Post-Finasteride Syndrome as an Epigenetic Post-Androgen Deprivation Syndrome: A potential pathological link between Drug-Induced Androgen Receptor Overexpression and Polyglutamine Toxicity

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Post-Finasteride Syndrome info & discussion forum

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Abstract

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/post-androgen-deprivation-syndrome-abstract/

Post-Finasteride Syndrome as an Epigenetic Post-Androgen Deprivation Syndrome: A potential pathological link between Drug-Induced Androgen Receptor Overexpression and Polyglutamine Toxicity

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Post-Finasteride Syndrome (PFS) is a rare and devastating disease encompassing persistent physiological, sexual, and neurological health problems following exposure to a 5alpha reductase inhibitor. The condition comprises a broad and variable clinical spectrum and is responsible for relationship breakdown, disability preventing work, isolation and suicide. Herein, the administrators of the patient support website propeciahelp.com summarise the current published research into PFS, add to the understanding of the condition, and present a mechanistic hypothesis to support further scientific investigation. We argue that PFS cannot be understood with exclusive consideration as to Finasteride and is of unappreciated significance to health and disease. More appropriately considered a Post-Androgen Deprivation Syndrome, patients are increasingly seeking support following exposure to diverse substances capable of anti-androgenic endocrine disruption including 5alpha reductase inhibitors, isotretinoin, serotonergic antidepressants, saw palmetto extract and concentrated phenolic compounds marketed as health supplements. A symptomatic and potentially mechanistic overlap between PFS and the polyglutamine disease Spinal and Bulbar Muscular Atrophy is discussed. Transgenic models illustrate that polyQ toxicity can be recapitulated through overexpression of the wild-type AR. Persistent AR overexpression has been established in symptomatic tissue of PFS patients and is a mechanistic consequence of androgen deprivation. We suggest that site-specific epigenetic changes induced by androgen deprivation may result in a pathological AR deregulation. The role of the androgen receptor as a ubiquitous and critical regulator in the physiological and neurological domains relevant to PFS symptomatology is reviewed. We urge clinical education to end psychosomatic misdiagnosis, aid patient management and ensure a genuinely informed consent before prescription of these substances to young men. We urge molecular-level investigation of PFS patients to achieve pathomechanistic understanding, discover safe therapeutic options and ultimately disease-modifying treatment. Discovery of predisposing genetic and epigenetic factors will aid in assessing the suitability of young patients for therapies with antiandrogenic modality, while promising significant translational insight to a range of disease states.

Post-Finasteride Syndrome, what makes it novel and propeciahelp.com

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Post-Finasteride Syndrome

Post-Finasteride Syndrome is a life-altering disease occurring rarely following therapeutic use of a 5-alpha reductase inhibitor such as Finasteride. PFS encompasses serious physical, neurological, and sexual symptoms of variable severity and distribution. Duration of use is not positively correlated with the severity or persistence of the symptoms of PFS, and although the condition can develop rapidly after many years of asymptomatic use, severely affected phenotypes can follow as little as one dose ?(Garreton et al., 2016; Than et al., 2018)?. The condition is currently without known predictive factors, disease-modifying treatment or effective therapeutic relief, and thus represents a serious and increasingly urgent unrecognised public health risk as online marketing for finasteride increases.

The diverse symptoms of PFS and their potential severity are not adequately appreciated by clinicians nor in medical literature ?(Traish, 2018)?. PFS presents heterogeneously, with variably severe symptoms from a broad constellation, in isolation or combination. Despite the significant interindividual differences in presentation, there are key commonalities in the disease behaviour. The health of the most severely affected patients is so profoundly impacted that they cannot continue their lives in a meaningful capacity. PFS is frequently causative of relationship breakdown, disability preventing work, isolation and suicide. Although of controversial practical application, Maslow's hierarchy of needs is a pervasive categorisation of motivating human needs ?(Kenrick et al., 2010)?. PFS, by this measure, can prove ruinous to the attainment of basic physiological needs in sleep and sex, safety needs in emotional security, financial security and health, and the interpersonal needs of friendships, intimacy and family.

Symptoms of PFS

Sexual dysfunction, including:

- Erectile Dysfunction
- Loss of libido
- Ejaculatory and orgasm disorders
- Clear, watery ejaculate
- Genital anaesthesia
- Post-orgasm exacerbation of symptoms

Symptoms of androgen-responsive tissue, including:

- Atrophy of penile tissue and penile deformation
- Venous leak, penile calcification, penile fibrosis
- Penile, testicular, perineal and prostate pain
- Testicular atrophy
- Muscle atrophy
- Muscular dysfunction, fasciculations, tremors
- Dry eyes
- Osteopenia, osteoporosis
- Tooth decay and tooth loss
- Skin pigmentation changes including darkened penile skin
- Thinned skin
- Dry skin
- Acceleration or deceleration of male pattern hair loss

Other physiological changes, including:

- Lessened beard growth and altered pigmentation
- Altered body temperature
- Gynecomastia
- Changes in fat distribution; Increased gynoid and android fat
- Alteration in allergic reactions

Neurological and Cognitive dysfunction, including:

- Depression, Anhedonia

- Memory failure (short term and long term)
- Cognitive impairment
- Anxiety and panic attacks
- Insomnia

Autonomic and sensory nervous system and somatic symptoms, including:

- Sinus arrhythmia, bradycardia, tachycardia
- Sleep apnoea (obstructive, central)
- Visual impairment and problems including visual snow
- Head pressure, vertigo and dizziness
- hearing difficulty and tinnitus
- Digestive impairment including dysmotility, pale stools, diarrhoea and constipation
- Numbness, tingling or stinging/burning sensations, often in distal extremities

Endocrine and metabolic alterations can include:

- Alteration in serum hormonal parameters including T, E, LH
- Deregulation between LH and T
- Low vitamin D3
- Increased triglycerides
- Increased creatine kinase
- Metabolic dysfunction, Insulin resistance, glucose intolerance
- Hyperbilirubinemia
- Decreased 3a-diol-G
- Lowered CSF neurosteroids

What makes PFS novel?

- Persistent and frequently permanent.
- Interindividually variable improvement or deterioration over course of disease progression.
- Disease ordinarily progresses in absence of the drug: Majority of cases involve rapid progressive onset or intensification of health problems that patients colloquially refer to as a "crash" after

cessation of drug.
- Heterogenous presentation: Differing symptoms and severities across patients with variable site-specific involvement.
- Severity is not positively correlated to length of exposure; severe multisystemically affected phenotypes occur after less than 1mg total.
- Atypical spatiotemporal involvement: More common in younger men taking lower dose for hair loss than older men using for BPH. Associated with greater disability in young men (FAERS data).
- Consequential endocrine fragility: Despite a frequent and curious symptomatic relief, severely affected patients liable to permanent phenotypical worsening following exposure to substances with antiandrogenic properties.

Characteristics inadequately explored in medical literature add significantly to the understanding of the condition and its peculiarity. While PFS is frequently mischaracterised as persistent side effects, in a majority of cases PFS involves the onset or intensification of health problems after cessation of the drug. This counter-intuitive phenomenon, which is often sudden and debilitating, is colloquially referred to as the "crash" by patients. Often, this follows a partial or sometimes even complete resolution of any side effects experienced on the drug. This is a remarkable and intrinsic novel characteristic so frequent that media coverage of the condition expresses awareness of the phenomenon ?(Morgans, 2018)?. The majority of PFS patients are younger men who have taken Finasteride 1mg, or a division of the 1mg or 5mg tablets, for treatment of AGA. This is represented in Adverse Drug Reaction (ADR) reports to the FDA FAERS scheme. FAERS data shows a markedly higher number of adverse event reports from this group, coherent with a higher incidence of associated disability ?(Baas et al., 2018)?. This is notably atypical in that ADRs are usually more common and severe in aged populations ?(Lavan & Gallagher, 2015)?. As finasteride is widely prescribed and PFS is proportionally very rare, there is likely to be a predisposition in consumers who develop PFS. The apparent prevalence in younger individuals, as well as reports of rapid development of the condition upon later rechallenge in previously asymptomatic or mildly symptomatic users further suggests the involvement of spatiotemporal factors, perhaps at the level of gene expression.

PFS is without a consistent biomarker, however patients with prior hormonal bloodwork will often report significant alterations to their serum hormonal profile following onset of the condition, including raised or reduced testosterone. Low luteinising hormone values is commonly reported. Additionally, low vitamin D and signs of metabolic alteration including increased triglycerides and elevated bilirubin can be frequently apparent. Basic urological evaluation may be subclinical or unrevealing, but this is not always the case and clinical evaluation of PFS patients describing a severe or total sexual dysfunction and penile changes who are clinically examined regularly receive relevant diagnoses including penile venous leak, microcalcifications, fibrosis and markers of neuropathy. These outcomes, are not dose dependent, often developing and progressing rapidly after cessation in severely affected patients who took only a single dose. Professor Daniel Stewart, a previously healthy man with no pre-existing mental or sexual dysfunction, developed PFS severely following little over one week of 1mg Finasteride. After cessation due to side effects he experienced the crash, developing sexual dysfunction, genital pain and atrophy,

severe muscle atrophy, weight loss, extreme fatigue, cognitive dysfunction, anxiety and insomnia. Daniel committed suicide at age 37 after suffering for eight months, writing to his family that "Finasteride has destroyed my mind and body". He had received a diagnosis of penile venous leakage ?(PFS Foundation, 2017)?.

Appreciation of PFS has often entailed a narrow clinical focus, and the reality is alarming drug-induced health problems that extend far beyond erectile dysfunction and depression. Given the diverse array of symptoms and lack of interdependence, it is in our view highly likely many consumers will have developed health problems they have failed to associate with the causative product due to the potential for insidious onset and counter-intuitive presentation after withdrawal. As of 2020, many symptoms are recorded in some capacity in medical literature, however the breadth is only apparent upon comprehensive review. Clinical characterisation of PFS in literature review is often incomplete and can be highly selective in line with the specialisation or hypotheses of the authors. The clear establishment of the multidomain symptom profile is therefore of paramount importance in line with increasing commentaries on the condition.

propeciahelp.com

Originating in 2003, propeciahelp is the largest and longest running website for patients suffering from persistent sexual, neurological and physiological side effects arising following use of the drug Finasteride (branded Propecia). Propeciahelp.com aims to provide a place of discussion for those affected by PFS. Propeciahelp's discussion forum is a vast record of PFS patient experiences and has been considered a source of clinical information ?(Diviccaro et al., 2020)?. Although the quality of discussion is variable, patient posts which provide clear accounts of individual symptoms, the manner of onset and disease progression are of clinical value. Submissions have been the subject of published attempts at recording and categorising the multi-system symptom profile ?(Walf et al., 2018)?.

In the absence of adequate clinical education regarding PFS, propeciahelp remains a key support to many patients. Along with the families of PFS patients who were driven to suicide by their symptoms, the administrative staff of propeciahelp assisted in the formation of the PFS foundation which has funded scientific research into the condition through charitable donations. To deliver a structured clinical characterisation of the condition, propeciahelp launched a comprehensive Post-Drug Syndrome Survey in March 2019 and recently passed 200 submissions from post-Finasteride patients experiencing persistent symptoms for a minimum of three months following cessation. We will seek to publish detailed results in the future.

As well as having designed and gathered the largest standardised self-reported dataset concerning PFS, over a decade operating the largest patient support website provides us with a unique insight into the clinical situation. The administrators of propeciahelp have herein summarised current research on PFS. We additionally present a contextual mechanistic hypothesis as basis for future investigation. The vital role of the AR in physiological domains relevant to the symptomatology of PFS is reviewed. This document is intended to aid those with scientific interest in understanding the condition and the practical expertise to uncover the molecular mechanisms underlying this remarkable disease.

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A summary of published research into PFS

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/a-summary-of-published-research-into-pfs/

In 2011, Traish et al. determined the possibility of a causal relationship between 5a-reductase inhibitor use and persistent sexual dysfunction in a subset of consumers. They reported the case of a young man who suffered significant sexual dysfunction, libido loss and a depressive symptomatology that continued 11 years after only weeks of exposure to finasteride for AGA ?(Traish et al., 2011)?. Irwig and Kolukula first characterised persistent sexual dysfunction in 71 otherwise healthy men who had used finasteride for AGA. 94% experienced low libido, 92% had erectile dysfunction, 92% developed decreased arousal, and 69% developed orgasm dysfunction. Compared with before use, mean sexual episodes per month dropped and sexual dysfunction score per Arizona Sexual Experience Scale increased ($P < 0.0001$) ?(Irwig & Kolukula, 2011)?. In a follow up report, 54 of these men were reassessed at a mean of 14 months following their initial interview dates. The mean age of the patients was 31 years and the mean age at assumption of finasteride was 26 years, with a mean duration of 23 months of use. Participants had no baseline sexual dysfunction or psychiatric conditions before use of finasteride. Persistent sexual side effects continued to be present in 96%. 89% of subjects continued to meet the definition of sexual dysfunction according to ASEX. Mean (± SD) total scores were 7.2±2.0 before finasteride, 22.2±2.6 after finasteride at the time of the interview, and 20.8±3.6 at reassessment. Severity of sexual dysfunction did not correlate to duration of finasteride use or duration of persistent effects. Irwig noted a broad range of commonly reported persistent effects beyond those formally assessed by the ASEX including decreased volume of ejaculate, loss of penile size and/or testicular size, testicular pain, prostatitis, penile curvature, reduced penile sensation, a reduction in spontaneous erections. Additionally, subjects reported difficulty sleeping, mental impairment, and depressive symptoms ?(Irwig, 2012b)?.

In a group of 61 PFS subjects who completed the BDI-II, rates of depressive symptoms were markedly higher (75%) than the control group (10%). While 3% of controls reported suicidal thoughts, this was significantly more frequent in PFS patients. 39% of PFS patients exhibited suicidality with 5% having chosen the statement "I would like to kill myself". Mean (± SD) scores from the 21-item BDI-II were 23.67 (± 12.56) in PFS patients and 5.93 (± 4.48) in the control group ($P < .0001$) ?(Irwig, 2012a)?. Irwig additionally reported a decrease in alcohol consumption in a cohort of 63 PFS patients compared to before use of finasteride. Mean alcoholic beverages consumed per week declined from 5.2±0.7 before finasteride to 2.0±0.3 after finasteride ($p < 0.0001$), consistent with observations regarding finasteride's attenuation of alcohol consumption in animal experiments ?(Irwig, 2013)?. Reporting androgen levels and semen parameters in 24 PFS patients, 13% were found to have low total testosterone and 13% had low serum DHT, however mean levels were close to other studies and could not explain the persistent symptoms. 16% (3 of 19) had severe oligospermia, whereas this finding would be expected in 3% of fertile-age men ?(Irwig, 2014)?. Considering the medical records of 6 men who committed suicide following use and cessation of finasteride, Irwig noted common symptoms of persistent sexual dysfunction and insomnia across all cases ?(Irwig, 2020)?.

Drasa et al. enrolled 35 patients with persistent sexual and nonsexual symptoms following use and cessation of finasteride for male pattern hair loss. Patients had an average age of 30 and mean use of finasteride was 24 months. Assessment was a mean of 12 months after discontinuation. ASEX completion with respect to before and after use of finasteride showed a mean increase of 14.75. 59% of patients experienced severe symptoms per the AMS. 68% of participants reported a worsening after cessation of the drug, and a trend of symptomatic worsening over the course of their condition was reported by 63%. Duration of use and symptom severity were not statistically associated ?(Drasa, 2014)?.

Ganzer et al. reported a characterisation of the persistent physical, psychological, and cognitive symptoms experienced by PFS patients who had used the drug for at least 3 months and experienced health problems after cessation of finasteride. The authors constructed a web-based questionnaire including ad-hoc questions based around a symptom profile generated from literature review and 100 private patients' reports to the author's practice. Demographic characteristics, data regarding use and cessation of the drug, and the onset of symptoms were also ascertained. Additionally, men were questioned as to the medical support they had sought and their satisfaction with their clinical assessment and treatments. 100 patients who had sought medical assistance were invited by email and additional patients were recruited from propeciahelp.com. No participant had a pre-existing sexual dysfunction or psychiatric condition. 93% reported having used the 1mg finasteride preparation. 84% of patients reported that they were asymptomatic during use of the medication and symptom onset began after cessation, rapidly so in 68% of patients. Respondents reported experiencing physical symptoms of fatigue (69%), muscle atrophy and weakness (56%), fasciculations (47%), decreased oil and sebum (41%), dry and thinned skin (68%), metabolic changes and increased fat deposition (54%). 14% of respondents reported a finding of raised fasting glucose and triglycerides. Sexual dysfunction included diminished libido (93%), loss of spontaneous and morning erections (89%), complete impotence (40%), reduced semen volume and ejaculatory force (82%), orgasm dysfunction (40%) and sexual anhedonia (70%). Penile atrophy (79%) scrotal atrophy (51%) and sensory changes were reported. 20% reported Peyronie's disease. Cognitive complaints were highly prevalent, including severe memory impairment (56%), mental cloudiness or brain fog (75%), impaired problem solving (69%) and attentional deficits (74%). Chronic insomnia was reported by 58% of men. Nearly three quarters of respondents reported increased anxiety, low mood, and anhedonia. Of concern, 63% of respondents had suicidal ideation and felt they could not keep living on with their extreme side effects. In terms of medical support, 50% had initially consulted a urologist while 62% saw their primary care provider. Physicians generally attributed physical symptoms to being of a psychological nature and recommended psychiatric consultation (69%). 93% of men were frustrated by clinical ignorance, inadequate recognition of the validity of their symptoms, and were dissatisfied with the medical care that they received. The authors conclude the aggregate multi-domain symptom profile could constitute a definable syndrome ?(Ganzer et al., 2014)?.

Chiriacò et al. conducted a similar retrospective evaluation. 79 men who had used finasteride for AGA and experienced persistent symptoms for a minimum of six months were asked to answer 100 ad-hoc questions, both a pre and post-finasteride ASEX questionnaire, and the Aging Male Symptom Scale

(AMS) questionnaire. Mean age of participants was 33. Finasteride had been taken for an average of approximately 2 years. All subjects were still symptomatic at assessment. 89.9% of participants noticed some symptoms during finasteride use, and the trend of symptoms after discontinuation was worsening in 62% of patients, with a trend of improvement reported in 13.9%. Sexual symptoms included loss of penile sensitivity (87.3%), decreased ejaculatory force (82.3%), decreased penile temperature (78.5%), reduced ejaculate volume (73.4%), reduction in penile dimension (65.8%), perineal tightness (45.6%). Other symptoms included anhedonia (75.9%), concentration problems (72.2%), loss of muscle tone and mass (51.9%), and increased body weight (48.1%). Post-finasteride ASEX score ranged from 13–30 (21.0 ± 2.67), with 78.5% having ASEX ?19 points indicating sexual dysfunction. This included 44.3% of patients indicating severe difficulty or incapability of getting/keeping an erection. Pre-finasteride ASEX score was far lower ($p < 0.001$) ranging 5–15 (7.7 ± 2.52), indicating no overt sexual dysfunction. Of 78 patients with available data, all had some signs of androgen deficiency per the AMS, with 60.3% with an AMS score of ?50 points indicating severe deficiency. The authors note the reports by their PFS patients suggest androgen deficiency across different tissues where 5alpha reductase is expressed at an average of four years after finasteride discontinuation, indicating that permanent changes occurred in the human body ?(Chiriacò et al., 2016)?.

Walf et al. sought to characterise persistent symptoms following finasteride treatment and its discontinuation by assessment of subjective patient reports on propeciahelp.com. 244 cases were isolated from discussions in a discrete time period. Walf et al. placed symptoms into four broad categories: Antiandrogenic effects, estrogenic effects, central effects and nonspecific adverse effects. Antiandrogenic adverse effects were described to be genital dysfunction, testicular dysfunction and infertility, accessory sexual or genitourinary organ dysfunction, psychosexual function, and hormonal function. Estrogenic AEs included breast cancer, breast neoplasm or breast mass, gynecomastia, breast pain, and increased serum estrogen. Central effects involved depression, anxiety, confusion and “brain fog”, insomnia and attentional difficulties. The nonspecific/severe AEs were defined as muscle twitching, lower back pain, weight gain, fatigue, numbness in the anal region, muscle spasms, excessive sweating, bleeding gums, tinnitus, hot flashes, irregular stool, scoliosis, and discoloration of the urine. While these presented heterogeneously, some individuals experienced adverse events across all categories ?(Walf et al., 2018)?.

In a retrospective control matched study, Di Loreto et al. evaluated expression of the androgen receptor and nerve density in multiple cell lines of prepuce tissue in PFS patients aged 29–43 years who had experienced persistent sexual symptoms for over 6 months, with the notable finding of persistent androgen receptor overexpression (Di Loreto et al., 2014). Patients had used finasteride for an average of 32 months and had stopped using an average of 56 months to the point of study, at which point all patients remained symptomatic. PFS patients self-reported symptoms including loss of penile sensation, erectile dysfunction, pain in the penis, scrotum or testes, penile tissue changes, reduced penile dimensions, and reduced volume of ejaculate. PFS cases experienced sexual dysfunction at point of interview per Arizona Sexual Experience Scale (22.5±2.78). PFS patients were additionally asked to complete the ASEX survey considering themselves before use of finasteride and these pre-finasteride scores indicated no pre-existing sexual dysfunction (7.6±1.92). Histological evaluation of nerve density revealed similarity with controls. Immunohistochemistry revealed a significantly higher percentage of

nuclear AR-positive epithelial cells in all cases (mean±SD, 80.6±8.63%) than in controls (mean±SD, 65.0±19.1%), P = 0.043. Stromal cells in all cases showed a significantly greater expression of AR in the nuclei compared to controls (mean±SD, 40.0±15.1% in cases versus 23.4±8.68% in controls), P = 0.023. Percentage of AR positive vessel smooth muscle cells did not differ significantly between the 2 groups. Averagely, AR positive cells in the 3 tissues was higher in cases than in controls. Di Loreto et al. speculate that the ostensibly permanent effects could be due to mechanisms of ageing prematurely induced by artificially reduced androgen levels with finasteride. They conclude a better understanding of the molecular events may inform possible therapies for these severe effects in young men of fertile age ?(Di Loreto et al., 2014)?. Although unreported in the manuscript, La Marra, co-author of the study, further elaborated on the data in a thesis centring on the investigation. He reported the percentages of AR positive cells are always higher in the cases than in the controls. He further reported positive correlations between the increase of AR levels in the epithelial and stromal cells and the decrease in ability/frequency to perform sexually per the AMS, the increase of AR in the vessels cells and the intensification of ASEX sexual dysfunction and physical exhaustion, and the increase of AR in the epithelial cells and the worsening of muscular weakness and feeling "burnt out" per AMS. La Marra noted that exogenous androgens do little to improve - and sometimes worsen - PFS symptoms, concluding that investigations should centre on epigenetic alterations relevant to the changed sensitivity of the AR ?(La Marra, 2010)?. Di Loreto's investigation was the first to report significant objective differences at the molecular level and it has subsequently been suggested that local AR levels could play a pathological role in PFS ?(Than et al., 2018; Traish, 2018)?.

Demonstrating multisystem involvement in absence of what the authors regarded to be the "typical" neurological and sexual complaints, Gupta et al. reported a 33 year old man with PFS who suffered itching, burning micturition, abdominal discomfort, skin rash, and seborrhoea after a first use of 0.5mg dutasteride for a month. These symptoms subsided with the adoption of exercise but had reoccurred and persisted after attempting AGA therapy with finasteride 1mg four years later. Keratotic follicular papules and pustules were apparent on his shoulders and back. Semen analysis revealed pus cells and moderate growth of Enterococcus faecalis following culture. Therapeutic attempts over the following years at three centres were not successful ?(Sharma et al., 2016)?. Motofei also reported an uncommon presentation in a 52 year old who presented with generalised vitiligo 2 months after cessation alongside symptoms including bilateral gynecomastia, sexual dysfunction and depression that were not present upon pre-treatment evaluation ?(Motofei et al., 2017)?.

Cecchin et al. reported a significantly higher occurrence of "extreme length" AR polymorphisms (CAG-rs4045402 and GGN-rs3138869) in PFS patients following finasteride use for AGA as compared to controls without AGA, suggestive of a potential genetic role in the development of AGA and PFS ?(Cecchin et al., 2014)?. Cauci et al. expanded on this in a subsequent study exploring the relationship of AR polyglutamine stretch-encoding (CAG) and polyglycine stretch-encoding (GGN) polymorphisms with the individual symptoms of PFS in 66 patients experiencing symptoms for a median of three years after cessation. Patients were asked to describe their trend of symptoms after discontinuation (improved, unchanged or worsening). 57.6% of PFS patients responded that their trend after was worsening. Androgen receptor polymorphisms were correlated to the frequency of several PFS symptoms. Patients

completed a bespoke symptom questionnaire in addition to the ASEX and the AMS. While total scores of the ASEX and AMS did not differ with length of (CAG)n and (GGN)n repeats, significant differences were found within individual PFS symptoms. Patients with shorter CAG repeat lengths (9-19) used finasteride for a shorter time than those with medium (20-24) or long (?25) repeat lengths, and 83.3% of this short CAGn group reported severe libido loss, scoring 5 on item 17 of the AMS. Increased body weight (>2kg) following use of finasteride was most associated with those with long CAG repeats. Interestingly, skin dryness showed a parabolic curvilinear profile, with short and long CAGn groups having higher frequencies (50% and 63.6% respectively) than the medium CAGn group (18.9%). Muscle spasms were found to be more frequent amongst long CAGn carriers (72.7%). Patients with long (>23) GGN repeats did not report experiencing scrotal pain compared with 34.1% of those with medium (23) GGN repeats and 32.7% of those with medium to short length (?23) repeats. Penile pain was likewise more often seen in those with short or medium rather than long GGN repeats (34.6% vs 7.1%). Long GGN repeats were also associated with a better phenotype regarding fatigue, loss of vitality, depression and the feeling of passing one's peak than those with medium repeats. Loss of perineal fullness was reported by 100% of men with short GGNn repeat lengths, 70.5% of men with medium GGN repeats and 57.1% of those with long repeats. The results of Cauci et al. suggest genetic involvement in the symptom profile of PFS, and the authors conclude the need for much more research into the pathophysiology, particularly with a precision medicine approach ?(Cauci et al., 2017)?.

In a clinical assessment of 24 PFS patients, Basaria et al. found no significant sequence variations in AR, SRD5A1 or SRD5A2. Depression scores were significantly higher in PFS patients via BDI, Hamilton Depression inventory and PHQ-9. PHQ-9 scoring was not significantly related to either the duration of finasteride use or the time since discontinuation of the drug. Some characteristics were measured and were not significantly different to controls. No hormonal correlate able to account for the pathological presentation was identified. Two fMRI measurements suggested neurobiological abnormalities PFS patients. fMRI of PFS patients' brains in response to erotic stimuli was conducted. Worsening IIEF scores correlated to increased activity in the neural areas the authors deemed to correspond with sexual arousal, while activity in brain regions associated with higher level cognitive and motivational networks decreased concomitantly, revealing a dissociation in activity that may be a marker of neural changes following use of finasteride. Blood-oxygen dependent activity in brain areas implicated in major depression were also identified in PFS patients with correlation to BDI scores pertaining to negative affect ?(Basaria et al., 2016)?. This study included limited gene expression assay of skin taken from the back of symptomatic patients and non-symptomatic finasteride users. Although the paper stated that "we did not find evidence of...significant alterations in expression of AR-dependent genes in the skin", this is not completely reflective of the statement in the study's supplementary appendix: "While the DESeq analysis determined there were statistically significant differences in a few of the androgen-regulated genes, the hierarchical clustering analysis revealed that the symptomatic and non-symptomatic subjects did not share the immediate cluster" (Basaria et al., 2016 appendix: methods).

Melcangi et al. Performed case-controlled clinical evaluations of 16 PFS patients aged 22-44 with a strong focus on the neurological presentation of the syndrome. Mean treatment duration was 1037 days with a range of 451–4697 days between cessation of finasteride and clinical evaluation. 50% of PFS

patients were deemed to suffer from major depressive disorder per screening with the Mini-International Neuropsychiatric Interview, and scores of Beck Depression Inventory and Beck Anxiety Inventory were significantly higher in those with MDD. Ten patients experienced severe ED per the IIEF15, while the remaining 6 exhibited mild to moderate ED. Ultrasound determination of testicular volume was calculated to be normal in patients. Objective markers of neuropathy were determined in 25% of patients via sensory evoked potentials of the pudendal nerve, while 75% of the patients had normal PN_SEPs. No evidence of metabolic, toxic, or inherited disease associated with peripheral nervous system damage was detected. Interestingly, depression scores were not correlated to PN_SEPs while sexual dysfunction scores were. The cerebrospinal fluid of 14 patients was analysed with comparison to 25 healthy age-matched controls. Significant differences were determined. Pregnenolone, isopregnanolone, progesterone and dihydroprogesterone were significantly decreased, while levels of dehydroepiandrosterone (DHEA), testosterone and 3?-diol were increased. Additionally, 17?-estradiol and DHT were decreased. Plasma determination showed differences to the CSF findings. In serum, pregnenolone, tetrahydroprogesterone, DHEA and T were significantly increased, while dihydroprogesterone was significantly decreased ?(Melcangi et al., 2017)?. This disruption in neurosteroids is notedly heterogenous and differed slightly to findings from their previous pilot study involving 3 PFS patients ?(Melcangi et al., 2013)?. Melcangi et al. later reported that the gene promoter of SRD5A2 was methylated in CSF samples of 9 of 16 PFS patients (age 34.5 ± 8.8 years) compared with 1 of 13 age-matched controls. Interestingly, the single control with SRD5A2 methylation had a diagnosis of normotensive hydrocephalus. Amongst PFS patients the methylation ranged from 15.4 to 100%. Neither depression, anxiety or erectile dysfunction scoring via validated scales were correlated to methylation status. Methylation was not found in blood DNA, demonstrating tissue specificity. SRD5A1 was found to be unmethylated across samples and groups ?(Melcangi et al., 2019)?.

Rubin et al. Performed penile duplex Doppler ultrasound examination with a high frequency probe during maximal pharmacologic erection on 27 PFS patients. Patients had a mean age of 31, no known cardiovascular risk factors, and had sexual dysfunction following use of finasteride. 26 of 27 patients (96%) demonstrated lack of homogeneity and hyperechoic/hypoechoic regions in erectile tissue. They concluded induced corporal smooth muscle apoptosis and fibrosis may represent a biologic pathophysiology responsible for impairing tissue expandability resulted in venoocclusive dysfunction and ED ?(Rubin et al., 2018)?. Mirabal et al. issued 25 patients with persistent symptoms following 5ari use for AGA and 25 controls a range of validated questionnaires related to self-reported symptomatology including the IIEF, the International Prostate Symptom Score (IPSS), the Patient Health Questionnaire-9 (PHQ-9) and the Androgen Deficiency in the Aging Male (ADAM). Post-5ari patients had significantly higher median scores compared with controls in the IIEF (35 vs 29, $p=0.035$), the IPSS (10 vs 3, $p < 0.01$), the PHQ-9 (10 vs 1, $p < 0.001$), and had significant differences in all questions of the ADAM. Penile duplex doppler ultrasound revealed vascular abnormalities in 17 (68%) post-5ari patients. Alarmingly, 2 (8%) of post-5ari patients committed suicide during and after the study. Mirabal et al. concluded that there may be persistent genitourinary, physical, psycho-cognitive, anti-androgenic and penile vascular changes after 5ARI discontinuation in addition to persistent sexual dysfunction ?(Mirabal, 2019)?.

Epidemiological research into PFS has thus far been limited to sexual dysfunction and depressive symptoms. Ali et al. used data mining techniques with FAERS data to conduct a retrospective pharmacovigilance disproportionality analysis. They analysed reports of sexual dysfunction and suicidal ideation between 1998 and 2013 in men aged 18-45 who had used low-dose finasteride. Supportive of survey research previously discussed, the data revealed that a strong signal of persistent sexual dysfunction and disproportional reporting of suicidal ideation. Most sexual dysfunction reports were serious, with 43.5% resulting in disability. 87% of incidences of suicidal ideation occurred in men also experiencing sexual dysfunction from low-dose finasteride. Most of these events were classed as serious (e.g., contributed to the patient's death, hospitalization, or disability). Ali note there is mechanistic plausibility in the link between finasteride and the risks of sexual dysfunction and suicidal ideation, and that the disproportional reporting could be symptoms of Post-Finasteride Syndrome. The authors conclude that, although a causal link cannot be inferred from this study due to the nature of the data, young men receiving low-dose finasteride for AGA are at risk of persistent sexual dysfunction that may lead to suicidal ideation ?(Ali et al., 2015)?.

Kiguradze et al. have provided a well-designed analysis of a large set of data from the Northwestern Medicine Enterprise Data Warehouse with sole regards to persistent erectile dysfunction following use of finasteride or dutasteride. They conclusively identified a strong and intrinsic association between debilitating persistent sexual dysfunction and exposure to low dose finasteride or dutasteride. Duration of 5-alpha reductase inhibitor exposure was a greater predictive risk factor for ED in young men than all other assessed factors. Of 4,284 young men, without prior sexual dysfunction, taking finasteride at a dose less than 1.25 mg/day, 34 (0.79%) developed persistent erectile dysfunction with a median 1,534 days after drug cessation (interquartile range of 651–2,351 days). Of 103 young men with new ED, 34 (33%) had new persistent erectile dysfunction ?(Kiguradze et al., 2017)?.

Through obtaining finasteride-related adverse events catalogued by the FAERS reporting system between April 2011 and October 2014, Fiuk et al. identified 105 women with finasteride-associated adverse events following use. These included typical PFS symptoms including dry eyes, sleep disturbances and suicidal ideation as well as hearing loss, renal failure, urosepsis, new incidences of breast cancer, haemorrhagic diathesis. They concluded female PFS patients represent a small but real subset of long term finasteride-related adverse events, and that further etiological investigation of this devastating syndrome is crucial ?(Fiuk et al., 2016)?.

In addition to the significant primary findings in PFS patients discussed, the subject is far more regularly the focus of literature review. Than et al. concluded that the existing evidence well supports the existence of persistent sexual, physical, neurological and central effects following 5alpha reductase inhibitor exposure, and that a growing understanding of the constellation of symptoms describing PFS can inform prescribing clinicians as to the risk and benefit of prescription ?(Than et al., 2018)?. Traish considered that the magnitude of the broad and serious symptomatology of the syndrome is inadequately appreciated. Persistent loss of libido and erectile dysfunction are recognised to be serious issues pertaining to quality

of life and wellbeing, as well as "signs of something terribly amiss with physiological process". Traish further deemed it imperative that the scientific and medical communities act now to seek a better understanding the pathophysiology of this serious and debilitating disorder, expand awareness amongst physicians and patients, and develop tools for treatment ?(Traish, 2018)?. Said and Mehta concluded that comprehensive literature review shows a disproportionately high number of men with 5-? reductase inhibitor-associated sexual dysfunction and infertility, and that though uncommon, broad sexual and reproductive symptoms that are both serious and persistent can occur. They note that while methodological concerns have been raised regarding the possibilities of recall and selection bias in the questionnaire-based study of PFS patients, their results parallel scientific observations about the long-term pathophysiological changes induced by finasteride, even after treatment discontinuation. They suggest physicians engage in productive conversation regarding the potential impact of these medications on their health and quality of life before 5alpha reductase inhibitor prescription ?(Said & Mehta, 2018)?.

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Finasteride Drug origin, pharmacology, AR structure and androgen action

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/finasteride-drug-origin-pharmacology-ar-structure-and-androgen-action/

Androgens, the androgen receptor and the expanding understanding of its role in health

Androgens are well appreciated for their critical developmental role in sexual differentiation ?(Forger, 2018)?, male characteristics, the development and maintenance of male sexual organs and sexual function ?(C J Bagatell et al., 1994; Podlasek et al., 2016; A. M. Traish, 2008; Yamada et al., 2006)?. However, androgens are now known to play a "pleiotropic role...in virtually all body systems" ?(Gibson et al., 2018)?. Gibson et al. identify four key areas in which the understanding of the role of androgens has evolved and expanded in the 21st century: Testosterone's recognition as a "Goldilocks" molecule, with too much or too little androgen signalling disrupting cellular homeostasis and proving deleterious to health, a dynamic and tissue specific regulation of intracrine androgen metabolism, an increased understanding of the role of androgens in female reproductive tissue, and the extensive role for androgen-mediated regulation in tissue beyond the reproductive system in both sexes ?(Gibson et al., 2018)?. At the tissue level, there are tightly controlled optimum levels for androgen concentrations. Owing to the crucial role of androgen intracrine biosynthesis and metabolism in the physiology of peripheral tissues in males and females, dysregulation can impair both local and systemic metabolic homeostasis ?(Carrie J. Bagatell & Bremner, 1996; Schiffer et al., 2018)?.

Nuclear receptors are ancient proteins well conserved across evolutionary time and are present across the Metazoa ?(King-Jones & Thummel, 2005)?. The effects of androgen steroids are primarily mediated through the Androgen Receptor ?(Verhoeven & Swinnen, 1999)?, a class I steroidal receptor protein which binds androgens as ligand in the cytoplasm, dissociates from chaperones and translocates to the nucleus ?(Davey & Grossmann, 2016; Ni et al., 2013; Tsai & O’Malley, 1994)?. The AR is ubiquitously expressed across most bodily tissues including the brain and nervous system, penis, testes, prostate, skeletal muscle, skin, liver, urinary bladder, gastrointestinal tract, arteries, kidneys, breast, uterus, bone, adrenal glands, and teeth ?(Dale et al., 2002; Fujimoto et al., 1994; Gannon et al., 2019; Heemers & Tindall, 2007; Khalil et al., 2018; Kimura et al., 1993; Mhaouty-Kodja, 2018; Ruizeveld de Winter et al., 1991; Schultheiss et al., 2003; Sinha-Hikim et al., 2004; Vanderschueren et al., 2014; Verhoeven & Swinnen, 1999; Wu et al., 2019; Xia et al., 2019)?. Significant evidence has demonstrated the AR is expressed across many areas of the brain in both sexes including the temporal, medial preoptic, hypothalamus, amygdala, bed nucleus of the stria terminalis, midbrain, frontal and prefrontal areas, cingulated gyrus, and limbic regions including the hippocampus, where it is critical to important

neurocognitive functions including reproductive behaviour, reward behaviour, learning, memory, spatial awareness and metabolic regulation ?(Beyenburg et al., 2000; Brock et al., 2015; Lu et al., 1998; Morford et al., 2018; Shah et al., 2004; Simerly et al., 1990; Tobiansky et al., 2018)?. The role of the AR in disease cannot be overstated ?(Koryakina et al., 2014)? owing to its role as an important hub mediating multiple cellular signals and functions ?(Lai et al., 2012)?.

The AR is coded from eight exons located in the long arm of the X-chromosome ?(J. Brand & M. Dehm, 2013; Lubahn et al., 1988)?, lacks a TATA and CCAAT box in the regulatory promotor, and is comprised of four distinct domains acting together to mediate genomic effects of androgens in target tissue. These are the N-terminal domain, the DNA binding domain, the hinge region, and the C-terminal ligand binding domain ?(Brinkmann et al., 1989; Lanciotti et al., 2019; Mangelsdorf et al., 1995; I J McEwan, 2004)?. The AR is regulated by ligand binding, interaction of functional domains (such as N/C terminal interaction), homodimerization and cofactor interactions ?(van Royen et al., 2012)?. The N-terminal domain is intrinsically disordered and exists as collections of conformers, allowing rapid impermanent structural alterations in response to the cellular environment and binding of multiple coregulators with distinct outcomes ?(Kumar & McEwan, 2012; I. McEwan & Monaghan, 2016)?. This region contains polymorphic glutamine and glycine tracts ?(Wadosky & Koochekpour, 2016)?. The ligand independent AF-1 surface in the N-terminal domain interacts with coregulators ?(Heinlein & Chang, 2002)?. More than 200 AR-interacting proteins with either coactivator or corepressor activities are known ?(Chang & McDonnell, 2005)?. The open structure of the ligand binding domain (LBD) adopts a compact structure when bound to agonists, which are then sealed within hydrophobic interior ?(Iain J. McEwan & Kumar, 2015)?. Helix 12 is repositioned to form a surface for transcription promoters ?(Hur et al., 2004)?. The LBD contains AF-2 which is pivotal to the ligand-dependent full activation of the androgen receptor ?(Narayanan et al., 2018)? and is affected by coregulators. The AF-2 has high affinity for a highly conserved 5-residue FQNLF motif in the N-terminal segment of the N-terminal domain. The LBD binding to this region facilitates activation, and molecular chaperones compete for binding and prevent activation of the AR in a delicate balance of protein-protein interaction that is seemingly regulatory of activity, solubility, concentration and AR turnover ?(Eftekharzadeh et al., 2019)?. A nonclassical zinc finger structure in the DNA Binding Domain functions to recognise and make contact with nucleotide sequences, while a second mediates dimerization on DNA ?(Iain J. McEwan & Kumar, 2015)?. The activation of the AR and targeting of androgen response elements results in increased transcription of a host of genes, many of which control cell growth, proliferation and regulation of apoptosis ?(Heemers & Tindall, 2007)?. Liganded AR also activates coregulators distinctly from its DNA binding capability ?(Slagsvold et al., 2001)?. The human AR has AREs and autoregulates its own gene in a tissue-specific manner ?(Hunter et al., 2018)?. The AR has functional roles beyond transcription, and nonclassical AR mediated actions occur via the ERK, SRC, PI3K, MEK and AKT pathways ?(Deng et al., 2017; Vanderschueren et al., 2014)?. Recently, ubiquitously expressed specific G protein-coupled receptors known as membrane androgen receptors have been described by which androgens mediate rapid intracellular actions and diverse nonclassical processes, eliciting significant physiological and behavioural effects in animals and humans within seconds or minutes ?(Balthazart et al., 2018; Foradori et al., 2008; Geniole et al., 2019; Kalyvianaki et al., 2019; Thomas, 2019; Thomas et al., 2018)?. Testosterone association to membrane AR exerts a rapid regulatory influence over classical genomic AR signaling ?(Deng et al., 2017; Li et al., 2018)?, and appreciation of these effects are therefore more accurately characterised as nonclassical as opposed to nongenomic ?(Balthazart et al., 2018)?. The rapid

nonclassical actions of the mAR ZIP9 are vulnerable to disruption by endocrine disrupting chemicals known to interfere with classical androgen signaling, and the toxicological consequences of this are currently unclear ?(Thomas & Dong, 2019)?.

The primary male steroid hormone and AR ligand testosterone is produced by the Leydig cells of the testes (Schiffer et al., 2018). Testosterone is synthesised from cholesterol (Miller, 1988) through a number of steps originating with p450 side-chain cleavage conversion to pregnenolone in the inner mitochondrial membrane (Selvaraj et al., 2018). Leydig cell production of testosterone is stimulated in response to the anterior pituitary releasing LH in response to a pulsatile release of LHRH by the hypothalamus, and testosterone regulates LHRH release via a negative feedback loop (Heemers & Tindall, 2007). Androgen signalling is amplified in target tissue through the metabolism of T to 5?-dihydrotestosterone (DHT). DHT is the most potent endogenous androgen (Pretorius et al., 2016; Rege et al., 2013), with a four-fold higher binding affinity for the androgen receptor (Gao et al., 2005) and a three-fold lower dissociation rate than that of testosterone (Wilson & French, 1976). Agonists form hydrogen bonds to the AR with high occupancy, with DHT bonding to residue Thr877 and testosterone bonding at Asn705 (Azhagiya Singam et al., 2019). DHT binding causes the AR to undergo conformational change to its DNA binding state (Kovacs et al., 1984), and increases synthesis and degradation of the AR protein (Syms et al., 1985). However, tissue-level factors regulating metabolism including local intracellular ligand concentrations influence binding in addition to relative ligand affinities, and as such DHT does not always bind preferentially compared with T (Swerdloff et al., 2017).

Circulating T is more important than serum DHT for optimizing the intracellular DHT concentrations due to the presence of a rate-limiting enzyme, 5a-reductase. Testosterone is metabolised to DHT irreversibly by the catalytic microsomal enzyme 5?-reductase type 2. 5AR2 is a hydrophobic membrane-bound protein comprised of 254-260 amino acid residues (Russell & Wilson, 1994). The 5?-reductase family of enzymes are diffusely expressed across a large number of tissues, and exert a profound effect on human health due to their regulation of steroid metabolism and metabolic functions including glucocorticoid clearance ?(Abdulmaged M. Traish et al., 2014)?. 5ar enzymes catalyze the reduction of the double bond in the A-ring at ?4,5 position in C-19 and C-21 steroids ?(Azzouni et al., 2012; Abdulmaged M. Traish et al., 2015)?.

Development and pharmacology of Finasteride

Loss of appropriate androgen signaling is associated with diverse detrimental effects in males, as evidenced by the well appreciated side effects of androgen deprivation therapy. ADT is known to induce bone problems, metabolic dysfunction, sexual dysfunction, reduction of penile and testicular size, gynecomastia, fatigue, vasomotor flushing, memory, cognitive and psychosocial impairments ?(Nguyen

et al., 2015)?. Heightened androgen action is directly implicated in pathologies including benign prostate hyperplasia, prostate cancer ?(Banerjee et al., 2018)?, bladder cancer ?(Gil et al., 2019; Liu et al., 2018)?, androgenic alopecia ?(Lai et al., 2012)?, lower urinary tract symptoms and polycystic ovary syndrome ?(Apparao et al., 2002)?. As 5alpha reductase is largely responsible for tissue DHT levels, 5alpha reductase inhibitor products can alleviate symptoms owing to reducing pathological androgen receptor activation. Significant increases in serum DHT via exogenous DHT administration have little effect on prostate DHT concentrations, prostate size, and lower urinary tract symptoms ?(Swerdloff et al., 2017)?. Considering misconceptions likely arising from the lowered serum levels following 5alpha reductase inhibitor therapy coinciding with symptomatic relief in these domains, Swerdloff et al. note this illustrates fundamentally important control mechanisms in androgen target tissues that finely regulate androgen synthesis and degradation pathways to maintain DHT homeostasis, to which circulating DHT levels are of much less importance than that of T ?(Swerdloff et al., 2017)?. Beyond these primary androgens, around 5-10% of serum androgens include dehydroepiandrosterone, androstenediol, and androstenedione, which can be produced by ACTH-regulated adrenal synthesis ?(Rainey et al., 2002)?.

The prostate is a strictly androgen dependent structure ?(Banerjee et al., 2018)?. The link between androgens and prostate growth was established in the mid-20th century ?(Nelson, 2016)?. Concurrently, androgens were understood to be both a strict requirement and driver of male pattern hair loss ?(Hamilton, 1942)?. The selective 5alpha-reductase type 2 inhibitor Finasteride is a 4-azasteroid that was developed as a treatment for benign prostate hyperplasia (BPH) and androgenic alopecia (AGA) by Merck. This programme followed Imperato-McGinley's identification and profiling of pseudohermaphroditism in males with genetic 5aR deficiency ?(Imperato-McGinley et al., 1974, 1991)?. These (46XY) males demonstrate at birth a marked ambiguity of external genitalia and are frequently raised as girls. However, a notable change occurred at puberty during which they developed a typical male phenotype, including virilisation of ambiguous genitalia into a functional penis and male psychosexual orientation regardless of prior female designation and rearing ?(Imperato-McGinley et al., 1974; Imperato-McGinley & Zhu, 2002)?. In adulthood this cohort display little body hair, minimal beard growth, no hairline recession, no acne and significantly smaller prostates. Finasteride clinical research and development leads viewed genetic 5ar2 deficiency as a predictive model for the chronic inhibition of the 5ar2 enzyme in the adult male ?(Stoner, 1990)? and that enzymatic inhibition with finasteride would mimic a genetic 5ar2 deficiency ?(GORMLEY et al., 1990)?. Without consideration as to the devastating outcomes for a subset of consumers, finasteride appears to be tolerated in most men.

Finasteride exhibits a highly unusual and nonlinear dose-response. Maximum DHT suppression is achieved after a single 1mg dose. It is markedly suppressive of DHT at all daily doses between 0.04 and 100mg over two weeks. Steady-state DHT levels were reduced to between 0.1-0.15ng/ml at all doses tested by Gormley et al, with DHT levels returning to pre-treatment levels within 14 days of cessation ?(GORMLEY et al., 1990)?. 0.05 to 5mg finasteride produces a 60% reduction in DHT in scalp skin. Similarly, a dose of approximately 0.2 mg of finasteride is not appreciably different to 5mg in terms of serum DHT reduction, suggesting this drug is profoundly effective at low doses ?(Frankel, 1999)?. Preferentially binding to the 5ar2 enzyme though with a notable lesser effect on 5ar1, finasteride is a pseudo-irreversible mechanism-based inhibitor that is exceptionally potent, specific, and unusually

efficient. The enzyme-bound inhibitor complex follows parallel reaction coordinates that proceed through closely related enolate intermediates as testosterone's reduction to DHT, with the two reactions proving divergent in the final step, as detailed by Bull et al ?(Bull et al., 1996)?.

No meaningful assessment of lasting sexual dysfunction was published during the clinical development of finasteride or dutasteride ?(Kiguradze et al., 2017)?. Meta-analysis of 34 clinical trials of Finasteride for use in androgenic alopecia discovered serious flaws, poor quality reporting and systematic bias ?(Belknap et al., 2015)?. None of the 34 articles considered had adequate safety reporting. Of 25 clinical trial reports with a control arm, none reported on blinding adequacy. 18 publications (53%) disclosed authors with conflicts of interest, while 19 articles (56%) received funding from a pharmaceutical manufacturer of finasteride. 12 articles (35%) did not disclose their funding. Nonsexual adverse drug events were not reported in 28 articles. One report found a clinically and statistically significant increase in Beck Depression Inventory Scores after exposure to finasteride but did not adequately assess adverse effects other than depression. Noting the flaws in reporting raised by Belknap, Lee et al. meta-analysed fifteen trials and nevertheless concluded a 1.55 fold increased risk of sexual dysfunction including erectile dysfunction, loss of libido and ejaculatory dysfunction with oral use of finasteride ?(Lee et al., 2018)?.

The typical physiological response to finasteride in animals and humans is not sufficient to account for PFS, its remarkable dose-independent severity, or the common worsening and progression following withdrawal. However, it is important that significant basic science evidence illustrates finasteride interacts with the broad physiological systems affected in PFS ?(Irwig & Kolukula, 2011)?. Use of finasteride is an identified risk factor for male infertility ?(Samplaski et al., 2019)? and has been associated with a variably reversible depletion in sperm count in humans at 5mg and 1mg doses ?(Amory et al., 2007; Samplaski et al., 2013)?. Recent animal research reveals not only lasting decreases in fertility parameters in finasteride exposed animals ?(Garcia et al., 2012)?, but a negative impact on the fertility of the next generation ?(Kolasa-Wolosiuk et al., 2015; Kolasa-Wo?osiuk et al., 2018, 2019)?. Reduced androgen levels in the offspring of finasteride treated adult male rats have been noted as similar to those reported in studies exploring the effects of prenatal exposure to the antiandrogenic endocrine disruptors flutamide and vinclozolin ?(Kolasa-Wo?osiuk et al., 2019; Ostby et al., 1999)?. In gerbils, low doses of Finasteride have been demonstrated to cause structural alterations in the prostates of both sexes, as well as lasting upregulation of the AR in the prostate epithelium of intrauterine exposed males, suggested to be a compensatory response to the low available DHT ?(Maldarine et al., 2019)?. 5alpha reductase inhibition induces erectile dysfunction in rats that is not fully reversed by washout ?(Öztekin et al., 2012; Pinsky et al., 2011)?. Histopathological evidence of marked atrophic changes in prostatic epithelial tissues, loss of penile smooth muscle content and prominent collagen deposition in penile cavernosal tissues has been reported in rats treated with either Finasteride or Dutasteride ?(Sahin Kilic et al., 2018; Shen et al., 2003; Zhang et al., 2013)?, suggesting direct deleterious effects on the penis and on erectile function.

Rats subchronically treated with finasteride for 20 days showed depressive behaviour and hippocampal alterations one month after withdrawal ?(Diviccaro et al., 2019)?. Additionally, disruption of

neurosteroids and steroid receptors, including an upregulation of the AR in the cerebral cortex, persisted a month after 20 days of low-dose finasteride treatment in rats, suggesting lasting structural and functional consequences on brain function ?(Giatti et al., 2015)?. Finasteride has broad consequences upon the formation of centrally active steroids and neurosteroids ?(Soggiu et al., 2016; Abdulmaged M. Traish, 2018)?. Neurosteroids are important to a range of central functions including HPA regulation and their dysregulation has a determinant role in neuropsychological abnormalities ?(Belelli & Lambert, 2005; Calogero et al., 1998; Camille Melón & Maguire, 2016; Carver & Reddy, 2013; Maguire, 2019)?. Allopregnanolone, determined to be low in the central nervous system of PFS patients ?(Melcangi et al., 2017)?, has a known role in increasing neurogenesis and neuronal cell survival, as well as reducing cell death in the hippocampus and midbrain ?(Diotel et al., 2018)?. Low or absent allopregnanolone is associated with psychological pathology including Post-Traumatic Stress Disorder (PTSD) ?(Pineles et al., 2018)? and major depressive disorder ?(Maguire, 2019)?. Finasteride is employed experimentally to abolish the formation of neuroactive steroids including allopregnanolone in models relevant to Tourette syndrome and PTSD ?(Cadeddu et al., 2019; Nagaya et al., 2015)?.

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PFS: Manifestation of a Post-Androgen Deprivation Syndrome following exposure to substances with antiandrogenic effects

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/pfs-manifestation-of-a-post-androgen-deprivation-syndrome-following-exposure-to-substances-with-antiandrogenic-effects/

Endocrine disruption

"Endocrine disruption" refers to a specific toxicity whereby natural and/or anthropogenic chemicals cause adverse health effects by disrupting the endogenous hormone system. An endocrine disruptor is defined by the World Health Organisation as “an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub) populations”. Potential endocrine disruptors can act on hormone receptors directly or interfere with proteins mediating hormonal delivery to target tissues and cells. They may act at low doses, exhibit non-monotonic dose-response relationships, cause tissue specific effects and differing endpoints ?(Bergman et al., 2012)?. There is broad potential for pharmaco/toxicodynamic influences from EDCs including alteration of receptor expression and interruption of the critical and complex feedback mechanisms regulating the endocrine system ?(Lagarde et al., 2015)?. It has been estimated that, in the EU, the cost associated with disease and disability reasonably attributable to EDC exposure is €157 billion, 1.23% of the European Union’s gross domestic product ?(Trasande et al., 2015)?. Health risks related to exposure to endocrine disruptors are typically underestimated and poorly characterised ?(Fucic et al., 2018)?.

There is now scientific consensus that, as well as disruptive effects during developmental windows, interference with the role of hormones during maintenance of physiological function in adult life can cause adverse effects ?(Solecki et al., 2016)?. An adverse effect in this context constitutes “a change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences” ?(Bergman et al., 2012)?. In this context, anthropogenic chemicals can represent pervasive environmental stressors ?(Latchney et al., 2017)?, and the marked sensitivity to endocrine-affecting substances common in PFS patients appears to us to be a manifestation of this increased susceptibility. Changes to the epigenome that can persist indefinitely after exposure to pharmaceutical products is an increasing area of consideration ?(Csoka & Szyf, 2009)?. Recent publications centring on epigenetics increasingly appreciate Finasteride in the context of endocrine disruptors, with respect to both PFS ?(Traish, 2018)? and in broader animal studies. Finasteride induces hypospadias and a permanent reduction in anogenital distance in adult male rats exposed during late gestation ?(Bowman et al., 2003)?. This effect on LABC weight is consistent with the effects of other antiandrogens such as flutamide, procymidone, vinclozolin, and linuron

?(McIntyre, 2001, 2002; Ostby et al., 1999; Wolf et al., 1999)?.

Despite the "clear endocrine disrupting activity" of 5-alpha reductase inhibitors, there is a paucity of information regarding the impact of non-clinical 5-alpha reductase inhibition ?(Patisaul & Belcher, 2017)?. Even with sole consideration of the known effects of very low doses of finasteride on development, the strong persistence of the drug in the environment and high photostability raises serious concerns about its widespread availability ?(Sammartino et al., 2013)?. The profound and devastating changes to physiological health manifesting as PFS in an adult subpopulation of fertile age following exposure to as little as 0.2mg of Finasteride should add significant and urgent public health concerns regarding its environmental toxicity as an EDC.

"PFS" following therapeutic use and cessation of other substances?

Importantly, patients are increasingly presenting to us suffering what is ostensibly clinically "post-finasteride syndrome" following use of drugs and substances including Isotretinoin, Serenoa repens (saw palmetto) extract, SSRI antidepressants, topical ketoconazole, topical minoxidil, and high-dose phenolic compounds marketed as health supplements including quercetin and milk thistle extract.

It is recognised that the syndrome termed Post-SSRI Sexual Dysfunction (PSSD) and PFS may share an etiological link. With focus on neurological symptoms, Giatti et al. presented a hypothesis that the impairment of overlapping signals of neuroactive steroids, dopamine and serotonin as potentially underlying the condition(s) ?(Giatti et al., 2018)?. In another consideration of the potential for a single syndrome underlying these presentations, Healy et al. analysed 300 patient responses to structured questions provided by and submitted to rxisk.org, an independent drug safety website. The cohort was comprised of patients suffering persistent sexual dysfunction following use of 5-ARIs, Isotretinoin and Serotonin Reuptake Inhibitors, with treatment duration ranging from a single dose to over 16 years. Overlap was seen in symptoms including ED, Libido loss, genital anaesthesia, difficulty achieving orgasm, pleasureless orgasm, premature ejaculation, emotional blunting, loss of nocturnal erections, penile or testicular pain, reduction of penis size, decreased testosterone, watery ejaculate, testicular atrophy, and other skin numbness. Across drug groups, the sexual dysfunction became markedly worse or even began after cessation of treatment in many instances. For all three drug groups there were reports of profound dysfunction appearing within days of stopping. while Finasteride and Isotretinoin are stopped abruptly, SSRIs are often tapered. Interestingly, three subjects on SSRIs reported an increasing loss of sexual function as the dose was tapered, suggesting that PSSD may be equally likely following abrupt or gradual discontinuation of an SSRI or SNRI. They conclude the need for comparative investigation in these cohorts and a systematic approach with structured symptom sets to establish the existence of a single syndrome ?(David Healy et al., 2018)?.

The antiandrogenic commonality of substances causing an ostensibly similar persistent syndrome

Accutane, Roaccutan, Generics (Isotretinoin)

Retinoids possess important antiandrogenic endocrine disrupting properties. Isotretinoin is a 3-cis-retinoic acid which is marketed under the brand name Accutane, Roaccutan, and as branded generic preparations. The main application is treatment of acne, which is strongly linked to androgenic activity in the skin ?(Melnik, 2017)?. Boudou et al. reported that after three months of isotretinoin treatment to six male patients with severe acne, complete resolution of acne was achieved in four patients and the remaining two patients improved significantly. No changes were recorded in serum testosterone but a significant decrease in DHT was observed. Androgen receptor status was investigated in back skin biopsies obtained in acne areas before and after three months of isotretinoin treatment. Treatment induced a 2.6-fold decrease in AR binding capacity constant (62 vs. 24 fmol/mg cytosolic protein), demonstrating a marked sensitivity of androgen receptor in the skin to oral isotretinoin. The authors concluded the data supported previous observations of DHT suppression and were consistent with the key role of the AR and DHT in acne, noting sebum is under androgen control and that androgen responsiveness of the pilosebaceous unit is implicated in acne pathogenesis ?(Boudou et al., 1995)?. Boudou et al. had previously illustrated that skin biopsies of eight men with severe acne treated with 3 months of isotretinoin "lost 80% of their ability to form 5 alpha-dihydrotestosterone (P <0.001)" ?(Boudou et al., 1994)?.

AR signal transduction is crucial to acne pathogenesis, stimulating the size of sebocytes and sebum production as well as proliferation of keratinocytes ?(Lai et al., 2012)?. IGF-1/PI3K/AKT-mediated inactivation of Forkhead box O1 (FoxO1) is vital to androgen receptor transactivation ?(Fan et al., 2007)?. FoxO1 is repressive of AR owing to FoxO1's inhibition of AR N/C terminal interaction (Q. Ma et al., 2009). IGF-1 has correlated to acne severity ?(Cappel, 2005)? and isotretinoin decreases IGF-1 ?(A.S. Karadag et al., 2009)?. As IGF-1 is inhibitory of AR ?(Palazzolo et al., 2009; Yanase & Fan, 2009)?, Karadag et al. hypothesised that a consequential nuclear increase in FoxO1 would significantly contribute to the downregulation of AR and thus a decrease of androgen-responsive gene transcription ?(Ayse Serap Karadag et al., 2015)?. As with other anti-acne therapies, Isotretinion enhances p53 expression ?(Melnik, 2017)?, which supresses AR expression ?(Alimirah et al., 2007; Shenk et al., 2001)?. Additionally, p53 activates and increases FoxO1 expression ?(Pappas et al., 2017)?. Human primary keratinocytes treated with isotretinoin show an increase in FoxO1 ?(Shi et al., 2018)?, and significant increases in nuclear levels of FoxO1 protein are reported in skin biopsies from acne patients following isotretinoin treatment ?(Agamia et al., 2018)?. In vitro evidence demonstrates all-trans retinoic acid profoundly downregulates the AR and abolishes the induction of androgen-induced functions ?(Ubels et al., 2002, 2003)?, suggesting a common androgen antagonism among retinoids. Taken together, there is significant evidence

for the conclusion that oral Isotretinoin exerts a potent antiandrogenic effect.

Antidepressants

SSRI/SNRI class antidepressants exert significant antiandrogenic activity and have been associated with reproductive toxicity in male rats and humans ?(Atli et al., 2017; Ilgin et al., 2017; Tanrikut et al., 2010)?. Fluoxetine is known to be endocrine disruptive, with evidence of nonmonotonic effects ?(Cunha et al., 2018; Vandenberg et al., 2012)?. Rats administered Fluoxetine display delayed sexual development and decreased sexual behaviours ?(Drugs@FDA, 2016)?. Griffin and Mellon found the enzymatic efficiency of 3?-HSD conversion of DHT to androstanediol increased 163-fold when the enzyme was incubated with fluoxetine and 63-fold with paroxetine ?(Griffin & Mellon, 1999)?, which greatly reduces intracellular DHT.

Using the H295R cell line, Hansen et al. demonstrated that commonly used SSRIs fluoxetine, paroxetine, citalopram, escitalopram, sertraline and fluvoxamine exert significant endocrine disrupting properties in vitro. Despite different steroidogenic enzymes being affected across the six different drugs, the outcome was the same in terms of a marked decrease in testosterone. Observing that the steroidogenic interruptions may partly explain some of the sexual disorders associated with SSRIs, Hansen et al. suggest that the endocrine disrupting potential of these drugs at pharmacologically relevant doses should encourage their careful use in therapy ?(Hansen et al., 2017)?. A similar decrease in testosterone in this cell line following exposure to five SSRI drugs had previously been reported ?(Jacobsen et al., 2015)?. Munkboel et al. demonstrated that steroidogenesis was significantly disrupted in rats exposed to therapeutic doses of sertraline. The most significant effects observed on testicular sex steroid production, particularly the Delta 4 steroidogenic pathway (comprising progesterone, 17-hydroxyprogesterone, Androstenedione, Testosterone, DHT). Testosterone production was significantly decreased in all 3 exposure groups, and DHT was significantly decreased in the testis, plasma and brain. A 53% decrease of testosterone was reported in testis of rats exposed to 5 mg/kg/day alongside a general decrease on the D4 axis. Munkboel et al. note that this corresponds to the human starting dose of 50mg per day and this pronounced effect suggests the possibility of significant consequences on reproductive and health endpoints. They conclude that men treated with sertraline should be monitored carefully for sexual dysfunction ?(Munkboel et al., 2018)?.

Serotonin is recognised to be inhibitory of both male and female sexual behaviour and function ?(Croft, 2017; Iovino et al., 2019; Olivier et al., 2010)?. SSRIs increase inhibition of serotonin reuptake ?(Ferguson, 2001)?, and increase serotonin by a downregulation of autoreceptors which otherwise act to inhibit serotonin release ?(Hagan et al., 2012; Neumaier, 1996)?. Both 5HT1a receptor knockdown and interference using siRNA molecules of has demonstrated antidepressant effects accompanied with greater increases in extracellular serotonin in response to either stress or fluoxetine ?(Ferrés-Coy et al., 2012)?.

Increased extracellular serotonin levels in the ventral hippocampus of 5HT1b knockout mice were observed in response to SSRI administration ?(Nautiyal et al., 2016)?. As well as reuptake inhibition, SSRIs have been observed to upregulate tryptophan hydroxylase ?(Kim et al., 2002)?, mediatory of serotonin production in non-neuronal and neuronal tissue ?(Walther, 2003; X. Zhang, 2004)?.

There is a well-studied and remarkable antagonism between testosterone and serotonin in terms of their behavioural effects that aligns with the significant impact of androgens on serotonergic activity in the brain ?(Ambar & Chiavegatto, 2009; Daly et al., 2001; Keleta et al., 2007; Martinez-Conde et al., 1985; Sundblad & Eriksson, 1997; L. Zhang et al., 1999)?. Testosterone promotes territorial behaviour, impulsivity, sexual behaviour and aggression ?(Bing et al., 1998; Kimura & Hagiwara, 1985; Svensson, 2003; Wu & Shah, 2011)?, whereas serotonin appears to exert opposite effects ?(Batty & Meyerson, 1980; Nelson & Chiavegatto, 2001; Olivier et al., 2010)?. Studer et al. demonstrated that while the pro-aggressive effect of testosterone is apparently independent of serotonin, the inhibitory effect of serotonin to dampen maladaptive aggression is "irrelevant" in the absence of testosterone. Additionally, inhibition of serotonin production failed to reinstate aggression in mice rendered hypoaggressive by early life brain AR knockout ?(Studer et al., 2015)?.

Recent evidence in tissue outside the brain shows that serotonin exerts a powerful downregulatory effect on the androgen receptor. BPH tissue has been observed to demonstrate AR upregulation ?(Izumi et al., 2013; Nicholson et al., 2013; P. Zhang et al., 2015)? as well as a significant depletion of 5-HT ?(Cockett et al., 1993)?. Carvalho-Dias et al explored the relationship between 5-HT and androgen signaling, demonstrating a clear inhibitory influence of serotonin on the androgen pathway, providing robust data from a number of elegant in vitro and in vivo observations. In vitro, 5-HT significantly inhibited rat prostate cell growth through a 5-HT1a and 5-HT1b mediated down-regulation of AR either with or without testosterone supplementation. In cultured human cell lines, proliferation of BPH epithelium and normal prostate stroma cells supplemented with testosterone was significantly reduced by 5-HT or specific 5-HT1a and 5HT1b agonists. Proliferation of normal prostate epithelium cells was not affected. Testosterone was observed to upregulate the AR in BPH epithelium and markedly in normal stroma, while 5-HT or specific 5-HT1a and 5HT1b agonists inhibited this upregulation. Importantly, the absence of an inhibitory action of 5HT or an agonist of either autoreceptor on viability and proliferation of normal epithelium cells, with or without testosterone supplementation, was coincidental with a complete absence of AR expression in these cells. They additionally demonstrated that tryptophan hydroxylase type 1 knockout mice exhibit a remarkable 37% higher prostate-to-body weight ratio compared to wild-type at 20 weeks without difference in overall body weight, with prostate histology revealing areas of hyperplasia in epithelium and stroma. These mice displayed significantly larger seminal vesicles than controls, supportive of negative androgenic regulation by 5HT beyond the prostate cell lines. qRT-PCR revealed increased AR levels in the dorsolateral prostate of Tph1?/? mice. Remarkably, 5HT treatment significantly reduced prostate weight and seminal vesicles near to that of controls, and reduced AR mRNA to levels comparable to controls ?(Carvalho-Dias et al., 2017)?.

Collectively, these in vitro and in vivo studies demonstrate that the inhibition of 5alpha reductase type 2 with finasteride and steroidogenic dysregulation with SSRIs have a clear mechanistic commonality: A considerable disruption to androgen signaling. As with isotretinoin, SSRIs exert antiandrogenic endocrine disruptive activity through distinct actions. Further supporting this hypothesis, a significantly affected patient registered on propeciahelp.com suffers the syndrome following over the counter use of 5-hydroxytryptophan, a serotonin precursor observed to increase excretion of 5-HIAA with significant interindividual variation ?(Joy et al., 2008)?. This is suggestive of increased production of serotonin following 5-HTP intake, which is the rationale underlying its supplemental use ?(Hallin et al., 2012)?.

Saw Palmetto (Serenoa repens)

Amongst propeciahelp membership, Serenoa repens (saw palmetto), an extract with markedly antiandrogenic properties commonly used in treatment of BPH and LUTS ?(Cicero et al., 2019)?, is the most prevalent alternative therapy causative of the syndrome. This is usually taken as a “natural” hair loss remedy. Although proportionally rarer, topical antiandrogenic products are causing patients to present with the syndrome, and these include finasteride, ketoconazole, the antiandrogen RU-58841 and minoxidil. In animals, Finasteride has been demonstrated to have significant systemic effects following topical application ?(Chen et al., 1995)?. Ketoconazole is antiandrogenic and suppressive of steroid production, exhibiting nonmonotonic activity. As with other imidazole azole class drugs, the extremely potent endocrine disruptive properties of ketoconazole are attracting increasing scrutiny given their prevalence as antifungal treatments ?(Munkboel et al., 2019)?. In vitro investigations have demonstrated minoxidil can directly bind to the AR, decrease transcriptional activity and interfere with AR function ?(Hsu et al., 2014)?. Additionally, minoxidil has been shown to significantly downregulate 5 alpha reductase type 2 expression in human keratinocytes ?(Pekmezci & Türko?lu, 2017)?. A 28 year old patient member of our site recently received a diagnosis of "5 alpha reductase inhibitor syndrome" after one week of oral quercetin-3-O-rutinoside under physician direction led to the rapid development of persistent symptoms including severe muscle loss, increased adiposity, osteoporosis of the hip and lumbar spine, severe penile atrophy, post orgasmic illness, impotence, anxiety, depression and insomnia. Polyphenols can be potent 5alpha reductase inhibitors ?(Hiipakka et al., 2002)? and antiandrogenic at the receptor level ?(Boam, 2015; Cicero et al., 2019; Kampa et al., 2017; Xing, 2001)?. Nordeen et al. noted the lack of data regarding purified concentrated flavonoid supplements, while providing evidence that two flavonoids, luteolin and quercetin, are "promiscuous endocrine disruptors" that demonstrate anti-androgenic effects, suggesting caution regarding the potential "peril" of supplementing these phenols far beyond the intake of a normal, healthy diet ?(Nordeen et al., 2013)?.

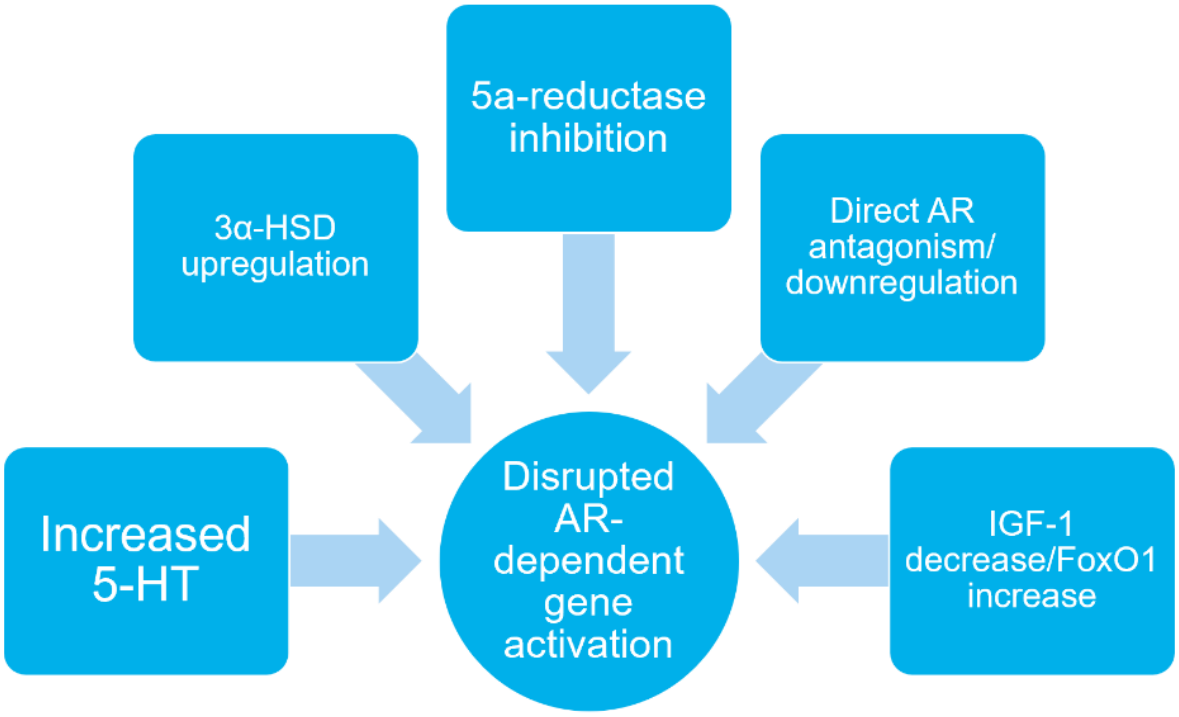

Fig. Finasteride, Accutane and SSRIs are all potent antiandrogenic endocrine disruptors.

While this large range of pharmaceutical and natural substances may seem broad and mechanistically distinct, the notable commonality is dramatic antiandrogenic endocrine disruption. Any treatments targeting the AR or suppressing androgens are known to have adverse effects on other critical physiological functions ?(Bourke et al., 2011)?. Narrow mechanistic perspectives often inform substance grouping for analysis of the risk of permanent male reproductive malformations and irreversible sexual disorders in the developing foetus. Through analysis of adverse outcome pathway networks, Kortenkamp illustrated that independent mechanistic effects from a very broad range of substances meet at nodal points in the network to result in common down-stream antiandrogenic effects and adverse outcomes. Kortenkamp suggested that - in addition to phthalates - substances capable of AR antagonism, cholesterol transporter down-regulation, and interruption or inhibition of steroidogenic or cholesterol synthesising enzymes should be included in an expanded consideration of substances capable of inducing male reproductive malformation. A non-exhaustive list of chemicals identified as a starting basis included vinclozolin, bisphenol A, finasteride, paracetamol, ibuprofen, ketoconazole and simvastatin (Kortenkamp, 2020).

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AR CAG Repeats and Spinal and Bulbar Muscular Atrophy

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/ar-cag-repeats-and-spinal-and-bulbar-muscular-atrophy/

The AR CAG repeat polymorphism influences tissue response to androgens

An increase in repeats of the cytosine-adenine-guanine (CAG) trinucleotide sequence in the N-terminal domain of the androgen receptor is inhibitory of appropriate transactivation function ?(Chamberlain et al., 1994)?, entailing weaker transcriptional activity ?(Singh et al., 2007)?. Patrizio et al reported a statistically significant association between longer CAG repeats and infertility (mean length 25) when compared with healthy controls (mean length 22), particularly apparent in those with extremely severe oligozoospermia ?(Patrizio et al., 2001)?. AR CAG repeat sequence length is associated with a higher risk of symptomatic late-onset hypogonadism in men ?(Hong et al., 2018; Kim et al., 2018)?. As well as physiological outcomes, the CAGn has been associated with evolutionary-relevant male life history strategies ?(Gettler et al., 2017)?.

Huhtaniemi et al. analysed valuable and unique data from the European Male Ageing Study, comprising AR CAG repeat lengths and endocrine and clinical characteristics of nearly 3000 men aged 40 –79. Coordinated by centres across Europe ?(Lee et al., 2009)?, this dataset benefits distinctly from standardisation and large sample size. Analysis revealed that, while below the 40 CAGn threshold considered denotive of SBMA ?(Spada et al., 1991)?, as the Exon 1 CAG repeat length extended, the length of the AR polyglutamine tract repeat correlated directly to all measures of serum testosterone (total, bioavailable, free) and strongly positively correlated to T and E2 in circulation. No symptoms or signs of androgen deficiency correlated to the CAG repeat length, suggesting that in the presence of greater polyQ expansion, deficiency of androgen action may be compensated for by a concomitant increase in the production of androgens under normal hypothalamic-pituitary-testicular axis conditions ?(Huhtaniemi et al., 2009)?. This compensation had similarly been hypothesised by Skjærpe et al. who also reported a positive association between CAG repeat length and free and total testosterone ?(Skjaerpe et al., 2008)?.

Although not universal, assumedly due to reasons including fluctuations in testosterone levels and the cross-sectional nature of some studies ?(Harkonen et al., 2003)?, this positive correlation of longer CAG stretches with free and total testosterone is well established ?(Crabbe et al., 2007; Gong et al., 2014; Harkonen et al., 2003; Krithivas et al., 1999; Owens et al., 2018; Stanworth et al., 2008)?. Khan et al. additionally observed this in a large cohort of 400 men ?(Khan et al., 2018)?. Their study noted that the

IIEF-15 scores negatively correlated to long CAGn repeats despite higher testosterone levels, concluding that long CAGn repeats impair the effects of testosterone, particularly on erectile function. Liu et al had previously reported, in a cohort of 478 Taiwanese males aged 41 to 83, that long CAGn repeats were an independent risk factor for erectile dysfunction in men with testosterone above 3.3ng/mL but, interestingly, not 3.3ng/mL or below ?(Liu et al., 2015)?. This finding was additionally corroborated by Tirabassi et al ?(Tirabassi et al., 2016)?. Speculatively, this evidence suggests higher testosterone may exert a negative physiological effect on tissues expressing expanded CAGn AR before reaching the repeat threshold of SBMA, in which toxicity is ligand dependent. The relationship between AR CAGn and optimal function is not strictly linear: Low repeat lengths are also associated with suboptimal function. In vitro investigations by Nenonen et al. revealed a 22 CAG genotype had the highest AR-mediated transcription with the least protein compared with 16 CAG and 28 CAG. ?(H. Nenonen et al., 2009)? In agreement, analysis of 4000 men revealed lengths close to this median confine a lower risk of infertility ?(H. A. Nenonen et al., 2010)?.

Despite the vital role of testosterone centrally ?(Santi et al., 2018)? and peripherally for male sexual function and maintenance ?(Corona et al., 2016; Traish, 2008)?, studies of healthy men have failed to denote a relevant testosterone threshold for erectile dysfunction ?(Lackner et al., 2011)?. Androgen-induced target activities are attenuated corresponding to the length of triplet residues ?(Zitzmann, 2008)? and the result of exogenous testosterone treatment is markedly modulated by CAG repeat polymorphism ?(Francomano et al., 2013)?. Owing to this relationship, it has been suggested that existing thresholds of hypogonadism and consequential indications are likely to be replaced with a continuum spanned by genetics and symptom specificity ?(Zitzmann, 2009)?. Recently, Escobedo et al. demonstrated the tandem CAG repeat sequence folds into a helical structure, with propensity of helicity correlating positively to sequence length. An accumulation of unconventional hydrogen bond donations from glutamine side chains to the main chain carbonyl of the residue at relative position i?4 confers a gain of stability to the polyQ helix and could provide a rationale for length-dependent impairment of transactivation function ?(Escobedo et al., 2019)?. Collectively, research illustrates that the available level of ligand is not an absolute determinant of optimum androgenic function, and much is dependent on its transcription factor in target tissues. The effect of agonists as beneficial or detrimental is determined specifically by the tissue of action ?(Narayanan et al., 2018)?.

SBMA

X-linked Spinal and Bulbar Muscular Atrophy, also known as Kennedy's disease, is a condition which effects multiple bodily systems and organs ?(Manzano et al., 2018; Sperfeld et al., 2002)?. SBMA is caused by an expansion of the CAG trinucleotide repeat polyglutamine tract in the first exon of the androgen receptor ?(Spada et al., 1991)?, with an excess of 38 repeats denotive of the pathogenesis ?(G. Querin et al., 2017)?.

SBMA is rare, occurring in 1 per 400,000 men per year ?(Fischbeck, 1997)?. This rarity has led to calls for the establishment of international multi-center networks to speed understanding and progress ?(Fratta et al., 2014; G. Querin et al., 2017)?. Poor clinical awareness, frequent improper diagnosis and confusion with other diseases likely result in an underestimated prevalence ?(G. Querin et al., 2017)?. In cohorts of 47 and 46 patients considered, 32% and 30% respectively had received an alternative diagnosis at first ?(Fratta et al., 2014; Rhodes et al., 2009)?. SBMA usually becomes notably symptomatic in middle age or later ?(Katsuno et al., 2012)?, however initial symptoms often begin in adolescence, long before clinical assessment ?(Sperfeld et al., 2002)?. In line with the inhibitory action of the polyglutamine tract on AR transactivation, tandem CAG repeat length has been correlated to androgen insensitivity in SBMA ?(Dejager et al., 2002)?. CAG repeat length correlates inversely with age at onset but does not always correlate to disease severity or progression ?(Doyu et al., 1992; Fratta et al., 2014; Andrew P. Lieberman et al., 2014; Rhodes et al., 2009)?. Epigenetic contributions to the late onset nature of SBMA are likely ?(Kondo et al., 2019)?. Progression is gradual and life expectancy is averagely insignificantly decreased ?(Chahin et al., 2008)?. The breadth of the clinical spectrum and involvement of testosterone target tissue likely reflects the ubiquitous expression of the androgen receptor throughout the central nervous system and peripheral tissues ?(H. Adachi, 2005)?. The complex clinical picture that results has been described by Manzano et al. as an "interplay between differentially affected tissues, which struggle to cooperate to maintain homeostasis" ?(Manzano et al., 2018)?.

Characteristic symptoms are proximal and distal weakness and proximal muscle atrophy. Bulbar muscle involvement accounts for dysarthria, dysphagia, hypernasality and decreased range of pitch and loudness ?(Pennuto & Rinaldi, 2018; G. Querin et al., 2017)?. Other common symptoms include fasciculations, cramps, tremor, reduced or absent deep tendon reflexes, loss of sensory functions in extremities, loss of vibratory sensation, tongue wasting, gynecomastia, sexual dysfunction, testicular atrophy and fertility problems including oligospermia/azoospermia. ?(Dahlqvist et al., 2019; Dejager et al., 2002; Fratta et al., 2014; Kennedy et al., 1968; Polo et al., 1996; G. Querin et al., 2017; Udd et al., 2009)?. Symptoms including gynecomastia, hand tremors, muscular cramps, myalgias, premature exhaustion during physical exercise and feet numbness can present before the onset of weakness ?(Finsterer & Scorza, 2019; Finsterer & Soraru, 2015)?. Libido loss presents and can be unappreciated due to the late onset ?(G. Querin et al., 2017)?. Abdominal obesity, dyslipidemia, glucose intolerance and liver problems represent a commonly seen metabolic involvement and these patients can frequently develop metabolic syndrome ?(Dejager et al., 2002; Pennuto & Rinaldi, 2018; G. Querin et al., 2017; Rosenbohm et al., 2018)?. Heart rhythm abnormalities including Brugada syndrome can occur ?(Araki et al., 2014; Giorgia Querin et al., 2015)?. Alterations in bone mineral density including lumbar density scores above controls, lumbar and/or femoral osteopenia, and osteoporosis are reported without correlation to LH, testosterone or vitamin D determinations. The frequency of lower urinary tract symptoms exceeds that of the general population significantly ?(Giorgia Querin et al., 2015)?. Interestingly, AR133Q knock-in mouse models exhibit significant atrophy and abnormal spontaneous myotonic discharges in the levator ani/bulbocavernosus (LABC) muscles, suggesting alteration to lower urinary tract muscle membrane excitability that could be responsible for the obstructive LUTS and associated death in these models ?(Yu, 2006)?. Hypospadias has been suggested as potentially underreported feature of the SBMA phenotype ?(Nordenvall et al., 2016)?.

While traditional focus has been on the muscular symptoms and long-associated motor neuron degeneration ?(Lombardi, Querin, et al., 2019)?, this can be misleading ?(Finsterer & Scorza, 2019; Sperfeld et al., 2002)?. The systemic, endocrinological and neuropsychological effects are now known to be of equal importance to both the clinical picture and the quality of life of patients ?(G. Querin et al., 2017; Giorgia Querin et al., 2018)?. SBMA can manifest in absence of neuromuscular complaints or symptoms, presenting with an endocrine phenotype comprising of symptoms including gynecomastia, testicular atrophy, hypercholesterolemia and diabetes mellitus ?(Battaglia et al., 2003)?. Nonclassical symptoms including erectile dysfunction can be cited by patients as amongst their most disabling symptoms ?(Fratta et al., 2014)?. Sexual dysfunction across domains including orgasm function, erectile function and satisfaction is commonly reported ?(Dahlqvist et al., 2019)?. In a large cohort of 73 patients, excluding ten patients who refused to answer, all patients were found to have mild-to-severe erectile dysfunction per IIEF (mean 15.9±7.6; range 0–25) ?(Giorgia Querin et al., 2015)?.

SBMA patients can display peculiar psychological characteristics including diffidence, marked emotional sensitivity and concentration problems ?(G. Querin et al., 2017)?. Soukup et al. reported systematic evidence of differing frontotemporal cognitive functioning in SBMA patients compared to age and education matched controls ?(Soukup et al., 2009)?. Despite similar intelligence per IQ assessment, SBMA patients were found to significantly underperform in a battery of neuropsychological tests. Interestingly, while this varied from mild to severe impairment and "astonishingly widespread", most were subclinical in expression. Executive function and short- and long-term memory were found to be domains exhibiting pronounced deficits, while attentional control was also deficient. Consistent with prefrontal deficits, Di Rosa et al. utilised control matched neuropsychological testing, reporting a significant weakness in cognitive empathy but not in areas of affective empathy in SBMA patients. They suggest even mild impairment in mentalising may have profound implications for interpersonal relations, particularly when such changes are not recognized as the consequence of neural processes ?(Di Rosa et al., 2014)?. In a small cohort of SBMA patients, Romigi et al. reported a decrease in both subjective and objective sleep quality parameters compared with healthy age and sex matched controls. 77.8% of SBMA patients subjectively experienced disturbed sleep per the Pittsburgh Sleep Quality Index. Objectively, time in bed, total sleep time and sleep efficiency were significantly lower in SBMA patients, with a significantly higher apnea-hypopnea index. SBMA patients showed periodic limb movements. Obstructive sleep apnea was evident in a majority of patients, REM sleep without atonia was observed in 22% of patients ?(Romigi et al., 2014)?.

Although CAG repeat length is not held to be strictly associated with severity, individual case reports of patients with abnormally long CAG repeat lengths present with severe phenotypes that have expanded the clinical understanding of SBMA. Grunseich et al. reported a 29-year-old SBMA patient with a long 68 CAG repeat expansion. The patient experienced early onset of multisystemic symptoms. He had been born with penile congenital abnormality. He developed gynecomastia by 16 and muscle weakness, fatigue after exercise, fasciculations, cramping, and tremor by age 18. He experienced ejaculation difficulties, testicular atrophy, burning neuropathic pain and dysesthesia in the feet and fingertips, reduced sweating and decreased facial hair growth. Tongue atrophy was noted, and weakness was observed in the

orbicularis oculi and orbicularis oris. He exhibited perioral fasciculations, severe limb weakness bilaterally, difficulty standing on his heels and ankles, and loss of temperature and vibratory sensation in the fingers and toes. Abnormalities were seen on muscle MRI. Evidence of autonomic dysfunction suggestive of small fiber dysfunction was determined, including negligible sweat responses and orthostatic tachycardia without blood pressure changes or symptoms ?(Grunseich et al., 2014)?. Similarly, Madeira et al., reported a phenotype of an exceptional 72 CAG repeat length. This man was 53 years old and underweight. He complained of shortness of breath, difficulty breathing while lying down and paroxysmal nocturnal dyspnea. He had a micropenis, small testicles and progressive testicular failure. Deep tendon reflexes were absent. Fasciculations, weakness and atrophy were apparent in the tongue, masseter muscles and limb muscles. Neck muscles were severely weakened. He had osteopenia, with low bone mass densities in the lumbar spine and femoral neck. He additionally had dyslipidaemia ?(Madeira et al., 2017)?. These phenotypical presentations highlight the broad effects associated with alteration of androgen-dependant signaling pathways.

Reliable biomarkers for SBMA remain a challenge ?(Manzano et al., 2018; Giorgia Querin et al., 2018)?, but common findings have been established. Creatine-Kinase will often be elevated ?(G. Querin et al., 2017)?. Testosterone, LH and FSH are generally found to be within normal bounds, although T and DHT can be high or low in some patients ?(Hashizume et al., 2012; Ni et al., 2015; Giorgia Querin et al., 2015; Rhodes et al., 2009)?. Patterns of androgen insensitivity per biomarkers are seen in some patients as per the Androgen Sensitivity Index, and have been reported to correlate positively with CAG repeats ?(Dejager et al., 2002; Giorgia Querin et al., 2015)?. High proportions of patients will show lipid and metabolic abnormality, including elevated total cholesterol, triglycerides, fasting glucose and insulin ?(Dejager et al., 2002; Francini-Pesenti et al., 2018; Guber et al., 2017; Giorgia Querin et al., 2015)?. Signs of non-alcoholic fatty liver disease including excess deposition of triacylglycerol in the liver have been reported as a near universal finding, even in patients with normal BMI ?(Guber et al., 2017)?. The observation that hepatic AR knockout models that develop steatosis and insulin resistance ?(Lin et al., 2008)?, as well as multisystem disruption of metabolic homeostasis, is suggestive of direct disease involvement in the observed NAFLD in SBMA patients. Serum hydroxyvitamin D was reported as low in a majority of patients in a large cohort ?(Giorgia Querin et al., 2015)?. Interestingly, the markers of neuronal damage phosphorylated neurofilament heavy chain and neurofilament light chain levels are not elevated in serum of SBMA patients or animal models and do not correlate with phenotypical severity ?(Lombardi, Bombaci, et al., 2019; Lombardi, Querin, et al., 2019)?.

Muscle involvement is diffuse. Myopathic evidence present upon muscle biopsy ?(Manzano et al., 2018)? is supportive of a conserved pathological mechanism that likely underlies a vast proportion of clinical manifestations ?(Baniahmad, 2015; G. Querin et al., 2017)?. In a 40-patient cohort, muscle fat content was significantly higher than controls in the semitendinosus, semimembranosus, biceps femoris longus, triceps surae and spared sartorius, gracilis, biceps femoris brevis, and tibialis anterior. Affected leg muscles showed greater involvement than arm muscles, and muscle fat content correlated to muscle strength and function tests, disease duration and severity, and creatine kinase and testosterone levels ?(Dahlqvist et al., 2019)?. White matter alterations in the corticospinal tracts, limbic system, brainstem and cerebellum have been demonstrated via quantitative brain imaging ?(Kassubek et al., 2007; Unrath et

al., 2010)?, while voxel based morphometry has identified gray matter atrophy in the frontal lobes and brainstem ?(Pieper et al., 2012)?. Skeletal muscle, known to be AR enriched, is a notable site of toxicity and tissue biopsy has demonstrated denervation, muscle fiber degeneration and myogenic changes in addition to neurogenic atrophy ?(Giorgia Querin et al., 2015; Sorarù et al., 2008)?. Somatosensory evoked potentials are regularly abnormal, while electromyography and nerve conduction study will often reveal low sensory nerve amplitudes, decreased compound motor action potentials and evidence of diffuse denervation ?(BUECKING, 2000; Kachi et al., 1992; Pennuto & Rinaldi, 2018; Polo et al., 1996)?. Broad involvement of sensory neurons and autonomic skin denervation were reported with abnormal sweat test results ?(Manganelli et al., 2007)?. These findings align with AR accumulation and degeneration in autonomic regions including the dorsal root ganglia ?(Antonini et al., 2000)?.

The mechanisms of PolyQ AR toxicity are yet to be fully elucidated but it appears that levels of AR expression are directly correlated to muscular atrophy ?(Manzano et al., 2018)?. Both testosterone or DHT binding to the polyQ AR and its subsequent translocation of the expanded protein to the nucleus is required for toxicity as demonstrated in vivo ?(Katsuno et al., 2002; Nedelsky et al., 2010; Takeyama et al., 2002)? and in vitro ?(Becker et al., 2000; Darrington et al., 2002; Stenoien et al., 1999; Walcott & Merry, 2002)?. Higher androgen levels in males are therefore responsible for the symptomatic presentation, and female carriers will ordinarily remain asymptomatic ?(Chevalier-Larsen, 2004; Schmidt et al., 2002)?. In humans, exogenous androgen administration does not usually relieve clinical symptoms ?(Neuschmid-Kaspar et al., 1996)? and has been reported to have reversibly worsened symptoms ?(Kinirons & Rouleau, 2008)?. Administrating testosterone to previously asymptomatic transgene SBMA female mice induces a distinct increase of symptoms similar to the level of untreated males, including progressive emaciation and motor dysfunction, pathological markers and nuclear localisation of pathogenic AR ?(Katsuno et al., 2002)?, demonstrating the androgen dependency of the pathology.

AR polyQ expansion involves a partial loss of the normal transcriptional activity of the AR ?(Chamberlain et al., 1994; Kazemi-Esfarjani et al., 1995; A. P. Lieberman, 2002; Mhatre et al., 1993)? and this contributes to the pathology. However, neither loss of AR function nor androgen ablation is adequate for the pathology, and men with complete androgen insensitivity syndrome do not exhibit neurological symptoms ?(Chivet et al., 2019; Quigley et al., 1992)?. As such, the disease entails a proteotoxic gain of function ?(A. P. Lieberman, 2002; Manzano et al., 2018; Nath et al., 2018; Pennuto & Rinaldi, 2018)?. The mutant AR disrupts many downstream pathways, and alteration of diverse cellular processes including transcription, RNA splicing, axonal transport, ion homeostasis, and mitochondrial function likely coalesce to cause toxicity ?(Borgia et al., 2017; Chua et al., 2015; Eftekharzadeh et al., 2019; Malik et al., 2019)?. Diffuse nuclear accumulation of mutant AR is frequent and extensive in SBMA, occurring in a wide array of CNS nuclei and visceral organs ?(H. Adachi, 2005; Doi et al., 2013; Katsuno et al., 2002)?. Nuclear accumulation of AR is reported to be important to the pathology ?(Nedelsky et al., 2010)?. Animal models have revealed export of the pathogenic AR protein is impaired in the absence of any cell-wide disruption of nucleocytoplasmic transport ?(Arnold et al., 2019)?. Significant age, hormone and CAG repeat length dependent impairment of multiple ubiquitin-proteasome genes have been demonstrated to result from a toxic gain of AR function, progressively compounding toxicity through a failure of polyQ AR clearance. Diminished expression of numerous components of the

ubiquitin-proteasome pathway including ubiquitin receptors, proteolytic subunits and assembly scaffold proteins were recently reported in skeletal muscle of AR113Q male mice. This involved significant reduction of ~30% of constitutive proteasome subunits and ~20% of E2 ubiquitin conjugating enzymes, with no upregulation observed and a non-significant trend towards reduced expression in many more subunits ?(Nath et al., 2018)?. This differentiates AR-mediated toxicity from skeletal muscle atrophy following cachexia, renal failure, surgical denervation, fasting, tumors, and diabetes, which all exhibit an up-regulation of proteasome subunits ?(Sacheck et al., 2006)?.

Using cell culture and animal models, androgen axis targeted therapeutic strategies have been explored. Androgen ablation and treatment with AR antagonists are beneficial and ameliorate the SBMA pathogenicity ?(Baniahmad, 2015)?, demonstrating phenotypical improvement beyond simply a slowing of the disease progression. The antiandrogen flutamide was protective of androgen-mediated toxicity across several SBMA models, preventing or reversing motor dysfunction of transgene models and extending the life of knock-in males significantly ?(Renier et al., 2014)?. Similarly, castration of AR97Q males dramatically prevented phenotypical presentation, with these mice showing significantly extended life, ameliorated muscle atrophy and body size reduction, virtually absent motor impairment, and markedly reduced nuclear AR staining intensities as compared to sham operated AR97Q mice displaying significant pathology ?(Katsuno et al., 2002)?. Castration was also remarkably effective in 112 and 113 glutamine models ?(Chevalier-Larsen, 2004; Nath et al., 2018)?. Leuprorelin has also been demonstrated as effective in transgenic mice ?(Katsuno et al., 2003)?. 14 years of prospective quantitative measurement of a single SBMA patient who underwent leuprolide acetate treatment for the initial 7 years before undergoing orchiectomy indicated that long term androgen deprivation slows disease progression when compared to existing control data ?(Hijikata et al., 2019)?. In transgenic mice, SBMA symptoms have been shown to be ameliorated through IGF-1 treatment or overexpression in muscle, which promotes AR degradation through phosphorylation by Akt ?(Palazzolo et al., 2009; Rinaldi et al., 2012)?. Treatment with genistein, an antiandrogenic soy isoflavone, was demonstrated to promote dissociation of the AR from the co-regulator ARA70 and attenuate pathology and improved survival in 97Q mouse models ?(Qiang et al., 2013)?. Modulation of activation function-2 of the AR with the compound MEPB rescued toxicity in a drosophila model of SBMA and showed a dose-dependent rescue from loss of body weight, rotarod activity and grip strength, neuronal loss, neurogenic atrophy and reversed testicular atrophy in a SBMA mouse model ?(Badders et al., 2018)?. It is likely that the new generation of Selective Androgen Receptor Degraders in development for use in castration resistant prostate cancer ?(Han et al., 2019; Ponnusamy et al., 2017)? will be of interest with regard to a potential treatment for SBMA. ASC-J9, an AR degrader enhancer with structural similarity to curcumin ?(Cheng et al., 2018)?, has already been shown to rescue SBMA motor symptoms and improve sexual function in transgenic 97Q mice ?(Yang et al., 2007)?.

In cell models, targeting the heat shock protein families, molecular chaperones to the AR, suppresses aggregation and enhances polyQ AR degradation, making them a potential therapeutic target ?(Bailey, 2002)?. Mutant AR forms a Hsp90 chaperone complex preferentially compared to wild type AR, and use of a Hsp90 inhibitor, Tanespimycin, has been demonstrated to be effective at degrading polyQ AR in vitro and in vivo modelling, markedly ameliorating motor impairment ?(Waza et al., 2005)?.

Tanespimycin, however, has broad interruptive effects and is not well tolerated ?(Yang et al., 2007)?, and Hsp90 inhibitors can induce the degradation of hundreds of client proteins that are likely needed for diverse processes ?(Eftekharzadeh et al., 2019)?. Recently, Eftekharzadeh et al. suggested that Hsp70 activation with small molecules such as JG-98 or JG-294 is a safer potential approach to leveraging protein quality control mechanisms to degrade the AR in SBMA and other androgen-mediated conditions ?(Eftekharzadeh et al., 2019)?. Hsp70 overexpression is similarly seen to significantly ameliorate SBMA symptoms in a transgenic mouse model by reducing the amount of nuclear-localized mutant AR protein ?(Hiroaki Adachi et al., 2003)?. Arimoclomol, a co-inducer of the heat shock response limited to stressed cells, has been observed to delay disease progression in a mouse model of SBMA through the prevention of motor neuron degeneration and alleviation of muscle atrophy ?(Rinaldi et al., 2015)?. Trehalose has been suggested as a potential therapeutic agent, and in vitro studies suggest beneficial effects resulting from increased autophagic clearance of the mutant AR ?(Cicardi et al., 2019)?. Sodium butyrate, a histone deacyletase inhibitor capable of modulating AR expression ?(Paskova et al., 2013)?, showed improvement in motor deficits and histopathological impairment of neurons and muscle within an narrow optimum dose window in transgenic mice ?(Minamiyama, 2004)?. Inhibition of Src kinase, a pathway upregulated by polyglutamine expansion and AR overexpression, has been demonstrated to mitigate toxicity in SBMA animal and cell models ?(Iida et al., 2019)?.

Given the significant advancement in the understanding of the pathological mechanisms, a move towards targeted molecular therapies addressing the systemic pathological processes is likely in the near future ?(Giorgia Querin et al., 2018)?. To achieve a disease modifying therapy for SBMA, Rinaldi et al. suggest a coordinated, collaborative effort of researchers with multiple areas of expertise, clinicians, the pharmaceutical industry and the involvement of patient groups ?(Rinaldi et al., 2015)?.

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AR deregulation as a key pathological driver of PFS?

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/ar-deregulation-as-a-key-pathological-driver-of-pfs/

Induced Wild Type AR Overexpression and the potential relevance of SBMA to PFS

As discussed, as the CAG trinucleotide sequence extends in the N-terminal domain of the AR, there is a consequent functional decline in transcriptional efficiency which is seemingly associated with a compensatory increase in androgen levels. However, at longer repeat lengths, high androgen levels can exert a deleterious and ultimately toxic response. Crucially, polyglutamine expansion is not the only way ligand-dependent toxicity can be conferred to the AR protein, and overexpression of the wild type AR can cause a paradoxical loss of function and toxic gain of function. This is reflective of evidence in other polyglutamine diseases that point to gain of native protein function underlying pathology ?(Paulson et al., 2017)?. It is now appreciated that balanced gene expression is vital for homeostasis, and overexpression of wild-type proteins causes disease states in humans ?(Ohshima et al., 2017; Shastry, 1995)?. Multiple studies demonstrate that, while seemingly paradoxical, sufficient increases in AR expression converge with loss of function phenotypes, with an inverse U?shaped curve representative of AR gene dose response in tissues. The pathological consequence of overexpression of the AR is therefore coherent with Prelich's observation that overexpression of proteins mimics a loss of function and interferes with its function antimorphically. The mechanisms by which overexpression causes a mutant phenotype is therefore of great importance to further understand ?(Prelich, 2012)?.

Generating mice overexpressing AR solely in skeletal muscle, Monks et al. reported the striking and seemingly counter-intuitive observation that overexpression of the Wild-Type androgen receptor recapitulates the pathological consequence of polyglutamine expansion despite a polyglutamine repeat tract comprised of 22 glutamines. Decreased viability was observed in males of all seven transgene lines but not in females. Interestingly, administration of flutamide to pregnant dams enhanced perinatal survival, suggesting prenatal androgen activation of the overexpressed AR, not the overexpression *per se*, is causative of death. Two transgenic mouse lines of differing WT AR copy number (L78 < L141) were characterised. L141 males exhibited a far more severe phenotype, corresponding to a significantly higher AR expression at the mRNA and protein level. Surviving L78 males were functionally comparable to wild type despite a lower body weight. However, L141 males exhibited a marked phenotype of lower body weight, curvature of the thoracic spine, severe deficits in motor function and muscle strength, and early death. Castration dramatically restored function in L141 mice, illustrating the androgen dependency of the toxicity. Remarkably, although L141 females were apparently unaffected by AR overexpression *per se*, when administered testosterone to the approximate circulating level of male mice, they rapidly developed a comparable disease phenotype to male L141 mice including motor dysfunction and muscle

atrophy. Over 9 days of T treatment was fatal to female L141 mice. L78 female mice did not become symptomatic or atrophic with T treatment, even for prolonged periods. This parallels the asymptomatic L78 male. This is strongly indicative that the degree of overexpression dictates severity of androgen-mediated toxicity and, as Monks et al. observe in several contexts, that overexpressed AR confers toxicity once activated by hormonal ligand ?(Monks et al., 2007)?.

Monks et al. compared differentially regulated genes in myogenic transgene mice and the SBMA AR97 and AR113Q models. Gene expression in the transgene AR-overexpressing muscle revealed similar deregulation to AR Knock-out muscle, further suggesting that a paradoxical loss of AR function results from overexpression of the androgen receptor. The finding of overexpression of WT AR reproducing a phenotype comparable to polyglutamine expansion was noted to be surprising and puzzling considering SBMA is associated with a loss of AR function whereas overexpression of the AR would typically be expected to enhance the function of androgen signaling ?(Mo et al., 2010)?. Further striking findings were provided through investigation of the contributions of native AR interactions to polyglutamine-expanded AR toxicity in Drosophila models. Nedelsky et al. determined that native interactions at AF-1 of the AR modify toxicity while AF-2 coregulator interaction and function is essential for toxicity. Expressing AR in the photoreceptor neurons and accessory pigment cells of the eyes of the developing flies, they demonstrated a polyglutamine length and ligand-dependent degenerative phenotype. While flies reared on normal food did not demonstrate pathology, a degenerative phenotype in the posterior margin of the eye occurred in flies reared on food containing DHT. This androgen and polyQ length dependent degenerative phenotype of atrophy and functional deficit was further demonstrated in larval tissues including salivary glands and motor neurons. Crucially, Nedeslky et al. reported that wild-type AR of a 12Q polyglutamine-length, when expressed at very high levels, resulted in an degenerative phenotype indistinguishable from that caused by expansion of the AR polyglutamine tract ?(Nedelsky et al., 2010)?. This reflected the dose dependency and pathological consequence of wild-type AR overexpression well reported by Monks et al. Furthermore, though generally weaker, expression analysis revealed a similar dysregulation in both AR12Q+DHT and AR52Q+DHT files, lending further support to a link between an amplification of native function and the toxicity induced by polyglutamine expansion and is supportive of a conserved mechanism. Interestingly, quantitative analysis did not reveal a correlation between the amount of high molecular weight species and neurodegeneration in their Drosophila model. This is in line with the lack of AR positive aggregates reported in transgenic mice that recapitulated the SBMA phenotype ?(Monks et al., 2007)?. The presence of aggregates was in previous decades presumed to be a driving factor in pathogenesis of SBMA, however this is no longer the case and a direct mechanistic involvement is controversial ?(Todd & Lim, 2013)?. Providing another parallel between the effect of polyglutamine expansion and wild type overexpression, Halievski et al. demonstrated that in mice expressing a human androgen receptor of 97 CAGs and the wild-type overexpressing myogenic mice, several common transcriptional effects were seen, such as robust downregulation of BDNF and NT-4 transcripts. Remarkably, similar effects were seen indistinctly across both synaptic and extrasynaptic domains, suggesting a broad effect and involvement of common deleterious AR-mediated mechanisms across cell types ?(Halievski et al., 2019)?.

While it might be expected AR overexpression would result in a hyper-masculine socio-sexual

phenotype, Swift-Gallant et al. demonstrated significant reductions of male-typical aggressive and sexual behaviours in transgene AR overexpressing mice. This non-linear androgen response was curiously reflective of loss of AR function. Interestingly, same-sex anogenital investigation was increased and male-typical preferences for female olfactory cues were disrupted in globally overexpressing mice but not mice only overexpressing AR in neural tissue, suggesting a direct role of non-neuronal AR in mediation of socio-sexual behaviours. A decrease in testosterone production is not a sufficient explanation for the mechanistic consequences of overexpression on masculine physiological and behavioural phenotypes and the many convergences with loss of function models, and reduced testosterone was not routinely observed in models of overexpression ?(Swift-Gallant et al., 2016)?. Monks and Swift-Gallant considered a uniform global loss of AR function unlikely, proposing a cellular mechanism that would be differentiated according to affected neurological or physiological tissue and system. This would implicate regional variations, possibly including site-specific cofactor influences and differential transcriptional effects resulting from regional epigenetic changes. Additionally, overexpression of AR has been suggested as a plausible mechanistic route to alteration in neurosteroid synthesis ?(Monks & Swift-Gallant, 2018)?.

Considerable evidence exists to support an overlapping androgen dependent toxicity in the contexts of AR polyglutamine tract expansion and overexpression of the wild-type AR, and a loss of function coincident to both insufficient and excessive AR signaling. It is therefore highly significant that both hypogonadism ?(Seftel, 2005)? and the multi-systemic symptom profile of SBMA ?(Querin et al., 2017)? bear a clear resemblance to the broad symptomatology of PFS. However, it is important to consider that there are notable areas of presentation and progression in which the disease states of PFS and SBMA differ. Neurocognitive symptoms are profoundly more severe in PFS than are reported in SBMA, although these domains of disease involvement are not without overlap as we have illustrated. Tongue atrophy is not reported in PFS. These differences are likely inherent to the aetiologies of the respective diseases: An endocrine disruption leading to epigenetic dysregulation in PFS and a genetic glutamine repeat sequence as causative factor in SBMA. While SBMA is a characteristically slow progressing condition, PFS can, in many cases, onset extremely rapidly with the discussed "crash". After this onset, an initial period of weeks or months during which the pathology is often rapidly progressive to what patients refer to as a "baseline" state occurs. Atrophy of androgen dependent tissue and physiological changes are often reported over this time. Beyond this, PFS is not always markedly progressive, with some patients experiencing improvement or stabilisation of their symptoms to variable points over subsequent months or years. As we will discuss, exogenous testosterone can sometimes cause symptomatic intensification, and significant and rapid phenotypical deterioration with additional symptomatic physiological domains can occur following exposure to further antiandrogenic endocrine disrupting substances. Previously discussed as the "crash", the majority patient experience of a intensification or development of symptoms after cessation of the drug may reflect the return of 5a-dihydrotestosterone to physiological levels in the presence of the newly uninhibited 5-alpha reductase enzymes. In the myogenic models discussed, when male physiological levels of androgens were administered to female L141 mice a severe disease state is rapidly induced, while the L78 mice were largely asymptomatic. A site-specificity and expression level-dependency of induced AR overexpression therefore serves as a compelling explanation for the large variation in the toxic post-drug phenotype, manifesting as either a continuation of on-drug side effects or, more commonly, the crash, which can vary from an onset of sexual dysfunction, libido loss, anxiety and depression to a devastating and disabling physiological and psychological alteration including cognitive impairment of executive function, derealisation, anhedonia, panic attacks, memory loss, total insomnia,

dysautonomia, atrophy of androgen-responsive tissue and metabolic changes.

A "malignancy switch" for the androgen receptor?

In the absence of serum endocrine or other toxicological findings that could account for the pathological features of PFS ?(Irwig, 2014; Melcangi et al., 2017)? we suggest a biological event during use of finasteride is causing an often permanent change in the ordinary metabolic function of cells through epigenetic alteration. Although this is controversial to suggest, the potential severity of the disease cannot be overstated, and in a a significant number of cases the health problems are severe, progressive, do not resolve with time and entail a peculiar endocrine fragility. We hypothesise underlying pre-existing genetic and/or epigenetic factors differentiate those who are prone to developing PFS, and this predisposition effects deleterious epigenetic modifications by means of a conserved mechanism upon significant reduction of intracellular androgen-dependent transactivation through various modes of action including but not limited to 5alpha reductase inhibition. These vectors include downregulation of AR mRNA, an induced increase of protein degradation, upregulation of enzymes capable of reducing endogenous AR ligand to inactive androgen metabolites and suppression of steroidogenic enzymes. We further suggest the necessary exposure and severity of symptomatic outcomes are dependent on interindividual differences within this/these underlying predisposing factor(s) and the resulting degree of persistent dysregulation of the androgen receptor on a site-specific basis.

The epigenetically determined fate of somatic cells is not terminal. Epigenetic barriers preservative of cellular integrity were famously visualised by Conrad Waddington's epigenetic landscape, which described a ball running down valleys in determination of its ultimate differentiated state ?(Slack, 2002)?. However, these can be overcome given the correct stimuli, and the past decades have seen rapid advancements in cellular reprogramming methods ?(MacArthur et al., 2009)?. As chemicals are capable of inducing reversal of cell lineage, Kanherkar et al. investigated the possibility of permanent epigenetic alterations occurring following exposure to pharmacological agents. HEK-293 cells cultured in the SSRI antidepressant citalopram revealed significant differential methylation in hundreds of genes. They proposed the term "pharmaceutical reprogramming" to describe a partial dysdifferentiation event resulting from drug-induced methylation changes that consequently alter cellular function and integrity ?(Kanherkar et al., 2018)?. Evidence demonstrates adult sex typical behaviour can be altered in mammals under certain conditions and may be a function of epigenetic maintenance and gene expression with behavioural impacts ?(McCarthy, 2019)?. In relation to androgen signalling, significant recent work has suggested that biologically meaningful differences that directly influence behaviour and function pertaining to sexual traits can arise from epigenetic alteration to the program of the androgen receptor ?(Schuppe et al., 2020)?.

As well as fibrotic changes in the penis, Enatsu et al. reported a reduction of AR and an increase in ER expression in the prostate of young rats administered dutasteride, speculating that an improper response to androgens upon restoration could underlie the sexual dysfunction in PFS owing to altered local receptor expression ?(Enatsu et al., 2016)?. This study demonstrated a deleterious influence exerted by 5alpha reductase inhibition in young rats that entailed morphological alterations to sexual organs and epigenetic remodelling that trended towards the effect of castration. However, many factors exclude the typical response to prolonged 5alpha reductase inhibition from being an applicable model for the behaviour of PFS. These include the rarity of PFS amongst 5ari users, the clinical picture of PFS including pathological development and/or progression of the disease following cessation, a prevalence in younger men using a lower dose, the brevity of exposure in some of the most severely affected cases, the commonly reported responses of PFS patients to trialled therapies, and the previously reported determination of persistent and significant upregulation of the AR in prepuce tissue of PFS patients. Nevertheless, the parabolic nature of AR expression would suggest Enatsu's hypothesis of an induced dysfunction in local androgen response owing to epigenetic remodelling is plausible. Finasteride has previously been shown to upregulate prostate epithelial AR significantly in BPH patients after 30 days of exposure ?(Hsieh et al., 2011)?. Corradi et al. demonstrated that Finasteride induced a persisting overexpression of the AR and important alterations in the tissue microenvironment of the prostate gland in young gerbils. Across three stages of postnatal development, the content and intensity of AR immunostaining were noticeably elevated, particularly in epithelial cell nuclei. Both the tissue changes and AR overexpression proved persistent. Interestingly, when contrasted with their respective control groups, a greater increase in AR nuclear intensity could be observed in the young (8% to 61.5%) Finasteride administered experimental group as opposed to the old Finasteride administered experimental group (66% to 72.5%) at the conclusion of the post-treatment phase ?(Corradi et al., 2009)?.

Coskuner et al, reviewing literature on persistent sexual symptoms in a subset of 5alpha reductase inhibitor users, considered tissue-specific epigenetic effects likely given the persistence of symptoms ?(Coskuner et al., 2019)?. In considering the mechanistic origins of the development of PFS following endocrine disruption with Finasteride, Traish proposed that androgen deprivation and depletion of the substrate precursors for the 3?-hydroxy-steroid dehydrogenases causative of a block in neurosteroidgenesis, attenuating the function of steroid and neurotransmitter receptors and inducing changes in the expression of a host of gene products, eliciting epigenetic changes manifested in histone acetylation, DNA methylation and upregulation of the AR. Traish thus suggests these changes, together with the consequent depletion of neurosteroids, manifest in the development of PFS in susceptible individuals ?(Traish, 2018)?. Di Loreto et al had previously suggested that it was tempting to speculate that PFS patients have triggered processes associated with advanced age by pharmaceutical androgen deprivation ?(Di Loreto et al., 2014)?. The natural decline of testosterone values with ageing has been well established ?(Kaufman & Vermeulen, 2005)?. PFS may thus represent an aberration of such processes, resulting as an adaptive epigenetic response to the pre-receptor disruption of androgen signaling during finasteride use.

Our stated hypothesis for PFS as an epigenetic adaption induced by pharmaceutically interrupted androgen signalling accounts for a deregulated epigenome and the onset and/or symptomatic

intensification following finasteride withdrawal, often after a brief resolution of symptoms, which standardised questionnaires including our own data indicate is an intrinsic feature of the syndrome (Propeciahelp Post-Drug Syndrome Survey: Data not provided). Cessation of finasteride will result in a surge in androgen production owing to the newly uninhibited 5a-reductase enzyme. Presuming a 60% reduction of basal DHT levels during finasteride use, cells epigenetically adapted to a depletion of androgenic signaling owing to the pharmacological reduction of DHT would be exposed to a 300% increase in DHT upon cessation. As molecular level investigation has revealed a persistent elevation in expression of the androgen receptor in symptomatic tissue of a PFS cohort, this may entail a deleterious ligand-dependent effect in alignment with the demonstrated in vitro and in vivo models discussed. Application of such a conceptual framework to the pathology of PFS is not unprecedented. Professor Charles Ryan explained the tissue response to testosterone in terms of a "bell curve" in his book The Virility Paradox. He wrote of PFS: "I think this is what we are seeing here. With a greater concentration of receptors, the organ becomes more sensitive to testosterone and at a certain point, paradoxically, that sensitivity may shut down" ?(Ryan, 2018)?.

We hypothesise that a loss of function and toxic gain of function manifests tissue specifically in a broad spectrum of clinical endpoints, from functional impairment to atrophy in affected tissues. In consideration of this, we would expect future gene expression analysis of symptomatic tissue in severely affected patients to reveal widespread dysregulation of gene expression. A consideration of how a dysregulation of the AR and associated epigenetic remodelling might occur as an aberrant result of antiandrogenic endocrine disruption, and how it may influence broader gene expression, is therefore necessary. This can be contextualised via known molecular mechanisms.

The most well recognised epigenetic adaptations occurring as a result of androgen deprivation therapy is in the context of castration resistant prostate cancer. As a driver of epithelial cell growth and proliferation as well as a fundamental aspect of prostate cancer progression, the androgen receptor axis has been the predominant therapeutic target in prostate cancer for over 75 years ?(Kim & Ryan, 2012; Takeda et al., 2018)?. Patients develop resistance to androgen deprivation therapy after a period of this first line treatment, a state with very poor prognosis known as castration resistant prostate cancer. Second generation antiandrogen treatments have been developed, however nearly all men also develop resistance to this, suggestive of a mechanistic response irrespective of the agent ?(Robinson et al., 2015)?. Although not always observed, amplification of the AR is the most common mechanism of castration resistance ?(Takeda et al., 2018)? and is the only consistent gene expression change associated with hormone refractory disease ?(Chen et al., 2003)?. The amplification of the AR occurs during androgen deprivation therapy ?(Friedlander et al., 2011; Visakorpi et al., 1995)? or antiandrogen treatment ?(Coutinho et al., 2016)? and represents an adaptive response to the low androgen environment ?(Perner et al., 2015; Ruggero et al., 2018; Teply et al., 2018)? that sensitizes cells to lower levels of hormone ?(Waltering et al., 2009)?. Interestingly, low, rather than high, endogenous testosterone levels have been associated with poor prognostic features in prostate cancer and disease reclassification during active surveillance ?(Amadi et al., 2018; San Francisco et al., 2014)?. Several lines of evidence suggest low levels of androgen may predispose to more aggressive tumours ?(Swerdloff et al., 2017)?. Gravina et al. provided evidence that epigenetic mechanisms can contribute to castration resistant phenotypes, demonstrating that

pca cell models in androgen-deprived medium or bicalutamide progressively increased DNMT expression, which increased in proportion to AR upregulation. These findings were verified in patient tissue. DMNT was additionally shown to be regulated by AR, as siRNA AR interference greatly reduced DNMT modulation ?(Gravina et al., 2011)?.

Chen et al. hypothesised that any one of a number of primary molecular events that alter AR activity and increase AR mRNA could represent a common final pathway for castration resistance in PCa. In support of this, it was demonstrated that LNCaP cells altered to express a threefold greater level of AR grew in low androgen concentrations whereas LNCaP cells did not unless supplemented with androgen, confirming that AR overexpression alone confers castration resistance. In addition, they demonstrated that the androgen receptor must bind its ligand to confer hormone-refractory growth. LBD mutant LNCaP constructs did not exhibit hormone-refractory growth beyond vector controls even at ten-fold increases of AR expression levels. Interestingly, AR antagonists, in the circumstance of overexpression, induced certain androgen regulated genes ?(Chen et al., 2003)?. This paradoxical response is reflected in the apparent vulnerability CRPC cells exhibit to supraphysiological androgens. Teply et al. demonstrated clinical response and short-lived resensitisation to enzalutamide through bipolar androgen therapy using exogenous testosterone ?(Teply et al., 2018)?. Similarly, Christensen et al. reported a remarkable clinical and prostate-specific antigen response to a combination of high doses of testosterone and radium 223 in a patient with metastatic CRPC whose disease had progressed while receiving a number of antiandrogenic therapies ?(Christensen et al., 2019)?. ctDNA consistently showed a high degree of AR amplification. These findings suggest that the switch to a hormone refractory state entails a markedly different response to ligand.

Large scale sequencing studies have shown over 90% of cases of advanced CRPC exhibit overexpressed or altered AR, alongside significant alteration to genes involved in histone rearrangement and chromatin modification ?(Barbieri et al., 2012; Braadland & Urbanucci, 2019; Grasso et al., 2012; Robinson et al., 2015; Taylor et al., 2010)?. Chromatin structure is at least partially definitive of a cell's transcriptional program, and determines vast networks of regulatory elements tissue-specifically ?(Pihlajamaa et al., 2015)?. Chromatin relaxation is part of an adaptive response that increases the probability of genomic access and transcription, and enables continued function in a situation in which sufficient androgens and androgen signaling are therapeutically reduced ?(Braadland & Urbanucci, 2019)?. Patterns of open chromatin differ in CRPC to BPH or PCa samples, with large interindividual variance in CRPC ?(Alfonso Urbanucci et al., 2017)?. Braadland and Urbanucci suggest that selective or adaptive remodelling occurs mainly upon treatment challenge with AR-targeted therapies ?(Braadland & Urbanucci, 2019)?. Sequencing in independent AR overexpressing models by Urbanucci et al. revealed genome wide increases in open confirmations of chromatin and an increased opening at androgen responsive binding sites. Androgens further increased this chromatin opening, suggesting ligand potentiates an AR-driven chromatin remodelling in the context of AR overexpression ?(Alfonso Urbanucci et al., 2017)?. This represents a potential "feed forward" mechanism in which the overexpressed AR further facilitates chromatin remodelling that allows the AR greater access and increased binding at the genome ?(Braadland & Urbanucci, 2019)?. Additionally, progression to CRPC entails a significant reprogramming of the AR cistrome ?(Pomerantz et al., 2015; Sharma et al., 2013)?.

Mechanistic alteration of master regulators of the epigenome have been established to play a key role via increasing AR transcriptional activity ?(Ruggero et al., 2018)?, and their behaviour can be context sensitive. The chromatin remodelling enzyme lysine-specific demethylase 1 has emerged as having a dual role given its context-sensitive promotive or repressive effects on AR ?(Cai et al., 2011; Metzger et al., 2005)?. High androgen levels have been demonstrated to cause AR-mediated recruitment of LSD1 to facilitate gene silencing via negative autoregulation of the AR gene ?(Cai et al., 2011)?, while in the context of CRPC this feedback loop is apparently broken given that low androgen levels drive AR overexpression ?(Ruggero et al., 2018)?. LSD1 coactivator or corepressor activity is influenced by post-transcriptional modifications, such as its phosphorylation status which can switch the enzymes substrate ?(Metzger et al., 2007; Shi et al., 2004)?. The tyrosine kinase Src, upregulated in CRPC ?(Siu et al., 2016)?, inactivates the AR corepressor LCoR that ordinarily downregulates AR in response to ligand. This subsequently activates AR at the chromatin level in CRPC ?(Asim et al., 2011)?. A large number of micro-RNAs have been identified to act as post-transcriptional regulators of the AR ?(Perner et al., 2015)?. The miRNA miR137 regulates an androgen-mediated feedback loop that inhibits a large network of crucial AR coregulators in normal prostate epithelia, while epigenetic loss of miR137 in CRPC leads to coregulator and, consequently, AR overexpression ?(Nilsson et al., 2015)?.

It is notable that, in contrast with other DNA binding elements, the AR is able to initiate epigenetic modification of chromatin by itself ?(Tewari et al., 2012)?. Higher AR levels increase AR's genome-wide binding to chromatin upon stimulation with low concentration of ligand ?(A Urbanucci et al., 2011)?. AR overexpression recruits AR and the basic epigenetic machinery to the chromatin to alter histones at AR binding sites and favour chromatin accessibility in the presence of low androgen levels ?(Alfonso Urbanucci et al., 2011)?. Chromatin remodeling proteins such as FOXA1 and HOXB13 are also known to co-localise with AR ?(Stelloo et al., 2017)? and are capable of recruiting acetylating and methylating coregulators including CBP/p300 and MLL ?(Braadland & Urbanucci, 2019)?. Many coregulators of the AR exert chromatin remodelling effects themselves ?(Bannister & Kouzarides, 2011)?, and there is evidence that the AR upregulates a number of its coregulators gene-specifically through varied mechanisms, including AIB1, CBP, MAK, BRCA1, ?-catenin, ATAD2, and MID1 ?(Perner et al., 2015; Alfonso Urbanucci et al., 2008, 2017)?. Several coregulators of the AR including p300, CBP and TIF2 have been shown to increase as a result of androgen deprivation ?(Agoulnik et al., 2006; Comuzzi et al., 2004; Heemers et al., 2007)?. Even a modest overexpression of AR can alter expression and amounts of AR coregulators ?(Chen et al., 2003)?, many of which are histone acetylating ?(Alfonso Urbanucci et al., 2011)?. Key bromodomain proteins, which locus-specifically affect chromatin opening, are androgen regulated and upregulated in AR overexpressing cells. These proteins participate in an AR deregulation-driven feedback loop that increases AR chromatin accessibility ?(Alfonso Urbanucci et al., 2017)?. The Jumonji C KDM4 histone lysine demethylases are overexpressed in CRPC, and KDM4B expression has been significantly correlated with AR. KDM4B influences chromatin and may induce relaxation in conditions of androgen deprivation that are relevant to progression to CRPC ?(Duan et al., 2019)?.

Gritsina et al. reviewed current knowledge regarding the function of AR signaling in driving target gene

repression and silencing by regulation of the epigenetic machinery. Ligand-bound AR binds to the enhancers and/or promoter elements of target genes and mediates assembly and recruitment of the repressive complexes, including histone deacetylases, lysine-specific demethylase 1, and enhancer of zeste homolog 2. AR directly and indirectly induces cascades involving the stabilisation of protein-protein interactions and recruitment of complexes responsible for the removal of acyl groups, demethylation, inhibition of transcriptional activators, and trimethylation, resulting in chromatin modifications that render gene regulatory elements inaccessible or silenced ?(Yu et al., 2019)?.

Taken together, research has identified a clear role for AR expression in genome-wide epigenetic status, along with the ability of the AR to recruit and drive the basic elements of the epigenetic machinery. Additionally, it is apparent that a refractory response to antiandrogenic treatment can occur irrespective of agent. With consideration to these findings, a potential feed-forward mechanism of AR overexpression, potentiated by androgens, may have significant mechanistic implications for the onset and progressive worsening of PFS with the "crash" after cessation of the medication, during which time the multi-systemic symptoms and physiological effects of the condition become apparent or intensify with significant interindividual variability in severity. This occurrence is most usually in a time frame of days or weeks, a timeframe correlating to the return and increase of endogenous DHT levels as the newly functional 5-alpha reductase enzyme is replenished. DHT has been demonstrated to alter the regulation of a number of AR coactivators gene-specifically depending on the level of the receptor, suggesting plausible involvement of coactivator regulation in a feedback loop potentiating increased AR signaling ?(Alfonso Urbanucci et al., 2008)?.

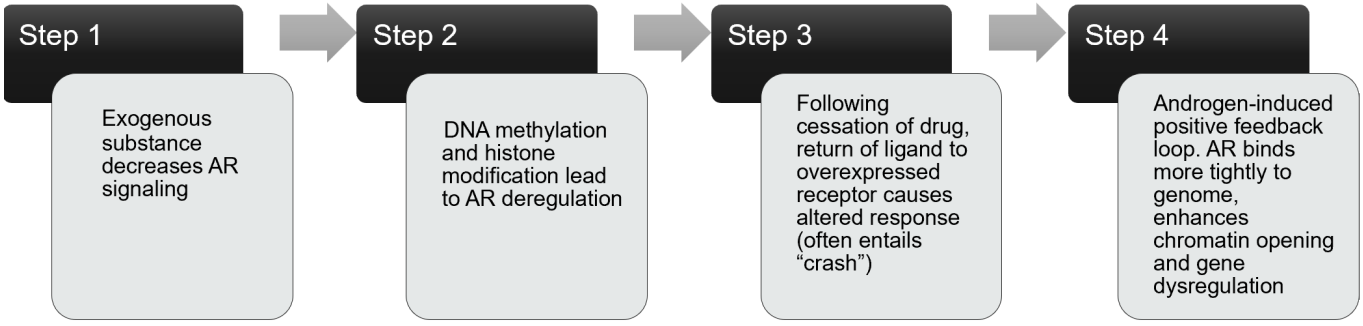

fig. A proposed basic mechanism in pathologically affected cells underlying the development of PFS.

As the transition to CRPC results from androgen deprivation or androgen-axis targeted treatment, an induction of AR deregulation could have relevance to the increased incidence of higher Gleason score prostate cancers in 5ari patients ?(Sarkar et al., 2019; Theoret et al., 2011; Traish et al., 2014; Van Rompay et al., 2018)?. It is of significance that, following three years of use and then cessation, finasteride has been demonstrated to accelerate the progression of male pattern hair loss significantly.

Using technologies unavailable at the time of finasteride's clinical approval, Van Neste recently reported the first evidence of what they describe as a "drug dependency" of terminal scalp hair follicles in AGA patients and a "post-finasteride rebound phenomenon" in patients who had stopped finasteride after 3 years of successful maintenance. During 3 years of finasteride use, 99%?100% terminal hair counts were recorded suggesting effective maintenance. However, while terminal hair was maintained on drug, within 30 months "off-drug" androgenic alopecia had significantly worsened, only 5.8% of terminal hair could be measured, with 94% having miniaturised and become unproductive. This is far in excess of the expected regression rates that were previously established in these patients and robustly predicted at 6% per year ?(Van Neste, 2019)?. It was previously reported that vertex dermal papilla cells in balding samples were 1.9 fold higher in AR expression than those from the occipital scalp ?(Kwon et al., 2004)?, and frontal follicles are 40% higher in AR expression in males compared with women ?(Sawaya & Price, 1997)?. Increased DNA methylation of the AR promoter in occipital follicles from men with AGA is suggestive of toxicity mediated by receptor levels ?(Cobb et al., 2011)?. In agreement, AGA models support an AR-mediated pathological process. Transgenic mice overexpressing human AR in the skin exhibit impaired hair regeneration when exposed to DHT, while hydroxyflutamide can abolish this effect ?(Crabtree et al., 2010)?. An adaptive increase in AR expression following androgen deprivation is therefore a plausible a mechanistic explanation for an increase in hormone sensitivity causative of the dramatic finasteride-induced progression of male pattern hair loss observed by Van Neste. Similarly, epigenetic amplification in PFS could reflect the common reports of a significant acceleration in MPB following development of the condition.

Therapeutic responses to androgens and antiandrogens in PFS

There is no known therapeutic approach for PFS ?(Than et al., 2018)? and no consistently safe or effective therapy has emerged from two decades of patient self-experimentation. Owing to the common PFS symptom profile ostensibly pointing towards decreased androgenic activity and low or hypogonadal levels of testosterone in some cases of PFS, many patients have undergone treatment with exogenous androgens. While this can be of benefit in some patients, it is very rare that this is complete or consistently effective even if a temporary improvement is observed in some symptoms. Remarkably, symptoms can be exacerbated by administration of androgens. This is well reported even in patients in whom PFS has caused a clinical hypogonadism. Patients receiving testosterone replacement therapy prior to PFS have reported a dramatic intolerance to exogenous androgens following the onset of the condition. Testosterone is ordinarily associated with a decrease in depression an improved verbal memory ?(Cherrier et al., 2014)? as well as anxiolytic effect in men, women and animals ?(McHenry et al., 2014)?. The reverse has been well reported in PFS patients, even when hypogonadal. Beyond cognitive symptoms, sexual dysfunction and physical symptoms such as muscle wastage can be exacerbated. This is highly remarkable and paradoxical. A patient who since committed suicide reported further rapid penile shrinking upon local application of topical DHT gel at a dosage of 5g per day with therapeutic intent. This is striking and paradoxical with consideration as to the known effect of DHT in increasing penile size ?(Arteaga-Silva et al., 2008; Becker et al., 2016; Choi et al., 1993)?. Patients will often report feeling no response at all to high doses of testosterone. Interindividually variable "saturation" points with regard

to androgen response ?(Morgentaler & Traish, 2009; Zitzmann, 2009)? have been hypothesised, and this may be of relevance to the therapeutic failure of testosterone in PFS. A threshold at which androgen-mediated toxicity reaches saturation has been observed with regard to the degree of symptoms seen in SBMA models ?(Chevalier-Larsen & Merry, 2011)?, in the toxic effect of DHT in SBMA motor neurons ?(Sheila et al., 2019)?, and in prostate cancer, in which testosterone therapy does not accelerate the disease progression despite androgen dependence ?(Morgentaler & Traish, 2009)?. In PFS, this reaction to exogenous ligand could plausibly be reflective of the degree of AR overexpression per site and per patient, and offers an explanation as to why more favourable partial responses to androgens are sometimes seen, while other patients can often rapidly worsen with raising androgen levels. Of note, it has been reported that an SBMA patient exhibited a notably similar reversible deterioration with androgen administration ?(Kinirons & Rouleau, 2008)?. Importantly, this would be in keeping with the observed responses of female transgenic mice overexpressing WT AR in skeletal muscle to exogenous testosterone equivalent to circulating male levels, which caused striking differences in deleterious physiological effects depending on the degree of AR overexpression ?(Monks et al., 2007)?.

Across the history of the propeciahelp forum, the most consequentially profound responses described entail significant modulation of symptoms by further exposure to substances that lower androgens through mechanisms including 5 alpha reductase inhibition, or substances that reduce concentrations of or inhibit AR. While rapid and severe worsening can occur, patients have equally often reported the dramatic return of function in the domains affected by PFS, usually temporarily. These are nearly always taken in the absence of the knowledge they are taking pharmaceuticals or natural extracts with antiandrogenic properties and are frequently sought out based upon their purported benefits in marketing and health editorials concerning relief of symptoms or through online reports from other patients. These have included zinc, quercetin, resveratrol, milk thistle, licorice root, turmeric/curcumin, sulforaphane, DIM, sodium butyrate, saw palmetto, tribulus terrestris, polyphenol rich products such as cacao nibs or pomegranate, and soy and soy isoflavones including genistein, all of which are notably antiandrogenic through various mechanisms ?(Agarwal et al., 2006; Boam, 2015; Cicero et al., 2019; De Amicis et al., 2019; Hiipakka et al., 2002; Jang et al., 2019; Kampa et al., 2017; Le et al., 2003; Sabbadin et al., 2019; Samykutty et al., 2013; Sandeep et al., 2015; Shiota et al., 2011; Xing, 2001)?. A remarkable overlap can be noted with nutraceuticals that are of increasing interest in the treatment of AR-mediated conditions and with substances or extracts causing patients to develop and present with PFS, as we have noted. Patients have independently described significant and remarkable multi-domain relief following use of AR antagonists including bicalutamide ?(Rice et al., 2019)?, and drugs with an antiandrogenic effects such as ibuprofen, paracetamol, dexamethasone, omeprazole, leuprolide acetate and mifepristone ?(Hoda et al., 2016; Inder et al., 2009; Kortenkamp, 2020; Kristensen et al., 2010; Song et al., 2004; Sørensen et al., 2016)?, and even finasteride itself. Recently, truvada, an antiretroviral medication combining tenofovir disoproxil and emtricitabine, has been reported to improve some PFS patients significantly in multiple symptom domains. Marketed as PrEP, truvada is a reverse transcriptase inhibitor. RTI drugs have been considered for potential therapeutic efficacy in hormonally refractive prostate cancer due to in vitro results suggesting the capability of Nevirapine to induce extensive reprogramming of gene expression, resensitizing cells to stimulation by extracellular ligand and consequentially re-establishing the efficacy of antiandrogen treatment with bicalutamide ?(Landriscina et al., 2009)??.

These common reports are highly remarkable and of relevance to the potential of a pathologic link between PolyQ toxicity and deleterious consequences of site-specific overexpression of the wild type androgen receptor. This would appear to be in alignment with functional rescue in SBMA models targeting the androgen pathway ?(Cortes & La Spada, 2018; Katsuno et al., 2003; Minamiyama, 2004; Nedelsky et al., 2010; Rinaldi et al., 2015)?, and the molecular level responses to androgens and antiandrogens in AR overexpressing CRPC as discussed.

It is of the utmost importance to establish that antiandrogenic therapeutic strategies are dangerous for PFS patients. Patients can persistently exacerbate or develop further symptoms in multiple domains of the condition upon rechallenge or subsequent exposure to substances with antiandrogenic effect. This often occurs after a dramatic improvement of existing multisystemic symptoms. In 2018, a PFS patient who had taken supplementary resveratrol described a profound reversal of symptoms including insomnia, erectile dysfunction, libido loss and fatigue shortly before taking his own life. We note a key vulnerability of this cohort to what we believe to be an aberrant epigenetic response following exposure to antiandrogenic substances. This vulnerability appears significantly exacerbated following initial development of PFS, and even phenol or isoflavone-rich foods have resulted in clear reports of persistent worsening or the triggering of further symptoms. PFS patients most at risk of this are, in our experience, those who present with severe phenotypes after short use of finasteride or a causative antiandrogenic substance. Therefore, until more is known regarding the molecular mechanisms underlying the development of PFS, we strongly urge physicians dealing with PFS patients to be aware of this unique and peculiar vulnerability to therapeutic substances or medicines with antiandrogenic modality. This is of relevance to both prescribed therapies such as SRI antidepressants and to self-driven “natural” therapeutic attempts that can involve high dose phenolic compounds or vitamins marketed as health supplements. Owing to the sometimes profound endocrine sensitivity induced by PFS, safely managing the condition can be a significant burden for patients.

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The role of the AR in areas relevant to the sexual dysfunction in PFS

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/the-role-of-the-ar-in-areas-relevant-to-the-sexual-dysfunction-in-pfs/

Libido, erectile function, and penile structural maintenance

Male libido and sexual desire is primarily androgen-mediated and strictly testosterone dependent. Considerable evidence supports libido loss as the clearest symptom of hypogonadism ?(Santi et al., 2018)?. Evidence regarding the role of other hormones is less clear ?(Corona et al., 2016)?. Male-typical behaviour requires AR signaling in adults, and AR inactivation in male mice causes a complete loss of male sexual behaviour alongside a significant reduction in aggression ?(Sato et al., 2004)?.

Phosphorylated endothelial nitric oxide synthase (eNOS) has a key facilitative role in physiological penile erection following initiation by neuronal nitric oxide synthase (nNOS) ?(Burnett, 2004)?. In human aortic endothelium cells, T rapidly induces eNOS activation and production of nitric oxide through AR-dependent induction of PI3-kinase/Akt signaling ?(Yu et al., 2010)?. Additionally, AR inactivation in mice demonstrates a dramatic reduction in nNOS expression in the hypothalamus, suggesting AR regulation of this neurotransmitter and its sexually relevant functions ?(Sato et al., 2004)?. A particularly common and important symptom of PFS is the loss of nocturnal and morning erections. This is a central mechanism of unconscious sexual arousability ?(Santi et al., 2018)?. Inactivation of the noradrenergic cells in the locus coeruleus in the brain stem, a site expressive of the AR, is a testosterone-dependant process ?(Bancroft, 2005)? that results in nocturnal penile tumescence.

Androgens are crucial to maintain male reproductive physiology and erectile function and are critical to the integrity and maintenance of the tunica albuginea, cavernous endothelium, cavernosal smooth muscle, and nerve structure and function ?(A. Traish & Kim, 2005; A. M. Traish, 2008; Zhang et al., 2013)?. Tissue integrity and structure is vital to venoocclusive function, and structural alteration will result in dysfunction that is both difficult to diagnose and challenging to treat ?(A. M. Traish, 2008)?. Castration of adult male rats significantly decreases penile length, girth, smooth muscle content and endothelial nitric oxide synthase activity, and this is reversible with testosterone administration ?(Halmenschlager et al., 2017; Hofer et al., 2015; Huh et al., 2018; A. M. Traish, 2008)?. Immunohistochemical study of stromal and endothelial human corpus cavernosum cells biopsied from potent males aged between 19 and 63 revealed age-independent high expression of the AR (74.9%) and low expression of ERa (11%). Cultured endothelial cells exposed to T or DHT showed dose-dependent and significant increases in

cellular metabolic activity than control groups with or without growth medium, while similar concentrations of estradiol or progesterone had no respective effect compared with controls ?(Schultheiss et al., 2003)?. This comparably reflects the testosterone-stimulated increase in proliferation reported in fetal smooth muscle cells ?(Crescioli et al., 2003)?, suggesting that peripheral androgen receptor function is important for maintenance of physiology and function of the endothelium in the adult human male penis. The significant expression of AR in penile tissue suggests its vulnerability to a proposed loss of function and potential toxic gain of function conferred by site-specific AR overexpression. This is of particular relevance to the progressive and often rapid penile atrophy after cessation of the drug experienced by some PFS patients that can occur after only one dose ?(Garreton et al., 2016)?. It is particularly relevant that PFS patients reporting this can have normal serum androgen levels ?(Irwig, 2014)?, or frequently relatively high - or intraindividually increased - levels of T.

In addition to venous leakage, clinical findings of calcification and atherosclerosis upon penile ultrasound are anecdotally reported findings following urological evaluation of PFS patients with atrophic changes to the penis. AR signaling is increasingly appreciated as involved in calcification and atherosclerotic lesions, in line with the well-appreciated heightened risk of cardiovascular disease in males, as recently reviewed by Takov et al ?(Takov et al., 2018)?. Vascular smooth muscle cells (VSMCs) provide structural integrity of blood vessels and control diameter via regulation of contraction and vasodilation ?(Metz et al., 2011)?. Zhu et al. reported significant expression of the AR in VSMCs and the presence of AR in calcified aortic and femoral artery tissue. In vitro investigation revealed striking induction of pro-calcificatory effects by both testosterone and DHT, and the lack of aromatase expression in these cells indicated direct mediation by AR signaling ?(Zhu et al., 2016)?. Arterial calcification and atherosclerosis has been associated with long term anabolic steroid abuse, hyperandrogenemia in women with polycystic ovary syndrome and postmenopausal women administered testosterone ?(Christian et al., 2003; Hak et al., 2007; Santora et al., 2006)?. However, in addition to pro-calcificatory effects, investigations have revealed that androgen induction of AR-mediated processes are atheroprotective ?(Son et al., 2010; Yu et al., 2010)?, further suggesting appropriate AR-mediated signaling is necessary for vascular health.

Testosterone treatment of rats during urethral wound healing increases myofibroblast proliferation and collagen deposition, and Hofer et al. speculate this may contribute to spongiofibrosis and stricture development ?(Hofer et al., 2015)?. Finasteride has recently been suggested as a potential therapy in myocardial infarction. Evidence of increased DHT and androgen-responsive gene expression in mouse models of myocardial infarction was reported, and treatment with finasteride markedly improved cardiac function and reduced fibroblast collagen secretion ?(Froese et al., 2018)?. Interestingly, prominent collagen deposition is reported in the corpus cavernosum of rats treated with either finasteride or dutasteride ?(Sahin Kilic et al., 2018)?, reflecting androgen deprivation and hypogonadism ?(El-Sakka, 2011; A. Traish & Kim, 2005)?, possibly indicative of a similar histopathological effect of both reduced or increased androgen signaling.

Hypospadias, a congenital penile deformation associated with prenatal endocrine disruption ?(Wolf et al.,

1999)? and decreased androgen signaling ?(Aschim et al., 2004)?, is associated with altered expression of the AR ?(Vottero et al., 2011)?. Loss of AR expression is not correlated to severity ?(Celayir, 2018)?. Interestingly, Qiao et al. reported that AR was significantly upregulated in the preputial skin of boys with severe hypospadias compared with boys without hypospadias or boys with mild hypospadias, the latter demonstrating a more moderate elevation in AR expression ?(Qiao et al., 2012)?.

Sperm count, motility, and semen consistency

AR dysregulation is a plausible causative factor for well-reported changes to sperm count, motility, semen consistency and ejaculate volume in PFS. AR action in the male reproductive system is functionally critical to sperm differentiation, maturation and survival. Targeted AR knockout in mice causes azoospermia and infertility ?(Krutskikh et al., 2011)?. The AR has been recently shown to be critical across the spermatogenesis and maturation processes. Androgen blockade inhibits differentiation to spermatocytes. In vitro cell culture and in vivo confirmations revealed that promyelocytic leukemia zinc-finger, an important gene in differentiation of spermatogonial stem cells. AR in Sertoli cells indirectly regulates ?1 integrin via GATA2 and WT-1, and ?1 integrin further binds to E-cadherin to regulate the fate of spermatogonial stem cells. DHT treatment of AR-overexpressing Sertoli cells demonstrated AR indirectly down-regulates WT-1, a key gene in spermatogenesis, via GATA2 ?(J. Wang et al., 2019)?. WT-1 is critical to spermatogenesis and deficiency is associated with male infertility ?(X. N. Wang et al., 2013)?. The human epididymis is a complex tubular structure in which spermatozoa functionally develop and reach maturity, serving as conduit to the vas deferens from the testis ?(Cornwall, 2008)?. AR is prominently expressed throughout the epididymis ?(SAR et al., 1990; Zhou et al., 2002)?, and the importance of the AR in this tissue is well established ?(Robaire & Hamzeh, 2011)?. The critical influence of the AR in human epidydimal cells has been confirmed by next generation deep sequencing protocols ?(Browne et al., 2019)?. The AR has been identified to regulate a functional transcriptional network of about 200 genes in the human caput epididymis epithelium and is therefore critically implicated in sperm maturation and fertility maintenance in men ?(Yang et al., 2018)?. The vas deferens fluid microenvironment is crucial to sperm transport and survival in the organ. In rats, vas deferens lumen size, fluid volume and osmolality have been demonstrated to be under the regulation of the AR, as was the expression of aquaporin isoforms AQP-1, AQP-2 and AQP-9. Testosterone was shown to increase water secretion and osmolality in this organ through the AR and was interrupted by Finasteride or Flutamide ?(Ramli et al., 2018)?.

Post-Orgasm illness and increased refractory period

Both a significantly increased refractory period and a post-orgasm modulation of symptoms is widely reported in PFS. Male accessory sex organs are responsive to prolactin. Post-orgasm increases in

prolactin are implicated in sex organ maintenance and functionality, whereas constant levels would prove deleterious ?(Hernandez et al., 2006)?. Prolactin administration has been observed to induce a dose-related increase of AR expression levels beyond levels explainable by organ weight increases in the testes, prostate and epididymis in male rats ?(BARAÑAO et al., 1982)?.

In male rats, AR mRNA levels in the ventral prostate were determined after consecutive ejaculations by Hernandez et al. AR, with a concurrent steady increase in AR mRNA, was significantly increased after one ejaculation (100% increase; $p < 0.05$). Levels were further highly increased after two and three ejaculations (200% and 300% increases respectively) to a total of 800%, returning to precopulatory levels rapidly after the fourth ejaculation. Interestingly, a rapid and significant copulation-induced induced increase in androgen receptor protein precedes higher expression of mRNA or serum elevation of testosterone, suggesting rapid regulatory processes. Additionally, testosterone reaching its maximal increase did not arrest the continual increase of AR mRNA, suggesting the existence of a balance of both gene transcription and stabilization in regards to AR-mRNA levels ?(Hernandez et al., 2007)?.

The paracrine influence of oxytocin ?(H. Nicholson, 1996)?, which systemically increases at orgasm ?(Ivell et al., 1997; OGAWA et al., 1980; Thackare et al., 2006)?, may be influential in the commonly reported modulation of PFS symptoms following orgasm, which can include severe multi-symptom worsening usually lasting a number of days. Administration of oxytocin to rats has been shown to increase testicular and epididymal weight, with a significant increase in 5alpha reductase activity in these organs ($P < 0.005$ and $P < 0.01$ respectively). In vitro homogenates incubated with oxytocin additionally showed significant increases in 5alpha reductase activity at low concentrations (10 pg/0.3-mg protein) ?(H. D. Nicholson & Jenkin, 1994)?. Oxytocin at physiological levels positively regulates the activity of type I and II 5alpha reductases in human prostate epithelial cells ?(S.J. Assinder, 2007)? and in LNCAP cell lines ?(Stephen J. Assinder et al., 2015)?. These results occurred at the level of post-translational protein activity and do not appear to regulate gene expression. Oxytocin is considered to be a potent growth inducer in prostate cancer ?(Xu et al., 2017)?. We hypothesise the increase in 5alpha-reductase activity and increased androgen receptor expression may explain a significant and widely anecdotally reported impact of orgasm on PFS symptoms.

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The role of the AR in areas relevant to the physiological symptoms of PFS

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/the-role-of-the-ar-in-areas-relevant-to-the-physiological-symptoms-of-pfs/

Muscle atrophy and muscular dysfunction

Evidence regarding the ligand- and dose-dependent atrophic consequences of AR overexpression in muscle have been discussed in a previous section. Muscle AR is a major determinant of muscle mass and function. Owing to this, selective androgen receptor modulators are in development with a focus on therapeutic application to diseases including muscle wasting and cachexia ?(Narayanan et al., 2018; Srinath & Dobs, 2014)?. In mice with AR knockout in satellite cells, the precursor cells of skeletal muscle, limb maximal grip strength is decreased by 7% despite similar mass, with altered fiber-type distribution observed in soleus muscles. The weight of the perineal LABC muscle is markedly reduced, weighing 52 percent less than control animals ?(Dubois et al., 2014)?. Significant levator ani weight reduction occurs in inducible ARKO mice in adulthood independent of earlier AR expression ?(Wu et al., 2019)?. It is well appreciated that both the innervating lower motor neurons and the skeletal muscle of the LABC are exquisitely sensitive to androgens ?(Z. Yu, 2006)?, highly expressive of AR ?(D. Ashley Monks & Holmes, 2017; Narayanan et al., 2018)? and androgen dependent for survival and function ?(N. Forger et al., 1993; N. G. Forger et al., 1992; Johansen et al., 2007; C. Jordan et al., 1997; C. L. Jordan et al., 1991; Douglas Ashley Monks et al., 2004; Schrøder, 1980; J. Xu et al., 2001)?. In female ovariectomized mice with consequently diminished pelvic muscles, two SARMs restored pelvic floor muscles to sham operated control weights, with a nonsignificant trend towards an overall increase in lean body mass ?(Ponnusamy et al., 2017)?. As a key site for histological analysis of AR-mediated toxicity ?(Nath et al., 2018)?, the pelvic floor muscle area is a promising site for biopsy and gene expression assay in PFS patients, as well as for less invasive study including EMG evaluation.

Defects in excitation contraction coupling and intracellular calcium homeostasis of skeletal muscle result in a wide range of myopathies including weakness, myalgia, cramping, muscle wasting, joint stiffness and exercise intolerance ?(Dowling et al., 2014)?. The AR is an important regulator of genes involved in muscle contraction, function, structure and calcium dynamics ?(Chivet et al., 2019)?. Using a computational biology approach, Chivet et al. identified androgen response elements in the enhancers, promoters, and 5’-untranslated regions of excitation-contraction coupling-related genes found to be dysregulated in their transcriptome analysis of AR100Q, AR113Q mice and SBMA patients. Restoration was achievable partly with castration and fully with suppression of polyQ AR using antisense oligonucleotides, suggesting a reversibility of the disruption. Importantly, these genes were found to be similarly dysregulated in castrated wild-type mice, establishing the key genes involved in muscle

contraction as being under the regulation of androgen signaling ?(Chivet et al., 2019)?.

Myostatin is a growth factor that strongly inhibits muscle growth ?(McPherron et al., 1997)?, and is under the regulation of AR signaling. Dubois et al. reported a >6-fold decrease in myostatin expression in levator ani muscle of satellite ARKO mice, as well as significant downregulation in the gastrocnemius. Additionally, a reduction of myostatin mRNA levels in orchiectomised mice could be fully reversed with testosterone or DHT administration, demonstrating that myostatin is androgen regulated ?(Dubois et al., 2014)?. However, Mendler et al. reported a strong suppression of myostatin mRNA levels by androgens in the skeletal muscle of young male rats. Considering the presence of ARE on the myostatin gene and the induction of androgen receptor coregulators by myostatin, they speculate that a negative feedback-loop exists between myostatin and androgen pathways ?(Mendler et al., 2007)?.

Skeletal and dental problems

Bone-related complaints are frequent, and diagnosis of osteopenia and osteoporosis are reported by PFS patients. All aspects of body composition are determined by the actions of sex steroids including in the skeleton. Body composition is generally more robust in men, and the risk of osteoporosis is approximately half that of women ?(Vanderschueren et al., 2014)?. Hypogonadal men have lowered bone mineral density that is normalised by exogenous testosterone treatment ?(Behre et al., 1997)?. In addition to ER, appropriate AR signaling is independently required for adult bone health and maintenance ?(J.-F. Chen et al., 2019)?. AR is ubiquitously expressed in human bone marrow in both sexes ?(Mantalaris et al., 2001)?. Detailed tissue specific and global studies of ARKO in bone have revealed a critical regulatory role for androgens in bone health and maintenance on a compartmental basis ?(Vanderschueren et al., 2014)?. Men with complete or partial androgen insensitivity syndrome have a reduced final height that is intermediate between ordinary males and females, as well as reduced lumbar spine density that cannot be compensated by estrogen replacement ?(Danilovic et al., 2006)?. The dramatic reduction in lumbar bone density in androgen insensitivity syndrome patients is not seen in men with 5alpha redutase type II insufficiency syndrome ?(Sobel et al., 2006)?. In Asian men with prostate cancer, 12 months of ADT with either combined GnRH agonist and bicalutamide therapy or GnRH monotherapy induces the same significant loss of bone mineral density ?(Joung et al., 2017)?. Collectively, this illustrates a direct role of the AR in human bone maintenance. To account for the potential of the confounding influence on developmental influences in lifelong ARKO models, Wu et al. developed an inducible ARKO model, demonstrating appropriate AR expression in adulthood is crucial for bone maintenance in adult male mice. Both pre and post-pubertal AR inactivation resulted in significant decreases in the mid-diaphyseal cortical area and cortical thickness in the tibia, as well as trabecular bone volume fraction in the metaphyseal region ?(Wu et al., 2019)?. The reduced cortical thickness was seen to be a "phenocopy" of previously reported models of lifelong AR inactivation ?(Almeida et al., 2017)?.

In a transgenic mouse model, Wiren et al. explored the consequences of targeted AR overexpression in differentiated osteoblasts, demonstrating that excess AR signaling results in a significantly negative consequences on bone matrix quality, biomechanical competence, fragility and strength, while reducing turnover and inhibiting osteoblastic formation ?(Wiren et al., 2008)?. In line with these findings, Aro et al. locally delivered a SARM via an implanted sustained-release matrix in a rat bone marrow ablation model. Contrary to the stated hypothesis of an anabolic effect on intramedullary osteogenesis, only the lowest dose had a negligible anabolic effect, while all higher doses resulted in a dose-dependent decrease in new bone formation around the implant and the bone/implant contact. This was noted to be reflective of overexpression models ?(Aro et al., 2015)?. These findings support the suggestion of Vanderschueren et al that neither too high nor too low AR activity is favourable for bone. Steffens et al. have demonstrated in rats that, as with low levels of testosterone following orchidectomy, supraphysiological doses also increase ligature-induced periodontal bone loss ?(Joao P. Steffens et al., 2012; Joao Paulo Steffens et al., 2015)?, plausibly reflecting the curvilinear dose relationship of AR signaling ?(Gibson et al., 2018)?.

Tooth loss and gum problems are frequent in PFS patients, with many reports of rapid degeneration of teeth, gum recession and the condition causing the need to undergo gingival grafts. Similarly, significantly affected male patients have reported progressive alterations to the jaw structure after cessation. This is notably reported by two brothers who developed PFS after only two weeks of use. It is therefore again highly significant that several lines of evidence suggest periodontal and gingival tissues, tissues responsible for teeth structure and gum health, are dependent on androgens and specifically AR signaling. AR inhibition has been demonstrated to significantly increase peridontal bone loss and impairs bone repair in female rats and is regulatory of inflammatory markers in gingival tissue ?(João Paulo Steffens et al., 2018, 2019)?. Minocyline can stimulate 5alpha reductase in gingival tissue, and combinatory administration with finasteride has suggested that some of the anabolic response to minocycline in these tissues are attributed to the AR pathyway ?(Soory & Virdi, 1998)?. Parkar et al. analysed numerous human peridontal ligament and gingival tissue samples as well as cultured cells for expression of AR. In contrast to ER which was not detected, AR was readily detected in a high proportion of tissue and all fibroblasts, suggesting a high and direct sensitivity to androgens in these tissues with implications for inflammation, connective tissue and bone repair processes ?(Parkar et al., 1996)?. AR is also highly expressed in human tooth pulp, with a greater expression in males than females, and is subject to hormonal manipulation in vitro. T was observed to significantly reduce AR content in tooth pulp, while E2 or androstenedione increased AR mRNA. This suggests, as with bone, this tissue is highly androgen responsive ?(Dale et al., 2002)?. Wang et al. systematically examined the mandibles of castrated rhesus macaques in prime and old age against those of control animals to determine the impact of low androgens on bone and teeth. A prevalence of periodontitis, significant alveolar bone recession and severe temporomandibular joint osteoarthritis was observed in the old castrates. Faces were indicated to be generally narrower by reduced distance between rami. Cortical bone of the mandibular body and rami was thinner, and molar teeth were slender in castrates. These findings collectively suggest the importance of androgens to development and maintenance of facial structure, skeletal and dental health in macaques ?(Q. Wang et al., 2015)?. In addition, androgens exert a significant nociceptive behavioural response and are protective against temporomandibular joint pain in castrated male and female rats, but not sham-operated males. This was demonstrated to be mediated by the AR and is independent of aromatisation to

estrogen or the organisational effects of androgens ?(Fanton et al., 2017)?.

Metabolic regulation

Androgens and the AR are increasingly appreciated as important regulators of metabolic function through actions across the body, and increasing evidence suggests an important influence on metabolic regulation through actions in neurons in hypothalamic and extra-hypothalamic sites in addition to peripheral tissues ?(Morford et al., 2018)?. As in broader evidence we have discussed, there appears to be a parabolic nature to androgen signaling in metabolic function, with high and low levels being detrimental in both sexes, although the parabola is shifted far to the right in males ?(Morford et al., 2018)?. Low androgens and androgen deprivation therapy for prostate cancer increase the risk of type 2 diabetes and obesity in men, and studies in humans and animal models have associated low androgens with hyperglycemia, decreased pancreatic ?-cell function, impaired fasting glucose, glucose intolerance, altered lipid profiles and metabolic syndrome ?(Morford et al., 2018; G. Navarro et al., 2016; I.-C. Yu et al., 2014)?. Central AR knockout in males causes late-onset insulin resistance, glucose intolerance, lipid accumulation in the liver and visceral obesity ?(I.-C. Yu et al., 2012)?. ARKO also induces leptin resistance ?(Fan et al., 2008)?. AR CAG repeat length is positively correlated with higher body fat content, increased leptin and hyperinsulinemia in men ?(Zitzmann et al., 2003)? owing to weaker AR signaling. Interestingly, the risk of type 2 diabetes was recently shown to be 30% greater over 11 years in men receiving either finasteride or dutasteride for BPH, without a difference between the drugs ?(Wei et al., 2019)?. Excessive androgen signaling is also detrimental to optimum metabolic function in males. Male powerlifters using anabolic steroids have diminished glucose tolerance secondary to insulin resistance when compared with non-steroid using athletes and sedentary weight men ?(COHEN & HICKMAN, 1987)?. In castrated rats administered high doses of testosterone, insulin resistance was observed, as with the castrated group. Castrated rats administered testosterone at a dosage that restored physiological levels abolished the perturbation of insulin sensitivity induced by castration, suggesting an appropriate "window" of androgen signaling is required for metabolic homeostasis in males ?(HOLMÄNG & BJÖRNTORP, 1992)?.

Hyperandrogenaemia in women results in metabolic effects strikingly coincident with hypogonadism in men, including predisposition to type 2 diabetes ?(Escobar-Morreale et al., 2014)?. In female mice fed a representative "Western" diet, chronic DHT administration predisposed subjects to type 2 diabetes due to activation of AR in the hypothalamus, which promoted hepatic insulin resistance. In these mice, increased AR signaling in pancreatic ? cells increased mitochondrial oxygen consumption and caused insulin hypersecretion, oxidative injury, and predisposed to secondary ? cell failure ?(G. Navarro et al., 2018)?. RNA-seq has identified a fold change >2 in the expression of 214 genes in AR-deficient islets, and that a third of these are proteins associated with cellular stress and inflammation, indicating a response to injury and emphasising the importance of appropriate AR signaling to ? cell health ?(W. Xu et al., 2017)?. Another study in adult female rats showed hyperinsulinemia due to elevated DHT occurs without alteration in the number or size of pancreatic islets or change in ?-cell area. Even though DHT treated

females had higher insulin levels than controls, they exhibited glucose intolerance with elevated plasma glucose. Ins1 was shown to have an ARE-like sequence that bound to AR upon DHT treatment, suggesting functional regulation of insulin by the AR and androgen. Additionally, skeletal muscle Ir?, the major utiliser of glucose, was downregulated in this model ?(Mishra et al., 2018)?. Independent of obesity, female mice eating a normal diet administered low-dose DHT exhibit impaired whole-body glucose metabolism consisting of glucose intolerance, hepatocyte AR-mediated insulin resistance, impaired gluconeogenic capacity and hyperinsulinemia. This was in addition to observations pertaining to reproductive dysfunction including acyclicity, decreased corpora lutea, and increased atretic follicles that were beyond the scope of the study ?(Andrisse et al., 2016)?. Reflective of evidence in animal models, 50-90% of women with PCOS, a condition characterised by pathological hyperandrogenemia, display insulin resistance and glucose intolerance ?(Morford et al., 2018; W. Xu et al., 2019)?. Testosterone levels robustly correlate with the degree of insulin resistance and ?-cell dysfunction in PCOS ?(Sahin et al., 2014; W. Xu et al., 2019)?. The Glucagon-Like Peptide-1 (GLP-1) receptor is widely expressed and also an important contributor to insulin and glucose homeostasis and ?-cell proliferation ?(Bullock et al., 1996)?. Zhu et al recently demonstrated that GLP-1R expression is under the regulation of androgen signaling, and that this regulation was mediated by the DHT AR complex binding to an AR motif in the Glp1r gene promoter region ?(Zhu et al., 2019)?.

Glucocorticoid steroids pleiotropically mediate a number of functions essential for life including stress-related and circadian functions, immune regulation, metabolic and energy regulation including gluconeogenesis, and control of glucose uptake ?(Kadmiel & Cidlowski, 2013)?. Spaanderman et al recently demonstrated that androgen receptor signaling strongly influences glucocorticoid receptor signaling in metabolic tissues. AR agonism was demonstrated to potentiate glucocorticoid signaling in white and brown adipocytes in vitro and in vivo, while AR antagonism attenuated GR in white adipose tissue and the liver. 11B-hydroxysteroid dehydrogenase type 1, critical to glucocorticoid homeostasis, was shown to be AR regulated. They also demonstrated increased glucocorticoid signalling enhanced fat mass and significantly reduced lean mass without significantly altering weight and induced hyperlipidaemia which was attenuated with the antiandrogen enzalutamide ?(Spaanderman et al., 2019)?.

Androgens, and appropriate proteomic quantity and status of AR, are crucially important to metabolic function and determinant of many aspects of metabolic health. Therefore, a dysregulated androgen receptor is a plausible mechanistic factor in the metabolic disturbances observed in PFS. Additionally, as recent findings implicate insulin receptor and glucagon-like peptide 1 expression in dopaminergic function and mood disorders (Mansur et al., 2018, 2019), the increasing appreciation of the regulation of androgen signaling upon metabolic systems may have functional relevance to the psychological disturbances in PFS.

Digestive complaints, dysmotility, bile acid synthesis and microbiome

Digestive complaints are frequent in PFS with dysmotility, diarrhoea, constipation, and pale stools well reported. Well appreciated sex differences exist in digestive conditions such as IBS, suggesting an influence of sex hormones ?(Y. S. Kim & Kim, 2018)?, and women are generally considered to be more disposed to functional gastroenterological disorders ?(Houghton et al., 2016)?. Interestingly, testosterone has been reported to be higher in male IBS patients than controls ?(B. J. Kim et al., 2008)?. González-Montelongo et al. demonstrated that the digestive tract is a key target of functionally relevant androgen action owing to the AR-mediated regulatory influence of intestinal smooth muscle transit ?(María C. González-Montelongo et al., 2010)?. Calcium sensitization and potentiation of contractile activity in ileal and colonic muscles is rapidly and powerfully induced by androgens at physiological concentrations through a strictly androgen-receptor dependent mechanism ?(Maria C. González-Montelongo et al., 2006; María C. González-Montelongo et al., 2010)? that induces non-genomic cellular signal cascades. These in turn increase ornithine decarboxylase and intracellular polyamines ?(María C. González-Montelongo et al., 2013)?, important modulators of intestinal peristalsis ?(Sánchez et al., 2017)?.

Dysregulation of bile acid metabolism can result in malabsorption and hyperbilirubinemia ?(Chiang, 2013)? which is a frequent serum abnormality reported by PFS patients. Aldo-keto reductase family 1 member D1 (AKR1D1), a ?4-3-oxosteroid 5?-reductase, is required to synthesise bile acid from cholesterol ?(Chiang, 2013)?. Upregulation of Peroxisome Proliferator-activated Receptor ? (PPAR?) has been demonstrated to markedly decrease AKR1D1 promotor transactivation and expression in vitro in HepG2 cells and in vivo, disrupting bile acid homeostasis ?(Valanejad et al., 2018)?. PPAR? also induces glucuronidation of bile acids, making this an important regulator of metabolism ?(Barbier et al., 2003)?. PPAR? has been demonstrated to be under direct regulation by androgens ?(Collett et al., 2000; Zhang et al., 2012)?, and this suggests androgen receptor dysregulation may have functional consequences on bile acid synthesis and metabolism due to crosstalk between these pathways.

Androgen dysregulation has been well demonstrated to induce changes in the microbiome composition, including mice models of hyperandrogenemia, castrated mice and PCa patients undergoing multiple different antiandrogen therapies ?(Guo et al., 2016; Harada et al., 2016; Sfanos et al., 2018; Sherman et al., 2018)?. The absence of species does not appear to affect the influence of androgens on composition ?(Torres et al., 2019)?. Additionally, the microbiome composition of Finasteride treated rats is shown to differ from control animals ?(Diviccaro et al., 2019)?.

Immune system and wound healing

For many patients PFS entails an alteration of immune responses, including intraindividual changes in the incidences of viral infection, fungal infections and the modulation of allergies. Various studies have

highlighted essential androgen regulation of the immune system ?(Lai, Lai, et al., 2012)?. Data indicates an extensive role for the AR in haematopoiesis ?(Mantalaris et al., 2001)?, and immune cell lines including neutrophils, mast cells, macrophages, B cells, T and Treg cells express AR ?(W. Chen et al., 2010; Ma et al., 2019; Mantalaris et al., 2001; Viselli et al., 1997; Walecki et al., 2015)?. Rodent studies have indicated that androgen signaling directly influences differentiation and function of T and B cells, central to the adaptive immune system, and possibly contributes to sex differences in autoimmune disorders ?(Gubbels Bupp & Jorgensen, 2018)?. Androgens and the AR have an increasingly appreciated role in thymopoiesis and T cell transcriptional function partly by modulation of thymic epithelial cells and affect thymic size and output ?(M. A. Brown & Su, 2019)?. Kadel and Kovats, reviewing the understanding of the regulation of sex hormones and viral immunity, suggest that receptor expression may underlie numbers of and functional regulation of innate immune cells in response to hormones ?(Kadel & Kovats, 2018)?. Further, sex differences in epigenetically imprinted regions of open or closed chromatin in hematopoietic stem cells may exist, and the sex-divergent epigenome may be responsive to the sex hormone environment ?(M. A. Brown & Su, 2019; Kadel & Kovats, 2018)?.

Neutrophils are significantly the most abundant granulocyte and form an vital part of the innate immune system, responding rapidly through chemotaxis to clear bacterial and fungal infections ?(Desai & Lionakis, 2018; Lai, Lai, et al., 2012)?. As well as phagocytic removal of cellular debris and pathogens, neutrophils secrete and scavenge a number of cytokines and chemokines that recruit and activate macrophages and monocytes in resolution of inflammation ?(Gordon & Taylor, 2005; Jones et al., 2016; Pham, 2006; Rittirsch et al., 2008)?. In men and women neutrophils strongly express AR at all stages of granulopoiesis from myeloblasts to mature neutrophils ?(Mantalaris et al., 2001)?. In humans, neutropenia can occur with antiandrogen treatment ?(Eaton & Blackmore, 2001; McDonnell & Livingston, 1994)? but neutrophil counts decrease more moderately following castration ?(Chuang et al., 2009)?.

With both in vivo and in vitro studies, Chuang et al. demonstrated that the AR exerts a direct and profound effect upon which neutrophil homeostasis is critically dependent. AR knockout mice are significantly more susceptible to infection. A 90% reduction of neutrophils is observed in male AR knockout and Tfm mice compared with wild type, while castration results in a less significant neutrophil reduction in blood and bone marrow, reflecting human findings. Exogenous androgens restored neutrophil levels in castrated WT mice, but not Tfm or AR knockout mice. Female mice have normal neutrophil levels in the presence of ten-fold lower androgen levels than males, whereas female AR knockout mice are neutropenic, suggesting a direct importance of the AR rather than androgens. It was further demonstrated that loss of AR results in defects in terminal differentiation of neutrophils, and AR restoration in AR knockout granulocyte-macrophage progenitor cells rescued the neutrophil maturation process. AR was also shown to be significantly important to neutrophil production mechanistically by regulation of granulocyte-colony stimulating factor (G-CSF) signaling. Loss of AR in granulocytes leads to suppression of G-CSF resulting from an increase in protein inhibitor of activated STAT protein 3 (PIAS3) binding to STAT3, which is rescued by AR in a dose-dependent manner, apparently without dependence on androgens. Thus, AR is required for G-CSF induction of ERK activation and consequent proliferation of granulocytes ?(Chuang et al., 2009)?. Higher androgen levels have been demonstrated to

impair the bactericidal abilities of neutrophils and increase the expression of anti-inflammatory cytokines IL10 and TGF?1 in a rat model of bacterial prostate inflammation, prolonging the inflammatory response ?(Scalerandi et al., 2018)?.

Slowed wound healing is very frequently reported in PFS. As with immune differences, sex differences exist in the speed of cutaneous wound healing, with males healing slower than females ?(Taylor et al., 2002)?. Higher androgen levels are observed to be inhibitory of cutaneous wound healing ?(Ashcroft & Mills, 2002; Fimmel & Zouboulis, 2005)?, and DHT is more potently inhibitory of upon re-epithelialization than testosterone ?(Gilliver et al., 2009)?. In line with findings in dermal wound healing, androgens were demonstrated to prolong healing in castrated rats administered testosterone following urethral surgery. Those administered testosterone had significantly increased neutrophils, higher macrophage counts, significantly higher immunomodulators such as TNF?, TGF?-1, VEGF? and IL-10, a more intense and longer inflammatory phase and an increase in myofibroblast proliferation and collagen tissue deposition in the delayed proliferative phase ?(Hofer et al., 2015)?. Following prostate resection, both castration ?(X.-J. Wang et al., 2017)? and finasteride ?(Ruizhe Zhao et al., 2017)? were seen to speed wound healing and induce re-epithelialization, while DHT enhanced macrophages TNF-? secretion through AR signaling. This extended the inflammatory phase, delaying and weakening the anti-inflammatory stage.

Mechanistic studies have revealed that the AR, and not androgens, are critical to the suppression of wound healing ?(Lai, Chang, et al., 2012)?. AR knockout males have markedly accelerated wound healing that is not reversed with DHT administration ?(Lai et al., 2009)?, demonstrating increased reepithelialisation, keratinocyte proliferation and matrix deposition. By contrast, AR knockout does not affect the wound healing rate in female mice ?(Yiwei Wang et al., 2016)?. In a model of autoimmune myocarditis, AR suppression with the AR degrader ASC-J9 promoted anti-inflammatory cytokines and M2 macrophage polarization via STAT3/SOCS3 regulation, suggesting ASC-J9s potential as a protective therapeutic in inflammatory cardiomyopathy ?(Ma et al., 2019)?. Local AR antagonists and degraders including ASC-J9 are reported to speed wound healing ?(Lai et al., 2009; Toraldo et al., 2012; Yiwei Wang et al., 2016)?. While AR has an upregulatory effect on TNF-? and CCR2 expression, suppressing cutaneous wound healing ?(Lai et al., 2009)?, TNF-? has been shown to increase in ARKO mice ?(Bourghardt et al., 2010)?. Androgens have been reported to be inhibitory of inflammatory cytokine production after haemorrhagic shock and burns ?(Lai, Lai, et al., 2012)?. In contrast to the discussed studies, testosterone has been shown to reduce TNF-? and IL-1? in hypogonadal men ?(Kalinchenko et al., 2010; Malkin et al., 2004)?. Men and women with rheumatoid arthritis have significantly decreased androgen levels in synovial fluid of inflamed tissue ?(Cutolo, 2009)?.

Considering the increased inflammatory markers in hypogonadism and the anti-inflammatory influence of testosterone in hypogonadal men, Traish et al. suggest that androgens may be necessary in maintaining inflammatory homeostasis ?(Traish et al., 2018)?. This would be in agreement with a "bell curve" effect of androgen signaling on cellular homeostasis and consistent with Gibson's description of the new

appreciation of testosterone as a "goldilocks molecule" ?(Gibson et al., 2018)?.

Dry Eye

Dry eye problems are extremely well reported in anecdotes on our forum and from post-finasteride, Accutane and SSRI patients. Androgens play a direct role in the development of lacrimal gland inflammation and aqueous-deficient dry eye disease ?(Morthen et al., 2019)?. Androgen deficiency is a major cause of dry eye, and this is particularly prevalent in women following the menopausal decrease in androgen levels ?(K. Li et al., 2017)?. Androgen administration alleviates dry eye symptoms and increases tear flow in Sjogren syndrome patients, suppresses inflammation in mice models of dry eye, and completely resolves symptoms in dry eye dogs ?(Morthen et al., 2019)?. Complete androgen insensitivity syndrome causes dry eye, meibomian gland dysfunction, lipid tear film layer instability and decreased mucous levels in humans ?(Mantelli et al., 2006)?. Finasteride has been used to generate a rat model of androgen deficient dry eye, downregulating the AR, disrupting androgen-influenced inflammatory homeostasis, and significantly increasing levels of the inflammatory cytokines IL-1?, IL-4, IL-6, IL-10, MMP-8, FasL and TNF-? in the lacrimal glands as compared with control rats ?(K. Li et al., 2017; S. Singh et al., 2014)?.

The androgen receptor mRNA and protein have been identified in epithelial cell nuclei of the human meibomian glands, lacrimal glands, cornea and conjunctiva ?(Rocha, 2000; Wickham et al., 2000)?. DHT has been demonstrated to significantly regulate the expression of approximately 3,000 genes in immortalized human meibomian gland and conjunctival epithelial cells ?(Khandelwal et al., 2012)?, including many related to inflammation and mucus production.

The testosterone-induced regulation of numerous immune related gene expressions in the lacrimal tissue of Sjogren syndrome and diabetic mouse models differed considerably, with a significant inflammatory effect of androgens in the diabetic mice model as opposed to the anti-inflammatory response seen in the Sjogren’s syndrome model. AR status was hypothesised as a possible mediating "on/off switch" for the microenvironment-dependent response ?(Morthen et al., 2019)?. Interestingly, hyperandrogenic PCOS patients experience dry eye, tear reduction and meibomian gland dysfunction ?(Baser et al., 2016; Bonini et al., 2007; Yuksel et al., 2015)?, lending further support to the suggestion that appropriate androgen signaling is required for inflammatory homeostasis. Local AR dysregulation in PFS could underlie the dry eyes and tear-related symptoms reported by patients.

Skin

Skin is an androgen-sensitive organ ?(Ashcroft & Mills, 2002)? and a major target of androgen action. The AR is expressed in human skin fibroblasts, basal cells, sebocytes, pilosebaceous units, sweat gland secretory cells, dermal papilla, and keratinocytes ?(Alesci & Bornstein, 2000; Pelletier & Ren, 2004)?. The AR has been shown to have a profound and determinant effect on the collagen content of the skin of the adult mouse in both genders ?(Markova et al., 2004)?. Immunohistochemical staining has shown that AR staining intensity and immunoreactivity correlates strongly with the height of the apocrine sweat secretory epithelium ?(Beier et al., 2004)?, and as low epithelium is associated with inactivity, this would suggest AR signaling has a direct role in sweat secretion ?(Ceruti et al., 2018)?. Androgens have been understood to be a leading factor in acne pathogenesis for nearly a century ?(J. B. HAMILTON, 1941)?, and androgen signaling influences both the sebaceous gland activity and inflammation associated with acne ?(Lai, Chang, et al., 2012)?. Comprised of sebocytes, the sebaceous gland is are important in production of sebum, the lipids comprising which are important in skin barrier function, water resistance, sun damage and UV resistance, and establishment of the commensal bacterial flora of the skin ?(Szöll?si et al., 2017)?. The sebaceous gland is capable of synthesising pregnenolone from cholesterol via p450 side chain cleavage ?(Thiboutot et al., 2003)? as well as metabolising androgens through enzymes including hydroxysteroid dehydrogenases and 5 alpha reductase type 1 ?(Szöll?si et al., 2017)?. The proliferative effects of androgens on sebocytes are dependent on the physiological site of localisation ?(Akamatsu et al., 1992)?. Recent in vitro investigation has demonstrated differentiation of immature sebocytes is under strong AR regulation, and lipid synthesis and storage is induced by androgens in an AR-dependent process. This was demonstrated to be independent of the presence of serum or other cofactors ?(Barrault et al., 2015)?.

Alteration in skin pigmentation and tanning response is very commonly reported in PFS patients and a case of PFS involving significant vitiligo was reported by Motofei et al. ?(Motofei et al., 2017)?. Early observations by Hamilton noted a poor tanning response to ultraviolet radiation in castrated men, and testosterone treatment would improve melanisation ?(J. HAMILTON, 1948)?. Androgens and the AR are involved in melanocyte biology and function, and melanocytes synthesise DHT ?(Slominski et al., 2004)?. Genital skin increases in pigmentation at puberty, and this increase in pigmentation is not seen in hypogonadal men ?(Köhn et al., 2000)?.

Cooper et al. reported three cases of myotonic dystrophy - a disease associated with low androgen levels - exhibiting androgen dependent diseases including acne, hidradenitis suppurativa, androgenetic alopecia and keratosis pilaris. They speculated a functional difference in AR may account for the frontal balding in myotonic dystrophy, and that in androgen-mediated conditions, the peripheral response to androgens differs between individuals, mediated by peripheral androgen receptors, with absolute levels of circulating androgens being of limited importance ?(Cooper et al., 2003)?.

Mitochondrial function

With broad physiological relevance, AR is an important regulator of overall mitochondrial function and is suggested to impact gene transcription through retrograde signaling ?(Bajpai et al., 2019)?. Testosterone had been hypothesised to regulate mitochondrial function owing to prior data including serum levels correlating with oxidative phosphorylation gene expression in skeletal muscle ?(Pitteloud et al., 2005)?. In a significant contribution to the understanding of the nonclassical role of the AR, Bajpai et al. demonstrated that the AR contains a mitochondrial localisation sequence and is imported into the mitochondria independent of association with ligand where it localises and regulates multiple processes via signaling cascades. Through a number of studies, they elucidated several roles for the AR in regulation of mitochondria. AR negatively regulates assembly factors of, and destabilises, oxidative phosphorylation supercomplexes. The AR is regulatory of the enzymatic activity of oxidative phosphorylation complexes and a large number of oxidative phosphorylation subunits. The AR regulates mitochondrial protein translation through control of the expression of nuclear ribosomal genes in the mitochondria. AR expression was shown to negatively correlate with mitochondrial DNA content and to TFAM (transcription factor A mitochondrial) protein content, which is regulatory of mitochondrial DNA. Mitochondrial stress was demonstrated to increase expression of the AR and its import into the mitochondria, suggesting an intricate link between both ?(Bajpai et al., 2019)?. Taken together, the well demonstrated impact on mitochondrial function would suggest aberrant AR signaling is capable of inducing significant mitochondrial dysfunction, which in turn could result in numerous detrimental effects at the cellular and consequently systemic level. This is of significance to the mechanistic overlap of wild-type gene amplification and polyglutamine expansion ?(D. A. Monks et al., 2007)? with consideration as to the aforementioned implication of mitochondrial dysfunction in SBMA. Beyond an indispensable role in cellular energy production, metabolism, apoptosis and proliferation ?(van der Bliek et al., 2017)?, mitochondria play a major role in aspects of health and disease ?(Chakrabarty et al., 2018; Ru?Zhou Zhao et al., 2019)? including t-cell and macrophage immune response ?(Liu & Ho, 2018)?, neurodegeneration and neuroprotection ?(Darryll M.A. Oliver & P. Hemachandra Reddy, 2019; P. A. Li et al., 2017)?, sensorineural hearing loss ?(Kamogashira et al., 2015)?, cardiomyopathy ?(Lorenzo et al., 2013)?, atherosclerosis ?(Hulsmans et al., 2012)?, macular degeneration ?(E. E. Brown et al., 2018)?, periodontitis ?(Y. Chen et al., 2019)?, non-alcoholic fatty liver disease ?(Simões et al., 2018)?, cancer ?(Higuchi et al., 2005; K. K. Singh & Modica-Napolitano, 2017)?, and normal aging ?(Y. Wang & Hekimi, 2015)?.

LH/T Deregulation

PFS patients often report atypical hormonal profiles, and in cases who had profiles from before exposure to finasteride, a significantly altered hormonal milieu is frequently apparent. Curiously, PFS patients commonly report LH disproportionately low in relation to Testosterone levels, and this has been noted in a studied cohort ?(Di Loreto, 2011)?. A feedback loop of hypothalamic gonadotropin-releasing hormone

(GnRH) and subsequent LH release from the pituitary stimulate male testosterone synthesis, which in turn negatively regulates GnRH release by acting on steroid receptors in Kiss1/NKB/Dynorphin (KNDy) neurons ?(V. M. Navarro et al., 2011; Ruka et al., 2016; Smith et al., 2005)?. Neural ARKO male mice show elevated levels of T ?(Raskin et al., 2009)?, and evidence from ERa knockout additionally illustrates that the AR plays the primary role in negative-feedback regulation of hypothalamic LH release ?(Wersinger et al., 1999)?.

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The role of the AR in areas relevant to the neurological and psychological symptoms of PFS

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/the-role-of-the-ar-in-neurological-and-psychological-symptoms-of-pfs/

Cognitive dysfunction, Anhedonia and Anxiety

Anxiety, loss of motivation, loss of aggression, lack of feelings of wellbeing, severe anhedonia and visuospatial and cognitive impairment are some the most frequent neuropsychological complaints in PFS. These can manifest with a profound severity and entail a devastating impact on quality of life. This is strongly suggestive of impairment in executive, reward and motivational circuitry in the brain. The important role of metabolite neurosteroids ?(Diotel et al., 2018)?, shown to be broadly deregulated in PFS ?(Melcangi et al., 2017)?, may have additional relevance to these symptomatic areas. However, this is beyond the scope of this review, which is focused upon a potential pleiotropic pathomechanism with direct relevance to the full clinical picture and underlying the pathology.

Low serum testosterone is strongly associated with an increase in depression in aging men ?(Ford et al., 2016)? and men undergoing ADT ?(Lee et al., 2014)?. Androgens have mostly anxiolytic and antidepressant properties in humans and animals ?(Liang et al., 2018; McHenry et al., 2014; Zarrouf et al., 2009)?. Androgens regulate gene expression in key areas of the brain that are fundamental to the etiology of depression and anxiety ?(McHenry et al., 2014)?. AR-deficient mice rapidly develop depressive-like behaviour with exposure to chronic mild stress ?(Hung et al., 2019)? and significant comparative reductions in AR in the hypothalamic paraventricular nucleus (PVN) has been identified in autopsied depression patients ?(Wang et al., 2008)?. Androgen administration has anti-depressive effects in middle-aged men with low testosterone levels ?(Amanatkar et al., 2014)?. Owens et al. reported significantly increased AR mRNA in the PFC of patients with bipolar disorder as surprising given the association of depression with low androgen levels but noted the association of excessive androgen signaling with psychological illness ?(Owens et al., 2019)?.

Impaired executive functioning and visuospatial abilities are the most frequently reported cognitive consequences of androgen deprivation therapy ?(Nelson et al., 2008)?. Additionally, multiple lines of evidence including in anabolic steroid abuse and polycystic ovary syndrome suggests increased androgen action is markedly associated with psychological illnesses including schizophrenia, psychosis, bipolar disorder, tics, anxiety and depression ?(Cesta et al., 2016; Piacentino et al., 2015; Wood, 2008)?. In an important review of the role of androgens in the mesolimbic system and of evidence that both high and

low androgen signaling causes cognitive impairment in both human and animals, Tobiansky et al. suggested that optimally required levels of androgen signaling are required within the mesolimbic system ?(Tobiansky et al., 2018)?. Mesolimbic areas crucial to executive function including the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC) express AR ?(Kritzer, 1997; Low et al., 2017; Tobiansky et al., 2018)?, areas which functionally align with the effects of androgens on behaviour ?(Kritzer, 1997)?. As the AR relevant to function in these areas is often not concentrated in neuronal nuclei, this has been traditionally difficult to quantify and easily overlooked. Executive functioning, which includes behavioural prioritisation of goal attainment, attention, inhibitory control and working memory, critically depends on PFC function ?(Tobiansky et al., 2018)?. Importantly, all major prefrontal cortical projections in the VTA are substantially AR enriched. Androgen signaling regulates the essential dopamine innervation of the PFC and regulates glutamate signaling, potentially through these circuits ?(Aubele & Kritzer, 2011)?. The NAc is critically involved in reward behaviour and is an integrative and convergent site for reward systems in the brain ?(Sesack & Grace, 2009)?. Neurons in the NAc respond to both excitatory and inhibitory afferents from the ventral hippocampus (vHPC) ?(Scudder et al., 2018)?. In the rat, AR is colocalised with dopamine neurons in the midbrain that project to the amygdala and nucleus accumbens ?(Creutz & Kritzer, 2004)?. In line with human studies suggesting an increase in testosterone raises striatal dopamine ?(Hermans et al., 2010)?, studies in the male rat have demonstrated AR-driven modulation of molecular measures of dopamine responsivity of the nigrostriatal pathway including regulating mRNA, levels of molecules involved in pre-synaptic dopamine synthesis, dopamine reuptake, packaging, breakdown and reception ?(Purves-Tyson et al., 2014)?. Dopamine is increased in reward regions of the rat brain in under 30 minutes ?(de Souza Silva et al., 2009)?, and the testosterone-induced effect on reward behaviour is abolished by administration of the dopamine receptor antagonist ?-flupentixol ?(Packard et al., 1998)?. Coincident with a sharp decline in voluntary physical activity, AR knockout mice show a substantial loss of dopamine and dopamine receptor expression in the striatum, with upregulation of mRNA levels of the metabolic enzymes monoamine oxidase A and B ?(Jardí et al., 2018)?. Alongside a significant reduction in voluntary activity, mice with knockout of hypothalamus-specific AR exhibited a large decrease in D? receptor mRNA and an increase in MOAB mRNA ?(Clarke et al., 2019)?. Interestingly, androgen-anabolic steroids significantly decrease D? receptor in the NAc ?(Kindlundh et al., 2001)? and testosterone administration impairs D? receptor-dependent set-shifting behaviour in rats ?(Wallin & Wood, 2015)?. DHT treatment inhibits the open-field induced dopamine increase in the PFC ?(Handa et al., 1997)?. This has important implications for cognitive functioning considering the importance of PFC functions. Loss of adequate D? receptor function in the PFC of Rhesus macaques causes cognitive deficits close to surgical ablation of the site ?(Brozoski et al., 1979; Tobiansky et al., 2018)?.

In late adolescent rats, finasteride remarkably decreases the activity of the dopaminergic system, exploratory and motor behaviours through decreasing DHT production and consequently androgen receptor activation on dopamine neurons in the Substantia nigra and VTA. Interestingly, this effect was not seen in older or younger rats ?(Li et al., 2017)?. The reported reduction in brain DHT of late adolescent rats had not been observed in younger rats in a previous study ?(Giatti et al., 2015)?, suggesting significant interruption in brain dopaminergic activity occurs when AR activation is inhibited during the time testosterone levels are at their natural peak ?(Li et al., 2017)?. This spatiotemporal observation of age-related difference is of potential relevance to the prevalence of PFS in young adult men of fertile age.

Androgens have been demonstrated to modulate the HPA stress response and modulate anxiety behaviours ?(Mhaouty-Kodja, 2018)?. While all metabolites of testosterone, including DHT, influence anxiety-like behaviours in animal models, aged male rats are more anxious than female counterparts. This difference is abolished by prepubertal orchiectomy, demonstrating this difference is androgen dependent ?(Domonkos et al., 2017)?. Evidence suggests the anxiolytic effect of T is mediated at least in part through the AR. Men treated with flutamide experience increased anxiety ?(Almeida et al., 2004)?. Intrahippocampal flutamide increases anxiety behaviour of intact and DHT-replaced male rats, but not when independently administered to gonadectomised rats ?(Edinger & Frye, 2006)?. Corticotropin-releasing hormone is an important regulator of the HPA axis and response. AR mediates regulation of corticotropin-releasing hormone mRNA in the PVN, possibly via AR-colocalising projecting neurons in the bed nucleus of the stria terminalis ?(Heck & Handa, 2019)?.

Williams et al. demonstrated sex differences in the resilience to stress-induced anhedonia in mice and revealed an androgen-mediated mechanism underlying lower vHPC-NAc excitability and correlated increase in subchronic stress resistance in male mice. Reduced sucrose preference following subchronic variable stress (SVS) was demonstrated to be female specific. Orchidectomy rendered male mice vulnerable to SVS-induced anhedonia. Testosterone to female mice was protective of SVS-induced anhedonia and decreased vHPC-NAc excitability in females. Ovariectomy, by contrast, did not affect female vHPC-NAc neuron excitability, suggesting direct mediation by the AR. It was determined that vHPC-NAc projection neurons, and many surrounding vHPC CA1 pyramidal cells highly express AR, and that bath application of the antiandrogen flutamide increased the excitability of cells ?(Williams et al., 2020)?, further suggesting interruption of androgen signalling conferred this susceptibility. The identification of this specific androgen-driven circuitry and its causal link to anhedonia suggests that a tissue-specific deregulation of the AR, as we propose in PFS, would have significant implications for dopaminergic signalling in the NAc and consequently anhedonia symptoms.

Providing a vital addition to the understanding of both the rapid effect of nonclassical androgen signaling on human social behaviour and the AR-dependency of testosterone's influence on aggression, Geniole et al. demonstrated that a single administration of testosterone to men with high-risk personality profiles increased aggression. This effect was negatively correlated with AR CAG repeat length, with shorter CAG repeat subjects exhibiting an enhanced effect. These effects were associated with increase reward feelings associated with aggression as opposed to anger associated with aggression, suggesting a rapid AR-mediated modulation of dopamine pathways in line with existing evidence ?(Geniole et al., 2019)?.

Conclusively, significant evidence indicates the curvilinear tissue response of androgen action is relevant to anxiety and mood ?(Owens et al., 2019)? as well as cognitive function ?(Tobiansky et al., 2018)?.

Memory and spatial processing

Severe memory impairment is a common and problem reported by PFS patients, with many extremely serious implications for the patient's life. The hippocampus is critical to a broad range of learning, memory, visual, spatial, and navigatory functions in mammals ?(Eichenbaum, 2017; Rolls & Wirth, 2018)?. In humans, CA1 neurons are crucial to memory formation and retrieval, as well as self-continuity, autonoetic consciousness and detailed memory revisitation ?(Bartsch et al., 2011)?. The AR is highly expressed in the hippocampus, particularly in CA1 pyramidal neurons. In addition to nuclear and cytoplasmic presence, AR is localised in spines, and synaptic AR rapidly responds to androgen, directly modulating spine density by kinase network activation ?(Hatanaka et al., 2015; Soma et al., 2018)?. Pyramidal CA1 neurons require NMDA receptors for spatial and temporal memory ?(Huerta et al., 2000)?. Neural AR deletion in mice impaired NMDAR activation and prevented temporal differentiation between objects seen, revealing hippocampal CA1 AR is critical for processing of visual temporal information, possibly through an observed modulation of glutamatergic transmission ?(Picot et al., 2016)?.

AR overexpression is demonstrated to strongly alter memory-related genes in the CA1 region ?(Ramzan et al., 2018)?. Finasteride has been demonstrated to significantly decrease brain DHT levels and reversibly reduce neurogenesis in the hippocampus of mice, affecting neuronal plasticity on a structural level ?(Römer et al., 2010)?. Hippocampal AR in humans is highly expressed in both sexes. Remarkably, this is of the same order of magnitude as AR expression in the prostate of BPH patients ?(Beyenburg et al., 2000)?. Multiple studies suggest androgens as important organisational modulators of hippocampal physiology that maintain active hippocampal functions throughout life ?(Hamson et al., 2016; Kerr et al., 1995)?. Perceived male sex-related advantages in spatio-visual and navigatory abilities have been attributed to androgens rather than evolutionary adaptation ?(Clint et al., 2012)?. Reports on the effects of androgens on spatial ability have provided contradictory results, suggestive of complex regulation ?(Shahrzad & Nasser, 2015)?. Men with Alzheimer's disease have lower brain testosterone, and findings suggest that low androgens may predispose to Alzheimer's ?(Rosario et al., 2011)?. In Alzheimer's models, testosterone has been demonstrated to exert a protective effect via an AR-mediated increase hippocampal neurons, synaptic plasticity and dendritic spine density ?(Jia et al., 2019)?. However, prelimbic testosterone injection causes impairment in spatial learning and memory in male Wistar rats ?(Gholaminejad et al., 2019)?. Clearly, crucial sites involved in learning, memory and spatial processing are markedly sensitive to alteration in androgen signaling.

Insomnia and sleep disordered breathing

PFS has driven patients to suicide through the rapid and persistent destruction of their ability to sleep. In

severely affected patients, this can be total. A patient who had resumed finasteride for a very short time with a stated aim of maintaining his hair for upcoming wedding photographs committed suicide after describing the rapid onset of extreme health complaints including debilitating anxiety and insomnia that prevented any sleep for a month. Severely affected patients often describe poor-quality, brief and interrupted sleep many years after brief use of the drug. This is an important and disabling symptom, the severity of which does not appear to be appreciated in literature. Additionally, patients have reported onset or worsening of sleep apnoea. Irwig found that insomnia was a common complaint in the medical records of 6 patients who committed suicide following use of Finasteride and development of persistent symptoms, and this was amongst their most debilitating symptoms ?(Irwig, 2020)?. Evidence suggests that, as well as low testosterone being associated with a decrease in sleep quality ?(Barrett-Connor et al., 2008)?, increased androgen signaling may be associated with sleep disruption and disordered breathing. Higher testosterone levels are associate with lower sleep intensity and higher ventilatory instability in men ?(Morselli et al., 2018)?, and whole genome methylation analysis has shown elevated AR protein is associated with obstructive sleep apnoea (OSA) via ventilatory instability ?(Chen et al., 2016)?. High dose exogenous testosterone can cause significant disruption of sleep to the extent of clinically relevant harm, as well as inducing and exacerbating OSA ?(Kim & Cho, 2019; Liu et al., 2003)?. Exogenous T has induced sleep apnoea in a female patient ?(Johnson et al., 1984)?. In the hyperandrogenic condition PCOS, meta-analysis of research has indicated a significant association of OSA with the syndrome ?(Helvaci et al., 2017)?. As previously mentioned, a high occurrence of sleep disorders has been reported in SBMA patients ?(Romigi et al., 2014)?. Androgens act locally in the suprachiasmatic nucleus, the hypothalamic structure controlling behavioural and physiological circadian rhythms, to influence plastic structural reorganisation and alter circadian period ?(Model et al., 2015)?. Androgen receptors are present in the suprachiasmatic nucleus, are regulated locally by androgens, and thus are an obvious site of action for a direct effect of androgen steroids ?(Karatsoreos & Silver, 2007)?. Significant clinical differences in the response of healthy men and women to a single dose of Olanzapine ?(Giménez et al., 2011)? suggest sex differences in the mechanisms regulating sleep (Mong & Cusmano, 2016). The exact influence of sex steroids over sleep remains an important knowledge gap ?(Mong & Cusmano, 2016)?.

Head pressure

A central and potentially causative role of androgen signaling was recently demonstrated in idiopathic intracranial hypertension (IIH), which entails an increase of CSF pressure. O'Reilly et al. identified a pattern of androgen excess in female IIH patients. Like human choroid plexus, rat cells expressed AR along with androgen-metabolising enzymes. It was demonstrated that testosterone drove CSF output in rodent choroid plexus cells ?(O'Reilly et al., 2019)?. O'Reilly et al. noted that while a determinant role for androgens in IIH may seem biologically implausible considering IIH occurs less frequently in men, androgens are now known to exert sexually dimorphic effects on metabolism. The metabolic phenotype of hypogonadal men resembles that of women with androgen excess, including an increased risk of type 2 diabetes, non-alcoholic fatty liver disease and cardiovascular mortality ?(Ding et al., 2006; Kautzky-Willer et al., 2016)?. O'Reilly et al. suggest epigenetic modifications to local androgen action or differences in AR signaling in both sexes as a plausible explanation, with IIH potentially representing a

distinctive manifestation of these sex specific differences ?(O'Reilly et al., 2019)?. Interestingly, male IIH patients are more likely to have symptoms typically associated with androgen insufficiency including obstructive sleep apnoea, erectile dysfunction and loss of libido ?(Fraser et al., 2010)?. As well, androgen deprivation therapy or hypogonadism can induce IIH symptomatology ?(Valcamonico et al., 2013)?. Although in males the metabolic parabola of AR signaling is shifted far to the right compared with females ?(Ding et al., 2006; Morford et al., 2018)?, significant increases in AR signaling in men are likely to recapitulate this symptomatology, and we therefore consider it plausible IIH occurs in PFS and contributes to commonly reported symptoms, including feelings of intense pressure in the head. In this context, it is of interest that the pilot study of Melcangi et al. evaluating CSF methylation in PFS patients and controls found only one member of the control group with methylation of SRD5A2, and this patient had normal-pressure hydrocephalus. The majority of PFS patient samples exhibited variable methylation of this gene ?(Melcangi et al., 2019)?.

Methylation of SRD5AR2

It is of interest that SRD5A2 was reported to be methylated in most CSF samples in a cohort of PFS patients. Interestingly, symptoms and severity per validated scales were found not to correlate to the observed methylation profiles ?(Melcangi et al., 2019)?. This is unlikely to represent a key factor in the pathological presentation when considering the symptomatic profile, novel factors of the condition and the lack of significant overlap between PFS and 5 alpha reductase insufficiency ?(Brinkmann et al., 2007; Imperato-McGinley et al., 1974)?.

5 alpha reductase type II is localised to many areas abundant in dopamine neurons and sites of projection, and finasteride has been considered for application in conditions associated with increased dopaminergic signaling including Parkinson's disease, Tourette's syndrome and schizophrenia ?(Castelli et al., 2013)?. Reduced D2 dopamine receptor binding in the nucleus accumbens has been reported in 5ar2 knockout mice. This was accompanied with behavioural deficits in aggressive, dominance, mating behaviours, along with reduced novelty seeking and risk taking. No anxiety-like, motoric or processing deficits were observed in these mice, and 5ar2 deficiency is not associated with sensorimotor deficit nor abnormalities in anxiety-like or reward-related behaviours ?(Mosher et al., 2018)?. Further, sexual desire is usually normal in human patients ?(Brinkmann et al., 2007)?. A role in neurosteroidgenesis could have some symptomatic relevance given their behavioural influences ?(Edinger & Frye, 2005; Ratner et al., 2019)?. However, hypotheses regarding the pathological alterations in PFS being localised to the nervous system do not plausibly account for the symptoms of patients, nor take appropriate account of reported evidence from investigations of peripheral tissues.

Evidence suggests that the methylation status of SRD5A2 is under regulatory influence of androgen

signaling. Both serum DHT and SRD5A2 mRNA in seminal vesicles have been demonstrated to significantly increase in inducible ARKO mice, demonstrating that SRD5A2 is regulated by the AR through local negative feedback ?(Wu et al., 2019)?. 5ar2 expression in the rat brain has been demonstrated to be under feed-forward regulation of androgens ?(Torres & Ortega, 2003)?. In the frog Silurana tropicalis, Bissegger and Langlois demonstrated that while SRD5A2 was not altered at the mRNA level, DNA methylation of SRD5A2 significantly increased in the testes and ovaries following treatment with DHT, suggesting androgen modulation of epigenetic mechanisms in both sexes. The methylation statuses of SRD5A1 and SRD5A3 were not changed following androgen exposure ?(Bissegger & Langlois, 2016)?.

One possible mechanistic influence of androgen signaling on methylation of SRD5A2 is the role of androgens in inflammatory regulation and a consequential influence on the methyltransferase enzyme DNA methyltransferase 1 (DNMT1). Kang et al. found a majority of BPH samples have methylation of the SRD5A2 promoter, with strong correlation between methylation and low or absent expression of 5alpha reductase 2 ?(Kang et al., 2018)?. Ge et al. reported that, in human prostate samples, DNMT1 regulates methylation of SRD5A2. The methylation of the promotor was shown to be increased by inflammatory mediators such as tumor necrosis factor ? (TNF-?), Nuclear factor-kappa B (NF-?B), and Interleukin-6 (IL-6) which upregulate DNMT1 expression. Inhibition of TNF-? restored the expression of SRD5A2 ?(Ge et al., 2015)?. In prostate cancer cells, androgen signaling crosstalk exists with inflammatory signaling (Malinen et al., 2017). As previously discussed, the AR has an upregulatory effect on TNF-? expression and is thus suppressive of cutaneous wound healing ?(Lai et al., 2009)?. DHT activates macrophage TNF-? secretion through AR signaling in prostatic urethral tissue ?(Zhao et al., 2017)?. In the CNS, epigenetic macrophage activation increases proinflammatory cytokines and chemokines, including TNF-? and IL-6 ?(Yin et al., 2017)?.

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Androgen mediated pleiotropy?

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/androgen-mediated-pleiotropy/

The case for diverse pathological effects arising from androgen-mediated pleiotropic mechanisms is increasingly clear beyond conditions already discussed such as PCOS and SBMA. The AR and its role in health is a fast-expanding research area of high priority ?(Takayama, 2017)?. The largest genome-wide association study to date in AGA research established a statistically significant positive association between AGA and other age and androgen related traits such as bone mineral density and early puberty, supporting a case for an androgen mediated pleiotropy underlying multiple conditions, as proposed by Yap et al ?(Yap et al., 2018)?. Considering the common androgenic pathogenesis of both AGA and BPH, Ramsamy et al. found that as the grade of AGA increased, there was an increase in the size of the prostate, with 66.7% of men evaluated experiencing severe AGA having an enlarged prostate ?(Subramaniyan et al., 2016)?. AGA patients are more prone to prostate enlargement and related symptoms ?(Monib et al., 2018)?.

Pleiotropic epigenetic factors can mediate a multi-system and clinically significant repression of AR expression. AIS type II is a type of Androgen Insensitivity Syndrome that presents clinically without mutation in the AR gene sequence ?(N. C. Hornig et al., 2016)?. Fewer than 40% of patients with diagnosed Partial AIS exhibit AR gene mutation, suggesting epigenetic involvement in androgen-insensitive phenotypes without sequence alterations. Hornig et al. recently provided a molecular diagnosis for the clinical presentation of AIS type II. Identifying significant reduction in AR mRNA levels in the genital fibroblasts of 57% of the cases, they additionally demonstrated methylation levels of two CpG sites in the proximal AR promoter region inversely correlated significantly to the expression of AR mRNA expression levels ?(Nadine C Hornig et al., 2018)?.

Noting the incomplete understanding of major chronic disease and the advancing understanding of the effects of androgens on major contributors to global mortality including immune function, cancer, cardiovascular disease and diabetes, Schooling considered the potential for androgens to be considered in a pleiotropic context to explain the higher vulnerability to disease mortality and earlier death observed in males than women. She suggests that "considering androgens as potential contributors to major diseases represents a major paradigm shift that flies in the face of individual level data from observational studies", and that a "rethink of the role of androgens, particularly, in immune function, cancer and cardiovascular disease, as potentially providing an underlying explanatory mechanism that could address the noted sex disparity in life expectancy, help identify new specific targets of intervention, explain unexpected side effects of commonly used drugs and eventually provide targets for precision medicine" ?(Schooling, 2015)?. In this context, PFS is likely to provide novel insights and considerable translational benefits to wider biological understanding and of mechanistic factors in better-recognised disease states.

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Current situation is dangerous

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/current-situation-is-dangerous/

An urgent clinical failure

> With [humility] comes not only reverence for truth, but also proper estimation of the difficulties encountered in our search for it. …[T]his grace of humility is a precious gift.
>
> *William Osler, Aequanimitas: with other addresses to medical students, nurses and practitioners of medicine, 1849-1919*

The stigma associated with sexual and mental dysfunctions, as well as a lack of medical support, are causing PFS to become a hidden epidemic. The scale and human cost of this failure cannot solely be attributed to pharmaceutical manufacturers. Rather, it is the result of a systemic clinical approach to ADRs that is not fit for purpose when considering a disease that manifests or progresses following withdrawal without a known biomarker. The staunch resistance patients continue to face in attempts to establish the very existence of the condition does not stem solely from the significant financial interest in antiandrogenic substances as first-line treatments in dermatology, but its ostensible implausibility given a remarkable reality and broad clinical endpoints. A perfect storm of novelty, rarity, and counter-intuitive clinical presentation compound clinical, pharmaceutical and regulatory failures to entrench a situation in which internet resources such as propeciahelp represent the only support for patients suffering profoundly following exposure to antiandrogenic endocrine disruptors. As symptoms vary between patients from moderate functional impairments to a life-threatening physiological and neuropsychological breakdown, this is an unsustainable situation that cannot continue.

Disturbingly, clinicians appear significantly more likely to report an ADR resulting from 5ari therapy in older men typically prescribed finasteride 5mg, despite the ADRs in this group being fewer and less frequently associated with lasting disability. Considering FAERS adverse event reports in the period April 2011 to October 2014, a significant majority of ADRs resulting from use of 1mg Finasteride by younger men were self-reported to the FDA despite a higher reported incidence of disability. Contrastingly, most side effects in older patients were reported by their doctors ?(Baas et al., 2018)?. With consideration to the alarming dissatisfaction amongst PFS patients with regards to clinical care reported by Ganzer et al. ?(Ganzer et al., 2014)?, this could indicate a widespread dismissal at the clinical level due to an erroneous assumption that patients' symptoms are not possible and/or psychosomatic in

nature. This would reflect the ubiquitous dissatisfaction of patients describing their experiences seeking help from primary care physicians and the ostensibly appropriate specialists in fields to which their symptomatology can generally be associated including urology and psychology. This deters patients with already stigmatising problems from professional engagement. This is extremely serious, as pharmacovigilant entities including the European Medicines Agency rely upon doctors to submit adverse event reports when reported by patients. Traish suggested that a misleading narrative that the condition does not exist has arisen from the current dearth of awareness and knowledge in the clinical community ?(Traish, 2018)? despite the body of literature suggesting epigenetic susceptibility in a subset of consumers ?(Traish, 2020)?. He notes that patients are frustrated by the perception in the medical community that such condition does not exist and that they are labelled to suffer from psychological disorder, rather than an organic disorder, attributed to the inhibition of a key biochemical pathway in steroid biosynthesis and metabolism. Traish suggests this, along with the lack of attention to improve care for afflicted patients, has "translated into loss of credibility and confidence by patients in their doctors and huge loss of faith in the medical community at large" ?(Traish, 2018)?.

As of 2020, the status quo in frontline care is presenting a perilous circumstance to both existing PFS patients and the wider public. Awareness of PFS as a clinical entity is unacceptably poor amongst the medical profession and education is urgently needed ?(Garreton et al., 2016; Traish, 2020)?. Failure to acknowledge the novelty and clinical scope of the pathology continues to delay progress towards etiological understanding. The fact that Vice media have demonstrated a deeper understanding of the post-withdrawal "crash" than medical literature is a matter of concern ?(Morgans, 2018)?. The consequence of this void in clinical understanding has not only led to a lack of basic science, but the potential for PFS patients to be prescribed therapies that can result in additional and permanent harm, including SSRI medications. It is deeply concerning that, instead of psychological support being offered as adjunctive care alongside appropriate recognition of what is a serious physiological disorder, doctors are frequently issuing rapid and inappropriate psychosomatic diagnosis for what is nearly always a striking and clear description of health problems never before experienced by the patient following taking and ceasing Finasteride. Healy et al. note that this is similarly the experience for patients suffering persistently after SSRI antidepressant use, commenting that even though patients report normal sexual function prior to use and neither depression nor anxiety can account for symptomatic presentations, "physicians appear to default to attributing problems a patient has after treatment to manifestations of an underlying nervous diathesis" ?(David Healy et al., 2018)?. This is unacceptable and unjustifiable given how deeply complex the issue is and how much there is yet to know regarding the physiological consequences of endocrine disruption with 5aris ?(Traish et al., 2015)?.

Psychosomatic misdiagnosis has, in extreme cases, caused patients to be deprived of their liberty through admission to psychiatric institutions. Patients have expressed feeling intense fear after being pressured into taking psychiatric drugs that have had a profound negative impact their condition. Routinely, additional stress, confusion and harm is caused to those suffering extreme symptoms by what is tantamount to "gaslighting" ?(Thomas, 2018)? by clinicians and psychologists. The combination of clinical arrogance and ignorance is egregious and difficult to excuse at this stage. Maksym concluded that the lasting consequences of antiandrogen therapy on the organism remain obscure, and can be highly

complex and multilateral, noting the extensive metabolism of steroid hormones in the central nervous system. They state that the presence of severe and persistent effects caused by the treatment of an aesthetic issue raises great concern for the clinician given the widespread use in young and healthy individuals, and that the low estimated prevalence of PFS cannot excuse nonvigilance ?(Maksym et al., 2019)?.

Those PFS patients who are most severely affected are those who are most vulnerable to these systemic failings. Many patients are very young, and young men left unable to function socially, work or continue their studies due to debilitating physiological and neurological symptoms can be left reliant on support from family and friends who cannot always understand or appreciate the etiology of their behavioural changes. Those around the patient will understandably defer to professional assessment, and simplistic misattribution is frequently the outcome. When physiological processes far beyond the patient's control are responsible, this psychosomatic misattribution by those in positions of medical authority unfamiliar with PFS or literature regarding the condition can often have devastating interpersonal consequences for patients already in an unimaginably desperate situation. The potential etiological overlap between the recognised persistent syndrome occurring rarely with serotonergic treatment and PFS is an emergent consideration in medical literature ?(David Healy et al., 2018; Giatti et al., 2018)?. Importantly, recent research has identified profound interruption of the androgen steroid pathway by SSRI antidepressants ?(Griffin & Mellon, 1999; Hansen et al., 2017; Jacobsen et al., 2015; Munkboel et al., 2018)?. In context of anecdotal reports from PFS patients of significant worsening following exposure to serotonergic drugs, an extremely cautious approach should therefore be taken when considering prescription of serotonergic medications to patients reporting enduring health problems not experienced prior to finasteride use.

Recognising a consistent and concerning failure in the clinical care of our patients, we issued Post-Finasteride patients the Short Assessment of Patient Satisfaction, a robust measure of patient satisfaction with their experience in clinical practice ?(Hawthorne et al., 2014)? as part of a wider survey. Patients were asked to complete the assessment once if they had seen only one professional with regards to PFS. If they had seen more than one clinical professional about PFS, we asked them to complete the questionnaire twice: Once considering their most positive experience with regards to an appointment, and once considering their most negative experience. After 170 submissions, the results were remarkable and alarming. The average score regarding even the most positive experiences PFS patients have had with a clinical appointment is on the verge between dissatisfaction and serious dissatisfaction, denoting that “severe and urgent failings” are the norm for PFS patients seeking healthcare support, and that the very best they can hope for is a dissatisfactory clinical outcome (Propeciahelp Post Drug Syndrome Survey: Data not provided). We will seek to publish this data in the future.

Disappointingly, PFS represents a neglected opportunity to broaden scientific understanding of biological mechanisms critical to human health and will undoubtedly bridge identified knowledge gaps in the understanding of endocrine disruption ?(Solecki et al., 2016)?. As well as a virtue, professional humility is important to being a good doctor ?(Chou et al., 2014; DuBois et al., 2013; Mahant et al., 2012; Wear,

2008)?, and the vast anecdotal experience of our patients attests to a widespread shortcoming in this regard. That physicians commonly deem what has happened to those suffering PFS as implausible or impossible is telling as to the biological significance of this disease. In his commentary stressing the importance of humility in medical professionals and scientists to avoid future harms, Ritterman notes that the "problem of mistaken ideas persisting despite scientific evidence to the contrary has been present since the onset of the scientific method…This problem is of particular concern in medical science, where outmoded ideas translate into excess morbidity and mortality" ?(Ritterman, 2017)?. What differentiates our remarkable situation from examples of historic medical ignorance such as this is that, in 2020, there exists compelling objective evidence which can be contextualised, as we have attempted to the best of our ability, in a broader framework of biological understanding. It is now abundantly clear that the androgen pathway has critical roles across the entire organism, and that understanding of the implications of this on health has expanded rapidly. With so much yet to be elucidated, and such profound effects described by a subpopulation of consumers for years, the arrogance faced by our patients when reporting their drug-induced symptoms is impossible to justify. "If the toxin is professional arrogance," Ritterman wrote, "the antidote is professional humility".

In the absence of the acknowledgement of the true scope of the condition, informed consent to the risk of PFS is never obtained from AGA patients commencing Finasteride therapy. Demand for - and marketing of - antiandrogenic hair loss remedies such as Finasteride is expanding, and an inevitable consequence will be more cases of PFS. As of 2020, emergent subscription services are engaging in social media advertising campaigns with modern production values. Hims present a video of young woman in a lab coat visibly laughing while saying that "anything (sic) can write anything on google". Another woman, also wearing a lab coat, assures consumers that "fewer than 1% of men actually experience side effects, but don't be scared; this happens to very few men, and we're here to help you if it does" ?(Hims, 2018)?. What that help consists of is difficult to infer, considering we nor professors engaged with the issue in the fields of neuroendocrinology, urology, andrology, steroid biology and psychology seeking an explanation as to this breakdown of expected function in the androgen pathway are aware of any effective and safe treatment. Manual are an internet-based prescription company who at time of writing advertise on social networks including the image sharing service Snapchat. They state on a web page intending to answer frequent questions about Finasteride that "Animal studies did not show negative effects on fertility." ?(Manual, 2019)?. As we have previously discussed, animal studies have entailed a deficiency in fertility parameters that is transgenerational ?(Garcia et al., 2012; Kolasa-Wo?osiuk et al., 2019)?. We are already receiving new PFS patients citing having taken finasteride after receiving the marketing of the companies mentioned. Considering increasing primary objective evidence in study of PFS patients, the multitude of deleterious molecular level effects in animal research and the numerous reviews stating that this is a rare and distinct clinical entity, those promoting Finasteride as a safe product for young men without warning of PFS can easily be likened to the tobacco executives of the 1980s. As public appreciation grew of the dangers associated with smoking, advertisement campaigns designed to obfuscate reality, including a smoker depicted to be saying "Please don't tell me my cigarette smoke is harmful to you. There's just no convincing proof that it is" (*?United States v. Philip Morris USA Inc.?*, 2006).

Certain dermatologists remain opposed to acknowledgement of what is physiologically happening to a

subset of consumers after taking finasteride. In a report of a single AGA patient without a depressive history who presented with sexual dysfunction following Finasteride withdrawal, Trüeb et al. presented a hypotheses that PFS is a "delusional disorder" ?(Trüeb et al., 2019)?. Trüeb suggests that the airing of a documentary on Swiss television may have had a psychosomatic influence on this patient and hypothesise the condition to be one of a "mass hysteria". The authors define mass hysteria as many people believing "obviously false and potentially distressing things based purely on hearsay". By their own definition, this does not apply to PFS considering basic science and animal research, as well as the outcomes of several case-controlled studies of PFS patients, which are not addressed. ADR data additionally refutes this suggestion: Ali et al. had previously considered the potential for bias due to stimulated reporting of persistent sexual dysfunction. Analysing FAERS adverse event data, Ali et al. acknowledged an increase in ADRs, but noted that significant signals with a 95% confidence interval lower limit of 2.0 or greater exists before and after 2011, irrespective of the public's knowledge of sexual dysfunction as a safety concern associated with finasteride. Ali et al. considered underreporting likely and the actual incidences of persistent sexual dysfunction to be potentially underestimated ?(Ali et al., 2015)?. Based upon their hypothesis and without any reported success in remediating the symptoms of their single patient, Trüeb et al. encourage the prescription of psychiatric medicines for an "underlying psychopathological disorder". First line treatments for depression ordinarily fail and have commonly worsened PFS patients as we have discussed. SSRIs are frequently antiandrogenic ?(Hansen et al., 2017; Jacobsen et al., 2015; Munkboel et al., 2018)? and are associated with a remarkably similar persistent cognitive, physiological and sexual dysfunction with the potential to represent a single syndrome ?(David Healy et al., 2018)?. As such, this baseless and irresponsible recommendation is not without the potential to result in harm to profoundly vulnerable patients should it influence clinical practitioners. It is interesting, however, that even in a commentary seeking to cast doubt on the existence of PFS as an organic condition, there is some awareness of a key novelty of the syndrome common to self-reports: The subsequential nature of onset or intensification frequently featured in patient reports ?(Trüeb et al., 2019)?. The author declares no conflict of interest despite stating that his private hair clinic continues to prescribe the drug after two decades of doing so.

Patient driven platforms cannot compensate for clinical disregard

While propeciahelp continues to provide as much support to patients as is feasible, this is a serious medical problem and patient-operated support platforms cannot possibly compensate for the entrenched failures in clinical practice that both patients and medical literature continue to highlight. Maksym et al. recognise the variable reporting in different healthcare settings is making the problem hard to evaluate ?(Maksym et al., 2019)?. Patients who have suddenly stopped visiting the propeciahelp forum are impossible to account for due to anonymity. Failure to achieve diagnosis of this syndrome and improper clinical inquiry means valuable medical records and investigation are usually non-existent or cannot be pursued in context. This is especially serious in the cases of those experiencing extremely severe and degenerative health problems, who can disappear suddenly and untraceably after expressing suicidality due to the extent of their symptoms. Clinical appreciation of PFS must be improved to provide patients accurate diagnosis and ensure the proper contextual documenting of patients with appropriate follow-up.

As severely affected patients are regularly left unable to work due to resultant disabilities, the lack of professional recognition is hampering their ability to receive much-needed financial support from welfare systems. Post-mortem study will likely be extremely beneficial to a mechanistic understanding of the induced epigenetic changes in PFS, and this is dependent on appropriate diagnosis and clinical profiling.

Clinical disregard and a dire need for hope compounds the potential for the exploitation of a vulnerable and often desperate cohort by individuals or businesses offering simplistic explanations and suggesting treatments. The risk of additional harms resulting from self-medication in attempts to relieve debilitating symptoms is significant, particularly amongst the worst affected. The inability of specialist doctors to provide answers or symptomatic relief drives some patients to embark upon self-experimentation. Patients will commonly express belief that supradietary doses of concentrated "natural" extracts, vitamins or minerals have a preferential safety profile as compared with that of pharmaceutical drugs in the attempted alleviation of PFS symptoms. In patients that can exhibit a novel fragility to any further disruption of the androgen pathway, therapeutic attempts with both clinically prescribed pharmaceuticals and self-sought nutraceuticals have led to permanent worsening and directly preceded completed suicide. It is urgent and imperative that clinicians presented with PFS patients inform the patient of a physiological vulnerability to substances with endocrine disruptive properties. This is particularly important for severely affected cases of PFS who present following a short exposure to Finasteride or other causative antiandrogenic substance.

A desperate need for improvement often results in a significant selection bias on the part of patients when considering other patient reports. This can often involve a rejection of the complex situation in favour of alternative health or pseudoscientific concepts. Strong views and poorly defined etiological conclusions can be rapidly formed. Significant heterogeneity in clinical endpoints results in many patients having a poor appreciation of the situation for other patients, or as indicative of a vast array of etiologically distinct disease states. A well-known parable describes a group of blind men touching an elephant. Grasping the tusk, one believes it to be a spear. Another touching its leg is sure it is a tree. A third man near the trunk asserts it is a snake, while the man touching its ear believes it to be a fan, and the tale concludes with vehement arguments based on a selective perception ?(Snyder & Ford, 1987)?. This analogy is appropriate and can be well observed. Mild to moderately affected patients can find reading the experiences and clinical condition of severely affected patients to be psychologically difficult, potentially owing to uncertainty surrounding their own prognoses. This contributes to an incohesive community and increases the difficulty of representing the true scale of the issue.

Propeciahelp’s volunteer staff, who are suffering ourselves, are placed in a deeply difficult situation in which we must constantly advise patients to be wary of theoretical proclamations and treatment suggestions online, while being aware that clinicians cannot currently provide practical help and often present an equal risk to PFS patients. It is our opinion that there will be serious questions to be answered in the future as to why such obstacles were faced in the clinical acknowledgement of a disease as deeply serious and biologically significant as Post-Finasteride Syndrome.

Regulatory activity is overdue

Reappraisal of the use cases for these substances is necessitated at the regulatory level, ensuring adequate warning and mandating informed consent as to the potential of developing this condition. PFS has no known predictive factors, unpredictable severity between patients, a complete absence of dose-dependence, and no available therapeutic options for any of the affected symptomatic domains. PFS does not conform to the presentation of known disease state and consumers are not placed to imagine the potential implications on their physiology, minds, and lives; an impact which cannot be overstated and is not currently widely appreciated at the clinical level. PFS patients almost invariably express shock and disbelief at what is happening to them. In this regard we support the conclusion of Motofei et al. insofar as the patient must be informed and consent to the full potential health risk. Motofei notes that this is especially important in aesthetic treatment, as therapy of AGA with dutasteride places treatment of an aesthetic condition on the same level as a life-threatening disease ?(Motofei et al., 2019)?. In the rare instance a consumer were so psychologically distraught by hair loss they would countenance the risk of irreparable physical damage and the permanent loss of sexual, neurological and physiological function, there is simply no excuse for the current situation in which consumers are not informed that this disease even exists as novel clinical entity with all it entails *per se*. Measures to address this must begin now. In particular, the dermatology profession should at a minimum address failure in assessing patient’s pre-treatment conditions, pursue a fully informed consent, and begin effective reporting of adverse events according to national and supranational guidelines. As we are discussing frontline drugs of the dermatology profession that represent a significant worldwide revenue, at this late stage we pragmatically recognise that regulatory action will have to precede any widespread self-initiated clinical responsibility. A simple truth can be represented by the words of Upton Sinclair: "It is difficult to get a man to understand something, when his salary depends upon his not understanding it" ?(Sinclair, 1994)?.

A good therapy should have tissue selectivity to the pathogenesis and not broadly interfere with other important processes in humans ?(Zheng et al., 2006)?. Finasteride interferes with fundamental and ubiquitous physiological processes ?(Traish, 2020)?, with PFS manifesting in some consumers as a disastrous and permanent result of this. Many scientific insights into the critical role of androgens across the body and brain were not appreciated at the time of its approval. While there is now significant post-marketing evidence and animal research illustrating the systemic influence and thus potential danger of finasteride, the evidentiary basis for its continued presentation as safe product is not robust ?(Belknap et al., 2015)?. Adverse reaction warnings in the product leaflet of Finasteride remain direly inadequate and do not include PFS as a distinct entity, do not mention the post-withdrawal development seen in the majority of PFS cases, nor most of the multi-systemic symptoms PFS entails. These are well recognised in publications centring on patient reports, as we have discussed, and it is noted that despite this evidence the leaflet continues to make little mention of the broad symptom profile ?(Walf et al., 2018)?. It is therefore unacceptable that consumers are still presented with a wolf in sheep's clothing. PFS is not imaginable by those thankfully able to take what it can strip away for granted: The emotional, physical

and intellectual joys of human experience, and, often, even the ability earn a subsistence income. Patisaul and Belcher suggest that, when considering risk from EDCs, the human brain performs a risk assessment as it would in anything else: "Using an imperfect calculus incorporating intuition, experience, a mix of facts (and more often fiction) combined with something like raw gut instinct", generally favouring short term benefit over the possibility of long term harm ?(Patisaul & Belcher, 2017)?. This "common sense" risk calculus is not adequate in the absence of accurate information, as it is novel amongst adverse drug reactions and astonishingly counter-intuitive. It is wholly unreasonable to presume consumers are placed to consider such an outcome as even the remotest possibility, particularly in absence of their doctors nor the product labelling making it abundantly clear that men are experiencing horrendous and progressive changes to the physiological structure and function of their bodies and minds as a result of taking as little as one tablet.

It cannot be emphasised strongly enough that we are primarily discussing finasteride prescribed as a cosmetic product. It is our strong contention that members of the public will rightly consider such an indication to be held to a considerably higher bar of safety than drugs for serious medical conditions, yet the de facto reality speaks to the opposite. Review after review now acknowledges evidential support for the existence of PFS and therefore the need for adequate consent to the potential risk to health and quality of life upon prescription of finasteride ?(Irwig, 2015; Maksym et al., 2019; Motofei et al., 2019; Said & Mehta, 2018; Than et al., 2018; Traish, 2020)?. In the absence of accurate clinical communication of the full risk to the patient, informed consent can never currently be obtained. Multidisciplinary scientific conclusion is not reflected in pharmacovigilant activity. The status quo begs the question: What precisely will it take to achieve the most basic of protections for the public? Discussing regulatory action in regards to endocrine disruptors for the protection of human health in their 2012 guidance to decision makers, the WHO describe that the 1973 United States ban on tetraethyl lead in gasoline followed "decades of inaction" during which children were continually exposed to a serious health risk. They suggest that "perhaps the answer is in making more use of the precautionary principle to ban or restrict chemicals in order to reduce exposure early, even when there are significant but incomplete data and before there is significant and long-lasting harm" ?(Bergman et al., 2012)?. Significant data exists with which conclude Finasteride is inestimably dangerous in a subpopulation, causes permanent harm, and that this is not positively correlated to duration of use. This justifies its withdrawal from sale as a cosmetic. Rosario and Bourke, discussing underappreciated cardiovascular risk associated with modern antiandrogen treatments in prostate cancer, suggest that in an era of media soundbytes and "wonder drugs" that men will insist on, the scientific community must respond and remain circumspect, with regulatory bodies, trial oversight committees, reviewers and editors having a duty of care "to ensure the correct health warnings go out alongside the positive messages" ?(Rosario & Bourke, 2020)?. If this is deemed the necessary response in the treatment of life threatening cancer, it is unfathomable that this vigilance should not be all the more appropriate to the prescription of antiandrogens to young healthy men for conditions like AGA and acne - conditions which are very mild in terms of androgen-mediated pathologies ?(Heemers & Tindall, 2007)?. Wolfgang Becker-Brüser, editor in chief of the German medical journal Arznei-Telegramm, recently stated that the “very serious side effects caused by finasteride [are] absolutely unacceptable for a lifestyle drug. Rationally, one cannot advocate for this medicine or justify the fact that it’s still on the market. Actually, it should be banned” ?(Südwestrundfunk, 2019)?.

Some authors continue to call for repeated placebo-controlled trials to determine the existence of persistent effects from finasteride, considering little else to be of sufficient evidential quality ?(Basaria et al., 2016; Diviccaro et al., 2020; Gray & Semla, 2019)?. Further study of this kind will not be enlightening nor practically useful to the scientific community, the PFS patient or consumer in the medium term, if ever. It is urgently necessary to acknowledge both the novel nature of the condition and the rarity of the syndrome ?(Traish, 2018)? for a pragmatic approach. Considering the medical history of 6 PFS patients who committed suicide, Irwig noted that a prospective study that may determine causality would likely require at least 10,000 participants in each arm and a duration of at least 5 years, making it practically and financially unfeasible ?(Irwig, 2020)?. It is very possible that even in such a trial, occurrence of PFS would not reach signal. Rarity, however, cannot and should not be construed to justify dismissal of the gravity of this condition ?(Maksym et al., 2019)?. This is particularly relevant with consideration to the unpredictability and dose-independence of PFS, and its atypical progression following withdrawal. Dismissal of retrospective studies is often attempted owing to a perceived lack of credibility in normal instances of ADR. This disease is not a normal ADR, to the point that existing drug reaction algorithms are unable to accommodate it ?(David Healy et al., 2018)?. As well as statistical rarity, objective differences at the molecular level in control study of patients are increasingly established in PFS. A pragmatic approach to any progress must take the reality of this issue into account, not defer to an arbitrary standard of perceived evidential quality appropriate to a more ordinary adverse drug reaction while patients continue to be driven to suicide by profound and unresolvable suffering. Insistence on the application of a formula that is not fit for purpose in this circumstance manifests as a dereliction of duty. This will be at the expense of lives that could be saved by the most basic of warnings. It is astonishing to consider that mechanistic elucidation may now plausibly precede acknowledgement of a syndrome that has been clinically reported by patients for two decades. Patients cannot continue to shoulder this global problem in lieu of clinicians.

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Research going forward

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/research-going-forward/

The clinical picture and molecular level understanding of PFS are not where they should be after decades of clear reports of profound suffering and suicides caused by exposure to a cosmetic product. Understanding of a disease, its basic molecular mechanisms, accurate experimental models with predictive value of the disease, and access to technologies for target validation are important for progress towards a therapy ?(Gashaw et al., 2011)? and we urge immediate steps to these ends. Finasteride is a potent endocrine disruptor that targets diverse tissues across the organism. The severity of the symptoms must be considered in parallel with scientific observations on the long-term physiological changes and post-withdrawal effects induced by finasteride and the vast array of physiological processes reliant on the appropriate function of the androgen pathway. Further study of PFS using a precision medicine approach is necessary ?(Cauci et al., 2017; Coskuner et al., 2019; La Marra, 2010; Traish, 2018)?. As patients and as patient advocates, we desperately need further molecular level investigation to be undertaken by functional geneticists, epigeneticists, scientists and epidemiologists engaged with both the emerging understanding of androgen signaling and appreciative of the full clinical and pathological picture of PFS. Although there is an increase in reported adverse events ?(Ali et al., 2015)? associated with use of Finasteride 1mg, the numbers of PFS patients are not clearly indicative of the problem when balanced against the millions using this drug. However, considering the multisystemic nature of the persistent health changes and the current void in clinical appreciation and scientific knowledge pertaining to this condition, it is extremely likely the number of young patients experiencing insidious health problems without attribution to a causative antiandrogen to be significant. We strongly advocate for a networked approach with a focus on epigenetic assay as a necessity to move towards mechanistic understanding and ultimately disease modifying treatment. Such an approach has been urged in SBMA and significant steps towards organisation are being achieved ?(Greensmith et al., 2019; Rinaldi et al., 2015)?. The advent of adaptive genome and epigenome editing technologies make a treatment feasible following the determination of key mechanistic factors at the molecular level. The suggestion of reversibility of gene dysregulation as a consequence of AR-mediated toxicity in models of other disease states, as discussed, is suggestive of eventual therapeutic possibility.

We recommend far more thorough clinical considerations of PFS patients, particularly severe phenotypes, to be conducted in line with the clinical findings known in androgen-mediated toxicity and the previously reported findings in PFS patients. Primary research must be directed towards the underlying biological differences in the patient cohort. Patients differ greatly in symptomatically affected physiological sites and symptomatic severity, so patient selection based on symptomatic presentation is important in the design of clinical research. We strongly urge that prior 5alpha reductase inhibitor, retinoid or serotonergic drug prescription and use be ascertained in completed incidences of young male suicides in North America and European nations. Currently, completed suicides that the patient themselves or their surviving families explicitly attribute to the physical, sexual and neuropsychological damage induced by

Finasteride are not appropriately attributed to the drug, as suicide is often occurring months or years after cessation when the drug is no longer in their body.

There are many avenues by which to pursue immediate clinical evaluation of PFS patients beyond appropriate basic endocrinological and urological evaluation, and these should account for the specific symptoms of individual patients. Serum creatine-kinase levels may be worthy of assessment during the post-withdrawal crash period or subsequent periods of muscle wasting, as some patients have reported elevated findings. Histological study of affected muscles, including the markedly AR-sensitive perineal muscles, would allow consideration of signs of atrophy and myogenic defects. Area calculation of the bulbocavernosus via ultrasonography has been suggested as a measure of decreased end-organ activity of androgens ?(Gupta et al., 2017)?, and this could potentially be a low-cost and non-invasive investigation in PFS patients who have experienced atrophic changes. Electromyography to assess abnormalities including signs of perineal muscle denervation may also be worthwhile. MRI protocols including localizer scans, T1-weighted imaging and 2-point Dixon sequences have proven a useful measure of muscle appearance and diffuse involvement in SBMA and could be useful in the phenotype profiling of PFS in patients with broad muscle atrophy. Dual-energy X-ray absorptiometry of bone including lumbar/thoracic spine, femur and sites of complaint, along with serum C-telopeptide testing to assess bone mineral density and trabecular bone health may be worthwhile in patients with bone-related symptomatology and who report structural alteration. Lipid profiling of patient cohorts would additionally provide insight into metabolic dysregulation.

Above all, a far greater focus on molecular level research and basic science is an overdue necessity. Due to low patient numbers, genome wide association study is unlikely to be a practical option, and full genome sequencing of existing PFS patients should be pursued to explore the potential of predisposing factors at the genomic level. Discovery of such genetic differences could eventually be used to screen for risk in young consumers considering use of antiandrogenic products or supplements. Proteomic study may yield insight into the mechanisms of toxicity. Assaying of gene expression data, study of chromatin structure and associated proteins, and methylome analysis of pathologically relevant tissues will advance understanding of deregulated genes as driving factors in this new and novel disease that develops following endocrine disruption. PFS patients are usually in good health prior to use of the associated antiandrogenic substance and can extraordinarily rapidly develop secondary disease states, many of which are associated with advanced age. Advancing the understanding of PFS is therefore likely to yield important mechanistic insights into a diverse array of pathologies. Comparative epigenetic profiling of patients suffering from the disease states following Accutane and SSRI antidepressant use could provide grounds for the wider consideration of the hypothesis regarding a common post-androgen deprivation syndrome and thus a ground-breaking discovery.

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Conclusion

by phadmin - Monday, March 30, 2020

https://www.propeciahelp.com/post-androgen-deprivation-syndrome-conclusion/

Post-Finasteride Syndrome represents a Post-Androgen Deprivation Syndrome following exposure to antiandrogenic endocrine disruptors and without specificity to finasteride. The common pharmacological interruption of steroid signaling and remarkably similar clinical endpoints may imply that a single mechanistic disease state occurs in predisposed consumers following the use of medications including dutasteride, isotretinoin and serotonergic antidepressants. The lasting and profound changes to physiological and neurological health are alarming and the permanence suggests that, in predisposed individuals, epigenetic reorganisation is possible in somatic cells and postmitotic neurons following significant interruption of androgen signaling. The past decade has seen broad appreciation that either excessive or insufficient androgen signaling can prove deleterious to cellular homeostasis and biologic function ?(Gibson et al., 2018)?. These mechanistic underpinnings trace back to the influential work of Charles Huggins in the mid-20th century ?(Huggins, 1965)?.

We hypothesise a clinically significant AR deregulation is an aberrant manifestation of a conserved mechanism of cellular adaptation to lowered levels of availability or potency of androgenic ligand or interruption of appropriate transactivation of androgen regulated genes. Potential mechanistic factors can be contextualised by the rapidly expanding understanding of the ability of the androgen receptor to affect the basic epigenetic machinery and the structure of chromatin in addition to its essential regulatory functions. Understanding the pathology may provide extremely valuable insight regarding an increasingly apparent androgen-mediated pleiotropy of relevance to a broad spectrum of disease states often associated with the ageing process. Scientific elucidation of predisposing genetic factors will aid in establishing urgent protections for the public. Regulatory level action is necessary and overdue. We ask the medical community to begin efforts towards education regarding this novel condition and to shoulder the clinical responsibility of accurate diagnosis and appropriate follow up of PFS patients.

This document was authored by axolotl and awor, the administrators of propeciahelp.com. We are extremely grateful for your time and consideration. If you are a specialised scientist working in next-generation sequencing, genomics, epigenetics or androgen receptor signaling and are interested in researching this devastating disease, please email us at: contact@propeciahelp.com.

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