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Invited commentary

A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients

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ABSTRACT

Fibromyalgia is a diffuse chronic pain condition that occurs predominantly in women and may be under-reported in men. Symptoms include a loss of feeling of well-being and generalized widespread flu-like muscle aches and pain that fail to resolve due to central sensitization of nociceptive neurons. It has commonalities with a myriad of other chronic pain conditions which include PTSD, "Gulf War Syndrome", and various stress-induced conditions caused, for example, by viral infection, emotional or physical stress, trauma, combat, accident or surgery. It is not understood why some individuals are susceptible to this condition and others are not. White et al., elsewhere in this issue, present a clinical feasibility study designed to test the hypothesis that 1) low or deficient testosterone serum levels are linked to a high risk for an inflamed nociceptive nervous system and resultant chronic pain states, and 2) a testosterone transdermal gel applied once a day by fibromyalgia patients can be an effective therapeutic against chronic pain. Here, a short profile of fibromyalgia is provided along with a brief summary of best practices currently recommended by clinical specialists. The link between testosterone and pain is then discussed, with an overview of scientific studies that lay the foundation for testosterone as a possible important additional therapeutic that has the potential to be safely administered and effective but also avoid the adverse effects of other therapeutics. Finally, novel mechanisms by which testosterone therapy is likely to down-modulate pain signaling are proposed.

Contents

Abbreviations: BBB, blood brain barrier; CNS, central nervous system; ENK, enkephalin; GABA, gamma-aminobutyric acid; HPA axis, hypothalamus, pituitary, adrenal endocrine axis; HPO axis, hypothalamus, pituitary, ovary endocrine axis; NSAID, nonsteroidal anti-inflammatory drug; OPIAD, opioid-induced androgen deficiency; PAG, periaqueductal gray neurons; RVM, rostral ventromedial medulla; SHBG, sex hormone binding globulin; SNRI, serotonin–norepinephrine reuptake inhibitor; SP, Substance P; SSRI, selective serotonin reuptake inhibitors.

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1. Commentary

1.1. Fibromyalgia is a disorder defined by "central sensitization".

Fibromyalgia is a diffuse non-focal chronic pain condition that occurs in 2–4% of the population, while the incidence among women aged 50–80 is even higher at 6–7% [1]. Fibromyalgia is thought to be stressor-induced, for example by a viral infection, physical or emotional stress, a traumatic accident, combat or surgery. Parallel phenomena are the chronic pain and fatigue found in syndromes such as Post Traumatic Stress Disorder (PTSD), "Gulf War Syndrome" and "Shell Shock". In this context, an allostatic load (stress) leads to a state of "distress" vs the healthy response of "eustress" [2,3]. A "wind-up" phenomenon in which repetitive activation of nociceptive nerves or C-fibers leads to augmented responses with additional input of nociceptive signals, associated early on with allodynia and hyperalgesia in fibromyalgia syndrome, results in neuronal plasticity and an altered pathologic state [4–6].

Specialists link this condition to a dysfunctional state of the nociceptive nervous system known as "central sensitization" and some investigators now use that term to describe fibromyalgia [7]. Normally, the nociceptive nervous system relays painful stimuli via peripheral sensory nerves to the CNS, and in time that pain is ultimately resolved by the down-modulation of both ascending and descending nociceptive signaling circuitry, allowing return to a healthy pain-free resting state. Some patients, however, fail to return to a pain-free state, even after the precipitating insult or stressor appears to have been resolved, causing clinicians to puzzle over why some patients get better and others don't. One possible explanation that is explored here, and tested in a companion paper in this issue, is a deficiency of testosterone in some individuals and not others.

The hallmarks of most peripheral inflammatory pain conditions are high WBC counts or local swelling, redness and soreness. In contrast, fibromyalgia patients have normal WBC counts, a normal erythrocyte sedimentation rate (which is usually elevated for inflammatory pain states in the clinic) and a lack of localized swelling or inflamed joints. Important early findings included the high levels of Substance P found in the cerebrospinal fluid of fibromyalgia patients [8,9], and the use of fMRI to evaluate altered patterns of cerebral activation and abnormally low pain thresholds when applying painful pressure to fibromyalgia patients compared with controls [10]. Substance P is of interest since it can amplify wind-up phenomena in chronic pain states and it has a pro-inflammatory effect on neutrophils, macrophages and lymphocytes [11]. Pathological features of chronic pain states within the nervous system include activated microglia within the spinal cord and activated sensory neuron-affiliated macrophages, as exemplified by cancer patients with chemotherapy-induced peripheral neuropathy [12]. Fibromyalgia is therefore best described as an inflamed nociceptive nervous system, distinctly different from various inflammatory states with high WBC counts in peripheral tissues.

1.2. Treatment guidelines for fibromyalgia patients

Current treatment guidelines for patients with fibromyalgia include patient education, exercise, cognitive behavioral therapy, CNS neurostimulatory therapies and pharmacologic therapies, which include NSAIDS, serotonin norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), tricyclic compounds, gabapentinoids, and the opioid antagonist naltrexone [7,13]. It is generally recognized, however, that these therapeutics can have suboptimal efficacy and/or adverse effects. NSAIDS are problematic when used for chronic conditions due to a significant risk for GI tract irritation; the side effects for anti-depressants such as SSRIs can be numerous and include risk of sexual dysfunction; and the gabapentinoids, including Pregabalin, have common side effects such as drowsiness, dizziness, fatigue, changes in libido and, for men, erectile dysfunction.

Opioids are sometimes prescribed but are now considered to be less effective for treating chronic pain than previously thought and their risk–benefit profile is poor due to serious adverse effects such as addiction, tolerance and opioid-induced hyperalgesia [7,14]. Opioids are also known to induce androgen deficiency (opioid-induced androgen deficiency, OPIAD) causing loss of libido and sexuality. Testosterone therapy in the presence of opioids has been used for treating the testosterone deficiency component in these patients, in combination with more aggressive opioid treatment for treating the pain component [15–18]. Testosterone therapy in the absence of exogenous opioids, however, has not been used for treating chronic pain in humans.

For the preliminary study described by White et al., elsewhere in this issue, the hypothesis was tested that testosterone therapy could be used to treat the chronic pain and fatigue of fibromyalgia patients without the well known side effects of currently prescribed pharmacologic agents. The rationale for using testosterone therapy resides in the combination of knowledge from diverse fields including reproductive endocrinology related to the gonadal steroid hormones, nociception, neuroendocrinology and reproductive immunology.

1.3. Preclinical and human studies causally link testosterone and pain

1.3.1. Gonadal steroid hormones and sexual dimorphisms

The function of androgens and their receptors, along with the knowledge that androgen receptors have been found and mapped out in the rodent brain, is associated with sexual differentiation during fetal development and reproductive behavior [19,20]. The relationship between testosterone and pain threshold has been investigated in animals [21–24], but the prevailing view has been that sex steroid hormones are involved early in the life of an animal to organize pain circuitry differentially by gender, resulting in the sexual dimorphisms observed for pain processing in adult males vs females [25]. No one has previously extended this concept further to consider whether exogenous sex steroid hormones, and testosterone in particular, can be used therapeutically to dampen pain in adult humans with low serum levels of testosterone and an inflamed nociceptive nervous system, even though serum free testosterone concentrations have been shown to be significantly decreased in premenopausal fibromyalgia patients relative to healthy volunteers [26].

1.3.2. Initial evidence of a role for testosterone in nociception

The discovery of aromatase-positive cells in the dorsal horn of the quail spinal cord [27] points to a role for testosterone in the regulation of pain threshold in adults. It is the dorsal horn where initial processing of pain sensation occurs (sensory neurons from the periphery synapse with CNS nociceptive relay neurons) and where transmission of nociceptive information to the thalamus and cerebral cortex via the anterolateral spinothalamic tract originates. Consistent with this, aromatase knockout (ArKO) mice unable to convert testosterone to 17β-estradiol have been shown to display increased nociceptive behaviors (decreased pain thresholds) upon challenge [28]. Thus, any testosterone/aromatase-dependent estrogen-mediated transcription of opiates, which has been shown to occur in the spinal and medullary dorsal horn [29–32], will not take place.

1.3.3. The inverse relationship between gonadal steroid hormones and inflammation

The concept that there is an inverse correlation between gonadal steroid hormones (estrogens, progestins and androgens) and inflammation, however, is well documented but underappreciated. First, at puberty, gonadal steroid hormone serum levels surge when the thymus correspondingly undergoes "involution", in which there is decreased thymic cellularity, decreased thymic cell development, and decreased thymic cell output to the periphery. Second, during pregnancy, an acute surge in gonadal steroid hormone serum levels results in further thymic involution, greatly decreased numbers of peripheral thymocytes

which might recognize the embryo as foreign and reject it, and consequently increased susceptibility to infection (rubella or rubeola viruses for example) which is well recognized in the clinic to be harmful to the fetus or abortogenic. Third, gonadectomy in animal models results in a reversal of thymic involution, restoration of thymic cellularity and thymic output and an increased T cell repertoire [33]. Finally, rescue of gonadectomy with exogenous hormones, reverses these events [34].

1.3.4. The inverse relationship between testosterone and hyperalgesia

Gonadectomy of male and female rats has been shown to result in increased pain responses (lower thresholds) to the formalin test, concomitant with decreased testosterone plasma levels; conversely, treatment of gonadectomized animals with testosterone resulted in decreased pain responses concomitant with increased testosterone plasma levels [22,23,35]. So, although testosterone and the sex steroid hormones in general have organizational effects on the CNS early in life [36], substantial evidence is consistent with the concept that testosterone can also modulate pain therapeutically in adult rodents, both male and female.

Animal studies have also shown that the state of pregnancy correlates with significantly increased pain thresholds mediated by endogenous opioid hormone production [37], at a time when testosterone levels are normally unusually high [38]. Data supporting a role for androgens and estrogens in up-regulating opiate production in the spinal dorsal horn nociceptive relay cells [21,27] provide one mechanistic basis for testosterone involvement in pain perception (Fig. 1, discussed in more detail below). Other sites within the nociceptive system appear to be important as well: androgen and estrogen receptors have also been localized to midbrain PAG neurons projecting to the medullary RVM in male and female rats [39–41], as well as male primates [42]; and the male rat locus coeruleus, an important site in the pons for brain synthesis of noradrenaline and involved in descending pain inhibition pathways, has also been found to be androgen receptor positive [39]. Neonatal castration of male rat pups was found to result in reduced analgesia in adults when morphine was injected into the PAG, and neonatal androgenization of female rat pups treated with testosterone propionate resulted in enhanced PAG morphine analgesia as adults [43,44].

1.3.5. Human brain imaging studies support a causal link between testosterone and pain

Consistent with the pre-clinical data above, brain imaging data support a role for androgens within the RVM in the brainstem of women [45]: In a group of contraceptive pill users with significantly reduced serum testosterone levels, fMRI activity in the RVM was significantly reduced and an overall altered central response to noxious stimulation was observed concomitant with decreased pain threshold upon heat stimulus challenge, whereas no correlation was found with reduced serum estrogen levels. Other retrospective studies have shown the incidence of pain was decreased in female-to-male transgender individuals treated with androgen, and increased in male-to-female transgender individuals whose serum androgen levels were pharmacologically lowered [46]. These studies support a role for testosterone in dampening pain and raising the pain threshold.

1.4. Inhibition vs facilitation of nociception

Investigators are gaining a fuller understanding of nociceptive pain (relevant to fibromyalgia patients) and the ascending/descending facilitation vs inhibition pathways between the midbrain periaqueductal gray neurons (PAG), the rostral ventromedial medulla (RVM) within the brain stem and the dorsal horn of the spinal cord that result in hyperalgesia vs dampening of pain and return to homeostasis [47–52]. Input into this system from the hypothalamus, amygdala, other neocortical areas as well as the dorsal horn provides nociceptive "context" that informs pain pathways. Opioid microinjection or electrical stimulation of the enkephalin rich and androgen receptor-positive PAG neurons excites neurons of the RVM, some containing serotonin, which project to and inhibit the firing of spinal pain-transmission neurons [53]. On-cells, off-cells and neutral cells within the RVM help regulate this complex process [54].

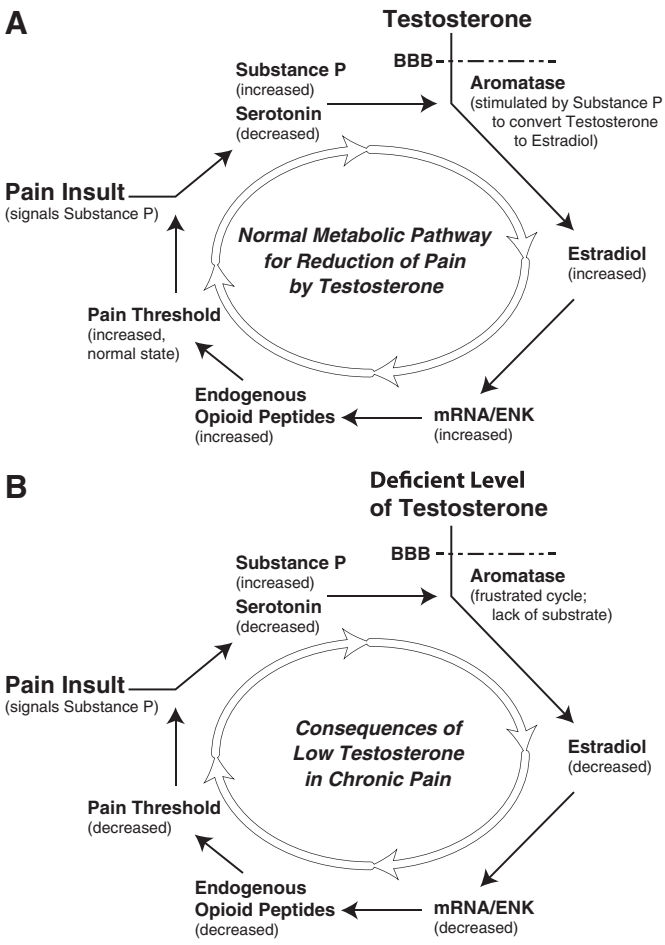

Fig. 1. Hypothesized signaling pathway for testosterone in relation to nociception in the CNS. A. In normal individuals, a painful/stressful stimulus up-regulates Substance P in the nociceptive relay neurons and serotonin levels drop, consistent with a loss of feeling of well-being [64]. Substance P has been found to stimulate aromatase [58], which would catalyze the conversion of testosterone to estradiol within the CNS, with subsequent upregulation of opiates and consequent dampening of pain. B. In fibromyalgia patients, deficient levels of testosterone are predicted to result in a "frustrated" cycle (due to lack of substrate) in which conversion of testosterone to estradiol is inadequate for induction of opiate-mediated dampening of nociceptive signals, resulting in abnormal chronic, diffuse, widespread pain. Estradiol, refers to 17-beta estradiol. See text for details and other hypothesized testosterone-based mechanisms.

1.4.1. Stress and the ability of testosterone to facilitate endocrine, nociceptive and immunologic cross-talk

Behavioral factors, stressors/threatening situations or behavioral needs can have anti-nociceptive effects that block otherwise nociceptive input, allowing the animal or individual to navigate between threat and safety/survival, including eating and reproduction [47]. In this context, we hypothesize the sex steroid hormone testosterone is well positioned to facilitate neuroendocrine "cross-talk" between reproductive, immunologic, HPA stress endocrine response and nociceptive relay neuron systems. Chronic stress or pain causes significant decreases in reproductive hormone production from both the adrenal gland (HPA axis) and ovary (HPO axis) [55], as observed in men undergoing military endurance/stress training [56] and in rats in response to formalin-induced tonic pain [57]. Exhaustion of testosterone responses to stressors then results in the hallmark symptoms for both testosterone deficiency and

fibromyalgia: chronic fatigue and muscle wasting or muscle dysfunction, and a low threshold for pain as hypothesized below.

1.5. Novel androgen deficiency hypothesis of chronic pain and central sensitization

Clinical data now support the hypothesis that testosterone therapy can decrease pain responses (White et al., elsewhere in this issue). Testosterone is more available (vs estrogen) to cross the blood brain barrier (BBB) free of sex hormone binding globulin (SHBG; it is testosterone that is unbound to SHBG that is bioactive), and was predicted to be the sex steroid hormone that is important for modulating the sensation of pain in the dorsal horn and other key sites within the CNS, acting therapeutically within the nociceptive neuronal environment to dampen an inflamed nociceptive nervous system.

One likely mechanism for the action of testosterone would involve dampened pain signaling within the dorsal horn: In normal individuals (Fig. 1A), a painful/stressful stimulus up-regulates Substance P which has been found to stimulate the enzyme aromatase [58], which then converts testosterone to estradiol within the CNS. Aromatase-positive neurons associate with nociceptive estrogen receptor+ neurons that are preproenkephalin mRNA+ [21,27,29,31], consistent with an up-regulation of opiates, eventual down-regulation of Substance P [59] and dampening of pain. In contrast, for fibromyalgia patients (Fig. 1B), their abnormally low testosterone levels, substantiated by others [26], are proposed here to result in a "frustrated" cycle whereby a lack of testosterone substrate fails to stimulate the aromatase enzyme. Enzymatic conversion of testosterone to estradiol by aromatase within the CNS is therefore inadequate for induction of endogenous opiate-mediated dampening of nociceptive signals, with the consequence that chronic, diffuse and widespread "wind-up" pain ensues. Relating to this, fibromyalgia patients' cerebrospinal fluid was found to have lower levels of the endogenous opioid peptide met-enkephalin-Arg6-Phe7 than that of normal individuals [60] in one report, higher levels in another report [61], and opioid receptors were changed as well [62]. The complex role of opioid peptides and their receptors is emphasized by the demonstration that exogenous opioids given over the long term can become hyperalgesic [14].

Other mechanisms proposed here by which testosterone is just as likely to dampen nociception include anatomic locations in the CNS other than the dorsal horn, for example at known centers of nociceptive neuron modulation such as the midbrain androgen receptor-positive PAG neurons that project to the on-cells and off-cells of the RVM, as mentioned above. In this case, testosterone is likely to act on PAG neurons to effect RVM on-cell/off-cell regulation and descending inhibition of pain. Additional mechanisms likely involve the non-classical non-genomic androgen receptor-mediated rapid actions known to modulate neuronal voltage- and ligand/neurotransmitter-gated ion-channels and transporters at neuronal synapses or elsewhere, acting directly or indirectly in a regulatory capacity [63]. For example, androgenic steroid effects on neuronal GABA-A receptors can be significantly more potent than benzodiazepines [63], which are used by some clinicians to treat fibromyalgia. Finally, it would be logical that androgens act to coordinate these nociceptive pathways as well as to coordinate between immunologic, neuro-endocrine and reproductive systems in order to allow the individual to navigate between response to threats from the environment (microbes and fight-or-flight), safety/survival, reproduction and baseline function.

Considering these mechanisms together, abnormally low testosterone levels are likely to result in amplified ascending/descending facilitation of nociception and reduced descending inhibitory control, resulting in a widening pain field and neuronal plasticity which can turn into the entrenched chronic pain states found in fibromyalgia patients. Pre-existing testosterone deficiency states due to exhaustion (environmental stress) and/or genetic predisposition may also help explain why some individuals are more susceptible to chronic pain than others. Treatment with testosterone is likely to benefit these patients, and that concept is supported by the preliminary study of White et al.

Potential conflicts of interest

HDW and TDR own shares of White Mountain Pharma, Inc. HDW had overall responsibility in the writing of this report and the decision to submit it for publication, and takes complete responsibility for the integrity of the report. White Mountain Pharma, Inc. has not influenced or biased the opinions expressed in this manuscript.

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