Effect of Sex Hormones on Migraine

Subjects: Health Care Sciences & Services

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Sex hormones and migraine are closely interlinked. Women report higher levels of migraine symptoms during periods of sex hormone fluctuation, particularly during puberty, pregnancy, and perimenopause. Ovarian steroids, such as estrogen and progesterone, exert complex effects on the peripheral and central nervous systems, including pain, a variety of special sensory and autonomic functions, and affective processing. A panel of basic scientists, when challenged to explain what was known about how sex hormones affect the nervous system, focused on two hormones: estrogen and oxytocin.

Keywords: sex hormones ; migraine ; estrogen ; oxytocin ; progesterone ; testosterone ; prolactin ; vasopressin

1. Sex Hormone Fluctuation as a Trigger of Migraine

Migraine tends to follow a classic temporal pattern throughout a cisgender woman's life that corresponds with sex hormone fluctuations during reproductive milestones in the female lifespan. Puberty is a key period with significant changes in sex hormone levels. Interestingly, in children and adolescents, the prevalence of migraine headaches is nearly equivalent in boys and girls [1], but during puberty, the prevalence of migraine between men and women diverges and is 3–4 times higher in women compared to men [2][3]. This sex difference corresponds to the onset of menarche and falls after menopause.

Migraine symptoms can be linked to menstrual cycle changes (menstrual migraine) and 18–25% of women with migraine experience migraine or headaches during menstruation [4]. Menstrual migraine can be associated with a higher frequency of migraine-accompanying symptoms and more frequent and severe migraine attacks [5]. A comparison of women with and without migraine shows that those with migraine are characterized by faster late-luteal-phase estrogen decline compared to women without migraine. Thus, the timing and rate of estrogen withdrawal has been proposed to be a marker of vulnerability to migraine in women [6]. Contraceptive pills reduce the number of migraine attacks, migraine days, pain scores, disability scores, and migraine medication use while reducing the frequency of aura, and lowering, but not eliminating, the risks of cardiovascular complications or other side effects [7][8][9]. Another strategy is to use estrogen supplementation with a pill, vaginal gel or patch during the menstrual week.

Migraine is a heterogeneous disease associated with many possible combinations of genetic defects which share a common phenotype of intermittent pain or other hypersensitivities. This accounts for the unpredictable response of migraineurs to medications and the effect of hormones on the nociceptive system is no exception.

Migraine disease has a complex relationship with pregnancy. For 8% of women with migraine, their headaches worsen during the first trimester. This is especially true for migraine without aura, which is more hormonally driven [10][11][12]. The majority of women with migraine generally experience reduced migraine symptoms by the third trimester [13]. However, many women have the acute onset of headaches during pregnancy.

Perimenopause, the period of two to eight years when menses first become irregular prior to the year after the end of menses, is a time when hormonal fluctuations are still occurring, and pre-existing migraine symptoms can remain unchanged, improve, or worsen [14][15][16]. In total, 8–13% of women report their first migraine during perimenopause [17][18]. However, many women see a decrease in headache prevalence during this period [19][20], most prominently in women who already suffer from migraine with aura [21]. For unexplained reasons, mid-facial pain and pressure and vestibular migraine can become prominent symptoms during perimenopause and menopause [22]. Hormone replacement therapy, or menopause replacement therapy (MRT), usually a continuous dosing of estrogen alone or estrogen plus progestin (ethinyl estradiol 5 µg combined with norethindrone acetate 1 mg, estradiol 1 mg combined with 0.5 mg norethindrone acetate, or transdermal estradiol combined with one-quarter or one-half of a 5 mg norethindrone daily) [23], remains an option, particularly for those women who have not had a hysterectomy because estrogen alone increases the risk of endometrial

cancer. Transdermal estrogen patches or gels can be efficacious and less risky than systemic estrogen replacement in treating migraine [4][16][24].

The bottom line is that current sex hormone supplements play a valuable role in mitigating the symptoms of migraine, but, because they are still associated with serious complications, especially migraine with aura, and exacerbate migraine symptoms in some, many medical professionals choose not to use hormone supplements in their migraine treatment plan. For example, plant-derived hormones (phytoestrogens) and the derivative bio-identical hormones are effective in reducing menstrual-related migraine headaches [25], but there is no rigorous scientific evidence that these supplements are safer or more natural compared to the current hormonal interventions. Phytoestrogen-containing foods, such as soy, are recommended over supplements, and all phytoestrogens should be avoided if there is a chance of pregnancy because these compounds might adversely affect the endocrine system. It is speculated that they might be safer in older women, such as those suffering from menopausal symptoms, particularly hot flashes [26][27], but currently there is not enough evidence to conclude that the benefits of phytoestrogens outweigh their potential health risks [28], and they do not appear to be ideal migraine preventive agents. Thus, since many women with migraine are unable to find an effective preventive therapy, there remains the challenge to understand how sex hormone supplements work, with the goal that select metabolites or synthetic derivatives might be both efficacious and safer than current hormonal therapies.

2. Which Sex Hormones Should Be the Target?

2.1. Estrogen

Estrogen plays a complicated role in migraine disease. Both drops and fluctuations in estrogen are associated with migraine symptoms, but its effect varies between individuals because of different receptors, metabolites, and interactions with other hormones. The dominant understanding of how crucial estrogen is in protecting individuals from migraine symptoms is what happens when estrogen levels decline: the estrogen withdrawal hypothesis. This hypothesis theorizes that drops in plasma estrogen trigger migraine attacks and neuroinflammation, eventually leading to chronic sensitization [29]. There are several possible mechanisms to explain his theory. One explanation is that estrogen suppresses pain by binding to estrogen receptor alpha (ER alpha) and estrogen receptor beta (ER beta), which are primarily associated with cell nuclei in the trigeminal ganglia. Activation of these nuclear receptors regulates inflammatory genes that ultimately suppresses cell excitability [30].

CGRP is believed to be among the critical neuropeptides responsible for the throbbing pain associated with a migraine attack and the neuroinflammation that causes both pain and that perhaps cause neuroplastic neural changes responsible for chronic central sensitization [31]. Specifically, estrogen may also increase neurogenic vasodilation and gene regulation.

While the estrogen withdrawal hypothesis focuses primarily on the trigeminal nerves, it is important to recognize the wider-ranging actions of estrogen in other parts of the body and brain [32]. A second mechanism to explain the estrogen withdrawal theory was demonstrated in an animal model where reduced levels of estrogen were shown to increase the frequency of cortical spreading depressions, the electrophysiological event believed to be responsible for triggering the trigeminal system and headaches, as well as auras [33].

2.2. Progesterone

Progesterone, the second major sex hormone, is produced in the ovaries, adrenal glands and placenta, and primarily helps maintain pregnancy. Progesterone with estradiol is found at the onset of menstrual migraines. Nonetheless, it is more likely that the withdrawal of estradiol, rather than progesterone, initiates migraine headaches. Instead, progesterone appears to protect neurons by suppressing neuroinflammation and reducing trigeminal nerve sensitivity.

It may be in the interplay with additional factors where progesterone plays an integral role in pain modulation. In a longitudinal study of fibromyalgia, it was high levels of progesterone and testosterone together that were associated with less pain [34]. Progesterone and testosterone are able to penetrate the blood-brain barrier and function as precursors for neurosteroids. There is an example of a progesterone derivative which enhances GABA function by modulating GABA receptors and, in turn, inhibits neuronal sensitivity [35][36].

Currently, synthetic progesterone is used as a form of birth control and a migraine preventive agent in the form of a continuous low dose of progestin. Bio-identical progesterone can be delivered in three formulations: orally, topically, and as a suppository. Progesterone may improve insomnia as a mild sedative, and improve sleep apneas by stimulating respiration [37].

2.3. Testosterone

A popular belief is that testosterone is the male hormone whereas estrogen is the female hormone. However, this is an oversimplification, as both estrogen and testosterone have important roles to play in individuals of either sex [38]. In both males and females, the balance between estrogen and testosterone production throughout life influences the function of both reproductive and nonreproductive organs [38].

Testosterone could be a potential therapeutic target, as it has an antinociceptive effect [39][40][41][42][43]. In animal studies, after gonadectomy or the blocking of testosterone receptors, animals appeared more sensitive to nociceptive stimuli [44][45][46][47][48]. The few human studies performed support an analgesic effect of testosterone, as higher testosterone levels are associated with lower experimental pain sensitivity [49]. Studies on the relationship of testosterone to migraine are few. Testosterone levels are lower in adults with migraine vs. without migraine, and are related to migraine severity. Interestingly, even when similar testosterone levels are found, men with migraine more frequently report symptoms of androgen deficiency compared to men with no migraine. However, one study found that no differences in testosterone levels were found in women with vs. without migraine, and that migraine pain intensity was not correlated with testosterone levels.

Testosterone appears to be able to effectively reduce symptoms by suppressing spreading depressions, increasing serotonin, stabilizing cerebral blood flow, and reducing cell excitability and neuroinflammation [50]. These metabolic effects may explain the findings that testosterone treatment can improve clinical pain and experimental pain sensitivity in patients with chronic pain, including in patients with temporomandibular joint pain, fibromyalgia, and migraine [51][52][53][54], and that testosterone treatment delivered by a subcutaneous implant significantly reduces migraine intensity [53].

2.4. Oxytocin

Oxytocin's (OT) therapeutic effects in migraine are complex and widespread in the nervous system, including at the level of the primary sensory neuron, spinal cord, and in a variety of brain regions associated with pain processing and modulation [55][56][57].

The effect of OT on migraine has been shown via a case report in which intravenous OT provided analgesia and migraine relief [58]. In addition, double-blind, placebo-controlled clinical studies have shown evidence that intranasal OT sprays are efficacious for treating migraine pain in adult men and women [55][59] and experimental-evoked pain in men [60]. A benefit of oxytocin as a treatment for migraine is that it is routinely administered intranasally for inducing labor, postpartum care, and for enhancing lactation, and its safety profile is well documented. In addition, intranasal oxytocin in humans has no major side effects [61].

OT is a neuropeptide that exerts its pain-inhibitory effects both at the level of the primary afferent fiber and in the central nervous system. The first mechanism is via the descending neural pathway from the paraventricular nucleus (PVN) to the dorsal horn of the spinal cord [62][63]. Signals from the PVN release oxytocin in the spinal dorsal horn that activate GABAergic interneurons in the dorsal horn which secondarily recruit other inhibitory GABAergic interneurons and suppress pain signals carried by ascending A-delta and C-fibers [64][65][66][67]. The second mechanism is where OT released from the supraoptic nucleus (SON) in the hypothalamus, periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and the spinal dorsal horn [68][69] modulates central endogenous pain pathways by raising nociceptive thresholds [70][71].

OTR mRNA and proteins are expressed in nociceptive C-fibers and Aδ-fibers in the adult rat trigeminal ganglia [72], and have a high level of co-expression with CGRP in trigeminal ganglia neurons [55]. OT dose-dependently blocks the release of calcitonin gene-related peptide (CGRP) from trigeminal afferent neurons innervating the dura in vitro [72].

2.5. Vasopressin

Arginine vasopressin (AVP) is a neuropeptide hormone that has an antidiuretic effect in low concentrations, but at higher concentrations it causes vasoconstriction. Together, these effects raise blood pressure. AVP also has a role in pain, behavior, platelet aggregation, and blood coagulation functions.

Much of AVP is synthesized in the SON of the hypothalamus and, while AVP is largely stored in and secreted from the pituitary, AVP-containing hypothalamic fibers are widely distributed in the CNS [73]. These fibers reach different centers in the brainstem and, in particular, the trigemminal nuclei. The AVP receptors (VP1 and VP2) are found in the trigeminal ganglion [72].

2.6. Prolactin

Prolactin (PRL) is a hormone that is responsible for lactation, breast development, and hundreds of other actions needed to maintain homeostasis. PRL is chemically related to growth hormones and placental lactogen hormones. In an animal model, high levels of prolactin increased meningeal trigeminal pain sensitivity by only affecting CGRP in female rodents [74].

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