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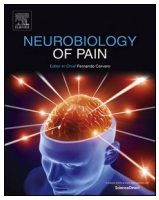

Review

The role of androgens in migraine pathophysiology

Adam J. Dourson [a,e], Rachel S. Darken [b], Thomas J. Baranski [c], Robert W. Gereau 4th [a,e], Whitney Trotter Ross [d], Hadas Nahman-Averbuch [a,e,*]

[a] Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA
[b] Department of Neurology, Washington University School of Medicine, St. Louis Missouri, USA
[c] Division of Endocrinology, Diabetes and Metabolism Washington University School of Medicine in St. Louis Missouri, USA
[d] Division of Minimally Invasive Gynecologic Surgery, Washington University in St. Louis, St. Louis, MO, USA
[e] Washington University Pain Center, Washington University School of Medicine, St. Louis, MO, USA

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ABSTRACT

Migraine affects ~12 % of the worldwide population and is more prevalent in females, which suggests a role of sex hormones in migraine pathophysiology. Most studies have focused on estrogen and progesterone, and the involvement of androgens has been less studied. However, due to the recent advances in androgen interventions, which could advance new androgen-based migraine treatments, it is critical to better understand the role of androgens in migraine. Testosterone, the most studied androgen, was found to have an antinociceptive effect in various animal and human pain studies. Thus, it could also have a protective effect related to lower migraine severity and prevalence. In this review, we discuss studies examining the role of androgens on migraine-related symptoms in migraine animal models. Additionally, we summarize the results of human studies comparing androgen levels between patients with migraine and healthy controls, studies assessing the relationships between androgen levels and migraine severity, and intervention studies examining the impact of testosterone treatment on migraine severity. Many of the studies have limitations, however, the results suggest that androgens may have a minor effect on migraine. Still, it is possible that androgens are involved in migraine pathophysiology in a subgroup of patients such as in adolescents or postmenopausal women. We discuss potential mechanisms in which testosterone, as the main androgen tested, can impact migraine. These mechanisms range from the cellular level to systems and behavior and include the effect of testosterone on sensory neurons, the immune and vascular systems, the stress response, brain function, and mood. Lastly, we suggest future directions to advance this line of research.

1. Introduction

Migraine is defined by the International Classification of Headache Disorders (ICH-D) as a highly prevalent and disabling disorder of recurrent headaches that last between 4 and 72 h, are unilateral, pulsating, with moderate or severe intensity, aggravated by routine physical activity, and are associated with nausea and/or photophobia, and phonophobia (2013). Several mechanisms for migraine have been proposed, including the involvement of sex hormones, which may have a role in migraine prevalence, severity, and management. Migraine is more prevalent in females, but this sex difference emerges only around puberty, at which time girls have a significant increase in migraine prevalence compared to boys (Stewart et al., 1991, Lipton and Bigal, 2005, King et al., 2011). For simplicity, this review will refer to individuals assigned as female at birth as “girls” or “women” and those assigned male at birth as “boys” or “men”, but it should be acknowledged the phenotypic presentation of sex and gender may differ in individuals. Puberty is a time of significant changes in sex hormone levels, with estrogen disproportionately increasing for girls and testosterone for boys. These changes in hormone levels provide a possible explanation for the difference in migraine prevalence between sexes (Nahman-Averbuch et al., 2023). Changes in migraine prevalence and severity are also observed during pregnancy, menopause, and menstrual cycle phases. During pregnancy, both an improvement and a worsening in migraine symptoms have been reported (Loder, 2007). Similarly, improvement, worsening, or no change in migraine symptoms have been reported during menopause (Ornello et al., 2021). Monthly sex hormone fluctuations during the menstrual cycle also relate to migraine

* Corresponding author at: Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA.
E-mail address: hadas@wustl.edu (H. Nahman-Averbuch).

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symptoms, especially in women with menstrual migraine, which is part of the ICHD-3 classification (2013). Mainstays of menstrual migraine management are interventions that reduce sex hormone fluctuations to reduce migraine symptoms (Ahmad and Rosendale, 2022).

Ovarian hormones have preferentially been studied in relation to migraine, and the role of androgens in migraine pathophysiology is less clear. Androgens are a group of sex hormones that, by binding to androgen receptors (ARs), play a key role in sexual differentiation, reproductive health and behavior, and body development and maintenance (Naamneh Elzenaty et al., 2022). Androgen synthesis involves the gonadotropin-releasing hormone (GnRH)-luteinizing hormone (LH) and follicular-stimulating hormone (FSH) axis (Sharma et al., 2022) (Fig. 1). In females, the ovaries and adrenal glands produce testosterone, while in males, most testosterone is produced in the testes. Testosterone can be converted to either dihydrotestosterone (DHT) via 5-alpha reductase or estradiol via aromatase (Handelsman, 2020, Naamneh Elzenaty et al., 2022). Testosterone and DHT are considered strong androgens. DHT has a greater affinity to the androgen receptor and, thus, is a more potent endogenous androgen than testosterone (Naamneh Elzenaty et al., 2022). DHT is a paracrine hormone and is formed by intracellular conversion of testosterone at primarily peripheral tissues involved in sexual maturation of males (Swerdloff et al., 2017, Kinter, 2024). Androgens in the blood can be bound or unbound. Dehydroepiandrosterone (DHEA), dehydroepiandrosterone- sulfate (DHEA-S), and androstenedione are either entirely or mainly bound to albumin, while DHT and testosterone are primarily bound to sex hormone binding globulin but also to albumin. About 1–2 % of testosterone in the blood is free and is considered readily available for action in target cells. Since testosterone is weakly bound to albumin, albumin-bound testosterone plus free testosterone is often referred to as bioavailable testosterone, while total testosterone is referred to as bound and unbound testosterone (Stanczyk, 2006, Kanakis et al., 2019).

In this review, we summarize the studies examining the role of androgens on migraine, including animal studies using migraine animal models, human studies assessing differences in androgen levels between patients with migraine and healthy controls, studies determining the relationships between androgen levels and migraine severity, and intervention studies examining the impact of testosterone treatment on migraine severity. We also discuss potential mechanisms in which testosterone, as the main androgen tested, can impact migraine.

2. Animal studies

Sex hormones have been discussed and tested to determine both their clinical and preclinical impact on pain (Mogil, 2012, Mogil et al., 2024). Androgens have been studied in multiple preclinical models of pain such as widespread muscle pain and activity-induced muscle pain (Lesnak et al., 2020, Lesnak et al., 2022), joint and inflammatory pain (Fanton et al., 2017, Poulaki et al., 2021), visceral pain (Ji et al., 2018), post-operative pain (Barbosa Neto et al., 2019), neuropathic pain (Saika et al., 2024), and hyperalgesic priming (Paige et al., 2020). Gonadectomy/orchiectomy is a medical procedure in which the gonads or testes, respectively, are removed to reduce systemic androgens and are often used in preclinical models to study the effects of testosterone on behavior. In an activity-induced muscle pain model, females and orchiectomized males display longer pain-like behaviors compared to intact males. Increasing testosterone levels by resistance training reduced pain phenotypes and an androgen receptor antagonist, flutamide, reversed this protection in intact males and females (Lesnak et al., 2020, Lesnak et al., 2022). In a hyperalgesic priming model, females and gonadectomized males displayed longer pain-like behaviors compared to intact males, which was partially reversed by testosterone replacement (Wangzhou et al., 2021). These examples indicate a role for androgens to regulate, and often reduce, nociception and persistent pain-like behaviors, but less has been studied in regard to migraine.

There are various proposed animal models of migraine (Begasse de Dhaem et al., 2023), but the role of testosterone has been tested in only two models (Table 1). In a genetic model of migraine using familial hemiplegic migraine type 1 mutant mice (R192Q), an orchiectomy increased cortical spreading depression (CSD, believed to underlie the phenomenon of migraine aura (Charles and Baca, 2013)) frequency. Treatment with testosterone for 21 days completely prevented the orchiectomy-induced increase in CSD susceptibility, and an androgen receptor blocker reversed the effect of testosterone treatment (Eikermann-Haerter et al., 2009). In contrast, a single dose of testosterone propionate administered one hour before electrophysiological recordings had no effect on CSD, and in wild-type mice, gonadectomy or testosterone replacement did not significantly alter CSD susceptibility (Eikermann-Haerter et al., 2009). In the nitroglycerine (NTG)-induced migraine model in mice (Alarcón-Alarcón et al., 2022), repeated administration of NTG leads to persistent mechanical allodynia, similar to that seen in human patients with migraine (Ashkenazi et al., 2007, Lovati et al., 2009). In this study, NTG-induced mechanical allodynia to the hind paw was unresolved in female mice at 20 days, yet was no longer present in males by day 18. However, in males that had undergone orchiectomy, allodynia was unresolved at 20 days, similar to intact females. Future studies are needed to determine if this effect persists for longer than 20 days and to investigate if the testosterone effect on

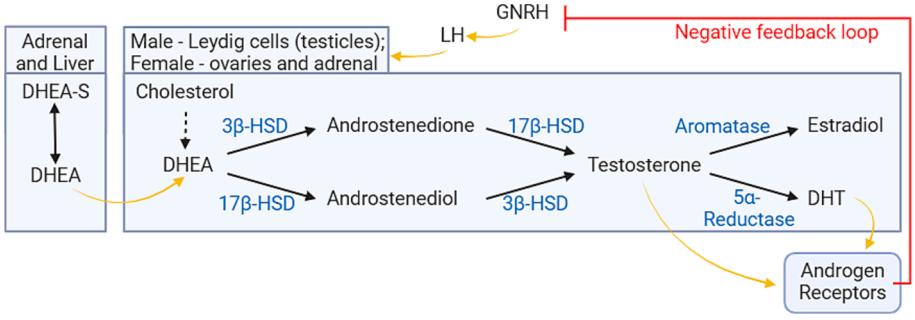

Fig. 1. Androgen synthesis. Androgen synthesis involves the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus which stimulates the secretion of luteinizing hormone (LH) and follicular-stimulating hormone (FSH) from the anterior pituitary (Sharma et al., 2022). In females, LH stimulates theca cells in the ovaries, producing a small amount of testosterone. In males, LH binds to specific receptors on Leydig cells in the testes to produce testosterone by regulating the conversion of cholesterol to pregnenolone. Pregnenolone is converted to dehydroepiandrosterone (DHEA), which is converted to androstenediol and androstenedione. The enzyme testosterone 17-beta-dehydrogenase converts these two hormones to testosterone(Miller and Auchus 2019, Naamneh Elzenaty et al., 2022). Testosterone can be transferred in the blood by binding to circulating plasma protein and activate androgen receptors or it can be converted to either dihydrotestosterone (DHT) via the enzyme 5-alpha reductase or estradiol via aromatase(Handelsman 2020, Naamneh Elzenaty et al., 2022). Testosterone and the other steroids have a negative feedback loop by inhibiting the release of GnRH, LH, and FSH from the hypothalamus and pituitary gland (Plant and Marshall 2001, Naamneh Elzenaty et al., 2022).

Table 1
The effects of androgen signaling on migraine-related phenotypes in animals.

Study	Species and model	Groups	Analyses	Results
Eikermann-Haerter et al., 2009	Mice with the FHM1 R192Q mutation (n = 4–19/group)	Male WT: Naïve, with orchiectomy, or with orchiectomy + testosterone treatment. Male R192Q: Naïve, with orchiectomy, with orchiectomy + testosterone replacement, or with orchiectomy + testosterone replacement and androgen receptor blocker flutamide.	Cortical spreading depression (CSD)	• WT animals had no change in CSD frequency across groups. • R192Q animals with orchiectomy had increased frequency of CSD compared to naïve R192Q mice. • Testosterone replacement reversed these effects and flutamine prevented this reversal.
Alarcon-Alarcon et al., 2021	Mice with NTG-induced migraine (n = 5–7/group)	• Female + vehicle/NTG Male + vehicle/NTG Male + vehicle/NTG with sham or orchiectomy Female + NTG with vehicle or testosterone treatment.	Hind paw von Frey	• Mechanical allodynia persisted longer in females (>20 days) compared to males (16 days). • Orchiectomy results in NTG associated mechanical allodynia for at least 20 days. • Females display reduced sensitivity after testosterone treatment.

allodynia is present also in the migraine associated areas such as the head and neck. Testosterone replacement in orchiectomized males or in females led to recovery by 18 days, similar to intact males (Alarcón-Alarcón et al., 2022). These studies demonstrate a probable relationship between androgen levels and pain models, including migraine, although limitations in these animal migraine models have been identified (Begasse de Dhaem et al., 2023), and there is a need to test this relationship in other models.

3. Human studies

Most of the relevant studies conducted in humans are observational studies comparing androgen levels between patients with migraine and healthy controls and correlating androgen levels with migraine severity or experimental pain sensitivity. Only a few interventional studies have examined the impact of testosterone treatment on migraine severity.

3.1. Differences in androgen levels between patients with migraine and healthy controls

There are disparate findings, depending on the patient population, on the relationship between androgen levels and migraines (Table 2). A few studies have found lower levels of testosterone in patients with migraine compared with healthy control participants with no migraine. This was found in women with migraine in the follicular and luteal phase (Li et al., 2018) and postmenopausal women with vestibular migraine (Tang et al., 2021). Men with chronic migraine had lower testosterone levels compared to published age-matched control (Shields et al., 2019). On the other hand, many other studies found no differences in testosterone levels between patients with migraine and healthy controls in populations of men and women (before, during, and after menopause) (Mattsson, 2002, Patacchioli et al., 2006, Aksoy et al., 2013, Solmaz et al., 2016, Li et al., 2018, van Oosterhout et al., 2018, Rustichelli et al., 2020, Al Asoom et al., 2021, Pan et al., 2024). Another study did not compare to a control group but found that testosterone levels in patients with migraine were within the normal range for women based on published age-matched controls (Epstein et al., 1975). A recent meta-analysis based on 3 of the above studies found overall no differences in testosterone levels between patients with migraine and healthy controls (Beech et al., 2023). Interestingly, even when similar testosterone levels are found, men with migraine more frequently report symptoms of androgen deficiency compared to men with no migraine (van Oosterhout et al., 2018).

The availability of circulating androgens is dependent on other steroid hormone levels. While the meta-analysis discussed above found no differences in testosterone levels between those with migraine and healthy controls, it did identify that cortisol levels are increased in patients with migraine (Beech et al., 2023). Other studies have similarly found that the testosterone/cortisol ratios were significantly lower in patients with chronic migraine than in healthy subjects due to higher cortisol levels (Patacchioli et al., 2006). Similarly, free testosterone levels were similar between men with episodic migraine without aura and healthy controls, but the testosterone/estradiol ratio was lower in men with migraine compared to controls (van Oosterhout et al., 2018). These findings suggest that the clinical significance of androgens may be due to androgen deficiency relative to other circulating steroid hormones.

Other androgens include androstenedione, DHEA, and DHEA-S. Androstenedione was examined in one study and no differences were found between patients with migraine and healthy controls (Mattsson, 2002). In women with episodic migraine, DHEA (but not DHEA-S) levels were found to be lower compared to controls (Koverech et al., 2019). In patients with chronic migraine, both DHEA and DHEA-S levels were lower compared to controls (Koverech et al., 2019). This study also found that patients with chronic migraine had lower DHEA and DHEA-S levels compared to patients with episodic migraine (Koverech et al., 2019). Another study found that the level of DHEA-S was lower in patients with migraine, and the cortisol/DHEA-S ratio was lower in the patient group, as cortisol levels in this study did not differ between the groups (Kokavec and Crebbin, 2010). However, contrasting results were found in a different study reporting a higher cortisol/DHEA-S ratio in patients with migraine compared to healthy controls, with no differences between patients and control participants in DHEA-S levels but with higher levels of cortisol in the patient group (Patacchioli et al., 2006).

3.2. Relationships between androgen levels and migraine severity or experimental pain measures

The results of these studies are summarized in Table 3. Overall, no relationships between testosterone levels and migraine characteristics, such as headache frequency, duration, or pain scores, were found in men or women (Aksoy et al., 2013, Li et al., 2018, Al Asoom et al., 2021, Tang et al., 2021). The only significant relationship was found between higher testosterone levels and lower migraine disability scores in postmenopausal women (Li et al., 2018). For experimental pain, no relationships were found between testosterone levels and heat pain thresholds or pain intensity ratings of noxious heat stimulus in men or women with migraine (Pan et al., 2024). For DHEA and DHEA-S, while one study found that higher DHEA and DHEA-S levels were related to lower migraine frequency and duration (years with migraine) in women with migraine (Rustichelli et al., 2021), other studies found no

Table 2
Differences in androgen levels between patients with *vs.* without migraine.

Study	Sample (age)	Androgen measure(s)	Results	Comments
Epstein et al., 1975	8 women with migraine	Testosterone *Plasma, collected between 8:30–10:00am*	Testosterone levels in all patients were within the range for normal women	
Mattsson 2002	15 women with migraine (61.4 ± 6.6) 45 women with no migraine (62.5 ± 7.2)	Total testosterone, free testosterone (calculated from SHBG and albumin levels), androstenedione *Blood collected between 9am-5 pm. Analysis using immunoassay*	No differences in testosterone and androstenedione between the groups (controlling for time of blood draw and oestradiol did not change the results)	Each patient had 3 controls matched for time since menopause and body mass index
Patacchioli et al., 2006	20 women with chronic migraine (49.6 ± 4.1) 20 women with no migraine (48.7 ± 3.3)	DHEA-S, testosterone *Saliva collected between 8:00 a.m. and 8:00p.m. Analysis with immunoenzymatic kits*	• No differences in DHEA-S and testosterone levels Higher cortisol/DHEA-S and cortisol /testosterone ratios in patients with chronic migraine compared to healthy controls	
Kokavec et al., 2010	8 women with migraine (46 ± 5) 8 women with no migraine (48 ± 4)	DHEA-S *Serum collected at 9:00 am. Analysis using immunoassay*	• Lower DHEA-S levels in patients compared to controls. • The cortisol:DHEA-S ratio was lower in patients.	The study also Included assessing the effect of ingestion of 75 g sucrose on hormones (no differences between the groups in the effect of sucrose on DHEA-S levels)
Aksoy et al., 2013	30 men with migraine (34.96 ± 1.30)31 men with tension type headache (35.54 ± 1.52)30 men with no migraine (35.54 ± 1.52)	Testosterone	No differences in testosterone levels between the groups.	
Li et al., 2018	119 patients with migraine (age range 13–61)30 controls with no migraine (age range 15–60)	Testosterone *Blood collected between 8 and 9 am. Analysis using chemiluminescence assay*	• Testosterone levels were lower in women with migraine in the follicular and luteal phases and in post menopause compared to controls. • No differences in testosterone levels in men	Comparisons included: *30 men with migraine vs. 5 men with no migraine* *Follicular phase- 52 women with migraine vs. 15 women with no migraine* *Luteal phase- 20 women with migraine vs. 5 women with no migraine* *Post menopause- 17 women with migraine vs. 5 women with no migraine* The study also included a group of patients with tension type headache
van Oosterhout et al., 2018	18 men with episodic migraine without aura (46.9 ± 16.4) 24 men with no migraine (48.5 ± 17.2)	Free testosterone (calculated from SHBG and albumin levels). *Serum collected at 9 am, 12 pm, 3 pm, and 6 pm. Analysis using immunoassay*	• No differences in free testosterone levels. Free testosterone/17β-estradiol ratio was lower in patients with migraine compared to controls	Total testosterone was also measured but no results are mentioned.
Koverech et al., 2019	19 women with episodic migraine (41.6 ± 16.2)51 women with chronic migraine and medication-overuse headache (51.6 ± 10.9) 31 women with no migraine (52.1 ± 17.8)	DHEA, DHEA-S *Plasma collected between 8 AM and 9 AM. Analysis using LC-MS/MS.*	• No differences in DHEA-S levels but lower DHEA in patients with episodic migraine compared to controls. • Lower DHEA and DHEA-S in patients with chronic migraine compared to controls. • Patients with chronic migraine had lower DHEA, DHEA-S compared to patients with episodic migraine	
Shields et al., 2019	14 men with chronic migraine without opioid or barbiturate overuse (36.1)	Total testosterone *Serum*	Men with migraine had lower testosterone levels compared to local laboratory normal values and published age- matched controls	
Rustichelli al., 2020	30 fertile women diagnosed with menstrually-related migraine without aura (age 33.5 ± 7.1)30 fertile women with no migraine (30.9 ± 7.9)30 menopausal women with migraine without aura (56.6 ± 4.5) 30 menopausal women with no migraine (56.1 ± 4.5)	Testosterone *Serum collected in the morning. Analysis using LC-MS/MS.*	No difference in testosterone levels	
Al Asoom et al., 2021	9 women with menstrual migraine (21.76 ± 2.73) 5 women with non-menstrual migraine (22.36 ± 4.48)21 women with no migraine (21.83 ± 2.02)	Testosterone *Serum collected during follicular and luteal phases and during and outside a headache attack. Analysis using immunosorbent assay*	• No differences between patients with migraine (combined menstrual and non-menstrual migraine) and healthy controls. • Higher testosterone levels in patients with menstrual migraine compared to healthy controls.	

(*continued on next page*)

Table 2 (*continued*)

Study	Sample (age)	Androgen measure(s)	Results	Comments
			• No differences between patients with non-menstrual migraine compared to healthy controls	
Rustichelli et al., 2021	30 fertile women with migraine without aura (33.5 ± 7.1) 30 fertile women with no migraine (30.9 ± 7.9)	DHEA, DHEA-S, *Serum. Analysis using LC-MS/MS*	Patients had lower levels of DHEA-S and DHEA.	
Tang et al., 2021	242 postmenopausal women with vestibular migraine (54.48 ± 5.93) 200 postmenopausal women with no migraine (55.02 ± 6.27)	Testosterone *Serum. Analysis using radioimmunoassay*	Testosterone levels were lower in patients compared with controls	
Pan et al., 2024	75 patients with migraine (31.1 ± 7.7, 30 men) 88 healthy controls (29.9 ± 7.7, 41 men)	Free testosterone *Saliva collected between 9:00 AM and 3:00 PM. Analysis using enzyme-linked immunosorbent assay*	No differences between patients and controls (men and women were compared separately)	

Mean and SD are presented for age unless otherwise stated. DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone sulfate, ELISA: enzyme-linked immunosorbent assay, LC-MS/MS: Liquid Chromatography with tandem mass spectrometry, SHBG: sex hormone binding globulin, VAS: visual analog scale.

Table 3
Relationships between androgen levels and migraine severity/experimental pain measure.

Study	Sample (age)	Androgen measure(s)	Migraine severity/ experimental pain measure (s)	Results
Aksoy et al., 2013	30 men with migraine (34.96 ± 1.30)	Testosterone	Headache duration	No correlations
Li et al., 2018	119 patients with migraine (age range 13–61) *30 men with migraine* *52 women with migraine in the follicular phase* *20 women with migraine in the luteal phase* *17 postmenopausal women with migraine*	Testosterone *Blood collected between 8 and 9 am. Analysis using chemiluminescence assay*	Pain intensity (VAS), Migraine disability, Headache frequency, Headache duration	• Testosterone levels were negatively correlated with migraine disability scores in the postmenopausal phase but not in men, or women in the follicular and luteal phase. • No correlations between testosterone levels and headache frequency, duration or pain intensity scores in any of the groups.
van Oosterhout et al., 2018	18 men with episodic migraine without aura (46.9 ± 16.4)	Free testosterone (calculated from SHBG and albumin levels). *Serum collected at 9 am, 12 pm, 3 pm, and 6 pm. Analysis using immunoassay*	Aging Males' Symptoms scale (includes items on aging and clinical testosterone deficiency)	No correlations
Koverech et al., 2019	19 women with episodic migraine (41.6 ± 16.2)51 women with chronic migraine and medication-overuse headache (51.6 ± 10.9)	DHEA, DHEA-S *Plasma collected between 8 AM and 9 AM. Analysis using LC-MS/MS.*	Migraine Disability Assessment Test Headache Impact test	No correlations
Al Asoom et al., 2021	9 women with menstrual migraine (21.76 ± 2.73) 5 women with non-menstrual migraine (22.36 ± 4.48)	Testosterone *Serum collected during follicular and luteal phases and during and outside a headache attack. Analysis using immunosorbent assay*	Migraine headache intensity (VAS)	No correlations
Kökönyei et al., 2021	23 patients with migraine without aura (27.61 ± 5.36, 18 women)	DHEA-S *Plasma. Analysis using ELISA*	Age at migraine onsetMigraine duration (years) ,Migraine frequency (average per month) .	No correlations
Rustichelli et al., 2021	30 fertile women with migraine without aura (33.5 ± 7.1)	DHEA, DHEA-S, *Serum. Analysis using LC-MS/MS*	Migraine frequency (migraine days/3 months)	Lower levels of DHEA and DHEA-S were related with higher years of migraine as well as higher migraine frequency
Tang et al., 2021	242 postmenopausal women with vestibular migraine (54.48 ± 5.93)	Testosterone *Serum. Analysis using radioimmunoassay*	Duration, frequency, and vestibular migraine severity (VAS)	No correlations
Pan et al., 2024	75 patients with migraine (31.1 ± 7.7, 30 men)	Free testosterone *Saliva collected between 9:00 AM and 3:00 PM. Analysis using enzyme-linked immunosorbent assay*	Heat pain thresholds and pain rating to a heat stimulus (10 s of 45 °C)	No correlations when tested only in men, only in women or in the combined group

Mean and SD are presented for age unless otherwise stated. DHEA: dehydroepiandrosterone, DHEA-S: dehydroepiandrosterone sulfate, ELISA: enzyme-linked immunosorbent assay, LC-MS/MS: Liquid Chromatography with tandem mass spectrometry, VAS: visual analog scale.

relationships with migraine frequency or disability (Koverech et al., 2019, Kökönyei et al., 2021).

3.3. Intervention studies

Seventy years ago, the efficacy of testosterone treatment on migraine symptoms was reported. In these observational publications, it was reported that daily methyl testosterone in various doses led to migraine relief in >80 % of patients (Moehlig and Gerisch, 1949, Moehlig, 1955). More recently, another study found significant improvement in migraine headache severity after testosterone therapy in women with symptoms of androgen deficiency and a chief complaint of migraine headache (Glaser et al., 2012) (Table 4). This study specifically evaluated testosterone delivered subcutaneously in a sustained-release pellet implant. There are also two case reports in which transgender men experienced improved migraine symptoms after initiating testosterone for masculinizing hormone therapy (Todd et al., 2023).

Danazol is a testosterone synthetic derivative that has androgenic effects and can increase testosterone levels (Nilsson et al., 1983). Danazol is mainly used for the treatment of endometriosis (Carlyle et al., 2020), however in letters to the editors, separate case reports described the effectiveness of danazol in reducing migraine severity in two patients (Calton and Burnett, 1984, Vincent, 1985). In addition, a larger study with 131 women with migraine headaches during the luteal phase found that danazol is mostly effective in improving migraine headache frequency and intensity for women >40 years old (Lichten et al., 1991). The described studies were not randomized, had no placebo control group, and some included a small number of patients.

Testosterone interventions can be delivered via intramuscular injection, transdermal gel or patches, subcutaneous implant/pellet, and oral capsules. Several years ago, a novel self-emulsifying drug delivery system (SEDDS) was developed (Bhat and Dobs, 2022). This new drug delivery system is reportedly easy to use and does not require intake with a high-fat-content meal in order to aid absorption and achieve desired levels (Bhat and Dobs, 2022). Medications of oral testosterone replacement therapy using SEDDS have been recently approved for hypogonadism, which is a condition in which significantly lower levels of testosterone are internally produced (Bhat and Dobs, 2022). The impact of testosterone on migraine severity should be tested using this new and advanced method of testosterone treatment.

4. Mechanisms underlying the impact of testosterone on migraine severity

Since most studies focused on testosterone, we discuss potential mechanisms in which testosterone impacts migraine prevalence and severity (Fig. 2). Bidirectional relationships may exist, such that migraine could also affect testosterone levels. However, we propose that the effect of migraine on testosterone levels is minor since most studies showed changes in migraine prevalence or severity following changes in testosterone (i.e., after testosterone treatment) or during times of known changes in sex hormone levels (i.e., during puberty, pregnancy, or menopause).

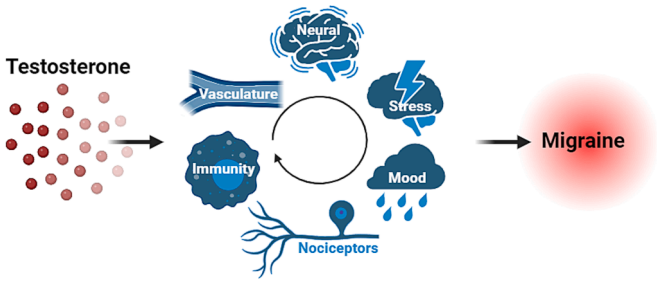

Fig. 2. Potential mechanisms involving the effect of testosterone on migraine. Testosterone may impact migraine via its effect on several factors. Diagramed is the effect of testosterone on the peripheral nervous, immune and vascular systems, the stress response, neural functions and mood, all of which can impact migraine. These factors can also interact with each other and further affect migraine.

4.1. Sensory neurons

Sensory neurons in the dorsal root ganglia (DRG) and the trigeminal ganglia (TG), which convey information sensed from the head and neck, transmit nociceptive signals to the brain. A key location in which TG neurons regulate migraine is the meninges surrounding the brain. However, the signaling pathways between neurons and local meningeal cells, such as immune cells, to mediate migraine are complex (Levy, 2009, Bolte et al., 2023; Louveau et al., 2015), and little is known about the role of androgen signaling in these cells (Fig. 3).

Androgen receptors are expressed highly in a variety of tissues and are important for many biological systems involving reproductive processes, muscle/bone development and repair, cardiac function, hematopoiesis, and more (reviewed by Davey and Grossmann (Davey and Grossmann, 2016)). Less well studied, due to relatively lower expression, are ARs in the peripheral nervous system. In mice, ARs begin to express in early embryonic stages in both TGs and DRGs (Young and Chang, 1998). Analysis of a species-harmonized single-cell RNA-sequencing atlas (Bhuiyan et al., 2024) reveals that the androgen receptor is expressed in mouse and human DRG neurons with lower expression in non-neuronal cell types. In the TG, it is expressed in ~30 % of both mouse and human neurons, although the level of expression within that proportion is lower than expected compared to antibody staining discussed below. Still, in humans, 12–28 % of TG nociceptors expressing voltage-gated sodium channels NaV1.7, NaV1.8, or NaV1.9 co-express AR. Importantly with respect to the potential impact on migraine, AR in the human TG is also co-expressed with CGRP (13.63 % co-express AR), Substance P (6.71 % co-express AR), and PACAP (13.67 % co-express AR). These neuropeptides, along with others, have been either directly linked or associated with migraine in animal models

Table 4
Androgens-related interventions effects on migraine.

Study	Sample (age)	Intervention	Migraine related measure(s)	Results
Lichten et al., 1991	131 women with hormonal related migraine unresponsive to standard medication (age range 20–51)	Danazol 200 mg twice daily *Month 1: hypoglycemic diet* *Month 2: diet + acetazolamide 125 mg daily* *Months 3 + 4: diet + acetazolamide + danazol*	Headache occurrence Headache frequency headache intensity	• 63 % reported 75 % decrease in headache. • Association between age and danazol treatment effect (75 % of patients < 40 years old had headache relief compared to 32 % of patients < 30 years old)
Glaser et al., 2012	27 women with symptoms of androgen deficiency and a chief complaint of migraine headache (47.4 ± 9.6)	Testosterone for 3 months, delivered subcutaneously in a sustained release pellet implant with a weight-based dose of 130 ± 19.7 mg (range 100–160 mg)	Headache intensity	Reduction in migraine headache severity after testosterone therapy

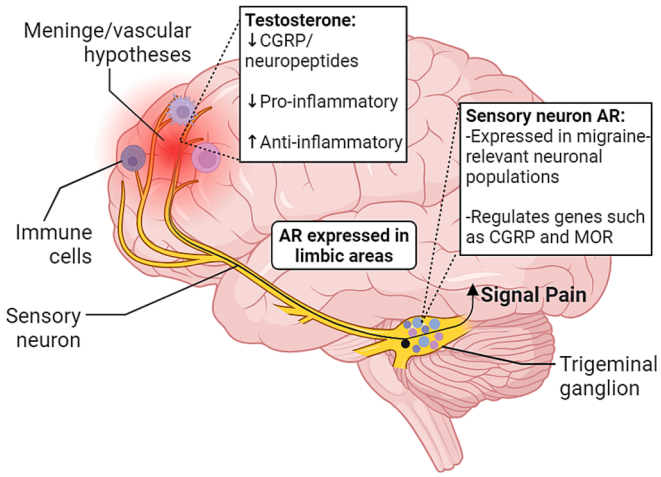

Fig. 3. Potential androgen signaling mechanisms contributing to the sensory component of migraine. Migraine is a multimodal disease that can be explained, in part, by sensory neuron innervation of the meninges from the trigeminal ganglia. In this space there are neuroimmune interactions, which testosterone has the ability to modulate by potentially decreasing neuronal release of CGRP and inflammation. Multiple sensory neuron subtypes express androgen receptors (AR) including nociceptors and cells containing neuropeptides important for migraine pathophysiology. Together, it may be that a reduction in testosterone contributes to migraine.

(Guo et al., 2021) and patients (Nicolodi and Del Bianco, 1990, Demartini et al., 2023, Alpuente et al., 2024). Revelations using this sequencing analysis imply that a proportion of the neurons suspected to contribute to migraine pathology have the potential to be modulated by testosterone, but this technique does not demonstrate protein availability nor a functional impact of AR on these neuronal subtypes.

Other methods allow assessing how testosterone and ARs can functionally affect sensory neurons. In male adult rats, about half of DRG lumbar six (L6) and sacral one (S1) neurons, which partially innervate visceral and reproductive organs, are immunoreactive for ARs, with about half of those also expressing calcitonin gene-related peptide (CGRP) (Keast and Gleeson, 1998, Herweijer et al., 2014). CGRP is important in meningeal migraine pathophysiology (reviewed elsewhere (Wattiez et al., 2020, Ray et al., 2021, Guan et al., 2023)) and a target for newly developed migraine therapies. In female swine, repeated testosterone injections decreased ovary innervating DRG neurons immunoreactive for CGRP/Substance P (SP) positive neurons but significantly increased the overall number of small and large diameter AR expressing neurons (Jana et al., 2016). *In vitro*, androgens enhanced neurite growth (Ward et al., 2021) and reduced the release of CGRP (Zhao et al., 2011) from DRG neurons. *In vivo*, these studies found that androgen receptors are necessary for axon regeneration (Ward et al., 2021), and DHT treatment results in reduced dermal CGRP levels in mice (Zhao et al., 2011). In the rat TG, AR is expressed in cells of all sizes, with enrichment in small to medium-diameter neurons (Lee et al., 2016). Testosterone may be physiologically relevant in TGs because AR was found to be a transcriptional regulator of the cannabinoid receptor type 1 (CB1) and the μ-opioid receptor which had increased expression after inflammation, which was blocked by flutamide (Lee et al., 2013, Lee et al., 2016). Both of these factors have been proposed as modulators of migraine pathology (DaSilva et al., 2014, Lo Castro et al., 2022). Together, these animal studies may suggest physiological relevant effects of androgens on sensory neurons as increasing the levels of androgens can reduce CGRP release by sensory neurons and increase μ-opioid receptor expression in TG neurons (Fig. 3). Important information would be gained from future analyses investigating how androgens change sensory neurons physiology and transcriptome.

4.2. Interaction with the immune system

The immune system has direct effects on the pathophysiology of migraine. Common treatments include dampening immune mediators to help manage migraine, such as nonsteroidal anti-inflammatory drugs (NSAIDs) (Pardutz and Schoenen, 2010), and newer therapeutics involving neuroimmune signaling pathways, such as targeting CGRP (Aguilar-Shea, Membrilla Md et al., 2022). The immune system is made up of a number of different cell types, many of which express AR, including hematopoietic stem cells, monocytes and macrophages, and neutrophils. In many cases, these cells respond to testosterone, often reducing inflammation (Gubbels Bupp and Jorgensen, 2018). In macrophages, an important cell type of the innate immune system, testosterone reduces mouse pro-inflammatory associated receptor toll-like receptor 4 (Rettew et al., 2008), and human macrophage proliferation *in vitro* (Cutolo et al., 2005). COX-2, an important target of NSAIDs is downstream of toll-like receptor 4 and thus, may be affected by testosterone (Chen et al., 2021). In castrated mice, there is an increase in the adaptive immune system T cells with signaling pathway changes similar to men undergoing androgen deprivation (Kissick et al., 2014). In men, higher testosterone levels relate to higher levels of the anti-inflammatory cytokine IL-10 and lower levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Maggio et al., 2005, Nettleship et al., 2007, Mohamad et al., 2019). In addition, in a random double-blind placebo-controlled study of men with androgen deficiency, testosterone replacement therapy decreased serum levels of the pro-inflammatory cytokines, IL-1β and TNFα, compared to placebo (Malkin et al., 2004). C-reactive protein is a common inflammatory biomarker that is elevated in patients with migraine (Lippi et al., 2014). High levels of C-reactive protein correlate to low levels of testosterone in men and to low levels of sex-hormone binding globulin in women in a population with major depressive disorder (Lombardo et al., 2024). Despite this evidence of testosterone reducing inflammation, men are more susceptible to severe infection than women (Gay et al., 2021) and transitioning men have reduced type-1 interferon response, but an increased monocytic pro-inflammatory response (Lakshmikanth et al., 2024). Also, there are cases in which there is no change in pro-inflammatory factors following testosterone replacement therapy (Ng et al., 2002). Additional studies will be necessary to reveal if there are particular testosterone-susceptible immune factors and how the context may impact the role of testosterone on immunity. These examples display what seems to be a predominant anti-inflammatory effect of testosterone on immune cells, which have been reviewed in depth recently (Gubbels Bupp and Jorgensen, 2018, Mohamad et al., 2019).

There are inconsistent results on the alterations in cytokine levels in patients with migraine compared to healthy controls, with reports of higher, lower, and no differences in both anti- and pro-inflammatory cytokines IL-10, IL-4, IL-6, TNF- α, and IL-1β (Thuraiaiyah et al., 2022). These inconsistent results are found in patients with migraine during the ictal and interictal phases(Thuraiaiyah et al., 2022). IL-17A is a proposed cytokine involved in migraine with both increased serum levels and the ability to cross the blood–brain barrier in the mouse NTG model (Chen et al., 2022). While the role of IL-17A on migraine causation is currently unknown, children with migraine have increased levels of IL-17A (Yang et al., 2024). In mice, IL-23/IL-17A induced mechanical sensitivity selectively in females and could be prevented by treating females with testosterone and, induced in males by treating males with an AR antagonist. These data indicate that mechanisms in females, such as IL-17A signaling, promote pain and possibly migraine, while testosterone actively prevents this sensitization (Luo et al., 2021).

4.3. Effects on the vascular system

Testosterone has a vasodilatory effect, and it can increase the relaxation of arteries and reverse the contraction effect of various agents such as prostaglandin or potassium chloride in animal models (Tep-

areenan et al., 2002, Jones et al., 2004, Herring et al., 2013). In patients with coronary artery disease, testosterone administration has a vasodilatory effect (Kang et al., 2002). Similarly, DHT and DHEA can also produce vasodilatation (Perusquía et al., 2018). The vasodilatory effect may be due to genomic actions such as gene express modifications, or nongenomic actions through noncanonical membrane bound proteins (Lorigo et al., 2020). However, interestingly, a few studies also found a vasoconstriction effect of testosterone (Ceballos et al., 1999, Ammar et al., 2004).

Understanding the impact of testosterone on migraine from a vascular mechanism is challenging. Vasodilatation has been considered a source for migraine headaches and medications that have a vasoconstriction effect have been developed and used to treat migraine (Jacobs and Dussor, 2016). However, this theory has been challenged as the administration of vasoactive intestinal peptide to patients with migraine caused vasodilatation but failed to evoke a headache (Rahmann et al., 2008). In addition, some vasoconstriction agents do not relieve migraine headaches and could even cause headaches (Brennan and Charles, 2010). Thus, it is unclear if vasodilatation is a cause of migraine headaches or if it is a secondary event of other migraine-related processes (Jacobs and Dussor, 2016, Levy et al., 2019). It is also possible that blood vessels have important roles in the pathophysiology of migraine, which are not related to dilation/constriction (Brennan and Charles, 2010, Jacobs and Dussor, 2016, Levy et al., 2019). Vascular cells respond to and release factors such as nitrous oxide that could contribute to migraine, particularly in the meningeal space (Jacobs and Dussor, 2016) (Fig. 3). Androgen receptors are expressed in blood vessel cells such as endothelial cells and vascular smooth muscle cells (Torres-Estay et al., 2015). Androgens have numerous effects on these cells, including stimulating nitrous oxide production (Yu et al., 2010) and promoting endothelial cells repair after injury (Cai et al., 2011). Together, it may be that testosterone contributes to vascular changes in migraine, although the exact mechanism and impact are not clear yet.

4.4. Brain function

Testosterone can cross the blood–brain barrier (Pardridge and Mietus, 1979, Banks, 2012) and acts on brain regions by binding to ARs. ARs are presented in the limbic system, which is involved in regulating emotion and behavior (Fig. 3). In this review, we focus on the amygdala and hypothalamus because they represent key testosterone targets (Kashon and Sisk, 1994, Cooke, 2006, Sarkey et al., 2008, Fernández-Guasti et al., 2022, Coolen et al., 2023) and are involved in pain processing and migraine pathophysiology (Simons et al., 2014, Burstein et al., 2015, Neugebauer, 2015, Russo et al., 2017, Thompson and Neugebauer, 2017, Zhang et al., 2023) and thus can mediate the effect of testosterone on migraine. Importantly, other brainstem and cortical brain regions could also be relevant; in healthy participants, testosterone levels were correlated with periaqueductal gray and rostral ventromedial medulla activation in response to noxious stimuli (Vincent et al., 2013) and orbitofrontal and anterior cingulate cortex activation in response to noxious stimuli was dependent on testosterone levels (Choi et al., 2017).

Amygdala activation in response to tasks and noxious stimuli is positively correlated with testosterone levels (Derntl et al., 2009, van Wingen et al., 2009, Manuck et al., 2010, Vincent et al., 2013, Heany et al., 2016). Moreover, in a social threat task in which angry, fearful, or happy faces are presented, amygdala activation is heightened after exogenous testosterone is given to healthy women (Hermans et al., 2008, van Wingen et al., 2009). For migraine, differences in amygdala structure and functional connectivity with various brain regions, including the somatosensory, prefrontal, cingulate, and insular cortices, are found in patients with migraine compared to healthy controls (Hadjikhani et al., 2013, Schwedt et al., 2013, Faria et al., 2015, Chen et al., 2017, Chong et al., 2017, Nahman-Averbuch et al., 2022, Zhang et al., 2023, Kosuge et al., 2024). Amygdala connectivity is also related to the response to migraine treatment. In adolescent with migraine, greater response to cognitive behavioral therapy is related to greater reduction in amygdala connectivity with the dorsolateral prefrontal cortex and paracingulate gyrus (Nahman-Averbuch et al., 2020). Moreover, the reduction in headache frequency after cognitive behavioral therapy was predicted by the baseline amygdala functional connectivity with frontal areas (Nahman-Averbuch et al., 2021). Together, these data suggest that the amygdala may be involved in migraine pathophysiology and is influenced by testosterone levels. The amygdala can also impact migraine indirectly via its involvement in anxiety regulation (McHenry et al., 2014).

The hypothalamus is another brain region that can mediate the effect of testosterone on migraine. The hypothalamus' role in migraine has been extensively studied, and it is thought to play a key role in migraine pathophysiology (Burstein et al., 2015). The hypothalamus is also involved in testosterone synthesis via the secretion of GnRH, which initiates the GnRH-LH/FSH- gonadal axis (Naamneh Elzenaty et al., 2022, Sharma et al., 2022). There is bi-directional activity between the hypothalamus and testosterone levels, as the hypothalamus structure changes in response to testosterone therapy in transgender males (Kranz et al., 2018). In patients with migraine compared to healthy controls, the hypothalamus resting state functional connectivity is increased with areas such as the cerebellum, medial prefrontal cortex, and caudate but decreased with areas such as the superior frontal gyrus, lingual gyrus, and fusiform gyrus (Moulton et al., 2014, Coppola et al., 2020, Schramm et al., 2023). Importantly, the hypothalamus exhibits a reduction in functional connectivity with the insula and brainstem areas immediately before a migraine headache attack and thus is thought to be involved in generating the headache (Schulte and May, 2016, Meylakh et al., 2020, Stankewitz et al., 2021).

4.5. Stress response

Patients with migraine report more life stressors (De Benedittis et al., 1990, Sauro and Becker, 2009). In addition, a speech stress paradigm evoked high physiological reactions in both patients with migraine and healthy controls, however, patients with migraine still had high pulse rates at the recovery phase which indicates a higher physiological response to stress (Holm et al., 1997). Moreover, a recent meta-analysis based on 10 papers found elevated cortisol levels for patients with migraine as compared to healthy controls (Beech et al., 2023). Sex differences in the relationships between stress and migraine severity are also found. Men with a high headache frequency had higher perceived stress (based on a survey) compared to men with a lower headache frequency, but this was not found for women (An et al., 2019).

Testosterone can suppress the activity of the hypothalamic–pituitary–adrenal axis, as there are opposing interactions between the hypothalamic–pituitary–adrenal and hypothalamic-pituitary–gonadal axes (Viau, 2002). In effect, higher testosterone levels can lower levels of glucocorticoids and other stress hormones (Viau and Meaney, 1996). In rats, stress induces visceral hypersensitivity as assessed using the visceral motor response (Ji et al., 2018). In females, this hypersensitivity was blocked by testosterone treatment or ovariectomy, and in males, it was exacerbated by estrogen treatment or orchiectomy (Ji et al., 2018). In rats, the animal's stress response can be modulated by whether they experience neonatal handling (NH) or not. Males are protected from stress-induced muscle pain as adults if they experience NH, but this effect was attenuated by orchiectomy or reduction of ARs by intrathecal injection. In females, NH was less protective against muscle pain, and ovariectomy and estrogen inhibitors did not significantly increase protection (Hermans et al., 2007). Together, these data suggest that testosterone has modulating roles on the stress response and cortisol levels, which can mediate multiple pain phenotypes, including migraine.

4.6. Mood

Anxiety and depression are comorbidities common in people living with chronic pain, including migraine (Minen et al., 2016, Vinall et al., 2016, Buse et al., 2020). There are bidirectional relationships between migraine and anxiety/depression, as individuals with migraine have an increased risk of elevated anxiety and depression scores, and individuals with anxiety and depression have an increased risk of being diagnosed with migraine (Giri et al., 2022). For patients with migraines, increases in headache frequency, intensity, and disability are observed in those with anxiety and depression compared to those without (Duan et al., 2023). Similar to migraine, mood disorders are more commonly diagnosed in women, and fluctuations in sex hormone levels are associated with diagnosis and symptoms of anxiety and depression (Reardon et al., 2009, Faravelli et al., 2013, McHenry et al., 2014). For men, anxiety and depression are more frequently diagnosed after initiation of treatments that reduce testosterone levels (Shores et al., 2004, DiBlasio et al., 2008). For menopausal women or for patients of both sexes with depression, testosterone treatment can improve symptoms of anxiety and depression (Shifren et al., 2000, Miller et al., 2009, Glaser et al., 2011, McHenry et al., 2014). Thus, the effect of testosterone on migraine could be via decreasing anxiety and depression symptoms.

5. Conclusion

Multiple studies in animals have shown a clear anti-nociceptive effect of testosterone, and intriguing, though limited, data in mouse models points to a protective role for testosterone in migraine pathogenesis. The current lack of additional animal studies to investigate testosterone and migraine is likely representative of an unmet need to develop better migraine animal models (see Begasse de Dhaem, for an overview of current models and their limitations (Begasse de Dhaem et al., 2023). As advances in the pathophysiology of migraine are achieved, it will be necessary to establish more relevant animal models with more accurate behavioral readouts. Animal studies should prioritize testing the head area since in patients with migraine, alterations in experimental pain sensitivity in some modalities are present only in the head/neck regions (Nahman-Averbuch et al., 2018). New technologies which track spontaneous pain-like behaviors, such as grimace (McCoy et al., 2024), will also increase the validity of migraine animal models. These methods may be more representative of the spontaneous pain during a headache attack rather than evoked experimental pain. Despite the limitations in animal models, the results on the effect of testosterone on migraine are more consistent than the results found in human studies. In humans, overall, androgen levels do not differ between individuals with or without migraine. Also, there is no consistent relationship between androgen levels and migraine severity, although comparing results among studies is challenging due to heterogeneous methodologies and variability in outcome measures. This may suggest that androgens may have a minor effect on migraine. However, most prior studies have limitations including small sample size, lack of controlling for key factors which can impact hormone levels, no blinding of the researchers to the participant group and not including a control group (Supp. Table 1). Thus, despite the lack of significant impact of androgen on migraine, there are many unanswered questions regarding the role of androgens in migraine pathophysiology. Androgens, specifically testosterone, given its direct effects on many of the players involved in migraine, may be involved in migraine pathophysiology in a sub-group of patients. A candidate sub-group is patients who have migraine onset or worsening during puberty or menopause as life periods with significant changes in sex hormone levels. In two studies that focused on postmenopausal women, testosterone levels were lower in women with compared to without migraine (Li et al., 2018, Tang et al., 2021). Although there is a large individual variability in testosterone levels, overall testosterone levels decline with age (Davison et al., 2005, Al-Azzawi and Palacios, 2009), and it is possible that postmenopausal women with migraine who have significantly lower levels of testosterone may benefit from testosterone therapy for migraine management. It is also possible individuals with an underlying susceptibility to migraine may respond differently to the same level of androgens/testosterone compared to other individuals, potentially resulting in a relative deficit with the same absolute levels (van Oosterhout et al., 2018). Testosterone may impact migraine via its effect on 1) sensory neurons and reducing CGRP levels, 2) the immune system by increasing anti-inflammatory and decreasing pro-inflammatory cytokines, 3) vascular system via its vasodilatation/vasoconstriction effects or by impacting vascular signaling, 4) reducing stress, 5) impacting brain limbic regions, such as the amygdala and hypothalamus, which are involved in pain processing and migraine pathophysiology, and 6) mood by reducing anxiety and depression (Fig. 2).

Future animal and human studies are needed to better understand the role of androgens in migraine pathophysiology. Additionally, there is a great need for consistency in the type of androgen measured (total, bioavailable, or free testosterone), methodologies used (immunoassays, mass spectrometry), and sample source (blood, saliva, urine) in order to compare among studies. Identifying how changes in androgen levels impact changes in migraine severity may guide the development of new treatments for migraine. In addition, studies determining the mechanisms underlying the effect of testosterone and other androgens on migraine are critical to understanding the potential anti-nociceptive effect of testosterone. Finally, animal experiments should directly assess the effect of androgens on sensory functions and migraine, without the caveats of a gonadectomy which has various biological effects (Hooper et al., 1986; Bensreti et al., 2023). Identifying mechanisms will allow for targeted therapies and improved management options for people living with migraines and potentially for those with other types of chronic pain.

CRediT authorship contribution statement

Adam J. Dourson: Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation. **Rachel S. Darken:** Writing – review & editing, Validation, Data curation. **Thomas J. Baranski:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Robert W. Gereau:** Writing – review & editing, Validation, Data curation. **Whitney Trotter Ross:** . **Hadas Nahman-Averbuch:** Writing – original draft, Visualization, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

- AJD: Acquisition of data, and drafting the article.
- RSD: Interpretation of data and revising the manuscript.
- TJB: The design of the study, interpretation of data, and revising the manuscript.
- RWG: Interpretation of data and revising the manuscript.
- WTR: The design of the study, interpretation of data, and revising the manuscript.

- HNA: The conception and design of the study, acquisition of data, interpretation of data and drafting the article

Appendix A. Supplementary data

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Further reading

The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia **33**(9): 629-808.