Sex Hormones and Glutamatergic Neurotransmission: A Review of the Literature

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Abstract

Glutamatergic dysfunction has been implicated in the pathophysiology of a variety of conditions, including epilepsy, chronic pain, multiple sclerosis, Alzheimer's, Parkinson's, and certain psychiatric conditions. This has led to interest in how to potentially modulate glutamatergic neurotransmission. Emerging research suggests an interactive effect between sex hormones and glutamatergic neurotransmission. The objective of this paper is to review the existing literature on sex differences in various neurological and psychiatric conditions, as well as known interactions between sex hormones and glutamatergic neurotransmission. This paper also summarizes what is known about the potential mechanisms for these effects, and the response to direct modulation of sex hormones in conditions where dysregulation of glutamate has been implicated in the pathophysiology. Scholarly papers were identified using academic databases, using the search terms “glutamate” “estrogen” “progesterone” “testosterone” “glutamate and sex hormone interaction” “glutamate and estrogen interaction” “glutamate and testosterone interaction” “glutamate and progesterone interaction,” and information was sought on the role of glutamate and sex hormones in conditions where glutamate is thought to be dysregulated. Papers were included in the review if they met the following criteria: peer reviewed original research from an academic journal that provided information on either: an interaction between glutamate and sex hormones, general hormonal interaction with neurotransmitters, or interaction within a specific neurological or psychiatric condition where dysregulation of glutamate has been implicated. The current evidence suggests that sex hormones can directly modulate glutamatergic neurotransmission, with specific protective effects against excitotoxicity noted for estrogen. Interestingly, two studies included here also demonstrated an effect of monosodium glutamate (MSG) consumption on sex hormone levels, which suggests the potential for a bi-directional effect. Overall, there is a good deal of evidence

suggesting a role for sex hormones, and specifically for estrogen, in the modulation of glutamatergic neurotransmission. Future research should evaluate how this information may be used to inform future treatment options.

1. Introduction

Dysregulation of glutamatergic neurotransmission has been implicated in many neurological and psychiatric disorders, including Alzheimer's (Scott et al., 2011; Fayed et al., 2011), Parkinson's (Griffith et al., 2008), epilepsy (Cavus et al., 2008), chronic pain, (Moloney et al., 2016), obsessive-compulsive disorder (Rosenberg et al., 2004), depression (Rosenberg et al., 2004), ADHD (Maltezos et al., 2014), and PMDD (Liu et al., 2015). Glutamate is the most common excitatory neurotransmitter in mammalian nervous systems and, as such, glutamatergic neurotransmission can influence wide-ranging brain functions (Yang et al., 2011). Emerging research has demonstrated the importance of sex hormones in the regulation of glutamatergic neurotransmission. Thus, it is important to understand how estrogens, progesterone, and testosterone influence normal neurological function, as well as their possible role in neurological and psychiatric conditions. It is widely hypothesized that hormones can affect neurotransmission in a way that is regulatory and protective. For example, a previous review summarized evidence that 17β-estradiol (the major estrogen released by the premenopausal ovary, hereafter "estrogen") assists in glutamate re-uptake, resulting in the hypothesis that estrogen could possibly be used therapeutically in disorders where excess glutamatergic excitation has been implicated (Lee et al., 2013).

Since abnormal glutamatergic neurotransmission has been associated with so many neurological and psychiatric conditions, it is important to understand how each sex hormone may influence this important aspect of nervous system dysfunction. Thus, this review aims to summarize current knowledge on the influence of estrogen, progesterone, and testosterone on glutamatergic neurotransmission. A few examples of psychiatric and neurological conditions where sex hormone interactions have been implicated, will be reviewed in order to inform potential future research directions.

2. Methods

Research articles were identified via scholarly databases, including PubMed, Google Scholar, and ProQuest, as well as from the American University Library database. Articles were included if they were original research from peer-reviewed academic journals that dealt with glutamate, estrogen, progesterone, testosterone, glutamate and sex hormone interactions, or the potential impact of glutamate and sex hormone interactions in the following conditions: Alzheimer's, Parkinson's, chronic pain, epilepsy, multiple sclerosis, OCD, ADHD, and PMDD.

3. Results

3.1 Glutamatergic Dysregulation and Excitotoxicity

Excitotoxicity occurs when elevated levels of glutamate overstimulate neurons, resulting in issues including neuronal death (Dong et al., 2009). This phenomenon has been implicated in epilepsy. Glutamate levels have been previously reported to increase during spontaneous seizures, and a higher seizure rate has been associated with decreased hippocampal volume. It is thus hypothesized that seizures may reduce protective mechanisms and increase vulnerability to excitotoxicity (Cavus et al., 2008).

Neurological disorders such as Alzheimer's, multiple sclerosis, and Parkinson's also may be due to glutamatergic dysfunction. Evidence tends to agree that glutamatergic excitotoxicity plays a role in the pathology of multiple sclerosis. In a magnetic resonance spectroscopy (MRS) study conducted at 3T, examining brain measures of glutamate, levels were seen to be higher in the white matter of multiple sclerosis patients in comparison to controls, with elevated levels also appearing in acute, but not chronic lesions (Srinivasan et al., 2005).

Glutamatergic excitotoxicity is not the only route to neural dysfunction. Altered glutamate levels have also been associated with different types of dysregulation. For example, MRS research on the role of brain glutamate in obsessive-compulsive disorder (OCD) has actually shown reduced glutamate-glutamine (Glx) levels in anterior cingulate cortex of afflicted individuals (Yücel et al., 2008).

MRS data measuring brain glutamate has also shown a reduction in the Glu/Cr ratio in patients with Parkinson's, suggesting that glutamate decreases in the cerebral cortex in Parkinson's patients (Griffith et al., 2008). Other data has shown similar glutamate decline in patients with Alzheimer's, with lower levels of brain glutamate in Alzheimer's patients as compared to patients with mild cognitive impairment or healthy controls (Fayed et al., 2011) Again, these findings examined together show a more complex role for glutamate in neurological diseases beyond excitotoxic effects. Thus, in the quest to identify optimal treatments for conditions where glutamate dysregulation has been implicated, it is important to consider other factors which may be able to affect glutamatergic neurotransmission.

3.2 Sex Differences in Neurological and Psychiatric Conditions

One of the first steps in identifying potential effects of sex hormones is to look for differential disease onset/outcomes based on biological sex assigned at birth. Sex differences in glutamatergic signaling have been reported in animal research using rats (Al-Suwailem et al., 2018), which suggests that sex hormones may have the ability to alter glutamatergic neurotransmission in humans. One study, investigating the overarching theory of higher Alzheimer's prevalence in females compared to males, found differences in comorbidity, mortality, and potential sex related differences in the rates of symptomatic progression (Sinforiani et al., 2010). Postmenopausal women have been estimated to have a 2-3-fold

increased risk of Alzheimer's as compared to men (Gao et al., 1998; Henderson, 1997), and menopause characteristically reduces estrogen and progesterone (Andersen et al., 1999; Sherwin, 1999), making these hormones of interest in regards to sex differences in the prevalence of Alzheimer's. Another study, investigating depression symptoms as a potential risk factor for Alzheimer's and dementia, presented results indicating a sex difference in depressive symptoms as a risk factor in the development of these two conditions (Dal Forno et al., 2005). A different epidemiological study disagreed, revealing no significant difference in mortality or prevalence of Alzheimer's by sex, once controlling for age. These authors suggested that longer life expectancy of females is the primary reason for a higher level of female Alzheimer patients (Hebert et al., 2001).

Sex differences have also been observed in quality of life, disease burden, and motor impairment of Parkinson's patients, with a greater impact being seen in males than females (Lubomski et al., 2014). Studies have also seen Parkinson's symptom presentation to differ by sex, with females more affected by non-motor symptoms than males and males more affected by the characteristic motor symptoms than females (Solla et al., 2012). Lower testosterone and estrogen concentrations have also been observed in male Parkinson's patients when compared to a control group (Nitkowska et al., 2015).

Sex differences also appear to have an effect in both the onset and disease progression of multiple sclerosis (MS). Epidemiological studies have been pointing to an increased frequency of MS in the general population, with one reporting a 50-year increase in the sex ratio reflective of an expanding number of females with MS (Orton et al., 2006). Other data agree that females are affected at higher rates, but also point out that males are at risk for worse prognosis; gray matter atrophy, indicative of neurodegeneration, has been observed in more areas of the brain in males

with MS, as compared to females with MS and healthy, age matched controls (Voskuhl et al., 2020).

Sex differences have also been observed in epilepsy. The frequency of occurrence for specific seizure types, epilepsy syndromes, and related lifestyle factors (Kishk et al., 2019) as well as quality of life factors (Yue et al., 2011) and epilepsy subtypes (Christensen et al., 2005), have been observed to vary by sex. It is also notable that females with epilepsy have higher rates of menstrual and endocrine disorders, and that hormones are seen to potentially influence seizures during pregnancy (Benson and Pack, 2020). Moreover, in catamenial epilepsy, where seizures increase at certain points in the menstrual cycle, hormonal changes are thought to directly affect seizure occurrence during pregnancy (Benson and Pack, 2020).

Similar differences are also apparent in depression, chronic pain, and pain severity, with females being significantly more affected than males (Munce and Stewart, 2007). Depression rates are higher in individuals with chronic pain, and females report higher levels of chronic pain in almost every condition examined, including fibromyalgia, migraines, and arthritis (Munce and Stewart, 2007). Epidemiological studies have also found sex differences in other psychiatric conditions of interest, such as a higher prevalence of anxiety in females as compared to males (McLean et al., 2011), and some suggestion of sex difference in OCD based on obsession/compulsion type, comorbidities, and related social factors (Labad et al., 2008); though not all studies have observed sex differences in OCD (Cherian et al., 2014). ADHD is also well known for the differential in occurrence by sex, with a higher prevalence and symptom burden in males (Mowlem et al., 2019). However, it should be noted that there is the possibility of underdiagnosis of ADHD in females with the condition due to inattention being more common than hyperactivity in females, thus potentially delaying diagnosis (Mowlem et al., 2019).

The sex differences noted in the above studies lend credence to the idea that sex hormones may play a modulatory role in diseases and disorders where glutamatergic dysregulation has been implicated. Thus, it is important to also examine cyclical changes in hormones and how they potentially modulate glutamatergic transmission.

3.3 Hormonal Cycle and Pregnancy Effects on Glutamatergic Neurotransmission

Changes in blood glutamate levels have also been investigated in healthy females across the menstrual cycle, where estrogen and progesterone naturally fluctuate. Based on evidence that glutamate can be neurotoxic, and that estrogen and progesterone may counter this effect, researchers hypothesized that these sex hormones may regulate blood and brain glutamate levels (Zlotnik et al., 2011). In this quasi-experimental study, 45 menstruating adult females with normal cycles (and no hormonal birth control interference) were recruited, and 4 total blood samples were taken from each female at 4 different hormonal points in the cycle. Single blood samples were taken from 31 adult males as controls. The concentration of glutamate, estrogen, progesterone, glucose, glutamate-oxaloacetate transaminase (GOT), and glutamate-pyruvate transaminase (GPT) (enzymes that perform glutamate transformation when the required co-substrates are available) were measured in the blood, with the plasma levels of the different hormones of interest being examined. At the start of menstruation, blood glutamate levels were lower in the females as compared to the one time point evaluated in the males. GOT and GPT levels were higher overall in the males and there was no change across the cycle in GOT/GPT concentrations in females (Zlotnik et al., 2011). Females had different blood glutamate levels based on the day the samples were taken, with samples collected on days 7, 12, and 21, as well as the first day of the cycle (see below). When these glutamate levels were examined according to hormonal changes, results showed that blood glutamate levels had an inverse correlation with

plasma progesterone and estrogen levels, so as estrogen and progesterone levels rose, glutamate levels were reduced. Estrogen levels peaked at the third collection point, when blood glutamate was the lowest, and there was a small drop by the fourth collection point. Despite this, estrogen levels at the start of menstruation were still higher than the levels at the first and second time points, corresponding to lower blood glutamate concentrations at the fourth point in comparison to the first and second points. Researchers noted this as significant, since their previous work has demonstrated a connection between lower blood glutamate and better neurological outcome in rats after traumatic brain injury (Zlotnik et al., 2011). Earlier work has also demonstrated a bell-shaped neuroprotective curve by progesterone, but results suggest a potentially stronger role for estrogen in regulating blood glutamate in comparison to progesterone (Stein, 2008).

Other research on the effect of estrogen/progesterone on blood glutamate levels has focused on pregnancy, another time of significant hormonal change. In a quasi-experimental design, 116 adult pregnant females were assigned to three groups, based on the trimester of pregnancy (Tsesis et al., 2013). Single blood samples were collected and concentrations of estrogen, progesterone, glutamate, GPT, and GOT were measured, while blood glucose was also checked upon collection. Results showed a significant reduction of blood glutamate between the first and second trimesters, without a significant reduction between the second and third trimesters. Estrogen and progesterone increased in the second trimester, and then further in the third, showing an inverse correlation, similar to what was found in the Zlotnik study. Researchers took the results to indicate that once blood glutamate is maximally reduced, additional hormones have a minor effect, noting a previously observed bell-shaped reduction effect from progesterone. This study found no significant changes in GOT throughout pregnancy, while GPT concentration had a slight decrease in the third trimester (Tsesis et al., 2013).

One more recent study was done to measure brain glutamate levels during pregnancy, stemming from an interest in the neurochemical basis of major depression during pregnancy (McEwen et al., 2021). Using MRS, this quasi-experimental design measured glutamate and other metabolite levels in the medial prefrontal cortex of 21 pregnant subjects in the third trimester as compared to 14 controls. This study also examined changes in gray matter, where glutamate is frequently found. No difference was observed between medial prefrontal cortex glutamate levels in pregnant and non-pregnant controls after adjustment for gray matter percentage, though a significant gray matter decrease in pregnant females was observed (McEwen et al., 2021).

Understanding the effect of hormonal fluctuations on psychiatric outcomes is also important in the context of puberty. Emotional problems have been shown to increase during puberty, with more negative outcomes in adolescent girls than boys (Oldehinkel et al., 2011). To date, no research has evaluated the association between pubertal hormonal fluctuation and glutamate levels. Understanding how estrogen and progesterone may play a role in brain structure and glutamatergic neurotransmission during puberty, a time of hormonal fluctuation, may be important for understanding what may be driving the symptoms of mental illness in this age group.

3.4. Potential Mechanisms of Interaction between Glutamate and Sex Hormones

3.4.1 Estrogen

Estrogen has been shown to be effective in protecting neurons from excitotoxicity caused by glutamate (Singer et al., 1996; Zhao and Brinton, 2006)). In vitro studies have demonstrated that estrogen (commonly abbreviated as E) can increase the uptake of glutamate in astrocytes, thereby helping to prevent excitotoxicity (Liang et al., 2002). Estrogen may be able to activate

signaling between metabotropic glutamate receptors through the stimulation of estrogen receptors, showing a potential interaction at the receptor level (Boulware, 2005).

The interaction and the mechanistic actions that take place between sex hormones and glutamatergic neurotransmission have also been examined in animal models. A study by Diano and colleagues in 1997 focused on AMPA glutamate receptors in the hypothalamus, septum, and amygdala of rats (Diano et al., 1997). It was hypothesized that gonadal steroid signals regulate the expression of glutamate receptors localized in the limbic and hypothalamic areas, and immunocytochemistry confirmed the co-expression of AMPA, GluR1/2/3, and androgen or estrogen receptors in the septum, amygdala, and hypothalamus of rats. Male and female rats were hormonally manipulated, and glutamate receptor expression was assessed. Results showed that estrogen and testosterone had a stimulatory effect on AMPA receptor expression in the hypothalamus, and that estrogen treatment also increased the presence of glutamate receptors in the hypothalamus, a change that was higher in females than males (Diano et al., 1997). This important study identified both co-localization of glutamate and androgen receptors and modulation of glutamate receptors in certain brain regions following treatment with estrogen.

Estrogen is also potentially neuroprotective against excitotoxicity induced by ischemia. Long-term administration of estrogen in rats was shown to protect visual and spatial memory affected by global ischemia, and acute estrogen administration protected visual memory and neuronal survival after induced global ischemia (Gulinello et al., 2006). Another study demonstrated that estrogen receptor α and β specific agonists were able to protect hippocampal CA1 neurons during ischemia (Miller et al., 2005).

A direct interaction between estrogen receptor α and metabotropic glutamate receptor 1a has also been observed in rats that underwent hormonal treatment, providing further evidence of estrogen receptor activity in hormonal and glutamatergic interaction (Dewing et al., 2007).

Another study supported this observation, reporting that estrogen treatment increased the internalization of both metabotropic glutamate receptor 1 and estrogen receptor α (Dominguez and Micevych, 2010). This data is in line with the existing hypothesis of an estrogen receptor/glutamate receptor signaling unit, indicating the involvement of specific receptors in the hormonal/glutamatergic interaction (Dominguez and Micevych, 2010).

Excitatory amino acid transporters may also be affected by sex hormones. The expression of GLT-1 and EAAT3, two transporters that assist in glutamate uptake, tends to increase after ischemia (where glutamate levels are known to be elevated), and mRNA and protein levels of these transporters are further increased by progesterone and estrogen as compared to ischemia alone (Nematipour et al., 2020). Increased glutamate transporter expression is protective against excitotoxicity, as it helps remove excess glutamate from the synaptic cleft. Thus, this may be a direct reason for the protective effect of these sex hormones.

Estrogen may also be protective against glutamate induced oxidative stress. Glutamate excitotoxicity is known to cause oxidative stress via the induction of reactive oxygen species and the downregulation of glutathione production (Murphy et al., 1989). A recent study demonstrated that co treatment with estrogen, when administering a glutamate injection, effectively reduced oxidative stress when compared to the glutamate injection alone (Khan et al., 2021).
In summary, there is strong animal data to suggest a colocalization and direct interaction between estrogen and glutamate.

It is noteworthy that in addition to the animal studies mentioned above, several independent laboratories have documented the effects of endogenous estrogen on brain injury, seizure activity and memory performance. Garcia-Segura et al., (1999) showed that peripheral administration of estrogen decreased excitotoxic cell death in rats and mice. This team and others

have gone on to show that much of this neuroprotection occurs via estrogen synthesis in reactive astrocytes at and around the site of damage (Garcia-Segura, 2008; Giatti et al., 2019).

Perhaps counterintuitively, neural estrogen levels seem to promote seizure activity in rats. More specifically, hippocampal levels of estrogen are higher in rats following kainic acid-evoked seizure activity, and treatment with an aromatase (*estrogen synthase*) inhibitor decreases kainic acid evoked seizure activity (Sato & Woolley, 2017). Neural estrogen synthesis has also been shown to support memory function in rats and songbirds. Estrogen delivered directly to the hippocampus increases spatial memory performance in rats (see Taxier et al., 2019), and inhibition of estrogen synthesis impairs spatial memory function in zebra finches (Bailey et al., 2013; 2017). Taken together, studies on multiple species suggest a strong interaction between estrogen and glutamate-dependent neural function.

3.4.2. Progesterone

Progesterone is a primary sex hormone, but as demonstrated in some of the research discussed above, it is often investigated alongside estrogen, rather than individually. Because of this, literature solely evaluating the effects of progesterone is lacking. Despite this difference in research quantity, some studies have provided evidence that progesterone should be an item of consideration when examining sex hormones and glutamatergic neurotransmission. For example, one *in vitro* study using cerebral cortex slices found progesterone to potentially have neuroprotective mechanisms that protected against glutamate induced toxicity through different pathways via activation of the neuroprotective mitogen-activated protein kinase (MAPK) and phosphoinositide-3 kinase (PI3-K) pathways. Furthermore, progesterone also increased brain-derived neurotrophic factor (BDNF) levels, which similarly have been shown to have neuroprotective properties (Kaur et al., 2007). Similarly, a study using hippocampal slices

reported that pre-treatment with progesterone reduced glutamate-induced elevations in intracellular calcium levels (Goodman et al., 2002). Another earlier *in vitro* study also demonstrated the potential ability of progesterone to enhance the inhibitory response of Purkinje cells to GABA (the main inhibitory neurotransmitter which counters glutamate excitation), while also suppressing excitation from glutamate to reduce excitotoxicity in the brain (Smith et al., 1987). Thus, progesterone is thought to have neuroprotective action, though more research using animal models is needed to better understand the effects of progesterone *in vivo*.

3.4.3 Testosterone

In addition to estrogen and progesterone, it is important to also consider the modulating effects of testosterone on glutamatergic neurotransmission. In 2004, the potential ability of testosterone to amplify excitotoxic damage to oligodendrocytes was tested (Caruso et al., 2004). It is notable that oligodendrocyte damage and death is a feature of multiple sclerosis, a disease which is more common in females, yet potentially more harmful to males, giving credence to results showing that testosterone may amplify damage (Werner et al., 2001 ;Voskuhl et al., 2020). Caruso and colleagues prepared oligodendrocyte cultures from rat forebrains, exposed them to testosterone for 24 hours, and then gave them a toxic pulse of AMPA with cyclothiazide or kainic acid for 15 minutes. Cultures were incubated for an additional 24 hours and assessed for oligodendrocyte death through lactate dehydrogenase release. AMPA treatments with both cyclothiazide and kainic acid were found to cause oligodendrocyte damage, and testosterone application was shown to enhance AMPA and kainate toxicity, even inducing slight toxicity in cultures that were not exposed to these glutamatergic agents. Testosterone amplified the increase in Ca2+ triggered by the activation of AMPA/kainite receptors, thus giving oligodendrocytes a lower threshold for damage (Caruso et al., 2004). This *in vitro* data showing increased

susceptibility to excitotoxicity upon treatment with testosterone is in opposition to more recent animal data showing that testosterone may be protective against neurodegeneration. In a 2019 experiment, Carteri and colleagues tested the protective effects of testosterone in an animal model of traumatic brain injury (Carteri et al., 2019). Mice were subjected to cortical impact and were then injected with testosterone or vehicle treatments. While the vehicle group showed Ca2+ driven mitochondrial damage, the testosterone treated group showed significantly reduced damage (Carteri et al., 2019).

Overall, there are few basic science studies examining the direct effects of testosterone, and the existing data is conflicting; thus, more mechanistic research is needed.

3.5 Implications for Neurological and Psychiatric Conditions

3.5.1 Alzheimer's, Parkinson's, and Multiple Sclerosis

Currently, there are no data examining the interaction between sex hormones and glutamate in MS, Alzheimer's, or Parkinson's disease. In 2018, Wickens, Bangasser, and Briand published a review on sex differences in psychiatric disease, and they included a section of the paper which also examined how sex-based differences in glutamatergic transmission may influence Alzheimer's outcomes; thus, readers are referred to this prior article (Wickens et al., 2018).

3.5.2 Epilepsy

As previously mentioned, catamenial epilepsy is characterized by seizure frequency changes at different points in the menstrual cycle (Benson and Pack, 2020). Other research has also demonstrated a strong glutamatergic component of epilepsy (Cavus et al., 2008). Data supports an effect of both estrogen and glutamate simultaneously on epilepsy, with one study

demonstrating that estrogen may be effective in upregulating GLT-1 transporters, downregulating glutamatergic neurotransmission, and increasing positive outcomes overall in rats induced to have epilepsy (Sarfi et al., 2017). In a study investigating astrocytes and estrogen in the epileptic condition, female rats were ovariectomized and injected with pilocarpine for seizure induction. Results were investigated in in ovariectomy only group (control), a lithium-pilocarpine ovariectomy group with no estrogen treatment, a lithium-pilocarpine ovariectomy group with low estrogen dose, a lithium-pilocarpine ovariectomy group with a high dose of estrogen, and a sham group treated with lithium, diazepam, atropine sulfate, and sesame oil. Seizure duration and mortality were lowered with estrogen treatment, alongside other effects indicating potential neuroprotective properties. Notably, glutamate content in the hippocampus actually increased in the low estrogen group in comparison to all other groups, but decreased in the high estrogen group. Overall, results from this study suggest a potential protective effect of estrogen in epilepsy, alongside the potential ability for estrogen to regulate glutamate levels and excitability of neurons in epileptic conditions (Sarfi et al., 2017).

3.5.3 Chronic Pain

Animal research on pain sensitivity and the influence of sex hormones on glutamatergic neurotransmission has yielded notable results. A study from Moloney and colleagues investigated how the estrous cycle influences excitatory amino acid transport and pain sensitivity in the context of early life stress (Moloney et al., 2016). The estrous cycle is the reproductive cycle experienced by female rats, a 4-to--5-day cycle that approximates the menstrual cycle in female humans (Ajayi and Akhigbe, 2020). During the proestrus phase, comparable to the follicular stage in human females, estrogen rises, and then quickly declines in the estrus phase as follicle stimulating hormone (FSH) peaks (Ajayi and Akhigbe, 2020). Moloney and colleagues

identified glutamatergic neurotransmission and excitatory amino acid transporters to be important in the body's pain processing mechanisms, while also being interactive with estrogen receptors. The aim of the study was to investigate maternal separation (early life stress) and the estrous cycle as potential effectors on visceral pain sensitivity and excitatory amino acid transporters (EAATs). Female rat pups underwent maternal separation to emulate early life stress, and colorectal distension to induce pain. Estrous cycle stage was determined, and animals were assessed for pain threshold and behaviors, while postmortem brain tissue EAATs were assessed as well. The early-life stress group exhibited a lower pain threshold and increased pain behavior in comparison to the non-stressed group, with both groups demonstrating the lowest pain threshold and highest total pain behaviors in the proestrus phase. There was also a significant effect of estrous-cycle variation on pain behavior and threshold. Furthermore, estrous cycle phase was shown to have a direct effect on EAAT function, with function being reduced in both the estrus and proestrus phases. The cycle effects in stressed and non-stressed rats were found to be completely opposite: EAAT function in stressed rats was inhibited in low estrogen cycle phases, while in non-stressed rats, EAAT function was inhibited in high estrogen states (Moloney et al., 2016).

In a different study on sex hormones, glutamatergic expression and pain, estrogen and testosterone were compared. This research from Ji et al. investigated the hypothesis that estrogen is pronociceptive (pain encouraging) and testosterone is antinociceptive (pain blocking) in a stress-induced rat hypersensitivity model, based on female predominance in pain conditions (Ji et al., 2018). Adult rats of both sexes were subjected to a forced swim condition to induce stress, and then underwent colorectal distension to induce pain from which visceromotor response could be recorded. Groups of male rats were administered estrogen, while groups of female rats were administered testosterone. Results showed that stress-induced hypersensitivity lasted longer in

females than it did in males, and ovariectomy blocked visceral hypersensitivity, while orchiectomy facilitated it. Estrogen injections in male rats were found to increase visceral hypersensitivity, while testosterone in female rats attenuated it. Estrogen injected into males was shown to increase excitatory glutamate ionotropic receptor NMDA subunit type 1 expression, and decrease inhibitory metabotropic glutamate receptor 2 expression, after the stressful forced swim scenario. Researchers took the data to suggest that estrogen facilitates stress induced visceral hypersensitivity, while testosterone attenuates it, potentially through modulation of glutamatergic neuronal activity in the spine (Ji et al., 2018).

3.5.4 OCD

In 2017, Karpinski et al published a review paper reviewing *in vivo* and human research on a variety of neurotransmitters in relation to gonadal hormones (including estrogen, progesterone, and testosterone) in the pathology of obsessive-compulsive disorder (OCD) (Karpinski et al., 2017). In this paper, the authors reviewed gonadal hormone interaction with the dopamine, glutamate, and serotonin systems, which have all been implicated in OCD. In the section on glutamate, it was determined that glutamate's involvement in OCD is still inconclusive, but that hormones and glutamate may still potentially play a role in OCD (Karpinski et al., 2017). Since the publication of this paper, there has been no new original research examining the multi-component interaction of sex hormones and glutamate in the development and course of OCD, and thus readers are referred to this prior review article for information on glutamate and sex hormone interaction in OCD.

3.5.5 ADHD

Another psychiatric condition in which both hormones and glutamate are of interest is attention-deficit/hyperactivity disorder (ADHD). To date, there are no studies examining the relation of hormones with glutamate levels and symptom severity in ADHD; thus, this review will consider publications on ADHD and glutamate, and ADHD and hormones, in a separate fashion. In one study on this topic based on glutamatergic abnormalities in Tourette's and ADHD, children with Tourette's, ADHD, or both, were recruited alongside healthy controls (Naaijen et al., 2017). Proton magnetic resonance spectroscopy (MRS) was used to investigate frontal-striatal circuit glutamate concentrations, and results showed no group differences in the concentration of glutamate in the anterior cingulate cortex (ACC) and striatum, with variation also being unrelated to sex, medication, IQ, presence of tics, or ADHD symptom severity. Interestingly, ACC glutamate concentrations were found to be positively correlated with obsessive-compulsive symptoms in the patients with Tourette's (Naaijen et al., 2017). While researchers acknowledge that this data is preliminary and inconclusive, they conclude that these findings open the door for research on glutamate concentrations and obsessive-compulsive symptoms manifesting in Tourette's.

Another study conducted in adults with ADHD did find differences in Glx in adults with ADHD as compared to controls. In this quasi-experimental study, conducted based on preliminary evidence of glutamatergic involvement in ADHD, 40 adults with ADHD (24 naïve to medication, 16 on stimulants) were compared with 20 healthy controls (Maltezos et al., 2014). Proton magnetic resonance spectroscopy data was collected from the caudate nucleus/striatum, dorsolateral PFC, and the medial parietal cortex (selected as a 'control' region) for signaling from Glx and other metabolites, including creatine, N-acetylaspartate, and choline. Results showed ADHD patients had significantly lower Glx, creatine, and N-acetylaspartate concentrations in the basal ganglia, and lower creatine concentrations in the dorsolateral PFC,

with no difference between treated and untreated patients. Interestingly, Glx in the lower basal ganglia of untreated ADHD patients was associated with inattention symptoms, with lower concentrations correlating with higher symptom severity. Researchers concluded that the reduction in Glx concentration in ADHD patients is not a brain-wide effect, but is present in some locations, adding to the evidence that glutamatergic abnormalities are associated with ADHD (Maltezos et al., 2014).

Other investigations on glutamate and ADHD have been sex specific. In one study from Ende et al., impulsivity and aggression in the anterior cingulate cortex of females with ADHD and Borderline Personality Disorder (BPD) patients were investigated in relation to GABA and glutamate (Ende et al., 2016). For this study, 78 female participants were recruited, 26 with BPD, 22 with ADHD, and 30 healthy controls. Participants were evaluated for impulsivity and aggression, and single voxel 1H MRS was performed at 3T to examine glutamate to creatine ratios and GABA levels in the anterior cingulate cortex of participants. GABA levels were found to be lower in patients with ADHD, and impulsivity measures were positively correlated with glutamate and negatively correlated with GABA, while aggression was negatively correlated with GABA. Both BPD and ADHD patients had higher impulsivity, anger, and aggression scores. Researchers took this as evidence that levels of GABA and glutamate are associated with self-reports of impulsivity. While these data may have been limited by small group size, there is evidence for a potential role of glutamate in symptoms associated with ADHD and BPD (Ende et al., 2016).

In a study from Roberts and colleagues, ADHD symptoms were shown to vary across the menstrual cycle in young adult females (Roberts et al., 2018). This study examined estrogen, progesterone, and testosterone in relation to ADHD symptoms in 32 regularly cycling females, who completed a baseline measurement for impulsivity, provided saliva samples every morning,

and completed an ADHD symptom checklist every day for 35 days. This within-person study showed that when estrogen decreased and progesterone or testosterone increased, there were heightened ADHD symptoms the next day, an effect magnified by already heightened baseline impulsivity. It was indicated that low estrogen and progesterone predicted higher symptoms, while variation in testosterone was linked with increased ADHD symptoms. Results also showed symptom changes in line with cycle changes, with a suggested increase in symptoms during the early follicular, early luteal, or post-ovulatory phases (Roberts et al., 2018). While researchers acknowledged limitations regarding the use of a nonclinical sample, limited diagnostic information, lack of comorbidity exploration, and use of self-report, it was concluded that the results demonstrate steroid effects in ADHD symptoms and suggest that ADHD symptoms can be hormonally variable within females.

Overall, while there is no literature directly addressing of the interaction between sex hormones and glutamatergic neurotransmission in ADHD, there is literature that establishes a speculative role of both glutamatergic components and sex hormone components independently in ADHD pathology. Given that there is a known influence of sex hormones on glutamatergic neurotransmission, and that both components are potentially factors in ADHD, more original research is needed to examine if this interaction has a role in the pathogenesis and symptomatic maintenance of ADHD. Involvement of the menstrual cycle in this research is also an interesting consideration and future research should measure hormonal variations and how these relate to glutamatergic neurotransmission.

3.5.6 PMDD

Premenstrual Dysphoric Disorder (PMDD) is an important disorder to consider when examining the interaction between sex hormones and glutamatergic neurotransmission. PMDD

directly involves the menstrual cycle and is therefore reactive to hormonal fluctuations. Two studies have evaluated glutamatergic dysregulation in PMDD. One study evaluated glutamate fluctuations across the menstrual cycle of females with PMDD in comparison to control subjects (Batra et al., 2008). They recruited 12 PMDD patients, along with 13 healthy controls, and all diagnoses were confirmed with symptoms monitored for 2 cycles. MRS was used to measure various metabolites in the prefrontal cortex, including Glx (glutamate and glutamine combined). A phase effect was observed, in which both the PMDD and control groups had lower levels of glutamate/Cr in the luteal menstrual phase than they did in the follicular menstrual phase; however, no significant difference in Glx levels were noted across groups. Similar results were produced when ovulation was taken into account. The study was limited by its small sample size, but it does provide evidence that glutamatergic fluctuations do occur with monthly hormonal fluctuations in females (Batra et al., 2008). Researchers suggested that females with PMDD may be more reactive to the phase related glutamatergic alterations, warranting further research.

A later study from 2015 also investigated brain measures of glutamatergic and GABA alterations in participants with PMDD (Liu et al., 2015). GABA is the main inhibitory neurotransmitter in the CNS, and as such, plays an important role in balancing out the excitatory effects of glutamate, making it also of interest. Twenty-two PMDD patients and 22 healthy controls were recruited, and GABA and Glx levels were measured with MRS in the anterior cingulate cortex, medial prefrontal cortex, and the left basal ganglia. In all PMDD subjects, an increase in symptom severity was reported in the luteal menstrual phase, in comparison to the follicular menstrual phase, and scans were performed in the late luteal phase. Results showed that GABA concentrations were lower in the PMDD participants than they were in the controls in the anterior cingulate cortex, medial prefrontal cortex, and left basal ganglia. Results also showed increased Glx levels in the anterior cingulate cortex and medial prefrontal cortex in

PMDD females as compared to healthy controls (Liu et al., 2015; Zia et al., 2014). This suggests GABA and Glx abnormalities in patients with PMDD, which supports the idea that glutamate dysregulation is involved in PMDD (including reduced conversion of excitatory glutamate into the inhibitory neurotransmitter GABA, which could indicate a vitamin B6 deficiency in this disorder (Jung et al., 2019). More work is needed to understand how sex hormones and glutamate/GABA may be affected in PMDD.

3.6 Monosodium Glutamate Effects on Sex Hormones and Bidirectional Effects

While this literature review is intended to characterize the effects of sex hormones on glutamatergic transmission, it is important to briefly note a potential bidirectional effect where exposure to monosodium glutamate (MSG) resulted in altered hormonal levels. In a study from 2014, female Sprague Dawley rats were divided into three groups (no treatment, just MSG, or MSG and Diltiazem, a calcium channel blocker used for high blood pressure) with the MSG administered orally (Zia et al., 2014). After 2 weeks, the serum levels of estrogen and progesterone were then assessed. In the group where just MSG was administered, there was an increase in serum estrogen and progesterone levels when compared to the group given only a laboratory diet. Diltiazem, as described above, prevented this effect, as the group administered both MSG and diltiazem did not experience a significant increase in sex hormones, potentially though a prevention of an overload of calcium in the cells (Zia et al., 2014). Testosterone has also been reported to fluctuate in response to MSG. In a different experiment, male rats were divided into 4 groups which were administered water or MSG solutions by gavage (with concentrations of 0.25, 3, or 6 g/kg MSG) daily for 30 days (Iamsaard, 2014). Reproductive organs were examined through removal and morphological assessment, testosterone through enzymatic immunoassay, and sperm count through sperm collection and concentration analysis.

While some reproductive aspects were unaffected, plasma testosterone levels were found to be significantly lower in the 3 g/kg and the 6 g/kg MSG groups when compared to the controls (Iamsaard, 2014). Thus, it is important to keep in mind that there may be a bidirectional effect present when examining the interaction between sex hormones and glutamate.

4. Conclusion

Glutamatergic excitotoxicity and dysfunction have been implicated in a multitude of different conditions. Interestingly, the prevalence of many of these conditions also differ based on sex, implying the potential role of sex hormones in these conditions. Interaction between glutamate and sex hormones has been observed in disorders such as epilepsy and chronic pain. Mechanistic studies have also demonstrated that estrogen may be protective through its modulation of glutamate receptors and transporters. Understanding how this interaction may take place in the body can help with the development of treatment plans, potentially through hormonal modulation, with the aim of reducing harmful glutamatergic dysfunction. Future research should focus on improving our understanding of the mechanism of effect for testosterone, pubertal hormone effects on glutamate levels, and glutamate and hormonal interactions in instances of Alzheimer's, Parkinson’s, MS, and OCD, to help illuminate potential treatment options. Overall, understanding the interaction between glutamatergic neurotransmission and sex hormones may provide important information on key hormonal intervention points to inform treatment for affected individuals.

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