Anxiety Disorders: Sex Differences in Serotonin and Tryptophan Metabolism

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 doi:10.20944/preprints201808.0487.v1

Abstract

Introduction: Anxiety disorders manifest in women more than in men by almost twofold. This narrative review aims to summarize the sex-related biological factors, which underpin anxiety, focusing on the interactions of sex and tryptophan/serotonin with anxiety.

Methods: A literature search was conducted using Google Scholar, PubMed/MEDLINE, Scopus, and EMBASE databases from inception until December 31, 2017.

Results: This review shows that sex may interact with many serotonin functions thereby modulating anxiety, including 5-HT1A and 5-HT2C receptors, 5-HT transporter and central 5-HT concentrations and metabolism. Sex-steroids modulate the expression of serotonin transporter genes, creating a difference in serotonin availability. Sex and estrous cycle phases lead to varying anxiety responses to tryptophan depletion. Testosterone, progesterone and estrogen are important factors in mediating sex differences in serotonin responses to anxiety-generating behavioral tests. At prenatal levels, there are sex-related differences in the reciprocal relationships between serotonin and the HPA-axis, which modulate anxiety-like behaviors. Activated immune-inflammatory pathways induce indoleamine-2,3-dioxynease (IDO) and the tryptophan catabolite (TRYCAT) pathway thereby increasing tryptophan degradation and increasing the production of TRYCATs including kynurenine and quinolinic acid, which may create an overall anxiogenic effect. The effects of immune activation on IDO are significantly more pronounced in women than men and therefore females may show increased levels of anxiogenic TRYCAT following immune challenge. Aberrations in the IDO-activated TRYCAT pathway are found in pregnant females and parturients and are associated with increased anxiety levels in the postnatal period.

 doi:10.20944/preprints201808.0487.v1

Conclusions: The results of this review underscore the necessity of studying the associations between serotonin and anxiety in both sexes taking into account the effects of immune activation on IDO and production of anxiogenic TRYCATs. Future anxiety research should focus on the interactions between serotonin/tryptophan and sex, sex hormones, the menstrual cycle, pregnancy, the HPA axis and the immune system through production of anxiogenic TRYCATs.

Keywords: sex; anxiety disorders; 5-HT; tryptophan; immune system; inflammation

 doi:10.20944/preprints201808.0487.v1

Introduction

Anxiety disorders include Panic Disorder (PD), Generalized Anxiety Disorder (GAD), Phobias, and Post-Traumatic Stress Disorder (PTSD). PD consists of unexpected panic attacks that happen often and unexpectedly [1]. In the United States (U.S) and Europe, PD occurs in roughly 2% - 3% of adults and adolescents in a 12-month period, and even less so in children under 14 (0.4%). It is important to note that the female population shows a gradual increase in the incidence of PD during adolescence, with females who have PD also showing more panic attacks than males with PD [1]. GAD is when an individual has an uncontrollable and excessive worry over a variety of events and activities that can lead to the interruption of social, occupational, and other spheres of life. In the U.S., there is a 0.9% incidence rate in a 12-month period, and in other countries, a 0.4% to 3.6% incidence rate. Again, note that females are twice as likely to have GAD and females make up 55%-60% of those diagnosed [1].

Phobias are classified as the fear or worry about a specific object or situation to the point of social, occupational, and other impairments in life [1]. Within a 12-month period, the incidence of phobias occurs at roughly 7%-9% in the U.S., around 6% in Europe, and 2%-4% in Asian, African, and Latin American populations. Most notably however, is that females are twice as likely to have phobias than males. Social phobias are characterized by an intense fear or worry of social situations where they are vulnerable to judgment from others. Social phobia appears in about 7% of individuals in the U.S. This phobia appears in approximately 2-5% of adults in the U.S. within a 12-month period and these rates decrease with age. Approximately twice as many women have a social phobia than men [1].

PTSD is the development of troublesome symptoms (distressing memories or dreams, dissociative reactions, intense distress, negative cognitions or mood etc.) following an exposure

 doi:10.20944/preprints201808.0487.v1

to a traumatic event [1]. PTSD has an incidence rate of 3.5% in U.S. adults, and 0.5%-1.0% in Europe and most Asian, African, and Latin American countries. Females exhibit a higher prevalence of PTSD and for longer periods of time than males [1]. Whatever the form of anxiety, the ratio of women to men is about 2 to 1. It is therefore particularly interesting to identify the biological components that can explain these differences.

A person's sex is a biological clarification as to whether they possess female or male reproductive organs and hormones. An individual's gender is a social construct in which they choose to identify by, either masculine or feminine, and can be different in varying cultures or environments. It is important to study how anxiety materializes in both sexes in order to learn how to treat anxiety in the most appropriate fashion. Moreover, recent research shows significant sex-related differences in the associations between the metabolism of serotonin (5-HT) and its precursor tryptophan, anxiety, the hypothalamic-pituitary-adrenal (HPA) axis and immune functions [2], and therefore studying the sex differences present in the manifestation of anxiety is important. Without further study, anxiety treatments would remain unspecified to people of certain sexes, meaning treatments may not be as effective, which would then lead to further health complications and worsening of symptoms. Therefore, the purpose of this review is to describe how serotonin and tryptophan interact with sex and other factors to affect anxiety levels.

Methods

This paper will discuss the sex differences and the interaction between anxiety and serotonin metabolism, not the gender differences. This review aims to foster the understanding of how serotonin and tryptophan levels can vary in different sexes, how serotonin and tryptophan interacts with sex hormones, pregnancy, the cortisol axis, and the immune system, and how that

 doi:10.20944/preprints201808.0487.v1

consequently affects the prevalence of anxiety disorders in an individual of a certain sex. We performed a literature search using Google Scholar, PubMed/MEDLINE, Scopus, and EMBASE databases from inception until December 31, 2017. The following keywords were used: sex (or menstrual cycle or sex hormones or pregnancy) and anxiety (or PD, GAD, PTSD or phobia); sex, anxiety and 5-HT (or tryptophan); sex, anxiety and biomarkers; sex, anxiety and immune (or inflammation); sex, anxiety and HPA-axis (or cortisol); and sex, anxiety and kynurenine (or quinolinic and xanthurenic acid); perinatal (or pre- and postpartum) anxiety and 5-HT (or tryptophan).

Overview of the serotonin metabolism

Serotonin has been studied for a long time and interest in it has increased in the past 20 years for a number of reasons: the introduction in clinical practice of the non-benzodiazepine anxiolytic buspirone, and the widespread use and success of antidepressants (Ads), in particular selective serotonin reuptake inhibitors (SSRIs), for treating anxiety disorders. The development of specific ligands for 5-HT receptors allows the visualization and the study of the multiplicity of 5-HT receptors and their functional role in disease. Further, the use of the tryptophan depletion technique in humans and molecular manipulation, and microdialysis studies in animals allows for a more rigorous assessment of the integrity of the 5HT-system in the CNS [3].

Serotonin is produced via the hydroxylation of tryptophan to form 5- hydroxytryptophan, and then the decarboxylation of the amino acid component to form serotonin (5-hydroxytryptamine or 5-HT) [4]. The amount of central 5-HT is in part determined by tryptophan availability in the plasma, which may be determined by the ratio of plasma tryptophan to other large neutral amino acid molecules, and free or total plasma tryptophan [2].

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The amount of tryptophan absorbed by the brain is determined by how much tryptophan is circulating in the body which is modifiable for example by carbohydrate or protein intake [2].

There are 14 types of serotonin receptors. Some serotonin receptors, for example 5-HT1A, are autoreceptors, which are receptors moderating the amount of neurotransmitter present in the synaptic cleft. If the autoreceptor senses that there is an excess of neurotransmitter in the synaptic cleft, the receptor will signal to the second messenger to terminate any further release of the neurotransmitter [5]. Therefore the 5-HT1A receptor, when stimulated, modulates serotonin release into the synaptic cleft and acts as a feedback mechanism. It mostly resides in the hippocampus, cortex, septum, and median raphe nucleus [4,6,7]. It can also be found on presynaptic and postsynaptic membranes [7]. The 5-HT2A receptor (5-HT2AR) is found in high density in the cortex, ventral striatum, hippocampus, amygdala, caudate nucleus, nucleus accumbens, and olfactory tubercle, with many signals arriving from the dorsal raphe nucleus (DRN) [7,8]. 5HT2AR is G protein-coupled and acts as a postsynaptic receptor [9]. Studies have shown that 5HT2AR signalling disruption leads to an increase in conflict-anxiety behavior, and that the restoration of 5HT2AR reverses the effects of the disruption [8].

Another important 5-HT receptor is the 5-HT2C receptor (5-HT2CR) [10]. The 5-HT2C receptor is G protein-coupled [11] and found on postsynaptic membranes [7]. A previous study found that the human gene HTR2C encodes for 5-HT2CR and is located on the X chromosome [7,12], suggesting that sexual polymorphisms can result from women having two X chromosomes and men having only one. This receptor plays an integral role in regulating dopamine in many areas of the brain, including the cortex, nucleus accumbens, hippocampus, amygdala, and basal ganglia [7]. 5-HT2CR may be a key component in the expression of anxiety. Kimura et al. (2009) [13] found that an overexpression of 5-HT2CR led to an increase in

 doi:10.20944/preprints201808.0487.v1

anxiety-like behavior following behavioral tests like the EPM and NOR. Furthermore Heisler et al. (2007) [14] discovered that a lack of 5-HT2CR led to a reduction in cortico-releasing hormone (CRH) neuronal activation following anxiety-inducing stimuli. Moreover, Strong (2012) [15] observed that 5-HT2CR is valuable in the expression of anxiety-like behavior in the dorsal striatum (DS) since the DRN projects to the DS where increases in 5-HT are mediated to control stress-induced behavior. In addition, activation of 5-HT2CR in the basolateral amygdala (BLA) is necessary for the expression of fear and interruption of learning in response to stress [15].

Lastly, the 5-HT3 receptor (5-HT3R) has also been found to play an important part in serotonergic turnover. 5-HT3R is most abundant in the hippocampus, amygdala, and upper surfaces of the cerebral cortex [7]. It is a ligand-gated ion channel residing on the membranes of presynaptic and postsynaptic neurons [16]. Studies have found that when 5-HT3R agonists are injected into the amygdala, there is an increase in avoidance behavior, and vice versa when 5-HT3R antagonists are injected [7]. Moreover, Bhatnagar et al. (2004) [17] determined that 5-HT3R-deficient female mice exhibited less anxiety than wild type (WT) females, since they spent more time on the open field test. Whereas 5-HT3R-deficient males spent less time than their WT counterparts, a behavior indicative of more anxiety. These results implicate 5-HT3R in the serotonergic mechanism and its relationship with anxiety. Therefore 5-HT1A, 5-HT2A, 5-HT2C, and 5-HT3 are all relevant receptors necessary in understanding the serotonergic system and its relationships with anxiety.

Serotonin and anxiety

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Disruptions in serotonergic systems have been associated with a variety of mental illnesses [18]. For example, serotonin is a key component in the manifestation of anxiety, proof of such is evident in its gene expression and transporter activity. Hariri et al. (2002) [19] discovered that individuals with one or both of the short alleles (s/*l* or s/s) transcribing for serotonin transporters (5-HTT), also known as SERT, showed higher levels of amygdala activity in response to a fearful stimulus when compared to their homozygous long allele control subjects. Furthermore, a study on polymorphisms in the serotonin-transporter-linked polymorphic region (5-HTTLPR) found that s/s monkeys exhibited more anxious behavior than monkeys with the long allele (*l*) [20]. Another study determined that serotonin transporter (SERT) synthesis failure led to anxiety-like behavior [21]. Olivier et al. (2008) [22] found that inactivating SERT removed sex differences in response behavior to anxiety-stimulating tests. Immunohistochemistry revealed that both male and female rats without SERT showed similar levels of basal extracellular serotonin. However, immunostaining found that there were no differences in DRN serotonin between rats with and without SERT [22].

The efficacy of serotonin-based drugs on treating anxiety-like symptoms also acts as evidence that serotonin is related to the manifestation of anxiety. For example, Venault et al. (2001) [23] found that treatment with SSRIs reduced anxiety-related balance impairments. Holmes et al. (2003) [24] determined that when a serotonin receptor antagonist was injected, 5-HTT deficient mice displayed anxiolytic behavior on the EPM as opposed to their counterparts [24]. On the other hand, Van der Wee et al. (2008) [25] reported that serotonergic abnormalities were not associated with clinical ratings of anxiety.

Tryptophan and Anxiety

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Tryptophan, being the amino acid precursor to serotonin, should also be taken into consideration when studying anxiety. Acute tryptophan depletion (ATD), as expressed in decreased levels of plasma tryptophan and hippocampal tryptophan, has been found to lead to increased anxiety-like behavior [26]. Robinson et al. (2012) [27] found that ATD increases anxiety-potentiated startle response in humans. Moreover, Silva et al. (2017) [28] demonstrated that a tryptophan-abundant diet led to greater levels of Fos-immunoreactivity (Fos-ir), and therefore brain activity, in areas of the brain responsible for mediating anxiety: the PFC, nucleus accumbens, paraventricular hypothalamus, arcuate and ventromedial hypothalamus, dorsolateral and dorsomedial periaqueductal grey, DRN, and median raphe nucleus (MRN). Hsiao et al. (2016) [29] found that TD led to increased activity in the sympathetic nervous system and decreased activity in the parasympathetic nervous system and that these effects were positively correlated with baseline anxiety scores. These studies show that altering levels of plasma tryptophan may affect the biological expression of anxiety.

More specifically ATD may exaggerate PD symptoms. For example, TD led to an enhanced level of panic in patients when 5% carbon dioxide was exposed to patients with PD [30]. Bell et al. (2011) [31] found that tryptophan-deficient individuals with PD had a return of panic symptoms following exposure to flumazenil, a benzodiazepine antagonist, despite cognitive behavioral therapy (CBT) treatment. A tryptophan-rich diet seemed to have a protective effect against panic whereas a tryptophan-poor diet led to an increase in panic in patients with PD [32]. This represents an increased vulnerability to anxiety in patients with tryptophan deficiency.

However, further complexities in the serotonergic system seem to arise as more research is conducted. For example Jans et al. (2010) [33] found that tryptophan depletion manifested

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behaviorally and neurochemically but in varying ways across different rat strains. Studies using healthy subjects found that males were not vulnerable to anxiety-like behavior following acute tryptophan depletion expressed by a decreased level of plasma tryptophan [34]. Acute tryptophan depletion and acute phenylalanine/tyrosine depletion (APTD) both produced an increase in heart rate, a behavior indicative of anxiety, in healthy women [35].

Sex and serotonin / tryptophan

Anxiety is the most abundant mental illness in the world, with approximately 7.3% or 1 in 13 people having anxiety of some form, with a majority of those being women [36]. Possible associations between serotonin/tryptophan and sex and between serotonin/tryptophan, sex, and anxiety are discussed in this section. For example, a chronic sugary diet decreased serotonin metabolism in the cortex and hypothalamus in female rats only [37]. Women had significantly more 5-HT1A receptors and significantly less 5-HTT binding potential than those of men in a substantial amount of brain regions [38], although Stein et al. (2008) [39] found disagreeing data using positron emission tomography (PET) scans from healthy subjects. Furthermore, Dawson et al. (2009) [40] concluded that the over-expression of the human SERT gene (hSERT) was able to modify glucose utilization in the medial striatum, globus pallidus, somatosensory cortex, mamillary body, and ventrolateral thalamus of females more so than males. These sex differences only just begin to highlight the complexities of the serotonergic mechanism and how certain factors can affect it.

Serotonin can also affect other systems and those effects may be mediated by sex. For example, Sachs et al. (2014) [41] found that female mice with dysfunctional tryptophan hydroxylase, an enzyme that synthesizes serotonin, had a decreased level of sucrose preference

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regardless of the stressor presented to them, a behavior indicative of anxiety. Females had a greater concentration of tritiated imipramine (IMI) than men in the right orbital cortex [42]. Since IMI targets the serotonergic system [43], it is implied that serotonin may act as a factor in determining sex differences. However, Nutt and Fraser (1987) [44] completed a study on patients with PD and found no differences in the concentration of [3H]imipramine in platelets between the sexes.

Some papers conclude that males have higher 5-HT functional activity in the ventromedial prefrontal cortex (vmPFC), amygdala, and insula than females since previous literature has exhibited females having acute reactions to serotonin challenges, suggesting possible serotonin upregulation [45]. Likewise, Misushima et al. (2006) [46] determined that males had higher levels of extracellular serotonin in the basolateral amygdala (BLA), but that females had higher levels of extracellular serotonin following 60 minutes of restrained stress overall. Whereas other papers show that females have higher levels of 5-HT synthesis, and consequently brain tryptophan concentrations, than males despite both being SERT deficient [47]. Christian et al. (2009) [48] stated similar findings that females had greater concentrations of 5-HTT available to the brain than males. Fehr et al. (2000) [49] genotyped male and female alcohol dependent patients, PD without agoraphobia, GAD, narcolepsy, and healthy controls and found that females in general had higher frequencies of 5-HT2C Serine 23 alleles than males. In depression, another affective disorder, there are significant inverse associations between the plasma ratio of tryptophan / competing amino acids (indicating the availability of plasma tryptophan to the brain) and self-rated depression, whereas in depressed men these associations were inverted a significantly differed from women [50].

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Contextual fear conditioning led to down-regulated 5-HT1A sensitivity in females, but MRN lesions down-regulated 5-HT1A sensitivity in males [6]. Grabe et al. (2005) [51] found an interaction between the short allele for the serotonin transporter gene (SLC6A4) and mental vulnerability to stress and chronic diseases. More specifically there was an interaction between the short allele, unemployment, and chronic diseases in females [51]. In addition, there are also interactions between sex and genotypes on the expression of neuroticism and agreeableness, the first of which is a trait associated with anxiety [52]. In other words, males with the short allele for 5-HTTLPR had a significant association with neuroticism scores. Moreover, para-chlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor, produced anxiolytic effects in males, which led researchers to believe the anxiogenic effects of serotonin were more evident in males [53]. Similarly, Naslund et al. (2013) [54] discovered that serotonin deficiency abolished sex differences present on the elevated plus maze (EPM). PCPA reduced serotonin levels and led to an increase in open arm entry and open arm time in males, but PCPA reduced closed arm entries in females. In a study that used rhesus monkeys, peer-only reared males had higher levels of 5-HIAA concentrations than females and their mother-reared counterparts [55]. In addition, 5-HIAA concentrations rose after an initial stressor was introduced, but eventually fell. These findings suggest that this serotonin metabolite interacts with sex and affects the expression of anxiety-related behaviors. 5-HT1A agonists may produce anxiolytic effects mostly in females, although males also exhibited decreases in anxiety-related behavior [56]. Overall, sex may interact with many serotonin functions, including receptor expression and 5-HT metabolism, to modulate anxiety.

Sex hormones, anxiety and serotonin / tryptophan

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With many differences in the response to serotonin between males and females, it is an appropriate assumption that these differences could be due to varying sex hormone levels like estrogen, testosterone, and progesterone. Studies found that there is a relationship between sex-steroids and the expression of serotonin transporter genes, creating a difference in serotonin availability [57]. Moreover, Gonzalez et al. (1994) [58] found that the effects of ritanserin, a 5-HT antagonist, manifested differently depending on the sex of the rat and their sex-steroid levels. Males with and without testosterone exhibited anxiogenic behavior in response to ritanserin injections, whereas females, androgenized or not, expressed anxiolytic behavior in response to ritanserin exposure [58]. Therefore it is implied that serotonin and testosterone affect male behavior in different ways.

Jans et al. (2007) [59] sought to test differences in serotonergic vulnerability by varying exposure to tryptophan and found that females showed more activity than males in a majority of anxiety-inducing behavioral tests. This increased level of activity in females was heightened by tryptophan depletion. Furthermore, females in metestrus/diestrus had increased activity in social interaction tests than their counterparts. Therefore, the study supports the notion that differences in sex and estrous cycle phases lead to varying behavioral responses to tryptophan depletion, allowing researchers to infer that sex, estrous cycle phases, and tryptophan levels play a key role in understanding the expression of anxiety. Other studies reported sex differences and variations in estrous phase to be associated with differing levels of serotonin following anxiety-producing behavioral tests. For example, Domínguez et al. (2003) [60] found that females on their first day of diestrus showed a greater level of aversion than males on the EPM. Interestingly both males and females had a decrease in serotonin following the EPM.

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In addition to differences in sex and estrous phases, testosterone and progesterone has also been found to possibly contribute to varying levels of serotonin in response to anxiety-inducing tests. Evidence from González et al. (1996) [61] suggests that testosterone inhibits the effects of 5-HT2 on exploration. In this study, a 5-HT antagonist decreased anxiety-like behavior in females, and a 5-HT agonist reduced anxiety in androgynous females, implying that neonatal 5-HT exposure leads to anxiogenic effects in females and anxiolytic effects in androgenized females, and no effect on males. Moreover, a 5-HT2 agonist decreased male and female sexual behavior in males and androgynous females respectively. This may indicate that that the 5-HT2 system inhibits the effects of testosterone on heterosexual orientation and sexual activity, and that this inhibition does not rely on genetic sex [61]. Likewise, Giltay et al. (2012) [62] established that high social anxiety is correlated with low testosterone levels in women. Díaz-Véliz et al. (1997) [63] found that the behavioral responses to ketanserin, a 5-HT2 receptor antagonist, varied depending on the sex, estrous cycle phase, ovariectomy, and ovarian hormone on the studied subject. More precisely, ketanserin only increased exploration on the EPM in diestrous females and ketanserin doses did not produce effects on males or ovariectomized females injected with progesterone. Therefore testosterone and progesterone, along with estrous cycle phases and estrogen levels, are important when it comes to understanding sex differences in serotonin responses to anxiety-generating behavioral tests.

Menstrual cycle, anxiety and serotonin / tryptophan

With clear associations between serotonin, estrogen, and anxiety, it is possible to assume connections between serotonin and the menstrual cycle. For example, Justice and Chappuis-Arndt (1976) [64] determined that, following exposure to an SSRI, females had less serotonin

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reuptake inhibition than males, as exhibited by higher percent 5-HT uptake levels in females. Furthermore, the amount of serotonin reuptake was greater at the start of menstruation and decreased as the cycle continued [64]. Wihlbäck et al. (2004) [65] performed a study using [3H]paroxetine, an SSRI, and [3H]lysergic acid diethylamide ([3H]LSD), a ligand for 5-HT2A receptors, to determine if binding for these two substances were altered during different phases of the menstrual cycle. It was determined that binding for both [3H]paroxetine and [3H]LSD were lower when progesterone levels were high during the mid-luteal phase, but higher when estradiol levels were high during the end of the follicular phase of the menstrual cycle [65]. The previously mentioned results are in concordance to Justice and Chappuis-Arndt (1976) [64]. On the other hand, Tam et al. (1985) [66] found that levels of 5-HT varied independent of menstrual cycle phases, and that these fluctuations in 5-HT did not correlate with fluctuations in anxiety. Further research will be necessary to determine the exact relationship between serotonin and the menstrual cycle.

There are also some data that alterations in 5-HT metabolism are associated with premenstrual syndrome (PMS). Su et al. (1997) [67] determined that HPA-axis activity was inhibited following exposure to a serotonin agonist in patients with PMS during both the follicular and luteal phases of their menstrual cycle. Menkes et al. (1994) [68] found that deficient levels of tryptophan led to an inflation of PMS symptoms, especially irritability. Therefore both serotonin and tryptophan are at least partially involved in the expression of PMS.

Pregnancy, anxiety and serotonin / tryptophan

Effects of serotonin on anxiety should be acknowledged in a prenatal context as well. In Vataeva et al. (2007) [69], PCPA was injected into pregnant mice to induce a serotonin deficit in

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the developing offspring. This deficit led to a change in the behavior of offspring, depending on the sex of the offspring: females exhibited a decrease in anxious behavior on the EPM and dark-light chamber, whereas males exhibited elevated anxiety [69]. This study stands as an example of how serotonin differentially affects males and females, even when those differences are manifested prenatally. Similarly, Whitaker-Azmitia et al. (1994) [70] found serotonin differences in recently-born subjects that were subjected to differing prenatal conditions; rat offspring had heightened levels of serotonin nerve density in the hippocampus and caudate recently after birth, but had a decrease in the cortex five days after birth as well as 30 days after birth, whether they received monoamine oxidase inhibitor medication (MAO-I) inhibitors until birth or until sacrifice (MAO-I sac). Although all rat pups developed at a normal rate with no changes in anxiety, MAO-I sac animals had more activity on postnatal day 30, as well as seizures and visual impairments, and both groups of rat pups had learning deficits on the passive-avoidance test [70]. This study suggests that the serotonergic mechanism is vulnerable during fetal development and that MAO-I inhibition leads to impulsive-like behaviors. Overall, it can be concluded that serotonin differences created during prenatal development led to differences in anxiety-like behavior post-birth. It would be advantageous to study sex differences in how serotonin and anxiety manifest to better specify treatments of anxiety to individuals of a specific sex. Forging a better understanding of anxiety in females who are pregnant or may become pregnant, allows for more effective treatment and therefore reduces the strain placed on a developing infant, giving it a better chance of survival.

Sex, anxiety, serotonin / tryptophan and the HPA-Axis

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Hek et al. (2013) [71] determined that adults with chronic anxiety had a decreased cortisol awakening response than their control counterparts. Mendelson and McEwen (1991) [72] found that there was an increase binding at 5-HT1A receptors in the Cornu Ammonis (CA) 4 region of the hippocampus and intra-pyramidal dentate gyrus, as well as an increase in the binding of the CA1 region of the hippocampus in females responding to stress; this sex difference was independent of estrous cycle phase. Furthermore, corticosterone (CORT) levels were also higher in stress-exposed females. The latter also showed a significantly greater decrease in CORT levels over time [72]. Healthy men show higher cortisol responses to 5-hydroxytryptophan, the direct precursor of serotonin, as compared to women with severe depression, where this association is reversed [73]. This indicates that the central activity of serotonin and its regulation of the HPA-axis differs between the sexes and additionally that affective disorders are accompanied by sex-related differences in the serotonergic modulation of the HPA-axis with a higher responsivity in females [73]. Such differences could perhaps play a role in the increased incidence of stress-related disorders and anxiety in women as compared to men. It can be concluded that both serotonin and CORT are associated in sex differentiated responses to stress and possibly to anxiety, and that these two factors could be cooperating, as they both rise in response to stress, in females especially.

Goel et al. (2014) [74] found that when a 5-HT1AR antagonist is administered in rats, there is a decrease in corticosterone in males only. However this antagonist also promoted greater levels of Fos activity in some serotonergic DRN cells in both males and females. Likewise, McEuen et al. (2009) [75] found that increases in 5-HT levels led to increased sensitivity to chronic SSRI administration via citalopram, an antidepressant and anxiolytic drug. Females had increased sensitivity to citalopram on the EPM. Before tail restraint tests, stress-

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sensitive corticotropin-releasing factor (CRF) receptor-2-deficient (R2KO) female mice displayed higher baseline corticosterone levels following citalopram administration. Both males and females exhibited a delay in their stress response due to the drug which allowed researchers to infer that the pharmacological capability to increase serotonin can override that of the HPA axis.

Serotonin and HPA-axis associations have also been studied in the context of prenatal development and early-life development. For example, Gutknecht et al. (2015) [76] found that fetal corticosterone metabolite levels rose in females without the neuronal tryptophan hydroxylase-2 (Tph2) gene in response to chronic mild stress (CMS), which could mean that the HPA-axis is more susceptible to stress when there are deficient levels of serotonin. This hypoactivity of the HPA-axis associated with a deficiency of serotonin was followed by a hyperactivity of HPA activity in response to CMS due to the deficient levels of serotonin. In addition, Van den Hove et al. (2014) [77] found that an increase in CORT originally caused by prenatal stress (PS), was weakened by subsequent CMS exposure in males. The DRN, hippocampus, and prefrontal cortex (PFC) of males were observed having changes in serotonin and tryptophan hydroxylase 2 (TPH2) immunoreactivity due to PS and CMS and a decrease of 5-HT was observed in the DRN.

The relationship between serotonin and the HPA-axis components during prenatal development continues at the level of serotonin and tryptophan genes as well. For example, in females the *s* allele was associated with an increase in adrenocorticotropic hormone (ACTH) levels and a decrease in cortisol levels in response to acute separation stress, but only if the female had a history of early life stress due to maternal deprivation [78]. This pattern is consistent in individuals with neuropsychiatric disorders like PTSD [79]. Barr et al. (2004) [78]

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thus supports the involvement of *5-HTT*LPR and the HPA-axis in stress responses and how early life stress can affect an individual's vulnerability to neuropsychiatric disorders, especially if that individual is female. Prenatal exposure to dexamethasone (DEX), a synthetic glucocorticoid, led to a chronic decrease in TpH2 mRNA in the caudal DRN of females [80]. To summarize, the relationship between serotonin and the HPA axis is present in the moderation of anxiety-like behaviors, even at prenatal levels.

Sex, anxiety, serotonin / tryptophan and neurotrophins / neuropeptides

Serotonin shows also interactions with brain-derived neurotrophic factor (BDNF), since BDNF supports the development of serotonin neurons. Ren-Patterson et al. (2006) [81] reported that female SERT x BDNF-deficient mice exhibited no increases in anxious behavior following the EPM, as opposed to males. Furthermore, female SERT x BDNF-deficient mice also had smaller reductions in serotonin levels in the hypothalamus along with other areas of the brain. This suggests that the interaction between SERT and BDNF modulates anxiety-like behaviors and that those behaviors differ depending on sex. Interestingly, intraventricular administration of BDNF increases the expression of a number of neuropeptides including the neuropeptide cholecystokinin (CCK) [82]. Abramov et al. (2004) [83] found that CCK(2) receptor-deficient female mice had increased concentrations of 5-HT2 receptors in the frontal cortex. These female mice did not exhibit anxiety-related behaviors following isolated-living and the EPM tests. Therefore, researchers concluded that mutations in CCK(2) affect 5-HT2 receptor levels to the extent that anxiety-related behaviors are reduced or eliminated in female mice [83].

Sex, anxiety and the TRYCAT pathway

 doi:10.20944/preprints201808.0487.v1

Aside from being the precursor to serotonin, tryptophan is also the precursor to kynurenine, one of the several tryptophan catabolites (TRYCATs) on the indoleamine (2,3)-dioxygenase (IDO) pathway associated with anxiogenic activity [2,84]. Tryptophan is degraded by either IDO or tryptophan 2,3-dioxygenase (TDO) to eventually lead to kynurenine, kynurenic acid (KA), quinolinic acid (QA) [83] and xanthurenic acid (XA) [2,84]. Increased activity of the TRYCAT pathway has been associated with anxiety, therefore understanding this pathway will prove informative to the understanding of the interaction between serotonin, anxiety, and sex.

In one study, researchers found that tryptophan-deficient females exhibited a greater response than males to a simulated public speaking test meant to induce anxiety [86]. Similarly, Badawy and Dougherty (2016) [87] conducted a study on the effects of tryptophan deficiency and tryptophan abundance on kynurenine and its derivatives and found that women have lower levels of tryptophan but that both sexes had similar levels of TRYCATs. In addition, Badawy and Dougherty (2016) [87] observed that kynurenic acid was lower in female Caucasians and that African-American and Hispanic women had lower levels of tryptophan oxidation products than men of each respective race. Maes et al. (2007; 2011) [2,84] found that increased degradation of tryptophan to TRYCATs following IDO activation was related to the presence of anxiety and depression symptoms. This is important as kynurenine and quinolinic acid (QA) possess anxiogenic effects. Similarly, higher levels of kynurenine and excreted xanthurenic acid (XA) were found to be positively correlated to levels of anxiety [88, 89]. Lapin et al. (1996) [90] found that QA reduced the duration of social interaction, as well as grooming behavior, in mice and is therefore inferred to have anxiogenic effects. Furthermore, Hoes and Sijben (1981) [91] used renal excretions to measure levels of XA and found that levels of XA measured at two-

 doi:10.20944/preprints201808.0487.v1

weeks post treatment with L-tryptophan regimens correlated with anxiety scores at 4 weeks post treatment.

In schizophrenia patients, there are highly significant associations between anxiety symptoms and IgA responses to noxious TRYCATs, including picolinic, XA, and QA acid, suggesting that anxiety may be driven by increased levels of these neurotoxic TRYCATs [92]. However, no sex-related differences were found in these associations between severity of anxiety and neurotoxic TRYCAT levels. Recently, significantly increased IgA responses to TRYCATs were reported in women with premenstrual syndrome, indicating that sex-hormones may modulate TRYCAT pathway activity [93]. Interestingly, premenstrual syndrome is thought to be associated with immune activation, inflammation (and thus an activated TRYCAT pathway) and disorders in serotonin metabolism [93].

Prenatal and postnatal development also affect tryptophan and the TRYCAT pathway. At the end of a pregnancy and during early puerperium, an increase in the ratio between kynurenine and tryptophan (indicating IDO activity) is associated with signs of inflammation [94]. In addition, anxiety-related symptoms during early puerperium were associated with the catabolic processes turning tryptophan into kynurenine [94]. Women with postpartum depression (PPD) show a 50% decrease in platelet serotonin levels [95]. The 5-HT system in perinatal depression subjects differs from that in other types of depression [96]. This may be explained by decreased synthesis of cerebral 5-HT in pregnancy following increased placental catabolism of tryptophan [97]. This may be explained by increased levels of stress hormones and immune-inflammatory activity during the perinatal period which drives tryptophan toward the TRYCAT pathway thereby causing increased TRYCATs but decreased 5-HT and melatonin levels [98]. The increase in plasma kynurenine and kynurenine / tryptophan quotient at the end of pregnancy and

 doi:10.20944/preprints201808.0487.v1

in the early puerperium are significantly associated with depression and anxiety symptoms in the early puerperium although these phenomena are not associated with later postpartum depression [94]. Another study measuring IgA and IgM responses to TRYCATs could not demonstrate a significant association between increased TRYCAT pathway activity at the end of term and prenatal/postpartum depression [93], although IgA responses to anthranilic acid were inversely associated with prenatal depression [93]. In addition, in women, body image satisfaction, which is associated with depressive and anxiety features, is strongly associated with activation of the TRYCAT pathway and especially with an index of quinolinic availability to the brain [99]. At the end of term pregnancy, TRYCAT pathway activity appears to be regulated by a complex network comprising inflammatory signals, nitrosative stress, bacterial translocation and regulatory autoimmune responses, pathways that are all associated with anxiety and depressive symptoms [93,100,101,102]. Overall, these studies indicate that aberrations in the TRYCAT pathway in pregnant females and parturients may be associated with increased anxiety and that sex, the menstrual cycle and PMS may have a profound effect on the TRYCAT pathway.

Sex, anxiety, TRYCAT pathway and immune activation

The immune system and its cytokines are also components needed to build an understanding of the relationship between kynurenine, serotonin/tryptophan, anxiety, and sex. Activation of immune-inflammatory responses, which are frequently observed in depression and anxiety disorders [2], stimulate IDO thereby causing a decrease in tryptophan and an increase in TRYCATs [2]. This immune-inflammatory response may affect anxiety-like behaviors since some TRYCATs including kynurenine and QA are anxiogenic. Furthermore, Maes et al. (2011) [2] reported greater IDO activation and TRYCAT generation following an immune challenge in

women than men. This demonstrates an interaction between sex, IDO activity and TRYCAT concentrations, which could all affect levels of anxiety. It can be hypothesized that a greater activation of IDO in women than men would mean that women may have an enhanced production of neurotoxic and anxiogenic TRYCATs and by inference more anxiety.

Perna et al. (2016) [103] explained that greater levels of inflammation markers like interleukin 6 (IL-6) were present alongside anxious behavior in general populations, and that there was a relationship between immune inflammation and lipopolysaccharides (LPS), which are derived from Gram-negative bacteria present in the gut. The presence of LPS has been known to cause anxiety and cognitive dysfunctions in healthy male subjects. Moreover, the relationship between LPS and immune inflammation can lead to further IDO activation and increased levels of kynurenine, further producing anxiety-like behaviors [103]. In pregnant females, significant associations were observed between LPS/antigens to different commensal Gram-negative bacteria and immune responses to TRYCATs, especially QA and the QA/KA ratio (indicating increased neurotoxic potential) [103]. Moreover, increased IgA responses to LPS/antigens of Pseudomonas aeruginosa predict postnatal anxiety some weeks later. Such results indicate that in pregnant females the TRYCAT pathway is activated by LPS of Gram-negative bacteria and that both TRYCATs and LPS may predict anxious behaviors.

Maes et al. (1998) [104] reported that stress-induced increases in the production ratio of interferon-γ / interleukin-10 in peripheral blood mononuclear cells are associated with stress-induced anxiety. Interestingly, most TRYCATS have anti-inflammatory effects by decreasing the interferon-γ / interleukin-10 production ratio [82]. Interleukin 10 (IL-10) is an anti-inflammatory cytokine, while interferon-γ is a pro-inflammatory cytokine that activates IDO [2,106]. QA, on the other hand has significant pro-inflammatory effects [84] and therefore may be accompanied

 doi:10.20944/preprints201808.0487.v1

by increased anxiety levels via effects on the interferon-γ / interleukin-10 production ratio. Labaka et al. (2017) [106] ascertained that although reduced hippocampal IL-10 is associated with anxiety-like behaviors in females exposed to acute social instability stress, differences in tryptophan, kynurenine, and 3-hydroxykynurenine did not follow a similar association. Németh et al. (2006) [107] demonstrated that increased levels of IDO led to a decrease in 5-HT and an increase in levels of TRYCATs like 3-hydroxykynurenine and QA, both of which are neurotoxic. This provides proof of a relationship between serotonin and the TRYCAT pathway and how they could affect anxiety. It can be hypothesized that when immune activation stimulates the production of IDO, tryptophan and serotonin decrease, anxiogenic TRYCATs increase, including kynurenine, XA and QA, thus leading to increased anxiety. Moreover, since IDO is more activated in women as compared with men, anxiety-related behaviors could be more expressed in women.

Conclusions

The interactions between sex, serotonin and anxiety can be mediated via serotonin receptors, tryptophan catabolism, sex hormones, the menstrual cycle, pregnancy, cortisol levels, and immune activity. Various serotonin receptors are associated with anxiety and show sex differences. More specifically, the 5-HT2C receptor plays an important role being that the gene that encodes for it is located on the X chromosome, and receptor activity has illustrated an ability to increase anxiety and a lack of activity shown to decrease cortico-releasing hormone. In addition, inactivation of SERT removed sex differences in response to anxiety-provoking stimuli and tryptophan depletion has been correlated with increased levels of anxiety, especially that of panic, and especially in women. Research studies also show that responses to a 5-HT2 receptor

antagonist depended on sex, estrous cycle phase, ovariectomy, and ovarian hormone levels of female rats. Furthermore, studies have found that females had less serotonin reuptake inhibition following exposure to an SSRI than males, and that serotonin reuptake was greater at the start of menstruation and decreased as the cycle progressed. The serotonergic mechanism is also vulnerable to changes prenatally, and such changes can increase anxiety. In addition, the HPA-axis is another factor involved with the interaction between serotonin, anxiety and sex; for example men exhibited decreased levels of corticosterone in response to a 5-HT1AR antagonist, but this same antagonist has been found to promote greater levels of Fos activity in some serotonergic DRN cells in both males and females. Neurotrophins like BDNF and neuropeptides like CCK have also been found to interact with the three factors in this study. Reports describe female SERT x BDNF deficient mice exhibiting smaller decreases in serotonin levels in various areas of the brain, and no increases in anxious behavior following anxiety-provoking stimuli, as opposed to SERT x BDNF deficient males. CCK(2)-deficient female mice had increased concentrations of 5-HT2 receptors in the frontal cortex and did not have anxiety-like behaviors following anxiety-provoking tests.

Another interacting component is the immune system; immune activation stimulates IDO production allowing for serotonin and tryptophan to decrease, and TRYCATs to increase, namely kynurenine, XA, and QA, creating encompassing anxiogenic effects. Following immune stimuli, IDO may be more activated in women than men with increased levels of anxiogenic TRYCATs. Therefore, any immune challenge may lead to more anxiety-like behaviors in women than men.

It is evident from this paper that more research is necessary to create a complete understanding of how sex, tryptophan, serotonin and anxiety interact. The hopes are that this

review brings attention to the necessity of studying tryptophan and serotonin in both sexes as well as the interactions that anxiety has with sex, serotonin/tryptophan, estrogen, testosterone, progesterone, the menstrual cycle, pregnancy, the HPA axis, TRYCATs, and the immune system. These convoluted interactions will act as a guide for future research as it is evident that there is still more to be learned.

Acknowledgements

This study was funded by Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University, grant number RA61/016 and Chulalongkorn University; Government Budget. The authors confirm that they do not have any conflicts of interest. All authors contributed to the writing of the paper.

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Key Terms

- PD= Panic Disorder
- GAD= Generalized Anxiety disorder
- PTSD= Post-Traumatic Stress disorder
- U.S.= United States
- 5-HT= 5-hydroxytryptamine, also known as serotonin
- HPA axis= hypothalamic-pituitary-adrenal axis
- Ads= antidepressants
- SSRIs= selective serotonin reuptake inhibitors
- CNS= central nervous system
- 5-HT1A receptor; 5-HT1AR= the "1A" serotonin receptor
- 5-HT2AR= the "2A" serotonin receptor
- DRN= dorsal raphe nucleus
- 5-HT2CR= the "2C" serotonin receptor
- CRH= cortico-releasing hormone
- DS= dorsal striatum
- BLA= basolateral amygdala
- 5-HT3R= the "3" serotonin receptor
- 5-HTT, SERT= serotonin transporters
- 5-HTTLPR= serotonin-transporter linked polymorphic region
- EPM= elevated plus maze
- ATD= acute tryptophan depletion
- Fos-ir= Fos-immunoreactivity

 doi:10.20944/preprints201808.0487.v1

- PFC= prefrontal cortex
- MRN= median raphe nucleus
- TD= tryptophan depletion
- CBT= cognitive behavioral therapy
- APTD= acute phenylalanine/tyrosine depletion
- hSERT= the human serotonin transporter gene
- IMI= tritiated imipramine
- vmPFC= ventromedial prefrontal cortex
- SLC6A4= a specific serotonin transporter gene
- PCPA= para-chlorophenylalanine
- PMS= premenstrual syndrome
- MAO-I= monoamine oxidase inhibitors
- CA, CA4= Cornu Ammonis 4
- CA1= Cornu Ammonis 1
- CORT= corticosterone
- CRF= corticotropin-releasing factor
- R2KO= receptor-2-deficient
- CMS= chronic mild stress
- PS= prenatal stress
- TpH2= tryptophan hydroxylase 2
- ACTH= adrenocorticotropic hormone
- DEX= dexamethasone
- mRNA= messenger ribonucleic acid

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- BDNF= brain-derived neurotrophic factor
- CCK= cholecystokinin
- TRYCATs= tryptophan catabolites
- IDO= indoleamine (2,3)-dioxygenase
- TDO= tryptophan 2,3-dioxygenase
- KA= kynurenic acid
- QA= quinolinic acid
- XA= xanthurenic acid
- LPS= lipopolysaccharides