Journal of Affective Disorders 190 (2016) 193–207

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

5-HTTLPR and gender differences in affective disorders: A systematic review

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ARTICLE INFO

Article history:
Received 27 May 2015
Received in revised form
12 September 2015
Accepted 15 September 2015
Available online 23 October 2015

Keywords:
5-HTTLPR
Affective disorders
Anxiety
Depression
Gender
Serotonin transporter
Stressful life events

ABSTRACT

Background: Serotonin transporter-linked polymorphic region (5-HTTLPR) variants have been extensively studied in psychiatric disorders. Although gender effects have been reported, they have not been comprehensively reviewed.

The aim of our study was to summarize literature findings on 5-HTTLPR and gender differences in affective disorders.

Methods: A systematic search of PubMed, ISI Web of Knowledge, and PsycINFO databases was performed for dates until January 2015. The included articles ($n=78$) analyzed the association between 5-HTTLPR and affective spectrum disorders, taking into account gender. The quality of each study was assessed through STROBE and CONSORT.

Results: 5-HTTLPR modulation of affective disorders varied by gender. The S allele (or SS genotype) seemed to be differently associated with an increased risk of depression, depressive symptoms, anxiety traits and symptoms, and symptoms of internalizing behavior among women and an increased risk of aggressiveness, conduct disorder and symptom counts of externalizing behavior among men. Moreover, the presence of stressful life events reinforced the association. Interestingly, these differences seemed to begin with adolescence and were not consistent among the elderly, suggesting a plausible role of hormonal fluctuations.

Limitations: The review is limited by the small number of included papers, due to the paucity of information in the literature regarding 5-HTTLPR and gender.

Conclusions: 5-HTTLPR variants may exert a differential modulation on a number of features depending on gender. Further studies are needed to more deeply investigate the effect of 5-HTTLPR × gender on the modulation of affective disorders.

Contents

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http://dx.doi.org/10.1016/j.jad.2015.09.027
0165-0327/

1. Introduction

The serotonergic system seems to act differently according to gender. Concerning humans, central nervous system (CNS) serotonin (5-HT) synthesis rates are approximately 50% higher among males than among females (Nishizawa et al., 1997). Furthermore, central spinal fluid 5-hydroxyindoleacetic acid (5-HIAA) is higher among women than in men, although this may reflect either enhanced serotonin neuron firing or enhanced metabolism (Brummett et al., 2008b; Williams et al., 2003). Both 5-HT1A (Costes et al., 2005) and 5-HT2 (Biver et al., 1996) receptor densities are lower in the brains of women than men, although such a difference may reflect either lower receptor expression or lower serotonin release competing with radioligand for binding. Studies in kinetic parameters of platelet serotonin uptake have moreover reported differences between genders: Km and Vmax showed lower values, and transporter efficiency (Vmax/Km) was 16% higher among women than among men (Banovic et al., 2010). However, females are often not considered in studies on platelet serotonergic parameters because of the possible confounding effect of the menstrual cycle. In addition, depressive symptoms after tryptophan depletion are significantly higher among women (Booij et al., 2005; Moreno et al., 2006). Higher serotonin transporter (5-HTT) availability has been reported among females compared to males (Staley et al., 2001). Considering antidepressant response, selective serotonin re-uptake inhibitors (SSRI) were found to be more effective among women than among men, though not unequivocally (Kornstein et al., 2002; Martenyi et al., 2001).

Concerning 5-HTT in rodent models, sex differences were reported as well. First, female rats have an overall higher level of 5-HT in the CNS than males. Moreover, in SERT-knocked out (KO) mice, the 5-HT1A autoreceptor is more extensively desensitized among females than males (Bouali et al., 2003; Li et al., 2000). In transgenic mice overexpressing human SERT (hSERT OVR), SERT binding levels were significantly increased in the brain in a region-dependent manner, and this pattern was more pronounced among females than among males (Dawson et al., 2009). Cerebral metabolism was significantly decreased in many brain regions in hSERT OVR female compared with wild-type female mice, whereas no difference was found among males. The ability of hSERT overexpression to modify cerebral metabolism was significantly higher among females than among males. In addition, female SERT −/− mice had greater increases (79%) in brain 5-HT synthesis than male −/− mice did (25%), a finding associated with higher brain tryptophan concentrations among females (Kim et al., 2005).

In humans, the 5-HTT is encoded by the *SLC6A4* single gene, positioned on chromosome 17, in location 17q11.1-12; the *SLC6A4* gene spans 31 kb and consists of 14 exons (Collier et al., 1996; Heils et al., 1996). Among the recognized polymorphisms of this gene, the polymorphism located in the transcriptional control region upstream of the coding sequence (5-HTTLPR) is thought to have the greatest influence on the modulation of human and non-human behavior. It consists of a 43-bp insertion or deletion; the deletion is characterized by a short variant (S), whereas the insertion is characterized by a long variant (L). The S variant reduces the transcriptional efficiency of the 5-HTT gene promoter, resulting in decreased 5-HTT expression and availability (Lesch et al., 1996). Furthermore, an A/G single nucleotide polymorphism (SNP; rs25531) in the repeat region was found to be functional. Rs 25,531 is mostly found in the L variant, further dividing it into L_A and L_G. This SNP may modulate 5-HTTLPR expression, with L_G alleles being equivalent to S alleles in expression (Wendland et al., 2006).

Studies examining the effect of 5-HTTLPR on affective disorders have shown interesting but sometimes inconsistent results.

In rhesus macaques, females carrying the S allele had increased stress-induced release of adrenocorticotropic hormone (ACTH) and decreased cortisol levels after separation, whereas heterozygous males had a higher ACTH response to separation than both homozygous groups (Barr et al., 2004): only peer-reared females with the rh5-HTTLPR S allele had increased ACTH and lower cortisol responses to stress.

In addition, in humans, the 5-HTTLPR polymorphism may influence the development of the 5-HT system according to gender rather than having a direct control on 5-HTT expression. In particular, the 5-HTTLPR genotype was reported to affect the binding to central 5-HT1A receptors among women but not among men (Lothe et al., 2009). Moreover, the SS genotype was found to be associated with lower 5-HIAA levels among men but was associated with higher levels among women (Williams et al., 2003). Similar sex differences in response to tryptophan infusion were reported: males with the L allele and females with the S allele showed higher increases in negative affect (Brummett et al., 2008b). Moreover, a sex by 5-HTTLPR interaction has been found to be related to cortisol secretion (Jabbi et al., 2007; Wust et al., 2009; Wankerl et al., 2010).

Based on the abovementioned evidence, the 5-HTTLPR genotype may have opposite effects on the behavioral characteristics of men and women, which may bias observed results.

To further understand and evaluate the role of gender in the modulation of the association between the 5-HTTLPR polymorphism and affective disorders, we performed a systematic review on all of the studies in humans considering gender on the association between 5-HTTLPR and affective spectrum disorders.