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Stressful Life Events and Depression: The Role of Serotonin Transporter Gene Polymorphism (5-HTTLPR)

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Abstract

A developing body of evidence shows that stressful life events have a significant causal association with the beginning of major depression episodes. Genetic factors impact on the experience of stressful life events, and these factors are connected with those that lead to development of major depression. Various research reports have shown that a functional polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) or 5-HTTLPR has the moderating influence on the correlation between stressful life events and depression. This article will review the literature assuming that genetic variation in serotonin transporter gene regulates the effects of stressful life events on the occurrence of major depression.

Keywords: Serotonin Transporter; Polymorphism; Depression; Stress

Introduction

Worldwide, depression is a commonest psychiatric disease and seriously disabling mental disorder [1]. About one in five individuals will experience a major depressive episode during their lifetime [1]. Depression is characterized by a depressed mood or anhedonia (loss of interest and pleasure) or both, for more than 2 weeks combined with several neurovegetative and cognitive symptoms including poor concentration, fatigue, irritability, and sleep and appetite disturbances [2,3]. The etiology of depression has not been completely clarified but a range of causes particularly complex interaction of various genes with subsequent exposure to a wide range of environmental risk factors such as childhood psychosocial adversity or enduring later psychosocial stress may lead to changes in the structure and function of brain related to major depression [4]. The pathophysiology of major depression has conventionally focused on the monoamine hypothesis that supposed depression as a probably result of reduced levels of the monoamine neurotransmitters including serotonin, dopamine and nor epinephrine and various antidepressant drugs act by acutely enhancement of their concentration [5–7]. Certain gene polymorphisms increase risk for depression in response to environmental stressors through several mechanisms such as metabolic regulation of neurotransmitters and their receptors, regulation of signaling transduction pathways in neurons and monitoring of synaptic contacts and amounts of certain kinds of neurons [8]. The most examined gene in major depression that likely influence on sensitivity to stress is one polymorphism of serotonin transporter gene [4].It has demonstrated that the short allele of the 5-HTT gene polymorphism decreases its transcriptional efficiency and causes reduced expression of 5-HTT and uptake of serotonin in lymphoblasts [9]. Several neuroimaging studies have reported positive relationships between increased activation of amygdala and short allele of 5-HTTLPR in healthy subjects and various stress related psychiatric disorders including social phobia, panic disorder and major depression when experiencing of stress induced by emotional stimuli [10]. Several studies have reported interactive effects of stress and polymorphism of the serotonin transporter gene as a risk factor for major depression [11–14]. Contemporary theories particularly diathesis-stress theories believe that genes related to the onset of depression interact with stressful life events to produce depression instead of directly influence on depression [15]. In this article, the author reviews findings related to impact of interaction of serotonin transporter (5-HTTLPR) genotype and stressful life events on the susceptibility to major depression.

Stressful Life Events and Depression

The association between stressful life experiences as the environmental risk factors and first onset or recurrence of depression has been consistently reported by several studies [16,17]. Hyper activation of hypothalamic-pituitary-adrenal (HPA) axis and subsequent enhanced cortisol levels in plasma and cerebrospinal fluid induced by exposure to stressful life events has proposed as a

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major causal risk factor for predicting onset of major depression and effective antidepressant treatments could return the function of the HPA axis [18–27]. Clinical evidence revealed that experience of stressful life events in depressive patients is 2.5 times higher when compared to controls; however community-based studies have reported happening of stressful life events before onset of depression only in 80% of patients [16]. Developing body of evidence has shown frequently occurrence of stressful life events before onset of an episode of major depression suggesting likely presence of a causal relationship between them [28]. A strongly association between daily stressful events and greater initial severity of depressive symptoms and fewer vegetative features has reported in both patients and non-patient' community samples [29].

Relationship between 5-HTTLPR, Stress and Depression

Human subjects have shown a wide variation in response to adversity induced by stressful life events [30]. Numerous studies have supported that development and prediction of major depressive disorder (MDD) are dependent to interaction between candidate gene polymorphisms and negative environmental risk factors [31]. Consistently, increased reactivity to stress has reported in the carriers of short allele of 5-HTTLPR by many researches in the field of neuroscience [10,32,33]. Functional variation in the serotonin transporter (SERT) gene also affects behavioral response to stress in animals and serotonin transporter knockout mice have shown increased activation hypothalamic- pituitary-adrenal axis in response to both physical and psychological stressors [34,35]. A well-known polymorphism in the promoter region of the serotonin transporter gene is 5-HTTLPR that has two alleles including a long allele (L) with 16 repeats and a short allele (S) with 14 repeats. S allele leads to lower transcriptional activity relative to L allele and causes a relative decrease in mRNA levels, binding and reuptake of serotonin [9,36,37]. A prospective-longitudinal study of a representative birth cohort demonstrated that carriers of the short allele of the serotonin transporter have more depressive symptoms and suicidality and may be especially vulnerable to depression when exposed to stressful life events than individuals homozygous for the long allele [38]. Caspi et al. (2003) have reported that interaction of serotonin transporter (5-HTTLPR) genotype and stressful life events impact on the prediction of major depression [38]. Several investigators replicated results of study of Caspi et al (2003) [12,39,40]. Homozygous and heterozygous carriers of the short allele of the 5-HTTLPR genotype show significantly greater incidence of major depression in response to stressful life events [29]. It has reported that under the high environmental stressor conditions including high exposure to hurricane and low social support, the low-expression variant of 5-HTTLPR increased the risk of major depression [14]. Kendler et al (2005) replicated the moderating effect of the 5-HTTLPR genotype in a sample of adult twins and reported results resembled those reported by Caspi et al. (2003) but found that 5-HTTLPR genotype moderates the sensitivity of individuals to the depressogenic effects of only common, mild stressors rather than the impact of rarer and severe life events [13]. It has found that hypothalamic-pituitary-adrenocortical (HPA) axis functioning and stress reactivity may account impact of interaction of genotype and exposure to life stress on the increased susceptibility to depression [41].

Impact of Interaction of Stressful Life Events and 5-HTTLPR Genotype on the Depression

Gene–environment interactions studies for depression suggest that both genes and environment are important risk factors for the development of major depressive disorder (MDD) [31]. Serotonergic system shows significant differences in patients with and without major depression and represents a strong genetic candidate for major depression and suicide [29]. It has revealed that Patients with major depression have fewer binding sites of 5-HTT gene in the brainstem, hypothalamus, occipital cortex and prefrontal cortex as well as in blood platelets [42]. Molecular genetic investigations on the risk of major depression have been focused principally on the serotonergic system particularly the serotonin transporter (5-HTT) that regulates the synaptic reuptake of serotonin [9,43]. A positive correlation has been found between the genetic risk factors for stressful life events and genetic risk factors for major depression [9,42]. Although one meta-analysis study did not support a direct relationship between the 5-HTTLPR and depression onset but it has reported that Individuals do not experience stressful life events at random and probability of experiencing stressful life events in the interpersonal and occupational/financial domains will increase with genetic risk factors for major depression in the women and genes can likely influence on the risk for psychiatric disorder by affecting individuals to select themselves into high risk environments [44,45]. The results of another meta-analysis study provided support for the presence of a statistically significant but small effect of the 5-HTTLPR genotype on susceptibility to depression with this possibility that the effect may be a result of an artifactual basis, rather than a biological origin [46]. However, contrary to the results of the smaller earlier meta-analyses, a more recent meta-analysis study assessed the relationship between 5-HTTLPR, stress, and depression and represents strong evidence that a serotonin transporter promoter polymorphism (5-HTTLPR) moderates the relationship between stress and depression [47].

Conclusion

Major depression is a multifactorial psychiatric disease and integration of both genetic and environmental risk factors contribute to the etiology of major depression. Experience of a stressful life event considerably increases the risk of a subsequent episode of major depression. One of the important genes that is involved in the serotonergic transmission is the serotonin transporter (5-HTT) gene that it's functional polymorphism linked promoter region (5-HTTLPR) has two allelic forms including long (l) and short (s) variants. Genetic polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) in interaction with stressful life events plays a crucial role in the predisposition to major depression. Individuals with one or two copies of the short allele of the 5-HTTLPR polymorphism have higher rates of depression, higher levels of depressive symptoms and more suicidality as a function of exposure to enhancing levels of stressful life events than do individuals who have one or two copies of the long allele. HPA-Axis and stress reactivity has proposed as a possible mechanism underlying the association between genotype, exposure to life stress, increased susceptibility to depression and predicting the onset of depression. Despite increasing evidence show that the 5-HTT gene moderates the association between life stress and depression, nevertheless controversy still remains and not all studies have reported this gene–environment interaction. Therefore, replication of findings related to impact of interaction of 5-HTTLPR polymorphism and stressful life events in the prediction of episodes of major depression is needed.

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