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EDITORIAL

Vulnerability to depression: what is the role of stress genes in gene × environment interaction?

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Vulnerability to depression has been linked to the interaction of genetic predisposition with stressful life events. This review considers the associations between serotonergic and hypothalamic–pituitary–adrenal (HPA) systems. We follow the standpoint of a previous Editorial Review (Bhagwagar & Cowen, *Psychological Medicine* 2008, **38**, 307–313) and consider another possible mechanism of vulnerability to depressive disorder, that is we suggest that the gene × environment interaction involves complex participation of serotonergic genes modulating response to stress through the HPA system.

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Introduction

Major depressive disorder (MDD) has a heterogeneous aetiology and the contribution of environmental factors is at least equivalent to that of genetic factors. A genetic diathesis predisposes individuals to the disorder in the context of life stressors (Kendler *et al*. 2001). Environmental factors are now taken into account in studies of MDD, which is not a trivial task because their evaluation is usually retrospective. Moreover, it is not explicit which stressful events are the most relevant, ranging from acute to chronic or traumatic stress events. The evidence suggests that the acute and recent stress is more relevant, compared with chronic and distal events (for a review see Monroe & Reid, 2008).

In the following sections we consider some of the possible factors that play a role in the gene–environment interaction relevant to the concept of vulnerability to MDD.

The serotonergic system

Serotonergic vulnerability (Jans *et al*. 2006) is an increased sensitivity to natural or experimental alterations of the serotonergic system, such as genetic factors, female gender, personality characteristics (neuroticism), environmental stress (prenatal stress, life experiences) or drug use. An insertion/deletion polymorphism in the serotonin transporter-linked promoter region 5-HTTLPR modulates serotonin transporter gene (SLC6A4) expression, where the short allele (S) is associated with lower expression levels compared to the long allele (L). Importantly, the risk for depression has been associated with an interaction of the S allele with stressful life events (Caspi *et al*. 2003). What are the neural mechanisms of such an interaction? Neuroimaging studies show that, in response to aversive visual signals, S allele carriers demonstrate amygdala hyperactivity and also altered connectivity between the pregenual anterior cingulate cortex (ACC) and the amygdala (for a meta-analysis see Munafo *et al*. 2008). In other words, people who genetically have low activity of 5-HTTLPR, and consequently are at risk for developing depression, demonstrate an overactivity of the amygdala to aversive signals. These experiments are regarded as modelling the brain's responsivity to potentially stressful environmental signals. A functional magnetic resonance imaging (fMRI) study (Canli *et al*. 2006) has indeed found that the life stress measure correlated positively with resting activation in the amygdala and hippocampus in S allele carriers and negatively in L allele carriers.

The literature indicating a net inhibitory effect of serotonin on amygdala activity (Stutzmann & LeDoux, 1999) seems to support this model. However, the bigger picture of major depression is far from clear. Thus, a recent meta-analysis has not confirmed a direct link between 5-HTTLPR and MDD (Kato, 2007). Levinson (2006) suggested that there were small positive associations between 5-HTTLPR and depression-related personality traits but not with MDD itself. Kato

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(2007) argued that, in depression, the previously reported positive findings of a gene–environmental interaction between 5-HTTLPR and stress were not replicated consistently. One reason for these discrepancies is that 5-HTTLPR polymorphisms are now found to be more complex than previously thought, with at least 14 alleles of the 5-HTTLPR. There are views that the 5-HTTLPR polymorphisms may not be directly associated with MDD but modulate the serotonergic response to stress (for a methodological review see Uher & McGuffin, 2007).

Stress and the hypothalamic–pituitary–adrenal (HPA) axis

Traditionally, studies of vulnerability to stress have focused on malfunctioning of the HPA system involving neuroendocrine metabolism. A large body of knowledge suggests that exposure to stress leads to hyperactivation of the HPA system, which, in people with a deficitary feedback mechanism, is followed by hypercortisolism. This hypercortisolism is present during depressive episodes, in remitted patients and in those at high risk, for example in children from affected families (Mannie *et al*. 2007). Importantly, the degree of hypercortisolism has been shown to predict the occurrence of depression in high-risk individuals (Harris *et al*. 2000; Halligan *et al*. 2007).

Two receptor subtypes, glucocorticoid and mineralocorticoid receptors (GR and MR respectively), contribute to the regulation of HPA activity. One of the models of depression (Pariante, 2006) suggests that the main neuroendocrinological abnormality is glucocorticoid resistance resulting from decreased GR function or expression in the brain. The hypercortisolism would be a compensatory mechanism aiming to overcome the glucocorticoid resistance. Thus, in a proportion of MDD patients, GR dysfunction might be the primary source of the HPA axis abnormalities. An elevated waking cortisol level might be part of an endophenotype predisposing a subject to the development of depression in the context of stressful life events.

HPA-related genes

Growing evidence is suggesting that some polymorphisms in the MR and GR genes may underlie vulnerability to depression.

Glucocorticoid receptor

A significant association of MDD with polymorphisms in the gene coding for the GR was observed in a Belgian sample (in the promoter region NR3C1-1, rs10482605), a Swedish sample (R23K, rs6190) and a German population (R23K) (van West *et al*. 2005; van Rossum *et al*. 2006). Kumsta *et al*. (2007) investigated 206 healthy subjects and associations between common GR gene (NR3C1) polymorphisms and HPA axis responses to psychosocial stress, using the Trier Social Stress Test (TSST). The study detected a significant association, but no clear aetiological relationship, between GR gene polymorphisms (ER22/23EK, N363S, BclI, 9β) and HPA axis regulation and on glucocorticoid sensitivity as well as a sex-specific impact (BclI GG, 9β AG) on responses to psychosocial stress. Recently, Bradley *et al*. (2008) showed that child abuse interacts with the corticotrophin-releasing factor type 1 receptor (CRF-R1) genotype to enhance risk for depression in adults, in two independent ethnically different populations. They suggested that alterations in CRF-R1 responsiveness during these early emotionally crucial periods could alter later risk for HPA axis overactivity and depression.

In sum, the GR- and CRF-coding genetic polymorphisms are likely to have a modulating (rather than a causal) effect in the development of MDD.

Mineralocorticoid receptor

In a cohort of healthy males (DeRijk *et al*. 2006), carriers of the minor allele of the MR gene variant I180V showed significantly higher salivary and total cortisol and also heart rate responses to the TSST than non-carriers. Kuningas *et al*. (2006) assessed the impact of cortisol levels and of variations in the MR and GR genes on depressive symptoms. They showed that the prevalence of depressive symptoms was dependent on a variation in the MR gene, where carriers of the MR-I180V single nucleotide polymorphism (SNP) had more depressive symptoms compared to the non-carriers.

Thus, several genes involved in modulation of HPA axis functioning may have a role in the mechanisms of vulnerability to MDD. The involvement of serotonergic genes in vulnerability has also been highlighted. The question arises: do these mechanisms of vulnerability operate independently? We believe there should be a common pathway where the serotonergic and HPA systems converge in developing vulnerability to depressive states. The functional links between these systems may provide some clues.

Links between 5-HT and HPA systems

Gotlib *et al*. (2008) has shown recently that cortisol response may be a crucial mechanism underlying the association between the 5-HTTLPR gene and exposure

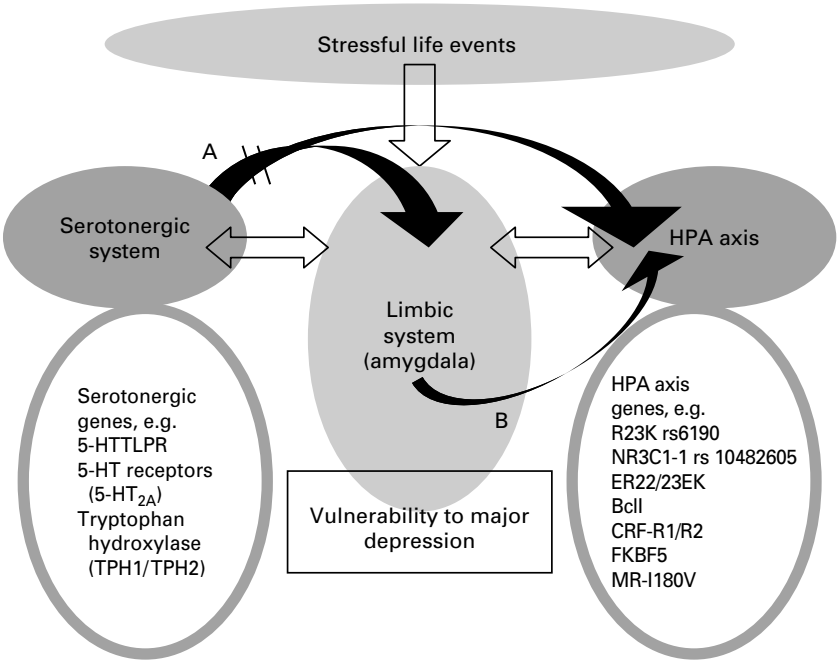

Fig. 1. Altered relationships between serotonergic, limbic and hypothalamic–pituitary–adrenal (HPA) systems underlie the vulnerability to depression. Reduced serotonergic inhibition (arrows A) is associated with overactivity in the amygdala and the HPA system. The overactive amygdala provides an additional boost to cortisol and corticotrophin-releasing factor production (arrow B). Genetic polymorphisms are associated with risk/vulnerability to depression. This diagram demonstrates the relationships between three systems underlying the vulnerability to depression. We acknowledge that there are several other systems involved (e.g. dopaminergic system, lateral, orbital frontal and cingulate circuits) but these are not the subject of this review.

to stressful events in increasing risk for depression. We consider below possible neural processes involved in such an interaction (Fig. 1).

It is well established that the activity of the amygdala is associated with the HPA axis through serotonergic projections to the hypothalamus (Weidenfeld *et al*. 2002), influencing the stress response (Herman *et al*. 2005). It has also been suggested that the central amygdaloid nucleus takes part in overproduction of CRF in melancholic patients with hypercortisolaemia (Reul & Holsboer, 2002).

However, the serotonergic system has been found to modulate HPA axis functioning: for example, studies with 5-HTT knockout mice have shown that one of the functions of the serotonin transporter is to restrain the HPA response to stress (Tjurmina *et al*. 2004; Murphy & Lesch, 2008). Jabbi *et al*. (2007) explored the influence of 5-HTTLPR polymorphisms on HPA axis reactivity using combined dexamethasone and CRF challenge, which is known to induce neuroendocrine states similar to stress-related clinical phenotypes. The study showed higher endocrine response in females homozygous for S allele of 5-HTTLPR which might contribute to the sex-related differences in MDD prevalence. Indeed, the same 5-HTTLPR polymorphisms also interacted with baseline measures of cortisol in determining susceptibility to MDD.

Conclusions

Given the above-mentioned close relationship between the amygdala, serotonergic transmission and the HPA axis, their concerted participation in limbic response to stress might be expected. This response may develop into an exaggerated reaction in people with low activity of 5-HTTLPR/elevated activity in the amygdala, where the hyperactive amygdala enhances HPA axis functioning; sustained hypercortisolism will follow, contingent on MR and GR gene expression.

Future studies of limbic brain modulation by genetic polymorphisms pertaining to serotonergic and HPA systems may tell us more about vulnerability to MDD.

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Declaration of Interest

None.

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