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Serotonin by stress interaction: a susceptibility factor for the development of depression?

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Abstract

A genetic predisposition to depression may be a potential risk factor in the development of depression. Although the neurobiological equivalent of the predisposition remains unclear, it seems as though the brain serotonin (5-HT) system plays an important mediating role. Therefore, individuals with a family history of depression (FH+) may be more likely to develop depression due to an innate vulnerability related to altered serotonergic neurotransmission in the brain. A major problem, however, is that the role of brain 5-HT in depression is complex and this serotonin-related innate vulnerability, by itself, is not sufficient enough to cause a depressive episode. In the search for additional factors, stress has received particular attention. Stressful life events influence and precede the onset of depression. Furthermore, depression is associated with stress hormone dysregulation and bidirectional interactions are thought to occur between stress-related changes in the neuroendocrine stress system and the 5-HT system. In the current review, we argue that healthy individuals with a positive family history of depression are more prone to develop depression due to a genetic 5-HT susceptibility, which deteriorates stress coping mechanisms and increases stress vulnerability.

Key words

depression, serotonin, 5-HT, stress

Introduction

Depression is one of the most common diseases in the world (Akiskal, 2005). Epidemiological studies suggest a lifetime prevalence of Major Depressive Disorder, which ranges from 5% to 17% (Rihmer and Angst, 2005). Additionally, its incidence is increasing. However, in spite of intensive research during the past decades, critical risk factors involved in the onset or development of depression have not been defined.

Genetic/family predisposition or 'susceptibility' to depression may be a potential risk factor in the development of depression. Family studies have shown that depression is two- to threefold more common in first-degree relatives compared to the general population (Sullivan *et al*., 2000; Kelsoe, 2005) and is also associated with early onset and higher levels of morbidity (Lieb *et al*., 2002). Twin studies, a powerful tool used to differentiate genetic and environmental influences, reveal a higher concordance rate for monozygotic twins than for dizygotic twins (Kendler and Gardner, 2001), which further corroborates the utility of genetic predisposition as risk factor in the development of depression. Although the neurobiological equivalent of this genetic predisposition remains unclear, it seems as though the brain serotonergic system serves an important mediating role (Owens and Nemeroff, 1994). Alterations in brain serotonergic function is thought to be involved in the onset and course of depression (Maes and Meltzer, 1995). Evidence suggests that individuals with a family history of depression (FH+) may be more 'genetically' susceptible to the development of depression; in some cases, this genetic susceptibility may involve allelic variation in genes that encode proteins that are critical in determining the overall level of serotonergic neurotransmission. A major problem, however, is that the role of brain serotonin in depression remains rather complex and it is unlikely that this neurotransmitter is entirely responsible for the pathogenesis of depression (Maes and Meltzer, 1995). Even though genetic vulnerability to depression, due to allelic variation in genes that influence serotonergic function, may constitute a likely risk factor in the development of depression, it does not seem to be the sole contributor. Based on previous data, stress has been suggested as an additional factor. Depression can be precipitated in susceptible individuals by a series of stressful life events. Indeed, individuals that frequently experience severe stressful life events, for instance loss, humiliation or defeat, are more likely to develop major depression relative to individuals who do not experience such major stressful events (Brown *et al*., 1987; Heim and Nemeroff,

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2001). However, even though major stress has frequently been found to precede the onset of depressive symptoms, this observation does not allow us to draw causal conclusions. We still need to know when and how stress may cause depressive symptoms and how biological mechanisms may interfere or be involved. Therefore, evidence detailing whether stress generates or promotes biological (brain) dysfunctions that are typically found in depression is required (Van Praag *et al*., 2004). This is indeed suggested by considerable evidence for dysfunctional stress hormone regulation in depressive patients and for complex interrelationships between the serotonergic system and neuroendocrine mechanisms involved in stress perception and stress adaptation (Arborelius *et al*., 1999; Holsboer, 2000; Markus, 2003; Van Praag, 2004). In addition, challenges to either the brain serotonergic system or neuroendocrine stress mechanisms involved in stress perception and adaptation may (further) interrupt the complex neurophysiological balance and promote the development of depression (Markus, 2003; Porter *et al*., 2004). Based on these new insights, it is assumed that serotonergic vulnerability (defined as a serotonergic system which is more vulnerable or sensitive to serotonergic alterations or dysregulations; this vulnerability may be genetically determined), particularly under major or prolonged stress exposure, may constitute a risk factor for depression. This may be particularly relevant for individuals with a positive family history of depression in which a genetic predisposition, possibly related to allelic variations in genes that influence the serotonergic system, may promote the development of depression in response to severe and continued stress exposure.

Serotonin involvement in depression

It is widely accepted that serotonin (5-hydroxytryptamine, 5-HT), a neurotransmitter involved in the regulation of emotion, mood, sleep and aggression, plays a key role in the onset and course of depression (Maes and Meltzer, 1995; Neumeister *et al*., 2004a). Evidence supporting reduced brain 5-HT function in depression comes from studies reporting lower plasma availability of the 5-HT precursor, tryptophan, for uptake into the brain, reduced cerebrospinal fluid (CSF) concentration of the serotonin metabolite 5-hydroxyindoleacetic (5-HIAA) and decreased platelet 5-HT uptake in depression (Maes and Meltzer, 1995; Neumeister *et al*., 2004a). Together, these studies suggest diminished brain 5-HT uptake and metabolism in depressive patients. In addition, disturbances of 5-HT receptor function have been described. The disturbances primarily involve altered postsynaptic 5-HT_{2A} receptor and presynaptic 5-HT_{1A} receptor functioning, which results in the dysregulation of 5-HT neurotransmission (Stahl, 1998). The state of the 5-HT_2 receptor system remains rather unclear with some studies reporting upregulation (e.g. Biegon *et al*., 1990; Pandey *et al*., 1990) and others reporting downregulation (Audenaert *et al*., 2001) of 5-HT_{2A} receptors in depression. This variability may indicate differing levels of 5-HT_2 dysfunction in varying areas of the brain. Depression is more consistently associated with presynaptic 5-HT_{1A} receptor upregulation and postsynaptic 5-HT_{1A} receptor downregulation (Maes and Meltzer, 1995; Van Praag *et al*., 2004). Additional, direct evidence of 5-HT_{1A} receptor pathology in depression comes from imaging studies using Positron Emission Tomography (PET) showing reduced 5-HT_{1A} receptor binding in depressed patients (Drevets *et al*., 1999; Sargent *et al*., 2000). However, these abnormalities do not seem to be specific for depression as they have also been found in patients with panic disorder with and without depression (Neumeister *et al*., 2004b). Moreover, involvement of other 5-HT receptor subtypes has not been clearly investigated due to a lack of specific receptor ligands.

In addition to 5-HT involvement in depression, allelic variations in the gene that encodes the 5-HT transporter protein (*5-HTT*) are currently being explored as genetic risk factors for depression (Mann *et al*., 2000; Neumeister *et al*., 2002). Five-HTT plays a crucial role in serotonergic neurotransmission by facilitating reuptake of 5-HT into the presynaptic neuron (Lesch *et al*., 1996; Neumeister *et al*., 2002). Fewer 5-HTT sites have been reported in functional imaging studies in depressive patients (Malison *et al*., 1998) as well as post-mortem studies (Mann *et al*., 2000), indicating less 5-HTT binding in depressive patients compared to healthy controls. The 5-HTT gene maps to chromosome 17q11.1-q12 (Lesch *et al*., 1994) and evidence revealed a 5-HTT gene-linked polymorphic region (*5-HTTLPR*) with two common alleles or variants: the short form (*s*) and the long form (*l*) (Heils *et al*., 1996). The short form of this variant is less active resulting in reduced transcriptional efficiency of the 5-HTT gene, decreased 5-HTT expression and reduced 5-HT uptake relative to the long form (Greenberg *et al*., 1999; Heils *et al*., 1996). The functional effect on 5-HT availability suggested an association between the *s* allele and depression-related phenotypes. Some data indeed reveal associations between the *s* allele and negative emotionality in adults (Lesch *et al*., 1996) and infants (Auerbach *et al*., 1999). Furthermore, individuals homozygous for the *s* allele are more likely to have multiple first-degree relatives with a history of depression (Joiner *et al*., 2003) and depressed patients (Collier *et al*., 1996) as well as suicide victims (Bondy *et al*., 2000) were more likely to carry an *s* allele. Moreover, it has been found that 3,4 methylenedioxymethamphetamine (MDMA, or Ecstasy) users carrying the *s* allele show abnormal emotional processing and higher depression scores compared to ecstasy users homozygous for the l-allele and control subjects carrying the *s* allele. MDMA binds to the 5-HTT preventing uptake and stimulating the release of 5-HT. These events cause long-term changes to the 5-HT system (Roiser *et al*., 2005). However, findings concerning an association between the *5-HTTLPR* polymorphism and depression have been inconsistent; most studies revealed an association between the *s* allele and depression (Collier *et al*., 1996; Neumeister *et al*., 2002; Joiner *et al*., 2003; Gonda *et al*., 2005; Gonda *et al*., 2006) but not all (Willis-Owen *et al*., 2005). Inconsistent results detailing the association between *5-HTTLPR* and depression may be due to ethnicity or gender effects on 5-HT neurotransmission (Williams *et al*., 2003). There is also a paradox in the observation that low 5-HT uptake resulting from the *5-HTTLPRs* allele may increase the likelihood of developing depression, whereas low 5-HT reuptake caused by selective serotonin reuptake inhibitors (SSRIs) is a well-accepted treatment for depression. The latter issue, however, may arise from the fact that the

reduced uptake of 5-HT caused by the *5-HTTLPRs* allele occurs throughout development and post-natal life and consequently may cause permanent changes in the developing brain, whereas SSRIs reduce 5-HT uptake only when actually administered mostly in adults when the brain is fully developed and less subjected to plasticity and structural-functional changes (Wurtman, 2005). Nevertheless, this paradox remains unresolved.

It seems as though a predisposition to altered 5-HT functioning in certain populations of healthy subjects appears to be a significant risk factor in the development of depression. Such a '5-HT vulnerability for depression' may particularly be involved in first-degree family members of depressed patients who appear to have a two- to threefold increased risk for the development of major depression (e.g. Reich *et al*., 1987; Sullivan *et al*., 2000). Support for diminished 5-HT functioning in these populations is derived from studies using the acute tryptophan depletion (ATD) strategy (Young *et al*., 1985). Brain 5-HT synthesis and activity is lowered by depletion of the amount of plasma tryptophan (TRP, precursor of 5-HT) relative to the sum of the other Large Neutral Amino Acids (LNAAs) for which tryptophan competes for uptake into the brain (Fernstrom and Wurtman, 1971; Maes and Meltzer, 1995). This is accomplished through administration of a balanced tryptophan-free (TRP–) amino acid mixture, which contains all essential amino acids except for tryptophan. This reduces the amount of plasma TRP as compared to the LNAAs (TRP/LNAA ratio) by raising incorporation of TRP into protein synthesis and, thus, increases competition of the LNAAs for which TRP competes for uptake into the brain (i.e. Gessa *et al*., 1974; Maes and Meltzer, 1995; Moja *et al*., 1991). Evidence for reduced 5-HT neurotransmission after ATD comes from PET imaging studies (Nishizawa *et al*., 1997) as well as from studies measuring CSF 5-HIAA concentrations (Nishizawa *et al*., 1997; Carpenter *et al*., 1998; Williams *et al*., 1999).

Healthy subjects with a positive family history of depression showed significantly greater depressed mood after ATD than healthy controls without a family history (Benkelfat *et al*., 1994; Klaassen *et al*., 1999). Further, tryptophan depletion is found to cause depressive relapse in depressive patients treated with (and responding to) monoamine oxidase inhibitors (MAOIs) or SSRIs (Delgado *et al*., 1990; Delgado *et al*., 1994; Delgado *et al*., 1999; for a review on tryptophan depletion in psychiatric populations see Bell *et al.*, 2001; Van der Does, 2001), whereas in healthy subjects mood lowering effects are not found or appear to be rather modest (e.g. Benkelfat *et al*., 1994; Bhatti *et al*., 1998; Klaassen *et al*., 1999). The mood-lowering findings of ATD in individuals with a FH+ and (remitted) depressive patients strongly support the assumption that 5-HT vulnerability may constitute an important risk factor for the development of depression. Moreover, the exclusive effects of ATD in first-degree relatives of depressive patients suggest that 5-HT susceptibility in these subjects may be genetically transmitted. In addition, Neumeister *et al*. (2002) suggested that the mood lowering effects of ATD may depend on the genotype for the *5-HTTLPR* and family history of depression because FH+ in combination with only one copy of the *s* allele promotes the depressogenic effects of ATD.

Previous evidence suggests that 5-HT vulnerability is a risk factor in the development of depression. In particular, individuals with a positive family history of depression may have an increased risk for depression due to a genetic vulnerability involving the 5-HT system. Despite the fact that this genetic vulnerability may promote the development of depression, the majority of individuals with a positive family history of depression do not develop depression (Sullivan *et al*., 2000). Gene–environment interactions have been suggested in the aetiology of depression. Because depression is often preceded by stress, researchers have hypothesized that a genetic vulnerability to depression, related to the serotonergic system, might be expressed only if an individual is exposed to stress (Van Praag, 2004). Hence, bidirectional interactions are proposed between the stress system and the serotonergic system. Ultimately, these interactions may induce serotonergic dysfunction and promote the development of a depressive disorder (Markus *et al*., 2000b; Van Praag *et al*., 2004).

Interaction stress, brain 5-HT and susceptibility for depression

Biological as well as psychological factors are involved in depression and recent data suggest that (genetic) 5-HT vulnerability and cognitive stress perceptions may mutually increase the risk of depression. In support of this assumption, interactions between 5-HT and the regulation of neuroendocrine stress mechanisms have been clearly reported. Interestingly, challenges of either system may reduce the function of the other (Porter *et al*., 2004).

In response to stress, the hypothalamic–pituitary–adrenal (HPA) axis is activated. The HPA axis constitutes the major stress-adaptation mechanism that, on the one hand, provides extra glucose for the sympathetic stress responses and behavioural action and, on the other hand, suppresses the stress response in order to re-establish a physiological balance (Ursin and Olff, 1993). The HPA axis consists of three components: the hypothalamus, the anterior pituitary and the adrenal cortex (Arborelius *et al*., 1999). Upon receiving various limbic inputs indicative of stress, cell bodies at the level of the paraventricular nucleus (PVN) of the hypothalamus are stimulated to enhance the release of corticotropin-releasing hormone (CRH). CRH, in turn, is the main modulator for cell bodies in the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) and related peptides that originate from the same precursor pro-opiomelanocortin. ACTH is secreted into the systemic circulation and stimulates the adrenal cortex to release glucocorticoid cortisol. Cortisol, in turn, re-establishes the internal balance of the nervous system and the body by exerting a variety of actions throughout the brain in order to terminate the stress response, recover from stress and prepare the organism for stress coping (Sapolsky, 1992; Ursin and Olff, 1993; Dinan, 1994). These effects of cortisol are regulated by fast and slow negative feedback mechanisms on several levels of the HPA axis resulting in reduced release of CRH and ACTH. Hence, cortisol binds to receptors at the level of the hippocampus, hypothalamus and pituitary to mediate negative feedback to the HPA axis (e.g. Fulford and Harbuz, 2005). Rapid feedback occurs within minutes primarily by inhibiting CRH and ACTH release at the level of the PVN and anterior pituitary (Steckler *et al.*, 1999).

Delayed feedback emerges 1–2 hours later via an inhibitory action of cortisol at the level of the hippocampus to prevent continued activation of the HPA axis (Fulfor and Harbuz, 2005).

There is ongoing evidence that the HPA system may be hyperactive in depression (for a detailed review on the role of the HPA system in depression see Steckler *et al*., 1999; Holsboer, 2000; De Kloet *et al*., 2005). In the majority of studies, half of depressive patients respond with hyperactivation of the HPA axis (Nestler *et al*., 2002). Disturbances in the function of the HPA axis result in increased levels of circulating ACTH, increased urinary cortisol excretion and increased levels of CRH in CSF (Holsboer, 2000; Van Praag, 2004). Neuroendocrine function tests have been used to investigate further abnormal HPA function. Depressive patients show reduced suppression of ACTH and cortisol after pre-treatment with 1–2 mg dexamethasone (i.e. the dexamethasone (DEX) suppression test) in comparison to healthy controls (e.g. Carroll, 1982). In depressive patients, the normal degree of cortisol suppression requires higher doses of dexamethasone suggesting that the cortisol-mediated negative feedback is changed to a higher set-point (Modell *et al*., 1997). Additionally, intravenous administration of CRH leads to an increased ACTH response but normal cortisol response in depressed patients compared to controls (Holsboer *et al*., 1986). More recently, a combined DEX–CRH test has been used to investigate abnormal HPA function. It was found that dexamethasone pre-treated depressed patients show enhanced ACTH and cortisol response to CRH compared to healthy controls (e.g. Rybakowski and Twardowska, 1999; Von Bardeleben and Holsboer, 1989). Moreover, the hormonal response pattern following the combined DEX–CRH test of individuals with a family history of depression were more comparable to the enhanced response typically found in depressed patients suggesting that the vulnerability for HPA axis abnormalities observed in depression may also be (at least partly) genetically determined (Holsboer *et al*., 1995; Modell *et al*., 1998).

Serotonin plays an important role in regulating HPA axis activity and stress coping and there are strong interrelationships between stress and serotonin function. In various animal models, it has been shown that serotonin is important in activating the HPA axis by stimulating CRF release, triggering ACTH release and stimulating corticosteroid secretion (Lefebvre *et al*., 1992; Fuller, 1996). The serotonergic activation of the HPA axis has also been suggested for humans (Dinan, 1996). Furthermore, in animals, it has been found that acute stress leads to a rise in brain 5-HT turnover by increasing TRP availability and stimulating tryptophan hydroxylase (e.g. De Kloet *et al*., 1982; De Kloet *et al*., 1983; Davis *et al*., 1995). The increased release of brain 5-HT is important because it enhances the negative feedback control of cortisol on the HPA axis, as a biological mechanism for stress adaptation (Nuller and Ostroumova, 1980; Van Praag *et al*., 2004). Conversely, dysfunctional brain 5-HT activity may deteriorate HPA function and reduces stress adaptation in animals (Seckl and Fink, 1991) and humans (Maes *et al*., 1991). In animals, continued stress exposure or chronic stress is found to have a negative influence on the 5-HT system and may increase 5-HT sensitivity or vulnerability as a compensatory response (Adell *et al*., 1988). The existence of a clear mutual relationship between reduced 5-HT function, reduced stress adaptation and subsequent increased vulnerability to mood deterioration was further suggested by findings that increases in brain 5-HT improve stress coping and, subsequently, lead to reduced depressive mood in healthy stress-susceptible subjects but not in controls (e.g. Markus *et al*., 1998; Markus *et al*., 2000a; Markus *et al*., 2000b). The link between serotonin, stress and depression has also been investigated in a study using ATD (Richell *et al*., 2005). Healthy subjects were more susceptible to the mood-lowering effect of uncontrollable stress exposure after ATD than placebo.

Based on these previous findings, 5-HT vulnerability for depression in healthy individuals with a positive family history may be accompanied by reduced stress coping mechanisms during exposure to acute stressful situations. As a consequence, the experience of severe prolonged stress in these vulnerable subjects may further challenge the 5-HT system which, in turn, may further increase 5-HT vulnerability (enhancing 5-HT dysfunction through extra- and intracellular messenger pathways including reduced 5-HT receptor gene expression) and ultimately increases the risk to develop depression. Support of the assumption that stress, in combination with 5-HT vulnerability, may increase the risk for depression comes from recent studies showing that *5-HTTLPR* can moderate the influence of stress on the onset of depression (Caspi *et al*., 2003; Kendler *et al*., 2005). For instance, Caspi *et al*. (2003) found that individuals carrying one or two short alleles of the *5-HTTLPR* were more sensitive to the depressogenic effects of stressful life events than individuals homozygous for the long allele. However, Kendler *et al*. (2005) found that the interaction between stressful life events and genotype resulted from an increased sensitivity to the depressogenic effects for individuals homozygous for the short allele. The gene–environment interaction has also been investigated in maltreated children (Kaufman *et al*., 2004). Maltreated children with the s/*s* genotype had higher depression scores than control children with the same genotype. Interestingly, this was also influenced by the social support the children experienced with only slightly increased scores for children with good social support and markedly increased depression scores for maltreated children without social support.

It should be mentioned that one study, which aimed to replicate these findings, failed to do so (Gillespie *et al*., 2005) and two studies could only replicate the findings partially (Eley *et al*., 2004; Grabe *et al*., 2005). Gillespie *et al*. (2005) did not find an interaction between *5-HTTLPR*, life events and depression and suggested the wide age range (19–78 years; only 20% were aged below 30) as a possible factor contributing to the negative findings. Eley *et al*. (2004) and Grabe *et al*. (2005) could replicate the findings in women only. However, very recently, Wilhelm *et al*. (2006) reported a significant interaction between the *5-HTTLPR*, adverse life events and major depression in a longitudinal study demonstrating that the *s* allele of the *5-HTTLPR* increases the likelihood of developing depression after exposure to multiple stressful life events. Moreover, human neuroimaging studies have shown that individuals carrying the *s* allele of *5-HTTLPR* exhibit a greater stress response in the amygdala in reaction to fearful stimuli compared to individuals homozygous for the *l* allele (Hariri *et al*., 2002; Hariri *et al*., 2005).

Conclusion and future directions

Biological as well as psychological factors are involved in depression and it seems as if serotonergic vulnerability, particularly in combination with stress, increases the likelihood of developing depression. Evidence suggests that bidirectional interactions between the neuroendocrine stress mechanisms and the brain serotonergic system are responsible for the increased vulnerability to depression after stressful life events.

The serotonergic vulnerability may be innate as suggested by family and twin studies but may also be acquired during development or later in life. Future research should clarify whether a polymorphism at the 5-HTT gene indeed reflects serotonergic vulnerability as suggested for family members of depressive patients. In addition, family members of depressive patients may be more prone to the depressogenic effects of stress than healthy individuals without a family history of major depression depending on 5-HTT genotype or earlier exposure to stress.

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