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Review

Vulnerability to lasting anxiogenic effects of brief exposure to predator stimuli: Sex, serotonin and other factors—Relevance to PTSD

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ABSTRACT

Lasting anxiogenic effects of predator stress in rodents may model aspects of post-traumatic stress disorder (PTSD). There is a link between genetic variation in the serotonin (5-HT) transporter (SERT) and anxiety in humans, prompting the generation of SERT knockout mice. This review brings together studies of SERT knockout male mice, normal female mice, and different 5-HT receptors in predator stress effects on anxiety. These studies provide for a link between vulnerability to the anxiogenic effects of predator stress and abnormalities of 5-HT transmission induced by a life long reduction in 5-HT reuptake in male mice, which creates a vulnerability like that seen in normal female mice. Data reviewed suggest abnormalities in 5-HT transmission contribute to vulnerability to lasting anxiogenic effects of species relevant stressors. To the extent to which predator stress effects model aspects of PTSD, and in the light of relevant human literature, these considerations implicate abnormalities of 5-HT transmission in vulnerability to PTSD per se, and as a potential contributor to enhanced female vulnerability to PTSD.

Contents

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1. Severe stress and affective psychopathology

1.1. Prevalence and vulnerability

Anxiety associated with traumatic stress is a serious problem in view of the fact that many in North America experience some form of traumatic stress in their lifetimes, and a smaller percentage of those (6.8%) may develop post-traumatic stress disorder (PTSD) (Kessler et al., 2005). PTSD can be a debilitating disorder characterized by three major symptom clusters: re-experiencing (intrusive reminiscence of the trauma), avoidance of trauma reminders/numbing, and increased arousal (such as enhanced startle) (Bremner, 1999). In addition, this condition is often comorbid with other disorders, including generalized anxiety and depression. PTSD is a difficult disorder to treat, and may persist over the patient's lifetime. Moreover, there are marked inter-individual differences in risk for PTSD, and females appear more vulnerable (Bremner, 1999; Kessler et al., 1995). Therefore, gaining knowledge about the neurobiological causes and vulnerability factors for PTSD is important to guide treatment options and perhaps lead to new, more effective treatments in the future.

1.2. Animal models based on associative fear learning

There is no ideal animal model to study the mechanisms of stress precipitation of affective disorder, or vulnerability to it, but some models are promising. Classical associative fear conditioning is one model in which studies have advanced understanding of neural mechanisms underlying acquisition and extinction of cued fear memories (Blair et al., 2001; Maren et al., 1994; Rogan et al., 1997; Schafe et al., 2001). There is growing interest in using this model to gain insights into mechanisms of onset of trauma reminiscence in PTSD (Elzinga and Bremner, 2002), and as a guide to post-stressor prophylactic intervention in humans (Pitman et al., 2002; Vaiva et al., 2003).

1.3. Animal models of sensitized fearfulness—predator stress

An important clinical observation is that non-associative sensitized fearfulness manifested as generalized anxiety is also a feature of PTSD (Pitman, 1997). As mentioned above, there are marked inter-individual differences in risk for PTSD, and females appear more vulnerable (Kessler et al., 1995). As such, animal models of sensitized fearfulness which show differential vulnerability and sex-related vulnerability may be particularly relevant to study of mechanisms of stress precipitation of affective disorder. In this context, changes in affect following exposure to species relevant life threatening circumstances provide models of stressor-induced affective psychopathology with ecological validity. Predator stimuli are clearly stressful for rodents. Exposure to natural predators and their odors induce a pattern of monaminergic and stress hormonal elevations in rats (Adamec et al., 1998) and mice (Belzung et al., 2001; Hayley et al., 2001). Furthermore, exposure of rats and mice to natural predators or to their odors induce anxiety-like states (e.g., Adamec and Shallow, 1993; Berton et al., 1998; Blanchard et al., 1990a, 2001; Dielenberg and McGregor, 2001; Kavaliers et al., 1994; Zangrossi and File, 1992b). For example, rats avoid cat odor sources (Dielenberg et al., 1999), and display high rates of risk assessment oriented toward the threatening odor (Blanchard et al., 1990b). When tested shortly after exposure to predator odors, rats display an anxiogenic response in the social interaction and elevated plus-maze (EPM) tests (Zangrossi and File, 1992a). Chronic exposure to rat odor in mice also induces anxiogenic responses in the EPM (Calvo-Torrent et al., 1999). Finally, anxiety-like behavior and risk assessment in the EPM is lastingly affected by predator stress, in both rats (Adamec, 2001; Adamec and Shallow, 1993) and mice (Calvo-Torrent et al., 1999).

Most of the post-stress anxiogenic effects of predator stress have been tested within relatively short times (h) after the stress. However, increased anxiety-like behavior resulting from unprotected exposure of rats to a cat can actually induce changes that are long lasting (3 weeks or more) (Adamec, 1997; Adamec and Shallow, 1993; Cohen et al., 1999, 2003) as measured in the EPM, light/dark box and acoustic startle tests (Adamec, 2003). For these and other reasons, predator stress has been suggested as a model some of the hyper arousal and generalized anxiety aspects of PTSD (Adamec, 1997; Adamec et al., 1998, 2006a, 2007). Interestingly, multivariate correlation analysis (path analysis) reveals that both the nature of the stressor (cat behavior toward the rats) and the defensive response of the rats to the cat are predictive of degree of anxiogenic response measured 1 week later (Adamec et al., 1998). Nature of response to traumatic stressors (such as certain dissociative symptoms (e.g., time slowing, derealization) and cognitive appraisal (e.g., belief that one is about to die)) as well as the severity of the stressor are also predictive of symptom severity in PTSD (Ikin et al., 2004; Marmar et al., 1994; McNally, 2003). Moreover, as mentioned above, not all people exposed to severe stress develop chronic PTSD (Kessler et al., 1995) consistent with differential vulnerability to respond to severe stress (Charney, 2004). Such differences in risk may be in part mediated by genetic variability between individuals, given evidence that genes contribute substantially to risk for anxiety disorder (Hettema et al., 2001). Encouragingly, a number of studies have shown that differential vulnerability to predator stress occurs in rats (Cohen et al., 2003, 2004). Rats may respond to predator stress with severe and lasting anxiety (in the EPM) and startle enhancement (about 25% of rats of several strains) or not at all (about 25%). The remainder show significant but milder effects. Finally, predator stress has neurobiological and neuropharmacological features which recommend it as a model of aspects of PTSD (for review see Adamec et al., 2006a). For example, there is evidence that predator stress induces lateralized lasting potentiation of right amygdala afferent and efferent neural transmission which likely mediates behavioral effects (Adamec et al., 2005b), paralleling right amygdala hyperexcitability in PTSD (Rauch et al., 2000, 2006). In addition propranolol given just after stress blocks lasting changes in affect in predator stressed rats (Adamec et al., 2007), paralleling a similar effect of immediate post-trauma propranolol on PTSD symptom severity measured months later in humans (Pitman et al., 2002; Vaiva et al., 2003).

2. Predator stress and murine anxiety–transgenic mice

The mouse provides a potentially very valuable approach to identify genetic factors underlying differences in predator stress reactivity. Of note, the applicability of gene knockout and transgenic technology in the mouse make this species a unique experimental tool (Cryan and Holmes, 2005). Recent findings demonstrate that lasting anxiogenic effects of predator stress are produced in various strains of (non-mutant) mice, as they are in rats. For example, 2–10 min exposures of CD-1 mice to rat odor (shavings) increases response to acoustic startle for at least 7 days (Hebb et al., 2003), similar to duration of effects seen in rats exposed to cats (Adamec, 1997; Adamec et al., 1999). Anxiogenic increases in EPM risk assessment following cat exposure have also been reported to last up to 7 days in male CFW mice (Adamec et al., 2004c).

2.1. Graded effects of predator stimuli, female mice and vulnerability

Extending the aforementioned work, recent studies with C57BL/6J mice demonstrated graded and lasting (7 days) effects of 10 min exposures to a cat (predator stress) or a room rich in cat odor only (room stress) in this commonly used inbred mouse strain (Adamec et al., 2006c). Anxiogenic effects were observed as increases in open arm avoidance in the EPM and in lighted chamber avoidance in the light/dark box. Although room stress was without effect on startle responses, cat exposure enhanced peak startle amplitudes. Intriguingly, female C57BL/6J mice were more susceptible to the effects of predator and room stress than males. Furthermore, sex differences were specific to the behavioral endpoint measure examined. Thus, females but not males responded to cat exposure with a lasting increase in average startle amplitude. In contrast predator stress increases in the different measure of peak startle amplitude were equivalent in males and females. Perhaps most interestingly, while predator stress produced increased EPM anxiety across the sexes, only females responded with an elevated anxiety response to room stress. These findings suggest that EPM anxiety in females is affected more by the milder stress of cat odor exposure. In other words, this form of predator stress may be able to model increased trauma vulnerability in females.

2.2. Serotonin transporter (SERT) dysfunction and vulnerability to stress effects on affect in humans and animals

The serotonin transporter (5-HTT, SERT) regulates serotonergic neurotransmission by clearing serotonin from the extracellular space (Blakely et al., 1991; Torres and Amara, 2007). SERT is an important initial target for the serotonin reuptake inhibitor class of antidepressants and anxiolytics. There is also increasing evidence implicating SERT in stress-related disorders. For example, levels of SERT have been found to be significantly less in the prefrontal cortex and amygdala of males and females with depression, as compared to controls (Oquendo et al., 2007; Parsey et al., 2006). However, it is not clear whether changes in SERT expression are a consequence of the disease, or an antecedent factor that increases vulnerability to stress.

In this context, there is evidence that genetic variation in SERT may predispose towards stress susceptibility. A common polymorphic variant in the regulatory region of the SERT gene (SLC6A4) has been associated with increased risk for stress-related disorders such as anxiety and depression. Specifically, a so-called short(s) allelic version of this polymorphism has been found to cause relatively reduced SERT brain expression and lesser serotonin reuptake in vitro (Lesch et al., 1996; Little et al., 1999). Individuals carrying this loss-of-function gene variant appear to be at modestly increased risk for trait anxiety, and are more likely to present with depression following exposure to stressful life events (Caspi et al., 2003; Kendler et al., 2005; Lesch et al., 1996). Comparable findings have been obtained in rhesus macaques carrying a homologue of the s allele and exposed to early life stress (peer rearing)—in which females exhibit enhanced stress hormone responses to stress (Barr et al., 2004). In a somewhat parallel finding in humans, females with the s allele in combination with life stressors (care giver stress or low childhood socioeconomic status) exhibited more severe symptoms of depression than comparable males (Brummett et al., 2008). Finally, and of particular interest to the current discussion, Lee et al. recently examined the association between the SERT s allele and PTSD in one hundred PTSD patients and one hundred ninety seven healthy controls using a case–control design. The frequency of the s allele was found to be significantly higher in PTSD patients than controls suggesting that this genotype was a risk factor for PTSD (Lee et al., 2005). For further reviews of the extensive literature linking SERT genotype with risk for stress-related disease (see Anguelova et al., 2003; Lotrich and Pollock, 2004; Rees et al., 1997; Serretti et al., 2007).

Targeted gene knockout of SERT in mice results in an array of phenotypic abnormalities characterized by increased anxiety-like behavior and exaggerated neuroendocrine responses to stress (Holmes et al., 2003b). SERT knockout mice exhibit increased anxiety-like behavior in tests such as the elevated plus-maze when tested in the light (Ansorge et al., 2004; Holmes et al., 2003a; Holmes and Hariri, 2003) but not when tested after handling under red light (Adamec et al., 2006b). Exposure to modest stress, including low maternal care, further enhances anxiety-like behavior in these mice (Adamec et al., 2006b; Carola et al., 2008). Thus, the stress vulnerability phenotype of these mutant mice to some extent mimics that of the human s allele.

Against this background, recent findings identify SERT and various serotonin receptor subtypes as key mediators of the aforementioned effects of predator stress (Adamec et al., 2004a,b, 2006b). We recently assessed the anxiogenic effects of predator stress in male SERT knockout mice (Adamec et al., 2006b). The knockout mice were backcrossed onto a C57BL/6J background, a strain in which males are insensitive to room stress (Section 2.1). Therefore, we tested the lasting effects of brief cat room exposure on affect in male SERT knockout mice (Adamec et al., 2006b). Three types of male mice were studied: homozygous SERT knockouts (SERT−/−, KO), heterozygous (SERT+/−, HET) and wild type (WT). Mice from each genotype were either handled, or exposed for 10 min to a large room in which a cat had been resident for 1 h (i.e., the same procedure used to differentiate room stress effects between non-mutant male and female C57BL/6J mice in Section 2.1). Handled controls were handled for 1 min on the day of cat room exposures outside of their home cage room area. They were not exposed to cat odors. Seven days later, all mice were tested for anxiety using the EPM. Results showed that, similar to previous results in non-mutant female C57BL/6J mice, room stress had a lasting anxiogenic effect (reduced open arm exploration in the EPM) in male SERT knockout mice relative to handled controls (combined across genotypes) (Adamec et al., 2006b). As expected, room stress was not sufficient to increase anxiety in male wild type mice. Changes in open arm exploration in stressed SERT knockout mice were not due to changes in general activity. Also (and again as was previously found in male non-mutant C57BL/6J mice (Adamec et al., 2006c)), room stress was without effect on peak or average startle amplitude in any genotype.

Taken together, these data demonstrate that the relatively mild stress of exposure to predator odor has a lasting impact on anxiety-like behavior in male SERT knockout mice highly reminiscent of that seen in female non-mutant C57BL/6J mice. Generally, this adds to a literature obtained across species showing that loss of SERT gene function increases vulnerability to stress. More specifically, enhanced sensitivity to predator stress in male SERT knockout mice raises the possibility that sex differences in sensitivity to predator stress may be driven vis-à-vis the serotonin system and suggests that SERT knockout mice may be a useful model to identify the mechanisms involved.

3. Clues to mechanisms of increased stress vulnerability arising from low functioning SERT polymorphisms

Of particular interest to the question of mechanisms of enhanced vulnerability to predator stress in SERT knockout mice are functional alterations in 5-HT receptors. SERT knockout mice exhibit a reduction in binding density and/or function of 5-HT1A

receptors in several brain areas, including the amygdala, and this reduction is especially prominent in females (Bouali et al., 2003; Fabre et al., 2000; Li et al., 2000, 2003, 2004, 1999). (*Note*: a reduction in 5-HT1A receptor binding is also found in human s allele carriers (David et al., 2005).) This sex difference may be driven by estrogen given evidence that 17β-estradiol downregulates 5-HT1A receptors in the rodent brain (Maswood et al., 1995; Osterlund et al., 2000; Trevino et al., 1999), and the finding that ovariectomy partially reverses 5-HT1A receptor downregulation in female SERT knockout mice (Bouali et al., 2003). There is also a sex-independent increase of binding density of 5-HT2A receptors in the amygdala of SERT knockout mice (Li et al., 2003). These changes are intriguing given data obtained from predator-stressed rats, which demonstrates that agonism of 5-HT1A receptors or antagonism of 5-HT2A receptors following stress interferes with the development of lasting anxiety-related changes (Adamec et al., 2004a,b). These findings support an important mechanistic role for 5-HT1A and 5-HT2A receptors in mediating the neuroplastic changes produced by predator stress that ultimately lead to increased anxiety.

The available evidence raises the possibility that an upregulation of 5-HT2A receptors could promote predator stress-induced anxiety. 5-HT2A receptor agonism activates CRF containing cells in rodent central amygdala and stimulates stress hormone release (ACTH and corticosterone) (Van de Kar et al., 2001). CRF is implicated in predator stress effects in mice in that post-stress block of CRF type 1 receptors prevents lasting increases in startle amplitude in WT C57 mice (Adamec, in preparation). Moreover, enhanced stress hormone release could also contribute to amplified effects of stress in that both mineral corticoid (MR) and glucocorticoid receptor (GR) block post-stress interferes with anxiogenic effects of predator stress in rats (Adamec et al., 2007).

A role for the 5-HT1A receptor is supported by a number of lines of evidence linking the receptor with limbic excitability and neural plasticity. Predator stress induces right hemisphere lateralized NMDA receptor dependent long lasting potentiation (LLP) of transmission in the amygdala (Adamec et al., 2005a). This right lateralized increase in transmission parallels the right lateralized enhanced amygdala responsiveness to negative affective provocation in positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies of PTSD patients (Rauch et al., 2000, 2006; Rauch and Shin, 1997; Shin et al., 1997). In the rat, this neuroplastic change caused by predator stress is observed both in afferent (ventral hippocampus to basolateral amygdala (BLA)) and efferent (central amygdala to lateral periaqueductal gray) pathways (Adamec et al., 2005a,b). In addition, the degree of LLP in these two pathways in the right hemisphere predicts up to eighty percent of the variance in the lasting anxiogenic effects of predator stress (Adamec et al., 2005b).

5-HT1A receptors represent excellent candidates as modulators of this form of limbic plasticity. 5-HT1A agonism can block NMDA receptor-dependent afferent LTP in rat BLA slices (Pollandt et al., 2003). This could possibly contribute to the aforementioned ability of 5-HT1A receptor agonists to prevent the development of anxiogenic-like effects of predator stress (Adamec et al., 2004a). Contrariwise, loss of 5-HT1A receptor function in SERT knockout mice, particularly females, might remove an important brake on stress-induced plasticity in this circuit, with detrimental consequences for sensitivity to the anxiety-related behavioral consequences of predator stress. Could similar pathological mechanisms be at play in humans?

There is preliminary evidence that a variant (single nucleotide polymorphism −1019C/G) in the human 5-HT1A receptor (HTR1A) gene is linked to risk for affective disorders (Huang et al., 2004; Lemonde et al., 2003). For example, among healthy volunteers, Stroebel et al. found a significant effect of this variant on trait harm avoidance and neuroticism (the −1019G being positively associated). These findings suggest a possible role of allelic variation in the 5-HT1A receptor in the development and modulation of anxiety and depression-related personality traits. This is of relevance to PTSD as neuroticism and harm avoidance are part of a syndrome of trait negative affectivity proposed as a predisposing factor to stress precipitated anxiety disorders (deGraaf et al., 2002; Fox et al., 2005; Rapee, 2002). 5-HT1A and SERT polymorphisms are together associated with a pattern of limbic and prefrontal cortical activation which is PTSD-like. fMRI studies of panic patients carrying either the 5-HT1A −1019G and/or SERT short(s) risk alleles reveal that fearful faces provoke decreased activation of right prefrontal cortex and increased amygdala activation (Domschke et al., 2006; Heinz et al., 2005; Pezawas et al., 2005). Consistent with these findings, reduced 5-HT1A autoreceptor density (visualized with PET) predicts fMRI-measured amygdala reactivity to fearful faces in normal volunteers (Fisher et al., 2006).

Collectively, these data lead to a model in which disturbances of 5-HT modulation of corticolimbic circuitry predisposes to stress-driven plastic changes underlying enhanced traumatic memory and generalized fear. This would be consistent with current models of PTSD, which posit reduced prefrontal activation coupled with enhanced amygdala reactivity (Rauch et al., 2000; Shin et al., 2001, 2005). For example, the right amygdala of PTSD suffers shows exaggerated activation to both trauma reminders and more general negative emotional stimuli (Rauch et al., 1997, 2000). Rauch et al. (2006) suggest that given the phenomenological parallels between fear conditioning and the pathogenesis of PTSD, PTSD may be characterized by exaggerated amygdala responses (subserving exaggerated acquisition of fear associations and expression of fear responses) and deficient frontal cortical function (mediating deficits in extinction and the capacity to suppress attention/response to trauma-related stimuli), as well as deficient hippocampal function (mediating deficits in appreciation of safe contexts and explicit learning/memory). This convergence of preclinical and clinical data bodes well for future studies using animal models such as predator stress exposure to elucidate the genetic and sex-related factors underlying PTSD.

4. Conclusions

Studies using the predator stress model have provided novel insights into the neural mechanisms causing enhanced sex- and genotype-related vulnerability to the effects of predator stress. Data from knockout mice lacking SERT suggests that SERT gene dysfunction coupled with alterations in 5-HT1A and 5-HT2A receptors may be one mechanistic pathway underlying the enhanced predator stress vulnerability observed in these mice. In turn, this may identify a possible common mechanism by which serotonergic abnormalities, such as impaired 5-HT1A receptor modulation of limbic neuroplasticity, contribute to increased predator stress susceptibility in female mice. These emerging findings from rodent models, together with experimental data from non-human primates and humans, serve to point to fruitful lines of inquiry regarding sex differences in stress vulnerability.

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