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Review

From non-pharmacological treatments for post-traumatic stress disorder to novel therapeutic targets

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ABSTRACT

The development of new pharmacological therapies starts with target discovery. Finding new therapeutic targets for anxiety disorders is a difficult process. Most of the currently described drugs for post-traumatic stress disorder (PTSD) are based on the inhibition of serotonin reuptake. The mechanism of action of selective serotonin reuptake inhibitors was already described in 1977 (Benkert et al., 1977). Now, almost 40 years later, we still rely on the same mechanism of action and more effective pharmacological therapies, based on other working mechanisms, are not on the market yet. Finding new molecular switches that upon modulation cure or alleviate the disorder is hampered by a lack of valid animal models. Many of the characteristics of psychiatric disorders are typically human and hence animal models feature only part of the underlying pathology. In this review we define a set of criteria for animal models of PTSD. First, we describe the symptomatology and pathology of PTSD and the current pharmacological and non-pharmacological treatment options. Next, we compare three often-used animal models and analyze how these models comply with the set of criteria. Finally, we discuss how resolving the underlying mechanisms of effective non-pharmacological treatments (environmental enrichment, re-exposure) may aid therapeutic target discovery.

Contents

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1. PTSD

Post-traumatic stress disorder (PTSD) results from exposure to a traumatic event, which evokes fear, helplessness, and horror. The diagnostic criteria are categorized into three clusters of symptoms: (1) Re-experiencing of the trauma, in the form of e.g. nightmares, spontaneous flashbacks, or memories kindled by stimuli with a slight resemblance to the traumatic event. (2) Avoidance of stimuli or situations reminding of the trauma. This can lead to avoidance of thoughts, people, or activities that might stir recollection of the traumatic event, but also loss of memory for aspects of the trauma, or even emotional numbness to avoid feelings or thoughts about the event. And (3), persistent symptoms of increased arousal that were not present before the trauma, such as an exaggerated startle response, the feeling of always being on guard (hypervigilance), irritability (outbursts of anger), but also difficulty with concentration, and sleeping problems (APA, 2013).

Not everybody exposed to severe trauma develops PTSD. Only a relatively small number (10–15%) of people that are exposed to a traumatic event will develop this severe anxiety disorder (Breslau et al., 1991; Resnick et al., 1993; Kessler et al., 1995, 2005). With this in mind, PTSD can be regarded as failure to recover from a traumatic event.

The etiology and symptomatology of PTSD reveal that several behavioral systems are involved: fear learning (conditioning), fear extinction, and behavioral senitization. Very likely, brain areas and neurotransmitter systems that regulate these behavioral systems are affected in PTSD. Brain imaging studies show that PTSD patients have increased amygdala reactivity during fear acquisition, have smaller hippocampal volume, and show a failure of activation of the medial prefrontal/anterior cingulate cortex with re-experiencing of the trauma, which is thought to be responsible for the failure of extinction seen in PTSD (for review see Francati et al., 2007). An enhanced activity of the noradrenergic system has been suggested to mediate the hyperarousal symptoms seen in PTSD patients (Southwick et al., 1997, 1999). Noradrenalin plays an important role in the (re-) consolidation of (fear) memory. Increased noradrenergic activity in the amygdala may also contribute to the aversive/intrusive memories of PTSD patients (Southwick et al., 1999). This idea is supported by animal studies showing that a beta-adrenoceptor agonist applied in the amygdala enhanced fear memory (Debiec and LeDoux, 2006; Debiec et al., 2011). The serotonergic (5-HT) system too is linked to the pathophysiology of PTSD (Krystal and Neumeister, 2009). Interplay between traumatic events and a polymorphism of the 5-HT transporter (the 5-HTTLPR genotype) has been reported to be a susceptibility factor for PTSD (Lee et al., 2005; Grabe et al., 2009; Xie et al., 2009). Moreover, in 20–30% of the patients treatment with selective serotonin re-uptake inhibitors (SSRIs) leads to full recovery (Bandelow et al., 2008).

Changes in the neuroendocrine system seem to underlie the enhanced stress sensitivity. Although not uniformly consistent across studies, hypo-cortisolism is observed in many PTSD patients (Yehuda, 2006b). Prospective studies suggest that low cortisol levels might be a predictive variable for the development of PTSD after exposure to trauma (Resnick et al., 1995; Yehuda et al., 1998). PTSD patients show an increased sensitivity for the negative feedback of the HPA-axis by glucocorticoids (Yehuda, 2001, 2006a). An enhanced function of glucocorticoid receptors might be responsible for this. Concentrations of corticotropin-releasing factor (CRF) are elevated in the cerebrospinal fluid of PTSD patients. Given the role of CRF in stress-related behavior (Britton et al., 1982; Swerdlow et al., 1989; Bijlsma et al., 2011) and startle behavior (Bijlsma et al., 2011), this neuropeptide is likely to be a major player in the pathophysiology of PTSD. Neuropeptide-Y (NPY) is an endogenous anxiolytic peptide that counteracts the effects of CRF in the amygdala (Heilig, 2004; Dimitrov et al., 2007). Interestingly, blood levels of NPY are positively correlated with PTSD symptom improvement (Yehuda et al., 2006). In the periphery, NPY represses the action of adrenalin and thus the lower NPY plasma levels in patients may contribute to the hyperarousal symptoms (Rasmusson et al., 2000). In conclusion, the pathophysiology of PTSD is complex and involves multiple brain areas and neurotransmitter systems. For reviews elaborating on the pathophysiology see Bremner et al. (2008), Martin et al. (2009), and Heim et al. (2010). Fig. 1 summarizes the brain circuits and neurotransmitters involved in the neuropathology of PTSD.

2. Pharmacological treatments of PTSD

Monoamine oxidase inhibitors (MAOI's) were one of the first classes of drugs used to treat PTSD. Some MAOI's are non-selective, while others selectively inhibit MAO-A, reducing primarily the breakdown of serotonin adrenalin and noradrenalin, or MAO-B, reducing the breakdown of dopamine. Studies with MAOI's show mixed results. While the irreversible and non-selective MAOI phenelzine was ineffective in one study (Shestatzky et al., 1988), a significant improvement was reported by Kosten et al. (1991). Brofaromine, a selective MAO-A inhibitor, did not exceed the effects of placebo in a study by Baker (Baker et al., 1995), while Katz et al. (1994) did find an effect, although this depended on the PTSD assessment scale that was used.

The effects of tricyclic antidepressants (TCA's) are modest. In 50% of combat-related PTSD patients, Amitriptyline had some effect on the avoidance symptoms (Davidson et al., 1990). Amitriptyline treatment was particularly beneficial for patients with less severe symptoms (Davidson et al., 1993).

The adverse side effects of MAOI's and TCA's limit their use in clinical practice. The development of selective serotonin re-uptake inhibitors (SSRI's) overcame many of these problems. The therapeutic effect of SSRI's was investigated in a number of studies. Some studies showed clear effects but even in those only 30% of the patients showed complete remission after three months (Ursano et al., 2004; Ipser et al., 2006; Stein et al., 2009). In a meta-analysis from the National Institute of Clinical Excellence (NICE) no clinically relevant differences were found between