CHAPTER 6

Psychosocial predator stress model of PTSD based on clinically relevant risk factors for trauma-induced psychopathology

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6.1 Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder which is unique in that it has a known etiological feature composed of a single trauma or repeated life-threatening experiences, such as wartime combat, a motor vehicle accident, rape or other assault to an individual or to a loved one (Diagnostic and Statistical Manual of Mental Disorders-V [DSM-V]). The horrific triggering experience(s) can transform a healthy individual into one with a cluster of debilitating symptoms, including hypervigilance, cognitive deficits and pathologically intense and intrusive memories of the trauma, which can persist for a lifetime. PTSD is not a modern disorder, as the symptoms of traumatized individuals have been described throughout recorded human history. For example, the biographer Plutarch wrote of PTSD-like symptoms involving chronic anxiety, sleep disturbances, and alcohol abuse of Gaius Marius, a Roman General in the first century BC, who was (Plutarch, 1920):

...tortured by his reflections and bringing into review his long wandering, his flights, and his perils, as he was driven over land and sea, he fell into a state of dreadful despair, and was prey to nightly terrors and harassing dreams ... since above all things he dreaded the sleepless nights, he gave himself up to drinking-bouts and drunkenness at unseasonable hours and in a manner unsuited to his years, trying thus to induce sleep as a way of escape from his anxious thoughts" (p. 594).
In the 19th century, the emotional and physical toll of combat on soldiers in the US Civil War was referred to as “soldier’s heart,” and following World War I, trauma symptoms were referred to as “shell shock,” because of the presumed relationship of the heightened anxiety and startle reactivity to the intense sounds and stress of combat. In 1952, the persistent effects of psychological trauma were formally termed “gross stress reaction” in DSM-I, and in 1980 the syndrome was given its contemporary nomenclature, “post-traumatic stress disorder,” with the publication of the DSM-III (Andreasen, 2010).

Logistical challenges and ethical restrictions limit the study of the biology of PTSD under controlled conditions in human subjects. Therefore, insight into the neurobiology and neuroendocrinology of the persistent effects of trauma on brain and behavior may be achieved indirectly through translational approaches involving the study of traumatic stress in animals. This approach has spawned a vast amount of research on the effects of exposing animals, primarily rodents, to strong stressful experiences followed by behavioral and physiological testing, which, in theory, provides insight into PTSD in traumatized people. However, we assert that there remain conceptual limitations to linking the study of stress in animals to generating a syndrome which resembles clinical features of PTSD. For example, people who experience a horrific event, as well as rats exposed to a painful shock, can have a strong memory of the trauma, but an emotional memory of an experience alone does not sufficiently represent the cluster of symptoms that define PTSD. PTSD develops from the inability to cope with the memory of the trauma; the memory itself is only one component of the entire syndrome. A multifaceted goal for any animal model of PTSD, therefore, is to administer a strong stressful (traumatic) experience to an animal, and then to demonstrate that the animal has a conditioned fear memory for that experience, and that the trauma produces a cluster of behavioral and biological abnormalities that resemble those found in people diagnosed with PTSD.

This chapter reviews a subset of research studies that have addressed this goal. First, we provide a description of the basic features of PTSD, followed by a global review of diverse preclinical approaches that have modeled PTSD. We then discuss our animal model of PTSD, which is based on predator exposure administered in the context of clinically relevant risk factors, including social instability. The pathological outcomes generated in our model may provide insight into behavioral and biological abnormalities that develop in the subset of traumatized people that develop PTSD, as well as to provide a model that optimizes the development of novel pharmacotherapies for PTSD.
6.2 General characteristics of PTSD

Individuals exposed to life-threatening trauma, such as wartime combat, motor vehicle accidents, or natural disasters, are at risk for developing PTSD. People who develop PTSD respond to a traumatic event with intense feelings of fear, helplessness, or horror and subsequently endure chronic psychological distress by repeatedly re-living their trauma through intrusive, flashback memories (Ehlers et al., 2004; Hackmann et al., 2004; Reynolds et al., 1999; Speckens et al., 2007). These characteristics of the disorder foster the development of other debilitating symptoms, including persistent anxiety, exaggerated startle and cognitive impairments, as well as a predisposition toward substance abuse and comorbid psychiatric disorders, such as major depressive disorder (Nemeroff et al., 2006; Stam et al., 2007).

Posttraumatic stress disorder is also characterized by a complex aberrant biological profile involving several physiological systems, including the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS; Krystal & Neumeister, 2009; Pervanidou et al., 2010; Vidovic et al., 2011; Zoladz & Diamond, 2013). For instance, although findings have been mixed, extensive work has reported abnormally low baseline levels of cortisol in PTSD, which has been associated with the presence of enhanced negative feedback of the HPA axis and an elevated density of glucocorticoid receptors in these individuals (Yehuda, 2005, 2009). The reduced basal cortisol levels with PTSD do not appear to reflect adrenal insufficiency, as PTSD patients display robust HPA axis responsiveness, as evidenced by greater cortisol levels in response to, and in anticipation of, acute laboratory stressors, compared with control subjects (Bremner et al., 2003; Liberzon et al., 1999; Elzinga et al., 2003). People with PTSD also demonstrate greater baseline and stress-induced elevations of SNS activity (Buekley & Kaloupek, 2001), as measured by elevated baseline heart rate (HR), systolic blood pressure (BP) and diastolic BP, findings that resonate with research reporting an association between PTSD and increased risk for cardiovascular disease (Boscarino & Chang, 1999; Kubzansky et al., 2007).

In response to traumatic reminders and standard laboratory stressors, people with PTSD display significantly greater increases in HR, BP, skin conductance, epinephrine, and norepinephrine than do control subjects. Another indication of accentuated SNS activity in PTSD patients is the exaggerated responsiveness (i.e., greater increases in HR, greater increases in BP, greater expression of anxiety-like behavior) they exhibit following administration of yohimbine, an α2-adrenergic receptor antagonist that leads to increased central norepinephrine activity (Bremner et al., 1996, 1997; Southwick et al., 1993, 1999). These findings, as well as evidence of greater norepinephrine levels in PTSD patients (Krystal & Neumeister, 2009; Amihaesei & Mungiu, 2012; Strawn & Geracioti,
2008), have suggested a major role for exaggerated noradrenergic activity in the hyperarousal component of PTSD (Strawn & Geracioti, 2008).

Whereas numerous brain regions contribute to the behavioral and physiological manifestations of PTSD, much of the research has focused on the involvement of three primary structures, the amygdala, prefrontal cortex (PFC) and hippocampus (Bremner, 2007; Pitman et al., 2012; Zoladz & Diamond, 2013). People with PTSD exhibit abnormal fear responses and diminished extinction of conditioned fear, which is suggestive of amygdala hyperactivity (Elzinga & Bremner, 2002; Koenigs & Grafman, 2009; Orr et al., 2000; Peri et al., 2000). Studies have also shown that PTSD patients have decreased PFC volume (Carrion et al., 2001; De Bellis et al., 2002; Fennema-Notestine et al., 2002; Rauch et al., 2003; Woodward et al., 2006; Yamasue et al., 2003) and reduced activation of the PFC in response to the presentation of trauma-related, or fear-eliciting, stimuli (Bremner et al., 1999; Britton et al., 2005; Lanius et al., 2001; Lindauer et al., 2004; Shin et al., 2004). PTSD patients are also impaired in tasks involving executive functioning, indicating impaired PFC functioning. Given the importance of the PFC in inhibiting amygdala-modulated emotional responses, reduced PFC activity in PTSD patients could promote amygdala hyperactivity, as well as the hypervigilance component of the disorder. Moreover, repeated activation of the traumatic memory, which would involve activation of the amygdala in conjunction with impaired PFC functioning, would contribute to traumatic memories becoming even more intrusive and debilitating over time.

Extensive work has also shown that people with PTSD have cognitive deficits that are suggestive of hippocampal dysfunction. This has been documented by reports of smaller hippocampal volume (Grossman et al., 2002; Liberzon et al., 2008; Nütt & Malizia, 2004; Shin et al., 2006) and impaired hippocampus-dependent learning and memory in PTSD patients (Bremner et al., 1995; Gilbertson et al., 2001). However, close scrutiny of the literature suggests that severe deficits in hippocampal functioning with PTSD are relatively uncommon, with numerous studies that have not provided evidence of a global hippocampal impairment of hippocampal functioning in PTSD (Zoladz & Diamond, 2013). Moreover, impaired hippocampal functioning may actually be a risk factor for, rather than an outcome of, PTSD (Gilbertson et al., 2002; Pitman et al., 2006).

In summary, clinical research has provided strong evidence of increased sympathetic activation which underlies the hypervigilance component of PTSD, as well as PFC and amygdala abnormalities. Thus, symptoms including impaired attention, working memory, and executive functioning all point to impaired PFC functioning in conjunction with hyper-responsiveness, and perhaps hypertrophy, of the amygdala in PTSD. However, whether there are hippocampus-specific deficits in PTSD remains to be determined.
6.3 Preclinical models of PTSD

Whereas clinical research is vital for the implementation of novel treatments, animal models of PTSD provide a crucial complementary component in this process. In addition to their key role in establishing the safety and initial efficacy of novel compounds, animal models are valuable in three key areas of treatment development. First, they allow the rapid, cost-effective development of proof of concept studies to identify the most promising pharmacological candidates that can block trauma-induced behavioral and physiological abnormalities. This approach, with direct molecular assays of neural tissue, can improve our understanding of the mechanism of action of these compounds. Second, animal research provides for the assessment of the effects of interventions initiated prior to, or soon after, trauma occurs, which provides the opportunity to develop preventive strategies that would be high risk, expensive and potentially unethical to undertake in people. Finally, animal studies provide for the study of direct tests for different PTSD comorbidities and risk factors that might influence treatment responses in people, such as early life abuse, gender, and traumatic brain injury.

The development of valid and informative animal models of psychiatric disorders, in general, and PTSD in particular, has been a challenge. The human response to trauma can be considered to be composed of two distinct components, both of which should be included in animal models of PTSD. First, the person with PTSD typically has a pathologically intense and intrusive memory for the traumatic experience. Hence, the person commonly avoids any cues associated with the traumatic experience. Therefore, an animal model should include a component in which the traumatized animal exhibits a powerful fear-provoking memory for the stressful experience. Second, in patients with PTSD there are numerous abnormalities in their physiology and behavior. That is, a person with PTSD not only exhibits an intense memory for the traumatic event which may last for a lifetime, he or she also experiences significant post-trauma changes in physiology and behavior, including comorbid psychiatric disorders such as depression. Therefore, a clinically relevant animal model of PTSD should generate a powerful memory of the traumatic experience, as well as persistent changes in physiology and behavior in common with people with PTSD.

Preclinical researchers have used several types of stressors to model aspects of PTSD in animals (Stam, 2007). Such stressors have included electric shock (Garrick et al., 2001; Li et al., 2006; Milde et al., 2003; Pynoos et al., 1996; Rau et al., 2005; Sawamura et al., 2004; Servatius et al., 1995; Shimizu et al., 2004, 2006; Siegmund & Woitak, 2007a,b; Wakizono et al., 2007), underwater trauma (Cohen & Zohar, 2005; Richter-Levin, 1998), stress–restress and single prolonged stress paradigms (Harvey et al., 2003; Khan & Liberzon, 2004; Kohda et al., 2007; Liberzon et al., 1997; Takahashi et al., 2006) and exposure to predators (Adamec & Shallow, 1993; Adamec et al., 1997, 1999a,b; 2006, 2007) or predator-related
cues (Cohen & Zohar, 2005; Cohen et al., 2000, 2006; Goswami et al., 2013). The stressors employed in these studies typically produce behavioral signs of anxiety that persist beyond the time of the stress experience, and in some cases, exaggerated startle, cognitive impairments, enhanced fear conditioning, resistance to fear extinction, and reduced social interaction.

Although these studies have reported physiological and behavioral changes resembling those observed in people with PTSD, most have utilized only a small set of assessments, such as stress-induced changes in anxiety, without assessing the extensive abnormalities that make up routine symptoms of PTSD. Moreover, many of these studies have evaluated stress-induced changes in responses for a relatively short period of time. Finally, it is quite rare to find animal models of PTSD that assess the animal’s memory for the traumatic experience; typically the stress exposure is used only to disturb post-stress brain and behavior, instead of assessing the memory for the trauma experience itself.

We consider all of the aforementioned approaches to have contributed toward our understanding of how traumatic stress changes aspects of behavior and physiology, in general, and how a subset have enhanced our understanding of the neurobiology and endocrinology of PTSD. In the following section, we discuss our psychosocial predator-based animal model of PTSD and how our findings may shed light on the development of novel pharmacotherapies for trauma, as well as neurobiological and endocrine abnormalities observed in people diagnosed with PTSD.

6.4 Psychosocial predator stress model of PTSD

Pioneering research by Caroline and Robert Blanchard described how rats exhibit a strong fear of a predator, such as a cat (Blanchard et al., 1975). Their work also contributed to the development of studies examining predator scent, provided, for example, by cat or fox urine, as a stress-provoking stimulus which can substitute for the live animal (Apfelbach et al., 2005; Rosen, 2004). Further evidence of the effectiveness of predator exposure as a means with which to generate a fear response are findings in which cat exposure or predator scent activates the HPA axis (Morrow et al., 2000). At a functional level, extensive research demonstrates that predator exposure exerts a profound impairment of spatial memory and a suppression of synaptic plasticity in the hippocampus (Diamond et al., 1999; Mesches et al., 1999; Park et al., 2008; Vanelzakker et al., 2011; Woodson et al., 2003; Zoladz et al., 2012). It has also been reported that live predator exposure can enhance synaptic plasticity in the amygdala (Vouimba et al., 2006). Therefore, the ethological relevance and potency of predator exposure provides a highly relevant approach toward producing an intense, purely psychological, fear response in rodent models of PTSD.
Based on these observations of the instinctual fear generated in rats by cat exposure, our group has published a series of studies based on a predator-exposure animal model of PTSD (Roth et al., 2011; Zoladz et al., 2008, 2012, 2013). The primary components of the PTSD model were based on trauma-induction features that are known to be associated with a greater susceptibility of a subset of traumatized people to develop PTSD. Specifically, a subset of the DSM-V criteria for the diagnosis of PTSD includes the following three conditions: PTSD can be triggered by an event that involves threatened death or a threat to one's physical integrity; a person's response to the event involves intense fear, helplessness, or horror; and in the aftermath of the trauma, the person feels as if the traumatic event were recurring, including a sense of re-living the experience. Therefore, in our work, rats are immobilized and placed in close proximity to a cat. As noted, rats have an instinctual and intense fear of cats (Blanchard et al., 1990, 2003, 2005; Hubbard et al., 2004); which, in theory, would be intensified by their inability to escape (Amat et al., 2005; Bland et al., 2006, 2007; Maier & Watkins, 2005). Although there is no physical contact between the rats and cat, the experience produces a profound physiological stress response in the rats, including elevated HR, BP and corticosterone levels.

A core symptom of PTSD is the repeated “re-experiencing” of the traumatic event that people with PTSD suffer in response to activation of intense and intrusive memories of their trauma. For this reason, we included a “re-experiencing” component in our animal model of PTSD by giving rats the second cat exposure 10 days after the first. Moreover, the first predator exposure occurs during the light cycle, and the second predator exposure occurs during the dark cycle, thereby adding an element of unpredictability as to when the rats might re-experience the traumatic event. A lack of predictability in one’s environment is a major factor in the development of PTSD, as well as to influence the later expression of PTSD symptoms (Orr et al., 1990; Regehr et al., 2007; Solomon et al., 1988, 1989).

The second cat exposure occurred 10 days after the first, based on findings of Chattarji’s group, who observed increased dendritic arborization of amygdala neurons 10 days after a single immobilization experience (Mitra et al., 2005). In theory, therefore, the second cat exposure on day 11 activated a sensitized amygdala with hypertrophied neurons, thereby reinforcing stress-induced changes in brain and behavior that would have been initiated by the first cat exposure. The second exposure of rats to the cat also relates to work showing that PTSD develops in some people only after they have repeated traumatic experiences and work revealing that prolonged exposure to trauma increases the likelihood of developing symptoms of PTSD (Gurvits et al., 1996; Resnick et al., 1995; Taylor & Cahill, 2002). Thus, the repeated inescapable cat exposure served as a powerful reminder of the stress experience, as well as a manipulation that potentially
increased the likelihood of the rats to exhibit physiological and behavioral sequelae that can be broadly applied to people who develop PTSD as a result of multiple traumatic experiences.

An additional risk factor for PTSD is insufficient social support and an unstable social life (Andrews et al., 2003; Boscarino, 1995; Brewin et al., 2000; Ullman & Filipas, 2001). Therefore, we included daily social instability in the model to increase the likelihood of producing long-lasting sequelae in the rats. Beginning with the day of the first cat exposure, the stressed rats are exposed to unstable housing conditions for the next 31 days. The rats are pair-housed, and every day, their cohort pair combination is randomly changed, which results in the stressed rats having different cage mates on a daily basis during the 31-day stress period. Following this 31-day stress period, the rats are given a battery of physiological and behavioral assessments to examine the development of PTSD-like sequelae in the animals. The social instability component is an integral component of the model, as predator exposure alone does not produce persistent PTSD-like changes in the behavior of the rats (Zoladz et al., 2008).

We have found that exposing rats to our psychosocial predator-based animal model of PTSD results in a number of physiological and behavioral abnormalities, all of which are remarkably similar to those observed in people with PTSD. For instance, 3 weeks after the second predator exposure, rats exposed to our animal model of PTSD exhibit reduced growth rate, reduced thymus weight, greater adrenal gland weight, increased anxiety, exaggerated startle, impaired memory, greater cardiovascular and hormonal reactivity to an acute stressor and an exaggerated physiological and behavioral response to the α2-adrenergic receptor antagonist, yohimbine (Zoladz et al., 2008). Importantly, these effects depended on the combination of both cat exposures and daily social instability. Thus two cat exposures in conjunction with social instability produced greater anxiogenic effects on rat behavior than either cat exposure or social instability alone (Zoladz et al., 2008).

As we mentioned earlier in this chapter, a pathologically intense memory of the trauma is a hallmark feature of PTSD. Therefore, it was important to include a method with which to measure the rat’s memory for the cat exposure experiences. To accomplish this goal, in recent work we measured the rat’s memory for trauma indirectly by placing the rat in a fear conditioning chamber immediately prior to each of the two cat exposures (Zoladz et al., 2012). It is notable that the rats were not exposed to any aversive stimuli while they were in the chamber. The rats were in the chamber for 3 minutes, and during the last 30 seconds of each exposure, they were presented with a tone. Then, they were removed from the chamber and immediately immobilized and given the 1-hour cat exposure. The strategy behind this manipulation was to use a form of classical conditioning, which traditionally involves the pairing of a neutral stimulus, such as a tone, with a strong stimulus, such as shock to the tail. An illustration of the entire sequence
Behavioral and physiological measurements (beginning on day 32)

Figure 6.1 General description of the timeline of events in the psychosocial predator stress model of post-traumatic stress disorder (PTSD). Rats were exposed to a fear-conditioning chamber and tone followed by immobilization and cat exposure on days 1 and 11; unstable housing occurring daily from the first day of cat exposure through day 31. Beginning on day 32, fear conditioning memory testing, as well as all behavioral and physiological assessments took place. (See color plate section for the color representation of this figure.)

As a result of the pairing of the two stimuli, cat-exposed rats exhibit evidence of memory by displaying fear when later exposed only to the tone. In our case, rats associated the chamber and the tone with the fear-provoking cat experience. The association that rats form between the chamber and cue with the cat is analogous to the panic response people with PTSD exhibit when they experience a cue, such as an odor or a sound, that reminds them of their traumatic experience. Our test of the rat’s memory of the cat was confirmed with the finding that psychosocially stressed rats exhibited significant immobility (fear memory-induced freezing) in response to being returned to the chamber, as well as the tone, paired with the cat exposures. These findings are illustrated in Figure 6.2. Thus, our animal model of PTSD is unique in that the rats stressed in this paradigm display a powerful memory for the context and cue associated with the predator stress experiences, and they exhibit physiological and behavioral symptoms that occur in people with PTSD.
Figure 6.2 Rats exhibited strong fear memory for the context and cue associated with cat exposure. On days 1 and 11, rats were exposed to the fear conditioning chamber for 3 minutes, which terminated with a 20-second tone, followed by immobilization of the rats, followed by cat exposure, which took place in another room. On day 32, rats were re-exposed to the original chamber (context memory) and tone (cue memory) in a different chamber, with an assessment of their conditioning fear (freezing). The group exposed to the chamber/tone followed by cat exhibited significantly greater freezing in response to re-exposure to the context (top) and cue (bottom) compared with the control group, which had not been exposed to the cat. (Data adapted from Zoladz et al., 2008, 2012.) (See color plate section for the color representation of this figure.)

As discussed, PTSD is characterized by an aberrant biological profile in multiple physiological systems. One of the most extensively researched physiological systems in people with PTSD is the HPA axis. Empirical investigations of the adrenal hormone, cortisol, have often reported abnormally low baseline levels of cortisol in PTSD patients. One explanation for the presence of low baseline cortisol levels in people with PTSD is that the disorder is associated with enhanced negative feedback inhibition of the HPA axis. Indeed, studies have reported that people with PTSD display an increased number and sensitivity of glucocorticoid receptors and an increased suppression of cortisol and adrenocorticotropic hormone (ACTH) following the administration of dexamethasone, a synthetic glucocorticoid (Duval et al., 2004; Goenjian et al., 1996; Grossman et al., 2003; Stein et al., 1997; Yehuda et al., 1995, 2002, 2004). Studies have also employed the dexamethasone-corticotropin-releasing hormone (CRH) challenge paradigm to
study abnormal HPA axis functioning in people with PTSD. An advantage of
this paradigm is that the subjects are treated with dexamethasone prior to CRH
administration, thereby activating negative feedback mechanisms before acute
HPA axis stimulation. Studies employing this paradigm have generally reported
reduced ACTH levels in dexamethasone-treated PTSD patients who were sub-
sequently administered CRH (de Kloet et al., 2006; Rinne et al., 2002; Strohle
et al., 2008).

Based on the clinical findings of abnormal HPA activity in PTSD, we examined
the effects of our animal model on rat corticosterone levels at baseline and
following dexamethasone administration. We found that, at baseline, psychoso-
cially stressed animals exhibited significantly lower corticosterone levels than
non-stressed rats. Following dexamethasone administration, psychosocially
stressed rats displayed a blunted increase in corticosterone levels and a more
rapid post-stressor recovery of those levels, relative to non-stressed control
animals, following administration of an acute stressor (Zoladz et al., 2012).
These findings bear resemblance to those from human studies employing the
dexamethasone–CRH challenge paradigm and suggest that our PTSD regimen
might result in enhanced negative feedback of the HPA axis.

One of the most promising areas of PTSD research is the study of the inter-
action of genetic and epigenetic factors with environmental stressors (Zoladz &
Diamond, 2013). Epigenetic alterations of the brain-derived neurotrophic factor
(BDNF) gene have been linked to brain functioning, memory, stress, and neu-
ropsychiatric disorders (Domschke, 2012; Zovkic & Sweatt, 2013). Therefore, we
examined whether there was a link between our model and BDNF DNA methy-
lation. We found that psychosocially stressed rats exhibited increased BDNF DNA
methylation in the dorsal hippocampus, with the most robust hypermethylation
detected in the dorsol CA1 subregion (Roth et al., 2011). On the other hand,
psychosocially stressed rats also displayed decreased methylation in the ventral
hippocampus (CA3). No changes in BDNF DNA methylation were detected in
the medial prefrontal cortex or basolateral amygdala. Finally, we also observed
decreased levels of BDNF mRNA in both the dorsal and ventral CA1 regions
of psychosocially stressed animals. These results provide evidence that traumatic
stress occurring in adulthood can induce CNS gene methylation and, specifically,
support the hypothesis that epigenetic marking of the BDNF gene may underlie
hippocampal dysfunction in response to traumatic stress. Furthermore, this work
provides support for the speculative notion that altered hippocampal BDNF DNA
methylation is a cellular mechanism underlying the persistent cognitive deficits
which are prominent features of the pathophysiology of PTSD.

One goal of our animal model of PTSD was to assess whether pharmacothera-
peutic agents can block the stress-induced abnormalities. We recently examined
the differential effectiveness of amitriptyline (tricyclic antidepressant), clonidine
(noradrenergic antagonist), and tianeptine (glutamate modulator) in blocking
the physiological and behavioral sequelae manifested by our psychosocial predator stress model (Zoladz et al., 2013). We found that while each of the drugs had some sort of therapeutic effects, tianeptine was the only agent to prevent the effects of chronic psychosocial stress on our entire battery of physiological and behavioral end-points. Specifically, tianeptine blocked the expression of fear-conditioned memory in psychosocially stressed rats when they were re-exposed to the context and cue that were paired with the two cat exposures, and also prevented the effects of psychosocial stress on anxiety, startle, cardiovascular reactivity, growth rate, adrenal gland weight and thymus weight. Importantly, these salutary effects of tianeptine occurred in the absence of any adverse side-effects. To emphasize that the design of our experiment had clinical relevance, we did not begin the administration of pharmacological agents until the day after the stress paradigm commenced (i.e., 1 day after the first cat exposure). Treatment beginning 24 hours after exposing rats to an intense stressor is potentially relevant to treatment applications begun in people within 24 hours of a traumatic experience. This strategy may also highlight the importance of beginning a treatment regimen as soon as possible after a person experiences trauma.

6.5 Summary: the challenge of modeling PTSD in animals

In this chapter we have addressed the challenge of translating stress research in animals to clinically relevant factors involved in PTSD. Too often, research on animals focuses on either the stress response alone or the memory of the stress procedure, as measured by fear conditioning, which we have suggested addresses only fragments of the broad spectrum of PTSD symptoms. We emphasized the importance of appreciating the range of clinically relevant features of PTSD, which includes the intrusive memory of the traumatic experience, in conjunction with risk factors, such as social support, and the chronic anxiety following trauma, because all components interact to influence whether or not a traumatized individual will develop PTSD. Hence, PTSD results from the impaired ability to cope with the traumatic experience and the memory it generated, rather than PTSD being composed of a strong memory of the trauma alone. We therefore developed an animal model of PTSD which is based on clinically relevant features of susceptibility of an individual to develop stress-induced psychopathology. Specifically, we administered predator exposure to immobilized rats to provide them with a life-threatening experience in conjunction with an inability to escape. In theory, this experience to the rat is analogous to the PTSD induction feature involving a condition that evokes fear and horror in conjunction with a life-threatening experience. However, despite the fact that
this experience provokes a powerful stress response in rats, cat exposure alone does not produce persistent PTSD-like abnormalities in behavior. It was only when we combined predator exposure with social instability that we observed persistent behavioral and physiological abnormalities in the rats, which are remarkably similar to those found in people diagnosed with PTSD, including a strong memory of the trauma, increased anxiety, exaggerated startle, impaired memory for new information, increased cardiovascular and hormonal reactivity to an acute stressor, abnormally low corticosterone levels, increased sensitivity to dexamethasone, and an exaggerated physiological and behavioral response to the α2-adrenergic receptor antagonist, yohimbine. Moreover, we have provided guidance for clinical research on PTSD with the finding of epigenetic modifications (methylation) of the BDNF gene in the hippocampus, which may provide the basis for impaired cognitive functioning in traumatized people. Finally, our work has identified the antidepressant tianeptine as a potentially useful pharmacological approach toward treatment of the cluster of symptoms found in PTSD.

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Queries in Chapter 6

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