

## The Neurobiology of Post-Traumatic Stress Disorder (PTSD): Perspectives and Trends

Sana Rehman<sup>1</sup>, Arunabha Ray<sup>1\*</sup>, Kavita Gulati<sup>2</sup> and Maaz Naqvi<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Hamdard Institute of Medical Sciences and Research, Hamdard University, New Delhi, India

<sup>2</sup>Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

**\*Corresponding Author:** Arunabha Ray, Professor, Department of Pharmacology, Hamdard Institute of Medical Sciences and Research, Hamdard University, New Delhi, India.

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### Abstract

Post-traumatic stress disorder (PTSD) is a complex neuropsychiatric condition that may develop after experiencing or witnessing a traumatic event. Anxiety and cognitive dysfunction are among the characteristic manifestations of PTSD. Gender and genetics are important determinants of the disease. Limbic brain areas like hippocampus, prefrontal cortex and amygdala and their neural connections are important neuroanatomical substrates, several hypotheses have been forwarded to explain the neurochemical basis of this disease, and a variety of pharmacological and non-pharmacological strategies are proposed for treatment. Classically, PTSD is characterized by monoaminergic and hypothalamo-pituitary-adrenal (HPA)-axis abnormalities, and glucocorticoid induced glutamate release is recognized as an important mediator of neurotoxicity. Recent studies have shown that 5-HT and nitric oxide (NO) may play a causal role in the neurobehavioral manifestations of PTSD, and nitrenergic mechanisms may have an important role in hippocampal degeneration and cognitive deficits. A major scientific effort is therefore devoted to unravel the complexly interacting neural mechanisms underlying PTSD with the aim to develop newer and improved therapeutic approaches. This review comprehensively assesses the neurobiology of PTSD, the existing lacunae in the understanding of the disease and explores possible strategies to improve the quality of treatment in this complex neurobehavioral illness. .

**Keywords:** PTSD; Limbic Brain; HPA-Axis; Neurotransmitters; Experimental Models

### Introduction

Stress and stress-related disorders are a major cause of morbidity and mortality around the world. In biology and medicine, stress is defined as any aversive stimulus that threatens the physiological milieu or allostatic balance and a combination of stressors (environmental and emotional) result in allostatic load which add to the pathogenesis of and vulnerability to disease. The brain plays a crucial role in interpreting and responding to potentially stressful insults and these acute and traumatic inescapable stressors can have lasting outcomes on brain and behavior. Anxiety and depression are by far the frequent psychopathologies seen after chronic stress exposures. Clinical and experimental studies showed that there is a fair association exists between anxiety and stress [1]. A positive correlation between anxiety disorders and a variety of stressful situations has also been proposed [2]. Anxiety is also sometimes referred to as the psychophysiological signal of the stress response. For example, neuroanatomical studies showed that the limbic brain areas (e.g. amyg-

dala, prefrontal cortex, etc.) through their complex neural networking, coordinate stress-related responses including anxiety [3]. Pharmacological studies have also shown that the neurochemical mechanisms involved in both anxiety and depression are complex [2,4]. Many stressors are known to result in anxiogenic responses that depend on the intensity as well as the duration of the aversive stimuli. These stressful inputs influence the endocrinal, neurobehavioral, and immune system and are differently influenced by the classical anti-stress medications or adaptogens [5]. The prototype anti-stress agents e.g. benzodiazepines, have been used as anti-anxiety agents in humans as well as in experimental animals. They act by augmenting GABA-ergic neurotransmission through an allosteric interaction at the benzodiazepine-GABA receptor complex and are effective in inducing HPA axis inhibition [6]. Furthermore, recently it is becoming evident that stress-induced anxiety-related responses are not fully attributable to the dysfunctions in the BZD-GABA receptor moiety, and many other complex interactive mechanisms could be involved [7]. Post-traumatic stress disorder (PTSD) is a debilitating neuropsychiatric disorder precipitated by stressful and traumatic events. The term was coined in the mid-1970s and is defined as a complex anxiety disorder that can develop after exposure to a stressful, traumatic and terrifying life events. Traumatic and stressful events that may spark PTSD comprise of violent personal assaults, accidents, natural or human-caused disasters, or military combat [8]. Though PTSD was classified as an anxiety disorder; however, the latest edition, DSM-V, includes PTSD in a new category called "trauma and stress-related disorders". In this brand-new category, we consider disorders with poor adaptation to a traumatic experience. Most recently, the global COVID-19 pandemic is also being proposed as one of the probable causes for the development of PTSD. The strikingly characteristic features of PTSD consist of anxiety, cognitive dysfunction, sleep disturbances and reduced social skills [9]. PTSD may develop instantly or several years after exposure to a serious stressful and traumatic event or any injury and is represented by re-experiencing, avoidance of associative stimuli and hyper-arousal. These symptoms, which can be both cognitive and non-cognitive, can be directly or indirectly pertinent to a state of disorganized emotional state and memory, leading to a disproportionate biobehavioural response that continues beyond stress or [10-12].

After the initial stressful experience, the PTSD victim subsequently re-experiences the traumatic incidents and emotions in their mind. These daunting invasive post-traumatic memories are ingrained in a cascade of adverse physiologic, psychological, and interpersonal outcomes. PTSD sufferers also exhibited a higher likelihood of developing habit-like comorbidities, such as alcoholism and drug addiction [13]. In PTSD individuals, dysregulation of HPA axis has been seen. Various studies have showed that stress and anxiety may analogously facilitate cognitive dysfunction via damaging hippocampal memory function. PTSD has been associated with decreased hippocampal volume and deterioration in the hippocampus-dependent declarative memory. Moreover, PTSD subjects exhibit differences in the structure as well as the activity of the dorsal striatum, relative to the healthy controls, and more relatedness between the hippocampus and striatum. Elevated levels of emotional arousal can also damage spatial memory mediated by hippocampus, and augment stimulus-response habit memory mediated by dorsolateral striatum [14,15].

The limbic brain plays a significant regulatory role in mediating stress related neuropsychiatric pathophysiology and complexly interacting neuropharmacological mechanisms have been postulated. In PTSD, both the hippocampus and the prefrontal cortex are the essential players with important roles for linking areas like the amygdala and the dorsal striatum. The hippocampus is notably responsible for the emotional disturbance induced memory dysregulation, while, the stress-related neuroendocrine function is influenced by the prefrontal cortex, and the interplay between cognition and emotional changes are influenced by the amygdala [15]. The medial prefrontal cortex also reportedly exerts an inhibitory influence over the amygdala, which is lost in PTSD, which results in the fear related symptoms [16]. Recent studies have shown that PTSD may be a systemic illness that affects not just the brain, but the entire biological system. Thus, disease signals likely span many biological domains, comprising of genes, proteins, cells, tissues, and organism-level physiological changes. Identification of such signals could help in diagnosis, treatment, and risk evaluation, and various molecular biomarkers have been established in potential PTSD patients [17].

### Genetic factors in PTSD

Following the exposure of traumatic event the heritability of the development of PTSD has been approximated to be at least 30 - 40% [18], suggesting a substantial influence of genetic risk factors in PTSD development. On one hand, when candidate-gene approaches are

driven by a prior hypotheses on PTSD risk, on the other hand, genome-wide association studies (GWAS) represent an untargeted approach, able to identify new molecular mechanisms underlying PTSD development [19]. Moreover, the detection of genetic markers associated with the risk to develop PTSD needs an adequate evaluation and due consideration of traumatic load, that accounts for a considerable proportion of the variability in PTSD vulnerability [20]. PTSD risk has been shown to be increased among offspring of parents with PTSD in few studies [21]. The largest study consisted a cohort of 6924 mothers and their children and found a considerable rise in the offspring PTSD in a dose-response relationship along with maternal symptoms of posttraumatic stress (ORs 1.2-1.6) [22]. Interestingly, parent-offspring transmission was extensively mediated through arise in trauma exposure among offspring of PTSD mothers. Genetic factors can contribute to PTSD liability in at minimum by four ways: (a) by determining the liability to trauma exposure; (b) by determining the PTSD risk independent of trauma exposure; (c) by determining other risk factors for PTSD (e.g. personality traits, or comorbidities); or (d) by a pleiotropic effect on two or more of these ways. The genetic interrelationship between the symptoms of PTSD and assaultive trauma was substantial. Interestingly, this correlation declined as the number of assaultive traumas attained big levels, persistent with the hypothesis that high doses of trauma can cause PTSD regardless of genetic vulnerability [23]. The factors underlying genetic effects on trauma exposure remains uncertain, though they may be mediated by personality traits (such as risk-taking) that raise the probability of exposure to the threatening environments. In candidate gene studies, attempts to detect specific genetic variants contributing to the heritability of PTSD have overwhelmingly targeted on biological candidate genes [24]. Specifically, genes engaged in monoaminergic neurotransmission and elements of the HPA axis have been frequently studied. The most commonly studied polymorphism has been a variable number tandem repeat (VNTR) in the promoter region of the serotonin transporter gene (SLC6A4), which encodes the target of serotonin reuptake inhibitors. This functional polymorphism, known as the 5HTTLPR, which is prevalent in European ancestry populations, with a frequency of approximately 45% for the so-called short (S) allele that is associated with decreased transcription of SLC6A4. Some significant associations have been documented between PTSD symptoms and other neurotransmitter and neuropeptide related genes including HRT2A, SLC6A3, DRD3, NPY, CNR1 and RGS2 [25]. Genome-wide association studies (GWAS) in PTSD showed that, in military veterans and their intimate partners, a genome-wide significant association between PTSD and an SNP in the retinoid-related orphan receptor gene (RORA) was exhibited [26]. Environment and gene interactions are also very important in PTSD, a neuropsychiatric disorder for which an environmental exposure is necessary. Moreover, other environmental exposures such as childhood maltreatment, poverty, and low social support, have been shown to enhance the PTSD risk among trauma-exposed individuals [27]. Studies on environment-gene interaction showed that PTSD have suffered from an array of drawbacks including a confined locus on a small number of polymorphisms and incomplete consideration of the timing, chronicity, or differential effect sizes of numerous exposures. Therefore, the role of unusual structural divergence remains undetermined. However, in the coming years, progress in determining the genetic basis of PTSD is expected to take a leap ahead with analyses of considerable samples. Using a stepwise approach of discovery, prioritization, validation, and testing gene expression, biomarkers predictive of high-stress states were defined. One of the ultimate biomarkers was identified as FKBP5, a well-determined gene involved in stress response. Data on these biomarkers were correlated with telomere length (TL), which is another well-identified biological marker of psychological stress. It has been shown that the newly identified predictive biomarkers such as NUB1, APOL3, MAD1L1, or NKTR were comparable or better predictors of stress than TL or FKBP5. Few of these biomarkers were the targets of existing drugs. Such pharmacogenomics approach showed that the finest comprehensive functional molecular stress biomarkers were FKBP5, DDX6, B2M, LAIR1, RTN4, and NUB1. This could lead to identification of leads for potential new drug candidates and natural compounds by adopting bioinformatics based drug repurposing approaches, such as calcium folinate and betulin. These advanced studies may result in improved diagnosis and treatment for stress disorders such as PTSD, leading to less adverse outcomes or negative incidences such as addictions, violence, and suicide [28].

### Gender and PTSD

PTSD is represented by a number of variations in stress-related neurotransmitter, neurohormonal, and immune system function. The lifetime prevalence of PTSD is around 10 - 12% in women and 5 - 6% in men. PTSD sub cluster scores exhibited to be high in women, e.g. for re-experiencing and anxious arousal [29]. Males and females exposed to different types of trauma, both in private life and at work

place such as police officers, with females being exposed to more high-impact trauma (such as sexual assault) than males, and at a very tender age [30]. Traumatic stress influence different brain are as in boys and girls at a different age group. In PTSD individuals, there is dysregulation of HPA axis. These HPA axis parameters may be influenced by the gonadal hormones in PTSD sufferers. Many experimental studies have showed a larger acute response of the HPA axis to stress in females when compared to males. It has been postulated that this rise in the response may be due to oestrogen because ovariectomized females have a stress response which is identical in magnitude when compared to the response of males. There are also variations in the stress response during different phases of their menstrual cycle. During the follicular phase of the cycle, the HPA axis stress response is less robust when compared with the stress response during the luteal phase. Thus, it is necessary to assess menstrual cycle and menopausal status while considering any gender-specific issues related biologic response in PTSD and other illnesses. Various studies have exhibited decrease in the hippocampal volume in PTSD individuals. In addition, females with PTSD have less memory loss and disruption of cognitive function than their male counterparts. Moreover, it has been seen that PTSD has persistently been in association with hyperactivity of amygdala, hypoactivity of ventromedial prefrontal cortex (vmPFC) and reduced communication (functional connectivity) between the amygdala and vmPFC, with less PFC control over the amygdala - thus providing an basis for the excessive fear response in PTSD. It has been explained that the oxytocin system, which has been associated with social support, fear and stress responses, possibly plays a sex-specific role in the stress response. In recently traumatized patients, it was found that the effects of administration of oxytocin on amygdala reactivity to emotional stimuli depend on stimulus and gender. In PTSD patients, sex-specific effects were seen after single oxytocin administration on the potential to decrease anxiety (fear learning) and fear expression by the amygdala: augment inhibitory control of the vmPFC over the centromedial nucleus in men and fewer excitatory dorsal anterior cingulate cortex projections to the basolateral nucleus in females. So, while these findings add to accumulating evidence that oxytocin administration could potentially augment treatment response in PTSD, there are different routes in males and females [31]. Thus, it has been concluded that there are some PTSD-specific gender differences in the biologic abnormalities.

### The neurochemistry of PTSD

#### Role of HPA axis and catecholaminergic pathways

In stress responses, hypothalamic-pituitary-adrenal (HPA)-axis and monoaminergic sympatho-adrenal system (SAS) play an essential role. Post-traumatic stress disorder (PTSD) is described as the abnormalities in the SAS and HPA-axis and understanding of SAS -HPA-axis responses may contribute to a better understanding of PTSD neurobiology. Various animal studies have shown that PTSD influences the HPA axis - thus eliciting regional-specific brain monoamine variations which bottom line the maladaptive behavior and other post stress-related incidents. A key point in the PTSD pathogenesis assumes to be within associative learning and other behavioral processes mediated by the hippocampus. However, while the catecholamines facilitate the availability of energy to vital organs, the glucocorticoids secreted from the adrenals have been assumed to play an essential role in containing the neural responses started by the stressor [32]. Following trauma exposure the extensive release of glucocorticoids may lead to hippocampal atrophy. Thus, it is possible that such glucocorticoid release due to acute exposure to trauma is just the first step in a cascade of events resulting in neurodegeneration and hippocampal atrophy along with subsequent memory deficits. This cascade may involve kindling and sensitization as well as a host of molecular messengers, both neuroprotective and neurotoxic, that will ultimately determine the progressive deterioration of neuronal function - eventually culminating in the behavioral pathology typical of PTSD. It is possible that decreased baseline cortisol reflects the net outcome of input to the hypothalamus from cortical and subcortical regions of the brain linked to elevated vigilance, trauma sensitization because of previous traumatic experiences, or genetic factors. Indeed, reduced levels of cortisol have been seen in the presence of high levels of catecholamine in PTSD patients. PTSD individuals fail to produce adequate cortisol levels for a long period of time to shut down stress-induced sympathetic nervous responses, hypothesizing that there is a magnified conditioned automatic reaction to thoughts related to the trauma, e.g. raised heart rate, skin conductance, raised blood pressure and anxiety. Modified noradrenergic transmission has also been implicated in a number of anxiety disorders. Acute and chronically stressed rats show apparent increase in noradrenergic activity in the prefrontal cortex and hippocampus [33]. The noradrenergic system acts as an arousal and alerting system and augments

transmission in many brain regions, interacting with corticotropin releasing factor (CRF). It plays an essential role in the amygdala where it mediates conditioned fear responses and augmenting the retrieval of fear memory. Likewise, mesolimbic dopaminergic pathways play an important role in states of fear and anxiety, though its relationship to clinical anxiety disorders is more complicated and poorly understood, as is its role in PTSD [32].

### Role of serotonin

In PTSD, disturbances in the HPA axis adversely influence the serotonergic (5-HT) system. Hippocampal 5HT<sub>1A</sub> receptors mediate anxiety and stress. Also, the 5HT<sub>2</sub> receptors in cortex are functionally anxiogenic and hamper the adaptation to stressors. The serotonergic system also has complementary effects on the HPA axis [34]. However, high synaptic serotonin levels after a stressful and traumatic event may expedite or worsen, anxiety through 5HT<sub>1A</sub> and/or 5HT<sub>2A</sub> receptors activation, and selective serotonin (5HT) reuptake inhibitors (SSRIs) weaken many of the debilitating symptoms of PTSD disorder. A study showed that SSRIs would be helpful in PTSD treatment, possibly by raising the concentration of synaptic 5HT, thus causing the downregulation of 5HT<sub>1A</sub> receptor and a reactive rise in the receptor affinity over a period of time. Indeed, hippocampal 5HT<sub>1A</sub> receptor downregulation is proposed to be the basis of the anxiolytic response to these drugs. 5HT thus plays an important role in the cognitive-behavioural changes evoked by time dependent sensitization (TDS; an experimental model for PTSD in rodents). During stress, the bidirectional effects of 5HT may bottom line the aberrant behaviour and neuropathology demonstrated in the TDS model and, possibly, in PTSD patients. Moreover, a broad understanding of 5HT action in the stress response, as well as in PTSD, needs further study. PTSD was linked with structural modifications in the hippocampus and prefrontal cortex that correlated fairly well with cognitive dysfunction, and serotonin (5HT) played an important role in these areas. Though, both anxiogenic and anxiolytic effects of 5-HT has been reported, and 5HT reuptake inhibitors are beneficial in the treatment, its role (5HT) in PTSD development remains uncertain. In an animal model of PTSD in rats, an apparent impairment in the spatial memory occurred together with raised 5HT<sub>1A</sub> receptor density (Bmax), reduced 5HT<sub>1A</sub> receptor affinity (Kd) and significantly raised 5HT<sub>2A</sub> receptor affinity. Fluoxetine, the selective 5HT uptake blocker prevented stress-induced cognitive dysfunction. Though, PCPA (p-chlorophenylalanine) the 5HT depleter, reversed stress-induced hippocampal 5HT<sub>1A</sub> receptor affinity alterations. Neither PCPA nor fluoxetine reversed stress effects on the affinity of 5HT<sub>2A</sub> receptor to its ligand. It was inferred that 5HT plays an essential part in the cognitive-behavioral changes evoked by repeated trauma. That increased 5HT activity may mediate hippocampal 5HT<sub>1A</sub> receptor changes evoked by stress, suggests a bidirectional role for 5HT in the PTSD development [35].

### Role of glutamate-NMDA receptor

Variations in the function of glutamatergic transmission and NMDA receptors have been proposed to play an important role in the causation of PTSD in humans [36]. The NMDA receptor is involved in the normal memory encoding processes, whereas, overstimulation of the NMDA receptor results in the formation of strongly embedded emotional memories through mobilization of free cytosolic Ca<sup>2+</sup> in excess. The glutamate-NMDA receptor plays a central role in the stress response in the Long-term Potentiation (LTP) and memory process and has been recently shown to be involved in PTSD and its treatment. In the hippocampal synapse, both stress and glucocorticoids have been found to raise the concentration of glutamate, proposed as a key mediator of glucocorticoid-induced neurotoxicity. PTSD is described by a loss of cognitive abilities with evidence for raised activity of glutamate. Moreover, stress and glucocorticoids not only raised the concentration of glutamate in the hippocampus, but glucocorticoids also specifically caused a rise in the glutamate accumulation in response to excitotoxic insults. Therefore, hippocampal damage, resulting from the effects of raised levels of glucocorticoids due to trauma exposure, will further enhance glutamate levels, thus facilitating neurotoxicity. It is thus clear that raised levels of glucocorticoids may trigger hippocampal damage but also it activate other neurotoxic pathways that may drive neuronal damage, over a period of time, following the traumatic event. It has been shown that overstimulation of the NMDA receptor might explain the neurodegeneration observed in PTSD individuals. Studies have shown that inhibition of glutamate reuptake, resulting in raised synaptic glutamate levels, ultimately leads to a reduction in NMDA receptor density, and has been suggested as a possible neuroprotective mechanism to counteract NMDA [37].

### Role of nitric oxide (NO)

NO is a unique and ubiquitous gasotransmitter molecule with complex pleiotropic functions in the CNS and its involvement in stress and stress related disorders has been proposed [37,38]. It is small gaseous molecule (MW 30Da) with a biological half-life of few seconds and quickly degraded to stable metabolites (nitrates and nitrites). Moreover, its high lipid solubility confers on it the unique ability to move rapidly within and between the cells. Nitric oxide synthases (NOS) exist in three isoforms that are either constitutive or inducible. All NOS isoforms are NADPH ( $\beta$ -nicotinamide adenine dinucleotide phosphate) and calmodulin dependent. GC (Guanyl Cyclase) activation by NO following glutamate-mediated activation of the NMDA receptor results in a rise in the second messenger - cGMP (cyclic guanosine monophosphate) which ultimately produces an effect on the neuronal function. The degradation of cGMP is inhibited by the phosphodiesterase (PDE) enzyme family, out of which PDE-3 and PDE-5 are proposed to be cGMP specific [37].

The role of NO in anxiety and related disorders has been extensively studied and both the preclinical and clinical data are available in this context. However, most of the study data findings that has been generated till date are equivocal to say the least [38,39]. Many study findings indicate that NO plays an essential role in anxiety-related disorders. Huge concentrations of NOS are found in brain regions involved in the diversity of anxiety and defensive behavior [40] and exposure to stressful stimuli has been found to bring about the NO-producing neurons activation in the amygdala, periaqueductal grey, hypothalamus, and pedunculo-pontine tegmental nucleus [41]. Glutamatergic activation of NMDA receptors stimulates a number of enzymes which includes NOS, cyclooxygenases, proteases, lipases, and protein kinases by invoking an influx of long-lasting (100 millisecond)  $Ca^{2+}$ -ion. These  $Ca^{2+}$  ions activate NOS in the presence of calmodulin which transforms the amino-acid, L-arginine to  $N\omega$ -hydroxy-L-arginine that is further transformed into NO and L-citrulline [37]. On the other hand, recent studies have shown that NO might play a role as an anti-stress agent by relieving stress induced anxiogenic, neuroendocrinal, visceral and immunological responses in both acute as well as chronic stress models. Gender based differences in stress responsiveness has also been found to be regulated by NO, and stress attenuating effects of various drugs have been referred to NO [38]. Since NO also possesses anti-oxidant properties and has the ability to suppress expression of iNOS, it may exert a neuroprotective effect. Moreover, by inhibiting its own formation and by down-regulation of the NMDA receptor by S-nitrosylation at the redox-sensitive site on the receptor, it can also negatively affect its own formation and activation. Thus, many behavioral and pharmacological studies have suggested dysfunction of NMDA-NO-cGMP system in anxiety states. Therefore, NMDA receptor antagonists, guanylate cyclase inhibitors, and NOS inhibitors, all were found to have apparent anxiolytic properties in the animal models of anxiety [37]. Further, since initial stimulation of constitutive NOS may follow acute stress, iNOS appears to play a more significant role during chronic stress [42].

Many studies have suggested that PTSD induces a complex neurobiological response in the hippocampus involving excitatory and inhibitory pathways. In particular, it results in a sustained rise in the hippocampal NOS activity along with the hippocampal NMDA receptors. Also, glucocorticoid synthesis inhibition (by ketoconazole) resulted in similar reduction of NOS activity. These highlighted the possible influence of NO in PTSD induced hippocampal degeneration and cognitive dysfunction. A study also found that NO and cGMP were significant neurobiological correlates in the response of the brain to repeated stress as found in PTSD, and may help to describe cognitive disturbances, anxiety and hippocampal degeneration shown in PTSD. Nevertheless, the exact role of these three NOS subtypes in the PTSD pathophysiology is still not clear [43]. Another study demonstrated that agmatine, a neurotransmitter substance associated with the L-arginine-NO pathway and produced endogenously by the decarboxylation of arginine by arginine decarboxylase, lessened the anxiety like behavior in rats in a PTSD experimental model [44]. This further suggests the involvement of the Arginine-NO nexus and associated signaling pathways in the regulation of PTSD.

### Role of GABA

In the CNS, the role of GABA as an inhibitory transmitters widely studied and various studies on the mechanisms of stress have found that GABA attenuates various stress responses and involved with various neuromodulators to neutralize the effects of stress in stress dis-

ease models [45,46]. PTSD-generated stimulation of hippocampal iNOS and the following down-regulation of NMDA receptors are probably associated with lowered GABA levels in the hippocampus. GABA occupies a crucial role in glutamatergic transmission via inhibition through presynaptic GABA-B heteroreceptors. Furthermore, the swim stress-induced hippocampal GABA release is augmented by NO, which could provide a protective mechanism to curb glutamate-NOS stimulation of PTSD. Acute stress results in an increase in the levels of GABA [47], an instantaneous response to attenuate the excitotoxic release of glutamate. However, under conditions of repeated trauma exposure, as with TDS (Time-Dependent Sensitization, an animal model of PTSD), the protective influence of GABA is not observed. Within this same context, it is relevant to state that NMDA receptor-mediated release of GABA is inhibited by NO [48], such that elevated levels of NO decreases neuronal GABA thereby causing unabated excitotoxic effects of glutamate.

### Role of neuro-immune interactions

Stress and stress related incidents are known to regulate the neuroendocrine-immune axis and complex immunological changes are manifested. Both innate and adaptive immune responses are affected by the stress and this is supported by both the preclinical and clinical studies. Psychoneuroimmunology is a discipline that studies interactions of brain and behaviour with the immune system function, and the HPA axis plays a crucial role in this [48,49]. Activation of the HPA axis releases stress hormones, including cortisol/corticosterone, and adrenergic hormones during stress and traumatic events, which in turn modulate the immune system through the release of cytokines which attach to their specific receptors on the white blood cells or on their precursors in the bone marrow, thymus, spleen or lymph node tissue. PTSD sufferers manifest an upregulation of the immune response, whereas those in the state of remission manifest a down regulation of the immune functioning, with reduction in T cells counts, activity of NK cell, and interferon gamma (IFN- $\gamma$ ) and interleukin 4 (IL-4) expression. Thus, the connection between the stress hormones secreted by the HPA axis, the immune system and the behavioural patterns are interactive and complex. Acute stress may exhibit an augmentation of the immune response, whereas chronic stress may exhibit a suppression of the immune pathways. However, in a recent study, Marshall (2004) [50] showed that chronic stress exhibits the concomitant enhancement and suppression of the immune response through variations in the expression pattern of cytokine. Th1 cytokines released by the CD4+ Th1 subsets stimulate the inflammatory cellular immune response that includes IL-12 and IFN- $\gamma$ . IL10 produced by adrenergic moieties due to stress suppress IFN- $\gamma$ . This helps in switching the cellular immune response to a Th2 anti-inflammatory response. There are studies which provide that this switch does not inevitably take place in absolute quantities but rather occurs proportionately with other Th2 cytokines e.g. IL-4 and IL-5. This switch occurs through the interaction of stress hormones from the stimulation of HPA axis and corticosteroids and sympatho-adrenal system. IL-10 is a powerful suppressor of Th1 helper cells and Th1 cytokines. Continuous rise in the levels of glucocorticoids and adrenaline due to flashbacks of PTSD results in the suppression of the Th1 cell activities and responses of the cellular immune system through inhibition of IFN- $\alpha$  production as well as the down regulation of cortisol receptors or TNF- $\alpha$ . Adoptive immune therapy linked with corticosteroid and catecholamine therapy could be an interesting alternative for the amelioration of immune suppression [51]. This would also be helpful in specific short- and long-term consequences that are connected with PTSD by restoring the equilibrium between the Th1 and Th2 immune responses.

### The COVID pandemic: Stimulus for PTSD

COVID-19 has rapidly become a global health emergency and attention has greatly been directed on both SARS-CoV2 infected patients and the physical as well as psychological status of the frontline medical personnel/caregivers. With the rapid growth of information technology, the influence on the psychological status spread more extensively through the so called "We Media," which is a naïve media approach [52]. Thus, COVID-19 is described as a challenge to the psychological state of both those who are experiencing it as well as the healthcare personnel. From the study findings of the SARS outbreak, it is pertinent that even after the COVID-19 outbreak is over, such challenges are possibly resulting into a secondary disaster due to psychological stress [53]. Severe psychological stress factors are well likely to trigger serious mental illnesses and precipitate post-traumatic stress disorder (PTSD). Undergoing and perceiving the suffering associated with COVID-19 can lead to increased prevalence of PTSD, resulting into serious distress and disability among COVID-19

survivors, their close family members, and frontline workers (medical and public health professionals, police personnel, etc.), and even among the general public exposed to this COVID anxiety. Although the best epidemic management and the ultimate care of patients of COVID-19 is the predominant approach worldwide, the ancillary psychological issues also needs immediate attention for early intervention and prevention of PTSD among the affected individuals. Exposure to such type of epidemics lead to a particular type of psychological trauma, which is classified into three groups. Firstly, those who are directly affected by disease and the traumatic event i.e. experiencing symptoms of disease like shortness of breath, alteration of conscious states, fear of death, tracheotomy/ventilatory support, etc. Secondly, those watching the patients of COVID-19 who are suffering, struggling and dying of the illness that has a direct and significant impact on the fellow patients, their family members as well as on the people who are directly providing medical care. Thirdly, those experiencing the realistic or unrealistic anxiety of contracting the infection, social isolation and the societal stigmatization. Epidemiological studies have found a high prevalence rate of mental health issues among the survivors, families of the sufferers, medical professionals, and the general people after an infectious disease epidemic, for example-SARS, MERS, Ebola, Flu, HIV/AIDS etc. A study on the outcomes of the psychological issues of infectious disease outbreak (after the 2003 SARS outbreak, the H1N1 outbreak in 2009, and occupational exposure to HIV) showed that the average prevalence of PTSD among health professionals was around 21% (10 to 33%), and 40% of them showed persistently high PTSD symptoms 3 years after exposure to stressful event. PTSD symptoms were also apparently more among exposed healthcare workers (HCWs) than the unexposed control group, specifically among allied HCWs, followed by the nursing staff and then the doctors [54]. The duration and level of exposure to psychological trauma was found to be the most dependable predictor of PTSD after an epidemic of an infectious disease. After studying the large number of people that are exposed to the current COVID-19 pandemic, it is suggested to provide urgent service to mental health along with the targeted approach for the prevention of PTSD among survivors and other people that are exposed to COVID-19.

### Current therapeutic approaches for PTSD and future strategies

PTSD is a complex brain disorder which follows exposure to a traumatic event. Brain areas like prefrontal cortex and hippocampus are the primary neuroanatomical substrates and symptoms are predominantly cognitive or non-cognitive in nature. Dysregulations of the HPA axis and sympathoadrenal system are proposed as the neurochemical basis for PTSD. Further, it is apparent that, since not all individuals exposed to trauma end up with PTSD, both prophylactic and therapeutic strategies are important for treatment [9,55]. Nevertheless, though several treatment options are practiced, none of them have proved to be sustainable. Both psychotherapy and pharmacotherapy have emerged as crucial treatment strategies for this complex brain disorder. In psychotherapy, cognitive therapy, exposure therapy and eye movement desensitization and reprocessing (EMDR) - all of which help in developing stress management skills and better coping strategies. Pharmacological strategies have been the major focus and have led to considerable amount of preclinical and clinical research for novel therapeutic alternatives. There is consensus that both pharmacotherapy and psychotherapy may complement each other for optimal treatment in PTSD. Such strategies include prophylactic treatments and use of pharmacotherapy as adjunctive treatment with established trauma-focused psychological therapies. Some of these established therapeutic approaches include modulation of stress induced angiogenesis and cognitive dysfunction by drugs like glucocorticoid, corticotropin-releasing factor and norepinephrine signaling modulators. A role for putative cognitive enhancers has also been proposed. Modulators for glucocorticoid receptors and glutamate signaling have also been proposed. Generally, treatment strategies are preventive (both primary and secondary) and/or curative. Primary prevention (pre-stress) is aimed at enhancing abilities to cope with stress, whereas, secondary prevention targets post-stress effects. Glucocorticoid receptor (GR) antagonists and CRF antagonists, as well as CCK antagonists influence the coping process as well as post-stress consolidation mechanisms and are likely to be effective as primary and secondary preventive agents. Additionally, adrenoceptor agonists (via presynaptic  $\alpha$ -2R) and antagonists (beta blockers) have also been shown to be effective in some PTSD cases, with differential efficacy. Benzodiazepines and NMDA-R antagonists have also been shown to provide beneficial effects in secondary prophylaxis (i.e. in post stress exposure). More recent studies have shown that opioids like morphine may reduce the incidences of PTSD development following psychological trauma. Treatment of established PTSD, however, is the major challenge and both non-cognitive and cognitive



symptoms are targeted. Selective Serotonin Reuptake Inhibitors (SSRIs) and other anti-depressants are the principal agents used for this purpose. 5-HT appears to be the neurotransmitter which regulates such PTSD manifestations. GR antagonists, adrenoceptor modulators and NMDA-R antagonists also help in attenuating developed PTSD. These drugs, although being effective, have some restrictions in the form of refractoriness to drug therapy, adverse effects on their long term use, and most important their psychological and physical dependence [56]. Therefore, there is a high need for the development of newer and/or safer drugs for PTSD treatment, specifically in the wake of this current global COVID 19 pandemic.

Targeting neuroanatomical substrates of PTSD is also an alternative approach. The disruption of amygdala functioning has been considered as an effective strategy for PTSD treatment. Unilateral amygdectomy, which has been shown to be effective treating temporal lobe epilepsy, has been proposed as an aggressive treatment option for intractable PTSD. A reversible and alternative approach is deep brain stimulation (DBS), in which electrodes are implanted to modulate neuronal activity. In fact, DBS has been used as an advanced technique for treating neurological and psychiatric diseases like Parkinson's disease, Obsessive compulsive disorder (OCD) and depression. Specifically, amygdala electrode implantation in DBS reduce symptoms of anxiety and stress. Amygdala specific pharmacotherapy is a more logistically feasible approach and is the outcome of recent research in cellular/molecular neuropsychiatry. Preclinical studies have shown that targeting specific ion channels localized in the amygdala can attenuate fear and anxiety - two of the principal manifestations of PTSD [16,57,58].

More recent studies have suggested that cannabinoids and histone deacetylase (HDAC) inhibitors may have a role to play in alleviating PTSD effects. Experimental data have also indicated that there is a possible role of brain derived neurotrophic factor (BDNF) and the BDNF gene in the pathophysiology of PTSD. Central injections of BDNF have been shown to attenuate PTSD like manifestations in animal models, which could be translated to PTSD therapy. For example, the development of small-molecule mimetics for the tropomyosin receptor kinase B (TrkB) receptor could become a potential new treatment option for PTSD. Molecular insights into the HPA axis functioning and GR dependent signaling abnormalities have shown that the GR co-chaperone, FKBP51 is dynamically regulated during PTSD, and the first selective FKBP51 antagonist has recently been developed and shown to reduce anxiety in animal models, which has the potential of being translated to the clinical scenario [59].

Medicinal plants have a history of providing effective and safe therapeutic agents to modern medicine since long. Such phytotherapeutic substances (plant extracts or phytomolecules), being natural agents are comparatively safer, therapeutically effective, pharmacoeconomically viable and readily available to the population at large [60]. Several studies have shown the possibility of adaptogenic medicinal plants and their active moieties in many experimental and models of stress-related disorders and proven to be of great clinical importance when compared to the conventional psychoactive drugs [61,62]. Recent studies have further shown that the endocannabinoid (eCB) system may be a potential target for developing therapeutic agents in PTSD. Cannabidiol (CBD), a phytocannabinoid constituent of *Cannabis sativa*, sans the psychotomimetic effects, has shown promise. Preclinical and clinical studies have shown that CBD, acting via the eCB system, attenuates emotional and cognitive disturbances and PTSD neurobehavioral symptoms with minimal adverse effects as compared to other contemporary pharmacological agents. These preliminary results point to the therapeutic potential of CBD for pharmacological treatment of PTSD [9]. Our most recent studies have shown that the traditionally used Indian medicinal plant, *Withania somnifera* (Ashwagandha, Indian Ginseng) attenuated neurobehavioral manifestations of PTSD in experimental models (Ray and co-workers, 2020, unpublished data).

Irrespective of the nature/type of treatment i.e. prophylactic or curative it is increasingly evident that both psychotherapy (counselling) and pharmacotherapy will complement each other in the treatment of PTSD. As most of these psychotherapeutic agents have untoward effects which could further complicate the PTSD scenario, a judicious assessment of risk versus benefit should be a important consideration. Both preclinical and clinical studies indicate that prophylaxis is possible but assessment of safety of therapeutic options

is a must. Also, such treatment may be particularly useful for specific populations e.g. disaster management personnel, armed forces etc. Therapies focused on trauma, fear/anxiety, cognitive dysfunction are likely to be more effective strategies in research. Neuroendocrinal and neurochemical biomarkers could be of assistance in both preclinical models and clinical trials during the process of drug development. Facilitation of alternative behavioural paradigms like new skills or reorienting memory and behavioral patterns could be exciting future treatment options for PTSD. This may also negate some of the deleterious issues associated with chronic drug administration like tolerance/dependence, addiction, and other adverse effects.

**Preclinical disease models of PTSD**

One of the major scientific tools used to gain insights into understanding physiological and neuronal mechanisms underlying neuropsychiatric diseases and treatment development is the use of preclinical animal models of human diseases. PTSD is a complex stress-related disorder and the understanding of the neurobiological, cellular and molecular mechanisms are central to the development of newer pharmacological strategies to alleviate the condition. Though several psychoactive agents are currently used for pharmacotherapy, the long-term treatment of this condition still remains far from satisfactory. Recently there has been considerable debate on the use of preclinical animal models for disorders like PTSD, and the relevance of these proposed models for understanding the pathophysiology of the condition has been questioned. Nevertheless, overall impression from the studies has indicated that animal models are indeed invaluable for understanding the PTSD disease process and some of the related manifestations like fear/anxiety and cognitive deficits. These models are also able to take into account the complexity of the human disease and differential responses to risk factors like stressors. However, it is imperative that inter-individual differences, sexual polymorphism, risk factors and manifestations of the disease should be given due consideration while selecting the model. Such studies have shown that experimental animal models for PTSD are not only invaluable in understanding basic mechanisms of CNS pathophysiology, but are also of translational value with reference to human disease. Such models are expected to unravel the physiological and pharmacological correlates in PTSD which should serve to reveal novel targets for drug development and provide a platform for novel drug testing. Several trauma and stress based models have been employed to evaluate potential drugs for PTSD, but the association between behavioural and neural correlates seems to be crucial for any model being tested. Exposure of animals to a variety of complex stressors results in many epigenetic, gene expression, and biochemical alterations and resultant modulations in activity in many brain areas is assumed to be associated with the neuropathology. Accordingly, several animal models have been documented, and sometimes a combination of models may also have to be used to express the true characteristics of PTSD [59,63]. Some of these commonly used models are summarized in the table 1.

Animal model	Procedure
Single prolonged stress: Single prolonged stress (SPS) or Time Dependent Sensitization (TDS)	Animals are exposed to a single session of prolonged stress (SPS), 2h restraint followed by a 20 min forced swim, followed by exposure to ether or halothane vapors until loss of consciousness
Fear conditioning response	Animals are exposed to brief series of tone-shock exposures. rodents learn to fear a specific cue (e.g., tone) through a pairing of the cue with a fear eliciting stimulus such as a foot shock. After several pairings, the rodent learns that the cue (e.g., tone) means a shock is coming, and it demonstrates a conditioned fear response to the cue, even when the shock no longer follows.
Stress-enhanced fear learning (SEFL)	Animals were received 15 (1 mA, 1 sec) foot-shocks; 3-8 m apart for a period of 90 min. Followed by a single (1 mA, 1 sec) foot-shock and level of fear was measured for five minutes. Pre-exposure to repeated foot shock in one context produces an enhancement of conditional freezing to cues associated with a single shock in a second distinct context.

Immobilization/restraint	This involve placing rodents in an enclosed chamber allowing for minimal or no movement for 2h.
Underwater trauma/Submersion stress	In this model, rats are forced to swim for 1 min. in a Morris water maze from which the platform has been removed. Afterwards, they are held under water for 30 sec.
Exposure to a short session of inescapable footshocks	Animals are exposed to a brief (15 min) session of inescapable foot shocks (e.g. 10 × 6s, 1 mA) inducing a gradually developing and long lasting change in behavioral responses to novel environmental stimuli.
Exposure to predators or predator odor	Laboratory Rodents are exposed to a predator (cat, snake,..) or predator odor, (TMT) trimethylthiazoline originally isolated from fox feces often in combination with other stressors and this will be exhibit innate aversion to this odor illustrated by freezing and withdrawing.
Chronic stress models (e.g. chronic variable stress, chronic social defeat, etc)	Exposure of rats or mice to less severe, but chronic or repeated stressful situations

Table 1: Preclinical models for PTSD\*

\*: Flandreu and Toth, 2018; Richter-Levin., et al. (2019).

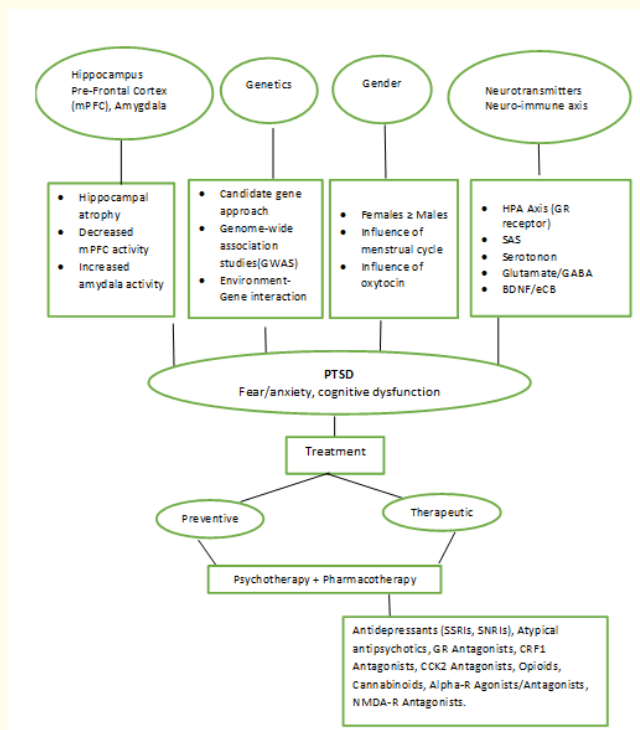


Figure 1: Schematic diagram summarizing pathophysiology and therapeutic options in PTSD (post-traumatic stress disorder).

SAS: Sympathoadrenal System; BDNF: Brain Derived Neurotropic Factor; eCB: Endocannabinoids; SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Selective Norepinephrine Reuptake Inhibitors; GR: Glucocorticoid Receptor; CRF: Corticotropin Releasing Factor; CCK: Cholecystokinin; NMDA: N-methyl-D-Aspartate Receptor.

## Conclusions and Perspectives

Stress related disorders consist of mental and physical over-reaction to environmental cues that are perceived as potentially harmful, engendered by past exposure to traumatic events. Stress disorders, such as post-traumatic stress disorder (PTSD), are prevalent, disabling and underdiagnosed. It is becoming increasingly apparent that PTSD may be a systemic illness, affecting not just the brain, but the entire body. Therefore, disease signals likely span multiple biological domains, including genes, proteins, cells, tissues, and organism-level physiological changes. Identification of these signals could aid in diagnostics, treatment decision-making, and risk evaluation. Brain substrates like the hippocampus and the prefrontal cortex regulate the neural circuits that are disturbed in PTSD. Experimental studies on neurochemical pathways show the association of PTSD and complex neurotransmitter interactions result in facilitation of learning and consolidating trauma related memories. Neuro-immune interactions may also be important in this regard. More recent studies have shown that novel stress related genetic biomarkers could help in prediction and management of PTSD. Therapeutic interventions are primarily pharmacotherapy (psychoactive drugs) and psychological counseling and are still far from satisfactory. Hence, the better understanding of the disease biology leading to identification of novel targets may be crucial for the development of newer and better therapeutic agents. In view of the fact that PTSD has been recognized as a multi-system disease, a multi-targeted approach is likely to be of benefit. In this context, medicinal plant derived products with multi-faceted properties could be potential agents worth investigating. A multi-disciplinary approach may lead to improved diagnosis and treatment for stress disorders like PTSD, reduce adverse outcomes and improve quality of life. A comprehensive overview of all aspects of PTSD is summarized in figure 1.

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