REVIEW ARTICLE

BIOLOGICAL MARKERS OF PSYCHOLOGICAL TRAUMA: A REVIEW

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ABSTRACT

To review current evidence on the patho-physiology of psychotrauma and its biological markers. The authors made a comprehensive literature search using internet databases, PubMed, Medline and google search engine, Am J Psychiatry, British Journal of Psychiatry, Arch Gen Psychiatry, J Neurosci, ISTSS journal for evidence for biological markers of Psychotrauma spanning over a period last 28 years, up to 1980. The key words used for the search were psychotrauma & biological marker. A total of 109 papers and articles were included in the study. The patho-physiology of psychotrauma involves a complex interplay between trauma-related factors and the neurobiological and psychosocial influences that determine individual differences in resilience and vulnerability. In psychotrauma, dysregulation of HPA axis takes place associated with changes in autonomic nervous system. The structures mostly related to psychotrauma are amygdala, hippocampus, anterior cingualte cortex, prefrontal cortex etc. The related hormones are CRF, ACTH, Cortisol, Catecholamines, Serotonin, GABA, Dopamine, Opioids, and Substance P.

Psychotrauma is not a mere psychological or a social pathology. There are clear & well-defined biological markers of the change seen in consequence to exposure to trauma. The understanding of patho-physiology of the consequent disorders is however still in infancy. This calls for consorted scientific enquiry into the biological basis of psychotrauma through rigorous methods.

INTRODUCTION

Psycho-Trauma (Trauma, Greek: "wound, injury"). A psychological trauma is a wound to the psyche due to an experience which has endangered one's life and threatened one's identity, integrity, honour & property. The experience is understood as a threat to one's physical and psychological well-being and is a sharp confrontation with death or a challenge to life. A traumatic experience leaves scars on the mind and the body of a human being. These can express themselves as involuntary flashbacks, reliving of the traumatic experiences, avoidance of cues related to the trauma and a state of hyper arousal or else lead to dissociation, depression, anxiety, somatization or medically unexplained symptoms which deeply impair day-to-day life. The most common & well-studied outcome of trauma is post traumatic stress disorder (PTSD).

A key question in trauma research is why some individuals develop PTSD following exposure to potentially traumatic events when others appear to experience few negative effects. Clinical profile of trauma survivors' depends upon the type & severity of the trauma, personality pattern of the individual, his/her coping abilities, social condition etc. i.e. his/her bio-psycho-social status. The study of biological markers has however focused most commonly on Posttraumatic stress disorder. Biological markers that influence the risk for developing PTSD therefore, may provide part of the answer to this question.

The rapid development of technical advances in the neurosciences has led to a better understanding of the molecular biology, neurotransmitter systems & neural circuitry involved in mental illness. The authors reviewed literature from internet on the biological marker associated with psychotrauma.

Exploring neuroendocrine function in patients with post-traumatic stress disorder (PTSD) may give insight into the pathogenesis of this stress-related disorder. One focus in the scientific literature has been on possible disturbances in the hypothalamic–pituitary–adrenal (HPA) axis[1]. During acute stress the HPA axis is activated; (Fig 1) the hypothalamus secretes corticotropin-releasing hormone (CRH) under the influence of serotonin from the

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amygdala. Subsequently, CRH stimulates the pituitary to release adrenocorticotropic hormone (ACTH), which results in the production of glucocorticoids (cortisol) in the adrenal cortex. Cortisol serves to stop many metabolic, neuronal defensive and immune reactions. Consequently energy can be mobilized to cope adequately with the stressor. Studies using psychological stress to stimulate the HPA axis have shown an exaggerated cortisol response in PTSD. (Fig. 2)

Well-defined chemical, structural, and immunological changes are evident. Biological markers in traumatic stress are poorly understood and inadequately researched. Rigorous scientific inquiry into biological markers of Psychotrauma is the need of the hour. Better understanding of the biological marker of stress could have a profound effect on its prevention & treatment.

A comprehensive literature search was made, using internet databases, PubMed, Medline and google search engine, Am J Psychiatry, British Journal of Psychiatry, Arch Gen Psychiatry, J Neurosci, ISTSS journal for evidence for biological markers of Psychotrauma spanning over a period last 28 years, up to 1980. The key words used for the search were psychotrauma & biological marker. A total of 109 papers and articles were included in the study. Since this was not a systematic review, the books published on the subject were not included in the study and no attempt was made to find literature beyond 1980.

Additional papers were found by hand searching the references of retrieved articles, previous systematic reviews and meta-analyses of PTSD.

It is evident that stress response is dysregulated in PTSD and influenced by neurochemical and neuroanatomic abnormalities and genetic vulnerabilities. Persistent alterations have been observed in physiologic reactivity and levels of specific stress - responsive neurochemicals. Neuroanatomic changes have also been reported. Findings from family and twin studies suggest a genetic vulnerability to PTSD[2].

The biological changes. reflected in psychotrauma may be grouped into four major heads, namely, Neurochemical, Structural, Immunological and Genetic changes

I. Neuro-chemical changes

a. Hypothalamic- Pituitary-Adrenal axis (HPA):

The Hypothalamic- Pituitary-Adrenal (HPA) axis plays a key regulatory function in the body, controlling all three systems through negative feedback inhibition. Cortisol is a major hormone of the HPA axis and is the primary stress hormone in the body. It is released when stimulated by Corticotropin Releasing Hormone (CRH) and inhibited via negative feedback acting at the hypothalamic and pituitary levels[3].

Intense psychological trauma such as sexual abuse can cause changes in the body's response to stress by increasing levels of CRH and dysregulating the HPA axis[4-6]. This results in a decreased number of CRH receptors in the anterior pituitary, decreased pituitary responsiveness to CRH, and disturbed negative feedback inhibition[7]. Reduced responsiveness to CRH causes over activation of the HPA axis and can disturb negative feedback by cortisol. Cortisol has widespread action and its dysregulation affects other neural systems including the mesocorticolimbic dopaminergic system, leading to inappropriate fear reactions and persistent mild depression[8].

Although the hypothalamic-pituitary-adrenal (HPA) axis appears to be dysregulated in individuals with PTSD4, the direction of the abnormality is unclear. Some studies report elevated cortisol levels, whereas others note low or normal levels[9,10]. Methodological and population differences across studies may account for these discrepancies. There have been reports of low cortisol levels[11] and heightened responsiveness to corticotropin-releasing factor (CRF)[9,12], raising the possibility that low cortisol levels prior to traumatic stress exposure elevate the risk of PTSD. There may also be gender differences in HPA axis activity

in PTSD[13], with heightened ACTH activity and adrenal cortisol response to CRF reported in women with PTSD compared with controls12. These results differ from earlier reports of low cortisol levels and blunted ACTH responses to CRF in men with PTSD[14].

b. Dexamethasone Suppression Test (DST):

In PTSD there is enhanced cortisol negative feedback inhibition of ACTH secretion at the level of the pituitary. Pituitary glucocorticoid receptor binding, rather than low adrenal output, is implicated as a likely mechanism for this effect[15]. The ACTH and cortisol responses to 0.50 mg of dexamethasone were assessed in 19 subjects (15 men and four women) with PTSD and 19 subjects (14 men and five women) without psychiatric disorder by Yehuda et al[15]. The subjects with PTSD showed greater suppression of ACTH (as well as cortisol) in response to dexamethasone.

A high level of cortisol suppression is associated with PTSD in subjects with personality disorder[16]. Major depression, gender, age when trauma (s) occurred, and a diagnosis of borderline personality disorder did not have significant main or interaction effects on cortisol suppression[16].

Enhanced cortisol suppression in response to dexamethasone has been associated primarily with parental PTSD status, with minimal contribution of subjects' own trauma-related symptoms. Enhanced cortisol negative feedback inhibition may be associated with PTSD because it is related to the PTSD risk factor of parental PTSD[17].

c. Corticotropin-Releasing Factor (CRF)

Corticotropin-releasing factor (CRF) plays an important role in mediating the mammalian stress response[18]. CRF released during stress[19] from nerve terminals originating in the paraventricular nucleus of the hypothalamus increases the secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary, which in turn stimulates release of cortisol from the adrenal[20]. Cortisol has a number of effects that are beneficial to short-term survival, including suppression of reproductive and immune function, promotion of analgesia, activation of the peripheral autonomic system, suppression of gastric motility and gastric acid secretion, and increases in total oxygen consumption and glucose and glucagon concentrations in plasma[20]. Chronic stress results in sustained increases in plasma glucocorticoid levels[21], with a potentiation of glucocorticoid responsiveness to subsequent stressors[22,23] and neuronal "hypersecretion" of CRF.

CSF concentrations of Corticotropin Releasing Factor (CRF) was found higher in the PTSD patients than in the comparison subjects. This group difference remained significant after covariance for age. Higher CSF CRF concentrations in patients with PTSD may reflect alterations in stress-related neurotransmitter systems. The higher CSF CRF concentrations may play a role in disturbances of arousal in patients with PTSD[24].

d. Cortisol

Psychological trauma is viewed in the DSM as linked in an essential way with a specific syndrome, that of posttraumatic stress disorder (PTSD)[25]. It has been proposed that PTSD demonstrates a paradoxical cortisol profile in comparison with the expected response to stress, with evidence of low basal cortisol levels in urine and plasma and enhanced negative feedback to dexamethasone[26-28]. The low cortisol levels were accompanied by increased catecholamine secretion in urine, leading to the claim that there is a disconnect between basal cortisol and catecholamine in individuals with PTSD[26,27].

But trauma per se does not lead to sustained increases in cortisol or catecholamine levels. Posttraumatic stress disorder is associated with higher catecholamine levels. In contrast, persons with PTSD had neither an increase nor a decrease in mean urinary cortisol levels. Women with PTSD and co-morbid Major Depressive Disorder had higher cortisol levels[28].

Circadian studies have found low peripheral basal cortisol concentrations in posttraumatic stress disorder (PTSD), whereas results of single time-point plasma and urinary

free cortisol studies have been variable[30,31]. found significantly higher in the subjects with

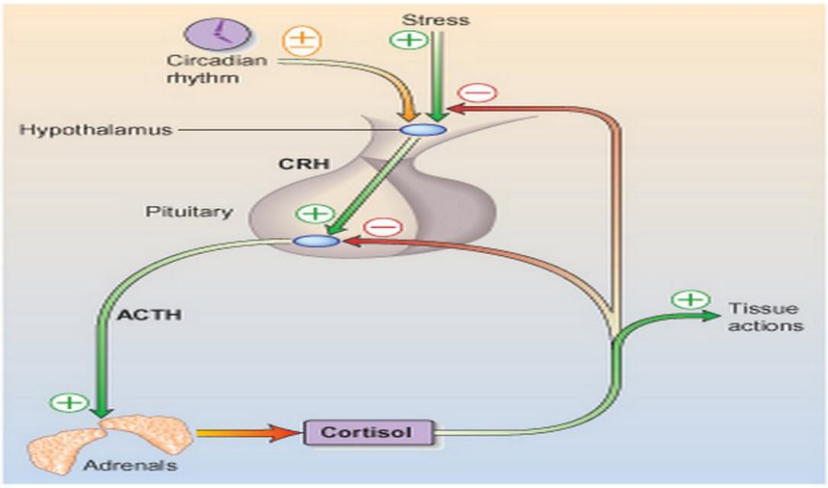

Figure 1: The HPA axis

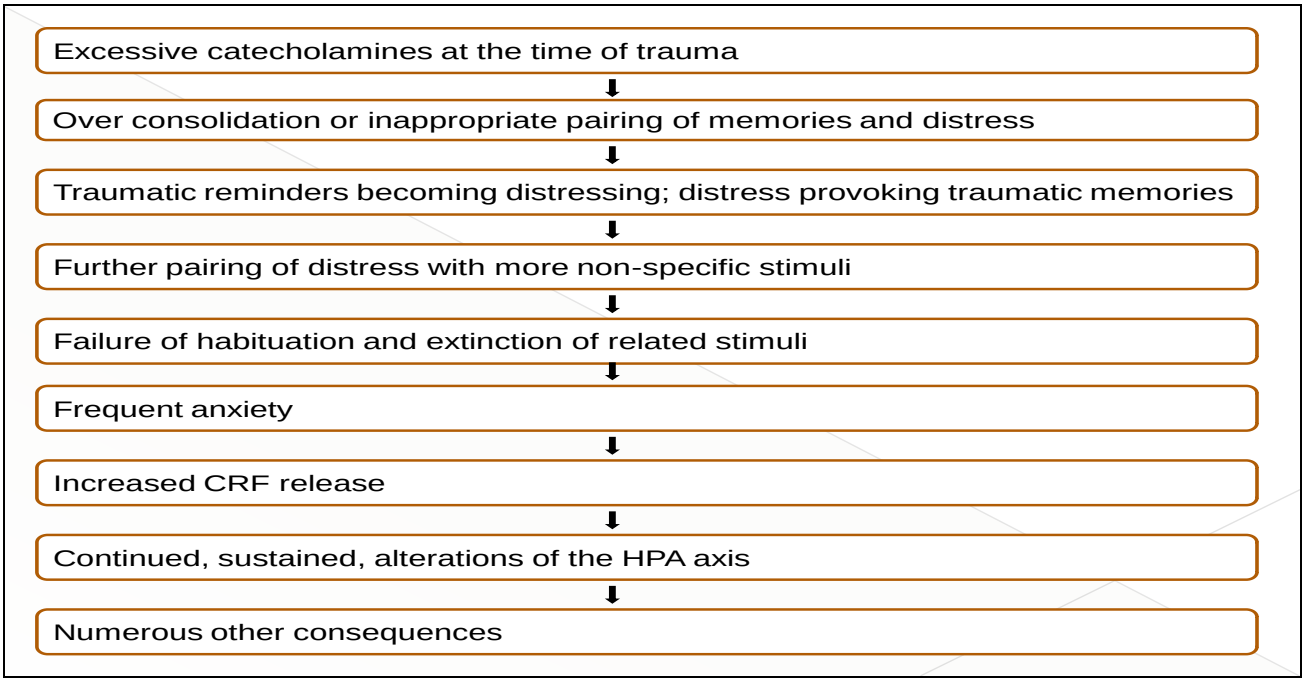

Figure 2: Neuroendocrine consequences after trauma

Given the elevation in CSF corticotropin-releasing hormone (CRH) in PTSD, even normal circulating cortisol levels could be considered low[32]. Cortisol enters the brain readily from plasma, but levels in the CSF cannot be inferred directly from peripheral measures[33-36].

Most of the studies measured the peripheral cortisol concentration. In one study[37], mean CSF cortisol concentrations were PTSD than in the normal volunteers, largely due to higher CSF cortisol concentration. No group differences were observed in either plasma ACTH or peripheral (plasma or urinary free) cortisol. Despite normal peripheral cortisol indices in the veterans with PTSD, their CNS exposure to cortisol was greater than that of normal comparison subjects.

Across 37 studies, 828 people with PTSD and 800 controls did not differ in cortisol levels.

Subgroup analyses revealed that studies assessing plasma or serum showed significantly lower levels in people with PTSD than in controls not exposed to trauma1.

e. Catecholamines

Catecholaminergic activity increases during stress, and research findings suggest that catecholaminergic dysfunction, especially in norepinephrine, may play a role in the development of specific PTSD symptoms. On exposure to stress, norepinephrine is rapidly released (Fig. 2) from the locus ceruleus, leading to elevations in heart rate and blood pressure and symptoms of increased arousal. Stress paradigms demonstrate increased noradrenergic and sympathetic activity in PTSD[38,39] and this hyperactivity may contribute to the core autonomic hyper arousal and re-experiencing symptoms. There may also be a relationship between increased norepinephrine activity and enhanced long-term memory for traumatic events and PTSD re-experiencing symptoms[40,41].

CSF norepinephrine concentrations were significantly higher in the men with PTSD than in the healthy men. Moreover, CSF norepinephrine levels strongly and positively correlated with the severity of PTSD symptoms. Plasma norepinephrine concentrations showed no significant relationship with the severity of PTSD symptoms[42].

f. Serotonin

Converging evidence supports a role for serotonergic dysregulation in PTSD[43]. Platelet paroxetine binding (a peripheral marker of serotonergic function) is lower in individuals with PTSD and may be a predictor of response to treatment with selective serotonin reuptake inhibitors (SSRIs)[44,45,46]. D-Fenfluramine, a serotonin releasing agent and reuptake inhibitor, was used to assess the integrity of the serotonergic system in PTSD through prompting of serotonin-mediated prolactin release. A low prolactin response to Dfenfluramine was observed in veterans with PTSD, and this response was inversely correlated with severity of PTSD symptoms and aggression[47] . Serotonin dysregulation is linked to specific PTSD symptoms, including aggression, impulsivity, depression, and suicidality[48] . The clinical efficacy of the SSRIs in the treatment of PTSD lends additional support to a role for serotonin in PTSD[49,50].

g. Dopamine

Dopamine is involved in control of locomotion, cognition, affect, and neuroendocrine secretion. Preclinical studies demonstrate that the mesocortical / mesoprefrontal and mesolimbic systems appear to be the dopaminergic neuronal systems most vulnerable to the influences of stress[51,52]. Clinical findings that support a role for dopamine in the stress response and in PTSD include the high rates of psychotic symptoms observed among individuals with PTSD[53] and the abnormally high concentrations of urinary dopamine (in addition to cortisol and norepinephrine) in children with PTSD after years of severe maltreatment[54]. Genetically determined changes in dopaminergic reactivity also may contribute to the risk of PTSD[55, 56].

Significantly higher mean levels of dopamine, epinephrine, and norepinephrine were found in persons with lifetime PTSD (with and without comorbid MDD), compared with persons with MDD alone or neither disorder[29].

h. Central Amino Acids

Excitatory glutaminergic and inhibitory GABA-ergic (γ-aminobutyric acid) pathways are implicated in encoding memory and may play a role in the patho-physiology of PTSD. Glutaminergic mechanisms are central to neuronal activation and cognitive functions, such as perception, appraisal, conditioning, extinction, and memory, all of which may be altered in PTSD[57]. A role for GABA is suggested in findings of a reduction in peripheral and central benzodiazepine receptors in subjects with PTSD[58,59,60], which may reflect an adaptive response to an overproduction of glucocorticoids in hyper arousal states. Consistent with this hypothesis are the elevated plasma levels of the GABA (A) antagonistic neurosteroid dehydroepiandrosterone (DHEA) in individuals with PTSD[61].

j. GABA

At 6 weeks and at 1 year, mean post trauma GABA levels were significantly lower among subjects who met all or nearly all criteria for PTSD than among those who did not. Among patients who met all or nearly all criteria for PTSD at 6 weeks, 75% of those with post trauma GABA levels above 0.20 mmol/ml no longer met criteria at 1 year. By contrast, among patients whose GABA levels were below 0.20 mmol/ml, 80% met all or nearly all criteria for PTSD at 1 year. Two-thirds of patients who met all or nearly all criteria for PTSD at 1 year also met criteria for major depressive disorder.

A plasma GABA level above 0.20 mmol/ml may protect against chronic PTSD and may represent a marker of recovery from trauma[62].

k. Opioids

Opioid system dysfunction is seen in the avoidance/numbing and hyper arousal symptoms of PTSD. Normally, stress-induced opioid activity inhibits both the HPA and norepinephrine systems, thus promoting recovery. In PTSD, abnormal levels of endogenous opioids and lower pain thresholds have been reported[63], suggesting a potential therapeutic role for opioid antagonists.

l. Substance P

Among its many actions, substance P has a major role in facilitating or transmitting nociceptive and stressful stimuli in the CNS[64,65,66]. Elevated CNS substance P concentrations are involved in both major depression and PTSD. Both depressed and PTSD patients had significantly elevated basal CSF substance P concentrations. The marked increase in CSF substance P concentrations during and after the symptom-provoking stimulus, but not after the neutral stimulus, implicates CNS release of substance P in the mechanism of acute PTSD symptoms[67].

II. Structural Changes

The amygdala has been implicated in PTSD in findings from MRI and single photon emission computerized tomography (SPECT) studies[68,69]. Functional MRI studies demonstrate alterations in other CNS regions in PTSD, including the anterior cingulate gyrus, the thalamus, and the medial frontal cortex[70,-72.] . Discrepancies in the neuroimaging literature may be explained by methodological differences across studies.

Amygdala

Recent research has focused on the role of specific CNS regions in the development of PTSD, although findings from neuroimaging studies to date are inconclusive[2]. Persons with PTSD may have alterations in brain regions central to the neurobiological fear response, specifically, the amygdala and the hippocampus. These structures are components of the limbic system, the area of the brain involved in the regulation of emotions, memory, and fear. The amygdala plays a role in threat assessment, fear conditioning, and emotional learning, and the hippocampus is implicated in learning, memory consolidation, and contextual processing. PTSD can be likened to a conditioned fear response, whereby an extreme threat becomes paired with a constellation of situational triggers, resulting in an abnormal fear response.

Hippocampus

Findings of reduced hippocampal volumes in PTSD have been reported in magnetic resonance imaging (MRI) studies[73-75] although this result is somewhat controversial, with conflicting findings published[76-78]. Neuroimaging evidence also suggests decreased hippocampal function[79] and flashback intensity has been linked to cerebral blood flow in this region[80].

Hippocampal atrophy can be associated with PTSD following combat trauma or childhood abuse. Such atrophy is demonstrable in both sexes and ranges from 5% to 26%[81]. Subjects with PTSD had 26% and 22% atrophy of the left and right hippocampi, respectively[82].

The question comes whether atrophy occurs prior to trauma, as a result of trauma, or as a result of the stress disorder following trauma81. In a recent prospective study, MRIs were carried out near the time of a trauma (in most cases, a serious car accident) and at intervals thereafter; a demonstration that individuals destined to develop PTSD already

had small hippocampi at the time of the trauma would confirm the predisposition idea. Instead, atrophy was not yet demonstrable among those succumbing to PTSD even 6 months after trauma[83].

As a second possibility, atrophy may arise as a result of the trauma itself. Such atrophy need not necessarily be demonstrable immediately after trauma; it must merely be that an even slowly emerging atrophy arises from biological features of the trauma, rather than of the posttraumatic period. Favoring this are findings hinting that atrophy is more a correlate of trauma itself, rather than of PTSD. One example concerned atrophy among victims of childhood abuse[84]; PTSD developed in a subset of individuals, but hippocampal volume in the non-PTSD trauma survivors did not differ from volume in subjects with PTSD[85]. As the second example, individuals who succumbed to PTSD following combat trauma were also those exposed to the most severe trauma. Thus, it is unclear whether it is trauma itself, or succumbing to PTSD afterward, which predicts atrophy[86].

Anterior Cingulate Cortex

The anterior cingulate cortex is involved in the extinction of conditioned fear responses and is implicated in the pathophysiology of PTSD[87]. Evidence for anterior cingulate dysfunction in adult PTSD comes from recent positron emission tomography studies. Studies comparing women who had been sexually abused as children and who had PTSD with women with a similar history who did not have PTSD found a lower level of anterior cingulate blood flow during traumatic script-driven imagery[88] and during memories of childhood sexual abuse[89]. A lower level of anterior cingulated blood flow has also been seen in Vietnam combat veterans with PTSD compared to those without PTSD during exposure to combat-related traumatic stimuli[90].

The lower N-acetylaspartate /creatine ratio in subjects with PTSD suggests that anterior cingulate neuronal metabolism may be altered in childhood PTSD. The ratio of N-acetylaspartate to creatine was significantly lower in the maltreated subjects with PTSD than in the comparison subjects.

Prefrontal Cortex

Medial prefrontal structures have been implicated in the pathophysiology of PTSD[91]. Several functional neuroimaging studies have demonstrated relatively diminished activation in the subcallosal[92,93], anterior cingulate[94-96], and medial frontal gyri[95,97] in PTSD. In addition, PTSD symptom severity is negatively correlated with blood flow in the medial frontal gyrus during traumatic imagery and recollection97. Furthermore, blood flow changes in the medial frontal gyrus appear to be negatively correlated with changes in the amygdala during traumatic imagery in PTSD[97]. These findings highlight the potential importance of interactions between the amygdale and medial prefrontal structures in this disorder. However, whether such interactions can be observed during the presentation of more general, affective stimuli unrelated to trauma is unknown.

III. Genetics

As mentioned earlier that a key question in trauma research is why some individuals develop PTSD following exposure to potentially traumatic events when others appear to experience few negative effects. Genetic factors influence who is at risk for developing PTSD and, therefore, may provide part of the answer to this question[98]. Evidence for genetic influences on PTSD comes from family, twin, and molecular genetic studies. If PTSD is genetic, family members of individuals with PTSD should have a higher prevalence of PTSD than do nonrelatives. Twin studies have examined the relative contribution of genetic and environmental influences on the variance in PTSD risk98.

Cambodian refugee children whose mother and father both had PTSD were five times more likely to receive the diagnosis than refugee children whose parents did not have PTSD[99]. Similarly, parents of children who developed PTSD in response to a serious physical injury were more likely to develop PTSD themselves[100]. Adult children of Holocaust

survivors with PTSD had a higher risk of PTSD following trauma compared to adult children of Holocaust survivors without PTSD[101].

The results of these studies suggest vulnerability to developing PTSD runs in families. However, PTSD may run in families for genetic or environmental reasons. Family members are both more genetically similar to each other and share more environmental exposures than do nonrelatives. Twin studies indicate that genetic influences account for about one third of the variance in PTSD risk[102,103]. That is, PTSD is approximately 30% heritable, indicating that genetic factors are important in the disorders' etiology. However, twin studies are limited in that they cannot tell us which genes are important in PTSD etiology.

Data from both pre-clinical research and family and twin studies implicate a genetic contribution to the development of PTSD[104]. Animals that are genetically predisposed to learned helplessness demonstrate cognitive deficits, analgesia, and HPA axis hypo-responsiveness in ways similar to those seen in people with PTSD[105]. A recent review of family and twin studies provides evidence to support a role for familial influences in the development of PTSD[106]. However, it remains unclear what vulnerabilities are inherited and how these may interact with the trauma experienced. Future research may focus on trait markers such as HPA axis hypo-function, increased arousal, and increased acoustic startle response[107,108].

IV. Immune System

Exposure to trauma can result in immune dysregulation, implicating the immune system in PTSD pathophysiology. Cytokine profiles in PTSD are similar to those observed in clinical chronic psychological stress models, although differences are noted in other immune parameters[109]. It remains unclear whether these changes are central or peripheral to the pathophysiology of PTSD. Investigations of the role of the immune system are also challenged by the inconsistent findings across studies.

CONCLUSION

Psychotrauma is not a mere psychological or a social pathology. There are clear & well defined biological markers of the change seen in consequence to exposure to trauma. The structures mostly related to psychotrauma are amygdala, hippocampus, anterior cingualte cortex, prefrontal cortex etc. The related hormones are CRF, ACTH, Cortisol, Catecholamines, Serotonin, GABA, Dopamin, Opioids, and Substance P. The understanding of patho-physiology of the consequent disorders is however still in infancy. This calls for consorted scientific enquiry into the biological basis of psychotrauma through rigorous methods.

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