



## REVIEW ARTICLE

# An insight on chronic unpredictable stress in association with pathophysiology, neurotransmitters, and experimental models

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### ABSTRACT

Stress is a common disorder affecting the normal functioning of the brain and behavior majorly in the prefrontal cortex and hippocampus region of the brain. Any long-term intrinsic and extrinsic stimulus evokes chronic stress-like conditions. Chronic stress reported enhancing the formation of reactive oxygen species, leading to mitochondrial cell death through the activation of the hypothalamic-pituitary axis which releases cortisol, excessive secretion of cortisol is responsible for alteration in glucose metabolism, and other neurological disorders such as anxiety, depression, multiple sclerosis, Alzheimer, and Parkinson's disease. The purpose of this review is to provide an insight into the various pathophysiological aspects along with neurotransmitters involved in chronic stress and its association with various neurological disorders. Along with this, we also provided a background on the various experimental models of chronic stress.

**KEY WORDS:** Anxiety, Chronic stress, Cortisol, Experimental models, Hypothalamic-pituitary axis, Neurological disorders

### INTRODUCTION

Stress is characterized by altered physical, mental (with impaired learning, decision making, and anxiety), and emotional behavior, leading to altered brain function and physiological changes of the body.<sup>[1-5]</sup> As per the literature, stress is divided into acute, chronic eustress, and distress.<sup>[6]</sup> In acute stress, the body will prepare itself to defend from unusual stress. Chronic stress occurs when the person is exposed to a longer duration of stress which, further, leads to various neurological disorders such as anxiety, depression, and disruption in memory also reported to affect the immune system.<sup>[7-9]</sup> Another stress that is good with positive feelings is "eustress" which means beneficial stress.<sup>[5,10]</sup> Last but not least is distress, in which the person has negative feelings or thoughts that can harm the body (including problems associated with work and financial difficulties).<sup>[11]</sup>

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As per the National Mental Health Survey of India 2015–2016, the neurotic and stress-related disorders in the female are 5.7% and in the male are 4.8%.<sup>[12]</sup> According to the 2019 CIGNA 360 wellbeing survey results, 82% of India's population are suffering from the high levels of stress. Moreover, chronic stress has been reported to have a very broad effect on behavioral and immunological responses.

### A NEUROPATHOLOGICAL CASCADE OF CHRONIC STRESS

The brain, the central organ of our body, is the major site that perceives and determines the behavioral and

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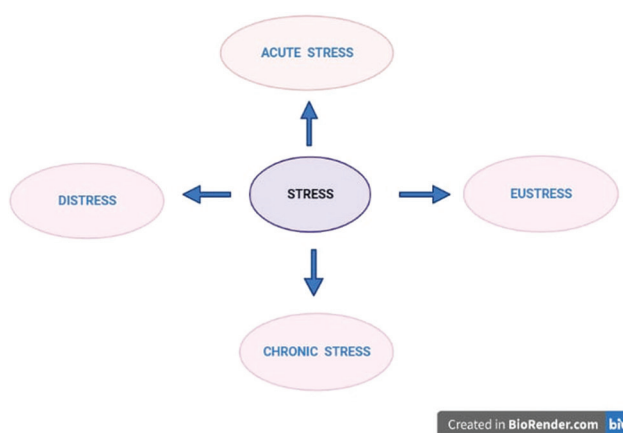
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physiological responses to the different stress conditions. The pathophysiological aspects behind chronic stress involve alterations of the hypothalamus-pituitary-axis (HPA), neuroinflammation or alteration of immune system pathways, and neurotransmitters alterations which are explained as follows –

### HPA pathway

Amygdala is a region in the brain that interprets the message. When the amygdala recognizes the danger, it directly drives a distress signal to the hypothalamus.<sup>[13]</sup> Hypothalamus is the command center in the brain. It also liaises with other parts of the body through the autonomic nervous system (ANS) and HPA. The HPA regulates the stress signal and in normal conditions, the HPA receives a signal which activates the paraventricular nucleus of the hypothalamus containing neurons. These neurons secrete corticotropin-releasing factor (CRF).<sup>[14]</sup> It is a peptide hormone which is also known as the corticotropin-releasing hormone (CRH), responsible for the stimulation of the pituitary gland containing proopiomelanocortin. This leads to the production of adrenocorticotrophic hormone (ACTH) and activation of the adrenal gland which secretes cortisol. Cortisol contributes a negative feedback mechanism to the hypothalamus to control the release of hormones. It is also responsible for the metabolism of glucose, immune function, and behavioral responses when it binds with glucocorticoid receptors [Figure 1].<sup>[15-17]</sup>

In chronic stressed conditions, there is excessive secretion of cortisol which impairs the binding of cortisol to glucocorticoid receptor and disrupts the negative feedback mechanism.<sup>[15]</sup> In normal conditions, cortisol inhibits the



**Figure 1:** The normal physiology of stress – activation of HPA axis which activates PVN of hypothalamus. These neurons secrete corticotropin releasing factor which leads to production of adrenocorticotrophic hormone and activation of adrenal gland which produces and secretes cortisol. Cortisol gives a negative feedback mechanism to hypothalamus to control the release of the hormones and thus maintains homeostasis.

constant secretion of CRH through a negative feedback mechanism when it is sufficient. CRH is responsible for the inflammatory responses from mast cells, also triggered by the nor-epinephrine release, upregulation of receptor-like glutamate, and N-methyl-D-aspartate receptors (NMDA).<sup>[18]</sup> Chronic stress can prolong and increase cortisol secretion, downregulates the glucocorticoid receptor, blocks the binding of cortisol, and develops insulin-resistant diabetes.<sup>[19]</sup>

### Immune system alterations

#### Cytokines

In acute stressed conditions after the release of cortisol, cortisol binds with the glucocorticoid receptor. Then, it binds with the specific sequence of DNA to regulate gene transcription. It also interferes with the signaling of transcription factors such as NF- $\kappa$ B and AP-1 and suppresses the inflammatory cytokines which are responsible for the inflammation, whereas, in chronic stress conditions, the release of inflammatory markers is increased which include interleukin (IL)-1 $\beta$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>[20-22]</sup>

#### Microglial activation

Chronic stress plays an important role in the activation of microglia.<sup>[23]</sup> Microglia are the macrophages that are present in central nervous system (CNS) and sensitive to brain injury and disease.<sup>[24]</sup> Any infection, ischemia, trauma, and neurodegenerative diseases or alteration in neuronal activity leading to any disturbance or loss of homeostasis in the brain that indicates a potential danger in CNS can bring changes in the shape of the microglial cell.<sup>[25]</sup> The stress may increase the level of cortisol or cytokines from the periphery leading to the activation of microglia. This will increase the pro-inflammatory markers in the CNS such as IL-1 $\beta$  and TNF- $\alpha$ . Further, these proceedings may cause atrophy of astrocytes and raise the level of IL-1 $\beta$ . The glucocorticoid receptor is downregulated, whereas the level of glutamate increases in the synaptic cleft by NMDA receptors. The calcium rises in neurons which are responsible for the degradation of the cytoskeleton of cells and increase the production of reactive oxygen species (ROS) and neuronal cell death. It is also responsible for neurodegenerative diseases and impairment of learning and memory.<sup>[26-29]</sup>

### Neurotransmitter alterations

Neurotransmitters play an important role in the pathophysiology of stress or chronic stress. These are the chemicals that are involved in the transmission of signals from one neuron to others in the body. The neurotransmitters which are altered in stressed conditions are dopamine, serotonin, glutamate, gamma-aminobutyric acid (GABA), adrenaline, and nor-adrenaline [Figure 2].

### NMDA

In chronic stress conditions, there is an increase in glutamate release which increases the intracellular calcium through activation of enzymes such as endonucleases, proteases, and oxidases. These enzymes degrade the cytoskeletal structure of the cell. The increase in intracellular calcium causes free radical generation which increases oxidative stress. An increase in oxidative stress damage the mitochondria and further can cause cell death.<sup>[18,19]</sup> Some studies may also reveal that chronic stress over activates GluN2B (an NMDA receptor subtype) which contains NMDA receptors in the prefrontal cortex (PFC). Chronic stress accumulates glutamate or blocks the uptake of glutamate developing depressive behaviors. The glutamatergic transmission through synaptic NMDA receptors (GluN1-/GluN2B) assists neuroprotection through extrasynaptic NMDA receptors that cause excitotoxicity [Figure 3].<sup>[30]</sup>

### Dopamine

DA is an important neurotransmitter that is responsible for various behavioral and biological functions in the CNS. It regulates the locomotor activity and neuroendocrine secretion.<sup>[31]</sup> There are many neurodegenerative disorders associated with dopamine neurotransmission. Many studies suggested that dopamine level is altered throughout chronic stressful events.<sup>[32-35]</sup> In chronic stress, the dopamine levels were remarkably reduced in the brain, hippocampus, and striatum. However, there is no significant difference in DA level in the amygdala. Decreased level of DA in the hippocampus in stressed conditions is due to reduced activity of enzyme cholinesterase and rise in the concentration of acetylcholine which increases impermanent (lasting for a short time) memory.<sup>[36,37]</sup> Dopamine generates ROS by the metabolism of mono amine oxidase (MAO) and

auto-oxidation. The molecular oxygen reacts with dopamine and thus forms semiquinones and quinones which later can cause depletion of GSH with continuous ROS generation. Further, dopamine turnover and metabolism rise which may produce hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) through MAO activity which can be responsible for lipid peroxidation in the neuronal membrane.<sup>[38]</sup>

### Serotonin

In the hypothalamus, serotonin is an important neurotransmitter for the regulation of stress. Receptors that are involved in stress are 5-HT1A and 5-HT2A receptors. These receptors are situated on neurons present in the paraventricular nucleus of the medial hypothalamus. It has been also found to arbitrate the release of stress hormones.<sup>[39,40]</sup> In chronic stress conditions, the level of serotonin decreases in the frontal cortex, striatum, and hippocampus. The reduced serotonin levels lead to the alteration in brain responses to chronic stress. The alteration in 5-HT transmission may also increase oxidative stress during CUS.<sup>[38]</sup>

### Glutamate

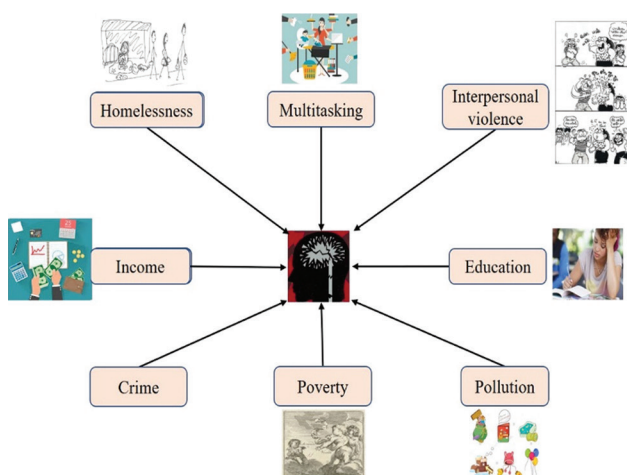
Glutamate is an excitatory neurotransmitter, which plays an important role in the body. In chronic stressed condition, the glutamate release is elevated.<sup>[41-43]</sup> Chronic stress also increases plasmalemmal glial-glutamate transporter 2 and vesicular glutamate transporter-1 (VGLUT-1), but the mechanism is unknown. VGLUT-1 plays an essential role in the regulation of the amount of glutamate in synaptic vesicles. The increase in glutamate concentration leads to excitotoxicity and further damage to cells.<sup>[44]</sup>

### GABA

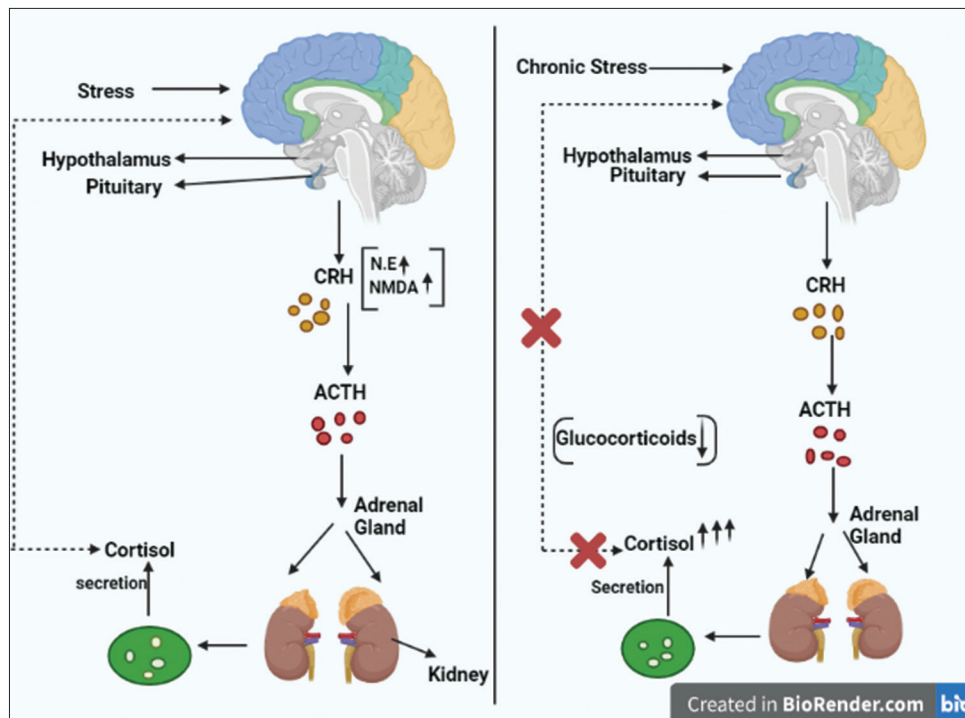
GABAergic neurons directly inhibit the paraventricular nucleus, also lowers the ACTH secretion in the hypothalamus, and further CRH release.<sup>[45]</sup> The GABAergic markers are altered due to chronic unpredictable stress. The glutamic acid decarboxylase expressions are reduced in both the PFC and hippocampus.<sup>[46]</sup> During stressed conditions, the GABAergic neurons are unable to control the secretions of ACTH and CRH.<sup>[45]</sup> Whereas the mechanisms behind the reduction of GABA content are not fully described.<sup>[46]</sup>

### Adrenaline

Adrenaline or epinephrine is also called as flight and fight hormone.<sup>[47]</sup> It is secreted by adrenal glands after a stressful event. It gives immediate action when we feel stressed.<sup>[48]</sup> During the stressed condition, it is secreted with noradrenaline. In acute stress conditions, both adrenaline and noradrenaline help to maintain homeostasis. The prolonged release of these catecholamines affects the psychological and physical outcomes of the body. It may also contribute to abnormal cardiac functions.<sup>[49,50]</sup>



**Figure 2:** Figure depicts alteration in different neurotransmitters release due to stress response which is dopamine, serotonin, glutamate, GABA, adrenaline and nor-adrenaline. The level of neurotransmitters which are increased during stress condition are – glutamate, adrenaline, nor-adrenaline and decreased are – GABA, serotonin, and dopamine.



**Figure 3:** Depicts activity of NMDA receptor in stress condition. The NMDA receptor is hyperactivated in stress condition which upregulates release of glutamate which causes extracellular accumulation of glutamate in CNS, further, it increases calcium influx in the cell. This is responsible for the generation of free radical cell and increase oxidative stress.

### Noradrenaline

The norepinephrine or noradrenaline level was increased in chronic stressed conditions.<sup>[51]</sup> The primary role of noradrenaline is to make people more aware, focused during the stressed condition. Like adrenaline, it is also secreted from the adrenal gland.<sup>[52]</sup> In stress conditions, the expression of the  $\alpha$ -adrenergic receptor is increased which results in decreased vascular tone. The impaired secretion of noradrenaline during stressed conditions also relays the nociceptive effect toward the spinal dorsal horn.<sup>[53,54]</sup> The altered norepinephrine level also causes sleeplessness, which slows healing of injury, anxiety, and gastrointestinal problems.<sup>[55]</sup>

### Neuromodulator alterations

#### Adenosine

Adenosine is a neuromodulator present in the brain and its level has been reported to be increased in stress conditions. The action of cytosolic adenosine deaminase (ADA) was remarkably decreased in stressed conditions.<sup>[56]</sup> ADA is an enzyme that regulates the level of adenosine.<sup>[57]</sup> Animal studies suggest that acute restraint stress leads to alteration in the level of adenosine in the brain. Thus, the cytosolic ADA activity is decreased that leads to an increase in extracellular adenosine levels through bidirectional transport of nucleoside. Adenosine is a nucleoside that acts through the purinergic P1 receptor and controls the neuronal activity in the brain. The purinergic signaling may act as a compensatory mechanism and maintain homeostasis.

Thus, the normal mechanism is that adenosine has anxiolytic effects and during stress plays an important role in counteracting stress.<sup>[56-58]</sup> The adenosine extracellular and nucleotides act on two types of purinoceptors, that is, P1 and P2. They are, further, subdivided into P1 -A1, A2A, A2B, A3, and P2 P2X, P2Y receptors. Extracellular nucleotide and nucleoside levels are controlled by a cascade of enzymes located on the cell surface called ectonucleotidases. The availability of ligands (ATP, AMP, ADP, and Adenosine) for purine receptors was controlled by ectonucleotidase cascade. Diphosphonucleosides and triphosphonucleosides hydrolyzed through the enzyme nucleoside triphosphate phosphohydrolase (NTPDases). The enzyme ecto-5'-nucleotidase hydrolyzes nucleoside monophosphates and produces adenosine.<sup>[56]</sup> Shreds of evidence have demonstrated that receptors of adenosine might be altered during chronic stress conditions. The extracellular ATP concentration and adenosine are also observed after the application of stressors in rodents.<sup>[59]</sup>

The interaction between antagonistic A2AR-D2R results in the formation of heterodimers, which regulate excitation of neurons and neurotransmitter release. A2AR trigger with stimulation of adenylyl-cyclase. Stimulation of adenylyl cyclase interferes with the signaling of the cAMP pathway through phosphorylation of PKA substrates such as CREB, DARPP-32, and also consequently increase the expression of various genes. The D2R activation impedes the effects of A2A receptor stimulation by inhibiting adenylyl cyclase.<sup>[58]</sup> The factors such as CRF, phospho cyclic AMP response

element-binding protein (CREB), and calcineurin are altered in chronic stressed conditions. The mRNA expression is increased for CRF and calcineurin and decreases pCREB in stressed conditions as compared to non-stressed. Most of the protein which gets downregulated in the brain are ALDOAA, PHB2, PGAM1B, SNCB, SLC25A5, CKM, ALDOCB, PVALB5, NME2B, and CKB as compared to normal conditions.<sup>[60]</sup>

### **BDNF**

BDNF is a key component for the development, perpetuation, plasticity, and survival of CNS neurons.<sup>[31]</sup> The BDNF is synthesized in the hippocampus and is regulated by different and hormone neurotransmitters. In a stressed condition, the BDNF mRNA expression is reduced.<sup>[61]</sup> Chronic stress increases the glucocorticoids and downregulates the glucocorticoid receptor and raises the level of stress hormones, causing a reduction in BDNF level. However, when the origin of the stress is stripped away, the hippocampus shows improvement in cognitive and synaptic deficits. Further, studies also demonstrated that decreased expression of BDNF increases the glutamate release, excitotoxicity of neurons, and also weakens the activation of phospholipase-C  $\gamma$ .<sup>[62,63]</sup>

## **ASSOCIATION OF CHRONIC STRESS WITH DIFFERENT NEUROLOGICAL CONDITIONS**

Chronic stress may lead to various neurological disease conditions such as anxiety and depression.<sup>[64]</sup> In various studies, spine retraction and dendritic atrophy were followed by chronic restraint stress. The monoaminergic neurotransmission, specifically NE acting at  $\alpha$ 1-adrenergic receptors and serotonin acting at 5-HT<sub>2A</sub> receptors, causes excitotoxicity through facilitating glutamatergic transmission from thalamocortical afferents in pyramidal cells.<sup>[65]</sup> Chronic stress interferes with monoaminergic neurotransmission, excitotoxic damage, and results in cognitive deficit.<sup>[66]</sup> Serotonin also facilitates glutamate transmission at pyramidal cell dendrites in the PFC.<sup>[67]</sup> Depletion of the cortical serotonergic system or wrecking of serotonin causes debts in reversal learning.<sup>[68,69]</sup> Exposure to chronic stress also produced a persistent rise in anxiety-like behavior. Anxiety is a prominent component of depression.<sup>[70,71]</sup> In anxiety, the level of GABA an inhibitory neurotransmitter is decreased, whereas the other neurotransmitters such as glutamate, serotonin, and noradrenaline are increased [Figure 4].<sup>[71]</sup>

### **Anxiety**

Studies suggest that in anxiety, the individual has fear-like symptoms.<sup>[72,73]</sup> Certain studies suggested a dual role of serotonin when serotonin is released from the dorsal raphe nucleus terminal decreases the learned anxiety while increases innate fear.<sup>[74]</sup> There is an increased level

of biogenic amines such as serotonin and dopamine in anxiety.<sup>[75]</sup>

### **Major depressive disorder**

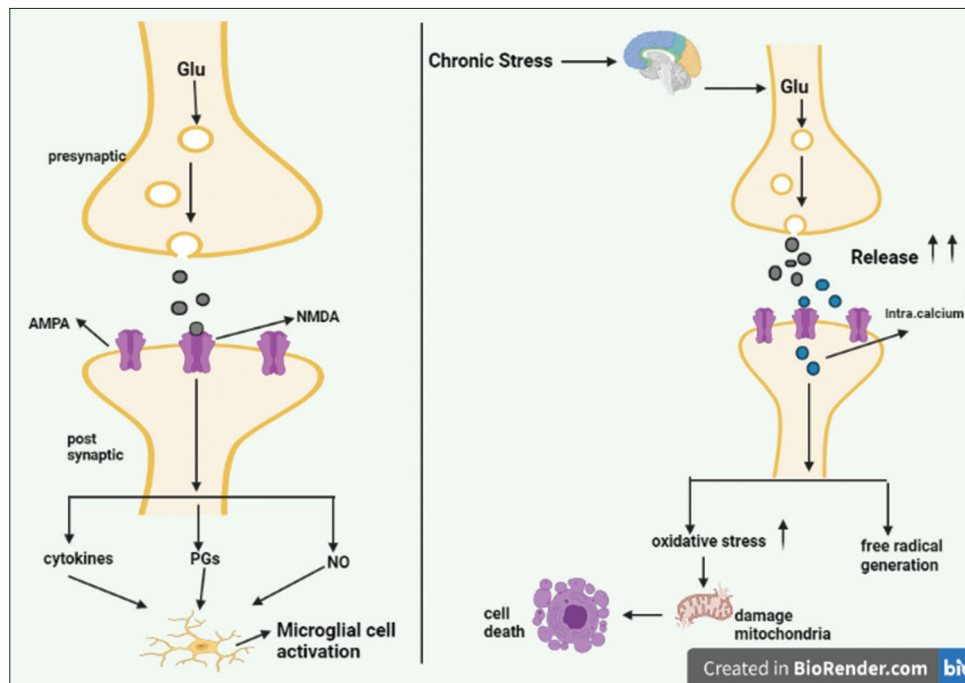
Clinical studies show that stressful events in life are important factors that are responsible for the development of depression.<sup>[76,64]</sup> In depression, biogenic amines such as serotonin, acetylcholine, noradrenaline, and dopamine play an important role. When stress is not controllable, the neurochemical utilization increases leading to the reduced level of these amines. The deficiency of these amines led to depression.<sup>[77]</sup> Studies have revealed that in major depressive disorder, the level of glutamate and GABA is altered, which prompt glutamatergic hyperactivity. GABA is an important inhibitory neurotransmitter which on activation fabricates antidepressant-like effects. Different regions of the brain involved in depression are the thalamus, hippocampus, amygdala, prefrontal, cingulate cortex, and striatum. On exposure to stress, the excitatory neurotransmitter glutamate release from presynaptic neurons subsequently binds with NMDA receptors, kainite receptors,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, and metabotropic receptors present at both pre- and postsynaptic cells, initiates pathways of downstream signaling. These lead to increased accumulation of calcium intracellularly and an increase in oxidative stress which is responsible for mitochondrial dysfunction, excitotoxicity of neurons, and neuronal death.<sup>[78-80]</sup> Various studies revealed that there is a decreased amount of GABA in plasma and CSF. The abnormalities in serotonin receptors are also seen in clinical studies especially in 5-HT<sub>2A</sub>. The metabolites of dopamine are also decreased like homovanillic acid which is also responsible for depression.<sup>[46,81,82]</sup>

### **Parkinson's disease**

Parkinson's disease is a neurodegenerative disease characterized by involuntary movements and decreased muscle strength.<sup>[83]</sup> Stress can affect the level of dopamine and its control of motor movements, whereas the increased production of glucocorticoids affects the compensatory mechanism of the impaired motor system. Dopamine is a principal neurotransmitter in the brain. DA is the precursor for other catecholamines.<sup>[84]</sup> Stress and increased level of cortisol or glucocorticoid cause the stimulation of pro-inflammatory cytokines leading to CNS inflammation.<sup>[85,86]</sup> Till now, there is no direct relationship has been proved between stress and PD.<sup>[78]</sup> However, studies suggest that chronic stress aggravates functional deficiency and leading to dopaminergic neuronal loss.<sup>[87]</sup> Psychological stress and raised levels of corticosterone lead to neuronal loss in the substantia nigra to an increased extent.<sup>[86]</sup>

### **Epilepsy**

Epilepsy is characterized by repeated seizures. As the discharge of corticosteroid increases, the convulsion



**Figure 4:** Depicting various neurological disorders which are associated with chronic stress. These include anxiety, major depressive disorder, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and epilepsy.

susceptibility and seizure rate also increase.<sup>[88]</sup> The preclinical studies showed that early life stress provokes seizures and further lead to epilepsy. It is caused due to hyperactivation of the HPA during stress conditions.<sup>[89]</sup> The stress leads to an impaired release of glutamate which contributes to the atypical firing of neurons in the brain. The evidence suggests that cortisol plays an important role in controlling seizures.<sup>[90-92]</sup> In epilepsy, there is inhibition of GABA levels causing hyperexcitable neurotransmission and an increase in CRH, leading to changes in neuronal structure and also inflammation.<sup>[93-95]</sup>

### Multiple sclerosis

Multiple sclerosis is an immune arbitrate inflammatory disease. It is indicated by the activation of microglia and cytotoxic mediator causing nervous tissue damage.<sup>[96]</sup> It is also characterized by neural and axonal loss.<sup>[97]</sup> In stressed conditions, there is a release of pro-inflammatory cytokines which increase oxidative stress. The increase in oxidative stress causes neurodegeneration.<sup>[98]</sup> Due to chronic stress, depletion of ATP takes place which leads to dysfunction of astrocyte and elevated level of glutamate causing neuronal death. The elevated level of glutamate leading to dysfunction of ion channels which further increases the calcium level- Change this as Glutamate excitotoxicity leads to dysfunctioning of Ion channels that further leads to increase in calcium ion. Further, these changes in conditions lead to mutation in mitochondrial DNA, making of proteolytic enzyme and activate apoptotic pathway.<sup>[99]</sup>

### Alzheimer's disease

Alzheimer's disease is a capacitating neurodegenerative disorder that leads to dementia. The previous studies revealed that in Alzheimer's the higher cortisol level increases the progression of the disease.<sup>[100-102]</sup> An increased Amyloid  $\beta$  ( $A\beta$ ) accumulation increases the burden in the brain.<sup>[100]</sup> An increase in the accumulation of  $A\beta$  causes the formation of plaques within the brain and also produces neurofibrillary tangles, neuronal loss. The normal function of  $A\beta$  is it acts as anti-oxidative, which regulates cholesterol.<sup>[103-105]</sup> The behavioral and psychological conditions change in AD due to disruption in neuronal circuits which arbitrate stress.<sup>[106]</sup>  $A\beta$  is produced from amyloid precursor protein by the proteolysis of  $\beta$ -secretase and by a  $\gamma$ -secretase enzyme.<sup>[107]</sup> The intracellular  $A\beta$  activates caspases through the process of mitochondrial stress. The activation of caspase cleaves tau, which causes conformational changes leading to paired helical filaments. Progressive aggregation of tau causes the disruption of the cytoskeleton and subsequently neuronal loss. The deposition of extracellular amyloid triggers reactive changes in glial cells and neuroinflammation that may also lead to neuronal loss by the creation of ROS, nitrous oxide, and other pro-inflammatory cytokines. Further, the increase in oxidative stress and inflammatory cytokines causes cognitive dysfunction and progression of Alzheimer's disease.<sup>[108-110]</sup>

### EXPERIMENTAL MODELS OF STRESS CONDITIONS

The experimental models are more commonly used to mimic the human disease conditions so as investigate the

therapeutic drug targets against the disease. The various experimental models have been used to mimic the stressful conditions to study the underlying mechanisms and it includes both rodent and non-rodent models.

### Rodent models

This model comprises vertebrates and mammals. The different models of stress include deprivation paradigm such as food, water deprivation, restraint; exposure to adverse environmental stimuli which includes hot and cold; pain paradigm – it is pain based paradigm including electric foot shock, tail pinch; pharmacologically-induced hyperalgesia (formalin, carrageenan); and fear and anxiety based paradigms which includes predator stress, models of social conflict, and disruption including social isolation.<sup>[111,112]</sup>

#### Food and water deprivation

The animals are underprivileged by both food and water. The deprivation of food produces humoral and behavioral alterations in response to stress.<sup>[111]</sup> Starvation induces changes in CRF by activating the HPA axis.<sup>[113]</sup> Food and water deprivation increases the level of basal plasma corticosterone level and decreases the levels of CRH mRNA in the paraventricular nucleus.<sup>[114]</sup> The animals were deprived for 12, 48 h once a week in water deprivation, whereas food deprivation is for 24 or 48 h earlier to their food and water intake.<sup>[115]</sup>

#### Restraint stress

Chronic restraint stress act as psychological stressors, in which an animal is placed in a small area. It produces cognitive deficits in the hippocampus and also changes its structure.<sup>[116]</sup> It activates the HPA axis and increases the corticosterone levels in serum. Furthermore, it increases anxiety levels and showed depressive behaviors in animal models. It also affects the hypothalamic gene expression, body weight, and food intake. It also showed an increase in plasma fatty acid, cholesterol level, and glycerol whereas reduction in plasma triglyceride.<sup>[117,118]</sup> The rats were restrained for 6 h regularly for 21 days.<sup>[119,120]</sup>

#### Cold exposure

Cold exposure activates certain systems such as the sympathoadrenal (SA) system and HPA or hypothalamo-pituitary-thyroid (HPT) system. The SA system activation alters the release of catecholamines; HPA enhances the release of cortisol, whereas HPT increases the release of thyroid hormones (T3 and T4). The T3 levels are elevated after chronic exposure to stress and act as a potent thermogenic substance, which maintains the body temperature during severe cold. Furthermore, prolonged stress decreased TRH mRNA, plasma TSH, and T4, T3 level. The exposure of cold temperature is at 4°C for 3 h.<sup>[121-123]</sup>

### Social isolation

Social isolation alters the functional and structural development of the brain. It also alters the behavior of rodent animals and enhances locomotor activity, anxiety-like, and aggressive behavior. It impairs memory and spatial learning.<sup>[124]</sup> It causes alterations in dopamine and serotonin systems in the nucleus accumbens, hippocampus, and PFC.<sup>[125]</sup> The animals were socially isolated for 1 or 3 weeks.<sup>[126,127]</sup>

#### Electric foot shock

In this method, the animal is administered several footshocks for some time (1–6 s). The range of shock lies between 0.1 and 0.25 mA.<sup>[128-130]</sup> Electric foot shock stress increases plasma ACTH and corticosterone levels. In the amygdala, CRF mRNA expression has been reported to be increased. It also increases the IL-6 in serum.<sup>[131,132]</sup>

#### Tail pinch

Tail pinch induces licking, gnawing, and eating behavior in rats.<sup>[133]</sup> In this method, the tail of a rat is pinched with a clamp. This method immediately produces stressful events.<sup>[134]</sup> It is widely used for the testing of analgesics.<sup>[135]</sup>

### Post-traumatic stress disorder

PTSD is a complex disorder, in which emotional learning and memory process dysfunctions that trigger fear responses in the absence of traumatic situations.<sup>[136]</sup> Different rodent models are used to mimic the effect of PTSD-induced trauma. These include single prolonged stress such as restraint stress<sup>[137,138]</sup> predator scent stress (the animal was placed on soiled cat litter for 10 min in a locked environment),<sup>[139]</sup> housing instability (animals are exposed to a predator),<sup>[140]</sup> and early life stress (induced through maternal isolation).<sup>[141]</sup>

### Non-rodent models

Non-rodent models are those which are other than vertebrates and mammals. Several non-rodent animals are used in research such as dogs, pigs, rabbits, and zebrafish. Among which, the zebrafish model is beneficial for the study of stress condition, as its neural systems are similar to humans.

#### Zebrafish

The zebrafish (*Danio rerio*) is widely used as an experimental model. It is an emerging model for the study of brain disorders such as anxiety,<sup>[142]</sup> depression, autism, psychosis, cognitive impairment.<sup>[143]</sup> The physiological system, structure, and function of the brain's neural system are similar to vertebrates. It is homologous to rodents and humans.<sup>[144,145]</sup> Zebrafish responds to a variety of different stressors like mammals. The different stressors include temperature changes such as cold and hot; exposure to predators, restraint, chasing, tank change, crowding, and increases the level of cortisol in the body which is an

important steroid (corticosteroid/stress hormone) in humans and animals.<sup>[146,147]</sup> This model is also used for the study of acid water,<sup>[148]</sup> organic pollutants,<sup>[149]</sup> and heavy metals.<sup>[150,151]</sup>

## FUTURE ASPECTS

Stress is the leading cause of many other conditions such as anxiety, depression, and dementia. Till now, there is no specific medication for the treatment of stress, but the conditions can be overcome by exploring the pathophysiological events associated with chronic stress. For the development of newer molecules that are effective in these conditions with lesser side effects, these rodent and non-rodent models are considered and more commonly used. Various pathophysiological pathways have been explored in chronic stress which includes HPA axis activation, SA medullary axis, NMDA receptor, an imbalance between neurotransmitters, and alterations in immune systems. But still, the exact underlying mechanism is unknown.

## CONFLICTS OF INTEREST

The author declares no conflicts of interest

## COMPLIANCE WITH ETHICAL STANDARDS

This is a review manuscript and ethical standards are not applicable in this study.

## ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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