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Review Article

Brain Physiology and Pathophysiology in Mental Stress

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Exposure to various forms of stress is a common daily occurrence in the lives of most individuals, with both positive and negative effects on brain function. The impact of stress is strongly influenced by the type and duration of the stressor. In its acute form, stress may be a necessary adaptive mechanism for survival and with only transient changes within the brain. However, severe and/or prolonged stress causes overactivation and dysregulation of the hypothalamic pituitary adrenal (HPA) axis thus inflicting detrimental changes in the brain structure and function. Therefore, chronic stress is often considered a negative modulator of the cognitive functions including the learning and memory processes. Exposure to long-lasting stress diminishes health and increases vulnerability to mental disorders. In addition, stress exacerbates functional changes associated with various brain disorders including Alzheimer's disease and Parkinson's disease. The primary purpose of this paper is to provide an overview for neuroscientists who are seeking a concise account of the effects of stress on learning and memory and associated signal transduction mechanisms. This review discusses chronic mental stress and its detrimental effects on various aspects of brain functions including learning and memory, synaptic plasticity, and cognition-related signaling enabled via key signal transduction molecules.

1. Introduction

Although stress is a necessary mechanism for survival, severe and/or long-term stress disrupts normal brain structure and function [1–4]. Mental stress, which may range in intensity from mild to severe posttraumatic stress disorder (PTSD), has been reported to impair memory [5–15] possibly by elevating excitatory amino acid and glucocorticoid levels, which in turn induce excitotoxicity and hippocampal atrophy [16].

The endocrinologist, Selye [17], defined "stress" as "the non-specific response of the body to any demand placed on it." The body's principal physiological responses to stressful stimuli are mediated by the sympathoadrenal system and the hypothalamic pituitary adrenocortical (HPA) axis, which are, in turn, mediated by the hippocampus [18–21]. Stress stimulates the release of corticotropin-releasing factor (CRF), from the hypothalamic paraventricular nucleus (PVN), into the hypophysial-portal circulation, where it induces the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary and glucocorticoids (cortisol in humans; corticosterone in rodents) from the adrenal glands [22].

The magnitude of the HPA stress response elicited by PVN neurons is limited by neuronal and hormonal mechanisms, which work together to maintain glucocorticoid levels within tolerable limits [23]. Three feedback loops prevent overshooting of the HPA axis: (a) the negative feedback of glucocorticoids to the anterior pituitary, hypothalamus, and hippocampus, (b) the ACTH feedback to the hypothalamus, and (c) the direct feedback of CRF to the hypothalamus.

Mental stress impairs cognitive function in animals and humans [6, 15, 24–32]. It is postulated that mental stress impairs learning and memory through the high adrenal glucocorticoid output known to occur during stressful episodes [33–35]. In humans and animals, the effects of glucocorticoids on memory are dose dependent [11, 36, 37] and determined by the binding of corticosteroids to two receptors in the brain: the type-1, high affinity, mineralocorticoid receptor and type-2, glucocorticoid receptor [38–40]. The mineralocorticoid receptors are mostly restricted to the hippocampus, but the glucocorticoid receptors are ubiquitously expressed in the brain, with high densities in the hippocampus, amygdala, and prefrontal cortex, where they mediate the feedback action

of glucocorticoids on stress-activated brain processes [41, 42]. Whereas mineralocorticoid receptors play an important role in the feedback control of the HPA axis, promoting maintenance of basal HPA activity, glucocorticoid receptors directly or indirectly regulate genes controlling development, metabolism, and immune function [39]. Thus, a balance in the expression of mineralocorticoid receptors and glucocorticoid receptors is necessary for maintaining cellular metabolism and cognitive functions, such as learning and memory [21]. Under normal conditions, selective activation of type-1 receptors by mild or moderate glucocorticoid levels enhances memory and increases long-term potentiation (LTP) [41]. However, during stress, activation of type-2 receptors by high glucocorticoid levels impairs memory [9, 32, 43] and suppresses LTP [24, 25, 28, 31, 32, 44–46].

Chronic stress influences the onset and/or severity of cognitive decline in various disorders [47], including Cushing's syndrome [48], posttraumatic stress disorder [49], hypothyroidism [28, 45], Alzheimer's disease [50–52], and depression [16, 53]. The physiological consequences of stress depend on the intensity and duration of the stressor and upon how an organism perceives and reacts to the noxious stimulus [54–56].

While acute stress-induced activation of mineralocorticoid receptors enhances LTP and memory consolidation, chronic stress-induced activation of glucocorticoid receptors inhibits LTP and impairs memory [57, 58]. The distinct responses induced by acute or chronic stress are due to a shift in the balance of mineralocorticoid receptor-glucocorticoid receptor occupation [55, 59]. In general, activation of mineralocorticoid receptors by low levels of corticosteroids produces low amplitude Ca^{2+} currents, which have an excitatory effect on hippocampal CA1 pyramidal cells, whereas activation of glucocorticoid receptors by high levels of corticosteroids enhances Ca^{2+} influx and inhibits CA1 pyramidal cell excitability [59].

The hippocampal formation, an important brain structure in learning and memory, is particularly vulnerable to stress hormones due to its high density of glucocorticoid receptors, in spite of its remarkable plasticity [16, 60]. Stress mediates a variety of effects on neuronal excitability, neurochemistry, and structural plasticity of the hippocampus [16]. For example, excessive glucocorticoids are associated with deleterious changes in hippocampal excitability, LTP, and cognitive abilities [61, 62]. The harmful effects of stress on memory have been confirmed by several studies in rodents and humans. Chronic psychosocial stress has been shown to impair hippocampus-dependent learning and memory in animal models [12, 15, 31, 50, 63, 64] and humans [64]. In addition, electrophysiological studies have shown that stress significantly impairs synaptic plasticity in the CA1 region of the hippocampus in urethane-anesthetized rats [30–32, 50] and in hippocampal slices [26]. Furthermore, other studies have shown that stress facilitates the induction of long-term depression (LTD) [29, 65].

The mechanisms mediating stress-induced impairment of cognition and synaptic plasticity are largely unknown. However, advances in animal and human studies have resulted in the establishment of various hypotheses. Based on studies in adult and older animals and humans, a "glucocorticoid cascade" hypothesis is introduced, which suggests that there is a relationship between cumulative exposures to high glucocorticoid levels and hippocampal atrophy [66]. This is supported by findings of studies in aged rats in which glucocorticoid hypersecretion is correlated with memory impairment and reduced hippocampal volume [67]. Furthermore, middle-aged rats exposed to high levels of glucocorticoids also developed memory impairment and hippocampal atrophy [68]. In an attempt to clarify the mechanism by which glucocorticoid levels correlate with hippocampal atrophy, a "neurotoxicity hypothesis" was developed [69]. This hypothesis suggests that prolonged exposure to glucocorticoids reduces the ability of neurons to resist insults, thus increasing the rate at which they are damaged.

2. The Stress Response

The physiologic response to stress consists of a rapid component and a slower one, acting in a coordinated temporal manner to reestablish homeostasis [70–72]. The rapid response is the activation of the sympathetic nervous system, which increases the levels of circulating norepinephrine and epinephrine and elevates the levels of norepinephrine in the brain. This is referred to as the "sympathetic-adrenomedullary system." The slower, longer-lasting response is activation of the HPA axis that begins with the release of CRF into the circulation from the paraventricular nucleus of the hypothalamus, which then stimulates the pituitary to release ACTH into the bloodstream. The released ACTH accelerates the discharge of glucocorticoids from the adrenal cortex.

The type-2 glucocorticoid receptors bind glucocorticoids at tenfold lower affinity than type-1 receptors. At the circulating low-basal glucocorticoid levels, type-1 receptors are already activated to a large extent. However, when the circulating glucocorticoid levels are elevated after stressful events, type-2 receptors are also activated. Glucocorticoid receptors are abundant throughout the brain. However, both receptor types are highly expressed in the hippocampus making it a target for stress hormone actions [72]. These nuclear receptors can act as transcription factors by binding to the DNA thus regulating gene expression [56]. In addition, glucocorticoids mobilize peripheral energy stores, diminish the immune response, and mediate the negative feedback control of the HPA axis [73]. Both the HPA axis and sympathetic-adrenomedullary system work in concert to coordinate adaptive responses to stressors. Regulation of the HPA axis occurs through negative feedback mechanisms in which high levels of glucocorticoids suppress the release of CRF.

In addition to glucocorticoids, other mechanisms are associated with the detrimental effects of stress on the hippocampus including excessive release of glutamate and repeated activation of glutamate NMDA receptors [74–77], modified interneuronal GABA inhibitory tone [78], and increased serotonergic tone [79]. Perception of stress also results in activation of preganglionic sympathetic neurons in the spinal cord, which activates neurons of the prevertebral or paravertebral ganglia that, in turn, project to effector organs,

including the blood vessels, heart, and glands including the adrenals. The consequent physiological changes include elevations in epinephrine and norepinephrine levels, peripheral vasoconstriction, increase in heart rate and vagal withdrawal, and increased energy mobilization [80].

3. Animal Models of Stress

Two major classes of experimental stressors have been in use to produce stress in animals. Various animal models have been used to study the two types of stress, physical and psychological, and their effects on brain functions, including learning and memory, have been discussed previously [81–83]. Animal models for physical stress including cold or hot environment, foot shock, noise, body vibration, exposure to high-altitude and immobilization stress are used to simulate physical stressors that are commonly faced by humans such as exposure to hot or cold environment [84–87]. Psychosocial stress models include social isolation by withdrawing the animal from a group housing, intruder aggression, which involves attack within unfamiliar territory by a dominant male, or disruption of social hierarchy by introducing new comers to a socially stable group. Other psychosocial models include maternal deprivation by separation of preweanling pups from their mother and exposure to predator where the subjects (rats or mice) are exposed to the sight and smell of a natural predator [12, 88–93]. Both physical and psychological stresses may be used to induce acute or chronic stress. Due to the social nature of psychosocial stress, the procedures are considered more naturalistic and species-typical than the artificial noxious stimulus procedures associated with physical stress models [86].

4. Effect of Stress on Structure and Function of the Brain

Stress has profound effects on the structure and function of the brain at the cellular and subcellular levels. The impact of stress on brain structure and function is influenced by a variety of factors including the duration and type of the stressor as well as age and sex of the animal [94–99]. The major areas of the brain most affected by stress are the hippocampus, prefrontal cortex, and amygdala, probably because these areas contain abundant glucocorticoid receptors. Additionally, neurons in these regions are known to be highly plastic, both functionally and structurally, in response to repetitive activation [100, 101]. Hence, neurons in the hippocampus, prefrontal cortex, and amygdala are highly sensitive to stressful stimuli, resulting in significant changes in their structure and function even at the molecular level [102, 103].

Most of the stress-induced structural changes involve the neuronal dendrites and synaptic spines. The stress-induced structural modification of dendrites and synaptic spines in neurons of certain regions of the brain may include cytoskeletal alteration involving actin filaments and microtubules [104–106]. Synaptic spines are specialized protrusions arising mostly from dendrite and are sites of synaptic connections. The number of synaptic spines reflects the extent of connectivity among neurons and may determine the amount of neurotransmitters released during activity in a particular brain region. With activity, branching of dendrites can proliferate and their spines increase in number, enlarge, and change shape forming strong synapses with larger postsynaptic densities indicating more receptor insertion [107]. Additionally, the presynaptic nerve terminals may change shape and increase in size. These changes can occur very quickly (in seconds); thus, dendrites and spines are vital agents for effecting immediate and long-term functional synaptic plasticity [77, 105, 108, 109].

Stress induces similar changes in structure and function of neurons in the hippocampus and prefrontal region but affects neurons of the amygdala differently. Even different areas in the hippocampus (e.g., area CA1 and dentate gyrus) may respond to stress differently [27, 45, 110–112]. The following is a brief discussion of the effect of stress on structural and functional synaptic plasticity in each of the three regions of the brain but with particular emphasis on the hippocampus. It is important to note that acute stress may have different effects on neuronal structures than chronic stress. In fact, chronic stress starts initially as acute stress, but then it is repeated for a long periods of time. This allows the system response to change significantly and, in some cases, even disappear [77].

4.1. Structure and Function of the Hippocampus during Stress. Chronic stress in experimental animals reversibly reduces branching of neurons, decreases densities of dendrites, and affects growth and shape of synaptic spines in neurons of various hippocampal regions [1, 74, 97, 110–119]. Similar structural changes have been reported in CA3 area of brains of humans who experience intense psychosocial stress [120].

Chronic psychosocial stress applied daily for 4–6 weeks in rats impairs spatial short-term memory but has no significant effect on learning or long-term memory [28, 31, 50, 121–123]. However, longer periods of psychosocial stress (>12 weeks) seem to adversely affect short-term as well as long-term memory [124, 125]. In correlation with memory impairment, chronic (4–6 weeks) psychosocial stress caused significant suppression of stimulation-evoked early phase long-term potentiation (E-LTP) of hippocampal area CA1, a cellular correlate of short-term memory [5, 15, 24, 31, 45, 50, 122, 125]. In contrast, the late phase LTP (L-LTP), which is believed to be the cellular correlate of long-term memory, was not significantly affected by chronic stress [126]. However, chronic stress facilitated the induction and markedly enhanced the magnitude of long-term depression (LTD) in area CA1 [29, 65, 122, 126–129]. Chronic stress, however, did not affect basal synaptic transmission of area CA1 as indicated by analysis of input/output (I/O) curves [29].

Investigation of the effect of chronic stress at the subcellular level has been accomplished by analyzing the molecular cascade involved in the expression of memory and synaptic plasticity. Chronic psychosocial stress severely diminished the basal levels of calcium calmodulin kinase II (CaMKII), which is the principal protein kinase essential for LTP maintenance [130]. Both total CaMKII and phosphorylated-(P-) CaMKII levels were decreased in the CA1 region of the hippocampus of chronically stressed rats. The finding that

P-CaMKII/CaMKII ratio in CA1 of chronically stressed rats was not changed suggested that the major cause of the decrease in P-CaMKII level might be an overall decrease in the total CaMKII protein levels. Alternatively, the decrease in basal levels of P-CaMKII in stressed rats could have resulted from a decrease of calmodulin level, a decrease of protein kinase-C (PKC) level, and/or an increase in the levels of calcineurin, a phosphatase essential for deactivation (dephosphorylation) of CaMKII [15, 31, 50]. These effects of signaling molecules are discussed further in later sections of this review.

Interestingly, the same protocol of chronic psychosocial stress that markedly impaired short-term memory and suppressed E-LTP of the hippocampal area CA1 did not block E-LTP of the dentate gyrus region of the same hippocampus [27, 45]. This could be due to two major findings; the first is the significantly decreased basal levels of calcineurin in the dentate gyrus of stressed rats, which as a consequence meant a reduction in the dephosphorylation of P-CaMKII in the LTP cascade of the dentate gyrus region. The other finding is that P-CaMKII levels remained unaffected despite the marked decrease in the total CaMKII level in the dentate gyrus region of chronically stressed rats. The decreased dephosphorylation resulting from the reduced calcineurin level was most probably responsible for maintaining adequate levels of P-CaMKII, which may explain the normal E-LTP seen in the dentate gyrus of chronically stressed rats [45].

Another critical molecule in the hippocampus that is negatively affected by chronic psychosocial stress is brain-derived neurotropic factor (BDNF) [32, 131]. The importance of BDNF in the expression of LTP has been demonstrated by the impairment of LTP in the presence of BDNF antibodies or BDNF scavenging protein [132–135]. Furthermore, a number of other factors are involved in modulating hippocampal dendritic and spine plasticity during chronic stress; they include the transmembrane glycoprotein M6a, the stress-related neuropeptide CRF, and the extracellular protease tissue plasminogen activator (tPA) [77, 112, 136–140].

4.2. Stress and the Prefrontal Cortex. The prefrontal cortex neurons appear to respond to stress in a sexually dimorphic manner. In the female, stress increases dendritic density, whereas in the male stress decreases branching and length of dendrites and causes loss of dendritic spines of pyramidal neurons of the medial prefrontal cortex (mPFC) [111, 141–152]. Interestingly, chronic stress-induced spine loss seems to be dependent on the type of spine where large, mushroom shaped spines are decreased but thin spines are increased [111, 146, 153]. These changes in the mPFC are seen in young rats but not in middle aged and aged animals [153].

Excitability of the mPFC neurons is altered as a result of stress-induced atrophy of apical dendrites, which correlates with deficits in the excitatory responses to inputs targeted at those dendrites [154]. It has been reported that chronic stress impacts synaptic plasticity by decreasing the magnitude of LTP in the mPFC [155]. Chronic stress impairs synaptic plasticity by reducing LTP magnitude in the hippocampal-PFC connection thus severely disrupting working memory and behavioral flexibility [147].

Certain morphological changes in the PFC can be seen with repeated exposure to mild stressors and also after acute but intense stress [156–158] indicating that this region is sensitive to both chronic and acute types of stress. Interestingly, while rats of all ages exhibit dendritic retraction with stress in the mPFC, these effects are reversible after a stress-free recovery period in young rats but not in old rats [151].

4.3. Structure and Function of the Amygdala in Stress. Interestingly, chronic stress increases length and number of spines, augments dendritic length, and increases branching points of dendrites of the basolateral complex (BLA) neurons without affecting those in the central nucleus of the amygdala [115, 159–164]. Acute stress, in contrast, does not affect the dendrites but may promote formation of new spines in the amygdalar neurons [162]. Another interesting difference between the amygdala and hippocampus and PFC is while the stress-induced structural atrophy in the hippocampus and mPFC is reversible, the stress-induced dendritic hypertrophy in the amygdala is persistent and remains a long time after termination of stress [165].

The stress-induced hypertrophy and hyperexcitability seen in the amygdalar neurons after stress indicate a strong correlation between structural and functional synaptic plasticity in the amygdala [166]. Intensely emotional experiences are generally thoroughly remembered through a process in which the amygdala plays a vital role [167, 168]. Such memory enhancement is encountered in both unpleasant and pleasurable events [167].

4.4. Interaction among Brain Regions. The stress-induced structural changes most likely contribute to changes in the electrical properties of neurons within the region as well as interactions among these regions. For example, stress inhibits the generation of LTP in the pathway between the hippocampus and the mPFC as well as in the pathway connecting the amygdala to the mPFC [169–172]. Furthermore, stress impacts the reciprocal pathway between the mPFC and the amygdala, such that there is inhibition of LTD and facilitation of LTP of this pathway [173].

Repetitive stimulation, which produces LTP, also swiftly promotes the formation of new spines and spine shape modification in contrast with LTD, which is associated with shrinkage or loss of spines [108]. Therefore, stress-induced changes in functional synaptic plasticity may be influenced by and may in turn impact structural plasticity. For example, by weakening hippocampal structure, stress may diminish activity in hippocampal afferents to the mPFC, which could in turn lead to fewer mPFC dendritic spines.

4.5. Molecular Mechanisms. Chronic stress is known to alter the levels of essential signaling molecules in the molecular cascades implicated in memory and LTP. Alterations in the levels and activities of these signaling molecules disrupt synaptic plasticity and memory and may be important in the pathogenesis of various disorders including stress. The impact of stress on signaling molecules critically important for both synaptic plasticity and memory is discussed in the following.

4.5.1. Calcium Calmodulin-Dependent Protein Kinase II (CaMKII). CaMKII is the most abundant protein kinase in the brain. Comprising up to 1% of total brain protein, CaMKII plays an essential role in the regulation of neuronal excitability and synaptic transmission as well as induction and maintenance of hippocampal LTP [174–176]. Elevation of the Ca^{2+} concentration in the postsynaptic region, as a result of glutamate NMDA receptor activation, stimulates several kinases, including CaMKII, which is critical for spatial memory and LTP [177–180]. Activation of CaMKII in the process of LTP induction is necessary and sufficient to generate LTP. The essential role of CaMKII in cognitive abilities and synaptic plasticity is indicated by a number of experiments. For example, CaMKII inhibitors (e.g., H-7) impair memory [181] and block LTP in hippocampal area CA1 [177, 182]. Additionally, CaMKII null mice exhibit significant deficits in memory and LTP, compared to wild-type animals [183, 184]. The activation of CaMKII persists even when Ca^{2+} reverts back to the normal physiological levels, due to its ability of autophosphorylation at amino acid Thr286. Thus, CaMKII has several features that make it an appealing candidate as a memory molecule: its ability to autophosphorylate and remain active even after the decline in intracellular Ca^{2+} concentrations, its abundance in the brain, and its wide spectrum of substrates.

Previous findings in this laboratory showed that chronic stress reduces the basal levels of P-CaMKII and the ratio of P-CaMKII/total CaMKII in the CA1 region of the hippocampus [32, 50]. In order for LTP to be properly maintained, the rate of autophosphorylation must exceed the rate of dephosphorylation. The basal levels of both total CaMKII and P-CaMKII are reduced after chronic stress in the CA1 region of the hippocampus [15]. Stress also blocks the high-frequency stimulation (HFS)-induced LTP and the attended increase in P-CaMKII, which confirms the critical role of P-CaMKII in the expression of LTP. This decrease of P-CaMKII in stressed rats could result from a decrease in calmodulin, PKCγ and/or an increase in calcineurin basal levels in the hippocampal area CA1 of stressed rats [15].

The significant impairment of learning, memory, and synaptic plasticity observed in behavioral and electrophysiological studies may also be associated with the failure of HFS to increase P-CaMKII production in stressed rats. Coupled with the reduced phosphorylation in the stressed animals, indicated by the decreased ratio of P-CaMKII/total CaMKII, the observed cognitive deficits may be due, at least partly, to curtailed CaMKII phosphorylation.

Stress, by social isolation, decreased phosphorylation at Thr286, thus, limiting CaMKII activity. Synaptosomal fraction from cortex of socially isolated animals exhibited decreased phosphorylation at Ser831 relative to that of control animals [185]. This effect, which lasted to a later developmental age, was prevented by RU486, an antagonist of glucocorticoid receptor [185]. Neonatal social isolation that caused downregulation of CaMKII activity is in line with the attenuation of LTP at age of 27 days by early life social isolation. Ser831 of GluR1 subunit of AMPA receptor is a target of CaMKII and is known to be phosphorylated during LTP [186]. Interestingly, certain forms of stress may upregulate CaMKII expression. For example, postnatal maternal deprivation and pubertal immobilization stress upregulate CaMKII [187]. The reason for this differential response is not well understood.

Stress seems to affect levels of CaMKII differently in distinct brain regions. For example, recently, we have shown that predator exposure stress in rats did not significantly change the P-CaMKII levels in the hippocampus, but markedly increased its levels in the amygdala (BLA region) and decreased its levels in the mPFC [92]. In other reports, we showed that psychosocial stress significantly decreased CaMKII levels in hippocampal area CA1 but not in the dentate gyrus area [27, 45, 50].

4.5.2. Calcineurin (PP2B). Protein phosphatases are responsible for the dephosphorylation and inactivation of previously phosphorylated protein molecules. Several protein phosphatases exist in hippocampal neurons, including calcineurin. The effects of calcineurin on learning and memory are said to be largely regulatory so as to limit the saturation of learning and its underlying synaptic processes. It has been reported that overexpression of calcineurin in the hippocampus results in detrimental effects on cognitive abilities. For instance, overexpression of calcineurin in the hippocampus attenuates hippocampus-dependent memory formation [188]. There are three major types of protein phosphatases in hippocampal neurons: PP1, PP2A, and PP2B (also known as calcineurin). Phosphatases PP1 and PP2A are very effective in dephosphorylating CaMKII at Thr286, thus reversing its constitutive activity to basal levels. Calcineurin is not only a potent inhibitor of postsynaptic activity in the hippocampus [127] but also is responsible for the expression of LTD. Activation of calcineurin by calcium-calmodulin (Ca^{2+}-CaM) leads to the activation of PP1, which in turn inactivates P-CaMKII [189, 190]. Additionally, despite the fact that much of the literature classifies phosphatases as a generic "off" switch that equilibrates the cellular environment after kinase activity is finished, calcineurin has been shown to both increase and decrease synaptic efficacy by modulating ion channels (e.g., L-type Ca^{2+} channels) and receptors (e.g., AMPA receptors) in addition to kinases (CaMKII, MAPK), transcription factors (e.g., CREB), and other phosphatases (e.g., PP1) [191].

Chronic psychosocial stress causes overexpression of calcineurin in area CA1 of the hippocampus [27, 32, 50, 192]. Interestingly, within the hippocampal formation, the dentate gyrus area seems to be relatively immune to the effect of moderately chronic stress in that chronic stress produced a significant decrease, rather than increase, in calcineurin levels. Thus, the dentate gyrus of chronically stressed rats seems to have a compensatory mechanism whereby calcineurin levels are reduced in order to maintain normal P-CaMKII levels, which may be responsible for the normal early LTP of the dentate gyrus in chronically stressed rats [27].

Other types of stressors may have different effects on the levels of calcineurin. For example, predator exposure stress produced no significant effect on the expression of

calcineurin in hippocampal area CA1, amygdala, or mPFC of rats [92]. Interestingly, calcineurin expression in the hippocampus of maternally deprived rats seems to be sex specific in that it is decreased in male but not female animals [193].

4.5.3. Brain-Derived Neurotrophic Factor (BDNF). The neurotrophic factor (BDNF) promotes various aspects of plasticity and survival of existing as well as newly born neurons in the central nervous system. This protein factor is expressed not only in brain tissue but also locally in exercised skeletal muscle [52, 194]. In addition to its action on neuronal survival and differentiation, BDNF has a role in the regulation of synaptic strength. It can act as an activity-dependent modulator of neuronal structure, and its release after tetanic stimulation modulates the induction and maintenance phase of LTP in the hippocampus [195, 196]. Experimental evidence supports the role of BDNF in memory processes. It has been shown that memory acquisition and consolidation are accompanied by an increase in BDNF mRNA expression and the activation of its receptor TrkB in the hippocampus [197]. Thus, BDNF plays a prominent role in learning and memory and synaptic plasticity [198].

Two major families of neurotrophic factors have been identified: the neurotrophins family and the glial cell line-derived neurotrophic factor (GDNF) family. The latter includes four members that have been identified so far: GDNF, neurturin, artemin, and persephin, all of which function through activation of receptor tropomyosin kinases (Trk). The neurotrophin family in mammals includes four members that have similar structure and biochemical characteristics and activate one or more of the three members of the TrK family of receptors. The four members are the nerve growth factor (NGF), which activates TrkA receptor, BDNF and neurotrophin-4/5 (NT-4/5), both of which selectively activate TrkB receptor, and neurotrophin-3 (NT-3) with high affinity for TrkC receptor. In addition, all neurotrophins activate, with low affinity, the tumor necrosis factor receptor, p75 neurotrophin receptor (p75(NTR)) [199–202].

Based on the observed changes in the hippocampus in response to stress, a "neurotrophic hypothesis" has been formulated to explain the mechanism of mood disorders due to a lack of trophic support in certain areas of the brain [203, 204]. BDNF is the major neurotrophin thought to be involved in this hypothesis. In general, evidence indicates reductions in BDNF protein level or its mRNA level in the hippocampus after acute and chronic stress [32, 205, 206]. Further, a similar decrease of BDNF in the dentate gyrus is seen after corticosterone administration [205]. Parallel reductions in BDNF levels are reported in the hippocampus [207–209] and PFC [208] of brains of depressed patients.

The trophic influence of glucocorticoids on the brain is related to the previous discussion. The complexity of the neurotrophins system is suggested by the finding that TrkB phosphorylation can also be induced by glucocorticoids in neurons [210] and that both BDNF and glucocorticoids can also regulate the release of CRF [211]. It is well known that prolonged glucocorticoid exposure is associated with dendritic atrophy and synaptic spine loss in adult brains. Although glucocorticoids are maligned because they are the hormones that initiate the stress responses, at normal circulating levels they have trophic effects on neurons [212]. Removing circulating glucocorticoids by adrenalectomy resulted in reduced dendritic density and even neuronal death. These changes in neuronal morphology were prevented when the adrenalectomized rats were treated with corticosterone. This suggests a trophic influence of glucocorticoids on the hippocampus. It has been shown that the trophic effects of glucocorticoids are due to activation of the specific BDNF TrkB receptor [211]. However, BDNF and glucocorticoids have different time courses in acting on the TrKB receptor in that BDNF causes immediate activation of the receptor, whereas glucocorticoids response is smaller but longer lasting [211].

Recent evidence revealed an important role for glucocorticoids in synaptic modulation to improve learning and memory. A single behavioral stressor improved performance in working memory tasks in rats, and short-term corticosterone treatment *in vitro* induced long-lasting potentiation of synaptic responses, which could be blocked with a glucocorticoid receptor antagonist [213, 214]. Additionally, corticosteroids are said to be involved in structural plasticity of neurons. *In vivo* studies showed that corticosterone administration enhanced dendritic spine formation in cortical regions and this effect was blocked by corticosterone deprivation [215].

It has been demonstrated by several studies that exposure to a variety of stressors both acute [216–218] and chronic [131, 219–221] can significantly downregulate both BDNF mRNA expression and protein levels in the hippocampus. However, in adrenalectomized animals restoration of basal levels of circulating corticosterone restores the stress-mediated repression of BDNF expression [205] suggesting a role for the basal circulating glucocorticoids in the effects of stress on hippocampal BDNF expression.

This decrease in BDNF expression is seen predominantly in the dentate gyrus and CA3 hippocampal areas [216, 219]. However, the duration of stress differentially influences BDNF expression with short-duration stressors of less than 60 min causing an increase in hippocampal BDNF expression and protein levels [222–224].

In contrast to its effects on the hippocampus, stress has been shown to cause an increase in BDNF expression in the frontal cortex [225–227], PVN [216], and amygdala [137, 227]. This differs from reports following glucocorticoids administration, which is largely associated with a decline in BDNF expression in cortical brain regions, including the frontal cortex [207, 228]. This suggests that stress effect may not be due to increased glucocorticoids levels alone.

4.5.4. Cyclic-AMP Response Element Binding Protein (CREB). CREB, a transcription factor that regulates the expression of CRE-containing genes, plays an essential role in the molecular mechanisms underlying synaptic plasticity processes, and regulates adaptive responses including memory consolidation, addiction, and synaptic refinement [229–231]. CREB signaling may play a central role in mediating the effects of chronic stress on neurogenesis, LTP, and calcium currents in the dentate gyrus area [232, 233].

The transcriptional activity of CREB occurs upon phosphorylation of the regulatory Ser133 residue by key protein kinases [234, 235]. In nerve cells, the depolarization-induced phosphorylation of Ser133 of CREB is critically dependent on Ca^{2+} influx-mediated activation of calcium calmodulin kinase IV (CaMKIV) [236]. Whereas activation of CREB is necessary and sufficient to generate L-LTP and long-term memory [237, 238], inactivation or blocking of CREB impairs synaptic plasticity, learning, and long-term memory [239–241]. For example, mice with mutations in CREB exhibit normal E-LTP and short-term memory but deficient L-LTP and long-term memory [239].

Reports on the impact of stress on CREB are inconsistent. For example, in chronically stressed rats, CREB phosphorylation has been reported to be significantly reduced in several brain regions, including the hippocampus [242, 243]. In mice, however, chronic psychosocial stress has been shown to stimulate CREB transcriptional activity in the brain [24]. Findings from this laboratory consistently showed that chronic psychosocial stress in rats did not significantly affect the basal expression of p-CREB or total CREB [52, 123, 244]. The contradictory findings are most probably the consequences of using different species of animals, different stress paradigms, and whether the analysis was done in a specific area of the brain or the whole brain tissue.

4.5.5. Calcium Calmodulin-Dependent Protein Kinase IV (CaMKIV). The transcriptional activator, CaMKIV, is expressed in the nuclei and cytosol of neurons in several brain regions, including the cortex, cerebellum, hippocampus, and amygdala [245–249]. CaMKIV activates several transcription factors, including CREB, and phosphorylates and regulates the function of a number of synaptic proteins, including synapsin 1 [250]. Induction of LTP by multiple-high-frequency stimulation causes an increase in the level of CaMKIV leading to phosphorylation and activation of CREB [251, 252]. Therefore, CaMKIV plays a modulatory role along with other signaling pathways to ultimately ensure activation of CREB. Indeed, mice with mutation in CaMKIV showed impaired late phase LTP, long-term memory, and CREB phosphorylation in the hippocampus but intact early phase LTP and short-term memory [253, 254].

The role of CaMKIV in mediating anxiety and stress-related behavior is suggested by examining CaMKIV knockout mice. These animals exhibit decreased anxiety-like behaviors and develop less stress-induced analgesia [255]. However, chronic psychosocial stress in rats produced no significant effect on the expression of CaMKIV [256].

5. Stress and Central Nervous System Disorders

Psychological stress is a major risk factor for the development and progression of a variety of diseases. Chronic exposure to stress diminishes health and increases susceptibility to mental disorders [257]. Moreover, stress aggravates existing functional deficits and structural alterations associated with various brain disorders including schizophrenia [258], Cushing's disease [259], hypothyroidism [15], Alzheimer's disease [50, 51], and cardiovascular disease [260, 261]. Long-term high concentrations of glucocorticoids will have indirect detrimental effects on the neurons, by engendering a metabolically adverse cellular environment, which increases their vulnerability to existing or impending insults such as Alzheimer's disease and Parkinson's disease [51, 262].

Severe and/or protracted stress causes overactivation and dysregulation of the HPA axis and induces negative effects on the brain morphology and chemistry [263] with serious consequences. The entire vast literature on the role of stress in various disorders is beyond the scope of this report; however, this section briefly reviews the effect of stress on selected brain disorders.

The effects of chronic stress on brain structure and function are similar to those of a variety of brain disorders including Alzheimer's' disease and Parkinson's disease. For example, stress or chronic corticosterone administration in animals compromised normal motor function [264] and exaggerated motor deficits in a rat model of Parkinson's disease [256] and exasperated or precipitated Alzheimer's disease phenotype [51, 52, 122, 192].

5.1. Stress-Dependent Cardiovascular Disorders. A growing body of literature suggests that chronic stress-induced activation of the sympathetic nervous system and the HPA axis may lead to inflammation, which plays an important role in the pathophysiology of a number of diseases including cardiovascular disorders. Tonic activation of the sympathetic nervous system may cause overt arterial hypertension and contribute to a high risk of cardiovascular diseases particularly in subjects with high-normal blood pressure [265].

Association between stress and hypertension and other cardiovascular diseases has been thoroughly investigated both in humans and in experimental animals. Even the fetus may suffer from consequences of psychosocial stresses during pregnancy. For example, it has been reported that stressors during pregnancy predispose the child at age 5–7 to higher blood pressure [266]. Psychosocial stressors enhance autonomic stimulation via the HPA axis, which increases circulating catecholamines and cortisol in humans. These heightened autonomic responses are associated with increased risk of hypertension and proinflammatory state and, consequently, development of coronary heart disease.

Hyperactivity of the sympathetic cardiovascular control is believed to contribute to high blood pressure in patients. Chronic psychosocial stress is associated with the onset and aggravation of ischemic heart disease and produces a greater increase in blood pressure in patients with labile hypertension than in normotensive subjects [267, 268]. Although stress-induced hypertension returns to normal within a few days of termination of stress, prolonged mild-moderate hypertension may contribute to atherosclerotic cardiovascular diseases [269] in addition to causing cognitive impairment [27]. Both genetic and stress-induced experimental forms of hypertension are known to include a significant neural component that contributes to the development and maintenance of this disease [260, 270].

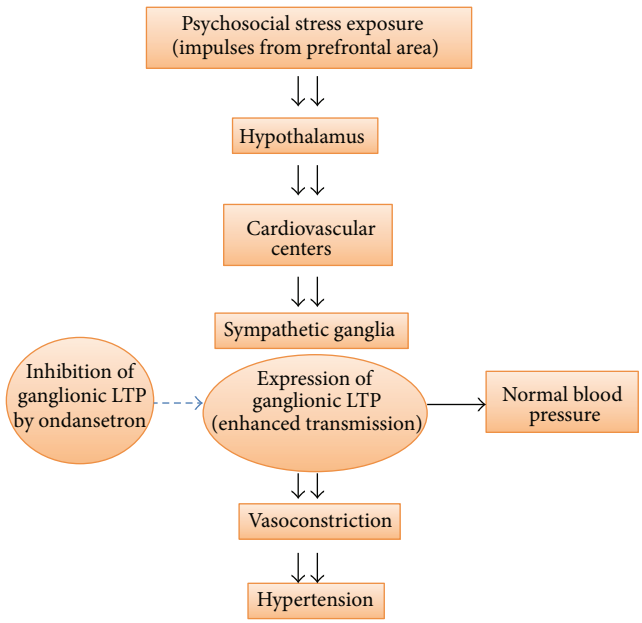

Figure 1: Chronic mental stress supplies the repetitive stimulation required for induction of ganglionic long-term potentiation (gLTP), which enhances impulses to blood vessels leading to vasoconstriction and hypertension. Treatment with 5-HT3 receptor antagonists normalizes blood pressure in chronically stressed animals. It is noteworthy to mention that such mechanism may be only one of several other contributing mechanisms in the development of hypertension.

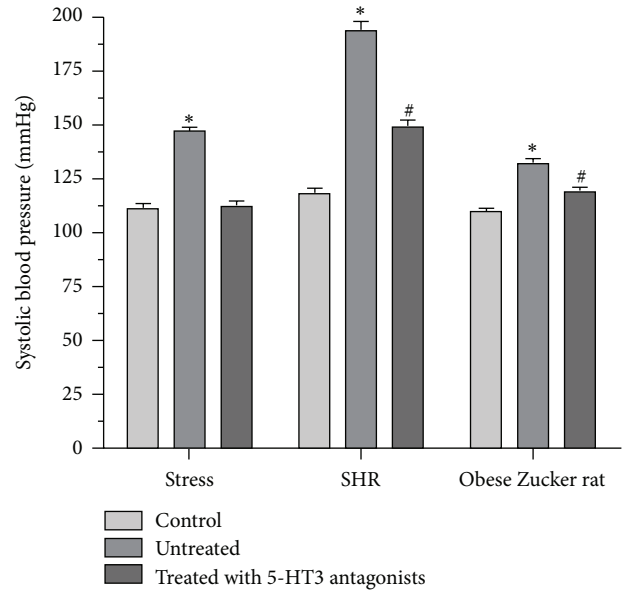

Figure 2: Chronic psychosocial stress caused elevation of blood pressure in normal animals and exacerbates existing hypertension in rat models of hypertension (spontaneous hypertensive rat "SHR" and obese Zucker rat). Note that treatment with 5-HT3 receptor antagonists, which block ganglionic LTP, inhibits the stress-induced component of hypertension. ∗ and # indicate significant difference from the other two groups ($P < 0.05$–0.01).

We have proposed that the stress-induced sustained increase in central sympathetic outflow to sympathetic ganglia may provide the repeated presynaptic activity required to express LTP in sympathetic ganglia, which in turn leads to a sustained increase in sympathetic tone to blood vessels, causing elevation of blood pressure [91] (see Figure 1).

Similar to the LTP of the hippocampus, ganglionic LTP has been demonstrated both *in vitro* and *in situ*, in a number of autonomic ganglia from vertebrates including mammalian, amphibian, and avian species [271]. Ganglionic LTP of the nicotinic pathway is an enduring increase in synaptic effectiveness that can be induced in ganglia following a short train of relatively high-frequency stimulation of the preganglionic nerve. As in LTP of the hippocampus, the expression of ganglionic LTP is thought to be the product of a complex set of events that involve several enzymes, modulators, and second messengers, involving both the postsynaptic and presynaptic regions [271].

The cardiovascular centers in the brain stem region are regulated by higher centers in the hippocampus, amygdala, and prefrontal lobe of the brain, which are said to have a profound impact on autonomic functions [272, 273]. Stress perception involves participation of the PFC, which consequently alters the cardiovascular functions by influencing the autonomic regulatory systems. The ability of the prefrontal cortex to influence the cardiovascular system response to stress has been demonstrated in pigs, where blocking the frontocortical-brain stem pathways prevents the development of lethal arrhythmias in psychosocially stressed pigs [274].

In vivo expression of LTP in autonomic ganglia is expected to enhance tonic efferent signals to an array of effector organs, including the heart, blood vessels, and glands, which result in modulation of the normal physiology of these organs. We have shown that expression of ganglionic LTP, which enhances activity of the sympathetic nervous system, may be responsible for the development and/or aggravation of stress-induced hypertension in animal models (Figure 2) [91, 126, 260, 271, 275–277]. Sustained elevation of sympathetic tone to the blood vessels and the heart may also lead to increased heart rate (clinically presents as palpitation) and arrhythmias, which may lead to death [277]. The function of the stress-induced elevation of blood pressure is unclear. We suggest that it may be involved in an adaptive mechanism to compensate for reduced blood perfusion reported in certain areas of the brain during stressful conditions [260, 278, 279].

5.2. Alzheimer's Disease. Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disease that was first characterized by the Bavarian psychiatrist Alois Alzheimer who published two seminal articles titled "A Characteristic Disease of the Cerebral Cortex" [280] and "On Certain Peculiar Diseases of Old Age" [281], which detailed the biographical, clinical, and neuropathological history of two patients with severe cognitive deficits and proteinaceous deposits as classic hallmarks of AD. The disorder was subsequently named after Alois Alzheimer [282, 283].

Alzheimer's disease is a multifactorial disease with both familial and sporadic forms. Familial AD is an autosomal dominant hereditary disorder with early onset before the age

of 65. A three-gene mutation has been identified as the cause of the familial form of the disease. A common feature of the disease-causing mutations in these genes is that they all involve the metabolism or stability of amyloid-beta (Aβ) protein believed to be a causing factor for AD. Fortunately, the familial AD is relatively rare with a frequency of less than 1% of total AD cases [284, 285]. In addition to age and genetic factors, chronic stress is a risk factor for AD [286, 287], since elevated glucocorticoid levels are correlated with increased Aβ deposition, enhanced Aβ-mediated neurotoxicity, and accelerated cognitive decline [21, 288–290].

The hippocampal complex of the brain is a particularly susceptible target in AD where early symptoms include significant impairment of the hippocampus-dependent cognitive abilities. Accumulating evidence suggests that elevation of glucocorticoid levels, as in chronic stress, increases neuronal vulnerability to age-related damages hence speeding up the progression of aging of the brain [291]. A possible explanation for this increased vulnerability is that age-associated deterioration of the hippocampal neurons may interfere with the negative feedback inhibition of the HPA axis and consequently result in elevated plasma glucocorticoid levels. Such enhanced levels of glucocorticoids have been observed in Alzheimer's patients [292, 293].

Furthermore, genetic studies indicate a link between glucocorticoids function and the risk for developing AD [294]. Studies in transgenic mice demonstrate that acute corticosterone treatment increased soluble and insoluble Aβ protein production *in vivo* [21]. Additional data from *in vitro* studies found that corticosterone treatment increased steady-state levels of amyloid precursor protein (APP) and β-APP cleaving enzyme (BACE). This increase was blocked by glucocorticoid antagonists indicating selective activation of glucocorticoid type-2 receptors [21]. Studies in animal models of AD provide corroborative evidence of stress-induced changes in AD. For example, exposure to chronic stress results in an increase in the levels of Aβ and/or Aβ-related proteins suggesting that stress may drive the APP enzymatic processing cascade to favor the amyloidogenic pathway [50, 295]. This prompted the proposition that stress may contribute to the development and/or maintenance of AD. Further support of this hypothesis comes from an epidemiological report that suggests stress as a risk factor for AD because elderly individuals who suffer psychological distress are more likely to develop the disorder than their age-matched, nonstressed individuals [21].

My laboratory group has conducted extensive studies on the impact of chronic psychosocial stress in rat models of AD phenotype at the behavioral, cellular, and subcellular levels [50, 192, 253, 296]. Particularly interesting is our novel subclinical or "at-risk" rat model of AD. This model was obtained by 14-day intracerebroventricular infusion of subpathogenic doses of Aβ protein by osmotic pumps. Treated rats were not different from control rats in every test conducted; thus the model was assumed to mimic preclinical, symptomless condition in humans. However, when these rats were subjected to chronic psychosocial stress before and during amyloids infusion, they exhibited clear AD phenotypes, including impaired learning and memory, suppressed LTP, and deficit of cognition-related molecular cascades similar to those seen in rats infused with full pathogenic doses of Aβ proteins (Table 1) (reviewed in [244]).

Table 1: Effects of chronic psychosocial stress on cellular and molecular neuronal functions in at-risk AD model in rats. Sub-Aβ (160 pmol/day; subpathogenic dose); Full Aβ (300 pmol/day; pathogenic dose) in CA1 area of the hippocampus; $\Downarrow$ decreased; $\Uparrow$ increased; $\Leftrightarrow$ no change compared to the control. Note that Sub-Aβ values are identical to control values (not shown) and that the presence of stress in sub-Aβ rats revealed full AD phenotype seen in Full Aβ.

	Stress	Sub-Aβ	Str/sub-Aβ	Full Aβ
P-CaMKII	$\Downarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
t-CaMKII	$\Leftrightarrow$	$\Leftrightarrow$	$\Leftrightarrow$	$\Leftrightarrow$
Calcineurin	$\Uparrow$	$\Leftrightarrow$	$\Uparrow$	$\Uparrow$
BDNF	$\Leftrightarrow$	$\Uparrow$	$\Uparrow$	$\Uparrow$
P-CREB	$\Leftrightarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
t-CREB	$\Leftrightarrow$	$\Leftrightarrow$	$\Leftrightarrow$	$\Leftrightarrow$
CaMKIV	$\Leftrightarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
Learning	$\Leftrightarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
Short-term memory	$\Downarrow$	$\Leftrightarrow$	$\Downarrow\Downarrow$	$\Downarrow$
Long-term memory	$\Leftrightarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
Early LTP magnitude	$\Downarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
Late LTP magnitude	$\Leftrightarrow$	$\Leftrightarrow$	$\Downarrow$	$\Downarrow$
LTD magnitude	$\Uparrow$	$\Leftrightarrow$	$\Uparrow\Uparrow$	$\Uparrow\Uparrow$

A number of reports have demonstrated that patients with AD exhibit HPA axis abnormalities [29–303]. In AD patients, the concurrent age-associated loss of hippocampal neurons and downregulation of glucocorticoid receptors cause severe dysregulation of the HPA system [304]. With aging, progressive failure of the negative feedback regulation of the HPA axis allows continued glucocorticoid release [68, 305, 306], which promotes hippocampal atrophy [307], excitotoxicity and neurotoxicity, [3, 306]. The combination of these adverse effects may reduce the ability of neurons to survive concurrent insults, thus exacerbating Aβ-mediated neurotoxicity and/or impairment of memory and LTP [24, 28, 55, 308, 309].

5.3. Parkinson's Disease. The impact of overactive HPA axis on various neurodegenerative diseases including Parkinson's disease (PD) is well known [310–313]. Parkinson's disease is a progressive neurodegenerative disorder with complex, multifactorial etiology, affecting around 1% of individuals over the age of 65, and hallmarked by loss of dopaminergic neurons of the nigrostriatal pathway and debilitating motor dysfunction [262, 314, 315]. Additionally, neuronal loss that occurs in other brain areas and protein accumulation could play a prominent role in the pathogenesis of PD. While the serious motor symptoms (rigidity, bradykinesia, resting tremor, and postural instability) are the obvious manifestations of the disease, a variety of nonmotor symptoms may also be present and together they can negatively affect the quality of life of patients. Depression seems to be one of the most common PD comorbidities, which may be masked by the psychomotor symptoms [316, 317].

The majority (90%) of cases of PD are sporadic with the remaining 10% may be due to a genetic origin (familial) [314]. In addition to aging, it is believed that a combination of genetic vulnerability and environmental factors, including stress, may be involved in the expression of the disease. Parkinsonism can also be precipitated by toxins, certain medications, central nervous system infection, and other disorders. Recently, inhibitors of the ubiquitin-proteasome system, including some environmental toxins, have been identified as possible factors for this disease [318].

While acute stress increases dopamine release as an essential measure to promote adaptation and survival, chronic stress decreases dopaminergic tone in various regions of the brain including PFC, striatum, nucleus accumbens, and frontal cortex [319, 320]. However, the effect of stress in the presence of already impaired dopaminergic system, as in PD, may have serious implications for the disease [315].

Unfortunately, the exact etiology of PD is currently unclear, but the primary risk factor for PD is aging, which may be accompanied by elevated levels of cortisol [321]. Interestingly, cortisol level is elevated in PD patients relative to healthy age-matched controls [322], which is an indication of the presence of stress. Plasma cortisol levels in PD patients can be lowered by acute treatment with levodopa, the drug of choice for treatment of PD [323], suggesting that stress is not merely a psychological reaction to being diagnosed with the disease and implying an association between dopaminergic system dysfunction and HPA axis hyperactivity [315]. Stress can transiently increase motor symptoms of PD, but it is unclear whether other behavioral changes associated with PD are also affected.

Severe stressors may bring about the development of PD later in life. For example, thirty-five years after release, prisoners of war showed a higher incident rate of PD development [324]. This, however, may be the product of the continuous form of traumatic stress, PTSD. It is believed that prolonged stress episodes may cause permanent damage to brain structure [325]. Accordingly, emergence of the PD clinical symptoms during a stressful period may indicate a preexisting subthreshold damage to the nigrostriatal system that has been intensified by stress. These neurological impairments were linked both to the degree of dopamine depletion and to the intensity of the stress [312].

High cortisol levels accelerate PD progression [262]. Pleasure responses were further reduced in PD patients after exposure to emotional stress, even though stress did not affect certain motor symptoms [326]. However, corticosteroids may also have neuroprotective effects by curbing harmful microglial reactivity [327].

5.4. Epilepsy. Epilepsy is a brain disorder characterized by periods of abnormal intense neuronal repetitive activity resulting in recurrent seizure episodes. The paroxysmal nature of epilepsy suggests the involvement of triggering factors. Stress is consistently identified as the most common trigger of seizures in patient perception studies, independent of the subtype of epilepsy reported [328–334]. In fact, one proposed theory for the etiology of epilepsy is that it is due to psychological causes such as stress, psychic trauma, and shock. Although the mechanism(s) by which stress causes or triggers epilepsy remained obscure, a number of theories have been proposed (reviewed in [335]).

Seizures can originate from different regions of the brain and can be generalized or localized (focal) depending on the type of epilepsy. The disease is frequently comorbid with other disorders, including anxiety, depression and cognitive and memory problems. In epilepsy the brain can undergo various changes at the cellular level including cell loss and widespread circuit abnormalities, alterations of synaptic properties, aberrant ion channels, inflammation, and changes in glial cell function [336].

Because of the subjective perception of stress, self-report studies in humans are not very reliable. However, correlational studies explored the relationship between stress and occurrence of seizures in populations affected by a common stressor. For example, investigation of the effect of a controlled evacuation from a flooded area in the Netherlands on patients with epilepsy revealed a strong relationship between the stressful situation and the frequency of seizures in the evacuated patients [337]. Similarly, during the 1991-1992 Croatian war, Bosnjak and colleagues [338] compared epileptic children with other epileptic children but from areas unaffected by war and reported a strong association between stress and seizure frequency.

Although human data on the association between stress and epilepsy are limited, a wealth of data from animal experiments on the effects of stress or glucocorticoids, albeit sometimes contradictory, exists in the literature. Experiments on the effect of corticosterone in various experimental epilepsy models yielded conflicting results. With so many different experimental variables, the contradictory findings are not surprising (reviewed in [334]).

With acute stress, the results have been variable depending on the epilepsy model and are, to some extent, sex dependent [334]. Depending on the seizure induction method and type of acute stressor used, acute stress is reported to both enhance and reduce seizure susceptibility [334]. Emotional stress is considered the most frequent self-reported seizure trigger [332]. For example, acute stress has been reported to exacerbate or even trigger an epileptic episode [329] as patients recount that the frequency of their seizures increases if they are exposed to stress [330, 339].

In contrast to acute stress, the results of the effects of chronic stress and early life stress on seizure susceptibility in experimental animals have been more consistent. Early life stress can result in lasting vulnerability to epileptogenesis in adult animals [340–342]. Various forms of psychiatric disorder have been reported in humans as a product of stress in early life, they include mood and anxiety disorders, schizophrenia and even dementia [71] in addition to increased vulnerability to limbic epilepsy in adult life [343–345].

Prenatal stresses and exposure to elevated corticosteroid blood levels impair hippocampal synaptic function and increase the rate of severe seizure and may enhance later seizure susceptibility in infant rats. In animal experiments, early life stress results in long-lasting augmentation of HPA axis responses to limbic seizures, in addition to cell loss in

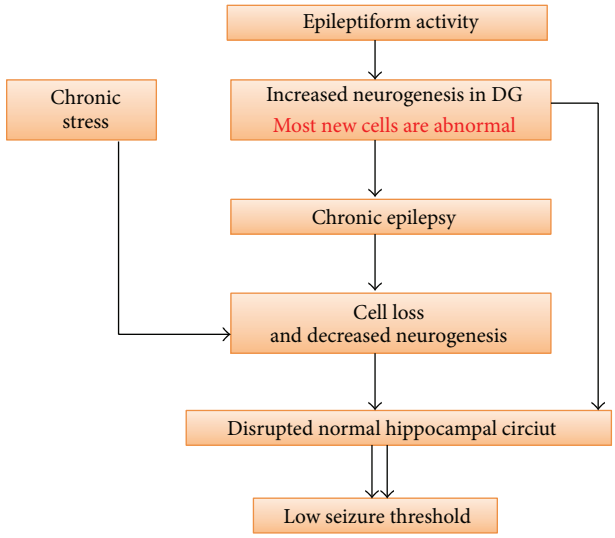

Figure 3: Chronic stress lowers seizure threshold in epileptic patients (DG = dentate gyrus).

hippocampal area CA3 and enhanced neurogenesis, in a sex-dependent fashion [345]. This may represent possible mechanisms by which early life stress promotes susceptibility to limbic epileptogenesis in rats and possibly to human mesial temporal lobe epilepsy and its associated psychiatric comorbidities. This most common form of focal epilepsy in adults [346] arises from limbic structures, including the hippocampus, which are vulnerable to the effects of stress [254, 347].

Accumulating evidence supports the role of stress hormones in the effect of stress on epilepsy. For example, administering exogenous corticosterone exacerbates the kindling model of epilepsy [348–350]. The involvement of stress hormones was indicated by the findings that glucocorticoid and mineralocorticoid receptors antagonists [349] as well as adrenalectomy or hypophysectomy reversed or slowed the effect on kindling in rats [351–354]. It appears that even CRF has proconvulsive activity. It has been reported that intracerebroventricular injections of CRF produced spontaneous seizures in rats [355–359].

Neurogenesis is important for hippocampal functions (for review see [360]). Chronic stress and depression are known to cause decreased granule cell neurogenesis in the dentate gyrus, whereas neurogenesis initially increases during the development of epilepsy but then decreases later in the disease. However, the majority of these nascent granule cells that are generated early in epilepsy assimilate abnormally [361]. Aberrant integration of new cells during the development of epilepsy may interfere with the ability of the dentate gyrus to curtail excessive excitatory activity from reaching hippocampal pyramidal cells, thus furthering seizure activity (Figure 3). Therefore, in spite of the opposing effects of stress and epilepsy on neurogenesis, both disorders may be epileptogenic. Because of these marked changes in dentate gyrus granule cell neurogenesis, it has been suggested that temporal lobe epilepsy develops when large numbers of granule cells integrate abnormally into the dentate gyrus [362] (reviewed in [363]).

6. Concluding Remarks

This paper reviews the current state of knowledge regarding the impact of mental stress on brain structure and function. The reader will see relatively more emphasis put on how chronic stress affects synaptic plasticity and its underlying molecular cascades. The review also discusses the effect of stress on certain disease conditions. The discussion of how stress impacts health conditions is obviously not comprehensive as chronic stress negatively impacts a wide variety of other disorders that are not discussed here due to space limitation. It is well known that chronic stress negatively impacts patients suffering from schizophrenia [364], Cushing's syndrome [365], thyroid hormone disorders [15, 366, 367], sleep disorders [368], Huntington's disease [369], and bipolar disorder [370, 371] among others.

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