Translational Brain Rhythmicity

Review Article

Studies on stress-induced modulation of long term potentiation in rodent hippocampus: what can we learn about pathogenesis of depression?

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Abstract

Long-term potentiation (LTP) reflecting continuous changes in synaptic efficacy is regarded as a cellular model of learning and memory. In this mini-review the data relating to hippocampal LTP alterations in rodent models of depression are analyzed to learn whether disturbances in LTP may be reliable markers of synaptic plasticity impairments underlying depressive and anxiety states. LTP disturbances result from synaptic reorganizations induced by multiple inter-related and mutually dependent events: hypothalamic-pituitary-adrenal axis disfunction; malfunction of neurotransmitter systems; failure to maintain the balance of neurotrophic systems; neuroinflammatory processes; disturbance in neurogenesis. Stable deficits in hippocampal LTP reflect the synapse-related basic mechanisms for cognitive and emotional behavioral deficits characterisic for depression/anxiety, and altered LTP is indicative of the development of stress-induced psychopathology.

Abbreviations: BDNF: Brain-Derived Neurotrophic Factor; BNST: Bed Nucleus of the Stria Terminalis; CB1: Cannabinoid Receptor1; CFC: Contextual Fear Conditioning; CMS: Chronic Mild Stress; CS: Corticosterone; CUS: Chronic Unpredictable Stress; DG: Dentate Gyrus; GluR: Glutamate Receptor; GRs: Glucocorticoid Receptors; HPA: Hypothalamic Pituitary Adrenal; LTD: Long-Term Depression; LTP: Long-Term Potentiation; MS: Maternal Separation; SI: Social Isolation Stress; UWT: Underwater Trauma

Literature

Chronic stress is considered to be a major risk factor in the development of mood diseases. In order to study mechanisms involved in the etiology of human affective disorders, there is an abundant use of various animal models based on different stress paradigms. Depressive disorders are the most common psychiatric pathology, and a great number of people who experience depression also experience anxiety. Sometimes, anxiety is more expressed than depression, while in many cases neither is clearly predominant. In rodent stress-based models anxiety and depression symptoms often are demonstrated in parallel.

Activity-dependent changes in synaptic strength are widely accepted as key mechanisms for information storage in the brain [1]. Long-term potentiation (LTP) is an electrophysiological phenomenon, an hours-lasting increase of postsynaptic potentials after tetanization. It is believed to reflect long-term changes in synaptic efficacy in distributed networks, associated with constant changes in the behavioral phenomena, which are often interpreted as the retention of information [2]. Thus, hippocampal LTP is regarded as a cellular model of learning and memory. Cognitive impairments and LTP impairments are increasingly recognized as events accompanying and reflecting experimental depression, anxiety and other experimental stress-related chronic psychological disorders, therefore, disturbances in LTP may be reliable markers of synaptic plasticity impairments underlying depressive and anxiety states. The dentate gyrus (DG) of the hippocampus is supposed to play a critical role in defining the impact of stress on hippocampal functioning. The DG is a dynamic structure susceptible to stress, its variable and complex stress response being reflected in changes of LTP and local circuit activity associated with the behavioral outcomes [3].

Structural and neurochemical changes in the hippocampus have been found in major depressive disorder, these changes being pivotal for regulation of mood and cognitive functions. Stressful life events, specifically inducing fear, provoke adaptive anxiety that can also lead to exaggerated states, forming a link of mental illnesses pathogenesis. These states are associated with alterations in dendritic and synaptic structure within specific brain regions, including the hippocampus, amygdala, and prefrontal cortex (PFC) [4]. Stress-induced structural plasticity underlies changes in hippocampal plasticity recorded using electrophysiological approaches. Exposure to experimental stress induces atrophy and cell loss in the hippocampus accompanied by decreased expression of neurotrophic/growth factors, while antidepressants reverse the effects of stress upregulating neurotrophic factor systems and neurogenesis in the adult hippocampus [5-7]. The key role of adult neurogenesis and its abnormalities in the development of depression have become widely debated during the last decade, the main bulk of the data that form the basis of this hypothesis having been obtained from rodent model experiments [8]. Hippocampal LTP is critically dependent on neurogenesis in the subgranular

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neurogenic niche. Linking depressive disorders to adult hippocampal neurogenesis, Schinder & Gage [9] have proposed a hypothesis about the contribution of specific features of newly generated neurons to hippocampal plasticity; later Perera *et al.* [10] speculated that stress-induced suppression of neurogenesis would uncouple emotions from external context leading to a negative mood state, its persistence inducing depression. Neuroinflammatory processes negatively affect both neurogenesis and synaptic plasticity [11,12]. For example, old autoimmune-prone cytokine B-cell-activating factor (BAFF) transgenic mice exhibit an anxiety-like phenotype associated with brain inflammation and decreased proliferation of newly formed neurons in the subgranular zone of the hippocampus; they also demonstrate an abnormal neuronal activation within the limbic system in response to mild anxiogenic stimuli and impaired neurogenesis-dependent and neurogenesis-independent LTP in DG [13]. These data support the idea that neuroinflammation, including inflammatory processes accompanying autoimmune diseases, may be associated with emotional disorders.

Tanti & Belzung [14] have analyzed relations of rodent depression models and of antidepressant therapies to adult neurogenesis along the septo-temporal axis of the hippocampus The dorsal hippocampus (septal part) is responsible for cognitive function (learning, memory and spatial navigation), while the ventral hippocampus (temporal part) is involved in the control of emotional and anxious behaviors and regulation of the neuroendocrine stress axis. Indeed, stress-response is different in the dorsal and ventral parts of hippocampus. Studies on rodent models of stress and depression in search of links between stress, psychiatric diseases and changes in the hippocampus (corticosteroid receptors, neurotransmitter systems, neurotrophins, neurogenesis, plasticity/LTP) strongly suggest a specific involvement of ventral hippocampus in the development of depression [15,16]. Expectedly, effects of stress on the neurogenic niche are restricted to the ventral hippocampus more frequently than they are evident in the dorsal part. In addition, the effects are also stage specific, and concern mostly neurogenesis rather than cell proliferation or survival [14]. Surprisingly, antidepressants: selective serotonin re-uptake inhibitors as well as non-pharmacological manipulations that are also endowed with antidepressant effects, such as environmental enrichment or physical exercise, act in a more uniform way on dorsal and ventral adult neurogenesis. Dine *et al.* [17] revealed a multifaceted high-anxiety neurophysiological endophenotype in the murine ventral hippocampus by applying electrophysiological techniques to brain slices from animals of the high anxiety-related behavior (HAB) and normal anxiety-related behavior (NAB) mouse model. Interestingly, basal neurotransmission at ventral hippocampal CA3-CA1 synapses was weaker in HAB as compared to NAB mice, while paired-pulse facilitation and LTP at these synapses were more pronounced in slices from HAB animals. Intranasal administration of neuropeptide S, a potential novel treatment option for anxiety, increased basal neurotransmission and reduced paired-pulse facilitation and LTP in slices from HAB animals shifting this endophenotype towards norm.

Stress exerts its effect on cognitive function and mood to the utmost through the actions on hypothalamo-pituitary-adrenal (HPA) axis, in particular *via* effects of stress hormone corticosterone (CS) on synaptic plasticity. Increased levels of CS affect hippocampal functioning *via* the glucocorticoid receptors (GRs). A number of studies reported stress-induced alterations in hippocampal LTP depending on the nature and duration of stress [18], however only few of these studies are directly linked to CS effects and confirm that stress paradigms used model depressive behaviors. Kamal *et al.* [19] showed that susceptibility to stress following social isolation stress (SI), in particular genetic background, has a major effect on the level of in vitro LTP impairment in the CA1 hippocampal area in mice. SI significantly increased CS levels. Chronic CS infusion in control mice phenocopied the LTP impairments observed in SI mice, while infusion of the GRs antagonist RU38486 rescued the LTP impairments induced by SI. Exposure of young rats to tail suspension stress for 30 s significantly increased serum CS and attenuated CA1 LTP in hippocampal slices [20]. This effect was mediated by CS-dependent increase in postsynaptic Zn^{2+} signal. The data suggest that changes in hippocampal function induced by acute stress may be a potential risk factor under chronic stress circumstances to induce depressive symptoms.

Along with disturbances in the HPA axis, the most common stress-related psychiatric disorders (depression and generalized anxiety) are underlain by dysfunctions of neurotransmitters systems, in particular serotoninergic (5-HT) and glutamatergic. Indeed, disturbances in 5-HT/HPA interactions at molecular and functional levels and related alterations of hippocampal neurogenesis are key links in the pathogenesis of psychoaffective disorders [21]. Studies on LTP in the hippocampal CA1 field in 5-HT-depleted rats suggest that the serotonergic mechanism is involved in the psychological stress-induced alteration in synaptic plasticity [22]. Epigenetic modulation of specific genes related to development of pro-depressive or antidepressive stress response (5HT transporter and receptors, corticotropin releasing hormone, glucocorticoid and their receptors, BDNF and other neurotrophic factors) may contribute to the formation of depressive endophenotypes [23].

Besides the monoamine system that has been the central focus of neurobiological research into depression and represents the major target of modern antidepressant drugs, dysfunction of the glutamatergic system has also emerged as a major pathological feature in depression. A most important excitatory neurotransmitter, glutamate, is a key player in synaptic plasticity phenomena, in particular LTP and new synapse formation. The experiments performed in cats and rats by Adamec *et al.* [24] confirmed that NMDA-dependent LTP of limbic system circuits controlling defensive behavior underlies stressor-induced permanent increases in anxiety-like behavior. Dysfunction of glutamate receptors (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid subtype of glutamate receptors, AMPAR; N-methyl-D-aspartate receptors, NMDAR and metabotropic glutamate receptors, mGluR) may account for alterations to multiple signal transduction pathways in depression [25]. Concepts supporting a NMDAR hypothesis of depression postulate that the pathogenesis of depression may arise from stressors inducing excessive NMDAR activity which acts at both cellular and regional levels stimulating the depressive phenotype. Such NMDAR dysfunction may lead to alterations of synaptic efficiency/LTP pathways in hippocampus and other regions (e.g. amygdala). Glutamatergic processes are essentially implicated in the pathophysiology and treatment of depression, including the antidepressant effects of NMDAR receptor antagonists. Kudryashova [26] has reviewed the data on the involvement of impairments of glutamatergic system functions in the development of depressive states in humans and animals and discussed the hypothesis on the contribution of excitotoxic damage to neurons in depression. An alternative hypothesis was also considered dealing with deadaptation of the mechanisms of presynaptic, including structural, plasticity due to a deficit of trophic factors. Indeed, the interrelations between glutamatergic system and neurotrophins may unify these hypotheses into one concept. CS released during stress

response is able to alter functional properties of synaptic glutamate receptors, in particular AMPAR and NMDAR responsible for the expression of synaptic plasticity. Stress levels of CS applied to adult rat hippocampal slices potentiated evoked NMDAR-mediated synaptic responses as well as facilitation of both LTP and long term depression (LTD) [27]. A CS-mediated slow-onset increase in GluN2A receptors in hippocampal synapses revealed in this study could be a homeostatic mechanism to normalize synaptic plasticity following fast-onset stress-induced facilitation.

Repeated stress is one of the environmental factors that precipitates and exacerbates depression and anxiety as well as cognitive impairments. A variety of approaches, first of all different types of stress applied to different rodents of different gender and age, make it difficult to compare the results from various groups. However, considering both sides of the coin, the diversity of existing models is quite positive since it allows performing targeted studies of selected neurobiological paradigms/mechanisms of depressive state development, as well as to investigate mechanisms of action and predict pharmacological profiles of potential antidepressants [28,29].

As compared to men, women have increased stress susceptibility and exhibit a nearly twofold increased risk of developing depression and anxiety disorders. Chronic stress, sex and 5-HT deficiency are recognized main risk factors in the development of aberrant emotional behavior typical for psychiatric diseases. Indeed, effects of stress on LTP are gender-specific. A study using a contextual fear conditioning (CFC) paradigm demonstrated that the females exhibited low anxiety-like behavior, and CFC increased extracellular 5-HT levels in the hippocampus only in the males. LTP in hippocampal CA1 was suppressed by CFC in the males only, and pretreatment with the 5-HT1A receptor agonists tandospirone suppressed LTP induction in the males, while synaptic responses to CFC and 5-HT1A receptor interventions were not observed in the females [30].

Chronic unpredictable stress (CUS) or chronic mild stress (CMS) paradigms are among most popular and relevant models of stress-induced depression/anxiety behaviors in rodents. As a rule, in these models rather mild stimuli are used more frequently than painful ones to induce depressive behaviors and anxiety. CUS in rats induced depressive-like behavior (diminished sucrose preference and reduced measures of locomotor activity), impaired LTP in the hippocampal CA1 region and significantly decreased synaptophysin mean density in the hippocampal CA3 region and respective mRNA levels [31]. Electroconvulsive stimulation improved CUS-induced behavioral effects, synaptophysin deficits and ameliorated LTP impairment. Changes in hippocampal synaptic plasticity were dependent on the duration of CUS, the functional changes at CA3-CA1 hippocampal synapses occurring earlier than the structural alterations. Qiao *et al.* [32] reported that CUS during three weeks induced depressive-like behaviors, impaired LTP induction, and decreased basal synaptic transmission at hippocampal CA3-CA1 synapses recorded in vivo; a decrease in density of dendritic spines in CA1 and CA3 pyramidal neurons and brain-derived neurotrophic factor (BDNF) level in the hippocampus accompanied changes in synaptic plasticity. After a two week CUS, some depressive-like behaviors were observed, accompanied by depressed basal synaptic transmission, enhanced LTP induction at the CA3-CA1 synapses and decreased BDNF. After a 7 day long CUS, most indices did not differ from control yet. CUS induced depressive-like behaviors and decreased the number of bromodeoxyuridine-labeled neural progenitor cells and doublecortin-positive immature neurons in the DG of mice [33]. Simultaneously, CUS impaired induction of neurogenesis-dependent LTP in the DG. Close relationship between behavioral, cellular and LTP deficits in CUS-exposed mice was further confirmed by prevention all of them by a chronic treatment with a monoacylglycerol lipase inhibitor JZL184.

Hippocampal microglial activation may play a causal role in chronic stress-induced cognitive and LTP disturbances. Liu *et al.* [34] demonstrated that a rat model of CUS induced a cognitive impairment in spatial memory and the Morris water maze test and a hippocampal LTP impairment accompanied by microglial activation and attenuated phosphorylation of glutamate receptor 1 (GluR1 or GluA1). Blockade of microglial activation by chronic treatment with minocycline before CUS prevented CUS-induced impairments of both spatial memory and LTP induction as well as increased phosphorylation of GluR1.

CMS significantly modified physiological and behavioral reactions, as observed by the impairment in avoidance extinction and LTP in the hippocampal-accumbens pathway, and the alterations in depression-like symptoms, such as coping with stress behavior, weight gain, and sucrose consumption [35]. Exposure to CMS produces downregulation of the cannabinoid 1 (CB1) receptor in the hippocampus of male rats. Enhancing cannabinoid signaling using the CB1/2 receptor agonist WIN55,212-2 and GRs antagonist RU-38486 prevented the CMS-induced alterations in extinction and plasticity. The involvement of endocannabinoids in the stress response and their putative contribution to the etiology of mood disorders were confirmed by Reich *et al.* [36] , who reported that CMS (21 d) in rodents significantly altered hippocampal endocannabinoid-mediated neurotransmission and synaptic plasticity in *in vitro* experiments (field potential recordings, LTP in hippocampal area CA1). The results suggest that CMS does not directly affect glutamatergic neurotransmission, rather CMS sensitizes CB1 function on GABAergic terminals, leading to less inhibition and an increase in excitatory neurotransmission. Interestingly, LTP-blocking property of WIN 55,212-5 shifted from being glutamate-dependent in non-stress animals to being GABA-dependent in CMS animals.

In addition to CUS/CMS, different paradigms of early life stress (including acute stress) are very popular models of depression/anxiety in adult rodents. Traumatic events during early life may affect the neural systems associated with memory function, including extinction, and, most importantly, lead to altered sensitivity to stress later in life. Exposure to chronic stress during the neonatal period is known to induce permanent long-term changes in the central nervous system and HPA axis reactivity that are associated with increased levels of depression, anxiety, and cognitive impairments. Neonatal proinflammatory stress (bacterial lipopolysaccharide or interleukin administration) induces "perinatal malprogramming" resulting in development of depression-like behaviors, associated with abnormalities in functioning of the HPA axis, impaired hippocampal neuroplasticity (LTP) and changes in hippocampus-dependent memory formation [37]. As compared to neocortex, hippocampus was shown to be more vulnerable to stress-induced inflammation and demonstrated persistent inflammatory response induced by chronic stress. This maladaptive inflammatory response was associated with a selective increase in hippocampal CS accumulation and changes in CS signaling [38].

Maternal separation (MS) paradigm in rodents is a validated model of early life stress associated with increased depression, anxiety, and cognitive impairments in adults. The neuronal and endocrine changes induced by MS are long lasting, and exaggerate the mild age-associated deficits. Sousa *et al.* [39] demonstrated that the baseline behavioral deficits of aged (70-week-old) control rats were further

aggravated by MS, indicating that early-life stress-induced continuous changes in anxiety-like behavior and hippocampal-dependent memory were maintained later in life. These differences were associated with impaired hippocampal plasticity: the magnitude of hippocampal LTP from Schaffer collaterals/CA1 synapses was significantly lower in aged MS animals than in age-matched controls. Early deprivation model which involves both dam and littermate deprivation is less investigated in comparison with classical MS. Zhang *et al.* [40] reported that this paradigm of early deprivation reduced threshold of LTP induction in hippocampal CA3-CA1 pathway, lowered CS, reduced anxiety and enhanced memory (better performance in social recognition and Morris water maze test). The authors suggested that the surprisingly diminished HPA axis response and facilitated hippocampal LTP may contribute to the anxiety-reducing and memory-enhancing effects of early deprivation, respectively.

An increased incidence of anxiety, depression and attention deficits in children is believed to be linked to psychological stress during pregnancy. Stress to a pregnant rat during the period when the foetal limbic and HPA axes develop induces anxiogenic and depressive behaviours as well as learning and attention deficits in the offspring. These consequences of prenatal/maternal stress depend on its intensity and timing as well as on offspring gender. For example, maternal stress increased CS levels in the foetal brain, reduced foetal testosterone and brain aromatase activity in males, while it altered brain catecholamine activity in females [41]. Learning deficits, reductions in hippocampal neurogenesis, LTP and dendritic spine density in the prefrontal cortex were more expressed in prenatally-stressed males, while anxiety, depression and increased response of the HPA axis to stress were more prevalent in females.

The sound stress during fetal life induced anxiety, efficiently disturbed both cognitive abilities and synaptic plasticity in male Wistar rats. It negatively affected the basic synaptic responses and led to a lower level of LTP assessed in the CA3-CA1 pathway of the hippocampus [42]. The offspring of pregnant females exposed to the noise stress had an elevated level of CS suggesting that changes in HPA axis might contribute to LTP disturbances. Using a chronic prenatal restraint stress model where the rat dams were immobilized for 45 min three times per day during the last week of pregnancy Yeh *et al.* [43] found that stress switched the direction of synaptic plasticity in hippocampal CA1 region, favouring low-frequency stimulation-induced LTD and depressing the induction of LTP by high-frequency stimulation in young (5-week-old) rat offspring, these changes disappearing at adulthood (8 weeks old). Interestingly, fostering of prenatal restraint stress offsprings to control dams did not alter the effects of stress on LTP and LTD. Prenatal stress-induced changes in LTP and LTD induction correlated with increases in non-cleaved pro-BDNF and decreases in the mature BDNF (mBDNF) levels as well as with decrease in the expression of tissue plasminogen activator, a protease involved in the extracellular conversion of pro-BDNF to mBDNF. In these experiments, no gender differences could be revealed.

Since the majority of stress stimuli in humans leading to psychopathology are of social nature, studies of consequences of social stress in adult animal models are very relevant. One of these models uses the resident-intruder paradigm, in particular social defeat in rats [44]. A differential effect of a brief double social defeat and repetitive social defeat stress on dendritic remodeling in hippocampal CA3 neurons has been described, this effect being associated with alterations of hippocampal LTP and LTD. Collins [45] suggested a conflict model, developed to generate a more naturalistic model of anxiety, utilizing two non-noxious stressors (predator (cat) odor and light), external stimuli eliciting typical, stimulus-specific, anxiety-related behaviors. Ex vivo induction of LTP within the CA1 region of the hippocampus was reduced following exposure to light stress, independent of presence, or absence, of odor. However, after a single presentation, LTP was diminished following either odor presentation or dual presentation of the stressors. LTP responses in hippocampus obtained from conflict-exposed animals were hemisphere-specific. Ardi *et al.* [46] examined the impact of an underwater trauma (UWT) reminder on anxiety-like behaviour, and electrophysiological indices in the hippocampus and the amygdala. The exposure to UWT by itself increased anxiety behaviour and paired-pulse inhibition in the DG. UWT reminder 24 h later resulted in an additional increase in anxiety behaviors and paired-pulse inhibition accompanied by impaired LTP in DG.

Data on the depression/anxiety-related effects of stress conditions on LTP in brain structures other than hippocampus are quite limited. CUS induced anhedonia associated with lower amplitude of field excitatory postsynaptic potential in the PFC [47]. Chronic restraint stress provoked receptor-mediated impairments to catecholaminergic facilitation of synaptic plasticity in the medial PFC (intra-infralimbic LTP) [48]. LTP-like response in the hippocampal-medial PFC pathway was associated with extinction retrieval of context-dependent fear memory. Early postnatal stress induced neurodevelopmental dysfunction of this neural circuit and impaired fear extinction later in life [49]. Chronic restraint stress facilitated synaptic plasticity in the anterior cingulate cortex (field excitatory postsynaptic potentials duration, paired-pulse ratios and LTP level) *via* increased excitability due to disinhibition of GABA(A) receptor signalling, which may underlie induction of stress-related behavioral hyper-locomotive activity [50]. Adamek [51] showed that LTP in periacqueducatal gray mediated stress induced increases in anxiety in rodents, as it did in the cat. Cocaine withdrawal enhanced NMDA receptors-dependent LTP induced by corticotropin-releasing factor at central amygdala glutamatergic synapses [52]. In the lateral amygdala LTP was dependent on the metabotropic glutamate receptor subtype 7 (mGlu7), an important presynaptic regulator of neurotransmission linked to anxiety and depression [53] and was gated by the striatal-enriched protein tyrosine phosphatase [54]. Thirty days after the last exposure to chronic restraint stress for 2 weeks late adolescent rats demonstrated increased anxiety, impaired LTP in the ventral subiculum-nucleus accumbens (NAc) pathway, impaired performance in the PFC-dependent object-recognition task and the hippocampal-dependent spatial version of this task, and significantly reduced expression of GRs in the amygdala, hippocampus, PFC, and NAc[55]. The bed nucleus of the stria terminalis (BNST), a subregion of the extended amygdala, is regarded as a relay of corticolimbic information to the paraventricular nucleus of the hypothalamus to directly influence the stress response. Conrad *et al.* [56] showed that chronic CS injections and chronic SI housing conditions induced anxiety-like behavior in mice, and chronically stressed mice also displayed a parallel blunting of LTP in the dorsal-lateral BNST. Conversely, acute SI housing had no effect on anxiety-like behavior but still resulted in a blunting of LTP in the BNST. Thus, acute and chronic stressors specifically affect synaptic plasticity in the BNST, these changes being not consistently associated with an increase in anxiety-like behavior.

Plasticity is a specific feature of the nervous system underlying key aspects of learning, memory, and repair. Dysregulation of neuroplasticity, in particular synaptic plasticity, contributes to numerous neuropsychiatric diseases. Discussing possible mechanisms

of ambiguous stress-reactivity of long-term plasticity [18], it has been concluded that vast unpredictability of stress induced modulation of synaptic plasticity has various reasons. In acute stress conditions, stress paradigms, severity, duration, and period of recording, brain structure and other factors enhancing uncertainty and unpredictability of stress response are important, their action is highly regulated by emotional experience, and changes of synaptic plasticity may be transient. Stress paradigms modeling depression/anxiety are dealing with chronic states, as are depressive and anxiety disorders in human. In this situation changes of synaptic plasticity are much more predictable and are accompanied by definite behavioral and molecular alterations. Indeed, behavioral manifestations of these pathologies reflect altered level of synaptic plasticity. In most clinically relevant models of depression/anxiety hippocampal LTP is a mirror of disturbed plasticity. LTP disturbances result from synaptic reorganizations induced by multiple inter-related and mutually dependent events, primarily: HPA axis disfunction affecting CS and its receptors in the brain; malfunction of neurotransmitter systems; failure to maintain the balance of neurotrophic factors and their receptors; neuroinflammatory processes; disturbance in neurogenesis (including proliferation, differentiation, and migration) modifying the appearance of new neurons. On the one hand, stable deficits in hippocampal LTP (as well as of LTP in other structures of the limbic system) reflect the synapse-related basic mechanisms for cognitive and emotional behavioral deficits characterisic for depression. On the other hand, altered LTP is indicative (or even predictive) of the development of stress-induced psychopathology, representing its distinctive biomarker useful for deeper studies of synaptic pathogenetic mechanisms of mental diseases.

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