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Therapeutic effects of environmental enrichment against chronic stress-induced cognitive-behavioral impairments: A comprehensive review of recent advances

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Chronic exposure to stress has been demonstrated to increase the risk of developing neuropsychiatric disorders. Given the importance of effective therapeutic ways to overcome stress-related deficits, the present review focused on the therapeutic effects of environmental enrichment (EE) against chronic stress-induced cognitive-behavioral impairments. Chronic stress exposure has been shown to modify neuronal function and morphology in corticolimbic structures such as the prefrontal cortex (PFC), hippocampus, and amygdala, three brain regions greatly involved in mood regulation, fear processing, and cognition. It has been reported that chronic stress reduces brain-derived neurotrophic factor (BDNF) levels and its mRNA expression on the PFC, suggesting that downregulation of BDNF is a possible mechanism that mediates the effect of stress on anxiety or depression-like behaviors. There is an increasing demand for findings of effective intervention methods for alleviating the detrimental effects of chronic stress. EE is a beneficial intervention for improving anxiety and depression-like behaviors. A large body of research revealed that exposure to EE improves several conditions, including degenerative diseases, epilepsy, traumatic brain injury, anxiety, and depression. This article will provide an overview by discussing the influences of chronic stress on cognitive function and beneficial therapeutic effects of environmental enrichment (EE) against chronic stress.

KEYWORDS

Anxiety; BDNF; chronic stress; corticolimbic; environmental enrichment; depression; cognitive-behavioral impairments.

Introduction

Stress has been reported as a nonspecific and adaptive response against environmental factors in which activation of the hypothalamus-pituitary-adrenal (HPA) axis leads to the elevation of glucocorticoid levels [1,2]. It is well-known that high levels of glucocorticoids can trigger impairment in cognitive performance and memory processes [3]. Short and long-lasting effects of stress hormones mediate mainly via glucocorticoids and alter cognitive functions via genomic and non-genomic mechanisms [4]. Stress related morphological and functional changes in brain following exposure to acute or chronic stress can play a major role in developing neuropsychiatric disorders [1]. Animal studies have demonstrated that stress can induce synaptic plasticity impairment, morphological remodeling, neurotoxicity, and also influence neurogenesis in the brain. In addition, all these stress-derived physiological effects can strongly influence cognitive functions [5]. Numerous studies have reported that

susceptible brain regions such as amygdala following acute or chronic exposure to stress can lead to long lasting adaptive changes in these areas [2,3]. Behavioral studies on laboratory animals have been reflected that stress has a profound effect on the brain, primarily in the cortico-limbic structures [6]. These alterations include a serious consequence of chronic stress on brain structures especially the hippocampus (HPC), one of the most vulnerable targets of stress [4]. Indeed, remarkable morphological and functional changes have been implicated in areas such as the prefrontal cortex (PFC), HPC, and amygdala that control higher cognitive functions, following prolonged stress [7]. Dysfunction in cortico-limbic circuits may contribute to stress-associated mental disorders, and chronic stress leads to cognitive impairments in these diseases [8].

It is widely established that exposure to stress is linked to neuroanatomical deficits in brain areas, adverse effects in brain anatomy and function [5, 6] and might actually lead to development of stress-related disorders [6, 7].

Importantly, the morphology of cortico-limbic areas seems to be succeptiable to the profound effects of stress and leads to alterations including the retraction of the CA3 region apical dendrites in the hippocampus [8, 9]. Besides behavioral and morphological changes, it has been shown that prolonged stress induces decrease in BDNF expression in PFC [7].

The relationship between chronic stress and impaired cognition has also been well reported in the literature [9]. This evidence suggests that impairment in brain functions following chronic stress can exert an important role in developing neurodegenerative disorders especially for anxiety like behaviors, mood disorders and post-traumatic stress disorder (PTSD) [10, 11,12]. The aim of the current study was to verify the detrimental effects of schronic stress on biochemical factors, brain structures, and stress oxidative and also possible beneficial effects of EE in individuals that were previously exposed to chronic stress. In this review, we will summarize the role of EE in stress-induced cognitive impairments and structural alterations after exposure to stress for a long time. We also discuss the role of EE on stress oxidative markers based on its therapeutic effects.

Effect of chronic stress on biochemical factors (BDNF, IGF-1, synapsin-1)

Brain derived neurotropic factor (BDNF)

Alternations in the expression of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT4/5), nerve growth factor (NGF), and insulin-like growth factor (IGF-1) are strongly linked to abnormal neural plasticity in the corticolimbic circuits involved in cognitive processing. Cell growth controlling, differentiation, maturation (through mitosis stimulation and DNA synthesis), metabolic processes (i.e., glucose uptake and protein production) as well as the role in synaptic plasticity are the main functions of IGF-1 in the brain Szczęsny. Given to the primary expression of IGF-1 receptors in synaptic areas, it has been assumed that cognitive dysfunction might be a result of impairments in the IGF-1 system [13].

BDNF is the most abundant neurotrophin in the brain with a wide range of functions including brain development, neurogenesis, and neuroplasticity has been widely studied as the main factor associated with learning and memory processes [14]. There is evidence suggesting that early exposure to stress has many effects on brain development, including learning and memory deficits in adulthood [15]. Therefore, these consequences at least in part leads to long-term changes in the BDNF pathway [16]. Additionally, several neurodegenerative diseases such as Alzheimer's disease (AD)

and other mental disorders, especially depression has closely correlated with alteed serum BDNF levels [17].

Overexpression of BDNF also causes both anxiolytic and antidepressant behavior. Previous research has shown that hippocampal BDNF is necessary for spatial memory improvement Ortiz and modifies synaptic activity both during brain development as well as in adulthood [18].

Recent data have indicated that alteration in BDNF expression, synaptic plasticity, and synapse dynamics are subsequently involved in anxio-depressive disorders. Besides distinct roles, the sensitization of pain pathways is related to BDNF in higher brain centers. BDNF regulates a wide variety of brain functions such as cognitive functions. For instance, hippocampal BDNF modulates glutamatergic and GABAergic activity [19]. These different roles of BDNF are not only merely because of its critical role in synaptic plasticity in the context of learning and memory, but also an impairment in learning and memory might result in alternations in BDNF level. It is considered that the high sensitivity of the hippocampus to stress-related diseases are associated with hippocampal dysfunctions due to the high sensitivity of this brain structure to stress [20].

Synapsin-1

Impaired brain plasticity has been considered to be the main consequence of depression so that both environmental and genetic risk factors might associate with development of this depressive-like behavior [20]. Synapsins are neuron-specific phosphoproteins and belong to the most abundant families of synaptic proteins comprising 1% of the total brain proteins. They mainly associate with the synaptic vesicle membrane at the cytoplasmic surface by significantly contributing synaptogenesis and neuronal plasticity, including the regulation of synapse development, modulation of neurotransmitter release, and formation of nerve terminals [19, 21,22]. Various isoforms of synapsin distributed in various neuronal types including synapsins I and II are the major isoforms in neurons Lucca, playing important roles in synapse formation whereby specifically anchoring of synaptic vesicles, depletion of the neurotransmitter at the inhibitory synapses is minimized [23]. Interestingly, both genetic and functional studies have demonstrated that synapsin genes are associated with developing several neurological disorders such as schizophrenia, bipolar disorder (BD), AD, multiple sclerosis (MS), Huntington's disease (HD), and epilepsy. In particular, depressive-like behavior has been linked with synaptic remodeling of the cortex and hippocampus of stressed animals, suggesting an important role of synapsin1 in synaptic formation [13,24]. Using chronic mild stress (CMS) model , a recent study show dissociation between synapsin1 expression levels and depressive-like behaviors [25].

Stress effects on stress oxidative

Oxidative stress is a major factor that can lead to tissue degeneration in CNS [10] via releasing reactive oxygen and nitric oxide species predominantly through microglia cells and macrophages , which results in activation express the respective enzymes necessary for their production, such as different nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases [11], and myeloperoxidase [12].

An increase in releasing glucocorticoids from the adrenal gland has already been verified in stress models induction [26]. Moreover, prolonged high levels of corticosterone can result in oxidative stress, with decrease in antioxidative enzymes activity and developing damage to the central nervous system (CNS) [27].

Oxidative stress is considered as an imbalance between the productions of reactive oxygen species (ROS)/reactive nitrogen species, which results in molecular and cellular damage [22]. High concentrations of ROS has been associated with age-related diseases progression via oxidative damage and interaction with mitochondria [13]. Oxidative stress is an important mechanism that has been identified as contributing factor pathogenesis of neurologic and psychiatric disorders [28]. Both preclinical and clinical studies suggest that a high level of cellular oxidative stress in the brain is associated with chronic physical or psychosocial stress [29]. Owing to the low antioxidant capacities of brain structures, the effects of oxidative stress are widespread and neurons are particularly vulnerable to this type of cellular stress induced by ROS production [30]. This type of cellular stress is characterized by an imbalance between the amount of ROS production and the capacity of antioxidant systems. Exact mechanisms of stress oxidative have connection with the onset and more recently been identified as a contributing factor in the progression of numerous psychiatric disorders [31].

A growing body of evidence been reported that highly vulnerable areas of brain to oxidative stress is linked with the corticolimbic structures such as the PFC, hippocampus, and amygdala [14,15], Furthermore, exposure to chronic restraint stress increases plasma levels of corticosterone, and then induces oxidative stress in the hippocampus and impaires spatial learning and memory [16]. Because of the widespread effects of oxidative stress and particularly low antioxidant capacities in the brain, neurons are attractive targets for oxidative damage induced by ROS excess [17].

Abundant evidence from preclinical and clinical studies suggests that increased cellular oxidative stress in the brain can be developed by prolonged physical or psychosocial stress Lucca. Therefore, oxidative stress has been implicated in the pathophysiology of several neurodegenerative disorders [32]. A critical role of oxidative stress in the development of age-related diseases including atherosclerosis, cardiovascular and neurodegenerative diseases, like AD, Parkinson, and psychiatric disorders such as depression is well documented [33]. Recent research echoes that oxidative stress also may play an important role in major depression as a mental disorder. Increasing levels of oxidative stress is directly associated with neurotransmitters imbalance observed in major depression. In other word, the pathophysiology of depression is strongly linked with oxidative stress products [18].

Additionally, stress-induced memory deficits is an outcome of activation HPA axis and altered neurotransmitters contents in the CNS which can lead to increase in the production of ROS, and subsequent brain oxidative damage [19].

Stress effects on cognition

Stress is a well-known adaptive response that threatens organism physiological or psychological homeostasis, resulting in psychic and behavioral changes alterations [20]. This environmental factor can exert a deteriorating effect on the functioning of an organism by its critical role in various diseases [17]. In addition, it is considered that behavioral alterations are common in stress-associated mental disorders [34].

Exposure to chronic stress results in learning and memory impairment, due to the susceptibility of brain regions involved in this process. The hippocampus, a primary structure for learning and memory, and also PFC are particularly susceptible to detrimental chronic stress effects. In other words, exposure to chronic stress results in impaired cognitive hippocampus-dependent functions [35]. For example, chronic stress

exacerbates the impairment in spatial memory as a consequence of lesions in the CA1 region of the hippocampus Broadbent [21]. As discussed earlier, the hippocampus is responsible for decreased learning and memory abilities following long-lasting exposure to stress. It is believed chronic stress is involved in the reduction of adult hippocampal neurogenesis, blocks LTP induction, down-regulates expression of neurotrophic factors, and exacerbates neuronal apoptosis in the hippocampus [36]. It has been reported that stress can affect cognitive performance and this association has also been extensively well reported in the literature [9].

Chronic stress can increase the risk of psychiatric disorders and stress-induced neuronal changes impair brain structures related to learning and memory [37]. It is clear from recent studies that prolonged stress can leave negatively impact on neural networks that affect cognitive function [38]. Also, stress-induced structural changes and neuronal damage in the hippocampus impair learning ability and memory function [22]. Chronic stress not only impaires brain functions such as synaptic plasticity, but also can heighten developing of cognitive deficits, especially for Alzheimer's disease outcomes following exposure to stress have been established [39,40] .

Stress effects on brain structures

Brain structures are vulnerable to stress induced alternations in function of medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), basolateral amygdala (BLA), and dorsal hippocampus (DHC). This changes are associated with mental disorders, working memory dysfunction, anhedonia Banasr, and anxiety-like behavior Bijlsma [41]. Data from literature proposed that chronic stress is linked with the pathogenesis of depression [42,43]. Sustained stimulation, caused by prolonged stressful events, disturbs the capacity to maintain homeostasis, resulting in psychopathological events. For instance, both neuronal ad morphological alterations are a well-established chronic stress resulting in the mPFC as recognized by apical dendritic retraction in pyramidal cells Radley [23]. Evidence also exists for stress-induced spine loss in the rodent mPFC Liu Radley. In contrast, chronic stress has also been shown to produces dendritic proliferation in BLA, and consistently leads to increased spine density in BLA. However, chronic stress can induce profound alternations in dendritic morphology and spine density in both PFC and hippocampus [9,44].

Environmental Enrichment

Environmental enrichment (EE) is a term referring to keeping the laboratory animals exposed to more physical and social stimuli than the standard condition [45]. Environmental enrichment can be divided into two types: physical and social forms [46]. In physical one, some structural changes are made including increasing the space in which the animal is kept (cage) and placing some tools of sport, play, exploration for the animal that provide the possibility of some controls in the environment [47]. Some of the tools used in this type of EE include a modified bed, plastic tunnels, wooden objects to chew, rope, running wheel, ball, ramp, ladder, and other similar toys. A socially enriched environment refers to keeping the animals in groups [46].

EE effects on biochemical factors

EE makes some changes in the expression of the genes which determine the neural structures of the cerebral cortex. At the molecular level, these positive changes result from the increased concentration of nerve growth factors of NGF, 3-NT, and BDNF neurotrophins [24]. EE also makes some changes in the activities of cholinergic neurons and the brain beta-adrenoceptor

system [48]. The ability of induction of long term potentiation (LTP) depends on NMDA glutamate channels. These glutamate channels play an important role in LTP induction. One of the cytoskeletal proteins which have a major role in the function of NMDA channels and binds them to the cell membrane is a scaffold protein named PSD-95. The other effect of EE is increasing proteins such as synaptophysin and PSD-95 in synapses [49]. EE has positive effects on neurogenesis and the increased neurogenesis caused by EE can be related to the increased vascular endothelial growth factor (VEGF) [50].

Chronic stress causes some changes in the hippocampus and hypothalamic pituitary adrenal (HPA) axis and suppresses neurogenesis in dentate gyrus neurons of the hippocampus. Long term increase of glucocorticoid (GC) hormones in the brain leads to damage and destruction of hippocampal neurons and consequently decreases the volume of the hippocampus. As a result, hippocampal atrophy caused by chronic stress and other destructive effects of stress can intensify the anxiety and depression symptoms [51]. It seems that EE decreases the destructive effects of stress on the brain and anxiety by affecting neurogenesis and improving the function of synapses. The cellular and molecular pathways through which EE can decrease the harmful effects of stress on the brain are not known yet. However, it is evident that under normal conditions, the hippocampus has an inhibitory effect on the production of corticotropin-releasing hormone (CRH) by paraventricular nucleus of the hypothalamus neurons. Hippocampal neuron damage caused by chronic stress and atrophy decreases this inhibitory effect and leads to the production of CRF and consequently, increased Adrenocorticotropic hormone and cortisol. Increased cortisol causes increased anxiety effects and damaging effects on the brain, and this vicious cycle will continue. Destruction of neurons and reduced hippocampal volume can justify the memory and learning disorders [25]. According to the studies, EE can decrease cortisol level, change the expression of neurotrophins in the brain and especially in the hippocampus, and increase neurogenesis [52]. EE alleviates stress-induced activation of the ERK-MAPK-CREB pathway and increases neuronal activity marker, including early growth response protein 1 (EGR-1), expression in the BLA [26]. These effects appear to be a support to the idea that EE blunts the amygdala response to stress, which would modulate pro-stress signals originated from the amygdala [26,27]. EE animals do not present these stress-related effects under baseline conditions [28]. Also, EE promotes release of other neurotrophins in the hippocampus as well, including VEGF, nerve growth factor (NGF), neurotrophin-3 (NT-3), IGF-1 and glial cell-derived neurotrophic factor (GDNF), under basal and stress conditions [29, 30]. As noted before, neurotrophins generally have a promoting role in neural survival and proliferation. BDNF and NGF specifically increase dendritic complexity, while VEGF increases angiogenesis and spinogenesis [31, 32, 33]. Therefore, contribution of these molecules are expected to be effective in the positive morphological alternations induced by EE in stress exposed animals [34].

EE-induced alterations of BDNF levels observed in both the prefrontal cortex hippocampus. EE stimulate BDNF expression in the prefrontal cortex under basal conditions, and alleviates stress-induced reduction in BDNF [35,36]. Protective effects are similar to those seen in the VEGF63 and IGF-1 [37] levels expression.

EE and oxidative stress markers

Because of the high sensitivity of brain tissue to oxidative stress, the imbalance of the oxidative state may hurt brain normal

function. The most common definition of oxidative stress is the disruption of the balance between oxidant and antioxidant factors. Under this condition, increased oxidant activity may cause disruption in the structural and functional activity of neurons and other brain cells. The previous studies demonstrated that due to cerebral hypoperfusion, increased free radicals and thiobarbituric acid reactive substances (TBARS) return back to normal range in the hippocampus of rats exposed to the EE. Exposure to EE before and after a 2-vessel occlusion model of cerebral hypoperfusion also has shown that alleviated cognitive impairment is associated with lipoperoxidation oxidative stress in the brain Cechetti. According to Ahmadalipour and colleagues [14], LTP abnormalities restored nearly to control in the dentate gyrus of rats which housing in EE condition before cerebral hypoperfusion induction. The study showed that the corticosterone level decreased in the serum of stressed rats, subjected to EE rather than the stressed control group. Stress condition induce the dendritic retraction of CA3 hippocampal pyramidal neurons [53].

Effect of EE on cognition

Several lines of evidence reported that living in an enriched condition is significantly effective in quality of life, cognition, and behavior. Putting new objects and various toys and running wheels in the rodents' cages makes the animals express the more seeking behaviors and physical activity for a longer period of time, and can be effective in the reduction of anxiety behaviors. On the other hand, a larger cage and housing with more roommates under EE increase social interactions and make the animals more exposed to social stimuli. Since sensory information is integrated into the hippocampus, an increase in sensory stimuli caused by EE can be a provocative agent for neurogenesis and maturation of other neurons and improve long-term potentiation (LTP) in hippocampal neurons. The offsprings of rats exposed to stress during pregnancy and kept in EE express less emotional responses in the face of difficult conditions. Also, they are more resistant against hormone-related stress harms and damages to cognitive functions caused by age growth [54].

Other studies have suggested that the mature rats that are kept in a standard environment and whose mothers have experienced different stresses during pregnancy express anxiety behaviors and tend to escape in the face of new situations; also, they have a high level of corticosterone secretion under stressful conditions. Whereas, the mature rats that are born of mothers exposed to different stresses during pregnancy but have grown in an enriched environment after birth express fewer anxiety behaviors and express an exploratory behavior in the face of new situations; they have less corticosterone secretion than EE group under stressful conditions. The rats kept in EE express more adjustability in the face of stressful conditions [55,56]. EE increases physical activity, the experience of learning, visual and somatosensory inputs, and social mutual effects [45]. It can increase neurogenesis and glycogenesis, cognition, and improvement of brain damages and neurodegeneration in rodents [57]. Astrocytes also respond to the enriched environment in a similar manner to the neurons [58]. Studies on animal models indicate that EE can reduce the harmful effects of psychological stress and mediate the adverse effects of stress and improve coping function [59].

EE effects on brain structures

The effects of EE on the morphology of the hippocampal neurons have been investigated in some related studies. In pregnant women

exposed to stress, EE prevents decreased dendritic spine density in their children which is caused by stress during pregnancy. The prevention of decreased dendritic spine density occurred accompanied by an increased function of spatial memory and also increased synaptophysin protein in the rats born to these mothers [60]. EE increases synaptic plasticity and intrinsic excitability in pyramidal neurons of the CA1 region of the hippocampus [6]. Transferring the rats from EE to the standard environment led to an increase of vulnerability, Corticotropin-releasing factor (CRF) mRNA levels, and cAMP response element-binding protein phosphorylation in the bed nucleus of the striaterminalis (BNST) [61].

Conclusion

Based on our current and previous findings, it can be concluded that chronic stress through reducing important neuronal growth factors and remodeling the limbic structures causes neuropsychiatric disorders. So, given the sensitivity of the animals to stress, environmental enrichment can be used as a non-pharmacological therapy to alleviate the harmful effects of stress. Findings from studies presented in this review could have important implications for the development of novel strategies for the treatment of stress-related disorders.

Conflicts of Interest

The authors state that they have no conflicts of interest to disclosure.

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