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Physical enrichment enhances memory function by regulating stress hormone and brain acetylcholinesterase activity in rats exposed to restraint stress

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ABSTRACT

To study the effects of stress on mental health activity is of great importance in neuropsychological studies as it may affect the lifelong performance related to brain and overall health and wellbeing of an individual. It is observed very often that exposure to stress during early life can alter the brain function which may reflect as cognitive disability. Impairment of memory is associated with increased oxidative stress which is due to enhanced production of free radicals that may lead to lipid peroxidation and disintegration of cell structure and functions. Exposure to enriched environment has shown to enhance spatial learning and memory, although the underlying mechanism covering the regulation of antioxidant capacity is limited. Here we investigated short and long term memory using Morris water maze before and after giving restraint stress procedure in rats exposed to social and physically enriched environment. Levels of malondialdehyde (MDA), activity of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and acetylcholinesterase (AChE) in brain tissue were estimated. Plasma corticosterone was also determined after decapitation. Results demonstrated that rats pre-exposed to physical along with social enrichment showed improved short and long term memory as compared to control group. However, restraint stress exerted differential effects in socially and physically enriched groups. Reduced lipid peroxidation and decreased activity of SOD, GPx and AChE were observed in physically enriched rats subjected to stress as compared to stressed rats kept in social environment. Levels of corticosterone were also found to be significantly reduced in rats kept in physically enriched environment. This study shows the beneficial effects of environmental enrichment on learning and spatial memory by reducing oxidative stress via reducing lipid peroxidation and regulation of antioxidant enzymes in rats.

1. Introduction

Early life events play an influential role on the mental health of an individual in adulthood. The early experiences that a person faced may alter the mental capability to cope with stressful situations throughout the life [1]. Living in a healthy and stimulated environment has shown to produce positive effects on brain function. It has been observed that the children that were developed in enriched conditions showed enhanced memory performance than the children who were raised in impoverished environment [2]. Non-enriched and non-stimulated environmental conditions may increase the vulnerability of brain abnormality in stressful situations [3]. Adverse events can enhance the responsiveness of stress which may lead to hyperactivity of hypothalamic-adrenal-pituitary (HPA)-axis. The stress-induced increased glucocorticoid levels has shown to mediate detrimental effects on brain functions via activating inflammatory responses which may lead to impaired learning and memory functions [4]. Abnormal levels of glucocorticoid have been implicated in the modulation of memory formation [5]. Glucocorticoids act by binding with high-affinity mineralocorticoid receptor (MR) and low-affinity glucocorticoid receptor (GR). These receptors control the activity of HPA-axis by negative feed mechanism. Increased activation of HPA-axis and reduced expression of MR have been found in mammals following the exposure of stress. Therefore, changes in these receptors are considered as more critical in regulating behavioral responses to stressors and may act as neural protective mechanism [6]. It has also been reported that expression of these receptors plays an important role to modify the behavioral responses. A high number of these receptors are present in hippocampus

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and prefrontal cortex making them sensitive for the deleterious effects of glucocorticoids [7]. Repeated exposure to stress leads to loss of inhibitory influence of MR and GR on HPA-axis which may lead to impaired learning and memory processes [8]. It has been hypothesized that experiencing an enriched environment from an early life may exhibit alterations of endocrine responses to stress leading to decreased adverse effects of stress in adulthood [9]. Rearing of animals in enriched stimulating environment from an early age has shown to produce long lasting effects on physiological, neurological and psychological wellbeing. Presence of physical stimulation along with social interaction have shown to reduce the severity of stress, wide-spreading addiction of various legal and illegal drugs and their related behavioral and biochemical deficits [10]. Environmental enrichment affects neuroplasticity processes such as neurogenesis through the production of neurotrophic growth factors. These processes induce greater synaptic responses such as increased number of extensions and branches of neuron [11]. Therefore, a healthy or stimulated environment may help to decrease the accelerated aging process due to stress and hence reduce the risk of senescence-associated memory loss [12].

Spatial memory associated with hippocampus is highly susceptible to the psychopathological condition of an individual [13]. Exposure to repeated stress interrupts in the formation of memory and thus adversely affects the performance during a particular learning task [14]. It has been observed that a chronic stress reduces the process of neurogenesis and potentiates inflammatory responses, oxidative stress and neuronal cell death leading to increased vulnerability of brain functions towards stress-related deficits. Exposure to stress leads to increased production of free radicals and aberrant activity of antioxidant enzymes [15]. Reactive oxygen species are usually generated by increased activity of mitochondrial enzymes and hyper-function of cytosolic NADPH oxidase under stressful situation [16]. It has also been reported that increased glucocorticoid levels induce increased production of NADPH oxidase-dependent reactive oxygen species in hippocampus leading to impaired learning and memory functions. Oxidative stress has been implicated in the development and progression of neurodegenerative diseases and aging [17]. Age-related memory loss and impaired brain functions are directly correlated with the production of free radicals and altered antioxidant enzyme activity in central nervous system [18]. Free radicals are neutralized by the activity of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) which are considered as a primary antioxidant defense system. It has also been reported that repeated stress causes increased lipid peroxidation and altered activity of antioxidant enzymes in hippocampus, prefrontal cortex and striatum which may lead to anomalous oxidation of biomolecules and early neuronal cell death [19–21].

The role of reduced cholinergic function has been widely implicated in memory loss following the stress exposure [21]. Repeated stress exposure reduces the negative feedback control of HPA-axis resulting in abnormally high levels of glucocorticoids. The interaction of glucocorticoid with cholinergic neurons in hippocampus has been suggested to have modulatory effect on memory formation [22]. The hyperactivity activity of HPA-axis and resulting oxidative stress has been hypothesized to induce increased degradation of cholinergic neurons leading to impaired memory processes [23]. Repeated stress exposure, via stress hormone, has also been associated with hippocampal damage and cognitive decline. Cholinergic loss in response to stress and hypersecretion of glucocorticoid has been reported previously [24]. Moreover, studies regarding age-related cognitive decline have suggested the role of increased glucocorticoid and cholinergic dysfunction. Impaired spatial learning and memory is one of the prominent behavioral deficit produced by stress-induced enhanced oxidative stress [25,26]. Whereas exposure to environmental enrichment on the other hand has been implicated in the enhancement of spatial learning and memory [27]. In light of above literature, the present study was designed to establish the role of enriched environment in repeated stress-induced memory loss and oxidative stress. Previously, effect of enriched environment on acute stress-induced alteration of glucocorticoid levels was investigated [28]. However, the role of enriched environment to cope with repeated stress and its relation with stress hormone and acetylcholinesterase (AChE) has not been investigated. Therefore, the study was further intended to evaluate the association of elevated levels of stress hormone and cholinergic function in different environmental conditions.

2. Material and methods

2.1. Animals

Locally bred adolescent male albino Wistar rats weighing about 200 g having the age of 4–5 mo, experimentally naive at the start of the study, were housed in a temperature and humidity controlled room and maintained on a 12 h light/dark cycle. Rats were given standard laboratory diet and water ad libitum, throughout the experimental protocol. All experiments were carried out in a balanced design to avoid influence of order and time. The experimental procedures were approved by the institutional ethics and animal care committee and performed in strict accordance with National Institute of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

2.2. Housing conditions

After habituation to the laboratory environment, rats were divided into four groups as Control, Stress, Enriched Environment (EE) and EE + Stress (n = 6 per group). All the rats were housed socially as a group of three rats per cage. Control and Stress groups were placed in standard cages (59 × 38 × 20 cm), while EE and EE + Stress groups were kept in enriched cages having the dimensions of 120 × 100 × 60 cm. Previous findings have suggested that duration of exposure plays an important role for the effectiveness of environmental enrichment. Bennett et al., [29] compared different durations of exposure of enrichment on memory function and they found more significant effects of continuous exposure rather than temporary or partial environmental enrichment. Therefore, in this study rats were kept in their respective environment for 24 h in order to provide continuous exposure to enriched environment. The physically enriched rats were provided with enrichment within the cage in the form of small sheltered house, four colorful toys, PVC pipe tunnels, and a running wheel. Toys were weekly replaced by other type of toys, whereas, remaining inanimate form of enrichment was kept constant till entire phase of study [30].

2.3. Restraint stress procedure

Animal model of restraint stress for one week has been used earlier to study the detrimental effects of stress exposure [30,31]. Hence, in this study Stress and EE + Stress groups were subjected to 2 h/day restraint stress for seven consecutive days in ventilated closed plastic tubes that allowed only mild lateral movements. The stress treatment was given after four weeks of pre-exposure to social or physically enriched environment.

2.4. Behavioral assessment of memory

Assessment of short term memory (STM) and long term memory (LTM) was performed by Morris water maze (MWM) task [32] before and after restraint stress procedure. The apparatus consisted of an open tank with diameters of 97 cm which was filled with water and made opaque with adding milk. A hidden opaque platform was placed at the end of tank. The experimental procedure consisted of three phases including training session, STM and LTM retention. During training session rats were allowed to swim inside the tank and locate the hidden