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RESEARCH ARTICLE

EFFECTS OF STRESS INDUCED CHRONIC DEPRESSION AND ANTIDEPRESSANT DRUGS ON CA4 REGION OF HIPPOCAMPUS IN ADULT ALBINO RATS

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ABSTRACT

1.By the middle of the last century the hippocampal formation started to be one of the most studied structures of the nervous system. The present study was conducted using 45 albino rats of either sex (150-200 gm) and divided into 3 equal groups. First group was control and received water and food ad-libitum, second group was experimental receiving chronic depression for 7 weeks by immobilization method, the third group received Flouxetine drug (1mg/kg body weight orally) for 4 weeks following chronic depression. The animals were sacrificed after the experiment, perfused with 10% formaldehyde, brains were dissected and tissue blocks were processed for paraffin embedding. Observations were made on 5 micron thick H and E stained sections. Estimation of neuronal density of CA4 regions was performed using Motic images plus 2.0 software. Neuronal density was markedly reduced (85.4 cells/cubic mm) in experimental group, as compared to control (110.5 cells/cubic mm). Neuronal density was enhanced to 144.3 cells /cubic mm in Treatment Group. Statistical analysis was done using students t-test and the significance was assessed. It was found that stress induced depression causes significant neuronal loss in CA4 region that can be significantly reversed by the pharmacological intervention.

INTRODUCTION

The Hippocampus is a part of limbic system and hippocampal formation, which also includes the Dentate Gyrus, Subiculum, and Entorhinal cortex. Extensive evidence implicates the hippocampus and related structures in the formation of episodic memories in humans [1] and in consolidating information into long-term declarative memory [2]. Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and physical well-being [3]. Dysthymia is a state of chronic depressed mood and is also a feature of borderline personality disorder. Loss of hippocampal neurons is found in some depressed individuals and correlates with impaired memory and dysthymic mood. MRI scans of patients with depression have revealed a number of differences in brain structure compared to those who are not depressed, meta-analyses have shown that there is evidence in favor of smaller hippocampal volume [4] and increased numbers of hyper intensive lesions [5]. There may be a link between depression and neurogenesis of the hippocampus [6]. Drugs may increase serotonin levels in the brain, stimulating neurogenesis and thus increasing the total mass of the hippocampus [7]. Brain derived neurotrophic factor (BDNF) is drastically reduced (more than threefold) in depressed individuals as compared to the normal. Antidepressant treatment increases the blood level of BDNF. It is involved in both the causation of depression and the mechanism of action of antidepressants [8].

MATERIALS AND METHODS

Animal model

After taking approval from Institutional Animal ethical committee which strictly follows international guidelines on the ethical use of animals. 45 adult albino rats of either sex 150-200 gm were maintained at 21ºC and given access to food and water ad libitum. Animals were randomly assigned into 3 equal groups:

Control Group (CG)
Depressed Group (DG)
Treatment Group (TG)

The cage was small, made up of steel wire, measuring 9''x 2.75'', it was an indigenous one which was designed to suit the experiment as described and depicted previously [9]. It was framed to provide adequate immobilization without giving any physical harm to the animal. It is of light weight and easy to carry, with no maintenance cost.

Experimental Procedure

Before the experiment animals were handled manually for one week to remove handling stress. The CG group received food and water. The DG group were immobilized by the rat immobilizer 3 times (30 minute each) a day for 7 weeks. The experiment was conducted between 10-11 am. The TG group received Fluoxetine 1mg/kg body weight once a day for 4 weeks after being immobilized for 7 weeks. Animals were anaesthetized by diethyl ether, and perfused intracardially with 10% formaldehyde. Brains were removed and hippocampus was dissected. Tissues processed with alcohol, xylene, and paraffin embedding was done. Blocks were made and 5 micron thin sections of identical regions were taken of different groups. Observations were made under 40x resolution by compound microscope after HandE staining. CA4 region was identified in the hilum of dentate gyrus and Neuronal density was compared in different groups using Motic 2.0 software. Statistical analysis was done using Student's T test.

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Observations

Behavioural

General activity of the rat was markedly reduced. And the struggle duration was also affected following prolonged immobilization for 7 weeks. Female rats were more active as compared to male rats following immobilization procedure.

Microscopic

CA4 region was identified in the hilum of dentate gyrus. The observations were made at 40x. The neuronal density was markedly reduced in DG and increased in TG as shown in Figure-1. Neuronal density per unit area was calculated and compared as shown in Table-1.

Table 1. Showing neuronal density of different groups Comparison of neuronal density in the CA4 region of different groups (cells/mm^2± S. E.)

Group	Ctrl	Ch.Dp	Ch.Tt
Neuronal Density	110.5 ± 4.6	85.4 ± 3.1	144.3 ± 9.6

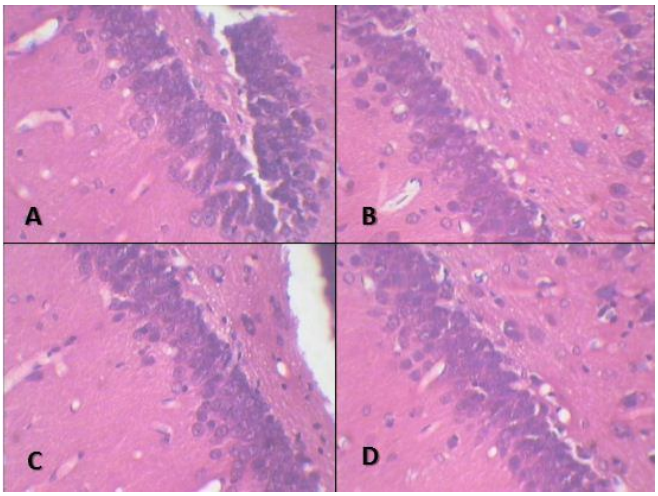

Figure 1. Sample photomicrographs Dentate Gyrus (A), of Control group (B) after Chronic Depression (C), and after Chronic Depression treatment (D). x 400, Hand E stain

DISCUSSION

This study showed fall in neuronal density in the selected area of hippocampus after immobilization stress leading to chronic depression, whereas antidepressants showed positive effects on the neuronal density of the selected area and causes significant increase in the neuronal density. Results of different research conducted over the past two decades in rats, monkeys, and humans indicate that the hippocampus is particularly susceptible to neuronal degeneration during normal aging [10]. Neuronal loss might be responsible for deficits in hippocampal-dependent learning and memory associated with advanced age [11]. Hippocampal neuron loss is widely viewed as a hallmark of normal aging. Many studies have shown that hippocampal volume decreases after depression [12], which can be reflected in the fall of neuronal densities as shown by the present study. By taking advantage of improved methods for quantifying neuron number, the present study assessed the changes in the neuronal density due to depression and treatment by antidepressants. Chronic stress has been shown to lead to degenerative changes affecting the apical dendrites of pyramidal neurons in field CA3 in rats, tree shrews, and monkeys [13]. Prolonged immobilization stress also leads to decreases in the number of neurons in hippocampal field CA3 in castrated rats [14]. As in present study chronic stress leads to highly significant fall in neuronal density. Fall in neuronal density and behavior changes finds support [15] suggesting that this neuronal loss may be responsible for memory impairment. However, studies reported by other investigators [16] does not support these results, and the question remains unresolved [17]. According to one study there is no convincing data demonstrating that stress has a neurotoxic action on the nervous system [18]. To conclude further research is needed to know the molecular mechanism and factors affecting neurogenesis/degeneration.

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