Available online at http://www.journalijdr.com

ISSN: 2230-9926

IJDR

International Journal of
DEVELOPMENT RESEARCH

International Journal of Development Research
Vol. 3, Issue, 05, pp.027-029, May, 2013

Full Length Research Article

EFFECTS OF STRESS INDUCED CHRONIC DEPRESSION AND ANTIDEPRESSANT DRUGS ON DENTATE GYRUS OF HIPPOCAMPUS IN ADULT ALBINO RATS

[1,*]Nazim Nasir and [2]Nidhi Sharma

[1]Department of Applied Medical Sciences, College of Applied Medical Sciences, KKU, Abha, KSA
[2]Department of Anatomy, Teerthankar Mahaveer Medical College, TMU, Moradabad, India

ARTICLE INFO

Article History:

Received 29th January, 2012
Received in revised form
12th March, 2013
Accepted 24th April, 2013
Published online 13th May, 2013

Key words:
Dentate gyrus,
Hippocampus,
Depression,
Fluoxetine,
Antidepressants.

ABSTRACT

The pilot study is conducted using 30 adult albino rats (150-200 gm). They were divided into one control and two experimental groups of equal numbers. Group 1 is Control (Ctrl), Group 2 is Chronic Depression (Ch.Dp) and Group 3 is Treatment Group (Ch.Tt) following Chronic Depression. Ctrl Group received food and water ad-libitum, Ch.Dp Group received Chronic Depression by immobilization method in a Rat Immobilizer for 7 weeks, whereas Ch.Tt Group received anti-depressant drug (Flouxetine 1mg/kg body weight orally) for 4 weeks following depression. All the rats were sacrificed after the experiment. They were perfused using formaldehyde, brains were dissected out and tissue blocks were made by paraffin embedding. Hippocampus was located in the groups (following H and E Staining) and identical areas were compared for neuronal density. Neuronal density was calculated in Dentate Gyrus using Motic images plus 2.0 Software. Neuronal density of control was 110.5 cells/cubic mm which was markedly reduced to 85.4 cells/cubic mm after chronic depression. Neuronal density was enhanced to 144.3 cells /cubic mm in Ch.Tt 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 Dentate Gyrus that can be significantly reversed by the pharmacological intervention.

INTRODUCTION

The hippocampus belongs to the limbic system and plays important role in the transformation of information, control and mediation of memory, emotion, learning, dreaming, attention, and arousal, and the perception and expression of emotional, motivational, sexual, and social behavior including the formation of loving attachments. It also plays a important role in spatial navigation. It contains two main interlocking parts: Ammon's horn and the Dentate Gyrus. Damage to the hippocampus can result from oxygen starvation (hypoxia), encephalitis, or medial temporal lobe epilepsy. In rodents, the hippocampus has been studied extensively as part of a brain system responsible for spatial memory and navigation. In humans, memory for words, passages, conversations, and written material is also significantly impacted, particularly with left hippocampal destruction (Frisk and Milner 1990). Newborn neurons are detected in the dentate gyrus of the hippocampus (Altman and Das 1965) and olfactory bulb (Pencea *et al*., 2001) of adult mammals, including monkeys (Gould *et al*., 1999). Hippocampal cells greatly alter their activity in response to certain spatial correlates, particularly as an animal moves about in its environment (Wilson and McNaughton 1994). Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and physical well-being. Depressed people may feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, or problems of concentrating, remembering details or making decisions; and may contemplate or attempt suicide. Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains or digestive problems that are resistant to treatment may be present. Dysthymia is a state of chronic depressed mood, the symptoms of which do not meet the severity of a major depressive episode. Dysthymia is also commonly a feature of borderline personality disorder. Loss of hippocampal neurons is found in some depressed individuals and correlates with impaired memory and dysthymic mood. Drugs may increase serotonin levels in the brain, stimulating neurogenesis and thus increasing the total mass of the hippocampus. This increase may help to restore mood and memory.

MATERIALS AND METHODS

Animal model: 30 adult albino rats 150-200 gm were maintained on a 12 h/ 12 h light/dark cycle at 22ºC and

Corresponding author: sahil9792003@gmail.com

given access to food and water ad libitum. All animal experiments were approved by the Institutional Animal ethical committee and were conformed to international guidelines on the ethical use of animals. Animals were randomly assigned into 3 equal groups of 10 animals each:

- Control Group (Ctrl)
- Depressed Group (Ch.Dp)
- Treatment Group (Ch.Tt)

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 (Nasir and Khan 2011). 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

The animals were handled manually for one week before the experiment to remove handling stress. The Ctrl group received food and water ad-libitum. The Ch.Dp group received immobilization 30 min per turn 3 times a day for 7 weeks. The experiment was conducted between 10-11 am to minimize diurnal variation/ circadian rhythm. The Ch.Tt group received Flouxetine 1mg/kg body weight once a day for 4 weeks for Ch.Dp group. Animals were sacrificed following anesthesia by diethyl ether, and perfused with 10% formaldehyde. Brains were dissected out and hippocampus was identified. Tissues were processed by different dilutions of alcohol, xylene, and paraffin embedding was done. Blocks were made and 5 micron thin sections were made of identical regions of different groups. H and E staining was done and observed under 40x resolution under compound microscope. Neuronal density was compared of dentate gyrus in different groups using Motic 2.0 software. Student's T test was applied and groups were compared to assess the significance.

Observations

Behavioural

The rats became sluggish when released from the cage. At the start of the experiment rat tried to bite the cage for a longer duration, noted as struggle time which reduces with repeated immobilization. It reflects rat's adaptation towards the external environment. In total, general activity was reduced markedly in depressed rats.

Microscopic

The Dentate Gyrus is located as interlocked with Ammon's Horn (Cornu Ammonis) also called as CA region. There as total 4 CA regions (CA1, CA2, CA3, CA4), whereas CA4 starts from hilum of Dentate Gyrus. The observations at 40x revealed reduced neuronal density in Ch.Dp and increased neuronal density in Ch.Tt as shown in figure-1. Quantitative estimate of neuronal density per unit area as compared to control group (Ctrl) the chronic depression (Ch.Dp) and the treatment group (Ch.Tt) showed significant changes in neuronal density (Table 1). Depression reduces neuronal density whereas treatment increases neuronal density. the observations conclude that depression affects Dentate Gyrus in the form of reduction in neuronal density which is somehow reversed by treatment with antidepressant drugs.

Table 1. Showing neuronal density of different groups

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

Comparison of neuronal density in the Dentate Gyrus of different groups (cells/mm^2 ± S. E.)

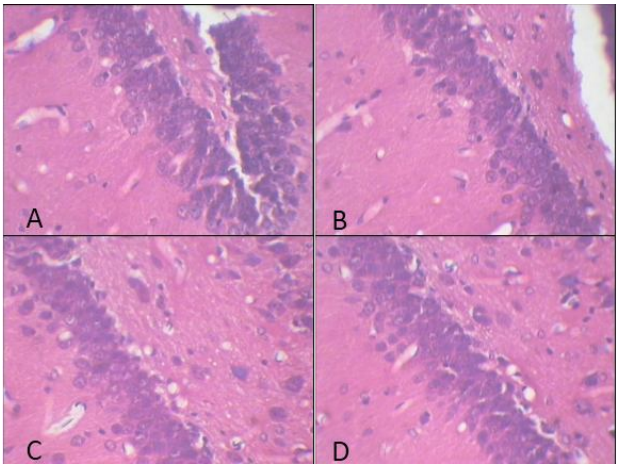

Figure 1. Sample photomicrographs Dentate Gyrus (A), of Control group (B) after Chronic Depression (C), and after Chronic depression treatment (D). x400, Hand E stain.

DISCUSSION

The present study was conducted to know the long term effects of depression over Dentate Gyrus of hippocampus and its response to standard treatment by Flouxetine. The study found that depression has an organic basis and is due to loss of neurons in the hippocampal region. Study also found that this loss was somewhat reversed by the use of antidepressant drug. The supportive researches shows the neuropil which is responsible for neuronal growth is down-regulated in depression, also there is loss of hippocampal volume during depression (Czéh et al., 2001). It was studied that chronic stress leads to degenerative changes and affects apical dendrites of pyramidal neurons in field CA3 in rats, tree shrews, and monkeys (McEwen and Magarinos 1997). As in present study chronic stress leads to highly significant fall in neuronal density. Fall in neuronal density and behavior changes are supported by (Kim and Diamond 2002; Calvo *et al*., 1998) which suggests that this neuronal loss may lead to memory impairment.

However, few studies do not support our results (Volmann-Honsdorf 1997), and the question remains unresolved (Bremner 2001). Neurogenesis in the adult hippocampus is restricted to the sub granular zone, and newborn neurons appear to migrate only as far as the nearby dentate granule layer. According to one study says that stress has no neurotoxic action on the nervous system (Bremner 2001). The vast majority of antidepressants in clinical use work by increasing the synaptic availability of monoamine neurotransmitters. Flouxetine increases serotonin and to nicely commensurate with the involvement of serotonin, there is some evidence that increased serotonin availability can stimulate cell proliferation in the hippocampus (Brezun and Daszuta 2000; Brezun and Daszuta 1999). To conclude further research is needed to know the molecular mechanism and factors affecting neurogenesis/degeneration.

REFRENCES

Altman J.; Das, G. D. "Post-natal origin of microneu-rones in the rat brain". Nature. 1965; 207: 953-956.

Bremner JD. “Hypotheses and controversies related to effects of stress on hippocampus: an argument for stress-induced damage of the hippocampus in patient with posttraumatic stress disorder.” Hippocampus. 2001; 11:121–124.

Brezun J and Daszuta Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricu-lar zone of adult rats A. Neurosci.1999; 89:999–1002.

Brezun JM and Daszuta A. Serotonin may stimulate gra-nule cell proliferation in the adult hippocampus, as Neural Precursors in Adult Hippocampus 259 observed in rats grafted with foetal raphe neurons. Eur J Neuro-sci. 2000b; 12: 391–396.

Calvo N, Martijena ID, Molina VA and Volosin M. Me-tyrapone pretreatment prevents the behavioral and neu-rochemical sequelae induced by stress. Brain Res. 1998; 800:227–235.

Czéh B, Michaelis T, Watanabe T, Frahm J, de Biurrun G, van Kampen M, Bartolomucci A, Fuchs E. Proc Natl Acad Sci USA. 2001; 98:12796–12801.

Frisk V. and Milner B. The role of the left hippocampal region in the acquisition and retention of story content. Neuropsychologia. 1990; 28, 349 –359.

Gould E, Reeves AJ, Fallah M, Tanapat P, Gross CG, Fuchs E. Hippocampal neurogenesis in adult Old World primates. Proc Natl Acad Sci USA. 1999; 96:5263–5267.

Kim JJ, Diamond DM .The stressed hippocampus, syn-aptic plasticity and lost memories. Nat Rev Neurosci. 2002; 3:453–462.

McEwen BS and Magarinos AM. “Stress effects on morphology and function of the hippocampus,” Ann. N.Y. Acad. Sci. 1997; 821:271–274.

Nasir N and Khan AA. Effects of Stress-induced Acute Depression and Antidepressant Drugs on CA3 Region of Hippocampus of Albino Rats. Current Neurobiol. 2011; 2: 31-34.

Pencea V, Bingaman KD, Freedman LJ, Luskin MB. Neurogenesis in the sub ventricular zone and rostral migratory stream of the neonatal and adult primate forebrain. Exp Neurol. 2001; 172: 1-16.

Volmann-Honsdorf GK, Flugge G and Fuchs E. “Chron-ic psychosocial stress does not affect the number of py-ramidal neurons in tree shrew hippocampus,” Neurosci. Lett.1997; 233:121–124.

Wilson MA and McNaughton BL. Dynamics of the hip-pocampal ensemble code for space. Science [Erratum] 1994; 261: 1055–1058.

****