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A Pharmacological Study to Explore Anti stress Potential of Statins

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Abstract

Objective: A pharmacological study to explore Anti stress Potential of Simvastatins in stress produced models of mice.

Method and Materials: Either sex of Wistar rats were used for studying the activity of statins (simvastatin) in stress condition and their activity in brain. Animals were divided into five groups and each groups having six animals. Freshly prepared alloxan (80 mg/kg) i.p. were given to fourth and fifth group to produced oxidative stress. first group received normal saline, second group received standard drug Piracetum (500 mg/kg) orally, third group received test drug simvastatin (50 mg/kg) orally and also fifth group received simvastatin (50 mg/kg) orally after treatment with alloxan (80 mg/kg.) and by using certain test like Marble burying and coock's pole climbing we find out the effect of our drugs in different groups of animals.

Result: With the help of investigation of biochemical parameters of different groups of animals we found out that simvavastatin showed significantly lowering the oxidative stress and enhancing the memory of rats. Evaluation of group second (standard group) were approximately same as groups third (treated by simvavastatin). And group fifth suppressed the oxidative stress induced by the alloxan.

Conclusion: Simvastatin significantly suppressed the oxidative stress and helpful in enhancing the memory.

Keywords: Oxidative stress, Simvasatin, Marble burying.

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INTRODUCTION

The word 'stress' is defined as "a state of affair involving demand on physical or mental energy." Stress is a condition which can disturb the normal physiological and psychological functions of an individual.

In medical parlance 'stress' is defined as a perturbation of the body's homeostasis. This demand on mind-body occurs when it tries to cope with incessant changes in life. Extreme stress_conditions, psychologists say, are detrimental to human health but in moderation stress is normal and, in many cases, proves useful. Stress, nonetheless, is synonymous with negative conditions.[1]

During stressful situations the energy requirement of the organism is increased resulting in enhance generation of free radicals that causes oxidation of nucleic acid and proteins. Free radical also damage biomembrane, reflected by increased lipid peroxidation, thereby compromising cell integrity and function. During this process, the ability of the body's defense system to combat the oxidative stress may diminish due to reduced antioxidants.[2] Stress also increases brain serotonin (5-HT) level. The ascending 5-HT neurons from raphe nuclei innervates hypothalamic and limbic sites and have an overall role in regulating secretions of Adrenocorticotropic hormone (ACTH) during stress.[3] Stress triggers a wide ranging set of bodily changes called the stress response or General Adaptation Syndrome (GAS). Hans Selye a pioneer in stress research introduced the concept of the GAS. Any stimulus that produces a stress is called a stressor. A stressor may be almost any disturbance – heat or cold, environmental poisons, toxins given off by bacteria during a raging infection, heavy bleeding from a wound or surgery, or a strong emotional reaction. When a stressor appears it stimulates the hypothalamus to initiate the GAS through two pathways. The first pathway produces an immediate set of responses called the alarm reaction. The second pathway called the resistance reaction is slower to start but its effects last longer.

MATERIALS AND METHODS

Materials

Statins and Piracetum were purchased from the local market of Mandsaur M.P.

Procurement and selection of animals

Male Albino mice weighing between 22-30 g of weight were obtained from B.R.N.C.P. Mandsaur Animal House. The animals were stabilized for 1 week; they were maintained in standard condition at room temp; 60 ± 5% relative humidity and 12 h light dark cycle. They had free access to food and water. Animals were acclimatized to laboratory conditions before the experiment. All the experiments were carried out between 09:00 and 15:00 h. The experimental protocols were approved by Institutional Animal Ethics Committee of B. R. Nahata College of Pharmacy, Mandsaur, (M.P.).[5]

Drugs and Treatment

According to literature survey Statins are given orally (50mg/kg) and alloxan dissolved in normal saline (80 mg/kg) and given intra peritoneal routes and Piracetum given at a dose of 500mg/kg p.o.[6]

Experimental Procedure- Mice were divided into five groups and each group having six animals and animals will be divided into following groups. Group-1: Normal control, received normal saline daily, Group-2: Standard group received Piracetum (500mg/kg p.o.),Group-3: Drug treated group (simvastatin) 50mg/kg by oral route, Group-4: Stress group, received Alloxan (80 mg/kg) i.p. and Group-5: Stress treated group, received Statin (50 mg/kg, orally) daily up to fourteen day.[7]

Induction of oxidative stress- Oxidative stress are produced by induction of freshly prepared alloxan monohydrate (80 mg/kg dissolve in sodium acetate buffer pH 4.5) i.p. to fourth and fifth group.[8]

Methods

Behavior Study: Marble Burying test and cook's pool climbing method.

Marble burying test: The test of burying behavior was performed in the animal housing room. Each rat were place singly into an acrylic cage (25_ 41_ 19 cm) with a bedding of 5 cm of fine sawdust (Altromin WH 3-4). There, it was kept for a 1-day habituation period. Then, four glass marbles (3.5 cm in diameter) were place in a row next to one of the 25 cm walls of the cage. The statuses of the marbles were monitored and time course of burying. During the first hour, measures were take every 15 min; thereafter, they were taken every hour.[9]

cook's pool climbing method: Cook's Pole climbing Response Apparatus served as the exteroceptive behavioral model to evaluate memory in rats. Conditioned avoidance response (C.A.R.) was taken as a parameter to evaluate memory in rats as described by Cook and Weidley (1957). We were used Dolphin company apparatus. It was completely digital design. The chamber for the animals is fabricated from clear Perspex sheet. The bottom of the chamber was fitted with chrome platted brass bars to make a grill. The apparatus was also equipped with light and sound for stimulating the animals. A shock can be applied to the animals through brass bars. The shock strength was 400V, 5Hz and 0.2 mA. This was built in the apparatus. One can apply the shock to the animals either manually

or up to the control set duration. Both the option was available on the front of the apparatus.[10]

Statistical Analysis

The statistical analysis were done using GraphPad Prism software demo version 5 and result will expressed in mean ± SEM and data were compaired by one way ANOVA followed by Dunnett's test and $p < 0.05$ considered as significant , $p < 0.01$very significant and $p< 0.001$ is considered as highly significant.[11]

RESULTS AND DISCUSSION

Biochemical Investigation

Estimation of CAT, SOD, GSH, LP level on rats brain.

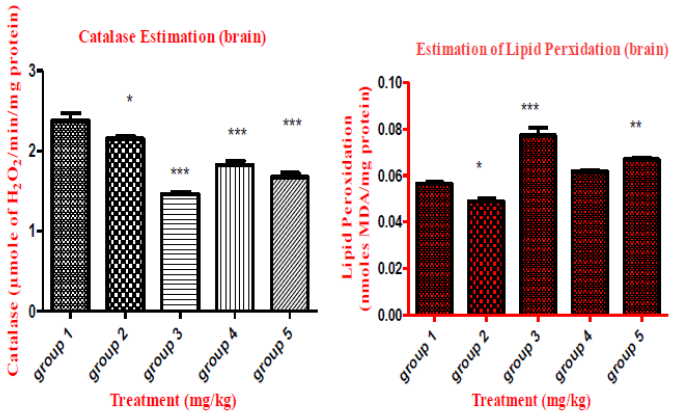

Fig 1:Effect of Statin (50 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on the Catalase & Lipid Peroxidation. *Significant P < 0.05, ** Very Significant P < 0.005, * Highly Significant P < 0.0001 as compared to that of Control group rats.**

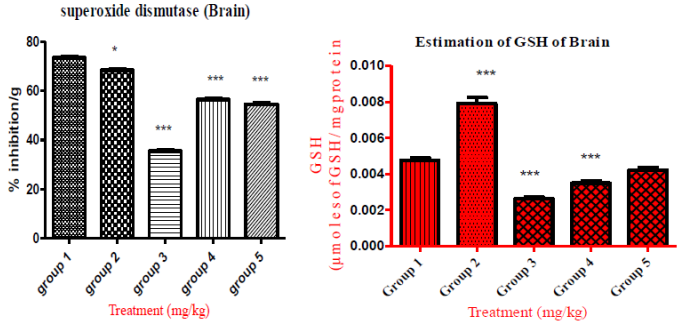

Fig 2: Effect of Statin (50 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on the SOD & GSH. *Significant P < 0.05, ** Very Significant P < 0.005, * Highly Significant P < 0.0001 as compared to that of Control group rats.**

Stress is known to induce alterations in various physiological and psychological responses even leading to pathological diseases. The stress induced effects are supposed to be an outcome of altered activity of different mechanisms such as Central neurotransmitter, Neurohormonal factors, particularly those linked with the pituitary-adrenal axis and free radical generation. Exposure to stress caused significant behavior and biochemical changes. Chronic immobilization stress is the most widely used method for assessing the antistress property of a novel compound. Stress may also cause oxidative stress and the formation of free radicals. Oxidative stress can cause cellular damage and neurodegeneration by inducing the reactive oxygen species (ROS) that oxidizes vital cellular components such as lipids, proteins and DNA. Stressed animals showed an early fall-off from the Rota-rod, increased anxiety response in mirror chamber, increased locomotor activity in actophotometer, hyperalgesic response and cognitive dysfunction with altered concentration and memory. Memory may be looked upon as an ability to remember past events. It is a complex process involving various parts of the brain, several neurotransmitters (GABA, ACh, E, NE, Glutamate etc.) and sensory organs.[12] Psychologists define memory as a capacity to retain information and later retrieve this information for day to day activities. Memory is comprised of following components: perception (sensation), registration, consolidation, storage, retrieval (recall) and decay.[13] It is observed that the process of decay of information or forgetting is a continuously active process and well learnt information is totally forgotten, if a conscious effort is not made to retain it e.g. we do not remember the poems and theorems, we had well crammed and rehearsed during our school days. Different parts of the brain contribute to different types of sensory (such as visual, olfactory etc) stimuli and different kinds of brain damage produce different types of amnesia (memory lose).[14] Hippocampus plays an important role in storing information and hippocampal damage results in serious learning as well as memory deficits .There are several types of memory such as sensory memory, short term memory, working memory, intermediate long term memory and long term memory. Long term memory is further sub classified into implicit (skill or procedural) memory and explicit (declarative) memory.[15] Explicit memory in turn can be further divided into semantic memory, episodic memory and photographic memory.[16] Oxidative stress and tissue damage are common phenomena linked to exposure to toxic agents and occurring in several diseases, including diabetes.[17] In our study the significant finding is that statin prevented the oxidative stress which is produced by the administration of alloxan and cause diabetes in our animals (rats). Alloxan administration produced a marked oxidative impact, as evidenced by the significant rise of lipid peroxidation products (TBARS) and the significant decline of endogenous antioxidants, including GSH content, and SOD and CAT activities, in the liver and brain.[18] The decrease in GSH level in both the liver and brain of alloxan-treated rats might be attributed to the inhibition of its regenerating enzyme glutathione reductase (GSHR), regression of the antioxidant recycling mechanism in diabetic and the direct reaction between GSH and ROS generated by alloxan .Additionally, tissue containing reduced SOD and CAT activities might have enhanced superoxide radicals and hydrogen peroxide which could

potentially inhibit GSH-R activity and consequently decreased GSH in the liver and brain.

Simvastatin reduces Rac-1 translocation and oxidative stress in endothelial cells exposed to high glucose and also Atorvastatin blunts vascular Rac-1 activity and oxidative stress in diabetes mellitus.[19] our experimental evidence further supports the concept that restriction of vascular oxidative stress is a fundamental goal in the treatment of diabetes mellitus.

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