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RESEARCH ARTICLE

Evaluations of Statins in Stress Conditions and Their Activity in Brain

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ABSTRACT

Objective: To study the activity of Statins in stress condition and their activity in brain.

Materials and Method: Wistar rats of either sex were used for studying the activity of statins (Atorvastatins) in stress condition and their activity in brain. Animals were divided into five groups and each groups having six animals. Freshly prepared alloxan (100 mg/kg) i.p. was 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 Atorvastatin (30 mg/kg) orally and also fifth group received atorvastatin (30 mg/kg) orally after treatment with alloxan (100 mg/kg.) and by using certain test like Marble burying and cook'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 atorvastatin 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 atorvastatin), and group fifth suppressed the oxidative stress induced by the alloxan.

Conclusion: Atorvastatin significantly suppressed the oxidative stress and was found helpful in enhancing the memory.

Keywords: Oxidative stress, Atorvastatin, Marble burying**,** oxidative stress

1. INTRODUCTION

Oxidative stress indicates the intracellular accumulation of reactive oxygen species and nitrogen compounds, mainly the so called reactive oxygen species (ROS). The major ROS variants are hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), superoxide ($\cdot O_2^+$), hydroxyl (OH), peroxyl (RO_2^+) and hydroperoxyl (HO_2^+) in mitochondrial respiration, ROS are generated in the electron chain, as a byproduct in the ATP generating process. This occurs in situation of enhanced oxidation of energy substract such as glucose and FFA, unless uncoupling compensates and prevents ROS formation. The enzyme NAD (P) H oxidase play a key role to stimulate ROS formation and it can be activated by various cytokines. [1] The mitochondrial mechanism involves increased levels of electron donors, mainly $FADH_2$ and NADH that are generated by the tricarboxylic acid cycle, and they will push electron into the protein complexes of mitochondria respiration chain .This will lead to electron pilling up in the mitochondrial electron transport chain, and eventually they will be donated to molecular oxygen generating superoxide, that subsequently can be degraded into hydrogen peroxide by magnese superoxide dismutase. [2] Interestingly, excessive amount of the ubiquitous biological messenger nitrogen oxide (NO) appear to have detrimental effects that are similar to those of ROS. Hyperglycemia- induced oxidative stress is likely to be of great importance in diabetes, particularly in patients whose glucose levels are poorly controlled. Importantly, further support is provided by a study showing that hyperglycemia- induced insulin resistance can be prevented by antioxidant treatment. The postprandial glucose peaks in type 2 diabetes, have a particular propensity to increase ROS formation in the vessel walls. This can be major importance for the development of micro- and macro vascular diabetes. [3, 4]

2. MATERIALS AND METHODS:

Materials

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Procurement of drug

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

Procurement and selection of animals

Male wistar rats weighing between 180-200 gm were obtained from B.R.Nanata College of pharmacy Mandsaur Animal House. The animals were stabilized for 1 week; they were maintained in standard condition. 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 (30mg/kg) and alloxan dissolved in normal saline (100 mg/kg) and given intra peritoneal routes and Piracetum given at a dose of 500mg/kg p.o. [6]

Experimental Procedure-

Rats were divided into five groups and each group having six animals and animals were 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 (Atorvastatin) 30mg/kg by oral route, Group-4: Stress group, received Alloxan (100 mg/kg) i.p. and Group-5: Stress treated group, received Statin (30 mg/kg, orally) daily up to fourteen day. [7]

Induction of oxidative stress- Oxidative stress are produced by induction of freshly prepared alloxan monohydrate (100 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 was 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 taken 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 was done using GraphPad Prism software demo version 5 and results were expressed in mean ± SEM and data was 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]

3. RESULT

Marble burring test: Reading of 15 min after treatment of drugs to different groups.

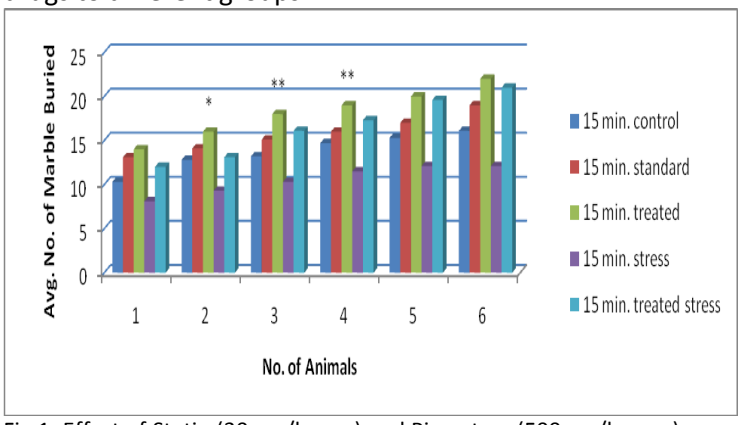

Fig 1: Effect of Statin (30 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on marble burying time at 15 min and from day 1 to day 12.The value are expressed in Mean±SEM *Significant P < 0.05, ** Very Significant P < 0.005, *** Highly Significant P < 0.0001 as compared to that of Control group rats. (Reading after 15 min)

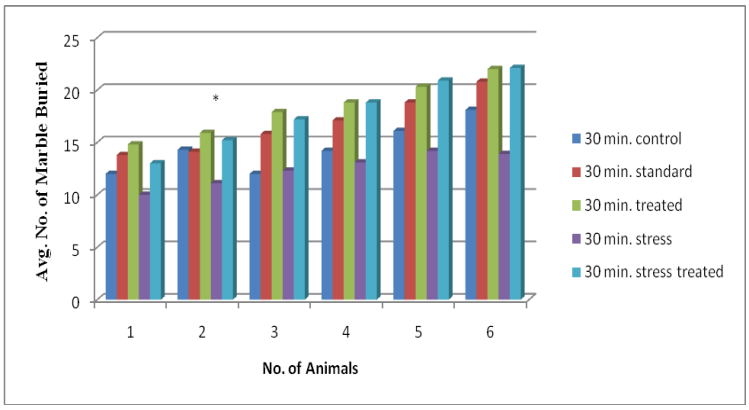

Fig 2: Effect of Statin (30 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on marble buying time at 30 min and from day to day 12. The value are expressed in Mean±SEM *Significant P < 0.05, ** Very Significant P < 0.005, *** Highly Significant P < 0.0001 as compared to that of Control group rats. (Reading after 30 min)

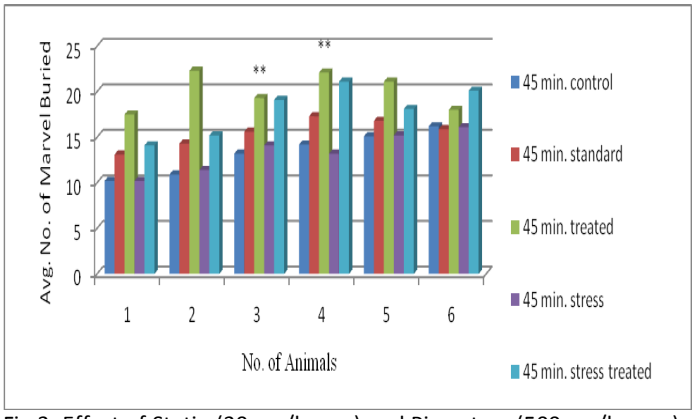

Fig 3: Effect of Statin (30 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on marble buying time at 30 min and from day to day 12. The value are expressed in Mean±S.E *Significant P < 0.05, ** Very Significant P < 0.005, *** Highly Significant P < 0.0001 as compared to that of Control group rats. (Reading after 45 min)

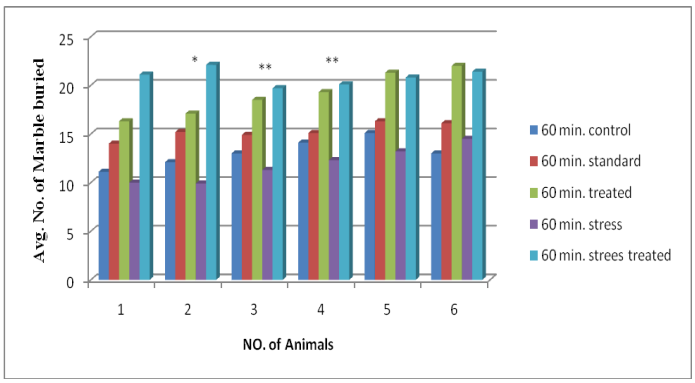

Fig 4: Effect of Statin (30 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on marble buying time at 30 min and from day to day 12. The value are expressed in Mean±S.E *Significant P < 0.05, ** Very Significant P < 0.005, *** Highly Significant P < 0.0001 as compared to that of Control group rats. (Reading after 60 min)

Biochemical Investigation

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

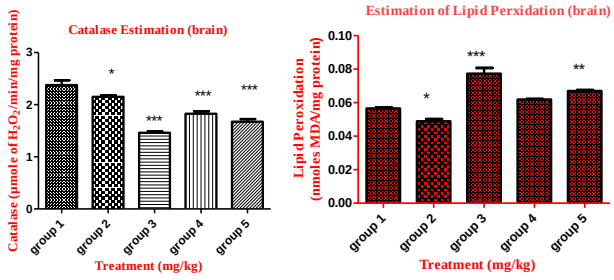

Fig 5: Effect of Statin (30 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on the Catalase & Lipid Peroxidation. *Significant P < 0.05, ** Very Significant P < 0.005, *** Highly Significant P < 0.0001 as compared to that of Control group rats.

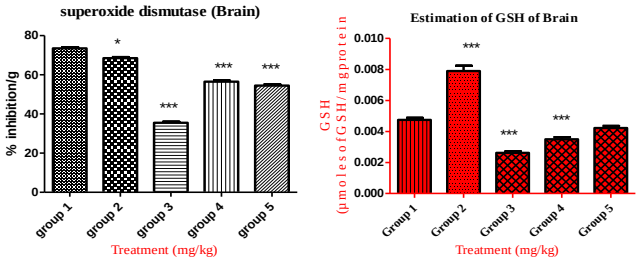

Fig 6: Effect of Statin (30 mg/kg *p.o*) and Piracetam (500 mg/kg, *p.o*) on the SOD & GSH. *Significant P < 0.05, ** Very Significant P < 0.005, *** Highly Significant P < 0.0001 as compared to that of Control group rats

4. DISCUSSION:

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.

Atorvastatin 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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Conflict of Interest: None Declared

