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Short Communication

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Antistress Potential of Simvastatins in Chronic Immobilization Stress

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Abstract

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

Method and Material

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.).[1]

Chronic Immobilization Stress- The animals in all the groups except control (normal) were subjected to immobilization stress daily in a prone position for 150 min for 5 consecutive days using simple adhesive tape (chronic stress). Animals were released by removing the tape after moistening with acetone.[2]

Result: With the help of investigation of biochemical parameters of different groups of animals we found that simvavastatin significantly lowered the stress and stressor.

Conclusion: Simvastatin significantly suppressed the stress.

Keywords: stress, Simvasatin, mirror chamber

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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[3].

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. Stress triggers a wide ranging set of bodily changes called the stress response or General Adaptation Syndrome (GAS).[4] 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.[5] 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.[6]

MATERIALS AND METHOD

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.).[7]

Chronic Immobilization Stress- The animals in all the groups except control (normal) were subjected to immobilization stress daily in a prone position for 150 min for 5 consecutive days using simple adhesive tape (chronic stress). Animals were released by removing the tape after moistening with acetone.[8]

Drugs and Treatment- Simvastatins was purchased from the local market of Mandsaur.

piracetum (400 mg/kg, i.p.) was administered 30 min, simvastatin (100 and 200 mg/kg, p.o.) and vehicle (1% CMC solution, p.o.) were administered 1 hour before subjected to chronic immobilized stress. Group-1 were treated as Normal (Unstressed),Group-2Control(Stressed) Group-3 smivastatins (40mg/kg, p.o.) Group-IV smivastatins (50mg/kg, p.o.) Group-V piracetam (400 mg/kg, i.p.)[9]

Method

Behavioral study: All the behavioral parameters were observed at the 6th day of chronic immobilization stress.

Measurement of Hyperalgesia

The hyperalgesia of animals were determined by Tail-flick method. In this method, the tip (last 1-2 cm) of the tail of animals were placed on the radiant heat source Analgesiometer). The tail withdrawal from the heat (flicking response) was taken as the end point (normal withdrawal time is 3-5 sec). A cut off period of 10-12 sec observed to prevent any damage to tail.[10]

Measurement of Anxiety

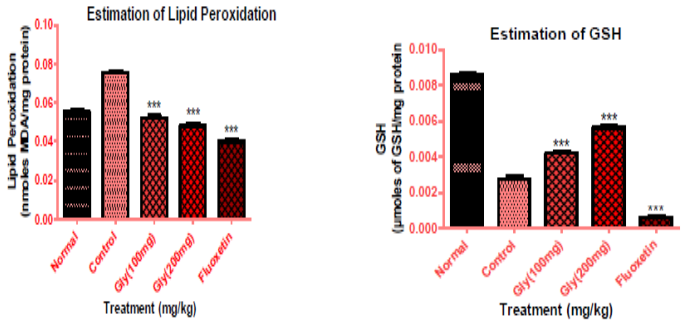
The anxiety level of various groups of mice was measured using mirror chamber and following parameters were recorded (i) Latency to enter the chamber (ii) Number of entries and time spent in mirror chamber .The mirror chamber consisted of a wooden chamber having a mirror enclosed within it. Animal were placed individually at the distal corner of the mirror chamber at the beginning of the test.[11]

Measurement of Locomotor activity

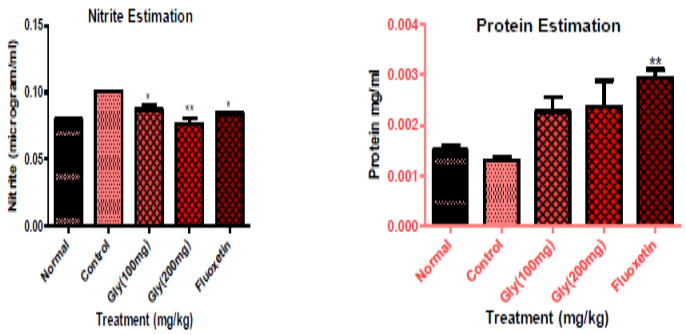
The locomotor activity was assessed using digital activity meter (Actophotometer). The activity meter consisted of an arena (29x22x22 cm) and operated on photoelectric cells that were connected in circuit with a counter. When the animal cuts off the beam of light falling on photoelectric cell, a circuit was recorded. After subjecting mice to the stress and 30 minute after drug administration mice were placed gently in this arena and number of counts (locomotor activity scores) recorded for 10 minutes.[12]

RESULT

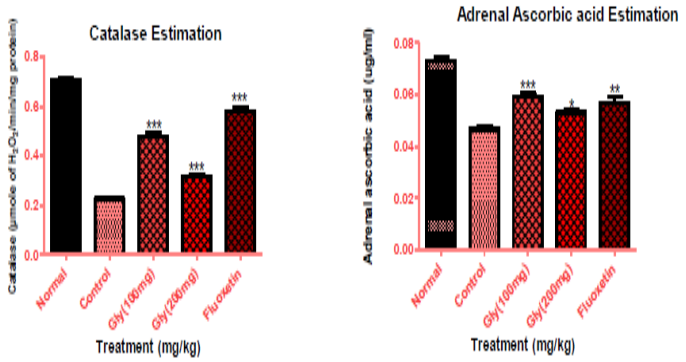
Biochemical Investigation Estimation of CAT, SOD, GSH, LP level on mice brain.



Effect of simvastatins (100 & 200 mg/kg, p.o.) on lipid peroxidation level in chronic immobilization stress induced biochemical alteration in the whole brain of mice. Values are express in Mean±SEM. P<0.05, ***Highly Significant as compare to Control group. (ANOVA followed by Dunnett's test), n=5.



Effect of simvastatins (100 & 200 mg/kg, p.o.) on nitrite level in chronic immobilization stress induced biochemical alteration in the whole brain of mice. Values are express in Mean±SEM. P<0.05, *Significant, **Very Significant as compare to Control group. (ANOVA followed by Dunnett's test), n=5.



Effect of simvastatins (100 & 200 mg/kg, p.o.) on catalase level in chronic immobilization stress induced biochemical alteration in the whole brain of mice. Values are express in Mean±SEM. P<0.05, ***Highly Significant as compare to Control group. (ANOVA followed by Dunnett's test), n=5.

DISCUSSION

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[13].

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.[14]

In the present study, chronic immobilization stress caused impairment of muscle co-ordination, locomotion, anxiety, cognitive functions and hyperalgesia.

Immobilization stress increases 2-3 fold of plasma corticosterone level due to activation of Hypothalamic-Pituitary-Adrenal axis (H-P-A axis) resulting in increased production of corticosterone. In humans and animals, adrenal cortex contains a higher concentration of ascorbic acid than other tissues and the acute administration of adrenocorticotropic hormone (ACTH) caused decrease in ascorbic acid levels.[15] Increased cortisol level has been linked with anxiety like behavior and painful responses in humans.

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.[16] 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. [17] Chronic immobilization stress also caused significant oxidative damage in animals brains indicated by increased lipid peroxidation, protein, nitrite activity and depleted reduced glutathione and catalase level in stressed brain.[18,19]

Daily treatment with simvastatins (100 & 200 mg/kg, p.o.) and piracetum (400 mg/kg, i.p.) causes significantly increased the fall-off time, decreased latency to enter in mirror chamber, decreased locomotor activity, decreased the hyperalgesic responses and prevented the memory dysfunction.

Simvastatins also significantly decreased the level of lipid peroxidation, protein, nitrite and increased the activity of endogenous antioxidants such as reduced glutathione and catalase in the brain. Simvastatins also reversed the decrease level of adrenal ascorbic acid in stressed animals.

Antistress activity of Simvastatins may be due to attenuating the H-P-A axis activation and free radical scavenging activity (Antioxidant activity).

In summary, the present study revealed that daily treatment with Simvastatins (100 & 200 mg/kg, p.o.) was effective in reversing chronic immobilization stress induced various behavioral and biochemical alteration in mice.

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