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STUDY OF THE EFFECT OF MELATONIN ON RETENTION OF CONDITIONED AVOIDANCE RESPONSE AND ON ENHANCEMENT OF SEROTONIN MEDIATED BEHAVIOURAL RESPONSES AFTER ELECTROCONVULSIVE SHOCK (ECS) ADMINISTRATION IN RATS

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ABSTRACT: Objectives: To obtain the data regarding the effects of melatonin on retention of conditioned avoidance response (CAR) and on enhancement of serotonin mediated behavioural responses after electroconvulsive shock (ECS) administration in rats. **Methods:** Forty rats after training for conditioned avoidance response by using Cook's pole climbing apparatus were divided in four groups with ten rats in each group and treatment duration was kept for ten days in all the groups. 1) **Control group-** distilled water (2ml daily) **2) ECS pretreated group-** single ECS daily (150 V, 50 Hz sinusoidal with intensity of 210 mA for 0.5 s through crocodile clip ear electrodes) **3) Melatonin group-** melatonin suspension (10 mg/kg/day, p.o.) daily **4) Test group-** Single ECS daily + melatonin suspension one hour after ECS (10mg/kg/day, p.o.).Then percentage of retention of conditioned avoidance response and number of lithium induced head twitches were calculated in each group on day 11. Data was analysed by chi square and student unpaired t test. **Results:** Findings show that administration of single ECS daily for consecutive 10 days results in enhancement of 5-HT-mediated behaviour (lithium-induced head twitches) and also led to disruption of the retention of CAR. Melatonin administration significantly increased the retention of conditioned avoidance response compared to control & ECS group. Also melatonin significantly prevented ECS induced attenuation of the retention of conditioned avoidance response. On the other hand, melatonin significantly retarded the ECS-induced enhancement of 5-HT-mediated behaviour. **Conclusion:** Melatonin by attenuation of enhancement of 5-HT mediated activity may be responsible for attenuation of disruptive effect on retention of conditioned avoidance behaviour by ECS.

INTRODUCTION: Melatonin is a hormone secreted from pineal gland. It is involved in the regulation of biological rhythms, in sleep regulation; it has potent antioxidant action and protects the organism from carcinogenesis and neurodegenerative disorders [1].

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Studies in mice show that melatonin administration may inhibit the appearance of neural cell abnormalities and the attendant memory disturbance which are observed in Alzheimer's disease (AD) [1]. Melatonin agonist agomelatine was shown to possess memory facilitating effects in the rat novel object recognisation task and both melatonergic agonist and 5-HT_{2C} antagonist properties could be involved in these effects [2]. This suggest that memory facilitating effect of melatonin may be mediated by retarding serotonegic (5-HT) transmission in brain in rats. Although AD once thought to result from a cholinergic deficit alone, researchers now believe that that multiple

neurotransmitters including dopamine,- noradrenaline, serotonin and glutamate have shown to be dysregulated in AD [3, 4, 5]. Evidences suggest that serotonergic transmission inhibits the memory performances and it is also suggested that blocking serotonergic transmission in brain is a possible mechanism to enhance the memory performances [6]. Lithium induced head twitches is useful animal model for quantifying 5-HT activity in the brain and screening of potential antagonists of 5-HT receptors [7].

Electroconvulsive shock therapy is associated with side effect of cognitive deficit which is associated with both anterograde and retrograde amnesia. These adverse effects are major factors limiting the use of ECT as the memory disturbances occur quite frequently [8]. Previous studies have shown that ECS was associated with increased serotonergic activity which might be causative factor in disruption of learning and memory performances [6]. Chronic administration of ECS for 8-10 days induces amnesia in animals by facilitating serotonergic transmission [9].

In view of above findings we had planned the study to assess the effects of melatonin in prevention of ECS induced disruption of memory performance and to evaluate the possible serotonergic mechanism through lithium induced head twitches as it is one of the established model to asesss the serotonergic mechanism in the central nervous system mechanism.

MATERIAL AND METHODS:

Experimental Animals: Male Sprague-Dawley rats which were weighed from 140-160g were used in the present study. The animals were maintained on standard laboratory diet and had free access to tap water supplied by Municipal Corporation. The rats were maintained under standard conditions of temperature (25ºC ± 5ºC) and relative humidity (55 ± 10%) and a 12/12 h light/dark cycle. The study was approved by institutional animal ethics committee.

Chemical / Drugs:

Study drug : Melatonin

Dose : 10 mg/kg body weight

Chemical used: Lithium chloride

double distilled water (vehicle)

Source: Both drug & chemical purchased from sigma

Conditioned avoidance response (CAR):

This model was used to study the effects of melatonin on working memory performance [10, 11]. The rats were trained for conditioned avoidance response by using Cook's pole climbing apparatus. Each rat was allowed to acclimatize for 2 min and was then exposed to a buzzer noise. After 5 s of putting on the buzzer, mild electric shocks were given through the stainless steel grid floor. The magnitude of the voltage was adequate (10 V) to stimulate the rat to escape from the floor and climb the pole. As soon as the rat climbed the pole, both the buzzer and foot-shock button were switched off. At least 10 such trials were given to each rat at an interval of 1 min per day for 10 days. After about 10 days training schedule, most of the rats learned to climb the pole within 5 s of starting the buzzer to avoid the electric foot shocks. Rats, avoiding the foot shocks in all 10 out of 10 trials, were considered to have developed conditioned avoidance response for further experiments. All trained rats were divided in 4 groups with 10 rats in each group and treatment duration was kept for 10 days in all the groups.

Group I- Control: Rats were given daily 2ml distilled water only.

Group II- ECS Pre-treated Group: Rats were administered single ECS daily (150 V, 50 Hz sinusoidal with intensity of 210 mA for 0.5 s through crocodile clip ear electrodes) for ten consecutive days.

Group III- Melatonin Group: Rats were administered melatonin suspension daily (10 mg/kg/day, p.o) only.

Group IV- Test Group: Rats were given single ECS daily as discussed earlier and melatonin suspension (10 mg/kg/day, p.o) one hour after ECS administration. On day 11, all rats were tested to see if they had retained the conditioned avoidance response. After 2 min of acclimatization period, each rat was exposed to the buzzer for 5 s. Ten such trials were given at an interval of 1 min,

without giving any foot shock. Rats, responding by climbing the pole when exposed to the buzzer noise, were considered to have retained the conditioned avoidance response.

Lithium induced head twitches:

This model was used to study serotonin (5-HT) induced behavioural changes [12].

The animals were divided into four groups of ten rats each as done in the previous model of conditioned avoidance response. Pre-treatment's in these four groups were carried out in the same manner as that of CAR.

This behavioural test was performed on day 11, 24 hours after the administration of last dose of pre-treatment according to their group respectively. The numbers of head twitches induced by injecting lithium hydrochloride (200 mg/kg, i.p) were counted during 10 min interval, starting immediately from the time of injecting lithium hydrochloride up to a period of 90 min[13].

Statistical analysis:

The result of the retention of CAR was analyzed by the chi-square test of proportion. Result from the lithium induced head twitches were analysed by using unpaired student's t test. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS:

Conditioned avoidance response:

The percentage of rats showing retention of conditioned avoidance response (CAR) was calculated in each group. The result is shown in **Fig. 1**. In group I (control group), 78% rats showed retention of CAR. In group II (ECS pre-treated group) 31% rats showed retention of CAR, and these decreases were statistically significant ($p<0.001$) compared to group I. In groups III (Melatonin group), 95 % rats showed retention of CAR, and these increases were statistically significant as compared to group I & II ($p<0.001$ & $p <0.001$ respectively). In groups IV (Test group-ECS + melatonin), 80% rats showed retention of CAR and this increase was statistically significant as compared to group II ($p<0.001$).

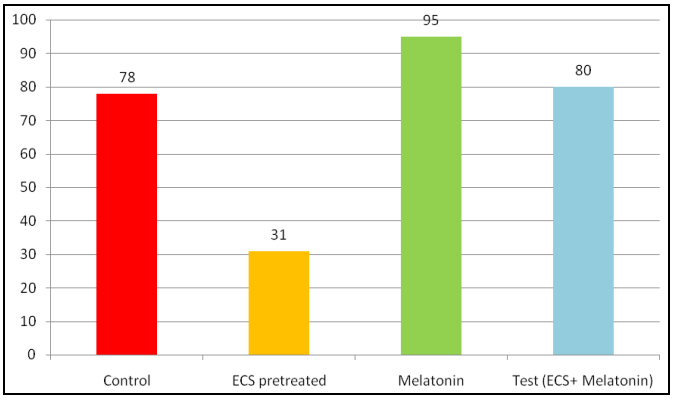

FIG.1: CONDITIONED AVOIDANCE RESPONSE

Lithium-induced head twitches:

The number of head twitches induced by injecting lithium chloride was counted every 10 min, starting immediately from the time of injection up to a period of 90 min. The results of this study are shown in **Fig. 2**. The maximum number of head twitches in different groups was seen between 41 and 50 min.

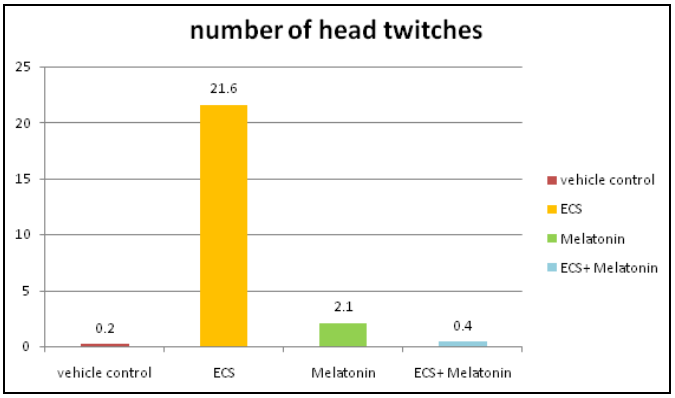

FIG.2: LITHIUM INDUCED HEAD TWITCHES

The maximum numbers of head twitches in different groups were compared. In the control group a score of 0.2 ± 0.05 (Mean ± SEM) was seen. In the ECS pre-treated group the score increased to 21.6 ± 6.56 and this increase was statistically significant as compared to control group ($p < 0.01$ ECS pre-treated Vs Control group). The melatonin group showed increase in head twitches to 2.1±0.9 which was not statistically significant in comparison with control ($p >0.05$ melatonin group Vs Control group). In the test group score was 0.4 ± 0.26 which was statistically significant decrease as compared to ECS pre-treated group ($p <0.01$ Test group Vs ECS pre-treated group).

DISCUSSION: Currently, our knowledge related to retention of memory appears to be limited. Several neurotransmitter systems that have different anatomical locations are involved in various aspects of memory [14]. Serotonergic system has also been implicated in this. Evidences suggest that serotonergic transmission inhibits the memory performances. Fenfluramine, a serotonin reuptake inhibitor and releasing agent which effectively increases serotonin levels, appeared to impair the memory. It is also suggested that blocking serotonergic transmission in brain is a possible mechanism to enhance the memory performances [6, 15].

The present study was planned to see if melatonin produced its action by significantly influencing serotonergic systems in the CNS, that might prove to be of therapeutic value in treating patients, not only of Alzheimer's disease but other neurodegenerative diseases also like Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease and brain trauma.

Our study shows that administration of single ECS daily for consecutive 10 days results in disruption of the retention of CAR in ECS group (group II) as compared to control group (group I) ($p<0.001$). This might be due to increase in monoamine mediated responses like increased serotonergic activity after ECS administration.

Melatonin significantly increased retention of conditioned avoidance response in test group where melatonin was given after ECS administration, (group IV) as compared to ECS only group. This might be due to attenuation of enhanced serotonergic mediated responses after ECS administration by melatonin ($p<0.001$).

Our study also shows that administration of single ECS daily for consecutive 10 days results in enhancement of 5-HT-mediated behaviour (lithium-induced head twitches) as compared to control group ($p < 0.001$ ECS pre-treated Vs Control group). This is in consistent with finding that ECS administration increases lithium induced head twitches [6]. On the other hand, melatonin significantly retarded the ECS induced enhancement of 5-HT-mediated behaviour ($p<0.001$ test group Vs ECS pre-treated group). The result of lithium-induced head twitches is in agreement with the fact that blocking serotonergic transmission in the brain is a mechanism to enhance the retention of conditioned avoidance response. Thus, the results in the present study suggests possible role of serotonergic system in memory modulating effects of melatonin.

CONCLUSION: It could be concluded that ECS administration leads to disruption of memory performance. Melatonin could prevent disruption of memory following ECS administration. Melatonin by attenuation of enhancement of 5-HT mediated activity may be responsible for attenuation of disruptive effect on retention of conditioned avoidance behavior by ECS. As ECT in humans is known to produce memory disruption, a possible potential therapeutic utility of melatonin to prevent memory disruption in such patient is worth considering.

LIMITATIONS OF STUDY: Our study has certain shortcomings. Small sample size of animals was selected for the study. Secondly, the effect of melatonin on other monoamine like dopamine, noradrenaline, mediated responses in rats could have been studied to elucidate the action of melatonin on other neurotransmitter mediated responses.

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CONFLICT OF INTEREST: The authors do not have any conflict of interest.

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