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To Study of the Effect of Melatonin on Noradrenaline Mediated Behavioural Responses after Electroconvulsive Shock (ECS) Administration

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Abstract

Objectives: To look for possible data regarding the effects of melatonin on noradrenaline mediated behavioral responses after Electroconvulsive Shock (ECS) administration in rats. **Methods:** Forty rats 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. 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). Clonidine induced sedation was used as a model to assess noradrenaline mediated behavioral changes. Clonidine induced sedation score was assessed 30 min after giving intraperitoneal injection of clonidine hydrochloride (100 µg/kg) in each group on day 11.Data was analysed by Mann-Whitney U test. **Results:** Findings show that administration of single ECS daily for consecutive 10 days results in enhancement of clonidine induced sedation. Melatonin group, administration of decreases clonidine induced sedation which may be due to modulation at noradrenergic neurotransmission. Also, melatonin significantly retarded the ECS-induced enhancement of clonidine induced sedation as seen in test group. **Conclusion:** ECS administration leads to enhancement in clonidine induced sedation. Melatonin administration could prevent enhancement in clonidine induced sedation which may be possibly due to modulation at the level of noradrenergic transmission at central nervbous system. This modulation in noradrenergic transmission might be of some therapeutic value in attenuation of disruption of memory following ECS administration. 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.

Keywords: Clonidine Induced Sedation, ECS, Melatonin, Noradrenaline

1. 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 neurodegenerative disorders[1]. Preclinical 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).1Melatonin agonist agomelatine was shown to possess memory facilitating effects in the rat novel object recognition task and both melatonergic and noradrenergic agonistic properties could be involved in these effects[2].

Although AD once thought to result from a cholinergic deficit alone, researchers now believe that multiple neurotransmitters including dopamine, noradrenaline, serotonin and glutamate have shown to be dysregulated in AD[3–5]. Evidences suggest that noradrenergic transmission facilitates the memory performances and it is also suggested that modulating noradrenergic transmission in brain is a possible mechanism to enhance the memory performances[4]. Clonidine induced sedation is useful animal model for quantifying NA activity in the brain[5].

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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 (Electroconvulsive Therapy) therapeutics as the memory disturbances occur quite frequently[6].

In view of above findings we had planned the study to assess the effects of melatonin on "ECS induced clonidine induced sedation", as this is one of the established models to assess the noradrenergic mechanism in the central nervous system and its possible correlation with memory deficit after ECT in humans.

2. Material and Methods

2.1 Experimental Animals

Male Sprague-Dawley rats which were weighed from 140-160 g 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 (25°C ± 5°C) and relative humidity (55 ± 10%) and a 12/12 h light/dark cycle. The study was approved by institutional animal ethics committee.

2.1.1 Chemical/Drugs

Study drug : Melatonin
Dose : 10mg/kg body weight
Chemical used:
Clonidine
double distilled water (vehicle)
Source : Both drug & chemical purchased from sigma Laboratories

Rats were divided in 4 groups with 10 rats in each groups 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.

2.1.2 Clonidine Induced Sedation

This model was used to assess noradrenaline-induced behavioral changes.

Procedure:

This behavioral test was performed on day 11, 24 hours after the administration of last dose of pre-treatment according to their group respectively. The degree of sedation was assessed 30 min after injection of clonidine hydrochloride (100 µg/kg, i.p)[6]. Sedation was assessed by removing rat from the cage and transferring them on to the laboratory shelf and observing for gross differences from the naïve rats. The following 6 indices were used and were scored on a 0-4 scale as follows:

- Lowered body posture (scored 0: if there was no change; scored 4: if the ventral surface of the abdomen touched the floor and the normal arched back was not distinctly visible).
- Slowness of gait (scored 0: if no change; increasing slowness increased the score; score 4: if the rat did not move at all).
- Depressed response of the rat to pressure by finger and thumb placed on either side of the body.
- Passivity (assessed by whether or not rat struggled when picked up gently by the dorsal fold of loose skin of neck).
- Impaired righting reflex (assessed by number of times the rat failed to land on all 4 feet when dropped 4 times from inverted position on to a tray of paddy husk).
- Ptosis (assessed by directly observing the eyes, scored 0: if the eyes were wide open; scored 4: if the eyes were shut).
- Scores for each index were summed for each dose group. The maximum possible score being 24.

2.1.3 Statistical Analysis

The result of the clonidine induced sedation was analyzed by the Mann Whitney U test (Non Parametric test for two groups). A value of $p < 0.05$ was considered to be statistically significant.

3. Results

After injecting clonidine (100µg/kg/i.p.) total sedation score was calculated as described before. The result has been shown in Table 1.

As can be seen in this table, the control group had a median sedation score of 5.0. In the ECS pretreated rats the median sedation score increased to 12.0 which was statistically significant ($p<0.001$) as compared to control group. In Melatonin pretreated group the median sedation score was 6.0 which was not statistically significant as compared to control ($p>0.05$). In Melatonin pretreated group the median sedation score was 6.0 which was

statistically significant as compared to ECS pretreated group ($p<0.001$). In test group the score was 7.0 which showed statistically significant difference ($p<0.001$) when compared with ECS pretreated group.

Table 1. Clonidine-induced sedation score

Groups (n=10)	Median Score
Control	5
ECS pretreated	12
Melatonin	6
ECS followed by Melatonin (Test group)	7

(NS- not significant, *- $p< 0.05$, ** $p < 0.01$, *** $p< 0.001$)

4. 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[7]. Animal experiments have generally shown that injecting norepinephrine to various brain regions at times when memories are encoded or shortly after the behavioural training could enhance memory performance[8,9]. Conversely, blocking adrenergic receptors (such as β-type) could have a decremental effect on memory[10,11] and prevent the increase of memory performance during concurrent injections of the agonist[12].

Our study showed that administration of single ECS daily for consecutive 10 days results in enhancement of clonidine induced sedation as compared to control group. On the other hand, melatonin significantly retarded the ECS induced enhancement of clonidine induced sedation in the test group. The result of clonidine induced sedation appears to be agreement with the fact that facilitating noradrenergic transmission in the brain result in enhancement of memory performance through modulation of synaptic plasticity[6]. Thus, the results in the present study suggest a possible role of noradrenergic neurotransmission in memory modulating effects of melatonin.

5. Conclusion

It could be possibly concluded that ECS administration leads to enhancement in clonidine induced sedation which might have detrimental effect on memory performance in therapy. Melatonin could prevent enhancement in clonidine induced sedation possibly due to modulation at noradrenergic neurotransmission which might also prevent disruption of memory following ECS administration. 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.

6. Limitations of Study

Our study has few shortcomings. Small sample size of animals was selected for the study. Secondly, the effect of melatonin on other monoamine like dopamine could have been evaluated in preclinical studies to elucidate the likely action of melatonin on other neurotransmitter mediated behavioural response which may be involved in modulation of memory performances.

7. Conflict of Interest

The authors do not have any conflict of interest.

8. References

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