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A Study on the Effect of Melatonin on Sexual Urge of Swiss Albino Male Mice

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ABSTRACT

Melatonin regulates the sleep-wake cycle, or circadian rhythms, in many animals, including humans. Produced at night by the pineal gland at the base of the brain, it makes us drowsy at night and, when levels drop in the morning, brings us back to alertness. Despite claims by supplement manufacturers, however, melatonin has shown mixed results as a treatment for disease, whether insomnia, Alzheimer's disease or cancer to decrease or compensate the effect of age and oxidative stress, taking melatonin and other antioxidative drugs is increased in developed countries. Popular supplement of melatonin found to have broader effects on various systems of body like reproductive system. Reproduction is something that has been studied very rigorously, and to identify a new peptide in that arena that seems to be playing such an important role is pretty phenomenal at this time. The present study aimed to investigate the effect of melatonin on the sexual urge of male Swiss albino mice by using Hebb William's maze, model D[1]. Mice were divided into four groups having equal number of males. Two groups of 6 weeks and other two groups are of 10 weeks of male mice. The entire four groups are separated from female by 15 days prior to experiment. The time taken by male mice to travel from chamber A to chamber B (which contained female mice) was recorded over a period of two months, for both melatonin-treated (0.002 mg/kg body weight) and untreated groups. Results clearly indicate that normal male group takes less time to reach the goal as compared to melatonin treated group. Although there was a continuous decline in the time taken by mice of both the groups to reach the goal but the decline was of greater magnitude in normal male mice. The result shows that melatonin has an inhibitory effect on the reproductive performance of the animal as well as it also affects endocrinological function of the body.

***Keywords**: Melatonin, Reproductive Performance, Sexual Urge, Endocrinological Function, Female Mice.*

Introduction

Despite enormous medical progress during the past few decades, the last years of life are still accompanied by increasing ill health and disability. The ability to maintain active and independent living for as long as possible is a crucial factor for ageing healthily and with dignity. To decrease or compensate the effects of age and oxidative stress, taking melatonin and other antioxidative drugs is increased in developed countries. Its effect on different parameters has already been studied. The most important and drastic gender differences in aging are related to the reproductive organs. In distinction to the course of reproductive ageing in women, with the rapid decline in sex hormones expressed by the cessation of menses, men experience a slow and continuous decline. This decline in endocrine function involves: a

decrease of testosterone, dehydro epiandrosterone (DHEA), estrogens, thyroid stimulating hormone (TSH), growth hormone (GH), IGF1, and melatonin. Now, it is very obvious that melatonin has an effect on sexual urge of organisms.

Melatonin is an endogenous hormone produced by the pinealocyte in the pineal gland during the dark hours (night) of the day –night cycle. Light suppresses the production of melatonin. Melatonin, has been shown to participate in a number of physiological process like regulation of reproduction (Reiter *et al.*, 1998), sleep (Waldheizer *et al.*, 1998) mood and behavior (Zu danova *et al.,* 1998) and circadian rhythm (Macchi and Bruce 2004) immune function and body temperature. In many species of animals, the pineal gland acts as "biological clock" (Wainwright, 1982). Melatonin alone has been shown to alter the phase of circadian rhythms (Turek and Gillette, 2004). It has been proposed as a "chronobiotic" (Armstrong, 1999). A chronobiotic is defined as a substance which can re-entrain short term dissociated and long-term desynchronized circadian rhythm (Armstrong, 1999).

While some studies (Santosh *et al*., 2020) indicate that melatonin may suppress excitatory input to GnRH neurons—potentially downregulating reproductive signaling, especially in prepubertal animals, other studies (Drago and Busa, 2000; Brotto and Gorzalka, 2000) report that melatonin facilitates sexual activity in adult male rats. These differing effects may reflect age-dependent, dose-dependent, or species-specific variations**,** or distinct mechanisms of melatonin action on central versus peripheral reproductive pathways.

Melatonin production has an impact on every stage of our life. Newborns produce very little of it and get it from mother milk. Then, at about three months of age—which is the stage of development when they start sleeping longer stretches at night and being more alert during the day—melatonin levels rise. From about the age of one, melatonin levels are more or less constant for a decade. Then, just before puberty, they go down sharply. Recent studies have demonstrated that this decline is the body's signal to the sex glands to set sexual maturation in motion. So clear is the signal meant to be, that a child who maintains unusually high levels of melatonin will experience a delay in the onset of pubescence. There have actually been rare cases, in which the melatonin level is so uncharacteristically high in adolescence that sexual maturation simply does not occur. Therefore, melatonin deserves serious attention for its impressive potency in sex drive.

Synthesis of melatonin also occurs in other areas of the body, including the retina, the gastrointestinal tract, skin, bone marrow and in lymphocytes, from which it may influence other physiological functions through paracrine signaling.

Melatonin also occurs in human milk (Illnerova *et al.*, 1993) and in a variety of common plant food (Dubbels *et al*., 1995). Such as Bananas beet, cucumber and tomato. The occurrence of melatonin in vegetation parallel the occurrence of it precursor compound serotonin, which as long been known to occur in plant material, particularly in tropical food.

Oral administration of melatonin causes significant decrease in sex hormones like serum estradiol, testosterone, and DHEAS concentrations in adult dogs. (Ashley *et al.,* 1999). Melatonin is known to inhibit male and female sex behavior, but this effect has been reported only after repeated administration of sustained doses of the hormone. Melatonin may exert opposite effects on male and female sex behavior depending on the dose and duration of treatment (Drago *et al.,* 1999). Melatonin protects against the effects of chronic stress on sexual behaviour in male rats (Brotto *et al*., 2001).

One of the animal's fundamental ability is to explore its environment to know where food water and mating partner etc. Therefore to investigate the age-dependent and dose-dependent effects of melatonin on sexual behavior in male Swiss albino mice, with a focus on its potential modulatory role on reproductive activity during early and late maturation, we used a laboratory model in which Swiss albino mice has to approach a particular place (goal) for a mating partner.

Materials and Methods

- **Animals**

Male Swiss albino mice were selected from an inbred colony and maintained on standard mice feed (Hindustan Lever Ltd., New Delhi) and water *ad labitum*. Mice were maintained at constant temperature (22±1 C) and light (12L:12D).

- **Drug**

Melatonin is a hormone, which is available in market in the form of tablets, named meloset. Each meloset tablet contains only melatonin (3mg) and not any other compound as stated in the ingredient table of tablet wrapper. Meloset tablet were purchased from Aristo Pharmaceutical and dissolve in drinking water to make an appropriate concentration before oral administration.

Experimental Protocol

Mice were divided into four groups having equal number of males. Two groups of 6 weeks and other two groups are of 10 weeks of male mice. The entire four groups are separated from female by 15 days prior to experiment. One group of each age group is treated with melatonin 15 days prior to experiment with dose 0.002mg/kg of b.wt in drinking water and continued till the end of the experiment. The maze used in our study is called HEBB WILLIAM MAZE, model D, a maze system consists of passages where only one leads to the goal while others comes to a dead end. In such experiments an essential feature for check out the sex urge by how fast the animal reach the goal *i.e.* female mice. Time taken by mice to reach from chamber A to chamber B (containing female) was recorded in all the groups. Time recorded on alternate days for two months. Body weights and brain weights of animals for both the groups were taken at three successive intervals, before treatment, after treatment and after learning at 6 week, 8 week and 12 week.

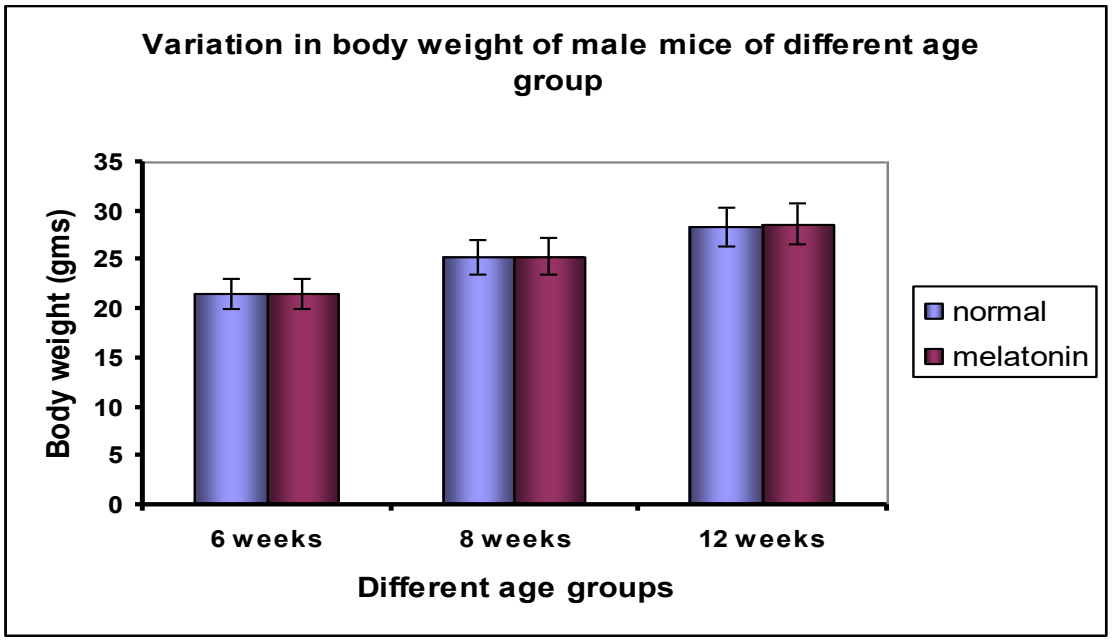
- **Observations:** The difference in learning time calculated in percentage has been depicted in the following tables:

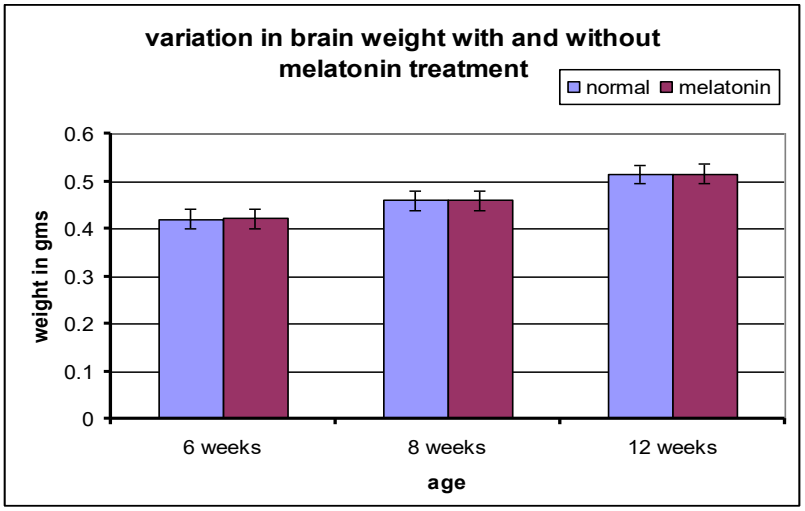
Table 1: For Male Mice Group of Age 6 Weeks

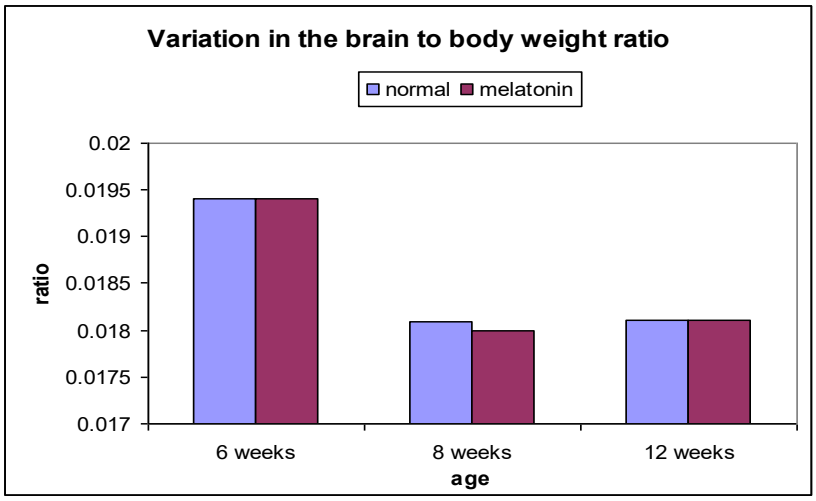
Groupss	Initial 20 Days	Upto 40 Days	Upto 60 Days
Normal	100 %	100 %	100 %
Melatonin Treated	131 %	132.05 %	133.25 %

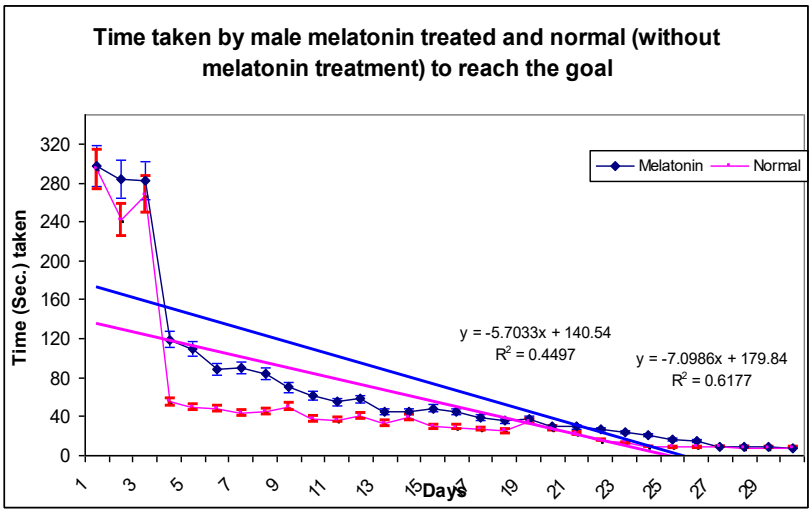
Table 2: For Male Mice Group of Age 10 Weeks

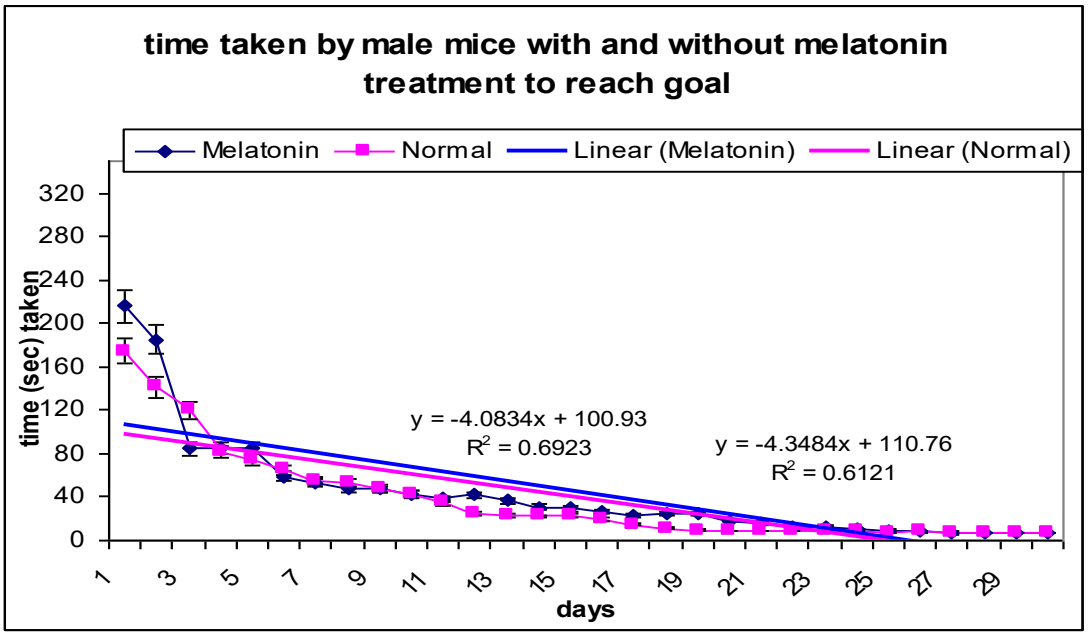
Groups	Initial 20 Days	Upto 40 Days	Upto 60 Days
Normal	100 %	100 %	100 %
Melatonin Treated	105.75 %	114.3 %	115.35 %




variation in brain weight with and without melatonin treatment
normal
melatonin
weight in gms
0.6
0.5
0.4
0.3
0.2
0.1
0
6 weeks
8 weeks
12 weeks
age


Variation in the brain to body weight ratio
normal
melatonin
ratio
0.02
0.0195
0.019
0.0185
0.018
0.0175
0.017
6 weeks
8 weeks
12 weeks
age


Time taken by male melatonin treated and normal (without melatonin treatment) to reach the goal
Melatonin
Normal
Time (Sec.) taken
320
280
240
200
160
120
80
40
0
y = -5.7033x + 140.54
R2 = 0.4497
y = -7.0986x + 179.84
R2 = 0.6177
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
Days



Results

Body weights of melatonin supplemented group were not significantly higher than the normal group. Also not significant difference existed in the brain weights of melatonin treated and normal mice.

Brain weight to body weight ratio is a measure of relative effectiveness of brain in relation to body weight. Brain to body weight ratio was also statistically non-significant between melatonin treated and normal mice.

Normal male mice show more sexual urge as compared to melatonin treated male mice. Although there was a continuous decline in the time taken by mice of both the groups to reach the goal. However, non-treated males showed better performance. Mice show aggressive behaviour as well as pseudo-sexual behaviour after shifting in cage. After pseudo-sexual behaviour they were serene and calm.

During the initial stage of experiment, animals of both the groups were unfamiliar with the maze. They go here and there, feel afraid, sniff the path before going forward, went to different partitions of the maze, sit there, come and go again. Then they gradually learnt the site of satisfaction. After 20 days a continuous decline in their timings to reach the goal has been noticed. This decline has been of greater magnitude in normal males than those of treated males. Normal Male mice took 33% less time than melatonin treated mice. However, after about 50 days of experiment, both normal male and treated male showed stabilization in their performance that is the average time for each group to reach the goal remain more or less same. It was the shortest time and did not decrease further. Now at this stage, the animal reached the goal with its full intensity with full knowledge of path without doing any error. At this time, there has been an almost steady state in the sexual urge of mice. The average difference occurred between normal male and treated male mice group during the whole experiment in their learning time is of 34%. This difference is significant as the regression coefficient has been very near to one as also shown by a diagonal trend.

Discussion

Melatonin has attracted increasing interest as a therapeutic agent for treating a range of medical conditions including cancer, cardiovascular disease, stress, jet lag, and sleep disorders. However, its use as an antigonadal or contraceptive agent remains a subject of debate. Its absorption and bioavailability vary widely; melatonin is absorbed in the small intestine, transported to the liver via the portal circulation, and largely metabolized to 6-hydroxymelatonin. The remaining unmodified hormone enters systemic circulation, with a serum half-life of approximately 35–50 minutes.

In this study, melatonin administered at a dose of 0.002 mg/kg body weight was found to be non-toxic. No statistically significant differences were observed in body weight, brain weight, or brain-to-body weight ratio between the treated and control groups. These findings suggest that the given dosage did not affect general growth or neural development. This aligns with the findings of Markova *et al*. (2003), who reported changes in body weight and organ parameters only after prolonged melatonin treatment in rats.

Behavioral analysis revealed that melatonin supplementation reduced sexual motivation in male Swiss albino mice. Treated mice consistently took longer (33–34%) to reach the female in the maze compared to untreated males. Although both groups showed improved performance over time due to learning, the treated group exhibited a slower learning curve. These results indicate a suppressive effect of melatonin on sexual behavior and goal-directed activity, particularly in mating-related contexts.

This inhibitory effect is supported by previous studies. Ashley *et al.* (1999) demonstrated that oral administration of melatonin led to a significant reduction in sex hormones such as estradiol, testosterone, and DHEAS in adult dogs. Similarly, Drago *et al*. (1999) showed that melatonin could exert opposing effects on male and female sexual behavior depending on the dose and treatment duration.

At the neuroendocrine level, melatonin is known to influence the hypothalamic-pituitary-gonadal (HPG) axis. It inhibits gonadotropin-releasing hormone (GnRH)-induced luteinizing hormone (LH) release, as shown in studies by Martin and Klein (1976) and Vanecek and Klein (1993). The suppression of GnRH signaling may occur through reduced phospholipase C activity and inhibition of calcium signaling, leading to diminished gonadotropin output and sexual behavior (Yamada *et al*., 1998).

Furthermore, melatonin has been shown to upregulate the production of gonadotropin-inhibitory hormone (GnIH), which directly counteracts the effects of GnRH. Bentley *et al*. (2003) and Kriegsfeld *et al.* (2006) demonstrated that melatonin stimulates GnIH expression, leading to decreased LH levels and reproductive suppression. In birds, the withdrawal of melatonin-producing organs decreased GnIH, which was restored upon melatonin administration. These findings support the dual role of melatonin in regulating reproductive timing and behavior through both central and peripheral pathways.

Culturally, practices like “amroli,” a traditional yogic method involving the ingestion of early-morning urine rich in melatonin, have been associated with enhanced calmness and mental clarity, possibly due to increased melatonin levels (Mills and Faunce, 1991). This anecdotal association aligns with melatonin’s known influence on mood, sleep, and hormonal regulation.

In summary, the present study demonstrates that low-dose melatonin does not significantly impact general growth parameters but does exert a clear inhibitory effect on male sexual motivation and learning behavior related to reproductive goals. These effects are consistent with previous findings and can be attributed to melatonin's modulation of reproductive hormone pathways through the suppression of GnRH and activation of GnIH. Thus, melatonin appears to influence sexual behavior in a dose- and age-dependent manner, supporting its potential role in reproductive regulation without inducing systemic toxicity.

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