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Acute low doses of melatonin stimulate rat sex behavior: the role of serotonin neurotransmission

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Abstract

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. The present experiments were performed in order to study the effects of acute treatment with low doses of melatonin on rat male and female sex behavior in a dose–response paradigm. After four mating tests with a receptive female, sexually active male rats of the Wistar strain were injected intraperitoneally (i.p.) with small doses of melatonin (10, 50 and 100 μg/kg) administered acutely 1 h before a 30-min mating test. Melatonin (50 and 100 ng/2 μl) or its analogs, 6-chloromelatonin (2 and 4 ng/2 μl) and 2-iodomelatonin (5 and 10 ng/2 μl) were also injected intracerebroventricularly (i.c.v.) 30 min before mating. Either treatments caused a reduction of the latency to the first mount, intromission and ejaculation. An increase in the frequency of mounts, intromissions and ejaculations was also observed. Inhibition of sexual activity was observed when a greater dose (1 mg/kg) of melatonin was repeatedly injected for 14 days. Female sex behavior, measured by the lordosis quotient in Wistar female rats, was not affected by acute treatment with the hormone, while it appeared to be inhibited by the repeated injection. The facilitating effect of acute i.p. or i.c.v. melatonin low doses on sexual activity of male rats was partially abolished by the pre-treatment with the non-selective melatonin antagonist, luzindole (0.25 mg/kg, injected subcutaneously), and totally suppressed by the injection of small quantities of serotonin or the $5H_{2A}$–$5H_{2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane into the amygdala. These results suggest that melatonin may exert opposite effects on male and female sex behavior depending on the dose and duration of treatment.

Keywords: Melatonin; Sex behavior, male; Sex behavior, female; 5-HT (5-hydroxytryptamine, serotonin); Ejaculation; Lordosis

1. Introduction

The vertebrate pineal gland rhythmically produces melatonin, a hormone involved in the regulation of several physiological and behavioral processes. The rate-limiting step in melatonin production is the *N*-acetylation of serotonin by arylalkylamine *N*-acetyltransferase (Coon et al., 1995) The activity of this enzyme seems to be under control of the suprachiasmatic nucleus (SCN) in the hypothalamus, that receives neural afference from the retina indicating daily light/dark alternance. Thus, SCN regulates melatonin synthesis in relation of environmental light. As a result, high levels of melatonin are produced in vertebrates during the dark part of the daily light–dark cycle.

The physiological and pharmacological effects of melatonin seem to be mediated by activation of high-affinity receptors, but may involve different neurotransmitters in the brain (Gaffori and Van Ree, 1985a; Tenn and Niles, 1995). In particular, serotonin has been often considered as a possible mediator of melatonin effects (Gaffori and Van Ree, 1985b; Eison et al., 1995). The main action of the hormone deals with adaptation of animal behavior, including sex behavior, to the length of the dark period of the circadian cycle, hence, to the seasons. Similar effects may be mimicked through the exogenous administration of melatonin. Animal studies show, for instance, that its chronic administration leads to inhibition of male sex behavior (Baum, 1968; Yamada et al., 1992) and the implantation of melatonin-containing pellets near the SCN in female rats reduces their lordosis reflex (De Catanzaro and Stein, 1984). Besides, melatonin is involved in sexual cycle of the female rat. In particular, it was observed that melatonin administered by intraperitoneal (i.p.) injection

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produces an inhibiting effect on the nervous structures involved in the regulation of sexual cycle of female rats (Diaz Lopez and Fernandez, 1984). All these experiments, however, were made using rather high doses of melatonin. Furthermore, to date no report is available on the effect of melatonin on male or female rat sex behavior after acute administration.

Purpose of the present study was to determine the influence of acute treatments with melatonin on rat male and female sex behavior in a dose–response paradigm. Drug doses were selected in a range rather lower than that used in previous experiments, and closer to physiological blood concentration of melatonin. Although the sexual effects of melatonin have been studied in a wide range of animal species (Bittman and Karsch, 1984; Lincoln and Ebling, 1985; Pitrosky et al., 1991; Mendonca et al., 1996), the rat was selected as the most studied species for behavioral experiments.

2. Materials and methods

2.1. Animals and surgery

Male rats of the Wistar strain (purchased from Charles River, Italy) weighing 350 ± 25 g were used throughout all experiments. A group of female rats of the same strain, weighing 150 ± 10 g was also used. Animals were kept three or four to a cage, at a constant temperature of 21°C, with food and water available ad libitum. At least, 1 week before the beginning of the experiments, they were housed under a reversed light–dark cycle (light on between 0300 and 1500 h). A group of male rats were subjected to the implantation of a plastic cannula (external diameter: 0.8 mm) into the cerebral ventricular system (foramen interventriculare, König and Klippel, 1963, A6360) and of stainless steel cannula (external diameter: 0.5 mm) into the right amygdala (König and Klippel, 1963, P3456). The operation was performed under a ketamine/xylazine general anesthesia. The correct insertion of the cannulas was checked in post-mortem examination injecting small quantities of Alcyan blue solution.

All experiments were carried out according to the European Communities Council Directive 86/609/EEC and efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Drugs

All drugs used in this study were supplied from Sigma (USA). Melatonin (*N*-acetyl-5-methoxytryptamine), 6-chloromelatonin (*N*[2-(6-chloro-5-methoxy-1*H*-indol-3-yl)ethyl]acetamide), 2-iodomelatonin (*N*-acetyl-2-iodo-5-methoxytryptamine), luzindole (*N*-acetyl-benzyltryptamine), serotonin (5-hydroxytryptamine hydrochloride) and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane were freshly dissolved in saline before administration. Estradiol benzoate (β-estradiol 3-benzoate) and progesterone (4-pregnene-3,20-dione) were dissolved in oil olive.

2.3. Male sex behavior analysis

Sexual activity of rats was evaluated after four selection mating tests with receptive females, at weekly intervals. Copulatory behavior was scored according to Beach (1956) utilizing an event recorder (Basile, Italy). The following behavioral parameters were considered for each animal: latency (in s) to the first mount, intromission and ejaculation; frequency (total number) of mounts, intromissions and ejaculations. Latency to the first mount and intromission was the time elapsing from the introduction of the female into the male's cage until the first mount or intromission, respectively. Latency of ejaculation was the time from the first intromission until the first ejaculation. Frequency of mounts and intromissions was the number of mounts or intromissions in a series; frequency of ejaculations was the total number of ejaculations during 30-min observation. Behavioral test was terminated after 30 min (1800 s). Mating tests were carried out during the late scotophase (10 h after the onset of darkness), under dim red light. After selection tests, animals were admitted to the experimental session if they have exhibited at least one ejaculation per each test.

Ovariectomized females, used as copulatory partners, were admitted to experimental session a week after bilateral operation. They were made sexually receptive by subcutaneous (s.c.) injection of estradiol benzoate (60 μg/kg in olive oil) followed 48 h later by a s.c. injection of progesterone (1 mg/kg in olive oil).

2.4. Female sex behavior

Females rats made receptive by the above procedure were exposed to an active male rat for a 30-min mating test. The lordosis quotient (number of lordoses by female/number of mounts by male) was measured utilizing an event recorder (Basile, Italy) according to the method described by Pfaff (1973).

2.5. Experimental design

2.5.1. Effects on male sex behavior

Acute injection of melatonin (10, 50 and 100 μg/kg) was made during the late scotophase, 1 h before mating test (i.e., 9 h after the lights were turned off). The hormone was freshly dissolved in saline and administered i.p. in a final volume of 1 ml. Control animals received an i.p. injection of saline alone with the same procedure and in the same volume. Melatonin (50 and 100 ng/2 μl) or its analogs 6-chloromelatonin (selective Mel1b melatonin receptor agonist, 2 and 4 ng/2 μl) and 2-iodomelatonin (non-selective melatonin receptor agonist, 5 and 10 ng/2

μl) were dissolved in saline and injected intracerebroventricularly (i.c.v.) 30 min before mating. In another experiment, groups of rats were repeatedly injected i.p. with melatonin (10, 50, 100 μg/kg or 1 mg/kg daily for 14 days), the last injection being made 1 h before the 30-min mating test. Repeated injections were always made during the late scotophase.

2.5.2. Effects on female sex behavior

Melatonin was injected to female rats i.p. at the doses of 10, 50 or 100 μg/kg 1 h prior to mating. The treatment was made acutely (1 h before the mating test) or repeatedly (every day for 14 days, 9 h after the light was turned off, the last injection being made 1 h before the mating test).

2.5.3. Role of melatonin and serotonin receptors

Two experiments were made in order to study the possible involvement of central melatonin and serotonin receptors in the behavioral effects of the hormone. Groups of male rats were treated acutely with melatonin (100 μg/kg, i.p. or 100 ng/2 μl, i.c.v.) 30 min after a pretreatment with the non-selective melatonin receptor antagonist, luzindole dissolved in a water:ethanol 1:2 solution and injected s.c. at the dose of 0.25 mg/kg in a total volume of 1 ml. Other animals were injected with saline i.p. or i.c.v. and luzindole s.c. Control rats received saline i.p. or i.c.v. and water:ethanol 1:2 solution s.c. injections in a total volume of 1 ml each. Mating activity was tested 1 h after i.p. melatonin or 30 min after i.c.v. melatonin. In the second experiment, groups of male rats received an i.p. or i.c.v. injection of melatonin and a simultaneous injection of serotonin (5 ng/1 μl, dissolved in saline) or the $5H_{2A}$–$5H_{2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (2 ng/1 μl, dissolved in saline) into the amygdala.

2.6. Statistical analysis

The one-way analysis of variance (one-way ANOVA) followed by the post-hoc Dunnett's test for multiple comparisons were used for the statistical analysis of data obtained for each behavioral item. A *P*-level of 0.05 or less was accepted as indicative of a significant difference (Rohlf and Sokal, 1978).

3. Results

3.1. Effects on male sex behavior

Acute i.p. injection of melatonin in sexually active male rats reduced the latency to the first mount, intromission and ejaculation and increased the frequency of mounts, intromissions and ejaculations (Table 1). This effect, however, did not appear to be dose-dependent. Similar results were observed after i.c.v. injection of melatonin and its analogs, 6-chloromelatonin and 2-iodomelatonin (as shown in Fig. 1A and B, where only ejaculation parameters are presented). Again, a reduced latency to the first ejaculation and an increased frequency of ejaculation were found but with no clear dose–response relationship. Repeated injection of melatonin to male rats in a dose-range of 10–100 μg/kg for 14 days failed to modify either the latencies to and the frequencies of sex behavior items (data not shown). In contrast, increased latencies and reduced frequencies were observed when a greater dose (1 mg/kg) of melatonin was injected for 14 days.

Table 1
Latency to the first mount, intromission, and ejaculation and frequency of mounts, intromissions and ejaculations in sexually active male rats after acute or repeated i.p. injection of melatonin (MEL)
Values are means ± S.E.M. of measures of time expressed in seconds (for latencies) and of total number of events over a 30-min mating test (for frequencies). Each experimental group included seven animals.

		Mount	Intromission	Ejaculation
Latency				
Acute	Saline	35 ± 3.0	48 ± 2.7	831 ± 90.1
	MEL 10 μg/kg	21 ± 1.9*	24 ± 2.9*	578 ± 57.9*
	MEL 50 μg/kg	22 ± 3.9*	21 ± 2.1*	339 ± 50.1*
	MEL 100 μg/kg	20 ± 2.9*	20 ± 2.0*	334 ± 41.0*
Repeated	Saline	34 ± 5.1	42 ± 3.1	811 ± 88.1
	MEL 1 mg/kg	156 ± 10.0*	167 ± 17.1*	1391 ± 123.1*
Frequency				
Acute	Saline	40 ± 3.0	42 ± 4.1	2 ± 0.1
	MEL 10 μg/kg	55 ± 3.2*	55 ± 3.8*	3 ± 0.1*
	MEL 50 μg/kg	53 ± 4.2*	54 ± 3.9*	3 ± 0.2*
	MEL 100 μg/kg	55 ± 3.9*	61 ± 3.3*	3 ± 0.1*
Repeated	Saline	38 ± 3.3	41 ± 4.0	2 ± 0.2
	MEL 1 mg/kg	11 ± 1.9*	15 ± 1.1*	0 ± 0.1*

*Significantly different as compared to saline-injected controls ($P < 0.05$, post-hoc Dunnett's test for multiple comparisons).

3.2. Effects on female sex behavior

Female rats acutely injected with melatonin at any of the doses used (10–100 μg/kg) did not show changes in the lordosis quotient as compared to control animals (data not shown). The repeated injection of melatonin, however, was followed by a dose-dependent decrease of the behavioral parameter (6.0 ± 0.5 for saline, 3.2 ± 0.2 for 10 μg/kg, 2.4 ± 0.2 for 50 μg/kg, 1.9 ± 0.1 for 100 μg/kg).

3.3. Role of melatonin and serotonin receptors

The non-selective melatonin receptor antagonist, luzindole injected alone at the dose of 0.25 mg/kg s.c. decreased latency to the first mount, intromission and ejaculation (Table 2). No effect was observed on the frequency of these behavioral parameters (data not shown). The

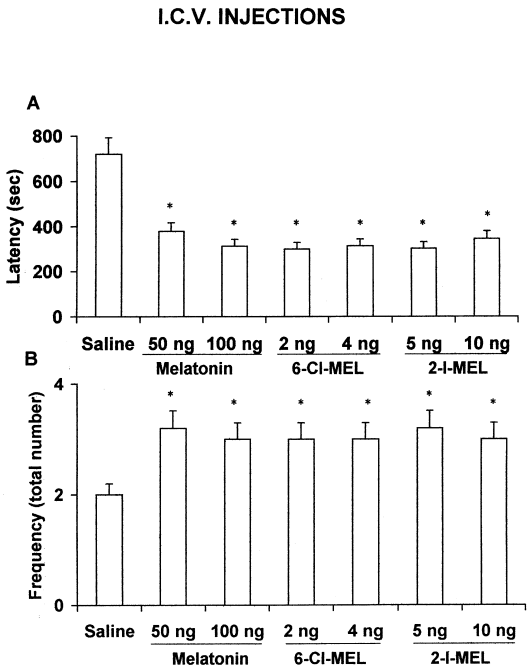

Fig. 1. Latency to the first ejaculation (A) and frequency of ejaculations (B) in sexually active male rats injected intracerebroventricularly (i.c.v.) with melatonin (50 and 100 ng/2 μl) or its alogs 6-chloromelatonin (6-Cl-MEL, 2 and 4 ng/2 μl) and 2-iodomelatonin (2-I-MEL, 5 and 10 ng/2 μl). Injections were made 30 min before a 30-min mating test. Values are means ± S.E.M. of time measures expressed in seconds (for latency) and of total number of events over a 30-min mating test (for frequency). Each experimental group included seven animals. * Significantly different as compared to saline-injected control animals ($P < 0.05$, post-hoc Dunnetts' test for multiple comparisons).

administration of luzindole made 30 min before the injection of melatonin (100 μg/kg, i.p. or 100 ng/2 μl, i.c.v.) prevented the effect of the latter on latency to the first mount and intromission. It failed to change the effect of the hormone on latency to the first ejaculation and on frequency of mounts, intromissions and ejaculations (data not shown). Furthermore, when i.p. or i.c.v. melatonin-treated male rats were simultaneously injected into the amygdala with serotonin or the $5H_{2A}$–$5H_{2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane, they showed a total suppression of the facilitating effect of melatonin on all parameters of sex behavior. In particular, intra-amygdala treatments inhibited the effect of melatonin on the latency to the first ejaculation and on frequency of ejaculations (Table 3). The injection of serotonin or 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane into the amygdala in i.p. or i.c.v. saline-treated animals induced an increase in latency to the first ejaculation and a decrease in the frequency of ejaculations.

Table 2
Effects of the non-selective melatonin receptor antagonist, luzindole (LUZ) on the latency to first mount, intromission and ejaculation in sexually active rats treated with melatonin (MEL)
Melatonin was injected acutely i.p. (100 μg/kg) or i.c.v. (100 ng/2 μl). Luzindole was administered s.c. at the dose of 0.25 mg/kg. Values are means ± S.E.M. of time measures expressed in seconds. Each experimental group included seven animals.

	Mount	Intromission	Ejaculation
Saline i.p. + vehicle s.c.	29 ± 2.0	30 ± 2.8	699 ± 70.1
Saline i.p. + LUZ s.c.	14 ± 1.1*	17 ± 1.9*	324 ± 28.1*
MEL i.p. + vehicle s.c.	19 ± 2.0*	20 ± 1.8*	321 ± 34.2*
MEL i.p. + LUZ s.c.	30 ± 3.4†	32 ± 2.2†	361 ± 40.1
Saline i.c.v. + vehicle s.c.	25 ± 3.1	38 ± 3.2	710 ± 61.2
Saline i.c.v. + LUZ s.c.	16 ± 1.4*	19 ± 2.3*	322 ± 21.2*
MEL i.c.v. + vehicle s.c.	17 ± 1.0*	19 ± 2.1*	313 ± 34.2*
MEL i.c.v. + LUZ s.c.	27 ± 3.2†	32 ± 3.3†	373 ± 31.1

* Significantly different as compared to saline/vehicle-injected controls ($P < 0.05$, post-hoc Dunnett's test for multiple comparisons).
† Significantly different as compared to MEL/vehicle-injected animals ($P < 0.05$, post-hoc Dunnett's test for multiple comparisons).

Table 3
Effects of serotonin or the $5H_{2A}$–$5H_{2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DIA) injected in the amygdala on the latency to first ejaculation and on frequency of ejaculations in sexually active rats treated i.p. or i.c.v. with melatonin (MEL)
Melatonin was injected acutely i.p. (100 μg/kg) or i.c.v. (100 ng/2 μl). Serotonin was or DIA were administered in the amygdala at the dose of 5 ng/1 μl and 2 ng/1 μl, respectively. Values are means ± S.E.M. of time measures expressed in seconds (for latencies) and of total number of events over a 30-min mating test (for frequencies). Each experimental group included seven animals.

		Latency	Frequency
Saline i.p. +	saline in the amygdala	747 ± 62.4	2 ± 0.1
	serotonin in the amygdala	979 ± 84.4*	0 ± 0.0*
	DIA in the amygdala	909 ± 81.1*	0 ± 0.0*
MEL i.p. +	saline in the amygdala	227 ± 22.9*	3 ± 0.3*
	serotonin in the amygdala	821 ± 34.2†	1 ± 0.1†
	DIA in the amygdala	861 ± 41.1†	2 ± 0.1†
Saline i.c.v. +	saline in the amygdala	810 ± 91.0	1 ± 0.1
	serotonin in the amygdala	952 ± 86.3*	0 ± 0.0*
	DIA in the amygdala	961 ± 87.1*	0 ± 0.0*
MEL i.c.v +	saline in the amygdala	312 ± 34.2*	3 ± 0.2*
	serotonin in the amygdala	922 ± 101.2†	1 ± 0.1†
	DIA in the amygdala	913 ± 94.2†	1 ± 0.1†

* Significantly different as compared to saline/saline-injected controls ($P < 0.05$, post-hoc Dunnett's test for multiple comparisons).
† Significantly different as compared to MEL/saline-injected animals ($P < 0.05$, post-hoc Dunnett's test for multiple comparisons).

4. Discussion

The physiology of reproduction in mammals seems to be under control of melatonin (Meyer and Theron, 1988; Tijmes et al., 1996). This hormone also exerts a profound influence on sex behavior. Chronic administration of melatonin leads to the inhibition of male sexual activity (Yamada et al., 1992). The implantation of a melatonin-containing beeswax pellet near the SCN in female rats reduced their lordosis reflex when exposed to the males (De Catanzaro and Stein, 1984). Besides, i.p. injection of melatonin inhibits the nervous structures involved in regu-

lation of the sexual cycle of the female rat (Diaz Lopez and Fernandez, 1984).

The present data confirm the inhibitory effect of repeated administration of melatonin on rat female sex behavior, but the original results concern the stimulatory effects of melatonin on male sexual activity when the hormone was administered acutely in a dose-range of 10–100 μg/kg in sexually active rats. In particular, the acute injection (but not the repeated administration) of low doses of melatonin administered either i.p. or i.c.v. or of its analogs, 6-chloromelatonin [selective Mel1b melatonin receptor agonist (Dubocovich et al., 1998)] and 2-iodomelatonin [non-selective melatonin receptor agonist (Dubocovich et al., 1998)] administered i.c.v. in the late scotophase enhanced the full pattern of male copulatory behavior including ejaculation. In contrast, the repeated injection of the hormone either failed to affect (with low doses) or inhibited (with a large dose) sexual activity of male rats. The duration of treatment may be essential for the type of action exerted by this hormone on mating behavior of male animals. Interestingly, the inhibitory effect of the pineal gland on the neuroendocrine reproductive axis seems to be due to a longer increased nocturnal peak of melatonin (Diaz Lopez et al., 1993). Thus, it is possible that long-term treatment with this hormone induces a suppression of sex behavior because it mimics a persistent peak of the hormone. Consistently with this hypothesis, the minimal effective quantity of infused melatonin inhibiting sexual activity in hamsters is 40 ng/h for 8 h per day, while an infusion of 6 h is not effective (Pitrosky et al., 1991). In contrast, the acute surge of melatonin may stimulate male and female sex behavior acting as an internal signal on the nervous structures involved in sexual processes such as amygdala, ventral hypothalamus, septal area and posterior cortex (Diaz Lopez et al., 1993). The doses of melatonin that were used here are far smaller than those used in other studies and seem to be closer to physiological blood concentration of the hormone. In fact, a larger dose (1 mg/kg) injected repeatedly inhibited male rat sex behavior under the same experimental conditions. Interestingly, the same inhibitory effect was found in a preliminary experiment where melatonin was injected acutely in a dose of 1 mg/kg (Drago, unpublished observation).

The repeated injection of melatonin during the late photophase or the late scotophase causes reduced weights of testes and seminal vesicles, and lowered plasma and testosterone levels. No effect is observed during the first 7 h of the scotophase (Lang et al., 1984). Thus, it is important that in the present experiments melatonin was injected either acutely or repeatedly 9 h after the onset of scotophase.

Low doses of melatonin were found to be effective in facilitating male sex behavior either after i.p. or i.c.v. injection. Its analogs, 6-chloromelatonin and 2-iodomelatonin were also active either after i.p. (Drago, unpublished observation) or i.c.v. administration. This may suggests that the behavioral action of these substances is mediated by central rather than peripheral mechanisms. No dose–response relationship was clearly found either after i.p. or i.c.v administrations for any of the substances examined in the dose-range selected for these experiments. However, it appears that on a dose basis the effect of analogs was greater than that of melatonin.

The physiological and pharmacological effects of melatonin seem to be mediated by activation of high-affinity receptors in the brain (Zawilska and Nowak, 1996; Sugden, 1998). In fact, the non-selective Mel1a/Mel1b melatonin receptor antagonist, luzindole reversed the stimulatory effect of melatonin on male sexual activity although failing to influence ejaculation parameters. This drug showed to exert per se a stimulatory activity on some male sex behavior parameters. These results are difficult to explain, but it should be remembered that luzindole exerts psychostimulant activity (Mogilnicka and Dubocovich, 1987). It is possible but unlikely that these effects depend on a pharmacological profile of the drug as agonist/antagonist on melatonin receptors (Dubocovich, 1988; Dubocovich et al., 1998). Interestingly, since both the selective Mel1b melatonin receptor agonist, 6-chloromelatonin and the non-selective melatonin receptor agonist, 2-iodomelatonin were found to be active in the present experiments, it is likely the Mel1b melatonin receptor is primarily involved in the behavioral effects of melatonin. Interestingly, the pharmacological profile of the human recombinant Mel1b melatonin receptor is similar to that of the functional presynaptic melatonin heteroreceptor of rabbit retina. Thus, a presynaptic mechanism is likely to be involved in the behavioral effects of melatonin when administered at low doses. Moreover, melatonin may influence the function of various neurotransmitters in the brain. Acute systemic melatonin reduces serotonin release in different brain areas in rats (Chuang and Lin, 1994), and, like some antidepressants, acts as a $5HT_{2A}$ antagonist (Eison et al., 1995). Injection of serotonin antagonists (methysergide or cyproheptadine) into the nucleus accumbens (NA) results in similar behavioral changes as found after treatment with melatonin, e.g., decreased locomotor activity and rearing, and increased grooming and sniffing behavior (Gaffori and Van Ree, 1985b). Also, administration of serotonin into the NA completely inhibited melatonin-induced behavioral responses. Serotonin suppresses sex reflexes (Marson and McKenna, 1994) and inhibits copulatory behavior of male rats (Ahlenius et al., 1980). In the present experiments, injections of serotonin or 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane into the amygdala induced per se inhibitory effects on male sex behavior. Thus, the stimulation of male sexual activity by acute injections of low doses of melatonin could be explained by an interference of the hormone with serotonergic neurotransmission. This hypothesis is supported by the total suppression of melatonin-induced sex behavior activation

found after injections of serotonin or the $5H_{2A}$–$5H_{2C}$ receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane into the amygdala. A serotonergic mechanism controlling male mating behavior through the involvement of central melatonin may exist in this area. Amygdala, together with the ventral hypothalamus, the septal area and the posterior cortex are the brain structures mainly involved in sexual processes in the male rat where melatonin signal may have a target (Diaz Lopez et al., 1993). The present experiments, however, are too preliminary to allow any conclusion on possible 5-HT_2 receptor subtypes and brain regions involved in the melatonin effects on sex behavior.

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