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Short communication

Melatonin facilitates short-term memory

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Abstract

The olfactory social memory test, based on the recognition of a juvenile rat by a male adult rat, was used to investigate whether melatonin influences memory. Intracerebroventricular (i.c.v.) injection of 1.1 nmol melatonin shortened recognition time, while the melatonin ML_1 receptor antagonist luzindole (1 nmol) exerted the opposite effect. The facilitating influence of melatonin was abolished in the presence of 0.5 nmol luzindole. The findings suggest that endogenous melatonin facilitates short-term memory.

Keywords: Memory, short-term; Melatonin; Luzindole; (Rat)

1. Introduction

The physiological significance of the hormone melatonin is obscure. Besides its involvement in circadian rhythms, melatonin is thought to influence physiological and behavioural processes, as well as neuroendocrine function (Krause and Dubocovich, 1990). Melatonin seems to affect passive and active avoidance learning, probably by reducing activity (Martini, 1971; Kovács et al., 1974), but this interpretation has been questioned (review article: Datta and King, 1980). Nevertheless, peripheral administration (Wong and Whiteside, 1968; Datta and King, 1980) and central microinjection of melatonin into the nucleus accumbens decrease locomotor activity and this effect has been attributed to interactions with the serotonin system (Gaffori and Van Ree, 1985). On the other hand, it has also been observed that melatonin improves shift worker's alertness during working hours (Folkard et al., 1993). Additionally, it has been found that the hormone reduces reaction time in patients with affective disorders (Sherer et al., 1985).

In the brain, melatonin binding sites have also been found in regions implicated in cognition and memory (Cardinalli et al., 1979; Weaver et al., 1989). Since melatonin ameliorates extinction of an active avoidance response, it has been proposed that the hormone inhibits memory, probably by affecting motility and/or adrenocorticotropin (ACTH) secretion (review article: Datta and King, 1980). Recently, at least two subtypes of melatonin receptors, ML_1 and ML_2, have been identified (Dubocovich, 1995; Reppert et al., 1996), luzindole being a full agonist at ML_1 receptors. To investigate the possible involvement of melatonin in cognitive processes, we centrally injected melatonin and luzindole alone or in combination and investigated their effects on short-term memory. For this purpose, we used the olfactory, social memory test, which is based on the recognition of a juvenile rat by a male adult rat (Carr et al., 1976; Thor and Holloway, 1982).

2. Materials and methods

Approximately 6 month old (400–500 g), male Sprague–Dawley rats were used as adult rats, and 1-month old (80–120 g) male Sprague–Dawley rats were used as juvenile rats. Experiments were carried out between 11:00 AM and 4:00 PM, as previously described (Prast et al., 1996). Briefly, drugs were injected i.c.v. into the right lateral ventricle through a cannula inserted under pentobarbital sodium (40 mg/kg, i.p.) and ketamine (50 mg/kg, i.p.) anaesthesia. After a recovery period of 4 days, an

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adult rat was placed for 10 min in the observation cage. Subsequently, a juvenile rat was exposed to the adult rat for 5 min and the time the adult rat took to investigate the juvenile rat was recorded. Social investigatory behaviour of the adult rat was defined as being close to (tip of nose within approximately 1 cm) or in direct contact with the juvenile while sniffing, following, nosing, grooming or generally inspecting any body surface of the juvenile (Thor and Holloway, 1982; Sawyer et al., 1984). After the first exposure, drugs were applied i.c.v. The second exposure followed 60 min (melatonin, or melatonin combined with luzindole) or 30 min (luzindole applied alone) after drug administration. The time necessary for recognition was recorded as mentioned above. Data were calculated as the ratio 'investigation duration during second contact/investigation duration during first contact' (RID), so as to minimize day-to-day changes in rat behaviour and to equalize individual differences between rats. When intervals between first and second contact were shorter than 30 min, the duration of recognition during the second contact was reduced (RID approximately 0.7). This did not occur when the intervals were longer than 45 min (RID approximately 1). For this reason, the effects of drugs expected to suppress memory were investigated after an interval of 30 min. When given alone, luzindole was dissolved in artificial cerebrospinal fluid (CSF), and melatonin alone or in combination with luzindole was diluted in CSF:ethanol (400:1). Volumes of 10 μl were injected over a period of 30 s. Control rats were treated with 10 μl of the respective vehicle i.c.v. (Prast et al., 1996). As a control for memory-dependent changes in investigation duration, an unknown juvenile rat was exposed to the adult rat after drug treatment. Statistical analysis was carried out by analysis of variance followed by a least-square difference test. Drugs used were melatonin (RBI, Natick, USA) and luzindole (Tocris Cookson, St. Louis, USA).

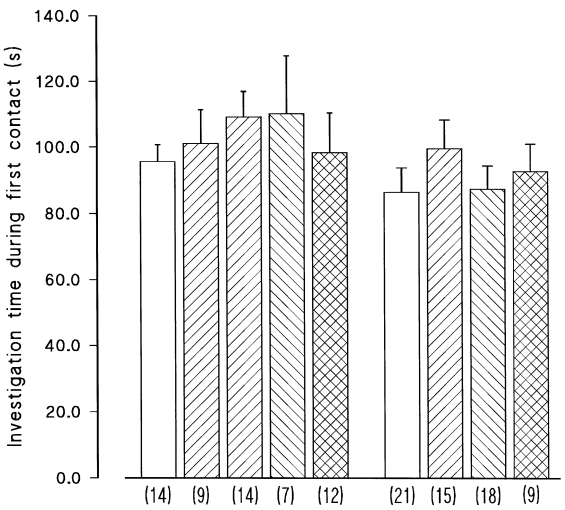

Fig. 1. Duration of social investigatory behaviour during the first contact of adult males with a juvenile male rat. Scale: time in seconds, means ± S.E.M., number of experiments in parentheses. The nine groups of rats are identical to those in Fig. 2.

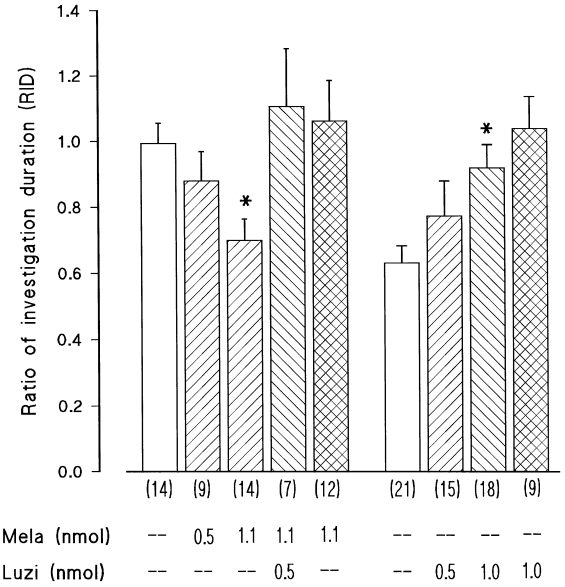

Fig. 2. Effects of melatonin and luzindole on the olfactory social memory test. Scale: 'ratio investigation duration during second contact to investigation duration during first contact' (RID). Mela: melatonin; Luzi: luzindole. Control rats (open columns) were treated with the vehicle. The 5th and 9th columns show the test for specificity of effects, in which an unknown juvenile rat was exposed to the adult rat during the second contact. Number of experiments in parentheses. $* P < 0.05$ vs. control value.

3. Results

During first contact, the time the adult rat spent investigating a juvenile rat was similar in all groups of animals (99 ± 5 s; mean value ± S.E.M. of group means, $n = 9$; Fig. 1). Injection of 0.5 nmol melatonin tended to shorten the second investigation time (RID 0.879 ± 0.168; Fig. 2), but this effect was statistically not significant ($P < 0.1$). Injection of 1.1 nmol melatonin shortened significantly the investigation time during the second contact with the same juvenile rat, thus reducing RID. When injected together with 0.5 nmol luzindole, melatonin (1.1 nmol) was ineffective. Given alone, 0.5 nmol luzindole did not influence RID. However, 1.0 nmol luzindole prolonged significantly the investigation time 30 min after drug injection. When an unknown juvenile rat was exposed to the adult rat during the second contact, neither melatonin nor luzindole influenced the investigation time, thus demonstrating the specificity of the observed effects (Fig. 2).

4. Discussion

The finding that recognition time was shortened by melatonin indicates that the hormone, centrally applied,

leads to a facilitation of short-term memory. The elimination of the melatonin-induced improvement of memory by the melatonin ML_1 receptor antagonist luzindole also underpins the specificity of the finding. Since luzindole, given alone, prolonged recognition time, it might be suggested that endogenous melatonin has a permanent, facilitatory influence on memory processes.

Our findings might be surprising in the light of results suggesting that melatonin has substantial but short-acting sedative-like properties in patients (Lieberman et al., 1984, 1985) and potentiates pentobarbitone-induced sleep in rats and mice (review article: Datta and King, 1980). However, at least in rats, i.p. administration of melatonin per se does not seem to influence the state of vigilance, as revealed by analysis of EEG power spectra (Tobler et al., 1994). Besides sedation elicited by melatonin, other memory-independent effects, such as a general reduction in motor activity, a decrease in emotionality and anxiolytic properties (Neville and McNaughton, 1986) have been reported. A depressant effect of melatonin has also been suggested on the basis of the antidepressant-like activity of luzindole, though melatonin itself is ineffective (Dubocovich et al., 1990).

However, the social interaction test renders it possible to differentiate specific, memory-enhancing properties of drugs from general, nonspecific effects. Nonspecific influences, such as impairment of alertness, are identified by exposing an unknown juvenile rat to the adult rats during the second contact. If nonspecific influences do not exist, the time of social investigation during the second contact is identical with the time during the first contact. Drugs which impair alertness greatly change the RID under these control conditions (Perio et al., 1989).

If this nonspecific influence is eliminated, then the RID of the social investigation test reflects short-time memory, based on olfactory recognition (Carr et al., 1976; Thor and Holloway, 1982; Sawyer et al., 1984). It has been shown that the RID is decreased and enhanced by drugs which facilitate and inhibit memory, respectively (Dantzer et al., 1987).

In the present study, neither melatonin nor luzindole changed the time spent investigating an unknown juvenile, indicating that these compounds do not influence alertness and do not possess other nonspecific properties. The facilitation of memory found seems to be consistent with the improved performance observed in patients (Folkard et al., 1993; Sherer et al., 1985), as mentioned in Section 1.

Previously, opposing findings have been reported concerning the influence of melatonin on memory. It has been found that melatonin affects avoidance by facilitating the extinction of learned responses, whereas memory acquisition is not influenced (Martini, 1971; Kovács et al., 1974; Datta and King, 1980). However, avoidance conditioning involves long-term memory. Moreover, the discrepancy between our results and those of earlier investigations might be due to differences in dosage, age of animals, time interval between injection of drug and observation and/or route of melatonin administration. It should also be emphasized that, in contrast to avoidance tests, the social investigation test is not stressful.

5. Conclusion

Our findings suggest that melatonin facilitates short-term memory, and that endogenous melatonin exerts a permanent facilitatory influence on memory processes. It remains to be clarified whether melatonin and luzindole exert similar effects in other memory tests when applied i.c.v. in rats and, most importantly, whether peripheral administration of the hormone also improves memory.

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