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REM Sleep Deprivation Changes Behavioral Response to Catecholaminergic and Serotonergic Receptor Activation in Rats

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MOGILNICKA E. *REM sleep deprivation changes behavioral response to catecholaminergic and serotonergic receptor activation in rats.* PHARMAC. BIOCHEM. BEHAV. 15(1) 149–151, 1981.—The effects of REM sleep deprivation (REMD) on apomorphine-induced aggressiveness and quipazine-induced head twitches in rats were determined. Forty-eight hr of REMD increased apomorphine-induced aggressiveness, and reduced (immediately after completing of REMD) or increased (96 hr after completing of REMD) quipazine-induced head twitches. Results are discussed in terms of similarity to pharmacological effects of other antidepressive treatments.

REM sleep deprivation Aggression Head twitches

ACCORDING to clinical investigations, sleep deprivation (of REM phase) may have an antidepressive therapeutic effect [18]. Hence, it seemed interesting to compare, applying pharmacological tests, the effects of sleep deprivation with the effects of chronically administered antidepressant drugs. We have demonstrated in our previous studies that REMD elicits in rats changes similar to those observed after chronic administration of antidepressants and electroshocks. Like imipramine, desipramine or electroshocks [7, 13, 17], REMD reduced density of ^{3}H-dihydroalprenolol and ^{3}H-imipramine binding sites in the rat cerebral cortex [9] and inhibited clonidine-induced sedation [11].

Taking into account the fact that catecholamines and serotonin (5-HT) are essential for sleep [6] and that antidepressive therapy (whether with antidepressants or with electroshocks) affects catecholaminergic and 5-HT-ergic systems, we decided to check whether the behavioral response to stimulation of these systems is altered in rats deprived of REM sleep.

Accordingly, the influence of REMD on apomorphine (APO), dopamine (DA)-agonist, was studied. Stereotypy and aggressive behavior served as the criteria of catecholaminergic activity; the activity of 5-HT-ergic system was evaluated by measuring head twitch response induced in rats by administration of quipazine.

METHOD

REM Deprivation

Male Wistar rats (200–250 g) were used for experiments. REMD was achieved using the water tank procedure. For experiments, two groups of animals were studied in parallel: in the first, the control group, rats were kept (for 48 hr) individually in dry transparent cages; in the second group, REMD was achieved by placing the animals on small platforms of 6 cm diameter surrounded by water—this condition permitted the occurrence of slow wave sleep but not of REM sleep [2]. Rats were deprived of REM sleep for 48 hr, beginning at 10 a.m. All rats—control and REM deprived animals—had unlimited access to food and water.

Stereotypy and Aggressiveness

Immediately or 96 hr after completing of a 48 hr lasting REMD, rats were placed individually in wire mesh cages (20×20×23 cm), injected with APO 0.5 mg/kg (dissolved in water) to assess stereotypy, or with a dose of 5 mg/kg SC to test aggressive behavior (10 min after the injection of APO the animals were paired). Stereotypy was assessed 30 min after APO injection using the scale 0–4 [4]. Fighting behavior was defined when both rats assumed upright posture standing on their hind legs, or when the animal forced its partner to assume different patterns of submissive posture. The number of rat pairs showing continuous or incidentally interrupted fighting was recorded and included in Table 1.

Head Twitches

Immediately or 48, 72 and 96 hr after completing of a 48 hr lasting REMD, rats were placed individually in wire mesh cages and, just after injection of quipazine 10 mg/kg IP, head twitches were recorded for 30 min. Quipazine hydrochloride was dissolved in 0.9% NaCl.

RESULTS

REMD did not affect the stereotypy induced by APO

TABLE 1

EFFECT OF 48 HR REM SLEEP DEPRIVATION (REMD) ON AGGRESSIVE BEHAVIOR INDUCED BY APOMORPHINE 5 mg/kg SC IN RATS

Treatment condition	Time (hr) after completing REMD	No. fighting pairs / No. pairs used	Positive response (%)
Control	0	0/5	0
REMD		5/5	100
Control	96	0/5	0
REMD		1/5	20

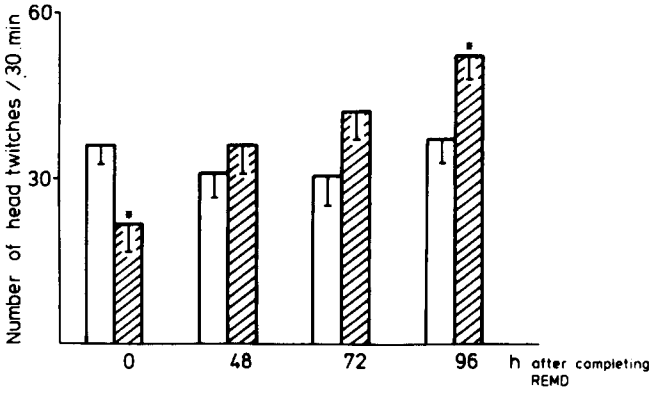

FIG. 1. Effects of a 48 hr REM sleep deprivation (REMD) on head twitches response in rats induced by quipazine. Quipazine (10 mg/kg IP) was given to control rats (white columns) or to REMD rats (hatched columns) immediately, 48, 72 or 96 hr after completion of REMD. The results are mean with SEM of data obtained from 11–12 rats. $*p<0.05$ (t-test).

neither immediately after completing of REMD nor 96 hr later (data not shown).

APO (5 mg/kg) apparently did not induce aggressiveness in control rats. A strong aggressive behavior after APO was observed in REMD animals when APO was given immediately but not 96 hr after completing of a 48 hr REMD (Table 1). Fighting occurred just after the pairing and persisted incessantly or with short breaks for about 1.5 hr.

As is shown in Fig. 1, REMD reduces the number of quipazine-induced head twitches if quipazine is administered immediately after completing of deprivation. However, if administration of quipazine is postponed for some time (48, 72, 96 hr) after completion of deprivation, the opposite effect is observed, i.e. quipazine increases the number of head twitches in REMD animals. This effect is statistically significant for quipazine administered after a delay of 96 hr.

DISCUSSION

In this study, we have confirmed the fact, noted by other authors [16], of increase by REMD of APO-induced aggression. We have also found that REMD changed the response to serotonergic stimulation, which was quantified by the number of quipazine-induced head twitches.

In the mechanism of pharmacologically induced aggression an important role is attributed to the DA-ergic and noradrenergic systems [14,15]. The potentiation of APO-induced aggression may be due to the enhanced function of the catecholaminergic system. It seems, however, that a 48 hr REMD potentiates APO-induced aggression by affecting the noradrenergic rather than the DA-ergic system, since REMD did not modify APO-induced stereotypy. This involvement of the noradrenergic system is further implicated by the results of our previous studies where we demonstrated that REMD abolished clonidine-induced sedation [11]. Similar results, i.e., potentiation of APO-induced aggression, were observed by Tufik *et al.* [16], though they observed, in addition, the enhancement of APO-induced stereotypy. From these results, they suggested that after REMD the supersensitivity of DA receptors occurs. They used, however, a longer period of REMD than we did; thus, it is possible that a 48 hr REMD is not sufficient to induce alterations in the DA-ergic system.

The influence of REMD on aggression is similar to the effect of other antidepressive treatments. We have demonstrated previously that chronic administration of antidepressants potentiates APO-induced aggression [8] or footshock-induced aggression [3,12] and that this effect was sustained for a considerable period of time (unpublished data). In the case of REMD, the potentiation of aggression was noticeable immediately after completion of 48 hr lasting deprivation; 96 hr later this effect disappeared. We think, that longer lasting REMD would induce more durable changes and that the potentiation of aggression would continue for a longer time, as it does after treatment with antidepressants. Recently, Hicks *et al.* [5] have shown that REMD increased aggression in rats in a "dose-dependent" manner: the effect of 4 days REMD was more pronounced and longer lasting than the effect of 2 days REMD.

In the second series of experiments, we have demonstrated that REMD modifies the response to the stimulation of 5-HT-ergic system: REMD reduced the behavioral response (head twitches) to quipazine if the drug was given immediately after completion of REMD; after a 96 hr delay, the head twitch response to quipazine was increased.

The similar pattern of alterations in the response to 5-HT-ergic stimulation was detected after treatment with antidepressants: chronic treatment with amitriptyline or imipramine inhibited head twitches induced in mice by 5-methoxydimethyltryptamine if this agent was given 1 hr after the last dose of antidepressant; after a 48 hr delay, the number of head twitches was increased [4]. We have also reported an increase in behavioral response to 5-hydroxytryptophan after a chronic treatment with mianserin, danitracen and amitriptyline [10]. The increased response of the 5-HT-ergic system, which is observed after REMD, suggests the occurrence of supersensitivity. De Montigny and Aghajanian [1] found this phenomenon after prolonged treatment with antidepressants. They showed that various antidepressants given chronically potentiated the response of forebrain neurons to electrically applied 5-HT. Recently, Vetulani *et al.* [17] have concluded that electroconvulsive treatment leads to the supersensitivity of the 5-HT-ergic sys-

tem in rats, since they demonstrated an increase in the density of ^{3}H-spiperone-labelled 5-HT receptors and potentiation of quipazine or 5-HTP-induced head shakes in animals treated with electroshocks.

The results obtained in this study indicate that in rats REMD induces changes in noradrenergic and 5-HT-ergic systems similar to those obtained with other antidepressive treatment, e.g., chronic administration of antidepressants or electroshocks.

This similarity indicates a potential application of REMD in the therapy of depression.

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