Effects of Parlodel on Sleep-Wake Cycles in Rats with MPTP-Induced Depressive Syndrome

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Chronic treatment with Parlodel normalized the parameters of REM sleep disturbed by multiple systemic administration of the dopaminergic neurotoxin MPTP, which is a novel model of depressive syndrome in rats. When administered prior to MPTP, Parlodel reduced the occurrence of REM sleep episodes, shortened duration of REM sleep, and prolonged REM sleep latency. It also reduced the percentage of REM sleep episodes in the total time of sleep.

Key Words: *REM sleep; depression; MPTP; Parlodel; rats*

Neuropathophysiological mechanisms of depression have not yet been sufficiently understood. In recent years, much attention is focused on central dopaminergic mechanisms of depression [1,5]. In patients, impairment of REM sleep (a sleep phase with rapid eye movements, or the paradoxical phase of sleep) has been considered as a biological correlate and a possible biological marker of developing depression [6, 7,10]. Alterations in the sleep-wake cycle, and specifically, REM sleep disturbances, resulting from decreased functional activity of the brain dopaminergic-system were observed in old people [5]. REM sleep impairment in rats similar to that in patients was reported on experimental model of depression induced by neonatal administration of clomipramine [14]. Previously, we have developed a new model of depression in rats by using multiple systemic administrations of the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [4]. It was found that chronic administration of MPTP increases the frequency of REM sleep episodes, reduces their latency, and increases both the duration of REM sleep and the percentage of REM sleep in the total sleep time [2]. Chronic administration of Parlodel, a bromocriptine derivative (D_2 dopamine receptor agonist), prevented the development of the behavioral depressive syndrome in rats [3]. In this study we investigated the effects of Parlodel on the parameters of REM sleep in rats with MPTP-induced depressive syndrome (DS).

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MATERIALS AND METHODS

The study was carried out on 22 male Wistar rats weighing 300-370 g. The animals were housed in pairs under standard conditions with natural light/dark cycle and free access to food and water. Electrical activity (EA) of the sensorimotor cortex, caudate-putamen, and dorsal hippocampus and EMG of neck muscles were recorded under conditions of free behavior via electrodes implanted as described elsewhere [2]. Electrical activity was recorded at 10.00-14.00 on days 5-6 after surgery, on days 3 and 12 of treatment, and 1 week after cessation. Substances were administered for 12 days in a volume of 1 ml/kg body weight. Four groups were formed: group 1 rats (n=6) received saline; group 2 rats (n=6) received saline perorally and MPTP (20 mg/kg intraperitoneally) 45-50 min after saline; group 3 rats (n=5) received Parlodel perorally (5 mg/kg) 45-50 min prior to intraperitoneal MPTP; group 4 rats (n=5) received Parlodel perorally and intraperitoneal saline 45-50 min after it. The interval between the administration of Parlodel (Bromocriptine mesylate) and MPTP was chosen on the basis of previous finding that the level of striatal dopamine peaked 1 h after bromocriptine administration [11]. Parlodel (Sandoz) was given as a suspension: crushed tablets were

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dissolved in 1-2 drops of Tween-80, adjusted to a required volume with saline, and administered by a syringe with a special attachment to prevent the damage to oral tissues. The neurotoxin MPTP (Institute of Pharmacology of the Russian Academy of Medical Sciences) was dissolved in saline immediately before administration.

The parameters of sleep-wake cycles were assessed as described elsewhere [2]. Minute records were analyzed and classified as sleep or wakefulness depending on the predominant activity. The onset of REM episode during slow-wave sleep was recognized by cortical desynchronization and decreased EA amplitude, synchronization of hippocampal EA within the θ-range, and by disappearance of the neck muscle tone. The number of REM episodes, the mean duration of episodes, the total time of REM sleep, and the percentage of the total time of sleep were computed. The latency of REM sleep was determined as the period from the onset of slow-wave sleep to the onset of REM sleep or as the period between two REM sleep episodes against the background of continuous slow-wave sleep. The mean latency of REM sleep was determined for each animal. We also calculated the mean time of wakefulness and slow-wave sleep and their percentage of the total time of observation.

The data were analyzed statistically using one-way and repeated-measures ANOVA (Primer software) with subsequent comparison of the means using Student—Newman—Keuls's test.

RESULTS

The rats treated with MPTP (group 2) showed a higher frequency of REM sleep episodes, longer total duration of REM sleep, and higher percentage of REM sleep in the total sleep time compared with other groups during treatment (days 3 and 12, Table 1).The groups did not differ in the mean duration of REM episodes. We did not compare the mean latencies of REM sleep during treatment in different groups because of initial significant intergroup difference in this parameter, which probably reflects its high individual variability. The latency of REM sleep was analyzed in each group

TABLE 1. REM Sleep Parameters (*M±m*)

Group		Time of observation			
		before treatment	day 3	day 12	one week after cessation
Number of episodes	1	5.4±0.4	6.8±0.6*	6.6±0.2**	5.4±0.7
	2	5.0±1.0[1]	11.6±2.3[+]	15.2±2.4[+°]	8.8±1.9
	3	5.2±0.5	6.0±0.8	7.2±1.5	6.6±1.1
	4	6.4±0.7	5.8±0.5	6.4±0.8	6.0±0.3
Total duration, sec	1	399.3±76.1	540.3±102.2**	632.6±43.0**	443.0±111.2
	2	511.6±137.6[1]	1155.8±58.9[+]	1367.0±180.8[+°]	738.2±185.3
	3	528.8±111.8	632.2±147.5	832.6±200.7	822.6±127.6
	4	543.2±63.5	496.6±77.8	607.2±127.3	494.4±106.8
The mean duration of episodes, sec	1	75.6±14.2	79.7±9.1	90.9±5.5	67.7±18.9
	2	84.3±18.5	112.2±16.7	91.7±4.4	84.5±9.2
	3	98.5±13.9	97.9±15.0	102.3±18.6	125.6±3.2
	4	85.3±4.2	84.8±10.9	94.9±15.6	79.9±13.9
Latency, sec	1	304.7±43.0	312.9±37.8	305.4±30.2	325.3±47.9
	2	347.0±82.2[2]	156.9±19.2[°]	157.6±26.6[°]	207.0±45.3[°]
	3	140.0±23.3	146.2±12.7	121.7±20.3	125.9±13.4
	4	202.2±17.9	193.8±18.8	264.5±29.5	242.4±23.6
Percentage of total sleep time	1	7.6±0.9	5.4±0.6***	6.8±0.8*	5.9±1.4
	2	4.9±1.0[1]	12.4±1.3[+]	14.5±3.0[+°]	8.5±1.9
	3	5.9±1.5	5.7±1.4	7.4±1.9	6.8±1.1
	4	5.7±1.3	7.1±1.0	7.1±1.6	6.0±0.7

Note. *$p<0.05$, **$p<0.01$; ***$p<0.001$, one-way ANOVA (comparison of 4 groups by 1 parameter); [1]$p<0.01$, [2]$p<0.01$ repeated measures ANOVA (comparison of one parameter values within the same group); $p<0.05$: [+]in comparison with similar parameters in other groups; [°]comparison with similar parameter before treatment in the same group (Student—Newman—Keuls's test after the analysis of variance).

TABLE 2. Parameters of Sleep-Wake Cycle (*M±m*)

Group		Time of observation			
		before treatment	day 3 of treatment	day 12 of treatment	one week after treatment
Sleep duration, percent of the total time of observation	1	63.8±1.8	67.8±5.5	68.0±2.9	60.2±5.4
	2	68.5±4.0	68.2±6.1	67.1±4.1	61.8±8.1
	3	64.6±2.9	62.2±8.1	65.9±6.1	73.8±5.2
	4	61.0±2.5	62.2±2.2	67.2±1.8	64.0±5.4
Mean duration of sleep episodes, min	1	10.9±0.5	12.7±1.4	11.8±1.4	10.0±0.9
	2	12.9±0.7	16.6±2.8	13.9±2.0	14.1±1.0
	3	13.0±1.7	9.6±1.5	11.7±1.9	10.8±1.4
	4	11.0±0.3	13.0±1.5	14.8±1.5	13.9±1.7
Duration of wakefulness, percent of the total time of observation	1	37.2±1.9	32.3±5.5	32.2±3.0	40.0±5.4
	2	31.5±4.0	32.3±5.3	33.0±4.1	42.3±7.3
	3	6.3±0.8	8.2±1.4	6.6±0.5	26.2±5.1
	4	39.0±2.4	37.8±2.2	32.8±1.8	36.0±5.4
Mean duration of wakefulness, min	1	6.7±0.4	6.7±1.6	5.8±0.6	7.3±1.2
	2	6.3±0.8	8.2±1.4	6.6±0.5	11.7±4.1
	3	7.7±0.5	6.5±1.2	6.0±0.8	3.7±0.6
	4	7.9±0.8	8.9±1.3	8.3±1.3	8.2±1.4

separately. Only group 2 rats showed changes in REM sleep parameters in the course of treatment: the number of REM episodes increased, their latency decreased, and both the total time of REM sleep and its contribution to the total time of sleep increased. One week after cessation of the treatment the latency of REM sleep in this group remained below the initial value.

In all other groups, including group 3 with combined administration of Parlodel and MPTP, all these parameters remained practically unchanged during treatment. For the entire experimental period we found no significant difference in the mean time of sleep and wakefulness and their proportion in the total time of observation between the groups or in one group at different times (Table 2).

Bromocriptine is clinically approved as an antidepressant [13,15]. Its antidepressive properties were also revealed in the model of ahedonia in rats exposed to chronic mild stress [12]. Previously, we have found that Parlodel produced an antidepressant effect on the model of depression induced by systemic MPTP administration in rats [3]. Parlodel prevented the appearance of behavioral signs of depression, such as reduced motor activity and water consumption, weight loss, reduced sacharose-to-water preference, and a high depression index. [3]. These findings suggest that this syndrome is associated with brain dopamine deficiency. In this study on the same model of depression we found that chronic administration of Parlodel prior to MPTP prevented the disturbance of REM sleep. The cholinergic structures of the brain stem, fronto-basal regions, hypothalamus, and amigdala are involved in the mechanisms of REM sleep induction, and these processes are modulated by central serotonin-, norepinephrine-, GABA-, and glycinergic systems [9]. The role of central dopaminergic neurotransmission in this modulation is less studied. The dopamine agonist apomorphine has been reported to prolong the latency of REM sleep and smooth this phase of sleep [8]. Our data suggest that MPTP-induced behavioral depression in rats and changes in REM sleep share the same pathophysiological mechanism: inhibition of the central dopaminergic system.

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