Effect of Parlodel on Brain Electrical Activity in Experimental Depressive Syndrome in Rats

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In rats with experimental MPTP-induced depressive syndrome, chronic administration of parlodel prevented epileptiform activity, an increase in δ-band and a decrease in α-band spectral powers in the caudate-putamen structures, and an increase in δ-band spectral power in the hippocampus.

Key Words: *depressive syndrome; parlodel; brain electrical activity; rats; pathological system*

We have previously shown that repeated systemic administration of 2-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP) to rats induces a depressive syndrome [6] characterized by suppression of major motivations and such symptoms as "behavioral despair" and ahedonia. MPTP-induced changes in REM-sleep parameters were similar to those in patients with endogenous depression [2], 70% animals developed epileptiform activity in the caudate-putamen (CP) structures [3]. We assumed that the MPTP-induced depressive syndrome in rats is determined by CP hyperactivation.

Parlodel, D_2 receptor agonist bromocriptine derivative exhibits antidepressant activity in both clinical practice [12,14] and experiments [11,15]. Our studies on the model of the MPTP-induced depressive syndrome also revealed that parlodel exerted an antidepressant effect on behavior [4] and prevented REM-sleep disturbance [1]. However, the effect of parlodel on electrical activity (EA) of subcortical brain structures during the formation of a depressive state has not been studied yet.

The present study was aimed at investigation of the effect of parlodel on the caudate-puitamen, hippocampal, and cortical EA in rats with an MPTP-induced depressive syndrome.

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MATERIALS AND METHODS

The study was carried out on 32 Wistar male rats weighing 270-350 g. The animals were housed in pairs under standard conditions with natural light/dark cycle and free access to food and water. EA of the sensorymotor cortex, CP, and dorsal hippocampus and EMG of neck muscles was recorded under conditions of free behavior via stereotaxically implanted electrodes [2,13]. All recordings (4 h each) were performed at the same day time by the method described previously [2]. The first recording was performed on days 5-6 postoperation (baseline), then the sessions were repeated on days 3-4 and 11-12 of treatment, which corresponded to the initial and final stages of depressive syndrome development, respectively, and a week after cessation (recovery). The last 10-min fragment of each EA record was stored on a TEAC MR-20 tape recorder for further computer processing. MPTP (the Institute of Pharmacology, Russian Academy of Medical Sciences) and parlodel (Sandoz) were prepared as described previously [4] and administered daily for 12 days in a volume of 1 ml/kg body weight. Group 1 rats (n=6) were given oral saline 45-50 min prior to intraperitoneal MPTP (20 mg/kg). Group 2 animals (n=5) received oral parlodel (5 mg/kg) followed by intraperitoneal MPTP after 45-50 min. Group 3 (n=5) received oral parlodel followed by intraperitoneal saline after 45-50 min, and group 4 (n=6) re-

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ceived only saline. Each group comprised animals participated in all recording sessions, *i.e.* EA spectral power was analyzed at all consecutive stages of depressive syndrome development. The EA spectral density within the frequency range from 1 to 30 Hz (1 Hz step) was assessed with a fast Fourier transform. The signal was input to a computer through an RTJ-820 analog-to-digital converter, the epoch for the analysis was 4 sec. EA spectral power was determined in all leads within the following frequency bands: δ_1 (0-2 Hz); δ_2 (2-4 Hz); θ_1 (4-6 Hz); θ_2 (6-8 Hz); α (8-13 Hz), β_1 (14-19 Hz), and β_2 (20-30 Hz). Individual spectra were processed and averaged as described [3]. The data were analyzed statistically using one-way and repeated measures ANOVA with a subsequent comparison of the means with a Student—Newman—Keuls test (Primer software). The location of subcortical electrodes was verified morphologically.

RESULTS

As shown previously, the formation of a depressive syndrome after MPTP administration is accompanied by an increase in the δ_1-band power of EA in CP (11.7±2.3% compared to 4.1±0.9% after saline administration) [3]. The present study revealed that this parameter after combined administration of parlodel and MPTP (4.9±0.7%) did not differ from the control (see above) and remained significantly lower than in the group treated with MPTP alone (Fig. 1, *a, b*; the groups were compared at a significance level of $p<0.05$). The δ_1-band power of EA in CP after administration of parlodel (8.8±0.9%) did not differ significantly from the corresponding value in other experimental groups.

We previously found that pronounced behavioral depression after MPTP treatment and following behavioral restoration were characterized by reduced α-band power [3]. In this study, the rats receiving parlodel combined with MPTP or saline exhibited no shifts in α-band power (Fig. 1, *a-d*).

Behavioral recovery in MPTP-treated rats was accompanied by enhanced δ_1-band power not only in MPTP [3], but also in parlodel-treated animals: in these groups δ_1-band power increased to 9.2±1.1% and 8.6±1.3%, respectively, and significantly ($p<0.05$) exceeded this parameter in the groups receiving parlodel-MPTP combination and saline (4.7±0.5% and 4.6±0.8%, respectively) (Fig. 1, *d*). In rats treated with parlodel-MPTP combination or parlodel alone, this period was characterized by increased β_1-power (14.4± 0.6% and 14.2±1.6%, respectively, *vs.* 8.4± 0.9% in the saline-treated group, $p<0.05$).

The analysis of hippocampal EA in rats treated with parlodel-MPTP combination or parlodel alone revealed no increase in the δ_1-band during the formation of MPTP-induced depressive syndrome, which was typical of rats receiving MPTP alone [3]. The relative powers of hippocampal EA in groups treated with MPTP, parlodel-MPTP, parlodel and saline were 7.7±0.7%, 3.6±0.7%, 2.9±0.5%, and 3.4±0.3%, respectively (the difference with the MPTP-group is significant at $p<0.05$).

In previous studies, the majority of animals treated with MPTP (70%) exhibited epileptiform activity in CP at the stages of pronounced depression and behavioral recovery [3]. In the corresponding period in the present study, only 1 of 5 animals receiving parlodel-MPTP showed a single episode of disorganized sharp-wave activity in CP without behavioral seizures. This episode lasted for 12 sec. No signs of epileptiform EA were observed in the groups treated with parlodel and saline.

We hypothesized that MPTP-induced depressive syndrome results from hyperactivation of CP brain structures that play a role of a pathological determinant for the pathological system of the depressive syndrome involving other brain structures, in particular hippocampus [3,5,6]. Apart from epileptiform activity, CP hyperactivation manifests itself in enhanced EA spectral power in the δ-band and its decrease in the α-band, which are the EEG-correlates of CP activation [8-10]. In this study, parlodel prevented epileptiform activity in the CP of MPTP-treated rats, the increase in the δ_1-band and decrease in the α-band spectral powers. Since parlodel also prevented behavioral manifestations of MPTP-induced depressive syndrome [4] and REM-sleep disturbances in MPTP-treated animals [2], we can associate the pathogenesis of the depressive behavioral syndrome under conditions of dopaminergic deficiency with CP hyperactivation.

The enhanced δ_1-band density in parlodel-treated animals during behavioral recovery in MPTP-treated rats is of special interest. Previously, we observed depressive components in rat behavior after parlodel administration (reduced motor activity and transient decrease in daily water consumption), which probably presents an adaptive response to chronic pharmacological stimulation of dopamine receptors [4]. The character and dynamics of parlodel-induced changes in the EA spectral power are similar to those in depressive syndrome, which suggests that plastic changes in CP dopamine receptors after their persistent activation are the main mechanism of the effects of parlodel.

In animals receiving parlodel alone or in combination with MPTP, the β_1-band spectral power of EA increased after cessation of the treatment was ceased. These changes in EA can reflect gradual dopaminergic activation characterized by enhanced EEG spectral power in the 19-30 Hz frequency range [7].

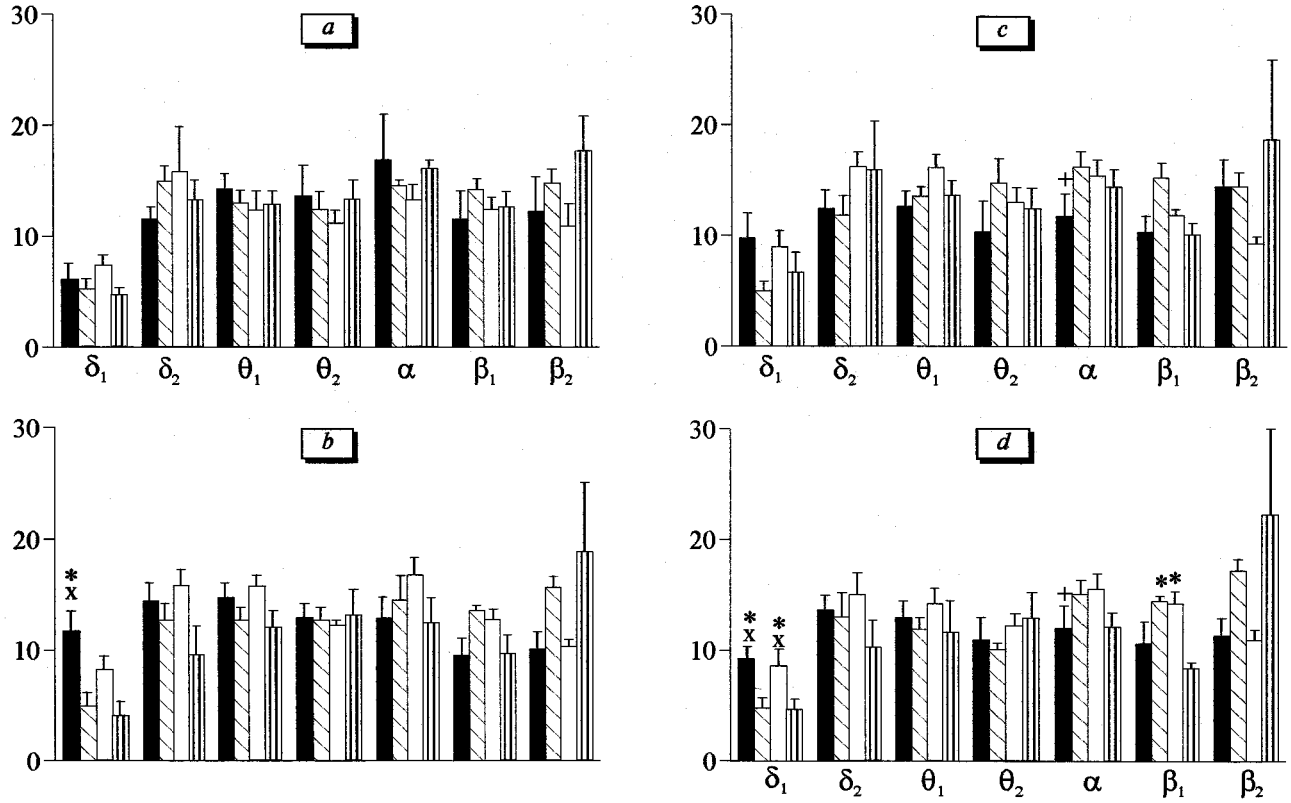

Fig. 1. Spectral power histograms of caudate-putamen electrical activity in rats. *a*: before treatment; *b*: on days 3-4 of treatment (formation of depressive syndrome in MPTP-treated animals); *c*: on days 11-12 of treatment (the pronounced depression in MPTP-treated animals); *d*: a week after cessation (recovery in MPTP-treated animals). Filled bars: group with MPTP; oblique shading: MPTP+parlodel; open bars: parlodel; vertical shading: saline. Significant difference at $p<0.05$: *compared to saline; ˣcompared to MPTP+parlodel; ⁺ compared to the baseline.

Our data showed that parlodel prevented changes in hippocampal EA typical of depressive syndrome, which suggests that the drug suppressed the formation of depressive syndrome pathological system.

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