Effect of Parlodel on the Development of a Depressive Syndrome Induced by Administration of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) in Rats

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Effects caused by the chronic administration of Parlodel on the development of behavioral signs of depression in rats are studied using the new model of depressive syndrome induced by the systemic administration of MPTP. Pretreatment with Parlodel prevents locomotor depression, weight loss, reduction of liquid intake, a decline of the preference of sucrose solution over water, and a rise of the depression index and promotes a quicker restoration of exploratory activity, i.e., it safeguards rats from manifestating the behavioral signs of MPTP-induced depression.

Key Words: *depressive syndrome; MPTP; Parlodel; rats*

Systemic administration of the specific dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rats results in the development of behavioral symptoms which are considered as a manifestation of the depressive syndrome [1]. The present investigation included a study of the effects of Parlodel (a brand name of bromocryptine, a D_2-receptor agonist) on the development of behavioral signs of depression in rats using a new model of depressive syndrome induced by chronic systemic administration of MPTP.

MATERIALS AND METHODS

Experiments were carried out on 24 male albino Wistar rats weighing 250-350 g. Animals were kept individually under standard vivarium conditions with a natural day-night cycle and food and water *ad libitum*.

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The effects of Parlodel on the development of behavioral signs of MPTP-induced depression were tested for oral administration of Parlodel followed by intraperitoneal injection of MPTP. In order that the test procedure be the same in all groups the experiment was performed as follows. The animals were divided into 4 groups with 6 rats in each group. MPTP-treated rats of the 1st group were injected with physiological saline (PS) 45-60 min prior to neurotoxin administration. Animals of the 2nd group were injected with Parlodel (bromocryptine mesylate) and 45-60 min later with PS intraperitoneally. The 3rd group of animals was treated with Parlodel followed 45-60 min later by MPTP. The interval between drug injections was chosen in light of the fact that bromocryptine has its maximal effect on the dopamine level in the stratum 1 h postadministration [3]. Animals of the 4th group were injected twice with MPTP according to the above scheme. MPTP was administered in a dose of 15 mg/kg and Parlodel at 5 mg/kg in a volume of 1 ml/mg body weight during 12 days. Oral administration was via a syringe with a special attachment

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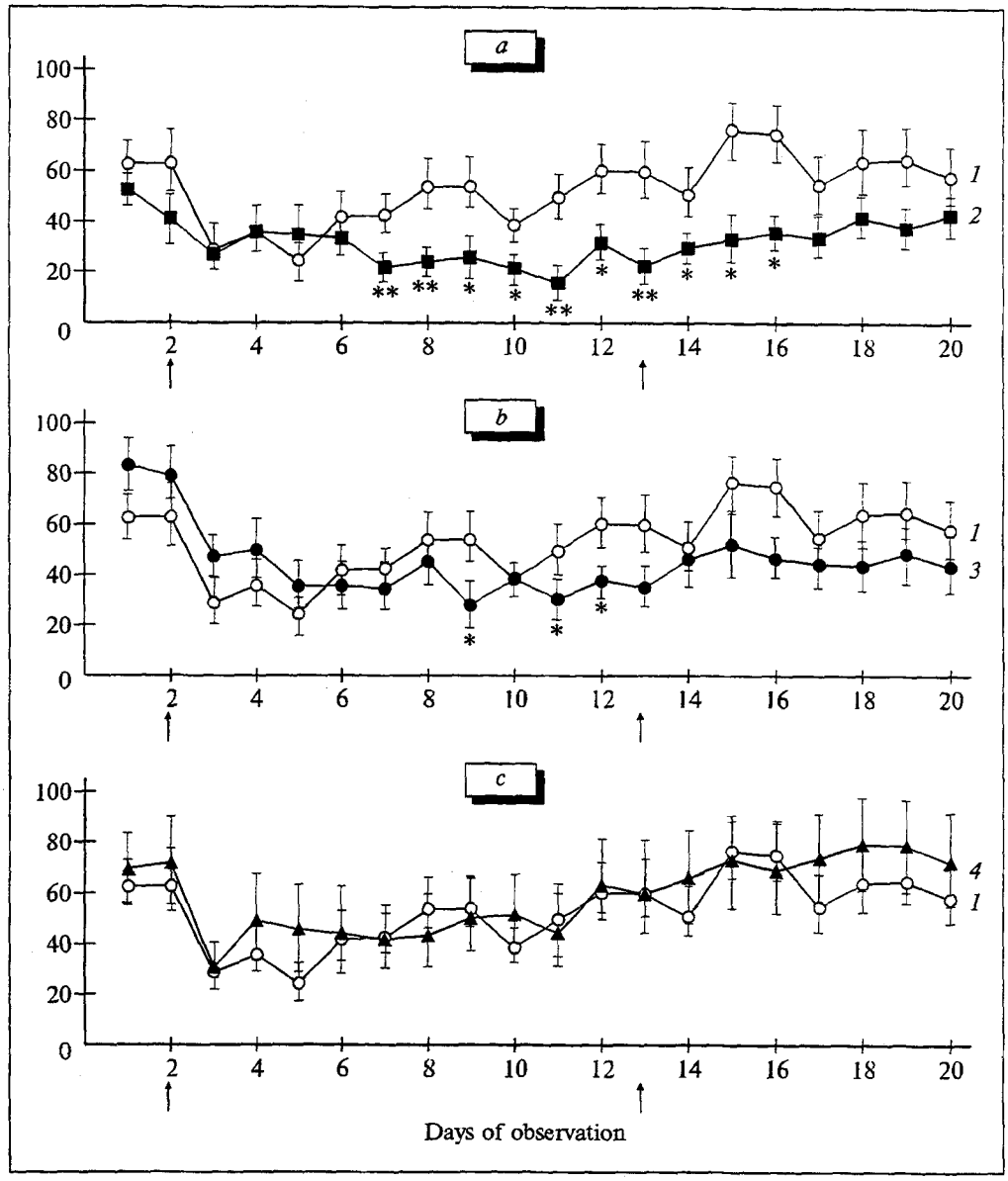

Fig. 1. Dynamics of daily liquid intake in groups of rats treated with MPTP (*a*), Parlodel (*b*), and their combination (c) as compared with the control. Here and on Fig. 2: $^{*}p<0.05$, $^{**}p<0.01$ as compared with the value of parameter on the same day in the control group with PS administration (according to the unpaired parametric Student *t* test). Arrows point to the first and last days of drug administration. *1*) administration of PS; *2*) of MPTP, *3*) of Parlodel, and *4*) combined administration of Parlodel and MPTP. Ordinate: Daily volume of liquid drunk, ml

which prevents damage to the oral soft tissues. Parlodel was used suspended as follows: tablets (Darnitsa Chemical-Pharmacological Conglomerate, Ukraine, in collaboration with Sandoz) pounded in a china mortar were dissolved in 1-2 drops of Tween-80 and diluted with PS to the required volume. MPTP (synthesized at the Research Institute of Pharmacology, Russian Academy of Medical Sciences) was dissolved in PS just prior to use.

Examination of animals using the method of multiparameter assessment of anxiety and phobic states in rats, in the open field test, and determination of daily liquid intake as well as the preference for 10% sucrose solution over water were performed as described previously [1]. The motor and exploratory activity of animals (studied in the open field test, during which the number of squares crossed and the number of upright postures were recorded for the first 3 min) as well as the anxiety and phobic level were determined 4 times: 1 week prior to the administration of drugs, on the 11th-12th day after the start of treatment, and 1 and 2 weeks after discontinuation of the drugs. The depression index (DI) was calculated as the ratio of the number of shortest immobilization periods (less than 6 sec) to the total number of active swimming periods during a 10-min-long forced swimming test performed as described previously [1] using the biorhythmic approach created by Shchetinin and co-authors [2]. DI was determined on the 8th day after the start of treatment and on the 11th day after its cessation.

Results were processed statistically using the nonpaired parametric Student *t* test, one-factor

analysis of variance (analysis 1) and analysis of variance for repeated measurements (analysis 2) by algorithms of Statgraphics and Primer software followed by comparison of mean values after Tukey (t_Q test).

RESULTS

Daily i.p. injection of MPTP at 15 mg/kg during 18 days results in reduced motor and exploratory activity, a lowered daily liquid intake and reduced preference of 10% sucrose solution over water, as well as in elevated DI for an unchanged anxiety-phobic level [1]. All these effects manifested themselves as early as 2 weeks after the onset of MPTP treatment and were preserved for at least a week after drug abolishment, which allowed us to restrict the period of neurotoxin administration to 12 days in the given study.

Lowered motor activity was found in the 1st group [$F(3.15)=5.01$, $p<0.05$, analysis 2] with a decrease of its mean value 1 week after cessation of MPTP as compared with the initial ($t_Q=5.23$, $p<0.05$). Exploratory activity was reduced [$F(3.15)=6.48$, $p<0.01$, analysis 2]; the effect was obtained 1 and 2 weeks after drug cessation ($t_Q=5.41$ and 5.28, $p<0.05$). A decreased daily liquid intake was noted in this group [$F(19.95)=2.66$, $p<0.001$, analysis 1] against the background of MPTP as compared to the initial level of intake. Daily liquid intake and preference of 10% sucrose solution over water in this group were diminished as compared to the corresponding parameters of the 4th group with PS administration against the background of MPTP during several days also after its discontinuation (Fig. 1, *a*; Fig. 2, *a*). The DI exceeded the control value in the forced swimming test against the background of MPTP in the group with PS injection (1.78±0.53 and 0.60±0.10, respectively, $p<0.05$) and did not differ from that after MPTP cessation (0.47±0.38 and 0.35±0.18, respectively, $p>0.05$). The anxiety-phobic level comprised initially in this group 8.6±1.1 points and did not change during the course of the observation. Weakly expressed extrapyramidal disorders manifested in body rigidity (a slight humpiness) were noted against the background of MPTP administration.

Thus, all previously obtained behavioral effects of the preparation were reproduced in the given study despite the slight modification of the MPTP administration scheme. The invariability of the anxiety-phobic level argues in favor of the phenomenological isomorphism of the model and of depressive disorders in parkinsonism, because phobic reactions are not characteristic of these kinds of pathology [4].

Reduced motor activity was found in the 2nd group [$F(3.12)=6.74$, $p<0.01$, analysis 2] with a decreased mean value noted both 1 and 2 weeks after Parlodel cessation ($t_Q=4.56$ and 6.08, respectively, $p<0.05$). Exploratory activity tended to diminish. Daily liquid intake against the background of Parlodel in this group was reduced as compared with the initial level [$F(19.76)=4.21$, $p<0.001$, analysis 1]. A decreased daily liquid intake was also noted on some days as compared to the PS-treated group (Fig. 1, *b*), but Parlodel did not affect the level of sugar preference (Fig. 2, *b*). The DI (0.69±0.31) did not exceed the control level in the group with PS administration either against the background of administration of the drugs (0.72±0.33) or after their discontinuation. The anxiety-phobic level in this group comprised initially 7.9±1.5 points and did not change throughout the observation.

Combined administration of Parlodel and MPTP in the 3rd group did not lower the motor activity as compared to the initial value against the background of drug administration and the decrease noted a week later was insignificant ($t_Q=3.44$, $p>0.05$). Exploratory activity [$F(3.15)=3.98$, $p<0.05$, analysis 2] was reduced and its mean value was decreased as compared to the initial data 1 week after abolishment ($t_Q=4.60$, $p<0.05$). Mild extrapyramidal disorders were found against the background of MPTP in this group, as in the 1st group. Combined administration of Parlodel and MPTP was not followed by a reduced daily liquid intake (Fig. 1, *c*) or by a significant decrease of sugar preference (Fig. 2, *c*) as compared to PS administration. It is to be noted that the absolute value of DI (1.26±±0.52), statistically the same as in the control, was more than unity against the background of drug administration, attesting to signs of behavioral depression in these animals [2]. After discontinuation of the drugs DI (0.44±0.23) did not differ from that in the PS-treated group. The anxiety-phobic level in this group initially comprised 8.3±1.7 points and did not change throughout the observation.

Rats of the 4th group showed a marked tendency toward a lower motor and, to a lesser degree, exploratory activity in repeated open field tests. The level of daily liquid intake somewhat decreased with the onset of PS administration and became stable toward the end of the observation period (Fig. 1), whereas the level of sugar preference was stable throughout the period (Fig. 2). The absolute DI value against the background of PS administration as well as after its discontinuation did not exceed unity. The anxiety-phobic level comprised initially 8.4±1.1 points and did not change throughout the observation in this group.

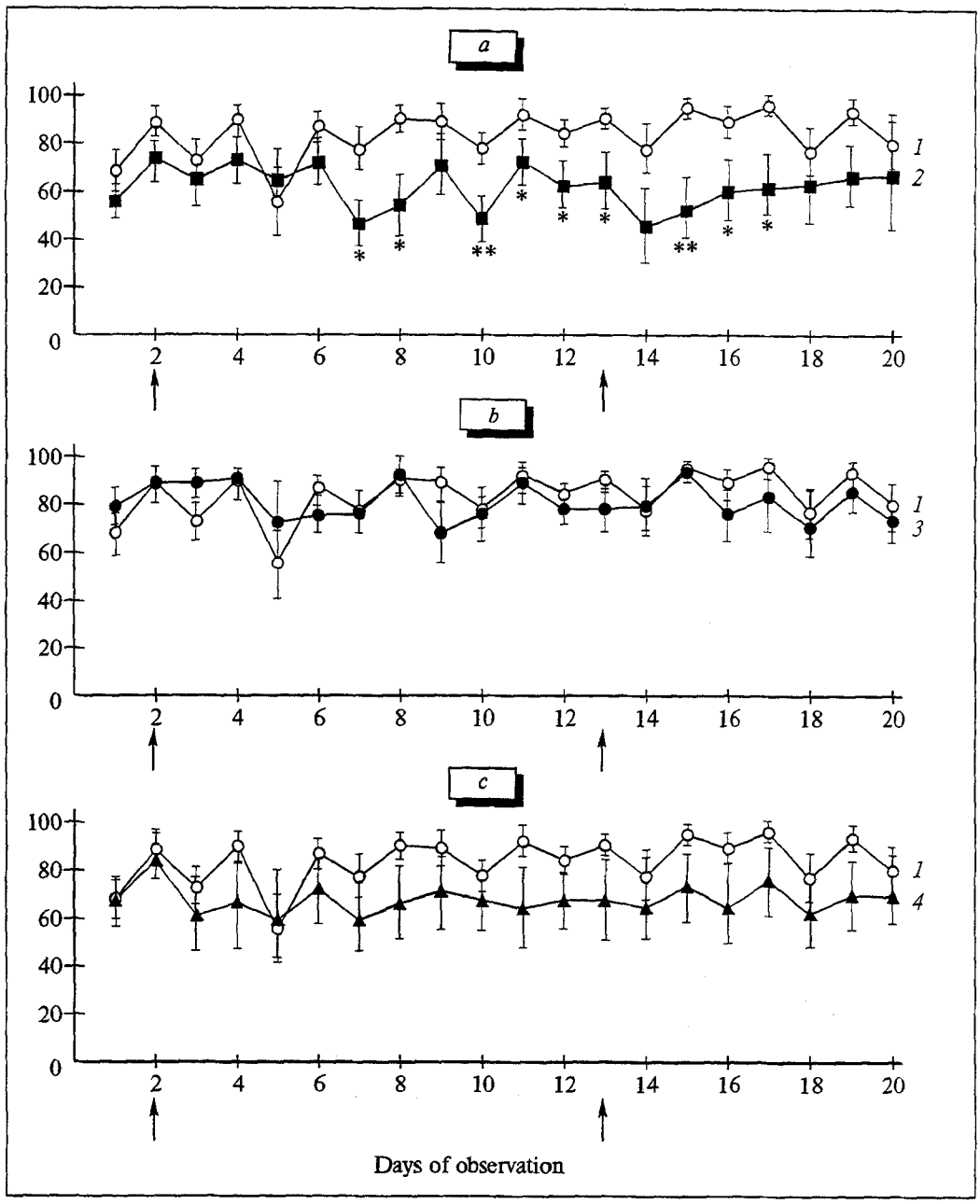

Fig. 2. Dynamics of 10% sucrose solution intake in groups of rats with administration of MPTP (*a*), of Parlodel (*b*), and their combination (*c*) as compared with the control. Ordinate: sucrose solution intake, % of total daily liquid intake.

A comparison of the mean weight of animals in corresponding examinations revealed differences only between the 1st and the 4th groups, namely against the background of MPTP administration, and after 1 week the mean weight of animals in the 1st group was lower than in the 4th (281.7±11.3 g and 334.0±11.6 g; 292.5±11.3 g and 340.0±11.7 g respectively, $p<0.05$), while after 2 weeks there were no longer any differences between these groups.

Clinically bromocryptine is known to produce an antidepressive effect [5,6]. The findings attest that chronic Parlodel treatment preceding MPTP administration according to the indicated scheme prevents the drop of motor activity, weight loss, reduction of total daily liquid intake, decrease of sugar preference over water, and increase of the DI and promotes a quicker restoration of the exploratory activity; in other words, it prevents the manifestation of behavioral depression in rats.

The lowered motor activity and, on some days, reduced daily liquid intake found in Parlodel-treated animals are noteworthy. We consider this to be an adaptive response to chronic pharmacological stimulation of the dopamine receptors.

The results confirm our previous assumption about the dopamine-deficiency-dependent nature of the experimental depressive syndrome in rats induced by systemic MPTP administration, and serve

as the first experimental evidence of the pharmacological isomorphism of this model of depression with the clinical forms of the disease.

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