GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Effects of Buspirone on Experimental Depressive Syndrome Induced by Systemic Administration of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) in Rats

N. A. Krupina, G. N. Kryzhanovskii, I. N. Orlova, and T. E. Iordanskaya

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 121, No. 5, pp. 489-494, May, 1996
Original article submitted March 16, 1995

It is shown that pretreatment with buspirone 45-60 min prior to MPTP administration performed daily for 12 days prevented or weakened the development of depressive symptoms in rats. Specifically, it prevented a reduction of daily water intake, weakened the preference for sugar solution over water, and, to a lesser degree, shortened the increase in the duration of immobilization and lowered the index of depression in the forced swimming test, but did not affect the drop in motor and exploratory activity.

Key Words: *depressive syndrome; MPTP; buspirone, rats*

As we showed recently in model experiments, the dopamine (DA) receptor agonist bromocriptine and the tricyclic antidepressant melipramine prevent or weaken the development of behavioral signs of depressive syndrome in rats induced by systemic administration of the neurotoxin MPTP and this syndrome is DA-deficiency dependent [2,3]. The development of depression is often related to dysfunction of the serotoninergic system due to the interaction between the serotoninergic and catecholaminergic brain systems [5,6,8]. There are data on the treatment of depression and neuroses of phobic-depressive origin with buspirone [8], a preparation which exhibits mixed receptor action, being both an agonist of the serotonin 5-HT_{1A} receptors and an agonist/antagonist of the D_2 DA receptors [11]. The aim of the present investigation was to study the effect of buspirone on the manifestation of MPTP-induced depressive syndrome in rats.

Laboratory of General Nervous System Pathology, Research Institute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow

MATERIALS AND METHODS

Experiments were carried out on 24 male albino Wistar rats weighing 270-420 g. The animals were kept individually under standard vivarium conditions with the natural day-night cycle and food and water *ad libitum*.

The effects of buspirone on the development of behavioral signs of MPTP-induced depression were tested as follows: animals of the 1st group (n=6) were injected intraperitoneally with buspirone at 1 mg/kg and 45-60 min later with MPTP at 20 mg/kg every day for 12 days. Rats of the 2nd group (n=6) were injected with physiological solution 45-60 min prior to neurotoxin administration. The 3rd group of animals (n=6) was treated with buspirone and then (45-60 min later) with physiological saline. Animals of the 4th group (n=6) were injected with

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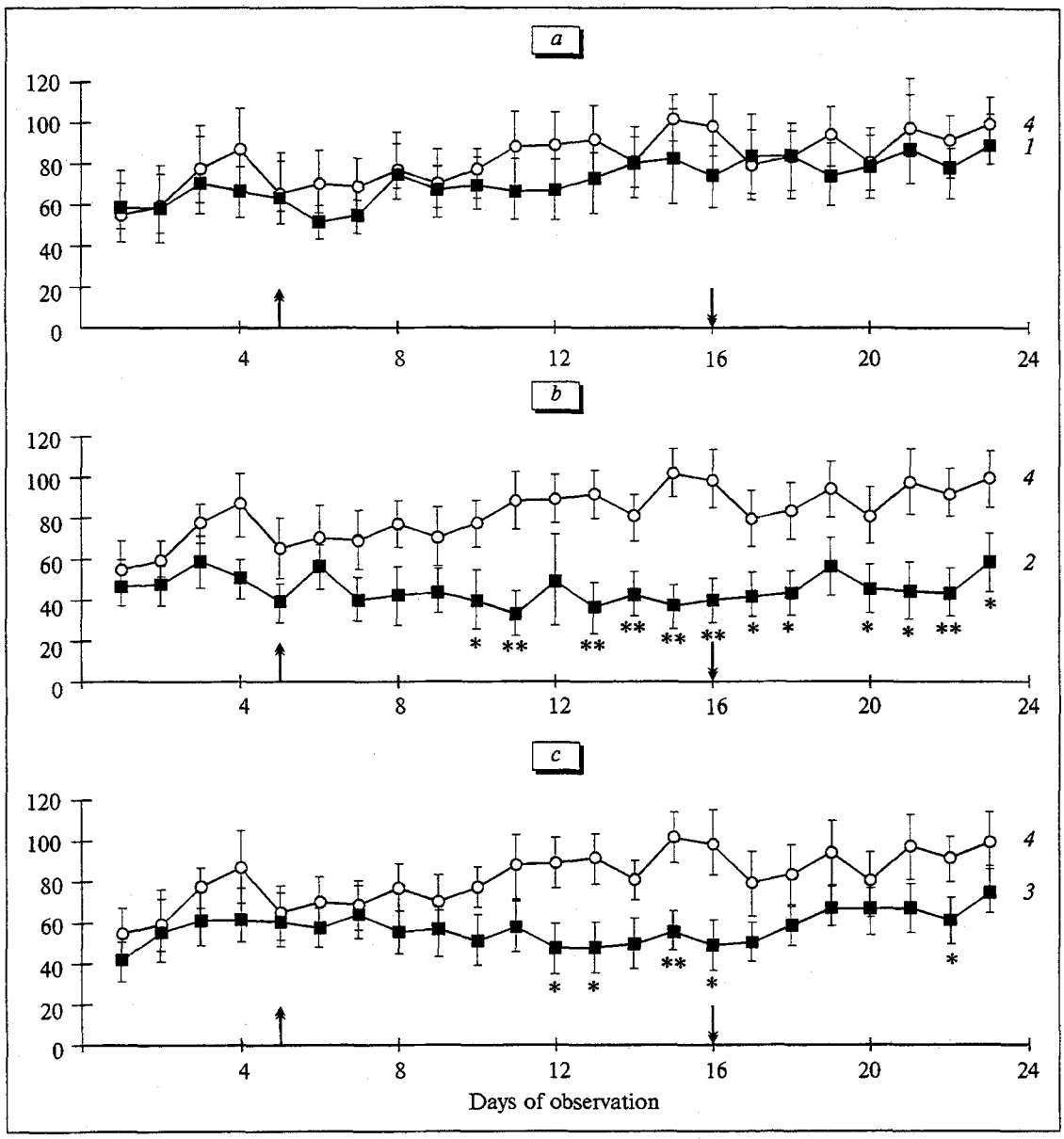

Fig. 1. Dynamics of daily liquid intake in groups of rats treated with buspirone and MPTP (*a*), MPTP and physiological saline (*b*), and buspirone and physiological saline (*c*) as compared with the control. Ordinate: volume of liquid drunk daily, ml. Here and in Fig. 2: $^{*}p<0.05$, $^{**}p<0.01$ as compared to the same–day parameter in the control group of rats administered physiological saline (unpaired parametric Student *t* test); arrows point to the first and last day of drug injection; curve number corresponds to the number of the group.

physiological sanline both times according to the same scheme. Thus, the experimental procedure was the same for all groups under study. The preparations were administered in a volume of 1 ml/kg body weight. Buspirone (synthesized at the Bogatskii Physicochemical Institute, Ukrainian Academy of Sciences) and MPTP (synthesized at the Research Institute of Pharmacology, Russian Academy of Medical Sciences) were dissolved in physiological saline just before use.

Study of the animals using the method of multiparameter assessment of anxiety and phobic states in rats (done here to take into account the possible anxiolytic effects of buspirone) and 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 [4]. The motor and exploratory activity of animals as well as the anxiety and phobic level were determined 4 times: 2-3 days prior to drug administration, on the 11th-12th day after the start of treatment, and 1 and 2 weeks after discontinuation of the drugs. On the 10th day after the start of treatment and on the

12th day after its cessation the duration of immobilization and the depression index (DI) (calculated as the ratio of the number of immobilization periods lasting up to 6 sec to the total number of active swimming periods) were determined in the forced swimming test.

The results were processed statistically using the Student t test (Statgraphics) and analysis of variance for repeated measurements REPEATED MEASURES ANOVA (RMA, Primer software) followed by comparison of mean values after Tukey (t_Q test).

RESULTS

The following behavioral changes were considered as criteria of the depressive state [2-4]: reduced daily intake of liquid (lowered level of motivation), weakened preference for 10% sucrose solution over water (development of ahedony), prolonged immobilization and increased DI in the forced swimming test (development of "behavioral despair"), and lowered motor and exploratory activity.

The daily intake of liquid in the 1st group of rats treated with buspirone and MPTP did not dif-

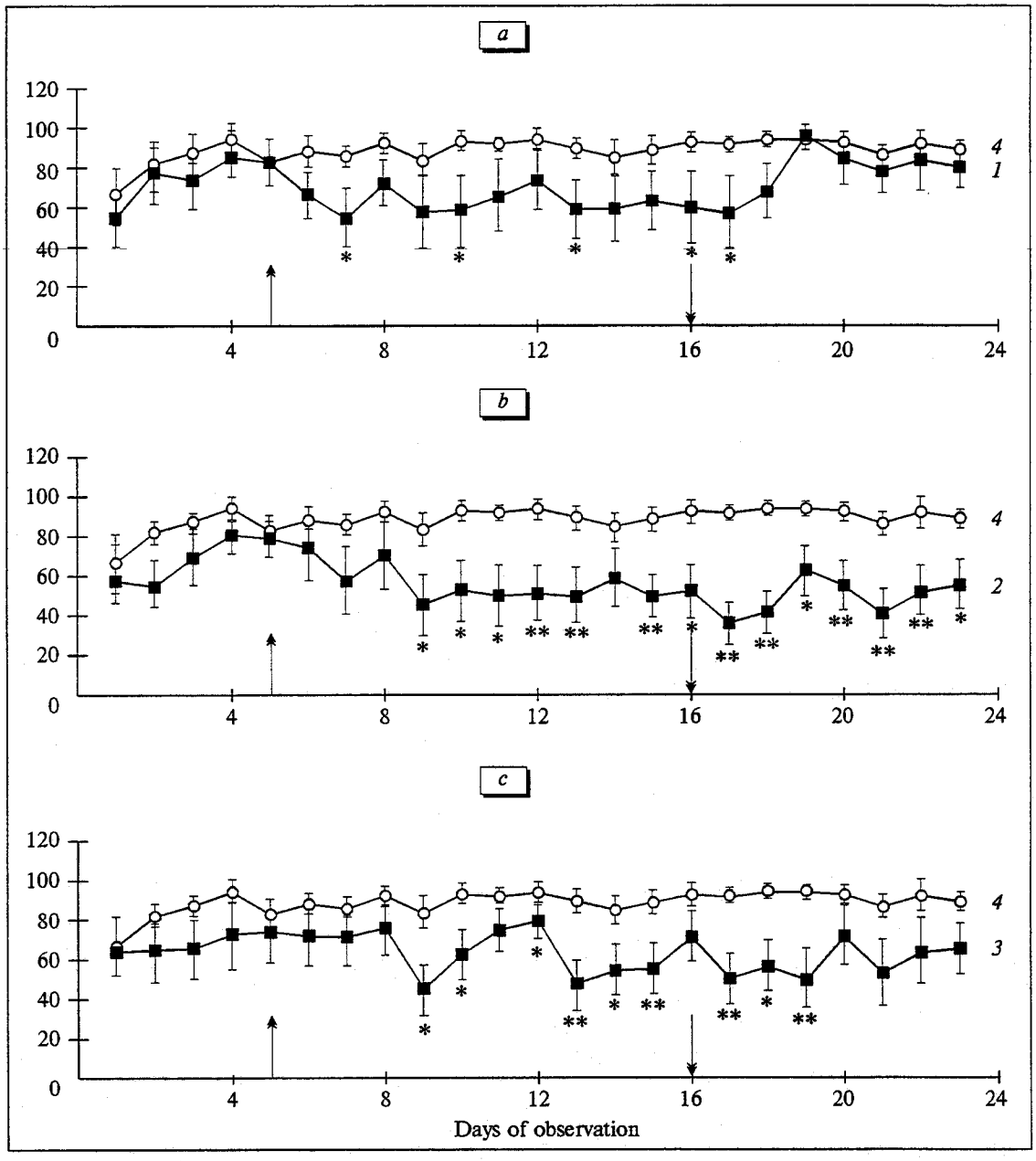

Fig. 2. Dynamics of 10% sucrose solution intake in groups of rats treated with buspirone and MPTP (*a*), MPTP and physiological saline (*b*), and buspirone and physiological saline (*c*) as compared with the control. Ordinate: % of sucrose solution intake in relation to total daily liquid intake.

TABLE 1. Duration of Immobilization and Depression Index in Rats Treated with Buspirone and MPTP (Group 1), MPTP and Physiological Saline (Group 2), Buspirone and Physiological Saline (Group 3), and Physiological Saline (Group 4) in the Forced Swimming Test (*M±m*)

Group of rats	Immobilization, sec		Depression index	
	during treatment	after treatment	during treatment	after treatment
1	20.0±11.3	7.2±3.8	2.52±1.64	1.00±0.52
2	20.3±7.3*	10.0±4.1	1.88±0.60*	0.75±0.28
3	0.3±0.2*	0.8±0.8	0.08±0.05*	0.08±0.08*
4	5.5±2.5	6.8±4.7	0.49±0.20	0.70±0.22

Note. *$p<0.05$, *$p<0.1$ as compared to the corresponding parameter in the group of rats treated with physiological saline (Student *t* test).

fer from that of the group administered physiological saline (Fig. 1, *a*), whereas the level of preference for sugar over water was lowered on some days against the background of drug administration and immediately after its discontinuation (Fig. 2, *a*). The duration of immobilization and DI against the background of drug administration and after did not differ significantly from the control values in the group receiving physiological saline (Table 1), but there was a wide spread in the individual values of these parameters in this group against the background of drug administration, which manifested itself in a high mean error. Motor activity was lowered ($F_{(3.15)}=8.26$, $p<0.05$, RMA) as compared to the baseline value in this group and its mean value was lower than the baseline level two weeks after discontinuation of the drugs ($t_Q=6.09$, $p<0.05$, Fig. 3, *a*). Exploratory activity was also lowered ($F_{(3.15)}=4.95$, $p<0.05$, RMA) and its mean value was lower than the initial 2 weeks after discontinuation of the treatment ($t_Q=4.10$, $p<0.05$, Fig. 3, *b*). Towards the end of treatment the animals of this group displayed mild extrapyramidal disorders in the form of humpiness. The anxiety-phobic level in the group comprised initially 6.4±1.2 points and did not change during the course of the observation.

In the 2nd group, administered physiological saline and MPTP, the daily liquid intake was decreased and the preference for 10% sucrose solution over water was weakened as compared to the corresponding values in animals treated with physiological saline both against the background of treatment and after discontinuation of the drugs (Figs. 1, *b*; 2, *b*). The duration of immobilization and DI in the forced swimming test against the background of drug administration exceeded control values ($p<0.1$ and $p<0.05$, respectively) in the group receiving physiological saline and did not differ from those after discontinuation of MPTP (Table 1). A decrease of motor activity was noted in this group ($F_{(3.15)}=3.55$, $p<0.05$, RMA). The mean value of motor activity 1 week after MPTP abolishment was lower than the baseline mean level in this group ($t_Q=4.03$, $p<0.05$, Fig. 3, *a*). The exploratory activity also diminished ($F_{(3.15)}=6.01$, $p<0.01$, RMA) and its mean

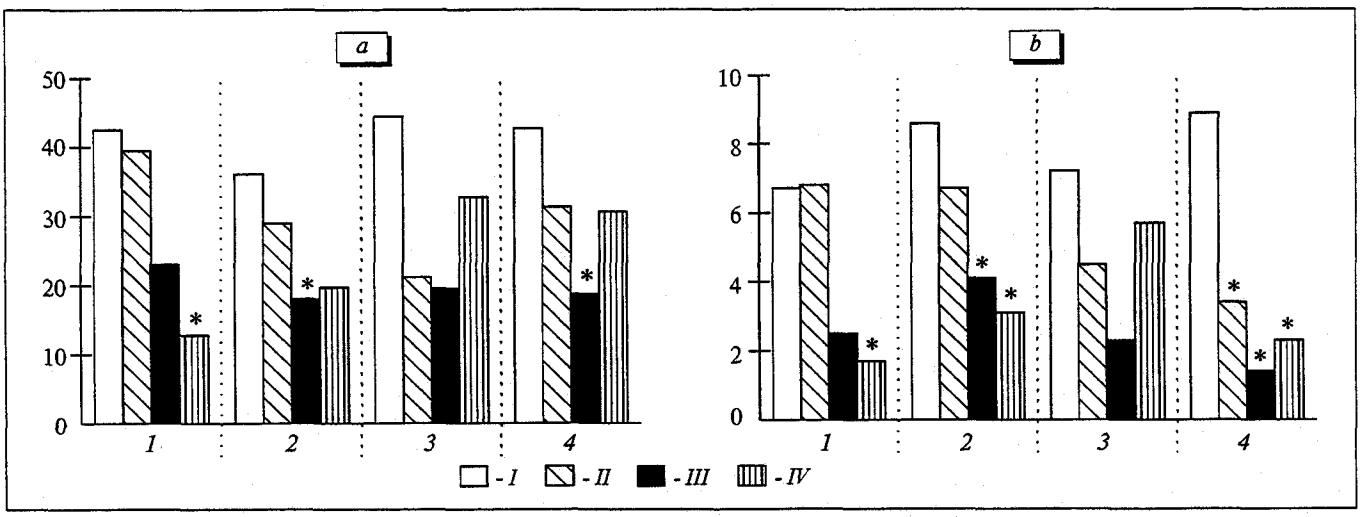

Fig. 3. Dynamics of motor (*a*) and exploratory (*b*) activity in groups of rats treated with buspirone and MPTP (*1*), MPTP and physiological saline (*2*), buspirone and physiological saline (*3*), and physiological saline (*4*). *I*) before treatment; *II*) 2 weeks after the start of treatment; *III*) 1 week after drug discontinuation; *IV*) 2 weeks after drug discontinuation. Ordinate: *a*) number of squares crossed; *b*) total number of upright postures during 3 min of observation. *$p<0.05$ for t_Q after RMA.

value differed from the initial level 1 and 2 weeks after the end of treatment (t_Q, respectively, 4.4 and 5.4, $p<0.05$ in both cases, Fig. 3, *b*). The anxiety-phobic level in this group initially comprised 7.5±1.2 points and did not change during the observation period. Towards the end of MPTP administration the animals manifested slight rigidity of the body and hind paws. Thus, MPTP caused the development of behavioral signs of depression in this study, just as in our previous investigations [2-4].

In the 3rd group of rats, administered buspirone and physiological saline, the daily intake of liquid as well as the preference of sucrose over water decreased as compared to the corresponding values in the group administered physiological saline both against the background of treatment and on some days after its discontinuation (Figs. 1, *c*; 2, *c*). A shortened immobilization and diminished DI were found in the forced swimming test as compared to the corresponding values in the group which received physiological saline ($p<0.1$ in both cases), whereas after buspirone was discontinued only the DI decrease was preserved ($p<0.05$, Table 1). Motor and exploratory activity did not fall off during the observation period ($F_{(3.15)}=2.22$, and $F_{(3.15)}=1.43$, $p>0.05$, RMA, respectively, Fig. 3, *a*, *b*). The anxiety-phobic level in the group was initially 6.9±0.9 points and did not change during the observation period.

The daily intake of liquid in the 4th group changed insignificantly and comprised 70-90 ml and the level of sucrose preference was a stable 85-90%. Immobilization during and after treatment lasted 5.5±2.5 and 6.8±4.7 sec, respectively, and DI comprised 0.5±0.2 and 0.7±0.2. A decrease of motor activity was also noted in this group ($F_{(3.15)}=4.67$, $p<0.05$, RMA) and its mean value was lower than the initial level 1 week after treatment ($t_Q=5.3$, $p<0.05$, Fig. 3, *a*). Exploratory activity was also diminished ($F_{(3.15)}=20.16$, $p<0.001$, RMA; t_Q consecutively, 7.3, 9.99, and 8.8, Fig. 3, *b*). The anxiety-phobic level in this group initially comprised 7.1±1.2 points and did not change during the observation period.

The findings attest that repeated administration of buspirone prevents the drop of the level of motivation, weakens the development of hedonic disorders, and reduces the manifestation of "behavioral despair" in rats with experimental depressive syndrome, confirming the antidepressant properties of the drug. However, buspirone does not prevent the diminishment of motor and exploratory activity in animals with MPTP-induced depression. It may be assumed that the mechanisms of lowered mobility and exploration in these animals differ from the pathogenic mechanisms of the other behavioral signs of depression studied.

The decrease of motor and exploratory activity in the group of rats administered physiological saline may be due to the stressful effect of the procedure of repeated administration [3]. In the groups of animals given buspirone and MPTP as well as MPTP and physiological saline the decrease of motor and exploratory activity probably resulted from the combined stressful effect of its administration and the direct effect of MPTP. In this case the fact that motor and exploratory activity did not fall off in the group administered buspirone and physiological saline may attest to the antistress effect of buspirone.

The effect of buspirone on DA-deficiency-dependent symptoms of MPTP-induced depression in animals can be explained in two ways: by the mediated effect on DA neurons of the nigrostriatum via phase presynaptic modulation of their activity using serotoninergic afferents running to the substantia nigra and striatum from the neurons of the dorsal suture nucleus, which have 5-HT_{1A}-autoreceptors [6,7], and by the direct effect on the D_2 DA receptors in the nigrostriatal system [1,10]. Since the agonist of D_2 DA receptors bromocriptine (proprietory name Parlodel) effectively prevents the development of all signs of depression in rats [2] and buspirone is evidently less effective, it may be assumed that the most likely mechanism of the antidepressant effect of buspirone in this model is its mediated modulating effect on the activity of the central DA-ergic system. It is known that the modulating effect depends on the functional state of catecholaminergic brain neurons [9]. The antidepressant effect of buspirone on the model of MPTP-induced depression and the noted diminishment of motivational behavior in rats treated with buspirone and physiological saline are due to the difference in the effect of buspirone on functionally altered and unaltered D_2 DA receptors.

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