PHARMACOLOGY AND TOXICOLOGY

Effect of Melipramine on the Development of Experimental Depressive Syndrome Induced by Systemic Administration of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)

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The effects of chronic administration of melipramine on the development of behavioral signs of depression in rats are studied using the model of a depressive syndrome induced by systemic administration of MPTP. Preadministration of melipramine prevents such MPTP-induced behavioral signs of depression in rats as decreased motor activity, reduced total daily liquid intake, reduced preference of sucrose solution over water, and increased depression index.

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

In a previous study concerning the effects of bromocriptine (an agonist of dopamine receptors, the basis of the pharmacopoeic preparation parlodel) using a new model of depressive syndrome in rats induced by systemic administration of the neurotoxin MPTP [2] we substantiated the dopamine-dependent nature of the development of this syndrome [1]. The present study continues the pharmacological analysis of the modelled depressive syndrome in rats and deals with the effects of the tricyclic antidepressant melipramine (MP) on the development of behavioral signs of depression induced by chronic systemic administration of MPTP.

MATERIALS AND METHODS

The study was performed on 25 male Wistar rats weighing 220-300 g. The animals were caged individually and kept under standard vivarium conditions with the natural day-night cycle and free access to food and water.

The effects of MP on the development of behavioral signs of MPTP-induced depression in rats were studied as follows: the rats (fixed with forceps) received a daily intramuscular injection of MP (10 mg/kg) to the hind paw followed 45-60 min later by an intraperitoneal injection of MPTP in a dose of 15 mg/kg (for which the rats were handled). To avoid any differences in experimental manipulations, in all experimental groups the study was performed according to the following scheme. The animals were divided into 4 groups. The rats of group 1 (n=7) received MPTP 45-60 min after intramuscular injection of physiological saline (PS). The animals of group 2 (n=6) were injected with MP and after 45-60 min received an intraperitoneal injection of PS. The animals of group 3 (n=6) were injected with MP and after 45-60 min with MPTP. Group 4 received two injections of PS according to the above scheme. The preparations were injected in a volume of 1 ml/kg body weight. A pharmacopoeic preparation

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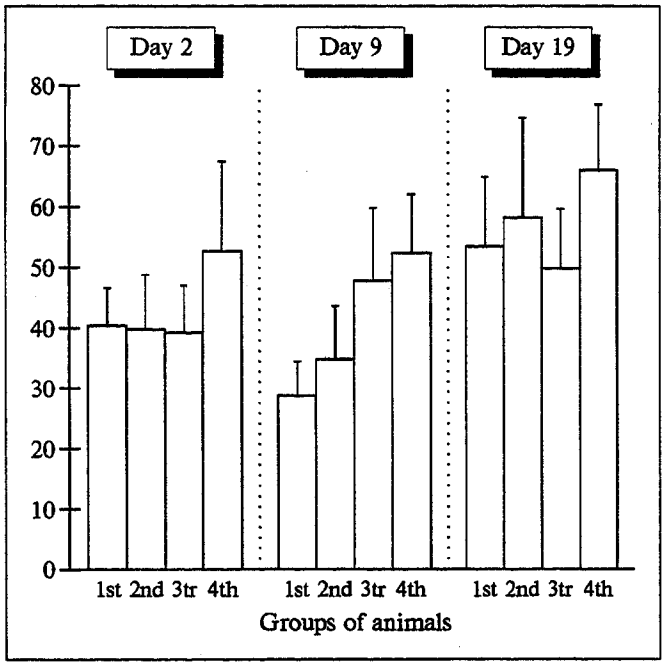

Fig. 1. Histogram of daily liquid intake in rats receiving MPTP (group 1), MP (group 2), and their combination (group 3) in comparison with rats receiving PS (group 4) at different times of observation. Days from the start of observation: day 2 – before treatment, day 9 – during treatment, and day 19 – after withdrawal. Ordinate: daily liquid intake (10% sucrose solution and water), ml. Here and in Fig. 2: *$p<0.05$ in comparison with the respective parameter in the control group treated with PS (unpaired parametric Student t test).

of MP (imipramine hydrochloride, in ampoules, Egis Pharmacological Plant) was used in the experiments. MP was adjusted to the necessary volume with PS. MPTP (synthesized at the Research Institute of Pharmacology, Russian Academy of Medical Sciences) was diluted with PS immediately before injection.

The multiparametric method of evaluating anxiety-phobic states in rats in the open field, as well as determination of daily liquid intake and preference of 10% sucrose over water were performed as described earlier [2]. Motor and exploratory activity as well as the anxiety-phobic level in rats were determined 5 times: 2-3 days before the first injection of the preparations, on days 11-12 of treatment, and 1, 2, and 3 weeks after cessation of the treatment. The forced swimming test [2] with a biorhythmological approach [3] was used for determination of the index of depression (ID), which represents the ratio of the number of immobilization periods lasting up to 6 sec to the number of periods of active swimming. ID was determined on day 9 of treatment and 12 days after its termination. Statistical processing of the results was performed using Student's unpaired parametric t test and analysis of variance for repetitive changes according to Statgraphics and Primer algorithms with comparison of the mean values after Tukey (t_Q test).

RESULTS

Earlier we showed that MPTP injected intraperitoneally in a dose of 15 mg/kg daily during 18 days reduced motor and exploratory activity in rats, daily liquid intake, and the preference of 10% sucrose over water, while it increased ID, the anxiety-phobic level being unaffected [2]. These effects manifested themselves no later than 2 weeks after the beginning of MPTP injections and persisted at least one week after termination of the treatment. Neither minor modifications of the scheme of MPTP administration in the study of the effects of parlodel on the development of MPTP-induced depressive syndrome in rats, dictated by requirements to comply with the procedure of experimental interventions in animals of all experimental groups, nor a shortened (to 12 days) administration of neurotoxin affected the main behavioral effects of the preparation [1].

In the present study we observed reduced motor activity in rats in group 1 [$F(4.24)=19.59$, $p<0.001$], the mean value also being decreased in comparison with the initial level at the end of the treatment and 1, 2, and 3 weeks after termination of MPTP (t_Q values were 7.10, 9.04, 9.62, and 7.25, respectively, $p<0.05$). Exploratory activity was suppressed [$F(4.24)=3.30$, $p<0.05$]: one week after termination of the treatment this parameter differed from the initial level ($t_Q=4.26$, $p<0.05$). The daily liquid intake and preference of 10% sucrose over water in this group were lower than the respective values in the group receiving PS against the background of MPTP (Figs. 1 and 2). In the group tested in forced swimming against the background of MPTP, ID was higher than the control value obtained in the group receiving PS (1.89±0.52 and 0.56±0.19, respectively, $p<0.05$) and did not differ from that after withdrawal of MPTP (0.82±0.39 and 0.50±0.18, respectively, $p>0.05$). The anxiety-phobic level in this group was 9.1±1.5 points and remained constant throughout the experiment. A slight rigidity of the body (slight humpiness) was observed in animals toward the end of MPTP administration.

Thus, in the present study, just as in the study on the effects of parlodel, some modification of the scheme of MPTP administration consisting in intramuscular injection of PS prior to the neurotoxin did not affect the reproduction of the MPTP-induced behavioral effects observed earlier.

In group 2 MP reduced motor activity [$F(4.16)=5.02$, $p<0.01$], the mean value of this parameter being decreased in comparison with the initial level both against the background of MP and 1, 2, and 3 weeks after its withdrawal (t_Q values were 5.02, 5.26, 5.16, and 4.35, respectively, $p<0.05$). The exploratory activity was also decreased [$F(4.16)=3.56$, $p<0.05$]: the mean value was lower than the initial level 1 and 2 weeks after withdrawal of the preparation (t_Q=4.42 and 4.64). The sugar preference was suppressed in comparison with the group injected with PS both against the background and after withdrawal of the preparation (Fig. 2), while a decline in daily liquid intake was noted only episodically after withdrawal of the preparations. ID did not differ from the control values (PS injections) either during treatment or after withdrawal of the preparations and constituted 0.98±0.19 and 0.36±0.17, respectively. The initial anxiety-phobic level in this group was 10.4±1.7 points and did not change throughout the experiment.

In group 3 (combined administration of MPTP and MP) no reliable suppression of motor activity was observed [$F(4.20)=2.07$, $p>0.05$], although such a tendency was noted. The exploratory activity was decreased [$F(4.20)=6.95$, $p<0.01$]: the mean value after all the above times was lower than the initial level (t_Q values were 5.56, 6.55, 5.75, and 5.56, respectively, $p<0.05$). At the end of injections in this group, similarly to the group receiving injections of MPTP, we observed slight extrapyramidal disturbances (rigidity of the hind legs). The sugar preference declines at the end of treatment and for some days after withdrawal (Fig. 2), while the daily liquid intake remained unchanged. The absolute value of ID (1.08±0.45) did not differ statistically from the control but exceeded unity, which points to a weakly expressed depressive component in the animal's behavior [3]. No differences in ID values in animals of this group (0.38±0.15) and animals injected with PS were observed after withdrawal of the preparations. The initial anxiety-phobic level in this group was 9.9±2.0 points and did not change throughout the experiment.

In group 4 motor activity was reduced [$F(4.20)=5.80$, $p<0.01$]: its mean value against the background of PS and 2 weeks after withdrawal was lower than the initial value (t_Q=5.49 and 6.15, respectively, $p<0.05$). The exploratory activity was also decreased during all studied periods [$F(4.20)=8.68$, $p<0.001$] (t_Q values were 5.91, 7.17, 6.99, and 5.22, respectively). Daily liquid intake and sugar preference in this group remained constant throughout the period of PS injections. The absolute value of ID did not exceed unity either during or after withdrawal of the treatment. The anxiety-phobic level, 10.9±1.7 points, did not change throughout the experiment.

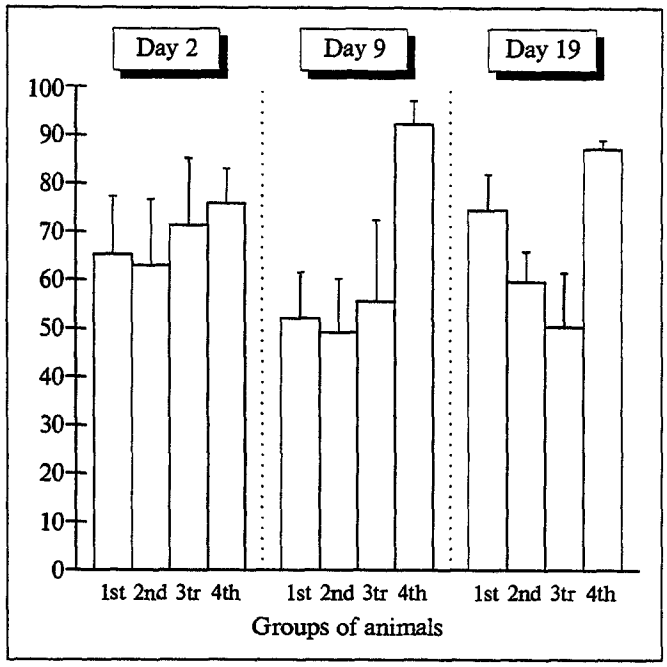

Fig. 2. Histogram of intake of 10% sucrose solution in rats receiving MPTP (group 1), MP (group 2), and their combination (group 3) in comparison with rats receiving PS (group 4) at different times of observation. Days from the start of observation: day 2 – before treatment, day 8 – during treatment, and day 21 – after withdrawal. Ordinate: intake of 10% sucrose solution, % of total volume drunk daily.

These data suggest that repeated injections of MP prevent the suppression of motor activity, daily liquid intake, and preference of sucrose solution over water and the increase of ID against the background of MPTP, i.e., they prevent the appearance of behavioral signs of depression in rats similarly to the previously studied effects of parlodel [1]. The data on the comparable of the efficacy of parlodel and MP in preventing the main behavioral symptoms of MPTP-induced depression in rats obtained using this new experimental model of depressive syndrome correlate with clinical data on the efficacy of both preparations against mood disturbances and retardation in psychogenic and endogenous depression [5]. Taking into account the fact that various stress factors may lead to a reduced dopamine content in the striatum [7], it may be assumed that multiply repeated daily procedure of PS injections places great stress on the animals. This is manifestesd in a reduced motor and exploratory activity, the level of which depends on the dopamine content in the central nervous system [6]. In animals of other groups this effect may be masked by the effect of MP and

MPTP. For instance, multiple injections of MP in the chosen dose to normal animals during 12 days are accompanied by a considerable impairment of behavioral characteristics: a stable reduction in both motor activity and sugar preference. Both effects remain after the end of treatment. Such impairment of behavioral characteristics in normal rats in response to MP may be related to the development of plastic alterations in the central nervous system due to the blockade of reuptake of norepinephrine, which is one of the main mechanisms of action of MP [5]. This is confirmed by the fact that the MP metabolite desipramine, a potent inhibitor of norepinephrine reuptake, accumulates and is retained in the brain for a long time after long-term administration [4]. In this case the adaptive response is realized through a reduced content of norepinephrine in the synaptic gap. This leads to motor and hedonic disturbances directly or indirectly related to the insufficient effect of norepinephrine [6].

These results together with the data on the efficacy of parlodel in the treatment of behavioral depression in rats obtained on the new model of MPTP-induced depressive syndrome attest to the pharmacological isomorphism of our new experimental model of depression with clinical forms of the disease.

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