PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

A New Model of the Depressive Syndrome Induced by Administration of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP) in Rats

G. N. Kryzhanovskii, N. A. Krupina, and V. G. Kucheryanu

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 119, № 2, pp. 125-128, February, 1995
Original article submitted April 11, 1994

Animals treated with MPTP neurotoxin displayed lowered motor and exploratory activity in the open field test, reduced daily intake of water with a preference for sugar solution over water, prolonged immobilization, and increased index of depression in the forced swimming test. The changes in rat behavior were preserved for at least a week after withdrawal of the drug. The data attest to the development of a state of lowered motivational activity combined with ahedony and "behavioral despair" in response to MPTP, making it possible to consider this state as a new experimental model of dopamine-dependent depressive syndrome in rats.

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

According to the data of the World Organization of Public Health, some 5% of the world population suffer from some kind of depression [7]. The creation of suitable experimental models of depression-like disorders in animals is important for the study of the pathophysiological mechanism of depressive states. However, in many respects the existing models [9] do not meet the criteria for phenomenologic and pharmacologic isomorphism with the corresponding clinical forms of depression.

The theory of generator and systemic mechanisms of neuropathological syndromes forms the basis of this study [3]. The neuropathophysiological base for hypokinesia and rigidity in rats with experimental parkinsonism caused by the administration of the specific dopaminergic neurotoxin MPTP is demonstrated to be the hyperactivity of nucleus caudatus neurons with the development of a generator of pathologically enhanced excitation [4]. The genesis of inactivation states in rats is also related to the activation of striatum mechanisms [5]. The motor and emotional-behavioral "freezing" that occurs in an inactivation state is the same as that observed in clinical manifestations of depression [1]. It may be assumed that the hyperactivity of limiting mechanisms of the striatum is the principal pathophysiological mechanism underlying the development of immobility in parkinsonism and of motor and mental inhibition in depressive disorders.

The aim of the present investigation was to examine the possibility of the development of behavioral depression in rats for chronic systemic administration of MPTP neurotoxin using a scheme less stringent than that required for the creation of a model of the parkinsonian syndrome.

MATERIALS AND METHODS

Experiments were carried out on 22 male albino Wistar rats weighing 250-370 g. Animals were kept

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

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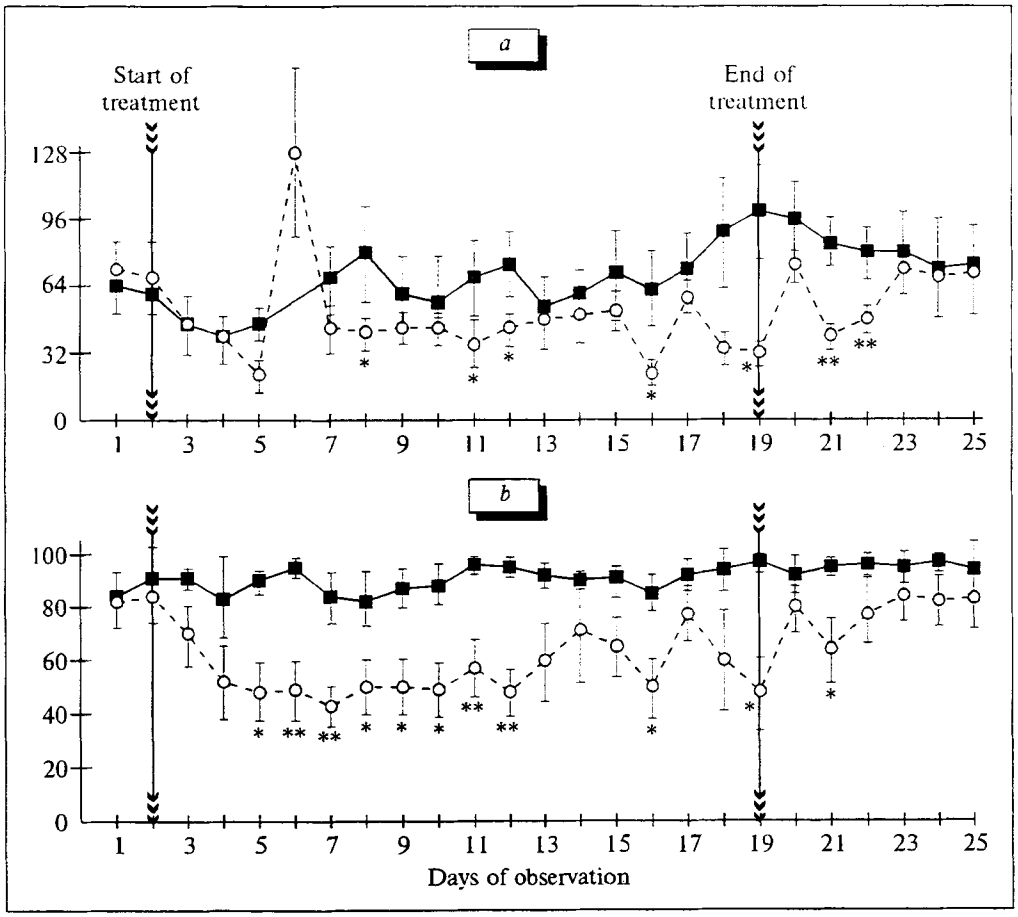

Fig. 1. Dynamics of the total liquid (*a*) and 10% sugar solution (*b*) intake in groups of rats treated with MPTP (broken line) or physiological saline (continuous line). Ordinate: *a*) volume of fluid drunk per day, ml; *b*) intake of sugar solution in % of total liquid intake per day. Here and in Fig. 2: * indicates $p<0.05$, ** $p<0.01$ with the significance of differences corresponding daily to the value of the parameter in the group of rats injected physiological saline (the Student *t* test).

individually under standard vivarium conditions. MPTP (Research Institute of Pharmacology, Russian Academy of Medical Sciences) was administered i.p. at 15 mg/kg (in 0.5 ml physiological saline per animal) daily during 18 days. Animals of the control group were injected physiological saline according to the same scheme.

Animals were examined by the method of multiparameter assessment of anxiety and phobic states in rats and in the open field test, as described previously [6]. 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 3 min) as well as the anxiety and phobic level were determined 6 times: 1 week prior to administration of to drugs, 1 and 2 weeks after the start of treatment (against the background of daily injections of MPTP), and 1 and 2 weeks after discontinuation of the drug. The structure and parameters of swimming behavior in the forced swimming test were assessed using the classic method [12] in a modification [8]. Each rat was placed in a vessel filled with water up to the 30-cm mark with a temperature of 24-25°C. The duration of active swimming, passive floating, and immobilization was recorded. 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 [8]. Each group of rats was examined twice at an interval of 3 weeks. An examination included two tests, performed one day apart. In the first series the experimental (n=5) and control (n=6) groups were tested on the 2nd and 3rd day after the start of treatment and on the 6th and 7th day after its cessation; in the second series the experimental (n=5) and control (n=6) rats were tested on the 14th and 15th day after the start of treatment and on the 14th and 15th day after its cessation drugs. The preference for 10% sugar solution over water was determined as follows. Each cage was equipped with two drinking bowls, one filled with plain water and the other with 10% sugar solution. Throughout 25 days of observation the volume of water and sugar solution drunk was monitored in each cage at the same time daily. Every day the bowls filled with fresh water and sugar solution were switched. The percent of sugar solution intake was calculated from the whole volume of liquid drunk in the groups of rats for each day of the experiment.

Results were processed statistically using the nonpaired parametric Student *t* test and analysis of

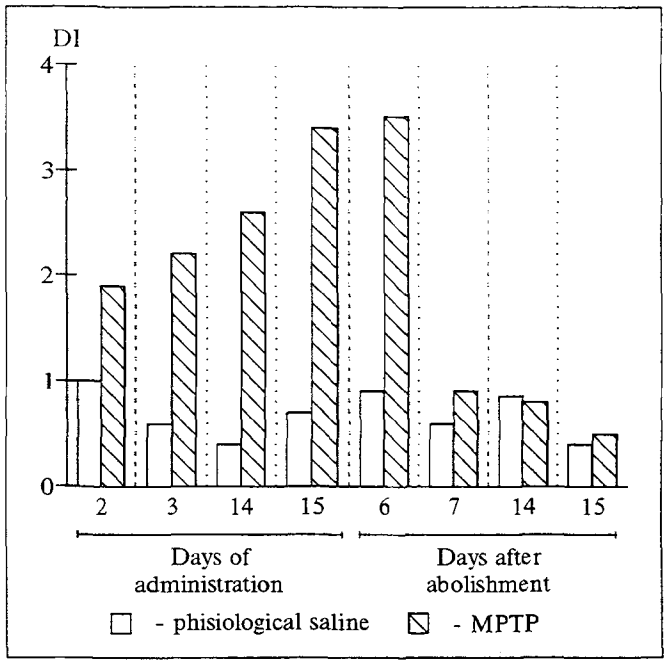

Fig. 2. DI changes in forced swimming test in rats against the background of MPTP administration and after abolishment of the drug. The broken line indicates the maximal value of DI allowed for animals with the absence of the depressive component in behavior.

variations for repeated measurements by algorithms of Statgraphics and Primer software followed by comparison of mean values after Tewkey (t_Q test).

RESULTS

The administration of MPTP resulted in reduced motor activity in the experimental group ($F(5.45)= =4.20$; $p<0.01$), the level of motor activity being decreased 2 weeks after the start of MPTP treatment as well as 1 and 2 weeks after abolishment ($p<0.05$ for all cases) as compared to the level of motor activity in the same group before treatment. Diminished exploratory activity was also found in the experimental group ($F(5.45)= =6.89$; $p<0.001$) and its level was lowered just 1 week after the start of drug administration as compared to the baseline findings ($p<0.05$). The effect was marked 2 weeks after the start of MPTP treatment ($p<0.05$) and was preserved for 1 and 2 weeks after treatment ($p<0.05$ for both cases). The control group showed a tendency toward lowered motor and exploratory activity in repeated open field tests.

The decrease of the motor and exploratory activity in the experimental group against the background of MPTP administration was accompanied by slight rigidity of the hind limbs (moving on raised paws) and of the body (a slight humpiness).

The anxiety-phobic level in the control and experimental groups initially comprised 5.33±0.83 ($n=6$) and 5.30±1.43 ($n=10$) points, respectively, and did not change on repeated examinations.

A difference in the total volume of water intake between the experimental and control groups of rats was noted against the background of MPTP administration and was preserved during 3 days after its abolishment (Fig. 1, *a*). The level of intake in the control group was stable throughout the observation period. A difference in sugar-water preference between the experimental and control groups was noted against the background of MPTP administration and for 2 days afterward (Fig. 1, *b*). A stable preference of 10% sugar solution over water was noted in the control group throughout the observation period.

Experimental rats showed a lowered duration of passive floating and prolongation of immobilization (Table 1) in the 1st series on the 3rd day of MPTP treatment. Control rats exhibited a complete change of the structure of swimming behavior in the 2nd series on the 14th day of MPTP treatment, namely increased duration of active swimming, decreased passive floating, and longer immobilization. Only the effects of shortened floating and prolonged immobilization were preserved on the 15th day.

The structure of swimming behavior in the experimental and control groups did not differ either on the 6th and the 7th days or on 14th and 15th days, although immobilization still tended to be prolonged in the experimental groups 2 weeks after the abolishment of MPTP. The DI in control groups did not exceed unity either against the background of physiological saline, or after it (Fig. 2). The DI in experimental groups exceeded the corresponding control level on the 2nd and 3rd as well as on the 14th and 15th days of MPTP administration. After MPTP treatment the DI in the experimental groups on the 6th and 7th days did not differ significantly from the control values, and on the 14th and 15th days of MPTP abolishment the DI did not exceed unity, as in control animals.

Thus, chronic administration of MPTP in rats was accompanied by the development of signs of behavioral depression, such as a decrease of motor and exploratory activity, a lowered level of water intake and of a preference for sugared over plain water, prolongation of immobilization, and a rise of DI in the forced swimming test.

Although reduced motor and exploratory activity in response to MPTP may be a sign of the hypokinesia characteristic for parkinsonism, the decrease of the total volume of water intake in experimental rats attests to a lowered level of motivation (for drinking, in this case), while the

disappearance of the preference for sugar water indicates the loss of pleasure emotions, i.e., of the ahedony typical for clinical manifestations of melancholic depression [10].

Prolonged immobilization in the forced swimming test testifies to the development of "behavioral despair" in experimental animals, which may be considered an experimental analog of despair, hopelessness, inactivity, and pessimism in clinical manifestations of the depressive syndrome. The rise of DI in such animals confirms the development of a depressive component in the behavior of experimental rats.

The aggregate of behavioral changes characteristic for depression was preserved for at least a week after the abolishment of MPTP. The complex of symptoms of depressed behavior attests to the existence of a certain phenomenological isomorphism of the experimental depressive syndrome in rats with clinical forms of depressive disorders.

Long-term electrostimulation of the striatum is known to reduce locomotion, which becomes desynchronized, and to boost DI [2]. Therefore, hyperactivation of striatal structures may underlie the observed complex of depressive symptoms in animals, which acquires properties of a pathological determinant under conditions of dopamine deficiency and leads to the formation of structurally different pathological systems, clinically manifesting either as the parkinsonian syndrome or as depression. Clinical and epidemiological investigations verify such an assumption [11].

The findings permit us to consider the behavioral changes in rats induced by MPTP as a new experimental model of dopamine-dependent depressive syndrome.

TABLE 1. Duration of Periods of Swimming Behavior in Rats against the Background of MPTP and Physiological Saline, sec ($M \pm m$)

Days after start of treatment	Physiological saline (n=6)	MPTP (n=5)
	Active swimming	
2	322.5±23.1	242.4±42.9
3	253.3±8.5	266.0±47.3
14	295.3±20.8	411.0±43.4*
15	261.3±28.7	348.0±43.5
	Passive floating	
2	261.2±25.9	310.4±39.8
3	321.8±14.7	231.0±23.2**
14	298.3±21.9	137.6±35.4**
15	330.0±28.6	179.8±35.3**
	Immobilization	
2	16.3±5.0	47.2±17.7
3	24.8±15.7	103.0±32.2*
14	6.3±3.2	51.4±14.6**
15	8.7±4.4	72.2±18.5**

Note. * indicates $p<0.05$, ** $p<0.01$; the significance of differences corresponds to the parameter in the group of rats treated with physiological saline (the Student t test); n: the number of animals.

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