MICROBIOLOGY AND IMMUNOLOGY

Disturbances in Humoral and Cell-Mediated Immunity in Rats with Experimental Depressive Syndrome Induced by Systemic Administration of 1-Methyl-4-Phenyl-1,2,3,6—Tetrahydropyridine

T. V. Davydova, V. G. Fomina, N. A. Krupina,* G. N. Kryzhanovskii,* V. A. Evseev, I. N. Orlova,* and T. E. Iordanskaya*

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 3, pp. 308-311, March, 1997
Original article submitted December 22, 1995

Changes in humoral and cell-mediated immunity are studied in rats with 1-methyl-4-phenyl-1,2,3,6—tetrahydropyridine (MPTP)-induced depressive syndrome. A decrease in the lymphocyte count and in absolute and relative T cell counts and absolute B cell counts in peripheral blood and an increase in serum concentration of circulating immune complexes (CIC) are demonstrated. Serum CIC content increases, while the relative count of peripheral blood T cells remains decreased two weeks after discontinuation of MPTP and normalization of rats' behavior. Serum CIC content decreases and T cell count normalizes one month after discontinuation of MPTP.

Key Words: *depressive syndrome; MPTP; rats; T and B cells; immune complexes*

The interactions between nervous and immune systems play an important role in the pathogenesis of depressions [2,3]. It was reported that in acute depression the activity of lymphocytes and the concentration of circulating immune complexes (CIC) are decreased [14] and the activity of natural killer cells is altered [10,12]. In patients with psychogenic depression, the relative counts of T suppressors and immature B cells are decreased, while the absolute count of B cells and the concentration of immunoglobulins G, A, and M and CIC are increased [5]. However, no distinct relationship has been revealed between the type of depression, major neurochemical alterations, and changes in immune reactivity. The investigation of the pathogenesis of immune disturbances in depression is hampered by the absence of adequate experimental model. Previously, it was shown that systemic administration of 1-methyl-4-phenyl-1,2, 3,6-tetrahydropyridine (MPTP), a toxin specific for dopaminergic neurons, to rats induces a dopamine deficiency-dependent depressive syndrome manifesting itself as reduced motivation, hedonic disorders, and "behavioral despair" [7,8]. The REM-sleep disorders typical of endogenous depression were observed in animals with experimental depressive syndrome [6]. The state induced in rats by systemic administration of MPTP can be regarded as a model of dopamine deficiency-dependent emotional and behavioral disorders typical of endogenous depression. Our objective was to study the dynamics of some parameters of humoral and cell-mediated immunity in rats with MPTP-induced depressive syndrome.

Laboratory of Neuroimmunopathology, *Laboratory of General Pathology of Nervous System, Institute of General Pathology and Pathophysiology, Russian Academy of Sciences, Moscow

0007-4888/97/0003-0267$18.00

MATERIALS AND METHODS

Experiments were performed on 28 male Wistar rats weighing 320-380 g. The animals were maintained in individual cages under standard vivarium conditions and natural light regime and had free access to food and water. MPTP was injected intraperitoneally in a daily dose of 20 mg/kg every day during a 13-day period. Control rats received an equal volume of normal saline. Experimental and control groups consisted of 14 rats. The preparation was dissolved in normal saline immediately before injection and administered in a volume of 1 ml/kg body weight. Daily consumption of water (motivation level), preference between water and 10% sucrose solution (hedonic disturbances), duration of immobilization in the forced swimming test ("behavioral despair"), and depression index (DI, a ratio between the number of more than 6-sec long immobilizations to the total number of swimming periods for a 10-min test) were determined as previously [7]. Daily consumption of water and preference between water and 10% sucrose were assessed during a 24-day period (4 days before, 13 during, and 7 days after administration of MPTP). Depression index was estimated on day 12 after administration of MPTP and on day 13 after MPTP discontinuation.

For determination of T and B cell counts and serum CIC concentration blood was collected from the caudal vein on day 13 of MPTP administration and 2 and 4 weeks after discontinuation of MPTP. Lymphocytes were isolated with the use of 3% gelatin and purified from erythrocytes by osmotic shock. T cells were identified by rosette formation with guinea pig erythrocytes [4]. B cells were identified by rosette formation with the sheep erythrocytes—antibodies—complement complex [9]. Serum concentration of CIC was determined by selective precipitation with polyethylene glycol [1].

The results were statistically processed by Student's t test and a single-factor analysis of variance with the use of a Statgraphics software.

RESULTS

Daily water consumption decreased in MPTP-treated rats ($F(23,298)=1.948$, $p<0.01$, single-factor analysis of variance) and remained stable (70-100 ml) throughout the entire experimental period in control rats ($F(23,312)=1.405$, $p>0.05$). The preference for 10%

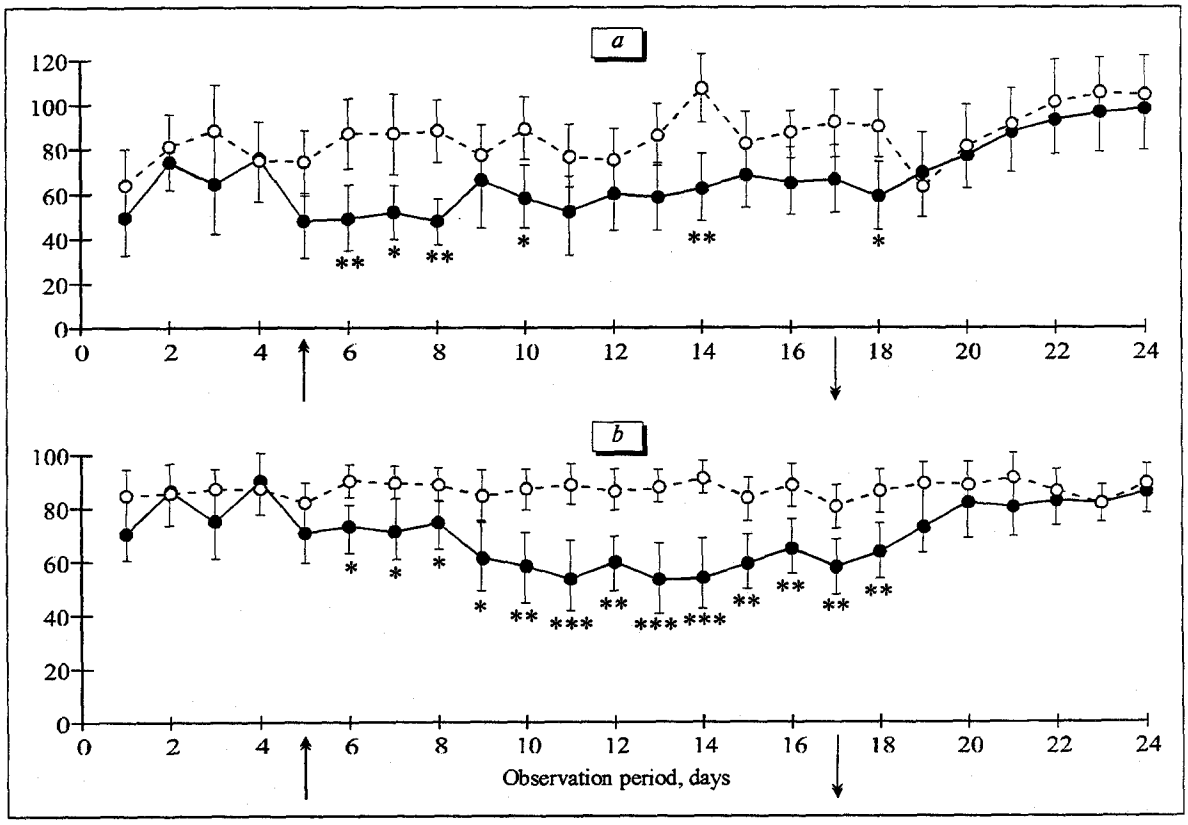

Fig. 1. Time course of water (*a*) and 10% sucrose (*b*) consumption in MPTP-treated (solid line) and control (broken line) rats. Ordinate: *a*) volume of water, ml; *b*) volume of sucrose solution, percent of total liquid consumption. The first and the last days of MPTP administration are indicated with arrows. Here and in Fig. 2: *$p<0.05$; **$p<0.01$; ***$p<0.001$ compared with the corresponding parameter in control rats.

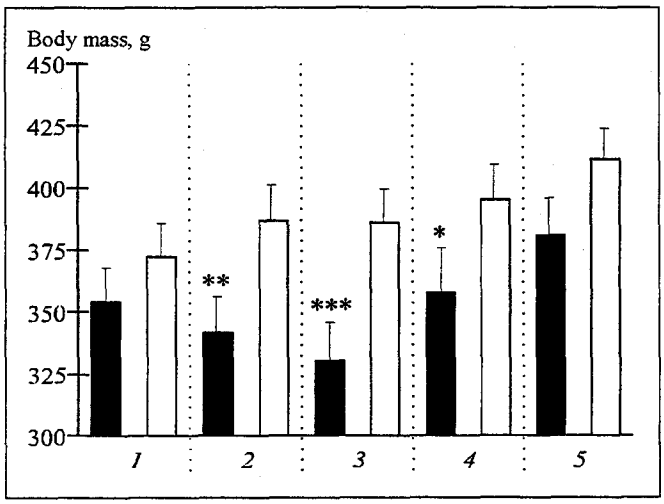

Fig. 2. Time course of body mass of MPTP-treated (black bars) and control (white bars) rats. Before (*1*), 7th (*2*), and 13th (*3*) day of MPTP administration; 1 (*4*) and 2 (*5*) weeks after MPTP discontinuation.

sucrose decreased in MPTP-treated rats ($F(23,298)=2.689$, $p<0.001$), while in control rats it remained at a high level (85-90%) ($F(23,312)=0.860$, $p>0.05$. The differences in these parameters were observed one day after discontinuation of MPTP (Fig. 1). These findings point to reduced motivation and hedonic disturbances in MPTP-treated rats.

In experimental rats, the immobilization periods in the forced swimming test were longer (39.3±5.1 *vs.* 6.1±1.5 sec in the control group, $p<0.001$), the latency of immobilization shorter (130.4±10.0 *vs.* 211.7±36.3 sec, $p<0.05$), while DI increased considerably (3.17±0.59 *vs.* 0.65±0.17, $p<0.001$) against the background of MPTP, indicating the development of "behavioral despair." These parameters returned to normal 2 weeks after discontinuation of MPTP: 6.3±1.5 *vs.* 7.0±4.4 sec ($p>0.05$) and 227.2±45.1 *vs.* 327.1±56.4 ($p>0.05$), respectively. There were no significant differences in DI: 1.01±0.24 *vs.* 0.48±0.12, $p>0.05$.

Thus, all MPTP-treated rats developed depressive syndrome manifesting itself as reduced motivation (daily water consumption), hedonic disturbances (decreased preference for sucrose solution), and/or "behavioral despair." In addition, body weight of experimental rats was lower compared with that of control rats (Fig. 2).

In MPTP-treated animals, the total lymphocyte count and absolute and relative counts of peripheral blood T cells and absolute count of B cells decreased, while serum concentration of CIC increased (Table 1). Changes in the immune status were most pronounced in rats with severe depression. After normalization of behavior (2 weeks after discontinuation of MPTP), serum CIC concentration increased, while the relative count of peripheral blood T cells remained at a low level. Normalization of T cell count and reduction in CIC concentration were observed 1 month after discontinuation of MPTP.

A decrease in the total lymphocyte and absolute T and B counts were observed in patients with severe endogenous depression [11,13]. In the present study, similar changes occurred in rats with experimental depressive syndrome. Previously, we showed that this syndrome is dopamine deficiency-dependent [7]. A decrease in the activity of the dopaminergic system leads to suppression of immune reactions [2,3]. It can be hypothesized that the revealed changes in immunological parameters of rats with experimental depressive syndrome are associated with dopamine deficiency. The increase in serum CIC content may result from increased production of autoantibodies, specifically, anti-neurotransmitter antibodies, which is probably associated with activation of autoimmune reactions in the organism.

TABLE 1. Counts of Peripheral Blood T and B Cells and Serum CIC Concentration in Rats with Experimental Depressive Syndrome

Parameter	MPTP administration		Weeks after discontinuation of MPTP			
			2		4	
	MPTP	normal saline	MPTP	normal saline	MPTP	normal saline
Leukocytes, mm^3	5350±542.8*	7250±367.0	9100±604.6*	7100±305.5	7250±160.9	7416.6±160.9
Lymphocytes, %	51.6±2.5*	66.0±3.8	51.5±1.8*	69.6±1.9	67.0±1.9	71.6±1.4
T cells, %	21.8±2.5*	36.6±2.7	32.5±2.3*	38.5±1.4	36.3±1.2	37.9±13
absolute count	618.1±101.5*	1730.3±174.6	1611.7±124.1	1905.2±122.5	1789.5±139.6	2009.0±71.5
B cells, %	14.5±1.6	14.0±1.1	13.8±0.9	14.5±1.1	16.5±1.4	15.3±0.8
absolute count	405.9±62.8*	656.7±62.3	735.9±59.9	735.9±59.9	796.1±71.4	811.0±45.3
CIC, arb. units	3.4±0.7*	1.5±0.2	6.0±0.4*+	0.6±0.1	3.1±0.3*	0.45±0.1

Note. $p<0.05$: *compared with corresponding parameter in control rats, +compared with the initial value in the group.

This study was supported by the Russian Foundation for Basic Research (project No. 95-04-13216).

REFERENCES

1. P. V. Baranovskii and V. S. Danilishina, *Lab. Delo*, No. 5, 62 (1983).
2. L. V. Devoino and R. Yu. Il'yuchenok, *Monoaminoergic Systems in the Regulation of Immune Reactions* [in Russian], Novosibirsk (1983).
3. L. V. Devoino and R. Yu. Il'yuchenok, in: *Neurotransmitter Systems in Psychoneuroimmunomodulation* [in Russian], Novosibirsk (1993), pp. 10-39.
4. *Immunological Methods* [in Russian], Moscow (1987).
5. N. A. Kornetov, in: *Psychogenic Depressions (Clinics and Pathogenesis)* [in Russian], Tomsk (1993), pp. 153-186.
6. N. A. Krupina, G. N. Kryzhanovskii, T. E. Iordanskaya, *et al.*, *Byull. Eksp. Biol. Med.*, **123**, No. 2, 138-142 (1997).
7. N. A. Krupina, I. N. Orlova, and G. N. Kryzhanovskii, *Byull. Eksp. Biol. Med.*, **120**, No. 7, 66-71 (1995).
8. G. N. Kryzhanovskii, N. A. Krupina, and V. G. Kucheryanu, *Zh. Vyssh. Nervn. Deyat.*, **45**, No. 2, 377-387 (1995).
9. C. R. Bianco, R. Patric, V. Nussenzmeig, *J. Exp. Med.*, **132**, 702-722 (1970).
10. D. L. Evans, C. A. Pedersen, and J. D. Folds, *Progr. Neuropsychopharmacol. Biol. Psychiatry*, **12**, 739-748 (1988).
11. Z. Kronfol, J. Silva, J. Greden, *et al.*, *Life Sci.*, **33**, 241-247 (1983).
12. K. I. Natban, D. L. Musselman, A. F. Schatzberg, and Ch. B. Nemeroff, *The American Psychiatric Press Textbook of Psychopharmacology* A. F. Schatzberg and Ch. B. Nemeroff (Eds.), Washington - London (1995), pp. 439-477.
13. S. J. Schleifer, S. E. Keller, S. G. Siris, *et al.*, *Arch. Gen. Psychiatry*, **42**, 129-133 (1985).
14. M. Stein, A. H. Miller, and R. L. Trestman, in: *Psychoneuroimmunology* R. Ader *et al.* (Eds.), New York (1991), pp. 897-930.

Antibody Spectrum to Membrane Phospholipids in Women with Recurrent Miscarriages

I. V. Ponomareva, V. I. Kulikov, G. I. Muzya, L. V. Van'ko, B. M. Sidel'nikova, and G. T. Sukhikh

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 123, No. 3, pp. 312-315, March, 1997
Original article submitted January 29, 1996

Immunoenzyme assay is developed for determination of IgM- and IgG-antibodies to 6 major human blood phospholipids. The antiphospholipid antibody spectra in pregnant and nonpregnant women with recurrent miscarriages and the dynamics of these antibodies during pregnancy are studied. Antibodies to phosphatidylserine, a phospholipid expressed on the surface of cytotrophoblast cells, are identified. It is demonstrated that the antiphospholipid antibody spectrum is important for clinical evaluation and prognosis of pregnancy.

Key Words: *antiphospholipid syndrome; antiphospholipid antibodies; immunoenzyme assay; recurrent miscarriages; phospholipids*

It is known that production of autoantibodies to membrane phospholipids is often associated with recurrent abortions, late toxemia, fetal growth retardation or intrauterine death, and thromboembolic complications.

Laboratory of Clinical Immunology, Department of Prophylaxis of Spontaneous Abortions, Research Center of Obstetrics, Gynecology, and Perinatology, Russian Academy of Medical Sciences; Laboratory of Lipid Biochemistry, Research and Manufacturing Center of Medical Biotechnology, Ministry of Health, Moscow

The incidence of pregnancy loss in patients with high titers of antiphospholipid antibodies (aPL) is 80-90% [1,4].

Antiphospholipid antibodies represent an antibody population heterogeneous by immunochemical specificity, which is related to the presence of several classes of membrane phospholipids (PL) with different structure and immunogenicity. The major membrane PL include neutral (phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin) and ne-

0007-4888/97/0003-0270$18.00