Substances Increasing the Extracellular Content of Dopamine in the Striatum Prevent the Development of Haloperidol Catalepsy in Rats

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The effects of substances which raise the extracellular level of dopamine in the striatum (amphetamine, pargyline, nomifenzine, sulpiride, piracetam, and L-DOPA) on the intensity of haloperidol-induced catalepsy were studied in rats. It was shown that elevation of the extracellular content of dopamine in the striatum hindered the development of haloperidol catalepsy in rats.

Key Words: *neuroleptics; dopamine; release; striatum; catalepsy*

In experiments with intracerebral microdialysis on freely moving rats it has been found that typical (cataleptogenic) and atypical (noncataleptogenic) neuroleptics are distinguished by their ability to boost the release and metabolism of dopamine (DA) in the striatum, as follows: atypical compounds raise the extracellular DA level to a greater (or equal) extent as compared to its metabolites, while the typical neuroleptics have a more marked effect on the metabolic indexes [7,12]. The clearly defined increase of DA release in the striatum under the action of noncataleptogenic neuroleptics suggests that it is this component which contributes to the formation of the atypical mode of action of the antipsychotropic agents.

Catalepsy induced by neuroleptics is known to be mainly due to blocking of the postsynaptic DA receptors in the striatum [13]. An increase of the extracellular DA content in the striatum may in turn lead to the development of competitive relationships between a neuroleptic and the endogenous ligand during their interaction with postsynaptic receptors. The results of such competition could be an unblocking of the postsynaptic DA receptors and, consequently, a decrease of the intensity of catalepsy. This study of the influence of substances increasing the extracellular DA content in the striatum on the expression of haloperidol catalepsy aimed at verifing this hypothesis.

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MATERIALS AND METHODS

The experiments were carried out on male Wistar rats weighing 200-250 g. Catalepsy was produced in rats by subcutaneous injection of haloperidol in a dose of 2 mg/kg. The degree of catalepsy was estimated 4 h later. The following criteria were used for assessing the intensity of catalepsy:

1) how long the animal held on with its forepaws to a horizontal bar of diameter 2 cm situated at a height of 10 cm;

2) how long the animal remained "straddled" between two cross-beams spaced at 15 cm at a height of 6 cm [2,11].

The intensity of catalepsy was expressed in points in terms of the time during which the animals kept a fixed pose according to the following scale: 0 (0-14 sec), 1 (15-29 sec), 2 (30-59 sec), and 3 (60 sec or more).

The following substances were used for the study: haloperidol (Janssen Pharmaceutica), pargyline (Serva), nomifenzine (RBI), sulpiride (Serva), L-

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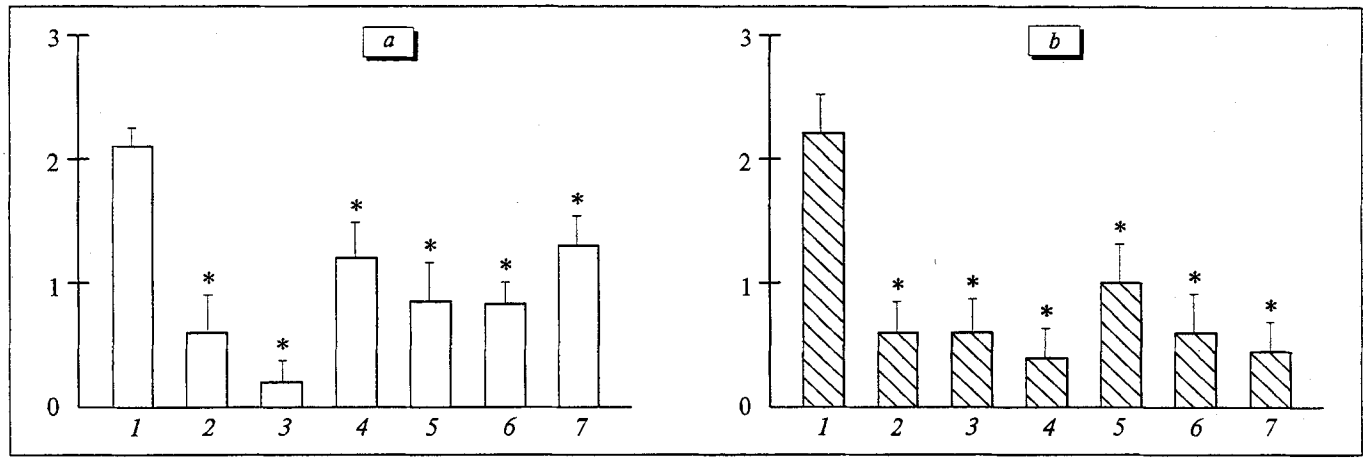

Fig. 1. Effect of substances on the intensity of catalepsy caused by haloperidol (2 mg/kg, subcutaneously) assessed by the time of clinging to the horizontal bar (*a*) and the "straddling" time (*b*). Ordinate: intensity of catalepsy, points. *1*) control; *2*) pargyline (25 mg/kg; *3*) nomifenzine (10 mg/kg); *4*) sulpiride (50 mg/kg); *5*) L-DOPA (50 mg/kg); *6*) amphetamine (2 mg/kg); *7*) piracetam (500 mg/kg). The drugs were administered intraperitoneally. The data are presented as $M \pm m$ ($n = 5-6$). *$p<0.05$ compared to the control according to the Wilcoxon–Mann–Whitney U test.

DOPA (Serva), amphetamine (Sigma), and piracetam (Russia). The drugs were administered intraperitoneally: pargyline (25 mg/kg) 2 h before and nomifenzine (10 mg/kg), sulpiride (50 mg/kg), L-DOPA (50 mg/kg), amphetamine (2 mg/kg), and piracetam (500 mg/kg) 40 min before estimation of catalepsy intensity.

The results of the study were processed using the nonparametric Wilcoxon—Mann—Whitney U test.

RESULTS

The results on the effect of the drugs on the intensity of haloperidol catalepsy depicted in Fig. 1 attest that all the substances inhibit to varying degrees catalepsy development in rats.

It is well known that the extracellular DA concentration can be increased in the striatum in the following ways: by boosting transmitter release (the potential-dependent one by blocking the terminal DA autoreceptors, of heteroreceptor influence; the potential-independent one by substances releasing DA with the aid of a carrier), by blocking the monoamine reuptake, activating biosynthesis, and by inhibiting monoamine oxidase (MAO) activity [4,5,9, 10,15]. Accordingly, the following substances were used for the study: sulpiride, an inhibitor of the terminal DA autoreceptors, which induces an additional increase of DA release in the rat striatum against the background of haloperidol [6]; piracetam, which boosts DA release in the striatum as a result of probable action on the glutamate receptors and involvement in the processes of heteroreceptor regulation [1]; amphetamine, which releases newly synthesized cytoplasmic DA as a result of an tetrodotoxin-insensitive process with the aid of a carrier [15], nomifenzine, an inhibitor of monoamine reuptake [5]; L-DOPA, a DA precursor [10]; and pargyline, an MAO inhibitor [9].

The doses and time intervals were chosen in accordance with the results of the microdialysis assays cited above, in which a marked increase of the extracellular DA content was reported for the striatum under the action of the above substances.

An anticataleptic effect was previously described in a number of reports [1,3,4] for L-DOPA, amphetamine, MAO inhibitors, blockers of DA reuptake, and piracetam. In spite of the possible involvement of other mechanisms, the weakening of haloperidol catalepsy found by us for the action of substances under conditions of a marked increase of the extracellular DA content confirms the above hypothesis. This suggests that the catalepsy caused by neuroleptics is the result of interaction of at least two processes, as follows: inhibition of postsynaptic DA receptors and a rise of the extracellular DA level in the striatum owing to blockade of the presynaptic DA receptors. It is noteworthy that even a relatively small increase of DA release (by 30-40% for piracetam [1]) may counteract catalepsy development in rats.

This observation suggests a high DA affinity of the postsynaptic receptors involved in the development of catalepsy under conditions of a lower or the same affinity of these receptors for cataleptogenic neuroleptics, their affinity for DA manifesting itself in the concentrations close to the basal extracellular concentration of the transmitter (4 nM, as reported elsewhere [14]). At the present time at least five subtypes of DA receptors are known: the D_1-like family (D_1 and D_5) and the D_2-like family (D_2, D_3, and D_4) [8]. All these subtypes may have a postsynaptic lo-

calization. According to published data [8,14], the affinity of only the D_3 receptors for DA and haloperidol is similar in the nanomolar range. This suggests their key role in the mechanism of haloperidol catalepsy development.

The results of this investigation attest that a rise of the extracellular DA content in the striatum prevents the development of haloperidol catalepsy in rats.

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Pharmacological Correction of Immune Disorders during Acute Poisoning with Dimethyl Dichlorovinylphosphate

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Experiments on mice revealed that the cholinesterase reactivator dipiroxime in a single dose of 15 mg/kg and retinol acetate in a dose stimulating thymus-dependent antibody production (3000 U per os daily for 3 days after poisoning) reverse the suppression of the main immune reactions caused by dimethyl dichlorovinylphosphate.

Key Words: *organophosphorus compounds; immunity; dipiroxime; retinol acetate*

Organophosphorus compounds (OPC) characterized by an anticholinesterase effect are among the xenobiotics causing widespread acute and chronic poisoning because of their extensive agricultural and household use as pesticides. There is also the possibility of OPC intoxication at chemical plants where they are produced. In addition, intoxication with anticholinesterase poisons may occur on a mass scale during accidents at chemical plants, specifically, at those engaged in the destruction of toxic OPC. Recently many publications have appeared that are devoted to studies of the immunotoxic effects of OPC [2,3,5,9]. The principal mechanisms of these effects have been disclosed [5], thus permitting a targeted pharmacological correction of postintoxication immunodeficiency in order to prevent various infectious complications and diseases. Our studies [5] suggest that reactivation of T-lymphocyte acetylcholineste-

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