LITERATURE CITED

1. V. B. Andreev, Yu. D. Ignatov, Z. S. Nikitina, and I. A. Sytinskii, Zh. Vyssh. Nerv. Deyat., 32, No. 3, 511 (1982).
2. V. V. Bul'on and É. A. Migas, Abstract of Proceedings of the 4th All-Union Conference on Biochemistry of Muscles [in Russian], Leningrad (1981), p. 13.
3. I. S. Zavodskaya and E. V. Moreva, Pharmacological Analysis of the Mechanism of Stress and Its Sequelae [in Russian], Leningrad (1981).
4. V. A. Ivanov, T. P. Semenova, T. M. Tret'yak, and E. A. Gromova, Neirokhimiya, 7, No. 2, 255 (1988).
5. Yu. N. Kozhevnikov, Vopr. Med. Khim., 35, No. 5, 2 (1985).
6. P. A. Kometiani, Neirokhimiya, 1, No. 4, 38 (1982).
7. F. Z. Meerson and M. G. Pshennikova, Adaptation to Stress Situations and to Physical Exercise [in Russian], Moscow (1988).
8. É. A. Migas, "Molecular bases of development of neurodystrophic lesions of the internal organs and their pharmacotherapy by means of antiphein derivatives," Author's Abstract of Dissertation for the Degree of Candidate of Biological Sciences, Leningrad (1984).
9. M. Nikolova, Med.-Biol. Inform. (Sofia), No. 3, 3 (1987).
10. V. P. Novikov, "Effect of some imidazole-dicarboxylic acid on energy metabolism of the myocardium in the presence of neurogenic damage," Author's Abstract of Dissertation for the Degree of Candidate of Biological Sciences, Leningrad (1984).
11. E. B. Okon, T. P. Semenova, and E. I. Grishchenko, Neirokhimiya, 5, No. 3, 290 (1986).
12. V. K. Pozdev, Byull. Éksp. Biol. Med., No. 5, 628 (1980).
13. I. D. Stal'naya and T. G. Garishvili, Modern Methods in Biochemistry [in Russian], Moscow (1977), pp. 66-68.
14. S. L. Stancheva and L. G. Alova, Farmakol. Toksikol., No. 3, 16 (1988).
15. A. H. Ennor and H. Rosenberg, Biochem. J., 51, 606 (1952).

SELECTIVE EFFECT OF NEUROLEPTICS ON DOPAMINE-DEPENDENT BEHAVIORAL DISTURBANCES IN RATS IN THE EXTRAPOLATION ESCAPE TEST

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The detection of antidopaminergic activity is a basic trend in neuroleptic screening. For this purpose the ability of substances to affect stereotyped behavior of rodents, induced by dopamine (DA) receptor agonists apomorphine, amphetamine, and L-dopa, has been studied [15]. Many known neuroleptics with phenothiazine and butyrophenone structure reduce, whereas classical antidepressants increase the intensity and duration of stereotyped reactions [9]. However, an atypical character of action of neuroleptics and antidepressants has been found in a series of benzamide derivatives. For instance, different doses of sulpiride and tiapride exhibit (according to clinical data) neuroleptic and antidepressive activity [7, 10]. However, the dose range within which they weaken stereotyped climbing on a net and strengthen stereotypy induced by amphetamine is identical [9, 15]. The antiemetic metoclopramide and the sedative sultopride have virtually no antipsychotic action [11, 15], but nevertheless they inhibit all forms of apomorphine and amphetamine stereotypy much more effectively than sulpiride [9, 15].

In view of these facts it is essential to discover more selective screening methods for neuroleptics and to make a more penetrating study of the mechanism of their antipsychotic effect. One approach to the solution of this problem is to study the effect of neuroleptics on memory processes, on the mechanisms of positive and negative reinforcement, and also on other complex psychological phenomena [13].

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TABLE 1. Effect of Psychotropic Drugs on Stereotyped Hyperactivity and Ability to Escape from an Acute Stress Situation by Rats Receiving L-Dopa

Substance, mg/kg	Number of rats	Percent of animals able to escape	p	p_1	Number of unsuccessful attempts to escape	p	p_1
Physiological saline (control)	80	90			5,7		
L-dopa 100	40	20**	<0,01		125**	<0,01	
L-dopa 100 + neuroleptics:							
chloropromazine, 1	10	80		<0,01	3,3		<0,01
trifluoperazine, 1	10	80		<0,01	5		<0,01
haloperiodol 0.1	20	90		<0,01	4		<0,01
cis-flupenthioxol, 1	10	50*	<0,05	<0,05	0,8		<0,01
clozapine, 12.5	10	60	<0,05	<0,05	49,4	<0,05	<0,05
sulpiride, 17	25	62	<0,05	<0,01	29,3	<0,05	<0,05
tiapride, 20	32	64		<0,01	12,5		<0,01
imipramine, 12.5	10	15*	<0,01		101*	<0,01	
desipramine, 30.0	20	50	<0,05	<0,05	10,2		<0,01
amitriptyline, 10	33	35	<0,01		113,0	<0,01	
nomifensine, 30	20	20	<0,01		63,0	<0,05	<0,05
quipazine, 4	10	20	<0,01		131,0	<0,01	
citalopram, 5	10	0	<0,01		70,7	<0,05	<0,05
phenazepam, 0.5	10	10	<0,01		23,0	<0,05	<0,05
piracetam, 200	20	5	<0,01		49,4	<0,05	<0,05
metaclopramide, 2	10	0	<0,01		110,0	<0,01	
sultopride, 8	20	50	<0,05	<0,05	33,8	<0,05	<0,01
ethmozine, 1	24	30	<0,01		112,0	<0,01	
3-hydroxybenzylhydrazine, 100	10	20	<0,01		49,3	<0,05	<0,01
	10	20	<0,01		115,0	<0,01	
	10	90	<0,01		35	<0,05	<0,01

Note. p) Significance of differences compared with control, p_1) compared with L-dopa alone. Asterisks indicate significance of differences between doses of substances: $p < 0.05$.

It was shown previously that investigative activity, leading to the discovery by animals of hitherto unknown versions of adaptive behavior, is clearly revealed by the extrapolation escape test (EET), suggested by Bondarenko [2]. In this test the ability of rats to respond to diving, the only possible way of escaping from an acute stress situation, is assessed (the animal is placed inside a cylinder which is partially immersed in water). Escape behavior under these conditions is facilitated by the action of tranquilizers [3] and nootropic drugs [6], and is totally disturbed, and replaced by stereotyped hyperactivity in the form of unsuccessful attempts to escape (jumping and clambering up the walls of the cylinder) by rats receiving L-dopa [5].

The aim of this investigation was to study the effect of neuroleptics belonging to various chemical groups and to compare it with the action of antidepressants, tranquilizers, and nootropic drugs on L-dopa-induced behavioral pathology in rats in the EET.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 220-250 g. The presence of escape (by diving) and of stereotyped hyperactivity (the number of unsuccessful attempts to escape) was estimated in the EET, using the method described previously [2-5]. Unlike in the previous study [4], 24 h before the pharmacological experiments the animals were subjected once to the EET, and rats initially unable to escape were eliminated. To enhance the central effect of L-dopa, it was injected together with benserazide (Madopar-125), a peripheral aromatic amino acid decarboxylase inhibitor [4, 5]. This preparation was suspended in 0.9% NaCl with the addition of Tween-80 and injected intraperitoneally in a volume of 0.2 ml/100 g body weight 60 min before testing. Neuroleptics chloropromazine, trifluoperazine, haloperidol, clozapine (Leponex), cis-flupenthixol, sulpiride, tiapril, and also their structural analogs not possessing antipsychotic activity, namely ethozine (a phenothiazine derivative), metoclopramide, and sultopride (Barnetil), were injected in the form of a suspension, with the aid of Tween-80, intraperitoneally in a volume of 0.2 ml/100 g body weight 10 min before L-dopa. The antidepressants imipramine, desipramine, amitriptyline, nomifensine, quipazine, and citalopram, and also the tranquilizer phenazepam, the nootropic drug piracetam, and the central aromatic amino acid decarboxylase inhibitor 3-hydroxybenzylhydrazine, were injected in a similar manner. The doses used and the number of experimental animals are indicated in Table 1. The results were subjected to statistical analysis, using the Wilcoxon–Mann–Whitney nonparametric test and Fisher's exact method.

EXPERIMENTAL RESULTS

The experiments showed that preliminary exposure of rats to the EET did not change the character of disturbance of their behavior following injection of L-dopa compared with that described previously [4, 5]. 3-Hydroxybenzylhydrazine, in a dose blocking DA synthesis in brain tissue, prevented the disturbance of escape behavior in EET by rats receiving L-dopa (Table 1). This points to a connection between this form of behavioral pathology and the increased concentration of brain 5-HT formed from exogenous L-dopa.

Among the psychotropic drug with different types of action, the classical and atypical neuroleptics, but not the various antidepressants or the tranquilizer phenazepam, had the strongest effect on escape behavior. Chloropromazine, trifluoperazine, and haloperidol restored escaping ability in 80-90% of the experimental animals, sulpiride, clozapine, and cis-flupenthixol did so in 60%, and tiapride in 50% of the animals (Table 1). This is in agreement on the whole with clinical data on the antipsychotic efficacy of each of the neuroleptics studied [1, 7]. The minimal effective doses of the neuroleptics did not exceed those for antagonism with stereotyped climbing on a net, induced by apomorphine (the most sensitive screening test for neuroleptics) [15]. Since in these doses their selective DA-blocking action was manifested, it can be postulated that it is this action which is essential for weakening the DA-dependent disturbance of escaping behavior in rats treated with L-dopa. Metoclopramide and sultopride, which also possess anti-DA-properties [9, 15], nevertheless did not prevent behavioral pathology in rats receiving L-dopa. This indicates the existence of additional factors essential for the mechanism of neuroleptic activity.

Neurochemical studies showed that low doses of sulpiride and haloperidol affect mainly DA-ergic neurons in zone A-10, but high doses – in zone A-9 [8]. Accordingly we studied the effect of high doses of sulpiride and haloperidol (50 and 1 mg/kg, respectively) on the behavior or rats receiving L-dopa. The data in Table 1 indicate reduction of the efficacy of these substances in high doses compared with lower doses. Thus the leading role in the mechanism of neuroleptic correction of escape behavior, disturbed by L-dopa, is evidently played by the DA-blocking action relative to the mesolimbic and mesocortical DA system. This hypothesis is confirmed by the absence of any positive effect on escape behavior of the selective nigrostriatal DA antagonist metaclopramide, and the presence of such activity in piracetam, which stimulates DA metabolism in the cortex (Table 1) [14].

Restoration of the ability of rats to carry escape behavior following administration of 3-hydroxybenzylhydrazine and neuroleptics was accompanied by weakening of stereotyped hyperactivity (Table 1). However, desipramine, nomifensine, sultopride, quipazine, and citalopram weakened stereotyped hyperactivity, but without thereby restoring the escape behavior of rats receiving L-dopa. Consequently, the selectivity of action of neuroleptics relative to stereotyped hyperactivity is considerably lower than pathology of investigative activity. Since potentiation of DA-mediation of A-10 neurons [12] is an important element of the mechanism of stereotyped hyperactivity, the pharmacological data obtained point to both similarities and differences with the presumed mechanism of disturbance of escaping behavior. Their common element is evidently the potentiation of mesolimbic DA-mediation under the influence of L-dopa.

By the use of EET we thus discovered a pharmacologically specific form of DA-dependent behavioral pathology in rats (disturbance of escaping ability), which can be selectively corrected by neuroleptics of varied chemical structure, including benzamide derivatives. This pathology was found to be highly sensitive to neuroleptics, and their activity as a whole was shown to correspond to their clinical efficacy.

LITERATURE CITED

1. G. Ya. Avrutskii, Modern Psychotropic Drugs and Their Use in the Treatment of Schizophrenia [in Russian], Moscow (1964).
2. N. A. Bondarenko, Abstract Lodged with the All-Union Institute of Scientific and Technical Information, No. 2038 (1980).
3. N. A. Bondarenko, A. V. Val'dman, and V. A. Kamysheva, Byull. Éksp. Biol. Med., No. 7, 35 (1981).
4. N. A. Bondarenko, Farmakol. Toksikol., No. 4, 31 (1985).
5. N. A. Bondarenko, I. I. Miroshnichenko, and V. S. Kudrin, Byull. Eksp. Biol. Med., No. 8, 168 (1988).
6. N. M. Savchenko, R. U. Ostrovskaya, and Yu. V. Burov, Byull. Éksp. Biol. Med., No. 8, 170 (1988).

7. G. Alfredsson, C. Härnryd, and E.-A. Wiesel, Psychopharmacology, 84, 237 (1984).
8. M. J. Bannon, A. S. Freedman, L. A. Chiodo, et al., New Direction in Behavioral Pharmacology, L. L. Iversen et al. (eds.), New York (1987), pp. 123-183.
9. R. Dall Olio, A. Vaccheri, O. Gandolfi, and N. Montanaro, Psychopharmacology, 90, 18 (1986).
10. M. Dufrague and Y. Collard, Lille Med., Suppl. 1, 92 (1979).
11. M. Dugas and M. F. Le Henzly, Neuropsychiat. Enf. Adolesc., 32, Nos. 10-11, 557 (1984).
12. O. Magnusson, C. J. Fowler, C. Köhler, and S.-O. Ogren, Neuropharmacology, 25, No. 2, 187 (1986).
13. R. Miller, Psychopharmacology, 92, 405 (1987).
14. L. K. Rago, Arch. Pharmacol., 318, 36 (1981).
15. P. Worms, The Benzamides: Pharmacology, Neurobiology, and Clinical Aspects, J. Rotrogen and M. Stanley (eds.), New York (1982), pp. 7-16.