Antineurotic Effect of the Hydrazide of O-β-Chlorethyl-para-N-Dimethylaminophenyl-Phosphinylacetic Acid (Amphasid)

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An novel organophosphorus compound, the hydrazide of O-β-chlorethyl-para-N-dimethylaminophenyl-phosphinylacetic acid (amphasid), was found to be an antineurotic agent. Amphasid restored exploratory activity in rats according to the open field test in experimental neurosis, raised the brain level of RNA and DNA lowered by stress, and reduced the concentration of malonic dialdehyde in the brain cortex of neurotized rats.

Key Words: *amphasid; antineurotic effect; brain biochemistry*

The increasing incidence of neurotic disorders which are among the most universal and least specific syndromes in relation to other mental diseases [2] calls for the creation of drugs which will act on different pathogenetic components of the neurosislike states. For clinical use it is important to have a preparation which combines tranquilizing and antidepressive properties [2].

Combination of these two features is reported in hydrazines of phosphorylated carbonic acids, among them in the derivative of their phosphabenzide [1,3,4]. This may be due both to the presence of a phosphorus atom in the molecule [16] and to the existence of a hydrazide group which imparts psychotropic activity to the compounds [5]. This warrants further elaboration of psychotropic drugs based on the above family of organophosphorus compounds. Amphasid, the hydrazide of O-β-chlorethyl-para-N-dimethylaminophenyl-phosphinylacetic acid, is a new representative of hydrazides of phosphorylated carbonic acids.

The aim of the present investigation was to study the antineurotic effect of amphasid.

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MATERIALS AND METHODS

The antineurotic activity of amphasid in a dose of 100 mg/kg and of the preparations of comparison seduxen (1.5 and 5 mg/kg) and melipramine (10 mg/kg) was assessed on 100 male Wistar rats using a model of chronic neurotization [9]. The behavioral reaction in the open field test was studied. The preparations were administered in the following two regimes: in a protective regime, daily for 15 days immediately after each stressing procedure, and in a "treatment" regime, during 7 days after completion of the 15-day neurotization. Testing in both regimes was performed 24 h after the last administration of preparations, after which the rats were decapitated. The relative adrenal mass was determined. Accumulation of lipid peroxidation products in the brain cortex was estimated according to the reaction with 2-thiobarbituric acid [7] and the level of nucleic acids (RNA and DNA) was measured as described elsewhere [8].

The results were treated statistically using Student's *t* test.

RESULTS

Stable changes of the behavioral reaction in the open field test (Table 1) were noted in the form of

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TABLE 1. Effect of Amphasid, Seduxen, and Melipramine Administered in a "Protective" Regime on the Indexes of Rat Behavior in the Open Field Test 24 h after Completion of the Neurotization Cycle (*M±m*)

Index of behavior during 3 min	Group of animals					
	control 1 (intact)	control 2 (neurotized)	neurotization+ amphasid	neurotization+seduxen, 1.5 mg/kg	neurotization+seduxen, 5 mg/kg	neurotization+melipramine
Horizontal activity (number of lines crossed)	13.4±1.5	6.3±1.6*	7.1±0.8	6.6±1.5	13.0±2.3**	4.1±0.9
Vertical activity (number of rearings)	10.3±0.9	4.4±1.1*	5.1±0.9	6.4±1.4	8.7±1.5**	2.9±1.0
Number of holes explored	5.9±0.8	1.5±0.6*	1.9±0.5	2.1±0.4	6.6±1.1**	1.5±0.5
Number of defecations	1.4±0.7	3.9±0.7*	2.2±0.9	2.4±0.8	2.0±0.4**	5.1±1.2
Increase in weight, g	+10.0	-11.8*	-2.5**	-5.7	-3.5**	-12.5
Relative mass of adrenals	0.18±0.01	0.22±0.01*	0.18±0.01**	0.18±0.01**	0.17±0.01**	0.16±0.01**
Malonic dialdehyde content, μmol/kg	28.7±2.7	67.1±13.6*	27.2±2.4**	29.0±2.9**	26.4±2.1**	44.1±3.1

Note. Here and in Table 2: $p<0.05$: *compared to control 1; **compared to control 2.

TABLE 2. Content of Malonic Dialdehyde and Nucleic Acids in the Brain Cortex in the Neurotized Rats after "Treatment" with Amphasid, Seduxen, and Melipramine (*M±m*)

Index	Group of animals				
	control 1 (intact)	control 2 (neurotized)	neurotization+ amphasid	neurotization+seduxen, 1.5 mg/kg	neurotization+melipramine
Malonic dialdehyde content, μmol/kg	31.8±1.7	45.5±4.7*	31.6±1.3**	32.7±1.9**	40.9±4.3
DNA content, mg%	6.1±0.6	4.6±0.1*	7.6±0.7**	6.3±0.8**	5.0±0.9
RNA content, mg%	16.0±1.0	10.0±1.0*	14.2±0.3**	15.7±0.9**	11.6±1.2

inhibition of exploratory motivation in the control group after the 15-day neurotization. Body weight loss, hypertrophy of the adrenal glands, an increase of the malonic dialdehyde level in the brain cortex, and a decrease of the RNA and DNA content were found in this group.

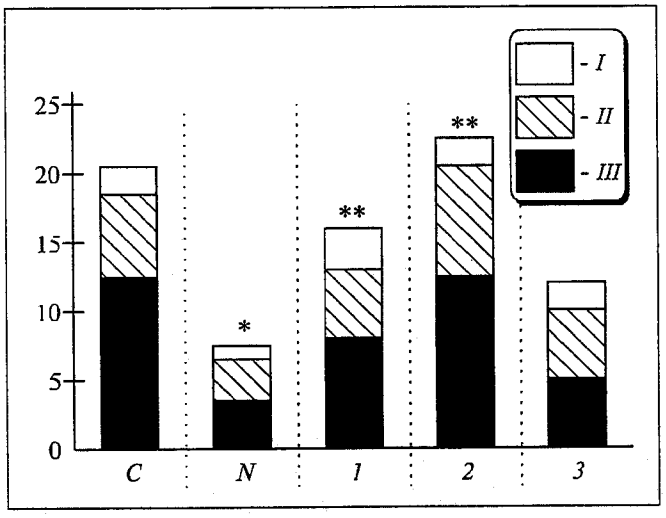

Fig. 1. Total indexes of exploratory activity of neurotized rats in the open field test after 7-day "treatment" with amphasid, seduxen, and melipramine. *C*: control 1 (intact); *N*: control 2 (neurotized); *1*) neurotization + amphasid; *2*) neurotization + seduxen (1.5 mg/kg); *3*) neurotization + melipramine. *I*) number of holes explored; *II*) number of rearings; *III*) number of lines crossed; $p<0.05$: *compared to control 1, **compared to control 2.

Amphasid and seduxen at 1.5 mg/kg administered in the protective regime did not influence the behavioral reactions in the open field test (Table 1) but somewhat lowered the other indexes of neurosis as follows: the animals lost less weight, the relative mass of the adrenal glands did not differ from that in the intact animals, and the malonic dialdehyde level was 55% below the control.

Seduxen in a dose of 5 mg/kg prevented the development of neurosis but caused a number of undesirable effects, such as muscle weakness, ataxia, and, after 2 weeks of administration, the appearance of aggressiveness and excitation.

Melipramine in the dose studied was ineffective against experimental neurosis.

Administration of distilled water to control rats in the "treatment" regime during one week did not induce a spontaneous restoration of the alterations induced by neurosis.

The administration of only amphasid or seduxen (1.5 mg/kg) to the neurotized rats for 7 days increased horizontal, vertical, and exploratory activity (Fig. 1). Both preparations lowered the elevated

level of malonic dialdehyde and restored the RNA and DNA content in the brain cortex (Table 2).

Thus, amphasid in both the protective and "therapeutic" regimes of use showed an antineurotic effect comparable to the effect of seduxen in a dose of 1.5 mg/kg (the maximal dose causing no side-effects), restoring motor-exploratory activity and normalizing the somatic and metabolic shifts.

REFERENCES

1. N. A. Blyukherova, in: *Pharmacology and Toxicology of Organophosphorus Compounds and Other Biologically Active Substances. Transactions of Kazan Medical Institute* [in Russian], Kazan (1974), pp. 118-122.
2. A. V. Val'dman and Yu. A. Aleksandrovskii, *Psychopharmacotherapy of Neurotic Disorders* [in Russian], Moscow (1987).
3. A. V. Val'dman, M. M. Kozlovskaya, I. V. Zaikonnikova, *et al., Byull. Eksp. Biol. Med.*, **89**, No. 3, 310-312 (1980).
4. I. V. Zaikonnikova, A. V. Val'dman, M. M. Kozlovskaya, and G. F. Rzhevskaya, *Farmakol. Toksicol.*, No. 3, 334-338 (1980).
5. V. E. Kolla and I. S. Berdinskii, *Pharmacology and Chemistry of Hydrazine Derivatives* [in Russian], Ioshkar-Ola (1976).
6. D. E. C. Corbridge, *Phosphorus. Bases for Chemistry, Biochemistry, and Technology*, Amsterdam (1980).
7. I. D. Stal'naya and T. G. Garshvili, *Modern Methods in Biochemistry* [in Russian], Moscow (1977).
8. R. R. Tsanev and G. O. Markov, *Biochemistry*, **25**, 151-159 (1960).
9. K. Hecht, A. Mechedova, K. Treptov, and T. Hecht, *Acta Biol. Med. Germ.*, No. 8, 867-879 (1976).