ar-treated group MDA was decreased by 22.3% ($p< 0.01$), which attests to probable antioxidant properties of the drug.

Thus, in our experiments mebicar exhibited a beneficial combination of adaptogenic, hypolipidemic, and, probably, antioxidant effects.

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Antidepressive Effect of O-β-Chloroethyl-para-N-Dimethylphosphinylacetic Acid (Amphazide)

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The antidepressive effects of O-β-chloroethyl-para-N-dimethylphosphinylacetic acid (amphazide) are demonstrated on CBWA tetrahybrid male mice using the "behavioral despair" and "conditioned helplessness" models. The pharmacological effect of a course of amphazide appears more rapidly than that of the tricyclic antidepressant melipramine. The serotonin-positive activity of amphazide manifests itself, in particular, in a heightened reaction of stressed mice to injection of 5-hydroxytryptophan.

Key Words: *organophosphorus compounds; antidepressant; serotonin-positive action*

The creation of new, highly effective antidepressants without marked side effects calls for exploiting original chemical classes. Of particular interest in this connection are the organophosphorus compounds without intrinsic anticholinesterase activity, among which neurotropic drugs [2], including antidepressants [1], are found.

The present study evaluates the antidepressant properties of O-β-chloroethyl-para-N-dimethylphosphinylacetate hydrazide (amphazide).

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MATERIALS AND METHODS

The experiments were carried out on inbred male mice, CBWA tetrahybrids, weighing 19-22 g. Antidepressant activity was assessed using the "behavioral despair" [5,9] and "conditioned helplessness" [8] models.

In the "behavioral despair" model, amphazide (90 mg/kg) was injected intraperitoneally 40 min before testing and then once a day during 10 days, and 24 hours after the last injection the animals were tested again.

In the model of "conditioned helplessness" the total time of escape delay and the total number of

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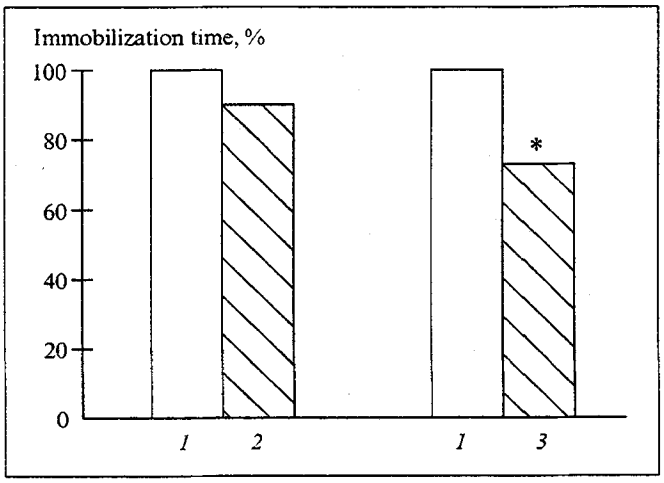

Fig. 1. Effect of amphazide on the duration of immobilization in mice in the "behavioral despair" test. *1*) control; *2*) amphazide (90 mg/kg) singly; *3*) amphazide (90 mg/kg) for 10 days; *$p<0.05$.

nonexecuted reactions were determined for subchronic daily intraperitoneal administration of amphazide (90 mg/kg), or the reference drugs melipramine (7 mg/kg) and pyrazidole (10 mg/kg). Control animals exposed (control 2) or not exposed (control 1) to unavoidable aversive stimulation were injected with twice-distilled water in the same volumes. To elucidate the role of serotoninergic processes in the mechanism of action of these drugs, on day 12 of treatment in this model all animals were intraperitoneally injected 5-hydroxytryptophan (5-HTP, 300 mg/kg) and after 20 min the number of "nods" was counted during 5 min [6].

The data were processed statistically [3].

RESULTS

A single injection of amphazide had no effect on the parameters of "behavioral despair", while a course of 10 injections shortened the duration of standstill periods (Fig. 1). This phenomenon as a manifestation of an antidepressive effect is consistent with the view that antidepressive activity can best be established with chronic (not single) administration of the agents [4]. Moreover, for one-time administration of antidepressants this test is especially sensitive to the norepinephrinergic component of their action, while the agents activating predominantly the serotoninergic system do not reduce the duration of immobilization.

Evaluation of the relative rate of development of the effects of amphazide and the reference drugs in the model of "conditioned helplessness" revealed some differences between these agents (Table 1). The animals preliminarily exposed to unavoidable stress demonstrated a reliable escape deficit in the next (after 24 hours) testing in a shuttle box, a deficit which persisted in subsequent testings on days 6 and 12.

When injected one time, none of the drugs shortened the escape latency, and only amphazide increased the number of accomplished escape reactions to the level observed in control 1.

The 6-day treatment with amphazide reliably improved all behavioral parameters, which did not differ from those in control 1, whereas pyrazidole reduced only the escape latency, and melipramine was ineffective. On day 12 of the experiment all behavioral parameters returned to normal not only in the amphazide-treated group, but also in the groups treated with the reference drugs. Thus, amphazide has the shortest latency of antidepressive action among the studied drugs.

An injection of 5-HTP markedly reduced the number of nods in stressed animals (control 2) in comparison with intact mice (control 1). This is in conformity with data on the pathogenetic role of the serotoninergic system in the development of behavioral disturbances in this model. Amphazide, pyrazidole, and melipramine not only restored the state of the serotoninergic system to the initial level, but

TABLE 1. Effect of Amphazide, Melipramine, and Pyrazidole on Escape Parameters in Mice Subjected to Preliminary Unavoidable Stress in the "Conditioned Helplessness" Model (*M±m*)

Group	Dose, mg/kg	Single administration		6-day administration		12-day administration	
		escape deficit, %	mean escape latency, sec	escape deficit, %	mean escape latency, sec	escape deficit, %	mean escape latency, sec
Control 1	-	17	10.1±1.3	16	9.5±0.9	17	8.8±1.0
Control 2	-	63*	16.1±1.6*	54*	15.4±1.7*	56*	15.2±1.5*
Amphazide	90	19**	12.1±1.5	2**	9.0±0.7**	1**	7.9±0.7**
Melipramine	7	43	13.5±1.8	29	11.8±1.5	11**	9.2±1.1**
Pyrazidole	10	39	13.6±1.1	18	10.0±1.4**	14**	8.0±0.6**

Note. $p<0.05$: *in comparison with control 1 (nonstressed animals), **in comparison with control 2 (stressed animals).

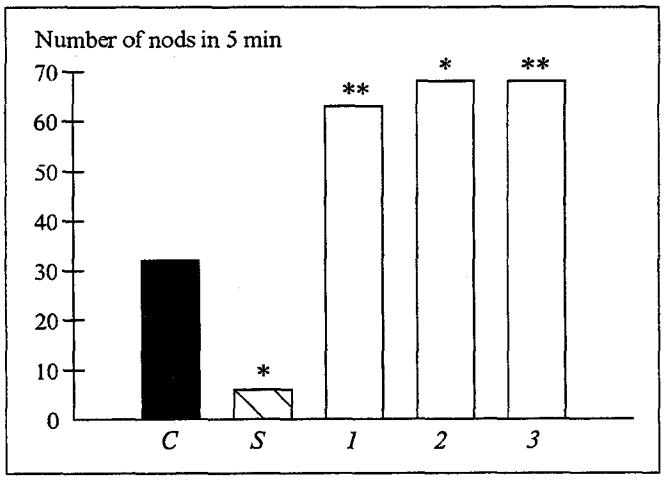

Fig. 2. Effect of amphazide, melipramine, and pyrazidole on the effects of 5-hydroxytryptophan (5-HTP) in mice exposed to unavoidable stress stimulation in a model of "conditioned helplessness". *C*: control; *S*: stressed mice+5-HTP; *1*) stressed mice+amphazide+5-HTP; *2*) stressed mice+melipramine+5-HTP; *3*) stressed mice+pyrazidole+5-HTP; $p<0.05$: *in comparison with the control; **in comparison with stressed mice.

even increased the number of nods in comparison with the nonstressed animals (Fig. 2).

Thus, amphazide exhibits an antidepressive activity comparable with the effects of the standard antidepressants melipramine and pyrazidole. An advantage of this drug is a more rapid development of the antidepressive effect. The serotonin-positive component is demonstrated to play a role in the realization of this effect.

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