the muscle in time Δt, Δv_S is the rate of shortening induced by it under these circumstances, a denotes acceleration, and m is a measure of inertia of the muscle + loading factor system. Analysis of the force–velocity relationship shows that momentary values of the rate of shortening V_S and the rate of development of tension V_T correlate closely with each other, i.e., with a certain approximation, $\Delta V_S = k\Delta V_T$, where k = const, and considering that $\Delta V_T = P/\Delta t$ and $a = k\Delta V_T/\Delta t^2$. But since k = const, the value of $P/\Delta t^2$ is perfectly suitable for use as the criterion of myocardial contractility, equally with acceleration of shortening a.

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EFFECT OF A 3-HYDROXYPYRIDINE DERIVATIVE MEMBRANE MODULATOR ON PHARMACOLOGICAL ACTIVITY OF SOME PSYCHOTROPIC DRUGS

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An intensive search for physiologically active compounds among the group of 3-hydroxypyridine derivatives is currently being undertaken and the mechanism of their action is being studied [12]. 3-Hydroxypyridine derivatives have been shown to be a promising class of neurotropic compounds with an original spectrum of pharmacological activity and mechanism of action that differs from those of other known preparations [5, 7, 11]. Antistressor, antiisochemic, antiarrhythmic, and anticonvulsant types of action have been found among 3-hydroxypyridine derivatives [8, 10]. Some workers [1, 10] associate the pharmacological activity of 3-hydroxypyridine derivatives with their ability to inhibit lipid peroxidation in biological membranes. Slowing oxidative reactions in membrane lipids by 3-hydroxypyridine derivatives has been shown to lead to changes in the composition and properties of the lipids [3]. This, in turn, is reflected in the structure of the membrane and its sensitivity to the action of xenobiotics and noxious factors, and it is also accompanied by changes in membrane function.

There is evidence in the literature that changes in phospholipid composition cause changes in activity of membrane-bound enxymes and, in particular, of adenylate cyclase and phosphodiesterase [2]. For example, administration of phospholipid liposomes, causing modification of the phospholipid composition of plasma membranes, modifies the conformation of adenylate cyclase, recognition and binding of hormones, and affinity of the enzyme for ATP [13]. These changes lead to an increase in activity of adenylate cyclase and its sensitivity to hormones. These results suggested that preliminary modification of the phospholipid composition of membranes by synthetic antioxidants of the 3-hydroxypyridine class could have a significant effect on the pharmacological activity of the psychotropic drugs.

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TABLE 1. Effect of Tranquilizers and Their Combinations with P-3-HP on Parameters of Rats' Behavior in Conflict Situation (M±m)

Experimental conditions	Dose, mg/kg	Number of times of taking water	Approaches to feeding bowl	Motor activity
Control	—	2,0±0,7	13,8±3,3	18,6±4,4
P-3-HP	25	3,2±1,2	13,0±2,2	15,0±2,6
Diazepam	0,5	6,4±1,5	10,1±3,0	19,6±4,1
P-3-HP + diazepam	25±0,5	12±1,3	11,6±2,6	22,7±4,1
Diazepam	2	14,2±4,2	7,8±5,0	11,2±7,4
Phenazepam	0,1	5,3±1,8	15,4±4,1	22,3±7,0
P-3-HP + phenazepam	25±0,1	16,1±6,7	17,6±4,8	24,0±3,7
Phenazepam	1,2	15,4±3,2	4,2±1,1	7,1±2,2
Calcium valproate	100	5,1±1,8	12,4±2,6	13,6±2,6
P-3-HP + calcium valproate	25±100	11,9±3,0	15,4±4,4	17,3±3,3
Calcium valproate	300	14,8±4,2	5,1±3,2	6,9±3,1

Legend. Recording time 20 min. Combinations of substances injected in accordance with first scheme.

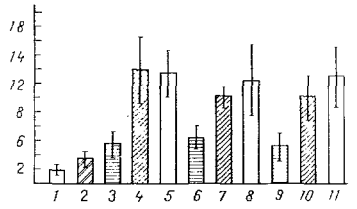

Fig. 1

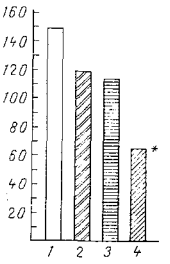

Fig. 2

Fig. 1. Potentiation of anxiolytic action of tranquilizers in a conflict situation by P-3-HP. Ordinate, number of times rats took water in conflict situation. 1) Control; 2) P-3-HP (25 mg/kg); 3) phenazepam (0.1 mg/kg); 4) P-3-HP (100 mg/kg+ 100 mg/kg+ 25 mg/kg) + phenazepam (0.1 mg/kg); 5) phenazepam (1.2 mg/kg); 6) diazepam (0.5 mg/kg); 7) P-3-HP (100 mg/kg+ 100 mg/kg+ 25 mg/kg) + diazepam (0.5 mg/kg); 8) diazepam (2 mg/kg); 9) calcium valproate (100 mg/kg); 10) P-3-HP (100 mg/kg+ 100 mg/kg+ 25 mg/kg) + calcium valproate (100 mg/kg); 11) calcium valproate (300 mg/kg). Substances injected in accordance with first scheme.

Fig. 2. Potentiation of sedative action of trifluoperazine by P-3-HP during recording of motor activity of mice in an Animex. Ordinate, mean number of movements by mouse in 10 min; 1) control; 2) P-3-HP (100 mg/kg); 3) trifluoperazine (0.5 mg/kg); 4) P-3-HP (100 mg/kg+ 100 mg/kg+ 25 mg/kg)+ trifluoperazine (0.5 mg/kg). Substances injected in accordance with first scheme. *P = 0.05.

The writers showed previously [11] that some 3-hydroxypyridine derivatives have a marked ability to potentiate the hypnotic action of barbiturates, and this is evidence in support of the above hypothesis. Data showing enhancement of the tremor-inducing action of arecoline under the influence of a membranotropic antioxidant of the 3-hydroxypyridine class also have been published [4].

The aim of the present investigation was an extensive study of the potentiating properties of 3-hydroxypyridine derivatives in relation to the psychotropic activity of drugs of different chemical structure and type of action: neuroleptics (chlorpromazine, trifluoperazine, reserpine), tranquilizers (diazepam, phenazepam,* calcium valproate), and a hypnotic (hexobarbital).

*7-Bromo-1,3-dihydro-5-(2'-chlorophenyl)-2H-1,4-benzodiazepin-2-one.

TABLE 2. Effect of Psychotropic Drugs and Their Combinations with P-3-HP on Motor Activity of Mice in Animex

Experimental conditions	Dose, mg/ kg	Parameters of motor activity			
		first 5 min	second 5 min	10 min	mean for one animal
Control	—	230	257	487	81,2
P-3-HP	10	306	305	611	101,8
P-3-HP	25	360	326	686	114,3
Control	—	332	261	593	98,7
Phenazepam	0,3	102	320	334	55,6
P-3-HP + phenazepam	10±0,3	223	7	230	38,3*
Control	—	362	345	707	117,8
Chlorpromazine	0,5	161	190	351	58,5
P-3-HP + chlorpromazine	10+0,5	162	129	291	48,5
P-3-HP + chlorpromazine	25+0,5	81	124	205	34,2 *
Control	—	331	296	627	104,5
Reserpine	1,0	105	63	168	28,7
P-3-HP + reserpine	10+0,1	28	14	42	7,0*

Legend. Substances administered in accordance with second scheme. *P = 0.05.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino mice (weight 18–24 g) and rats (weight 180–250 g). To assess the tranquilizing effect, the method of a conflict situation created in rats by collision between pain and food reflexes [6] was used. The general depressant action of the drugs was tested in mice by recording motor activity in an actograph (Ugo Basile, Italy). Motor activity was recorded for 10 min (two periods each of 5 min). The hypnotic effect was judged by the ability of the drugs to cause the mice to fall into the side position, and the latent period of sleeping and awakening was recorded [6]. Each dose of the substance was tested on 8–12 animals.

The test substances were injected intraperitoneally, allowing for their peak of action: hexobarbital 5 min, phenazepam and diazepam 40 min, calcium valproate 1 h, and chlorpromazine, trifluoperazine, and reserpine 2 h before the experiment began. An alkyl-substituted 3-hydroxypyridine (P-3-HP), injected intraperitoneally in two variants, was used as the antioxidant. The first scheme of administration was 100 mg/kg twice on the day before the experiment and a subthreshold dose of 25 mg/kg 30 min before administration of the test substances before the experiment; the second scheme was 100 mg/kg 4 h before, and subthreshold doses (10, 25, and 50 mg/kg) 40 min after administration of the test substances.

EXPERIMENTAL RESULTS

Preliminary injection of P-3-HP according to the first scheme on the day before the experiment considerably potentiates the effects of the psychotropic drugs. In the conflict situation, under the influence of P-3-HP, definite potentiation of the anxiolytic effects, both of the classical tranquilizers of the benzodiazepine series (diazepam and phenazepam) and of an atypical tranquilizer with a GABA-ergic mechanism of action (calcium valproate), was observed (Table 1, Fig. 1). For example, whereas phenazepam in a dose of 0.1 mg/kg increased the basic parameter of behavior during conflict (the number of times of taking water, despite accompanying painful stimulation) by 2.5 times, and P-3-HP alone in a dose of 25 mg/kg increased it by 1.6 times after preliminary administration of P-3-HP this parameter was increased eightfold. To obtain a similar anxiolytic effect from phenazepam alone, the dose of the tranquilizer would have to be increased to 1.2 mg/kg, i.e., by 12 times. Marked potentiation of the anxiolytic effect by preliminary administration of P-3-HP also was observed when other tranquilizers were used: diazepam and calcium valproate (Table 1, Fig. 1).

Definite potentiation of the effects of the psychotropic drugs after preliminary administration of P-3-HP also was observed when their sedative action was assessed during recording of motor activity in the Animex. A single dose of P-3-HP or trifluoperazine (0.5 mg/kg) was found to cause only a small, not statistically significant, reduction of the animals' motor activity (Fig. 2). Meanwhile administration of the neuroleptic preceded by the antioxidant reduced motor activity threefold.

In the next series of experiments, in which P-3-HP was injected on the day of the experiment, significant potentiation of the sedative action of chlorpromazine, reserpine, and phenazepam also was observed when motor activity was recorded in the Animex (Table 2).

Under the influence of P-3-HP a considerable increase was observed in the duration of barbiturate sleep. For instance, after injection of hexobarbital alone, in a dose of 50 mg/kg, mice assumed the side position, in which they remained for 18.9 ± 4.1 min, whereas, after combined administration of hexobarbital and P-3-HP, the duration of sleep was increased to 34.1 ± 7.8 min. It will be recalled that P-3-HP alone did not induce the side position, either in a dose of 50 mg/kg or in an increased dose of 300 mg/kg. Prolongation of hexobarbital sleep by preliminary injection of P-3-HP was due mainly to an increase in the awakening time of the animals and by a lesser degree to shortening of the latent period of falling asleep.

The use of psychotropic drugs preceded by P-3-HP thus led to considerable enhancement of their activity – anxiolytic, sedative, and hypnotic. Potentiation of activity after preliminary P-3-HP was observed when the psychotropic drugs and antioxidant were used in subthreshold doses, with which their specific effect could hardly be observed, and in some cases P-3-HP also enhanced manifestations quite untypical of the antioxidant, even in subtoxic doses.

The results suggest that the mechanism of interaction between these substances is not additive in type, but involves potentiation of the effects of the drugs by the antioxidant. Potentiation in this case has a broad spectrum of action, since P-3-HP potentiates different manifestations of action (anxiolytic, sedative, hypnotic) of different psychotropic drugs, belonging to different classes, as regards both chemical structure (phenothiazines, benzodiazepines, barbiturates, valproate) and mechanisms of action, and also their clinical application (neuroleptics, tranquilizers, hypnotics).

The results demonstrate the universality and nonspecificity of the potentiation mechanism, which is probably not associated with any concrete, specific level of interaction of the drug with systems of the body or with pharmacokinetic conversions of the drugs.

The mechanism of action of P-3-HP on the pharmacological effects of psychotropic agents is evidently based on its membrane-modulating effect, namely its action on the physicochemical properties and phospholipid composition of biological membranes, which may be accompanied, as was shown in [4], by a change in sensitivity and functional activity of synaptic membranes. Considering the profile and mechanisms of action of the substances tested, it can be postulated that modification of relations between drug and membrane, causing potentiation of the pharmacological effect, takes place, in particular, at the level of the GABA-benzodiazepine-barbiturate complex.

Thus, the ability of membrane-active compounds of the 3-hydroxypyridine class to potentiate effects of psychotropic drugs, revealed experimentally, opens up new prospects for deliberate modification of the spectrum of action of these therapeutic substances in clinical practice.

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