ANTIOXIDANTS L-TOCOPHEROL, EMOXYPINE, AND MEXIDOL MODIFY THE EFFECT OF ANTIDEPRESSANTS IN MICE

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Therapy in cases of resistant depression, related both to features of the main disorder and to the presence of additional somatic and/or other (nonaffective) psychic diseases in adult patients (especially of senile age), frequently require nontraditional approaches [1, 2]. Senility, as well as the development of somatic or psychosomatic pathology, can be considered as deterioration of the functions of organs and systems caused to a considerable extent by a strong pathogenic factor such as lipid peroxidation (LPO) under oxidant stress conditions [2, 3]. Taking into account that such changes in the organism may lead to the development of depressive states poorly treated by the existing methods, we believe that it would be expedient to combine the traditional antidepressant therapy with antioxidant agents in order to reduce the age-related activation of LPO processes in the brain.

In order to check the validity of this suggestion, we have experimentally studied the effect of some antioxidants on the characteristics of model depressive states and the influence of these antioxidants on the activity of well-known antideressants in these states.

EXPERIMENTAL PART

The experiments were performed on a group of male and female mice weighing 18 – 22 g. We have studied the interaction of three antioxidants (L-tocopherol, emoxypine, and mexidol) with the antidepressants pyrazidole and tetrindole in the following standard tests: avoidance of forced swim (emotional-stressor behavioral test) [4]; horizontal and vertical locomotor activity and stereotypy (open field behavioral test); reserpine (2.5 mg/kg, i.p.) antagonism (blepharopthosis test [5]); and hyperthermia induced by L-DOPA (200 mg/kg, i.p.).

L-tocopherol (5 mg/kg), emoxypine and mexidol (10 and 25 mg/kg), pyrazidole (10 and 25 mg/kg), and tetrindole (2.5 and 10 mg/kg) were introduced in mice either separately or in certain antioxidant–antidepressant combinations.

TABLE 1. Effect of Antioxidants and Their Combinations with Pyrazidole and Tetrindole on the Activity of Mice in Emotional-Stressor Test for Escape from Water

Treatment		Daily dose, mg/kg (p.o.; 5 days)	Number of water wheel rotations per mice (first 6 min after immersion)	
			$M \pm m$	P
Distilled water	$n = 20$	–	38 ± 3.3	
L-Tocopherol	$n = 20$	5	54 ± 4.0	< 0.05
Emoxypine	$n = 20$	10	44 ± 2.1	
	$n = 30$	25	49 ± 1.8	< 0.05
Mexidol	$n = 20$	10	37 ± 1.2	
	$n = 30$	25	45 ± 1.6	> 0.05
Pyrazidole	$n = 20$	10	47 ± 2.8	> 0.05
	$n = 20$	25	49 ± 1.4	< 0.05
L-Tocopherol + Pyrazidole	$n = 20$	5 10	49 ± 2.0	< 0.05
Emoxypine + Pyrazidole	$n = 20$	25 10	50 ± 2.5	< 0.05
Mexidol + Pyrazidole	$n = 20$	25 10	48 ± 1.2	< 0.05
Tetrindole	$n = 40$	2.5	43 ± 2.8	
	$n = 20$	10	57 ± 4.0	< 0.05
L-Tocopherol + Tetrindole	$n = 30$	5 2.5	58 ± 4.2	< 0.05
Emoxypine + Tetrindole	$n = 20$	25 2.5	58 ± 3.4	< 0.05
Mexidol + Tetrindole	$n = 20$	25 2.5	49 ± 2.1	< 0.05

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TABLE 2. Effect of Antioxidants and Their Combinations with Pyrazidole and Tetrindole on the Horizontal and Vertical Activity and Stereotypy of Mice in Open-Field Test

Treatment		Daily dose, mg/kg (p.o.; 5 days)	Number of movements, % of control ($M \pm m$)		
			horizontal	vertical	stereotypy
Distilled water	$n = 10$	–	100	100	100
L-Tocopherol	$n = 9$	5	80.4 ± 10.2	91.6 ± 21.4	97.8 ± 12.3
Emoxypine	$n = 10$	25	86.7 ± 11.4	92.3 ± 17.9	91.8 ± 13.6
Mexidol	$n = 9$	25	83.9 ± 14.6	87.2 ± 15.2	98, 11 ± 16.7
Pyrazidole	$n = 9$	25	101.3 ± 15.1	103.6 ± 27.1	114.7 ± 19.7
L-Tocopherol + Pyrazidole	$n = 10$	5 25	84.9 ± 16.8	69.1 ± 21.8	105.7 ± 18.8
Emoxypine + Pyrazidole	$n = 8$	25 25	89.3 ± 19.8	88.7 ± 16.8	96.5 ± 13.4
Mexidol + Pyrazidole	$n = 8$	25 25	92.4 ± 19.4	91.4 ± 17.2	101.1 ± 16.9
Tetrindole	$n = 8$	10	91.6 ± 11.2	111.2 ± 12.7	111.8 ± 15.1
L-Tocopherol + Tetrindole	$n = 11$	5 10	86.2 ± 15.3	99.0 ± 26.4	120.6 ± 14.8
Emoxypine + Tetrindole	$n = 9$	25 10	87.6 ± 14.8	93.9 ± 18.5	98.4 ± 16.4
Mexidol + Tetrindole	$n = 9$	25 10	90.4 ± 12.5	95.6 ± 13.8	106.4 ± 19.6

In the behavioral tests (forced swim, open field), the drugs were introduced over a period of five days; the tests using analyzers (reserpine, L-DOPA) were performed upon a single treatment. The tests were carried out one hour after the last (or single) drug administration. The experimental data were statistically processes using the Student method.

RESULTS AND DISCUSSION

In the forced swim test, it was established that separate treatment with antioxidants L-tocopherol (5 mg/kg) and emoxypine (25 mg/kg), as well as with antidepressants pyrazidole (25 mg/kg) and tetrindole (10 mg/kg), leads to an increase in the number of active attempts to escape from water (Table 1). Lower doses of the same drugs produced no statistically significant changes in the behavior of animals in the test groups as compared to the untreated control. Mexidol in the maximum dose (25 mg/kg) showed only a tendency to increasing the activity of test mice. In the case of joint administration with antioxidants, pyrazidole and tetrindole increased the activity of mice even in doses not producing significant effects in the case of separate administration (10 and 2.5 mg/kg, respectively).

The data presented in Table 2 show that the antioxidants and antidepressants neither separately nor jointly produced any statistically significant influence on the locomotor activ-

TABLE 3. Effect of Antioxidants and Their Combinations with Pyrazidole and Tetrindole on the Temperature Response to L-DOPA in Mice

Treatment		Dose, mg/kg (p.o.)	Rectal temperature (°C) 30 min after L-DOPA injection (200 mg/kg, i.p.; 20°C)	
			$M \pm m$	P
Distilled water	$n = 12$	–	36.4 ± 0.3	
L-Tocopherol	$n = 12$	5	37.0 ± 0.3	> 0.05
	$n = 6$	10	38.6 ± 0.46	< 0.05
Emoxypine	$n = 18$	10	38.5 ± 0.36	< 0.05
Mexidol	$n = 12$	10	38.7 ± 0.24	< 0.05
Pyrazidole	$n = 12$	5	37.2 ± 0.22	> 0.05
	$n = 12$	10	38.2 ± 0.22	< 0.05
L-Tocopherol + pyrazidole	$n = 12$	5 5	37.8 ± 0.24	< 0.05
Tetrindole	$n = 12$	2.5	37.4 ± 0.32	> 0.05
	$n = 12$	5	38.0 ± 0.34	< 0.05
L-Tocopherol + tetrindole	$n = 10$	5 2.5	37.9 ± 0.28	< 0.05

TABLE 4. Effect of Antioxidants and Their Combinations with Pyrazidole and Tetrindole on the Reserpine-Induced Blepharopthosis in Mice

Treatment		Dose, mg/kg (p.o.)	Blepharopthosis rate 4 h after reserpine injection (2.5 mg/kg, i.p.)	
			$M \pm m$	P
Distilled water	$n = 12$	–	3.8 ± 0.18	
L-Tocopherol	$n = 12$	5	3.7 ± 0.14	
Emoxypine	$n = 12$	25	3.2 ± 0.32	> 0.05
Mexidol	$n = 12$	25	3.7 ± 0.2	
Pyrazidole	$n = 12$	25	2.3 ± 0.21	< 0.05
L-Tocopherol + Pyrazidole	$n = 12$	5 25	3.2 ± 0.32	> 0.05
Emoxypine + Pyrazidole	$n = 9$	25 25	3.0 ± 0.4	> 0.05
Mexidol + Pyrazidole	$n = 12$	25 25	3.1 ± 0.36	> 0.05
Tetrindole	$n = 18$	2.5	0.6 ± 0.18a	< 0.001
L-Tocopherol + Tetrindole	$n = 12$	5 2.5	2.5 ± 0.4a′	< 0.05
Emoxypine + Tetrindole	$n = 10$	25 2.5	1.6 ± 0.22a″	< 0.01
Mexidol + Tetrindole	$n = 9$	25 2.5	2.4 ± 0.4a‴	< 0.05

Note: Differences between a and a', a'', and a''' are statistically significant for $P < 0.05$.

ity in the range of doses studied. It can be suggested that the drug-induced increase in the activity of mice observed in the emotional-stressor behavioral test is probably related to some metabolic effects increasing the functional capacity of the organism.

As can be seen from the data in Table 3, L-DOPA induced hyperthermia on the background of emoxypine and mexidol (10 mg/kg), pyrazidole (10 mg/kg), and tetrindole (5 mg/kg), while separate pretreatment with L-tocopherol and both antidepressants in lower doses showed only a tendency to the development of hyperthermia in test mice. However, pretreatment with the subthreshold dose of L-tocopherol in combination with the subthreshold doses of pyrazidole or tetrindole made the hyperthermic effect of L-DOPA reliably reproducible. The combinations of emoxypine and mexidol with pyrazidole or tetrindole were not studied, since these antioxidants could separately produce a significant increase in the L-DOPA effect.

The data in Table 4 show that antioxidants in the dose range studied did not influence the reserpine-induced blepharopthosis in mice, but decreased the antireserpine action of antidepressants.

From an analysis of the experimental results, it follows that L-tocopherol, emoxypine, and mexidol decrease the immobilization of mice in the forced swim test and enhance the L-DOPA hyperthermia. From this we infer that these antioxidants are capable of potentiating the effects mediated by the noradrenergic system.

The antioxidant-induced decrease in the antireserpine activity of antidepressants is probably related to modification of the metabolism of reserpine and/or of the neurochemical processes caused by this agent (related predominantly to the serotoninergic system).

In concluding, we believe that adding antioxidant to antidepressants in the clinical practice may increase the efficacy of treatment of resistant depressions and reduce the formation of such resistance, especially in senile age.

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