ANTIDEPRESSANT—ANTICONVULSANT INTERACTION MANIFESTED IN TESTS OF ANTICONVULSANT AND ANTIRESERPINE ACTIVITY

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The use of anticonvulsants, namely carbamazepine (Finlepsin) and sodium valproate (Convulex), in the treatment of affective disorders has recently been described [1, 4, 9].

Both these anticonvulsants possess GABA-ergic activity. It is claimed that their therapeutic effect may be connected with an activating effect on brain GABA-ergic systems [5, 7]. At the same time these substances affect monoaminergic transmission in neurons in certain parts of the brain. By increasing the concentration of serotonin and other biogenic amines, they may reduce neuronal excitability by a feedback mechanism, and thereby potentiate GABA-ergic inhibition [6].

Of the two anticonvulsants named above, carbamazepine gives the most constant antipsychotic effect.

In continuation of our previous investigation of the anticonvulsant activity of a number of antidepressants, in this investigation we studied the effect of the combined use of anticonvulsants and antidepressants on the convulsant action of thiosemicarbazide (an inhibitor of glutamate decarboxylase) and on the depressant effect (hypothermia and ptosis) of reserpine in mice.

EXPERIMENTAL METHODS

Experiments were carried out on albino mice of both sexes weighing 18-20 g. In the investigation of the anticonvulsant effect, antidepressants pyrazidol (Pirlindol) and (or) imipramine were given internally 45 min before, and the anticonvulsants carbamazepine and (or) sodium valproate 30 min before subcutaneous injection of thiosemicarbazide (20 mg/kg). The latent period of onset of convulsions and death (in min) and also the number of surviving mice were recorded.

To investigate the antireserpine (as one parameter of the antidepressant) effect, antidepressants were given internally 60 min before, and anticonvulsants 45 min before, intraperitoneal injection of reserpine (2.5 mg/kg). Effects of reserpine were assessed 4 h after its injection. Blepharoptosis was determined by the method in [8] and the rectal temperature was measured with an electrothermometer. The doses of the drugs are indicated in Tables 1 and 2.

The numerical results were subjected to statistical analysis by Student's test.

RESULTS

It will be clear from Table 1 that carbamazepine, in doses of 25, 40, and 50 mg/kg, and sodium valproate in doses of 200, 250, and 300 mg/kg appreciably lengthen the latent period of onset of convulsions and death from thiosemicarbazide in mice. Carbamazepine, in doses of 40 and 50 mg/kg, and sodium valproate in doses of 250 and 300 mg/kg protected 40-60% of the animals against death.

Imipramine and pyrazidol, in doses of 50 mg/kg, had a weak anticonvulsant action: They delayed the onset of thiosemicarbazide convulsions only a little and did not prevent death of

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TABLE 1. Effect of Anticonvulsants and Antidepressants on Convulsant Action of Thiosemicarbazide in Mice (M ± m)

Preparations	Dose, mg/kg	Number of mice	Convulsant action of thiosemicarbazide: latent period of onset of convulsions, min	% of control	latent period of onset of death, min	% of control	mice without convulsions, number	%	surviving mice, number	%
Distilled water	—	80	53,0±1,7	100	72,0±5,5	100	0/80	0	2/80	2,5
Carbamazepine	25	30	70,0±2,1*	132	120,0±7,2	167*	1/30	3	3/30	10
	40	40	114,0±11,8*	215	179,0±10,9	249[a]	5/40	13	18/40	45[c]
	50	30	119,0±8,6*	224	252,0±11,3	350[b]	4/30	13	18/30	60[d]
Sodium valproate	200	20	78,0±3,4*	147	113,0±9,8	157*	0/20	0	2/20	10
	250	30	89,0±5,4*	168	132,0±8,1	183*	4/30	13	12/30	40
	300	50	109,0±10,0*	205	170,0±2,7	236*	10/60	17	26/60	43
Pyrazidol	50	60	74,0±1,8*	127	94,0±5,2	129**	—	—	5/60	8
Pyrazidol + carbamazepine	25 + 25	10	70,0±4,3	132	135,0±11,9	188*	0/10	0	2/10	20
	40	30	125,0±8,6	236	207,0±7,2	288[a1]	4/30	13	20/30	67
	50	30	139,0±10,8	250	284,0±10,4	394 [b1]	4/30	13	19/30	63
Imipramine	50	30	66,0±2,0**	113	69,0±3,4	95	—	—	4/30	14,6
Imipramine + carbamazepine	25 + 25	20	126,0±10,4	238	227,0±12,3	315[a2]	4/20	20	17/20	85 [c1]
	50	30	121,0±5,9	228	265,0±9,5	368	6/30	20	27/30	90 [d1]
Pyrazidol + sodium valproate	25 + 200	10	78,0±6,5	147	109,0±7,6	151	0/10	0	1/10	10
	250	10	85,0±9,2	160	149,0±17,3	203	1/10	10	3/10	30
	300	30	85,0±6,4	160	156,0±15,8	216	2/30	6	8/30	27
Imipramine + sodium valproate	25 + 250	10	112,0±13,6	211	125,0±7,5	174	1/10	10	3/10	30
	300	40	100,0±9,0	187	153,0±13,1	213	6/40	15	21/40	53

Note. Differences between a, a_1, and a_2, b and b_1, c and c_1, and d and d_1 significant at the $P < 0.05$ level. *$P < 0.001$, **$P < 0.01$. Dose of first drug shown in parentheses (in mg/kg body weight).

the animals. In a smaller dose (25 mg/kg) these drugs did not affect the action of thiosemicarbazide. In this same dose, however, the antidepressants potentiated the anticonvulsant effect of carbamazepine. Pyrazidol significantly lengthened the latent period of onset of death of the animals whereas imipramine increased the number of surviving animals compared with results obtained by the use of carbamazepine alone. The antidepressants had virtually no effect on the anticonvulsant effect of valproate.

Table 2 gives data on the antireserpine activity of the antidepressants, anticonvulsants, and combinations of the two. The antidepressants pyrazidol and imipramine, in a dose of 10 mg/kg (internally), reduced hypothermia and ptosis induced by reserpine. Carbamazepine, in a dose of 50 mg/kg, also reduced blepharoptosis due to reserpine. In a dose of 25 mg/kg, carbamazepine did not affect the action of reserpine. Valproate, in doses of 200-300 mg/kg, appreciably enhanced reserpine-induced hypothermia.

Combined administration of carbamazepine with pyrazidol or with imipramine significantly increased antagonism between the antidepressants in relation to reserpine-induced blepharoptosis. Valproate did not potentiate the antireserpine activity of the antidepressants.

Combined administration of the anticonvulsant carbamazepine and the antidepressants pyrazidol and imipramine thus revealed synergism in their action against both anticonvulsant and antireserpine activity. The combined use of antidepressants and valproate had no such effect but, on the contrary, valproate potentiated the hypothermic action of reserpine.

The mechanism of action of anticonvulsants is not completely clear. It has been suggested that it may differ for different drugs. The anticonvulsant effect of carbamazepine, a structural analog of the tricyclic antidepressant opipramol, is linked with selective depression of neuronal activity in certain areas of the cerebral cortex, with consequent improvement of inhibition [7]. The effect of carbamazepine may be mediated through monoaminergic transmission by its effect on GABA-ergic structures. This explains to some extent the synergism in the action of carbamazepine and the antidepressants, which have a marked effect on monoaminergic mediation. The mechanism of the action of valproate is explained by its

TABLE 2. Effect of Anticonvulsants and Antidepressants on Action of Reserpine in Mice (M ± m)

Preparations	Dose, mg/kg	Number of mice	Effect of reserpine 4 h after intraperitoneal injection (2.5 mg/kg)				
			hydrothermia, °C	Δt	P	blepharoptosis	P
Distilled water	—	36	30,2±0,3	—	—	3,8±0,1	—
Sodium valproate	10	36	32,4±0,4	2,2	<0,001	2,8±0,2[a]	<0,001
Imipramine	10	24	33,0±0,4	2,8	<0,001	2,8±0,2[a1]	<0,001
Carbamazepine	50	30	29,7±0,3	—0,5	>0,05	2,9±0,1	<0,001
Sodium valproate	200	30	28,7±0,4	—1,5	<0,01	3,3±0,1	>0,05
Pyrazidol + carbamazepine	10+50	36	32,6±0,3	2,4	<0,001	2,1±0,2 b	<0,001
Imipramine + carbamazepine	10+50	24	33,4±0,3	3,2	<0,001	1,9±0,2 b_1	<0,001
Pyrazidol + sodium valproate	10+200	36	32,4±0,3	2,2	<0,001	2,3±0,2	<0,001
Imipramine + sodium valproate	10+200	12	31,6±0,8	1,4	>0,05	2,4±0,4	<0,001

Note. Differences between a and b and a_1 and b_1 significant at the $P < 0.01$ level.

GABA-ergic action. Under the influence of valproate, a marked increase in the GABA concentration is observed in certain discrete regions of the brain [3, 7]. This effect is evidently insensitive to the action of antidepressants, at least in acute experiments.

This investigation may provide experimental evidence in support of the efficacy of carbamazepine (Finlepsin) in the treatment of affective states.

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CHANGES IN PRESYNAPTIC RELEASE, BUT NOT REUPTAKE, OF BIOAMINES INDUCED BY LONG-TERM ANTIDEPRESSANT TREATMENT

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The basis of the thymoleptic effect of the tricyclic and many other antidepressants is evidently elevation of the synaptic concentration of noradrenalin (NA) and serotonin (5-HT). This effect is realized both by inhibition of reuptake [5] and intensification of presynaptic release [3] of these monoamines. These changes in function of noradrenergic and serotoninergic synapses are observed after a single dose of antidepressant, but their clinical effect develops only during a course of administration [1]. The retarded development of the therapeutic effect is attributed [2] to adaptive changes in the receptor profile and sensitivity of the nerve cell to monoamines, arising during a course of antidepressant therapy. However,

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