PHARMACOLOGY

THE ANTICALCIUM ACTION OF SOME ANTIDEPRESSANTS

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Ability to reduce the entry of Ca^{2+} into the cell and thereby to inhibit excitation processes in it is a property of several substances of different chemical structure [1, 6]. To a certain degree it has also been observed in some tricyclic antidepressants [4]. The same phenomenon is partly reflected in the presence of some degree of antiarrhythmic activity in antidepressants, but the opinion has also been expressed that the antidepressive action itself is linked with an effect on calcium channels. Another important point is that the antidepressive effect is characteristic to some degree also of typical calcium antagonists, especially verapamil [8, 9].

It was interesting to study the presence of anticalcium activity in Russian antidepressants tetrindole, pyrazidol (pirlindole), inkazan, azaphene, and the imported preparation moclobemide, which are reversible type A MAO inhibitors, and also imipramine, an inhibitor of neurotransmitter reuptake, and to compare it with the action of verapamil.

EXPERIMENTAL METHOD

In experiments on male and female albino mice weighing 20-25 g the effect of the antidepressants was studied on mortality of the animals after intravenous injection of $CaCl_2$ into them in a dose of 330 mg/kg (LD_{85}), in the form of a 3% aqueous solution. The duration of the injection was 2-3 sec. The antidepressants for study and verapamil were administered internally in doses of 5, 10, 25, and 50 mg/kg 60 min before injection of $CaCl_2$.

In experiments on male albino rats weighing 200-230 g, anesthetized with urethane (1 g/kg, intraperitoneally) the effect of the antidepressants on arrhythmia induced by $CaCl_2$ was studied. The antidepressants chosen for study, with the exception of tetrindole, were injected intravenously as an aqueous solution 5 min before, and tetrindole in the form of an aqueous suspension was given internally 1 h before injection of $CaCl_2$ (300 mg/kg, in the form of a 10% aqueous solution, intravenously). The electrocardiogram (EOG) was recorded in lead II immediately after injection of $CaCl_2$, and 5, 10, and 15 min later.

The results were subjected to statistical analysis by the chi-square test.

In experiments in vitro on an isolated segment of guinea pig intestine the effect of the antidepressants was studied on the spasmogenic action of $CaCl_2$ and KCl. These results were subjected to statistical analysis by the method of regression analysis and calculation of the concentration of the antidepressants inhibiting the spasmogenic effect of the agonists by 50% (IC_{50}).

EXPERIMENTAL RESULTS

As Table 1 shows, tetrindole in doses of 10-50 mg/kg caused a dose-dependent decrease in mortality of the mice after receiving an injection of a toxic dose of $CaCl_2$ to the same degree as verapamil. Pyrazidol and moclo-

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TABLE 1. Effect of Intravenous Injection of Antidepressants and Verapamil on Lethal Effect of $CaCl_2$ in Mice

Preparations, mg/kg		Ratio of number of mice dying after injection of $CaCl_2$ (300 mg/kg, intravenously) to number of mice receiving the dose	Number of mice dying, %
Distilled water (control)		100/115	87
Tetrindole	5	15/20	75
	10	28/40	70*
	25	24/40	60*
	50	22/40	55*
Pyrazidol	5	24/30	80
	10	40/50	80
	25	32/40	80
	50	26/40	65*
Inkazan	5	18/20	90
	10	24/30	80
	25	30/40	75
	50	18/20	90
Azaphene	10	24/30	80
	25	18/20	90
	50	18/20	90
Moclobemide	10	24/30	80
	25	30/40	75
	50	26/40	65*
Imipramine	10	30/40	75
	25	16/20	80
	50	15/20	75
Verapamil	5	16/20	80
	10	30/40	75
	25	18/30	60*

Legend. Here and in Table 2: *$p < 0.05$.

TABLE 2. Effect of Intravenous Injection of Antidepressants and Verapamil on Arrhythmic Action of $CaCl_2$ in Rats

Preparations, mg/kg (IV)		Ratio of number of rats with lethal ventricular fibrillation after injection of $CaCl_2$ to number of rats receiving the dose	Number of rats with lethal ventricular fibrillation, %
Distilled water	—	10/10	100
Tetrindole Per os	1	8/10	80
Pyrazidol	2,5	5/10	50*
	2,5	10/10	100
	5,0	8/10	80
	10,0	6/10	60
Inkazan	5,0	10/10	100
	10,0	8/10	80
Azaphene	5,0	10/10	100
	10,0	10/10	100
Moclobemide	5,0	10/10	100
	10,0	8/10	80
Imipramine	5,0	10/10	100
	10,0	10/10	100
Verapamil	1,0	6/10	60
	2,5	5/10	50*

bemide had an equal (65%) protective effect, only in a dose of 50 mg/kg. Inkazan, azaphene, and imipramine had no protective effect.

Table 2 shows that of all the antidepressants tested only tetrindole in a dose of 2.5 mg/kg protected 50% of the rats against the development of ventricular fibrillation, and the death of the animals which followed it. The antiarrhythmic effect of tetrindole was similar to that of verapamil when the latter was injected intravenously in a dose of 2.5 mg/kg. When pyrazidol was used in a dose of 10 mg/kg a tendency was noted for the number of rats with lethal ventricular fibrillation to decrease. The remaining antidepressants were inactive.

The anticalcium action of tetrindole, as the most active drug with regard to the parameters studied, also was investigated in experiments on an isolated segment of guinea pig intestine with respect to its effect on the spasmogenic reaction to addition of $CaCl_2$ ($5 \cdot 10^{-4}$ g/ml) to the calcium-free, potassium-depolarizing Ringer's perfusion solution (KCl concentration $1.7 \cdot 10^{-3}$ g/ml) or to the addition of KCl ($2 \cdot 10^{-3}$ g/ml) to the standard Ringer's perfusion solution. Comparison with verapamil was investigated. In these experiments IC_{50} of tetrindole for its effect on spasmogenic reactions induced by $CaCl_2$ and KCl was $1 \cdot 10^{-6}$ and $2 \cdot 10^{-6}$ g/ml respectively, whereas verapamil had effects of similar strength in a concentration of $1 \cdot 10^{-8}$ and $2 \cdot 10^{-8}$ g/ml respectively. The results of these experiments point to a significantly weaker antagonistic action of tetrindole than of verapamil on voltage-dependent Ca channels in the smooth-muscle tissue of the intestine. In analogous experiments by other workers [3] several known calcium antagonists also exhibited very different spasmolytic activity: for instance, IC_{50} of nifedipine for the abolition of calcium spasm of the intestine was $1 \cdot 10^{-10}$ g/ml, whereas for cinnarizine it was $1 \cdot 10^{-7}$ g/ml.

Differences in affinity for different tissues, and also in the mechanism of the anticalcium effects, are known for calcium antagonists and have been explained by the chemical heterogeneity of this group of compounds [6].

Thus, under the conditions of this investigation, not all our antidepressants that were studied had anticalcium activity. Imipramine, azaphene, and inkazan exhibited no activity in the tests used, whereas pyrazidol, moclobemide and, in particular, tetrindole were active to some degree or other.

Since the Russian preparations pyrazidol and tetrindole have been used as effective antidepressants, the question of the contribution of their anticalcium effect to the mechanism of their antidepressive action merits attention. We know that transmembrane Ca^{2+} transport plays an important role in the function of cells of the nervous system, including in the process of mediator secretion [4, 6].

Different neurotransmitters facilitate both opening and closing of the Ca-channels and, in turn, calcium antagonists change the biogenic monoamine levels [5]. Recently, incidentally, calcium antagonists have attracted attention as agents of neuronal protection against the destructive action of excess of Ca^{2+} in cerebral pathology [2, 7, 10].

Our investigations do not provide adequate grounds for assessing the direct action of pyrazidol and tetrindole on transmembrane Ca^{2+} transfer in cells of the CNS. Further investigations are needed for this purpose. Nevertheless, it can be postulated that the data on the anticalcium effect of these preparations, especially tetrindole, will help to explain the central action of this original antidepressant, and will also provide a basis for consideration of its possible neuronal-protective activity in pathological (senile and presenile-ischemic, hypoxic, etc.) states of the nervous system.

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