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Imipramine and electroshock threshold (**)

Introduction

Despite its close chemical relationship to chlorpromazine, imipramine was found to exert quite opposite clinical effects. Accordingly, it has been used in the treatment of various types of depression.

Whereas chlorpromazine does not influence the electroshock convulsive seizure ([8]), imipramine prevents the occurrence of the tonic phase of the electroshock convulsions ([10], [12]).

In a previous paper ([4]) we have reported that the marked increase in electroshock threshold, provoked by amphetamine, was completely prevented by pretreatment with reserpine, moderately enhanced in presence of increased brain serotonin and catecholamine levels, but very markedly enhanced in presence of selectively increased brain dopamine levels.

The present paper deals with the effect of imipramine on the electroshock threshold and its possible mechanism of action in this respect.

Material and Methods

The experiments were performed in 64 unanæsthetized rabbits, weighing from 1.6 to 2.1 kg, according to the previously described technique ([3], [4]).

The effect of imipramine (1) on the electroshock threshold was studied in intact animals, in animals with lowered brain 5-hydroxytryptamine and catecholamine

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(1) Imipramine [N-(γ-dimethylaminopropyl-)-imino-dibenzyl hydrochloride, Tofranil(R), G 32883 [5-carbamyl-dibenz (b, f)-azepine] and G 35020 [desmethylimipramine, Pertofran(R)] were kindly supplied by Geigy A. G., Basle, reserpine [Serpasil(R)] by Ciba A. G., Basle, iproniazid [Marsilid(R)] and *l*-dihydroxyphenylalanine by F. Hoffmann-La Roche Ltd., Basle, Switzerland, and α-methyl-m-tyrosine by Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey, U.S.A.

levels, i.e. after reserpine, in animals with increased brain 5-hydroxytryptamine and catecholamine levels, i.e. after iproniazid, in animals with selectively and markedly increased brain dopamine levels, i.e. after pretreatment with reserpine + iproniazid + *l*-dihydroxyphenylalanine ([2]), and finally in animals with a complete and selective loss of brain noradrenaline, i.e. after pretreatment with α-methyl-*m*-tyrosine ([1]).

Results

Our experimental observations have been summarized in Table I. It can be seen that imipramine considerably increases the electroshock threshold, since as much as 12 W. sec., vs. 0.2 W. sec. in controls, had to be given in order to elicit,

TABLE I.

Experimental conditions [Drug (dose in mg/kg, route of administration, time of administration before electroshock)]	% Increase (+) or decrease (—) of electroshock threshold (average values in groups of 10 animals)
Imipramine (5, i.v., 4 min)	+ 5.900
Reserpine (1, i.v., 24 hrs)	
+ Imipramine (5, i.v., 5 min)	+ 75
Iproniazid (100, i.p., 24 hrs)	
+ Imipramine (5, i.v., 5 min)	+ 13.750
Reserpine (1, i.v., 21 hrs)	
+ Iproniazid (100, i.p., 13 hrs)	
+ *l*-Dihydroxyphenylalanine (50, i.p., 1 hr)	
+ Imipramine (5, i.v., 5 min)	+ 15.000
α-Methyl-*m*-tyrosine (50, i.v., 13 hrs)	
+ Imipramine (5, i.v., 5 min)	+ 15.000

in only 30% of cases, a typical convulsive seizure. A similar, though somewhat less pronounced increase in electroshock threshold occurred after administration of the imipramine analogue G 32883, whereas desmethylimipramine was found to be inactive in this respect.

The increase in electroshock threshold, provoked by imipramine, does not occur in reserpinized animals. It is noteworthy that the respiratory and cardiovascular changes, occurring in these animals upon the administration of electroshock, show a spontaneous return to normal, without a need for artificial respiration and administration of pressor substances, as required in animals pretreated with reserpine only or with reserpine + amphetamine ([3], [4]).

As further shown in Table I the increase of electroshock threshold, induced by imipramine, was even more marked after pretreatment with iproniazid and especially after pretreatment with reserpine + iproniazid + *l*-dihydroxyphenylalanine.

Finally, it is noteworthy that the imipramine-induced increase in electroshock threshold still occurs in case the brain noradrenaline stores have been completely and selectively depleted by pretreatment with α-methyl-*m*-tyrosine.

Discussion

Sigg ([10]) has reported that the intraperitoneal injection of 30 mg/kg of imipramine in mice prevents in 75% of cases the tonic phase of supramaximal electroshock, applied 15 minutes after the imipramine administration.

The present experiments, in which the minimal electroshock method was used, confirm and extend these observations. They show that the intravenous injection of 5 mg/kg of imipramine in rabbits, given 5 minutes before the electroshock, provokes in all animals a very marked increase of the electroshock convulsion threshold.

The protective action exerted by imipramine against the acute respiratory (apnea) and cardiovascular (circulatory collaps) alterations, which are known to occur upon application of electroshock in reserpinized rabbits, is not due to its anticholinergic properties, since atropinization does not prevent these alterations ([7]). Neither is it related to a respiratory stimulation, since imipramine rather depresses respiratory movements, at least in cats ([10]). This action should be more likely attributed to the potentiation of the noradrenaline effects by imipramine, as shown by Sigg ([10]) and Vernier et al. ([12]). This would also explain the prolongation of the arterial hypertension, which may be observed upon application of electroshock in imipramine pretreated rabbits ([8]).

Various investigators have tried to uncover the pharmacological basis for the potent antidepressant properties of imipramine, which would also provide a clear-cut and qualitative differentiation from chlorpromazine. Maxwell and Palmer ([6]) observed in rats that low doses of imipramine have a distinct stimulant effect, whereas higher doses provoke a chlorpromazine-like sedation. In rabbits, imipramine produced a complete reversal of reserpine induced ptosis, as well as an increase in alertness and reactivity.

According to Vernier et al. ([12]), on the other hand, the antidepressant properties of imipramine should be related to its antagonism of tetrabenazine sedation and reserpine hypothermia, and to its potentiation of noradrenaline hypertension and of amphetamine hypermotility. In this connection, attention should be drawn to the fact that suitable doses of chlorpromazine may also antagonize the reserpine induced hypothermia and ptosis, and prolong the noradrenaline pressor effect ([5]). Accordingly, credit should be rather given to the relationship between the antidepressant effect of imipramine and its potentiation of amphetamine hypermotility, which is in agreement with the observation of Stein and Seifter ([11]) that the increase in self-stimulation, provoked by methamphetamine in rats, is enhanced by imipramine, but prevented by chlorpromazine.

Our experimental observations further suggest that amphetamine and imipramine induce an increase in electroshock threshold through the same dopamine me-

diated mechanism, e.g. by provoking a sensitization towards dopamine. This would also explain why imipramine facilitates the effect of amphetamine on spontaneous motor activity.

SUMMARY

Imipramine was found to provoke a very marked increase of the electroshock convulsion threshold in rabbits. This increase does not occur in reserpinized animals, but is even more pronounced, as reported previously for amphetamine, in presence of increased brain dopamine levels.

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