J. Pharm. Pharmac., 1966, **18**, 443–448 Received January 17, 1966

Effect of desipramine on directly or indirectly elicited catecholamine pressor responses in rats*

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Desipramine enhances the pressor effect induced by noradrenaline, adrenaline, dopamine and dimethylphenylpiperazinium in pithed rats, while indirectly acting sympathomimetic amines, such as tyramine and phenethylamine were inhibited. With a similar degree of noradrenaline potentiation, desipramine was more effective than cocaine as an inhibitor of the tyramine pressor response. Desipramine, but not cocaine, was effective in blocking the hypertension induced by small doses of reserpine in animals pretreated with tranylcypromine.

SEVERAL authors (Sigg, 1959; Sigg, Soffer & Gyermek, 1963; Loew, 1964; Kaumann, Basso & Aramandia, 1965, and others) have observed in cats, dogs and rabbits an increased sensitivity of peripheral adrenergic responses after a treatment with antidepressant drugs such as imipramine and desipramine. On the basis of these observations it was proposed that a potentiation of central adrenergic effects may explain the antidepressant activity of these compounds (Sigg, 1959; Sulser, Bickel & Brodie, 1964). A biochemical basis for this hypothesis was established by experiments which showed an inhibition of the uptake of catecholamines after treatment with imipramine-like agents (Hertting, Axelrod & Whitby, 1961; Thoenen, Huerlimann & Haefely, 1964; Iversen, 1965a,b).

Since previous pharmacological and biochemical studies with antidepressant drugs have been made in these laboratories with rats (Garattini, Giachetti, Jori, Pieri & Valzelli, 1962; Garattini & Valzelli, 1962; Jori & Garattini, 1965; Jori, Paglialunga & Garattini, 1965) it was decided to use rats in an investigation of the influence of desipramine on blood pressure responses to sympathomimetics or to drugs known to act through releasing catecholamines.

Reserpine induces hypertension in animals pretreated with monoamine oxidase inhibitors (Chessin, Kramer & Scott, 1957; Garattini, Fresia, Mortari & Palma, 1960). This hypertension has been interpreted as the result of the peripherally released catecholamines which are not rapidly metabolised at the site of release because of the inhibition of the monoamine oxidase. Since Cuenca, Salvá & Veldecasas (1964) observed an inhibition exerted by desipramine on the initial pressor action of guanethidine and bretylium, whose effect is also thought to be mediated by catecholamines (Gillis & Nash, 1961), it was of interest to investigate the influence of desipramine on this effect of reserpine.

Materials and methods

Male Sprague–Dawley rats, 250–300 g, were anaesthetised with ether. Both carotid arteries were ligated after cannulation of the trachea.

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* Partially supported by a grant from J. R. Geigy S.A., Basle.

Animals were then pithed and maintained by artificial respiration. Blood pressure was recorded from a cannulated carotid artery by means of a pressure transducer (Statham P 23A) and displayed on an ink-writing Grass Polygraph. Injections of 0·1 or 0·2 ml were given into the cannulated right femoral vein.

Other experiments were made to observe the pressor effect of reserpine in animals pretreated with monoamine oxidase inhibitors. Sprague–Dawley rats, 300 g, were anaesthetised with urethane, 1·25 g/kg i.p., and the left carotid artery was cannulated for recording blood pressure.

Tranylcypromine, 5 or 10 mg/kg, was injected i.p. either 60 min or 5 hr before the intravenous injection of reserpine. Other monoamine oxidase inhibitors used were pheniprazine, 10 mg/kg, and iproniazid, 100 mg/kg, given 18 hr before the experiment.

Results

EFFECT OF DESIPRAMINE AND COCAINE ON THE BLOOD PRESSURE RESPONSES INDUCED BY INJECTED AMINES OR DIMETHYLPHENYLPIPERAZINIUM

Groups of five or more pithed rats received noradrenaline or adrenaline at doses of 0·05 and 0·1 μg/rat until consistent responses were obtained. Desipramine, 3 mg/kg, was then injected intravenously and the pressor responses elicited by the catecholamines were again determined 30 min after the drug. The responses to the two amines were significantly increased. The pressor response to dopamine, 20–40 μg, was also enhanced by desipramine while the response to dopa, 2 mg, was unaffected. These results are summarised in Table 1.

TABLE 1. EFFECT OF DESIPRAMINE ON PRESSOR RESPONSE ELICITED BY ADRENALINE HYDROCHLORIDE, NORADRENALINE BITARTRATE, DOPAMINE, DOPA PHENETHYLAMINE OR DIMETHYLPHENYLPIPERAZINIUM IN PITHED RATS. (TIME BETWEEN DESIPRAMINE AND PRESSOR RESPONSES WAS 30 MIN). DOSES ARE EXPRESSED AS SALTS

No. of experiments	Pressor agent	Dose μg/rat i.v.	Pressor response in mm Hg ± s.e.		Statistical significance (P)
			Saline	Desipramine 3 mg/kg i.v.	
5	Noradrenaline	0·05	39 ± 4	72 ± 8	=0·01
5	,,	0·10	55 ± 7	101 ± 13	=0·01
4	Adrenaline	0·05	20 ± 3	38 ± 3	=0·01
4	,,	0·10	44 ± 8	76 ± 10	=0·05
5	Dopamine	10	34 ± 3	53 ± 2	=0·01
5	,,	20	50 ± 4	70 ± 8	=0·01
5	Dopa	2,000	55 ± 4	58 ± 6	>0·05
10	DMPP	20	33 ± 10	65 ± 13	=0·05
10	DMPP	40	46 ± 6	105 ± 10	<0·01
4	Phenethylamine	50	25 ± 3	4 ± 4	<0·05

The effect of desipramine on noradrenaline was less consistent when animals were not pithed but anaesthetised with urethane.

Dose-response curves to noradrenaline were shifted to the left after treatment with desipramine or cocaine (Fig. 1). On the other hand the pressor effect of tyramine was antagonised (Fig. 2). The dose-response

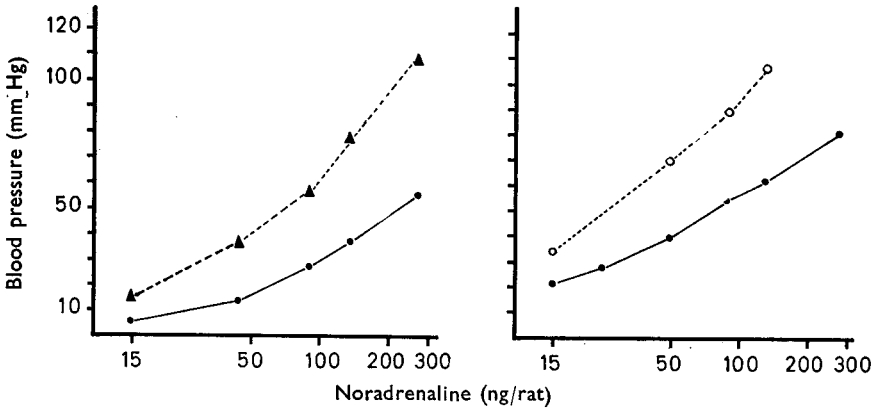

FIG. 1. Potentiation of blood pressure response to noradrenaline by previous treatment with desipramine (▲- - - -▲), 3 mg/kg, or cocaine (○- - - -○), 5 mg/kg, in pithed rats. Control ●—●. The curves obtained in a single rat are representative of a typical response.

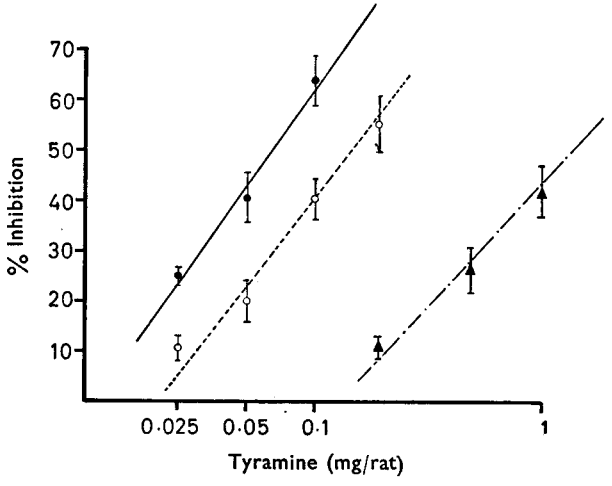

FIG. 2. Inhibition of blood pressure response to tyramine by previous treatment with desipramine (▲- · -▲), 3 mg/kg, or cocaine (○- - - -○), 5 mg/kg, in pithed rats. Control ●—●. Vertical bars represent the standard error of the mean.

curves are parallel and desipramine shifts the curve more to the right than cocaine. The pressor response to phenethylamine, 50 μg, was also antagonised by desipramine (see Table 1).

In nine experiments desipramine enhanced the blood pressure response induced by 20–40 μg of the ganglion stimulant 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) (see Table 1). This is in agreement with the data obtained by Osborne & Sigg (1960) who worked with imipramine in anaesthetised dogs.

EFFECT OF COCAINE AND DESIPRAMINE ON THE BLOOD PRESSOR RESPONSE INDUCED BY RESERPINE IN RATS TREATED WITH A MONOAMINE OXIDASE INHIBITOR

In intact animals pretreated with tranylcypromine, 5 mg/kg i.p., 60 min before the experiment, reserpine, 250 μg/kg, induced a sustained increase of the systolic blood pressure which was inhibited by desipramine (see Fig. 3) but unaffected by cocaine. Similar results were obtained using pithed rats.

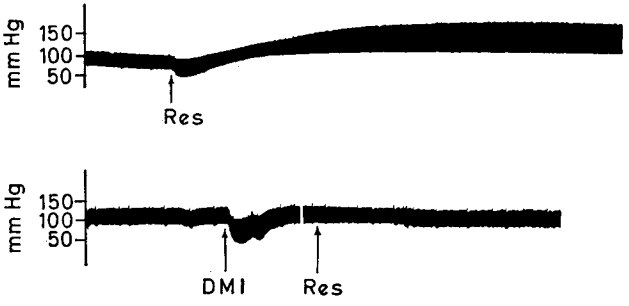

FIG. 3. Effect of desipramine (DMI), 3 mg/kg i.v., on the hypertensive response elicited by reserpine (Res), 250 μg/kg i.v., in rats pretreated 60 min before the experiment with tranylcypromine, 5 mg/kg i.p. Immediately after tranylcypromine administration, animals were anaesthetised with urethane.

When 5 hr elapsed after the tranylcypromine pretreatment, the pressor action of reserpine was smaller and occurred only with a larger dose, 2·5 mg/kg. This response was unaffected by desipramine. Similar results were obtained when pheniprazine and iproniazid were given 18 hr before reserpine (see Table 2).

TABLE 2. EFFECT OF DESIPRAMINE ON THE PRESSOR RESPONSE INDUCED BY RESERPINE IN RATS TREATED WITH MONOAMINE OXIDASE INHIBITOR. (TIME BETWEEN DESIPRAMINE OR COCAINE AND RESERPINE WAS RESPECTIVELY 30 AND 10 MIN)

No. of animals	Pretreatment i.p. mg/kg	Time after MAO inhibitor	Compound mg/kg i.v.	Reserpine mg/kg i.v.	Pressor responses in mm Hg ± s.e.	P
9	Tranylcypromine 5	60 min	Saline	0·25	79 ± 9	<0·01
9	,, 5		Desipramine 3	0·25	11 ± 4	
6	Tranylcypromine 5	60 min	Saline	0·25	68 ± 11	>0·05
5	,,		Cocaine 3	0·25	50 ± 13	
11	Tranylcypromine 10	5 hr	Saline	2·5	45 ± 7	>0·05
6	,,		Desipramine 3	2·5	28 ± 5	
8	Pheniprazine 10	18 hr	Saline	2·5	26 ± 2	>0·05
7	,,		Desipramine 3	2·5	27 ± 4	
6	Iproniazid 100	18 hr	Saline	2·5	39 ± 14	>0·05
6	,,		Desipramine 3	2·5	20 ± 7	

The difference in response to reserpine between the 60 min tranylcypromine-treated rats and the 5 hr tranylcypromine-treated, 18 hr pheniprazine-treated or 18 hr iproniazid-treated rats may be accounted for by the activity of tranylcypromine itself inhibiting noradrenaline uptake (Iversen, 1965a). This activity may have dispersed 5 hr after administering the drug. Iproniazid does not inhibit noradrenaline uptake (Iversen, 1965a).

Discussion

The ability of desipramine to potentiate noradrenaline and adrenaline and to antagonise the pressor effect of certain indirectly acting sympathomimetic amines such as tyramine and phenethylamine in pithed rats has been demonstrated in the present work.

As previously mentioned desipramine prevents the uptake of catecholamines (Hertting & others, 1961; Iversen, 1965a,b), particularly at low concentrations (Iversen, 1965c) presumably by inhibiting the active transport mechanism. The potentiation of noradrenaline and adrenaline may therefore be explained at least in part by the inhibition of uptake, an important mechanism for terminating the action of catecholamines (Koelle, 1959; Dengler, Spiegel & Titus, 1961; Rosell, Kopin & Axelrod, 1963).

Dimethylphenylpiperazinium is known to act at sympathetic ganglia to induce a release of catecholamines at the nerve ending. The potentiation of the dimethylphenylpiperazinium pressor response by desipramine may therefore also be related to an inhibition of catecholamine uptake. Furthermore it has been demonstrated that desipramine enhances the effect of electrical stimulation of the peripheral sympathetic system (Haefely, Huerlimann & Thoenen, 1964).

The effect of indirectly acting sympathomimetic amines is generally attributed to a release of noradrenaline from tissue stores (Carlsson, Rosengren, Bertler & Nilsson, 1957; Burn & Rand, 1958). The inhibition by desipramine or cocaine of responses to indirectly acting sympathomimetics may therefore be related to a decreased access of these amines to the noradrenaline storage sites. Imipramine congeners inhibit catecholamine depletion induced by tyramine (Kaumann & Basso, 1965) and desipramine prevents the uptake of tyramine (Matsumoto, Costa & Brodie, 1964).

From these data it is evident that desipramine shows a pattern of effects comparable with that shown by cocaine. Data from the literature, confirmed by this experimental work, demonstrate that cocaine potentiates the action of noradrenaline, adrenaline and dimethylphenylpiperazinium but inhibits the effect of tyramine and phenethylamine. In these experiments desipramine can be distinguished from cocaine only by its inhibition of the pressor effect of reserpine elicited 60 min after administration of a monoamine oxidase inhibitor.

Both desipramine and cocaine only slightly affect the hypertension induced by reserpine in rats when reserpine was given several hours after the monoamine oxidase inhibitor.

Further work is required to elucidate the reason for the hypertension induced by reserpine being greater—60 min after, compared with 5 hr after—than treatment with a monoamine oxidase inhibitor.

In conclusion the data presented show that in rats the interaction of desipramine and catecholamines or drugs acting through a catecholamine release is compatible with the hypothesis that this antidepressant drug inhibits amine uptake.

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