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Observations on the interactions between desipramine and reserpine on adrenergic transmission in the rat

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The time course of the impairment of the adrenergic transmission induced by reserpine has been examined on the inferior eyelid of the rat pretreated with desipramine. Desipramine given before reserpine is able to counteract, in a dose-dependent manner, the impairment induced in the first hours after reserpine. On the contrary, desipramine has only a limited effect, not dose-dependent, when given after the reserpine treatment.

Desipramine and other tricyclic antidepressant drugs are able to anatagonize many of the central and peripheral effects of reserpine. Of the various symptoms induced by reserpine, ptosis has been regarded as a sign of its central action, and the ability of drugs to prevent reserpine-induced ptosis has been proposed as a screening test for antidepressant activity (Chen, 1964). However, Fielden & Green (1965); Schmidt, Küsel & Dal (1968) have reported evidence that reserpine-induced ptosis is produced by a peripheral rather than by a central mechanism. Tedeschi (1967) showed this ptosis to be brought about by three different mechanisms: (i) increased outflow over the facial nerve (blepharospasm); (ii) reduced outflow via superior sympathetic nerves secondary to both central and peripheral action; (iii) retraction of the eyeball into the orbit. Since the blockade of the sympathetic motor innervation seems to be more responsible than other mechanisms for the reserpine ptosis, we decided to study the effect of desipramine on reserpine-induced impairment of the adrenergic transmission at the level of the eyelid contraction elicited by the stimulation of the sympathetic trunk.

METHODS

Male Sprague Dawley rats, 250–300 g, were used.

Electrical stimulation of the sympathetic trunk

The rats were anaesthetized with urethane (1·25 g/kg intraperitoneally). The head of the rat was immobilized in a head holder, the trachea cannulated and the cervical sympathetic nerve dissected free and placed over shielded platinum electrodes. Preganglionic stimulation of the right superior cervical sympathetic chain elicits a retraction of the inferior (Gertner, 1956) and superior (Morpurgo, 1968) eyelid of the rat. Retraction of the inferior eyelid was thus recorded by means of a thread connected to a Grass force displacement transducer FTO3 fed into a writing unit of a Grass Polygraph. The electrical stimulation was delivered from a S4 Grass stimulator at square wave pulses of 1 ms duration, at supramaximal voltage and

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varying frequencies. Animals were injected with reserpine before anaesthesia and with desipramine either before or after anaesthesia.

Ptosis. Observations were made on unanaesthetized animals following the same schedule of treatment used for adrenergic transmission. Ptosis was evaluated according to Rubin, Malone & others (1957).

Drugs. Reserpine (Serpasil vials—CIBA), and desipramine HCl (Geigy).

RESULTS

Eyelid contraction

The effects of reserpine on the contraction of the inferior eyelid induced by electrical stimulation of the sympathetic trunk were recorded and plotted in graphs (Fig. 1). Recordings made 4, 8 or 24 h after administration of two doses of reserpine

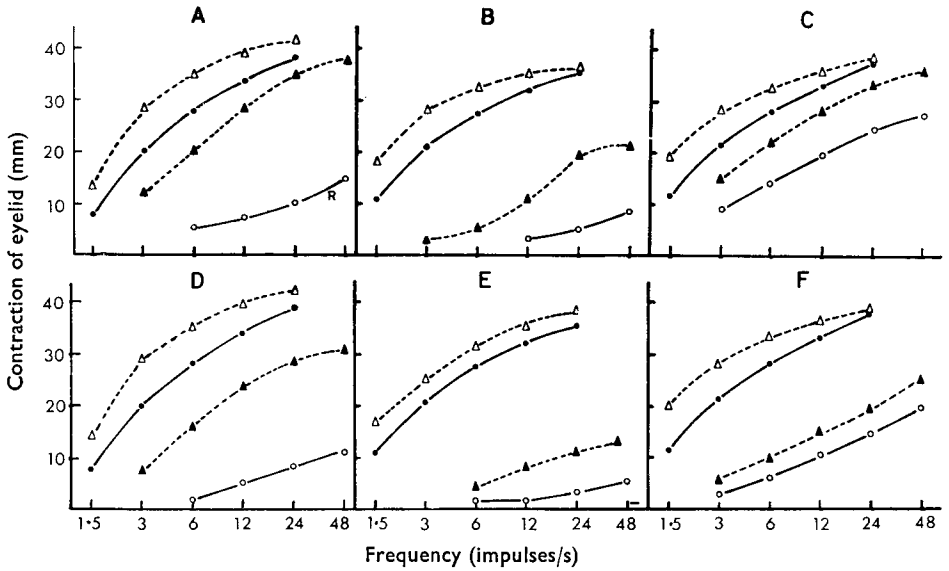

FIG. 1. Effect of desipramine on the impairment of adrenergic transmission induced by reserpine in the rat lower eyelid, after stimulation of the superior cervical sympathetic nerve. Parameters of stimulation were 7V, 1 ms for 15 min every 3 min. Desipramine (15 mg/kg, i.p.) was given 1 h before reserpine and the test made at 4 h after reserpine A, D; 8 h after reserpine B, E; 24 h after reserpine C, F. ●——● = control. ○——○ = reserpine. △- - - -△ = desipramine. ▲——▲ = desipramine + reserpine. *P*-values for animals treated with reserpine and compared with desipramine + reserpine and for A, B, D $<0{\cdot}01$; for E $<0{\cdot}05$. Reserpine was administered intravenously at the dose of 0·25 mg/kg in A, B, C and at dose of 1 mg/kg in D, E, F.

show a marked impairment of the adrenergic transmission. Reserpine pretreatment results in a shift of the frequency response curve to the right, and in a decrease of the maximal response. The effect was related to the dose and time of pretreatment, being maximal after 8 h. Control animals receiving desipramine alone showed a frequency-response curve (to the electrical stimulation of the sympathetic trunk) slightly shifted to the left confirming previous data on the cocaine-like effect of desipramine.

The antagonism of desipramine to reserpine was then examined following two schedules of desipramine treatment: one group of animals received desipramine before reserpine and recordings of the sympathetic transmission were made at the same time as animals treated with reserpine alone. The antagonist action of

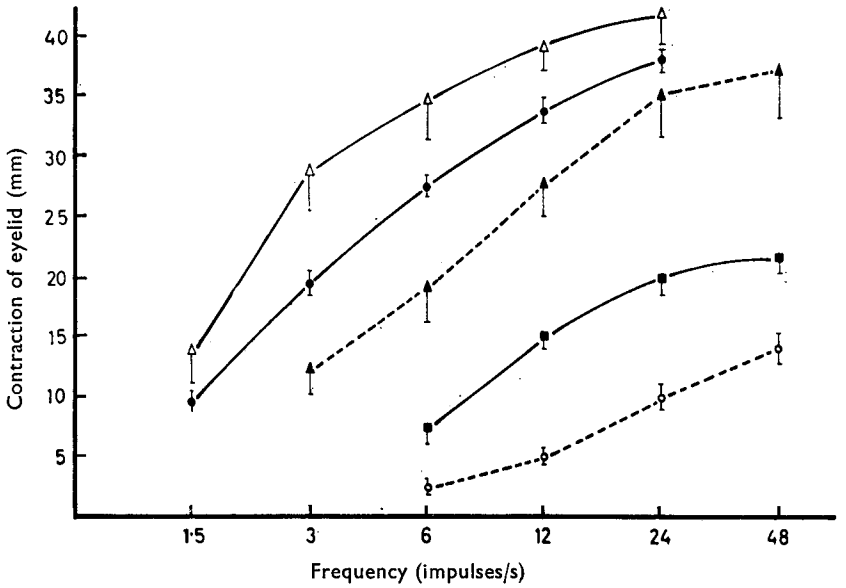

FIG. 2. Effect of desipramine given before or after reserpine (0·25 mg/kg, i.v.) on the contraction of the lower eyelid. Test made 4 h after reserpine. ●——● control, △- -△ desipramine, ○——○ reserpine. ▲- - - -▲ desipramine given 1 h before reserpine. ■——■ desipramine given 3 h after reserpine.

desipramine is marked in the first hours but gradually subsides and at 24 h it has disappeared (Fig. 1). In the second schedule, desipramine was given when the adrenergic transmission was already impaired by reserpine (Fig. 2). Fig. 3 summarizes the results obtained from the two schedules.

In reserpinized animals, desipramine is still able to increase the sympathetic response but the increase is not dependent on the dose over the doses studied. On the contrary, pretreatment with desipramine leads to a dose-dependent antagonism of reserpine being almost complete with the highest dose of desipramine (15 mg/kg).

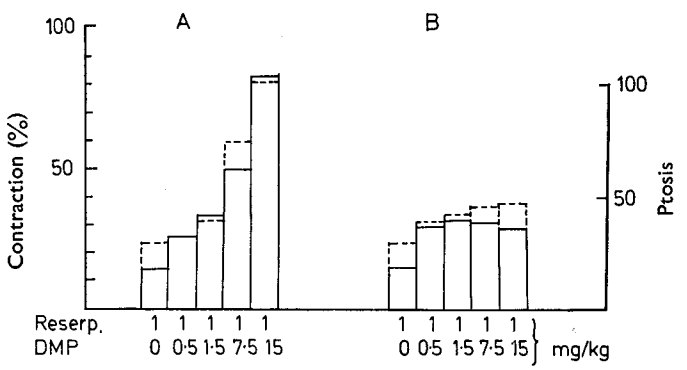

FIG. 3. Effect of various doses of desipramine on the impairment of adrenergic transmission (7V, 1 ms, 12 Hz) and ptosis in the rat lower eyelid induced by reserpine. Columns in solid lines indicate % contraction of the lower eyelid induced by the stimulation of the sympathetic trunk. Columns in broken lines refer to ptosis which is reported as reciprocal of the score values × 100.

Ptosis

The schedule of treatment was similar to that described for the sympathetic transmission. Intact animals received desipramine either before or after reserpine and the extent of ptosis, scored on a 0–4 scale (Rubin & others, 1957), was evaluated 4 h after the administration of reserpine (Table 1). The time course of the ptosis and the inhibition induced by desipramine is roughly correlated with the impairment of the adrenergic transmission as shown in Fig. 3 where the reciprocal of ptosis is superimposed on eyelid retraction.

Definite inhibition of ptosis related to the dose of desipramine can be demonstrated when it is administered before reserpine. When ptosis is already established desipramine has little activity and its effect is not related to the dose (Table 1).

Table 1. *Effect of desipramine on the ptosis* induced by reserpine* (1 mg/kg, i.v.).

	Dose of desipramine (mg/kg, i.p.)	Desipramine given 1 h before reseripine	Desipramine given 3 h after reserpine
Reserpine	0	4·00	4·00
Reserpine + desipramine	1·5	3·06 ± 0·28	2·91 ± 0·14
	7·5	1·66 ± 0·22	2·58 ± 0·1
	15	1·21 ± 0·41	2·55 ± 0·1

* Ptosis was evaluated according to Rubin & others (1957), 4 h after reserpine.

DISCUSSION

The experiments described show that the impairment of adrenergic transmission and ptosis induced by reserpine can be prevented or delayed by desipramine in a dose-dependent relation provided it is given before reserpine. Doses of desipramine between 0·5 and 15 mg/kg, given after reserpine however, caused a small increase in the size of the response of the eyelid to the stimulation of the sympathetic trunk and induced an opening of the eyes that was not related to dose. In both situations, there was a good correlation of ptosis and the contraction of the inferior eyelid.

The difference in the action of desipramine, before and after reserpine, suggests that in these two situations it is exerting two different mechanisms according to whether noradrenaline stores are depleted or replenished. The potentiation induced in reserpinized animals by desipramine may well be due to the blockade of re-uptake of noradrenaline into adrenergic neurons (cocaine-like effect), which the drug is known to cause (see Iversen, 1967).

The dose-dependent anatagonism obtained when desipramine is given before reserpine suggests that, as well as an action at the neural membrane, the drug may exert another effect on the rate of release of catecholamines by reserpine. It has been shown that the rate of catecholamine release induced by reserpine in the heart and brain is lowered by desipramine (Manara, Algeri & Sestini, 1967; Sulser, Owens & others, 1969). The same effect could operate on the stores present in the sympathetic nerve terminals of the eyelid and may explain the more pronounced antagonistic effect of desipramine in the first hours of impairment of the adrenergic transmission induced by reserpine.

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