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Potentiation by desipramine of the pressor and depressor effects of dopamine

Imipramine and desipramine are known to potentiate the peripheral effects of noradrenaline and other amines. These facts supported the hypothesis relating the antidepressant action of imipramine to the activation of adrenergic mechanisms in the brain (Sigg, 1959).

The demonstration of the inhibition of catecholamine uptake in peripheral tissues and in the brain by imipramine-like drugs (Dengler & Titus, 1961; Glowinski & Axelrod, 1964) has provided a biochemical basis for the suggested mechanism of their antidepressant effect (Sulser, Bickel & Brodie, 1964) and the interactions with endogenous amines.

Tricyclic antidepressants potentiate the inhibitory effects of noradrenaline at the synaptic level (Cairncross, McCulloch & others, 1967; Kądzielawa, Gawęcka & Kądzielawa, 1967, 1968; Kądzielawa & Widy-Tyszkiewicz, 1969). We have found that imipramine and desipramine activate the depressor action of dopamine and we now report an analysis of this effect.

Male rats, 250–350 g; guinea-pigs, 400–500 g; rabbits, 3–3·5 kg, and cats, 2·8–3·5 kg were anaesthetized with urethane (25% soln) at doses of 0·7 ml/100 g, subcutaneously for rats and 0·9 ml/100 g for guinea-pigs; 1·7 g/kg, intraperitoneally for rabbits and 1·0/kg for cats. Blood pressure was recorded from cannulated carotid common artery by means of a mercury manometer. Drugs were dissolved in normal saline and injected through a polythene cannula in the femoral vein. In rats and guinea-pigs the amount of injected solution did not exceed 0·1–0·2 ml/100 g. Desipramine hydrochloride and dopamine hydrochloride was used in these experiments. The doses refer to the salts. In guinea-pigs, rats and rabbits dopamine (2·5–30 μg/kg) produced an acute fall in blood pressure, with gradual recovery to normal values in few minutes, depending upon the dose used. In cats anaesthetized with urethane, dopamine (10–30 μg/kg) induced a biphasic response; an acute and short lasting increase in blood pressure followed by a decrease in pressure lasting for 2–5

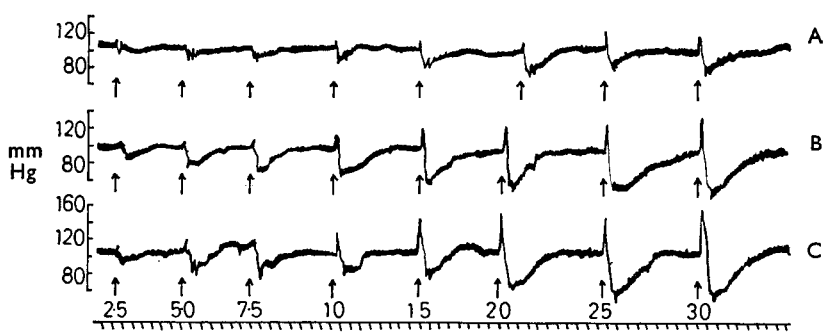

FIG. 1. The influence of a sequence of doses of dopamine (in μg/kg) on the blood pressure in a cat anaesthetized with urethane. A, Before, B, 30 min and C, 90 min after i.v. desipramine (6 mg/kg). Time marker in min.

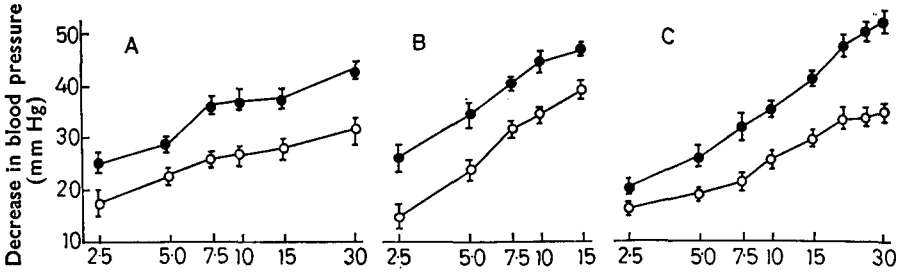

FIG. 2. Potentiation by desipramine (6 mg/kg) of the depressor effect of dopamine in animals anaesthetized with urethane: A. Rabbits (15 exp.). B. Guinea-pigs (25 exp.). C. Cats (14 exp.). —○—, Normal response to dopamine, —●—, the effect of a sequence of dopamine doses applied 30 min following desipramine. Abscissa: doses of dopamine (μg/kg) in log scale.

min (Fig. 1A). In cats anaesthetized with chloralose (80 mg/kg, i.p.) dopamine (10–30 μg/kg) induced a pressor response, which was dominant, with a secondary depressor effect, this action is similar to that seen after adrenaline.

Desipramine (3–6 mg/kg) potentiated both the pressor and depressor effects of dopamine (Fig. 1). The potentiation of the depressor effects of dopamine in the three species anaesthetized with urethane is illustrated in Fig. 2. The near parallel shift of the dose-response curves indicates a true potentiation and the results are statistically significant with $P < 0.01$ for 7·5–30 μg/kg doses of dopamine.

Bonaccorsi & Garattini (1966) noted a potentiation by desipramine (3 mg/kg) of the pressor response to dopamine (10 and 20 μg/kg) in pithed rats. Previously only Eble (1964) has mentioned the augmentation by imipramine (2 mg/kg) of both the systemic pressor and depressor effects of dopamine (10 and 20 μg/kg) in dogs anaesthetized with pentobarbitone.

According to Løvtrup (1967) imipramine is a membrane stabilizer comparable to chlorpromazine. Present results suggest that both the inhibitory and excitatory effects of dopamine (or other amines) in the brain can be accentuated by imipramine and desipramine. This may be a factor in the mechanism of action of tricyclic antidepressants as well as in the modification in electrophysiological responses to monoamine precursors (Kądzielawa & Widy, 1970).

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February 21, 1971

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