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Effects of desipramine and cocaine on sympathetic responses in the pithed rat

Desipramine blocks the uptake of noradrenaline into sympathetic nerve endings (Hertting, Axelrod & Whitby, 1961; Iversen, 1965), and this has been accepted as the explanation for enhancement by desipramine of responses to adrenergic nerve stimulation and to exogenous noradrenaline. However, *in vitro* experiments with large doses of desipramine have demonstrated depression of sympathetic responses attributed to α-receptor blockade (Bonaccorsi & Hrdina, 1967; Bassett, Cairncross & others, 1969; Scriabine, 1969). Bonaccorsi & Hrdina (1967) reported that desipramine did not reduce responses to intravenous injections of noradrenaline in pithed rats. We now report the effects of desipramine and cocaine on the pressor responses to both intravenous injections of noradrenaline and sympathetic nerve stimulation in the pithed rat preparation described by Gillespie & Muir (1967). Desipramine was compared with cocaine since the latter drug does not have α-receptor blocking activity, but blocks uptake into sympathetic nerve endings (Muscholl, 1961).

The area of the pressor responses to sympathetic nerve stimulation and noradrenaline were measured by planimetry. The responses after desipramine or cocaine were calculated as a percentage of the mean control response. The results are illustrated in Fig. 1. Desipramine and cocaine in doses up to 2 mg/kg enhanced the pressor responses to sympathetic stimulation and intravenous noradrenaline. With higher doses the effects of the two drugs differed: cocaine continued to enhance the pressor responses whereas maximal enhancement was obtained with 2 mg/kg of desipramine and the enhancement was less with higher doses. The effect of both drugs on noradrenaline released from sympathetic nerve endings was far greater than the effects on injected noradrenaline. However, unlike Bonaccorsi & Hrdina (1967), some potentiation of injected noradrenaline by desipramine was demonstrated: the mean area of the pressor response to injected noradrenaline was 207 $\pm$ 47% of control with 2 mg/kg of desipramine. Unlike cocaine, the sharp cut off in the potentiating action of desipramine above 2 mg/kg can possibly be explained in terms of its dual action, namely: blockade of noradrenaline uptake demonstrated at low doses, and α-receptor blockade demonstrated at higher doses.

Desipramine antagonized calcium-induced contractions in a dose dependent manner (Bonaccorsi & Hrdina, 1967) so its blocking action in high doses could be due to a combination of α-receptor blockade and a membrane stabilizing effect.

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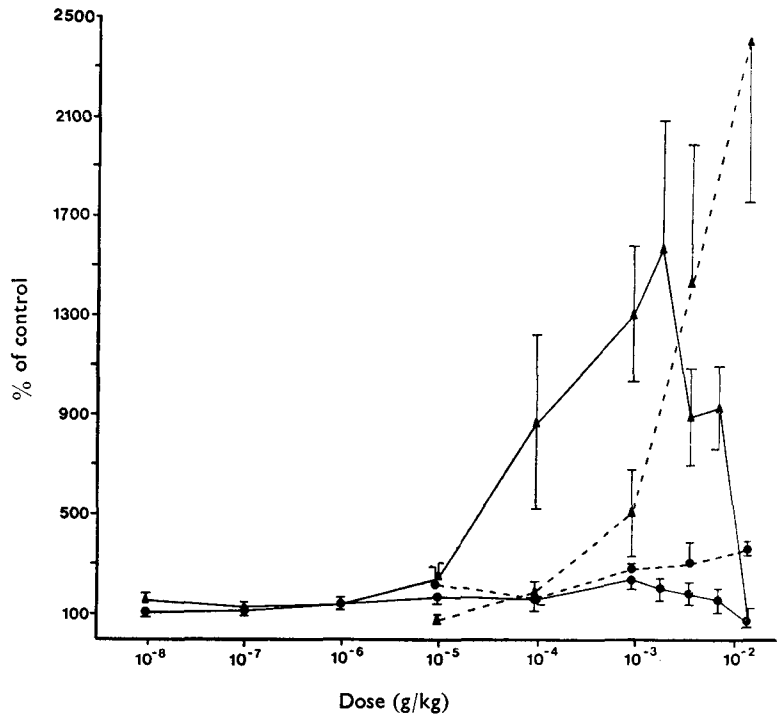

FIG. 1. Pithed rat preparation. The effect of various concentrations of desipramine and cocaine on the area of the pressor response to sympathetic nerve stimulation and to intravenous noradrenaline, expressed as a percentage of the area of the control responses: ●——●, desipramine and noradrenaline; ▲——▲, desipramine and sympathetic stimulation; ●- - -●, cocaine and noradrenaline; ▲- - -▲, cocaine and sympathetic stimulation. The vertical bars represent standard errors.

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