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Sensitivity changes to noradrenaline in the guinea-pig vas deferens induced by amphetamine, cocaine and denervation

Recently de Moraes & Carvalho (1968) and Carvalho, Martins & de Moraes (1970) provided strong evidence that amphetamine is an indirectly-acting sympathomimetic amine that induces presynaptic supersensitivity to noradrenaline. Amphetamine is known to inhibit noradrenaline uptake (Axelrod, Hertting & Potter, 1962; Burgen & Iversen, 1965; Häggendal & Hamberger, 1967). The current theory of the action of cocaine is that the drug produces competitive saturation of the noradrenaline uptake into adrenergic nerves (Furchgott, Kirpekar & others 1963; Draskóczy & Trendelenburg, 1968) by impairing amine uptake by the adrenergic nerves (Langer & Trendelenburg, 1969). On the other hand, the sensitizing action of cocaine cannot be attributed solely to this action

Guinea-pigs 450–600 g were killed by a blow on the back of the neck and decapitated. The vas deferens was suspended in a water-jacketed bath containing 18 ml of modified Krebs-bicarbonate solution (Huković, 1961), maintained at 31° and bubbled with 5% carbon dioxide in oxygen. Dose-response curves for noradrenaline were obtained by the single dose method and constructed from recording of isotonic contractions obtained by means of a frontal writing level on a kymograph. Two control dose-response curves were always determined on each vas deferens before the treatment of the tissue with the sensitizing agent. Tissues were sensitized to noradrenaline with amphetamine or cocaine during 20 min. Repetition of dose-response curves at intervals less than 20 min occasionally resulted in erratic responses. (−)-Noradrenaline bitartrate (+)-amphetamine sulphate and cocaine hydrochloride were dissolved in distilled demineralized water which contains 0·02 mM of ascorbic acid. Noradrenaline, cocaine and amphetamine were expressed as molar concentrations of the bases. In some of the animals the vas deferens was denervated according to Birmingham (1967). Fourteen days after surgical sympathectomy the animals were killed and the vas deferens prepared as described.

The dose-response curves to noradrenaline determined on the preparation before and after the exposure to amphetamine 10^{-4} M, and to cocaine (10^{-5} M) and after surgical denervation and amphetamine (10^{-4} M) are shown in Fig. 1. It is apparent that after the treatment with amphetamine the dose-response curve of the preparation to noradrenaline is shifted to the left by more than 2 log units without increase in the maximum control response; this we have found before (Carvalho, Martins & de Moraes, 1970). After treatment with cocaine or surgical denervation, amphetamine shifts the dose-response curve to noradrenaline to the left only by factors of 20 and 18 respectively, although cocaine and surgical sympathectomy increased the maximum control response (Table 1).

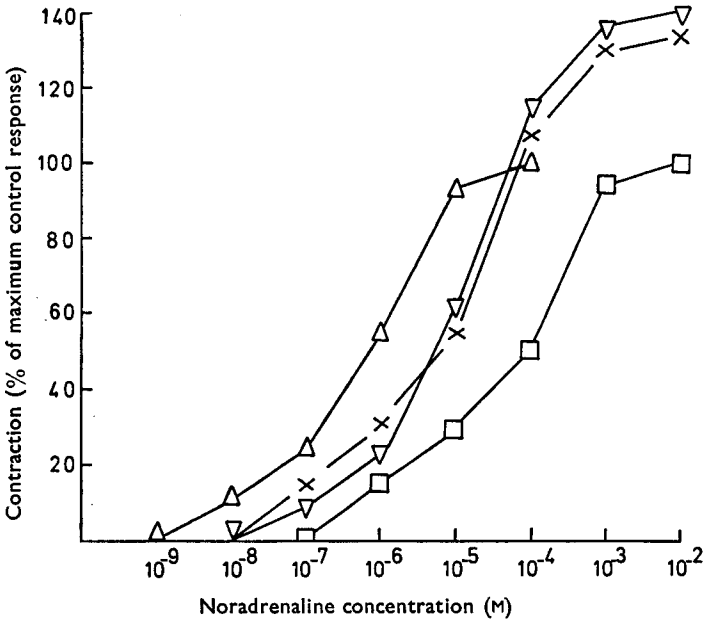

FIG. 1. Dose-response curves of noradrenaline determined in the isolated guinea-pig vas deferens. (□) control; (△) after exposure to 10^{-4} M amphetamine; (▽)after 10^{-5} M cocaine followed by 10^{-4} M amphetamine (×) 2 weeks after surgical denervation followed by 10^{-4} M amphetamine.

TABLE 1. *The effect of various procedures on the response of the guinea-pig isolated vas deferens to noradrenaline*

Agent and procedure	n	EC50 (Mean ± s.e.)	Relative sensitivity to nor adrenaline	Maximum response (mean ± s.e.) mm
Control	10	3·986 ± 0·028	1	48·6 ± 0·6
10^{-4} M Amphetamine	5	6·150 ± 0·035	146	47·4 ± 1·9[a]
10^{-5} M Cocaine	5	4·950 ± 0·080	9·5	123·3 ± 1·1[b]
2 weeks after surgical denervation	8	4·700 ± 0·018	5	120·5 ± 2·6[b]
10^{-5} M Cocaine and 10^{-5} M amphetamine	5	5·300 ± 0·086	20	124·2 ± 1·8[b]
2 weeks after surgical denervation and 10^{-4} M amphetamine	8	5·250 ± 0·015	18	119·4 ± 2:1[b]

n Number of experiments.
[a] Value not significantly different from control ($P > 0·05$).
[b] Values significantly different from control values ($P < 0·05$) EC50 molar concentration of noradrenaline producing 50% of the maximum effect.

The sum of evidence presented strongly favours the conclusion that amphetamine induces presynaptic supersensitivity to noradrenaline in the guinea-pig isolated vas deferens. The sensitizing action of the drug was reduced by cocaine and is dependent on the functional integrity of the adrenergic nerves. It has been suggested that cocaine produces supersensitivity to noradrenaline not only by inhibiting the noradrenaline uptake but also by changing the conformation of the receptor area and thus, probably increasing the efficiency of the drug-receptor complex (Barnett, Greenhouse & Taber, 1968; Reiffenstein, 1968; Varma & McCullough, 1969). In view of these facts it is suggested that the site of the sensitizing action of amphetamine

is presynaptic, there is probably an impairment of the noradrenaline uptake into the adrenergic nerves. Cocaine and surgical denervation inhibit the uptake of noradrenaline but they also seem to sensitize the isolated vas deferens by a "deformation" of the receptor area, thus altering receptor kinetics to allow increased receptor utilization.

Department of Pharmacology and Therapeutics S. DE MORAES
Faculty of Veterinary Medicine, F. V. CARVALHO
University of São Paulo, Brasil. R. D. WEHRLE

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Pentazocine and nikethamide antagonism

Pentazocine, a benzomorphan derivative, is in increasing use for the relief of pain. Like all analgesics it is capable of producing respiratory depression in man and possibly in some other species also. Because pentazocine is itself an opiate antagonist, respiratory depression produced by it cannot be reversed by nalorphine. It therefore seemed worth while to examine the possibility of using nikethamide to reverse the respiratory depression produced by pentazocine.

The respiratory minute volume of rabbits was measured with the aid of the Gaddum Respiration Recorder by methods described previously (Hunter, Pleuvry & Rees, 1968).

In a preliminary trial, pentazocine, 4 mg/kg, produced in rabbits significant respiratory depression in most animals. The administration of nikethamide, 25 mg/kg, produced a sharp increase in respiratory minute volume and a less distinct increase in respiratory rate in animals given 4 mg/kg of pentazocine 7 min previously (Table 1). The simultaneous administration of nikethamide and pentazocine produced significantly less depression of respiratory minute volume, but not of rate, than pentazocine alone. A dose of nikethamide of 25 mg/kg was also capable of producing an increase in respiratory minute volume and rate of respiration in an animal depressed by morphine (Table 1).

These findings point the way to the treatment of an emergency in which the administration of pentazocine produces an unexpectedly severe depression of respiration in the human subject.

Since this work was begun Kallos & Smith (1968) showed that naloxone can reverse the respiratory depression produced by pentazocine in human volunteers, and this finding is amply backed by experimental evidence in animals. Until naloxone