RESEARCH PAPERS

THE PRESSOR ACTION OF GUANETHIDINE IN THE SPINAL CAT

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Guanethidine has a marked pressor action in the spinal cat. Doses of 2–4 mg./kg. produce a greater increase in blood pressure than doses of 8–16 mg./kg. Large doses of guanethidine (16 mg./kg.) inhibit the pressor action of small doses (2 mg./kg.). Guanethidine potentiated the pressor action of noradrenaline but inhibited that of tyramine. The degree of inhibition of tyramine increased with the dose of guanethidine, but was inversely related to the pressor action of guanethidine.

IN the anaesthetised dog or cat guanethidine produced sympathomimetic actions of approximately 45 min. duration (Maxwell, Plummer, Schneider, Povalski and Daniel, 1960; McCubbin, Kaneko and Page, 1961). When the sympathomimetic actions of the drug subsided a prolonged hypotension was observed. This paper describes the pressor action of guanethidine in the spinal cat.

EXPERIMENTAL

Cats were anaesthetised with ether and made spinal as described by Burn (1952). Blood pressure was recorded from the right carotid artery and drugs were injected into a femoral vein.

Drugs: Tyramine hydrochloride, (−)-noradrenaline bitartrate and 2-(octahydro-1-azocinyl)ethyl guanidine sulphate (guanethidine) were dissolved in 0·9 per cent w/v aqueous NaCl before each experiment. Doses have been expressed as weights of base.

RESULTS

Although there was no significant regression of pressor action on dose for guanethidine, a small dose of the drug (2–4 mg./kg.) produced a greater increase in blood pressure than a large dose (8–16 mg./kg.), $P<0{\cdot}001$ (Table I*a* and Fig. 1). In most of these experiments a single injection of guanethidine was made, but when the drug was tested more than once in a cat, the amount injected did not exceed 4 mg./kg. except for the final injection, and injections were separated by intervals of at least 45 min. In one cat a first injection of 4 mg./kg. guanethidine produced a rise in blood pressure of 98 mm. Hg and a second injection of the same dose 45 min. later produced a rise in blood pressure of 95 mm. Hg. In two other experiments, however, 16 mg./kg. guanethidine inhibited the pressor action of a subsequent injection of 2 mg./kg. of the drug, $P<0{\cdot}01$ (Table I*b*).

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In most experiments the pressor actions of tyramine and noradrenaline were recorded before and after the injection of guanethidine. Submaximal doses of tyramine and noradrenaline were injected alternately, the dose of tyramine being selected to produce a rise in blood pressure of between 40 and 80 mm. Hg. When reproducible responses were obtained

TABLE I

EFFECT OF INTRAVENOUS INJECTIONS OF GUANETHIDINE ON SENSITIVITY TO NORADRENALINE AND ARTERIAL BLOOD PRESSURE IN SPINAL PREPARATIONS OF CATS

Numerical values are means ± s.e. of the mean. Number of observations in brackets

	Dose (mg./kg.)	Sensitisation to noradrenaline $\left(\frac{\text{Initial dose noradrenaline}}{\text{equipressor dose after guanethidine}}\right)$	Rise in blood pressure (mm. Hg)
a.	2–4	4·8 ± 0·9 (5)	119·0 ± 6·9 (9)
	8–16	4·6 ± 1·4 (7)	66·2 ± 7·3 (9)
b.	2	—	123·8 ± 9·5 (5)
	2 after prior injection of 16 mg./kg.	—	34·0 ± 2·0 (2)

to these amines guanethidine was injected and the preparation rested until the blood pressure reached a steady level. Half an hour after guanethidine the same dose of tyramine and a reduced dose of noradrenaline were injected and their actions on blood pressure compared with the effects produced by these amines initially. Guanethidine

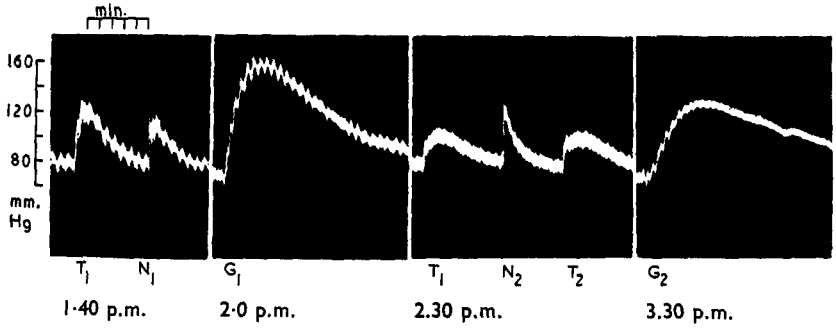

FIG. 1. Arterial blood pressure of spinal cat. The subscripts mark intravenous injections of 250 μg. tyramine (T_1), 2 μg. noradrenaline (N_1), 4 mg./kg. guanethidine (G_1), 0·25 μg. noradrenaline (N_2), 750 μg. tyramine (T_2), and 8 mg./kg. guanethidine (G_2).

potentiated the action of noradrenaline but inhibited that of tyramine, confirming the results of Maxwell, Plummer, Povalski and Schneider (1960). After guanethidine the response to tyramine changed very little with increasing dosage (Fig. 1). The per cent inhibition of the pressor action of tyramine increased with the dose of guanethidine (Fig. 2).

DISCUSSION

McCubbin and others (1961) suggested that the sympathomimetic actions of guanethidine resulted from a release of endogenous catecholamines since the rise in blood pressure and the vasoconstriction in a

denervated perfused hind limb of the dog after guanethidine were abolished with phentolamine or by pre-treatment with reserpine. It has been shown, moreover, in the rabbit and cat that guanethidine selectively depleted heart and spleen noradrenaline (Cass, Kuntzman and Brodie, 1960). However, the sympathomimetic actions of guanethidine were of shorter duration than the depletion of noradrenaline.

The prolonged release of a substance in the body may be mimicked by its infusion. When adrenaline or noradrenaline was infused into an animal for several hours the sympathomimetic actions declined during

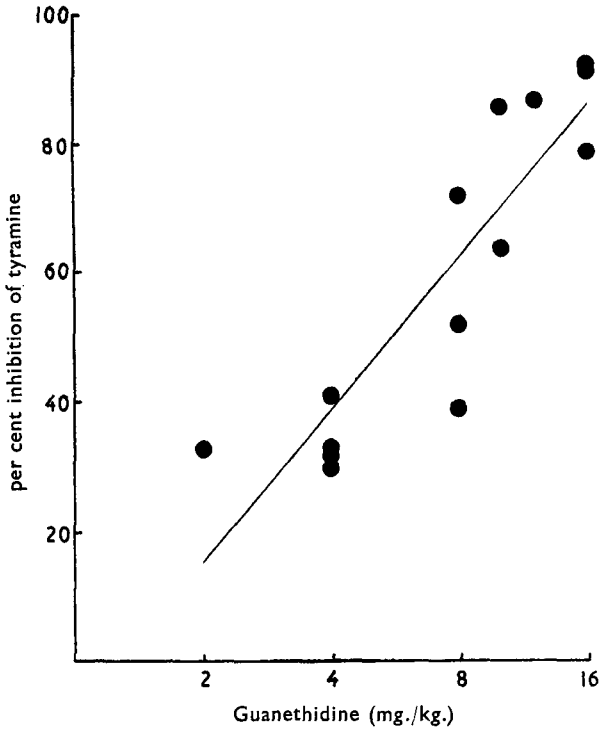

FIG. 2. Inhibition by guanethidine of the pressor action of tyramine in spinal preparations of cats. The calculated regression is significant at the 1 per cent level.

the infusion (Draškoci, Feldberg and Haranath, 1960; Lever, Mowbray and Peart, 1959). The discrepancy between the duration of sympathomimetic actions and the depletion of noradrenaline from heart and spleen did not therefore conflict with the hypothesis of McCubbin and others (1961) that the sympathomimetic actions of guanethidine were the outcome of the release of endogenous catecholamines.

In the present experiments a small dose of guanethidine (2–4 mg./kg.) produced a greater rise in blood pressure than a large dose (8–16 mg./kg.). It seemed unlikely that this was due to an action on catecholamine receptors since large and small doses of guanethidine potentiated the

pressor action of noradrenaline to the same extent (Table Ia). But, it could be explained if the small dose released more catecholamines than the large dose. If this was so, a large dose of guanethidine must inhibit its own action as a catecholamine releaser. The inhibition by a large dose of guanethidine of the pressor action of a small dose of guanethidine lends support to this hypothesis.

The pressor action of tyramine may be produced indirectly by the release of endogenous catecholamines (Lockett and Eakins, 1960a and b). This action would not be seen after a prior release of the amines or in

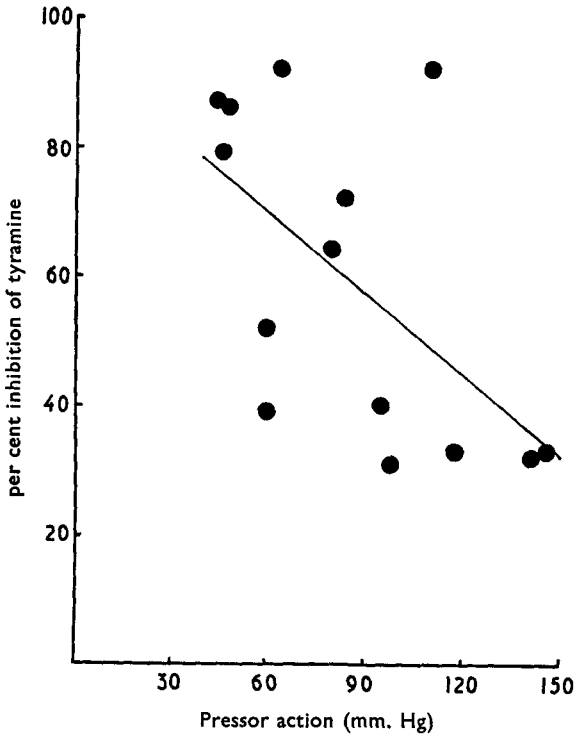

FIG. 3. Relation of pressor action of guanethidine to the ensuing inhibition of tyramine in spinal preparations of cats. The calculated regression is significant at the 5½per cent level.

the presence of an inhibition of catecholamine release. When guanethidine produced a large rise in blood pressure, indicative of a release of catecholamines, the corresponding inhibition of tyramine was small; tyramine was more effectively inhibited by doses of guanethidine which had a smaller pressor effect (Fig. 3). This suggests that inhibition by guanethidine of the pressor action of tyramine was not the outcome of a massive release of catecholamines from the tissues, but was the result of a change in the state of the tissue catecholamines so that their release by tyramine was inhibited.

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