Indirect sympathomimetic actions of dopamine

SIR,—Dopamine, the immediate precursor of noradrenaline, has direct sympathomimetic actions although there are reports which suggest that dopamine acts partly indirectly (Bülbring & Burn, 1938; Bejrablaya, Burn & Walker, 1958; Strömblad, 1960; Farmer, 1965). The acute administration of cocaine, or pretreatment with reserpine, enhances the response of smooth muscle structures to directly acting amines and decreases the response to indirectly acting amines (Tainter & Chang, 1927; Burn & Rand, 1958). Thus the response of the nictitating membrane, heart rate and blood pressure of spinal cats to graded doses of dopamine and their modification by cocaine or reserpine has been determined.

Cats weighing 2–3·5 kg were anaesthetised with halothane and made spinal by the method of Burn (1952). The movements of the right nictitating membrane were recorded with an isotonic, frontal writing point, lever (tension 7 g 15× magnification). Blood pressure was recorded from the right femoral artery with a mercury manometer. The heart rate was measured by a Devices Tachograph unit. Reserpine, 3 mg/kg, was administered intraperitoneally in 20% ascorbic acid 24 hr before the experiment. Cocaine hydrochloride, 5 mg/kg, was given as a slow intravenous injection 30 min before starting the dose-effect curve for dopamine.

The results are shown in Fig. 1. Table 1 compares the effects of cocaine and reserpine on the response of nictitating membrane, heart rate and blood pressure to dopamine, with the effect on response of these tissues to tyramine and noradrenaline taken from Fleming & Trendelenburg (1960).

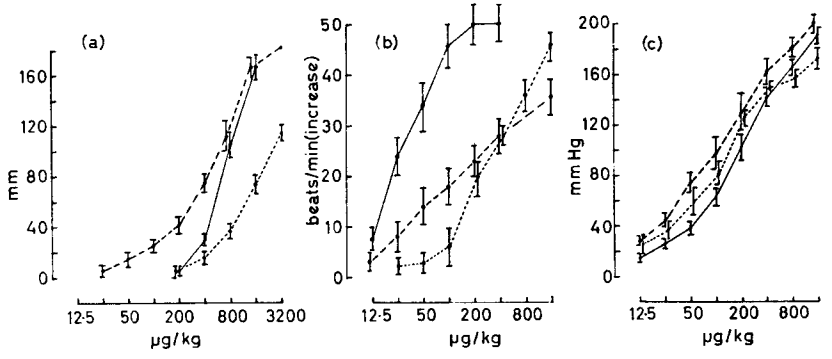

FIG. 1. Dose effect curves for dopamine on (a) nictitating membrane, (b) heart rate, (c) blood pressure of spinal cats. Each response is mean ± s.e. for 4 cats. ●———● control. ●- - - - - ●, resperpine pretreated (3 mg/kg/24 hr). ●— — —●, after cocaine 5 mg/kg i.v.

It is clear from the results in the Table that dopamine must be classified as a sympathomimetic amine with both direct and indirect actions. The extent to which the sympathomimetic response in the intact animal may be attributed to direct or indirect action depends upon the tissue studied. For instance the action of dopamine on the heart and nictitating membrane is mainly indirect whilst the vasopressor action is partly direct and partly indirect.

It has been suggested that dopamine might accumulate in sympathetic nerves and be released as a false transmitter after prolonged inhibition of the enzyme

TABLE 1. EFFECTS OF COCAINE AND RESERPINE ON THE RESPONSE OF CAT NICTITATING MEMBRANE, HEART RATE AND BLOOD PRESSURE TO DOPAMINE COMPARED WITH THE EFFECT OF THE RESPONSE OF THESE TISSUES TO TYRAMINE AND NORADRENALINE (FLEMING & TRENDELENBURG, 1960)

Catechol-amine	Nictitating membrane		Heart rate		Blood pressure	
	Cocaine	Reserpine	Cocaine	Reserpine	Cocaine	Reserpine
Dopamine	Small doses (25–400 μg/kg) Increase. Maximum 4 fold	Decrease Maximum 4 fold	Decrease 8 ×	Decrease 8 ×	Increase 2 ×	Increase 1½
Nor-adrenaline	Increase 30–60 ×	No change	Increase	Increase	Increase 5 ×	Increase 5 ×
Tyramine	Decrease 2 ×	Very marked decrease	Decrease 10 ×	Abolished	Decrease 3 ×	Very marked decrease

monoamine oxidase (Farmer, 1965). Support for the hypothesis that dopamine can act as a false transmitter has since been demonstrated by Thoenen, Haefely, Grey & Hurlimann (1965). These authors observed that dopamine was released from the cat spleen in response to electrical stimulation of sympathetic nerves after treatment with the β-oxidase inhibitor disulphiram. The ability of dopamine to displace noradrenaline, i.e. to act indirectly, may partly account for the fall in noradrenaline content of certain tissues of cats treated with the monoamine oxidase inhibitor nialamide (Davey, Farmer & Reinert, 1963) or tissues of rats treated with the β-oxidase inhibitor disulphiram (Musacchio, Kopin & Snyder, 1964).

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References

Bülbring, E. & Burn, J. H. (1938). *J. Physiol., Lond.*, **91**, 459–473.
Bejrablaya, D., Burn, J. H. & Walker, J. (1958). *Br. J. Pharmac. Chemother.*, **13**, 461–466.
Burn, J. H. & Rand, M. J. (1958). *J. Physiol. Lond.*, **144**, 314–336.
Burn, J. H. (1952). *Practical Pharmacology*, Oxford: Blackwell.
Davey, M. J., Farmer, J. B. & Reinert, H. (1963). *Br. J. Pharmac. Chemother.*, **20**, 121–134.
Farmer, J. B. (1965). *J. Pharm. Pharmac.*, **17**, 640–646.
Fleming, W. & Trendelenburg, U. (1960). *J. Pharmac. exp. Ther.*, **133**, 41–51.
Musacchio, J., Kopin, I. J. & Snyder, S. (1964). *Life Sci.*, **3**, 769–775.
Strömblad, B. C. R. (1960). *Br. J. Pharmac. Chemother.*, **15**, 328–331.
Tainter, M. L. & Chang, D. K. (1927). *J. Pharmac. exp. Ther.*, **39**, 193–207–2038.
Thoenen, H., Haefely, W., Grey, K. F. & Hurlimann, A. (1965). *Life Sci.*, **4**, 2033.