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The response of an isolated artery to sympathomimetic amines

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The rabbit ear central artery preparation responded with contractions to noradrenaline, dopamine, tyramine, octopamine, phenylethylamine, β-phenylethanolamine and periarterial sympathetic nerve stimulation. Noradrenaline, dopamine and nervous stimulation gave monophasic responses. Tyramine and octopamine gave biphasic responses consisting of an initial fast contraction followed by a second contraction of slow onset and long duration. Phenylethylamine and phenylethanolamine also gave biphasic responses, but the second contraction was of quick onset and short duration of action and often merged with the first contraction. Cocaine, superior cervical ganglionectomy and reserpinization reduced the second phase of the contraction to tyramine, octopamine and phenylethylamine. The second phase of the response to phenylethanolamine was reduced by reserpine but not by cocaine or denervation.

A BIPHASIC response of the isolated central artery of the rabbit ear to tyramine has been described by Farmer (1966). It was concluded that this biphasic response consists of a primary phase probably due to a direct α-receptor stimulation and a secondary phase due to release of catecholamines from stores within the sympathetic neurone. The aim of the present investigation was to examine, qualitatively and quantitatively, a number of chemically related sympathomimetic amines on the isolated artery preparation. The responses of the artery to noradrenaline, dopamine, tyramine, octopamine, β-phenylethylamine, β-phenylethanolamine and periarterial nerve stimulation and their modification by sympathetic denervation, reserpine, cocaine are described. Although the responses of this tissue to noradrenaline and tyramine have previously been described they are included in these experiments to enable a direct comparison of all these amines on one tissue to be made.

Experimental

METHODS

Lop-eared or semi-lop-eared rabbits weighing 2·0–5·0 kg were anaesthetized with pentobarbitone 30 mg/kg injected intravenously. The central artery of the ear was cannulated and removed according to de la Lande & Rand (1965). The arterial segment, usually 4–5 cm long, was perfused with McEwen solution delivered from a constant output pump (Watson-Marlow). The artery was also immersed in McEwen solution, both solutions being maintained at 37° and gassed with oxygen 95%, carbon dioxide 5%. Perfusion pressure was measured with a Devices blood pressure transducer recording on a Devices multi-channel recorder. Periarterial nerve stimulation was by means of bipolar platinum electrodes. Trains of impulses of supramaximal voltage and 1·0 msec pulse width were delivered for 5 sec from a Palmer electronic square-wave stimulator.

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Injections of drugs dissolved in McEwen solution were given into a rubber connection close to the artery.

The maximum dose volume used was 0·1 ml. The total doses of the drugs expressed in terms of their salts is given in all figures. Dose-response curves to the sympathomimetic amines and frequency response curves for periarterial nerve stimulation (2, 5 and 10 cycles/sec) were determined on each artery. In experiments using denervated arteries the superior cervical ganglia of the rabbits were removed 7 to 10 days before the animal was used. Reserpine, 2·5 mg/kg was administered intraperitoneally, dissolved in 20% ascorbic acid in distilled water, 19 hr before the arteries were used. In experiments using cocaine the drug was added to the perfusion fluid to give a concentration of 10 μg/ml.

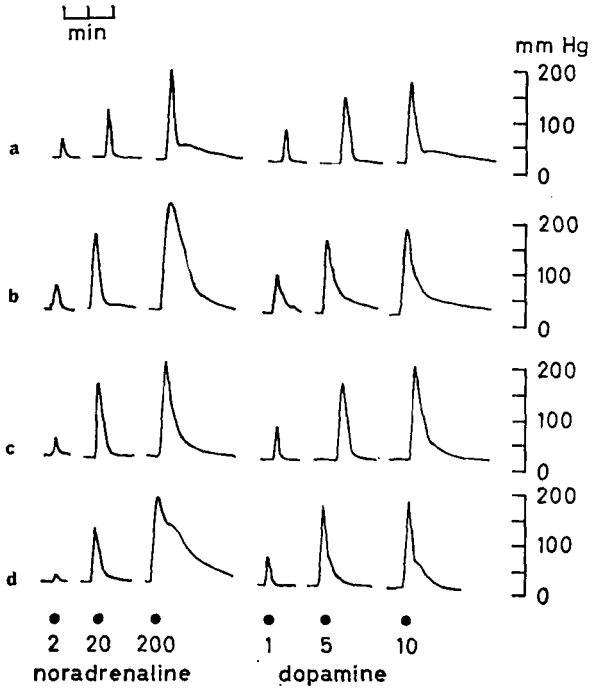

FIG. 1. (a) The response of an isolated central ear artery of the rabbit to noradrenaline (2, 20 and 200 ng) and dopamine (1, 5 and 10 μg). (b) The effect of superior cervical ganglionectomy on responses of an isolated ear artery to the same doses of noradrenaline and dopamine as used in the control experiments. (c) The effect of reserpine pretreatment (2·5 mg/kg 19 hr before experiment) on responses of an isolated ear artery to the same doses of noradrenaline and dopamine as used in the control experiments. (d) The effect of cocaine (10 μg/ml in perfusion fluid) on responses of an isolated ear artery to the same doses of noradrenaline and dopamine as used in the control experiments.

DRUGS

(−)-Noradrenaline bitartrate, dopamine hydrochloride, tyramine hydrochloride, (±)-octopamine hydrochloride, β-phenylethylamine hydrochloride, (±)-β-phenylethanolamine hydrochloride, cocaine hydrochloride

and reserpine. Solutions of all sympathomimetic amines contained 1 μg/ml ascorbic acid as an antioxidant.

RESPONSES OF THE ISOLATED ARTERY TO SYMPATHOMIMETIC AMINES AND SYMPATHETIC NERVE STIMULATION

In 10 arteries, dose-response curves to noradrenaline, dopamine, phenylethylamine, phenylethanolamine, tyramine, octopamine and periarterial sympathetic nerve stimulation at 2, 5 and 10 cycles/sec were obtained. Dopamine produced a monophasic response, like noradrenaline, but was some 50 times less potent. The slope of the dose response curve for dopamine was the same as for noradrenaline (Fig. 1a). Octopamine gave a monophasic response at low doses (5 and 10 μg) and in this respect was approximately 1000 times less potent than noradrenaline.

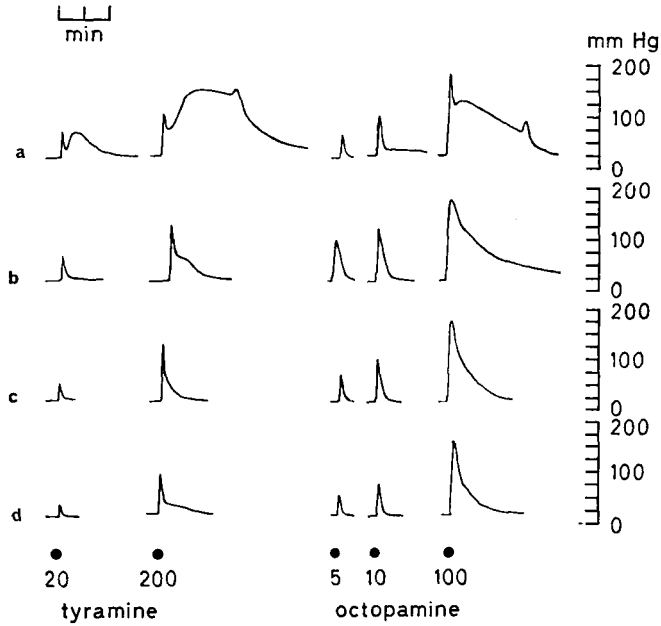

FIG. 2. (a) The responses of an isolated central artery of the rabbit ear to tyramine (20 and 200 μg) and octopamine (5, 10, 100 μg). (b) The effect of superior cervical ganglionectomy on responses of an isolated ear artery to the same doses of tyramine and octopamine as used in the control experiments. (c) The effect of reserpine pretreatment (2·5 mg/kg, 19 hr before experiment) on responses of an isolated ear artery to the same doses of tyramine and octopamine as used in the control experiments. (d) The effect of cocaine (10 μg/ml in perfusion fluid) on responses of an isolated ear artery to the same doses of tyramine and octopamine as used in the control experiments.

At higher dose levels (100 μg) octopamine elicited a biphasic response, the second phase was prolonged but less intense than the first phase (Fig. 2a). Phenylethylamine and phenylethanolamine produced monophasic responses at low dose levels (10 μg) and were of a similar potency to octopamine; however, a biphasic response at higher dose-levels was observed

with phenylethylamine and phenylethanolamine but the response was not clearly differentiated into two phases (Fig. 3a). The second phase was of similar magnitude to the first phase at any given dose-level, but was of shorter duration than that observed with either tyramine or octopamine. The maximum response that could be obtained with phenylethylamine was only 50% of that obtainable with noradrenaline.

THE EFFECT OF SUPERIOR CERVICAL GANGLIONECTOMY ON RESPONSES OF THE ISOLATED ARTERY TO SYMPATHOMIMETIC AMINES AND SYMPATHETIC NERVE STIMULATION

The superior cervical ganglia of four rabbits were removed one week to 10 days before the animals were used for experiments. On the eight arteries, dose-response curves to noradrenaline, dopamine, β-phenylethylamine, phenylethanolamine, tyramine and octopamine were obtained. No responses were obtained to periarterial nerve stimulation at 2, 5 or

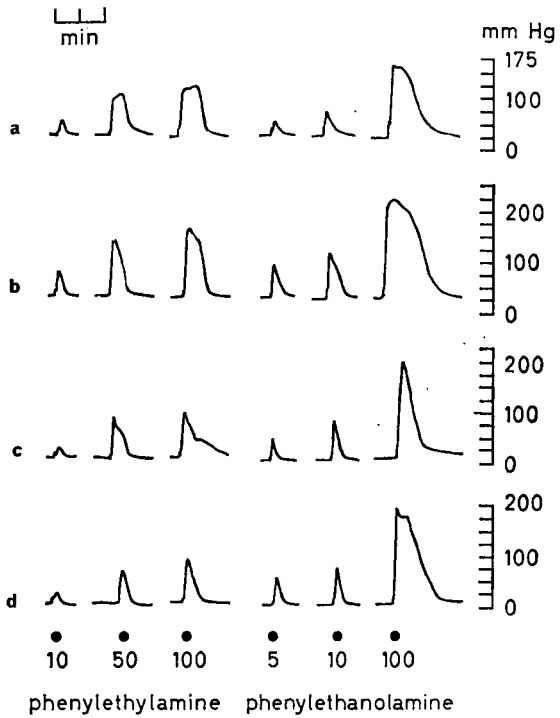

FIG. 3. (a) The response of an isolated central artery of the rabbit ear to phenylethylamine (10, 50 and 100 μg) and phenylethanolamine (5, 10, 100 μg). (b) The effect of superior cervical ganglionectomy on responses of an isolated ear artery to the same doses of phenylethylamine and phenylethanolamine as used in the control experiments. (c) The effect of reserpine pretreatment (2·5 mg/kg, 19 hr before experiment) on responses of an isolated ear artery to the same doses of phenylethylamine and phenylethanolamine as used in the control experiments. (d) The effect of cocaine (10 μg/ml in the perfusion fluid) on responses of an isolated ear artery to the same doses of phenylethylamine and phenylethanolamine as used in the control experiments.

10 cycles/sec (Fig. 4b). Responses to high doses of noradrenaline and dopamine were enhanced by denervation, but in the case of dopamine this potentiation was not significant (Fig. 1b). As described previously, tyramine, octopamine, phenylethylamine and phenylethanolamine elicited biphasic constrictions of the artery preparation. Sympathetic denervation enhanced the first phase of the response to these amines and reduced the second phase, although the reduction in the second phase was not marked with phenylethanolamine (Figs 2b and 3b).

THE EFFECT OF RESERPINE PRETREATMENT ON RESPONSES OF THE ISOLATED ARTERY TO SYMPATHOMIMETIC AMINES AND SYMPATHETIC NERVE STIMULATION

Four rabbits were pretreated with reserpine (2·5 mg/kg) 19 hr before the experiments were made. Dose-response curves were obtained on eight arteries to noradrenaline, dopamine, phenylethylamine, phenylethanolamine, tyramine and octopamine. The responses to noradrenaline, dopamine, and the primary phase of the responses to tyramine, octopamine, phenylethylamine and phenylethanolamine was not significantly altered by pretreatment with reserpine (Figs 1c, 2c, 3c). The second phase of the responses to the above amines were much reduced or

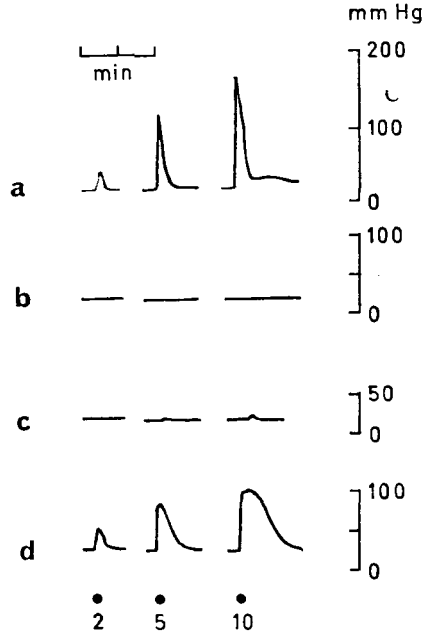

FIG. 4. (a) The response of an isolated central ear artery of the rabbit to periarterial nerve stimulation (2, 5, 10 cycles/sec). (b) The effect of superior cervical ganglionectomy on responses of an isolated central ear artery to the same frequencies of nervous stimulation as used in control experiments. (c) The effect of reserpine pretreatment (2·5 mg/kg, 19 hr before experiment) on responses of an isolated central ear artery to the same frequencies of nervous stimulation as used in control experiments. (d) The effect of cocaine (10 μg/ml) in perfusion fluid on responses of an isolated central ear artery to the same frequencies of nervous stimulation as used in control experiments.

absent (Figs 2c, 3c). The response to sympathetic nerve stimulation was also absent (Fig. 4c).

THE EFFECT OF COCAINE ON RESPONSES OF AN ISOLATED ARTERY TO SYMPATHOMIMETIC AMINES AND SYMPATHETIC NERVE STIMULATION

Eight arteries were perfused with McEwens solution containing 10 μg/ml cocaine hydrochloride, and dose-response curves to noradrenaline, dopamine, phenylethylamine, phenylethanolamine, tyramine and octopamine were determined after perfusion for 2–3 hr. The responses to periarterial nerve stimulation were significantly reduced by cocaine, the effect being greater at higher rates of stimulation (Fig. 4d). Responses to noradrenaline were unaffected in height by cocaine, but increased in duration (Fig. 1d). Responses to dopamine were not altered by cocaine (Fig. 1d). The primary phase of the response to the four other amines was not altered, however the second phase of the response to tyramine, octopamine, and phenylethylamine were much reduced (Figs 2d, 3d). The second phase of the response to phenylethanolamine was not altered by cocaine (Fig. 3d).

Discussion

Three types of response to sympathomimetic amines have been observed on the isolated central artery ear preparation of the rabbit. Firstly, a monophasic response was produced by noradrenaline and dopamine. Secondly, a well differentiated biphasic response was produced by tyramine and octopamine. Thirdly, a poorly differentiated biphasic response in which the second phase of contraction was of rapid onset and short duration, produced by β-phenylethylamine and phenylethanolamine. Phenylethylamine was also of interest because the maximum response obtainable was considerably smaller than that obtainable with noradrenaline.

Superior cervical ganglionectomy, reserpinization and the addition of cocaine to the perfusion fluid all produced significant reductions in the second phase of the response to tyramine, octopamine and phenylethylamine. These results suggest that the second phase of the response to tyramine, octopamine and phenylethylamine is produced by a release of noradrenaline from tissue stores. The evidence for such an action of phenylethanolamine was by no means as clear cut since only reserpine pretreatment affected the response to this amine; denervation and cocaine having little effect. However the decreased response of the artery after reserpine pretreatment confirms the observation of Burn & Rand (1958) who observed that this amine was without action on the perfused hindleg of the reserpine pretreated dog.

The primary phase of the response to all amines used was enhanced by denervation. This may be expected in the absence of an adrenergic innervation. Reserpine potentiated the action of all amines with the exception of β-phenylethylamine and β-phenylethanolamine. The preferential inhibition of uptake of amines into adrenergic nerves by reserpine

can possibly explain these results. No potentiation of the primary phase of the response to any of the sympathomimetic amines was observed in the presence of cocaine. These results are surprising since cocaine is known to inhibit neuronal uptake of sympathomimetic amines. However the method of administration, by the injection into perfusion fluid of the sympathomimetic amines, is not an ideal way to show marked changes in sensitivity since equilibrium conditions cannot occur.

References

Burn, J. H. & Rand, M. J. (1958). *J. Physiol., Lond.*, **144**, 314–336.
de la Lande & Rand, M. J. (1965). *Aust. J. exp. Biol. med. Sci.*, **46**, 639–656.
Farmer, J. B. (1966). *Br. J. Pharmac. Chemother.*, **28**, 340–347.