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The action of tyramine on the rabbit ear artery

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1. The vasoconstrictor potency of extraluminal tyramine on the isolated perfused rabbit ear artery is considerably greater than that of intraluminal tyramine.

2. Chronic denervation, which caused the noradrenergic storage structures in the medial-adventitial border of the artery to disappear, reduces the potency of extraluminal tyramine more than that of intraluminal tyramine so that the difference in potency for the two routes of administration tends to disappear. Cocaine exerts a greater inhibitory effect on responses to extraluminal tyramine than on those to intraluminal tyramine.

3. It is concluded that the indirect component plays a more prominent part in the responses to extraluminal tyramine than in those to intraluminal tyramine. This conclusion is supported by analysis of the diphasic response of the artery to intraluminal injection of tyramine under perfusion conditions which permit intraluminal fluid to mix with the extraluminal fluid. Evidence is presented that the first phase of the response is mediated by intraluminal tyramine, and the second phase by extraluminal tyramine.

The central artery of the rabbit ear displays a marked difference between its sensitivities to intraluminal and extraluminal noradrenaline. Because the sympathetic nerves are distributed exclusively at the border of the media and the adventitia, the difference in sensitivity to intraluminal and extraluminal noradrenaline has been explained in terms of the relative positions of the nerves, and the smooth muscle, in the artery wall (de la Lande & Waterson, 1967).

The distribution of sympathetic nerves also has implications to the action of tyramine on the artery. There is considerable evidence (reviewed by Trendelenburg, 1963) that the sympathomimetic action of tyramine on smooth muscle is largely indirect and that the indirect component is mediated by release of noradrenaline from its storage sites. Intraluminally and extraluminally applied drugs must diffuse through different regions of the artery wall to reach the sympathetic nerves, so the possibility arises that tyramine which is applied to the intima may not achieve the same concentration in the region of the artery containing the sympathetic nerves (that is, the biophase of the noradrenergic storage sites) as tyramine which is applied to the adventitia. To explore this possibility we have compared the vasoconstrictor potencies of intraluminal and extraluminal tyramine on the basis that the vasoconstrictor response to tyramine will depend on the concentration which the drug attains in the biophase of the storage sites.

Farmer (1966) has shown that intraluminal injections of tyramine cause a biphasic constrictor response of the artery, the first phase of which is an effect on the smooth muscle, and the second phase the indirect response mediated by sympathetic nerves. Under the conditions of perfusion used by Farmer, the intraluminally applied drug escapes into the extraluminal fluid bathing the artery. As part of the present study we have investigated the possibility that the two constrictor phases described by Farmer may reflect separate intraluminal and extraluminal actions of tyramine.

Methods

The principle of the method of perfusing the isolated artery of the rabbit ear was that of de la Lande & Rand (1965) in which Krebs bicarbonate solution at 37° C is pumped at a constant rate through the lumen of the artery. The artery is suspended in a 10 ml. organ bath containing Krebs bicarbonate solution. Constriction of the artery causes an increase in perfusion pressure which is recorded by a mercury manometer. Under the conditions employed by de la Lande & Rand, the intraluminal fluid escapes into the extraluminal fluid before draining away through the overflow tube of the organ bath. The modification used in the present study was that of de la Lande, Cannell & Waterson (1966) in which an artery segment, 1–2 cm in length, is taken from the base of the ear where there are no side branches, and is cannulated at its distal as well as the proximal end.

The intraluminal fluid escapes through the distal cannula and does not come in contact with the extraluminal fluid. The artery is suspended vertically in the organ bath, and fixed in position by the proximal (lower) cannula. The artery increases in length as it constricts. To prevent the artery folding or kinking as it lengthened and thus mechanically obstructing flow through the lumen, the upper cannula was not rigidly fixed in position but instead was attached to a writing lever under 0.4–0.8 g tension.

Absence of leakage between the intraluminal and extraluminal fluid compartments was routinely tested at the beginning of each experiment by observing the level of the extraluminal fluid in the organ bath, and at the end of each experiment by perfusing the artery intraluminally with 1% Evans blue dye and examining the extraluminal fluid for the appearance of dye. About one artery in six displayed evidence of leakage, usually through a side branch not detected during dissection; such arteries were rejected. Other points of procedure common to all experiments were: (i) rates of intraluminal perfusion were between 6 and 8 ml./min; these rates were associated with resting levels of perfusion pressures of between 10 and 30 mm mercury; (ii) intraluminal and extraluminal solutions were at 37° C and gassed with 95% oxygen and 5% carbon dioxide; (iii) drugs were added in volumes of 0.05–0.2 ml./10 ml. of intraluminal or extraluminal media.

Because of dead space in the perfusion system, drugs added to the intraluminal reservoir required 35 to 70 sec (depending on the dead space volume and flow rate) to reach the artery. These estimates were based on the time intervals between commencing perfusion of Evans blue 1% and its first appearance in the outflow from the artery. As reported in an earlier study, Evans blue does not attain its final steady concentration in the outflow for a further period of up to 30 sec (de la Lande, Frewin & Waterson, 1967).

In a few experiments, tyramine was injected into the intraluminal perfusion stream immediately proximal to the artery. In such cases injection volumes were between 0.05 and 0.2 ml.

Comparison of responses

The use of the double cannulated artery permits the vasoconstrictor response to tyramine added to the extraluminal bathing medium to be compared with that to tyramine added to the intraluminal perfusing media (through the intraluminal reservoir). In view of our experience that the sensitivity of perfused arteries to noradrenaline changed considerably during the first hour of perfusion after which it remained constant for at least 4 hr, experiments on tyramine were routinely commenced after the artery had been perfused for 1 hr. Intraluminal and extraluminal tyramine was applied alternately to the artery at intervals ranging in different arteries from 10 to 30 min following wash out of the previous dose. Tyramine was allowed to remain in contact with the artery until constriction was maximal; in most arteries periods of 5–6 min sufficed. The ratio of the sensitivities of the artery to intraluminal and extraluminal tyramine was established in a similar fashion to that described for noradrenaline (de la Lande, Cannell & Waterson, 1966; de la Lande, Frewin & Waterson, 1967). Concentration-response curves to intraluminal and to extraluminal tyramine were obtained, and the ratio of the concentrations producing constriction of equal magnitude (the dose ratio) was determined. The dose ratio $\frac{\text{intraluminal tyramine}}{\text{extraluminal tyramine}}$ is referred to as the sensitivity ratio (de la Lande, Frewin & Waterson, 1967); a sensitivity ratio of 10 means that a ten-fold greater concentration of intraluminal tyramine was required to produce responses equal in magnitude to those produced by extraluminal tyramine. The ratio of the sensitivities of two separate arteries—for example, a denervated and a control artery—to the one stimulant, for example, extraluminal tyramine, was also expressed by the corresponding sensitivity ratio. Where the curves under comparison differed in slope, the sensitivity ratio was expressed as the range of the maximum and minimum observed values of the ratio. Where progressive changes in sensitivity to either extraluminal or intraluminal tyramine prevented establishment of concentration-response curves, the sensitivity ratio was estimated at one level of response only (see **Results**).

Denervation

In three experiments, the responses of arteries which had been denervated by removal of the superior cervical ganglion 2–3 weeks previously were compared with the artery from the opposite ear which had not been denervated. Denervation was carried out by the method described by de la Lande & Rand and the effectiveness of denervation was routinely tested by comparing the responses of the denervated and control artery to periarterial electrical stimulation (de la Lande & Rand, 1965).

Drugs

Concentrations of (*l*)-noradrenaline bitartrate are expressed in terms of the base; those of tyramine hydrochloride and cocaine hydrochloride are expressed in terms of the salts.

Results

Nature of responses

The responses to intraluminal and extraluminal tyramine were examined in thirty arteries. In the majority of arteries, the response to extraluminal tyramine

comprised an increase in perfusion pressure which commenced within 10–50 sec of adding the drug to the organ bath and reached a maximum after a further 30–180 sec according to the magnitude of the response. The constriction was either sustained at the maximum value or declined slowly for the period of contact between drug and artery; the perfusion pressure returned to its resting value promptly on washout of drug and only in rare instances did the time for recovery exceed 1 to 3 min. The responses to intraluminal tyramine were similar in shape and time course to those to extraluminal tyramine, with the qualification that the onset was further delayed by the period of time required for the drug to reach the artery from the perfusion reservoir.

The shapes of the responses occasionally varied in that the sustained phase of large responses was interrupted by rapid oscillations in the perfusion pressure. This type of response was observed consistently in five arteries, and was more prominent with intraluminal than extraluminal tyramine. The shapes and time courses of the responses illustrated in Fig. 2, however, were typical of those observed in most arteries. Compared with the responses to noradrenaline, which were described in earlier studies (de la Lande, Cannell & Waterson, 1966; de la Lande, Frewin & Waterson, 1967), those to tyramine were characterized by more gradual attainment of the peak level of constriction.

Sensitivity

The responses to repeated application of intraluminal and extraluminal tyramine at various levels of concentration were examined in twenty-four arteries. In each artery the sensitivity to extraluminal tyramine was considerably greater than that to intraluminal tyramine. The difference in sensitivity was particularly marked in the early stages of perfusion (between the first and second hours of perfusion) at which stage it was a common finding that extraluminal tyramine 2 μg/ml. caused an increase in perfusion pressure of the order of 40–100 mm mercury whereas intraluminal tyramine failed to elicit a response in concentrations of 5 μg/ml. Spontaneous changes in sensitivity occurred in most arteries. These consisted of a decline in sensitivity to extraluminal tyramine, and either no change or an increase in sensitivity to intraluminal tyramine. As a result, the difference between intraluminal and extraluminal sensitivity often tended to become less marked during the course of an experiment. In some arteries, the spontaneous changes in sensitivity prevented establishment of concentration-response curves. In others the sensitivity to one of the stimulants—for example, intraluminal tyramine—was sufficiently steady throughout the perfusion to enable the mean of the first few responses to constant concentrations of the second stimulant (extraluminal tyramine) to be used as a guide to the sensitivity ratio prevailing early in the experiment. In twelve arteries, spontaneous changes in sensitivity were minor and it was possible to base the estimates of sensitivity ratios on concentration-response curves to both intraluminal and extraluminal tyramine. Examples of curves which were considered satisfactory and which included a wide range of responses in two arteries (experiments Nos. 9 and 10 in Table 1) are shown in Fig. 1. It will be noted that extraluminal tyramine is more potent than intraluminal tyramine at all levels of response, despite differences between the slopes and shapes of the curves under comparison. The sensitivity ratios for each of the twelve arteries are summarized in Tables 1 and 2. Sensitivity ratios based on one response level for a further six arteries

are also included in Tables 1 and 2. The latter ratios refer not only to arteries where spontaneous changes in sensitivity vitiated one of the concentration-response curves, but also to arteries in which the response to intraluminal tyramine in the highest concentration tested failed to exceed the level of the smallest response to extraluminal tyramine (for example, Fig. 4). Although the ratios quoted in Tables 1 and 2 range from 1.3 to >50, most fall within the narrower range of 3 to 12. The range shown for estimates on individual arteries is an indication that the concentration-response curves were often not parallel. In these cases the value of the ratio was influenced by the level of response employed in its estimate. It will be noted, however, that the levels of responses on which the ratios in Tables 1 and 2 are based ranged from threshold effects—of the order of 3 mm of mercury—to

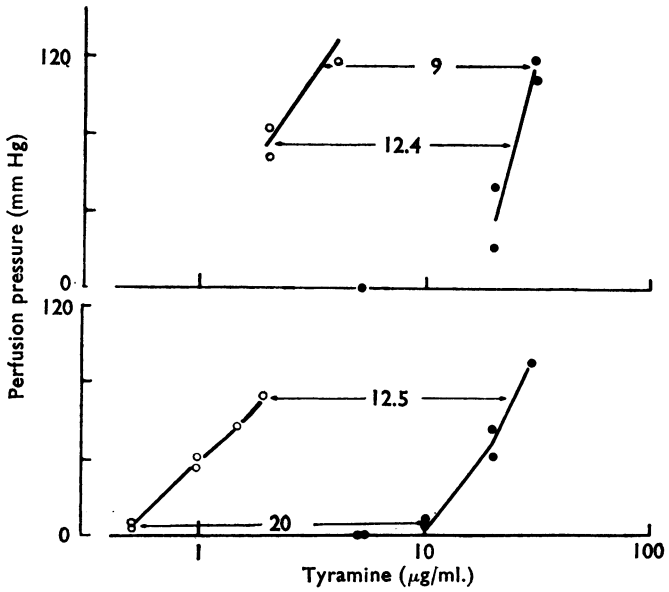

FIG. 1. Concentration-response curves to intraluminal tyramine (●) and extraluminal tyramine (○). Upper and lower graphs refer to arteries Nos. 9 and 10 in Table 1 respectively. The minimum and maximum values of the sensitivity ratios for each artery are shown.

TABLE 1. *Sensitivity ratios.* $\frac{\textit{Intraluminal tyramine}}{\textit{Extraluminal tyramine}}$

Expt. No.	1	2	3	4	5	6
Ratio	1·3–2·8	2·6–3·0	3·1	3·3–4·9	3·3–5·1	2·6–5·0
Response range (mm Hg)	4–50	16–40	76–168	8–82	4–30	3–100
Expt. No.	7	8	9	10	11	
Ratio	3·3–5·3	4·2–4·8	9–12·4	12·5–20	30–37·5	
Response range	24–116	17–76	76–116	5–68	3–20	
Expt. No.	12	13	14	15		
Ratio	5	7·1	10	12·5		
Response level	20	26	8	12		

Note: A sensitivity ratio of 10 means that a ten-fold greater concentration of intraluminal tyramine was required to produce the same response as extraluminal tyramine. Maximum and minimum values of the ratios are given, together with the range of the responses over which the ratios were measured.

168 mm of mercury increases in perfusion pressure. Every innervated artery displayed greater sensitivity to extraluminal than intraluminal tyramine so it must be assumed that this difference in sensitivity was not simply a function of the level of response.

Effect of cocaine

In four arteries cocaine, 1 μg/ml., was added before tyramine, or during the sustained constrictor response to tyramine. The effect of both extraluminal cocaine (added to the organ bath) and intraluminal cocaine (added to the perfusion reservoir) was examined separately in each artery. Cocaine greatly reduced or abolished responses to extraluminal tyramine, but had either a much smaller inhibitory effect, or no effect on those to intraluminal tyramine. The more marked effect on extraluminal tyramine occurred regardless of the route of application of cocaine (Fig. 2).

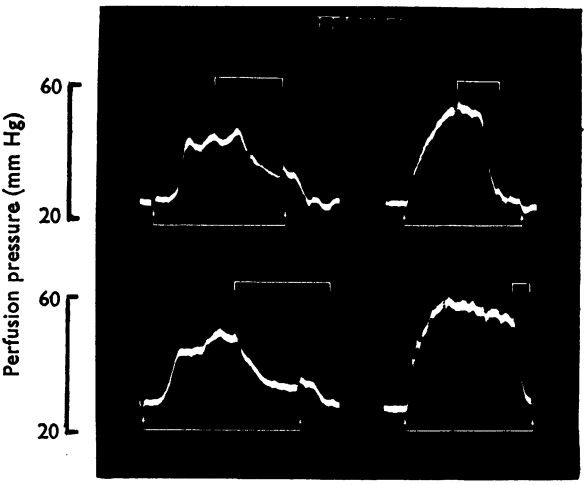

FIG. 2. Responses of an artery to intraluminal tyramine, 5 μg/ml. (top left and bottom left) and extraluminal tyramine, 1.5 μg/ml. (top right and bottom right). The white bars indicate the period of application of cocaine, 1 μg/ml., added intraluminally (top left and right), and extraluminally (bottom left and right). Period of application of tyramine shown as ⌊⌋, and of cocaine shown as ⌐¬. Time trace, min.

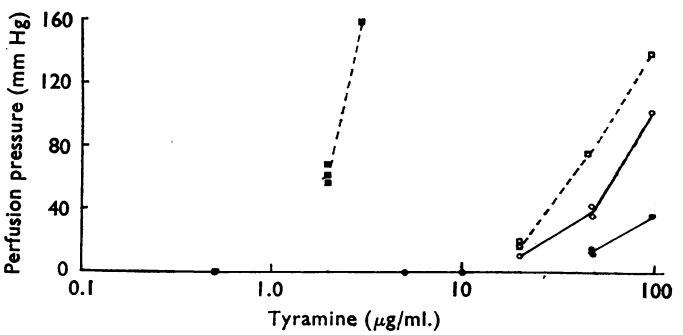

FIG. 3. Concentration-response curves to tyramine of a denervated artery (open symbols) and of its control artery (closed symbols). ——, Intraluminal tyramine; - - - -, extraluminal tyramine.

Denervation

In three experiments, the effects of tyramine on an artery denervated by removal of the superior cervical ganglion 2–3 weeks previously were compared with its effects on the (control) artery from the opposite ear which had not been denervated. Concentration-response curves are illustrated in Fig. 3 and the results are summarized in Table 2. The main feature is that, compared with its action on the corresponding control arteries, extraluminal tyramine is much less active in the denervated arteries so that there is now little difference between sensitivity to intra- and extra-luminal tyramine. Another characteristic difference between denervated and control arteries was the relative slowness of the response of the former to extraluminal tyramine ; the slow response is evident in Fig. 4. In accord with previous observations, the denervated arteries also displayed greatly enhanced sensitivity to extraluminal noradrenaline, but only a small increase in sensitivity to intraluminal noradrenaline compared with the control arteries (Table 2). In order to avoid interaction between the two drugs, noradrenaline was applied to the artery only after sensitivity to tyramine was established.

Response to injected tyramine

Farmer (1966) presented evidence that the response of the ear artery to an injection of tyramine comprised an immediate transient constriction due to a direct effect of the drug on arterial smooth muscle, followed by a prominent secondary constriction which was mediated by the release of noradrenaline (indirect effect). Under the conditions employed by Farmer, drug escapes into the extraluminal fluid

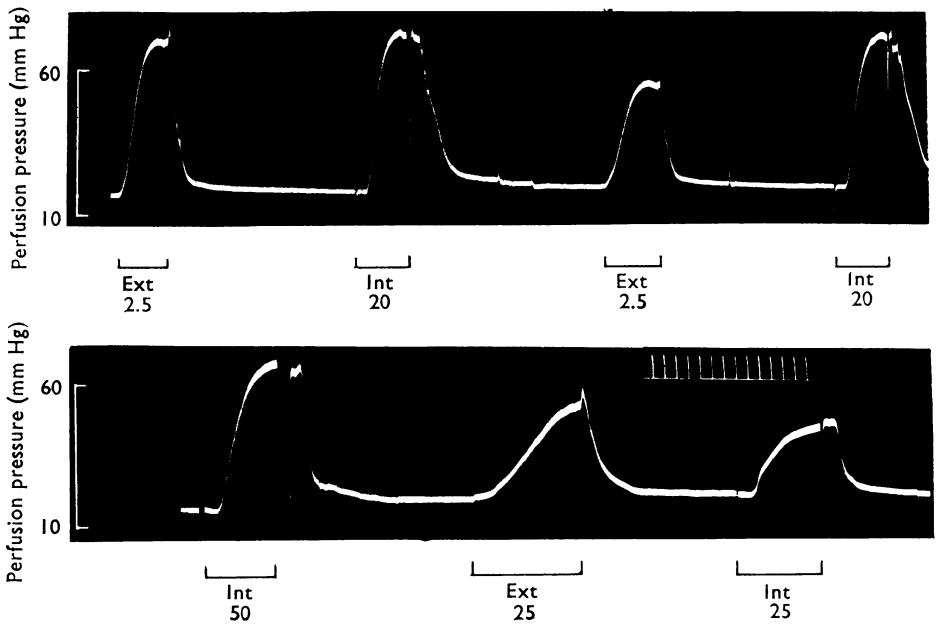

FIG. 4. Responses of a denervated artery (bottom panel) and its control artery (top panel) to extraluminal (EXT) and intraluminal (INT) tyramine in the concentrations shown in μg/ml. Time trace, min.

TABLE 2. *Sensitivity ratios in control and denervated arteries*

	Expt. 1	Intraluminal tyramine / Extraluminal tyramine Expt. 2	Expt. 3
Control	>50 (63)	3·9–6·4 (20–50)	10 (22)
Denervated	1·1–1·8 (15–110)	1·1 (40–130)	0·74–0·9 (18–52)
		Control artery / Denervated artery	
Intraluminal tyramine	2·3–2·4 (12–36)	0·25–0·64 (35–52)	0·95–1·1 (20–70)
Extraluminal tyramine	0·03–0·05 (63–135)	0·11–0·14 (40–85)	0·08 (22)
Intraluminal noradrenaline	1·8 (40)	1·6–2·1 (30–77)	1–1·3 (41–59)
Extraluminal noradrenaline	28–34 (25–42)	42–51 (10–60)	12–12·1 (37–70)

Figures in brackets refer to level of response or range of responses in mm Hg at which sensitivity ratios were measured.
The sensitivity ratios are based on concentrations of the drugs producing responses equal in magnitude (see **Methods**), with the exception that in experiments 1 and 2 intraluminal noradrenaline was given by injection so that the ratios here are based on doses instead of concentrations. A ratio of less than one means that the denervated artery is less sensitive than the control.
The concentrations of drugs employed in the control arteries were: extraluminal tyramine 1–10 μg/ml.; intraluminal tyramine 20–100 μg/ml.; extraluminal noradrenaline 50–400 ng/ml.; intraluminal noradrenaline 5–10 ng ml. (expt. 3 only).
Doses of intraluminal noradrenaline in experiments 1 and 2 were 5–10 ng.

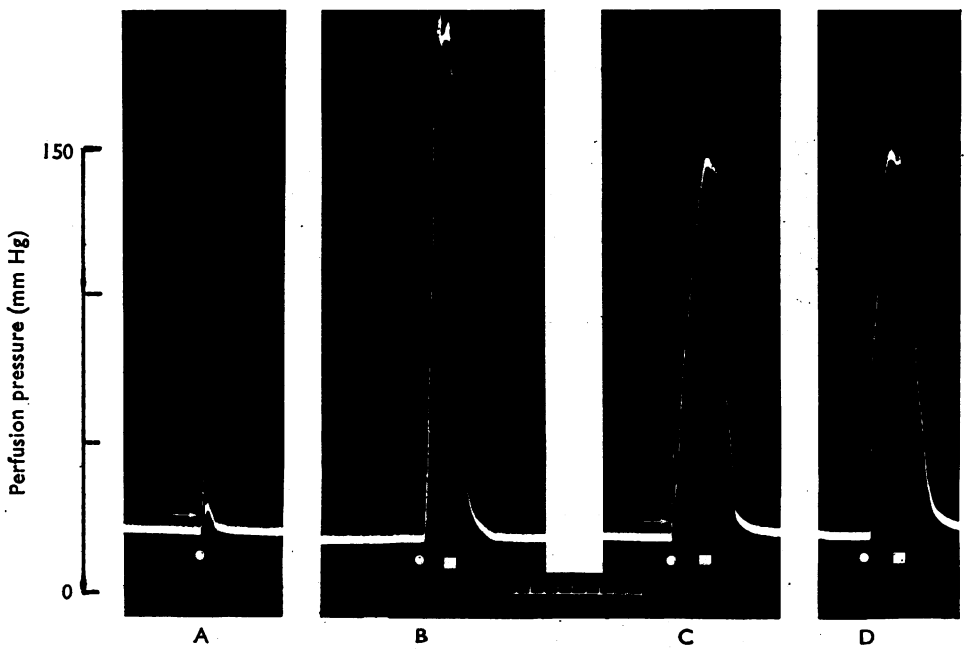

FIG. 5. Effect of tyramine in an artery where mixing of intraluminal perfusate with extraluminal fluid was prevented (A and B), and permitted (C and D). A and C, Injection of 100 μg of tyramine into the perfusion stream. B and D, Addition of 100 μg of tyramine to the extraluminal fluid (extraluminal fluid volume, 10 ml.). ●, Injection or addition of tyramine; ■, wash out of extraluminal fluid to remove tyramine. Time trace, min. Arrows indicate height of injection artefact, that is, the increase in pressure caused by the injection volume 0.1 ml. It is partially obscured by the immediately following initial transient constrictor phase of the response to the tyramine.

following its passage through the lumen of the artery. In view of the high sensitivity of the artery to extraluminal tyramine observed in the present study, it seemed likely that the secondary constriction observed by Farmer was due to the response of the artery to the tyramine which had escaped into the extraluminal fluid. The following observations indicated that this was the case. In each of three arteries which were double cannulated to avoid mixing of intraluminal and extraluminal fluids, the response to an injection of tyramine into the perfusion stream (intraluminal tyramine) was diphasic, the main feature of which was the initial transient constriction. This was extremely rapid in its onset and in its rate of decline from the peak value, and was followed by a small, slower constriction (secondary response) (Fig. 5A). The same amount of tyramine added to the extraluminal fluid caused sustained constriction which was much greater in magnitude (Fig. 5B). After washout of tyramine the outflow of the intraluminal perfusion fluid was returned to the extraluminal fluid by appropriate adjustment of the outflow cannula or by removing the latter cannula entirely. An injection of tyramine into the perfusion stream now caused a diphasic response in which the rapid transient constriction was little different in magnitude to that previously obtained, but the secondary response was now very much greater (Fig. 5C). The latter response was reproduced by adding tyramine to the extraluminal fluid only (Fig. 5D). It may be noted that, under the conditions of perfusion (Figs. 5C and D) the extraluminal fluid was being continuously displaced by the intraluminal fluid.

Discussion

The results indicate that the constrictor potency of tyramine is influenced by its route of application to the artery. Thus extraluminal tyramine is considerably more potent than intraluminal tyramine and is highly sensitive to the effects of cocaine and of denervation. These findings are consistent with an assumption that the noradrenergic storage sites play a major part in the constrictor response to extraluminal tyramine. This assumption also receives support from Farmer's earlier evidence, based on the effects of cocaine and denervation, that the secondary phase of the constrictor response to an intraluminal injection of tyramine is indirectly mediated (Farmer, 1966). We have shown that the secondary phase is greatly reduced when escape of tyramine into the extraluminal fluid is prevented, and that the secondary response is reproduced by the same quantity of tyramine added directly to the extraluminal fluid—that is, the " secondary " phase is largely the response to extraluminal tyramine.

The quantitative importance of the action of tyramine on the storage sites is indicated by the findings that denervation of three arteries was associated with a reduction of sensitivity to extraluminal tyramine ranging from approximately four-fold to more than fifty-fold (Table 2). The residual constrictor activity in the denervated artery presumably represents the direct effect of tyramine—constriction mediated by receptors in the smooth muscle. It is of interest that the denervated arteries displayed little difference in their sensitivity to intraluminal and extraluminal tyramine. Intraluminal tyramine was less sensitive to the effects of denervation and cocaine than extraluminal tyramine so it seems likely that the direct effects are of greater quantitative importance in the constrictor action of intraluminal tyramine.

The greater potency of extraluminal tyramine implies that the concentration which tyramine achieves in the region of the noradrenergic storage sites—medial-adventitial

border—depends on the particular surface of the artery to which tyramine is applied. A possible explanation is that as the tyramine diffuses across the artery from the lumen and approaches the outer border of the media, it is diluted by the tyramine-free solution bathing the adventitia. Such a diluting effect must inevitably occur at some point between the surface of the artery to which the drug is applied and the opposite surface. Other factors contributing to the low activity of intraluminal tyramine may be the presence of permeability or enzymic barriers. The presence of a permeability barrier seems unlikely for several reasons. In the denervated arteries there is little difference between the potencies of intraluminal and extraluminal tyramine, suggesting that the drug attains the same concentration in the media of the denervated artery irrespective of the surface to which it is applied. We have shown in an earlier study (de la Lande, Frewin & Waterson, 1967) that denervation has the same effect on the action of noradrenaline: it tends to eliminate the effect of the route of application to the artery on constrictor potency, again pointing to the probability that when the influence of the nerve terminals is eliminated, drugs diffuse equally well from either surface into the media. We have observed also that intraluminal cocaine potentiates the constrictor action of extraluminal noradrenaline to approximately the same extent as does extraluminal cocaine, and a potentiation of extraluminal noradrenaline by intraluminal cocaine occurs rapidly as though the cocaine penetrates rapidly from the intima to the noradrenaline storage sites (de la Lande, Frewin & Waterson, 1967).

Another possible explanation of the findings on tyramine is that there is an enzymic barrier between the lumen and the adventitia. We have recently demonstrated that extra-neuronal monoamine oxidase is present throughout the media of the ear artery (de la Lande & Jellett, unpublished); in other words, monoamine oxidase occurs in the region when it may be expected to exert a major influence on the amount of tyramine reaching the medial-adventitial border from the lumen of the vessel. Current studies on the interaction between tyramine and monoamine oxidase inhibitors may shed further light on this possibility.

The relation between our findings and those of Luduena (1963) on the whole ear is not clear. Luduena found little difference between the constrictor activity of tyramine in rabbit ears before and after reserpine perfusion, or in ears from control and reserpine-pretreated rabbits, and concluded that the constrictor activity is direct. The ear is a complete vascular bed, however, and it is possible that areas beyond the central artery are more sensitive to the direct effect of tyramine and we have shown elsewhere that the sensitivity of the whole ear and that of the central artery may differ markedly to vasoconstrictor drugs (de la Lande & Waterson, 1968). Furthermore, Luduena used single injections of tyramine, and it is possible that under these conditions very little tyramine escaped into the extracellular space to act on the noradrenergic storage structures. Hence it is possible that the response used by Luduena as a measure of tyramine's action corresponded more to that elicited by intraluminal perfusion in the present study.

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