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Effects of oxyfedrine on isolated portal vein and other smooth muscles

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Summary

1. Oxyfedrine (0·01—1·0 μg/ml), inhibited spontaneous myogenic activity in rat isolated portal vein and carbachol-induced contractions of rat isolated uterus, and relaxed the rabbit duodenum and the guinea-pig tracheal chain preparation. These actions were prevented by the β-adrenoceptor blocking drug alprenolol. Oxyfedrine was a relatively weak β-adrenoceptor stimulant (10–100 times less active than isoprenaline) but its actions were more prolonged.

2. In the same concentrations, oxyfedrine reduced or prevented the inhibition of myogenic activity of the rat portal vein induced by isoprenaline and by repeated doses of oxyfedrine itself, acting as a partial agonist at β-adrenoceptor sites.

3. Oxyfedrine, 1–12 μg/ml increased myogenic activity in the rat portal vein. This effect was not due to direct or indirect stimulation of α-adrenoceptors (because it was unaffected by phentolamine) or to potentiation of acetylcholine or 5-hydroxytryptamine.

4. Oxyfedrine (>20 μg/ml) inhibited spontaneous myogenic activity in the portal vein and relaxed the saphenous vein contracted with noradrenaline. This spasmolytic effect of the drug was not due to β-adrenoceptor stimulation or to inhibition of phosphodiesterase since it was unaffected by alprenolol and by concentrations of imidazole which antagonized the effects of the active phosphodiesterase inhibitor, papaverine. In the portal vein this effect of oxyfedrine was similar to that of the calcium inhibitor iproveratril; some of the effects of oxyfedrine on venous smooth muscle may be mediated through effects on calcium transport.

Introduction

L-3-Methoxy-(1-hydroxy-1-phenylisopropylamino)-propriophenone hydrochloride (oxyfedrine) is an aminoketone synthesized by Thiele, Schimassek & von Schlichtegroll (1966). In isolated hearts it has metabolic and mechanical effects which are similar to those of the β-adrenoceptor stimulants except that, unlike isoprenaline and noradrenaline, oxyfedrine causes increased tolerance to anoxia and inhibition of phosphodiesterase activity (Kukovetz & Pöch, 1970). *In vitro*, heart rate, cardiac output, contractile force, left ventricular dP/dt_{max} and pulmonary arterial pressure and blood flow are increased by oxyfedrine (Thalinger & Lefer, 1970; Turnheim & Kraupp, 1971; Moore & Parratt, 1972; Szekeres, Udvary & Madarász, 1972). Ventricular wall tension and heart size are reduced and local myocardial blood flow increased. In contrast to the effect of catecholamines, myocardial metabolic heat production is decreased (Moore & Parratt, 1972). This suggests an increase in

myocardial efficiency. In further contrast to isoprenaline, oxyfedrine markedly increases blood flow and oxygen consumption in experimental myocardial infarcts (Ledingham, McArdle & Parratt, 1972 ; Parratt & Ledingham, 1972) and possesses membrane stabilizing properties (Papp & Szekeres, 1972 ; Marshall, Ledingham & Parratt, unpublished observations).

The few published studies on the effects of oxyfedrine on isolated smooth muscle have shown that the guinea-pig trachea and rat uterus are relaxed by the drug, that these effects are prolonged and that they are mediated partly by β-adrenoceptors (Beckett & Foster, 1972). Oxyfedrine appears also to be a partial agonist at α-adrenoceptor sites (Osswald & Guimarães, 1971 ; Beckett & Foster, 1972) and to possess a ' papaverine-like ' action (Osswald & Guimarães, 1971). In the present work the effects of oxyfedrine on smooth muscle have been examined, with particular attention to the rat isolated portal vein.

Methods

Rat portal vein, dog saphenous vein circular strips and rabbit duodenum

These smooth muscle preparations were set up in a 10 ml organ bath containing Krebs solution (composition, g/litre: NaCl, 6·9 ; KCl, 0·34 ; $NaHCO_3$, 2·1 ; $MgCl_2$, 0·11 ; NaH_2PO_4, 0·15 ; $CaCl_2$, 0·6 ; dextrose, 1·0) at 37° C. The solution was bubbled with a mixture of 5% carbon dioxide and 95% oxygen. Contractions were recorded isometrically with Ugo-Basile strain-gauges, Devices pre-amplifiers and a two-channel recorder. The resting tensions were 0·5 g except for the rabbit duodenum when it was 1·0 g.

Rat uterus

Uteri were removed from rats in natural oestrous. Each horn was split and the resulting halves were suspended in de Jalon's solution (composition g/litre: NaCl, 9·0 ; KCl, 0·4 ; $NaHCO_3$, 0·5 ; $CaCl_2$, 0·07 ; dextrose, 0·5) bubbled with 95% O_2, 5% CO_2 at 32° C, under 0·5 g tension. Recording was as above.

Guinea-pig tracheal chain

The guinea-pig trachea was removed and cut into rings, four of which were sewn together forming a chain. This was suspended in Krebs–Henseleit solution (composition, g/litre: NaCl, 6·9 ; KCl, 0·33 ; $NaHCO_3$, 2·1 ; $MgSO_4$, 0·29 ; KH_2PO_4, 0·16 ; $CaCl_2$, 0·6 ; dextrose, 1·0 ; ascorbic acid, as an antioxidant, 0·2) bubbled with 95% O_2, 5% CO_2 at 37° C. The tension of the developing spontaneous tone was maintained at 0·5 g and recorded as above. Equilibrium state was achieved after one hour.

Drugs

The drugs used were (−)-noradrenaline hydrochloride (Sigma) ; (−)-isoprenaline bitartrate (Wyeth) ; cocaine hydrochloride (Macfarlane Smith) ; 5-hydroxytryptamine creatine sulphate (B.D.H.) ; alprenolol (Hässle) ; phentolamine mesylate (Ciba) ; acetylcholine chloride, carbachol, procaine hydrochloride and papaverine (B.D.H.) ; iproveratril hydrochloride (Pfizer) ; oxyfedrine hydrochloride (Geigy). Except where otherwise stated, all concentrations quoted in the text are final bath

concentrations, calculated as base. All drugs were made up in 0·9% w/v NaCl solution (saline). The pH of the oxyfedrine dilutions was adjusted to 6·5 before addition to the organ bath.

Results

Preliminary experiments with the rat portal vein showed that oxyfedrine had at least three separate actions on venous smooth muscle. In low concentrations spontaneous myogenic activity was inhibited and frequency slightly increased. With intermediate concentrations a stimulant effect was observed and with still higher concentrations there was pronounced inhibition of activity. These actions are illustrated in Figure 1. The purpose of the investigation was to analyse these three components of activity.

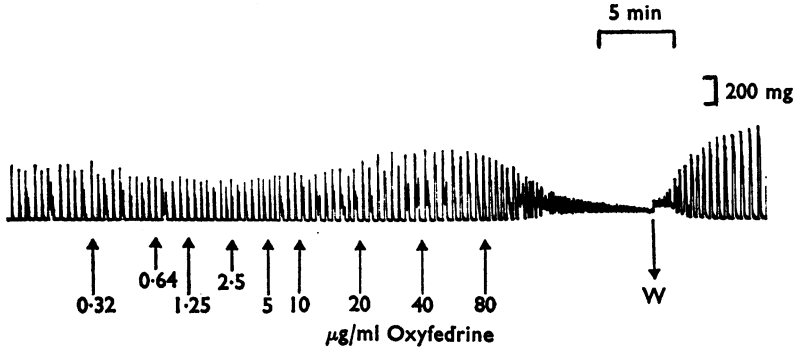

FIG. 1. The effect of increasing concentrations of oxyfedrine on the rat isolated portal vein. W=wash.

Inhibition of the rat portal vein; evidence for interaction with β-adrenoceptors

A total of ninety-six preparations was used. With concentrations of oxyfedrine from 0·01 to 1·0 μg/ml there were dose-dependent decreases in the amplitude of spontaneous activity with increases in frequency of contraction. Responses were rapid in onset, of short duration and similar to the effects of isoprenaline (5–10 ng/ml). They differed from those of procaine (100–250 μg/ml) which decreased both amplitude and frequency. The maximum inhibition of amplitude obtained with oxyfedrine was always less than 25% (Fig. 2) and occurred with a bath concentration of about 0·5 μg/ml. This was in contrast to the inhibitory effect of isoprenaline on spontaneous activity which was complete at a concentration of 20 ng/ml. Inhibition of spontaneous activity induced by oxyfedrine was prevented by the β-adrenoceptor blocking drug alprenolol in a concentration (0·5 μg/ml) which also prevented the inhibitory effect of isoprenaline. Stimulation of spontaneous activity was often observed with these concentrations of oxyfedrine in the presence of alprenolol (Fig. 2).

There was evidence that in this tissue, and in these concentrations, oxyfedrine was acting as a partial agonist at β-adrenoceptors. After oxyfedrine had been washed out of the bath the addition of similar doses of the drug failed to inhibit spontaneous activity and the inhibition induced by isoprenaline (8 ng/ml) was either

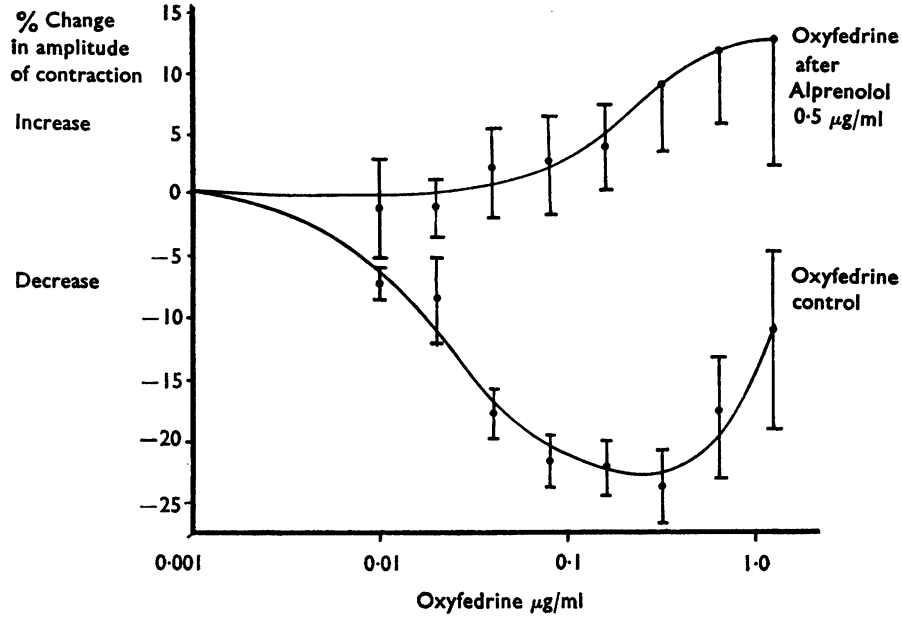

FIG. 2. The effect of alprenolol (0·5 μg/ml) on the relationship between amplitude of the spontaneous contractions of the rat isolated portal vein (16 preparations) and oxyfedrine concentration. Points are means of 6 (upper curve) or 10 (lower curve) observations ± S.E.M.

prevented or reduced. Log-dose response curves for isoprenaline were shifted to the right after oxyfedrine.

It was clear from these experiments with the portal vein that interaction with β-adrenoceptor sites was one component of the smooth muscle actions of oxyfedrine. This component was further examined in a number of other preparations.

(a) *Rabbit duodenum.* Oxyfedrine (0·1–5 μg/ml; 19 preparations) depressed the amplitude of pendular movement in the rabbit duodenum. The effect was similar to that of isoprenaline (Bowman & Hall, 1970), and of the phosphodiesterase inhibitor quazodine (Parratt & Winslow, 1971), in that inhibition was slow in onset and that no overshoot in contraction height was observed on washing. This is in contrast to the effects of α-adrenoceptor stimulation (Bowman & Hall, 1970). It was consistently observed that recovery of pendular movement, after washing out oxyfedrine, was considerably slower than that after isoprenaline. This is illustrated in Figure 3. Since the oxyfedrine response was abolished by alprenolol (0·5 μg/ml) it can be concluded that this action on the rabbit duodenum is mediated through β-adrenoceptors, which in this preparation have been classified as β_1. Parallel log-dose response curves for isoprenaline and oxyfedrine ($P>0·8$) were consistent with both drugs acting at β-adrenoceptors. Oxyfedrine was about ten times less active than isoprenaline.

(b) *Rat uterus.* In 6 preparations sub-maximal contractions induced by carbachol (0·2–0·8 μg/ml) were almost completely inhibited by both oxyfedrine (0·8 μg/ml) and by isoprenaline (0·01 μg/ml). Oxyfedrine was about 100 times less active than isoprenaline on this preparation and the effect of both drugs was prevented by the prior administration of alprenolol (0·05 μg/ml). The carbachol-induced contraction recovered after a single washing of isoprenaline from the

tissue but recovery from oxyfedrine was considerably slower and required several washings.

(c) *Guinea-pig tracheal chain.* Oxyfedrine (6 preparations) inhibited spontaneous muscle tone in concentrations from 0·1 to 3·2 μg/ml. Oxyfedrine was about 100 times less active than isoprenaline and the effects of both drugs were

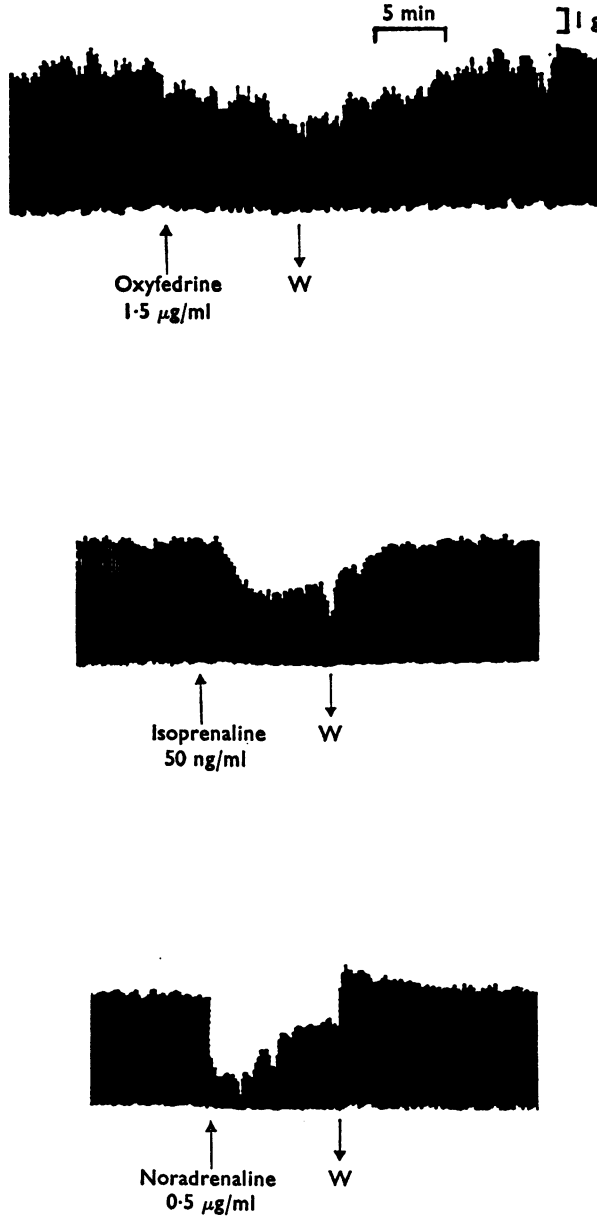

FIG. 3. The effects of (from above) oxyfedrine (1·5 μg/ml), isoprenaline (50 ng/ml) and noradrenaline (0·5 μg/ml) on the rabbit isolated duodenum. In contrast to noradrenaline, the inhibition produced by oxyfedrine and isoprenaline was slow to develop and there was no overshoot on washing. (W=wash). Recovery of spontaneous activity was much slower after oxyfedrine than after isoprenaline.

prevented by alprenolol (0·5 μg/ml). Recovery of tone after oxyfedrine relaxation took more than 2 hours. Recovery after maximum isoprenaline relaxation (which occurred with a bath concentration of 16 ng/ml) took only 15–20 minutes.

The stimulant effect of oxyfedrine on the rat portal vein

In concentrations of 1–12 μg/ml (or less in the presence of alprenolol) oxyfedrine increased the amplitude of the spontaneous contractions of the rat portal vein (Fig. 1). The frequency of spontaneous activity was slightly reduced. This response was similar to that produced by acetylcholine (0·15 μg/ml) and noradrenaline (1 μg/ml), except that stimulant doses of these two agonists also increased frequency of contraction and elevated the baseline. Oxyfedrine-induced stimulation of the rat portal vein was relatively slow in onset, with a maximum effect after a tissue contact time of 5 to 8 min and was not affected by phentolamine in a concentration (2 μg/ml), which prevented the increase in spontaneous activity induced by noradrenaline.

There is some evidence (Grobecker, Hellenbrecht, Lemmer, Palm & Schmid, 1972; Westermann, Neuvonen, Onken & Vapaatalo, 1972) that part of the effect of oxyfedrine on the cardiovascular system is mediated through the release of noradrenaline. For example, bethanidine reduces the increase in heart rate and left ventricular dP/dt_{max} which result from the administration of oxyfedrine to anaesthetized cats (Moore & Parratt, unpublished observations). Despite the fact that oxyfedrine-induced stimulation of spontaneous activity in the rat portal vein was not prevented by low doses of phentolamine, it was decided to see if responses to noradrenaline could be potentiated by oxyfedrine in this tissue as they are in the isolated rat vas deferens (Mackenzie, unpublished observations). Whereas the effect of noradrenaline was markedly potentiated by cocaine (1–10 μg/ml), no such potentiation was observed with oxyfedrine in eight preparations with concentrations up to 50 μg/ml.

The effect of oxyfedrine on the contraction of the portal vein induced by acetylcholine (0·15 μg/ml), was investigated in four preparations. No potentiation was observed with concentrations of oxyfedrine up to 10 μg/ml. 5-Hydroxytryptamine (0·15 μg/ml), which stimulates this preparation, was also not potentiated by oxyfedrine (10 μg/ml).

The inhibitory effect of high concentrations of oxfedrine

When the concentration of oxyfedrine was increased above 20 μg/ml a marked inhibition of the amplitude of spontaneous contractions of the portal vein resulted (Fig. 1). This was associated with an increase in frequency and was unaffected by alprenolol (0·5 μg/ml). Kukovetz & Pöch (1970) have shown that, at very high concentrations (10^{-3}M), oxyfedrine inhibits phosphodiesterase. If this action was responsible for the marked inhibition of myogenic activity in the portal vein, one would expect it to be reversed by imidazole. In seven preparations imidazole (300 μg/ml) did not antagonize the inhibition produced by oxyfedrine (50 μg/ml), although imidazole (300 μg/ml) antagonized inhibition produced by the active phosphodiesterase inhibitor, papaverine (10 μg/ml; Fig. 4).

An additional piece of evidence that makes it unlikely that the spasmolytic effect of oxyfedrine in this preparation is due to inhibition of phosphodiesterase is that oxyfedrine never potentiated, at any dose level, the effects of isoprenaline.

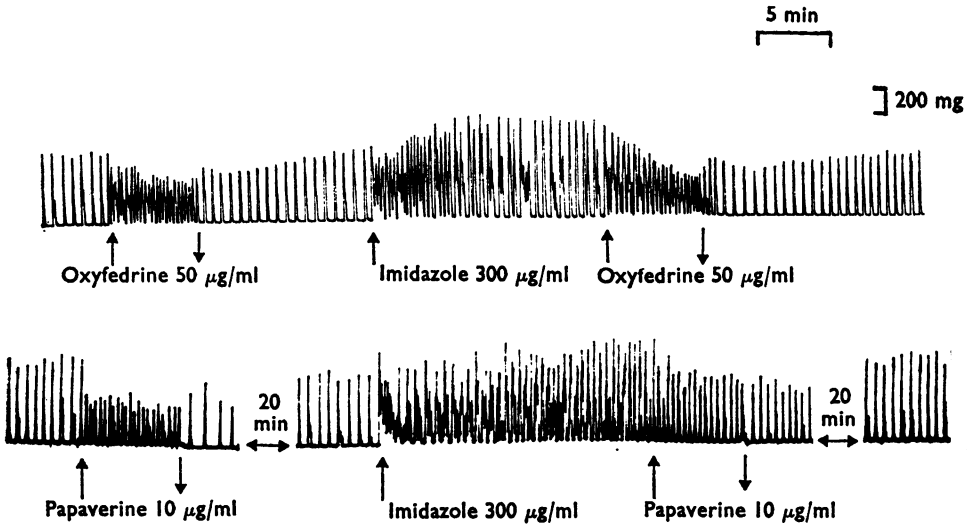

FIG. 4. Failure of imidazole (300 μg/ml) to influence the inhibitory action of a high concentration (50 μg/ml) of oxyfedrine (top trace) whilst antagonizing the inhibitory effect of the phosphodiesterase inhibitor papaverine (10 μg/ml, lower trace) on the rat isolated portal vein.

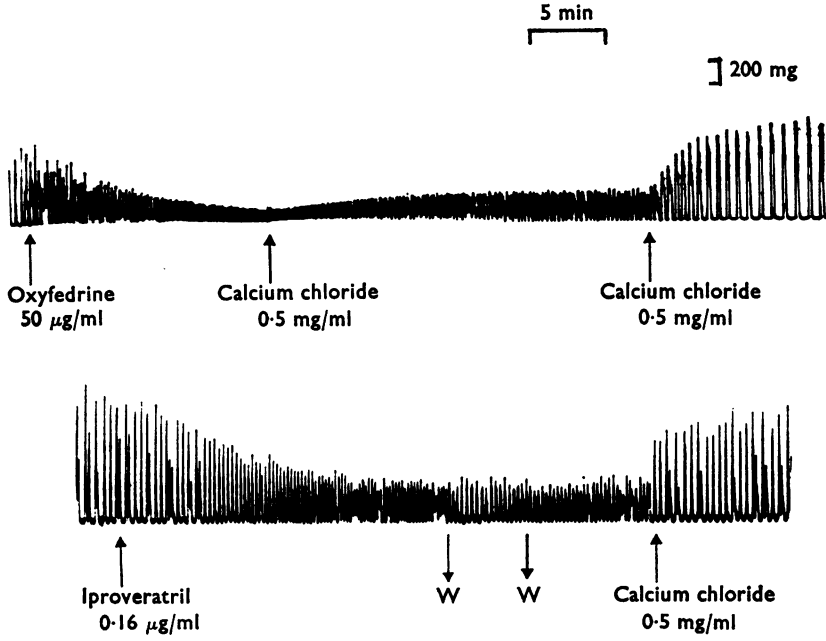

FIG. 5. The effect of raising the calcium concentration (×1·8) on the inhibitory response of oxyfedrine (50 μg/ml, top trace) and of iproveratril (0·16 μg/ml, lower trace) on the rat isolated portal vein. (W=wash.)

In five portal vein preparations the effect of iproveratril (0·02–0·5 μg/ml), a known inhibitor of calcium influx into mammalian cardiac muscle fibres (Fleckenstein, 1971), were examined. The effects (Fig. 5) were similar to those observed with high concentrations of oxyfedrine (20–80 μg/ml). There was a decrease in tension and an increase in the frequency of contractions with an iproveratril con-

centration of 0·16 μg/ml. When the $CaCl_2$ concentration was increased by 0·5 mg/ml to higher levels (1·1 to 1·6 mg/ml) the effects of both iproveratril and oxyfedrine were reversed (Fig. 5).

A spasmolytic effect of oxyfedrine was also demonstrated in a vein preparation which does not usually possess spontaneous activity or inherent tone. Thus in concentrations up to 40 μg/ml, oxyfedrine (except in one preparation when a slight contraction occurred) had no effect on the dog saphenous vein (11 preparations). However, contractions induced by noradrenaline (0·2–0·4 μg/ml) could be antagonized both by isoprenaline (0·02 μg/ml) and by oxyfedrine (0·1–3·0 μg/ml) when these substances were given either before noradrenaline, or at the height of the noradrenaline-induced contraction. The effect of isoprenaline could be prevented by alprenolol (0·05 μg/ml) and this is evidence for the presence of β-adrenoceptors in this preparation. In contrast, oxyfedrine antagonism of noradrenaline contraction was not prevented by similar concentrations of alprenolol. A further point of difference between isoprenaline and oxyfedrine in this preparation was the considerable prolongation of action of the aminoketone.

Discussion

These experiments demonstrate that oxyfedrine has at least three distinct actions on isolated smooth muscle. Firstly, it is a partial agonist at β-adrenoceptor sites. Like isoprenaline, it inhibited spontaneous activity in the portal vein, inhibited carbachol-induced contractions of the rat uterus, relaxed the rabbit duodenum and inhibited spontaneous tone in the guinea-pig tracheal chain preparation. Each of these actions was prevented, as were those of isoprenaline, by the β-adrenoceptor blocking drug alprenolol. Oxyfedrine was 10 to 100 times less active than isoprenaline, but its action was considerably more prolonged and it was much more difficult to obtain full recovery on washing. The reason for this persistent agonist action at β-adrenoceptor sites (guinea-pig trachea, rabbit duodenum and rat uterus) is not clear but is probably related to the high lipophilic property of the methoxypropriophenone part of the molecule (Thiele *et al.*, 1966). This leads to marked tissue accumulation (Beckett & Foster, 1972).

In concentrations similar to those that stimulated β-adrenoceptors oxyfedrine, in the rat portal vein, reduced or prevented the inhibition of spontaneous activity induced by both isoprenaline and by repeated doses of oxyfedrine itself. The antagonism was specific since nitrite inhibition was unaltered and log-dose response curves for isoprenaline were shifted to the right (indicative of competitive antagonism). In the portal vein, oxyfedrine acted as a partial agonist at β-adrenoceptor sites, where these receptors have been classified as β_2 (Mackenzie, unpublished observations). A β-adrenoceptor blocking action of oxyfedrine has also been demonstrated in the guinea-pig trachea and rabbit duodenum (Beckett & Foster, 1972), in isolated atrial and perfused heart preparations (Bosse & Schaum, 1969 ; Osswald & Guimarães, 1971) and in the femoral vascular bed (Sakai, 1970).

With concentrations rather higher than those required to stimulate β-adrenoceptors in the portal vein, oxyfedrine increased the amplitude of spontaneous contractions. This effect, which was slow in onset, could be demonstrated with rather lower concentrations of oxyfedrine in the presence of alprenolol (Fig. 2). This stimulation of portal venous smooth muscle is unlikely to be due to potentiation of

endogenously released noradrenaline since oxyfedrine, unlike cocaine, failed to potentiate the effects of noradrenaline. In high concentrations, isoprenaline also increases spontaneous activity in the portal vein (Johansson, Jonsson, Axelsson & Wahlström, 1967 ; Parratt & Winslow, 1971). This is an effect at α-adrenoceptor sites and is prevented by phenoxybenzamine (Johansson *et al.*, 1967). Because the increase in activity observed with oxyfedrine was not prevented by phentolamine in a concentration which abolished the response to exogenous noradrenaline, it is unlikely that oxyfedrine's stimulant effect on the portal vein is mediated through α-adrenoceptors. In other preparations, oxyfedrine has been reported to possess weak anticholinesterase activity (Sakai, Akima & Matsushita, 1972) and also to inhibit the uptake of 5-hydroxytryptamine by human thrombocytes (Grobecker *et al.*, 1972). Potentiation of acetylcholine and 5-hydroxytryptamine stimulant responses on the rat portal vein were not observed with concentrations of oxyfedrine which markedly increased inherent activity. It is unlikely, therefore, that this stimulant effect of oxyfedrine is mediated through either of these agents.

In still higher concentrations (above 20 μg/ml) oxyfedrine inhibited the amplitude of spontaneous contractions of the portal vein, an effect which could not be prevented by β-adrenoceptor blockade. An alprenolol-resistant and prolonged spasmolytic effect was also demonstrated on the saphenous vein. We could find no evidence of phosphodiesterase inhibition by oxyfedrine, the responses being unaffected by imidazole in concentrations which antagonized the response to the active phosphodiesterase inhibitors quazodine (Parratt & Winslow, 1972) and papaverine. However, there was some similarity between the effects on the portal vein of high concentrations of oxyfedrine and those of iproveratril. With both drugs there was a decrease in tension and an increase in frequency of contractions. Iproveratril has been shown by Fleckenstein (1971) to inhibit excitation-contraction coupling in cardiac muscle, probably by blocking Ca^{++} channels in the fibre membrane. In guinea-pig taenia coli and portal venous preparations, Golenhofen & Lammel (1972) have recently shown that iproveratril suppressed electrical and mechanical activity in parallel and that these effects were similar to those of calcium removal. These authors concluded that in smooth muscle the mechanism of action of iproveratril is similar to that in heart muscle. In the present experiments the effects of both iproveratril and of oxyfedrine could be reversed by raising the external calcium concentration. There is some direct evidence (Noack & Greeff, 1971) that oxyfedrine inhibits the uptake of calcium into heart mitochondria. Although the effects of drugs on calcium accumulation by mitochondria are small compared with those on calcium uptake by microsomes (Kübler & Shinebourne, 1971), such a general effect of oxyfedrine on calcium transport could explain both the stimulant and spasmolytic effects of the drug on venous smooth muscle, particularly as longitudinal muscle in the rat portal vein has an abundance of mitochondria (Ts'ao, Glagov & Kelsey, 1970). By decreasing calcium uptake to storage sites within the smooth muscle cell, oxyfedrine would, initially, make more calcium available for the contraction and relaxation processes. This would increase tension, though not necessarily frequency of contractions. If, in addition, calcium influx across the cell membrane were inhibited (as it is by iproveratril), this would eventually result in decreased activity and a reduction in muscle tension. These are precisely the effects seen with oxyfedrine. Such a mechanism would also be one explanation for the decrease in contractile force seen with large doses of oxyfedrine in the cat papillary muscle preparation (Thalinger & Lefer, 1970).

These results may contribute to an understanding of the mechanism by which oxyfedrine decreases left ventricular end-diastolic pressure in anaesthetized, but essentially normal, experimental animals (Moore & Parratt, 1972) and in dogs following acute ligation of a branch of the left coronary artery (Ledingham *et al.*, 1972; Marshall, Ledingham & Parratt, unpublished). Although much of this effect is presumably secondary to myocardial stimulation, it could in part be due to a dilator effect of oxyfedrine on capacitance vessels.

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