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Actions of quazodine (MJ1988) on smooth muscle

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Summary

1. Quazodine (MJ1988 ; 6,7-dimethoxy-4-ethyl-quinazoline) relaxed a variety of vascular and extravascular smooth muscle preparations and antagonized, non-competitively, several substances which contract smooth muscle.

2. This activity was not due to β-adrenoceptor stimulation or to α-adrenoceptor blockade.

3. On the rabbit duodenum, the inhibitory effect was qualitatively similar to that of theophylline and was antagonized by the phosphodiesterase potentiator, imidazole.

4. The activity of quazodine was similar to, but up to 18 times greater than, that of theophylline and it is suggested that at least part of its activity on vascular and extravascular smooth muscle is due to inhibition of phosphodiesterase.

Introduction

Quazodine (MJ1988 ; 6,7-dimethoxy-4-ethyl-quinazoline) is one of a series of alkyl or aralkyl substituted quinazolines with cardiac stimulant and bronchodilator properties (Lish, Cox, Dungan & Robbins, 1964). In experimental animals, the administration of quazodine results in pulmonary and coronary vasodilatation, an increase in cardiac output and a reduction in peripheral vascular resistance (Aviado, Folle & Pisanty, 1967 ; Carr, Cooper, Daggett, Lish, Nugent & Powers, 1967 ; Parratt & Winslow, 1971). Amer & Browder (1971) showed that quazodine is a potent inhibitor of the phosphodiesterase responsible for converting cyclic adenosine 3′,5′ monophosphate to 5′ adenosine monophosphate. In the experiments described in this paper, the effects of quazodine on several smooth muscle preparations were investigated. Theophylline was used for comparison since, in broken cell preparations, it also inhibits phosphodiesterase (Butcher & Sutherland, 1962).

Methods

Unless otherwise stated, all preparations were set up in a 5 ml organ bath and the bathing solution were gassed with a mixture of 5% carbon dioxide in oxygen.

Guinea-pig vas deferens

The tissue was set up in a 100 ml organ bath containing Krebs solution (composition, g/l.: NaCl, 6·9 ; KCl, 0·34 ; $NaHCO_3$, 2·1 ; $MgCl_2$, 0·11 ; NaH_2PO_4, 0·15 ; $CaCl_2$, 0·06 ; glucose, 1·0). The bath temperature was maintained at 32° C to avoid spontaneous activity. Contractions were recorded on smoked paper using a strain-

gauge transducer and a moving coil galvanometer (Ugo Basile). The resting tension was 1 g. The tissue was stimulated transmurally with platinum electrodes using the method described by Birmingham & Wilson (1963) who demonstrated that responses to transmural stimulation are due mainly to excitation of postganglionic adrenergic fibres. Rectangular pulses of 0·5 ms duration at 5–50 Hz and at supramaximal strength were applied until a maximum response was obtained (from 5 to 45 s). Five minutes were allowed from the end of one stimulation period to the start of the next.

Cat tracheal chain

The technique used was that of Akasu (1952). Three rings of approximately 3 mm width were cut from each trachea and tied together to form a chain which was set up in an organ bath containing Krebs solution. The bath temperature was 37° C and a tension of 0·5 g was applied to the tissue. Since the tracheal chains had very little tone, contractions were produced with acetylcholine, and the inhibitory drugs were added to the bath before, or during, the effect of acetylcholine.

Rat vas deferens

The vasa deferentia were removed from rats weighing 200–400 g. They were suspended in Tyrode solution (composition, g/l.: NaCl, 8·0 ; KCl, 0·2 ; $MgCl_2$, 0·1 ; $CaCl_2$, 0·2 ; NaH_2PO_4, 0·05 ; $NaHCO_3$, 1·0 ; glucose, 1·0), which was maintained at 32° C to avoid spontaneous activity. A tension of 1 g was applied to the tissue.

Rabbit aortic strip

Adult Dutch strain rabbits of either sex were used. The descending aorta was cut spirally to produce lengths of smooth muscle approximately 3 mm wide and 3 cm long, and these were suspended in Krebs solution at 37° C. A resting tension of 3 g was applied to the tissue. This preparation has been described in detail by Furchgott & Bhadrakom (1953).

Guinea-pig ileum

The ileum was removed from male guinea-pigs weighing 400–900 g, and pieces of approximately 3 cm length were cut from the distal region. The tissue was suspended in Tyrode solution maintained at 37° C. A tension of 0·5 g was applied and isotonic contractions were recorded on smoked paper by means of an isotonic frontal writing lever.

Rat uterus

Uteri were removed from rats previously injected with stilboestrol (0·1 mg/kg) and suspended in de Jalon's solution (composition, g/l.: NaCl, 9·0 ; KCl, 0·4 ; $NaHCO_3$, 0·5 ; $CaCl_2$, 0·07 ; glucose, 0·5) at 32° C. A tension of 0·5 g was applied to the tissue and isotonic contractions were recorded on smoked paper by means of a frontal writing lever.

Rabbit duodenum

Segments approximately 3 cm long were suspended in Krebs solution at 37° C. A tension of 3 g was applied to the tissue to prevent the development of background

tone. Drug responses consisted of alterations in pendular movement without a concomitant alteration in the baseline (Lum, Kermani & Heilman, 1966). Pendular movements were recorded on smoked paper either isometrically or isotonically by means of a strain gauge and a moving coil galvanometer. No qualitative differences were observed between the results obtained with the two types of recording and, therefore, no distinction has been made in describing the results.

Rat portal vein

Portal veins were removed from female rats weighing 200–500 g and immersed in Krebs solution. The temperature was maintained at 37° C, a tension of 0·5 g was applied to the tissue and spontaneous contractions were recorded isometrically on smoked paper.

Drugs used were (−)-adrenaline hydrochloride, (−)-noradrenaline hydrochloride, (−)-phenylephrine hydrochloride and imidazole (Sigma); (−)-isoprenaline bitartrate (Wyeth); theophylline, acetylcholine chloride, histamine dihydrochloride, serotonin creatine phosphate and potassium chloride (B.D.H.); phentolamine mesylate (Ciba); quazodine (Mead Johnsohn); alprenolol (Hassle). Except where otherwise stated, all drug concentrations are expressed as μg/ml (final bath concentrations).

Results

Quazodine (1·0 μg/ml or greater) induced relaxation in all the smooth muscle preparations studied.

Evaluation of the inhibitory action of quazodine

Cumulative log dose-response curves to acetylcholine (on cat trachea) and to noradrenaline (on rat vas deferens and rabbit aortic strip) were constructed in the absence and presence of quazodine. Figure 1 shows examples of results obtained. Although quazodine caused a parallel shift to the right of the log dose-response curves, the maximum contractor response which could be elicited in each preparation was reduced. Similar sets of curves were obtained using theophylline. PD'_2 values for theophylline and quazodine were calculated according to the method of Ariens, Simonis & van Rossum (1964). These are listed in Table 1. The PD'_2 values for quazodine, calculated from experiments on the guinea-pig ileum, were similar for three different agonists (acetylcholine, histamine and 5-hydroxytryptamine). This is indicative of non-specific antagonism. On all the preparations in which the effect of quazodine was compared with that of theophylline (rat vas deferens, rabbit aortic strip and cat tracheal chain), quazodine was a more potent inhibitor than theophylline. The order of tissue sensitivity to quazodine was rat vas deferens>guinea-pig ileum>rabbit aortic strip>cat tracheal chain.

Electrically stimulated guinea-pig vas deferens

Frequency-response curves were plotted from experiments on twenty-six preparations in which stimulation frequencies of 5, 10, 20, 25 and 50 Hz were applied. Concentrations of quazodine (5 μg/ml or greater) caused a shift to the right and a slight flattening of the curves at frequencies below 50 Hz. The results of ten such experiments are summarized in Fig. 2a. Responses to low frequency stimulation were inhibited more than were those to high frequency stimulation; this can be

seen clearly when percentage inhibition is plotted against stimulation frequency (Fig. 2b). In eight more preparations the responses to noradrenaline (25–250 μg/ml), acetylcholine (25–250 μg/ml), and potassium chloride (1·25–2·5 mg/ml)

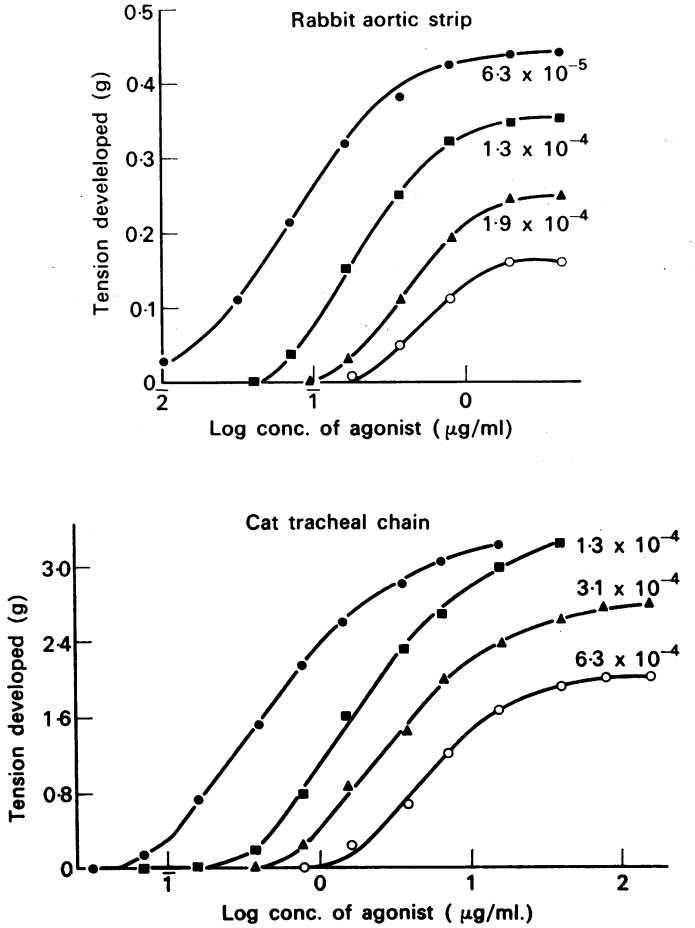

FIG. 1. Effects of quazodine on cumulative log dose-response curves to noradrenaline (rabbit aortic strip) and to acetylcholine (cat tracheal chain). Quazodine produces a parallel shift to the right and depresses the maximum contractor response that can be elicited in both preparations. Molar concentrations of quazodine used are shown above the curves.

TABLE 1. *PD'_2 values for quazodine and theophylline on various isolated smooth muscle preparations*

Antagonist	Agonist	Cat tracheal chain	Rat vas deferens	Rabbit aortic strip	*Guinea-pig ileum
Quazodine	Acetylcholine	3·45±0·11			4·06±0·08
Quazodine	Histamine				4·16±0·12
Quazodine	Serotonin				4·32±0·13
Quazodine	Noradrenaline		4·36±0·16	3·89±0·11	
Theophylline	Acetylcholine	2·31±0·04			
Theophylline	Noradrenaline		3·3±0·11	2·62±0·08	

The values are the mean values ± S.E. of results obtained from five to nine preparations. * PD'_2 values for quazodine were calculated from antagonism of a concentration of agonist which produced 50–80% of the maximum contractile response.

were also shown to be inhibited by comparable concentrations of quazodine (10–50 μg/ml).

Cat tracheal chain

In seven preparations, contractions of the trachea were induced with acetylcholine (0·2–1·0 μg/ml). In each preparation quazodine (20, 50, 100 and 150 mg/ml), and noradrenaline and adrenaline (0·05, 0·1, 0·2, 0·3 and 0·4 μg/ml), added 1 min after acetylcholine, produced relaxation. The mean reductions in tension were plotted against the log of the drug concentrations. The lines of best fit were calculated and the slopes of the log dose-response curves, thus obtained for each drug, were compared. The slopes for adrenaline and noradrenaline were comparable, and both were significantly less than that obtained for quazodine. In six preparations, the inhibitory response evoked by quazodine (50–100 μg/ml) was not reduced by the β-adrenoceptor blocking agent propranolol (0·1 μg/ml). The same concentration of propranolol completely blocked the inhibitory responses to adrenaline (0·1–0·3 μg/ml) or noradrenaline (0·1–0·3 μg/ml).

Rat uterus

Quazodine (1–40 μg/ml) inhibited or abolished the contractor response of the uterus to acetylcholine (0·2–10 μg/ml).

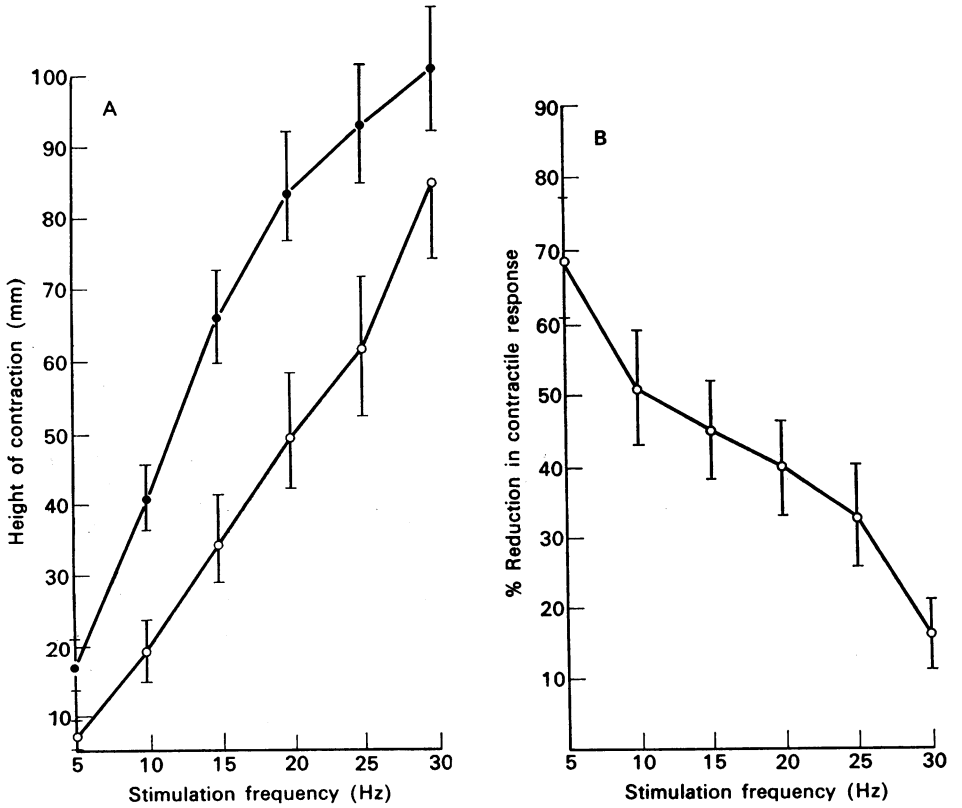

FIG. 2. Effect of quazodine (25 μg/ml) on the frequency–response curve of the isolated guinea-pig vas deferens subjected to transmural electrical stimulation. The responses are inhibited in the presence of quazodine (A), particularly at low frequency stimulation (B). Each point is the mean of ten experiments ± S.E.

Rabbit duodenum

In sixty preparations, quazodine (15–100 μg/ml: $6{\cdot}7 \times 10^{-5}$ to $4{\cdot}5 \times 10^{-4}$M) depressed the amplitude of the pendular movements and this effect was accompanied by a reduction in frequency. In twelve of these preparations smaller concentrations of quazodine (5–10 μg/ml: $2{\cdot}2 \times 10^{-5}$ to $4{\cdot}5 \times 10^{-5}$M) increased the amplitude of the spontaneous contractions and again reduced the frequency. In the remaining forty-eight preparations all concentrations of quazodine ($2{\cdot}2 \times 10^{-5}$ to $4{\cdot}5 \times 10^{-4}$M) depressed the spontaneous activity. Similar, variable, dose dependent effects were seen with theophylline. The inhibitory response produced by quazodine resembled that produced by isoprenaline (0·004–0·1 μg/ml) and by theophylline (100–600 μg/ml: $5{\cdot}1 \times 10^{-4}$ to 3×10^{-3}M) rather than those produced by adrenaline (0·004–0·04 μg/ml), noradrenaline (0·004–0·02 μg/ml) or phenylephrine (0·2–0·6 μg/ml). Figure 3 shows typical responses to each of the six drugs. The inhibitory

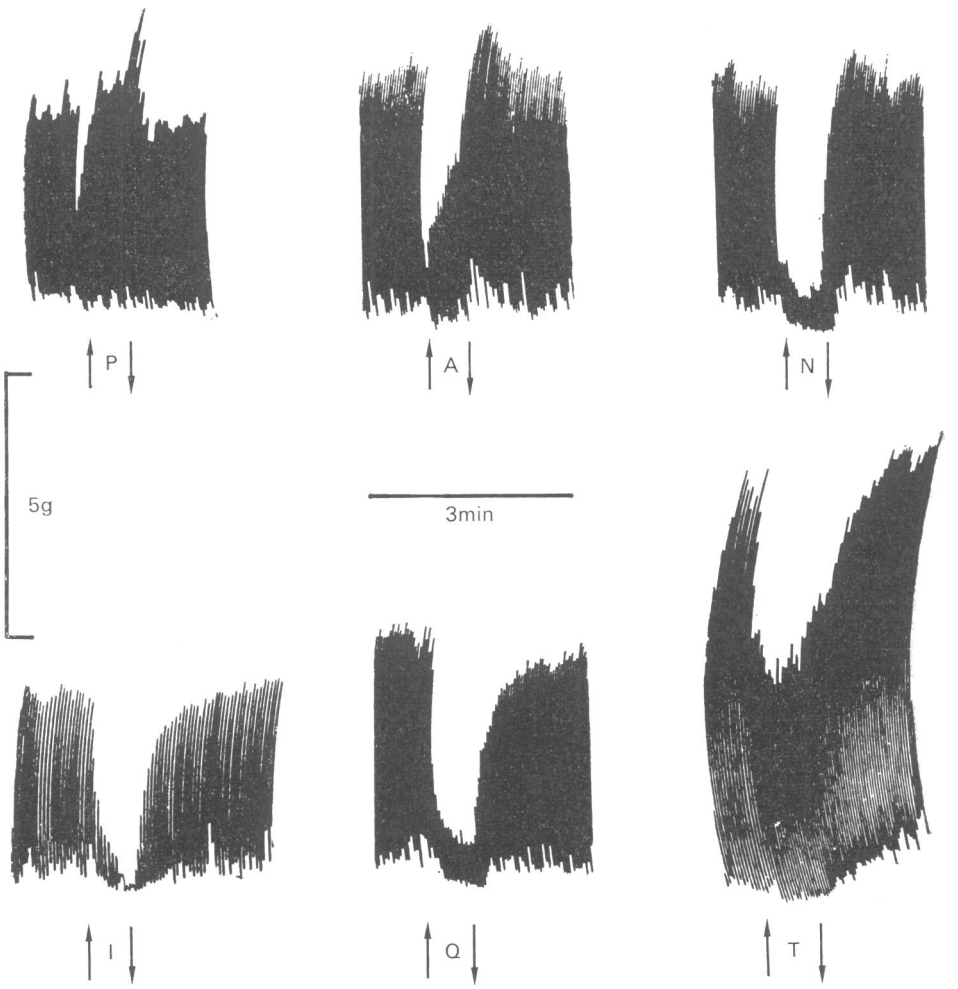

FIG. 3. Effects of phenylephrine (P, 0·2 μg/ml), adrenaline (A, 0·02 μg/ml), noradrenaline (N, 0·02 μg/ml), isoprenaline (I, 0·06 μg/ml), quazodine (Q, 100 μg/ml) and theophylline (T, 400 μg/ml) on pendular movements of the isolated rabbit duodenum. Drugs were added at the arrows and washed out at the inverted arrows. Qualitatively, the response to quazodine was similar to that produced by isoprenaline and by theophylline.

responses to quazodine, theophylline and isoprenaline were relatively slow in onset and were relatively slow to recover when the drugs were washed out of the bath. In contrast, the responses to noradrenaline, adrenaline and phenylephrine recovered rapidly on washing, and with adrenaline and phenylephrine an overshoot in contraction height was usually observed. Bowman & Hall (1970) also noted these differences in the responses to sympathomimetic amines.

In seven preparations the effects of quazodine were unaltered by propranolol (0·2 μg/ml), phentolamine (0·2 μg/ml) or by combinations of these drugs which reduced or abolished responses to catecholamines.

Quazodine (10–80 μg/ml: $4{\cdot}1 \times 10^{-5}$ to $3{\cdot}6 \times 10^{-4}$M) and theophylline (10–80 μg/ml: $5{\cdot}1 \times 10^{-5}$ to 4×10^{-4}M) augmented the inhibitory response of the duodenum to isoprenaline (0·004–1·0 μg/ml). The results of eight experiments are summarized in Fig. 4. Potentiation of isoprenaline could be produced with concentrations of quazodine or theophylline which, by themselves, had very little effect.

Although quazodine (20–80 μg/ml) augmented the inhibitory effects of isoprenaline, it inhibited those of phenylephrine in each of seven preparations. Theophylline produced similar effects, as also noted by Bowman & Hall (1970).

In each of twelve preparations the effects of theophylline (100–200 μg/ml) were additive with those of quazodine (10–100 μg/ml). In each of nine preparations, imidazole (40–200 μg/ml) antagonized the inhibitory response to quazodine (10–70 μg/ml).

Log dose-response curves to quazodine before and after addition of theophylline, and before and after addition of imidazole, are shown in Fig. 5. It can be seen that

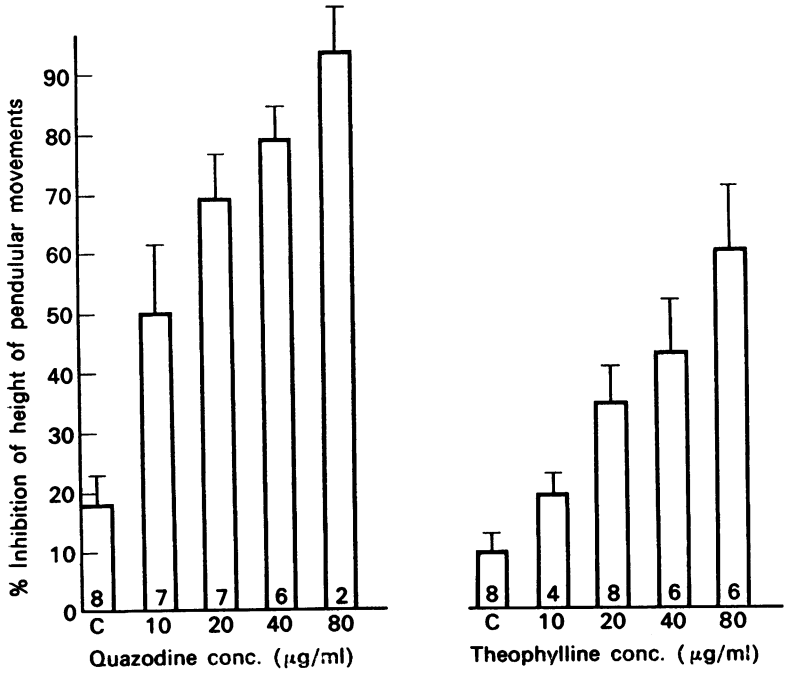

FIG. 4. Potentiation by quazodine and theophylline of the inhibitory effects of isoprenaline (0·004–1·0 μg/ml) on pendular movements of the isolated rabbit duodenum. C represents the control responses to isoprenaline in the absence of quazodine or theophylline. The numbers in the columns are the number of observations and results are expressed as mean ± S.E.

theophylline shifted the log dose-response curve to the left and, in preparations where quazodine increased the height of the pendular movements, this effect was reduced or reversed when quazodine was given after theophylline. Imidazole shifted the log dose-response line to the right, and with low concentrations of quazodine where an inhibitory response had previously been obtained, this response was converted, in the presence of imidazole, to one of stimulation. This effect is also illustrated in Fig. 5.

Rat portal vein

The spontaneous contractions of the portal vein were reduced in amplitude by quazodine (4 μg/ml or greater). The frequency of the spontaneous contractions was usually reduced. The inhibitory response again resembled that produced by theophylline or isoprenaline although the latter, in large doses, produced an increase in the height of the spontaneous contractions. Such stimulation was never observed

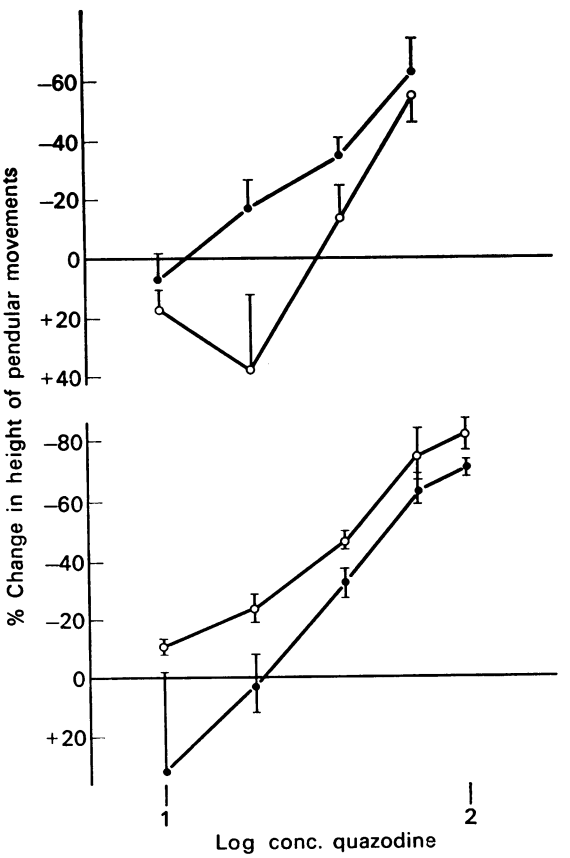

FIG. 5. Effects of imidazole and theophylline on the action of quazodine on the pendular movements of the isolated rabbit duodenum. The upper diagram shows log dose–response curves to quazodine in the absence and in the presence of imidazole (40–200 μg/ml). The log dose–response curve to quazodine was shifted to the right in the presence of imidazole and lower doses of quazodine, which previously caused inhibition of pedular movements, increased the height of the contractions. The lower diagram shows log dose–response curves to quazodine in the absence and in the presence of theophylline (100–200 μg/ml). The log dose–response curve was shifted to the left and low doses of quazodine, which initially produced an increase in the height of the pendular movements, caused a decrease in the presence of theophylline.

with quazodine or theophylline. Typical responses to quazodine and theophylline are illustrated in Fig. 6. The response to quazodine was unlike that produced by phentolamine (0·2 μg/ml), in that the latter, while inhibiting the response to added noradrenaline, did not reduce the size of the spontaneous contractions (Fig. 6).

On eight preparations, the inhibitory response to quazodine was not blocked by the β-adrenoceptor blocking agent alprenolol in doses (0·1 μg/ml) which inhibited the response to isoprenaline (0·04–0·2 μg/ml).

In seven experiments log dose-response curves were obtained for quazodine (4–80 μg/ml: $1{\cdot}8 \times 10^{-5}$ to $3{\cdot}6 \times 10^{-4}$M) and theophylline (10–200 μg/ml: $5{\cdot}1 \times 10^{-5}$ to $1{\cdot}0 \times 10^{-3}$M) both for inhibition of the height of spontaneous contractions and the inhibition of the contractor response to noradrenaline (0·2 μg/ml). The mean slope was calculated for each drug on both types of response and it was found that the slopes for quazodine and theophylline were not significantly different.

Figure 7 shows the effects of increasing the extracellular concentration of Ca^{++} on the inhibitory response of the portal vein to quazodine and on the inhibition of

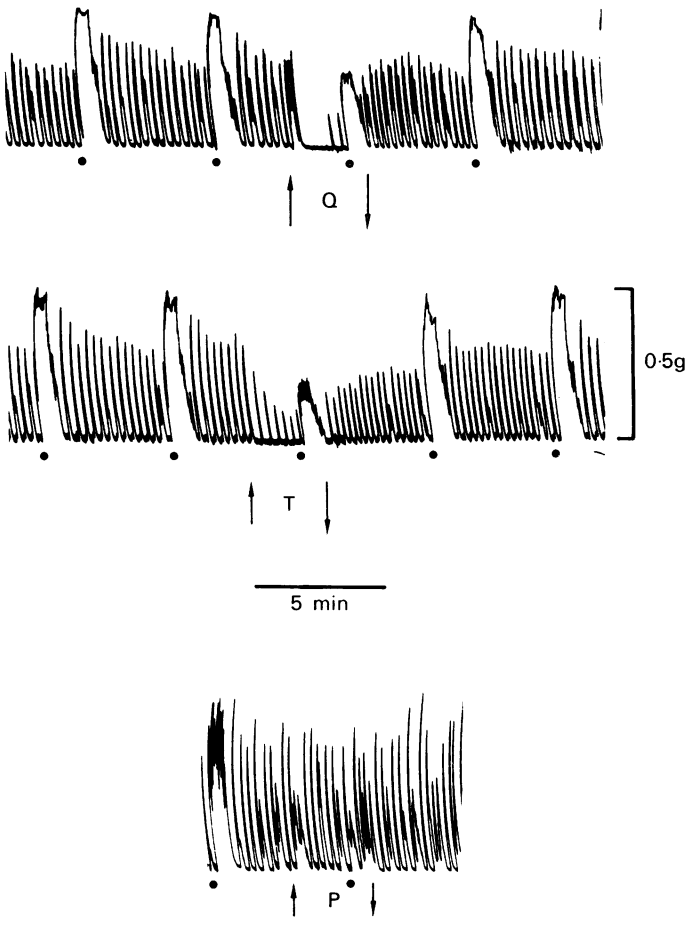

FIG. 6. Effects of quazodine (Q, 40 μg/ml), theophylline (T, 80 μg/ml) and phentolamine (P, 0·2 μg/ml) on spontaneous contractions of the isolated rat portal vein and on the contractor response to noradrenaline (0·2 μg/ml at ●). The responses to quazodine and theophylline were similar in that both the contractor responses to noradrenaline and the spontaneous contractions were reduced. Phentolamine abolished the response to noradrenaline but failed to influence spontaneous activity.

the contractor response to noradrenaline produced by quazodine. As the Ca^{++} concentration increases, the inhibitory action of quazodine on the height of the spontaneous contractions and on the response to noradrenaline is decreased.

Discussion

Quazodine relaxed the smooth muscle in all the preparations studied. It also potentiated isoprenaline-induced inhibition of the isolated rabbit intestine, and opposed α-adrenoceptor mediated effects of noradrenaline on rat and guinea-pig vasa deferentia, rabbit aortic strip, and rat portal vein. Quazodine also potentiates isoprenaline-induced vasodilatation, and reduces vasoconstrictor responses to adrenaline, noradrenaline and phenylephrine in the anaesthetized rat (unpublished observations). None of the effects of quazodine were modified by β-adrenoceptor antagonists, indicating that its actions are not mediated through β-adrenoceptors. These observations, together with those demonstrating a stimulant action on the heart (Lish *et al.*, 1964 ; Aviado *et al.*, 1967 ; Carr *et al.*, 1967 ; Parratt & Winslow, 1971), show that quazodine has a spectrum of pharmacological activity similar to that of methylated xanthines, such as theophylline, which was used for comparison in many of the present experiments. Indeed, synergism between theophylline and quazodine was evident in the rabbit duodenum. Other experiments demonstrating

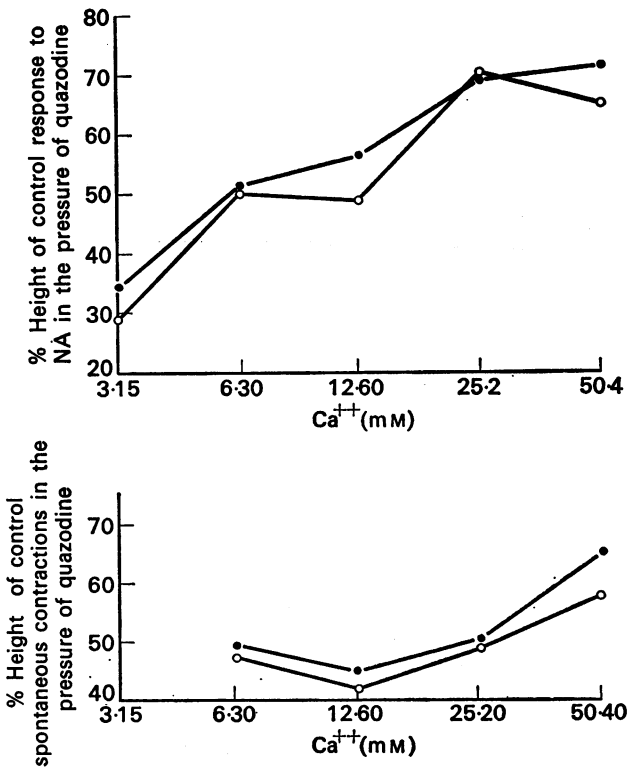

FIG. 7. Effects of extracellular Ca^{++} concentration on the inhibitory effects of quazodine (10 and 20 μg/ml) on spontaeous contractions and on the contractor response to noradrenaline (0·2 μg/ml) of the isolated rat portal vein. As the extracellular Ca^{++} concentration was increased the inhibitory effects of quazodine were decreased.

similar actions of theophylline have been described by Northover (1968), McNeill, Barnes, Davis & Hook (1969), Wilkenfeld & Levy (1969) and Bowman & Hall (1970).

Many of the effects of isoprenaline and of theophylline are mediated by increased cellular concentrations of cyclic adenosine-3′,5′-monophosphate (cyclic AMP) (Sutherland, Robison & Butcher, 1969; Butcher & Sutherland, 1962; Robison, Butcher & Sutherland, 1967; Turtle, Littleton & Kipnis, 1967). Isoprenaline produces this effect by activating adenyl cyclase, the enzyme which converts ATP to the cyclic nucleotide. Theophylline achieves a similar effect by inhibiting phosphodiesterase, the enzyme which catalyses the breakdown of cyclic AMP. The common end result (increased cyclic AMP concentrations) accounts for the similarities between the effects of isoprenaline and theophylline, and for the synergism between them. Amer & Browder (1971) have recently shown that, in different broken cell preparations quazodine inhibits phosphodiesterase and is between 1·2 and 6 times more potent than theophylline in this respect. This action of quazodine is therefore probably the basis for the changes in myocardial contractility it produces and for at least part of its effect in smooth muscle. The relative potencies of quazodine and theophylline, both as phosphodiesterase inhibitors and in producing contractility changes, are compatible with this suggestion. In our experiments quazodine was up to 18 times more potent, on a molar basis, than theophylline in relaxing the rabbit duodenum. Further evidence that the effects of quazodine depends on its ability to inhibit phosphodiesterase was obtained in this study by the use of imidazole. In broken cell preparations, imidazole activates phosphodiesterase (Butcher & Sutherland, 1962), and was found in the experiments described here to inhibit the action of quazodine.

Increased extracellular concentrations of Ca^{++} inhibit the actions of theophylline and of diazoxide, another phosphodiesterase inhibitor, on aortic strips and on the isolated mesenteric artery preparation (Wohl, Hausler & Roth, 1968; McNeill *et al.*, 1969). In the experiments described here, raised Ca^{++} concentrations counteracted the actions of quazodine on the rat portal vein and it is possible that quazodine, in some way reduces the amount of free Ca^{++} available for contraction, so that relaxation or inhibition of spontaneous activity results.

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