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A comparison of the cardiovascular actions of AQ 110 with those of isoprenaline and salbutamol

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Summary

1. AQ 110 is a β-adrenoceptor agonist which, like isoprenaline and salbutamol, acts directly on the receptors.

2. Compared with isoprenaline, AQ 110 has relatively stronger actions on bronchial and vascular smooth muscle (β_2-adrenoceptors) than stimulant effects on heart muscle (β_1-adrenoceptors). The β_2-selectivity of AQ 110 is, however, much less than that of salbutamol, mainly due to the weak cardiac actions of the latter.

3. At doses which were equipotent in decreasing the bronchoconstrictor effect produced by a standard dose of 5-hydroxytryptamine, AQ 110 had marginally less hypotensive action than salbutamol and considerably less than isoprenaline.

4. Although AQ 110, unlike salbutamol, possesses a catechol group it was found not to be a substrate for catechol-O-methyl transferase and this is considered to account for its significantly prolonged action, compared with isoprenaline, *in vivo*.

Introduction

Sympathomimetic agents used in the relief of bronchospasm have long been known to produce circulatory side-effects. These are especially marked with the classical β-adrenoceptor agonist, isoprenaline. Following their observation that a series of catecholamines showed differences in cardiac and bronchodilator predominance, Lands and his co-workers (Lands & Brown, 1964; Lands, Arnold, McAuliff, Luduena & Brown, 1967) proposed a subdivision of β-adrenoceptors into a β_1 group in heart muscle and a β_2 group in bronchial and vascular smooth muscle. Subsequently, a number of β_2-selective agents structurally related to isoprenaline were discovered, for example soterenol (Dungan, Cho, Gomoll, Aviado & Lish, 1968), salbutamol (Cullum, Farmer, Jack & Levy, 1969).

Another group of compounds which have been investigated for their β_2-selectivity are the 1-substituted 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines. Of these, AQ 110 was found to be the most potent bronchodilator and had, moreover, less cardiovascular action than isoprenaline (Sato, Yamaguchi & Kiyomoto, 1967). In the present paper, the circulatory effects of AQ 110 are compared with those of isoprenaline and salbutamol. The formulae of these substances are illustrated in Fig. 1, in which the resemblance of AQ 110 to papaverine and papaveroline (desmethyl papaverine) is also shown.

Methods

Anaesthetized cats

Adult cats were anaesthetized by intraperitoneal injection of sodium pentobarbitone (30 mg/kg). Subsequent drugs were introduced into the jugular vein. Bronchial resistance was measured using the method of Konzett & Rössler (1940) modified by the inclusion of an Ether low-pressure transducer (type UP1) in the circuit. The activity of the test compounds was assessed by their antagonism to the bronchoconstrictor effect of a standard dose of 5-hydroxytryptamine (5-HT). Blood pressure was monitored using an Ether transducer (type BP15) connected to a cannula in the right common carotid artery. Heart rates were measured from the blood pressure recordings. In one experiment the blood pressure could be stabilized by the use of a compensator (of the type described by Krayer & Verney, 1936) connected to a side arm on the arterial cannula. Two cats were injected intraperitoneally with reserpine (5 mg/kg), 18-24 hr before the experiment.

Isolated tissues

Guinea-pig heart. The isolated hearts were perfused by Langendorff's method with oxygenated Ringer-Locke solution warmed to 37° C. Drug solutions were injected into the aortic cannula in a volume not exceeding 0·02 ml. The contractile force of the heart was registered on a pen recorder via a mechano-electronic transducer (which used an RCA 5734 valve) connected to the cardiac apex.

Perfused rabbit ear. After cannulation of the central artery, the organ was perfused from a constant height (50 cm fluid) with Krebs-Henseleit solution (modified by the addition of ascorbic acid 38·46 mg/l. and disodium edetate 10 mg/l.) warmed to 37° C and aerated with 5% carbon dioxide in oxygen. The venous outflow was measured by means of a Thorpe drop counter, resetting every 10 s, and recorded on a kymograph. Drug solutions were introduced into a chamber near the inflow to the ear in volumes of 0·01 or 0·02 ml, which did not produce significant effects

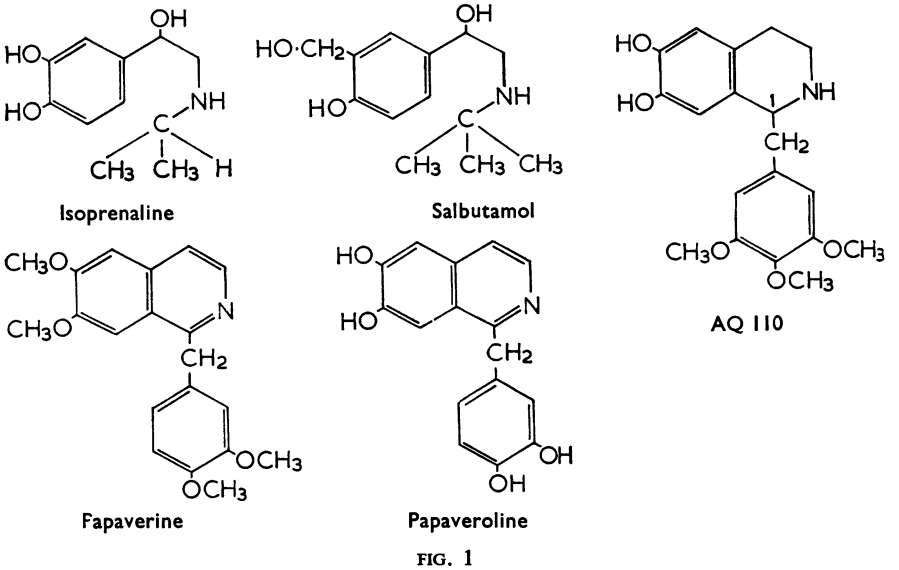

FIG. 1

on the recording system. To provide a background for vasodilator action, a suitable dose of noradrenaline was added to the perfusion fluid.

Isolated rabbit ear artery. A 1·5–2 cm length from the proximal end of the central artery, free of side branches, was cannulated and perfused by the method of de la Lande & Rand (1965). The perfusion fluid was " modified " Krebs-Henseleit solution (see above) aerated with 5% carbon dioxide in oxygen and warmed to 37° C. The flow rate varied between 7–15 ml/min in different preparations. Changes in perfusion pressure were monitored by an Ether blood pressure transducer (BP 15), just proximal to the arterial cannula, which traced the pulses produced by the roller pump on a pen recorder. Drug solutions were injected into the short length of rubber tubing connecting the transducer to the cannula in volumes not exceeding 0·2 ml, which produced only evanescent changes on the tracing. Again, noradrenaline was added to the perfusion fluid in suitable dosage to provide adequate vasoconstrictor tone. In some animals one ear was denervated by excision of the superior cervical ganglion 6–10 days before the experiment.

Rabbit vessel strip preparations. Spiral strips, 2–3 cm long, from the portal (anterior mesenteric) vein and descending thoracic aorta were suspended in " modified " Krebs-Henseleit solution in a 10 ml bath at 37° C. Aeration was maintained with 5% carbon dioxide in oxygen. Recordings were made on a kymograph using frontal isotonic levers with 3–4 fold amplification. After an equilibration period of 2 hr, drug solutions were added to the bath in 0·01–0·1 ml volumes. Following washout slight tension was applied, especially to the aortic preparations, if necessary, so that the lever was at the baseline ready for the next drug application 15–30 min later. Drug concentrations are expressed as final bath concentrations (g/ml) of free base.

Drugs

Concentrated drug solutions were made in deionized water ; in the case of catecholamines, they also contained 0·1 N HCl. They were stored at 8° C and diluted freshly as required either in distilled water or the appropriate salt solution. The following drugs were used: acetylcholine perchlorate (B.D.H.) ; AQ 110 ; desmethylimipramine hydrochloride (Geigy) ; 5-hydroxytryptamine creatinine sulphate (B.D.H.) ; isoprenaline sulphate (Burroughs Wellcome) ; propranolol hydrochloride (I.C.I.) ; (−)-noradrenaline bitartrate (Koch-Light) ; reserpine (CIBA) ; phentolamine methyl sulphate (B.D.H.) ; salbutamol (Allen & Hanburys) ; tyramine hydrochloride (B.D.H.).

Results

Effects on anaesthetized cats

Bronchial resistance. The relative potencies of isoprenaline, salbutamol and AQ 110 as antagonists of the bronchoconstrictor action of 5-HT are shown in Figs. 2 and 3. It can be seen from Fig. 2 that 200 ng salbutamol or AQ 110 produced a degree of inhibition intermediate to those resulting from 50 ng and 100 ng isoprenaline but lasting about twice as long. At 400 ng doses, salbutamol and AQ 110 produced inhibition comparable with 250 ng isoprenaline but even greater persistence. AQ 110 not only outlasted salbutamol but produced its maximum effect for significantly longer. Complete inhibition of the 5-HT response (Fig. 3) resulted after 500 ng

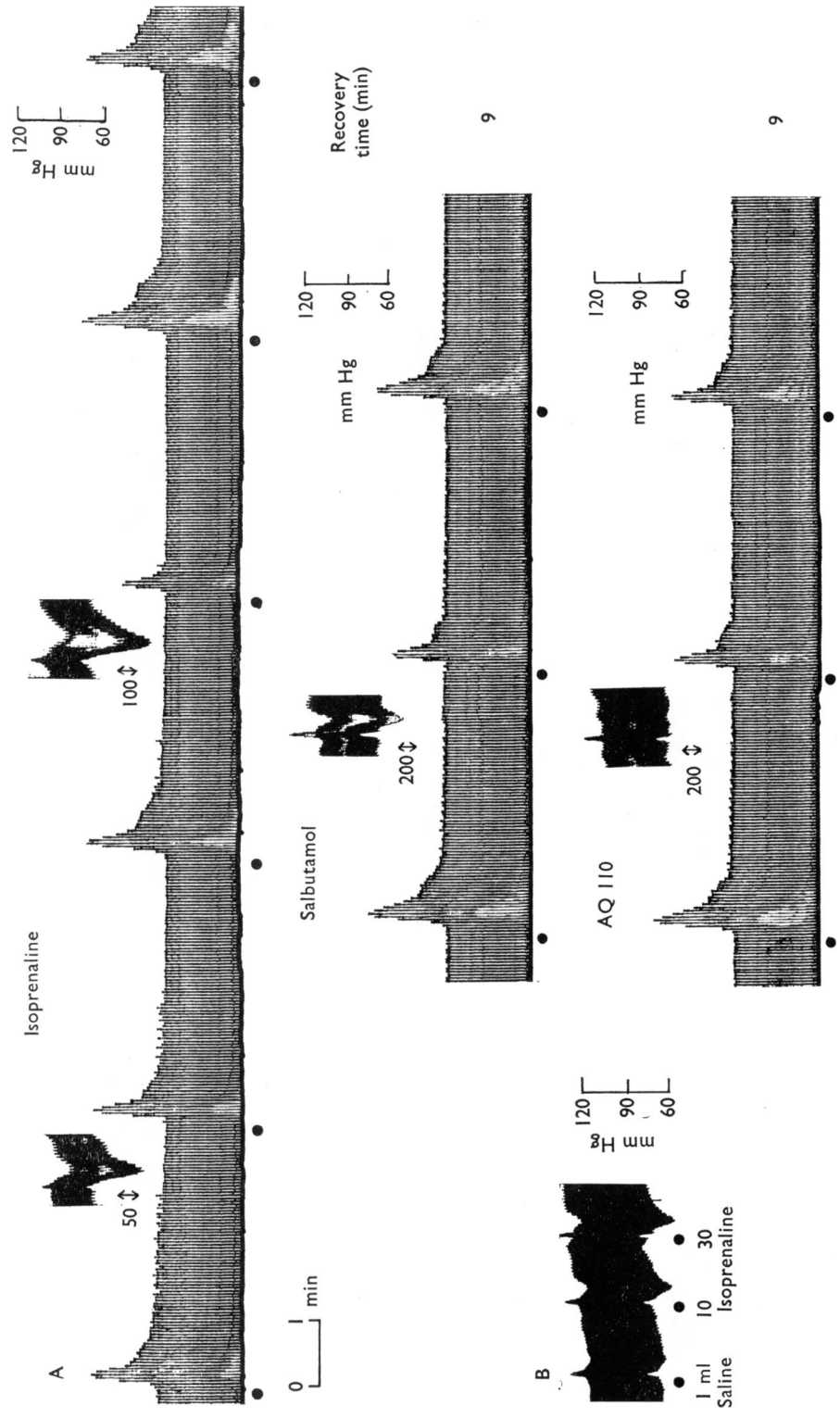

FIG. 2. Cat 2·9 kg. A, Antagonism by isoprenaline, salbutamol and AQ 110 of the bronchoconstrictor response to 15 μg 5-hydroxytryptamine (●) given intravenously every 4 min. The antagonist (dose in ng) was administered in 1 ml 0·9% NaCl 1 min before a 5-hydroxytryptamine injection. Recovery time indicates the period following the antagonist injection for the bronchoconstrictor effect to return to its original form. Inset, blood pressure effects of the doses of isoprenaline, salbutamol and AQ 110. B, Blood pressure effects produced by 1 ml 0·9% NaCl, 10 ng and 30 ng isoprenaline for comparison with the salbutamol and AQ 110 responses.

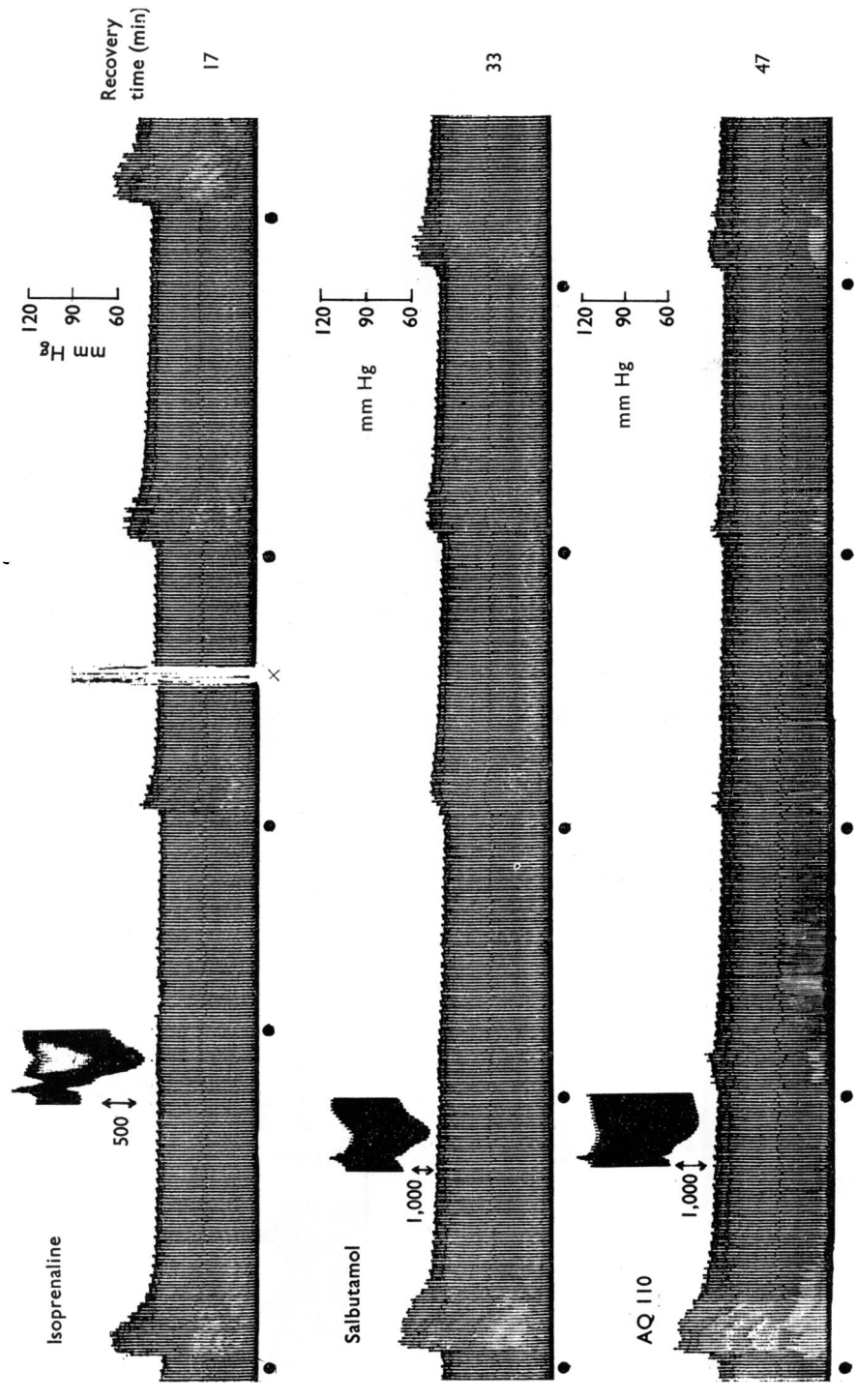

FIG. 3. Cat, as Fig. 2. Effects of larger doses of isoprenaline, salbutamol and AQ 110. Note in the top tracing that the isoprenaline and second and fifth 5-hydroxytryptamine injections were given 1 min late in the cycle and that at × the tracheal cannula was cleared.

isoprenaline or 1 μg salbutamol. AQ 110 was slightly less active than the latter and took longer to produce its maximum effect; however, its duration was much greater. Similar ratios for degree and duration of inhibition were obtained in eleven direct comparisons of the three drugs over a range of doses from 10 ng–1 μg. From these, the mean dose-ratios to produce equal % inhibitions of the 5-HT response were found to be: isoprenaline, 1; salbutamol, 3·0 $\pm$ 0·5 (S.E. of mean); AQ 110 3·4 $\pm$ 0·3. AQ 110 was significantly longer-lasting than salbutamol, which itself had a much greater duration of action than isoprenaline.

Cardiovascular actions. Figures 2 and 3 also show that at doses which were equipotent in diminishing the 5-HT response, the hypotensive effects of isoprenaline were more marked than those of either salbutamol or AQ 110. Inconsistent results, possibly due to tachyphylaxis, were obtained if consecutive doses were given more frequently than 5, 15 or 20 min for isoprenaline, salbutamol and AQ 110 respectively. Furthermore, cross-tolerance to the other two drugs also occurred. Thresholds for the hypotensive effects were: isoprenaline 10–50 ng; salbutamol, 125 ng–1 μg; AQ 110, 200 ng–1 μg. Comparison of equihypotensive doses in fourteen experiments from threshold up to 20 μg gave the following mean dose-ratios: isoprenaline, 1; salbutamol, 8·8 $\pm$ 0·8; AQ 110, 9·9 $\pm$ 0·9. The larger doses of the drugs, especially AQ 110, tended to have longer-lasting effects. This aspect is well illustrated in Fig. 4, where it can be seen that the action of 20 μg AQ 110, which gave a maximum fall of diastolic blood pressure similar to that of 2 μg isoprenaline or 20 μg salbutamol, was considerably prolonged. In addition, this large dose of AQ 110 characteristically increased the pulse pressure more than isoprenaline and salbutamol by virtue of a greater increase in systolic blood pressure. The hypotensive effects of isoprenaline, AQ 110 and salbutamol were antagonized by propranolol (Fig. 5). It was found that the smallest dose of propranolol required to abolish the

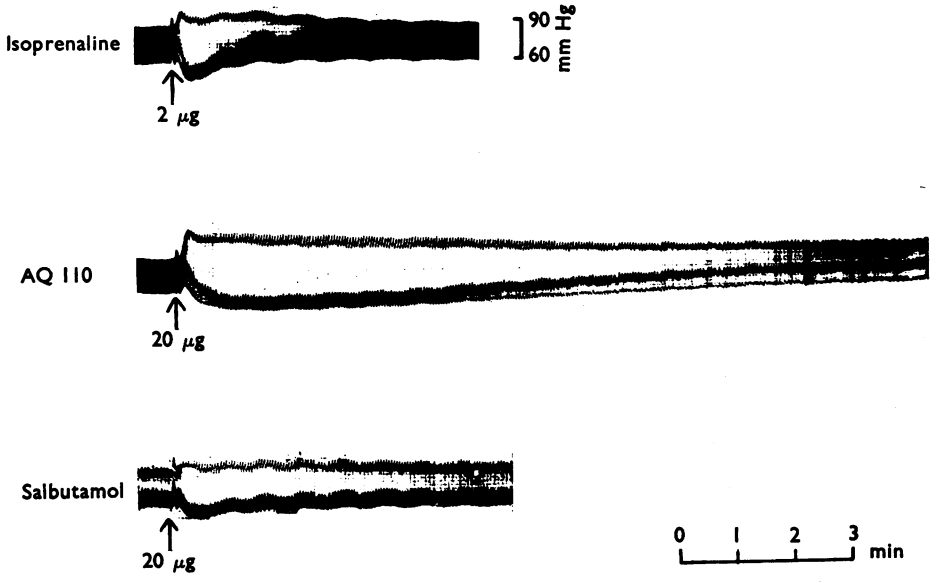

FIG. 4. Effects of large doses of isoprenaline, AQ 110 and salbutamol on the blood pressure of an anaesthetized cat (2·8 kg). This animal had been given reserpine (5 mg/kg, intraperitoneally) 18 hr before the experiment, but the tracings are also characteristic of those obtained in cats which had not been pretreated with reserpine.

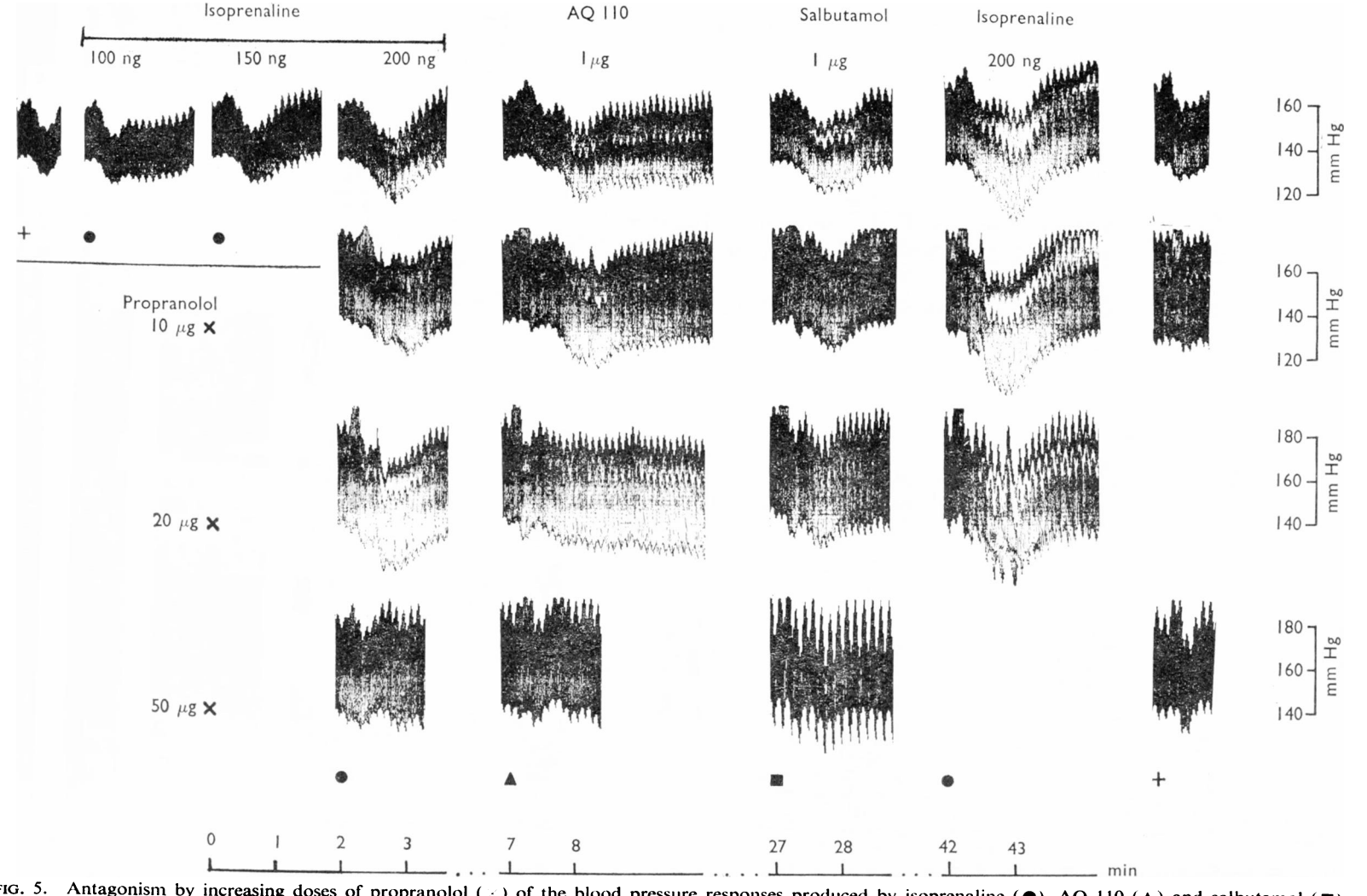

FIG. 5. Antagonism by increasing doses of propranolol (×) of the blood pressure responses produced by isoprenaline (●), AQ 110 (▲) and salbutamol (■) in an anaesthetized cat (2·8 kg). Control injections (+) of 0·9% NaCl. The top row of tracings compares the effects of doses of the three agonists given at appropriate intervals. Subsequent rows show the effects of propranolol (10 μg., 20 μg and 50 μg respectively) on the responses to one dose of isoprenaline, AQ 110 and salbutamol given respectively 2 min, 7 min and 27 min after the propranolol. The preparation was allowed to recover its response to isoprenaline (shown in second column from the right) before administering a further dose of propranolol.

hypotension caused by a given dose of isoprenaline usually also completely blocked an equihypotensive dose (5–10 times as much) of AQ 110 or salbutamol and, in general, that a given dose of propranolol antagonized equipotent doses of the three agonists to a similar degree.

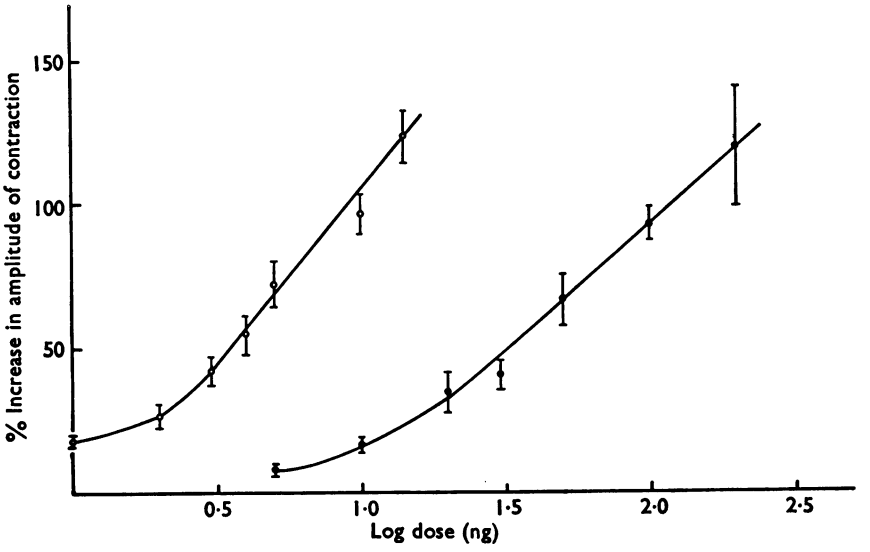

FIG. 6. Log dose-response curves for isoprenaline (○, 1–20 ng) and AQ 110 (●, 5–200 ng) on the amplitude of contraction of the isolated guinea-pig heart (Langendorff preparation). Each point represents the mean % increase obtained in eight separate preparations ±S.E.

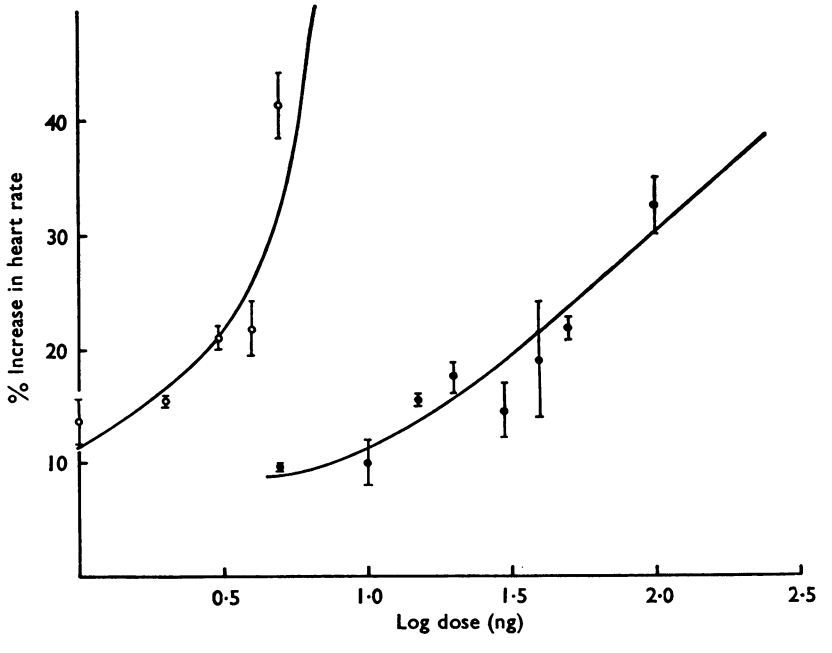

FIG. 7. Log dose-response curves for isoprenaline (○, 1–5 ng) and AQ 110 (●, 5–100 ng) on the heart rate of the isolated guinea-pig heart (Langendorff preparation). Each point represents the mean % increase obtained in six separate preparations ±S.E.

AQ 110 produced an immediate tachycardia which was prolonged with higher doses. For example, in the experiment illustrated in Fig. 4 the increase in heart rate occurred before the diastolic blood pressure had fallen, persisted in the absence of any decrease in the mean or pulse pressure and was still present 11 min later when the diastolic pressure had returned to its initial value. The tachycardia could occur with doses of AQ 110 which were below the hypotensive threshold and still took place after stabilization of the blood pressure. A dose-response relationship for the increase in heart rate in the whole animal was not established.

The above effects of isoprenaline, salbutamol and AQ 110 and their relative potencies were not altered in reserpine-treated preparations. The cardiovascular responses, in the whole animal, to AQ 110 were unaffected by the prior administration of either 1 mg phentolamine or 0·5 mg desmethylimipramine (which blocked the circulatory effects of 300 μg tyramine).

Effects on isolated tissues

Guinea-pig heart. Isoprenaline, AQ 110 and salbutamol produced positive inotropic and chronotropic actions. Those of salbutamol, however, were negligible except at very high concentrations. Figures 6 and 7 show log dose-response curves for the inotropic and chronotropic effects, respectively, of isoprenaline and AQ 110. The curves, though not parallel, show isoprenaline to have 8–11 times the inotropic activity and 10–16 times the chronotropic activity of AQ 110 over most of the dosage range studied. These ratios were not significantly different when hearts from reserpinized animals were used. In the absence of results at higher doses, it is not possible to state whether AQ 110 is acting as a partial or full agonist in respect of these actions. The effects of AQ 110 were much more prolonged than those of isoprenaline. The inotropic and chronotropic effects of isoprenaline and AQ 110 were blocked by propranolol and, in general, a given dose of the latter antagonized equipotent doses of isoprenaline and AQ 110 to a similar degree.

Perfused rabbit ear. Only seven direct comparisons of the three drugs were made and Fig. 8 shows the most common result obtained—that 100 ng isoprenaline gave a similar response to 1 μg AQ 110 or 1 μg salbutamol. These effects were abolished by 20 μg propranolol. Note that at the doses compared in Fig. 8, AQ 110, unlike salbutamol or isoprenaline, exerted a marked inhibition of subsequent isoprenaline action for 20–25 min.

Isolated rabbit ear artery. As seen from Fig. 9, which shows a representative series, AQ 110 was roughly equipotent with isoprenaline as a vasodilator in this preparation, whilst salbutamol was about ten times weaker. From more than twenty direct comparisons of the three drugs, over a range from 2 μg–4 mg, mean equiactive dose-ratios were found to be: isoprenaline, 1 ; AQ 110, $1{\cdot}5 \pm 0{\cdot}1$; salbutamol, $11{\cdot}0 \pm 1{\cdot}1$. Similar ratios were obtained in preparations from innervated or chronically denervated rabbit ears. It was found that AQ 110 and salbutamol, especially in the higher doses, depressed the responses to subsequent injections of either themselves or isoprenaline for periods up to 30 min.

Rabbit portal (anterior mesenteric) venous and thoracic aortic strips. Isoprenaline at final bath concentrations of 10^{-7} to 2×10^{-6} g/ml produced relaxation of tone in the *portal vein.* This was usually accompanied by a decrease in the amplitude of spontaneous activity (Fig. 10A, B, C) but could occur without any change

in this parameter (Fig. 10D). These effects were blocked by propranolol (10^{-6} g/ml). Higher concentrations of isoprenaline (from 4×10^{-6} to 10^{-5} g/ml) characteristically produced a biphasic response (initial relaxation followed by contraction) which was converted into a pure contraction by propranolol (10^{-6} g/ml) or became a simple relaxation following phentolamine (10^{-6} g/ml). When the isoprenaline concentration exceeded 10^{-5} g/ml, contraction of the vein was obtained. On the *thoracic aorta,* isoprenaline produced only contraction ; the threshold concentration was most commonly $1\text{–}4 \times 10^{-6}$ g/ml (Fig. 10B, C), although some preparations

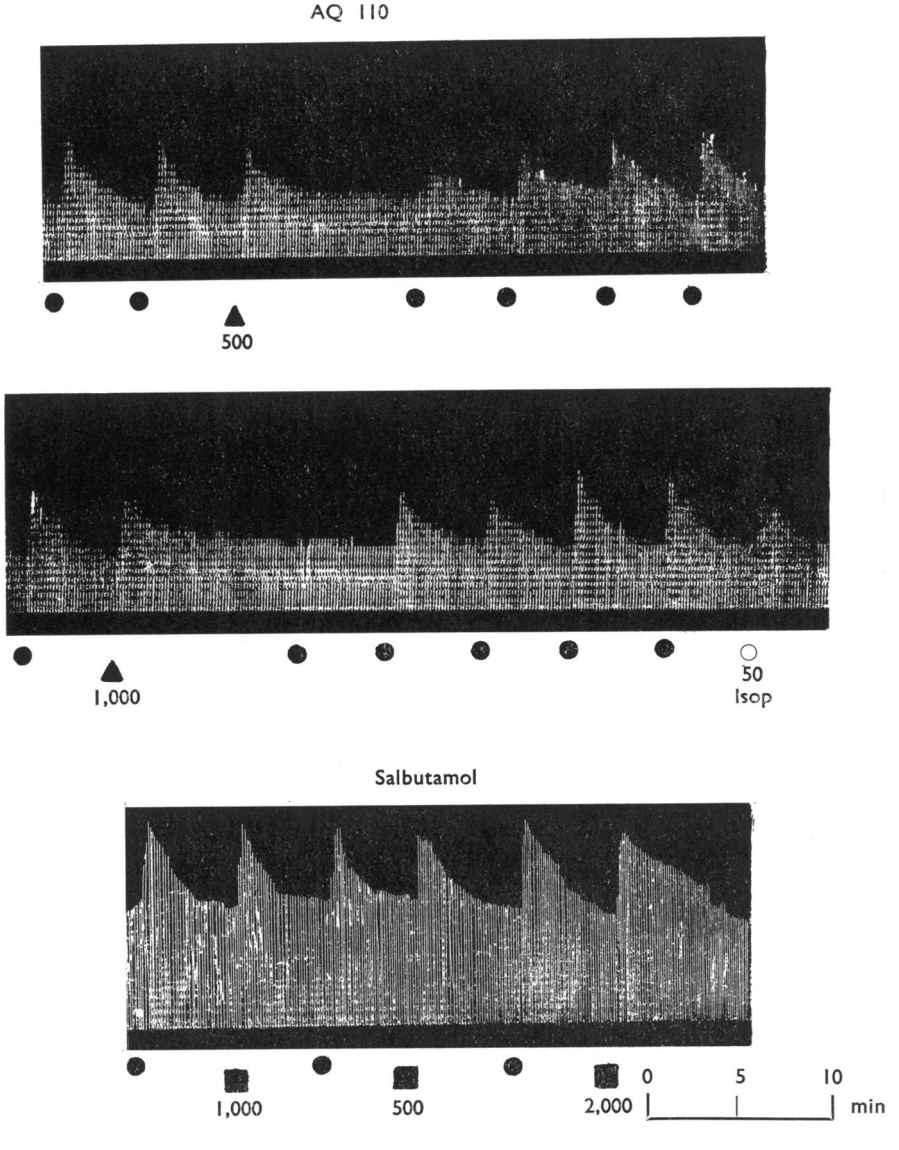

FIG. 8. Effects of different doses (in ng) of AQ 110 (▲) and salbutamol (■) on the flow of perfusion fluid through an isolated rabbit ear compared with those resulting from 100 ng isoprenaline (●) and, in the centre tracing, 50 ng isoprenaline (○, Isop). The perfusate contained 20 ng/ml noradrenaline to provide a background of vasoconstriction. A rise in the tracing profile indicates an increase in fluid flow.

were more sensitive (Fig. 10D). AQ 110 and salbutamol produced only contraction of the vein and no significant effect on the thoracic aorta ; this is shown in Fig. 10A. From a small series of six comparisons, mean equipotent dose-ratios for portal vein contraction were found to be: isoprenaline, 1 ; AQ 110, $5{\cdot}0 \pm 2{\cdot}5$; salbutamol, 137 ± 39. Phentolamine (4×10^{-6} g/ml) reversed this isoprenaline effect on the vein, that is, converted it to a relaxation, and inhibited the salbutamol contraction. However, as the AQ 110 response could often not be repeated even after an interval of 70 min without drug application, its disappearance after phentolamine was not conclusive of an effect on α-adrenoceptors. The contraction produced by isoprenaline on the thoracic aorta was also abolished by phentolamine.

Whilst relaxant effects of AQ 110 and salbutamol on both vessels and isoprenaline on the thoracic aortic strips could not be shown directly, they manifested themselves after the vessels had been contracted with noradrenaline, 5-HT or acetylcholine. Occasionally, there was a small initial contraction, but the relaxant actions predominated and were compared as in Fig. 11. From a small series of comparisons, mean equipotent dose-ratios for relaxation of the vessels were found to be: *portal vein:* isoprenaline, 1 ; AQ 110, $4{\cdot}0 \pm 1{\cdot}2$; salbutamol, $47{\cdot}6 \pm 7{\cdot}9$; *thoracic aorta:* isoprenaline, 1 ; AQ 110, $10{\cdot}4 \pm 3{\cdot}1$; salbutamol, $10{\cdot}6 \pm 2{\cdot}1$. These

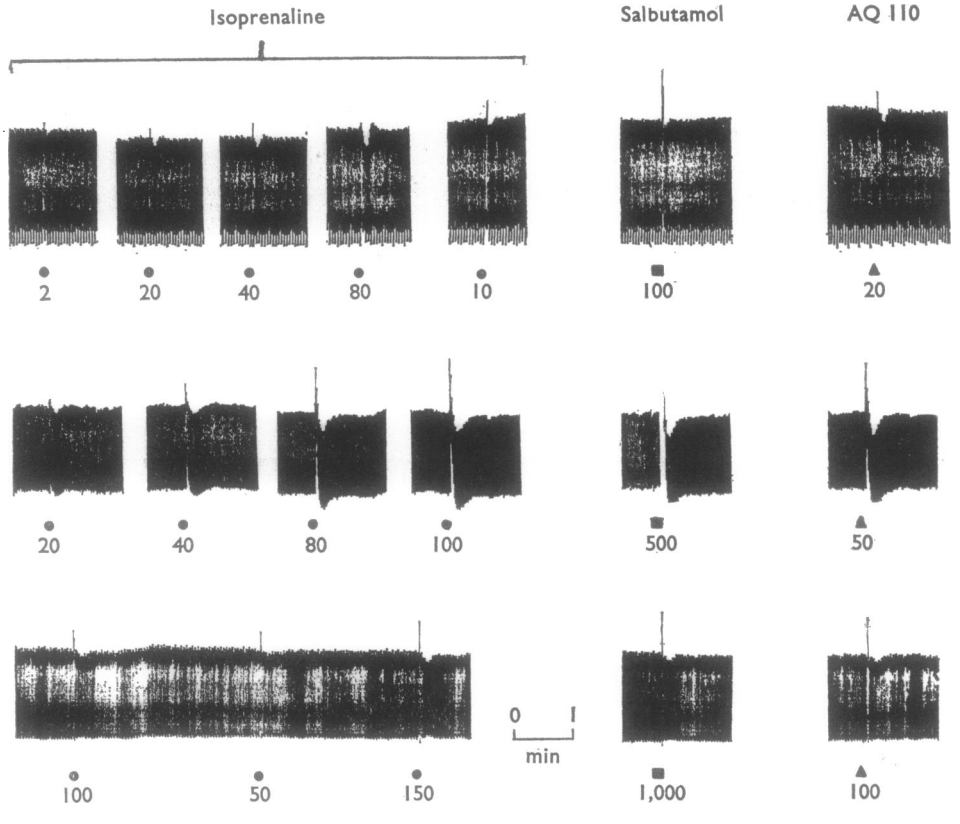

FIG. 9. Isolated ear arteries from three rabbits (separate horizontal rows). Effects of various doses (in μg) of isoprenaline (●), salbutamol (■) and AQ 110 (▲) on the perfusion pressure. A fall in the tracing profile indicates a decrease in pressure. Artefacts on injection are volume effects (less than 0·2 ml, except for the 500 μg salbutamol injection, which was 1 ml).

effects were antagonized by propranolol. However, there was a difficulty here as the antagonist itself in final bath concentrations $\geqslant 10^{-5}$ g/ml produced a relaxation of the vessels which had to be allowed to level off, if possible, before the agonist could be applied. Figure 12 shows that a dose of propranolol which blocked isoprenaline relaxation of the portal vein also blocked equipotent doses of AQ 110 and salbutamol. Similar results were obtained on other portal venous and aortic strip preparations.

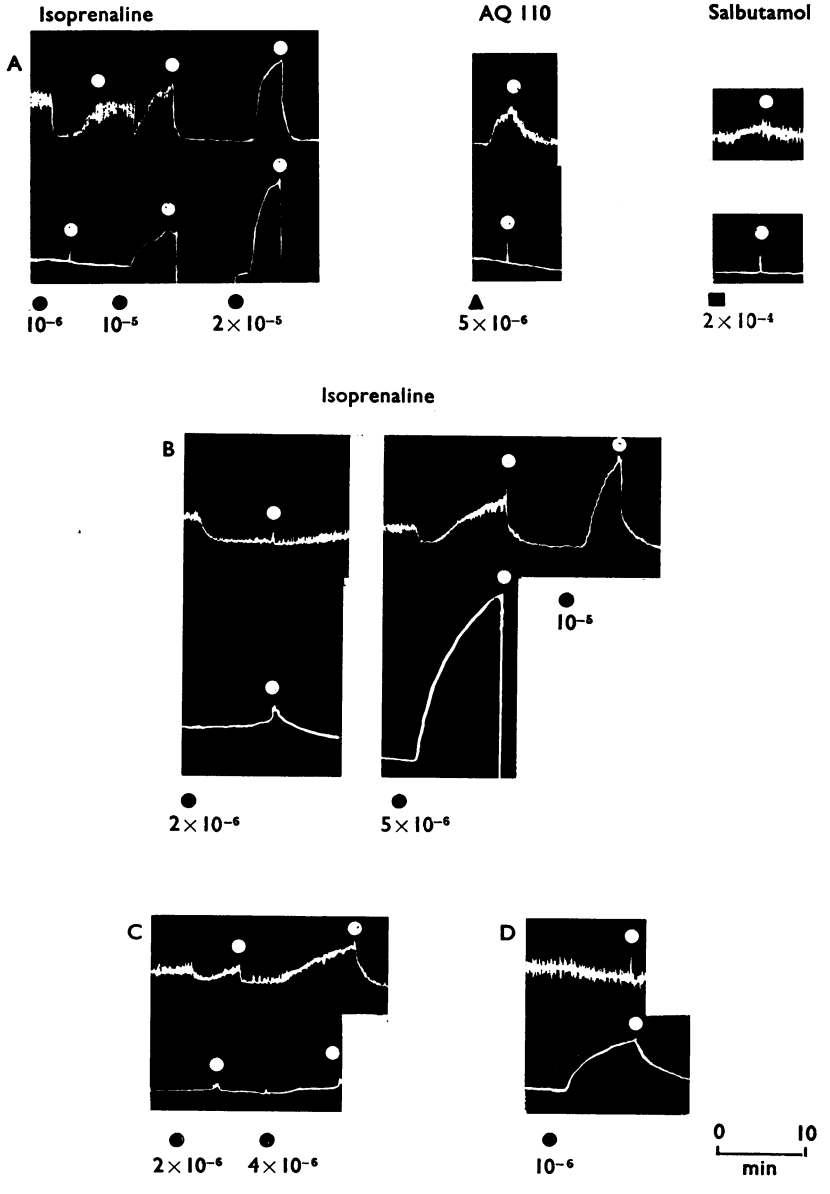

FIG. 10. Drug effects on spiral strips of rabbit portal vein (upper tracing of each vertical pair) and thoracic aorta (lower tracing). A, Isoprenaline (●) compared with AQ 110 (▲) and salbutamol (■); B–D, isoprenaline only. Figures below tracings indicate final bath concentrations (g/ml) as free bases; white dots on tracings indicate washout.

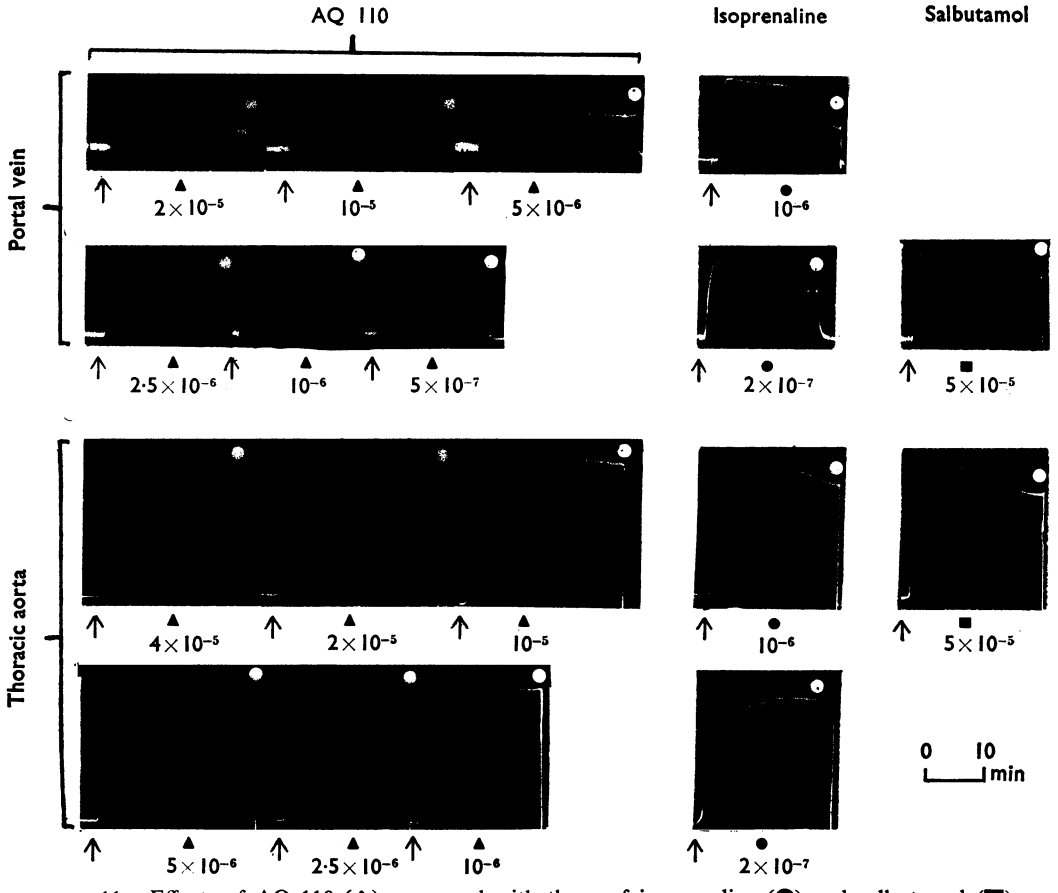

FIG. 11. Effects of AQ 110 (▲) compared with those of isoprenaline (●) and salbutamol (■) on spiral strips of rabbit portal vein or thoracic aorta following contraction of the vessel with 10^{-7} g/ml noradrenaline (at arrows). Each experiment began 30 min after the preceding washout (indicated by white dot on tracing). Figures below tracings indicate final bath concentrations (g/ml) of AQ 110, isoprenaline or salbutamol as free bases.

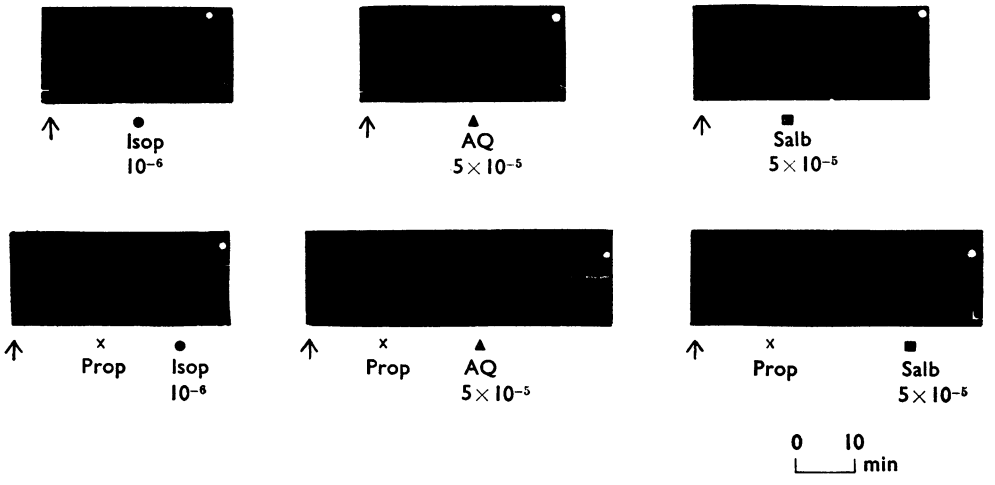

FIG. 12. Antagonism by propranolol of the relaxations produced on spiral strips of rabbit portal vein by isoprenaline (●, Isop), AQ 110 (▲, AQ) and salbutamol (■, Salb). In each tracing the vessel was first contracted with 5×10^{-7} g/ml noradrenaline (at arrows). The upper row of tracings shows the effects before and the bottom row after the administration of 10^{-5} g/ml propranolol (×, Prop). Intervals between successive tracings, 30 min; doses as final bath concentrations (in g/ml); white dots on tracings indicate washout.

It was again noted that the duration of drug effects on these vessels was generally more prolonged with AQ 110 and salbutamol than with isoprenaline.

Relative potencies of isoprenaline, AQ 110 and salbutamol on the experimental variables studied

Table 1 shows mean equipotent doses of AQ 110 and salbutamol for the different actions studied in this paper, compared with isoprenaline as unity in each case. Both AQ 110 and salbutamol showed β_2-selectivity in that they had relatively stronger relaxant effects on bronchial and vascular smooth muscle than stimulant effects on the heart. Salbutamol was by far the more β_2-selective due to its extremely weak cardiac action. In the whole animal, however, the relatively stronger action of AQ 110 on the heart accompanied by only a slightly greater vasodilation resulted in a fall of blood pressure which was marginally less than that produced by salbutamol. The α-adrenoceptor effects of the three drugs on the portal vein should be noted.

Discussion

It is apparent that AQ 110 is a β-adrenoceptor agonist. It was found to have positive inotropic and chronotropic effects, to be a peripheral vasodilator and to produce hypotension. All these effects were antagonized by propranolol. Like isoprenaline and salbutamol, AQ 110 appeared to act directly on β-adrenoceptors rather than indirectly by release of catecholamines for the following reasons. First, the positive inotropic and chronotropic effects and the hypotension were unaffected by reserpine pretreatment. Second, the denervated rabbit ear artery showed no diminution in relative response to the three drugs compared with the innervated vessel. Finally, desmethylimipramine did not modify the cardiovascular responses to AQ 110 in the whole animal.

TABLE 1. *Equipotent doses of AQ 110 and salbutamol relative to isoprenaline (= 1) on the different experimental variables*

		AQ 110		Salbutamol	
Preparation and effect		Mean equipotent dose ± S.E.	*n*	Mean equipotent dose ± S.E.	*n*
Guinea-pig heart					
Positive inotropic effect	β_1	8–11*	56	>500‡	3
Positive chronotropic effect	β_1	10–16†	48		
Anaesthetized cat					
Fall in blood pressure		9·9 ± 0·9	14	8·8 ± 0·8	14
Antagonism of 5-HT bronchoconstriction	β_2	3·4 ± 0·3	11	3·0 ± 0·5	11
Perfused rabbit ear					
Vasodilation	β_2	10·0 ± 1·7	7	10·0 ± 1·5	7
Rabbit ear artery					
Dilation	β_2	1·5 ± 0·1	24	11·0 ± 1·1	22
Rabbit thoracic aortic strip					
Relaxation	β_2	10·4 ± 3·1	8	10·6 ± 2·1	7
Rabbit portal venous strip					
Relaxation	β_2	4·0 ± 1·2	12	47·6 ± 7·9	9
Contraction	α	5·0 ± 2·5	6	137 ± 39	6

n, Number of observations. *Range only (from Fig. 6). †Range only (from Fig. 7). ‡Insufficient data for a more accurate value.

The immediate therapeutic interest in AQ 110 concerns its potency as a bronchodilator. While Iwasawa & Kiyomoto (1967) found, using guinea-pig tracheal chain, that this substance had about 10 times the relaxant activity of isoprenaline, our results indicate that AQ 110, given intravenously to the anaesthetized cat, has about one-third the potency of isoprenaline in inhibiting a bronchoconstrictor dose of 5-HT. We find salbutamol to have a similar relative potency ; which lies between the values found for that substance by Cullum *et al.* (1969) in the anaesthetized guinea-pig and tracheal chain, respectively equipotent and one-tenth as active as isoprenaline. Cullum *et al.* (1969) further found that the bronchodilator action of salbutamol in the anaesthetized guinea-pig lasted two to three times as long as an equiactive dose of isoprenaline. We have confirmed this in the anaesthetized cat and shown that equiactive doses of AQ 110 last even longer.

Isoprenaline acts as a strong agonist both on the β_1-adrenoceptors in heart muscle and the β_2-adrenoceptors in bronchial and vascular smooth muscle ; that is it shows no β_1- or β_2-selectivity. Cullum *et al.* (1969) showed salbutamol to be a selective β_2 agonist, especially on bronchial muscle, with very little cardiac action. We find AQ 110 to show some β_2-selectivity. This is less than that of salbutamol due to the relatively stronger cardiac actions of AQ 110 (*vide infra*). However, in the whole animal, these actions mitigate the depressor effect which is, accordingly, slightly less with AQ 110 than with salbutamol.

On the isolated guinea-pig heart, isoprenaline has marked positive inotropic and chronotropic effects. These actions are appreciably less with AQ 110 and extremely small with salbutamol, as Cullum *et al.* (1969) also found using guinea-pig atria. These workers also noted that the dose-response curves for increases in rate and tension in the atria produced by salbutamol were less steep and reached a lower maximum than those for isoprenaline. The similar possibility of a partial agonist action for AQ 110 on the heart is suggested by the fact that our cardiac dose-response curves for this drug were less steep than those for isoprenaline. The direct positive chronotropic effect of AQ 110 is considered to be an important element in the tachycardia produced in the whole animal for the following reasons. The increase in heart rate could be produced by doses below the depressor threshold or could be present concomitantly with a stabilized blood pressure. With larger doses, the tachycardia could occur without any fall in mean or pulse pressure, could precede the decrease in diastolic pressure and often persisted after the latter had recovered. The extent to which reflex mechanisms contributed to the tachycardia in the whole animal was not determined, but this element must have been present when an appreciable blood pressure fall was produced. A fall in pulse pressure was unusual with AQ 110 ; usually there was no change or, with higher doses, a rise. This latter was achieved by an increase in systolic pressure which suggests that, at these doses of AQ 110, the cardiac effects were still increasing whereas the vasodilation had reached its zenith.

The depressor action of AQ 110, like those of isoprenaline and salbutamol, is due to a decrease in the total peripheral resistance. Because of the chemical resemblance of AQ 110 to papaverine (Fig. 1), a vasodilator action independent of the β_2-adrenoceptors was carefully sought, but we could find no evidence for such an effect. The hypotension in the whole animal, the vasodilation in the rabbit ear and the relaxant effects on the portal vein and thoracic aorta produced by AQ 110, salbutamol and

isoprenaline were all specifically antagonized by propranolol. On the perfused rabbit ear, AQ 110 and salbutamol were one-tenth as active as isoprenaline: this vasodilator ratio between salbutamol and isoprenaline is similar to that found by Cullum *et al.* (1969) on the skinned hind limb of the dog. Using the isolated ear artery, the relative potency of AQ 110 was found to be significantly increased (Table 1). This would suggest a greater vasodilator effect on the artery than on the other vascular components of the rabbit ear. This conclusion may not be justified, however, because the dosage used on the isolated artery was very much higher than that found necessary for the perfused ear.

The action of isoprenaline on the portal vein of the rabbit has two antagonistic components—an α-adrenoceptor stimulation producing contraction and a β_2-effect causing relaxation. These effects may be separated in at least two ways. First, by the lower threshold of the β-action. This was clearly described by Sutter (1965). Secondly, by the predominance of the β-action after the vessel has been pharmacologically contracted (*vide infra*). On the thoracic aorta only the α-effect is seen. Salbutamol exhibits only the α-effect on the vein and no action on the aorta. AQ 110 acts similarly, but that the contraction of the vein is an α-effect, though likely, has not been proved. However, after either vessel has been contracted pharmacologically, β-effects predominate—occasionally preceded by a slight, evanescent contraction. The α-actions on the peripheral circulation seem unimportant in the whole animal as the blood pressure responses remained unaffected by the administration of phentolamine. The presence of α-effects in a predominantly β_2-selective agent has previously been reported for soterenol (Dungan *et al.*, 1968).

The duration of action of AQ 110 was consistently found, in all the preparations studied, to be appreciably longer than that of isoprenaline and significantly longer than that of salbutamol. The negligible effect of desmethylimipramine on the cardiovascular responses in the whole animal shows that, like isoprenaline, AQ 110 is insignificantly removed by Uptake_1 into the nerve terminal. Cullum *et al.* (1969) found that salbutamol was not a substrate for catechol-O-methyl transferase (COMT), the enzyme mainly responsible for isoprenaline inactivation. This is not unexpected, as salbutamol has no catechol group. AQ 110 does have such a group, yet we found (unpublished data) that it was neither a substrate for nor a significant inhibitor of COMT. The absence of this latter activity, present in papaveroline (desmethyl papaverine, Burba & Murnaghan, 1965), was confirmed by the failure of AQ 110, even in large doses, to potentiate any of the effects of isoprenaline. In fact, the opposite occurred in all the preparations used, viz. the effects of isoprenaline were diminished if the drug was administered immediately after AQ 110. This tachyphylaxis was more marked the larger the initial dose of the agonist, suggesting desensitization, and was greater following AQ 110 and salbutamol than after isoprenaline. This strengthens our view that these three drugs compete at or near the same receptor locus and that AQ 110 and salbutamol are removed more slowly from this site of action than is isoprenaline. Although AQ 110 has a catechol group, which should react with COMT, the bulky substituent on the 1-position may interfere to prevent this: papaveroline has two catechol groups. Finally, the fact that equiactive doses of isoprenaline, AQ 110 and salbutamol were antagonized *to the same degree* by a given dose of the specific competitive β-antagonist, propranolol, further suggests (van Rossum, 1963) that the three agonists are interacting with the same receptors.

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