Br. J. Pharmac. (1972), **46**, 375–385.

Pharmacological actions of a new β-adrenoceptor agonist, MJ-9184-1, in anaesthetized cats

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Summary

1. The effects of (−)-isoprenaline and the new β-adrenoceptor agonist, MJ-9184-1, on the lungs, on the cardiovascular system, and on slow contracting skeletal muscle have been compared in cats under chloralose anaesthesia.

2. Both amines reduced the increases in airways resistance produced by 5-HT, depressed incomplete tetanic contractions of the soleus muscle, lowered the blood pressure and produced an increase in heart rate. In comparison with (−)-isoprenaline, MJ-9184-1 had a long duration of action.

3. The effects of MJ-9184-1 and (−)-isoprenaline were antagonized by the β-adrenoceptor antagonist, propranolol.

4. MJ-9184-1 was approximately half as potent as (−)-isoprenaline in its effects on pulmonary resistance and soleus muscle contractility, and one seventh as potent in producing chronotropic effects in the heart.

5. These results suggest that MJ-9184-1 possesses some specificity as a β_2 receptor stimulant.

Introduction

On the basis of the differing relative potencies of a number of sympathomimetic amines in producing β-adrenoceptor mediated effects in different tissues, Lands and his co-workers have proposed that β-receptors may be subclassified into two types, β_1 and β_2 receptors (Lands, Arnold, McAuliff, Luduena & Brown, 1967, and for reviews see Paton, 1969, and Raper & McCulloch, 1971).

From a clinical standpoint, the use of β_2-receptor agonists as sympathomimetic bronchodilators may be advantageous in that the side effect of tachycardia, which is due to β_1-receptor stimulation, may be avoided. However, skeletal muscle tremor which has also been noted as a side-effect (Legge, Gaddie & Palmer, 1971 ; Beumer, 1971) may be unavoidable in that, like the bronchodilator actions of the amines, it appears to be due to β_2-receptor stimulation (Bowman & Nott, 1970 ; Brittain, Jack & Ritchie, 1970).

In a series of ring substituted *N*-alkylethanolamines which possess β-receptor stimulant activity, increasing the bulk of the substituent on the amine nitrogen generally enhances agonistic potency, and also increases the relative specificity of the compounds for β_2 as opposed to β_1-receptor effects (Ariens, 1967 ; Lands & Brown, 1967 ; Brittain *et al.*, 1970).

* On leave from the Department of Pharmacology, University of Singapore.
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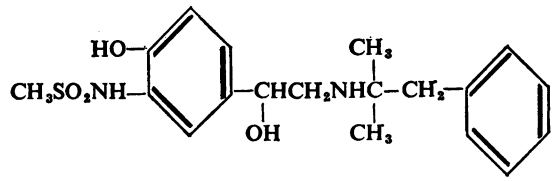

FIG. 1. 2'-Hydroxy-5'-[1-hydroxy-2-(2-methyl-1-phenyl-2-propylamino) ethyl] methanesulphonanilide hydrochloride (MJ-9184-1).

In the present experiments some cardiovascular, bronchial and skeletal muscle effects of MJ-9184-1 (Fig. 1) and of (−)-isoprenaline have been compared in anaesthetized cats. Some metabolic responses to MJ-9184-1 have been described by Rigglio, Comer & Roth (1972).

Methods

Adult cats of either sex were anaesthetized by the intraperitoneal injection of a mixture of chloralose (80 mg/kg) and sodium pentobarbitone (6 mg/kg). The trachea was cannulated but, except in experiments involving measurement of respiratory effects, the animals were allowed to breathe spontaneously. Body temperature was maintained at $37 \pm 0{\cdot}5°$ C by means of a thermostatically controlled electric heating blanket (Epil, Edinburgh). Drugs were injected through a cannulated brachial vein. Traces of the various parameters mentioned below were made with Grass (Type 7 and 79) ink writing pen recorders.

Cardiovascular system

General arterial blood pressure was recorded from a common carotid artery in experiments where contractions of the soleus muscle were recorded, and in the remaining experiments from a femoral artery with a Statham (model P23AC) pressure transducer. Heart rate was recorded with a Grass (model 7P4C) tachograph triggered by the arterial pulse.

Soleus muscle

The cat was laid prone on the operating table and the soleus muscle prepared for the recording of muscle contractions as described by Bowman & Nott (1970). The soleus nerve was stimulated with rectangular pulses of 100 μs duration and of about twice the strength necessary to evoke a maximal twitch. A pulse train of 8 Hz frequency was evoked for 1 s every 10 s. Isometric muscle tension was recorded with a Grass (model FT03) strain gauge. A resting tension of between 60 and 100 g was applied to the muscle and maintained at a constant level throughout each experiment.

Airways resistance

The method employed was adapted from that of Amdur & Mead (1958) as described by Bowman & Rodger (1972). Constant, submaximal bronchoconstrictor responses were induced by the intravenous injection of 5-hydroxytryptamine (5-HT) at 20 min intervals.

The increase in airways resistance in response to 5-HT was calculated from the

flow rate and the transpulmonary pressure at isovolumic points on the tidal volume record as described by Amdur & Mead (1958). The basis of this assessment is that at points of equal volume during a respiratory cycle the elastic forces contributing to the total lung resistance are equal. Therefore between two such points, any change in the transpulmonary pressure in conjunction with the change in airflow yields an assessment of the resistance to airflow in the lungs and bronchial passages.

In these experiments heart rate, arterial blood pressure and contractions of the soleus muscle were recorded simultaneously.

Expression of results

In the text, except where otherwise stated, results are expressed as the mean ± standard error.

The drugs used were (−)-isoprenaline bitartrate (Wyeth), MJ-9184-1 (Mead Johnson), bethanidine sulphate (Burroughs Wellcome), (±)-propranolol hydrochloride (Imperial Chemical Industries), 5-hydroxytryptamine creatinine sulphate (5-HT, B.D.H.). Stock solutions were freshly prepared and were diluted with 0·9% w/v NaCl solution immediately before injection. The doses quoted refer to the bases.

Results

Cardiovascular system

MJ-9184-1 produced vasodepressor and positive chronotropic responses in the anaesthetized cat. These effects were abolished by the prior injection of propranolol (0·5 mg/kg). The tachycardia produced by MJ-9184-1 was long lasting, responses to 0·1 μg/kg of the amine taking 30–45 min to return to control levels. Therefore, in experiments in which the effects of (−)-isoprenaline and MJ-9184-1 were compared, two or more cumulative dose-response curves for (−)-isoprenaline were first established, after which effects of cumulatively administered MJ-9184-1 were recorded. Each dose was injected at the peak of the rise in heart rate produced by the previous dose in the series. With both amines cumulative dosage was continued until a maximal rise in heart rate was attained (Fig. 2b). Control studies with (−)-isoprenaline showed that similar rises in heart rate were produced by single injections of the drug and by the equivalent total cumulative dose. Cumulative dose-response curves were recorded at 30–40 min intervals and found to be reproducible.

Fig. 2a shows dose response curves from an experiment in which the rises in heart rate produced by (−)-isoprenaline and MJ-9184-1 were compared. With each dose of (−)-isoprenaline in the series, the maximum increase in heart rate occurred 30 to 50 s from the time of injection, whereas with MJ-9184-1 responses reached a peak in 2 to 4·5 minutes. In 6 experiments the maximal heart rate following administration of MJ-9184-1 was 164 ± 8 beats per min, and of (−)-isoprenaline, 164 ± 7 beats per minute. These corresponded to rises in heart rate of 42 ± 9 and 46 ± 7 beats/min, respectively. Figure 3 shows the mean results from these experiments. Responses are expressed as percentages of the maximal rise in heart rate produced by (−)-isoprenaline plotted against the total cumulative log dose of the amines. The potency ratio for chronotropic activity was established at 50% of the maximum rise in heart rate produced by (−)-isoprenaline. On a weight basis

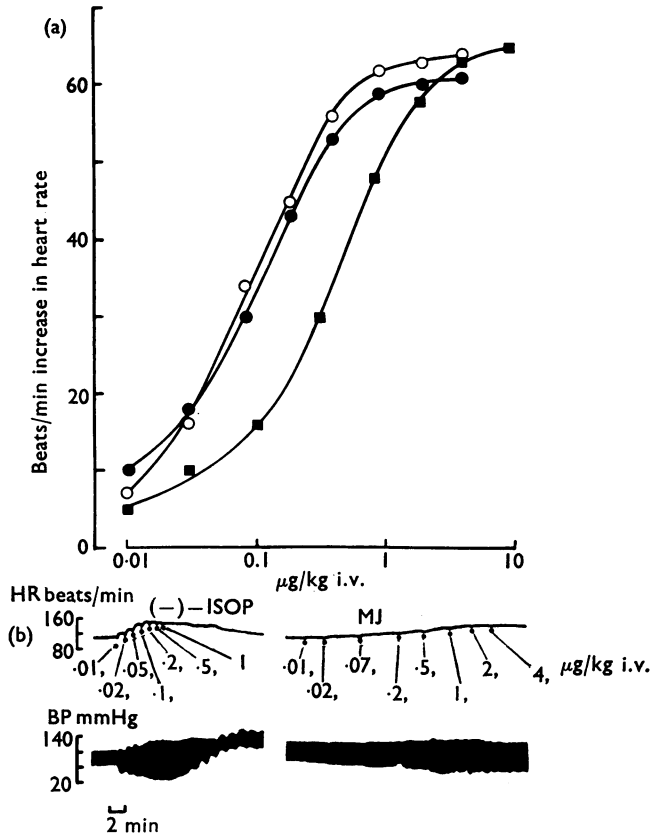

FIG. 2. Effects of (−)-isoprenaline and MJ-9184 on heart rate and blood pressure of the anaesthetized cat. (a) Results from an experiment in which two cumulative dose-response curves for (−)-isoprenaline (○ and ●) were followed by one for MJ-9184-1 (■). Increases in heart rate are expressed as absolute rises (beats per min) above control resting heart rate, and doses as the total cumulative doses administered. (b) Traces from parts of the experiment graphically represented above. Upper records: heart rate (HR, beats per min); lower records: blood pressure (BP, mmMg; 1 mmHg≡1·333 mbar). (−)-Isoprenaline ((−)-ISOP) injected cumulatively produced a maximal increase in heart rate of 48 beats/min and a maximal fall in diastolic blood pressure of 45 mmHg. Following the final dose in the series, the time for half recovery from the fall in diastolic blood pressure was approximately 1·5 min and from the rise in heart rate approximately 6 minutes. Following the cumulative administration of MJ-9184-1 (MJ), the maximal increase in heart rate was 46 beats/min and fall in diastolic blood pressure 40 mmHg. The time to half recovery from the final administered dose of MJ-9184-1 was approximately 50 min for diastolic blood pressure and 150 min for the effects on heart rate.

MJ-9184-1 was found to be 6·8 ± 2·2 times less potent than (−)-isoprenaline. After the maximal chronotropic response to (−)-isoprenaline had been produced the heart rate returned to control levels. For (−)-isoprenaline the time to half return was 6 to 20 min in different experiments. In two experiments with MJ-9184-1, the time to half return was 125 and 190 minutes. In the remaining experiments, propranolol (0·5 mg/kg), injected intravenously 5 min after the final dose of MJ-9184-1 in the series, completely antagonized the persistent positive chronotropic effect of MJ-9184-1 within 5 to 10 minutes.

The possibility that part of the chronotropic response to (−)-isoprenaline or MJ-9184-1 was due to a reflex rise in cardiac sympathetic tone, resulting from the

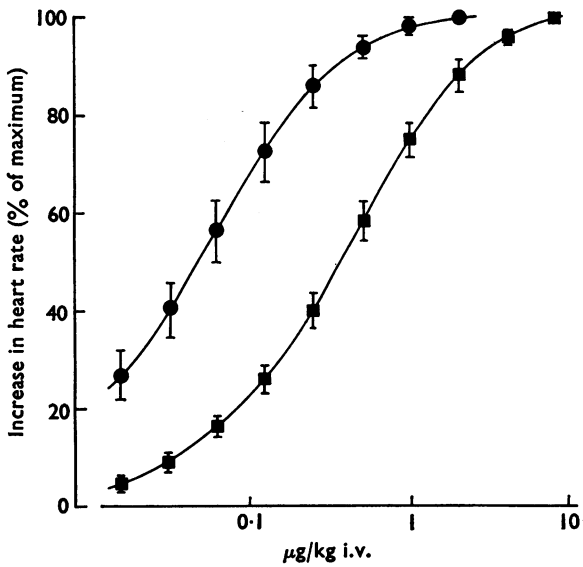

FIG. 3. Mean (±S.E.) results from 6 experiments showing the effects of (−)-isoprenaline (●) and MJ-9184-1 (■) on heart rate. Responses are expressed as percentages of the maximal increase produced by (−)-isoprenaline in each experiment.

vasodepressor action of the amines, was investigated in 6 experiments. After control cumulative dose-response curves to (−)-isoprenaline had been established, bethanidine (2–4 mg/kg) was injected intravenously. Within 30 min adrenergic neurone blockade was present as shown by the abolition of the carotid occlusion reflex. Cumulative dose-response curves to (−)-isoprenaline were then re-established and were followed by a dose-response curve to MJ-9184-1. In 6 experiments the mean dose of (−)-isoprenaline required to produce 50% maximal chronotropic activity was 0·055 ± 0·005 μg/kg before and 0·088 ± 0·019 μg/kg after adrenergic neurone blockade. There is no significant difference ($0{\cdot}1<P<0{\cdot}125$) between these means. After administration of bethanidine, comparison of dose response curves at 50% of the maximal response showed that on a weight basis, MJ-9184-1 was 5·6 ± 1·5 times less potent than (−)-isoprenaline in producing a positive chronotropic response. This value does not differ significantly ($0{\cdot}3<P<0{\cdot}5$) from that obtained in experiments performed in the absence of bethanidine.

During the cumulative administration of (−)-isoprenaline, depressor responses were of a shorter duration than were the rises in heart rate, while with MJ-9184-1, vasodepression was maintained at each dose level injected in the series. The maximum falls in diastolic blood pressure produced by (−)-isoprenaline and MJ-9184-1 were similar. Due to the differing time courses of the depressor responses to the two amines, accurate potency ratios could not be established. However, when comparing the minimum doses of (−)-isoprenaline (0·33 ± 0·05 μg/kg) and MJ-9184-1 (1·2 ± 0·3 μg/kg) required to produce a maximal fall in diastolic blood pressure, MJ-9184-1 was approximately 4 times less potent than (−)-isoprenaline. In animals pretreated with bethanidine, depressor responses to (−)-isoprenaline were of longer duration than those found in untreated animals. In these experiments MJ-9184-1 was also found to be about 4 times less potent than (−)-isoprenaline.

Soleus muscle

MJ-9184-1, like adrenaline and isoprenaline (Bowman & Zaimis, 1958), produced a decrease in the tension and duration of the maximal twitch, and a pronounced decrease in the fusion of incomplete tetanic contractions of the cat soleus muscle.

The effect of MJ-9184-1 and (−)-isoprenaline on contractions of the soleus muscle were recorded during cumulative dose administration of the amines as described by Nott & Raper (1972). Figure 4 shows the results from one of the experiments. MJ-9184-1 possessed a long duration of action on the soleus muscle,

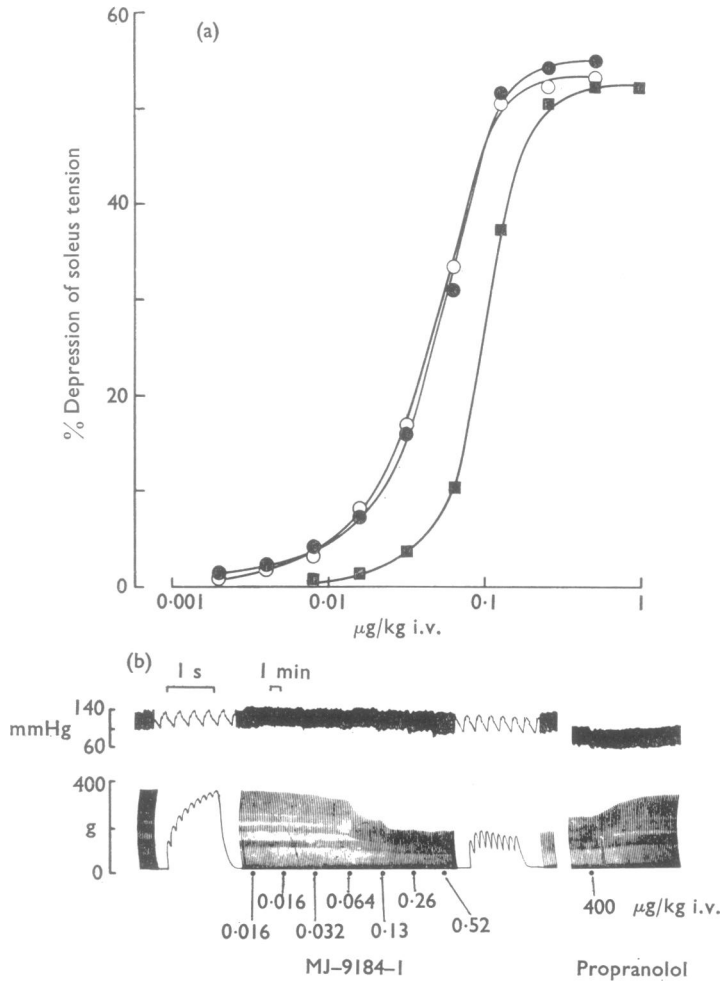

FIG. 4. Depression of submaximal tetanic contractions of the cat soleus muscle by (−)-isoprenaline and MJ-9184-1. (a) Results from an experiment in which two cumulative dose-response curves for (−)-isoprenaline were established in the order ○ and ●, and followed by a cumulative dose-response curve for MJ-9184-1 (■). Responses are expressed as a percentage reduction from control and doses as total cumulative doses administered. (b) Part of the experiment graphically represented above. Contractions of a soleus muscle were evoked by stimulating the motor nerve at a frequency of 8 Hz for 1s every 10 seconds. The pen recording includes two contractions recorded on fast moving paper. The upper record is of general arterial blood pressure. MJ-9184-1 was injected cumulatively with the doses shown. The half recovery time for the effect of MJ-9184-1 on the soleus contractions was 90 minutes. Propranolol antagonized the effect of MJ-9184-1. Time between panels is 95 minutes.

and therefore, in these experiments, dose-response curves for (−)-isoprenaline were first established, after which the responses to MJ-9184-1 were obtained. (−)-Isoprenaline caused a maximum depression of developed tension of 52·2 ± 2·5% and the time to half return from the maximal response to (−)-isoprenaline was 3·5–4·5 minutes. The maximal depression produced by MJ-9184-1 was 99·9 ± 0·8% of that produced by (−)-isoprenaline (= 100%) in the same experiments. Following the cumulative dose of MJ-9184-1 just large enough to cause maximal depression, the time to half return of responses was 15 to 45 minutes. When doses two to four times greater than those required for maximal responses were used, the time to half return was 1·5 hours. Figure 5 shows the means of the results from dose response determination in all six experiments. Relative potencies calculated at 50% of the maximal depression of the soleus muscle contraction showed that on a weight basis, MJ-9184-1 was 2·7 ± 0·4 times less potent than (−)-isoprenaline. The intravenous injection of the β-receptor antagonist propranolol (0·5 mg/kg) reversed the depression of the muscle contractions produced by MJ-9184-1 (Fig. 4).

Respiratory system

In each experiment, bronchoconstrictor responses to 5-HT were produced at 20 min intervals. The dose of 5-HT chosen (1 to 10 μg/kg in different experiments) was sufficiently large to produce a considerable degree of bronchoconstriction, but was insufficient to cause appreciable changes in blood pressure, heart rate or soleus muscle contractions. With doses of 5-HT greater than 20–50 μg/kg, there was a decrease in the fusion of incomplete tetanic contractions of the soleus muscle. This

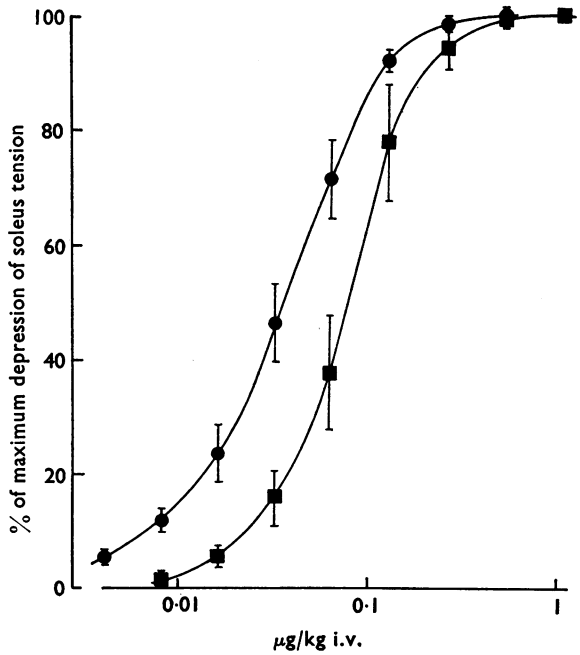

FIG. 5. Mean (±S.E.) results from 6 experiments showing the effects of (−)-isoprenaline (●) and MJ-9184-1 (■) on incomplete tetanic contractions of the cat soleus muscle. Responses are expressed as percentages of the maximal depression produced by (−)-isoprenaline in each experiment, and doses as total cumulative doses administered.

was probably a consequence of endogenous catecholamine release, since the effect could be blocked by the prior injection of the β-receptor antagonist propranolol.

After at least two control responses to 5-HT had been obtained, a dose of MJ-9184-1 or (−)-isoprenaline was injected some 20 min later. The next dose of 5-HT in the series was injected when the effects of the sympathomimetics on heart rate and on contractions of the soleus muscle were at their maximum. This was 30 to 50 s after the injection of (−)-isoprenaline and 2 to 4·5 min after the injection of MJ-9184-1. In each experiment this procedure was repeated, and the effects of three or more doses of MJ-9184-1 and (−)-isoprenaline were tested. The sympathomimetics reduced the increase in airways resistance produced by 5-HT. Dose-response curves were plotted; increases in the airways resistance in the presence of (−)-isoprenaline or MJ-9184-1 were expressed as a percentage reduction of that produced by 5-HT alone. The bronchoconstrictor responses to 5-HT returned to control levels within 20 min of the injection of (−)-isoprenaline. The effects of MJ-9184-1 were much longer lasting. In 8 experiments, responses to 5-HT returned to control levels 40 to 80 min after injections of 0·1 to 0·2 μg/kg of MJ-9184-1.

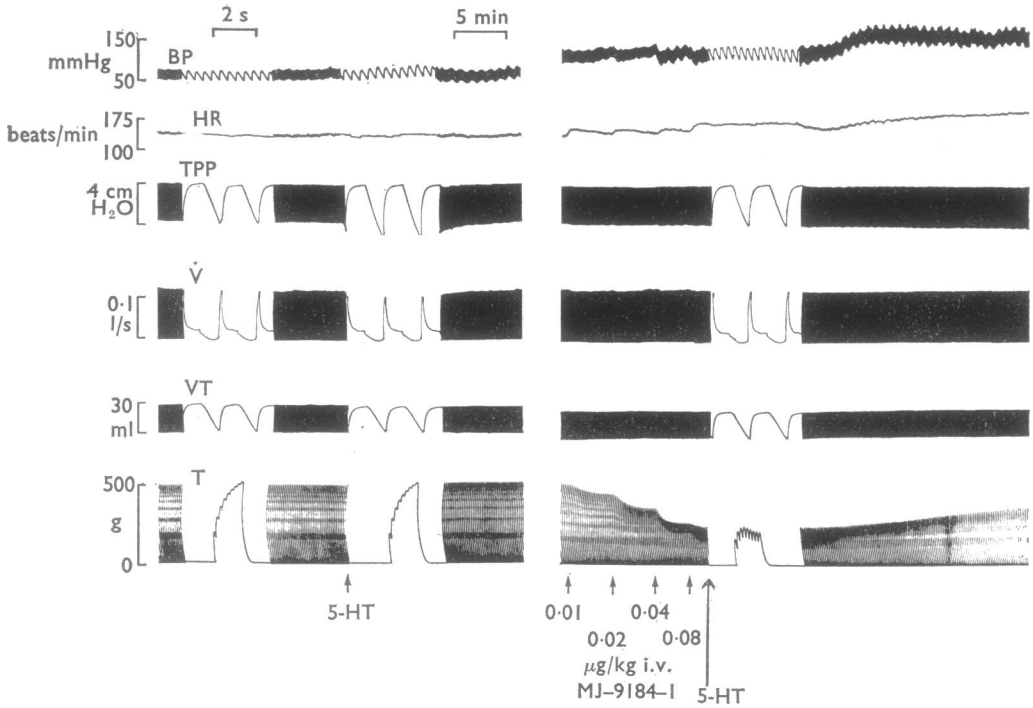

FIG. 6. Effects of MJ-9184-1 on bronchoconstrictor responses to 5-HT. Traces, from the top: general arterial blood pressure (BP), heart rate (HR), transpulmonary pressure (TPP), air flow ($\dot{V}$), tidal volume (VT), and incomplete tetanic contractions of the soleus muscle (T) in response to motor nerve stimulation at 8 Hz for 1 s every 10 seconds. Fast records were made during a control period, at the peak of activity of 5-HT alone, and at the peak of activity of 5-HT after injection of MJ-9184-1. Following 5-HT (2·5 μg/kg i.v.) transpulmonary pressure increased and air flow decreased. The maximum effects occurred within 8 to 12 s of 5-HT administration. MJ-9184-1 was administered cumulatively to produce a total dose of 0·15 μg/kg i.v. This dose of MJ-9184-1 produced a fall in diastolic blood pressure of 20 mmHg, an increase in heart rate of 35 beats/min and a reduction of 52% in contractility of the soleus muscle. After MJ-9184-1 the effects of 5-HT on transpulmonary pressure and air flow were almost abolished, the calculated increase in airways resistance being reduced by 96%.

Figure 6 illustrates results from an experiment in which the bronchoconstrictor effects of 5-HT were antagonized after a total cumulative dose of 0·15 μg/kg MJ-9184-1. Figure 7 shows dose-response curves for the effects of MJ-9184-1 and (−)-isoprenaline on 5-HT-induced increased airways resistance from one of the 8 experiments performed.

In all experiments dose-response curves for MJ-9184-1 and (−)-isoprenaline were close to parallel. MJ-9184-1 was 2·4 ± 0·4 times less potent than (−)-isoprenaline on a weight basis in causing a 50% reduction in the bronchoconstrictor response to 5-HT.

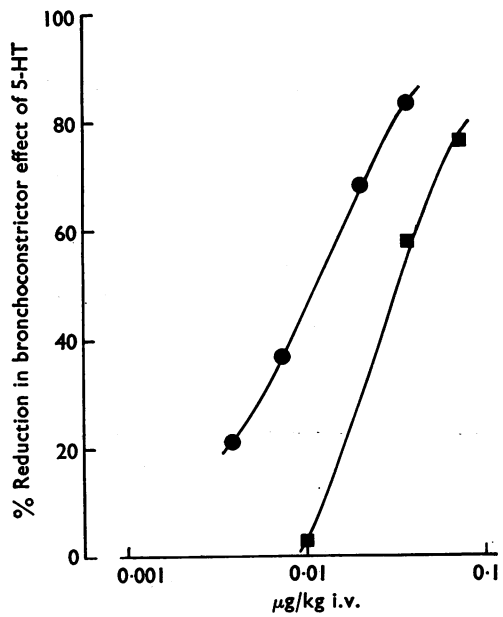

FIG. 7. Dose response curves from a typical experiment in which the effects of (−)-isoprenaline (●) and MJ-9184-1 (■) were compared for their ability to reduce the increase in airways resistance produced by 5-HT (5 μg/kg i.v.). Each point represents the effect produced by a single dose of a sympathomimetic expressed as a percentage reduction of the control response to 5-HT.

Discussion

Table 1 shows the doses of (−)-isoprenaline and MJ-9184-1 required to reduce 5-HT-induced increases in airways resistance by 50%, and to produce 50% of the maximal increase in heart rate and depression in soleus muscle contractility. The dose of a sympathomimetic required to reduce the effect of 5-HT on airways resistance is dependent on the degree of bronchoconstriction induced, which in turn, is dependent on the sensitivity of the cat and on the dose of 5-HT used (Bowman & Rodger, 1972). However, the potency ratio of MJ-9184-1 and (−)-isoprenaline was consistent from one experiment to another and was thus independent of the degree of bronchoconstriction induced by 5-HT. With (−)-isoprenaline, all doses sufficient to reduce 5-HT-induced changes in airways resistance also produced a depression in the contractions of the soleus muscle, and a rise in heart rate. Similar effects were produced with the highest doses of MJ-9184-1 used; however, at lower

TABLE 1. *Effects of (−)-isoprenaline and MJ-9184-1 on airways resistance, heart rate and soleus muscle contractility in the cat*

		Reduction in 5-HT-induced increase in airways resistance	Increase in heart rate*	Depression in soleus contractions
Mean dose (μg/kg i.v.) required for 50% maximal effect	(−)-isoprenaline	0·016±0·005	0·055±0·005	0·041±0·007
	MJ-9184-1	0·041±0·013	0·37 ±0·06	0·089±0·019
Mean relative potency [(−)-isoprenaline=1]	By weight	0·42 ±0·07	0·15 ±0·05	0·37 ±0·05
	Molar	0·71 ±0·12	0·27 ±0·09	0·66 ±0·09

All values expressed as mean±S.E. of at least 6 experiments. * Determined before bethanidine; no significant change after bethanidine.

dose levels, bronchodilator effects and effects on the soleus muscle, although accompanying each other, were not associated with tachycardia.

It has been suggested that cardiac stimulant effects are subserved by β_1-receptors, whereas bronchodilation and effects on skeletal muscle are due to stimulation of β_2-receptors (Lands *et al.*, 1967 ; Lands, Luduena & Buzzo, 1967 ; Bowman & Nott, 1970). Differential selectivity for β_1-receptors in the heart and for β_2-receptors in bronchial and skeletal muscle is apparent when comparing potency ratios of MJ-9184-1 and (−)-isoprenaline in the present experiments (Table 1). The potency of MJ-9184-1 relative to that of (−)-isoprenaline is similar with respect to bronchodilatation and activity in depressing soleus contractility. However, there is wider separation between potencies of MJ-9184-1 and (−)-isoprenaline in producing tachycardia.

In conclusion, MJ-9184-1 is a long acting β-receptor agonist with a relatively selective action on β_2-receptors. This selectivity of action suggests that in comparison with (−)-isoprenaline it might produce bronchodilation with less likelihood of concomitant cardiac side effects. However, its potent effects on skeletal muscle suggest that, if it is used as a bronchodilator, skeletal muscle tremor may be produced in some patients.

We thank Mr. J. Houston for technical assistance and Mead Johnson, Co., and Wyeth & Bro. Ltd. for gifts of drugs. We are indebted to the Wellcome Foundation for a grant towards apparatus, and to the Medical Research Council for a grant towards animals. One of us (I. W. R.) was in receipt of a Medical Research Council Scholarship.

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(*Received May 30, 1972*)