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INVESTIGATION OF THE MECHANISM OF PROPRANOLOL-INDUCED BRONCHOCONSTRICTION

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1 Dose-related increases in airways resistance (R_{aw}) and decreases in dynamic lung compliance (C_{dyn}) were recorded in guinea-pigs and rats following intravenous injection of propranolol and of the cardioselective β-adrenoceptor blocking drugs, atenolol and practolol.

2 The bronchoconstriction reached a peak in 2 to 4 min and subsided within 15 min. Repeated injections caused identical responses in the airways.

3 The isomer (+)-propranolol, which has only weak β-adrenoceptor blocking activity, produced identical responses when given alone or when given after a dose of the racemate, sufficient to cause measurable β-adrenoceptor blockade in the lungs.

4 After the initial bronchospasm had subsided, the β-adrenoceptor blocking drugs and the isomer, (+)-propranolol, produced potentiation of the bronchoconstrictor effects of 5-hydroxytryptamine and histamine.

5 Both the bronchospasm and the potentiation occurred in adrenal demedullated rats.

6 The results indicate that the bronchoconstrictor effects of these drugs are unrelated to β-adrenoceptor blockade in the airway smooth muscle.

Introduction

The observation that the β-adrenoceptor blocking drug, (±)-propranolol, could cause bronchoconstriction was made shortly after its introduction into clinical use. Initially this bronchoconstrictor effect was reported in asthmatics (McNeill, 1964) but subsequent investigation showed that propranolol could also cause bronchospasm in normal subjects (McNeill & Ingram, 1966; Stone, Sarkar & Keltz, 1973; Kumana, Marlin, Kaye & Smith, 1974). Similar bronchoconstrictor effects have been reported with other β-adrenoceptor blocking drugs, including those of the cardioselective type (Macdonald & McNeill, 1968; Powles, Shinebourne & Hamer, 1969; Johnsson, Svedmyr & Thiringer, 1975; Skinner, Palmer & Kerridge, 1975).

It has generally been assumed from the clinical studies that the bronchospasm is due to the blockade of β-adrenoceptors in the smooth muscle thus removing a sympathetic bronchodilator drive to the airways (Macdonald, Ingram & McNeill, 1967). However, because it has been difficult to reproduce the bronchoconstrictor effects in animals, no detailed study of the mechanism of action has been undertaken.

It was therefore decided to look for a method which would record the bronchoconstrictor effect of the β-adrenoceptor blocking drugs in animals. The sensitive recording method, devised by Mead & Whittenberger (1953) and modified by Green & Widdicombe (1966), was found to be suitable in guinea-pigs and rats. The results obtained show that there is apparently no correlation between the bronchospasm and the blockade of β-adrenoceptors in the lung produced by the β-adrenoceptor blocking drugs. A preliminary account of this work has been presented to the British Pharmacological Society (Maclagan & Ney, 1977).

Methods

Guinea-pigs (400 to 1100 g) of the Dunkin Hartley strain supplied by David Hall or Redfern; and rats (390 to 850 g) of two strains, either Sprague–Dawley supplied by Charles River, or Chester Beatty bred at The Royal Free Medical School, were used. They were lightly anaesthetized with urethane (1.25 g/kg) or pentobarbitone sodium (40 mg/kg) injected intraperitoneally and they breathed spontaneously. The right carotid artery was cannulated for the measurement of blood pressure and a cannula was placed in the left jugular vein for the injection of drugs.

Airways resistance (R_{aw}) and dynamic lung com-

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pliance (C_{dyn}) were measured by the subtractor method of Mead & Whittenberger (1953) modified by Green & Widdicombe (1966). A polythene cannula of known resistance to flow, was placed in the trachea and connected in series with a Fleisch pneumotachograph (Serial No. 4/0). Airflow ($\dot{V}$) through the Fleisch head was measured with a differential air pressure transducer (Statham PM15ETC) and this flow signal was integrated to give the tidal volume (V_T). Transpulmonary pressure (TPP) was recorded with a second Statham pressure transducer (PM5E) which measured the pressure difference between the tracheal cannula and a cannula sealed in the intrapleural cavity.

The TPP signal, on the x axis, was continuously plotted against the $\dot{V}$ signal on the y axis of an oscilloscope so that a 'loop' was displayed for each breath. The V_T signal was passed through a potentiometer to earth and the resulting output was also connected to the x axis, using a differential amplifier. By adjusting the potentiometer, a part of the V_T signal, proportional to the C_{dyn}, could be electrically subtracted from the TPP leaving only the pressure required to overcome the flow of air through the airways. This point is reached when the oscilloscope 'loop' becomes a straight line, whose slope provides a measure of the airways resistance according to the equation:

$$R_{aw} = \text{slope} \times \frac{\text{TPP cmH}_2\text{O/division}}{\dot{V}\text{ls}^{-1}\text{/division}}.$$

The slope of the line was measured directly from the oscilloscope, during the inspiratory phase of each breath, with a rotating protractor mounted on the screen. Subtraction of the cannula resistance from this value gave the airways resistance.

The value of the V_T signal which had been subtracted, was recorded on a counter (numbered from 0 to 1000) attached to the potentiometer and from this value the C_{dyn} could be calculated as follows:

$$C_{dyn} = \frac{1000}{1000 - \text{potentiometer reading}} \times \frac{V_T\,\text{ml/division}}{\text{TPP cmH}_2\text{O/division}}.$$

The $\dot{V}$ signal was calibrated using a Rotameter Series 1100, range 0.1 to 1.2 $ls^{-1}s^{-1}$ (GEC Elliott Process Instruments), the V_T using a 1 ml syringe and the TPP using an industrial water manometer Type 504 range 0 to 7.5 cmH_2O (Airflow Developments Ltd.). The calibrations were made at the beginning and end of each experiment and the resistance of the tracheal cannula was measured from the oscilloscope (range 11.5 to 35 $cmH_2O\,l^{-1}\,s^{-1}$). In all experiments a permanent record of the signals was made with a pen-recorder and values of airways resistance and compliance could also be calculated from these traces.

Experiments on adrenal demedullated rats

In these experiments 10 male albino Sprague–Dawley litter-mates were used. Adrenal enucleations were performed on 5 of the rats as described by Evans (1936). This involved removal of the cortex and medulla, leaving the capsule and some adhering cells which rapidly regenerate. For 14 days after this operation the rats were given 0.9% w/v NaCl solution in place of drinking water. Sham-operations were performed on the remaining 5 rats but their adrenals were only exposed and not removed. The acute experiments were performed 3 months after the adrenal enucleations when the rats weighed between 600 to 850 g. By this time the cortex had regenerated (Buckingham & Hodges, 1975).

In order to determine that the adrenal enucleations had been complete and that there was no medullary tissue capable of producing catecholamines in the regenerated adrenal glands, fluorescence histochemistry was carried out. At the end of the acute experiments, the adrenal tissue was removed and frozen in isopentane cooled in liquid nitrogen. The procedure for the visualization of both adrenaline and noradrenaline by the formaldehyde-induced fluorescence method (Falck & Owman, 1965) was followed. The sodium borohydride test was used to determine the specificity of the fluorescence (Corrodi, Hillarp & Jonsson, 1964).

Drugs

Drugs were made up in 0.9% w/v NaCl solution (saline) and injected in a volume not exceeding 0.2 ml. All β-adrenoceptor blocking drugs were injected slowly and washed in with 0.2 ml of saline. The following drugs were used: histamine acid phosphate (BDH), 5-hydroxytryptamine creatinine sulphate (BDH), atropine sulphate (BDH), isoprenaline sulphate (Burroughs Wellcome), quinidine sulphate (Burroughs Wellcome). The β-adrenoceptor blocking drugs (±)-propranolol, practolol and atenolol and the isomer (+)-propranolol were supplied by ICI. Addition of ascorbic acid to the solutions of isoprenaline sulphate was not possible because this vehicle caused changes in the respiratory pattern. Consequently fresh isoprenaline solutions were prepared every 60 min and it was shown that the solution was stable for this period of time as reproducible bronchodilator responses could be obtained to repeated test doses.

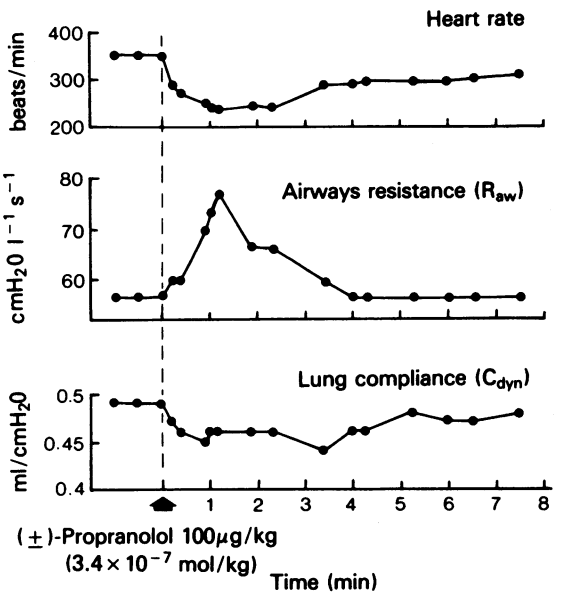

Figure 1 Time course of the bronchoconstriction and bradycardia produced by (±)-propranolol 3.4 × 10^{-7} mol/kg in a guinea-pig. The airways resistance (R_{aw}; $cmH_2O\ l^{-1}\ s^{-1}$), dynamic lung compliance (C_{dyn} ml/cmH_2O) and heart rate (beats/min) are plotted on the ordinate scale against time on the abscissa scale.

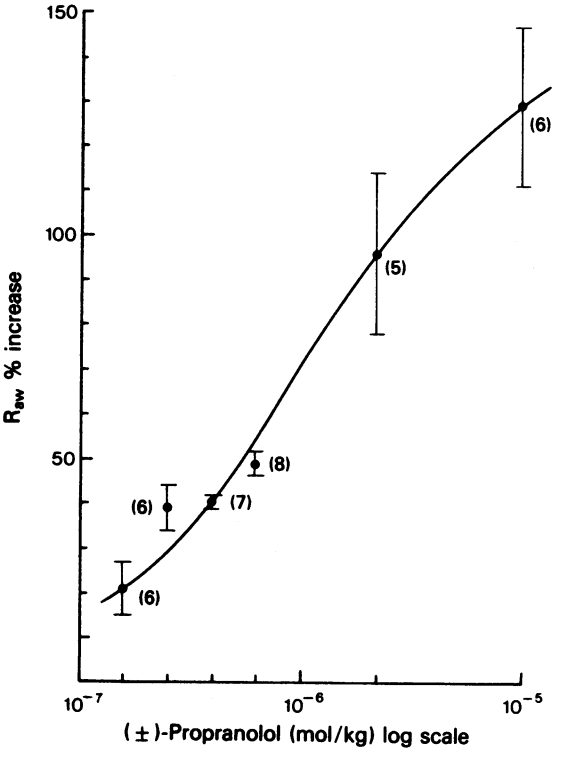

Figure 2 The effect of (±)-propranolol on airways resistance in guinea-pigs. The increases in R_{aw}, expressed as % changes, with reference to the value immediately before injection of the drug, are plotted on the ordinate scale, against dose of propranolol on a log scale on the abscissae. Values are mean results; vertical bars give s.e. mean and the numbers in parentheses refer to the number of observations.

Results

The resting values of airways resistance were comparable in the two species used in these experiments, guinea-pigs (mean R_{aw} = 44.3 ± 6.3, n = 23) and rats (R_{aw} = 42 ± 3.7, n = 13). In general the smaller animals had higher resistance values. The dynamic lung compliance was also of the same order of magnitude in the two species (mean C_{dyn} for guinea-pigs was 0.98 ml/cmH_2O ± 0.18, n = 23; and for rats C_{dyn} = 0.65 ± 0.09, n = 13).

The resting values recorded from animals anaesthetized with urethane were compared with those obtained in the sodium pentobarbitone anaesthetized animals and no significant differences were found between the two groups. In addition, the choice of anaesthetic did not affect the responses of the airways to the various drugs used in these experiments and the results in this paper include data obtained with both anaesthetics.

Effect of (±)-propranolol on the airways

Intravenous injection of the racemic mixture of propranolol caused a rapid and short lasting increase in airways resistance and a corresponding decrease in dynamic lung compliance. Similar results were obtained in guinea-pigs and rats and of the figures selected for this paper, four illustrate the effects recorded in guinea-pigs and three show the results in rats. The bronchoconstriction produced by 3.4 × 10^{-7} mol/kg (±)-propranolol in a guinea-pig is shown in Figure 1. When larger doses of propranolol were given the bronchospasm was more prolonged but the effect never lasted more than 15 min after injection, even at the highest dose used (1.7 × 10^{-5} mol/kg).

The propranolol-induced increase in R_{aw} was dose-related (Figure 2) as was the decrease in C_{dyn}. The percentage changes in resistance were consistently larger than the percentage changes in compliance; for example, a dose of 3.4 × 10^{-6} mol/kg of propranolol (shown in Figure 2) caused a 96% ± 18 (n = 5) increase in R_{aw} whereas the mean decrease in C_{dyn} for this dose was only 11.2% ± 3 (n = 5). In rats the increase in R_{aw} produced by this dose of (±)-proprano-

lol was 81.2% ± 13.4 ($n = 5$), while the decrease in C_{dyn} was 12.98% ± 3.42 ($n = 5$).

It was also notable that when repeated injections of the same dose of (±)-propranolol were given to any animal, the resulting bronchonconstrictions were always of the same magnitude and at no time was any tachyphylaxis to the drug observed in the lung. However, the bradycardia produced by (±)-propranolol outlasted the effect on the lung and consequently successive doses of propranolol caused variable effects on the heart-rate, depending on the time interval between injections.

Effects of the cardioselective β-adrenoceptor blocking drugs

Practolol and atenolol also produced dose-dependent bronchoconstrictions which followed an identical time-course to those produced by propranolol. Figure 3 compares the effect of these three drugs and shows that atenolol caused greater increases in R_{aw} than propranolol, whereas practolol had less effect and these differences were statistically significant (Student's t test).

Effect of (+)-propranolol

The effect of intravenous injection of (+)-propranolol which has only weak β-adrenoceptor blocking activity, was investigated.

The results showed that the degree of bronchoconstriction produced by (+)-propranolol was not significantly different from that produced by the racemate; for example, in rats, a dose of 3.4×10^{-7} mol/kg (+)-propranolol gave a mean 35.2% ± 2.15 ($n = 26$) increase in R_{aw} which is comparable to the increase of 39.3% ± 5.3 ($n = 10$) produced by the same dose of the racemate. The time course of the bronchospasm was also identical for the two drugs and as with the racemate it was found that there was no tachyphylaxis to the (+)-propranolol-induced bronchospasm. These points are illustrated for one rat in Figure 4.

Relationship between β-adrenoceptor blockade and bronchoconstriction

The relationship between β-adrenoceptor blockade and bronchoconstriction was studied by comparing the bronchospasm and blockade produced by an injection of the racemate, (±)-propranolol.

The degree of β-adrenoceptor blockade produced in the heart and lungs by (±)-propranolol, was assessed by measuring the antagonism of isoprenaline-induced bronchodilatation and tachycardia, in five rats and four guinea-pigs. The lower sections of Figure 5 show the responses of the heart and lungs

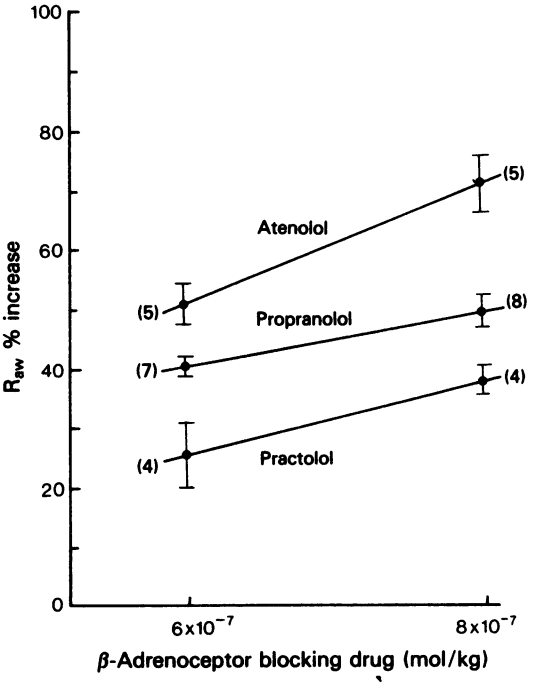

Figure 3 Comparison of the effect of (±)-propranolol, atenolol and practolol on airways resistance in guinea-pigs. Values are plotted as in Figure 2. The bronchoconstriction produced by atenolol is significantly greater and that produced by practolol is significantly less than the effect of (±)-propranolol. ($P < 0.02$ at both dose levels compared with mean values for (±)-propranolol; Student's t test).

to test doses of isoprenaline before and after 3.4×10^{-6} mol/kg (±)-propranolol in a rat. The upper section of the figure shows the bronchospasm which occurs immediately after the injection of the β-adrenoceptor blocking drug. There is a marked difference between the duration of the bronchospasm, which subsides in a few minutes, and the duration of the β-adrenoceptor blockade in the lungs which lasts for nearly 1 h.

In another series of experiments the bronchoconstrictor effect of (+)-propranolol was studied after administration of a dose of the racemate sufficient to cause β-adrenoceptor blockade. The degree of the blockade was again assessed by measuring the antagonism of test doses of isoprenaline. Identical results were obtained in two guinea-pigs and four rats and the responses recorded in one rat are shown in Figure 4. Repeated injection of (+)-propranolol caused a consistent degree of bronchoconstriction (top section) both before and during the β-adrenoceptor blockade produced in the airways and heart by (±)-propranolol (lower sections).

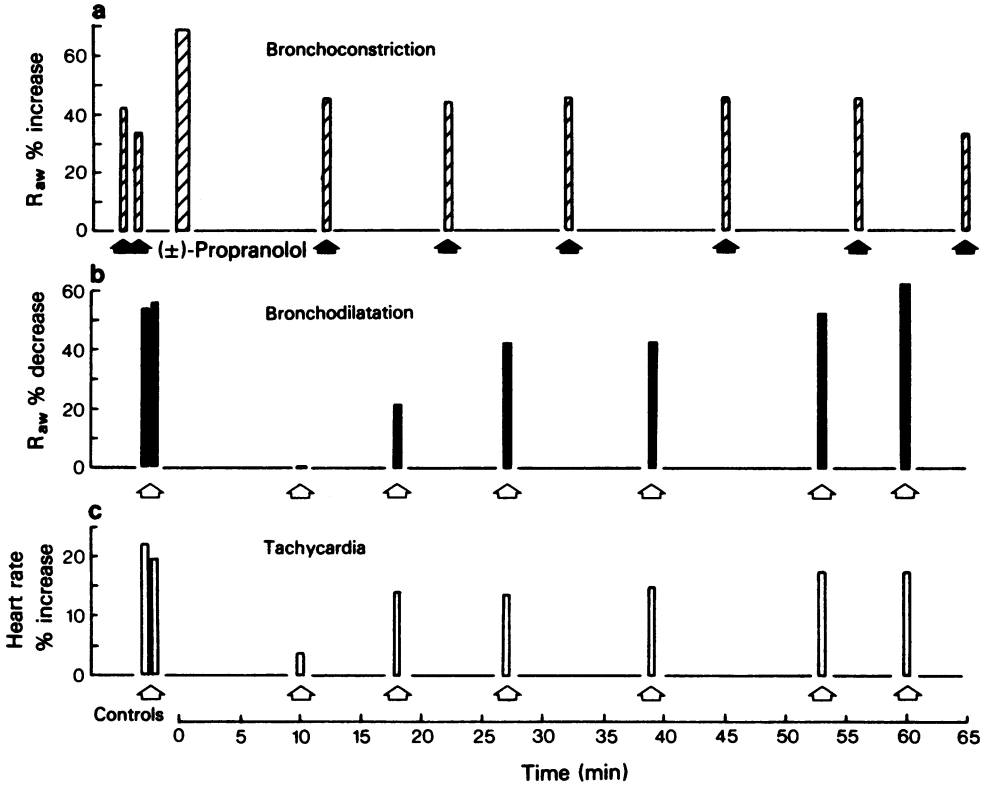

Figure 4 Bronchoconstrictor responses to (+)-propranolol before and after β-adrenoceptor blockade induced by (±)-propranolol 3.4×10^{-6} mol/kg in a rat. The degree of β-adrenoceptor blockade in the heart and lungs, produced by the racemate, was assessed with test doses of isoprenaline. The bronchodilatation (b) and tachycardia (c) produced by isoprenaline (open arrows, 1 μg/kg) and the bronchoconstriction (a) produced by (+)-propranolol (solid arrows, 3.4×10^{-7} mol/kg) and (±)-propranolol are plotted as in Figure 5. The bronchoconstrictor responses to test doses of (+)-propranolol were constant throughout the experiment despite the production of β-adrenoceptor blockade by the racemate.

Adrenal demedullated rats

The effects of intravenous (+)-propranolol were also studied in adrenal demedullated rats in which it caused bronchoconstriction which was not significantly different from that obtained in sham-operated control rats (Figure 6). The time course of the response was also unaltered. Adrenal tissue, removed at the end of these experiments was examined by fluorescence microscopy and the absence of catecholamines in the adrenal demedullated rats was confirmed.

Effect of atropine

The possibility that the β-adrenoceptor blocking drugs might be initiating a reflex bronchoconstriction was investigated by measuring the increases in airways resistance before and after atropine. Table 1 shows that atropine (1 mg/kg) did not alter the degree of bronchoconstriction induced by propranolol in guinea-pigs. The time course of the response was also unaffected.

Effect of quinidine

The effect of quinidine sulphate (i.v.) was recorded in guinea-pigs. It was found that while injection of quinidine resulted in considerable decreases in heart rate and blood pressure, similar to those produced by (±)-propranolol, no changes in the resting R_{aw} or C_{dyn} were observed at any dose level tested from 3.4×10^{-7} to 2×10^{-6} mol/kg.

Potentiation of histamine and 5-hydroxytryptamine-induced bronchoconstriction

In all the experiments described in this paper, it was found that the bronchoconstrictor responses to histamine and 5-hydroxytryptamine (5-HT) were greatly

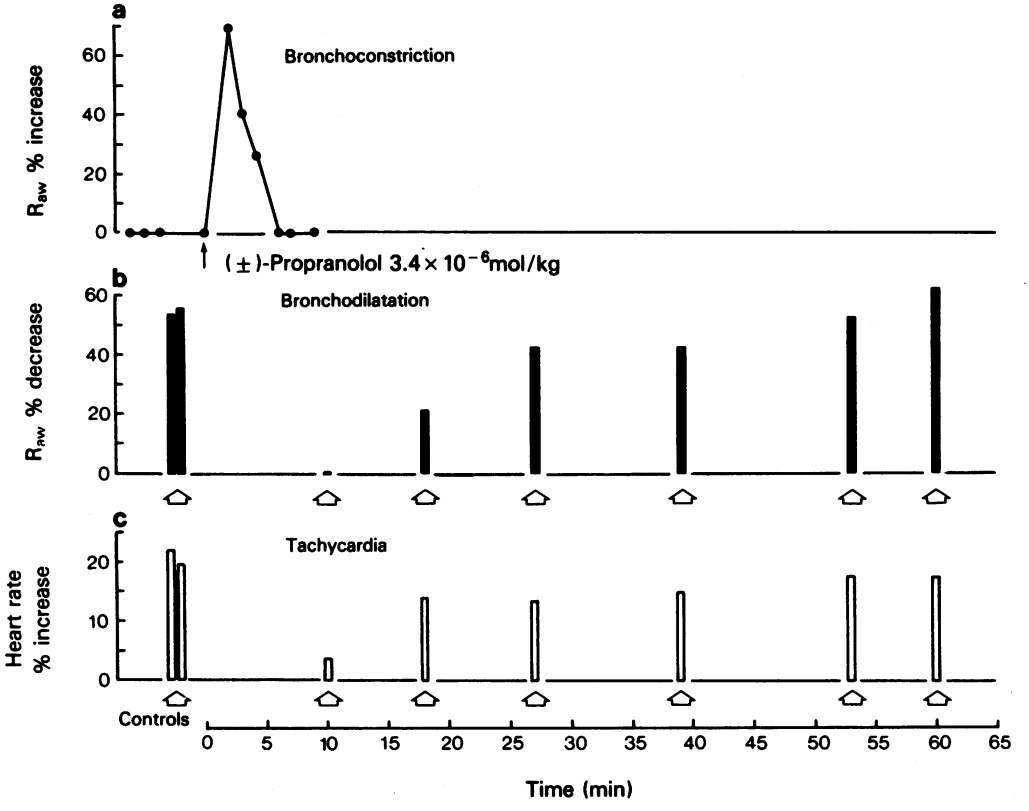

Figure 5 Comparison of the time course of the bronchoconstriction and β-adrenoceptor blockade produced by (±)-propranolol in a rat. The antagonism of the bronchodilatation (% decrease in R_{aw}, b) and tachycardia (% increase in heart rate, c) produced by repeated test doses of isoprenaline (1 μg/kg i.v. at open arrows) were used to assess the onset and duration of β-adrenoceptor blockade in the airways and in the heart. Injection of (±)-propranolol 3.4 × 10^{-6} mol/kg caused blockade which lasted approximately 1 h, wherease the bronchoconstriction (% increase in R_{aw}, a) was short lasting.

increased after injection of any of the β-adrenoceptor blocking drugs. This potentiation was seen after the initial bronchospasm induced by the β-adrenoceptor blocking drugs had subsided and it lasted for several hours.

Table 1 The effect of (±)-propranolol in guinea-pigs in the presence of atropine

Dose of (±)-propranolol (mol/kg)	*% increase in airways resistance (R_{aw}) Before*	*After atropine (1 mg/kg)*
6×10^{-7}	40.5 ± 1.7	39.0 ± 3.6*
	$n = 7$	$n = 5$
8×10^{-7}	49.1 ± 2.8	47.2 ± 2.8**
	$n = 8$	$n = 5$

Results are given (±) s.e. mean; n = number of observations. The mean values after atropine are not significantly different from the controls at either dose level (* $P > 0.8$; ** $P > 0.7$).

Further investigation showed that the isomer, (+)-propranolol, produced a similar potentiation of histamine and 5-HT-induced responses, while causing no measurable β-adrenoceptor blockade in the lungs. The potentiation was also observed in the group of adrenal demedullated rats.

Discussion

The results described in this paper have shown that by the use of a sensitive method it was possible to record bronchoconstriction in guinea-pigs and rats after administration of small doses of the β-adrenoceptor blocking drugs. With this method (Green & Widdicombe, 1966), the effects of drugs could be recorded simultaneously in the large airways, measured as changes in airways resistance, and in the small airways, measured as changes in lung compliance. It was found that the percentage increase in

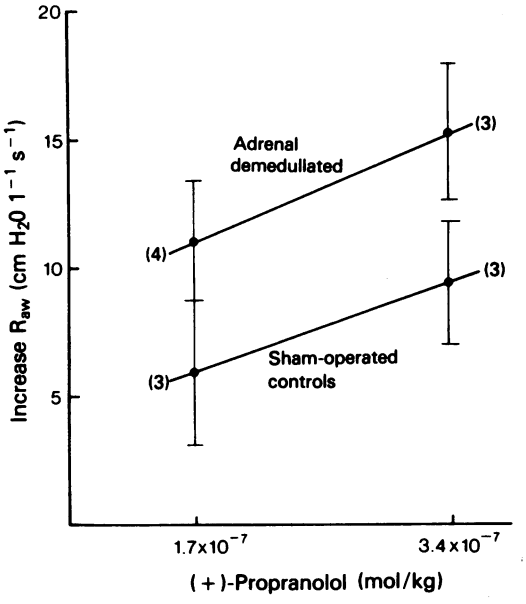

Figure 6 Comparison of the effect of (+)-propranolol on airways resistance in adrenal demedullated and sham-operated control rats. Absolute changes in R_{aw} ($cmH_2O\,l^{-1}\,s^{-1}$) are plotted on the ordinate scale against dose of (+)-propranolol on the abscissa scale. Values are mean results, vertical bars give s.e. mean and the numbers in parentheses refer to the number of observations.

resistance produced by the β-adrenoceptor blocking drugs was always larger than the corresponding decrease in compliance, suggesting that these drugs act mainly on the large airways. This may explain why there have been so few reports demonstrating the bronchoconstriction induced by the β-adrenoceptor blocking drugs in animals, since the recording methods of the Konzett & Rössler type (1940), which have been most frequently used to evaluate the effects of drugs on the lungs, are based on measurements of tidal volume and therefore primarily record changes in the smaller airways. Those workers who used resistance measurements to record changes in the larger airways, were able to obtain bronchoconstriction with moderate doses of a number of β-adrenoceptor blocking drugs in guinea-pigs (Advenier, Boissier & Giudicelli, 1972; Giudicelli, Boissier, Dumas & Advenier, 1973).

In the present experiments it was shown that, as with propranolol, the cardioselective β-adrenoceptor blocking drugs, atenolol and practolol, also caused bronchoconstriction, despite the fact that they have less blocking activity on β_2-adrenoceptors in the airway smooth muscle. This raised doubts about the mechanism of the bronchoconstriction. The subsequent finding that the weak β-adrenoceptor blocking isomer, (+)-propranolol (Howe & Shanks, 1966), produced comparable bronchospasm to the racemate was an indication that the response might not be due to β-adrenoceptor blockade. It is interesting to note that, although the mechanism underlying the bronchoconstrictor effect was not investigated, Advenier *et al.* (1972) also found that (+)-propranolol caused bronchoconstriction in guinea-pigs.

Further investigation of the relationship between the bronchoconstriction and β-adrenoceptor blockade produced by (±)-propranolol in the guinea-pigs and rats in the present experiments, showed that the bronchospasm was short-lasting, while the β-adrenoceptor blockade had a much longer time course. As a result, successive injections of the drug, every 10 or 15 min, caused repeated and identical bronchospasms, but only added to the blockade in a cumulative manner. The marked differences in the time course of the bronchoconstriction and β-adrenoceptor blockade produced by a dose of (±)-propranolol, suggests that there is little correlation between these two responses. This was supported by the finding that the isomer, (+)-propranolol, caused similar bronchoconstrictions whether it was given alone or in the presence of a measurable β-adrenoceptor blockade produced by the racemate, (±)-propranolol.

The effect of (+)-propranolol was also investigated in adrenal demedullated rats, because it has been shown that this species lacks a noradrenergic innervation to the airway smooth muscle (El-Bermani, McNary & Bradley, 1970; Fillenz & Woods, 1970), and thus by removing the adrenal medulla the rats are also deprived of a major source of circulating catecholamines. Consequently, in the acute experiments, the influence of catecholamines on the airways was minimal. The ability of (+)-propranolol to cause bronchoconstriction in these animals indicates that this effect is unlikely to be due to the antagonism of a sympathetic influence on the airways via β-adrenoceptors.

It would appear, from the results described in this paper, that the bronchoconstriction produced by the β-adrenoceptor blocking drugs is unrelated to β-adrenoceptor blockade in the airway smooth muscle.

The β-adrenoceptor blocking drugs possess a number of properties unrelated to their receptor blocking effect, including a membrane stabilizing action, intrinsic sympathomimetic activity, an action on the central nervous system and an inhibitory action on catechol-*O*-methyltransferase (COMT). It is unlikely that such secondary actions are responsible for the bronchoconstrictor effects reported here, since neither practolol nor atenolol have membrane stabilizing effects (Dunlop & Shanks, 1968; Barrett, 1977), atenolol does not cross the blood brain barrier (Barrett, 1977) and, of the drugs used, only practolol has

intrinsic sympathomimetic activity (Dunlop & Shanks, 1968) and can inhibit COMT (Kenakin & Black, 1978); yet all three drugs can cause bronchospasm. It also seems unlikely that the haemodynamic changes, which these drugs can produce, contribute to the bronchoconstriction as the results showed that quinidine, which has similar cardiac depressent effects to propranolol, did not produce bronchospasm.

It is well known that in this type of lightly anaesthetized preparation various substances such as histamine, 5-HT, prostaglandins and sulphur dioxide can elicit a parasympathetically-mediated, reflex bronchoconstriction. This has been confirmed in several laboratories by showing that the bronchospasm induced by these agents can be antagonized by atropine or vagotomy (Hansen & Zipf, 1960; de Kock, Nadel, Zwi, Colebatch & Olsen, 1966; Karczewski & Widdicombe, 1969; Mills & Widdicombe, 1970; Gold, Kessler & Yu, 1972).

The finding that atropine did not alter the propranolol-induced bronchoconstriction indicates that the response is not mediated via parasympathetic bronchoconstrictor nerves to the airway smooth muscle. Thus propranolol could not be eliciting a reflex effect in the same way that histamine does. This result also appears to rule out the possibility that the production of micro-emboli, oedema or changes in blood gas tension are responsible for the bronchoconstriction, since bronchospasm induced by these means is antagonized by atropine or vagotomy (Nadel & Widdicombe, 1962; Richardson & Widdicombe, 1969; Mills, Sellick & Widdicombe, 1969; Glogowska & Widdicombe, 1973).

In man, the bronchospasm which these β-adrenoceptor blocking drugs cause limits their clinical usefulness, especially in asthmatic patients. It would therefore seem important to know whether the bronchoconstrictor response which has been obtained in the present animal experiments is similar to the type of response which occurs in man. There is some evidence to suggest that this may be so. It could be argued that the experimental conditions used in man are not comparable to those used to record airways resistance in small animals. However, the whole body plethysmograph method can be used to record R_{aw} in man and this is comparable to the method used in the present experiments. By use of the whole body plethysmograph it has been shown that the onset of the response after intravenous injection is comparable in man and animals although the effects tend to last longer in man (McNeill & Ingram, 1966). In addition, it has been shown that the cardioselective β-adrenoceptor blocking drugs can cause bronchospasm in man as in animals (Macdonald & McNeill 1968) and this is also supported by the results of Skinner *et al.* (1975) and Marlin, Kumana, Kaye, Smith & Turner (1975) using less sensitive measurements of FEV_1 and PEFR. There are indications from some of the clinical studies that the bronchoconstriction may also be unrelated to β-adrenoceptor blockade in the airways. This is suggested by the finding that: (a) after a dose of a cardioselective drug sufficient to cause bronchospasm, the β-adrenoceptors respond normally to isoprenaline (Dierckx, Gillard & Gossart 1976): this has also been shown with the less sensitive methods (Powles *et al.*, 1969; Johnsson *et al.*, 1975); (b) doses of practolol and acebutolol (Skinner *et al.*, 1975) and of propranolol and alprenolol (Tivenius & Nyberg, 1969) which produce equipotent β-adrenoceptor blockade in the lungs, produce different degrees of bronchoconstriction.

Another similarity between the present experiments and the observations made in man, is that the response to any bronchoconstrictor agent such as histamine, 5-HT, prostaglandins or methacholine, is potentiated after administration of β-adrenoceptor blocking drugs. This potentiation is easily demonstrated and has been widely reported in man (Zaid & Beall, 1966; Bouhuys, Douglas & Guyatt, 1971; Nicolaescu, Manicatide & Stroescu, 1972) and in animals (Collier, James & Piper, 1965; Collier & James, 1967; Dennis & Douglas, 1970; McCulloch, Proctor & Rand, 1967; Diamond, 1972; Douglas, Dennis, Ridgeway & Bouhuys, 1973).

The potentiation was confirmed in the animal experiments outlined in this paper using both (±)-propranolol and the cardioselective β-adrenoceptor blocking drugs. It was also obtained with the isomer (+)-propranolol and occurred in the adrenal demedullated rats, which suggests that this is another effect which cannot be attributed to β-adrenoceptor blockade in the airway smooth muscle. The results of Nicolaescu *et al.* (1972) in asthmatic patients, suggest that, in man as in animals, the potentiation may be unrelated to β-adrenoceptor blockade. They showed that a β-adrenoceptor agonist was equally effective in reversing acetylcholine-induced bronchospasm before and during the phase of potentiation produced by practolol.

The evidence discussed above indicates that the effects of the β-adrenoceptor blocking drugs in the lungs of guinea-pigs and rats, described in this paper, may be similar to the effects produced in man. Such an animal model might be of use in screening the β-adrenoceptor blocking drugs for their bronchoconstrictor actions. Until now the determination of the relative potency on β_1- and β_2-adrenoceptors has been used as an indication of the potential bronchoconstrictor activity of these drugs during clinical use. However, as the present results suggest that there is no correlation between β-adrenoceptor blockade and bronchospasm, this criterion for selection may be inappropriate.

Further experiments are required in order to eluci-

date the mechanism of the bronchoconstriction and potentiation of histamine and 5-HT-induced bronchospasm produced by the β-adrenoceptor blocking drugs. Since the lung is a source of several bronchoconstrictor substances which may be released by various stimuli (Piper, 1977) it is possible that any one or more of these mediators may be involved.

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