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Propranolol-induced airway hyperreactivity in guinea-pigs

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1 In anaesthetized, spontaneously breathing guinea-pigs, enhanced bronchoconstrictor responses ($\uparrow R_L$) to histamine were measured following intravenous injection of practolol, (±)-propranolol, (+)- and (−)-propranolol.

2 Propranolol enhanced not only histamine- but 5-hydroxytryptamine (5-HT)-induced bronchoconstrictions and its effects lasted up to 2 h.

3 This increased airway sensitivity was not due to β-adrenoceptor blockade because: (a) similar effects were produced by racemic propranolol and its two isomers (+)- and (−)-propranolol and (b) whilst equal doses of (±)- and (+)-propranolol produced the same potentiation of histamine bronchoconstriction, only (±)-propranolol also caused a measurable β-adrenoceptor blockade in the airways.

4 The enhanced histamine- and 5-HT-induced bronchoconstrictions were antagonized by the leukotriene antagonist FPL 55712 and by the lipoxygenase/cyclo-oxygenase inhibitor BW755c.

5 The results demonstrate that endogenously released leukotrienes can produce not only a direct bronchospasm but may enhance the effects of other bronchoconstrictor agents.

6 The relevance of this leukotriene-mediated hyperreactivity to the non-specific airway hyperreactivity seen in asthmatics is discussed.

Introduction

Bronchoconstriction has been reported in asthmatics following administration of a variety of β-adrenoceptor blocking drugs (Skinner, Palmer & Kerridge, 1975; Benson, Berrill, Sterling, Decalmer, Chatterjee, Croxson & Cruickshank, 1977). In addition to the initial bronchospasm, these drugs have been found to increase the sensitivity of the airways to other bronchoconstrictor agents such as histamine and acetylcholine (Zaid & Beall, 1966; Bouhuys, Douglas & Guyatt, 1971). Although these effects have generally been attributed to blockade of airway β-adrenoceptors (Macdonald, Ingram & McNeill, 1967), similar observations with the cardioselective β-blockers has led to the suggestion that other factors might be involved (Nicolaescu, Manicatide & Stroescu, 1972).

Investigation of the initial bronchoconstrictor effect of the drugs in guinea-pigs, showed that (±)-propranolol and its isomer (+)-propranolol were equipotent bronchoconstrictor agents (Maclagan & Ney, 1979). As the (+)-isomer has only 1/60–1/100 of the β-adrenoceptor blocking potency of the racemate (Howe & Shanks, 1966), it was concluded that the bronchospasms were not due to β-adrenoceptor blockade of the airways, but to a non-specific effect of the drugs.

In the same experiments an enhancement of bronchoconstrictor responses to histamine by (±)- and (+)-propranolol was observed and the mechanism of this increase in airway sensitivity has now been investigated in more detail by comparing the effects of racemic, dextro and laevo propranolol and the cardioselective agent, practolol on the guinea-pig airway. Since lipoxygenase products have recently been implicated in *in vitro* models of enhanced airway reactivity in the guinea-pig (Adcock & Garland, 1980; Mitchell, 1982), their possible role in propranolol-induced hyperreactivity was determined, using the leukotriene antagonist FPL 55712 (Augstein, Farmer, Lee, Sheard & Tattersall, 1973) and the combined lipoxygenase/cyclo-oxygenase inhibitor, BW755c (Higgs, Copp, Denyer, Flower, Tateson, Vane & Walker, 1978). A preliminary account of this work has been presented to the British Pharmacological Society (Ney, 1983).

Methods

Guinea-pigs (310–700 g; of either sex) of the Dunkin Hartley strain (KFM, Switzerland), were anaesthetized with urethane (1.25–1.5 g kg^{-1} i.p. and i.m.) and allowed to breathe spontaneously. The right carotid artery was cannulated for the measurement of blood pressure and the left jugular vein for the injection of drugs. In some experiments infusions of histamine were given and for these the right jugular vein was also cannulated.

The animals were prepared for the measurement of lung resistance and compliance as described by Maclagan & Ney (1979). The tracheal cannula was connected in series with a Fleisch pneumotachograph (4/0) and airflow measured using a differential pressure transducer (Statham PM15ETC). This flow signal ($\dot{V}$) was then integrated to give the tidal volume (V_T). Transpulmonary pressure (TPP) was recorded with a Statham pressure transducer (PM5E) which measured the pressure difference between the tracheal cannula and a cannula sealed in the pleural cavity.

Mean lung resistance (R_L) and compliance (C_{dyn}) were determined by the method of Amdur & Mead (1958) using a Buxco Pulmonary Mechanics Analyser Model 6 (Buxco Electronics Inc., Sharon, Conn.). R_L was calculated from the pressure and flow changes between isovolume points in the same breath ($R_L = TPP/\dot{V}$) and the dynamic lung compliance from the volume and pressure changes between points of zero flow in each breath ($C_{dyn} = V_T/TPP$). Values of R_L and C_{dyn} were recorded on a chart recorder together with the respiratory rate of the animal, in breaths per minute, derived from the V signal. The end tidal CO_2 of the guine-pig was monitored throughout the experiment using an IL 200 CO_2 monitor (Ingold, Zürich) and was maintained between 3–4% CO_2.

All drugs, except FPL 55712 and BW755c, were made up in 0.9% w/v NaCl solution (saline). They were injected in a volume not exceeding 0.2 ml and at a constant rate by means of an infusion pump (B. Braun, Melsungen). Solutions of FPL 55712 were made up in 0.02 M NaOH and BW755c in 0.08 M tartaric acid. Drugs used were: histamine dihydrochloride (Fluka AG), 5-hydroxytryptamine creatinine sulphate (Fluka A.G.), (±)-, (−)- and (+)-propranolol, practolol (ICI), FPL 55712 (sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4-H-l-benzopyran-2-carboxylate) and BW755c (3-amino-l-[*m*(trifluoromethyl)-phenyl]-2-pyrazoline).

All doses are expressed as the base.

Expression of results

Bronchoconstriction R_L was calculated in $cmH_2O\,l^{-1}\,s$ and C_{dyn} in ml cmH_2O^{-1}. Bronchoconstrictions were measured as increases in R_L and decreases in C_{dyn} and expressed as the percentage change compared to the resting levels. Except where indicated, the bronchoconstrictions have been expressed in terms of the change in R_L.

Airway sensitivity The degree of airway sensitivity was determined by comparison of the response to the bronchoconstrictor agent (histamine or 5-HT) before and after different drug treatments. The mean control bronchoconstriction in each animal was ascribed a value of 100% and subsequent post-treatment responses in the same animal were expressed as a percentage of the control.

Results

The basal lung resistance (R_L) in the guinea-pigs used in these experiments was 121.8 ± 5.5 $cmH_2O\,l^{-1}\,s$ ($n = 50$) with a range from 70–240 $cmH_2O\,l^{-1}\,s$ and the mean resting compliance (C_{dyn}) was 0.50 ± 0.012 ml cmH_2O^{-1} ($n = 50$); range 0.25–0.95 ml cmH_2O^{-1}.

In these animals the bronchoconstrictor response to histamine, 1–4 μg kg^{-1} i.v., before drug treatment

Table 1 Comparison of the effects of (±)-propranolol, (+)-propranolol and practolol on histamine-induced bronchoconstriction in the guinea-pig

Drug	*Dose* (mg/kg i.v.)	n	*Histamine bronchoconstriction* (as % of control response*) max ↑ R_L	60 min
(±)-Propranolol	0.1	3	233 ± 48	153 ± 56
(+)-Propranolol	0.1	5	221 ± 35	196 ± 55
Practolol	0.1	3	201 ± 34	151 ± 25

*Control response in each animal = 100% (see Methods).
The histamine dose was 1–4 μg kg^{-1} i.v.
All values are means ± s.e.mean.

was between 50 and 280% ↑ R_L with a mean increase of 143 ± 12% ↑ R_L ($n = 33$).

Effects of β-adrenoceptor blocking drugs on histamine-induced bronchoconstriction

Intravenous injection of (±)-propranolol (0.1 mg kg^{-1} i.v.) resulted in a two fold increase in histamine-induced bronchoconstrictions. The same dose of the (+)-isomer and the cardioselective agent, practolol, produced a similar enhancement of the histamine bronchospasm (Table 1). The maximum effect was seen 15 min after injection of the blocking agent and there was still some degree of enhancement 60 min later.

Comparison of the effect of (±)-, (+)- and (−)-propranolol

The ability of (±)-propranolol to increase the airway sensitivity to histamine was compared with that of both its isomers, (+)- and (−)-propranolol. Following injection of 0.5 mg kg^{-1} i.v., all three drugs significantly enhanced the response to histamine compared to saline-treated control animals (Table 2) and there was no difference between their effect.

Time course of the propranolol-induced increase in airway sensitivity

In Table 2, the increased airway sensitivity is compared at 15, 30, 45 and 60 min after injection of propranolol and shows that, at this dose, the histamine response is still considerably potentiated after 1 h. The time course of the effect is illustrated in more detail for one guinea-pig in Figure 1. The % ↑ R_L ($cmH_2O\,l^{-1}\,s$) in response to histamine, is plotted for the controls (mean of three challenges) and at 15 min intervals after injection of (+)-propranolol (0.5 mg kg^{-1} i.v.). The potentiated response was seen at 15 min and lasted up to 2 h. Following histamine challenge a decrease in C_{dyn} was also measured and this too was enhanced by propranolol. The time-course of this potentiation parallelled that of the resistance changes (Figure 2).

Measurement of β-adrenoceptor blockade in the airways

Experiments were carried out to compare the degree of β-adrenoceptor blockade produced in the airways by (±)- and (+)-propranolol. The effect of isoprenaline was measured indirectly as the antagonism of a histamine-induced bronchoconstriction. Histamine was infused i.v. (1.1 to 4.4 μg kg^{-1} min^{-1}) to produce a long-lasting increase in lung resistance (R_L) and increasing doses of isoprenaline were injected until the resting level of R_L was restored. On completion of the cumulative dose-response curve for isoprenaline the histamine infusion was stopped and 15 min later (±)- or (+)-propranolol, 0.5 mg kg^{-1}, was given i.v. After a further 5 min the histamine infusion was restarted. Since this dose of propranolol at least doubles the response to histamine, the second infusion was made with half the concentration of histamine used in the control period

Table 2 Comparison of the effect of (±)-, (+)- and (−)-propranolol on histamine-induced bronchoconstriction

Propranolol	*Dose* (mg kg^{-1} i.v.)	n	*Histamine bronchoconstriction* (% of control)†			
			15	30	45	60 min
(±)	0.5	4	255** ±28	190 ±34	207* ±39	174*§ ±32
(+)	0.5	5	266*** ±10	196*** ±11	194*‡ ±25	209‡ ±78
(−)	0.5	4	233 ±58	265** ±30	206*** ±23	203* ±36
NaCl	0.2 ml	4	94 ±10	110 ± 4	99§ ±13	100§ ± 4

†Control response = 100% in each animal (see Methods)

The histamine dose used was 1–4 μg kg^{-1} i.v. and all results at the four time points after propranolol treatment are means ± s.e.mean.

The difference from the control (NaCl) group is symbolised by: *$P<0.05$; **$P<0.01$; ***$P<0.001$; Student's t test.

‡$n = 4$; §$n = 3$.

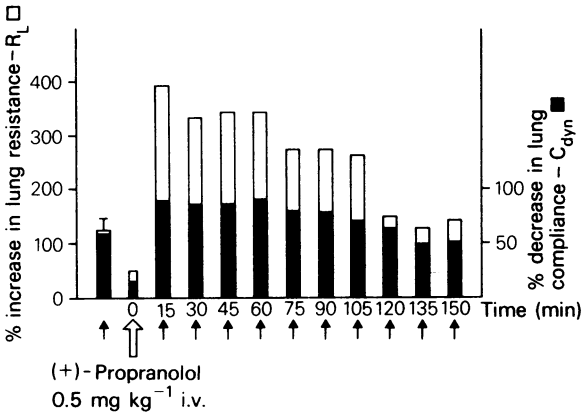

Figure 1 Time-course of the enhancement of histamine-induced bronchoconstriction by (+)-propranolol. The responses to histamine challenge (2 μg kg^{-1} i.v. at closed arrows) are plotted against time before and after (+)-propranolol administration (0.5 mg kg^{-1} i.v. open arrow). Open columns represent the % increase in R_L and closed columns the % decrease in C_{dyn}. The response to histamine before (+)-propranolol is the mean of three separate challenges (s.e.mean shown as vertical bar). (+)-Propranolol itself produced a small bronchospasm (shown by the small column at $t = 0$ min) which subsided before rechallenge with histamine. The enhanced histamine response was seen 15 min after propranolol treatment and was maintained for the next 60 min before gradually declining to control levels.

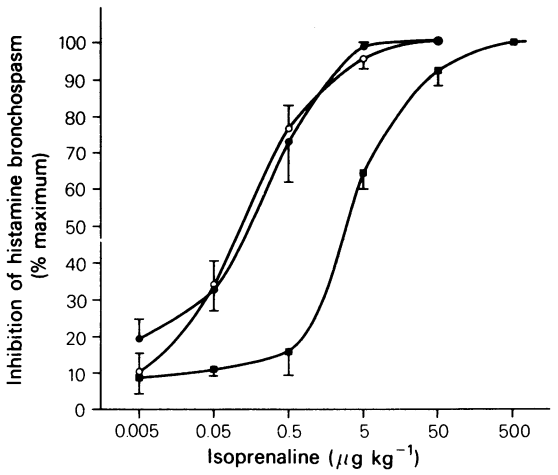

Figure 2 Comparison of the effect of (±)-propranolol and (+)-propranolol on responses to isoprenaline in guinea-pig airways. The effect of isoprenaline was measured as the reduction in a histamine-induced increase in lung resistance (R_L) and for each dose this is expressed as a percentage of the maximum inhibition produced: (○) show the response to isoprenaline in the control period ($n = 7$); (●) show the response after (+)-propranolol (0.5 mg kg^{-1} i.v.; $n = 3$) and (■) show the response after (±)-propranolol (0.5 mg kg^{-1} i.v.; $n = 4$). All points are means and vertical bars give s.e.mean. The difference between isoprenaline responses in (±)- and (+)-propranolol-treated guinea-pigs was significant at 0.05 ($P < 0.05$), 0.5 ($P < 0.01$) and 5.0 μg kg^{-1} ($P < 0.001$) (Student's t test).

(i.e. 0.55 to 2.2 μg kg^{-1} min^{-1}) so that the increase in R_L was approximately the same during both infusions.

Figure 2 shows the dose-response curves to isoprenaline in the absence and presence of (±)- and (+)-propranolol. At this dose (0.5 mg kg^{-1}) (±)-propranolol produced a twenty fold shift of the isoprenaline dose-response curve whilst, at the same dose, (+)-propranolol had no effect.

Enhancement of 5-hydroxytryptamine-induced bronchoconstriction

To determine whether the increase in bronchoconstrictor responses by propranolol was specific for histamine or was due to a non-specific increase in airway sensitivity, the effect of (+)-propranolol on 5-HT-induced bronchospasms was investigated. The mean bronchoconstrictor response to 5-HT (3–6 μg kg^{-1} i.v.) was 101 ± 17.3% ↑ R_L ($n = 4$) and following 0.5 mg kg^{-1} (+)-propranolol, this was increased to 235 ± 48.5 ↑ R_L ($n = 4$).

Effects of FPL 55712 and BW755c on the increased airway sensitivity produced by (+)-propranolol

The mechanism of the propranolol-induced increase

Table 3 Effect of FPL 55712 on (+)-propranolol-induced enhancement of histamine bronchoconstriction

Propranolol	*Dose* (mg kg^{-1} i.v.)	*Histamine bronchoconstriction* (% control)* *Maximum response*	n	*1 min after FPL 55712*	n
(+)	0.1	221 ± 35	(5)	94 ± 6.5	(2)
(+)	0.5	338 ± 103	(5)	106 ± 35	(3)
NaCl	0.2 ml	102.5 ± 11.5	(4)	93 ± 16	(3)

*Control response = 100% in each animal (see Methods). The histamine dose was 1–3 μg kg^{-1} i.v. and FPL 55712 was given i.v., 1 mg kg^{-1}, 1 min before histamine challenge. All values are means ± s.e.mean.

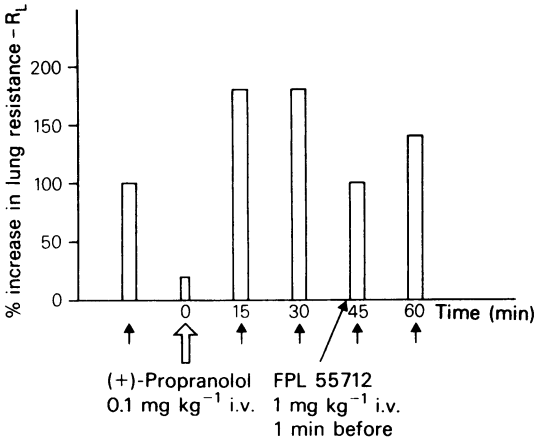

Figure 3 Effect of FPL 55712 on the enhanced response to histamine in a (+)-propranolol-treated guinea-pig. Challenge with histamine (1.5 μg kg^{-1} i.v., closed arrows) in the control period resulted in a 100% increase in R_L (± 0; $n = 3$). Injection of (+)-propranolol (0.1 mg kg^{-1} i.v., open arrows) caused a 20% increase in R_L and decrease in C_{dyn} (latter not shown). Enhanced responses to histamine were recorded 15 and 30 min later and then FPL 55712 (1 mg kg^{-1}) injected i.v. 1 min before the next histamine challenge. The subsequent bronchospasm was reduced to control levels, but, after a further 15 min, the enhanced response was partially restored.

in airway sensitivity was investigated by use of the leukotriene antagonist, FPL 55712 (Augstein *et al.*, 1973) and the combined lipoxygenase/cyclooxygenase inhibitor, BW755c (Higgs *et al.*, 1978). Following potentiation of the histamine response by (+)-propranolol, FPL 55712 (1 mg kg^{-1} i.v.) was injected 1 min before the next histamine challenge. Figure 3 illustrates the time course of this experiment in one guinea-pig. Immediately after administration of FPL 55712, the histamine-induced bronchoconstriction was reduced to control levels but 15 min later the potentiated response was partially restored. Similar results obtained in guinea-pigs treated either with 0.1 or 0.5 mg kg^{-1} i.v. (+)-propranolol are summarised in Table 3. FPL 55712 had no effect on histamine responses in the absence of (+)-propranolol.

In a second series of experiments, 5-HT-induced bronchoconstrictions were potentiated by (+)-propranolol (0.5 mg kg^{-1} i.v.) and BW755c (5 mg kg^{-1}) was injected 5 min before the next 5-HT challenge. This subsequent bronchoconstriction was reduced to pre-propranolol levels (Table 4). The 5-HT-induced bronchoconstrictions were unaffected by BW755c in the absence of (+)-propranolol.

Discussion

The experiments presented in this paper demonstrate an enhancement of responses to bronchoconstrictor agents by the β-adrenoceptor blocking drugs. This was observed by measuring changes in lung resistance and compliance in anaesthetized, spontaneously breathing guinea-pigs. Earlier work had suggested that this enhanced sensitivity was not due to β-adrenoceptor blockade (Maclagan & Ney, 1979) and this has been confirmed by the present experiments showing that equal doses of (±)-, (+)- and (−)-propranolol produced similar enhancement of histamine responses although the dextro isomer had no β-adrenoceptor blocking effect in the airways.

In these experiments, propranolol increased not only the bronchoconstrictor responses to histamine but also those to 5-HT, indicating that it was increasing airway sensitivity in a non-specific manner. Similar potentiation of a range of bronchoconstrictor agents has been reported, including histamine and acetylcholine, in the guinea-pig (Collier, James & Piper, 1965; McCulloch, Proctor & Rand, 1967; Douglas, Dennis, Ridgeway & Bouhuys, 1973); and citric acid spray and antigen challenge in dogs (Hirshman, Downes, Leon & Peters, 1981) although some workers have been unable to show an effect (Snapper, Braasch, Ingram, Loring & Drazen, 1981). However, all these authors used only the racemic

Table 4 Effect of BW 755c on 5-hydroxytryptamine (5-HT)-induced bronchoconstrictions

Treatment	n	*5-HT bronchoconstriction* (% control)* *Maximum response*	*5 min after BW 755c*
(+)-Propranolol 0.5 mg kg^{-1}	4	243 ± 36	141 ± 44
NaCl 0.2 ml	4	100	103.5 ± 26.5

*Control response = 100% in each animal (see Methods).
The dose of 5-HT was 3–8 μg kg^{-1} i.v. and BW 755c was injected i.v. 5 mg kg^{-1} 5 min before 5-HT challenge.
All values are means ± s.e.mean.

form of propranolol and consequently attributed the increased reactivity to β-adrenoceptor blockade whilst the present studies show that it is due to a non-specific effect of the drug.

Increased bronchoconstrictor effects of histamine or methacholine have also been reported following administration of propranolol to asthmatics and patients with allergic rhinitis (Zaid & Beall, 1966; McGeady, Conboy & Townley, 1968). Nicolaescu *et al.* (1972) showed that treatment with propranolol and the cardioselective drug, practolol, produced a similar degree of potentiation of acetylcholine bronchospasms in their patients and they therefore proposed that the increased sensitivity might not be due to β-adrenoceptor blockade. In a more extensive double blind study, Ruffin, Frith, Anderton, Kumana, Newhouse & Hargreave (1979) compared the effects of propranolol on histamine bronchoconstriction with those of the β_1-selective drugs, metoprolol and timolol. The drugs were given in equivalent cardiac blocking doses, assessed from heart rate measurements, yet despite the corresponding differences in their β_2-antagonistic properties, all three enhanced histamine responses to the same extent.

These clinical findings with the cardioselective β-adrenoceptor blocking drugs suggest that, as demonstrated in the experiments reported here in the guinea-pigs, β-adrenoceptor blockade may not be responsible for the increased sensitivity to bronchoconstrictor agents in man. Therefore the relevance of determining the relative antagonistic potency of the drugs on β_1- and β_2-adrenoceptors, as an indicator of their potential airway effects, is questionable.

The role of leukotrienes in the propranolol-induced increase in airway sensitivity in the guinea-pig, was demonstrated by the inhibition of the potentiated bronchoconstrictor responses by the leukotriene antagonist, FPL 55712 and the combined lipoxygenase/cyclo-oxygenase inhibitor, BW755c. The leukotrienes are known to cause bronchoconstriction *in vivo* and *in vitro* (Drazen, Austen, Lewis, Clark, Goto, Marfat & Corey, 1980; Hanna, Bach, Pare & Schellenberg, 1981) but the present experiments show that they may also act to enhance the effects of other bronchoconstrictor agents. Recent observations of an indomethacin-induced potentiation of histamine and arachidonic acid contractions of guinea-pig (Adcock & Garland, 1980; Mitchell, 1982) and human (Adcock & Garland, 1982) airway smooth muscle *in vitro*, have suggested that other lipoxygenase products may also increase airway reactivity. *In vitro*, this appears to be a sensitizing effect on airway smooth muscle, but since in the present *in vivo* experiments, histamine and 5-HT bronchoconstrictions are partly mediated via a parasympathetic reflex, the level at which the enhancement of bronchoconstrictor effects occurs cannot be defined. However, it is clear that lipoxygenase products may be important in the regulation of airway contraction and could consequently contribute to the non-specific hyperreactivity which is characteristic of asthma.

The evidence in this paper points in particular to a role for the leukotrienes in increased airway sensitivity. Since the effects of propranolol in the guinea-pig are analogous to those of the β-adrenoceptor blocking drugs in asthmatics, these findings may be of direct relevance to the mechanism of airway hyperreactivity in asthma. Thus this model of propranolol-induced hyperreactivity in guinea-pigs *in vivo* may prove suitable for studying the phenomenon of asthmatic hyperreactivity.

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