

Anti-Anaphylactic and Bronchodilating Action of a Beta-Adrenoceptor Stimulator, KWD 2131, in Human Lung Tissue

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The beta-adrenoceptor stimulating agent KWD 2131 has been studied with regard to inhibitory effect on allergen-induced histamine release from passively sensitized human lung tissue and relaxing effect on contracted small (diameter = 1 mm) and large (diameter > 3 mm) isolated human bronchi. The dose for 50% inhibition of the allergen-induced histamine release was 2×10^{-11} M. The potency of KWD 2131 was approximately 0.15 times that of terbutaline and 0.05 times that of isoprenaline in this respect. The bronchodilating potency of KWD 2131 was 0.02–0.03 times that of terbutaline. The data indicate that KWD 2131 is a compound with preferably anti-anaphylactic potency in the human lung.

Key words: adrenergic beta-receptor agonists; histamine release; lung.

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Sympathomimetic amines have been found to inhibit anaphylactic histamine release in a variety of tissues and cell preparations, e.g. human and primate lung tissue (1, 4), human leucocytes (6) and guinea pig lung (10, 2). The inhibitory effect is antagonized by β -adrenoceptor blocking agents (β -blockers), indicating that β -adrenoceptors are involved. Judging from the rank order of β -receptor stimulants (β -stimulants) with regard to anti-anaphylactic potency (7, 13) and PA_2 values for different β -blockers on this parameter (3, 7) the β -adrenoceptors mediating the inhibitory effect on histamine release do not easily fit into the β_1 - β_2 -receptor scheme proposed by Lands (5). This difficulty was further emphasized by the recent finding that a new β -stimulant KWD 2131 with the same anti-anaphylactic potency as the β_2 -

selective stimulant terbutaline in the guinea pig lung was comparatively less potent as a relaxing agent on the guinea pig trachea (14). In the present study the anti-anaphylactic and bronchorelaxing properties of terbutaline and KWD 2131 in human lung tissue were compared to elucidate whether KWD 2131 has a preferably anti-anaphylactic action also in this tissue.

MATERIAL AND METHODS

Chemicals. d'1-Isoprenaline sulphate (Sigma), terbutaline sulphate (AB Draco, Sweden), 1-(3, 5-dihydroxyphenyl)-2-[(1, 1-dimethyl-2-hydroxyethyl)-amino] ethanol sulphate (KWD 2131, AB Draco, Sweden), propranolol (ICI Ltd, England), birch pollen allergen extract (Vitrum Laboratories, Sweden). The allergen was dialysed against Tyrode's

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solution and aliquots were stored at -20°C until used. Other material used was purchased from standard commercial sources.

Histamine release. The histamine release from human lung tissue was studied as previously described (12). Fresh and macroscopically normal lung tissue from cancer patients undergoing lung resection was chopped and rinsed in Tyrode's solution. Tissue samples of 100 mg (duplicates) were then passively sensitized by incubation for 18 h at room temperature in reaginic serum (1:25 dilution) from a patient allergic to birch pollen. After washing the tissue, samples were incubated in Tyrode's solution for 10 min at 37°C . Drugs were then added, and 5 min later birch pollen allergen. The incubation continued for an additional period of 20 min. Then the media were pipetted off and the tissue rinsed with Tyrode's solution. 3 ml of 0.1 M HCl were added and the tissue was boiled for 10 min. The histamine of the incubation fluids and tissue extracts was determined according to the fluorometric method of Shore et al. (11). The β -stimulants did not interfere with the histamine assay. The effect of drugs on the histamine release was expressed as per cent inhibition. Control histamine release (no allergen added) was deducted prior to this calculation.

Isolated human bronchi. Human lung tissue from three patients undergoing intervention for lung tumour was used. The patients had no diagnosed obstructive lung disease. Airways of various size were carefully dissected free from surrounding tissue. Those with a diameter >3 mm were cut helically and mounted as strips with a length of 20–30 mm. These preparations are referred to as large airways in the following.

Small airways, with diameters ≈ 1 mm were prepared as tube segments with a length of 5 mm. They were placed over two steel rods allowing the recording of the circular tension (9). Isometric tension changes were recorded with strain gauge transducers (Grass FT 03).

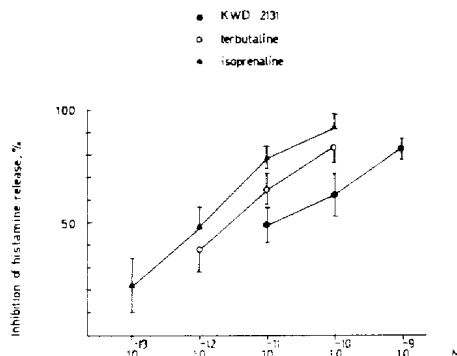


Fig. 1. The effect of KWD 2131, isoprenaline and terbutaline on the allergen-induced release of histamine from chopped human lung tissue passively sensitized with serum from a patient allergic to birch pollen. Per cent inhibition, mean value $\pm$ is presented.

The preparations were mounted in jacketed, temperature controlled (37°C) organ baths containing 30 ml of Krebs' solution. Increased tone was induced in the preparations with pilocarpine, $1\text{ }\mu\text{g/ml}$, or carbacholin, $0.05\text{ }\mu\text{g/ml}$. These agents were present in the baths when the β -stimulants were added cumulatively. After washing, repeated dose-response evaluations could be made in each preparation. From the dose-response curves obtained on each bronchial preparation the dose for 30% of maximum relaxation was extrapolated for the β -stimulants studied, and the potency ratio was calculated.

RESULTS

Inhibition of histamine release

When the passively sensitized human lung tissue was challenged with an extract of birch pollen, $0.5\text{ }\mu\text{g/ml}$, histamine (15.3–36.7%, $n=6$) was released into the incubation fluid. The control release without allergen was 0–4.3% ($n=6$) of the tissue content of histamine. When the β -stimulants KWD 2131, terbutaline and isoprenaline were added to the lung preparations 5 min prior

Table 1
Potency of KWD 2131 relative to terbutaline for relaxation of isolated human bronchi

	Potency ratio, mean and range	
	Airways $\phi > 3$ mm	Airways $\phi = 1$ mm
Terbutaline	1	1
KWD 2131	0.029 (0.050-0.022)	0.022 (0.033-0.018)
<i>n</i>	6	5

to allergen the histamine release was suppressed in a dose-dependent way (Fig. 1). An inhibitory effect was obtained with a rather low concentration of β -stimulant, 10^{-13} , -10^{-9} M. All drugs produced about the same maximum inhibition but isoprenaline was more potent than terbutaline, which in turn was more potent than KWD 2131. The extrapolated dose producing 50% inhibition of the histamine release was about 9×10^{-13} M, 3×10^{-12} M and 2×10^{-11} M for isoprenaline, terbutaline and KWD 2131 respectively. Thus, the potency of KWD 2131 was about 0.15 times that of terbutaline and 0.05 times that of isoprenaline.

Relaxation of human bronchi

Six large and five small airways were obtained from three patients. All preparations contracted when pilocarpine, 1 μ g/ml, or carbacholine, 0.05 μ g/ml, were added to the baths. Graded relaxant responses were obtained when KWD 2131 or terbutaline were added cumulatively. When maximum relaxation had been obtained with KWD 2131, terbutaline was added. This did not relax the bronchi further indicating that KWD 2131 and terbutaline relaxed the preparation to the same maximum level. The dose-response curves for terbutaline and KWD 2131 were similar. Concentrations of KWD 2131 needed for bronchial relaxation were in the range of 10^{-5} - 10^{-4} M. Potency ratios for KWD 2131 as related to the action of terbutaline are given in Table 1. On large

airways the potency of KWD 2131 was 0.029 times that of terbutaline while on small airways it was 0.022 times that of terbutaline.

DISCUSSION

The results show that the β -stimulants KWD 2131 and terbutaline inhibit allergen-induced release of histamine from passively sensitized human lung tissue, and relax isolated contracted human bronchi. Our data with isoprenaline agree with previous results by Assem & Schild (1) who found isoprenaline effective in the concentration range 10^{-12} - 10^{-9} M, in contrast to Orange et al. (8) who used higher concentrations, 10^{-8} - 10^{-6} M, to produce inhibition of histamine release.

In addition, a marked discrepancy was found between the concentration range for anti-anaphylactic effect and that for bronchial relaxation respectively, a difference not noted in the actively sensitized guinea pig lung/pilocarpine-contracted trachea system (14). A comparative study on the effective anti-anaphylactic concentrations of isoprenaline in passively and actively sensitized guinea pig lung tissue showed no striking difference between the two systems (2). Thus it is conceivable that the high anti-anaphylactic potency of the β -stimulants observed in the human lung preparations reflect a species difference in this respect rather than differences in sensitization procedures.

In the guinea pig lung the compound KWD 2131 was equipotent to terbutaline as an inhibitor of anaphylactic histamine release but less potent as a dilator of the isolated trachea (14). Thus in this species the pharmacological profile of KWD 2131 is that of a preferentially anti-anaphylactic compound as compared with terbutaline. The ratio anti-anaphylactic potency/tracheo-dilating potency of KWD 2131 relative to that of terbutaline was 30 in the guinea pig. In the human lung the corresponding ratio was 5, or 7.5 depending on the size of bronchi studied. Thus, the data from the human lung experiments indicate that KWD 2131 is a compound with preferably anti-anaphylactic property, but less so than in the guinea pig lung.

The synthesis of β -stimulants possessing selective anti-anaphylactic mode of action offers an interesting possibility to study the role of β -receptor-mediated anti-allergic effects in the prophylactic treatment of allergic disorders. A study of the effect of subcutaneously administered KWD 2131 on changes in bronchial resistance to inhalation of specific allergen in asthmatics is in progress (Pegelow & Strandberg, 1979).

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