

Cutaneous Responses to Allergen after Local Pretreatment with Beta-Adrenoceptor Stimulating and Blocking Agents

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β -Adrenoceptor stimulating agents possess anti-allergic effects *in vitro* and *in vivo*. To study the mechanism of action further we compared in 10 atopic subjects the effects on allergen-induced cutaneous reactions of intradermally (i.d.) injected prenalterol (1-10 μ g) terbutaline (2.5-250 ng) and KWD 2131 (100 ng-2.5 μ g), i.e. compounds with preferential actions on β_1 -, β_2 -adrenoceptors and on β -adrenoceptors not fitting this classification. All injections were given according to a double-blind design. Terbutaline and KWD 2131 produced a dose-dependent inhibition of the skin reactions induced by injecting horse dander allergen 5 min later. Terbutaline was about 20 times as potent as KWD 2131 whereas prenalterol was inactive. Propranolol fully blocked the anti-allergic effect produced by terbutaline.

The results suggest that the cutaneous anti-allergic effect of β -adrenoceptor-stimulating drugs is mediated via activation of β_2 -adrenoceptors, possibly on the mast cell, resulting in inhibition of mediator release.

Key words: allergen; KWD 2131; prenalterol; terbutaline.

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In a previous investigation intradermal (i.d.) pretreatment of atopic subjects with terbutaline was found to suppress the skin reactions elicited by i.d. injected allergen in a dose-dependent manner (3). In contrast terbutaline did not inhibit the flare reactions to histamine and compound 48/80 and only weakly suppressed wealing following injection of these compounds. These findings suggested an inhibitory action of terbutaline on the allergen-induced release of vasoactive substances and on the capillary permeability changes caused by released mediator substances.

In the present investigation the mechanism of action of the anti-allergic effect has been studied further by comparing the capability of three β -adrenoceptor stimulating

compounds with differences in receptor specificity to antagonize the allergen-induced cutaneous reactions in atopic individuals. Thus the effect of prenalterol (S-(-)-1-(4-hydroxyphenoxy)-3-isopropylaminopropanol-2 hydrochloride), a compound acting predominantly on β_1 -adrenoceptors (1) according to the classification of Lands et al. (5), and KWD 2131 {(1 - (3,5 - dihydroxyphenyl) - 2 - (1,1 - dimethyl - 2 - hydroxyethyl) - amino} ethanol sulphate, a compound with β -adrenergic actions in the guinea pig but with preference for neither β_1 -nor β_2 -adrenoceptors (7), were related to that of terbutaline. In addition, the effect of the β -adrenoceptor blocking agent propranolol on the allergen-induced response was studied as well as its interference with the action of terbutaline.

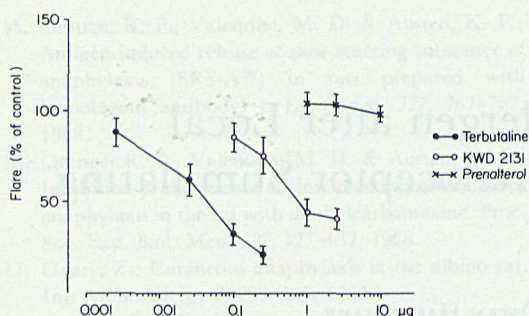


Fig. 1. Dose-response relations for the effect of terbutaline, KWD 2131 and prenalterol on the allergen-induced flare response measured 15 min after injection of the allergen. The compounds were injected 5 min prior to allergen (mean $\pm$ s.e.; $n=10$).

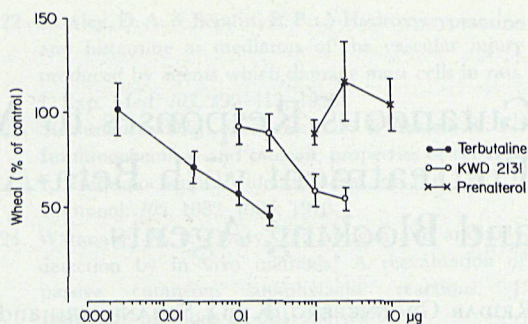


Fig. 2. Dose-response relations for the effect of terbutaline, KWD 2131 and prenalterol on the allergen-induced weal response measured 15 min after injection of the allergen. The compounds were injected 5 min prior to allergen (mean $\pm$ s.e.; $n=10$).

MATERIAL AND METHODS

Skin responses to allergen were studied in 16 volunteering atopic subjects, aged 19–38 years, with a history of allergic rhinitis and/or bronchial asthma and a positive skin test to horse dander. A RAST test to horse dander was positive in the majority of the participants. No patient exhibited dermatographism or suffered from atopic dermatitis and patients were not allowed any medication for 48 h prior to the experiments. The study was approved by the Karolinska Hospital ethics committee.

The horse dander allergen was injected i.d. in a dose producing approximately a flare response corresponding to that of the ED_{50} for histamine as previously determined in each individual. Using a double-blind technique, skin sites on the back were pretreated in a random fashion with the drugs used followed by injection of the allergen with a micrometer syringe 5 min later. Physiological saline (0.02 ml) was injected 5 min prior to allergen as a control injection. The technique used for the injections has been described in detail elsewhere (3). The resulting flare and weal responses were outlined with a marking pen on the skin 15 min after injection of the allergen and measured by planimetry. The areas obtained for the control injections were compared with the corresponding areas after

i.d. injection of the different compounds (expressed as per cent of control values) and the differences were analyzed by the Student's *t*-test.

Terbutaline (Bricanyl®, Draco, Lund, Sweden), KWD 2131 (Draco, Lund, Sweden), prenalterol (Hässel, Mölndal, Sweden) and propranolol (Inderal®, ICI-Pharma, Gothenburg, Sweden) were dissolved in sterile physiological saline containing 10% (v/v) Sörensen phosphate buffer ($Na_2HPO_4 + KH_2PO_4$, 67 mM) pH 7.4. In the doses used i.d. injections of the drugs *per se* elicited no visible vascular effects.

Dilutions of horse dander allergen (Vitrum, Stockholm, Sweden) were prepared by the hospital pharmacy each week using physiological saline with 0.3% phenol. The same batch of allergen was used throughout the study.

RESULTS

The concentrations of allergen needed to produce flare reactions of a size similar to that produced by the ED_{50} for histamine varied between 10^{-10} – 10^{-3} w/v due to differences in reactivity of the allergic subjects. The areas (mm^2) of the flare and weal responses were 990 ± 40 and 63 ± 3 respectively (mean $\pm$ s.e.). The mean coefficient of variance for the

control injections was 17.4% (flare) and 21.8% (weal).

In 10 atopic individuals i.d. pretreatment of the skin with terbutaline (2.5–250 ng) and KWD 2131 (100 ng–2.5 μ g) 5 min prior to allergen injection produced a dose-dependent inhibition of the allergen-induced cutaneous responses. Terbutaline was about 20 times more potent (ID_{50}) than KWD 2131 in this respect. The inhibition of the reactivity was approximately equally pronounced in all individuals independent of individual reactivity. Prenalterol (1–10 μ g) was inactive (Figs. 1 and 2).

The inhibitory effect of 100 ng terbutaline on the flare and weal responses to allergen was abolished by 100 ng propranolol when the two drugs were injected in a mixture 5 min prior to the allergen (Fig 3). When propranolol and terbutaline were injected in a dose ratio 1 : 5 propranolol still counteracted the inhibitory action of terbutaline on the flare response significantly ($P < 0.01$), whereas the effect on the weal reaction was only weakly influenced (Fig 4). Propranolol (20, 100 ng) injected alone prior to the allergen had no effect on the weal and flare responses.

DISCUSSION

Terbutaline was previously shown to be a potent inhibitor of the allergen-induced flare and weal responses in atopic skin (3). The present experiments further suggest that the anti-allergic effect of β -adrenoceptor stimulating compounds is related to their β_2 -adrenoceptor stimulating properties. Thus a highly selective β_1 -adrenoceptor stimulant, prenalterol, was inactive in comparatively high doses. Like terbutaline, KWD 2131 inhibited the allergen-induced reaction in a dose-dependent manner but it was considerably less potent. Similar results were obtained when the inhibitory action of the two compounds on allergen-induced histamine release from passively sensitized human lung fragments was compared (6).

In contrast, KWD 2131 was as potent an inhibitor as terbutaline of anaphylactic histamine release from guinea pig lung tissue, whereas it was a less potent bronchodilator (7). In the guinea pig the anti-allergic effect of β -adrenoceptor stimulants may well be mediated via β -adrenoceptors separable from β_2 -adrenoceptors but in the human this concept is not favoured by our data. In this context it may be mentioned that salbutamol and fenoterol are essentially equipotent to terbutaline as inhibitors of allergen-induced cutaneous reactions in man, which further emphasizes the β_2 -adrenoceptor site of action (Grönneberg, unpublished results).

Terbutaline suppresses the allergen-induced weal and flare responses markedly in doses that cause no inhibition of the flare and only weak antagonism of the weal to histamine (3). These data were taken to indicate a dual mechanism of action for the anti-allergic effect of terbutaline, i.e. inhibition of the release of vasoactive mediator substances from the skin mast cells and antagonism of an increased capillary permeability due to released mediators. With this interpretation of the results it is difficult to reconcile the seemingly differential effect of propranolol on the inhibitory action of terbutaline on the flare and weal response to allergen respectively. Both responses were fully restored when an equivalent dose of propranolol was given concomitantly with terbutaline but in contrast to the effect on wealing the flare response was restored also when the ratio of propranolol to terbutaline was lowered. Possibly for technical reasons, the flare response with its larger size and two-dimensional appearance lends itself better to this kind of quantitative experimentation. Alternatively, the inhibitory effect of terbutaline on the weal response might be more resistant to propranolol treatment due to the possible dual inhibitory action of terbutaline in this case, i.e. inhibition of mediator release and permeability changes. The main conclusion rests, however, that propranolol counteracts the terbutaline-induced inhibition of cutaneous responses to

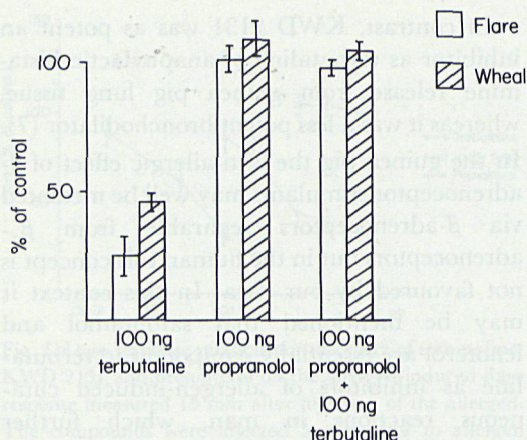


Fig. 3. Effects of 100 ng terbutaline and 100 ng propranolol injected alone, or as a mixture, on the flare and weal responses induced by allergen. The compounds were injected 5 min prior to the allergen. The flare and weal areas were measured 15 min after injection of the allergen (mean $\pm$ s.e.; $n=8$).

allergen and does not enhance these responses *per se*.

That β -adrenoceptor stimulants may inhibit mast cell mediator release as well as diminish increased capillary permeability *in vivo* has been amply demonstrated by experiments in the rat (2). When peritoneal anaphylaxis was induced by i.v. administration of egg albumin after i.p. injection of rat IgE serum, pretreatment with β -adrenergic stimulants was found to reduce the amounts of histamine released and the amounts of i.v. injected dye extravasated into the peritoneal cavity.

In conclusion the present data suggest that the inhibitory action of β -adrenoceptor stimulating compounds on allergen-induced cutaneous responses is mediated via activation of β_2 -adrenoceptors, possibly on the mast cell. The demonstration that the inhibitory effect may be elicited also on oral administration of terbutaline further supports the hypothesis that the anti-allergic effect of these drugs may be of clinical relevance (4).

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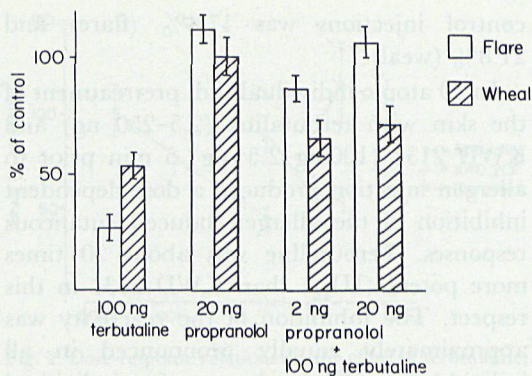


Fig. 4. Effects of 100 ng terbutaline and 2 and 20 ng propranolol injected alone, or as a mixture, on the flare and weal responses induced by allergen. The compounds were injected 5 min prior to allergen. The flare and weal areas were measured 15 min after injection of the allergen (mean $\pm$ s.e.; $n=10$).

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