

Systemic adrenaline attenuates skin response to antigen and histamine

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Summary

Six atopic subjects received either adrenaline (0.3 ml of 1 mg/ml), subcutaneously over the deltoid muscle, or saline on 2 separate days. After 10 min, histamine and antigen were injected intradermally in the forearm. Adrenaline significantly inhibited the flare of histamine and both the flare and weal of antigen ($P < 0.05$). This anti-allergic action of adrenaline occurred with a dose that we have previously shown produces plasma concentrations at the upper limit of the physiological range in resting normal subjects.

Introduction

Systemically administered β_2 -agonists, theophylline and corticosteroids have previously been shown to have no influence on the skin response to either intradermal antigen or histamine [1–4]. However, if the area of skin to be challenged is pre-treated with an injection of a β_2 -agonist, then this high local concentration attenuates the response to intradermal antigen [5–8].

Adrenaline is established as an effective treatment of acute urticaria and we, therefore, studied the effect of systemic adrenaline on intradermal antigen- and histamine-induced weal and flare. The dose of adrenaline chosen has been previously shown to produce venous plasma levels at the upper limit of the physiological range in resting subjects [9]. This experiment can, therefore, be interpreted as relevant to adrenaline acting either as a drug or as a circulating hormone.

Subjects and methods

Six atopic subjects (two males) aged 23–35 years received either 0.3 ml saline or 0.3 ml of 1 mg/ml adrenaline subcutaneously over the deltoid muscle on 2 separate days in

Table 1. Effect of systemic adrenaline or placebo on the weal-and-flare response to intradermal antigen and histamine

		Adrenaline	Saline
Histamine	Weal	0.08 (0-0.28)	0.11 (0-0.44)
	Flare	0.25 (0-1.53)	3.20 (0-8.42)*
Antigen	Weal	0.12 (0-0.86)	0.37 (0.13-1.54)*
	Flare	3.02 (0-8.44)	7.64 (2.37-13.77)*

Results are the median (range) in cm², $n=6$.

* $P<0.05$, Wilcoxon matched pairs signed rank sum test, saline *vs* adrenaline.

randomized order. Ten minutes later, intradermal skin-prick challenges with histamine (1% solution) and either grass pollen or house dust mite (Bencard, U.K.) were performed in duplicate on the forearm with Morrow Brown needles [10]. The choice of antigen depended on the previously determined skin sensitivity of the individual. The skin tests were placed 3 cm on either side of the mid-point of the flexor aspect of the forearm. After 15 min the weal-and-flare responses were recorded by an independent observer. The weals were traced in ink and transferred to paper using 'sellotape'. The flares were traced directly onto acetate sheets. The areas were calculated by planimetry and the results analysed by Wilcoxon signed-rank sum test. The study was approved by the hospital ethics committee.

Results

Table 1 summarizes the weal-and-flare responses to antigen and histamine. Adrenaline reduced the median area of antigen-induced weal to 32% of control, and the flare to 40%, compared with control. The corresponding figures for histamine were 73% for weal and 8% for flare.

Discussion

Adrenaline differs from other β_2 -agonists in that, when given systemically in doses used clinically, it is capable of inhibiting both histamine and antigen skin challenges. Compared with a previous study, where high doses of intravenous adrenaline were shown to have the same effect [11], the present study used a small dose of subcutaneous adrenaline, which gives venous plasma levels in the physiological range [9]. Phenylephrine does not affect the response to intradermal skin tests [11] and this makes alpha stimulation alone an unlikely explanation of this action. Although oral β_2 -agonists are ineffective, high concentrations of locally injected β_2 -agonists are effective inhibitors of histamine and antigen challenge; this is blocked by beta-receptor antagonists [6]. Topical application of a β_2 -agonist has also been shown to protect against antigen challenge in the nose [12] and further, intravenous salbutamol is an inhibitor of skin anaphylaxis in rats [13]. It is, therefore, likely that adrenaline is acting by β_2 -receptor stimulation, but this does not explain why adrenaline is so active at low concentrations compared with other β_2 -agonists. Adrenaline may be having a specific anti-allergic effect, since *in-vitro* it can prevent IgE-induced histamine release from human lung [14, 15].

Endogenous adrenaline may have a powerful protective influence on the airway [16, 17], but it is difficult to dissociate this from its bronchodilator action. By using skin-challenge testing the present experiment highlights the capacity of adrenaline, at plasma concentrations at the upper limit of the physiological range [9], to diminish immediate hypersensitivity.

When selecting compounds with potential use as β_2 -stimulants it may be advantageous to select those with this anti-allergic effect of adrenaline in addition to their ability to bronchodilate. Skin testing provides a simple method of screening for this property.

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