

Differential effects of skin nerves on allergic skin inflammation

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Allergic skin disorders can be affected by neurogenic

signals, e.g.

atopic dermatitis and urticaria are often reported to be exacerbated

by stress. In

support of this view, we have recently shown that sensory nerves and neuropeptides in murine skin contribute significantly to the development of allergic inflammatory responses (1). However, there is very limited information on the role of sensory nerves in the modulation of allergic inflammation in human skin. To address this, we have assessed all four major features of allergic skin inflammation (rubor, calor, tumor and pruritus) in the absence of functional sensory nerves as well as in normal skin.

Forty-eight volunteers with sensitizations to common inhalant allergens were included in this study, which was approved by the ethics committee of Charité – Universitätsmedizin Berlin. Skin prick tests (SPTs) were performed in each subject with a relevant allergen, histamine and saline on both volar forearms. Lidocaine/prilocaine cream (EMLA[®], AstraZeneca, Wedel, Germany), and vaseline (Winthrop[®], Winthrop Arzneimittel, Fürstentfeldbrück, Germany) were applied double blind to the test areas of the left and the right forearm, respectively, 1 h prior

Sensory skin nerves can differentially modulate allergic inflammatory reactions.

to testing, and the treated areas were covered using a self-adhesive dressing (Tegaderm[™], 3M, Neuss, Germany). After SPTs, size of developing erythema, increases in skin temperature, wheal development, and intensity of pruritus were assessed at various time points after SPTs.

The pharmacologic inhibition of cutaneous nerves differentially affected allergic inflammatory responses in human skin. Lidocaine/prilocaine treatment most prominently reduced the flare reaction associated with allergic skin inflammation (Fig. 1A), whereas hyperthermia and wheal formation were less inhibited (Fig. 1B,C). Lidocaine/prilocaine treatment did not affect pruritus responses following allergic skin inflammation (Fig. 1D). Interestingly, lidocaine/prilocaine treatment had very similar effects on histamine-induced skin responses (Fig. 1E–H).

These findings indicate that cutaneous sensory nerves differentially affect allergic inflammatory skin responses. Specifically, our observations demonstrate that the pharmacologic inhibition of sensory nerves in the skin by topical application of lidocaine/prilocaine results in an almost complete inhibition of erythema, a moderate reduction of hyperthermia and wheal development, and in no changes in pruritus.

It is well known that neuropeptides released from sensory nerves, i.e. substance P, vasoactive intestinal polypeptide (VIP), calcitonin gene-related peptide (CGRP) or nerve growth factor (NGF), can activate mast cells (MCs) (2), and we have previously shown in mice that denervation of the skin leads to reduced MC-dependent allergic inflammation (1). However, the neurogenic modulation of allergic skin responses observed in this study is, at least in part, caused by effects downstream of MC activation, as lidocaine/prilocaine treatment reduces erythema,

hyperthermia and wheals almost identically in allergen- and histamine-induced skin inflammation.

The observed dramatic reduction of the erythema in the lidocaine/prilocaine-treated skin in our investigations indicates that sensory nerves are almost exclusively responsible for rubor, whereas wheal development is far less altered after pharmacologic inhibition of skin nerves, confirming the prominent role of histamine and other MC products in this response. These findings are in line with previous investigations showing that erythema but not wheal development is reduced by topical analgesics (3–5). While the effect on pruritus has been controversially discussed in the literature, we observed that allergen- and histamine-induced pruritus were virtually unaffected by the treatment. Lidocaine/prilocaine cream is a potent topical analgesic that efficiently blocks the pain associated with SPTs; therefore, these data indicate that specific pruriceptive sensory nerve fibres exist in the skin, which are unresponsive to EMLA[®] treatment. This hypothesis is in line with the current concept that pruritus is a distinct sensation independent from pain and that specific pruriceptive histamine-sensitive sensory nerves are involved in the perception of itch (6).

In this study, we report – for the first time – a quantitative assessment of all four features of allergic skin inflammation (i.e. rubor, calor, tumor, and pruritus) in allergen- and histamine-induced skin responses in the absence and presence of fully functional sensory skin nerves, and we show that sensory skin nerves differentially modulate allergic inflammatory reactions in human skin.

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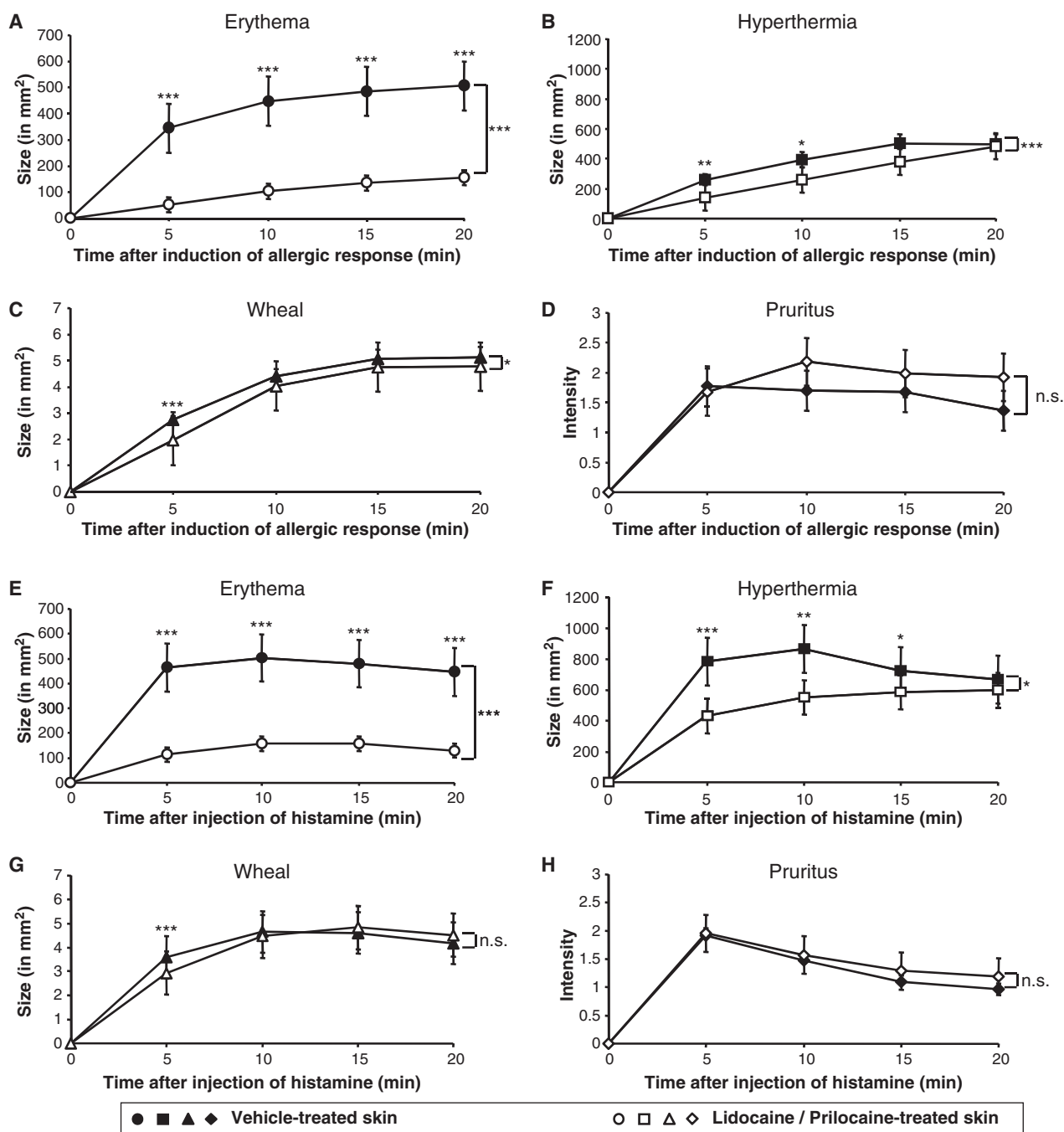


Figure 1. Sensory skin nerves contribute differentially to allergic and histamine-induced skin inflammation. Effects of sensory nerve inhibition by topical treatment with the local anesthetics Lidocaine/prilocaine (EMLA®) on the development of erythema (A, E), hyperthermia (B, F), wheal (C, G), and pruritus (D, H) in cutaneous allergic responses induced by skin prick testing (A–D) or histamine (E–H). Data represent means $\pm$ SEM, $n = 48$. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, ns = not significant. Erythematous areas were calculated using the formula $\text{area} = \pi \times r_1 \times r_2$, with r_1 = the radius for the largest diameter and r_2 = the radius for the orthogonal diameter to the largest diameter. To assess increases in skin temperature, hyperthermic skin areas were measured using an infrared camera and a volumetric optical scanning system was used to determine the lesion volume. Pruritus intensity was quantified using a Likert scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

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