

High-concentration topical capsaicin may abolish the clinical manifestations of allergic contact dermatitis by effects on induction and elicitation



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ABSTRACT

Allergic contact dermatitis (ACD) is a common skin condition caused by a type-IV hypersensitivity reaction. Even though ACD is considered as a T-cell mediated disease, indications exist that peptidergic nerve fibers at the site of allergen exposure and associated with the draining lymph node play a prominent role in both induction and elicitation of ACD. This neuro-immune cross talk seems to rely on neuropeptides such as Substance P secreted by nerve fiber terminals. It is hypothesized that local complete or partial cutaneous denervation/defunctionalization of peptidergic fibers in humans could be a feasible approach towards treating allergic contact dermatitis. Recently, human experimental protocols for prominent, temporary defunctionalization of peptidergic fibers have been published relying on prolonged application of 8% topical capsaicin patches. Combined with human experimental ACD models the importance of peptidergic nerve fibers in the induction and elicitation phases of ACD could be accurately established. Understanding the role of cutaneous peptidergic fibers in the pathogenesis and potentially of ACD and how contact sensitization can be modulated by topical defunctionalization of these fibers could lead to new approaches to treatment for ACD. In patients with localized ACD occurring to an allergen that is difficult or unfeasible to evade this would have particular relevance.

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Introduction

Allergic contact dermatitis (ACD) is a highly prevalent and potentially debilitating condition elicited by allergens/haptens such as nickel, fragrances or hair dyes [1–5]. Pathoetiologically, ACD is a type-IV-hypersensitivity reaction initiated when allergens come into contact with the skin and interact with structural and antigen-presenting immune cells (APCs) as well as cutaneous peptidergic nerve fibers (CPNF) [2–4,6]. In response to the allergen, the APCs and surrounding structural cells produce co-stimulatory factors locally and within 24 h the APCs migrate to the associated lymph nodes. Here, antigen-presentation occurs and elicits an immune response towards Tc1/Th1 and Tc17/Th17 T-cells in a process where inflammatory co-stimulation appears to be important to overcome innate immune-regulation [4,5,7,8]. After the induction phase, elicitation of ACD occurs when the antigen is reintroduced. Elicitation starts with reuptake and re-presentation of the

allergen by APCs to allergen-specific T-cells. This leads to an inflammatory response involving local macrophages, keratinocytes, mast-cells and CPNF causing release of cytokines and T-cell-attracting chemokines [5,9–11]. This is followed by a pronounced infiltration of allergen-specific and non-specific T-cells (basophils, eosinophils and mast cells partake) releasing TNF- α and GM-CSF [5,12]. These factors combined in a positive loop-like manner, give rise to the clinical picture of ACD with infiltration, edema, erythema, itch, pain (the two latter mediated by C-/A δ -fibers) and neuronal sensitization [3,4,1,10].

Hypothesis

In light of the summarized evidence, it is hypothesized that topical high-concentration capsaicin-induced defunctionalization/ablation of peptidergic C-fibers in humans can abolish or greatly diminish both induction and elicitation of allergic contact dermatitis locally. While much lower concentrations of topical capsaicin have long been employed to alleviate ACD symptoms such as itch [14,15], we specifically hypothesize that prolonged application of high concentrations may directly hamper ACD pathogenesis in its entirety.

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Evaluation of the hypothesis

CPNF are in direct contact with APCs and release a number of inflammatory and vasoactive molecules in response to epicutaneously applied antigens and irritants [5,13]. Activation also occurs in response to endogenous processes and CPNF have been proposed to play a role in the symptomatology and pathogenesis of inflammatory dermatoses such as psoriasis [16–18]. Upon activation, peptidergic neurons secrete neuropeptides such as calcitonin-gene related peptide (CGRP), Substance P (SP), and corticotropin-releasing hormone (CRH) [6,19–22]. In turn, vasodilation and extravasation occurs and neighboring cells responsive to neuropeptides (mast-cells, keratinocytes, APCs, macrophages, and endothelial cells) secrete histamine, interleukin-1 (IL-1), interleukin-6, interleukin-8, interleukin-12 (IL-12), nerve growth-factor (NGF), tryptase, etc. [6,18,19,22–24] (Fig. 1). Many of these substances cause neuronal sensitization, but perhaps more importantly in the context of ACD, they modulate the immunological reaction mounted in response to the allergen exposure: 1) IL-1,

CGRP and histamine facilitates diapedesis and inflammation [22], 2) SP activates APCs leading to the antigen-specific immune responses, production of Th1-cytokines, and increased infiltration of eosinophils [12], and 3) IL-12 from APCs and keratinocytes released in response to neuropeptides potentiate the immune response towards Th1-cells [22,25–27]. Much of this signaling is thought to rely on positive-feedback involving or initiated by CPNF and certain contact sensitizers such as dinitrochlorobenzene (DNCB) directly activate receptors on CPNF associated with inflammation, itch, and pain [13]. Notably in this context, it is well-established that repeated applications of low concentration topical capsaicin diminish neurogenic inflammation, itch, and pain associated with various irritants [14,15,28,29].

Strong evidence showing involvement of CPNF comes from rodent studies where ablation of CPNF was performed prior to ACD-challenges [30–32]. In a murine ACD-model, Beresford et al. 2004 utilized both a general and peptidergic specific neurotoxin (capsaicin) to ablate fibers. Subsequently, DNCB was applied to denervated and control areas. Both total and peptidergic-specific neuronal ablation resulted in an almost complete inhibition of both

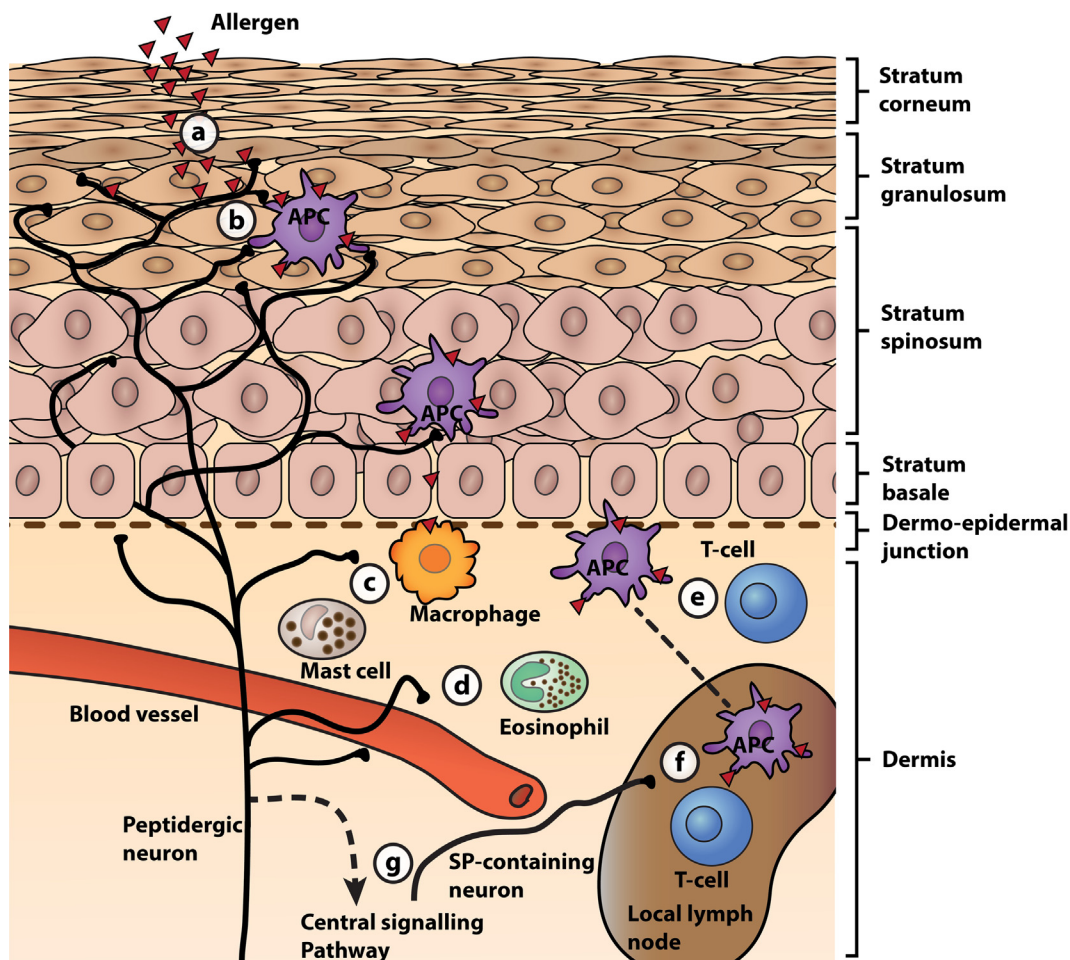


Fig. 1. Hypothesis illustration - neurogenic processes influencing allergic contact dermatitis elicitation. Steps: a) an allergen/hapten penetrates the stratum corneum and comes into contact with keratinocytes, APCs (foremost epidermal Langerhans cells), and in some cases activates peptidergic fibers directly; b) APCs processes the allergen and a peptidergic response wherein Substance P is released commence. This inflammatory response modulates APC activity directly and indirectly through paracrine signaling to keratinocytes; c) the release of neuropeptides in the vicinity of mast cells cause degranulation leading to the release of variety of inflammatory mediators such as histamine and leukotrienes leading to itch and sensory sensitization. Moreover, these substances induce chemotaxis, extravasation, and leads to macrophage activation and release of interleukins, such as IL-6, further potentiating the inflammatory response (macrophage activity is also directly tuned by neuropeptide release); d) the antidromic neurogenic response extents via the entire terminal branch. Consequently, release of CGRP from terminals in the vicinity of capillaries cause vigorous vasodilation leading to extravasation of eosinophils and other immune cells; e and f) APCs attracts and activate local e) and lymph node residing f) T-cells eliciting the vigorous T-cells response characteristic of ACD. Subsequently, infiltration and intensity of the response is likely tuned by co-inflammatory stimulation; g) as proposed by Shepherd et al. (2005) a central signaling pathways initiated by cutaneous peptidergic fibers might modulate efferent signaling mediated by Substance P to the local lymph node and hereby regulate the T-cell response (8).

ACD-induction and effector responses. This effect was localized to the pretreated denervated areas, and subsequent systemic capsaicin-induced peptidergic ablation had similar effects to the local treatment, indicating a fiber-specific mechanism. Moreover, control experiments showed that APCs in the area had not been damaged and that migration of APCs to the draining lymph nodes was not impeded [31]. The demonstrated inability of sensitized T-cells to evoke an ACD-response in a capsaicin-denervated area suggests that CPNF are crucial to local chemotaxis, infiltration and/or APC behavior in the effector stage. The findings are aligned with earlier observations from studies on wound healing in denervated areas [33,34] and supported by the fact that intradermal administration of exogenous SP-agonists enhances ACD, while SP-antagonists impair ACD-development [35–37]. Lastly, a central signaling-axis from peripheral fibers (at the site of the challenge) to the CNS and then via efferent fibers innervating the drainage lymph nodes has also been suggested to underlie the denervation-induced inhibition of ACD [30,32].

How to test hypothesis

The use of high-concentration topical capsaicin (8%, Qutenza, Astellas) was approved for neuropathic pain conditions in 2009 and recently experimental protocols with prolonged application have proven successful in establishing a pronounced temporary functional blockade of peptidergic C-fibers in humans [38,39]. Combined with a standardized model of ACD using DNCB or squaric-acid dibutyl-ester the presented hypothesis could be effectively and safely tested in healthy volunteers [3].

Consequences of the hypothesis

ACD is one of the most frequent occupation-related diseases and remains a major treatment challenge, especially in cases where avoiding the inciting allergen is arduous. Understanding the role of CPNF and neurogenic inflammation in the pathogenesis and potentially how contact sensitization can be modulated by topical defunctionalization of CPNF could lead to novel treatment approaches for ACD. This would be particularly relevant in cases with localized ACD occurring to an allergen that is difficult or unfeasible to evade.

Author contributions

All authors contributed in the conception, writing and discussion of this hypothesis manuscript. HHA wrote the initial manuscript draft. The final version of the manuscript was approved by all authors.

Conflict of interest

None of the authors have conflicts of interest to declare.

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