

Short communication

TRPV1-mediated itch in seasonal allergic rhinitis

Background: Patients with allergic rhinitis may be abnormally sensitive to stimulation of the ion channel transient receptor potential vanilloid-1 (TRPV1).

Aim of the study: To examine effects of various TRP ion channel activators on sensory symptoms in allergic rhinitis prior to and during seasonal allergen exposure.

Methods: Nasal challenges were carried out with the TRPV1-activators capsaicin, anandamide and olvanil. Moreover, challenges were performed with mustard oil (allylisothiocyanate) and cinnamaldehyde as well as menthol, activators of TRPA1 and TRPM8, respectively. Nasal symptoms were monitored after each challenge and compared with symptoms reported following corresponding sham challenges. Symptoms recorded after challenge prior to pollen season were also compared with challenge-induced symptoms during pollen season.

Results: The TRPV1, TRPA1 and TRPM8-activators produced sensory symptoms dominated by pain and smart. During seasonal allergen exposure, but not prior to season, TRPV1-activators also induced itch. Furthermore, the seasonal challenge to the TRPV1-activator olvanil was associated with rhinorrhoea.

Conclusion: Patients with allergic rhinitis feature an increased itch response to TRPV1 stimulation at seasonal allergen exposure. We suggest that this reflects part of the hyperresponsiveness that characterizes on-going allergic rhinitis. Intervention with the TRPV1-signalling pathway may offer potential treatments of this condition.

**L. Alenmyr¹, E. D. Högestätt¹,
P. M. Zygmunt¹, L. Greiff²**

Departments of ¹Clinical Chemistry and Pharmacology and ²ORL, Head & Neck Surgery, Lund University Hospital, Lund, Sweden

Key words: airways; allergy; sensory neurons; transient receptor potential ion channels.

Lisa Alenmyr, MD
Department of Clinical Chemistry and Pharmacology
Lund University Hospital
SE-221 85 Lund
Sweden

Accepted for publication 23 September 2008

Transient receptor potential vanilloid-1 (TRPV1) is an ion channel localized to primary sensory neurons and known for mediating the pungency of capsaicin. In experiments involving TRPV1-knockout mice, Shim et al. (1) demonstrated that histamine administered subcutaneously produced lesser symptoms in TRPV1-knockout than in wild-type animals. Furthermore, in wild-type mice, treatment with a TRPV1-antagonist reduced histamine-induced effects (1). Histamine is well known to induce nasal itch in man, and the H1-receptor is co-expressed with TRPV1 on afferent neurons of the nasal mucosa in guinea-pigs (2). Accordingly, part of the biological effect of histamine, e.g. in allergic rhinitis, may be mediated by TRPV1.

We have previously shown that nasal administration of the TRPV1-activator capsaicin produce greater pain and smart responses late into the pollen season compared with prior to the season (3). Similarly, Kowalski et al. (4) reported greater symptoms (congestion and rhinorrhoea) in response to capsaicin during the pollen season than after the season. However, whether or not these findings can be extended to other TRP ion channels on sensory neurons, e.g. TRPA1 and TRPM8, has not been studied. It also remains unknown whether or not these TRP ion channels are involved in mediating nasal itch, which is a prominent symptom in allergic rhinitis.

In the present study, we exposed patients with on-going allergic rhinitis to nasal challenges that stimulate the ion channels TRPV1 (capsaicin, anandamide, olvanil), TRPA1 (mustard oil, cinnamaldehyde) and TRPM8 (menthol). The latter ion channels define subpopulations of TRPV1-positive and TRPV1-negative sensory neurons (5–7). The challenges were carried out prior to as well as during seasonal allergen exposure and we focused our analysis on sensory symptoms, notably itch.

Material and methods

Ten patients with intermittent allergic rhinitis (aged 21–35 years) were subjected to sensory nasal challenges before and during seasonal allergen exposure. All patients had a history of strictly seasonal allergic rhinitis and a positive skin prick test to birch pollen allergen. No drugs were allowed during the course of the study and for a period of 1 month before the first visit. The local ethics committee approved the study and informed consent was obtained from all subjects.

Daily pollen counts were obtained from a regional pollen trap. Active challenges were carried out on six separate days (24-h washout periods) prior to and approximately 2 weeks into the birch pollen season. The challenges were delivered as lavages using a pool-device (3). The daily active challenge was preceded by two 30-s isotonic saline lavages (carried out to remove mucosal surface liquids that might have accumulated for an unknown period of time

and to produce a stable baseline) and by a control/sham challenge. The active and sham challenges were kept in the nasal cavity for 5 min.

The active challenges were capsaicin (1.0 μ M), anandamide (100 μ M), olvanil (1.0 μ M), cinnamaldehyde (100 μ M), allylisothiocyanate (100 μ M) and menthol (1.0 mM). These concentrations of activators produce robust and almost maximal effects on their respective cloned TRP-ion channel (5–7). The sham/control solution was ethanol (1.0%) in isotonic saline and all active challenges were dissolved in this solution. The order of the challenges was randomized for each individual.

The patients scored symptoms after each control/sham challenge and after each active challenge. Accordingly, pain, smart, itch, heat, cold and rhinorrhoea, respectively, were assigned a score reflecting the severity of the symptom: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms and 3, severe symptoms.

Data are described as median levels with interquartile range (IQR). Observations between sham and active challenge prior to and during the pollen season, respectively, were compared using the Wilcoxon-signed rank test. This test was also used for analysis of observations between active challenges prior to and during the pollen season. *P*-values < 0.05 were considered significant.

Results

Seasonal pollen counts revealed moderate allergen exposure and the patients reported mild-to-moderate symptoms of allergic rhinitis (data not shown).

Compared with sham challenge, capsaicin produced pain or smart and a sensation of heat prior to ($P \leq 0.01$) as well as during ($P < 0.01$) seasonal allergen exposure (Table 1). Furthermore, this challenge produced a significant sensation of itch during the season ($P < 0.05$), but not prior to the season (Fig. 1A, Table 2). Several subjects reported rhinorrhoea after capsaicin challenge prior to and during the season, but these changes were not statistically significant.

For olvanil, a significant smart response was recorded prior to ($P < 0.01$) as well as during the pollen season ($P < 0.05$) (Table 1). In addition, olvanil produced significant rhinorrhoea, pain and itch responses during the season ($P < 0.05$), but not prior to the season (Fig. 1B, C). Some subjects reported smart after anandamide challenge, but this effect failed to reach statistical significance (Table 1).

Table 1. Median scores (IQR) of pain and smart (range 0–6) recorded following sham and active challenge, respectively, prior to and during the pollen season

	Prior to the pollen season		During the pollen season	
	Sham	Active challenge	Sham	Active challenge
Capsaicin	0 (0–0)	4 (3–4.5)	0 (0–0)	4 (3–5.5)
Anandamide	0 (0–0)	0 (0–1)	0 (0–1)	1 (0–2)
Olvanil	0 (0–0)	1 (0–1)	0 (0–0)	1 (0–3)
Mustard oil	0 (0–0)	3 (1–3.5)	0 (0–0)	2 (1–4)
Cinnamaldehyde	0 (0–0)	0 (0–1.5)	0 (0–0)	0 (0–2)
Menthol	0 (0–0)	2 (0.5–3)	0 (0–0)	3 (1–4)

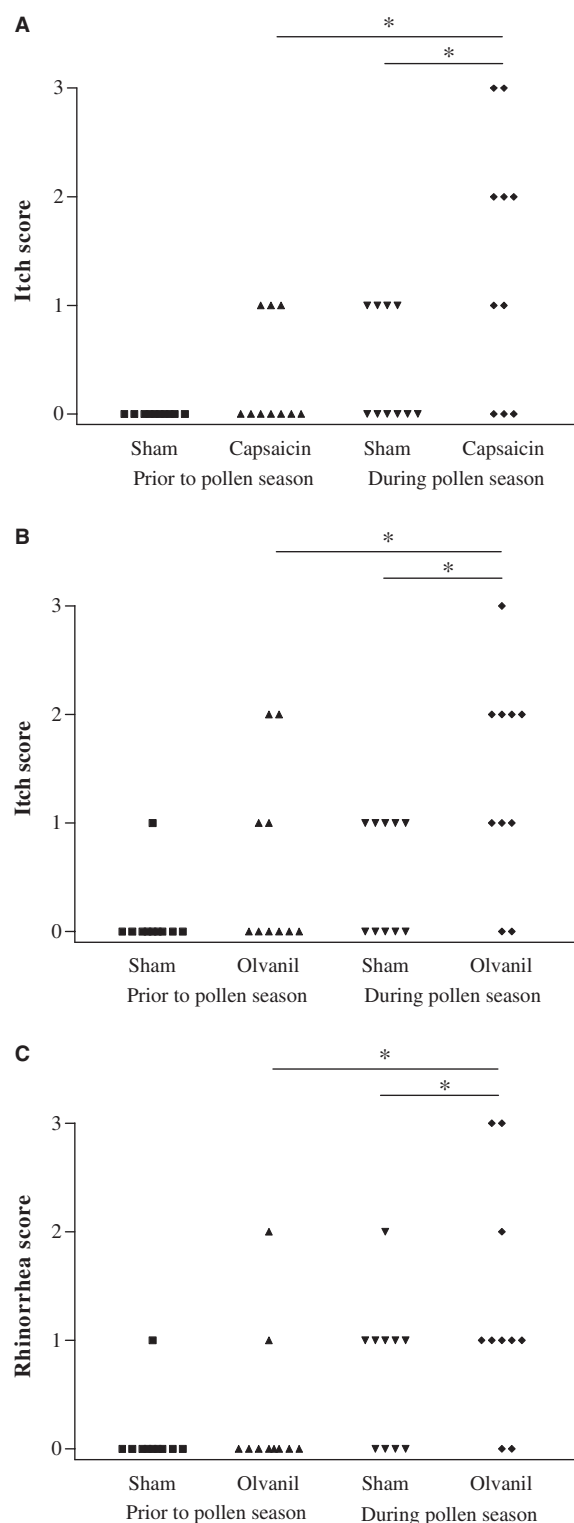


Figure 1. Individual symptom scores following sham and active challenge prior to and during the pollen season. Capsaicin and olvanil induced itch responses (A, B) and olvanil produced rhinorrhoea (C) during the pollen season, but not prior to the season, compared with sham challenges. Reported itch and rhinorrhoea during active challenge were also larger during the pollen season than prior to the season.

Table 2. Median scores (IQR) of itch (range 0–3) recorded following sham and active challenge, respectively, prior to and during the pollen season

	Prior to the pollen season		During the pollen season	
	Sham	Active challenge	Sham	Active challenge
Capsaicin	0 (0–0)	0 (0–1)	0 (0–1)	1.5 (0–2.5)
Anandamide	0 (0–0)	0 (0–1)	1 (0–2)	1.5 (0–3)
Olvanil	0 (0–0)	0 (0–1.5)	0.5 (0–1)	1.5 (0.5–2)
Mustard oil	0 (0–0)	0 (0–1)	0 (0–1.5)	1 (1–2.5)
Cinnamaldehyde	0 (0–0)	0 (0–1)	0 (0–1.5)	1 (1–1.5)
Menthol	0 (0–0.5)	0 (0–1)	0 (0–1)	1 (0–1)

As shown by paired comparisons with sham, the TRPA1 activators produced a pain or smart response prior to as well as during the pollen season ($P < 0.05$) (Table 1). For menthol (activator of TRPM8), significant smart/pain responses were observed prior to as well as during the pollen season ($P < 0.05$) (Table 1) along with a sensation of coolness ($P < 0.01$). The TRPA1 and TRPM8 activators did not elicit any significant itch responses, neither before nor during pollen season.

Discussion

In the present study we report that activation of TRPV1 by capsaicin and olvanil in the nasal mucosa evokes itch in patients with allergic rhinitis at seasonal allergen exposure, but not outside the pollen season. The observation may reflect the sensory hyperresponsiveness that characterizes airway inflammation in on-going allergic rhinitis (3, 4) and asthma (8). Based on observations in inflammatory bowel disease (9), it may be hypothesized that the increased TRPV1-responsiveness reflects upregulation of TRPV1 associated with the inflammatory process. The present finding that activation of TRPA1, which is expressed on a subpopulation of TRPV1-positive neurones (5), was unable to trigger seasonal itch suggests that nasal itch is mediated by TRPA1-independent neuronal pathways in man. It is unlikely that the TRPA1 activators failed to reach their target, because they produced pain or smart both before and during the pollen season.

In contrast to capsaicin and olvanil, the endogenous TRPV1-activator anandamide neither induced itch nor pain or smart. The discrepant effects might be explained by several factors, including extensive mucosal metabolism of anandamide and differences in mucosal penetration *in vivo*. The latter possibility might also explain why cinnamaldehyde and mustard oil had different effect profiles in the present study (Table 2). Furthermore, the

study is of a low power and we may not entirely exclude seasonal differences involving other TRP-ion channels than TRPV1.

Histamine, acting on H1-receptors, is a key mediator of itch in allergic rhinitis. For example, at acute allergen exposure, antihistamine treatment abolishes nasal symptoms, including itch/sneezes (10). Our present observation suggests that TRPV1 may also mediate itch in allergic rhinitis, specifically at sustained seasonal exposure. Importantly, histamine, as suggested by Shim et al. (1), may act via TRPV1 and tentatively produce itch. This is in agreement with findings in human skin where capsaicin desensitizes the histamine-responsive nerves (11); activation of the phospholipase C and A₂ signalling pathways may provide potential molecular mechanisms for such a TRPV1-dependent pruritogenic action of histamine (1, 12–14). Importantly, other mediators associated with allergic inflammation, including bradykinin, may also act via TRPV1 and tentatively produce itch (12, 13). Taken together, the present and previous observations provide a rationale for evaluating the effect of TRPV1-antagonists on airway symptoms, such as itch and sneezes, in patients with allergic rhinitis.

The present observations indicate that TRPV1-pathways mediate rhinorrhoea. This is in agreement with a previous report on glandular secretion after nasal challenge with capsaicin (15). Taken together, available observations suggest that TRPV1-stimulation can induce a reflex action that results in glandular secretion, a response associated with but not specific for airway inflammation. Importantly, as discussed above, this action may contribute to rhinorrhoea and the mediators of the response may be histamine as well as other inflammatory products.

We conclude that patients with on-going allergic rhinitis may feature increased itch to TRPV1-activation at seasonal allergen exposure. The finding suggests that TRPV1-pathways may contribute to the pathophysiology of allergic rhinitis and that this particular ion channel may be of interest as a treatment target. Further studies are warranted to elucidate mechanisms involved in TRPV1-mediated nasal itch as well as in allergen-induced nasal itch/sneezes. Tentatively, such studies may involve the employment of selective TRPV1-antagonists.

Acknowledgments

This study was supported by grants from Swedish Research Council (2007-3095), Medical Faculty of Lund University (ALF), Cancer- och Allergifonden, Stiftelsen Astma- och Allergiförbundets forskningsfond.

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