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Do products containing menthol exacerbate allergic rhinitis? A narrative review

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Abstract. – The aim of this paper is to review whether products containing menthol exacerbate allergic rhinitis. A literature survey was performed on PubMed, Google and Google Scholar concerning allergic rhinitis (AR).

Allergic rhinitis is an inflammatory condition of the nasal mucosa characterized by wheeze, congestion, nasal pruritus and discharge, or any combination thereof. Menthol is a naturally occurring phytochemical, with the formula C10H20O. The L-isomeric form creates the typical odor of peppermints and causes a sensation of coolness when applied to the skin or mucosae. Inhaling menthol vapor is known to affect the respiratory system in a number of different ways. The cooling agent, menthol, is also recognized as a trigger for asthma, AR and urticaria. The menthol molecule stimulates the TRPM8 receptor and may stimulate histamine release in a dose-dependent manner from RBL-2H3 cell cultures. The addition of menthol to products produces symptomatic relief in some patients by providing an impression of freer nasal air flow. It does this by stimulating cold receptors on branches of the fifth cranial nerve.

Menthol is capable of provoking allergic hypersensitivity reactions and disorders, including asthma, AR and urticaria. It may also trigger an anaphylactic response. The use of menthol-containing products is best avoided in cases where an allergic disorder exists.

Key Words:
Menthol, Allergic rhinitis, Nasal mucosa, Inflammatory condition.

Introduction

Allergic rhinitis (AR) is an inflammatory condition of the nasal mucosa characterised by wheeze, congestion, nasal pruritus and discharge, or any combination thereof[1]. Although AR does not usually cause mortality, except if it is accompanied by an anaphylactic reaction or severe asthmatic state, it is associated with considerable morbidity[2]. The clinical presentation of AR involves nasal discharge, pruritus, blockage of the nose and postnasal drip[2].

Inhaling menthol vapour is known to affect the respiratory system in a number of different ways. Knowledge of its effects mainly comes from studies in animals and human infants. New-borns exposed to menthol frequently experience transient apnoea[3], whilst guinea pigs exposed to inhaled L-menthol and cold air had a lowered respiratory rate[4]. This chapter addresses how menthol affects allergic disorders in general, but especially AR. A literature survey was performed in the PubMed, Google, and Google Scholar.

Characteristics of Menthol

Menthol is a naturally occurring phytochemical, with the formula $C_{10}H_{20}O$. The L-isomeric form creates the typical odour of peppermints and causes a sensation of coolness when applied to the skin or mucosae. Research focused on understanding how menthol produces the feeling of cold has identified specialised cold receptors on the endings of fifth cranial nerve, which respond both to low temperature and to specific molecules, including menthol, that are termed cooling agents. When menthol is inhaled, it makes the nose feel less congested thanks to interaction with receptors on the fifth cranial nerve[5,6].

This phenomenon was studied by research involving subjects inhaling vapour consisting of solely L-menthol in crystalline form. The L-isomer possesses 45-fold greater activity than the D-isomer in the stimulation of trigeminal cold receptors. The sensation of cold occurs virtually without delay. The sensation of cold can also be totally obliterated experimentally[7].

These properties have led to the use of L-menthol as an agent capable of producing a feeling of

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coolness and a non-specific analgesic effect. The perception of cold has been firmly linked to stimulation of the specialised cold receptor protein TRPM8, which is principally expressed on Aδ and C fibres. The molecular basis for menthol-induced analgesia is considerably harder to account for, and several competing hypotheses have been advanced to account for it[8-11]. L-menthol is a common ingredient in a variety of medications, such as skin ointments, where it is used to treat localised inflammation or arthralgia, in soothing throat lozenges and in nasal sprays, where it acts as a decongestant and has an anti-inflammatory effect on the upper respiratory tract in cases of coryza or flu-like illness. The USA FDA characterises L-menthol as a compound capable of localised relief, including from itching, and as a cough-suppressant[12]. L-menthol has been shown in a murine model to produce a limited but significant increase in mucosal blood flow[10,13]. This effect may be because some 15% of dorsal root ganglionic fibres express TRPV1, in addition to TRPM8. Alternatively, it may be caused by physiological alteration of flow through the capillary bed[11,14,15]. L-menthol may also produce hypersensitive reactions to cold[16,17].

Menthol may increase the uptake of other agents when included in combined pharmaceutical preparations. A safety warning has therefore been given that raised absorption by this mechanism may mean that previous evaluation of the safety of an agent may be invalid when administered with menthol[18].

Pathophysiological Aspects

The transient receptor potential cation channel subfamily M (melastatin) member 8 (TRMP8) protein is a channel permitting passage of various cations through the cell membrane. Cell culture studies[19] have shown that this molecule is expressed by the RBL-2H3 basophilic leukaemia cell line. Cells exposed to menthol, or low temperatures, responded by increasing the flow of calcium ions through the channel. An antagonist agent acting on TRPM8 was able to reverse this flow. Furthermore, histamine release also occurs in a dose-dependent fashion when menthol activates these cells. The release of histamine and the exchange of calcium ions were both completely inhibited when silencing RNA (siRNA) was used to downgrade the synthesis of TRPM8. Additionally, when menthol was injected subcutaneously, pruritus occurred, which typically indicates the release of histamine. This pruritus was also inhibited when an antagonist to TRPM8 was administered[19].

The barrier function of the nasal mucosa depends on autonomic nervous signalling, itself affected by sensory input from the tactile sensory nerve fibres. Perception of pain and the sensation of cold occurs *via* Aδ fibres, which have a thin layer of myelin for insulation. If the mucosa is covered over by mucus, for example, the sensory fibres no longer perceive the flow of air, and this causes the patient to feel the nose is blocked and breathing is difficult. If menthol stimulates the receptors on Aδ fibres, the patient mistakenly feels as though the nose has become unblocked and breathing is easier. The rapid stimulation of Aδ fibres is followed by a more delayed C-fibre activation[20].

C-fibres, which sense pain, carry sensory information from various organs and the deep blood vessels within the submucosa. Stimulation results in release of substance P, which then causes upgraded expression of E-selectin and VCAM by the vascular endothelium. This situation results in an increased level of leucocytic infiltration, a feature occurring late in cases of rhinitis and indicating a poor prognosis. It is noteworthy that, in allergic subjects, administration of substance P leads to altered mRNA levels for interleukins 1 to 6, TNFα and γ-interferon, whereas in non-allergic subjects these substances only cause an alteration in the level of interleukin-6 and its messenger RNA[20].

The sensation of the nose being clearer which follows inhalation of menthol is thus produced by this agent directly stimulating fibres of the fifth cranial nerve, including those responsive to cold stimuli[21]. The sensory fibres of the ethmoid nerve with sensitivity to temperature participate in the control of respiratory rate in a significant way[22]. The cold receptor proteins are within a family of proteins termed the transient receptor potential channels[9]. The dorsal root ganglion fibres express TRPM8[23]. It appears that these proteins are the route by which menthol creates an impression of cold temperature within the nose. A potential function of TRPM8 is also to sense the flow of air through the upper respiratory tract. When cold receptors are stimulated under normal physiological conditions, the mucosal blood supply increases as vessels dilate, providing the surface with heat to transfer to the inhaled air passing to the lungs. This mechanism is

the opposite of that seen in the skin, where cold temperature causes the vascular bed to contract its vessels in an attempt to minimise heat loss to the environment[24].

Menthol and Allergy

Menthol is a constituent in many different food items, breath fresheners, mouthwashes or dentifrices. Its chemical structure is that of a cyclic alcohol, with the systematic name 2-isopropyl-5-methyl cyclohexanol. It is known that both asthma and urticaria can be triggered by exposure to menthol[25].

Hypersensitivity responses and urticaria have been frequently linked to exposure to cold. The cooling agent, menthol, is also recognised as a trigger for asthma, AR, and urticaria[19].

Menthol has a pleasant, characteristic taste and this accounts for its wide range of applications. However, despite the generally recognised propensity of menthol to trigger allergic dermatitis through a type IV reaction, it was not until 1964[26,27] that the initial report of allergy linked to menthol use appeared in the literature.

The literature also contains several reports[25,28,29] linking menthol – included as a constituent in e.g., dentifrices – with asthma. An article by Andersson and Hindsén[25] linked a case of rhinitis to use of products containing menthol, such as toothpaste. Their case concerned a male aged 44 years, who complained of headaches, nasal inflammation, and asthma. He observed that, whenever he used a dentifrice, rhinitis was triggered. This supposition was confirmed by positivity of the nasal provocation test. The authors concluded that this allergic hypersensitivity was linked to menthol, which then cross-linked and activated mast cells within the nasal epithelium. It was thus a true allergy. The patient responded to antihistamine treatment and intranasal application of corticosteroids.

There are several case reports[30] in the literature of contact dermatitis occurring in infants and children triggered by menthol in peppermint-flavoured products. Morton et al[31] describe reactions to menthol in the oral cavity, including a variety of oral disorders such as ulcer formation or a lichen-like growth.

There is a case report[32] concerning an infant aged 2 months exhibiting an allergy to an *eau de cologne* where menthol was a constituent. Perfumes or toilet waters are both liable to cause respiratory symptoms in individuals who have asthma. Furthermore, they are a frequently identified cause of contact dermatitis[33,34].

Conclusions

Menthol is capable of provoking allergic hypersensitivity reactions and disorders, including asthma, AR, and urticaria. It may also trigger an anaphylactic response. The menthol molecule stimulates the TRPM8 receptor and may stimulate histamine release in a dose-dependent manner from RBL-2H3 cell cultures. The addition of menthol to products produces symptomatic relief in some patients by providing an impression of freer nasal air flow. It does this by stimulating cold receptors on branches of the fifth cranial nerve. Despite this helpful effect in terms of symptomatic relief, the use of menthol-containing products is best avoided in cases where an allergic disorder exists.

Conflict of Interest
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Ethical Approval
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