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Thermo sensitive TRPM8 channel and its role in cold induced airway symptoms

Jana Plevkova[1], Zuzana Biringerova[2], Silvia Gavliakova[1]

[1]Department of Pathological Physiology, JFM CU, Martin, Slovakia
[2]Anesthesiology and Intensive Medicine Clinic of JFM CU & University Hospital, Martin, Slovakia
Email: jplevkova@gmail.com

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ABSTRACT

It is generally accepted that environmental factors can significantly influence respiratory system. Cold is one of these factors. Understanding of the reaction of airways to cold air is very important tool leading to improvement in management of cold induced rhinitis, cold induced asthma, exercise induced asthma, and exacerbation of chronic airway diseases induced by cold exposure. Despite the airways are protected against cold air by powerful heat and moisture exchanging counter current system within the nose, they are still at the risk of onset and development of cold induced symptoms mainly if this mechanism is insufficient, exposed person hyperventilates or is breathing subfreezing air. Some of the mechanisms involved in cold air induced reactions are understood quite well, but some of them are still discussed as they have not been satisfactorily explained, yet. Most discussed mechanisms by which cold air may induce respiratory symptoms include direct cooling and exsiccation of mucosal surface with subsequent hypertonicity of superficial fluid layer and interactions between the trigeminal and the vagus nerve at the central level. Molecular background for such a reaction may rely on the presence of thermo sensitive channels, mainly TRPM8, expressed on airway afferent nerves, which initiate response to cold air, giving a rise to autonomic responses like bronchoconstriction, cough, dyspnoea, chest tightness, mucus secretion and mucosal swelling. Identification of targets for cold action in the airway may help to identify potent antagonists which may prevent or reverse cold induced reactions sharing possibility for clinical application.

Keywords: Cold Air; Airways; Thermo Sensation; TRPM8; Cold; Hypertonicity

1. INTRODUCTION

Cold air is unlikely to be a causal factor initiating airway and lung diseases but it could be a symptom trigger. The mechanisms beyond cold air-provoked respiratory symptoms vary considerably and mainly depend on the individual susceptibility and the ventilation level during the cold exposure. Understanding of the reaction of airways to cold air is very important tool leading to improvement in management of problems such are cold induced rhinitis, cold induced asthma, exercise induced asthma, and exacerbation of chronic airway diseases (for example COPD) induced by cold exposure [1].

There is an excellent review about cold induced airway symptoms by Koskela [2], which is describing broad spectrum of airway symptoms related to cold air exposure, and discussing possible mechanisms responsible for onset and development of cold exposure consequences.

Cold exposure in patients with allergic or vasomotor rhinitis may induce mucosal congestion, oedema, hypersecretion and sneezing. In case that lower airways are exposed to cold air, it may lead to dyspnoea, chest tightness, cough or bronchoconstriction. There is a hypothesis that reaction to cold represents the high end of a spectrum of compensatory mechanisms activated to preserve the water/temperature homeostasis of the airway mucosa [1] **Figure 1**.

Although the cold is very important provoking stimulus regarding the airways, the mechanisms of its action in respiratory system are not completely understood. The new point in understanding of cold action in airways is identification of thermosensitive channels, relevant for low temperature detection. Inhibitors of these channels may have potential clinical applications in subjects hypersensitive to cold in general.

2. PROTECTION AGAINST COLD AIR

A major function of the nose is to warm and humidify the inhaled air, thus preventing adverse effects of cold on respiratory system. In wide range of external temperatures, including breathing cold air of subfreezing temperature, the average temperature of the airstream in the

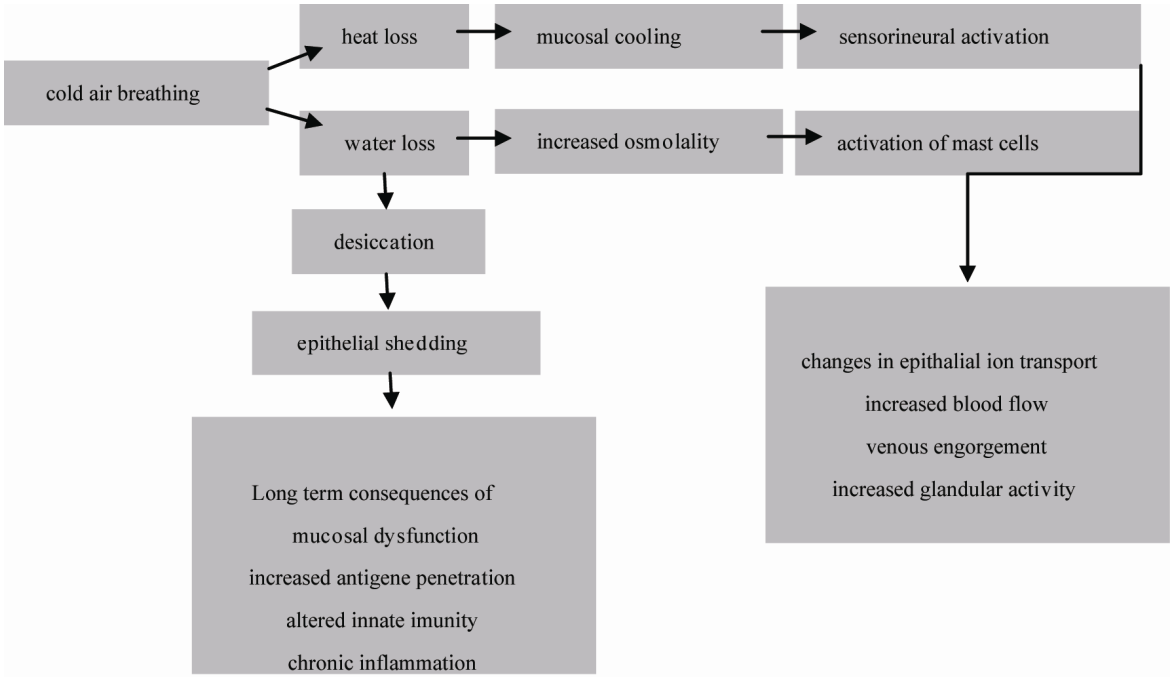

Figure 1. represents the effects induced by cold air inhalation. What is important to note, that these effects are present mainly in persons with reduced ability to condition inhaled air, or are exposed to cold air or hyperventilation repeatedly, like sportsmen. Cold air induced changes are augmented in persons with pre existed airway disease, for example allergic rhinitis.

nasopharynx is approximately 30˚C - 32˚C, and the saturation of that air is almost 100%. Final conditioning of the inhaled air is completed within the lower airways prior it reaches the alveolar space [3].

The major contributor to the nasal air conditioning of inhaled air is the counter—current heat/moisture exchanging mechanism of the nasal mucosa. The air entering the nose is heated and moisturised same time. The nasal cavity is divided by the septum and turbinates into particular nasal passages thus allowing close contact of the air stream with the mucosal surface. Molecules of the superficial fluids evaporate toward the airstream according osmotic gradient. At basal conditions, during the inspiratory phase, small osmotic gradients are probably generated by the movement of water from the liquid to vapour phase [4,5].

During the expiration these processes run in opposite direction—it means heat is conducted back to the mucosal surface and water condensates. However this countercurrent mechanism is not absolutely perfect, and some heat and moisture get lost with the expiratory airstream. Loss of heat and superficial fluid is immediately compensated by the vascular capillary bed conducting heat to the mucosa by means of blood perfusion, also contributing to production of the superficial fluids by means of glandular output and capillary transudation. Turbulent airflow in the nasal cavity mixtures the air with water vapours thus significantly enhancing the air conditioning process [1].

Increase of minute ventilation up to 40 l/min in adults during physical exercise leads to switch from nasal to oral breathing. Air conditioning in case of oral breathing (obstruction of the nose with inability to inhale throughout the nose, talking, singing, exercising) is limited, because oral cavity does not provide as effective mechanism as the nasal cavity does, so the lower airways may be endangered by the risk of inhalation of dry and cold air. Contribution of lower airways to the final air conditioning is also limited because the structure of lower airway does not allow heat and moisture exchange in such extent due to structural differences when comparing to nasal mucosa. Mucosa in lower airways is therefore prone to cooling and exsiccation due to limited heat and moisture supplementation mainly in the case of oral breathing and/or hyperventilation due to exercise [6,7].

Cooling of the skin can be enhanced not only by cooling of the ambient air but also by increasing the movement of air across the skin. In the airways, the equivalent for wind is hyperpnoea/hyperventilation, which means that cooling of the airways is enhanced by increasing the airflow. Therefore, hyperpnoea of temperate air shares similar effects as the inhalation of cold air. Hyperpnoea of cold air may cause the fluid to evaporate more rapidly than it can be replaced. This would lead to drying and hypertonicity of the fluid layer. Therefore, while the effect of cold air on the skin is mainly cooling, the effect

on the airways is cooling and drying [2].

Some of the reactions to cold are believed to be a consequence of dysregulation of heat/moisture balance within the mucosa after cold exposure, because mucosal blood flow increases to conduct more heat via the blood stream, thus leading to congestion and possibly oedema of musocas with increased glandular activity to compensate loss of superficial fluids. These reactions are manifested as nasal blockage due to congestion of mucosa and/or runny nose and in lower airways by increased airways resistance due to mucosal oedema and bronchoconstriction with dyspnoea, wheezing and mucus hypersecretion [7,8].

Define abbreviations and acronyms the first time they are used in the text, even after they have been defined in the abstract. Abbreviations such as IEEE, SI, MKS, CGS, sc, dc, and rms do not have to be defined. Do not use abbreviations in the title or heads unless they are unavoidable.

3. MOLECULAR BACKGROUND FOR COLD ACTION IN THE RESPIRATORY SYSTEM-TRPM8 RECEPTOR

Body surface cold exposure gives rise to a rich spectrum of sensations that range from pleasantly cool to painful. At normal temperatures, innocuous cold thermoreceptors exhibit spontaneous activity, while exposure to very low temperature with possible hazards for the body activates cold nociceptors. The recent identification of several ion channels with marked sensitivity to cooling provides a molecular framework to understand the transduction mechanisms for cold temperatures by sensory endings [9]. How does the thersmosensation work within the airways? Clearly, the lowest temperature air enters the nasal cavity and moving towards alveolar space the air gets warmer up to body temperature. Thermal mapping of airways showed that temperatures in the lower airways unlikely drop below 20˚C [10].

Cation channels that act as the cold receptors have been identified and cloned. These include the transient receptor potential melastine 8 (TRPM8) and the transient receptor potential ankyrin 1 (TRPA1), the later regarded as a nociceptor and the former as a gentle cooling and menthol sensing receptor **Figure 2**. So far, transient receptor potential melastatin 8 (TRPM8), a nonselective cation channel of the transient receptor potential super family [11], is the best candidate for the transduction of moderate cold, because it fits with the concept of the temperatures the airways are usually exposed to. These channels are expressed selectively in a subpopulation of cold-sensitive primary sensory neurons with specific electrophysiological properties [11]. Electrophysiological

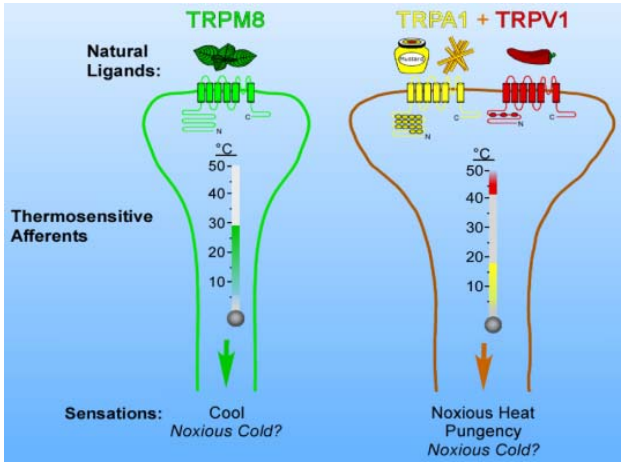

Figure 2. represents thermo sensitive airway afferents, which are expressed on trigeminal nasal afferents and also vagal nodose and jugular fibers. These channels are also activated by number of natural ligands.

studies have showed that TRPM8 is highly permeable for Ca^{2+} and its activation increases intracellular concentration of calcium ions, either by the influx from the extracellular compartment, and by the release of calcium ions from the intracellular stores. TRPM8 had been also identified within the trigeminal afferents and vagal sensory nerve endings [12]. The channels are activated by innocuous cold with threshold temperatures of 25˚C, with maximal response at 10˚C and by exposure to cooling compounds such as menthol or icilin. Additional evidence for TRPM8-independent cold transduction mechanisms has been reported in damaged sensory endings [13]. Despite significant advances in our understanding of cold thermotransduction, the role of TRPM8 channels in defining the sensory modality, temperature activation threshold, and spontaneous discharge of native cold receptors should be studied in more details.

Despite vagal and somatosensitive nerve endings belong to different systems, they may share same or very similar molecular backgrounds for activation. Therefore it is not surprising that small proportion of vagal afferent neurons innervating lower airways express TRPM8 receptor, as it have been demonstrated on 7% of vagal fibres in lower airways by calcium imaging, and on 16% of fibres by retrograde labelling and electrophysiological studies [12]. Detail distribution of TRPM8 expressing nerve endings within the airways had not been identified yet however it is believed they are distributed mainly in the larynx, trachea and main bronchi, where the airstream temperature may fall to less than 25˚C (TRPM8 threshold) mainly in case of inadequate air conditioning (oral breathing, exposure to subfreezing air, or physical exercise in cold weather). Their expression on most peripheral fibres had not been proven yet, as well as their role in most peripheral airway, because the temperature

within the most peripheral airways gets to the ≈37˚C, which is too high temperature for TRPM8 to be activated.

Activation of TRPM8 by innocuous cold temperatures results to the activation of parasympathetic pathways including nasal airways (trigeminal branches also contain parasympathetic fibres) and lower airways. The response mediated by TRPM8 activation leads to increase of fluid output caused both by increased glandular activity and increased vascular permeability with mucosa oedema and hyperaemia [11].

4. COLD AIR INDUCED RESPONSES

Nasal or facial skin exposure to cold air induces an engorgement of the venous sinuses in the nasal submucosa, which leads to congestion, sneezing and, especially, rhinorrhoea both in healthy and rhinitic subjects. However, these responses are greater in subjects with upper and/or lower airways hyperresponsiveness [1].

The cold exposure targets are located mainly on the facial skin and nasal mucosa that are undoubtedly exposed the lowest temperature from all exposed airway regions. How is it possible, that facial/nasal cold exposure could initiate reflex changes also within the lower airways?

The studies on the effect of nasal cooling on the lower airways are contradictory, sharing conflicting evidence. Facial cooling caused by –5˚C to –20˚C ambient air combined with wind provokes an immediate 3% - 10% fall in FEV1, in healthy subjects as well as in subjects with asthma and COPD [14]. Some investigators have found cooling of the nose to provoke a slight bronchoconstriction; other investigators reported no changes of airway resistance after upper airways cold exposure. Different results may reflect different methods that had been used to apply cold stimulus to the upper airway region. This reflex response had been provoked only in case of nasal breathing, whereas cooling of the oral cavity is not capable to initiate changes of lower airway resistance. Also cooling of the pharynx and larynx induces bronchoconstriction in cats [15].

This reflex bronchoconstriction is believed to be a part of nasobronchial reflex [16] and it does not provoke breathing difficulties in a person with normal lung function. However, for a subject with impaired lung functions these responses may be of clinical significance [17]. Nasobronchial reflex is contradictory issue, but based on the animal and also human studies it may be concluded that trigemino—vagal reflex interactions contribute significantly to cold induced reflex responses of lower airways.

The most popular hypothesis suggests that inhalation of cold air leads to significant fluid loss from the superficial layer causing its hyperosmolarity. The cells that respond to hyperosmolarity are eosinophils and the mast cells, however direct mechanisms responsible for activation of these cells is not entirely clear. The background for such activation may rely on neuro-immune relationships, which are characterized by the recruitment of immune cells after stimulation of afferent nerves due to TRPM8 channel activation (see later). It had been also shown that cold exposure increases level of inflammatory mediators—histamine, kinins, prostaglandins PGD2, mainly released from mentioned cell populations [18]. These mediators are known to be potent bronchoconstrictors and some of them may decrease threshold for activation of vagal cough mediating fibres thus contributing to appearance of cough as a one of the lower airway cold induced symptoms [19]. Increased concentration of inflammatory mediators in lavage fluids had been demonstrated in samples obtained after cold exposure from the nose and the lower airways as well [18] documenting the cold induced mediator release.

Cold air induced bronchoconstriction can be effectively attenuated by heat moisture-retaining masks. These masks may be regarded as the best physiological way to treat this problem: as the user exhales, heat and moisture are trapped within the mask. During the subsequent inhalation, cold air is warmed and humidified as it travels through the mask.

Cold air inhalation induced bronchoconstriction could be attenuated by various anti-asthma drugs including inhaled β2-adrenergic agonists, nedocromil sodium and leukotriene receptor antagonists a long-term treatment with inhaled corticosteroids attenuates the response to cold air, indicating that this response is associated also with the degree of asthmatic inflammation [20].

Another studies possibly explaining cold induced airway narrowing demonstrated that cooling of the lower airways may induce vasoconstriction in the bronchial mucosa, followed by reactive hyperaemia and oedema, which would narrow the airways.

Besides bronchoconstriction, cold air hyperventilation also provokes coughing in susceptible persons. Therefore cough, as a reflex response may arise from lower airway after cold exposure, most likely because of mucosal superficial fluid hypertonicity. Hypertonic saline is very effective tussigenic stimulus during experimental challenge, so we can assume, naturally developed hypertonicity over the mucosal surface after cold exposure, or hyperventilation may effectively induce coughing [19].

Prolonged and/or repeated exposure to cold dry air or repeated hyperventilation with subsequent airway cooling may induce also structural changes, however these are reversible and vanished after the sport related hyperventilation or cold air exposure had been terminated [21].

Animal studies have shown that repeated cooling and desiccation of peripheral airways leads to a loss of cili-

ated epithelium, thickening of the lamina propria with increased concentrations of inflammatory cells. So, experimental studies suggest that airway cooling can damage the airway epithelium and, if repeated, can lead to changes in the airway's wall structure and function. These changes may represent a physiological adaptive response to an abnormal stress on airways [22].

There are also studies documenting structural changes within airways in subjects exposed to cold air or repeated hyperventilation episodes like athletes, skiers, swimmers, and long distance runners [23].

5. CONCLUSIONS

Cold induced upper and lower airways responses, as well as exacerbation of chronic respiratory diseases by cold exposure seem to have also molecular background—TRPM8 and/or TRPA1 channels activation on sensory nerves, epithelial cells and possibly other target sites within the airways. Identification of effective and potent antagonists of these receptor channels would provide a tool with possible clinical application for prevention and treatment of cold induced changes in the airways, mainly in persons with reduced ability to condition air, or persons constantly exposed to cold environment and/or hyperventilation during extreme physical exercising.

Identification of the molecular background of the cold action in airways may help our understanding of this clinically important issue, hopefully with benefits for our patients.

6. ACKNOWLEDGEMENTS

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