

Mechanisms of increased airway sensitivity to occupational chemicals and odors

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Purpose of review

Airway symptoms induced by chemicals and odors are common problems that are also reported after contact with substances normally regarded as nontoxic. This article reviews current findings and opinions regarding mechanisms of increased airway sensitivity to occupational chemicals and odors.

Recent findings

Individuals exposed to organic solvents during work had more nasal irritation and lower threshold to pyridine odor compared with a nonexposed control group. Six percentage of a general population in Sweden had pronounced airway chemical sensitivity and augmented capsaicin cough sensitivity, known to reflect the sensory nerve reactivity of the airways. The cough sensitivity was associated with changed levels of nerve growth factor in nasal lavage and such patients had longstanding symptoms influencing their working capacity. Positron emission tomography activation studies with several different odorants showed in patients with odor-associated symptoms an odorant-related increase in activation of the anterior cingulate cortex and cuneus–precuneus in comparison with a control group.

Summary

In subgroups of individuals with airway symptoms induced by chemicals and odors, there seems to be a sustainable physiological mechanism behind the reactions. An increased vulnerability to stress cannot be neglected as a confounding factor in some sensitive individuals.

Keywords

airway symptoms, capsaicin, environment, occupational chemicals, odors

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Introduction

Airway reaction to chemical stimuli and odors is an essential protective physiological mechanism to prevent inhaling harmful substances, but it may also be a symptom of diseases of the nose and lungs. In the general population, self-reported odor intolerance, often called chemical sensitivity, is a frequent symptom with a reported prevalence of 16–33% [1–4].

Sensory irritation

The expression ‘sensory irritation’ is based on airway and eye symptoms in relation to certain odors, chemicals or environments and may serve as a comprehensive term for this phenomenon. An odor stimulates the sense of smell but may also evoke sensory irritation due to a trigeminal nerve reaction. This happens if the odor concentration is high enough or if the trigeminal threshold is lowered. Normally the sensitivity of olfaction is much higher

compared with the concentrations needed to evoke sensory irritation [5,6]. The typical trigeminal reaction is the sensory irritation in the airways and eyes that sniffing on ammonia may induce.

Volatile organic compounds (VOC) emitting from building materials may activate the sense of smell as well as sensory irritation. Some VOCs (oxidation products of alkenes) in the office environment can contribute to eye and airway symptoms under certain conditions and low relative humidity [7]. This study reported that odor thresholds for many VOCs are probably considerably lower than previously known and that low relative humidity exacerbates the sensory irritation impact. All of the sensory irritating species have not yet been identified and whether ultrafine and fine particles enhance the sensory irritation is not clarified. In accordance with this, sensory irritation was also reported more often among hospital workers in relation to dry air and unpleasant odors than in office environments [8].

Laboratory technicians, exposed to organic solvents during work, had lower threshold to pyridine odor compared with a nonexposed control group, and they also complained more of work-induced sensory irritation-like nasal symptoms [9]. The results indicate a measurable influence on a physiological function from a certain work environment and encourage further studies.

A mixed group of individuals with self-reported chemical hypersensitivity also rated the pyridine stimuli to be more intense and unpleasant, and sensory irritation was the perceptual dimension found to correlate most strongly with chemical hypersensitivity [10]. No group differences, however, were found in cortical activity assessed with the amplitudes of chemosensory event-related potentials (ERPs), between chemical-sensitive and non-sensitive individuals.

It is well established that individuals complaining of sensory irritation do not have an IgE-mediated reaction towards perfume or other irritating substances, though the symptoms may be misinterpreted as allergy. A recent study aimed to investigate whether basophils from patients with respiratory symptoms related to perfume released more histamine in the presence of perfume, as compared with healthy volunteers [11^{••}]. In both groups, incremental perfume concentrations showed a positive and significant dose–response effect on the release of histamine. The dose–response curve was substantially steeper in the patient group, and at the highest perfume concentration the basophils released significantly more histamine in patients as compared with the healthy control subjects. The results indicate a possible mechanism in airway reactions to perfume that have so far been unknown, though the importance of the findings needs to be further clarified.

A commonly raised question regarding the mechanisms behind sensory irritation is whether the symptoms are dependent on augmented vulnerability to stress. Measuring cortisol levels in smell-annoyed individuals and comparing the values with a control group did not show significant changes regarding cortisol secretion over 5 days but there seemed to be a minor relation to increased psychological activation in terms of self-reported stress [12]. When comparing groups of smell-annoyed individuals, electrically annoyed and a control group, the electrically annoyed showed strongly elevated scores on 5/6 scales within the trait anxiety/neuroticism personality dimension, while the smell-annoyed group had a slight elevation on only one anxiety scale [13]. Individuals in this group reported low satisfaction with their work situation, including more frequent fatigue after work and a higher, and often unfulfilled, need for recovery. This may reflect the problems from occupational odor that the sensitive individuals have to tackle

in their daily living, and these two studies do not support a theory of increased psychological activation as a major cause of sensory irritation.

Sensory hyperreactivity

Sensory hyperreactivity (SHR) is a discrete entity of individuals with airway sensory irritation. SHR is defined as a combination of increased cough sensitivity to inhaled capsaicin [14,15] and a high score on the Chemical Sensitivity Scale for Sensory Hyperreactivity, which measures behavioral consequences of self-reported odor sensitivity [16]. A suggested explanation of SHR is hyperreactivity of the sensory nerves of the entire airways, in accordance with the increased cough response to inhaled capsaicin, which is known to reflect the sensory nerve reactivity of the airways [17,18]. Common symptoms are heavy breathing, difficulty in getting air, cough, hoarseness, phlegm, nasal blockage, rhinorrhea, and eye irritation [3,14,19[•]]. SHR is a frequent problem that affects more than 6% of the adult population in Sweden [3].

A recent longitudinal study has shown that patients with SHR (but with no bronchial obstruction) had persistent airway symptoms and enhanced capsaicin cough sensitivity lasting several years [19[•]]. During a 5-year follow-up, three of 17 patients were granted a pension, while 11 patients had problems with their working capacity because of their sensitivity to chemical agents; six of these patients were periodically on sick leave because of their symptoms, alone or together with other conditions.

Patients with SHR had changed levels of nerve growth factor (NGF) in nasal secretions after capsaicin inhalation, and the changes correlated with the capsaicin cough sensitivity [20]. This supports a theory of a neuro-chemical imbalance as a cause of SHR. In that study, after capsaicin inhalation challenge targeting the lower airways, the symptom scores for rhinitis had a strong correlation with an increase in NGF found in nasal lavage. This finding may not be surprising since the nasal mucosa may have produced the factor being analysed. The mechanisms behind the reaction are unclear. It could have been reflex-mediated, however, a small amount of capsaicin could have reached the nose ‘backwards’ or, since the patients did not use a nose clip, some of the nebulized solution could have been dispersed and inhaled through the nose.

In summary, SHR may be described as an ‘airway hyperalgesia’ where the sensory nerve reactivity is estimated by a standardized inhalation test with capsaicin.

Capsaicin and transient receptor potential ion channels

In recent years, there has been an increasing interest in the family of transient receptor potential (TRP) ion

channels. They are important means for multiple organ systems to interact with their environment [21^{••},22,23[•]]. They respond to temperature, noxious stimuli, stretch, osmolarity and pain, among others, and may be involved in different diseases due to an increased level of channel expression.

Capsaicin, used in the diagnostics of SHR, is the main pungent ingredient in chilli and elicits a burning sensation by activating the cloned transient receptor potential vanilloid-1 receptor (TRPV1) [24]. The TRPV1 is expressed in the airways and eyes in a subpopulation of sensory neurons. This receptor, belonging to one of the six subfamilies of TRP channels, is not only activated by capsaicin but also by noxious stimuli and heat, and is potentiated by extracellular acidic pH, and interacts with vanilloid-like compounds [25–27,28^{••}]. The ability to be activated by various stimuli has given the receptor the epithet of ‘the promiscuous receptor’ [29[•]]. Patients with chronic cough have shown a five-fold increase of TRPV1-staining nerve profiles and, furthermore, a significant correlation between capsaicin tussive response and the number of TRPV1-positive nerves [30]. There are data indicating that specific TRPV1 antagonists could be useful in treating disorders like pain, chronic cough and irritable bowel syndrome [28^{••}].

Multiple chemical sensitivity

In 1987, Cullen described ‘The worker with multiple chemical sensitivities’ [31]. Multiple chemical sensitivity (MCS) was defined as ‘an acquired disorder characterized by recurrent symptoms referable to multiple organ systems. These symptoms occur in response to demonstrable exposure to chemically unrelated compounds at doses far below those known to cause harmful effects in the general population. No single widely accepted test of physiological function has been shown to correlate with symptoms.’

This definition is a general definition of MCS and may cover a number of conditions in patients with various symptoms and undiagnosed disorders. The debate regarding MCS is ongoing. In the USA, MCS has been rejected as an established organic disease [32]. Several authors claim that MCS is caused by psychiatric disorders or is a consequence of psychological factors, and the term ‘MCS’ is often replaced with ‘Idiopathic environmental intolerances’ [33,34]. There is a lack of objective provocation studies that prove true reactions to odors [35]. This may support the suggestion that there could be salient psychological mechanisms operating that lead sufferers to respond when they are aware of the exposure, and that behavioral conditioning could be an important mechanism in the pathogenesis of MCS.

In contrast to the above-mentioned lack of objective provocation studies of MCS, a recent study investigated whether subjects with MCS could have an increased odor–signal response in the odor-processing neuronal circuits [36[•]]. Positron emission tomography activation studies with several different odorants were carried out in a group of patients with MCS and compared with a control group. The study also included online measurements of respiratory frequency and amplitude and heart-rate variations by recording R wave intervals on the surface electrocardiogram. The MCS subjects activated odor-processing brain regions less than controls, despite the reported, and physiologically indicated (decreased R wave intervals) distress. In parallel, they showed an odorant-related increase in activation of the anterior cingulate cortex and cuneus-precuneus. The abnormal patterns were observed only in response to odor signals. The results from this study can have different interpretations and further research is needed to understand this better.

There is a resemblance between SHR and MCS, but the diagnosis of SHR implies that just one organ is affected—the airways—while in MCS, symptoms from multiple organs are involved. Some patients with SHR, however, also complain of more general symptoms such as sweating, dizziness, headache, and fatigue, bordering on a diagnosis of MCS [37].

Increased odor sensitivity in asthma

Asthma is characterized by variable airflow obstruction, airway inflammation, bronchial hyperresponsiveness (BHR), and reversibility even if the disease concept has been questioned [38]. The asthmatic BHR is often well described as bronchial obstruction induced by methacholine, histamine and cold or dry air [39,40]. The BHR remains, at least to some degree, even if the underlying asthmatic inflammation is successfully treated with inhaled steroids [41,42,43[•]]. In a recent study, BHR was found in more than 30% of the population compared with an asthma prevalence of less than 10% [44].

Population-based studies of the prevalence of odor intolerance indicate an overrepresentation in asthma as well as rhinitis [1,45]. It is common, however, to attribute the asthmatic hyperresponsiveness, followed by bronchial constriction, to a ‘general hypersensitivity of the airways’ towards all kinds of irritating environmental stimuli like chemicals and odors rather than to odor sensitivity such as occurs in nonasthmatic subjects, though the scientific evidence to support these assumptions is weak [46,47]. Sensory irritation, estimated from questionnaires, seems to be more common in asthma, but whether this sensitivity actually results in airway narrowing is not known since provocation studies with common irritants such as

perfume are rare. Atopic subjects with such sensitivity, however, had increased cough sensitivity to capsaicin compared with nonsensitive atopic subjects and healthy controls [48], indicating another mechanism behind the hypersensitivity to chemicals and odors in asthma and allergy.

Conclusion

Exposure to occupational chemicals and odors is an inevitable and frequently occurring part of daily living and also in work places normally regarded as 'clean', such as office environments. There is a wide range of prevailing definitions and expressions regarding eye and airway symptoms induced by chemicals and odors, which may illustrate the difficulties this research field has to tackle. Though there are new findings indicating sustainable physiological reactions as a cause to the symptoms in certain subgroups, the possible influence of psychological factors cannot be neglected. Since the group reporting symptoms seems to be both huge and heterogeneous, there is a need for further careful studies to clarify different subgroups and characteristics.

Acknowledgements

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 191–192).

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