NeuroToxicology 60 (2017) 92–98

Contents lists available at ScienceDirect

NeuroToxicology

Symptoms from masked acrolein exposure suggest altered trigeminal reactivity in chemical intolerance

Anna-Sara Claeson*, Linus Andersson

Department of Psychology, Umeå University, Umeå, Sweden

ARTICLE INFO

Article history:
Received 12 December 2016
Received in revised form 22 March 2017
Accepted 23 March 2017
Available online 27 March 2017

Keywords:
Human exposure
Acrolein
Chemical intolerance
TRPA1
Trigeminal reactivity

ABSTRACT

Background: Chemical intolerance (CI) is a widespread occupational and public health problem characterized by symptoms that reportedly result from low-levels of chemical exposure. The mechanisms behind CI are unknown, however modifications of the chemical senses (rather than toxic processes) have been suggested as key components. The aim of this study was to investigate whether individuals with self-reported CI report more sensory irritation during masked acrolein exposure compared to controls without CI.

Methods: Individuals with CI ($n = 18$) and controls without CI ($n = 19$) were exposed in an exposure chamber. Each participant took part in two exposure conditions – one with heptane (the masking compound), and one with heptane and acrolein at a dose below previously reported sensory irritation thresholds. The exposures lasted for 60 min. Symptoms and confidence ratings were measured continuously throughout the exposure as were measurements of electrodermal activity and self-reported tear-film break-up time. Participants were blind to exposure condition.

Results: Individuals with CI, compared with controls reported greater sensory irritation in the eyes, nose and throat when exposed to acrolein masked with heptane. There was no difference during exposure to heptane.

Conclusions: Masked exposure to acrolein at a concentration below the previously reported detection threshold is perceived as more irritating by individuals with CI compared with controls. The results indicate that there is altered trigeminal reactivity in those with CI compared to controls.

1. Introduction

Chemical intolerance (CI) is a widespread occupational and public health problem characterized by symptoms that reportedly result from low-levels of chemical exposure. Sufferers are often forced to make extensive, unwanted changes in their lives to avoid as yet medically unexplained symptoms. Failure to cope with the illness is common, and results in suffering, occupational and financial hardship, and isolation (Gibson et al., 2011; Söderholm et al., 2011). Headache, irritability and concentration difficulties are examples of general symptoms that sufferers attribute to be caused by exposure to everyday chemicals, such as perfumes or cleaning agents, but localized reactions also occur, such as irritation of the mucosa of the eyes, nose, and throat (Andersson et al., 2009a,b). The estimated prevalence of CI ranges from a low percentage of individuals to one fifth of the population, depending on its definition and severity (Berg et al., 2008; Caress and Steinemann, 2004; Johansson et al., 2006; Kreutzer et al., 1999). Multiple chemical sensitivity (MCS) and idiopathic environmental intolerance (IEI) are labels that are commonly used for severe cases. Considerably more women than men report experiencing CI (Sears, 2007). The affliction is often comorbid with other environmental intolerances (e.g., sick building syndrome) and other medically unexplained symptoms (Palmquist et al., 2013). Although the mechanisms behind CI are unknown, various theories highlight that alterations in chemical sensory transduction and neural processing (rather than for example, toxic processes) serve as key components (see Dantoft et al., 2015 for a review).

The detection of chemicals in the upper airways is mediated by the olfactory and trigeminal nerves. Stimulation of the olfactory nerve results in what is commonly referred to as smell, whereas stimulation of the trigeminal nerve evokes sensations such as irritation and pain. Individuals with CI generally react to odors at concentrations below currently known sensory irritation thresholds. Despite such reports, no differences in olfactory thresholds

* Corresponding author at: Department of Psychology, Beteendevetarhuset, Umeå University, 90 1 87 Umeå, Sweden.
E-mail address: Anna-Sara.Claeson@umu.se (A.-S. Claeson).

http://dx.doi.org/10.1016/j.neuro.2017.03.007
0161-813X/

have been identified (Doty et al., 1988; Papo et al., 2006). There is some evidence of lower trigeminal thresholds in CI (Andersson et al., 2009a,b). Such an effect is, however, absent in other studies (Papo et al., 2006). Individuals with CI often react in the same way to both active and masked exposures, across several different conditions (Dalton, 2012; Das-Munshi et al., 2006). Due to the paucity of evidence on sensory alterations, it has been postulated that expectancy effects, stress and negative affectivity are possible causes of CI symptoms. Investigating the reactions to masked exposure is of importance in CI research, as a positive outcome would greatly contribute to the current understanding of the underlying systems that mediate symptoms.

Neurogenic inflammation (i.e., inflammation produced by alterations or activations of unmyelinated c-fibers) is another theoretical explanation for CI, but it has yet to be thoroughly investigated (Bascom et al., 1997; Meggs, 1999). Neurogenic inflammation is an axon reflex mechanism that follows noxious activation of the peripheral nervous system. Environmental chemicals (such as acrolein) might stimulate nociceptors in the nasal and oral cavities, retina, and throat, and they evoke sensations of pungency via the trigeminal nerve. During this process, pro-inflammatory mediators, known as neuropeptides (e.g., substance P), are released (Chiu et al., 2012). Almost all neural inflammatory pathways incorporate TRPV1 and TRPA1 (TRP = transient receptor potential), which are two receptors situated on the trigeminal nerve endings. These receptors provide a mechanism through which to link exposures of low concentrations of organic compounds to various health effects (Bessac and Jordt, 2008). TRPV1 is activated by different compounds for example capsaicin, the pungent ingredient in chilli pepper (Bessac and Jordt, 2010; Caterina et al., 1997; Lehmann et al., 2016). This compound has been implicated in symptom induction in a sub-category of CI referred to as sensory hyperreactivity (SHR), which is possibly mediated by trigeminal hyperreactivity (Millqvist et al., 1998). On the other hand, TRPA1 is activated by compounds present during environmental exposures (e.g., formaldehyde). The compounds contain a special reactive group (an electrophilic group) and they form reversible covalent bonds with the TRPA1 receptor (which is different from what occurs with other known receptors) (Bautista et al., 2006). Initial high-level chemical exposure and/or tissue damage may heighten the sensitivity of the receptor through inflammatory signaling pathways and it has been proposed that the channel could be involved in conditions like reactive airways dysfunction syndrome (RADS) or MCS (Bessac and Jordt, 2008). Also, endogenously produced inflammatory mediators (e.g., bradykinin) have been shown to activate TRPA1 (Wang et al., 2008) which suggests that individuals with inflammatory conditions may be more sensitive toward compounds that react with the TRPA1 receptor.

Only a few earlier exposure studies involving individuals with CI have used such reactive compounds, and that might explain the lack of a difference – or the minor differences – identified between individuals with and without CI (Andersson et al., 2009a,b; Hillert et al., 2007; Osterberg et al., 2003; Papo et al., 2006). Acrolein constitutes a suitable chemical that can be used to investigate the impact of reactive compounds in CI. It has an acrid, pungent odor, with sensory irritating effects on the mucous membranes, especially in the eyes (Gomes et al., 2001); formed during incomplete combustion (e.g., of wood fuel, tobacco or food), and it is also formed as a chemical reaction by-product in indoor air (Weschler, 2006). Acrolein has been shown to act directly on the TRPA1 receptor situated on the trigeminal nerve endings ultimately inducing neurogenic inflammation (Andrè et al., 2008; Bessac and Jordt, 2008). Individuals with CI often report symptoms that result from various levels of exposures to acrolein (e.g., such as through cooking fumes or motor vehicle exhaust; Berg et al., 2009). Acrolein is also suspected to contribute to chronic airway diseases (Bein and Leikauf, 2011; Geppetti et al., 2010). In a recent study, the sensory irritation that resulted from acrolein exposure was found to be time-dependent (Claeson and Lind, 2016a). Such time-dependence has further been shown for other TRPA1- agonists, and it might be due to accumulation of the compound at the receptor (Cain et al., 2010). TRPA1 channels are not only gated by environmental irritants, but also by endogenously produced inflammatory agents, such as prostaglandins or 4-hydroxynonenal (4-HNE; Bautista et al., 2013; Wang et al., 2008). The mechanism by which the TRPA1 receptor is activated (e.g., covalent bonding) renders it plausible that the irritation experienced following exposure depends on the reactivity of the compound, the exposure duration, and the state of the exposed individual (e.g., the presence of stress or inflammation).

Therefore, the aim of this study was to investigate whether CI implies the existence of a lower symptom detection threshold to masked acrolein exposure when compared with controls without

Table 1
Demographic overview and reported symptoms in the self-reported chemical intolerance group (CI) and the control group (α-level <0.05).

	CI (n = 18)	Controls (n = 19)	p-value[a]
Sex (n; women/men)	13/5	13/6	Ns
Age (years; mean ± SD)	42 ± 13	40 ± 13	Ns
Perceived stress questionnaire (PSQ)	0.36 (0.16)	0.30 (0.16)	Ns
Chemical sensitivity scale (CSS)	69.4 (11.6)	49.7 (11.6)	<0.001
Reported no of symptoms during the last 3 months, mean (±SD)			
Airway, out of 9	0.29 (0.3)	0.11 (0.1)	<0.01
Eye, out of 1	0.50 (0.5)	0.21 (0.4)	Ns
Skin, out of 3	0.16 (0.3)	0.30 (0.2)	Ns
Gastrointestinal, out of 3	0.8 (0.2)	0.3 (0.1)	<0.05
Head related, out of 3	0.8 (0.2)	0.4 (0.1)	Ns
Cardiac, nausea and dizziness, out of 5	0.7 (0.2)	0.1 (0.1)	<0.05
Cognitive and affective, out of 10	1.8 (0.4)	2.7 (0.7)	Ns
Reported diagnoses (n)			
Asthma/allergy	5	1	
Chronic sinusitis	0	0	
Disease in joints/muscles	3	1	
Irritable bowel syndrome (IBS)	3	1	
High blood pressure	0	6	
Chronic fatigue syndrome	1	2	
Depression	1	1	
Migraine	2	2	

[a] Independent samples t-test between the groups. Ns = non-significant.