Prostaglandins, Leukotrienes and Essential Fatty Acids 121 (2017) 60–67

Contents lists available at ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Levels of oxylipins, endocannabinoids and related lipids in plasma before and after low-level exposure to acrolein in healthy individuals and individuals with chemical intolerance

Anna-Sara Claeson[a,*], Sandra Gouveia-Figueira[b], Jenny Häggström[c], Christopher J. Fowler[d], Malin L. Nording[b]

[a] Department of Psychology, Umeå University, Sweden
[b] Department of Chemistry, Umeå University, Sweden
[c] Umeå School of Business and Economics, Department of Statistics, Umeå University, Sweden
[d] Department of Pharmacology and Clinical Neuroscience, Umeå University, Sweden

ARTICLE INFO

Keywords:
Oxylipins
Endocannabinoids
Plasma
Human exposure
Acrolein
Chemical intolerance

ABSTRACT

Oxylipins and endocannabinoids play important biological roles, including effects upon inflammation. It is not known whether the circulating levels of these lipids are affected by inhalation of the environmental pollutant acrolein. In the present study, we have investigated the consequences of low-level exposure to acrolein on oxylipin, endocannabinoid and related lipid levels in the plasma of healthy individuals and individuals with chemical intolerance (CI), an affliction with a suggested inflammatory origin. Participants were exposed twice (60 min) to heptane and a mixture of heptane and acrolein. Blood samples were collected before exposure, after and 24 h post-exposure. There were no overt effects of acrolein exposure on the oxylipin lipidome or endocannibinoids detectable in the bloodstream at the time points investigated. No relationship between basal levels or levels after exposure to acrolein and CI could be identified. This implicates a minor role of inflammatory mediators on the systemic level in CI.

1. Introduction

Acrolein is a highly reactive volatile organic compound (VOC) present in cigarette smoke, smoke from fires, automobile exhaust, and smog. It has an acrid, pungent odor with sensory irritating effects at low concentrations on the mucous membranes, especially in the eyes [1], but has also been shown to interact with the nasal epithelia and produce nasal irritation [2]. The compound is found both in outdoor and indoor air, but is present at higher concentrations indoors. Indoor air concentration ranges from < 0.05–29 μg/m^3, higher levels have been found in restaurant kitchens and bakeries (0.02–0.6 mg/m^3;[3]). Indoor air levels are often below Swedish occupational threshold values (0.2 mg/m^3, limit value and 0.7 mg/m^3 ceiling value, [4]) but such concentrations have nevertheless been shown to induce sensory irritation in a time dependent manner [5–7].

The time-dependency and low threshold of sensory irritation detection of acrolein are probably due to the interaction with the TRPA1-receptor, a member of the large family of Transmembrane Receptor Potential channels (TRP) [8]. The TRP channels are primary transducers of incoming external stimuli such as noxious cold or heat and pain and a variety of noxious compounds and environmental stimuli activate TRPA1 specifically. A unique feature of the TRPA1 channel is that sensory irritation is produced through covalent binding and this modification can lead to irritation at low exposure levels and to sensitization of the person being exposed [9]. TRPA1 has a central role in inflammation and function both as a detector and instigator of inflammation. Furthermore, acrolein has been shown to cause pain and neurogenic inflammation upon stimulation [10,11]. Neurogenic inflammation is an axon reflex mechanism following noxious activation of the peripheral nervous system. An important trigger is the chemosomatosensory system, which is activated by chemical exposure (sensory irritants) that stimulates nociceptors in the nasal and oral cavities, retina and throat, and evokes sensations of pungency via the trigeminal nerve. In this process pro-inflammatory mediators such as prostaglandins and substance P, are released to produce vasodilatation, edema, and other manifestations of inflammation. TRPA1 do not only initiate the production of certain inflammatory mediators by interaction with environmental irritants, but are also regulated by agents produced endogenously during stress and/or inflammation [11,12].

Oxylipins (e.g. prostaglandins, leukotriens and thromboxanes) and

* Correspondence to: Department of Psychology, Umeå University, 901 87 Umeå, Sweden.
E-mail address: Anna-Sara.Claeson@umu.se (A.-S. Claeson).

http://dx.doi.org/10.1016/j.plefa.2017.06.004
Received 21 September 2016; Received in revised form 5 June 2017; Accepted 12 June 2017

endocannabinoids (e.g. *N*-arachidonoylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG)) are lipid mediators formed from unsaturated fatty acids, which are involved in the signaling system during inflammation. Lipids from a variety of different metabolic pathways (cyclooxygenase [COX], lipoxygenase [LOX], Cytochrome-P_{450} [CYP]) have been shown to both direct and indirect regulate different TRP-channels, including the TRPA1 [13]. These compounds are part of a complex pattern of pro- and anti-inflammatory signals produced to keep homeostasis and are therefore important in relation to afflictions with suspected inflammatory origin.

Chemical intolerance (CI), affect between 9% and 33% of the population, the variability in prevalence depends largely on the wide variety of definitions and severity [14–17]. Multiple chemical sensitivity (MCS) or idiopathic environmental intolerance (IEI) are labels commonly used for severe cases, although the criteria are based on self-reports only. Irrespective of definition the affliction has been shown to have a great impact on the quality of life [18]. Symptoms are reported in relation to low-level exposures and there is currently no established dose-response relationship between exposure to certain compounds and reports of symptoms. One commonly used explanation for CI is that low-level inflammation or dysregulation of the immune system makes the mucous membranes more sensitive towards chemical exposures [19]. There is some empirical support for a difference in the basal levels of certain immunological mediators suggestive of elevated inflammatory activity in individuals with MCS [20,21]. However, there are few exposure studies that involves individuals with CI with focus on inflammation and the results are contradictory. Elevated levels of substance P in plasma were found both before and after exposure to VOCs in the CI group compared to controls [22,23]. However, a recent study involving individuals with MCS and exposure to low-levels of n-butanol did not find support for upper airway inflammation in response to the exposure or in the baseline levels [24].

The role of TRPA1 as a key regulator of signals derived from inflammatory mediators together with the time dependence on sensory irritation at low concentrations makes it interesting to investigate levels of inflammatory lipids in relation to low-level exposures from common sensory irritants that interact with the TRPA1 receptor, such as acrolein. A large inter-individual variation in the response to acrolein has been found in earlier studies [6]. The differences in reaction might be due to the presence or absence of lipid mediators known to modulate the response from certain TRP- channels [13]. The purpose of this study was to investigate if potential effects of acrolein exposure on oxylipin, endocannabinoid and related lipid levels were detectable in the blood stream of healthy individuals and individuals with CI. Heptane exposures were performed for comparison. A second objective was to test the relationship between individual factors such as self-reported CI and circulating lipid levels before and after exposure to acrolein.

2. Methods

2.1. Subjects and study design

Participants with CI and healthy controls were recruited through advertisement in the local newspaper and through billboard advertisement. A total of 37 individuals (26 women and 11 men) were included in the study of whom 18 (13 women and 5 men) answered yes to the question “Are you getting symptoms from odorous/pungent chemicals (not limited to certain buildings), such as perfumes and cleaning agents, in doses that you were not getting symptoms from before or that you believe most other people are not getting symptoms from?”. These participants were regarded as chemically intolerant. The Chemical Sensitivity Scale (CSS; [25]) verified that the CI group also had affective reactions and behavioural disruptions by odorous/pungent substances to a larger extent than the control group ($p < 0.001$, see table 1). The Perceived Stress Questionnaire (PSQ [26]) were used to quantify the extent of subjectively perceived stress during the previous 4 weeks and there were no difference in reported stress between the groups ($p = 0.29$). The CI group reported significantly more airway and cardiac/nausea/dizziness symptoms ($p < 0.05$). The participants are further described in Table 1. Pregnancy and smoking constituted exclusion criteria for participants in both groups. Prior to exposure, the participants were screened for anosmia (also constituting an exclusion criterion) using the Connecticut Chemosensory Clinical Research Centre Threshold Test [27]. Dilution step 6 was used as the cut-off (*n*-butanol 0.44% v/v). All participants had a normal sense of smell according to the test. The calculation of sample size was based on a previous study on individuals with MCS and immunological mediators [20].

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

	CI (n = 18)	Controls (n = 19)	p-value
Sex (n; women/men)	13/5	13/6	1[a]
Age (years; mean ± SD)	42 ± 13	40 ± 13	0.64[b]
Perceived stress questionnaire (PSQ) (Mean ± SD)	0.36 (0.16)	0.30 (0.16)	0.29[b]
Chemical sensitivity scale (CSS) (Mean ± SD)	69.4 (11.6)	49.7 (11.6)	0.00[b]
Reported no of symptoms, mean (± SD)			
Airway, mucosae and skin, out of 11	0.29 (0.3)	0.11 (0.1)	0.05[a]
Gastrointestinal, out of 3	0.8 (0.2)	0.3 (0.1)	0.13[a]
Head related, out of 3	0.8 (0.2)	0.4 (0.1)	0.57[a]
Cardiac, nausea and dizziness, out of 5	0.7 (0.2)	0.1 (0.1)	0.02[a]
Cognitive and affective, out of 10	1.8 (0.4)	2.7 (0.7)	0.55[a]
Reported diagnoses (n)			
Asthma/allergy	5	1	0.18[a]
Chronic sinusitis	0	0	1[a]
Disease in joints/muscles	3	1	0.60[a]
Irritable bowel syndrome (IBS)	3	1	0.60[a]
High blood pressure	0	6	0.02[a]
Chronic fatigue syndrome	1	2	1[a]
Depression	1	1	1[a]
Migraine	2	2	1[a]

[a] Fisher's exact test.
[b] Independent samples *t*-test between the groups. Ns = non-significant.

Each participant took part in two exposure conditions, one with only heptane and one with acrolein and heptane. The exposures were executed in a balanced design. All exposures occurred between breakfast and lunch and at the same time for both conditions to avoid influence from diurnal variations in metabolite concentration. Blood samples to assess systemic effects were taken at 3 occasions for each exposure (N = 6 in total for each individual), before exposure, directly after the exposure and at 24 h post-exposure. These time points were chosen due to practical reasons and earlier studies indicating an inflammatory response within 24 h post exposure [28,29]. During exposure, magnitude estimation of sensory irritation of the eye, nose and throat together with confidence were rated every 5 min to monitor participants experience during exposures. Self-reported tear-film break up time (BUT) was measured before and immediately after the exposures and electrodermal activity (EDA) were recorded throughout the exposures. A detailed description on the methodology used for collection of self-reported ratings during exposure and results is published elsewhere [30]. The acrolein exposure was shown to elicit symptoms characteristic of CI in the CI group and to produce the expected group differences.

2.2. Exposure chamber and stimulus material

Participants were exposed twice (2 × 60 min) in a controlled exposure chamber (1.5 × 0.9 × 2.0 m). Carbon filtrated air entered the chamber through an inlet at floor-level and exited in the ceiling. The air exchange rate was set to 7.5 times/hour (approximately 330 L/minute), the mean temperature during exposure was 21 °C ± 1 °C and the mean