ORIGINAL CONTRIBUTION

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Peripheral and central levels in nasal trigeminal sensitization and desensitization*

G. Brand[1] and L. Jacquot[2]

[1] Laboratoire de Neurosciences, Université de Franche-Comté – Place Leclerc 25000 Besançon, France
[2] Monell Chemical Senses Center, 3500 Market Street – Philadelphia, PA, 19104 - USA

SUMMARY

In order to investigate the role of central and peripheral mechanisms in nasal trigeminal sensitization/desensitization processes, the present work recorded psychophysical (intensity ratings) and psychophysiological (skin conductance) responses to allyl isothiocyanate volatile nasal stimulation - during normal breathing - in monorhinal condition after a controlateral stimulation of the other nostril. Insofar as both nostrils are anatomically separated, modifications in responses can be interpreted as a central regulation process. Results showed that sensitization was clearly related to central mechanisms contrarily to desensitization which depended only of peripheral level.

Key words: sensitization, desensitization, mustard oil, allyl isothiocyanate, trigeminal stimuli, skin conductance

INTRODUCTION

Most chemical nasal stimuli have the propensity to stimulate receptors of the olfactory nerve (Cranial Nerve I) located in the upper recesses of the nasal cavity and free nerve endings of the trigeminal nerve (Cranial Nerve V) [(1)]. Sensations derived from the trigeminal nerve are somatosensory and include burning, stinging, itching, tickling, cooling, warming and pain sensations [(2)]. Repeated or continuous olfactory stimulation is well known to elicit adaptation processes revealed by psychophysical measures, i.e. decrease of perce ived intensity and by psychophysiological measures, e.g. decrease of skin conductance response (SCR) amplitudes. In contrast, repeated trigeminal stimulation induces differential responses according to inter-stimulus intervals (ISIs) and the nature of chemical stimuli [(3)]. Specifically, trigeminal stimuli can produce increases in rated intensity with short ISI, a phenomenon called sensitization and moreover, with long ISI repeated trigeminal stimuli can produce markedly decreases intensity, a phenomenon named desensitization.

Sensitization and desensitization by a chemical irritant have been principally investigated on the cutaneous receptors and the tongue. The first psychophysical evidence of such an effect in the oral cavity came from Stevens and Lawless [(4)], who observed that when capsaicin (or piperine) was presented twice at the same concentration within a short interval, the second presentation produced a more intense sensation than the first. Subsequently, other studies have dealt with the question of sensitization/desensitization by chemical irritants but few studies concerned the nasal cavity [(5-7)]. A first study using capsaicin [(8)] has shown sensitization when a second stimulus was delivered shortly after (<1 min) the first stimulus and desensitization when the second stimulus was delivered >3-4 min later. More recently [(9)], the same process has been demonstrated with allyl isothiocyanate (mustard oil). In this latter study, psychophysical (intensity ratings) and psychophysiological (SCR recordings) were strongly correlated. In contrast, successive nasal stimulations with acetic acid produced a self-desensitization whatever ISI duration [(10)].

A neurophysiological point of view assumes that sensitization/desensitization processes occur at peripheral level corresponding to C-fibers (unmyelinated) and A-delta fibers (myelinated) activation, two major fiber systems that participate in the afferent chemosensitive innervation of the nasal epithelium [(11,12)]. Both kinds of fibers are activated by the intracellular accumulation of protons, which modify the membrane conductance [(13)]. However, it has been suggested for a long time that central mechanisms could be in part responsible of both sensitization and desensitization processes [(14)]. These central mechanisms could occur in the same manner that those involved in the regulation of pain sensation [(15)]. Until now, no experiment has assessed the peripheral and central mechanisms involved in the sensitization/desensitization nasal trigeminal processes. Thus, the aim of the present study was to investigate the response, acute effects and time-course of sensitization/desensitization to allyl isothiocyanate volatile nasal stimulation during normal breathing in monorhinal condition after a controlateral stimulation of the other nostril. Indeed, insofar as both nostrils are anatomically separated, modifications in responses can be interpreted as involving central regulation process. As the sensitization and desensitization processes are related to ISI, a short (45s) and a long (3m30s) ISIs were tested according to previous data obtained in this field.

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MATERIALS AND METHODS

Subjects

Twenty female students participated in the experiment. Subjects were taken from within a single gender because nasal chemoreception is known to depend on gender. Women were selected owing to the fact that this population appears generally more homogeneous than the male population with respect to nasal chemoreception, especially olfactory perception [16]. Their age ranged from 21 to 31 years (mean age 23 years, 2 months). All subjects were right-handed, non smokers and none had a history of nasal-sinus disease. The study was conducted in accordance with the Declaration of Helsinki – Hong Kong and approved by an ethic committee.

Nasal stimulus

The nasal stimulus was allyl isothiocyanate (AIC) [Sigma – C_4H_5NS, mol. Wt. 99.15) diluted at 25% in mineral oil, a concentration higher than the standardized detection thresholds [17]. The nasal stimulus under liquid form was presented in a glass tube (7.5 cm high; 1 cm in diameter at the opening) filled with 4 ml of liquid. The tube was presented to the subject during a limited period of 2s (one inspiration) at a distance of 1 cm from the nostril using a holder to avoid any olfactory or thermic interference from the experimenter's hand.

Procedure

The subjects were comfortably seated in a quiet room. Before the experiment, a control auditory stimulation (440 Hz, 60 dB, 1s) was used for the dial readings and adjustment of the baseline in order to zero the Galvanic Skin Response (GSR) amplifier. Then, visual cues were excluded by a blindfold and auditory cues by a soundproof helmet. Additionally, the breathing cycle (mouth open) was recorded with a Minigraph Lafayette instrument (Model 76107 equipped with pneumo bellows) and monitored in order to present the nasal stimulus at the outset of inspiration and to check that the inspiration amplitude did not change during the experiment. The nasal stimulus was delivered to one nostril and the other nostril was blocked with a nose plug. The side tested first was randomized. For each subject, the full experiment was divided in four sessions occurring on four different days, in relation to the inter-stimulus interval (i.e. short ISI of 45s and long ISI of 3m30s) and to the nostril first stimulated. Each session started with a 5-minute rest period and lasted approximately 20-30 min. After the Skin Conductance Response (SCR) recordings, the subjects were asked to note the intensity of stimuli on a scale ranging from 0 (not perceived) to 10 (very high).

SCR recordings

The SCR, expressed in microSiemens (μS), was recorded from the left hand with a MacLab system (GSR amplifier; ADInstruments) interfaced with a computer. The GSR amplifier provided a low constant voltage (22 mV at 75 Hz). Skin preparation consisted of washing the hand in soapy water, followed by rinsing and thorough drying. Bipolar electrodes were attached with a Velcro strip to the palmar surface of the middle phalanges of the first and second left fingers. When the electrodes were in position, the subject was told not to move and asked to relax to establish good baseline conductivity.

Data analysis

According to the classical recommendations [18], and previously published studies [19-23] SCR data were as follows: phasic stimulus-elicited SCR amplitudes referring to the first response were > 0.02 μS, with a minimal slope of 0.01 μS/s which occurred within an interval of 0.5 – 4 s after the onset of the stimulus. The amplitude was scored from the inflection point to peak. The observations of a response occurring during a modified inspiration were excluded.

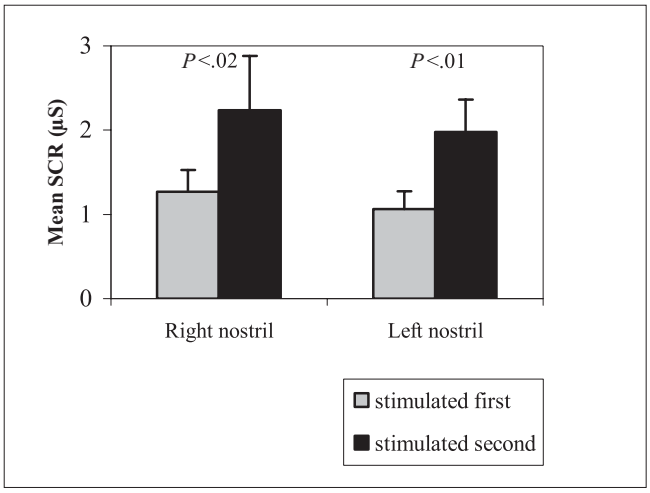

Figure 1. Mean SCR amplitudes (μS) recorded in monorhinal condition before and after a previous controlateral nostril stimulation (Short ISI of 45 s).

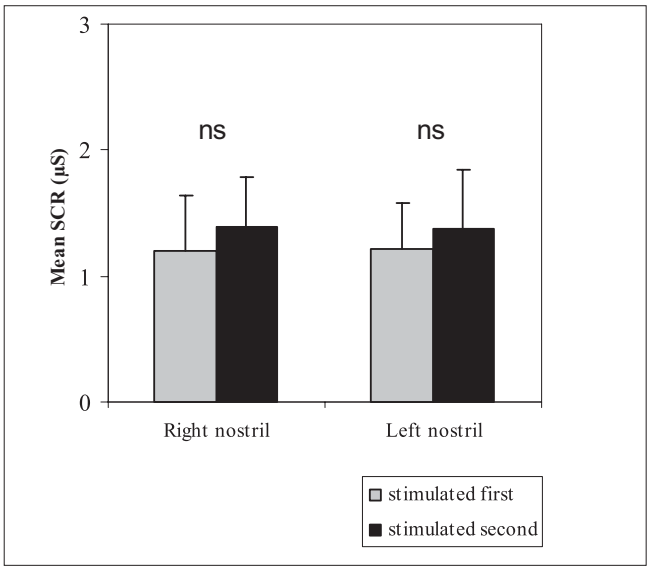

Figure 2. Mean SCR amplitudes (μS) recorded in monorhinal condition before and after a previous controlateral nostril stimulation (Long ISI of 3 min 30 s).

Statistics

Student's t-test (paired) and correlation coefficient were used for statistical analyses. A criterion of α=0.05 was used for all comparisons and non-significant results were noted as *ns*. The arithmetic mean and the standard deviation (SD) were included.

RESULTS

SCR amplitudes - Short ISI (45 s)

Results are reported in Figure 1. For the right nostril, the SCR amplitudes obtained after the left nostril stimulation (m = 2.237, SD = 0.64) were significantly higher (t = 2.543, $p < 0.023$) than those obtained when the right nostril was first stimulated (m = 1.268, SD = 0.26). In the same way, for the left nostril the SCR amplitudes obtained after the right nostril stimulation (m = 1.975, SD = 0.39) were significantly higher (t = 2.766, $p < 0.015$) than those obtained when the left nostril was first stimulated (m = 1.066, SD = 0.21).

SCR amplitudes – Long ISI (3 m 30 s)

Results are reported in Figure 2. For the right nostril, the SCR amplitudes obtained after the left nostril stimulation (m = 1.395, SD = 0.39) were not significantly different (t = 0.542, ns) than those obtained when the right nostril was first stimulated (m = 1.202, SD = 0.43). In the same way, for the left nostril the SCR amplitudes obtained after the right nostril stimulation (m = 1.381, SD = 0.46) were not significantly different (t = 0.420, *ns*) than those obtained when the left nostril was first stimulated (m = 1.208, SD = 0.37).

Intensity ratings – Short ISI (45 s)

Results are reported in Figure 3. For the right nostril, the intensity ratings noted after the left nostril stimulation (m = 7.73, SD = 0.40) were significantly higher (t = 2.41, $p < 0.03$) than those obtained when the right nostril was first stimulated (m = 6.26, SD = 0.61). In the same way, for the left nostril the intensity ratings noted after the right nostril stimulation (m = 8.26, SD = 0.33) were significantly higher (t = 4.58, $p < 0.0004$) than those obtained when the left nostril was first stimulated (m = 6.46, SD = 0.25).

Intensity ratings – Long ISI (3 m 30 s)

Results are reported in Figure 4. For the right nostril, the intensity ratings noted after the left nostril stimulation (m = 6.46, SD = 0.42) were not significantly different (t = 0.361, *ns*) than those obtained when the right nostril was first stimulated (m = 6.66, SD = 0.44). In the same way, for the left nostril the intensity ratings noted after the right nostril stimulation (m = 5.87, SD = 0.56) were not significantly different (t = 1.233, *ns*) than those obtained when the left nostril was first stimulated (m = 6.67, SD = 0.39).

DISCUSSION

Using the pungent volatile nasal stimulus allyl isothiocyanate, the results of the present study indicated that the responses (SCR amplitude and intensity ratings) obtained for one nostril were significantly higher after controlateral nostril stimulation when the ISI was short (45s). In contrast, when the ISI was long (3m30s) no difference occurred in responses (SCR amplitudes and intensity ratings) before and after previous controlateral nostril stimulation. These findings are similar irrespective of the nostril tested first, in accordance with previously published work which compared psychophysiological as well as psychophysical responses between both nostrils [21]. Moreover, psychophysiological and psychophysical results lead to the same conclusion.

A previous experiment showed that sensitization and desensitization processes following birhinal allyl isothiocyanate stimulation were related to ISI [9] in the same way as oral stimulation [24].

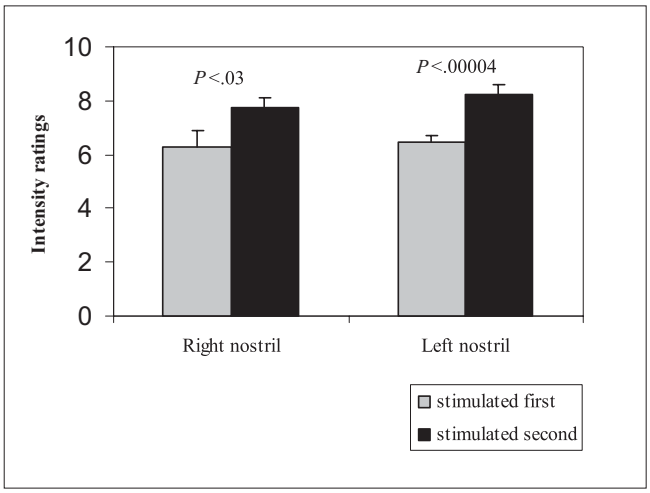

Figure 3. Mean intensity ratings recorded in monorhinal condition before and after a previous controlateral nostril stimulation (Short ISI of 45s).

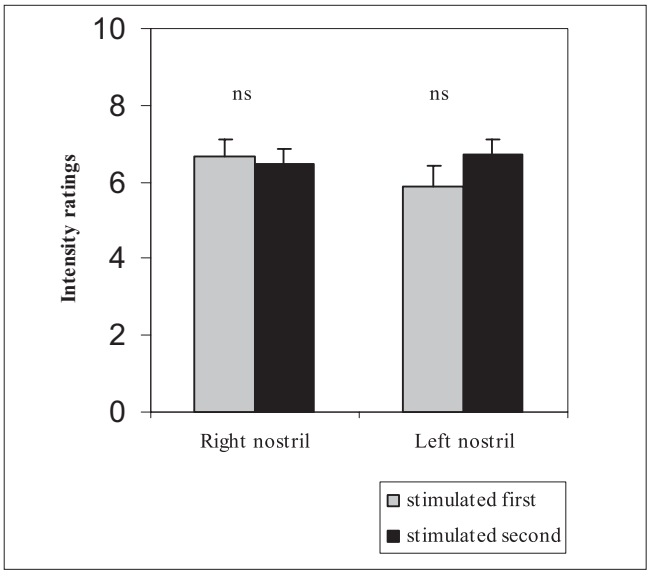

Figure 4. Mean intensity ratings recorded in monorhinal condition before and after a previous controlateral nostril stimulation (Long ISI of 3m30s).

Specifically, responses increased with short ISIs and decreased with long ISIs. The findings of the present study indicate that nasal trigeminal sensitization process seems to also take place at central level and not exclusively at peripheral level. In the same way, the findings indicate that nasal trigeminal desensitization could only occur at peripheral level insofar as no difference appears with a long ISI in responses, before and after previous controlateral nostril stimulation.

Most studies investigating the irritant properties of mustard oil have been conducted on hairy skin [25-28]. Mustard oil applied to the skin induces pain sensation followed by sensitization specifically characterized by hyperalgesia and allodynia [28]. However, responses to AIC applied to the skin differed from those obtained with AIC inhaled via the nasal cavity [23]. The difference is due in a great part to the better accessibility of irritant to nociceptive endings in nasal epithelium compared with skin tissue.

From a peripheral point of view, allyl isothiocyanate probably activates both C- and A-delta fibers insofar as a previous experiment [29] indicated that the subjects noted equally stinging and burning sensations following an AIC stimulation. C-fibers are preferentially involved in the mediation of burning sensations and A-delta fibers preferentially in stinging sensations [30]. Moreover, it is well known that messages mediated by C-fibers and A-delta fibers differ in their response to repeated stimuli [31,32]. In contrast, it is not known if allyl isothiocyanate activates specific receptors such as vanilloid receptors (VR1) for capsaicin [33], cold menthol receptors (CMR-1) for menthol [34] or whether AIC activates nerve endings via a non-specific action onto the membrane [35]. Sensitization is largely mediated by progressive spatial recruitment of nociceptors as the chemical diffuses through epithelial tissue, especially onto the skin. Desensitization involves cellular processes leading to reduced excitability of the nociceptor nerve endings. Although both sensitization and desensitization processes may occur simultaneously, it must be noted that allyl isothiocyanate quickly diffuses through the nasal epithelium (contrary to capsaicin, for instance, which diffuses slowly through the epithelium) and probably all the receptors are recruited after an initial application [24]. In this respect, central elicitation of sensitization, as demonstrated in this experiment, could be hypothesized. The trigeminal system activation indicates possible harmful compounds action; the central sensitization could be interpreted as a reinforcement of protective reflexes. In contrast, with a long ISI (3m30s), the desensitization process observed in bilateral nasal stimulation with AIC [9] did not occur in the present experiment. This fact suggests that the desensitization process is not related to central mechanisms and probably results from peripheral inactivation of nerve endings following repeated stimulations.

From a central point of view, it has been shown that while initiation of central sensitization depends on input from sensitized peripheral pathways, central sensitization can be maintained independently of peripheral input [36]. As in the regulation of pain via the trigeminal system described in a recent study [37], this central process could occur in the trigeminal ganglion (first-order neurons), in the trigeminal nucleus (second-order neurons) and in the thalamus (third order neurons). The sensitization is currently explained as a summation of the successive inputs into the brain.

In this field, further research must delineate the central and peripheral levels in cross-sensitization and –desensitization insofar as it could influence smell-related behaviours [38,39]. Some studies have been focused on this topic in the oral cavity [24,40] and in the nasal cavity [10]. However, only peripheral explanations based on nociceptor recruitment have been hypothesized [41].

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Dr G. Brand
Laboratoire de Neurosciences,
Université de Franche-Comté
Place Leclerc 25000
Besançon
France

E-mail: gerard.brand@univ-fcomte.fr