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Trigeminal sensitization and desensitization in the nasal cavity: a study of cross interactions*

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SUMMARY

Chemical irritation in the human nasal cavity is poorly documented. In this field, an important issue concerns the differential responses produced by successive stimulation. Repeated identical chemical irritant stimuli can produce increases or decreases in responses (two phenomena known as self-sensitization or self-desensitization). In the same way, different molecules can interact and produce cross-sensitization or cross-desensitization. The aim of this study was to contribute to this question using two specific molecules, acetic acid (AA) and allyl isothiocyanate (AIC). As the self-sensitization and -desensitization for AIC is known, a first experiment in the present work investigated the response, acute effects and time course of sensitization or desensitization to acetic acid. A second experiment tested the responses of acetic acid after a previous stimulation with allyl isothiocyanate (mustard oil) and inversely with a short inter-stimulus interval (ISI of 45s). A third experiment similar to the second used a long inter-stimulus interval (ISI of 3min30). Twelve healthy subjects participated in the study using psychophysical (intensity ratings) and psychophysiological (skin conductance response) measurements. Firstly, the results showed that repeated nasal stimulation with acetic acid produced a self-desensitization whatever the ISI. Secondly, the results showed a cross-desensitization of allyl isothiocyanate by previous acetic acid stimulation. In contrast, previous stimulation with allyl isothiocyanate had no effect on the following acetic acid response. These findings confirm that trigeminal sensitization and desensitization in the nasal cavity do not follow the same processes in relation to molecules used.

Key-words: chemical irritation, trigeminal sensitivity, sensitization, desensitization, autonomic activation, skin conductance.

INTRODUCTION

Many investigations have described several aspects and characteristics of chemical irritation [1], principally on the cutaneous receptors and the tongue. Comparatively, few studies have dealt with the question of chemical irritation in the nasal cavity although the publications over the last few years have been trying to overcome this [2]. In this field, an important issue concerns the differential responses produce by successive stimulation. Indeed, it is well established that repeated stimuli with odors and tastes typically show a decrease in rated stimulus intensity if the inter-stimulus interval (ISI) is brief. In contrast, it has been demonstrated - especially on the skin and the tongue - that chemical irritant stimuli can produce increases or decreases in rated intensity (two phenomena known as sensitization and desensitization) during repeated stimulation in relation to the ISI and depending on the type of irritant. A wide variety of volatile chemicals stimulate nasal trigeminal nerve endings leading to a sensation of irritation. However, few specific molecules have been studies in the field of sensitization/desensitization in the nasal cavity. Cain [3] showed that the perceived irritation produced by n-butyl alcohol grew significantly stronger over three sniffs. Subsequently, Cometto-Muniz and Cain [4] reported that the irritation produced by ammonia intensified as the duration of a sniff was increased from approximately 1.25 sec to 3.75 sec. In contrast isoamyl butyrate, an odorous compound that produces no perceptible irritation, resulted in no significant increase in odor intensity under identical conditions. Psychophysical studies with capsaicin [5] have shown sensitization when the stimuli were delivered during short ISIs. On the contrary, capsaicin produced desensitization in the nasal cavity if the ISI was longer than three or four minutes [6]. Recently, Brand and Jacquot [7] investigated the response, acute effects and time-course of sensitization and desensitization to allyl isothiocyanate (mustard oil) nasal stimuli. The experiment employed psychophysical (intensity ratings) and psychophysiological (skin conductance response) measurements. The results showed that successive nasal stimulation with allyl isothio-

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cyanate produced increased perceived intensity after a short period of time (less than 2 minutes) whereas the stimuli delivered after more than 3 minutes produced a markedly decreased perceived intensity of irritation.

In the same way, different molecules can interact and produce cross-sensitization or cross-desensitization. Cain and Murphy [8] presented CO2 before amyl butyrate in order to see if sequential presentation of irritant before odor would alter the pattern of inhibitory responses. It appeared that irritation inhibited odor but only by about one-fourth the amount noted with simultaneous presentation. Cross interaction in the human nasal cavity between irritants has been poorly studied. Only Geppetti et al. [9] demonstrated that desensitization by capsaicin decreased irritation by citric acid. Thus, the aim of the present work was to investigate the cross interaction between two irritants, when acetic acid (AA) was delivered before allyl isothiocyanate (AIC) and inversely. The specific molecules, acetic acid and allyl isothiocyanate were tested in this study, because both are known to act through the trigeminal nerve [10], both are non toxic and widely used as flavoring agents in a variety of foods in many countries. The literature on stinging and burning sensations with acetic acid and allyl isothiocyanate is poorly documented. The preliminary data which indicated that allyl isothiocyanate leads to a burning sensation [11] and acetic acid leads to a stinging sensation [12] must be confirmed. The perceptual characteristic is important from a neurophysiological point of view. Indeed, free nerve endings of the ophthalmic and maxillary divisions of the trigeminal nerve (CN V) are distributed throughout the nasal mucosa and olfactory epithelium. Two major fiber systems C-fibers (unmyelinated) and Adelta-fibers (myelinated) participate in the afferent chemosensitive innervation of the nasal epithelium [13,14]. It seems that C-fibers are preferentially involved in the mediation of burning sensations and Adelta-fibers preferentially in stinging sensations [15]. Interestingly, responses mediated by C-fibers and Adelta-fibers differ in their response to repeated stimuli [10,16,17]. At short intervals, burning sensations increase whereas no such summation has been reported for stinging sensations which decrease in relation to the desensitization of Adelta-fibers [18].

In consideration of the importance of the type of sensation in the explanation of the cross interactions between the stimuli, a first study (Study 1) evaluated with a psychophysical method the stinging and burning sensations of both AA and AIC stimuli. As a previous experiment explored the effect of repetitive stimulation with allyl isothiocyanate [7] a second study (Study 2) tested in a first experiment the perceptual characteristics of intensity irritation level during repeated stimulation with acetic acid. A second experiment investigated the response of allyl isothiocyanate after a nasal stimulation with acetic acid and inversely (response of AA after AIC stimulation) with a short inter-stimulus interval of 45s. A third experiment replicated the second experiment with a long inter-stimulus interval of 3 min 30s. Both ISIs (45s and 3 min 30s) were chosen according to their differential sensitization/desensitization effects observed in previous works. From a methodological point of view, the most widely reported method of assessing sensitization/desensitization in humans has been to use psychophysical tests [19].

In the present work both psychophysical (self rating of perceived intensity) and psychophysiological (skin conductance response - SCR) measures were used. SCR recording was added because it was considered to be a reactivity measure in terms of arousal and affect or basic emotion. SCR related to the autonomic nervous system has long been used to assess the level of arousal during specific tasks or stimuli, including nasal stimuli. The studies were conducted in accordance with the Helsinki/Hong Kong Declaration.

MATERIAL AND METHODS

Nasal stimulations

Two specific types of nasal stimuli were used in both studies. One was allyl isothiocyanate (AIC) [C4H5NS Mol.Wt.: 99.15], and other was acetic acid (AA) [C2H4O2 Mol.Wt.: 60.1]. The properties of both molecules are summarized in Table I. The dilutions of the stimuli were prepared in mineral oil. The concentration used was 25%, which is a suprathreshold higher than the standardized detection thresholds [20]. The nasal stimulus in liquid form was presented in a bottle (7.5 cm high; 1 cm in diameter at the opening) filled with 3 ml of liquid. The bottle, in birhinal stimulation, was presented to the subject during a limited period of 2 seconds (one inspiration) at a distance of 1 cm from nostrils using a holder to avoid any olfactory or thermic interference with the experimenter's hand.

Study 1. Method

A group of 20 subjects (10 females, 10 males; mean age 23 years 7 months) was tested. The subjects were asked to note the intensity of burning and stinging sensations for both acetic acid (one day) and allyl isothiocyanate (another day) stimuli on a scale ranging from 0 to 10 unit (0, not perceived; 10 very high). The Student t-test (related samples) was used for statistical analyses. Non-significant results were noted as NS.

Study 2. Method

Subjects

A group of 12 subjects (6 females, 6 males) different from Study 1, participated in Study 2. Their ages ranged from 21 to 25 years (mean age 22 years 8 months). All subjects were dextrals, non smokers and reported normal smell sensitivity, and none of them had a history of nasal/sinus disease or extensive exposure to chemicals with potential olfactory or trigeminal toxicity.

Procedure

Three experiments carried out between 10:00 and 12:00 a.m. on three different days. Each experiment included two sessions separated with a rest period of 30 min. duration.

Table 1. Properties and concentration of allyl isothiocyanate and acetic acid.
* The American Chemical Society's Chemical Abstracts Service (CAS) registry number

						Concentration used		
Chemical	Company	CAS*	Molecular formula	Mol.wt	Density g/cm3	(% v/v)	g/cm3	mol/ cm3
Allyl isothiocyanate	Sigma	57-06-7	C4H5NS	99.15	1.02	25	2.55 x 10-1	2.57x10-3
Acetic acid	Sigma	64-19-7	C2H402	60.1	1.05	25	2.62 x 10-1	4.36x10-3

The first experiment was separated in two similar sessions; session 1 as psychophysical rate and session 2 as psychophysiological recording. In both sessions, the test tube with acetic acid was presented five times at a constant interval of 45s and the sixth presentation 3 min 30 after the fifth. In a second experiment, two nasal stimuli were delivered with an inter-stimulus interval of 45s. In session 1, the order of stimulation was AA - AIC and in session 2 the order was AIC - AA. In a third experiment, the same conditions as the second experiment were used, but the inter-stimulus varied with an interval of 3 min 30s.

Psychophysical estimation and psychophysiological recordings

In order to note the perceived intensity of the stimulus, a scale ranging from 0 to 100 (0, not perceived; 100, very high) was used. In session 1 of the first experiment, the subjects noted the perceived intensity of the stimulation after each tube presentation. In the second and the third experiment, the subjects were asked to note the perceived intensity of both stimuli after the SCR recordings. The breathing cycle (mouth closed) of the subjects was recorded with a Minigraph Lafayette instrument (Model 76107 equipped with pneumo bellows) in order to check that the inspiration amplitude did not change during the experiment. The subjects which produced an inspiratory stop reflex (flat line on the breathing cycle recording) during the stimulation were excluded from the sample. The breathing cycle monitoring was also used in order to present the nasal stimulus at the outset of inspiration.

The procedure of the SCR recording sessions was the same as that previously described in other published works [7,21,22]. As all the subjects were right-handed, the SCRs were recorded on the non dominant left hand according to the classical recommendations [23]. SCR data were as follows: phasic stimulus-elicited SCR amplitudes referring to the first response were equal to or greater than 0.02 μS with a minimal slope of 0.01 μS/s which occurred within an interval of 0.5 – 4s after the onset of the stimulus. For each of the observed SCR following the stimulation, the compound response was scored from the inflection point to peak. If more than one response occurred in the interval (0.5 – 4s), only the first one was scored. The observations of a response occurring during a modified inspiration were excluded.

Data analyses

Data were statistically evaluated with a computer program (Statview II) using an analysis of variance (ANOVA) with repeated measures for experiment 1. *Post hoc* analyses following significant ANOVA effects were conducted using Scheffe tests. A criterion of ü=0.05 was used for the comparisons. Student's t-tests (paired and independent) were used for statistical analyses of experiments 2 and 3. The arithmetic mean and the standard deviation were respectively noted as *m* and *sd*. The non significant analyses were noted as NS.

RESULTS

Study 1

The psychophysical estimation of stinging and burning sensations (Figure 1) indicated that the results were different in relation to the stimulus. Stinging rate for acetic acid (m=8.22; SD=1.15) was significantly higher than burning rate (m=3.12; SD=0.4) (t=18.16; p<0.0001). In contrast, for allyl isothiocyanate stinging rate (m=6.34; SD=0.83) and burning rate (m=7.51; SD=0.76) were not significantly different (t=1.81; NS). Moreover, the stinging rate for acetic acid was significantly higher than that for allyl isothiocyanate (t=4.622; p<0.001). Inversely, the burning rate for allyl isothiocyanate was significantly higher than that for acetic acid (t=14.13; p<0.0001).

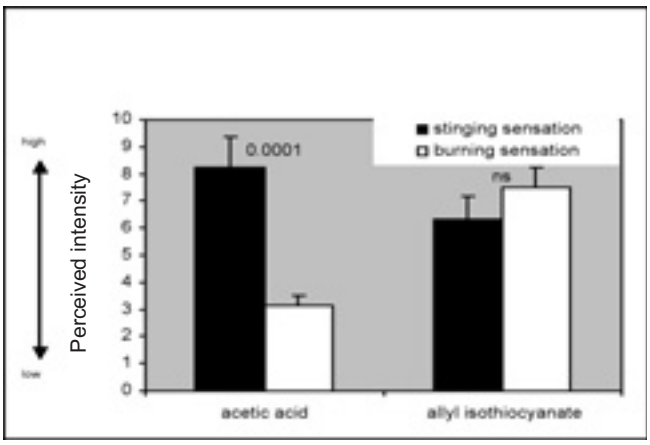

Figure 1. Psychophysical estimation of stinging and burning sensations for acetic acid (AA) and allyl isothiocyanate (AIC).

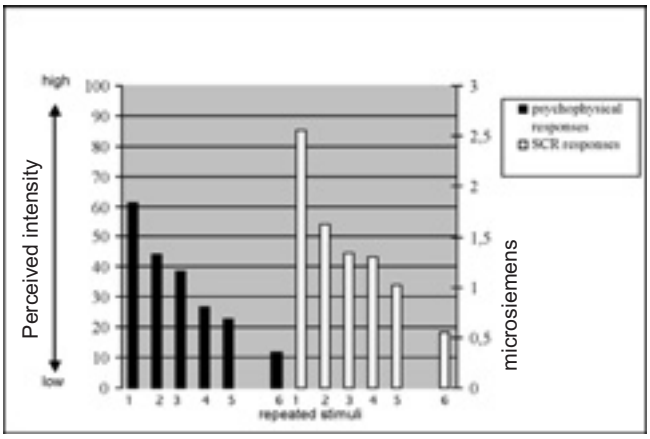

Figure 2. Psychophysical (rating scale) and psychophysiological responses (SCR amplitude) during repeated stimuli with acetic acid in the nasal cavity.

Table 2. Scheffe post hoc tests between psychophysical responses during successive stimuli with acetic acid ($p<0.05$).

	2	3	4	5	6
1	7,06	12,07	28,94	36,33	59,49
2		NS	7,41	11,36	25,56
3			3,29	6,06	17,2
4				NS	5,44
5					2,84

Table 3. Scheffe post hoc tests between psychophysiological responses during successive stimuli with acetic acid ($p<0.05$).

	2	3	4	5	6
1	2,4	4,14	4,16	6,61	11,28
2		NS	NS	NS	3,27
3			NS	NS	NS
4				NS	NS
5					NS

Study 2

First experiment: The results of the first experiment which recorded the psychophysical (session 1) and psychophysiological (session 2) responses during repeated stimuli with acetic acid are reported in Figure 2. For session 1, the data indicated that the mean values of intensity ratings regularly decreased during the stimulation with a constant ISI of 45s. Moreover, the score of the sixth stimulus which was delivered 3 min 30 after the fifth appeared to be lower. The ANOVA yielded significant differences for the intensity ratings [$F(1.11)=74.98$ $p<0.0001$] in session 1. Scheffe *post hoc* tests (Table 2) showed that the first stimulus ($m=61.25$; $sd=10.4$) produced a significantly higher score than all the following stimuli. In the same way, Scheffe *post hoc* tests showed significant differences between all the stimuli except between the second and the third and between the fourth and the fifth. For session 2, the data indicated that the mean values of SCR amplitudes regularly decreased in the same way as the intensity ratings of session 1. The ANOVA also yielded significant differences [$F(1.11)=12.729$ $p<0.0001$] and similarly, the first stimulus ($m=2.55$; $sd=1.51$) produced a significantly higher SCR amplitude than all the following stimuli (Table 3). In contrast, there was no significant difference between the other stimulations except between the second and the sixth.

Second experiment: The results are reported in Figure 3a for acetic acid responses and in Figure 3b for allyl isothiocyanate responses. The *t-test* showed that the responses for acetic acid were not significantly different when delivered before or after an allyl isothiocyanate stimulation (ISI 45s) as well as for the psychophysical estimation ($t=0.84$ NS) and for the psychophysiological response ($t=0.756$ NS). In contrast, the *t-test* showed that the responses for allyl isothiocyanate were significantly lower when delivered after an acetic acid stimulation as well as for the psychophysical estimation ($t=7.483$ $p<0.0001$) and for the psychophysiological responses ($t=4.240$ $p<0.001$).

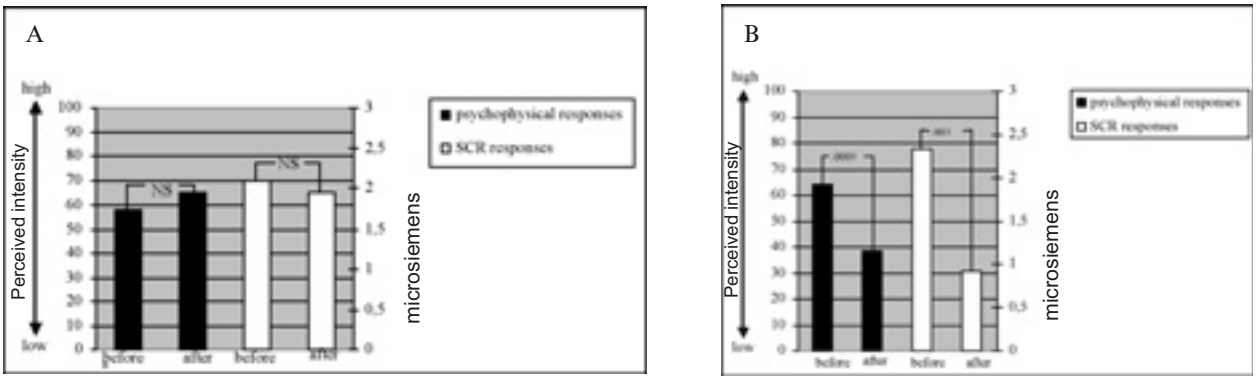

Figure 3. (a) Mean of psychophysical (rating scale) and psychophysiological (SCR amplitude) responses for acetic acid before and after (45s) an allyl isothiocyanate stimulation in the nasal cavity. (b) Mean of psychophysical (rating scale) and psychophysiological (SCR amplitude) responses for AIC before and after (45s) an acetic acid stimulation in the nasal cavity.

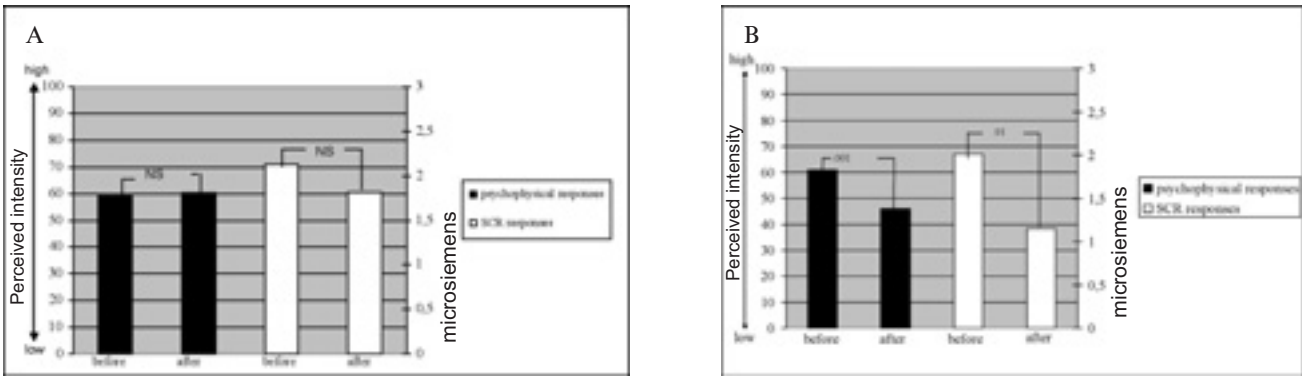

Figure 4. (a) Mean of psychophysical (rating scale) and psychophysiological (SCR amplitude) responses for acetic acid before and after (3min30) an allyl isothiocyanate stimulation in the nasal cavity. (b) Mean of psychophysical (rating scale) and psychophysiological (SCR amplitude) responses for AIC before and after (3min30) an acetic acid stimulation in the nasal cavity.

Third experiment: The results are reported in Figure 4a for acetic acid responses and in Figure 4b for allyl isothiocyanate responses. The *t-test* showed that the responses for acetic acid were not significantly different when delivered before or after an allyl isothiocyanate stimulation (ISI 3 min 30) as well as for the psychophysical estimation ($t=0.302$S NS) and psychophysiological response ($t=1.779$ NS). In contrast, the *t-test* showed that the responses for allyl isothiocyanate were significantly lower when delivered after an acetic acid stimulation as well as for the psychophysical estimation ($t=4.377$ $p<0.001$) and for the psychophysiological responses ($t=3.651$ $p<0.01$).

DISCUSSION

The psychophysical data of Study 1 indicate that stinging and burning sensations differ in relation to the trigeminal stimulus. In the nasal cavity, acetic acid clearly induces stinging sensation with very low burning sensation whereas allyl isothiocyanate simultaneously induces burning and stinging sensations. Interestingly, acetic acid induces a higher stinging sensation than allyl isothiocyanate and inversely allyl isothiocyanate induces a higher burning sensation than acetic acid.

The results of the Study 2 indicate that repeated nasal stimulation with acetic acid produced a decrease in perceived intensity and in the same way a decrease in SCR amplitudes. Moreover, the self acetic acid desensitization in the nasal cavity appears not to depend on the period of time between the stimuli insofar as this work tested a short (45s) and a long (3 min 30) ISI. These findings for acetic acid contrast with the results previously obtained with allyl isothiocyanate [7] which showed a self sensitization and a self desensitization related to the ISI, i.e. a clear sensitization when the ISI is short (less than 2 minutes) and a markedly desensitization when the ISI is longer than 3 min 30. The results concerning the cross interactions between acetic acid and allyl isothiocyanate showed that a previous stimulation with allyl isothiocyanate did not affect the response to acetic acid whatever the inter-stimulus interval. On the contrary, the results indicated that a previous stimulation with acetic acid led to a clear desensitization of allyl isothiocyanate response if the ISI was brief or long. The comparative results concerning the psychophysical estimation and psychophysiological responses are in agreement with previous studies [7,21,24,25] which showed a strong correlation between both measures.

These findings confirm that self sensitization and self desensitization in the nasal cavity with irritants which stimulate the trigeminal nerve do not follow the same processes in relation to the molecule used. Allyl isothiocyanate presents the same properties as capsaicin or piperine [19,26,27] and differs with acetic acid. In the oral cavity, such self desensitization has been demonstrated with menthol [28] or nicotine [29]. This fact could be related to the type of fibers involved and the self desensitization of acetic acid indicated that Adelta-fibers could mediate the responses especially since this molecule gave a clear stinging sensation.

The cross desensitization of allyl isothiocyanate following acetic acid whereas this was not the case with allyl isothiocyanate before acetic acid, raise a more complex question. No such effect has been reported in the nasal cavity in a normal breathing condition. Only Geppetti et al. [9] using a direct application to the nasal mucosa, observed a reduction of pain induced by citric acid after an application of capsaicin. In the mouse, capsaicin stimulation in the nasal cavity produced a decrease in irritation by n-propanol and ethylene [30]. In the oral cavity, it has been demonstrated that capsaicin stimulation induces a decrease in irritation by NaCl [31-33], by ethanol [19], citric acid [31], pentanoic acid [34] and by nicotine [29].

The non reversibility of the cross desensitization between allyl isothiocyanate and acetic acid indicates that the relationship between molecules which stimulated the trigeminal nerve is complex and partially understood especially from a neurophysiological point of view. The effect of acetic acid which reduces the allyl isothiocyanate response would seem to require that both molecules activate a common set of trigeminal fibers. The cellular mechanisms underlying such a non-reciprocal cross desensitization are not known and warrant further inves-

tigation. In this field, the peripheral mechanisms could not only be the ones which play a role in the cross interaction. Indeed, it has been suggested for a long time that central neural mechanisms could be in part responsible to the processes of sensitization and desensitization [8]. Thus, concurrently to the neurophysiological explanations, further research using monorhinal stimulation is needed to investigate if there is a contralateral effect between the two nostrils in chemical irritant molecule cross-interactions.

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