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SHORT COMMUNICATION

Loss of Olfactory Function Leads to a Decrease of Trigeminal Sensitivity

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Abstract

Healthy controls were compared to patients with decreased olfactory sensitivity ($n = 32$) to investigate interactions between the olfactory and trigeminal systems. Amplitudes of chemo-somatosensory event-related potentials in response to suprathreshold trigeminal stimuli (CO_2) were found to be smaller in patients ($P < 0.05$) indicating a decrease of trigeminally mediated sensations. **Chem. Senses 21: 75–79, 1996.**

Introduction

Most chemical stimuli produce both trigeminal (e.g. stinging, cooling) and olfactory sensations (Elsberg *et al.*, 1935; Doty *et al.*, 1978; Cain and Murphy, 1980; Kobal and Hummel, 1991). As a consequence, much research has been performed on the modulation of olfactory sensations by concomittant trigeminal activation (Cain and Murphy, 1980; Bouvet *et al.*, 1987; Caprio *et al.*, 1989; Finger *et al.*, 1990). In contrast, there are only few reports focusing on the olfactory modulation of trigeminally mediated sensations. Walker and Jennings (1991) reported an increase of nasal irritation thresholds for acetic acid, propionic acid and amyl acetate in anosmics. In addition, Cometto-Muniz and Cain (1995) mentioned preliminary data obtained in anosmics indicating that pungency thresholds were higher compared to healthy controls. Similar findings had already been obtained in experimental animals (Silver *et al.*, 1985; Henton *et al.*, 1969; Walker *et al.*, 1979). On a suprathreshold level, Kobal and co-workers (Kobal and Hummel, 1988; Livermore *et al.*, 1992) demonstrated in normosmics that trigeminal stimuli are perceived as more intense when they were accompanied by olfactory stimulation; specifically, both H_2S and vanillin produced an increase of the perceived intensity of CO_2-stimuli.

Thus, the hypothesis presently tested was as to whether the ongoing activation of the olfactory system leads to an increase of responses to trigeminal stimuli. One way to address this question is to compare responses in normosmic subjects with responses in patients with decreased olfactory sensitivity. As a prerequisite of this investigation the stimulants used must not produce a simultaneous olfactory sensation; to our knowledge only CO_2 meets these criteria (Hummel *et al.*, 1991; Thürauf *et al.*, 1991). To approach

the problem, chemo-somatosensory event-related potentials (CSSERP) were used as an electrophysiological measure of trigeminal activity (Kobal and Hummel, 1989).

Methods, results and conclusions

Chemosensory function in 16 patients with olfactory disorders (hyposmia or anosmia) was compared to 16 healthy controls matched for both sex and age [patients: age 20–64 years (mean 50 years), controls: age 19–68 years (mean 51 years)]. The study was approved by the local ethics committee; it was performed in accordance to the Declaration of Helsinki/Hong Kong.

The patients' olfactory function was assessed by means of a squeeze bottle test which allowed for a lateralized presentation (Kobal *et al.*, 1992). Patients were tested for odor discrimination (eight pairs of odorants) and detection of an odorant (thresholds for phenylethyl alcohol). Using a triple-forced-choice paradigm the subjects had to indicate the bottle which contained an odorant different from the two other presentations. Odor identification was investigated with eight common odors. After presentation the patients were requested to identify each odor by means of a multiple choice of graphical symbols. All tests were performed for the left nostril. Individual results of the three subjective tests were collapsed to a single mean score (Cain and Rabin 1989). Groups of healthy subjects and patients with olfactory disturbances were built according to both their history (see Table 1 for patients' characteristics) and their performance in the subjective tests (controls had a score >4).

For trigeminal stimulation CO_2 was used (15 stimuli of 52% v/v, duration 200 ms, stimulus rise time ≤20 ms, interstimulus interval 30–40 s). It is regarded to specifically activate trigeminal fibers (Kobal *et al.*, 1989; Hummel *et al.*, 1991; Thürauf *et al.*, 1991). An olfactometer was employed which delivered CO_2 without altering mechanical or thermal conditions at the stimulated mucosa (Kobal, 1985; Kobal and Hummel, 1988). This monomodal chemical stimulation is achieved by mixing pulses of the stimulants in a constantly flowing air stream (140 ml/s) with controlled temperature (36.5°C) and humidity (80% RH). The air-stream was led into the nasal cavity by way of a teflon tubing (6 cm length, 3 mm inner diameter). Subjects were comfortably seated in an air-conditioned room. White noise of approximately 50 dB SPL (ERA stimulator, Tönnies) prevented them from hearing the switching process. Stimuli were applied non-synchronously to breathing. EEG (bandpass 0.2–30 Hz; sampling frequency 250 Hz; segments of 2048 ms duration) was recorded from position Cz referenced to linked earlobes; this position was chosen since the signal-to-noise ratio for CSSERPs is greatest at this particular site (Hummel *et al.*, 1992; Livermore *et al.*, 1992). Blink artifacts were registered from Fp2 (10/20 classification). Averaging yielded late nearfield event-related potentials. The peak-to-peak amplitudes P1N1 and N1P2, and the latencies of P1, N1 and P2 were measured (Kobal and Hummel, 1988). Differences between the two groups of patients were analysed by means of *t*-tests (program SPSS/PC+).

Table 1 Characteristics of patients with olfactory disturbances

Sex	Age	Score	History
Female	21	3.1	Unknown
Female	54	1.0	Trauma
Female	56	0.5	Trauma
Female	64	0.0	Whiplash injury
Female	51	1.3	Influenza
Female	54	2.3	Influenza
Female	56	1.7	Trauma
Female	56	3.3	Influenza
Male	20	1.5	Whiplash injury
Male	30	0.0	Trauma
Male	55	1.2	Exposition to solvents
Male	63	0.4	Unknown
Male	38	2.0	Trauma
Male	59	3.7	Exposition to pesticides
Male	60	1.7	Unknown
Male	63	4.0	Trauma

Healthy subjects exhibited larger mean amplitudes compared to patients with a decreased olfactory sensitivity (Figure 1; Table 2). This became significant for amplitude P1N1 ($t = 2.22$, $P < 0.05$). No significant effect was found for peak latencies. These results indicate that a loss of olfactory sensibility is accompanied by a simultaneous decrease of trigeminal chemosensitivity. Although the patients' mean CSSERP amplitudes were generally smaller compared to healthy controls, it is interesting to note that the significant difference between the two groups appeared for the earlier amplitude P1N1. This indicates that the interaction between the olfactory and trigeminal systems is predominantly aimed towards the processing of exogenous stimulus characteristics such as stimulus intensity. This hypothesis is derived from experiments where early ERP components were shown to reflect the processing of exogen-

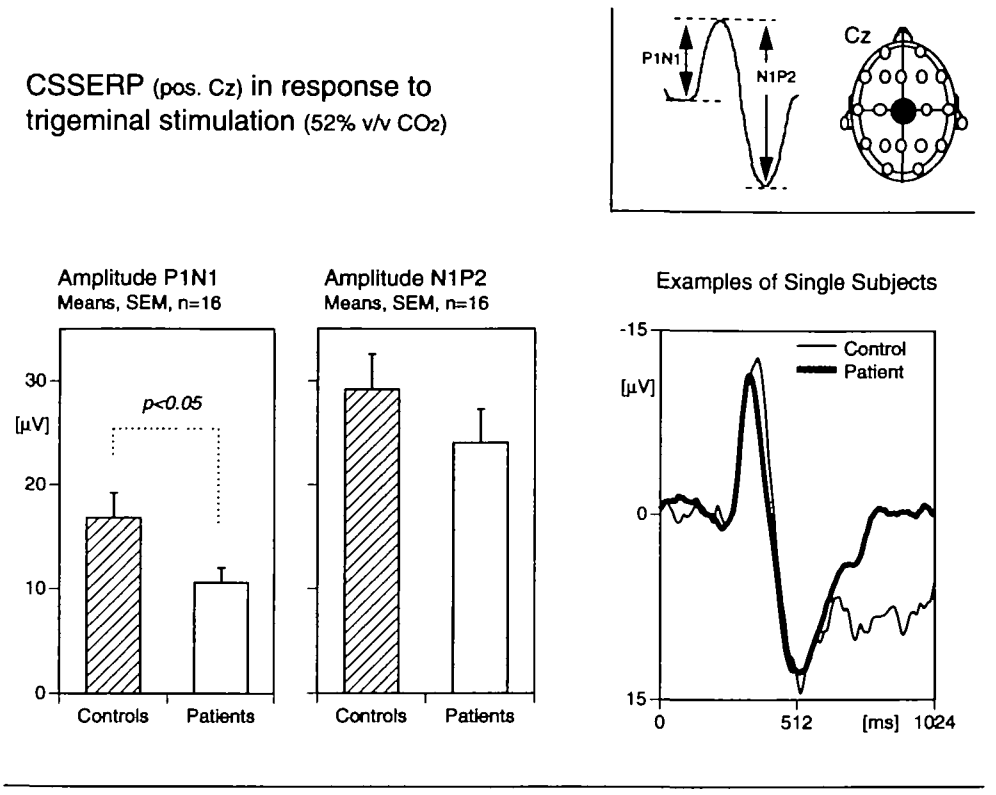

Figure 1 Means and standard errors of CSSERP amplitudes P1N1 and N1P2 (n = 16) obtained in controls and patients (recording position Cz; 52% v/v CO_2). Amplitudes recorded in patients with decreased olfactory sensitivity were significantly smaller compared to healthy controls ($P < 0.05$) To the right responses of two representative subjects are presented (control: 51 years, male; patient: 55 years, male). The insert illustrates both the CSSERP's peak-to-peak amplitudes and the location of the recording position Cz.

Table 2 Chemosomatosensory event-related potentials (pos Cz, 52% v/v CO_2)

	A-P1N1		A-N1P2		A-P2		T-N1		T-P2	
Stimulus	M	*SEM*	M	*SEM*	M	*SEM*	M	*SEM*	M	*SEM*
Controls	16.8	2.4	29.2	3.4	298	13	380	12	560	18
Patients	10.6	1.4	24.1	3.2	299	21	376	21	554	26

Means [M], standard errors of means [SEM], n = 16; A-P1N1, A-N1P2: peak-to-peak amplitudes P1N1 and N1P2; T-P1, T-N1, T-P2: latencies of peaks P1, N1, and P2; (see Figure 1 for definition of CSSERP peaks).

ous stimulus characteristics as opposed to later ERP components (Hummel *et al.*, 1992; Livermore *et al.*, 1992).

Based on work in experimental animals it may be hypothesized that these interactions take place in the thalamus (e.g. rat: mediodorsal nucleus) where convergence between olfactory and trigeminal afferents occurs. Inokuchi *et al.* (1993) showed that single neuronal responses following odorant stimulation were enhanced after trigeminal afferent activity was blocked with a local anesthetic. However, aside from higher order CNS sites (Stone, 1969) interactions might also take place at the mucosa. Analogous to the concept that olfactory responses might be modified by an axon reflex of trigeminal afferents lying in the olfactory epithelium (Bouvet *et al.*, 1987; Finger *et al.*, 1990; Livermore *et al.*, 1993) it should also be considered that olfactory afferent activity may influence trigeminal input via neurosecretory changes. Given that the olfactory epithelium appears to cover a larger part of the nasal cavity than previously thought

(Knecht *et al.*, 1995) these hypothetical effects merit further investigation by measures such as the electro-olfactogram (Hummel and Kobal, 1995). On a cortical level interactions between the two chemosensory systems may be assessed with magnetic source imaging techniques (Huttunen *et al.*, 1986; Kobal *et al.*, 1993; Kettenmann *et al.*, 1995) which allow the evaluation of the CSSERP's cortical generators.

In the light of the present data, studies performed on gender differences in the perception of trigeminal stimuli may have to be reanalysed. Specifically, the results of Becker *et al.* (1993) indicated that women perceive trigeminal stimuli more strongly than men. However, since female subjects perceived olfactory stimuli also to be stronger compared to male subjects, the observed differences after trigeminal stimulation may rather be interpreted as an epiphenomenon of gender-related differences regarding the chemical senses. Another consequence of the interaction between the olfactory and the trigeminal nerves relates to the diagnostics of smell disorders where an evaluation of trigeminal responses should be included as they are an integral part of odor perception.

Taken together, the present study is the first to indicate on an electrophysiological basis that a loss of olfactory sensibility in humans produces a decrease of the perception of trigeminal stimuli. However, since the possibility remains that a trauma itself produces a decrease of CSSERP amplitudes due to local demyelination, fibrosis etc., it might be instructive to compare the results from this paper with CSSERPs recorded in head-injured normosmics. Beyond that aspect, future studies will additionally have to focus on the localization of the site where this hypothetical interaction takes place. It will be interesting to see whether concomittant olfactory stimulation modifies trigeminal input from cutaneous (Livermore *et al.*, 1993) or ocular sites (Cometto-Muniz and Cain, 1995) in a similar manner as the naso-trigeminal input is influenced.

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