Rhinological reactions in persons with self-reported chemical sensitivity (SCS)

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ABSTRACT

In persons reporting chemical sensitivity (sCS), investigations about nasal function and biomediators in nasal secretion under controlled exposures are rare. Therefore, anterior rhinomanometry and acoustic rhinometry was applied in 12 sCS and 12 controls before and after exposures to ethylbenzene and 2-butanone in four sessions close to the current German TLVs and near odour thresholds. Concentrations of eosinophil cationic protein (ECP), myeloperoxidase (MPO), interleukin (IL-)1β, substance P (SP), and neurokinin A (NKA) were measured in nasal secretion after exposures. Regardless of substance and dose the flow-values in anterior rhinomanometry significantly decreased across the session exclusively in the sCS group. A corresponding result could not be observed in the acoustic rhinograms. The biomediator concentrations were not affected by the exposures. The rhinomanometric result suggests general somatic reactions to the exposure in the sCS subjects. Further examinations need to be performed to confirm the results and clarify underlaying pathomechanisms in sCS persons.

INDEX TERMS

Biomarker; Chemical sensitivity; Nasal mucosa; Solvent

INTRODUCTION

Tight buildings and sick building syndrome (SBS) may be possible causes of multiple chemical sensitivity (MCS) (Ashford and Miller, 1991; Welch and Sokas, 1992). Both environmental syndromes show similar symptom complexes (Montgomery and Reasor, 1993). Since the symptoms of MCS are triggered by very low concentrations of chemicals, with respect to olfactory thresholds, the intranasal chemoreceptive sense might be involved in the pathophysiology of MCS. Nasal pathology may be a prominent feature of MCS (Meggs and Cleveland, 1993).

Based on these suggestions, the present study follows the hypothesis that nasal function may be (more) affected by chemical irritants in chemically sensitive persons than in not sensitive persons. Therefore, the aim of this study was to examine nasal function dependent on a controlled chemical exposure in chemically sensitive persons and controls.

For objectifying and quantifying of nasal reactions anterior active rhinomanometry (measurement of pressure-flow relation in the nasal airways) and acoustic rhinometry (calculation of cross-sectional areas of the upper airways using an acoustic signal) were used. Additionally, the concentrations of the cellular mediators eosinophil cationic protein (ECP), myeloperoxidase (MPO), and interleukin 1β (IL-1β) as well as the neurotransmitters substance P (SP) and neurokinin A (NKA) in the nasal secretion were examined to cover the spectrum of neurogenic as well as antigen-driven, immune-mediated inflammation (Bachert *et al*., 1999, 2001). For the generation of controlled exposure ethylbenzene (EB) and methyl

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ethyl ketone (MEK, 2-butanone) were used as solvents to vary the irritative potency. MEK is suspected to be more potent than EB (Cometto-Muñiz and Cain, 1993, 1995).

METHODS

Subjects

A random sample of 122 male students was investigated with a standardized questionnaire composed of 67 items about chemical and general environmental sensitivity (Kiesswetter *et al*., 1997) to select 15 students reporting chemical sensitivity (sCS) and 15 controls. sCS was defined by confirming at least one out of eight questions describing strong physical responses to environmental chemicals with a rating ≥4 on a six-point rating scale. After exclusion of subjects with asthma, allergic rhinitis or chronic diseases, 24 healthy male students (mean age 26.04 ± 4.58 years), 12 sCS and 12 age-matched controls, voluntarily participated in the study. None of the subjects reported any type of olfactory impairment. All subjects responded adequately to olfactory event-related potentials to H_2S and chemosensory event-related potentials to CO_2 (Kobal and Hummel, 1994). The study protocol was approved by the ethic committee of the Institute of Occupational Physiology at the University of Dortmund, Germany. All participants gave written informed consent.

Exposure

The experiments were carried out in an exposure laboratory (spatial dimensions 4.80 × 2.65 × 2.27 m (ca. 29 m^3)) at the Institute of Occupational Physiology at the University of Dortmund, Germany. Inside the laboratory, four PC workplaces were located separated by three vertical boards, which were equipped with a computer monitor and various response panels for symptom rating and neurobehavioral tests. During exposure, air exchange rate was ca. 250 m^3/h, average relative humidity in the laboratory ca. 40% and mean temperature ca. 25°C. Subjects were exposed for 4 h to low and high concentrations of EB and MEK. According to the German regulation for short-term exposures (DFG, 1999), distinct peaks with concentrations twice the German TLV (EB: 200 ppm; MEK: 400 ppm) were combined during the session with low levels near the odour threshold (EB: 10.3 ± 1 ppm; MEK: 9.6 ± 0.5 ppm). Integration of the concentration data yielded mean exposure levels of 98.3 ± 71.8 ppm for EB and 188.6 ± 150.1 ppm for MEK. Thus, the time-weight average concentrations did not exceed the exposure limits of EB (100 ppm) and MEK (200 ppm).

Anterior Active Rhinomanometry and Acoustic Rhinometry

For anterior active rhinomanometry, the computer-based system from Atmos Inc., Lenzkirch, Germany, was used. The data were checked by the so-called CAR (computer aided rhinomanometry) from Bachert and Feldmeth (1988).

Acoustic rhinograms were recorded by the PC-based Eccovision (Model AR-1003) from E. Benson Hood Laboratories Inc., Pembroke, MA, USA (Seaver *et al*., 1995) with a standardized application method (Wiesmüller *et al.*, 2000).

In a separate room, both measurements (acoustic rhinometry always before anterior active rhinomanometry) were applied twice in all subjects and in each session: (i) after a 30-min acclimatization period before the exposure session in the laboratory (pre-exposure) and (ii) immediately after the exposure session in the laboratory (post-exposure).

Biomediators in Nasal Secretion

Thirty minutes after the exposure session, a pre-weighted paper disc was applied to nasal septum-mucosa during rhinoscopy for exactly 60 s. This procedure was repeated twice and performed in each nasal cavity. Afterwards, the disc was weighed and 4 ml physiological NaCl solution was added, samples were stored for 2 h at –20°C. Then the discs were pressed

in the solution using a plastic pipette head. After centrifugation (4000 rpm, 5 min) the liquid was divided into 250 µl portions over 12 Eppendorf® caps and stored at –80ºC. MPO and IL-1β were measured in duplicate using commercial ELISA kits (R&D, Minneapolis, MN, USA), ECP by the CAP system (Pharmacia, Uppsala, Sweden), NKA and SP by RIA (Peninsula Laboratories, Belmont, CA, USA). Measurements were recalculated based on secretion weights per samples.

Statistical Analysis

For anterior rhinomanometry, the flow-value of inspiration at 150 pa from both nasal cavities was taken (FLOW). For acoustic rhinometry, three parameters from the measurements were extracted: (1) volume of the nose between 0 and 8 cm from nose tip (VOL_{08}), (2) minimal cross-sectional area (MCA) between 1.6 and 2.84 cm from nose-tip (MCA_1), where the nasal valve is located, and (3) MCA between 3.5 and 6.5 cm from nose-tip (MCA_2), where the inferior turbinate is expected. Repeated measures ANOVA with between-subject factors was used to test the effects on the before mentioned target parameters for the different factor combinations (SAS, 1994). Type of solvents and exposure levels were investigated as within-subject factors, whereas sensitivity group and daytime are between-subject factors. In case of the biomarkers, difference scores for the baseline-corrected ratings and percentage changes (Δ%) were calculated. For comparison, a possible interaction of the within-subject factor exposure levels and the between-subject factor sensitivity group Mann–Whitney *U*-test was used (SPSS, 1999). In all cases, significance levels were set at $\alpha \leq 0.05$.

RESULTS

Table 1 shows that the only significant difference for the target parameters FLOW, VOL_{08}, MCA_1, and MCA_2 was observed for the between-subject factor 'group' (df = 1, *F*-value = 4.72, *p*-value = 0.042). The sMCS group showed a decrease of the flow-values (FLOW) in anterior rhinomanometry compared to a slight increase in the control group. The baseline flow-values in both groups showed no significant difference (sCS group: adjusted mean, 764.72 ml/s and 95% confidence interval, 699.38–830.07 ml/s; control group: adjusted mean, 716.05 ml/s and 95% confidence interval, 649.16–782.95 ml/s).

Table 1 Means of relative differences of rhinomanometric target parameter FLOW and rhinometric target parameters VOL_{08}, MCA_1, and MCA_2 and variance analysis results (df = 1, *F*-value = 4.72, *p*-value = 0.042)* for between-subject (group, daytime) and within-subject (solvent, level) factors, each adjusted for the other factors (for abbreviations, see Methods)

Factors	Subfactors	Target parameters (%)			
		FLOW	VOL_{08}	MCA_1	MCA_2
Group	SCS	–12.93*	–0.78	4.07	6.81
	Control	5.74*	–0.90	4.64	4.88
Daytime	Morning	–6.53	–2.86	3.47	4.90
	Afternoon	–0.11	1.41	5.31	6.64
Solvent	Ethylbenzene	–4.66	–0.38	5.98	6.10
	2-Butanone	–2.30	–1.30	3.10	5.49
Level	Low	–1.55	–2.05	–0.95	–2.77
	High	–5.31	0.28	9.58	14.08

For NKA only 25% of the samples exceeded the detection level. A frequency analysis of these NKA values yielded comparable proportions for the different exposure conditions. The explorative analysis of the ECP data showed that 27% of the samples were below detection level (BDL). A frequency analysis of these BDL-values yielded comparable proportions for the different exposure conditions. Regarding inter-individual differences sCS-subjects showed

a higher proportion of BDL-values (50% < BDL) than the controls (12.5% < BDL). To ensure that this parameter could be analysed BDL-values were substituted by 1.99 μg/l.

The concentrations of ECP, MPO, IL-1β, and SP were not systematically influenced by the exposure conditions. The group differences of the percentage changes (Δ%) of the high-exposure condition compared to the low exposure condition for EB and MEK are given in Table 2. With the exception of ECP after EB, exposure the percentage changes for all values of the sCS group were numerically greater than those of the control subjects. However, none of these differences reached the level of statistical significance.

Table 2 Medians of the percentage changes of the examined biomediators and Mann–Whitney *U*-test results (for abbreviations, see Methods)

Biomediator	Solvent	Median of Δ%[a]		*p*-Values (*U*-tests)
		Controls	sCS	
ECP	EB	0.0[b]	–51.5	0.114
	MEK	–40.0	12.7	0.130
MPO	EB	–5.2	16.8	0.923
	MEK	–46.8	31.3	0.284
IL-1β	EB	6.4	8.9	0.722
	MEK	–36.0	62.5	0.182
SP	EB	–14.1	-3.2	0.761
	MEK	–34.9	-4.2	0.091

[a]Compared to low condition; [b]negative values = higher concentrations during low exposure condition, and positive values = higher concentrations during high exposure condition.

DISCUSSION

Studies on objective measurements of nasal function under controlled exposures to solvents showed different results: Koren *et al.* (1992) demonstrated an increase of neutrophils in nasal lavage in 14 healthy subjects after exposure to 25 mg/m^3 of Mølhave's VOC mixture (Mølhave and Moller, 1979). Lundqvist *et al.* (1992) could not show any significant reaction in anterior rhinomanometry and acoustic rhinometry in seven healthy persons under exposures to diethylamine. Mølhave *et al.* (1993) could not show any significant reaction in 10 healthy subjects in acoustic rhinometry during exposures to Mølhave's VOC mixture and different air temperatures. Doty *et al.* (1988) observed in 18 MCS affected persons (12 women, 6 men, average age 46.1 years) regardless of exposure to phenyl ethyl alcohol (PEA) and MEK a significant higher total nasal resistance on in- and exhalation than in 18 matched controls before and after the exposure sessions. Exposure to olfactory threshold levels of MEK resulted in significantly increased nasal resistance in the MCS and control group. Following exposure to PEA, only females with MCS showed a decrease of nasal resistance.

That we could not observe exposure-dependent reactions in anterior rhinomanometry and acoustic rhinometry in the healthy controls might be due to (1) a weak sensitivity of the mucous membranes to the exposed substances, (2) a too short exposure duration, (3) missing measurements during the exposure, (4) a too short follow-up after exposure, and/or (5) overlay of dose-dependent effects of the individual nasal cycle. But probably also the limited irritative potency of the substances combined with their limited concentration in the inhaled room air provided the results described.

Reasons for the differences between the results of Doty *et al.* (1988) and our observations may be that our self-reported MCS group was not highly intolerant and comparable to a population-based than a clinically representative sample for MCS.

The decrease of nasal flow only in the sCS group regardless of substance and dose suggest a somatic reaction which may be explained by an increased density of c-fibre neurons in nasal

mucosa, a damaged mucosa barrier between airway and nerve fibres, an increased production of neuropeptides and prostanoids or an increased, respectively, augmented inflammation (Meggs, 1999; Sanico *et al.*, 2000). Other explanations may be a neural sensitization (Bell *et al.*, 1999), conditioning (Siegel and Kreutzer, 1997) or interactions of both and habituation (Bell *et al.*, 1999). Regarding the discussed MCS concepts, a dose–response relationship was not expected.

That a corresponding result to the rhinomanometric measurements could not be observed in the acoustic rhinograms demonstrates that the anterior rhinomanometry with the algorithm CAR is more sensitive for exposure dependent nasal function disturbances than acoustic rhinometry what may be due to diverse methodical difficulties (for details, see Wiesmüller *et al.*, 2000).

That the concentrations of the investigated biomediators were not affected by the investigated exposures can be explained by strong intrapersonal variations (Steerenberg *et al.*, 1996). Therefore, further studies should employ pre-exposure measurements. Probably, the irritating and odorous potential of both substances may lay closer together than assumed in the literature (Cometto-Muñiz and Cain, 1993, 1995). Also the selection of sensitive biomarkers must be taken into account. Exposure duration and the postulated irritant potency of the substances might be insufficient to trigger inflammatory processes in the nasal mucosa.

CONCLUSION AND IMPLICATIONS

The results must be confirmed, other chemicals investigated, and pathophysiological examinations carried out to get explanations for the observations in our study. Nevertheless, in contrast to the recommendations of Light and Bessa (1999), chemical sensitivity should be considered for healthy buildings as suggested by Nakai *et al*. (2002).

ACKNOWLEDGEMENTS

The authors thank the participants in the study, Wobbeke Weistenhöfer, Peter Jedrusik, and Peter Demes for the medical monitoring, as well as Nicola Schmidt, Dieter Giller, Christian Lippmann, Beate Aust, and Torsten Meyer for technical assistance. Funding: German Research Council (Deutsche Forschungsgemeinschaft (DFG)), grant number SE535-5-1.

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