Chemical Senses Vol.19 no.4 pp.359–364, 1994

SHORT COMMUNICATION

Functional imaging of effects of fragrances on the human brain after prolonged inhalation

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Abstract. Beside olfactory or trigeminal stimulation of chemosensory receptor-cells some results in published literature suggest that fragrances show a direct affect on the brain. The effect of the fragrance 1,8-cineol, which was described in literature as 'stimulating', on regional and global cerebral blood flow (rCBF and gCBF) in the human brain after prolonged inhalation was investigated. The results show an increase of global-CBF without preference to primary or secondary olfactory centres after an inhalation-time of 20 min.

Introduction

The olfactory and trigeminal stimulating effects of fragrances were described in several studies. Alteration of the behavioural aspect of mice, namely locomotor activity, was demonstrated after inhalation of lavender oil, rosemary oil and 1,8-cineol (Kovar *et al.*, 1987; Ammon, 1989; Buchbauer *et al.*, 1993a,b). An increase of locomotor activity was also observed in mice after oral administration of rosemary oil and its main component, 1,8-cineol, with a positive correlation to blood-level (Kovar *et al.*, 1987). This suggests at least a partial direct pharmacological action of 1,8-cineol in mice. Studies with Contingent Negative Variation (CNV) (Walter *et al.*, 1964) also show a stimulative effect of rosemary oil in humans (Kubota *et al.*, 1992). The regional and global functional alterations in the brain caused by olfaction or pharmacological actions are not exactly known yet. One indirect parameter for measurement of brain-function is regional cerebral blood-flow (= rCBF). Using positron emission tomography (PET) for their studies Sugano (1989, 1992) reported odour effects on rCBF and Zatorre *et al.* (1992) found a significant increase of rCBF during short-time inhalation of fragrances in primary olfactory centers (Benninghoff, 1985). Following on from these studies it was decided to examine changes of rCBF in humans after prolonged inhalation of 1,8-cineol.

Material and methods

In total eight neurologically healthy subjects aged between 20 and 30 years were examined. In addition, one clinically tested (with olfactory and trigeminal substances) anosmic person joined in the study. Regional cerebral blood flow (= rCBF) was measured with stable Xe-enhanced computed tomography (= XeCT), a three-dimensional, high-resolution rCBF-measurement-method for clinical routine, which

Table I. Regions for specific evaluation and comparison

Primary olfaction	Olfaction associated	Mainly other function than olfaction
Fronto-basal (cortex piriformis) Temporo-medio-basal (cortex piriformis)	Thalamus	Latero-frontal Parietal cortical (exclusively brodman area 1 and 2) Occipital Nucleus lentiformis

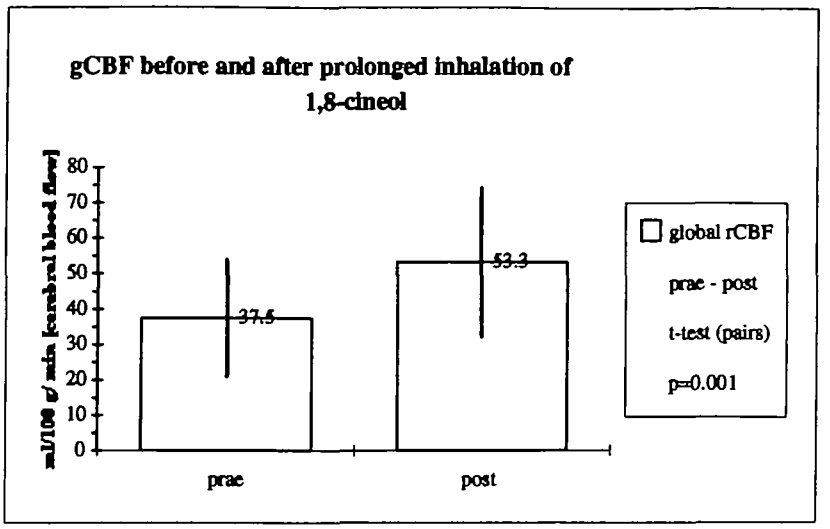
Reference: Benninghoff, 1985.

allows direct analysis of regional blood flow within investigated brain-structures (Gur *et al.*, 1992; Kety and Schmidt, 1948; Tomita and Gotoh, 1981; Yonas *et al.*, 1984a,b, 1991). All measurements were performed on a spiral-CT-scanner (Somatom PLUS, Siemens, Erlangen). The matrix-resolution of XeCT was 256 × 256 voxels. During the examination stable Xenon-gas was inhaled through a closed breathing-circuit in a concentration of 30%. The Xe-gas is a freely diffusible contrast medium for CT-measurement. The rest of the gas-mixture contained 50% oxygen and approximately 19% nitrogen from the normal air. An optimized wash in/out protocol of 3/4 min (= total inhalation-time of Xe-gas-mixture: 7 min) was used for rCBF-calculations (Bidabe *et al.*, 1990; Sadao *et al.*, 1992; Shigeki *et al.*, 1992). Four slices with 8 mm thickness in axial CT-angulation were evaluated simultaneously. The images showed frontal, temporal, occipital and parietal lobe, the basal-ganglia-region and the thalami, and allowed rCBF-analysis within each of these regions. Frontobasal regions seem to be primarily involved in olfaction and parts of the thalami secondarily (Benninghoff, 1985; Zatorre *et al.*, 1992). The other analysed regions should contribute preferentially to other cerebral performances (Table I). Additionally, the global cerebral blood flow was estimated. Two series were performed: one before and another one after inhalation of 1,8-cineol (99%, Aldrich-Chemie, Germany) over a period of 20–25 min to guarantee adequate time for uptake of the substance (Ammon, 1989; Kovar *et al.*; 1987). During the inhalation-period and the second examination the air was passed over 2 ml of 1,8-cineol which was introduced into the breathing circuit.

Results

For statistical analysis the software-package of SPSS 4.0 was used. In a first step the global CBF before and after inhalation of 1,8-cineol in eight subjects was investigated showing a significant increase of g-CBF after inhalation of the fragrance (*t*-test,[dependent pairs], $P = 0.001$, Table II and Fig. 1). (This could not be demonstrated in follow-up-examinations, performed for standardization of our method with an equal protocol, but without any fragrance.) An additional experiment with an anosmic person also showed increase of global CBF (Fig. 2). In a second step the characteristics of regional CBF values within defined regions (see Table I) were analysed. No statistically provable preference for one of the analysed regions after prolonged inhalation could be found (ANOVA n.s. between regions).

Table II. Global increase of rCBF-values after prolonged inhalation of 1,8-cineol



Discussion

Testing a hypothesis of direct influence of a fragrance on human CNS is difficult, mainly because of limited abilities to separate stimulations of olfactory and trigeminal sensations from possible direct effects. However, an uptake of essential oils into blood in measureable concentrations was shown under various application-conditions, even when the respiratory tract was bypassed (e.g. application as a massageoil-component) in humans (Jäger *et al.*, 1992). In the study presented here activity in human brain before and after application of 1,8-cineol was estimated indirectly by rCBF-measurement. The fragrance was inhaled for approximately 23 min between two rCBF-examinations to guarantee positive blood-concentration of the fragrance during the second rCBF-series. Olfaction should lead to an activation of olfactory centers (Zatorre *et al.*, 1992). The results of our study show a significant global increase of CBF after prolonged inhalation without preference to specific or unspecific regions. This could indicate an unspecific, but direct effect of 1,8-cineol, where in connection with data about uptake of this fragrance after inhalation with appearance of positive blood-levels (Kovar *et al.*, 1987) a transport to the central nervous system via blood could become a conceivable hypothesis. A current study of our group with close blood-level control during prolonged inhalation of different fragrances aims to clarify this point.

The results with an anosmic person who also underwent this examination were interesting. This subject showed the same rCBF-reactions as the other ones although she proved to be a total anosmic in clinical tests (anosmia especially for 1,8-cineol was also tested). Although this single case should not be overestimated the similarity of rCBF-findings with the tested collective in this study is obvious. However, the current results are one of the first steps in analysing direct interactions of fragrances with the human brain, but since the data of this study is in good concordance with findings of

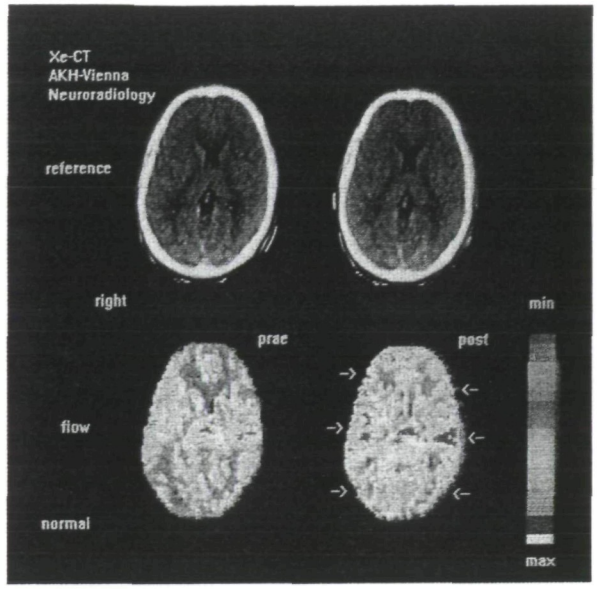


Fig. 1. Normal subject: the two images in the upper row, called reference, show the direct morphological correlate in nativ-CT to the XeCT-rCBF-flow-maps below. Comparison of the reference-images demonstrates measurement within the same slice before and after inhalation. Both left images show the anatomical and functional situation before prolonged inhalation of 1,8-cineol. On the post-inhalation scans (right images) global increase of rCBF-values is seen (expansion of yellow and red-coded flow areas).

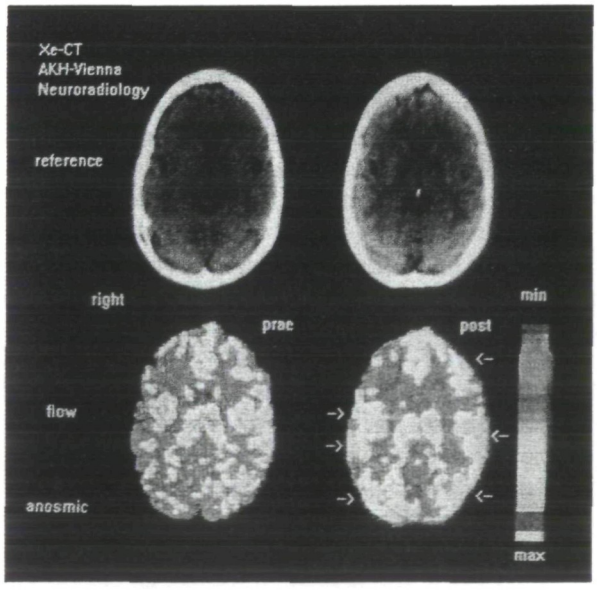


Fig. 2. The flow-pattern of an anosmic person shows the same global increase of rCBF-values after prolonged inhalation of 1,8-cineol as the subjects in the tested group in this study (widening of yellow- and red-coded flow areas in the post-inhalation-flow-map right and below).

other experiments (e.g. Jäger *et al.*, 1992; Našel *et al.*, 1993), the possibility of direct 'pharmacological'-like effects of fragrances, as 1,8-cineol in this study, could be a conceivable hypothesis and worth further examination.

Acknowledgements

This work was supported by grants from the Bürgermeister-fund of the City of Vienna. Also we owe thanks to the Dragoco Comp., Vienna-Liesing, for their interest in our work.

References

Ammon,H.P.T. (1989) Phytotherapeutika in der Kneipp-Therapie. *Therapiewoche*, **39**, 117–127.

Benninghoff,A. (1985) Anatomie-Makroskopische und mikroskopische Anatomie des Menschen. In: Fleischhauer,K., Staubesand,J. and Zenker,W. (eds) 13/14. edn, vol. 3. Urban & Schwarzenberg, München, pp. 363–390.

Bidabe,A.M., Gense de Beaufort,D., Gin,A.M. and Caille,J.M. (1990) Measurement of cerebral blood flow by the stable Xenon computerized Tomography. *Method J. Neuroradiol.*, **17**, 103–124.

Buchbauer,G., Jirovetz,L., Jäger,W., Plank,Chr. and Dietrich,H. (1993a) Fragrance compounds and essential oils with sedative effects upon inhalation. *J. Pharm. Sci.*, **82**, 660–664.

Buchbauer,G., Jirovetz,L., Czejka,M., Našel,C. and Dietrich,H. (1993b) New results in aromatherapy research paper given at the *24th International Symposium on Essential Oils*, July 21–24, 1993, Berlin.

Gur,D., Good,W., Johnson,D. and Sashin,D. (1992) A comparison of Xe/CT-CBF derived values using simulated and biological measurements. In: *Abstracts of the Second International Conference on Xe/CT-CBF*, Nov. 23–26 1992, Fukuoka Japan, p. 13.

Jäger,W., Buchbauer,G., Jirovetz,L. and Fritzer,M. (1992) Percutaneous absorption of lavender oil from a massage oil. *J. Soc. Cosmet. Chem.*, **43**, 49–54.

Kety,S.S. and Schmidt,C.F. (1948) The nitrous oxide method for quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. *J. Clin. Invest.*, **27**, 476–483.

Kovar,K.A., Gropper,B., Friess,D. and Ammon,H.P.T. (1987) Blood levels of 1,8-cineol and locomotor activity of mice after inhalation and oral administration of rosemary oil. *Planta Med.*, **53**, 315–318.

Kubota,M., Ikemoto,T., Komaki,R. and Imai,M. (1992) Odor and emotion—effects of essential oils on contigent negative variation. In: Woidich,H. and Buchbauer,G. (eds) *Proceedings of the 12th International Congress of Flavours, Fragrances and Essential Oils*. Austrian Association of the Flavour and Fragrance Industry, Vienna, 456–461.

Našel,C., Našel,B., Buchbauer,G., Samec,P., Heimberger,K. and Schindler,E. (1993) Alteration of cerebral blood flow caused by inhalation of fragrances (abstract). *Neuroradiology*, **35**, 50.

Sadao,S., Takeshi,K., Hideki,K., Shigeo,T., Hayao,S. and Nobuo,T. (1992) Adequate rate of Xenon inhalation in the end-tidal gas-sampling method. In: Yonas,H. (ed.) *Cerebral Blood Flow Measurement with Stable Xenon-Enhanced Computed Tomography*, Raven Press, New York.

Shigeki,N., Tetsuo,Y., Shiro,K., Masaaki,H., Teiichi,T. and Haruhide,I. Optimization of the Inhalation Protocol. In Yonas,H. (ed.) *Cerebral Blood Flow Measurement with Stable Xenon-Enhanced Computed Tomography*. Raven Press Ltd., New York.

Sugano,H. (1989) Effects of odor on mental function (abstract). *Chem. Senses*, **14**, 303.

Sugano,H. (1992) Psychophysiological studies of fragrance. In: Van Toller,S.P. and Didd,G. (eds) *Fragrance: the Psychology and Biology of Perfume*. Elsevier Applied Science, London, pp 221–228.

Tomita,M. and Gotoh,F. (1981) Local cerebral blood flow values as estimated with diffusible tracers: validity of assumptions in normal and ischemic tissue. *J. Cereb. Blood Flow and Metab.*, **1**, 403–411.

Walter,W.G., Cooper,R., Aldridge,V.J., McCallum,W.C. and Winter,A.L. (1964) Contingent negative variation: an electric sign of sensorimotor association and expectancy in the human brain. *Nature*, **203**, 380–384.

Yonas,H., Good,W.F., Gur,D., Wolfson,S.K.Jr, Latchaw,R.E., Good,B.C., Leanza,R. and Miller,S.L. (1984a) Mapping cerebral blood flow by xenon-enhanced computed tomography: clinical experience. *Radiology*, **152**, 443–442.

Yonas,H., Wolfson,S.K.,Jr, Gur,D., Latchaw,R.E., Good,W.F., Leanza,R., Jackson,D.L., Janetta,P.J. and Reinmuth,O.M. (1984b) Clinical experience with the use of xenon-enhanced CT blood flow mapping in cerebral vascular disease. *Stroke*, **15**, 443–450.

Yonas,H., Gur,Sc., Johnson,D.W. and Latchaw,R.E. (1991) Xenon/CT cerebral blood flow analysis. In: Latchaw,R.E. (ed.) *MR and CT Imaging of the Head, Neck and Spine* Vol II, 2nd edn. Mosby Year Book, 1991, pp. 109–126.

Zatorre,R.J., Jones-Gotman,M., Evans,A.C. and Meyer,E. (1992) Functional localization and lateralization of human olfactory cortex. *Nature*, **360**, 339–340.

Received on December 9, 1993; accepted on April 13, 1994