Chem. Senses 27: 23–29, 2002

Olfactory Discrimination Ability for Aromatic Odorants as a Function of Oxygen Moiety

Matthias Laska

Department of Medical Psychology, University of Munich Medical School, Goethestraße 31, D-80336 Munich, Germany

Correspondence to be sent to: Matthias Laska, Institut für Medizinische Psychologie, Ludwig-Maximilians-Universität, Goethestraße 31, D-80336 München, Germany. e-mail: laska@imp.med.uni-muenchen.de

Abstract

To assess the significance of the type of oxygen moiety on odor quality of aromatic compounds, I tested the ability of human subjects to distinguish between odorants sharing a benzene ring and the same total number of carbon atoms but differing in their functional groups. Phenyl ethanol, phenyl acetaldehyde, phenyl methyl ketone, methyl benzoate and phenyl acetic acid, were employed. In a forced-choice triangular test procedure 20 subjects were repeatedly presented with all possible binary combinations of the five odorants, and asked to identify the bottle containing the odd stimulus. I found (i) that as a group, the subjects performed significantly above chance level in six of the tasks whereas they failed to do so with the four other tasks; (ii) marked interindividual differences in discrimination performance, ranging from subjects who were able to significantly distinguish between all 10 odor pairs to subjects who failed to do so with the majority of the tasks; and (iii) that odor pairs that involved methyl benzoate or phenyl methyl ketone were significantly easier to discriminate than those that involved phenyl acetaldehyde or phenyl ethanol, and thus there was a clear dependence of discriminability on type of functional group. Additional tests of the degree of trigeminality of the five aromatic substances indicated that the discriminability of the odor pairs is indeed due to differences in odor quality. A comparison of the present results with those of an earlier study that employed aliphatic odorants suggests that functional oxygen-containing groups may generally be an important determinant of the interaction between the stimulus molecule and the olfactory receptor, and thus may generally be a molecular property affecting odor quality in a substance class-specific manner. The poorer discriminatory performance of the subjects with aromatic odorants compared with corresponding aliphatic substances suggests that the structure of the alkyl rest attached to a functional group may also play a crucial role for recognition of ligands at the olfactory receptor and thus for odor quality.

Introduction

The multidimensionality of the chemical world presents a real challenge to the olfactory system of any species. However, most of the animal species investigated so far are capable of perceiving and discriminating between a large variety of odors (Hildebrand and Shepherd, 1997). This raises the question of how the olfactory system achieves this—in some cases amazingly well developed—ability to recognize different odor qualities.

It is now widely agreed that the cascade of events leading to odor recognition begins with differential interaction of odor molecules with different types of olfactory receptors (Malnic *et al*., 1999). It is also widely accepted that both the overall shape and size of an odor molecule as well as the nature and disposition of its functional group(s) play a crucial role in the interaction occurring between stimulus and receptor (Weyerstahl, 1994; Rossiter, 1996).

Although a considerable number of psychophysical studies have tried to reveal, and have generally reported, some correlations between odor quality and molecular properties (Pilgrim and Schutz, 1957; Moskowitz and Barbe, 1977; Dravnieks, 1985; Jeltema and Southwick, 1986; Cain *et al*., 1998), most of these studies have failed to provide quantitatively useful data as they have usually relied on enumerative description and thus have a strong subjective component, have an unproven ability to discern small differences and are indeterminate regarding the extent of individual differences (Wise *et al*., 2000).

Recently, Laska and colleagues have begun to systematically assess odor structure–activity relationships using discrimination procedures which avoid the disadvantages of subjectivity, context dependence and poor resolution, allow for examination of individual differences and yield non-negotiable answers with potential archival value (Laska and Freyer, 1997; Laska and Teubner, 1998, 1999a,b; Laska *et al*., 1999, 2000). With regard to the first structural feature determining the degree of interaction between stimulus and olfactory receptor—overall size and shape of the molecule—they could show a significant negative correlation between

olfactory discrimination performance (and thus odor quality) and structural similarity of odorants in terms of differences in carbon chain length in all major classes of oxygen-containing aliphatic compounds.

With regard to the second structural feature affecting the strength and character of odorants—nature and disposition of functional group(s)—Laska *et al.* (Laska *et al.*, 2000) have recently shown human subjects to have a well-developed ability to discriminate between aliphatic odorants sharing the same number of carbon atoms but differing in their oxygen moieties. Further, they demonstrated that functional groups affected odor quality in a substance class-specific manner.

In an extension of this study I decided to test the ability of human subjects to distinguish between aromatic odorants that are identical in structure except for their oxygen moieties. The aim of this was to help clarify whether the correlation between type of functional group and olfactory discriminability found with aliphatic odorants could also be found with substances sharing a benzene ring rather than a linear and unbranched carbon chain. Further, a comparison of the results of the present study and the earlier one should help to evaluate the impact of the structure of the alkyl rest on discriminability and thus odor quality.

Thus, the aims of the present study are twofold: (i) to provide data on the olfactory discrimination ability of human subjects for aromatic odorants sharing the same number of carbon atoms but differing in their functional groups; and (ii) to assess whether the effect of type of oxygen moiety on discriminability and thus odor quality of aromatic odorants is substance-class specific.

Experiment 1: discriminability of odorants

Materials and methods

Human subjects

A total of 20 healthy, unpaid volunteers (two males and 18 females), 23–39 years of age (median = 28 years), participated in the study. None of the subjects had any history of olfactory dysfunction. They were informed as to the aim of the experiment and provided written consent. The study was performed in accordance with the Declaration of Helsinki/Hong Kong.

Odorants

A set of five odorants was used (Table 1). They comprised aromatic substances sharing the same number of carbon atoms but differing in their oxygen moiety (alcohol, aldehyde, ketone, carboxylic acid and ester, respectively). All substances were obtained from Merck (Darmstadt, Germany) and had a nominal purity of at least 99%. They were diluted using diethyl phthalate (Merck) as the solvent. In an attempt to ensure that the odorants were of approximately equal strength when presented in squeeze bottles, intensity matching was performed by a panel of six subjects using a 8.7 g/l solution of isoamyl acetate as the reference and adopting a standardized psychophysical procedure (ASTM, 1975).

Table 1 Substances and concentrations used (g/l)

No.	Substance	Conc.	Sum formula	Chemical class
1	2-phenyl–1-ethanol	102.0	$C_8H_{10}O$	alcohol
2	phenyl acetaldehyde	10.8	C_8H_8O	aldehyde
3	phenyl methyl ketone	1.0	C_8H_8O	ketone
4	methyl benzoate	10.9	$C_8H_8O_2$	ester
5	phenyl acetic acid	10.0	$C_8H_8O_2$	carboxylic acid

Test procedure

A 20 ml aliquot of each odorant was presented in a 250 ml polyethylene squeeze bottle equipped with a flip-up spout. Subjects were instructed as to the manner of sampling and at the start of the first session were allowed time to familiarize themselves with the bottles and the sampling technique. Care was taken that the flip-up spout was only a short distance (1–2 cm) from the nasal septum during sampling of an odorant in order to allow the stimulus to enter both nostrils.

In a forced-choice triangular test procedure 20 subjects were asked to compare three bottles and identify the one containing the odd stimulus (Lawless and Heymann, 1998). Additionally, after each decision, subjects were asked whether their choice was based predominantly on perceived differences in odor quality or on perceived differences in odor intensity. Each bottle could be sampled twice, with an inter-stimulus interval of 10 s. Sampling duration was restricted to 1 s per presentation in order to minimize adaptation effects. The sequence of presentation of the stimulus pairs was systematically varied between sessions and individual subjects, while taking care that the presentation of a given odorant as the odd or even stimulus was balanced within and between sessions. In order to control for possible cross-adaptation effects, the order in which the stimuli of a given triad were sampled was systematically varied between sessions. Approximately 30 s were allowed between trials and no feedback regarding the correctness of the subjects' choice was given.

Ten different stimulus pairs, i.e. all possible binary combinations of the five odorants, were presented twice per session, and testing was repeated in four more sessions each 1–3 days apart, enabling 10 judgements per stimulus pair and panelist to be collected.

Data analysis

The criterion for an individual subject to be regarded as capable of discriminating a given odor pair was set at seven or more out of 10 decisions correct (two-tailed binomial test, $P < 0.05$). Accordingly, the criterion for the group of

subjects to be regarded as capable of discriminating a given odor pair was set at 13 or more out of 20 subjects performing significantly above chance (two-tailed binomial test, $P < 0.01$).

Comparisons of group performance across tasks were made using the Friedman two-way analysis of variance (ANOVA). When the ANOVA detected differences between tasks, this was then followed by pairwise Wilcoxon signed-rank tests for related samples to evaluate which tasks were involved (Siegel and Castellan, 1988). Frequencies in discrete categories were compared using the χ^2 test. All data are reported as mean ± SD.

Results

General discrimination performance

Figure 1 summarizes the mean performance of 20 subjects in discriminating between the 10 odor pairs. As a group, the human subjects performed significantly above chance level in six of the 10 tasks, whereas they failed to do so with the remaining four tasks. Interindividual variability was high, particularly in odor pairs that more than a few of the panelists were unable to distinguish above chance (cf. SDs in Figure 1). However, the ANOVA detected significant differences in the group's performance between tasks (Friedman, $P < 0.001$) and subsequent pairwise tests revealed that the four odor pairs that were not discriminated above chance at the group level (1–2, 1–5, 2–5 and 3–4; cf. Table 1) were significantly more difficult to distinguish compared with the six odor pairs which the group of subjects were able to discriminate (Wilcoxon, $P < 0.05$ for all pairs). Accordingly, only 1–5 out of 20 subjects failed to significantly distinguish between the latter group of odor pairs, whereas 9–17 out of 20 subjects were unable to discriminate the former group of odor pairs. With only few exceptions (which always involved odor pair 2–3), the odor pairs that were significantly discriminated at the group level did not differ significantly from each other in their degree of discriminability (Wilcoxon, $P > 0.05$). Similarly, with only few exceptions (which always involved odor pair 1–5), the odor pairs that were not significantly discriminated at the group level did not differ significantly from each other in their degree of discriminability (Wilcoxon, $P > 0.05$).

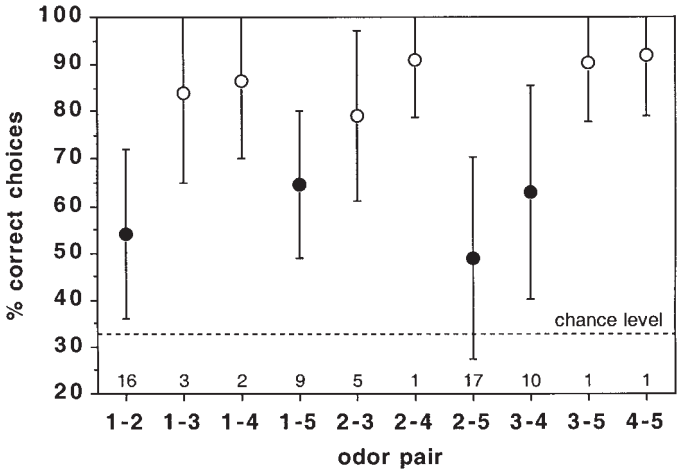

Figure 1 Performance of 20 subjects in discriminating between aromatic odorants with the same number of carbon atoms but different functional groups. Each data point represents the percentage (mean ± SD) of correct choices from 10 decisions per odor pair and subject. The figures above the abscissa indicate the number of subjects that failed to perform above chance in the corresponding task. The names of substances for each odor pair are given in Table 1.

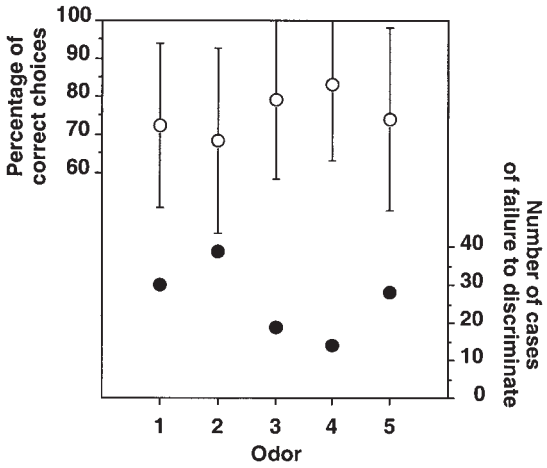

Figure 2 Discriminability of the five aromatic substances. Open symbols represent the percentage (mean ± SD) of correct choices across the four tasks that involved a given odorant. Filled symbols indicate the number of cases in which a given odorant was involved when an odor pair was not significantly discriminated by a subject. The names of substances are given in Table 1.

Discriminability of the individual odorants

Figure 2 illustrates the discriminability of the individual odorants. The number of times that a given odorant was involved when subjects failed to significantly discriminate an odor pair (Figure 2, lower panel) ranged from only 14 with odor no. 4 (methyl benzoate) to 39 with odor no. 2 (phenyl acetaldehyde) and thus differed significantly between stimuli (χ^2, $P < 0.05$). Likewise, the mean scores of correct decisions across the four tasks that involved a given odorant (Figure 2, upper panel) differed significantly between stimuli (Friedman, $P < 0.05$). Subsequent pairwise comparisons revealed that odor no. 4 (methyl benzoate) was more readily discriminated than the four other odorants (Wilcoxon, $P < 0.05$), and that odor no. 3 (phenyl methyl ketone) was more readily discriminated than odors no. 1 (phenyl ethanol) and no. 2 (phenyl acetaldehyde).

Interindividual differences

Interindividual differences in subjects' ability to discriminate between the 10 odor pairs were quite large. The percentage of errors ranged from only 11% for the best-performing subject up to 41% for the worst. Accordingly, the best panelist was able to significantly distinguish all 10

odor pairs whereas the poorest-performing subject failed to do so with six of the 10 tasks.

Training effects

The mean performance of the group of 20 subjects across the five test sessions was quite stable. Error rates did not differ significantly between sessions (Friedman, $P > 0.05$), and thus no training or learning effects at the group level were found.

Odor intensity

With all 10 odor pairs <16% of decisions were reported to be based upon perceived differences in odor intensity rather than odor quality (cf. Test procedure). Altogether, 91.0% of decisions were reported to be based upon perceived differences in odor quality.

None of the statistical comparisons mentioned above led to significantly different results when the decisions reported to be based upon perceived differences in odor intensity rather than odor quality were removed from the data set.

Experiment 2: trigeminality of odorants

The results of experiment 1 showed that the ability of human subjects to discriminate between aromatic substances on the basis of differences in oxygen moiety was substance specific.

In order to elucidate whether the nasal trigeminal system contributed to this performance, I assessed whether the substances differ in their degree of trigeminality by testing subjects' ability to localize the side of monorhinal stimulation. This simple method has been shown adequate to reliably quantify the trigeminal impact of odorants (Berg *et al.*, 2000).

Materials and methods

Subjects

A total of 10 healthy, unpaid volunteers (two males and eight females), 23–39 years of age (median = 27 years), participated in the study. All subjects had already participated in experiment 1. They were chosen on the basis of availability and not on the basis of their performance in the previous experiment.

Odorants

The same set of five odorants as in experiment 1 was used (Table 1). The substances were diluted using diethyl phthalate (Merck) as the solvent to the same concentrations as in experiment 1.

Test procedure

Using a custom-made squeezer, air from two 250 ml polyethylene squeeze bottles was applied to the right and the left nostril of a subject. One bottle contained 40 ml of an odorant whereas the other bottle contained 40 ml of the odorless solvent. Both bottles were equipped with a flip-up spout which for testing was fitted with a handmade Teflon nose-piece. Care was taken that the nose-pieces were in direct contact with the nostrils during sampling in order to ensure that each stimulus entered one nostril only. Presentation of an odorant was synchronized with the subject's inhalation and the squeezer was calibrated to deliver 20 ml of air to each nostril.

In a forced-choice test procedure 10 subjects were asked to identify the side of stimulation with an odorant. The sequence of presenting the stimuli was systematically varied between sessions and individual subjects while taking care that the presentation of a given odorant to the left or the right nostril was balanced within and between sessions. Approximately 30 s were allowed between trials and no feedback regarding the correctness of the subjects' choice was given. The five stimuli were presented five times per session and testing was repeated in three more sessions, each 1–3 days apart, enabling 20 judgements per stimulus and panelist to be collected.

Data analysis

The criterion for an individual subject to be regarded as capable of localizing the side of monorhinal stimulation with a given odorant was set at 14 or more out of 20 decisions correct (two-tailed binomial test, $P < 0.05$). Accordingly, the criterion for the group of subjects to be regarded as capable of localizing a given odorant was set at eight or more out of 10 subjects performing significantly above chance (two-tailed binomial test, $P < 0.05$).

Comparisons of group performance across tasks and sessions were made using the Friedman two-way analysis of variance. When the ANOVA detected differences between tasks or sessions, this was then followed by pairwise Wilcoxon signed-rank tests for related samples to evaluate which tasks or sessions were involved (Siegel and Castellan, 1988). All data are reported as mean ± SD.

Results

General localization performance

Figure 3 summarizes the mean performance of 10 subjects in localizing the side of monorhinal stimulation with phenyl ethanol, phenyl acetaldehyde, phenyl methyl ketone, methyl benzoate and phenyl acetic acid when presented at the same concentrations as in experiment 1. As a group, the human subjects clearly failed to perform significantly above chance in all five tasks, with 8–10 out of 10 individuals not reaching the criterion of at least 14 out of 20 decisions correct. Accordingly, an ANOVA failed to find significant differences in group performance between tasks (Friedman, $P > 0.05$).

Interindividual differences

Interindividual differences in subjects' ability to localize the side of monorhinal stimulation were comparatively small (cf. SDs in Figure 3), and altogether there was only one case of an individual subject scoring 80% correct choices (corresponding to a 1% level of significance) with one of the five

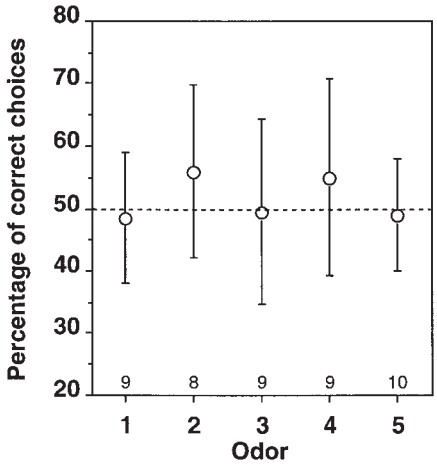

Figure 3 Performance of 10 subjects in correctly localizing the side of monorhinal stimulation. Each data point represents the percentage (mean ± SD) of correct choices from 20 decisions per odor pair and subject. The dashed line indicates the chance level of performance. The figures above the abscissa indicate the number of subjects that failed to perform significantly above chance in the corresponding task.

substances (methyl benzoate). The percentage of overall correct choices ranged from 63% for the best-performing subject to 44%. Even the best panelist was only able to localize two out of five substances at a 5% level of significance, whereas the majority of subjects failed to do so with all five tasks.

Training effects

The mean performance of the group of 10 subjects across the four test sessions was quite stable. Error rates did not differ significantly between sessions (Friedman, $P > 0.05$), and thus no training or learning effects at the group level were found.

Discussion

The results of this study demonstrate that the ability of human subjects to discriminate between aromatic odorants sharing the same number of carbon atoms but differing in their oxygen moieties is (i) clearly dependent on the type of functional group involved; and (ii) poorer than that for corresponding aliphatic substances (Laska *et al*., 2000).

Prior to a discussion of these findings, it seems appropriate to consider whether the performance of the human subjects shown in the present study was indeed based on the ability of the olfactory system to discern between odor qualities, or whether other sensory systems or other talents of the olfactory system may have been involved.

The possibility that the nasal trigeminal system might have contributed to the discrimination of odorants (Doty, 1995) can be excluded for two reasons: firstly, recent psychophysical studies have shown nasal pungency thresholds, mediated by the trigeminal nerve, of human subjects to be generally at least two and up to four orders of magnitude higher than odor thresholds, mediated by the olfactory nerve (Cometto-Muniz and Cain, 1995; Cometto-Muniz *et al*., 1998a,b). Thus, although congenitally anosmic subjects have been shown to possess at least a coarse ability to distinguish between highly concentrated odorants using information provided by their fifth cranial nerve (Laska *et al*., 1997), the dilutions employed here (cf. Table 1) are likely to prevent trigeminal involvement in the discrimination of stimuli. Secondly, the results of experiment 2 clearly demonstrate that the substances used here had little, if any, trigeminal-stimulating properties at the concentrations tested and that in any case the stimuli did not differ in their degree of trigeminality.

Although the possibility that differences in perceived odor intensity might have contributed to the discrimination performance cannot be ruled out completely, this seems quite unlikely as the attempt to present stimuli at equal subjective intensities was confirmed by the fact that in the critical discrimination tasks >90% of the subjects' decisions were reported to be based on perceived differences in odor quality rather than odor intensity (cf. Test procedure). Further, the few instances in which perceived differences in odor intensity were reported seem to mirror a subject's difficulty to discriminate at all, as error rates in such cases tended to be higher than the usually reported differences in odor quality. The same tendency for higher error rates with reports of perceived differences in odor intensity rather than odor quality as a choice criterion has been found in studies assessing the discriminability of members of homologous series of aliphatic compounds (Laska and Freyer, 1997; Laska and Teubner, 1998, 1999b; Laska *et al*., 1999) and of terpenes (Laska and Teubner, 1999a). Therefore, it seems reasonable to assume that the discrimination scores found here reflect the ability of the human olfactory system to distinguish between odor qualities.

The most important finding of the present study is that the ability of human subjects to distinguish between aromatic odorants solely on the basis of oxygen-containing functional groups is clearly substance-class specific. It was apparent that the aromatic ester and ketone were more easily discriminated from the other stimuli than aromatic substances with the same number of carbon atoms but with a functional alcohol or aldehyde group (cf. Figures 1 and 2).

Exactly the same rank order of discriminability as in the present study, ketone ≥ carboxylic acid > alcohol ≥ aldehyde, was found in a recent study that employed the same paradigm with aliphatic (rather than aromatic) odorants sharing the same number of carbon atoms and differing only in their oxygen moiety (Laska *et al*., 2000). Here, too, the odor pair ketone versus carboxylic acid was most readily distinguished, and the odor pairs alcohol versus aldehyde and aldehyde versus carboxylic acid yielded the lowest percentages of correct discriminations. Unfortunately, esters were not included in that study. However, in contrast to the earlier study, in which all odor pairs tested were clearly

discriminable above chance at the group level, the present study showed that several combinations presented considerable difficulties to the subjects and were not discriminated above chance (cf. Figure 1). This suggests that both the oxygen moiety and the molecular structure of the alkyl rest—straight-chained in the case of the aliphatic substances, ring-like in the case of the aromatic substances—affects discriminability and thus odor quality of the stimuli. Recent studies using optical imaging techniques lend support to this supposition as they, too, have reported both molecular structural features mentioned to be important for odor recognition in olfactory systems as diverse as those of mammals (Uchida *et al*., 2000) and insects (Sachse *et al*., 1999) at the level of the first olfactory neuropil, i.e. the olfactory bulb and the antennal lobe, respectively.

Although I cannot rule out completely the possibility that the poor discriminability of the odor pair phenyl acetaldehyde versus phenyl acetic acid may, at least in part, be due to the fact that the former substance is rather unstable in the presence of oxygen and easily converted to the latter substance, this seems unlikely as the subjects' discriminatory performance with this odor pair did not deteriorate across sessions but was poor from the start.

One hypothetical explanation for the corresponding substance class-specificity of discriminability and thus qualitative similarity observed with both aliphatic and aromatic substances is that the presence of certain oxygen moieties, such as an ester or keto group, might lead to more specific interactions with olfactory receptors, and/or that stimulus molecules bearing such functional groups might interact with a smaller subset of receptors compared with stimuli with functional alcohol or aldehyde groups. This idea is supported by electrophysiological findings that show that certain odor molecules interact with a larger number of olfactory receptors than others (Sicard and Holley, 1984). The molecular mechanism possibly underlying this phenomenon is related to differences in the dipole qualities of the oxygen moieties, as keto or carboxylic groups, for example, are stronger dipoles than alcohol groups when attached to the same alkyl radical (Beets, 1982).

One possible means to test this hypothesis is to assess the molecular receptive ranges of identified olfactory receptors for sets of substances that are similar to the one employed here using cellular recording techniques. The recently accomplished cloning, functional expression and characterization of olfactory receptor types in rats (Zhao *et al*., 1998) and humans (Hatt *et al*., 1999) provide the tool with which to perform such studies.

At the level of the olfactory bulb, Katoh *et al.* (Katoh *et al.*, 1993) recorded responses from rabbit single mitral cells following stimulation with a set of aromatic compounds with various substituents and found a clear dependence of response patterns on type of functional group. Although the authors mainly employed non-oxygen-containing substituents, their findings are in line with the present results as they, too, point to a key role for dipole quality of functional groups in the interaction between stimulus and receptor.

The finding of the present study that the olfactory discriminability of aromatic substances on the basis of oxygen moiety was markedly poorer than that for corresponding aliphatic substances (Laska *et al*., 2000) may, at least in part, be explained by the fact that the ring-like structure of aromatic compounds leads to more stable and thus less flexible molecular conformations than the linear backbone of aliphatic compounds. As the interaction of an odor molecule with an olfactory receptor is considered to be a multipoint attachment process (Ohloff, 1994), the higher flexibility of a straight-chained alkyl rest should allow for more options of hydrogen bonding than a stiff, ring-like alkyl rest (Afshar *et al*., 1998). This supposition is supported by theoretical considerations that emphasize the role of both flexibility and overall structure of apolar parts of an odor molecule for the specificity of the directed dipole–dipole interaction or hydrogen bonding underlying the interaction between stimulus and receptor (Yoshii and Hirono, 1996; Chastrette and Rallet, 1998).

Taken together, the findings of the present study provide evidence for a clear dependence of olfactory discriminability of aromatic substances on type of oxygen moiety. In agreement with an earlier study that employed aliphatic substances, the results support the assumption that functional oxygen-containing groups may generally be an important determinant of the interaction between stimulus molecule and olfactory receptor, and therefore may generally be a molecular property affecting odor quality in a substance-class-specific manner. At the same time, a comparison of the results of the two studies shows that the structure of the alkyl rest attached to a functional group may also play a crucial role in the recognition of ligands at the olfactory receptor and thus of odor quality.

Acknowledgements

I thank the panelists for their willingness to participate in this study, and the Deutsche Forschungsgemeinschaft for financial support (La 635/10-1).

References

Afshar, M., Hubbard, R.E. and **Demaille, J.** (1998) *Towards structural models of molecular recognition in olfactory receptors.* Biochimie, 80, 129–135.

ASTM (1975) *Standard recommended practice for referencing suprathreshold odor intensity*. Am. Soc. Testing Materials (Phil.), E, 544–575.

Beets, M.G.J. (1982) *Odor and stimulant structure.* In Theimer, E.T. (ed.), Fragrance Chemistry—The Science of the Sense of Smell. Academic Press, New York, pp. 77–122.

Berg, J., Hummel, T., Huamg, G. and **Doty, R.L.** (2000) *Trigeminal impact of odorants assessed with lateralized stimulation.* Chem. Senses, 25, 793–794.

Cain, W.S., de Wijk, R.A., Lulejian, C., Schiet, C. and **See, L.C.** (1998)

Odor identification: perceptual and semantic dimensions. Chem. Senses, 23, 309–326.

Chastrette, M. and **Rallet, E.** (1998) *Structure–minty odour relationships: suggestion of an interaction pattern.* Flavor Fragr. J., 13, 5–18.

Cometto-Muniz, J.E. and **Cain, W.S.** (1995) *Relative sensitivity of the ocular trigeminal, nasal trigeminal and olfactory systems to airborne chemicals*. Chem. Senses, 20, 191–198.

Cometto-Muniz, J.E., Cain, W.S. and **Abraham, M.H.** (1998a) *Nasal pungency and odor of homologous aldehydes and carboxylic acids.* Exp. Brain Res., 118, 180–188.

Cometto-Muniz, J.E., Cain, W.S., Abraham, M.H. and **Kumarsingh, R.** (1998b) *Trigeminal and olfactory chemosensory impact of selected terpenes.* Pharmacol. Biochem. Behav., 60, 765–770.

Doty, R.L. (1995) *Intranasal trigeminal chemoperception.* In Doty, R.L. (ed.), Handbook of Olfaction and Gustation. Marcel Dekker, New York, pp. 821–833.

Dravnieks, A. (1985) Atlas of Odor Character Profiles. American Society for Testing and Materials, Philadelphia, PA, Data Series 61.

Hatt, H., Gisselmann, G. and **Wetzel, C.** (1999) *Cloning, functional expression and characterization of a human olfactory receptor.* Cell. Mol. Biol., 45, 285–291.

Hildebrand, J.G. and **Shepherd, G.M.** (1997) *Mechanisms of olfactory discrimination: converging evidence for common principles across phyla*. Annu. Rev. Neurosci., 20, 595–631.

Jeltema, M.A. and **Southwick, E.W.** (1986) *Evaluation and applications of odor profiling*. J. Sens. Stud., 1, 123–136.

Katoh, K., Koshimoto, H., Tani, A. and **Mori, K.** (1993) *Coding of odor molecules by mitral/tufted cells in rabbit olfactory bulb. II. Aromatic compounds.* J. Neurophysiol., 70, 2161–2175.

Laska, M. and **Freyer, D.** (1997) *Olfactory discrimination ability for aliphatic esters in squirrel monkeys and humans*. Chem. Senses, 22, 457–465.

Laska, M. and **Teubner, P.** (1998) *Odor structure–activity relationships of carboxylic acids correspond between squirrel monkeys and humans*. Am. J. Physiol., 274, R1639–R1645.

Laska, M. and **Teubner, P.** (1999a) *Olfactory discrimination ability of human subjects for ten pairs of enantiomers*. Chem. Senses, 24, 161–170.

Laska, M. and **Teubner, P.** (1999b) *Olfactory discrimination ability for homologous series of aliphatic alcohols and aldehydes*. Chem. Senses, 24, 263–270.

Laska, M., Distel, H. and **Hudson, R.** (1997) *Trigeminal perception of odorant quality in congenitally anosmic subjects.* Chem. Senses, 22, 447–456.

Laska, M., Trolp, S. and **Teubner, P.** (1999) *Odor structure–activity relationships compared in human and non-human primates.* Behav. Neurosci., 113, 998–1007.

Laska, M., Ayabe-Kanamura, S., Hübener, F. and **Saito, S.** (2000) *Olfactory discrimination ability for aliphatic odorants as a function of oxygen moiety.* Chem. Senses, 25, 189–197.

Lawless, H.T. and **Heymann, H.** (1998) *Discrimination testing.* In Lawless, H.T. and Heymann, H. (eds.), Sensory Evaluation of Food—Principles and Practices. Chapman & Hall, London, pp. 117–139.

Malnic, B., Hirono, J., Sato, T. and **Buck, L.B.** (1999) *Combinatorial receptor codes for odors.* Cell, 96, 713–723.

Moskowitz, H.R. and **Barbe, C.D.** (1977) *Profiling of odor components and their mixtures.* Sens. Processes, 1, 212–226.

Ohloff, G. (1994) Scent and Fragrances. The Fascination of Odors and their Chemical Perspectives. Springer, Berlin.

Pilgrim, F.J. and **Schutz, H.G.** (1957) *Measurement of the quantitative and qualitative attributes of flavor.* In Chemistry of Natural Food Flavors. Quartermaster Food Container Institute, Chicago, IL, pp. 47–58.

Rossiter, K.J. (1996) *Structure–odor relationships.* Chem. Rev., 96, 3201–3240.

Sachse, S., **Rappert, A.** and **Galizia, C.G.** (1999) *The spatial representation of chemical structure in the antennal lobe of honeybees: steps towards the olfactory code*. Eur. J. Neurosci., 11, 3970–3982.

Sicard, G. and **Holley, A.** (1984) *Receptor cell responses to odorants: similarities and differences among odorants*. Brain Res., 292, 283–296.

Siegel, S. and **Castellan, N.J.** (1988) Nonparametric Statistics for the Behavioral Sciences. McGraw-Hill, New York.

Uchida, N., **Takahashi, Y.K., Tanifuji, M.** and **Mori, K.** (2000) *Odor maps in the mammalian olfactory bulb: domain organization and odorant structural features.* Nature Neurosci., 3, 1035–1043.

Weyerstahl, P. (1994) *Odor and structure.* J. Prakt. Chem., 336, 95–109.

Wise, P.M., Olsson, M.J. and **Cain, W.S.** (2000) *Quantification of odor quality.* Chem. Senses, 25, 429–443.

Yoshii, F. and **Hirono, S.** (1996) *Construction of a quantitative three-dimensional model for odor quality using Comparative Molecular Field Analysis (CoMFA)*. Chem. Senses, 21, 201–210.

Zhao, H., Ivic, L., Otaki, J.M., Hashimoto, M., Mikoshiba, K. and **Firestein, S.** (1998) *Functional expression of a mammalian odorant receptor.* Science, 279, 237–242.

Accepted September 6, 2001