STRUCTURE-ACTIVITY RELATIONSHIPS IN HUMAN CHEMORECEPTION pdf

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St ruct u re-act ivity relationships in chemoreception by human olfaction H. Boelens Groen van Prinstererlaan 21, GB Hmzen Nil, The Netherlands. Every living organism needs information for the maintenance of its life and species.

Show Context Citation Context This makes the musk problem somewhat more difficult. Because of the subjective nature of the tes Nitroanilines, sulphamates, oximes, isocoumarins and dipeptides, Chemical Senses , " The previously introduced conceptual parameters a, 6, u and S to describe the stereochemical requirements for organic compounds to taste sweet, were now applied to another series of sweeteners and to some well-known potent substances. With the help of an adapted STERIMOL computer program, the positions of relevant, hydrophobic side chains were determined in ureas, sac-charins, tryptophans, chlorosugars and acesulfame derivatives in relation to their AH-B moieties. The results obtained were compared with previous findings for five other homologous series of sweeteners. There is evidence to suggest that 6-substituted acesulfame derivatives and saccharin employ the same receptor site. In the dulcin series of the urea derivatives, two AH-B moieties can be distinguished: It is remarkable that the average 6 positions belonging to sweeteners with similar AH-B moieties are located very close to each other. D-tryptophan, which is 19 times sweeter than sucrose on a molar basis, becomes dramatically sweeter when one or two chlorine atoms are introduced at one or both positions 5 and 6 of the benzene nuc Result by unknown authors " Suppose you are a lock smith and you are attempting to infer the most general required shape that a key must have in order to open the supply room door. If you knew this required shape, you could predict, by examin If you knew this required shape, you could predict, by examining any key, whether that key could unlock the door. What makes your lock smith job difficult is that the staff members are uncooperative. Instead of showing you which key on their key chains opens the supply room door, they just hand you their entire key chain and ask you to figure it out for yourself! Instead, you must examine the shapes of all of the keys on the key rings and infer the answer. We call this kind of learning problem the multiple instance problem. It arises in complex applications of machine learning where the learning system has partial or incomplete knowledge about each training example. This situation is depicted in Fig. Each object is typically represented as a fixedlength.

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2: nys bio lab questions Manual

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Advanced Search Abstract We tested the ability of human subjects to distinguish between enantiomers, i. In a forced-choice triangular test procedure 20 subjects were repeatedly presented with 10 enantiomeric odor pairs and asked to identify the bottle containing the odd stimulus. These findings support the assumption that enantioselective molecular odor receptors may only exist for some but not all volatile enantiomers and thus that chiral recognition of odorants may not be a general phenomenon but is restricted to some substances. Introduction Chiral recognition of substances, i. Discrepant enantiomer effects are well-established, with numerous examples in drug effectiveness e. Caldwell, , taste perception e. The first molecular event in odor perception is the interaction of an odorant with a receptor. As olfactory receptors have been identified as proteins, i. Ohloff, , although the number of cases reported in which the differences are small seems inconsistent with the large differences found in other biological interactions between body tissues and dextro- and levo- forms of the same compounds. There are also reports of identically smelling enantiomeric odor pairs Theimer et al. The situation is even more complicated by findings of chiral isomers in which one form has a distinct odor quality whereas the other form is odorless Simmons et al. Surprisingly few studies, on the other hand, have directly tested the discriminability of chiral odorants, although this method largely avoids the disadvantages of comparatively poor resolution, subjectivity, likely context dependence and semantic ambiguity Cain and Olsson, Even fewer studies using discrimination procedures have assessed whether inter- or intraindividual variability in discrimination performance rather than perceptual differences between antipodes may at least partly account for the sometimes widely differing findings with the same chiral odor pairs. To the best of our knowledge, only one study so far has investigated the discrimination performance of humans for an array of enantiomeric odorants Jones and Elliot, Unfortunately, the authors of this study reported only the total number of correct discriminations pooled from all their subjectsâ€”drawing statistically invalid conclusions as to discriminability of a given chiral odor pair due to an inflated number of observationsâ€”and gave only cursory information with regard to inter- or intraindividual variability of performance. Given the continuing uncertainty in the field of chiral recognition of odorants and the possible importance of enantioselectivity for our understanding of the molecular mechanisms underlying the interaction between odor stimulus and olfactory receptor, we decided to test the ability of human subjects to distinguish between 10 pairs of enantiomers. Materials and methods Subjects Twenty healthy, unpaid volunteers 14 females and 6 males , 22â€”37 years of age, participated in the study. All were non-smokers and none had any history of olfactory dysfunction. All subjects had previously participated in a clinical test of olfactory function and were found to be normosmic. All subjects had also previously served in olfactory discrimination tests and were familiar with the basic test procedure. They were informed about the aim of the experiment and provided written consent. Odorants A set of 20 odorants comprising 10 pairs of enantiomers was used Table 1. They were diluted using diethyl phthalate Merck, Darmstadt, Germany as the solvent. The enantiomers of a given pair were presented at equal concentrations in order to assess whether differences in perceived intensity rather than differences in perceived odor quality contributed to discrimination performance cf. In an attempt to ensure that the different enantiomeric odor pairs were of approximately equal strength when presented in squeeze bottles, intensity matching was performed by a panel of six subjects adopting a standardized psycho-physical procedure ASTM, Test procedure A 40 ml aliquot of each odorant was presented in a ml polyethylene squeeze bottle equipped with a flip-up spout which for testing was fitted with a handmade Teflon nose-piece. 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 to ensure

that the nose-piece was only a short distance 1â€”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 to identify the one containing the odd stimulus. Additionally, after each decision, subjects were asked whether their choice was predominantly based 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 at least 10 s. Sampling duration was restricted to 1 s per presentation in order to minimize adaptation effects. The sequence of presenting the stimulus pairs was systematically varied between sessions and individual subjects while ensuring that the presentation of a given odorant as 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. The 10 stimulus pairs were presented twice per session and testing was repeated in four more sessions, each 1â€”3 days apart, enabling 10 judgements per stimulus pair and panelist to be collected. Comparisons of group performance across tasks or sessions were made using the Friedman two-way analysis of variance. When ANOVA detected differences between tasks, this was then followed by pairwise Wilcoxon signed-rank tests for related samples to evaluate which tasks were responsible Siegel and Castellan, Results Figure 1 summarizes the mean performance of 20 subjects in discriminating between the 10 enantiomeric odor pairs. Interindividual variability was high, particularly in tasks that were not significantly discriminated at the group level cf. SDs in Figure 1. Accordingly, between 12 and 19 out of 20 subjects failed to significantly distinguish between the antipodes of the former group of substances, whereas only 2 or 3 out of 20 subjects were unable to discriminate the enantiomers of the latter group of substances. Figure 2 shows the distribution of individual performance in discriminating between the 10 enantiomeric odor pairs. Accordingly, the best panelists were able to significantly distinguish 6 out of 10 enantiomeric odor pairs whereas the poorest-performing subject failed to do so with all tasks but one. Figure 3 shows the mean performance of the 20 subjects across the five test sessions. The three enantiomeric odor pairs that were significantly discriminated at the group level yielded the lowest percentages of perceived intensity as the choice criterion, with 3. This simple method has been shown to reliably quantify the trigeminal impact of odorants Berg et al. Materials and methods Subjects Ten healthy, unpaid volunteers seven females and three males , 22â€”37 years of age, participated in the study. Two of the subjects had already participated in experiment 1. The substances were diluted, using diethyl phthalate as the solvent, to the same concentrations as in experiment 1. Test procedure Using a custom-made squeezer, air from two ml polyethylene squeeze bottles was applied to the right and to 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. 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 ensuring that the presentation of a given odorant to the left or the right nostril was balanced within and between sessions. The six stimuli were presented five times per session and testing was repeated in three more sessions, each 1â€”3 days apart, enabling 20 judgements per stimulus and panelist to be collected. Comparisons of group performance across sessions were made using the Friedman two-way analysis of variance, and comparisons of group performance between tasks involving the antipodes of a given substance were made using the Wilcoxon signed-rank test for related samples Siegel and Castellan, As a group, the human subjects failed to perform significantly above chance in all six tasks, with between 5 and 10 out of 10 individuals not reaching the criterion of at least 14 out of 20 decisions correct. Interindividual variability was low cf. Figure 6 shows the mean performance of the 10 subjects across the four test sessions. For each stimulus, a geometric dilution series using diethyl phthalate as the solvent was prepared, starting at a concentration of 1. Stem dilutions were designated step 1, and subsequent dilutions step 2, 3 and so forth. Bottles containing the pure diluent served as blanks. Care was

taken that the nose-piece was only a short distance 1â€”2 cm from the nasal septum during sampling of an odorant in order to allow the stimulus to enter both nostrils. Detection thresholds were determined using a triangular test procedure in which panelists were presented with three randomly arranged bottles, two of which contained pure diluent and the third the stimulus Laska and Hudson, ; Laska et al. In order to minimize adaptation effects, testing followed an ascending staircase procedure. Each bottle could be sampled twice per trial, with an inter-stimulus interval of at least 10 s. Panelists were required to decide whether there was no difference between the bottles or identify one as containing the stimulus. If both choices were correct, this was provisionally recorded as the threshold dilution. However, if these had been preceded by one correct and one incorrect choice, the previous dilution was again tested, and if both choices were then correct this was taken as the threshold. In this way, thresholds for the six odorants were determined for each panelist. Testing was repeated in four more sessions, each 1â€”3 days apart, taking care to systematically vary the order in which the six odorants were presented across sessions. Data analysis Comparisons of group performance across sessions were made using the Friedman two-way analysis of variance. When ANOVA detected differences between tasks, this was then followed by pairwise Wilcoxon signed-rank tests for related samples to evaluate which sessions were responsible. Comparisons of group performance between tasks involving the antipodes of a given substance were made using the Wilcoxon signed-rank test for related samples Siegel and Castellan, Results Figure 7 shows the mean detection thresholds of 10 subjects for each of the six odorants tested across five sessions. Interindividual variability was comparatively low, as can be inferred from the SDs in Figure 7 , which ranged from 0. The same is true for the antipodes of limonene. Discussion The results of this study demonstrate that the ability of human subjects to discriminate between enantiomeric odor pairs is substance-specific and thus not a generalizable phenomenon. They are also in line with reports which assigned the same verbal labels to the antipodes of menthol Doll and Bournot, ; Beets, ; Eccles, , citronellol Maas et al. The few studies which have so far used discrimination procedures to assess the ability of humans to detect differences between enantiomeric odor pairs are generally in agreement with our findings. Jones and Velasquez , Pike et al. Using a triangular test procedure similar to the one employed here, Cowart also found that humans are unable to discriminate between the antipodes of fenchone. In the only study so far that has employed an array of chiral odor pairs, Jones and Elliot reported the ability of human subjects to discriminate between enantiomers to be both substance-specific and subject-specific. Their finding of 2-butanolâ€”which was significantly discriminated by only 1 out of 20 subjects in our studyâ€”to be discriminable from its mirror image, however, was based on invalid statistics as the authors applied binomial tests to the total number of correct responses pooled from all subjects. Converted to percentages, their summed score for this odor pair corresponds to The same authors reported large differences in discrim- ination performance between subjects. We also found considerable interindividual variability both with individual odor pairs cf. SDs in Figure 1 and across tasks cf. This suggests that the substance-specificity of the ability to discriminate between enantiomeric odor pairs is a robust phenomenon. It is well-established that both the olfactory and trigeminal systems contribute to the perception of the majority of odorants Doty, The results of experiment 2, however, strongly suggest that the substances used here had little if any trigeminal-stimulating properties at the concentrations tested and that in any case the antipodes of a given substance did not differ in their degree of trigeminality. Thus, the possibility of trigeminal involvement in the discrimination of the three enantiomeric odor pairs in question can be excluded. 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 alcohols Laska and Trolp, and carboxylic acids Laska and Teubner, A final aspect of the present study is the finding that no generalizable conclusions can be drawn from our data as to odor structureâ€”activity relationships which would allow us to predict whether or not a given pair of enantiomers can be olfactorily discriminated. However, it was apparent that two of the three substances whose optical isomers were significantly distinguished carvone and limonene share a propenyl group at the chiral center and thus it would be worthwhile to include other enantiomeric odor pairs

which show this structural feature in future studies of olfactory discrimination performance. Similarly, membership of a certain chemical class is not a predictor of whether or not the antipodes of a substance are discriminable as, for example, carvone, fenchone and camphor are all carbonyl compounds but differ significantly in their discriminability cf. A more biological explanation of why some enantiomeric odor pairs can be discriminated whereas others cannot is that enantioselectivity of the human olfactory system may be restricted to substances for which both optical isomers are widely present in our natural odor world. There is accumulating evidence that the mammalian olfactory system, analogous to the immune system, may be capable of increasing the expression of molecular receptors that are responsive to a given odorant after repeated exposure to that stimulus Wang et al.

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3: - NLM Catalog Result

Srivastava, Sanjay Structure-activity relationship studies in medicinal chemistry and drug design Doctor of Philosophy, Case Western Reserve University, , Chemistry Structure activity relationship studies is a very important part of drug design in medicinal chemistry. These involved the study of antisecretory and cytoprotective antiulcer compounds, where chemical functionalities relevant to antiulcer action were identified. A successful attempt was also made at designing new multidrug resistant reversal drugs in another project, where the designed compounds were actually experimentally tested for verification of their predicted activity. The study led to the identification of four new active compounds. A problem relating to the study of dose-response was also addressed and a method was established for scaling activity data using a modified logit curve equation. In another project, the mispairing of guanine as a result of its C-8 substitution was studied. A new hypothesis was proposed which shows that C-8 substitution of guanine leads to an oxidized structure which could favorably pair both with cytosine and thymine with equal ease giving rise to possible mutation. As expression levels of RR are high during cell replication, RR has long been considered an attractive drug target for a range of proliferative diseases, including cancer. Many drugs targeting RR, such as the standard treatment for pancreatic cancer gemcitabine, are nucleoside analogues which irreversibly inhibit RR and exhibit a wide range of off-target effects that lead to unwanted toxicity in healthy cells. Developing reversible, non-nucleoside inhibitors which target RR more specifically may reduce this unwanted toxicity. In order to identify non nucleoside inhibitors, a moderate throughput screening method was developed targeting a protein-protein interface on the inactive human RR hexamer. Through a combination of in silico screening and biochemical assays, ten unique non-nucleoside compounds were shown to inhibit RR with mid-micromolar enzymatic IC50s. One phthalimide-based compound was found to inhibit RR noncompetitively, in agreement with binding to the targeted protein-protein interface. While NSAAH-E-3A was shown to demonstrate nanomolar cytotoxicity in multiple cancer cell lines, additional studies in healthy bone marrow progenitor cells showed no cytoxicity until micromolar doses were used data provided by Dr. A library of 25 hydrazone analogues, designed using medicinal chemistry and structure-based drug design, were synthesized for the purpose of structure-activity relationship SAR studies. The SAR studies identified key chemical moieties in the hydrazone scaffold based on potency toward hRR in cell-free inhibition assays. These results were then used to design a second-generation library, replacing the metabolically unstable acyl hydrazone backbone with heterocyclic ring systems. A library of five 1,2,3-triaozle analogs and ten 1,3,4-oxadiazole analogs were rationally designed with the aim of improving pharmacokinetic properties such as aqueous solubility and specificity towards RR. John Pink , suggesting that the cellular cytotoxicity observed for Oxa F may be primarily attributed to inhibition of RR and not to interactions with off-target enzymes. Oxa F is also predicted to have better aqueous solubility and membrane permeability than the initial lead NSAAH-E-3A, indicating that this compound is a promising lead compound for development of non nucleoside cancer chemotherapeutics.

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To gather this information all animals possess senses. By means of these senses they can communicate with their environment. With the senses of smell and taste the animal-world communicates via chemicals. Chemical communication plays an important role in finding food and in interindividual relations social and sexual and in detecting danger. With the chemical senses one may assume that a chemical substance or mixture interacts with a biological system resulting in a response. For centuries attempts have been made to correlate the structures of odourant molecules with their olfactory responses. After a study of the structural features of these compounds some general remarks with respect to the primary olfaction process can be made. These general remarks are discussed below. The discovery of a multigene family of odourant receptors as a molecular basis for odour recognition by Buck and Axel Cell, Vol. From our studies we can make the following remarks regarding the primary process of odour perception. Receptor sites seem to be flexible and dynamic, and odourant molecules are either flexible or rigid. Therefore, both may contribute to an optimal fit. Different fit-possibilities may exist with flexible odourant molecules more odour aspects for one molecule. One odourant molecule interacts with one receptor site. If a receptor site could interact with a large number of molecules, structure-activity relationships would not exist. Both the odourant molecule and the receptor site are chirally active. Since humans can distinguish between optical isomers R and S enantiomers , some type of a diastereo-isomeric interaction between optical active stimulus and optical active receptor site has to occur. The interaction between stimulus and receptor site may be only electronic strong polar molecules , or steric spherical molecules , but is usually a combination of both factors. The first interaction association can often be electronic dipole interaction, van der Waals forces, hydrogen bridges , but this is not always necessary alkanes, spherical molecules. Some parts of the molecule are important only as steric, or spacefilling, elements possible replacement of polar by apolar groups. The generation of the impulse may be either direct or indirect due to enzymatic processes. The generated impulse is a function of the electronic interaction stimulus to site and the space occupied at the receptor site. Detailed studies about structure-activity relationships in human olfaction are available.

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