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Rapid Olfactory Adaptation Induced by Perithreshold Odorant Concentrations in Human Observers

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Abstract A recent study from our laboratory described the development and use of a novel psychophysical method to characterize the onset time course of rapid olfactory adaptation (Smith et al., Chem Senses 35:717–725 2010). In the present study, we used this same approach to measure adaptation-induced changes in olfactory sensitivity following exposure to different self-adapting perithreshold-level stimuli. We used a custom-built liquid-dilution olfactometer to estimate two-odor discrimination thresholds for 600-ms presentations of a vanilla odorant alone and 500 ms after the onset of a 1,500-ms simultaneous vanilla adapting stimulus. Our previous findings suggest that a 500-ms exposure to a suprathreshold stimulus is sufficient to induce an asymptotic level of rapid olfactory adaptation in most participants. Twenty normosmic college-aged volunteers (ages 18–24; 14 females) served as subjects in this experiment. Thresholds were initially estimated for the 600-ms vanilla target alone, then compared in the presence of a simultaneous adapting stimulus set to 0.25, 0.5, 1.0, or 2.0 times the participant's initial threshold to assess the effects of adapting odorant level on adaptation magnitude. The results suggest that significant decreases in odorant sensitivity were evident even with subthreshold adapting odorant levels, but that the magnitude of adaptation was unaffected by adapting odorant concentration.

Keywords Odor adaptation · Perithreshold odorant concentration · Subthreshold odorant concentration · Odor threshold · Human odor perception

Introduction

Olfactory receptors are exposed to non-stop, complex chemical signals. From moment to moment, the volatile environment varies in chemical composition and concentration and olfactory receptors are responsible for isolating biologically relevant odors from background noise. At the olfactory periphery, the process of odor adaptation serves to suppress or inhibit responses to extended and or repeated stimulation; by shifting the concentration–response curve to the higher odor concentrations, the process of adaptation maintains the olfactory sensory neuron's (OSN) dynamic range and enhances detection of novel or transient odors.

Physiological studies have shown that adaptation is a complex, time-dependent process. Calcium imaging studies of in vivo OSN cilia have identified at least three calcium-dependent negative-feedback loops that compensate for sustained olfactory stimulation (Getchell and Shepherd 1978a, b; Kurahashi and Shibuya 1990; Kurahashi and Menini 1997; Leinders-Zufall et al. 1997, 1998, 1999; Zufall and Leinders-Zufall et al. 1997, 1998, 2000; Reisert and Matthews 1999, 2000; Munger et al. 2001; Kelliher et al. 2003; Boccaccio et al. 2006; Lecoq et al. 2009). Interestingly, at least one of these processes can be engaged, independent of cellular firing, at subthreshold levels of odor stimulation (Leinders-Zufall et al. 1999; Zufall and Leinders-Zufall 2000).

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At suprathreshold stimulation levels, one consistent feature of odor-induced adaptation, physiological or perceptual, is concentration dependence; the higher the odor concentration, the greater the magnitude of the resulting adaptation (cf., Dalton 2000). Correspondingly, in a previous study (Smith et al. 2010) we described use of a new, simultaneous stimulus paradigm to characterize the onset time course of perceptual rapid olfactory adaptation in human observers. In that work, we also showed that the magnitude of the observed adaptation was adapting odor concentration dependent (Smith et al. 2010). Moreover, we also observed anecdotal evidence suggesting subthreshold-level odorants could likewise produce measurable levels of odor adaptation. Using our simultaneous stimulus paradigm, observers were asked to detect a brief, 600-ms vanilla target odorant presented simultaneously with a self-adapting stimulus. The onset time course of odor adaptation is estimated as the increase in threshold for a brief target stimulus as a function of adapting stimulus onset to target odorant onset delay (i.e., at different points along the adaptation contour; Smith et al. 2010). To characterize the effects of absolute adapting odorant level on adaptation-induced threshold increases, adapting odorant concentrations were fixed at 1%, 5%, and 30% (volume/volume). Because the adapting odorant level was fixed at predetermined absolute concentrations in this condition, rather than *relative* to each subject's threshold, the adapting odorant level of 1% v/v was *below threshold* for some subjects. Yet, our analysis showed that in some of those subjects, the subthreshold adapting odorant produced a systematic increase in threshold qualitatively similar, but smaller in magnitude, to those shown for suprathreshold adapting stimuli (Smith et al., unpublished observations). These observations suggest that, like the calcium measures of single OSN responses (Leinders-Zufall et al. 1999; Zufall and Leinders-Zufall 2000), *perceptual* sensitivity may likewise be affected by exposure to subthreshold odors.

The influence of subthreshold concentration odorants on odor adaptation was first addressed by Amirov (1959). In that work, he compared thresholds for peppermint oil and camphor presented in either increasing or decreasing concentrations. On trials where the concentration of the odorant was gradually and continuously increased until detected by the observer, thresholds were relatively higher than when the rate of odorant increase was slower. Amirov interpreted this effect as being due to the lower concentrations of the odorant, before the odorant concentration was sufficiently high for detection, producing an apparent degree of odor adaptation. An unexplained finding was that adaptation was larger, and more common in patients reporting infections (influenza and catarrh), than in normosmic participants (Amirov 1959).

In the present experiment, we sought to determine whether or not perithreshold-level odorants are capable of producing measurable levels of odor adaptation. The magnitude of adaptation was estimated by comparing threshold for the detection of vanilla extract alone, with thresholds for the same target odor when presented simultaneously in four perithreshold levels of a 1,500-ms vanilla adapting stimulus. The results show that perithreshold-level, self-adapting odorants can produce significant levels of odor adaptation.

Materials and Methods

Subjects Twenty participants (six male, 14 female; 18–24 years) reporting no olfactory or respiratory complaints participated in this study. Prior to participation, individuals completed a brief questionnaire that screened for prohibitive respiratory conditions, such as a history of allergies, nasal infections, nasal surgery, or smoking. In addition, participants who exhibited an unusually high baseline threshold for the vanilla target stimulus alone, 20% volume/volume (v/v) or greater, were excluded from further study. Such a high detection threshold would not permit a sufficient range of odor concentrations to indicate significant changes in sensitivity related to the presence of the adapting odorant.

All experimental procedures were approved by the Institutional Review Board of the University of Florida.

Olfactometer The experiments were conducted using a custom-designed automated, liquid-dilution olfactometer. A schematic of the apparatus is shown in Fig. 1. A PC-based program with a graphic user interface controlled the olfactometer, and participants used a hand-held response box with an LCD screen to receive instructions and respond during the experiment. Two independent, charcoal-filtered air streams, controlled by solenoid pinch valves, constituted the stimulus and carrier streams; the stimulus stream controlled release of gas-phase odorants from the saturation bottles, while the carrier stream directed these stimuli to the subject. Flow rates, 0.27 L/min for the carrier and 4.1 L/min for the stimulus, were selected to optimize the odorant onset rapidity at the nose (Smith et al. 2010).

A third charcoal-filtered, high-flow-rate air stream, approximately 6 L/min, was inserted upstream of all odorants and served to flush residual odors out of the stimulus delivery air stream and into the evacuation system after each stimulus presentation. Saturation bottles for each odorant type (target, control, and adapting) occupied fixed positions within the stimulus delivery system in order to maintain consistent relative travel times and onset odor delays to the nose. During trials, all stimuli were delivered to the nose via a vented, composite nasal mask (St. Croix Sensory; Lake Elmo, MN, USA). The odorant clearance line from the mask contained a small, DC fan that served to

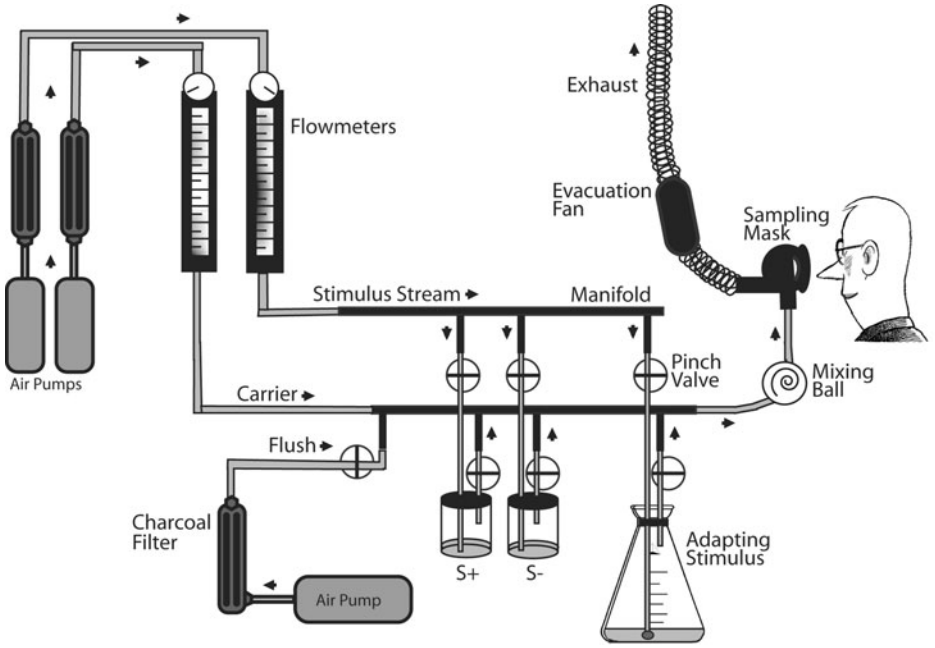

Fig. 1 Schematic depiction of olfactometer. Ambient room air was pumped separately through charcoal filters and into separately controlled stimulus and carrier air streams. A third charcoal-filtered air stream was inserted upstream of the experimental stimuli to flush the manifold and mask after each stimulus presentation. Presentation and relative timing of adapting and target stimulus presentation was controlled by a series of pinch valves which delivered the stimuli into the carrier stream, through a mixing ball and to the sampling mask. The odorants were evacuated by an inline fan. To ensure consistent, relative stimulus timing the S+ (target+diluent) and S− (diluent alone) saturation bottles were fixed in position on the manifold upstream from the adapting odorant

draw the odorants from the delivery lines, through the mask and to the central evacuation system.

Odorants Pure vanilla extract, purchased in bulk (Gordon Food Service, Grand Rapids, MI, USA), was used as the base for all odorant dilutions in this study. The extract contains 35% ethanol, which the subjects report not-detecting at low concentrations. Vanilla extract is an easily recognizable, pleasant odor and was chosen in favor of pure vanillin because detection thresholds for vanillin in solution are too high to allow a sufficient dynamic range for threshold increases to indicate significant changes in sensitivity related to the presence of the adapting odorant.

The stock odorants were stored in a refrigerator under inert gas (nitrogen) to prevent oxidation. Serial dilutions of the vanilla extract, using deionized water (DH_2O) as a diluent, constituted both target and adapting stimuli. Ten milliliters of the liquid-phase vanilla odorant, placed in a 500-mL glass saturation jar, served as a target stimulus. Likewise, 10 mL of the diluent alone was placed in a 500-mL glass saturation jar and served as the control stimulus. Because of the relatively longer presentation time, adapting stimulus dilutions were of necessarily higher volume (100 mL) and were contained within a larger saturation bottle (3,000 mL). Target (S+; vanilla in DH_2O diluent) and control (S−; DH_2O) stimuli each consisted of a single, 600-ms presentation of volatilized odorant. Adapting stimuli were 1,500-ms presentations of vanilla diluted in DH_2O.

As illustrated in Fig. 1, solenoid pinch valves briefly bubbled the stimulus stream through a tube submerged in liquid-phase odorant to produce volatilized stimuli that filled the headspace before introduction into the carrier stream and presentation to the subject. Concentration here refers to the v/v concentration of the liquid-phase odorant in the saturation bottle, rather than stimulus concentration at the subject's nose; odorant concentration at the subject's nose is relatively unimportant as *relative* changes in threshold, not absolute threshold, are of interest in this study of odor adaptation.

Psychophysical Methods During the experimental session, participants held the response box in one hand and secured the nasal mask over their nose with the other. The response box's LCD screen presented instructions indicating experimental conditions, observer response requests, and feedback concerning response accuracy. With the nasal mask secured, the subject initiated a trial sequence, by depressing and holding a "ready" response key. Once depressed, the LCD screen instructed the participant to slowly exhale for 3 s. Following the exhalation period, the response box LCD screen instructed the participant to inhale slowly and continuously for 3 s. The adapting stimulus, as well as the target or control, was presented during this inhalation period.

Individual trials required participants to discriminate dilutions of the target vanilla odorant (S+) from the control stimulus (S−). This discrimination task is similar to the two-bottle discrimination paradigm employed by a number of psychophysical researchers (Bodyak and Slotnick 1999; Laska and Seibt 2002; Hernandez-Salazar et al. 2003). Immediately following the 3-s sampling period, subjects reported detection of the S+ odorant by pressing a green response key, or failure to detect the S+ odorant (i.e., "detection" of the S− odorant) by pressing a red response key. The response box provided immediate feedback to the subject for both correct and incorrect responses.

Target stimuli were presented in mixed blocks of 20 trials, 10 S+ and 10 S− stimuli, in quasi-random order. A subject's correct response percentage, for both correct detection and correct rejection, was calculated and a participant was judged to have detected a given dilution when they could accurately discriminate a concentration at 85% or greater within a block, for two consecutive blocks. After successfully passing a dilution, the process was repeated with a more dilute target concentration in the subsequent blocks. Likewise, if the participant was unable to accurately discriminate the target vanilla order at a given concentration from the diluent alone, the target odorant concentration was increased on the following block of trials.

Figure 2 illustrates the stimulus conditions employed in this study. During the initial phase of testing, detection threshold for the vanilla target was estimated (Fig. 2, top line). To estimate the threshold alone, the participant was asked to discriminate the S+ from S− in the presence of a null adapting stimulus (DH_2O) so that all stimulus conditions, save for the presence of the vanilla in the adapting odorant, were identical to all subsequent test conditions. The estimated target alone threshold served as both a baseline against which adaptation would be measured, but also served to permit adapting odorant levels to be set relative to threshold (Smith et al. 2010).

All subsequent experimental conditions involved the presentation of a vanilla target in the presence of a simultaneous vanilla adapting odorant; in this condition, the participant discriminated the S+ from S− in the presence of a low-level adapting stimulus. The adapting odorant to target onset delay was fixed at 500 ms for all testing and adapting odorant concentrations were 2.0, 1.0, 0.5, or 0.25 times baseline threshold concentration. The 500-ms onset delay was chosen because previous work showed this onset delay produced an approximate asymptotic level of adaptation (Smith et al. 2010). Adapting odor presentation order was randomized within and across subjects. To ensure that changes in threshold were not due to long-term exposure to the odorants during the experiment, we re-estimated thresholds intermittently throughout the session. If a participant exhibited any systematic changes in threshold over the course of the test session, the experiment was stopped and

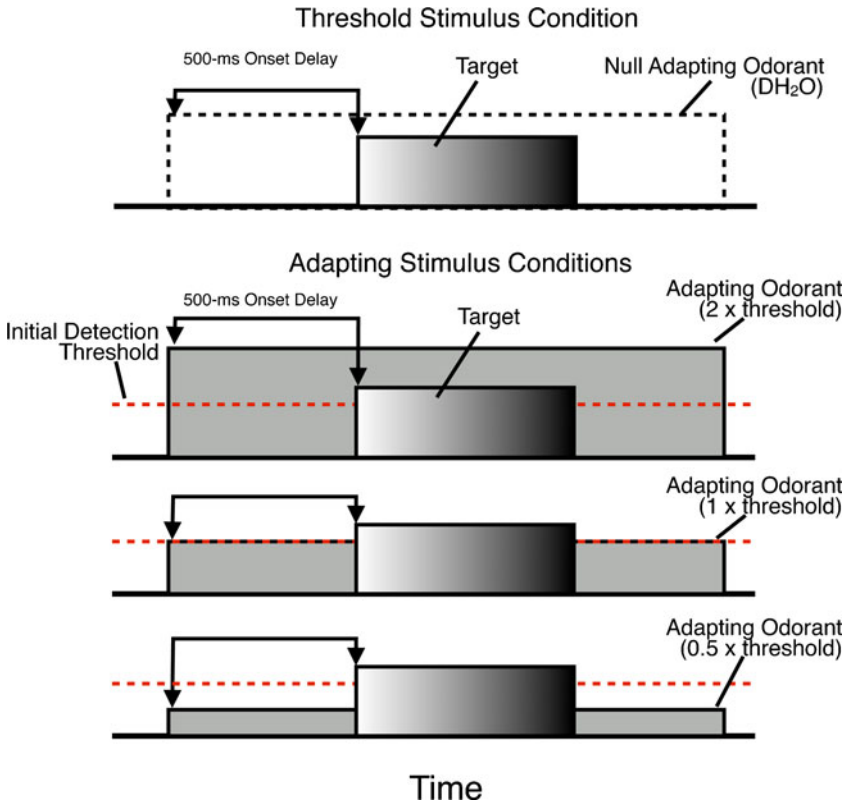

Fig. 2 Schematic of stimulus conditions employed in the simultaneous presentation paradigm. A subject's threshold was initially assessed for the target odor alone, in the presence of a null background (*top line*). In subsequent trials, the target odor was presented simultaneously with a 500-ms adapting-to-target onset delay (*lower three lines*). The adapting odorant concentration was set relative to each participant's threshold (2.0, 1.0, 0.5, or 0.25 times threshold)

the subject's data were not used in further analyses. No subject, however, exhibited such long-term effects. Due to time constraints, all adapting stimulus concentrations could not be tested on every participant. We addressed this limitation, however, through the quasi-random ordering of adapting stimuli, and employed a Wilcoxon signed-rank test to examine differences between experimental conditions.

Results

Initial baseline threshold estimates for the target odorant alone ranged across participants from 1% v/v to 10% v/v, with a median of 5% v/v. Adapting stimulus concentrations across conditions, therefore, varied from 0.25% v/v to 20% v/v, depending on a participant's baseline threshold and the relative adapting odorant concentration employed.

Figure 3 presents median thresholds across subjects, plotted as a function of the adapting stimulus concentration. Median baseline threshold was computed for 20 subjects, with nine subjects for the 0.25 times adapting odorant concentration, 10 subjects for the 0.5 times threshold concentration, 11 for the 1.0 times threshold concentration, and six for the 2.0 times concentration. Thresholds for the target stimulus alone, measured in the presence of a simultaneous "null" (DH_2O-diluent alone) adapting stimulus, served both to permit the setting of adapting odorant concentration relative to threshold for each subject and as the baseline against changes in threshold in the presence of the simultaneous adapting odorant could be quantified. When estimated in the presence of perithreshold-level adapting odorants, threshold increases, relative to baseline, were observed for all four adapting odorant concentrations. As compared with a median baseline threshold of 5% v/v, median thresholds across subjects in the 0.25, 0.5, 1.0, and 2.0 times threshold conditions were 40% v/v, 80% v/v, 100% v/v, and 60% v/v, respectively. Median thresholds for the target stimulus alone (baseline) and the 2.0 times threshold adapting condition in the present study are consistent with results under the same stimulus conditions from our previous work (Smith et al. 2010). Results from a Wilcoxon signed-rank test identified a significant deviation from baseline threshold for each adapting odorant condition: suprathreshold, 2.0 times baseline ($z=-2.21$, $p=0.027$); threshold-level, 1.0 times baseline ($z=-2.68$, $p<0.007$); and both 0.5 times baseline ($z=-2.81$, $p<0.005$) and 0.25 times ($z=-2.67$, $p=0.008$) subthreshold conditions. Threshold estimates for each adapting odorant level were significantly increased as compared with thresholds for the target odorant alone; however, there was no significant effect of adapting odorant level (2.0, 1.0, 0.5, and 0.25 times threshold) on thresholds.

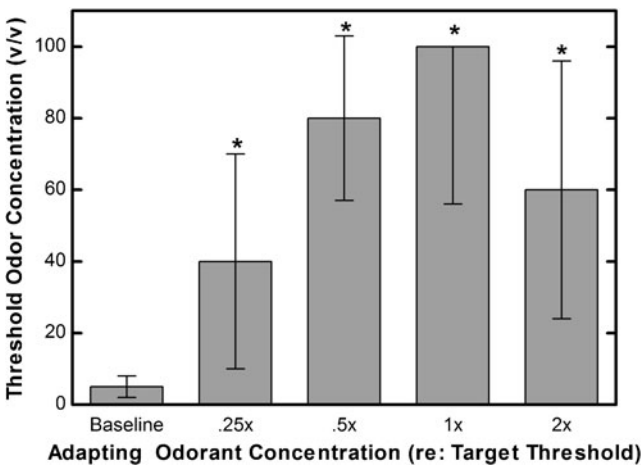

Fig. 3 Median detection thresholds measured alone (baseline) and in the presence of adapting odorants set to 0.25, 0.5, 1.0, and 2.0 times threshold. A 500-ms null stimulus (DH_2O) served as the adapting odorant in the baseline condition. *Error bars* represent interquartile ranges

Discussion

Previous work from our laboratory has shown that perceptual thresholds for brief target odorants, estimated in the presence of a relatively long-duration, simultaneous adapting odorant, are increased in a manner that is dependent on adapting-odorant concentration (Smith et al. 2010). Those results agree well with both psychophysical and physiological findings reported by other groups using different, non-simultaneous adapting stimuli (cf., Dalton 2000). In our initial work, however, adapting odorant concentration was fixed at 1%, 10%, or 30% v/v, irrespective of an individual observer's threshold. As a consequence, because the mean threshold for all participants was 6.1% v/v, the lowest level adapting odorant concentration employed, 1.0% v/v, was likely below detection threshold for a number of the participants; nevertheless, increases in target stimulus threshold were routinely observed with these presumably subthreshold adapting odorants. As such, the objective of the present study was to characterize the effect of perithreshold adapting odorant levels on perceptual odor detection threshold.

Using the same stimulus paradigm employed in our earlier work, the present results demonstrate that sub- and near-threshold-level adapting odorants are capable of producing significant increases in odor threshold for brief, simultaneous target stimuli. Measured in the presence of perithreshold concentration odorants, thresholds were, in general, increased in a manner that was similar in magnitude to those observed in the presence of supra-threshold adapting stimuli (Smith et al. 2010). In the present study, the mean threshold for the target alone was

5.5% v/v, and 45.6% v/v, 69.0% v/v, 60.5% v/v, and 55.8% v/v, respectively, when estimated in the presence of 0.25, 0.5, 1.0, and 2.0 times threshold adapting conditions. In the previous work, the vanilla extract target alone threshold was 6.1% v/v, and, when measured in the presence of a simultaneous adapting odorant set to twice threshold, increased to an approximate asymptotic level of 50% v/v. The present data confirm earlier, unpublished observations that suggest that perithreshold-level stimuli can activate receptor adaptation and increase perceptual thresholds for the self-adapting stimuli.

The vanilla extract used in this study does contain 35% ethanol, which may have stimulated trigeminal receptors. Because we were measuring relative changes in threshold, the ethanol was present in all stimulus conditions. Recent work from our laboratory (Yoder et al. 2011) suggests that, employing the same olfactometer and stimulus conditions, trigeminal odorants produce relatively less adaptation, with a relatively longer onset time course, at comparable odorant concentrations. Therefore, it is unlikely that the presence of ethanol at peri- and subthreshold levels would have impacted our findings.

These data are also consistent with a previous study by Amirov (1959). In that study, thresholds measured using both an ascending and descending method of limits were compared. Threshold estimates were relatively higher when using ascending odorant concentrations than when using descending concentrations, an effect he interpreted as demonstrating the adaptive effects subthreshold odorants have on perceptual threshold.

With the single exception noted above, psychophysical and behavioral investigations of olfactory adaptation have employed suprathreshold level odorants (cf., Pryor et al. 1970; Stone et al. 1972; Cain and Polak 1992; Pierce et al. 1996). A defining characteristic of those studies has been the relationship between adapting odorant concentration and the magnitude of the observed adaptation (cf., Dalton 2000). Although our earlier report also showed increases in the magnitude of the observed adaptation with adapting odorant concentration (Smith et al. 2010), the present data, however, suggest that there is little effect of perithreshold odorant concentration on odor adaptation magnitude (Fig. 3). Yet, this finding is consistent with several previous reports analyzing effects of sub- and perithreshold odorants on both olfactory and gustatory perception (Lopetcharat 2003; Miyazawa et al. 2008a, b; Labbe et al. 2007; Labbe and Martin 2009). Lopetcharat (2003) demonstrated that subthreshold-level odorants could alter the perceived intensity of a second odor in both binary and tertiary mixtures. Whether the subthreshold odorant produced suppression or enhancement depended upon a number of factors, such as functional group and relative polarity of the stimuli. Likewise, Miyazawa and colleagues (2008a) measured the effects of exposure to perithreshold concentrations of acetic and butyric acid on odor detection thresholds for maple lactone. Their findings showed that the presence of either carboxylic acid in subthreshold concentration produced statistical decreases in thresholds for maple lactone. Labbe et al. (2007) showed that presentation of subthreshold concentrations of the odorant ethyl butyrate could enhance the sweetness of sucrose in human observers.

The intra- and cross-modal interaction of sub- or perithreshold chemical stimuli with suprathreshold odors or tastants appears to be dependent on familiarity with, or the "congruence" of the two stimuli (Dalton et al. 2000; Miyazawa et al. 2008a, b; Labbe et al. 2007). For example, in the Lopetcharat (2003) study, the type of subthreshold effect observed, whether enhancing or additive, was dependent on odor chemical similarity and was lost when carbon chain length varied by more than two atoms. Similarly, Dalton et al. (2000) also suggested that the integration of subthreshold taste and odor stimuli was dependent on previous experience with the combined stimuli. Therefore, in the present study, because we employed a self-adapting vanilla odorant, stimulus conditions should have been optimized to observe sub- and/or perithreshold-level odorant interactions.

These new psychophysical adaptation data can be explained by known physiological mechanisms. Adaptation at the level of the OSN cilia is a complex product of, at least, three different processes that can be distinguished by both biochemistry and time constants (Leinders-Zufall et al. 1997, 1998, 1999; Zufall and Leinders-Zufall 1998, 2000). Analyses of the intracellular, molecular pathways responsible for OSN adaptation have demonstrated that at least two of these processes, short-term adaptation and desensitization, can be activated by subthreshold levels of stimulation, decreasing the sensitivity of the OSN to continued stimulation, without activating cellular transduction processes (Leinders-Zufall et al. 1999; Zufall and Leinders-Zufall 2000). Based on the brief adapting to target odorant onset delays employed in this stimulus paradigm, we have previously argued that the observed threshold increases are a result of rapid adaptation—an interpretation also supported by these new data. Continuing studies seek to further relate perceptual phenomena to underlying physiological mechanisms.

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