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Psychophysical and Behavioral Characteristics of Olfactory Adaptation

Pamela Dalton

Monell Chemical Senses Center, Philadelphia, PA 19104, USA

Correspondence to be sent to: Pamela Dalton, Monell Chemical Senses Center, 3500 Market Street, Philadelphia, PA 19104, USA. e-mail: pdalton@pobox.upenn.edu

Abstract

Sensory adaptation allows organisms to reach behavioral equilibrium with the ambient environment and respond primarily to changes in stimulation. Given its functional significance, it is not surprising that adaptation in the olfactory system exhibits many of the same characteristics as adaptation in other sensory systems, including vision. Repeated or prolonged exposure to an odorant typically leads to stimulus-specific decreases in olfactory sensitivity to that odorant, but sensitivity recovers over time in the absence of further exposure. Psychophysical analysis shows that olfactory adaptation results in elevations in odor thresholds and in reduced responsiveness to suprathreshold stimulation. Further, the magnitude of the decrease and the time course of adaptation and recovery are dependent on the concentration of the odor and on the duration of exposure. It is generally agreed that olfactory adaptation can occur at multiple levels in the olfactory system and can involve both peripheral (receptor level) and more central (post-receptor) components. Evidence for peripheral and central involvement comes from studies showing that monorhinal stimulation results in adaptation in both the ipsilateral and contralateral nostril, although the degree of adaptation in the ipsilateral nostril is more profound and recovery is slower. Additional evidence for central involvement comes from studies that have found relatively small decreases in peripheral response following repeated stimulation despite substantial reductions in perceived intensity. Most psychophysical studies of adaptation, however, have not differentiated the peripheral and central processes. Although relatively few in number, studies of the parametric features of olfactory adaptation in both vertebrate (e.g. rat) and invertebrate (e.g. *Drosophila, Caenorhabditis elegans*) animal models appear to replicate the findings in psychophysical studies of adult humans. Despite the broad overall similarity of olfactory adaptation to adaptation in other sensory systems, olfactory adaptation exhibits some unique features. Adaptation in olfaction has been shown to be very long-lasting in some cases and may be modulated by the contribution of pre-neural events and physico-chemical properties of the odorant molecules that govern diffusion to receptor sites and post-receptor clearance.

Introduction

In humans and animals, the olfactory system is bombarded by an extraordinarily diverse range of chemical stimulation. In order to maintain high sensitivity yet remain responsive to a wide range of odorants and concentrations, organisms must possess some means of adjusting the response of their olfactory system. This process is known as adaptation, and is a common feature in all sensory modalities. Adaptation in olfaction allows the olfactory system to maintain equilibrium with the odorant concentrations in the ambient environment, yet respond appropriately to the appearance of novel odors or changes in odorant concentration. Adaptation kinetics can also enhance sensitivity to time-varying stimulation, an important advantage in the detection of natural stimuli which are often in the form of highly heterogeneous odor plumes.

The phenomenon of olfactory adaptation has historically been investigated using behavioral, psychophysical and (in animals) electrophysiological techniques. As research on olfactory adaptation extends to examinations of cellular and molecular mechanisms, it becomes increasingly important to relate the findings from these investigations to the characteristics of adaptation obtained from studies of perception and behavior. In this attempt, however, it is likely that we need to exercise prudence when relating outcomes at such diverse levels of analysis. Although we presume (and rightly so) that perception and experience are related to neural activity or events in some fashion, we are cautioned by the psychophysicist Donald Laming that 'the relationship may not be sufficiently simple that it is helpful to think of the intensity of sensation as being a direct or isomorphic reflection of some internal level of neural activity' (Laming, 1997). Indeed, previous attempts to relate neural activity to perceptual experience in other modalities have met with mixed results. If the subjective perception of stimulus intensity is based on the level of neural activity, then one could expect a substantial correlation between the psychophysical functions for neural activity and perceived stimulus intensity. In fact, a study by Knibestöl and Vallbo described by Laming (Laming, 1997) that compared the responses from single afferent fibres in the median or ulnar nerve of human subjects to varying degrees of tactile stimulation with simultaneous estimates of the subjective magnitude of this stimulus revealed a negligible correlation between these measures ($r = 0.04$) (Laming, 1997). Thus, we must proceed with caution when rejecting or embracing relationships between single unit recordings and sensation intensity.

At the present time, considerably more is known about the influences of olfactory adaptation on perception and behavior than is known about the relationship between these behaviors and the underlying neural events. Thus, this review presents an overview of the general features of olfactory adaptation in order to identify the perceptual and behavioral characteristics that will need to be accounted for and integrated with findings from more peripheral levels of analysis.

This paper first reviews the psychophysical and behavioral measures that have been used to index olfactory adaptation in both human and animal studies. This is followed by a description of the parametric features of olfactory adaptation (e.g. specificity, concentration and duration-dependnce). Important to any attempt to relate cellular processes to perceptual phenomena is a review of the few studies that have used psychophysical techniques to investigate the locus of the adaptation process. The review concludes with a brief discussion of non-receptor level processes (e.g. odorant deposition/clearance and cognitive modulation of response) that can influence the degree of adaptation to odors.

Measures of olfactory adaptation

In general, adaptation is defined as the waning of response with stimulus repetition. As in other sensory modalities, the decrease in sensitivity or response to an odor stimulus following repetitive stimulation can be indexed using a variety of psychophysical or behavioral methods. For example, adaptation produces stimulus-specific decreases in odor sensitivity and, in humans or animals, this decrease is most commonly measured by obtaining estimates of the absolute detection threshold before and after repetitive or prolonged exposure to an odor (Pryor *et al.*, 1970).

Adaptation also reduces the perceived intensity of an odor, a phenomenon that can be observed after even a few breaths of an odorant. In studies of human olfactory perception, such changes are measured by asking subjects to scale or rate the intensity of the odor stimulus (Cain, 1969, 1970) or to match the intensity of the odor stimulus to a stimulus in another modality (Ekman *et al.*, 1967). Exposure-induced adaptation can also increase an individual's reaction time to detect an odor, suggesting that the amount of stimulus information that must be accrued for odor detection to occur is increased under conditions of adaptation. Although reaction times are a promising and ecologically relevant measure of adaptation and response to odors, this measure has seen infrequent use in human studies. Finally, adaptation can diminish the behavioral responsiveness to an odor (Colbert and Bargmann, 1995), measures which are most commonly used in studies of adaptation in pre-linguistic humans or non-human species.

Drawing inferences about the locus of the adaptation process from differences among these measures is not straightforward. For example, the term 'adaptation' has typically been used to describe the waning of response when the process is peripheral and sensory (as in retinal adaptation), whereas the term 'habituation' has been used to describe reductions in response that reflect more central processes. It is obvious, however, that a change in behavior or perceived intensity can reflect either a change in the peripheral response (which we traditionally interpret as a change in sensitivity or 'adaptation') or a decrease in evocability at the perceptual or behavioral level, even if the stimulus elicits the same neural response. In practice, these distinctions are rarely clear-cut. Most investigations of behavioral changes in response to an odorant, particularly in simple organisms, have not sought to distinguish whether the observed changes reflect peripheral or central processes.

Parametric features of adaptation

Adaptation in olfaction shares a number of features with adaptation in other sensory systems. For example, the magnitude and rate of adaptation have been shown to depend upon the concentration and duration of exposure to the target odorant. In addition, a decrease in sensitivity or intensity to the target odorant that does not generalize to all odorants is necessary in order to distinguish adaptation from a more general system dysfunction following exposure. Below I review a number of studies that illustrate the general features of the adaptation process. An analysis of the characteristics of olfactory adaptation from studies of olfaction in humans and *Drosophila* also illustrates the fact that olfaction can be studied at different levels of analysis, with a focus on behavior.

From simple organisms to humans, the duration of exposure to an odor has been shown to affect both the degree of adaptation and the rate of recovery. For example, recent investigations of olfactory adaptation in nematodes (Colbert and Bargmann, 1995) and *Drosophila* larvae (Wuttke, 1999; Wuttke and Tompkins, 2000) have revealed exquisite sensitivity to the duration of exposure to an odorant. The basic paradigm involves placing the to-be-tested organisms in the center of a Petri dish on which a disk impregnated with odorant and a disk impregnated with water have been placed diametrically opposite one another. *Drosophila* larvae are responsive to most, if not all, odorants that have been tested. In their unadapted state they will readily crawl to the disk with the odorant. However, following an adapting exposure, they will distribute themselves randomly on both the odorant-impregnated and the blank disk, and a response index can be calculated by subtracting

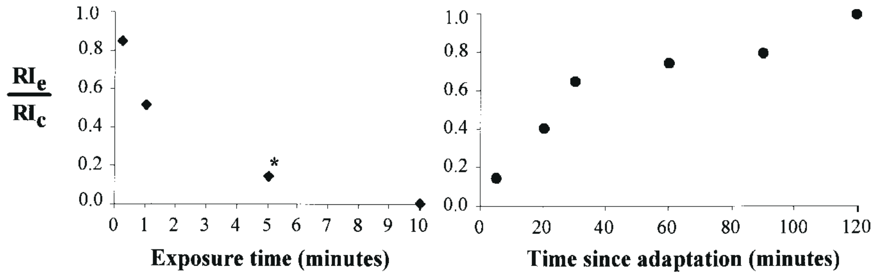

Figure 1 The effect of pre-exposure duration to the odorant on the degree of adaptation among *Drosophila* larvae. The response index (RI) was calculated by subtracting the number of larvae that crawled to the blank disk from the number of larvae that crawled to the odorant disk and dividing by the number of larvae that moved from the starting position. Increasing durations of pre-exposure to the odorant greatly reduced the number of larvae that responded to the odorant disk during a 5 min test period. Adapted from (Wuttke, 1999).

the number of larvae on the control disk from the number of larvae on the stimulus disk, standardized by the total number of larvae that moved in any direction.

For *Drosophila* larvae that had 5 min of pre-exposure to proprionic acid, benzaldehyde or ethyl acetate, the chemotaxic response was significantly suppressed to those odorants relative to larvae that only received pre-exposure to clean air. Importantly, however, these effects appeared dependent upon exposure duration. As shown in Figure 1, 1 min of odorant exposure did not decrease responsiveness to the odorant significantly. However, as the duration of pre-exposure increased (up to 10 min), so too did the degree of adaptation.

A second characteristic of adaptation that can be demonstrated using this same paradigm is that the observed degree of adaptation depends upon the concentration of the adapting odorant. As the adapting odor concentration is increased, the number of larvae that respond to the test odorant is decreased (Figure 2); at sufficiently high concentrations, there is no evidence that larvae can discriminate the test odorant from the blank (Wuttke, 1999).

Stimulus features such as concentration and exposure duration produce comparable influences on the adaptation process in humans. In numerous studies that have examined adaptation and recovery to a wide variety of odorants, it has been shown that although the decline in perceived intensity follows a characteristic exponential decay function, the rate and degree of adaptation and the temporal kinetics of recovery are both concentration- and duration-dependent (Cain, 1974; Berglund, 1974). At the extreme, where studies have used prolonged exposure durations, the level of adaptation can rise to the level of the adapting stimulus and yield the impression that the odor has completely disappeared (de Wijk, 1989).

The relationship between the adapting concentration and the test concentration is also an important determinant of the magnitude of perceived adaptation, with the perception of weaker concentrations showing greater perceptual suppression than stronger concentrations. As illustrated by the data collected by Stone and colleagues (Figure 3), adaptation steepens the slope of the psychophysical function relating concentration to perceived intensity across a wide variety of odorants, consistent with findings in other modalities (Stone *et al.*, 1972).

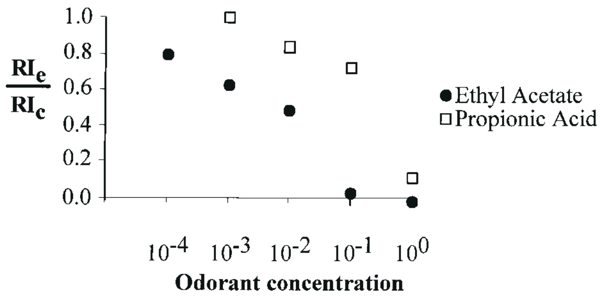

Figure 2 The effect of odorant concentration on the degree of adaptation to that odor among *Drosophila* larvae. The RI was calculated as in Figure 1. Pre-exposure to stronger concentrations of the adapting odorant significantly reduced the number of larvae that responded to the odorant disk, thereby demonstrating adaptation. Adapted from (Wuttke, 1999).

A third defining feature of olfactory adaptation is that the exposure-induced decrease in sensitivity or perceived intensity is specific to the adapting odorant. Although adaptation to one odor may generalize to a small subset of other chemicals that share structural or perceptual features with the adapting odorant [i.e. cross-adaptation (Pierce *et al.*, 1996)], in general, self-adaptation is more profound than any observed cross-adaptation (Köster, 1971). Dalton and colleagues tested a group of workers who had daily occupational exposure to acetone and a matched group of controls for their sensitivity and rated intensity of acetone and another control compound (Dalton *et al.*, 1997; Wysocki *et al.*, 1997). The workers rated the odor of acetone as much weaker than did the controls; workers also exhibited elevated detection thresholds for acetone. However, no differences among groups were found to the control odorants (butanol and phenylethyl alcohol), suggesting that the adaptation observed from exposure to acetone did not generalize to all odorants.

The temporal kinetics of recovery from adaptation may differ when viewed at the neural versus the perceptual level. For example, the duration of adaptation at the periphery

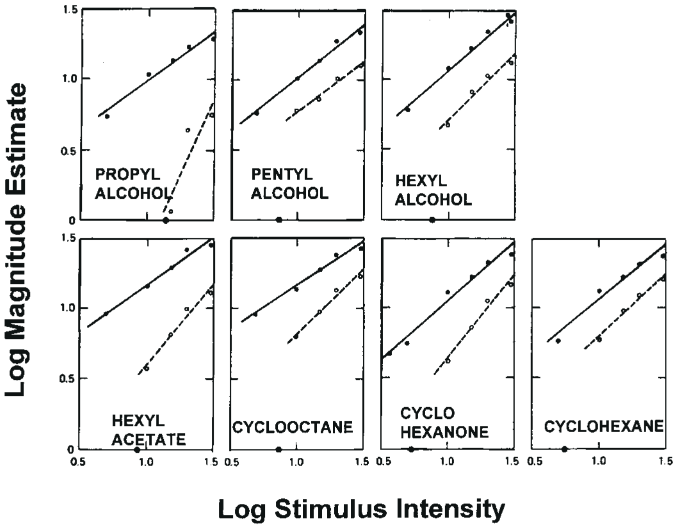

Figure 3 The relationship between the adapting concentration and the test concentration of an odorant for a variety of chemicals with different physical properties. As a general rule, test concentrations that were weaker than the adapting stimulus showed more suppression than did concentrations that were stronger than the adapting stimulus; this interaction between adapting and test odorant concentration produces an increase in the exponent (steepening) of the psychophysical function during adaptation. Figure reprinted from (Stone *et al.*, 1972), with permission.

that is considered 'long-lasting' is on the order of minutes (Zufall and Leinders-Zufall, 1997), yet both anecdotal and experimental examples of perceptual adaptation appear much more durable, with decreased sensitivity often persisting for hours beyond the original exposure (Gagnon *et al.*, 1994; Colbert and Bargmann, 1995). Moreover, there is evidence that repetitive exposure can induce a form of adaptation of even longer duration. Dalton and Wysocki found that when individuals were exposed to odors in their homes for 6 h per day for 2 weeks, recovery to baseline olfactory sensitivity for the adapting odor did not occur for >2 weeks following the last exposure (see Figure 4) (Dalton and Wysocki, 1996). The neural basis, if any, for such persistence remains unclear.

Locus of adaptation

Exploiting the duality of the inputs to the olfactory modality (that is, separate nares leading to separate groups of olfactory receptors with convergence at the level of the olfactory bulb) provides investigators with an important strategy for examining the contributions of peripheral (receptor) and central (bulb and cortex) structures on the process of olfactory adaptation. One nostril can be exposed to an odorant for some duration and then threshold or suprathreshold sensitivity can be tested to the same or the opposite nostril (Köster, 1971; Cain, 1977).

Using this methodology, Stuiver showed that, after adapting one side of the nose to 2-octanol or *m*-xylene, recovery to baseline sensitivity, measured at threshold, was always faster for the contralateral side (Stuiver, 1958). Similar results can be found at suprathreshold levels. Cain tested the effects of unilateral adaptation to linalyl acetate or a diluent on the perceived intensity of different concentrations of the adapting odorant (Cain, 1977) and found that the reduction in perceived intensity was always greater for the ipsilateral than for the contralateral nostril (Figure 5), although perception for both was attenuated relative to an unadapted nostril. Although it is possible that some of the adaptation in the contralateral nostril can be explained by retronasal olfactory stimulation during exhalation, these results at least suggest that both peripheral and central structures are involved in the process of olfactory adaptation. Although the CNS substrate for effects of contralateral adaptation on unilateral intensity ratings is not clear, fibers projecting topographically from the accessory olfactory nucleus on each side to the contralateral olfactory bulb provide evidence of communication between the ipsilateral and contralateral olfactory pathways in the CNS (Shipley and Adamek, 1984).

Non-sensory influences on adaptation

Finding varying degrees of concordance between peripheral neural responses and an organism's measured sensitivity or responsivity is not merely evidence that dissociations exist in the conductance or transmission of the neural activity to the brain. In fact, there are numerous other factors, from preneural events to cognitive processes, that hold the potential to significantly influence the degree and rate of adaptation and recovery to an odorant.

A complexity in olfaction, unlike in vision or hearing, is the fact that chemical stimulation does not terminate after removal of the stimulus. Thus, while some degree of observed olfactory adaptation could be due to changes in the response characteristics of the receptors, another contribution to decreased sensitivity could be due to a delay in signal termination because the chemical stimulus has not been cleared from the peri-receptor environment. Both within- and across-individuals, differences in odorant clearance, and therefore the degree of adaptation and recovery, could result from differences in the physico-chemical properties of various odorants or variation in peri-neural clearance mechanisms such as nasal submucosal blood flow, nasal mucociliary clearance and expiratory desorption (Dalton and Scherer, 1999). Studies are currently underway to evaluate the role of many of these variables on the adaptive response.

Additionally, research has shown that post-sensory cognitive processes can exert a considerable influence on the magnitude and degree of adaptation when measured by subjective intensity estimates. Individuals who were given a negative characterization about the consequences of exposure to an odorant, whether through experimenter-provided instructions (Dalton, 1996) or the verbal cues or behavior of

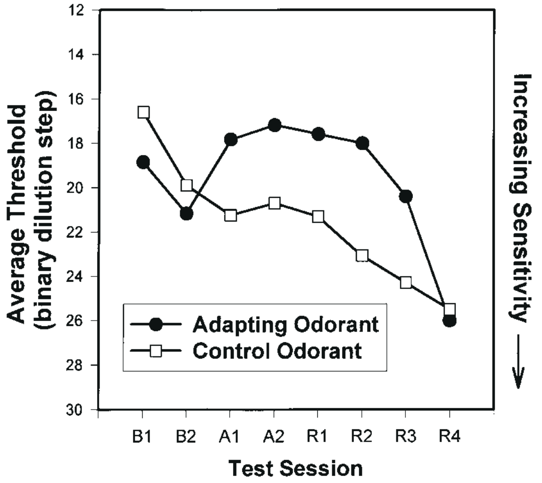

Figure 4 The effect of long-term exposure to an odorant on sensitivity as measured by olfactory thresholds. 10 subjects were exposed for two weeks in their home to a single odorant (half were exposed to benzyl acetate, BA, and half to geraniol, G); at weekly intervals they were given threshold tests for their adapting odorant (BA or G) and a control odorant (the alternate odor). B1 and B2 refer to baseline tests, prior to odorant exposure; A1 and A2 refer to tests during adaptation phase; and R1–R4 refer to tests following removal of the odorant from their home (recovery). Thresholds were significantly elevated to the exposure odorant, but not to the control odorant. Moreover, sensitivity to the adapting odorant did not return to baseline for most subjects until three weeks after the odorant had been removed from their home (P. Dalton, unpublished data).

a confederate subject (Dalton *et al.*, 1999), showed much less adaptation across a 20 min exposure than did individuals who were exposed to the same odor but who were given a neutral or positive characterization of the odorant. Yet, detection thresholds obtained before and after exposure showed adaptation effects (i.e. were elevated) for all groups, suggesting a dissociation between the peripheral signals and the central signals that provide input to each type of response.

Summary

The perceptual characteristics of olfactory adaptation have been described in numerous behavioral and psychophysical experiments. Nevertheless, fundamental questions remain regarding many of the determinants of the adaptation process and the dominant locus (peripheral versus central) of olfactory adaptation. Parallel investigations of the temporal kinetics and mechanisms of adaptation at the cellular and perceptual levels that it is now possible to pursue in both animal and human models (Rawson *et al.*, 1997; Zufall and Leinders-Zufall, 1997; Reisert and Matthews, 1999) promise to advance our understanding about the process of olfactory adaptation—a fundamental type of noncontingent learning that allows organisms to accommodate and remain responsive to a dynamic olfactory environment.

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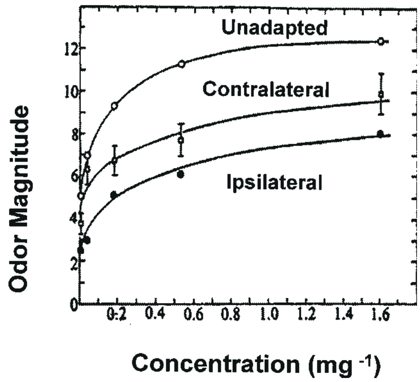

Figure 5 The effect of unilateral adaptation on the perceived intensity of the ipsilateral versus the contralateral nostril. When one nostril was adapted to linalyl acetate (LA), the subjective magnitude of varying concentrations of LA presented to the ipsilateral nostril were significantly lower than the magnitude of the LA when presented to the contralateral nostril. When the subjective magnitude of LA was rated following unilateral adaptation to clean air, both (ipsi- and contralateral) nostrils showed effects of adaptation. Reprinted from (Cain, 1977), with permission.

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