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Olfactory Adaptation

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Introduction

Summary

Introduction

The phenomenon of olfactory adaptation reflects itself in a temporary decrease in olfactory sensitivity following stimulation of the sense of smell. Olfactory adaptation can be seen in increases in odor thresholds and decreases in odor intensities. Adaptation poses issues that require understanding in their own right, such as the magnitude of desensitization, the time-course of desensitization and recovery to normal sensitivity, and ultimately the mechanisms responsible for these phenomena. In principle, however, the study of adaptation could also provide important clues regarding receptor specificity. Behind this hope lies the expectation that stimuli impinging upon many receptors in common will induce substantial cross-adaptation (where the adapting stimuli differ from the test stimuli), whereas stimuli impinging on very few receptors in common will not. Unfortunately, the picture that emerges from studies of cross-adaptation in regard to this issue is far from clear.

A general consideration in the study of olfaction is the precise production and delivery of the stimulus. Chemical substances cannot be generated and directed to the target sensory organs as easily and accurately as, for example, tones or lights. On the other hand, olfactory experiments that artificially control every variable (onset of stimulus, flow, humidity, temperature, duration, site of stimulation, offset of stimulus) may produce results difficult to reconcile with realistic situations. After all, there is evidence that natural sniffing

gives optimum odor perception for humans (Laing, 1983). Such considerations take on special importance in the study of adaptation. In studies of the time–course of adaptation, natural sniffing produces temporal variations in the stimulus. Such variations undoubtedly have consequences for how likely an odor is to fade over time or how readily one stimulus may desensitize a person to another (Berglund, 1974). The pulsatile nature of the stimulus, though ecologically realistic, may obscure physiologically relevant differences between odorants. In the future, a comparison of adaptation during continuous flow to the receptors with that during natural sniffing could reveal what, if anything, the pulsatile character of natural sniffing obscures or perhaps sharpens. Recently developed olfactometers (Kobal, 1985) now permit relatively comfortable exposure to continuous stimulation for at least minutes (See Chapter 8).

In this chapter we discuss findings from studies of olfactory adaptation with regard to odor thresholds, perceived odor intensities, odor quality, reaction times to odors, sensitivity across odors, and pungent or irritant effects of odorants.

Specific questions addressed include the following:

1) What is the time–course of adaptation when measured at the threshold level? That is, does desensitization occur rapidly? Is the final effect large? Does recovery occur quickly or slowly?

2) Is the time–course of adaptation different between threshold and suprathreshold stimulation? Are rate of adaptation and recovery concentration–dependent at suprathreshold levels?

3) Do the time–course of adaptation and the time–course of recovery vary meaningfully from odorant to odorant?

4) Does the perceived magnitude of an odorant predict its potency as an adapting stimulus?

5) Does adaptation reflect itself in measures other than perceived intensity and detection, e.g., reaction times and judgments of odor quality?

6) Does adaptation to one odorant generalize broadly to other odorants, i.e., is cross–adaptation a broad or narrow effect?

7) Does cross–adaptation show symmetry? That is, if exposure to one substance causes desensitization to another, will exposure to the second cause a comparable desensitization to the first?

8) Do adaptation and cross–adaptation cause changes in odor quality?

9) Do adaptation and cross–adaptation reflect effects at just the olfactory receptors?

10) Does vulnerability to adaptation vary from one group of subjects to another?

I. <u>Effects on Thresholds.</u>

Olfactory thresholds rise — that is, absolute olfactory sensitivity diminishes — as a result of adaptation. As noted by Stuiver (1958), the extent to which this occurs depends principally on two factors: adaptation <u>time</u> and the <u>concentration</u> of the adapting stimulus. Figure 1 illustrates the relationship between the rise in olfactory threshold (expressed as multiples of unadapted threshold concentration) and the adapting time for various adapting concentrations of the odorant 2-octanol. The increase in threshold with adaptation time is more pronounced with high adapting concentrations. At first, adaptation produces a steep rise in the threshold and, over time, the increase in threshold becomes progressively smaller.

Insert Figure 1 about here

If the adaptation time is long enough, the olfactory threshold can apparently rise to the concentration of the adapting stimulus and, according to some studies, the adapting stimulus may eventually no longer be perceived. This has been called the adaptation time required for the cessation of smell (ATCS) (de Wijk, 1989; Elsberg and Levy, 1935; Mullins, 1955; Stuiver, 1958; Woodrow and

Karpman, 1917). As Figure 2 shows, ATCS increases with the concentration of the adapting stimulus and varies with the test odorant.

Insert Figure 2 about here

In real situations, perception of an odor over long periods of time presumably depends on the level of attention that the subject pays to a stimulus and on the manner of breathing, i.e., inhaling in such a way as to maximize odor magnitude though not necessarily on every breath (Cain, 1974b). Level of attention most likely varies with odor quality and context. For example, pleasant or neutral odors probably drift from attention quicker than unpleasant odors, which can be quite persistent. The issue of whether or not odors truly completely disappear — that is, produce complete adaptation — remains unresolved (Engen, 1982). Ideally, studies of olfactory adaptation should employ a methodology that minimizes expectations and controls the odor–reporting criterion of a subject. As discussed in the next section, the method of stimulus presentation (stimulus delivery interrupted by normal breathing vs. continuous presentation) may be one influence whether or not complete disappearance of the odor sensation occurs.

Köster (1971), employing m–xylene as the stimulus, found that even very low adapting concentrations (i.e., those between 2 and 4 times the unadapted threshold) and smelled for one sniff, will decrease the percentage of positive responses to test stimuli of the

same level as the adapting concentration. This adaptation effect held despite a 60 sec interval between adapting and test stimuli. Köster's experiments highlight how changes in sensitivity due to adaptation go on more or less continuously throughout everyday life with its fluctuations of volatile organic chemicals from materials, bodies, foods, vegetation, etc. It is relatively easy to find some functional value in continuous modulation of sensitivity. Presumably, a nose more or less at equilibrium with its surroundings will stand ready to respond to or bring to consciousness changes in the composition of the airborne chemical environment (see Berglund, 1974).

No studies of the time–course of changes in absolute sensitivity have answered the question of whether rate of change varies meaningfully from one substance to another or depends in a systematic fashion on physicochemical and molecular properties of odorants. Stuiver's measurements suggest that adaptation to 2–octanol may progress more rapidly than adaptation to m–xylene, and that may take more time to recover than m–xylene. Since Stuiver's astonishingly extensive results came mainly from a comparison of two odorants and the use of himself as a subject, their generality is unknown. Recovery of sensitivity is on the other side of the coin from adaptation. Stuiver (1958) adapted the nose to one or another level of an odorant until no smell sensation was perceived, and then followed the time–course of recovery toward original olfactory sensitivity. Figure 3 depicts how the thresholds approached the value of the unadapted threshold concentration (value of 1 on the ordinate) as recovery time increased. Recovery of sensitivity was fast

in the beginning and slower afterwards, a result also found by Köster (1971) for a number of other odorants. Stuiver's curves imply that after adaptation following strong stimulation, full recovery may take hours.

Insert Figure 3 about here

Berglund and colleagues (Berglund, Berglund, Engen, and Lindvall, 1971) adapted subjects with concentrations below and above a classically measured threshold for hydrogen sulfide (H_2S), and then measured the proportion of hits (correct detections) and false alarms to subsequent presentations of near–threshold H_2S concentrations. The concentration of the adapting stimulus affected hit rate in an expected manner: the highest hit rate occurred after the weakest adapting stimulus, whereas the lowest occurred after the strongest adapting stimulus. False alarm rate was high throughout testing, at least 15% and often 30%, even when subjects received immediate feedback about the correctness of their responses. (False alarm rates can vary over a wide range depending on a priori probability of presentation of a stimulus, payoff matrix, and other factors that may alter a subject's decision criterion. What we might call the baseline case of 50% probability of presentation and a symmetrical payoff matrix will rarely lead to rates of false alarm of 15–30 % outside of olfaction.) The results show that odor perception is a difficult signal–detection task, and highlight the need to consider the olfactory response as detection of a signal in a very noisy background. It is conceivable that earlier results obtained by classical

techniques may have been influenced to some degree by the lack of control of the response criterion. This situation has particular relevance to the results of Stuiver (1958), who often served as his own subject. In light of this criterion issue, the observations of Stuiver need to be confirmed.

Arguing that the presentation of an adapting stimulus may raise the criterion for calling a test stimulus odorous independent of any change in sensitivity, Corbit and Engen (1971) employed a signal detection procedure (Green and Swets, 1966) to assess the influence of adaptation on thresholds for homologous alcohols. They also found the decrement in sensitivity observed in threshold studies after self-adaptation; however, some facilitation (i.e., <u>decrease</u> in the threshold) after cross-adaptation with certain stimulus pairings was also noted. The phenomenon of cross-facilitation has considerable potential importance for the understanding of olfaction and arguably could only be demonstrated convincingly at near threshold levels by the techniques of signal detection theory. (Cross-adaptation is discussed in Section V.) Unfortunately, in what is perhaps the most labile of the senses, with high background noise level which invites a critical role for decision criterion, psychophysical techniques compatible with signal detection theory have seen hardly any use.

If seen just as broad outlines of the process of adaptation and recovery, what can data such as that described above tell us? They indicate the approximate rates at which stimulation causes desensitization and at which recovery occurs in absence of

stimulation. However, since studies of the influence of physicochemical properties of the stimulus (e.g., solubility factors) on adaptation have not been made, these observations tell us little about the degree to which adaptation reflects neural or preneural events.

II. Effects on suprathreshold odor intensities.

It is much easier to study the time–course of adaptation at suprathreshold than at threshold levels. Measurement of a threshold at the end of an adaptation period before significant recovery has begun requires many adaptation trials per subject and a tremendous investment of time. This problem exists whether one uses classical psychophysical techniques or more modern detection techniques. In the case of suprathreshold judgments, particularly those obtained using cross–modality matching, for example matching finger span or magnitude of handgrip to perceived odor intensity (see Chapter 8), subjects can register the strength of sensation without any interruption of exposure. Using finger–span to chart the magnitude of odor sensation over time, Ekman and colleagues (Ekman, Berglund, Berglund, and Lindvall, 1967) found an exponential decay of the perceived intensity of H_2S for constant concentrations ranging from 0.7 to 6.4 ppm (Figure 4). Rate of adaptation tended to decrease with increasing concentration. Results from individual subjects showed that often the odor sensation did not disappear completely even after 15 min of stimulation. Recovery was fast at first, though

remained incomplete even 3 to 4 min after cessation of adaptation. There was a tendency for speed of recovery to increase with the concentration of the adapting stimulus.

Insert Figure 4 about here

Cain (1974b) followed up the work of Ekman et al. (1967) with a comparison of rates of adaptation across the odorants propanol, ozone, eugenol, and butyl acetate. Perceived intensity declined exponentially as in the previous investigation. Rate of decline varied little from one odorant to another and, as in the previous work, tended to decrease with increasing odorant concentration. The functions approached an asymptote in the vicinity of 30–40 % of initial perceived magnitude by about 4 min. Berglund, Berglund, and Lindvall (1978) found similar asymptotic perceived intensity (25–40 %) and little difference in rate of adaptation for the malodors H_2S, dimethyl disulfide, and pyridine.

The effect of adaptation on suprathreshold odor magnitude can be observed via a transformation of the psychophysical function relating stimulus concentration to perceived odor intensity. Cain and Engen (1969) found that as the level of adaptation increased, so did the steepness of the psychophysical function, a finding compatible with that shown in other modalities such as brightness vision. Adaptation was achieved by having the subject take some breaths of an adapting concentration just prior to sampling each of several target concentrations. The increase in slope results from the

proportionally larger reduction in perceived odor intensity of the lower concentrations compared to the higher concentrations, a result obtained in various experiments with other odorants (Cain and Polak, 1992; Pryor, Steinmetz, and Stone, 1970; Stone, Pryor, and Steinmetz, 1972; Todrank, Wysocki, and Beauchamp, 1991). Not uncommonly, the perceived intensity of high test concentrations may show no change after adaptation to a low or moderate adapting concentration.

The steepening of the psychophysical function under adaptation is essentially compatible with the notion that adaptation puts the nose more or less in equilibrium with the ambient environment and ready to respond to changes in stimulation. Such steepening is also compatible, however, with simple pharmacological or physiological models of molecular site–filling.

Cain (1970; see also Cain and Engen, 1969) used the transformation of the psychophysical function as an outcome variable to address the question of whether adapting stimuli matched in perceived intensity cause the same degree of self–adaptation. The positive answer obtained to the question implied internal consistency between perceived intensity and adapting potential. Hence, whatever properties determine the perceived intensity of a particular stimulus, also determine its effect as a self adapting stimulus. Cain and Polak (1992) similarly obtained a positive answer to the question (see Figure 5).

Insert Figure 5 about here

There are instances where psychophysical functions for odor intensity show local flattening at the lowest concentrations of test stimuli. Quite possibly, such an outcome again reflects the relatively high false alarm rate for olfaction. In this case, the "false alarm" reveals itself in an inflated rating rather than in the mere claim of positive detection. These ratings may mask the "true" form or curvature of the psychophysical functions at low levels and may imply more stability than warranted in the exponential decay functions for the time–course of suprathreshold adaptation. The issue has more than just theoretical relevance in various instances. Figures 6 and 7 show the ratings of periodic visitors and occupants of an environmental chamber to the odorant pyridine injected at various constant rates (injection begun at time indicated by arrow) (Cain, Leaderer, Cannon, Tosun, and Ismail, 1987). These measurements were design to learn how well workers in a confined space might react to a leak of inert gas odorized with pyridine. The higher the rate of injection, the sooner and more abrupt were the changes in ratings above background (some background odor came undoubtedly from the bodies of the occupants). Occupants where not required to sniff the air continuously but only when they needed to make their periodic judgments (5 min intervals). Nevertheless, the occupants exhibited the effects of adaptation in their somewhat compressed judgments compared to those of the visitors, who sat in unodorized surroundings between judgments. The degree of adaptation measured in this environmentally more–or–less realistic circumstances

(e.g., smelling of ambient odorized air rather than air delivered to the nose via an olfactometer, and absence of a requirement to sniff on every inhalation) seemed smaller than expected. This proved even more the case when occupants judged constant concentrations of pyridine (Figures 8 and 9). Although the occupants exhibited a general net reduction in rated intensity, their functions differed only a small amount from those of visitors.

Insert Figures 6, 7, 8, and 9 about here

How should we interpret the results with pyridine, particularly those in Figure 8? Should we conclude that under environmentally realistic circumstances adaptation has a negligible effect on perceived intensity? Is its unpleasant character responsible for its continued effectiveness? Is pleasantness a crucial variable to explore? If pleasantness matters, then it would seem that adaptation must be controlled largely in the central nervous system where presumably pleasantness is discerned. Do the demand characteristics of the psychophysical experiment give an unrealistic picture of the decay?

Quite possibly, for stimuli of environmental or ecological importance, complete adaptation may not occur when subjects are breathing freely. As pointed out by Köster and de Wijk (1991), experiments in awake animals (rabbits) showed a respiration–related synchronization of mitral cell activity in the olfactory bulb, resulting in activation during inhalation and inhibition during exhalation (Chaput and Panhuber, 1982). This effect conceivably prevents complete

adaptation during normal breathing. Of course, the specific odorant used may also prove crucial in influencing adaptation. For example, substances that stimulate both the olfactory and trigeminal nerves probably are less likely to produce complete adaptation than substances which stimulate, for the most part, the olfactory nerve (see Section VIII). As far as we could tell, however, pyridine at the concentrations studied in the chamber had not trigeminal effects.

An environmental chamber investigation of the odor and irritation (in eyes, nose, and throat) produced by airborne formaldehyde vapors found that both types of sensations increased with time (potentiation) at relatively low concentrations, but decreased (adaptation) at relatively high concentrations (Cain, See, and Tosun, 1986). Irritation of the eyes, nose, and throat was more resistant to adaptation than was odor (see Section VIII), an outcome also found using a mixture of volatile organic compounds (Hudnell, Otto, House, and Mølhave, 1992). As discussed below (Section VII), there are indications that mixtures exhibit less adaptation than single substances (Schiet and Cain, 1990).

III. Effects on reaction time.

Electrophysiological investigations in animals have found the latency of the gross olfactory receptor potential, termed the electroolfactogram (EOG), to fall between 100 and 400 msec

(Ottoson, 1956; van As, Kauer, Menco, and Köster, 1985). The latency of this initial electrical activity may largely reflect preneural events such as diffusion of molecules through mucus to receptor sites. Latencies obtained from recordings of single receptor cells have offered little refinement of this picture since they are quite variable, both among odorants and among cells stimulated with the same odorant (see Gesteland, 1976; Getchell, Heck, DeSimone, and Price, 1980).

de Wijk (1989) measured reaction times of 1000 to 1500 msec to odorous stimuli at moderate to high concentrations. Reaction times of this order are quite long compared to values of around 500 to 600 msec found by other investigators (Cain, 1976). Nevertheless, even these reaction times are long relative to those seen in other senses (e.g., for sound, an analogous reaction time is about 170 msec; Kohfeld, Santee, and Wallace, 1981). Irrespective of the absolute values measured in any given experiment, changes in reaction time could in principle provide a relatively simple index of magnitude of adaptation. de Wijk (1989) found that both self–adaptation and cross–adaptation increased olfactory reaction time. One of the most intriguing phenomena had to do with the relative stability of reaction time under adaptation. The stimulus geraniol, which had a long reaction time in the unadapted case, showed a smaller relative increase than hexane, which had a short reaction time in the unadapted case. After adaptation, however, both had the same (lengthened) reaction time. Another curious phenomenon concerned cross–facilitation. de Wijk found it in magnitude estimations but not in

reaction times. Hence, a subject would find a test stimulus stronger smelling when presented after a cross–adapting stimulus, but the latency of the response would be longer, just as if cross–adaptation had occurred. This suggests an unusual origin for the phenomenon of cross–facilitation, a phenomenon that appears regularly enough to be taken quite seriously.

IV.   <u>Effects on Odor Quality</u>

Odor quality may vary with odor intensity. A stimulus such as ethyl mercaptan, which is used as a warning agent for LP gas, smells like scallions when quite weak, like skunk when stronger, and like rotten eggs when stronger still. Little has been said or apparently observed about changes in quality from adaptation–induced changes in perceived intensity. Both the issue of why quality varies with intensity and whether it does with adaptation have importance. So too does the question of whether quality changes as a result of cross–adaptation (Cain, 1988). Cross–adaptation can lead to changes in quality when a single odorant is used as the adapting stimulus and a mixture that includes the adapting odorant is used as the test stimulus. The quality of the mixture will then shift away from that of the adapting stimulus and toward that of the other components (de Wijk, 1989). When the cross–adapting and test stimuli are both single constituents, however, there seems to be little if any alteration in quality. This matter has not been subjected to actual experimentation, but those who have sought to convince themselves

that cross–adaptation–induced changes should occur have found the stability of quality impressive. If we can assume such stability to be essentially correct, then we may ponder its implications.

In color vision, prior adaptation to monochromatic light of 580 nm (yellow) will make a monochromatic light of 610 nm (orange) seem red, and adaptation to 630 nm (red) can make the orange light (610 nm) seem yellow. Such shifts occur because of the breadth of spectral sensitivity of the three types of individual cones. Similar effects occur in taste. Why not in smell too? One possibility is that sensitivity to any given molecule (odorant) is distributed broadly across receptor cells, such that many cells will respond to an odorant. These cells will also respond to another odorant, but the distribution of sites across the cells would differ from that for the first odorant. This would mean that a given cell might prove much more sensitive to odorant A than to odorant B. Another cell might prove much less sensitive to odorant A. Another, a little more sensitive, etc., until many different combinations of relative sensitivity would be found. Under this kind of arrangement, prior presentation of odorant A would reduce the detectability or perceived magnitude of odorant B, but would not necessarily change its quality. With enough different kinds of receptor elements (protein molecules), each distributed more or less independently across receptor cells, but with multiple types of elements on any given cell, the pattern of the neural message (and hence quality) would be preserved in a statistical sense in spite of the desensitizing influence of a cross–adaptation. This picture is compatible with the known facts that there are not obvious

functionally different types of receptor cells, that there are many different types of receptor sites (protein molecules), and that cells will show all varieties of cross–adaptation, no cross–adaptation, and cross–facilitation (see Baylin and Moulton, 1979).

As a methodological matter we can note that irrespective of any shifts in quality that might be found to occur, any claims of such shifts need to control for the influence of context. For example, a recent study found a shift in odor quality when a "conditioning" stimulus <u>followed</u> a test stimulus and thereby provided context without accompanying adaptation (Lawless, Glatter, and Hohn, 1991).

V. <u>Self–adaptation vs. Cross–adaptation</u>

The absence of gross and pervasive changes in odor quality suggests at the least that olfactory receptors are not organized into a very small number that can be disabled as a class by cross–adaptation. What then can be learned from studies of cross–adaptation? One thing is that cross–facilitation is not likely just a fluke. Results of a study on olfactory thresholds for three aliphatic alcohols (1–propanol, 1–butanol, and 1–heptanol) under no adaptation and under all possible combinations of adapting and test stimuli showed the usual decrement in sensitivity (i.e., rise in the thresholds) typical of self– and cross–adaptation studies. In addition, a facilitation of detection (i.e., decrement in the thresholds) with certain stimulus

pairings was also observed (Corbit and Engen, 1971). Specifically, heptanol facilitated the detection of the other two odorants.

A previous study demonstrated similar facilitatory effects with infants when 1–octanol served as adapting stimulus, and 1–propanol and 1–butanol served as test stimuli (Engen and Bosak, 1969). Failure to produce facilitation in mixtures of those same stimuli led to the conclusion that the effect depends on the appropriate temporal pairing of the long– and short–chain alcohols (adapting and test stimuli, respectively). Differences in the rate of penetration in the mucosa, probably due to differences in water solubility of the odorants, were seen as a possible reason for the facilitation. In fact, however, there have been no good theories to account for cross–facilitation.

Based on his extensive results on adaptation and cross–adaptation in the vicinity of threshold, Köster (1971) formulated a number of rules concerning these phenomena. The most important ones can be summarized as follows (Köster and de Wijk, 1991):

"1. No adapting substance enhances the sensitivity to another substance.

2. No other substance reduces the sensitivity to a given odorous substance to a larger degree than that substance itself.

3. An odorous substance may have a larger adapting effect on the sensitivity to another substance than it has on the sensitivity to itself.

4. Most cross–adaptational relationships are non–reciprocal (i.e., asymmetric). One substance influences the sensitivity to another substance to a larger degree than the second one influences the sensitivity to the first one.

5. The sensitivity to an odorous substance which self–adapts rather strongly is usually also reduced strongly by other odorous substances."

Although the last four of these rules are in accord with the general literature, the first rule contradicts the findings of cross–facilitation by some investigators (Corbit and Engen, 1971; de Wijk, 1989; Engen and Bosak, 1969). One possibility is that novelty or contrast effects operate in the instances of facilitation found in the literature (Köster and de Wijk, 1991). As noted in Section IV, contrast (or context) may produce shifts in odor quality (Lawless, Glatter, and Hohn, 1991).

In order to test the hypothesis of whether cross–adaptation is more likely to occur for perceptually similar than dissimilar odors, a recent investigation addressed the issue of the effects of adaptation to a single odor on the sensitivity to similar and dissimilar odors (Todrank, Wysocki, and Beauchamp, 1991). In this study, identification (rather than detection) thresholds, and perceived intensities, constituted the responses of choice. In general, the outcome supported the hypothesis, and also confirmed that cross–adaptation is frequently asymmetric, even between perceptually similar odorants.

Cross–facilitation between odorants has been also reported at suprathreshold odor intensities (de Wijk, 1989). This phenomenon is more likely at low concentrations of the adapting and test stimuli, whereas at high concentrations cross–adaptation tends to predominate (Berglund, Berglund, and Lindvall, 1978).

Recently, two structurally different substances with almost identical bitter chocolate odors (trimethyl pyrazine, TMP, and 2–propionyl–3–methyl furan, PMF) were examined for self– and cross–adaptation effects on psychophysical functions of perceived intensity (Cain and Polak, 1992). As previously found for the odorants 1–propanol and 1–pentanol (Cain, 1970), the stimulus–response functions for TMP and PMF became steeper under conditions of cross– and self–adaptation since the adaptation conditions weakened the intensity of low test concentrations proportionally more than higher ones (Figure 5). Even for these perceptually similar odors, cross–adaptation was less effective than self–adaptation. Adapting stimuli of the two compounds at matched intensity levels caused equivalent self–adaptation and equivalent, though weaker, cross–adaptation. Another experiment in the same study confirmed that TMP and PMF produced equal amounts of self– and cross–adaptation to each other, though not on three other test stimuli: anethole, ethyl butyrate, and 2,3 pentanedione. PMF showed a bit more effectiveness as cross–adapting stimuli on these three chemicals than TMP.

As in the case of self–adaptation, reaction times to odors become longer after cross–adaptation (de Wijk, 1989). With the exception noted for the first of Köster's rules for adaptation, the rest proved to be valid also for reaction time measurements to odorants presented at suprathreshold intensities. In fact, increases in adaptation time from three to five seconds failed to affect the perceived intensity of the test stimuli, but led to longer reaction times to those same stimuli. This demonstrates the sensitivity of reaction time as an indicator of olfactory adaptation.

Electrophysiological experiments in animals show that <u>olfactory receptors</u> exhibit decreased excitability when an odorous stimulus is presented either continuously (Getchell and Shepherd, 1978) or repeatedly within a limited period of time (Baylin and Moulton, 1979; Ottoson, 1956; van Boxtel and Köster, 1978). The number of evoked action potentials in single unit recordings from the salamander olfactory receptors decreases and their pattern changes after cross–adaptation. As in the case of human studies, these effects are often asymmetric when adapting and test odorant are switched (Baylin and Moulton, 1979).

Single–unit recordings from <u>olfactory bulb neurons</u> in rats were analyzed (Mair, 1982) in an attempt to seek an electrophysiological basis for the phenomena of cross–facilitation seen in some human experiments. Successive presentations of the same stimulus evoked similar patterns of activity during each presentation. Some neurons exhibited increased (facilitative) and others decreased (suppressive)

excitability in the adapted state. In cross–adaptation trials, the number, but not the pattern, of action potentials evoked by the second odorant differed from the unadapted state. Again, some neurons exhibited increased and others decreased excitability in the cross–adapted condition, and, as with the peripheral receptors, instances of asymmetrical cross–adaptation were noted. The study concluded that neurons in the olfactory bulb differ in both the type (facilitative or suppressive) and extent of adaptation evoked by a given odorant.

VI.   Ipsi–lateral vs. contra–lateral adaptation: implications for locus of adaptation

One strategy for addressing the relative roles of peripheral (i.e., olfactory receptors) and central (i.e., olfactory bulb) structures in the production of olfactory adaptation entails (i) adapting one side of the nose to an odorant, and (ii) testing threshold or suprathreshold sensitivity to the odorant on the same (ipsilateral) and opposite (contralateral) sides of the nose (Cain, 1977; Elsberg and Levy, 1935; Köster, 1971; Stuiver, 1958).

An early threshold study using coffee and citral as stimuli showed that monorhinal adaptation for 30 to 180 sec to one of these odorants resulted in longer recovery times in the ipsilateral than in the contralateral side (Elsberg and Levy, 1935). In a later threshold study, Stuiver (1958) adapted one side of the nose with

either m–xylene or 2–octanol; the time required to regain the original sensitivity was measured in both the same and the other nostril (Stuiver, 1958). As Figure 10 illustrates, both sides of the nose exhibited adaptation, but the effect was weaker on the contralateral side, which regained its former sensitivity much sooner than the ipsilateral side. Similar findings were found by Köster (1971) for m–xylene.

Insert Figure 10 about here

Psychophysical functions for the odorant linalyl acetate obtained under conditions of no adaptation, ipsilateral adaptation, and contralateral adaptation reveal that similar results can be found at suprathreshold levels (Figure 11) (Cain, 1977). That is, both ipsi– and contralateral adaptation reduce the perceived odor magnitude of linalyl acetate throughout the range of concentrations tested, with ipsilateral adaptation producing a larger decrease than contralateral.

Insert Figure 11 about here

In another experiment, differences between ipsi– and contra–lateral adaptation again revealed themselves in the direction mentioned: ipsilateral more effective than contralateral, but only in measurements of perceived odor intensity, not in measurements of odor reaction times (de Wijk, 1989). This led to the conclusion that the mechanisms underlying such differences become operational at later stages of stimulus processing, approximately 0.4 to 6 sec after

the start of stimulation, since this is the time over which stimulus processing for perceived intensity takes place. Reaction times, on the other hand, reflect stimulus processing during the first 0.4 sec of stimulation (de Wijk, 1989).

Stuiver (1958) concluded that thresholds measured immediately after adaptation are highly dependent upon the product of intensity (reflected by the odorant concentration) and time of adaptation (I x T), whereas thresholds measured after 100 sec of recovery vary only with the fourth root of such product, $(I \times T)^{1/4}$. Figure 12 shows that when both the amount and duration of stimulus used to provoke adaptation are large (large C x T, where C = adapting concentration and T = time of adaptation), the differences between the threshold measured immediately after adaptation and that measured after 100 or 200 sec of recovery are also large. Such differences are much smaller when low amounts of odorant are used to provoke adaptation. This means that the relatively fast, central component of adaptation plays a proportionally much smaller role at low stimulus amounts. We conclude that, in order to minimize the influence of the central component of adaptation, one should employ a stimulus of low intensity, adapt for a short duration, and allow some time for recovery before making the measurement (Köster, 1971).

Insert Figure 12 about here

The differences that have been found between the adaptation of the ipsilateral and contralateral sides of the nose presumably

reflect, at least in part, (i) the degree of peripheral neural involvement in adaptation (absent when the contralateral side is tested), and (ii) attenuation in the effectiveness of the adapting stimulus stemming from the transfer of influence to the contralateral side. These results point towards the existence of two adaptation processes: a peripheral one, characterized by a slow recovery, and a more central one, characterized by a faster recovery. It should be noted that the speed of recovery mentioned here refers to olfactory function as assessed psychophysically, not to electrophysiological or other properties of the respective neural structures.

It is of interest to note in this context that both multiunit (Ottoson, 1956) and single–unit (Getchell and Shepherd, 1978) electrophysiological recordings in animals suggest that olfactory receptors adapt relatively slowly. Measurements of general receptor activity (electroolfactogram, EOG) and of olfactory bulb unit activity during the course of a single continuous odor presentation reveal decrements in the response with time at both levels (Potter and Chorover, 1976). When brief periods without stimulation are introduced between odor presentations, the response of the receptors regains its original level, but bulbar mitral cells do not. Such persistent decrement in response within the bulb is thought to represent a more central process and was termed "habituation" by Potter and Chorover (1976). When the olfactory bulb is cut off from some of its central connections, mitral cells become hyperactive, hyperresponsive, habituate more rapidly, show longer recovery times, and markedly reduced their synchronization to the inhalation cycle as

compared to the intact bulb. These results suggest that while habituation of the mitral cell activity does not depend on centrifugal inputs per se, those inputs exert an inhibitory control that modulates and tunes the mitral cells' response characteristics.

VII. Adaptation and mixtures of odorants

Very few studies have adapted the olfactory system to mixtures of odorants and tested its subsequent sensitivity to each of the mixture components. Similarly, only a few studies have adapted the system to one component of a mixture and then tested for the sensitivity to the mixture. In one such study, de Wijk (1989) employed four odorants (geraniol, 1–8 cineole, hexane, and 1–butanol) to test selected combinations of self– and cross–adapting conditions for the single substances and for binary mixtures. Perceived odor intensities and reaction times were measured. de Wijk found that it is possible to alter the odor quality of the binary mixture, shifting it towards one component, by adapting to the other component. Also, the adapting effect of a binary mixture (e.g., AB) on one of the components (e.g., A) was related to the self– (i.e., A on A) and cross– (i.e., B on A) adapting effects that each of the components exerted on the test stimulus. In turn, the adapting effect of a single odorant on a mixture (e.g., A on AB) was related to the self– (i.e., A on A) and cross– (i.e., A on B) adapting effects that the single odorant exerted on each of the components of the mixture.

In an investigation where subjects were exposed to the odorants in an environmental chamber, binary mixtures of the compounds cineole, geraniol, heliotropine, hexyl salicylate, and linalyl acetate exhibited more resistance to adaptation than the single components (Schiet and Cain, 1990). Thus, mixtures proved more resilient to adaptation, showing more perceptual durability. The generality of this provocative outcome awaits further testing across other compounds, under different conditions of adaptation, and, particularly, beyond two–component mixtures.

VIII. Adaptation and trigeminal attributes of odorants

Studies of the olfactory sense have to deal with the fact that virtually all odorous compounds trigger not only olfactory sensations — Cranial Nerve (CN) I — but also pungent sensations mediated by free nerve endings of the trigeminal nerve (CN V) within the nasal mucosa. Sensations mediated via CN V include stinging, irritation, tingling, freshness, burning, piquancy, and prickliness, among others. (See Chapter 37).

Olfactory adaptation can be influenced by the simultaneous activation of CN V. Such influence is minimized by avoiding strong trigeminal stimulants (e.g., ammonia), by using only low concentrations of substances — CN I thresholds are, as a rule, lower than CN V thresholds (Cometto–Muñiz and Cain, 1990; Cometto–Muñiz and Cain, 1991b; Cometto–Muñiz and Cain, 1993; Cometto–

Muñiz and Cain, 1994; Doty, 1975), or, even, by asking participants to assess separately odorous and pungent attributes (e.g., Cain, 1976; Cain, 1981; Cometto–Muñiz and Hernández, 1990). Nevertheless, a most revealing approach to separate olfactory from trigeminal inputs entails testing of individuals lacking CN V sensitivity (Cain, 1974a), or lacking CN I sensitivity (i.e., anosmics) (Cometto–Muñiz and Cain, 1991a; Cometto–Muñiz and Cain, 1992; Cometto–Muñiz and Cain, 1993; Cometto–Muñiz and Cain, 1994; Doty, 1975; Doty, Brugger, Jurs, Orndorff, Snyder, and Lowry, 1978).

One investigation explored the course of adaptation to butyl acetate using the constant–sensation procedure, employing two subjects with total unilateral destruction of the trigeminal nerve, as well as ten normal controls (Cain, 1974a). Over the course of more than 5 min, normal controls kept increasing the concentration of the odorant in order to maintain perceived intensity at the initial level, implying that they became progressively adapted. One of the two neurectomized subjects showed a significantly higher degree of adaptation in the deficient side (the one with no trigeminal sensitivity), which suggests that an intact CN V can indeed act to slow down the adaptation process. The other neurectomized subject showed virtually no adaptation with either nostril.

When normal subjects were asked to rate separately the perceived magnitude of odor and irritation (pungency) from the same concentrations of 1–butanol after three breaths, the odor intensity diminished (implying adaptation) compared to that after one breath,

whereas pungency increased (implying temporal integration or summation) compared to that after one breath (Figure 13) (Cain, 1976).

Insert Figure 13 about here

In a comparative study of a pungent (ammonia) vs. a benign (isoamyl butyrate) odorant, the perceived magnitude of the former increased with inhalation time (from 1.25 to 3.75 sec), while that of the latter remained stable (Cometto–Muñiz and Cain, 1984). Furthermore, when subjects assessed separately the perceived odor and the perceived pungency of a low and a high ammonia concentration, presented at the shortest (1.25 sec) and at the longest (3.75 sec) inhalation times, only pungency increased with time (which suggests temporal integration) (Figure 14).

Insert Figure 14 about here

In summary, the evidence indicates that odorants capable of eliciting trigeminal attributes (i.e., pungency) will cause less adaptation than those that do not evoke such pungency.

IX. Cellular and Molecular Mechanisms of Adaptation.

Despite the fact that a number of advances in understanding the olfactory process have occurred at the molecular level (Breer,

1991), psychophysical experiments on adaptation and cross–adaptation have not shed much light on the molecular events involved.

Recent studies at the receptor level in newts and salamanders have confirmed that through a G protein–coupled mechanism (Bruch, 1990; Jones and Reed, 1989), an increase in intracellular cyclic adenosine 3',5'-monophosphate (cAMP) (Pace, Hanski, Salomon, and Lancet, 1985; Sklar, Anholt, and Snyder, 1986) or 1,4,5–inositol triphosphate (IP$_3$) (Boekhoff, Tareilus, Strotmann, and Breer, 1990; Restrepo, Miyamoto, Bryant, and Teeter, 1990) acts as a secondary messenger signal for the odorant–induced depolarization of the olfactory neuron and activation of cation–selective conductance (Firestein, Darrow, and Shepherd, 1991; Kurahashi, 1990; Kurahashi, Kaneko, and Shibuya, 1990; Lowe and Gold, 1993). After a few seconds, the current activated by an increased cAMP in whole–cell patch clamp preparations decreases to a plateau or, in some cases, to zero, as does the current elicited by maintained steps of odor stimulus (Firestein, Shepherd, and Werblin, 1990). In excised patches, no desensitization to cAMP is observed (Dhallan, Yau, Schrader, and Reed, 1990; Nakamura and Gold, 1987), suggesting that desensitization to odors either occurs at steps in the olfactory cascade prior to the channel or requires some intracellular factor absent in excised patches (Firestein, Darrow, and Shepherd, 1991). According to Firestein et al. (1991), the decay in the odor–induced current appears to be the result of (i) the inherent GTPase activity of the olfactory G protein and (ii) the hydrolysis of cAMP by

phosphodiesterase (PDE). Selective blocking experiments on these two processes have suggested that the rate setting step in the decline of the current is the hydrolysis of cAMP by the PDE (Firestein, Darrow, and Shepherd, 1991).

Other studies using the whole–cell patch clamp technique have shown a response decay in olfactory receptor cells attributed to inactivation of odorant–activated conductance (Kurahashi and Shibuya, 1990). Recovery after inactivation — determined with double pulse experiments — depended on the duration of a resting interval. The inactivation of the odorant–activated conductance was only observed when the external medium contained Ca^{2+}. In addition, the odorant–activated conductance led to permeation of Ca^{2+} into the cell, and a rise in the internal concentration of the Ca^{2+}–sequestering agent ethyleneglycol–bis–(ß–aminoethyl)–N,N,N',N'–tetraacetic acid (EGTA) inhibited the activation. Altogether, these observations suggest that Ca^{2+} influx mediates the decay of the olfactory response to prolonged stimulation, i.e., adaptation (Kurahashi and Shibuya, 1990).

The molecular mechanism of termination of the olfactory signal in the very short time–range (milliseconds to a few seconds) is a matter of debate. Some investigators have suggested an enzymatic biotransformation of the odorant itself, perhaps through a uridin diphosphate (UDP) glucuronosyl transferase reaction resulting in a major change in solubility and chemical properties of the odorant (Lazard, Zupko, Poria, Nef, Lazarovits, Horn, Khen, and Lancet,

1991). Other investigators favor a termination via phosphorylation reactions catalyzed by specific protein kinases: the cAMP pathway could be turned off by kinase A, whereas the IP_3 cascade could be turned off by kinase C (Boekhoff and Breer, 1992).

There is emerging evidence for a role of cyclic guanosine 3',5'-monophosphate (cGMP) in olfactory signaling, particularly in the adaptation phenomenon. Recent experiments have shown significantly reduced second messenger responses to odorants in rat cilia upon pre-treatment with permeable derivatives of cGMP (Breer and Boekhoff, 1992). This falls into register with electrophysiological studies on isolated bullfrog olfactory epithelia showing an attenuation of the net inward current induced by odorants upon pre-treatment with permeable cGMP analogs (Persaud, Heck, DeSimone, Getchell, and DeSimone, 1988).

The olfactory adaptation phenomena should be seen not only as a desensitizing mechanism but also as a way to maximize the detection of <u>new</u> signals in a constant chemical background as suggested by electrophysiological experiments in lobsters (Borroni and Atema, 1988; Borroni and Atema, 1989; Voigt and Atema, 1987; Voigt and Atema, 1990).

X. <u>Clinical implications</u>.

Olfactory adaptation bears relevance to clinical testing of olfaction from two perspectives. First, it is important that clinical procedures avoid olfactory adaptation, particularly threshold tests. One way to avoid adaptation entails use of a suitable interstimulus interval (i.e., a suitable time between the presentation of successive stimuli). If the stimuli presented are close to threshold, an interval of 60 or even 30 sec may be sufficient (Doty, Gregor, and Settle, 1986), although this may depend upon the stimuli used and the testing conditions (Köster, 1971). Prolonging the interstimulus interval has to be balanced against the time available to measure threshold. Time may be plentiful in the laboratory, but not in the clinic (Cain, Cometto–Muñiz, and de Wijk, 1992).

Second, olfactory adaptation, *per se* , may shed light on some olfactory pathologies and thereby add information in the clinical assessment of olfactory function. Although the pitfalls of the different methods to produce and evaluate adaptation, as discussed in this chapter, and the evasiveness of the effect itself presently preclude the wide–spread clinical use of tests of olfactory adaptation, future research on this point may mitigate such problems.

Recent studies of olfactory adaptation and recovery in the elderly have found that the elderly are more prone to olfactory adaptation and are slower to recover from it than the young (Stevens, Cain, and Oatley, 1989; Stevens, Cain, Schiet, and Oatley, 1989). It remains to be investigated if diseases known to affect the olfactory sense manifest themselves in any particularly relevant

manner in terms of olfactory adaptation (see Doty, Bartoshuk, and Snow Jr., 1991).

Summary

Olfactory adaptation exerts its influence in almost all aspects of the functioning of the sense of smell. An adapted olfactory sense is characterized by elevated odor thresholds, reduced responses to suprathreshold sensations, slower reaction times to odors, and, sometimes, a shift in perceived odor qualities. The presence of trigeminal properties (i.e., pungency) in an odorous stimulus slows the adaptation process. Studies of olfactory adaptation, perhaps even more than any other aspect of human smell function, need to control for subject bias and expectations. Presently, standardized clinical tests of olfaction do not include an olfactory adaptation component, largely because of practicality considerations. Recent reports show that aging speeds olfactory adaptation and slows recovery. In view of this, it might prove revealing to explore olfactory adaptation in patients with diseases known to affect the sense of smell and compare the results with those obtained in matched control subjects.

Acknowledgements

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<u>Figure Legends</u>

<u>Figure 1</u>. Increase in the threshold for 2-octanol during adaptation to various stimulus concentrations. Both adapting concentrations (parameter) and threshold concentrations are expressed as multiples of the unadapted threshold concentration. (From Stuiver, 1958.)

<u>Figure 2</u>. Relation between concentration of adapting stimulus (expressed as multiples of the unadapted threshold concentration) and adaptation time required for the cessation of the smell sensation (ATCS) for 2-octanol and m-xylene. (From Stuiver, 1958.)

<u>Figure 3</u>. Relation between decrease of threshold and recovery time for various adaptation times and adapting intensities. The adapting intensities are equal to the threshold concentrations when recovery begins. The adaptation times (sec) used are shown to the right of the curves. (From Stuiver, 1958.)

<u>Figure 4</u>. Group data describing adaptation and recovery. The unbroken curves represent the exponential adaptation function fitted to these data. The dashed curves have been drawn to indicate the general trend of the recovery process. (From Ekman, Berglund, Berglund, and Lindvall, 1967 by permission of Scandinavian University Press.)

Figure 5. Families of psychophysical functions for the odor intensity of trimethyl pyrazine (TMP) and 2-propionyl-3-methyl furan (PMF) under various conditions of self-adaptation and of cross-adaptation of one substance by the other. (From Cain and Polak, 1992 by permission of Oxford University Press.)

Figure 6. How visitors rated the intensity of pyridine over time at five injection rates, including zero. The arrow shows the time when pyridine injection began. The data points are means plus or minus one standard error. Filled circles represent values significantly greater than corresponding control values, $p < 0.01$. (From Cain, Leaderer, Cannon, Tosun, and Ismail, 1987.)

Figure 7. How occupants rated the intensity of pyridine. The time scale refers to the point where occupants entered the chamber. The arrow shows the time when pyridine injection began. The data points are means plus or minus one standard error. Filled circles represent values significantly greater than corresponding control values, $p < 0.01$. (From Cain, Leaderer, Cannon, Tosun, and Ismail, 1987.)

Figure 8. How visitors rated the intensity of pyridine when they entered the chamber periodically after it had reached a steady state concentration. (From Cain, Leaderer, Cannon, Tosun, and Ismail, 1987.)

Figure 9. How occupants rated the intensity of pyridine over time when they entered and remained in the chamber after it had reached a steady state concentration. (From Cain, Leaderer, Cannon, Tosun, and Ismail, 1987.)

Figure 10. The recovery of one nose side when the same nose side has been adapted (I) and the recovery of the nose side which has not been adapted (II). For m–xylene, an adapting concentration of 70 times the absolute concentration was injected during 80 seconds, for d–octanol a concentration 50 times the absolute threshold concentration during 100 seconds before recovery started. (From Stuiver, 1958.)

Figure 11. Psychophysical functions for linalyl acetate obtained when test concentrations succeeded the diluent (no adaptation, empty circles) and when they succeeded and adapting stimulus (0.53 mg/l) on the same side (ipsilateral adaptation, filled circles) or on the opposite side (contralateral adaptation, squares). The vertical bars represent the standard error of the difference between the results for no adaptation and contralateral adaptation (upper bars) and between the results for contralateral adaptation and ipsilateral adaptation (lower bars). (Reprinted with permission from Nature (Cain, 1977) Copyright (1977) Macmillan Magazines Limited.)

Figure 12. The threshold concentration as a function of the quantity of odorous material used for the adaptation, for same

recovery time. The recovery time is given at the curves. Odorant used was 2–octanol. (From Stuiver, 1958.)

Figure 13. Psychophysical functions for odor and for irritation after exposures of one breath (solid lines) or three breaths (dashed lines). Upper portion depicts functions for individual subjects and lower portion depicts functions for the group. (From Cain, 1976 by permission of Academic Press.)

Figure 14. Perceived odor, pungency, and total intensity (geometric means ± standard errors) for two concentrations of ammonia inhaled for two durations. (From Cometto–Muñiz and Cain, 1984 by permission of Oxford University Press.)

FIGURE 1
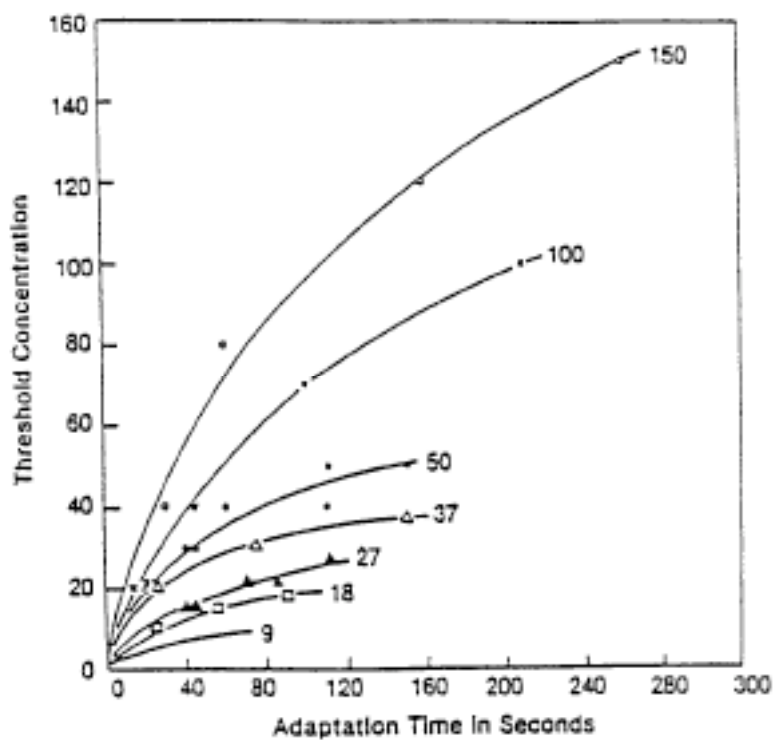
FIGURE 2

FIGURE 3

FIGURE 4

Time (min) of olfactory adaptation and recovery

FIGURE 5

CONCENTRATION ($\mu g/l$)
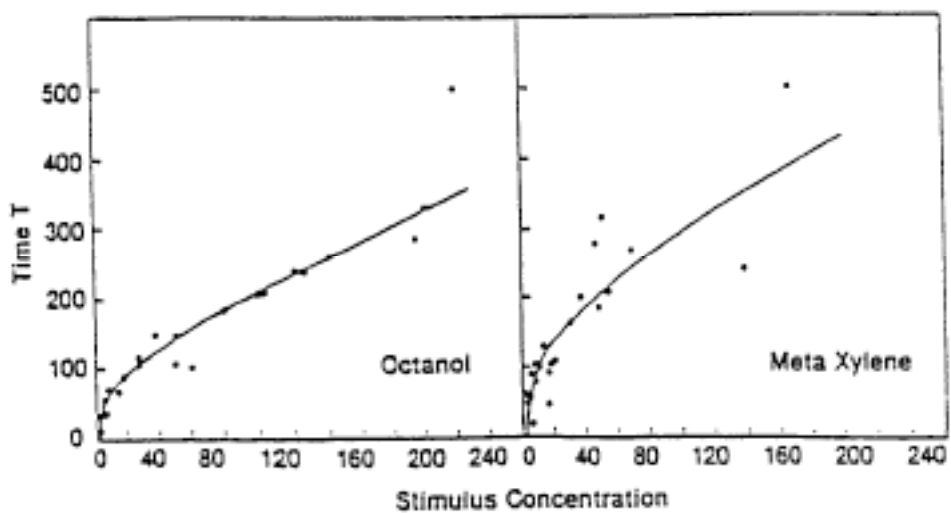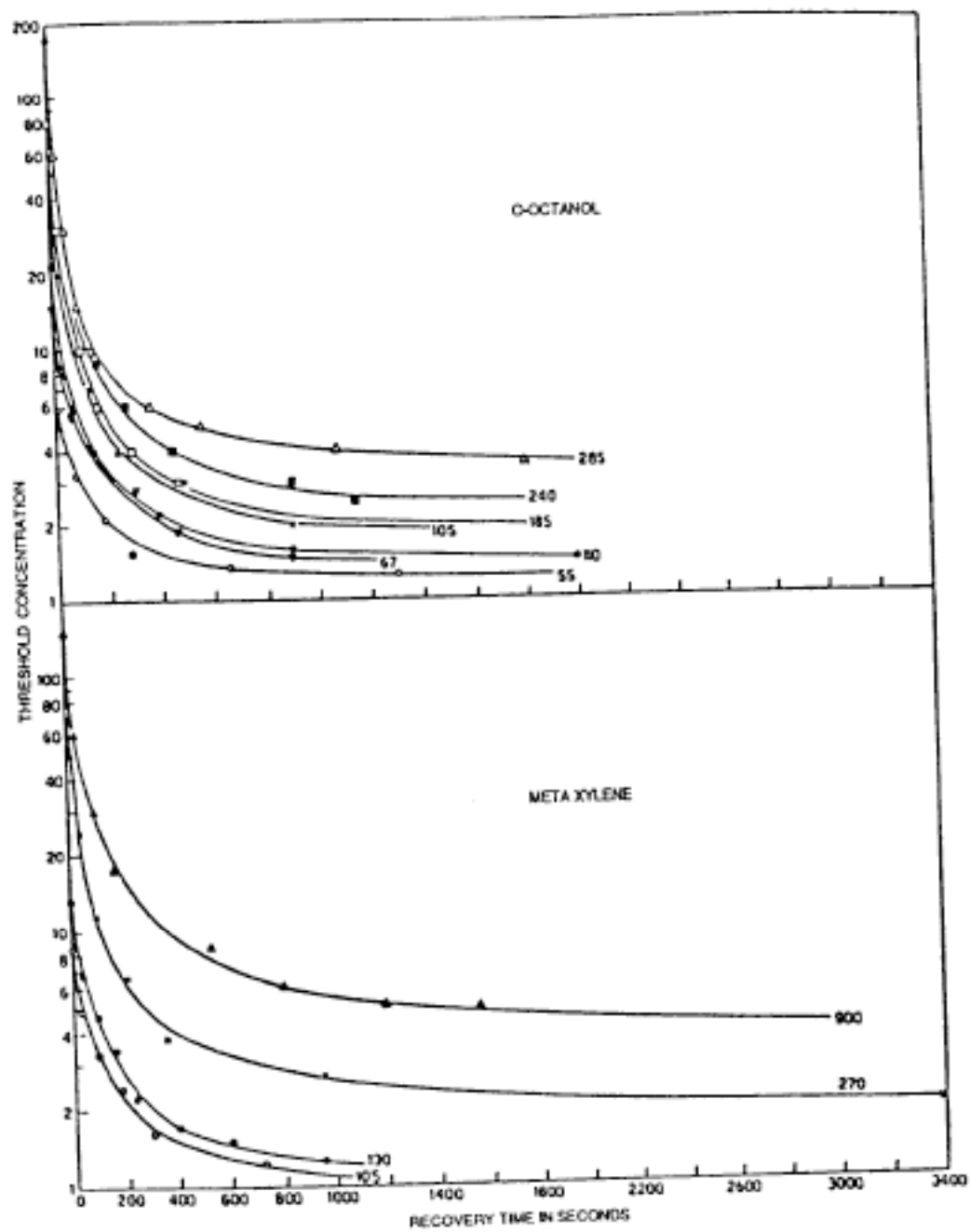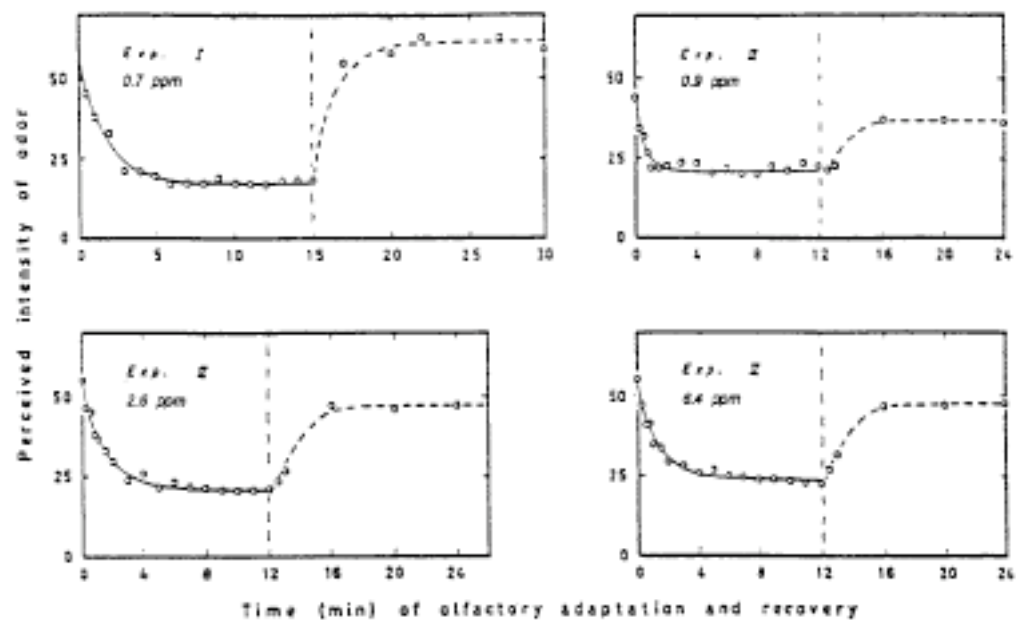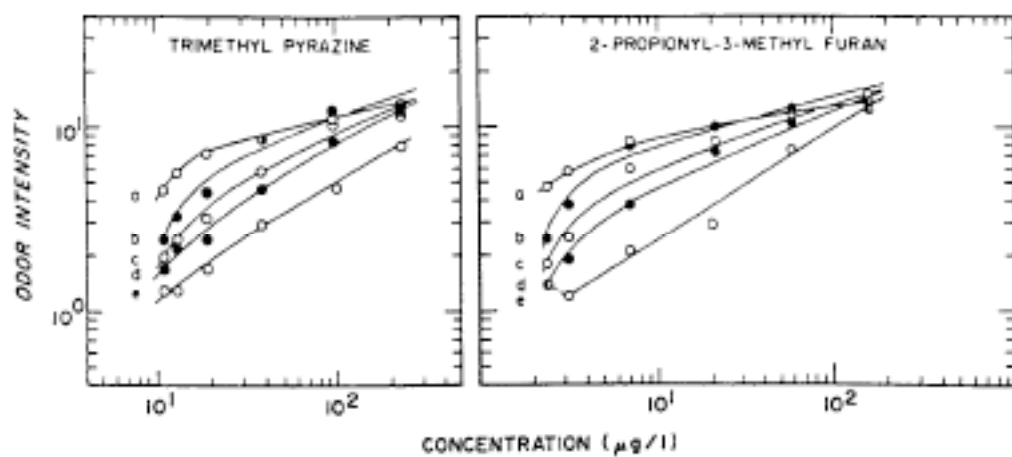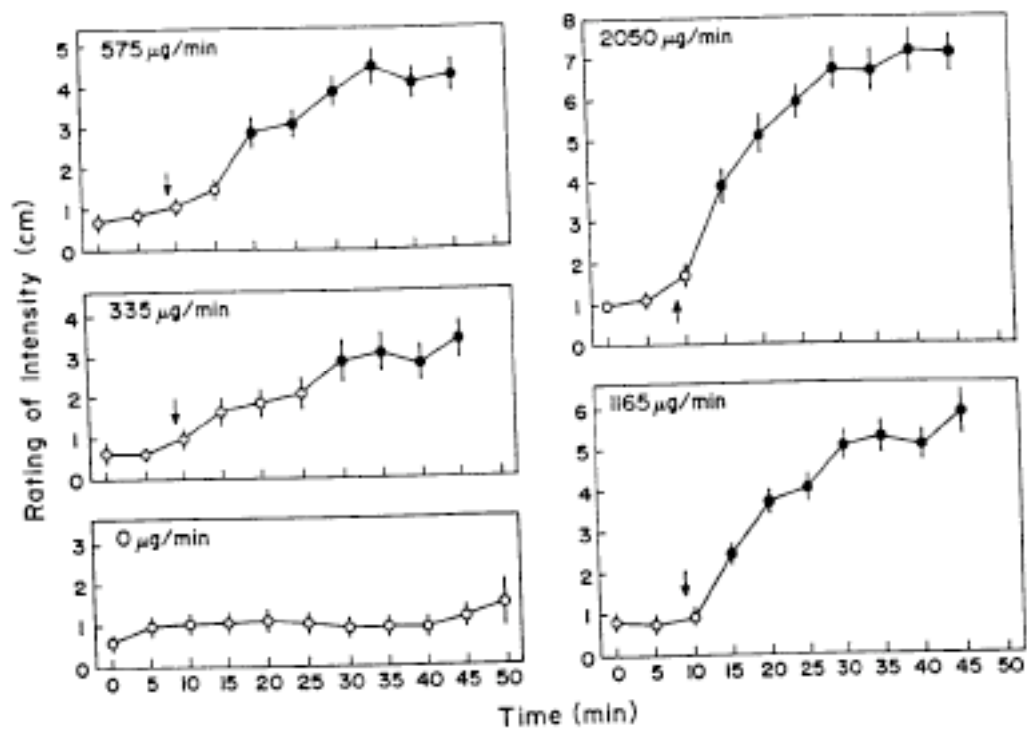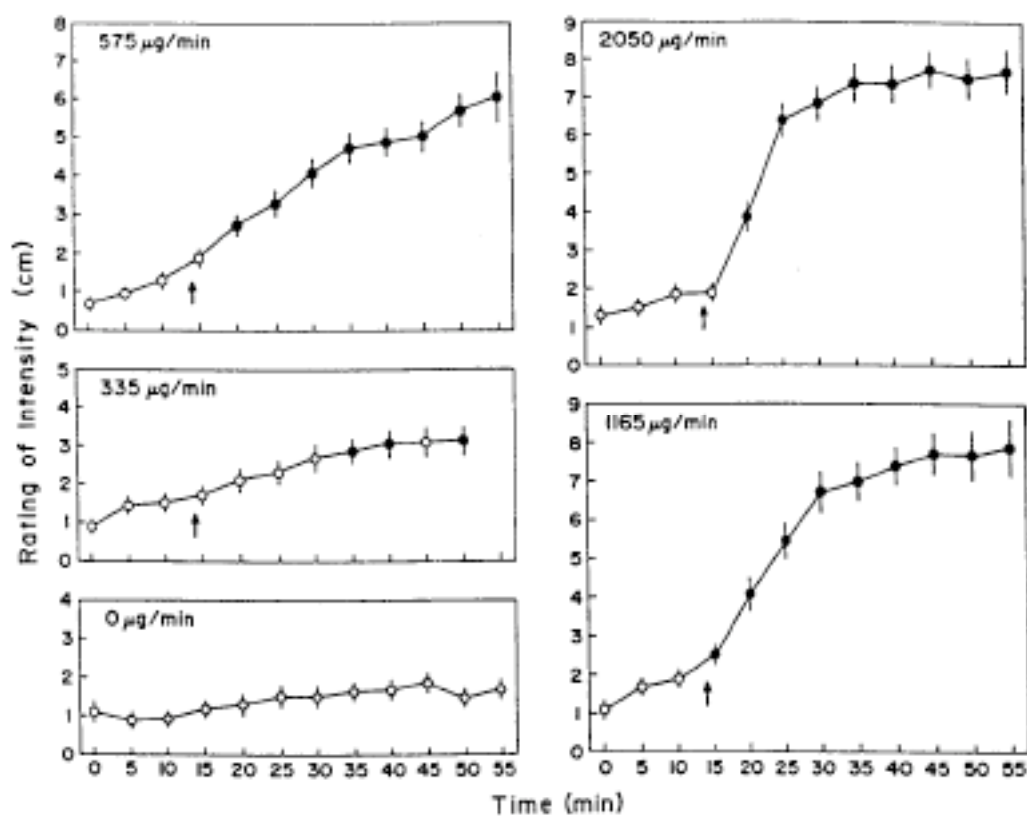
FIGURE 6

FIGURE 7

FIGURE 8
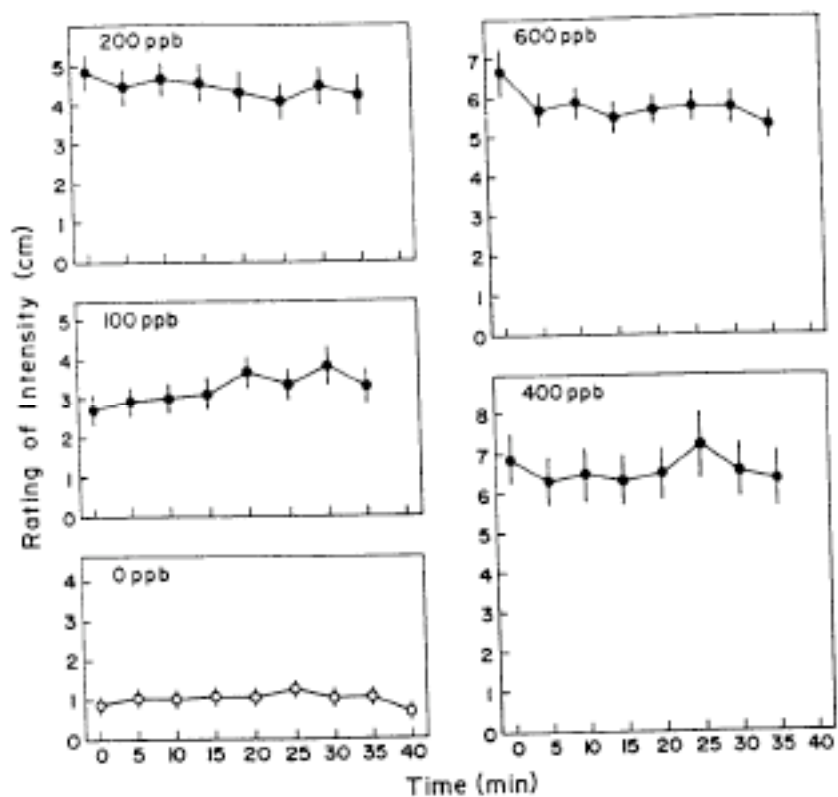
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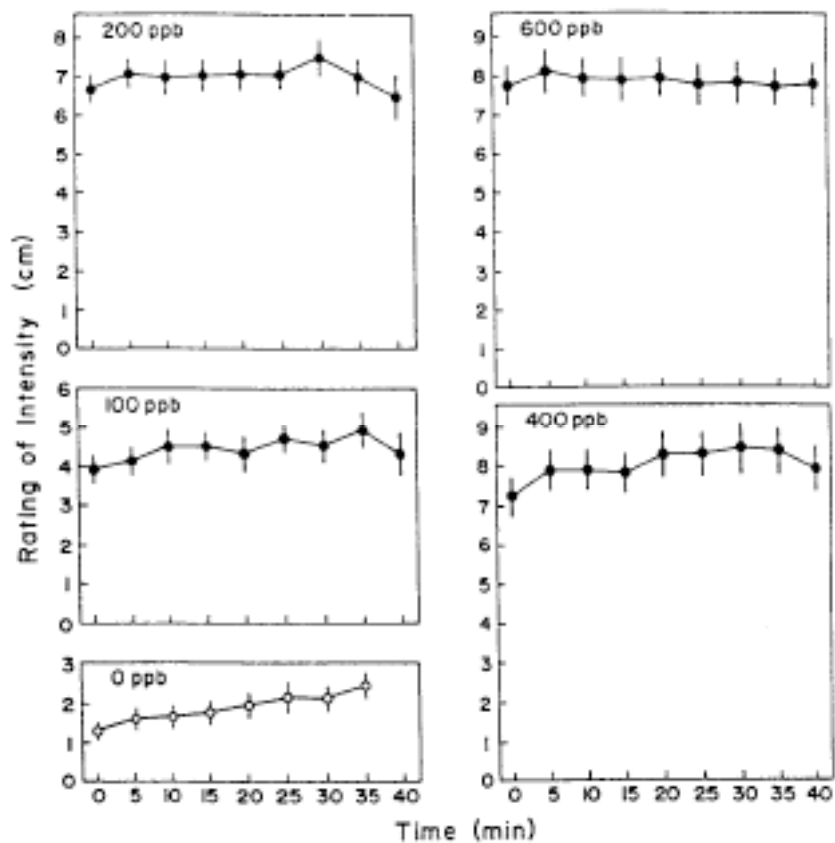
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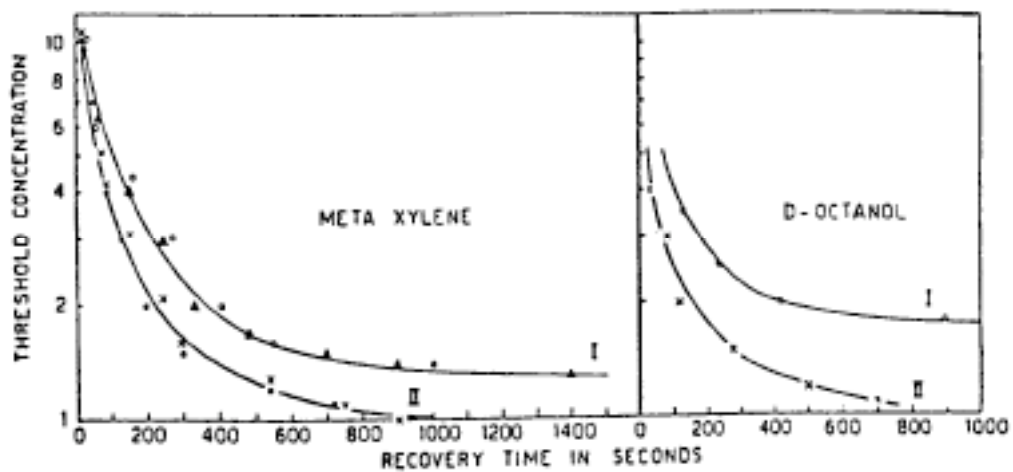
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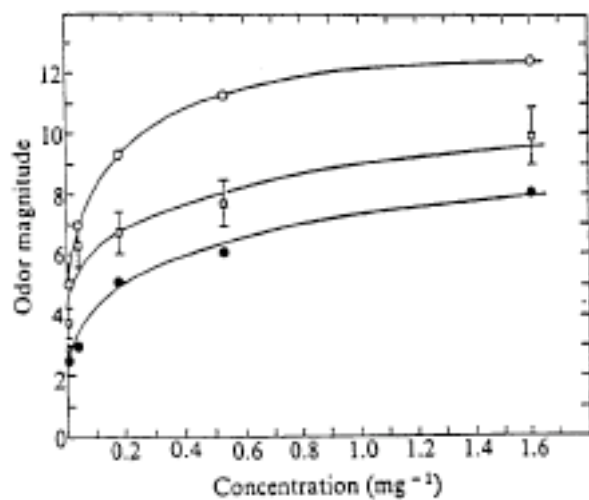
FIGURE 12

FIGURE 13

FIGURE 14