Experience Modifies Olfactory Acuity: Acetylcholine-Dependent Learning Decreases Behavioral Generalization between Similar Odorants

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Perceptual learning has been demonstrated in several thalamo-cortical sensory systems wherein experience enhances sensory acuity for trained stimuli. This perceptual learning is believed to be dependent on changes in sensory cortical receptive fields. Sensory experience and learning also modifies receptive fields and neural response patterns in the mammalian olfactory system; however, to date there has been little reported evidence of learned changes in behavioral olfactory acuity. The present report used a bradycardial orienting response and cross-habituation paradigm that allowed assessment of behavioral discrimination of nearly novel odorants, and then used the same paradigm to examine odorant discrimination after associative olfactory conditioning with similar or dissimilar odorants.

The results demonstrate that associative conditioning can enhance olfactory acuity for odors that are the same as or similar to the learned odorant, but not for odors dissimilar to the learned odorant. Furthermore, scopolamine injected before associative conditioning can block the acquisition of this learned enhancement in olfactory acuity. These results could have important implications for mechanisms of olfactory perception and memory, as well as for correlating behavioral olfactory acuity with observed spatial representations of odorant features in the olfactory system.

Key words: adaptation; perceptual learning; piriform cortex; olfaction; olfactory memory; scopolamine

Experience can shape both behavioral and physiological responses to sensory input. Both associative conditioning and, in some cases, simple stimulus exposure have been shown to modify receptive fields of sensory neurons and associated behavioral sensory abilities in most sensory modalities (Gibson, 1953; Gilbert et al., 2001). For example, training an owl monkey to discriminate between different frequencies of punctate tactile stimulation of the finger both modifies somatosensory cortex single-unit response patterns to the trained stimulus frequencies and enhances behavioral performance in the discrimination task (perceptual learning) (Recanzone et al., 1992). These modified cortical receptive fields are believed to underlie the enhanced behavioral discrimination that occurs after perceptual learning (Gilbert et al., 2001).

In the olfactory system, experience has also been shown to modify neural response patterns to learned odors. Associative conditioning in young rats modifies both olfactory bulb glomerular activity and mitral/tufted cell odor-evoked responses to the learned odor (Leon, 1987; Wilson and Sullivan, 1994). In mature animals, associative olfactory learning has been shown to modify odor-evoked activity in the main olfactory bulb (Viana DiPrisco and Freeman, 1985; Kendrick et al., 1992), anterior olfactory nucleus (Hamrick et al., 1993), and piriform cortex (Litaudon et al., 1997; Datiche et al., 2001). Furthermore, simple odor habituation has also been shown to modify receptive fields of both

mitral/tufted cells and piriform cortex neurons (McCollum et al., 1991; Wilson, 2000).

Despite this wealth of data showing experience-dependent effects on olfactory system physiology, it is not known whether these learned physiological changes are translated into changes in behavioral discriminability of odorants (i.e., olfactory acuity). That is, do learning-induced changes in odor representation in the olfactory system affect the ability to discriminate those odors at a behavioral level? This is an important issue as work progresses toward quantifying spatial representations of odorant quality, usually relying on stimulation with novel odorants (Johnson et al., 1999; Rubin and Katz, 1999; Uchida et al., 2000), and correlating those spatial representations with behavioral performance in learned discrimination tasks (Linster and Hasselmo, 1999).

One difficulty in addressing the issue of whether, or how, learning changes behavioral olfactory acuity is obtaining a behavioral paradigm that allows determination of olfactory acuity to novel (or nearly novel) odors (i.e., a task that does not specifically require extensive training of the animal to the odorants before

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discrimination can be assessed). Toward that end, we have recently developed a habituation/cross-habituation paradigm that allows determination of olfactory acuity after minimal exposure to the odorants (Fletcher and Wilson, 2001). Odor-evoked heart-rate bradycardia orienting responses are used as the behavioral measure. These responses require no initial procedural training, are expressed in response to the initial presentation of an odorant stimulus, and show relatively rapid habituation with minimal cross-habituation to molecularly dissimilar odorants (Fletcher and Wilson, 2001).

Using a homologous series of ethyl esters, the present report examined behavioral cross-habituation/generalization between odorants before and after associative conditioning. The results suggest that olfactory conditioning significantly enhances olfactory acuity for similar odorants. Given the well-described role of acetylcholine (ACh) muscarinic receptors in olfactory memory and odorant processing (Ravel et al., 1994; DeRosa and Hasselmo, 2000; Wilson, 2001b), we also examined whether these conditioning effects could be prevented by muscarinic receptor blockade.

MATERIALS AND METHODS

Subjects. Young male and female Long–Evans hooded rats (17–21 d of age) were used as subjects. Animals were born to females from Charles River Laboratories (Wilmington, MA) and were housed in polypropylene cages on a 12 hr light/dark cycle, with food and water available *ad libitum*. Animal care protocols were approved by the University of Oklahoma Institutional Animal Care and Use Committee in accordance with National Institutes of Health guidelines.

Cardiac orienting response. Bilateral, subcutaneous silver chloride recording electrodes were implanted under isoflurane anesthesia. Topical lidocaine was applied at the site of electrode implantation to minimize discomfort to the animal. When animals had completely recovered from the anesthesia, they were placed in the Plexiglas testing chamber on top of a stainless-steel grid (6 × 15 × 12 cm) and allowed a 15 min habituation period before testing began.

A constant airstream entered the chamber from the side at 4 liters per minute, to which odorants could be added with a flow-dilution olfactometer. A vacuum line vented the odor from the chamber. Instantaneous heart rate was calculated from the interbeat interval of electrocardiogram recordings as described previously (Fletcher and Wilson, 2001) using Spike2 software (CED, Inc., Cambridge, UK). Baseline heart rate was determined from 10 consecutive heartbeats before odor presentation. Bradycardia orienting response magnitude was determined as the maximal heart rate decrease (averaged over 10 consecutive heartbeats) from baseline within 10 sec of odor onset (Fletcher and Wilson, 2001).

Stimulus delivery. The stimulus-delivery apparatus was identical to that described by Fletcher and Wilson (2001), with humidified, filtered air passing through syringe filters saturated with specific odorants via a flow dilution olfactometer (1:10 dilution). The odorants used were ethyl butyrate (E4), ethyl valerate (E5), ethyl heptanoate (E7), ethyl octanoate (E8), isoamyl acetate (AA) (Sigma-Aldrich, St. Louis, MO), and peppermint extract.

Cross-habituation in naive animals. Animals were presented with a series of different odors to determine baseline responses. As reported previously (Fletcher and Wilson, 2001), not all animals displayed orienting responses to all odors; thus, this initial screening allowed determination of which odors to use as well as determination of initial response magnitudes. One effective odor was then pseudorandomly chosen to be the habituation stimulus. Stimuli (4 sec duration) were presented at a 30 sec interstimulus interval for 10 or 15 repetitions or until the average of the last three trial blocks was <50% of the baseline response for that odor, depending on the experiment. After habituation, animals were presented with a molecularly dissimilar odor or a homologous odor differing by 1 or 4 carbons from the habituation odor to test for cross-habituation. Each animal was tested on a single pair of odorants. The final self- and cross-habituation magnitudes were calculated as a percentage of the initial responses.

Associative conditioning effects on cross-habituation. Conditioning took place in the chamber described above, through which footshocks were delivered. All trained animals were given 15 trials of the S$^+$ odor (4 sec
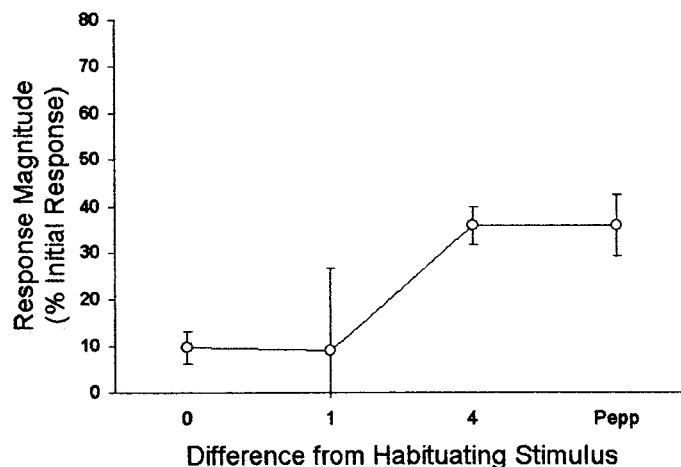

Figure 1. Discrimination of novel ethyl esters of different carbon chain lengths. The amount of self-habituation (0 carbon difference) was determined by the average of the last three self-trials during habituation as a percentage of the initial response. The response magnitude to the cross-habituated odor is expressed as a percentage of the initial response to the cross-habituated odor [1, 4, or peppermint (*Pepp*)]. Animals displayed significantly less cross-habituation to esters differing by 4 carbons or to peppermint than to esters differing by 1 carbon. Error bars denote the SE.

duration) paired with footshocks (1 sec duration, 0.5 mA) at odor offset and 15 randomly interspersed trials of peppermint odor not paired with footshock (S$^-$). Cardiac orienting responses were not recorded during training. Immediately after conditioning, animals were returned to their home cages until testing the next day.

Like the naive animals, the animals tested the following day were given presentations of two odors to determine baseline response magnitudes. Selected odors and their relationship to the conditioned odors varied, as described below in Results. In the majority of cases, the S$^+$ odor was not selected to be the habituation odor, although no difference in self-habituation was observed regardless of which odor was chosen. Animals were considered habituated when the average of the last three trial blocks was <50% of the baseline response for that odor. After habituation, animals were presented with a different odor to test for cross-habituation.

Pharmacological manipulations. Before associative conditioning as described above, animals were given intraperitoneal injections of scopolamine-hydrobromide (HBr) (Sigma) or saline as a control. Fifteen minutes before conditioning began, 0.2 mg/kg scopolamine-HBr, 0.5 mg/kg scopolamine-HBr, or saline was administered. Animals were then associatively conditioned as described above and returned to their home cage until habituation/cross-habituation testing 24 hr later. No drugs were administered during the determination of baseline response magnitudes or during the habituation phase of the experiment.

Analyses. Orienting response magnitudes and baseline heart rate were analyzed with ANOVAs and *post hoc* comparisons. One animal from the novel discrimination experiment and two animals from the scopolamine experiment were excluded from final analyses as statistical outliers because their final responses were >3 SDs from the mean of their respective groups (Barnett and Lewis, 1994).

RESULTS

Examination of cross-habituation between relatively novel similar and dissimilar odorants revealed that animals did not discriminate between ethyl esters differing by a single carbon ($n = 12$ animals) but did discriminate between ethyl esters differing by 4 carbons ($n = 17$), as evidenced by less cross-habituation, and between ethyl esters and peppermint ($n = 17$). All animals in this experiment received 10 4 sec presentations of the habituating stimulus. Self-habituation (0-carbon difference from the habituating stimulus) did not vary between groups; thus these values were combined across groups for statistical analysis. As shown in Figure 1, cross-habituation levels to esters that were 1 carbon
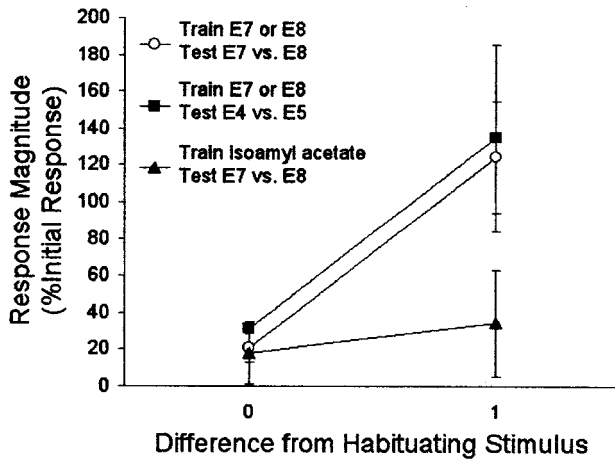
Figure 2. Discrimination of ethyl esters differing by 1 carbon after associative conditioning. Response magnitudes to the self-habituated (0) and cross-habituated (1) odors are expressed as a percentage of the initial response. One group of animals was trained to E7 or E8 and then tested for discrimination of E7 versus E8 (○). Another group was trained to E7 or E8 and then tested with E4 versus E5 (■). The last group was trained to a structurally different odor, isoamyl acetate, and then tested with E7 versus E8 (▲). After training to a similar ester, animals were capable of discriminating ethyl esters. Animals were unable to discriminate E7 versus E8 after conditioning to isoamyl acetate.

different from the habituation stimulus were similar to that of the habituation stimulus itself, whereas cross-habituation to esters that were 4 carbons different or to peppermint was substantially less (ANOVA: main effect of odor, $F_{(1,43)} = 4.18$, $p < 0.05$; *post hoc* Fisher's tests revealed significant differences between the response magnitude to the 4-carbon difference and peppermint stimuli from both the self-habituation/0-carbon difference and the 1-carbon difference, $p < 0.05$).

However, aversive conditioning to an ester 24 hr before the cross-habituation test significantly enhanced discrimination between esters that were 1 carbon apart (Fig. 2). Animals were associatively conditioned with E7, E8, or AA as the S^+ and then tested 24 hr later on their ability to discriminate a 1-carbon difference in esters. After 24 hr, animals received 15 habituation trials and were tested for cross-habituation. Animals conditioned with E7 or E8 as the S^+ were tested for discrimination of E7 versus E8 ($n = 6$) or E4 versus E5 ($n = 6$). Animals conditioned to AA as the S^+ were also tested for discrimination of E7 versus E8 ($n = 6$). Animals were able to discriminate ethyl esters after training to a similar ester but were unable to discriminate E7 versus E8 (1-carbon difference) after conditioning to isoamyl acetate, similar to the untrained animals described above (ANOVA: $F_{(2,30)} = 10.62$, $p < 0.05$; *post hoc* Fisher's tests revealed a significant difference between self-habituation and cross-habituation in both the ester-trained and ester-tested groups, $p < 0.05$, but not between the amyl acetate-trained and ester-tested group).

Finally, the enhanced odorant discrimination and decreased cross-habituation produced by associative conditioning could be blocked by systemic injection of scopolamine-HBr (0 mg/kg, $n = 9$; 0.2 mg/kg, $n = 5$; 0.5 mg/kg, $n = 6$) before the associative conditioning. (No drug was present during the habituation testing on the following day.) Analysis of the discrimination data revealed both a significant main effect of dose (ANOVA: $F_{(2,34)} = 7.09$, $p < 0.05$) and a significant main effect of odor (ANOVA: $F_{(2,34)} = 6.39$, $p < 0.05$) on cross-habituation, with *post hoc*
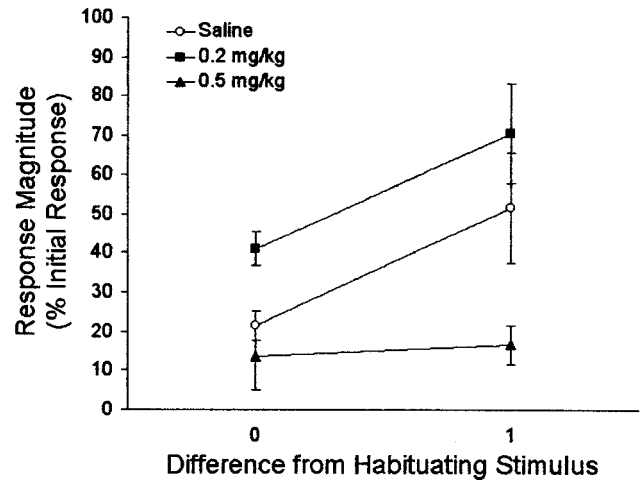

Figure 3. Discrimination of E7 and E8 after systemic injection of scopolamine-HBr before conditioning. Animals receiving 0.5 mg/kg scopolamine displayed significantly less discrimination and more cross-habituation of the esters than did the saline controls, while having similar levels of self-habituation. Scopolamine was only present during associative training, and not during the cross-habituation testing.

Fisher's tests confirming significantly better discrimination and less cross-habituation in the saline and 0.2 mg/kg scopolamine groups than the 0.5 mg/kg scopolamine group ($p < 0.05$). As described in Materials and Methods, in this experiment the number of habituation trials given was determined by on-line visual evaluation of the extent of habituation of odor-evoked bradycardia. Although there were no differences in the average number of habituation trials across dosages (mean habituation trials: saline, 26.2 ± 1.2; 0.2 mg/kg scopolamine, 23.4 ± 2.5; 0.5 mg/kg scopolamine, 29.7 ± 1.4; ANOVA: $F_{(2,18)} = 1.97$, $p = 0.17$, NS), clearly the 0.2 mg/kg scopolamine animals did not attain the levels of self-habituation expressed by the saline and 0.5 mg/kg scopolamine animals, and showed minimal cross-habituation (Fig. 3). However, the 0.5 mg/kg scopolamine animals did show levels of self-habituation that were similar to those seen for the saline animals, yet these two groups displayed significantly different levels of cross-habituation.

To determine whether scopolamine affected conditioned fear responses, baseline (pre-odor) heart rates of conditioned animals with and without scopolamine were compared. Habituation testing was performed in the same context as the aversive conditioning. Animals that received conditioning had a significantly greater baseline heart rate before the discrimination test than nonconditioned animals, and there were no differences in heart rate between animals given saline or animals given scopolamine [baseline heart rate: naive, 444.74 ± 5.70 beats per minute (BPM); conditioned, no injection, 530.85 ± 5.04 BPM; conditioned-saline, 529.63 ± 10.64 BPM; conditioned-scopolamine (0.2 mg/kg), 543.68 ± 9.15 BPM; conditioned scopolamine (0.5 mg/kg), 530.87 ± 8.36 BPM; ANOVA: $F_{(4,91)} = 41.75$, $p < 0.05$]. *Post hoc* Fisher's tests revealed that all conditioned groups had significantly higher baseline heart rates than the naive animals ($p < 0.05$).

DISCUSSION

The present results demonstrate that olfactory acuity for similar odorants can be enhanced by previous experience with those odorants, and that acquisition of this learned enhancement can be

impaired by the ACh muscarinic receptor antagonist scopol-amine. These findings are similar to perceptual learning phenom-ena described in thalamocortical sensory systems (Gilbert et al., 2001).

Perceptual learning

Perceptual learning is a form of implicit memory wherein the ability to discriminate differences between stimuli (perceptual acuity) can be enhanced with training (Gibson, 1953; Gilbert et al., 2001). This change in acuity is different from an experience-dependent change in detection threshold (Wysocki et al., 1989; Dalton and Wysocki, 1996), although changes in detection thresh-old may also occur. Perceptual learning, as described in other sensory systems, has several characteristics (for review, see Gil-bert et al., 2001): (1) the learned changes in perceptual acuity are primarily specific for the trained stimuli, although there can be some transfer to similar stimuli; (2) the learned changes are long-lasting; (3) the learned changes generally do not occur after passive stimulation, but require attention by the animal; (4) the attentional component of the learning can be mimicked by acti-vation of cholinergic systems; and (5) the learned behavioral changes are often correlated with changes in cortical receptive fields.

The results described here match remarkably well the charac-teristics of perceptual learning described for other sensory sys-tems. First, aversive conditioning to an ethyl ester enhanced discrimination of that ester from similar esters. There was some transfer of the training effect to other esters [e.g., training to ethyl octanoate (E8) enhanced discrimination of E4 from E5, but training to a completely different odorant (isoamyl acetate) did not transfer to ethyl ester discrimination]. Thus, there is some specificity in the learning effect. The lack of training specificity within esters is potentially related to the hierarchical processing of odorant features observed in optical imaging data of odor-evoked spatial patterns of activity (Uchida et al., 2000). Uchida et al. (2000) suggest that odorant features may include both primary features (such as functional groups) and secondary features (such as carbon chain length). If this is correct, then perhaps associative conditioning to esters enhances coding of all esters or odors including that functional group, whereas training to a different odorant with different functional groups has no effect on esters (as shown in the current data). Current work is underway to more fully examine the nature of potential hierarchical coding in ol-faction using more diverse odorant sets and odorant mixtures.

A second similarity of the current data with perceptual learning in other sensory systems is that the learning effect was long-lasting, with olfactory acuity enhanced for at least 24 hr after training. Thus, it seems unlikely that simple, rapid changes in olfactory receptor neuron sensitivity (Zufall and Leinders-Zufall, 2000) account for the findings; rather, the data suggest a change in central olfactory circuits.

Third, although the present results do not definitively identify whether associative conditioning is necessary for enhanced olfac-tory acuity or whether passive odor exposure is sufficient, they do demonstrate that administration of scopolamine during training, at a dose that does not impair fear conditioning to the context (Anagnostaras et al., 1999; this study), prevents experience-induced acuity enhancement. ACh has been reported to modu-late behavioral odor habituation (Hunter and Murray, 1989), performance in delayed-match-to-sample olfactory tasks (Roman et al., 1993; Ravel et al., 1994), and interference or generalization between behavioral and piriform single-unit odor representations

(DeRosa and Hasselmo, 2000; Linster et al., 2001; Wilson, 2001b); in addition, ACh reportedly modifies synaptic efficacy and plasticity in piriform cortical circuits (Hasselmo and Bower, 1992; Saar et al., 2001). Thus, the present results extend the role of ACh in olfactory memory to implicit, perceptual learning. In fact, perceptual learning may be a critical component of some of these previously described cholinergic-dependent behavioral phenomena.

Several other lines of recent evidence also suggest a role for perceptual learning in odor-discrimination performance (Rabin, 1988). For example, Cleland et al. (2002) have demonstrated recently that the ability of animals to discriminate odors is task dependent. Rats generalize between similar odorants more in simple habituation tasks (similar to what was observed here) than in rewarded tasks. The data presented here extend these findings by demonstrating that previous experience in a rewarded task (aversive conditioning) modifies a subsequent discrimination per-formance in an unrewarded (habituation) task. Thus, the repre-sentation of the odorant and perceptual acuity may be modified by perceptual learning and can later be expressed in other tasks and contexts.

Locus of olfactory perceptual learning

In the mammalian olfactory system, molecular/odorant features are extracted by a large family of olfactory receptors within the olfactory epithelium (Buck and Axel, 1991) and then spatially represented by odorant-specific spatial patterns of glomerular activity across the olfactory bulb (Johnson et al., 1999; Rubin and Katz, 1999; Uchida et al., 2000). Thus, for example, focal clusters of olfactory bulb glomeruli may be responsive to specific molec-ular functional groups and/or specific hydrocarbon chain lengths. When comparing spatial patterns evoked by different odorants, it is apparent that some odorants have highly overlapping patterns, whereas others are quite distinct. This has led to predictions about the behavioral discriminability of odorants (olfactory acu-ity) based on a similarity of spatial patterning (Linster and Has-selmo, 1999; Laska and Hubener, 2001). The output neurons of the olfactory bulb, mitral/tufted cells, project directly to the piriform (olfactory) cortex. Neurons within the piriform cortex have enhanced odor-discrimination abilities compared with mi-tral/tufted cells (Wilson, 2000, 2001a), and thus presumably also contribute significantly to behavioral olfactory acuity.

In thalamocortical sensory systems, perceptual learning is be-lieved to be primarily a cortical phenomenon, occurring through changes of receptive fields of neurons from primary to higher order cortices (Gilbert et al., 2001). In olfaction, however, odor-ant responses in both the olfactory bulb and the piriform cortex can be modified by experience (Viana DiPrisco and Freeman, 1985; Leon, 1987; Kendrick et al., 1992; Wilson and Sullivan, 1994; Litaudon et al., 1997; Faber et al., 2000; Datiche et al., 2001), and plasticity in both structures is modulated by ACh (Elaagouby and Gervais, 1992; Ravel et al., 1994; Hasselmo and Barkai, 1995; Saar et al., 2001; Wilson, 2001b). Associative learn-ing can modify glomerular representation of odorant features in both rats (Wilson and Sullivan, 1994) and invertebrates (Faber et al., 2000) and can also modify mitral/tufted cell odorant response patterns in an odorant-selective manner (Wilson and Sullivan, 1994). Furthermore, odorant receptive fields of piriform cortex neurons are very dynamic, expressing highly odorant-specific experience-induced changes (Wilson, 1998, 2000) in a cholinergic-dependent manner (Wilson, 2001b). Either or both of these structures may play a critical role in perceptual learning of olfactory acuity.

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