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Cholinergic modulation of sensory representations in the olfactory bulb

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Abstract

We present a computational model of the mammalian olfactory bulb (OB) designed to investigate how cholinergic inputs modulate olfactory sensory representations. The model integrates experimental data derived from diverse physiological studies of cholinergic modulation of OB circuitry into a simulation of bulbar responses to realistic odorants. Experimentally-observed responses to a homologous series of odorants (unbranched aliphatic aldehydes) were simulated; realistic cholinergic inputs to the OB model served to increase the discriminability of the bulbar responses generated to very similar odorants. This simulation predicted, correctly, that missing cholinergic inputs to the OB would result in greater generalization between similar aliphatic aldehydes. Based on the assumption that the overlap between the neural representations of two sensory stimuli is predictive of their perceptual similarity, we tested this prediction in a behavioral experiments with rats. We show that, indeed, rats with selective lesions of cholinergic neurons that project to the OB and cortex discriminate less well between aliphatic aldehydes with similar carbon chain lengths than do rats that received sham lesions.

Keywords: Olfactory bulb; Acetylcholine; Computational modeling; Behavior; Rat; Feedback inhibition; Lateral inhibition; Horizontal limb of the diagonal band of Broca; Odorants; Homologous series

1. Introduction

The olfactory bulb (OB) is the first relay structure for olfactory sensory information in vertebrates. Primary olfactory sensory neurons (OSNs) within the olfactory epithelium project to two classes of relay neurons within the bulb, mitral and tufted cells, which in turn convey the resulting representation to more central olfactory structures. Experimental data and modeling suggest that the circuitry of the OB plays a critical role in feature extraction, noise reduction and contrast enhancement of sensory information within the odor-evoked signal cascade (for review see Laurent, 1999; Mori, Nagao, & Yoshihara, 1999; Scott, Wellis, Riggott, & Buonviso, 1993). These signal processing phenomena are thought to derive from the interactions of mitral and tufted cells with two main classes of inhibitory local bulbar interneurons, known as periglomerular cells and granule cells (Fig. 1(A)). These interneurons interact with mitral and tufted cells within two distinct layers of the OB. In the glomerular layer, periglomerular cells are excited directly by primary OSNs and indirectly via dendrodendritic synapses from mitral cell primary dendrites; they in turn inhibit mitral cell primary dendrites within the same glomerulus via dendrodendritic synapses and in neighboring glomeruli via lateral axonal projections. Granule cells, in contrast, are excited by mitral cell secondary dendrites and inhibit these same secondary dendrites at reciprocal synapses within the external plexiform layer. Furthermore, the OB also integrates information communicated via centrifugal projections from numerous central structures, including olfactory cortex, basal forebrain and the brainstem (for review see Halasz, 1990; Price, 1987; Shipley, 1995). In particular, a cholinergic projection from the horizontal limb of the diagonal band of Broca (HDB), which has been shown to innervate the OB (for review see Halasz & Shepherd, 1983; Le Jeune & Jourdan, 1993; Macrides, Davis, Youngs, Nadi, & Margolis, 1981; Zaborszky, Carlsen, Brashear, & Heimer, 1986), has been investigated in terms of its proposed roles in olfactory sensory processing.

Lesions of the HDB, as well as local or systemic injections of the muscarinic cholinergic antagonist scopolamine, decrease performance in a number of olfactory behavioral tasks, including olfactory habituation (Hunter & Murray, 1989), olfactory short-term memory (Ravel, Elaagouby, & Gervais, 1994; Ravel, Vigouroux, Elaagouby, & Gervais, 1992) and the discrimination of overlapping

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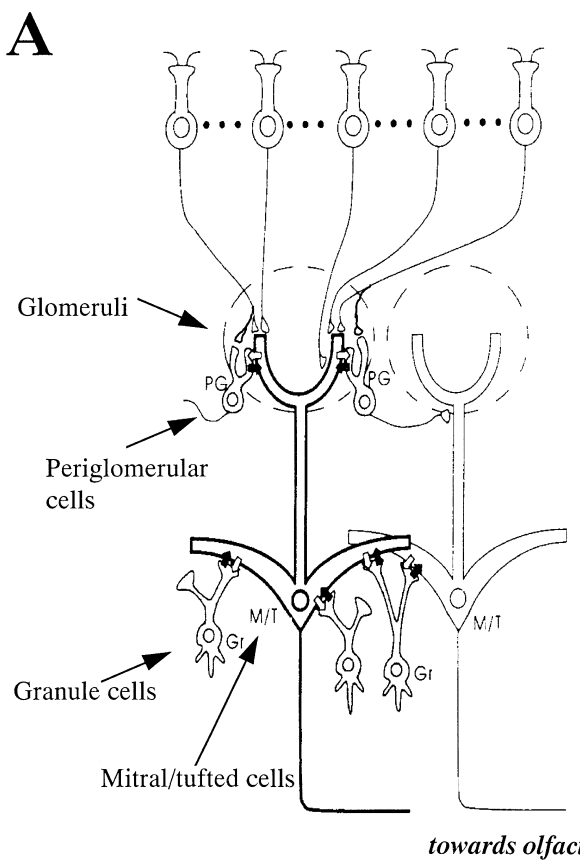

B

(3) CHO	Propylaldehyde	
(4) CHO	*n*-Butylaldehyde	
(5) CHO	*n*-Valeraldehyde	
(6) CHO	*n*-Hexylaldehyde	
(7) CHO	*n*-Heptylaldehyde	
(8) CHO	*n*-Octylaldehyde	

Fig. 1. (A) Schematic illustration of neurons and neural connectivity in the olfactory bulb. Adapted from Shepherd (1998). For a detailed review of bulbar circuitry also see Shipley (1995). (B) Molecular structures of the unbranched aliphatic aldehyde series used in the present experiments.

olfactory stimuli (De Rosa & Hasselmo, 2000; De Rosa, Hasselmo, & Baxter, 2001). Based on these data and on electrophysiological studies of the modulatory effects of cholinergic agonists within the OB, we have constructed theoretical models of the functional role of acetylcholine in olfactory stimulus processing (Linster & Gervais, 1996; Linster & Hasselmo, 1997). A consistent and critical prediction of these models has been that cholinergic modulation of local inhibitory circuits within the OB could sharpen the responses of mitral/tufted cells to odor stimuli and consequently reduce overlap between the neural representations of chemically similar odorants (Linster & Hasselmo, 1997). We here present functional predictions based on studies performed using specific olfactory stimuli: unbranched aliphatic aldehydes (Fig. 1(B)). We show that, in our model, the overlap between mitral cell responses to aldehydes with neighboring carbon chain lengths increases in the absence of cholinergic modulation of inhibition, predicting that the perceptual similarities between *n*-aliphatic odorants with similar carbon chain lengths would be increased by the disruption of centrifugal cholinergic projections to the OB. Finally, we test this prediction in a behavioral experiment in which cholinergic inputs to rats' OBs were specifically lesioned by injecting 192 IgG-saporin, a lesioning agent selective for cholinergic neurons (Wiley, Oeltmann, & Lappi, 1991), into the HDB.

2. Cholinergic modulation in the olfactory bulb model

Our OB model has been extensively described elsewhere; the equations used herein are the same as those previously presented (Linster & Gervais, 1996; Linster & Hasselmo, 1997). Here, we will briefly describe the model as well as the experimental data on which our implementation of the modulation of inhibition within the OB has been based.

The model includes four categories of neurons: OSNs, mitral cells (tufted cells are not included in the model), periglomerular cells, and granule cells, connected as described earlier and as shown in Fig. 2. All neurons were represented as single compartments except for mitral cells, which were represented by two compartments (the primary dendritic arborization and the secondary dendrites). Each compartment was characterized by a membrane time constant which can be regarded as the mean product of the membrane capacitance and the membrane input resistance. All neurons in the model produced discrete spikes for output, computed according to the instantaneous spiking probability, a continuous, bounded function of the membrane potential. Excitatory and inhibitory interactions between neurons were modeled by multiplying the presynaptic activity with a synaptic weight; the values for these synaptic weights were chosen from a random distribution

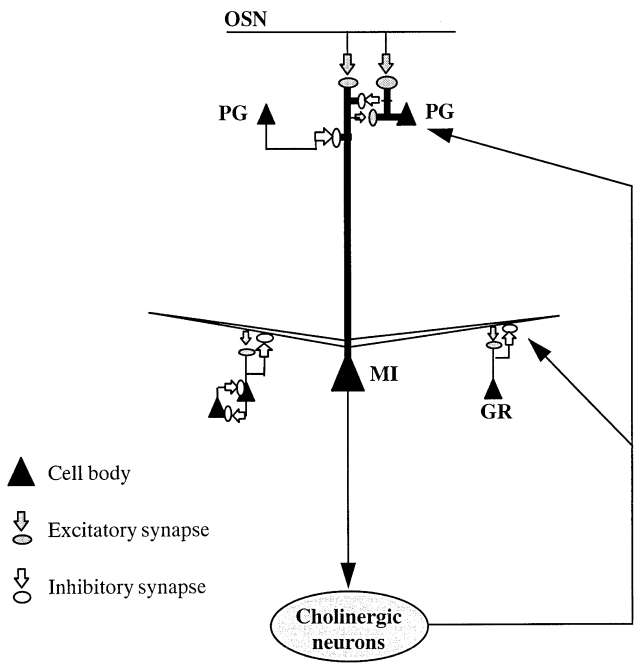

Fig. 2. Schematic illustration of the neural circuitry implemented in the OB model. The circuitry associated with a single glomerulus is depicted. One model OSN, tuned to a restricted range of odorants and representing a population of similarly tuned OSNs in the mammalian nose, projects to each glomerulus, wherein it synapses with the primary dendrites of mitral cells (MI) and periglomerular cells (PG). In the model, 15 glomeruli are modeled; one mitral cell, one periglomerular cell, and one granule cell are associated with each glomerulus. Within each glomerulus, periglomerular and mitral cells interact via dendrodendritic recurrent synapses; periglomerular cells are excited by mitral cells which they in turn inhibit. In addition, periglomerular cells send an axon to inhibit the mitral cells of two neighboring glomeruli on either side. Mitral cell secondary dendrites, which can span up to one third of the OB, interact with 10 neighboring granule cells (GC). Cholinergic modulatory inputs excite periglomerular cells and reduce the inhibitory effect of granule cells onto mitral cell secondary dendrites. In each case, the degree of modulation is regulated by OB output activity via a regulatory feedback loop. Detailed circuitry and equations for the model are described in (Linster & Hasselmo, 1997).

around the mean in order to introduce noise into the model (see Linster & Hasselmo, 1997, for parameter values).

In the model, odor components are represented in a 15-dimensional, discrete odorant space; each odorant stimulus corresponds to a particular point in this space. Fifteen OSNs with overlapping molecular response properties can be differentially activated by these odorant components. These OSNs are differentially sensitive to multiple odor components: each OSN has a maximal (unity) sensitivity to one molecule (i.e. at the center of its gaussian sensitivity curve), while its sensitivity to surrounding molecules is described by a gaussian function with $\sigma = 2$ odors. The 15 OSNs each project onto one of 15 glomeruli, which are arranged in a one-dimensional circular axis of odorant similarity. Within each glomerulus, incoming OSNs synapse onto the primary dendrites of mitral cells as well as onto periglomerular cell dendrites (Fig. 2). Mitral cell primary dendrites also excite periglomerular cells. Periglomerular cells, in turn, inhibit their associated mitral cell dendrites, and also project lateral connections into neighboring glomeruli (spanning a radius of up to two neighboring glomeruli) within which they also inhibit mitral cell primary dendrites. Mitral cell secondary dendrites project laterally and excite granule cells, which in turn inhibit mitral cells; each mitral cell indirectly interacts in this manner, via granule cells, with the secondary dendrites of mitral cells within a range of up to ten neighboring glomeruli (five in each direction). In addition, granule cells locally interact with each other through mutually inhibitory connections; these feedback inhibitory interactions project to three neighboring granule cells in each direction.

The electrophysiological effects of cholinergic modulation in the OB in vivo (either by infusion of cholinergic agonists or by electrical stimulation of the HDB) can be summarized as follows: (i) an increase of the spontaneous activity of periglomerular cells and (ii) a decrease of the inhibitory action on mitral cells by granule cells (Elaagouby & Gervais, 1992; Elaagouby, Ravel, & Gervais, 1991; Kunze, Shafton, Kemm, & McKenzie, 1992; Kunze, Shafton, Kemm, & McKenzie, 1991, 1992; Nickell & Shipley, 1988; Ravel, Akaoka, Gervais, & Chouvet, 1990). Recently, Castillo, Carleton, Vincent, and Lledo (1999) have also demonstrated multiple effects of cholinergic modulation on mitral, periglomerular and granule cells in an OB slice preparation. The results from this study corroborate the in vivo data, demonstrating (i) activation of periglomerular and mitral cells by nicotinic cholinergic agonists and (ii) an inhibitory effect of muscarinic cholinergic agonists on the firing activity of granule cells. Based on the experimental data gathered in vivo and in vitro, we have implemented the cholinergic modulation of inhibition in the model both at the level of periglomerular cells and at the level of granule cells. Specifically, centrifugal cholinergic inputs directly excite periglomerular cells in the model, and also reduce the inhibitory connection strengths from granule cells to mitral cells. (The experimental data gathered in vivo and in vitro propose different effects of acetylcholine on granule cells; since both proposed mechanisms lead to the disinhibition of mitral cells, and no functional differences between these mechanisms have yet been proposed, we here use only one of the proposed mechanisms: modulation of the granule-mitral synapse.) As we have shown before (Linster & Gervais, 1996; Linster & Hasselmo, 1997), the excitation of periglomerular cells increases lateral inhibition among mitral cells and consequently reduces the number of mitral cells responding with increased spike rates to a given stimulus, whereas reduction of the inhibitory action of granule cells increases the firing rate of activated mitral cells. If the degree of cholinergic modulation is directly dependent on the level of OB output activity, a feedback regulation loop between mitral cell activation and centrifugal cholinergic modulation is generated (Fig. 2). In the model, such a feedback loop can (i) ensure a constant

average number of activated mitral cells, relatively independent of the complexity of the stimulus, (ii) lead to constant average spike rates within the active mitral cells, and (iii) reduce the overlap between neural responses to similar input patterns, thus enhancing the discriminability of similar odorant stimuli at the output of the OB. Thus, this model predicts that centrifugal cholinergic input, when regulated by activity in the olfactory system and acting via modulation of local inhibitory circuits, could serve to modulate discrimination between similar olfactory stimuli over a wide range of possible odorants.

3. A model for odor similarity

In order to behaviorally test the model's prediction that acetylcholine modulates olfactory discrimination between similar stimuli, we require a model system for graded odor similarity that can be applied both in behavioral experiments and in the model, that is, a set of odorants that can be ordered in a series such that nearest neighbors in the series are more perceptually similar to one another than are more distant neighbors. Ideally, mitral cell responses to such odorants would also be known, in order to more strictly constrain the model and improve the accuracy of its representation of the neural responses to such an odorant series. Several years ago, Mori and co-workers proposed that mitral cells in particular regions of the anesthetized rabbit OB responded preferentially to unbranched aliphatic aldehydes with a specific number of carbons in the aliphatic chain (Fig. 1(B); Imamura, Mataga, & Mori, 1992; Yokoi, Mori, & Nakanishi, 1995). These neurons would respond with increased spiking activity to the application of any of a group of aldehydes with similar chain lengths (e.g. a cell that responded most strongly to an aldehyde with 5 carbons would also increase its spike rate somewhat in response to aldehydes with 4 and 6 carbons). However, such a neuron would be inhibited by aldehydes with more dissimilar numbers of carbons (i.e. the cell described earlier might be inhibited by unbranched aldehydes containing 3 or 7 carbons; Yokoi et al., 1995). Subsequently, a number of imaging studies (Johnson, Woo, Hingco, Pham, & Leon, 1999; Meister & Bonhoeffer, 2001) have shown that responsive olfactory glomeruli are often commonly activated by aliphatic odorants with neighboring carbon chain lengths, in concordance with the single-cell recordings performed in rabbits. A consequence of this is that odorants with carbon chains of neighboring lengths will activate overlapping populations of neurons, and furthermore that the overlap between the populations of neurons activated by two unbranched aliphatic odorants with similar carbon chain lengths would be greater than that evoked by two such odorants with dissimilar carbon chain lengths. For this model to be directly applicable to behavioral data, however, greater degrees of overlap between the neural populations activated by two odorants should predict increased perceptual similarities between these odorants. In the last few years, we and others have shown that unbranched aliphatic aldehydes are indeed perceived as more similar when they have similar numbers of carbons in their carbon chains (Laska, Galizia, Giurfa, & Menzel, 1999; Linster & Hasselmo, 1999), and that, in rats, similarities between glomerular activation patterns in response to straight-chain carboxylic acids can predict behaviorally perceived similarities among these odorants (Cleland, Morse, Yue, & Linster, 2002; Johnson et al., 1999; Meister & Bonhoeffer, 2001).

Based on the experimental data reviewed earlier, we suggest that a defined series of unbranched aliphatic aldehydes, among other straight-chain homologous series, constitutes a useful model system for ordered odorant similarity that can be used to directly relate the predictions arising from our computational model to experimental behavioral observations, as well as to physiological responses at both the individual mitral cell and broad glomerular activation levels (Imamura et al., 1992; Johnson et al., 1999; Kashiwadani, Sasaki, Uchida, & Mori, 1999; Linster & Hasselmo, 1999; Meister & Bonhoeffer, 2001; Yokoi et al., 1995). Accordingly, we have implemented responses to unbranched aldehydes with 3- to 8-carbon chains in our model and simulated the effects of eliminating cholinergic inputs on the representation of these odorants by OB mitral cells. For present purposes, we are restricting our analyses to a single dimension of odorant similarity; consequently, the additional responsivity of aldehyde-sensitive OSNs to (e.g.) branched aldehydes and/or non-aldehydes is neglected.

4. Effects of cholinergic modulation on model mitral cell responses to aliphatic aldehydes

In order to simulate mitral cell responses to aliphatic aldehydes, we programmed OSNs to respond preferentially to an aldehyde with a given chain length, and to a lesser extent to neighboring aldehydes. Specifically, OSN response profiles as a function of carbon chain length were modeled by gaussian functions with $\sigma = 2.0$. As previously detailed (Linster & Gervais, 1996; Linster & Hasselmo, 1997), and as shown in Fig. 2, each sensory neuron projects to a single glomerulus and activates mitral cell primary dendrites and a periglomerular cell within that glomerulus. The mitral cell primary dendrite also directly excites the periglomerular cell within its glomerulus, while the periglomerular cell inhibits the mitral cell primary dendrite and those of its 'near' neighbors. Granule cells are activated indirectly via excitatory inputs from active mitral cell secondary dendrites and feedback inhibition upon mitral cells. Consequently, the overall response pattern of each individual mitral cell to an odorant stimulus, as shown in Fig. 3, is shaped by the inhibitory actions of periglomerular and granule cells in addition to the excitatory

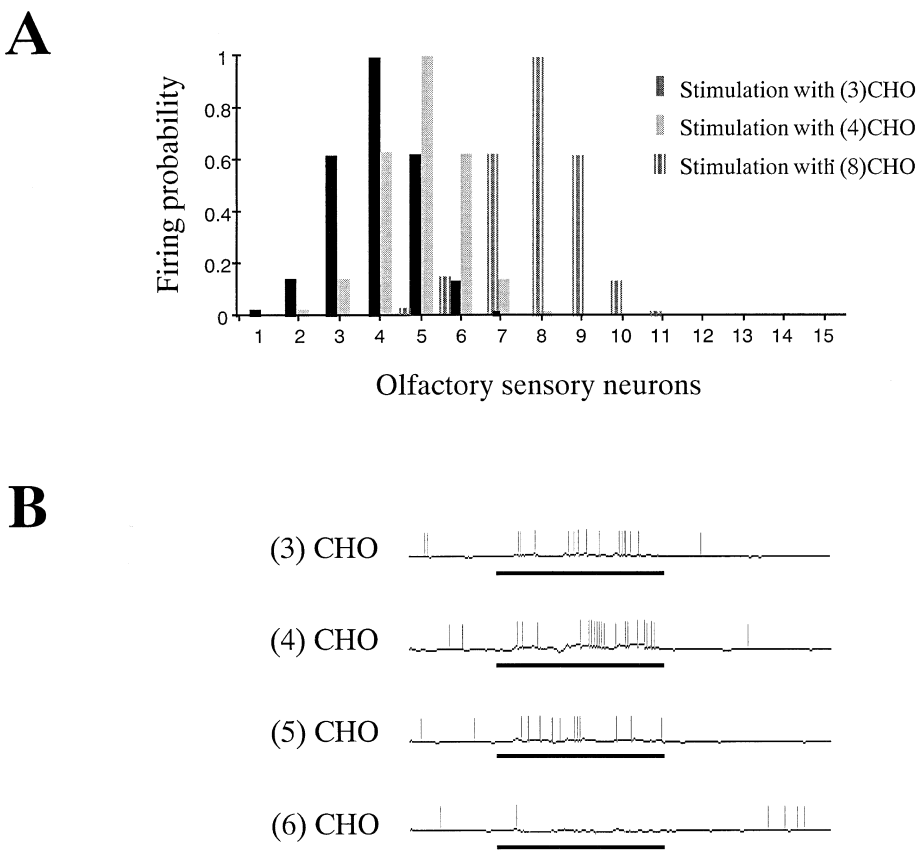

Fig. 3. Response patterns to aliphatic aldehydes. (A) Firing probabilities of the 15 model OSNs (inputs to the 15 glomeruli) in response to stimulation with (3)CHO, (4)CHO and (8)CHO. These OSN response profiles were modeled as a function of carbon chain length using gaussian functions with $\sigma = 2.0$. Consequently, each OSN responds maximally to a single aldehyde, and less strongly as the carbon chain length difference between the stimulating odor and the odor evoking the maximal response increases. (B) Response patterns of one selected model mitral cell to each of four aliphatic aldehydes. Membrane potential and action potentials are shown; the duration of odor stimulation is indicated by the line underneath each trace. This mitral cell responds most strongly to (4)CHO, is activated to a lesser degree by (3)CHO and (5)CHO, and is inhibited by (6)CHO.

input from its associated OSN. Furthermore, while the response profile of each mitral cell is based on the odorant specificity of its associated OSN, it is additionally influenced by lateral inhibitory input from neighboring glomeruli. Consequently, for example, the model mitral cell shown in Fig. 3 responds preferentially to the 4-carbon aldehyde odorant (4)CHO, is activated to a lesser degree by (3)CHO and (5)CHO, and is inhibited by (6)CHO.

In the simulations presented here, we directly compare the responses of all 15 mitral cells to each of the aldehyde odor stimuli used. As shown in Fig. 4(A), under control conditions (i.e. with an intact cholinergic feedback loop between the central cholinergic neurons and the neurons of the OB), overlapping populations of mitral cells respond to odorants with neighboring carbon chain lengths. The degree of overlap between the responses to two odorants was derived from the mean firing rates of the mitral cells in response to these odorants. Specifically, for each odor response, a 15-dimensional vector was constructed from the mean firing rates of mitral cells associated with each of the 15 glomeruli during a 120 ms stimulus application. Fig. 4(B) shows an example of such a vector representation of three neighboring aldehydes in a two-dimensional (i.e., two-glomerular) space. The overlap between any two odor representations was quantified as the normalized scalar product of the two resulting vectors (Linster & Hasselmo, 1997); this product tends towards 0.0 when the two vectors are orthogonal (non-overlapping) and towards 1.0 when the two vectors are fully overlapping. Using the normalized scalar product, we compared the activity patterns in response to (3)CHO to those in response to all other odors in the stimulus ensemble ((4)CHO–(8)CHO). For each pair of odor stimuli, the simulation was run 50 times and the mean overlap was calculated from the individual scalar products. To test how a deficit in cholinergic modulation would affect the representation of these odorants, we then performed the same simulations with suppressed cholinergic modulation; i.e. we inactivated the feedback loop between the cholinergic neurons and the OB in the model. Under these conditions, more mitral cells responded to each odor presentation, and fewer mitral cells were suppressed by odors that would have inhibited their activity in the presence of cholinergic feedback (Fig. 4(C)).

Both curves in Fig. 4(D) show that the overlap between the neural responses to two straight-chain aldehyde odorant stimuli decreases as the difference between the carbon chain

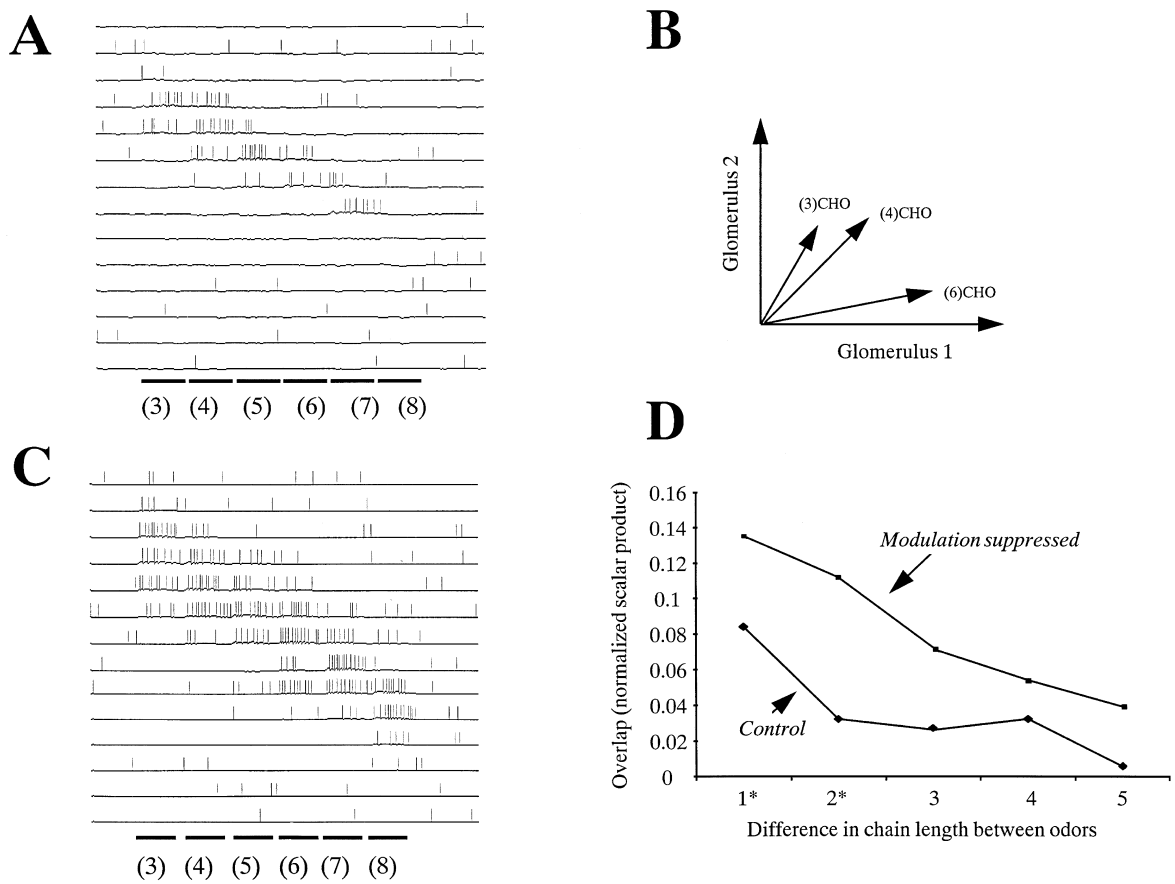

Fig. 4. (A) Response patterns of model mitral cells to stimulation with aliphatic aldehydes with carbon chain lengths varying from three to eight in the presence of intact cholinergic feedback modulation. Membrane potential fluctuations and action potentials are shown; the identities and durations of odor stimuli are indicated by the lines underneath the traces. Each odor stimulation lasted 120 ms, the approximate duration of one inhalation cycle during normal respiration in rats. (B) Illustration of the vector representation of neural responses for a two-dimensional (i.e. two-glomerular) example. For each odor stimulation, the population response of the model is represented as a vector, the magnitude and direction of which is determined by the average firing rates of the mitral cells associated with each glomerulus (here, we illustrate responses to two similar odors, (2)CHO and (3)CHO, and one less-similar odor, (6)CHO). The overlap between two population responses can then be represented as the normalized scalar product between the two corresponding vectors. (C) Simulation of the responses to aliphatic aldehydes with carbon chain lengths varying from three to eight after elimination of cholinergic modulatory input. Membrane potential fluctuations and action potentials are shown; the identities and durations of odor stimuli are indicated by the lines underneath the traces. Each odor stimulation lasted 120 ms. (D) Overlap between the response patterns of all mitral cells in the model in response to aliphatic aldehydes with varying differences in carbon chain lengths. Each data point depicts the normalized scalar product calculated from the vectors of mitral cell firing rates in response to odorants differing by a given number of carbons. To generate these curves, the response to (3)CHO was compared with the response to each of the other odorants ((4)CHO–(8)CHO). The lower curve (*Control*) is the mean of 50 simulations per odorant with intact feedback modulatory regulation, the upper curve (*Modulation Suppressed*) is the mean of 50 simulations per odorant with suppressed cholinergic modulation. Asterisks indicate those odor pairs for which a significant difference ($p < 0.05$) was found between the two conditions.

lengths of the two odorants increases. Comparison of the normalized scalar products (overlap) between odorant pairs under *control* and *suppressed modulation* conditions shows that when modulation is suppressed, the overlap between closely related odor stimuli increases significantly (Fig. 4(D) asterisks: statistically significant differences in overlap for 1- and 2-carbon differences in chain lengths, two-tailed *t*-test, $p < 0.05$), whereas the overlap between less closely related stimuli is correspondingly less affected (Fig. 4(D): 3- to 5-carbon differences in chain lengths). If our simulations accurately model the physiological processes underlying odor perception, then a reduction in the overlap of two neural representations should correspond to the behaviorally-measured decreases in perceived similarities of the two corresponding odors (Linster & Hasselmo, 1999). Furthermore, these results would then predict that when cholinergic modulation is suppressed, closely related aliphatic aldehydes should be perceived as more similar than they would be under normal conditions, whereas perception of less similar odorants should not be so affected.

5. Behavioral effects of missing cholinergic inputs to the olfactory system

In order to test the prediction that acetylcholine modulates the perceived similarities between aliphatic aldehydes, we trained rats with pharmacologically-specific

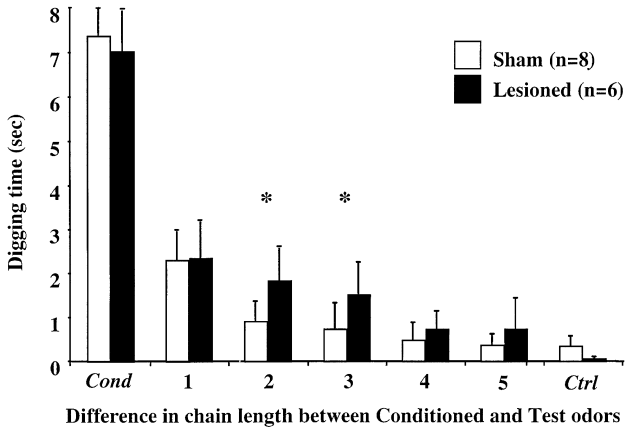

Fig. 5. Results from behavioral experiments. The graph depicts mean digging times (in seconds) of two groups of rats (Sham and Lesioned) as a function of the difference in carbon chain lengths between the conditioned and test odorants, as well as the responses to the conditioned odor itself (*Cond*) and to the highly dissimilar control odorant *n*-amyl acetate (*Ctrl*). Asterisks indicate test odorants for which a significant difference ($p < 0.05$) between the response levels of the two groups was found.

lesions of HDB cholinergic neurons on a olfactory behavioral task which enables the measurement of perceived odor similarities in rats, in collaboration with Dr Mark Baxter and Ms Patricia Garcia (Harvard University) and Dr Michael Hasselmo (Boston University). The behavioral task and lesioning techniques have been described in detail elsewhere (Linster, Garcia, Hasselmo, & Baxter, 2001; Linster & Hasselmo, 1999; Linster & Smith, 1999). Briefly, two groups of rats were trained in this experiment. The first group received 192 IgG-saporin lesions of cholinergic neurons within the HDB, while the second group received sham lesions. These lesions resulted in the specific elimination of cholinergic projections to the OB and olfactory cortex. Rats were conditioned to dig in a dish filled with bedding to recover food reinforcement (a small piece of sweet cereal). The rats had to learn to choose between a scented cup that contained reinforcement and an unscented cup that contained only bedding. We trained rats on a series of aliphatic aldehydes ((3)CHO to (8)CHO; Fig. 1(B)) and tested all combinations of pairwise generalization between these different odorants. To control for non-specific responses to odorants, we also tested rats' responses to an unrelated control odorant, *n*-amyl acetate; to control for non-specific digging, an unscented cup containing only bedding was also present during all tests. On each day, each rat was trained on one of the six test aldehydes (the 'conditioned odor') and its responses to each of the six aldehydes were subsequently tested. Generalization was quantified as the amount of time spent digging in response to a test odor relative to that rat's response to the conditioned odor (in the absence of reward); it can be thought of as the degree to which rats 'confuse' the test odorant with the conditioned odorant, and constitutes a measure for similarities in perception (Cleland et al., 2002). For analysis, generalization measurements were grouped by differences in chain lengths—that is, generalizations between (3)CHO and (6)CHO (a 3-carbon difference in chain length, including generalization from each to the other) were combined with generalizations between (4)CHO and (7)CHO and between (5)CHO and (8)CHO (Fig. 5).

When tested on generalization between *n*-aliphatic odorants of different carbon chain lengths, both groups of rats performed similarly in response to the conditioned odor (Fig. 5, *Cond*), as well as in response to the control odor (*n*-amyl-acetate; Fig. 5, *Ctrl*). This demonstrates that neither the acquisition of the conditioned odorant nor the discrimination of very dissimilar odorants were significantly affected by the cholinergic lesions. Similarly, no significant differences were observed in the responses to adjacent test odorants, or those to test odorants differing by four or more carbons. Significant differences were observed, however, in the responses to test odorants differing by two or three carbons from the conditioned odor ($p < 0.05$ by simple mean effects calculation). In these cases, the responses of the lesioned rats were significantly higher to these test odorants, indicating that they were more likely to confuse them with the conditioned odor than were the sham operated rats.

The results from this behavioral experiment accord with the predictions from the simulations described earlier: suppressing cholinergic modulation resulted in increased perceptual overlap between similar, but not dissimilar, odorants. There remain quantitative differences between the model predictions and behavioral results; notably, while the behavioral responses of the two groups of rats differed significantly when two odors differed by two or three carbons, significant corresponding differences arose in the model when the two odors differed by one or two carbons.

6. Conclusion

We have described a computational model of the OB originally designed to investigate how known neuromodulatory inputs could regulate odor representation in the OB. The model relies on the regulation of the activity of cholinergic neurons by activity in the neurons of the OB. Although there is no evidence for direct connections from the OB to the HDB, we have recently shown that neurons in the HDB can be modulated by electrical stimulation of OB output fibers, suggesting that a pathway exists through which the OB could regulate the levels of cholinergic modulation projecting back to it (Linster & Hasselmo, 2000). Indeed, candidate projections to the HDB have been proposed from the olfactory cortex and the anterior cortical nucleus of the amygdala, both of which receive direct input from the OB (see Russchen, Amaral, & Price, 1985 for review). Additionally, while we have focused on the effects of acetylcholine, modulation of local interneuronal inhibition within the OB is mediated by a number of different centrifugal inputs to the OB (e.g. efferent projections from

olfactory cortex and noradrenergic inputs from the locus coeruleus), and thus may also be productively investigated using the present computational model.

Electrophysiological evidence for mitral cell and glomerular response patterns to aliphatic aldehydes which resemble 'molecular receptive fields' led us to investigate whether similarities between neural response patterns in the OB could predict perceptual similarities between odorants (Linster & Hasselmo, 1999). The present model was used to integrate these diverse physiological data into a simulation of OB responses to realistic odorants; this simulation predicted, correctly, that missing cholinergic inputs to the OB would result in greater generalization between similar aliphatic aldehydes. The success of this prediction is highly encouraging to future studies seeking to take advantage of the complementary interactions between computational modeling and experimental results.

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