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Receptive Fields in the Rat Piriform Cortex

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Current models of odor discrimination in mammals involve molecular feature detection by a large family of diverse olfactory receptors, refinement of molecular feature extraction through precise projections of olfactory receptor neurons to the olfactory bulb to form an odor-specific spatial map of molecular features across glomerular layer, and synthesis of these features into odor objects within the piriform cortex. This review describes our recent work on odor and spatial receptive fields within the anterior piriform cortex and compares these fields with receptive fields of their primary afferent, olfactory bulb mitral/tufted cells. The results suggest that receptive fields in the piriform cortex are ensemble in nature, highly dynamic, and may contribute to odor discrimination and odor memory.

Introduction

A receptive field can be defined as that portion of the sensory world (or range of specific energies) to which a neuron responds (Hartline, 1938; Mountcastle, 1957). Depending on the sensory system, receptive fields can be described in terms of location on the body surface, a range of frequencies of vibrations induced in the inner ear, a range of wavelengths or spatial locations of light impinging on the retina, or a set of odorant molecules contacting the olfactory receptor sheet. In the classic view, receptive fields of peripheral neurons divide a sensory stimulus into components or features which can be assembled through convergence into more complex receptive fields in higher order neurons (Hubel and Wiesel, 1962) and/or through binding within oscillatory networks resulting in perceptual wholes (Singer, 1999).

In most sensory systems, receptive fields can be described along rational, or at least ordinal, scales, wherein relationships between stimuli (and between receptive fields) can be quantified and relatively easily organized. Identification of retinotopic, tonotopic and somatotopic maps of cortical receptive fields are an obvious consequence of these quantifiable stimuli, and have provided great insight into how those sensory systems (e.g. mammalian thalamocortical sensory systems) function. It should also be noted that receptive fields of a single neuron may be described along more than one dimension; for example, a visual cortical neuron may have a binocular or monocular receptive field (dimension 1) for contrast edges of a particular range of orientations (dimension 2).

A hindrance to understanding the olfactory system has been the relative lack of insight into what the appropriate scalar is for describing odorant molecules (Wise *et al.*, 2000) and, in turn, describing olfactory neuron receptive fields. It has been unclear along what dimension or with what features the olfactory system operates to discriminate and respond to odors (Amoore, 1970). However, since the relatively recent discoveries that olfactory receptor neurons express one of a large set of G-protein-coupled odor receptor proteins and that receptor neurons expressing similar proteins project in a precise manner to converge on individual main olfactory bulb (MOB) glomeruli [for reviews see Shepherd and Buck (Shepherd, 1994; Buck, 1996)], there has been significant progress toward identifying the dimensions and units of odor space. For example, recent work has extended older work (Dethier, 1954; Doving, 1966; Cain, 1970) to suggest that carbon chain length, structural conformation and the presence of functional groups, such as hydroxyl and carboxyl groups, may be important molecular features recognized by olfactory receptors and encoded by MOB neurons (Sato *et al.*, 1994; Mori and Yoshihara, 1995; Malnic *et al.*, 1999; Rubin and Katz, 1999; Johnson and Leon, 2000; Scott *et al.*, 2000).

Specifically, receptive fields of both olfactory receptor neurons and olfactory bulb mitral/tufted cells have been mapped along the dimension of carbon chain length of specific organic molecules. Individual mammalian olfactory receptor neurons (Sato *et al.*, 1994; Malnic *et al.*, 1999) and mitral/tufted cells (Imamura *et al.*, 1992; Yokoi *et al.*, 1995) respond with excitation to sequential series of carbon chain lengths with longer and shorter chains outside of the cell's receptive field. In mitral/tufted cells, these receptive fields often include inhibitory surrounds (Meredith, 1986; Wilson and Leon, 1987) to the longest and shortest effective stimuli (Yokoi *et al.*, 1995; Mori *et al.*, 1999).

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Most detailed models of primary olfactory (piriform) cortex function were developed prior to the discovery of the large olfactory receptor gene family and subsequent molecular mapping of receptor projections to the MOB (Haberly 1985; Lynch, 1986; Bower, 1991). However, in general these models include the concept of convergence of information about odor features (or odor mixture components) via afferent and/or association fibers onto individual piriform cortex neurons. Theoretical receptive fields of these cortical neurons, then, include ensembles of molecular features (or odors) resulting in the ability to discriminate between 'whole' odors. These models also include a strong plasticity component that is important not only for olfactory memory, but also for the association of particular components within the odor ensemble to be discriminated (Haberly 1985; Lynch, 1986; Bower, 1991).

The present review briefly describes recent descriptions of receptive fields and receptive field plasticity in the rat anterior piriform cortex (aPCX) from our laboratory. These aPCX receptive fields are compared with receptive fields in mitral/tufted cells and with cortical receptive fields in thalamocortical systems in order to extract basic similarities and differences between sensory receptive fields in the olfactory system and thalamocortical systems.

Functional Anatomy of Rat aPCX

The mammalian primary olfactory cortex differs substantially from other mammalian sensory systems in several ways that could result in important differences in cortical receptive fields. First, there is no thalamic relay between initial central processing and the olfactory cortex. In thalamocortical systems, the thalamic relay can sharpen sensory information through response amplification and enhanced lateral inhibition before the information enters the cortex (Sherman, 1993). This thalamic processing could thus help refine cortical receptive fields. A second major difference between the olfactory system and thalamocortical systems is that piriform cortex anatomy (see below) results in a spatial and temporal wave of afferent activation of the cortex, rather than the more synchronous activation produced by thalamic input to other sensory cortices. The dynamics and mechanisms of this input wave have been described (Ketchum and Haberly, 1993). However, the consequences of wave activation on cortical receptive fields have not yet been explored, but may be expected to have significant effects on local intracortical interactions, such as potential inhibitory surrounds.

In contrast to these two differences between olfactory cortex and thalamocortical systems, there are a number of important similarities. As in thalamocortical systems, where there are cortico-thalamic feedback systems, there is strong cortical-olfactory bulb feedback. In fact, the majority of centrifugal input to the olfactory bulb comes from olfactory cortical areas (Haberly, 1998). Feedback of this sort can allow rapid, experience-dependent changes in gain control and receptive field dynamics of the more peripheral structure, which in turn can influence subsequent cortical receptive fields [e.g. the visual system (Murphy and Sillito, 1987; Cudeiro *et al.*, 2000)]. The second major similarity between the olfactory cortex and thalamocortical systems is the presence of strong cortico-cortical associational connections. Association fibers in the visual system, for example, connect individual cortical columns, as well as whole cortical regions such as primary and secondary visual cortices. In the olfactory cortex, association systems also connect both proximal and distal regions of the cortex, and are bidirectional (Haberly and Price, 1978; Datiche *et al.*, 1996).

Excellent descriptions of piriform cortex anatomy exist (Shipley and Ennis, 1996; Haberly, 1998), thus only a brief outline is included here. The piriform cortex is a three-layered cortical structure, with the primary input consisting of mitral cell axons forming the lateral olfactory tract (LOT) which runs along the cortical surface. LOT axons branch and terminate in superficial layer I (Ia) on apical dendrites of the principal cortical neurons, and superficial (somas in layer II) and deep (somas in layer III) pyramidal neurons. A third class of pyramidal-like neurons is the semilunar neurons, with cell bodies located in superficial layer II, no basal dendrites, and multiple apical dendrites extending into layer Ia. Association and commissural inputs terminate on cortical pyramidal cell apical dendrites in layer Ib and basal dendrites in III. A number of different interneurons exist in both layers I and III.

Odor responses in layer II/III neurons are short-latency and, in awake (McCollum *et al.*, 1991) or urethane-anesthetized rats (Wilson, 1998a), most commonly excitatory (Figure 1). Intracellular recordings reveal large odor-evoked depolarizations (Nemitz and Goldberg, 1983; Wilson, 1998a), in phase with the respiratory cycle (Wilson, 1998a). These depolarizing post-synaptic potentials can evoke single or multiple action potentials, with instantaneous frequencies within odor-evoked spike trains generally of 50–100 Hz, although occasionally reaching 300 Hz (Wilson, 1998a). Subthreshold oscillations of ~30–60 Hz can also sometimes be observed riding respiratory-entrained post-synaptic potentials (Figure 1).

Spatial Receptive Fields in Rat aPCX

Cortical spatial receptive fields have been described most thoroughly in the somatosensory and visual systems. Within these systems, cortical responses are dependent not only on the quality (e.g. light touch/deep touch, or wavelength) of the stimulation, but also on the spatial location of the stimulus on the receptor sheet. Spatial receptive fields can contribute to both stimulus localization and stimulus identification.

In the olfactory system, given the nature of stimulus

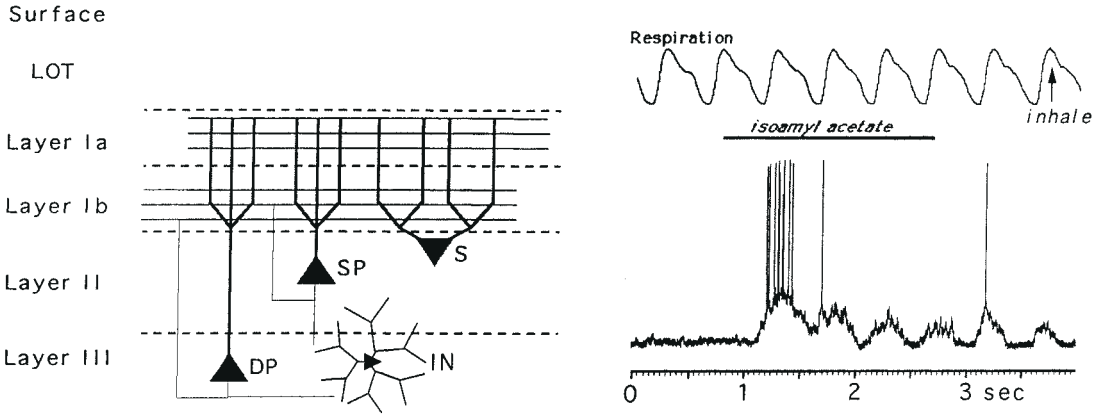

Figure 1 Schematic of basic anatomical organization of the anterior piriform cortex (right) and an example of an aPCX neuron response to odor (left). Input from the ipsilateral MOB (mitral cell axons) enters the aPCX via the lateral olfactory tract (LOT) which terminates in layer Ia on apical dendrites of the principle aPCX neurons, deep pyramidal (DP), superficial pyramidal (SP) and semilunar cells (S). Associational and commissural inputs terminate within layers Ib and III. Excitability is controlled through interneurons (IN) in layers I and III. For a more thorough description see Haberly (Haberly, 1998). In freely breathing, urethane-anesthetized rats, layer II/III neurons respond to odors generally with large depolarizations in phase with the respiratory cycle. These depolarizing synaptic potentials can give rise to spike trains and/or subthreshold oscillations.

access to the receptor sheet and the intermixed spatial distributions of receptor proteins across the receptor sheet (Ressler *et al.*, 1993; Vassar *et al.*, 1993), olfactory cortical spatial receptive fields would appear less useful. However, each olfactory receptor sheet is divided into different zones, each expressing a different subpopulation of receptor proteins and projecting to roughly segregated regions of the MOB. Furthermore, there are two separate olfactory receptor sheets (left and right nasal passages) which are relatively well isolated from each other. Thus, the anatomical basis for cortical spatial receptive fields does exist in the olfactory system. We have begun examining spatial receptive fields in aPCX by describing the ability of aPCX neurons to discriminate ipsilateral and contralateral odor stimulation (binaral receptive fields).

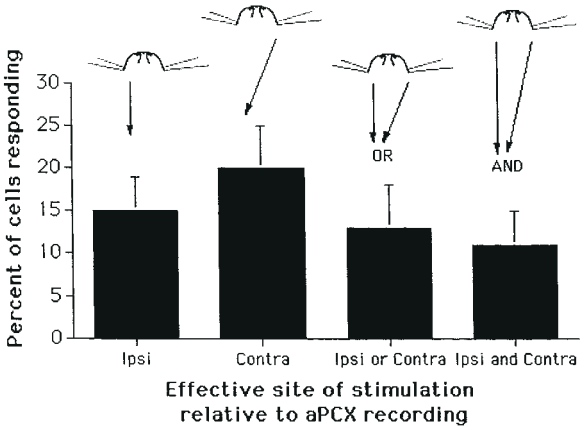

Figure 2 Spatial receptive fields in aPCX neurons. In freely breathing, urethane-anesthetized rats, approximately similar proportions of layer II/III neurons were responsive only to odors delivered to the ipsilateral naris; only to odors delivered to the contralateral naris; to odors delivered to either naris; or only to odors delivered bilaterally (Wilson, 1997).

Description

The commissural inputs to aPCX (see above) are sufficient to drive odor responses in aPCX single-units (Wilson, 1997). Odor responses can be evoked in aPCX layer II/III single-units by unilateral stimulation of the contralateral naris or by bilateral odor stimulation following reversible lesions of the ipsilateral MOB (Wilson, 1997). Based upon responses to unilaterally delivered odors, at least four categories of spatial receptive fields can be described in aPCX neurons. Individual cells may respond selectively to ipsilateral stimulation, selectively to contralateral stimulation, to either ipsi- or contralateral stimulation or require bilateral stimulation. With the odor set used by us (Wilson, 1997), each of these spatial receptive field categories were approximately equally represented in aPCX (Figure 2).

The anatomical bases for differential spatial receptive fields is not known. Cells selectively responsive to ipsilateral stimulation, however, may belong to the semilunar class of pyramidal-like neurons. These superficial layer II neurons have large dendritic spines concentrated within layer Ia, and thus presumably receive primarily ipsilateral LOT input (Haberly, 1983). In fact, survival of semilunar neurons requires ipsilateral LOT input. Ipsilateral olfactory bulb lesions or LOT sectioning results in selective apoptosis of semilunar neurons within hours (Heimer and Kalil, 1978; Lopez-Mascaraque and Price, 1997), with no detected effect on contralateral neurons.

The role of aPCX binaral spatial receptive fields in odor processing is also not known. Humans appear incapable of localizing unilaterally delivered, purely olfactory stimulation to one nasal passage or the other (Kobal *et al.*, 1989). Rats, which have laterally directed external nares and respiratory airflow (Wilson and Sullivan, 1999), and can follow odor

trails, could potentially use bilateral comparisons of odor intensity or quality to localize odorants. Other potential roles of binaral spatial receptive fields include signal amplification (Bennett, 1968) and bilateral access to olfactory memories (Kucharski and Hall, 1987).

In addition to demonstrating that commissural connections are capable of driving odor responses in the aPCX, the existence of at least four distinct categories of binaral spatial receptive fields suggests a potentially high degree of specificity in local afferent terminations within the aPCX. In fact, mitral cell afferents to the ipsilateral aPCX show patchy termination patterns (Ojima *et al.*, 1984; Buonviso *et al.*, 1991), and recent mapping of c-fos immunoreactivity in response to odors suggests odor-specific spatial patterns of activity within the aPCX (Illig and Haberly, 2000). Given that different odors evoke unique spatial patterns of activity across the olfactory bulb (Jourdan *et al.*, 1980; Guthrie *et al.*, 1993; Mori *et al.*, 1999; Rubin and Katz, 1999; Johnson and Leon, 2000; Xu *et al.*, 2000), aPCX neurons may also demonstrate 'spatial receptive fields' for activity within the olfactory bulb. Thus, differential odor responsiveness may in fact be indicative of a form of spatial receptive field wherein individual aPCX neurons are differentially responsive to specific spatial locations within the olfactory bulb, in addition to the observed differential responsiveness between olfactory bulbs.

Plasticity

Spatial receptive fields in both the somatosensory and visual systems can be modified by experience (Buonomano and Merzenich, 1998). Functional plasticity of spatial receptive fields in aPCX has not been examined, although neuroanatomical data suggest a basis for experience-dependent plasticity. For example, the relative width of layers Ia (ipsilateral LOT fibers) and Ib (associational/commissural fibers) can be modified by olfactory bulb or LOT lesions during development. Olfactory bulb lesions in neonates results in a reduction of layer Ia width and a compensatory increase in width of layer Ib (Friedman and Price, 1986; Westrum and Bakay, 1986). Similar, though less dramatic, results can be produced with unilateral olfactory deprivation during development (Wilson *et al.*, 2000). Furthermore, unilateral olfactory deprivation reduces dendritic complexity of ipsilateral semilunar neurons (Wilson *et al.*, 2000). These activity-dependent changes in both presynaptic termination zones and post-synaptic dendritic targets could have significant effects on spatial receptive fields in the aPCX.

Molecular Receptive Fields in Rat aPCX

Description

Work on a variety of species has shown that neurons in the olfactory cortex respond to multiple, diverse odors (Haberly, 1969; Tanabe *et al.*, 1975; Nemitz and Goldberg, 1983; McCollum *et al.*, 1991; Duchamp-Viret *et al.*, 1996; Wilson, 2000a). A complete description of aPCX neuron molecular receptive fields, such as that performed with olfactory receptor neuron (Sato *et al.*, 1994; Malnic *et al.*, 1999; Kaluza and Breer, 2000) and mitral cell (Imamura *et al.*, 1992) responses to homologous series of organic compounds with different functional groups, has not been done at this time. However, as shown in Figure 3, stimulation with alkane odorants reveals that, similar to mitral cells, aPCX neurons can discriminate odors based on carbon chain length (Wilson, 2000a). Mitral cells with similar molecular receptive fields are spatially organized within the olfactory bulb, such that particular spatial locations within the olfactory bulb are somewhat more responsive to one class of odor than to another (Mori *et al.*, 1999). At present it is unknown whether there is any spatial organization or clustering of aPCX neurons with similar molecular receptive fields, although recent c-fos mapping suggests there may be (Illig and Haberly, 2000).

An important difference between mitral cell and aPCX neuron molecular receptive fields appears to be how the receptive fields are derived. Mitral cells appear to respond to particular molecular features, and thus may respond to many odors if each of those odors contains the appropriate feature, similar to proposed ORN responses (Sato *et al.*, 1994; Malnic *et al.*, 1999). Cross-habituation studies (Figure 4) show that mitral cells demonstrate strong cross-habituation between alkane odors (Wilson, 2000b), as would be expected if mitral cells are simply responding to the presence of a single feature that both odors have in common. aPCX neurons, on the other hand, appear to respond to multiple odors as independent stimuli. Thus, in cross-habituation studies in the aPCX there is minimal cross-habituation between alkane odors (Wilson, 2000a,b), or even between binary mixtures and their components (Wilson, 2000a).

This underlying difference in molecular receptive fields of mitral and aPCX neurons may be derived from the difference in afferent input to these two cells types, and, in fact, could be predicted from olfactory cortex models (Haberly 1985; Lynch, 1986; Bower, 1991). That is, mitral cells receive afferent input from a single glomerulus that is the target of receptor neurons primarily expressing the same receptor gene (Ressler *et al.*, 1994; Vassar *et al.*, 1994) with potentially similar or identical molecular receptive fields (Bozza and Kauer, 1998). Thus, if receptor neurons and their associated mitral cells respond to a set of odors because each member of that set contains a similar molecular feature, then habituation to that feature should reduce responsiveness to all members of the set (strong cross-habituation). On the other hand, the piriform cortex has been proposed to act as a combinatorial array, with each neuron responding to a particular odor due to its unique combination of features [the odor-specific pattern of activated glomeruli and the convergence of mitral cell axons (Haberly 1985; Lynch, 1986; Bower, 1991; Mori *et al.*,

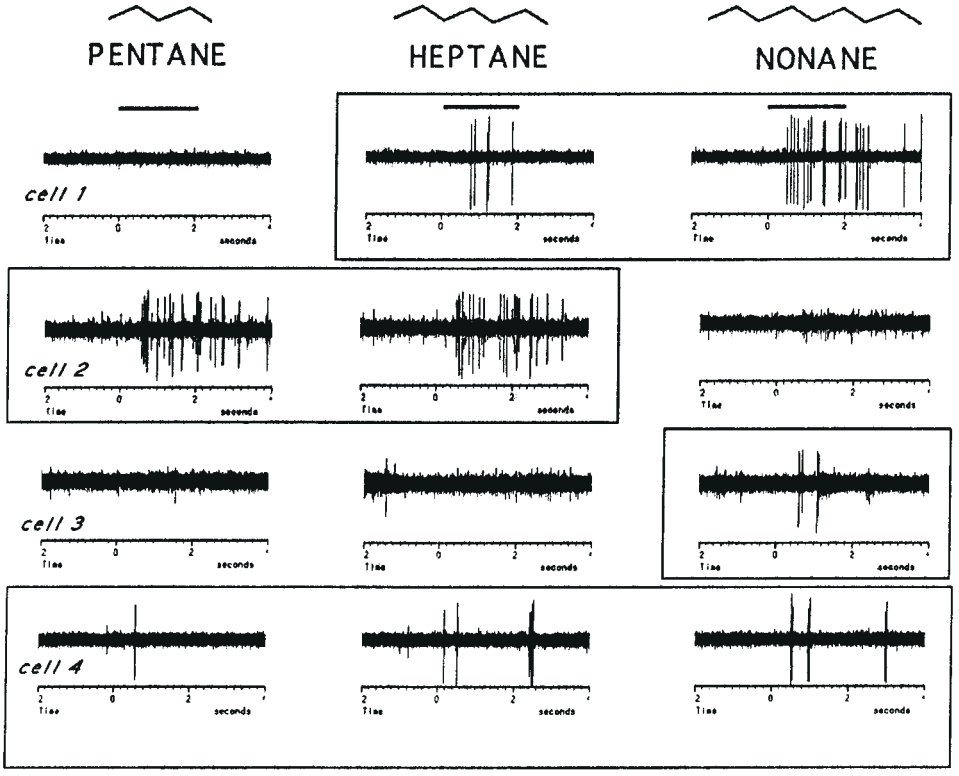

Figure 3 Odor/molecular receptive fields in aPCX neurons. Examples of response patterns of aPCX layer II/III neurons in freely breathing, urethane-anesthetized rats to alkane odorants. These neurons displayed excellent discrimination of carbon chain length, similar to that reported for mitral cells of the MOB (Mori *et al.*, 1999).

1999)]. That is, the piriform cortex odor response is dependent on the combination of features, not a single feature. Thus, habituation to one combination (one odor) should have relatively little effect on other combinations (weak cross-habituation). Association fibers within the cortex (Haberly 1985; Bower, 1991; Hasselmo and Bower, 1992) and feedback to the olfactory bulb could further enhance the difference between different input combinations. Behavioral work supports this view of ensemble coding in piriform cortex. Lesions of the piriform cortex impair discrimination/memory of complex odor cues but have no effect on simple odor cue discrimination/memory (Staubli *et al.*, 1987).

Plasticity

Molecular receptive fields of aPCX neurons can be rapidly and selectively modified by experience. In both awake (McCollum *et al.*, 1991) and anesthetized (Wilson, 1998a) rats, aPCX neuron response to odors habituates rapidly. This habituation can occur despite relatively maintained input from mitral cells (Wilson, 1998a). One potential mechanism of this rapid filtering of mitral cell input by aPCX neurons is synaptic depression of LOT inputs to aPCX neurons that is correlated with odor habituation (Wilson, 1998b). A similar mechanism has been proposed at thalamocortical synapses in the visual system to account for habituation to contrast gratings (Finlayson and Cynader, 1995). Association fibers are also capable of experience-dependent plasticity (Kanter and Haberly, 1990; Hasselmo and Barkai, 1995; Stripling and Patneau, 1999); however, their role in odor response plasticity has not been examined.

As noted above, the habituation in aPCX is highly odor specific. Stimulus-specific habituation has been reported in other sensory cortices, such as the auditory cortex (Weinberger, 1995). This specificity could be important for filtering background odorants while allowing maintained response to dynamic, biologically relevant stimuli (Dalton, 2000). Odor-specific plasticity such as this may also play a role in storing odor memories, and in experience-dependent shaping of odor receptive fields. It should be noted that the studies described here have used odor stimuli that are novel to the animals tested. Receptive fields for odors that have acquired significance through associative conditioning or other behaviorally relevant exposure may have different properties than those described here (Wilson *et al.*, 1987).

Conclusions

As in thalamocortical sensory systems, primary olfactory (piriform) cortex neurons display classic receptive fields. These receptive fields map properties along both spatial and

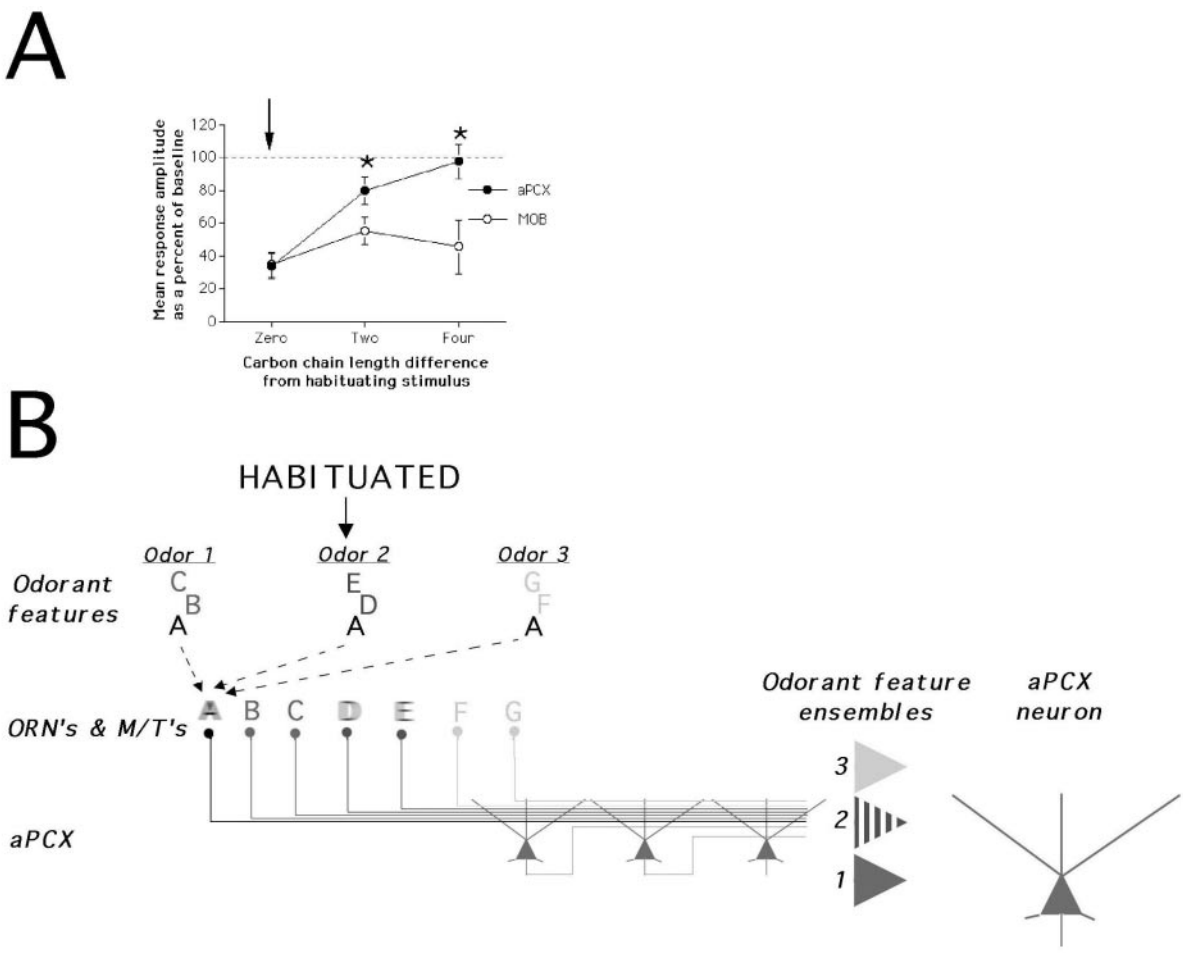

Figure 4 **(A)** A comparison of cross-habituation to alkane odors between MOB mitral/tufted cells and aPCX layer II/III neurons in freely breathing, urethane-anesthetized rats. aPCX neurons showed significantly less cross-habituation than mitral cells to odors differing by two or four carbons in length (Wilson, 2000b). **(B)** Simplified schematic representation of odor coding in olfactory receptor neurons (ORNs), MOB mitral/tufted (M/T) cells and aPCX neurons. Both M/T cell 'A' and the aPCX neuron have similar receptive fields, responding to all three odors. M/T cell 'A' responds to all three odors because each contains feature 'A'. Neurons in the aPCX, however, may have receptive fields based on odorant feature ensembles which are created through afferent and association fiber termination patterns. Thus, the aPCX neuron shown also responds to all three odors. This difference in the underlying basis for receptive fields results in cross-habituation (blurred letters and dashed lines) in M/T cell 'A' to all odors shown following habituation to one odor (Odor 2), and selective habituation (minimal cross-habituation) in the aPCX neuron (hatched arrowhead).

molecular dimensions. The molecular receptive fields are dynamic and capable of experience-dependent plasticity that is highly odor specific. Both the time-course and odor specificity of aPCX receptive field plasticity differ from that expressed by the primary cortical afferent, mitral cells, which suggests a form of higher order processing within the aPCX. Based on cross-habituation studies, aPCX neurons appear to be capable of much greater odor discrimination than olfactory bulb mitral cells and appear to display synthetic or combinatorial characteristics.

In thalamocortical sensory systems, cells expressing similar receptive fields are located near to each other within the cortex, resulting in organizations such as somatotopic or retinotopic maps. Odotopic maps for molecular features have been described in the mammalian MOB (Xu *et al.*, 2000). At present, it is unknown whether similar odotopic maps exist within the piriform cortex (Cattarelli *et al.*, 1988), although recent work using c-fos immunohistochemistry and stimulation patterns designed to avoid habituation suggest that odor-specific spatial patterns of aPCX may occur (Illig and Haberly, 2000).

Finally, in addition to odor sensitivity, activity within the piriform cortex is also influenced by neuromodulatory input from the horizontal limb of the diagonal band [acetylcholine (Hasselmo and Bower, 1992; Linster *et al.*, 1999; Chabaud *et al.*, 2000)], the locus coeruleus [norepinephrine (Datiche and Cattarelli, 1996; Hasselmo *et al.*, 1997)] and a variety of other state-dependent or sensory inputs (Schoenbaum and Eichenbaum, 1995; Chabaud *et al.*, 2000). How these diverse inputs combine to shape and modulate receptive fields and odor processing in primary olfactory cortex remains to be explored.

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