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Action Potentials that Go the Distance

Dendrodendritic inhibition between mitral and granule cells in the olfactory bulb is thought to play an important role in olfactory discrimination. In this issue of *Neuron*, Xiong and Chen (2002) explore the propagation of action potentials along the secondary dendrites of mitral cells and their modulation by dendrodendritic inhibition.

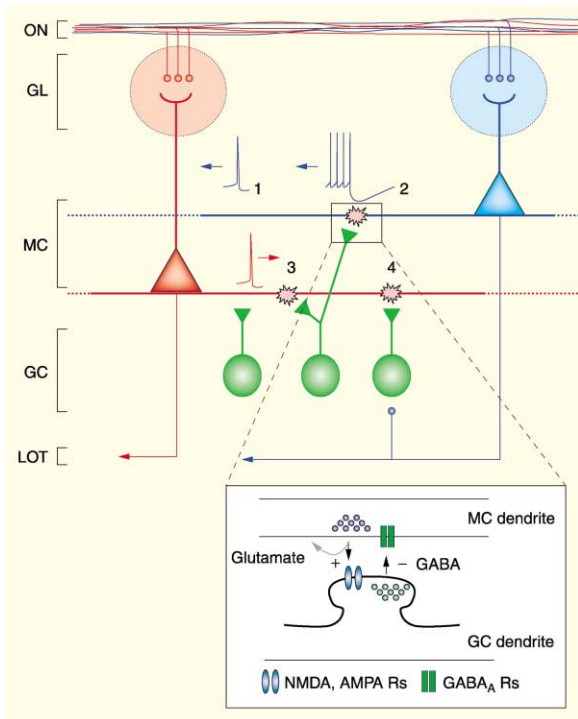
How we perceive the world is of course determined by how the brain processes information from specialized peripheral sensory neurons that reside in sensory sheets such as the retina, cochlea, skin, or olfactory epithelium. In the cases of vision, audition, and touch, the projection to higher centers is, at least in its outlines, a relatively straightforward spatial reflection of the organization of the peripheral tissue and the dimensional reality of the world. In addition, the stimuli themselves can also be represented by a spatial function because their physical energy varies along a single dimension (frequency, wavelength, or pressure). The olfactory sense, however, confronts a somewhat different challenge. The stimulus is a vapor with no immediate spatial component and the stimulus energy is the chemical energy of binding which varies along multiple dimensions. Does this mean higher processing levels in the olfactory system use strategies that differ from those in other sensory systems, for example in the circuitry designed for stimulus enhancement, sharpening, and filtering? Recent studies in the microcircuitry of the olfactory bulb, one of which appears in this issue of *Neuron*, are providing some insight into these intriguing questions.

Olfactory receptor neurons (ORNs) synapse in the main olfactory bulb (MOB), where the earliest stages of olfactory processing are thought to occur. Axon terminals of ORNs form excitatory synapses onto primary dendrites of mitral and tufted cells (MC and TC, respectively), in a specialized structure of neuropil termed the

glomerulus. Each MC and TC in the mammalian MOB sends a single primary dendrite to a glomerulus and has secondary dendrites which can extend laterally for long distances around the bulb (Shepherd and Greer, 1998). The ordered organization of the glomeruli and associated MCs has allowed physiologists and molecular biologists alike to gain a better understanding of how olfactory information may be processed in the MOB (Mombaerts, 1999; Mori et al., 1999). Several studies indicate that each ORN expresses only one or a few receptors, from a large repertoire, and ORNs expressing the same receptor converge onto one or two glomeruli in the bulb. Furthermore, diverse physiological studies indicate that different odors induce distinct patterns of glomerular activation in the MOB (Mori et al., 1999; Kauer and White, 2001). The importance of these spatial odor maps and how they relate to the perception of smell is still a matter of debate (e.g., Laurent, 1999), but it is well accepted that local inhibitory circuits in the bulb shape the odor-induced activity of output neurons (MCs and TCs).

Two types of intrinsic neurons in the MOB, periglomerular (PG) and granule cells (GC), modulate the activity of MCs and TCs through dendrodendritic synapses. PG cell dendrites contact the primary dendrites of MCs and TCs in the glomerulus and their axons can extend onto neighboring glomeruli (Shepherd and Greer, 1998). The role of these cells in olfactory processing is poorly understood. In contrast, dendrodendritic synapses between secondary dendrites of MCs and dendrites of GCs have been well characterized. Release of glutamate from secondary dendrites of MCs, through the activation of NMDA and AMPA receptors, induces the release of GABA from the dendrites of GCs. Activation of GABA_A receptors in the MC secondary dendrite produces an inhibitory postsynaptic potential (IPSP) (Schoppa et al., 1998). Recent studies have indicated that activation of dendrodendritic synapses is dependant on action potential propagation throughout the secondary dendrites of MC (Isaacson and Strawbridge, 1998; Schoppa et al., 1998).

In this issue of *Neuron*, Xiong and Chen (2002) elegantly show that the extent of action potential propagation in secondary dendrites of MCs is regulated by inhibitory synapses, using Ca²⁺ increase as a reporter of action potential propagation. Moreover, they show that action potentials propagate throughout the length of the secondary dendrite with little or no attenuation. This latter finding contrasts a previous report by Margrie et al. (2001), who found that the action potential attenuated quickly in the proximal half of the dendrite. The nature of this discrepancy deserves further study, although differences in the recording conditions may account for at least some of it. The degree of dendrodendritic inhibition is larger in *in vivo* experiments, suggesting that some of the circuitry involved in inhibition is not present in the slice preparation (Margrie et al., 2001). Despite this difference, one important aspect of these studies is that they show that the size and extent of propagation of the Ca²⁺ signal, and thus the number of activated dendrodendritic synapses depends on the number of action potentials (Margrie et al., 2001; Xiong and Chen, 2002). Thus, stronger inputs will enable action potentials to travel further in the dendrite and inhibit the activity of MCs in other distant regions of the MOB. An interesting



Action Potential Propagation and Inhibitory Synapses in Secondary Dendrites of Mitral Cells

proposition by Xiong and Chen is that recurrent inhibition in the proximal region of the secondary dendrite will have a direct effect on the firing pattern of the output neuron while inhibition in distal regions will have a greater role in lateral inhibitory effects on other cells.

These results could be summarized in the following manner (see Figure). A single action potential can travel throughout the length of the secondary dendrite of an MC (1). In the slice preparation, a single action potential rarely induces an IPSP, unless Mg^{2+} ions are removed, to allow NMDA receptor activation. A stronger activation of the cell will produce an IPSP as the action potentials propagate along the dendrite (2). Since each GC can have dendrodendritic contacts with other MCs, GCs are able to inhibit action potential propagation in the secondary dendrites of neighboring MCs (3). This lateral inhibition is thought to play an important role in olfactory discrimination (Mori et al., 1999) as it can suppress weak responses in neighboring MCs. Another way these action potentials can be gated is by IPSPs produced by direct activation of the GC, either by axon collaterals from MCs (4) or by incoming fibers from other brain regions (i.e., olfactory cortex, not shown). In addition, recent studies have indicated that spillover of glutamate can activate autoreceptors in the MC secondary dendrites (Isaacson, 1999). It has been proposed that this excitation may allow synchronous activity of mitral cells in vivo (Isaacson, 1999; Schoppa and Westbrook 2001). The interplay between this self-excitation and dendrodendritic inhibition, which in turn could lead to olfactory oscillations, may have a relevant role in olfactory processing and awaits further studies (Laurent, 1999).

Optical recordings of stimulus-induced activity show

patterns of glomerular excitation that range over wide areas of the olfactory bulb. It seems likely that the micro-circuitry of the cells, and in particular the involvement of the widely projecting lateral dendrites of MCs, play a critical role in correlating and refining this relatively raw input from the periphery, enabling us to make sense of the more than 500 chemical components that constitute the smell of coffee.

Ricardo C. Araneda and Stuart J. Firestein
Department of Biological Sciences
Columbia University
New York, New York 10027

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Should Bad Workmen Always Blame Their Tools?

In this issue of *Neuron*, Beauchamp and colleagues (2002) differentiated brain regions in humans that are selectively responsive to viewing motion: (1) of humans, (2) of tools/utensils, and (3) in general. Active regions were the superior temporal sulcus, middle temporal gyrus, and MT/V5, respectively. This study provides impetus for future work in motion perception and its relationship to apraxia.

Both human and nonhuman primates possess excellent high-level motion processing skills, including the ability to infer the actions not only of their conspecifics, but also those of other species. These neural mechanisms are not only essential for survival (i.e., aiding in the evasion of predators and achieving successful procreation), but are also the cornerstone in the ability to form and maintain successful social relationships (reviewed by Adolphs, 1999; Allison et al., 2000). Human primates have also evolved considerable skills not only with the use of tool and utensils, but also with their manufacture as well, quite unparalleled in nonhuman primates.

Single-unit electrophysiological studies in nonhuman