Membrane and synaptic properties of pyramidal neurons in the anterior olfactory nucleus

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McGinley MJ, Westbrook GL. Membrane and synaptic properties of pyramidal neurons in the anterior olfactory nucleus. J Neurophysiol 105: 1444–1453, 2011. First published December 1, 2010; doi:10.1152/jn.00715.2010.—The anterior olfactory nucleus (AON) is positioned to coordinate activity between the piriform cortex and olfactory bulbs, yet the physiology of AON principal neurons has been little explored. Here, we examined the membrane properties and excitatory synapses of AON principal neurons in brain slices of PND22–28 mice and compared their properties to principal cells in other olfactory cortical areas. AON principal neurons had firing rates, spike rate adaptation, spike widths, and I–V relationships that were generally similar to pyramidal neurons in piriform cortex, and typical of cerebral cortex, consistent with a role for AON in cortical processing. Principal neurons in AON had more hyperpolarized action potential thresholds, smaller afterhyperpolarizations, and tended to fire doublets of action potentials on depolarization compared with ventral anterior piriform cortex and the adjacent epi leptogenic region preependopiriform nucleus (pEN). Thus, AON pyramidal neurons have enhanced membrane excitability compared with surrounding subregions. Interestingly, principal neurons in pEN were the least excitable, as measured by a larger input conductance, lower firing rates, and more inward rectification. Afferent and recurrent excitatory synapses onto AON pyramidal neurons had small amplitudes, paired pulse facilitation at afferent synapses, and GABAB modulation at recurrent synapses, a pattern similar to piriform cortex. The enhanced membrane excitability and recurrent synaptic excitation within the AON, together with its widespread outputs, suggest that the AON can boost and distribute activity in feedforward and feedback circuits throughout the olfactory system.

METHODS

Slice preparation. Brain slices were prepared from C57BL/6J mice (300 μm, Leica VT 1200S) at PND22–28, which is after the development of basic properties of excitation in piriform cortex (Schwob et al. 1984; Franks and Isaacson 2005). Isoflurane-anesthetized mice were euthanized by decapitation. The brain was cut coronally at the midline and sagitally at the midline. The right hemisphere was mounted on an acrylic block specially machined so that slices contained the AON, APCvR, and pEN, and layering within these regions was easily discerned. Dissection and slicing were conducted in ice-cold carbogenated saline (in mM): 83 NaCl, 26.2 CaCl2, 26.2 NaHCO3, 2.5 KCl, 1 Na2HPO4, 3.3 MgSO4, 0.5 CaCl2, 22 glucose, 72 sucrose. Slices were incubated in the dissection solution (33°C for 35–45 min) and subsequently placed at room temperature (also in dissection solution, for 30–150 min) until recording. All animal handling and experimental procedures were approved by the Institutional Animal Care and Use Committee at Oregon Health and Science University in accordance with National Institutes of Health guidelines for ethical treatment of animals.

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Targeting principal neurons. Recordings of AON neurons were restricted to the broad cell body layer of the lateral part of the AON, deep to the axodendritic layer that borders the lateral olfactory tract (LOT) and posterior from pars externa of AON. This region, known as pars principalis, has three anatomical subdivisions. We largely recorded from pars lateralis with possibly a few recordings in pars ventroposterioralis or pars dorsalis. For simplicity, we refer to the recorded area as AON. Principal neurons in AON were targeted based on morphology, having a teardrop-shaped cell body, and one or two tapering apical dendrites oriented toward the pial surface. Periform pyramidal neurons were targeted in the deep half of layer II (layer IIb) to avoid semilunar neurons (Suzuki and Bekkers 2006). Principal neurons in pEN were targeted based on multipolar morphology (Tseng and Haberly 1989). A few neurons that had membrane physiology consistent with fast-spiking GABAergic interneurons (McGinley, unpublished observations) were excluded from analysis.

Electrophysiological recording. Voltage and current clamp data were low-pass filtered online at 10 kHz and acquired at 25 kHz using a Multiclamp 700b amplifier (Molecular Devices). Recordings were further low-pass filtered offline (2 kHz) except for calculations of the series resistance and curve fits to charging transients. Neurons with high series resistance (>20 Ω) or unstable recordings were excluded from further analysis. Series resistance in the bath was 11.8 ± 0.4 Ω (n = 230). In most experiments, a potassium-based pipette solution was used. The pipette solution contained (in mM): 135 K-gluconate, 5 NaCl, 10 HEPES, 12 phosphocreatine, 3 MgATP, 0.3 NaGTP, 0.1 EGTA, 0.025 CaCl2 (pH, 7.3; 285 mOsm). The bath solution (33°C) contained (in mM): 119 NaCl, 26.2 NaHCO3, 2.5 KCl, 1 NaH2PO4, 1.0 MgSO4, 2.0 CaCl2, and 22 glucose (300 mOsm). In some experiments, as indicated, R-CPP (5 μM), picrotoxin (100 μM), or CGP55845 (10 μM) were included in the bath to block NMDA, GABAA, or GABAB receptors, respectively. The calculated potassium reversal potential was −105 mV. Voltage measurements were not corrected for the calculated liquid junction potential (16.3 mV). Series resistance was corrected in current clamp recordings. For whole cell voltage clamp of synaptic responses, the compensation was not corrected for the calculated liquid junction potential (16.3 mV). Series resistance was corrected in current clamp recordings. For whole cell voltage clamp of synaptic responses, the compensation was not corrected for the calculated liquid junction potential (16.3 mV). Series resistance was corrected in current clamp recordings. For whole cell voltage clamp of synaptic responses, the compensation was not corrected for the calculated liquid junction potential (16.3 mV).

For analysis of membrane properties, neurons were recorded across regions in the same slices, often in pairs, to avoid variability or artificial differences resulting from slice condition. We applied a family of 21 evenly spaced current steps to each neuron (starting from rest, 800-ms duration, 5-s pause between steps, 2–3 repetitions per cell) with amplitudes ranging from −2.5 to +2.5 times the rheobase in each neuron (15- to 30-pA increments). Rheobase was defined as the amplitude of the smallest depolarizing current step that elicited one or more action potentials on most trials. Single action potentials at rheobase were scored as 1.25 Hz in step that elicited one or more action potentials on most trials.

Passive cable analysis. For cable analysis of dendritic structure, we used the half-and-stick model of Rall (1969) with procedures outlined by Jackson (1992). An average of 20–50 charging transients, from depolarizing and hyperpolarizing voltage pulses, were fit with sums of three exponentials (see Supplementary Methods; Supplemental Material for this article is available online at the Journal website.).

Statistics. Data are presented as means ± SE. Statistical comparisons were made with the two-tailed Student’s t-test or ANOVA (F statistic and P value reported) followed by Tukey’s post hoc (P value reported) for multiple comparisons, or Friedman ANOVA was used, and the χ2 value is reported. Statistics were calculated using OriginPro 8 (OriginLab, Northampton, MA).

RESULTS

Active properties of principal neurons in olfactory cortical subregions. Despite its large size and extensive interconnectivity across the mammalian olfactory system, the physiological properties of AON neurons have not been reported. Thus, we performed whole cell recordings from 122 neurons in AON to assess their membrane properties and compared them with pyramidal neurons in layer IIb in rostral and caudal ventral anterior periform cortex (APCV-C and APCV-CR, respectively, n = 52) and principal neurons in pEN (n = 21; Fig. 1A). An example family of voltage responses to current steps, for a typical neuron from each region, is shown in Fig. 1B. Principal cells in all regions responded to depolarizing currents with a pattern of accommodating action potentials. Hyperpolarizing currents produced modest voltage sags, suggesting activation of a small Ih component.

To quantitatively compare membrane properties, we randomly chose nine neurons from AON, six neurons from layer IIb of APCV-C, seven neurons from layer IIb of APCV-CR, and nine neurons in pEN for more detailed analysis. I-V relationships are shown in Fig. 1C. I-V curves had similar slopes near rest, as reflected in the slope conductance at −85 mV (Fig. 1D), although there was a small but significant difference between pEN and APCV-C (F = 4.7; P < 0.01). I-V curves differed more substantially at −105 mV (F = 7.1, P < 0.001), where pEN neurons showed more inward rectification (Fig. 1D). The larger conductance in pEN neurons at hyperpolarized voltages was reflected in the twofold larger “difference” conductance than all other regions (subtraction of slope conductances) for pEN vs. APCV-C (F = 8.5; P < 0.005). The inward rectification in pEN probably did not result from Ih, because the voltage sag was small in all regions (Fig. 1E; see Fig. 2B). Furthermore, the time constant of the sag was not different between regions (F = 0.56, P = 0.91; AON, 132 ± 6 ms; APCV-CR, 137 ± 19 ms; APCV-C, 141 ± 26 ms; pEN, 125 ± 27 ms).

Action potentials in principal neurons across regions, measured at threshold (Fig. 2, A and B, gray traces), had similar amplitudes (peak - threshold; F = 3.7; P = 0.29; AON, 86.9 ± 2.0 mV; APCV-CR, 81.6 ± 1.4 mV; APCV-C, 82.9 ± 1.4 mV; pEN, 82.3 ± 1.4 mV) and half widths (F = 4.3; P = 0.23; AON, 1.31 ± 0.07 ms; APCV-CR, 1.21 ± 0.07 ms; APCV-C, 1.29 ± 0.06 ms; pEN, 1.35 ± 0.04 ms). These values are typical of pyramidal neurons in cerebral cortex (Larkman and Mason 1990; Krahe and Gabbiani 2004). The current necessary to trigger an action potential (rheobase) was similar in AON and periform pyramidal neurons, but larger in pEN (Fig. 2C; F = 7.9; P < 0.05), consistent with the larger slope conductance in

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pEN. AOC pyramidal neurons had a lower threshold for action potential initiation (F = 9.2; P < 0.05; Fig. 2D) and a smaller afterhyperpolarization (F = 11.2; P < 0.01; Fig. 2E) than pyramidal neurons in piriform cortex, which would be expected to enhance firing.

To analyze intrinsic firing patterns, we calculated f-I curves for principal neurons across regions. F-I curves were shallower in pEN (Fig. 3A), mirroring the differences in rheobase shown in Fig. 2. Furthermore, average firing rates at threshold, and at 2.5× rheobase, were lower in pEN than in all other regions (F = 5.7; P < 0.005; F = 10.3; P < 0.02; Fig. 3, C and D). The percent of neurons that fired bursts (2 or more APs) at threshold was also lowest in pEN (0%) and highest in AON (78%) compared with piriform cortex (APCV_R, 50%; APCV_C, 38%). Firing rates in all regions adapted to long current pulses, as shown for AON (Fig. 3B). However, there was a rostral-to-caudal decrease in adaptation across AON and APC (Fig. 3E; F = 8.4, P < 0.05), whereas pEN neurons had comparable adaptation to AON (Fig. 3E). These results suggest enhanced excitability in the rostral corner of piriform cortex.

Passive properties of principal neurons. To understand how differences in passive properties contribute to the shaping of activity, we analyzed passive charging transients in re-
responses to voltage steps from rest, in neurons from each region (Fig. 4A, inset). Three time constants were necessary to accurately fit charging transients (Fig. 4A), suggesting substantial dendritic charging (Rall 1969). Differences between regions in time constants and their associated amplitudes suggested a more extended electrotonic structure in AON (Supplementary Fig. 1). Therefore, we applied a uniform cable and lumped soma model and extracted passive parameters (Rall 1969).

Fig. 2. Action potentials in principal neurons across regions have similar shapes, except for AP thresholds and afterhyperpolarization (AHP) in AON. A: voltage response (top) for 3 current steps (bottom) in a typical neuron from the AON. Red line indicates a transmembrane voltage of −80 mV. Gray traces are at rheobase in this neuron (160 pA). B: left, an example of the action potential waveform at rheobase (enlarged from A) illustrating the voltage threshold (c) and action potential half-width (bar). At top right is a further enlargement of the threshold region (same action potential) illustrating the AHP (bar). At bottom right, hyperpolarized step (enlarged from A) showing the calculation of sag (b/a). A single exponential was fit to the sag time course (red dotted curve and tau). C: the amount of current necessary to trigger an action potential (rheobase) was similar for principal neurons across subregions (left 3 bars). pEN neurons had a higher rheobase (right bar). Recording region indicated below the x-axis. D: neurons in AON had consistently hyperpolarized action potential thresholds compared with pyramidal neurons in piriform cortex. E: the AHP measured relative to AP threshold. Pyramidal neurons in AON had consistently smaller AHPs compared with piriform cortex. * P < 0.05; ** P < 0.01; *** P < 0.001.

Fig. 3. Regional differences in firing rates and the extent of firing rate adaptation in principal neurons. A: the average firing rate vs. current amplitude (f-I curve) reveals lower firing rates in pEN neurons. B: examples (gray symbols) and average (black) of instantaneous firing rates (1/Δt) for 14 AON pyramidal neurons during current application at 2.5× rheobase. Inset shows an example AON firing pattern (top) in response to a current step at 2.5× rheobase (400 pA, bottom). Red bar indicates the interspike interval (Δt) for the 7th AP interval. Scale bars apply to inset. C: the average firing rate (at rheobase) is smallest in pEN, reflecting a tendency to fire only 1 action potential at threshold. D: the average firing rate at 2.5× rheobase (first 10 action potentials) was lower in pEN neurons. E: principal neurons in all subregions showed firing rate adaptation. Neurons in AON and pEN showed more firing rate adaptation than neurons in APCV-C. Neurons in APCV-R showed intermediate firing rate adaptation. * P < 0.05; ** P < 0.02; *** P < 0.01; **** P < 0.005.
1969; Jackson 1992). The dendritic length (in units of length constants) was longest in AON and decreased in the rostro-caudal direction (Fig. 4B; F = 6.0, P < 0.005). The membrane time constant (τmem) also showed a rostro-caudal gradient (F = 6.1, P < 0.002; AON, 4.8 ± 0.5 ms; APCV-R, 5.3 ± 0.7 ms; APCV-C, 8.9 ± 1.4 ms; pEN, 8.8 ± 0.9 ms), such that the membrane time constant was slower in APCV-C than in AON (P < 0.02). pEN neurons had a membrane time constant comparable to APCV-C neurons (P = 0.99998) and slower than AON neurons (P < 0.01). The somatic-to-dendritic resistance ratio (ρ) was larger in AON and intermediate in pEN (Fig. 4C; F = 17.2, P < 2E-7). These results suggest a greater filtering of dendritic inputs in AON pyramidal neurons.

Weak single fiber LOT inputs to AON and APCV. Afferent and associational synapses in piriform cortex show distinct features thought to be important for cortical function, in terms of plasticity, modulation, and synaptic strength (Bower and Haberly 1986; Hasselmo and Bower 1990, 1992; Tang and Hasselmo 1994; Linster and Hasselmo 2001; McNamara et al. 2004; Franks and Isaacsen 2006). To examine the synaptic properties of AON pyramidal neurons, we measured the strength of single afferent inputs from the LOT using minimal stimulation (Raastad et al. 1992). Single shocks (0.1 Hz) of low amplitude (3–10 V) evoked failures on some trials and successes on other trials. In 14 of 18 neurons, we isolated a single shock strength at which similar amplitude successes occurred on some trials, and failures occurred on other trials, indicating that the successes resulted most likely from a single fiber input (Fig. 5A). The amplitude of the single fiber input with the potassium-based pipette solution was 16.1 ± 2.4 pA (Fig. 5B). For the remaining four neurons, a small increase in shock strength (≥1 V) resulted in an abrupt transition from all failures to all successes, thus providing a least-upper-bound (LUB) estimate of the single fiber input strength. The LUB estimate of 28.4 ± 3.5 pA was larger than the well-isolated single fiber input estimates (P < 0.02), suggesting that LUB estimates represented the recruitment of multiple fibers. To address the possibility that our single fiber measurements were underestimates because of reduced voltage clamp control with a potassium-based pipette solution, we used a cesium-based internal solution in six additional neurons. In five of six neurons, threshold stimulation indicated a single fiber amplitude of 28.5 ± 7.0 pA. The remaining neuron had a LUB estimate of 57.3 pA. These values were larger than with a potassium-based solution (P < 0.02) but not as large as the single fiber input strengths previously reported in piriform cortex (Franks and Isaacsen 2006).

To compare LOT input strengths between AON and piriform pyramidal neurons, we recorded pyramidal neurons in APCV in response to minimal stimulation of the LOT. Successful threshold stimulation was achieved in four of five piriform pyramidal neurons. The single fiber input strength was 17.4 ± 4.8 pA, not different from the value obtained in AON (P = 0.82; Fig. 5B). The remaining piriform pyramidal neuron had a LUB estimate of 40.9 pA. Similarly, the single fiber amplitude, with a cesium-based solution, was 33.4 ± 8.7 pA (n = 4), larger than with intracellular potassium (P < 0.05), and not different from cesium-loaded AON neurons (P = 0.6). To further evaluate the strength of single fiber inputs, we performed graded stimulation in five AON principal neurons and six piriform pyramidal neurons. The EPSC amplitude increased gradually with shock strength (Fig. 5, C and D), consistent with the results of minimal stimulation. Our results indicate that LOT inputs to AON and APCV are weak under the conditions of our experiments, similar to afferent synapses in neocortex (Bruno and Sakmann 2006) and the analogous synapses in locusts (Jortner et al. 2007).

In addition to LOT inputs, we examined local excitatory interactions between AON neurons. Extensive recurrent interactions between AON neurons. Extensive recurrent interactions between AON neurons. Extensive recurrent interactions between AON neurons. Extensive recurrent interactions between AON neurons.
excitatory connectivity is a hallmark of cortical regions including the piriform cortex (Tsodyks et al. 2000; Holmgren et al. 2003; Haberly and Price 1978; Luskin and Price 1983b; Johnson et al. 2000). In paired recordings of AON principal neurons using potassium electrodes, 3 of 18 pairs exhibited an excitatory monosynaptic connection in one direction (see Fig. 6; 3 of 36 possible connections, or 8.3%), which is similar to layer 2/3 of neocortex (Holmgren et al. 2003). These recurrent connections had small EPSC amplitudes (26 ± 12 pA; see Fig. 6A), also similar to neocortex (Tsodyks and Markram 1997; Holmgren et al. 2003).

Short-term plasticity and pathway-specific GABA_B modulation in AON. LOT synaptic inputs to piriform pyramidal neurons show paired pulse facilitation (Bower and Haberly 1986; Hasselmo and Bower 1992). Furthermore, and unlike recurrent excitatory connections, LOT inputs to piriform pyramidal neurons lack presynaptic GABA_B receptors (Tang and Hasselmo 1994). We looked for these patterns in AON. For LOT inputs to AON principal neurons, paired pulse stimulation (interstimulus interval, ISI, 50–1,000 ms) evoked paired pulse facilitation for short ISIs (Fig. 7A) that was unaffected by GABA_B receptors (P = 0.31; Fig. 7B). With a potassium-based internal solution, the EPSC amplitude was reduced by a small amount in baclofen (Fig. 7C), suggesting postsynaptic shunting or filtering due to GABA_B receptors. Consistent with this interpretation, baclofen shifted the holding current with a potassium-based (Fig. 7D) but not cesium-based (Fig. 7D) solution and reduced the input resistance with a potassium-based (n = 3; χ^2 = 6; P < 0.05; control, 69.7 ± 14.6 MΩ; baclofen, 48.1 ± 6.0 MΩ; CGP55845, 78.4 ± 9.7 MΩ) but not with a cesium-based pipette solution (n = 3; χ^2 = 4.7; P = 0.10; control, 232 ± 53 MΩ; baclofen, 195 ± 42 MΩ; CGP55845, 261 ± 46 MΩ). The small effect of GABA_B receptors in cesium may reflect a small drift in EPSC amplitude as well as the presence of postsynaptic cesium-permeable GIRK channels (Hommers et al. 2003).

Another characteristic of the piriform cortex is the selective suppression of recurrent excitatory synapses by GABA_B receptors (Tang and Hasselmo 1994). We observed a similar pattern in AON. Baclofen markedly reduced polysynaptic activity evoked by LOT stimulation in the presence of GABA_A and NMDA receptor antagonists, which were used to unmask recurrent fast excitation (Supplementary Fig. 2A; unpublished observations). The polysynaptic bursts of activity were restored in CGP55845 (Supplementary Fig. 2A). Paired pulse stimulation of the LOT (ISI, 0.2–5 s) resulted in paired pulse depression of bursts for short ISIs (Supple-
mentary Fig. 2B) that was partially relieved by CGP55845 (Supplementary Fig. 2B). These results indicate that endogenous GABA<sub>B</sub> receptors suppress associational excitation in AON.

DISCUSSION

Intrinsic membrane and synaptic properties influence the circuit dynamics of cortical networks. Our results indicate that AON pyramidal neurons share many of the properties of principal neurons in the piriform cortex as well as other areas of cerebral cortex. However, there were regional differences that may provide insight into region-specific functions in the olfactory system. In particular, AON neurons showed enhanced excitability, whereas the epileptogenic pEN showed diminished excitability compared with piriform cortex. Lateral olfactory tract inputs from olfactory bulb to AON and ventral anterior piriform cortex were weak, suggesting that afferent activation of these regions requires highly synchronous sensory input.

Regional differences in excitability. Only a few physiological studies have included the AON (Boulet et al. 1978; Kucharski and Hall 1987; McNamara et al. 2004; Lei et al. 2006; Kikuta et al. 2008, 2010) and none have explored their physiology with whole cell recording. AON pyramidal neurons had enhanced membrane excitability at threshold, and at 2.5 or 10 × rheobase, compared with piriform pyramidal neurons. Pyramidal neurons in neocortex and hippocampus show a range of excitable properties, consistent with the differences we observed between AON and subregions of piriform cortex (Larkman and Mason 1990; Krahe and Gabbiani 2004). Burst firing in AON was not as pronounced as for thalamic relay neurons (Jahnsen and Llinas 1984). Afterhyperpolarization (AHP) amplitudes in piriform pyra-
Axonal and dendritic neurons are affected by learning (Cohen-Matsliah et al. 2010), thus the smaller AHP in AON may reflect different intrinsic plasticity (Liraz et al. 2009; Cohen-Matsliah et al. 2010). The membrane properties were surprisingly uniform for pars principalis pyramidal neurons, which project to piriform cortex. Other subregions (pars externa and pars medialis) that project exclusively to the olfactory bulb were not explored, and thus could exhibit different membrane properties. It is also possible that there are differences between subregions within pars principalis (Meyer et al. 2006), as our recordings were focused primarily on pars lateralis. It should also be noted that our experiments were performed on juvenile animals (P22–28) because of the limits of whole cell recording, thus it is possible that there will be differences in older animals.

Perhaps surprisingly, pEN neurons were less excitable than the other regions we explored. The pEN, also called the “area tempestas,” is a known epileptogenic locus within the olfactory system (Piredda and Gale 1985; Ekstrand et al. 2001). pEN principal neurons had a pronounced inward rectification, consistent with a higher expression of IRK and/or GIRK channels. In olfactory cortex, neurons, rather than glia, may buffer extracellular potassium, during local increases in extracellular potassium such as seizures (Howe et al. 2008). Therefore, a high potassium buffering capacity of pEN neurons could be important in controlling excitation. Pyramidal neurons in the neocortex and hippocampus have a large \( I_h \), particularly in dendrites where \( I_h \) is thought to normalize or scale synaptic inputs (Williams and Stuart 2000). Although it has been reported that piriform pyramidal neurons do not express \( I_h \) inputs (Williams and Mitchell 2008), therefore, a more passive and compact dendritic tree in piriform pyramidal neurons compared with neocortex (Bruno and Sakmann 2006) and at the analogous olfactory synapse in the locust (Jortner et al. 2007). As our experiments were restricted to AON and APCD, single fiber inputs to posterior piriform cortex and/or APCD may be stronger, possibly to compensate for a reduction in the number of LOT inputs. Furthermore, a distinct class of principal neuron in piriform cortex, semilunar neurons, receive stronger LOT input than pyramidal neurons (Suzuki and Bekkers 2006), perhaps because of stronger single fiber inputs. As expected, single fiber inputs were larger with a cesium-compared with a potassium-based electrode solution, reflecting an improved voltage clamp of dendritic inputs (but see Williams and Mitchell 2008).

The role of the AON in olfaction. The AON is integrated into the excitatory circuit of piriform cortex (Luskin and Price 1983a; unpublished observations) and shares with piriform cortex and neocortex in exhibiting weak synaptic strengths as well as pathway-specific, short-term plasticity and modulation by GABA<sub>B</sub> receptors (Bruno and Sakmann 2006; Tsodyks and Markram 1997; Bower and Haberly 1986; Hasselmo and Bower 1990, 1992; Tang and Hasselmo 1994; Linster and Hasselmo 2001; McNamara et al. 2004). The membrane properties of pyramidal neurons in AON were typical of cerebral cortex (Larkman and Mason 1990; Krahe and Gabbiani 2004). However, common properties of AON and piriform cortex are not shared by all targets of the olfactory bulb (Chiang and Strowbridge 2007; Suzuki and Bekkers 2006), and the role of inhibitory neuronal populations in these regions remains largely unexplored.

The precise role of olfactory areas in processing information is still a topic of debate (Kay and Sherman 2007; Fontanini and Bower 2006; Cleland 2010). The AON was originally considered a nuclear structure because it has only two distinct layers (Herrick 1924). However, pars principalis contains a large population of neurons with pyramidal morphology (Brunjes et al. 2005; Brunjes et al. 2009), and recent evidence is more consistent with a contribution of AON to a range of cortical functions (Haberly 2001; Brunjes et al. 2005). Individual neurons in AON respond to multiple distinct odor mixtures as well as several chemically unrelated components of individual mixtures (Lei et al. 2006). Commisural pathways connecting the AON allow contralateral recall of memories (Haberly and Price 1978; Kucharski and Hall 1987). AON neurons can change their preferred side following unilateral nares occlusion (Kikuta et al. 2008), and neurons in pars externa receive excitation from one bulb and inhibition from the other (Kikuta et al. 2004).
These functions, together with the current results, are inconsistent with a view of the AON as a simple relay, but rather as a module of olfactory cortex.

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