

## Inhibitory interneurons in the piriform cortex

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### Summary

1. The piriform cortex (PC) is the largest subdivision of the olfactory cortex and the first cortical destination of olfactory information. Despite the relatively simple anatomy of the PC and its obvious appeal as a model system for the study of cortical sensory processing, there are many outstanding questions about its basic cell physiology. Here, we review what is known about GABAergic inhibitory interneurons in the PC.

2. GABA-containing neurons in the PC are morphologically diverse, ranging from small neurogliaform cells to large multipolar forms. Some of these classes are distributed across all three main layers of the PC, while others have a more restricted laminar expression.

3. Distinct and overlapping populations of GABAergic basket cells in Layers II and III of the PC express different combinations of calcium-binding proteins and neuropeptides. Few Layer I interneurons express any of the molecular markers so far examined.

4. The intrinsic firing properties of one or two types of putative PC interneurons have been measured, and inhibitory postsynaptic responses have been recorded in PC pyramidal cells following extracellular stimulation. However, little is known about the physiology of identified subtypes of interneurons.

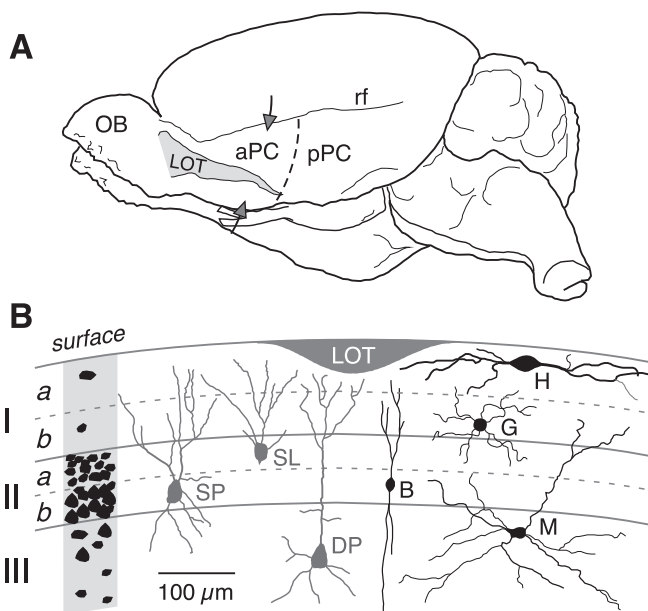
5. In view of the likely importance of PC interneurons in olfactory learning, olfactory coding and epileptogenesis, further study of their properties is likely to be highly informative.

### Introduction

Olfactory cortex is usually defined as those regions that receive monosynaptic input from the olfactory bulb. The largest of these regions is the piriform cortex (from the Latin *pirum*, pear), sometimes called primary olfactory cortex. The piriform cortex (PC) is a phylogenetically-ancient, strongly-laminated cortex with only 3 main layers (*cf.* 6 in the neocortex). Its comparatively simple anatomy, coupled with an increasing understanding of the inputs it receives from the olfactory bulb, have lead to a growing interest in the PC as a model system in which to study cortical sensory processing.<sup>1-4</sup>

As in other cortical areas, the PC contains glutamate-releasing principal neurons and a much smaller number of GABA-releasing inhibitory interneurons. The principal neurons, particularly those in the densely-packed input layer of the PC, Layer II (Fig. 1B), have been studied in

some detail.<sup>4-10</sup> In contrast, much less is known about inhibitory interneurons in the PC. The aim of this review is to bring together what is currently known about PC interneurons in an attempt to foreshadow and stimulate future work in this area.



**Figure 1. Schematic diagram of the location and anatomy of the piriform cortex.** *A*, Ventrolateral aspect of the rat brain, showing the olfactory bulb (OB), lateral olfactory tract (LOT), and the locations of the anterior and posterior piriform cortex (aPC and pPC, respectively), which are approximately demarcated by the dashed line. rf, rhinal fissure. A coronal slice of the aPC, taken between the arrows, shows the laminar structure illustrated schematically in panel B. *B*, The three main layers of the PC. At left is a schematic representation of the density of neuronal somata in each layer, showing the high density of mainly principal cells in Layer II, and a lower density of neurons in Layers I and III. Schematic diagrams of the dendritic trees of the two main types of Layer II principal cells (SP, superficial pyramidal; SL, semilunar) and one type of Layer III principal cell (DP, deep pyramidal) are shown in grey. Schematic diagrams of the dendritic trees of four types of GABAergic interneurons are shown in black (B, bitufted; G, neurogliaform; H, horizontal; M, multipolar). The scale bar is approximate. Adapted from Neville and Haberly (2004).<sup>1</sup>

Intensive work in the hippocampus and neocortex has revealed a large diversity in interneuron classes in these brain regions.<sup>11-14</sup> In order to make sense of this diversity, interneurons are commonly categorised under three main headings: morphology, molecular markers, and physiology.<sup>15</sup> We will make use of these headings in our review of what is currently known about PC interneurons. We will finish by briefly reviewing the possible involvement of PC interneurons in olfactory learning, olfactory coding, and epilepsy.

### Morphology

The rodent PC is located bilaterally in the ventrolateral forebrain, where it receives direct input from the olfactory bulb *via* the lateral olfactory tract (LOT; Figure 1A). The PC is commonly divided into anterior (aPC) and posterior (pPC) regions, with the boundary at the caudal end of the LOT.<sup>16</sup> A coronal slice taken from the aPC has the typical trilaminar structure shown schematically in Figure 1B. Layer I contains many axons and dendrites but only a few neuronal somata. The more superficial part (Layer I *a*) receives afferent axons from the LOT, whereas the deeper part (Layer I *b*) receives associational fibres from within the PC. Layer II is densely packed with the somata of glutamatergic principal neurons, the main input cells of the PC, and, again, is often divided into superficial (*a*) and deep (*b*) sublaminae. Layer III contains a lower density of neuronal somata and, like Layer I *b*, a high density of associational fibres.

The location of the soma and shape of the dendritic tree have traditionally been used to classify interneuron morphology, and these do provide clues about the synaptic inputs received by interneurons and their likely function. This approach has been applied in the PC, where interneurons with dendrites restricted to specific laminae have been identified (see below).<sup>1</sup> More recently, however, the pattern of axonal projections of interneurons has been regarded as more informative.<sup>14</sup> By this criterion, interneurons are of two main types, perisoma-targeting and dendrite-targeting. In the PC, a population of GABAergic basket cells has been identified in Layers II and III, the axons of which are known to target the somata of principal cells located in Layer II.<sup>16</sup> Little is known about the axonal projections of other classes of interneurons in the PC.

The majority of the sparse neurons in Layer I appear to be GABAergic.<sup>17,18</sup> In Layer I *a* of the aPC, close to the LOT, are found large horizontal cells with their moderately-spiny dendrites mostly confined to Layer I *a* (H, Figure 1B).<sup>19-21</sup> Hence, horizontal cells would receive most of their excitatory input from the LOT, and so might provide feedforward inhibition onto principal cell dendrites.<sup>17</sup> Distributed throughout Layer I are small, globular neurogliaform cells with thin, smooth dendrites and axonal arbors that ramify locally (G, Figure 1B).<sup>17,20</sup> Finally, Layer I also contains larger multipolar cells with dendrites that extend further than those of neurogliaform cells, although their form is very variable (M, Figure 1B).<sup>17,20,22</sup>

In Layer II, estimates of the fraction of GABA-

containing interneurons range from <15% in aPC of opossum<sup>17</sup> to >30% in pPC of rat.<sup>18,22</sup> A common type of interneuron in Layer II is the large multipolar cell (M, Figure 1B).<sup>1</sup> This has long sparsely-spiny dendrites and axons that branch into widespread arbors. Many of these cells have profuse axonal arborizations in Layer II, with evidence of perisomatic boutons, *i.e.* they are most likely to be basket cells.<sup>16,22</sup> The same class of cell is also common in Layer III, particularly in the more superficial regions closer to Layer II. Presumably these cells are important for feedback-inhibition onto the Layer II principal neurons. A second class of basket cell, also found in Layer II and upper Layer III, is a bipolar or bitufted form with vertically-oriented smooth dendrites that can extend into Layer I *a* (B, Figure 1B).<sup>16,17,22</sup> With this morphology, these cells could provide both feedforward and feedback perisomatic inhibition of Layer II neurons.<sup>1,17</sup>

Layers II and III also contain small neurogliaform cells similar to those in Layer I. Finally, deeper Layer III contains a variety of smooth multipolar cells with their dendrites largely restricted to Layer III and an unknown axonal arborization (M, Figure 1B).<sup>1,23</sup>

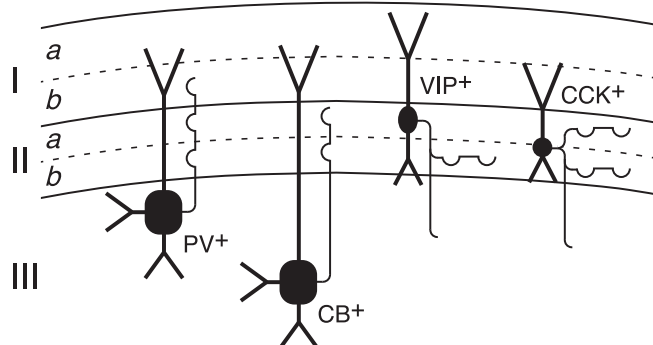
To sum up, interneurons in the PC are characterised by morphological diversity, as in other cortex, but a number of broad classes can be identified. These include small neurogliaform and large multipolar cells, which are found in all layers, and horizontal cells, which are largely confined to Layer I *a*.

### Molecular markers

Interneurons are commonly classified by their expression of two types of molecular markers: calcium-binding proteins and neuropeptides. Although the physiological role of these proteins in interneurons is often unclear, they nevertheless have empirical value as convenient tags.<sup>12,14</sup> The calcium-binding proteins parvalbumin (PV), calbindin (CB) and calretinin (CR) are reasonably reliable markers of interneurons and many in the hippocampus and neocortex express at least one.<sup>12</sup> In those regions, PV<sup>+</sup> interneurons tend to be perisoma-targeting cells, whereas CB<sup>+</sup> and CR<sup>+</sup> interneurons are often dendrite-targeting.<sup>12,14</sup> The best-characterised interneuron neuropeptides are somatostatin (SOM), cholecystokinin (CCK), neuropeptide Y (NPY) and vasoactive intestinal peptide (VIP).<sup>14,24</sup> SOM<sup>+</sup> interneurons in the neocortex are mainly dendrite-targeting, whereas CCK<sup>+</sup> interneurons in the hippocampus mainly target the soma.<sup>25</sup>

Focusing first on calcium-binding proteins, a strongly layer-dependent expression is apparent in the PC (Figure 2). No PV<sup>+</sup> or CB<sup>+</sup> interneurons are found in Layer I<sup>16,26</sup>, and the small number of CR<sup>+</sup> cells may be excitatory.<sup>22,27</sup> In contrast, in Layer II ~25% of interneurons are PV<sup>+</sup> and ~10% are CB<sup>+</sup>, with most (~90%) of the CB<sup>+</sup> cells also expressing PV.<sup>26</sup> In Layer III an even larger proportion of interneurons contains these proteins, although the relative frequency of PV<sup>+</sup> and CB<sup>+</sup> interneurons is reversed: ~80% of cells are CB<sup>+</sup> and ~50% are PV<sup>+</sup>, with most (~95%) of the PV<sup>+</sup> cells also expressing CB.<sup>16,26</sup> These CB<sup>+</sup> and/or

PV<sup>+</sup> neurons have various morphologies, ranging from globular to large multipolar.<sup>16,22</sup> Interestingly, many of them give rise to prominent perisomatic boutons in Layer II, identifying them as the Layer II/III basket cells described above.<sup>16,22,26</sup> Layers II and III also contain small numbers of CR<sup>+</sup> interneurons with bipolar or tufted morphologies and unknown axonal projections.<sup>22</sup>



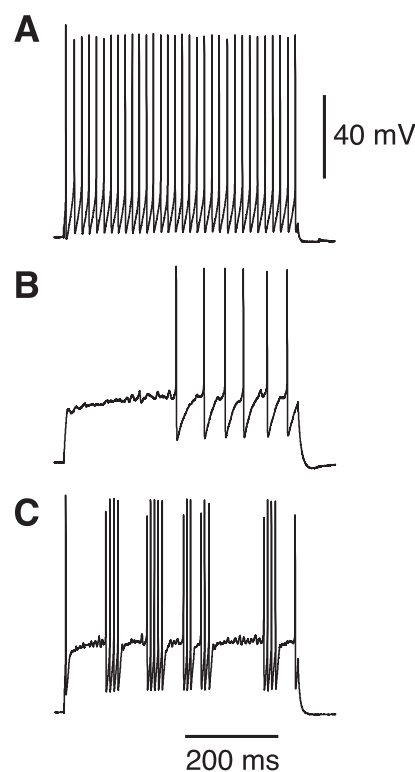
**Figure 2.** Schematic illustration of the distribution of neurons expressing different molecular markers (PV, parvalbumin; CB, calbindin; VIP, vasoactive intestinal peptide; CCK, cholecystinin). The thin lines represent axons, which mostly form basket synapses (represented by semi-circles), with fewer synapses in Layer III. Only a subset of 'typical' cell types is shown.

Turning to the neuropeptides, NPY, SOM, VIP and CCK are all expressed more sparsely in the PC than the calcium-binding proteins<sup>16</sup> but, again, there is a pronounced laminar specificity in their distributions.<sup>28-30</sup> Similar to the calcium-binding proteins, few neuropeptide-positive neurons are found in Layer I and most are confined to Layers II and III.<sup>16,30</sup> VIP<sup>+</sup> GABAergic neurons are mostly bitufted cells with their somata located in Layer II *a* (Figure 2).<sup>16,29</sup> Their axonal arbors form extensive perisomatic contacts, mostly in Layer II *b*, identifying them as a subtype of basket cell, but they also send axons into Layer III. CCK<sup>+</sup> GABAergic neurons often have small globular morphologies with their somata distributed throughout Layer II and, occasionally, in Layer III (Figure 2).<sup>16,28</sup> Larger multipolar CCK<sup>+</sup> cells are also seen, particularly in Layer III. Like the VIP<sup>+</sup> cells, CCK<sup>+</sup> neurons form extensive axonal arbors around somata in Layer II, with some collaterals in Layer III. Hence, these neurons are also basket cells. Little information is available about the morphologies of NPY- or SOM-containing interneurons in the PC.

In summary, PC interneurons can express different combinations of calcium-binding proteins and neuropeptides, as in other brain regions. Expression of these molecular markers is strongly laminar-specific in the PC, being more common in the deeper layers (Layers II and III) and often associated with basket cells.

## Physiology

The electrophysiological properties of interneurons can be divided into two categories: intrinsic and extrinsic. Intrinsic properties include resting potential, input resistance, and the firing pattern of action potentials (APs) evoked by a long current step at the soma. In the neocortex, interneuron APs are consistently briefer than those of excitatory cells<sup>31</sup>, but their firing pattern varies widely between interneuron types. Many descriptive terms have been used, *e.g.* fast-spiking, late-spiking, irregular spiking (Figure 3).<sup>15,32</sup> Extrinsic properties typically refer to the behaviour of synaptic and gap junction connections between pairs of interneurons or between interneurons and excitatory cells. For example, inhibitory synaptic currents between neocortical interneurons can vary in their kinetics and short-term plasticity.<sup>33,34</sup>



**Figure 3.** Examples of different patterns of action potential firing in response to a current step, recorded in interneurons in slices of mouse PC using the whole-cell patch clamp technique. **A**, Fast-spiking cell in Layer III. **B**, Late-spiking cell in Layer I. **C**, Irregular-spiking cell in Layer III. (Suzuki and Bekkers, unpublished data.)

Intrinsic properties of PC interneurons were first described in *in vivo* experiments using both extracellular and sharp intracellular recordings.<sup>35-37</sup> These described repetitively-firing putative interneurons in the deeper part of Layer III. Since then there have been only a few reports on the intrinsic properties of PC interneurons in slices. Regular-spiking putative interneurons of unknown morphology at the Layer II/III border have been described

using sharp electrodes,<sup>38,39</sup> and the passive and firing properties of Layer III non-pyramidal cells have been measured using whole-cell patch clamping.<sup>23</sup> These experiments confirmed that some interneurons have higher input resistances ( $\sim 85 \text{ M}\Omega$  *cf.*  $\sim 60 \text{ M}\Omega$ ) and smaller AP widths (0.5 ms *cf.* 1.4 ms) than pyramidal cells, and are able to fire at higher rates ( $\sim 3 \times$ ). In another series of experiments using extracellular unit recordings,  $\alpha_1$ -adrenoceptor and monoamine receptor agonists have been reported to directly depolarize Layer II/III putative interneurons, increasing inhibitory drive onto PC pyramidal cells.<sup>8,38,40</sup>

Extrinsic (synaptic) properties of PC interneurons were first inferred from *in vivo* experiments describing both feedback and feedforward inhibition onto PC pyramidal cells.<sup>10,35,37</sup> Subsequent work done in slices has focused on recording inhibitory postsynaptic potentials (IPSPs) and currents (IPSCs) in pyramidal cells following extracellular stimulation. Interestingly, IPSPs tend to be depolarizing at rest in Layer II pyramidal cells because these cells have strongly negative resting potentials ( $\sim -75 \text{ mV}$ ).<sup>1,4</sup> The functional consequences of this have not been explored. It has been reported that IPSCs in pyramidal cells have two kinetically-distinct components with decay time constants  $\sim 10 \text{ ms}$  and  $\sim 40 \text{ ms}$ , with the latter more prominent in the dendrites.<sup>41-43</sup> Using local extracellular stimulation and focal application of antagonist, it was also concluded that two largely independent circuits generate GABAergic inhibition in the perisomatic and distal dendritic regions.<sup>43</sup> Laminar differences in neuromodulation of IPSPs have also been reported. For example, cholinergic<sup>44</sup> and muscarinic<sup>45</sup> agonists inhibit IPSPs produced by Layer I *b* stimulation more than those produced by Layer I *a* stimulation.

To summarise, regular-firing action potentials have been recorded in putative interneurons in the PC, and some of the kinetic and neuromodulation properties of inhibitory synaptic responses have been reported. A more systematic study of the neurophysiology of identified interneurons remains to be done.

## Function

Although there is ample circumstantial evidence for the role of interneurons in the normal operation of the PC, the details of their participation remain speculative. Broadly speaking, interneurons could control three different components of the neuronal network: (i) dendritic inputs; (ii) axonal outputs; and (iii) long-range connections between interneuron assemblies.<sup>22</sup>

An example of PC interneuron control of dendritic inputs is their participation in the induction of long-term potentiation (LTP) in the PC, which is thought to be important for olfactory learning.<sup>46</sup> Associative LTP between afferent (LOT) and associational inputs onto Layer II pyramidal cells can be induced only when GABAergic inhibition in the dendrites is blocked, suggesting that dendrite-targeting interneurons normally exercise a veto over this form of plasticity.<sup>47,48</sup> Hence, cholinergic or monoaminergic modulation of inhibitory input in the

dendrites could modulate olfactory learning.<sup>41,49</sup>

Interneuron control of long-range connections is suggested by the prominence of electrical oscillations in the PC when it is performing an olfactory task.<sup>50,51</sup> Similar oscillations are seen in the hippocampus and neocortex, where the participation of interneurons has been established.<sup>52,53</sup> It is possible that networks of interneurons in the PC, as in other brain regions, provide a global clock that synchronizes the firing of action potentials, a process that may be important for olfactory coding.<sup>54,55</sup>

A final example of function is provided by interneuron involvement in a brain pathology, epilepsy. The PC, like the hippocampus, is strongly epileptogenic.<sup>56</sup> Unsurprisingly, inhibition has been shown to limit excessive excitability in the PC in several models of epilepsy.<sup>57-59</sup> For instance, in an *in vivo* kindling model it was shown that a precisely-timed IPSP is critical for limiting excessive excitation in PC pyramidal cells.<sup>60</sup>

In conclusion, this brief review of inhibitory interneurons in the PC has shown that this field is in many respects a *terra incognita*. However, it has already been established that the PC contains a rich and fascinating fauna of interneurons, the study of which is certain to be important for our future understanding of olfactory processing.

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