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A blanket of inhibition: functional inferences from dense inhibitory connectivity

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The function of neocortical interneurons is still unclear, and, as often happens, one may be able to draw functional insights from considering the structure. In this spirit we describe recent structural results and discuss their potential functional implications. Most GABAergic interneurons innervate nearby pyramidal neurons very densely and without any apparent specificity, as if they were extending a 'blanket of inhibition', contacting pyramidal neurons often in an overlapping fashion. While subtypes of interneurons specifically target subcellular compartments of pyramidal cells, and they also target different layers selectively, they appear to treat all neighboring pyramidal cells the same and innervate them massively. We explore the functional implications and temporal properties of dense, overlapping inhibition by four interneuron populations.

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Introduction

Although functional inhibition was discovered more than half a century ago [1], there is still vigorous debate as to what exactly inhibitory neurons (INs) do. Even for the paradigmatical example of a clearly defined IN population, the chandelier cells, it is still unclear whether they are actually inhibitory [2] or excitatory [3], or whether their function could be a mixed one, depending on the state of the network [4]. To make this problem more complicated, GABAergic interneurons belong to many different subtypes, and their function is unlikely to be homogeneous or simple.

However recent data suggest that some INs project densely to nearby principal cells (PCs). To gather information that could constrain hypotheses about IN function we review recent studies on network the connectivity of five IN populations that together encompass ~85% of all neocortical INs: (1) Parvalbumin containing INs (PVs), which are virtually always fast spiking cells (FSs) with particularly rapid action potentials. Because of the high overlap between FS and PV groups [5–8], we use only the term PV for simplicity. (2) Chandelier cells (ChCs), also known as axo-axonic cells [9,10•,11]. (3) Neurogliaform cells (NGFCs) [12,13••], (4) Somatostatin containing INs (SOMs) [14] and (5) Vasoactive Intestinal Peptide containing INs (VIPs) [15]. Of these five populations PVs, NGFCs, SOMs and VIPs show virtually no overlap with each other [15–17], while some ChCs contain parvalbumin [11]. All studies reviewed here were performed in rats or mice.

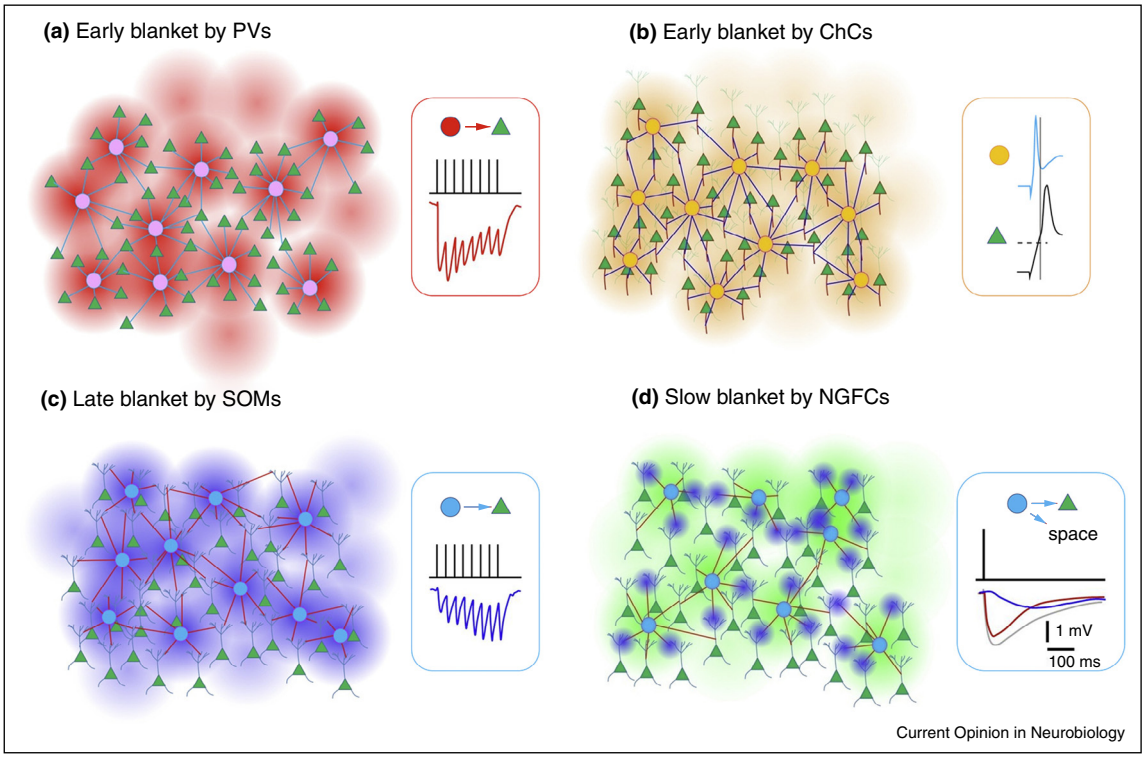
Blanket inhibition

This term describes the dense and unspecific innervation of local PCs by INs, i.e., restricted to immediate intralaminar territories covered by their axons. PVs and SOMs project densely to PCs within a 200 μm radius (Fig. 1). This dense innervation pattern was demonstrated in living IN-GFP brain slices across multiple cortical areas and developmental stages using two-photon glutamate uncaging [18••,19••]. The connection probabilities decayed with distance but at peak, at around 100 μm intersomatic distances, were ~80% for both IN types and in some recordings *all* INs within 200 μm of a PC were connected to it demonstrating highly overlapping inhibitory connectivity. Given that many axons are cut in slice, we expect these INs project to essentially every PC around them in the intact brain. Since these studies showed that a given PC receives inhibitory input from most PVs and SOMs around it, it stands to reason that any PV or SOM inhibits most PCs around it unspecifically. Before these studies, compatible but less comprehensive results had been reported, using paired electrical recordings [20].

The connectivity between INs is less well understood. Some studies report a high degree of connectivity between PVs, from PVs to SOMs and SOMs to PVs [21–23] (but see [5] and [24••] for smaller estimates of PV → PV and PV → SOM). Thus the dense inhibitory blankets from PVs and SOMs to PCs might extend to INs too, with the clear exception that SOMs virtually never inhibit each other.

A recent study of ChCs found that, within their local axonal territorie, they also project densely to local PCs [10•]. Nearly 50% of AISs within 200 μm from a ChC soma were apposed by a cartridge. This could be a

Figure 1



Blanket inhibition by the different subtypes of interneurons. **(a)** Early blanket inhibition by PVs. Inset shows depressing nature of its synaptic dynamics. **(b)** Early blanket inhibition by ChCs. Inset shows early activation of ChCs (blue) compared to PCs (black) after layer 1 stimulation (copied with permission from Ref. [4]). **(c)** Late blanket inhibition by SOMs. Inset shows facilitating synaptic dynamics. **(d)** Slow blanket inhibition by NGFCs. Inset: Gray trace represents total inhibitory current while blue is a $GABA_B$ receptor component and red is the difference. Green triangles represent PCs, and circles in each panel represent INs projecting to PCs.

significant underestimate of the real connectivity because of the technical caveats and stringent analysis methods employed (discussed in detail in [10•]). Indeed, some areas within the ChC axonal fields had cartridges apposing nearly every AIS. Consistent with the lack of selectivity, an average of 4 ChCs were estimated to innervate any given AIS, indicating an overlapping pattern of inhibition. Dense innervation of virtually every PC AIS by ChCs in piriform cortex has also been observed [25]. Thus, ChCs appear similar to PVs and SOMs in terms of their local blanket inhibition. Nevertheless, it would be important to study ChC connectivity with a similar method used on PVs and SOMs [18••,19••] to reveal the functional density of this blanket inhibition.

A final case for a 'blanket' inhibitory innervation can be made for NGFCs, which mediate a spatially extreme form of blanket inhibition by forming presynaptic boutons that are not directly opposed to postsynaptic densities of other cells and secrete GABA into the neuropil some micrometers away from the functionally postsynaptic cells. This innervation strategy, showering cortical circuits with GABA, presumably accounts for the 87% connection probability observed from NGFCs to nearby neurons within 100 μm [13••]. NGFCs additionally modulate synaptic transmission within their axonal field [13••] and inhibit cells with more distant somata that have distal dendrites within the NGFC axonal fields [26]. Working through presynaptic $GABA_B$ receptors, NGFCs can decrease the effect of repetitive synaptic events [13••]. A high degree of connectivity was observed in another recent study on layer 4 NGFCs, although presynaptic modulation of synaptic transmission upon thalamic stimulation was found only on PV-to-PC synapses but not on excitatory synapses formed by thalamocortical afferents which also contain presynaptic $GABA_B$ receptors [12]. This discrepancy might be simply due to presence of the whole PV soma-to-dendritic domain within the NGFC axonal cloud, rather than spatial specificity in the distribution of release sites within the NGFC axonal field.

Early and late blanket inhibition

Subtypes of INs have different temporal properties in their firing and synaptic dynamics and also target separate subcellular compartments of PCs. Because of dynamic changes and variance of synaptic weights [27], blanket