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Review article

Functional dissection of inhibitory microcircuits in the visual cortex

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ABSTRACT

Cerebral cortex contains various types of GABAergic neurons exerting local inhibition. Although the number of GABAergic inhibitory neurons is much smaller than glutamatergic excitatory neurons, they show greater diversity in their morphological and physiological properties. Genetic markers for distinct subclasses of GABAergic neurons have been identified, and technical advances achieved in the past few decades have brought about a demonstration of a unique function of each sub-class of GABAergic neurons in the cortex. In particular, visual processing in the cortex requires inhibitory function of various GABAergic neurons. Here, we summarize current understandings on the function of inhibitory neurons in the cortex, especially focusing on their roles in visual processing.

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1. Introduction

The cerebral cortex is subdivided into several areas with specialized features through which animals can maintain various cognitive abilities. Many types of neurons are intermingled in the cortex, and interaction between them structures neural circuits that rapidly process cognitive information. In particular, the importance of GABAergic inhibition during cortical processing has been proposed for decades. GABAergic neurons form specific connectivity patterns in cortical microcircuits, which have important roles in regulating the excitatory outputs of cortical neurons. The level and type of cortical inhibition determine the saliency of stimuli as well as transmission efficiency of the information (Fishell and Rudy, 2011; Isaacson and Scanziani, 2011; Kepecs and Fishell, 2014). GABAergic inhibition is also important for regulating neuronal synchrony, synaptic plasticity, and response selectivity (Isaacson and Scanziani, 2011). Furthermore, abnormal function of inhibitory circuits has been suggested as the cause of many neurological disorders, such as epilepsy, schizophrenia, anxiety disorder, and Alzheimer's disease (Moult and Harvey, 2009). Thus, clear understanding on the function of GABAergic neurons in the cortex is critical for curing cognitive declines in the patients with those disorders.

The GABAergic interneurons occupy 20–30% of the overall cortical neurons, and they were found to be varying extensively in terms of their morphological, genetic, and electrophysiological characteristics (Markram et al., 2004; Petilla Interneuron Nomenclature et al., 2008; Xu et al., 2010). The cell-type specific function of cortical

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inhibitory neurons has been revealed recently in different cortical areas. In particular, genetic markers of specific GABAergic neurons have been discovered extensively, and targeting them for optogenetic manipulation or calcium imaging became a powerful tool for elucidating the function of each inhibitory neuron *in vivo*. Many pioneering researches have been performed in the visual cortex, and the results so far suggest that GABAergic inhibition has crucial roles in every step of the visual processing. Not only does GABAergic inhibition help the formation of receptive field properties of individual neurons but also regulates oscillatory activity of the cortical network. Here, we discuss the roles of GABAergic neurons in the visual cortex in shaping properties of visual responses and visual perception. We review first the characteristics of their own receptive field properties and next their influences on the formation of receptive field properties of neighboring excitatory neurons. Then, we further discuss the roles of GABAergic neurons in modulating network activity of cortical neurons, which in turn changes brain states dynamically.

2. Emergence of receptive field properties in the primary visual cortex

It was illustrated for the first time by Hubel and Wiesel in their 1950s studies that neurons in the primary visual cortex (V1) are tuned to certain orientations of the visual stimuli (i.e. orientation selectivity) (Hubel and Wiesel, 2009). They proposed a model of a neural circuit that can form the orientation selectivity of V1 neurons. In this model, excitatory neurons in the lateral geniculate nucleus (LGN) project to simple cells in the layer 4 of V1 with a spatial arrangement of the ON–OFF receptive fields. This model of a feed-forward input was supported by mapping receptive field structures in LGN and V1 through simultaneous recordings (Ferster and Miller, 2000). Recent studies in the mouse model further support the idea that tuned thalamo-cortical innervations determine the orientation selectivity of V1 neurons (Li et al., 2013; Lien and Scanziani, 2013). These results match with the revised model of the feed-forward inputs from the LGN that determines orientation selectivity; i.e. it can be explained by holistic pattern of the axonal innervation from the LGN to the V1 rather than by the selective convergence of multiple thalamic neurons to a single V1 neuron with spatially restricted receptive field structures (Jin et al., 2011; Reid and Alonso, 1995).

After the initial finding on the emergence of orientation selectivity in the V1 neurons, it has long been discussed whether the inhibitory neurons in the cortex can shape the orientation-selective response of V1 neurons (Shapley et al., 2003; Sillito, 1975). Although the excitatory inputs seem to be sufficient to generate the orientation selectivity (Nelson et al., 1994), blocking local GABAergic inputs in the cortex clearly broadened the orientation tuning curve of V1 neurons (Sillito, 1975). This evidence supported the idea that inhibition in the cortex is important for shaping orientation selectivity. Next question was whether the inhibitory inputs are also tuned to specific orientations. The observation of cross-orientation suppression, the suppression of neuronal responses to the preferred orientation when the perpendicular orientation stimuli are presented together, suggested a model that the inhibitory inputs are either tuned to the perpendicular orientation or almost untuned (broadly responding to all orientations) (DeAngelis et al., 1992; Morrone et al., 1982). Based on these experimental observations, computational modeling studies further suggested that these broadly tuned or orthogonally tuned inhibitory inputs are required for the contrast-invariant orientation tuning of V1 neurons that maintain tuning width invariantly across the stimuli intensities (Lauritzen and Miller, 2003; Sompolinsky and Shapley, 1997).

In order to prove this model experimentally, orientation tuning of excitatory and inhibitory synaptic inputs was measured separately in a single V1 neuron through the patch-clamp recording *in vivo*. It turned out that the inhibitory inputs are tuned to similar orientation as that of the excitatory inputs (i.e. iso-orientation inhibition) (Anderson et al., 2000; Hirsch et al., 1998). These results strongly opposed the importance of inhibition in determining the orientation selectivity of V1 neurons and suggested that cross-orientation suppression and contrast-invariant orientation tuning of V1 neurons can be explained without any inhibition (Finn et al., 2007; Priebe and Ferster, 2006, 2008). However, it is still unclear whether the cortical inhibition does not play any roles in shaping these receptive field properties of V1 neurons (MacEvoy et al., 2009). Recent studies have compromised contradicting ideas on the role of inhibition in shaping orientation selectivity by proposing a model of broadly tuned inhibition (Isaacson and Scanziani, 2011; Li et al., 2012b). In this model, inhibitory inputs are broadly tuned to the iso-orientations, to which excitatory inputs are tuned more selectively, and this inhibition can sharpen the orientation selectivity of V1 neurons by hyperpolarizing the membrane potential of the neuron. With inhibition, weak excitatory inputs at non-preferred orientations cannot induce spike output of the neuron anymore, and the neuron in turn spikes selectively only at the preferred orientations (Fig. 1).

3. The orientation selectivity of GABAergic neurons

While overall inhibitory inputs to an orientation-selective neuron have been suggested to be broadly tuned, it was unclear whether individual GABAergic neurons show distinct receptive field properties in the visual cortex. Although anatomical and physiological studies have suggested greater diversity in GABAergic neurons than glutamatergic neurons, measuring the receptive field properties of specific inhibitory neurons intermingled with many other neurons was not trivial due to technical limitations in isolating activity of specific GABAergic neurons *in vivo*. Traditional approach for classification of neuronal types was based on the shape of action potentials from the recorded neurons. For example, GABAergic neurons are fast-spiking (FS) with narrower action potentials and pyramidal neurons are regular-spiking (RS) with broader action potentials. By adapting this technique of sorting neuronal types, it has been revealed that the FS GABAergic neurons in cat V1 exhibit various degrees of orientation selectivity (some with very selective responses; others with non-selective). On the other hand, those in rodent V1 generally have very low orientation selectivity (Cardin et al., 2007; Niell and Stryker, 2008; Nowak et al., 2003). These results suggested the idea that orientation selectivity of GABAergic neurons might vary depending on the presence of orientation columns in V1. GABAergic neurons within a specific orientation column might show selective response to the preferred orientation of that column, as they receive excitatory inputs from the neighboring neurons that are tuned to that orientation.

Although the FS neurons were identified as GABAergic neurons, not all GABAergic neurons were FS neurons (Xu et al., 2010). Thus, the criterion on the shape of spikes was not able to account for isolation of responses from all the cortical GABAergic neurons. Recent advances in mouse genetics as well as development of two-photon microscopy for *in vivo* calcium imaging allowed researchers to overcome this difficulty in identification of overall GABAergic neurons. For instance, *in vivo* calcium imaging with two-photon microscopy can be done with transgenic mice whose GABAergic neurons express fluorescent protein GFP (e.g. GAD67-GFP) (Sohya et al., 2007). In this study, receptive fields of GFP-expressing GABAergic neurons were directly measured by calcium imaging under the two-photon microscopy after uploading calcium indi-