

Network-Level Control of Frequency Tuning in Auditory Cortex

Highlights

- Frequency tuning in auditory cortex of mice is shaped by lateral inhibition
- Lateral inhibition is due to the suppression of recurrent excitation
- Somatostatin-expressing interneurons trigger network suppression
- Auditory cortex operates as an inhibition-stabilized network (ISN)

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In Brief

Kato et al. show that lateral inhibition shapes frequency tuning in primary auditory cortex via an unconventional mechanism: non-preferred stimuli suppress recurrent excitation. Somatostatin-expressing interneurons are critical for triggering this indirect form of cortical inhibition.

Network-Level Control of Frequency Tuning in Auditory Cortex

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SUMMARY

Lateral inhibition is a fundamental circuit operation that sharpens the tuning properties of cortical neurons. This operation is classically attributed to an increase in GABAergic synaptic input triggered by non-preferred stimuli. Here we use *in vivo* whole-cell recording and two-photon Ca²⁺ imaging in awake mice to show that lateral inhibition shapes frequency tuning in primary auditory cortex via an unconventional mechanism: non-preferred tones suppress both excitatory and inhibitory synaptic inputs onto layer 2/3 cells (“network suppression”). Moreover, optogenetic inactivation of inhibitory interneurons elicits a paradoxical increase in inhibitory synaptic input. These results indicate that GABAergic interneurons regulate cortical activity indirectly via the suppression of recurrent excitation. Furthermore, the network suppression underlying lateral inhibition was blocked by inactivation of somatostatin-expressing interneurons (SOM cells), but not parvalbumin-expressing interneurons (PV cells). Together, these findings reveal that SOM cells govern lateral inhibition and control cortical frequency tuning through the regulation of reverberating recurrent circuits.

INTRODUCTION

In sensory cortical areas, neurons sharply tuned to particular features of sensory stimuli underlie precise representations of the external world. For example, pyramidal cells in visual cortex respond selectively to visual stimuli with a certain orientation or size, those in rodent somatosensory cortex prefer particular directions of whisker deflection, and neurons in auditory cortex fire selectively to certain sound frequencies. Revealing the factors governing cortical tuning properties is fundamental for understanding how sensory information is encoded in the brain.

The excitatory synaptic input driving tuned pyramidal cell activity comes from two main sources: afferent thalamic inputs and recurrent synapses between pyramidal cells themselves that amplify thalamic input (Li et al., 2013; Lien and Scanziani,

2013). While excitation broadly defines the tuning of pyramidal cell spike output, stimulus selectivity can be further refined by inhibitory synaptic input (Isaacson and Scanziani, 2011; Priebe and Ferster, 2008). Cortical inhibition is mediated by a variety of local GABAergic interneurons that are highly interconnected with pyramidal cells as well as each other (Pfeffer et al., 2013; Tremblay et al., 2016). However, the precise synaptic mechanisms by which interconnected excitatory and inhibitory circuits generate pyramidal cell tuning properties are not established.

Lateral inhibition, first described in photoreceptors (Hartline et al., 1956), is a basic circuit operation that can sharpen cortical tuning properties (Isaacson and Scanziani, 2011; Priebe and Ferster, 2008). In this operation, pyramidal cells firing in response to stimuli in their receptive fields recruit local interneurons, which in turn suppress firing of other neurons with different receptive fields. In a classical model, lateral inhibition narrows tuning of individual neurons when non-preferred stimuli recruit inhibitory synaptic input more strongly than excitation. In other words, lateral inhibition occurs when synaptic inhibition is more broadly tuned than excitation. Indeed, differences in the tuning broadness of excitation and inhibition have been proposed to enforce odor selectivity in olfactory cortex (Poo and Isaacson, 2009) as well as selectivity for the size (Adesnik et al., 2012) and orientation (Liu et al., 2011; but see Tan et al., 2011) of visual stimuli in visual cortex.

Interestingly, in primary auditory cortex the extent to which lateral inhibition contributes to frequency tuning as well as the synaptic mechanisms underlying suppressive effects of non-preferred stimuli are a matter of debate. For example, studies in primates, cats, and rodents using two-tone protocols have found that firing to preferred frequencies can be suppressed when preceded by tones that are octaves different (Calford and Semple, 1995; Li et al., 2014; Phillips and Cynader, 1985; Sadagopan and Wang, 2010; Sutter et al., 1999). Although two-tone suppression is typically attributed to GABAergic inhibition produced by the first sound, synaptic depression of excitatory input has also been shown to contribute to suppressed activity in this paradigm (Wehr and Zador, 2005). More typical of classic lateral inhibition, single tones at non-preferred frequencies have also been found to cause suppression of spontaneous neuronal firing in awake primates (O’Connell et al., 2011; Sadagopan and Wang, 2010). However, these reports of response suppression are difficult to reconcile with intracellular recordings of sound-evoked synaptic responses in rodent auditory cortex. For instance, studies have found completely

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