Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Broad Inhibition and Local Disinhibition Characterize Local Cortical Circuits

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Review of Karnani et al.

The term "blanket of inhibition" has been proposed to explain the dense and indiscriminate inhibitory connectivity of several classes of GABAergic interneurons with nearby pyramidal neurons (Karnani et al., 2014). This inhibition is extensive in both space and time. The inhibition extends the length of the somatodendritic axis of pyramidal neurons, with parvalbumin-expressing interneurons (PVs) projecting predominantly to the perisomatic region and somatostatin-expressing interneurons (SOMs) projecting to the dendritic trees. While PVs display a rapid-onset, transient inhibition via fast-spiking activity that depresses over time, SOMs produce a slowly recruited, persistent inhibition that can increase several fold in response to high-frequency input (Karnani et al., 2014). In an article recently published in *The Journal of Neuroscience*, Karnani et al. (2016a) asked how information is propagated through the cortex given that such a pervasive stronghold of inhibition exists. They provide evidence of a functional "hole" in the blanket of inhibition that occurs via a disinhibitory circuit composed of vasoactive intestinal peptide-expressing interneurons (VIPs), SOMs, and pyramidal neurons.

Karnani et al. (2016a) first used optogenetic inactivation to confirm that SOMs mediate disynaptic lateral inhibition between pyramidal neurons in acute slices from the primary visual cortex (V1) and primary somatosensory cortex (S1). Specifically, they showed that depolarizing one pyramidal neuron caused disynaptic inhibition of a nearby pyramidal neuron, and silencing SOMs eliminated this inhibition. They then showed that optogenetic activation of VIPs significantly reduced SOM-mediated lateral inhibition, mimicking the effect of optogenetic inactivation of SOMs. Using *in vivo* calcium imaging, the authors demonstrated a correlation between spontaneous activity in VIPs and pyramidal neurons, as well as a correlation between visually evoked activity in the two cell types. For both cases, the correlation was distance dependent, exhibiting the highest correlation within a 50 μm radius. These data indicate that VIPs and pyramidal neurons are connected within the same local circuit and are involved in the handling of the same input.

To ensure the directionality of this VIP–pyramidal neuron connection, Karnani et al. (2016a) used visual stimulation and calcium imaging to detect changes in the activity of putative pyramidal neurons while optically stimulating single VIPs. Less than 1% of all recorded pyramidal neurons were inhibited when VIPs were activated, and disinhibited pyramidal neurons were located significantly closer to the stimulated VIP than all other imaged cells, suggesting a highly localized disinhibitory effect of VIP stimulation. Indeed, plotting the change in stimulus-evoked activity during VIP activation as a function of distance revealed an ~120–180 μm radius of disinhibition for a single VIP. These data suggest that VIPs disinhibit a local region of pyramidal neurons by inhibiting local SOMs within that same region.

Other recent work by Jackson et al. (2016) expands on the significance of the disinhibitory circuit discussed by Karnani et al. (2016a) to include its role in network activity. Jackson et al. (2016) found that VIPs were activated during periods of locomotion, visual stimulation, immobility, and light anesthesia; and VIP activation was most highly correlated with overall levels of network activity. The decreases in SOM activity demonstrated during high-activity states, such as free running in V1 (Fu et al., 2014) and during whisking in S1 (Gentet et al., 2012), may therefore be explained by increased inhibition of SOMs by VIPs. To further elucidate the role of VIPs in network activity, Jackson et al. (2016) silenced VIPs via the inhibitory DREADD (designer receptors exclusively activated by designer drug) hM4Di and found reduced spontaneous activity in pyramidal neurons across all previously discussed behavioral states. The reduction in spontaneous network activity in the absence of VIP output suggests a functional role for VIPs in amplifying network activity through the disinhibitory circuit char-

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acterized in the study by Karnani et al. (2016a).

A functional role for VIP-mediated disinhibition in larger network computation was also characterized in another publication by Karnani et al. (2016b). In that study, the authors expanded on the proposed disinhibitory circuit by examining the coactivity within local populations of VIPs and SOMs, and their participation in cooperative subnetworks within a spatial domain. *In vivo* calcium imaging revealed both spontaneous and evoked coactivity of several VIPs within a local population, and that the firing of a few VIPs could quickly recruit the firing of several other VIPs within a local population. Similar behavior was found for SOMs. Karnani et al. (2016b) optogenetically stimulated putative pyramidal neurons and found that their activation produced temporally nonoverlapping EPSPs in SOMs and VIPs, suggesting that temporally distinct excitatory inputs drive the activity of each interneuron subtype independently. Karnani et al. (2016b) hypothesized that unison activity of a selective interneuron subtype may arise through mechanisms such as population-specific local excitation or GABAergic disinhibition and may serve to amplify inhibition onto specific targets during certain behavioral demands. Thus, activation of VIPs within the disinhibitory circuit of Karnani et al. (2016a) may recruit additional VIPs and cause this disinhibitory circuit to act on a network level in certain scenarios, introducing an additional level of complexity. Further investigation is needed to elucidate how orchestrated networks of different interneuron subtypes may selectively drive inhibition and influence computation through disinhibitory networks.

The selective inhibition of SOMs within this disinhibitory circuit is curious given the interconnectedness within interneuronal networks. SOMs inhibit PVs in V1 (Pfeffer et al., 2013; Karnani et al., 2014), which calls into question whether the inhibition of SOMs by VIPs simultaneously relieves the inhibition of PVs, thereby increasing the somatic inhibition of pyramidal neurons via a VIP → SOM → PV → pyramidal neuron circuit. That is, inhibition would be concurrently heightened at the soma but relieved in the dendrites, with uncertain implications for pyramidal neuron output yet to be explored. Inhibition of a small subset of PVs by VIP activation has been reported (Pi et al., 2013), which, although minor, could possibly counteract this. The compartmentalization of SOM projections onto the dendritic tree suggests that the selective disinhibition of these cellular compartments may play a specialized function that is not achievable by relieving the shunting inhibition around the soma exerted by PVs. Synaptic input onto the dendrites is integrated into an outgoing signal very differently than input near the soma, due to inherent cable properties of the neuron, and involves regenerative processes, including Na^+ spikes, Ca^{2+} spikes, and NMDA spikes that can result in supralinear integration of synaptic input (Häusser et al., 2000). The increased firing in pyramidal neurons with VIP activation during visual stimulation shown in the study by Karnani et al. (2016a) could be explained by this type of supralinear integration, as NMDA spikes can enhance action potential generation in cases of sensory stimulation (Palmer et al., 2014). One possible specialized function for the dendritic compartmentalization of this disinhibitory circuit could be enhancing the selectivity for specific stimuli or situations given that dendritic spikes have been shown to enhance orientation tuning in the visual cortex (Smith et al., 2013).

An alternative function for this disinhibitory circuit has been proposed to function at the subcellular level and emphasizes the computational processes performed by dendritic branches of pyramidal neurons (Yang et al., 2016). Yang et al. (2016) propose that while SOM–pyramidal neuron connectivity is highly dense and indiscriminate at the cellular level, as seen within the blanket of inhibition (Fino and Yuste, 2011), connectivity is actually sparse when examined at the subcellular level (i.e., individual dendritic branches). Yang et al. (2016) developed a computational model that suggests that this VIP-induced disinhibitory circuit promotes pathway-specific gating of input into individual dendritic branches, allowing nonlinear integration of synaptic input from specific excitatory pathways while suppressing excitatory input from other pathways. The authors suggest that the simultaneous activation of excitatory inputs clustered on the dendritic branch of a pyramidal neuron and disinhibition of that same branch allows local supralinear depolarization and amplification of the excitatory input that arrives there. When disinhibition is not colocalized with excitation, this supralinearity is "gated off" and input is suppressed. This pathway-specific gating is achieved in their model via one of the following two scenarios: excitatory input that targets a sparse, selective subset of VIPs or excitatory input that indiscriminately targets VIPs and only a selective subset of SOMs. The first scenario with excitatory input selectively engaging VIPs is more consistent with the evidence from the study by Karnani et al. (2016b) that VIPs and SOMs receive distinct excitatory inputs. Yang et al. (2016) hypothesize that the amplification of input onto specific dendritic branches, but not others, via pathway-specific gating transmits stimulus selectivity for corresponding input pathways that could be linked with complex tasks or context-dependent behaviors. The connection between network activity and this disinhibitory circuit as discussed in the study by Jackson et al. (2016), is an interesting consideration for the emphasis of this model on dendritic computation, as the NMDAR component of dendritic integration is highly based on network activity (Major et al., 2013).

Future studies aimed to identify aspects of behavior mediated through VIP-induced disinhibition will allow a comprehensive understanding of how interneuronal activity facilitates the propagation of selective information throughout the neocortex. When combined with computational models incorporating additional interneuron subtypes, multiple cortical layers, or distinct long-range inputs, a more complete picture of how inhibitory interneurons interact to shape cortical activity will be achieved. The work presented by Karnani et al. (2016a) provides direct experimental evidence for localized holes in the blanket of inhibition through the disinhibitory role played by VIPs. In this way, disinhibition through VIP activity may play a central role in several states of cortical processing, at both the level of individual dendrites and in cooperative subnetworks of interneurons in the neocortex.

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