This Week in The Journal

Cortical VIP-Expressing Neurons Disinhibit Principal Cells

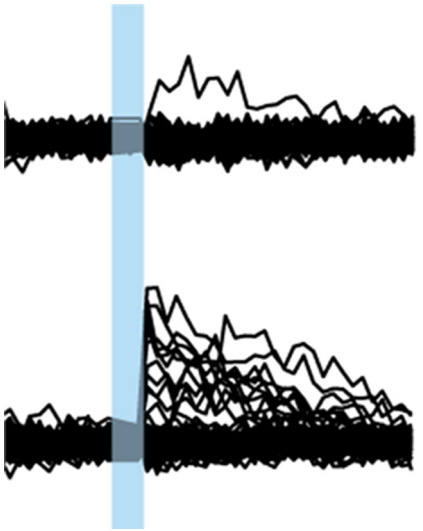
Mahesh M. Karnani, Jesse Jackson, Inbal Ayzenshtat, Azadeh Hamzehei Sichani, Kasra Manoocheri, et al.

(see pages 3471–3480)

Multiple types of GABAergic interneurons influence cortical circuits. Parvalbumin-expressing interneurons inhibit nearly all surrounding principal neurons via perisomatic synapses, while somatostatin-expressing (SOM) interneurons innervate the distal dendrites of principal cells. In contrast, interneurons that express vasoactive intestinal peptide (VIP) rarely target principal cells, but instead inhibit SOM neurons. VIP neurons have therefore been proposed to release principal cells from inhibition. Karnani et al. now demonstrate that this is the case.

The authors first confirmed that SOM neurons mediate disynaptic inhibition between principal cells in layer 2/3 of mouse visual cortex: activating principal cells produced inhibition in nearby principal cells, and this inhibition was blocked by silencing SOM neurons. Next, they showed that activating VIP neurons mimicked the effect of silencing SOM neurons, that is, it blocked disynaptic inhibition between principal cells. The authors went on to demonstrate that VIP neurons inhibited nearby SOM neurons. Finally, they showed that optogenetic activation of VIP neurons during visual stimulation increased responses of some nearby principal cells, affecting cells up to $\sim$120 μm away.

These results strongly suggest that activation of VIP interneurons leads to disinhibition of nearby principal cells in visual cortex. This disinhibition might work together with the widespread inhibition provided by SOM- and parvalbumin-expressing interneurons to ensure that only a small number of principal cells are activated by a stimulus. It may also influence the timing of principal neuron firing. In addition, because VIP cells are activated by long-range projection neurons from other cortical areas, they may increase local excitability under specific circumstances, for example, when the animal is walking (Fu et al. 2014 Cell 156, 1139–1152) or receiving reinforcement (Pi, et al. 2013 Nature 503: 521). Future studies in which VIP neurons are inhibited in behaving animals should help elucidate the function of disinhibition and deepen our understanding of cortical circuits.



Principal neuron responses to visual stimulation (blue bar) in awake mice were greater when VIP neurons were activated using two-photon optogenetic stimulation (bottom traces) than during visual stimulation alone (top traces). See Karnani et al. for details.

The Role of the Amygdala in Fear

Sahib S. Khalsa, Justin S. Feinstein, Wei Li, Jamie D. Feusner, Ralph Adolphs, et al.

(see pages 3559–3566)

The amygdala is essential for generating appropriate responses to potential threats. During fear conditioning in rodents, information about conditioned and unconditioned stimuli converge in the basal and lateral nuclei of the amygdala. These nuclei project to the central nucleus, which in turn projects to the hypothalamus and brainstem to elicit appropriate responses, such as freezing and increased heart rate.

The human amygdala is also activated during fear conditioning and when people view frightening stimuli. But the most compelling evidence that the amygdala is required for generating the feeling of fear comes from rare cases of people who lack substantial portions of the amygdala. One such patient displayed no fear-related physiological responses and reported no feelings of fear when confronted with stimuli that frighten most people. She also reported that she felt no fear when she was threatened outside the lab, for example, when she was robbed at knife point (Feinsteinet al. 2011 Curr Biol 21:34). Although this patient remembered being afraid as a child (before she lost amygdala function), the only time she reported feeling fear as an adult was when she inhaled 35% CO_2. In fact, she and two other patients lacking amygdala nuclei experienced fear and panic attacks—as well as increases in respiratory rate, heart rate, and skin conductance responses—during a CO_2 challenge (Feinstein, et al. 2013 Nat Neurosci 16:270).

These results raise the possibility that while the amygdala is necessary for generating fear responses to external stimuli, it is unnecessary for generating fear to internal cues. Khalsa et al. provide more evidence for this hypothesis. They found that two of these patients lacking amygdala function felt fear after receiving the peripherally acting β-adrenergic agonist isoproterenol. Moreover, one of the patients had a panic attack. As expected, isoproterenol increased heart rate in patients as well as controls, but interestingly, patients were slower to notice the increased heart rate. Skin conductance responses were also increased in both patients and controls.

These results indicate that interoceptive signals acting in the periphery can induce fear in humans with amygdala damage. It is important to note, however, that the lesions in these patients predominantly affect the basolateral nuclei, sparing the central nucleus. Ideally, future experiments using functional imaging will identify which brain regions are activated by fear-inducing interoceptive stimuli and thus provide clues about neural circuitry underlying the experience of fear.

This Week in The Journal is written by Teresa Esch, Ph.D.