This Week in The Journal

Kynurenic Acid Disrupts Excitatory-Inhibitory Balance in Prefrontal Cortex

Eden Flores-Barrera, Daniel R. Thomases, Daryn K. Cass, Ajay Bhandari, Robert Schwarcz, et al.

(see pages 7921–7929)

The cognitive disruptions seen in schizophrenia and other mental illnesses are rooted in the prefrontal cortex (PFC), and the onset of such symptoms has been linked to dysregulation of excitatory-inhibitory signaling there. Now, Flores-Barrera et al. have elucidated a potential molecular underpinning of this dysregulation in rats. At the center of the mechanism is kynurenic acid (KYNA), an astrocyte-derived metabolite of tryptophan that is abnormally elevated in the brains of people with schizophrenia. KYNA, normally present at nanomolar concentrations in the cortex, negatively modulates alpha-7 nicotinic type acetylcholine receptors (α7nAChR) found on GABAergic neurons. At levels present in schizophrenics, KYNA also competes for the glycine coagonist site of the NMDA-type glutamate receptor, potentially interfering with signaling in cortical circuits and perhaps contributing to cognitive disruption (see Timofeeva and Levin, 2011). Animal studies have shown that KYNA elevation indeed compromises executive function (see Pershing et al., 2015), but how remained unknown.

In the current study, the researchers painstakingly recorded the effects of manipulating KYNA in normal rats. They infused the prefrontal cortex in vivo with 50, 100, or 300 nM KYNA and then recorded local field potentials following 10, 20, and 40 Hz trains of stimuli to the ventral hippocampus. They saw KYNA-dose- and stimulus-frequency-dependent disruption of inhibitory PFC processing of incoming hippocampal signals. To tease apart just how KYNA affected processing, the authors applied 7Cl-KYNA, which blocks the NMDAR glycine site but not α7nAChRs; LFPs were indistinguishable from controls. Infusion of the α7nAChR antagonist MLA, however, affected LFPs similarly to KYNA, suggesting that KYNA exerted its effects through α7nAChRs. To determine the role played by GABA, the researchers then made whole-cell patch-clamp recordings from layer V pyramidal neurons in PFC slices. Application of 300 nM KYNA decreased the number of spontaneous, GABAergic inhibitory postsynaptic currents (IPSCs), although their amplitude remained stable. They concluded that GABAergic drive was reduced via KYNA's actions on presynaptic α7nAChRs, whereas glutamatergic inputs were not affected. Application of the α7nAChR allosteric modulator Indiplon prevented the disruption by KYNA, supporting the idea that slightly elevated KYNA decreases α7nAChR signaling at GABAergic neurons, effectively shifting the excitatory-inhibitory balance in the PFC. The findings might provide an avenue to target the cognitive disruptions seen with schizophrenia.

A rodent forages for food—a complex behavior that depends on basal ganglia processing. According to new work from Rainwater et al., striatal GPR88 plays a key role in that processing.

Striatal GPR88 Helps Mice Weigh Costs, Benefits of Food Seeking

Aundrea Rainwater, Elisenda Sanz, Richard D. Palmiter, and Albert Quintana

(see pages 7939–7947)

Performing homeostatic behaviors critical to our survival—seeking respite from the cold, finding food—requires coordination of motor activity that begins in the basal ganglia, a group of brain structures including the striatum, thalamus, globus pallidus, and cortex. In advance of coordinating motor movements, factors such as the nutritional benefit of a food must be weighed against the effort necessary to procure it. The striatum is thought to be particularly important as an information-integrating center that weighs these competing needs and guides foraging in mice, but the neural processes underlying complex food-finding behaviors are not understood.

Rainwater et al. suspected that GPR88, an orphan G protein-coupled receptor the group previously showed to be enriched in the striatum, might play a role in food-seeking foraging behavior. GPR88 is found in both D1- and D2-type dopaminergic medium spiny neurons of the striatum, and mice lacking the receptor display increased neuronal excitability and behavioral differences associated with striatal function (see Quintana et al., 2012). Recently, humans were identified with nonsense mutations in the GPR88 gene who presented with motor and learning disabilities (Alkufri et al., 2016). Following that lead, the current study sought to examine the effects of GPR88 loss in mice on food-seeking behavior.

In an effort to vary the effort needed to find food in the laboratory setting, the researchers trained mice to press a lever to receive a food pellet reward. Mice lacking GPR88 were slower to learn to lever press, but by the end of training the groups were indistinguishable, including in a progressive ratio lever-pressing paradigm and a test where one of two available levers did not deliver a reward pellet. Wild-type and knockout mice also both preferred a lever that delivered more nutrient-dense pellets. The groups differed, however, when the effort required or the reward delivered varied. Compared with mice lacking GPR88, wild-type mice preferred a lever that delivered three pellets over a lever that delivered only one pellet, and they preferred a lever that required only three versus nine lever presses to deliver food. Viral delivery of a *Gpr88* rescue gene to the dorsal striatum normalized those differences, indicating a role for GPR88 in striatal processing of cost-benefit analysis in food acquisition.

This Week in The Journal was written by Stephani Sutherland, Ph.D.