This Week in The Journal

Stable Chloride Microdomains Set Potential of GABA channels

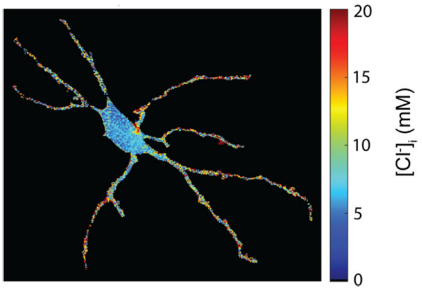
Negah Rahmati, Kieran P. Normoyle, Joseph Glykys, Volodymyr I. Dzhala, Kyle P. Lillis, et al.

(see pages 4957–4975)

GABAergic receptors form the cornerstone of inhibitory synaptic signaling in the brain. Classically, ionotropic $GABA_A$ receptors pass inward chloride-dominated currents, effectively dampening neural activity by stabilizing or hyperpolarizing the cell's membrane potential. A more positive reversal potential could lead to loss of inhibition or, in some circumstances, even tip GABA's effect toward neural excitation. The direction of current—and its effect on the cell—depends on the balance of chloride ions on either side of the membrane, which is generally thought to be consistent throughout a given cell. But for years, researchers have reported a range of reversal potentials through $GABA_A$ channels. Now Rahmati, Normoyle, et al. definitively show that the variation depends on stable intracellular chloride microdomains that arise from variations in structural anionic biopolymers such as the cytoplasmic protein actin.

The authors used an array of techniques to measure chloride concentration in hippocampal pyramidal neurons, including two-photon microscopy of ratiometric, transgenic chloride-sensitive fluorophores, and fluorescence lifetime imaging of chloride-sensitive dyes. Fluorophore imaging indicated that subcellular concentration of chloride varied significantly across a single neuron, and that these microdomains remained stable over time, even following a large transient chloride flux. In addition, the authors made electrophysiological recordings from an individual pyramidal cell while stimulating presynaptic interneurons, each of which made a synapse on the same pyramidal neuron. Remarkably, each interneuron evoked GABAergic currents with unique chloride reversal potentials over a 23 mV range.

Although chloride microdomains have been investigated for decades, inquiry has often centered around the impact of ion transporters on chloride equilibrium. But here, the authors follow up on their 2014 finding that impermeant ions, such as those locked up in polymers, contribute to chloride homeostasis. In the current study, the researchers imaged single hippocampal neurons while blocking the cation–chloride cotransporters (CCCs) NKCC1 and KCC2 and saw no effect on the chloride microdomain distribution, suggesting they were not determined by local variations in cation–chloride transport rates. When they manipulated actin dynamics to favor depolymerization, however, microdomains were disrupted, presumably due to reorganization of the large, negatively charged macromolecules. The microdomains allow a single neuron to respond differently to multiple GABAergic interneurons and perhaps to each individual synaptic input. The consequence could be a functional expansion of GABA signaling to include not only hyperpolarization but potentially amplification of excitatory signals.



Resolution of subcellular chloride microdomains in a hippocampal neuron.

Dietary Protein Preference Reflected in VTA Activity

Giulia Chiacchierini, Fabien Naneix, Kate Zara Peters, John Apergis-Schoute, Eelke Mirthe Simone Snoeren, et al.

(see pages 5080–5092)

Protein intake is critical to the health and survival of animals, as some amino acids needed for cellular functions cannot be made by the body. Paradoxically, a dearth of dietary protein can lead to obesity due to increased caloric intake. Rodents on a low-protein diet develop a strong preference for protein over carbs, but the neural links between dietary protein and feeding behaviors remain unknown. Now, Chiacchierini, Naneix et al. wanted to trace the neural substrates of behavioral control of protein intake. A logical neural substrate was the ventral tegmental area (VTA), a midbrain structure known to participate in controlling feeding behaviors including food preferences. To test that, the authors used fiber photometry, which uses calcium imaging as a proxy for neuronal firing, to track neural activity in the VTA in rats fed varying levels of dietary protein.

The researchers injected rats in the VTA with a virus expressing the calcium-sensitive fluorescent protein GCamP6s under control of the synapsin promoter to confer neuronal specificity, then implanted the VTA with an optic fiber. Some rats were then switched from a normal, 14% protein diet to a protein-restricted diet (PR) containing 5% casein. Rats were trained to distinguish between flavored liquids containing either casein (protein) or maltodextrin (carbohydrate); the researchers then recorded VTA activity while the rats drank either solution. Rats on the nonrestricted diet showed no difference in VTA activity while sipping the casein or maltodextrin, but in PR rats, VTA responses were higher while sipping protein compared to carbohydrate. When the rats were presented with both liquids at once, PR rats showed a strong preference for casein, whereas control rats did not.

When rats' diets were switched from nonrestricted to PR, they rapidly developed a preference for the protein solution, given a choice. Conversely, the protein preference subsided over several weeks in rats switched from PR to a nonrestricted diet. Interestingly, the VTA activity associated with protein status lagged behind the change in preference, leaving a sort of dietary imprint on the brain. It remains unclear whether the VTA activity plays a causal role in protein-seeking behavior, but the authors suggest it may reflect the reward value of each food to help guide choices.

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