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This Week in The Journal

Kainate Receptor GluK1$_b$ Subunit Interacts with Gαo

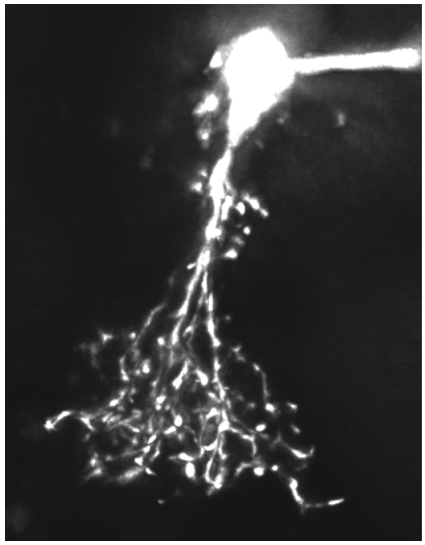
Izabela Rutkowska-Wlodarczyk, M. Isabel Aller, Sergio Valbuena, Jean-Charles Bologna, Laurent Prézeau, et al.

(see pages 5171–5179)

Kainate receptors (KARs) have the structure of ionotropic glutamate receptors, but unlike AMPA and NMDA receptors, KARs can activate metabotropic signaling as well as passing ionic current. Several metabotropic effects of KARs have been demonstrated, including inhibition of voltage-sensitive calcium channels, inhibition of glutamate and GABA release, and inhibition of the slow afterhyperpolarization current (I_{AHP}). All these effects are blocked by pertussis toxin and involve phospholipase C, suggesting they are mediated by Go proteins, but how KARs activate G-proteins has remained an open question.

To answer this question, Rutkowska-Wlodarczyk et al. performed a proteomic analysis on mouse brain homogenates and identified proteins that interacted with the intracellular C-terminal portion of GluK1$_b$, a KAR subunit. They found 22 proteins that specifically interacted with GluK1$_b$, including the α subunit of Go. When coexpressed in neuroblastoma cells, GluK1$_b$ and Gαo were partially colocalized. Furthermore, fluorescence was reconstituted when cells were transfected with the C- and N-terminal fragments of yellow fluorescent protein fused to Gαo and GluK1$_b$, respectively, indicating that Gαo and GluK1$_b$ are closely apposed *in vivo*. Additional experiments using bioluminescence resonance energy transfer demonstrated that glutamate activated Go in GluK1$_b$-expressing HEK cells. Finally, kainate-induced reduction of I_{AHP} in dissociated mouse dorsal root ganglion (DRG) neurons was abolished by knocking out GluK1, but not by knocking out GluK5, the only other KAR subunit expressed in these cells.

These data strongly suggest that direct interaction between GluK1$_b$ and Gαo underlies KAR metabotropic signaling, at least in DRG neurons. How this interaction activates Gαo remains puzzling, given that the structure of GluK1$_b$ is unlike that of other G-protein-coupled receptors. Moreover, what determines whether ionotropic or metabotropic signaling dominates in a given setting remains unknown. Defining the interaction domains of GluK1$_b$ and Gαo and identifying other interacting proteins should help to answer these questions.



An AII amacrine cell recorded in a retinal slice. The frequency of spontaneous EPSCs in these cells is elevated in diabetic rats. See the article by Castilho et al. for details.

Hyperglycemia Reduces Inhibitory Feedback to Rod Bipolar Cells

Áurea Castilho, António F. Ambrósio, Espen Hartveit, and Margaret L. Veruki

(see pages 5422–5433)

Retinopathy is common in people with diabetes, and diabetic retinopathy is the most common cause of blindness in young and middle-aged adults. Diabetic retinopathy was originally thought to stem from disruption of the microvasculature of the retina, but accumulating evidence indicates that hyperglycemia may directly alter retinal function. For example, electroretinographic recordings reveal changes in photoreceptor, bipolar cell, and amacrine cell responses before microvascular damage is detected in diabetic patients, as well as in a rat model of type 1 diabetes. Such studies have also suggested that the rod pathway is particularly sensitive to hyperglycemic insult.

To investigate the cellular and molecular basis of diabetic retinopathy, Castilho et al. recorded from rod-pathway cells in retinal slices from rats made diabetic by administering a toxin that targets pancreatic insulin-producing cells. They examined a microcircuit comprising rod bipolar cells (RBCs) and their postsynaptic targets: AII amacrine cells, which convey information from rods to cone bipolar cells; and A17 amacrine cells, which provide GABAergic inhibitory feedback to RBCs. An increase in the frequency of spontaneous EPSCs (sEPSCs) in AII and A17 amacrine cells suggested that release of glutamate from RBCs was elevated in retinas from diabetic rats. The increase in sEPSC frequency in AII amacrines was replicated in control retinas by inhibiting $GABA_C$ receptors or blocking feedback inhibition from A17 cells to RBCs. Because these blockers did not further increase sEPSC frequency in retinas from diabetic rats, loss of A17-mediated tonic inhibition of RBCs likely underlies the increased sEPSC frequency in diabetic animals. Thus, despite increased excitatory input, the inhibitory output of A17 amacrine cells appeared to be reduced. This was attributable to a decrease in the single-channel conductance of AMPA receptors and decreased glutamate-induced calcium influx in A17 amacrines.

Together, these results suggest that loss of insulin and/or the resulting hyperglycemia reduces the expression of calcium-permeable AMPA receptors in A17 amacrine cells, thus reducing GABA release and inhibitory feedback to RBCs. Disruption of this microcircuit may contribute to early visual disturbances in diabetics. What other retinal cells are affected in the early stages of diabetes and how hyperglycemia might drive such changes remain to be determined.

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

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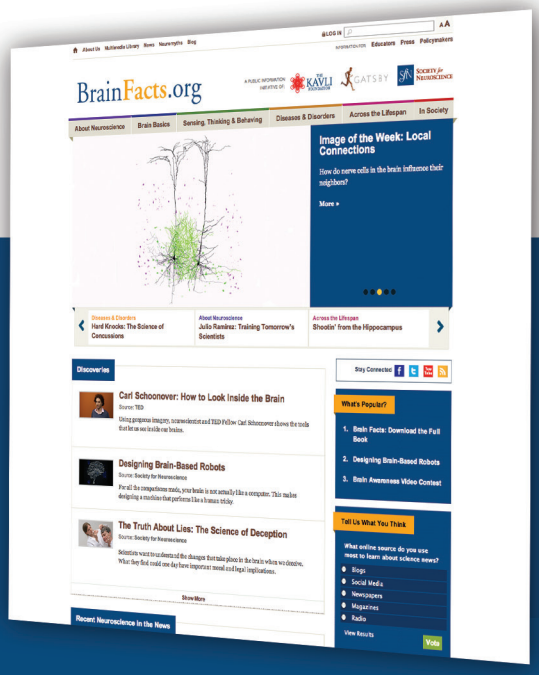

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