Generally Physiological

Of ghrelin, cone cultivation, dinoflagellate eyes, and the cyanobacterial circadian clock

This month’s installment of Generally Physiological considers inhibition of calcium channels through distinct agonist-dependent and -independent GHSR1a pathways, how rods support cone survival, the complex origins of a chimeric “eye” in a unicellular eukaryote, and the role of a metamorphic protein in the cyanobacterial circadian clock.

Inhibiting presynaptic calcium channels

Ghrelin, the only known orexigenic peptide, signals through GHSR1a (growth hormone secretagogue receptor type 1a), a GPCR with high constitutive activity, to modulate neurotransmitter release from presynaptic nerve terminals. In this issue, noting that activation of various GPCRs leads to the inhibition of presynaptic voltage-gated calcium channels (see Weiss and Zamponi), López Soto et al. explored the effects of constitutive and ghrelin-dependent GHSR1a signaling on Ca\textsubscript{2.1} and Ca\textsubscript{2.2} function in primary cultures of hypothalamic neurons and when heterologously expressed in HEK 293 cells. Intriguingly, they found that, although both constitutive and agonist-dependent GHSR1a signaling inhibited Ca\textsubscript{2.1} and Ca\textsubscript{2.2} activity, they did so through distinct mechanisms involving different signaling pathways. Whereas ghrelin signaled through a G\textsubscript{4} pathway to rapidly and reversibly inhibit Ca\textsubscript{2} currents, constitutive GHSR1a signaling led to a long-lasting inhibition of current associated with a decrease in the surface expression of Ca\textsubscript{2.1} and Ca\textsubscript{2.2} through a pathway involving G\textsubscript{i/o}. Both constitutive and agonist-dependent GHSR1a signaling decreased GABA release from hypothalamic neurons, suggesting that GHSR1a signaling could promote the disinhibition (and thereby the activation) of postsynaptic neurons.

Cone cultivation

Although the rods and cones of the human retina serve different functions, with the rods mediating image-forming vision in dim light and the cones required for high resolution color vision, the two classes of photoreceptors are interdependent. Thus, loss of rods in the genetic disorder retinitis pigmentosa leads to the subsequent degeneration of cones and thereby to blindness. Lack of rod-derived cone viability factor (RdCVF) contributes to cone degeneration; however, the mechanism whereby RdCVF promotes cone viability has been unknown (see Krol and Roska, 2015). Aït-Ali et al. (2015) used far-Western analysis of cone-enriched cultures from chicken embryos to identify the transmembrane protein basigin-1 as binding to RdCVF, and then determined that silencing basigin-1 decreased RdCVF-mediated cone survival. The glucose transporter GLUT1 communoprecipitated with basigin-1 from chicken retina, and FRET analysis of labeled GLUT1 and basigin-1 confirmed their interaction. RdCVF stimulated basigin-1-dependent glucose uptake, and increasing the extracellular glucose concentration (from 15 to 30 mM) enhanced RdCVF-mediated cone survival. RdCVF increased intracellular ATP concentration and, intriguingly, pharmacological analysis indicated that this involved stimulation of aerobic glycolysis. The authors thus propose that RdCVF promotes cone survival by signaling through basigin-1 to enhance glucose uptake and aerobic glycolysis.
Keeping an eye on dinoflagellates

Remarkably, the complex, multicellular structure that makes up the “camera-type” vertebrate eye is echoed by the eye-like ocelloids of the unicellular warnowiid dinoflagellates, with components analogous to the cornea, the lens, and the retina. Gavelis et al. (2015) combined single-cell and single-organelle genomics with electron microscopy to determine that the ocelloid is, in fact, a complex structure incorporating components with endogenous origins and organelles with distinct endosymbiotic origins. Intriguingly, both endosymbiotic components are repurposed from organelles known chiefly for their roles in metabolism. Thus, the ocelloid “cornea” is formed from mitochondria, and the ocelloid “retina” is made up of anastomosing plasmids (originating through endosymbiosis with a red alga). In a thoughtful commentary, Richards and Gomes (2015) consider the evolutionary context of the work, discussing other eukaryotic microorganisms with eye-like structures.

A folding clock?

The circadian clock in cyanobacteria depends on an oscillator comprised of three proteins, KaiA, KaiB, and the ATPase KaiC, which interact to give rise to a circadian cycle of KaiC phosphorylation: KaiA promotes KaiC (auto)phosphorylation, whereas KaiB inhibits KaiA and promotes KaiC (auto)dephosphorylation. Chang et al. (2015) determined that, when bound to KaiC, the secondary structure of KaiB (βαββαβα, defined as the folded-switched state, fsKaiB) was distinct from that in free solution (βαββααβ, defined as the ground state, gsKaiB), identifying KaiB as a metamorphic protein, a rare class of proteins that reversibly switch between different folded conformations under native conditions. A KaiB mutant with increased propensity to assume the fsKaiB form bound to the KaiB-binding domain of KaiC far more rapidly than wild-type KaiB did and disrupted KaiC phosphorylation rhythms in vitro and in cyanobacterial reporter strains. In addition to its role in determining KaiC phosphorylation status, KaiB also regulates the antagonistic clock output enzymes SasA and GkA, competing with SasA for binding to KaiC. SasA is stimulated by binding to KaiC, and KaiB variants that favored the fsKaiB conformation decreased SasA signaling and increased GkA signaling. The authors thus propose that the rare transition to fsKaiB enables its binding to KaiC, enabling the inhibition of KaiA to initiate KaiC dephosphorylation, and outcompeting SasA to link timekeeping with output in the cyanobacterial circadian clock. In a separate study by a different group, Abe et al. (2015) explored the role of the slow ATPase activity of KaiC in determining the frequency of the cyanobacterial circadian clock.

Elizabeth M. Adler
Executive Editor, JGP
eadler@rockefeller.edu

REFERENCES


The warnowiid dinoflagellate ocelloid is a complex structure, made up of components with endogenous and distinct endosymbiotic origins. (Reprinted by permission from Macmillan Publishers, Ltd. T.A. Richards and S.L. Gomes. Nature. http://dx.doi.org/10.1038/nature14630, copyright 2015.)

Model for KaiB fold switching in linking timekeeping and output of the cyanobacterial circadian clock. (From Chang et al. 2015. Science. http://dx.doi.org/10.1126/science.1260031. Reprinted with permission from AAAS.)

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