Generally Physiological

Of BK regulation, repurposed taste receptors, and arrestin recruitment

This month's installment of *Generally Physiological* considers the effects of the BK β2 subunit on chromaffin cell firing properties, how hummingbirds taste nectar, and arrestin recruitment to G protein–coupled receptors (GPCRs).

Of BK and bursting behavior

Large conductance calcium- and voltage-activated potassium (BK) channels are found in numerous tissues, where they serve distinct physiological functions. Splice variants of the pore-forming BK α subunit, which are subject to distinct posttranslational modifications, and its regulation by various auxiliary subunits contribute to the functional diversity of BK channels and complicate our ability to understand the role they play in any given cellular context. In this issue, Martinez-Espinosa et al. used mice lacking the BK β2 subunit (β2 KO mice) to explore the functions of BK channels bearing this subunit in adrenal chromaffin cells. BK channels can mediate either predominantly inactivating currents or largely noninactivating currents in chromaffin cells, properties thought to depend on variable expression of the β2 subunit (which not only mediates BK inactivation but also shifts its gating to more negative potentials). Martinez-Espinosa et al. (2014) analyzed current and firing properties of chromaffin cells from wild-type mice and β2 KO mice and determined that BK inactivation was abolished in the latter. The ability of chromaffin cells to fire repetitively in response to constant current injection was reduced with loss of β2, consistent with the predicted effects of the shift in BK gating on BK activation and recovery of Na^+ channels from inactivation. Unexpectedly, however, loss of β2 was associated with an increase in spontaneous burst firing, an observation which enabled the authors to make the intriguing proposal that loss (or down-regulation) of β2 might decrease evoked secretion of catecholamines but, paradoxically, enhance basal release.

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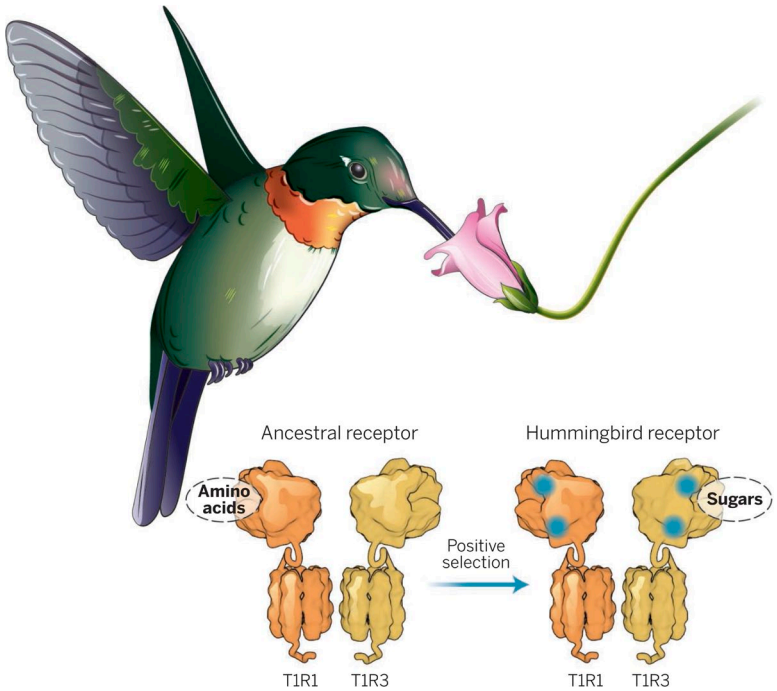
Sweet or savory?

T1R GPCRs mediate sweet and savory taste in vertebrates, with the T1R1–T1R3 heterodimer acting as the savory (umami) taste receptor and the T1R2–T1R3 sensing sweet tastes. Thus, many obligate carnivores, like cats, lack T1R2 and do not consume glucose, sucrose, or fructose (see Jiang and Beauchamp [2014]). Similarly, chickens and turkeys, which also lack T1R2, fail to show a preference for sugars, leading Baldwin et al. (2014) to wonder about the mechanisms underlying sugar perception in

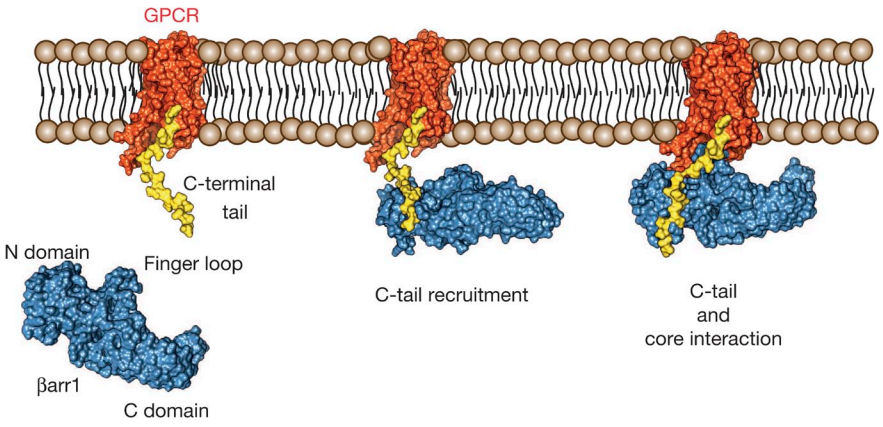


The hummingbird T1R1–T1R3 receptor mediates the response to sweet tastes, having evolved from the T1R1–T1R3 receptor for amino acids. (From P. Jiang, G.K. Beauchamp, *SCIENCE* 345:878 (2014). ILLUSTRATION: V. ALTOUNIAN/*SCIENCE*.)

birds that subsist on a sugar-rich diet (such as hummingbirds). Having identified genes encoding T1R1 and T1R3 but not T1R2 in whole-genome analyses of 10 birds with different diets, Baldwin et al. (2014) cloned T1R receptors from chickens, hummingbirds, and swifts and used a heterologous expression system to determine their responses to sugars and amino acids. Whereas T1R1–T1R3 heterodimers from chickens and swifts (insectivorous birds closely related to hummingbirds), like those from primates, rodents, and fish, responded to amino acids but not sugars, hummingbird T1R1–T1R3 responded to such carbohydrates as glucose, sucrose, and fructose. Moreover, preference assays indicated that the molecular recognition properties of hummingbird T1R1–T1R3 were important for hummingbird taste behaviors. Analyses of hummingbird–chicken T1R3 chimeras identified 19 nonconsecutive amino acid residues from the extracellular "Venus flytrap" ligand-binding domain as sufficient to confer sensitivity to sucrose. Two of these sites showed evidence of positive selection, and three were in the putative ligand-binding pocket. The authors thus conclude that hummingbirds have evolved a new sugar receptor, thereby regaining the ability to perceive sweet tastes.

Recruiting β-arrestins

Although named for their relationship with G proteins, GPCRs also interact with the β-arrestins, which desensitize receptor signaling through G proteins and also transduce a G protein–independent signaling pathway. Recent structural data has provided insight into GPCR activation; the structural bases of β-arrestin recruitment, however, remain less well understood. After obtaining a stable complex of a β_2 adrenergic receptor chimera (β_2V_2R) bound in a functional conformation to β-arrestin 1, Shukla et al. (2014) used chemical cross-linking in combination with single-particle negative-stain electron microscopy and hydrogen–deuterium exchange mass spectrometry to visualize the complex and characterize GPCR–β-arrestin 1 interactions. They concluded that arrestin engagement involves a biphasic mechanism, involving an initial interaction between the N-terminal domain of arrestin and the phosphorylated C-terminal domain of the GPCR. This initial recruitment enables a second interaction, involving the arrestin finger loop and the GPCR core, leading to a longitudinal arrangement of arrestin on the cytoplasmic side of the receptor that would block its interaction with G proteins and thereby induce desensitization.



Model for GPCR recruitment of β-arrestin 1 (βarr1). GPCR, orange; phosphorylated C-terminal tail, yellow; β-arrestin 1, blue (Reprinted by permission from Macmillan Publishers, Ltd. A.K. Shukla et al. 2014. *Nature*. http://dx.doi.org/10.1038/nature13430, copyright 2014.)

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REFERENCES

Baldwin, M.W., et al. 2014. *Science.* 345:929–933. http://dx.doi.org/10.1126/science.1255097

Jiang, P., and G.K. Beauchamp. 2014. *Science.* 345:878–879. http://dx.doi.org/10.1126/science.1259175

Martinez-Espinosa, P.L., et al. 2014. *J. Gen. Physiol.* 144:275–295. http://dx.doi.org/10.1085/jgp.201411253

Shukla, A.K., et al. 2014. *Nature.* 512:218–222. http://dx.doi.org/10.1038/nature13430