Generally Physiological

Of antisense, antibodies, K⁺ channels, and jejunal metabolism

This month’s installment of Generally Physiological focuses on endogenous regulation of K⁺ channels by antisense, K⁺ channel targeting by antibodies, and the effects of gastric bypass surgery on metabolism.

Is antisense regulation of Kcna2 a pain?
A decrease in the abundance of voltage-dependent K⁺ channels in dorsal root ganglion (DRG) neurons can result in enhanced excitability and aberrant firing, contributing to neuropathic pain after peripheral nerve injury (see Han and Jan, 2013). But why should nerve injury decrease K⁺ channel expression? Noting that long noncoding RNAs have been implicated in the regulation of gene expression, Zhao et al. (2013) determined that the DRG of various mammals contained long noncoding RNA transcripts (Kcna2 antisense RNA) complementary to the RNA encoding the voltage-dependent potassium channel Kcna2. In situ hybridization revealed that expression of Kcna2 antisense RNA increased after nerve injury, whereas that of Kcna2 mRNA and Kcna2 decreased. Further analysis indicated that nerve injury increased abundance of the transcriptional activator MZF1, which bound to a consensus sequence found in the Kcna2 antisense RNA gene promoter but not that of the Kcna2 gene, to stimulate Kcna2 antisense RNA expression. Overexpression of Kcna2 antisense RNA decreased expression of DRG Kcna2 mRNA and protein and increased the excitability of large- and medium-sized DRG neurons. Moreover, Kcna2 antisense RNA promoted hypersensitivity to mechanical stimuli and cold in mice (indicative of neuropathic pain), whereas a Kcna2 sense fragment that blocked nerve injury–induced increase in Kcna2 antisense RNA and the accompanying decrease in Kcna2 mRNA and protein attenuated such hypersensitivity. Thus, the authors conclude that Kcna2 antisense RNA represents an endogenous regulator of the Kcna2 channel in DRG and a potential target in the therapy of neuropathic pain.

Targeting K⁺ channels with antibodies
Kcna2 is only one of the many voltage-gated K⁺ (Kv) channels present in electrically excitable cells. Although the different Kv channel subtypes have distinct subcellular distributions and functional properties, the lack of subtype-selective inhibitors has made teasing out their specific contributions to cellular physiology—and pathophysiology—a challenge. In this issue, in an ingenious approach to this problem, Sack et al. attached a porphyrin moieties to a monoclonal antibody directed against an epitope on the external face of the Kv4.2 channel to create an immunotoxin selectively targeted to Kv4.2. The unconjugated antibody did not itself inhibit Kv4.2 current; however, patch-clamp analysis of cells heterologously expressing Kv channels indicated...
that, after incubation with the antibody–porphyrin conjugate, photostimulation irreversibly inhibited Kv4.2 current. Although photostimulation produced some collateral damage, the specificity for Kv4.2 over Kv4.3 or Kv2.1 was greater than that achieved with other methods currently in use. Moreover, the study by Sack et al. (2013) provides proof-of-principle of a viable technique for using monoclonal antibodies to selectively target and inhibit individual Kv channel subtypes.

Rerouting glucose metabolism
Gastric bypass surgery provides an effective approach to treating obesity-related diabetes and, remarkably, glucose homeostasis improves even before substantial weight loss has taken place. In the Roux-en-Y gastric bypass (RYGB) procedure, the gut is reconfigured so that food passes directly from a small gastric pouch to the jejunum, bypassing the duodenum and most of the stomach. Thus, the jejunal segment attached to the gastric pouch (called the Roux limb) is exposed to undigested food that would not normally make its way to this part of the intestine (see Berthoud, 2013). Noting that rodent and human studies have indicated that the Roux limb undergoes hypertrophy and hyperplasia, Saeidi et al. (2013) used a rat model of RYGB to investigate the mechanism of enhanced glycemic control. Comparisons of the metabolic profile and patterns of gene and protein expression of the Roux limb compared with that in sham-operated rats indicated that the Roux limb underwent metabolic reprogramming of glucose metabolism, consistent with increased anabolic demands associated with the increased growth of the reconfigured segment. Positron emission tomography-computed tomography (PET/CT) scanning using 2-deoxy-2-[18F]fluoro-d-glucose ([18F]FDG) indicated that there was an increase in intestinal glucose uptake, and biodistribution analysis indicated that, after RYGB, the intestine became a major tissue for glucose use. Experiments in which a section of jejunum was interposed between the esophagus and stomach (without the other anatomical changes involved in RYGB) were consistent with the hypothesis that the morphological and metabolic changes found with RYGB were triggered by exposure of the Roux limb to undigested nutrients. The authors thus propose that morphological and metabolic changes in the Roux limb secondary to exposure to undigested food contribute to the improvement in glycemic control after gastric bypass surgery.

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REFERENCES