Endo-neuro-endocrine incretin pathways

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IN RESPONSE TO NUTRIENT INTAKE, glucagon-like peptide-1 (GLP-1) is secreted from endocrine cells in gastrointestinal mucosa primarily in the distal ileum and colon (3). Numerous actions of GLP-1 have been described, including reduction of blood glucose via several complementary mechanisms and inhibition of gastric emptying. Several recent reviews discuss these actions in some detail (3–7, 10).

Messenger RNA and GLP-1 peptide are also found in several locations in the central nervous system (8, 9, 11). Centrally, GLP-1 is believed to act as a neurotransmitter, and it forms part of one or more anorexigenic circuits (8, 9, 11). Most often, however, GLP-1 is considered as an incretin—a hormone released from the gut that augments postprandial, glucose-induced insulin secretion and glucose disposal (10).

With respect to the incretin function of GLP-1, there are several issues that are not well understood. For instance, how does GLP-1, which has a short half-life and is secreted into the hepatic portal circulation, convey signals to β-cells in the pancreas? Certainly β-cells possess GLP-1 receptors, but how does the peptide get there in sufficient amounts? One obvious possibility is that the effect of GLP-1 to augment insulin secretion is neurally mediated. This possibility was tested several years ago by Balkan and Li (2), who showed in rats that ganglionic blockade, but not muscarinic blockade, inhibited augmentation of insulin secretion when both glucose and GLP-1 were given into the portal circulation. When GLP-1 was given intravenously, ganglionic blockade was no longer effective. Consequently the authors concluded that portal and peripheral GLP-1 activated different pathways leading to augmented insulin secretory response to a glucose load.

In this issue of the American Journal of Physiology- Regulatory, Integrative and Comparative Physiology, a paper by Ahren (1) reports studies using a complementary approach. Mice were subjected to gastrointestinal deafferentation by neonatal capsaicin and then were studied as adults. Threshold and saturating doses of GLP-1 were administered intravenously, and the results are consistent with dual endocrine-neural and endocrine signaling. Importantly, potential confounds such as β-cell desensitization by capsaicin and nonspecific responses to capsaicin were excluded by appropriate in vivo and in vitro control studies. By use of multiple doses, peripheral administration of GLP-1, and an extensive set of controls, this study has changed and increased our understanding of the regulation of glucose-induced insulin secretion by neurally and hormonally transduced signals from the gut.

REFERENCES