Glucagon-like peptide-1 (GLP-1): a piece of the incretin puzzle.

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Editorial

Endocrinology has a history of naming hormones for their biological action before they are isolated, with secretin and cholecystokinin as notable examples. Experimental support for incretin came from the finding that plasma insulin levels accompanying the oral intake of glucose were greater than those observed when glucose was given intravenously (1). The concept was extended to other food components and other islet hormones; with the general mechanism referred to as the entero–insular axis. Then the terms gluco-incretin, lipo-incretin, and amino-incretin emerged. Although neural mechanisms could contribute to the incretin phenomenon in some species, the effect is thought to be mainly hormonal. For example, pancreas transplants without innervation efficiently reverse the diabetic state.

The search for incretin has focused upon a variety of insulinotropic peptides of gut origin. Early candidates included secretin, gastrin-releasing peptide, vasoactive intestinal peptide and cholecystokinin, but none of these appear to be active at physiological concentrations. Glucose-dependent insulinotropic polypeptide (GIP), also known as gastric inhibitory peptide, continues to be an important incretin candidate (2). GIP, which is present in the duodenum and upper jejunum, is released into plasma by the oral intake of glucose or fatty acids. Moreover, concentrations of GIP in the physiological range can stimulate insulin secretion.

Recently, glucagon-like peptide-1 (GLP-1) has emerged as another major incretin candidate. The cloning of the glucagon gene provided the surprising information that the glucagon prohormone contains two glucagon-like peptides, GLP-1 and GLP-2. There are two truncated forms, GLP-1 (7-37) and GLP-1 (7-36) amide, which for simplicity's sake are both called GLP-1. Both have been found to be remarkably potent insulin secretagogues. The predominate truncated form in plasma is the 7-36 amide, which mostly comes from the L cells of the distal ileum and colon; the mechanisms that cleave proglucagon in pancreatic alpha cells appear to make little, if any, GLP-1. In 1987, a study in humans provided evidence that physiological levels of GLP-1 achieved during eating were insulinotropic (3). An unavoidable weakness of the study was uncertainty about which GLP-1 species were recognized by the radioimmunoassay, a problem which still plagues the field. In this issue of *The Journal,* Wang and co-workers from the same group in London provide an important advance, showing that the GLP-1 antagonist exendin (9-39) given to rats before a standard meal produces lower insulin levels and higher glucose levels (4). Exendin (9-39) is a fragment of a peptide found in venom of Gila monsters that binds tightly to the GLP-1 receptor without agonistic activity. Much work remains to be done before the relative contributions of GLP-1 and GIP to incretin or gluco-incretin activity in humans are established. The finding of GIP in the proximal gut and GLP-1 in the distal portions is difficult to make sense of, but there must be some kind of coordination of both the release of these peptides and their activation of insulin secretion.

The GLP-1 story continues to provide surprises and lessons. For example, the preoccupation with glucose as the dominant mediator of insulin secretion is evolving to the realization that real-life secretion with meals requires the complex coordination of multiple effectors. The beta cell is exposed to gradual and usually modest increases in glucose accompanied by rising concentrations of GLP-1 and GIP that presumably produce the critical increases in cyclic AMP required to potentiate the effects of glucose upon insulin secretion. Other secretagogues operating through different mechanisms must also be involved. An unexpected finding emerged when workers exploring the pharmacological effects of GLP-1 found that glucose uptake by muscle was enhanced through mechanisms other than increased insulin secretion (5). In addition, inhibition of gastric emptying has been demonstrated recently. These pharmacological effects may be important now that the possibility of using GLP-1 or an analogue as a drug to enhance insulin secretion in non–insulin-dependent diabetes mellitus is receiving so much attention (6).

The present study by Wang and co-workers (4) is an example of the fruits provided by advances in the fields of peptide chemistry and ligand–receptor interaction. The discovery of the receptor antagonist exendin (9-39) has produced a tool which provides strong evidence that GLP-1 has incretin activity in rodents. Hopefully, this tool can now be used in humans to define the insulinotropic and possible extrapancreatic effects of GLP-1. Also, because incretins have such obviously important effects upon islet secretion, pursuit of their possible contribution to the pathogenesis of non–insulin-dependent diabetes mellitus must continue. We can look forward to more pieces of the puzzle falling into place in the near future.

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