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EDITORIAL

Role of Incretins in Pancreas Growth and Development

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The incretin hormones (glucagon-like peptide 1: GLP-1; cholecystokinin: CCK; and glucose-dependent insulinotropic polypeptide: GIP) are released from endocrine cells in the distal ileum and the colon [1, 2, 3] in response to nutrient intake. GLP-1, GIP and CCK enhance insulin secretion from pancreatic beta cells and also contribute to maturation [4, 5, 6, 7, 8] of fetal beta cells.

GLP-1 is a peptide hormone, derived from post-translational processing of the proglucagon gene in the L cells of the small intestine. The cloning of the proglucagon gene has shown us that this glucagon pro-hormone contains two glucagon-like peptides; GLP-1 and GLP-2. Furthermore, there are two truncated forms of GLP-1; GLP-1 (7-37) and GLP-1 (7-36) amide, both of which are generally referred to as GLP-l. Both have been found to be potent insulin secretagogues which bind to a seven transmembrane domain, G-protein coupled receptor. The predominant truncated form in plasma is the 7-36 amide, which is produced by the L cells of the distal ileum and the colon. The mechanisms which cleave proglucagon to glucagon in pancreatic alpha-cells appear to make little, if any, GLP-1 peptide. Although it is not well understood how GLP-1, which has a very short half-life and is secreted into the hepatic portal circulation, convey signals to the beta cells in the pancreas, several possible mechanisms have been discussed [9, 10,11]. Studies in mice lacking receptors for incretin hormones [12, 13] have shown that incretins are involved in stimulation of insulin secretion from pancreatic beta cells, the inhibition of hepatic gluconeogenesis by suppression of glucagon secretion and the inhibition of gastrointestinal motility. GIP was first identified due to its effect on gastric acid secretion and therefore initially called 'gastric inhibitory polypeptide'. Only subsequently was it shown to stimulate insulin as well. When a nutrient passes through the gut, unlike intravenous glucose administration, humans secret more insulin. This gut-mediated augmentation of insulin secretion is referred to as the "incretin effect". Experiments in diabetic patients have shown a marked decrease of the gut-mediated augmentation of insulin secretion, suggesting that a defect in incretin response may contribute to the patho-physiology of type 2 diabetes. Intriguing evidence from animal models suggests a marked effect on beta cell proliferation and neogenesis. GLP-1 agonists have also been shown to reduce apoptosis in pancreatic beta cells [14, 15, 16].

CCK, another gastrointestinal peptide, plays important role in regulating exocrine pancreatic secretion, gallbladder contractility, gastrointestinal motility and neural modulation of appetite. The multiple actions of CCK are mediated by the G protein-coupled CCK receptor. CCK is produced by cells localized in the small intestine and has been shown to be important during the development and maturation of the pancreas [7, 17, 18]. CCK was originally purified from

the porcine intestine as a 33-amino acid peptide with an amidated carboxy-terminal pentapeptide (Gly-Trp-Asp-Met-Phe-NH2), which is identical to gastrin. Because of this high similarity between CCK and gastrin, each of these ligands is known to bind with either receptor. Therefore, it is also difficult to discriminate CCK using antibodies. Furthermore, gastrin circulates in the blood at concentrations which are 10 to 100 fold greater than CCK, thereby making it difficult to ascertain the circulating concentrations and the mechanism of action of these ligands. Since the discovery of CCK, many different molecular forms have been identified [reviewed in 19]. However, the CCK octapeptide (CCK-8), consisting of the carboxy terminal 8 amino acids of CCK, is the most biologically potent small peptide form of CCK. In this issue, Kuntz *et al*. demonstrate that CCK-8 can induce proliferation of islet beta cells leading to an increase in islet beta cell mass in mice [20]. Similar to this effect of CCK, GLP-1 (as well as exendin-4) has been shown to expand islet cell mass primarily by proliferation of the pre-existing islet cells. These studies demonstrate that incretin hormones have tremendous potential for studies which aim to increase the islet beta cell mass, especially in conditions of elevated glucose concentrations as discussed in this issue by Kuntz *et al*. [20]. Since recent studies in genetically engineered mice [21] have demonstrated that beta cells in adult mouse are generated primarily, if not exclusively, from pre-existing insulin-expressing cells and not largely from precursor/stem cells, studies that demonstrate mechanisms, which would influence proliferation of adult beta cells will help in regulating islet beta cell mass *in vivo* and *in vitr*o. Since incretin hormones have been known to be important in islet beta cell maturation as well as in proliferation, use of these incretins as supplements to *in vitro* cultures of islets and islet-progenitor cells may help us in obtaining better islet cell populations for transplantation in order to cure type 1 diabetes.

Keywords Cholecystokinin; Diabetes Mellitus, Type I; Diabetes Mellitus, Type II; Gastric Inhibitory Polypeptide; Islets of Langerhans

Abbreviations CCK: cholecystokinin; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide 1

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