CCK, gastrin and diabetes mellitus

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The classical concept of gastrointestinal hormones as being just local regulators of digestive juice secretion and gut motility has proven far too narrow and is now considered obsolete. Instead, the new biology suggests that gastrointestinal hormones should be viewed as general intercellular messengers in the body [1]. Both the hormones and their receptors are widely expressed also outside the digestive tract; and accordingly, gut hormones exert a large specter of regulatory functions all over the body after being secreted in multiple different ways from a variety of different cell types (e.g., endocrine, neurocrine, paracrine, myocrine, autocrine and spemioocrine secretion).

An extraintestinal function that has aroused particular interest is the effect of gastrointestinal hormones on growth and secretion from pancreatic islet cells. The interest is of cell biological and physiological nature, but it is heavily spurred by the question of its significance for the development and treatment of Type 1 and Type 2 diabetes mellitus. Today, the effect is called the incretin effect, and the gut hormones that stimulate insulin secretion are classified as incretins. An obvious question in this context is also whether insulinotropic gut hormones may serve as biomarkers for some type of diabetes mellitus.

The incretin idea is more than 110 years old, as Ernest Starling already, in 1905, suggested that secretin not only stimulates bicarbonate secretion from the exocrine pancreas,

but also hormone secretion from the endocrine pancreas [2]. The name ‘incretin’ was coined in 1932 by the Belgian physiologist Jean La Barre [3]. But incretin first became an operative concept after it became possible to measure insulin directly in plasma using radioimmunoassay technology in the 1960s. Thus, in 1964 McIntyre *et al.* and Elrick *et al.* were the first to show that oral glucose induced a considerably higher insulin response than intravenous glucose, even at similar blood glucose concentrations [4,5]. Hence, their results proved the existence of a gut hormonal mechanism that stimulated insulin secretion. In the following decades, the incretin interest gradually focused on two more recently discovered gut hormones: GIP and GLP-1. Today, incretin has essentially become synonymous with these two hormones [6,7], not least since GLP-1 analogs have become successful drugs in the treatment of Type 2 diabetes [8,9].

It is beyond doubt that GLP-1 and GIP are essential incretins. But there are nevertheless reasons to ask whether the two hormones alone can explain the entire incretin effect, and – consequently – whether other gastrointestinal hormones might deserve reconsideration as drug candidates in the treatment of both Type 1 and Type 2 diabetes mellitus [10]. The question addresses the fundamental understanding of the role of hormones in the digestive tract. We have to realize that none of the gut endocrine cells is collected in well-defined glandular struc-

Jens F Rehfeld

Department of Clinical Biochemistry,
Rigshospitalet, University of
Copenhagen, 9 Blegdamsvej, DK-
2100 Copenhagen, Denmark
Tel.: +45 354 530 18
Fax: +45 354 528 80
jens.f.rehfeld@regionh.dk

tures in mammals. On the contrary, the endocrine cells are spread throughout significant stretches in the gastrointestinal mucosa as single cells intermingled with, for instance, other endocrine cells. Sometimes the endocrine cells are spread in a gradient-like manner. Although, for example, somatostatin cells occur evenly throughout the stomach and the small intestinal mucosa, the gastrin cells have the highest density in the antral mucosa and in the proximal duodenum. But in fact gastrin cells are also present with low density in the jejunal and ileal mucosa. This illustrates why most or all gut hormones are released during food intake, often also for long periods (hours) in variable patterns.

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We have also to realize that gut hormones often interact with their effect on the target cells. The classic example is how CCK potentiates the effect of secretin on pancreatic bicarbonate secretion. The mechanism is through different receptors on the target-cell membrane, and subsequent intracellular crosstalk between different signal-transduction pathways. Many different gut hormones are expressed – as they are – in order to cope with the intake of food, which for most people come in meals of highly variable size and composition. The hormonal regulation of digestion also interacts with the dense neuronal network of the gut, where some neurons use gut hormonal peptides as transmitters, as well known for CCKs, neurotensins and tachykinins.

In relation to the incretin effect, a mixed meal with significant amounts of protein, fat and complex carbohydrates will release several more gut hormones than just GIP and GLP-1. Such a meal also releases considerable amounts of insulin, even though the blood glucose concentrations increase only slightly. As mentioned, however, the traditional way of measuring the incretin effect of gut hormones has, since 1964, been based on oral intake of a pure solution of plenty (50–75 g) of glucose. But that is an artificial and unphysiological way of evaluation. It contrasts strongly the daily intake of mixed meals that varies considerably with size and composition.

In addition, some gastrointestinal hormones other than GIP and GLP-1 have obvious connections with the growth and secretion from the endocrine pancreas. It may be in the form of specific receptors expressed on the islet-cell membranes; of intraislet occurrence of peptidergic neurons; and of additional gut hormone

containing cells in some stages of islet development, where the particular gut hormone may stimulate growth of, for instance, insulin cells in a paracrine manner [11–13].

Gastrin and CCK are examples of such other gut hormones with affinity for islet cell function. Human islet cells are well equipped with gastrin/CCK_B (~CCK₂) receptors [11,14]; gastrin is expressed in significant amounts of fetal and neonatal pancreatic islets [13]; and CCK peptides are present and presumably released from intraislet neurons [12]. Moreover, nesidioblastosis and increased insulin secretion have been found in patients with endogenous hypergastrinemia [15,16]; and exogenous CCK and gastrin peptides stimulate insulin secretion both with and without intravenous glucose [12,17]. A reason why CCK and gastrin – in spite of the described insulinotropic effect and the association with islet cells – have not been taken seriously as incretin candidates is probably the small release of gastrin and CCK after the unphysiological test, oral intake of pure glucose. But recently, they have nevertheless re-entered the scene of incretins.

In 2008, Suarez-Pinzon *et al.* [18] reported that treatment of nonobese diabetic mice with a combination of GLP-1 and gastrin stimulated islet cell growth and insulin secretion to an extent that completely restored normoglycemia. Nonobese diabetic mice are models of Type 1 diabetes, and the study revealed that the insulinotropic effects on the mice of GLP-1 and gastrin were negligible when they were administered separately. In combination, however, even with gastrin in very small doses, the incretin effect was remarkable. Since then, additional studies have confirmed the results of combining GLP-1 with gastrin or CCK peptides [19,20] in experimental treatment of Type 1 diabetes. Also proton-pump inhibitor-induced hypergastrinemia has been reported to improve glycemic control in patients with Type 2 diabetes [21], a result that of course requires confirmation. Anyway, gastrin and CCK are again in focus as candidates for drug development in a combinatorial treatment of diabetes mellitus.

Returning to the question of endogenous CCK and gastrin as biomarkers of some diabetes types, available evidence indicates so far that the secretion of CCK and gastrin in both the fasting state and after food intake is normal in Type 1 as well as Type 2 diabetes. But there is a remarkable shortage of detailed studies. We need further studies which should also examine patients with the effect of GLP-1 derived drugs on CCK and gastrin secretion in patients with Type 2 diabetes.

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