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Review

Glucagon-like peptides 1 and 2 in health and disease: A review

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ABSTRACT

The gut derived peptides, glucagon-like peptides 1 and 2 (GLP-1 and GLP-2), are secreted following nutrient ingestion. GLP-1 and another gut peptide, glucose-dependent insulinotropic polypeptide (GIP) are collectively referred to as 'incretin' hormones, and play an important role in glucose homeostasis. Incretin secretion shares a complex interdependent relationship with both postprandial glycemia and the rate of gastric emptying. GLP-1 based therapies are now well established in the management of type 2 diabetes, while recent literature has suggested potential applications to treat obesity and protect against cardiovascular and neurological disease. The mechanism of action of GLP-2 is not well understood, but it shows promise as an intestinotropic agent.

Contents

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1. Introduction

Glucagon-like peptides 1 and 2 (GLP-1 and GLP-2) are gut-derived peptides secreted from specialized entero-endocrine 'L' cells located predominantly in the distal small intestine and colon, following exposure to ingested nutrients. They share with glucagon a common precursor molecule, proglucagon, but exhibit a diverse range of functions, both complementary and divergent. GLP-1 was discovered only 30 years ago, but its actions are now exploited in the management of type 2 diabetes, with a number of GLP-1 based drugs on the market. Apart from its insulinotropic and glucagonostatic properties, GLP-1 influences the function of multiple organ systems; chief among these are effects on gastrointestinal motility, and likely cardio-protective and neuro-protective effects. GLP-2, on the other hand, has intestinotropic properties and is likely to be useful in the management of chronic intestinal disorders such as short bowel syndrome and possibly inflammatory bowel disease. This review provides an overview of various aspects of these important gut peptides and summarizes their role in health and disease.

2. Discovery of glucagon-like peptides

The discovery of glucagon-like peptides 1 and 2 (GLP-1 and GLP-2) was the result of a deliberate and protracted search to characterize the gastrointestinal factors involved in blood glucose homeostasis, and capitalized on scientific advances, including radioimmunoassays and gene sequencing. The work of Bayliss and Starling [7], Moore and Edie [39], and others in the early 1900s had hinted that factors derived from the intestinal mucosa played a role in determining glycemic control in both health and diabetes. La Barre reported in 1932 that an extract from duodenal mucosa lowered the blood glucose concentration in rabbits and dogs when given orally [70], although such an outcome is difficult to explain on the basis of current knowledge, given that peptides are rendered ineffective when given by mouth. He named the substance, 'incrétine' or 'incretin'.

In the subsequent decades, the role of the gastrointestinal tract in regulating glucose homeostasis was seriously undermined by the work of influential American researcher Ivy and co-workers [26]. They reported that infusing duodenal extracts intravenously or stimulating the small intestine with hydrochloric acid did not lower blood glucose concentrations in fasting animals [76–78]. However, in discrediting the 'incretin theory', they failed to appreciate a number of characteristics of an 'incretin' which were subsequently defined by Creutzfeldt [25] as: (1) secretion following ingestion of nutrients, especially glucose; (2) glucose-dependency, i.e. the glucose-lowering activity of the incretins persists only when blood glucose levels are elevated; and (3) that glucose-lowering by stimulation of insulin takes place at physiological concentrations achieved following ingestion of nutrients.

By the 1960s, it became possible to measure circulating insulin concentrations due to the development of specific and sensitive radioimmunoassay (RIA) techniques. In 1964, Mcintyre et al. [87] and Elrick et al. [42], working independently, renewed interest in the incretin concept by reporting that an oral glucose load considerably amplified the plasma insulin response, when compared to an intravenous glucose infusion that resulted in comparable blood glucose concentrations. This phenomenon is known as the 'incretin effect'.

In 1970, Brown and co-workers published a paper on the enterogastrone (i.e. inhibitory to gastric secretion and motility) properties of a gut-based peptide at supraphysiological levels, which they named 'gastric inhibitory polypeptide' (GIP) [15]. However, it was soon recognized that GIP had the capacity to stimulate insulin secretion at physiological doses, and it was renamed 'glucose-dependent insulinotropic polypeptide' [37]. GIP can be therefore considered the first known 'incretin' hormone [5].

In 1983, Ebert et al. showed persistence of more than 50% of the incretin effect in rats after complete removal of GIP by radioadsorption, and therefore predicted the existence of additional insulinotropic factors derived from the gut [38]. Around this time, with the aid of gene sequencing techniques, Lund et al. [82] and Bell et al. [9] sequenced the proglucagon gene in anglerfish and humans respectively; this gene was shown to encode not only the 29 amino acid peptide, glucagon, but also other smaller peptides, including glicentin, oxyntomodulin, intervening peptides and, importantly, two additional sequences bearing 50% homology to glucagon. These were named glucagon-like peptides 1 and 2 (GLP-1 and GLP-2). GLP-1 was shown to have considerable insulinotropic activity at physiological levels [69,131], and thus became the second known incretin. GLP-2 does not have insulinotropic activity [131], but has generated substantial interest as an intestinal growth factor [35].

3. Precursor gene and receptors

A single gene, the preproglucagon gene (Gcg), is responsible for the production of glucagon and glucagon-like peptides in mammals. It belongs to the group of genes encoding the hormones of the pituitary adenylate cyclase-activating polypeptide (PACAP)/glucagon superfamily – a group of nine bioactive peptides that also includes GIP and secretin. Gcg is located on the long arm of chromosome 2 (2q36-q37) and consists of six exon regions, with exons 3, 4 and 5 encoding for glucagon, GLP-1 and GLP-2 respectively [132]. Gcg, is thought to have undergone repeated exon duplication during mammalian evolution – it has been suggested that the origin of glucagon dates from some one billion years ago, while diversification 700 million years ago resulted in GLP-1 and GLP-2 [62]. Expression of Gcg is evident in a number of organs including the pancreas (alpha cells of the islets of Langerhans), intestine (entero-endocrine L cells, especially in the distal small intestine and the colon), and the central nervous system (caudal brainstem and hypothalamus) [32,96]. Transcription of Gcg results in a common messenger RNA (mRNA) for the three peptides [5].

Translation of the common mRNA results in a 180 amino acid precursor, proglucagon [152]. It is, however, at the post-translational stage that diversification takes place, resulting in organ-specific peptide profiles – while glucagon is the major peptide produced from proglucagon in the pancreas, glucagon-like peptides are produced in the intestine and brain. Prohormone convertase (PC) enzymes are responsible for this differential peptide profile [12,123]. In the pancreatic alpha cells, the enzyme PC 2 produces the end-products glucagon [124], intervening peptide-1, glicentin-related polypeptide, and major proglucagon fragment. While glucagon plays a well-described role in glucose homeostasis, none of the other peptides has a known role in human physiology. On the other hand, PC 1 and 3 acting in the intestinal L cells and in the central nervous system respectively result in the products GLP-1, GLP-2, intervening peptide 2 (IP-2), glicentin and oxyntomodulin [123]. Oxyntomodulin suppresses appetite and leads to weight loss in humans, and is capable of increasing the intrinsic heart rate in rats [136]. While glicentin has intestinotropic effects in rodents [99], there is no known physiological role for IP-2 (see Fig. 1). A recent study found increased PC 2 positive cells in intestinal biopsies of type 2 diabetes patients compared with healthy controls [67]. The authors have suggested that the gut, particularly in patients with type 2 diabetes, could be an additional source of glucagon aside from the pancreas. This finding needs further