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Review

Glucagon – Early breakthroughs and recent discoveries

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ABSTRACT

Glucagon was discovered in 1922 as a hyperglycemic factor in the pancreas. During its early history up to 1970, glucagon was shown to increase circulating glucose through stimulating glycogenolysis in the liver. It was also shown to be a constituent of islet non-β cells and to signal through G protein coupled receptors and cyclic AMP. Furthermore, its chemical characteristics, including amino acid sequence, and its processing from the preproglucagon gene had been established. During the modern research during the last 40 years, glucagon has been established as a key hormone in the regulation of glucose homeostasis, including a key role for the glucose counterregulation to hypoglycemia and for development of type 2 diabetes, and today glucagon is a potential target for treatment of the disease. Glucagon has also been shown to be a key factor beyond glucose control and involved in many processes. For the coming, future research, studies will be focused on α-cell biology beyond glucagon, hyperglucagonemia in other conditions than diabetes, its involvement in the regulation of body weight and energy expenditure and the potential of glucagon as a target for other diseases than type 2 diabetes, such as type 1 diabetes and obesity. This review summarizes the more than 90 years history of this important hormone as well as discusses potential future research regarding glucagon.

Contents

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Introduction

Glucagon has emerged as a key hormone for the regulation of glucose homeostasis and for development of type 2 diabetes, and glucagon is a potential target for treatment of the disease. Glucagon is also a key factor beyond glucose control and involved in many processes. Here the more than 90 years history of this important hormone is summarized along with the results of the modern glucagon science as well as outlook for the future research.

Early breakthroughs

Identification of glucagon

Following the discovery by von Mering and Minkowski that pancreatectomy results in hyperglycemia and diabetes in dogs [1] several researchers worked to isolate the putative antidiabetic factor in the pancreas. Murlin was one of those pioneers. He had started working in 1912 on aqueous extracts of the pancreas and showed, together with Kramer when they were working at the Cornell University Medical College, that when alkali was administered together with the pancreatic extracts to pancreatectomized dogs, urine glucose completely disappeared. After the move to University of Rochester, Murlin intensified his work in October 1921 [2]. He then found that, besides the glucose lowering ability of pancreatic extracts, pancreas contains also a factor which raises glucose. This discovery was performed in December 1922 when an extract was injected in two pancreatectomized dogs and found to raise blood sugar after three hours (from 21.1 to 32.8 mmol/l and from 7.8 to 21.7 mmol/l, respectively). The results were repeated four days later when the extract was injected in normal rabbits with similar results. It was therefore concluded that a hyperglycemic substance exists in the pancreas and this putative substance was named glucagon [3]. This name, however, was not used in general until the 1950s; in the meantime "the hyperglycemic factor of the pancreas" was more commonly used.

Characterization of glucagon effect and cellular origin

Studies in the 1930s and 1940s aimed at further characterizing the hyperglycemic effect of pancreatic extracts and it was shown that following intravenous injection, circulating glucose rose within a few minutes to reach a peak after 5–10 min. Then the glucose-lowering effect of insulin remaining in the extracts reduced glucose. Main effort in characterization of the glucagon effect was performed by Bürger and Brandt at Bonn University who also aimed at isolating glucagon from insulin in the preparations [4]. Although producing a partially purified extract with hyperglycemic property, Bürger and Brandt never succeeded to completely dissociate this factor from insulin and, in fact, concluded that insulin and glucagon must be closely related. Further studies by Sutherland and de Duve showed that the hyperglycemic factor of the pancreas stimulated glycogenolysis from liver slices in vitro and characterized the source of this factor [5]. They then found that its occurrence in the pancreas followed the distribution of islets and that it remained in pancreatic extracts from alloxan-treated animals. They thus presented evidence that glucagon is an islet hormone produced in non β-cells, using modern language, which is the basis of our present-day understanding of the islet topography with the glucagon producing α-cells in close apposition to the insulin-producing β-cells (Fig. 1). Both these researchers received the Nobel price; Sutherland in 1971 for the discovery of cyclic AMP and de Duve in 1974 for the discovery of lysosomes and other cell organelles.

Characterization of glucagon structure

During the 1950s attempts to isolate and characterize the structure of the hyperglycemic factor of the pancreas was intensified in the Lilly Research Laboratories in Indianapolis by a research group led by Staub. They successfully crystallized a pancreatic material for which they applied the name glucagon [6]; hereafter the name glucagon was used for a specific and identified factor. In later work, the purification and crystallization of glucagon was described in detail [7] and in 1957 the complete amino acid sequence of the hormone was reported [8].

Processing from the preproglucagon gene

In 1983, Bell and coworkers at the University of Chicago established the structure of the human preproglucagon gene [9]. The gene was found to encode proglucagon which consists of 160 amino acids and is expressed mainly in pancreatic α cells, in the gut L cells and in the brain. Later studies have established that these cells exhibit differential posttranslational processing of this prohormone. In the pancreatic α-cells, through the action of proconvertase 2, the main products are glucagon together with glucagon related

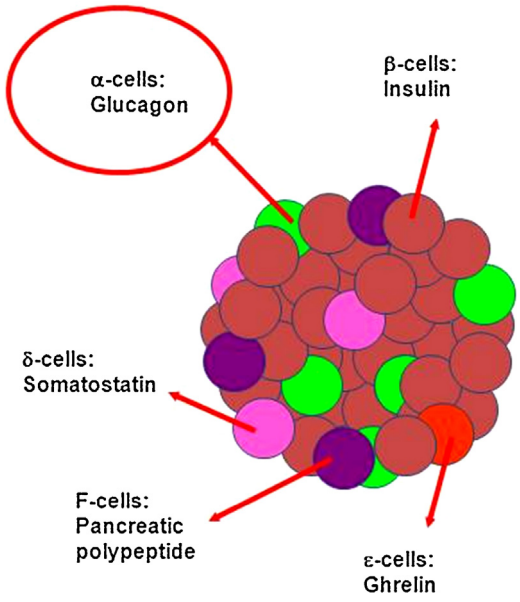

Fig. 1. Schematic view of pancreatic islet anatomy with the glucagon producing α-cells in close apposition to insulin-producing β-cells, somatostatin-producing δ-cells, pancreatic polypeptide producing F cells and ghrelin-producing ε-cells as based on comparative and developmental morphological studies [85].