Review Article

Historical Perspectives of Glucagon's Discovery and Early Research

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Abstract

This review article looks at the historical journey of the discovery of glucagon and the initial stages of research that paved the way for a comprehensive understanding of its physiological significance. Glucagon, an essential peptide hormone produced by the pancreas, plays a pivotal role in maintaining glucose homeostasis. Tracing the trajectory of its discovery from its initial identification to the unraveling of its complex functions, this article offers a detailed analysis of the early scientific endeavors, and collaborations that contributed to shaping our understanding of glucagon's pivotal role. By exploring the historical context, controversies, and advancements, this review sheds light on the evolution of endocrinological knowledge and its profound implications for diabetes research and treatment strategies.

Keywords: Diabetes, endocrinology, glucagon, glucose homeostasis, historical research, hormone discovery, insulin, pancreatic hormones, therapeutic applications

Introduction

Glucagon, an enigmatic subject of study, embarked on a journey marked by serendipity and scientific intrigue. It is interesting that Glucagon was actually identified from early insulin preparations as an impurity that caused, causing a surge in blood glucose levels and even increased mortality.[1,2] Kimball and Murlin christened the hormone as Glucagon (GLUCose-AGONist), embodying its capacity to elevate glucose levels in depancreatized dogs. But it took a quarter of a century before Sutherland and De Duve succeeded in purifying the elusive hormone.[3]

Glucagon is a 29-amino acid linear peptide hormone and it is emerged as a crucial regulator in the intricate balance of metabolic equilibrium. Principally secreted by the pancreatic α cells, it shares an ancestral lineage with GLP-1 and GLP-2, owing to their common precursor, proglucagon. This intriguing molecular relationship fuels the orchestration of metabolic processes that reverberate across multiple organ systems.

These peptides share substantial sequence similarity, collectively constituting the glucagon family—a distinctive subset within the secretin-glucagon superfamily. Amidst this familial framework, the foundational structure of glucagon is best known in vertebrates. Manifesting its

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role as the principal hyperglycemic hormone, glucagon orchestrates a delicate equilibrium alongside insulin. Its action includes the promotion of gluconeogenesis and glycogenolysis, leading to elevation in blood glucose levels. While its impact is most marked within the liver, the influence of glucagon extends to various bodily organs, including adipose tissue, pancreas, brain, and kidney.[4]

Glucagon's Unveiling: Pioneers of Discovery

The trajectory of glucagon research spans across several decades, tracing its roots back to a pivotal moment in medical history. In 1921, the discovery of insulin by Banting and Best came with an intriguing observation—pancreatic extracts wielded not just one, but a duality of hyperglycemic and hypoglycemic properties.[5]

Two years later, Murlin et al[6] carved a distinct identity for one of these properties. Isolating a pancreatic extract with hyperglycemic activity, they christened this entity "glucagon" (GLUCose-AGONist). This naming marked the inception of an endeavor that would unravel the intricate workings of a powerful hormone.

The year 1948 saw a monumental breakthrough. Sutherland and de Duve's efforts culminated in the isolation of glucagon within the pancreatic α-cells, providing a new layer of understanding to its intricate localization.[7] This milestone paved the way for deeper exploration, fueled by the establishment of the amino acid sequence of glucagon in 1956 by Bromer *et al.*[8]

The year 1959 ushered in yet another critical development—the inception of a radioimmunoassay for glucagon by Unger *et al.*[9] This innovation breathed life into quantification, enabling researchers to measure and comprehend the hormone's dynamic presence.

Glucagon, then became a subject of intense scrutiny. An ensemble of animal models—from mice and rats to dogs, pigs, and nonhuman primates— were studied in scientific research on the hormone. This led to outcomes across myriad animal models while the findings in humans accentuated the profound translational value of investigating glucagon's role in physiology.

Thus, the tale of glucagon research navigates a historical tapestry, embellished with key discoveries and innovations. A testament to the enduring intrigue of hormonal orchestration, this research journey underscores the profound impact of glucagon in the intricate narrative of human health.

Guardian of Glucose Equilibrium: Discovery of Glucagon's Essential Role

Embedded within the pancreatic islets, the A-cells, also known as α (alpha)-cells, give rise to a pivotal polypeptide hormone known as glucagon. This hormone's primary risk is in preventing a perilous plunge in blood glucose levels, thus safeguarding the delicate equilibrium that fuels our physiological processes.[10] Unlocking its therapeutic potential, glucagon emerges as an integral player, initially derived from the pancreases of bovines or pigs, and later synthesized through the alchemy of recombinant DNA.

Glucagon is secreted in response to hypoglycemia and its response is regulated by both endocrine and autonomic pathways.[10]

Glucagon also combines with adenylate cyclase leading to surge of glycogenolysis and gluconeogenesis within the hepatocytes.[11]

Simultaneously, the adipose tissue is activated when lipolysis is also summoned into action.[12]

The hormone's action extends beyond metabolism as it works on the smooth muscles with a rise in cyclic AMP.[13]

However, it's in the realm of therapeutic intervention that glucagon's impact truly resonates. In individuals with diabetes managed with insulin, glucagon's role is significant as it is the hormone that protects against hypoglycemia. The reversal of hypoglycemia, a perilous state often challenging diabetic individuals, finds its resolution through glucagon's intervention.

Unger[14] added further light on glucagon's role in the intricate web of metabolic perturbations. This understanding led to a new horizon—developing antagonists targeting the glucagon receptor.

Amid this canvas, peptidic antagonists like desHis1, desPhe6, and Glu9 glucagon amide step forward, as crafted by Ying *et al.* were of interest.[15]

However, the spotlight was soon seized by an even more riveting narrative—non-peptidic antagonists described by Madsen *et al.*,[16] Ladouceur *et al.*, thereby leading to further therapeutic innovation.[17]

In the ever-evolving tale of glucagon which is not just a hormone but a protagonist—glucagon is a guardian of balance and a beacon of hope for those grappling with the intricacies of diabetes. From its intricate biochemical footwork to its therapeutic potential, glucagon's narrative remains poised to play an increasingly bigger role in the management of diabetes and possibly weight reduction as triple agonist therapy in the form of retatrutide, etc.

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Conflicts of interest

There are no conflicts of interest.

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