Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(2)

Role of Glucagon in The Metabolic Response: Review

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ARTICLE INFO

Article history:
Received
10 November 2022

Accepted
28 February 2023

Manuscript ID:
JSOCMED-101122-22-3

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Historically, glucagon is the counter-regulatory hormone of insulin. Glucagon secretion is induced by fasting conditions or hypoglycaemia to increase glucose levels. Glucagon is the dominant product of alpha cells in the islet and was first identified in 1923 during an attempt to purify insulin, where it was identified as a contaminant hyperglycaemia factor. Further research determined that the hyperglycaemic action of glucagon is mediated by increased hepatic glycogenolysis and gluconeogenesis to increase endogenous glucose production. Insulin and glucagon as opposing hormones work together for glycaemic control. Diabetic hyperglycaemia is caused by increased impaired insulin action and inappropriately elevated glucagon levels. This review summarizes an important function of glucagon is its role as a regulator of glucose homeostasis. Increased plasma glucagon levels lead to increased hepatic glucose production. The balance between insulin and glucagon is responsible for maintaining euglycaemia conditions. In conditions of hypoglycaemia, increased glucagon secretion leads to increased hepatic glucose production through a number of cellular mechanisms including suppression of glycogenesis and glycolysis and stimulation of glycogenolysis and gluconeogenesis.

Keywords

Glucagon, Metabolic response, Hormone of insulin.

How to cite: Tona AI, Syukri M. Role of glucagon in the metabolic response. *Journal of Society Medicine*. 2023;2(2): 44-48. **DOI: https://doi.org/10.47353/jsocmed.v2i2.62**

INTRODUCTION

Glucagon is a peptide consisting of 29 amino acids with varied biological actions including glucose homeostasis. The GCG gene encodes the glucagon precursor proglucagon. Proglucagon consists of 160 amino acids and is expressed in certain neurons in the brainstem, intestinal L cells, and pancreatic alpha cells. Several bioactive peptides such as glucagon-like-peptide (GLP-1 and GLP-2) are cut from proglucagon by prohormone convertases at tissue-specific patterns. With prohormone convertase 2 (PC2) proglucagon is cut at pancreatic alpha cells to form glucagon [1].

Glucagon (proglucagon 33-61) results from the processing of proglucagon (PG-160) with prohormone convertase 2 (PC2) dependent. In the intestine, PG is processed by PC1/3 activity to form glycentine (1-69) which is further cleaved into pancreatic glycentine-related polypeptide (GRPP) and oxintomodulin (33-69). N-terminal direct antibodies will also cross-react with oxytomodulin where as C-terminal antibodies react with proglucagon 1-61 and finally antibodies developed against the central region of glucagon are potentially bound to all the aforementioned peptides. Measurement of glucagon may require a sandwich ELISA technique targeting both terminals (Fig. 1).

Glucagon is secreted in response to various metabolic signals such as changes in blood glucose concentrations, certain amino acids, and possibly free amino acids and in response to stress such as activation of the sympathetic nervous system. Glucagon receptor antagonists are used to lower blood glucose levels in patients with type 2 diabetes mellitus and glucagon co-agonists such as incretin hormone lose weight in patients with diabetes mellitus who are overweight. Besides glucose homeostasis, glucagon also plays a role in lipid and amino acid metabolism. In humans, blood glucose levels are reciprocally correlated with glucagon

secretion. One of the intrinsic pathways proposed to cause glucagon secretion induced hypoglycaemia is the decreased ATP/ADP ratio which paradoxically slightly increases KATP channel activity leading to increased voltage-dependent activity of calcium P/Q channels and calcium ion influx. In response to carbohydrate intake, GLP-1 which has glucagonostatic effects, as well as GLP-2 and GIP which have glucagonotropic effects are secreted. Paracrine signals elicited by glucose in pancreatic delta cells and beta cells also inhibit glucagon secretion. Somatostatin and insulin secreted in response to increased glucose concentration inhibit glucagon secretion. Glucokinase, which is expressed in alpha cells also plays a role in glucagon secretion of glucose regulation. Some other intra-islet factors that impact the regulation of glucagon secretion are urocortin-3, zinc, GABA/L-glutamate, GABA, amylin, and ephedrine while extra-islet factors that contribute to the regulation of glucagon secretion include GLP-1, GLP-2, GIP, ghrelin, and gastrin, as well as sodium-glucose-co-transporter 2 (SGLT-2) inhibitors. Measurement of glucagon can be done by chromatography and mass spectrometry [1,2].

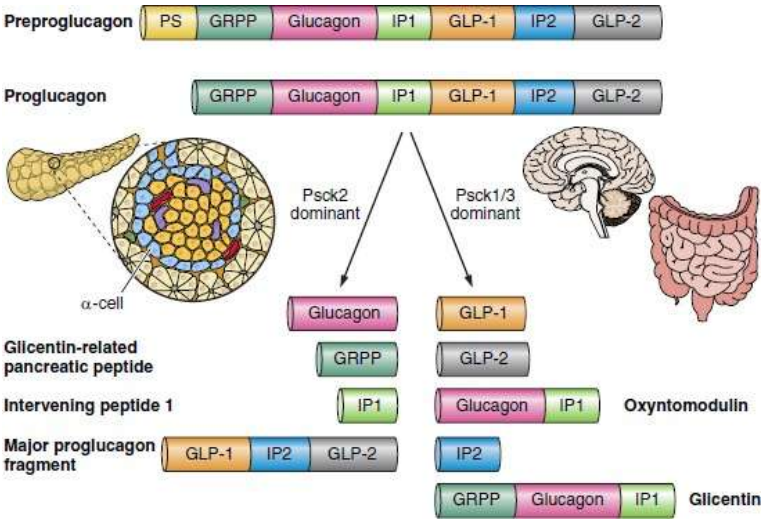

Figure 1. Glucagon Processing and Measurement

Although glucagon levels initially increase after the onset of fasting, concurrent with a decrease in glycaemia, with prolonged fasting (>3 days) circulating glucagon levels decline progressively to post-prandial values even though blood glucose remains low. Glucagon administration to hypoglycaemic people who have been fasting for >3 days does not produce any significant change in glycaemia due to depletion of glycogen stores. Low plasma glucose is not always associated with increased glucagon levels, thus making it likely that hypoglycaemia is not the primary stimulation for pancreatic islet alpha cell secretory function. The amino acid arginine, an alpha cell secretagogue can induce a significant increase in circulating glucagon independent of glycaemia. Decreased glucagon action on hepatocytes leads to hyperaminoacidemia which is a predisposing factor for alpha cell hyperplasia and hyperglucagonemia. Glutamine, arginine and alanine are potent inducers for glucagon secretion. Glucose increases beta cell activity and secretion of insulin products, zinc, gamma aminobutyric acid and suppresses alpha cell function through direct paracrine inhibition of beta cell mediated signalling to alpha cells. The secretory activity of delta cells also inhibits glucagon through somatostatin [2,3].

An important function of glucagon is its role as a regulator of glucose homeostasis. Increased plasma glucagon levels lead to increased hepatic glucose production. The balance between insulin and glucagon is responsible for maintaining euglycaemia conditions. In hypoglycaemic conditions, increased glucagon secretion leads to increased hepatic glucose production through a number of cellular mechanisms including suppression of glycogenesis and glycolysis and stimulation of glycogenolysis and gluconeogenesis. When glucagon binds to the 7 transmembrane receptors on the cell plasma membrane it causes conformational changes that activate the Gαs protein. This results in an increase in cAMP levels through the activation of

adenylate cyclase to stimulate the activation of protein kinase A and cAMP response element binding (CREB) protein. CREB is responsible for inducing the transcription of glucose-6 pospatase and PEPCK (pospoenolpyruvate carbokycinase) for gluconeogenesis. PKA activation leads to intracellular events for additional CREB phosphorylation. During short periods of fasting (<12 hours), glucose levels are maintained through the process of glycogenolysis and then gluconeogenesis after glucagon stores are depleted. Glucagon stimulates hepatic amino acid metabolism leading to increased amino acid flux into hepatocytes and provides substrate in the form of gluconeogenic amino acids [1,2] (Fig. 2)

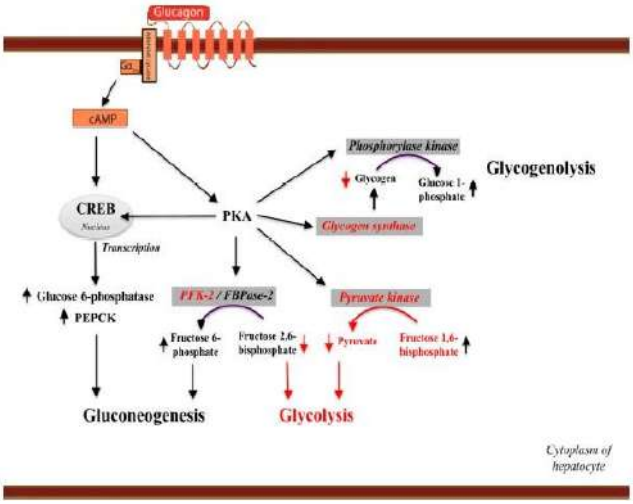

Figure 2. Effects of Glucagon on Hepatic Glucose Production.

Glucagon is a potent stimulus for hepatic amino acid turnover by inducing an increase in urea cycle enzyme activity. Through the cAMP-PKA-CREB protein-mediated effect, glucagon regulates several urea cycle enzymes at the transcriptional level. Glucagon also activates the amino acid transporter system A on the hepatocyte membrane, allowing increased amino acid uptake and substrate availability for ureagenesis. Glucagon regulates the transcription of N-acetyl-glutamate synthetase which plays a role in the process of ureagenesis. Glucagon acutely regulates hepatic amino acid metabolism through increased ureagenesis. Inhibition of glucagon signalling leads to decreased expression of genes involved in hepatic amino acid uptake and metabolism causing hyperaminoacidemia.

Glucagon secretion is strongly and rapidly stimulated by protein-containing foods. When only carbohydrates are ingested, plasma glucagon concentration will decrease in healthy individuals almost to zero while high protein meals are associated with a marked increase of glucagon secretion. Studies of genetic or pharmacological ablation of glucagon receptor signalling in mice have consistently associated hyperglucagonemia, hyperaminoacidemia, and hyperaminoacidemia-induced alpha cell hyperplasia. This endocrine feedback loop where glucagon induces hepatic amino acid metabolism and amino acids stimulate glucagon secretion is called the hepatic-alpha cell axis. Glucagon receptor block also increases the expression of several amino acid transporters on the plasma membrane of pancreatic alpha cells [3,4]

Inhibition at the glucagon receptor results in negative effects on lipid-related processes. Patients given glucagon receptor antagonists had increased total cholesterol, hepatic fat fraction, and weight gain compared to the control group. Glucagon mainly acts on hepatocytes, with the highest expression of glucagon receptors found in the liver. Glucagon might regulate lipid metabolism through hepatic signalling. When glucagon binds to its receptor in hepatocytes, cAMP is activated resulting in the accumulation and activation of CREB protein. As a result, transcription of carnitine acyl transferase (CPT- 1) will increase enabling the conversion of fatty acids to acylcarnitine where beta oxidation is activated to produce acetate [5].

Acetate and CoA react to form acetyl-CoA which in turn reacts with oxaloacetate to form citrate and then enters the citric acid cycle. As a result, hepatic glucagon signalling increases fatty acid catabolism, inhibits

glycolysis, and stimulates the citric acid cycle. When glucagon binds to its receptor in hepatocytes, PKA-dependent phosphorylation will be induced causing the inactivation of acetyl-Co-A carboxylase which functions to catalyse the formation of malonyl-CoA. Malonyl-CoA inhibits CPT-1 so beta oxidation decreases malonyl-CoA levels leading to the conversion of free fatty acids to beta oxidation rather than re-esterification to triglycerol. Glucagon decreases de novo fatty acid synthesis and release of very small density lipoproteins. Glucagon signalling increases the AMP/ATO ratio required to activate AMP-activated kinase causing transcriptional activation of PPAR-α (peroxisome proliferator- activated receptor) for induction of transcription of beta oxidation-related genes such as CPT-1 and acetyl-CoA oxidase [6,7].

CONCLUSION

This review summarizes an important function of glucagon is its role as a regulator of glucose homeostasis. Increased plasma glucagon levels lead to increased hepatic glucose production. The balance between insulin and glucagon is responsible for maintaining euglycaemia conditions. In conditions of hypoglycaemia, increased glucagon secretion leads to increased hepatic glucose production through a number of cellular mechanisms including suppression of glycogenesis and glycolysis and stimulation of glycogenolysis and gluconeogenesis.

DECLARATIONS

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This research has received no external funding.

COMPETING INTERESTS

None.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

None

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