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Regulation of Glucose Metabolism by Glucagon: A Review

KEYWORDS: Glucagon, Glucose metabolism, Blood glucose homeostasis

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ABSTRACT *The aim of this article was to review the relationship between glucagon hormone and glucose metabolism. Glucagon secreted by the alpha cells of Langerhans, of pancreas, plays an important role in the regulation of blood glucose by producing antagonistic effects on insulin action. The primary target for glucagon action is on liver hepatocyte and promotes the production of glucose by increasing Glycogenolysis and Gluconeogenesis.*

INTRODUCTION:

GLUCAGON SYNTHESIS:

Glucagon is a 29 – amino acid peptide hormone, is an extremely efficient hyperglycaemic agent, processed from proglucagon. Proglucagon is expressed not only in the pancreas, but also in the other tissues such as enteroendocrine cells in the digestive tract and in the brain. All mammalian glucagon's appear to have the same structure. Human preproglucagon is a 179-amino-acid protein that is found in pancreatic A cells, in L cells in the lower gastrointestinal tract, and in the brain. However the processing of proglucagon differs among tissues and is proteolytically processed in the alpha cells in a cell – specific manner[1]. The 2 main products of proglucagon processing are glucagon in the A-cells of the pancreas and glucagon-like polypeptides 1 and 2 (GLP-1 and GLP-2). GLP-1 and GLP-2 have no definite biologic activity by themselves. However, GLP-1 is a potent stimulator of insulin secretion that also increases glucose utilisation[2]. Up to now glucagon – binding sites have been identified in multiple tissues, including liver, brain, pancreas, kidney, intestine, and adipose tissues[3]. The role of glucagon in maintaining the blood glucose homeostasis depends on structure and the expression of glucagon and glucagon receptor genes.

GLUCAGON IS A POTENT REGULATOR OF GLUCOSE METABOLISM IN VIVO:

Among all the hormones, glucagon plays a major role in glucose homeostasis in vivo. Administration of exogenous glucagon increases glucose levels in fasted or fed animals [4] by stimulating the hepatic RNA and protein breakdown and the effect was greater after 24 hrs and observed the glucose output from intact perfused rat livers[5]. Similar observations were made in humans. Glucagon administration is used clinically to treat hypoglycemia in humans. Similarly, glucagon also stimulates glucose output from primary hepatocytes by regulation of expression of the phosphoenol pyruvate carboxylase gene in cultured rat hepatocytes [6] and observed in rats had high saturated fat diet produces greater hepatic glucose production comparable with rats on standard diet[7]. The effect of glucagon can occur within 5-6 minutes and dissipate rapidly. The predominant site of glucagon degradation is the liver which degrades as much as 80% of the circulating glucagon in one pass[8]. Multiple evidences shown that glucagon is a sensitive and is the major key and timely regulator of glucose homeostasis in vivo. Small doses of glucagon are sufficient to raise significant glucose levels in the blood[9].

MOLECULAR MECHANISM FOR GLUCAGON-MEDIATE GLUCOSE REGULATION:

Glucagon and GLP-1 peptide receptor binding in the target cells activates the adenyl cyclise enzyme that leads to increased formation of cyclic AMP which mediates the effects of the hormone. This leads to subsequent activation of protein kinase A (PKA) and therefore increased breakdown of glycogen and an increase in plasma glucose. However, it was found that some of the glucagon receptors located on the same hepatic cells to activate phospholipase C, production of inositol 1,4,5-triphosphate, and subsequent release of intracellular calcium[10].

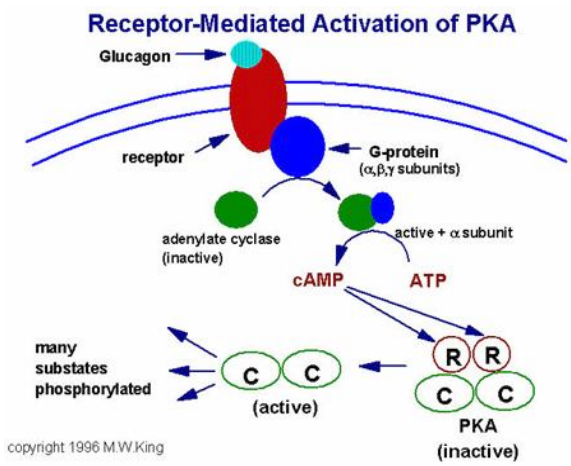

Fig: 1. Mechanism of glucagon action

The glucagon regulates hepatic glucose output by activating PKA, leading changes in glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis. The principle physiological effects of glucagon are mediated in liver.

GLYCOGENOLYSIS:

POTENTIATION OF GLYCOGENOLYSIS:

Overall, glucagon signaling promotes glycogenolysis and, at the same time, inhibits glycogen synthesis in the liver. When glucose levels are low in the blood, glucagon activated PKA (protein kinase A) phosphorylates and activates glycogen phosphorylase kinase phosphorylates resulting in increased glycogen breakdown (glycogenolysis) and the production of glucose – 6 – phosphate. G-6-P is then converted into glucose by glucose-6-phosphatase (G-6-Pase), increasing the glucose pool for hepatic output [11].

INHIBITION OF GLYCOGENESIS:

In addition to promoting glycogenolysis, glucagon inhibits glycogen synthesis by regulating glycogen synthase in the liver. Glycogen phosphorylase and glycogen synthase is regulated by phosphorylation but in an opposite fashion. Gluca-

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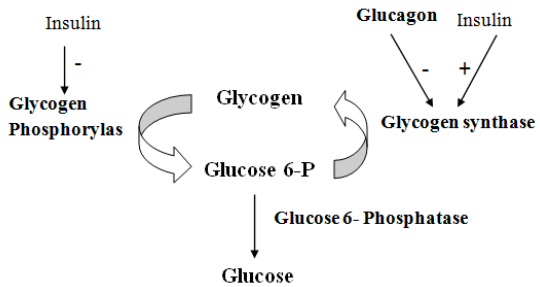
gon induces glycogen synthase phosphorylation and inhibits glycogen synthase activity in the liver[12].

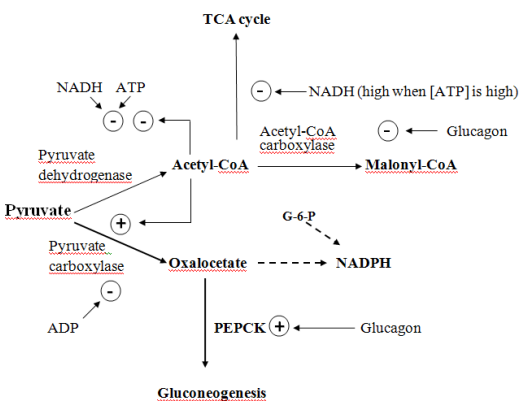


Fig/Chart 2: Inhibition of glycogenesis

GLUCONEOGENESIS:

Potentiation of gluconeogenesis:

In addition to affecting glycogen metabolism, glucagon regulates blood glucose homeostasis through a process known as gluconeogenesis and decreasing glycolysis. The liver is the major site of gluconeogenesis where lactate, pyruvate, glycerol, and certain aminoacids are converted into glucose through by means of gluconeogenesis. The most important function of gluconeogenesis is play a major role in conditions of starvation, in diabetic state or when stored glycogen is depleted.



Fig/Chart 3: Potentiation of gluconeogenesis

The above chart shows the sequence of reactions by which pyruvate, and probably enters the cell by various carrier-mediated plasma membrane transport systems. Lactate and most aminoacids are converted in the cytoplasm of the cells. Alanine may also be trans aminoacid to pyruvate in the mitochondria. It has been suggested that mitochondrial metabolism of alanine contributes significantly in the production of glucose from this amino acid. Phosphoenolpyruvate carboxykinase (PEPCK) catalyzes the conversion of oxaloacetate into phosphoenolpyruvate, an early and rate-limiting step in the pathway of hepatic gluconeogenesis Glucagon treatment has been shown to increase the PEPCK mRNA level in the liver or hepatocytes[13]. Recent studies suggest that glucagon action on liver is mediated by the activation of adenyl cyclase and the PKA pathway. PKA activation leads to phosphorylation of cAMP response element-binding (CREB) protein. The phosphorylated CREB protein in turn [14] regulates gluconeogenesis mainly by the up-regulation of key enzymes such as glucose-6-phosphatase (G6PC) and phosphoenolpyruvate carboxykinase(PCK). Pyruvate a glucogenic molecule which is directly converted to oxaloacetate by pyruvate carboxylase. Oxalo acetate escapes the mitochondria as malate, which is then reoxidised to oxaloacetate. The fate of mitochondrial oxaloacetate is depending in larger part on the distribution of enzyme phosphoenolpyruvate carboxylase(PEPCK)[15]. Since oxaloacetate was not metabolised directly, glucagon stimulates PEPCK, which converts later oxaloacetate into phosphoenolpyruvate. PCK mediates the conversion of oxalacetate into phosphoenolpyruvate while G6PC regulates glucose production from glucose-6-phosphate. FBP1 is responsible for the conversion of fructose-1,6-biphosphate (F(1,6) P2) into fructose-6-phosphate (F6P). Its activity is regulated by glucagon since this hormone decreases the intracellular levels of fructose-2,6-biphosphate (F(2,6)P2), an allosteric inhibitor of FBP1[16].

INHIBITION OF GLYCOLYSIS:

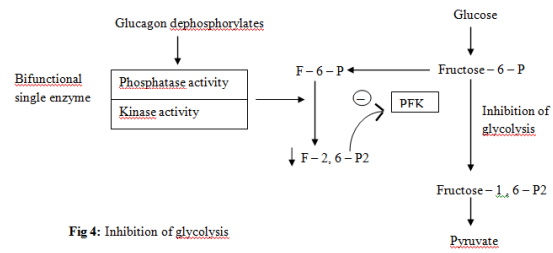


Fig 4: Inhibition of glycolysis

Fig 4: Inhibition of glycolysis

In addition to increasing gluconeogenesis, glucagon inhibits glycolysis. Glucagon also dephosphorylates the bifunctional regulates enzymes, which decreases the levels of fructose - 2, 6 - biphosphate. This intermediate inhibits the activity of 6 phosphofructo kinase1(PFKI) and inhibits the process of glycolysis[17]. In addition glucagon inhibits glycolysis by several mechanism. Glucagon decreases the activity of the rate – limiting and irreversible reaction of phosphorylating F6P to fructose – 1, 6 – biphosphate, which is catalysed by the enzyme PFK – 1 and thereby inhibits the process of glycolysis. Glucagon inactivates the enzyme pyruvate kinase which catalyses the transfer of the phosphate group from phosphoenolpyruvate to ADP, producing pyruvate and ATP, the last step in the glycolysis pathway. Glucagon inactivates pyruvate kinase through phosphorylation of phosphofructokinase – 2/ fructose biphosphatase [18, 19]. The inhibition of pyruvate kinase by glucagon results in decreased glycolysis and increased gluconeogenesis.

CONCLUSION:

During the last two decades, significant progress has been made in understanding and analysing the action of glucagon at the receptor level. Glucagon plays a major role in glucose homeostasis in vivo. Administration of exogenous glucagon increases glucose levels in fasted or fed animals. Similarly, glucagon also stimulates glucose output from primary hepatocytes in culture and observed in rats had high saturated fat diet produces greater hepatic glucose production comparable with rats on standard diet. Glucagon increases hepatic glucose output by inceasing glycogenolysis and gluconeogenesis. Glucagon regulates metabolism during interdigestive and fasting period. Glucagon and GLP-1 peptide receptor binding in the target cells and the key metabolic enzymes mediates the effects of the hormone. The glucagon regulates hepatic glucose output by activating PKA, leading changes in glycogenolysis, glycogenesis, gluconeogenesis, and glycolysis. Recent studies shows that by antagonizing glucagon action or by neutralizing the hormone or blocking the action of the glucagon receptor may represent a new avenue for intervention of diabetes and related metabolic disorders.

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