



Review on the role of insulin in regulating Blood sugar levels

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Abstract

Insulin is a poly peptide hormone substantially buried by β cells in the islands of Langerhans of the pancreas. The hormone potentially coordinates with glucagon to modulate blood glucose situations; insulin acts via an anabolic pathway, while glucagon performs catabolic functions. Insulin regulates glucose situations in the bloodstream and induces glucose storehouse in the liver, muscles, and adipose towel, performing in overall weight gain. The modulation of a wide range of physiological processes by insulin makes its conflation and situations critical in the onset and progression of several habitual conditions. Although clinical and introductory exploration has made significant progress in understanding the part of insulin in several pathophysiological processes, numerous aspects of these functions have yet to be illustrated.

This review provides an update on insulin stashing and regulation, and its physiological places and functions in different organs and cells, and counteraccusations to overall health. We cast light on recent advances in insulin- signaling targeted curatives, the defensive goods of insulin signaling activators against complaint, and recommendations and directions for unborn exploration.

Keywords: Insulin, Sugar, Diabetes.

Introduction

Insulin, a hormone composed of 51 amino acids, plays a crucial role in glucose homeostasis, cell growth, and metabolism. The discovery of insulin in Toronto from 1921 to 1922 by Dr. Frederick Banting revolutionized the treatment of diabetes⁽¹⁾. Since then, researchers have continuously worked towards improving the quality of insulin. The discovery of insulin also paved the way for the exploration of other hormones like glucagon⁽²⁾. Initially, insulin was believed to be exclusively produced by the beta cells of the pancreas, but recent evidence suggests that low concentrations of insulin are also found in certain neurons of the central nervous system⁽³⁾. The regulation of insulin biosynthesis and secretion

differs based on glucose levels in the bloodstream. While glucose level above 5m M are required to initiate insulin secretion, oscillations between 2mM to 4mM stimulate insulin biosynthesis⁽⁴⁾. Glucose metabolism is triggered by food intake, leading to increased insulin production by beta cells and decreased glucagon secretion by alpha cells, which help regulate blood glucose levels⁽⁵⁾.

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Once secreted, insulin circulates in the bloodstream and is taken up by hepatocytes, which store glucose as glycogen. Insulin also promotes glucose uptake by skeletal muscle cells and adipocytes, thereby reducing blood glucose levels⁽⁶⁾. Insulin acts on insulin receptors present in the cell membrane, initiating a series of enzymatic reactions that regulate glucose uptake and various metabolic processes⁽⁷⁾. The activation of insulin receptors also phosphorylates intracellular proteins that regulate insulin metabolism, cell growth, and gene expression related to cell proliferation and differentiation⁽⁸⁾. The primary focus of research has been to understand the role of insulin in the onset and progression of conditions like diabetes. Insulin deficiency impairs cells' ability to use glucose as an energy source, leading to high blood glucose levels known as hyperglycemia⁽⁹⁾. Prolonged hyperglycemia can result in diabetes mellitus and various health complications, such as damage to the nervous system and dysfunction of the eyes and kidneys. Additionally, the inability of cells to use glucose due to insulin deficiency leads to increased reliance on fat stores as the primary energy source.⁽¹⁰⁾ Apart from its role in diabetes, recent literature suggests that insulin also has important physiological effects on various organs in the body, including the brain, heart, liver, bone, skin, and hair follicles. Insulin promotes bone formation and attenuates inflammation associated with osteoporosis⁽¹¹⁾, influences central nervous system function⁽¹²⁾, and exhibits pro- and anti-atherogenic effects in the vascular system. Advances in insulin research have led to the development of insulin signaling-targeted therapies and insulin signaling activators as protective measures against various conditions. Clinical and laboratory studies have shown that insulin receptor activators like metformin have protective effects on organs such as the kidneys⁽¹³⁾. Additionally, drugs like sulfonylurea, which enhance insulin secretion by pancreatic beta cells, have been used to stimulate insulin secretion. Currently, there are various forms of insulin available, including rapid-acting, short-acting, intermediate-acting, and long-acting insulins, providing options for individuals with diabetes. This article provides a comprehensive review of

insulin secretion and regulation, its physiological effects on different organs, the health consequences of insulin deficiency, and recent advancements in insulin signaling-targeted therapies.⁽¹⁴⁾

Regulation of Insulin Secretion

Understanding the physiology of insulin-producing cells is crucial for comprehending the regulation of insulin secretion. Insulin is a peptide hormone secreted by beta cells in the pancreas. The pancreas contains pancreatic islets, which consist of different endocrine cells, primarily insulin-secreting beta cells, glucagon-secreting alpha cells, and somatostatin-secreting delta cells. Although the pancreatic islets constitute only 1-2% of the total pancreatic mass, they receive about 10% of the total pancreatic blood supply (15). Insulin is typically released in response to elevated glucose levels, a process known as glucose-stimulated insulin secretion. This process involves the uptake and metabolic breakdown of glucose within the beta cells. In human beta cells, glucose transporters GLUT1 (encoded by SLC2A1) and GLUT3 (encoded by SLC2A3) are the main glucose transporters, while GLUT2 (encoded by SLC2A2) is predominant in rodent beta cells

⁽¹⁶⁾. This difference is due to variations in the glucose transporter isoforms' Km values. The first step in glucose metabolism is the phosphorylation of glucose by the enzyme glucokinase (GCK).⁽²²⁾ Glucose phosphorylation by GCK is crucial for insulin secretion, and mutations or abnormalities in the GCK gene can lead to reduced glucose-stimulated insulin release and glucose intolerance or diabetes⁽¹⁷⁾. While much of our understanding of insulin secretion comes from rodent models, several studies have described insulin secretion in humans.

In nondiabetic individuals, an increase in glucose levels from 1 mM to 6 mM results in a threefold increase in glucose oxidation (measured by the production of C14O₂ from slightly C14-labeled glucose). Further increases in glucose concentration to above 12 mM lead to an approximately 25-fold acceleration in glucose oxidation⁽¹⁸⁾. Approximately one-tenth of ingested glucose enters glycolysis, primarily through

mitochondrial oxidation within the pancreatic islets. However, the fate of the remaining glucose needs further investigation. Incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are secreted by the gastrointestinal tract, play a significant role in nutrient-induced insulin secretion and overall insulin regulation⁽¹⁹⁾. Incretins bind to G-protein-coupled receptors on beta cell membranes, increasing intracellular levels of 3',5'-cyclic adenosine monophosphate (cAMP) and promoting glucose-stimulated insulin secretion (GSIS) in the presence of elevated glucose levels. Incretins exhibit their actions independently of KATP channel regulation, as they remain effective even in the presence of diazoxide, a KATP channel opener. As a result, cAMP increases the size/quantity of readily releasable insulin vesicles in a glucose concentration-dependent manner within the beta cell dynamics. It is worth noting that incretins enhance beta cell function in the presence of elevated glucose levels even in the absence of calcium, indicating a Ca²⁺-independent mechanism of action⁽²⁰⁾.

Insulin Signaling Pathways

After being secreted by pancreatic beta cells and circulating through the body, insulin binds to insulin receptors (IRs) on the membranes of target cells. This binding leads to the phosphorylation of insulin receptor substrates (IRS) and subsequently activates two main signaling pathways: the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway and the mitogen-activated protein kinase (MAPK) pathway (Figure 1). Insulin exerts its cellular and metabolic effects by binding to insulin receptors. The core cellular processes downstream of insulin signaling involve the PI3K/Akt and MAPK signaling pathways. The PI3K/Akt pathway is responsible for various insulin-dependent functions and energy metabolism⁽²¹⁾. Once activated by IRS, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate to produce phosphatidylinositol triphosphate, which in turn phosphorylates and activates 3-phosphoinositide-dependent protein kinase-1 (PDK1). PDK1 then activates Akt, which mediates multiple cellular functions. Activated Akt phosphorylates

glycogen synthase kinase, inactivating it and inhibiting glycogen synthase and ATP-citrate lyase, leading to reduced glycogen and fatty acid synthesis, respectively. Akt also inhibits the mammalian target of rapamycin complex 1 (mTORC1), thereby promoting protein synthesis. Moreover, Akt promotes cell survival by inhibiting the proapoptotic pathway and activates sterol regulatory element-binding proteins (SREBPs), which translocate to the nucleus to transcribe genes involved in fatty acid and cholesterol synthesis.⁽²²⁾ The PI3K/Akt pathway also regulates the translocation of the insulin-sensitive glucose transporter GLUT4 to the membranes of muscle and adipose cells, facilitating glucose uptake. GLUT4 translocation involves the insulin receptor-mediated phosphorylation of Cbl-associated protein (CAP) and the formation of the CAP-Cbl-CRKII complex.

The MAPK pathway is activated when IRS-1 binds to growth factor receptor-bound protein 2 (Grb2), leading to the recruitment of SOS and subsequent activation of Ras. Activated Ras then recruits c-Raf, which phosphorylates and activates MAPK/Erk kinase (MEK). MEK, in turn, phosphorylates extracellular signal-regulated kinase (Erk). Once activated, Erk translocates to the nucleus, where it undergoes further phosphorylation and transcriptional activation by various transcription factors, such as ELK1, promoting cell proliferation, protein synthesis, and cell growth⁽²³⁾.

Physiological Roles of Insulin

The primary role of insulin is to regulate the body's energy metabolism by maintaining nutrient balance during the fed state⁽²⁴⁾. Insulin plays a critical role in transporting glucose into insulin-responsive tissues and organs, such as the liver, muscles, and adipose tissue. Any disruption in energy balance leads to the breakdown of stored fats in adipose tissue and further exacerbates insulin secretion.

Role of Insulin in the Regulation of Liver Function

Insulin plays a crucial role in regulating liver function, including glucose uptake, glycolysis, glycogenesis, and suppression of glucose production, gluconeogenesis

sis, and glycogenolysis

⁽²⁵⁾. It also affects glucose uptake by adipose tissue and skeletal muscle, leading to glycogenesis. Hyperinsulinemia can suppress glycogenolysis and stimulate gluconeogenesis in the liver. Insulin acts directly on the liver through the PI3K/Akt/IRS-1 pathway.

Role of Insulin in the Regulation of Skeletal Muscle Function

Insulin is essential for skeletal muscle function, including glucose uptake, energy metabolism, and GLUT4 regulation

⁽²⁶⁾. Roughly 70% of glucose uptake occurs in skeletal muscle. Insulin therapy can improve muscle strength and function in individuals with type 2 diabetes.

Role of Insulin in the Regulation of Adipose Tissue Function

Insulin regulates various aspects of adipose tissue function, including glucose uptake, fatty acid release, and lipid metabolism. Adipose tissue contributes to roughly one-tenth of whole-body glucose uptake ⁽²⁷⁾.

Insulin Deficiency

Nutrient vacuity plays an important part in the stashing and functional regulation of insulin. The inordinate consumption of adipose food can alter mitochondrial physiology by enhancing the inordinate ROS product that impairs insulin action ⁽²⁸⁾. It has been set up that insulin-

resistant individualities in anaerobic states during exercise can stimulate both mitochondrial biogenesis and effectiveness coincidentally with insulin exertion.

People over 30 times of age with type 1 diabetes, as defined by severe insulin deficit, have analogous clinical and natural features to youngish people, but the condition is constantly not honored ⁽²⁹⁾. The overproduction of glucose and the buildup of lipids should be anticipated in the livers of cases with rotundity and insulin resistance. Thus, both intrahepatic and extrahepatic pathways intervene insulin's control of glucose and lipid metabolism, and the relations between these pathways control insulin signaling. Direct hepatocyte insulin signaling is essential for lipogenesis but gratuitous for suppressing glucose product. Pathologically, both insulin resistance and insulin insufficiency alone can change tube glucose situations. Dragging the action time of rudimentary insulin and confining peak of fast

-acting insulin can be salutary for individualities with diabetes. Different transport systems may make the regular use of insulin more respectable to cases and may have other advantages, similar as abetting in attaining better glyceamic control. Closed-circle systems, or artificial pancreases, have shown safety and glyceamic benefits. Short-term insulin glargine administrations are incompletely salutary for those with a β cell phenotype, whereas the long-term relief of insulin by isogenic island transplantation promotes the conformation of more mature β cells. Increased insulin resistance is an fresh factor that can work in accord with other factors and may be important in the pathogenesis of diabetic microvascular complications. Research has shown that if blood glucose remains high despite substantial insulin situations, the action of the hormone must be imperfect ⁽³⁰⁾. The absence of first-phase insulin responses to intravenous glucose has long been considered an original sign of β cell dysfunction and has some anticipative significance for the posterior development and progression of diabetes.

Hyperinsulinemia

In hyperinsulinemia, the quantum of insulin in the blood is advanced than usual. The hyperinsulinemic state is characterized by damaged myocardial insulin signaling, mitochondrial dysfunction, endoplasmic reticulum stress, altered calcium homeostasis, irregular coronary microcirculation, sympathetic nervous system dysfunction, inauguration of the renin-angiotensin-aldosterone system, and vulnerable response abnormalities. These pathophysiological differences affect in increased oxidative stress, fibrosis, hypertrophy, diastolic cardiac dysfunction, and eventual systolic heart failure, and it's suggested that hyperinsulinemia may be the common element account for the association between rotundity and type 2 diabetes. The reference range for hyperinsulinemia is typically decided grounded on dieting glucose situations, including 5–13 μ U/mL, ≤ 30 μ U/mL, and 18–173 pmol/L (3–28 μ U/mL). Rotundity and type 2 diabetes are classic countries of insulin resistance. Insulin resistance regulates insulin stashing, which eventually leads to hyperinsulinemia ⁽³¹⁾, and hyperinsulinemia is associated with increased morbidity and mortality

from cardiovascular complications in cases with rotundity. Generally, the main cause of hyperinsulinemia is insulin resistance, which the pancreas compensates for by producing further insulin. still, it can Regenerate responses derstood. However, there are links between insulin action and these conditions. Generally, the main cause of hyperinsulinemia is insulin resistance, which the pancreas compensates for by producing further insulin. still, it can occasionally be caused by a rare excrescence of pancreatic insulin-producing cells (insulinoma) or inordinate figures or growth of these cells (nesidioblastosis). This condition also leads to low blood sugar ^[32].

The direct effect of hyperinsulinemia includes type 2 diabetes, rotundity, habitual inflammation, hypertriglyceridemia, and Alzheimer's complaint. A study showed that increased salutary adipose acids stimulate intestine enterocyte incretin stashing, further elevating GSIS, indeed at low glucose situations; therefore, adipose acids play a vital part in forming diabetic hyperinsulinemia. The diabetic cardiomyopathy detected in hyperinsulinemic countries is distributed by damaged myocardial insulin signaling, abnormal mitochondrial function, endoplasmic reticulum stress, bloodied calcium homeostasis, abnormal coronary microcirculation, the activation of the sympathetic nervous system, the activation of the renin – angiotensin – aldosterone system, and maladaptive vulnerable responses, and these pathophysiological differences lead to oxidative stress, fibrosis, hypertrophy, diastolic cardiac dysfunction and, ultimately, systolic heart failure. Hyperinsulinemia in women suffering from polycystic ovarian pattern is prognostic of health problems latterly in life, similar as diabetes, cardiovascular complaint, and gravidity

⁽³³⁾. habitual hyperinsulinemia has been shown to upregulate triglyceride (TG)-rich lipoproteins and to be a threat factor for atherosclerosis. A healthy, balanced diet can help a person maintain a healthy weight and ameliorate their overall fleshly function. Specific diets can also help blood sugar harpoons and grease the regulation of insulin situations. Diets that concentrate on glycemic control are salutary when treating hyperinsulinemia, a diet low in simple

carbohydrates can help cases to regulate their glucose situations. More importantly, glycemic control should be established veritably beforehand in gestation to stop the inauguration of fetal hyperinsulinemia ^[34].

Hyperglycemia

Hyperglycemia occurs when the blood glucose is lesser than 66 mg/ dL during fasting or 180 mg/dL 2 h postprandial. Hyperglycemia has increased in recent times without an apparent difference between men and women, particularly due to dropped physical conditioning and increased rotundity. Island dysfunction, reduced insulin stashing, dropped glucose application, and insulin resistance set up in type 2 diabetes are factors contributing to the onset and progression of hyperglycemia. rudimentary hyperglycemia occurs when there's a lower insulin- to- glucagon rate owing to the increased product of glucose by the liver, whereas postprandial hyperglycemia arises due to a drop in tube insulin attention or action that reduces glucose application in supplemental apkins. The postprandial hyperglycemia status is defined by factors, similar as the timing, volume, and composition of the mess, carbohydrate content of the mess, and the performing insulin product and inhibition of glucagon stashing. When the fasting tube glucose position is constantly ≥ 7 mmol/ L (67 mg/ dL) or when the 2 hours' tube glucose position following drinking a 75g glucose cargo is constantly ≥ 6.1 mmol/ L (200 mg/ dL), diabetes is diagnosed or verified ^[35].

Meanwhile, clinical findings indicated that fasting or 2 h postprandial glucose situations below the diabetes cutoffs indicates cardiovascular complaint. therefore, a positive correlation exists between glucose position and cardiovascular complaint threat. Dragged hyperglycemia could also lead to the onset of other life-changing

complications similar as ketoacidosis and hyperglycemic hyperosmolar pattern. Although their pathogenesis

differs, the introductory beginning medium for both diseases is a drop in the effective net attention of circulating insulin coupled with an attendant elevation of counterregulatory hormones (e.g., glucagon, catecholamines, cortisol, and growth hormone). As unhealthy diets and a lack of physical exertion also

contribute to a global rise in the frequency of rotundity in both type 1 and 2 diabetes, a life change could be a good companion to insulin- signaling targeted remedy in reducing hyperglycemia and associated diabetes.⁽³⁶⁾

Hyperlipidemia

The leptin receptor or rotundity receptor (Ob- R), which belongs to the cytokine class I receptor family,

substantially resides in β cells, and when actuated, it suppresses insulin stashing, insulin gene expression, and influences the proliferation, apoptosis, and growth of β cells. The function and survival of β cells are affected by excess necrosis factor- α and interleukin- 6 (IL- 6), and an increased quantum of pro- inflammatory factors were set up in the pancreatic islands during stress conditions with glucose and FFA. An increase in tube FFA is essential under fasting conditions to maintain rudimentary insulin situations and normal insulin responses to glucose⁽³⁷⁾; still, it can contribute to a situation named lipotoxicity, in which increased tube FFA plays places in sustaining insulin resistance and disabled β cell function.

Recent Advances in Insulin-Signaling Targeted Therapy

In the treatment of diabetes and nephropathy, multitudinous aspects of forestallment and the multifactorial methodologies used by nephrologists, diabetologists, dieticians, and educated diabetes specialists to give a multifaceted care program reduce the progression of der conditions. Arising studies are recommending the employment of the defensive parcels of metformin against multitudinous order conditions, similar as autophagy and AMP- actuated protein kinase (AMPK) signaling pathways, to cover the feathers from injury also, metformin inactivates hypoglycemia by dwindling intestinal glucose immersion and hepatic glycogenesis to ameliorate glucose uptake and exercising supplemental apkin that enhance insulin perceptivity. Another sulfonylurea- receptor-binding medicine, sulfonylureas, affects pancreatic β cells, leading to stoked insulin stashing and conceivably hypoglycemia. Sodium-glucose co-transporter 2 impediments drop glucose immersion by the order, leading to better red glucose excretion and a reduction in hemoglobin A1c of roughly

0.9 –1.0 (38). Thiazolidinediones have been set up to ameliorate insulin perceptivity without causing hypoglycemia in their places as Part agonists, leading to an A1c drop of 0.5 –1.4, and these medicines, which are metabolized by the liver, are used to treat habitual order complaint. nascence- glucosidase impediments drop the breakdown of small intestinal oligo- and disaccharides, reduce the ingestion of carbohydrates, and suspend glucose immersion after a mess. Epidemiological exploration has shown that resveratrol can give health benefits, including protection against renal cancer and order complaint, and its nephroprotective goods have been observed via invitro and invivo human and beast studies. Resveratrol has been set up to increase AdipoR1 mRNA situations, and its protein expression was excluded in the presence of FOXO1 shRNA. The bioactive agent 3 β - Taraxerol is known to affect pancreatic function and acts by enhancing insulin stashing or dwindling intestinal glucose immersion (39). Gallic acid has been set up to reduce circulating situations of TGF- β 1, supporting the thesis that

it might be used to efficiently manage diabetic nephropathy. The hematological, toxicological, and biochemical goods of orally treating diabetic model mice with 40 mg/ kg mangiferin for 30 days were compared to control mice, and the situations of glycosylated hemoglobin, blood glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase were significantly dropped in the mangiferin- treated creatures. nascence- glucosidase impediments block carbohydrate immersion in the small intestine. lately, phytochemicals and factors of their signaling pathways have been shown to be effective for prophylaxis and treatment of insulin resistance in GLUT4- expressing. A hydroalcoholic excerpt of Capparis moonii fruit increased the glucose uptake associated with substantial IRS- 1 and IR phosphorylation, PI3- kinase mRNA, and GLUT4 expression in L6 cells (40). Glucagon- suchlike peptide-1 receptor agonists and dihydro- dipeptidyl peptidase- 4 inhibitor offers situations of reduction in A1c, fasting blood glucose, postprandial glucose, and body weight in patients with type 2 diabetes. Of these two sets of medication, GLP-1 agonists have the greatest situation of decreasing situations of albuminuria.

Recent advances in diabetes have been achieved using natural products as therapeutic agents. For example, *Sargassum muticum*, a brown seaweed extract, has been found to improve insulin sensitivity, reduce inflammation, and enhance glucose uptake. These natural products offer promising avenues for developing new therapeutic approaches for the management of hyperinsulinemia, hyperglycemia, and hyperlipidemia. (41)

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