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Review on the role of insulin in regulating Blood sugar levels

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Abstract

Insulin is a poly peptide hormone substantially buriedb y 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 Bantingr evolutionized the treatment of diabetes[(1)]. Since then, researchers have continuouslyworkedtowardsimprovingthequality 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 suggeststhat low concentrationsof insulinare also foundin certain neuronsofthe centralnervous system [(3)]. The regulation of insulin biosynthesis and secretion differs based on glucose levels in the bloodstream. While glucose level sabove 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,whichstoreglucoseasglycogen.Insulin alsopromotesglucoseuptakebyskeletalmusclecells andadipocytes,therebyreducingbloodglucoselevels [6].Insulinactsoninsulin receptorspresentinthecell membrane, initiating a series of enzymatic reactions that regulate glucose uptake and various metabolic processes[7].Theactivationofinsulinreceptorsalsoph osphorylatesintracellularproteinsthatregulateinsuli n metabolism,cellgrowth,andgeneexpressionrelatedt ocellproliferationanddifferentiation [8].Theprimary 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 varioushealthcomplications,suchasdamagetothene rvoussystemanddysfunctionoftheeyesandkidneys. 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]
Apartfromitsroleindiabetes,recentliteraturesuggest sthatinsulinalso hasimportantphysiologicaleffects onvariousorgansinthebody,includingthebrain,heart ,liver,bone,skin,andhairfollicles.Insulinpromotes bone formation and attenuates inflammation associated with osteoporosis [11], influences central nervous systemfunction[12],andexhibitspro-andanti-atherogeniceffectsinthevascularsystem.Advancesi ninsulin research have led to the developmentof 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, drugslikesulfonylurea,whichenhanceinsulinsecreti onbypancreaticbetacells,havebeenusedtostimulate insulinsecretion.Currently,therearevariousformsofi nsulinavailable,includingrapid-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,thehealthconsequencesofinsulindeficiency, andrecentadvancementsininsulinsignaling-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-secretingalphacells,andsomatostatin-secretingdeltacells.Althoughthepancreaticislets constituteonly1- 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 phosphorylationbyGCKiscrucialforinsulinsecretio n,andmutationsorabnormalitiesintheGCKgenecan leadtoreducedglucose-stimulatedinsulinreleaseandglucoseintoleranceordi abetes[17].Whilemuchofour understandingofinsulinsecretioncomesfromrodent models,severalstudieshavedescribedinsulinsecreti on 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 increasesinglucoseconcentrationtoabove12mMlea dtoanapproximately25-foldaccelerationinglucose oxidation [18]. Approximately one-tenth of ingested glucose enters glycolysis, primarily through

mitochondrialoxidationwithinthepancreaticislets. However,thefateoftheremainingglucoseneedsfurther 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 eveninthepresenceofdiazoxide,aKATPchannelopener.Asaresult,cAMPincreasesthesize/quantityof readilyreleasableinsulinvesiclesinaglucoseconcentration-dependentmannerwithinthebetacelldynamics. It isworth noting that incretinsenhance betacell function inthe presenceof 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)onthemembranesoftargetcells.Thisbindingleadstothephosphorylationofinsulinreceptor 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).Insulinexertsitscellularandmetaboliceffectsbybindingtoinsulinreceptors.Thecorecellularprocesses 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).PDK1thenactivatesAkt,whichmediatesmultiplecellularfunctions.ActivatedAktphosphorylates glycogen synthase kinase, inactivating it and inhibiting glycogen synthase andATP-citratelyase, leading to reducedglycogenandfattyacidsynthesis,respectively.Aktalsoinhibitsthemammaliantargetofrapamycin 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/Aktpathwayalsoregulatesthetranslocationoftheinsulin-sensitiveglucosetransporterGLUT4tothemembranes 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.

TheMAPKpathwayisactivatedwhenIRS-1bindstogrowthfactorreceptor-boundprotein2(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 phosphorylationandtranscriptionalactivationbyvarioustranscriptionfactors,suchasELK1,promotingcell proliferation, protein synthesis, and cell growth [23].

Physiological Roles of Insulin

Theprimaryroleofinsulinistoregulatethebody'senergymetabolismbymaintainingnutrientbalanceduringthefedstate[24].Insulinplaysacriticalroleintransportingintracellularglucosetoinsulin-responsivetissues 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, andsuppressionofglucoseproduction,gluconeogene

sis,andglycogenolysis [25].Italsoaffectsglucoseuptake 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].Roughly70%ofglucoseuptakeoccursinskeletal muscle.Insulintherapycanimprovemuscle strength and function in individuals with type 2 diabetes.

Role of Insulin in the Regulation of Adipose Tissue Function

Insulinregulatesvariousaspectsofadiposetissuefunction,includingglucoseuptake,fattyacidrelease,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 consumptionofadipose foodscan altermitochondrialphysiologybyenhancingthe inordinate ROS product thatimpairsinsulinaction [28].Ithasbeensetupthatinsulin-resistantindividualitiesinanaerobicstateduring exercise can stimulate both mitochondrial biogenesis and effectiveness coincidently with insulin exertion. Peopleover30timesofagewithtype1diabetes,asdefinedbysevereinsulindeficit,haveanalogousclinical and naturalfeaturesto youngish people,butthecondition isconstantly nothonored [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 timeofrudimentaryinsulinandconfiningpeaksoffast-actinginsulincanbesalutaryforindividualitieswith diabetes.Differenttransportsystemsmaymakethere gularuseofinsulinmorerespectabletocasesandmay have other advantages, similar as abetting in attaining better glycemic control. Closed-circle systems, or artificial pancreases, have shown safety and glycemic benefits. Short-term insulin glargine administrations areincompletelysalutaryforthosewithaβcellphenotype,whereasthelong-termreliefofinsulinbyisogenic 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

Inhyperinsulinemia,thequantumofinsulininthebloodisadvancedthanusual.Thehyper insulinemicstate ischaracterizedbydamagedmyocardialinsulinsignaling,mitochondrialdysfunction,endoplasmicreticulum 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,including5–13μU/mL,≤30μU/mL,and18–173pmol/L(3–28μU/mL).Rotundityand 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 hyperinsulinemiaisinsulinresistance,whichthepancreascompensatesforbyproducingfurtherinsulin.still, it can Regenerate responsederstood. 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,adiposeacidsplayavitalpartinformingdiabetichyperinsulinemia.Thediabeticcardiomyopathy detected in hyper insulinemic 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 nervoussystem,the activation of the renin – angiotensin – aldosterone system, and maladaptive vulnerable responses, and these pathophysiological differences lead tooxidativestress,fibrosis,hypertrophy,diastoliccardiacdysfunctionand,ultimately,systolicheartfailure.Hyperinsulinemia in women suffering from polycystic ovarian pattern is prognostic of health problems latterlyinlife,similarasdiabetes,cardiovascularcomplaint,andgravidity [33].habitualhyperinsulinemiahas 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 carbohydratescanhelpcasestoregulatetheirglucosesituations.Moreimportantly,glycemiccontrol 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. Hyperglycemiahasincreased in recenttimeswithoutan apparentdifferencebetween 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 factorscontributingtotheonsetandprogressionofhyperglycemia.rudimentaryhyperglycemiaoccurswhen 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 insulinproductandinhibitionofglucagonstashing.Whenthefastingtubeglucosepositionisconstantly≥7 mmol/ L(67 mg/ dL) or when the 2 hours'tube glucose position following drinking a 75g glucose cargo is constantly ≥63.1 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 andcardiovascularcomplaintthreatDraggedhyperglycemiacouldalsoleadtotheonsetofotherlife-changing complicationssimilarasketoacidosisandhyperglycemichyperosmolarpattern.Althoughtheirpathogenesis differs, the introductory beginning medium for both diseases is a drop in the effective net attention of circulating insulin coupled with a attendant elevation of counterregulatory hormones (e.g., glucagon, catecholamines, cortisol, and growth hormone. As unhealthy diets and a lack of physical exertion also

contributetoaglobalriseinthefrequenceofrotunditan dbothtype1andIIdiabetes,alifechangecouldbe 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, substantiallyresidesinβcells,andwhenactuated,itsu ppressesinsulinstashing,insulingeneexpression,and influencestheproliferation,apoptosis,andgrowthofβ cells.Thefunctionandsurvivalofβcellsareaffected by excrescence necrosis factor- nascence and interleukin- 6 (IL- 6), and an increased quantum ofpro- inflammatory factors were set up in the pancreatic islands during stress conditions with glucose and FFA. An increase in tube FFAis essential under fasting conditionsto maintain rudimentary insulin situations and normal insulin responses to glucose (37); still, it can contribute to a situation named lipotoxicity, in which increased tube FFAplays 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 multifacetedcareprogramreducetheprogressionofor derconditions.Arisingstudiesarerecommendingthe employment of the defensive parcels of metformin against multitudinous order conditions, similar as autophagy andAMP- actuated protein kinase (AMPK) signaling pathways, to cover the feathers from injury also,metforminactivateshypoglycemiabydwindlin gintestinalglucoseimmersionandhepaticglycogene sis toameliorateglucoseuptakeand exercisingsupplementalapkinsthatenhanceinsulinp erceptivity.Another sulfonylurea- receptor-binding medicine, sulfonylureas, affects pancreatic β cells, leading to stoked insulin stashing and conceivably hypoglycemia. Sodium-glucoseco-transporter 2 impediments drop glucose immersionbytheorder,leadingtobetteredglucoseexc retionandareductioninhemoglobinA1cofroughly 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 anA1c 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 nephroprotectivegoodshavebeenobservedviainvitr oandinvivohumanandbeaststudies.Resveratrolhas been set up to increaseAdipoR1 mRNAsituations, and its protein expression was excluded in the presence of FOXO1 shRNA. The bioactive agent 3β- 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- Î21, 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 glycosylatedhemoglobin,bloodglucose,alanineami notransferase (ALT),aspartateaminotransferase (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 factorsoftheir signaling pathwayshave been shown tobe effective forprophylaxisand treatment of insulin resistance in GLUT4- expressing.Ahydroalcoholic excerpt of Capparis moonii fruit increased the glucose uptake associated with substantial IRS- 1 and IR phosphorylation, PI3- kinase mRNA, and GLUT4 expressioninL6cells(40).Glucagon-suchlikepeptide-1receptoragonistsanddiidro-dipeptidyl peptidase-4inhibitorsoffersituationsofreductioninA1c,fasting bloodglucose,postprandialglucose,andbodyweight in patientswith type 2 diabetes. Of these two sets of medication, GLP-1 agonistshave the greatest situation of decreasing situations of albuminuria.

Recent advances in diabetes have been achieved using natural productsastherapeuticagents.For example, Sargassum muticum,a brown seaweed extract, hasbeen found toimproveinsulinsensitivity,reduceinflammation,andenhanceglucoseuptake.Thesenaturalproductsoffer promising avenues for developing new therapeutic approaches for the management of hyperinsulinemia, hyperglycemia, and hyperlipidemia. (41)

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