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Review

The PI3K/AKT pathway in obesity and type 2 diabetes

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Abstract

Obesity and type 2 diabetes mellitus are complicated metabolic diseases that affect multiple organs and are characterized by hyperglycaemia. Currently, stable and effective treatments for obesity and type 2 diabetes mellitus are not available. Therefore, the mechanisms leading to obesity and diabetes and more effective ways to treat obesity and diabetes should be identified. Based on accumulated evidences, the PI3K/AKT signalling pathway is required for normal metabolism due to its characteristics, and its imbalance leads to the development of obesity and type 2 diabetes mellitus. This review focuses on the role of PI3K/AKT signalling in the skeletal muscle, adipose tissue, liver, brain and pancreas, and discusses how this signalling pathway affects the development of the aforementioned diseases. We also summarize evidences for recently identified therapeutic targets of the PI3K/AKT pathway as treatments for obesity and type 2 diabetes mellitus. PI3K/AKT pathway damaged in various tissues of the body leads to obesity and type 2 diabetes as the result of insulin resistance, and in turn, insulin resistance exacerbates the PI3K/AKT pathway, forming a vicious circle.

Introduction

The prevalence of obesity has grown at an alarming rate although specific public health policies and treatment efforts have been developed to resist the obesity epidemic [1], potentially leading to increased numbers of patients affected by complications of obesity, such as the most devastating type 2 diabetes mellitus (T2DM) [2]. T2DM is also a metabolic disease characterized by chronic hyperglycaemia, along with various comorbidities, such as cardiovascular disease, obesity, microangiopathy and renal failure [3]. Diabetic hyperglycaemia is caused by a decrease in insulin sensitivity, resulting in excessive insulin production, and current therapies either increase insulin sensitivity or introduce exogenous insulin. Unfortunately, these treatments currently cannot ensure long-term glycaemic control or reverse the progress [4].

In the chronically obesity, the prevalence of diabetes significantly increased, which is four times higher than the general population [5]. 80% of people with T2DM are obese or overweight, chronically obese patients, have a greater chance of developing diabetes. Both obesity and T2DM are associated with insulin resistance [6]. However, current therapies are not well designed for the effective treatment of obesity and diabetes. Thus, further researches related to the mechanism of obesity and diabetes need to be identified.

Phosphoinositide 3-kinase (PI3K) was discovered in 1985 and identified as a previously unknown phosphoinositide kinase [7, 8]. After decades of researches, the PI3K/AKT pathway is still worth studying due to its multiple functions. PI3K/AKT signalling plays a central role in cellular physiology by mediating growth factor signals during organismal growth and critical cellular processes, such as glucose homeostasis, lipid metabolism, protein synthesis and cell proliferationand survival[9]. This review mainly focuses on the mechanisms by PI3K/AKT signalling regulates

metabolism in normal physiology and morbid conditions, such as obesity and T2D.

Upstream molecules in The PI3K/AKT pathway

PI3Ks are a family of lipid kinases that phosphorylate phosphatidylinositol, which is a component of eukaryotic cell membranes [10]. Based on differences in sequence homology and lipid substrate preference, PI3Ks are divided into three classes (classes I, II, and III). Among these classes, PI3K class I is the most thoroughly researched due to its various activities [8]. Class I PI3K is a heterodimer and is divided into class IA and class IB, according to differences in the molecular structure [11]. The ligands, including growth factors, cytokines and hormones, activate receptor tyrosine kinases (RTKs) and G-protein-coupled receptors (GPCR), activate PI3K. RTKs recruit class I PI3Ks to the plasma membrane, which relieves the inactivation function of p85 and p110 to activate the protein [12, 13]. GPCRs directly interact with PI3Ks through Gα or Gβγ subunits. Meanwhile, RTKs and GPCRs also activates Ras to subsequently activates PI3K [14]. Activated Class I PI3K phosphorylates the substrate phosphatidylinositol 4,5-biphosphate (PIP2) to form phosphatidylinositol 3,4,5-triphosphate (PIP3) on intracellular membranes, subsequently recruiting signalling proteins, including AKT[15]. PIP2 is synthesized by class II PI3Ks using PIP as substrate [16]. Phosphatase and tensin homologue (PTEN), a main negative regulator of the PI3K, dephosphorylates PIP3 to generate PIP2 [17].

AKT contains three domains: pleckstrin homology (PH), middle kinase and regulatory carboxy-terminal domain, of which PH domain regulates the membrane AKT translocation [9]. According to differences in serine/threonine residues, AKTs are divided into three isoforms (AKT1, AKT2 and AKT3). AKT1 expresses ubiquitously, AKT2 mainly expresses in insulin-sensitive tissues, such as skeletal muscle, adipose tissues and liver, and AKT3 expresses in the testes and brain [9, 18]. AKT is activated through two pivotal phosphorylation processes. First, phosphorylation of the threonine 308 (AKT1) in the kinase domain by phosphoinositide-dependent protein kinase 1 (PDK1) initiates the activation process [19], subsequent phosphorylation at serine 473 (AKT1) in the carboxy-terminal regulatory domain through mTOR complex 2 (mTORC2)[17, 20], which is activated by a PI3K-dependent mechanism, completely activates AKT [21]. Similar phosphorylation events are observed at corresponding residues in AKT2 (T309 and S474) and AKT3 (T305 and S472) [22]. Phosphorylation of both residues is necessary for maximum activation of AKT. Protein phosphatase 2A (PP2A) [23] and PH domain leucine-rich repeat protein phosphatases (PHLPP1 and PHLPP2) [24] dephosphorylate AKT T308 and S473, respectively, leading to AKT inactivation. Recently, endomembranes that contain PIP3 and PIP2 have also been shown to directly contribute to AKT activation [25, 26].

Although several studies have reported an absolute requirement for PI3K in AKT activation, AKT activation has also been suggested to be mediated by a PI3K-independent mechanism [27]. However, researchers have not firmly established whether functional AKT activation occurs in the absence of productive PI3K signalling and thus this topic requires further study.

Downstream effectors

Downstream effectors, including protein and lipid kinases, transcription factors, regulators of small G proteins and vesicle trafficking, metabolic enzymes, E3 ubiquitin ligases, cell cycle regulators, and many other effectors, are regulated through serine and/or threonine phosphorylation by AKT (Fig. 1) [22]. Those effectors share a common minimal sequence motif, Arg-Xaa-Arg-Yaa-Zaa-Ser-Hyd [28]. Through effect-tors, AKT has important roles in many cellular processes, such as apoptosis, cell survival, cell cycle progression and metabolism. The downstream effectors are described in a previous review [22]. Here, we mainly describe downstream effectors involved in metabolism.

AKT regulates glucose and lipid metabolism. Activated AKT2, which is primarily expressed in insulin-responsive tissues, promotes translation of glucose transporter 4 (GLUT4). And the direct target of AKT is a substrate of 160 kDa (AS160), also known as TBC1D1 [29]. In intracellular compartments, AKT converts glucose to glucose 6-phosphate by stimulating hexokinase. AKT regulates two processes by glycolysis Glucose 6-phosphate and glycogen synthase kinase 3 (GSK3) to produce cellular energy via glycolysis and promotes glycogen production by inhibiting [30]. FoxO proteins, particularly FoxO1, are the main target of AKT and affect energy homeostasis throughout body [31]. FoxO1 and peroxisome proliferator-activated receptor-coactivator 1α (PGC1α) coordinately regulate gene expression to increase gluconeogenesis and fatty acid oxidation [32]. On the other hand, FoxO1 induces the expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase gene (G6PC), subsequently increases gluconeogenesis [33]. AKT directly inhibits FoxO1, reducing glucose levels [31], FoxO1

simultaneously activates AKT to increase energy production and inhibits mTOR complex 1 (mTORC1) to reduce lipid and protein production [34]. Finally, GSK3 inhibits glycogen synthase (GS), which promotes glycogen synthesis. AKT exerts an inhibitory effect on GSK3 by phosphorylation of GSK3 [35]. AKT regulates lipid metabolism through sterol regulatory element-binding proteins (SREBP), which increases cholesterol and fatty acid accumulation, including SREBP-1c, SREBP-1a, and SREBP-2[18, 34]. Therefore, PI3K/AKT regulates glucose metabolism through FoxO1 and GSK-3 and lipid metabolism through mTORC1 and SREBP.

PI3K/AKT pathway in skeletal muscle

Approximately 90% of insulin-stimulated glucose utilization occurs in skeletal muscle and plays an important role in regulating glucose metabolism and energy homeostasis [36]. Insulin regulates skeletal muscle metabolism by promoting glucose transport, glycogen synthesis and protein synthesis through PI3K/AKT signalling pathway (Fig. 2).

Previous research has found knockout or knockdown of AKT or IRS adaptor proteins obviously reduce insulin-induced glucose uptake, whereas overexpression of AKT increases glucose uptake [37]. AKT directly phosphorylates AS160, inducing GLUT4 translocation, which translocated to the plasma membrane from storage vesicles and transports glucose in skeletal muscle following stimulation of insulin and AKT [38, 39]. GagAKT, constitutively activated form of AKT, promotes glycogen synthesis in L6 myotubes [40]. Following study found activated AKT increases glycogen synthesis in skeletal muscle, activating glycogen synthase (GS) to redirect glucose-6-phosphate to glycogen and inhibiting GSK-3[41]. In skeletal muscle, insulin stimulates protein synthesis and accelerates mRNA translation by regulating the initiation steps of protein translation [42]. AKT-mediated mTORC1 activation regulates a number of downstream effectors proteins through phosphorylation, including the well-characterized effectors p70 ribosomal S6 protein kinase-1 (S6K1) and eukaryotic translation initiation factor-4E (eIF4E)-binding protein-1 (4E-BP1), to increase protein synthesis [43, 44]. Obesity is associated with several processes in skeletal muscle metabolism, leading to insulin resistance. Insulin resistance refers to a

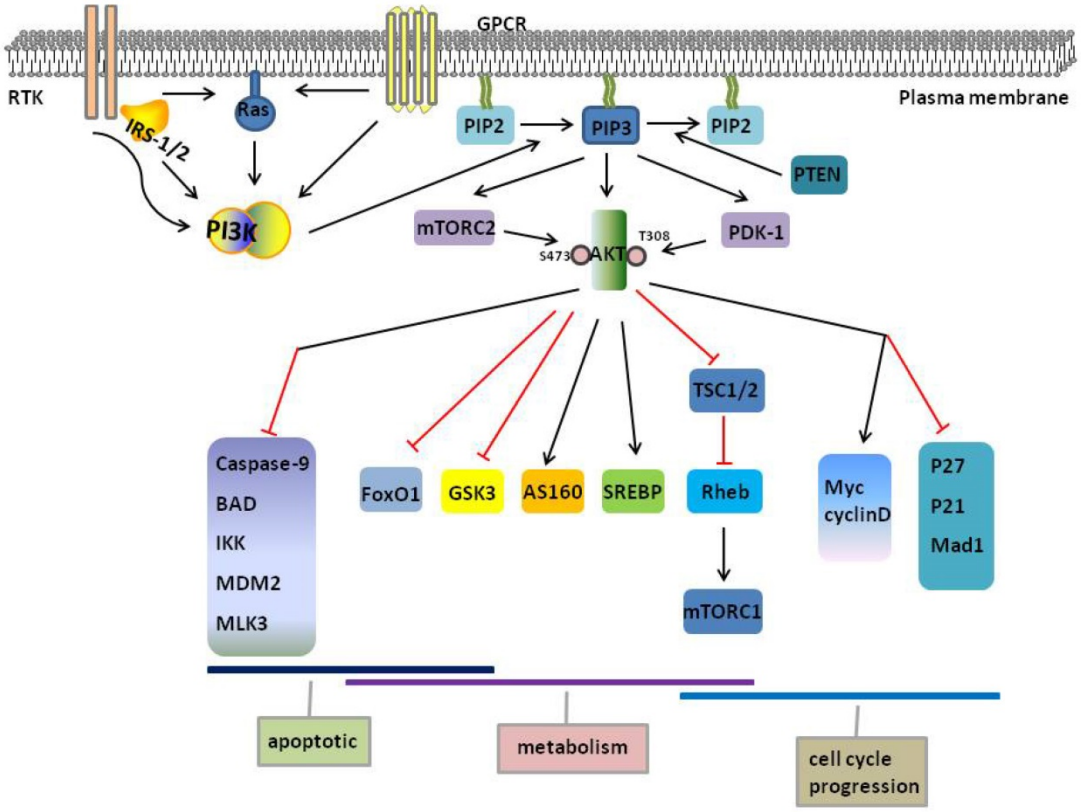

Figure 1. PI3K/AKT pathway. PI3K activates AKT, and AKT phosphorylates downstream substrates that are involved in the regulation of diverse cellular functions, including apoptotic, metabolism and cell cycle progression. As illustrated by these targets, a high degree of functional versatility and overlap exists amongst AKT substrates. Red and black line indicates inhibition and activation respectively. AKT, protein kinase B; AS160, Akt Substrate of 160 kDa; FoxO1, Forkhead box O1; GSK3, glycogen synthase kinase 3; GPCR, G-protein-coupled receptors; IRS-1/2,insulin receptor substrate-1/2; IKK, IkB-kinase; MAD1, MAX dimerization protein 1; MDM2, murine double minute 2; MLK3, mixed lineage kinase 3; mTORC1/2, mTOR complex 1/2; PDK1, phosphoinositide-dependent protein kinase 1; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, Phosphatase and tensin homologue; RTK, receptor tyrosine kinases; SREBP, sterol regulatory element-binding proteins; TSC1/2, tuberous sclerosis complex 1/2.

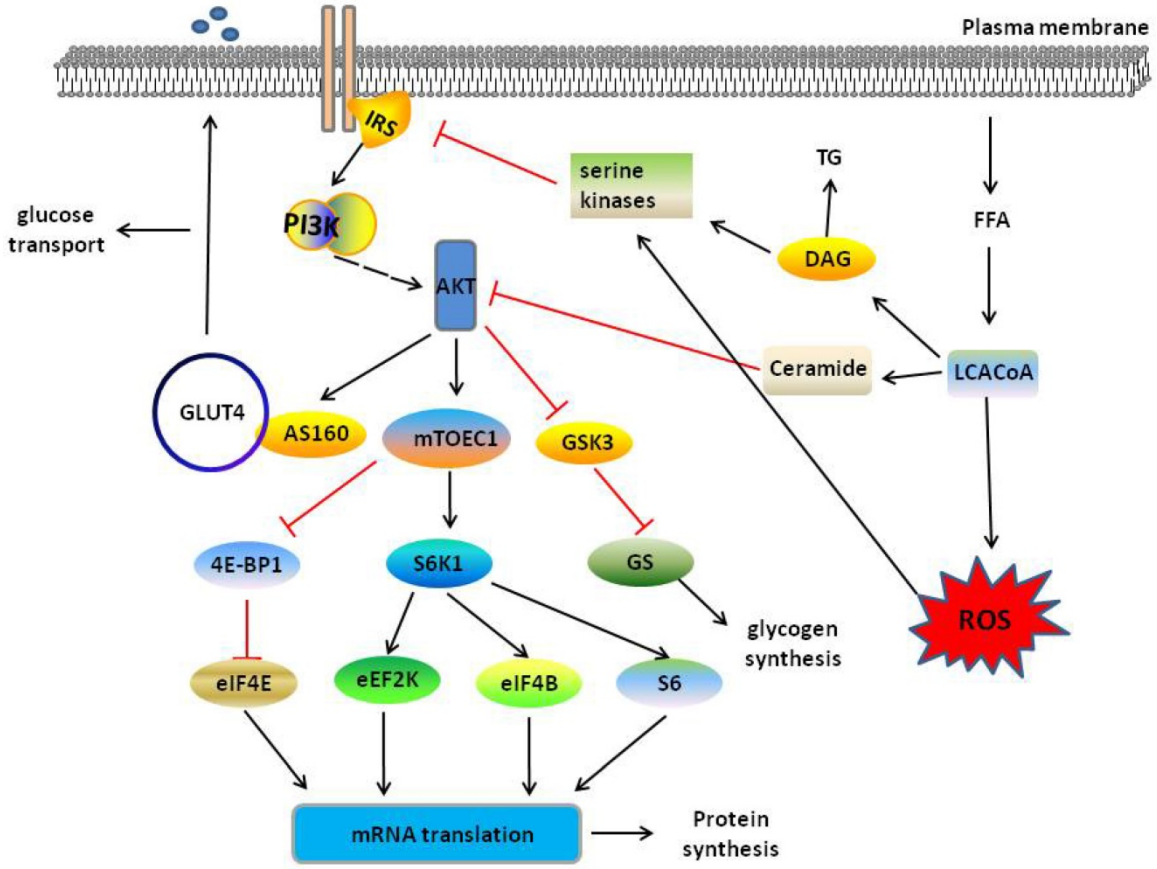

Figure 2. PI3K/AKT pathway in muscle tissue when normal state and insulin resistance. In normal sate, insulin mediates PI3K/AKT pathway and then regulates glucose transport through activating AS160, glycogen synthesis through inhibiting GSK3 and protein synthesis through activating S6K1 or inhibiting 4E-BP1. When the excess FFAs enters into skeletal muscle, FFAs forms LCACoAs, and then partitioned to the TAG or toward the mitochondria for oxidation fatty acid, which inhibits PI3K/AKT signalling and leads to skeletal muscle insulin resistance. Red and black line indicates inhibition and activation respectively. See text for detailed descriptions.

blunted response to insulin in organs and as an important marker of T2DM [45]. Therefore, dysfunctional PI3K/AKT-mediated glucose transport and glycogen synthesis play an important role in the development of obesity and T2DM.

Under normal conditions, FFAs enter the skeletal muscle through fatty acid translocase/CD36 and fatty acid-binding protein, and then forms long chain fatty acid CoAs (LCACoAs), which are then partitioned to the synthesis of lipids (TAG) or toward the mitochondria for oxidation [46]. Excessive lipid production and impaired disposal may promote the development of insulin resistance and diabetes in the skeletal muscle [47, 48]. In early studies, insulin resistance was thought to be accompanied by excessive intramyocellular lipid (IMCL) levels [49], and improved insulin sensitivity observed in subjects with T2DM by reduced IMCL levels [50]. Recently, muscle lipid intermediates, such as LCACoAs, ceramides and diacylglycerol (DAG), were shown to be the cause of insulin resistance [46, 48] instead of IMCL [51]. In the presence of insulin resistance, the level of free fatty acids increases in the body resulting in the accumulation of intramyocellular lipids, such as DAG and ceramides [52]. DAG activates serine kinases phosphorylates and inhibits the signal transduction capacity of IRS-1[53]. Ceramides disturb insulin signalling by AKT, leading to reduction of glucose utilization [54]. Mitochondria-dependent mechanisms also cause insulin resistance. Excessive fatty acid oxidation in the mitochondria via the tricarboxylic acid (TCA) cycle and the electron transport chain (ETC) increases the production of fatty acid metabolites and reactive oxygen species (ROS), subsequently activated intracellular stress kinases to inhibit IRS-1 and possibly exerting effects on insulin signalling from GLUT4 translocation to unknown points downstream of AKT and AS160 function [46, 55] (Fig. 2). Excessive lipid intermediate production and the mitochondria disorder, impair the insulin-AKT pathway, leading to insulin resistance in skeletal muscle, and ultimately affect development of obesity and T2DM.

PI3K/AKT pathway in adipose tissue

Adipose tissue has two main functions: energy storage and endocrine function, which plays an important role in maintaining body energy balance,

including protecting tissues and organs from cold and hot, thermogenesis and the production of various hormones/cytokines that are collectively referred to as cytokines [56, 57]. Insulin-AKT signalling regulates the metabolism of adipose tissues by promoting glucose utilization, protein synthesis, and lipogenesis. Insulin stimulates the utilization of approximately 10% of glucose in adipose tissue, glucose metabolism in adipose tissue impacts other tissues through its extra-adipose actions [58].

Although most of the lipid stored in adipose tissues is derived from the diet, the adipocytes are fully capable of synthesizing new fatty acids from excessive substrates through *de novo* lipogenesis (DNL), and fatty acids are then transferred into TGA and eventually exported as very low density lipoproteins (VLDLs) for storage and utilization by peripheral tissues [56]. The two major enzymes of DNL, fatty acid synthase and acetyl CoA carboxylase, are abundantly expressed in adipose tissues under the control of SREBP-1c [56]. In normal physiology, feeding is able to activate synthesis of SREBP-1c via insulin-dependent pathway (mTORC1) or insulin-independent pathway (carbohydrate response element binding protein (ChREBP)) [59, 60]. But insulin pathway is require for expression of SREBP-1c mRNA in obesity or T2DM [60].

PI3K/AKT signalling pathway promotes lipid biosynthesis and inhibits lipolysis. The substrate SREBP, which regulates fatty acid synthase and cholesterol-related genes [18, 61], and FOXO1, which regulates lipolysis by controlling the expression of adipose triglyceride lipase (ATGL) [62], are primary substrates for AKT-mediated lipid metabolism [63]. In the feeding state, SREBP-1c is regulated by four pathways: activated AKT stimulates liver X receptor (LXR), which is require for SREBP-1c transcription [64]; activated AKT stimulates mTORC1 to activate SREBP-1c transcription, and mTORC1 also inhibits Lipin-1, which decreases the half-life of nuclear SREBP-1c [65, 66], and activates S6K1, which promotes SREBP-1c maturation [67, 68]; activated AKT suppresses insulin-induced gene 2A (INSIG2A), which strongly promotes the maturation of SREBP-1c precursors into nuclear forms [69]; and activated AKT inhibits GSK3, which extends the half-life of SREBP-1c [70]. In the fasting state, acute lipolysis is induced by β-adrenergic signalling, leading to cAMP accumulation and subsequent PKA-mediated phosphorylation of hormone sensitive lipase (HSL) and perilipin [71]. In the fed state, PI3K/AKT inhibits protein kinase A (PKA) and thus suppresses lipolysis. AKT-independent, PI3K-dependent pathway also regulates adipocyte lipolysis by directly regulating PKA [72], AKT regulate FoxO1 through three pathway: reducing the expression of the rate-limiting lipolytic enzyme (ATGL), which is responsible for triacylglycerol hydrolase activity (ATGL) [62]; reducing the expression of interferon regulatory factor 4 (IRF4), which promotes lipolysis, at least in part, by inducing the expression of the lipases HSL and ATGL [71]; phosphorylating phosphodiesterase 3b (PDE3B) to reduce intracellular cAMP levels and PKA activity, thus inhibiting lipolysis in adipocytes [73].

Obesity is associated with insulin resistance. Abnormal glucose metabolism caused by insulin resistance in adipose tissues impacts other tissues through its extra-adipose actions. For example, specifically knockdown of GLUT4 in adipose tissues resulted in insulin resistance in skeletal muscle and liver instead of adipose tissues [74]. When the synthesis ability of adipose tissues decreases and fat degradation increases, the release of free fatty acids (FFAs) increases, thus reducing circulating adiponectin levels and lipid oxidation in extra-adipose tissues. However, this process triggers the ectopic accumulation of lipids and subsequently causes lipotoxicity and insulin resistance [75]. How does insulin resistance occur in adipose tissues?

The synthesis and secretion of adiponectin, tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6), which enhance lipolysis by reducing perilipin and fat-specific protein 27 levels [76]. The increased in subjects with obesity-induced inflammation, aggravating insulin resistance [77]. In the presence of adipose hypertrophy, insulin resistance also occurs because of the expansion of adipose tissues exceeds their storage capacity [45, 78, 79]. Additionally, adipose hypertrophy increases tissue immune cell infiltration, fibrosis, and lipolysis, reduces IRS-1 activation and AKT-induced glucose uptake, and exacerbates systemic insulin resistance and the development of T2DM [79, 80]. Therefore, adipocytokines and adipose hypertrophy cause insulin resistance by blocking PI3K/AKT-mediated inhibition of lipolysis attenuating the capacity of glucose utilization, and weakening the capacity of SREBP to promote lipid synthesis.

PI3K/AKT pathway in the liver

Most of the extracellular glucose is produced in the kidneys and liver, and only the liver acutely responds to insulin by reducing glucose levels [81]. In the fasting sate, glucose is primarily utilized in the liver for gluconeogenesis and glycogenolysis then transported to various tissues while suppressing the synthesis of new fatty acids [82]. In the fed state, the PI3K/AKT signalling pathway reduces hepatic glucose production (HGP) and glycogenolysis,

increases glycogen synthesis and the synthesis of fatty acids for storage and subsequent utilization by other tissues [82, 83].

In previous studies, insulin suppressed PEPCK and G6PC expression, which are known to increase hepatic gluconeogenesis by activating the PI3K/AKT pathway [84-86]. However, insulin was recently shown to inhibit gluconeogenic gene expression [87]. Additionally, those mice still maintained the normal postprandial state, even in the absence of canonical liver insulin signalling [85, 87]. Based on these results, AKT may not only be an indispensable intermediate for insulin action, extrahepatic insulin may be stimulated by other pathways to regulate glucose metabolism in the liver. Three pathways may mediate cell-nonautonomous effects on hepatic glucose metabolism [88]. First, insulin action in the hypothalamus through K (ATP) channels decrease expression of G6PC and hepatic glucose production (HGP) in liver [89, 90]. Subsequently, insulin acts in agouti-related peptide (AgRP) neurons through PI3K-PIP3 signalling to control this process [91]. However, further studies should be carried on because the action of insulin in brain may not common in all species [92, 93]. Second, insulin functions through the AKT pathway to inhibit lipolysis and decrease circulating FFA levels in adipose tissues, which suppressing HGP in the liver, even in the absence of hepatic insulin signalling [82, 94]. Third, insulin functions through the AKT pathway suppress α-cell glucagon secretion in the brain, which reducing HGP levels in the liver [92, 95, 96]. All three pathways require the insulin-PI3K pathway regulate to HGP, regardless of whether insulin functions in the brain, liver or adipose tissues (Fig. 3).

The PI3K/AKT pathway also mediates lipid synthesis. Overexpression of SREBP-1c in the liver selectively induces the expression of lipogenic, but has no effect on cholesterol synthesis genes. AKT has been reported to modulate the mTORC1-S6K1 pathway to regulate SREBP-1c expression in the liver [97]. AKT suppresses the expression of INSIG2A, a liver-specific transcript encoding the SREBP-1c inhibitor INSIG2, through an mTORC1-independent pathway [98]. However, in the absence of AKT2, the activation of mTORC1 and SREBP-1c is not sufficient to drive postprandial lipid generation [99]. Thus AKT-mediated mTORC1-dependent and –independent pathways are required for lipogenesis. The role of FoxO1 in liver lipid metabolism is less well studied; some studies have shown that FoxO1 is directly associated with insulin-promoted expression of fat genes in the liver, whereas others have reported a permissive role for FoxO1 in these processes [100-102]. However, AKT-dependent activation of mTORC1 was recently shown to be required for DNL, but recently inhibition of FoxO1 also is required and sufficient for DNL [82]. Further studies are required to reconcile the relationships between the mTORC1-

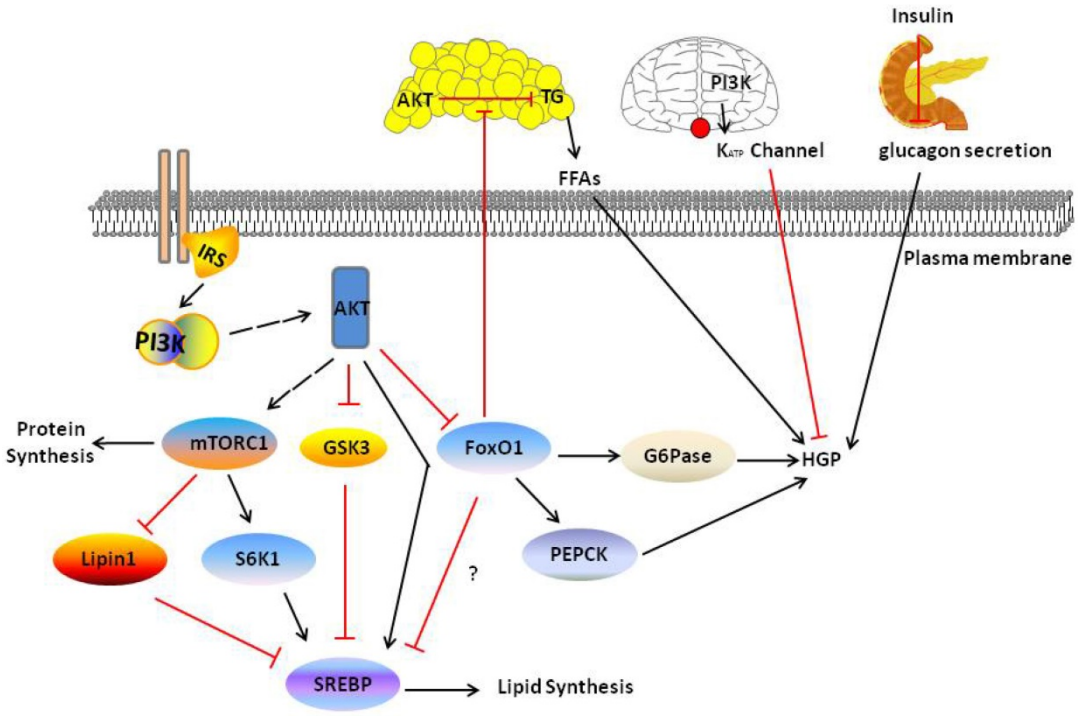

Figure 3. PI3K/AKT pathway in liver and other tissue mediate liver metabolism. PI3K/AKT signal increase DNL in four ways: activating S6K1 and SREBP, inhibiting Lipin1 and GSK3. And inhibits HGP through directly inhibiting FoxO1 or indirectly other tissue PI3K/AKT signaling including adipose, brain and pancreas. Red and black line indicates inhibition and activation respectively. See text for detailed descriptions.

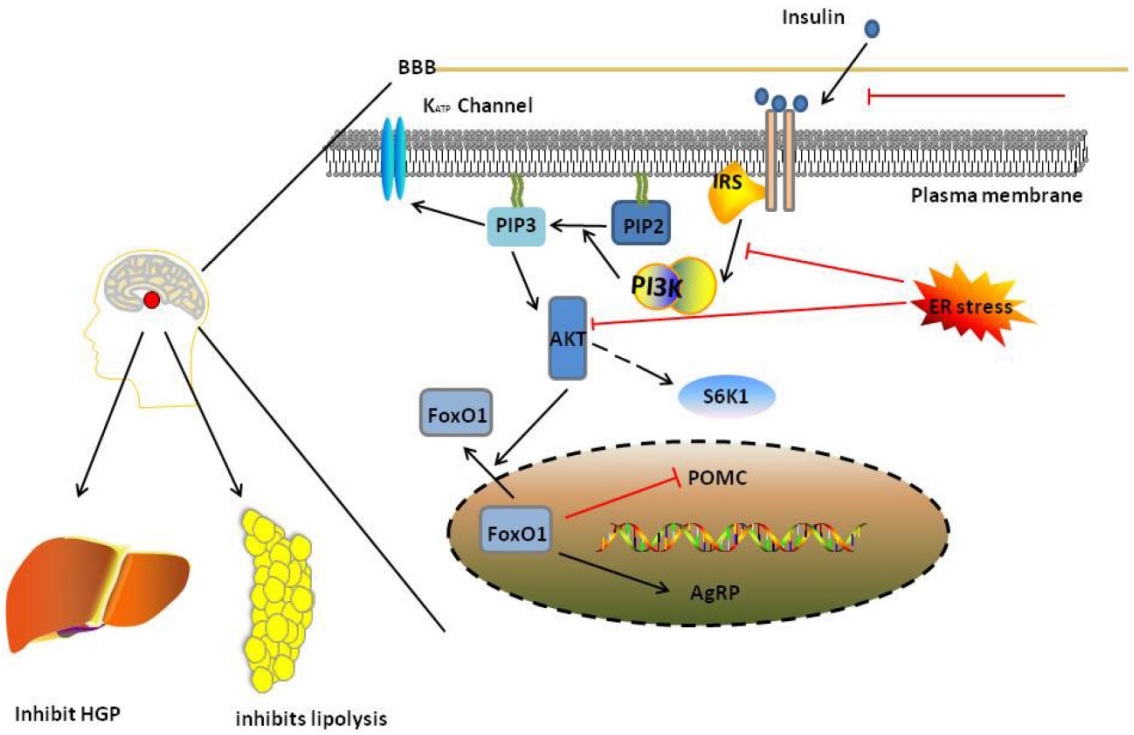

Figure 4. PI3K/AKT pathway in normal state and insulin resistance. In normal state, ligand activates PI3K/AKT signalling which inhibits food intake in hypothalamus. And the signalling also inhibits HGP through regulate liver and inhibit lipolysis through regulate adipose tissue. And when the ligand can not pass through BBB, and the ER stress occurs, insulin resistance would occurs in brain, leading to damage PI3K/AKT pathway. Red and black line indicates inhibition and activation respectively. See text for detailed descriptions.

dependent pathway, INSIG2-dependent pathway and FoxO1 pathway (Fig. 3).

In obesity, the blunted response of adipose tissues leads to decreased FFA uptake and glucose utilization, resulting in ectopic accumulation in other tissues [103]. Ectopic accumulation of lipids in the liver is highly correlated with insulin resistance and non-alcoholic fatty liver disease (NAFLD) [104]. Meanwhile, excessive oxidation of FFAs increases the hepatic acetyl-CoA content and thus activates pyruvate carboxylase, which is required for gluconeogenesis [45], and increases DAG levels, which impair PI3K/AKT pathway and exacerbate insulin resistance [48, 105]. Chronic metabolic inflammation and endoplasmic reticulum (ER) stress also impair hepatic insulin-AKT signalling and subsequently causes insulin resistance [106, 107].

Hepatic glycogen synthesis decreases during hepatic insulin resistance due to decreased insulin-PI3K signalling [48]. However, contradictory findings are observed in insulin-mediated DNL and HGP: why does insulin normally stimulate DNL but inhibit HGP in hepatic insulin resistance. Two possible mechanisms have been reported: in the first, the liver displays selective insulin resistance in which the actions of insulin are suppressed in HGP but are normal in DNL [108]. And recent study finds Irs2-knockout mice develop 'selective insulin resistance', whereas mice lacking in Irs1, or both Irs1 and Irs2, develop 'total insulin resistance', which indicates the IRS 1/2 are the cause of insulin selective resistance [109]; in the second, hepatic insulin signalling remains intact but the cell-nonautonomous pathway may be blocked, which is mentioned on above, resulting in increased HGP during insulin resistance [82]. Others recent study also proved this hypothesis [85, 87]. The first statement can be interpreted as insulin resistance caused by the integrity of the substrate IRS1/2. The two possible mechanisms are, in fact, that insulin signals are intact and both cause increased HGP and DNL when insulin resistance.

PI3K/AKT pathway in the brain

Previously, insulin-sensitive organs included the skeletal muscle, liver and adipose tissues. The brain has recently been reported to be an insulin-sensitive organ, and its function in glucose metabolism and energy regulation has also been recognized.

Leptin is the most important hormone reported to date that regulates food intake and energy balance [110]. In the hypothalamic arcuate nucleus (ARC), anorexigenic proopiomelanocortin (POMC) and orexigenic AgRP coordinately regulate food intake and energy expenditure, as well as peripheral tissue glucose homeostasis and energy partitioning through insulin, leptin and nutrients [111]. The leptin activity-mediated IRS-PI3K pathway was observed in

the IRS2-deficient mice [112]. Leptin requires intact PI3K signalling to promote hypothalamic expression of POMC genes and inhibit expression of the NPY and AgRP genes [113, 114]. In a subsequent study, leptin and insulin were shown to coordinately regulate FoxO1 activity, increasing the expression of NPY and AgRP and suppressing POMC expression [115, 116]. Recently, Gpr17, the target of FoxO1, was shown to regulate feeding and sensitivity through insulin and leptin in AgRP neurons [117, 118]. However, leptin and insulin-mediated PI3K signalling was only shown to play a role in POMC expression in the presence of short-term alterations in leptin levels. In the presence of persistent excess energy availability, leptin signalling activates other pathways, such as STAT3 or SH2-containing tyrosine phosphatase, to predominantly regulate food intake in POMC neurons [90, 113, 119]. The PI3K/AKT signalling pathway plays an important role in glucose homeostasis mediated insulin and leptin actions in the hypothalamus and is thought to exert less important effects on food intake [120].

mTOR, a well-known phosphorylation target of AKT, specifically binds to Rheb GTPase with GTPase-activating protein (GAP) activity, which directly activates mTORC1[121]. As shown in a previous study, acute activation of mTOR1 promotes the ability of hypothalamic neural circuits to sense the nutritional milieu and regulate feeding [122, 123]. According to a recent study, mTOR1 is dispensable for the regulation of feeding behaviour and energy metabolism [124], and chronic activation of mTOR1 interferes with the hypothalamic neurons that regulate feeding and energy balance [125]. However, mTOR1 signalling is required for glucose homeostasis in the hypothalamus [126, 127]. One way to regulate HGP is that S6K1, a downstream molecule of mTOR1, regulates HGP, modulates neuronal excitability and peripheral lipid metabolism in POMC neurons, regulates the insulin sensitivity of skeletal muscle via AgRP neurons [128]. Another way to regulate HGP is PI3K-stimulated generation of PIP3 in AgRP neurons, which activates K (ATP) channels, decreasing G6PC expression in the liver [91]. Compared with POMC, AgRP plays a more important role in the long-term regulation of glucose metabolism [91]. The selective inactivation of IR in AgRP neurons in mice results in an inability to suppress HGP whereas only a deficiency in both leptin and IRs in POMC neurons resulted in systemic insulin resistance [45, 129]. Acute activation of AgRP neurons decreases insulin-stimulated glucose uptake and insulin sensitivity by increasing myostatin expression, a muscle-related gene expressed in brown adipose tissue that causes insulin resistance [130]. Recently, Another ligand, glucagon-like peptide (GLP-2), it was recently shown to play a key role in the control of HGP through the PI3K/AKT pathway[131], suggesting that in addition to insulin and leptin, GLP-2 also regulates HGP through PI3K/AKT signalling.

Leptin and insulin-mediate PI3K/AKT signalling is impaired in the brains of obese subjects with insulin resistance [132]. There are two reasons for this: first, the transport of insulin through the blood brain barrier is impaired in obese subjects [45]. second, brain insulin action is attenuated or even diminished in response to both endogenous and exogenous insulin stimulation [133], which impairs hypothalamic AKT activation due to ER stress and the activation of inflammatory pathways [134]. Both factors contribute to the development of insulin resistance in the brain (Fig. 4). Insulin resistance in the brain is followed by disorders of glucose metabolism, such as hepatic glucose production and glucose transport, occurring in other insulin-sensitive organs and may eventually lead to systemic insulin resistance.

Three functions of the PI3K/AKT pathway are disturbed in insulin resistance in the brain. First, PI3K generates PIP3, which regulates GHP through K (ATP) channels in the hypothalamus. Insulin signalling is blocked during insulin resistance in the brain due to increased protein kinase C (PKC) activity, ER stress and inflammation [134, 135], which blocks the ability of PI3K to generate PIP3. Second, in hypothalamic neurons, FoxO1 upregulates AgRP/NPY expression and downregulates POMC expression under normal conditions, which is inhibited by AKT. In response to insulin resistance in the brain, overexpression of FoxO1 in POMC neurons leads to obesity and hyperphagia [136]. Third, according to studies by Ono et al. [137] and Um, S. H et al. [138], activation of S6K1, a downstream effector of mTORC1, in hypothalamic neurons leads to hepatic insulin resistance because it decreases the stimulation of IRS-1 and AKT.

PI3K/AKT pathway in the pancreas

The pancreas is mainly composed of four types of cells, of which pancreatic β cells are vitally important in maintaining glucose homeostasis by producing and secreting insulin in response to the blood glucose concentration [58]. Insulin regulates β cell function and insulin secretion through the PI3K/AKT pathway.

Insulin was not previously thought to exert an effect on insulin synthesis, differentiation and secretion in pancreatic cells. However, insulin has consistently been shown to play an important role in pancreatic cells [139], mainly through PI3K/AKT

signalling. β cell-specific knockout of IRS2 or the IR, which disrupts of insulin signalling in pancreatic β cells, reduces the pancreatic insulin content, β cell mass and glucose-stimulated insulin secretion, followed by the development of a phenotype similar to T2DM [140, 141]. Activation of the PI3K/AKT pathway promotes insulin secretion form pancreatic β cells [142, 143]. Overexpression and constitutive activation of AKT in pancreatic β cells results in an increase in the β cell mass, proliferation and cell size, which are mediated by signalling intermediates downstream of AKT, such as FoxO1, GSK3 and mTOR1, providing further evidence for the role of AKT in pancreatic cells [144]. In contrast, overexpression of a kinase dead mutant in β cells, which reduced AKT activity by 80%, results in a lack of insulin secretion [145]. In addition, the PI3K/AKT pathway prevents lipotoxicity in pancreatic β cells by inhibiting FoxO1, which is abundantly expressed in pancreatic β cells and promotes FFA-induced β cell apoptosis [146, 147].

Obesity and T2DM are associated with insulin resistance. In insulin resistance, the activity of β cells are increased, boosting the release of additional insulin to maintain normal glucose tolerance, resulting in the development of hyperinsulinemia [148]. Glucose tolerance is impaired in response to β cell dysfunction in insulin resistance, resulting in the development of T2DM [149]. In obese subjects, excess levels of circulating FFAs, which are caused by a blunted response of adipose tissues, impairs the function of β cells [150]. This finding also explains why obese individuals readily develop to T2DM. In obesity and T2DM, the insulin-mediated PI3K/AKT pathway is also blocked, which reduces insulin secretion and β cell function [58]. This condition further aggravates insulin resistance by affecting other tissues.

Therapeutic targets

The PI3K/AKT signalling pathway regulates cell proliferation, differentiation, metabolism, and cytoskeletal reorganization, leading to apoptosis and cancer cell survival. Therefore, the pathway is associated with various diseases, such as obesity, diabetes and cancer. The table mainly summarizes recent target treatments which related to PI3K/AKT pathway for obesity and type 2 diabetes (Table 1). In normal condition, PI3K/AKT is activated in regulating the function of the body. When excessive energy intake occurs, the PI3K/AKT pathway is suppressed. At this point, activation of the PI3K/AKT pathway alleviates obesity and insulin resistance. However, when the regulation of PI3K is disturbed, such as overexpression and mutation, it can cause many human diseases (obesity, cancer, etc.) [151]. At this point, the pharmacological inhibition of PI3K is an effective and safe anti-obesity and anti-cancer intervention that can reverse the negative effects of human diseases [152].

Table 1. Summary of targeting PI3K/AKT pathway in the treatment of obesity and T2DM

Key cell type/tissue	target	Mechanism	Effect	References
C57BL/6 mice HepG2 cell	FAM3A	Activates PI3K/AKT signaling	inhibits hepatic gluconeogenesis	[153]
db/db mice HFD-induced diabetic mice	Dapper1	Activates PI3K/Akt in an insulin-independent manner	attenuates hepatic gluconeogenesis and lipogenesis in T2D	[154]
Streptozocin-induced diabetic mice db/db mice HepG2 cell	ATP synthase β subunit (ATPSβ)	Activates PI3K/Akt pathway	promotes hyperglycemia	[155]
db/db diabetic mice HepG2 cell	Bone morphogenetic protein-7 (BMP-7)	Activates PDK1 and AKT strengthens insulin signaling	improves glucose uptake promotes peripheral insulin resistance	[156]
Streptozotocin-induced diabetic db/db mice Pancreatic beta-cell	glial cell line-derived neurotrophic factor (GDNF)	Activates phosphorylation of AKT	improves glucose tolerance and β cell mass	[157, 158]
Pancreatic beta-cell	nuclear factor erythroid 2-related factor 2 (Nrf2)	Through PI3K/AKT pathway	Enhances glucose-stimulated insulin secretion in β-cell and insulin sensitivity	[159]
Male C57BL/6J mice HepG2 cell	Irisin	Activate PI3K/Akt/FOXO1 and PI3K/Akt/GSK3 pathway	Reduces gluconeogenesis and increase glycogenesis	[160]
Streptozotocin-induced diabetic mice	amniotic fluid stem cells (AFSC)	Activates the IR/PI3K/Akt signaling pathway preserving	promoting endogenous β-cell functionality and proliferation.	[161]
C57BL/6 mice HepG2 cell	glycerol kinase (Gyk)	Decreases the expression of FoxO1	reduced expression of G6Pase and PEPCK	[162]
C57BL/6 mice	NPC1L1	Regulates the AKT-FOXO1-PEPCK/G6Pase pathway	reduced expression of G6Pase and PEPCK	[163]
MCF7-tet OFF Sesn2F cells	Sestrins (Sesn1/2/3)	through activation of AMPK and mTORC2, which is necessary for activation of AKT	Regulate both glucose and lipid metabolism	[164, 165]
Mesenchymal stem cells	Apelin 13	Activate PI3K/AKT signaling pathways	enhance the efficacy of MSCs in cell therapy of diabetes	[166]
C57BL/6 mice HepG2 cell	miR-451	regulate the AKT-FOXO1-PEPCK/G6Pase pathway	promote gluconeogenesis and promote glucose homeostasis	[162]
C57BL/6 mice HepG2 cell	GSK-3	Global inhibition of GSK-3	improves insulin sensitivity and hepatic glycogen deposition significantly	[35, 167]

Key cell type/tissue	target	Mechanism	Effect	References
C57BL/6 mice HEK293 Cells HepG2 cell	miR-423-5p	Repress the FAM3A-ATP-Akt pathway	Promote gluconeogenesis and hyperglycemia	[168]
Agrp-specific FoxO1 knockouts by mating Agrp-ires-Cre-transgenic mice with $Foxo1^{loxP/loxP}$ mice	Gpr17	Reduce expression of FoxO1	Improved glucose homeostasis, and increased sensitivity to insulin and leptin	[117, 118]
PHLPP-1 knockout (KO) C57BL/6 mice	PHLPP	PHLPP inhibits PI3K/AKT signaling	As inhibitor of AKT	[169, 170]
PB-Cre4 mice PTENloxP/loxPmice	PTEN	PTRN inhibits PIP3, thus reduces activation of AKT	As inhibitor of PI3K	[152, 171]

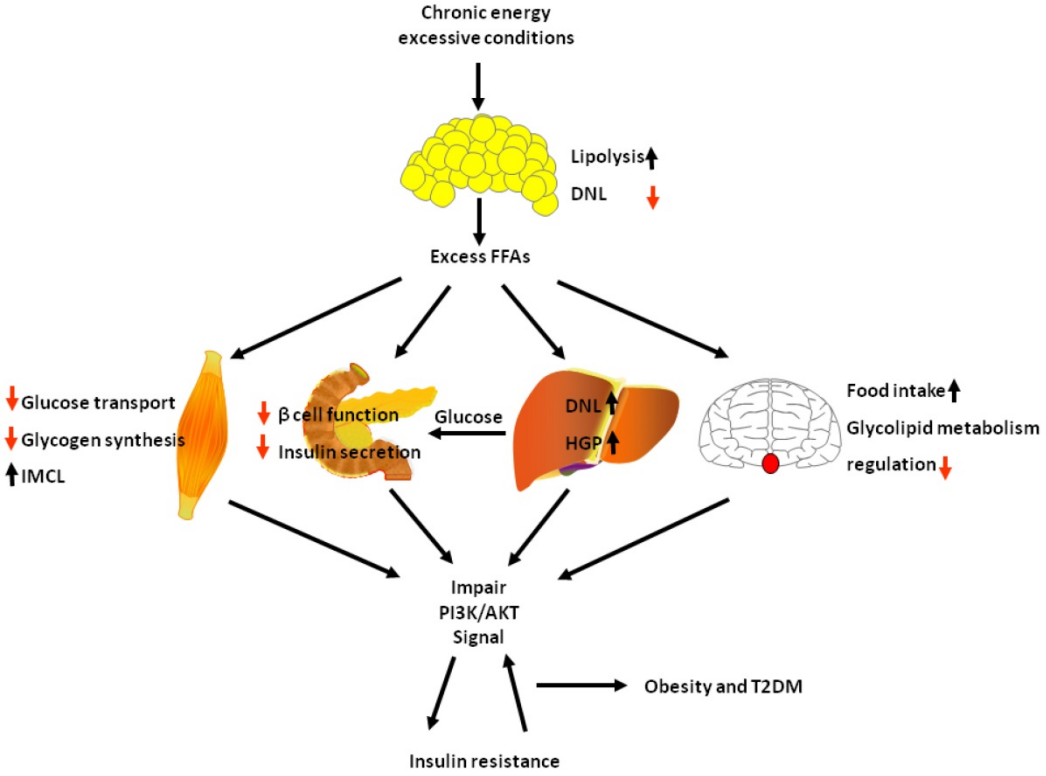

Figure 5. In chronic energy excessive conditions, the causes of insulin resistance. In chronic energy excessive conditions, lipid accumulation is saturated and results in an increase in lipolysis in adipose tissue, causing excess FFAs. Lipid ectopic accumulation in skeletal muscle causes reduce of glucose transport and glycogen synthesis; excess circulating FFAs also destroy β cell function and insulin secretion; and in liver, insulin action is normal, but inhibition of extra-hepatic insulin signalling and lipid ectopic accumulation causes increase of HGP and excess insulin causes increasing DNL; and in brain, excess FFAs causes glucose and lipid metabolism disorder. All those ultimately impair PI3K/AKT signal, causing insulin resistance, and insulin resistance further exacerbates PI3K/AKT signalling, forming a vicious circle. Black arrow indicates activation or augment. Red arrow indicates reduction.

Conclusion

Many ligands such as leptin, insulin, GPL, growth factors act on PI3K/AKT pathway and play a variety of physiological roles. Insulin is the main ligand for PI3K/AKT pathway to regulate metabolism, others only account a small part for metabolism. In obesity and diabetes, insulin guided multiple pathways to regulate lipid and glucose metabolism. Among them, PI3K/AKT is the main pathway of insulin. PI3K/AKT signalling pathway exists various organs in the body and plays an important role in a variety of physiological functions. Here we describe the metabolic functions of PI3K/AKT signalling pathway in the brain, liver, muscle, adipose and pancreas play a role in the metabolism, and the relationship between obesity and diabetes. Under physiological conditions, insulin secreted immediately after a meal activates PI3K/AKT signalling pathway, which increases glucose utilization and reduces gluconeogenesis in liver and muscle, increases body lipid deposition thus reduces FFA circulation in adipose tissue, increases insulin production in the pancreas, regulates lipid and glucose metabolism balance, reduce appetite in the brain. However, in chronic energy excessive conditions as observed in obesity, sustained excess circulating FFAs consistently harm other tissue: lipid accumulation is saturated and results in an increase in lipolysis in adipose tissue, further aggravating content of circulating FFAs; lipid ectopic accumulation in skeletal muscle causes reduce of glucose transport and glycogen synthesis, leading to glucose metabolism unbalance; excess circulating

FFAs also destroy β cell function and insulin secretion; and in liver, insulin action is normal, but inhibition of extra-hepatic insulin signalling and lipid ectopic accumulation causes increase of HGP and excess insulin causes increasing DNL. All of those would impair PI3K/AKT signal then causing insulin resistance, and insulin resistance further exacerbates PI3K/AKT signal, forming a vicious circle. Finally, the vicious circle would lead to obesity and T2DM (Fig. 5).

Over the past decade, people have made a surprising understanding of the regulation and function of PI3K/AKT signalling pathway. There is no doubt that PI3K/AKT signalling is closely related to metabolism. And manipulation of PI3K/AKT signalling and its downstream molecule are promising therapeutic target for the treatment of obesity and T2DM. However, the PI3K/AKT pathway is still complex and still needs a lot of energy to study.

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Abbreviations

PI3K, Phosphoinositide 3-kinase; AKT, protein kinase B; T2DM, type 2 diabetes mellitus; RTKs, receptor tyrosine kinases; GPCR, G-protein-coupled receptors; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, Phosphatase and tensin homologue; PDK1, phosphoinositide-dependent protein kinase 1; mTORC2, mTOR complex 2; PP2A, Protein phosphatase 2A; PHLPP1, PH domain leucine-rich repeat protein phosphatises 1; GLUT4, glucose transporter 4; GSK3, glycogen synthase kinase 3; FoxO, forkhead box O; PGC1α, peroxisome proliferator-activated receptor-coactivator 1α; PEPCK, phosphoenolpyruvate carboxykinase; G6PC, glucose-6-phosphatase gene; SREBP, sterol regulatory element-binding proteins; IGF-1, insulin-like growth factor 1; KLF14, Krüppel-like factor 14; GS, glycogen synthase; UCP1, uncoupling protein 1; HDL, high density lipoprotein; S6K1, S6 protein kinase-1; 4E-BP1, eukaryotic translation initiation factor-4E binding protein-1; eIF4F, Eukaryotic translation initiation factor 4F; eIF4B, eukaryotic translation initiation factor 4B; eEF2K, eukaryotic elongation factor-2 kinase; eEF2, elongation factor 2; FFAs, free fatty aids; LCACoAs, long chain fatty acid CoAs; IMCL, intramyocellular lipid; DAG, diacylglycerol; TCA, tricarboxylic acid; ETC, electron transport chain; ROS, reactive oxygen species; DNL, *de novo* lipogenesis; VLDLs, very low density lipoproteins; ChREBP, carbohydrate response element binding protein; ATGL, adipose triglyceride lipase; LXR, liver X receptor; INSIG2A, insulin-induced gene 2A; HSL, hormone sensitive lipase; PKA, protein kinase A; IRF4, interferon regulatory factor 4; PDE3B, phosphodiesterase 3b; IL-6, interleukin 6; NAFLD, non-alcoholic fatty liver disease; ER, endoplasmic reticulum; ARC, arcuate nucleus; POMC, proopiomelanocortin; AgRP, agouti-related peptide; VMH, ventral medial nucleus; TH, tyrosine hydroxylase; JAK2, Janus kinase 2; STAT3, Signal transducer and activator of transcription 3; GAP, GTPase-activating protein; GLP-2, glucagon-like peptide; HGP, hepatic glucose production; PKC, protein kinase C.

Competing Interests

The authors have declared that no competing interest exists.

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