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Review

Akt activation: A potential strategy to ameliorate insulin resistance

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ABSTRACT

Insulin resistance is a hallmark of type 2 diabetes and obesity while the mechanism remains unclear. Current therapy to treat type 2 diabetes is metformin, the 5′-monopho sphate-activated protein kinase (AMPK) activator, owing to the ability to augment peripheral glucose uptake. However, metformin also displays limitations, as AMPK activation remains intact and regular in most type 2 diabetes and metformin does not seem to facilitate peripheral insulin resistance. Evidence has shown that PI3K-Akt/PKB pathway could be induced via insulin and act as an important effector. Akt/PKB is capable of inducing a great number of downstream molecules, such as translocating glucose transporters GLUTs to the cell membrane thus increase glucose uptake. Hence, any defect in Akt/PKB pathway along with the downstream molecules could lead to insulin resistance. Inositol pyrophosphates, synthesized by inositol hexakisphosphate (IP_6) kinase 1 (IP6K1) and competitive with 3,4,5-bisphosphate (PIP_3) to bind the PH domain of Akt/PKB, demonstrate the ability to inhibit Akt signaling. In addition, IP6K1 knockout mice present increased insulin sensitivity and obesity resistance, indicating a novel therapeutic target in confronting insulin resistance. Taken together, we conclude that Akt activation is another potential strategy to ameliorate insulin resistance.

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1. Introduction

Type 2 diabetes is a multifactorial disease, hallmarks of which are recognized as β-cell defections, increased hepatic gluconeogenesis, mitochondrial dysfunctions and also insulin resistance, a common feature in type 2 diabetes, obesity and cardiovascular diseases [1,2]. Despite prominent development in related signaling pathways and involved molecules, the exact mechanism of insulin resistance remains unclear [3]. Primary to insulin resistance is the low effectiveness of uptake and utilization of glucose along with aberrations in lipid metabolism. Insulin resistance appears in liver, skeleton muscle, adipose in the pathologic process of pre-diabetes since these tissues are targets of insulin in the glucose metabolism [4]. Systematic insulin resistance in type 2 diabetes can induce inflammation [5], dyslipidemia and disorder of mitochondrial biogenesis [3,6].

Similar to type 2 diabetes, obesity has also become a worldwide problem currently with the number of the overweight population rapid increased. Obesity-related health problems desiderate therapies. These metabolic syndromes could lead to cardiovascular and cerebrovascular diseases [7], which are the top of various causes of death with around 16 millions death each year across the world [8].

Insulin resistance, as the main symptom of both diseases, is the key to understand and raise therapies to ameliorate diabetes and obesity. Contemporary treatments for type 2 diabetes target at AMPK, which plays an important role in responding to insulin [9]. AMPK is supposed to regulate glycogen synthesis, fatty acid synthesis and oxidation [10]. The application of metformin, a potent activator of AMPK, intends to suppress hyperglycemia and upregulate glucose uptake [11,12].

2. Targeting AMPK treatment: restrictions and challenges

AMPK, the crux molecule regulating complicated energy metabolism, is recognized as a core in type 2 diabetes and other metabolic syndromes. AMPK, which is expressed in various organs related to metabolism, could be induced via various stimulations including hormones, cellular stress and movement and substances effecting cellular metabolism. Researches on genetics and pharmacology indicate that AMPK is essential to maintain glucose balance [13]. The activation of AMPK could ameliorate metabolic dysfunctions triggered by type 2 diabetes.

In diverse species, AMPK exists as a heterotrimer complex consisting of a catalytic subunit α and two further regulatory subunits β and γ. Each of these subunits has isoforms expressed by different genes [14]. N-terminal of α subunit consists of a conservative site Thr^{172}, the phosphorylation of which is integrant in the activation of AMPK. Subunit γ is composed of 4-cystathionine-b-synthase domains to form two bateman domains that can bind adenosine triphosphate (ATP) or adenosine monophosphate (AMP) [15,16]. The increased ratio of AMP and ATP activates AMPK. Thus, all metabolic stresses disturbing energy balance through interfering ATP production can induce AMPK activation [15]. Most understood stimulators are hypoxia and contractile activity of muscles that provide a rationale that exercise is of benefit in improving type 2 diabetes (Fig. 1) [17].

Sensitized AMPK reduces the pathologic level of type 2 diabetes and may augment glycogen synthesis in skeletal muscle [18]. Metformin, a well-known drug to treat diabetes, is also recognized as an activator of AMPK. Metformin displays various mechanisms in treating diabetes, including suppressing hepatic gluconeogenesis via phosphorylation of cAMP-response element binding protein (CREB) , decreasing appetite of patients, reducing intestinal carbohydrate absorption, increasing peripheral glucose uptake and inhibiting Krebs cycle through AMPK activation [19–21]. However, metformin-induced activation of AMPK does not appear to facilitate peripheral insulin resistance, which is considered to occur prior to hepatic insulin resistance [14,22]. What's more, lower absorption of carbohydrate in intestine is now reckoned to induce oxidative stress which might result in cardiovascular complications [23]. Besides, previous work illustrated that the administration of metformin in diabetic patients at a dose of 2550 mg/day for 3–4 months had little impact on insulin

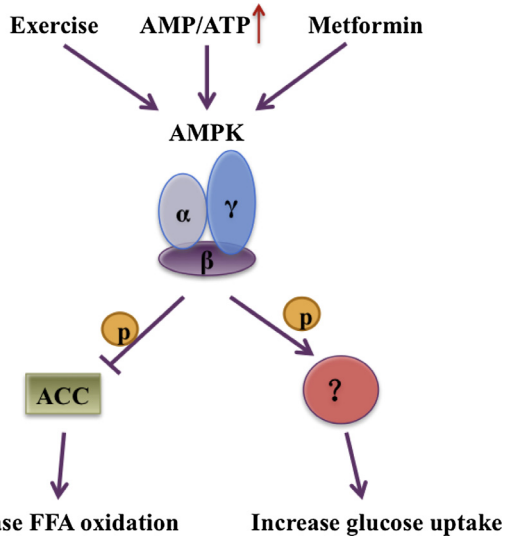

Fig. 1 – Factors induce AMPK pathway and important downstream reactions. AMPK phosphorylates 1-Aminocyclopropanecarboxylic Acid (ACC), decreases Malonyl-CoA, and increases free fatty acid (FFA) oxidation. AMPK may increase glucose uptake via phosphorylating unknown proteins.

receptor substrate-1 (IRS-1), class IA phosphatidylinositol-3 (PI3) kinase (PI3K), or Akt/protein kinase B (PKB) activity in skeletal muscle [24], consistent with the data reported by Karlsson et al. [25]. Impaired glucose tolerance could be reversed via intervention of a healthier lifestyle while metformin acts ineffectively and finitely [26]. It is reported that in endometrial stromal cells, PI3K and GLUT4 expression once increased in response to insulin were then diminished after the treatment of metformin [27]. In addition, Akt phosphorylation was inhibited by metformin [27]. What's more, it is interesting that AMPK activation remains normal in type 2 diabetes [28,29]. McBride et al. [30] found that AMPKα2 knockout mice appear a systematic insulin resistance, indicating the important function of AMPK in regulating insulin sensitivity. On the contrary, skeletal muscle of transgenic mice (AMPK-mutant) appears to respond normally to insulin in vitro. The aberrations of AMPK do not seem to influence basal nor insulin-stimulated deoxyglucose uptake. Moreover, deficiency in AMPK activity displays no obvious change in the steady-state levels of muscle GLUT4 [31]. Fujii et al. also established muscle-specific transgenic mice with cDNAs of inactive AMPKα2 (α2iTG) and found glucose tolerance was only effected slightly in the mutant mice, indicating that AMPK is not an important mediator of insulin sensitivity in skeletal muscle [32,33].

There is no doubt that AMPK is the current target of medicine like metformin that is extensive-utilized in treating type 2 diabetes and the activation of AMPK indeed brings a great number of expected effects to tissue and body. Nevertheless, there is no distinct difference of AMPK activation and subunits expression in diabetes or nondiabetes [34]. Consequently, the future drug discovery should not only concentrate on the activation of particular molecules contributing to the traditional insulin signaling pathway, but those become visibly abnormal in insulin-resistant tissue while responding to insulin.

2.1. *PI3K-Akt pathway acts as an important effector of insulin*

PI3K is an intracellular phosphatidyl inositol kinase, which has serine/threonine (Ser/Thr) kinase activity. PI3K consists of the catalytic subunit p110 and the regulatory subunit p85 [35]. There are three categories of PI3K with different structures and functions. Among these types, the most widely studied is type I PI3K. One of the primary effectors of PI3K downstream signaling network is Akt, also regarded as PKB, a serine/threonine kinase [36]. Three isoforms of Akt/PKB are reckoned as Akt1/PKBα, Akt2/PKBβ and Akt3/PKBγ, each of which has different major functions. Akt1 plays a role in regulating body size and adipogenesis [37], Akt2 disruptions could result in severe insulin resistance and diabetes, along with lipoatrophy [38] and Akt3 functions in brain and neuronal cell size [39]. It is known that Akt promotes cellular survival and growth particularly in cancer as PI3K-Akt signaling pathway is abnormally activated [40], whereas Akt inhibition might also lead to hyperglycemia. Akt2 knockout mice display severe insulin resistance following the development of diabetes rather than Akt1 and Akt3 knockout mice [41].

Growth factors like insulin induce PI3K-Akt activation [27]. After receiving signals from tyrosine kinase (PTK) or G protein-coupled receptor, the regulatory subunit p85 is recruited to the membrane then the combination of p85 and p110 transforms phosphatidylinositol 4, 5-bisphosphate (PIP_2) to PIP_3 [42]. PIP_3 can bind the pleckstrin homology (PH) domain of Akt thus transfer Akt to the membrane from cytoplasm. The following process is that Akt is activated by 3′-phosphoinositide-dependent kinase 1 (PDK1) through the phosphorylation of Thr^{308} and Ser^{473} [14,43].

The activation of PI3K-Akt signaling pathway could induce a number of molecules downstream. It is known that Akt functions in facilitating insulin resistance through inhibiting glucose release from hepatocytes [44]. Akt can translocate GLUTs, specific glucose transporters, to the membrane thus increase glucose uptake [45,46]. The phosphorylation of β subunit tyrosine of insulin receptor then leads to insulin receptor substrate (IRS) phosphorylation and activation. Binding of IRS with p85 ulteriorly results in PI3K-Akt activation and other downstream targets [47]. Thus, PI3K-Akt/PKB pathway plays a distinctly essential role in glucose transfer stimulated by insulin.

3. Insulin resistance is associated with defects in PI3K-Akt signaling pathway

The activated Akt participates in the metabolic functions of insulin mainly through three marked ways: (1) The translocation of GLUTs especially GLUT4, which serves as the major transporter in skeletal muscles and lipocyte. (2) Glycogen synthase kinase 3 (GSK3) is a key kinase involved in hepatic glucose metabolism, which inhibits glucose synthase (GS) activity via phosphorylation [48]. Upon inactivation, hepatic glucose production is reduced thus promotes glycemia in the body. GSK3 is also known as an important substrate of Akt/PKB [49], and its two isomers GSK3α and GSK3β both contain Akt phosphorylation sites. The expression of GSK3β increases in the insulin-resistant tissues of aged and obese mice, which indicates the reciprocal function of GSK3 and Akt/PKB [50]. (3) The well-known theory elicits that obesity is closely related to the pathologic process of insulin resistance in the whole body. Apart from this, Guilherme et al. [51] demonstrate that peroxisome proliferators activated receptor coactivator (PGC-1α) pathway decreases in (pre)diabetic state, resulting in lipid-induced insulin resistance. However, Akt/PKB could phosphorylate PGC-1α to inhibit free fatty acid (FFA) oxidation and gluconeogenesis therefore modulate hepatic glycolipid metabolism [52]. Thus, undesirable interferences in any section of the pathway could affect the transduction of insulin, then influence glucose uptake. In this state, insulin resistance might be determined as defects in the transduction of insulin signal.

Cho et al. [53,54] state that the response of liver and skeletal muscle to insulin recedes to different degree in Akt2/PKBβ knockout mice compared with the wild type. Thereunto, hepatic glucose production is reduced with monished absorption of glucose in skeletal muscle, indicating Akt2/PKBβ plays a dominant role in maintaining euglycemia. In addition, they illustrate that knockdown or knockout of Akt2/PKBβ isoform

in mice leads to insulin resistance and diabetic-like symptoms [53]. The similar work has been accomplished in humans. Karen Tan et al. [55] find that a mutation in Akt2/PKBβ could cause a syndrome of severe insulin-resistant diabetes and integrant lipid dysfunction. However, the mutations do not seem to be a rational cause for insulin resistance as mutations are uncommon and on rare occasions.

3.1. *Inositol pyrophosphates produced in response to insulin inhibit Akt signaling*

Insulin receptor, belonging to the family of tyrosine kinase receptors, is widely distributed in mammalian cell membranes. There are two α subunits totally exposed out the membrane and two transmembrane subunits known as β, the binds between which are disulfide bond [56]. After the combination of insulin and its receptor, the activated receptor phosphorylates the IRS on tyrosine sites then activates PI3K-Akt pathway. IRS, existing mainly in insulin-sensitive tissues, is the key signal protein in mediating insulin and its functions [57]. Different types of IRS (IRS-1, IRS-2, IRS-3, IRS-4) expressed in various tissues and cells participate in distinct signal transductions to exert their functions. Aberrations of IRS-1 phosphorylation or expression can result in insulin resistance [58]. There are studies suggesting that insulin resistance in skeletal muscle from type 2 diabetic patients is associated with impaired signal transduction at the level of IRS-1 [59–62]. Another important substrate of Akt is AS160, first found in 3T3L1 adipocytes, a 160 kDa protein containing a Rab GTPase-activating protein (GAP) domain [63]. Phosphorylation of AS160 and GLUT4 trafficking could be regulated by Akt2, thus serve as an association with membrane [64]. Consequently, any disruption of IRS-PI3K-Akt-AS160 transduction could interfere insulin signaling further resulting in insulin resistance. As such, there is a well-characterized feedback mechanism that insulin could induce ribosomal protein subunit 6 kinase (S6K1), the downstream protein of mTOR complex 1 (mTORC1), to phosphorylate seine residues of IRS-1 thus inhibit it [65].

Besides the understanding of the negative-feedback mechanism, Chakraborty et al. find another process, central of which is inositol pyrophosphates [50]. Inositol pyrophosphates, also known as inositol diphosphates [5-PP-I(1,2,3,4,6)P5,heredesignatedIP7] and bisdiphosphoinositol tetrakisphosphate ($[PP]_2$-IP_4, IP_8), which are generated by inositol hexakishosphate (IP_6) kniases (IP6Ks) with three subtypes (Fig. 2) [66]. Unlike the most perceivable inositol phosphate, inositol-1, 4, 5-trisphosphate (IP_3), acting as an important second messenger in regulating Ca^{2+} signal [67], inositol pyrophosphates IP_7 and its producer IP6Ks have come into view in recent years.

The sizable family of inositol pyrophosphates plays a significant role in various fields while many functions as well as exact mechanism of signal transduction remain uncertain. The binding of IP_3 to IP_3 receptor, a typical mechanism, which induces the opening of calcium channel through a conformational change of the channel structure, is an explicit mechanism of inositol phosphate family [68]. Besides, many binding partners for inositol phosphates have also been identified, especially for the lipid phosphatidylinositols. These

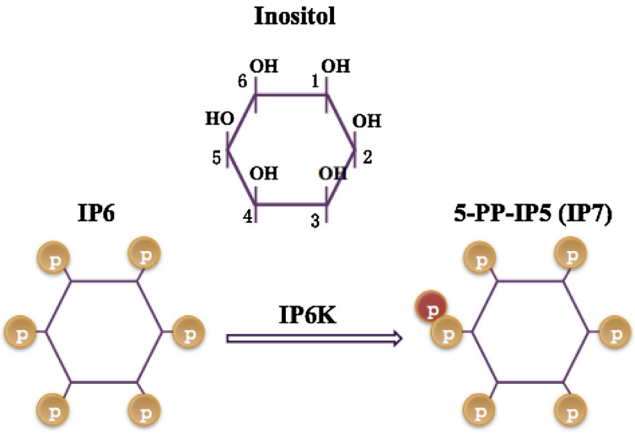

Fig. 2 – The structure of inositol, IP_6 and IP_7. IP_6 can be transformed to IP_7 via inositol hexakishosphate kniases IP6Ks.

binding sites include pleckstrin homology (PH), phagocyte oxidase homology (PX) or FYVE (for Fab1, YOTB, Vac1 and EEA1) protein domains [69].

Zhang et al. [70] investigate IP6Ks inhibition on bone marrow-derived mesenchymal stem cells (BM-MSCs) and found that aged BM-MCSs produced more IP_7 and the expression of Thr^{308} phosphorylation of Akt was significantly decreased. Previous research shows that there seems to be a competitive relation between IP_7 and PIP_3 in order to bind the PH domain of Akt [71]. Luo et al. [50,71] suspected that IP_7 might restrain Akt directly via binding to its PH domain as Akt lacking PH domain fails to be suppressed. The authors established a cell model of serum-starved mouse embryonic fibroblast (MEFs) to determine IP_7 level reacting to insulin-like growth factors-1 (IGF-1) and find that Akt phosphorylation at Thr^{308}/Ser^{473} induced by insulin-like growth factors-1 increased in IP6K1 knockout mouse embryonic fibroblast, coincident with phosphorylation augments of the downstream protein GSK3β and S6K1. In other words, the translocation of Akt to the cell membrane is inhibited and so does the phosphorylation by PDK1. Conversely, the knockout or knockdown and selective inhibition of IP6K1 do increase the number of PIP_3 binding to the PH domain of Akt. Moreover, when preparations are pre-incubated with PIP_3, the number of IP_7 binding to the PH domain of Akt gets reduced thus decreases the replacement of PIP_3. IP_7 potently suppresses Akt phosphorylation while IP_5 and IP_6 display much less inhibitive activity let alone inactive IP_3 and IP_4. These indirect evidences bring many presumptions on the exact mechanisms whereby IP_7 inhibits Akt (Fig. 3). It is reported that the family of inositol pyrophosphates exert their functions by binding to a chaperone proteins [72] or PH domains [71] and phosphorylating proteins as NSR1, a nucleolar protein involved in ribosome assembly and export [73]. In consideration with the potent inhibitory activity of IP_7 rather than IP_4, which also displays competitive activity in the PH domain. It seems that the inhibition not only depends on binding to the PH domain of Akt. During the activation, PDK1 and Akt form a complex *in vivo* [74] and PIP_3 seems to help convert Akt to the PH-out

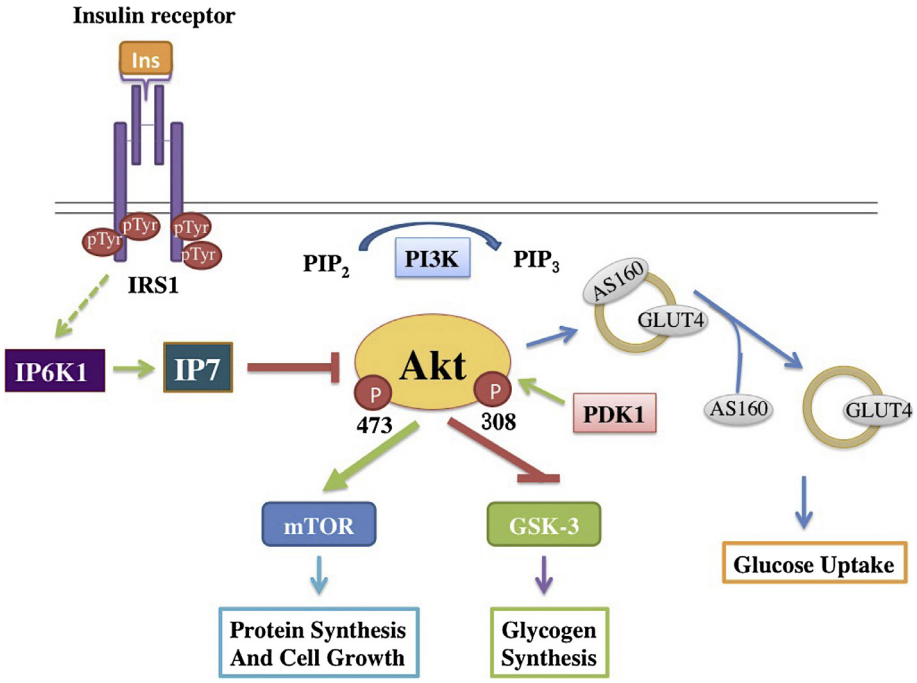

Fig. 3 – IP_7 produced by IP6K1 could suppress Akt and affect its downstream pathways.

conformation for the phosphorylation by PDK1 whereas IP_7 appears to act conversely. How does IP_7 rigorously exert its functions in this process remains perplexing.

4. Depletion of IP6K1 leads to insulin hypersensitivity and obesity resistance

Three subtypes of IP6Ks (IP6K1, IP6K2, IP6K3) exert distinct functions. IP6K2 seems to exert the apoptotic-promoting and growth-suppressing function. A reduction in IP6K2 expression abrogated interferon-beta induced apoptosis while IP6K2-knockout mice display increased susceptibility to carcinogen-induced squamous cell carcinoma as well as aerodigestive tract carcinoma when treating with the oral carcinogen 4-nitroquinoline-1-oxide (4NQO) [75–77]. IP6K3 was reported to impact brain function via interacting with the cytoskeletal proteins spectrin and adducin. Furthermore, IP6K3-knockout mice display weakened motor learning and coordination [78]. In addition, overexpression of three subtypes all led to analogous augments in exocytosis [79]. However, insulin hypersensitivity and glucose tolerance were observed in IP6K1-knockout mice rather than other subtype-knockout mice. Moreover, the same phenomenon did not occur in other two subtypes of IP6Ks.

Chakraborty et al. [50] state that loss of IP6K1 in mice reinforces Akt activation and thus improves glucose uptake in skeletal muscle and adipose tissue. Furthermore, IP6K1 KO mice show a resistance to obesity with lean bodies and decreased white adipose tissues. Decreased insulin level in blood along with the regular glucose content indicates insulin super sensitivity. The authors performed hyperinsulinemic-euglycemic clamp experiment and found the insulin sensitivity of IP6K1 KO mice was twice of that in wild type.

Illies et al. [80] created a model of pancreatic β cells with IP6K1 knockdown via RNAi and found diminution in insulin secretion, following the defective mice model lacking C-terminal catalytic domain of IP6K1 established by Rashna Bhandari et al. [81]. They found the mutant mice became visibly smaller with lower weight compared to the wild type despite normal food intake. Furthermore, insulin content in the plasma also got a striking decrease in the mutant mice, consistent with Illies's results. It is documented that inositol pyrophosphates are known to play an essential role in controlling vesicular trafficking and mediating endocytosis [82,83]. Notably, the secretion of insulin is exactly through vesicular, which may give a theoretical evidence to explain the decreased insulin secretion. Thus, depletion of IP6K1 contributes to diminished insulin secretion from pancreatic β cells resulting in lower circulating insulin. However, the glucose remains constant regardless of decreased peripheral insulin content indicating increased glucose uptake into skeletal muscle and adipose tissues. What's more, resistance to obesity induced by high-fat diets (HFD) in IP6K1 KO mice may result from activated Akt, which in turn phosphorylates and restrains GSK-3β. It is reported that IP6K1 could bind and stimulate GSK3 enzymatic activity in a non-catalytic fashion and behavioral alterations of IP6K1 knockout mice resemble those of GSK3 mutants [84]. Moreover, leptin level goes down in the serum indicating the augmented leptin sensitivity as well. Lipid droplets are visible in wild type mice while being much less in IP6K1 KO mice, suggesting a hopeful field in treating obesity [81]. The overexpression of Akt in skeletal muscle leads to insulin sensitivity, skeletal muscle hypertrophy and hepatic fatty acid oxidation, thus decreases fat accumulation [85] (see Fig. 4).

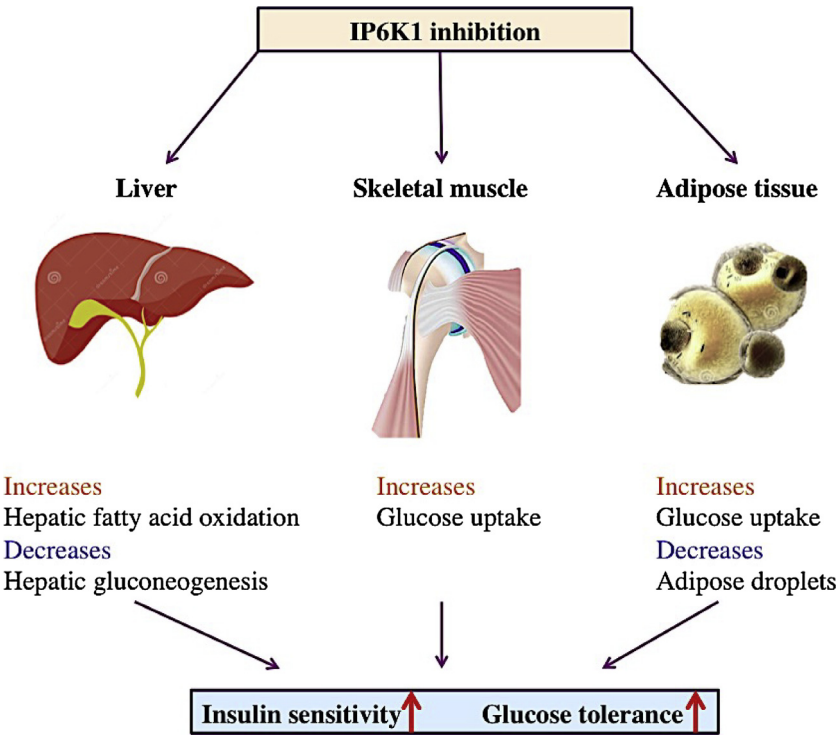

Fig. 4 – Depletion of IP6K1 increases insulin sensitivity and glucose tolerance.

4.1. *Lower level of IP6K1 may ameliorate insulin resistance and obesity*

Insulin resistance is a multifactor dysfunction that leads to defect of insulin function, which, in turn, results in other undesired metabolic alterations. From other perspective, insulin resistance is the diminution sensitivity of insulin-targeted organs in response to insulin. In addition, the lower sensitivity of insulin is regarded as the major pathogenesis in diabetes and obesity. Facilitating insulin sensitivity has become a fresh thought in developing new drugs, as insulin secretion is intact under many circumstances. From above, IP6K1 KO mice display a lean body phenotype, increased insulin sensitivity, increased glucose uptake and glucose tolerance. Moreover, TNP, N^2-(*m*-(trifluoromethyl)benzyl), N^6-(*p*-nitrobenzyl) purine, a known inhibitor of IP6K, could lead to the increment of Akt phosphorylation no matter under which condition (normoxic or hypoxic) [70]. Thus, it suggests that lower level of IP6K1 could become a research spot in treating insulin resistance and obesity due to elevated Akt activity.

5. Conclusions and perspectives

Targeting IP6K1-IP_7-Akt-GSK3β stream, a novel cascade in studying insulin resistance, is supposed to exert therapeutic effect on treating type 2 diabetes and obesity. As we have discussed in the previous sections, IP6K1 knockout mice show a normal glucose content, leaner body and resistance to high-fat diets induced obesity when comparing with the wild type. Moreover, the mutant mice display greater decrease of blood glucose levels indicating hypersensitivity of insulin. The improved Akt activity contributes to elevated glucose uptake in skeletal muscle hence maintains euglycemia, implying IP6K1 a potential target. We have published a number of nutrients, also designated as mitochondrial nutrients, coming from natural sources that do ameliorate insulin resistance [3,86,87]. Some of nutrients may exactly point at inositol pyrophosphates, thus a possibility of future proposal and further researches are warranted.

However, there might be some unfavorable effects when utilizing these inhibitors. As is reported, Akt signaling leads to increased cellular growth and survival, which is most recognized in cancer [36]. Thus, the overexpression of Akt may lead to tumor formation though there were no spontaneous tumors appearing in 2-year-old IP6K1 knockout mice (roughly equivalent to 75–80 years of human life) [50]. Moreover, the IP6K1 knockout mice weigh around 15–20% less than the wild type and spermatogenesis is partly inhibited in males [81,88]. More importantly, the diminished insulin secretion could also become a vital problem despite normal glucose content as insulin itself functions in various physiological activities. Nonetheless, the reduced circular insulin is possible due to a lower requirement of insulin whereby increased insulin sensitivity and more effective glucose disposal. Throughout these current problems, further research needs to be done especially on the presumed deficiency. Targeting AMPK pathway and the energy metabolism with the developed medicine metformin is a current therapy to treat type 2 diabetes. Both AMPK and PI3K-Akt pathways, which contain signal divergence and crosstalk with other essential signaling cascades, demonstrate a great impact on insulin resistance. However, the exact pathogenesis of insulin resistance remains deciphering.

Identifying new molecules that impact insulin signaling and the potential mechanisms is primary to develop more effective therapies. It was documented that migration, incasion and growth of tumor could be limited when IP6K1 levels was reduced [77]. What's more, these "big molecules" also play a part in mediating ATP concentration via the ratio of glycolysis and mitochondrial metabolism [89]. Though IP6K1 has been already discovered for 20 years, there are only a small number of published literatures focusing on IP6K1 knockout or knockdown mice and insulin resistance. These literatures delineate a hopeful field in confronting insulin resistance. For further study of IP6K1, stable animal models with IP6K1 inhibited rather than totally knockout need to be established. Moreover, it remains unclear that whether inositol pyrophosphates species exert characteristic functions via binding specific sites and the mechanism how they could acquire specificity from the precursor.

Reckoning on age-related insulin resistance, mitochondria, which have vital functions in regulating various biological metabolisms, are supposed to play an important part. Excessive reactive oxygen species (ROS) produced by mitochondria causes oxidative stress, which could be common detected in type 2 diabetes. There are findings using *Saccharomyces cerevisiae* mutants to examine the potential roles of inositol pyrophosphates in respond to cell damage caused by excessive reactive oxygen species. Yeast lacking kcs1 [the *S. cerevisiae* IP6K] displays increased resistance to cell death caused by H_2O_2, coinsident with a sustained activation of DNA repair mechanisms [90]. Inositol pyrophosphates are elucidated participating in the control of intracellular ATP concentration [91]. These findings indicate underlying connection between IP6K1 and mitochondria. Yet the exact mechanism how IP6K1 can affect mitochondria is a novel question to be interpreted. Based on the proposed studies, we are looking forward to the next decades of inositol pyrophosphates.

Conflict of interest

The authors declare there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2017.10.004.

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