Cross Roads between Insulin and Adiponectin Pathways: APPL1 Perspective

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Abstract

Type 2 diabetes mellitus (T2DM) is one of the leading causes of mortality and morbidity worldwide. Insulin plays a very important role in glucose metabolism hence disturbance in the insulin signaling cascade can induce insulin resistance and is associated with the development of T2DM. Adiponectin possesses insulin-sensitizing effect and is an important link between obesity, insulin resistance and the development of type 2 diabetes. APPL1 plays a critical role in the cross-talk between adiponectin- and insulin-signaling pathways and may be a novel mechanism for the insulin-sensitizing effect of adiponectin. This mini review centres on the insulin sensitising action of adiponectin with APPL1 as a major player and its role in T2DM.

Keywords: Type 2 Diabetes Mellitus (T2DM); Insulin; Adiponectin; APPL1

Adipose tissue which was previously described as an organ to store excessive fat has now been established as an endocrine organ which secretes biologically active substances known as adipocytokines. Adiponectin is an adipocytokine who's antiatherogenic, antidiabetic and anti-inflammatory functions are well documented. Various studies have found a strong inverse association between adiponectin and an increased risk of type 2 diabetes mellitus (T2DM). T2DM is highly prevalent and is one of the leading causes of mortality and morbidity worldwide. The rising global tide of obesity, physical inactivity, and energy dense diet has resulted in an unprecedented increase in the number of patients with T2DM [1-4]. T2DM is characterized mainly by systemic insulin resistance which results in hyperglycaemia and dyslipidaemia. Insulin resistance is defined as the condition in which normal amount of insulin is inadequate to produce a normal biological response i.e. insulin mediated glucose uptake [5-7]. It is widely agreed in the field that obesity is a major cause of impaired insulin signaling and therefore the development of insulin resistance. It has been reported that with increasing level of obesity the secretion of adipose specific peptide adiponectin reduces [8-12]. However, it is not fully understood how adiponectin causes the development of insulin resistance. Many molecular mechanisms are proposed, including ER stress, oxidative stress, dysregulation of lipid homeostasis (including FFA homeostasis), mitochondrial dysfunction, hypoxia and others. However, now several evidences suggest that obesity-induced changes in adipose tissue and its affect on adiponectin and insulin signaling may also be a key cause of insulin resistance [13,14].

Insulin signaling in T2DM

At the level of cell, the mechanism that is responsible for the development of insulin resistance in T2DM is the disruption of the insulin signaling pathway in insulin-responsive cells (adipocytes, myocytes, hepatocytes and β-cells). Hence, disruption of this insulin signaling cascade can induce insulin resistance and is associated with the development of T2DM [15].

Insulin normally initiates its physiological effects by binding to a high affinity specific insulin receptor of the tyrosine kinase (TK) superfamily located on the plasma membrane of muscles and adipose tissue [16,17].

Insulin binds to the extracellular α subunit of the insulin receptor, resulting in conformational change enabling ATP to binding to the intracellular component of the β subunit of its receptor and the phosphorylation of the β subunit of tyrosine kinase thus enabling tyrosine phosphorylation of the insulin receptor substrates (IRS) proteins [18]. Phosphorylation of IRS proteins results in binding of IRS with regulatory subunit of phosphatidylinositol 3-kinase (PI 3-kinase) which then acts via serine and threonine kinases, PI dependent protein kinases 1 and 2 (PIPD 1 and 2) and Akt/protein kinase B (PKB), protein kinase C (PKC). PI3K-Akt activation rapidly increases glucose transport through the regulated trafficking of the glucose transporter GLUT4 from intracellular stores to the cell surface in adipose tissue and muscle, [19,20] and glucose uptake occurs. Studies on insulin resistance in insulin signaling pathway has majorly implicated on IRS1/2, PI3K and PKB [21] principally due to the defects observed at the levels of IRS proteins, Akt- PI3K and PKB [22-25].

Excess nutrient intake causes ER stress and subsequently reduce protein synthesis, which leads to the phosphorylation and activation of JNK, inducing serine phosphorylation of IRS 1 and 2 and insulin resistance. In cultured hepatocytes, treatment with high concentrations of glucose augmented IRS serine phosphorylation and impaired insulin-stimulated AKT phosphorylation [26]. Moreover, intracellular lipid accumulation can also impair insulin signaling by inducing multiple serine phosphorylation of IRS [27]. Ser/Thr phosphorylation of IRS proteins is S6K-dependent, which results in the dissociation of IR: IRS [28] and IRS: PI3K [29] complexes. This reduces the capacity of IRS proteins to undertake further insulin-stimulated Tyr phosphorylation and leads to disruptive insulin signaling [30]. Free fatty acids, stress, and inflammation [31-35], hypoadiponectemia, are some of the factors responsible for an increased serine phosphorylation of IRS-1.

Interestingly, in adipose tissue of obese, insulin-resistant humans and animals adiponectin secretion decreases and secretion of TNF-α, increases which are both associated with increased S6K activity which may lead to Ser/Thr phosphorylation of IRS and disruptive insulin signaling.

Adiponectin

Adiponectin possesses insulin-sensitizing effect and can be an important link between obesity, insulin resistance and the development of T2DM [36]. The level of plasma adiponectin has been reported to be reduced in obese humans, particularly those with visceral obesity, and correlate inversely with insulin resistance [37-45]. In obese patients, visceral body fat affect health conditions, through an abnormal production of adipocytokines.

Adiponectin, a hormone secreted mainly by adipose tissue, and has the highest plasma concentrations of a circulating protein. The adiponectin polypeptide molecule is secreted into circulation in three oligomeric isoforms: a low molecular-weight trimer, an intermediate-molecular weight hexamer and a high molecular weight (HMW) complex [46]. Some studies suggest that the HMW isoform is most biologically active, and that lower levels of this form are associated with diabetes mellitus and coronary artery disease [47-49].

Adiponectin plays a pivotal role in energy metabolism; concentration of both total adiponectin and high molecular weight (HMW) decreases in obesity and increases after weight loss [50-53]. Drolet., *et al.* demonstrated an inverse relationship between mean adipocytes diameter and adiponectin secretion. AdipoR1 and AdipoR2 expression is significantly decreased in T2DM and obesity state [54].

Adiponectin exerts its insulin sensitizing effects by activation of AMP-activated protein kinase (AMPK), p38 mitogen activated protein kinase (MAPK), peroxisome proliferator activated receptor α (PPAR-α) [36] mediated by the membrane receptor proteins AdipoR1 and Adipo R2, which specifically bind to adiponectin [55].

AMPK has a vital role in the maintenance of cellular status and adiponectin mediated stimulation of AMPK increases glucose uptake and fatty acid oxidation leading to decreased glucose and lipid levels in vivo. Though p38 MAPK regulates several processes, recently it has been reported that adiponectin activated p38 MAPK has a role in glucose uptake and fatty acid oxidation also [56]. Moreover, PPAR-α is involved only in fatty acid metabolism and not in glucose uptake.

Adiponectin elicits a number of downstream signaling events. APPL1 which is highly hydrophilic adaptor protein consisting of multiple structural and functional domains including BAR, PH, PTB, and coiled coil (CC) which interacts with the adiponectin receptor and

mediates adiponectin signaling and its effect on energy metabolism and insulin sensitivity [57,58]. In cultured skeletal muscle cells, suppression of APPL1 expression diminishes adiponectin-induced glucose uptake and GLUT 4 translocation [59]. On the other hand, ove-rexpression of APPL1 enhances the stimulatory actions of adiponectin in glucose metabolism in muscle [59]. APPL1-mediated signaling activates AMPK and thus promote fatty oxidation [60,61] In addition to the AMPK pathway, APPL1 also mediates adiponectin-induced activation of the p38 MAPK pathway [59] and its impact on the anti-inflammatory actions of adiponectin [62].

APPL 1 in crosstalk between insulin and adiponectin pathways

APPL1is expressed in all insulin-sensitive tissues (liver, skeletal muscle and adipose) which also have adiponectin receptors. APPL1 plays a critical role in the cross-talk between adiponectin- and insulin-signaling pathways and may be a novel mechanism for the insu-lin-sensitizing effect of adiponectin [59].

APPL1 modulates the substrate specificity and activity of Akt [63-67] and IRS, and so plays a central role in mediating the peripheral actions of insulin. APPL1 also interacts with IR and deletion of APPL1 reduces the IR-IRS signaling, suggesting that APPL1 serves as the platform for the interaction between IRS and the receptor [68].

The capability of adiponectin to reduce the phosphorylation of p70 S6 kinase (S6K) is the explanation for adiponectin-insulin cross-talk [69]. IRS-1 tyrosine phosphorylation and downstream insulin signaling are negatively correlated to S6K activation [70,71]. The inhi-bition of S6K mediated by adiponectin enhances the ability of insulin to stimulate IRS-1 tyrosine phosphorylation and subsequent Akt phosphorylation and insulin-signaling activation. APPL1 potentiates the effect of insulin on IRS1/2, by suppressing the negative effect of S6K on IRS1, promotes insulin-stimulated tyrosine phosphorylation of IRS1, but not the IR [69].

Conclusion

To summarize, APPL1 is a requisite element in regulation of insulin via the IRS and Akt thus suggesting that APPL1 is a principal con-troller of adiponectin and insulin action. The role of APPL 1 in crosstalk between insulin and adiponectin pathways in diabetes cannot be ignored.

Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

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