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Adiponectin and Insulin Crosstalk: The Microvascular Connection

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Abstract

Adiponectin exerts both vasodilatory and insulin-sensitizing actions and its levels are decreased in the insulin resistant humans and animals. The mechanisms underlying the adiponectin's insulin-sensitizing effect have been extensively investigated but remain largely unclear. Muscle microvasculature critically regulates muscle insulin action by modulating insulin delivery to the microvessels nurturing the muscle cells and the trans-endothelial insulin transport. We have recently reported that adiponectin exerts its insulin-sensitizing effect via recruiting muscle microvasculature, expanding the endothelial surface area, and increasing insulin delivery to and thus action in muscle. The current review focuses on the microvascular connection between the adiponectin and insulin crosstalk.

Introduction

Adiponectin is the most abundant adipokine and circulates as both full-length and globular forms in the plasma (Hu et al., 1996; Maeda et al., 1996; Nakano et al., 1996; Scherer et al., 1995). The full-length adiponectin (fAd) accounts for the vast majority of the circulating adiponectin while the globular adiponectin (gAd), the C-terminal domain proteolytic product of the fAd, exists in a much smaller amount in human plasma (Fruebis et al., 2001). Unlike other adipokines, ample evidence from both laboratory animal and human studies has confirmed that adiponectin has an insulin-sensitizing action and its levels are decreased in animals or humans with obesity and insulin resistance (Arita et al., 1999; Berg et al., 2001; Combs et al., 2001; Fruebis et al., 2001; Hotta et al., 2000; Kadowaki et al., 2006; Weyer et al., 2001; Yamauchi et al., 2001). Furthermore, adiponectin exerts a beneficial effect on the cardiovascular system (Fesus et al., 2007) and hypoadiponectinemia is independently associated with endothelial dysfunction in both humans and animals (Cao et al., 2009; Iwashima et al., 2004; Kumada et al., 2003; Ouchi et al., 2003; Schmid et al., 2011; Tan et al., 2004; Torigoe et al., 2007).

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In rodent models of obesity and insulin resistance, replenishment of adiponectin not only improves endothelial function but also significantly ameliorates insulin resistance (Lee et al., 2012; Ohashi et al., 2006; Xing et al., 2013; Yamauchi et al., 2001). These strongly suggest a close coupling and crosstalk between adiponectin and insulin signaling. However, the underlying pathophysiology remains unclear despite intensive investigations. In a recent study we reported that muscle microvasculature plays a critical role in adiponectin-mediated enhancement of insulin action in muscle (Zhao et al., 2013). Here we summarize current knowledge on the crosstalk between adiponectin and insulin in the regulation of glucose metabolism with a focus on the role of muscle microvasculature.

The interactions between adiponectin and insulin signaling pathways

Adiponectin acts mainly via two receptors (AdipoR1 and AdipoR2) to exert a variety of biological effects (Yamauchi et al., 2003). AdipoR1 is most abundant in the skeletal muscle with high affinity for gAd, whereas AdipoR2 is predominantly expressed in the liver that has higher affinity for fAd (Kadowaki et al., 2006; Yamauchi et al., 2003). Both AdipoR1 and AdipoR2 are expressed in endothelial cells (Tan et al., 2004). An additional adiponectin receptor T-Catherin has also been identified which only binds the hexameric and high-molecular-weight adiponectin but not the trimeric or globular adiponectin (Hug et al., 2004). While the exact signaling pathways transducing the adiponectin receptor signals to the downstream molecules remain largely unknown, adaptor protein containing pleckstrin homology, phosphotyrosine binding (PTB) domain and leucine zipper motif 1/2 (APPL1/2), endoplasmic reticulum protein 46 (ERp46), activated protein kinase C1 (RACK1) and protein kinase CK2β have all been identified to directly interact with the adiponectin receptors and mediate adiponectin actions (Buechler et al., 2010), including the activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor (PPAR) α which increase fatty acid oxidation and glucose uptake in muscle and the induction of nitric oxide (NO) production via AMPK-stimulated phosphorylation of endothelial NO synthase (eNOS) at serine 1177 (human) or 1179 (bovine) and serine 633 in endothelial cells (Chen et al., 2003; Chen et al., 2009; Yamauchi et al., 2002; Yoon et al., 2006). Adiponectin also promotes the formation of heat shock protein (HSP) 90 and eNOS complex, which is required for the maximal activation of eNOS (Xi et al., 2005).

Insulin binds to its membrane receptors and exerts its biological actions via the phosphatidylinositol 3-kinase (PI-3 kinase) and mitogen-activated protein kinase (MAPK) signaling pathways. Insulin activates the insulin receptor tyrosine kinase that subsequently phosphorylates insulin receptor substrates (IRS) and activates PI-3 kinase and protein kinase B (PKB or Akt)(Taniguchi et al., 2006), leading to the membrane translocation of glucose transporter 4 (GLUT4) and glucose uptake in myocytes and the phosphorylation of eNOS at serine 1177/1179 and NO production in endothelial cells (Montagnani et al., 2001; Taniguchi et al., 2006; Zeng and Quon, 1996). On the contrary, MAPK pathway regulates gene expression and cell proliferation and growth. In endothelial cells, it mediates endothelial-1 (ET-1) production/secretion by the endothelial cells (Ferri et al., 1995; Muniyappa et al., 2007). While NO dilates the blood vessels by relaxing the smooth muscle layer, ET-1 is a potent endogenous vasoconstrictor.

It has long been noted that there is a crosstalk between adiponectin and insulin signaling pathways that occurs at multiple levels. AdipoR1 and R2 serve as the predominant receptors for adiponectin's metabolic actions as simultaneous disruption of both AdipoR1 and AdipoR2 abolishes adiponectin's insulin sensitizing actions, resulting in increased tissue triglyceride content, inflammation and oxidative stress and leading to insulin resistance and glucose intolerance (Yamauchi et al., 2007). It appears that APPL1, an AdipoR1/R2 adaptor protein, is a critical node linking adiponectin receptor and its downstream signaling. It mediates adiponectin-stimulated AMPK activation which reduces mammalian target of rapamycin (mTOR)/p70 S6 kinase-mediated serine phosphorylation of insulin receptor substrate (IRS) proteins and enhances insulin-stimulated IRS tyrosine phosphorylation and Akt phosphorylation in skeletal muscle cells and eNOS activation and NO production in endothelial cells (Cheng et al., 2007; Deepa and Dong, 2009; Wang et al., 2007). APPL1 enhances insulin-stimulated activation of Akt and suppression of gluconeogenesis in hepatocytes and eNOS activation and NO production in enthelial cells via by blocking the association of Akt, a major signaling intermediate in the insulin signaling pathway, with its endogenous inhibitor tribble 3 (TRB3) through a direct competition (Cheng et al., 2009; Saito et al., 2007; Wang et al., 2011b). In adipocytes and muscle cells APPL1 forms a complex with Akt2 that dissociates upon insulin stimulation to regulate insulin-stimulated GLUT4 membrane translocation (Cheng et al., 2009; Saito et al., 2007; Wang et al., 2011b). APPL1 also facilitates the binding of IRS1/2 to the insulin receptor (Ryu et al., 2014). In addition, adiponectin-mediated up-regulation of hepatic IRS-2 expression via a macrophage-derived interleukin 6-dependent pathway has also been implicated as an underlying mechanism (Awazawa et al., 2011). To date, these crosstalks have largely been used to explain the insulin-sensitizing effect of adiponectin. Inasmuch as evidence thus far has mostly focused on the effects of adiponectin and insulin crosstalk on the metabolic effects of insulin, the effect on insulin's mitogenic actions are not well studied.

Microvasculature critically regulates insulin action in muscle

Skeletal muscle is a major organ regulating body energy metabolism and accounts for approximately 80% of insulin-stimulated whole body glucose disposal during euglycemic insulin clamp (DeFronzo and Tripathy, 2009). The muscle microvasculature plays a pivotal role in the regulation of insulin action in muscle. For insulin to act on muscle cells, it first has to be delivered into the capillaries nurturing the muscle cells after being secreted by the pancreatic β-cells and then transported through the capillary endothelium to enter the interstitial space before they can bind to the myocyte insulin receptors to exert its metabolic actions (Rasio, 1982). Studies employing lymphatic sampling, microdialysis or radio-labeled insulin uptake techniques have all confirmed that insulin delivery to the muscle is rate-limiting for insulin action in muscle and this process is significantly blunted in the insulin resistant states (Herkner et al., 2003; Holmang et al., 1997; Yang et al., 1989).

Microcirculation encompasses all vessels <150 μm in diameter, including arterioles, capillaries, and venules. It regulates tissue function by delivering adequate amount of nutrients, oxygen and hormones and providing sufficient endothelial surface area for their exchanges between the plasma and tissue interstitium. In the resting state only ~30% of the capillaries in muscle are being perfused but in response to an increased demand such as

exercise more capillaries are being perfused via the relaxation of the pre-capillary terminal arterioles, a process termed microvascular recruitment (Honig et al., 1982). The resultant increase in muscle microvascular blood volume, i.e., the expansion of the endothelial exchange surface area, in muscle could markedly increase the extraction of nutrients, oxygen, and hormones such as insulin from the plasma to muscle interstitium and facilitates the removal of metabolic wastes. Using either 1-methylxanthine extraction or contrast-enhanced ultrasound method, investigators have repeatedly shown that muscle microvascular blood volume is being actively regulated. Thus far, multiple factors have been shown to increase muscle microvascular blood volume, including exercise, muscle contraction, insulin, angiotensin 1–7, angiotensin II type 1 receptor blockers, resveratrol, glucagon-like peptide-1, ranolazine and adiponectin (Chai et al., 2011; Chai et al., 2014; Fu et al., 2014; Fu et al., 2013; Inyard et al., 2009; Inyard et al., 2007; Rattigan et al., 1997; Subaran et al., 2014; Vincent et al., 2002; Wang et al., 2011a; Zhao et al., 2013). Not surprisingly, all these factors have been shown to possess insulin sensitizing property. However, it appears that only vasodilatation of the muscle microvasculature is associated with improved insulin actions. Indeed, infusion of nitroprusside or bradykinin during a euglycemic-hyperinsulinemic clamp did not enhance insulin-mediated limb glucose uptake in either normal or obese humans despite a marked increase in limb blood flow (Laine et al., 1998; Natali et al., 1998; Nuutila et al., 1996). Though treatment of obese hypertensive patients with prazosin for 12 weeks is associated with an increase in insulin-mediated glucose disposal during insulin clamp (Pollare et al., 1988), clinically either α-adrenergic receptor or calcium channel blockers are not associated with significant improvement in insulin sensitivity in patients with hypertension. Certainly the blood pressure lowering effect of these agents can decrease the capillary perfusion pressure thus mitigate the effect of microvascular perfusion on insulin action. This possibility remains to be examined.

We and others have confirmed that muscle microvasculature critically regulates insulin's metabolic action in the muscle and insulin regulates its own delivery to and thus actions in muscle by recruiting capillaries in muscle and facilitating its own trans-endothelial transport (Barrett et al., 2009; Chai et al., 2011; Chai et al., 2014; Fu et al., 2014; Fu et al., 2013; Premilovac et al., 2013; Vincent et al., 2004; Wang et al., 2008; Zhao et al., 2013). Insulin's microvascular and metabolic actions appear to be closely coupled. Insulin-mediated microvascular recruitment precedes insulin-stimulated glucose disposal in muscle and blockade of insulin's microvascular action with NOS inhibitor L-NAME decreases insulin-stimulated steady-state glucose disposal by up to 40% (Vincent et al., 2003; Vincent et al., 2002). This process is clearly impaired in the presence of insulin resistance. Indeed, impaired insulin-mediated microvascular recruitment has been demonstrated in obese and diabetic animals (Clerk et al., 2007; Wallis et al., 2002), obese humans (Clerk et al., 2006) and humans or animals receiving systemic infusions of tumor necrosis factor α or lipid (Liu et al., 2009; Wang et al., 2013; Youd et al., 2000). That insulin-mediated microvascular recruitment occurs before its metabolic action in muscle and all factors causing metabolic insulin resistance tend to also induce microvascular insulin resistance strongly suggests that microvascular insulin resistance may contribute to the pathogenesis of metabolic insulin resistance in muscle and therefore muscle microvasculature could be a therapeutic target for the prevention and management of insulin resistance and diabetes(Liu, 2013).

Crosstalk between adiponectin and insulin: The microvascular connection

Adiponectin is a potent vasodilator and, similar to insulin, its vasodilatory effect is mediated via a NO-dependent mechanism (Cheng et al., 2007; Schmid et al., 2011; Xi et al., 2005). Inasmuch as adiponetin's vasodilatory actions have been repeatedly demonstrated in conduit arteries and resistance arterioles (Cheng et al., 2007; Schmid et al., 2011; Xi et al., 2005), its effect on the microvasculature was unknown prior to our recent study published in Circulation Research(Zhao et al., 2013). While the conduit arteries regulate arterial plasticity and compliance and the resistance arterioles regulates blood pressure and total blood flow to tissues, it is the microvasculature that provides the needed exchange surface area for tissue to extract nutrients, oxygen and hormones from the plasma. As mounting evidence strongly suggests that muscle microvasculature is a critical regulatory site for insulin's metabolic action and adiponectin has both vasodilatory and insulin-sensitizing actions, we sought to define whether adiponectin modulates muscle microvascular recruitment thus insulin delivery and action in muscle. To this end, we gave overnight fasted, adult male Sprague-Dawley rats gAd or fAd intraperitoneally and determined the effects of adiponectin on muscle microvascular recruitment, insulin-mediated whole body glucose disposal, and muscle insulin uptake. We found that both fAd and gAd were able to significantly recruit muscle microvasculature but gAd appeared to be more potent. This effect was paralleled by a 30–40% increase in muscle insulin uptake and ~30% increase in insulin-stimulated whole body glucose disposal. All these effects were completely abolished in the presence of NOS inhibition by simultaneous administration of L-NAME suggesting that adiponectin exerts its microvascular and insulin-sensitizing actions via a NO-dependent mechanism. Thus our data provide first-hand evidence that adiponectin enhances insulin action via recruiting muscle microvasculature and increasing muscle insulin uptake and strongly support the view that muscle microvasculature is the missing link in the crosstalk between adiponectin and insulin (Figure).

Perspective

Patients with type 2 diabetes and obesity have endothelial dysfunction and insulin resistance and are prone to developing hypertension and cardiovascular complications, which contribute significantly to the morbidity and mortality seen in this patient population. Adiponectin has both insulin-sensitizing and salutary vascular actions and its levels are decreased in patients with and animal models of diabetes and insulin resistance. Mounting evidence thus far has confirmed a critical role of muscle microvasculature in the regulation of insulin action and our recent study demonstrates that adiponectin improves muscle insulin action by potently recruiting muscle microvasculature and expanding the endothelial exchange surface area within muscle via a NO-dependent mechanism, leading to increased muscle insulin delivery, uptake and action. Thus, our results provide a new perspective on the mechanisms underlying the insulin-sensitizing action of adiponectin and together with other evidence suggesting that microvascular insulin resistance may contribute to the pathogenesis of metabolic insulin resistance raise the possibility that adiponectin replenishment and/or improving microvascular insulin responses could be effective therapeutic strategies in the prevention or treatment of insulin resistance, type 2 diabetes, and associated cardiovascular complications.

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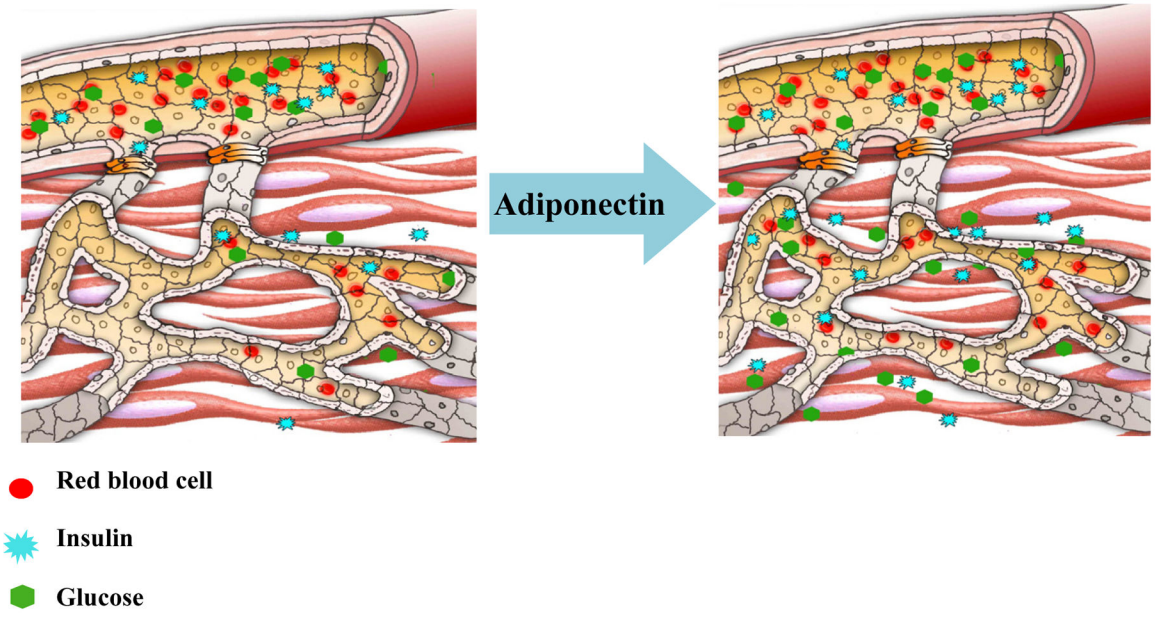

Figure.

Schematic diagram of adiponectin's effects on microvascular recruitment and insulin delivery in muscle.