Does adiponectin mimic exercise?

Physical inactivity is one of the major causes of type 2 diabetes, and exercise training contributes substantially to both the prevention and treatment of this disease. Physical exercise affects many biochemical characteristics of skeletal muscle and thereby influences energy metabolism of the whole body. Although the mechanism by which the biochemical properties of skeletal muscle adapt to physical exercise is not completely understood, recent evidence suggests that peroxisome proliferator-activated receptor-γ (PPARγ) coactivator 1α (PGC-1α) plays a key role in this process. The expression of PGC-1α in skeletal muscle is rapidly induced in response to physical exercise, and forced expression of this molecule in cultured cells or in skeletal muscle of mice elicits biochemical changes similar to those induced by exercise, including upregulation of the expression of genes associated with energy metabolism (such as those for the insulin-sensitive glucose transporter 4, as well as for various enzymes of oxidative phosphorylation and fatty acid oxidation). Furthermore, PGC-1α plays an important role in the biogenesis of mitochondria, which is also induced by physical exercise. Mitochondrial function is thought to be a key determinant of insulin sensitivity and of predisposition to type 2 diabetes. These various observations suggest that a pharmacological therapy that upregulates PGC-1α in skeletal muscle would be a promising option for the treatment or prevention of type 2 diabetes. A recent study by Iwabu et al. has shown that signaling by adiponectin and one of its receptors is a potential target for such exercise-mimicking drugs.

Adiponectin is an adipocyte-derived hormone that possesses a variety of biological activities including antidiabetic, anti-atherogenic and anti-inflammatory actions. Two structurally related cell surface receptors that interact with adiponectin have been identified and termed adiponectin receptor 1 (AdipoR1) and AdipoR2. Although these receptors contain seven transmembrane domains similar to those of members of the G protein-coupled receptor (GPCR) family, their structural topology is opposite to that of GPCR in that their NH2-terminus is located inside of the cell and their COOH-terminus outside of the cell. Several signaling molecules are activated on AdipoR ligation, but the links between these molecules and the receptors remain unclear. AdipoR1 is expressed in a wide range of tissues including skeletal muscle, whereas AdipoR2 is expressed predominantly in the liver. Mice lacking either AdipoR1 or AdipoR2 develop insulin resistance and mild glucose intolerance, whereas those lacking both receptors manifest severe glucose intolerance, showing that AdipoR1 and AdipoR2 mediate the glucose-lowering effect of adiponectin in a coordinated manner.

To understand the tissue-specific roles of the adiponectin-AdipoR system, Iwabu et al. generated mice with an AdipoR1 deficiency, specifically in muscle. These mice develop insulin resistance and glucose intolerance, as do those with an AdipoR1 deficiency in the entire body, suggesting that skeletal muscle is the major organ in which AdipoR1 exerts its effect on glucose metabolism. Signaling from AdipoR1 was previously shown to stimulate adenosine monophosphate-activated protein kinase (AMPK), and the activity of this kinase was indeed attenuated in skeletal muscle of the mice lacking AdipoR1 in this tissue. Given that AMPK suppresses the activity of the protein kinase S6K1, which contributes to inhibition of insulin signaling, the reduced activity of AMPK might explain in part the insulin resistance of mice with an AdipoR1 deficiency in muscle.

Interestingly, Iwabu et al. found that the expression of PGC-1α was downregulated in the skeletal muscle of their mice with muscle-specific AdipoR1 deficiency. Consistent with this observation, the expression of genes regulated by PGC-1α, such as that for insulin-sensitive glucose transporter 4 as well as those related to the function and biogenesis of mitochondria to fatty acid oxidation or to the lowering of oxidative stress, was also reduced in skeletal muscle of these mice. Reflecting these changes in gene expression, fatty acid oxidation was impaired, triglyceride content was increased and the abundance of mitochondria was reduced in skeletal muscle of the mutant animals. All these phenotypic alterations in skeletal muscle are thus likely to be largely responsible for the development of insulin resistance.

Iwabu et al. further showed that treatment of cultured myocytes with adiponectin increased the expression of PGC-1α in an AdipoR1-dependent manner, consistent with the notion that AdipoR1 is a regulator of PGC-1α. However, AMPK appeared not to contribute to this upregulation of PGC-1α, showing that an unidentified signaling pathway mediates this process. Muscle contraction is associated with stimulation of various signaling pathways including Ca2+-dependent signaling, which is thought to contribute to the induction of PGC-1α. Iwabu et al. found that adiponectin induces Ca2+ influx into cultured myocytes and subsequently activates Ca2+- and calmodulin-dependent protein kinase kinase β (CaMKKβ) signaling. Knockdown of CaMKKβ or chelation of Ca2+ attenuated the adiponectin-induced expression of PGC-1α, showing that Ca2+-dependent signaling plays an
important role in this effect of adiponectin. Although AMPK is well established as a signaling molecule that functions downstream of AdipoR1, the mechanism by which AdipoR1 activates AMPK has been unclear. The activity of AMPK is regulated by phosphorylation, and CaMKKβ is a kinase that functions upstream of AMPK in some cell types. Iwabu et al. have now shown that adiponectin-induced Ca²⁺ influx and the subsequent downregulation of both the abundance of AdipoR1 in cultured cells resulted in insulin sensitivity. However, disruption of the signaling that leads to an improvement in adiponectin, AdipoR1 might transmit a signal that leads to an improvement in insulin sensitivity through AdipoR1. Alternatively, even in the absence of adiponectin, AdipoR1 might transmit a signal that leads to an improvement in insulin sensitivity. However, disruption of AdipoR1 in cultured cells resulted in downregulation of both the abundance of Ca²⁺ channels by forming heteromeric complexes with coreceptors. It will thus be of interest to determine whether AdipoR1 requires a similar coreceptor to trigger Ca²⁺ influx. Although muscle contraction is associated with Ca²⁺ signaling in myocytes, it is unclear how this signaling is initiated. Does AdipoR1 contribute to exercise-related Ca²⁺ signaling in skeletal muscle? Although the circulating concentration of adiponectin does not change markedly during short-term exercise, it remains possible that the function of AdipoR1 is influenced by exercise. Iwabu et al. found that physical exercise increased the mitochondrial content of skeletal muscle in mice with muscle-specific AdipoR1 deficiency, however, showing that exercise is capable of increasing the number of mitochondria in the absence of AdipoR1. Aside from the unresolved question of whether or not AdipoR1 participates in the exercise-induced adaptation of skeletal muscle, the similarity of adiponectin-AdipoR1 signaling to signaling induced by physical exercise suggests that the adiponectin-AdipoR1 system is a promising target for exercise-mimicking drugs. A search for activators of AdipoR1 might thus identify new drugs for both the treatment and prevention of type 2 diabetes.

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