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Adiponectin Receptor Signaling: A New Layer to the Current Model

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DOI 10.1016/j.cmet.2011.01.012

Adiponectin and its receptors, AdipoR1 and AdipoR2, regulate glucose and fatty acid metabolism partly via activation of AMP-activated protein kinase (AMPK). Recent work in *Nature Medicine* (Holland et al., 2011) suggests that adiponectin stimulates ceramidase activity through AdipoR1 and AdipoR2, an activity potentially involved in promoting cell survival.

Adiponectin is a major insulin-sensitizing adipokine (Berg et al., 2001; Fruebis et al., 2001; Yamauchi et al., 2001). Adiponectin levels are decreased in cases of obesity and type 2 diabetes, a finding that has attracted enormous interest in the scientific community. Adiponectin stimulates AMP-activated protein kinase (AMPK), and this action has been implicated in its insulin-sensitizing function in liver and muscle (Yamauchi et al., 2002; Nawrocki et al., 2006). Both adiponectin receptors, AdipoR1 and AdipoR2 (Yamauchi et al., 2003), mediate the major part of the insulin-sensitizing action of adiponectin in liver, while AdipoR1 primarily does so in muscle (Yamauchi et al., 2007; Iwabu et al., 2010). Although it was previously shown that AdipoR1 and AdipoR2 regulate glucose and fatty acid metabolism partly via activation of AMPK, Ca^{2+}, and PPARα signaling pathways, it was not known whether these signaling pathways are sufficient to explain the pleiotropic actions of adiponectin. This study adds ceramide signaling as a new pathway involved in mediating such pleiotropic effects.

Scherer and colleagues also confirm that adiponectin ameliorates insulin resistance induced by a high-fat diet (HFD) in an AdipoR1- or AdipoR2-dependent fashion (Holland et al., 2011). Interestingly, they demonstrate that adiponectin lowers cellular ceramide levels via activation of ceramidase, which converts ceramide to sphingosine, an effect that appears to be dependent on activation of AdipoR1 or AdipoR2. They found that in liver, overexpression of adiponectin, AdipoR1, or AdipoR2 reduces hepatic ceramide levels and improves insulin sensitivity, while deficiency of adiponectin increases hepatic ceramide levels and exacerbates insulin resistance. Because increased ceramide levels correlate with impaired insulin action in muscle (Savage et al., 2007), it is tempting to speculate that the relationship between adiponectin-induced changes in ceramide levels and those in insulin sensitivity may be causal; this hypothesis should be examined experimentally.

Accumulation of ceramide has also been implicated in both β cell decompensation and heart failure induced by a HFD. This may be due to reduced ceramidase activity associated with reduced sphingosine, leading to reduced sphingosine 1-phosphate (S1P), a potent inhibitor of apoptosis generated via phosphorylation of sphingosine by sphingosine kinase. Scherer and colleagues use their elegant model of conditionally induced apoptosis to demonstrate that adiponectin both increases S1P and protects from apoptotic cell death induced by either palmitate or C2-ceramide in cardiac myocytes and pancreatic β cells (Holland et al., 2011). Because this protection is reversed by either an inhibitor of ceramide biosynthesis or S1P itself, it seems likely that adiponectin-induced S1P generation protects cardiac myocytes and β cells from cell death.

In this study, adiponectin significantly reduced hepatic ceramide levels and blood glucose levels in mice deficient in LKB1, an upstream activator of AMPK, which had increased basal hepatic ceramide levels and blood glucose levels compared to controls (Holland et al., 2011). From these data, they argue that adiponectin reduces hepatic ceramide levels independent of AMPK. No evidence yet exists to support this claim, as it may be difficult to draw a conclusion on the role of AMPK per se in decreasing glucose levels or on the role of adiponectin on lowering ceramide in this system. Moreover, the activation of AMPK and Ca^{2+} signaling pathways occurs within minutes after adiponectin stimulation, whereas activation of ceramidase appears to occur within a half hour, raising some question of whether ceramidase is the most upstream event following AdipoR1 or AdipoR2 activation.

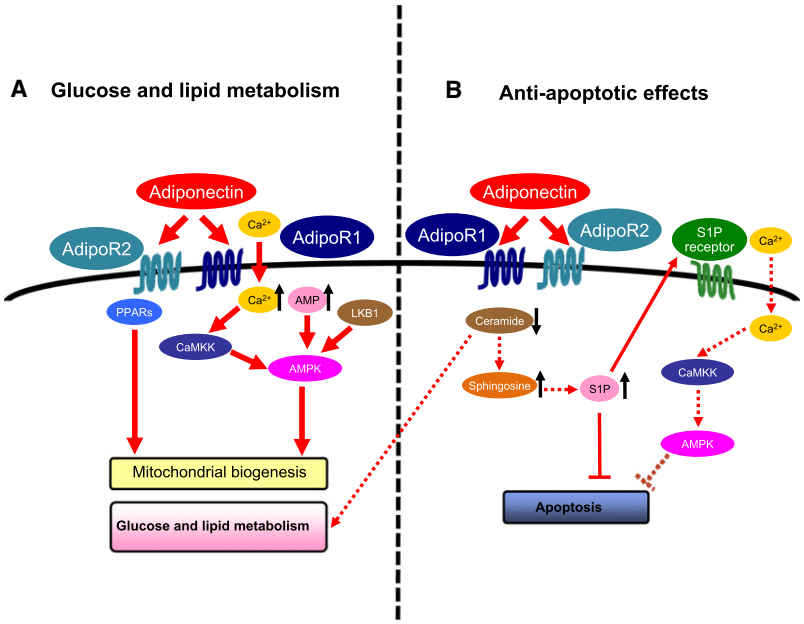

Figure 1. Adiponectin-Mediated Intracellular Signaling Pathways via AdipoR1 and AdipoR2
(A and B) Glucose and lipid metabolism regulated by adiponectin occurs within minutes, while antiapoptotic effects regulated by adiponectin occur within a half hour. Solid lines indicate pathways with reported cause-effect relationship, while hashed lines indicate those without. In skeletal muscle and liver, adiponectin stimulates AMPK, extracellular Ca^{2+} influx, and PPARα, which are involved in glucose and lipid metabolism in part via mitochondrial biogenesis (A). In this study, Holland et al. (2011) propose that in cardiac myocytes, β cells, and liver, adiponectin reduces levels of ceramide and increases those of S1P, which may be implicated in antiapoptosis (B). This may also be implicated in glucose and lipid metabolism, although the latter is only a parallel effect at present.

AdipoR1 and AdipoR2 belong to the progesterone and adiponectin Q receptor (PAQR) family. Some PAQR family members have been reported to contain sequence homology with alkaline ceramidase, and transfection of the yeast PAQR Izh2p enhances ceramidase activity in the cell. Indeed, transfection of cDNAs encoding AdipoR1 or AdipoR2 significantly enhanced ceramidase activity, and this activity was further enhanced by adiponectin in HEK293 cells (Holland et al., 2011).

While this study reveals an involvement of ceramide pathway downstream of AdipoR1 and AdipoR2 in pleiotropic actions of adiponectin, several points need to be clarified in future investigations. First, it is unclear whether and to what extent alterations of hepatic ceramide levels regulated by adiponectin-AdipoR1/AdipoR2 may be causally implicated in the regulation of insulin sensitivity. Second, as Scherer and colleagues acknowledge, it remains largely unknown whether adiponectin-AdipoR1/AdipoR2-activated ceramidase pathway is independent, parallel, or even an upstream pathway of AMPK or Ca^{2+} signaling. This point could be addressed through a detailed time course of these signals in response to adiponectin. Inducible ablation of AMPK, rather than ablation of LKB1, could also determine the role of AMPK on adiponectin-induced changes in ceramide levels in liver as well as in muscle, another important organ in the regulation of glucose and fatty acid metabolism. Last, even though AdipoR1 and AdipoR2 play roles in the regulation of ceramidase activity, it should next be determined whether the ceramidase activity is intrinsic to the receptor or whether ceramidase is indirectly activated upon adiponectin stimulation via an unknown mechanism.

This study shows that AdipoR1 and AdipoR2 mediate not only metabolic actions but also the antiapoptotic actions of adiponectin. In order for adiponectin to regulate these pleiotropic biological actions, it appears to regulate more diverse and complex pathways, such as ceramide and S1P downstream of AdipoR1 and AdipoR2, in addition to those originally identified, such as AMPK, Ca^{2+}, and PPARα (Yamauchi et al., 2003; Iwabu et al., 2010). It will be important to determine upstream, downstream, or even circuit relationships of these complex pathways as well as to correlate each of the signals to the downstream pleiotropic actions of adiponectin. This work has added a new layer to the working model for adiponectin-induced signaling pathways via AdipoR1 and AdipoR2 (Figure 1). This new knowledge adds to our fundamental understanding of this pleiotropic adipokine and to the development of versatile treatment strategies toward obesity-linked diseases such as type 2 diabetes.

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