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Review

The role of AMP-activated protein kinase in regulating white adipose tissue metabolism

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ABSTRACT

AMP-activated protein kinase (AMPK) is a heterotrimeric enzyme that plays a major role in the maintenance of energy homeostasis in various organs and tissues. When activated, AMPK can induce substrate catabolism and shut down energy-consuming anabolic pathways to increase intracellular ATP availability. Even though most of these effects have been described in muscle and liver, several studies have provided compelling evidence that AMPK also plays an important role in the regulation of white adipose tissue (WAT) glucose and lipid metabolism. In fact, the effects of acute and chronic AMPK activation in the WAT induce profound changes in adiposity with important implications for the treatment of obesity and its related metabolic disorders. This review discusses the role of AMPK in the regulation of white adipocyte metabolism with respect to energy storage and release, gene expression, mitochondrial biogenesis, oxidative capacity, cell differentiation, and the potential impact on whole-body adiposity and energy homeostasis.

Contents

1. Introduction

The white adipose tissue (WAT) is the major energy reservoir in mammals and plays a critical role in the maintenance of whole-body energy homeostasis. The WAT is mainly composed of white adipocytes (35–75% of all cells), with the remaining being comprised of stromal vasculature tissue containing fibroblasts, endothelial cells, blood cells, macrophages, pericytes, and preadipocytes among others (Cinti, 2009). White adipocytes are specialized and differentiated spherical cells with a great capacity to store lipids in the form of triacylglycerides (TAGs) for subsequent release of fatty acids (FAs) under conditions of high metabolic demand (i.e. exercise) or negative energy balance (i.e. food restriction). From a metabolic perspective, the main classical functions of white adipocytes are: (a) lipid synthesis and storage from a variety of substrates; and (b) TAG breakdown (lipolysis) and exportation of FAs (Cinti, 2009; Bays et al., 2008). However, adipocytes also express and secrete various factors called adipokines (i.e. leptin and adiponectin) that exert autocrine, paracrine, and endocrine effects in the body (Bays et al., 2008). Of particular interest is leptin, a 16 kDa protein that is secreted mainly by adipocytes proportionally to the size of adipose tissue mass and nutritional status (Considine and Caro, 1997; Frayn et al., 2003). Leptin relays information to the central

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nervous system (CNS) regarding energy availability in the organism, which allows the CNS to make continuous adjustments in food intake and energy expenditure to regulate fat mass and body weight in the long-term (Bays et al., 2008; Leibel, 2008). Importantly, the expression and release of leptin by adipocytes has been reported to depend on the amount of glucose that is up-taken and metabolized by these cells (Mueller et al., 1998). Therefore, mechanisms that alter glucose uptake and metabolism in the WAT can affect the ability of this tissue to express and release leptin and potentially other adipokines, which can have a major impact on whole-body energy homeostasis. In this context, we (Gaidhu et al., 2006; Anthony et al., 2009; Gaidhu et al., 2009., Gaidhu et al., 2010a,b; Gaidhu et al., 2011) and others (Garton and Yeaman, 1990; Salt et al., 2000; Daval et al., 2005; Gauthier et al., 2008) have reported that the cellular energy sensor AMPK plays an important role in regulating adipocyte glucose and lipid metabolism. Once activated, AMPK can quickly alter the uptake, storage, and oxidation of various substrates in the adipocyte (Gaidhu et al., 2006, 2009). AMPK also has the ability to regulate the expression in the adipocyte of several genes involved in the control of cellular differentiation (Habinowski and Witters, 2001; Lin et al., 2011) and mitochondrial biogenesis (Gaidhu et al., 2009). The rapid metabolic adjustments (Gaidhu et al., 2006) along with the long-term gene expression effects of AMPK (Gaidhu et al., 2009, 2011) have a profound impact not only on WAT metabolism, but also on whole-body energy homeostasis (Winder et al., 2000; Narkar et al., 2008; Gaidhu et al., 2011). These observations have opened up the possibility of using nutritional and pharmacological approaches to manipulate AMPK activity within the WAT with great potential implications for the treatment of metabolic disorders such as obesity and type 2 diabetes (Gaidhu and Ceddia, 2009, 2011).

2. Structure and functional role of AMPK subunits in the WAT

AMPK is a well-conserved heterotrimeric enzyme composed of a catalytic (α) and two regulatory (β and γ) subunits. Multiple isoforms of each mammalian subunit exist (α1, α2, β1, β2, γ1–γ3) and are differentially expressed in various tissues enabling the potential formation of 12 heterotrimer combinations that are thought to exhibit differences in subcellular localization and tissue-specific signaling functions (Hardie, 2007). The N-terminus portion of the α catalytic subunit of AMPK has a serine/threonine protein kinase domain, while the C-terminal region contains the β-binding domain required for the formation of the heterotrimer complex (Elbing et al., 2006). The β subunit serves as a scaffold that allows the assembly of the αβγ complex, and also contains the glycogen binding domain (GBD), which is a member of the isoamylase-N domain family usually found in enzymes that metabolize the α1 → 6 branch of glycogen and starch (McBride et al., 2009). Recent studies provide evidence that the existence of the GBD allows AMPK to also act as a cellular sensor of glycogen that regulates the rate of synthesis and breakdown of this fuel source (McBride et al., 2009). Although this may play an important role in the regulation of glycogen metabolism in liver and skeletal muscle (McBride and Hardie, 2009), the importance for adipose tissue metabolism remains undetermined. The γ subunit of AMPK has four cystathionine β-synthase sequence repeats (CBS domains), which are small motifs found in tandem pairs also referred to as Bateman domains. The CBS sequences provide sites for the binding of the regulatory nucleotides AMP, ADP and ATP (Xiao et al., 2007, 2011).

Analysis of various rat tissue extracts revealed that AMPK activity was highest in liver followed by the mammary gland, lungs, adrenal gland, macrophages, adipose tissue, and heart, while the lowest activity was detected in brain and skeletal muscle (Davies et al., 1989). However, this study did not discriminate which AMPK catalytic subunit predominated in each of the tissues analyzed (Davies et al., 1989). Subsequent studies in male C57Bl/6 mice reported that AMPK activity in brown adipose tissue (BAT) was 3-fold higher than in liver, a finding that was secondary to a high level of expression of the α1 isoform (Mulligan et al., 2007). Similarly, in WAT from mice (Daval et al., 2005; Mulligan et al., 2007) and humans (Lihn et al., 2004) heterotrimeric complexes containing the α1 subunit accounts for most of the activity of this kinase. This is also in line with our observations that overexpressing a kinase dead mutant of the α1 catalytic (KD-AMPK-α1) prevents the effects of the purine nucleoside adenosine analog AMPK activator 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) on glucose uptake and metabolism in primary rat adipocytes (Gaidhu et al., 2010b).

Interestingly, it has been reported that, as a result of an enhanced lipid accumulation in adipocytes but not in other tissues, mice lacking AMPK-α2 show increased fat mass when fed a high-fat diet (Villena et al., 2004). Food intake and energy expenditure in mice lacking AMPK-α2 did not differ from those of wild-type mice. Moreover, the increase in adipose mass was due to an enlargement of the preexisting adipocytes without any alterations in adipocyte number or differentiation (Villena et al., 2004). These findings indicated that the AMPK-α2 could potentially play an important role in the regulation of adiposity. However, since this mouse model had whole-body deletion of AMPK-α2 (Viollet et al., 2003), the obese phenotype could be secondary to alterations in glucose and lipid metabolism due to the lack of AMPK α2 activity in other peripheral tissues such as liver and skeletal muscle. Also, in the study by Villena et al. (2004) no data was provided regarding whether a compensatory up-regulation in AMPK-α1 took place in the WAT and other tissues, which could, either directly or indirectly, have affected adiposity. In another study in which mice with whole-body deletion of AMPK-α1 (AMPK-$\alpha1^{-/-}$) were analyzed (Bauwens et al., 2011), AMPK-α2 activity in BAT, WAT, and liver was significantly greater in AMPK-$\alpha1^{-/-}$ than wild-type mice. Furthermore, loss of AMPK-α1 in WAT had no effect on P-ACC levels, indicating that compensatory up-regulation of AMPK-α2 was sufficient to maintain P-ACC at normal levels (Bauwens et al., 2011). Furthermore, studies of mice lacking the β1 subunit of AMPK (AMPK-$\beta1^{-/-}$) revealed a phenotype of reduced body weight and fat mass under both low and high fat diets, despite increased insulin-stimulated lipogenesis in the WAT (Dzamko et al., 2010). These findings could suggest an important role for the β1 subunit of AMPK in the regulation of adiposity. However, while AMPK-α1 and α2 activities were substantially reduced in liver, no significant differences were found for these variables in the WAT. Therefore, the alterations in fat mass in AMPK-$\beta1^{-/-}$ mice appear to be secondary to the reduced food intake that was also reported in these animals (Dzamko et al., 2010). Additional studies in which each of the α and β subunits of AMPK are deleted specifically in the WAT will be required in order to determine whether or not they play important roles in regulating WAT metabolism and adiposity *in vivo*.

The α1 and α2 isoforms share 90% amino acid sequence homology within the catalytic site, but much less identity (61%) elsewhere. Also, major differences in the COOH-terminal tails of α1 and α2 sequences exist (Stapleton et al., 1996), suggesting that these catalytic subunits could selectively interact with proteins within this region and confer tissue-specific differences with respect to the formation of heterotrimers, metabolic regulation, and sub-cellular localization. In this context, studies in a transformed cell line derived from rat pancreatic β-cells (INS-1 cells) reported that AMPK-α2 and α1 heterotrimers elicited 5- and 2-fold increases in activity in the presence of AMP, respectively (Salt et al., 1998). Furthermore, a significant proportion of AMPK complexes containing the α2 subunits, but not α1, were reported to