Obesity: The role of hypothalamic AMP-activated protein kinase in body weight regulation

Woo Je Lee, Eun Hee Koh, Jong Chul Won, Min-Seon Kim, Joong-Yeol Park, Ki-Up Lee

Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Song-Pa P.O. Box 145, Seoul 138-600, Republic of Korea

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Abstract

Obesity is rapidly increasing and is of great public health concern worldwide. Although there have been remarkable developments in obesity research over the past 10 years, the molecular mechanism of obesity is still not completely understood. Body weight results from the balance between food intake and energy expenditure. Recent studies have found that hypothalamic AMP-activated protein kinase plays a key role in regulating these processes. Leptin, insulin, glucose and alpha-lipoic acid have been shown to reduce food intake by lowering hypothalamic AMP-activated protein kinase activity, whereas ghrelin and glucose depletion increase food intake by increasing hypothalamic AMP-activated protein kinase activity. In addition, this enzyme plays a role in the central regulation of energy expenditure. These findings indicate that hypothalamic AMP-activated protein kinase is an important signal molecule, which integrates nutritional and hormonal signals and modulates feeding behavior and energy expenditure.

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1. Introduction

The prevalence of obesity is rapidly increasing around the world. Obesity is a major risk factor for numbers of disorders, including diabetes, hypertension and heart disease. In the United States alone, it has been estimated that about 300,000 deaths each year, and US$117 billion in direct and indirect annual costs, result from obesity (Stein & Colditz, 2004). Although the past 10 years have been the golden age of obesity research, including the discovery of leptin (Zhang et al., 1994) and the leptin receptor gene (Tartaglia et al., 1995), the molecular mechanism of obesity is not yet completely understood. It seems likely that insights into weight-regulatory pathways will accelerate the identification of molecular targets, eventually enabling the development of safe and effective pharmaceuticals for obesity.
Here, we briefly summarize current understandings of the molecular mechanisms of obesity, focusing on recent studies from our group and others on the role of hypothalamic AMP-activated protein kinase (AMPK) in the regulation of food intake and energy expenditure.

2. Pathogenesis

2.1. Genetics

The heritability of obesity is high, approximately equivalent to the heritability of height and greater than that of almost every other condition that has been studied. Single gene defects, including defects in the leptin, leptin receptor, melanocortin 4 receptor (MC4R) and proopiomelanocortin (POMC) genes, have been identified in rare cases of severe obesity.

2.2. Fat cell biology

Adipose tissue is the major storage organ for surplus energy. It is now clear that adipose tissue is a complex and highly active metabolic and endocrine organ. Leptin is a representative adipocyte-derived hormone that signals information about the body’s energy status from the adipose tissue to the brain. Although it is now well known that leptin-deficient ob/ob and leptin receptor-deficient db/db mice develop severe obesity, leptin deficiency is very rare in humans, and most obese individuals have increased plasma leptin concentrations, suggesting that they are leptin resistant. In addition to secreting leptin, adipose tissue secretes a variety of bioactive peptides, collectively called adipocytokines, including tumor necrosis factor (TNF)-alpha, adiponectin, plasminogen activator inhibitor (PAI)-1, interleukin (IL)-6 and angiotensinogen. The expression profile of adipocytokines in subcutaneous adipose tissue and that in visceral adipose tissue are different. Adiponectin, PAI-1, IL-6 and angiotensinogen are mainly in the latter. The change in these important adipocytokines by visceral obesity is regarded as the cause of the detrimental metabolic effects.

Recently, the physiologic role of adiponectin has received considerable attention. Adiponectin has been shown to reduce insulin resistance and atherosclerotic processes and to increase fatty acid oxidation rates (Havel, 2004). The actions of adiponectin are considered to be due to the activation of AMPK through the recently cloned adiponectin receptor (Yamauchi et al., 2003). Unlike other adipocytokines, plasma adiponectin levels are reduced in accordance with body (visceral) fat mass (Havel, 2004). TNF-alpha, which increases in obesity and inhibits the insulin signal, is considered to be a key factor in the regulation of adiponectin production.

2.3. Energy expenditure

Body weight results from the balance between food intake and energy expenditure. The sympathetic nervous system is activated in response to excess energy or a cold environment. Mice with deletions of the genes encoding the three adrenergic β receptor subtypes (Bachman et al., 2002) developed severe obesity as a result of their inability to increase energy expenditure in response to a high calorie diet. In rodents, uncoupling protein (UCP)-1 in brown adipose tissue is the main regulator of basal energy expenditure, and the expression of this protein is increased by adrenergic stimulation. In humans, however, the main regulator of energy expenditure is not yet known. The UCP-1 homologues, UCP-2 and UCP-3, which are expressed in human tissues, were formerly thought to be the main regulators of energy expenditure. Indeed, hyper-expression of UCP-2 and UCP-3 was shown to increase energy expenditure and to reduce body fat. These proteins, however, may not be the major regulators of whole body energy expenditure, in as much as mice deficient in either protein did not develop obesity (Flier, 2004).

2.4. Nutrient sensing in the hypothalamus and feeding regulation

The neural system that regulates body weight and appetite is centered in the hypothalamus, which coordinates both afferent sensing and efferent action signals. Long-term afferent signals, such as leptin and insulin, sense the long-term status of body energy stores, whereas short-term (meal-related) afferent signals, derived from the gut, are involved in regulating the onset or termination of individual meals (Flier, 2004).

Neuronal cells, which sense nutrient availability, trigger feeding behavior. Intracerebroventricular (ICV) administration of glucose or long chain fatty acid has been found to inhibit food intake (Obici et al., 2002),
whereas central administration of 2-deoxyglucose (2-DG), a non-metabolizable glucose analogue or mercaptoacetate, an inhibitor of fatty acid oxidation, elicits feeding behavior (Sergeyev, Broberger, Gorbatyuk, & Hokfelt, 2000).

Several signaling pathways are thought to be involved in mediating nutrient-induced feeding. For example, central administration of the fatty acid synthase (FAS) inhibitors cerulenin and C75 reduce food intake, but this can be prevented by the co-administration of the acetyl-CoA carboxylase (ACC) inhibitor TOFA (Loftus et al., 2000). This result suggests that malonyl CoA, an intermediate metabolite between ACC and FAS, may be an anorexigenic signal (Fig. 1). In contrast, inhibition of hypothalamic carnitine palmitoyl transferase-1 (CPT-1) reduces food intake (Obici, Feng, Arduini, Conti, & Rossetti, 2003). From these findings, it has been suggested that increased cytosolic concentrations of long chain fatty acyl CoA (LCAC) may serve as an anorexigenic signal. Like pancreatic β-cells, some neurons in the ventromedial (VMH) and arcuate nuclei (ARC) of the hypothalamus have glucose-sensing machinery, including GLUT2, glucokinase and the ATP-sensitive potassium (KATP) channel (Yang, Kow, Funabashi, & Mobbs, 1999). The anorexic hormones leptin and insulin can activate the KATP channel in glucose-responsive hypothalamic neurons (Spanswick, Smith, Mirshamsi, Routh, & Ashford, 2000).

2.5. Role of hypothalamic AMPK

AMPK is an enzyme that acts as an intracellular energy sensor (Kahn, Alquier, Carling, & Hardie, 2005). AMPK is activated when the energy status of a cell is low. When activated, AMPK inhibits ATP-consuming pathways (e.g., fatty acid synthesis) and activates ATP-generating pathways (e.g., fatty acid oxidation and glycolysis), thus maintaining energy balance within cells. AMPK activation in skeletal muscle enhances glucose uptake and mitochondrial fatty acid oxidation (Kahn et al., 2005). In the liver, AMPK activation suppresses endogenous glucose production (Kahn et al., 2005). In pancreatic β-cells, AMPK seems to antagonize the effect of glucose on insulin secretion and to induce β-cell apoptosis (Kefas et al., 2003).

![Fig. 1. Possible mechanism by which decreased hypothalamic AMP-activated protein kinase (AMPK) activity reduces food intake. The reduction in hypothalamic AMPK activity in response to feeding-inhibiting factors, such as leptin, insulin, glucose and alpha-lipoic acid (α-LA), increases acetyl-CoA carboxylase (ACC) activity. Increased ACC activity leads to increase in malonyl-CoA levels, which in turn inhibits carnitine palmitoyltransferase-1 (CPT-1) and mitochondrial β-oxidation of long chain fatty acyl CoA (LCAC). Recent studies have suggested that increases in malonyl-CoA and/or LCAC levels in the hypothalamus decrease food intake (Anderson et al., 2004; Loftus et al., 2000; Obici et al., 2003).](image-url)
whereas activation of this enzyme has been reported to play a favorable role in preserving β-cell function under lipid overloading conditions (Diraison et al., 2004).

Recent studies (Andersson et al., 2004; Kim et al., 2004; Minokoshi et al., 2004) have demonstrated that AMPK activity in hypothalamic neurons is altered by various factors and mediates their feeding effects. Hypothalamic AMPK activity is regulated by nutritional availability in hypothalamic neurons. For example, administration of 2-DG increases hypothalamic AMPK activity, while co-administration of an AMPK inhibitor, compound C, inhibited the 2-DG-induced glucoprivic feeding (Kim et al., 2004). Conversely, ICV administration of glucose or restoration of food intake has been found to decrease hypothalamic AMPK activity (Minokoshi et al., 2004). AMPK activity is reduced by ICV administration of anorexigenic hormones, such as insulin and leptin, but increased by ICV administration of the orexigenic hormone ghrelin (Andersson et al., 2004; Minokoshi et al., 2004). In the hypothalamic paraventricular nucleus, AMPK activity is decreased by the melanocortin receptor agonist MT-II but increased by the melanocortin receptor antagonist agonist-related protein (AgRP). Taken together, these findings indicate that AMPK is part of the common signaling pathway by which various factors regulate feeding behavior. That is, hypothalamic AMPK activity is reduced by feeding-inhibiting factors and increased by feeding-stimulating factors.

Although the mechanism by which AMPK activity in hypothalamic neurons affects feeding behavior is still not fully understood, the leptin-induced reduction in hypothalamic AMPK activity was shown to decrease feeding by down-regulating expression of the orexigenic hormones neuropeptide Y (NPY) and AgRP (Minokoshi et al., 2004). Alternatively, changes in AMPK activity may affect feeding via changes in intracellular malonyl CoA concentrations and CPT-1 activity (Loftus et al., 2000; Obici et al., 2003; Fig. 1).

3. Therapy

Sibutramine and orlistat, which regulate food intake and lipid absorption, respectively, are the two currently approved anti-obesity drugs. Both of these drugs,
however, are less than satisfactory because of their limited efficacy and unfavorable side effects. Thus, there is a need for more effective and safer therapeutic agents for obesity.

We recently demonstrated that alpha-lipoic acid (α-LA) has anti-obesity effects mediated by the suppression of hypothalamic AMPK activity (Kim et al., 2004). α-LA is an essential cofactor of mitochondrial pyruvate and ketone body dehydrogenase. In addition, α-LA enhances glucose metabolism in insulin-resistant rat skeletal muscle, and shows potent antioxidant activity by chelating transition metal ions and increasing cytosolic glutathione and vitamin C levels. Administration of α-LA to rodents reduces food intake and body weight, as well as stimulating whole-body energy expenditure. We have shown that central administration of very small amounts of α-LA increased UCP-1 mRNA in brown adipose tissue, whereas co-administration of an AMPK activator, 5′-aminoimidazole-4-carboxamide ribonucleoside (AICAR), prevented the α-LA-induced enhancement of energy expenditure and UCP-1 expression, indicating that these effects are mediated by α-LA-induced inhibition of AMPK (Kim et al., 2004). Finally, in contrast to its effects on the hypothalamus, α-LA increased glucose uptake and fatty acid oxidation in skeletal muscle by activating AMPK (Lee et al., 2005).

The mechanism by which α-LA decreases hypothalamic AMPK activity is presently unknown. However, α-LA has been found to stimulate glucose transport and ATP synthesis in peripheral tissues (Yavorsky, Somrkat, Ramdal, Trischler, & Klip, 2000), and it may decrease hypothalamic AMPK activity by increasing glucose uptake and/or metabolism in the hypothalamus.

Drugs that can both reduce appetite and increase energy expenditure may be ideal for regulating body weight. Therefore, α-LA may be a promising new drug for the treatment of human obesity (Fig. 2). The effects of α-LA on energy expenditure, however, may be limited to rodents, which possess active brown adipose tissues.

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References


