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# The Role of AMP-Activated Protein Kinase in Obesity

Blerina Kola · Ashley B. Grossman · Márta Korbonits

Department of Endocrinology, Barts and the London, Queen Mary's School of Medicine and Dentistry,  
University of London, London, UK

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## Abstract

AMP-activated protein kinase (AMPK) is a major regulator of energy metabolism at both the cell and at the whole body level. Numerous genetic and obesity models as well as human studies have suggested a role for AMPK in the physiological regulation of fatty acid and glucose metabolism, and in the regulation of appetite. Changes in AMPK activity have been reported in obesity, type 2 diabetes, the metabolic syndrome and cardiovascular disease, which jointly represent a major health and economical problem worldwide. Whether AMPK changes are one of the causes or the consequence of these pathological conditions remains a matter of debate, but AMPK clearly represents a major potential pharmacological target in the treatment of these conditions.

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Obesity is a major health and economic problem in both Western and developing societies. Its continuing rise in prevalence, 20% in England and 30% in USA [1, 2] seems to be unstoppable despite multiple efforts to attempt to halt this trend. Obesity is characterised by multiple metabolic changes such as insulin resistance, dyslipidaemia and hypertension. The diseases arising as a consequence of obesity such as type 2 diabetes (T2D), cardiovascular disease and certain cancers, are increasingly important causes of morbidity and mortality. In the last decades, a huge amount of research has been dedicated to the study of the complex pathophysiology of obesity and to the research for new medical therapies.

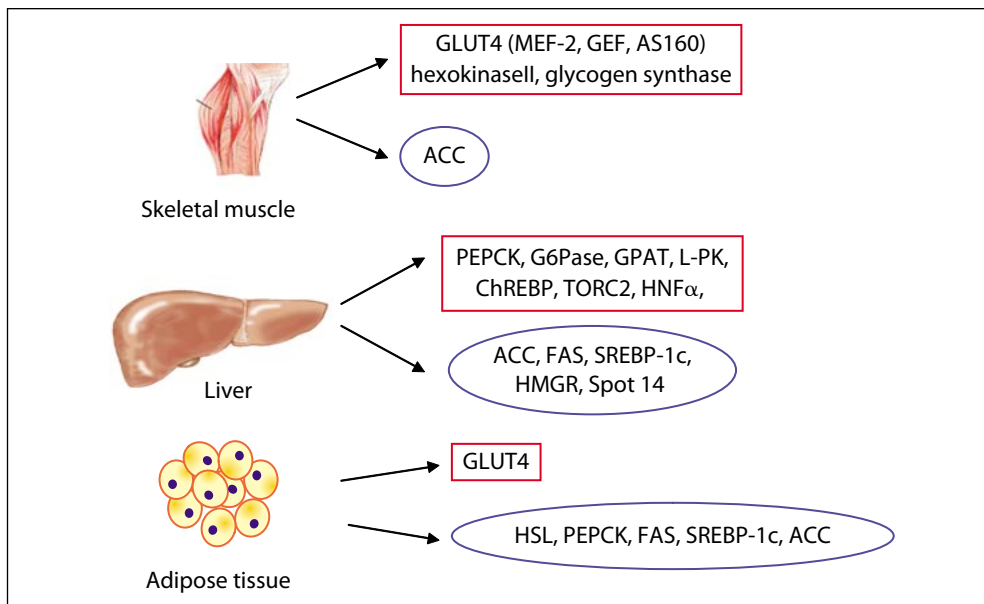
AMP-activated protein kinase (AMPK) has emerged in the last years as a major regulator of cell and whole body metabolism. Numerous papers have reported evidence for its role in the regulation of appetite, of body weight and of metabolism [3–5]. Therefore, it is natural to consider AMPK as a major player in the development of obesity. The AMPK complex is an evolutionally conserved serine/threonine heterotrimer kinase complex consisting of  $\alpha$ -,  $\beta$ - and  $\gamma$ -subunits [for detailed reviews see 5, 6]. AMPK is

activated by cellular stress, which depletes cellular ATP leading to a concomitant rise in AMP. AMP activates AMPK by three distinct mechanisms: (a) allosteric activation, (b) stimulation of phosphorylation of the  $\alpha$ -subunit on Thr172 by upstream kinase(s) [LKB1 and calmodulin kinase kinase- $\alpha$  or - $\beta$  and recently a new possible AMPK kinase candidate, the transforming growth factor- $\beta$ -activated kinase (TAK1), which phosphorylates AMPK on Thr-172 in HeLa cells [7], has been reported], and (c) inhibition of dephosphorylation by protein phosphatases [5, 8–10]. Cellular stresses that cause a rise in the AMP/ATP ratio include metabolic poisons (arsenite, oligomycin), oxidative stresses, hypoxia, low glucose, muscle contraction and nutrient deprivation. Osmotic stress also activates AMPK even without a change in the AMP/ATP ratio. Once activated, AMPK switches off anabolic pathways such as gluconeogenesis, glycogen, fatty acid, triglyceride, cholesterol and protein synthesis (mTOR-p70SK-E2 pathway), and switches on catabolic pathways such as glycolysis, glucose uptake, and fatty acid oxidation. It also leads to mitochondrial biogenesis, which improves the ATP synthesis capacity of the cell [11]. Metabolic changes induced by AMPK are both acute changes due to phosphorylation of key enzymes and longer-term effects on the expression of genes involved in metabolic regulation. AMPK, through several mediators, plays a role in various physiological and pathological processes in different tissues (fig. 1). Therefore, it was logical to hypothesise that abnormal AMPK activity would be present in conditions of deregulated energy balance, such as obesity and T2D.

## **Role of AMPK in Normal Physiology**

### *Role of AMPK in Skeletal Muscle Metabolism*

Skeletal muscle is the major site of glucose uptake [12], a process that is mainly stimulated by insulin but also by other alternative pathways. Exercise stimulates glucose uptake in the skeletal muscle independently of the insulin pathway and AMPK appears to be the mediator of this effect, primarily in the glycolytic white muscle. These conclusions derived from studies in which in vivo AMP-mimetic 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) treatment stimulated glucose uptake [13]. The effect was not inhibited by the inhibition of the insulin-dependent PI3K pathway and was additive to insulin-stimulated glucose uptake [14]. AICAR also stimulates glucose transporter GLUT4 expression [15, 16] and its translocation to the cell membrane in rat skeletal muscles [17]. Chronic AMPK activation also increases the expression of hexokinase II, the first enzyme of the glycolysis pathway [18] and inactivates glycogen synthase [19]. The effect of AMPK is fibre dependent and is different in resistance (weight lifting) or endurance (distance running) exercise. AMPK stimulates glucose uptake and GLUT4 expression/transport in fast-twitch (glycolytic, white) muscle but not in slow-twitch (oxidative, red) muscle [20]. AMPK in muscle is activated during exercise, probably as a result of the exercise-induced IL-6 release, a cytokine which activates AMPK in isolated rat muscles [21]. Moreover, it seems that



**Fig. 1.** Metabolic targets of AMPK in muscle, liver and adipose tissues. AMPK regulates the expression and phosphorylation of enzymes and genes involved in glucose and lipid metabolism. GLUT4 = Glucose transporter 4; MEF-2 = myocyte enhancer factor-2; GEF = GLUT4 enhancer factor; AS-160 = Akt-substrate-of-160 kDa; ACC = acetyl-coenzyme A carboxylase; PEPCK = phosphoenolpyruvate carboxykinase; G6Pase = glucose-6-phosphatase; GPAT = glycerol-3-phosphate acyl-transferase; L-PK = L-pyruvate kinase; ChREBP = carbohydrate response element-binding protein; TORC2 = transducer of regulated CREB activity 2; HNF $\alpha$  = hepatic nuclear factor  $\alpha$ ; FAS = fatty acid synthase; SREBP-1c = sterol regulatory element binding protein-1; HMGR = 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HSL = hormone-sensitive lipase.

only endurance exercise and not resistance exercise can induce AMPK activation [20, 22]. AMPK activation in endurance exercise could also explain the lack of muscle hypertrophy in distance running in contrast to weight lifting. This is possibly due to the effect of AMPK on the mTOR pathway [20]. The mTOR pathway stimulates protein synthesis and hence cell growth and hypertrophy in response to growth factors and amino acids. Therefore, AMPK inhibition of this pathway would result in inhibition of protein synthesis and lack of muscle hypertrophy. AMPK also stimulates fatty acid oxidation in muscle. This results in lower lipid deposition and increases the ability of the muscle to meet energy needs by increasing glucose uptake and fatty acid oxidation as well. Studies with transgenic animals (AMPK  $\alpha$ 1 and  $\alpha$ 2 knockout mice, muscle-specific over-expression of dominant negative AMPK  $\alpha$ 2, AMPK  $\gamma$ 3 knockout, muscle-specific over-expression of AMPK  $\gamma$ 3 and muscle-specific over-expression of AMPK  $\gamma$ 3 R225Q overactive mutant and skeletal muscle-specific LKB1 knockout [for detailed descriptions, see 20, 23]), have provided further evidence for AMPK being the main mediator, although not the only one, of the adaptations (i.e. increased

glucose uptake, fatty acid oxidation, inhibition of glycogen synthesis) of skeletal muscle in response to exercise.

#### *Role of AMPK in Liver Metabolism*

The liver is the major site for storage and release of carbohydrates and for fatty acid synthesis. It responds to fasting with increased glucose output and increased fatty acid oxidation, while in post-prandial conditions liver glucose uptake increases with consequent glycogen and triglyceride synthesis [24]. AMPK regulates liver lipid and glucose homeostasis via phosphorylation of multiple enzymes (e.g. ACC1 – ↓ lipid synthesis, ACC2 – ↑ lipid oxidation, 3-hydroxy-3-methylglutaryl-coenzyme A reductase – ↓ cholesterol synthesis, glycerol-3-phosphate acyltransferase – ↓ glycerolipid synthesis), and influences the expression of genes involved in gluconeogenic, glycolytic and lipogenic processes and their upstream regulators [for a comprehensive review on the topic, see 25]. Therefore, overall AMPK activation in the liver results in inhibition of gluconeogenesis, fatty acid, triglyceride and cholesterol synthesis, and stimulation of fatty acid oxidation. Changes in hepatic metabolism are certainly present in obesity and T2D. Elevated glucose production by the liver is the major cause of fasting hyperglycaemia, and it is possible that AMPK activation by decreasing gluconeogenesis and cholesterol synthesis could be beneficial in these patients. Nevertheless, one needs to be cautious as AMPK activation, by increasing fatty acid oxidation and ketogenesis, might lead to ketoacidosis, and by inhibiting protein synthesis might lead to a negative nitrogen balance together with enhanced urea synthesis [25].

#### *Role of AMPK in Adipose Tissue Metabolism*

Adipose tissue has been considered for decades simply as an energy storage organ, while in the last years it has emerged as an active endocrine organ, which by secreting several proteins, known as adipokines, contributes to the regulation of appetite and metabolism. AMPK  $\alpha$ 1 subunit is the prevalent AMPK subunit expressed in the adipose tissue [26 and our own unpublished data]. AMPK regulates lipogenesis and lipolysis in adipose tissue. Activation of AMPK in rodent adipocytes leads to a decreased fatty acid uptake, decreased triglyceride synthesis and increased fatty acid oxidation via inhibition of ACC1 and ACC2 and, as in the liver, inhibition of the expression of lipogenic genes [27, 28].

During fasting, lipolysis is activated in adipose tissue in order to provide fatty acids and glycerol as fuels for peripheral tissues, but reports on the effect of AMPK activation on lipolysis are contradictory. There is evidence that AMPK activation, either by AICAR or by over-expression of a constitutively active AMPK isoform or by biguanide treatment, has an inhibitory effect on lipolysis [26, 29]. In conditions where lipolysis is activated, such as fasting and exercise, AMPK is also activated but as a feedback mechanism this activation leads to inhibition of lipolysis, which is an energy-consuming process for the adipocytes [27]. Furthermore, in the AMPK  $\alpha$ 1 knockout mice, the size of the