EJE PRIZE 2017

Hypothalamic AMPK: a golden target against obesity?

Miguel López

Department of Physiology, NeurObesity Group, CIMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria and CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Santiago de Compostela, Spain

Correspondence
should be addressed
to M López

Email
m.lopez@usc.es

Abstract

AMP-activated protein kinase (AMPK) is a cellular gauge that is activated under conditions, such as low energy, increasing energy production and reducing energy waste. Centrally, the AMPK pathway is a canonical route regulating energy homeostasis, by integrating peripheral signals, such as hormones and metabolites, with neuronal networks. Current evidence links hypothalamic AMPK with feeding, brown adipose tissue (BAT) thermogenesis and browning of white adipose tissue (WAT), as well as muscle metabolism, hepatic function and glucose homeostasis. The relevance of these data is interesting from a therapeutic point of view as several agents with potential anti-obesity and/or antidiabetic effects, some currently in clinical use, such as nicotine, metformin and liraglutide are known to act through AMPK, either peripherally or centrally. Furthermore, the orexigenic and weight-gaining effects of the worldwide use of antipsychotic drugs (APDs), such as olanzapine, are also mediated by hypothalamic AMPK. Overall, this evidence makes hypothalamic AMPK signaling an interesting target for the drug development, with its potential for controlling both sides of the energy balance equation, namely feeding and energy expenditure through defined metabolic pathways.

*European Journal of
Endocrinology*
(2017) **176**, R235–R246

Living organisms need to sense energy

The survival of living organisms is due to their continuous exchange of energy with the environment. Intracellularly, there are thousands of different metabolic processes that underlie energy production and utilization. Heterotrophs, such as mammals, obtain energy from organic compounds, mainly carbohydrates, fats and proteins, which are oxidized to release energy that is then stored as ATP. Indeed, every living cell can be considered to contain an energy-storing 'battery', the main components being ATP and ADP, interconverted

by the reaction $\text{ATP} \leftrightarrow \text{ADP} + \text{P}$. Discharging the battery therefore leads to an increase in intracellular ADP levels. As the reaction is reversible ($2\text{ADP} \leftrightarrow \text{ATP} + \text{AMP}$), AMP levels rise markedly when the ADP:ATP ratio increases during the energy consumption. Thus, under conditions of insufficient intracellular energy, there is an associated rise in AMP levels. An efficient evolutionary criterion for a functional intracellular energy gauge would therefore be necessary to sense the ratio of either ADP:ATP or AMP:ATP (1, 2, 3, 4).

Invited Author's profile

Dr Miguel López PhD is currently Associate Professor in Department of Physiology at the School of Medicine and the Research Centre of Molecular Medicine and Chronic Diseases (CIMUS) of the University of Santiago de Compostela, Spain. His research has focused on the regulation of energy balance and obesity, with his current interest on hypothalamic AMPK and energy sensing in the modulation of energy balance and metabolism.

Figure 1

Structure, regulation and the role of AMPK. AMP-activated protein kinase (AMPK) is a heterotrimer consisting of a catalytic α subunit and two regulatory subunits, β and γ . AMPK is the downstream component of a kinase cascade that acts as a gauge of cellular energy levels, being activated through increased phosphorylation of Thr172 within the catalytic α subunit by upstream liver kinase B1 (LKB1) and Ca^{2+} /calmodulin-dependent protein kinase kinase β (CaMKK β). In addition to activation by phosphorylation, AMPK is allosterically activated by AMP, which induces phosphorylation at Thr172 by LKB1 and CaMKK β and also inhibits dephosphorylation by protein phosphatases such as protein phosphatase 2C alpha (PP2C α). Other upstream factors modulate AMPK activity (see main text) but have been omitted to simplify the figure. AMPK is a counter-regulatory intracellular switch, switching off (red lines) ATP-consuming

AMPK and the regulation of cellular energy metabolism

In 1987, David Carling and Grahame Hardie first demonstrated that apparently two different protein kinases that inhibited enzymes involved in *de novo* fatty acid and cholesterol synthesis (acetyl-CoA carboxylase and hydroxymethylglutaryl-CoA reductase respectively) were in fact the same protein (5). As each enzyme had formerly been shown to be activated by AMP (6, 7), they re-named them both as AMP-activated protein kinase (AMPK) (8). AMPK is now established as the principal energy sensor in eukaryotic cells and is unquestionably one of the most important discoveries in biomedical sciences in the last 30 years. In fact, 3 decades later, AMPK is considered the principal (and probably sole) energy sensor in eukaryotic cells, a concept that has been extended to a more global view in which AMPK has a wide range of effects at the cellular and whole-body levels, regulating, besides metabolism, cell growth, mitosis, apoptosis, cell polarity, autophagy, inflammation, immune function and cancer (4, 9, 10, 11).

AMPK: the master energy sensor

AMPK is a highly conserved serine/threonine kinase; certainly, orthologs of AMPK subunits have been found in all eukaryotic kingdoms, including protists, fungi, plants and animals (1, 9). AMPK is a heterotrimer complex comprising a catalytic α ($\alpha 1$, $\alpha 2$) subunit with a conventional serine/threonine protein kinase domain and two regulatory subunits, β ($\beta 1$, $\beta 2$) and γ ($\gamma 1$, $\gamma 2$, $\gamma 3$) (Fig. 1), encoded by different genes (1, 4, 9, 12, 13). Briefly, AMPK is activated by phosphorylation of Thr172 of the α subunit, a process that can be allosterically induced by AMP (but not ADP) (14) and catalyzed by several upstream kinases,

processes, while switching on (green arrows) catabolic processes that produce ATP. In several brain areas, such as the hypothalamus, AMPK acts to monitor nutritional and hormonal signals and consequently to regulate energy balance at the whole-body level. Thus, activation of AMPK increases energy (food) intake and decreases energy expenditure (thermogenesis). Red and green lettering represents inhibitory and stimulatory stimuli respectively. AgRP, agouti-related peptide; BMP8B, bone morphogenetic protein 8B; CCK, cholecystokinin; CNTF, ciliary neurotrophic factor; GLP-1, glucagon-like peptide-1; T3, 3,3',5-triiodothyronine.

such as liver kinase B1 (LKB1) (15, 16), the pseudokinase STRAD, the scaffold protein mouse protein-25 (MO25) (17, 18, 19), and calmodulin-dependent kinase kinases (CaMKKs), especially CaMKK β (20, 21, 22). AMP and ADP not only facilitate phosphorylation at Thr172 by LKB1 and CaMKK β (14, 15, 16, 23), but also inhibit dephosphorylation by protein phosphatases, such as protein phosphatase 2C α (PP2C α ; with AMP being 10-fold more potent than ADP and both being antagonized by ATP) (13, 24, 25). Ca²⁺-dependent and AMP-dependent pathways occur independently. Thus, a rise in Ca²⁺ leads to the activation of CaMKK β , which increases Thr172 phosphorylation and activation of AMPK (26). Finally, a mechanism modulating AMPK independent of AMP and phosphorylation/dephosphorylation processes has been proposed. Cell-death-inducing like-effector A (CIDEA) forms a complex with the β subunit of AMPK, which elicits an ubiquitination-mediated degradation of AMPK, reducing its activity (27) (Fig. 1). A more detailed description of AMPK structure and regulation is beyond the scope of the present review but has been excellently reviewed elsewhere (1, 4, 9, 28, 29, 30).

AMPK is activated in situations that lead to a reduction in intracellular energy levels, such as hypoxia and hypoglycemia, or to those that increase ATP utilization, such as muscle contraction or food deprivation (1, 2, 3, 4, 29, 30). As a result of changes in the ratio of adenine nucleotides, AMPK is phosphorylated leading to ATP-consuming processes, such as fatty acid synthesis being switched off and catabolic processes, such as fatty acid oxidation being switched on. The overall effect of AMPK activation is therefore to produce ATP and restore AMP:ATP and ADP:ATP, allowing balanced rates of catabolism and ATP usage and thus maintaining cellular energy homeostasis (1, 2, 3, 4, 29, 30). Catabolic processes such as mitochondrial biogenesis and autophagy (mitophagy) are turned on (31, 32, 33, 34). AMPK also regulates anabolic processes, with AMPK switching off all anabolic pathways virtually, such as the biosynthesis of lipids, carbohydrates, proteins and ribosomal RNA, when the cellular energy status is diminished (1, 2, 3, 4, 29, 30).

Hypothalamic AMPK and regulation of food intake

The first evidence implicating hypothalamic AMPK in the modulation of energy balance was demonstrated by David Carling and Caroline Small groups stating that AMPK played a role in the regulation of feeding (35).

In their seminal paper, they showed that key hormones controlling food intake, such as leptin and ghrelin, modulated hypothalamic AMPK and that activation of AMPK at this level increased appetite (35). Parallel work by Barbara Kahn and colleagues showed that AMPK is highly expressed in the arcuate (ARC), dorsomedial (DMH), paraventricular (PVH), and ventromedial (VMH) nuclei, as well as in the lateral hypothalamic area (LHA) (36); importantly, they also demonstrated that modulation of hypothalamic AMPK formed part of an adaptive change in the physiological regulation of feeding (36). Thus, fasting increases but refeeding inhibits the AMPK activity in many hypothalamic regions (35, 36, 37). Moreover, at the whole-body level, activation of hypothalamic AMPK leads to increased feeding and weight gain, whereas its inhibition leads to hypophagia and weight loss (36).

In keeping with this physiological evidence, genetic models have demonstrated a key role for hypothalamic AMPK in the modulation of feeding. Initially, it was shown that inhibition of hypothalamic AMPK with AMPK dominant negative (AMPK-DN) isoforms decreases mRNA expression of the orexigenic neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY) in the ARC. However, over-expression of an AMPK constitutively active (AMPK-CA) isoform elevates the fasting-induced expression of AgRP and NPY in the ARC as well as expression of melanin-concentrating hormone (MCH) in the LHA (36). It has been currently reported that AMPK modulates the expression of NPY and pro-opiomelanocortin (POMC) by regulating autophagy (38). These data were taken to suggest that AMPK exerts nucleus-specific effects on feeding control, an idea that was subsequently confirmed by the generation of mice with a conditional deletion of the catalytic subunit of AMPK α 2 specifically in POMC or AgRP neurons of the ARC. Interestingly, both mouse models display divergent phenotypes in terms of energy balance; while AMPK α 2-POMC KO mice developed obesity due to hyperphagia, AMPK α 2-AgRP KO mice developed an age-dependent lean phenotype (39). However, despite the unquestionable role of AMPK in the regulation of feeding, several lines of evidence suggest that the chronic effects of hypothalamic AMPK manipulation on body mass are more closely related to altered energy expenditure than to food intake (see below) (40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50).

Notably, most actions of AMPK in the hypothalamus relate to mediation of hormonal effects. Both orexigenic and anorexigenic hormones converge on hypothalamic AMPK to modulate appetite. The consensus view is that while the main anorexigenic factors inhibit hypothalamic

Figure 2

Brain AMPK is a canonical regulator of energy balance. AMP-activated protein kinase (AMPK) acts in the hypothalamus to modulate whole-body energy homeostasis and body weight. AMPK senses several nutritional and hormonal stimuli to regulate food intake, hepatic glucose and possibly lipid metabolism, brown adipose tissue (BAT) thermogenesis, browning of white adipose tissue (WAT), glucose homeostasis and lipid and glycogen synthesis in skeletal muscle. The actions of hypothalamic AMPK on peripheral tissues/organs are mediated by specific regulation of the sympathetic (SNS) and parasympathetic nervous systems (PSNS). The fact that inhibition of hypothalamic AMPK leads to anorexia and increased thermogenesis (and therefore elevated energy expenditure) makes it an interesting target for drug development, with its potential for controlling both sides of the energy balance equation. 3V, third ventricle; AgRP, agouti-related peptide; ARC, arcuate nucleus of the hypothalamus; BMP8B, bone morphogenetic protein 8B; DMH, dorsomedial nucleus of the hypothalamus; GLP-1, glucagon-like peptide-1; LHA, lateral hypothalamic area; NPY, neuropeptide Y; PVH, paraventricular nucleus of the hypothalamus; T3, 3,3',5-triiodothyronine; VMH, ventromedial nucleus of the hypothalamus.

AMPK, the vast majority of orexigenic hormones activate it (40, 41, 42, 43, 44, 45, 46, 47, 48) (Figs 1 and 2). For example, physiological appetite inhibitors such as leptin (35, 36, 51), insulin (36, 52), glucagon-like peptide-1 (GLP-1) (46, 53), estradiol (E2) (45, 54) and ciliary neurotrophic factor (CNTF) (55), inhibit hypothalamic AMPK. In contrast, activation of hypothalamic AMPK is caused by orexigenic signals such as adiponectin (56, 57), glucocorticoids (58), ghrelin (35, 37, 59, 60, 61, 62), cannabinoids (59, 63) and AgRP (36). Resistin (RSTN), despite its anorectic effect, activates hypothalamic AMPK (64).

The fact that hypothalamic AMPK has emerged as a key modulator of food intake is of interest because several pharmacological factors with well-established impacts on feeding, such as melanocortin receptor agonists (including melanotan II; MTII) and nicotine, exert their actions by inhibiting hypothalamic AMPK (36, 44, 65). In contrast, antipsychotic drugs (APDs), such as olanzapine, well known for their orexigenic and obesity-prone properties, activate hypothalamic AMPK (66, 67, 68, 69). Overall, the evidence suggest that central AMPK is a potential target for the treatment of obesity, an idea that is reinforced by AMPK's effects on energy expenditure (40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50) (see below).

Hypothalamic AMPK and regulation of thermogenesis

The hypothalamus also plays a major role in the regulation of brown adipose tissue (BAT) thermogenesis through the sympathetic nervous system (SNS). BAT is activated by increased firing of sympathetic neurons, leading to release of noradrenaline and activation on β 3-adrenergic receptors (β 3-AR) (70, 71, 72, 73, 74). Within the hypothalamus, the VMH was the first hypothalamic location to be identified as important in BAT thermogenic activity (75). The VMH is connected to other brainstem regions linked to the regulation of BAT, such as raphe pallidus (RPa) and the inferior olive (IO), which control sympathetic activation of BAT (70, 71, 72, 73).

Recent evidence has demonstrated that hypothalamic AMPK is a major regulator of BAT thermogenesis through its modulation of the SNS. By analyzing the central effects of thyroid hormones (THs) on energy homeostasis, we demonstrated that central specific administration of 3,3',5-triiodothyronine (T3) within the VMH (but not in the ARC) promotes a profound thermogenic response that is associated with decreased AMPK activity in the VMH and, importantly, elevated sympathetic firing in brown fat (41, 49, 76, 77). Notably, targeted administration

of adenoviruses harboring AMPK-CA isoforms to the VMH reduced the activation of BAT and prevented the weight loss, which is usually associated with central T3 action, in a feeding-independent but uncoupling protein 1-dependent manner (41, 49). The significant aspect of such an integrative mechanism is that it constitutes a canonical circuit that is non-exclusive for THs and mediates the effects of other thermogenic molecules. For example, central administration of E2 inhibits AMPK through estrogen receptor alpha (ER α), selectively in the VMH (but not in the ARC), leading to feeding-independent activation of thermogenesis in brown fat through the SNS (45, 78). Again, virogenetic activation of AMPK in the VMH (but not in the ARC) prevented an E2-induced increase in BAT-mediated thermogenesis and weight loss (45). Notably, fluctuations in E2 levels during the estrous cycle and pregnancy also modulate this integrated AMPK network, indicating its physiological relevance (45, 78). Current evidence shows that bone morphogenetic protein 8B (BMP8B) acts centrally and that its thermogenic effect is dependent on the activation status of AMPK in the VMH. In fact, BMP8b-induced thermogenesis can be completely prevented by AMPK-CA isoforms within the VMH (43, 50), as well as with pharmacologic antagonist or genetic deletion of orexin (OX) in the LHA (50). If OX neurons in the LHA also mediate THs and/or E2 is currently unknown, but seems likely when considering the similitude in thermogenic response and the known neuroanatomical connections.

Together, these findings demonstrate that hormonal regulation of the VMH AMPK-(LHA OX)-SNS-BAT axis is an important determinant of energy balance (47, 48) and suggest that dysregulation of this axis might account for common changes in energy homeostasis associated with alterations in thyroid and ovarian status, together with impaired BMP8B function (41, 43, 45, 78). In this context, recent data have also indicated that VMH AMPK could be an interesting target for the treatment of obesity. For example, nicotine, the main bioactive compound of tobacco, stimulates thermogenesis and weight loss through AMPK in the VMH (44, 65). More importantly, liraglutide, a GLP-1 agonist currently used clinically for the treatment of type 2 diabetes (T2D), exerts a potent central thermogenic action, in addition to inducing browning of WAT, by modulating AMPK specifically in the VMH among tested hypothalamic sites (46). Again, that effect is accompanied by significant weight loss (46). Further studies are necessary to address the sub-cellular mechanisms and neuronal networks involved in the VMH AMPK-(LHA OX)-SNS-BAT axis.

Review	M López	Hypothalamic AMPK and obesity	176:5	R240

AMPK modulators and metabolic disorders

AMPK has become a potential therapeutic target in metabolic diseases involving impaired eating behaviors, including obesity, T2D and some lipodystrophies. Although activation of AMPK can be expected to lead to a reduction of ectopic lipid storage in liver and muscle with an improvement in insulin sensitivity, it can also affect energy homeostasis in a tissue-specific manner. AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) was one of the first-described direct activators of AMPK (79). However, despite its improving glucose tolerance and reducing circulating triglycerides (TG) and free fatty acids (FFA) (80), its poor bioavailability and short half-life make it unlikely to be used in humans (81). Other direct AMPK activators, such as 991 and A-769662, are more potent and some studies have found reductions in plasma glucose and lipid levels (82). However, side effects related to cell cycle progression (83) also make these direct AMPK activators unlikely to be used therapeutically.

Reduced ectopic lipid storage and increased insulin sensitivity can be driven by increasing glucose uptake by skeletal muscle (33, 84) or inhibiting glucose production in the liver (85). Various AMPK activators are currently used to ameliorate high glucose levels in T2D. Metformin, a synthetic biguanide, activates AMPK indirectly by inhibiting the mitochondrial respiratory chain (86, 87). Metformin reduces glycated hemoglobin HbA1c by 2% in T2D patients, with very few side effects, simultaneously reducing the risk of cardiovascular diseases (88) and certain types of cancer (89). Its main action is to inhibit the hepatic glucose production (90), which appears to be LKB1 dependent and therefore is mediated by an indirect activation of AMPK, as LKB1-null animals do not have reduced levels of glucose (18, 91). Recent reports have also shown that metformin exerts its AMPK-independent effects in the liver (92). In contrast, mice with acetyl-CoA carboxylase (ACC) mutations are refractory to the lipid and glucose-reducing effects of metformin (93). In addition to metformin, thiazolidinedione compounds, such as rosiglitazone and pioglitazone, also produce a dramatic increase in AMP in skeletal muscle, which results in a rapid activation of AMPK (94). These drugs also seem to activate AMPK indirectly, through peroxisome proliferator-activated receptor- γ (PPAR γ), which in turn stimulates adiponectin secretion (95). Other drugs, such as liraglutide and exenatide (the synthetic form of exendin-4), have been designed to mimic the action of GLP-1 to increase insulin sensitivity (96). Liraglutide has been reported to have opposing effects on AMPK. Although

it increases AMPK phosphorylation in endothelium (reducing inflammation) (97, 98), heart (99), liver and muscle (enhancing insulin sensitivity) (100, 101), and WAT (102), it decreases AMPK phosphorylation in pancreatic β cells (leading to their proliferation) (103) and in the hypothalamus (leading to anorexia and increased BAT thermogenesis) (46). Exendin increases hepatic AMPK phosphorylation, thus ameliorating steatosis (104).

As well as these synthetic compounds, there are naturally occurring molecules that have also been shown to elicit metabolic benefits through AMPK activation. Resveratrol, for example, found in the skin of red grapes, has been shown to activate AMPK indirectly and increase muscle glucose uptake (105), possibly by increasing intracellular Ca²⁺ levels and thus activating CaMKK β (106). Resveratrol has also been reported to reduce lipid accumulation in the liver in an AMPK-dependent manner, as these effects are blunted when AMPK is genetically blocked (107). Quercetin, the most abundant flavonoid, is thought to have metabolically protective roles. Thus, it has been reported to exert an anti-adipogenic action mediated by activation of AMPK and its substrate ACC (108). In the same context, there is evidence to suggest that quercetin positively affects glucose metabolism in both liver and muscle through an insulin-independent mechanism involving AMPK activation (109). Quercetin also appears to have beneficial effects by protecting against cholesterol-induced neurotoxicity (110, 111). Other plant-derived compounds, such as rooibos and berberine, improve glucose homeostasis and reduce cholesterol levels, with these benefits being attributed to activation of AMPK in liver (112, 113), muscle (114) and adipose tissue (113, 115).

It is notable that patients with metabolic disorders, such as T2D, insulin resistance and obesity are at an increased risk of developing cancer (116). Since AMPK activation inhibits anabolism leading to cell arrest, it is logical to speculate that AMPK might prevent tumor progression. As AMPK mutations leading to tumorigenic processes are rare, in humans, it seems more likely that defective upstream effectors or downstream targets of AMPK will be found to be causative. In this context, inactivation of LKB1 induces activation of mTORC1, which promotes cell growth and proliferation (18, 91), whereas mutations in LKB1 prevent activation of AMPK, causing Peutz-Jeghers syndrome, which is a risk factor for developing cancer (18). It has been shown that inactivation of AMPK enhances the aerobic glycolysis that is likely to cause activation of oncogenes and inhibition of tumor suppressors (117). Thus, activation of AMPK has

been suggested as a possible therapy in cancer. Indeed, evidence suggests that the AMPK activator metformin can reduce the tumor size (89). In contrast, high levels of pACC have been found in prostate cancer cells, implicating activated AMPK in prostate cancer (118). Since AMPK activation is inhibited when energy levels are in a normal fed state, continued AMPK activation might be essential for the survival of cancer cells. Further studies are necessary to understand the role of AMPK in the cell cycle and in the development of cancer. In this context, very recent evidence shows that AMPK plays a major role in regulating glycolysis and cell survival in response to mitophagy during mitotic arrest (11).

Is hypothalamic AMPK a realistic therapeutic target against obesity?

Obesity causes thousands of deaths per year worldwide, directly and indirectly due to comorbidities including cancer, cardiovascular disease and T2D, and yet, it is the most preventable epidemic (96, 119, 120, 121). However, despite significant investments in education and public engagement, government-led policies are relatively ineffective. This is shown in the World Health Organization (WHO)'s latest report, which states that globally, 13% of adults are obese. In healthy individuals, maintaining normal weight is a matter of lifestyle. However, such apparent simplicity also necessitates an understanding of how the body manages what, how, when and why we eat, as well as how we expend calories. Each of these functions is carried out by different hormones and peptides that respond to the various physiological states occurring in arousal and sleep, with some having circadian rhythms.

Data accrued over the last decade have demonstrated an unequivocally key role of hypothalamic AMPK in the regulation of both parts of the energy balance equation, i.e. feeding and energy expenditure (40, 42, 47, 48). Activation of AMPK in peripheral organs is one of the mechanisms of the widely used antidiabetic drug, metformin (for an extensive review see (87)). However, central activation of AMPK would not give the best outcome in treatment for obesity as it would increase feeding while decrease BAT thermogenesis due to its differential regulation in the periphery (122) and centrally (36, 37, 40, 42, 47, 48). Inhibition of AMPK in peripheral tissues would also have deleterious consequences, worsening insulin resistance and developing diabetes. However, the best strategy would be to specifically target hypothalamic AMPK that also looks to be a highly complex task. The use of nanoparticle

or exosome approaches (123) might be an option, but directing them to specific hypothalamic populations, e.g. to AMPK neurons in the VMH (whose inhibition could promote anorexia, and increase thermogenesis and weight loss) (Fig. 2), seems challenging. Another alternative might be optogenetic modulation of hypothalamic AMPK neurons, which has already been elegantly achieved in rodents (124). However, the implementation of optogenetics for hypothalamic intervention in humans also seems a distant possibility. Perhaps a more realistic strategy would be to use peptide conjugates (with other peptides or steroid hormones) (120, 121, 125, 126, 127) in a targeted approach. For example, a chimera containing GLP-1 plus an estrogen, (125) or glucagon plus T3 (127), would allow quite a precise targeting of AMPK neurons in the VMH, although the fact that other neuronal populations would be affected (128) would limit specificity.

Overall, such restraints raise some doubts about the translatability of the data into clinical practice. Even if hypothalamic AMPK can be specifically targeted, other questions and potential problems emerge. In my view, the most relevant issue to address is that of the long-term consequences of targeting AMPK in the brain. Considering the central role of AMPK on lipid and glucose metabolism, how would neurons respond to sustained AMPK inhibition? Would they survive? In this sense, recent data have shown that impaired lipid metabolism in neurons leads to lipotoxicity, endoplasmic reticulum stress, and leptin and insulin resistance (129, 130, 131, 132, 133, 134, 135), which would be a deleterious side effect. Would their modulation affect other hypothalamic-mediated physiological processes such as regulation of endocrine axes? (61). A substantial amount of work will be necessary to address these questions and to understand the molecular and neural mechanisms upstream and downstream of central AMPK fully, itself a fascinating endeavor for the years to come.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The research leading to this work has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 281854-the *ObERStress* project, Xunta de Galicia (2015-CP079 and 2016-PG068), MINECO co-funded by FEDER (SAF2015-71026-R and BFU2015-70454-REDT/*Adipoplast*). CIBER de Fisiopatología de la Obesidad y Nutrición is an initiative of ISCIII.

Review	M López	Hypothalamic AMPK and obesity	176:5	R242

Acknowledgements

The manuscript was edited for English language by Dr Pamela V Lear (University of Oxford). The author humbly thanks the European Society of Endocrinology and the *European Journal of Endocrinology* for this award. The author is indebted to my master, colleague and friend Carlos Diéguez, for his constant support, generosity and inspiration. The author would also like to thank my 'scientific brother', Rubén Nogueiras, for his friendship and the constant stimulus that working alongside him for many years has brought. The author is also grateful to Antonio Vidal-Puig for profoundly changing my view of science by making it broader and more professional, as well as to Manuel Tena-Sempere and Kamal Rahmouni for educating me in Physiology, their generosity and their friendship. The author is grateful to all my students and postdocs for the enthusiasm and dedication they have brought to the work every day. Finally, the author feels indebted beyond words to my wife and three daughters, my parents and my sister.

References

- Carling D, Mayer FV, Sanders MJ & Gambin SJ. AMP-activated protein kinase: nature's energy sensor. *Nature Chemical Biology* 2011 **7** 512–518. (doi:10.1038/nchembio.610)
- Ruderman NB, Carling D, Prentki M & Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. *Journal of Clinical Investigation* 2013 **123** 2764–2772. (doi:10.1172/JCI67227)
- Hardie DG, Carling D & Gambin SJ. AMP-activated protein kinase: also regulated by ADP? *Trends in Biochemical Sciences* 2011 **36** 470–477. (doi:10.1016/j.tibs.2011.06.004)
- Hardie DG. AMP-activated protein kinase: maintaining energy homeostasis at the cellular and whole-body levels. *Annual Review of Nutrition* 2014 **34** 31–55. (doi:10.1146/annurev-nutr-071812-161148)
- Carling D, Zammit VA & Hardie DG. A common bicyclic protein kinase cascade inactivates the regulatory enzymes of fatty acid and cholesterol biosynthesis. *FEBS Letters* 1987 **223** 217–222. (doi:10.1016/0014-5793(87)80292-2)
- Yeh LA, Lee KH & Kim KH. Regulation of rat liver acetyl-CoA carboxylase. Regulation of phosphorylation and inactivation of acetyl-CoA carboxylase by the adenylate energy charge. *Journal of Biological Chemistry* 1980 **255** 2308–2314.
- Ferrer A, Caelles C, Massot N & Hegardt FG. Activation of rat liver cytosolic 3-hydroxy-3-methylglutaryl coenzyme A reductase kinase by adenosine 5'-monophosphate. *Biochemical and Biophysical Research Communications* 1985 **132** 497–504. (doi:10.1016/0006-291X(85)91161-1)
- Hardie DG, Carling D & Sim TR. The AMP-activated protein kinase – a multisubstrate regulator of lipid metabolism. *Trends in Biochemical Sciences* 1989 **14** 20–23. (doi:10.1016/0968-0004(89)90084-4)
- Hardie DG. AMPK – sensing energy while talking to other signaling pathways. *Cell Metabolism* 2014 **20** 939–952. (doi:10.1016/j.cmet.2014.09.013)
- Carling D & Viollet B. Beyond energy homeostasis: the expanding role of AMP-activated protein kinase in regulating metabolism. *Cell Metabolism* 2015 **21** 799–804. (doi:10.1016/j.cmet.2015.05.005)
- Domenech E, Maestre C, Esteban-Martinez L, Partida D, Pascual R, Fernández-Miranda G, Seco E, Campos-Olivas R, Pérez M, Megias D *et al.* AMPK and PFKFB3 mediate glycolysis and survival in response to mitophagy during mitotic arrest. *Nature Cell Biology* 2015 **17** 1304–1316. (doi:10.1038/ncb3231)
- Xiao B, Heath R, Saiu P, Leiper FC, Leone P, Jing C, Walker PA, Haire L, Eccleston JF, Davis CT *et al.* Structural basis for AMP binding to mammalian AMP-activated protein kinase. *Nature* 2007 **449** 496–500. (doi:10.1038/nature06161)
- Xiao B, Sanders MJ, Underwood E, Heath R, Mayer FV, Carmena D, Jing C, Walker PA, Eccleston JF, Haire LF *et al.* Structure of mammalian AMPK and its regulation by ADP. *Nature* 2011 **472** 230–233. (doi:10.1038/nature09932)
- Gowans GJ, Hawley SA, Ross FA & Hardie DG. AMP is a true physiological regulator of AMP-activated protein kinase by both allosteric activation and enhancing net phosphorylation. *Cell Metabolism* 2013 **18** 556–566. (doi:10.1016/j.cmet.2013.08.019)
- Woods A, Johnstone SR, Dickerson K, Leiper FC, Fryer LG, Neumann D, Schlattner U, Wallimann T, Carlson M & Carling D. LKB1 is the upstream kinase in the AMP-activated protein kinase cascade. *Current Biology* 2003 **13** 2004–2008.
- Hardie DG. The LKB1-AMPK pathway-friend or foe in cancer? *Cancer Cell* 2013 **23** 131–132. (doi:10.1016/j.ccr.2013.01.009)
- Hawley SA, Boudeau J, Reid JL, Mustard KJ, Udd L, Mäkelä TP, Alessi DR & Hardie DG. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. *Journal of Biology* 2003 **2** 28. (doi:10.1186/1475-4924-2-28)
- Shaw RJ, Kosmatka M, Bardeesy N, Hurley RL, Witters LA, DePinho RA & Cantley LC. The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. *PNAS* 2004 **101** 3329–3335. (doi:10.1073/pnas.0308061100)
- Alessi DR, Sakamoto K & Bayascas JR. LKB1-dependent signaling pathways. *Annual Review of Biochemistry* 2006 **75** 137–163. (doi:10.1146/annurev.biochem.75.103004.142702)
- Hawley SA, Pan DA, Mustard KJ, Ross L, Bain J, Edelman AM, Frenguelli BG & Hardie DG. Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase. *Cell Metabolism* 2005 **2** 9–19. (doi:10.1016/j.cmet.2005.05.009)
- Hurley RL, Anderson KA, Franzone JM, Kemp BE, Means AR & Witters LA. The Ca²⁺/calmodulin-dependent protein kinase kinases are AMP-activated protein kinase kinases. *Journal of Biological Chemistry* 2005 **280** 29060–29066. (doi:10.1074/jbc.M503824200)
- Woods A, Dickerson K, Heath R, Hong SP, Momcilovic M, Johnstone SR, Carlson M & Carling D. Ca²⁺/calmodulin-dependent protein kinase kinase-beta acts upstream of AMP-activated protein kinase in mammalian cells. *Cell Metabolism* 2005 **2** 21–33. (doi:10.1016/j.cmet.2005.06.005)
- Oakhill JS, Steel R, Chen ZP, Scott JW, Ling N, Tam S & Kemp BE. AMPK is a direct adenylate charge-regulated protein kinase. *Science* 2011 **332** 1433–1435. (doi:10.1126/science.1200094)
- Davies SP, Helps NR, Cohen PT & Hardie DG. 5'-AMP inhibits dephosphorylation, as well as promoting phosphorylation, of the AMP-activated protein kinase. Studies using bacterially expressed human protein phosphatase-2C alpha and native bovine protein phosphatase-2AC. *FEBS Letters* 1995 **377** 421–425. (doi:10.1016/0014-5793(95)01313-X)
- Steinberg GR, Michell BJ, van Denderen BJ, Watt MJ, Carey AL, Fam BC, Andrikopoulos S, Proietto J, Görgün CZ, Carling D *et al.* Tumor necrosis factor alpha-induced skeletal muscle insulin resistance involves suppression of AMP-kinase signaling. *Cell Metabolism* 2006 **4** 465–474. (doi:10.1016/j.cmet.2006.11.005)
- Sanders MJ, Grondin PO, Hegarty BD, Snowden MA & Carling D. Investigating the mechanism for AMP activation of the AMP-activated protein kinase cascade. *Biochemical Journal* 2007 **403** 139–148. (doi:10.1042/BJ20061520)
- Qi J, Gong J, Zhao T, Zhao J, Lam P, Ye J, Li JZ, Wu J, Zhou HM & Li P. Downregulation of AMP-activated protein kinase by Cidea-mediated ubiquitination and degradation in brown adipose tissue. *EMBO Journal* 2008 **27** 1537–1548. (doi:10.1038/emboj.2008.92)

Review	M López	Hypothalamic AMPK and obesity	176:5	R243
28	Carling D, Thornton C, Woods A & Sanders MJ. AMP-activated protein kinase: new regulation, new roles? <i>Biochemical Journal</i> 2012 445 11–27. (doi:10.1042/BJ20120546)	Cuenca S <i>et al.</i> BMP8B increases brown adipose tissue thermogenesis through both central and peripheral actions. <i>Cell</i> 2012 149 871–885. (doi:10.1016/j.cell.2012.02.066)		
29	Ross FA, Mackintosh C & Hardie DG. AMP-activated protein kinase: a cellular energy sensor that comes in 12 flavours. <i>FEBS Journal</i> 2016 283 2987–3001. (doi:10.1111/febs.13698)	44	Martinez de Morentin PB, Whittle AJ, Ferno J, Nogueiras R, Diéguez C, Vidal-Puig A, López M. Nicotine induces negative energy balance through hypothalamic AMP-activated protein kinase. <i>Diabetes</i> 2012 61 807–817. (doi:10.2337/db11-1079)	
30	Hardie DG, Schaffer BE & Brunet A. AMPK: an energy-sensing pathway with multiple inputs and outputs. <i>Trends in Cell Biology</i> 2016 26 190–201.	45	Martinez de Morentin PB, Gonzalez-Garcia I, Martins L, Lage R, Fernández-Mallo D, Martínez-Sánchez N, Ruiz-Pino F, Liu J, Morgan DA, Pinilla L <i>et al.</i> Estradiol regulates brown adipose tissue thermogenesis via hypothalamic AMPK. <i>Cell Metabolism</i> 2014 20 41–53. (doi:10.1016/j.cmet.2014.03.031)	
31	Egan DF, Shackelford DB, Mihaylova MM, Gelino S, Kohnz RA, Mair W, Vazquez DS, Joshi A, Gwinn DM, Taylor R <i>et al.</i> Phosphorylation of ULK1 (hATG1) by AMP-activated protein kinase connects energy sensing to mitophagy. <i>Science</i> 2011 331 456–461. (doi:10.1126/science.1196371)	46	Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, Villarroya F, Serrano M, Fernø J, Salvador J, Escalada J <i>et al.</i> GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. <i>Diabetes</i> 2014 63 3346–3358. (doi:10.2337/db14-0302)	
32	Kim J, Kundu M, Viollet B & Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. <i>Nature Cell Biology</i> 2011 13 132–141. (doi:10.1038/ncb2152)	47	Lopez M, Nogueiras R, Tena-Sempere M & Dieguez C. Hypothalamic AMPK: a canonical regulator of whole-body energy balance. <i>Nature Reviews Endocrinology</i> 2016 12 421–432. (doi:10.1038/nrendo.2016.67)	
33	O'Neill HM, Maarbjerg SJ, Crane JD, Jeppesen J, Jørgensen SB, Schertzer JD, Shyroka O, Kiens B, van Denderen BJ, Tarnopolsky MA <i>et al.</i> AMP-activated protein kinase (AMPK) beta1beta2 muscle null mice reveal an essential role for AMPK in maintaining mitochondrial content and glucose uptake during exercise. <i>PNAS</i> 2011 108 16092–16097. (doi:10.1073/pnas.1105062108)	48	Martinez de Morentin PB, Urisarri A, Couce ML & Lopez M. Molecular mechanisms of appetite and obesity: a role for brain AMPK. <i>Clinical Science</i> 2016 130 1697–1709. (doi:10.1042/CS20160048)	
34	Hardie DG, Ross FA & Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. <i>Nature Reviews Molecular Cell Biology</i> 2012 13 251–262. (doi:10.1038/nrm3311)	49	Alvarez-Crespo M, Csikasz RI, Martinez-Sanchez N, Diéguez C, Cannon B, Nedergaard J & López M. Essential role of UCP1 modulating the central effects of thyroid hormones on energy balance. <i>Molecular Metabolism</i> 2016 5 271–282. (doi:10.1016/j.molmet.2016.01.008)	
35	Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, Bloom SR, Carling D & Small CJ. AMP-activated protein kinase plays a role in the control of food intake. <i>Journal of Biological Chemistry</i> 2004 279 12005–12008. (doi:10.1074/jbc.C300557200)	50	Martins L, Seoane-Collazo P, Contreras C, González-García I, Martínez-Sánchez N, González F, Zalvide J, Gallego R, Diéguez C, Nogueiras R <i>et al.</i> A functional link between AMPK and orexin mediates the effect of BMP8B on energy balance. <i>Cell Reports</i> 2016 16 2231–2242. (doi:10.1016/j.celrep.2016.07.045)	
36	Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foulfelle F, Ferré P, Birnbaum MJ <i>et al.</i> AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. <i>Nature</i> 2004 428 569–574. (doi:10.1038/nature02440)	51	Gao S, Kinzig KP, Aja S, Scott KA, Keung W, Kelly S, Strynadka K, Chohnan S, Smith WW, Tamashiro KL <i>et al.</i> Leptin activates hypothalamic acetyl-CoA carboxylase to inhibit food intake. <i>PNAS</i> 2007 104 17358–17363. (doi:10.1073/pnas.0708385104)	
37	Lopez M, Lage R, Saha AK, Pérez-Tilve D, Vázquez MJ, Varela L, Sangiao-Alvarellos S, Tovar S, Raghay K, Rodríguez-Cuenca S <i>et al.</i> Hypothalamic fatty acid metabolism mediates the orexigenic action of ghrelin. <i>Cell Metabolism</i> 2008 7 389–399. (doi:10.1016/j.cmet.2008.03.006)	52	Namkoong C, Kim MS, Jang PG, Han SM, Park HS, Koh EH, Lee WJ, Kim JY, Park IS, Park JY <i>et al.</i> Enhanced hypothalamic AMP-activated protein kinase activity contributes to hyperphagia in diabetic rats. <i>Diabetes</i> 2005 54 63–68. (doi:10.2337/diabetes.54.1.63)	
38	Oh TS, Cho H, Cho JH, Yu SW & Kim EK. Hypothalamic AMPK-induced autophagy increases food intake by regulating NPY and POMC expression. <i>Autophagy</i> 2016 12 2009–2025. (doi:10.1080/15548627.2016.1215382)	53	Seo S, Ju S, Chung H, Lee D & Park S. Acute effects of glucagon-like peptide-1 on hypothalamic neuropeptide and AMP activated kinase expression in fasted rats. <i>Endocrine Journal</i> 2008 55 867–874. (doi:10.1507/endocrj.K08E-091)	
39	Claret M, Smith MA, Batterham RL, Selman C, Choudhury AI, Fryer LG, Clements M, Al-Qassab H, Heffron H, Xu AW <i>et al.</i> AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. <i>Journal of Clinical Investigation</i> 2007 117 2325–2336. (doi:10.1172/JCI31516)	54	Tsai YC, Lee YM, Lam KK, Wu YC, Yen MH & Cheng PY. The role of hypothalamic AMP-activated protein kinase in ovariectomy-induced obesity in rats. <i>Menopause</i> 2010 17 1194–1200. (doi:10.1097/gme.0b013e3181dfca27)	
40	Lage R, Dieguez C, Vidal-Puig A & Lopez M. AMPK: a metabolic gauge regulating whole-body energy homeostasis. <i>Trends in Molecular Medicine</i> 2008 14 539–549. (doi:10.1016/j.molmed.2008.09.007)	55	Steinberg GR, Watt MJ, Fam BC, Proietto J, Andrikopoulos S, Allen AM, Febbraio MA & Kemp BE. Ciliary neurotrophic factor suppresses hypothalamic AMP-kinase signaling in leptin-resistant obese mice. <i>Endocrinology</i> 2006 147 3906–3914. (doi:10.1210/en.2005-1587)	
41	Lopez M, Varela L, Vazquez MJ, Rodríguez-Cuenca S, González CR, Velagapudi VR, Morgan DA, Schoenmakers E, Agassandian K, Lage R <i>et al.</i> Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. <i>Nature Medicine</i> 2010 16 1001–1008. (doi:10.1038/nm.2207)	56	Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T <i>et al.</i> Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. <i>Cell Metabolism</i> 2007 6 55–68. (doi:10.1016/j.cmet.2007.06.003)	
42	Schneeberger M & Claret M. Recent insights into the role of hypothalamic AMPK signaling cascade upon metabolic control. <i>Frontiers in Neuroscience</i> 2012 6 185. (doi:10.3389/fnins.2012.00185)	57	Wen JP, Liu CE, Hu YT, Chen G & Lin LX. Globular adiponectin regulates energy homeostasis through AMP-activated protein kinase-acetyl-CoA carboxylase (AMPK/ACC) pathway in the	
43	Whittle AJ, Carobbio S, Martins L, Slawik M, Hondares E, Vázquez MJ, Morgan D, Csikasz RI, Gallego R, Rodriguez-			

Review	M López	Hypothalamic AMPK and obesity	176:5	R244

- hypothalamus. *Molecular and Cellular Biochemistry* 2010 **344** 109–115. (doi:10.1007/s11010-010-0534-2)
- 58 Shimizu H, Arima H, Watanabe M, Goto M, Banno R, Sato I, Ozaki N, Nagasaki H & Oiso Y. Glucocorticoids increase neuropeptide Y and agouti-related peptide gene expression via adenosine monophosphate-activated protein kinase signaling in the arcuate nucleus of rats. *Endocrinology* 2008 **149** 4544–4553. (doi:10.1210/en.2008-0229)
- 59 Kola B, Farkas I, Christ-Crain M, Wittmann G, Lolli F, Amin F, Harvey-White J, Liposits Z, Kunos G, Grossman AB *et al.* The orexigenic effect of ghrelin is mediated through central activation of the endogenous cannabinoid system. *PLoS ONE* 2008 **3** e1797. (doi:10.1371/journal.pone.0001797)
- 60 Andrews ZB, Liu ZW, Wallingford N, Erion DM, Borok E, Friedman JM, Tschöp MH, Shanabrough M, Cline G, Shulman GI *et al.* UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. *Nature* 2008 **454** 846–851. (doi:10.1038/nature07181)
- 61 Sangiao-Alvarellos S, Varela L, Vazquez MJ, Da Boit K, Saha AK, Cordido F, Diéguez C & López M. Influence of ghrelin and growth hormone deficiency on AMP-activated protein kinase and hypothalamic lipid metabolism. *Journal of Neuroendocrinology* 2010 **22** 543–556. (doi:10.1111/j.1365-2826.2010.01994.x)
- 62 Lage R, Vazquez MJ, Varela L, Saha AK, Vidal-Puig A, Nogueiras R, Diéguez C & López M. Ghrelin effects on neuropeptides in the rat hypothalamus depend on fatty acid metabolism actions on BSX but not on gender. *FASEB Journal* 2010 **24** 2670–2679. (doi:10.1096/fj.09-150672)
- 63 Kola B, Hubina E, Tucci SA, Kirkham TC, Garcia EA, Mitchell SE, Williams LM, Hawley SA, Hardie DG, Grossman AB *et al.* Cannabinoids and ghrelin have both central and peripheral metabolic and cardiac effects via AMP-activated protein kinase. *Journal of Biological Chemistry* 2005 **280** 25196–25201. (doi:10.1074/jbc.C500175200)
- 64 Vazquez MJ, Gonzalez CR, Varela L, Lage R, Tovar S, Sangiao-Alvarellos S, Williams LM, Vidal-Puig A, Nogueiras R, López M *et al.* Central resistin regulates hypothalamic and peripheral lipid metabolism in a nutritional-dependent fashion. *Endocrinology* 2008 **149** 4534–4543. (doi:10.1210/en.2007-1708)
- 65 Seoane-Collazo P, de Morentin PB, Ferno J, Diéguez C, Nogueiras R & López M. Nicotine improves obesity and hepatic steatosis and ER stress in diet-induced obese male rats. *Endocrinology* 2014 **155** 1679–1689. (doi:10.1210/en.2013-1839)
- 66 Ikegami M, Ikeda H, Ishikawa Y, Ohsawa M, Ohashi T, Kai M, Kamei A & Kamei J. Olanzapine induces glucose intolerance through the activation of AMPK in the mouse hypothalamus. *European Journal of Pharmacology* 2013 **718** 376–382. (doi:10.1016/j.ejphar.2013.08.006)
- 67 Ikegami M, Ikeda H, Ohashi T, Ohsawa M, Ishikawa Y, Kai M, Kamei A & Kamei J. Olanzapine increases hepatic glucose production through the activation of hypothalamic adenosine 5'-monophosphate-activated protein kinase. *Diabetes, Obesity and Metabolism* 2013 **15** 1128–1135. (doi:10.1111/dom.12148)
- 68 Skrede S, Martins L, Berge RK, Steen VM, Lopez M & Ferno J. Olanzapine depot formulation in rat: a step forward in modelling antipsychotic-induced metabolic adverse effects. *International Journal of Neuropsychopharmacology* 2014 **17** 91–104. (doi:10.1017/S1461145713000862)
- 69 He M, Zhang Q, Deng C, Wang H & Huang XF. Olanzapine-activated AMPK signaling in the dorsal vagal complex is attenuated by histamine H1 receptor agonist in female rats. *Endocrinology* 2014 **155** 4895–4904. (doi:10.1210/en.2014-1326)
- 70 Cannon B & Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiological Reviews* 2004 **84** 277–359. (doi:10.1152/physrev.00015.2003)
- 71 Morrison SF, Madden CJ & Tupone D. Central neural regulation of brown adipose tissue thermogenesis and energy expenditure. *Cell Metabolism* 2014 **19** 741–756. (doi:10.1016/j.cmet.2014.02.007)
- 72 Contreras C, Gonzalez F, Ferno J, Diéguez C, Rahmouni K, Nogueiras R & López M. The brain and brown fat. *Annals of Medicine* 2015 **47** 150–168. (doi:10.3109/07853890.2014.919727)
- 73 Contreras C, Nogueiras R, Dieguez C, Medina-Gomez G & Lopez M. Hypothalamus and thermogenesis: heating the BAT, browning the WAT. *Molecular and Cellular Endocrinology* 2016 **438** 107–115. (doi:10.1016/j.mce.2016.08.002)
- 74 Seoane-Collazo P, Ferno J, Gonzalez F, Diéguez C, Leis R, Nogueiras R & López M. Hypothalamic-autonomic control of energy homeostasis. *Endocrine* 2015 **50** 276–291. (doi:10.1007/s12020-015-0658-y)
- 75 Perkins MN, Rothwell NJ, Stock MJ & Stone TW. Activation of brown adipose tissue thermogenesis by the ventromedial hypothalamus. *Nature* 1981 **289** 401–402. (doi:10.1038/289401a0)
- 76 Lopez M, Alvarez CV, Nogueiras R & Dieguez C. Energy balance regulation by thyroid hormones at central level. *Trends in Molecular Medicine* 2013 **19** 418–427. (doi:10.1016/j.molmed.2013.04.004)
- 77 Martinez-Sanchez N, Alvarez CV, Ferno J, Nogueiras R, Dieguez C & Lopez M. Hypothalamic effects of thyroid hormones on metabolism. *Best Practice and Research Clinical Endocrinology and Metabolism* 2014 **28** 703–712. (doi:10.1016/j.beem.2014.04.004)
- 78 Martinez de Morentin PB, Lage R, Gonzalez-Garcia I, Ruiz-Pino F, Martins L, Fernández-Mallo D, Gallego R, Ferno J, Señaris R, Saha AK *et al.* Pregnancy induces resistance to the anorectic effect of hypothalamic malonyl-CoA and the thermogenic effect of hypothalamic AMPK inhibition in female rats. *Endocrinology* 2015 **156** 947–960. (doi:10.1210/en.2014-1611)
- 79 Sullivan JE, Brocklehurst KJ, Marley AE, Carey F, Carling D & Beri RK. Inhibition of lipolysis and lipogenesis in isolated rat adipocytes with AICAR, a cell-permeable activator of AMP-activated protein kinase. *FEBS Letters* 1994 **353** 33–36. (doi:10.1016/0014-5793(94)01006-4)
- 80 Iglesias MA, Ye JM, Frangioudakis G, Saha AK, Tomas E, Ruderman NB, Cooney GJ & Kraegen EW. AICAR administration causes an apparent enhancement of muscle and liver insulin action in insulin-resistant high-fat-fed rats. *Diabetes* 2002 **51** 2886–2894. (doi:10.2337/diabetes.51.10.2886)
- 81 Fogarty S & Hardie DG. Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. *Biochimica et Biophysica Acta* 2010 **1804** 581–591. (doi:10.1016/j.bbapap.2009.09.012)
- 82 Cool B, Zinker B, Chiou W, Kifle L, Cao N, Perham M, Dickinson R, Adler A, Gagne D, Iyengar R *et al.* Identification and characterization of a small molecule AMPK activator that treats key components of type 2 diabetes and the metabolic syndrome. *Cell Metabolism* 2006 **3** 403–416. (doi:10.1016/j.cmet.2006.05.005)
- 83 Moreno D, Knecht E, Viollet B & Sanz P. A769662, a novel activator of AMP-activated protein kinase, inhibits non-proteolytic components of the 26S proteasome by an AMPK-independent mechanism. *FEBS Letters* 2008 **582** 2650–2654. (doi:10.1016/j.febslet.2008.06.044)
- 84 Merrill GF, Kurth EJ, Hardie DG & Winder WW. AICA riboside increases AMP-activated protein kinase, fatty acid oxidation, and glucose uptake in rat muscle. *American Journal of Physiology* 1997 **273** E1107–E1112.
- 85 Lochhead PA, Salt IP, Walker KS, Hardie DG & Sutherland C. 5-Aminoimidazole-4-carboxamide riboside mimics the effects of insulin on the expression of the 2 key gluconeogenic genes

Review	M López	Hypothalamic AMPK and obesity	176:5	R245
	PEPCK and glucose-6-phosphatase. <i>Diabetes</i> 2000 49 896–903. (doi:10.2337/diabetes.49.6.896)	100	Yamazaki S, Satoh H & Watanabe T. Liraglutide enhances insulin sensitivity by activating AMP-activated protein kinase in male Wistar rats. <i>Endocrinology</i> 2014 155 3288–3301. (doi:10.1210/en.2013-2157)	
86	Hawley SA, Ross FA, Chevtzoff C, Green KA, Evans A, Fogarty S, Towler MC, Brown LJ, Ogunbayo OA, Evans AM <i>et al.</i> Use of cells expressing gamma subunit variants to identify diverse mechanisms of AMPK activation. <i>Cell Metabolism</i> 2010 11 554–565. (doi:10.1016/j.cmet.2010.04.001)	101	Li Z, Ni CL, Yao Z, Chen LM & Niu WY. Liraglutide enhances glucose transporter 4 translocation via regulation of AMP-activated protein kinase signaling pathways in mouse skeletal muscle cells. <i>Metabolism</i> 2014 63 1022–1030. (doi:10.1016/j.metabol.2014.05.008)	
87	Foretz M, Guigas B, Bertrand L, Pollak M & Viollet B. Metformin: from mechanisms of action to therapies. <i>Cell Metabolism</i> 2014 20 953–966. (doi:10.1016/j.cmet.2014.09.018)	102	Shao Y, Yuan G, Zhang J & Guo X. Liraglutide reduces lipogenic signals in visceral adipose of db/db mice with AMPK activation and Akt suppression. <i>Drug Design, Development and Therapy</i> 2015 9 1177–1184. (doi:10.2147/DDDT.S79175)	
88	Haffner S, Temprosa M, Crandall J, Fowler S, Goldberg R, Horton E, Marcovina S, Mather K, Orchard T, Ratner R <i>et al.</i> Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. <i>Diabetes</i> 2005 54 1566–1572. (doi:10.2337/diabetes.54.5.1566)	103	Miao XY, Gu ZY, Liu P, Hu Y, Li L, Gong YP, Shu H, Liu Y & Li CL. The human glucagon-like peptide-1 analogue liraglutide regulates pancreatic beta-cell proliferation and apoptosis via an AMPK/mTOR/P70S6K signaling pathway. <i>Peptides</i> 2013 39 71–79. (doi:10.1016/j.peptides.2012.10.006)	
89	Buzzai M, Jones RG, Amaravadi RK, Lum JJ, DeBerardinis RJ, Zhao F, Viollet B & Thompson CB. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. <i>Cancer Research</i> 2007 67 6745–6752. (doi:10.1158/0008-5472.CAN-06-4447)	104	Xu WW, Guan MP, Zheng ZJ, Gao F, Zeng YM, Qin Y & Xue YM. Exendin-4 alleviates high glucose-induced rat mesangial cell dysfunction through the AMPK pathway. <i>Cellular Physiology and Biochemistry</i> 2014 33 423–432. (doi:10.1159/000358623)	
90	Owen MR, Doran E & Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. <i>Biochemical Journal</i> 2000 348 607–614. (doi:10.1042/bj3480607)	105	Breen DM, Sanli T, Giacca A & Tsiani E. Stimulation of muscle cell glucose uptake by resveratrol through sirtuins and AMPK. <i>Biochemical and Biophysical Research Communications</i> 2008 374 117–122. (doi:10.1016/j.bbrc.2008.06.104)	
91	Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, Montminy M & Cantley LC. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. <i>Science</i> 2005 310 1642–1646. (doi:10.1126/science.1120781)	106	Vingtdex V, Giliberto L, Zhao H, Chandakkar P, Wu Q, Simon JE, Janle EM, Lobo J, Ferruzzi MG, Davies P <i>et al.</i> AMP-activated protein kinase signaling activation by resveratrol modulates amyloid-beta peptide metabolism. <i>Journal of Biological Chemistry</i> 2010 285 9100–9113. (doi:10.1074/jbc.M109.060061)	
92	Miller RA, Chu Q, Xie J, Foretz M, Viollet B & Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. <i>Nature</i> 2013 494 256–260. (doi:10.1038/nature11808)	107	Zang M, Xu S, Maitland-Toolan KA, Zuccollo A, Hou X, Jiang B, Wierzbicki M, Verbeuren TJ & Cohen RA. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor-deficient mice. <i>Diabetes</i> 2006 55 2180–2191. (doi:10.2337/db05-1188)	
93	Fullerton MD, Galic S, Marcinko K, Sikkema S, PuliniLkunnil T, Chen ZP, O'Neill HM, Ford RJ, Palanivel R, O'Brien M <i>et al.</i> Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. <i>Nature Medicine</i> 2013 19 1649–1654. (doi:10.1038/nm.3372)	108	Ahn J, Lee H, Kim S, Park J & Ha T. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. <i>Biochemical and Biophysical Research Communications</i> 2008 373 545–549. (doi:10.1016/j.bbrc.2008.06.077)	
94	Krentz AJ, Bailey CJ & Melander A. Thiazolidinediones for type 2 diabetes. New agents reduce insulin resistance but need long term clinical trials. <i>BMJ</i> 2000 321 252–253. (doi:10.1136/bmj.321.7256.252)	109	Eid HM, Nachar A, Thong F, Sweeney G & Haddad PS. The molecular basis of the antidiabetic action of quercetin in cultured skeletal muscle cells and hepatocytes. <i>Pharmacognosy Magazine</i> 2015 11 74–81. (doi:10.4103/0973-1296.149708)	
95	Kubota N, Terauchi Y, Kubota T, Kumagai H, Itoh S, Satoh H, Yano W, Ogata H, Tokuyama K, Takamoto I <i>et al.</i> Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. <i>Journal of Biological Chemistry</i> 2006 281 8748–8755. (doi:10.1074/jbc.M505649200)	110	Lu J, Wu DM, Zheng YL, Hu B, Zhang ZF, Shan Q, Zheng ZH, Liu CM & Wang YJ. Quercetin activates AMP-activated protein kinase by reducing PP2C expression protecting old mouse brain against high cholesterol-induced neurotoxicity. <i>Journal of Pathology</i> 2010 222 199–212. (doi:10.1002/path.2754)	
96	Tuduri E, Lopez M, Dieguez C, Nadal A & Nogueiras R. Glucagon-like peptide 1 analogs and their effects on pancreatic islets. <i>Trends in Endocrinology and Metabolism</i> 2016 27 304–318. (doi:10.1016/j.tem.2016.03.004)	111	Martinez de Morentin PB, Gonzalez CR & Lopez M. AMP-activated protein kinase: 'a cup of tea' against cholesterol-induced neurotoxicity. <i>Journal of Pathology</i> 2010 222 329–334. (doi:10.1002/path.2778)	
97	Hattori Y, Jojima T, Tomizawa A, Satoh H, Hattori S, Kasai K & Hayashi T. A glucagon-like peptide-1 (GLP-1) analogue, liraglutide, upregulates nitric oxide production and exerts anti-inflammatory action in endothelial cells. <i>Diabetologia</i> 2010 53 2256–2263. (doi:10.1007/s00125-010-1831-8)	112	Brusq JM, Ancellin N, Grondin P, Guillard R, Martin S, Saintillan Y & Issandou M. Inhibition of lipid synthesis through activation of AMP kinase: an additional mechanism for the hypolipidemic effects of berberine. <i>Journal of Lipid Research</i> 2006 47 1281–1288. (doi:10.1194/jlr.M600020-JLR200)	
98	Krasner NM, Ido Y, Ruderman NB & Cacicedo JM. Glucagon-like peptide-1 (GLP-1) analog liraglutide inhibits endothelial cell inflammation through a calcium and AMPK dependent mechanism. <i>PLoS ONE</i> 2014 9 e97554. (doi:10.1371/journal.pone.0097554)	113	Beltran-Debon R, Rull A, Rodriguez-Sanabria F, Iswaldi I, Herranz-López M, Aragonès G, Camps J, Alonso-Villaverde C, Menéndez JA, Micol V <i>et al.</i> Continuous administration of polyphenols from aqueous rooibos (<i>Aspalathus linearis</i>) extract ameliorates dietary-induced metabolic disturbances in hyperlipidemic mice. <i>Phytomedicine</i> 2011 18 414–424. (doi:10.1016/j.phymed.2010.11.008)	
99	Inoue T, Inoguchi T, Sonoda N, Hendarto H, Makimura H, Sasaki S, Yokomizo H, Fujimura Y, Miura D & Takayanagi R. GLP-1 analog liraglutide protects against cardiac steatosis, oxidative stress and apoptosis in streptozotocin-induced diabetic rats. <i>Atherosclerosis</i> 2015 240 250–259. (doi:10.1016/j.atherosclerosis.2015.03.026)	114	Cheng Z, Pang T, Gu M, Gao AH, Xie CM, Li JY, Nan FJ & Li J. Berberine-stimulated glucose uptake in L6 myotubes involves	

Review	M López	Hypothalamic AMPK and obesity	176:5	R246

- both AMPK and p38 MAPK. *Biochimica et Biophysica Acta* 2006 **1760** 1682–1689. (doi:10.1016/j.bbagen.2006.09.007)
- 115 Kim SH, Shin EJ, Kim ED, Bayaraa T, Frost SC & Hyun CK. Berberine activates GLUT1-mediated glucose uptake in 3T3-L1 adipocytes. *Biological and Pharmaceutical Bulletin* 2007 **30** 2120–2125. (doi:10.1248/bpb.30.2120)
- 116 Dossus L & Kaaks R. Nutrition, metabolic factors and cancer risk. *Best Practice and Research Clinical Endocrinology and Metabolism* 2008 **22** 551–571. (doi:10.1016/j.beem.2008.08.003)
- 117 Faubert B, Boily G, Izreig S, Griss T, Samborska B, Dong Z, Dupuy F, Chambers C, Fuerth BJ, Viollet B *et al.* AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo. *Cell Metabolism* 2013 **17** 113–124. (doi:10.1016/j.cmet.2012.12.001)
- 118 Park HU, Suy S, Danner M, Dailey V, Zhang Y, Li H, Hyduke DR, Collins BT, Gagnon G, Kallakury B *et al.* AMP-activated protein kinase promotes human prostate cancer cell growth and survival. *Molecular Cancer Therapeutics* 2009 **8** 733–741. (doi:10.1158/1535-7163.MCT-08-0631)
- 119 Dietrich MO & Horvath TL. Limitations in anti-obesity drug development: the critical role of hunger-promoting neurons. *Nature Reviews Drug Discovery* 2012 **11** 675–691. (doi:10.1038/nrd3739)
- 120 Clemmensen C, Muller TD, Finan B, Tschop MH & DiMarchi R. Current and emerging treatment options in diabetes care. *Handbook of Experimental Pharmacology* 2016 **233** 437–459.
- 121 Tschop MH, Finan B, Clemmensen C, Gelfanov V, Perez-Tilve D, Müller TD & DiMarchi RD. Unimolecular polypharmacy for treatment of diabetes and obesity. *Cell Metabolism* 2016 **24** 51–62. (doi:10.1016/j.cmet.2016.06.021)
- 122 Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Müller C, Carling D & Kahn BB. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature* 2002 **415** 339–343. (doi:10.1038/415339a)
- 123 Milbank E, Martinez MC & Andriantsitohaina R. Extracellular vesicles: pharmacological modulators of the peripheral and central signals governing obesity. *Pharmacology and Therapeutics* 2016 **157** 65–83. (doi:10.1016/j.pharmthera.2015.11.002)
- 124 Yang Y, Atasoy D, Su HH & Sternson SM. Hunger states switch a flip-flop memory circuit via a synaptic AMPK-dependent positive feedback loop. *Cell* 2011 **146** 992–1003. (doi:10.1016/j.cell.2011.07.039)
- 125 Finan B, Yang B, Ottaway N, Stemmer K, Müller TD, Yi CX, Habegger K, Schriever SC, García-Cáceres C, Kabra DG *et al.* Targeted estrogen delivery reverses the metabolic syndrome. *Nature Medicine* 2012 **18** 1847–1856.
- 126 Finan B, Yang B, Ottaway N, Smiley DL, Ma T, Clemmensen C, Chabenne J, Zhang L, Habegger KM, Fischer K *et al.* A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nature Medicine* 2015 **21** 27–36. (doi:10.1038/nm.3761)
- 127 Finan B, Clemmensen C, Zhu Z, Stemmer K, Gauthier K, Müller L, De Angelis M, Moreth K, Neff F, Perez-Tilve D *et al.* Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell* 2016 **167** 843–857. (doi:10.1016/j.cell.2016.09.014)
- 128 Shughrue PJ, Lane MV & Merchenthaler I. Comparative distribution of estrogen receptor-alpha and -beta mRNA in the rat central nervous system. *Journal of Comparative Neurology* 1997 **388** 507–525. (doi:10.1002/(sici)1096-9861(19971201)388:4%3C507::aid-cne1%3E3.0.co;2-6)
- 129 Zhang X, Zhang G, Zhang H, Karin M, Bai H & Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. *Cell* 2008 **135** 61–73. (doi:10.1016/j.cell.2008.07.043)
- 130 Ozcan L, Ergin AS, Lu A, Chung J, Sarkar S, Nie D, Myers MG Jr & Ozcan U. Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metabolism* 2009 **9** 35–51. (doi:10.1016/j.cmet.2008.12.004)
- 131 Martinez de Morentin PB & Lopez M. 'Mens sana in corpore sano': exercise and hypothalamic ER stress. *PLoS Biology* 2010 **8**.
- 132 Martinez de Morentin PB, Varela L, Ferno J, Nogueiras R, Dieguez C & Lopez M. Hypothalamic lipotoxicity and the metabolic syndrome. *Biochimica et Biophysica Acta* 2010 **1801** 350–361. (doi:10.1016/j.bbalip.2009.09.016)
- 133 Contreras C, Gonzalez-Garcia I, Martinez-Sanchez N, Seoane-Collazo P, Jacas J, Morgan DA, Serra D, Gallego R, Gonzalez F, Casals N *et al.* Central ceramide-induced hypothalamic lipotoxicity and ER stress regulate energy balance. *Cell Reports* 2014 **9** 366–377. (doi:10.1016/j.celrep.2014.08.057)
- 134 Contreras C, Gonzalez-Garcia I, Seoane-Collazo P, Martínez-Sánchez N, Liñares-Pose L, Rial-Pensado E, Fernø J, Tena-Sempere M, Casals N, Diéguez C *et al.* Reduction of hypothalamic ER stress activates browning of white fat and ameliorates obesity. *Diabetes* 2017 **6** 87–99. (doi:10.2337/db15-1547)
- 135 Gonzalez-Garcia I, Ferno J, Dieguez C, Nogueiras R & Lopez M. Hypothalamic lipids: key regulators of whole body energy balance. *Neuroendocrinology* 2016. (doi:10.1159/000448432)

Received 9 November 2016

Revised version received 26 January 2017

Accepted 22 February 2017