Biochemical and Biophysical Research Communications 421 (2012) 1–3

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

Inositol polyphosphate multikinase: An emerging player for the central action of AMP-activated protein kinase

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ARTICLE INFO

Article history:
Received 20 March 2012
Available online 7 April 2012

Keywords:
AMPK
IPMK
Energy homeostasis
Food intake

ABSTRACT

AMP-activated protein kinase (AMPK) is an essential enzyme indispensable for energy sensing and metabolic homeostasis at both the cellular and whole-body levels. Phosphorylation of AMPK, a key step for its activation, is known to be regulated by upstream kinases such as liver kinase B1 (LKB1) and calmodulin-dependent protein kinase kinase-beta (CaMKKβ). Recent evidence shows that inositol polyphosphate multikinase (IPMK), which possesses both inositol phosphate kinase and lipid inositol kinase activities, can physiologically regulate AMPK signaling in cultured cells and in the arcuate nucleus. IPMK-mediated regulation of AMPK occurs through the dynamic protein interactions of IPMK with AMPK in response to glucose availability. Here we review and discuss a novel role for the hypothalamic IPMK signaling in the control of AMPK and central energy homeostasis.

1. Introduction

The increasing rates of obesity and associated metabolic disorders have stimulated efforts to identify the mechanisms underlying energy homeostasis. Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a highly conserved cellular energy sensor that plays a pivotal role in multiple metabolic processes [1]. AMPK within the hypothalamus has been shown to control whole body energy balance by integrating peripheral and central energy signals [2]. Although the molecular details of these interactions are not fully understood, it is known that alterations in hypothalamic AMPK activity lead to changes in feeding behavior, body weight and metabolism [3,4]. Thus, understanding the signaling components driving changes in hypothalamic AMPK may provide new therapeutic targets for the treatment of obesity and related metabolic syndromes.

AMPK is a heterotrimeric protein kinase consisting of a catalytic (α) subunit and two regulatory (β, γ) subunits. Activation of AMPK requires phosphorylation of the α subunit [5]. The γ subunit contains two sites that bind metabolic nucleotides (e.g. AMP, ADP, and ATP), in an antagonistic manner to promote or inhibit phosphorylation in response to changing energy levels [6,7]. The activity of AMPK is also controlled by upstream kinases. Liver kinase B1 (LKB1) has been suggested to continuously phosphorylate AMPK, an action that is rapidly reversed in the absence of AMP [8]. Another upstream kinase, calmodulin-dependent protein kinase kinase-beta (CAMKKβ) activates AMPK in the presence of high cytosolic calcium [9]. Recent evidence indicates AMPK is also modulated by inositol signaling through the direct protein interaction of inositol polyphosphate multikinase (IPMK) with AMPK [10].

2. A role for inositol and IPMK in metabolism

Inositol is a naturally-occurring glucose isomer and a key nutrient of the human diet. Abnormalities in the level or metabolism of inositol have been implicated in various diseases, including diabetes [11]. Water-soluble inositol polyphosphates (IPs) function as signaling messengers to mediate a variety of physiological processes, such as growth and apoptosis [12]. The various IPs are generated by inositol phosphate kinases sequentially phosphorylating different sites on the inositol phosphate ring. Snyder and his associates first identified IPMK as an enzyme essential for the physiologic synthesis of IP5 [Ins(1,3,4,5,6)P5], which is a precursor to all the inositol polyphosphates [12]. Additionally, IPMK is a lipid inositol kinase that can phosphorylate phosphatidylinositol-4,5-bisphosphate (PIP2) at the three position to generate phosphatidyl inositol-3,4,5-trisphosphate (PIP3), thus regulating the physiologic level of PIP3, a key second messenger for the activation of Akt/protein kinase B (PKB) signaling pathway [13].

Potential roles for IPMK in energy homeostasis were implied by its earlier identification in budding yeast where IPMK was cloned as a key component of the arginine sensor for governing the expression of genes involved in arginine metabolism [14,15]. In

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http://dx.doi.org/10.1016/j.bbrc.2012.04.010

seeking mammalian functions for IPMK, Kim et al. [16] recently reported that IPMK is a novel mammalian target of rapamycin (mTOR) cofactor and a critical determinant of amino acid-induced mTOR Complex 1 (mTORC1) signaling. Depletion of mouse IPMK in mouse embryonic fibroblast (MEFs) markedly reduces amino acid-induced mTORC1 activation and decreases cell size, comparable to the effects of depletion of raptor, a key element of mTORC1 signaling in response to amino acids. In budding yeast, a role for IPMK as a chaperone for the Arg80/Mcm1 transcription complex is critically dependent upon a short consecutive sequence of polyaspartates that is absent in mammalian IPMK. In contrast, mammalian IPMK orthologs possess a unique amino terminal extension of 31–60 amino acids that is required for the regulation of amino acid-induced mTORC1 signaling by IPMK. This mammalian specific, amino terminus of IPMK mediates the direct binding of IPMK to mTOR and stabilizes the mTOR-raptor interaction [16].

3. IPMK, a new AMPK regulator

Bang et al. [10] recently established a role for IPMK in controlling cell metabolism that is not restricted to Akt/mTOR, but is further extended to AMPK signaling. Both IPMK mRNA and protein levels in the hypothalamus are lowered in fasted mice but are markedly increased by re-feeding. Conditional deletion of hypothalamic IPMK gene in the arcuate nucleus (Arc) by stereological injection of Cre recombinase increases hypothalamic AMPK signaling under ad libitum conditions. IPMK null mouse embryonic fibroblasts also exhibit augmented AMPK signaling in a low glucose condition, accompanied by the loss of dynamic regulation of AMPK activity in response to glucose availability. IPMK-mediated AMPK signaling appears to depend on the physical interaction between IPMK and AMPK. IPMK is a novel AMPK binding protein and its binding to AMPK is dynamically changed by glucose level. Glucose deprivation for 2 h markedly decreases IPMK-AMPK binding, which is fully restored by 30 min of glucose repletion. Glucose treatment stimulates phosphorylation of IPMK at tyrosine-174(Y174), which enables IPMK to strongly interact with AMPK and regulates AMPK signaling responses to glucose. Overexpression of IPMK peptides responsible for AMPK binding not only interrupts the increased IPMK–AMPK interaction elicited by glucose treatment but also abolishes the dynamic changes of AMPK activity in response to glucose level. These findings lead to the following model: in low glucose, phosphorylated IPMK-Y174 level becomes decreased, and subsequently AMPK can interact with and be phosphorylated by its upstream kinases such as LKB1. In this scenario, high glucose facilitates phosphorylation of IPMK-Y174 and increases IPMK–AMPK binding affinity, thereby interfering with the regulatory action of LKB1 and thus controlling AMPK signaling [10].

4. IPMK–AMPK interact to alter food intake

In order to assess the role of hypothalamic IPMK in the control of energy homeostasis, we further investigated the effects of IPMK deletion within the Arc on AMPK signaling and food intake under fasted/re-fed conditions. When mice were fasted overnight, IPMK falls to low levels and active AMPK levels [as measured by phosphorylated AMPK-T172 (pAMPK)] are increased in both GFP-control and Cre–GFP groups (Fig. 1A). As expected, re-feeding decreases pAMPK and elicits increased food intake in GFP-control mice (Fig. 1). Interestingly, Cre–GFP mice had lower pAMPK levels and lower food intake after re-feeding compared with GFP-control mice. According to our current model, these findings lead to the following interpretation: re-feeding recovers hypothalamic IPMK levels and stimulates IPMK–AMPK interactions which modulate

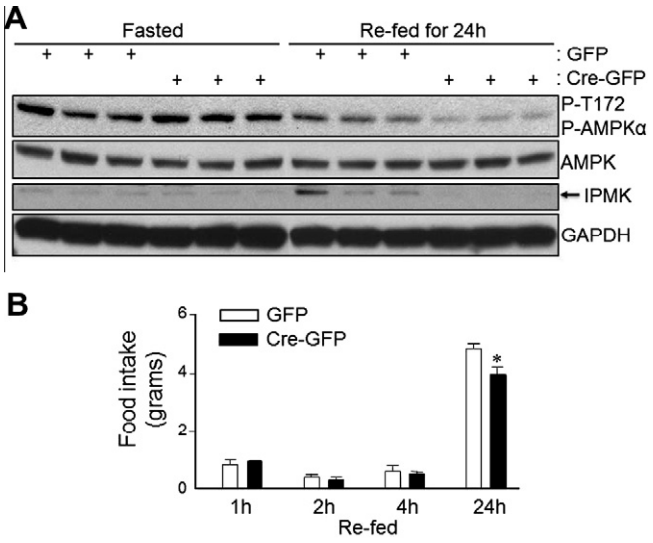

Fig. 1. Effects of IPMK on AMPK signaling and food intake. *IPMK*$^{lox/lox}$ mice were injected into the Arc with an adenovirus expressing either GFP (n = 10) or Cre–GFP recombinase (n = 10), as described (Section 2). Fasted mice were re-fed for indicated times. AMPK signaling (A) and food intake (B) were measured. Food intake was analyzed using a two-way repeated measures ANOVA with group (GFP or Cre–GFP) as the between-subject factor and time as the within-subject factor using Number Crunching Statistical Software (NCSS v 2000; Kaysville, UT). Newman–Keuls post hoc tests were used when appropriate. Data are presented as mean ± SEM. * Represents a significant difference from the GFP group ($p < 0.05$).

the phosphorylation status of AMPK (Fig. 2). In the absence of IPMK, phosphorylated AMPK appears to become much more susceptible to a protein phosphatase and thus rapidly dephosphorylated. Thus, the deletion of IPMK manifests the decreased pAMPK and reduced food intake upon re-feeding. These data suggest IPMK as a physiological player in the activation of AMPK in the Arc and the concomitant increase in food intake following food deprivation.

5. IPMK–AMPK: a potential target of pharmacological therapies

The IPMK–AMPK interaction in response to glucose availability within the Arc is an important finding because the upstream molecules that signal changes in glucose and alter AMPK activation have not been defined. Even though LKB1 and CAMKKβ play a role in central and peripheral AMPK activity, their role in hypothalamic AMPK regulation has not been fully identified [17]. Many of the

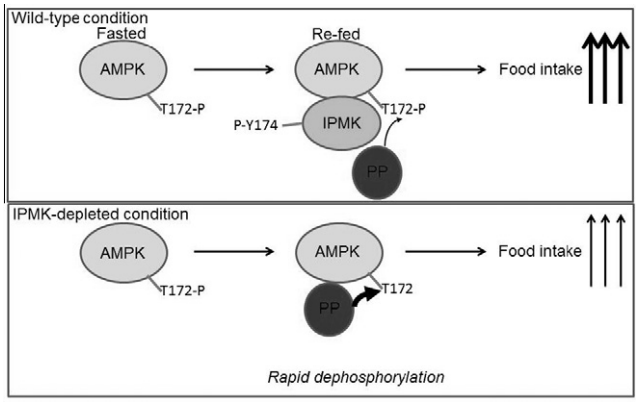

Fig. 2. A model depicting a role for hypothalamic IPMK. Under the fasting condition, AMPK is highly phosphorylated and subsequently activated. Re-feeding increases protein level of IPMK and association of IPMK with AMPK. AMPK becomes gradually dephosphorylated by protein phosphatases such as PP2C. In the absence of IPMK, dephosphorylation of AMPK is accelerated, which reduces food intake.

cells of the Arc are inhibited by high levels of glucose [18] and IPMK would allow for a mechanism by which glucose-inhibited neurons can alter AMPK activity even with decreased calcium.

We know that IPMK is phosphorylated in response to an increase in glucose levels, but the mechanism by which this occurs is unknown. Identifying a glucose-activated tyrosine kinase in Arc neurons will be of primary interest in dissecting upstream signaling events for IPMK and related AMPK signaling. Although many cells use glucose transporters to move glucose into a cell, Arc neurons do not appear to utilize this mechanism. Cells excited by high glucose require ATP-sensitive potassium channels and those that are inhibited by a drop in glucose use an unidentified chloride channel, but the relationship between these cellular changes and IPMK have not been investigated [19].

Arc AMPK activation plays a role in controlling multiple pathways for food intake, body weight and metabolism. Understanding the upstream molecules in the control of AMPK may help to identify how a wide variety of energetic signals are able to be integrated in the Arc and maintain energy balance. Future studies differentiating the cell types in the hypothalamus (e.g. NPY/AgRP and POMC neurons, glucose excited/inhibited) and upstream signals of IPMK may help to elucidate how Arc cells differentially respond to changes in glucose availability and alter AMPK function as well as food intake. Accordingly, drugs perturbing IPMK actions on hypothalamic AMPK may have therapeutic relevance in the fields of eating disorders (i.e. anorexia nervosa) and metabolic syndrome (i.e. obesity, type 2 diabetes).

Disclosure

There are no conflicts of interest to declare.

Acknowledgments

The authors would like to thank Drs. Timothy H. Moran and Solomon H. Snyder for their critical review of this manuscript. This work was supported by National Institute of Diabetes Digestive and Kidney Diseases Grants DK-19302 (to Timothy Moran) and DK-092126 (to M.J.D), the US Public Health Service Grant DA-00266 and Research Scientist Award DA-00074 (to Solomon H. Snyder) and The Jan Coffin Childs Memorial Fellowship (to S.K).

References

[1] B.B. Kahn, T. Alquier, D. Carling, D.G. Hardie, AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism, Cell Metab. 1 (2005) 15–25.

[2] P. Blanco Martinez de Morentin, C.R. Gonzalez, A.K. Saha, L. Martins, C. Dieguez, A. Vidal-Puig, M. Tena-Sempere, M. Lopez, Hypothalamic AMP-activated protein kinase as a mediator of whole body energy balance, Rev. Endocr. Metab. Disord. 12 (2011) 127–140.

[3] Y. Minokoshi, T. Alquier, N. Furukawa, Y.B. Kim, A. Lee, B. Xue, J. Mu, F. Foufelle, P. Ferre, M.J. Birnbaum, B.J. Stuck, B.B. Kahn, AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus, Nature 428 (2004) 569–574.

[4] U. Andersson, K. Filipsson, C.R. Abbott, A. Woods, K. Smith, S.R. Bloom, D. Carling, C.J. Small, AMP-activated protein kinase plays a role in the control of food intake, J. Biol. Chem. 279 (2004) 12005–12008.

[5] S.A. Hawley, M. Davison, A. Woods, S.P. Davies, R.K. Beri, D. Carling, D.G. Hardie, Characterization of the AMP-activated protein kinase kinase from rat liver and identification of threonine 172 as the major site at which it phosphorylates AMP-activated protein kinase, J. Biol. Chem. 271 (1996) 27879–27887.

[6] J.W. Scott, S.A. Hawley, K.A. Green, M. Anis, G. Stewart, G.A. Scullion, D.G. Norman, D.G. Hardie, CBS domains form energy-sensing modules whose binding of adenosine ligands is disrupted by disease mutations, J. Clin. Invest. 113 (2004) 274–284.

[7] B. Xiao, M.J. Sanders, E. Underwood, R. Heath, F.V. Mayer, D. Carmena, C. Jing, P.A. Walker, J.F. Eccleston, L.F. Haire, P. Saiu, S.A. Howell, R. Aasland, S.R. Martin, D. Carling, S.J. Gamblin, Structure of mammalian AMPK and its regulation by ADP, Nature 472 (2011) 230–233.

[8] D.G. Hardie, Sensing of energy and nutrients by AMP-activated protein kinase, Am. J. Clin. Nutr. 93 (2011) 891S–896.

[9] S.A. Hawley, D.A. Pan, K.J. Mustard, L. Ross, J. Bain, A.M. Edelman, B.G. Frenguelli, D.G. Hardie, Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase, Cell Metab. 2 (2005) 9–19.

[10] S. Bang, S. Kim, M.J. Dailey, Y. Chen, T.H. Moran, S.H. Snyder, S.F. Kim, AMP-activated protein kinase is physiologically regulated by inositol polyphosphate multikinase, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 616–620.

[11] B.J. Holub, Metabolism and function of myo-inositol and inositol phospholipids, Annu. Rev. Nutr. 6 (1986) 563–597.

[12] A. Chakraborty, S. Kim, S.H. Snyder, Inositol pyrophosphates as mammalian cell signals, Sci. Signal. 4 (2011) re1.

[13] D. Maag, M.J. Maxwell, D.A. Hardesty, K.L. Boucher, N. Choudhari, A.G. Hanno, J.F. Ma, A.S. Snowman, J.W. Pietropaoli, R. Xu, P.B. Storm, A. Saiardi, S.H. Snyder, A.C. Resnick, Inositol polyphosphate multikinase is a physiologic PI3-kinase that activates Akt/PKB, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 1391–1396.

[14] J. Bechet, M. Grenson, J.M. Wiame, Mutations affecting repressibility of arginine biosynthetic enzymes in *Saccharomyces cerevisiae*, Eur. J. Biochem. 12 (1970) 31.

[15] A.R. Odom, A. Stahlberg, S.R. Wente, J.D. York, A role for nuclear inositol 1,4,5-trisphosphate kinase in transcriptional control, Science 287 (2000) 2026–2029.

[16] S. Kim, S.F. Kim, D. Maag, M.J. Maxwell, A.C. Resnick, K.R. Juluri, A. Chakraborty, M.A. Koldobskiy, S.H. Cha, R. Barrow, A.M. Snowman, S.H. Snyder, Amino acid signaling to mTOR mediated by inositol polyphosphate multikinase, Cell Metab. 13 (2011) 215–221.

[17] M. Claret, M.A. Smith, C. Knauf, H. Al-Qassab, A. Woods, A. Heslegrave, K. Piipari, J.J. Emmanuel, A. Colom, P. Valet, P.D. Cani, G. Begum, A. White, P. Mucket, M. Peters, K. Mizuno, R.L. Batterham, K.P. Giese, A. Ashworth, R. Burcelin, M.L. Ashford, D. Carling, D.J. Withers, Deletion of Lkb1 in pro-opiomelanocortin neurons impairs peripheral glucose homeostasis in mice, Diabetes 60 (2011) 735–745.

[18] X. Fioramonti, S. Contie, Z. Song, V.H. Routh, A. Lorsignol, L. Penicaud, Characterization of glucosensing neuron subpopulations in the arcuate nucleus: integration in neuropeptide Y and pro-opio melanocortin networks?, Diabetes 56 (2007) 1219–1227

[19] Z. Song, B.E. Levin, J.J. McArdle, N. Bakhos, V.H. Routh, Convergence of pre- and postsynaptic influences on glucosensing neurons in the ventromedial hypothalamic nucleus, Diabetes 50 (2001) 2673–2681.