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# Regulation of Food Intake by Fuel Sensors

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## Abstract
Adenosine 5'-Monophosphate (AMP) - Activated Protein Kinase (AMPK), mammalian Target of Rapamycin (mTOR), Peroxisome Proliferator Activated Receptors (PPARs) have been reported to serve as an intracellular fuel sensors to regulate cell metabolism. Fuel sensors are involved in sensing of nutrient availability and metabolic hormones, thereby contribute to control of appetite. This review summarizes the recent advances on the modulation of food intake by fuel sensors.

**Keywords:** Food intake; Fuel sensors; AMPK; mTOR; PPARs.

## Introduction

Food intake is the most basic and complex behavior of human beings and animals to maintain life activities. After being digested and absorbed, the food provides the body with necessary energy and nutrients [1]. Increased availability of nutrients is tightly coupled with nutrient-sensing mechanisms that in turn activate energy consumption and decreases in appetite. The availability of nutrients and metabolic hormones can be sensed at hypothalamic sites or directly in peripheral tissues such as gastrointestinal tract, skeletal muscle and fat [2]. Central nervous system that regulate appetite, energy expenditure, and endogenous glucose production and respond to input from nutritional and hormonal-related signals that convey information regarding both body energy stores and current energy availability. In response to nutritional and hormonal signals, adaptive changes occur that promote energy homeostasis and the maintenance of blood glucose levels in the normal range. Adenosine 5'-Monophosphate (AMP) - Activated Protein Kinase (AMPK), mammalian Target of Rapamycin (mTOR), Peroxisome Proliferator Activated Receptors (PPARs) have been referred to as energy sensors due to its regulatory properties for energy homeostasis. Defects in fuel sensing system are implicated in the link between obesity and type 2 diabetes [3]. Thus, we summarize the roles of fuel sensors such as AMPK, mTOR and PPARs in the regulation of food intake in this review.

## 1. Adenosine 5'-Monophosphate (AMP) - Activated Protein Kinase (AMPK)

### 1.1 AMPK: Structure, Regulation

Adenosine 5'-Monophosphate-Activated Protein Kinase (AMPK), known as the "energy sensor", exactly feels the changes of cellular energy status [4]. AMPK exists as a heterotrimer comprising a catalytic α subunit and regulatory β and γ subunits, which are essential to AMPK activity. α subunit is encoded by multiple genes (α1, α2), while β subunit is also encoded by β1 and β2 genes, instead γ1, γ2 and γ3 encode γ subunit [4, 5]. The α subunit contains an N-terminal kinase domain with a kinase activation domain and a C-terminal domain, among them the C-terminal domain is to form a complex with α and γ. The β subunits also contain a carbohydrate binding domain in center, and a C domain which is connecting with α and γ subunits.

The γ subunits of AMPK contain four repeats of a sequence motif of about 60 residues; originally termed as a CBS domain , and each form a bateman domain binds two molecules of AMP or ATP [4-6]. In mammals, an upstream kinase(s) named liver kinase B1 (LKB1) activate AMPK directly by phosphorylating the Thr172 in AMPKα1 subunit [7]. Besides artificial synthesis of nonspecific agonist 5-Aminoimidazole-4-Carboxamide Riboside (AICAR), a kind of adenosine analogue, also can activate AMPK [8]. Although increasing the ratio of AMP/ATP is the classical pathway to activate AMPK, yet there are still many hormones, cytokines and some extracellular ligands play a role in AMPK signaling pathway, for example leptin, ghrelin, Adiponectin and other metabolic hormones also will influence the activation of AMPK [9].

### 1.2 Role of AMPK in the Regulation of Food Intake

As an evolutionarily conserved sensor of cellular energy status, AMPK plays a critical role in systemic energy balance. AMPK integrates nutritional and hormonal signals in peripheral tissues and the hypothalamus [10]. The hypothalamus, especially hypothalamic arcuate nucleus and paraventricular nucleus, is the main organ of central nervous system to regulate appetite [11]. Neurons in the hypothalamus can sense a variety of neuroendocrine and metabolic signals to regulate the body's energy supply and demand balance [11]. Recent findings indicate that hypothalamic AMPK is an important signal molecule, which integrates nutritional and hormonal signals and modulates feeding behavior and energy expenditure. 2-deoxyglucose(2-DG) [12, 13], glucose depletion [14], streptomycin [12], ghrelin [15], AgRP [16], pioglitazone [17, 18], salvianolic acid A [19] and olanzapine [20] increase food intake by enhancing hypothalamic AMP-activated protein kinase activity, whereas glucose [16], leptin [16], insulin [21], melanocortin receptor agonists [12], alpha-lipoic acid [14], fatty acid synthase FAS inhibitor C75 [22 - 24], thiamine [25] and C1q /TNF [26] have been shown to reduce food intake by lowering hypothalamic AMP-activated protein kinase activity.

Hypothalamic AMPK is affected by nutritional availability in hypothalamic neurons, more specifically, intracerebroventricular (i.c.v.) administration of glucose decreases hypothalamic AMPK activity, whereas inhibition of intracellular glucose utilization through the administration of 2-deoxyglucose increases hypothalamic AMPK activity and appetite. Moreover, 2-deoxyglucose-induced hyperphagia is reversed by inhibiting hypothalamic AMPK [12, 13]. Alpha-lipoic acid (alpha-LA), a cofactor of mitochondrial enzymes, decreases hypothalamic AMPK activity but active AMPK in skeletal muscles. Inhibition of AMPK activation in the hypothalamus decrease energy intake and activation of peripheral tissues AMPK increase fatty acid oxidation and enhanced insulin sensitivity [22]. H1R agonist, 2-(3-trifluoromethylphenyl) histamine, suppresses food intake via the inhibition of AMPK in the mediobasal hypothalamus, which can be blocked by olanzapine [20]. Thiamine deficiency induces anorexia by inhibiting hypothalamic AMPK [25]. Leptin-induced reduction in hypothalamic AMPK activity was shown to decrease feeding by down-regulating expression of the orexigenic hormones neuropeptide Y (NPY) and agouti gene-related protein (AgRP) [27]. Akieda-Asai S et al. [28] also report that coinjection of CCK and leptin reduces food intake via reduced AMPK phosphorylation and increased amphetamine-regulated transcript (CART) and thyrotropin-releasing hormone (TRH) in the hypothalamus. Melanocortin (MC) 4 receptor pathway potently inhibits appetite and at least partially mediates the anorexigenic effect of leptin [16]. In contrast, injection of ghrelin in vivo, which increases food intake, stimulates AMPK activity and enhances NPY expression in the hypothalamus [29]. Interestingly, ghrelin also has been reported to inhibit AMPK activity in liver and epididymal fat [30]. C75, a fatty acid synthase inhibitor, reduces food intake via hypothalamic AMP-activated protein kinase [22 - 24]. Inhibition of Carnitine Palmitoyltransferase 1 (CPT1), which is inhibited physiologically by malonyl-CoA, reduces food intake [15, 31]. Hormonal induced changes in AMPK activity leading to changes in ACC phosphorylation activity, which in turn would alter malonyl-CoA levels to regulate food intake. Taken together, these results provide the demonstration that hypothalamic AMPK is directly involved in regulating food intake and implicate it as a potential target for therapeutic agents aimed at reducing body weight [15].

In the peripheral metabolic tissues, AMPK contributes to the reconstruction of the energy imbalance by the regulation of the peripheral metabolic tissue and organs. Targeted deletion of C1q/TNF-related protein 9 increases food intake, decreases insulin sensitivity, and promotes hepatic steatosis in mice, which attributes to the reduced AMPK of skeletal muscle [26].

## 2. Mammalian Target of Rapamycin (mTOR)

### 2.1 mTOR: Structure, Regulation, and Functions

Extensive investigations indicate that the Target of Rapamycin (TOR) is a conserved Ser/Thr kinase (289kDa) that regulates cell growth and metabolism in response to environmental cues. Two mTOR complexes are known to exist, termed TOR Complex 1 (TORC1) and TORC2 [32]. Mammalian TORC1 (mTORC1) contains mTOR, mLST8, raptor, which is activated by nutrients, growth factors, and cellular energy, and is inhibited by the rapamycin. mTORC1 positively regulates anabolic processes, such as protein synthesis, ribosome biogenesis, transcription, lipid synthesis, nucleotide biosynthesis while inhibiting catabolic processes such as autophagy.

mTORC2 contains mTOR, mLST8, mSIN1, rictor, and is activated by growth factors via association with ribosomes [33]. TSC1 and TSC2 are tumor suppressor genes that are mutated in the disease TSC [34]. The proteins TSC1 and TSC2 form a tight complex in the cell to negatively regulate mTOR activity [35]. Well characterized down-stream targets of mTORC1 are ribosomal protein S6 kinase (S6K), eukaryotic translation initiation factor 4E (eIF4E) binding proteins (4E-BPs) [33]. mTOR promotes cell growth by promoting protein translation and increasing the number of cells after activation. The cells with the brisk mTOR function are customarily able to gain growth advantage and emerge a greater volume [36].

### 2.2 Nutrients and mTOR Activity

In mammalian cells, co-over expression of TSC1 and TSC2 prevents amino acid dependent activation of S6K1 which strongly suggests that TSC1 and TSC2 are required for amino acid–induced signaling through mTOR [37]. Branched-chain amino acid leucine has a stimulatory effect on assembly of the eIF4F complex, a key component in the mRNA binding step in translation initiation, as assessed by the phosphorylation status of the eIF4E binding protein 4E-BP1 and by the association of eIF4E with 4E-BP1 and eIF4G. Leucine also has a stimulatory effect on the phosphorylation status of eIF4G as well as S6K1 and its downstream substrate S6 [38]. Rapamycin and nutrient deprivation have similar effects on the activity of S6 kinase 1 (S6K1) and 4E-BP1, but the relationship between nutrient- and rapamycin-sensitive pathways is unknown [39]. The glycolytic inhibitor 2-deoxyglucose (2-DG) was more effective in inhibiting S6K1 Thr389 phosphorylation and S6K1 activation than was the mitochondrial inhibitor rotenone. 2-DG-induced reduction in ATP concentrations appears to selectively influence signaling to S6K1 and 4E-BP1 [40]. It is generally considered that AMPK is more sensitive to ATP than mTOR, because the concentration of AMP in the cell is much lower than ATP. AMPK may be a primary intracellular energy of physiological receptor, and the increase of AMPK activity can inhibit the mTOR signal transduction pathway. Further studies show that AMPK has the ability to reduce mTORC1 signal transduction by TSC2 phosphorylation, leading to the enhancement of GAP activity [41].

### 2.3 Effects of mTOR on Energy Intake

In Drosophila, activation of drosophila p70/S6 kinase activity in neurons led to attenuated hunger response by fasted larvae, whereas its down-regulation triggered fed larvae to display motivated foraging and feeding [42]. In mammals, rapamycin, a typical inhibitor of mTOR, increase the feeding of high fat fed C57BL/6J mice [43]. In rats, mTOR signaling components colocalizes with neuropeptide Y and proopiomelanocortin neurons in the arcuate nucleus. Central administration of leucine increases hypothalamic mTOR signaling and decreases food intake and body weight. The hormone leptin increases hypothalamic mTOR activity, and the inhibition of mTOR signaling blunts leptin's anorectic effect [44]. Moreover, Zhang et al. [45] have found that mTOR signaling in the dorsal motor nucleus of the vagus (DMNV) neurons also regulates both the nutrient and the hormonal signals for the modulation of food intake. S6K, a down-stream target of mTOR, is also a physiologically relevant nutrient sensor and a critical mediator required for appropriate feeding and metabolic responses that maintain energy balance. MBH S6K up regulation is associated with an increased sensitivity to anorexigenic stimuli (refeeding, leptin) and a decreased sensitivity to orexigenic stimuli (fasting, high fat diet), while the reciprocal pattern of responses occurs during MBH S6K downregulation [46]. In addition to leucine and leptin, cilliary neurotrophic factor (CNTF) and Bone morphogenetic protein 7 (BMP7) also suppress food intake. CNTF induces the phosphorylation of STAT3 via mTORC1 in neuroblastoma cells. BMP7 inhibit food intake, which was mediated, at least in part, by a central rapamycin-sensitive mTOR-p70S6 kinase pathway [47]. All these findings suggest that mTOR plays an important role in central neuronal control of nutrient intake and energy balance. However the means by which peripheral cellular mTOR signaling is integrated with hypothalamic neuronal activity is unclear. Xu et al. [48] firstly report that mTOR signaling molecules express selectively in nearly all gastric X/A like cells, about 1/3 of G cells, but not in D cells. Furthermore, gastric mTOR inhibits the production of ghrelin while promotes nesfatin synthesis, which in turn acts to initiate food intake [49, 50]. These studies support the concept that peripheral fuel sensor also plays an essential role in food intake. In sum, the existence of a fuel-sensing pathway within the central and peripheral organs may provide opportunities for the therapy of obesity.

## 3. Peroxisome Proliferator Activated Receptors (PPARs)

Peroxisome Proliferator-Activated Receptors (PPARs) are members of the nuclear hormone receptor super family of ligand-activated transcription factors. Three PPAR isotypes have been identified: α, β (also called δ) and γ. PPARs play essential roles in the regulation of lipid-activated gene transcription, lipid metabolism, and inflammation and cell differentiation [51].

Administration of the thiazolidinedione, a PPARγ ligand, increased food intake in rats in a dose-dependent manner [52]. PPARγ agonist pioglitazone transiently increased and the PPARα agonist fenofibrate transiently decreased food intake, PPARα/γ dual activator ragaglitazar had no impact on feeding [53]. PPARγ activation increases both food intake and feed efficiency, resulting in net accumulation of subcutaneous body fat. The impact of PPARγ activation on feeding and feed efficiency appears to be partially independent because ragaglitazar completely counteracts the orexigenic actions of PPARγ activation without marked impact on feed efficiency [53].

Fenofibrate administration also normalized the daily food efficiency of mice treated with Rosiglitazone [54]. The effects of PPARs on food intake also confirmed by PPAR subtypes gene null mice. Food intake increased in PPARα knockout mice when compare to control littermates [55]. Food consumption normalized for body weight indicated that the male PPARβ null mice consumed more energy than wild-type controls [56]. Energy intake after a high fat diet was significantly lower in PPARγ+/− than in wild type [57]. This phenomenon was confirmed by brain specific PPARγ null mice, during high-fat diet (HFD) feeding, food intake was reduced and energy expenditure increased in PPARγ brain knockout (BKO) mice compared to control littermates, resulting in reduced weight gain. Excess weight gain induced by HFD feeding depends in part on the effect of neuronal PPARγ signaling to limit thermo genesis and increase food intake [58]. Although literatures illustrate that PPARs regulate appetite, the molecular mechanism still need further exploration, which was mediated, at least in part, by the regulation of hormonal production. For instance, PPARα agonist fenofibrate transiently decrease food intake. Inhibition of appetite by fenofibrate is associated with anorexigenic cholecystokinin release [59]. PPARβ/δ agonist GW501516 and GW0742 stimulate the synthesis and secretion of hormone GLP-1, a peptide which function is inhibiting food intake [60].

## Conclusion

In summary, fuel sensing mechanism in both central nervous system and peripheral organs are critical for energy homeostasis. In the central nervous system, Glucose, leptin and insulin, act on the hypothalamic neurons to inform the energy metabolism regulating center of the energy status. Peripheral fuel sensor such as mTOR is selectively expressed in a subpopulation of gastrointestinal endocrine cells and its activity is reciprocally related with the energy level, thus the peripheral fuel sensor integrating the energy supply with the food intake and energy metabolism by alteration of hormones production. Defining the mTOR signaling pathway to regulate the production of metabolic hormones such as ghrelin, nesfatin, GLP-1, would shift therapeutic focus to Peripheral gastrointestinal targets [49, 50, 61]. Further studies will aim to advance our understanding of intracellular processes in the fuel sensing and to provide new information on the integration of cellular activities with overall nutrient availability. Results of these new investigations will yield new insights relevant to treatment strategies for human obesity and diabetes.

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## References

1. Woods SC, Seeley RJ, Porte D, Schwartz W (1998) Signals that regulate food intake and energy homeostasis. Science 280: 1378-1383.
2. Obici S, Rossetti L (2003a) Minireview: nutrient sensing and the regulation of insulin action and energy balance. Endocrinology 144: 5172-5178.
3. Schwartz MW, Porte D (2005) Diabetes, obesity, the brain. Science 307: 375-379.
4. Kahn BB, Alquier T, Carling D, Hardie DG (2005) AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. Cell Metabolism 1: 15-25.
5. Hardie DG (2003a) Minireview: the AMP-activated protein kinase cascade: the key sensor of cellular energy status. Endocrinology 144: 5179-5183.
6. Hardie DG, Scott JW, Pan DA, Hudson ER (2003b) Management of cellular energy by the AMP-activated protein kinase system. FEBS letters 546: 113-120.
7. Lizcano JM, Goransson O, Toth R, Deak M, Morrice NA et al. (2004) LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1. The EMBO Journal 23: 833-843.
8. Lochhead PA, Salt IP, Walker KS, Hardie DG, Sutherland C (2000) 5-aminoimidazole-4-carboxamide riboside mimics the effects of insulin on the expression of the 2 key gluconeogenic genes PEPCK and glucose-6-phosphatase. Diabetes 49: 896-903.
9. Hardie DG (2008) AMPK: a key regulator of energy balance in the single cell and the whole organism. International Journal of Obesity 32: S7-S12.
10. Kalra SP, Dube MG, PU S, XU B, Horvath TL, et al. (1999) Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocrine Reviews 20: 68-100.
11. Schwartz MW, Woods SC, Porte D, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 404: 661-671.

12. Kim MS, Lee KU (2005) Role of hypothalamic 5′-AMP-activated protein kinase in the regulation of food intake and energy homeostasis. Journal of Molecular Medicine 83: 514-520.
13. Sergeyev V, Broberger C, Gorbatyuk O, Hokfelt T (2000) Effect of 2-mercaptoacetate and 2-deoxy-D-glucose administration on the expression of NPY, AGRP, POMC, MCH and hypocretin/orexin in the rat hypothalamus. Neuroreport 11: 117–121.
14. Kim MS, Park JY, Namkoong C, Jang PG, Ryu JW, et al. (2004) Anti-obesity effects of α-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase. Nature Medicine 10: 727-733.
15. Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, et al. (2004) AMP-activated protein kinase plays a role in the control of food intake. Journal of Biological Chemistry 279: 12005-12008.
16. Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, et al. (2004) AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 428: 569-574.
17. Matsuura N, Asano C, Nagasawa K, Ito S, Sano Y, et al. (2015) Effects of pioglitazone on cardiac and adipose tissue pathology in rats with metabolic syndrome. International Journal of Cardiology 179: 360-369.
18. Quaresma PGF, Reencober N, Zanotto TM, Weissmann L, Matos AHB, et al. (2015) Pioglitazone treatment increases food intake and decreases energy expenditure partially via hypothalamic adiponectin/adipoR1/AMPK pathway. International Journal of Obesity. DOI: 10.1038/ijo.2015.134.
19. Qiang G, Yang X, Shi L, Zhang L, Chen B, et al. (2015) Antidiabetic Affect of Salvianolic Acid A on Diabetic Animal Models via AMPK Activation and Mitochondrial Regulation. Cellular Physiology and Biochemistry 36: 395-408.
20. He M, Zhang Q, Deng C, Wang H, Lian L, et al. (2014) Hypothalamic histamine H1 receptor-AMPK signaling time-dependently mediates olanzapine-induced hyperphagia and weight gain in female rats. Psychoneuroendocrinology 42: 153-164.
21. Minokoshi Y, Kim YB, Peroni OD, Fryer LGD, Muller C, et al. (2002) Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature 415: 339-343.
22. Kim EK, Miller I, Aja S, Landree LE, Pinn M, et al. (2004) C75, a fatty acid synthase inhibitor, reduces food intake via hypothalamic AMP-activated protein kinase. J Biol Chem 279: 19970–19976.
23. Landree LE, Hanlon AL, Strong DW, Rumbaugh G, Miller LM, et al. (2004) C75, a fatty acid synthase inhibitor, modulates AMP-activated protein kinase to alter neuronal energy metabolism. J Biol Chem 279: 3817–3827.
24. Loftus TM, Jaworsky DE, Frehywot GL, Townsend CA, Ronnett GV, et al. (2000) Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. Science 288: 2379–2381.
25. Liu M, Alimov AP, Wang H, Frank JA, Katz W, et al. (2014) Thiamine deficiency induces anorexia by inhibiting hypothalamic AMPK. Neuroscience 267: 102-113.
26. Wei Z, Lei X, Petersen PS, Aja S, Wong GW, et al. (2014) Targeted deletion of C1q/TNF-related protein 9 increases food intake, decreases insulin sensitivity, and promotes hepatic steatosis in mice. American Journal of Physiology-Endocrinology and Metabolism 306: E779-E790.
27. Hardie DG, Ashford MLJ (2014) AMPK: regulating energy balance at the cellular and whole body levels. Physiology: 29: 99-107.
28. Akieda-Asia S, Poleni PE, Date Y (2014) Coinjection of CCK and leptin reduces food intake via increased CART/TRH and reduced AMPK phosphorylation in the hypothalamus. American Journal of Physiology-Endocrinology and Metabolism 306: E1284-E1291.
29. Wortley KE, Anderson KD, Garcia K, Murray JD, Liu R, et al. (2004) Genetic deletion of ghrelin does not decrease food intake but influences metabolic fuel preference. Proceedings of the National Academy of Sciences of the United States of America 101: 8227-8232.
30. Kang S, Moon NR, Kim DS, Kim SH, Park S (2015) Central acylated ghrelin improves memory function and hippocampal AMPK activation and partly reverses the impairment of energy and glucose metabolism in rats infused with β-amyloid. Peptides 71: 84-93.
31. Obici S, Feng Z, Arduini A, Conti R, Rossetti L (2003b) Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. Nat Med 9: 756–761.
32. Wullschleger S, Loewith R, Hall MN (2006) TOR signaling in growth and metabolism. Cell 24: 471-484.
33. Albert V, Hall MN (2015) mTOR signaling in cellular and organismal energetics. Current Opinion in Cell Biology 33: 55-66.
34. Van Slegtenhorst M, De Hoogt R, Hermans C, Nellist M, Janssen S, et al. (1997) Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science 277: 805-808.
35. Kwiatkowski DJ (2003) Tuberous sclerosis: from tubers to mTOR. Annals of Human Genetics 67: 87-96.
36. Kim DH, Sarbassov DD, Ali SM, King JE, Latek RR, et al. (2002) mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell 110: 163-175.
37. Kimball SR, Jefferson LS (2006a) New functions for amino acids: effects on gene transcription and translation. The American Journal of Clinical Nutrition 83: 500S-507S.

38. Kimball SR, Jefferson LS (2006b) Signaling pathways and molecular mechanisms through which branched-chain amino acids mediate translational control of protein synthesis. The Journal of Nutrition 136: 227S-231S.
39. Peng T, Golub TR, Sabatini DM (2002) The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. Molecular and Cellular Biology 22: 5575-5584.
40. Dennis PB, Jaeschke A, Saitoh M, Fowler B, Kozma SC, et al. (2001) Mammalian TOR: a homeostatic ATP sensor. Science 294: 1102-1105.
41. Inoki K, Li Y, Xu T, Guan KL (2003) Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes & Development 17: 1829-1834.
42. Wu Q, Zhang Y, Xu J, Shen P (2005) Regulation of hunger-driven behaviors by neural ribosomal S6 kinase in Drosophila. Proceedings of the National Academy of Sciences of the United States of America, 102: 13289-13294.
43. Chang GR, Chiu YS, Wu YY, Chen WY, Liao JW, et al. (2009) Rapamycin protects against high fat diet induced obesity in C57BL/6J mice. J Pharmacol Sci 109: 496-503.
44. Cota D, Proulx K, Smith KAB, Kozma SC, Thomas G, et al. (2006) Hypothalamic mTOR signaling regulates food intake. Science 312: 927-930.
45. Zhang W, Zhang C, Fritze D, Chai B, Li J, et al. (2013) Modulation of food intake by mTOR signalling in the dorsal motor nucleus of the vagus in male rats: focus on ghrelin and nesfatin-1. Experimental Physiology 98: 1696-1704.
46. Blouet C, Ono H, Schwartz GJ (2008) Mediobasal hypothalamic p70 S6 kinase 1 modulates the control of energy homeostasis. Cell Metab 8: 459-467.
47. Takei N, Furukawa K, Hanyu O, Sone H, Nawa H, et al. (2014) A possible link between BDNF and mTOR in control of food intake. Frontiers in Psychology, DOI: 10.3389/fpsyg.2014.01093.
48. Xu G, Li Y, An W, Zhao J, Xiang XX, et al. (2010) Regulation of gastric hormones by systemic rapamycin. Peptides 31: 2185-2192.
49. Li Z, Xu G, Li Y, Zhao J, Mutholland MW, et al. (2012) mTOR-dependent modulation of gastric nesfatin-1/NUCB2. Cellular Physiology and Biochemistry 29: 493-500.
50. Xu G, Li Y, An W, Li S, Guan Y, et al. (2009) Gastric mammalian target of rapamycin signaling regulates ghrelin production and food intake. Endocrinology 150: 3637-3644.
51. Kersten S, Desvergne B, Wahli W (1999) Peroxisome proliferator-activated receptors: nuclear control of metabolism 1. Endocrine Reviews 20: 649-688.
52. Schoonjans K, Auwerx J (2000) Thiazolidinediones: an update. The Lancet 355: 1008-1010.
53. De Vos P, Lefebvre AM, Miller SG, Guerre-Millo M, Wang K, et al. (1996) Thiazolidinediones repress ob gene expression in rodents via activation of peroxisome proliferator-activated receptor gamma. Journal of Clinical Investigation 98: 1004.
54. Carmona MC, Louche K, Nibbeline M, Prunet B, Bross A, et al. (2005) Fenofibrate prevents Rosiglitazone-induced body weight gain in ob/ob mice. International Journal of Obesity 29: 864-871.
55. Guerre-Millo M, Rouault C, Poulain P, Andre J, Poitout V, et al. (2001) PPAR-α-Null Mice Are Protected From High-Fat Diet-Induced Insulin Resistance. Diabetes 50: 2809-2814.
56. Peters JM, Lee SST, Li W, Ward JM, Gavrilova O, et al. (2000) Growth, adipose, brain, and skin alterations resulting from targeted disruption of the mouse peroxisome proliferator-activated receptor β(δ). Molecular and Cellular Biology 20: 5119-5128.
57. Kubota N, Terauchi Y, Miki H, Tamemoto H, Yamauchi T, et al. (1999) PPARγ mediates high-fat diet–induced adipocyte hypertrophy and insulin resistance. Molecular Cell 4: 597-609.
58. Lu M, Sarruf DA, Talukdar S, Sharma S, Li PP, et al. (2011) Brain PPAR-[gamma] promotes obesity and is required for the insulin-sensitizing effect of thiazolidinediones. Nature Medicine 17: 618-622.
59. Park MK, Han Y, Kim MS, Seo E, Kang S, et al. (2012) Reduction of Food Intake by Fenofibrate is Associated with Cholecystokinin Release in Long-Evans Tokushima Rats. Korean J Physiol Pharmacol 16: 181–186.
60. Daoudi M, Hennuyer N, Borland MG, Touche V, Duhem C, et al. (2011) PPARβ/δ activation induces enteroendocrine L cell GLP-1 production. Gastroenterology 140: 1564-1574.
61. Xu G, Li Z, Ding L, Tang H, Guo S, et al. (2015) Intestinal mTOR regulates GLP-1 production in mouse L cells. Diabetologia 58: 1887-1897.