Diabetol Int (2012) 3:109–112
DOI 10.1007/s13340-012-0088-5

COMMENTARY

# Hypothalamic Sirt1 and regulation of food intake

**Tadahiro Kitamura · Tsutomu Sasaki**

Received: 17 July 2012 / Accepted: 20 July 2012 / Published online: 22 August 2012
© The Japan Diabetes Society 2012

**Keywords** Obesity · Hypothalamus · Sirt1 · Diabetes · Leptin · Insulin

The hypothalamus controls food intake [1]. It regulates food intake by integrating information on nutritional status from periphery through nutrients, hormones, and autonomic nervous system. Previous studies revealed that numerous neuropeptides are expressed in the hypothalamus and contribute to the neural networks that regulate food intake. Among them, the melanocortin system—which consists of proopiomelanocortin (POMC), agouti-related peptides (AgRP), and melanocortin receptors—is the most fundamental system regulating food intake. POMC is a precursor for alpha-melanocyte-stimulating hormone (α-MSH), which is an agonist for melanocortin type 4 receptor (MC4R), and AgRP is an inverse agonist for MC4R and counteracts the function of α-MSH. In fact, POMC-null mice [2] and MC4R-null mice [3] are obese, and cases of highly obese humans with MC4R gene mutations have been reported [4–6].

Within the hypothalamus, the arcuate nucleus (ARC), paraventricular nucleus (PVN), and lateral hypothalamic (LH) area are centers for controlling food intake. ARC is the "first-order center" for regulating food intake. It is located at the mediobasal hypothalamus, where the blood–brain barrier is quite permissive, making ARC the place for sensing nutrients and hormone levels. ARC contains two types of neurons: anorexigenic POMC and orexigenic AgRP. These neurons project axons to the "second-order centers," which are located in PVN and LH, and competitively regulate the activity of these nuclei [7, 8].

The most-studied feeding-related hormone is leptin. In the hypothalamic neurons, leptin activates the Janus kinase 2–signal transducer and activator of transcription 3 (JAK2-STAT3) pathway, leading to nuclear translocation of phosphorylated STAT3. STAT3 suppresses food intake by transactivating the anorexigenic *Pomc* gene and transrepressing the orexigenic *Agrp* gene. Insulin is also known as a central regulator for food intake. Neuron-specific insulin receptor knockout mice exhibit increased food intake and obesity [9]. Insulin signaling is transmitted from the insulin receptor to phosphoinositide 3-kinase (PI3K), which subsequently activates a serine/threonine kinase protein kinase B (Akt). FoxO1 is a transcription factor and one of the substrates for Akt. Phosphorylation of FoxO1 by Akt results in cytoplasmic shuttling from the nucleus, thereby inactivating FoxO1 as a transcription factor [10]. FoxO1 is expressed in ARC AgRP and POMC neurons, and FoxO1 in these neurons are located in the nucleus under fasted condition but is shuttled to cytoplasm by feeding [11, 12]. Overexpression of constitutively active FoxO1 in the mediobasal hypothalamus of rats by adenoviral microinjection leads to loss of feeding inhibitory effect of leptin and results in body weight gain [11]. Hypothalamus-specific constitutively active FoxO1 knockin mice also have increased food intake and decreased energy expenditure, and consequently these mice develop obesity [13].

Silent mating type information regulation 2 homolog (sirtuin 1; Sirt1) is a nicotinamide adenine dinucleotide ($NAD^+$)-dependent deacetylase and serves as an energy sensor [14]. Sirt1 is the mammalian ortholog of Sir2, which is crucial for caloric-restriction-induced longevity [15–17]. Sirt1 is expressed in POMC and AgRP neurons in ARC and

T. Kitamura (✉) · T. Sasaki
Metabolic Signal Research Center, Institute for Molecular and Cellular Regulation, Gunma University,
3-39-15 Showa-machi, Maebashi, Gunma 371-8512, Japan
e-mail: kitamura@gunma-u.ac.jp

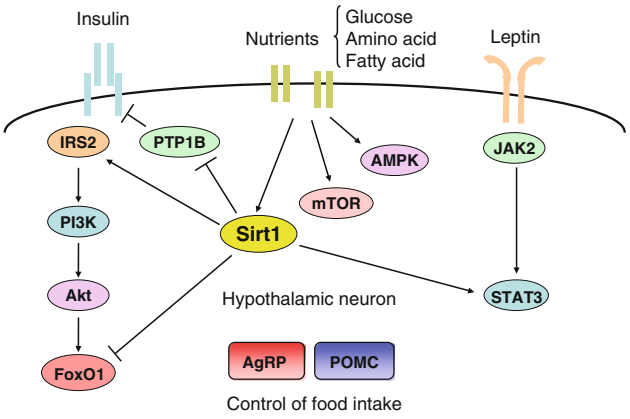


**Fig. 1** Hormones, nutrients, and neuropeptides controlling food intake. Insulin and leptin control food intake via regulating neuropeptides in the hypothalamus. Nutrients, such as glucose, amino acids, and fatty acids, regulate feeding. Nutrient-sensing proteins, such as adenosine-monophosphate-dependent protein kinase (AMPK), mammalian target of rapamycin (mTOR), and silent mating type information regulation 2 homolog (sirtuin 1; Sirt1) also participate in controlling food intake. Cross-talk among these molecules implicates more complex mechanisms for food intake control

other hypothalamic nuclei that are important for regulating food intake [18, 19]. There are several reports indicating that Sirt1 affects insulin signaling by modulating the downstream effectors (Fig. 1). For example, Sirt1 deacetylates insulin receptor substrate 2 (IRS2) in hepatocytes, which enhances insulin-induced tyrosine phosphorylation of IRS2 [20]. Sirt1 also decreases transcription of protein tyrosine phosphatase 1B (PTP1B), which results in increased tyrosine phosphorylation of insulin receptor in hepatocytes and myocytes [21]. We also previously reported that Sirt1 deacetylates FoxO1 in pancreatic $\beta$ cells, enhancing FoxO1 ubiquitination and thereby decreases FoxO1 protein level [22]. Furthermore, Nie et al. [23] reported that Sirt1 deacetylates STAT3, a downstream effector of leptin signaling, and inhibits STAT3 transcriptional activity. If the same mechanism for Sirt1 regulation of insulin and leptin signaling exists in the hypothalamus, Sirt1 should also play an important role in the central regulation of food intake. Therefore, we and others investigated the role of hypothalamic Sirt1 in regulating food intake.

There is conflicting information on how feeding regulates hypothalamic Sirt1 protein. We found that Sirt1 protein level decreases with fasting in the hypothalamus but not in the cerebral cortex [18]. This hypothalamic Sirt1 response to food intake is lost in diet-induced obese mice. Furthermore, Sirt1 is ubiquitinated in the hypothalamic cells in vitro and in vivo, and fasting increases hypothalamic Sirt1 ubiquitination [18]. On the other hand, Satoh et al. found that dietary restriction increases Sirt1 protein level in the dorsomedial hypothalamus (DMH) and LH [24]. Ramadori et al. [19], found that fasting increased the Sirt1 protein level strictly in the hypothalamus within the brain, which is contrary to our finding.

There are also varying reports on physiological effects of hypothalamic Sirt1 on food intake. In our observation, Sirt1 suppressed hyperphagia and body weight gain induced by overexpression of constitutively active FoxO1 in the mediobasal hypothalamus by adenovirus microinjection, but the effect of hypothalamic Sirt1 overexpression on food intake was not observed in normophagic mice [18]. Satoh et al. [24], observed no change in food intake in their brain-specific Sirt1 transgenic mice, but these mice showed increased physical activity. Intracerebroventricular injection of Sirt1 inhibitor (Ex-527) suppressed food intake [25, 26]. Furthermore, AgRP neuron-specific Sirt1-knockout mice have decreased electric responses of AgRP neurons to ghrelin and decreased food intake [26]. Meanwhile, POMC neuron-specific Sirt1 knockout mice exhibit unchanged food intake, but these mice are hypersensitive to diet-induced obesity due to reduced energy expenditure [27]. We also observed that POMC neuron-specific Sirt1 knockin mice have increased energy expenditure and decreased body weight gain (authors' unpublished data).

Further investigation is required to clarify the role of hypothalamic Sirt1 in regulating food intake and energy balance. Sirt1 is expressed in most neurons, and it is quite possible that Sirt1 in the different parts of the brain contributes differently to food intake control. Therefore, manipulation of Sirt1 specifically in certain types of neurons or nuclei is important. Interestingly, Sirt1 expression level decreases with age only in ARC but not in DMH, PVN, or ventromedial hypothalamus (VMH) [28]. Aging and high-fat diet reduces Sirt1 expression and activity in a number of tissues [29, 30]. It is possible that the age-dependent loss of Sirt1 in ARC contributes to increased obesity with age, and obesity further accelerates the loss of Sirt1 function in ARC, causing dysregulation of energy balance. The pharmacological activation of Sirt1 confers life span extension in mice fed a high-fat diet [31, 32], but overexpression of Sirt1 in transgenic mice fed a normal diet does not extend life span [33]. These data implicate that Sirt1 promotes health and life of mammals under excessive nutrient conditions but not in normal conditions.

Hypothalamic control of food intake is regulated not only by hormones, such as insulin and leptin, but also by nutrients, such as glucose, amino acids, and FAs. The molecular mechanisms by which these factors control food intake have been uncovered in the past 10 years. Amino acids activate mammalian target of rapamycin (mTOR) signaling in the hypothalamus and suppress food intake [34]. AMP kinase, which also serves as an energy sensor for cells, stimulates food intake [35]. Cross-talk

among adenosine-monophosphate-dependent protein kinase (AMPK), mTOR, FoxO1, and Sirt1 have been reported in different experimental systems [36–39], and it is quite possible some of these signaling cross-talks may be functional in the hypothalamus (Fig. 1). We hope that clarifying the molecular mechanism of Sirt1 in controlling food intake will contribute to the development of a new strategy to treat obesity and metabolic syndrome.

## References


1. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000; 404:661–71.
2. Yaswen L, Diehl N, Brennan MB, Hochgeschwender U. Obesity in the mouse model of pro-opiomelanocortin deficiency responds to peripheral melanocortin. Nat Med. 1999;5:1066–70.
3. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA, Cone RD, Smith FJ, Campfield LA, Burn P, Lee F. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell. 1997; 88:131–41.
4. Vaisse C, Clement K, Guy-Grand B, Froguel P. A frameshift mutation in human MC4R is associated with a dominant form of obesity. Nat Genet. 1998;20:113–4.
5. Yeo GS, Farooqi IS, Aminian S, Halsall DJ, Stanhope RG, O'Rahilly S. A frameshift mutation in MC4R associated with dominantly inherited human obesity. Nat Genet. 1998;20:111–2.
6. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med. 2003;348:1085–95.
7. Bagnol D, Lu XY, Kaelin CB, Day HE, Ollmann M, Gantz I, Akil H, Barsh GS, Watson SJ. Anatomy of an endogenous antagonist: relationship between Agouti-related protein and proopiomelanocortin in brain. J Neurosci. 1999; 19:RC26.
8. Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD. Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. Neuron. 1999;24:155–63.
9. Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR. Role of brain insulin receptor in control of body weight and reproduction. Science. 2000;289:2122–5.
10. Biggs WH 3rd, Meisenhelder J, Hunter T, Cavenee WK, Arden KC. Protein kinase B/Akt-mediated phosphorylation promotes nuclear exclusion of the winged helix transcription factor FKHR1. Proc Natl Acad Sci U S A. 1999;96:7421–6.
11. Kitamura T, Feng Y, Kitamura YI, Chua SC Jr, Xu AW, Barsh GS, Rossetti L, Accili D. Forkhead protein FoxO1 mediates Agrp-dependent effects of leptin on food intake. Nat Med. 2006;12:534–40.
12. Fukuda M, Jones JE, Olson D, Hill J, Lee CE, Gautron L, Choi M, Zigman JM, Lowell BB, Elmquist JK. Monitoring FoxO1 localization in chemically identified neurons. J Neurosci. 2008; 28:13640–8.
13. Kim HJ, Kobayashi M, Sasaki T, Kikuchi O, Amano K, Kitazumi T, Lee YS, Yokota-Hashimoto H, Susanti VY, Kitamura YI, Nakae J, Kitamura T. Overexpression of FoxO1 in the hypothalamus and pancreas causes obesity and glucose intolerance. Endocrinology. 2012;153:659–71.
14. Imai S, Armstrong CM, Kaeberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature. 2000;403:795–800.
15. Kaeberlein M, McVey M, Guarente L. The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. Genes Dev. 1999;13:2570–80.
16. Tissenbaum HA, Guarente L. Increased dosage of a sir-2 gene extends lifespan in Caenorhabditis elegans. Nature. 2001;410: 227–30.
17. Rogina B, Helfand SL. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. Proc Natl Acad Sci USA. 2004;101:15998–6003.
18. Sasaki T, Kim HJ, Kobayashi M, Kitamura YI, Yokota-Hashimoto H, Shiuchi T, Minokoshi Y, Kitamura T. Induction of hypothalamic Sirt1 leads to cessation of feeding via agouti-related peptide. Endocrinology. 2010;151:2556–66.
19. Ramadori G, Lee CE, Bookout AL, Lee S, Williams KW, Anderson J, Elmquist JK, Coppari R. Brain SIRT1: anatomical distribution and regulation by energy availability. J Neurosci. 2008;28:9989–96.
20. Zhang J. The direct involvement of SirT1 in insulin-induced insulin receptor substrate-2 tyrosine phosphorylation. J Biol Chem. 2007;282:34356–64.
21. Sun C, Zhang F, Ge X, Yan T, Chen X, Shi X, Zhai Q. SIRT1 improves insulin sensitivity under insulin-resistant conditions by repressing PTP1B. Cell Metab. 2007;6:307–19.
22. Kitamura YI, Kitamura T, Kruse JP, Raum JC, Stein R, Gu W, Accili D. FoxO1 protects against pancreatic beta cell failure through NeuroD and MafA induction. Cell Metab. 2005;2: 153–63.
23. Nie Y, Erion DM, Yuan Z, Dietrich M, Shulman GI, Horvath TL, Gao Q. STAT3 inhibition of gluconeogenesis is downregulated by Sirt1. Nat Cell Biol. 2009;11:492–500.
24. Satoh A, Brace CS, Ben-Josef G, West T, Wozniak DF, Holtzman DM, Herzog ED, Imai S. SIRT1 promotes the central adaptive response to diet restriction through activation of the dorsomedial and lateral nuclei of the hypothalamus. J Neurosci. 2010;30:10220–32.
25. Cakir I, Perello M, Lansari O, Messier NJ, Vaslet CA, Nillni EA. Hypothalamic Sirt1 regulates food intake in a rodent model system. PLoS ONE. 2009;4:e8322.
26. Dietrich MO, Antunes C, Geliang G, Liu ZW, Borok E, Nie Y, Xu AW, Souza DO, Gao Q, Diano S, Gao XB, Horvath TL. Agrp neurons mediate Sirt1′s action on the melanocortin system and energy balance: roles for Sirt1 in neuronal firing and synaptic plasticity. J Neurosci. 2010;30:11815–25.
27. Ramadori G, Fujikawa T, Fukuda M, Anderson J, Morgan DA, Mostoslavsky R, Stuart RC, Perello M, Vianna CR, Nillni EA, Rahmouni K, Coppari R. SIRT1 deacetylase in POMC neurons is required for homeostatic defenses against diet-induced obesity. Cell Metab. 2010;12:78–87.
28. Lafontaine-Lacasse M, Richard D, Picard F. Effects of age and gender on Sirt 1 mRNA expressions in the hypothalamus of the mouse. Neurosci Lett. 2010;480:1–3.
29. Sasaki T, Maier B, Bartke A, Scrable H. Progressive loss of SIRT1 with cell cycle withdrawal. Aging Cell. 2006;5:413–22.
30. Ramsey KM, Mills KF, Satoh A, Imai S. Age-associated loss of Sirt1-mediated enhancement of glucose-stimulated insulin secretion in beta cell-specific Sirt1-overexpressing (BESTO) mice. Aging Cell. 2008;7:78–88.
31. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA.

Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006;444:337–42.
32. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell. 2006;127:1109–22.
33. Herranz D, Munoz-Martin M, Canamero M, Mulero F, Martinez-Pastor B, Fernandez-Capetillo O, Serrano M. Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. Nat Commun. 2010;1:1–8.
34. Cota D, Proulx K, Smith KA, Kozma SC, Thomas G, Woods SC, Seeley RJ. Hypothalamic mTOR signaling regulates food intake. Science. 2006;312:927–30.
35. Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foufelle F, Ferre P, Birnbaum MJ, Stuck BJ, Kahn BB. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature. 2004;428:569–74.
36. Canto C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, Elliott PJ, Puigserver P, Auwerx J. AMPK regulates energy expenditure by modulating $NAD^+$ metabolism and SIRT1 activity. Nature. 2009;458:1056–60.
37. Canto C, Jiang LQ, Deshmukh AS, Mataki C, Coste A, Lagouge M, Zierath JR, Auwerx J. Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. Cell Metab. 2010;11:213–9.
38. Chen CC, Jeon SM, Bhaskar PT, Nogueira V, Sundararajan D, Tonic I, Park Y, Hay N. FoxOs inhibit mTORC1 and activate Akt by inducing the expression of Sestrin3 and Rictor. Dev Cell. 2010;18:592–604.
39. Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, Turk BE, Shaw RJ. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol Cell. 2008;30:214–26.