Identification of a novel interorgan mechanism favoring energy storage in overnutrition

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While body weight is essentially determined by the balance of energy intake and energy consumption, it is not necessarily the case that changes in daily food intakes and exercise directly reflect changes in body weight. In recent years, it has been revealed that numerous metabolic interactions between organs, which are organized by the brain, function as a feedback mechanism, and are involved in maintaining body weight homeostasis against excess energy intake. On the other hand, since obesity has seen an explosive increase in this age of plenty, there must be other interactions between organs working as feedforward mechanisms favoring weight gain. However, no such interaction has yet been demonstrated. Recently, we discovered a new interorgan neural network, from the liver, which may represent the feedforward mechanism.[1] Under conditions of excessive energy intake, changes in glucose metabolism occur in the liver with increased expression of hepatic glucokinase (GK) and the induction of neuronal signal transmission via the afferent vagus nerve. These signals are received by the medulla and result in inactivation of sympathetic nerve to brown adipose tissue (BAT), thereby suppressing thermogenesis in BAT and promoting adiposity. Furthermore, the efficacy of the liver-to-BAT interaction differs among mouse strains and these differences may contribute to determining the obesity predispositions of various strains. In conclusion, this novel interorgan neuronal relay system functions to suppress energy expenditure when energy intake is increased, and thus, is considered to be a thrifty mechanism operating on the whole body level. During periods when sufficient food was not always available, this system worked in favor of survival. However, in the current age of plenty, it is assumed to work as a mechanism flipping a metabolic switch toward obesity.

Obesity is a common cause of lifestyle-related diseases such as diabetes, hyperlipidemia and hypertension. Therefore, it is important to elucidate the mechanisms(s) regulating body weight. Body weight homeostasis requires that a quickly available energy source is stored in the body under uncertain circumstances in which food cannot always be obtained. On the other hand, excessive accumulation of fat leads to reduced activity, which is disadvantageous in escaping from predators. Therefore, based on the stored and supplied amounts of energy, eating behavior and energy expenditure must be accurately regulated. This body weight regulation is achieved by multiple mechanisms which consist of interorgan/tissue communications.[2] For these communications, humoral factors, including adipokines, are known to be important. For instance, leptin is secreted from white adipocytes according to the quantity of stored triglyceride and suppresses food intake and increases energy expenditure via the hypothalamus. Thus, the leptin system is a major feedback mechanism working against excessive energy intake and thereby functions to maintain body weight homeostasis.[3]

In addition to humoral factors such as leptin, recent studies have demonstrated that the neuronal network plays

an important role in body weight homeostasis as a feedback mechanism preventing excessive energy intake and enhancing energy expenditure.[4] We also revealed that afferent neuronal signals are transmitted according to alterations in fat accumulation in intraabdominal organs, such as adipose tissue and the liver, to the brain, leading to suppressed food intake and enhanced energy expenditure, respectively.[5,6] If these feedback mechanisms consisting of humoral and neuronal pathways were to function without fail, body weight could not keep rising and obesity would never develop. However, the incidence of obesity is actually rising worldwide at an alarming rate. Therefore, there must be a feedforward mechanism(s) which perturbs the feedback mechanisms, thereby initiating body weight gain when energy intake is excessive.

GK catalyzes the first and rate-limiting step of glycolysis, i.e., the glucose to glucose-6-phosphate reaction in hepatocytes and its expression in the liver is strongly induced by insulin. We observed that hepatic GK expression was upregulated by a high-fat diet prior to obesity development. Several studies have shown that liver-specific GK overexpression actually affects body weights in mice, although the results are seemingly inconsistent; weight gain has been demonstrated,[7] while weight loss has also been reported.[8,9] Collectively, we speculated that hepatic GK upregulation followed by enhanced glucose metabolism influences systemic energy metabolism but how hepatic GK expression affects energy metabolism remained unclear. Therefore, in our recent study,[1] we enhanced hepatic glycolysis by inducing selective expression of GK in the mouse liver using an adenovirus-mediated gene transfer system, and then examined the effects of changes in liver glucose metabolism on the whole-body energy balance as well as energy expenditure in BAT, which is known to be responsible for thermogenesis. BAT specifically expresses uncoupling protein 1 (UCP1), a thermogenic molecule, and consumes energy as heat through the uncoupling of oxidative phosphorylation. Until recently, BAT was considered to exist in rodents and human neonates but not in human adults. However, recent reports have demonstrated that functionally active BAT is present in adult humans[10] and that the amount and activity of BAT correlate inversely with body weight.[11]

First, we expressed GK in the livers of mice receiving a normal diet (GK mice) and analyzed the interorgan network originating from the liver. Seven days after adenovirus transfer, as expected, increased glycogen accumulation was observed. Surprisingly, we found that expressions of thermogenic molecules such as UCP1 were decreased in BAT, and that these decreases were actually accompanied by suppressed thermogenesis. In addition, metabolic signals triggered by hepatic GK induction were transmitted to the brain via the afferent vagal nerve, leading to inactivation of sympathetic nerve to BAT, thereby suppressing adaptive thermogenesis in BAT. Thus, the liver–brain–BAT system reduces energy expenditure, in response to increased energy intake, on the whole-body level, indicating that this system functions as a feedforward mechanism favoring energy storage (**Fig. 1**).

When examining the effects of alterations in thermogenesis, especially BAT thermogenesis, on body weights of mice, environmental temperatures are an important consideration.[12,13] Thermogenesis in individuals can be divided into two types, "non-shivering thermogenesis (mainly carried out by BAT)" and "shivering thermogenesis (mainly carried out by skeletal muscle)". It should be noted that the non-shivering thermogenesis by BAT is more efficient than thermogenesis governed by other tissues. While diet-induced adaptive thermogenesis is solely mediated in a non-shivering manner by BAT, cold-induced adaptive thermogenesis is mediated by both non-shivering and shivering mechanisms.[13] In cold (i.e., subthermoneutral) environments, extra thermogenesis, irrespective of its origin, is needed to maintain body temperature homeostasis. If BAT-derived heat is available, it is used. If it is not available, other inefficient heat sources must be used to compensate for BAT dysfunction, leading to increased energy consumption. In contrast, at thermoneutrality where no extra heat production is needed, the reduction in BAT thermogenesis directly affects whole-body energy metabolism (i.e., body weight).

Therefore, thermoneutral conditions have been used to evaluate the direct effects of BAT thermogenesis reduction on whole-body energy metabolism. Feldmann et al. clearly demonstrated the significance of thermoneutrality in evaluating the effects of BAT thermogenesis reduction on body weight using UCP1 knockout mice.[14] In their study, UCP1 knockout mice showed an obese phenotype under thermoneutral environmental conditions. This body weight gain was due to suppression of diet-induced adaptive thermogenesis by BAT. On the other hand, UCP1 knockout mice did not show an obese phenotype, instead having reduced body weight gain, in subthermoneutral environments.[14] Thus, to maintain body temperature, more energy is consumed by inefficient thermogenesis involving tissues other than BAT, resulting conversely in suppression of body weight gain.

In addition to UCP1 knockout mice, these paradoxical body weight changes affected by environmental temperatures are also observed in other mouse models featuring reduced thermogenesis in BAT, such as type II 5'-deiodinase[15] and thyroid hormone receptor-α knockout mice.[16] These results indicate that marked suppression of BAT thermogenesis commonly suppresses body weight gain under subthermoneutral conditions. Moreover, these environmental temperature-dependent body weight alterations are also observed in GK mice. These results further support the marked reduction in BAT thermogenesis in GK mice. As aforementioned above, however, effects of liver-specific GK overexpression on body weight were seemingly inconsistent among several studies.[7-9] In our study,[1] opposite impacts of hepatic GK induction on adiposity were dependent on environmental temperature. Therefore, although more precise examinations will be required, the difference in environmental temperatures may resolve the previously reported conflicting results.

Whether mice should be housed under thermoneutral conditions to best mimic the thermal conditions experienced by humans has been a point of argument.[17] In discussing this point, we should keep in that the effects of ambient temperature on features of energy metabolism, such as food intake and oxygen consumption, depend
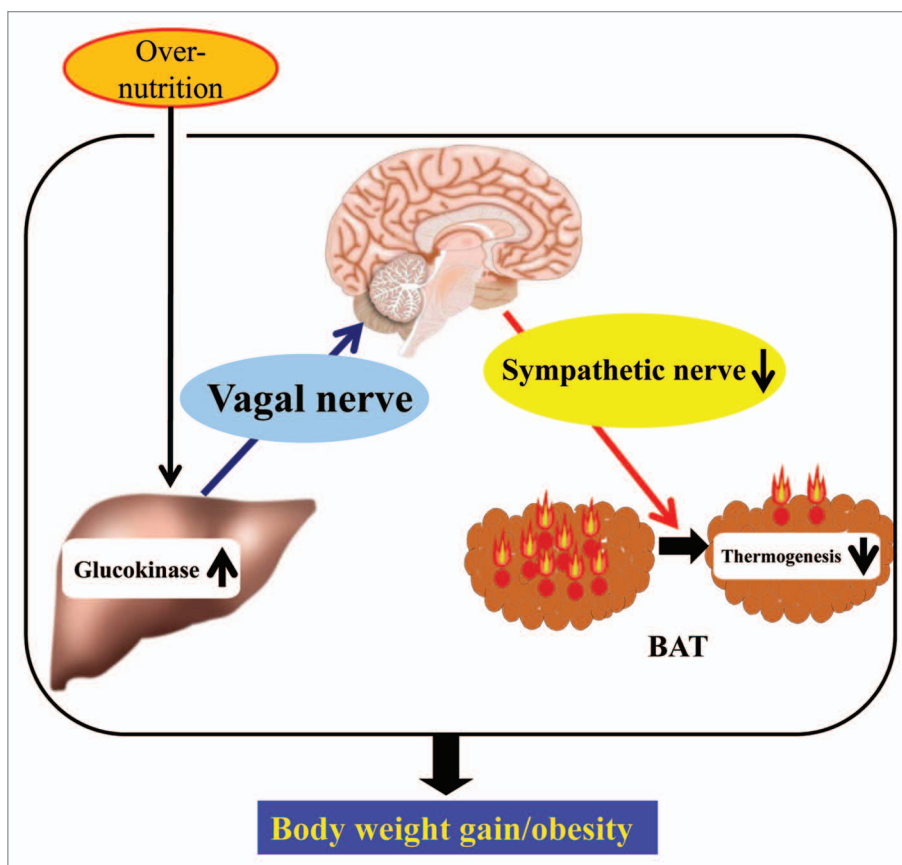
Figure 1. A schematic presentation of the novel "thrifty" mechanism operating on the whole-body level. Hepatic GK expression via a neuronal relay system, consisting of afferent vagal and efferent sympathetic nerves, suppresses BAT adaptive thermogenesis. This system may function as a feedforward mechanism favoring energy storage under conditions of excess energy intake.

on body surface area/mass ratios. In fact, both food intake and oxygen consumption were much higher in mice kept under subthermoneutral conditions (23 °C), with each being about 1.6-fold higher than in mice under thermoneutral conditions (30 °C).[18] In contrast, in rats, food intake and oxygen consumption under subthermoneutral conditions (23 °C) were similar to those under thermoneutral conditions (30 °C).[18] These results suggest that animals having much smaller surface area/body mass ratios, such as humans, are essentially free of thermal stress, even under subthermoneutral conditions. Consequently, when using murine models, thermoneutral conditions should be maintained so as to mimic human physiology, since thermal stress-free conditions are required for studying BAT thermogenesis.

As described above, hepatic GK expression suppressed BAT thermogenesis, resulting in weight gain under thermoneutral conditions. In addition, endogenous GK expression is upregulated in the early stage of overnutrition. Therefore, this liver–brain–BAT intertissue mechanism is considered to contribute to triggering body weight gain and flipping a metabolic switch promoting obesity. In contrast, it is well known that sympathetic outflow is increased in both obese animal models and human subjects. We previously reported that lipid accumulation induced by PPARγ expression in the liver increases sympathetic outflow and UCP1 upregulation in BAT.[6] Thus, under chronic high fat diet-fed conditions as lipids accumulate in the liver, another neuronal mechanism(s) activating sympathetic nerves may function. The possible interplay among neuronal signals in the brain under conditions of chronic overnutrition merits detailed analysis.

We further examined the relationship between the neuronal liver–brain–BAT feedforward mechanism and the leptin system, representing the humoral homeostatic feedback mechanism that works against overnutrition. In GK mice, as in controls, leptin administration altered NPY and POMC expressions in the hypothalamus and suppressed food intake. In contrast, the leptin-induced BAT adaptive thermogenesis was attenuated via sympathetic inactivation by hepatic GK expression. More detailed examinations revealed this blockade of the leptin signaling pathway to occur downstream from the hypothalamus and to suppress neuronal activity in the rostral raphe pallidus in the medulla, which contains the sympathetic premotor neurons responsible for thermogenesis in BAT. Thus, this liver–brain–BAT feedforward system suppresses the feedback mechanism, leading to marked weight gain.

Degrees of weight gain in overnutrition differ markedly among humans.[19] Among mouse strains, the degrees of weight gain in response to a high-fat diet load also differ,[20] and different degrees

of diet-induced adaptive thermogenesis are reportedly involved in weight gain differences.[21,22] Viewing these results collectively, we hypothesized that the liver–brain–BAT feedforward system may modulate obesity predisposition under conditions of over-nutrition. Therefore, we compared endogenous GK expression in the liver and UCP1 expression in BAT between obesity-prone and obesity-resistant mice after 1 wk of high-fat diet feeding. Hepatic GK expressions were more markedly enhanced in obesity-prone than in obesity-resistant mouse strains. In addition, UCP1 expression in BAT was found to correlate inversely with hepatic GK expression in these mouse strains. Furthermore, hepatic GK overexpression in obesity-resistant mice promoted weight gain, while hepatic GK knockdown in obesity-prone mice attenuated weight gain with increased BAT thermogenesis. These results demonstrate that how strongly the liver–brain–BAT system works can explain the differences among murine strains in terms of obesity predisposition.[1]

Ours is the first study to provide evidence that there is a feedforward mechanism favoring weight gain under conditions of excess energy intake. Because food supplies are often unstable in natural environments, surplus energy storage as fat is believed to work in favor of survival of the individual when starvation is an occasional threat. Therefore, this feedforward mechanism is regarded as "thrifty mechanism" operating on the whole-body level. On the other hand, in times of chronic excessive eating as seen in today's society, this system triggers weight gain and consequently may contribute to the onset of obesity. While future experiments are needed to elucidate which step(s) in the cascade of glucose metabolism in the liver leads to changes in vagal nerve activity and whether this thrifty mechanism functions in adult humans, suppression of this feedforward mechanism would potentially lead to preventive and therapeutic strategies for obesity in this era of excess.

Disclosure of Potential Conflicts of Interest

References

1. Tsukita S, Yamada T, Uno K, Takahashi K, Kaneko K, Ishigaki Y, et al. Hepatic glucokinase modulates obesity predisposition by regulating BAT thermogenesis via neural signals. Cell Metab 2012; 16:825-32; PMID:23217261; http://dx.doi.org/10.1016/j.cmet.2012.11.006
2. Yamada T, Oka Y, Katagiri H. Inter-organ metabolic communication involved in energy homeostasis: potential therapeutic targets for obesity and metabolic syndrome. Pharmacol Ther 2008; 117:188-98; PMID:18006064; http://dx.doi.org/10.1016/j.pharmthera.2007.09.006
3. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. Nature 2006; 444:847-53; PMID:17167472; http://dx.doi.org/10.1038/nature05483
4. Katagiri H, Yamada T, Oka Y. Adiposity and cardiovascular disorders: disturbance of the regulatory system consisting of humoral and neuronal signals. Circ Res 2007; 101:27-39; PMID:17615379; http://dx.doi.org/10.1161/CIRCRESAHA.107.151621
5. Yamada T, Katagiri H, Ishigaki Y, Ogihara T, Imai J, Uno K, et al. Signals from intra-abdominal fat modulate insulin and leptin sensitivity through different mechanisms: neuronal involvement in food-intake regulation. Cell Metab 2006; 3:223-9; PMID:16517409; http://dx.doi.org/10.1016/j.cmet.2006.02.001
6. Uno K, Katagiri H, Yamada T, Ishigaki Y, Ogihara T, Imai J, et al. Neuronal pathway from the liver modulates energy expenditure and systemic insulin sensitivity. Science 2006; 312:1656-9; PMID:16778057; http://dx.doi.org/10.1126/science.1126010
7. Ferre T, Riu E, Franckhauser S, Agudo J, Bosch F. Long-term overexpression of glucokinase in the liver of transgenic mice leads to insulin resistance. Diabetologia 2003; 46:1662-8; PMID:14614559; http://dx.doi.org/10.1007/s00125-003-1244-z
8. Wu C, Kang JE, Peng LJ, Li H, Khan SA, Hillard CJ, et al. Enhancing hepatic glycolysis reduces obesity: differential effects on lipogenesis depend on site of glycolytic modulation. Cell Metab 2005; 2:131-40; PMID:16098830; http://dx.doi.org/10.1016/j.cmet.2005.07.003
9. Hariharan N, Farrelly D, Hagan D, Hillyer D, Arbeeny C, Sabrah T, et al. Expression of human hepatic glucokinase in transgenic mice liver results in decreased glucose levels and reduced body weight. Diabetes 1997; 46:11-6; PMID:8971074; http://dx.doi.org/10.2337/diabetes.46.1.11
10. Saito M, Okamatsu-Ogura Y, Matsushita M, Watanabe K, Yoneshiro T, Nio-Kobayashi J, et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. Diabetes 2009; 58:1526-31; PMID:19401428; http://dx.doi.org/10.2337/db09-0530
11. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009; 360:1509-17; PMID:19357406; http://dx.doi.org/10.1056/NEJMoa0810780
12. Tschöp MH, Speakman JR, Arch JR, Auwerx J, Brüning JC, Chan L, et al. A guide to analysis of mouse energy metabolism. Nat Methods 2012; 9:57-63; PMID:22205519; http://dx.doi.org/10.1038/nmeth.1806
13. Cannon B, Nedergaard J. Nonshivering thermogenesis and its adequate measurement in metabolic studies. J Exp Biol 2011; 214:242-53; PMID:21177944; http://dx.doi.org/10.1242/jeb.050989
14. Feldmann HM, Golozoubova V, Cannon B, Nedergaard J. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. Cell Metab 2009; 9:203-9; PMID:19187776; http://dx.doi.org/10.1016/j.cmet.2008.12.014
15. Castillo M, Hall JA, Correa-Medina M, Ueta C, Kang HW, Cohen DE, et al. Disruption of thyroid hormone activation in type 2 deiodinase knockout mice causes obesity with glucose intolerance and liver steatosis only at thermoneutrality. Diabetes 2011; 60:1082-9; PMID:21335378; http://dx.doi.org/10.2337/db10-0758
16. Pelletier P, Gauthier K, Sideleva O, Samarut J, Silva JE. Mice lacking the thyroid hormone receptor-alpha gene spend more energy in thermogenesis, burn more fat, and are less sensitive to high-fat diet-induced obesity. Endocrinology 2008; 149:6471-86; PMID:18719022; http://dx.doi.org/10.1210/en.2008-0718
17. Speakman JR, Keijer J. Not so hot: Optimal housing temperatures for mice to mimic the thermal environment of humans. Mol Metab 2013; 2:5-9; http://dx.doi.org/10.1016/j.molmet.2012.10.002
18. Overton JM, Williams TD. Behavioral and physiologic responses to caloric restriction in mice. Physiol Behav 2004; 81:749-54; PMID:15234180; http://dx.doi.org/10.1016/j.physbeh.2004.04.025
19. Wijers SL, Saris WH, van Marken Lichtenbelt WD. Recent advances in adaptive thermogenesis: potential implications for the treatment of obesity. Obes Rev 2009; 10:218-26; PMID:19021870; http://dx.doi.org/10.1111/j.1467-789X.2008.00538.x
20. West DB, Boozer CN, Moody DL, Atkinson RL. Dietary obesity in nine inbred mouse strains. Am J Physiol 1992; 262:R1025-32; PMID:1621856
21. Prpic V, Watson PM, Frampton IC, Sabol MA, Jezek GE, Gettys TW. Adaptive changes in adipocyte gene expression differ in AKR/J and SWR/J mice during diet-induced obesity. J Nutr 2002; 132:3325-32; PMID:12421846
22. Surwit RS, Wang S, Petro AE, Sanchis D, Raimbault S, Ricquier D, et al. Diet-induced changes in uncoupling proteins in obesity-prone and obesity-resistant strains of mice. Proc Natl Acad Sci U S A 1998; 95:4061-5; PMID:9520493; http://dx.doi.org/10.1073/pnas.95.7.4061