Cell. Mol. Life Sci. (2009) 66:3023–3027
DOI 10.1007/s00018-009-0062-y

Cellular and Molecular Life Sciences

REVIEW

Upper intestinal lipids regulate energy and glucose homeostasis

Grace W. C. Cheung · Andrea Kokorovic · Tony K. T. Lam

Received: 29 April 2009 / Revised: 25 May 2009 / Accepted: 27 May 2009 / Published online: 10 June 2009

Abstract Upon the entry of nutrients into the small intestine, nutrient sensing mechanisms are activated to allow the body to adapt appropriately to the incoming nutrients. To date, mounting evidence points to the existence of an upper intestinal lipid-induced gut–brain neuronal axis to regulate energy homeostasis. Moreover, a recent discovery has also revealed an upper intestinal lipid-induced gut–brain–liver neuronal axis involved in the regulation of glucose homeostasis. In this mini-review, we will focus on the mechanisms underlying the activation of these respective neuronal axes by upper intestinal lipids.

Keywords Intestine · Brain · Lipid-sensing mechanisms · Food intake · Glucose production

G. W. C. Cheung and A. Kokorovic contributed equally to this review.

G. W. C. Cheung · A. Kokorovic · T. K. T. Lam
Department of Physiology, University of Toronto, Toronto M5S 1A8, Canada

T. K. T. Lam
Department of Medicine, University of Toronto, Toronto M5S 1A8, Canada

G. W. C. Cheung · A. Kokorovic · T. K. T. Lam
Toronto General Research Institute, University Health Network, Toronto M5G 1L7, Canada

T. K. T. Lam (✉)
MaRS Centre, Toronto Medical Discovery Tower, Room 10-706, 101 College Street, Toronto, ON M5G 1L7, Canada
e-mail: tony.lam@uhnres.utoronto.ca

Introduction

The gut has, of late, been receiving increasing attention due largely to its recently discovered role as the first line of metabolic defense against energy excess and glucose imbalance. Following a meal ingestion, the upper intestine senses an accumulation of long-chain fatty acids—an integral component of many dietary fats—and sends signals to the central nervous system (CNS) to regulate food intake [1], and more recently revealed, glucose production [2]. The focus of this mini-review is on the underlying mechanisms responsible for relaying the lipid-induced signal to the CNS, and the subsequent attenuation of food intake and glucose production that ensues.

Gut–brain axis

Over the past decades, accumulating evidence suggests that upper intestinal lipids suppress food intake in rats and humans through a neuronal network [3–7]. As lipids enter the duodenum, lipids in the form of triglycerides are hydrolyzed by lipases into fatty acids and glycerol. Previous studies in humans demonstrated that the inhibition of gastrointestinal lipases reduced the lipid-induced satiation, suggesting that the hydrolysis of lipids into fatty acids is essential to inhibit food intake [3, 4]. With the establishment that the generation of fatty acids is a required step in the lipid-induced satiation, some studies have examined whether fatty acids per se are sufficient to induce satiation. It was found that intraduodenal fatty acids can suppress energy intake in rats and humans [8–12]. However, the length of the acyl chain of the fatty acids is an important factor in eliciting the satiation effect. In particular, only long-chain fatty acids (LCFAs) with 12 or more carbons

can suppress energy intake [8–10], whereas short and medium chain fatty acids with 11 or fewer carbons are unable to elicit the same effect [11, 12]. As LCFAs accumulate in the duodenum, they stimulate the release of cholecystokinin (CCK) from I cells that line the mucosa of the duodenum [13].

Cholecystokinin is a peptide hormone that has been shown to be directly involved in the regulation of energy balance. As a mediator of the intestinal-lipid-induced satiety effect, exogenous CCK has also been shown to suppress food intake in rodents, primates and humans [14–22]. Evidence suggests that lipid-induced CCK mediates the satiety effect through a neuronal network [5, 23]. There are two types of CCK receptors: CCK-A and CCK-B receptors, which reside in the periphery (predominantly in the gastrointestinal system) and brain, respectively [1]. The binding of CCK to CCK-A receptors is essential in satiation since inhibition of CCK-A receptors by both pharmacological and genetic means attenuated the lipid-induced inhibitory effects on food intake [3, 6, 7, 10]. Together, these studies reveal that upper intestinal lipids trigger satiation via the mediation of CCK (Fig. 1).

Moreover, the intraduodenal co-infusion of lipids with tetracaine, a local anesthetic that inhibits neuronal activation, prevented the upper intestinal lipid-induced satiation effects. The failure of upper intestinal lipids to elicit satiation in the presence of tetracaine suggests that neuronal activation in the duodenum is required for upper intestinal lipids to suppress feeding behavior [5]. Interestingly, vagal afferent fibers have been found in the lamina propria of the mucosa [24], and CCK-A receptors have been located on capsaicin-sensitive vagal afferents [25, 26]. Collectively, it is plausible that lipid-induced CCK acts through a paracrine action by binding to CCK-A receptors on the vagal afferents innervating the duodenum. Furthermore, the involvement of the vagus nerve has been supported by the finding that subdiaphragmatic vagotomy abolished the ability of upper intestinal lipids to suppress feeding [27]. Consistent with the finding that CCK-A receptors are located on capsaicin-sensitive vagal afferents, the capsaicin-sensitive afferent branch of the vagus nerve was found to be responsible for the lipid-induced satiation effects [23]. Together, upper intestinal lipids may activate CCK-A receptors on the C-fibers of the subdiaphragmatic vagal afferents innervating the duodenum to induce satiation (Fig. 1).

By activating the subdiaphragmatic vagus nerve, nutrient signals arrive at the nucleus of the solitary tract (NTS) and activate the neurons in this hindbrain region [23]. Upper intestinal lipids could therefore suppress food intake by activating the NTS via the vagus nerve. Although the existence of a lipid-induced gut–brain axis is now clear, mechanisms at various levels remain to be elucidated. It is also important to point out that there are at least two emerging classes of lipids that could potentially act in the intestine to regulate food intake: The first is the PPAR-alpha ligand oleoylethanolamide, which suppresses feeding [28, 29], and the second are the cannabinoid receptor agonists anandamide and 2-arachidonoylglycerol, which increase feeding [30]. The underlying mechanisms that mediate the feeding control of these two classes of lipids remain to be uncovered, but the neuronal network and CCK signaling may play an important role [31–33].

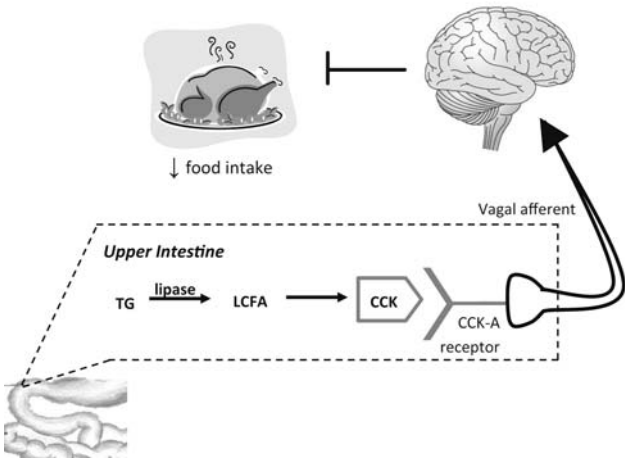

Fig. 1 Lipid-induced gut-brain axis. Lipids enter the upper intestine in the form of triglycerides (*TG*). TG is then digested by lipases to form long-chain fatty acids (*LCFA*). The accumulation of LCFA leads to the release of cholecystokinin (*CCK*). As CCK is released, it binds to CCK_A receptors on the vagal afferents. Ultimately, nutrient signals from the upper intestine will reach the nucleus of the solitary tract in the brain to suppress food intake

Brain–liver axis

Given that signals initiated in the upper intestine transmit input to the brain, it is important to understand the signaling that takes place at the level of the brain. It has been demonstrated that the hypothalamus can sense hormones and nutrients, including insulin [34] and fatty acids [35], respectively, to regulate hepatic glucose production and maintain glucose homeostasis. It does so by triggering vagal efferent signals to the liver in what is termed the brain–liver axis.

The effects of insulin on glucose homeostasis were initially thought to be exerted exclusively on peripheral organs. However, recent evidence has implicated the brain as being an important insulin-sensing organ. Studies have shown that direct administration of insulin into the hypothalamus decreases hepatic glucose production, an effect that requires the activation of ATP-sensitive potassium channels [34, 36]. The decrease in glucose production is attributed to the activation of hepatic vagal efferent fibers.

In animals with selective hepatic branch vagotomy, the effect of insulin on glucose production could not be recapitulated [36]. Specifically, the insulin-induced decreases in gluconeogenesis and liver enzyme mRNA expression involved in hepatic glucose output were abolished in animals with hepatic vagotomy [36].

Direct infusion of the LCFA oleic acid into the third cerebral ventricle decreases hepatic glucose production [35]. Consistently, the inhibition of hypothalamic lipid oxidation increases long-chain fatty acyl-coenzyme A (LCFA-CoA) levels and lowers glucose production [37]. Similar to central insulin sensing, the fatty acid-mediated decrease in glucose production requires the activation of ATP-sensitive potassium channels [35, 38]. Moreover, it has been determined that vagal efferent signals to the liver are required for the effect of hypothalamic fatty acids on glucose production [38]. In animals treated with selective hepatic vagotomy, central increases in lipid did not suppress glucose production and, analogous to the insulin studies, hepatic glucose fluxes and liver enzyme expression remained unchanged [38].

From the previous studies, it is evident that hypothalamic fatty acid sensing in part maintains glucose homeostasis. These studies, however, administered LCFA directly into the hypothalamus, thereby raising the concern of whether the effects are of physiological relevance. Hence, studies were conducted to test the effects of circulating fatty acids on glucose homeostasis. In the presence of a physiological rise in the levels of circulating lipids, inhibition of hypothalamic fatty acid esterification to generate LCFA-CoA with triacsin C administration or hepatic vagotomy negated the inhibitory effects of hypothalamic lipids on glucose production [39]. This led to a rise in glucose production and a disruption in glucose homeostasis in the presence of an elevation in circulating lipids. In summary, hypothalamic sensing of circulating lipids is required to counteract the direct lipid-induced stimulation on hepatic gluconeogenesis [40]. The physiological relevance of hypothalamic lipid-sensing mechanisms in glucose regulation during fasting remains unclear. However, it is important to note that in spite of the elevation in circulating fatty acids during fasting, the level of hypothalamic LCFA-CoA (which is an important signal to decrease hepatic glucose production; see above) is decreased [41]. Thus, the drop in hypothalamic LCFA-CoA levels during fasting should shut off the restraining effect on hepatic glucose production by the brain and lead to a rise in glucose production. This working hypothesis clearly remains to be tested.

Together with the aforementioned results, these data propose a role for hypothalamic LCFA as critical regulators of glucose production, an effect that is mediated via the activation of the efferent branch of the hepatic vagal nerve.

Gut–brain–liver axis

With the findings that gut–brain and brain–liver axes exist to regulate energy and glucose homeostasis, respectively, our laboratory has recently tested the existence of a lipid-induced gut–brain–liver neuronal network in the regulation of glucose homeostasis [2]. First, we administered lipid to the duodenum, and a reduction of glucose production was observed. After establishing that upper intestinal lipids can regulate glucose homeostasis by suppressing glucose production, we examined the mechanisms involved. Co-infusions of lipids with triacsin C or tetracaine into the duodenum and vagal deafferentation experiments were performed to demonstrate that the acute accumulation of the lipid metabolite in the duodenum, LCFA-CoA, is required to activate vagal signaling and suppress glucose production. By verifying that the vagus nerve plays a role in mediating the lipid-induced glucose production suppression effect, we investigated whether vagal signals from the intestine are sent to the NTS. Upper intestinal lipids failed to suppress glucose production when we prevented the activation of *N*-methyl D-aspartate (NMDA) receptors in the NTS, providing evidence that NTS NMDA receptors are required for gut lipid-induced glucose production suppression effect. Lastly, a hepatic vagotomy was performed to demonstrate that upper intestinal lipid signals are relayed from the NTS to the liver via the hepatic vagal innervation. Altogether, these experiments support the existence of an upper intestinal lipid-induced gut–brain–liver neuronal axis (Fig. 2), which represents one of the first lines of metabolic defenses against nutrient excess to provide metabolic balance by down-regulating glucose production on nutrient exposure.

Various mechanisms remain to be elucidated to gain a complete understanding of how upper intestinal lipids regulate glucose homeostasis through the intestine–brain–liver neuronal network. Nonetheless, in combination with the previously mentioned gut–brain neuronal axis in the regulation of energy homeostasis, lipid-induced activations of the gut–brain and gut–brain–liver neuronal networks allow transient control of energy and glucose homeostasis upon the ingestion of lipids.

Effect of high-fat diets

Although both the gut-brain and gut-brain–liver neuronal axes play a role in down-regulating energy and glucose homeostases, respectively, these two neuronal networks seem to be malfunctioning in response to high-fat feeding.

Interestingly, despite that upper intestinal lipids can induce satiation through the gut–brain neuronal network in normal rodents and humans, it was observed that in rats fed

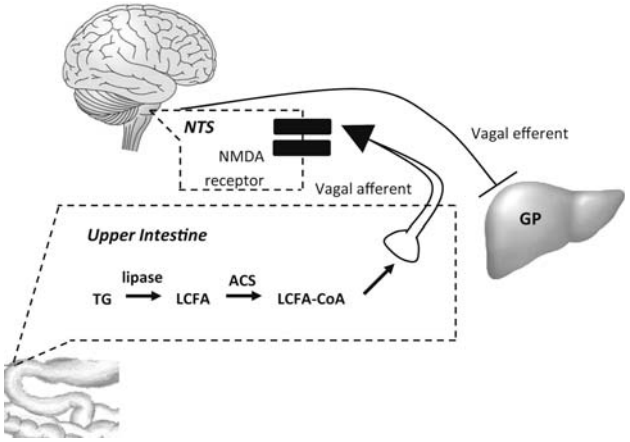

Fig. 2 Lipid-induced gut–brain–liver axis. As lipids enter the upper intestine in the form of triglycerides (*TG*), TG molecules are being digested by lipases. The digestion of TG leads to the release of free fatty acids. In particular, long-chain fatty acids (*LCFA*) are esterified into long-chain fatty acyl-coenzyme A (*LCFA-CoA*) by acyl-coenzyme A synthetase (*ACS*). The accumulation of LCFA-CoA will result in the activation of vagal afferents innervating the duodenum. The activation of the vagal afferent leads to the stimulation of *N*-methyl D-aspartate (*NMDA*) receptors in the nucleus of the solitary tract (*NTS*) of the brain. The NTS will then relay signals to the liver through the hepatic vagal efferent and suppress glucose production (*GP*) ultimately

with high-fat diets for 3 weeks, they had diminished sensitivities to intestinal LCFA-induced satiation [42]. The amount of reduction in the ability of LCFA to inhibit further food intake was dependent on the fat content of diet [42], meaning a higher fat content was associated with more impairment in the ability of intestinal LCFA to inhibit food intake. This observation suggests that the overconsumption of lipids may actually lead to an impairment of the gut-brain neuronal network that regulates energy homeostasis, such that duodenal fatty acids may no longer suppress food intake in individuals who are adapted to high-fat diets. Moreover, intraduodenal LCFA infusion failed to increase neuronal activations in the NTS in high-fat diet-fed rats (at least 2 weeks) as opposed to low-fat diet-fed rats [43]. Interestingly, the levels of oleylethanolamide, anandamide and 2-arachidonoylglycerol in the intestine are also affected in obese Zucker rats as well as rats that are fed with a high-fat diet for 1 week [44, 45]. Hence, the functioning of the lipid-induced gut–brain neuronal network that regulates energy balance seems to be defected in response to high-fat feeding. Similarly, the lipid-induced gut–brain–liver neuronal network in the regulation of glucose homeostasis also seems to be impaired following the adaptation to high-fat diets. In rats fed with high-fat diets in as little as 3 days, intraduodenal lipid infusion failed to suppress glucose production [2]. Future studies are required to dissect the underlying mechanisms responsible for the deleterious effects on duodenal lipids to regulate energy and glucose homeostasis in response to high-fat feeding.

In summary, upper intestinal lipids regulate energy and glucose homeostasis through the activation of the gut-brain and gut-brain-liver neuronal circuitries, respectively. However, the functioning of these neuronal circuitries may become defective in response to high-fat feeding. Therefore, future directions involve the elucidation of the complete mechanisms in these neuronal circuitries will increase the understanding of glucose and energy homeostatic regulation as it pertains to obesity and diabetes research.

Acknowledgments T. Lam is supported by grants from the Canadian Institutes of Health Research (CIHR, MOP-82701 and 86554). G. Cheung is supported by a graduate studentship from the Banting and Best Diabetes Centre at the University of Toronto (BBDC). A. Kokorovic is supported by a grant from the BBDC. T. Lam holds the John Kitson McIvor Chair in Diabetes Research at the Toronto General Research Institute and the University of Toronto. We apologize to colleagues whose work has not been specifically referenced due to space limitations.

References

1. Cummings DE, Overduin J (2007) Gastrointestinal regulation of food intake. J Clin Invest 117:13–23
2. Wang PY, Caspi L, Lam CK, Chari M, Li X, Light PE, Gutierrez-Juarez R, Ang M, Schwartz GJ, Lam TK (2008) Upper intestinal lipids trigger a gut–brain–liver axis to regulate glucose production. Nature 452:1012–1016
3. Matzinger D, Degen L, Drewe J, Meuli J, Duebendorfer R, Ruckstuhl N, D'Amato M, Rovati L, Beglinger C (2000) The role of long chain fatty acids in regulating food intake and cholecystokinin release in humans. Gut 46:688–693
4. Feinle C, O'Donovan D, Doran S, Andrews JM, Wishart J, Chapman I, Horowitz M (2003) Effects of fat digestion on appetite, APD motility, and gut hormones in response to duodenal fat infusion in humans. Am J Physiol Gastrointest Liver Physiol 284:G798–G807
5. Greenberg D, Smith GP, Gibbs J (1990) Intraduodenal infusions of fats elicit satiety in sham-feeding rats. Am J Physiol 259:R110–R118
6. Lieverse RJ, Jansen JB, Masclee AA, Rovati LC, Lamers CB (1994) Effect of a low dose of intraduodenal fat on satiety in humans: studies using the type A cholecystokinin receptor antagonist loxiglumide. Gut 35:501–505
7. Matzinger D, Gutzwiller JP, Drewe J, Orban A, Engel R, D'Amato M, Rovati L, Beglinger C (1999) Inhibition of food intake in response to intestinal lipid is mediated by cholecystokinin in humans. Am J Physiol 277:R1718–R1724
8. Covasa M, Ritter RC (2001) Attenuated satiation response to intestinal nutrients in rats that do not express CCK-A receptors. Peptides 22:1339–1348
9. Feltrin KL, Little TJ, Meyer JH, Horowitz M, Rades T, Wishart J, Feinle-Bisset C (2007) Effects of lauric acid on upper gut motility, plasma cholecystokinin and peptide YY, and energy intake are load, but not concentration, dependent in humans. J Physiol 581:767–777
10. Schwartz GJ, Whitney A, Skoglund C, Castonguay TW, Moran TH (1999) Decreased responsiveness to dietary fat in Otsuka

Long-Evans Tokushima fatty rats lacking CCK-A receptors. Am J Physiol 277:R1144–R1151
11. Feltrin KL, Little TJ, Meyer JH, Horowitz M, Smout AJ, Wishart J, Pilichiewicz AN, Rades T, Chapman IM, Feinle-Bisset C (2004) Effects of intraduodenal fatty acids on appetite, antropyloroduodenal motility, and plasma CCK and GLP-1 in humans vary with their chain length. Am J Physiol Regul Integr Comp Physiol 287:R524–R533
12. McLaughlin J, Grazia LM, Jones MN, D'Amato M, Dockray GJ, Thompson DG (1999) Fatty acid chain length determines cholecystokinin secretion and effect on human gastric motility. Gastroenterology 116:46–53
13. Moran TH, Kinzig KP (2004) Gastrointestinal satiety signals II. Cholecystokinin. Am J Physiol Gastrointest Liver Physiol 286:G183–G188
14. Cox JE (1996) Effect of pyloric cuffs on cholecystokinin satiety. Physiol Behav 60:1023–1026
15. Gibbs J, Young RC, Smith GP (1973) Cholecystokinin elicits satiety in rats with open gastric fistulas. Nature 245:323–325
16. Gibbs J, Falasco JD, McHugh PR (1976) Cholecystokinin-decreased food intake in rhesus monkeys. Am J Physiol 230:15–18
17. Kissileff HR, Pi-Sunyer FX, Thornton J, Smith GP (1981) C-terminal octapeptide of cholecystokinin decreases food intake in man. Am J Clin Nutr 34:154–160
18. Kraly FS, Carty WJ, Resnick S, Smith GP (1978) Effect of cholecystokinin on meal size and intermeal interval in the sham-feeding rat. J Comp Physiol Psychol 92:697–707
19. Moran TH, Ameglio PJ, Schwartz GJ, McHugh PR (1992) Blockade of type A, not type B, CCK receptors attenuates satiety actions of exogenous and endogenous CCK. Am J Physiol 262:R46–R50
20. Moran TH, Baldessarini AR, Salorio CF, Lowery T, Schwartz GJ (1997) Vagal afferent and efferent contributions to the inhibition of food intake by cholecystokinin. Am J Physiol 272:R1245–R1251
21. Weatherford SC, Chiruzzo FY, Laughton WB (1992) Satiety induced by endogenous and exogenous cholecystokinin is mediated by CCK-A receptors in mice. Am J Physiol 262:R574–R578
22. Woltman T, Castellanos D, Reidelberger R (1995) Role of cholecystokinin in the anorexia produced by duodenal delivery of oleic acid in rats. Am J Physiol 269:R1420–R1433
23. Monnikes H, Lauer G, Bauer C, Tebbe J, Zittel TT, Arnold R (1997) Pathways of Fos expression in locus ceruleus, dorsal vagal complex, and PVN in response to intestinal lipid. Am J Physiol 273:R2059–R2071
24. Berthoud HR, Patterson LM (1996) Anatomical relationship between vagal afferent fibers and CCK-immunoreactive enteroendocrine cells in the rat small intestinal mucosa. Acta Anat (Basel) 156:123–131
25. Moran TH, Smith GP, Hostetler AM, McHugh PR (1987) Transport of cholecystokinin (CCK) binding sites in subdiaphragmatic vagal branches. Brain Res 415:149–152
26. Moran TH, Norgren R, Crosby RJ, McHugh PR (1990) Central and peripheral vagal transport of cholecystokinin binding sites occurs in afferent fibers. Brain Res 526:95–102
27. Sclafani A, Ackroff K, Schwartz GJ (2003) Selective effects of vagal deafferentation and celiac-superior mesenteric ganglionectomy on the reinforcing and satiating action of intestinal nutrients. Physiol Behav 78:285–294
28. Hansen HS, Diep TA (2009) *N*-acylethanolamines, anandamide and food intake. Biochem Pharmacol [Epub ahead of print]
29. Schwartz GJ, Fu J, Astarita G, Li X, Gaetani S, Campolongo P, Cuomo V, Piomelli D (2008) The lipid messenger OEA links dietary fat intake to satiety. Cell Metab 8:281–288
30. de Kloet AD, Woods SC (2009) Minireview: endocannabinoids and their receptors as targets for obesity therapy. Endocrinology 150:2531–2536
31. Gomez R, Navarro M, Ferrer B, Trigo JM, Bilbao A, Del AI, Cippitelli A, Nava F, Piomelli D, Rodriguez de FF (2002) A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. J Neurosci 22:9612–9617
32. Burdyga G, Lal S, Varro A, Dimaline R, Thompson DG, Dockray GJ (2004) Expression of cannabinoid CB1 receptors by vagal afferent neurons is inhibited by cholecystokinin. J Neurosci 24:2708–2715
33. Thabuis C, Tissot-Favre D, Bezelgues JB, Martin JC, Cruz-Hernandez C, Dionisi F, Destaillats F (2008) Biological functions and metabolism of oleoylethanolamide. Lipids 43:887–894
34. Obici S, Zhang BB, Karkanias G, Rossetti L (2002) Hypothalamic insulin signaling is required for inhibition of glucose production. Nat Med 8:1376–1382
35. Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L (2002) Central administration of oleic acid inhibits glucose production and food intake. Diabetes 51:271–275
36. Pocai A, Lam TK, Gutierrez-Juarez R, Obici S, Schwartz GJ, Bryan J, Aguilar-Bryan L, Rossetti L (2005) Hypothalamic K (ATP) channels control hepatic glucose production. Nature 434:1026–1031
37. Obici S, Feng Z, Arduini A, Conti R, Rossetti L (2003) Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. Nat Med 9:756–761
38. Pocai A, Obici S, Schwartz GJ, Rossetti L (2005) A brain–liver circuit regulates glucose homeostasis. Cell Metab 1:53–61
39. Lam TK, Pocai A, Gutierrez-Juarez R, Obici S, Bryan J, Aguilar-Bryan L, Schwartz GJ, Rossetti L (2005) Hypothalamic sensing of circulating fatty acids is required for glucose homeostasis. Nat Med 11:320–327
40. Caspi L, Wang PY, Lam TK (2007) A balance of lipid-sensing mechanisms in the brain and liver. Cell Metab 6:99–104
41. He W, Lam TK, Obici S, Rossetti L (2006) Molecular disruption of hypothalamic nutrient sensing induces obesity. Nat Neurosci 9:227–233
42. Covasa M, Ritter RC (1999) Reduced sensitivity to the satiation effect of intestinal oleate in rats adapted to high-fat diet. Am J Physiol 277:R279–R285
43. Covasa M, Grahn J, Ritter RC (2000) Reduced hindbrain and enteric neuronal response to intestinal oleate in rats maintained on high-fat diet. Auton Neurosci 84:8–18
44. Artmann A, Petersen G, Hellgren LI, Boberg J, Skonberg C, Nellemann C, Hansen SH, Hansen HS (2008) Influence of dietary fatty acids on endocannabinoid and *N*-acylethanolamine levels in rat brain, liver and small intestine. Biochim Biophys Acta 1781:200–212
45. Izzo AA, Piscitelli F, Capasso R, Aviello G, Romano B, Borrelli F, Petrosino S, Di MV (2009) Peripheral endocannabinoid dysregulation in obesity: relation to intestinal motility and energy processing induced by food deprivation and re-feeding. Br J Pharmacol [Epub ahead of print]