Disease Models & Mechanisms 5, 583-587 (2012) doi:10.1242/dmm.009902

Brain–gut–adipose-tissue communication pathways at a glance

Chun-Xia Yi[1] and Matthias H. Tschöp[1,*]

One of the 'side effects' of our modern lifestyle is a range of metabolic diseases: the incidence of obesity, type 2 diabetes and associated cardiovascular diseases has grown to pandemic proportions. This increase, which shows no sign of reversing course, has occurred despite education and new treatment options, and is largely due to a lack of knowledge about the precise pathology and etiology of metabolic disorders. Accumulating evidence suggests that the communication pathways linking the brain, gut and adipose tissue might be promising intervention points for metabolic disorders. To maintain energy homeostasis, the brain must tightly monitor the peripheral energy state. This monitoring is also extremely important for the brain's survival, because the brain does not store energy but depends solely on a continuous supply of nutrients from the general circulation. Two major groups of metabolic inputs inform the brain about the peripheral energy state: short-term signals produced by the gut system and long-term signals produced by adipose tissue. After central integration of these inputs, the brain generates neuronal and hormonal outputs to balance energy intake with expenditure.
Miscommunication between the gut, brain and adipose tissue, or the degradation of input signals once inside the brain, lead to the brain misunderstanding the peripheral energy state. Under certain circumstances, the brain responds to this miscommunication by increasing energy intake and production, eventually causing metabolic disorders. This poster article overviews current knowledge about communication pathways between the brain, gut and adipose tissue, and discusses potential research directions that might lead to a better understanding of the mechanisms underlying metabolic disorders.

[1]Institute for Diabetes and Obesity, Helmholtz Centre for Health and Environment and Technical University Munich, Munich, Germany
*Author for correspondence (matthias.tschoep@helmholtz-muenchen.de)

Introduction

For survival and reproduction, the body has developed an intricately balanced system to efficiently control energy homeostasis at multiple levels. In short, the brain continually monitors the systemic metabolic state and adjusts behavior, as well as humoral and neuronal outputs to peripheral effector organs, to ensure an appropriate energy supply. If the central nervous system (CNS) senses a caloric shortage or surplus, the brain orchestrates responses that alter food intake, nutrient partitioning and physiological functions such as hepatic glucose production, adiposity and thermogenesis. Efficient maintenance of the delicate homeostatic balance of energy, glucose and lipid metabolism largely depends on system-wide synchronicity of metabolic processes that can only be achieved by central regulatory influences and master circuits in the brain. Disruption of such synchronicity, or failure of any of the key components of this system, are common pathophysiological causes of metabolic disorders such as obesity and diabetes.

The most well-studied metabolic sensing region in the forebrain is the hypothalamus, where a number of nuclei such as the arcuate nucleus (ARC) and ventromedial hypothalamus (VMH) express high levels of receptors that bind adipokines (cell signaling molecules secreted by adipose tissue, such as leptin) and gut hormones. Central leptin resistance, one of the major causes of obesity, is caused by defective leptin sensing in these brain regions (Gautron and Elmquist, 2011). In the hindbrain, the nucleus tractus solitarius (NTS)–dorsal motor nucleus of the vagus (DMV) complex is the best-studied brain area with respect to detection of metabolic feedback, especially from the gastrointestinal system via vagal afferents or the circulation (Berthoud et al., 2006).

In this article and the accompanying poster, we provide an overview of current knowledge regarding coordinated system-wide connections that maintain energy homeostasis, highlighting how disruptions in metabolic sensing and integration between the brain, white adipose tissue (WAT) and the gastrointestinal system can contribute to metabolic disorders. Although we focus here on brain–gut–adipose-tissue communication pathways, it is important to acknowledge that other important CNS-peripheral communications (such as those involving muscle and brown adipose tissue) also contribute to energy homeostasis.

Signals to the brain from the gastrointestinal system

During embryogenesis, the parasympathetic ganglia of both the gut and the brain originate from the neural crest. This common origin could explain why many gut-secreted hormones and peptides and their receptors are also found in the brain; indeed, many hormones produced by the gastrointestinal tract are referred to as brain-gut hormones.

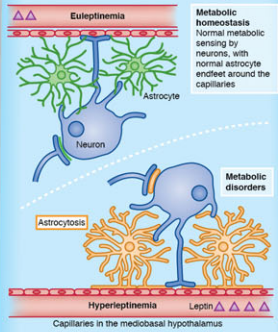
DMM Disease Models & Mechanisms dmm.biologists.org

Brain–gut–adipose-tissue communication pathways at a glance

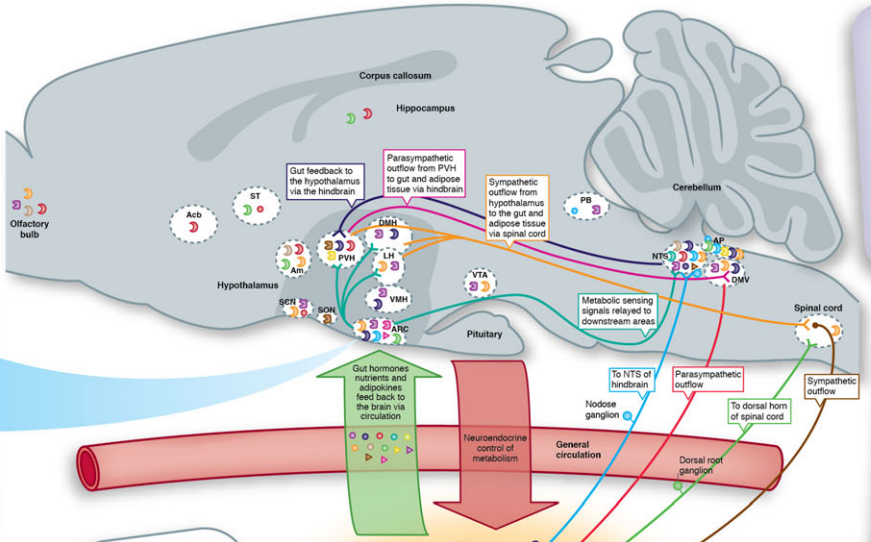
Chun-Xia Yi and Matthias H. Tschöp

Takeda

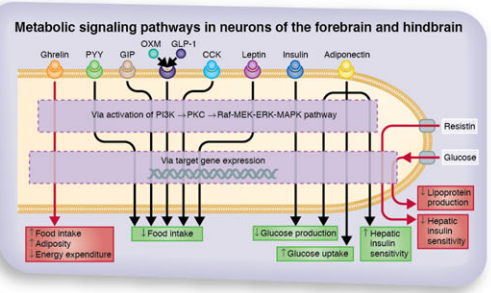
Astrocytes in the ARC are involved in metabolic hormonal sensing



Metabolic feedback in the brain involves not only neurons, but also astrocytes that are situated between neurons and the circulation. Impaired feedback responses to gut hormones or adipokines via the circulation can involve abnormalities of astrocytes. For example, exposure to a high-fat diet induces astrocytosis (an increase in astrocytic components) between blood vessels and neurons, including POMC neurons in the ARC of the mediobasal hypothalamus, which are important in metabolic sensing. This hampers the ability of POMC neurons to sense metabolic hormonal feedback, and can contribute to leptin resistance.



Metabolic signaling pathways in neurons of the forebrain and hindbrain



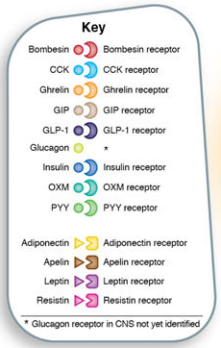
Origin and action of adipokines and gut- and pancreas-derived factors affecting metabolism

Factor	Major cell or tissue origin	Major target brain regions	Major CNS and peripheral functions
Gut- and pancreas-derived factors			
Bombesin	Stomach, ST, SCN	Acb, Am, PVH and NTS	Suppresses appetite
CCK	Intestine and brain (CCK8)	Vagal sensory terminals and hindbrain	Suppresses appetite, stimulates release of digestive enzymes and bile acids
Ghrelin	Stomach	OB, hypothalamus, midbrain (VTA), hindbrain and spinal cord	Increases appetite and adiposity, stimulates release of growth hormone
GIP	Duodenum K cells	OB, Am and NTS	Induces insulin secretion
GLP-1	Intestine	Pancreas, hypothalamus	Suppresses appetite, induces insulin secretion and promotes insulin sensitivity
Glucagon	Pancreas	No clear CNS target	Suppresses appetite and stimulates hepatic glucose production
Insulin	Pancreas	ARC and VMH	Regulates hepatic glucose production
OXM	Colon (oxyntic cells)		Suppresses appetite and inhibits meal-stimulated gastric acid secretion
PYY	Intestine and colon	ST, Am, ARC and AP	Suppresses appetite and inhibits meal-stimulated gastric acid secretion
Adipokines			
Adiponectin	Adipocytes	PVH and other location unidentified	Increases fatty acid oxidation and insulin sensitivity
Apelin	Adipocytes and stomach	PVH and SON	Suppresses appetite
Leptin	Adipocytes	Variable region in hypothalamus, midbrain (VTA) and hindbrain	Suppresses appetite and stimulates energy expenditure
Omentin	Stromal vascular cells (visceral fat)	No clear CNS target	Enhances insulin-stimulated glucose uptake
RBP4	Adipocyte and hepatocytes	No clear CNS target	Decreases insulin sensitivity
Resistin	Adipocytes (and hypothalamus?)	ARC	Inhibits liver insulin sensitivity
Visfatin	Adipocytes	No clear CNS target	Increases insulin sensitivity

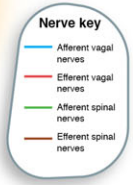
Signals to the brain from gastrointestinal system

Nutrient digestion and absorption trigger the secretion of satiety hormones, which stimulate vagal sensory nerves to provide feedback to the brain and initiate termination of feeding. Gut hormones also influence the brain via the circulation. This information is integrated at different levels and related to regulatory areas, such as the PVH of the hypothalamus, to maintain systemic metabolic homeostasis through modulating neuroendocrine and autonomic outputs. Defective or weakened signal feedback by the brain in response to satiety and nutrients can cause over-feeding and dis-inhibition of liver glucose production.

Key



Nerve key



Autonomic and neuroendocrine outputs to gastrointestinal system

The autonomic nervous system uses sympathetic and parasympathetic outflow to balance peripheral energy production and expenditure. Through projections to the lower autonomic center in the hindbrain and spinal cord, pre-autonomic neurons located in the PVH can mediate autonomic outflows to different parts of the gastrointestinal system and regulate glucose and lipid metabolism in different organs and tissues. Feedback from gut hormones to the hypothalamic autonomic control center in the PVH can also influence the neuroendocrine output via the pituitary. The neuroendocrine-derived hormones can then interact with peripheral metabolic hormones, such as insulin, in the liver and other tissues to regulate metabolism.

Signals to the brain from white adipose tissue

In addition to acting as a lipid store and energy source, WAT acts as an endocrine organ. WAT-derived adipokines (such as leptin) communicate with other peripheral organs as well as the brain to coordinate metabolic homeostasis. Under physiological conditions, adipokines inform the brain about long-term energy storage, and guide the brain's control of energy balance and long-term regulation of body weight. Impaired adipokine-feedback pathways (such as brain leptin resistance) are a key underlying mechanism of obesity and metabolic syndrome.

Autonomic and neuroendocrine outputs to white adipose tissue

The dominant autonomic-WAT connections are neuronal sympathetic outputs that initiate lipid mobilization in WAT. This sympathetic outflow can be generated from the higher autonomic center in the PVH or the lower center in the hindbrain and spinal cord. The rate of lipolysis stimulated by this 'hardwired' sympathetic outflow (mainly through releasing norepinephrine) is greater than that stimulated by epinephrine released by the adrenal medullary. Deficient stimulation of lipid mobilization caused by dysfunction of the sympathetic autonomic nervous system can contribute to obesity.

Abbreviations: Acb, nucleus accumbens; Am, amygdala; AP, area postrema; ARC, arcuate nucleus; CCK, cholecystokinin; DMH, dorsomedial hypothalamus; DMV, dorsal motor vagus nucleus; ERK, extracellular signal-regulated kinase; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; LH, lateral hypothalamus; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; NTS, nucleus of solitary tract; OXM, oxyntomodulin; PB, parabrachial nucleus; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; POMC, proopiomelanocortin; PVH, paraventricular nucleus of the hypothalamus; PYY, peptide YY; RBP4, retinol binding protein 4; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; ST, stria terminalis; VMH, ventromedial hypothalamus; VTA, ventral tegmental area; WAT, white adipose tissue.

This article is part of a special issue on obesity: see related articles in Vol. 5, issue 5 of *Dis. Model. Mech.* at http://dmm.biologists.org/content/5/5.toc

Disease Models & Mechanisms **(2012) 5, 583-587**

Under CNS guidance, the gut is in charge of energy intake. Energy homeostasis can be well maintained only when the brain-gut circuit is synchronized. This synchronization is achieved by neuronal and humoral interaction between the brain and gut. In the gastrointestinal tract, nutrient digestion and absorption trigger the secretion of gut satiety signals such as cholecystokinin (CCK), peptide YY (PYY) and glucagon like peptide-1 (GLP-1) for stimulation of vagal sensory nerves to provide feedback to the brain (Berthoud, 2008). Vagal sensory terminals also express receptors for other gut hormones and peptides that are involved in metabolic regulation. The NTS in the hindbrain is one of the major processors of vagal afferent signals, as evidenced by the finding that upper intestinal lipids inhibit hepatic glucose production through a vagal-NTS circuit (Wang et al., 2008). Additionally, gut hormones and nutrients can influence several specific brain regions and neurons via the circulation. These factors reach these regions and neurons via transporters across either the blood-brain barrier (BBB) and/or less BBB-protected circumventricular organs where neurons can sense blood-borne signals more directly (Cottrell and Ferguson, 2004; Gross, 1992). Among these regions, the NTS–area postrema (AP) complex in the hindbrain and the ARC in the forebrain are two of the major targets of gut hormones; insulin, produced in the pancreas, and ghrelin, produced in the stomach, are among the best studied gut hormones acting in these brain areas (Kojima et al., 1999; Obici et al., 2002; Pocai et al., 2005; Tschöp et al., 2000). In response to gut hormones and nutrient signals, these brain areas relay the information to other key regulatory areas, such as the paraventricular nucleus (PVH) of the hypothalamus (to maintain systemic metabolic homeostasis by modulating neuroendocrine and autonomic outputs) and the suprachiasmatic nuclei [SCN; where the central biological clock is located (Yi et al., 2006)] (to synchronize the behavior and physiology of the whole body and balance the sympathetic and parasympathetic autonomic outflow). Defective or weakened signal feedback by the brain in response to satiety and nutrients from the gut could cause over-feeding and dis-inhibition of liver glucose production, and thereby promote metabolic diseases (Berthoud, 2002).

Autonomic and neuroendocrine outputs to the gastrointestinal system

The autonomic system uses sympathetic and parasympathetic outflow to balance peripheral energy production and expenditure. Pre-autonomic neurons located in the PVH project to the lower autonomic centers in the hindbrain and spinal cord and mediate autonomic outflow to different parts of the gut system. Good examples of these autonomic-center–gut connections are the parasympathetic outflow conveying the central insulin effect on liver glucose production (Obici et al., 2002; Pocai et al., 2005), and the central glucose-sensing effect on liver lipoprotein secretion (Lam et al., 2007). In contrast, activation of the sympathetic nervous system normally antagonizes peripheral insulin sensitivity. In WAT, this antagonism triggers free fatty acid (FFA) release; in liver, it stimulates glucose production via gluconeogenesis and glycogenolysis; in muscle, it increases FFA oxidation, decreases glucose oxidation and glycogen synthesis, and results in reduced glucose uptake. Abnormal elevation of sympathetic outflow could be caused by overactivation of orexin neurons under conditions of sleep deprivation (Yi et al., 2009), lack of inhibition of neuropeptide Y neurons in the ARC in the mediobasal hypothalamus (van den Hoek et al., 2008), or dysregulation of the melanocortin receptor in diverse populations of cells in the forebrain and hindbrain (Skibicka and Grill, 2009).

Feedback from gut hormones to the hypothalamic autonomic control center in the PVH can also influence neuroendocrine output. Most of the neuroendocrine-derived hormones (e.g. epinephrine, glucocorticoids, thyroid hormones and growth hormone) also counteract insulin's action in the liver and other tissues (Yi et al., 2010).

Signals to the brain from white adipose tissue

Adipose tissue not only dynamically accumulates and releases lipids, but also acts as an endocrine organ. Adipose tissue produces adipokines that inform the brain about whole-body long-term energy-storage status, and the tissue drives the brain's control of energy balance and the long-term regulation of body weight. In terms of adipose tissue crosstalk with the CNS, the best studied adipokine is leptin (Halaas et al., 1995; Maffei et al., 1995), although adiponectin, resistin and apelin are also well studied with respect to their specific signaling pathways and functionalities in the CNS (Banerjee et al., 2004; Kadowaki et al., 2006; Pope et al., 2012; Rajala et al., 2004; Singhal et al., 2007; Steppan et al., 2001). It is not yet clear whether other adipokines, including those recently identified [such as retinol binding protein 4 (RBP4), visfatin and omentin], are involved in adipose-tissue–brain communication.

Leptin sensing in the CNS is necessary for feeding and energy expenditure regulation. It also acts as a natural antagonist of the gut hormone ghrelin. In addition to adipokines, WAT also communicates with the brain via neuronal inputs (Bartness et al., 2010b). The inability to sense leptin signals (leptin resistance) in key areas in the hypothalamus and hindbrain is thought to be one of the underlying mechanisms in the development of obesity. Generally, leptin resistance can cause the brain to misunderstand long-term energy stores and, as a result, initiate extra energy production – i.e. overfeeding (hyperphagia) and glucose production (hyperglycemia), which are typical symptoms of metabolic disorders.

Autonomic and neuroendocrine outputs to white adipose tissue

The dominant autonomic-WAT connections are neuronal sympathetic outputs that initiate lipid mobilization in WAT. This sympathetic outflow can be generated from the higher autonomic center in the PVH or the lower centers in the hindbrain and spinal cord. The rate of lipolysis stimulated by this 'hardwired' sympathetic outflow (mainly by releasing norepinephrine) is greater than that stimulated by epinephrine released by the adrenal medulla. Loss of autonomic control from the PVH [for instance by lesion of the nuclei (Foster et al., 2010)] can increase the accumulation of lipids in WAT without influencing lipid mobilization. This indicates that obesity could be caused by excess energy deposition owing to malfunction of the sympathetic autonomic nervous system.

Astrocytes in the ARC are involved in metabolic hormonal sensing

Although the CNS as a whole has been well studied with respect to its role in detecting and integrating metabolic signals, the roles

of specific cell types, such as astrocytes, have not. Astrocytes are a major class of macroglial cells that occupy up to 50% of the total brain volume. Beyond their classical roles in neuronal proliferation and differentiation, modulation of synaptic efficacy, and maintenance of ionic and neurotransmitter homeostasis, astrocytes also express adipokine receptors, including leptin receptors (Pan et al., 2008). Thus, a defect in adipokine signals to the brain would affect both neurons and astrocytes. For example, in response to a high-fat diet, astrocytes display increased expression of leptin receptors (Hsuchou et al., 2009). In addition, a high-fat diet induces astrocytosis, causing an increase in astrocytic components between the blood vessels and the anorexigenic proopiomelanocortin (POMC) neurons in the ARC of the mediobasal hypothalamus (Horvath et al., 2010). Notably, leptin's role in directing the inhibition of food intake occurs in part through signaling in POMC neurons (Seeley et al., 1997). In obesity, although leptin concentration is increased in the circulation (hyperleptinemia), the reactive astrocytes with their enlarged ensheathments hamper the POMC neurons' ability to sense leptin in blood vessels, which might contribute to leptin resistance.

In addition to astrocytes, another important non-neuronal cell type involved in metabolic sensing is the tanycyte, which resides along the wall of the third ventricle. Owing to their expression of glucose transporter 2 (García et al., 2003), tanycytes are thought to be involved in glucosensing from the cerebral spinal fluid in the brain ventricle system.

Perspectives

For accurate and timely monitoring of the peripheral metabolic state, certain areas are developed by the brain to more directly sense the metabolic feedback from the energy input site (the gastrointestinal system) and the energy storing site (WAT). These short-term and long-term inputs are integrated at different levels within the CNS, and are incorporated into neuroendocrine and autonomic outputs to balance energy intake and expenditure. A malfunction at any level in this input-output circuit could contribute to a homeostasic imbalance and contribute to metabolic disorders.

Recent progress has been made in the treatment of metabolic syndrome through a combinational strategy, integrating different gut hormones and/or adipokines, while eliminating their potential side effects (Day et al., 2009). However, there are still many unknowns that make therapeutic strategies problematic. For example, before we completely understand the mechanism of leptin resistance (for which cell specificity and intracellular signaling have yet to be clarified), leptin cannot be used to treat obesity. Another important unanswered question is how we can target the autonomic system to modulate energy homeostasis. In the past, efforts have been made to determine whether there are specific circuits between autonomic neurons and peripheral organs and tissues. For instance, are the liver and pancreas controlled by the same or different groups of pre-sympathetic neurons (Kreier et al., 2006)? Are there neurochemical characteristics specific to each subtype of pre-autonomic neuron that enable their connections to peripheral organs or tissues (Bartness et al., 2010a; Oldfield et al., 2007; Oldfield et al., 2002)? Is it possible to target specific subtypes of pre-autonomic neurons to manipulate their output to specific peripheral organs or tissues? Improved neuroanatomical and neurophysiological methods, combined with genetic tools, will be helpful in addressing these questions and will improve the outlook for anti-obesity therapy.

This article is part of a special issue on obesity: see related articles in Vol. 5, issue 5 of Dis. Model. Mech. *at http://dmm.biologists.org/content/5/5.toc.*

COMPETING INTERESTS

The authors declare that they do not have any competing or financial interests.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

REFERENCES

Banerjee, R. R., Rangwala, S. M., Shapiro, J. S., Rich, A. S., Rhoades, B., Qi, Y., Wang, J., Rajala, M. W., Pocai, A., Scherer, P. E. et al. (2004). Regulation of fasted blood glucose by resistin. *Science* **303**, 1195-1198.

Bartness, T. J., Shrestha, Y. B., Vaughan, C. H., Schwartz, G. J. and Song, C. K. (2010a). Sensory and sympathetic nervous system control of white adipose tissue lipolysis. *Mol. Cell. Endocrinol.* **318**, 34-43.

Bartness, T. J., Vaughan, C. H. and Song, C. K. (2010b). Sympathetic and sensory innervation of brown adipose tissue. *Int. J. Obes.* **34 Suppl. 1**, S36-S42.

Berthoud, H. R. (2002). Multiple neural systems controlling food intake and body weight. *Neurosci. Biobehav. Rev.* **26**, 393-428.

Berthoud, H. R. (2008). The vagus nerve, food intake and obesity. *Regul. Pept.* **149**, 15-25.

Berthoud, H. R., Sutton, G. M., Townsend, R. L., Patterson, L. M. and Zheng, H. (2006). Brainstem mechanisms integrating gut-derived satiety signals and descending forebrain information in the control of meal size. *Physiol. Behav.* **89**, 517-524.

Cottrell, G. T. and Ferguson, A. V. (2004). Sensory circumventricular organs: central roles in integrated autonomic regulation. *Regul. Pept.* **117**, 11-23.

Day, J. W., Ottaway, N., Patterson, J. T., Gelfanov, V., Smiley, D., Gidda, J., Findeisen, H., Bruemmer, D., Drucker, D. J., Chaudhary, N. et al. (2009). A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat. Chem. Biol.* **5**, 749-757.

Foster, M. T., Song, C. K. and Bartness, T. J. (2010). Hypothalamic paraventricular nucleus lesion involvement in the sympathetic control of lipid mobilization. *Obesity* **18**, 682-689.

García, M. A., Millán, C., Balmaceda-Aguilera, C., Castro, T., Pastor, P., Montecinos, H., Reinicke, K., Zúñiga, F., Vera, J. C., Oñate, S. A. et al. (2003). Hypothalamic ependymal-glial cells express the glucose transporter GLUT2, a protein involved in glucose sensing. *J. Neurochem.* **86**, 709-724.

Gautron, L. and Elmquist, J. K. (2011). Sixteen years and counting: an update on leptin in energy balance. *J. Clin. Invest.* **121**, 2087-2093.

Gross, P. M. (1992). Circumventricular organ capillaries. *Prog. Brain Res.* **91**, 219-233.

Halaas, J. L., Gajiwala, K. S., Maffei, M., Cohen, S. L., Chait, B. T., Rabinowitz, D., Lallone, R. L., Burley, S. K. and Friedman, J. M. (1995). Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* **269**, 543-546.

Horvath, T. L., Sarman, B., García-Cáceres, C., Enriori, P. J., Sotonyi, P., Shanabrough, M., Borok, E., Argente, J., Chowen, J. A., Perez-Tilve, D. et al. (2010). Synaptic input organization of the melanocortin system predicts diet-induced hypothalamic reactive gliosis and obesity. *Proc. Natl. Acad. Sci. USA* **107**, 14875-14880.

Hsuchou, H., He, Y., Kastin, A. J., Tu, H., Markadakis, E. N., Rogers, R. C., Fossier, P. B. and Pan, W. (2009). Obesity induces functional astrocytic leptin receptors in hypothalamus. *Brain* **132**, 889-902.

Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K. and Tobe, K. (2006). Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J. Clin. Invest.* **116**, 1784-1792.

Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H. and Kangawa, K. (1999). Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* **402**, 656-660.

Kreier, F., Kap, Y. S., Mettenleiter, T. C., van Heijningen, C., van der Vliet, J., Kalsbeek, A., Sauerwein, H. P., Fliers, E., Romijn, J. A. and Buijs, R. M. (2006). Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. *Endocrinology* **147**, 1140-1147.

Lam, T. K., Gutierrez-Juarez, R., Pocai, A., Bhanot, S., Tso, P., Schwartz, G. J. and Rossetti, L. (2007). Brain glucose metabolism controls the hepatic secretion of triglyceride-rich lipoproteins. *Nat. Med.* **13**, 171-180.

Maffei, M., Fei, H., Lee, G. H., Dani, C., Leroy, P., Zhang, Y., Proenca, R., Negrel, R., Ailhaud, G. and Friedman, J. M. (1995). Increased expression in adipocytes of ob RNA in mice with lesions of the hypothalamus and with mutations at the db locus. *Proc. Natl. Acad. Sci. USA* **92**, 6957-6960.

Obici, S., Zhang, B. B., Karkanias, G. and Rossetti, L. (2002). Hypothalamic insulin signaling is required for inhibition of glucose production. *Nat. Med.* **8**, 1376-1382.
Oldfield, B. J., Giles, M. E., Watson, A., Anderson, C., Colvill, L. M. and McKinley, M. J. (2002). The neurochemical characterisation of hypothalamic pathways projecting polysynaptically to brown adipose tissue in the rat. *Neuroscience* **110**, 515-526.
Oldfield, B. J., Allen, A. M., Davern, P., Giles, M. E. and Owens, N. C. (2007). Lateral hypothalamic 'command neurons' with axonal projections to regions involved in both feeding and thermogenesis. *Eur. J. Neurosci.* **25**, 2404-2412.
Pan, W., Hsuchou, H., He, Y., Sakharkar, A., Cain, C., Yu, C. and Kastin, A. J. (2008). Astrocyte leptin receptor (ObR) and leptin transport in adult-onset obese mice. *Endocrinology* **149**, 2798-2806.
Pocai, A., Lam, T. K., Gutierrez-Juarez, R., Obici, S., Schwartz, G. J., Bryan, J., Aguilar-Bryan, L. and Rossetti, L. (2005). Hypothalamic K(ATP) channels control hepatic glucose production. *Nature* **434**, 1026-1031.
Pope, G. R., Roberts, E. M., Lolait, S. J. and O'Carroll, A. M. (2012). Central and peripheral apelin receptor distribution in the mouse: species differences with rat. *Peptides* **33**, 139-148.
Rajala, M. W., Qi, Y., Patel, H. R., Takahashi, N., Banerjee, R., Pajvani, U. B., Sinha, M. K., Gingerich, R. L., Scherer, P. E. and Ahima, R. S. (2004). Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. *Diabetes* **53**, 1671-1679.
Seeley, R. J., Yagaloff, K. A., Fisher, S. L., Burn, P., Thiele, T. E., van Dijk, G., Baskin, D. G. and Schwartz, M. W. (1997). Melanocortin receptors in leptin effects. *Nature* **390**, 349.
Singhal, N. S., Lazar, M. A. and Ahima, R. S. (2007). Central resistin induces hepatic insulin resistance via neuropeptide Y. *J. Neurosci.* **27**, 12924-12932.
Skibicka, K. P. and Grill, H. J. (2009). Hypothalamic and hindbrain melanocortin receptors contribute to the feeding, thermogenic, and cardiovascular action of melanocortins. *Endocrinology* **150**, 5351-5361.
Steppan, C. M., Bailey, S. T., Bhat, S., Brown, E. J., Banerjee, R. R., Wright, C. M., Patel, H. R., Ahima, R. S. and Lazar, M. A. (2001). The hormone resistin links obesity to diabetes. *Nature* **409**, 307-312.
Tschöp, M., Smiley, D. L. and Heiman, M. L. (2000). Ghrelin induces adiposity in rodents. *Nature* **407**, 908-913.
van den Hoek, A. M., van Heijningen, C., Schröder-van der Elst, J. P., Ouwens, D. M., Havekes, L. M., Romijn, J. A., Kalsbeek, A. and Pijl, H. (2008). Intracerebroventricular administration of neuropeptide Y induces hepatic insulin resistance via sympathetic innervation. *Diabetes* **57**, 2304-2310.
Wang, P. Y., Caspi, L., Lam, C. K., Chari, M., Li, X., Light, P. E., Gutierrez-Juarez, R., Ang, M., Schwartz, G. J. and Lam, T. K. (2008). Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. *Nature* **452**, 1012-1016.
Yi, C. X., van der Vliet, J., Dai, J., Yin, G., Ru, L. and Buijs, R. M. (2006). Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. *Endocrinology* **147**, 283-294.
Yi, C. X., Serlie, M. J., Ackermans, M. T., Foppen, E., Buijs, R. M., Sauerwein, H. P., Fliers, E. and Kalsbeek, A. (2009). A major role for perifornical orexin neurons in the control of glucose metabolism in rats. *Diabetes* **58**, 1998-2005.
Yi, C. X., la Fleur, S. E., Fliers, E. and Kalsbeek, A. (2010). The role of the autonomic nervous liver innervation in the control of energy metabolism. *Biochim. Biophys. Acta* **1802**, 416-431.

Forthcoming DMM articles

For articles published online ahead of print see http://dmm.biologists.org/content/early/recent
Sign up for email alerts (eToC) at http://dmm.biologists.org/cgi/alerts/etoc

New Research Online

- **A mathematical model of weight loss under total starvation and implications of the genetic architecture of the modern obesity epidemic for the thrifty-gene hypothesis.** John R. Speakman and Klaas R. Westerterp
- **Age-related changes in core body temperature and activity in triple-transgenic Alzheimer's disease (3xTgAD) mice.** Elysse M. Knight, Timothy M. Brown, Sarah Gümüsgöz, Jennifer C. M. Smith, Elizabeth J. Waters, Stuart M. Allan and Catherine B. Lawrence
- **Mutation of *sec63* in zebrafish causes defects in myelinated axons and liver pathology.** Kelly R. Monk, Matthew G. Voas, Clara Franzini-Armstrong, Ian S. Hakkinen and William S. Talbot

Forthcoming Review Articles

- **Clinical Puzzle: Do stroke models model stroke?** Philipp Mergenthaler and Andreas Meisel
- **Primer: Zebrafish models flex their muscles to shed light on muscular dystrophies.** Joachim Berger and Peter D. Currie
- **Perspective: Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases.** Jean E. Vance