SYMPOSIUM REPORT

Hypothalamic leptin regulation of energy homeostasis and glucose metabolism

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Growing evidence suggests that food intake, energy expenditure and endogenous glucose production are regulated by hypothalamic areas that respond to a variety of peripheral signals. Therefore, in response to a reduction in energy stores or circulating nutrients, the brain initiates responses in order to promote positive energy balance to restore and maintain energy and glucose homeostasis. In contrast, in times of nutrient abundance and excess energy storage, key hypothalamic areas activate responses to promote negative energy balance (i.e. reduced food intake and increased energy expenditure) and decreased nutrient availability (reduced endogenous glucose production). Accordingly, impaired responses or 'resistance' to afferent input from these hormonal or nutrient-related signals would be predicted to favour weight gain and insulin resistance and may contribute to the development of obesity and type 2 diabetes.

(Received 30 April 2007; accepted after revision 19 June 2007; first published online 21 June 2007)
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The hypothalamus is a brain region thought to play a critical role in the regulation of energy homeostasis. Early support for a central role of the hypothalamus in feeding emerged from lesioning studies. Lesions of the ventromedial hypothalamus were shown to cause hyperphagia and obesity (Hetherington & Ranson, 1940) while lesions of the lateral hypothalamus caused reduced food intake and leanness (Anand & Brobeck, 1951). Since then, a large and compelling body of evidence, first hypothesized by Kennedy over 50 years ago (Kennedy, 1953), suggests that body adiposity is regulated by circulating factors that are released in proportion to body fat mass and act in the brain to maintain energy balance. Two hormones postulated to act as these 'adiposity' signals are insulin and leptin. Both hormones circulate at levels proportional to body fat (Bagdade *et al.* 1967; Considine *et al.* 1996) and interact with their respective receptors to regulate food intake and energy expenditure (Baskin *et al.* 1988, 1999). Central administration of either hormone reduces food intake and body weight (Woods *et al.* 1979; Campfield *et al.* 1995) while conversely, deficiency of either hormone results in hyperphagia (Zhang *et al.* 1994; Sipols *et al.* 1995). Recent evidence suggests, however, that in addition to playing a critical role in the regulation of energy homeostasis, insulin and leptin may also play an important role in the hypothalamic control of glucose metabolism (Fig. 1).

Hypothalamic insulin action and control of peripheral glucose metabolism

Well known for its effects on peripheral tissues, the pancreatic hormone insulin also regulates blood glucose levels through its action in the brain. Support for this assertion stems in part, from mice with neuron-specific deletion of either the insulin receptor or insulin receptor substrate-2 (IRS-2), an intracellular mediator of insulin signalling. These mice display a mildly obese, hyperphagic and insulin-resistant phenotype (Bruning *et al.* 2000; Kubota *et al.* 2004; Lin *et al.* 2004) establishing a requirement for neuronal insulin signalling in energy homeostasis and glucose metabolism. Furthermore, rescue of insulin receptor function selectively in liver and pancreatic beta-cells prevents the development of diabetes in insulin receptor-deficient mice when combined with concomitant expression of insulin receptor in brain (Okamoto *et al.* 2004). In rats, infusion of insulin into either the 3rd ventricle or directly into mediobasal hypothalamus (in the area of the arcuate nucleus (ARC)) reduces hepatic gluconeogenesis by increasing liver insulin sensitivity (Obici *et al.* 2002*c*). Intrahypothalamic

This report was presented at *The Journal of Physiology* Symposium on Obesity and the central nervous system, Washington, DC, USA, 1 September 2007. It was commissioned by the Editorial Board and reflects the views of the author.

 DOI: 10.1113/jphysiol.2007.135590

insulin infusion also improves insulin sensitivity in mice (Inoue *et al.* 2006). Similarly, increasing hypothalamic phosphatidylinositol 3-kinase (PI3K, a major intracellular mediator of insulin action) signalling by overexpression of either IRS-2 (which links insulin receptors to PI3K) or the PI3K target, protein kinase B (PKB/Akt, an enzyme activated by PI3K) increases peripheral insulin sensitivity in rats with uncontrolled diabetes induced by streptozotocin (STZ-DM) (Gelling *et al.* 2006). Combined with evidence that both antisense 'knockdown' of insulin receptors in the area of the ARC and local infusion of a PI3K inhibitor cause peripheral insulin resistance in rats (Obici *et al.* 2002*a*,*c*; Gelling *et al.* 2006), these data collectively implicate insulin signalling in the CNS for the regulation of both body weight and glucose metabolism.

The mechanism by which insulin action in the brain lowers plasma glucose levels appears to involve activation of ATP-sensitive potassium (K_{ATP}) channels on ARC neurons (Obici *et al.* 2002*c*; Pocai *et al.* 2005*a*). This conclusion stems from studies in which the ability of either intracerebroventricular (I.C.V.) or systemic insulin administration to inhibit hepatic glucose production (GP) is prevented by selective administration of a K_{ATP} channel blocker (glybenclamide) into the ARC. Conversely, local infusion of a K_{ATP} channel opener into the ARC mimics the effect of insulin on endogenous GP, suggesting that circulating insulin inhibits GP, at least in part, via a mechanism that involves activation of hypothalamic K_{ATP} channels. Since the ability of insulin to suppress endogenous GP is impaired in mice lacking the sulphonylurea receptor 1 subunit (SUR1) (Pocai *et al.* 2005*a*), activation of K_{ATP} channels in the mediobasal hypothalamus appears to be both necessary and sufficient to explain the central effects of insulin on hepatic GP.

In addition to the ARC, the hypothalamic ventromedial nucleus (VMN) is implicated in the physiological control of both glucose metabolism and energy balance. Szabo and colleagues showed in the 1980s that microinjection of insulin into the VMN lowers blood glucose levels via an autonomic mechanism involving the vagus nerve (Iguchi *et al.* 1981). Subsequently, leptin administration into the VMN was shown to markedly increase glucose uptake into skeletal muscle and adipose tissue (Haque *et al.* 1999; Minokoshi *et al.* 1999), further implicating VMN neurons in the control of peripheral insulin action, and recent studies established that leptin signalling in VMN neurons is required for intact control of energy homeostasis (using Cre-loxP technology to delete leptin receptors from these cells) (Dhillon *et al.* 2006). The VMN is enriched in 'glucose-sensing' neurons (Song & Routh, 2005; Kang *et al.* 2006) that are essential for autonomic and hormonal responses to hypoglycaemia (McCrimmon *et al.* 2005; Tong *et al.* 2007) and this glucose-sensing function is dependent on K_{ATP} channel activation (McCrimmon *et al.* 2005), similar to the effects of both insulin and leptin on ARC neurons (Spanswick *et al.* 2000; Pocai *et al.* 2005*a*).

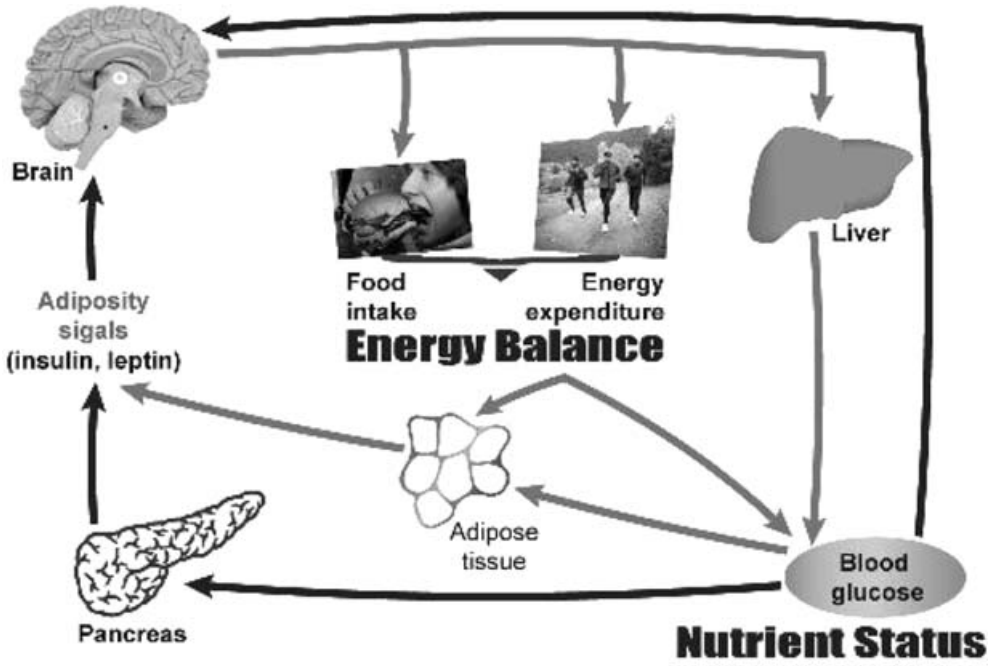

Figure 1. Model depicting the central control of energy homeostasis and glucose metabolism
Neuronal systems sense input from adiposity signals (e.g. insulin and leptin) and nutrient-related signals (FFAs) and activate responses to regulate food intake, energy expenditure and hepatic glucose production (adapted from Schwartz & Porte, 2005).

Lastly, IRS-2 is concentrated in the VMN as well as in the ARC (Pardini *et al.* 2006) and insulin-mediated K_{ATP} channel activation is PI3K dependent in ARC neurons. Taken together, these observations support the hypothesis that, like the ARC, VMN neurons sense and integrate input from both hormonal (insulin, leptin) and nutrient-related (glucose) signals to regulate autonomic outflow, energy intake and peripheral insulin action via signal transduction mechanisms resembling those utilized by ARC neurons.

How a signal from the hypothalamus mediates changes in peripheral insulin sensitivity remains an active area of study. One hypothesis proposes a key role for communication between hypothalamus and hindbrain areas that control autonomic outflow to the liver and other tissues via the vagus nerve. Specifically, activation of descending projections from ARC neurons to the hindbrain is proposed to increase hepatic insulin sensitivity via activation of vagal efferent fibres supplying the liver (Fig. 2). This hypothesis is supported by evidence that hepatic branch vagotomy attenuates the suppression of GP following intrahypothalamic infusion of insulin, free fatty acids (FFAs) or a K_{ATP} channel opener, whereas there was no effect of selective vagal deafferentation (Pocai *et al.* 2005*a*,*b*). Whether additional mechanisms link hypothalamic nutrient and hormone sensing to the control of glucose metabolism in peripheral tissues is a key question that awaits further study.

Hypothalamic leptin and glucose metabolism

Leptin binding to the 'long' or 'signalling' isoform of the leptin receptor, lepr^b, results in activation of Jak2 (Janus-Kinase), which in turn phosphorylates lepr^b, resulting in the recruitment and tyrosine phosphorylation of the transcription factor signal transducer and activation of transcription-3 (STAT3) (Howard & Flier, 2006). Phospho-STAT3 dimers then translocate to the nucleus and activate the transcription of various target genes including suppressor of cytokine signalling-3 (SOCS-3), a signalling inhibitor that blocks lepr^b activation of Jak-STAT signalling (Howard & Flier, 2006). Recent data suggest that like insulin, leptin is also capable of activating the IRS–PI3K pathway (Niswender *et al.* 2001; Niswender *et al.* 2003) and that this effect, like activation of the Jak-STAT pathway, is required for leptin regulation of food intake (Niswender *et al.* 2001). Therefore, hypothalamic PI3K signalling may play a critical role in leptin, as well as insulin, action on energy and glucose homeostasis.

Although changes of food intake and body adiposity can clearly affect insulin sensitivity in peripheral tissues, several observations suggest that leptin regulation of glucose homeostasis occurs independently of its effects on food intake. For example, impaired glucose metabolism characteristic of genetic models of leptin deficiency occurs regardless of whether the animals are obese (e.g. *ob/ob* mice) (Zhang *et al.* 1994) or lean (e.g. various models of lipodystrophy due to defective adipocyte development) (Shimomura *et al.* 1999), and leptin treatment corrects these metabolic abnormalities via a mechanism that cannot be explained by changes of food intake or body weight (Schwartz *et al.* 1996; Shimomura *et al.* 1999). Therefore, deficient leptin signalling appears to have severe consequences for glucose metabolism that are independent of, and additive to, its effects on energy intake or body fat content. Moreover, the brain is implicated as a key target for the glucose-lowering action of leptin, as I.C.V.

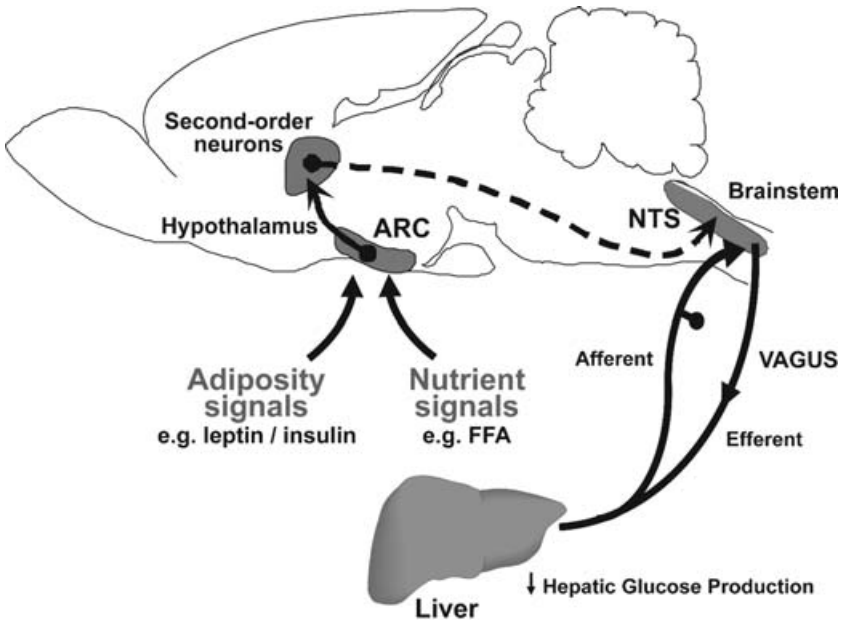

Figure 2. Model of the hypothalamic regulation of hepatic glucose production
Both insulin activation of the IRS-PI3K pathway and increased concentration of LCFA-CoA levels in the ARC are proposed to activate second-order neurons that project to hindbrain areas. In response to this input, output of motor neurons of the vagus nerve that supply the liver is increased (adapted from Pocai *et al*. 2005*b*). ARC, arcuate nucleus; NTS, nucleus of the solitary tract; FFA, free fatty acids.

administration of leptin rescues the insulin resistance and diabetes phenotype of lipodystrophic mice at doses that are ineffective when administered peripherally (Asilmaz *et al.* 2004). Thus, leptin signalling appears to be required for intact glucose metabolism, and recent evidence implicates the ARC as a key site mediating this effect.

Using a combination of gene targeting and viral gene therapy to rescue leptin receptors in the hypothalamus of mice that otherwise lack these receptors, Elmquist and colleagues found that while ARC-directed leptin receptor gene expression reduced food intake and body fat mass only modestly, it effectively normalized blood glucose and insulin levels (Coppari *et al.* 2005). Our recent work using Koletsky (fa^k/fa^k) rats that develop obesity, hyperphagia, glucose intolerance and insulin resistance due to genetic absence of all leptin-receptor protein (Takaya *et al.* 1996; Ernsberger *et al.* 1999) extends these findings. We found that restoring leptin receptors selectively to the ARC of Koletsky rats using an adenoviral gene therapy approach dramatically improved peripheral insulin sensitivity, even when the effects of food intake and body weight were prevented by pair-feeding (Morton *et al.* 2005). Reduced leptin signalling in the hypothalamus therefore contributes to impaired glucose metabolism in animals that lack a leptin signal. Furthermore, this response to ARC-directed leptin receptor gene therapy appears to depend, at least in part, on PI3K signalling, since it is attenuated by prior I.C.V. infusion of a PI3K inhibitor. Conversely, ARC-directed expression of a constitutively active mutant of PKB mimicked the insulin-sensitizing effect of restored hypothalamic leptin signalling in these animals (Morton *et al.* 2005). These findings suggest that hypothalamic leptin signalling is an important determinant of peripheral insulin sensitivity and that the underlying neuronal mechanism involves PI3K. This conclusion is further supported by studies of mice (*s/s*) in which the endogenous leptin receptor gene was replaced with a mutant allele that cannot signal via the Jak-Stat pathway, but otherwise functions normally (Bates *et al.* 2003, 2005). These animals develop severe hyperphagia and obesity, but unlike *db/db* mice, exhibit only mild disturbances of glucose homeostasis that can be prevented by caloric restriction (Bates *et al.* 2005). These results suggest that although leptin-receptor-mediated JAK-STAT signalling is essential for regulation of food intake and body weight, this is not the case for leptin regulation of glucose metabolism. Rather, leptin-stimulated PI3K signalling appears to mediate this effect.

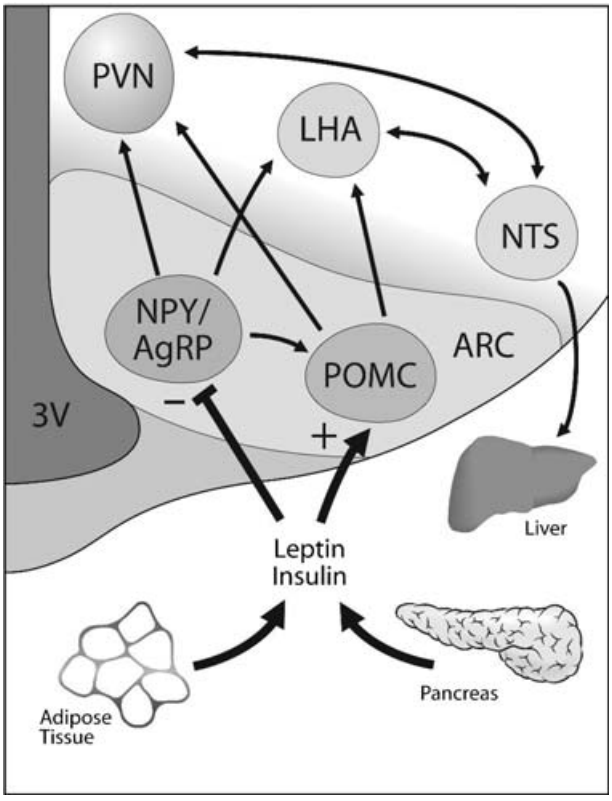

Figure 3. Model of the hypothalamic neurocircuits involved in glucose metabolism
Insulin and leptin act in the arcuate nucleus (ARC) to inhibit NPY/AgRP neurons and activate pro-opiomelanocortin (POMC) neurons. Both neuronal subsets project to other hypothalamic areas including the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA). Activation of neuronal projections from these hypothalamic neurons to hindbrain areas, such as the nucleus of the solitary tract (NTS), generates a vagal signal to the liver to regulate hepatic glucose production. 3V, third ventricle.

The hypothalamic ARC contains distinct neuronal subsets that can potently regulate food intake, energy expenditure and insulin sensitivity. Two well characterized neuronal populations in this area express both insulin and leptin receptors, are regulated by both insulin and leptin, and exert opposing effects on energy balance and glucose metabolism. One of these subsets are neurons containing neuropeptide Y/agouti-related peptide (NPY/AgRP), peptides that potently stimulate food intake and reduce energy expenditure and these cells are inhibited by leptin and insulin. The other subset contains neurons that express the melanocortin precursor, pro-opiomelanocortin (POMC), which unlike NPY/AgRP neurons, are stimulated by input from leptin and act on melanocortin receptors (Mc3/4r) to reduce food intake (Schwartz & Porte, 2005). In addition to the release of NPY, NPY/AgRP neurons stimulate feeding by reducing melanocortin signalling via release of AgRP, an endogenous melanocortin 3/4 receptor antagonist (Ollmann *et al.* 1997; Shutter *et al.* 1997). In addition to these well characterized effects on energy balance, recent evidence suggests that both neuronal populations may also be important in the central regulation of glucose metabolism. For example, central administration of NPY causes insulin resistance even when its effects on food intake are prevented (Marks & Waite, 1997; van den Hoek

et al. 2004), and similar responses are elicited following chronic I.C.V. infusions of the melanocortin 3/4 receptor antagonist, SHU9119 (Adage *et al.* 2001), while central infusion of the melanocortin receptor agonist, MTII, has the opposite effect (Obici *et al.* 2001). Collectively, these observations support the hypothesis that in addition to having potent effects on energy balance, ARC neurons also participate in the control of insulin sensitivity in peripheral tissues (Fig. 3). Since leptin-receptor gene therapy directed to the ARC reduces hypothalamic *Npy* mRNA levels (Morton *et al.* 2003), reduced signalling by NPY/AgRP neurons may contribute to the improvement of insulin sensitivity induced by hypothalamic leptin receptor gene therapy in our studies.

Nutrient-related signals

The CNS is thought to sense and respond not only to input from adiposity signals such as insulin and leptin, but also to nutrient-related signals. One putative hypothalamic signal of nutrient availability is the intracellular accumulation of long-chain fatty acyl-CoA (LCFA-CoA) molecules. Consistent with this hypothesis, both I.C.V. administration of the monounsaturated FFA, oleic acid, and local inhibition of lipid oxidation due to increased malonyl CoA levels (either using a fatty acid synthase (FAS) inhibitor or an inhibitor of carnitine palmitoyl-transferase-1 (CPT-1), a key regulator of β-oxidation), decreases both food intake and GP (Loftus *et al.* 2000; Obici *et al.* 2002*b*; Lam *et al.* 2005). Conversely, hypothalamic reduction of LCFA-CoA levels by local infusion of adeno-associated virus expressing malonyl coenzyme A decarboxylase (MCD, an enzyme responsible for malonyl CoA degradation), causes obesity and insulin resistance in rats (He *et al.* 2006). These effects of FFA on hepatic GP appear to mimic the effect of central insulin on peripheral insulin sensitivity, and the mechanism is similarly suggested to require central activation of K_{ATP} channels and increased vagal outflow to the liver (Pocai *et al.* 2005*b*).

In contrast to LCFA-CoA, the enzyme AMP-activated protein kinase (AMPK) is a fuel sensor that is activated in response to depletion of cellular ATP. Besides its role in the periphery, hypothalamic AMPK is thought to play an important role in control of energy balance. Activation of hypothalamic AMPK stimulates food intake and body weight while, conversely, suppression of its activity has the opposite effect (Minokoshi *et al.* 2004). Moreover, hypothalamic AMPK activity is inhibited by central administration of glucose, insulin and leptin, as well as by physiological conditions such as re-feeding, while it is activated by interventions that stimulate food intake including I.C.V. ghrelin or fasting (Xue & Kahn, 2006). These data support the hypothesis that fuel sensors in the hypothalamus respond to changes in circulating nutrients and play a key role in the regulation of both energy homeostasis and glucose metabolism.

Conclusions

Based on the current literature, an emerging model suggests that when confronted with reduced nutrient availability, there is an adaptive, hypothalamic response that increases hepatic GP to meet the metabolic needs of the body. This metabolic response occurs in parallel with hypothalamic responses that stimulate food intake, and it appears to involve similar peripheral circulating factors, signal transduction molecules and neurocircuitry as those implicated in energy homeostasis. This is an important concept, as insulin resistance in peripheral tissues is common in obesity and type 2 diabetes, and the mechanism underlying this resistance involves impaired activation of PI3K. Since convergent signal transduction (e.g. via the IRS-PI3K signalling pathway) and termination (e.g. SOCS-3) mechanisms mediate neuronal actions of insulin and leptin, defects within a single biochemical pathway can potentially cause resistance to the central actions of both hormones. This, in turn, can be predicted to induce hyperphagia, weight gain, hepatic insulin resistance and glucose intolerance. This model is supported by evidence that both heterozygous SOCS-3-deficient mice and neuronal cell-specific SOCS-3 conditional knockout mice display increased leptin sensitivity, and are protected against the development of obesity on a high fat diet (Howard *et al.* 2004; Mori *et al.* 2004). Thus, neuronal SOCS-3 (which can disrupt signalling via both the JAK-Stat and PI3K signalling pathways) appears to play a physiological role to favour positive energy balance and weight gain by limiting the hypothalamic response to input from adiposity-related hormones. This model is further supported from evidence that diet-induced obesity is associated with impaired behavioural and hypothalamic responses to insulin, leptin and FFA (El-Haschimi *et al.* 2000; Morgan *et al.* 2004; De Souza *et al.* 2005). Taken together, these findings indicate that reduced hypothalamic input from adiposity- and nutrient-related signals occurs in common forms of obesity and are sufficient to impair both energy homeostasis and glucose metabolism. Whether such defects cause or are associated with the development of obesity, insulin resistance and diabetes in humans is an important scientific question.

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Acknowledgements

The author thanks Michael W. Schwartz (University of Washington) for helpful discussion and advice. G.J.M. was funded by the Clinical Nutrition Research Unit and Diabetes Endocrinology Research Center of the University of Washington