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Regulation of peripheral metabolism by substrate partitioning in the brain

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Metabolic flexibility is required to adapt to changes in fuel availability

All organisms and cell types adapt to fuel availability, though some cell types are more adaptable than others. Because glucose is the ultimate product of photosynthesis and thus the basis of virtually all bioenergetic economy, most cell types and organisms are optimized to use glucose to produce energy, and thus will use glucose preferentially when it is present. For example when both glucose and lactose are present, glucose inhibits lactose metabolism, but when lactose is the sole source of carbon lactose metabolism is induced. Indeed, studies of the molecular mechanisms by which *E. coli* adapts to metabolize lactose continue to elucidate surprisingly informative mechanisms [1-3]. Yeast too will preferentially metabolize glucose, and when excess glucose is present, will convert some of the glucose to

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ethanol in a process called fermentation, to be metabolized subsequently when glucose is no longer freely available. In animals a similar process occurs, in which glucose is the main source of energy during the active period (in humans during the day, in rodents at night), some of the excess glucose is converted to lipid stores, and then lipid stores are used by some tissues during the sleep phase or during prolonged nutritional deprivation. As with the lac operon, studies examining the mechanisms mediating these metabolic switches continue to yield surprising results.

In contrast to other cell types, neurons are relatively dependent on glucose as a source for cellular metabolism [4]. Thus the main deleterious effects of hypoglycemia encountered due to insulin therapy in diabetic patients are neurological symptoms including seizure and coma [5, 6]. Because of this unique dependence mechanisms have evolved for the brain to sense levels of blood glucose and produce robust systemic responses to correct blood glucose.

Neurons sensitive to glucose regulate peripheral glucose and lipid homeostasis

The earliest evidence that the brain controls blood glucose levels was Claude Bernard's famous observation that damage to the floor of the fourth ventricle in the brain produced a rapid and sustained increase in urinary glucose [7]. Many studies have corroborated this observation with a variety of manipulations; for example sustained elevations of blood glucose appear after many pharmacological manipulations directed toward the brainstem [8]. Similarly, the rapid induction of hyperglycemia and feeding produced by infusing the glucose metabolism inhibitor 5-thioglucose into either the lateral or the fourth ventricle appears to be mediated at least in part by glucose-sensing neurons in the brainstem [9].

On the other hand neurons located in the ventromedial hypothalamus (VMH) have long been implicated in the control of not only blood glucose, but energy balance as well. Some of the earliest evidence for the function of these neurons arose from hypothalamic tumors in patients, which were observed to produce a wide variety of impairments including obesity and diabetes. Subsequent studies demonstrated that lesions in the VMH in a wide range of species produce hyperphagia, weight gain, and impaired regulation of blood glucose [10-14]. The discovery of neurons in this brain area that are uniquely sensitive to glucose [15-19] suggested that a major function of these neurons is to sense and regulate plasma glucose levels, to ensure adequate glucose supply to the brain.

As indicated above, neurons normally prefer to use glucose as their main source of energy [4]. Thus during nutritional deprivation other tissues can relatively easily adapt to use free fatty acids to produce ATP via beta oxidation, while preserving glucose for utilization by neurons. A question of considerable interest is how complex organisms monitor and respond to nutritional deprivation, since impairments in this system could plausibly cause pathologies such as obesity and diabetes when nutritional resources are not limiting. A major and conserved signal of glucose sufficiency is the insulin/insulin-like pathway, which serves this function across a wide range of species including *C. elegans* [20], *Drosophila* [21], and of course mammals. In mammals insulin is produced by glucose-sensing pancreatic beta cells and when released promotes glucose metabolism and lipid synthesis in

relevant insulin-sensitive tissues; insulin also inhibits glucose and lipid release from relevant storage organs (mainly liver and adipocytes, respectively). Thus when glucose is readily available (usually during the active period), pancreatic beta cells release insulin to promote glucose utilization and nutrient storage in the form of glycogen and lipids, and when glucose is less available (usually during the period of sleep) insulin levels drop leading to release of glucose and lipids from storage. These direct actions of insulin were until recently thought to be the primary mediators of the switch from glucose metabolism to alternative substrates, especially free fatty acids. However it is now appreciated that actions of insulin on hypothalamic neurons play a major role in peripheral metabolic switching [22].

Nutritional deprivation also produces a characteristic set of neuroendocrine “counterregulatory” responses to preserve nutritional resources, including reduction of reproductive hormones [23], reduced thyroid hormone [24], reduced IGF-1 [25], and increased glucocorticoids as well as glucagon, and epinephrine [26-29]. A key signal mediating these neuroendocrine responses to nutritional deprivation is the adipose-derived hormone leptin, reflecting adipose stores, acting on hypothalamic neurons expressing the leptin receptor [30]. However, it should be noted that these same neuroendocrine responses are produced when blood glucose levels fall below about 2.5 mM glucose (normal blood glucose levels is about 4-5 mM) even when plasma leptin and insulin are normal or even elevated [31]. Similarly, although insulin serves as a key signal to stimulate peripheral glucose disposal, insulin-induced hypoglycemia reduces peripheral glucose disposal even though insulin (and leptin) are elevated [32].

Furthermore fasting can induce hypothalamic responses that are independent of changes in leptin or insulin [33] mediated at least in part by reduced glucose metabolism [34]. Indeed, hypoglycemia or 2-deoxyglucose (2-DG), which blocks local glucose metabolism, mimics the neuroendocrine and metabolic responses to fasting or leptin deficiency, and these responses are independent of changes in leptin or insulin [23, 24, 26].

The counterregulatory responses to hypoglycemia increase the availability of blood glucose, in part by increasing hepatic glucose production, but also by reducing metabolism in peripheral organs to preserve blood glucose for brain use. VMH neurons plausibly mediate these effects on glucose metabolism since electrical stimulation of the VMH but not the lateral hypothalamus increases glucose metabolism in peripheral tissues, mediated by enhanced sympathetic activity [35, 36]. Consistent with the results of genetic inhibition of VMH glutamate release [37], infusion of glutamate into the VMH also enhances peripheral glucose metabolism [36]. Increased peripheral glucose metabolism from VMH stimulation does not entail increased glucose transporters, in contrast to insulin-induced glucose uptake [38]. Associated with increased glucose metabolism, VMH stimulation also increases BAT temperature [39], likely reflecting hypothalamic mediation of hypothermia induced by 2DG [40]. Infusion of leptin specifically into the VMH also induces peripheral glucose metabolism [41] through enhancement of sympathetic nervous activity [42].

These studies were complemented by our studies demonstrating that in leptin-deficient mice, which are characterized by reduced expression of hypothalamic POMC [43], transgenic restoration of POMC completely normalized blood glucose, associated with normalization

of hepatic gluconeogenesis [44]. Furthermore, infusion of glucose into the hypothalamus acutely reduces hepatic glucose output [45] as well as circulating triglycerides by reducing hepatic secretion of TG-VLDL [46]. Some effects of hypothalamic glucose to reduce hepatic glucose output may require conversion to lactate [47], implicating a glial mechanism [48]. Taken together these studies demonstrate that activity of glucose-sensitive hypothalamic neurons promotes peripheral glucose metabolism and reduces peripheral glucose production, especially by the liver.

This hypothesis has been substantially supported by studies from the laboratory of Sherwin and colleagues. The ventromedial hypothalamus (VMH) was historically implicated as the main site of glucose-sensing neurons [15-19], and lesions of the VMH produce diabetic [49] and obese phenotypes [12]. In this historical context the VMH, sometimes referred to as the mediobasal hypothalamus (MBH), encompassed an area including both the ventromedial nucleus (VMN) and arcuate nucleus (AN), as well as the neuron-poor area between them, since most lesion and infusion studies could not adequately distinguish between these populations. Sherwin and colleagues also demonstrated that VMH lesions prevent the counterregulatory responses to hypoglycemia [50]. Furthermore localized reduction of glucose metabolism in the VMH by the metabolic inhibitor 2-deoxyglucose (2-DG) produced a robust counterregulatory response that largely mimicked the response to whole-body hypoglycemia [51]. This study was particularly informative because the 2-deoxyglucose was radiolabelled, allowing the investigators to assess the extent of spread from the infusion site. This analysis indicated that confining the 2-DG to the ventromedial nucleus (VMN) was sufficient to produce counterregulatory responses similar to those produced by whole-body hypoglycemia [51]. Conversely local infusion of glucose [52] or lactate [53] into the VMH blocked counterregulatory responses to whole-body hypoglycemia. These studies clearly demonstrated the key role of glucose-sensing neurons in the VMH in sensing and regulating blood glucose levels.

The mechanisms by which VMH neurons sense glucose leading to counterregulatory responses appear to be quite similar to those by which pancreatic beta cells sense glucose, entailing glucose metabolism mediated by the rare pancreatic form of glucokinase [17, 19, 54, 55]. Similarly, blocking K-ATP channels mimics the effect of glucose in glucose-excited neurons [17] and selectively blocking K-ATP channels in the VMH blocks counterregulatory responses to hypoglycemia {Evans, 2004 #8657} whereas activating K-ATP channels in the VMH enhances those responses {Chan, 2007 #8658}. The activation of counterregulatory responses by VMH neurons appears to be mediated in part by disinhibition, since hypoglycemia reduces VMH GABA, GABA agonists block counterregulatory responses, and GABA antagonists enhance counterregulatory responses [56]. These data support the hypothesis that counterregulatory responses during hypoglycemia are mediated in part by reduced activity of glucose-stimulated GABA-ergic neurons in the VMH. Counterregulatory responses to hypoglycemia were also impaired by genetic inhibition of glutamate transmission specifically the Sf-1 neurons (expressed in VMN but not arcuate nucleus) [37]. Of particular importance, this study also demonstrated that blood glucose levels were also relatively lower during fasting in mice with impaired glutamate transmission in Sf-1 neurons associated with impaired induction of hepatic gluconeogenic gene expression [37]. Since acute hypoglycemia is probably rarely

encountered under normal circumstances in the wild, these observations suggest that neuroendocrine and autonomic responses to acute hypoglycemia probably reflect systems evolved to adapt to more commonly encountered caloric deficits, supporting that mechanisms mediating responses to hypoglycemia and nutritional deprivation overlap (see below for molecular evidence supporting this hypothesis).

Free fatty acids are robustly metabolized by the brain

As indicated above, the normal rhythms of substrate availability require metabolic adaptations of most cells to maximum glucose metabolism and lipid synthesis when glucose is available during the active period and switch from glucose metabolism to alternative fuels, mainly free fatty acids, when nutrients are less available during the inactive/sleep period or after prolonged fasting due to lack of nutritional resources. Historically it has been assumed that the brain is a major exception [57] and does not metabolize free fatty acids to any significant extent and thus relies largely on glucose or ketone metabolism [58] during a prolonged fast. Several early studies infusing radiolabelled palmitate in ad lib fed animals reported that relatively small amounts of palmitate are oxidized in vivo [59].

More recent studies however have it is absolutely clear that the brain is capable of robust beta oxidation under at least some circumstances. One of the first studies to assess beta oxidation in the brain was by Geyer et al., who demonstrated that labeled octanoic acid was metabolized to carbon dioxide in vitro by brain slices about as efficiently as liver slices [60]. Based on these and several other studies, a thorough review in 1961 concluded that at least in vitro brain tissue can support beta oxidation, though the importance of beta oxidation in vivo was less clear [61]. Addressing this issue Little et al. demonstrated that infusing radiolabelled palmitate into the brain did lead to the production of radiolabelled carbon dioxide [62]. In fact octanoic acid is so robustly metabolized in brain that it was suggested as a marker for brain activity [63]. A widely cited paper indicated that astrocytes, but not oligodendrocytes or neurons, support beta oxidation [4]. This study demonstrated that all three cell types metabolized ketones (acetoacetate or 3-hydroxybutyrate) at rates 7-9 times higher than glucose, and that astrocytes metabolized free fatty acids (octanoate and palmitate) at even higher levels than ketones [4]. This was an in vitro study derived cells from the developing rat, so it could be argued that metabolism of these cell types is optimized for the high-fat low-carbohydrate composition of mother's milk during nursing. Nevertheless similar metabolic demands are made on cell types during fasting in adults, and molecular evidence clearly indicates a metabolic shift in the brain away from glucose utilization and toward beta oxidation, especially in the hypothalamus [34]. Similarly CNTF robustly induces beta oxidation in astrocytes [64]. Therefore these metabolic capabilities may not be limited to the developing stage but may be inducible by nutritional restriction.

Although it could be argued that in vitro studies may not reflect the limitations that might be encountered by free fatty acids cross the blood-brain barrier, there appear to be ample fatty acid transporters in the brain to allow rapid crossing of the blood brain barrier (for example, in the choroid plexus, a major site of import for many hormones and nutrients into the brain [65]). Furthermore radiolabelled free fatty acids rapidly equilibrate with the brain pool of FA-CoA [66], demonstrating that transport and metabolism of FFAs into the brain occurs

rapidly and robustly. Similarly radiolabelled octanoate, myristic acid, and linoleic acid rapidly cross the blood-brain barrier in adults [67]. Another study indicated that about 50% of palmitic acid that enters the brain is metabolized by beta oxidation [68]. More definitely, use NMR Ebert et al. demonstrated that the metabolism of octanoate, one of the most abundant free fatty acids in the blood, constitutes as much as 20% of total brain oxidative metabolism [69]. One reason that early studies may not have detected significant brain beta oxidation from some substrates may be that the studies were carried out in ad lib fed animals, whereas fasting significantly increases transport of free fatty acids across the blood brain barrier [70].

Free fatty acids oppose effects of glucose on the activity of hypothalamic neurons

One of the first reports indicating that hypothalamic neurons sense lipids was by Oomura et al. (who also discovered that hypothalamic neurons sense glucose) [71]. This study indicated that free fatty acids (palmitate and oleic acid) produce the opposite effects on neurons as glucose on glucose-inhibited neurons in the lateral hypothalamus and glucose-excited neurons in the ventromedial hypothalamus [71]. These observations were consistent with the normal physiology of the system since increased glucose is normally a signal of nutritional sufficiency and free fatty acids are normally elevated during nutritional deprivation (an exception is the consumption of high-fat meals which in most species including humans is mainly a modern phenomenon with pathological consequences, as discussed below). Thus for example, exemplifying a general if not universal biochemical principle of substrate competition [3], free fatty acids and glucose inhibit metabolism of each other [72]. Therefore it would be expected that these two types of nutrients would produce opposite effects on neurons whose function is to monitor nutritional status and regulate metabolic function accordingly. Nevertheless subsequent reports indicated a much more complex relationship between effects of glucose and effects of free fatty acids on hypothalamic neurons [73]. Some of these differences could be attributable to different concentrations of glucose and free fatty acids used to assess responsiveness of the hypothalamic neurons. Subsequent in vivo studies suggested that oleic acid in the hypothalamus inhibits glucose production and food intake via activation of K-ATP channels [74]. While activation of K-ATP channels would be expected to oppose effects of glucose in hypothalamic neurons, consistent with the opposing effects reported by Oomura et al. [71], effects on glucose production were not consistent with the hypothesis that free fatty acids serve as a signal for nutritional deprivation. Contributing to the lack of clarity in the field was the question of whether free fatty acids were sensed by hypothalamic neurons via metabolism, as is the case for glucose, or possibly through a cell surface receptor such as FAT/CD36 [75]. One study suggested that both beta oxidation and non-metabolic effects contribute to electrical effects of palmitate on hypothalamic neurons [75].

Since the brain has historically not been thought to support significant metabolism of free fatty acids by beta oxidation [57], and because there are many kinds of free fatty acids, there had been few studies addressing the functional significance of hypothalamic beta oxidation in regulating peripheral metabolism. Thus it is perhaps not surprising that one of the first

studies clearly implicating hypothalamic beta oxidation in regulating peripheral metabolism arose through serendipity. Loftus et al. had developed inhibitors of fatty acid synthase as possible treatments for cancer, based on the hypothesis that cancer cells might require relatively elevated levels of fatty acid synthesis [76]. Although these inhibitors exhibited relatively limited anti-tumor activity, one, C75, produced profound anorexia [76]. Normally anorexia would be considered an undesirable and common iatrogenic effect of a novel drug, but to the credit of these investigators they assessed the mechanism mediating the anorectic effect. These studies revealed that C75 produced anorexia by enhancing the levels of hypothalamic malonyl coA [76]. The classic effect of malonyl CoA (produced by and serving as a signal for glucose metabolism) in the periphery is to block the enzyme Carnitine palmitoyl transferase (Cpt1), especially the liver isoform Cpt1a, and thus block metabolism of free fatty acids by beta oxidation [77]. Based on these observations Ruderman et al. hypothesized that this mechanism may also occur in hypothalamic neurons expressing glucokinase [77]. Loftus et al. concluded that their studies with C75 supported this hypothesis [76]. Thus despite general consensus that the brain does not support significant beta oxidation [57], these studies clearly indicated that beta oxidation in the hypothalamus plays an essential role in regulating energy balance, particularly in glucose-sensing neurons which we demonstrated express the pancreatic form of glucokinase [17, 78], later corroborated by more extensive analysis [19].

In a series of studies these investigators and their colleagues further corroborated the importance of hypothalamic malonyl-CoA in regulating energy balance and glucose homeostasis [79-85]. For example, they demonstrated that fasting decreases hypothalamic malonyl-CoA (thus increasing hypothalamic beta oxidation), whereas feeding rapidly increases hypothalamic malonyl-CoA [82]. As expected i.c.v. infusion of C75 caused a rapid increase in malonyl-CoA, and preventing this rapid increase blocked effects of C75, including the reduction of hypothalamic AgRP and NPY and increase of hypothalamic POMC, both of which plausibly mediate effects of C75 on energy balance [82]. Of particular interest, central administration of C75 induced a rapid increase in skeletal beta oxidation, mediated by sympathetic activation of skeletal Ppar-alpha [86], which promotes beta oxidation. Interestingly, some effects of leptin may also depend on hypothalamic beta oxidation, since blocking the effect of leptin to increase hypothalamic acetyl-CoA carboxylase (which synthesizes malonyl-CoA) blocks effects of leptin [87].

The importance of hypothalamic beta oxidation in regulating glucose homeostasis was subsequently confirmed by Obici et al., who demonstrated that inhibiting hypothalamic Cpt1a (which they called Cpt1L, for the liver form) reduced food intake and hepatic glucose output [88]. Similarly, experimental enhancement of hypothalamic malonyl-CoA decarboxylase, which degrades malonyl-CoA, thus activating hypothalamic beta oxidation, leads to obese phenotypes and impaired glucose homeostasis [85, 89]. Furthermore the pro-obesity phenotypes mediated hormone ghrelin, which acts on hypothalamic neurons, entail induction of Cpt1a and inhibition of Cpt1a activity blocks effects of ghrelin [90] possibly mediated by neurons in the VMN [91, 92].

Our interest in the role of hypothalamic beta oxidation arose from examination of hypothalamic molecular responses to hypoglycemia and fasting, which preliminary studies

suggested entailed induction of hypothalamic Cpt1a (but not Cpt1c) and reduction in glycolysis [93]. While assessing molecular mechanisms mediating the suppression of counterregulation by estradiol, we observed that estradiol inhibited hypothalamic Cpt1a, plausibly contributing to counterregulatory failure by increasing reliance on glycolysis [94]. Similarly we observed that repetitive hypoglycemia also reduced hypothalamic expression of Cpt1a in association with counterregulatory failure [95]. We also confirmed the induction of Cpt1a by fasting in the hypothalamus, but not the cortex [34]. Beta oxidation is likely particularly important in POMC and AgRP neurons, which produce peroxisomes that support beta oxidation [96]. Finally, we have corroborated the results of Obici et al. and demonstrated that chronically enhanced expression of hypothalamic Cpt1a via AAV-mediated gene transfer produces robust obese phenotypes, including hyperphagia and enhanced blood glucose (Yang et al., submitted).

Thus although historically the brain was thought not to support beta oxidation, there is now overwhelming support that even human brains support beta oxidation under certain conditions, including Type 1 diabetes and nutritional deprivation [97]. In vivo studies consistently demonstrate that hypothalamic beta oxidation is associated with obese phenotypes, such that conditions that either directly [88] or indirectly [76, 79-85, 89, 98] reduce beta oxidation reduce obese phenotypes, while increasing hypothalamic beta oxidation promotes obese phenotypes (Yang et al., submitted). Thus in vivo studies suggest that hypothalamic lipid metabolism serves as a signal for nutritional deprivation, consistent with early reports that lipids and glucose produce opposite effects on hypothalamic glucose-sensing neurons and [71] and consistent with molecular evidence that fasting induces beta oxidation [34]. Later in vitro studies were not as consistent, probably because effects of free fatty acids on hypothalamic neuronal activity are highly dependent on ambient glucose concentrations [99].

Although astrocytes robustly support beta oxidation there is less evidence that neurons support beta oxidation [4]. Nevertheless peroxisomes are expressed in specific neuronal populations in the hypothalamus, including POMC and AgRP neurons, with more peroxisomes associated with obese phenotypes [96]. Furthermore enhanced hypothalamic expression of malonyl-coenzyme A decarboxylase produced obese phenotypes apparently by enhancing hypothalamic beta oxidation [89]. Since this gene was transferred using a neurotropic AAV vector, it is highly likely that its effects were mediated by neurons, and thus on neuronal beta oxidation. Using a similar AAV vector, we have also observed that direct activation of beta oxidation by enhanced expression of Cpt1a targeted to the VMN produces obese phenotypes, again almost certainly via actions on neuronal beta oxidation (Yang et al., submitted). It is plausible, as has been previously proposed [77] that beta oxidation in neurons may be largely confined to neurons that function to sense nutrient state and regulate peripheral metabolism, e.g., glucokinase-expressing glucose-sensing neurons [17, 19], which also largely overlap with neurons sensitive to leptin [34].

The molecular mechanisms mediating effects of free fatty acids on hypothalamic function remain to be determined. As suggested above, hypoglycemia produces similar metabolic [31] and molecular [95] effects as produced by fasting [34, 100]. In turn, metabolic responses to fasting require Ppar-alpha [100-103]. Therefore mice in which Ppar-alpha has

been ablated exhibit relative hypoglycemia after an overnight fast [101]. The control of glucose metabolism by Ppar-alpha is mediated by the brain, not the liver [104, 105]. For example, replacing Ppar-alpha in the liver of Ppar-alpha knockout mice does not reverse the elevated whole-body glucose metabolism in these mice but activating Ppar-alpha in the brain reduces whole-body glucose metabolism [104]. This observation led the authors to conclude that “the alteration in adipocyte glucose metabolism in the knockout mice may result from the absence of PPARalpha in the brain” [104]. Similarly, pharmacological activation of Ppar-alpha specifically in the hypothalamus reverses peripheral hypoglycemia observed in FASKO mice [105]. Likewise, many responses to fasting are mediated by hypothalamic neurons through leptin signaling [30] which in turn depends on glucose metabolism [34, 106]. We have recently reported that acute hypoglycemia induces many genes in the hypothalamus that are targets of the transcription factor Ppar-alpha, and the induction of these genes is correlated with endocrine responses [95]. These observations led us to hypothesize that many whole-body responses to hypoglycemia and fasting are mediated by Ppar-alpha in the VMH [95]. Since Ppar-alpha activity is induced by free fatty acids, and nutrient sensing in hypothalamic neurons controls peripheral Ppar-alpha gene expression and corresponding target genes via the sympathetic nervous system [86], these observations suggest that hypothalamic free fatty acids may produce peripheral responses to fasting via induction of peripheral Ppar-alpha.

A major question is how hypothalamic beta oxidation promotes obese phenotypes and increases peripheral glucose homeostasis. In a series of studies Rossetti and colleagues supported the hypothesis that hypothalamic beta oxidation enhances hepatic glucose output by metabolizing long-chain fatty acids, including oleic acid [74, 88, 89, 107, 108]. Conversely, these investigators argued that hypothalamic oleic acid reduces hepatic glucose output by activation of hypothalamic K-ATP channels [74, 88, 89, 107, 108]. While attractive this hypothesis poses some problems. For example under ordinary circumstances, certainly in rodents in which these studies were done, circulating levels of free fatty acids are elevated during the fasted state, and reduced in the fed state [109, 110]. The exception to this circumstance would be consumption of a high-fat diet. However both circumstances promote, rather than reduce, obese phenotypes and hepatic glucose output. On the other hand some evidence supports that hypothalamic beta oxidation promotes obese phenotypes by reducing hypothalamic glucose sensing [111], consistent with substrate competition observed in the periphery [77]. Furthermore promotion of obese phenotypes by hypothalamic beta oxidation appears to be mediated by reduction in reactive oxygen species [96], consistent with a reduction in glucose metabolism [112]. Of course these two mechanisms are not necessarily mutually exclusive and could be linked if long-chain fatty acids such as oleic acid enhance glucose metabolism. On the other hand, oleic acid and glucose produce opposite effects on K-ATP channel function (consistent with the opposing actions of these nutrients in many systems), while apparently having the same effect on hepatic glucose output. Further studies will be required to resolve these apparent inconsistencies.

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References

1. Ozbudak EM, et al. Multistability in the lactose utilization network of *Escherichia coli*. *Nature*. 2004; 427(6976):737–40. [PubMed: 14973486]
2. Lewis M. The lac repressor. *C R Biol*. 2005; 328(6):521–48. [PubMed: 15950160]
3. Mobbs CV, et al. Secrets of the lac operon. Glucose hysteresis as a mechanism in dietary restriction, aging and disease. *Interdiscip Top Gerontol*. 2007; 35:39–68. [PubMed: 17063032]
4. Edmond J, et al. Capacity for substrate utilization in oxidative metabolism by neurons, astrocytes, and oligodendrocytes from developing brain in primary culture. *J Neurosci Res*. 1987; 18(4):551–61. [PubMed: 3481403]
5. Cryer PE, Fisher JN, Shamoon H. Hypoglycemia. *Diabetes Care*. 1994; 17(7):734–55. [PubMed: 7924788]
6. Mohseni S. Hypoglycemic neuropathy. *Acta Neuropathol (Berl)*. 2001; 102(5):413–21. [PubMed: 11699552]
7. Bernard C. Influence de la section des pédoncules cérébelleux moyens sur la composition de l'urine. *Compte Rendus des seances de la Societe de biologie et de ses filiales*. 1849:14.
8. Feldberg W, Pyke D, Stubbs WA. Hyperglycaemia: imitating Claude Bernard's piqure with drugs. *J Auton Nerv Syst*. 1985; 14(3):213–28. [PubMed: 2866209]
9. Ritter RC, Slusser PG, Stone S. Glucoreceptors controlling feeding and blood glucose: location in the hindbrain. *Science*. 1981; 213(4506):451–2. [PubMed: 6264602]
10. Hetherington AW, Ranson SW. Hypothalamic lesions and adiposity in the rat. *Anatomical Record*. 1940; 78:149–172.
11. Debons AF, Krimsky I. Regulation of food intake: role of the ventromedial hypothalamus. *Postgrad Med*. 1972; 51(5):74–8. [PubMed: 5025224]
12. Goldman JK, et al. Early metabolic changes following destruction of the ventromedial hypothalamic nuclei. *Metabolism*. 1980; 29(11):1061–4. [PubMed: 7432170]
13. Komeda K, Yokote M, Oki Y. Diabetic syndrome in the Chinese hamster induced with monosodium glutamate. *Experientia*. 1980; 36(2):232–4. [PubMed: 6989622]
14. Bergen HT, Monkman N, Mobbs CV. Injection with gold thioglucose impairs sensitivity to glucose: evidence that glucose-responsive neurons are important for long-term regulation of body weight. *Brain Res*. 1996; 734(1-2):332–6. [PubMed: 8896843]
15. Oomura Y, et al. Glucose and osmosensitive neurones of the rat hypothalamus. *Nature*. 1969; 222(190):282–4. [PubMed: 5778398]
16. Orzi F, et al. Local cerebral glucose utilization in controlled graded levels of hyperglycemia in the conscious rat. *J Cereb Blood Flow Metab*. 1988; 8(3):346–56. [PubMed: 3366796]
17. Yang XJ, et al. Hypothalamic glucose sensor: similarities to and differences from pancreatic beta-cell mechanisms. *Diabetes*. 1999; 48(9):1763–1672. [PubMed: 10480606]
18. Song Z, et al. Convergence of pre- and postsynaptic influences on glucosensing neurons in the ventromedial hypothalamic nucleus. *Diabetes*. 2001; 50(12):2673–81. [PubMed: 11723049]
19. Dunn-Meynell AA, et al. Glucokinase is the likely mediator of glucosensing in both glucose-excited and glucose-inhibited central neurons. *Diabetes*. 2002; 51(7):2056–65. [PubMed: 12086933]
20. Kimura KD, et al. daf-2, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. *Science*. 1997; 277(5328):942–6. [PubMed: 9252323]
21. Clancy DJ, et al. Extension of life-span by loss of CHICO, a *Drosophila* insulin receptor substrate protein. *Science*. 2001; 292(5514):104–6. [PubMed: 11292874]
22. Scherer T, et al. Brain insulin controls adipose tissue lipolysis and lipogenesis. *Cell Metab*. 2011; 13(2):183–94. [PubMed: 21284985]
23. Nagatani S, et al. Reduction of glucose availability suppresses pulsatile luteinizing hormone release in female and male rats. *Endocrinology*. 1996; 137(4):1166–70. [PubMed: 8625885]
24. Schultes B, et al. Acute and prolonged effects of insulin-induced hypoglycemia on the pituitary-thyroid axis in humans. *Metabolism*. 2002; 51(10):1370–4. [PubMed: 12370861]

25. Fontana L, Klein S, Holloszy JO. Effects of long-term calorie restriction and endurance exercise on glucose tolerance, insulin action, and adipokine production. *Age (Dordr)*. 2010; 32(1):97–108. [PubMed: 19904628]
26. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes*. 1991; 40(2):223–6. [PubMed: 1991573]
27. Maggs DG, Sherwin RS. Mechanisms of the sympathoadrenal response to hypoglycemia. *Adv Pharmacol*. 1998; 42:622–6. [PubMed: 9327979]
28. Baker D, et al. Hypoglycemia and glucose sensing. *Diabetologia*. 1997; 40:B83–B88. [PubMed: 9345653]
29. Cryer PE. Hierarchy of physiological responses to hypoglycemia: relevance to clinical hypoglycemia in type I (insulin dependent) diabetes mellitus. *Horm Metab Res*. 1997; 29(3):92–6. [PubMed: 9137976]
30. Ahima RS, Flier JS. Leptin. *Annu Rev Physiol*. 2000; 62:413–37. [PubMed: 10845097]
31. Hoffman RP. Sympathetic mechanisms of hypoglycemic counterregulation. *Curr Diabetes Rev*. 2007; 3(3):185–93. [PubMed: 18220670]
32. Cohen N, et al. Counterregulation of hypoglycemia. Skeletal muscle glycogen metabolism during three hours of physiological hyperinsulinemia in humans. *Diabetes*. 1995; 44(4):423–30. [PubMed: 7698511]
33. Mizuno TM, et al. Fasting regulates hypothalamic neuropeptide Y, agouti-related peptide, and proopiomelanocortin in diabetic mice independent of changes in leptin or insulin. *Endocrinology*. 1999; 140(10):4551–7. [PubMed: 10499510]
34. Poplawski MM, et al. Hypothalamic responses to fasting indicate metabolic reprogramming away from glycolysis toward lipid oxidation. *Endocrinology*. 2010; 151(11):5206–17. [PubMed: 20881243]
35. Takahashi A, Shimazu T. Hypothalamic regulation of lipid metabolism in the rat: effect of hypothalamic stimulation on lipogenesis. *J Auton Nerv Syst*. 1982; 6(2):225–35. [PubMed: 6757306]
36. Sudo M, Minokoshi Y, Shimazu T. Ventromedial hypothalamic stimulation enhances peripheral glucose uptake in anesthetized rats. *Am J Physiol*. 1991; 261(3):E298–303. Pt 1. [PubMed: 1887876]
37. Tong Q, et al. Synaptic glutamate release by ventromedial hypothalamic neurons is part of the neurocircuitry that prevents hypoglycemia. *Cell Metab*. 2007; 5(5):383–93. [PubMed: 17488640]
38. Shimazu T, et al. Role of the hypothalamus in insulin-independent glucose uptake in peripheral tissues. *Brain Res Bull*. 1991; 27(3–4):501–4. [PubMed: 1959052]
39. Minokoshi Y, Okano Y, Shimazu T. Regulatory mechanism of the ventromedial hypothalamus in enhancing glucose uptake in skeletal muscles. *Brain Res*. 1994; 649(1–2):343–7. [PubMed: 7953650]
40. Pelz KM, et al. Monosodium glutamate-induced arcuate nucleus damage affects both natural torpor and 2DG-induced torpor-like hypothermia in Siberian hamsters. *Am J Physiol Regul Integr Comp Physiol*. 2008; 294(1):R255–65. [PubMed: 17959707]
41. Minokoshi Y, Haque MS, Shimazu T. Microinjection of leptin into the ventromedial hypothalamus increases glucose uptake in peripheral tissues in rats. *Diabetes*. 1999; 48(2):287–91. [PubMed: 10334303]
42. Haque MS, et al. Role of the sympathetic nervous system and insulin in enhancing glucose uptake in peripheral tissues after intrahypothalamic injection of leptin in rats. *Diabetes*. 1999; 48(9):1706–12. [PubMed: 10480598]
43. Mizuno TM, et al. Rapid Communication: Hypothalamic pro-opiomelanocortin mRNA is reduced by fasting and in ob/ob and db/db mice, but is stimulated by leptin. *Diabetes*. 1998; 47(2):294–297. [PubMed: 9519731]
44. Mizuno TM, et al. Transgenic neuronal expression of proopiomelanocortin attenuates fasting-induced hyperphagia and reverses metabolic impairments in leptin-deficient obese mice. *Diabetes*. 2003; 52(11):2675–2683. [PubMed: 14578285]

45. Lam TK, et al. Regulation of blood glucose by hypothalamic pyruvate metabolism. *Science*. 2005; 309(5736):943–7. [PubMed: 16081739]
46. Lam TK, et al. Brain glucose metabolism controls the hepatic secretion of triglyceride-rich lipoproteins. *Nat Med*. 2007; 13(2):171–80. [PubMed: 17273170]
47. Kokorovic A, et al. Hypothalamic sensing of circulating lactate regulates glucose production. *J Cell Mol Med*. 2009; 13(11-12):4403–8. [PubMed: 19040414]
48. Tsacopoulos M, Magistretti PJ. Metabolic coupling between glia and neurons. *J Neurosci*. 1996; 16(3):877–85. [PubMed: 8558256]
49. Shimazu T, Fukuda A, Ban T. Reciprocal influences of the ventromedial and lateral hypothalamic nuclei on blood glucose level and liver glycogen content. *Nature*. 1966; 210(41):1178–9. [PubMed: 5964188]
50. Borg WP, et al. Ventromedial hypothalamic lesions in rats suppress counterregulatory responses to hypoglycemia. *J Clin Invest*. 1994; 93(4):1677–82. [PubMed: 8163668]
51. Borg WP, et al. Local ventromedial hypothalamus glucopenia triggers counterregulatory hormone release. *Diabetes*. 1995; 44(2):180–4. [PubMed: 7859938]
52. Borg MA, et al. Local ventromedial hypothalamus glucose perfusion blocks counterregulation during systemic hypoglycemia in awake rats. *J Clin Invest*. 1997; 99(2):361–5. [PubMed: 9006005]
53. Borg MA, et al. Local lactate perfusion of the ventromedial hypothalamus suppresses hypoglycemic counterregulation. *Diabetes*. 2003; 52(3):663–6. [PubMed: 12606506]
54. Sanders NM, Dunn-Meynell AA, Levin BE. Third ventricular alloxan reversibly impairs glucose counterregulatory responses. *Diabetes*. 2004; 53(5):1230–6. [PubMed: 15111491]
55. Levin BE, et al. Ventromedial hypothalamic glucokinase is an important mediator of the counterregulatory response to insulin-induced hypoglycemia. *Diabetes*. 2008; 57(5):1371–9. [PubMed: 18292346]
56. Chan O, et al. ATP-sensitive K(+) channels regulate the release of GABA in the ventromedial hypothalamus during hypoglycemia. *Diabetes*. 2007; 56(4):1120–6. [PubMed: 17251273]
57. Speijer D. Oxygen radicals shaping evolution: why fatty acid catabolism leads to peroxisomes while neurons do without it: FADH/NADH flux ratios determining mitochondrial radical formation were crucial for the eukaryotic invention of peroxisomes and catabolic tissue differentiation. *Bioessays*. 2011; 33(2):88–94. [PubMed: 21137096]
58. Owen OE, et al. Brain metabolism during fasting. *J Clin Invest*. 1967; 46(10):1589–95. [PubMed: 6061736]
59. Allweis C, et al. The oxidation of uniformly labelled albumin-bound palmitic acid to CO₂ by the perfused cat brain. *J Neurochem*. 1966; 13(9):795–804. [PubMed: 5928224]
60. eyer RP, Matthews LW, Stare FJ. Metabolism of emulsified trilaurin (-C1400-) and octanoic acid (-C1400-) by rat tissue slices. *J Biol Chem*. 1949; 180(3):1037–45. [PubMed: 18139198]
61. Fritz IB. Factors influencing the rates of long-chain fatty acid oxidation and synthesis in mammalian systems. *Physiol Rev*. 1961; 41:52–129. [PubMed: 13702156]
62. Little JR, Hori S, Spitzer JJ. Oxidation of radioactive palmitate and glucose infused into the cortical subarachnoid space. *Am J Physiol*. 1969; 217(4):919–22. [PubMed: 5824329]
63. Rowley H, Collins RC. [1-14C]Octanoate: a fast functional marker of brain activity. *Brain Res*. 1985; 335(2):326–9. [PubMed: 4005560]
64. Escartin C, et al. Activation of astrocytes by CNTF induces metabolic plasticity and increases resistance to metabolic insults. *J Neurosci*. 2007; 27(27):7094–104. [PubMed: 17611262]
65. Ho HT, Dahlin A, Wang J. Expression Profiling of Solute Carrier Gene Families at the Blood-CSF Barrier. *Front Pharmacol*. 2012; 3:154. [PubMed: 22936914]
66. Rapoport SI. In vivo labeling of brain phospholipids by long-chain fatty acids: relation to turnover and function. *Lipids*. 1996; 31:S97–101. Suppl. [PubMed: 8729102]
67. Spector R. Fatty acid transport through the blood-brain barrier. *J Neurochem*. 1988; 50(2):639–43. [PubMed: 3335863]

68. Miller JC, Gnaedinger JM, Rapoport SI. Utilization of plasma fatty acid in rat brain: distribution of [¹⁴C]palmitate between oxidative and synthetic pathways. *J Neurochem.* 1987; 49(5):1507–14. [PubMed: 2889801]
69. Ebert D, Haller RG, Walton ME. Energy contribution of octanoate to intact rat brain metabolism measured by ¹³C nuclear magnetic resonance spectroscopy. *J Neurosci.* 2003; 23(13):5928–35. [PubMed: 12843297]
70. Ishiwata K, et al. A brain uptake study of [1-(¹¹C)]hexanoate in the mouse: the effect of hypoxia, starvation and substrate competition. *Ann Nucl Med.* 1996; 10(2):265–70. [PubMed: 8800460]
71. Oomura Y, et al. Effect of free fatty acid on the rat lateral hypothalamic neurons. *Physiol Behav.* 1975; 14(04):483–6. [PubMed: 1135293]
72. Randle PJ. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabetes Metab Rev.* 1998; 14(4):263–83. [PubMed: 10095997]
73. Le Foll C, et al. Characteristics and mechanisms of hypothalamic neuronal fatty acid sensing. *Am J Physiol Regul Integr Comp Physiol.* 2009; 297(3):R655–64. [PubMed: 19535676]
74. Obici S, et al. Central administration of oleic Acid inhibits glucose production and food intake. *Diabetes.* 2002; 51(2):271–5. [PubMed: 11812732]
75. Migrenne S, et al. Brain lipid sensing and nervous control of energy balance. *Diabetes Metab.* 2011; 37(2):83–8. [PubMed: 21185213]
76. Loftus TM, et al. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science.* 2000; 288(5475):2379–81. [PubMed: 10875926]
77. Ruderman NB, et al. Malonyl-CoA, fuel sensing, and insulin resistance. *Am J Physiol.* 1999; 276(1):E1–E18. Pt 1. [PubMed: 9886945]
78. Yang XJ, et al. Metabolic pathways that mediate inhibition of hypothalamic neurons by glucose. *Diabetes.* 2004; 53(1):67–73. [PubMed: 14693699]
79. Pizer ES, et al. Malonyl-coenzyme-A is a potential mediator of cytotoxicity induced by fatty-acid synthase inhibition in human breast cancer cells and xenografts. *Cancer Res.* 2000; 60(2):213–8. [PubMed: 10667561]
80. Kumar MV, et al. Differential effects of a centrally acting fatty acid synthase inhibitor in lean and obese mice. *Proc Natl Acad Sci U S A.* 2002; 99(4):1921–1925. [PubMed: 11854492]
81. Shimokawa T, Kumar MV, Lane MD. Effect of a fatty acid synthase inhibitor on food intake and expression of hypothalamic neuropeptides. *Proc Natl Acad Sci U S A.* 2002; 99(1):66–71. [PubMed: 11756683]
82. Hu Z, et al. Hypothalamic malonyl-CoA as a mediator of feeding behavior. *Proc Natl Acad Sci U S A.* 2003; 100(22):12624–9. [PubMed: 14532332]
83. Kim EK, et al. C75, a fatty acid synthase inhibitor, reduces food intake via hypothalamic AMP-activated protein kinase. *J Biol Chem.* 2004; 279(19):19970–6. [PubMed: 15028725]
84. Landree LE, et al. C75, a fatty acid synthase inhibitor, modulates AMP-activated protein kinase to alter neuronal energy metabolism. *J Biol Chem.* 2004; 279(5):3817–27. [PubMed: 14615481]
85. Hu Z, et al. A role for hypothalamic malonyl-CoA in the control of food intake. *J Biol Chem.* 2005; 280(48):39681–3. [PubMed: 16219771]
86. Cha SH, et al. Inhibition of hypothalamic fatty acid synthase triggers rapid activation of fatty acid oxidation in skeletal muscle. *Proc Natl Acad Sci U S A.* 2005; 102(41):14557–62. [PubMed: 16203972]
87. Gao S, et al. Leptin activates hypothalamic acetyl-CoA carboxylase to inhibit food intake. *Proc Natl Acad Sci U S A.* 2007; 104(44):17358–63. [PubMed: 17956983]
88. Obici S, et al. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nat Med.* 2003; 9(6):756–61. [PubMed: 12754501]
89. He W, et al. Molecular disruption of hypothalamic nutrient sensing induces obesity. *Nat Neurosci.* 2006; 9(2):227–33. [PubMed: 16415870]
90. Andrews ZB, et al. UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. *Nature.* 2008; 454(7206):846–51. [PubMed: 18668043]
91. Lopez M, et al. Hypothalamic fatty acid metabolism mediates the orexigenic action of ghrelin. *Cell Metab.* 2008; 7(5):389–99. [PubMed: 18460330]

92. Lage R, et al. Ghrelin effects on neuropeptides in the rat hypothalamus depend on fatty acid metabolism actions on BSX but not on gender. *FASEB J.* 2010
93. Mobbs CV, et al. Mining microarrays for metabolic meaning: nutritional regulation of hypothalamic gene expression. *Neurochem Res.* 2004; 29(6):1093–103. [PubMed: 15176466]
94. Cheng H, Isoda F, Mobbs CV. Estradiol impairs hypothalamic molecular responses to hypoglycemia. *Brain Res.* 2009; 1280:77–83. [PubMed: 19445909]
95. Poplawski MM, Mastaitis JW, Mobbs CV. Naloxone, but not valsartan, preserves responses to hypoglycemia after antecedent hypoglycemia: role of metabolic reprogramming in counterregulatory failure. *Diabetes.* 2011; 60(1):39–46. [PubMed: 20811039]
96. Diano S, et al. Peroxisome proliferation-associated control of reactive oxygen species sets melanocortin tone and feeding in diet-induced obesity. *Nat Med.* 2011; 17(9):1121–7. [PubMed: 21873987]
97. Page KA, et al. Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia. *Diabetes.* 2009; 58(5):1237–44. [PubMed: 19223595]
98. Kuhajda FP, et al. Synthesis and antitumor activity of an inhibitor of fatty acid synthase. *Proc Natl Acad Sci U S A.* 2000; 97(7):3450–4. [PubMed: 10716717]
99. Levin BE, et al. Metabolic sensing and the brain: who, what, where, and how? *Endocrinology.* 2011; 152(7):2552–7. [PubMed: 21521751]
100. Makowski L, et al. Metabolic profiling of PPARalpha–/– mice reveals defects in carnitine and amino acid homeostasis that are partially reversed by oral carnitine supplementation. *FASEB J.* 2009; 23(2):586–604. [PubMed: 18945875]
101. Xu J, et al. Peroxisome proliferator-activated receptor alpha (PPARalpha) influences substrate utilization for hepatic glucose production. *J Biol Chem.* 2002; 277(52):50237–44. [PubMed: 12176975]
102. Xu J, et al. Peroxisomal proliferator-activated receptor alpha deficiency diminishes insulin-responsiveness of gluconeogenic/glycolytic/pentose gene expression and substrate cycle flux. *Endocrinology.* 2004; 145(3):1087–95. [PubMed: 14670991]
103. Vaitheesvaran B, et al. Advantages of dynamic "closed loop" stable isotope flux phenotyping over static "open loop" clamps in detecting silent genetic and dietary phenotypes. *Metabolomics.* 2010; 6(2):180–190. [PubMed: 20445758]
104. Knauf C, et al. Peroxisome proliferator-activated receptor-alpha-null mice have increased white adipose tissue glucose utilization, GLUT4, and fat mass: Role in liver and brain. *Endocrinology.* 2006; 147(9):4067–78. [PubMed: 16777972]
105. Chakravarthy MV, et al. Brain fatty acid synthase activates PPARalpha to maintain energy homeostasis. *J Clin Invest.* 2007; 117(9):2539–52. [PubMed: 17694178]
106. Su H, et al. Glucose Enhances Leptin Signaling through Modulation of AMPK Activity. *PLoS One.* 2012; 7(2):e31636. [PubMed: 22359610]
107. Lam TK, Schwartz GJ, Rossetti L. Hypothalamic sensing of fatty acids. *Nat Neurosci.* 2005; 8(5):579–84. [PubMed: 15856066]
108. Pocai A, et al. Restoration of hypothalamic lipid sensing normalizes energy and glucose homeostasis in overfed rats. *J Clin Invest.* 2006; 116(4):1081–91. [PubMed: 16528412]
109. Richieri GV, Kleinfeld AM. Unbound free fatty acid levels in human serum. *J Lipid Res.* 1995; 36(2):229–40. [PubMed: 7751810]
110. Sonnenberg GE, et al. Plasma leptin concentrations during extended fasting and graded glucose infusions: relationships with changes in glucose, insulin, and FFA. *J Clin Endocrinol Metab.* 2001; 86(10):4895–900. [PubMed: 11600559]
111. Wortman MD, et al. C75 inhibits food intake by increasing CNS glucose metabolism. *Nat Med.* 2003; 9(5):483–5. [PubMed: 12724740]
112. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001; 414(6865):813–20. [PubMed: 11742414]

KEY POINTS

- All organisms must adapt to changing nutrient availability, with nutrient surplus promoting glucose metabolism and nutrient deficit promoting alternative fuels (in mammals, mainly free fatty acids).
- In mammals these complex metabolic adaptations are orchestrated by nutrient-sensing neurons in the ventromedial hypothalamus.
- At least some hypothalamic neurons can metabolize free fatty acids via beta oxidation, and that beta oxidation generally opposes effects of glucose on hypothalamic neurons.
- Hypothalamic beta oxidation promotes obese phenotypes including enhanced hepatic glucose output.
- The molecular mechanisms mediating the competition between glucose and lipid oxidation in the hypothalamus remain to be established but probably entail regulation of the Ppar family of transcription factors.

Synopsis

All organisms must adapt to changing nutrient availability, with nutrient surplus promoting glucose metabolism and nutrient deficit promoting alternative fuels (in mammals, mainly free fatty acids). In mammals these complex metabolic adaptations are orchestrated by nutrient-sensing neurons in the ventromedial hypothalamus. Historically neurons in the ventromedial hypothalamus were known primarily for their essential role in regulating energy balance because destruction of this brain area produces robust obesity and associated impairments in glucose homeostasis. For several decades a key property of these neurons was thought to be their ability to sense glucose, but this “glucostat” hypothesis fell out of favor more than 40 years ago. More recently the role of leptin and insulin in regulating the relevant hypothalamic neurons has been emphasized. However in the last 20 years it has become increasingly clear that a major function of glucose-sensing neurons in the hypothalamus is to regulate blood glucose. When these neurons sense glucose levels are too low (about 50 mg/dl) they activate robust counterregulatory responses to enhance glucose production, primarily from liver, and reduce peripheral metabolism. Historically it has been thought that the brain relied minimally on free fatty acids for energy production, although it has long been known that astrocytes can robustly metabolize free fatty acids. More recently it has become clear that at least some hypothalamic neurons can metabolize free fatty acids via beta oxidation, and that beta oxidation generally opposes effects of glucose on hypothalamic neurons. Thus hypothalamic beta oxidation promotes obese phenotypes including enhanced hepatic glucose output. One mechanism mediating these effects of hypothalamic beta oxidation may be a reduction in the accumulation of long-chain fatty acids that may serve to activate signaling systems such as PKC isoforms. Another mechanism may be that beta oxidation inhibits glucose metabolism, which itself is a signal for nutritional sufficiency. The molecular mechanisms mediating the competition between glucose and lipid oxidation in the hypothalamus remain to be established but probably entail regulation of the Ppar family of transcription factors.