Published in final edited form as:

Trends Endocrinol Metab. 2013 October ; 24(10): 488–494. doi:10.1016/j.tem.2013.05.007.

Metabolic mystery: Aging, obesity, diabetes and ventromedial hypothalamus

Charles V. Mobbs*, Cesar L. Moreno, and Michael Poplawski

Departments of Neuroscience, Endocrinology, and Geriatrics, and the Friedman Brain Institute, Mount Sinai School of Medicine, New York, NY 10029

Abstract

We propose that energy balance, glucose homeostasis, and aging are all regulated largely by the same nutrient-sensing neurons in the ventromedial hypothalamus (VMH). Although the central role of these neurons in regulating energy balance is clear, their role in regulating glucose homeostasis has only become more clear recently. It is the latter function that may be most relevant to aging and lifespan, by controlling the rate of glucose metabolism. Specifically, glucose-sensing neurons in VMH promote peripheral glucose metabolism, and dietary restriction, by reducing glucose metabolism in these neurons, reduces glucose metabolism of the rest of the body, thereby increasing lifespan. Here we discuss recent studies demonstrating the key role of hypothalamic neurons in driving aging and age-related diseases.

Keywords

Lifespan; glucose metabolism; dietary restriction

Glucose metabolism, not respiration, drives aging and determines lifespan

It is a truth universally acknowledged that metabolism drives aging. Indeed this intuition is so compelling that it may seem almost a tautology, equivalent to the proposition that life drives aging. The hypothesis that various aspects of metabolism drive aging is supported by studies of the robust effects of dietary restriction to increase lifespan in a wide range of species [1]. While for decades it was assumed that dietary restriction increases lifespan by reducing respiration, more recent studies have suggested that, rather than a decrease, an increase in respiration may be required for the life-extending effects of dietary restriction [2] and glucose restriction [3].

© 2013 Elsevier Ltd. All rights reserved.

*charles.mobbs@mssm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Excess nutrition and lifespan

A remarkable aspect of the protective effects of dietary restriction is that not only is lifespan extended, virtually all age-related impairments and diseases are also reduced, including cancer [4] and models of neurological diseases [5, 6]. In considering mechanisms mediating the protective effects of dietary restriction (i.e., nutritional deficit) during aging, it is useful to consider the contrary condition: the deleterious effects of nutritional excess (i.e., obesity and diabetes). Obesity is the major risk factor for diabetes, and as the Diabetes Control and Complications Trial (DCCT) and similar trials have conclusively demonstrated, the cause of pathology in diabetes is excess glucose [7]. While the deleterious effects of obesity and diabetes are so familiar as to appear almost intuitively obvious, this intuition is misleading. In fact, the opposite is the more obvious: without nutritional resources, life is impossible. Conversely, it is not at all obvious why excess nutritional resources should be deleterious. For the vast majority of cells, metabolism is driven by demand, not supply; most steps in glycolysis, especially rate-limiting steps such as hexokinase, are inhibited by ATP or other indicators of cellular energy status [8]. In short this is what we call the metabolic mystery: why is moderate excess nutritional resources widely deleterious, yet moderate deficit of nutritional resources is widely protective?

Of course it is possible that mechanisms driving aging and processes mediating the protective effects of dietary restriction and the deleterious effects of excess nutritional resources are completely independent [1]. On the other hand, it may be heuristically useful to apply Occam's razor and assume common mechanisms mediating this apparent continuum. If so, the most likely molecular component of such a hypothetical continuum would be glucose, since it has been conclusively demonstrated that even moderately elevated glucose drives pathologies caused by diabetes [7]. Glucose toxicity appears to entail a final common metabolic pathway driving oxidative stress [9]. While obesity might cause pathologies independent of frank diabetes, post-prandial glucose and insulin excursions are almost certainly exaggerated in obesity, likely leading to increased glucose metabolism in many tissues.

A related consideration is the hypothesis that dietary restriction is only protective in the artificial circumstance of "metabolically morbid" and "sedentary, obese, glucose intolerant" aging animals that occur under laboratory conditions [10]. As indicated above, the mechanisms by which such a metabolic state exacerbates such a wide range of pathologies including cancer and neurological disease, are largely unknown and likely fall on a continuum with those of dietary restriction. However dietary restriction appears to be protective even in the absence of such metabolically morbid pathologies. While the "metabolically morbid" description certainly applies to aging Sprague-Dawley rats, the standard mouse strain for aging, C57Bl/6J does not become obese during aging, and actually exhibits improved glucose tolerance during aging [11]. Similarly, producing obesity by a high-fat diet in mice, shortens lifespan much less than dietary restriction increases lifespan [12]. Furthermore dietary restriction is highly protective in *C. elegans* [13], *Drosophila* [14], and even yeast [15], which show no evidence of metabolic morbidity during aging. Nevertheless we agree with the hypothesis that the mechanisms by which obesity and

diabetes reduce lifespan largely overlap with the mechanisms by which dietary restriction increases lifespan, though these mechanisms remain to be elucidated.

Glucose metabolism and aging

The most conclusive evidence that glucose metabolism drives aging is in yeast, in which reduction of glucose concentrations increases lifespan [15]. Almost as conclusive is that in *C. elegans* inhibition of glucose metabolism increases lifespan [3], whereas elevated glucose reduces lifespan [16]. Of particular interest, glucose shortens lifespan at least in part by inhibiting daf-16, the worm ortholog of the FOXO family of transcription factors, the same mechanism by which the insulin-like pathway shortens lifespan [16]. Furthermore, protective effects of dietary restriction are blocked by inhibiting the transcriptional co-activator cAMP response element-binding protein (creb)-binding protein (Cbp), which also blocks the switch from glucose utilization to less toxic alternative metabolic pathways especially lipid metabolism [6]. Equally compelling, in Snell dwarf mice, which are deficient in IGF-1 and are long-lived, glucose metabolism is reduced by about 50% whereas blood glucose levels are reduced by only about 25% [17]. Conversely, lipid (oleic acid) metabolism is elevated about 20% in these mice and is associated with a 50% reduction in tissue triacylglycerol levels [17]. Other genetically dwarf mice exhibit similar metabolic profiles [18]. Interestingly, in humans with Type 2 diabetes, intensive insulin therapy is associated with increased 5-year mortality, suggesting that deleterious effects of insulin-stimulated glucose metabolism are greater than protective effects of reducing blood glucose [19].

The hypothesis that glucose metabolism drives aging (or at least limits lifespan) is supported by the discovery that reductions in the Insulin-like growth factor 1 IGF1/insulin signaling pathways in *C. elegans* [20], *Drosophila* [21], mice [22], and possibly humans [23], results in increased lifespan and reduced age-related pathologies. Since the canonical function of insulin is to enhance glucose metabolism, the observation that inactivation of the insulin/IGF1 receptor strikingly increases lifespan supports the hypothesis that glucose metabolism limits lifespan.

While it is clear that insulin/IGF1 signaling drives key aspects of the aging process, it is not clear whether glucose metabolism mediates these effects or whether reduced insulin/IGF1 signaling mediates effects of dietary restriction. While the latter is an appealing hypothesis, it was initially undermined by reports that in a genetic model of dietary restriction in the worm, mutations in the *eat-2* gene (encodes for a nicotinic acetylcholine receptor subunit that functions in the pharyngeal muscle), and the *daf-2* gene (the worm ortholog of IGF-1 receptor in the worm), produce additive effects on lifespan. Also, extension of lifespan by the *eat-2* mutation did not require activity of the *daf-16* gene, while extension of lifespan by the *daf-2* gene did [24], suggesting that these factors extend lifespan by independent mechanisms. Similarly, dietary restriction increased lifespan of the long-lived growth hormone (GH)-deficient dwarf mouse [22], leading these investigators to conclude that dietary restriction and the IGF1 pathway increase lifespan through at least partially distinct mechanisms. On the other hand, for other protocols of dietary restriction in which lifespan is optimized, life extension does require *daf-16* [6]. Long-lived dwarf mice [17] and several

models of long-lived *C. elegans* [25] are also characterized by relatively reduced glucose metabolism. These data suggest that at least one common pathway by which both dietary restriction and reduced insulin-IGF1 signaling increases lifespan is by reducing glucose metabolism. Conversely, this implies that glucose metabolism drives at least some key aspects of the aging process, as is the case with pathologies produced in diabetes [9].

Can glucose metabolism be toxic during aging?

The hypothesis that glucose metabolism drives aging implies that glucose metabolism is more toxic than alternative pathways. This hypothesis is supported by evidence that dietary restriction entails a metabolic switch away from glucose utilization and toward beta oxidation [26, 27]. Of particular importance, inhibition of Cbp prevents this switch and also prevents the protective effects of dietary restriction [6]. A key element of this model is that the protective effects of dietary restriction do not require reduction in metabolic rate, that is, the mechanism is “ATP-neutral”. In fact, generation of ATP from glucose metabolism requires less oxygen per ATP molecule than generation of ATP from lipid metabolism, but also produces more oxidative stress [26, 27]. Therefore the protective effects of dietary restriction may actually require increased oxygen consumption, consistent with reported results [2, 3]. The precise mechanisms by which glucose metabolism is relatively more toxic than lipid, amino acid, or ketone metabolism are complex. However mechanisms mediating toxic effects of glucose metabolism probably entail increased production of oxidative stress (in part due to increased NADH), reduced ability to counter oxidative stress (in part due to reduced production of NADPH), reduced turnover of oxidized protein and lipids, a pattern originally observed in VMH but probably exhibited by most tissues [26, 27] (Figure 1).

VMH neurons determine glucose homeostasis, energy balance, and lifespan

If glucose metabolism drives at least some aspects of the aging process as it does for diabetes, what determines glucose metabolism? For the vast majority of cells, glucose metabolism is determined by demand, subject to neuroendocrine regulation: glycolysis is highly regulated by the cellular energy state, so elevated glucose within normal range does not by itself increase glucose metabolism. Furthermore reducing blood glucose does not by itself increase lifespan [28]. For insulin-sensitive tissues such as liver [29], muscle [30], and fat [31], insulin is the main determinant of glucose metabolism, mediated through several mechanisms that enhance glycolytic capacity. However, insulin-sensitive tissues are not the tissues that produce the main morbidity and mortality in diabetes or aging. For example the main complications of diabetes are peripheral neuropathy, retinopathy, and nephropathy, and there is little evidence that these tissues are nearly as responsive to insulin as are liver, muscle, and adipose tissue. Similarly a major cause of morbidity during aging is neurodegeneration, and in general insulin does not stimulate glucose metabolism in neurons. This suggests the potential importance of extra-pancreatic mechanisms regulating glucose metabolism in both aging and diabetes. Such mechanisms would presumably, like pancreatic beta cells, exhibit the rare property of responding to changes in glucose supply as well as other changes in nutritional state. In *C. elegans*, protective effects of dietary restriction are mediated by only 2 neurons, the ASI nutrient- and chemosensory neurons that are the sole

source of TGF-beta [32]. We hypothesize that the most likely equivalent of these neurons in mammals are the glucose-sensing neurons in the VMH. For purposes of this review we use the term “VMH” to include both the ventromedial nucleus and the adjacent arcuate nucleus, and neurons expressing Pro-opiomelanocorticotropin (POMC) that are adjacent to the ventromedial nucleus, since most studies (including lesion, stimulation, infusion, and microdissection) cannot functionally distinguish between these areas (see Glossary).

The VMH as an energy sensor

The VMH has been implicated as a key area regulating (and, therefore presumably sensing) energy balance at least since 1940, when Hetherington and Ranson reported that lesions in the VMH produced robust increases in adiposity [33]. Electrical stimulation of VMH neurons rapidly increases blood glucose and decreases liver glycogen production, which is associated with increased epinephrine and glucagon release but no change in insulin [34]. Similarly, stimulation of the VMH increases glucose uptake in brown adipose tissue, muscle, and liver, but not in white adipose tissue [35]. Conversely, ablation of VMH neurons leads to a rapid (within 10 minutes) increase in insulin secretion, comparable to the effect of glucose itself, and which is dependent on the vagus nerve [36]. Collectively, these data suggest that neurons in the VMH play a major role in regulating glucose homeostasis, both directly through the autonomic nervous system and indirectly by regulating insulin and glucagon secretion. We note that many other parts of the brain impinge on energy balance directly and indirectly (like the hippocampus), but we focus on VMH neurons because there are far more data supporting a role for these neurons in the regulation of glucose metabolism than for any other area of the brain.

The VMH and glucose sensing

A particularly informative variant of the classic lesion studies is that the compound gold-thio-glucose, when injected peripherally in mice, produces a highly specific lesion in the VMH that causes obesity, and, in some strains, diabetes [37]. This lesion requires the glucose moiety and can be prevented by either hyperglycemia or glucose derivatives, supporting the hypothesis that the relevant neurons are particularly sensitive to, and likely regulated by, glucose. Interestingly, free fatty acids (FFAs) oppose the effects of glucose on hypothalamic neuronal activity, an observation consistent with the hypothesis that glucose serves as a positive signal of nutritional resources whereas FFAs, which are released during fasting, serves as a negative signal of nutritional resources [38]. The physiological significance of these glucose-sensing neurons was demonstrated by the observation that infusion of the glycolytic inhibitor 2-deoxyglucose produces a rapid and robust increase in epinephrine and glucagon that act to increase blood glucose [39], whereas infusion of glucose into the same area prevents these counterregulatory responses to whole-body hypoglycemia [40]. As in pancreatic beta cells, the ability of hypothalamic neurons to sense glucose demand is mediated by the pancreatic form of glucokinase [41]. Thus, it is of particular interest that glucokinase in the VMH is required for counterregulatory responses to whole-body hypoglycemia [42]. Consistent with these observations, infusion of leptin, another positive signal of nutritional resources, into the VMH, but not lateral hypothalamus, robustly increases glucose uptake in brown adipose tissue, skeletal muscles, and heart, but not white adipose tissue, mediated by the sympathetic nervous system [43]. Taken as a whole, these

studies clearly indicate that positive signals of nutritional resources, glucose and leptin, in the VMH, reduce hepatic glucose output and increase peripheral glucose metabolism.

Similar to effects of glucose and leptin, inhibition of the enzyme carnitine palmitoyltransferase I (Cpt1a) and thus inhibition of FFAs beta oxidation in the VMH reduces hepatic glucose output [44]. Similarly, the pro-obese phenotypes (e.g., hyperphagia), promoted by the gut orexigenic peptide ghrelin, requires Cpt1-mediated beta oxidation in hypothalamic neurons [45]. Furthermore, fasting induces the mobilization and metabolism of lipids in the hypothalamus that are required for molecular responses to fasting [46]. Consistent with these observations, Cpt1a in the VMH is induced by fasting in the VMH but not the cortex, rapidly reversed 4 hours after feeding [47]. FFAs are normally elevated by fasting, leading to the activation of the nuclear receptor peroxisome proliferator-activated receptor (Ppar)-alpha, which then induces Cpt1a (stimulating metabolism of FFAs) as well as genes that inhibit glucose metabolism, such as pyruvate dehydrogenase kinase, isozyme 4Pdk4 (PDK4) [48].

Ppar-alpha and Cbp determine VMH glucose metabolism and, thereby, glucose metabolism, energy balance, and lifespan

A single episode of hypoglycemia induces several Ppar-alpha target genes in the VMH, and the induction of these genes is preferentially lost after antecedent hypoglycemia which impairs counterregulatory responses to hypoglycemia [49]. Furthermore, Ppar-alpha knockout mice exhibit elevated whole-body glucose metabolism that is not reversed by replacing Ppar-alpha in the liver, but is reversed by activating Ppar-alpha in the brain [50]. This observation suggested that the increased glucose metabolism in Ppar-alpha knockout mice “may result from the absence of PPARalpha in the brain” [50]. Furthermore, pharmacological activation of Ppar-alpha specifically in the hypothalamus reverses peripheral hypoglycemia observed in fatty acid synthase (FAS) knockout mice [51]. Since hypothalamic expression of even more Ppar-alpha target genes is induced by fasting [47], these observations led to the hypothesis that protective effects of dietary restriction are mediated in part via activation of Ppar-alpha in the VMH by FFAs that are abundant in those conditions.

A key co-factor required for Ppar-alpha activity is the co-transcriptional activator Cbp [52]. Indeed, expression of Cbp in the VMH genetically, correlates positively with lifespan, and inhibition of Cbp blocks the protective effects of dietary restriction during aging, including lifespan extension [6]. Consistent with its coactivation with Ppar-alpha, Cbp is necessary for the protective effect of dietary restriction to switch from glucose utilization to beta oxidation [6]. Based on its function as a histone acetyltransferase, the HDAC inhibitor sodium butyrate mimics the effect of dietary restriction to increase lifespan and reduce proteotoxicity in a model of Alzheimer’s disease [6]. A molecule highly similar to butyrate, the ketone 3-beta-hydroxybutyrate, protects against oxidative stress, and a ketogenic diet, which enhances plasma levels of this ketone, reversed diabetic nephropathy [53]. It is therefore of particular interest that this same ketone is, like butyrate, an HDAC1 inhibitor that is also induced by dietary restriction [54]

Taken together these results suggest that some of the protective effects of dietary restriction are due to increased blood levels of 3-beta-hydroxybutyrate, which would amplify the protective effects of Cbp in the VMH [53]. Thus increased hypothalamic Cbp activity (either by increased expression or enhanced efficacy due to HDAC inhibition) would be expected to reduce hypothalamic glucose metabolism, leading to increased lifespan by reducing peripheral glucose metabolism. Interestingly, the mouse strain exhibiting the highest expression of Cbp in the VMH, C57Bl/6J, not only lives the longest, but also exhibits the most robust obese phenotypes (including elevated plasma glucose) on a high-fat diet, relative to A/J mice, the strain with the lowest expression of VMH Cbp [55]. Consistent with its role in promoting the switch from glucose metabolism to lipid metabolism [6], these observations suggest a surprising aspect of the metabolic mystery: long-lived genotypes under optimum (low-fat) conditions are also most susceptible to obesity and hyperglycemia under (high-fat) excess nutrient conditions.

Two recent studies have supported this model. In one study, administration of ghrelin, which induces appetite, to mice in which food was matched to normal controls, protected against pathology (improved cognition, reduced accumulation of amyloid beta and inflammation) in mouse model of Alzheimer's disease [56]. Since ghrelin promotes appetite at least in part by enhancing lipid metabolism (thus effectively reduces glucose metabolism) in hypothalamic neurons [45], these studies are consistent with the hypothesis that reduced hypothalamic glucose metabolism mediates at least some of the effects of dietary restriction on models of neurodegeneration. An even more striking study demonstrated that reducing inflammation specifically in the hypothalamus extends lifespan and reduces a wide range of age-related impairments, including on cognition, sarcopenia, endurance, and bone mass [57]. Since local inflammation enhances glycolysis of microglial cells [58], these studies are generally consistent with the hypothesis that hypothalamic glycolysis drives aging in the periphery.

Concluding remarks and future directions

Taken together the results described above suggest the hypothesis that neurons in the VMH control not only energy balance and glucose homeostasis but also lifespan, largely by controlling whole-body glucose metabolism (in part directly through the autonomic nervous system, in part by regulation of growth hormone/IGF1 and insulin secretion). Thus nutrient-sensitive neurons in the VMH may constitute the equivalent of the two ASI neurons that mediate the protective effects of dietary restriction on lifespan in *C. elegans* [32]. The VMH neurons that may correspond to ASI neurons probably include POMC neurons, as POMC expression is reduced in leptin-deficient ob/ob mice and genetic correction of this reduction completely corrects glucose homeostasis in ob/ob mice, in part by regulating hepatic transcriptional mechanisms [59]. However, BDNF and Sf-1 neurons in the VMN, which are stimulated by glucose and inhibition of which causes obesity [60] likely also play a role, plausibly in part by reciprocally activating POMC neurons, which in turn play a dominant role in regulating peripheral glucose homeostasis [61, 62] (Figure 2). A cumulative and persistent effect of glucose to activate these and POMC neurons, and possibly reduce Ppar-alpha and Cbp activity, may also drive increased glucose metabolism during aging, potentially accounting for weight loss, impaired counterregulation, and anorexia that occurs late in life [26].

Acknowledgments

We thank Penny Dacks, Fumiko Isoda, Esther Kim, Minhua Zhang, and Kelvin Yen for their many contributions to the ideas developed in this review. The studies described herein were supported by R01 HD060914 (CVM) and 1F31AG042299 (CM).

Glossary

ASI neurons	A pair of symmetrical chemosensory neurons in <i>C. elegans</i> necessary and sufficient to mediate protective effects of dietary restriction on lifespan
Brain-derived neurotrophic factor (BDNF)	A neurotrophic factor which, in the hypothalamus, is expressed largely or perhaps entirely in the ventromedial nucleus
Dietary restriction	Any of several restrictions of food intake (most commonly in rodents a reduction in caloric intake of about 25%) that increases life span
Pro-opiomelanocorticotropin (POMC)	A gene expressed in a small number of neurons in the ventromedial hypothalamus, partly in the arcuate nucleus and extending to just the outside of the ventromedial nucleus. The gene encodes a polypeptide precursor whose most important product, alpha-MSH, regulates energy balance and glucose homeostasis
Steroidogenic factor 1 (Sf-1)	A transcriptional factor, which, in the hypothalamus, is expressed largely or exclusively in neurons in the ventromedial nucleus. Ablation of Sf-1 prevents the development of the ventromedial nucleus and produces obesity
Ventromedial hypothalamus (VMH)	A small region at the base of the brain, just above the pituitary, that senses nutritional state, destruction of which causes obesity. This area includes the ventromedial nucleus and the arcuate nucleus, and is sometimes referred to as the medial basal hypothalamus

References

1. Fontana L, et al. Extending healthy life span--from yeast to humans. *Science*. 2010; 328:321–326. [PubMed: 20395504]
2. Lin SJ, et al. Calorie restriction extends *Saccharomyces cerevisiae* lifespan by increasing respiration. *Nature*. 2002; 418:344–348. [PubMed: 12124627]
3. Schulz TJ, et al. Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. *Cell Metab*. 2007; 6:280–293. [PubMed: 17908557]
4. Minor RK, et al. The arcuate nucleus and neuropeptide Y contribute to the antitumorigenic effect of calorie restriction. *Aging Cell*. 2011; 10:483–492. [PubMed: 21385308]
5. Mouton PR, et al. Caloric restriction attenuates amyloid deposition in middle-aged dtg APP/PS1 mice. *Neurosci Lett*. 2009; 464:184–187. [PubMed: 19699265]

6. Zhang M, et al. Role of CBP and SATB-1 in aging, dietary restriction, and insulin-like signaling. *PLoS Biol.* 2009; 7:e1000245. [PubMed: 19924292]
7. Pop-Busui R, et al. DCCT and EDIC studies in type 1 diabetes: lessons for diabetic neuropathy regarding metabolic memory and natural history. *Curr Diab Rep.* 2010; 10:276–282. [PubMed: 20464532]
8. Moreno-Sanchez R, et al. Metabolic control analysis: a tool for designing strategies to manipulate metabolic pathways. *J Biomed Biotechnol.* 2008; 2008:597913. [PubMed: 18629230]
9. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001; 414:813–820. [PubMed: 11742414]
10. Martin B, et al. “Control” laboratory rodents are metabolically morbid: why it matters. *Proc Natl Acad Sci U S A.* 2010; 107:6127–6133. [PubMed: 20194732]
11. Leiter EH, et al. Aging and glucose homeostasis in C57Bl/6J male mice. *FASEB J.* 1988; 2:2807–2811. [PubMed: 3044905]
12. Mizuno T, et al. Obesity over the life course. *Sci Aging Knowledge Environ.* 2004; 2004:re4. [PubMed: 15201431]
13. Greer EL, Brunet A. Different dietary restriction regimens extend lifespan by both independent and overlapping genetic pathways in *C. elegans*. *Aging Cell.* 2009; 8:113–127. [PubMed: 19239417]
14. Clancy DJ, et al. Dietary restriction in long-lived dwarf flies. *Science.* 2002; 296:319. [PubMed: 11951037]
15. Lin SJ, et al. Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*. *Science.* 2000; 289:2126–2128. [PubMed: 11000115]
16. Lee SJ, et al. Glucose shortens the life span of *C. elegans* by downregulating DAF-16/FOXO activity and aquaporin gene expression. *Cell Metab.* 2009; 10:379–391. [PubMed: 19883616]
17. Brooks NL, et al. Low utilization of circulating glucose after food withdrawal in Snell dwarf mice. *J Biol Chem.* 2007
18. Bartke A, Westbrook R. Metabolic characteristics of long-lived mice. *Front Genet.* 2012; 3:288. [PubMed: 23248643]
19. Gerstein HC, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med.* 2011; 364:818–828. [PubMed: 21366473]
20. Kimura KD, et al. *daf-2*, an insulin receptor-like gene that regulates longevity and diapause in *Caenorhabditis elegans*. *Science.* 1997; 277:942–946. [PubMed: 9252323]
21. Tatar M, et al. A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science.* 2001; 292:107–110. [PubMed: 11292875]
22. Bartke A, et al. Extending the lifespan of long-lived mice. *Nature.* 2001; 414:412. [PubMed: 11719795]
23. Guevara-Aguirre J, et al. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *Sci Transl Med.* 2011; 3:70ra13.
24. Lakowski B, Hekimi S. The genetics of caloric restriction in *Caenorhabditis elegans*. *Proc Natl Acad Sci U S A.* 1998; 95:13091–13096. [PubMed: 9789046]
25. Fuchs S, et al. A metabolic signature of long life in *Caenorhabditis elegans*. *BMC Biol.* 2010; 8:14. [PubMed: 20146810]
26. 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]
27. Guarente L. Mitochondria--a nexus for aging, calorie restriction, and sirtuins? *Cell.* 2008; 132:171–176. [PubMed: 18243090]
28. McCarter R, et al. Plasma glucose and the action of calorie restriction on aging. *J Gerontol A Biol Sci Med Sci.* 2007; 62:1059–1070. [PubMed: 17921417]
29. Zhou XY, et al. Insulin regulation of hepatic gluconeogenesis through phosphorylation of CREB-binding protein. *Nat Med.* 2004; 10:633–637. [PubMed: 15146178]
30. Yamada T, et al. {beta}-Hydroxybutyrate inhibits insulin-mediated glucose transport in mouse oxidative muscle. *Am J Physiol Endocrinol Metab.* 2010; 299:E364–373. [PubMed: 20516259]

31. Mizuno TM, et al. Specific preservation of biosynthetic responses to insulin in adipose tissue may contribute to hyperleptinemia in insulin-resistant obese mice. *J Nutr.* 2004; 134:1045–1050. [PubMed: 15113943]
32. Bishop NA, Guarente L. Two neurons mediate diet-restriction-induced longevity in *C. elegans*. *Nature.* 2007; 447:545–549. [PubMed: 17538612]
33. Hetherington AW, Ranson SW. Hypothalamic lesions and adiposity in the rat. *Anatomical Record.* 1940; 78:149–172.
34. Shimazu T, Ishikawa K. Modulation by the hypothalamus of glucagon and insulin secretion in rabbits: studies with electrical and chemical stimulations. *Endocrinology.* 1981; 108:605–611. [PubMed: 7004860]
35. Shimazu T, et al. Role of the hypothalamus in insulin-independent glucose uptake in peripheral tissues. *Brain Res Bull.* 1991; 27:501–504. [PubMed: 1959052]
36. Berthoud HR, Jeanrenaud B. Acute hyperinsulinemia and its reversal by vagotomy after lesions of the ventromedial hypothalamus in anesthetized rats. *Endocrinology.* 1979; 105:146–151. [PubMed: 446404]
37. Karasawa H, et al. Obesity-induced diabetes in mouse strains treated with gold thioglucose: a novel animal model for studying beta-cell dysfunction. *Obesity (Silver Spring).* 2011; 19:514–521. [PubMed: 20706204]
38. Moreno C, et al. Regulation of Peripheral Metabolism by Substrate Partitioning in the Brain. *Endocrinol Metab Clin North Am.* 2013; 42:67–80. [PubMed: 23391240]
39. Borg WP, et al. Local ventromedial hypothalamus glucopenia triggers counterregulatory hormone release. *Diabetes.* 1995; 44:180–184. [PubMed: 7859938]
40. Borg MA, et al. Local ventromedial hypothalamus glucose perfusion blocks counterregulation during systemic hypoglycemia in awake rats. *J Clin Invest.* 1997; 99:361–365. [PubMed: 9006005]
41. Yang XJ, et al. Metabolic pathways that mediate inhibition of hypothalamic neurons by glucose. *Diabetes.* 2004; 53:67–73. [PubMed: 14693699]
42. Levin BE, et al. Ventromedial hypothalamic glucokinase is an important mediator of the counterregulatory response to insulin-induced hypoglycemia. *Diabetes.* 2008; 57:1371–1379. [PubMed: 18292346]
43. 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; 48:1706–1712. [PubMed: 10480598]
44. Obici S, et al. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. *Nat Med.* 2003; 9:756–761. [PubMed: 12754501]
45. Andrews ZB, et al. UCP2 mediates ghrelin's action on NPY/AgRP neurons by lowering free radicals. *Nature.* 2008; 454:846–851. [PubMed: 18668043]
46. Kaushik S, et al. Autophagy in Hypothalamic AgRP Neurons Regulates Food Intake and Energy Balance. *Cell Metab.* 2011; 14:173–183. [PubMed: 21803288]
47. Poplawski MM, et al. Hypothalamic responses to fasting indicate metabolic reprogramming away from glycolysis toward lipid oxidation. *Endocrinology.* 2010; 151:5206–5217. [PubMed: 20881243]
48. Muoio DM, et al. Peroxisome proliferator-activated receptor- α regulates fatty acid utilization in primary human skeletal muscle cells. *Diabetes.* 2002; 51:901–909. [PubMed: 11916905]
49. Poplawski MM, et al. Naloxone, but not valsartan, preserves responses to hypoglycemia after antecedent hypoglycemia: role of metabolic reprogramming in counterregulatory failure. *Diabetes.* 2011; 60:39–46. [PubMed: 20811039]
50. Knauf C, et al. Peroxisome proliferator-activated receptor- α -null mice have increased white adipose tissue glucose utilization, GLUT4, and fat mass: Role in liver and brain. *Endocrinology.* 2006; 147:4067–4078. [PubMed: 16777972]
51. Chakravarthy MV, et al. Brain fatty acid synthase activates PPAR α to maintain energy homeostasis. *J Clin Invest.* 2007; 117:2539–2552. [PubMed: 17694178]
52. Takahashi N, et al. Overexpression and ribozyme-mediated targeting of transcriptional coactivators CREB-binding protein and p300 revealed their indispensable roles in adipocyte differentiation

- through the regulation of peroxisome proliferator-activated receptor gamma. *J Biol Chem*. 2002; 277:16906–16912. [PubMed: 11884404]
53. Poplawski MM, et al. Reversal of diabetic nephropathy by a ketogenic diet. *PLoS One*. 2011; 6:e18604. [PubMed: 21533091]
54. Shimazu T, et al. Suppression of oxidative stress by beta-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science*. 2013; 339:211–214. [PubMed: 23223453]
55. Surwit RS, et al. Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. *Metabolism*. 1995; 44:645–651. [PubMed: 7752914]
56. Dhurandhar EJ, et al. Hunger in the absence of caloric restriction improves cognition and attenuates Alzheimer's disease pathology in a mouse model. *PLoS One*. 2013; 8:e60437. [PubMed: 23565247]
57. Zhang G, et al. Hypothalamic programming of systemic ageing involving IKK-beta, NF-kappaB and GnRH. *Nature*. 2013; 497:211–216. [PubMed: 23636330]
58. Voloboueva LA, et al. Inflammatory response of microglial BV-2 cells includes a glycolytic shift and is modulated by mitochondrial glucose-regulated protein 75/mortalin. *FEBS Lett*. 2013; 587:756–762. [PubMed: 23395614]
59. Mizuno TM, et al. Transgenic neuronal expression of proopiomelanocortin attenuates fasting-induced hyperphagia and reverses metabolic impairments in leptin-deficient obese mice. *Diabetes*. 2003; 52:2675–2683. [PubMed: 14578285]
60. Unger TJ, et al. Selective deletion of Bdnf in the ventromedial and dorsomedial hypothalamus of adult mice results in hyperphagic behavior and obesity. *J Neurosci*. 2007; 27:14265–14274. [PubMed: 18160634]
61. King BM. The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. *Physiol Behav*. 2006; 87:221–244. [PubMed: 16412483]
62. Sternson SM, et al. Topographic mapping of VMH --> arcuate nucleus microcircuits and their reorganization by fasting. *Nat Neurosci*. 2005; 8:1356–1363. [PubMed: 16172601]

Outstanding Questions Box

- What are the hypothalamic cell types that mediate effects of PPAR-alpha and Cbp on energy balance, glucose metabolism, and lifespan?
- Are protective effects of dietary restriction due to increased FFAs and/or increased ketones, especially beta-hydroxybutyrate?
- Do hypothalamic Cbp and/or Ppar-alpha (or Ppar-gamma) mediate protective effects of dietary restriction and the ketogenic diet?
- Do hypothalamic Cbp and/or Ppar-alpha (or Ppar-gamma) mediate counter-regulatory responses to hypoglycemia and fasting?

Highlights

- The metabolic mystery highlights the remarkable fact that even moderately excess nutritional resources are broadly toxic, whereas moderately reduced nutritional resources are broadly protective.
- Many studies have shown that neurons in the ventromedial hypothalamus (VMH) regulate energy balance, and more recently, glucose homeostasis.
- It is increasingly clear that glucose metabolism drives key aspects of the aging process, as well as diabetic complications.
- We propose that nutrient-sensing neurons in the VMH also impinge on the aging process by regulating peripheral glucose metabolism, and that dietary restriction is protective by reducing glucose metabolism in these neurons.

Figure 1. Steps in the metabolic switch for glucose to FFA utilization

During energy deficit, including dietary restriction, an overall decrease of glucose utilization is accompanied by a switch to alternative fuels, predominantly fatty acids. Molecular evidence of this switch has been observed in VMH and liver, and probably occurs in most other tissues as well. Evidence for this switch includes the induction of pyruvate dehydrogenase (Pdk), which disconnects glycolysis from the Krebs cycle; instead pyruvate is converted to lactate at the expense of NADH. On the other hand, fatty acid catabolism is promoted, as suggested by fatty acid transporters into the cell (Fatp) and the mitochondria (Cpt1a). Accordingly, this switch also includes an activation of the Ppar family, transcription factors whose main physiological function is to effect this metabolic switch. A major physiological effect of reducing glycolysis and increasing fatty acid oxidation is the reduction of oxidative stress. First, glucose shunted through the pentose pathway results in a major production of anti-oxidative NADPH, which is also increased in the Krebs cycle during energy deficit by NADP-dependent Isocitrate dehydrogenase activity. Second, an overall reduction of NADH is sequential to reduced glycolysis, decreasing radical-producing complex I activity while favoring complex II, which does not produce free radicals. Other effects of this metabolic switch are to increase protein and lipid turnover, thus reducing the presence of oxidized macromolecules.

Figure 2. Proposed model of neurons in the VMH that regulate energy balance, glucose homeostasis, and lifespan

Glucose and leptin stimulate SF1 and POMC neurons in the VMH. These neurons stimulate each other forming a loop, which in addition to gene memory, perpetuates an increase of glucose metabolism in peripheral tissues. This activity in the VMH increases glucose uptake and metabolism in several tissues, while increasing insulin secretion, and decreasing hepatic glucose output.