Published in final edited form as:

Front Neuroendocrinol. 2013 April ; 34(2): 95–106. doi:10.1016/j.yfrne.2012.12.001.

Role of the hypothalamus in mediating protective effects of dietary restriction during aging

Penny A. Dacks^{1,2}, Cesar L. Moreno¹, Esther S. Kim¹, Bridget K. Marcellino¹, and Charles V. Mobbs^{1,3}

¹Department of Neurosciences and Friedman Brain Institute, Mount Sinai School of Medicine, New York, NY 10029

²Alzheimer's Drug Discovery Foundation, New York, NY 10019

Abstract

Dietary restriction (DR) can extend lifespan and reduce disease burden across a wide range of animals and yeast but the mechanisms mediating these remarkably protective effects remain to be elucidated despite extensive efforts. Although it has generally been assumed that protective effects of DR are cell-autonomous, there is considerable evidence that many whole-body responses to nutritional state, including DR, are regulated by nutrient-sensing neurons. In this review, we explore the hypothesis that nutrient sensing neurons in the ventromedial hypothalamus hierarchically regulate the protective responses of dietary restriction. We describe multiple peripheral responses that are hierarchically regulated by the hypothalamus and we present evidence for non-cell autonomous signaling of dietary restriction gathered from a diverse range of models including invertebrates, mammalian cell culture, and rodent studies.

Keywords

dietary restriction; caloric restriction; aging; ventromedial hypothalamus; autonomic; glucose metabolism

1. Introduction

Dietary restriction (DR) has been shown to extend lifespan and slow aging in highly divergent taxa including yeast, worms, spiders, flies, fish, mice, and rats [57]. DR can also protect against age-related diseases, including cancer [79, 201, 210–212], kidney disease [38], and models of Alzheimer's disease [226] [207] [152] [144] [217] [160] [223] [29], Parkinson's disease [50] [83] [123], Huntington's disease [192] [49], stroke [120] and other neurodegenerative diseases [27, 179]. Whether lifespan extension will extend to primates is currently unclear. Nevertheless, many of the physiological responses to DR are shared between humans, non-human primates, and other mammals including decreased cardiovascular disease risk factors, improved glucose regulation, decreased body temperature, and decreased inflammation [57] [190] [59] [214] [5].

© Â© 2XXX Elsevier Inc. All rights reserved

³Corresponding author: Telephone: 212-659-5929; FAX: 212-849-2510; 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.

While all cells in principle are capable of responding to nutritional availability [138], animals optimize responses to nutritional deficits by coordinating organ and tissue responses. In mammals the most important cells organizing responses to nutritional deficit are arguably the nutrient-sensing neurons of the ventromedial hypothalamus (VMH) which includes both the ventromedial nucleus and the arcuate nucleus [1, 53]. Neurons in these areas of the brain regulate neuroendocrine and autonomic nervous system control of glucose homeostasis, energy balance, and growth hormone (and thus insulin-like growth factor). They may also regulate the response of body temperature to nutritional deprivation through signaling with the preoptic area/anterior hypothalamus [11]. All of these systems are altered during nutritional deficit and potentially contribute to the protective effects of DR. In this review, we develop the hypothesis that nutrient-sensing neurons in the VMH mediate protective effects of DR.

2. Dietary Restriction Overview

DR elicits complex interacting pathways, many of which have been proposed to mediate protective effects [188]. For example, several signaling pathways are decreased including growth hormone (GH) and its downstream effector insulin-like growth factor-1 (IGF-1) [184], insulin [122], glucose metabolism [88], body temperature [32], inflammation [56], and mTOR activity [91]. In contrast, glucocorticoid secretion is increased [75, 97]. Since glucocorticoid secretion is also induced by other forms of stress in addition to DR [176], the latter observation has been used to support the hypothesis that protective effects of DR are due to hormesis, the phenomenon by which low levels of toxic insults can actually enhance functionality, presumably by inducing protective mechanisms [121]. While there may be some merit to this hypothesis, the majority of responses to DR are not generally induced by other stressors, so we do not further explore the applicability of hormesis.

For example, several signaling pathways are decreased including growth hormone (GH) and its downstream effector insulin-like growth factor-1 (IGF-1) [184], insulin [122], glucose metabolism [88], body temperature [32], inflammation [56], and mTOR activity [91]. In contrast, glucocorticoid secretion is increased [75, 97]. Since glucocorticoid secretion is also induced by other forms of stress in addition to DR [176], the latter observation has been used to support the hypothesis that protective effects of DR are due to hormesis, the phenomenon by which low levels of toxic insults can actually enhance functionality, presumably by inducing protective mechanisms [121]. While there may be some merit to this hypothesis, the majority of responses to DR are not generally induced by other stressors, so we do not further explore the applicability of hormesis.

Age-related impairments occur in probably all cell types and tissues mediated by mechanisms largely specific to those tissues (e.g., ovarian atresia and thymic involution [137, 213]). Furthermore mechanisms to respond to nutrient supplies also probably exist in all cell types and tissues (e.g., as with the lac operon, the presence of metabolites often induces the machinery necessary for their metabolism and reduces alternative metabolic pathways [138]). Similarly, as described in detail below, mechanisms producing circadian rhythms are also present in most cell types. Nevertheless these mechanisms may be highly influenced and effectively controlled by neuroendocrine mechanisms, as is the case with circadian rhythms. Herein we make the case that nutrient-sensing hypothalamic neurons mediate many effects of dietary restriction on cellular function during aging.

3. Evidence from invertebrates that protective effects of DR require cell non-autonomous nutrient sensing neurons

As with aging mechanisms in general, much of the most compelling evidence for mechanisms mediating protective effects of DR derives from elegant experiments in non-mammalian model organisms. These studies have demonstrated that extension of lifespan by DR either requires or is heavily modulated by small populations of nutrient sensing cells.

The best evidence that nutrient-sensing neurons mediate protective effects of DR derives from studies in *C. elegans* focusing on two ASI sensory neurons that regulate endocrine signals and peripheral metabolism in response to food availability [14]. Based on the known protective effects of the mammalian anti-oxidant transcription factor Nrf-1 [143], Bishop *et al.* hypothesized and demonstrated that DR lifespan extension in *C. elegans* requires Skn-1, the *C. elegans* homolog of Nrf-1 [14]. Remarkably, DR only induced Skn-1 in 2 neurons, the ASI chemo-nutrient sensory neurons. Ablation of these neurons blocked effects of DR to increase lifespan, and expressing Skn-1 only in these neurons completely supported protective effects of DR to increase lifespan [14]. Skn-1 specifically in these neurons alone also mediated effects of DR on whole-body oxygen consumption [14]. This seminal study demonstrated in *C. elegans* that nutrient sensing neurons regulate the metabolism of the entire body and are sufficient to mediate effects of DR on lifespan.

Further evidence that nutrient-sensing neurons mediate protective effects of DR comes from a series of elegant studies in *Drosophila* by Partridge and colleagues. In the adult brain of *Drosophila*, median neurosecretory (MNC) cells respond to nutrient availability by producing insulin-like peptides (DILPs). Although ablation of these cells does not affect feeding, it does block the effects of food availability on lifespan and fecundity [25]. Partial ablation of MNC cells increases lifespan, increases fasting glucose, increases lipid and carbohydrate storage in peripheral tissues, and reduces fecundity [24, 25]. Furthermore, although the loss of DILPs from MNCs is partially compensated for by up-regulation of DILP6 in fat bodies, the effects of DR on longevity and fecundity require DILPs produced by neurons [70]. Thus MNCs in *Drosophila* and ASI neurons in *C. elegans* share many features and suggest that such sensory cells can regulate lifespan independent of food intake.

Sensory cells controlling lifespan may sense nutritional state through both caloric and chemosensory mechanisms. In both *Drosophila* and *C. elegans*, exposure to nutrient-derived odors partially blocks the protective effects of DR on lifespan without affecting feeding [109] [156] [189]. Furthermore, DR increases lifespan when initiated in aged worms but this effect is independent of calorie intake because animals at this age no longer consume bacterial food [189]. The non-caloric signal of these effects is unknown, but several studies have demonstrated that a defect in sensory signaling can extend lifespan without altering food intake. These defects have included defective sensory cilia [9], a mutation in the odorant receptor Or83b [109] or the carbon dioxide olfactory sensor Gr63a [156], loss of sensory G proteins [105], or ablation of sensory cells [24, 25] [14] [4]. Although the ablation of either gustatory or olfactory neurons extends lifespan in *C. elegans*, the effects of gustatory neurons are completely daf-16 dependent while the olfactory neuron effects are not, indicating that sensory cells in *C. elegans* can modulate longevity via more than one circuit [4].

Several of the studies discussed above report that, in invertebrates, nutrient sensing cells may regulate longevity and DR through effects on whole-body metabolism [109] [14] [24], nutrient storage and availability [156] [24], and stress resistance [109] [24]. Together, these invertebrate studies indicate that small populations of nutrient sensing cells regulate peripheral responses to nutritional state as well as lifespan extension by DR.

As with all model organism experiments, it is unclear whether these principles from invertebrate animals will be translatable to humans and mammals. Nevertheless, many components of the responses to DR, including lifespan extension and/or health benefits, are similar across invertebrates and mammals [58]. Mammalian *in vitro* studies support the idea that intracellular responses to DR can be elicited in a non-cell-autonomous manner. Culturing mammalian cells with serum from rats, monkeys, or humans subjected to DR activates intracellular responses that mimic some effects of DR, including reduced cell proliferation, increased oxidative stress tolerance, increased stress response genes, increased Sirt1 expression, and decreased responses to TNFalpha [5, 44, 46].

4. Evidence that hypothalamic neurons are required for responses to DR or DR mimetics

If nutrient sensing cells mediate lifespan extension by DR, as suggested by the invertebrate studies, which mammalian cell types correspond to ASI neurons in *C. elegans* and MNC cells in *Drosophila*? A major clue is that ASI neurons (along with a few others) promote satiety in *C. elegans* [85]. In mammals, the classic “satiety” center of the brain is the ventromedial hypothalamus (VMH; including neurons in the ventromedial nucleus as well as the arcuate nucleus). Damage to this area causes loss of satiety and obesity (the classic “VMH” or simply “hypothalamic” obesity syndrome [21]). We have demonstrated that VMH neurons also exhibit many molecular and functional similarities to pancreatic beta cells [218]. For example, VMH neurons are uniquely sensitive to stimulation by glucose [148, 218], and stimulation of VMH neurons stimulates peripheral glucose metabolism [77, 131, 132, 173, 186, 194–196]. Interestingly, both ASI and MNC cells also exhibit many molecular and functional similarities to pancreatic beta cells including sensitivity to nutrients, production of insulin-like peptides, and promotion of glucose utilization [150]. We hypothesize that ancestral cellular precursors to VMH neurons and pancreatic beta cells supported functions similar to those of ASI and MNC neurons. However, over the course of evolution (perhaps due to greater body size of vertebrates), the cells diverged into two populations of glucose stimulated cells: one in the pancreas relatively near the intestinal site of nutrient absorption, and one in the hypothalamus at the site of hierarchical control of glucose homeostasis.

Lesion studies have supported that the protective effects of DR require nutrient sensing neurons in the VMH. DR normally suppresses tumorigenesis in rodents but this protective effect was blocked in two separate mouse models of impaired function of the VMH arcuate nucleus: lesion of the arcuate nucleus with monosodium glutamate or genetic deletion of a key arcuate neuropeptide NPY [133]. Arcuate nucleus ablation also blocked the DR suppression of fasting blood glucose in the monosodium glutamate model and the DR-induced increase of blood adiponectin in the NPY knockout model [133]. In another study, VMH lesions blocked the effect of DR to reduce resting energy expenditure [205]. These lesion studies, although not conclusive, indicate that the VMH is required for DR to protect against cancer and elicit major systemic changes in energy balance and glucose homeostasis.

Genetic manipulations in mice have also demonstrated that hypothalamic gene expression can be required for some protective responses to either DR or putative pharmacological mimetics of DR like resveratrol and rapamycin. The deacetylase Sirt2 is reported to mediate the protective effects of DR (glucose deprivation) in yeast [110] and its homolog sirtuins have been implicated in mediating metabolic responses to DR and fasting in mammals [34]. Two weeks of DR induced Sirt1 in the dorsomedial and lateral hypothalamus, though not the VMH, and transgenic mice with overexpression of SIRT1 in neurons enhanced the neurobehavioral response to fasting and DR [177]. In another study, improvements of glucose homeostasis by central or peripheral resveratrol, a DR mimetic and a putative

activator of SIRT1, were blocked by the inhibition of SIRT1 in the hypothalamus, possibly via glucose-sensing neurons [99]. Based on these data, it has been speculated that SIRT1 specifically in the hypothalamus may regulate aging [162].

Hypothalamic neurons may also mediate the protective effects of another putative DR mimetic, rapamycin, which extends lifespan in mice [78, 129] and protects against tumorigenesis [7] and age-related cognitive deficits [119]. The protective effects of rapamycin are believed to occur through its inhibition of the mTOR nutrient-sensing pathway [78]. Gene expression analysis indicates that DR suppresses hypothalamic mTOR [216] while feeding and central leptin treatment activate hypothalamic p70 S6 kinase 1 α (S6K), an effector of mTOR [15]. Over-activation of S6K in the mediobasal hypothalamus (that includes the VMH) was shown alter energy metabolism and cold tolerance [15]. Importantly, experimental over-activation of S6K in the mediobasal hypothalamus blocked the metabolic and feeding changes responses to fasting and the onset of metabolic syndrome and sustained overeating in response to a high-fat diet [15]. To our knowledge, no studies have similarly tested the role of hypothalamic S6K on responses to DR. However, the data suggest that hypothalamic mTOR and S6K are critical for metabolic responses to altered nutritional state.

The extent to which hypothalamic neurons mediate responses to dietary restriction in humans remains to be fully addressed, but the role of the hypothalamus in coordinating the body's responses to nutritional status appear to be largely similar to other mammals. For example, the role of hypothalamic neurons in regulating neuroendocrine functions and energy balance was first discovered in humans with hypothalamic tumors, and such tumors, called craniopharyngioma, are well-documented to produce similar metabolic impairments as occurs in animals with hypothalamic lesions [171]. Similarly deficiency in leptin, which largely acts through nutrient-sensing neurons in the VMH, produces largely the same metabolic and neuroendocrine impairments in humans as observed in leptin-deficient mice [141]. Since some recent studies failed to observe protective effects of dietary restriction in mice [108] and non-human primates [125], and since despite likely caloric restriction in many human populations throughout history there has never been a documented case of the expected life extension, it seems quite likely that the optimum caloric restriction for humans has never been discovered, and likely never will be. Nevertheless in view of the conservation of the relevant regulatory mechanisms, we hypothesize that pharmacological approaches activating these mechanisms may still be protective in humans.

5. VMH neurons integrate sensing of nutritional state to promote peripheral glucose utilization and inhibit hepatic glucose production

A major motivation to propose that the VMH is a hierarchical mediator of lifespan extension by DR is that it is a hierarchical regulator of many systemic responses to nutrient intake and energy balance. An example of this top-down control is glucose homeostasis.

Much of the evidence for how mammals maintain glucose homeostasis derives from studies of responses to acute peripheral hypoglycemia (e.g., blood glucose below 50 mg/dl). Acute peripheral hypoglycemia produces many of the same neuroendocrine responses as DR including reduction of reproductive hormones [146], reduced thyroid hormone [180], reduced IGF-1 [57], and increased glucocorticoids as well as glucagon, and epinephrine [10, 43, 80, 117]. The combined effect of all these responses is to produce a “counterregulatory” response to hypoglycemia that increases blood glucose, by increasing hepatic glucose production and reducing peripheral (e.g., muscle) glucose metabolism as well [39].

In contrast to neurons in most areas of the brain, the activity of neurons in the VMH is sensitive to variations within the physiological range of glucose concentrations [52, 148, 149, 191, 218]. Neuroendocrine and autonomic responses to hypoglycemia appear to be mediated largely or entirely by these glucose-sensing neurons in the VMH. For example, ablation of VMH neurons blocks counterregulatory responses to hypoglycemia [18]. Moreover, reducing glucose metabolism in the VMH induces peripheral counterregulatory responses [19] while increasing glucose [16] or lactate [17] levels in the VMH prevents counterregulatory responses to hypoglycemia. Furthermore, blocking K-ATP channels mimics the effect of glucose in glucose-excited cells [218] and selectively blocking K-ATP channels in the VMH blocks counterregulatory responses to hypoglycemia [54] whereas activating K-ATP channels in the VMH enhances those responses [36]. 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 [36]. 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 in the Sf-1 neurons of the VMN [199]. Of particular importance, the blood glucose levels in these mice were relatively low after 24 hours of fasting and this change was associated with impaired induction of hepatic gluconeogenic gene expression [199]. Since acute hypoglycemia is probably rarely encountered under normal circumstances, these observations suggest that neuroendocrine and autonomic responses to acute hypoglycemia probably reflect systems evolved to adapt to more commonly encountered caloric deficits. This is consistent with the observation that some mechanisms mediating responses to hypoglycemia and DR overlap (see below for molecular evidence supporting this hypothesis).

Another line of evidence for the hypothalamic control of systemic glucose homeostasis originates from our studies in leptin-deficient mice. These mice are characterized by reduced expression of hypothalamic POMC [135]. Transgenic restoration of POMC completely normalized blood glucose, associated with normalization of hepatic gluconeogenesis [134]. Furthermore, infusion of glucose into the hypothalamus of normal mice acutely reduces hepatic glucose output [103]. Taken together these studies demonstrate that activity of glucose-stimulated hypothalamic neurons promotes peripheral glucose metabolism through hepatic glucose output.

The hypothalamus can maintain blood glucose homeostasis and increase blood glucose availability 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 [194, 195]. Consistent with the results of genetic inhibition of VMH glutamate release [199], infusion of glutamate into the VMH also enhances peripheral glucose metabolism [194]. Increased glucose metabolism from VMH stimulation does not entail increased glucose transporters, in contrast to insulin-induced glucose uptake [186]. Associated with increased glucose metabolism, VMH stimulation also increases brown adipose tissue temperature [132], likely reflecting hypothalamic mediation of hypothermia induced by 2DG [153] (see below). Infusion of leptin specifically into the VMH also induces peripheral glucose metabolism [131] through enhancement of sympathetic nervous activity [77]. Thus, the VMH can regulate whole-body glucose homeostasis both through

hepatic glucose output and through peripheral cellular glucose metabolism, at least in rats, the species in which these studies were carried out.

6. Examples of hypothalamic top-down control of peripheral cell-autonomous signaling: examples from insulin, circadian rhythms and leptin

Insulin

While VMH neurons clearly regulate peripheral glucose metabolism, glucose metabolism is also regulated by insulin in some tissues and locally (cell autonomously) in all tissues. Thus an important question is the quantitative importance of the VMH in regulating peripheral glucose metabolism compared to these other factors. Many processes are regulated hierarchically both locally and by the hypothalamus, yet hypothalamic regulation is often dominant. For example, insulin secretion is regulated autonomously by glucose metabolism in the pancreatic beta cell in vitro [124]. Nevertheless, in vivo VMH neurons exert major control via the autonomic nervous system over pancreatic secretion of insulin. Insulin secretion increases 4-fold within 30 minutes after VMH lesions, with no change in blood glucose, dependent on the vagus nerve [198]. The magnitude of this change in insulin secretion is comparable to or greater than that produced by glucose alone in vivo [145] suggesting that VMH neurons play an important role in regulating regulation of insulin secretion. Moreover, VMH neurons can regulate insulin sensitivity in peripheral tissues. For example, mice lacking FoxO1 specifically in SF-1 neurons of the VMH had improved glucose tolerance due to improved insulin sensitivity in skeletal muscle and heart [95]. Similarly, even though glucose metabolism is generally driven locally by cellular demand (e.g., reduction of ATP), the effect of insulin on glucose metabolism is dominant in insulin-sensitive cells. Therefore it is plausible that VMH neurons contribute significantly to regulating glucose metabolism during aging and under conditions of dietary restriction.

Leptin

Another example of the hypothalamic top-down control of peripheral cell-autonomous signaling is leptin. Leptin is key hormone for the regulation of energy balance and metabolism. Although peripheral fat cells release the hormone and peripheral tissues contain leptin receptors that elicit intracellular responses in metabolism and other pathways[2], leptin receptors in the VMH have critical functions in leptin-regulated energy balance. The loss of leptin receptors from AgRP/NPY neurons of the VMH of young mice caused obesity due to transient hyperphagia and decreased energy expenditure [202] and restoration of leptin signaling in leptin-deficient mice was sufficient to reverse the phenotypes of leptin deficiency including obesity, diabetes, and infertility [47, 202]. People and animals with obesity are often leptin resistant and intranasal delivery of leptin in rats has been shown to reduce food intake and increase energy expenditure in lean and diet-induced obese rats without increasing serum leptin levels [181, 182].

Circadian clocks

A third example of hypothalamic hierarchical control is the circadian clock. Most tissues of the body have an internal “clock” with intracellular circadian rhythms of gene expression and activity that can maintain rhythmic behavior in vitro. However, the internal clocks in these tissues oscillate with different phases and have been referred to as “slave oscillators” because they require the hypothalamus to synchronize tissues of the body and maintain population-based amplitude of oscillation [222], reviewed by Froy and Miskin (2010) [62] and by Reppert and Weaver (2002) [164]. For example, ablation of the suprachiasmatic nucleus (SCN) of the hypothalamus blocks circadian rhythm in behavior and grafting SCN

tissue into arrhythmic hamsters with SCN ablation restores a circadian rhythm that is dependent on the genotype of the grafted SCN tissue rather than the genotype of the host animal [161]. The circadian rhythm can be altered by changes in nutritional state [35, 128] and coordinated whole-body responses to nutritional state and timing appear to require regions of the hypothalamus [63] [35, 128].

DR effects on circadian rhythm may contribute to the health and lifespan consequences of DR [61]. DR increases the amplitude of circadian changes in locomotor activity in older rhesus monkeys [209]. Changes in the circadian rhythm or wheel running and body temperature have also been shown in rodents [35, 128]. Epidemiological evidence from humans suggests that shift work increases the risk of obesity and age-related disease including diabetes, cardiovascular disease, and cancer (reviewed in [8, 61]. In humans and mice, disruption of circadian rhythm has metabolic consequences including altered leptin and insulin levels [178] [93]. Lifespan in hamsters and mice is decreased by disruption of circadian rhythm [87] [45] [51] [101] and lifespan can be extended by successful grafting of fetal SCN into intact adult hamsters that have age-related impairment in circadian rhythm [87].

7. Examples of hypothalamic top-down control of two specific DR responses: growth hormone/IGF-1 signaling and body temperature

Growth hormone/IGF-1

Of the systemic responses to DR, which ones are hierarchically regulated by the hypothalamus? One likely candidate is IGF-1. The potential role of IGF-1 and related hormones and homologs in lifespan and the protective effects of DR have been covered by many extensive reviews [12] [13] [58]. Here we note only that the hypothalamus regulates GH release from the pituitary, which in turn hierarchically regulates the release of IGF-1 from the liver (Figure 1). Hypothalamic regulation of GH release occurs through several pathways. The most commonly known circuits involve the hypothalamic expression of growth-hormone releasing hormone (GHRH) and somatostatin. During DR, serum GH in rats and sheep corresponds with GHRH mRNA levels in the arcuate nucleus of the mediobasal hypothalamus [81, 187][119][22]. GH release is also regulated by other hypothalamic peptides including ghrelin, thyrotropin-releasing hormone, pituitary adenylate cyclase-activating peptide, and gonadotropin-releasing hormone (reviewed in [6]). These systems may be complemented by hypothalamic control of the autonomic nervous system, such that resection of the vagus nerve was shown to blunt GH release in response to GHRH and decreased basal IGF-1 and GH levels [3]. In summary, if the protective effects of DR are mediated by reduced GH/IGF-1 signaling in mammals, this reduction is probably achieved through hypothalamic responses to DR.

Body temperature

DR decreases body temperature in humans [190], non-human primates [104], and some though not all mice [166, 167]. Similarly, hypoglycemia and glucopenia can reduce body temperature in humans [60, 140] and other species [169] [20, 31, 153]. Reducing temperature dramatically increases lifespan in poikilothermic (cold-blooded) animals [40, 84, 112–116, 206, 220] but the effect in mammals has been challenging to determine. The most convincing evidence comes from Conti and colleagues, who produced transgenic mice with overexpression of uncoupling protein 2 (UCP2) specifically in the lateral hypothalamus [41]. This manipulation led to chronic reduction of body temperature by about 0.3 °C because the elevation of UCP2 produced a local increase in temperature at the area of the hypothalamus that hierarchically regulates body temperature based on local thermosensory

neurons and peripheral temperature information. Although the transgenic mice consumed equal calories as wild-type controls, they lived 12% (males) and 20% (females) longer [41].

The degree to which reduced body temperature mediates the protective effects of DR is unclear. One group of rhesus macaques on DR exhibited decreased body temperature [104] and health benefits with young-onset CR such as decreased cancer incidence but not increased lifespan [125], strong evidence that it is not a major contributor to lifespan in these animals. On the other hand, analysis of mortality curves indicated that, in mice, lifespan extension by DR resembles lifespan extension by decreased body temperature in that both reduce the age-associated acceleration of mortality rate [41]. One rodent study reports that increasing ambient temperature blocked lifespan extension by DR, primarily through effects on lymphoma rates in a lymphoma-prone mouse strain [100]. Moreover, body temperature correlates with longevity in humans [172] and across genders in C57Bl/6J mice [175], and two long-lived rodent models exhibit decreased body temperature [86, 215]. Thus although the evidence clearly indicates that reduction in temperature is not the major mechanism by which DR increases lifespan, a role for temperature cannot yet be completely ruled out.

The circuitry by which DR reduces body temperature is uncertain but, in homeotherms like mammals, the hypothalamus is almost certainly involved. There are numerous pathways by which nutritional status influences whole-body temperature through hypothalamic mechanisms. These have been recently reviewed in depth by Bartfai & Conti so we will not review these here other than to state that several of these proposed pathways involve nutrient sensing and/or glucose-sensing neurons, including those in the arcuate nucleus of the hypothalamus [11].

Whether or not thermoregulation is a critical protective component of DR, it is certainly an important yet often overlooked variable in experimental design of DR studies. DR of rats in a cool environment (12°C) caused greater weight loss and suppressed oxygen consumption compared to DR rats kept at a thermoneutral environment (30°C) [55]. Standard laboratory environments are usually below the thermoneutral zone of most rodents [170] and thus require additional energy costs to maintain core temperature by shivering or non-shivering thermogenesis. Since lifespan extension by DR correlates with fuel efficiency across strains of mice, defined as the ability to maintain growth and body weight independently of calories [166], it is possible that some discrepancies in lifespan extension by DR may be due to variations in laboratory conditions that alter heat exchange including animal size and strain as well as environmental factors such as ambient temperature, air flow, bedding, and individual versus group housing [170].

8. Decreased glucose metabolism, a protective component of DR

During DR, there is a relative metabolic shift from glucose to the use of other fuel substrates including free fatty acids and ketone bodies [138]. Reducing glucose is sufficient to increase lifespan in flies [200] while reducing glucose metabolism increases lifespan in *C. elegans* [183]. In mammals, DR reduces average plasma glucose levels [122] and genes that increase lifespan entail reduction in whole-body glucose homeostasis [23]. Conversely elevated glucose reduces lifespan in humans [69] and *C. elegans* [107, 183] suggesting that the protective effects of DR may be mediated by a reduction in glucose metabolism [122, 136]. On the other hand, genetic reduction of plasma glucose in mice by overexpression of glucose transporters in muscle does not increase lifespan [127]. Therefore the reduction in glucose levels by DR is not sufficient, though it may be necessary, to mediate the full protective effects of DR on lifespan in animals. We suggest however that DR also reduces glucose metabolism via neuroendocrine and autonomic regulation by glucose-sensing VMH neurons.

In support of this hypothesis, many studies indicate that glucose toxicity is mediated by glucose metabolism [26]. The metabolism of glucose, relative to alternative substrates, preferentially produces oxidative stress, in part because it preferentially produces NADH (relative to FADH₂ and NADPH), which is oxidized at Complex 1, the main mitochondrial source of reactive oxygen species [138]. Glucose metabolism is also more efficient than alternative energy sources because NADH metabolism produces more ATP per carbon bond [138]. This may explain why increased respiration has been reported to be associated with the protective effects of DR in some [14, 111], though not all [90] studies. During DR, the metabolism of glucose is decreased relative to other substrates, supporting that DR does not increase lifespan by reducing metabolic rate per se [126].

Although the shift in metabolism from glucose to other substrates could be protective through decreased oxidative stress, recent studies indicate that increased oxidative stress does not always reduce lifespan [154]. Our own studies indicate that increasing oxidative stress by inactivation of SOD isoforms has no effect on lifespan and specifically no effect on life extension by DR [221]. However, these studies do not address if DR extends lifespan by specifically reducing oxidative stress produced by glucose metabolism, which will in general entail different compartmentalization and cellular targets than oxidative stress produced by other processes. Reducing glucose metabolism also has other protective effects independent of oxidative stress [138], including AMPK induction of autophagy [208].

Glucose sensitive neurons in the VMH are ideally situated to hierarchically regulate the systemic metabolic shift from glucose to other substrates during DR. Much of the evidence for this is described above. Glucose sensing neurons in the VMH share similarities with the ASI neurons in *C.elegans* and the MNC cells in *Drosophila* that mediate effects of DR on lifespan, as described above. VMH nutrient sensing neurons regulate peripheral glucose metabolism through the sympathetic nervous system [77, 195], and reduced hepatic glucose production. VMH control of neuroendocrine systems could also contribute to this effect, as sex steroids [168], thyroid hormone [139], and IGF-1 [74] stimulate glycolysis, whereas glucocorticoids inhibit glycolysis [155]. VMH neurons are required for peripheral metabolic responses to fasting [199] and hypoglycemia [16, 18] (see above). Many of these peripheral metabolic responses also occur during DR [72, 73], fasting [158] and hypoglycemia [157].

9. Molecular mechanisms mediating hypothalamic responses to DR

This review argues that glucose-sensing neurons in the VMH hierarchically mediate many key protective mechanisms produce by DR. If this hypothesis is correct, then a major question is what are the components of hypothalamic nutrient sensing and molecular signaling that mediate the key responses to DR? In this section, we will discuss evidence for a metabolic shift from glucose to other fuel substrates. In addition, we will discuss several molecular candidates that may be involved in hypothalamic responses to dietary restriction such as peroxisome proliferator-activated receptor alpha (Ppar-alpha), FoxO1, mammalian target of rapamycin (mTOR) and Creb-binding protein (Cbp) (Figure 1).

As described above, there is strong evidence that the glucose-stimulated neurons in the VMH mediate neuroendocrine responses to hypoglycemia and that many of these neuroendocrine responses also occur during DR [16, 18, 19, 54]. However, DR and hypoglycemia are not identical and the reduction in blood glucose during DR is not sufficient to activate the neuroendocrine responses to DR [127]. Nevertheless, glucose-sensing VMH neurons are positioned to respond to other plasma signals of energy balance that are altered during DR such as decreased leptin and ketone bodies [16, 18, 19, 54, 127]. Reduced leptin and glucose may synergize to affect VMH neuronal activity since leptin enhances hypothalamic responses to glucose [158] and hypothalamic glucose metabolism is

required for leptin signaling [193] [158]. Specifically, glucose deprivation or blocking glucose metabolism specifically blocks molecular responses (phosphorylation in the JAK-STAT pathway) to leptin but not GH [193].

Free fatty acids are elevated by DR [118] and may heighten the VMH neuronal response to decreased glucose by reducing the hypothalamic glucose metabolism that is a critical component of glucose sensing in these neurons [218, 219]. Specifically, free fatty acids can activate Ppar-alpha, although this effect varies by the chain length and saturation of the free fatty acids impacts the activation of Ppar-alpha[65]. We have recently observed that both fasting [158] and hypoglycemia [157] induce Ppar-alpha target genes. In turn, activation of Ppar-alpha promotes fatty acid beta-oxidation and reduces glucose metabolism [33, 165]. Furthermore, activation of hypothalamic Ppar-alpha reduces peripheral glucose metabolism [98] and activation of hypothalamic Ppar-alpha reduces glucose metabolism in the periphery [98]. The complex potential role of Ppar-alpha and free fatty acids in impacting hypothalamic glucose metabolism was covered in a recent review [142].

In addition to free fatty acids, DR increases plasma ketones in humans [118] and we have shown that ketones block glucose metabolism in hypothalamic neurons [37]. Thus, an increase in either fatty acids or ketone bodies would be expected to decrease hypothalamic glucose metabolism which would in turn be expected to reduce peripheral glucose metabolism [77, 131, 132, 153, 186, 194, 195, 199]. This circuit would tend to be self-perpetuating, possibly explaining why some long-term protective metabolic effects of DR persist even after return to ad lib feeding [118].

Evidence for the metabolic shift from glucose to fatty acid metabolism in the hypothalamus originates, in part, from studies on a large panel of hypothalamic genes induced both by acute nutritional deprivation [158] and acute hypoglycemia [157]. Some of these responses overlap with the genes induced by chronic DR [71]. The gene expression pattern indicated reduced hypothalamic glucose metabolism relative to other fuel sources (e.g. increased fatty acid beta oxidation) [157, 158]. Chronic DR produces a similar metabolic shift away from glycolysis and toward the use of alternate fuels in heart [106], liver [73], as well as the hypothalamus and other brain regions [71]. This molecular profile is also reflected in whole-body metabolism, since chronic DR produces a rapid shift toward greater 24-hour fat oxidation (accompanied by increased fatty acid synthesis) relative to ad lib fed animals [28].

The hypothalamic expression of Creb-binding protein (Cbp) may be an important mediator of the protective effects of DR [223]. We have demonstrated in two independent groups of animals that expression of Cbp in the VMH, but not liver or fat accounts for over 80% of lifespan in 5 strains of mice [223]. In contrast, hypothalamic expression of other genes implicated in aging did not significantly correlate with lifespan (mammalian orthologs to sirtuins, daf-16/FoxO3a, pha-4/FoxA, rheb-1, hsf-1, skn-1/NFE2, hif-1, and *aak-2/ampk*). The relevance of this robust correlation of Cbp is supported by our studies in *C.elegans* that showed that the induction of Cbp is required for protective effects of DR, including lifespan extension, and also for the animals' metabolic switch away from glycolysis and toward beta-oxidation [223].

Cbp is a co-activator of Ppar-gamma [197] and Ppar-alpha [48] as well as FoxO1/daf-16 [147]. The FoxO1/daf-16 transcription factor, which is inhibited by insulin-like signaling and whose induction is required for the protective effects of insulin-like signaling, is also necessary for the protective effects of some, though not all, protocols of DR [67, 223]. FoxO1 appears to mediate some neuroendocrine hypothalamic responses to fasting [30, 96]. In addition, the loss of FoxO1 specifically from SF-1 neurons of the ventromedial hypothalamus resulted in lean mice with increased energy expenditure and improved

glucose tolerance with improved insulin sensitivity in skeletal muscle and heart [95]. The response to 24-hour fasting was also altered in these mice with increased weight loss and a blunted decrease in energy expenditure during the fast [95]. The role of hypothalamic FoxO1 the responses to specifically DR remain to be assessed.

Cbp is also induced by reduced insulin-like signaling and is required for the protective effects of this reduction [174, 223]. Cbp is also a co-activator of cyclic AMP-response element binding protein (Creb), a transcription factor that directs hepatic counter-regulatory responses to hypoglycemia by promoting gluconeogenesis and glycogenolysis [82]. In contrast to the co-activity of Cbp with these transcriptional co-activators, Cbp activity is inhibited by CtBP through an NADH-dependent mechanism [94, 185] that may mediate molecular effects of glucose and the inhibition of those effects by ketones [66]. Interestingly, Creb in the brain is required for DR to induce Sirt-1 and associated metabolic and neuroprotective responses [64]. Since Cbp is required for Creb activity [102], these results suggest that Cbp also mediates effects of DR on Sirt-1 transcription. Of further interest, Ctbp represses Sirt1 through a nutrient-dependent pathway [225]. Mechanisms mediating effects of DR on Sirt-1 transcription are of increasing interest since recent studies suggest that sirtuin activity may be independent of NAD⁺ availability [225]. Recent studies also suggest that protective effects of resveratrol, previously thought to act through Sirt-1, may actually be mediated through the elevation of cAMP [151] which would enhance Cbp activity.

The protective effects of DR may also involve hypothalamic expression of mTOR (mammalian target of rapamycin). Inhibition of the TOR pathway increases lifespan in *C. elegans* [89, 203], flies [92] yeast [159], and mice [78, 129]. DR inhibits TOR activity and produces many effects (e.g., reduced protein synthesis) similar to inhibiting TOR activity [76]. Of particular interest, inhibition of TOR activity and DR did not produce additive effects on lifespan [76], suggesting that protective effects of DR are mediated by inhibition of mTOR. The effects of DR on hypothalamic gene expression are consistent with a role for mTOR in protective effects of DR [216]. Selective inhibition of hypothalamic mTOR activity produced similar molecular and behavioral effects as DR [15, 42]. One mechanism by which DR may inhibit hypothalamic mTOR is through the activation of hypothalamic AMPK, which mediates some effects of glucose and leptin on hypothalamic function [130]. Induction of AMPK also appears to be required for some, though not all, protective effects of DR [67, 68]. Finally, as indicated above, DR induces Sirt1 in the hypothalamus and hypothalamic Sirt1 appears to mediate at least some effects of DR in mice [99, 177].

One major candidate involved in inhibition of molecular effects of glucose is the transcriptional co-repressor C-terminal binding protein (CtBP) [66], which is regulated by NADH [224]. Free fatty acids inhibit glucose metabolism and induce beta oxidation mainly by activating the peroxisome proliferator-activated receptor (Ppar) family of transcriptional co-activators [165], which we observed also seems to mediate some molecular responses to hypoglycemia [157]. Indeed, chronic DR also induces the Pparcoactivator PGC-1alpha [163]. Finally, glucocorticoids inhibit brain glucose utilization [155], possibly in part by inducing Ppar activity [204]. Thus hypothalamic responses to fasting and DR may involve several key protein molecular mechanisms involving Cbp, Creb, CtBP, mTOR, sirtuins, FoxO, and Ppars (Figure 1).

14. Conclusion

A small number of nutrient-sensing cells in *C. elegans* (ASI neurons) [14] and *Drosophila* (MNC cells) [25] largely or entirely regulate the protective effects of DR to increase lifespan. A similar system has been neither proven nor disproven yet in mammals, but it is

known that mammalian hypothalamic neurons mediate many responses to nutritional state and deprivation, including some responses to DR. VMH neurons share features of ASI and MNC neurons and mediate neuroendocrine and autonomic responses to low glucose and leptin. Several lines of evidence suggest that glucose metabolism in the hypothalamus (primarily VMH) drives glucose metabolism and glucose levels in the brain and periphery. Based on these and other data, we hypothesize that DR decreases glucose metabolism in the hypothalamus and that this effect mediates the reduction of glucose metabolism in the periphery, thus slowing aging in these tissues. It's possible that this system involves hypothalamic expression of Cbp, which has been shown in mice to predict lifespan across strains. On the other hand, hypothalamic neurons also mediate effects of nutrients to reduce temperature and the GH/IGF-1 pathway. Taken together these observations support that hypothalamic neurons have the potential to regulate many metabolic and protective effects of DR during aging. If so, then the VMH nutrient sensing neurons may eventually be a useful target for the development of calorie restriction mimetics to protect against age-related disease. Advances in molecular technology may enable the studies needed to fully elucidate the role of the hypothalamus and nutrient sensing cells as top-down hierarchical regulators of the protective responses of DR.

Acknowledgments

We would like to thank Dr. Andrew Dacks for his feedback on the manuscript and his skilled editing of our figures. This work was supported by the NIH National Institute of Diabetes and Digestive and Kidney Diseases and The Klarman Family Foundation, Boston, MA. PA Dacks was supported by the Hilda and Preston Davis Foundation.

Works Cited

- [1]. Ahima RS, Flier JS. Leptin, *Annu Rev Physiol.* 2000; 62:413–437.
- [2]. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS. Role of leptin in the neuroendocrine response to fasting. *Nature.* 1996; 382:250–252. [PubMed: 8717038]
- [3]. Al-Massadi O, Trujillo ML, Senaris R, Pardo M, Castela C, Casanueva FF, Seoane LM. The vagus nerve as a regulator of growth hormone secretion. *Regul Pept.* 2011; 166:3–8. [PubMed: 21056594]
- [4]. Alcedo J, Kenyon C. Regulation of *C. elegans* Longevity by Specific Gustatory and Olfactory Neurons. *Neuron.* 2004; 41:45–55. [PubMed: 14715134]
- [5]. Allard JS, Heilbronn LK, Smith C, Hunt ND, Ingram DK, Ravussin E, de Cabo R. In vitro cellular adaptations of indicators of longevity in response to treatment with serum collected from humans on calorie restricted diets. *PLoS One.* 2008; 3:e3211. [PubMed: 18791640]
- [6]. Anderson LL, Jętkinija S, Scanes CG. Growth hormone secretion: molecular and cellular mechanisms and in vivo approaches. *Exp Biol Med (Maywood).* 2004; 229:291–302. [PubMed: 15044712]
- [7]. Anisimov VN, Zabezhinski MA, Popovich IG, Piskunova TS, Semchenko AV, Tyndyk ML, Yurova MN, Rosenfeld SV, Blagosklonny MV. Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice. *Cell Cycle.* 2011; 10:4230–4236. [PubMed: 22107964]
- [8]. Antunes LC, Levandovski R, Dantas G, Caumo W, Hidalgo MP. Obesity and shift work: chronobiological aspects. *Nutr Res Rev.* 2010; 23:155–168. [PubMed: 20122305]
- [9]. Apfeld J, Kenyon C. Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. *Nature.* 1999; 402:804–809. [PubMed: 10617200]
- [10]. Baker D, Evans M, Cryer P, Sherwin R. Hypoglycemia and glucose sensing. *Diabetologia.* 1997; 40:B83–B88. [PubMed: 9345653]
- [11]. Bartfai T, Conti B. Molecules affecting hypothalamic control of core body temperature in response to calorie intake. *Front Genet.* 2012; 3:184. [PubMed: 23097647]

- [12]. Barzilai N, Bartke A. Biological approaches to mechanistically understand the healthy life span extension achieved by calorie restriction and modulation of hormones. *J Gerontol A Biol Sci Med Sci*. 2009; 64:187–191. [PubMed: 19228789]
- [13]. Berryman DE, Christiansen JS, Johannsson G, Thorner MO, Kopchick JJ. Role of the GH/IGF-1 axis in lifespan and healthspan: lessons from animal models. *Growth Horm IGF Res*. 2008; 18:455–471. [PubMed: 18710818]
- [14]. Bishop NA, Guarente L. Two neurons mediate diet-restriction-induced longevity in *C. elegans*. *Nature*. 2007; 447:545–549. [PubMed: 17538612]
- [15]. Blouet C, Ono H, Schwartz GJ. Mediobasal hypothalamic p70 S6 kinase 1 modulates the control of energy homeostasis. *Cell Metab*. 2008; 8:459–467. [PubMed: 19041762]
- [16]. Borg MA, Sherwin RS, Borg WP, Tamborlane WV, Shulman GI. Local ventromedial hypothalamus glucose perfusion blocks counterregulation during systemic hypoglycemia in awake rats. *J Clin Invest*. 1997; 99:361–365. [PubMed: 9006005]
- [17]. Borg MA, Tamborlane WV, Shulman GI, Sherwin RS. Local lactate perfusion of the ventromedial hypothalamus suppresses hypoglycemic counterregulation. *Diabetes*. 2003; 52:663–666. [PubMed: 12606506]
- [18]. Borg WP, During MJ, Sherwin RS, Borg MA, Brines ML, Shulman GI. Ventromedial hypothalamic lesions in rats suppress counterregulatory responses to hypoglycemia. *J Clin Invest*. 1994; 93:1677–1682. [PubMed: 8163668]
- [19]. Borg WP, Sherwin RS, During MJ, Borg MA, Shulman GI. Local ventromedial hypothalamus glucopenia triggers counterregulatory hormone release. *Diabetes*. 1995; 44:180–184. [PubMed: 7859938]
- [20]. Branco LG. Effects of 2-deoxy-D-glucose and insulin on plasma glucose levels and behavioral thermoregulation of toads. *Am J Physiol*. 1997; 272:R1–5. [PubMed: 9038984]
- [21]. Bray GA, Inoue S, Nishizawa Y. Hypothalamic obesity. The autonomic hypothesis and the lateral hypothalamus. *Diabetologia*. 1981; 20:366–377. [PubMed: 7014333]
- [22]. Brogan RS, Fife SK, Conley LK, Giustina A, Wehrenberg WB. Effects of food deprivation on the GH axis: immunocytochemical and molecular analysis. *Neuroendocrinology*. 1997; 65:129–135. [PubMed: 9067990]
- [23]. Brooks NL, Trent CM, Raetzsch CF, Flurkey K, Boysen G, Perfetti MT, Jeong YC, Klebanov S, Patel KB, Khodush VR, Kupper LL, Carling D, Swenberg JA, Harrison DE, Combs TP. Low utilization of circulating glucose after food withdrawal in snell dwarf mice. *J Biol Chem*. 2007; 282:35069–35077. [PubMed: 17905742]
- [24]. Broughton SJ, Piper MD, Ikeya T, Bass TM, Jacobson J, Driege Y, Martinez P, Hafen E, Withers DJ, Leivers SJ, Partridge L. Longer lifespan, altered metabolism, and stress resistance in *Drosophila* from ablation of cells making insulin-like ligands. *Proc Natl Acad Sci U S A*. 2005; 102:3105–3110. [PubMed: 15708981]
- [25]. Broughton SJ, Slack C, Alic N, Metaxakis A, Bass TM, Driege Y, Partridge L. DILP-producing median neurosecretory cells in the *Drosophila* brain mediate the response of lifespan to nutrition. *Aging Cell*. 2010; 9:336–346. [PubMed: 20156206]
- [26]. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001; 414:813–820. [PubMed: 11742414]
- [27]. Bruce-Keller AJ, Umberger G, McFall R, Mattson MP. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Ann Neurol*. 1999; 45:8–15. [PubMed: 9894871]
- [28]. Bruss MD, Khambatta CF, Ruby MA, Aggarwal I, Hellerstein MK. Calorie restriction increases fatty acid synthesis and whole body fat oxidation rates. *Am J Physiol Endocrinol Metab*. 2010; 298:E108–116. [PubMed: 19887594]
- [29]. Cai H, Cong WN, Ji S, Rothman S, Maudsley S, Martin B. Metabolic dysfunction in Alzheimer's disease and related neurodegenerative disorders. *Curr Alzheimer Res*. 2012; 9:5–17. [PubMed: 22329649]
- [30]. Cakir I, Perello M, Lansari O, Messier NJ, Vaslet CA, Nillni EA. Hypothalamic Sirt1 regulates food intake in a rodent model system. *PLoS One*. 2009; 4:e8322. [PubMed: 20020036]

- [31]. Carnio EC, Almeida MC, Fabris G, Branco LG. Role of nitric oxide in 2-deoxy-D-glucose-induced hypothermia in rats. *Neuroreport*. 1999; 10:3101–3104. [PubMed: 10549830]
- [32]. Carrillo AE, Flouris AD. Caloric restriction and longevity: effects of reduced body temperature. *Ageing Res Rev*. 2011; 10:153–162. [PubMed: 20969980]
- [33]. Chakravarthy MV, Zhu Y, Lopez M, Yin L, Wozniak DF, Coleman T, Hu Z, Wolfgang M, Vidal-Puig A, Lane MD, Semenkovich CF. Brain fatty acid synthase activates PPARalpha to maintain energy homeostasis. *J Clin Invest*. 2007; 117:2539–2552. [PubMed: 17694178]
- [34]. Chalkiadaki A, Guarente L. Sirtuins mediate mammalian metabolic responses to nutrient availability. *Nat Rev Endocrinol*. 2012; 8:287–296. [PubMed: 22249520]
- [35]. Challet E. Interactions between light, mealtime and calorie restriction to control daily timing in mammals. *J Comp Physiol B*. 2010; 180:631–644. [PubMed: 20174808]
- [36]. Chan O, Lawson M, Zhu W, Beverly JL, Sherwin RS. ATP-sensitive K(+) channels regulate the release of GABA in the ventromedial hypothalamus during hypoglycemia. *Diabetes*. 2007; 56:1120–1126. [PubMed: 17251273]
- [37]. Cheng H, Isoda F, Belsham DD, Mobbs CV. Inhibition of agouti-related peptide expression by glucose in a clonal hypothalamic neuronal cell line is mediated by glycolysis, not oxidative phosphorylation. *Endocrinology*. 2008; 149:703–710. [PubMed: 17974626]
- [38]. Choudhury D, Levi M. Kidney aging--inevitable or preventable? *Nat Rev Nephrol*. 2011; 7:706–717. [PubMed: 21826079]
- [39]. Cohen N, Rossetti L, Shlimovich P, Halberstam M, Hu M, Shamooh H. Counterregulation of hypoglycemia. Skeletal muscle glycogen metabolism during three hours of physiological hyperinsulinemia in humans. *Diabetes*. 1995; 44:423–430. [PubMed: 7698511]
- [40]. Cohet Y. Epigenetic influences on the lifespan of the *Drosophila*: existence of an optimal growth temperature for adult longevity. *Exp Gerontol*. 1975; 10:181–184. [PubMed: 810356]
- [41]. Conti B, Sanchez-Alavez M, Winsky-Sommerer R, Morale MC, Lucero J, Brownell S, Fabre V, Huitron-Resendiz S, Henriksen S, Zorrilla EP, de Lecea L, Bartfai T. Transgenic mice with a reduced core body temperature have an increased life span. *Science*. 2006; 314:825–828. [PubMed: 17082459]
- [42]. Cota D, Proulx K, Smith KA, Kozma SC, Thomas G, Woods SC, Seeley RJ. Hypothalamic mTOR signaling regulates food intake. *Science*. 2006; 312:927–930. [PubMed: 16690869]
- [43]. Cryer PE. Hierarchy of physiological responses to hypoglycemia: relevance to clinical hypoglycemia in type I (insulin dependent) diabetes mellitus. *Horm Metab Res*. 1997; 29:92–96. [PubMed: 9137976]
- [44]. Csiszar A, Labinskyy N, Jimenez R, Pinto JT, Ballabh P, Losonczy G, Pearson KJ, de Cabo R, Ungvari Z. Anti-oxidative and anti-inflammatory vasoprotective effects of caloric restriction in aging: role of circulating factors and SIRT1. *Mech Ageing Dev*. 2009; 130:518–527. [PubMed: 19549533]
- [45]. Davidson AJ, Sellix MT, Daniel J, Yamazaki S, Menaker M, Block GD. Chronic jetlag increases mortality in aged mice. *Curr Biol*. 2006; 16:R914–916. [PubMed: 17084685]
- [46]. de Cabo R, Furer-Galban S, Anson RM, Gilman C, Gorospe M, Lane MA. An in vitro model of caloric restriction. *Exp Gerontol*. 2003; 38:631–639. [PubMed: 12814798]
- [47]. de Luca C, Kowalski TJ, Zhang Y, Elmquist JK, Lee C, Kilimann MW, Ludwig T, Liu SM, Chua SC Jr. Complete rescue of obesity, diabetes, and infertility in db/db mice by neuron-specific LEPR-B transgenes. *J Clin Invest*. 2005; 115:3484–3493. [PubMed: 16284652]
- [48]. Delerive P, De Bosscher K, Besnard S, Vanden Berghe W, Peters JM, Gonzalez FJ, Fruchart JC, Tedgui A, Haegeman G, Staels B. Peroxisome proliferator-activated receptor alpha negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF-kappaB and AP-1. *J Biol Chem*. 1999; 274:32048–32054. [PubMed: 10542237]
- [49]. Duan W, Guo Z, Jiang H, Ware M, Li XJ, Mattson MP. Dietary restriction normalizes glucose metabolism and BDNF levels, slows disease progression, and increases survival in huntingtin mutant mice. *Proc Natl Acad Sci U S A*. 2003; 100:2911–2916. [PubMed: 12589027]
- [50]. Duan W, Mattson MP. Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. *J Neurosci Res*. 1999; 57:195–206. [PubMed: 10398297]

- [51]. Dubrovsky YV, Samsa WE, Kondratov RV. Deficiency of circadian protein CLOCK reduces lifespan and increases age-related cataract development in mice. *Aging (Albany NY)*. 2010; 2:936–944. [PubMed: 21149897]
- [52]. Dunn-Meynell AA, Routh VH, Kang L, Gaspers L, Levin BE. Glucokinase is the likely mediator of glucosensing in both glucose-excited and glucose-inhibited central neurons. *Diabetes*. 2002; 51:2056–2065. [PubMed: 12086933]
- [53]. Elmquist JK, Elias CF, Saper CB. From lesions to leptin: hypothalamic control of food intake and body weight. *Neuron*. 1999; 22:221–232. [PubMed: 10069329]
- [54]. Evans ML, McCrimmon RJ, Flanagan DE, Keshavarz T, Fan X, McNay EC, Jacob RJ, Sherwin RS. Hypothalamic ATP-sensitive K⁺ channels play a key role in sensing hypoglycemia and triggering counterregulatory epinephrine and glucagon responses. *Diabetes*. 2004; 53:2542–2551. [PubMed: 15448082]
- [55]. Evans SA, Parsons AD, Overton JM. Homeostatic responses to caloric restriction: influence of background metabolic rate. *J Appl Physiol*. 2005; 99:1336–1342. [PubMed: 15932959]
- [56]. Fontana L. Neuroendocrine factors in the regulation of inflammation: excessive adiposity and calorie restriction. *Exp Gerontol*. 2009; 44:41–45. [PubMed: 18502597]
- [57]. 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; 32:97–108. [PubMed: 19904628]
- [58]. Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. *Science*. 2010; 328:321–326. [PubMed: 20395504]
- [59]. Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, Holloszy JO. Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. *Am J Physiol Endocrinol Metab*. 2007; 293:E197–202. [PubMed: 17389710]
- [60]. Freinkel N, Metzger BE, Harris E, Robinson S, Mager M. The hypothermia of hypoglycemia. Studies with 2-deoxy-D-glucose in normal human subjects and mice. *N Engl J Med*. 1972; 287:841–845. [PubMed: 5071962]
- [61]. Froy O. Circadian rhythms, aging, and life span in mammals. *Physiology (Bethesda)*. 2011; 26:225–235. [PubMed: 21841071]
- [62]. Froy O, Miskin R. Effect of feeding regimens on circadian rhythms: implications for aging and longevity. *Aging (Albany NY)*. 2010; 2:7–27. [PubMed: 20228939]
- [63]. Fuller PM, Lu J, Saper CB. Differential rescue of light- and food-entrainable circadian rhythms. *Science*. 2008; 320:1074–1077. [PubMed: 18497298]
- [64]. Fusco S, Ripoli C, Podda MV, Ranieri SC, Leone L, Toietta G, McBurney MW, Schutz G, Riccio A, Grassi C, Galeotti T, Pani G. A role for neuronal cAMP responsive-element binding (CREB)-1 in brain responses to calorie restriction. *Proc Natl Acad Sci U S A*. 2012; 109:621–626. [PubMed: 22190495]
- [65]. Gani OS. I, Molecular recognition of long chain fatty acids by peroxisome proliferator-activated receptor α . *Med Chem Res*. 2009; 18:8–19.
- [66]. Garriga-Canut M, Schoenike B, Qazi R, Bergendahl K, Daley TJ, Pfender RM, Morrison JF, Ockuly J, Stafstrom C, Sutula T, Roopra A. 2-Deoxy-D-glucose reduces epilepsy progression by NRSF-CtBP-dependent metabolic regulation of chromatin structure. *Nat Neurosci*. 2006; 9:1382–1387. [PubMed: 17041593]
- [67]. 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]
- [68]. Greer EL, Dowlatshahi D, Banko MR, Villen J, Hoang K, Blanchard D, Gygi SP, Brunet A. An AMPK-FOXO pathway mediates longevity induced by a novel method of dietary restriction in *C. elegans*. *Curr Biol*. 2007; 17:1646–1656. [PubMed: 17900900]
- [69]. Groeneveld Y, Petri H, Hermans J, Springer MP. Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. *Diabet Med*. 1999; 16:2–13. [PubMed: 10229287]

- [70]. Gronke S, Clarke DF, Broughton S, Andrews TD, Partridge L. Molecular evolution and functional characterization of *Drosophila* insulin-like peptides. *PLoS Genet.* 2010; 6:e1000857. [PubMed: 20195512]
- [71]. Guarnieri DJ, Brayton CE, Richards SM, Maldonado-Aviles J, Trinko JR, Nelson J, Taylor JR, Gourley SL, DiLeone RJ. Gene profiling reveals a role for stress hormones in the molecular and behavioral response to food restriction. *Biol Psychiatry.* 2012; 71:358–365. [PubMed: 21855858]
- [72]. Hagopian K, Ramsey JJ, Weindruch R. Caloric restriction increases gluconeogenic and transaminase enzyme activities in mouse liver. *Exp Gerontol.* 2003; 38:267–278. [PubMed: 12581790]
- [73]. Hagopian K, Ramsey JJ, Weindruch R. Influence of age and caloric restriction on liver glycolytic enzyme activities and metabolite concentrations in mice. *Exp Gerontol.* 2003; 38:253–266. [PubMed: 12581789]
- [74]. Hall JL, Gibbons GH, Chatham JC. IGF-I promotes a shift in metabolic flux in vascular smooth muscle cells. *Am J Physiol Endocrinol Metab.* 2002; 283:E465–471. [PubMed: 12169439]
- [75]. Han ES, Levin N, Bengani N, Roberts JL, Suh Y, Karelus K, Nelson JF. Hyperadrenocorticism and food restriction-induced life extension in the rat: evidence for divergent regulation of pituitary proopiomelanocortin RNA and adrenocorticotrophic hormone biosynthesis. *J Gerontol A Biol Sci Med Sci.* 1995; 50:B288–294. [PubMed: 7545529]
- [76]. Hansen M, Taubert S, Crawford D, Libina N, Lee SJ, Kenyon C. Lifespan extension by conditions that inhibit translation in *Caenorhabditis elegans*. *Aging Cell.* 2007; 6:95–110. [PubMed: 17266679]
- [77]. Haque MS, Minokoshi Y, Hamai M, Iwai M, Horiuchi M, Shimazu T. 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]
- [78]. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature.* 2009; 460:392–395. [PubMed: 19587680]
- [79]. Hart RW, Turturro A. Dietary restrictions and cancer. *Environ Health Perspect.* 1997; 105(Suppl 4):989–992. [PubMed: 9255593]
- [80]. Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes.* 1991; 40:223–226. [PubMed: 1991573]
- [81]. Henry BA, Rao A, Tilbrook AJ, Clarke IJ. Chronic food-restriction alters the expression of somatostatin and growth hormone-releasing hormone in the ovariectomised ewe. *J Endocrinol.* 2001; 170:R1–5. [PubMed: 11431163]
- [82]. Herzig S, Long F, Jhala US, Hedrick S, Quinn R, Bauer A, Rudolph D, Schutz G, Yoon C, Puigserver P, Spiegelman B, Montminy M. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. *Nature.* 2001; 413:179–183. [PubMed: 11557984]
- [83]. Holmer HK, Keyghobadi M, Moore C, Menashe RA, Meshul CK. Dietary restriction affects striatal glutamate in the MPTP-induced mouse model of nigrostriatal degeneration. *Synapse.* 2005; 57:100–112. [PubMed: 15906381]
- [84]. Hosono R, Mitsui Y, Sato Y, Aizawa S, Miwa J. Life span of the wild and mutant nematode *Caenorhabditis elegans*. Effects of sex, sterilization, and temperature. *Exp Gerontol.* 1982; 17:163–172. [PubMed: 6213421]
- [85]. Hukema RK, Rademakers S, Dekkers MP, Burghoorn J, Jansen G. Antagonistic sensory cues generate gustatory plasticity in *Caenorhabditis elegans*. *EMBO J.* 2006; 25:312–322. [PubMed: 16407969]
- [86]. Hunter WS, Croson WB, Bartke A, Gentry MV, Meliska CJ. Low body temperature in long-lived Ames dwarf mice at rest and during stress. *Physiol Behav.* 1999; 67:433–437. [PubMed: 10497963]
- [87]. Hurd MW, Ralph MR. The significance of circadian organization for longevity in the golden hamster. *J Biol Rhythms.* 1998; 13:430–436. [PubMed: 9783234]

- [88]. Ingram DK, Roth GS. Glycolytic inhibition as a strategy for developing calorie restriction mimetics. *Exp Gerontol.* 2011; 46:148–154. [PubMed: 21167272]
- [89]. Jia K, Chen D, Riddle DL. The TOR pathway interacts with the insulin signaling pathway to regulate *C. elegans* larval development, metabolism and life span. *Development.* 2004; 131:3897–3906. [PubMed: 15253933]
- [90]. Kaeberlein M, Hu D, Kerr EO, Tsuchiya M, Westman EA, Dang N, Fields S, Kennedy BK. Increased life span due to calorie restriction in respiratory-deficient yeast. *PLoS Genet.* 2005; 1:e69. [PubMed: 16311627]
- [91]. Kapahi P, Chen D, Rogers AN, Katewa SD, Li PW, Thomas EL, Kockel L. With TOR, less is more: a key role for the conserved nutrient-sensing TOR pathway in aging. *Cell Metab.* 2010; 11:453–465. [PubMed: 20519118]
- [92]. Kapahi P, Zid BM, Harper T, Koslover D, Sapin V, Benzer S. Regulation of lifespan in *Drosophila* by modulation of genes in the TOR signaling pathway. *Curr Biol.* 2004; 14:885–890. [PubMed: 15186745]
- [93]. Karatsoreos IN, Bhagat S, Bloss EB, Morrison JH, McEwen BS. Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. *Proc Natl Acad Sci U S A.* 2011; 108:1657–1662. [PubMed: 21220317]
- [94]. Kim JH, Cho EJ, Kim ST, Youn HD. CtBP represses p300-mediated transcriptional activation by direct association with its bromodomain. *Nat Struct Mol Biol.* 2005; 12:423–428. [PubMed: 15834423]
- [95]. Kim KW, Donato J Jr. Berglund ED, Choi YH, Kohno D, Elias CF, Depinho RA, Elmquist JK. FOXO1 in the ventromedial hypothalamus regulates energy balance. *J Clin Invest.* 2012; 122:2578–2589. [PubMed: 22653058]
- [96]. Kitamura T, Feng Y, Kitamura YI, Chua SC Jr. Xu AW, Barsh GS, Rossetti L, Accili D. Forkhead protein FoxO1 mediates Agrp-dependent effects of leptin on food intake. *Nat Med.* 2006; 12:534–540. [PubMed: 16604086]
- [97]. Klebanov S, Diais S, Stavinoha WB, Suh Y, Nelson JF. Hyperadrenocorticism, attenuated inflammation, and the life-prolonging action of food restriction in mice. *J Gerontol A Biol Sci Med Sci.* 1995; 50:B79–82.
- [98]. Knauf C, Rieusset J, Foretz M, Cani PD, Uldry M, Hosokawa M, Martinez E, Bringart M, Waget A, Kersten S, Desvergne B, Gremlich S, Wahli W, Seydoux J, Delzenne NM, Thorens B, Burcelin R. 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]
- [99]. Knight CM, Gutierrez-Juarez R, Lam TK, Arrieta-Cruz I, Huang L, Schwartz G, Barzilay N, Rossetti L. Mediobasal hypothalamic SIRT1 is essential for resveratrol's effects on insulin action in rats. *Diabetes.* 2011; 60:2691–2700. [PubMed: 21896928]
- [100]. Koizumi A, Wada Y, Tuskada M, Kayo T, Naruse M, Horiuchi K, Mogi T, Yoshioka M, Sasaki M, Miyamaura Y, Abe T, Ohtomo K, Walford RL. A tumor preventive effect of dietary restriction is antagonized by a high housing temperature through deprivation of torpor. *Mech Ageing Dev.* 1996; 92:67–82. [PubMed: 9032756]
- [101]. Kondratov RV, Kondratova AA, Gorbacheva VY, Vykhovanets OV, Antoch MP. Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. *Genes Dev.* 2006; 20:1868–1873. [PubMed: 16847346]
- [102]. Kwok RP, Lundblad JR, Chrivia JC, Richards JP, Bachinger HP, Brennan RG, Roberts SG, Green MR, Goodman RH. Nuclear protein CBP is a coactivator for the transcription factor CREB. *Nature.* 1994; 370:223–226. [PubMed: 7913207]
- [103]. Lam TK, Gutierrez-Juarez R, Pocai A, Rossetti L. Regulation of blood glucose by hypothalamic pyruvate metabolism. *Science.* 2005; 309:943–947. [PubMed: 16081739]
- [104]. Lane MA, Baer DJ, Rumpler WV, Weindrich R, Ingram DK, Tilmont EM, Cutler RG, Roth GS. Calorie restriction lowers body temperature in rhesus monkeys, consistent with a postulated anti-aging mechanism in rodents. *Proc Natl Acad Sci U S A.* 1996; 93:4159–4164. [PubMed: 8633033]

- [105]. Lans H, Jansen G. Multiple sensory G proteins in the olfactory, gustatory and nociceptive neurons modulate longevity in *Caenorhabditis elegans*. *Dev Biol*. 2007; 303:474–482. [PubMed: 17187771]
- [106]. Lee CK, Allison DB, Brand J, Weindruch R, Prolla TA. Transcriptional profiles associated with aging and middle age-onset caloric restriction in mouse hearts. *Proc Natl Acad Sci U S A*. 2002; 99:14988–14993. [PubMed: 12419851]
- [107]. Lee SJ, Murphy CT, Kenyon C. 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]
- [108]. Liao CY, Rikke BA, Johnson TE, Diaz V, Nelson JF. Genetic variation in the murine lifespan response to dietary restriction: from life extension to life shortening. *Aging Cell*. 2010; 9:92–95. [PubMed: 19878144]
- [109]. Libert S, Zwiener J, Chu X, Vanvoorhies W, Roman G, Pletcher SD. Regulation of *Drosophila* life span by olfaction and food-derived odors. *Science*. 2007; 315:1133–1137. [PubMed: 17272684]
- [110]. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*. *Science*. 2000; 289:2126–2128. [PubMed: 11000115]
- [111]. Lin SJ, Kaerberlein M, Andalis AA, Sturtz LA, Defossez PA, Culotta VC, Fink GR, Guarente L. Calorie restriction extends *Saccharomyces cerevisiae* lifespan by increasing respiration. *Nature*. 2002; 418:344–348. [PubMed: 12124627]
- [112]. Liu RK, Leung BE, Walford RL. Effect of temperature-transfer on growth of laboratory populations of a South American annual fish *Cynolebias bellottii*. *Growth*. 1975; 39:337–343. [PubMed: 1183853]
- [113]. Liu RK, Walford RL. Increased growth and life-span with lowered ambient temperature in the annual fish, *Cynolebia adloffi*. *Nature*. 1966; 212:1277–1278.
- [114]. Liu RK, Walford RL. The effect of lowered body temperature on lifespan and immune and non-immune processes. *Gerontologia*. 1972; 18:363–388. [PubMed: 4618218]
- [115]. Liu RK, Walford RL. Mid-life temperature-transfer effects on life-span of annual fish. *J Gerontol*. 1975; 30:129–131. [PubMed: 1123529]
- [116]. Loeb J, Northrop JH. Is there a temperature coefficient for the duration of life? *Proc Natl Acad Sci U S A*. 1916; 2:456–457. [PubMed: 16586628]
- [117]. Maggs DG, Sherwin RS. Mechanisms of the sympathoadrenal response to hypoglycemia. *Adv Pharmacol*. 1998; 42:622–626. [PubMed: 9327979]
- [118]. Mahoney LB, Denny CA, Seyfried TN. Caloric restriction in C57BL/6J mice mimics therapeutic fasting in humans. *Lipids Health Dis*. 2006; 5:13. [PubMed: 16709251]
- [119]. Majumder S, Caccamo A, Medina DX, Benavides AD, Javors MA, Kraig E, Strong R, Richardson A, Oddo S. Lifelong rapamycin administration ameliorates age-dependent cognitive deficits by reducing IL-1 β and enhancing NMDA signaling. *Aging Cell*. 2012; 11:326–335. [PubMed: 22212527]
- [120]. Manzanero S, Gelderblom M, Magnus T, Arumugam TV. Calorie restriction and stroke. *Exp Transl Stroke Med*. 2011; 3:8. [PubMed: 21910904]
- [121]. Masoro EJ. The role of hormesis in life extension by dietary restriction. *Interdiscip Top Gerontol*. 2007; 35:1–17. [PubMed: 17063030]
- [122]. Masoro EJ, McCarter RJ, Katz MS, McMahan CA. Dietary restriction alters characteristics of glucose fuel use. *J Gerontol*. 1992; 47:B202–208. [PubMed: 1430849]
- [123]. Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, Gerhardt GA, Grondin R, Roth GS, Mattison J, Lane MA, Carson RE, Cohen RM, Mouton PR, Quigley C, Mattson MP, Ingram DK. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. *Proc Natl Acad Sci U S A*. 2004; 101:18171–18176. [PubMed: 15604149]
- [124]. Matschinsky FM. Banting Lecture 1995. A lesson in metabolic regulation inspired by the glucokinase glucose sensor paradigm. *Diabetes*. 1996; 45:223–241. [PubMed: 8549869]

- [125]. Mattison JA, Roth GS, Beasley TM, Tilmont EM, Handy AM, Herbert RL, Longo DL, Allison DB, Young JE, Bryant M, Barnard D, Ward WF, Qi W, Ingram DK, de Cabo R. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*. 2012; 489:318–321. [PubMed: 22932268]
- [126]. McCarter R, Masoro EJ, Yu BP. Does food restriction retard aging by reducing the metabolic rate? *Am J Physiol*. 1985; 248:E488–490. [PubMed: 3157325]
- [127]. McCarter R, Mejia W, Ikeno Y, Monnier V, Kewitt K, Gibbs M, McMahan A, Strong R. Plasma glucose and the action of calorie restriction on aging. *J Gerontol A Biol Sci Med Sci*. 2007; 62:1059–1070. [PubMed: 17921417]
- [128]. Mendoza J, Drevet K, Pevet P, Challet E. Daily meal timing is not necessary for resetting the main circadian clock by calorie restriction. *J Neuroendocrinol*. 2008; 20:251–260. [PubMed: 18088363]
- [129]. Miller RA, Harrison DE, Astle CM, Baur JA, Boyd AR, de Cabo R, Fernandez E, Flurkey K, Javors MA, Nelson JF, Orihuela CJ, Pletcher S, Sharp ZD, Sinclair D, Starnes JW, Wilkinson JE, Nadon NL, Strong R. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J Gerontol A Biol Sci Med Sci*. 2011; 66:191–201. [PubMed: 20974732]
- [130]. Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foufelle F, Ferre P, Birnbaum MJ, Stuck BJ, Kahn BB. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature*. 2004; 428:569–574. [PubMed: 15058305]
- [131]. Minokoshi Y, Haque MS, Shimazu T. Microinjection of leptin into the ventromedial hypothalamus increases glucose uptake in peripheral tissues in rats. *Diabetes*. 1999; 48:287–291. [PubMed: 10334303]
- [132]. Minokoshi Y, Okano Y, Shimazu T. Regulatory mechanism of the ventromedial hypothalamus in enhancing glucose uptake in skeletal muscles. *Brain Res*. 1994; 649:343–347. [PubMed: 7953650]
- [133]. Minor RK, Lopez M, Younts CM, Jones B, Pearson KJ, Anson RM, Dieguez C, de Cabo R. The arcuate nucleus and neuropeptide Y contribute to the antitumorigenic effect of calorie restriction. *Aging Cell*. 2011; 10:483–492. [PubMed: 21385308]
- [134]. Mizuno TM, Kelly K, Pasinetti GM, Roberts JL, Mobbs CV. 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]
- [135]. Mizuno TM, Kleopoulos SP, Bergen HT, Roberts JL, Priest CA, Mobbs CV. 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; 47:294–297. [PubMed: 9519731]
- [136]. Mobbs CV. Neurotoxic effects of estrogen, glucose, and glucocorticoids: Neurohumoral hysteresis and its pathological consequences during aging. *Reviews of Biological Research on Aging*. 1990; 4:201–228.
- [137]. Mobbs CV, Gee DM, Finch CE. Reproductive senescence in female C57BL/6J mice: ovarian impairments and neuroendocrine impairments that are partially reversible and delayable by ovariectomy. *Endocrinology*. 1984; 115:1653–1662. [PubMed: 6541567]
- [138]. Mobbs CV, Mastaitis JW, Zhang M, Isoda F, Cheng H, Yen K. 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]
- [139]. Moeller LC, Dumitrescu AM, Refetoff S. Cytosolic action of thyroid hormone leads to induction of hypoxia-inducible factor-1 α and glycolytic genes. *Mol Endocrinol*. 2005; 19:2955–2963. [PubMed: 16051672]
- [140]. Molnar GW, Read RC. Hypoglycemia and body temperature. *Jama*. 1974; 227:916–921. [PubMed: 4405862]
- [141]. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997; 387:903–908. [PubMed: 9202122]

- [142]. Moreno C, Yang L, Dacks PA, Isoda F, Poplawski M, Mobbs CV. Regulation of peripheral metabolism by substrate partitioning in the brain. *Endocrinology and Metabolism Clinics of North America*. in press.
- [143]. Motohashi H, Yamamoto M. Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends Mol Med*. 2004; 10:549–557. [PubMed: 15519281]
- [144]. Mouton PR, Chachich ME, Quigley C, Spangler E, Ingram DK. Caloric restriction attenuates amyloid deposition in middle-aged dtg APP/PS1 mice. *Neurosci Lett*. 2009; 464:184–187. [PubMed: 19699265]
- [145]. Muzumdar R, Ma X, Atzmon G, Vuguin P, Yang X, Barzilai N. Decrease in glucose-stimulated insulin secretion with aging is independent of insulin action. *Diabetes*. 2004; 53:441–446. [PubMed: 14747296]
- [146]. Nagatani S, Bucholtz DC, Murahashi K, Estacio MA, Tsukamura H, Foster DL, Maeda KI. Reduction of glucose availability suppresses pulsatile luteinizing hormone release in female and male rats. *Endocrinology*. 1996; 137:1166–1170. [PubMed: 8625885]
- [147]. Nasrin N, Ogg S, Cahill CM, Biggs W, Nui S, Dore J, Calvo D, Shi Y, Ruvkun G, Alexander-Bridges MC. DAF-16 recruits the CREB-binding protein coactivator complex to the insulin-like growth factor binding protein 1 promoter in HepG2 cells. *Proc Natl Acad Sci U S A*. 2000; 97:10412–10417. [PubMed: 10973497]
- [148]. Oomura Y, Ono T, Ooyama H, Wayner MJ. Glucose and osmosensitive neurones of the rat hypothalamus. *Nature*. 1969; 222:282–284. [PubMed: 5778398]
- [149]. Orzi F, Lucignani G, Dow-Edwards D, Namba H, Nehlig A, Patlak CS, Pettigrew K, Schuier F, Sokoloff L. Local cerebral glucose utilization in controlled graded levels of hyperglycemia in the conscious rat. *J Cereb Blood Flow Metab*. 1988; 8:346–356. [PubMed: 3366796]
- [150]. Park D, Jones KL, Lee H, Snutch TP, Taubert S, Riddle DL. Repression of a Potassium Channel by Nuclear Hormone Receptor and TGF-beta Signaling Modulates Insulin Signaling in *Caenorhabditis elegans*. *PLoS Genet*. 2012; 8:e1002519. [PubMed: 22359515]
- [151]. Park SJ, Ahmad F, Philp A, Baar K, Williams T, Luo H, Ke H, Rehmann H, Taussig R, Brown AL, Kim MK, Beaven MA, Burgin AB, Manganiello V, Chung JH. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell*. 2012; 148:421–433. [PubMed: 22304913]
- [152]. Patel NV, Gordon MN, Connor KE, Good RA, Engelman RW, Mason J, Morgan DG, Morgan TE, Finch CE. Caloric restriction attenuates A β -deposition in Alzheimer transgenic models. *Neurobiol Aging*. 2005; 26:995–1000. [PubMed: 15748777]
- [153]. Pelz KM, Routman D, Driscoll JR, Kriegsfeld LJ, Dark J. 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:R255–265. [PubMed: 17959707]
- [154]. Perez VI, Bokov A, Van Remmen H, Mele J, Ran Q, Ikeno Y, Richardson A. Is the oxidative stress theory of aging dead? *Biochim Biophys Acta*. 2009; 1790:1005–1014. [PubMed: 19524016]
- [155]. Plaschke K, Muller D, Hoyer S. Effect of adrenalectomy and corticosterone substitution on glucose and glycogen metabolism in rat brain. *J Neural Transm*. 1996; 103:89–100. [PubMed: 9026380]
- [156]. Poon PC, Kuo TH, Linford NJ, Roman G, Pletcher SD. Carbon dioxide sensing modulates lifespan and physiology in *Drosophila*. *PLoS Biol*. 2010; 8:e1000356. [PubMed: 20422037]
- [157]. 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; 60:39–46. [PubMed: 20811039]
- [158]. Poplawski MM, Mastaitis JW, Yang XJ, Mobbs CV. Hypothalamic responses to fasting indicate metabolic reprogramming away from glycolysis toward lipid oxidation. *Endocrinology*. 2010; 151:5206–5217. [PubMed: 20881243]
- [159]. Powers RW 3rd, Kaeblerlein M, Caldwell SD, Kennedy BK, Fields S. Extension of chronological life span in yeast by decreased TOR pathway signaling. *Genes Dev*. 2006; 20:174–184. [PubMed: 16418483]

- [160]. Qin W, Chachich M, Lane M, Roth G, Bryant M, de Cabo R, Ottinger MA, Mattison J, Ingram D, Gandy S, Pasinetti GM. Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (*Saimiri sciureus*). *J Alzheimers Dis*. 2006; 10:417–422. [PubMed: 17183154]
- [161]. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. *Science*. 1990; 247:975–978. [PubMed: 2305266]
- [162]. Ramadori G, Coppari R. Does hypothalamic SIRT1 regulate aging? *Aging (Albany NY)*. 2011; 3:325–328. [PubMed: 21464518]
- [163]. Ranhotra HS. Long-term caloric restriction up-regulates PPAR gamma co-activator 1 alpha (PGC-1alpha) expression in mice. *Indian J Biochem Biophys*. 2010; 47:272–277. [PubMed: 21280563]
- [164]. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. *Nature*. 2002; 418:935–941. [PubMed: 12198538]
- [165]. Ribet C, Montastier E, Valle C, Bezaire V, Mazzucotelli A, Mairal A, Viguerie N, Langin D. Peroxisome proliferator-activated receptor-alpha control of lipid and glucose metabolism in human white adipocytes. *Endocrinology*. 2010; 151:123–133. [PubMed: 19887568]
- [166]. Rikke BA, Liao CY, McQueen MB, Nelson JF, Johnson TE. Genetic dissection of dietary restriction in mice supports the metabolic efficiency model of life extension. *Exp Gerontol*. 2010; 45:691–701. [PubMed: 20452416]
- [167]. Rikke BA, Yerg JE 3rd, Battaglia ME, Nagy TR, Allison DB, Johnson TE. Strain variation in the response of body temperature to dietary restriction. *Mech Ageing Dev*. 2003; 124:663–678. [PubMed: 12735906]
- [168]. Rivenzon-Segal D, Boldin-Adamsky S, Seger D, Seger R, Degani H. Glycolysis and glucose transporter 1 as markers of response to hormonal therapy in breast cancer. *Int J Cancer*. 2003; 107:177–182. [PubMed: 12949791]
- [169]. Rocha PL, Branco LG. Physiological significance of behavioral hypothermia in hypoglycemic frogs (*Rana catesbeiana*). *Comp Biochem Physiol A Mol Integr Physiol*. 1998; 119:957–961. [PubMed: 9773488]
- [170]. Romanovsky AA, Ivanov AI, Shimansky YP. Selected contribution: ambient temperature for experiments in rats: a new method for determining the zone of thermal neutrality. *J Appl Physiol*. 2002; 92:2667–2679. [PubMed: 12015388]
- [171]. Roth C, Wilken B, Hanefeld F, Schroter W, Leonhardt U. Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. *Eur J Endocrinol*. 1998; 138:89–91. [PubMed: 9461323]
- [172]. Roth GS, Lane MA, Ingram DK, Mattison JA, Elahi D, Tobin JD, Muller D, Metter EJ. Biomarkers of caloric restriction may predict longevity in humans. *Science*. 2002; 297:811. [PubMed: 12161648]
- [173]. Sakata T, Kurokawa M. Feeding modulation by pentose and hexose analogues. *Am J Clin Nutr*. 1992; 55:272S–277S. [PubMed: 1728839]
- [174]. Samuelson AV, Carr CE, Ruvkun G. Gene activities that mediate increased life span of *C. elegans* insulin-like signaling mutants. *Genes Dev*. 2007; 21:2976–2994. [PubMed: 18006689]
- [175]. Sanchez-Alavez M, Alboni S, Conti B. Sex- and age-specific differences in core body temperature of C57Bl/6 mice. *Age (Dordr)*. 2011; 33:89–99. [PubMed: 20635153]
- [176]. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev*. 1986; 7:284–301. [PubMed: 3527687]
- [177]. Satoh A, Brace CS, Ben-Josef G, West T, Wozniak DF, Holtzman DM, Herzog ED, Imai S. SIRT1 promotes the central adaptive response to diet restriction through activation of the dorsomedial and lateral nuclei of the hypothalamus. *J Neurosci*. 2010; 30:10220–10232. [PubMed: 20668205]
- [178]. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A*. 2009; 106:4453–4458. [PubMed: 19255424]

- [179]. Schroeder JE, Richardson JC, Virley DJ. Dietary manipulation and caloric restriction in the development of mouse models relevant to neurological diseases. *Biochim Biophys Acta*. 2010; 1802:840–846. [PubMed: 20472058]
- [180]. Schultes B, Oltmanns KM, Kern W, Born J, Fehm HL, Peters A. Acute and prolonged effects of insulin-induced hypoglycemia on the pituitary-thyroid axis in humans. *Metabolism*. 2002; 51:1370–1374. [PubMed: 12370861]
- [181]. Schulz C, Paulus K, Johren O, Lehnert H. Intranasal leptin reduces appetite and induces weight loss in rats with diet-induced obesity (DIO). *Endocrinology*. 2012; 153:143–153. [PubMed: 22128019]
- [182]. Schulz C, Paulus K, Lehnert H. Central nervous and metabolic effects of intranasally applied leptin. *Endocrinology*. 2004; 145:2696–2701. [PubMed: 15016717]
- [183]. Schulz TJ, Zarse K, Voigt A, Urban N, Birringer M, Ristow M. Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. *Cell Metab*. 2007; 6:280–293. [PubMed: 17908557]
- [184]. Sell C. Caloric restriction and insulin-like growth factors in aging and cancer. *Horm Metab Res*. 2003; 35:705–711. [PubMed: 14710349]
- [185]. Senyuk V, Sinha KK, Nucifora G. Corepressor CtBP1 interacts with and specifically inhibits CBP activity. *Arch Biochem Biophys*. 2005; 441:168–173. [PubMed: 16122695]
- [186]. Shimazu T, Sudo M, Minokoshi Y, Takahashi A. Role of the hypothalamus in insulin-independent glucose uptake in peripheral tissues. *Brain Res Bull*. 1991; 27:501–504. [PubMed: 1959052]
- [187]. Shimokawa I, Fukuyama T, Yanagihara-Outa K, Tomita M, Komatsu T, Higami Y, Tuchiya T, Chiba T, Yamaza Y. Effects of caloric restriction on gene expression in the arcuate nucleus. *Neurobiol Aging*. 2003; 24:117–123. [PubMed: 12493557]
- [188]. Sinclair DA. Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev*. 2005; 126:987–1002. [PubMed: 15893363]
- [189]. Smith ED, Kaerberlein TL, Lydum BT, Sager J, Welton KL, Kennedy BK, Kaerberlein M. Age- and calorie-independent life span extension from dietary restriction by bacterial deprivation in *Caenorhabditis elegans*. *BMC Dev Biol*. 2008; 8:49. [PubMed: 18457595]
- [190]. Soare A, Cangemi R, Omodei D, Holloszy JO, Fontana L. Long-term calorie restriction, but not endurance exercise, lowers core body temperature in humans. *Aging (Albany NY)*. 2011; 3:374–379. [PubMed: 21483032]
- [191]. Song Z, Levin BE, McArdle JJ, Bakhos N, Routh VH. Convergence of pre- and postsynaptic influences on glucosensing neurons in the ventromedial hypothalamic nucleus. *Diabetes*. 2001; 50:2673–2681. [PubMed: 11723049]
- [192]. Steinkraus KA, Smith ED, Davis C, Carr D, Pendergrass WR, Sutphin GL, Kennedy BK, Kaerberlein M. Dietary restriction suppresses proteotoxicity and enhances longevity by an hsf-1-dependent mechanism in *Caenorhabditis elegans*. *Aging Cell*. 2008; 7:394–404. [PubMed: 18331616]
- [193]. Su H, Jiang L, Carter-Su C, Rui L. Glucose Enhances Leptin Signaling through Modulation of AMPK Activity. *PLoS One*. 2012; 7:e31636. [PubMed: 22359610]
- [194]. Sudo M, Minokoshi Y, Shimazu T. Ventromedial hypothalamic stimulation enhances peripheral glucose uptake in anesthetized rats. *Am J Physiol*. 1991; 261:E298–303. [PubMed: 1887876]
- [195]. Takahashi A, Shimazu T. Hypothalamic regulation of lipid metabolism in the rat: effect of hypothalamic stimulation on lipogenesis. *J Auton Nerv Syst*. 1982; 6:225–235. [PubMed: 6757306]
- [196]. Takahashi A, Sudo M, Minokoshi Y, Shimazu T. Effects of ventromedial hypothalamic stimulation on glucose transport system in rat tissues. *Am J Physiol*. 1992; 263:R1228–1234. [PubMed: 1481931]
- [197]. Takahashi N, Kawada T, Yamamoto T, Goto T, Taimatsu A, Aoki N, Kawasaki H, Taira K, Yokoyama KK, Kamei Y, Fushiki T. 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]

- [198]. Tokunaga K, Fukushima M, Kemnitz JW, Bray GA. Effect of vagotomy on serum insulin in rats with paraventricular or ventromedial hypothalamic lesions. *Endocrinology*. 1986; 119:1708–1711. [PubMed: 3530723]
- [199]. Tong Q, Ye C, McCrimmon RJ, Dhillon H, Choi B, Kramer MD, Yu J, Yang Z, Christiansen LM, Lee CE, Choi CS, Zigman JM, Shulman GI, Sherwin RS, Elmquist JK, Lowell BB. Synaptic glutamate release by ventromedial hypothalamic neurons is part of the neurocircuitry that prevents hypoglycemia. *Cell Metab*. 2007; 5:383–393. [PubMed: 17488640]
- [200]. Troen AM, French EE, Roberts JF, Selhub J, Ordovas JM, Parnell LD, Lai CQ. Lifespan modification by glucose and methionine in *Drosophila melanogaster* fed a chemically defined diet. *Age (Dordr)*. 2007; 29:29–39. [PubMed: 19424828]
- [201]. Turturro A, Hart R. Dietary alteration in the rates of cancer and aging. *Exp Gerontol*. 1992; 27:583–592. [PubMed: 1426091]
- [202]. van de Wall E, Leshan R, Xu AW, Balthasar N, Coppari R, Liu SM, Jo YH, MacKenzie RG, Allison DB, Dun NJ, Elmquist J, Lowell BB, Barsh GS, de Luca C, Myers MG Jr. Schwartz GJ, Chua SC Jr. Collective and individual functions of leptin receptor modulated neurons controlling metabolism and ingestion. *Endocrinology*. 2008; 149:1773–1785. [PubMed: 18162515]
- [203]. Vellai T, Takacs-Vellai K, Zhang Y, Kovacs AL, Orosz L, Muller F. Genetics: influence of TOR kinase on lifespan in *C. elegans*. *Nature*. 2003; 426:620. [PubMed: 14668850]
- [204]. Vidal-Puig AJ, Considine RV, Jimenez-Linan M, Werman A, Pories WJ, Caro JF, Flier JS. Peroxisome proliferator-activated receptor gene expression in human tissues. Effects of obesity, weight loss, and regulation by insulin and glucocorticoids. *J Clin Invest*. 1997; 99:2416–2422. [PubMed: 9153284]
- [205]. Vilberg TR, Keesey RE. Ventromedial hypothalamic lesions abolish compensatory reduction in energy expenditure to weight loss. *Am J Physiol*. 1990; 258:R476–480. [PubMed: 2309937]
- [206]. Walford RL, Liu RK, Troup GM, Hsiu J. Alterations in soluble/insoluble collagen ratios in the annual fish, *Cynolebias bellottii*, in relation to age and environmental temperature. *Exp Gerontol*. 1969; 4:103–109. [PubMed: 5389540]
- [207]. Wang J, Ho L, Qin W, Rocher AB, Seror I, Humala N, Maniar K, Dolios G, Wang R, Hof PR, Pasinetti GM. Caloric restriction attenuates beta-amyloid neuropathology in a mouse model of Alzheimer's disease. *Faseb J*. 2005; 19:659–661. [PubMed: 15650008]
- [208]. Wang Q, Liang B, Shirwany NA, Zou MH. 2-Deoxy-D-glucose treatment of endothelial cells induces autophagy by reactive oxygen species-mediated activation of the AMP-activated protein kinase. *PLoS One*. 2011; 6:e17234. [PubMed: 21386904]
- [209]. Weed JL, Lane MA, Roth GS, Speer DL, Ingram DK. Activity measures in rhesus monkeys on long-term calorie restriction. *Physiol Behav*. 1997; 62:97–103. [PubMed: 9226348]
- [210]. Weindruch R. Effect of caloric restriction on age-associated cancers. *Exp Gerontol*. 1992; 27:575–581. [PubMed: 1426090]
- [211]. Weindruch R, Albanes D, Kritchevsky D. The role of calories and caloric restriction in carcinogenesis. *Hematol Oncol Clin North Am*. 1991; 5:79–89. [PubMed: 2026570]
- [212]. Weindruch R, Walford RL. Dietary restriction in mice beginning at 1 year of age: effect on lifespan and spontaneous cancer incidence. *Science*. 1982; 215:1415–1418. [PubMed: 7063854]
- [213]. Weindruch RH, Kristie JA, Cheney KE, Walford RL. Influence of controlled dietary restriction on immunologic function and aging. *Fed Proc*. 1979; 38:2007–2016. [PubMed: 437143]
- [214]. Weiss EP, Fontana L. Caloric restriction: powerful protection for the aging heart and vasculature. *Am J Physiol Heart Circ Physiol*. 2011; 301:H1205–1219. [PubMed: 21841020]
- [215]. Westbrook R, Bonkowski MS, Strader AD, Bartke A. Alterations in oxygen consumption, respiratory quotient, and heat production in long-lived GHRKO and Ames dwarf mice, and short-lived bGH transgenic mice. *J Gerontol A Biol Sci Med Sci*. 2009; 64:443–451. [PubMed: 19286975]
- [216]. Wu P, Jiang C, Shen Q, Hu Y. Systematic gene expression profile of hypothalamus in calorie-restricted mice implicates the involvement of mTOR signaling in neuroprotective activity. *Mech Ageing Dev*. 2009; 130:602–610. [PubMed: 19647013]

- [217]. Wu P, Shen Q, Dong S, Xu Z, Tsien JZ, Hu Y. Calorie restriction ameliorates neurodegenerative phenotypes in forebrain-specific presenilin-1 and presenilin-2 double knockout mice. *Neurobiol Aging*. 2008; 29:1502–1511. [PubMed: 17499883]
- [218]. Yang XJ, Kow LM, Funabashi T, Mobbs CV. Hypothalamic glucose sensor: similarities to and differences from pancreatic beta-cell mechanisms. *Diabetes*. 1999; 48:1763–1672. [PubMed: 10480606]
- [219]. Yang XJ, Kow LM, Pfaff DW, Mobbs CV. Metabolic pathways that mediate inhibition of hypothalamic neurons by glucose. *Diabetes*. 2004; 53:67–73. [PubMed: 14693699]
- [220]. Yen K, Mobbs CV. Dietary Restriction and Cold Temperature Both Acutely Reduce Senescence in *C. elegans* Open Longevity. *Science*. 2007; 1:8–13.
- [221]. Yen K, Patel HB, Lublin AL, Mobbs CV. SOD isoforms play no role in lifespan in ad lib or dietary restricted conditions, but mutational inactivation of SOD-1 reduces life extension by cold. *Mech Ageing Dev*. 2009; 130:173–178. [PubMed: 19059428]
- [222]. Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Slepka SM, Hong HK, Oh WJ, Yoo OJ, Menaker M, Takahashi JS. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proc Natl Acad Sci U S A*. 2004; 101:5339–5346. [PubMed: 14963227]
- [223]. Zhang M, Poplawski M, Yen K, Cheng H, Bloss E, Zhu X, Patel H, Mobbs CV. Role of CBP and SATB-1 in aging, dietary restriction, and insulin-like signaling. *PLoS Biol*. 2009; 7:e1000245. [PubMed: 19924292]
- [224]. Zhang Q, Piston DW, Goodman RH. Regulation of corepressor function by nuclear NADH. *Science*. 2002; 295:1895–1897. [PubMed: 11847309]
- [225]. Zhang Q, Wang SY, Fleuriel C, Leprince D, Rocheleau JV, Piston DW, Goodman RH. Metabolic regulation of SIRT1 transcription via a HIC1:CtBP corepressor complex. *Proc Natl Acad Sci U S A*. 2007; 104:829–833. [PubMed: 17213307]
- [226]. Zhu H, Guo Q, Mattson MP. Dietary restriction protects hippocampal neurons against the death-promoting action of a presenilin-1 mutation. *Brain Res*. 1999; 842:224–229. [PubMed: 10526115]

- Dietary restriction involves non-cell-autonomous signaling and nutrient sensing cells
- Hypothalamic nutrient sensing neurons may regulate protective effects of dietary restriction
- Hypothalamic transcription factors regulate metabolic responses to dietary restriction

Figure 1.

During DR, neurons in the hypothalamus may respond to changes in glucose, other fuel substrates, and hormones such as leptin and insulin. In response, hypothalamic metabolites, transcription factors, and other proteins may alter their activity and interact to regulate hypothalamic activity and output.