Published in final edited form as:
Trends Endocrinol Metab. 2012 April ; 23(4): 179–185. doi:10.1016/j.tem.2012.01.002.

Metabolic Actions of Hypothalamic SIRT1

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Abstract

The hypothalamus is a small structure located in the ventral diencephalon. Hypothalamic neurons sense changes in circulating metabolic cues (e.g.: leptin, insulin, glucose), and coordinate responses aimed at maintaining normal body weight and glucose homeostasis. Recent findings indicate that a nicotinamide adenine dinucleotide (NAD^+)-dependent protein deacetylase (namely, SIRT1) expressed by hypothalamic neurons is crucial for mounting responses against diet-induced obesity and type 2 diabetes mellitus (T2DM). Here, the repercussions of these findings will be discussed and particular emphasis will be given to the potential exploitation of hypothalamic SIRT1 as a target for the treatment of the rapidly-spreading metabolic disorders of obesity and T2DM. The possible roles of hypothalamic SIRT1 on regulating metabolic ageing processes will also be addressed.

Keywords

Hypothalamus; SIRT1; aging; metabolism; obesity; diabetes; insulin; skeletal muscle

SIRT1: An ancient metabolic-sensor protein with modern value

Silent Information Regulator 2 (SIR2; also known as mating-type regulator 1) of yeast *Saccharomyces cerevisae* is the first sirtuin protein being discovered (1). Orthologs of SIR2 can be found in several organisms as for example mammals, plants, bacteria, worms, flies, and fish. Humans and rodents have seven orthologs of SIR2, named SIRT1 to SIRT7 (2). Mammalian sirtuins are found in virtually all tissues, yet they are selectively localized at the subcellular level. In fact, SIRT3, 4 and 5 are localized to the mitochondrion, SIRT1, 6 and 7 are nuclear, and SIRT2 (and possibly SIRT1) is cytosolic (3). Because of their broad distribution in nature, it has been proposed that sirtuins exert important protective roles aimed at guaranteeing organismal survival, hence the suggested reason for their conservation throughout evolution (3-7).

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Conflict of Interest Statement
The author of this manuscript has no conflict of interests to declare.

Sirtuins are enzymes able to exert deacetylation and/or mono-ADP ribosylation of their target proteins (6, 8, 9). Very recently, novel enzymatic activities have been attributed to this class of proteins, as SIRT5 was found to also have protein lysine desuccinylase and demalonylase functions (10, 11). Therefore, it is possible that these proteins carry out other yet-to-be-identified types of post-translational modifications. Of note, sirtuins use nicotinamide adenine dinucleotide (NAD^+) as co-substrate (6, 8, 9). And, due to their dependence on NAD^+ and the fact that targets of sirtuins include histones, transcription factors, cofactors, proteins involved in oxidative phosphorylation, circadian clock regulators and many others (3), these enzymes are thought to link the redox status to gene expression, activity, and fate of the cell. Therefore, sirtuins are to be considered *bona fide* metabolic-sensor proteins as for example mammalian target of rapamycin (mTOR) and AMP-activated kinase (AMPK), two proteins that also are evolutionarily well-conserved.

It must be noted however that, in addition to changes in the amounts of available NAD^+, the activity of sirtuins is also influenced by other modifications as for example by changes in their association/dissociation status with other proteins (e.g.: deleted in breast cancer-1) (12) and/or following their own post-translational modification(s) (e.g.: adrenergic-meditated phosphorylation of SIRT1 has been shown to change its catalytic activity) (13). Thus, an emerging view is that variations in the activity of sirtuins could also occur independently of changes in cellular levels of NAD^+; provided that the amount of NAD^+ is sufficient to guaranteeing the execution of their enzymatic actions.

Owing to their metabolic-sensor status, interests on this class of proteins significantly mounted over the last decade. Indeed, it has been proposed that sirtuins are the molecular link between calorie-restriction (CR) and the improved health and longevity brought on by this feeding regimen; an idea still much debated (14, 15). Regardless to the actual roles (if any) of sirtuins on ageing, the activity of SIRT1 (the focus of this review) seems to increase in several but not all tissues following CR or fasting (16-20). In these low-energy states, SIRT1 has been suggested to be crucial for carrying out physiological adaptive responses, as for example the switch from glucose to lipid oxidation in skeletal muscle (21) and liver (22), the increase in hepatic glucose production (19), and the mobilization of lipids from adipose tissue (23). In addition, SIRT1 appears to be important for executing physiological adaptive responses to high-energy states, as for example after prolonged feeding on hypercaloric diets (24-27). The latter function is of particular relevance to modern human physiology and pathophysiology, as people often feed on hypercaloric diets that cause obesity (Box 1) and type 2 diabetes mellitus (T2DM; Box 2) (28). Thus, SIRT1 could represent an ideal molecular target for the treatment of diet-induced obesity and T2DM (see below).

Metabolic diseases and the hypothalamus

We are in the midst of an epidemic of metabolic diseases; indeed it is estimated that hundreds of million people are affected by either obesity, or T2DM, or both. This is most likely one of the worst man-made epidemics and the result of the introduction of low-cost, easily-accessible calorie-rich foods, combined with reduced needs to performing physical activity. It must be noted however that some, albeit rare, forms of obesity and/or T2DM have a strong genetic underlying origin, as most clearly illustrated by the phenotypes displayed by rodents and humans homozygous for loss-of-function mutation in the leptin or the leptin receptor gene (29-33).

To effectively diminish the incidence of obesity and/or T2DM, changes in feeding habits and lifestyles could be all is needed. However, this seemingly simple approach appears to be much harder to accomplish than anticipated, likely because of socio-economical, environmental, and cultural reasons. Thus, understanding the endogenous mechanisms that

prevent the insurgence of increased body adiposity and impaired glucose homeostasis induced by chronic feeding on hypercaloric foods (hereafter referred to as diet-induced metabolic imbalance), and the reasons why these defense pathways are going awry in nowadays environment, is of paramount medical importance.

A critical anatomical site in which cells able to monitor changes in energy status of the body and trigger responses aimed at maintaining metabolic homeostasis are found is the hypothalamus (Figure 1). Located in the ventral diencephalon, the hypothalamus borders with the optic chiasm (rostrally), the optic tracts and cerebral peduncles (laterally) and the mammilary bodies (caudally). Numerous types of cells and neurons populate the hypothalamus. Some of these hypothalamic neurons secreted peptide that stimulate food intake (orexigenic neurons) whereas others produce appetite suppressant molecules (anorectic neurons). One classical example of neuronal types that are morphologically very similar and anatomically located in the same hypothalamic site but exert opposite effects on feeding behavior is represented by the pro-opiomelanocortin (POMC) and the agouti-related peptide (AgRP) neurons. Indeed, the peptide α-melanocyte stimulating hormone (α-MSH) secreted from POMC neurons activates whereas AgRP inhibits melanocortin 3 and 4 receptors (MC3R and MC4R). As a result, α-MSH suppresses feeding whereas AgRP promotes food intake (34-37). Of note, POMC and AgRP neurons are oppositely regulated by circulating metabolic cues as for example the adipose-tissue-secreted hormone leptin that activates POMC neurons (38) and inhibits AgRP neurons (39-41). In addition to POMC and AgRP neurons that reside in the arcuate nucleus of the hypothalamus (ARH), neurons in other hypothalamic nuclei are also crucial for maintaining normal metabolic homeostasis. Another example of these metabolically-relevant cells is represented by neurons expressing steroidogenic factor 1 (SF1). SF1 neurons are present in the ventromedial hypothalamic nucleus (VMH) and known to respond to changes in circulating leptin and other metabolic cues (42). As AgRP and VMH neurons project to POMC neurons (43), it is likely that VMH and ARH neurons communicate to each other as part of an elaborated neuronal circuitry underlying normal metabolic homeostasis (Figure 1).

A key homeostatic behavioral adaptation against diet-induced metabolic imbalance is reduced amounts of ingested food; an effect that is in part mediated by leptin action on SF1-expressing neurons (42). Other defense mechanisms include increased energy expenditure; a homeostatic autonomic adaptation triggered by POMC- and SF1-expressing neurons (24, 25, 42, 44). By engaging the sympathetic nervous system, these hypothalamic neurons enhance amount and activity of the calorie-burning brown adipocytes in several fat depots (25, 44), including the interscapular brown adipose tissue (iBAT; a prominent tissue located between the shoulder blades in rodents) and visceral and subcutaneous depots previously thought to be only made of calorie-stockpiling white adipocytes (45-49). Unfortunately, in modern societies, the search for calorie-rich foods induced by stress and/or hedonic/reward pathways may override homeostatic behavioral adaptation, thus shift the energy balance towards the accruing arm, and hence favor the development of obesity and/or T2DM (50). Also, chronic feeding on a hypercaloric diet leads to altered metabolic-sensing (e.g.: glucose- and leptin-sensing) mechanisms in hypothalamic neurons responsible for safeguarding normal energy and glucose homeostasis; another defect that likely contribute to the impairment of the aforementioned homeostatic behavioral and autonomic adaptations hence leading to obesity and T2DM (51-53).

Hypothalamic SIRT1: An endogenous weapon in the arsenal against metabolic imbalance

Because obesity and T2DM probably emerged long time after sirtuins first appeared in nature (3, 7), it seems that is by serendipity that the ancient protein SIRT1 exerts protecting

actions against diet-induced metabolic imbalance (24-26). Interestingly, the metabolic effects of SIRT1 are cell-type-specific and environment dependent. Indeed, the reported roles of SIRT1 on body weight are disparate. For example, it was recently shown that SIRT1 deletion or overexpression in selected hypothalamic neurons such as POMC or SF1 neurons does not bring about any changes on body weight or adiposity in mice that are fed on a regular chow diet, while it impacts these parameters in the hypercaloric diet feeding context (24, 25). Specifically, these data indicate that in POMC and SF1 neurons, SIRT1 is a key molecule that selectively and properly controls homeostatic autonomic (energy expenditure) adaptations against diet-induced obesity (24, 25). Interestingly, while SIRT1 in POMC neurons is required for normal BAT-like remodeling of the perigonadal fat depot, SIRT1 in SF1 neurons seems to induce futile cycles in skeletal muscle (24, 25). These results also indicate that SIRT1 in POMC and SF1 neurons does not regulate food intake in either normal or hypercaloric diet feeding contexts (24, 25). SIRT1 in other, non-POMC and non-SF1 hypothalamic neurons, may however affect feeding behavior. Indeed, Cakir and colleagues showed that reduced hypothalamic SIRT1 contents suppresses food intake in rodents fed a regular diet (54), an effect likely due to diminished SIRT1 activity in AgRP neurons (55). Thus, from a therapeutic perspective, the aforementioned results would suggest that SIRT1-activating compounds effective in restraining body weight gain must target only SF1 and POMC neurons, while avoiding the AgRP-expressing neuronal group. Another possible advantage brought on by avoiding harnessing SIRT1-dependent pathways in AgRP neurons is to help reduce the risks of developing psychotropic side effects that are typical untoward actions of anorectic anti-obesity drugs (28) (Box 1).

In addition to protecting against dietary obesity, hypothalamic SIRT1 is also important for mounting homeostatic responses against dietary diabetes. In fact, mice overexpressing SIRT1 only in SF1 neurons are protected from developing diet-induced insulin resistance in skeletal muscle and hyperglycemia whereas mice lacking SIRT1 in these same neurons are more prone to develop dietary diabetes (24). Furthermore, intracerebroventricular delivery of resveratrol, a natural polyphenolic molecule known to activate SIRT1 (56, 57), improves dietary diabetes in rodents (58) via mechanisms that require the presence of SIRT1 in hypothalamus (59). Collectively, these results indicate that the “ancient” SIRT1 in hypothalamic neurons is crucial for triggering effective defense responses against the development of diet-induced metabolic imbalance (Figure 2).

Metabolic actions of SIRT1 in peripheral tissues

In addition to the brain, SIRT1 is expressed in virtually every peripheral tissue of the mammalian body. And, a large body of literature has established peripheral SIRT1 as an important regulator of metabolic function. Interestingly, the reported roles of peripheral SIRT1 on glucose homeostasis appear to be distinct and tissue-specific. For example, several studies indicate that hepatic SIRT1 is a main molecule for triggering gluconeogenic function. In fact, hepatocytes overexpressing SIRT1 have higher contents of mRNAs whose product are enzymes of the gluconeogenic pathway, compared to hepatocytes containing normal SIRT1 levels (26). These findings are in agreement with data shown by Shulman and colleagues, who reported that rats affected by T2DM and bearing reduced levels of liver SIRT1 have lower hepatic glucose production and improved diabetes, compared to controls (60). Also, SIRT1 is known to deacetylate and thus activate peroxisome proliferator activated receptor γ (PPARγ) coactivator 1α (PGC-1α) that stimulates the expression of gluconeogenic genes (19). Therefore, at a first glance, the results that either pharmacologically- or genetically-induced whole-body SIRT1 activation protects from dietary diabetes appear at odds with data indicating SIRT1 as a positive regulator of hepatic gluconeogenic function (26, 27, 61, 62). One possible explanation for this apparent conundrum is that SIRT1 actually does not activate but rather inhibits hepatic

gluconeogenesis, as suggested by Montminy and collaborators (63). However, in case SIRT1 is indeed a positive regulator of the gluconeogenic program, its activation in liver should be avoided in diabetic subjects who frequently have increased hepatic gluconeogenesis. On the other hand, considering the fact that this enzyme in myocytes has been suggested to positively regulate fatty acid oxidation, enhance O_2 consumption (21, 64), and potentiate the insulin sensitizing actions of adiponectin (65), SIRT1 activation in skeletal muscle is expected to be beneficial for the treatment of diabetes. The roles of SIRT1 in adipocytes on glucose metabolism are currently uncertain. SIRT1 suppresses the secretion of the insulin sensitizer hormone adiponectin from adipocytes (66). Also, by inhibiting the activity of PPARγ (a key regulator of adipogenesis) SIRT1 exerts an inhibitory effect on adipocyte differentiation and fat tissue accrual (23). Reduced fat mass is usually accompanied with reduced levels of leptin that is a positive regulator of glucose homeostasis as clearly indicated by the remarkable beneficial results of leptin therapy on glycemic control in lipodystrophic humans (67, 68). Therefore, based on the aforementioned results, activation of SIRT1 in adipocytes is expected to cause the very negative combination of reduced leptin and adiponectin levels that should bring about increased insulin resistance and hyperglycemia; an effect that is clearly unwanted in diabetic subjects. Future investigation directed to assess the real contribution of SIRT1 in liver, skeletal muscle, and adipose tissue in mediating the anti-diabetic actions of resveratrol and other SIRT1-activating compounds are therefore warranted.

The roles SIRT1 exerts on body lipid metabolism are also peculiar. Recently, Qiang and colleagues reported that addition of an extra copy of *Sirt1* gene engenders a predisposition to developing more severe aortic atherosclerotic lesions in mice fed on a cholesterol-rich diet; an effect probably mediated by increased hepatic lipid synthesis and secretion (69). These results are in line with previous findings showing that SIRT1 deletion causes reduced hepatic and circulating lipid levels (70) but are at odds with results of Pfluger and collaborators indicating that high-fat-diet-induced hepatic lipid accumulation is diminished in a different SIRT1 overexpressor mouse model (62). Differential SIRT1 overexpression in various tissues could explain the diverse outcomes observed by Qiang and colleagues and Pfluger and collaborators. Interestingly, SIRT1 overexpression only in endothelial cells has been suggested to protect against atherosclerotic lesions (71). Therefore, it appears as if SIRT1-activating compounds should not target the liver but perhaps the endothelium, if they are to exert positive actions against diet-induced atherosclerosis.

Does hypothalamic SIRT1 regulate ageing processes?

The answer to this question may depend on the environment the organism lives in. For example, the amount and type of food ingested greatly impacts the ageing process, as clearly demonstrated by the fact that CR prolongs lifespan in organisms from yeasts to monkeys (72-77) and by inference likely in humans as well. In contrast, hypercaloric feeding causes metabolic imbalance, accelerates the pace of ageing thus causing shorten mammalian lifespan (27). Because a significant proportion of the human population currently lives in obesogenic and diabetogenic environments in which calorie-rich foods are easily and inexpensively available (28), the roles of hypothalamic SIRT1 on ageing should be investigated in the context of hypercaloric feeding if these studies are to be relevant to the physiology and pathophysiology of nowadays humans.

Ageing processes are multiple and heterogeneous. For example, an age-dependent tendency to a decline in BAT content and activity in fat depots, and reduced insulin sensitivity, are components of the metabolic aging process. These defects are thought to increase the probability of developing diseases in which age is a risk factor as for example obesity and T2DM (78). Because SIRT1 is known to affect metabolic function and several groups have

shown that brain-mediated mechanisms link changes in energy intake to lifespan (79-81), hypothalamic SIRT1 seems to be perfectly placed to coordinate metabolic ageing processes. Indeed, studies indicate that at least two facets of metabolic ageing are controlled by hypothalamic SIRT1 in the obesogenic and diabetogenic hypercaloric feeding environment. As mentioned above, BAT content and activity in humans varies with age; they are both high early-on in life, while they tend to decrease by age (46, 82). This effect has also been observed in mice (78). Interestingly, young-adult mice lacking SIRT1 only in POMC neurons have reduced BAT in perigonadal fat, and as such possess an aged-like perigonadal fat at a young age (25). This defect is physiologically relevant as it predisposes to developing obesity (25). Impaired insulin sensitivity is also associated with ageing and a process that appears also to be influenced by hypothalamic SIRT1. In fact, young-adult mice lacking SIRT1 only in SF1 neurons have reduced skeletal muscle insulin sensitivity, and as such possess aged-like skeletal muscle at a young age (24). Conversely, aged mice overexpressing SIRT1 only in SF1 neurons have enhanced skeletal muscle insulin sensitivity and therefore display young-like skeletal muscle at an old age (24). This SIRT1-in-SF1-neuron-skeletal-muscle circuitry is physiologically relevant as it protects against the development of diet-induced T2DM (24).

Therefore, despite the recent controversy pertinent to the putative role of sirtuins on promoting longevity (14), the abovementioned results would suggest that, in mammals, the metabolic-sensor protein SIRT1 in metabolic-sensing hypothalamic neurons is a crucial component of the mechanisms underlying mammalian lifespan; at least in obesogenic and diabetogenic environments. Future studies will be required to establish the role (if any) of hypothalamic sirtuins on longevity in mammalian organisms. These studies will need to include measurements of lifespan in mice bearing POMC- and/or SF1-neuron-specific loss- or gain-of-function mutations in *Sirt1*.

Concluding remarks

Recent findings have indicated that SIRT1 in POMC and SF1 neurons protects against dietary metabolic defects such as obesity and T2DM. The roles of SIRT1 in peripheral tissues on metabolic regulation have also been investigated. However, while some findings support, others counter, the idea that SIRT1 activation in specific peripheral tissues is beneficial in the context of metabolic diseases. Based on the findings discussed above, it seems reasonable that ways to delivering SIRT1 agonists selectively in specific cells (e.g.: POMC- and SF1-expressing neurons, myocytes and endothelial cells) should be developed. The cellular selectivity of these compounds would in theory guarantee that only the beneficial effects of SIRT1 activation, for example improved body adiposity and diabetes in obesogenic and diabetogenic environments, are achieved, while the deleterious ones, such as changes in food intake, increases in glucose and lipids outputs from the liver, are avoided. Unfortunately, cell-selective SIRT1-activating drugs are not yet available. Future efforts should be made to find means by which these drugs are tailored in a cell-specific manner if only the beneficial effects of SIRT1 activation are to be achieved.

To better understand the biology and physiological relevance of mammalian sirtuins, several outstanding questions will also need to be addressed. These include the following: i) what are the intracellular mechanisms by which SIRT1 in hypothalamic neurons promotes anti-obesity and -T2DM actions? Some data are already available and indicate that this protein regulates the sensitivity of hypothalamic neurons to hormones (e.g. leptin) and neuropeptides (e.g.: orexin) (24, 25). However, much more needs to be done to fully elucidate the intracellular pathways regulated by SIRT1 in hypothalamic neurons; ii) how is the activity of hypothalamic SIRT1 regulated by hypercaloric feeding? It is indeed interesting and somewhat counterintuitive that a protein known to be activated in the low-

energy state is key for preventing diseases induced in the high-energy state (a condition in which the activity of SIRT1 is predicted to be reduced). One possible explanation for this apparent conundrum is that the activity of SIRT1 in the hypothalamic neurons that have been studied is actually increased following high-fat diet feeding. This counterintuitive regulation of SIRT1 could be due to the fact that high-fat diet feeding leads to an increase in NAD^+ in those neurons and/or to hormonal changes that bring about post-translation modification(s) of SIRT1 that ultimately lead to enhanced activity. Alternatively, SIRT1 activity is suppressed in those neurons following high-fat diet feeding; yet the residual SIRT1 activity is required for mounting appropriate responses against diet-induced obesity and diabetes. As mentioned above, no data are currently available to support of reject either hypotheses; thus, future experiments will be required to address this important question; iii) why the effects of genetic manipulation of hypothalamic SIRT1 are mainly observed in the high-energy state? As discussed above, one possible explanation is that SIRT1 in hypothalamic neurons is more active following high-fat diet feeding. Other possibilities include the following: in the chow-fed state compensatory mechanisms are able to counterbalance the defects brought on by lack of SIRT1 in hypothalamic neurons. This phenomenon could explain the lack of metabolic imbalance in mutants fed on a chow diet. However, in the context of high-fat diet feeding these compensatory mechanisms may not be able to prevent the whole-body metabolic effects caused by lack of SIRT1 in hypothalamic neurons. Supporting this notion are data indicating that chow-fed mice lacking SIRT1 only in SF1 neurons have reduced insulin sensitivity in skeletal muscle; yet they display normal glycemia. This is explained (at least in part) by the fact that insulin sensitivity is, on the other hand, enhanced in the liver; an aberrancy that may well be part of compensatory mechanisms aimed at maintaining blood glucose levels normal in chow-fed mutants. In the high-fat-feeding state, insulin sensitivity is reduced in the skeletal muscle but not up-regulated in liver, hence the manifestation of hyperglycemia in mice lacking SIRT1 only in SF1 neurons fed on a high-fat diet (24). Because the available data are not sufficient to support of reject these hypotheses, additional experiments will be required to address this important question; iv) does hypothalamic SIRT1 regulate lifespan? Experiments aimed at determining if the lifespan of mice lacking or overexpressing SIRT1 in discrete hypothalamic neuronal groups are already in process. While we wait for these experiments to be concluded, the idea that the metabolic-sensor protein SIRT1 in metabolic-sensing POMC and/or SF1 neurons is a crucial component of the mechanisms underlying mammalian lifespan seems to be an exciting possibility.

In summary, regardless to whether hypothalamic SIRT1 governs lifespan or not, current data pinpoint this enzyme in hypothalamic POMC and SF1 neurons as an attractive molecular target for drugs aimed at treating the rapidly-spreading metabolic disorders of obesity and T2DM.

Acknowledgments

This work was supported by the American Heart Association (Scientist Development Grant to R.C.) and the National Institutes of Health (DK080836 to R.C.). I thank Drs. Giorgio Ramadori and Claudia R. Vianna at The University of Texas Southwestern Medical Center, Dallas, TX, USA for suggestions and critical reading of the manuscript.

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Text box 1

Obesity: disease characteristics.

Obesity is a metabolic disorder characterized by a positive energy imbalance. This defect is due to increased food intake (hyperphagia), or reduced energy expenditure (hypometabolic rate), or both. Of note, even small changes in food intake and/or energy expenditure over a long period of time could cause obesity (28). The World Health Organization indicates that an adult with a Body Mass Index (BMI = body weight in kilograms divided by the square of the height in meters) equal or greater than 30 is obese. Due to its high incidence and serious co-morbidities as for example heart disease and diabetes, obesity is a serious threat to human health. With the exception of very rare monogenic forms (e.g. leptin or leptin receptor loss-of-function mutations), the primary defects causing this metabolic disease are still incompletely understood (83). Nevertheless, a common feature of obese people is elevated levels of circulating leptin indicating that resistance to the hormone is in part involved in the etiology of the disease. This leptin resistance is very likely caused by chronic feeding on hypercaloric diets (52) and precludes the use of leptin as a therapeutic tool against obesity, as clearly indicated by the fact that obese individuals respond poorly to leptin treatment (84, 85). Thus, obesity is a very difficult disease to treat and another major roadblock for the development of effective anti-obesity drugs is the anatomical overlap between brain circuitries controlling feeding and hedonic/reward pathways. Therefore, drugs aimed at curtailing food intake often cause serious psychotropic side effects as for example increased risk of developing depression and/or suicidal thoughts (28). Another untoward effect of anti-obesity drugs is detrimental action on the cardiovascular system. For example, increased incidence of valvular heart defects were observed after administration of fenfluramine-phentermine and an increased risk of myocardial infarction and stroke were seen after treatment with sibutramine (86, 87).

Text box 2

Type 2 diabetes mellitus: disease characteristics.

Type 2 diabetes mellitus (T2DM) is an illness characterized by insulin resistance and elevated blood levels of glucose (hyperglycemia), insulin (hyperinsulinemia) and lipids (hypertriglyceridemia) (88). Due to its high incidence and serious co-morbidities as for example heart disease, higher risk of developing cancer (e.g.: pancreatic and hepatic tumors), retinopathy, and nephropathy, T2DM is a serious threat to human health. Several treatments are available to patients with T2DM. Probably, the most widely prescribed anti-T2DM drug is metformin, a biguanide that suppresses glucose output from the liver (89, 90). Other anti-T2DM drugs include thiazolidinediones, synthetic ligands to the nuclear receptor/transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) known to increase insulin sensitivity (91), as well as insulin and insulin secretagogues (e.g.: sulphonylureas). Although metformin does not cause major side effects, thiazolidinediones have been shown to cause harmful effects on the heart while insulin and sulphonylureas are prone to induce hypoglycemia. Furthermore, it is common that the dose of each of the current anti-T2DM drugs (alone or in combination) tend to increase with the progression of the disease hence causing an increase in the likelihood of inducing side effects (92).

Outstanding Questions box

- What are the intracellular mechanisms by which SIRT1 in hypothalamic neurons promotes anti-obesity and -T2DM actions?
- How is the activity of hypothalamic SIRT1 regulated by hypercaloric feeding?
- Why the effects of genetic manipulation of hypothalamic SIRT1 are mainly observed in the high-energy state?
- Does hypothalamic SIRT1 regulate lifespan?

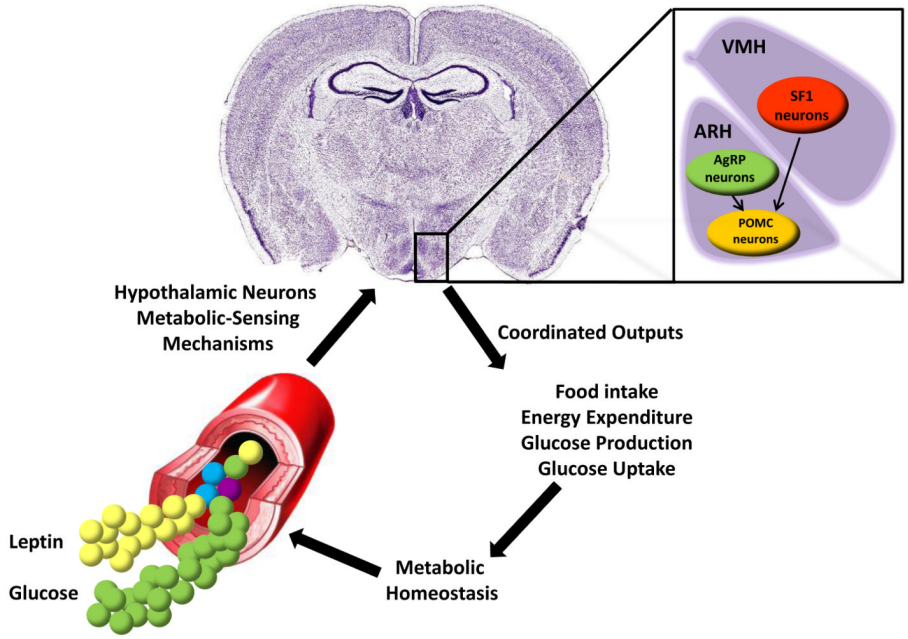

Figure 1. A model depicting hypothalamic-mediated control of metabolic homeostasis

AgRP and POMC neurons in the hypothalamic arcuate nucleus (ARH) and SF1 neurons in the ventromedial hypothalamic nucleus (VMH) are able to detect fluctuations in circulating levels of metabolic cues (e.g.: leptin and glucose) and to coordinate responses (e.g.: changes in food intake, energy expenditure, glucose production from the liver and glucose uptake by the skeletal muscle) aimed at maintaining normal body weight and glucose balance. Depicted are also projections from AgRP and VMH neurons to POMC neurons.

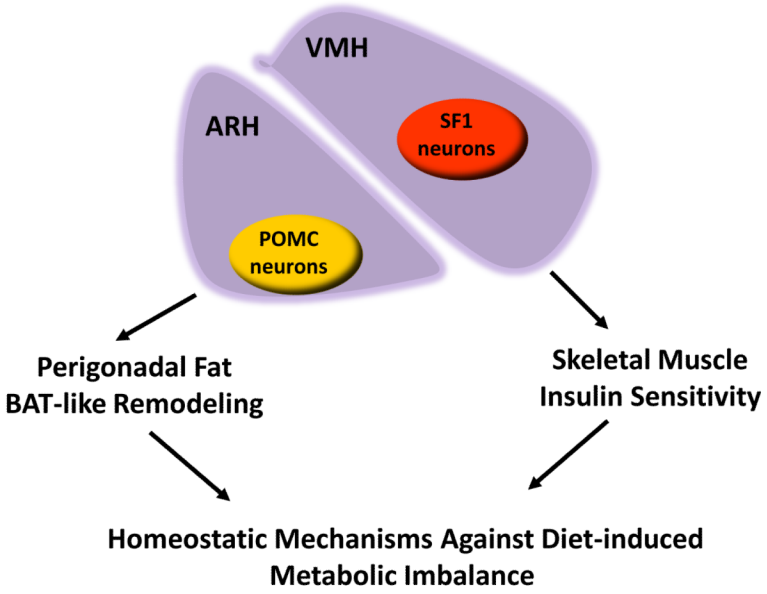

Figure 2. SIRT1 in POMC and SF1 neurons is a crucial molecule for triggering efficacious responses against diet-induced metabolic imbalance

Hypothalamic arcuate nucleus (ARH) POMC neurons selectively govern brown adipose tissue (BAT)-like remodeling of perigonadal fat while ventromedial hypothalamic nucleus (VMH) SF1 neurons selectively control skeletal muscle insulin sensitivity. The proper execution of these hypothalamic-mediated actions requires the presence of SIRT1 in POMC and SF1 neurons.