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Pharmacological Manipulations of CNS Sirtuins: Potential Effects on Metabolic Homeostasis

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Abstract

Sirtuins are deacetylases and/or mono-ADP-ribosyltransferases found in organisms ranging from bacteria to humans. These enzymes use oxidized nicotinamide adenine dinucleotide (NAD^+) and a long array of different proteins (e.g.: histones, transcription factors, cofactors, members of the electron transport chain, etc.) as substrates. Sirtuins-mediated reactions yield deacetylated proteins, nicotinamide (NAM) and 2′-O-acetyl-ADP-ribose (O-AADPr) or mono-ADP-ribosylated proteins and NAM. As these post-translational modifications change the activity of their targets and sirtuins depend on NAD^+ to function, these enzymes are thought to link metabolic statuses with cellular gene expression, activity and fate; as such sirtuins are thought to be *bona fide* metabolic-sensor proteins. Due to their diverse targets, sirtuins affect metabolism, senescence, longevity, circadian rhythms and many other biological and physiological programs. In this review we focus on their known roles on metabolic homeostasis with particular emphasis on their functions in neurons within the central nervous system (CNS). We also touch upon the possible metabolic outcomes of pharmacological manipulations of CNS sirtuins.

Keywords

Brain; Sirtuins; Metabolism; Homeostasis; Pharmaceutical; Metabolic-sensor proteins

1. Introduction

The name sirtuins stems from Silent Information Regulator 2 (SIR2), the first protein of this family being discovered in the yeast *Saccharomyces cerevisae* in 1979; however SIR2 was originally given a different name: mating-type regulator 1, as mutations in this gene cause sterility [1]. Sirtuins are present in many different species including bacteria, yeasts, worms, flies, fishes, rodents, plants and up to humans, suggesting that this class of proteins has been highly-conserved throughout evolution [2–4]. Seven SIR2's orthologs (SIRT1-7) have been found in mammals [5]. All sirtuins use NAD^+ as co-substrate to mediate deacetylation and/or mono-ADP ribosylation of target proteins [4,6,7]; nevertheless, not all sirtuins seem able to exert both enzymatic activities. In fact, SIRT1 and 5 have not been reported to have robust

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mono-ADP ribosylation activity whereas SIRT2, 3, 4 and 6 exert both types of post-translational modifications [7–12].

Sirtuins are widely expressed through the mammalian body but appear to be selectively localized at the subcellular level: SIRT3, 4 and 5 are mitochondrial, SIRT1, 6 and 7 are mainly nuclear and SIRT2 is mainly cytosolic (Figure 1) [12–21]. Perhaps because SIRT1 was first described to be an histone deatelytase [4], sirtuins have been classified as class III hystone deacetylases [22]. However, mitochondrial sirtuins are not known to be involved in nuclear chromatin metabolism and sirtuins' substrates are not limited to histones but include transcription factors, cofactors, proteins involved in oxidative phosphorylation (OXPHOS) and many others. Subunits of nuclear factor-κB (NF-κB), members of the forkhead box-containing protein type O subfamily (FOXOs), peroxisome proliferator activated receptor γ (PPARγ), PPARγ coactivator 1α (PGC1α), acetyl-CoA synthetases (AceCSs), glutamate dehydrogenase (GDH), circadian clock regulators BMAL1 and PER2 are just some of their known targets [12,23–30]. Considering the tight connection between normal circadian rhythms and whole-body metabolic homeostasis [31–34], it is not surprising that SIRT1's targets include key components of the metabolic and core clock machineries [23,24]. Also, further bolstering the idea that reversible acetylation is a broad and evolutionarily highly-conserved post-translational modification [35], mitochondrial sirtuins modulate the activity of core proteins of the electron transport chain (e.g.: SIRT3 acts on complex I) or key enzymes of acetate and urea cycles (e.g.: SIRT3 acts on AceCS2 whereas SIRT5 on carbamoyl phosphate synthetase 1) [17,30,36].

Due to their dependence on the oxidized form of NAD, sirtuins have been suggested to be important molecular links between redox status and cellular gene expression, activity and fate. Sirtuins are therefore to be considered *bona fide* metabolic-sensor proteins similar to mammalian target of rapamycin (mTOR) and AMP-activated kinase (AMPK). These metabolic-sensor proteins share some important features: i) they are highly-conserved throughout evolution as their orthologs can be found in prokaryotes, single-celled eukaryotes, lower metazoans and humans; ii) their activity is regulated by energy status and hence their activation (as for AMPK and sirtuins) or inhibition (as for mTOR) following calorie-restriction has been suggested to underlie the beneficial effects of this feeding regimen. This idea is supported by studies showing that activation of AMPK or sirtuins or inhibition of mTOR results in prolonged life-span, one of the most striking effects of calorie-restriction [3,37–41]. Spurred by the aforementioned results and the fact that SIR2 (or its orthologs in worms and flies) is required for the effects on longevity of compounds known to activate sirtuins (e.g.: resveratrol) [42–46], this pathway has attracted a great deal of attention in recent years. Indeed, sirtuins have been proposed to be "the" target to harness pharmacologically in order to slow down the pace of ageing and defend against age-related diseases, including metabolic dysfunctions [9, 42,47,48]. Below we discuss the mechanisms through which sirtuins (particularly SIRT1) affect metabolic homeostasis. We also survey emerging new roles for brain sirtuins against metabolic imbalances caused by hypercaloric feeding.

2. Actions of sirtuins in metabolically-relevant peripheral tissues

First we must state what we mean by metabolically-relevant tissues. All types of cells utilize fuels to function and therefore all tissues rely on metabolic reactions to exert their actions. However, some tissues impact whole-body metabolism more profoundly than others. For example, the cerebellum and the cerebral motor cortex mainly govern coordination and ambulatory movements whereas the hypothalamus controls body weight and glucose homeostasis. We include hypothalamus along with caudal brainstem, pituitary, adrenal and thyroid glands, entero-endocrine cells, liver, endocrine pancreas, skeletal muscle and adipose tissues in the list of metabolically-relevant sites.

We begin with parsing sirtuins' actions in the **liver**. Hepatic glucose and lipid metabolism are vastly controlled at the transcriptional level with PGC1α and β, liver X receptor (LXR), sterol response element binding proteins, FOXO-1, hepatocyte nuclear factor 4 alpha, and PPARs playing pivotal roles in these programs [49–57]. By deacetylating and thus activating PGC-1α, FOXO-1 and LXR, SIRT1 induces gluconeogenesis and fatty acid β-oxidation; these actions are physiologically relevant as demonstrated by the fact that liver-specific deletion (or downregulation) of SIRT1 causes hypoglycemia and hypersensitivity to diet-induced hepatic steatosis [58–61]. Because PGC1α and FOXO-1 link fasting to increased hepatic heme biosynthesis [62], it would be interesting to explore if SIRT1's antagonists can be used therapeutically in hepatic porphyrias. The functional roles of the other nuclear and cytosolic sirtuins in liver are yet to be established although the severe hypoglycemia seen in SIRT6 deficient mice [16] may indicate that this sirtuin could also be directly implicated in controlling liver glucose metabolism. As for the mitochondrial sirtuins, SIRT5 has been shown to deacetylate carbamoyl phosphate synthetase 1 (an enzyme of the urea cycle) and prevent hyperammonemia after fasting [17]. SIRT3 and 4 may be physiologically relevant to prevent genotoxic-induced cell death as these two sirtuins (but not others) have been suggested to mediate resistance to toxins following nutrient restriction, when liver mitochondrial NAD^+ levels increase [63]. In **skeletal muscle,** SIRT1 enhances mitochondrial activity, fatty acid β-oxidation and insulin sensitivity. These actions are, at least in part, *via* activation of PGC-1α–dependent pathways and inhibition of protein tyrosine phosphatase 1B, a negative regulator of the insulin receptor signaling cascade [64,65]. It is worth noting that some of the anti-diabetic effects of orally-delivered SIRT1's activators have been proposed to be mediated by this tissue due to the fact that skeletal muscles from treated animals display enriched mitochondria [66, 67]. Because this tissue is the most important site for glucose disposal in the mammalian body and SIRT6 deficient mice suffer of severe hypoglycemia [16], SIRT6 in myocytes may also be relevant for overall glucose homeostasis. As for the mitochondrial sirtuins, reduced SIRT3 amount has been found in skeletal muscle of diabetic mice [68]; however this seems to be secondary to diabetes because glucose and insulin homeostasis is normal in the absence of SIRT3 [36,69]. In **pancreatic β-cells** SIRT1 profoundly improves glucose stimulated insulin secretion and body glucose tolerance *via* a mechanism that involves suppression of uncoupling protein 2 (UCP2) [70]. However, another sirtuin seems to exert opposite effects in these cells as SIRT4 downregulates insulin secretion in response to amino acids through ADP-ribosylation of glutamate dehydrogenase (a mitochondrial enzyme that converts glutamate into α-ketoglutarate) [12,13]. The physiological significance of these somewhat puzzling results is not completely understood. In **adipose tissue,** SIRT1 reduces lipogenesis and adipogenesis through a mechanisms involving deacetylation and hence repression of PPARγ [71]. These specialized functions are probably important to allow the organism to cope with periods of reduced energy intake as enhanced SIRT1 activity is expected to mobilize free fatty acids from adipocytes and thus render chemical energy available to other tissues.

Although great advances regarding our understanding of the molecular actions of sirtuins have been made, a comprehensive knowledge of the roles these enzymes exert at the whole-body organism level is lacking. For instance, the fact that systemic pharmacological activation of SIRT1 has been proposed to be an effective anti-diabetic treatment is somewhat counterintuitive considering the fact that SIRT1 positively regulates gluconeogenesis in hepatocytes [25,72]. Therefore, the whole-body beneficial effects of pharmacological (or genetically-mediated) SIRT1 activation may be, at least in part, driven by cell non-autonomous mechanisms. Part of these mechanisms may include metabolic interplay between white adipose tissue and other organs as suggested by the fact that mice overexpressing SIRT1 display increased circulating levels of adiponectin [72]. Our recent studies would also suggest an important role for brain SIRT1 as central delivery of resveratrol improved glucose/insulin homeostasis in a food-intake-and body-weight-independent fashion in diet-induced diabetic rodents (see section 3) [73].

3. Metabolic actions of brain sirtuins

All mammalian sirtuins are expressed in the brain [12,16,17,20,74–76]; however, there is a dearth of information about what cell types each of the seven sirtuins are express in. Knowledge is limited to SIRT1 being expressed in CNS neurons and glial cells [74,77] whereas SIRT2 seems to be expressed exclusively by cells of the oligodendrocyte lineage [75,76]. Moreover and most importantly, the physiological roles of CNS sirtuins are still poorly understood. SIRT1 is thought to exert neuroprotective actions against states such as Alzheimer's disease and amyotrophic lateral sclerosis [78,79]. Also SIRT1 may contribute to the positive effects of NAD^+ against the program of axonal degeneration [80]. Conversely, inhibition of SIRT2 has been shown to protect against conditions characterized by aggregation of misfolded proteins (as for example in Parkinson's disease) whereas SIRT1 overexpression appears to be beneficial in this context [81–83]. To date, knowledge regarding the physiological roles of SIRT3, 4, 5, 6 and 7 in brain is lacking. Therefore, because we are in the very early stages regarding our understanding of brain sirtuins' biological and physiological roles, the outcomes of long-term treatments using pan-sirtuins activators are currently uncertain; especially considering recent findings indicating that SIRT1 does not protect neurons but actually sensitizes them to oxidative damage [84]. Not to mention the fact that O-AADPr (a product of sirtuins-mediated deacetylation) binds to transient receptor melastatin-related ion channel 2, hence enhancing the ability of this cation channel to cause cell death following oxidative stress [85,86]. It is thus important to consider not only the post-translational effects on their targets, but also to fully understand what actions other products of sirtuins enzymatic reactions exert.

Despite the fact that it may be difficult to disentangle actions on neuroprotection from the ones on metabolic functions (especially in the ageing context), below we will discuss the available information about the roles that sirtuins in brain neurons exert on the overall control of body energy and glucose balance. First, we need to briefly introduce the mechanisms through which central neurons govern metabolic homeostasis (due to space limitations we suggest reading other reports for a more detailed elucidation of these CNS-dependent homeostatic pathways [87,88]). In addition to specialized sensory neurons in the caudal brainstem that orchestrate acute responses to food ingestion (e.g.: meal termination), other neurons (mainly located in hypothalamus) coordinate long term energy and glucose balance [89]. For example, hypothalamic neurons are equipped with sensing-mechanisms that allow these cells to link extracellular fluctuations in hormonal and nutrient levels to changes in their gene expression, firing rate and overall activity. Physiological relevant hypothalamic sensing-mechanisms include (hormonal) leptin-, insulin-, and (nutrient) glucose-, lipid-sensing pathways. Indeed, it has been shown that genetic manipulations of each of these aforementioned sensing-mechanisms in restricted hypothalamic neurons lead to changes in body energy and/or glucose balance [90–95]. Because SIRT1 is known to affect molecular components of these sensing-mechanisms in peripheral tissues as for example UCP2 in the pancreas [70] (UCP2 negatively regulates glucose-sensing in neurons [92] as well as in pancreatic β-cell [96]), it is formally possible that this enzyme may affect these pathways in brain neurons also.

SIRT1 is widely expressed throughout the neuraxis but more abundantly expressed in areas known to govern metabolic functions as the hypothalamus and caudal brainstem nuclei [74]. Also, SIRT1 is present in cells firmly established as important regulators of body weight and glucose homeostasis as for example neurons belonging to the central melanocortin system [74,92,93,97]. Furthermore, SIRT1 activity in brain (particularly in hypothalamus and caudal brainstem) has been shown to be influenced by changes in energy availability and that these modulations are aberrant in obesity [74,98]. Recently, it has been shown that knockdown of SIRT1 in hypothalamus causes reduced feeding in rats [99]. Collectively, these findings indicate that SIRT1 is a molecular component of brain-mediated control of body metabolic functions.

Additional clues on the metabolic roles of brain sirtuins were provided by our recent study in which the hypothesis that CNS mediates the anti-diabetic actions of resveratrol was directly tested [73]. Resveratrol is a natural occurring polyphenolic compound (found in the skin of red grapes and other plants) known to directly activate SIRT1 by binding it at a region spanning amino acids 183-225 [9,44]. It has been shown that resveratrol lowers glycemia and improves insulin sensitivity when orally-delivered to animal models of type 2 diabetes [48,66], nevertheless, the mechanisms and sites of actions have not been established. However, our work pinpoints the brain as a main site for reveratrol's metabolic effects. Indeed, CNS resveratrol delivery improved diet-induced hyperglycemia and hyperinsulinemia; an effect that we speculated is, at least in part, *via* brain SIRT1 activation and reduced CNS inflammation [73]. Because it is formally possible that resveratrol also activates SIRT6, resveratrol's anti-inflammatory effects could be twofold: one direct inhibitory action on NF-kB *via* SIRT1-mediated deacetylation of RelA/p65 [29,73,77] and one indirect action on promoter regions of NF-kB's targets *via* SIRT6-mediated deacetylation of histone 3 and hence transcriptional silencing at these sites [100]. Despite robust evidences indicating that resveratrol directly activates SIRT1 [44,101], *per contra* this contention has recently been questioned [102–104]. Therefore, there are doubts regarding whether sirtuins play central or marginal roles in mediating resveratrol's metabolic effects [102]. Future studies in which resveratrol is delivered centrally in mice lacking SIRT1 (and/or SIRT6) only in specialized CNS neurons are thus warranted. Furthermore, as resveratrol indirectly activates AMPK [105,106], and that AMPK has been proposed to be the molecular link between resveratrol administration and improved metabolism [107], similar approaches, using animal models lacking AMPK only in selected CNS neuronal populations will also be required to establish the real contributions of this metabolic-sensor protein. Pitfalls of these experiments may be the presence of metabolic phenotypes in mice lacking SIRT1 (or AMPK) in brain centers rendering the interpretation of results more arduous. This is indeed likely considering that knockdown of SIRT1 in hypothalamus causes reduced feeding in rats [99] and mice with neuron-specific AMPK-deletion display metabolic aberrancies [108].

Albeit we and others have not found obvious deleterious effects of chronic resveratrol treatment [48,66,73], still one of the potential drawbacks of pharmacological manipulations of SIRT1 activity in CNS may relate to the potential loss of normal circadian oscillations in SIRT1 activity [23,24]. Because SIRT1 regulates circadian clock oscillatory mechanisms and altered function of circadian clock genes leads to metabolic abnormalities [31–34] one may predict that constitutively activated (or inhibited) SIRT1 activity would unlock the intertwined circadian clock and metabolic systems [109]. This effect would likely lead to altered energy and glucose homeostasis. However, despite the fact that SIRT1's roles on circadian clock pathways have been established, these rely on studies using mouse embryonic fibroblasts and by *in vivo* analysis of the liver [23,24]. Whether SIRT1 in central neurons is also involved in coordinated clock function (as for example in the suprachiasmatic nucleus, where SIRT1 is abundantly expressed [74]) remains to be seen. Also, *Sirt1* mRNA is found in the dorsomedial hypothalamic nucleus [74], a brain site proposed to link cycles of food intake to circadian rhythms [110]. Analyses of animal models lacking or overexpressing SIRT1 in selected neuronal populations are currently underway and results from these experiments will help decipher the physiological importance of this metabolic-sensor protein in specialized CNS neurons.

In normal feeding conditions, inflammatory NF-kB signaling is almost absent in hypothalamic neurons [111]. Conversely, chronic hypercaloric diet triggers this pathway robustly, an effect that is deleterious for appropriate hypothalamic neuronal hormonal-sensing and body energy and glucose homeostasis [112]. These findings led to the notion that endogenous (or exogenous) molecules able to suppress hypothalamic NF-kB signaling could be used to fight diet-induced metabolic dysfunctions. For reasons mentioned above, means to increase SIRT1

and/or 6 activities could therefore represent ideal avenues to achieve these goals. Results from our CNS resveratrol delivery study would indeed bolster this contention as diet-induced hypothalamic NF-kB signaling, hyperglycemia and hyperinsulinemia were all almost normalized in treated mice [73]. However, one caveat of our experiment is that CNS resveratrol delivery lasted 5 weeks thus precluding us to evaluate long-term effects of this pharmacological treatment. Because one of the many actions of NF-kB is to promote cell survival [113], seen from another prospective, activation of this signaling pathway in the context of hypercaloric diet may be a critical, adaptive event to prevent neuronal damage and cell death. Therefore, in the long run, chronic activation of SIRT1 and/or 6 could paradoxically lead to neuronal loss. Thus, before drugs targeting brain sirtuins are thought to be employed in the clinic, we need to investigate potential outcomes differences between acute *versus* chronic activation (or inhibition) of these enzymes.

4. Concluding Remarks

Calorie-restriction is a feeding regimen of ~30% fewer calories an organism would normally intake without causing malnutrition. In virtually every species calorie-restriction has been tested on, the outcomes were virtually unanimously positive. These include improved cardiovascular, brain and metabolic functions (even in non-human primates [114]) and prolonged life-span [48,115,116]. Obviously, if only one molecular pathway were to mediate these effects, harnessing it pharmacologically would represent an ideal approach to extend lifespan without the burden of undergoing calorie-restriction diets. Furthermore, such pathway could be exploited to fight age-related diseases as for example diabetes mellitus. Sirtuins have been proposed to be such a target [9,42,47,48,101,117,118]. Interestingly, specialized neurons are required for calorie-restriction-induced longevity in worms [119]. Also, a brain SIRT1 component is likely involved in mediating effects of this dietary protocol as suggested by lack of increased ambulatory activity in calorie-restricted *Sirt1* null mice [120]. Thus, it is not too far-fetched to imagine that sirtuins in CNS neurons could mediate, at least in part, the beneficial effects of calorie-restriction in mammals. It is clear that major advances in the near future will come from studies of mouse models in which sirtuins are manipulated in a neuron-specific fashion. Also, results from ongoing human clinical trials of resveratrol or other and more specific SIRT1 activators [121] will help determine if these treatments are without undesired side effects. Because obesity, diabetes and other age-related diseases share a common underlying inflammatory component, the anti-inflammatory actions of sirtuins may likely represent the link between calorie-restriction and improved metabolic functions and extended life-span. Ironically, after almost a century is passed since calorie-restriction was shown to exert beneficial effects, we now find ourselves dissecting the relevance of molecular mechanisms orchestrated by sirtuins in the hope these can be exploited to treat diseases brought about by hypercaloric feeding and that were barely seen one century ago (e.g.: diabetes mellitus and obesity). Whether sirtuins in the brain play crucial defensive roles against these metabolic conditions (Figure 2) is still to be directly tested, but we anticipate that interest and excitement to tackle these questions will soon increase in pace.

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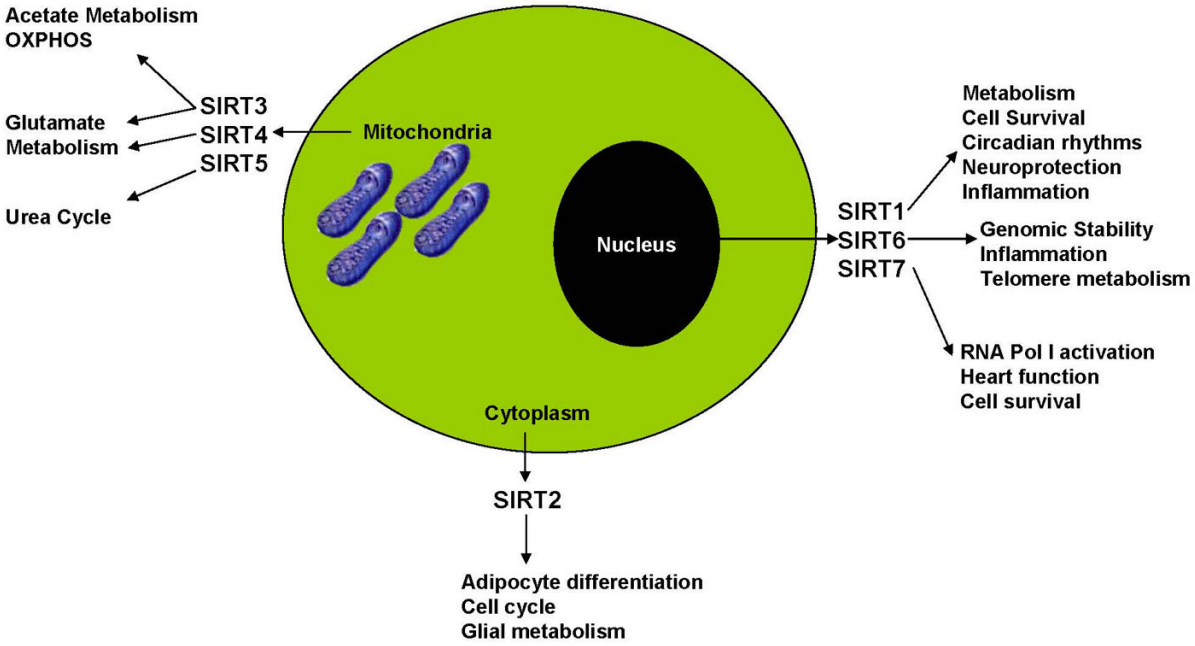

Figure 1. The diverse roles and subcellular localizations of mammalian sirtuins

SIRT1, 6 and 7 are mainly nuclear, SIRT2 is mainly cytosolic, and SIRT3, 4 and 5 are found only in mitochondria. Some authors have reported shuttling of SIRT1 and 2 from the nucleus to the cytosol and *vice versa* [122,123].

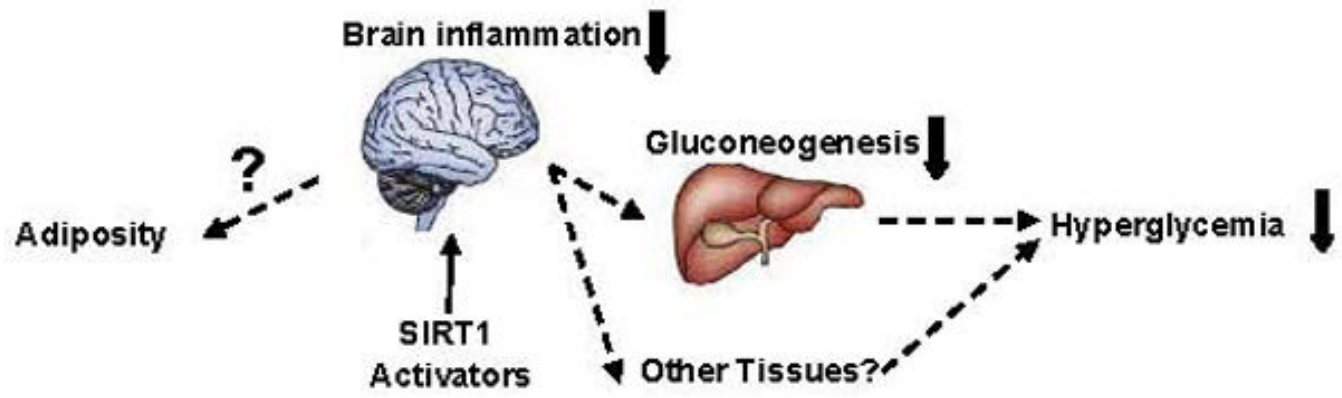

Figure 2. Proposed effects of CNS-restricted delivery of SIRT1 activators

Following chronic hypercaloric feeding mammals usually develop brain inflammation, diabetes and obesity. We predict that delivery of SIRT1 activators into the brain would ameliorate brain inflammation and consequentially hyperglycemia in part *via* reduced hepatic gluconeogenesis. Perhaps CNS-specific SIRT1 activation approach would also improve energy imbalance leading to reduced body adiposity.