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Review

Cross-talk between SIRT1 and endocrine factors: effects on energy homeostasis

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ABSTRACT

The mammalian sirtuins (SIRT1-7) are a family of highly conserved nicotine adenine dinucleotide (NAD^+)-dependent deacetylases that act as cellular sensors to detect energy availability. SIRT1 is a multifaceted protein that is involved in a wide variety of cellular processes. SIRT1 is activated in response to caloric restriction, acting on multiple targets in a wide range of tissues. SIRT1 regulates the role of multiple hormones implicated in energy balance, including glucose and lipid metabolism. Here, we review the relevant role of SIRT1 as a mediator of endocrine function of several hormones to modulate energy balance. In addition, we analyze the potential of targeting SIRT1 for the treatment of obesity and type 2 diabetes mellitus.

Contents

1. Introduction

The sirtuins are a family of highly conserved nicotine adenine dinucleotide (NAD^+)-dependent deacetylases. While research into the cellular energy sensor sirtuin 1 (SIRT1) was initially focused on aging, its interest is also turning toward its relevant ability to modulate energy balance and metabolism. Indeed, a link between energy metabolism

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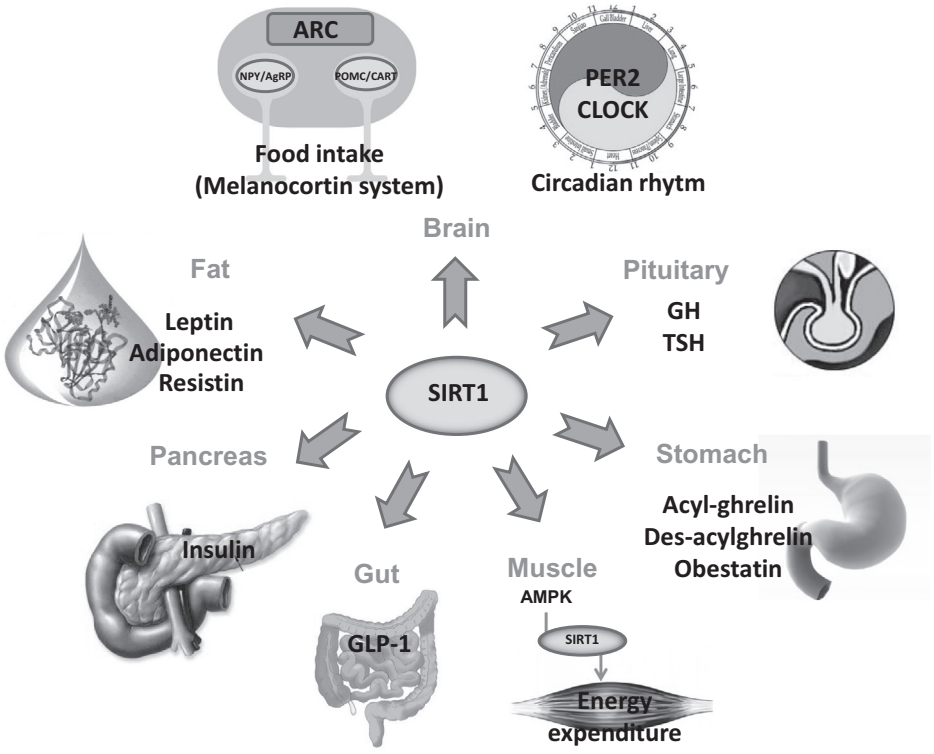

Fig. 1. SIRT1 couples the deacetylation of a number of transcription factors and co-factors to the cleavage of NAD^+, an indicator of cellular metabolic status, playing a vital role in metabolism as a mediator of endocrine function of several hormones to modulate energy balance.

and senescence has been described and calorie restriction (CR), which is defined as the restriction of food intake without malnutrition, is indicated as one of the best physiological methods to extend life spam and moderate age-associated pathologies such as diabetes, cancer or some cardiovascular pathologies (Colman et al., 2009; Fontana et al., 2004; Imai et al., 2000; Lin et al., 2002). These beneficial effects have been described in a wide variety of species such as yeast, flies, worms, rodents, monkeys and humans (Boily et al., 2008; Bordone et al., 2007; Colman et al., 2009; Fontana et al., 2004; Imai et al., 2000; Lin et al., 2002) even though others did not replicate those results (Harper et al., 2006; Mattison et al., 2012; Ramsey et al., 2000).

There are many different pathways that activate SIRT1. At present, there are a wide variety of natural and synthetic SIRT1 activators. Among the natural activators the most potent is the polyphenol resveratrol (RSV), a natural polyphenol that is produced by various plants such as red grapes, peanuts and berries that produces a variety of beneficial metabolic actions *in vivo* (Lagouge et al., 2006; Milne et al., 2007). RSV improves insulin sensitivity and increases insulin secretion and mitochondrial function (Gerhart-Hines et al., 2007), decreases adiposity and glucose levels and prolongs life spam (Baur et al., 2006; Milne et al., 2007). In addition, several small synthetic molecule activators such as SRT1720 or SRT2104, were developed and their metabolic beneficial effects were described (Libri et al., 2012; Mitchell et al., 2014; Venkatasubramanian et al., 2013; Yao et al., 2014). These molecules are structurally far away from RSV, however they are 1000 times more potent and its bioavailability is improved compared to the natural compounds (Milne et al., 2007).

2. SIRT1 as a mediator of neuroendocrine function

2.1. SIRT1 in the brain: mediator of neural function

SIRT1 is expressed in almost all tissues studied including the mammal brain (Al Massadi et al., 2013; Coppari, 2012). The relevant role of SIRT1 in metabolism led to the study of its regulation in sites of the brain that control energy balance, specifically in the hypothalamus where SIRT1 is widely expressed. CR stimulates SIRT1 expression also at the central level, specifically in the dorsomedial nucleus (DMN) and lateral hypothalamus (LH) (Satoh et al., 2010). Correspondingly, over-expression of SIRT1 specifically in the brain induces higher physical activity and increased levels of the neuronal marker c-fos, in the same hypothalamic sites in mice (Satoh et al., 2013). Moderate CR in SIRT1 transgenic (Tg) mice induces higher levels of Orexin type 2 receptor (Ox2r) in the DMN and LH, whereas this response is blunted in SIRT knockout (KO) mice. This is supported by *in vitro* data, demonstrating that SIRT1 together with Nk2 homebox-1 upregulates the Ox2r promoter expression in a dose-dependent manner in primary hypothalamic cultured cells (Satoh et al., 2013).

Neural SIRT1 action comprises the control of food intake by the melanocortin system and the maintenance of circadian rhythms (Cakir et al., 2009; Chang and Guarente, 2013; Dietrich et al., 2010; Velasquez et al., 2011). Recently, cumulative evidences suggest that SIRT1 is implicated in the regulation of endocrine function acting as a mediator of the most relevant hormones implicated in energy balance (Fig. 1).

2.1.1. SIRT1 and the melanocortin system

Pharmacological or genetic inhibition of SIRT1 in the central nervous system (CNS) decreases food intake and body weight (Cakir et al., 2009; Dietrich et al., 2010). Ex-527, a specific SIRT1 inhibitor, has been shown to decrease food intake and body weight after intracereboventicular (icv) administration in adult rats and this effect is reversed by coadministration of SIRT1 activator 3 (SA3) (Cakir et al., 2009). Additionally, SIRT1 repression in the hypothalamic arcuate nucleus (ARC) by using small interfering RNA (siRNA), decreases food intake and body weight (Cakir et al., 2009). The anorexigenic action of Ex-527 is blocked by the coadministration of the melanocortin