Central Nervous System Regulation of Metabolism - The Role of Mammalian Sirtuins

“Metabolic Disorders; Sirtuins; Hypothalamus; Energy Balance; Insulin Sensitivity”

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Abbreviations
ARC: Arcuate Nucleus; POMC: Pro-Opiomelanocortin; CART: Cocaine and Amphetamine-Regulated Transcript; NPY: Neuropeptide Y; AgRP: Agouti-Related Protein

The growing worldwide epidemic of obesity and related chronic diseases are characterized by impairment in the homeostatic regulation of energy balance. Substantial evidence indicates that the brain, in particular the hypothalamus, plays a fundamental role in this process [1]. The hypothalamus is a critical regulator of a vast array of physiological and behavioral functions, including food intake and energy expenditure, satiety, body temperature, reproductive physiology, and also circadian rhythms. This brain region is composed of various heterogeneous nuclei that together integrate peripheral nutrient and hormonal signals and orchestrate adaptive physiological responses. The hypothalamic arcuate nucleus (ARC) contains two neuronal populations essential for the regulation of food intake: the anorexigenic pro-opiomelanocortin/cocaine and amphetamine-regulated transcript (POMC/CART) neurons, which decrease food intake, and the orexigenic neuropeptide Y/Agouti-related protein (NPY/AgRP) neurons, which promote food intake [2]. These “first-order” neurons respond directly to peripheral signals and project to other nuclei of the hypothalamus, and in turn to other brain areas, to ensure the maintenance of physiological conditions [3]. Consumption of high fat diets leads to the disruption of these hypothalamic neuronal circuits and the inability to respond appropriately to fluctuations in energy availability, thus contributing to the development of metabolic dysfunction. This is characterized by the activation of several inflammatory and stress pathways [4], leading to hypothalamic injury [5], and also to impaired insulin and leptin sensitivity [6].

Given the exponential growth of metabolic disorders and the associated economic burden, there is an urgent need to develop novel therapeutic approaches for these conditions [7]. The mammalian sirtuins have emerged in recent years as potential targets to prevent or counteract metabolic disorders [8]. Sirtuins are a highly conserved family of NAD+ dependent deacetylases, with seven isoforms (SIRT1-7) [9]. The activity of these enzymes is regulated by fluctuations in nutritional availability. In general, NAD+ levels increase in response to caloric restriction, fasting, and exercise, consequently promoting sirtuin activation [10]. In contrast, under conditions of energy excess, such as obesity, NAD+ levels drop and sirtuin activity decreases. Sirtuins have a ubiquitous distribution, being widely expressed in several peripheral tissues, such as the liver, adipose tissue and skeletal muscle, and are also abundantly expressed in the central nervous system [11]. Moreover, sirtuins display distinct subcellular localization, with SIRT1, 6 and 7, predominantly localized in the nucleus, SIRT3, 4 and 5, present
in mitochondria, and SIRT2 mainly localized in the cytosol.

Research over the past 15 years has firmly established the mammalian sirtuins as major players in sensing and coordinating stress responses and has implicated these proteins in age-related diseases, such as metabolic disorders, cancer, and neurodegeneration [12]. Besides their well-known roles in peripheral tissues, sirtuins have also been reported to play a crucial role, mainly related to metabolic regulation, in the CNS [11]. SIRT1 is the best characterized of all mammalian sirtuins. This enzyme has been shown to be involved in feeding control and to have a protective effect against metabolic imbalance [13]. SIRT1 overexpression in forebrain, particularly in striatum and hippocampus, caused an increase in fat accumulation accompanied by a decrease in energy expenditure [14]. SIRT1 activity modulation in the brain also lead to a decrease in AgRP neurons activity and promoted the inhibitory output of POMC neurons [15]. Moreover, SIRT1 deficiency in POMC neurons [16], and in steroidogenic factor-1 (SF-1) neurons [17], caused a positive energy balance, with an increase in body weight and an impairment in energy expenditure. SIRT3, which has critical roles in mitochondrial function, was shown to regulate neuronal activity in response to metabolic stress, induced by exercise and caloric restriction [18]. Deletion of nuclear SIRT6 caused the development of obesity through an absent regulation of chromatin structure and gene expression by its deacetylase activity [19].

Taken together, these results support the modulation of mammalian sirtuins activity as a potential strategy to prevent or treat metabolic disorders [20]. Several pharmacological sirtuin activators, such as the natural polyphenolic compound resveratrol or synthetic molecules such as pyridine derivatives, have already been tested [21], but further studies are required to fully understand the central metabolic roles of sirtuins and the homeostatic impact of their modulation.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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