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Role of Reactive Oxygen Species in Hypothalamic Regulation of Energy Metabolism

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To understand the etiology of metabolic disorders, including obesity and type II diabetes, it is essential to gain better insight into how stored and available energy sources are monitored by the central nervous system. In particular, a comprehension of the fine cellular interplay and intracellular mechanisms that enable appropriate hypothalamic and consequent endocrine and behavioral responses to both circulating hormonal and nutrient signals remains elusive. Recent data, including those from our laboratories, raised the notion that reactive oxygen species (ROS) generation is not merely a by-product of substrate oxidation, but it plays a crucial role in modulating cellular responses involved in the regulation of energy metabolism. These review summarizes the published recent data on the effect of ROS levels in the regulation of neuronal function, including that of hypothalamic melanocortin neurons, pro-opiomelanocortin and neuropeptide Y-/agouti related peptide-neurons, in the modulation of food intake.

Keywords: Hypothalamus; Leptin resistance; Peroxisomes; Pro-opiomelanocortin; Reactive oxygen species

The hypothalamus detects a variety of peripheral and central metabolic signals, and generates an adequate degree of molecular and behavioral actions to control energy balance through complex and interconnected signal cascades [1-5]. Within the hypothalamus, the arcuate nucleus, located at its medial base portion around the third ventricle, contains at least two distinct neuronal populations controlling energy balance and defined as melanocortin system: the orexigenic neuropeptides agouti-gene-related protein (AgRP) and neuropeptide Y (NPY) containing neurons, and the anorexigenic neuropeptide pro-opiomelanocortin (POMC) expressing neurons. Both the AgRP/NPY and the POMC neurons have been identified as main regulators of appetite, satiety, and the regulation of energy expenditure.

Many circulating signals including peripheral hormones influence energy homeostasis either by activating or inhibiting the activity of these two antagonistic neuronal populations. The activation of POMC neurons by leptin, for example, triggers the release of alpha-melanocyte stimulating hormone (α-MSH) from their axon terminals, which in turn activates melanocortin 4 receptors (MC4R), leading to suppressed food intake. Simultaneously, leptin suppresses the activity of arcuate nucleus NPY/AgRP neurons [3], which otherwise would antagonize the effect of α-MSH on MC4Rs through the release of AgRP [4]. The arcuate neurons, also defined as "first order neurons," project to the so-called "second order neurons" in several hypothalamic areas including the paraventricular nucleus, ventromedial nucleus, dorsomedial nucleus, and lateral hypothalamic area [5]. From these areas, neurons then project to, among others, the nucleus of the solitary tract in the brain-

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stem and the dorsomotor nucleus of the vagus, where the descending hypothalamic inputs are integrated with peripheral afferent inputs from the liver and gastrointestinal tract.

In the last 2 decades, much has been learned about the control of feeding behavior and of its neuronal substrate in the hypothalamus, the melanocortin system [6-9]. One of the remaining enigmas is the neurobiological substrate of leptin resistance, a mechanism that entails the inability of increased leptin levels to promote a decreased feeding and body weight in diet-induced obese (DIO) subjects [10,11]. Many have argued that leptin resistance is the consequence of impaired activation of anorexigenic POMC neurons by elevated leptin levels during obesity and that this mechanism involves altered intracellular signaling cascades triggered by leptin. These include leptin-activated signal transducer and activator of transcription 3-promoted suppressor of cytokine signaling 3 accumulation [12]. PTP1B, endoplasmic reticulum stress, and inflammatory signals may also participate in the inhibition of LEPR-B signaling in obesity [11]. However, until recently, there was no conclusive neurobiological proof for impaired synaptic transmission in the melanocortin system in DIO animals [13]. In contrast, several, neurobiologically relevant components of the melanocortin system do not exhibit a clear leptin resistance [14,15]. Thus, the underlying cause for the impaired correlation between elevating leptin levels, POMC neuronal activity and feeding during diet-induced obesity remains elusive.

Recent data, including that from our laboratories [16,17], argued that reactive oxygen species (ROS) generation is not merely a by-product of substrate oxidation, but instead, plays a critical role in regulating neuronal responses. For example, when NPY/AgRP-expressing neurons are activated during negative energy balance, ROS levels are not increased in these cells despite increased firing and substrate utilization [16] possibly because of the activation of a mitochondrial protein, uncoupling protein 2. If ROS generation is uncontrolled in NPY/AgRP cells, neuronal firing of these cells is impaired [16]. In contrast, during positive energy balance, when glucose levels are elevated and POMC neurons are firing at high levels, ROS accumulates in these POMC cells [16]. However, during negative energy balance (such as fasting or before a meal), ROS levels in POMC neurons are reduced and these neurons are silent. Thus, it appears that POMC activation is driven by ROS [16,18]. The increased ROS level in POMC neurons is likely an important regulator of neuronal activation leading to cessation of feeding, increased energy expenditure supported by increased sympathetic tone to the brown fat and decreased gluconeogenesis and glucose output by the liver. In support of this idea is the observation that when ROS scavengers were selectively placed in the mediobasal hypothalamus, feeding behavior and cellular events associated with fasting were promoted [17]. The meal-associated activation of POMC neurons and related behaviors and autonomic regulation occur repeatedly within a day [16]. These short-term ROS peaks appear to be fundamental for evoking a proper behavioral, endocrine and autonomic response to nutrient intake. Furthermore, when we correlated ROS levels in POMC neurons with circulating leptin levels, a positive correlation was found. However, this correlation was lost in DIO mice. Furthermore, in DIO mice an increase in peroxisome proliferating receptor (PPAR) γ mRNA levels in the hypothalamus and a concomitant increase in the number of peroxisome in POMC neurons have been observed [19]. Peroxisomes are important cellular organelles which function is to breakdown long chain fatty acid and to produce important antioxidative enzymes including catalase, enzyme responsible for the neutralization of ROS. Thus, it is conceivable that during high fat diet, characterized by elevating leptin and insulin levels and high levels of nutrients including glucose and fatty acids, the steady high levels of ROS levels in POMC neurons may induce the proliferation of peroxisomes that by neutralizing ROS levels may reduce their levels and affect POMC neuronal activity. Indeed, when PPARγ was pharmacologically inhibited in high fat fed mice a reduction in food intake and an increase in POMC activity were observed. On the other hand, when PPARγ was pharmacologically activated in lean mice, an increase in food intake was found [19].

In summary, proper functioning of the hypothalamic POMC neurons is necessary for peripheral glucose metabolism, and intracellular ROS generation is fundamental for proper functioning of POMC neurons. Thus, during times of overnutrition, when high levels of substrates are available and thus higher levels of ROS generated, a cellular mechanism is activated to maintain ROS to a level that would not induce cellular damage. However, the activation of this same protective mechanism, i.e., peroxisomal proliferation, by reducing ROS levels, will decrease the ability of these neurons to respond to increase levels of circulating leptin.

Future studies will further delineate this mechanism that unmask a previously unknown hypothalamic cellular process associated with peroxisomes and ROS in the central regulation of energy metabolism in states of leptin resistance.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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