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Seminario

Neurons in Energy Balance: A Tale of Mitochondria and Primary Cilia in the Hypothalamus

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The hypothalamus plays a central role in regulating food intake and energy expenditure, thereby maintaining body weight. When this regulatory system is impaired, it can lead to obesity.

We recently found that chronic high-fat diet consumption increases the phosphorylation of the mitophagy protein PINK1 in the hypothalamus, while concurrently reducing the presence of primary cilia on hypothalamic neurons. These observations led us to explore the roles of mitophagy and the primary cilium in hypothalamic energy homeostasis, with a particular focus on Agouti-related peptide (AgRP) neurons, which are key orexigenic regulators.

Using AAV-mediated gene silencing, we observed that downregulation of PINK1 in AgRP neurons leads to increased body weight and impaired glucose tolerance. In contrast, loss of the primary cilium in AgRP neurons, using the same technical approach, has a modest effect on body weight but causes a pronounced deterioration in glucose tolerance.

Our findings highlight the critical roles of PINK1-dependent mitophagy and the primary cilium in AgRP neurons in maintaining metabolic homeostasis. These components may represent promising therapeutic targets for the treatment of metabolic disorders such as obesity and type 2 diabetes.