# Sirtuin's Action on the Hypothalamic Melanocortin System is Enabled by UCP2

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The discovery of sirtuins and their role in cellular function and whole body physiology raised the possibility that promotion of this pathway in peripheral tissues may diminish disease states and prolong healthy lifespan. Sirtuins are NAD+-dependent class III deacetylases, highly conserved across species. Promotion of the action of SirT1, the mammalian ortholog of Sir2, has been associated with increased survival of various species mimicking the effects of calorie restriction, a form of negative energy balance. Here we show that a central regulatory component in energy metabolism, the hypothalamic melanocortin system, is affected by sirtuins whereby they promote the activity and connectivity of this neuronal circuitry that is characteristic of negative energy balance. Suppression of SirT1 activity centrally decreases the inhibitory tone on the anorexigenic POMC neurons triggered either by negative energy balance or by the gut hormone, ghrelin, leading to decreased food intake. This action of sirtuins requires an appropriate shift in mitochondrial redox state in the hypothalamus, because in the absence of such adaptation enabled by the mitochondrial protein, UCP2, sirtuin-induced cellular and behavioral responses are impaired. Because the hypothalamic melanocortin system is a key regulator of peripheral tissue function, the present data argues for a major role of a central mode of action of sirtuins on whole body physiology. These results provide a novel mechanism via which SirT1 activity contributes to negative energy balance that is characteristic of calorie restriction, the mechanism SirT1 is thought to mimic in prolonging healthy life.

**Supported by** grants from CNPq and NIH.
**Key words** food intake, calorie restriction, aging, obesity.