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Novel anti-obesity effects of alpha-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase

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Body weight is maintained at a relatively constant level over days and months despite variability in food intake and physical activity. To achieve energy homeostasis, the hypothalamus receives information related to energy surplus or shortage from the periphery and controls food intake and energy expenditure. Leptin, an adipocyte derived hormone, is a principal mediator that signals the brain about the stored energy status. Increased leptin signaling in the brain prevents excess energy stores by suppressing food intake and increasing energy expenditure. In addition, insulin and nutrients themselves, such as glucose and free fatty acids, also regulate food intake.

AMP-activated protein kinase (AMPK) is a heterotrimeric serine/threonine protein kinase and a major cellular regulator of lipid and glucose metabolism. AMPK is activated when cellular energy is depleted. Activation of AMPK in skeletal muscle increases glucose uptake. In addition, AMPK activation increases fatty acid oxidation by inhibiting acetyl CoA caroboxylase (ACC) activity and decreasing malonyl CoA levels. AMPK is expressed in the central nervous system (CNS), but little is known about its role in the CNS.

Alpha-lipoic acid (α-LA) is a naturally occurring short chain fatty acid containing two sulfur molecules and is an essential cofactor of mitochondrial respiratory enzymes.

α-LA has a powerful antioxidant capacity and is used clinically for treatment of diabetic neuropathy. α-LA is a unique antioxidant because it has beneficial effects on fuel metabolism; it enhances glucose transport into the skeletal muscle of lean and insulin-resistant obese animals.

We found that α-lipoic acid, a cofactor of mitochondrial enzymes, decreased hypothalamic AMPK activity and caused a profound weight loss in rodents by reducing food intake and enhancing energy expenditure. Activation of hypothalamic AMPK reversed the effects of α-lipoic acid on food intake and energy expenditure. Intracerebroventricular administration of glucose decreased hypothalamic AMPK activity whereas inhibition of intracellular glucose utilization by 2-deoxyglucose administration increased hypothalamic AMPK activity and food intake. When an AMPK inhibitor was co-administered, the 2-deoxyglucose-induced hyperphagia was reversed.

Our findings indicate that hypothalamic AMPK plays an important role in the central regulation of food intake and energy expenditure and that α-lipoic acid exerts novel anti-obesity effects by suppressing hypothalamic AMPK activity.