**Title:**

Rapamycin Ameliorates Age-Dependent Obesity Associated with Increased mTOR Signaling in Hypothalamic POMC Neurons

**Abstract:**

The prevalence of obesity in older people is the leading cause of metabolic syndromes. Central neurons serving as homeostatic sensors for bodyweight control include hypothalamic neurons that express pro-opiomelanocortin (POMC) or neuropeptide-Y (NPY) and agouti-related protein (AgRP). Here, we report an age-dependent increase of mammalian target of rapamycin (mTOR) signaling in POMC neurons that elevates the ATP-sensitive potassium (KATP) channel activity cell-autonomously to silence POMC neurons. Systemic or intracerebral administration of the mTOR inhibitor rapamycin causes weight loss in old mice. Intracerebral rapamycin infusion into old mice enhances the excitability and neurite projection of POMC neurons, thereby causing a reduction of food intake and body weight. Conversely, young mice lacking the mTOR-negative regulator TSC1 in POMC neurons, but not those lacking TSC1 in NPY/AgRP neurons, were obese. Our study reveals that an increase in mTOR signaling in hypothalamic POMC neurons contributes to age-dependent obesity.