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Disruption of intraflagellar transport in leptin receptor-Expressing neurons leads to obesity via transcription 3 signaling

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Abstract

The primary cilium is a cellular organelle that serves as a signaling hub for most vertebrate cells including neurons. The assembly of the primary cilium depends on intraflagellar transport (IFT), and the mutations disrupting the IFT process result in loss of cilia. Disruption of the primary cilium results in obesity in both humans and mice, but the molecular mechanism underlying this phenotype remains to be elucidated. It is well known that leptin, a fat-derived hormone, exerts pleiotropic effects on energy balance and neuroendocrine functions. Mice defective in leptin or its receptor [leptin receptor, isoform b (LepRb)] exhibit severe obesity, infertility, and reduced linear growth. LepRb activates the transcription factor Stat3 and this signaling is required for leptin regulation of energy balance but not reproduction and linear growth.To investigate the contribution of the primary cilium to leptin regulation in *vivo,* we generated mice in which IFT was disrupted specifically in LepRb neurons after the onset of leptin receptor expressions, which resulted in loss of primary cilia in LepRb neurons. We showed that the mutant mice were hyperphagic and severely obese, but with increased linear growth and normal fertility. The mutant mice also developed impaired glucose tolerance and leptin resistance at an early age. Furthermore, the leptin induced Stat3 response was impaired in mutant mice independently of obesity. Our results suggest that the primary cilium is required for LepRb-Stat3 signaling to regulate energy balance, but not to regulate fertility and linear growth.

Biography

Yi Wang has completed her PhD from the University of Sydney, Australia, and is doing her postdoctoral training in Dr Vaisse's lab the University of California, San Francisco. Dr Vaisse's laboratory has described the first gene mutations causing human obesity. This laboratory has also studied the molecular determinant of this leptin-melanocortin pathway and was the first to determine the essential role of signal transducer and activator of transcription 3 (Stat3) signaling through the leptin receptor for the maintenance of long-term energy homeostasis.