A NOVEL, EVOLUTIONARILY CONSERVED NEUROENDOCRINE CILIARY SIGNAL REGULATING OBESITY

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Background: Pediatric obesity in a worldwide epidemic with long-lasting impacts on physical and psychological health. Obesity development is multifactorial, and most monogenic cases of obesity have been linked to mutations in genes that function in the hypothalamus. Recent work has shown that these proteins localize to the primary cilium – an organelle that serves as a central hub for integrating signaling pathways. Disruption of cilia result in disorders called ciliopathies, and often manifest with obesity. How disrupted ciliary function leads to obesity remains poorly understood. One such monogenic syndrome results from mutations in the gene Tubby. Tubby is most highly expressed in hypothalamic neurons, and human mutations in Tubby are associated with pediatric obesity. How Tubby regulates adiposity is currently unknown. Studies in mice, the nematode C. elegans, and the fruit fly Drosophila have shown that Tubby inactivation causes increased peripheral lipid stores. Furthermore, Tubby regulates trafficking of G protein-coupled receptors (GPCRs) to neuronal cilia, leading us to examine if defective neurociliary receptor trafficking may be causative in Tubby obesity.

Materials/Methods: C. elegans and Drosophila strains were obtained from respective stock centers and raised on standard media. Tubby mice were obtained from the Jackson Lab, raised on standard chow. Labeled animals were visualized by confocal microscopy and transmission electron microscopy (TEM).

Results: Employing a combinatorial approach using C. elegans, Drosophila and mice, we observed that Tubby was expressed in the hypothalamus but not in the adipose tissue and liver, and localizes at the base of primary cilia. Selective neuronal inactivation of Tubby was sufficient to induce lipid accumulation in adipose tissue and liver cell non-autonomously. Tubby loss of function resulted in increased lysosomal biogenesis and decreased turnover in adipose tissue and liver, as well as large lysosomal vesicles with undigested substrates, suggestive of a block in autophagy. Tubby mutants failed to correctly localize the GPCR serotonin receptor Ser-5 to sensory cilia, and neuropeptide expression was globally downregulated in Tubby mutants, consistent with a neuroendocrine axis of lysosomal and lipid metabolic regulation.

Conclusions: Together, these results reveal an ancient, evolutionarily conserved neuroendocrine signaling axis that communicates from the brain to metabolically active tissues to coordinate lipid storage through lysosomal regulation.

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