Abstract

The epidemic dimensions obesity and secondary diseases like T2D have assumed, pose a strain on the modern society, human health and healthcare system. An increasingly sedentary lifestyle and easy access to highly calory dense food, play a crucial role in this alarming development. With projections estimating over 50% of the population to be overweight or obese by 2035, understanding the molecular basis of obesity and metabolic dysfunction, is now more important than ever. The arcuate nucleus of the hypothalamus plays a key role in integrating energetic information about the organism and formulating responses such as modulating energy expenditure or peripheral metabolism (e.g. hepatic glucose production) to the nutritional state. Recently it has been shown that AgRP neurons in the ARH can induce autophagy in the liver.

The here presented data show that acute 4h fasting and 4h optogenetic stimulation of AgRP neurons induce hepatic ER-phagy mediated by FAM134B, while chemogenetic inhibition of AgRP neurons blunts this process. Acute fasting or i.p. Dexamethasone fails to induce autophagy and FAM134B mediated ER-phagy in the absence of hepatic GR. While optogenetic stimulation of AgRP neurons fails to induce autophagy in the absence of GR, FAM134 dependent ER-phagy-flux upon AgRP neuron stimulation has yet to be determined. Hepatic PPARGC1α knockout bluntes autophagy, but not ER-phagy in the liver upon fasting, but not Dexamethasone treatment or optogenetic AgRP neuron stimulation. Hepatic knockout of PPARα or FOXO1 do not affect autophagy flux in 4h fasted mice. Hepatic FAM134B knockdown results in ER dilation and increases in protein accumulation upon 4h fasting compared to control animals. Additionally, loss of hepatic FAM134B increases mitochondria/ER contact sites. In hepatic FAM134B knockdown animals, ER-stress markers remain unchanged. However, expression of mitochondrial stress markers was reduced upon 4h fasting compared to fasted control animals, despite the fact that mitochondrial morphology, determined by TEM imaging, was unaffected by loss of hepatic FAM134B. A ProteoFlux measurement revealed several potential target proteins of FAM134B mediated degradation possibly involved in lipid metabolism and ER-vesicular budding, which are currently under further investigation.

Conclusively, this study confirms that hepatic bulk-autophagy induced by acute AgRP neuron activity depends on hepatic GR. While acute fasting induced hepatic autophagy is mediated by PPARGC1α, AgRP dependent hepatic autophagy is not. Selective hepatic ER-phagy mediated by FAM134B is dependent on hepatic GR, however, the dependency in AgRP neuron activity remains unclear. Lastly, loss of FAM134B in the liver induces ER-dilation, increased mitochiondria/ER contact sites and transcriptional changes potentially suggesting changes in mitochondrial stress resistance. Investigation of downstream targets will reveal the implications of hepatic FAM134B mediated ER-phagy and on cellular and systemic homeostasis.