and weight regain will be important in evaluating the therapeutic potential of this pathway for weight loss.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Remote control of autophagy and metabolism in the liver

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Systemic control of homeostatic processes is of fundamental importance for survival and adaptation in metazoans. In this issue of *Cell Metabolism*, Chen and colleagues identify and methodically dissect a signaling cascade that is mobilized by the agouti-related peptide (AgRP)-expressing neurons in the hypothalamus, to ultimately modulate autophagy and metabolism in the liver upon starvation.

Autophagy in the liver serves diverse and vital functions, including energy production, detoxification, proteostasis, and regulation of basic hepatic functions, including gluconeogenesis, glycogenolysis, and β-oxidation of fatty acids. Thus, it comes as no surprise that perturbation of liver autophagy has been implicated in the pathogenesis of life-threatening diseases, such as hepatocellular carcinoma, non-alcoholic fatty liver disease (NAFLD), and cirrhosis.[1]

The regulation of autophagy in the liver is complex and involves several signaling mechanisms and feedback loops. Both intrinsic and extrinsic pathways converge to tightly regulate and fine-tune liver autophagy, in response to environmental cues and internal organismal physiological states.[2–4] Specific centers in the brain function as receivers and integrators of nutrient and energy availability signals, emanating from the periphery, and in turn, coordinate homeostatic and metabolic processes in key organs, such as the liver, to counter nutrient deprivation. Several studies have identified the agouti-related peptide (AgRP)-expressing and the pro-opiomelanocortin (POMC)-expressing neurons in the arcuate nucleus of the hypothalamus (ARH) as key mediators of long-range, systemic regulation of organismal physiology, under conditions of food scarcity.[5] However, whether and how these neurons might control autophagy in the liver was unclear. With their recent analysis, Chen and colleagues now reveal a chain of events that links the starvation-induced activation of AgRP neurons in the central nervous system (CNS) to the upregulation of autophagy and the

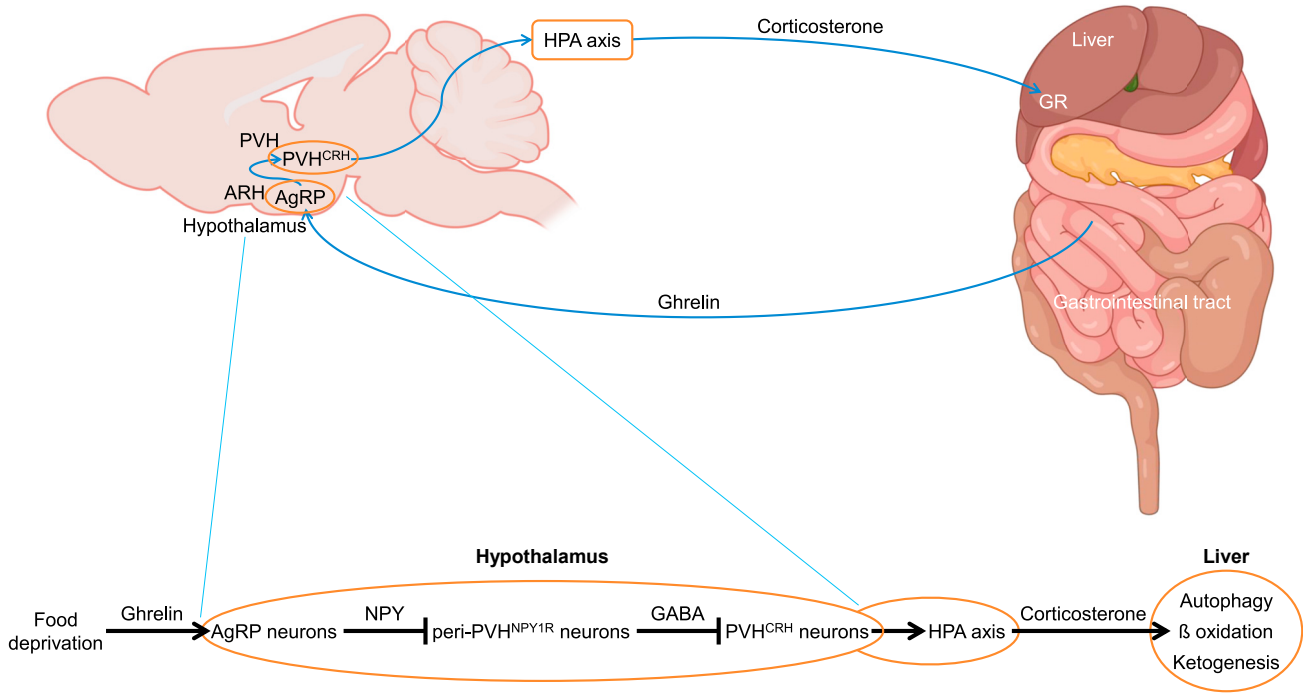

Figure 1. Non-cell-autonomous regulation of autophagy and metabolism in the mouse liver by AgRP neurons in the hypothalamus

Agouti-related peptide (AgRP)-expressing neurons, located in the arcuate nucleus of the hypothalamus (ARH), are exposed to signals in the circulation that convey information about the state of nutrient availability. One such signaling molecule is ghrelin, a hormone produced by enteroendocrine cells of the gastrointestinal tract upon food deprivation. Activation of AgRP neurons by starvation causes the sequential disinhibition of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVH). CRH neurons are controlled by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), released by peri-PVH neurons projecting into the PVH. These neurons express the neuropeptide Y receptor 1 (NPY1R) and become inhibited by NPY, released by activated AgRP neurons, which project in the peri-PVH area of the hypothalamus. Thus, starvation, sensed by AgRP neurons, results in the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the consequent increase in the concentration of circulating corticosterone. In turn, corticosterone signaling through the glucocorticoid receptor (GR) modulates autophagy and metabolism in the liver. Schematics of the mouse brain and gastrointestinal tract have been generated in BioRender (https://www.biorender.com).

reprogramming of metabolism in the liver of mice.[6]

In addition to the physiological stimulus of fasting, the authors utilized an arsenal of optogenetic and chemogenetic tools, coupled with sophisticated genetic manipulations, to robustly activate AgRP neurons and interrogate neuronal circuitry in the hypothalamus. They observed pronounced induction of autophagy, as well as a shift of liver metabolism toward β-oxidation of fatty acids and ketogenesis.

Nutrient depletion signals are conveyed from the gastrointestinal tract to the CNS by ghrelin, an orexigenic peptide hormone, which activates AgRP neurons that express specific ghrelin receptors (GhSRs).[7] Intracerebroventricular, but not intraperitoneal, injection of ghrelin was sufficient to induce autophagy in the liver, indicating that ghrelin acts in the CNS to modify hepatic metabolic processes (Figure 1). Notably, the capacity of both ghrelin and food deprivation to modulate liver autophagy and metabolism diminishes with age, thus weakening energy homeostasis in old animals.

How do AgRP neurons exert their regulatory influence on autophagy in the liver, remotely? Chen and colleagues examined the involvement of neuropeptide Y (NPY), one of the neurotransmitters released by hypothalamic AgRP neurons, in relaying starvation signals downstream, toward the liver. Indeed, the authors found that NPY is necessary for autophagy induction and metabolic adaptations in the liver upon nutrient depletion. The next link in the signaling chain, on the way from the CNS to the liver, are neurons targeted by AgRP neuron projections, in and around the paraventricular nucleus of the hypothalamus (PVH). Importantly, the authors find that GABAergic, peri-PVH neurons, which express the neuropeptide Y receptor 1 (NPY1R), likely become inhibited by NPY, released from AgRP neurons. As a consequence of peri-PVH^{NPY1R} neuron inhibition, corticotropin-releasing hormone (CRH) neurons in the PVH, which are innervated by peri-PVH^{NPY1R} neurons, become disinhibited, triggering the hypothalamic-pituitary-adrenal (HPA) axis and causing a rise in the levels of circulating corticosterone. In essence, inhibition of the inhibitory GABAergic peri-PVH neurons, by NPY released from AgRP neurons, de-represses GABA receptor-expressing PVH^{CRH} neurons to eventually engage the HPA axis and the production of corticosterone. In turn, circulating corticosterone signals through its cognate glucocorticoid receptor (GR) in liver cells to increase hepatic autophagy and adjust liver metabolism in response to starvation (Figure 1).

It is worth noting that, in contrast to the forebrain, where autophagy is paradoxically suppressed upon nutrient deprivation, the hypothalamus responds in a classical manner to starvation by upregulating autophagy.[8] This distinctive autophagic

response in the hypothalamus, as opposed to other areas of the brain, subserves the synthesis of the orexigenic AgRP in the AgRP neurons, contributing to neuropeptide-mediated acute induction of autophagy in the liver. However, the incoming signals and mechanisms that control autophagy in the hypothalamus are not entirely clear. Increased expression of the brain-derived neurotrophic factor (BDNF) upon starvation has been shown to repress autophagy in the forebrain.[9] By contrast, BDNF is depleted in the hypothalamus under fasting conditions.[10] Thus, attenuated BDNF signaling, due to lack of food, may contribute to increased autophagic activity in the hypothalamus.

In summary, the study of Chen and colleagues elegantly delineates a signaling cascade that connects the activation of specific neurons in the hypothalamus with the induction of autophagy in the liver. The authors have also investigated gene expression and metabolic modifications in the liver following activation of AgRP neurons. This analysis revealed that the liver executes a multifaceted choreography of adaptations involving lipid mobilization and ketogenesis, in addition to autophagy induction.[6] Therefore, perception of nutrient depletion by specialized neuronal circuits of the hypothalamus and liver metabolism is causally linked via a homeostatic pathway that orchestrates physiological acclimatization to dietary restriction. Importantly, the non-cell-autonomous regulation of liver autophagy by AgRP neurons is highly dynamic, with short-term fasting being sufficient for the consequent activation of these neurons and elevation of hepatic autophagy. Such agility toward the coordinated rewiring of metabolism in the liver may afford animals a pro-survival advantage in their natural habitat, where food availability is rather haphazard.

The findings of Chen and colleagues offer a solid foundation upon which to expand with further research on the important ramifications of systemic regulation of autophagy and metabolism by the hypothalamus. As the authors themselves note, it is not clear what type of cargo is predominately degraded in the liver upon corticosterone-mediated induction of autophagy. A prospective preference for a specific substrate (for example, mitochondria, peroxisomes, lipids, proteins, etc.) would provide significant insights pertinent to the physiological scope of long-range, non-cell-autonomous regulation of autophagy by the CNS. It would also prompt additional interesting inquiry about the specific molecular mechanisms underlying the implementation of any such preference. Finally, given the abundant evidence implicating enhanced autophagy in longevity,[11] a question that now becomes relevant is what part of the lifespan-extending effect associated with regimes and interventions, such as caloric or dietary restriction and low insulin signaling, is contributed by systemically imposed versus cell-autonomous upregulation of autophagy. In this regard, a potential differential requirement would critically inform therapeutic strategies, aiming to battle obesity, type 2 diabetes, and age-associated pathologies.

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DECLARATION OF INTERESTS

The author declares no competing interests.

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