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Unbiased identification of sucrose-responsive neuronal circuits in control of glucose metabolism

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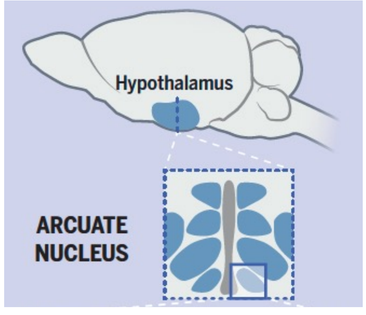
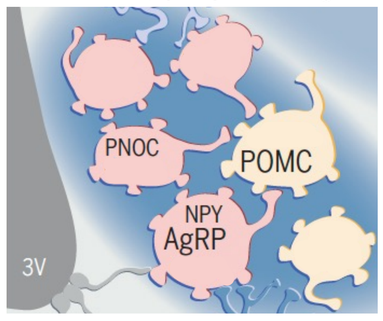
Background



The central nervous system (CNS) plays a crucial role in regulating glucose metabolism and energy homeostasis; therefore, alterations within the CNS can be correlated with metabolic dysfunction and potentially lead to diseases like obesity or diabetes.

An area essential for homeostatic regulation is the mediobasal hypothalamus and especially its ventral part, the **arcuate nucleus (ARC)**. Within the ARC, there are genetically, anatomically, and functionally diverse populations of neurons that adapt the physiological processes of the organism to its energy state.

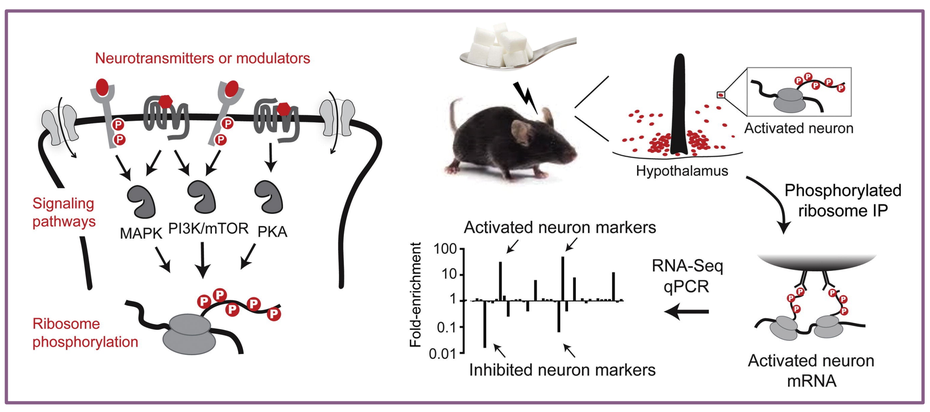


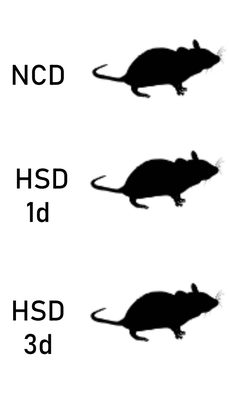
In the ARC, peripheral signals are integrated via orexigenic and anorexigenic like the agouti-related peptide/neuropeptide-Y (AgRP/NPY) or the pro-opiomelanocortin (POMC) expressing neuronal subpopulations, respectively.

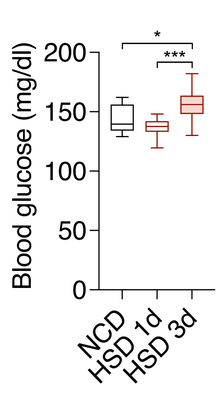
As recently demonstrated, neurons specifically activated upon a high-fat diet are prepronociceptin (PNOC) expressing neurons in the ARC.

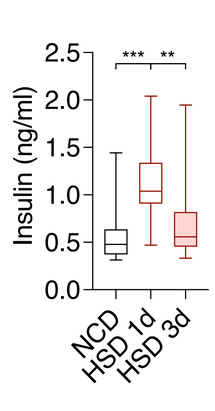
We investigated if there are neurons in the ARC exclusively activated by consumption of hypercaloric sweet diet.

Identification strategy



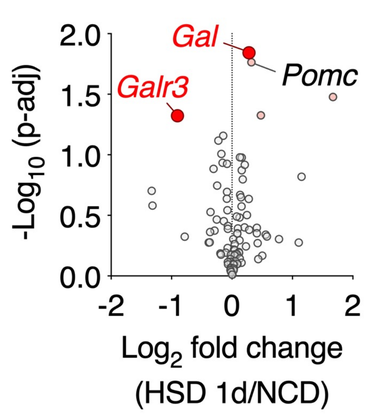


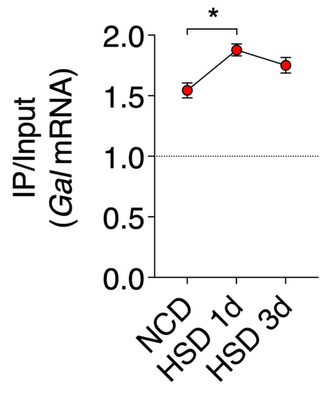


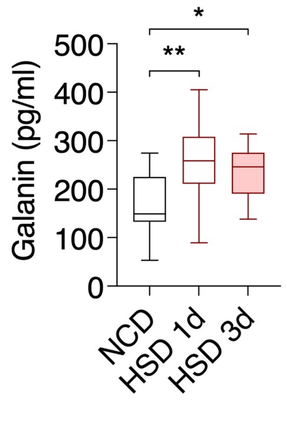


Phosphorylated ribosome profiling of the mediobasal hypothalamus of animals with access to high-sucrose diet (HSD; see box) and analysis of dietary effect on metabolic markers. Experimental groups had *ad libitum* access to either normal chow diet (NCD), 1 day or 3 days access to HSD. HSD increased serum glucose and insulin levels, dependent on duration of access. n=15, *p<0.05, **p<0.01 and ***p<0.001

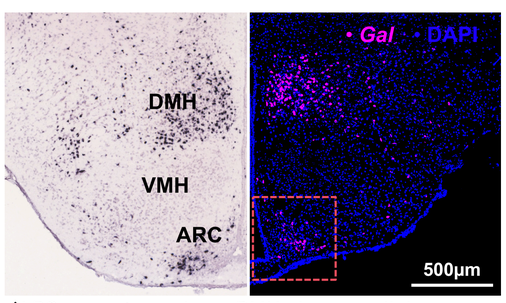
High-sucrose diet feeding activates galanin neurons in the ARC



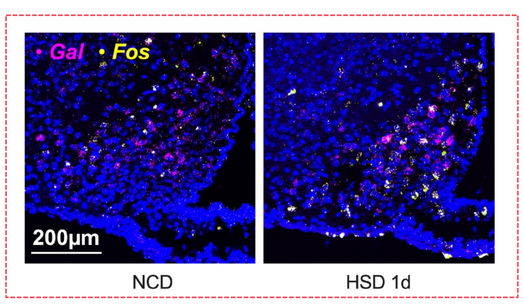


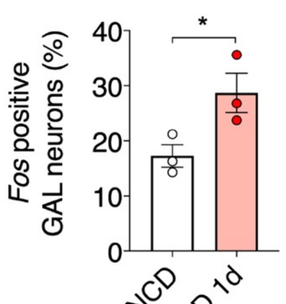


Enrichment of galanin (Gal) in hypothalamic neurons and serum during HSD feeding. Within the mediobasal hypothalamus, the 1-day access to HSD led to a significant upregulation of neuropeptide genes, like *Gal* and *Pomc*, and a downregulation of *Gal3r*. While *Gal* mRNA expression was significantly increased after only 1-day access to HSD, heightened levels of circulating serum GAL were detected in mice with both 1-day and 3-day access to HSD, when compared to data from animals with NCD access. n=12/13; *p<0.05 and **p<0.01



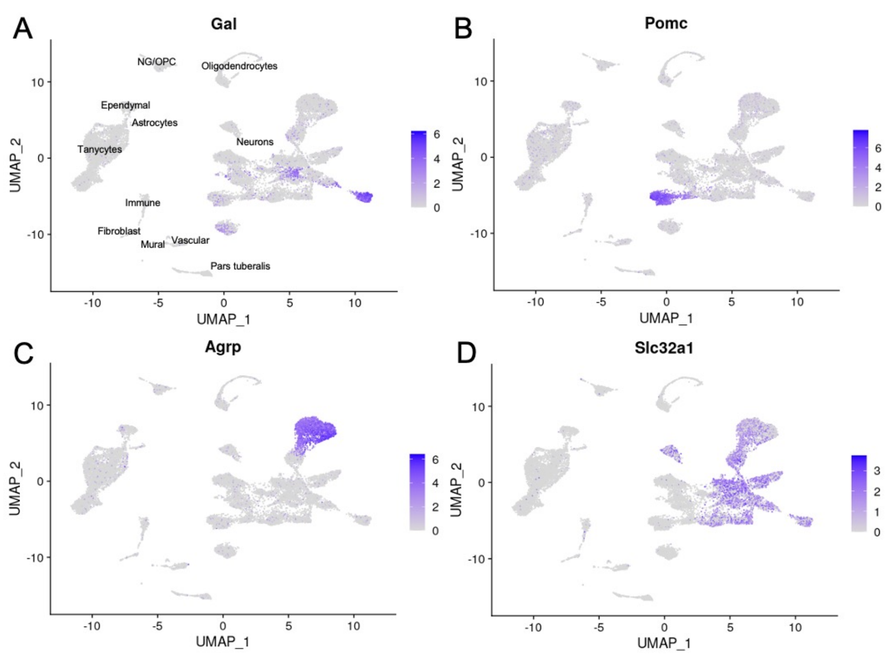
(ARC, arcuate nucleus; DMH, dorsomedial hypothalamus; VMH, ventromedial hypothalamus)





HSD feeding activates *Gal*-expressing neurons within the ARC. *In situ* hybridization for *Gal* mRNA in the mouse hypothalamus. ARC staining for *Gal* and the activity marker *Fos* showed increased co-localization after 1d access to HSD, hence an activation of GAL neurons after HSD consumption. n=3, *p<0.05.

GAL^{ARC} neurons are distinct from the classical feeding-regulatory neurons



***Gal*-expressing neurons in the ARC are GABAergic but distinct from the neuronal Pomc and AgRP subpopulations.** Single-cell sequencing data of the ARC – median eminence complex showed neuronal expression of GAL (A), Pomc (B), AgRP (C) and GABA (D).

Summary and outlook

Our experiments reveal that acute HSD feeding activates galanin-expressing neurons in the arcuate nucleus of the hypothalamus (GAL^{ARC} neurons).

Importantly, the role of GAL^{ARC} neurons in the regulation of feeding and energy homeostasis is still unknown and remains to be addressed.

Therefore, we will characterize short- and long-term consequences of GAL^{ARC} neuronal activity and define the role of GAL^{ARC} neurons in the regulation of peripheral metabolism and metabolic sensing.

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Declaration of interests:
The authors declare no competing interests.

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