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Supplementary information

Advances in appetite regulation by the arcuate nucleus

In the format provided by the authors and unedited

Supplemental Table. Five key publications in 2024 on arcuate nucleus-mediated appetite regulation.

Publication	*Identification*	*Physiological or Pathological Mechanism*	*Therapeutic Approach*	*Metabolic Benefits*
Henschke S, et al. *Science*. 2024 Apr 26;384(6694):438-446. (reference 2)	Sensory food perception, refeeding and POMC neuron activation promotes phosphorilation of MFFS131 in the liver.	Sensory food perception initiates an anticipatory mechanism for incoming nutrients, triggering activation of POMC neurons, which control HGP through AKT-dependent phosphorylation of MFFS131.	Targeting liver-specific AKT-dependent MFFS131 phosphorylation to reinstate effective HPG supression in T2DM.	Liver MFFS131 phosphorylation enables rapid metabolic adaptation of liver mitochondria, including (insulin action) enhanced suppression of HGP.
Benevento M, et al. *Nature.* Apr;628(8009):826-834 (2024). (reference 3)	A neurocircuitry linking heat exposure to feeding via α-tanycytes.	Upon thermal challenge, PBN glutamatergic neurons directly activate α-tanycytes, which release VEGFA, leading to food restriction via anorexigenic inputs onto dopamine and AgRP neurons in the arcuate nucleus.	Targeting activity of tanycytes (and/or VEGFA content in the arcuate nucleus) as a non neuronal weight loss (obesity) or weight gain (anorexia) strategy?	Limiting food intake for hours as a thermodefensive mechanism that restores metabolic balance during heat stress (for example, during fever or disease).
Tan, H.L, et al. *Nature* https://doi.org/10.1038/s41586-024-08108-2 (2024). (reference 6)	A new leptin-targeted population of BNC2-expressing neurons in the arcuate nucleus with anorexigenic properties.	The initiation of feeding activates BNC2 neurons via the LepR-STAT3 phosphorylation pathway, which triggers direct (monosynaptic) inhibition of AgRP neurons and leading to acute suppression of food intake.	Activation of BNC2 neurons acts as a counterregulatory (inhibitory) direct target of AgRP circuitry, which might potentially mitigate overeating-driven obesity.	LepR in BNC2 neurons is required for the full effects of leptin (i.e., satiety and systemic glucose control, independently).
Zhang, et al. *Nature* https://doi.org/10.1038/s41586-024-08164-8 (2024). (reference 8)	Stochastic cAMP signalling in PVH^{MC4R} neurons to regulate satiety.	The PVH decodes hunger (NPY) and satiety (αMSH) signals from arcuate nucleus neurons, with MC4R neurons integrating these signals by modulating their intracellular cAMP levels, leading to the calibration of satiation.	Combining MC4R agonists with NPY antagonists or PDE inhibitors (targeting cAMP levels) might enhance weight loss effectiveness.	The gradual accumulation of neuropeptide signals integrates real-time caloric intake estimates, modulating PVH^{MC4R} neuron activity to control the rate of satiation throughout a meal.
Beddows CA, et al. *Nature.* 2024;633:914–922 (2024). (reference 9)	Pathological PNN deposition in the arcuate nucleus – disease target.	(1) Augmented aggrecan deposition in the arcuate nucleus around AgRP neurons (neurofibrosis), impairing insulin signaling in the brain of DIO mice. (2) Inflammation is a key contributor of neurofibrosis development.	(1) Enzymatic PNN digestion (via chABC or Fluorosamine – a small-molecule inhibitor) reinstates insulin entry in the arcuate nucleus and induces disease remission in DIO and T2DM mice. (2) Delivering anti-infammatory agents (TNFR1α and soluble TGFβR) reduces neurofibrosis.	Abrogation of neurofibrosis leads to the restoration of AgRP neuron function, directly benefiting glucose metabolism and attenuating insulin resistance, even in leptin-deficient mice.

AgRP: Agouti-related protein; AKT: Protein kinase B; BNC2: Basonuclin 2; cAMP: Cyclic adenosine 3′,5′-monophosphate; chABC: Chondroitinase ABC DIO: Diet-induced obesity; HGP: Hepatic glucose production; LepR: Leptin receptor; MC4R: Melanocortin 4 receptor; MFFS131; Phosphorylation of serine 131 of the mitochondrial fission factor; αMSH: α-melanocyte-stimulating hormone; NPY: Neuropeptide Y; PBN: Parabrachial nucleus; PDE: cyclic nucleotide phosphodiesterase; PNN:

perineuronal net; POMC: Proopiomelanocortin; PVH: Paraventricular nucleus of hypothalamus; STAT3: signal transducer and activator of transcription 3; T2DM: Type 2 diabetes mellitus; VEGFA: Vascular wndothelial growth factor A.

References:

Henschke, S. *et al.* Food perception promotes phosphorylation of MFFS131 and mitochondrial fragmentation in liver. *Science* **384**, 438–446 (2024).

Benevento, M. *et al.* A brainstem–hypothalamus neuronal circuit reduces feeding upon heat exposure. *Nature* **628**, 826–834 (2024).

Tan, H. L. *et al.* Leptin-activated hypothalamic BNC2 neurons acutely suppress food intake. *Nature* (2024) doi:10.1038/s41586-024-08108-2.

Zhang, S. X. *et al.* Stochastic neuropeptide signals compete to calibrate the rate of satiation. *Nature* (2024) doi:10.1038/s41586-024-08164-8.

Beddows, C. A. *et al.* Pathogenic hypothalamic extracellular matrix promotes metabolic disease. *Nature* **633**, 914–922 (2024).