7. ottobre

I neurocircuiti che regolano l'assunzione del cibo

Non c'è umiliazione più violenta della fame.
Pranab Mukherjee

Il mantenimento del peso corporeo è regolato attraverso una complessa rete di segnali neuronali, ormoni e *interazioni intestino-cervello* che consentono l'adattamento all'assunzione di cibo e al dispendio energetico. Definire la *natura dei neurocircuiti sottostanti* e il modo in cui viene ottenuta la regolazione del feedback sono importanti per comprendere ***lo sviluppo dell'obesità e le patologie ad essa correlate, come il diabete mellito di tipo 2 e le malattie cardiovascolari***.

Il metabolismo sistemico deve essere costantemente adattato alla variazione dell'assunzione di cibo e anche essere preparato ai cambiamenti previsti nella disponibilità dei nutrienti. Pertanto, il cervello integra *molteplici segnali omeostatici* con numerosi segnali che predicono future deviazioni nell'approvvigionamento energetico. Recentemente è stata rivelata la nostra comprensione dei percorsi neurali alla base di questi principi regolatori, nonché della loro convergenza nell'ipotalamo come coordinatore chiave dell'assunzione di cibo, del dispendio energetico e del metabolismo del glucosio. Questi progressi stanno cambiando la nostra visione del controllo della fisiologia metabolica dipendente dal cervello.

Esiste una popolazione sempre crescente di individui in sovrappeso e obesi che mostrano la predisposizione a una serie di disturbi associati all'obesità, come il diabete mellito di tipo 2, le malattie cardiovascolari, alcuni tipi di cancro e i disturbi neurodegenerativi.

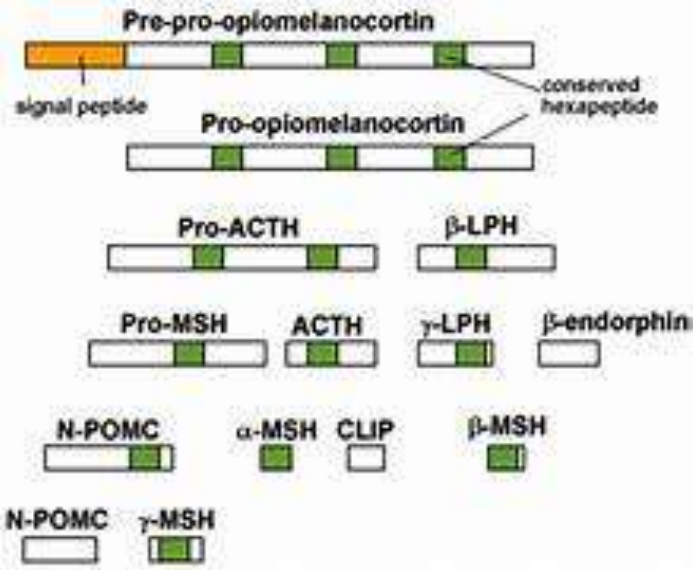
Poiché sia *l'omeostasi energetica* che il metabolismo periferico sono coordinati attraverso il cervello, è urgentemente necessario definire *i meccanismi neurobiologici* di base della regolazione metabolica e definire come le alterazioni in questi percorsi promuovano lo sviluppo dell'obesità e l'insorgenza di disturbi metabolici associati all'obesità per ideare interventi terapeutici per questi disturbi prevalenti. malattie.

Il nucleo arcuato (ARC) dell'ipotalamo integra molteplici input ormonali e neuronali, segnalando la disponibilità di nutrienti dell'organismo. Il nucleo di questo sistema di controllo ipotalamico comprende ***due popolazioni neuronali***, che esercitano funzioni quasi opposte nella regolazione del comportamento alimentare, del dispendio energetico e del metabolismo del carburante.

I neuroni del peptide correlato all'agouti (AgRP) vengono attivati in condizioni di deficit energetico, sono inibiti dai segnali di comunicazione del carburante leptina e insulina e promuovono il foraggiamento e il consumo di cibo.

La proteina correlata all'agouti (AgRP), chiamata anche peptide correlato all'agouti , è un neuropeptide prodotto nel cervello dal neurone AgRP/NPY. È sintetizzato in corpi cellulari contenenti neuropeptide Y (NPY) situati nella parte ventromediale del nucleo arcuato nell'ipotalamo. [5] AgRP è co-espresso con NPY e agisce per aumentare l'appetito e diminuire il metabolismo e il dispendio energetico. È uno degli stimolatori dell'appetito più potenti e duraturi. Negli esseri umani, il peptide correlato all'agouti è codificato dal gene AGRP **.**

I neuroni pro-opiomelanocortina (POMC) si attivano negli stati di bilancio energetico positivo e nei cambiamenti ormonali associati e riducono l'assunzione di cibo e aumentano il dispendio energetico. Un'intensa ricerca negli ultimi 20 anni ha rivelato che le alterazioni in questo circuito sono causalmente collegate allo sviluppo dell'obesità nei modelli murini e negli esseri umani. e il metabolismo del carburante.



La pro-opiomelanocortina (POMC) è un proormone che con opportuni tagli (effettuati tramite proconvertasi) di modificazione e maturazione proteolitica origina vari tipi di ormoni peptidici quali ACTH (corticotropina), β-lipotropina, γ-lipotropina, α-MSH, β-MSH e β-endorfina. Il suo *processamento avviene nella ghiandola pituitaria (ipofisi): più precisamente nel lobo anteriore maturano ACTH e β-lipotropina e nel lobo intermedio vengono sviluppati gli altri ormoni nominati in precedenza.*

I recenti sviluppi di *metodi di sequenziamento dell'RNA a singola cellula* e a singolo nucleo ad alto rendimento hanno consentito la definizione di sottopopolazioni cellulari con una risoluzione molecolare senza precedenti. L'applicazione di queste tecnologie ha recentemente portato all'identificazione di numerose popolazioni di cellule neuronali e non neuronali che regolano l'assunzione di cibo e il metabolismo nell'ipotalamo.

In parallelo, gli approcci ai sistemi molecolari funzionali hanno consentito di delineare non solo il ruolo funzionale di questi tipi cellulari appena identificati nel controllo del metabolismo, ma anche la definizione dell'organizzazione della rete neuronale e la valutazione della loro attività negli animali che si comportano liberamente.

Questi esperimenti hanno rivelato che i neuroni regolatori del metabolismo sono modulati su diverse scale temporali, inclusa la percezione sensoriale dei segnali alimentari, segnali postgestivi che provengono dal tratto gastrointestinale e mediatori ormonali più a lungo termine. L'integrazione di questi segnali serve a mettere a punto l'adattamento metabolico e i comportamenti associati in modo allostatico.

Questi studi hanno ampiamente fatto avanzare la nostra conoscenza dei principi fondamentali del controllo del metabolismo dipendente dal sistema nervoso centrale. Hanno inoltre consentito la definizione di nuove strategie per combattere le malattie metaboliche.

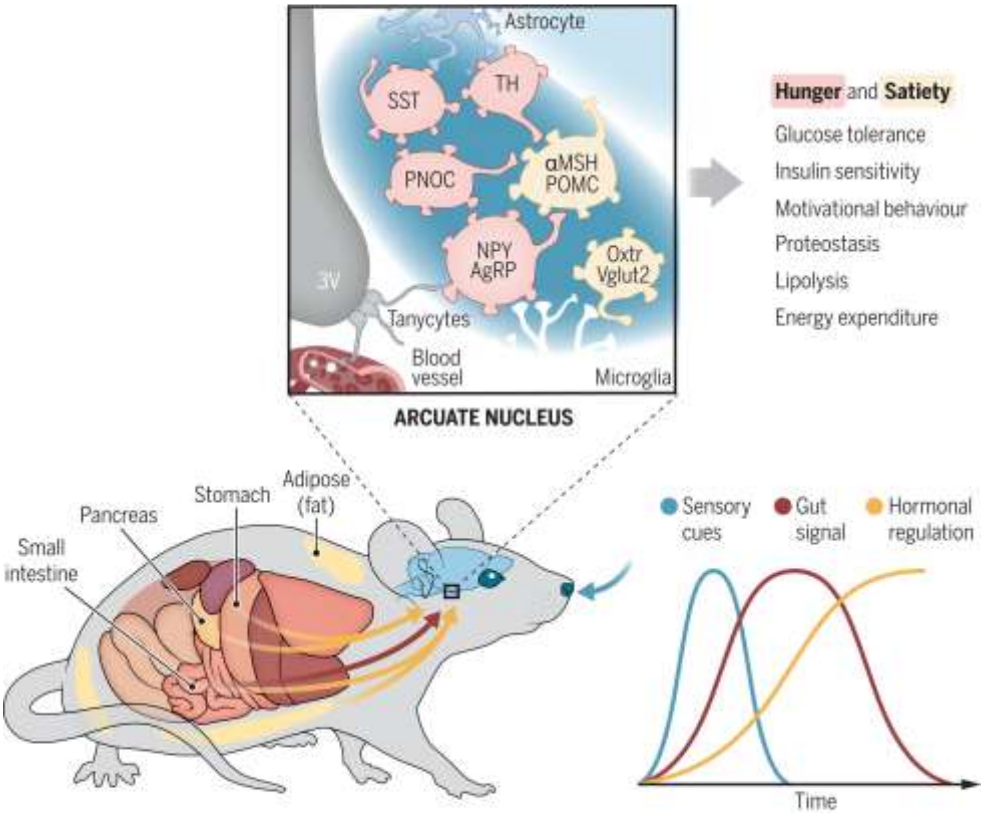
Jeans Brüning e Henning Fenselau *del Department of Neuronal Control of Metabolism, Max Planck Institute for Metabolism Research*

nel report

Brüning JC, Fenselau H.
Integrative neurocircuits that control metabolism and food intake.
Science. 2023 Sep 29;381(6665):eabl7398

Descrivono i percorsi che sono alla base dell'assunzione di cibo, del dispendio energetico e del metabolismo sistemico, in alcuni **modelli murini** e discutono di come questa conoscenza fornisca nuovi bersagli terapeutici per trattare l'obesità nell'uomo

Integrazione ipotalamica dei segnali legati al cibo nel controllo metabolico.



I principali tipi di cellule neuronali che promuovono la fame e la sazietà nell'ipotalamo integrano segnali correlati ai nutrienti in diversi tempi: (i) sulla percezione sensoriale del cibo, (ii) segnali post-ingestivi derivati dall'intestino e (iii) segnali ormonali che comunicano lo stato energetico dell'organismo. Oltre all'alimentazione, questi neurocircuiti adattano anche molteplici comportamenti e altri parametri fisiologici nei tessuti periferici in base allo stato energetico dell'organismo.

Conclusione

L'ulteriore espansione di questi sviluppi consentirà una visione più olistica dei tipi cellulari regolatori del metabolismo e dei neurocircuiti conservati non solo nei modelli di roditori ma anche negli esseri umani.

Queste nuove conoscenze aiuteranno a definire come la loro deregolamentazione sia legata allo sviluppo di disturbi metabolici. Inoltre, tali studi aiuteranno a chiarire la modalità d'azione di nuove e promettenti terapie anti-obesità.

Questi includono gli ***agonisti del recettore del glucagon-like peptide-1 (GLP-1)*** e i ***poliagonisti di nuova concezione*** per diversi recettori dei peptidi derivati dall'intestino, per i quali studi clinici hanno fornito prove di un'efficacia promettente nella riduzione del peso corporeo e nel miglioramento metabolico.

Riferimenti fondamentali e propedeutici

W. B. Cannon, [Homeostasis adaptations]. *An. Med. Ateneo Ramon Cajal Mex.* **3**, 1–9 (1945) [Homeostasis adaptations].

P. Sterling, Allostasis: A model of predictive regulation. *Physiol. Behav.* **106**, 5–15 (2012).

G. C. Kennedy, The role of depot fat in the hypothalamic control of food intake in the rat. *Proc. R. Soc. Lond. Ser. B* **140**, 578–596 (1953).

Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, J. M. Friedman, Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425–432 (1994).

M. Tschöp, D. L. Smiley, M. L. Heiman, Ghrelin induces adiposity in rodents. *Nature* **407**, 908–913 (2000).

J. C. Brüning, D. Gautam, D. J. Burks, J. Gillette, M. Schubert, P. C. Orban, R. Klein, W. Krone, D. Müller-Wieland, C. R. Kahn, Role of brain insulin receptor in control of body weight and reproduction. *Science* **289**, 2122–2125 (2000).

M. Blüher, Obesity: Global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* **15**, 288–298 (2019).

E. K. Speliotes et al., Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **42**, 937–948 (2010).

R. J. F. Loos, G. S. H. Yeo, The genetics of obesity: From discovery to biology. *Nat. Rev. Genet.* **23**, 120–133 (2022).

J. M. Friedman, A war on obesity, not the obese. *Science* **299**, 856–858 (2003).

J. T. Clark, P. S. Kalra, S. P. Kalra, Neuropeptide Y stimulates feeding but inhibits sexual behavior in rats. *Endocrinology* **117**, 2435–2442 (1985).

T. L. Horvath, F. Naftolin, S. P. Kalra, C. Leranth, Neuropeptide-Y innervation of beta-endorphin-containing cells in the rat mediobasal hypothalamus: A light and electron microscopic double immunostaining analysis. *Endocrinology* **131**, 2461–2467 (1992).

A. Jais, J. C. Brüning, Arcuate nucleus-dependent regulation of metabolism-pathways to obesity and diabetes mellitus. *Endocr. Rev.* **43**, 314–328 (2022).

R. Dali, J. Estrada-Meza, F. Langlet, Tanycyte, the neuron whisperer. *Physiol. Behav.* **263**, 114108 (2023).

M. Porniece Kumar, A. L. Cremer, P. Klemm, L. Steuernagel, S. Sundaram, A. Jais, A. C. Hausen, J. Tao, A. Secher, T. Å. Pedersen, M. Schwaninger, F. T. Wunderlich, B. B. Lowell, H. Backes, J. C. Brüning, Insulin signalling in tanycytes gates hypothalamic insulin uptake and regulation of AgRP neuron activity. *Nat. Metab.* **3**, 1662–1679 (2021).

W. Bakker, M. Imbernon, C. G. Salinas, D. H. Moro Chao, R. Hassouna, C. Morel, C. Martin, C. Leger, R. G. P. Denis, J. Castel, A. Peter, M. Heni, W. Maetzler, H. S. Nielsen, M. Duquenne, M. Schwaninger, S. Lundh, W. F. Johan Hogendorf, G. Gangarossa, A. Secher, J. Hecksher-Sørensen, T. Å. Pedersen, V. Prevot, S. Luquet, Acute changes in systemic glycemia gate access and action of GLP-1R agonist on brain structures controlling energy homeostasis. *Cell Rep.* **41**, 111698 (2022).

M. Duquenne, C. Folgueira, C. Bourouh, M. Millet, A. Silva, J. Clasadonte, M. Imbernon, D. Fernandois, I. Martinez-Corral, S. Kusumakshi, E. Caron, S. Rasika, E. Deliglia, N. Jouy, A. Oishi, M. Mazzone, E. Trinquet, J. Tavernier, Y.-B. Kim, S. Ory, R. Jockers, M. Schwaninger, U. Boehm, R. Nogueiras, J.-S. Annicotte, S. Gasman,

J. Dam, V. Prévot, Leptin brain entry via a tanycytic LepR-EGFR shuttle controls lipid metabolism and pancreas function. *Nat. Metab.* **3**, 1071–1090 (2021).

S. Yoo, D. Cha, D. W. Kim, T. V. Hoang, S. Blackshaw, Tanycyte-independent control of hypothalamic leptin signaling. *Front. Neurosci.* **13**, 240 (2019).

C. García-Cáceres, C. Quarta, L. Varela, Y. Gao, T. Gruber, B. Legutko, M. Jastroch, P. Johansson, J. Ninkovic, C. X. Yi, O. Le Thuc, K. Szigeti-Buck, W. Cai, C. W. Meyer, P. T. Pfluger, A. M. Fernandez, S. Luquet, S. C. Woods, I. Torres-Alemán, C. R. Kahn, M. Götz, T. L. Horvath, M. H. Tschöp, Astrocytic insulin signaling couples brain glucose

J. G. Kim, S. Suyama, M. Koch, S. Jin, P. Argente-Arizon, J. Argente, Z.-W. Liu, M. R. Zimmer, J. K. Jeong, K. Szigeti-Buck, Y. Gao, C. Garcia-Caceres, C.-X. Yi, N. Salmaso, F. M. Vaccarino, J. Chowen, S. Diano, M. O. Dietrich, M. H. Tschöp, T. L. Horvath, Leptin signaling in astrocytes regulates hypothalamic neuronal circuits and feeding. *Nat. Neurosci.* **17**, 908–910 (2014).

L. Varela, B. Stutz, J. E. Song, J. G. Kim, Z.-W. Liu, X.-B. Gao, T. L. Horvath, Hunger-promoting AgRP neurons trigger an astrocyte-mediated feed-forward autoactivation loop in mice. *J. Clin. Invest.* **131**, e144239 (2021).

S. Kohnke, S. Buller, D. Nuzzaci, K. Ridley, B. Lam, H. Pivonkova, M. A. Bentsen, K. M. Alonge, C. Zhao, J. Tadross, S. Holmqvist, T. Shimizu, H. Hathaway, H. Li, W. Macklin, M. W. Schwartz, W. D. Richardson, G. S. H. Yeo, R. J. M. Franklin, R. T. Karadottir, D. H. Rowitch, C. Blouet, Nutritional regulation of oligodendrocyte differentiation regulates perineuronal net remodeling in the median eminence. *Cell Rep.* **36**, 109362 (2021).

M. Valdearcos, J. D. Douglass, M. M. Robblee, M. D. Dorfman, D. R. Stifler, M. L. Bennett, I. Gerritse, R. Fasnacht, B. A. Barres, J. P. Thaler, S. K. Koliwad, Microglial inflammatory signaling orchestrates the hypothalamic immune response to dietary excess and mediates obesity susceptibility. *Cell Metab.* **26**, 185–197.e3 (2017).

C. García-Cáceres, E. Balland, V. Prevot, S. Luquet, S. C. Woods, M. Koch, T. L. Horvath, C.-X. Yi, J. A. Chowen, A. Verkhratsky, A. Araque, I. Bechmann, M. H. Tschöp, Role of astrocytes, microglia, and tanycytes in brain control of systemic metabolism. *Nat. Neurosci.* **22**, 7–14 (2019).

J. N. Campbell, E. Z. Macosko, H. Fenselau, T. H. Pers, A. Lyubetskaya, D. Tenen, M. Goldman, A. M. J. Verstegen, J. M. Resch, S. A. McCarroll, E. D. Rosen, B. B. Lowell, L. T. Tsai, A molecular census of arcuate hypothalamus and median eminence cell types. *Nat. Neurosci.* **20**, 484–496 (2017).

R. A. Romanov, A. Zeisel, J. Bakker, F. Girach, A. Hellysaz, R. Tomer, A. Alpár, J. Mulder, F. Clotman, E. Keimpema, B. Hsueh, A. K. Crow, H. Martens, C. Schwindling, D. Calvigioni, J. S. Bains, Z. Máté, G. Szabó, Y. Yanagawa, M.-D. Zhang, A. Rendeiro, M. Farlik, M. Uhlén, P. Wulff, C. Bock, C. Broberger, K. Deisseroth, T. Hökfelt, S. Linnarsson, T. L. Horvath, T. Harkany, Molecular interrogation of hypothalamic organization reveals distinct dopamine neuronal subtypes. *Nat. Neurosci.* **20**, 176–188 (2017).

D. Atasoy, J. N. Betley, H. H. Su, S. M. Sternson, Deconstruction of a neural circuit for hunger. *Nature* **488**, 172–177 (2012).

Q. Tong, C. P. Ye, J. E. Jones, J. K. Elmquist, B. B. Lowell, Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance. *Nat. Neurosci.* **11**, 998–1000 (2008).

M. J. Krashes, B. P. Shah, S. Koda, B. B. Lowell, Rapid versus delayed stimulation of feeding by the endogenously released AgRP neuron mediators GABA, NPY, and AgRP. *Cell Metab.* **18**, 588–595 (2013).

X. Zhang, A. N. van den Pol, Hypothalamic arcuate nucleus tyrosine hydroxylase neurons play orexigenic role in energy homeostasis. *Nat. Neurosci.* **19**, 1341–1347 (2016).

S. Spencer, C. B. Saper, T. Joh, D. J. Reis, M. Goldstein, J. D. Raese, Distribution of catecholamine-containing neurons in the normal human hypothalamus. *Brain Res.* **328**, 73–80 (1985).

B. J. Everitt, T. Hökfelt, J. Y. Wu, M. Goldstein, Coexistence of tyrosine hydroxylase-like and gamma-aminobutyric acid-like immunoreactivities in neurons of the arcuate nucleus. *Neuroendocrinology* **39**, 189–191 (1984).

P. J. Keller, W. Lichtensteiger, Stimulation of tubero-infundibular dopamine neurones and gonadotrophin secretion. *J. Physiol.* **219**, 385–401 (1971).

Z. A. Knight, K. Tan, K. Birsoy, S. Schmidt, J. L. Garrison, R. W. Wysocki, A. Emiliano, M. I. Ekstrand, J. M. Friedman, Molecular profiling of activated neurons by phosphorylated ribosome capture. *Cell* **151**, 1126–1137 (2012).

A. Jais, L. Paeger, T. Sotelo-Hitschfeld, S. Bremser, M. Prinzensteiner, P. Klemm, V. Mykytiuk, P. J. M. Widdershooven, A. J. Vesting, K. Grzelka, M. Minère, A. L. Cremer, J. Xu, T. Korotkova, B. B. Lowell, H. U. Zeilhofer, H. Backes, H. Fenselau, F. T. Wunderlich, P. Kloppenburg, J. C. Brüning, PNOCARC neurons promote hyperphagia and obesity upon high-fat-diet feeding. *Neuron* **106**, 1009–1025.e10 (2020).

S. Pinto, A. G. Roseberry, H. Liu, S. Diano, M. Shanabrough, X. Cai, J. M. Friedman, T. L. Horvath, Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* **304**, 110–115 (2004).

M. A. Cowley, J. L. Smart, M. Rubinstein, M. G. Cerdán, S. Diano, T. L. Horvath, R. D. Cone, M. J. Low, Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* **411**, 480–484 (2001).

A. R. Rau, S. T. Hentges, GABAergic inputs to POMC neurons originating from the dorsomedial hypothalamus are regulated by energy state. *J. Neurosci.* **39**, 6449–6459 (2019).

L. Vong, C. Ye, Z. Yang, B. Choi, S. Chua Jr., B. B. Lowell, Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. *Neuron* **71**, 142–154 (2011).

Y. Qi, N. J. Lee, C. K. Ip, R. Enriquez, R. Tasan, L. Zhang, H. Herzog, Agrp-negative arcuate NPY neurons drive feeding under positive energy balance via altering leptin responsiveness in POMC neurons. *Cell Metab.* **35**, 979–995.e7 (2023).

C. Zhan, J. Zhou, Q. Feng, J. E. Zhang, S. Lin, J. Bao, P. Wu, M. Luo, Acute and long-term suppression of feeding behavior by POMC neurons in the brainstem and hypothalamus, respectively. *J. Neurosci.* **33**, 3624–3632 (2013).

L. Yaswen, N. Diehl, M. B. Brennan, U. Hochgeschwender, Obesity in the mouse model of pro-opiomelanocortin deficiency responds to peripheral melanocortin. *Nat. Med.* **5**, 1066–1070 (1999).

A. W. Xu, C. B. Kaelin, G. J. Morton, K. Ogimoto, K. Stanhope, J. Graham, D. G. Baskin, P. Havel, M. W. Schwartz, G. S. Barsh, Effects of hypothalamic neurodegeneration on energy balance. *PLOS Biol.* **3**, e415 (2005).

H. Krude, H. Biebermann, W. Luck, R. Horn, G. Brabant, A. Grüters, Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat. Genet.* **19**, 155–157 (1998).

Y. Aponte, D. Atasoy, S. M. Sternson, AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nat. Neurosci.* **14**, 351–355 (2011).

M. Koch, L. Varela, J. G. Kim, J. D. Kim, F. Hernández-Nuño, S. E. Simonds, C. M. Castorena, C. R. Vianna, J. K. Elmquist, Y. M. Morozov, P. Rakic, I. Bechmann, M. A. Cowley, K. Szigeti-Buck, M. O. Dietrich, X.-B. Gao, S. Diano, T. L. Horvath, Hypothalamic POMC neurons promote cannabinoid-induced feeding. *Nature* **519**, 45–50 (2015).

N. Biglari, I. Gaziano, J. Schumacher, J. Radermacher, L. Paeger, P. Klemm, W. Chen, S. Corneliussen, C. M. Wunderlich, M. Sue, S. Vollmar, T. Klöckener, T. Sotelo-Hitschfeld, A. Abbasloo, F. Edenhofer, F. Reimann, F. M. Gribble, H. Fenselau, P. Kloppenburg, F. T. Wunderlich, J. C. Brüning, Functionally distinct POMC-expressing neuron subpopulations in hypothalamus revealed by intersectional targeting. *Nat. Neurosci.* **24**, 913–929 (2021).

H. Fenselau, J. N. Campbell, A. M. J. Verstegen, J. C. Madara, J. Xu, B. P. Shah, J. M. Resch, Z. Yang, Y. Mandelblat-Cerf, Y. Livneh, B. B. Lowell, A rapidly acting glutamatergic ARC→PVH satiety circuit postsynaptically regulated by α-MSH. *Nat. Neurosci.* **20**, 42–51 (2017).

L. Engström Ruud, M. M. A. Pereira, A. J. de Solis, H. Fenselau, J. C. Brüning, NPY mediates the rapid feeding and glucose metabolism regulatory functions of AgRP neurons. *Nat. Commun.* **11**, 442 (2020).

Y. Chen, R. A. Essner, S. Kosar, O. H. Miller, Y.-C. Lin, S. Mesgarzadeh, Z. A. Knight, Sustained NPY signaling enables AgRP neurons to drive feeding. *eLife* **8**, e46348 (2019).

N. Balthasar, L. T. Dalgaard, C. E. Lee, J. Yu, H. Funahashi, T. Williams, M. Ferreira, V. Tang, R. A. McGovern, C. D. Kenny, L. M. Christiansen, E. Edelstein, B. Choi, O. Boss, C. Aschkenasi, C. Y. Zhang, K. Mountjoy, T. Kishi, J. K. Elmquist, B. B. Lowell, Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell* **123**, 493–505 (2005).

A. S. Garfield, C. Li, J. C. Madara, B. P. Shah, E. Webber, J. S. Steger, J. N. Campbell, O. Gavrilova, C. E. Lee, D. P. Olson, J. K. Elmquist, B. A. Tannous, M. J. Krashes, B. B. Lowell, A neural basis for melanocortin-4 receptor-regulated appetite. *Nat. Neurosci.* **18**, 863–871 (2015).

T. Branco, A. Tozer, C. J. Magnus, K. Sugino, S. Tanaka, A. K. Lee, J. N. Wood, S. M. Sternson, Near-perfect synaptic integration by nav1.7 in hypothalamic neurons regulates body weight. *Cell* **165**, 1749–1761 (2016).

K. W. Williams, L. O. Margatho, C. E. Lee, M. Choi, S. Lee, M. M. Scott, C. F. Elias, J. K. Elmquist, Segregation of acute leptin and insulin effects in distinct populations of arcuate proopiomelanocortin neurons. *J. Neurosci.* **30**, 2472–2479 (2010).

B. Y. H. Lam, I. Cimino, J. Polex-Wolf, S. Nicole Kohnke, D. Rimmington, V. Iyemere, N. Heeley, C. Cossetti, R. Schulte, L. R. Saraiva, D. W. Logan, C. Blouet, S. O'Rahilly, A. P. Coll, G. S. H. Yeo, Heterogeneity of hypothalamic pro-opiomelanocortin-expressing neurons revealed by single-cell RNA sequencing. *Mol. Metab.* **6**, 383–392 (2017).

L. Steuernagel, B. Y. H. Lam, P. Klemm, G. K. C. Dowsett, C. A. Bauder, J. A. Tadross, T. S. Hitschfeld, A. Del Rio Martin, W. Chen, A. J. de Solis, H. Fenselau, P. Davidsen, I. Cimino, S. N. Kohnke, D. Rimmington, A. P. Coll, A. Beyer, G. S. H. Yeo, J. C. Brüning, HypoMap-a unified single-cell gene expression atlas of the murine hypothalamus. *Nat. Metab.* **4**, 1402–1419 (2022).

A. Secher, J. Jelsing, A. F. Baquero, J. Hecksher-Sørensen, M. A. Cowley, L. S. Dalbøge, G. Hansen, K. L. Grove, C. Pyke, K. Raun, L. Schäffer, M. Tang-Christensen, S. Verma, B. M. Witgen, N. Vrang, L. Bjerre

Knudsen, The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J. Clin. Invest.* **124**, 4473–4488 (2014).

C. Quarta, M. Claret, L. M. Zeltser, K. W. Williams, G. S. H. Yeo, M. H. Tschöp, S. Diano, J. C. Brüning, D. Cota, POMC neuronal heterogeneity in energy balance and beyond: An integrated view. *Nat. Metab.* **3**, 299–308 (2021).

M. Feldman, C. T. Richardson, Role of thought, sight, smell, and taste of food in the cephalic phase of gastric acid secretion in humans. *Gastroenterology* **90**, 428–433 (1986).

J. LeBlanc, M. Cabanac, Cephalic postprandial thermogenesis in human subjects. *Physiol. Behav.* **46**, 479–482 (1989).

M. L. Power, J. Schulkin, Anticipatory physiological regulation in feeding biology: Cephalic phase responses. *Appetite* **50**, 194–206 (2008).

B. K. Anand, R. V. Pillai, Activity of single neurones in the hypothalamic feeding centres: Effect of gastric distension. *J. Physiol.* **192**, 63–77 (1967).

E. Arnauld, J. du Pont, Vasopressin release and firing of supraoptic neurosecretory neurones during drinking in the dehydrated monkey. *Pflugers Arch.* **394**, 195–201 (1982).

S. Maddison, R. I. Horrell, Hypothalamic unit responses to alimentary perfusions in the anesthetised rat. *Brain Res. Bull.* **4**, 259–266 (1979).

L. A. Gunaydin, L. Grosenick, J. C. Finkelstein, I. V. Kauvar, L. E. Fenno, A. Adhikari, S. Lammel, J. J. Mirzabekov, R. D. Airan, K. A. Zalocusky, K. M. Tye, P. Anikeeva, R. C. Malenka, K. Deisseroth, Natural neural projection dynamics underlying social behavior. *Cell* **157**, 1535–1551 (2014).

G. Cui, S. B. Jun, X. Jin, M. D. Pham, S. S. Vogel, D. M. Lovinger, R. M. Costa, Concurrent activation of striatal direct and indirect pathways during action initiation. *Nature* **494**, 238–242 (2013).

J. Y. Cohen, S. Haesler, L. Vong, B. B. Lowell, N. Uchida, Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* **482**, 85–88 (2012).

J. N. Betley, S. Xu, Z. F. H. Cao, R. Gong, C. J. Magnus, Y. Yu, S. M. Sternson, Neurons for hunger and thirst transmit a negative-valence teaching signal. *Nature* **521**, 180–185 (2015).

Y. Chen, Y. C. Lin, T. W. Kuo, Z. A. Knight, Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell* **160**, 829–841 (2015).

Y. Mandelblat-Cerf, R. N. Ramesh, C. R. Burgess, P. Patella, Z. Yang, B. B. Lowell, M. L. Andermann, Arcuate hypothalamic AgRP and putative POMC neurons show opposite changes in spiking across multiple timescales. *eLife* **4**, e07122 (2015).

Y. Chen, Z. A. Knight, Making sense of the sensory regulation of hunger neurons. *BioEssays* **38**, 316–324 (2016).

M. L. Andermann, B. B. Lowell, Toward a wiring diagram understanding of appetite control. *Neuron* **95**, 757–778 (2017).

R. J. Seeley, K. C. Berridge, The hunger games. *Cell* **160**, 805–806 (2015).

S. M. Sternson, A. K. Eiselt, Three pillars for the neural control of appetite. *Annu. Rev. Physiol.* **79**, 401–423 (2017).

Y. Chen, Y. C. Lin, C. A. Zimmerman, R. A. Essner, Z. A. Knight, Hunger neurons drive feeding through a sustained, positive reinforcement signal. *eLife* **5**, e18640 (2016).

A. S. Garfield, B. P. Shah, C. R. Burgess, M. M. Li, C. Li, J. S. Steger, J. C. Madara, J. N. Campbell, D. Kroeger, T. E. Scammell, B. A. Tannous, M. G. Myers Jr., M. L. Andermann, M. J. Krashes, B. B. Lowell, Dynamic GABAergic afferent modulation of AgRP neurons. *Nat. Neurosci.* **19**, 1628–1635 (2016).

J. Berrios, C. Li, J. C. Madara, A. S. Garfield, J. S. Steger, M. J. Krashes, B. B. Lowell, Food cue regulation of AGRP hunger neurons guides learning. *Nature* **595**, 695–700 (2021).

I. E. de Araujo, T. Lin, M. G. Veldhuizen, D. M. Small, Metabolic regulation of brain response to food cues. *Curr. Biol.* **23**, 878–883 (2013).

G. T. Dodd, S. J. Kim, M. Méquinion, C. E. Xirouchaki, J. C. Brüning, Z. B. Andrews, T. Tiganis, Insulin signaling in AgRP neurons regulates meal size to limit glucose excursions and insulin resistance. *Sci. Adv.* **7**, eabf4100 (2021).

S. M. Steculorum, J. Ruud, I. Karakasilioti, H. Backes, L. Engström Ruud, K. Timper, M. E. Hess, E. Tsaousidou, J. Mauer, M. C. Vogt, L. Paeger, S. Bremser, A. C. Klein, D. A. Morgan, P. Frommolt, P. T. Brinkkötter, P. Hammerschmidt, T. Benzing, K. Rahmouni, F. T. Wunderlich, P. Kloppenburg, J. C. Brüning, AgRP neurons control systemic insulin sensitivity via myostatin expression in brown adipose tissue. *Cell* **165**, 125–138 (2016).

C. Brandt, H. Nolte, S. Henschke, L. Engström Ruud, M. Awazawa, D. A. Morgan, P. Gabel, H.-G. Sprenger, M. E. Hess, S. Günther, T. Langer, K. Rahmouni, H. Fenselau, M. Krüger, J. C. Brüning, Food perception primes hepatic ER homeostasis via melanocortin-dependent control of mTOR activation. *Cell* **175**, 1321–1335.e20 (2018).

H. Tsuneki, M. Sugiyama, T. Ito, K. Sato, H. Matsuda, K. Onishi, K. Yubune, Y. Matsuoka, S. Nagai, T. Yamagishi, T. Maeda, K. Honda, A. Okekawa, S. Watanabe, K. Yaku, D. Okuzaki, R. Otsubo, M. Nomoto, K. Inokuchi, T. Nakagawa, T. Wada, T. Yasui, T. Sasaoka, Food odor perception promotes systemic lipid utilization. *Nat. Metab.* **4**, 1514–1531 (2022).

C. López-Otín, M. A. Blasco, L. Partridge, M. Serrano, G. Kroemer, Hallmarks of aging: An expanding universe. *Cell* **186**, 243–278 (2023).

W. Chen, O. Mehlkop, A. Scharn, H. Nolte, P. Klemm, S. Henschke, L. Steuernagel, T. Sotelo-Hitschfeld, E. Kaya, C. M. Wunderlich, T. Langer, N. L. Kononenko, P. Giavalisco, J. C. Brüning, Nutrient-sensing AgRP neurons relay control of liver autophagy during energy deprivation. *Cell Metab.* **35**, 786–806.e13 (2023).

J. M. Pinto, K. E. Wroblewski, D. W. Kern, L. P. Schumm, M. K. McClintock, Olfactory dysfunction predicts 5-year mortality in older adults. *PLOS ONE* **9**, e107541 (2014).

Y. Livneh, R. N. Ramesh, C. R. Burgess, K. M. Levandowski, J. C. Madara, H. Fenselau, G. J. Goldey, V. E. Diaz, N. Jikomes, J. M. Resch, B. B. Lowell, M. L. Andermann, Homeostatic circuits selectively gate food cue responses in insular cortex. *Nature* **546**, 611–616 (2017).

L. R. Beutler, Y. Chen, J. S. Ahn, Y.-C. Lin, R. A. Essner, Z. A. Knight, Dynamics of gut-brain communication underlying hunger. *Neuron* **96**, 461–475.e5 (2017).

N. Goldstein, A. D. McKnight, J. R. E. Carty, M. Arnold, J. N. Betley, A. L. Alhadeff, Hypothalamic detection of macronutrients via multiple gut-brain pathways. *Cell Metab.* **33**, 676–687.e5 (2021).

Z. Su, A. L. Alhadeff, J. N. Betley, Nutritive, Post-ingestive signals are the primary regulators of AgRP neuron activity. *Cell Rep.* **21**, 2724–2736 (2017).

H. R. Berthoud, W. L. Neuhuber, Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci.* **85**, 1–17 (2000).

S. J. Brookes, N. J. Spencer, M. Costa, V. P. Zagorodnyuk, Extrinsic primary afferent signalling in the gut. *Nat. Rev. Gastroenterol. Hepatol.* **10**, 286–296 (2013).

H. R. Berthoud, L. A. Blackshaw, S. J. Brookes, D. Grundy, Neuroanatomy of extrinsic afferents supplying the gastrointestinal tract. *Neurogastroenterol. Motil.* **16** (Suppl 1), 28–33 (2004).

G. J. Dockray, Enteroendocrine cell signalling via the vagus nerve. *Curr. Opin. Pharmacol.* **13**, 954–958 (2013).

F. M. Gribble, F. Reimann, Enteroendocrine Cells: Chemosensors in the Intestinal Epithelium. *Annu. Rev. Physiol.* **78**, 277–299 (2016).

C. M. Mazzone, J. Liang-Guallpa, C. Li, N. S. Wolcott, M. H. Boone, M. Southern, N. P. Kobzar, I. A. Salgado, D. M. Reddy, F. Sun, Y. Zhang, Y. Li, G. Cui, M. J. Krashes, High-fat food biases hypothalamic and mesolimbic expression of consummatory drives. *Nat. Neurosci.* **23**, 1253–1266 (2020).

W. Han, L. A. Tellez, M. H. Perkins, I. O. Perez, T. Qu, J. Ferreira, T. L. Ferreira, D. Quinn, Z.-W. Liu, X.-B. Gao, M. M. Kaelberer, D. V. Bohórquez, S. J. Shammah-Lagnado, G. de Lartigue, I. E. de Araujo, A neural circuit for gut-induced reward. *Cell* **175**, 665–678.e23 (2018).

J. Kupari, M. Häring, E. Agirre, G. Castelo-Branco, P. Ernfors, An atlas of vagal sensory neurons and their molecular specialization. *Cell Rep.* **27**, 2508–2523.e4 (2019).

L. Bai, S. Mesgarzadeh, K. S. Ramesh, E. L. Huey, Y. Liu, L. A. Gray, T. J. Aitken, Y. Chen, L. R. Beutler, J. S. Ahn, L. Madisen, H. Zeng, M. A. Krasnow, Z. A. Knight, Genetic identification of vagal sensory neurons that control feeding. *Cell* **179**, 1129–1143.e23 (2019).

E. K. Williams, R. B. Chang, D. E. Strochlic, B. D. Umans, B. B. Lowell, S. D. Liberles, Sensory neurons that detect stretch and nutrients in the digestive system. *Cell* **166**, 209–221 (2016).

R. B. Chang, D. E. Strochlic, E. K. Williams, B. D. Umans, S. D. Liberles, Vagal sensory neuron subtypes that differentially control breathing. *Cell* **161**, 622–633 (2015).

Q. Zhao, C. D. Yu, R. Wang, Q. J. Xu, R. Dai Pra, L. Zhang, R. B. Chang, A multidimensional coding architecture of the vagal interoceptive system. *Nature* **603**, 878–884 (2022).

D. Borgmann, E. Ciglieri, N. Biglari, C. Brandt, A. L. Cremer, H. Backes, M. Tittgemeyer, F. T. Wunderlich, J. C. Brüning, H. Fenselau, Gut-brain communication by distinct sensory neurons differently controls feeding and glucose metabolism. *Cell Metab.* **33**, 1466–1482.e7 (2021).

W. S. Kim, S. Hong, M. Gamero, V. Jeevakumar, C. M. Smithhart, T. J. Price, R. D. Palmiter, C. Campos, S. I. Park, Organ-specific, multimodal, wireless optoelectronics for high-throughput phenotyping of peripheral neural pathways. *Nat. Commun.* **12**, 157 (2021).

J. M. Kefauver, A. B. Ward, A. Patapoutian, Discoveries in structure and physiology of mechanically activated ion channels. *Nature* **587**, 567–576 (2020).

D. Usoskin, A. Furlan, S. Islam, H. Abdo, P. Lönnerberg, D. Lou, J. Hjerling-Leffler, J. Haeggström, O. Kharchenko, P. V. Kharchenko, S. Linnarsson, P. Ernfors, Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. *Nat. Neurosci.* **18**, 145–153 (2015).

A. Mercado-Perez, A. Beyder, Gut feelings: Mechanosensing in the gastrointestinal tract. *Nat. Rev. Gastroenterol. Hepatol.* **19**, 283–296 (2022).

C. Alcaino, K. R. Knutson, A. J. Treichel, G. Yildiz, P. R. Strege, D. R. Linden, J. H. Li, A. B. Leiter, J. H. Szurszewski, G. Farrugia, A. Beyder, A population of gut epithelial enterochromaffin cells is mechanosensitive and requires Piezo2 to convert force into serotonin release. *Proc. Natl. Acad. Sci. U.S.A.* **115**, E7632–E7641 (2018).

A. J. Treichel, I. Finholm, K. R. Knutson, C. Alcaino, S. T. Whiteman, M. R. Brown, A. Matveyenko, A. Wegner, H. Kacmaz, A. Mercado-Perez, G. B. Gajdos, T. Ordog, M. Grover, J. Szurszewski, D. R. Linden, G. Farrugia, A. Beyder, Specialized mechanosensory epithelial cells in mouse gut intrinsic tactile sensitivity. *Gastroenterology* **162**, 535–547.e13 (2022).

L. Bai, N. Sivakumar, S. Yu, S. Mesgarzadeh, T. Ding, T. Ly, T. V. Corpuz, J. C. R. Grove, B. C. Jarvie, Z. A. Knight, Enteroendocrine cell types that drive food reward and aversion. *eLife* **11**, e74964 (2022).

M. Hayashi, J. A. Kaye, E. R. Douglas, N. R. Joshi, F. M. Gribble, F. Reimann, S. D. Liberles, Enteroendocrine cell lineages that differentially control feeding and gut motility. *eLife* **12**, e78512 (2023).

F. A. Duca, T. M. Z. Waise, W. T. Peppler, T. K. T. Lam, The metabolic impact of small intestinal nutrient sensing. *Nat. Commun.* **12**, 903 (2021).

C. Ran, J. C. Boettcher, J. A. Kaye, C. E. Gallori, S. D. Liberles, A brainstem map for visceral sensations. *Nature* **609**, 320–326 (2022).

H. J. Grill, M. R. Hayes, Hindbrain neurons as an essential hub in the neuroanatomically distributed control of energy balance. *Cell Metab.* **16**, 296–309 (2012).

C. Zhang, J. A. Kaye, Z. Cai, Y. Wang, S. L. Prescott, S. D. Liberles, Area postrema cell types that mediate nausea-associated behaviors. *Neuron* **109**, 461–472.e5 (2021).

C. W. Roman, V. A. Derkach, R. D. Palmiter, Genetically and functionally defined NTS to PBN brain circuits mediating anorexia. *Nat. Commun.* **7**, 11905 (2016).

C. W. Roman, S. R. Sloat, R. D. Palmiter, A tale of two circuits: CCKNTS neuron stimulation controls appetite and induces opposing motivational states by projections to distinct brain regions. *Neuroscience* **358**, 316–324 (2017).

I. Aklan, N. Sayar Atasoy, Y. Yavuz, T. Ates, I. Coban, F. Koksalar, G. Filiz, I. C. Topcu, M. Oncul, P. Dilsiz, U. Cebecioglu, M. I. Alp, B. Yilmaz, D. R. Davis, K. Hajdukiewicz, K. Saito, W. Konopka, H. Cui, D. Atasoy, NTS catecholamine neurons mediate hypoglycemic hunger via medial hypothalamic feeding pathways. *Cell Metab.* **31**, 313–326.e5 (2020).

M. Q. Ludwig, W. Cheng, D. Gordian, J. Lee, S. J. Paulsen, S. N. Hansen, K. L. Egerod, P. Barkholt, C. J. Rhodes, A. Secher, L. B. Knudsen, C. Pyke, M. G. Myers Jr., T. H. Pers, A genetic map of the mouse dorsal vagal complex and its role in obesity. *Nat. Metab.* **3**, 530–545 (2021).

G. D’Agostino, D. J. Lyons, C. Cristiano, L. K. Burke, J. C. Madara, J. N. Campbell, A. P. Garcia, B. B. Land, B. B. Lowell, R. J. Dileone, L. K. Heisler, Appetite controlled by a cholecystokinin nucleus of the solitary tract to hypothalamus neurocircuit. *eLife* **5**, e12225 (2016).

R. P. Gaykema, B. A. Newmyer, M. Ottolini, V. Raje, D. M. Warthen, P. S. Lambeth, M. Niccum, T. Yao, Y. Huang, I. G. Schulman, T. E. Harris, M. K. Patel, K. W. Williams, M. M. Scott, Activation of murine pre-proglucagon-producing neurons reduces food intake and body weight. *J. Clin. Invest.* **127**, 1031–1045 (2017).

D. I. Brierley, M. K. Holt, A. Singh, A. de Araujo, M. McDougle, M. Vergara, M. H. Afaghani, S. J. Lee, K. Scott, C. Maske, W. Langhans, E. Krause, A. de Kloet, F. M. Gribble, F. Reimann, L. Rinaman, G. de Lartigue, S. Trapp, Central and peripheral GLP-1 systems independently suppress eating. *Nat. Metab.* **3**, 258–273 (2021).

C. R. Boychuk, K. C. Smith, L. E. Peterson, J. A. Boychuk, C. R. Butler, I. D. Derera, J. J. McCarthy, B. N. Smith, A hindbrain inhibitory microcircuit mediates vagally-coordinated glucose regulation. *Sci. Rep.* **9**, 2722 (2019).

I. E. de Araujo, Gustatory and homeostatic functions of the rodent parabrachial nucleus. *Ann. N. Y. Acad. Sci.* **1170**, 383–391 (2009).
C. A. Campos, A. J. Bowen, C. W. Roman, R. D. Palmiter, Encoding of danger by parabrachial CGRP neurons. *Nature* **555**, 617–622 (2018).

D. Y. Kim, G. Heo, M. Kim, H. Kim, J. A. Jin, H.-K. Kim, S. Jung, M. An, B. H. Ahn, J. H. Park, H.-E. Park, M. Lee, J. W. Lee, G. J. Schwartz, S.-Y. Kim, A neural circuit mechanism for mechanosensory feedback control of ingestion. *Nature* **580**, 376–380 (2020).

J. L. Pauli, J. Y. Chen, M. L. Basiri, S. Park, M. E. Carter, E. Sanz, G. S. McKnight, G. D. Stuber, R. D. Palmiter, Molecular and anatomical characterization of parabrachial neurons and their axonal projections. *eLife* **11**, e81868 (2022).

M. W. Schwartz, E. Peskind, M. Raskind, E. J. Boyko, D. Porte Jr., Cerebrospinal fluid leptin levels: Relationship to plasma levels and to adiposity in humans. *Nat. Med.* **2**, 589–593 (1996).

R. C. Frederich, A. Hamann, S. Anderson, B. Löllmann, B. B. Lowell, J. S. Flier, Leptin levels reflect body lipid content in mice: Evidence for diet-induced resistance to leptin action. *Nat. Med.* **1**, 1311–1314 (1995).

J. Friedman, The long road to leptin. *J. Clin. Invest.* **126**, 4727–4734 (2016).

H. Cui, M. López, K. Rahmouni, The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nat. Rev. Endocrinol.* **13**, 338–351 (2017).

C. Bjørbaek, J. K. Elmquist, J. D. Frantz, S. E. Shoelson, J. S. Flier, Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol. Cell* **1**, 619–625 (1998).

J. P. Thaler, C.-X. Yi, E. A. Schur, S. J. Guyenet, B. H. Hwang, M. O. Dietrich, X. Zhao, D. A. Sarruf, V. Izgur, K. R. Maravilla, H. T. Nguyen, J. D. Fischer, M. E. Matsen, B. E. Wisse, G. J. Morton, T. L. Horvath, D. G. Baskin, M. H. Tschöp, M. W. Schwartz, Obesity is associated with hypothalamic injury in rodents and humans. *J. Clin. Invest.* **122**, 153–162 (2012).

M. D. Dorfman, J. P. Thaler, Hypothalamic inflammation and gliosis in obesity. *Curr. Opin. Endocrinol. Diabetes Obes.* **22**, 325–330 (2015).

L. Ozcan, A. S. Ergin, A. Lu, J. Chung, S. Sarkar, D. Nie, M. G. Myers Jr., U. Ozcan, Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab.* **9**, 35–51 (2009).

A. Jais, J. C. Brüning, Hypothalamic inflammation in obesity and metabolic disease. *J. Clin. Invest.* **127**, 24–32 (2017).

C. M. Nasrallah, T. L. Horvath, Mitochondrial dynamics in the central regulation of metabolism. *Nat. Rev. Endocrinol.* **10**, 650–658 (2014).

M. C. Vogt, L. Paeger, S. Hess, S. M. Steculorum, M. Awazawa, B. Hampel, S. Neupert, H. T. Nicholls, J. Mauer, A. C. Hausen, R. Predel, P. Kloppenburg, T. L. Horvath, J. C. Brüning, Neonatal insulin action impairs hypothalamic neurocircuit formation in response to maternal high-fat feeding. *Cell* **156**, 495–509 (2014).

S. Park, A. Jang, S. G. Bouret, Maternal obesity-induced endoplasmic reticulum stress causes metabolic alterations and abnormal hypothalamic development in the offspring. *PLOS Biol.* **18**, e3000296 (2020).

A. A. van der Klaauw, S. Croizier, E. Mendes de Oliveira, L. K. J. Stadler, S. Park, Y. Kong, M. C. Banton, P. Tandon, A. E. Hendricks, J. M. Keogh, S. E. Riley, S. Papadia, E. Henning, R. Bounds, E. G. Bochukova, V. Mistry, S. O'Rahilly, R. B. Simerly, J. E. N. Minchin, I. Barroso, E. Y. Jones, S. G. Bouret, I. S. Farooqi, INTERVAL, UK10K Consortium, Human semaphorin 3 variants link melanocortin circuit development and energy balance. *Cell* **176**, 729–742.e18 (2019).

S. B. Heymsfield, A. S. Greenberg, K. Fujioka, R. M. Dixon, R. Kushner, T. Hunt, J. A. Lubina, J. Patane, B. Self, P. Hunt, M. McCamish, Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. *JAMA* **282**, 1568–1575 (1999).

J. Liu, J. Lee, M. A. Salazar Hernandez, R. Mazitschek, U. Ozcan, Treatment of obesity with celastrol. *Cell* **161**, 999–1011 (2015).

W. Ghusn, A. De la Rosa, D. Sacoto, L. Cifuentes, A. Campos, F. Feris, M. D. Hurtado, A. Acosta, Weight loss outcomes associated with semaglutide treatment for patients with overweight or obesity. *JAMA Netw. Open* **5**, e2231982 (2022).

A. C. Rupp, A. J. Tomlinson, A. H. Affinati, W. T. Yacawych, A. M. Duensing, C. True, S. R. Lindsley, M. A. Kirigiti, A. J. MacKenzie, J. Polex-Wolf, C. Li, L. B. Knudsen, R. J. Seeley, D. P. Olson, P. Kievit, M. G. Myers Jr., Suppression of food intake by Glp1r/Lepr-coexpressing neurons prevents obesity in mouse models. *J. Clin. Invest.*e157515 (2023).

I. Merchenthaler, M. Lane, P. Shughrue, Distribution of pre-pro-glucagon and glucagon-like peptide-1 receptor messenger RNAs in the rat central nervous system. *J. Comp. Neurol.* **403**, 261–280 (1999).

K. M. Heppner, M. Kirigiti, A. Secher, S. J. Paulsen, R. Buckingham, C. Pyke, L. B. Knudsen, N. Vrang, K. L. Grove, Expression and distribution of glucagon-like peptide-1 receptor mRNA, protein and binding in the male nonhuman primate (*Macaca mulatta*) brain. *Endocrinology* **156**, 255–267 (2015).

C. B. Jensen, C. Pyke, M. G. Rasch, A. B. Dahl, L. B. Knudsen, A. Secher, Characterization of the glucagonlike peptide-1 receptor in male mouse brain using a novel antibody and in situ hybridization. *Endocrinology* **159**, 665–675 (2018).

M. H. Tschöp, B. Finan, C. Clemmensen, V. Gelfanov, D. Perez-Tilve, T. D. Müller, R. D. DiMarchi, Unimolecular polypharmacy for treatment of diabetes and obesity. *Cell Metab.* **24**, 51–62 (2016).

J. P. Frías, M. J. Davies, J. Rosenstock, F. C. Pérez Manghi, L. Fernández Landó, B. K. Bergman, B. Liu, X. Cui, K. Brown, SURPASS-2 investigators, tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N. Engl. J. Med.* **385**, 503–515 (2021).

T. D. Müller, M. Blüher, M. H. Tschöp, R. D. DiMarchi, Anti-obesity drug discovery: Advances and challenges. *Nat. Rev. Drug Discov.* **21**, 201–223 (2022).

J. P. H. Wilding, R. L. Batterham, M. Davies, L. F. Van Gaal, K. Kandler, K. Konakli, I. Lingvay, B. M. McGowan, T. K. Oral, J. Rosenstock, T. A. Wadden, S. Wharton, K. Yokote, R. F. Kushner; STEP 1 Study Group, Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. *Diabetes Obes. Metab.* **24**, 1553–1564 (2022).

K. Grzelka, H. Wilhelms, S. Dodt, M.-L. Dreisow, J. C. Madara, S. J. Walker, C. Wu, D. Wang, B. B. Lowell, H. Fenselau, A synaptic amplifier of hunger for regaining body weight in the hypothalamus. *Cell Metab.* **35**, 770–785.e5 (2023).

J. A. Sahel, E. Boulanger-Scemama, C. Pagot, A. Arleo, F. Galluppi, J. N. Martel, S. D. Esposti, A. Delaux, J.-B. de Saint Aubert, C. de Montleau, E. Gutman, I. Audo, J. Duebel, S. Picaud, D. Dalkara, L. Blouin, M. Taiel, B. Roska, Partial recovery of visual function in a blind patient after optogenetic therapy. *Nat. Med.* **27**, 1223–1229 (2021).

C. J. Magnus, P. H. Lee, J. Bonaventura, R. Zemla, J. L. Gomez, M. H. Ramirez, X. Hu, A. Galvan, J. Basu, M. Michaelides, S. M. Sternson, Ultrapotent chemogenetics for research and potential clinical applications. *Science* **364**, eaav5282 (2019).

L. E. Mickelsen, M. Bolisetty, B. R. Chimileski, A. Fujita, E. J. Beltrami, J. T. Costanzo, J. R. Naparstek, P. Robson, A. C. Jackson, Single-cell transcriptomic analysis of the lateral hypothalamic area reveals molecularly distinct populations of inhibitory and excitatory neurons. *Nat. Neurosci.* **22**, 642–656 (2019).

L. Madisen, A. R. Garner, D. Shimaoka, A. S. Chuong, N. C. Klapoetke, L. Li, A. van der Bourg, Y. Niino, L. Egolf, C. Monetti, H. Gu, M. Mills, A. Cheng, B. Tasic, T. N. Nguyen, S. M. Sunkin, A. Benucci, A. Nagy, A. Miyawaki, F. Helmchen, R. M. Empson, T. Knöpfel, E. S. Boyden, R. C. Reid, M. Carandini, H. Zeng, Transgenic mice for intersectional targeting of neural sensors and effectors with high specificity and performance. *Neuron* **85**, 942–958 (2015).

L. E. Fenno, C. Ramakrishnan, Y. S. Kim, K. E. Evans, M. Lo, S. Vesuna, M. Inoue, K. Y. M. Cheung, E. Yuen, N. Pichamoorthy, A. S. O. Hong, K. Deisseroth, Comprehensive dual- and triple-feature intersectional single-vector delivery of diverse functional payloads to cells of behaving mammals. *Neuron* **107**, 836–853.e11 (2020).

MINIMALISMO FOSSE

L'autore, drammaturgo e poeta norvegese **Jon Fosse** è stato nominato vincitore del Premio Nobel per la letteratura. Il presidente del comitato Nobel Anders Olsson ha detto è

"uno scrittore fantastico in molti modi". "Ti tocca così profondamente quando lo leggi, e quando hai letto un'opera devi continuare"

"Ciò che lo rende speciale è la vicinanza nella sua scrittura. Tocca i sentimenti più profondi che provi - ansie, insicurezze, domande sulla vita e sulla morte - cose con cui ogni essere umano si confronta fin dall'inizio.

"In questo senso penso che arrivi molto lontano e che ci sia una sorta di impatto universale in tutto ciò che scrive. E non importa se si tratta di teatro, poesia o prosa: ha lo stesso tipo di fascino su questo argomento fondamentale." umanità."

I suoi romanzi, ha detto l'accademia, sono "fortemente ridotti a uno stile che è diventato noto come 'minimalismo Fosse'