the potential advantage of this local scaling mechanism. Their simulations showed that branch-specific synaptic scaling prevents extreme firing rates and increases the information processing capability of the neuron.

Overall, the study by Barnes et al. reveals a phenomenon that may have broad implications. It shows a negative correlation between spine density and spine size within a dendritic segment. Similar observations have been made previously. An electron microscopy study (Bourne and Harris, 2011) suggests that, after induction of long-term potentiation in hippocampal CA1 dendrites, the loss of both excitatory and inhibitory synapses was counterbalanced by an increase in synaptic surface area of remaining synapses. More recently, Oh and colleagues showed that in hippocampal slice culture, induced structural potentiation of multiple spines on the same dendrite drove the nearby inactive spine to weaken and shrink (Oh et al., 2015). Together with these previous works, the current study suggests homeostatic plasticity at the dendritic level, which may be regulated jointly by local molecular signaling and the limited availability of cellular resources.

The branch-specific synaptic scaling corroborates the idea that the dendritic branch is a key unit of neural information processing. Previous works suggest that local dendritic spikes can be initiated within dendritic branches, which is related to compartmentalized changes in branch excitability (Losonczy et al., 2008). Together with nonlinear integration of synaptic inputs onto a dendritic segment (London and Häusser, 2005), a single neuron may be functionally equivalent to a two-layer neural network (Poirazi et al., 2003), an idea exploited in this paper.

The exciting idea of dendritic branch-specific homeostatic plasticity propels us to ask many further questions. What is the physiological target to be maintained along each dendritic branch? What molecular signaling contributes to the branch specificity? Given the plethora of plasticity mechanisms operating at synaptic, dendritic, and whole-cell levels, how do they coordinate to function synergistically? Tackling these questions will require research across multiple organizational levels of the nervous system, from signaling pathways to neuronal networks.

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A Synaptic Basis for GLP-1 Action in the Brain

Sandrine Lefort,[1,2] Matthias H. Tschöp,[1,2] and Cristina García-Cáceres[1,2,*]
[1]Helmholtz Diabetes Center and German Center for Diabetes Research (DZD), Helmholtz Zentrum München, München, Germany
[2]Division of Metabolic Diseases, Department of Medicine, Technische Universität München, München, Germany
*Correspondence: garcia-caceres@helmholtz-muenchen.de
https://doi.org/10.1016/j.neuron.2017.10.034

Unraveling the brain control of metabolism may generate opportunities to discover novel precision medicines for obesity and diabetes. In this issue of *Neuron*, Liu et al. (2017) identify a novel glucagon-like peptide (GLP)-1 receptor-dependent signaling process that exerts anorexigenic action via the regulation of AMPA receptor subunit composition in the hypothalamus.

Appropriate adaptation of feeding behavior is of paramount importance for survival. Complex and motivated behaviors such as food intake rely in part upon intricate neuronal networks communicating through fast and reliable synaptic connections. These circuits are not immutable and can adapt their synaptic strength and connectivity in response to environmental fluctuations, either external (e.g., sensory stimulation) or autonomic (e.g., energy demands). Therefore, the plasticity mechanisms endowing neuronal circuit malleability are essential for the restructuration and the functionality of neural circuits, as well as the regulation of synaptic transmission capabilities.

Using a wide array of techniques, Liu et al. (2017) now uncovered the involvement of cell-type-specific connectivity of nucleus tractus solitarius-paraventricular nucleus (NTS-PVN) projections, as well as the cellular and molecular NTS-to-PVN GLP-1 signaling mechanisms in the regulation of food intake and energy balance. The PVN is recognized as a major autonomic control center critically involved in the regulation of systemic energy homeostasis and feeding behavior.

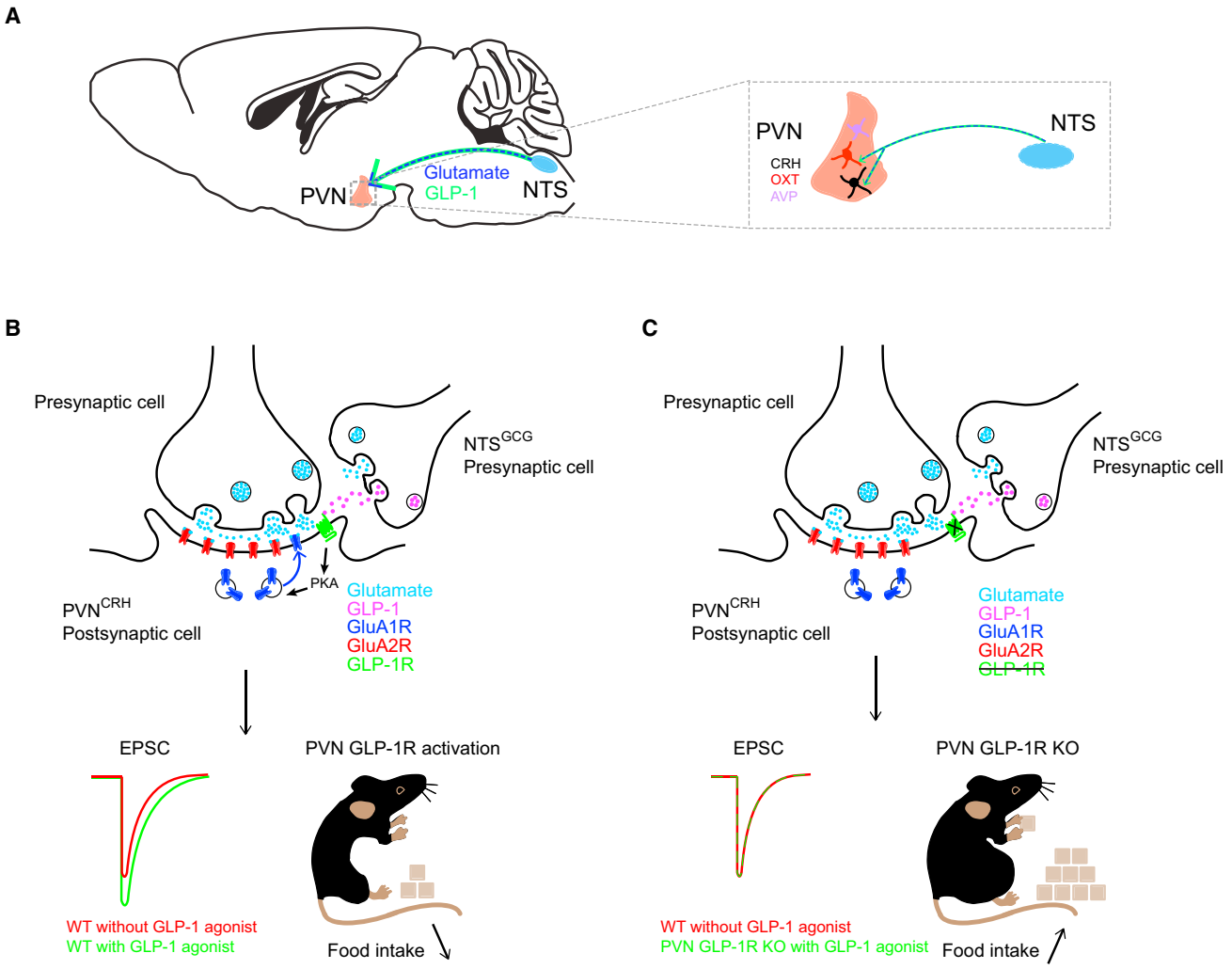

Figure 1. Hindbrain GLP-1 Signaling to PVN Neurons Reduces Food Intake by Regulating AMPAR Trafficking

(A) Pathways connecting glucagon-like peptide-1 (GLP-1)-producing neurons in the nucleus tractus solitarius (NTS^{GCG}) with neuronal populations from the paraventricular nucleus of the hypothalamus (PVN). CRH, corticotropin-releasing hormone; OXT, oxytocin; AVP, arginine-vasopressin.

(B) Enhanced AMPAR trafficking and excitability upon GLP-1R signaling on postsynaptic PVN^{CRH} neurons lead to a decrease in food intake. This effect is independent of presynaptic glutamate release from NTS^{GCG} neurons.

(C) Impact of genetic disruption of GLP-1R expression on postsynaptic AMPA-mediated current in PVN^{CRH} neurons. A global, postnatal GLP-1R knockout in PVN neurons induces obesity.

Neuronal populations in the PVN are highly diverse as defined by neuroanatomy, function, and molecular diversity, including expression of specific cellular markers (Swanson and Sawchenko, 1983). Previous studies postulated that the governing physiological and behavioral roles of the PVN are sensibly influenced by endogenous GLP-1 originating from the NTS preproglucagon gene (*Gcg*) neuronal projection and pharmacological manipulation of GLP-1 signaling in this hypothalamic nucleus (Katsurada et al., 2014). However, which specific PVN GLP-1 receptor (GLP-1R)-expressing neuronal population and molecular mechanisms involved were unclear to date. Therefore, this study sheds new lights on our current understanding and the physiological relevance of these circuits governing feeding behavior. These new perspectives are based on new anatomical and functional characterization of hypothalamic neuronal circuit organization, as well as the molecular mechanisms involved in the modulation of GLP-1-derived NTS postsynaptic transmission.

Liu et al. (2017) are the first to confirm that chemogenetic activation of NTS^{GCG} neuronal population recruits PVN^{CRH} neurons in a GLP-1-dependent manner. Channelrhodopsin2-assisted circuit mapping of NTS^{GCG} projections in the PVN combined with electrophysiological recordings further demonstrates a direct and functional excitatory glutamatergic connection between NTS^{GCG} and PVN^{CRH} neurons (Figure 1A). Finally, viral retrograde monosynaptic anatomical tracings reveal that more than half of the GLP-1-producing NTS neuronal population is presynaptic to PVN^{CRH} neurons. Here, Liu et al. (2017) further investigate the physiological relevance of NTS-to-PVN GLP-1R signaling in feeding behavior by stimulating or inhibiting NTS^{GCG} axon terminals

in the PVN. While inhibition of NTS^{GCG} fibers in this hypothalamic nucleus increases food intake, photostimulation-induced GLP-1 release in the PVN reduces food consumption in a presynaptic glutamate-independent manner. This observation indicates that NTS^{GCG} glutamatergic signaling in PVN^{CRH} neurons is not required for the GLP-1-mediated suppression of food intake. Interestingly, the level of PVN^{CRH} neuronal activity seems to be critical in regulating food intake, since chemogenetic activation of this neuronal population alone induces an anorexigenic effect, while chemogenetic silencing combined with GLP-1R signaling prevents the GLP-1-mediated decrease in feeding normally observed. Therefore, NTS-GLP-1 signaling refines the excitatory synaptic transmission at PVN^{CRH} neurons to ultimately curb food intake (Figure 1B). These results clearly reveal that GLP-1 released from NTS^{GCG} neurons regulates PVN^{CRH} neuronal excitability that might mediate the activation of the specific downstream signaling cascade potentially involved in reducing feeding.

Neuromodulation modifies neuronal circuits via either changes in synaptic transmission or changes in intrinsic membrane properties (Nadim and Bucher, 2014). Here, Liu et al. (2017) use Exendin-4 (Exn4), a specific agonist of GLP-1Rs, in *ex vivo* brain slices to investigate the influence of this incretin on synaptic transmission. Activation of GLP-1R induces an increase only in spontaneous excitatory postsynaptic current (sEPSC) and miniature excitatory postsynaptic current (mEPSC) amplitude in PVN^{CRH} neurons without changes in frequency, suggesting a postsynaptic action of GLP-1 specifically at excitatory synapses. Further, they extracellularly stimulate afferent inputs into the PVN and record evoked EPSCs (eEPSCs) from PVN^{CRH} neurons to determine the molecular mechanisms underlying the GLP-1R-dependent changes observed in PVN^{CRH} synaptic strength. An increase in both AMPA/NMDA ratio and rectification index demonstrates that calcium-permeable GluA1-containing AMPA receptors (AMPARs) are recruited postsynaptically (Figures 1B and 1C) and perturbations of such GluA1R subunit trafficking prevents the GLP-1R-mediated effect on the PVN^{CRH} excitatory tone. Further, GLP-1R signaling is reported to induce the phosphorylation of GluA1 at S845 via the PKA pathway. Thus GLP-1R signaling modifies excitatory synaptic transmission via cellular mechanisms akin to the ones involved in long-term synaptic plasticity (Roche et al., 1996).

Building on their discovery of such an acute effect of GLP-1 on synaptic transmission and feeding behavior, Liu et al. (2017) combined an inducible Cre-dependent viral recombination approach in *GLP-1R*$^{f/f}$ mice to specifically knock down GLP-1R expression in PVN neurons postnatally in order to investigate the relevance of PVN GLP-1R signaling for the regulation of food intake. Contrary to a recent observation dismissing the role of GLP-1R in feeding behavior, Liu et al. (2017) find that the postnatal loss of GLP-1R in PVN neurons induces a body weight gain resulting from an increase in food intake without changes in energy expenditure. Further, glucose tolerance and insulin sensitivity occur due to this diabetic phenotype. The discrepancy between both studies might be explained by the timing of GLP-1R removal in the PVN, with only a postnatal knockdown in this hypothalamic area being necessary to observe the effects on food intake. Although NTS^{GCG} neurons preferentially synapse onto PVN^{CRH}—and, to a lesser extent, oxytocin (OXT)-PVN-expressing neurons—and regulate their neuronal excitability, a specific removal of GLP-1R either in PVN^{CRH} or PVN^{OXT} neurons does not affect feeding behavior, suggesting that concomitant GLP-1R signaling at least onto these two PVN neuronal populations might be required for the regulation of food intake and energy homeostasis.

In summary, recent discoveries by Liu and colleagues uncover that endogenous GLP-1 released from NTS^{GCG} neurons suppresses food intake through an increase in PVN^{CRH} neuronal excitability. Indeed, GLP-1 derived from NTS leads to enhanced postsynaptic AMPAR trafficking in the PVN that presumably mediates the long-term GLP-1-dependent effect on food intake. However, the feedback mechanisms involved in terminating the GLP-1-mediated increase in PVN^{CRH} excitatory synaptic transmission, which then are necessary to maintain proper metabolism homeostasis, remain to be investigated. Apart from actions on PVN^{CRH} neurons, GLP-1 also affects feeding behavior and homeostasis via actions in mesolimbic nuclei, including modulation of excitatory synaptic transmission (Alhadeff et al., 2012; Wang et al., 2015). Given the considerable expression of GLP-1R throughout the brain, further work like the insightful studies presented here will be needed to disentangle the complex cellular and molecular mechanisms by which this gut and neuropeptide influence the neurobiology of food intake and energy balance. G-protein-coupled receptors (GPCRs) have emerged as promising drug targets for therapeutic purposes (Gurrath, 2001), with GLP-1 agonists being particularly effective in treating diabetes and obesity, either as monotherapy or as basis for unimolecular polyagonists (Campbell and Drucker, 2013; Tschöp et al., 2016). Therefore, a systematic investigation of the neuropeptide signaling cascade and specific modulation of neuronal activities is of immediate translational relevance for ongoing efforts to stop the obesity and diabetes pandemics.

CONFLICTS OF INTEREST

M.H.T. is a scientific advisor for and is receiving research support from Novo Nordisk.

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