A Local Rebalancing Act Leads to Global Benefit

Ju Lu[1] and Yi Zuo[1,*]
[1]Department of Molecular, Cell and Developmental Biology, University of California, Santa Cruz, Santa Cruz, CA 95064, USA
*Correspondence: yizuo@ucsc.edu
https://doi.org/10.1016/j.neuron.2017.11.001

Barnes et al. (2017) reveal that in the visual cortex of sensory-deprived mice, dendritic spine enlargement correlates with recent spine loss from the same dendritic branch. Such branch-specific homeostatic plasticity highlights dendritic branches as key computational units.

The mammalian nervous system constantly faces a challenge: to function adaptively and stably in an ever-changing environment. The configuration of the nervous system, i.e., the presence and strength of synaptic connections among neurons, perpetually undergoes modifications. Such flexibility, exemplified by Hebbian synaptic plasticity, is central to the animal's ability to adapt to experiences, to learn new skills, and to store memories. However, Hebbian forms of plasticity, which are positive-feedback processes, are inherently destabilizing (Abbott and Nelson, 2000). Therefore, the nervous system must possess homeostasis, "the trick of maintaining stability," in the words of the great physiologist Walter B. Cannon, just as any other physiological system does. The mechanisms that enable the nervous system to remain stable without being static, collectively termed "homeostatic plasticity," have thus attracted much attention of neuroscientists (Turrigiano, 2017).

Homeostatic plasticity encompasses a variety of mechanisms operating at different spatial and temporal scales with complex molecular underpinnings (Turrigiano, 2017). One important form of homeostatic plasticity is synaptic scaling at excitatory synapses in the central nervous system. Synaptic scaling regulates the strength of synapses across the whole neuron to compensate for perturbations to neuronal activities, so as to restore the neuron's average firing rate to the baseline value (Turrigiano et al., 1998). Although it is the best understood form of homeostatic plasticity, many questions remain. Does synaptic scaling occur homogenously across all synapses of a neuron (i.e., globally), or is it compartmentalized to individual dendritic arbors? Does synaptic scaling occur in inhibitory neurons *in vivo*? If so, is the process analogous to that in excitatory neurons?

Combining *in vivo* two-photon imaging, pharmacology, and slice electrophysiology, Barnes and colleagues endeavored to investigate whether homeostatic modulation of synaptic strength could occur at the level of individual dendritic branches (Barnes et al., 2017). They focused on excitatory synapses onto two types of neurons in the monocular zone of mouse visual cortex: a subset of spiny layer (L) 2/3 inhibitory neurons (largely neuropeptide Y-positive, labeled by GFP under the *GAD65* promoter) and a subset of L5 excitatory pyramidal neurons (labeled by GFP under the *Thy1* promoter). They deprived visual input to the cortex unilaterally in adult mice by surgically removing one eye (monocular enucleation, ME). As commonly practiced in *in vivo* two-photon imaging experiments, the authors used the emergence and disappearance of dendritic spines as a proxy for the formation and elimination of excitatory synapses, and measured spine sizes as a proxy for synaptic strength.

Barnes and colleagues first found that, following ME, the average size of dendritic spines on L5 pyramidal neurons increased within 24 hr, while the size of those on L2/3 inhibitory neurons increased after 48 hr. The authors then took a three-pronged approach to show that the observed spine enlargement is consistent with TNF-α signaling-dependent synaptic scaling. First, they pharmacologically inhibited TNF-α *in vivo* and found that spine enlargement was blocked as expected. Second, they conducted electrophysiological recordings on acute brain slices from ME mice and observed an increase in miniature excitatory postsynaptic current amplitude in both excitatory and inhibitory neurons. Finally, as synaptic scaling is associated with an increase in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluA2, the authors performed immunohistochemistry against GluA2, showing that ME increased the level of GluA2 in spines, as predicted by synaptic scaling.

Interestingly, the authors found that, in both excitatory and inhibitory neurons, only approximately half of analyzed dendritic branches underwent significant spine enlargement, defined as more than 10% increase in average spine size and more than 45% of associated spines enlarged by at least 10%. The proportion of such dendritic branches is greater than the expectation of a random allotment of enlarged spines, indicating a dendritic branch-level specificity of spine enlargement. Furthermore, dendritic branches sharing a common node (sibling branches) did not always exhibit spine enlargement together. What mechanisms underlie such specificity? To address this question, the authors first examined dendritic calcium transients by imaging dendrites labeled with the genetically encoded calcium indicator GCaMP6f in awake, head-fixed mice. They did not find significant differences in suprathreshold activity between sibling branches. Next they looked into spine density changes following ME. They found that the branches undergoing significant spine enlargement exhibited a decrease in spine density; the net loss of spines preceded the enlargement of remaining spines. This observation led the authors to hypothesize that the spine enlargement (and the putative synaptic strengthening) occurs to compensate the loss of synaptic inputs and restore the local output level. Finally, the authors developed a two-layer neural network model (Poirazi et al., 2003) to investigate

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.

REFERENCES

Abbott, L.F., and Nelson, S.B. (2000). Nat. Neurosci. *3* (*Suppl*), 1178–1183.

Barnes, S.J., Franzoni, E., Jacobsen, R.I., Erdelyi, F., Szabo, G., Clopath, C., Keller, G.B., and Keck, T. (2017). Neuron *96*, this issue, 871–882.

Bourne, J.N., and Harris, K.M. (2011). Hippocampus *21*, 354–373.

London, M., and Häusser, M. (2005). Annu. Rev. Neurosci. *28*, 503–532.

Losonczy, A., Makara, J.K., and Magee, J.C. (2008). Nature *452*, 436–441.

Oh, W.C., Parajuli, L.K., and Zito, K. (2015). Cell Rep. *10*, 162–169.

Poirazi, P., Brannon, T., and Mel, B.W. (2003). Neuron *37*, 989–999.

Turrigiano, G.G. (2017). Philos. Trans. R. Soc. Lond. B Biol. Sci. *372*, 20160258.

Turrigiano, G.G., Leslie, K.R., Desai, N.S., Rutherford, L.C., and Nelson, S.B. (1998). Nature *391*, 892–896.

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.