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Review

Homeostatic Plasticity of Subcellular Neuronal Structures: From Inputs to Outputs

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Neurons in the brain are highly plastic, allowing an organism to learn and adapt to its environment. However, this ongoing plasticity is also inherently unstable, potentially leading to aberrant levels of circuit activity. Homeostatic forms of plasticity are thought to provide a means of controlling neuronal activity by avoiding extremes and allowing network stability. Recent work has shown that many of these homeostatic modifications change the structure of subcellular neuronal compartments, ranging from changes to synaptic inputs at both excitatory and inhibitory compartments to modulation of neuronal output through changes at the axon initial segment (AIS) and presynaptic terminals. Here we review these different forms of structural plasticity in neurons and the effects they may have on network function.

Balancing Change and Stability

Neurons come in all shapes and sizes [1]. A bird's-eye view of a neuron will show complex dendritic and axonal morphologies that vary dramatically depending on neuron type and developmental stage [2,3]. While these differing morphologies may underlie important functional roles for neurons in a given circuit, neurons also possess an immense capacity to change both their structure and function [4]. It is this capacity for change that allows neurons – and wider neural circuits – to store information and adapt to the environment. How neurons in the brain perform this job is an area of intense research that has yet to find a definite structural correlate. Whereas wholesale structural rearrangement of dendrites and axons occurs mainly during development, subtler changes occur in adult neurons, with the most compelling evidence so far suggesting that the number and strength of synaptic connections change in response to experience-driven neuronal activity [5,6]. These changes in synaptic connectivity are thought to be the principal form of information storage in the brain, endowing organisms with the ability to learn [6,7]. However, this high level of ongoing plasticity comes at a price. Highly plastic systems are inherently unstable, as positive feedback loops emerge that can drive networks to extreme levels of activity that are detrimental to the organism [8]. Neurons, therefore, have the complex task of finding the right balance between plasticity and stability. To solve the stability problem, different strategies exist that allow neurons to maintain their excitability within reasonable bounds – a set of safeguards designed to avoid extremes while retaining the ability to build a circuit and store information. Under the general term of homeostatic plasticity they encompass numerous subcellular modifications that ultimately control function at both the single-cell and network level. These structural modifications span a very broad spatial domain that can range anywhere from the subnanometre to the micrometre scale [9] and that require different imaging modalities.

Trends

Structural plasticity in response to chronic changes in activity occurs at synaptic inputs at the level of both excitatory and inhibitory compartments. Although opposite in direction, they act to normalise the overall activity of the network in a homeostatic manner.

The output of neurons is also influenced by important structural modifications. The axon initial segment, where action potentials are initiated, undergoes changes in either length or position to fine-tune neuronal excitability.

Presynaptic terminals, which provide the final stage in neuronal output through the release of neurotransmitter, also show structural alterations that match their postsynaptic partners.

Overall, there appear to be multiple forms of plasticity that occur during chronic changes in activity, which together serve to stabilise network function.

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For example, structural changes that result in complete removal or addition of spines are easily visualised by light microscopy whereas changes in synaptic strength might be accompanied by subtler structural modifications at the molecular level that can be observed only with ultrastructural imaging. Here we will focus on structural alterations that lie beyond the molecular level and cause visible changes in neuronal morphology, since we currently have a more complete picture of their role in homeostatic plasticity both *in vitro* and *in vivo*. We review how both input and output structures in neurons are modulated to maintain relatively stable levels of neuronal excitability. Specifically, we focus on synaptic connections (inputs) and the AIS (output), both of which have been shown to undergo important structural modifications in response to chronic activity changes (Figure 1). Finally, we discuss the link between the structure and function of these subcellular compartments and their role in controlling the overall excitability of neurons and circuits.

The Synapse

The chemical synapse is a bicellular unit comprising a presynaptic terminal and a postsynaptic compartment separated by a synaptic cleft. Although the cleft is only 20–30 nm across, the experimental gulf between the two sides of the synapse has historically been quite large. Mainly due to technical limitations, studies looking at structural forms of plasticity tend to focus on either postsynaptic or presynaptic elements but rarely the two together. The fact that there is a strong correlation between the structure [2,3,10,11] and function of pre- and postsynaptic elements [4,12–14] lends further credence to studies that focus on one compartment only, but care should be taken as this functional correlation may not hold true in all conditions [5,6,12,15]. We have therefore divided this section into its constituent parts: excitatory postsynaptic spines, inhibitory postsynaptic compartments and presynaptic boutons. From these studies a consensus view of the structural changes that occur at the synapse as a whole is gradually beginning to emerge.

Postsynaptic Excitatory Compartments: Dendritic Spines

Dendritic spines are small protrusions that cover the dendrites of most vertebrate excitatory cell types. They typically comprise a neck that extends no more than 2 μm from the dendritic shaft and ends in a small bulb. Spines are thought to increase neuronal connectivity by allowing the dendrite to reach a larger number of axons within the same space [4,6,7].

From a functional perspective, dendritic spines allow cells to isolate their inputs and perform linear and nonlinear summation of inputs [8,16]. As the mediators of most of the excitatory inputs to neurons, spines possess a huge complement of postsynaptic receptors and signalling machinery. They exhibit variable sizes and shapes depending on their location on the dendritic tree [9,17] and are also highly dynamic (Box 1). Because of their role as mediators of synaptic

Box 1. Turnover of Dendritic Spines

Dendritic spines are not static; they grow, retract, shrink, and form anew throughout the lifetime of an organism [72]. These turnover rates vary between neuron types and can be affected by learning, disease, and sensory experience. The balance between formation and elimination of spines determines the density of spines along a dendritic branch. Thus, while the density of dendritic spines may be constant, turnover rates can be relatively high provided the rates of formation and elimination are balanced.

Following the development of *in vivo* imaging techniques, the morphology of spines has been tracked in the intact brain and even in awake, behaving mice. Two pioneering studies in this area [18,73] repeatedly imaged dendritic spines in cortical neurons to provide the first measurements of turnover rates *in vivo*. The overall conclusion from these experiments was that cortical neurons appeared to have two populations of spines: those that remained stable and did not turn over and a more dynamic set of spines that showed rapid turnover rates of a few days. Interestingly, a more recent study using two-photon microendoscopy to image pyramidal cell dendritic spines in the hippocampus showed a distinct lack of stable spines, all of them turning over with a mean lifetime of 1–2 weeks [74]. In addition, the developmental stage of the organism also affects spine turnover [40,75,76], such that younger animals have a much larger proportion of dynamic spines compared with the more stable spines found in adults.