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Deconstructing the synapse

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Abstract

While the role of protein synthesis in synaptic plasticity and memory is well-established, protein degradation processes have been less studied. A seminal 2003 Nature Neuroscience paper showed that ubiquitin-dependent degradation of synaptic proteins is engaged during activity-regulated synaptic remodeling.

It is often the case that pivotal studies seem rather obvious in hindsight. Pioneering studies in the 1960s demonstrated that memory consolidation requires protein synthesis, with subsequent work showing that activity-dependent transcription and translation are critical for long-term forms of synaptic plasticity such as long-term potentiation (LTP) and long-term depression (LTD)[1]. Surprisingly, the role of protein degradation and turnover in synaptic plasticity and memory was not well studied until the late 1990s and early 2000s, even though the crucial role for ubiquitin-dependent degradation of proteins in diverse cellular processes had been well-established[2]. A hint that this pathway was important for normal synaptic function and cognition came from the identification of the *UBE3A* gene as the basis for Angelman syndrome[3]. Ube3a is an E3 ligase, an enzyme that catalyzes ubiquitin conjugation to specific substrates, which is the final step in sending proteins to be degraded by the proteasome.

In a tour-de-force single-author paper in 2003, Michael Ehlers showed that proteins in the postsynaptic density (PSD) underwent reversible, bidirectional changes—including ubiquitin-dependent degradation—that dramatically remodeled PSD composition in response to neuronal activity[4]. Groundbreaking work by Gina Turrigiano had shown that chronic changes in neuronal activity result in scaling up or down of synaptic strength in a homeostatic manner that maintained the overall output of the neuron[5]. Ehlers used a similar approach, blocking or increasing activity in cultured cortical neurons for days and measuring protein levels and turnover rates. Strikingly, the expression of proteins that went up with increased activity also went down with inhibition of activity (Fig. 1a). Other sets of proteins exhibited the opposite expression pattern, suggesting that specific modules of proteins act in cohort together. Neuronal activity also affected global protein turnover rates: high activity led to accelerated turnover and low activity the converse. While the turnover rate does not distinguish between protein degradation and trafficking, neuronal activity also led to dramatic changes in the ubiquitin conjugation of PSD proteins. Blocking proteasome-

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Competing interests

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mediated protein degradation mimicked the effects of low activity and prevented changes induced by high activity, suggesting that activity-dependent PSD remodeling was primarily due to the ubiquitin pathway.

At the time, the prevailing model of activity-dependent synapse remodeling centered on gene expression and protein synthesis. The remarkable finding that the turnover and degradation of so many PSD proteins was regulated by activity level led to a number of conceptual changes in the mechanisms underlying synaptic plasticity. For example, Ehlers speculated that synaptic remodeling might be controlled by a few “master organizing molecules” such as Shank and GKAP. This concept has gained experimental evidence recently, with new proteomics and super-resolution imaging techniques revealing discrete nanodomains within the PSD that consist of specific complexes of proteins[6]. While the functional significance of these complexes remains unclear, emerging studies show that postsynaptic nanoclusters are partnered with presynaptic complexes into nanocolumns that allow fidelity of synaptic transmission[7]. Turnover of specific sets of complexes during synapse remodeling would allow rapid fine tuning of synaptic strength without whole-scale changes to the PSD. Master scaffolds could be the ‘seed’ for recruiting specific receptors and trafficking machinery to these complexes. Further work is needed to determine how the localization and expression of these scaffolds is regulated by neuronal activity and by regulated degradation.

Studies based on Ehlers’ findings went on to show that proteasomes themselves are regulated by neuronal activity[8]. NMDA receptor activation results in the redistribution of proteasomes from dendritic shafts to synaptic spines, providing a mechanism for synapse-specific protein degradation. Further work showed that CaMKII, one of the most abundant PSD proteins, acts as a structural scaffold to localize proteasomes at synapses[9]. Synaptic activity results in T286-autophosphorylation of CaMKIIα, enabling binding to proteasomes. The translocation of phosphorylated CaMKIIα to synapses after stimulation leads to the localization of proteasomes to spines. This process is critical for activity-induced PSD protein turnover, although the mechanism by which large protein complexes like proteasomes are transported into spines remains to be elucidated.

One limitation of these studies is their relevance for in vivo synaptic plasticity and memory processes. Evidence that synapse remodeling occurs in vivo came from experiments that showed an increase in ubiquitin-dependent protein degradation and specific ubiquitination of key PSD proteins, such as Shank, after memory retrieval in a fear conditioning task[10]. Interestingly, blocking protein degradation did not affect reconsolidation of memory but did affect extinction. This supports the idea that memory retrieval may result in synapse remodeling that allows further learning and updating by creating a labile memory window.

A prime characteristic of late-phase LTP is sensitivity to protein synthesis inhibition. Interestingly, blocking protein degradation has a similar effect in disrupting the maintenance of late-phase LTP. Paradoxically, however, if both protein synthesis and degradation are blocked simultaneously, maintenance of LTP is preserved[11]. This highlights the need for balanced and coordinated protein expression at synapses but also raises critical questions on the role of the dynamic turnover of proteins in synaptic plasticity and memory. If neither

synthesis nor degradation occurs, does this ‘lock’ information storage so that further updating cannot occur?

It is clear that the ubiquitin-dependent degradation pathway is critical for normal synaptic function and cognition, as a number of E3 ligases are mutated in neurological disorders[12], including the *PARK2* and parkin mutations that cause Parkinson’s disease. Moreover, the regulation of protein stability and degradation may also play critical roles in cognitive phenotypes associated with neurodevelopmental disorders. One example is the finely controlled expression of the immediate early gene *Arc*, a master regulator of synaptic plasticity[13]. Blocking Arc ubiquitination in vivo disrupts long-term depression (LTD), resulting in deficits in reversal learning[14]. Arc expression is also altered in *Ube3a*-mutant mice, disrupting homeostatic scaling of AMPA receptors[15]. It remains unclear how specific E3 ligases target their substrates at specific synapses during synaptic plasticity or how specific protein complexes in the PSD are coordinated by ubiquitination of master scaffolds. There is also little known about the signaling pathways that control the localization and activity of specific E3 ligases in neurons. Synapses undergo dramatic activity-dependent remodeling and pruning during development. Does degradation of PSD proteins play a role in synapse elimination?

Considering that synapses contain hundreds of proteins, it is amazing that the levels of these proteins are so finely controlled in the face of constantly fluctuating neuronal activity (Fig. 1b). How do individual synapses know and remember their precise strength? It has long been hypothesized that there are ‘slots’ for receptors that are stable in the face of constant protein turnover. Experimental evidence for what maintains these slots or their composition is lacking, although master PSD scaffolds may subserve this function. Beyond the slot hypothesis, set points are even sensitive to receptors with different conductance and charge, for example when calcium-permeable AMPA receptors are replaced by calcium-impermeable subunits. Elucidating the homeostatic set points that tune the balance of protein synthesis and degradation at synapses will be key to understanding the mechanisms that underlie synaptic plasticity.

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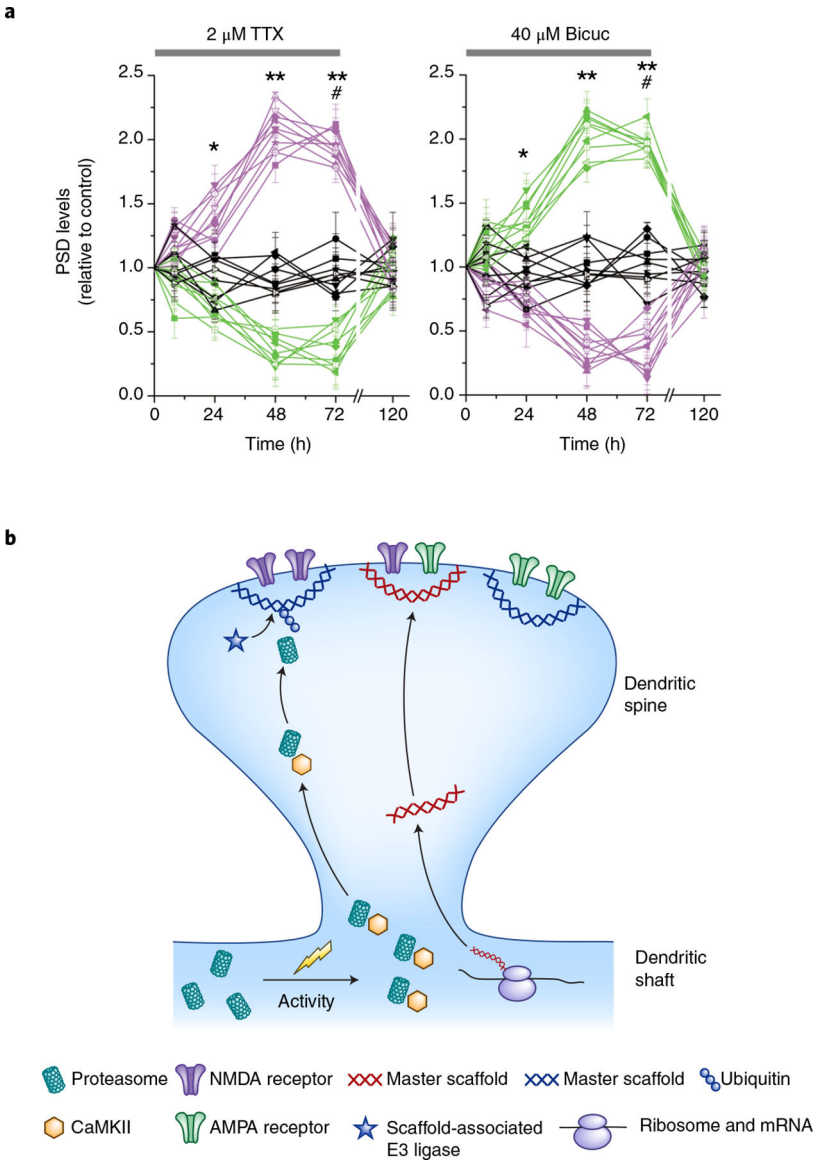

Fig. 1 |. activity-dependent remodeling of synaptic proteins.

a, Chronic changes in neuronal activity result in bidirectional changes in the expression of specific PSD proteins at synapses resulting from local synthesis or degradation. TTX, tetrodotoxin; bicuc, bicuculline. Image reproduced from ref.[4], Nature Publishing Group. **b**, Synaptic activity autophosphorylates CaMKIIα, which recruits proteasomes to synapses allowing efficient degradation of proteins locally. Specific master-scaffolds (blue; e.g., Shank, GKAP) within nanodomains of the synapse are selectively ubiquitinated by E3 ligases, which are recruited by an unknown mechanism. The degradation of these scaffolds alters the composition of neurotransmitter receptors, altering the strength and function of the synapse. In tandem with degradation, other specific master scaffolds (red; e.g., PSD-95) are locally translated in dendrites in response to activity leading to an increase in expression.