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Synaptic Plasticity: Importance of Proteasome-Mediated Protein Turnover

Dispatch

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The ubiquitin-proteasome system regulates protein degradation in every eukaryotic cell. Recent work has shown that protein turnover mediated by the ubiquitin-proteasome system plays a key role in synaptic plasticity.

Neurons use a variety of cellular mechanisms to regulate components required for synaptic transmission and plasticity, including post-translational modifications such as protein phosphorylation, protein compartmentalization into microdomains and protein turnover through regulation of protein synthesis and degradation. Considerable attention has been paid to protein-synthesis-dependent events in synaptic plasticity, exemplified by screens to identify genes induced by activity and learning paradigms [1,2] and reports on the role of local protein synthesis in synaptic plasticity [3,4].

If protein synthesis regulates synaptic transmission, then the local concentrations of certain proteins must be critical for plasticity. This predicts that degradation of these regulatory proteins would also affect synaptic plasticity. The ubiquitin-proteasome system provides a mechanism for regulating protein degradation: it consists of a tightly controlled cascade of enzymes, the activities of which result in ligation of a small protein, ubiquitin, to lysine residues of specific substrates and the subsequent degradation of the ubiquitinated substrate proteins by the 26S proteasome (Figure 1).

A requirement for the ubiquitin-proteasome system in neuronal function has already been demonstrated through analysis of neurological diseases. Proteasome function is impaired in Alzheimer's disease [5] and Parkinson's disease [6]. Mutations in proteins in the ubiquitin-proteasome system lead to ataxia in mice [7] and Angelman's syndrome in humans [8,9]. Expression of mutant Angelman ubiquitin ligase in mice leads to defective long-term potentiation [10]. Patients with schizophrenia show a decrease in expression of genes encoding proteins involved in ubiquitin-mediated protein degradation [11].

Although these studies show that the ubiquitin-proteasome system is important for brain function, the mechanisms and timeframe over which regulated protein degradation by the ubiquitin-proteasome system is important has been unclear. As reported recently in *Current Biology*, two recent studies by Speese *et al.* [12] and Zhao *et al.* [13] have tested the potential involvement of the ubiquitin-proteasome system in synaptic transmission and plasticity over a short timescale. Their results show that the components of the ubiquitin-proteasome system are present at synapses, and that they regulate synaptic transmission and plasticity on a time scale of minutes; they appear to do so by restricting the accumulation of proteins required for synaptic transmission. This means that increases in synaptic efficacy can operate by increasing levels of these restricted proteins. A third recent paper, by Watts *et al.* [14], shows that the ubiquitin-proteasome system is required for major restructuring of neuronal dendritic arbors and axonal projections in central nervous system during insect metamorphosis.

Speese *et al.* [12] used genetic and pharmacological methods to manipulate the ubiquitin-proteasome system at the *Drosophila* neuromuscular junction, and tested the effect of these manipulations on the strength of synaptic transmission. Speese *et al.* [12] found that pharmacological blockade of the ubiquitin-proteasome system, or presynaptic expression of a dominant-negative mutant form of a proteasome subunit, led to the selective accumulation of Dunc13A. Dunc13 is potentially a particularly relevant target protein: levels of UNC13 family proteins are known to control the strength of synaptic transmission, by effects on synaptic vesicle priming, in *Caenorhabditis elegans*, *Drosophila*, mice and *Xenopus*. In electrophysiological assays, Speese *et al.* [12] found that proteasome inhibitors increased evoked synaptic transmission at the *Drosophila* neuromuscular junction. These results suggest that protein degradation by the ubiquitin-proteasome system affects synaptic transmission over a short timescale of about 30 minutes. They further suggest that the net outcome of inhibiting the ubiquitin-proteasome system is to enhance transmission.

Zhao *et al.* [13] investigated the function of protein degradation by the ubiquitin-proteasome system at the sensori-motor neuron synapse in *Aplysia*. This synapse is known to show serotonin-mediated long-term facilitation *in vitro*. The authors were able to show that, in this system, the ubiquitin-proteasome system operates both presynaptically and postsynaptically. They found that treatment with inhibitors of the ubiquitin-proteasome system led to an increase in the glutamate-evoked response at this synapse, indicative of an increase in glutamate receptor number or responsivity, and also to increases in neurite process outgrowth and in presynaptic bouton numbers. It is possible that the increased synaptic transmission results from the increased bouton number. These observations indicate that protein degradation by the ubiquitin-proteasome system may affect synaptic transmission by tapping into known mechanisms of synaptic plasticity such as regulation of glutamate receptor transport, neurite process outgrowth and synaptogenesis.

Consistent with earlier evidence that protein translation is required for serotonin-mediated long-term facilitation in *Aplysia*, Zhao *et al.* [13] found that translational inhibitors counteract the effect of proteasome inhibition. This result serves to strengthen the

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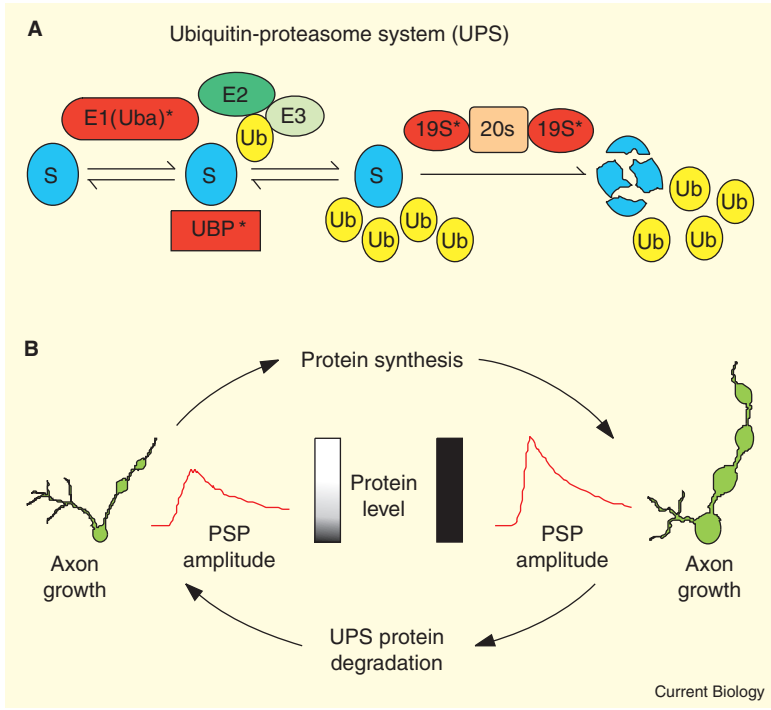

Figure 1. The ubiquitin-proteasome system.
(A) A substrate protein (S) is bound to ubiquitin (Ub) through the sequential activities of a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2) and a ubiquitin ligase (E3). Polyubiquitinated proteins are degraded by the proteasome, which has two 19S subunits and a 20S subunit. (B) A diagram illustrating the pleotropic effects of protein synthesis and protein degradation on multiple parameters in neurons which affect synaptic plasticity.

idea that it is a balance between protein synthesis and degradation that sets the levels of specific proteins which are at nodal positions in biochemical networks regulating synaptic plasticity.

The recent work of Watts *et al.* [14] shows that the ubiquitin-proteasome system has a role in the reorganization of axon projections during development. During insect metamorphosis, neurons in the central nervous system undergo large-scale structural changes in dendritic and axonal projections. Watts *et al.* [14] found that blocking the ubiquitin-proteasome system during metamorphosis in *Drosophila* prevents dendrite and axon pruning, so that the hormone-mediated renovation of the nervous system that normally occurs during pupation is prevented.

These three new papers [12–14] make several new contributions. One is to show that the ubiquitin-proteasome system directly regulates synaptic transmission through an action at the synaptic terminal. Secondly, they show the short time course over which ubiquitin-proteasome-mediated protein degradation can affect synaptic transmission and plasticity. Thirdly, the work on *Drosophila* reveals a specific role for ubiquitin-proteasome-mediated turnover of Dunc13 in neuromuscular junction plasticity. Fourthly, the work on *Aplysia* shows that the ubiquitin-proteasome system likely operates in both presynaptic and postsynaptic compartments to regulate synaptic transmission and plasticity. And finally, the work on insect metamorphosis shows that the ubiquitin-proteasome system is required for the degeneration-style axon pruning required for large-scale reorganization of central nervous system projections.

The full complement of proteins targeted for degradation by the ubiquitin-proteasome system has not been identified. It seems that these proteins will have positive and negative functions in synaptic transmission and plasticity. It is now essential to identify other proteins whose lifetime at the synapse is regulated by the ubiquitin-proteasome system. Understanding the full constellation of protein synthesis, targeting, post-translational modification and degradation will provide essential information for understanding the spatial and temporal dynamics of biochemical events controlling synaptic plasticity.

Given the widespread use of the ubiquitin-proteasome system in a variety of cellular events, one major dilemma in the field concerns specificity of the protein degradation. The work of Watts *et al.* [14] suggests that specificity of the ubiquitin-proteasome system likely derives from specific combinations of ubiquitin conjugating (E2) and ubiquitin ligase (E3) enzymes. Database searches indicate that there are more than thirty distinct E2s and fifty E3s in flies. Vertebrates certainly have many more. If these enzymes work combinatorially to modify protein substrates then it is easy to see how spatial and temporal specificity could arise in regulation of the ubiquitination of substrates and the operation of the ubiquitin-proteasome system in controlling protein degradation.

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