Nature Reviews Neuroscience | AOP, published online 5 january 2011; doi:10.1038/nrn3175

SYNAPTIC PLASTICITY

Ubiquitin activates synaptic plasticity

Ubiquitylation of synaptic proteins and their subsequent degradation by the proteasome is thought to be a key mechanism for the regulation of synaptic plasticity. Ubiquitylation can also alter protein function by modifying interactions between proteins or by modulating protein activity; however, less is known about the roles of these non-proteolytic functions of ubiquitin in synaptic plasticity. Kandel and colleagues now show that ubiquitin-mediated modification of the activity of cytoplasmic polyadenylation element-binding protein 3 (CPEB3) regulates hippocampal-based long-term memory storage.

> “inhibition of NEURL1A function … impaired long-term potentiation (LTP) and long-term depression (LTD) at hippocampal synapses and reduced hippocampus-dependent memory formation.”

The E3 ubiquitin ligase Neuralized facilitates long-term memory function in flies. Here the authors examined the role of its mouse orthologue, Neuralized-like protein 1A (NEURL1A), in synaptic function. They found that inhibition of NEURL1A function by the expression of a dominant negative form of the protein in the adult mouse forebrain impaired long-term potentiation (LTP) and long-term depression (LTD) at hippocampal synapses and reduced hippocampus-dependent memory formation. Overexpression of NEURL1A had the opposite effect.

The facilitatory effect of NEURL1A on synaptic plasticity prompted the authors to examine its effects on synapse numbers and composition. They found that NEURL1A overexpression increased the density of dendritic spines and functional synapses, and increased the synthesis of the AMPA receptor subunits glutamate receptor 1 (GLUA1) and GLUA2 in hippocampal CA1 pyramidal neurons.

To investigate the mechanisms by which NEURL1A exerts these effects, the authors used immunoprecipitation to identify proteins with which it interacts. CPEB3, which is a known regulator of protein synthesis and a functional orthologue of the prion-like CPEB protein in *Aplysia* spp., was shown to interact with and be ubiquitylated by NEURL1A. The authors found that non-ubiquitylated CPEB3 negatively regulates the translation of GLUA1 and GLUA2 but that the NEURL1A-mediated addition of a single ubiquitin molecule to CPEB3 modulates its activity so that it promotes the synthesis of these proteins and the formation of dendritic spines.

These findings demonstrate a non-proteolytic role for ubiquitylation in the regulation of synaptic plasticity, highlighting the complex and wide-ranging effects of this post-translational modification.

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ORIGINAL RESEARCH PAPER Pavlopoulos, E. *et al.* Neuralized1 activates CPEB3: a function for nonproteolytic ubiquitin in synaptic plasticity and memory storage. *Cell* **147**, 1369–1383 (2011)