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IMAGE SOURCE

NEUROTRANSMISSION

# Playing tag!

The ubiquitin proteasome system (UPS) has been implicated in modulating presynaptic and postsynaptic physiology by protein degradation. Rinetti and Schweizer now show that the dynamic ubiquitlyation of presynaptic proteins also regulates synaptic transmission independently of degradation by the UPS.

The tagging of proteins with ubiquitin in mammalian cells involves hundreds of enzymes that confer specificity. This led the authors to hypothesize that protein ubiquitylation — in addition to having a role in degradation — may modulate synaptic activity.

First, the authors tested the effect of proteasome inhibitors (MG132 and clasto-lactacystin β-lactone) on synaptic transmission in cultured rodent hippocampal neurons. They measured the changes in frequency (reflecting a presynaptic effect) and amplitude (reflecting a postsynaptic effect) of miniature postsynaptic currents (mPSCs) before and after application of the proteasome inhibitors. They observed changes in the frequency but not in the amplitude of inhibitory and excitatory mPSCs within 10 minutes of inhibitor application, which indicates that the UPS regulates presynaptic release.

The protein synthesis inhibitor cycloheximide did not alter the effect of MG132. Furthermore, the authors showed that MG132 did not affect the levels of two key proteins implicated in neurotransmitter release: UNC13 homologue B (also known as MUNC13), a vesicle-priming protein, and RIMS1 (regulating synaptic membrane exocytosis protein 1; also known as RIM1), a protein that modulates vesicle fusion. These results suggest that the MG132-triggered increase in mPSC frequency is independent of protein synthesis and degradation.

To test whether ubiquitylation of proteins is a prerequisite for this effect, the authors blocked protein ubiquitylation (without blocking the degradation of ubiquitylated proteins) by using two inhibitors of the E1 ubiquitin-activating enzyme. Surprisingly, both inhibitors increased neurotransmitter release, changing the frequency but not the amplitude of mPSCs.

These results suggest that, in addition to mediating protein degradation, the UPS regulates neurotransmitter release by dynamically changing the ubiquitylation of presynaptic proteins. It remains to be seen whether this mechanism regulates synaptic transmission *in vivo*.

*Claudia Wiedemann*

**ORIGINAL RESEARCH PAPER**
Rinetti, G. V. & Schweizer, F. E. Ubiquitination acutely regulates presynaptic neurotransmitter release in mammalian neurons. *J. Neurosci.* **30**, 3157–3166 (2010)
**FURTHER READING**
Tai, H.-C. & Schuman, E. M. Ubiquitin, the proteasome and protein degradation in neuronal function and dysfunction. *Nature Rev. Neurosci.* **9**, 826–838 (2008)