SYNAPTIC PLASTICITY

Neuroligin 1 does the splits

> NLGN1 cleavage can be induced by neuronal activity or by binding with NRX1β

Neuroligins are postsynaptic adhesion proteins that are essential for synaptic function, but little is known about their precise role and regulation. Neuroligin 1 (NLGN1) is located postsynaptically at glutamatergic synapses, where it binds to the presynaptic adhesion protein neurexin 1β (NRX1β). Now, two new papers shed light on the function and regulation of NLGN1.

Suzuki *et al.* detected several NLGN1 polypeptide fragments in immunoblots of rat brains and mouse primary cortical neuronal cultures, which suggests that NLGN1 undergoes proteolytic processing. Experiments with different enzyme inhibitors revealed that the metalloproteinase ADAM10 cleaves off NLGN1's extracellular domain (that is, the soluble, amino-terminal fragment (NTF)) and that γ-secretase cleaves off the intracellular domain from the remaining membrane-tethered fragment of the protein.

How is NLGN1 cleavage regulated? Peixoto *et al.* found that depolarization (induced by treating dissociated cortical cultures with KCl) rapidly reduced NLGN1 levels at synapses and increased levels of the NTF. Additional treatment with an NMDA receptor antagonist prevented this effect, and both papers showed that incubating cultures with NMDA increased NTF levels. In addition, NTF levels increased when Suzuki *et al.* added soluble NRX1β to the culture medium. Thus, NLGN1 cleavage can be induced by neuronal activity or by binding with NRX1β, and this provides a mechanism for the regulation of NLGN1 levels on the neuronal membrane.

The two studies also provided *in vivo* evidence for activity-induced regulation of NLGN1 cleavage. The authors induced seizures in mice by injecting them with pilocarpine and found that this increased levels of the NTF of NLGN1 in the forebrain (Suzuki *et al.*) and in the hippocampus (Peixoto *et al.*).

Peixoto *et al.* found that inhibition of the matrix metalloproteinase MMP9 prevented depolarization-induced NLGN1 cleavage in cortical cultures. Moreover, *MMP9*-knockout mice did not exhibit seizure-induced and sensory experience-evoked NLGN1 cleavage, both of which were robust in wild-type mice. Nevertheless, basal NLGN1 NTFs could be detected in the brains of *MMP9*-knockout mice. It is possible that MMP9 is required for activity-induced cleavage of NLGN1, whereas basal cleavage is mediated by ADAM10, as shown by Suzuki *et al.*

What is the functional consequence of activity-induced NLGN1 cleavage? Glutamate uncaging experiments by Peixoto *et al.* revealed that NLGN1 cleavage occurs only in activated dendritic spines. The authors found that acute NLGN1 cleavage destabilized NLGN1's presynaptic binding partner NRX1β. Furthermore, electrophysiology experiments showed that NLGN1 cleavage reduced excitatory neurotransmission by decreasing the probability of neurotransmitter release. In agreement with this, blocking NLGN1 cleavage increased presynaptic release probability. This suggests that NLGN1 cleavage acts as a retrograde signal that modifies glutamate transmission.

Cleavage of NLGN1 also had postsynaptic effects on dendritic spines. Suzuki *et al.* overexpressed different cleavage forms of the protein in rat dentate gyrus granule cells. Overexpression of full-length NLGN1 increased spine density, as did overexpression of the membrane-tethered carboxy-terminal fragment of NLGN1, but not overexpression of the intracellular domain (that is, the product of cleavage by γ-secretase). In addition, Suzuki *et al.* found that transfecting rat primary hippocampal neurons with a mutant, cleavage-deficient form of NLGN1 increased spine numbers. Together, these findings suggest that acute activity-induced cleavage of NLGN1 acts as a local homeostatic mechanism to regulate structural and functional synaptic plasticity at individual synapses.

Mutations in neurexin and neuroligin genes have been associated with autism. These two new studies suggest that alterations in proteolytic processing of NLGN1 could have a role in the pathophysiology of this condition and possibly point to a mechanism for the link between epilepsy and autism.

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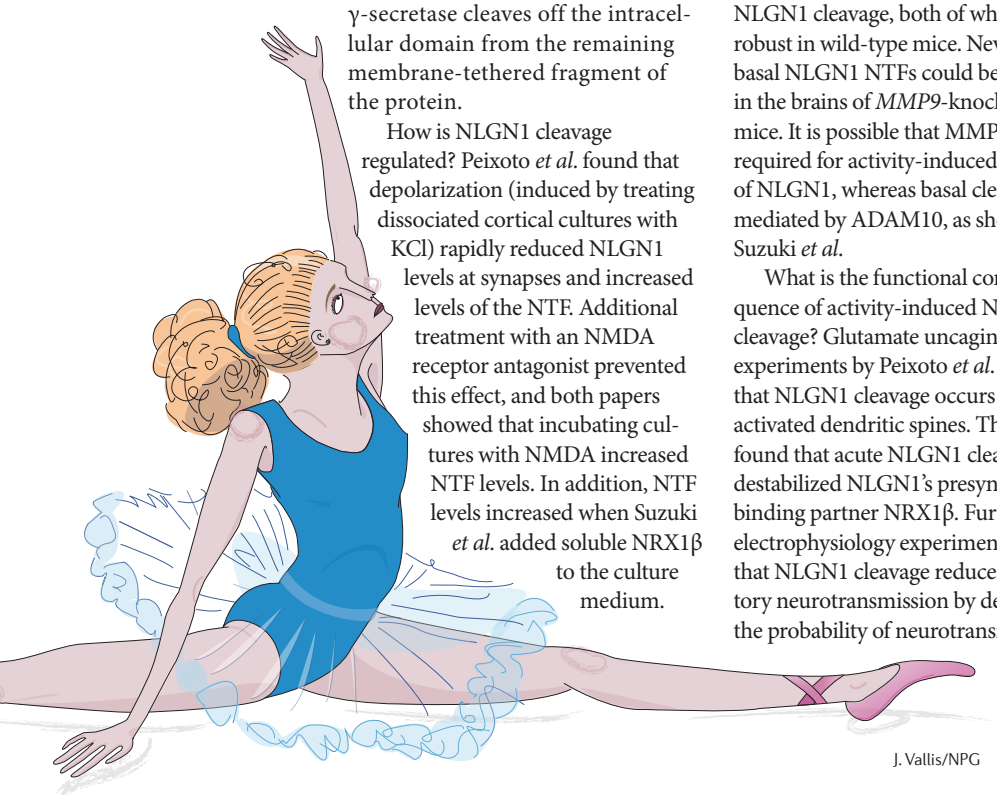

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ORIGINAL RESEARCH PAPERS Suzuki, K. *et al.* Activity-dependent proteolytic cleavage of neuroligin-1. *Neuron* **76**, 410–422 (2012) | Peixoto, R. T. *et al.* Transsynaptic signaling by activity-dependent cleavage of neuroligin-1. *Neuron* **76**, 396–409 (2012)