SYNAPTOGENESIS

Selective stabilization

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Neuroligins (NLs) are transmembrane postsynaptic molecules that bind to β-neurexins expressed in presynaptic cells. Far from merely bridging the synaptic cleft, NLs are actively involved in synaptogenesis in the mammalian brain, as they have been shown to trigger pre- and postsynaptic differentiation. However, it is unclear whether neuroligins mediate the initial establishment of synapses (contact initiation), as has been shown in cell cultures, or the subsequent validation and specification (inhibitory or excitatory) of synapses, as studies in NL-knockout mice suggest. Südhof and colleagues have now shed new light on this issue, and have reconciled previous *in vivo* and *in vitro* data.

The authors showed that in cultured hippocampal neurons overexpression of NL-1 increased the number of functional excitatory synapses. This effect was independent of alternative splicing of NL-1 and, most importantly, was activity dependent — chronic blockade of *N*-methyl-D-aspartate (NMDA) receptors or of the downstream signalling molecule calmodulin kinase II suppressed the synapse-boosting effect of NL-1 — suggesting that NL-1 has a crucial role in the activity-dependent stabilization of transient synaptic contacts.

These findings are in agreement with previous data from NL-1-knockout mice, which showed that NL-1 is essential for synaptic function rather than for the induction of synapses. Electrophysiological recordings now show that there is also a decrease in excitatory synaptic transmission in hippocampal slices from NL-1-knockout mice, demonstrating that NL-1 acts selectively on excitatory synapses *in vivo* as well as *in vitro*.

In contrast, NL-2 overexpression in hippocampal neurons increased the number of functional inhibitory synapses in an activity-dependent manner, and a complementary phenotype was observed in the analysis of NL-2-deficient neurons.

Mutations in NLs are associated with cognitive disorders such as autism, which involves an imbalance between excitatory and inhibitory connections between neurons. When the authors examined the effects of an autism-related single amino-acid substitution in the extracellular domain of NL-1, they found a dramatic decrease in synapse density and excitatory neurotransmission. The fact that this construct had a stronger effect than an NL-1 mutant in which the entire extracellular domain was substituted suggests that this residue is particularly important for NL-1 function.

These data support the idea that NLs 1 and 2 act downstream of the initiation of synapse formation and selectively mediate the activity-dependent stabilization of excitatory and inhibitory synapses, respectively. The precise mechanism by which different NL isoforms selectively stabilize specific types of synapse remains to be determined.

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ORIGINAL RESEARCH PAPER Chubykin, A. A. *et al.* Activity-dependent validation of excitatory versus inhibitory synapses by neuroligin-1 versus neuroligin-2. *Neuron* **54**, 919–931 (2007)