SYNAPTogenesis

Neurexins and new synapses

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Synaptogenesis depends on the clustering of postsynaptic proteins in line with the appropriate presynaptic axon terminals. In the formation of both glutamate- and GABA (γ -aminobutyric acid)-containing synapses this process relies on interactions between presynaptic neurexins and postsynaptic neuroligins. Writing in *The Journal of Neuroscience*, Craig and colleagues report that the expression of differentially spliced variants (leading to the formation of different mature mRNA molecules and therefore different proteins) of neurexins influences the types of synapse that develop by altering neurexin–neuroligin binding affinities.

Hippocampal neurons cluster neuroligin 2 (red) on dendrites at sites of contact with co-cultured COS cells expressing neurexin 1 β containing the splice site 4 insert (blue). The induced clusters of GABAergic postsynaptic components lack synapsin (green), unlike interneuronal synapses. Image courtesy of Y. Kang, X. Zhou and A. M. Craig, University of British Columbia, Canada.

Neurexins are a set of transmembrane cell adhesion molecules that reside on the presynaptic membrane and comprise six main isoforms and numerous naturally occurring splice variants. It is possible that presynaptic expression of specific neurexin isoforms promotes development of specific types of postsynaptic machinery. However, all six isoforms are expressed in a differential but overlapping fashion in different classes of neuron, which indicates that the type of presynaptic isoform is not likely to regulate the assembly of different types of postsynaptic machinery. Nevertheless, there is a single splice site (splice site 4, or S4) on β -neurexins, located on the LNS (laminin, neurexin, sex hormone-binding protein) domain, that is both necessary and sufficient for synaptogenesis, and so deserves particular consideration.

Craig and co-workers investigated the effects on the interactions between neurexins and neuroligins of adding a 30 amino acid insertion at S4 on neurexin 1 β . The results revealed a complex picture: rather than simply disrupting neurexin–neuroligin binding, addition of the S4 inserts impaired the development of glutamatergic but not GABAergic synapses. Specifically, the S4 insertion led to a reduction in the cluster-

ing of the glutamatergic postsynaptic protein PSD-95 and neuroligins 1, 3 and 4. By contrast, clustering of the GABAergic postsynaptic proteins gephyrin and neuroligin 2 was unaffected.

Moreover, the addition of the S4 insert significantly decreased binding between neurexin 1 β and neuroligin 1, whereas neurexin 1 β and neuroligin 2 binding remained unaffected. This indicates that the formation of glutamatergic synapses is more sensitive than GABAergic synapse development to modifications in β -neurexin splicing.

These findings support the idea that neurexin splice variations are important for maintaining the balance between the development of excitatory and inhibitory synapses. It will be interesting to determine whether such splice variations affect neurotransmitter-specific synaptogenesis throughout brain development.

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ORIGINAL RESEARCH PAPER Graf, E. R. et al. Structure function and splice site analysis of the synaptogenic activity of the neurexin-1/ β LNS domain. *J. Neurosci.* **26**, 4256–4265 (2006)

FURTHER READING Graf, E. R. et al. Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. *Cell* **119**, 1013–1026 (2004)