

Small-angle X-ray scattering and neutron contrast variation reveal the arrangement of synaptic proteins implicated in autism

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In the central nervous system, synapses allow neurons to form interconnected neural circuits that must be highly regulated to ensure the appropriate responses to different stimuli. Neuroligins are postsynaptic cell adhesion proteins that associate with their presynaptic partners, the neurexins, in the formation of synapses. Different forms of these proteins (isoforms) are associated with different neural pathways. Using small-angle solution scattering, we determined a low-resolution structure of the extracellular region of free neuroligin1 and its complex with β -neurexin. We also show that the globular domains of several neuroligin isoforms dimerize through a four-helix bundle typical of the cholinesterases. The region connecting the globular neuroligin domains to the cell membrane appears elongated, projecting radially from the globular domains. X-ray scattering and neutron solvent matching experiments demonstrate that two neurexin monomers associate with a neuroligin dimer at symmetric locations such that the complex is $\sim 20\text{\AA}$ longer than neuroligin alone. Our structure delineates the topological arrangements of different neuroligin domains and the synaptic disposition of the partnering molecules. As mutations of neurexin and neuroligin genes appear linked to autism and mental retardation, these structures provide a framework for understanding altered structure and recognition function of these synaptic proteins in developmental disorders.