Mechanistic Insights into Neurotransmitter Release and Presynaptic 3 Plasticity from the Crystal Structure of Munc13-1 C1C2BMUN

Munc13-1 acts as a master regulator of neurotransmitter release, mediating docking-priming of synaptic vesicles and diverse presynaptic plasticity processes. It is unclear how the functions of the multiple domains of Munc13-1 are coordinated. The crystal structure of a Munc13-1 fragment including its C_1, C_2B and MUN domains (C_1C_2BMUN) reveals a 195 Å-long multi-helical structure with the C_1 and C_2B domains packed at one end. The similar orientations of the respective diacyglycerol- and Ca^{2+}-binding sites of the C_1 and C_2B domains suggest that the two domains cooperate in plasma-membrane binding and that activation of Munc13-1 by Ca^{2+} and diacylglycerol during short-term presynaptic plasticity are closely interrelated. Electrophysiological experiments in mouse neurons support the functional importance of the domain interfaces observed in C_1C_2BMUN. The structure imposes key constraints for models of neurotransmitter release and suggests that Munc13-1 bridges the vesicle and plasma membranes from the periphery of the membrane-membrane interface. Details of the hurdles faced during the challenging structure determination will also be provided, which included high crystal non-isomorphism, severe data anisotropy and low resolution.

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