RESEARCH ARTICLE SUMMARY

NEUROSCIENCE

A synthetic synaptic organizer protein restores glutamatergic neuronal circuits

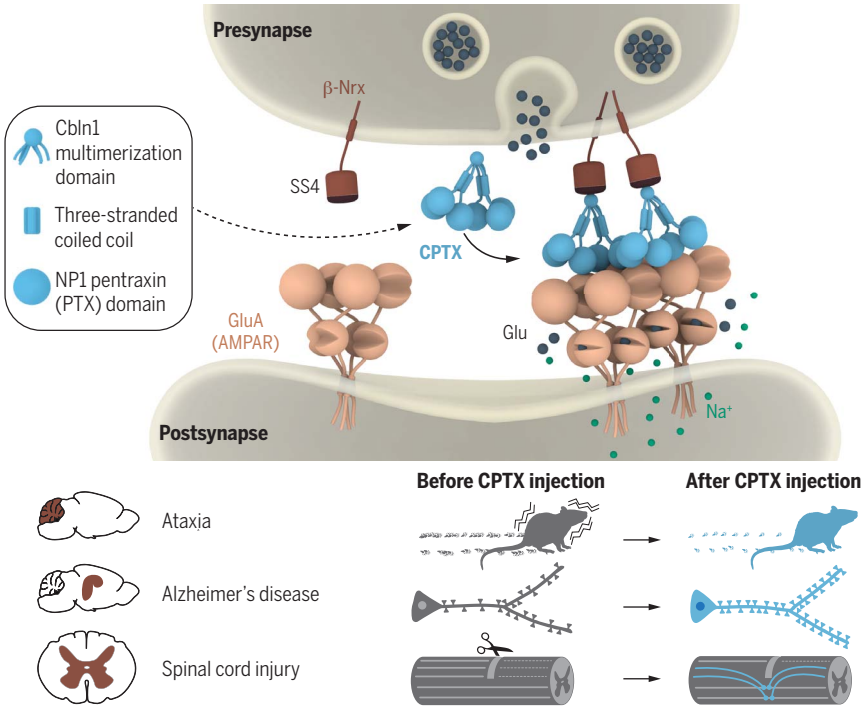
Kunimichi Suzuki*, Jonathan Elegheert*, Inseon Song*, Hiroyuki Sasakura*, Oleg Senkov, Keiko Matsuda, Wataru Kakegawa, Amber J. Clayton, Veronica T. Chang, Maura Ferrer-Ferrer, Eriko Miura, Rahul Kaushik, Masashi Ikeno, Yuki Morioka, Yuka Takeuchi, Tatsuya Shimada, Shintaro Otsuka, Stoyan Stoyanov, Masahiko Watanabe, Kosei Takeuchi, Alexander Dityatev†, A. Radu Aricescu†, Michisuke Yuzaki†

INTRODUCTION: Synapses are fundamental structural and functional units within neural circuits, where they define the connectivity between neurons and provide avenues for communication. At a molecular level, synapses are highly dynamic and their remodeling is essential for all aspects of brain physiology. However, errors in this process can happen and often lead to an imbalance of excitatory and inhibitory signaling. This is thought to be a major cause of neuropsychiatric or neurological disorders, including autism spectrum disorders, epilepsy, schizophrenia, and Alzheimer's disease. Thus, molecular tools to control the number and/or function of synapses would be highly desirable. Physiologically, synapse formation is driven by synaptic organizer proteins. Among these, extracellular scaffolding proteins (ESPs) such as cerebellin-1 (Cbln1) and neuronal pentraxin-1 (NP1) are distinctive in that they could rapidly induce synapse differentiation by binding pre- and/or postsynaptic cell surface proteins at the synaptic cleft. We hypothesized that synthetic molecules that would combine structural features of Cbln1 and NP1 could be used to efficiently reverse the loss of excitatory synapses and promote the structural and functional recovery of damaged neuronal circuits in animal models of neurological disease.

RATIONALE: NP1 recruits postsynaptic AMPA-subtype ionotropic glutamate receptors (AMPARs), responsible for excitatory neurotransmission, through its pentraxin domain. However, NP1 does not seem to induce presynaptic specializations in vivo. By contrast, Cbln1 promotes presynaptic differentiation by interacting with the cell adhesion molecule neurexin (Nrx) through its N-terminal multimerization domain, but cannot bind AMPARs. Guided by structural information, we developed a hexameric synthetic soluble ESP, termed CPTX, which includes the multimerization domain of Cbln1 and the pentraxin domain of NP1. We hypothesized that CPTX should induce Nrx–CPTX–AMPAR transsynaptic molecular bridges, and thus accumulate and align presynaptic vesicle release machinery and postsynaptic neurotransmitter receptors.

RESULTS: Recombinant CPTX selectively bound presynaptic Nrx containing the spliced sequence 4 [Nrx(+4)] with nanomolar affinity and most AMPAR subtypes with micromolar affinity. When administered to cerebellar granule cells and hippocampal neurons in vitro, CPTX acted as a bidirectional synapse organizer and induced excitatory pre- and postsynaptic sites. In vivo, CPTX increased the number of functional excitatory synapses and improved gait performance upon injection into the cerebellum of the ataxic *Cbln1*-null and *GluD2*-null mice. Furthermore, when injected into the hippocampus of 5xFAD mice, a model of familial Alzheimer's disease, CPTX restored dendritic spine numbers, excitatory synaptic transmission, and long-term potentiation and improved hippocampus-dependent learning. Finally, in mouse models of spinal cord injury, single injections of CPTX into the damaged tissue were sufficient to reorganize excitatory circuits and restore locomotion for more than 7 to 8 weeks.

CONCLUSION: We developed a synthetic, structure-guided, synaptic organizer termed CPTX, which induced functional and structural excitatory synapses in the cerebellar, hippocampal, and spinal cord neuronal circuits in vivo. Molecular components involved in excitatory synapses are considerably different among neuronal circuits. Rationally designed ESPs targeting distinct pre- and postsynaptic molecules may be useful to modulate neural circuit connectivity. This approach may inspire the development of a variety of innovative molecular tools for basic neuroscience as well as the treatment of neurological disorders. ■



Structure-guided design and applications of the synthetic synapse organizer CPTX. CPTX combines structural elements from the endogenous synaptic organizers Cbln1 and NP1 to bridge presynaptic neurexins (Nrxs) and postsynaptic AMPA receptors (AMPARs) across the synaptic cleft. CPTX can rapidly induce the formation of excitatory synapses and efficiently reorganize and functionally restore neuronal circuits in mouse models of ataxia, Alzheimer's disease, and spinal cord injury.

The list of author affiliations is available in the full article online.
*These authors contributed equally to this work.
†Corresponding author. Email: alexander.dityatev@dzne.de (A.D.); radu@mrc-lmb.cam.ac.uk (A.R.A.); myuzaki@keio.jp (M.Y.)
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