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Building synapses: Using a synthetic approach to bridge synaptic membranes.

Authors

Kim, Christina K
Kolodkin, Alex L
Shen, Kang
et al.

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Building synapses: Using a synthetic approach to bridge synaptic membranes

Christina K. Kim, Alex L. Kolodkin, Kang Shen*, Garret D. Stuber
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EVALUATION OF

Landmark

A synthetic synaptic organizer protein restores glutamatergic neuronal circuits

Suzuki *et al*.
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Synapses are specialized cellular junctions essential for communication between neurons. Synapse loss occurs in many neurodegenerative diseases. Harnessing our molecular knowledge of the development and maintenance of synapses, Suzuki *et al.* present the first comprehensive attempt to use a synthetic protein to bridge the pre- and postsynaptic membranes[1]. They show that this powerful approach can stimulate the formation of pre- and postsynaptic specializations *in vitro*, rescue synaptic deficits of mutant mice *in vivo*, and ameliorate synapse loss and behavioral abnormalities in both Alzheimer's disease and spinal cord injury mouse models.

EVALUATION BY

Christina K. Kim

University of California, Davis
Protein engineering, synthetic biology, and neuroscience

Alex L. Kolodkin

The Johns Hopkins School of Medicine
Developmental neuroscience

Kang Shen*

Stanford University; Howard Hughes Medical Institute
Developmental and cellular biology of the neuron

Garret D. Stuber

University of Washington
Behavior-related neural circuitry, plus synaptic function and dysfunction in the brain

***Corresponding author and primarily responsible for drafting the consensus evaluation:**
Kang Shen (kangshen@stanford.edu)

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Background

The integrity of synaptic networks is key to the normal function of nervous systems. Molecular mechanisms of synaptogenesis have been studied intensely over the last four decades. In recent years, extrasynaptic scaffolding proteins (ESPs) were discovered to play important roles in bridging the pre- and postsynaptic membranes in the synaptic cleft by directly binding to synaptic proteins. The cerebellin (Cbln) family of ESPs is essential for the development and maintenance of multiple types of synapses[2]. Using ESPs to slow down or even reverse synapse loss in neurodegenerative or injury conditions has not been attempted.

Main contributions and importance

The Suzuki *et al*. paper is a landmark in several ways.

First, it describes a synthetic protein (CPTX) that can directly augment select synaptic connections. CPTX contains a neurexin binding domain derived from Cbln and an AMPA receptor binding domain from neuronal pentraxins. Based on structural information and affinity measurements, the design of CPTX allows it to bind directly to select pre- and postsynaptic components, therefore bridging these synaptic membranes (Figure 1).

Second, the authors present convincing evidence that CPTX induces the formation of excitatory pre- and postsynaptic sites *in vitro*. Remarkably, injecting CPTX into the cerebellum of *Cbln1* mutant mice resulted in the rescue of synapse formation and motor coordination phenotypes in these mutants. Furthermore, CPTX has synaptogenic effects in the hippocampus: the authors were able to restore dendritic spine numbers and alleviate defects in long-term potentiation and cognition in an Alzheimer's disease model. CPTX also restores synapses and promotes long-term improvement of motor function in a mouse spinal cord injury model. The remarkable ability of CPTX to ameliorate excitatory synaptic deficits in a wide range of diseases and injury conditions suggests potential broad applicability.

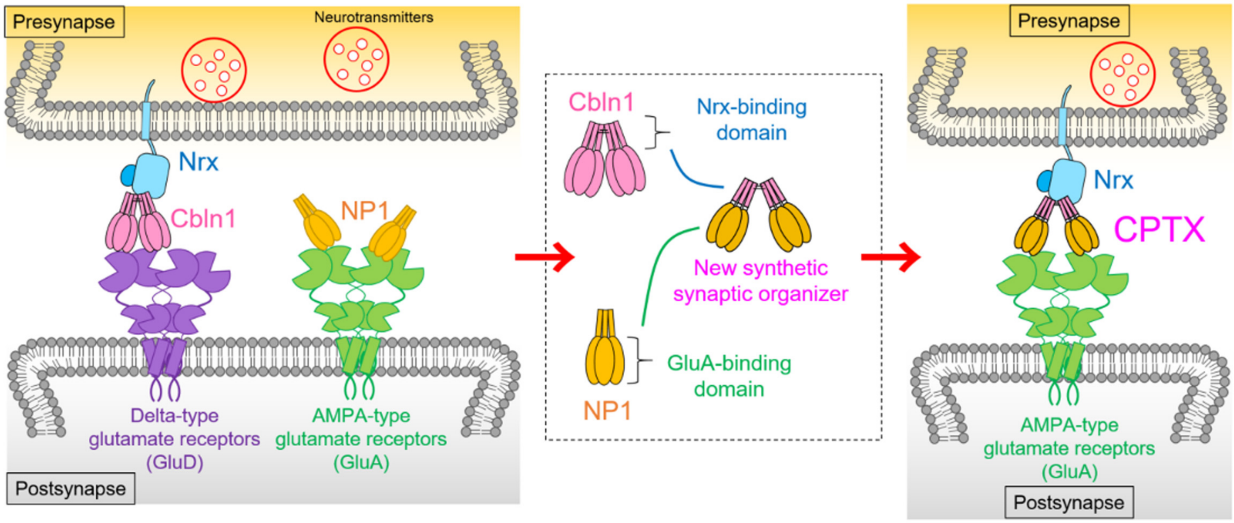

Figure 1. Structure of CPTX and how it bridges pre- and postsynaptic membranes

Image showing how CPTX, by incorporating elements of the Cbln1 and NP1 endogenous synaptic organizers, is able to form a bridge across the synaptic cleft between neurexins (Nrxs) on the presynaptic side and postsynaptic AMPA receptors (AMPARs). This image was reproduced with kind permission from M. Mizutani, K. Suzuki, and M. Yuzaki.

In addition to demonstrating the ability of CPTX to augment synaptic connections in different areas of the central nervous system, the modular structure of CPTX provides a design template for the development of new synaptic organizers to stimulate the growth and stabilization of other synapses in the future. The broad spectrum of research approaches and experimental systems used in this paper establishes a pipeline for such projects.

Open questions

The robust *in vitro* and *in vivo* activities of CPTX suggest that it is likely to impact many glutamatergic synapse types. Understanding the specificity of the activity of CPTX in different glutamatergic synapses will be an important step toward developing this molecule as a therapeutic agent. While the authors demonstrated the ability of CPTX to build and restore synapses, how it affects the existing synaptic networks is not understood. Since regulation of synaptic strength is key to neural plasticity and learning and memory, moving forward it will be important to investigate how CPTX impacts existing synapses and the balance of excitation and inhibition.

As a potential therapeutic agent, several aspects of the activity and pharmacodynamics of CPTX need to be studied further. Exactly how stable is CPTX once injected into the brain or spinal cord? This will dictate CPTX administration frequency and might impact whether recombinant protein or a virus-based delivery system is used. Another question is the lifespan of these newly formed synapses. This paper showed some promising results, since connections made by CPTX in the spinal cord injury model led to behavioral improvement that lasted for at least 8 weeks. Similar experiments testing the potential long-lasting effects of CPTX elsewhere in the nervous system and for different neuronal functions will further our understanding of the biological activities of such molecules.

The modular nature of CPTX provides a design template for new synaptic organizers targeting other types of synapses (i.e., GABAergic, cholinergic, or monoaminergic). The feasibility of such novel synaptic organizers will be tested by future experiments.

Conclusion

Suzuki *et al*. took a bold approach to develop a recombinant protein using their knowledge of ESPs. Using CPTX, they achieved direct bridging of pre- and postsynaptic membranes to build glutamatergic synapses *in vitro* and *in vivo* and presented convincing evidence that this molecule can restore synaptic connections in disease and injury models. This landmark study demonstrates the tantalizing possibility that we may be able to address synaptic loss associated with disease and injury by harnessing the power of synthetic biological molecules.

References

1. Landmark

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