Signal peptides' novel role in glutamate receptor trafficking and neural synaptic activity

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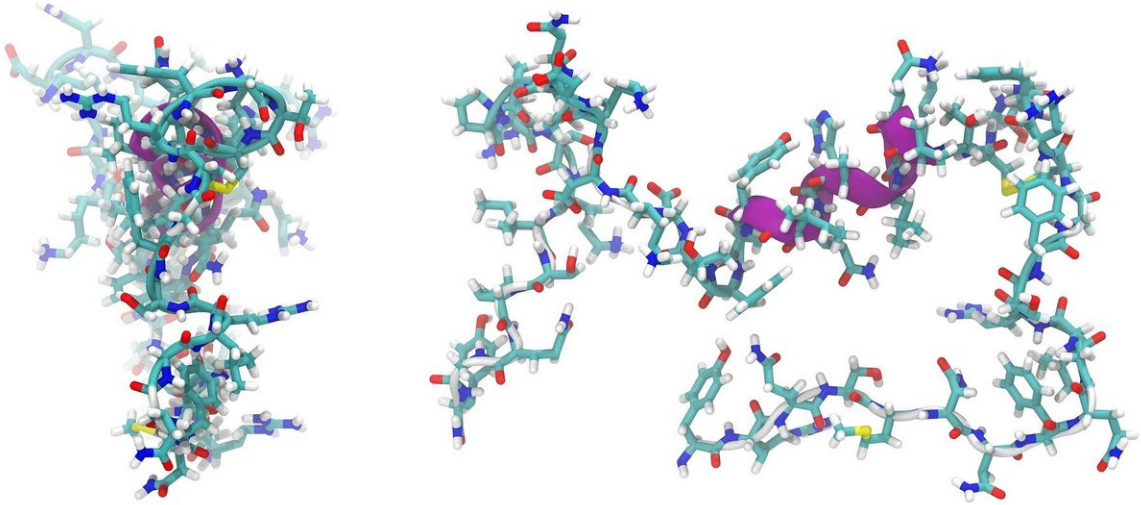

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Glutamate is the major excitatory neurotransmitter in the brain, and the postsynaptic expression level of glutamate receptors is a critical factor in determining the efficiency of information transmission and the activity of the neuronal network. Therefore, glutamate receptor trafficking is critical to the physiological function of human brain circuitry.

It is known that KAR-type glutamate receptors are closely related to many neurological disorders. Dr. Sheng Nengyin at the Kunming Institute of Zoology of the Chinese Academy of Sciences has long been devoted to studying the regulation of KAR trafficking. His previous studies have revealed that in neurons the trafficking performance of KAR subunits GluK1 and GluK2 are totally different, and it is the amino acid sequences of their extracelluar domains that determine their distinct trafficking capability.

To resolve the molecular machinery, the Neural Synaptic Mechanism and Function group led by Dr. Sheng Nengyin, in collaboration with Dr. Shi Yun's Lab at the Model Animal Research Center of Nanjing University, made serial chimeric GluK1-GluK2 receptors based on their conserved structures. The study was published in *Nature Communications*.

Researchers applied electrophysiological techniques to hippocampal slice cultures to analyze the synaptic responses mediated by these receptors. They unexpectedly found a crucial inhibitory role for the signal peptide in GluK1 trafficking.

Signal peptides are N-terminal residues of newly synthesized secretory or membrane proteins. Generally, they are regarded as "cellular address codes" for intracellular trafficking, localization and secretion.

When GluK1 signal peptide was replaced by that of GluK2, GluK2 signal peptide reversed the previous synaptic trafficking incapability. The resultant GluK1 (SPGluK2) receptor potentiated synaptic responses similar to wild-type GluK2, and this potentiation was suppressed by coexpressed GluK1 signal peptide in the same neurons.

Furthermore, they found that the inhibitory function of GluK1 signal peptide requires the presence of the N-terminal domain, since GluK1

successfully trafficked to synapses and neuronal surfaces if the N-terminal domain was replaced with the corresponding sequences of GluK2.

Biochemical studies revealed that GluK1 signal peptide directly interacts with its N-terminal domain (ATD). Therefore, the researchers proposed a model whereby the cleaved signal peptide, in a trans manner and behaving as a ligand of GluK1, binds to GluK1 ATD and forms an inhibitory complex regulating GluK1 forward trafficking in neurons.

This study has revealed a signal peptide function for glutamate receptor trafficking and uncovered a novel trafficking mechanism for glutamate receptors. It provides the theoretical basis for further study of synaptic transmission and plasticity, as well as the pathological mechanism of related neurological disorders.

The human brain has around 10 billion neurons. The neural synapses are the basic connection units transferring information between them. Neurotransmitters, which are released by presynaptic neurons, diffuse into the synaptic cleft and bind to the corresponding receptors on postsynaptic neurons. By doing so, they regulate neuronal activity and accomplish information transmission. Any deregulation of this process is regarded as a leading cause of neurological disorder.

More information: Gui-Fang Duan et al. Signal peptide represses GluK1 surface and synaptic trafficking through binding to amino-terminal domain, *Nature Communications* (2018). DOI: 10.1038/s41467-018-07403-7

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