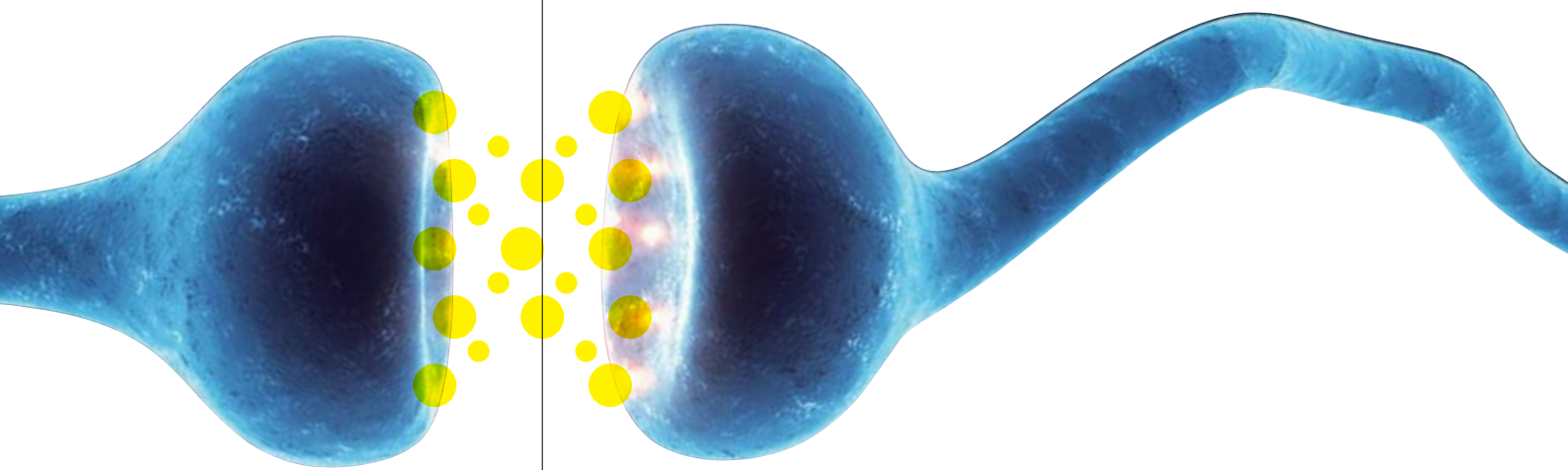
Center for Synaptic
Brain Dysfunctions

Super-resolution imaging reveals two distinct subsynaptic regions at inhibitory synapses, which are most likely specialized for synaptic transmission and adhesion

Identifying New Territories in the Synapse by Super-Resolution Imaging



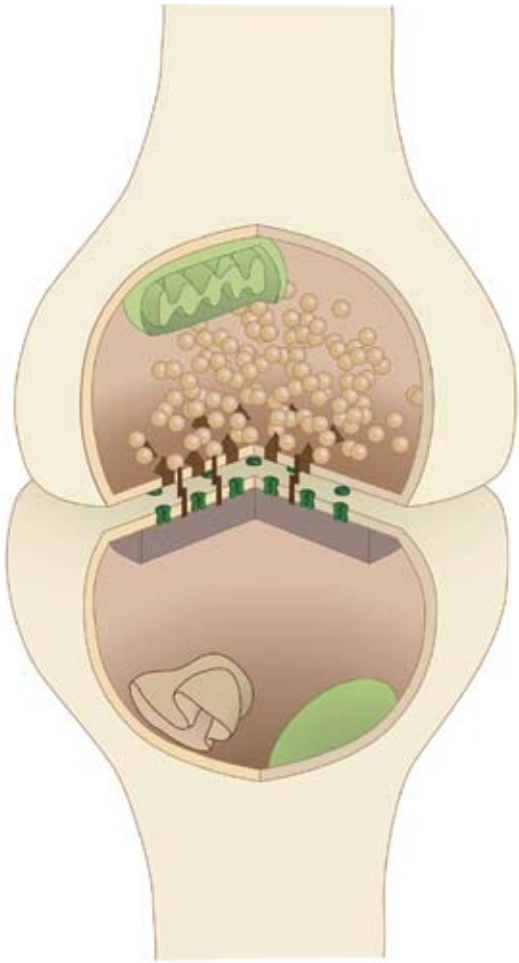
Neuronal synapses mediate synaptic transmission through postsynaptic neurotransmitter receptors. We found a subsynaptic region at inhibitory synapses that mainly contains synaptic adhesion molecules but not receptors, suggesting that neuronal synapses have two distinct regions specialized for synaptic transmission and synaptic adhesion.

Backgrounds and Research Trends • Neuronal synapses mediate excitatory or inhibitory synaptic transmission through the binding of presynaptically released neurotransmitters to postsynaptic receptors and subsequent initiation of postsynaptic responses. In order to facilitate this process efficiently, presynaptic nerve terminals must interact with postsynaptic partners and form a stable adhesive structure, in which synaptic cell adhesion molecules play critical roles.

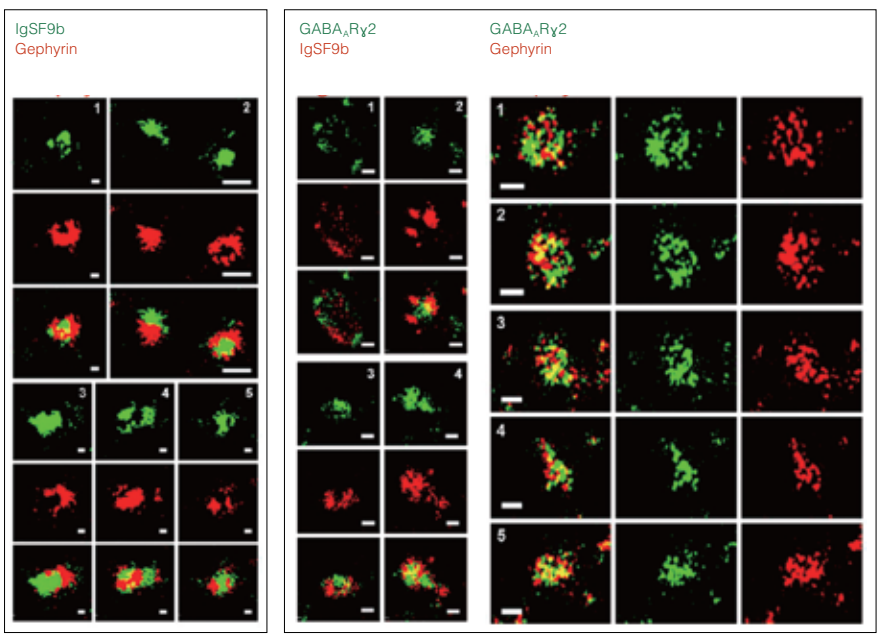
However, it remains unclear how proteins involved in synaptic transmission (i.e., receptors) and synaptic adhesion (i.e., adhesion molecules) are distributed in synaptic spaces. These proteins could be randomly distributed in synapses, or they may be concentrated in specific subsynaptic regions for certain purposes.

Recent studies on excitatory synapses have reported that postsynaptic receptors and receptor-associated proteins are concentrated in discrete subsynaptic clusters rather than being randomly distributed. However, the distribution patterns of synaptic adhesion molecules have not been determined in these synapses. Moreover, the subsynaptic distribution patterns of both receptors and adhesion molecules at inhib-

The synapse that makes contact with a nerve cell releases neurotransmitters that transmit signals. Synapses stimulate or inhibit nerve signals.



IgSF9b and gephyrin/GABAA receptors localize to distinct subsynaptic domains at inhibitory synapses.



itory synapses have remained largely unexplored.

Major Research • We have identified a novel synaptic adhesion molecule termed IgSF9b that is enriched at inhibitory synapses. IgSF9b proteins were more abundant in interneurons than other types of neurons. In addition, we found by super-resolution imaging that IgSF9b is present mainly in a subsynaptic domain that is distinct from neighboring subsynaptic domains enriched with inhibitory receptors (GABA receptors) and receptor-associated proteins (gephyrin).

These findings suggest that inhibitory synapses are composed of two distinct subsynaptic domains, one for synaptic transmission and the other for synaptic adhesion. The reason for this unexpected synaptic organization is unclear at present. However, this organization may promote the rapid and efficient formation of inhibitory synapses by simply joining two distinct domains, assuming that the individual domains are preassembled. This would also enhance the speed and efficiency of inhibitory synapse disassembly.

Future Prospects • Many questions remain regarding subsynaptic organization. For instance, it remains to be determined whether a subsynaptic organization similar to that of interneurons is observed at inhibitory synapses in other types of neurons. Furthermore, it is unclear whether all synaptic adhesion molecules localize to the adhesive subsynaptic domain, because neuroligin 2, a well-known inhibitory adhesion molecule, was more closely associated with GABA receptors and gephyrin. Lastly, more direct experiments are required to test whether preassembled subsynaptic domains are present and whether they form and eliminate inhibitory synapses efficiently.

Reference • Woo et al. (2013). "The adhesion protein IgSF9b is coupled to neuroligin 2 via S-SCAM to promote inhibitory synapse development". *Journal of Cell Biology,* 201:929-944.