JGP Journal of General Physiology

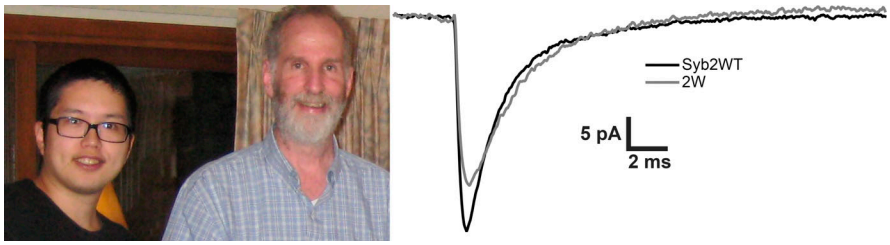
RESEARCH NEWS

Dissecting neurotransmission with artificial synapses

Ben Short

***JGP* study demonstrates how recordings from neuron–HEK cell cocultures provide a clearer picture of the factors involved in synaptic transmission.**

Resolving the rapid series of steps involved in synaptic transmission and assessing the contributions of different molecules to each of them is an enormous challenge. In this issue of *JGP*, Chiang et al. show that the process can be studied with greater resolution at the artificial synapses formed between neurons and cocultured human embryonic kidney (HEK) cells (1).



Chung-Wei Chiang (left), Meyer Jackson (right), and colleagues studied synaptic transmission between hippocampal neurons and cocultured HEK cells. Mutations in the SNARE protein synaptobrevin 2 alter the shape of mEPSCs generated in HEK cells, an effect made clearer by the absence of dendritic filtering in this artificial system.

Meyer Jackson and colleagues at the University of Wisconsin School of Medicine and Public Health are particularly interested in exocytosis. Though this process can be measured directly in endocrine cells, its role in controlling the dynamics of synaptic transmission can be difficult to separate from all the downstream steps required to elicit a response in the postsynaptic neuron. "We wanted to study a surrogate synapse with a simplified response to neurotransmitter that would allow us to focus on vesicle release with greater resolution," Jackson explains.

For years, researchers have studied synaptogenesis by transfecting HEK cells with a handful of postsynaptic factors that enable them to assemble functional synapses when cocultured with neurons (2, 3). Jackson realized that these artificial synapses lack two key sources of variability that can obscure the contribution of vesicle release to synaptic transmission. First, the postsynaptic apparatus of neuron–HEK synapses is consistent and can be precisely controlled (in contrast to regular synapses, where the molecular composition may vary from synapse to synapse). Second, the compact shape of HEK cells greatly reduces the influence of dendritic filtering, the phenomenon by which synaptic inputs take varying lengths of time to reach the cell body, depending on the location of the synapse within the dendritic arbor.

Jackson and colleagues, including first author Chung-Wei Chiang, transfected HEK cells with four postsynaptic proteins—the AMPA receptor subunit GluA2, the adhesion molecule neuroligin 1, the scaffold protein PSD-95, and the accessory factor stargazin—and cocultured them with hippocampal neurons (1). The researchers then measured the miniature excitatory postsynaptic currents (mEPSCs) evoked in the HEK cells by the spontaneous release of single synaptic vesicles from neighboring neurons.

The mEPSCs generated at these artificial synapses were larger and faster than mEPSCs produced by regular, neuron–neuron synapses (though they involved comparable amounts of charge, suggesting that the vesicle populations are similar at both types of synapse).

Notably, the rise rate of mEPSCs in HEK cells was faster and less variable, in keeping with the absence of dendritic filtering and the consistent, shorter distance between the artificial synapses and the HEK cell body. This allowed Chiang et al. (1) to resolve the contribution of vesicle release to mEPSC dynamics using mutant versions of the SNARE protein synaptobrevin 2 that impede the flux of neurotransmitters through synaptic fusion pores (4). These mutant proteins decreased the rise rate and decay rate of mEPSCs at artificial synapses. "However, the effect was much clearer in HEK cells

bshort@rockefeller.edu.

than we'd previously seen in neurons," Jackson says.

Chiang et al. (1) were also able to resolve the contribution of postsynaptic receptors to mEPSC shape, but Jackson is most interested in using the neuron–HEK coculture system to investigate synaptic vesicle release in more detail. "It opens up a new approach that will allow us to study synaptic exocytosis more precisely and look for much subtler effects," Jackson says. For example, Jackson hopes to explain why mutations in some exocytotic proteins have major effects on endocrine cells but little to no effect at synapses.

References

1. Chiang, C.W., et al. 2021. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202012849
2. Fu, Z., et al. 2003. *J. Neurophysiol.* https://doi.org/10.1152/jn.00647.2003
3. Sara, Y., et al. 2005. *J. Neurosci.* https://doi.org/10.1523/JNEUROSCI.3165-04.2005
4. Chiang, C.W., et al. 2018. *J. Neurosci.* https://doi.org/10.1523/JNEUROSCI.0721-18.2018