

## Neuroscience 201A Reading

### Module 3 – Synaptic Transmission

#### Books/Book Chapters:

Fain G (2014) *Molecular and Cellular Physiology of Neurons*, 2<sup>nd</sup> edition, Harvard University Press, Chapters 8-10. We will cover the material in Chapters 9 and 10 sparingly.

Sheng M, Sabatini BL, Südhof TC, eds. (2012) *The Synapse*, Cold Spring Harbor, NY. (*Excellent book; perhaps worth adding to your library if you end up focusing on synapses for your thesis work. The previous version, 2001, is also good but dated.*)

Johnston D, Wu SM-S (1995) *Foundations of Cellular Neurophysiology*, MIT Press, Cambridge, Massachusetts, Chapters 11-13.

Kandel ER, Schwartz JH, Jessell TM (2012) *Principles of Neural Science*, 5th edition, McGraw Hill, New York, New York, Chapters 10, 11, 12, 14.

Nicholls JG, Martin AR, Fuchs PA, Brown DA, Diamond ME, Weisblat DA (2012) *From Neuron to Brain*, 5<sup>th</sup> edition, Sinauer, Sunderland, Massachusetts, Chapters 9-12.

Purves D, Augustine GJ, Fitzpatrick D, Hall WC, LaMantia A-S, White LE, eds. (2012) *Neuroscience*, 5<sup>th</sup> edition, Sinauer Associates, Inc., Sunderland, Massachusetts, Chapters 5, 6.

#### Review Articles:

Eggerman E, Bucurenciu J, Goswami SP, Jonas P (2012) Nanodomain coupling between Ca<sup>2+</sup> channels and sensors of exocytosis at fast mammalian synapses. *Nat Rev Neurosci* 13:7-21.

Fiorvante D, Regehr W (2011) Short-term forms of presynaptic plasticity. *Curr Opin Neurobiol* 21: 269-274.

Kavalali E (2015) The mechanisms and functions of spontaneous transmitter release. *Nature Rev Neurosci* 16: 5-16.

Kochubey O, Lou X, Schneggenburger R (2011) Regulation of transmitter release by Ca<sup>2+</sup> and synaptogagmin: insights from a large CNS synapse. *Trends Neurosci* 34: 237-246.

Neher E, Taschenberger H (2012) Transients in global Ca<sup>2+</sup> concentration induced by electrical activity in a giant nerve terminal. *J Physiol* 591:189-195.

Pang ZP, Südhof TC (2010) Cell biology of Ca<sup>2+</sup>-triggered exocytosis. *Curr Top Cell Biol.* 22: 596-505.

Rudolph S, Tsai M-C, von Gersdorff, H, Wadiche J (2015) The ubiquitous nature of multivesicular release. *Trends Neurosci* 38: 428-438.

Schneggenburger R, Rosenmund C (2015) Molecular mechanisms governing  $\text{Ca}^{2+}$  regulation of evoked and spontaneous release. *Nature Neurosci* 18: 935-941.

Südhof TC (2012) The presynaptic active zone. *Neuron* 75:11-25.

Assigned Paper for Discussion:

Kawaguchi S-Y, Sakaba T (2015) Control of inhibitory synaptic outputs by low excitability of axon terminals revealed by direct recording. *Neuron* 85: 1273-1288.

Study Questions for Discussion:

This paper presents a different story for the basis of short term depression than that presented in lecture. What is the take-home message of this paper?

The synapses studied (largely) by the authors are ones made in long-term cultures. On p. 1273, the authors state "These neurons form synapses similar to that observed in intact preparations." What is the evidence that these connections resemble those in the animal? Do PCs appear similar in culture and in the animal (see Fig. 1)?

On page 1273 (second column near bottom) the authors say "PC axons are relatively thick and can faithfully transmit sodium APs up to over 200 Hz." What do they mean by "thick," and what is the connection between "thick" and a high rate of AP transmission.

What is the small molecular weight "classical" transmitter at synapses between PCs and neurons in the deep cerebellar nuclei? Permeability to which ion(s) are enhanced by this transmitter? How do the authors arrange in this preparation for the current carried by this ion to be inward?

The authors voltage-clamped PCs and used the clamp circuitry to elicit trains of APs at varying frequency (p. 1274, second column). Does the use of voltage steps in the cell body influence the shape of the signal in the terminal? Put another way, are the signals that reach the terminal really action potentials?

At the end of the first section of the Results, the authors, in referring to Figure 1, state that "the depression might be due ... to ... altered  $\text{Ca}^{2+}$  influx, conduction failure, or attenuation of APs." Why can we rule out conduction failure, based on the results in Figure 1?

The  $C_m$  measurements produce signals that greatly outlast the period of stimulation (Fig. 2). The authors state (p. 1275, column 2) that "a continuous increase in  $C_m$  was observed lasting for approximately 1s after the depolarization ceased, probably reflecting asynchronous release." How long do you think that these signals last? Is there any evidence for or against the suggestion that asynchronous release explains the signal? Do you think that these signals are an "artifact?"

The calcium uncaging experiments (Fig. 2) suggest to the authors that there is a  $\sim 4^{\text{th}}$  power relationship between peak  $[\text{Ca}^{2+}]_i$  and release. What is the evidence for this?

Early in the paper the authors support the notion that depression in PC-DCN synapses is not depletion-based by arguing that  $p_v$  (probability of release of a docked/primed vesicle) is small. What evidence do they have that  $p_v$  is small?

Figure 3B compares an IPSC evoked by stimulating the terminal with an “artificial action potential” and the average spontaneously occurring mIPSC. Is this homologous to the “direct” approach of measuring quantal content? What is the source of events that give rise to mIPSCs? Can you make out “evenly spaced peaks” in Fig. 3C?

What are the inward current transients in Figure 4A (right)?

What does Figure 3I show?

The authors use antibodies against voltage-depend sodium channels to conclude that labeling is “sparse” in the terminals compared to the nodes of Ranvier (p. 1281, first column). Do you think that this evidence adds materially to the physiological evidence presented earlier?

One of the bits of evidence suggesting in other systems that depletion of releasable vesicles is at least partly responsible for depression is that there is a consistent relationship between  $p_v$  and depression: anything that increases E/IPSC size by altering  $p_v$  also increases depression. In one instance the authors look at the effects of increasing  $[Ca^{2+}]_o$  from 2 to 4 mM (Supplemental Fig. 6H). What happens? What do they say about this experiment in the legend to figure S6? What do they say about it in the Results (p. 1283, first column)? Why does the TEA result, cited on p. 1283, suggest that depletion is not playing a role in this system?

There is a very interesting development on pp. 1282-3, starting with the passage “Because cultured PC axon terminals fired at ~5 Hz at rest ...” (p. 1282, second column, second full sentence). How do they account for this basal firing in their slice experiments, where evidently there is no basal firing? What happens when they abandon the attempt to account for it (Suppl Fig 6)?

What’s your overall assessment of this paper? The principal contribution of this paper is NOT that it supports a non-depletion model for depression at this synapse, since that was accepted more than a decade ago. What is the contribution(s) of this paper? What aspects of the paper prompted the editors to publish in in *Neuron*? What was the elapsed time from initial submission to acceptance?