Late Switch for Post-Tetanic Potentiation: Once Again It’s Ca^{2+}. Focus on “An Increase in Calcium Influx Contributes to Post-Tetanic Potentiation at the Rat Calyx of Held Synapse”

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Many prior studies have documented the role of calcium in the induction of posttetanic potentiation (PTP). In this issue of the Journal of Neurophysiology (p. 2868–2876), Habets and Borst now elucidate the effect of Ca\(^{2+}\) on vesicle pool size and a 3.5 power-law between Ca\(^{2+}\) and imaged. By using a very sensitive, cooled, and low-noise photon-multiplier tube (PMT), a judicious choice of low-noise Ca\(^{2+}\) indicators to increase the signal-to-noise ratio, and a pinhole imaging only the focal plane to reduce the background even further, they resolve the time course of the Ca\(^{2+}\) rise during a single presynaptic action potential (AP). Due to this technical improvement they found that after PTP induction a presynaptic AP triggers a 15% larger Ca\(^{2+}\) influx added onto an increased basal Ca\(^{2+}\) level. Assuming an increased vesicle pool size and a 3.5 power-law between Ca\(^{2+}\) influx and release the authors estimate that this surprising increase in Ca\(^{2+}\) influx is sufficient to explain the amount of enhanced transmitter release during PTP. It is also noteworthy that this increase in Ca\(^{2+}\) influx occurred over a similar time course as PTP.

PTP of synaptic inputs is a long studied form of synaptic plasticity, entailing an increase of synaptic strength for up to several minutes after prolonged tetanic stimulation. PTP was first reported in 1941 by Feng in a series of pioneering experiments on the frog neuromuscular junction (NMJ) (Feng 1941). Remarkably, this solitary scientist carried out this work in his Peking lab while war raged at his doorstep. Subsequent studies of the NMJ revealed that the magnitude of PTP was dependent on the number of stimuli in the tetanus, that PTP could be induced independently of Na\(^{+}\) influx, that the time course of PTP decay was accelerated at higher temperatures, and that PTP was associated with an intra-terminal accumulation of Ca\(^{2+}\) during the tetanus (Rosenthal 1969; Weinreich 1971). It was concluded that PTP could be quantitatively accounted for by an increase in release probability rather than an increase in the readily releasable pool of quanta.

Later studies used the crayfish NMJ where a large nerve terminal allows paired recordings of the presynaptic terminal and postsynaptic muscle (Wojtowicz and Atwood 1985) and imaging of ionic changes in the presynaptic terminal (Delaney and Tank 1994; Zhong et al., 2001). These studies revealed that PTP involves a prolonged rise in Na\(^{+}\) and Ca\(^{2+}\) within the terminal, without significant changes in the presynaptic action potential waveform after the tetanus. However, little is known about the underlying cellular mechanisms that trigger PTP besides the notion that presynaptic Ca\(^{2+}\) signaling and possibly phosphorylations are involved (Brager et al. 2003). Three recent publications have begun to tackle this issue anew using the calyx of Held synapse (Habets and Borst 2005, 2006; Korogod et al. 2005) in the mammalian brain stem where paired recordings are also feasible.

PTP exhibits an apparent Ca\(^{2+}\) sensitivity in the nano- to low micromole range during its decay, which coincides with an increase in mini-excitatory postsynaptic current (EPSC) frequency. In addition, the ease of induction of PTP varies during development, with increasingly more prolonged stimulation needed for more mature synapses (Korogod et al. 2005) maybe due to the increased expression of Ca\(^{2+}\)-binding proteins (Felmy and Schneggenburger 2004). Interestingly, PTP could not be induced during whole cell patch clamp of the presynaptic terminal but could again be induced after withdrawal of the patch pipette (Korogod et al. 2005). This remarkable resurrection of PTP, after a few minutes of resting the intact calyx, argues for the necessity of a small regenerative soluble messenger to induce or maintain PTP. In fact, during paired whole cell recordings at this synapse, one observes only posttetanic depression after a tetanus (Forsythe et al. 1998). An apparent discrepancy between recent studies concerns the time course of PTP with Habets and Borst (2005) finding that PTP decays in the range of \(\leq 10\) min, whereas Korogod et al. (2005) reported a decay time course of maximally 1 min. This may be due to the different induction protocols: 20 Hz for 5 min (Habets and Borst 2005) and 100 Hz for 2–10 s for Korogod et al. (2005). Another disagreement was the change in vesicle pool size after PTP. Habets and Borst (2005) found a 30% increase, whereas Korogod et al. (2005) find no significant change. Again, this may be due to the different induction protocols. Nevertheless, both groups agree that PTP is mostly due to an increased release probability.

The new work of Habets and Borst (2006) adds an important piece to the puzzle of PTP. However, several key questions remain unresolved. At other synapses, AP-broadening is a powerful mechanism for increasing transmitter release (Geiger and Jonas 2000). Habets and Borst (2006) suggest that AP-broadening may play a role in PTP. However, substantial AP broadening was not observed before at the calyx, at least for short stimulus trains (Korogod et al. 2005). In this respect, it would be of interest to know how much AP-broadening is...
necessary to increase the Ca\(^{2+}\) influx by 15% and if such AP-broadening would be detectable. Alternatively, Ca\(^{2+}\) currents could be increased by a Ca\(^{2+}\)-dependent facilitation without substantially altering the AP-width. Other unexplained observations are the increases in two distinct transmission delays. The time between stimulation and arrival of the AP is apparently prolonged due to a change in membrane excitability. In addition, the synaptic delay itself is increased. The authors speculate that AP broadening could lead to longer synaptic delays by altering the kinetics of Ca\(^{2+}\) influx. However, it remains possible that the increase in delay is independent of AP broadening. Clearly, more studies are needed to elucidate these results, especially because PTP at the avian ciliary ganglion calyx synapse does not involve presynaptic AP broadening (Martin and Pilar 1964).

Habets and Borst (2006) also found that Ca\(^{2+}\) buffering affects the strength of PTP because PTP was nearly an order of magnitude weaker when Oregon Green bis-(\(\rho\)-aminophenoxo)-N,N,N',N'-tetraacetic acid (OGB) was used than when the lower affinity buffer Fluo-4 was employed. The affinity of the buffer will also affect the Ca\(^{2+}\) signal during the tetanic induction period of PTP. So it may be important to separate the effects of the Ca\(^{2+}\) signals during tetanic induction leading to PTP from the elevated basal Ca\(^{2+}\) signal that remains during the PTP itself. Fluo-4, a fast buffer, is supposed to extend the time course of PTP, so it might become saturated during the induction period leading to an overshoot of the Ca\(^{2+}\) concentration, whereas OGB might be more effective in buffering the Ca\(^{2+}\) signal during tetanic stimulation. This putative overshoot of Ca\(^{2+}\) during tetanic induction might trigger intracellular signaling cascades leading to PTP. If so, OGB or EGTA-like buffers might reduce PTP via a more efficient buffering during the tetanus. This might indicate that the Ca\(^{2+}\) signal during tetanic stimulation is probably more relevant than has been recognized so far and the slow decay of elevated Ca\(^{2+}\) may only be necessary for PTP’s maintenance. Nevertheless, in spite of all these caveats, the work by Habets and Borst (2006) leads to a new direction for tackling the problem of PTP by using improved Ca\(^{2+}\) measurements in a mostly unperturbed synaptic terminal.

REFERENCES


