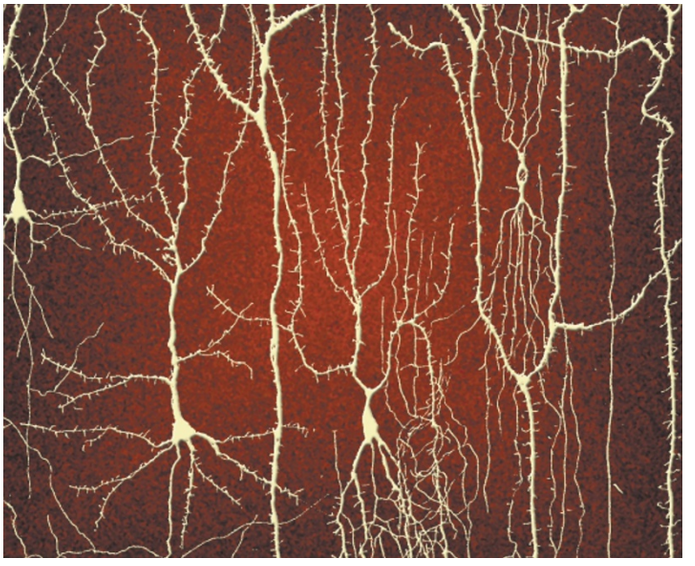
HIGHLIGHTS

SYNAPTIC PHYSIOLOGY

A fresh look at paired-pulse facilitation

When a presynaptic neuron receives two stimuli in rapid succession, the postsynaptic response will commonly be larger for the second than for the first pulse — a phenomenon known as paired-pulse facilitation (PPF). Now here's an easy question for every neurophysiologist: what is the mechanism responsible for PPF? Although most people will quickly point in the direction of 'residual calcium', the story is actually much more complicated. For example, theoretical considerations had led to the suggestion that PPF could also arise from the partial saturation of a calcium buffer, although the empirical evidence behind this idea has been limited. But now Rozov *et al.* have found solid experimental support for this suggestion at the contacts between pyramidal neurons and bitufted cells in rat neocortex.

The authors elicited PPF at this synapse and measured the effect of two buffers that have different calcium-binding kinetics — EGTA (slow) and BAPTA (fast). They observed that, whereas EGTA blocked facilitation by chelating residual calcium, relatively low concentrations of BAPTA did not affect PPF or, if anything, tended to increase it. How can we explain this paradoxical effect? Rozov *et al.* argue that the calcium that enters the terminal after the first pulse partially saturates the fast buffer BAPTA. As a result, less BAPTA is available to chelate calcium after the second pulse and a slight increase in PPF is observed.



Does this partial-saturation-based mechanism have physiological relevance? This issue is particularly important for neurons that express proteins such as calretinin or calbindin, which could act as fast buffers owing to their ability to bind calcium with high affinity. In this regard, it's interesting that Rozov *et al.* found that EGTA did not block the slight increase in facilitation elicited by BAPTA when both buffers were present simultaneously. So, one can predict that if PPF were insensitive to EGTA under normal conditions at a given synapse, this would be a good indication that partial buffer saturation might make a more important contribution to facilitation than residual free calcium. But independently of this consideration, the findings of Rozov and his colleagues make a compelling case for the need to revisit our beliefs on PPF, a plastic phenomenon that we normally take for granted.

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References and links

ORIGINAL RESEARCH PAPER Rozov, A. *et al.* Transmitter release modulation by intracellular Ca^{2+} buffers in facilitating and depressing nerve terminals of pyramidal cells in layer 2/3 of the rat neocortex indicates a target cell-specific difference in presynaptic calcium dynamics. *J. Physiol.* **531**, 807–826 (2001)

FURTHER READING Neher, E. Usefulness and limitations of linear approximations to the understanding of Ca^{2+} signals. *Cell Calcium* **24**, 345–357 (1998) | Zucker, R. S. Increased Ca^{2+} buffering enhances Ca^{2+}-dependent process. *J. Physiol.* **531**, 583 (2001)

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