

# The mechanisms of multi-component paired-pulse facilitation of neurotransmitter release at the frog neuromuscular junction

Mukhamedyarov M., Grishin S., Zefirov A., Palotás A.  
*Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia*

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## Abstract

We have studied the mechanisms of paired-pulse facilitation (PPF) of neurotransmitter release in isolated nerve-muscle preparations of the frog cutaneous pectoris muscle. In normal extracellular  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_o$ , 1.8 mM), as the interpulse interval was increased from 5 to 500 ms, PPF decayed as a sum of two exponential components: a larger but shorter first component (F1) and a smaller but more prolonged second component (F2). In low  $[\text{Ca}^{2+}]_o$  (0.5 mM), both F1 and F2 increased, and a third "early" component (Fe) appeared whose amplitude was larger and whose duration was shorter than F1 or F2. In the presence of the "fast"  $\text{Ca}^{2+}$  buffer BAPTA-AM, Fe disappeared, whereas F1 and F2 decreased in amplitude and duration. In contrast, the "slow"  $\text{Ca}^{2+}$  buffer EGTA-AM caused a decrease of Fe and reduction or complete blockade of F2, without any changes of F1. In solutions containing  $\text{Sr}^{2+}$  (1 mM), the magnitude of Fe was decreased, F1 was significantly reduced and shortened, but F2 was unaffected. Application of the calmodulin inhibitor W-7 (10  $\mu\text{M}$ ) at normal  $[\text{Ca}^{2+}]_o$  produced a marked decrease of F2, and at low  $[\text{Ca}^{2+}]_o$ , a complete blockade of Fe. These results suggest that PPF at frog motor nerve terminals is mediated by several specific for different PPF components intraterminal  $\text{Ca}^{2+}$  binding sites, which trigger neurotransmitter release. These sites have a higher affinity for  $\text{Ca}^{2+}$  ions and are located farther from the release-controlling  $\text{Ca}^{2+}$  channels than the  $\text{Ca}^{2+}$  sensor that mediates phasic release. © 2009 Springer-Verlag.

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## Keywords

Calmodulin, Neuromuscular junction, Neurotransmitter release, Paired-pulse facilitation, Short-term synaptic plasticity