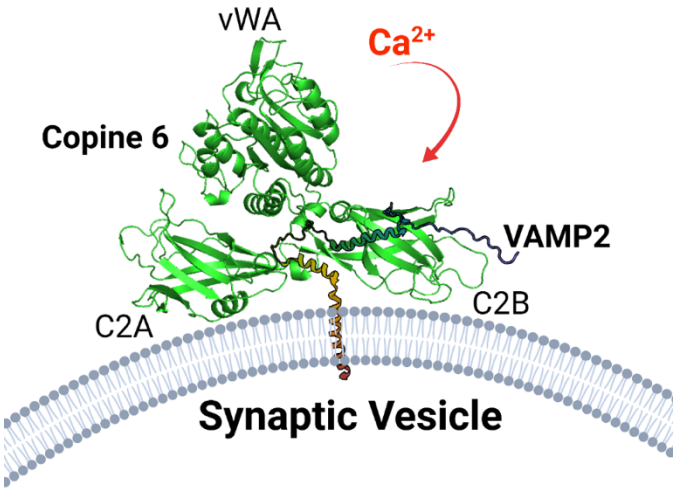
Converging mechanisms for calcium regulation of SNARE-dependent membrane fusion: EF-hand proteins and copines

Mehedi Hasan[1] and Mikhail Khvotchev[2,*]

[1] Department of Biochemistry, Faculty of Science, Mahidol University, Bangkok, Thailand; mehedihasan.saj@student.mahidol.edu
[2] Department of Biochemistry and Center for Neuroscience, Faculty of Science, Mahidol University, Bangkok, Thailand; mikhail.khv@mahidol.edu
* Correspondence: mikhail.khv@mahidol.edu

Abstract: Calcium-triggered membrane fusion is essential for nervous and endocrine system function and likely operates in many if not all nonneuronal cells. Similar to other types of membrane fusion, it critically depends on SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) proteins, however SNARE protein function is not directly regulated by calcium. Instead, calcium activates specialized sensor proteins, which initiate or suppress membrane fusion by direct action on SNARE proteins. Broad range of calcium-membrane fusion coupling kinetics dictates the presence of multiple calcium sensors with distinct calcium-binding properties. Using a combination of in vitro biochemistry and bioinformatics we demonstrate that the juxtamembrane linker in the v-SNARE protein VAMP2 is highly conserved in evolution and is required for interaction with several calcium sensor proteins. We identify novel calcium-dependent VAMP2 linker-binding proteins that belong to EF-hand protein superfamily and build molecular models of VAMP2 complexes with C2 domain sensor protein copine 6 and EF-hand protein calmodulin. Thus, distinct calcium-binding proteins converge on the conserved juxtamembrane linker in VAMP2 and enable calcium regulation of VAMP2-dependent membrane fusion.

Graphical abstract:



Keywords: SNARE protein; calcium sensor; membrane fusion; synaptic transmission; molecular docking; EF-hand; C2 domain; copine

Funding: This research received no external funding.

Acknowledgments: This research was supported by the Department of Biochemistry and Faculty of Science, Mahidol University. We thank current members of the Department of Biochemistry for help and encouragement. We thank Prof. Ege Kavalali (Vanderbilt Brain Institute and the Department of Pharmacology, Vanderbilt University, Nashville, USA) for support and discussions.

Conflicts of Interest: The authors declare no conflict of interest.