



SEMINARIO PRESENCIAL

Viernes, 25 de Octubre de 2024
12:30 h. Instituto Cajal - CSIC

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HOW IS NEUROTRANSMITTER RELEASE TRIGGERED IN MICROSECONDS

Abstract

Great advances have been made to understand the molecular mechanisms underlying neurotransmitter release, but two central questions have remained unanswered: how is membrane fusion induced and how does Ca^{2+} help to trigger fusion in microseconds. Thus, it is known that the SNARE proteins syntaxin-1, SNAP-25 and synaptobrevin form a tight four-helix bundle called the SNARE complex that brings the synaptic vesicle and plasma membranes together, but bringing membranes into contact is not sufficient for fusion. It is also clear that the Ca^{2+} sensor synaptotagmin-1 triggers fast release in cooperation with the SNAREs, but the mechanism of action of synaptotagmin-1 is unknown. Our all atom molecular dynamics simulations now suggest that extension of the SNARE helices into the juxtamembrane sequences preceding their transmembrane regions initiates fast, microsecond scale membrane fusion because it catalyzes encounters of the hydrophobic acyl chains of lipids from both membranes at the polar bilayer interface. Our simulations, together with NMR and FRET data, also suggest that helical extension into the juxtamembrane regions is hindered by energy barriers and that synaptotagmin-1 acts as a lever that, upon Ca^{2+} influx, facilitates such extension by re-orienting on the membrane and pulling the SNARE complex.

Affiliation and short bio

Josep Rizo was born in Barcelona, Spain, in 1959. He received a B.Sc. degree in Organic Chemistry in 1981 from the University of Barcelona. He became interested in quantum field theory and statistical mechanics, which led him to obtain a second B.Sc. degree, this time in theoretical physics, from the same University in 1988. During the 1982-1988 period, he also obtained M.Sc. and Ph.D. degrees in organic chemistry from the University of Barcelona, working in the laboratories of Ernest Giralt and Enrique Pedrosa on ^{13}C NMR spectroscopy and peptide synthesis. In 1989 he started postdoctoral research in the laboratory of Lila Gierasch at UT Southwestern, working on conformational studies of peptides by NMR spectroscopy and molecular dynamics, as well as protein NMR and protein folding. He established his independent research group in 1995 at UT Southwestern. The main focus of his research is the study of the mechanisms of neurotransmitter release and intracellular membrane fusion using structural biology, a variety of biophysical techniques and reconstitution approaches. He has made multiple key contributions to this field and is currently a Professor in the Departments of Biophysics, Biochemistry and Pharmacology.

Related publications with the topic

Rizo, J.; Sari, L.; Qi, Y.; Im, W.; Lin, M. M., All-atom molecular dynamics simulations of Synaptotagmin-SNARE-complexin complexes bridging a vesicle and a flat lipid bilayer. *Elife* 2022, 11, e76356.

Rizo, J.; Sari, L.; Jaczynska, K.; Rosenmund, C.; Lin, M. M., Molecular mechanism underlying SNARE-mediated membrane fusion enlightened by all-atom molecular dynamics simulations. *Proc Natl Acad Sci U S A* 2024, 121 (16), e2321447121

Jaczynska, J., Esser, V., Xu, J., Sari, L., Lin, M. M., Rosenmund, C., and Rizo, J. A lever hypothesis for Synaptotagmin-1 action in neurotransmitter release. *Biorxiv* 599417 (Preprint). June 18, 2024. Available from: <https://www.biorxiv.org/content/10.1101/2024.06.17.599417v1>.

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