Life Sciences Seminar

A Comparison of vesicle mobility in hippocampal and cerebellar mossy fiber synaptic terminals

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Hippocampal and cerebellar mossy fiber terminals (hMFTs and cMFTs) form some of the largest synapses in the central nervous system, having numerous varicosities, active zones (AZs) and thousands of synaptic vesicles. However, despite a similar morphology on a gross anatomical level, cMFTs and hMFTs exhibit distinct functional properties with respect to synaptic transmission, plasticity and their roles within their respective neural networks. To investigate whether vesicle mobility might play an important role in the functional distinction of these two large synapses, we performed fluorescence recovery after photobleaching (FRAP) experiments on hMFTs and cMFTs in brain slices from VGLUT1-Venus knock-in mice. Our results show a 9-fold lower vesicle mobility in hMFTs compared to cMFTs. Moreover, the immobile-vesicle fraction is at least twice as large in hMFTs compared to cMFTs, which may explain in part the lower vesicle mobility in hMFTs. Bath application of roscovitine, a CDK5 inhibitor, produced a larger reduction of the immobile-vesicle fraction in hMFTs compared to cMFTs, suggesting synapsin-based vesicle binding in hMFTs but not cMFTs. Next, we investigated whether structural properties of hMFTs and cMFTs underlay the 9-fold difference in vesicle mobility. Quantitative analysis of electron micrograph (EM) data indicates the vesicle density is similar in hMFTs and cMFTs, and therefore cannot account for the difference in vesicle mobility. Monte Carlo FRAP simulations confirm the immobile-vesicle fraction is larger in hMFTs (58%) compared to cMFTs (25%). While a larger immobile-vesicle fraction can account for the lower vesicle mobility in hMFTs, due to steric and hydrodynamic interactions, our analysis indicates it can only account for a 2 to 3-fold reduction in vesicle mobility. This suggests Dcyto, the diffusion constant of a single vesicle within the cytomatrix, is lower in hMFTs than in cMFTs, by about 3-fold. Finally, to investigate the effects of a lower vesicle mobility in hMFTs on synaptic transmission, we simulated vesicle diffusion in the vicinity of AZs, where vesicle locations and AZ geometries were derived from 3D EM reconstructions. Results show an ~2-fold higher vesicle supply rate to AZs in hMFTs compared to cMFTs at early times (< 2 ms), due to a larger AZ surface area (~4-fold larger), and comparable supply rates at intermediate (100 ms) and late times (50-100 s). Hence, the larger AZ surface area in hMFTs counteracts the lower vesicle mobility, resulting in a vesicle supply rate comparable to that in cMFTs.

Thursday, November 14, 2019 03:00pm - 04:00pm
Mondi Seminar Room 2, Central Building

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