Applying Nanocommunication Modeling to Understand Calcium Ion Influx in Neurons and Impact on Kinesin Axonal Transport of BDNF Vesicles

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The most common cause of dementia, Alzheimer's disease (AD), is an age-influenced chronic neurodegenerative progression affecting communication across multiple scales. Subcellular nano-molecular changes within neurons along with extracellular neurofibrillary plaques or tangles combine to disrupt inter-neural signaling and induce gradual loss of brain cognitive function. The subcellular initiating causes and factors influencing progression of AD would benefit by mathematical modeling of events to assist in understanding events in chemical signaling dysregulation that underlies changes to both intra- and inter-neural connectivity. The dysregulation of intracellular Ca^{2+} is known to play a role in AD early pathology along with amyloid-β (Aβ) oligomers that act on receptors to dysregulate calcium influx. Calcium signaling affects the transport of NTFs, such as the critical Brain Derived Neurotrophic Factor, BDNF. The "Calcium hypothesis of AD", proposes that aberrant Ca^{2+}signaling occurs prior to accumulation of hyper-phosphorylated tau (p-tau) and observance of cognitive decline. A recent study of BDNF transport defects in neurons supports this hypothesis and reveals a spatiotemporal progression of impairment of fast axonal transport, FAT, that correlates with Ca^{2+} elevation. In this work we apply new models that allow us to incorporate nanoscale communication events when addressing complex multi-scale cellular biological events. We model two events that are 1) rates of Ca^{2+} influx into neurons through receptors at the dendritic-soma membrane and 2) predict those elevated internal Ca^{2+} ion–levels that impact dense core-vesicle-BDNF microtubule loading onto kinesins and NTF-transport within the region of the axon initial segment (AIS). Our findings reveal new information on how the number and type of membrane receptors are involved in Ca^{2+}internalization rates (setting up a worse case scenario in which influx is maximized) as well as Ca^{2+} influenced changes to the dynamics of dense core vesicle-BDNF- cargo capture, transport and release. We have begun to include more complex structural axonal elements such as microtubule (MT) bundles and the presence of junctures at overlapping MT ends along the length of axons, to better structurally and functionally represent the impact of nano-microscale axonal complexity in Ca^{2+} ion regulated NTF dynamics. Our model is tested against recently published data on BDNF transport in neurons providing proof of concept.