New functional cAMP compartment in neuroprotection organized by AKAP6

P-03.1-03

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Neuronal survival and axon growth is known to be regulated by cAMP signaling. Last decades of research showed that cAMP signaling in neurons is highly compartmentalized, however besides dendritic and synaptic regulation, only few functional subcellular compartments in terms of molecular architecture have been identified so far. cAMP signaling is largely orchestrated by multimeric complexes called A-kinase anchoring proteins (AKAPs) that locally target PKA and other signaling molecules to specific compartments. These complexes are thought to serve as nodal points for signaling integration for pro-survival and pro-regenerative upstream stimuli. By using new PKA sensors for live-cell FRET imaging and molecular tools to specifically alter local cAMP level, we demonstrated that perinuclear compartment organized by AKAP6 is necessary for hippocampal neurons outgrowth and survival. Displacement of AKAP6-associated phosphodiesterase 4D3 (PDE4D3) with competing peptide (4D3-mCherry) significantly enhanced local cAMP elevations and promoted neuronal extension in the absence of any additional stimuli. Contrary, increasing PDE4D3 hydrolytic activity by targeting constitutively active enzyme to this compartment dramatically reduced length of axons and neuronal survival. In addition, in vivo delivery of 4D3-mCherry using AAV2 increased retinal ganglion cell survival following optic nerve injury. Our findings provide a demonstration of a new, functionally distinct neuronal compartment that regulate cAMP-dependent neuroprotection and axon growth and may be therapeutically targeted with AAV-based gene therapy.

Supported by National Science Center grant no. 2019/33/B/NZ4/00587