Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad – 500 046

Webinar

Roles for Neuronal Excitability and Bioenergetics in the Regulation of Longevity

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Mitochondrial ATP production is a well-known regulator of neuronal excitability. In this talk, I will describe a mechanism by which depolarized neurons elevate the somatic ATP/ADP ratio in *Drosophila* glutamatergic neurons. I will show that depolarization increases phospholipase- Cβ (PLCβ) activity by promoting the association of the enzyme with its phosphoinositide substrate. Augmented PLCβ activity led to greater release of endoplasmic reticulum (ER) Ca^{2+} via the inositol trisphosphate receptor (IP_3R), which in turn, stimulated mitochondrial Ca^{2+} uptake and ATP synthesis.

Expression of a gene encoding, an ALS-causing variant of an ER membrane protein, VAPB, decouples mitochondrial ATP production from neuronal activity. Due to a combination of diminished ATP production and elevated ATP consumption — established outcomes in ALS neurons — the levels of ATP in mutant neurons are unable to keep up with the bioenergetic burden of depolarization. The resulting paucity of ATP results in diminished extrusion of cytosolic Ca^{2+}, defects in synaptic vesicle release, and chronic depolarization.

Sustained depolarization of neurons in models of ALS and tauopathy led to untrammelled PLCβ–IP_3R activation, and a dramatic shortening of *Drosophila* lifespan. Investigation of the underlying mechanisms revealed that increased sequestration of Ca^{2+} into endolysosomes was an intermediary in the regulation of lifespan by IP_3Rs. Manipulations that either lowered PLCβ/IP_3R abundance or attenuated endolysosomal Ca^{2+} overload restored animal longevity. Collectively, our findings demonstrate that depolarization-dependent regulation of PLCβ–IP_3R signalling is required for modulation of the ATP/ADP ratio in healthy glutamatergic neurons, whereas hyperactivation of this axis in chronically depolarized glutamatergic neurons shortens animal lifespan by promoting endolysosomal Ca^{2+} overload.

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