Study uncovers role of mitochondrial energy production in dopaminergic neurons

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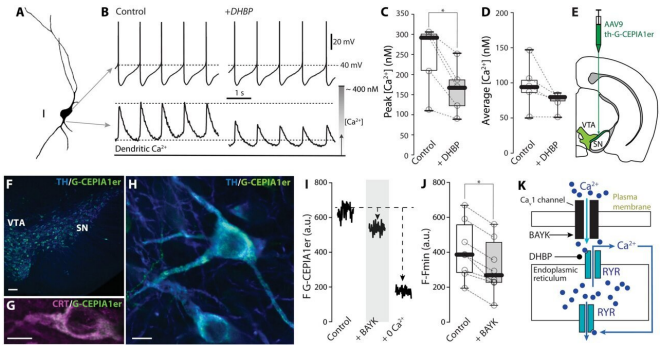

Ca^{2+} entry through Ca_v1 Ca^{2+} channels triggered ER Ca^{2+} release. (A) Representative reconstruction of a Fura-2–filled SNc dopaminergic neuron (scale bar, 20 ?m). (B) Representative whole-cell current clamp recordings (top) and 2PLSM traces of cytosolic Ca^{2+} oscillations (bottom) in SNc neurons loaded with Fura-2, before and after application of RYR antagonist DHBP. (C and D) Box plots summarizing the average amplitude of cytosolic Ca^{2+} oscillations and average Ca^{2+} concentration in dopaminergic neurons in control conditions and after DHBP bath application; DHBP significantly decreased the amplitude of cytosolic Ca^{2+} oscillations (n = 5, N = 5; P = 0.0312, one-tailed Wilcoxon matched-pairs signed rank test). (E) Cartoon representing the AAV delivery strategy to induce expression of G-CEPIA1er in midbrain dopaminergic neurons; modified from the Allen Mouse Brain Atlas, online version 1, 2008 (https://atlas.brain-map.org/). (F to H) Immunofluorescence images showing the expression of G-CEPIA1er in dopaminergic neurons stained for TH and the colocalization of G-CEPIA1er with the ER marker calreticulin (CRT); scale bars, 100 ?m (F) and 10 ?m (G and H). (I) Representative 2PLSM imaging time series showing the effect of application of Ca_v1 Ca^{2+} channel (Ca_v1)–positive allosteric modulator Bay K8644 (BAYK) on dendritic ER Ca^{2+} in SNc dopaminergic neurons expressing G-CEPIA1er. (J) Quantification of the effect of BAYK on dendritic ER Ca^{2+} measured with G-CEPIA1er (n = 8, N = 7; P = 0.0039, one-tailed Wilcoxon matched-pairs signed rank test). (K) Cartoon illustrating the effect of Ca^{2+} entry through Ca_v1 channels on RYR Ca^{2+} release and the targets of BAYK and DHBP. Box plots indicate first and third quartiles, thick center lines represent medians, and whiskers indicate the range. a.u., arbitrary units. *P Science

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Northwestern Medicine investigators have discovered that dopaminergic neurons in the substantia nigra utilize a specific ion channel to meet anticipated energy needs, according to findings published in *Science Advances*.

The study, led by D. James Surmeier, Ph.D., chair and the Nathan Smith Davis Professor of Neuroscience, sheds light on how this "anticipation" may stress mitochondria, which can ultimately cause the loss of these neurons with aging and neurodegenerative disease.

A major function of substantia nigra dopaminergic neurons is to modulate goal-directed movement. Their loss or decline causes movement to slow, which is a key symptom of Parkinson's disease.

To function properly, dopaminergic neurons require adenosine triphosphate (ATP) produced by mitochondria. The question Surmeier's team grappled with was how neuronal function influenced ATP synthesis. They started with the idea that neuronal action potentials or "spikes" were critical to this linkage, but precisely how spikes might control mitochondria energy production was unknown.

In the current study, investigators used non-invasive methods to monitor spiking in dopaminergic neurons and mitochondrial function at the same time. This was done using antibiotics to create small holes in the membrane of dopaminergic neurons, allowing electrical activity to be monitored and manipulated without disturbing mitochondria.

Using advanced microscopy and genetically encoded sensors, the investigators were able to monitor signaling inside the neurons during spiking.

They also used genetic strategies to delete key proteins that served to bridge events at the plasma membrane to events deep inside the cell.

This methodology revealed that dopaminergic neurons use calcium entering at each spike through a specific class of ion channel in the neuron's plasma membrane—Cav1 channels—to adjust ATP production to match their spiking rate.

"This control system 'anticipates' bioenergetic need, preventing episodes in which the cell runs out of gas and has to stop to refill its tank. This is of organismal importance because if these dopaminergic neurons stop spiking, the whole animal stops moving. Obviously, keeping this from happening if we were being chased or were chasing dinner would be to our advantage," Surmeier said.

Investigators also found that calcium enhances ATP production through two complementary mechanisms. The first mechanism involves calcium entering the matrix of the mitochondria to stimulate the tricarboxylic acid cycle, which helps drive cellular respiration and ATP synthesis. The other mechanism is mediated by calcium-stimulated enzymes outside the matrix that push metabolites into the matrix to support ATP production.

The discovery of these mechanisms improves the understanding of how neurons match energy production to activity and avoid "blackouts" caused by energy depletion. While this system helps dopaminergic neurons function efficiently, it also has a downside, according to Surmeier.

"While this control system is important for the efficient operation of many neurons, it can increase their stress. Over time, this high level of oxidant stress can damage the mitochondrial powerplant," Surmeier said.

Surmeier added that therapeutically targeting and "tuning down" this calcium channel may reduce Parkinson's disease risk and slow disease progression, a strategy his team is currently investigating.

"Although our initial study was focused on the cell body, the most vulnerable part of the dopaminergic neuron is its axon. We're now examining whether the same 'anticipatory' mechanisms are engaged there. If this turns out to be the case, we have a strategy for lowering axonal stress level just enough to keep them functioning into old age. This should allow us to slow or stop progression in Parkinson's disease," Surmeier said.

More information: Enrico Zampese et al, Ca 2+ channels couple spiking to mitochondrial metabolism in substantia nigra dopaminergic neurons, *Science Advances* (2022). DOI: 10.1126/sciadv.abp8701

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