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MEETING ABSTRACT

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L-type calcium channel-mediated Ca²⁺ influx exerts regulatory control of the mitochondrial ATP synthase in cultured hippocampal neurons

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Background: Calcium is a major regulator of mitochondrial ATP synthesis. The Ca²⁺ influx during neuronal activity stimulates mitochondrial metabolism, which appears to provide a mechanism how the neurons cope with the energetic burden. However, little is known about any source specificity regarding the responsible cytosolic Ca²⁺ rises. One candidate for providing regulatory Ca²⁺ rises is the L-type family of voltage-gated calcium channels (LTCCs, or Ca_v1.x channels).

Methods: In this study we investigated the impact of modulating LTCC-mediated Ca²⁺ influx on mitochondrial function, which was assayed using Perceval, a genetically encoded fluorescence indicator of ATP/ADP ratio, and TMRM (tetramethylrhodamine methyl ester), an indicator of the mitochondrial membrane potential (Ψ_{mt}). Furthermore, we employed oligomycin to probe the operational mode of the mitochondrial ATP synthase. Neuronal activity was stimulated by elevating extracellular K⁺ or by application of the GABA_A receptor antagonist bicuculline. The activity of LTCCs was modulated by application of an agonistic (Bay K8644) or an antagonistic dihydropyridine (isradipine).

Results: Our results demonstrate that LTCC-mediated Ca²⁺ influx regulates the ATP synthase in a bimodal manner, with moderate mitochondrial Ca²⁺ elevations exerting a stimulatory effect, whereas higher Ca²⁺ elevations induce a switch to reverse-mode operation. We provide evidence, that the stimulatory effect involves Ca²⁺-induced Ca²⁺ release from intracellular stores, whereas the switch to reverse-mode operation requires nitric oxide formation.

Discussion: Our results suggest that LTCCs are physiological regulators of mitochondrial function. LTCCs are able to promote mitochondrial ATP synthesis or to turn mitochondria into consumers of ATP.

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Keywords: L-Type calcium channels – mitochondria – ATP synthase – calcium – neuron – hippocampus

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