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Role of astrocyte mitochondria in opioid withdrawal.

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Astrocyte mitochondria play negligible role in ATP production but are essential for intercellular interactions and maintaining extracellular level of different metabolites such as glutamate and lactate. Astrocytes express mu opioid receptors, and chronic opiate treatment alters astrocyte morphology and/or physiology. Given importance of astrocyte mitochondria in astrocyte-neuron interaction, we evaluated whether astrocyte mitochondria are involved in mediating analgetic and behavioral effects of morphine. Impaired oxidative phosphorylation in astrocytes was produced in adult male and female mice by astrocyte-specific deletion of the nuclear gene, *Cox10*, that encodes for the accessory protein of the complex IV, the protoheme:heme-*O*-farnesyl transferase. Conditional deletion of *Cox10* gene in astrocytes decreased expression of COX10 and Cytochrome *c* oxidase subunit I (MTCO1) of Complex IV, resulting in reduced oxidative phosphorylation without alterations in glycolysis. No changes in general activity, anxiety or basic learning and memory were noted in *Cox10* cKO in mice, nor *Cox10* deletion in astrocytes alter acute analgesic effects of morphine. In contrast, *Cox10 cKO* mice exhibited significantly decreased morphine-induced conditioned place preference. In addition, *Cox10 cKO* mice demonstrated significantly increased physical signs of naloxone-precipitated withdrawal and naloxone-precipitated conditioned place aversion (CPA) that was still present in *Cox10 cKO* mice six weeks after cessation of naloxone treatment. This work for the first time shows that astrocyte mitochondria can play a critical role in mediating the behavioral effects of opioids, including aversion produced by opioid withdrawal. Our results suggest that astrocyte bioenergetics could be targeted as treatment for prevention of opioid dependence relapse.