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T3-induced enhancement of mitochondrial Ca2+ uptake as a boost for cellular metabolism

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Thyroid hormones are the main regulators of cellular metabolism, conveying their action via regulation of expression changes. Thereby, the biologically active triiodothyronine (T3) induces the expression of genes to enhance mitochondrial metabolic function. Notably, mitochondrial Ca2+ is essential to the function of Ca2+-dependent matrix dehydrogenases and, thus, mitochondrial respiration. However, just few genes are controlled in their expression by thyroid hormones, among others the uncoupling proteins 2 and 3 (UCP2/3). The biologically T3 induces upregulation of UCP2/3 in various cell types. In the current study, we studied the impact of T3 on [Ca2+]mito homeostasis. T3 induced a significant upregulation in mRNA expression of UCP2 and UCP3 and of protein arginine methyltransferase 1 (PRMT1) in HeLa cells after 3 h. Live-cell imaging in HeLa cells expressing mitochondrial-targeted Ca2+ biosensors revealed that short-time incubation (3 h) with T3 elevates basal [Ca2+]mito and causes increased [Ca2+]mito uptake upon Ca2+ depletion of the endoplasmic reticulum (ER), while cytosolic Ca2+ levels remained unchanged. Also T3-induced enhancement of mitochondrial Ca2+ uptake depends on the mitochondrial Ca2+ uniporter (MCU), UCP2, and PRMT1 that are essential for increased mitochondrial ATP ([ATP]mito) production after T3 treatment. T3's impact on [Ca2+]mito correlates with the expression and activity of UCP2, MCU und PRMT1 and translates into increased [ATP]mito. Increases in mitochondrial ATP and [Ca2+]mito supply the production of reactive oxygen species (ROS). We revealed that enhanced mitochondrial Ca2+ uptake is essential to elevate mitochondrial ROS production after 3 h of T3 incubation. These results suggest that mitochondrial Ca2+ homeostasis is essential for the role of T3 in controlling metabolic activity.