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Thyroid hormone action in mitochondria

C Wrutniak-Cabello [1], F Casas, G Cabello

Affiliations

Affiliation

1 UMR Différenciation Cellulaire et Croissance (INRA, Université Montpellier II, ENSAM), Unité d'Endocrinologie Cellulaire, INRA, 2 Place Viala, 34060 Montpellier Cedex 1, France.

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Abstract

Triiodothyronine (T3) is considered a major regulator of mitochondrial activity. In this review, we show evidence of the existence of a direct T3 mitochondrial pathway, and try to clarify the respective importance of the nuclear and mitochondrial pathways for organelle activity. Numerous studies have reported short-term and delayed T3 stimulation of mitochondrial oxygen consumption. Convincing data indicate that an early influence occurs through an extra-nuclear mechanism insensitive to inhibitors of protein synthesis. Although it has been shown that diiodothyronines could actually be T3 mediators of this short-term influence, the detection of specific T3-binding sites, probably corresponding to a 28 kDa c-Erb Aalpha1 protein of the inner membrane, also supports a direct T3 influence. The more delayed influence of thyroid hormone upon mitochondrial respiration probably results from mechanisms elicited at the nuclear level, including changes in phospholipid turnover and stimulation of uncoupling protein expression, leading to an increased inner membrane proton leak. However, the involvement of a direct mitochondrial T3 pathway leading to a rapid stimulation of mitochondrial protein synthesis has to be considered. Both pathways are obviously involved in the T3 stimulation of mitochondrial genome transcription. First, a 43 kDa c-Erb Aalpha1 protein located in the mitochondrial matrix (p43), acting as a potent T3-dependent transcription factor of the mitochondrial genome, induces early stimulation of organelle transcription. In addition, T3 increases mitochondrial TFA expression, a mitochondrial transcription factor encoded by a nuclear gene. Similarly, the stimulation of mitochondriogenesis by thyroid hormone probably involves both pathways. In particular, the c-erb Aalpha gene simultaneously encodes a nuclear and a mitochondrial T3 receptor (p43), thus ensuring coordination of the expression of the mitochondrial genome and of nuclear genes encoding mitochondrial proteins. Recent studies concerning the physiological importance of the direct mitochondrial T3 pathway involving p43 led to the conclusion that it is not only involved in the regulation of fuel metabolism, but also in the regulation of cell differentiation. As the processes leading to or resulting from differentiation are energy-consuming, p43 coordination of metabolism and differentiation could be of significant importance in the regulation of development.

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