

Tata J R, Ernster L, Lindberg O, Arrhenius E, Pedersen S & Hedman R.

The action of thyroid hormones at the cell level. *Biochemical J.* 86:408-28, 1963.
[Wenner-Gren Institute. University of Stockholm. Sweden]

A simultaneous analysis of mitochondrial respiration and phosphorylation, protein synthesis by ribosomes, and cytosolic enzymes of rat liver and muscle disproved the then widely accepted hypothesis that thyroid hormones regulated basal metabolic rate by uncoupling oxidative phosphorylation. Instead, this work provided a novel explanation, now firmly established, that all *physiological* actions of thyroid hormones are mediated via a selective regulation of synthesis of cellular proteins. [The *SCI*® indicates that this paper has been cited in over 490 publications.]

Thyroid Dogma Disputed

Jamshed R. Tata
Medical Research Council
National Institute for Medical Research
Mill Hill
London NW7 1AA
England

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In the early 1960s it was widely believed that the thyroid hormones, L-thyroxine (T4) and triiodo-L-thyronine (T3), regulated metabolic activity by uncoupling oxidative phosphorylation or directly interacting with one of the components of the respiratory chain. This paper challenged that concept and suggested an alternative explanation that has stood the test of time.¹

As a young postdoc in 1959, then at the National Institute for Medical Research, Mill Hill, England, I met Lars Ernster at a joint meeting of British and Scandinavian Biochemical Societies in Turku, Finland. He described the action of several uncoupling agents including dinitrophenol and thyroxine in terms of their interaction with mitochondria at different steps of the oxidative phosphorylation pathway. I suggested that there was something odd that

a hormone that controls both growth and basal metabolic rate (BMR) should act in this manner, whereupon Ernster asked me to seek an alternative explanation in his laboratory at the Wenner-Gren Institute in Stockholm. Using relatively small, near-physiological doses of the two thyroid hormones (in some cases 1,000 times less than previously used!), which promoted growth and elevated BMR, we followed as a function of time the reversal by hormone administration of the effects of thyroidectomy in young rats. For the first time, we measured simultaneously oxidative phosphorylation, the levels of individual dehydrogenases, ATPase, cytochromes, and cytochrome oxidase in mitochondria from both liver and muscle as well as various steps of protein synthesis *in vitro* and also the activity of several cytosolic enzymes. The results were unequivocal. The metabolic activity of thyroid hormone could not be explained by a disruption of mitochondrial structure and function. Instead the increase in oxygen consumption and growth by thyroid hormones could best be explained by a selective increase in mitochondrial enzymes via a selective control of protein synthesis.

The above conclusion was contrary to the accepted dogma of thyroid hormone action, especially as such top biochemists of the early 1960s as Lipmann, Martius, Lehninger, and Lardy had expounded it. Fortunately, evidence supporting the idea of thyroid hormones as regulators of ATP generation by controlling protein synthesis was not long in coming. Upon my return to Mill Hill, I soon showed that inhibitors of protein and nucleic acid synthesis blocked both the calorogenic and metabolic actions of thyroid hormones.² The timing of this observation was particularly propitious as it enabled C.C. Widnell and me to show that thyroid hormones acted via transcriptional control,³ a general mechanism underlying the action of all growth and developmental hormones.^{4,5}

Looking back, it gives me particular pleasure to see that conclusions that went against the then current dogma of hormone action were first published in a nontrendy journal. I am convinced that luck and good timing had something to do with this.

1. Tata J R. Biological action of thyroid hormones at the cellular and molecular levels. (Litwack G & Kritchevsky D, eds.) *Actions of hormones on molecular processes*. New York: Wiley, 1964. p. 58-131. (Cited 235 times.)
2. ———. Inhibition of the biological action of thyroid hormones by actinomycin D and puromycin. *Nature* 197:1167-8, 1963. (Cited 145 times.)
3. Tata J R & Widnell C C. Ribonucleic acid synthesis during the early action of thyroid hormones. *Biochemical J.* 98:604-20, 1966. (Cited 440 times.)
4. Tata J R. The action of growth and developmental hormones. (Goldberger R F & Yamamoto K R, eds.) *Biological regulation and development*. New York: Plenum Press, 1983. Vol. 3B. p. 1-58.
5. ———. The search for the mechanism of hormone action. *Perspect. Biol. Med.* 29:S185-S204, 1986.

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