DIFFERENTIAL ACTION OF THYROID HORMONES ON ENZYME LEVELS OF THE DPN AND TPN SPECIFIC ISOCITRATE DEHYDROGENASE

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Analysis of mitochondrial enzyme patterns in relation to the thyroid state has shown that thyroid hormones induce enzymes specialized in oxidative, energy-yielding (catabolic) processes (Drabkin, 1950; Maley, 1957; Lee et al., 1959; Kadenbach et al., 1963; Kadenbach and Klingenberg, in preparation), and repress enzymes of the synthetic, energy consuming (anabolic) pathways (Kadenbach et al., 1963; Kadenbach and Klingenberg, in preparation). The functional separation of catabolic and anabolic pathways was recently again recognized at the step of isocitrate dehydrogenation (Goebell and Klingenberg 1963 a,b). Here a unique example is afforded, since one common metabolic step, the oxidative decarboxylation of d-isocitrate to α-ketoglutarate, is conducted via the DPN system for the catabolic purpose and via the TPN system for the anabolic one.

This paper describes the induction of DPN-specific isocitrate dehydrogenase (D-IDH) and a simultaneous depression of the TPN-specific isocitrate dehydrogenase (T-IDH) in mitochondria from different tissues of the rat under the influence of thyroid hormones in vivo. With this finding further evidence is provided for the action of thyroid hormones in promoting the catabolic and repressing the anabolic pathways as well as for the specific roles of D-IDH and T-IDH in catabolism and anabolism.

Methods

Mitochondria were prepared from the tissues of two rats. Extracts were prepared and the enzyme activities estimated as

described elsewhere for the D-IDH (Goebell and Klingenberg, 1963c) and for the T-IDH by Delbrück et al. (1959). The TPN content (sum of TPN and TPNH) in mitochondria was determined by the procedure of Klingenberg and Slenczka (1959). The cytochrome a content was measured by absorption spectrophotometry in intact mitochondria (Schollmeyer and Klingenberg, 1962).

Results

In figure 1 the activities of mitochondrial D-IDH and T-IDH are given for several tissues in various thyroid states in the rat. In the mitochondria of all tissues tested, with the exception of brain, hyperthyroidism causes an increase of the activity of D-IDH whereas the T-IDH decreases. In hypothyroidism the effects are opposite; the D-IDH diminishes and the T-IDH is elevated. The effects are most pronounced in liver where the enzyme activities of the D-IDH rises about 4-fold and the T-IDH decreases to 1/3 progressing from the hypo- to the hyperthyroid state. Appreciable effects are also demonstrated in skeletal muscle, kidney and heart, whereas no effects are observed in brain.

Figure 2 demonstrates the percentage increase or decrease in hyper- and hypothyroidism compared to the normal values of D-IDH and T-IDH. The figure also shows the changes in the content of TPN and of cytochrome a in mitochondria as compared with the normal level. The cytochrome a content gives a measure of the oxidative capacity of mitochondria. The TPN content has been regarded as a measure of the synthetic activity of mitochondria (Klingenberg, 1963). The D-IDH activity changes in the same direction as the cytochrome a content. Both the activity of the T-IDH and the TPN content change in the opposite direction.

Discussion

The presented results concerning the influence of thyroid hormone level on the activities of DPN- and TPN specific isocitrate dehydrogenases are of interest not only in elucidating the mechanism of thyroid action but they also may afford an example of the control of enzyme induction and repression by the metabolic state in general. The conclusion that thyroid hormones induce catabolic (oxidative) processes has been drawn from the increase of oxidative enzymes such as succinate

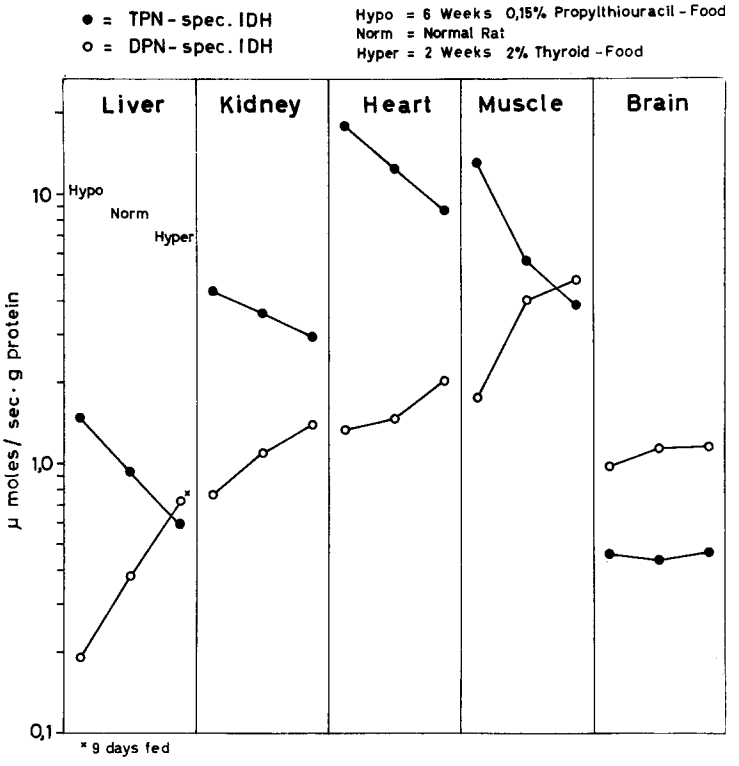

Figure 1

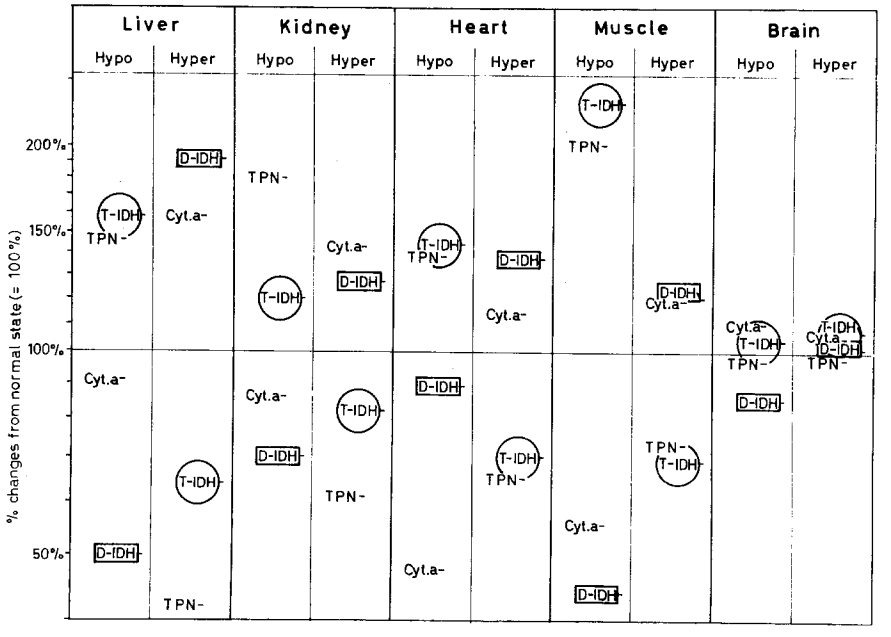

Figure 2

dehydrogenase, α-glycerophosphate oxidase and cytochromes b, c and a (Kadenbach and Klingenberg, in preparation). The repression of synthetic pathways by thyroid hormones is deduced mainly from the very strong decrease of the TPN content in mitochondria. These views on the action mode of thyroid hormones receive further support from the finding that these hormones decrease the T-IDH whereas the D-IDH is elevated. Thus, a hormonal regulation of metabolism is demonstrated simultaneously by opposite alteration of the enzyme activities according to the catabolic and anabolic requirements.

An analogous case to the isocitrate dehydrogenases is the couple of DPN and TPN specific glutamate dehydrogenases described in Neurospora crassa (Sanwal and Lata, 1962) and yeast (Holzer and Hierholzer, 1963). Here the simultaneous repression and induction of the two dehydrogenases in response to the glutamate or NH_4^+ concentration offered has been reported.

The induction of D-IDH illustrates that enzyme induction or repression can be understood only when the exact role of the enzyme in metabolism is known. Thus the induction of D-IDH under the influence of thyroid hormones is in contrast to the depression of the activity of other DPN-linked dehydrogenases such as the malate dehydrogenase (Kadenbach and Klingenberg, in preparation). This can be understood on the assumption that D-IDH is a regulatory enzyme, since it is activated by ADP (Goebell and Klingenberg, 1963 c). Therefore D-IDH acts in a nonequilibrium step, whereas malate dehydrogenase establishes an equilibrium (Hohorst, Kreutz and Bücher, 1959). The metabolic step controlled by D-IDH activity could be rate limiting in the citric acid cycle and therefore should increase when the metabolic rate is elevated. In contrast, the equilibrium step as catalyzed by malate dehydrogenase would not limit the metabolic flow rate even on a certain decrease of enzyme activity.

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