The Metabolism and Function of Dehydroepiandrosterone

Henry A. Lardy*, Padma Marwah, and Ashok Marwah, Department of Biochemistry, University of Wisconsin, Madison, Wisconsin, 53726, USA

The mitochondrial electron transport system oxidizes NADH and the energy liberated is captured in the formation of three equivalents of ATP from ADP and inorganic phosphate. In 1958 two groups (Bücher and Estabrook) reported that insect muscle oxidized NADH by a path that skipped the first phosphorylation step. Naturally, that would result in the energy not captured as ATP to be released as heat. The thyroid hormone is highly thermogenic and we found it to increase the Bücher system 20-fold in rat liver.

Dehydroepiandrosterone (DHEA), the most abundant steroid in the human body is also thermogenic and it also induces the Bücher system. The induction of mitochondrial glycerophosphate dehydrogenase serves as a good assay for activity of DHEA and its metabolites. Using that assay we established that DHEA is converted metabolically to 7α hydroxy DHEA then to 7-oxo DHEA which is reduced to 7-β-hydroxy DHEA and the latter is hydroxylated to form 7-β-16α-dihydroxy DHEA. These steroids exhibit increased activity (enzyme induction, memory restoration) as they undergo these sequential changes.

7-oxo DHEA is non-toxic to rats, mice, monkeys, and humans. It restores memory in old mice and causes weight loss in obese animals and humans. Another product of DHEA metabolism is androstenediol (A-diol) DHEA in which the 17-keto is reduced to 17-β-hydroxy. A-diol was known to have weak estrogen activity but in 1998 we found it to be a full-blown androgen that did not require structural alteration to become active. Most importantly we found that A-diol's androgenic activity was not inhibited by the anti-testosterone compounds that are currently used to treat prostate cancer. We proposed that A-diol was supporting prostate cancer growth in the so-called "androgen-independent" stage that is fatal.

Our postulate has been confirmed by Japanese clinicians who found that androstenediol is concentrated in the prostate when the cancer no longer responds to anti-testosterone agents.