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Defects in Hepatic Mitochondrial F_1F_0ATPase of the NIDDM-prone BHE/cdb rat

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The BHE/cdb rat is a specific strain of rat that mimics the human who develops impaired glucose tolerance and then non-insulin dependent diabetes mellitus (NIDDM) with age. Detailed studies of BHE/cdb rat compared to Sprague Dawley rat have shown that hepatic gluconeogenesis and lipogenesis are increased in BHE/cdb rat fed an unrefined diet and these processes are further increased when an energy-rich refined diet is fed. One of the challenges in working with this rat stock has been the detection the genetic error. Recent studies have shown that a mitochondrial DNA (mtDNA) mutation exists in the BHE/cdb rat. The hepatic mtDNA has a base substitution in the area that codes for subunit 6 of the F_1F_0ATPase. The inferred amino acid substitution in F_0 moiety could have an effect on the functional characteristics of F_1F_0ATPase that likely can explain the characteristics of the BHE/cdb rat.

The functional assessment of F_1F_0ATPase from BHE/cdb and Sprague Dawley rats was studied.. The responsiveness of hepatic mitochondria isolated from hyperthyroid and control Sprague Dawley and BHE/cdb rats were performed. Hyperthyroidism was induced through the addition of thyroxine (T_4) to the diet (2mg/kg of diet). Oxidative phosphorylation with the addition of ADP was studied by polarographic measurement. Dose response curves of state 3 and state 4 respiration, respiratory control (RC) ratio and ADP:O ratio to calcium levels (0 to 400 nmole/mg of mitochondrial protein) were generated. Mitochondria from BHE/cdb rats were more sensitive to calcium addition than mitochondria from SD rats. Thyroxine treatment potentiated this strain difference. The differences in the state 4 respiration, the respiratory control (RC) values, and the ADP:O ratios showed that the thyroxine-treated BHE/cdb rats were more uncoupled and less efficient with respects to aberrant F_1F_0ATPase.

What was unique in this work was the evidence of a strain differences in functional F_1F_0ATPase which showed that the BHE/cdb rat had a combined defect in the proton conductance and coupling of ATP synthesis. This study suggests that the defects in F_1F_0ATPase due to mtDNA mutation could have relevance to the development of glucose intolerance and subsequent degenerative disease.