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Effects of Dietary Fat on Mitochondrial Composition and Function in the NIDDM-Prone Rat

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The BHE/Cdb rat is an animal that mimics human NIDDM. It develops moderate hyperglycemia and impaired glucose tolerance as it ages as well as a number of diabetic complications. Along with these metabolic features is a decrease in efficiency of ATP synthesis. Recent studies have shown that mtDNA mutation exists in the BHE/Cdb rat. The hepatic mtDNA has a base substitution at position 523 in the area that codes for subunit 6 of the F_1F_0ATPase. This mutation effects on proton conductance and efficiency of ATP synthesis. Although there is a strong genetic element, NIDDM has a multifactorial etiology in which environmental factors like diet are important modifiers. In addition, mitochondria have a dual bilayer membrane structure that surrounds the OXPHOS system. The lipids in these membranes serve to regulate the activity of the membrane bound components. Thus, the fluidity of the lipid bilayer is a modifying factor in the synthesis of ATP using the energy of the proton gradient developed by the respiratory chain. One might anticipate a change in the lipid composition of membranes by diet. Such a change in lipid composition of the mitochondrial membrane could alter the properties of the membrane bound components. It is thus speculated that the composition of the phospholipids present in the membrane could have had an effect on the regulation of OXPHOS. To answer this question, it was studied OXPHOS by isolated mitochondria from BHE/Cdb rats fed a 6% coconut oil or corn oil diet in the presence of graded levels of added calcium. It was also determined F_1F_0ATPase activity and the fatty acid composition of the mitochondria. The coconut oil diet fed to the BHE/Cdb rat potentiated this rat's genetic tendency for mitochondrial dysfunction by altering the lipid milieu. The rats fed coconut oil had more saturated phospholipid fatty acids than rats fed corn oil. While no differences in ATPase activity was observed between mitochondria from rats fed coconut oil and rats fed corn oil, there was a marked differences in regulation of OXPHOS. Perturbation of the membrane lipid through the feeding of hydrogenated coconut oil affected mitochondrial coupling. The differences in the state 4 respiration, the respiratory control (RC) values, and the ADP/O ratios showed that the rats fed coconut oil were more uncoupled and less efficient with respect to mitochondrial ATP synthesis than the rats fed corn oil. This was manifested as an increased responsive to calcium. Mitochondria from rats fed coconut oil were more

sensitive to calcium addition as judged by losses in OXPHOS than mitochondria from rats fed corn oil. The present results lead to conclusion that the lipid milieu can be manipulated by diet by so doing, and understanding of the importance of the lipid milieu in regulation of OXPHOS in these animals predestined to develop NIDDM can be gained.