

EFFECTS OF CALORIE RESTRICTION ON MITOCHONDRIAL FUNCTION

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Oxidative stress resulting from a gradual shift in the redox status of tissues is thought to be an important mechanism underlying the aging process. Calorie restricted (CR) feeding that extends survival in rodents is recognized to slow the rate of accrual of age-related oxidative stress. It not fully understood how this is achieved but it has been proposed that mitochondria play a pivotal in the aging process, for these organelles are considered to be the main producers of reactive oxygen species (ROS). In a study of mitochondria isolated from a range of tissues of BN male rats maintained on 55% control food intake from 2 months of age, a significant reduction in ROS generation was observed. This effect was seen for a range of tissues at all ages studied. However, no depression in mitochondrial respiration rate during either non-phosphorylating or phosphorylating respiration was induced by CR feeding, indeed a significant increase in the rate of respiration was observed in brown fat mitochondria. Therefore the depression in mitochondrial ROS generation is not considered to be a simple rate effect. To identify the functional mechanism underlying the reduced ROS generation, detailed studies of mitochondrial bioenergetics have been completed. An increase in the proton leak of the inner mitochondrial membrane was maintained throughout the life span of CR rats that was associated with a 10-15% decrease in the membrane potential maintained under state 4 respiration conditions. Re-feeding, or an elevation of circulating plasma insulin concentrations prior to mitochondrial isolation in CR animals decreased the proton leak rate. The enhanced proton conductance in CR animals could not be explained by a modification of the lipid composition of the mitochondrial membrane. It may reflect changes in the surface area of the inner mitochondria membrane and/or transporter activity, such as the adenine nucleotide translocator.