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CHRONIC VITAMIN E SUPPLEMENTATION: EFFECT ON SURVIVAL, NEUROLOGICAL PERFORMANCE, OXIDATIVE STRESS, AND MITOCHONDRIAL MARKERS OF AGING

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Vitamin E supplementation (4.3 g d,l-α-tocopherol acetate/kg of mice food) from 28 wk of age to the end of male mice lives increased 25% and 20 % median and maximal lifespan. The used level of vitamin E in the diet corresponds to a daily intake of about 10 mg vitamin E/mouse. The neurological performance, tightrope and T-maze tests, was highly improved in aged mice supplemented with vitamin E. Brain and liver mitochondria were isolated and submitochondrial particles were prepared from young and old male mice. Chronic treatment with vitamin E prevented the aging-associated mitochondrial changes: 1) decreased oxidative stress markers, such as protein carbonyl and TBARS contents; 2) prevented the aging-associated decline in mitochondrial membrane enzyme activities: NADH-dehydrogenase, cytochrome oxidase, and mitochondrial nitric oxide synthase. The retard in the decline of brain mitochondrial enzyme activities observed in mice supplemented with vitamin E is correlated with both an increased mice survival and an improved quality of behavior with better neuromuscular and exploratory performances. Chronic vitamin E supplementation prevented neurological impairments associated to aging and increased mice lifespan. The effects are likely to lye on a molecular mechanism given by a decreased oxidative stress that retards the age-associated loss of mitochondrial functions.

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USING DNA MICROARRAYS TO INVESTIGATE THE IMPACT OF ANTIOXIDANTS AND CALORIC RESTRICTION ON THE AGING PROCESS IN THE HEART

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We evaluated the efficacy of three dietary interventions started at middle age to retard the aging process in mice. These were supplemental α-lipoic acid (LA) or coenzyme Q10 (CQ) and caloric restriction (CR, a positive control). LA and CQ had no impact on longevity or tumor patterns compared to control mice fed the same number of calories, whereas CR increased maximum lifespan by 13% ($p < 0.0001$) and reduced tumor incidence. To evaluate these interventions at the molecular level, we used microarrays to monitor the expression of 9,977 genes in hearts from young and old (30-month-old) mice. LA, CQ and CR inhibited age-related alterations in the expression of genes involved in the extracellular matrix, cellular structure, and protein turnover. However, unlike CR, LA and CQ did not prevent age-related transcriptional alterations associated with energy metabolism. LA supplementation lowered the expression of genes encoding major histocompatibility complex (MHC) components and of genes involved in protein turnover and folding. CQ increased expression of genes involved in oxidative phosphorylation and reduced expression of genes involved in the complement pathway and several aspects of protein function. Our observations suggest that supplementation with LA or CQ results in transcriptional alterations consistent with a state of reduced oxidative stress in the heart, but that these dietary interventions are not as effective as CR in inhibiting the aging process in the heart.

S15-82

LOSARTAN AMELIORATES RENAL MITOCHONDRIAL DYSFUNCTION IN STREPTOZOTOCIN-INDUCED DIABETES AND IN AGING

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To test whether antihypertensive drugs could attenuate kidney mitochondrial dysfunction in diabetes, 32 Sprague-Dawley rats were divided into groups: STZ (65 mg streptozotocin/kg, IP); CON (saline, IP); STZ+Los, (streptozotocin IP and 30 mg losartan/kg/d in drinking water); STZ+Am (streptozotocin IP and 3 mg amlodipine/kg/d in drinking water). Losartan and amlodipine treatments started 30 d prior to streptozotocin, and lasted 4-mo. Blood pressure was higher in STZ than in the other groups; glycemia was higher in STZ, STZ+Los, and STZ+Am than in CON. Kidney mitochondria H_2O_2 production in STZ and STZ+Am was 23% higher than in STZ+Los and CON, resting state membrane potential, and Mn-SOD were higher in STZ than in the other groups. In STZ and STZ+Los, mtNOS activity was 75% and 96% lower than in CON. In STZ+Am, mtNOS activity was 3.5 times higher than in CON. Mitochondrial piruvate in STZ was 5-times higher than in CON; and about 50% higher than in STZ+Los and STZ+Am. In STZ, STZ+Am, and STZ+Los, kidney GSH was 91% , 74% and 30% lower than in CON, respectively. In CON, STZ+Los, and STZ+Am, GSH/GSSG was 17-times higher than in STZ. Results in streptozotocin-induced diabetes suggest associations between mitochondrial function and angiotensin-II receptor inhibition; and between piruvate overproduction and mitochondrial oxidant generation. Supported with grants to CGF from University of Buenos Aires (B042), ANPCYT (PICT-01-08951), and CONICET (0738/98).