that tissue glycine depletion is a common feature of healthy aging. Supplementation of old mice with glycine efficiently improved age-related decline of mitochondrial respiratory function in skeletal muscle and prevented a gene program associated with protein catabolism observed in control-treated animals. In conclusion, GlyNAC is safe and well-tolerated and may selectively increase glutathione levels in older subjects with oxidative stress and glutathione demand. Our data further suggest that glycine may support mitochondrial function independently of NAC.

LOSS OF ISCHEMIC TOLERANCE WITH AGE: CAN WE PROTECT AN OLD KIDNEY

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The most abundant and vulnerable cohort of patients with acute kidney injury (AKI) is represented by the older people. It is well-known, the kidney tissue undergoes some changes with age, both at the morphological and molecular level. Therefore, when treating AKI in older patients, it is necessary to take into account the morphofunctional features of aging kidney tissue and metabolic alterations. We have shown that the kidney of old rats does not perceive signals from the most well-known protective approaches such as ischemic preconditioning (IPC) and caloric restriction (CR). Although the old kidney did not develop more severe AKI after ischemia, we found no pronounced effect on attempts to increase its resistance by IPC and CR. Analysis of the mechanisms underlying this loss of tolerance has shown that the most affected pathways are the mechanism of mitochondrial quality control, the effectiveness of autophagy, and the proliferative potential of kidney cells. However, several protective pathways activated in the young kidney were also active in the old one in response to the CR. In particular, an increase in SIRT1 deacetylase, antiapoptotic Bcl-xL, and a decrease in oxidative stress were observed. Our results show that some defense systems demonstrating their effectiveness in young organisms lose their beneficial effect in old organisms, while others still can be activated by protective approaches. Thus, it is necessary to carefully analyze the possibilities of increasing ischemic tolerance for old organisms. This work was supported by the Russian science foundation (grant #21-75-30009).

METFORMIN PRESERVES MITOCHONDRIAL INTEGRITY AT OLD AGE IN MALE RATS.

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Metformin is being deployed in clinical trials to ameliorate aging in older humans who do not have diabetes. In C. elegans, metformin treatment at old ages exacerbated mitochondrial dysfunction, led to respiratory failure, and shortened lifespan. Metformin is a commonly used, well-tolerated treatment for diabetes in older adults. Mitochondrial effects of metformin treatment in aged mammals has not been sufficiently investigated. We hypothesized that metformin treatment would not be toxic to older mammals. To define a therapeutic dose in aged hybrid rats, we evaluated two doses of metformin (0.1%, 0.75% of the diet) at 30-months of age. Body mass decreased at the 0.75% dose. Neither dose affected mortality between 30- and 34-months of age. We assessed mitochondrial quality, quantity, and function in aged rats treated with metformin at the 0.75% dose by measuring mitochondrial DNA copy number, deletion mutation frequency, and respirometry in skeletal muscle and heart. In skeletal muscle, we observed no effect of metformin on quadriceps mass, mtDNA copy number or deletion frequency. In the heart, metformin treated rats had higher mtDNA copy number, lower cardiac mass and no effect on deletion frequency. Metformin treatment resulted in lower mitochondrial complex I activity in both heart and quadriceps. Metformin did not compromise mitochondrial integrity, was well tolerated, and may have cardiac benefits to rats at old ages.

SUCCESSFUL EXOGENOUS EXPRESSION OF ATP8, A MITOCHONDRIAL ENCODED PROTEIN, FROM THE NUCLEUS IN VIVO.

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Replicative errors, inefficient repair, and proximity to reactive oxygen species production sites make the mitochondrial DNA (mtDNA) susceptible to damage with time. mtDNA mutations accumulate with age and accompany a progressive decline in organelle function. We lack molecular biology tools to manipulate mtDNA, thus we explore the possibility in vivo of utilizing allotopic expression, or the re-engineering mitochondrial genes and expressing them from the nucleus, as an approach to rescue defects arising from mtDNA mutations. This study uses a mouse model with a mutation in the mitochondrial ATP8 gene that encodes a protein subunit of the ATP synthase. We generated a transgenic mouse with an epitope-tagged recoded and mitochondrial-targeted ATP8 gene expressed from the nucleus. Our results show that the allotopically expressed ATP8 protein in the transgenic mice is robustly expressed across all tested tissues, successfully transported into the mitochondria, and incorporated into ATP synthase. We are currently evaluating if allotopic expression of ATP8 will functionally rescue the behavioral and bioenergetic defects in ATP8 mutant mice. Translating allotopic expression technology into a mammal and demonstrating systemic functional rescue will lend credence to utilizing allotopic expression as a gene therapy in humans to repair physiological consequences of mtDNA defects that may accumulate with age.

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CANCER AND AGING

EXPLORING SPIRITUALITY, LONELINESS AND HRQOL IN HISPANIC CANCER CAREGIVERS

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