at 48 hrs with hydrogen peroxide (10 uM) and examined changes in MALAT1 expression. MALAT1 was significantly decreased with H2O2 treatment, whereas miR-34a is increased in C2C12 cells after hydrogen peroxide exposure. Age-related muscle atrophy mediated by ROS may therefore result in part from related mechanisms involving miR-34a activity: an increase in miR-34a targeting Sirt1 resulting from p53 activation and an increase in miR-34a bioavailability resulting from a decline in miR-34a "sponging" due to ceRNA MALAT1 depletion. These findings suggest that therapeutic interventions increasing MALAT1 expression in muscle may potentially enhance the preservation of muscle mass with aging.

EFFECTS OF GLYCINE AND N-ACETYLCYSTEINE ON GLUTATHIONE LEVELS AND MITOCHONDRIAL ENERGY METABOLISM IN HEALTHY AGING

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Glutathione is an intracellular antioxidant that neutralizes reactive oxygen species and prevents tissue damage. Dietary supplementation with the glutathione precursors glycine and n-acetylcysteine supports the maintenance of normal glutathione levels in several age-related diseases, but the optimal doses and their efficacy in healthy elderly are not established. We report results from a randomized controlled clinical trial in 114 healthy volunteers (mean age = 65 years) receiving glycine and n-acetylcysteine (GlyNAC) at three different doses for two weeks (1.2g/1.2, 2.4g/2.4g, 3.6g/.3.6g of each amino acid). Older subjects showed increased oxidative damage and a lower reduced-to-oxidized glutathione ratio (GSH:GSSG) compared to young subjects, but unchanged total glutathione levels. GlyNAC did not increase levels of circulating glutathione compared to placebo treatment, the primary study endpoint. However, stratification analyses suggest that subjects with high oxidative stress and low glutathione status responded with glutathione generation. We find that unrelated to glutathione status, healthy aging was associated with lower levels of fasting glycine that can be increased towards those observed in young subjects with supplementation. Using preclinical models, we find 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.