discussing mechanisms underlying Glutathione deficiency and validation of a novel nutritional intervention based on supplementing glycine and N-acetylcysteine (GlyNAC) to correct Glutathione deficiency in older-humans. Dr. Sekhar will present the results of a pilot 16-week pilot randomized, placebo-controlled, double-blind clinical trial in older humans investigating the effect of supplementing GlyNAC (vs. placebo) to improve Glutathione levels and oxidative-stress in 24 older-humans and 12 young-humans on impaired mitochondrial fuel-oxidation (MFO) and other defects. The trial met its primary objective that that GlyNAC supplementation (and not placebo) significantly improved Glutathione deficiency and corrected impaired MFO (and defects in its molecular regulation), and also significantly improved gait-speed (increased 19% increase to match young-humans), muscle-strength, exercise-capacity, and lowered oxidative-stress (80%) inflammation (IL-6 83%, TNF-alpha 58%), and insulin-resistance (68%). Dr. Taffet will discuss age-induced diastolic heart failure, and the effect of supplementing GlyNAC (vs. NAC alone) in aged 24-month old mice with diastolic heart-failure, impaired myocardial MFO and cardiac-inflammation. Collectively this symposium on Glutathione and Aging will highlight the discovery that supplementing GlyNAC to correct Glutathione deficiency in older-humans has significant health benefits, and could be a novel nutritional-intervention in aging.

GLUTATHIONE DEFICIENCY AND OXIDATIVE STRESS IN AGING: METABOLIC MECHANISM AND TARGETED INTERVENTION

Farook Jahoor,[1] George E. Taffet,[1] and Rajagopal V. Sekhar[1], *1. Baylor College of Medicine, Houston, Texas, United States*

The free-radical theory of aging suggests that age-related functional decline is mediated by increases in free-radical induced oxidative-stress. Cells normally depend on antioxidants for protection against oxidative-stress. Glutathione is the most abundant endogenous intracellular antioxidant protein composed of 3 amino-acids, cysteine, glycine and glutamic-acid, and is known to be deficient in older-humans. We investigated Glutathione kinetics in older humans using a stable-isotope tracer-based approach, and found that compared to younger humans, older-humans had severe Glutathione deficiency as a result of decreased synthesis caused by limited availability of glycine and cysteine, and associated with elevated oxidative-stress. Orally supplementing glycine and cysteine (provided as N-acetylcysteine) at doses of 1.33mmol/kg/d and 0.81mmol/kg/d respectively for 2-weeks corrected their intracellular deficiency, normalized Glutathione synthesis rates and lowered oxidative-stress to levels in younger controls. These results suggest that short-term supplementation of GlyNAC at these doses can successfully correct intracellular Glutathione deficiency in older-humans.

CORRECTING GLUTATHIONE DEFICIENCY AND MITOCHONDRIAL DYSFUNCTION IN OLDER HUMANS: A RANDOMIZED CLINICAL TRIAL

Rajagopal V. Sekhar,[1] Premranjan Kumar,[1] Jean W. Hsu,[1] James Suliburk,[1] George E. Taffet,[1] Charles G. Minard,[1] Farook Jahoor,[1] and Chun Liu[1], *1. Baylor College of Medicine, Houston, Texas, United States*

Aging is associated with impaired mitochondrial fatty-acid oxidation (MFO) due to unknown mechanisms, and interventions are lacking. We hypothesized that impaired MFO in aging occurs due to Glutathione-deficiency and tested this in a randomized, placebo-controlled double-blind clinical-trial in 24 older-humans (71.1y) and 12 young-controls (25.5y) using calorimetry, muscle-biopsy and tracer-protocols. Older-humans received either GlyNAC (Glycine 1.33mmol/kg/d and N-acetylcysteine 0.83mmol/kg/d as Glutathione precursors) or isonitrogenous-placebo for 16-weeks; young-controls received GlyNAC for 2-weeks. Compared to young-controls, older humans had significantly lower Glutathione, impaired MFO, lower gait-speed and physical-function, and higher oxidative-stress, inflammation and insulin-resistance. GlyNAC supplementation in older-humans significantly improved and restored MFO; increased gait-speed (19%,) and physical-function; and decreased oxidative-stress (TBARS 80%), inflammation (IL-6 83%; TNF-alpha 58%), and insulin-resistance (HOMA-IR 68%), but young-controls were unaffected. These data provide proof-of-concept that GlyNAC supplementation could improve the health of older-humans by correcting Glutathione-deficiency and mitochondrial-defects to improve gait-speed, oxidative-stress, inflammation and insulin-resistance.

GLUTATHIONE, INFLAMMATION, MITOCHONDRIAL FAT OXIDATION AND DIASTOLIC HEART FUNCTION IN OLD MICE

George E. Taffet,[1] K A. Cieslik,[1] R V. Sekhar,[1] Celia A. Pena Heredia,[2] Dale J. Hamilton,[2] and Mark L. Entman[1], *1. Baylor College of Medicine, Houston, Texas, United States, 2. Houston Methodist Hospital, Houston, Texas, United States*

Impaired diastolic function is a risk factor for diastolic heart failure, may limit exercise performance, and is common in aging in both people and animals. This diastolic dysfunction seems to be associated with cardiac inflammation, fibrosis and impaired mitochondrial fatty acid metabolism. Old (24-28 m) mice fed a GlyNAC supplemented diet for 8 weeks were compared to those on control diet, and had dramatic improvement in all these parameters. For example, ATP generation from fatty acids with five-fold higher in the GlyNAC supplemented mice. In vitro studies compared NAC with GlyNAC and demonstrated the benefits only with supplementing both amino acids as compared to NAC alone. These data suggest that GlyNAC may have a role in improving cardiac function thus improving exercise tolerance and quality of life for older people.

SESSION 2200 (SYMPOSIUM)

CREATIVITY IN LATER LIFE: PERSPECTIVES ON ITS FORMS AND MEANINGS

Chair: Carolyn E. Adams-Price, *Department of Psychology Mississippi State University, Starkville, Mississippi, United States*

Discussant: Danielle K. Nadorff, *Mississippi State University, Starkville, Mississippi, United States*

Over the past 15 years, gerontologists have become increasingly interested in identifying activities that increase