(R)-alpha-lipoic acid reverses the age-related loss in GSH redox status

(R)-alpha-lipoic acid reverses the age-related loss in GSH redox status in post-mitotic tissues: evidence for increased cysteine requirement for GSH synthesis

Suh JH, Wang H, Liu RM, Liu J, Hagen TM.
Source

Department of Biochemistry and Biophysics, Linus Pauling Insitute, Oregon State University, USA.
Abstract

Age-related depletion of GSH levels and perturbations in its redox state may be especially deleterious to metabolically active tissues, such as the heart and brain. We examined the extent and the mechanisms underlying the potential age-related changes in cerebral and myocardial GSH status in young and old F344 rats and whether administration of (R)-alpha-lipoic acid (LA) can reverse these changes. Our results show that GSH/GSSG ratios in the aging heart and the brain declined by 58 and 66% relative to young controls, respectively ($p < 0.001$). Despite a consistent loss in GSH redox status in both tissues, only cerebral GSH levels declined with age ($p < 0.001$). To discern the potential mechanisms underlying this differential loss, the levels and the activities of gamma-glutamylcysteine ligase (GCL) and cysteine availability were determined. There were no significant age-related changes in substrate or enzyme levels, or GCL activity when saturating amounts of substrates were provided. However, kinetic analysis of GCL in brains of old rats displayed a significant increase ($p < 0.05$) in the apparent [Km] for cysteine (Km cys) vs. young rats (84.3+/-25.4 vs. 179.0+/-49.0; young and old, respectively), resulting in a 40% loss in apparent catalytic turnover of the enzyme. Thus, the age-related decline in total GSH appears to be mediated, in part, by a general decrement in GCL catalytic efficiency. Treating old rats with LA (40 mg/kg body wt; by i.p.) markedly increased tissue cysteine levels by 54% 12 h following treatment and subsequently restored the cerebral GSH levels. Moreover, LA improved the age-related changes in the tissue GSH/GSSG ratios in both heart and the brain. **These results demonstrate that LA is an effective agent to restore both the age-associated decline in thiol redox ratio as well as increase cerebral GSH levels that otherwise decline with age.**