Glutathione Metabolism during Aging and in Alzheimer Disease

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ABSTRACT: The concentration of glutathione (GSH), the most abundant intracellular nonprotein thiol and important antioxidant, declines with age and in some age-related diseases. The underlying mechanism, however, is not clear. The previous studies from our laboratory showed that the age-dependent decline in GSH content in Fisher 344 rats was associated with a downregulation of glutamate cysteine ligase (GCL), the rate-limiting enzyme in *de novo* GSH synthesis. Our recent studies further indicated that the activity and mRNA content of glutathione synthase (GS), which catalyzes the second reaction in *de novo* GSH synthesis, were also decreased with age in some tissues. No age-associated change was observed in glutathione reductase or γ-glutamyl transpeptidase activities. Also, although GSH content declined with age in both male and female mice, male mice experienced more dramatic age-associated decline in many tissues/organs than female mice. Furthermore, we found that GSH content was significantly decreased in the red blood cells from male Alzheimer disease patients, which was associated with decreases in GCL and GS activities. Finally, we showed that estrogen increased GSH content, GS and GR activities, and GCL gene expression in the liver of both male and female mice. Taken together, our results suggest that (1) GCL plays a critical role in maintaining GSH homeostasis under both physiological and pathological conditions; (2) decreased GSH content may be involved in AD pathology in humans; and (3) estrogen increases GSH content in mice by multiple mechanisms.

KEYWORDS: glutathione; aging; gender; glutamate cysteine ligase; γ-glutamylcysteine synthetase; Alzheimer disease; estrogen

The mechanism underlying aging, an inevitable biological process that affects most living organisms, is still an area of significant controversy and so is the mechanism for neurodegenerative diseases. Reactive oxygen species (ROS), generated endogenously or exogenously, cause damages to DNA, RNA, lipids, and proteins. Accumu-

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