Review

Elevation of glutathione as a therapeutic strategy in Alzheimer disease ☆

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a r t i c l e i n f o

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a b s t r a c t

Oxidative stress has been associated with the onset and progression of mild cognitive impairment (MCI) and Alzheimer disease (AD). AD and MCI brain and plasma display extensive oxidative stress as indexed by protein oxidation, lipid peroxidation, free radical formation, DNA oxidation, and decreased antioxidants. The most abundant endogenous antioxidant, glutathione, plays a significant role in combating oxidative stress. The ratio of oxidized to reduced glutathione is utilized as a measure of intensity of oxidative stress. Antioxidants have long been considered as an approach to slow down AD progression. In this review, we focus on the elevation on glutathione through N-acetyl-cysteine (NAC) and γ-glutamylcysteine ethyl ester (GCEE) as a potential therapeutic approach for Alzheimer disease. This article is part of a Special Issue entitled: Antioxidants and Antioxidant Treatment in Disease.

1. [illegible]

Alzheimer disease (AD) is a largely sporadic, age-related neurode-

Thus, glutathione-S-conjugates are not readily formed or exported, possibly increasing HNE levels in the cell [16].

Post-translational modification of proteins by glutathionylation is re-

from starting the therapies in the late stages of AD, not monitoring drug levels and markers for the in vivo therapeutic effect of the drug, not utilizing a multi-antioxidant approach that covers both lipophilic and hydrophilic areas of the cell or recycle the oxidized antioxidants back to the reduced state, and not taking into account the basal redox status of the subjects in the trials [10,73,74]. These limitations must be taken into consideration when determining if an antioxidant therapy would be beneficial in slow or preventing the progression of MCI and AD.

4. γ- ( )

Another effective means for increasing biosynthesis of GSH is GCEE (Fig. 5) [75]. γ-Glutamylcysteine formation is the rate-limiting step for the biosynthesis of GSH. Providing γ-glutamylcysteine bypasses the feed-back inhibition by GSH on γ-glutamylcysteine synthetase (GCS), the enzyme that catalyzes production of γ-glutamylcysteine. Attachment of an ethyl ester moiety allows γ-glutamylcysteine to more easily cross the cell membrane and blood–brain barrier (BBB). Protection against myocardial ischemic–reperfusion and myocardial dysfunction in Se-deficient rats was afforded by GCEE [76,77]. GCEE is able to increase brain and mitochondrial GSH levels and protect synaptosomes, neuronal cells, and mitochondria against peroxynitrite damage [78,79]. Neuronal cells were also protected against Aβ(1–42)-induced protein oxidation, loss of mitochondrial function, and DNA fragmentaion by GCEE upregulation of GSH. GCEE did not, however, disrupt Aβ(1–42) fibril formation [80,81]. Aβ(1–42) is known to deplete GSH cellular levels which can lead to neuronal death. However, 24 h after Aβ(1–42) addition, GSH and GCS levels increase intracellularly, offering protection against Aβ(1–42)-induced apoptosis in cortical neurons [82–84]. Recently, i.p. injections of GCEE protected against kainic acid induced ROS and downregulated c-fos mRNA in the cortex and hippocampus of rats [85]. GCEE may react di-

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