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TITLE

Therapeutic Potential and Anti-amyloidosis Mechanisms of Tert-butylhydroquinone for Alzheimer's Disease

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Alzheimer's disease (AD) is a major cause of dementia in the elderly with no effective treatment. Accumulation of amyloid beta peptide (Aβ) in the brain, one of the pathological features of AD, is considered to be a central disease-causing and disease-promoting event in AD. In this study, we show that feeding male APP/PS1 transgenic mice, a well-established mouse model of AD, with a diet containing phenolic antioxidant tert-butylhydroquinone (TBHQ)for 6 weeks increased the concentration of glutathione (GSH), an important antioxidant, and suppressed the expression of NADPH oxidase 2 (Nox2) as well as lipid peroxidation in the brain. Most importantly, we show that TBHQ diet dramatically reduced brain Aβload, which was associated with inhibition of the expression of plasminogen activator inhibitor-1 (PAI-1), a redox sensitive protease inhibitor which plays a critical role in brain Aβ accumulation in AD. This was accompanied by increases in the activities of tissue type and urokinase type plasminogen activators (tPA and uPA) as well as plasmin. Moreover, we show that TBHQ diet increased the expression of low density lipoprotein related protein-1 (LRP-1), a multi ligand endocytotic receptor involved in transportingAβ out of the brain, and plasma Aβ40 and Aβ42 levels. No significant effect of TBHQ diet on the amounts of alpha- and beta-C-terminal fragmentsor full-length APP was detected. Collectively, our data suggest that TBHQ may have therapeutic potential for AD through increasing brain antioxidant capacity/reducing oxidative stress level, which leads to inhibition of PAI-1 expression and thereby stimulation of Aβ degradation/clearance from the brain