Low Dose Pioglitazone Attenuates Oxidative Damage in Early Alzheimer’s Disease by Binding mitoNEET: Transcriptome-To-Reactome™ Biosimulation of Neurons

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ABSTRACT

Oxidative damage (OD) is considered to be a central component in the progression of Alzheimer’s disease (AD). 8-hydroxyguanosine (8-OHG), a readily oxidized ribonucleic acid found in AD, was used as a biomarker to investigate the role of OD in the progression of the disease. A disruption in two critical Thioredoxin-Dependent Peroxiredoxin System components, peroxiredoxin-3 (Prx-3) and thioredoxin (Trx), may serve as a source of the increased accumulation of OD observed in AD. We demonstrate that OD, in the form of 8-OHG, was quantitatively most significant during the earliest stage of AD [$F(3,25) = 5.08$, $p < .01$]. A drastic decline in mitochondrial protein levels of Prx-3 [$F(3,25) = 8.74$, $p < .01$] and Trx [$F(3,25) = 4.33$, $p < .05$] were also observed across the progression of the disease. We then tested the efficacy of pioglitazone, a thiazolidinedione class drug aimed to delay onset of AD by acting on mitoNEET. Our results showed a significant reduction in the oxidized variant of mitoNEET within the incipient population when a 0.8mg dose was simulated in silico ($p = 0.0242; \alpha < .05$).

Keywords: 8-hydroxyguanosine, mitoNEET, Oxidative Stress, Peroxiredoxin-3, Pioglitazone, Reactive Oxygen Species, Thiazolidinedione, Thioredoxin, Transcriptome-To-Reactome

DOI: 10.4018/IJKDB.2015010103
INTRODUCTION

Late-onset Alzheimer’s disease (AD) is a progressive neurodegenerative disease characterized by a gradual ongoing deterioration in cognition, memory, and functional aptitude, resulting in a steep behavioral decline (Castellani, 2011). The importance of this disorder cannot be understated given that AD is the most common form of dementia in adults over age 65 (Lovell & Markeysberry, 2007), is the sixth leading cause of death in the United States, and currently affects more than 44 million people globally (Alzheimer’s Disease International, 2016). Further exacerbating the issue, currently there are no known FDA approved preventative therapies or effective medication to slow the progression of AD. With increases in human longevity and lack of effective treatment, it has been estimated that by 2050, AD will affect more than 16 million Americans alone (Brookmeyer et al., 2007; Smith, 1998; Ziegler-Graham et al., 2008). Over the last decade, emerging evidence strongly suggests a key involvement of oxidative stress in the progression of neurodegenerative diseases, particularly AD (Moreira et al., 2008; Nunomura et al., 2001; Pohanka, 2013). Disruption of critical biological reduction pathways, such as the Thioredoxin-Dependent Peroxiredoxin System (TDPS), may serve as a source of the increased accumulation of oxidative damage observed in the progression of AD. Our research group takes advantage of a computational intact biological network to investigate the role of oxidative damage across the earliest stage of AD compared to an aged matched control population, as well as explore the protein levels and reaction activity of two critical components of the TDPS, Peroxiredoxin-3 (Prx-3) and Thioredoxin (Trx), through the progression of the disease. As a follow up study, our team then tested the efficacy of low-dose pioglitazone, a thiazolidinedione (TZD) class drug, to reduce localized oxidative stress. Pioglitazone is a peroxisome proliferator-activated receptor-γ (PPARγ) agonist approved by the FDA for treatment of diabetes mellitus. Now it is being re-targeted at mitoNEET and repurposed to delay onset of AD in an ongoing phase 3 clinical trial.

Oxidative stress is caused by a physiological imbalance between the production and removal of cytotoxic free radicals within the cell, consequently leading to cellular damage, subsequent degradation, and rebalancing of the oxidative response system (Sies, 1991). Oxidative stress, specifically reactive oxygen species (ROS), is defined as a critical stressor of the biological system, whereas the resultant oxidative damage is characterized as the system’s strain. These stressors drastically shift the homeostatic environment of the cells resulting in macromolecular degradation and neuronal apoptosis (Dubinina et al., 2015; Kannan, 2000). Neural tissue is extremely susceptible to oxidative imbalances due to several factors that promote the formation of reactive species such as, “high rate of oxygen consumption, enrichment of polyunsaturated fatty acids, relative paucity of antioxidant system, and high content of transition redox metals” (Shan et al., 2007, pp. 2753). Because of the high metabolic demands of these cells, mitochondria are critical organelles within neural tissue, which is extremely dependent on oxidative phosphorylation for its metabolic requirements (Moreira et al., 2008). However, many highly reactive end products are produced during oxidative phosphorylation, and as a result, mitochondrial respiration serves as a major source of endogenous ROS within a biological system (Kong & Lin, 2010; Moreira et al., 2008).

The biological stress caused by these highly reactive end products is exemplified as macromolecular oxidative damage to lipids, proteins, nuclear deoxyribonucleic acids (DNA), and ribonucleic acids (RNA) (Shan et al., 2007). Due to the single stranded nature of RNA as well as the lack of protective histone proteins and intramolecular hydrogen bonding, it is thought that RNA is more susceptible to oxidative damage from ROS than DNA (Bregeon & Sarasin, 2005; Li et al., 2006). Hofer et al. (2006) validated this conjecture by demonstrating a greater rate of oxidation in RNA compared to DNA when exposed to cytotoxic hydrogen peroxide.
Implementation of Case Costing with Ontario Case Costing Initiative (OCCI)
Thuy Thi Thanh Hoang (2014). Research Perspectives on the Role of Informatics in Health Policy and Management (pp. 79-88).
www.igi-global.com/chapter/implementation-of-case-costing-with-ontario-case-costing-initiative-occi/78690?camid=4v1a

Exerting Cost-Sensitive and Feature Creation Algorithms for Coronary Artery Disease Diagnosis
www.igi-global.com/article/exerting-cost-sensitive-feature-creation/74695?camid=4v1a