Journal Club

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Bolstered Neuronal Antioxidant Response May Confer Resistance to Development of Dementia in Individuals with Alzheimer's Neuropathology by Ameliorating Amyloid- β -Induced Oxidative Stress

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Review of [Fracassi et al.](#)

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide. It is characterized by cognitive decline and concomitant dementia, primarily resulting from progressive degeneration of cortical and hippocampal neurons. AD is definitively diagnosed postmortem by the analysis of two major histopathological features in brain tissue. These disease hallmarks are amyloid plaques, resulting from the accumulation and intercellular deposition of amyloid- β (A β) peptide, and neurofibrillary tangles (NFTs), consisting primarily of intracellular aggregates of the hyperphosphorylated microtubule protein tau (Hardy and Higgins, 1992). A prevailing theory regarding AD pathogenesis is the amyloid hypothesis, which posits that AD pathophysiology is initiated by the accumulation of A β peptides as a result of an imbalance between A β production and clearance (Selkoe and Hardy, 2016). While deposition of insoluble A β plaques was previously considered the initial cause of neuronal dysfunction in AD, more recent evidence suggests that small soluble A β oligomers are the primary pathogenic species (Shankar et

al., 2008; Selkoe and Hardy, 2016). Notably, one consequence of oligomeric A β is thought to be the aberrant accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that precedes neurodegeneration, and some have suggested that synaptic dysfunction in AD is the result of A β -induced oxidative stress (Forero et al., 2006; Ansari and Scheff, 2010; Cheignon et al., 2018). In support of this hypothesis, synapses are particularly vulnerable to oxidative insult. ROS/RNS damage membrane- and vesicle-associated lipids through peroxidation, and they modify synaptic proteins through cysteine oxidation, tyrosine nitration, and other post-translational modifications; these modifications eventually contribute to the loss of dendritic spines and synaptic degeneration (Forero et al., 2006; Ansari and Scheff, 2010). Yet the precise mechanisms through which neurons are impacted by A β aggregate-induced oxidative stress remain unclear, and the question of whether A β accumulation is causative or consequential in AD remains contentious.

Arguing against the amyloid hypothesis, some individuals maintain intact cognitive ability throughout their lives, yet display widespread AD neuropathology on postmortem analysis of brain tissue (Price et al., 2009; Maarouf et al., 2011; Zolochovska and Tagliatela, 2016). These individuals,

termed as being nondemented with Alzheimer's neuropathology (NDAN), exhibit extensive A β plaques and NFTs that are comparable to those of individuals with advanced AD, yet they score normally on cognitive assessments and show no clinical signs of dementia. While several studies have sought to assess this anomaly, there remains no consensus regarding the mechanisms that counteract A β -induced cognitive dysfunction in NDAN patients, or whether the presence of extensive AD histopathology represents an early preclinical event in AD pathogenesis (Pike et al., 2007; Price et al., 2009; Bjorklund et al., 2012; Zolochovska et al., 2018).

Considering the above, a recent study by Fracassi et al. (2021) in *The Journal of Neuroscience* sought to determine whether the oxidative state of neurons and glia is related to the resistance to cognitive decline in NDAN patients. The authors hypothesized that NDAN individuals, though having elevated production of reactive oxygen species as a result of A β accumulation, also have a more efficacious antioxidant response, which increases their ability to cope with oxidative stress relative to AD patients. To test this hypothesis, the authors performed a comparative analysis of postmortem frontal cortex tissue from AD, NDAN, and age-matched

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control individuals, using quantitative immunofluorescence to analyze the distribution and relative abundance of markers for oxidative damage, as well as critical enzymes involved in the antioxidant response.

Consistent with previous findings, the authors found that NDAN tissues exhibited extensive A β plaque distribution, comparable to that of the AD group, while age-matched control tissue was negative for amyloid pathology. In contrast, levels of 8-oxo-2'-deoxyguanosine (8-oxo-dG) and 4-hydroxy-2-nonenal (4-HNE), two indicators of oxidative damage, were much higher in AD tissue relative to NDAN, and levels in NDAN patients were comparable to those in age-matched control tissue. Additionally, the authors found that in each condition, regardless of the relative intensity of each marker, 8-oxo-dG and 4-HNE levels were much higher in neurons than in astrocytes, consistent with the idea that neurons are generally more susceptible to oxidative damage (Forero et al., 2006; Ansari and Scheff, 2010). Notably, the distribution of 8-oxo-dG, an oxidized derivative of deoxyguanosine and a major product of DNA oxidation, was primarily cytoplasmic in all conditions, suggesting selective oxidative modification of cytosolic and mitochondrial nucleic acids. This finding supports the existence of a pathologic cycle in which increased ROS production by mitochondria in AD leads to further perturbation of mitochondrial function through the modification of mitochondrial DNA, and this drives additional ROS formation and eventual damage to synapses (Moreira et al., 2010).

To probe whether the apparent resistance to A β -induced oxidative stress in NDAN tissue was the result of increased antioxidant activity, the authors measured the relative levels of the following two major antioxidant enzymes: superoxide dismutase 2 (SOD2), which converts superoxide (a by-product of mitochondrial respiration) to hydrogen peroxide; and catalase (CAT), which breaks down hydrogen peroxide to water and oxygen. Globally, levels of SOD2 were drastically reduced in the AD group relative to NDAN and control groups, and this was confirmed by Western blot analysis of isolated synaptosomes. Given that SOD2 is responsible for scavenging mitochondrial superoxide, this result further supports the idea that perturbations of mitochondrial function are central to the pathogenesis of AD.

Interestingly, although the SOD2 expression level was similar between

NDAN and control groups, it differed in its cellular distribution; SOD2 was predominantly localized to neurons in NDAN tissue, whereas expression in both AD and control groups was highest in glial cells. Furthermore, though total CAT levels were significantly higher in AD samples than in NDAN and control samples, it was predominantly localized to astrocytes in AD brain; indeed, although CAT levels were highest in astrocytes regardless of condition, a significant downregulation of neuronal CAT was observed in AD relative to NDAN and control neurons. These results suggest that impaired antioxidant activity in AD neurons may be independent of the presence of A β aggregates. However, it is possible that A β is responsible for the downregulation of antioxidant enzymes in AD, but NDAN neurons are resistant to this effect.

To further investigate the oxidative status of NDAN neurons, they analyzed the distribution and relative abundance of the following two critical regulators of the antioxidant response that were previously shown to be modulated in AD: peroxisome proliferator-activated receptor α (PPAR α), a nuclear receptor protein that regulates lipid metabolism; and PPAR γ coactivator 1- α (PGC1 α), a transcriptional coactivator that regulates multiple antioxidant response pathways and modulates mitochondrial biogenesis (Wenz, 2013). In line with the results for SOD2, PGC1 α levels were lower in AD tissue than in NDAN and control tissues, and it was primarily neuronal in NDAN tissue, whereas it was enriched in astrocytes in AD and control samples. Similarly, although total PPAR α levels were highest in AD tissue, the distribution was primarily astrocytic with a corresponding decrease in neuronal PPAR α relative to NDAN and control.

Finally, the authors performed quantitative RT-PCR to measure levels of miRNA-485, an upstream regulator of PGC1 α that has been previously shown to negatively modulate its expression (Lou et al., 2016). Consistent with the immunofluorescence and Western blot data for PGC1 α , Fracassi et al. (2021) found that AD individuals have significantly increased expression of miRNA-485 relative to NDAN and control individuals, providing a possible mechanism for the specific downregulation of PGC1 α in AD tissue.

Together, these results suggest that NDAN neurons express unusually high levels of antioxidant response enzymes. This may endow them with a bolstered neuronal antioxidant response that efficiently

counteracts A β -induced redox imbalance, conferring protection from A β -induced oxidative stress and, hence, preventing the development of dementia.

If the upregulation of neuronal PGC1 α (and consequently, SOD2) is sufficient to protect against A β -induced oxidative stress, then prophylactic activation of PGC1 α and/or SOD2 expression in individuals predisposed to developing AD may be of therapeutic benefit. In support of this, the compounds 17 β -estradiol and resveratrol have been identified to exert neuroprotective effects *in vitro* by upregulation of PGC1 α and SOD2, respectively (Robb and Stuart, 2011; De Marinis et al., 2013). Additionally, dietary supplementations of resveratrol have been shown to upregulate SOD2 expression in the mouse brain and reduce amyloid pathology in a mouse model of AD (Robb et al., 2008; Karuppagounder et al., 2009). As well, PGC1 α activators induce the expression of neuroglobin, an antioxidant enzyme that has been shown to confer protection against A β -induced oxidative stress by sequestering ROS/RNS and maintaining mitochondrial integrity (Li et al., 2008; de Vidania et al., 2020; Fiocchetti et al., 2021). However, it is possible that a combination of antioxidant response activators is required to show therapeutic benefit for AD, as the efficacy of resveratrol alone in protecting against AD-associated cognitive decline has yet to be determined in clinical trials (Turner et al., 2015).

Further research is needed to understand the regulatory mechanisms of the antioxidant response in NDAN neurons, such as what genetic and/or environmental factors play a role in adapting to A β -associated redox imbalance, and whether supplementation with antioxidant enzyme activators is sufficient to protect against oxidative damage in AD. However, the study by Fracassi et al. (2021) provides key insights as to the ability of NDAN individuals to resist AD-associated cognitive decline by increased antioxidant enzyme expression.

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