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Review

The Emerging Role of Glutathione in Alzheimer's Disease

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Abstract. With millions of older individuals presently suffering from Alzheimer's disease (AD) worldwide, AD is an unduly common form of dementia that exacts a heavy toll on affected individuals and their families. One of the emerging causative factors associated with AD pathology is oxidative stress. This AD-related increase in oxidative stress has been attributed to decreased levels of the brain antioxidant, glutathione (GSH). In this article, we review the role of GSH in AD from a pathological as well as a diagnostic point of view. We recapitulate the literature that has assessed the role of GSH in AD onset and progression. We discuss the various methodologies through which alterations in GSH levels might be monitored, and highlight the yet uncharted potential of assaying GSH levels *in vivo* with magnetic resonance spectroscopy in AD therapeutics and prognostics. Finally, the present manuscript integrates findings from various studies to elucidate the possible molecular mechanisms through which disruptions in GSH homeostasis may contribute to AD pathology.

Keywords: Alzheimer's disease, amyloid-β peptide, biomarker; glutathione, oxidative stress

INTRODUCTION

Alzheimer's disease (AD) is no longer an obscure enigma; with about 1 in 85 individuals over the age of 65 years predicted to be suffering from AD by 2050 [1], it is an unfortunately common and debilitating neurodegenerative disorder. Given the prevalence and impact of AD, there is a pressing need for development of reliable diagnostic biomarkers that can detect the disease pathology at its incipient stages, i.e., at or even prior to the onset of the ineluctable behavioral and cognitive deficits associated with AD. Development of such early biomarkers entails identification of the earliest pathological changes induced by AD onset. While research in the fields of genetics and molecular biology has offered insight into the underlying neuropathology of AD, our understanding of the causative events leading to development of neurofibrillary tangles, amyloidogenesis, and neurodegeneration is still incomplete. Recent research has evidenced the role of oxidative stress (OS) in AD pathogenesis [2, 3]. There is increasing evidence that the mechanisms leading to the development of AD pathology and consequent neuronal death are a result of increased OS [2, 4, 5]. Various human studies have reported elevated DNA and protein oxidation in brains of AD subjects [6–9]. Recently, it has been shown that brains from patients with mild cognitive impairment (MCI), the prodromal stage of AD [10, 11], also have increased protein oxidation and lipid peroxidation as compared to age-matched controls [12–14]. Levels of OS markers, such

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as isoprostanes, neuroprostanes, acrolein, and hydroxynonenal (HNE), have also been found to be elevated significantly in MCI and AD brains [15, 16]. As MCI is considered to be the transition zone between normal cognition and AD [11], this finding suggests that OS is instrumental to the progression of AD. Furthermore, oxidative damage in brains of AD patients appears to be directly correlated with presence of the hallmark AD pathology, i.e., amyloid-β (Aβ) oligomers. Indeed, protein oxidation has been shown to occur in the brain regions presenting the most severe histopathology, such as Aβ-rich hippocampus and inferior parietal lobe, but not in the cerebellum which contains low amounts of Aβ [17]. Moreover, the levels of these oxidation markers have been shown to correlate with increasing stage of AD progression [9].

As such, the last decade has witnessed AD research focused on delineating biomolecules that reliably reflect pathology-induced alterations in the brain OS status. Elevated oxidative damage in AD has been postulated to be a consequence of altered levels and activities of antioxidant enzymes in the brain. Studies have documented a significant reduction in the antioxidant defenses of AD as well as MCI patients, as assessed from the plasma or serum of these patients [18, 19]. One of the key causes for AD pathology-related increase in OS has been shown to be a decrease in levels of the antioxidant glutathione (GSH: l-glutamyl-l-cysteinyl-glycine) [20, 21]. In this review, we focus on the potential of GSH as a biomarker for AD. We present evidence from literature for alterations in brain GSH during AD onset and progression. We summarize the currently available methods for detection of brain GSH levels and emphasize the scope and relevance of *in vivo* brain GSH detection via magnetic resonance spectroscopy (MRS) in AD therapeutics and prognostics in terms of its key advantages—noninvasive, quick, and accurate *in vivo* quantification of GSH in specific brain regions and potential for longitudinal tracking. Finally, we address the putative underlying mechanisms through which GSH and OS may regulate AD pathology.

GSH AND AD

GSH is a major endogenous enzyme-catalyzed antioxidant that plays a fundamental role in detoxification of reactive oxygen species (ROS) and regulates the intracellular redox environment [22, 23]. It is present at high concentrations of 1–2 mM within the brain [24], and its intracellular equilibrium has been shown to be important for health and function of brain cells [23]. Various animal studies have consistently shown that GSH deficiency in the brain leads to increased OS-associated damage to the brain [25–27]. Various *in vitro* and *in vivo* studies have evidenced a neuroprotective role of GSH against a wide variety of oxidative insults (for review, see [28, 29]). Neuronal cells have been shown to be particularly vulnerable to ROS damage due to the reduced GSH content [30]. Studies have shown that GSH is involved in nullifying the toxic effect of ROS in neuronal cells and its depletion leads to increased apoptotic signaling and consequent neuronal death [31].

Literature evidences a key role for GSH in the pathogenesis of various aging-related neurodegenerative disorders, including AD [20, 31, 32]. AD-associated reductions in GSH levels have been documented in both *in vitro* [33] and *in vivo* animal models of AD [34]. A recent study longitudinally assessed the GSH redox state, i.e., ratio of reduced GSH to its oxidized form, glutathione disulphide (GSSG), in blood samples as well as in the brains of transgenic AD (AD-Tg) mice at different time-points with respect to wild type control mice [35]. The study revealed that the GSH/GSSG ratio in AD-Tg brains decreased with increase in AD pathology, with lowered GSH/GSSG ratio right before the onset of amyloid plaques followed by a continual increase in GSSG and associated decrease of GSH/GSSG ratio in brains of AD-Tg mice [35].

A majority of postmortem analyses of brains from AD patients have also corroborated findings from AD animal models and documented depleted levels of GSH [36–38]. In contrast, earlier postmortem studies have reported no change in GSH content [39, 40], or elevated levels of GSH [41] in brains of AD patients. These dissenting results might be a consequence of non-homogeneity in the stage of AD progression between studies or an artifact of different postmortem sample collection and analysis techniques. Postmortem analyses of AD brains containing the ε4 allele of apolipoprotein E (ApoE) gene, an allele associated with earlier and more severe expression of AD pathology [42, 43], has shown that the extent of GSH reduction in AD is dependent on the presence and the number of ApoE ε4 alleles, with GSH levels being the lowest in homozygous ε4 brains [36]. This finding provides strong support for early disruptions in GSH homeostasis during development of AD pathology. Moreover, *in vitro* studies have shown that application of exogenous Aβ fibrils to cell cultures of various cell types leads to intracellular GSH depletion [44–48].

Using *in vitro* mixed neuronal cultures, Aβ addition has been shown to induce GSH depletion in both astrocytes and neurons [47, 48]. These studies further reinforce the notion that AD pathology is associated with disruptions in GSH homeostasis.

In addition to alterations in GSH levels, studies have also demonstrated AD-related changes in GSH pathway enzymes. The levels of glutathione-S-transferase (GST), an enzyme that catalyzes the reaction between GSH and nucleophilic compounds such as HNE [32], has been shown to be significantly reduced in several key brain regions as well as the ventricular cerebrospinal fluid (CSF) of autopsied AD subjects [49]. MCI patients have also been shown to exhibit reduced GST activity levels along with decreased GSH/GSSG ratio [50]. Further, polymorphisms in genes involved in GSH metabolism, such as GST omega genes, have been associated with increased risk and earlier age-of-onset of AD [51, 52]. On the other hand, postmortem human studies have demonstrated that mRNA levels of glutathione peroxidase (GPx) and glutathione reductase enzymes, which are involved in GSH antioxidant activity with free radicals [32], are elevated in the hippocampus and inferior parietal lobe of AD patients [53]. This increase in mRNA as well as activity levels of GPx has been suggested to reflect compensatory gene responses to GSH depletion [53]. Taken together, these findings provide cumulative proof that AD pathology is associated with reduced GSH levels. Furthermore, they also present suggestive evidence that an impaired capacity to synthesize GSH is a vulnerability factor for AD.

GSH AS A BIOMARKER FOR AD

Various lines of evidence indicate that brain OS is a key underlying factor behind AD etiology. GSH levels have been consistently shown to reflect the OS status. Furthermore, the literature reviewed thus far reveals a strong correlation between AD pathology and reduced GSH levels. These findings have spurred the development of assays for GSH levels as a biomarker for AD. Several methodologies have been developed to assess GSH levels in peripheral biological samples, such as blood. Recent progress in technology has also enabled noninvasive *in vivo* measurement of GSH directly in different brain regions using MRS. We discuss the latest findings from studies utilizing these various GSH measurement methodologies and evaluate their relative potential in serving as a reliable measure of GSH levels.

Detection of GSH in blood

Of the various peripheral tissues, blood is able to reflect well the physiological changes in various body organs and systems, including the brain [54]. As much as 500 ml of CSF is thought to make its way into blood daily [54]. As such, blood levels of various biomarkers can indirectly reflect pathology-induced alterations in brain levels. Moreover, the ease of blood extraction and analysis further increases the value of blood-based biomarkers. Studies have reported decrease in blood plasma levels of GSH in AD as well as MCI subjects [55–58]. A study that assessed alterations in various OS-related biomarkers for AD alongside other neurodegenerative disorders showed that in AD patients both total GSH as well as the GSH/GSSG ratio in plasma decreased in relation to AD progression [57]. A recent study demonstrated that MCI patients that progressed to AD also displayed a significant decrease in peripheral blood GSH/GSSG ratio compared to stable non-progressing MCI [59].

Moreover, GSH/GSSG ratio has also been shown to correlate with cognitive performance of AD patients as assessed by Mini-Mental Status Exam (MMSE) [57]. Another study that assessed the relationship between plasma aminothiols and AD also showed that while plasma GSH levels between controls and AD subjects were not significantly different, GSH levels were, nevertheless, an independent predictor of cognitive function in AD patients as assessed by both MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale scores [60]. Further, a linear correlation has been demonstrated between increased GSSG levels in the blood and decreased cognitive status of AD patients [61]. Together, these studies indicate that the total blood GSH content by itself might provide significant information on the oxidative status of the brain, and reflect onset and progression of AD disease pathology.

In vivo detection of GSH in brain with MRS imaging

Aforementioned studies suggest that GSH levels from blood can indicate alterations in OS status. There is, however, an obvious conceptual issue in utilizing GSH levels in blood as an indicator of AD pathology onset in the brain since these levels reflects systemic OS status and would not be a reliable indicator of early-stage GSH alterations within key brain regions that might be associated with onset, or increased risk of onset, of AD pathology. Up until recently, the absence

of an *in vivo* quantitative measure of OS status within specific regions of the brain has been a major deterrent in the progress of both fundamental as well as clinical AD research. GSH can be detected by various measurement sequences in proton (^{1}H) MRS, such as double quantum coherence filtering [62], and MEscher-GArwood PRESS (MEGA-PRESS) pulse sequences ([63, 64]; for detailed review of GSH estimation through MRS, including comparison of various MRS techniques, please refer to [65]).

Estimation of GSH via MRS allows for noninvasive, quick, and reliable quantitation of GSH levels in specific brain regions. Yet, in spite of the availability and clear advantages of this technique, there have been very few studies that have thus far utilized this technology to assess the modulation of GSH levels in different brain regions with respect to AD onset and progression. Only two studies have quantified brain GSH levels with MRS in animal models of AD. An *in vitro* MRS on cortical extracts of AD-Tg mice at 19 months of age, a timepoint when Aβ deposits are widespread, documented a 36% decrement in GSH levels in the cerebral cortex [66]. Another study on a mouse model of chemically-induced AD also showed a similar ∼37% reduction of GSH levels in the hippocampal regions using *in vivo* MRS [67].

Recently, we pioneered the use of MRS for GSH detection and quantitation in human subjects with AD. We employed MEGA-PRESS MRS to assess the *in vivo* distribution of GSH in brains in cognitively normal human subjects as well as patients with MCI and with AD [68]. Using this technology, we were able to detect a clear GSH signal in the brain. Our study revealed a region-specific distribution of GSH within the brain, with GSH levels in parietal cortex > frontal cortex > hippocampus cerebellum [68]. In addition to region-specificity, we also observed gender dependence in GSH distribution in brains of healthy subjects. The mean GSH content was found to be relatively higher in healthy female subjects as compared to healthy male counterparts, with significantly higher levels in frontal and parietal regions of the female subjects [68].

Moreover, GSH levels were found to be depleted in AD in a gender-specific manner, with significant reduction of GSH levels in the right frontal cortex of AD female patients and in the left frontal cortex of AD male patients as compared to their respective healthy young counterparts [68]. Our findings are consistent with postmortem studies that show decreased GSH levels in brains with AD pathology [36–38, 50]. Both postmortem human studies as well as our *in vivo* brain MRS study clearly demonstrate that GSH level alterations in AD are specific to key brain regions, such as frontal cortex, which are known to be susceptible to AD pathology. These findings not only underscore the importance of assessing GSH levels *in vivo* within specific brain regions, but also provide compelling evidence that GSH levels may indeed reflect onset of AD pathology. A recent study [69] also utilized MRS to measure GSH levels in the cingulate of MCI patients. Interestingly, the study found an increase in cingulate GSH levels of MCI patients compared to healthy controls [69]. Furthermore, the study evidenced an inverse correlation between cingulate GSH levels and cognitive processing tests [69]. While the findings of this study are in disagreement with observations from other animal model [34] and postmortem human studies [36–38], as well as our preliminary findings, it is important to note the difference in methodologies used for GSH quantitation. While specialized pulse sequences, such as MEGAPRESS, edit the MRS signal to highlight the GSH peak, thereby allowing for accurate and unambiguous quantitation, the PRESS sequence used for GSH measurement in this study assesses GSH levels in the presence of all neurometabolites, and is therefore more prone to quantitation errors [65]. However, it is feasible that the observed GSH increase in the cingulate region is indicative of an initial compensatory response to increased OS in MCI patients. In addition, this discrepant observation of GSH increase in AD may also be reconciled in context of feasible regional differences in molecular response to oxidative challenge and/or GSH metabolism [39]. For instance, the activity of the pentose phosphate pathway responsible for production of NADPH and consequently, for maintenance of adequate levels of GSH has been shown to be differentially altered in different brain regions of AD subjects [39, 70]. Similarly, glutathione reductase has been shown to be differentially expressed in brains of AD subjects [53, 71]. Longitudinal studies that correlate GSH levels in different brain regions to MCI and AD progression will be able to determine the precise course of GSH during AD progression.

POTENTIAL OF GSH QUANTITATION WITH MRS AS A BIOMARKER

With growing evidence that slow accrual of AD pathology precedes symptomatic onset of AD by many years, focus of diagnostic AD research has centered on distinguishing normal aging from the earliest asymptomatic stages of AD. Based on the widely accepted

supposition that Aβ deposition is the earliest detectable event in AD pathology, current early diagnostic biochemical biomarkers primarily include determination of Aβ load, either biochemically in the CSF or by using positron emission tomography imaging [57, 72], in addition to phosphorylated tau levels in CSF and the canonical structural atrophy-based markers which serve as indicators of AD pathology-related neurodegeneration [73–76]. However, recent evidence strongly supports the notion that along with Aβ oligomerization, elevated OS is a key early pathological event in AD [77–80].

In vivo MRS is a powerful noninvasive imaging technique that can divulge vital information about essential cellular properties such as OS and pH, as well as membrane and energy metabolism, thereby providing a much needed platform for identification of causal molecular processes involved in AD pathology [65, 81, 82]. Recent developments in MRS spectra have enabled *in vivo* quantification of GSH from specific brain regions [81]. Only a small handful of studies have assessed *in vivo* brain GSH levels by MRS in patients with CNS conditions—epilepsy [83, 84], schizophrenia [85–87], multiple sclerosis [88, 89], bipolar disorder [90, 91], and mood depressive disorder [91, 92]. Recent work has added to this body of work by assessing GSH levels in brains of MCI and AD patients [68, 69].

In vivo quantitation of GSH with MRS offers numerous advantages over other estimation methodologies: not only is GSH estimation through MRS noninvasive, it also allows for quick and reliable quantitation of GSH levels in specific brain regions. While detection of GSH alterations in blood and other peripheral tissues or even CSF is likely to give an indication of acute changes in GSH levels, these methodologies are unlikely candidates for monitoring subtle alterations in GSH within specific brain regions that might be suggestive of AD pathology onset. The noninvasive profiling of GSH levels within the brain with MRS also enables crucial longitudinal leverage on assessing GSH level alterations along various stages of disease progression.

While the present evidence strongly suggest that GSH monitoring with MRS could ultimately be developed to be an important diagnostic tool for AD, it is important to bear in mind that the number of studies that have assessed AD-associated GSH modulation in the brain with MRS are very limited. Additionally, GSH alterations are not limited to AD pathology, but have been shown to be associated with a variety of other neurodegenerative diseases. Accordingly, GSH quantitation cannot be exclusively used as a differential diagnostic biomarker for AD.

However despite these limitations, GSH monitoring with MRS holds promise as an investigative and therapeutic tool in AD research. Monitoring of GSH levels in addition to the other neurochemicals affected in AD can allow for earlier detection of AD as well as enhance the diagnostic accuracy of AD through differentiating between AD and other dementias. As such, *in vivo* quantification of GSH with MRS holds tremendous promise as a putative biomarker for AD diagnostics. Given the outlined advantages and potential of this technology, future large scale longitudinal studies that assess the prognostic accuracy of GSH quantitation with regard to AD onset and progression are warranted.

MOLECULAR MECHANISMS BEHIND OS AND ALTERED GSH LEVELS IN AD

The last hundred years have seen a multitude of publications in the field of AD research that have attempted to unravel the etiopathology of AD. While it is beyond the scope of this review to discuss all the current literature, we will briefly discuss the key findings that have shed light on the involvement of OS in AD pathology and the role of GSH therein.

OS in AD pathology: Relationship between OS and Aβ

There is widespread acknowledgment that Aβ peptide oligomerization is a key initiating factor in AD (for comprehensive reviews, see [93, 94]). Recent research has also highlighted a pivotal role for OS in AD pathogenesis [77–79, 95]. A substantial body of *in vitro* and *in vivo* studies have evidenced that Aβ aggregates can generate free radicals, leading to induction of OS and neurotoxicity [4, 95–98]. An *in vitro* study analyzed the role of GSH cycle in Aβ-induced OS by adding Aβ fragments to NT2 rp cells, which have a normal mitochondrial electron transport chain, and NT2 r0 cells, which lack functional mitochondria [45]. The authors demonstrated that while r0 cells had inherently elevated ROS due to mitochondrial dysfunction, Aβ fragments only induced ROS generation in rp cells [45], thus confirming the involvement of mitochondria in Aβ-induced ROS. It is to be noted that some studies have suggested a contradictory role for Aβ as a potent antioxidant [99, 100]. Neuronal cells with elevated Aβ have been shown to exhibit decreased oxidative damage [78]. It has accordingly been suggested that

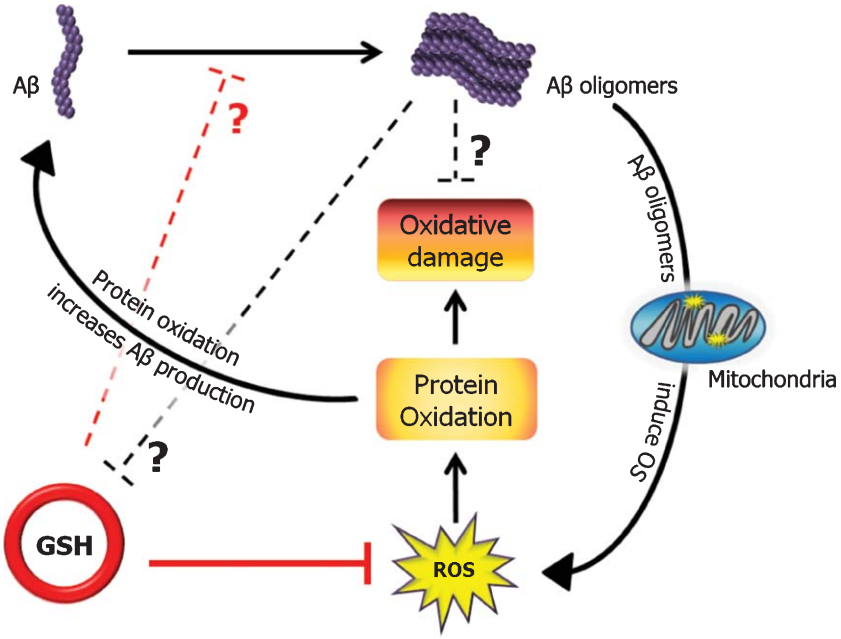

Fig. 1. Schematic depicting the complex interplay between oxidative stress (OS) and amyloid-β (Aβ) peptides and the potential role of glutathione (GSH) in regulating Alzheimer's disease (AD) pathology. Numerous studies have shown that Aβ oligomers induce mitochondrial reactive oxygen species (ROS) formation [96, 97]. It is to be noted that while some studies have suggested a contrary antioxidant role for Aβ oligomers [78], these studies are preliminary in nature. ROS formation leads to oxidative modification of various cellular proteins, thereby affecting their function. Recent studies suggest that oxidation of proteins involved in Aβ peptide formation can, in turn, increase Aβ production [106]. GSH is a potent antioxidant that has been shown to attenuate Aβ-induced oxidative damage [109, 110]. Preliminary *in vitro* evidence also suggests that GSH may be directly involved in attenuating AD pathogenesis [111–113]. Finally, *in vitro* studies have provided preliminary evidence that Aβ may directly disrupt GSH cycle homeostasis and lead to GSH depletion [44–48]. Arrows ends indicate a positive/stimulatory effect, whereas flat ends are indicative of a negative/inhibitory effect. Dashed lines with question mark are indicative of preliminary evidence that remains to be corroborated.

Aβ production occurs as a compensatory response to increased OS [100]. Furthermore, tau accumulation in AD has also been proposed to reflect a pathological consequence of oxidative imbalances, with neuronal death shown to precede tangle formation, and tau accumulation shown to lower oxidative damage [78, 101]. At present, it is difficult to coalesce these preliminary findings that evidence an antioxidant role for Aβ with the well-established oxidative role of Aβ oligomers.

In addition to being the proposed key downstream mediator of Aβ-induced toxicity, accruing evidence also supports the notion that OS plays a significant causative role in the development and exacerbation of AD pathologies, such as Aβ plaques and tau tangles [77, 78, 80, 102, 103]. Exposure to OS has been shown to induce Aβ production in neuronal cells [104]. OS leads to oxidation of several key proteins, thereby modulating their activity and impinging upon several cellular functions [105]. Oxidation of proteins involved in production and/or regulation of Aβ can directly affect Aβ production and consequent oligomerization [80, 102, 106]. For instance, it has been shown that oxidation-induced dysfunction of Pin-1, which is involved in both Aβ production as well as tau phosphorylation [106, 107], can lead to increased tangle and plaque formation [106, 108].

The literature summarized above suggests a bidirectional and causal relation between Aβ and OS. At the present stage, it remains unresolved as to whether these pathologies, i.e., Aβ and OS, are discrete occurrences that progress in lockstep or they reflect a sequential stream of pathological events, and more studies are required to better understand their chronological role in the physiopathology of AD triggering. Taken together, these findings present a possible scenario whereby the bidirectional interaction between Aβ and OS may result in a vicious positive feedback cycle whereby Aβ oligomers induce formation of ROS, which in turn appear to enhance the amyloid cascade by promoting Aβ synthesis and aggregation through oxidation of key proteins (Fig. 1).

Role of GSH in AD pathology

As discussed above, various studies have evidenced AD pathology-induced disruptions in GSH homeostasis; however, it remains unclear whether these alterations are causative in AD pathology or secondary to other events leading to neurodegeneration. Presence of GSH has been shown to be neuroprotective and attenuate Aβ-induced oxidative damage via HNE in neuronal cells [109]. Similarly, addition of GSH precursor has also been shown to significantly reduce Aβ-induced protein oxidation in neuronal cells [110]. Conversely, presence of Aβ has been shown to lead to GSH depletion in various *in vitro* cell models of AD [44–48]. Further, it has been demonstrated that this Aβ-induced disruption in GSH cycle homeostasis is dependent on presence of functional mitochondria [45]. These findings confirm an inversely correlative link between Aβ production and GSH levels (Fig. 1) and evidence the involvement of GSH in Aβ-induced toxicity.

Given the above presented evidence that demonstrate 1) decreased plasma as well as brain GSH levels with aging, 2) a negative correlation between AD and GSH levels, and 3) decreased GSH levels in AD pathology-susceptible brain regions, it is feasible that depletion of GSH serves as one of the key factors in induction of elevated OS, thereby exacerbating AD pathology. In such a scenario, alterations in GSH levels would be expected to occur *a priori* to emergence of other OS markers; as such, assessing changes in GSH levels within key brain regions might present an early indication of AD pathology. Future longitudinal research that combines MRS-based GSH quantitation and positron emission tomography-based amyloid imaging in the brain will be able to disambiguate the chronological interrelationship between Aβ, OS, and GSH in AD pathogenesis.

Interestingly, research has also suggested a direct pathogenic role for GSH in AD. *In vitro* studies that examined the effect of GSH on aggregation and fibrillation of amyloidogenic proteins have demonstrated that GSH significantly attenuates fibril formation [111, 112]. An *in vitro* biochemical study directly assessed whether GSH levels modulate Aβ-mediated cytotoxicity by exogenous addition of Aβ peptides to human neuroblastoma cells [113]. The study revealed that depletion of GSH levels not only augmented Aβ-associated cell death but also potentiated Aβ accumulation [113]. These data lend further support to the position that AD-associated alterations in GSH are not simply indicative of increased free radical-induced stress, but play a causal role in AD pathogenesis [113]. It is hypothetically possible that GSH, directly or indirectly, inhibits Aβ oligomerization and accumulation within neuronal cells (Fig. 1). However, what direct interactions, if any, exist between Aβ peptides and GSH is presently unknown and needs to be addressed.

CONCLUSION

In this review, we have discussed the putative role of GSH in AD pathology and explored its potential as an early biomarker for AD. AD-associated changes in GSH homeostasis appear to be more than simply a consequence of escalating disease pathology; they are closely associated with, and perhaps even causal in, AD onset and progression. As such, it is imperative to parse the underlying molecular mechanisms that lead to GSH depletion in AD and define the precise role of GSH in AD etiopathology. Delineating the role of GSH in AD pathogenesis will not only augment our understanding of the underlying mechanisms responsible for AD, it will also help target the key molecular components involved in inducing AD pathology, thereby aiding in the development of effective therapeutic agents for the treatment of AD. Moreover, modulation of GSH levels may, in itself, afford a means of attenuating, or even circumventing, AD pathology. Indeed, recent research efforts have centered on finding potential approaches for maintaining or restoring GSH levels in AD patients [55, 114].

In conclusion, there is a growing recognition of the involvement of GSH in etiopathogenesis of AD. GSH may well emerge as a linchpin in AD pathogenesis and open new avenues for AD diagnostics as well as targeted therapeutics. Future AD research needs to center on disambiguating and temporally delineating the respective roles of GSH and OS in AD pathology, as well as validating GSH as a biomarker for AD.

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