AN UNCONVENTIONAL HYPOTHESIS OF OXIDATION IN ALZHEIMER'S DISEASE: INTERSECTIONS WITH EXCITOTOXICITY

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1. ABSTRACT

There are two major lines of investigation from which a connection has been traditionally drawn between chemical oxidation and Alzheimer's disease. First, a major risk factor for AD is age, and oxidative stress has long been a component of general hypotheses about biological aging. The second line of reasoning is a corollary of the Amyloid Hypothesis, the assumption that the amyloid beta-peptide (A-beta) which comprises AD's pathognomic plaques is a key mediator of the neurodegeneration occurring in this disorder. Under many experimental conditions, A-beta has been shown to evoke oxidative damage to tissues, cells, and biomolecules; even the redox properties of the peptide itself have been hotly debated.   These two modalities of conjecture intersect under the Inflammatory Hypothesis of AD, as inflammation produces oxidation, old age is associated with elevation in inflammatory events, and A-beta can further exacerbate such inflammatory reactions in brain cells. This review discusses these arguments about the pathogenesis of AD and how they might be generalized to other neurodegenerative conditions.   But, additional speculation is offered in the form of an inclusionary mechanism that may be specific and novel enough to qualify as a third line of theory; namely, the possibility that inflammatory reactions in microglia-- activated by A-beta or other factors among the "usual suspects"-- initiate programmed oxidation that is converted to the neuron-specific stress of excitotoxicity.

2. OXIDATION AND AGING

Whether by cause or effect, old age is associated with a propensity for oxidative damage in every species analyzed. It is possible that this is a simply issue of exposure. Reactive oxygen species (ROS) are generated by both nonenzymatic reaction and by the intricate enzymology of oxidative phosphorylation. Thus, biological molecules begin to accumulate exposure to oxidative forces from the moment they are synthesized. Biomolecules differ in their innate vulnerabilities to oxidative stress, but most can be replaced on an appropriate schedule. In the case of our genetic blueprints of chromatin, continuity of the same molecule is favorable. So, mechanisms have evolved by which DNA can be repaired, replaced in parts rather than *in toto*. One of the most prevalent and mutagenic alterations spawned by ROS is 8-hydroxy 2'-deoxyguanosine (8-OHdG), and enzymes even exist to handle such modifications specifically, e.g., oxoguanine glycosylase (OGG1). Nevertheless, occasional deficiencies in repair and the sheer number of repairs that must be made logically accumulate over time. In addition, there is evidence that old age may be accompanied by a deficiency in antioxidants/repair mechanisms (1) coupled with an increase in metabolic errors that produce radicals (2). Therefore, aging may involve an oxidative vicious circle.

By and large, DNA repair mechanisms are quite efficient for nuclear chromatin. However, mitochondrial DNA is much more vulnerable, even at younger ages of an organism (3). Predictably, aging is associated with an accumulation of mutations in mitochondrial DNA (4). Mitochondrial DNA repair mechanisms either increase or remain unchanged in old age (5), suggesting that the repair mechanisms simply start out far inadequate of need. An intriguing aspect of mitochondrial mutation is the degree of "microevolution" that can occur within a tissue or even a single cell. Because mitochondria divide, mutations may be carried forth to create a mosaicism within a cell or among cells within a tissue (6). A mutation that is detrimental to the resident cell or organism may actually confer a replicative advantage to the mitochondrial

chromosome bearing it, or a proliferative advantage to that individual mitochondrion, resulting in selective accumulation of these lineages (7).

Oxidative damage is not limited to DNA, and while some oxidized proteins and lipids can be replaced, this is not always a sufficient to answer to the problem when the damage takes an active rather than passive role in degeneration. In particular, some lipid peroxidation products have a strong propensity for amplification through their own oxidizing capacity (8). Acrolein is a particularly potent toxic product of lipid peroxidation. Considerable attention has also been given to 4-hydroxynonenal (HNE). However, HNE adducts on neurofilament proteins do not vary with age (9). Oxidization of a protein can alter its activity to an actively detrimental state. For instance, the NMDA receptor has a redox-sensitive site that suppresses channel conductance in the oxidized state (10); though NMDA receptors are an important component of excitotoxicity, their activation is also critical in most models of memory acquisition. Oxidization of proteins can facilitate denaturation, fostering partially unfolded tertiary structures that more readily form aggregates (11). Oxidative formation of a disulfide bridge is credited with fostering the aggregation of the microtubule-associated protein tau into paired-helical filaments that makeup neurofibrillary tangles (12), suggested to be actively detrimental at least by their presence in Alzheimer's disease, frontotemporal dementias, and a host of other neurological conditions. Finally, oxidized proteins not only accumulate but also promote the accumulation of other proteins by active and dominant inhibition of proteases (13).

3. OXIDATION AND THE BRAIN

The brain appears to be particularly vulnerable to oxidation. For one, energy metabolism in the brain is among the highest of any organ, creating extraordinary opportunities for free radical generation. Second, DNA repair mechanisms do not seem to be elevated correspondingly. The levels of 8-OHdG in brain are relatively high (14), and increase with age (3). In addition, the degree to which mitochondrial levels of 8-OHdG exceed those of nuclear DNA is higher in brain than other tissues: 23:1 in brain versus 6:1 in liver and 16:1 in heart, for instance (3). Activities for the repair enzymes OGG1 and endonuclease III homologue 1 (NTH1) are no higher in brain than in any other tissue (15), even though the generation of their substrates occurs at a much higher relative rate in brain. Protein carbonyls were found to be elevated in the brains of older humans (16).

Aging of the nervous system appears to be a limiting factor for lifespan. Overexpression of a life-extending *daf* transgene in the neurons of *C. elegans* is sufficient to elicit the phenotype of whole-body expression (17). Although the *daf* gene is connected to metabolic generation of oxidants only by conjecture, superoxide dismutase can have a similar cell-type sufficiency in Drosophila, where its expression in neurons can extend lifespan by 40% (18).

4. OXIDATION IN ALZHEIMER'S DISEASE

The unique stresses of aging and oxidation on the brain, coupled with the age dependency of Alzheimer's disease have spurred a strong interest in the potential role for oxidation in this disorder. Early studies sought evidence of oxidized molecules; e.g., thiobarbituric acid-reactive substances (TBARS), a measure of lipid peroxidation (19). An elevation of oxidant-responsive genes and antioxidant enzymes also suggests an ongoing oxidative stress in Alzheimer's disease (20, 21). Positive evidence of oxidation in Alzheimer's has fueled hypotheses about irregularities in the metabolism of metals, including iron (22). In some of the most technically defensible work to date (23), microparticle-induced X-ray emission indicated a two-fold elevation of iron in the parenchyma of Alzheimer brain versus controls, and the levels in plaques were even further elevated beyond that of parenchyma; copper and zinc were also dramatically higher in this analysis.

Much of the evidence for oxidation in Alzheimer's disease has suffered from the same caveat as most other aspects of neuropathology: analysis of end-stage disease makes it difficult to distinguish a seminal, causative abnormality from late-occurring results of the pathological process. For instance, it is known that the blood-brain barrier is compromised as the brain parenchyma suffers severe degeneration. This fact has been offered to discredit early studies showing a small increase in aluminum in Alzheimer brains. But, if a consequence of the disease process on the blood-brain barrier can permit a red-herring accumulation of aluminum, does the same caveat apply to iron? The answer may depend on where one looks. Accumulation of iron in the classical neuropathological structures of Alzheimer's disease, plaques and neurofibrillary tangles, appears to occur rather late in the disease. In contrast, cytosol of vulnerable neurons shows a higher index of 8-OHG immunogenicity in patients newly diagnosed with Alzheimer's disease versus those that have progressed farther (24), and Down's syndrome individuals too young to have significant A-beta deposition show elevated 8-OHG, as well (25). This cytosolic 8-OHG immunoreactivity was interpreted to represent ROS attack of RNA, and the oxidative damage to RNA in Alzheimer's was confirmed by others more recently (26).

The role of iron in Alzheimer's disease may be related to a complex debate on the role of vascular damage itself in the disorder's etiology. Certainly, petechial hemorrhages permit a significant amount of iron to escape the vascular compartment and contaminate brain parenchyma. If they do not actually cause Alzheimer's disease, brain infarcts can at least encourage diagnosis (27), and it is possible that a subset of Alzheimer's cases have a vascular component to their etiology. The difference between classical vascular dementia and Alzheimer's disease seems clear to most neuropathologists, but some have suggested this reflects a qualitative distinction imposed (perhaps, artificially) upon a quantitative difference. It is possible that chronic recurrence of small

hemorrhagic events permits the development of a cummulative pathology that is quite different from the acute damage one sees after a single, severe stroke or even cerebral artherosclerosis. It could be instructive that while certain mutations in the -beta-amyloid precursor protein (beta-APP) cause a dementia we have termed "Alzheimer's," other alterations of the same protein can result in a hemorrhagic dementia (28). Could these be differences of degree rather than mechanism?

Perhaps, there would be no better evidence for a role of oxidation in Alzheimer's disease than the therapeutic success of antioxidants. Alzheimer models, primarily those of transgenic mice carrying a mutated human beta-APP gene, have been encouraging in this regard. Although it also exerts some anti-inflammatory effects, curcumin is a potent polyphenolic antioxidant and can inhibit the formation of A-beta plaques in a transgenic mouse model (29). Similarly positive effects on A-beta deposition and/or behavioral deficits have been noted with melatonin (30), *Ginko biloba* extract (31), and vitamin E (32). Even a transgenic model in the nematode has been useful in this regard, demonstrating beneficial effects of *Ginko* (33). Evidence of such therapeutic promise in humans is still limited to post-hoc epidemiological evidence, such as an analysis that indicated high-dose supplementation of both vitamin E and vitamin C reduce the risk for Alzheimer's disease (34).

4.1. THE AMYLOID-BETA PEPTIDE AND OXIDATION

The central role of A-beta in Alzheimer's disease research is undeniable. Whatever role in the development and progression of the disease is eventually attributed to A-beta, many investigations have been inspired by the Amyloid Hypothesis. And the connections between this peptide and cellular oxidation are still an important aspect of these studies. Indeed, much of the legitimacy of A-beta as a key factor in Alzheimer's derives from its ability to evoke the types of oxidative stress found in pathological specimens. When applied to cultures neurons or neuronal cell lines, A-beta can elevate superoxide, hydrogen peroxide, 4-HNE, peroxynitrite, protein carbonyls, and DNA damage (35, 36). Furthermore, A-beta can stimulate ROS production as a component of inflammatory mechanisms in other cell types such as microglia (below). Some have even suggested that A-beta is itself an autonomous source of oxidants when dissolved in an oxygenated aqueous solution (37). Others have questioned this chemistry, arguing that some trace amount of copper or iron must be present to catalyze oxidation from A-beta (38). Still others have found circumstances under which A-beta can function as an *anti*oxidant (39-41), inspiring the heretical hypothesis that the true trigger of Alzheimer's disease is an incipient oxidative stress and that the accumulation of A-beta merely represents a compensatory response.

The role of oxidation in the production of A-beta, or its conversion to toxic forms, is controversial as well. As mentioned above, cellular oxidation can generally lead to aggregation of proteins and/or a deficiency in proteolysis that permits accumulation. For example, oxidation facilitates an accumulation of ApoE proteins inside lysosomes and ApoE4 accumulates more readily than ApoE3 (42), relationships perhaps related to the genetic linkage of the ApoE4 gene allele to an elevated risk for Alzheimer's. *In vitro* studies indicate that alpha-synuclein, a component of neuritic plaques that also has relevance to Parkinson's disease, is likewise aggregated by oxidative conditions (43). Similarly, evidence suggests that cellular oxidation facilitates the formation A-beta aggregates from the beta-secretase-cleaved intermediate termed C99 (44). However, oxidation of a critical methionine (Met_{35}) results in a form of A-beta ("Met_{ox}A-beta") that is greatly diminished in its tendency to aggregate and acquire -beta-sheet secondary structure (45, 46). The resolution of this discrepancy may lie in differential effects on the small peptide versus its larger precursor (or intermediate fragments thereof); oxidation may be important for aggregation only because of its denaturing effect, less important for a peptide than for the larger precursor. Conceivably, oxidative stress in a cellular environment could oxidize other residues in beta-APP or C99 without hitting the methionine that will eventually become A-beta's Met_{35}, and this could alter the protein's conformation or cellular localization in a way that would facilitate proteolytic processing, aggregation of the more aminoterminal residues of A-beta, or both. Indeed, one might expect Met_{35} to be relatively protected from some oxidants while residing in the plasma membrane bilayer.

Most data and the resulting hypotheses suggest that toxicity of A-beta depends on some form of aggregation into oligomers or fibrils. Thus, it was surprising when Barnham *et al.* (47) reported that the unaggregated Met_{ox}A-beta still exerts neurotoxicity and suggested that this results from the abilities of both aggregated, unoxidized A-beta and Met_{ox}A-beta to produce hydrogen peroxide during the reduction of Cu(II). Butterfield and coworkers found that Met_{ox}A-beta was not neurotoxic, though it did lead to decreased values in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay (48), a phenomenon that may be an artifact of A-beta's ability to remove MTT reaction product from cells (49). This group also departs from the Barnham *et al.* report by contending that Met_{ox}A-beta is fully capable of forming fibrils, confirming work by others (50).

Despite some inconsistencies, all these studies implicating Met_{35} in the oxidative potential of A-beta agree on one thing: metals such as Cu(II) and Fe(II) *can* facilitate the generation of free radicals from full-length A-beta. The coordination site requires histidines in the aminoterminal half of the peptide, so the A-beta$_{25-35}$ often used experimentally does not reduce Cu(II); its toxicity involves an oxidant that may be metal-independent yet still dependent on Met_{35} (48). Protection against A-beta toxicity has been documented in many models for antioxidants like vitamin E and catalase. But a metal chelator, clioquinol, shows benefits as well. This antibiotic crosses the blood-brain barrier and has an affinity for divalent metals that appears to fall between that of A-beta

and more essential metal-binding proteins; therefore, it might be expected to have favorable tissue distribution without stripping the body of essential levels of Zn, Cu, and Fe. Clioquinol lessens A-beta toxicity in culture (47), inhibits A-beta deposition in transgenic mice (51), and a phase II clinical trial showed encouraging results in Alzheimer patients (52).

4.2. ALZHEIMER'S DISEASE AND INFLAMMATION: AN HYPOTHESIS EXTENDED

4.2.1. Role for microglia in Alzheimer's disease

In addition to any neurodegenerative effects A-beta has directly on neurons, untoward consequences can also arise from its proinflammatory activation of glial cells. Chief participants are the microglia, resident products of the monocytic lineage. And, it is clear that microglia can alter the function and output of astrocytes and neurons, such that elaborate cycles of inflammatory sequelae are perpetuated. Anti-inflammatory drugs have shown promising effects in delaying the onset or slowing the progression of Alzheimer's disease (53-55) or its counterpart in transgenic mice (56-59). One of the first clues that inflammatory mechanisms are operative in Alzheimer's disease came from the discovery of microglia overexpressing IL-1 in senile plaques (60). Although the correlation of total plaque number with degree of dementia is questionable, the subset of plaques showing inflammatory involvement is linked significantly to severe dementia (61). Furthermore, the presence of inflammatory markers is closely associated with loss of synapses (61), one of the most consistent and logical correlates of dementia (62, 63). A-beta and other factors elevated in Alzheimer's disease have been shown to be capable of direct activation of microglia (64, 65).

Of course, proinflammatory activation of microglia plays a beneficial role in many circumstances, and their actions in AD may not be entirely harmful. It is becoming increasingly accepted that plaques may be in a state of flux (66); certainly, the accumulation of A-beta that seeds them depends as much on removal rates as it does on A-beta production. If microglia contribute to the removal of soluble or aggregated A-beta, it may not be complete suppression of their activation that would provide the greatest benefit. Studies with cultured cells have indicated that microglia are quite efficient at removing naked A-beta deposited on a substrate. It is only when astrocytes add chondroitin sulfate proteoglycan to the mix that microglia become stymied in their role as "garbage collectors" (67), suggesting that the astrocytes that almost universally surround senile plaques are actually interfering with attempts at clearance by microglia. Observations made in transgenic mouse models of AD also complicate the role of microglia. It is now widely appreciated that immunization of beta-APP-transgenic animals against A-beta results in lower plaque burdens. In the plaques that remain, microglia laden with A-beta-immunoreactive material are found in and around the deposits (68). And, in a case study of a human patient immunized against A-beta, robust inflammation was associated with an apparent removal of plaques (69). The appearance of inflammatory markers

suggests microglial activation; possibly, they are participating in Fc-mediated phagocytosis of A-beta (70). In AD, absent antibodies and an Fc-mediated mechanism, microglia may be stuck in an unproductive activation, unable to remove the A-beta but continuing to produce the untoward products of inflammation.

4.2.2. The microglial oxidative burst

As the resident mononuclear phagocytes of the CNS, microglia retain the potential for many responses associated with macrophages, including phagocytosis, expression of proinflammatory cytokines and chemokines, and a robust signal-directed production of ROS. Activation usually results in a high production of superoxide, hydrogen peroxide, nitric oxide (NO), and their reaction products (71). This results from an oxidative burst, orchestrated by the assembly of a multi-subunit complex with NADPH oxidase activity. In the classically defined pathway, a small GTPase (Rac1 or Rac2), activated by a surface receptor-binding event, recruits the p47, p67, and p40 *phox* subunits to the membrane to join with the membrane-bound flavocytochrome subunits, gp91$_{phox}$ and p22$_{phox}$ and form the active oxidase complex. This NADPH oxidase catalyzes the unusual reaction of taking an electron from NADPH to reduce extracellular molecular oxygen to superoxide. Because of its membrane localization, NADPH releases much of its superoxide to the extracellular space where it is converted to hydrogen peroxide by nonenzymatic dismutation. However, it is now clear that intracellular oxidative bursts can occur, producing superoxide in the cytosol (72). A-beta activates the oxidative burst in several types of leukocytes, including microglia (73).

Regardless of the role of the oxidative burst in killing infectious agents or clearing debris, the generation of superoxide places a distinct stress on the microglial cell of origin. Conversion of cytosolic superoxide to hydrogen peroxide is rapidly catalyzed by superoxide dismutases. Some hydrogen peroxide is reduced by catalase, but sufficient protection is facilitated by the auxiliary actions of glutathione peroxidase. The latter enzyme consumes reduced glutathione, and while glutathione reductase can replenish its levels, there may be an additional requirement for *de novo* synthesis of glutathione under the extreme conditions of an oxidative burst. Further, glutathione S-transferases are important for terminating the ROS chain of events at the point of lipid peroxidation, and this class of enzyme effectively takes glutathione "out of circulation" through covalent modification of toxic lipids such as 4-HNE. Therefore, periods of intense ROS production-- including inflammatory oxidative bursts-- create a need for new glutathione. This molecule is synthesized from cysteine, which is supplied to cells from exogenous sources in its oxidized form: cystine. Thus, the intense production of ROS during inflammatory activation of mononuclear phagocytes requires a large influx of cystine.

Availability of cystine is regulated largely by the metabolism of homocysteine to cystathionine, then cysteine. This transsulfuration system seems to include intricate crosstalk and feedback regulation that makes each
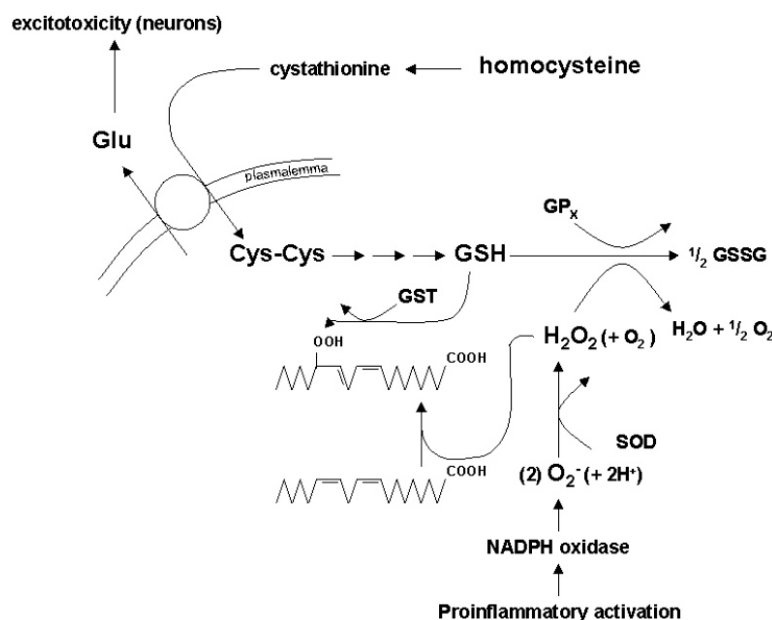
Figure 1. Schematic representation of hypothesis. Events are depicted within a microglial cell that has been activated. Proinflammatory stimulus triggers an oxidative burst that results in an elevation of superoxide, hydrogen peroxide, and lipid peroxidation. Reduced glutathione (GST) is consumed or oxidized by the actions of glutathione S-transferase (GST) or glutathione peroxidase (GPx), respectively. The consumption of GSH is at least partially alleviated by *de novo* production from cysteine, which enters the cell as cystine via the cystine/glutamate antiporter. The resultant expulsion of glutamate elevates extracellular levels of this powerful excitotoxin.

member of the pathway responsive to oxidative conditions (74). Interestingly, high homocysteine levels have been associated with conditions that involve inflammation, especially in the elderly, such as atherosclerosis (75) and arthritis (76). It is yet unclear whether hyperhomocysteinemia is causative for atherosclerosis or is merely an indicator of another risk. The connection of inflammation to cardiovascular disease is now well established, and it is possible that hyperhomocysteinemia contributes to atherosclerosis via exacerbation of inflammation. As activated macrophages produce a large amount of ROS, their responsiveness may be limited by their ability to survive these oxidative conditions; if homocysteine provides an elevated capacity for glutathione replenishment, it may "turn loose the reins" on inflammatory actions of sclerotic macrophages.

4.2.3. Excitotoxic consequences

To the extent that survival of its own oxidative burst requires the microglia to synthesize glutathione, the cell generates a chemical gradient of cystine across its membrane. Importing cystine for production of glutathione relies on the X_C exchange system: a cystine/glutamate antiporter (Figure 1). One result of this process is the export of glutamate, a profoundly consequential event in the CNS. Microglial activation results in release of glutamate, and this event has been documented to result from cystine/glutamate exchange (77, 78).

Glutamate is the most widely used excitatory neurotransmitter in the CNS, but it also possesses the most neurotoxic potential. Because of the potential for glutamate-stimulated excitotoxicity, both release of glutamate and its clearance from interstitial space are tightly regulated in the brain, such that typical concentrations of glutamate in extracellular fluid are subnanomolar (79). Five subtypes of glutamate transporters have been identified and characterized by molecular cloning. Astrocytes are responsible for most of the uptake of extracellular glutamate (80). Sodium-dependent transporters (GLAST and GLT-1) contribute most of the rapid clearance of glutamate from synapses, providing the kinetic precision and signal-to-noise ratios necessary for proper synaptic signaling. Once inside astrocytes, glutamate is aminated by glutamine synthase. Glutamine is released by the astrocytes for uptake by presynaptic neurons. The neurons then convert the glutamine back into glutamate, coincident with sequestration in synaptic vesicles, so that they may sustain suitable reserves of neurotransmitter. This cycle is critical to ensure the homeostasis of glutamatergic neurotransmission. Glutamate uptake declines with aging (81-83), and glutamine synthase is one of the most specifically carbonylated proteins in Alzheimer's disease (16). Indeed, glutamate transporters are among the more biologically relevant targets of detrimental oxidation (84, 85).

Glutamate activates multiple classes of receptor at both pre- and post-synaptic sites. NMDA receptors are ligand- and voltage-gated channels that conduct both sodium, calcium, and zinc. Under normal conditions, they are thought to play primarily a modulatory role, controlling mechanisms that potentiate or dampen a given synapse.

Excessive activation of NMDA receptors leads to large influxes of calcium that initiate synaptic and dendritic degeneration, as well as necrotic and apoptotic modes of cell death (86, 87). Besides ion conductance, consequence of robust NMDA receptor activation include the production of superoxide and peroxynitrite (88). Coupled with ROS produced by the microglial burst, this oxidative stress could inactivate glutamate transporters on neighboring astrocytes, compromising the most important means of regulating glutamate and thus fostering a vicious circle of neuronal injury. The same is likely for peroxynitrite, which can also inhibit glutamate transporters (89).

Regardless of whether glutamate uptake is compromised, the microglial release of glutamate may be sufficient to initiate neurotoxicity when its signal is potentiated by a coagonist at an allosteric site on the NMDA receptor. Full activation of the NMDA receptor requires a ligand binding to a site distinct from that which binds glutamate. The most extensively studied ligand for this site is glycine. Later, it was determined that dextrorotatory serine is at least three times as potent at this "glycine" site (90-92). Proinflammatory activation of microglia elevates their production of D-serine, probably through a transcriptional induction of the racemase that generates D-serine from L-serine; the enzyme is also overexpressed in Alzheimer's disease hippocampus (93). Age-related changes in NMDA receptors particularly impact the glycine/D-serine binding site (94), possibly as a consequence of elevated ambient levels of D-serine. This possibility is supported by analysis of the brains of senesence-accelerated (SAMP8) mice (95).

5. CONCLUSIONS

There is a wealth of evidence that oxidative mechanisms are operative in the pathogenesis of age-related neurodegeneration. Indeed, a dependence on oxidation may be the most attractive explanation for the age dependency of Alzheimer's disease and related disorders. From basic elements of vascular delivery of nutrients and oxygen to the specialized energy requirements of electromotive neurons, the brain and its proper function are at great risk from the detrimental aspects of cellular oxidation. However, few hypotheses seem to incorporate nonneuronal cell types in their consideration of oxidative damage to the brain. The physiological purposeful production of superoxide and secondary ROS by microglia is a source of oxidative stress for bystander cells. But, neurological function is at particular risk from one of the unfortunate consequences of this event. Within the mechanisms set in place to protect the microglial cell from its own oxidative products there is the opportunity for release of glutamate, a molecule that would probably be welcomed as an energy source in any other tissue but which represents to the brain a secondary challenge adding insult to injury. Therapeutic promise may lie in acknowledgement of this relationship and the design of antioxidant protections targeted at inflammatory events. Then again, it is possible that this would only exacerbate other consequences of a prolonged and robust inflammatory cascade. Only time and empirical investigation can resolve the implications.

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