these two results suggest that L1-dependent neural migration or axon growth could be disrupted during crucial periods of development in fetuses exposed to alcohol. Further investigation of the expression and function of L1 in models of fetal alcohol syndrome is clearly warranted.

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Radical AGEing in Alzheimer's disease

Mark A. Smith, Lawrence M. Sayre, Vincent M. Monnier and George Perry

The pathological presentation of Alzheimer's disease, the leading cause of senile dementia, involves regionalized neuronal death and an accumulation of intracellular and extracellular filamentous protein aggregates that form lesions termed neurofibrillary tangles and senile plaques, respectively. Several independent parameters have been suggested as the primary factor that is responsible for this pathogenesis, including apolipoprotein ϵ genotype, hyperphosphorylation of cytoskeletal proteins, or metabolism of amyloid β. However, at present, no one theory explains adequately the host of complex biochemical and pathological facets of the disease. Recent findings suggest that age-related increases in oxidative stress and protein glycation either individually, or more probably in a synergistic manner, could, exclusive of the other theories or in concert with them, account for all aspects of Alzheimer's disease.

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OXYGEN-DERIVED free radicals are formed as by-products of respiration and oxidative metabolism in all aerobic organisms (Fig. 1). The one-electron reduction of O_2 produces the superoxide-anion radical, which is converted rapidly to O_2 and H_2O_2 by superoxide dismutase. Hydrogen peroxide, which is also a normal by-product of several enzymatic two-electron oxidations, is reduced to H_2O by peroxidases or is disproportionated to O_2 and H_2O by catalase, or both. In certain instances (for example, ischemia, reperfusion and neutrophil respiratory burst), H_2O_2 persists, and is involved in transition metal-ion-catalyzed (and possibly superoxide stimulated) production of diffusible or 'site-specific' hydroxyl radicals, or both. Hydroxyl radicals are highly toxic and can initiate lipid peroxidation as well as create protein- or polynucleotide-centered free radicals by hydrogen-atom abstraction. Oxyradical-induced modification of protein is associated with fragmentation, increased susceptibility to proteolysis and, especially at lower oxygen concentrations, crosslinking reactions[1].

Normally, the cell has an adequate supply of protective mechanisms that quench radicals (vitamins C and E and glutathione), and reduce the products of free-radical chain autoxidations[2]. However, when there is a compromise in the levels of cellular antioxidants or accelerated production of reactive oxygen species, or both, a state of 'oxidative stress' results that can cause permanent cellular damage.

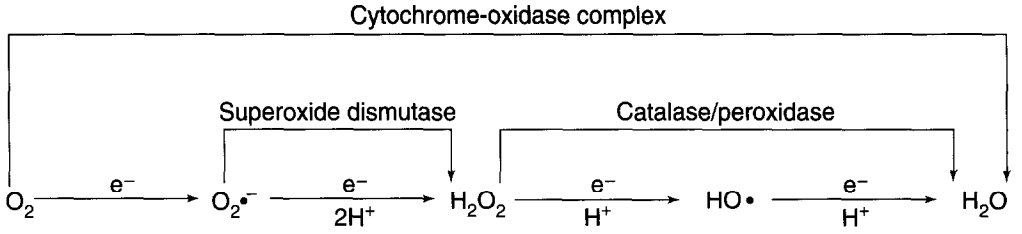

Fig.1. ***Pathways for the biological reduction of molecular oxygen.*** The electron reduction of molecular oxygen is shown in four steps, with indication of the transformations that are catalyzed enzymatically. The superoxide dismutase reaction generates O_2 and H_2O_2 and, when occurring non-enzymatically, generates reactive singlet O_2.

Advanced glycosylation end products (AGEs) are a family of complex, evolved post-translational modifications that are initiated by condensation of reducing sugars with protein amino groups via the Maillard reaction[3]. Although most work focuses currently on a role of AGE in diabetes, it has become increasingly clear that glycation of proteins occurs *in vivo* in non-diabetic aged individuals also[4]. In addition, oxidative stress increases the frequency of hydroxyl-radical-induced autoxidation of unsaturated membrane lipids. Reduced metal ion-mediated fragmentation of the resulting lipid hydroperoxides releases reactive aldehydes which can modify proteins in an adduct-evolutionary manner that almost parallels that seen in AGE (Ref. 5). Modification by AGE or products of lipid peroxidation will have the most effect on lysine-rich proteins, frequently with neutralization of the charge, and consequent alteration of protein–protein electrostatic interactions, and occassionally with intra- and intermolecular crosslinking (Fig. 2).

Synergy of AGE and oxidative stress-induced protein damage

Although AGE modifications or oxidative-stress mechanisms can lead individually to pathological modifications of neuronal proteins, these two factors together result in synergistically accelerated protein damage[6,7] (Fig. 2). Indeed, formation of adducts, and evolution in AGE modification of proteins, is accelerated by oxygen in a process that is called glycoxidation[8]. The condensation of reducing sugars with protein amino groups and subsequent Amadori rearrangement leads to the equilibrium presence of redox-active enediol and enol-enamine moieties that can catalyze the NADH-dependent reduction of O_2 to superoxide[9]. Such redox-cycling action can result in site-specific damage at the protein loci of sugar attachment, as exemplified by the fact that glycated proteins invariably contain oxidative modifications[6,10]. In addition, glycation of membrane lipids can be a mechanism for initiating lipid peroxidation[11], which adds to that resulting from oxidative stress. Evidence for such a scenario is that malondialdehyde, a major product of lipid peroxidation whose concentration is increased in neurofibrillary tangle (NFT)-containing neurons, is induced by AGE-modification of cultured cell lines[12]. Overall, modification of proteins by oxidation, glycation, and products of lipid peroxidation, can occur in both additive and synergistic mechanisms.

Old age is essential for Alzheimer's disease

One of the most important, yet often overlooked, aspects of the etiology and pathogenesis of Alzheimer's disease is that the disease is an age-related condition[13]. Indeed, even in individuals with a genetic predisposition, the disease rarely develops before age 55. An age-related penetrance is found also in a number of other chronic diseases, including cancer, rheumatoid arthritis, atherosclerosis, emphysema, cirrhosis and diabetes, that share the commonality that free-radical damage is implicated as a key pathogenic factor.

Growing evidence suggests that aging is associated with an increase in the adventitious production of oxygen-derived radicals, and also with a decreased ability to defend against the accumulation of free radicals. A gradual increase in free radicals, whose formation is compatible with a persistent state of oxidative stress, might underlie the damage of cellular components in an age-dependent manner[14]. Aging is also associated with an increase in AGE modifications which, for example, increase linearly with age in human skin[15]. Another important effect of aging is the decrease in protein turnover[16], and subsequent accumulation of damaged proteins that would normally be removed rapidly[17]. It is of note that aggregates of abnormal proteins[18,19], such as NFT and senile plaques, are the only definitive criteria used in the post-mortem diagnosis of Alzheimer's disease.

Radical generation and oxidative stress in Alzheimer's disease

Several potential sources of oxidative stress should be considered in the pathogenesis of Alzheimer's disease. First, the concentration of iron, a potent catalyst of oxyradical generation, is increased in NFT-bearing neurons[20]. Second, increased concentrations of iron would result in increased protein modifications, that are catalyzed by metal ions, by reducing sugars[14,21,22]. Third, microglia cells are activated and increased in number in Alzheimer's disease, and represent a major source of free radicals[23]. Fourth, the increased concentrations of aluminum in NFT-laden neurons have a stimulatory effect on iron-induced lipid peroxidation[24]. Membrane disturbances that are observed in degenerating neurons and neurites, perhaps as a result of lipid peroxidation, are expected to lead to an influx of Ca^{2+} which would destabilize the cytoskeleton and activate specific enzymes[25]. These enzymes would further potentiate membrane peroxidation and consequent free-radical propagation[26]. Finally, a novel hypothesis that regards the role of free radicals in Alzheimer's disease suggests that amyloid-β fragments form free-radical peptides spontaneously in a metal-independent mechanism[27], and induces the

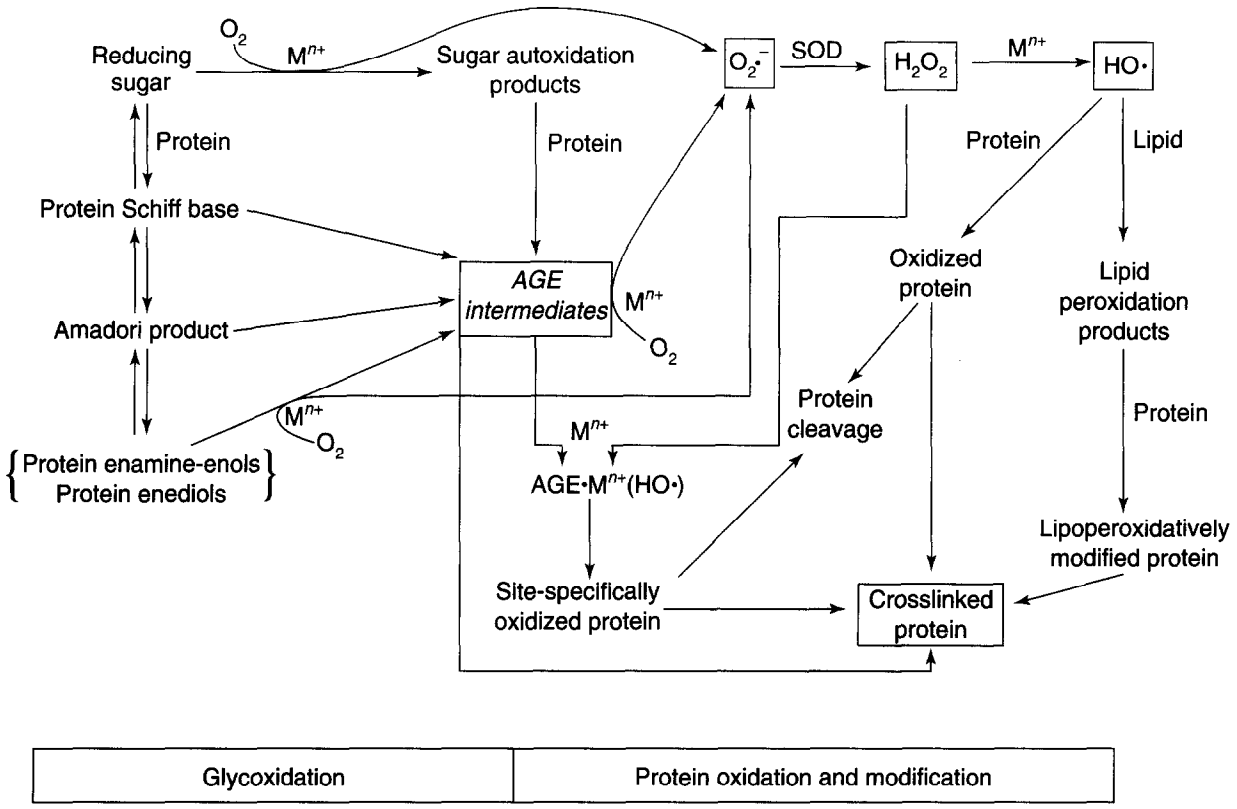

Fig. 2. ***Modification of proteins by glycation, autoxidation and reactive aldehydes that are generated from lipid peroxidation.*** *Protein modification and protein–protein crosslinking by glycation, autoxidation and reactive aldehydes that are generated from lipid peroxidation is a synergistic process; in particular, glycation and lipoperoxidative modification involve the adduction of redox-active moieties that potentiate free-radical autoxidation.*

accumulation of reactive oxygen species in cultured neurons[28–30] and synaptosomes[31].

Several protease inhibitors (for example, α_1-antitrypsin, α_1-antichymotrypsin and antithrombin), and proteases (for example, α_1-trypsin, thrombin, cathepsins B and D) are found in association with the pathological lesions of Alzheimer's disease, and proteolytic imbalance has been hypothesized to be responsible for many of the salient features of Alzheimer's disease[32]. Such an imbalance might occur upon inactivation of α_1-antitrypsin, arising from oxidation of the reactive center methionine[33], in a pathogenic mechanism that is similar to that described in emphysema[34].

There is a close association between increased levels of the antioxidant enzymes, superoxide dismutase[35] and heme oxygenase-1 (Ref. 36), and the cytoskeletal abnormalities found in Alzheimer's disease. Apparently, normal neurons do not show increased antioxidant markers, suggesting a strong correlation between cytoskeletal abnormalities and oxidative stress. This observation appears to indicate a response of the cell to increased oxidative stress, although the increased amount of superoxide dismutase might not necessarily be protective if there is no concomitant increase in catalase (Fig. 1). The enzymatic oxidation of heme by heme oxygenase-1 to generate biliverdin, a potent antioxidant progenitor[37], also indicates a cellular response to oxidative stress. However, this reaction results in the stoichiometric production of carbon monoxide also, which has neurotransmitter properties[38], and thus its possible pharmacologic effects should be considered[36].

Specific neuronal vulnerability

Neurons seem to be especially vulnerable to oxidative stress and free-radical damage, since they contain low levels of glutathione, a major antioxidant that is responsible for removal of cytosolic peroxides[39]. Furthermore, neuronal membranes contain a high proportion of free-radical-susceptible polyunsaturated fatty acids compared with normal plasma membrane, making them more susceptible to peroxidative damage. Moreover, any oxidative stress in neurons would undoubtedly be exacerbated by the very high consumption of oxygen that is required for the brain. It is of interest is to note that the cellular toxicity of amyloid β is related directly to free-radical damage in that vitamin E, a free-radical scavenger, prevents neuronal death induced by amyloid β directly[40]. Additionally, neuronal vulnerability might partly reflect free-radical damage to glutamate transporters that would potentiate glutamate excitotoxicity and, thus, might elicit selective neuronal degeneration[41].

Compared with other cellular proteins, neurofilaments and cytoskeletal proteins such as τ have relatively long half-lives, and contain high proportions of lysine residues. Therefore, while the lysine residues of neurofilaments have been implicated in supramolecular cytoskeletal organization, the presence of these multiple lysine-derived amino groups is probably the single most important feature that renders them particularly susceptible to cumulative oxidative damage, as well as modification by AGE and lipid-peroxidation products. Indeed, neurofilaments are the targets for modification by amine-directed neurotoxic chemicals that disrupt neurofilament transport[42].

The problem of insolubility

τ Protein and amyloid β, the main protein components of NFTs and senile plaques, respectively, are soluble in non-diseased conditions. However, in Alzheimer's disease, it is well accepted that these two proteins can become highly insoluble. Therefore, one, and possibly crucial, event in Alzheimer's disease is a decrease in the solubility of specific cellular proteins. The mechanism(s) responsible for protein insolubility and subsequent formation of lesions is thought to involve altered proteolytic metabolism[43] or specific post-translational modifications that include both enzymatic (for example, γ-glutamyl transaminase[44]) and non-enzymatic (for example, free radical-[45] or glycation-induced[12,46–49]) crosslinking events.

Several post-translational protein modifications characterize proteins that are found in Alzheimer's disease, including phosphorylation[18], isomerization[50], racemization[51] and crosslinking[12,44–49,52–54]. Although hyperphosphorylation of τ, racemization, isomerization, or aberrant protein processing, leading to increased levels of amyloid β, might rationalize the initial deposition of protein aggregates, this would constitute a non-covalent aggregation, which alone cannot confer the observed levels of insolubility. However, the proposal that protein insolubility is a direct consequence of covalent-crosslink formation is now supported by direct experimental evidence from studies *in vivo* and *in vitro* that, taken together, suggest that free-radical mechanisms are involved. First, proteins from NFTs and senile plaques tend to run as multimers or are unable to enter SDS–PAGEs (Refs 53 and 54). Second, several AGE modifications are found in close association with NFTs and senile plaques[48]. Modifications of AGE are associated with crosslink formation, decreased protein solubility, and increased protease resistance[55], that is, the same biochemical features that are displayed by the pathological lesions found in Alzheimer's disease[53,54,56]. The loss of skin elasticity in old age is one demonstrable effect of increased protein crosslinking. Third, the τ component of NFTs, but not τ from control brain, contains AGE modifications[12,46]. Fourth, *in vitro*, AGE-modified amyloid β induces aggregates which act as 'seeds' (as do senile plaques)[57] for the further deposition of soluble amyloid β[47]. Fifth, oxidation of amyloid β by free radicals can also generate insoluble protein aggregations[45].

Whereas AGE modification of protein involves the attachment of multifunctional residues with significant crosslinking capacity, only certain types of oxidative damage will lead to covalent protein crosslinking (Fig. 2). The generation of carbonyl reactivity, which has become a general indicator of protein oxidation, reflects in large part α-ketoamides that are formed by α-carbon hydroxylation and cleavage of the protein backbone[14]. The formation of aggregates of increased molecular weight must thus represent mainly the production of side-chain carbonyls arising from δ-hydroxylation of arginine and proline and ε-hydroxylation of lysine. Aldol condensation between resulting aldehyde groups or Schiff-base condensation with other lysines, or both, leads to intra- and intermolecular covalent crosslinks. The high susceptibility of τ protein to oxidation-induced crosslinking is not surprising in light of its unusual abundance of proline and lysine residues.

Taken together, these data suggest that insolubility is best explained by covalent crosslinking that is induced by a combination of protein oxidation, modification by AGEs and products of lipid peroxidation, that serve collectively to cement pre-existing non-covalent protein aggregates. Indeed, the synergistic mechanisms that result in covalent crosslinking would alter the biochemical and physical properties of proteins to those that are characteristic of Alzheimer's disease pathology (Fig. 2).

It is important, however, to appreciate that while glycation of amyloid β and τ might be involved causally in the neurodegenerative processes of Alzheimer's disease, the chronology of AGE modification is unknown and might not be an initiating event in disease pathogenesis. Some data are consistent with a scheme where glycation of amyloid β occurs after crosslinking and aggregation and after amyloid β has damaged neurons. For example, synthetic amyloid β, in the absence of sugars and without glycation, forms fibrillar aggregates that damage and kill neurons in culture[41,58,59]. Notwithstanding such data, modification by AGEs is probably an early event *in vivo*, since both diffuse senile plaques[48] and paired helical filament (PHF)-τ are glycated[12,46] and are considered to be two of the earliest pathological changes in Alzheimer's disease[60,61].

Concluding remarks

The evidence presented here suggests that modification of the proteins that accumulate in Alzheimer's disease by reactive oxygen species, sugars, and lipid-peroxidation products, plays a direct role in the etiology and pathogenesis of the disease. Therefore, in addition to the commonly accepted notions on the pathogenetic profile of Alzheimer's disease, including hyperphosphorylation[61], apolipoprotein ε genotype[62], and mutations of the β-protein precursor[43], stochastic mechanisms of protein damage by oxidative stress and the Maillard reaction[63] must now be added. Moreover, while all of these hypotheses are probably important for specific aspects in the pathogenesis of Alzheimer's disease, and therefore should all be considered in any realistic model of the disease, oxidative modification and AGE-related changes might be involved in any stage of the disease. Indeed, it must be remembered that Alzheimer's disease is an age-related condition with an incidence that parallels closely increases in cellular oxidative stress and formation of glycation- and lipoperoxidation-derived protein modifications.

Factors other than oxidative stress and glycation might initiate Alzheimer's disease by altering amyloid and neuronal cytoskeletal proteins in a way that predisposes them toward permanent oxidative-stress-related damage. This interpretation is attractive in that individual variation in susceptibility to these complications would be explained by variations in individual antioxidant competence. Indeed, it will be interesting to see whether future studies demonstrate links between Alzheimer's disease and metabolic disturbances of glucose metabolism or imbalances in detoxification of free-radicals or reactive oxygen species. In any event, the body of

evidence summarized here suggests that the therapeutic use of free-radical scavengers, antioxidants, and metal-ion chelators should be investigated thoroughly.

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