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Reactive Aldehydes and Neurodegenerative Disorders

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ÖZET:
Reaktif aldehitler ve nörodejeneratij hastalıklar

Nörodejeneratif hastalıklara olan ilgi özellikle son birkaç yılda belirgin bir şekilde artma göstermektedir. Fakat bu artan özel ilgiye rağmen, Alzheimer hastalığı (AH), Parkinson hastalığı (PD), multiple skleroz (MS) ve amiyotrofik lateral skleroz (ALS) gibi norodejeneratif hastalıkların patolojik mekanizmaları kesin olarak aydınlatılamamıştır. Endojen reaktif aldehitlerin (malondialdehit [MDA], 4-hydroxynonenal[HNE], acrolein, 3-aminopropanal [3-AP], formaldehit ve methylglyoxal) bu hastalıklardaki rolü için giderek artan kanıtlar vardır. Bu reaktif aldehitlerin çok çeşitli kaynaklar tarafından üretildiği ve hem in vitro hem de in vivo olarak çok sayıda nörotoksik ve gliotoksic özelliklere sahip olduğu gösterilmiştir. Bu makalede reaktif aldehitler ve bunların nörodejeneratif hastalıkların altında yatan patolojik süreçler ile ilgili bağlantılarını oluşturan kanıtlar ele tartışılmıştır.

Anahtar sözcükler: Nörodejeneratif hastalıklar, lipid peroksidasyon, malondialdehid, 4-hidroksinonenal, akrolein, formaldehid, metilglioksal, 3-aminopropanal, reaktif aldehidler, Alzheimer hastalığı, Parkinson hastalığı, multiple skleroz, amiyotrofik lateral skleroz

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ABSTRACT:
Reactive aldehydes and neurodegenerative disorders

Interest in neurodegenerative disorders has increased markedly in the last several decades; however, the exact pathological mechanisms of disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) remain to be elucidated. There is increasing evidence for the role of endogenous reactive aldehydes (including malondialdehyde [MDA], 4-hydroxynonenal [HNE], acrolein, 3-aminopropanal [3-AP], formaldehyde and methylglyoxal) as common mediators of neurodegeneration. These reactive aldehydes are produced by a wide variety of sources and have been shown to possess a multitude of neurotoxic and gliotoxic properties in vitro and in vivo. Evidence for accumulation of reactive aldehydes in and possible linkage to pathological processes underlying the above neurodegenerative disorders is discussed.

Key words: Neurodegenerative disorders, lipid peroxidation, malondialdehyde, 4-hydroxynonenal, acrolein, formaldehyde, methylglyoxal, 3-aminopropanal, reactive aldehydes, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis

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INTRODUCTION

The past several decades have seen an explosion of research into potential common neurodegenerative mechanisms underlying the pathological conditions seen in Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS). Studies of patients afflicted by these neurological disorders have shown a trend for elevated free and protein-bound reactive aldehydes to be present in cerebrospinal fluid (CSF), brain and spinal cord tissues (1). As such, it has been suggested that a possible link may exist between the excess production of these endogenous toxins and the pathogenesis involving selective neuronal and/or glial cell loss seen in neurodegeneration. With current therapy options marred by adverse effects, small therapeutic windows, and poor clinical efficacy, investigation of the toxic aldehyde pathways is warranted for development of future interventions.

The presence of reactive aldehydes in tissue is commonly interpreted as an increase in oxidative stress from lipid peroxidation (2). This process involves damage

of membrane polyunsaturated fatty acids by reactive oxygen species (ROS), producing α,β-unsaturated aldehyde compounds such as 4-hydroxynonenal (HNE), acrolein, and malondialdehyde (MDA) (3-5). However, other sources of reactive aldehydes include: metabolism of monoamines and polyamines; pyrimidine catabolism; carbohydrate glycation reactions; myeloperoxidase metabolism of tyrosine, threonine, and serine; extracellular matrix reactions of lysyl oxidase; and intermediary metabolic reactions involving amino acids, phospholipids, and carbohydrates (6). Normal cellular oxidation of the polyamines spermine, spermidine and 1,3-propanediamine to putrescine by polyamine oxidase, spermine oxidase and diamine oxidase yields hydrogen peroxide (H2O2) and the reactive aldehydes 3-aminopropanal (3-AP), 3-acetamidopropanal (3-AAP), 4-aminobutanal (4-AB) and acrolein as by-products (6). In addition, formaldehyde and methylglyoxal are produced from the precursors methylamine and aminoacetone, respectively, by primary amine oxidase (PAO; formerly called semicarbazide-sensitive amine oxidase, SSAO) (7).

Although production of reactive aldehydes may be augmented during pathological conditions, it is also important to consider alterations in aldehyde detoxification. The reactive aldehydes are known to be metabolized by three major pathways: conjugation by glutathione transferases, oxidation by aldehyde dehydrogenases, and reduction by aldo-keto reductases (6). Lipid peroxidation aldehydes and formaldehyde are primarily metabolized by the first two processes, while aminoaldehydes are known to be inactivated by aldehyde dehydrogenase (6). Methylglyoxal is detoxified by glutathione-dependent glyoxylase I and II enzymes (8).

MECHANISMS OF TOXICITY

Reactive aldehydes have a relatively long life span, allowing them to disperse to a wide range of intracellular and/or extracellular targets from their source of synthesis (4). The chemical reactivity of the aldehyde in question, and therefore its cellular action, is dependent on the functional groups present. All of the compounds named above possess an aldehyde group; however the aminoaldehydes, 3-AP, 3-AAP, and 4-AB, also contain an amine group, while acrolein, HNE, and MDA possess a carbon-to-carbon double bond and a hydroxyl group.

i) Acrolein, 4-Hydroxynonenal (HNE) and Malondialdehyde (MDA)

Reactive aldehydes produced as a result of lipid peroxidation are strong electrophiles and can react rapidly with nucleophilic compounds (especially those containing thiol or amino functional groups) in free amino acids, amino acid residues of proteins, nucleobases of nucleic acids, and aminophospholipids (4). The formation of these adducts (mostly irreversible) can lead to multiple deleterious events such as: inhibition of DNA, RNA, and protein synthesis; disruption of protein and cell membrane function; imbalance of calcium homeostasis; and interference with cell respiration and glycolysis pathways (4,9,10). Although acrolein exhibits the strongest electrophilic properties of the mentioned aldehydes and is estimated to be 100-fold more reactive with nucleophilic molecules than HNE (4), MDA and HNE are produced in much greater quantities (11).

The role of lipid peroxidation aldehydes in cytotoxicity has been closely tied with the mitochondria, as this organelle is the site of free radical formation and its membrane is a significant source of arachidonic and linoleic acids for the production of α,β-unsaturated aldehydes (12). Although all three aldehydes cause mitochondrial toxicity, their effects are exerted through different targets. Acrolein is a potent inhibitor of state 3 brain mitochondrial respiration via interaction with the phosphate transporter and/or adenine nucleotide translocase, but does not significantly alter the activity of mitochondrial complexes I-V (12). The findings suggest that acrolein does not disrupt baseline levels of cellular respiration but generates toxicity during conditions of energy stress by obstructing increases in respiration (12). Acrolein does not appear to directly induce apoptosis via mitochondrial permeability transition or cytochrome c release into the cytosol (12). HNE has been found to inhibit brain mitochondrial complexes II and III (13), while MDA inhibits complexes I, II, and V (14). As a result, HNE and MDA both cause diminished complex I- and II-linked state 3 respiration and destabilization of mitochondrial membrane potentials (13,14). Due to the high stability of adducts, long-term mitochondrial destabilization with HNE or MDA may deplete cellular energy levels under pathological conditions (13).

Acrolein and MDA also act as an inhibitors of brain

mitochondrial pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH) by forming adducts with sulfhydryl groups on lipoic acids present in the enzyme complexes (14,15). These enzymes play vital roles in oxidative phosphorylation and the Kreb's cycle by regulating the reduction of NAD+ to NADH. Although HNE was found to inhibit both enzymes in rat heart mitochondria (16), its ability to inactivate KGDH was lacking in brain cultures (13), suggesting tissue-specific toxicity. The concentration ranges for significantly impairing rat brain mitochondrial functions are comparable for all three aldehydes (12-14), but HNE and acrolein are considered to be more toxic in other cellular processes (4).

In cultured primary rat hippocampal neurons, both HNE and acrolein produced time- and concentration-dependent cell death, with the latter exhibiting greater toxicity (10,17). Aldehyde interference with plasma membrane Na^+/K^+-ATPase resulted in membrane depolarization, opening of voltage-gated channels, Ca^{2+} influx into the cytosol and subsequent activation of apoptotic cascades (10,17). Dizocilpine maleate (MK-801) and 2-amino-5-phosphonopentanoic acid (APV), antagonists of the glutamatergic NMDA receptor, were found to be protective against neuronal HNE toxicity, implying that HNE may further excitotoxicity by amplifying NMDA receptor activation or increasing glutamate release (17).

A recent investigation of HNE-induced apoptosis in cultured primary cortical neurons found that the aldehyde contributed to the activation of multiple cell cycle-related proteins, including phospho-p53, and cyclins D1 and D3 (18). The authors suggested that conflicting signals may derail cellular processes, resulting in a time-dependent activation of the apoptosis effector protease caspase-3 (18). HNE was also demonstrated to associate with proteasomes, thereby diminishing clearance of oxidized proteins and increasing accumulation of ubiquitinated proteins and protein-carbonyl adducts (19), as well as causing time- and concentration-dependent synaptosomal membrane protein conformational changes and increases in membrane fluidity (20).

As products of already-existing oxidative stress, the aldehydes acrolein, HNE, and MDA act to perpetuate the cycle of ROS damage by forming adducts with (and deactivating) the cellular antioxidant glutathione (4,21). MDA was also found to decrease the antioxidant activity of the superoxide dismutase (SOD) enzyme (14), while mitochondrial complex III inhibition (as seen with HNE) is known to amplify production of ROS (22).

ii) 3-Aminopropanal (3-AP) and 4-Aminobutanal (4-AB)

Reactive by-products of polyamine metabolism are thought to be a large source of aldehyde load in neurodegeneration, with 3-AP being the predominant aminoaldehyde formed from this process (6). It is believed that the presence of an amino group allows 3-AP (and 4-AB) to enter and accumulate within the lysosome, while the aldehyde group exerts toxicity by interaction with thiols on the lysosomal membrane proton pump (23-25). Leakage of lysosomal proteases into the cytosol is proposed to initiate apoptosis via mitochondrial damage and subsequent release of cytochrome c, but necrosis will occur if the extent of aminoaldehyde toxicity is enough to rupture the lysosome (25). Unlike glial cells, which exhibit apoptosis at lower concentrations of 3-AP and necrosis at higher concentrations (23-25), neuronal cultures were shown to be especially sensitive to 3-AP as even low concentrations of the agent induced mixed apoptosis and necrosis (24,26). The lysosomotropic properties of 3-AP were confirmed when the addition of NH3, resulting in elevation of lysosomal pH and reduction of 3-AP trapping within the lysosome, was found to be protective against 3-AP toxicity (25). While 3-AP is the major product of polyamine metabolism, a recent study investigated the toxicity of additional by-products of this pathway, namely acrolein, 3-AAP, 4-AB and H_2O_2. Using a rat retinal cell line, it was determined that acrolein and H_2O_2 possessed the greatest toxicity, which was almost twice that of 4-AB or 3-AP (6). This finding is consistent with the theory that acrolein and H_2O_2 exert direct mitochondrial damage, while 4-AB and 3-AP indirectly cause destabilization of the mitochondria via lysosomal degradation. No significant toxicity was found for 3-AAP, indicating that acetylation of the free amino group prevents aminoaldehydes from entering the lysosomes and damaging their membrane structure (6).

iii) Formaldehyde and Methylglyoxal

Formaldehyde and methylglyoxal are produced by PAO located on the extracellular membrane or in the cytoplasm

of endothelial, vascular smooth muscle and adipocyte cells (7). Their precursors, i.e. methylamine and aminoacetone respectively, are readily available from normal metabolism of creatine and derivation from threonine or glycine, respectively (7). There is also some evidence that choline may be metabolized to methylamine (27), which can then be converted to formaldehyde via PAO. Formaldehyde or methylglyoxal can interact with free amino or amide groups to form irreversible methylene bridges, thus enabling dose-dependent covalent cross-linking between proteins or between proteins and single-stranded DNA (7).

The formation of protein-protein or protein-DNA adducts may inactivate vital enzymes and result in deleterious cellular processes, as evidenced by neuronal apoptosis in rat prefrontal cortex following introduction of formaldehyde (28). Incubation with formaldehyde has been reported to cause a time- and concentration-dependent decrease in cell viability for cultured primary rat cortical neurons and astrocytes (29); the authors found that formaldehyde produced a differential effect on glutamate regulation for neuronal and glial cell cultures, upregulating glutamate transporter -1 (GLT-1) expression in neurons while significantly decreasing GLT-1 expression in astrocytes (29). Considering that glial cells outnumber neurons ten-to-one, a marked decrease of glial glutamate uptake and subsequent increase of extracellular glutamate levels may potentiate mechanisms of excitotoxicity. In cortical astrocytes, formaldehyde was also shown to cause an acute activation of stress-related mitogen-activated protein kinases (MAPKs) such as p38 MAPK and extracellular signal-related kinase 1/2 (ERK 1/2) (29). In cortical neurons, formaldehyde increased activation of p38 MAPK and caspase-9, while decreasing the activation of the serine/threonine protein kinase AKT (29) (caspase-9 and p38 MAPK induce the mitochondrial apoptosis pathway, while AKT is a marker of neuronal survival).

Acute treatment of human neuroblastoma cells with methylglyoxal induced production of ROS, cell membrane depolarization and glutamate release, resulting in increased vulnerability to excitotoxic insults (30). In the same study, chronic methylglyoxal treatment caused mitochondrial membrane depolarization, leading to attenuated intracellular ATP production and compromised cell viability (30). These results support the concept of a contribution of long-term methylglyoxal accumulation to mitochondrial dysfunction and decreased energy production in cellular stress.

RELEVANCE TO ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is an age-related neurodegenerative condition exhibiting initial symptoms of memory impairment followed by progression to further loss of executive function over a span of approximately 10 years (31). It is the most prevalent form of dementia in the elderly, characterized by the presence of frontal cortex and hippocampal extracellular β-amyloid neuritic plaques, intracellular neurofibrillary tangles containing hyperphosphorylated tau protein and severe loss of nucleus basalis cholinergic neurons (31).

i) Acrolein, 4-Hydroxynonenal (HNE) and Malondialdehyde (MDA):

There is compelling evidence for the presence of oxidative stress in AD pathogenesis as lipid peroxidation markers have been found to be significantly elevated in the blood, CSF, hippocampus, pyriform cortex and amygdala of AD patients (32-35). Concentration of MDA was increased in the erythrocytes, serum and plasma of AD subjects (36-40), as well as in the serum of individuals exhibiting mild cognitive impairment (41). However, one investigation found that AD patients exhibited higher levels of plasma HNE, but not MDA, in comparison to controls (42). Post-mortem levels of extractable HNE and acrolein were found to be significantly increased in the amygdala, hippocampus and parahippocampal gyrus of late-stage AD patients, with concentrations of acrolein reaching approximately 5-fold higher amounts than HNE for the aforementioned tissues (10, 43). Immunoreactivity for HNE-histidine Michael adducts was also found to be present in greater intensity in the perikarya of hippocampal pyramidal cells in subjects with the disorder (44).

Concentrations of HNE and acrolein were also reportedly increased (although not always reaching statistical significance) in the hippocampus/parahippocampal gyrus, superior and middle temporal gyrus, and cerebellum of patients with mild cognitive impairment and early AD (45). These results were corroborated by the finding of increased hippocampal and inferior parietal lobule HNE levels in individuals with mild cognitive impairment (46), as well as the identification of 11 HNE-modified proteins in these brain regions (47). A separate study revealed excessive

HNE binding to the tumor suppressor and transcription factor p53, a protein considered to play a major role in regulation of neuronal apoptosis, in both mild cognitive impairment and AD (48). Furthermore, there were significantly increased post-mortem levels of protein-bound HNE and extractable acrolein in the hippocampus/parahippocampal gyrus of patients with preclinical AD pathology at autopsy but normal ante-mortem performance on neuropsychological tests (49). By means of proteomic analysis, the brains of individuals exhibiting clinical symptoms of early AD were demonstrated to contain 6 inferior parietal lobule proteins that were excessively bound by HNE and normally carry out functions in the domains of neuronal communication, antioxidant defense, energy metabolism and neurite outgrowth (50). These studies suggest that oxidative stress and lipid peroxidation are events that occur early in the development of the disease and prior to onset of significant clinical symptoms. It also appears that HNE may exacerbate neuronal death by de-regulating normal function of cellular proteins involved in a wide variety of homeostatic processes.

The cleavage of the membrane-bound amyloid precursor protein to β-amyloid peptides is considered to play a central role in AD pathogenesis. These peptides aggregate to form oligomers, protofibrils and fibrils that eventually make up the extracellular neuritic plaques. The smaller soluble oligomers appear to be the most neurotoxic form of the β-amyloid peptide (51), possibly owing to their ability to enter the mitochondrial lipid bilayer where lipid peroxidation can subsequently take place (52). In a culture of primary rat hippocampal neurons, the addition of β-amyloid1-42 was shown to directly stimulate formation of HNE at concentrations sufficient for induction of cell death (17). Furthermore, an increase of rat brain MDA levels was observed following intraventricular and intrahippocampal injection of β-amyloid1-40 (53,54) as well as intrahippocampal injection of β-amyloid1-42 (although not reaching statistical significance in the latter case) (55). Incubation of MDA with β-amyloid1-40 was shown to dose-dependently potentiate oligomerization and fibrillization of the peptide, while HNE was able to significantly enhance β-amyloid1-40 aggregation only at higher concentrations (56). However, a separate study suggested that HNE covalently modifies β-amyloid1-40 and promotes its aggregation into protofibrils while inhibiting the formation of less-toxic mature fibrils (57). HNE was also demonstrated to covalently modify the β-amyloid peptide at 3 His residues by Michael addition, resulting in increased affinity of the peptide for the lipid membrane and transition to a fibril-like conformation once attached to the membrane (58).

Another central characteristic of AD brain neuropathology is the presence of intracellular neurofibrillary tangles primarily composed of hyperphosphorylated tau microtubule-associated protein. Adducts of acrolein, HNE, and MDA were determined to be highly concentrated in neurofibrillary tangles of AD brains (59-61). It is intriguing that acrolein was able to induce tau hyperphosphorylation in both human neuroblastoma cells and in primary cultures of mouse embryo cortical neurons via the p38 stress-activated kinase (62). Furthermore, the lipid peroxidation product HNE, but not MDA, was demonstrated to cross-link tau proteins and induce cytotoxicity in neuroglial cultures (63).

Of particular relevance to AD, HNE selectively causes a reduction of choline acetyltransferase activity in neuroblastoma cells by binding to active site histidine residues, while sparing acetylcholinesterase activity (43). This finding was further substantiated when basal forebrain injections of HNE in rats reduced basal forebrain and hippocampal choline acetyltransferase activity by 60-80%, resulting in death of basal forebrain cholinergic neurons and impaired performance of the animals in visuospatial memory tasks (64). These observations are consistent with the decline of cholinergic activity seen in AD.

A study examining DNA oxidation in AD brains found increased numbers of oxidized bases in the frontal, temporal, and parietal lobes in comparison to age-matched controls (65, 66). The damage was amplified in mitochondrial DNA, with nearly 10-fold greater oxidation of mitochondrial than nuclear bases (65). HNE can bind to lysine residues of histones, thereby altering their conformations and decreasing histone affinity for DNA strands (67). Acrolein can bind to DNA bases directly, with AD patients exhibiting 2-fold higher levels of nuclear DNA acrolein-guanosine adducts in the hippocampal region (11). The following processes may lead to increased vulnerability of DNA to oxidative damage or interruptions in transcription and gene expression seen in AD.

In addition to increased production of lipid peroxidation aldehydes, the accumulation of these toxic compounds is amplified by their impaired metabolism. Patients with AD had decreased levels of the enzyme glutathione transferase (responsible for the detoxification of acrolein, HNE and

MDA) in the CSF, parahippocampal gyrus and amygdala (68). The activity of glutathione transferase was not affected in the cerebellum, implying that the impairment of aldehyde detoxification is localized to regions exhibiting AD.

ii) 3-Aminopropanal (3-AP) and 4-Aminobutanal (4-AB)

Although there have been no direct investigations of aminoaldehyde toxicity in AD patients, the polyamine pathways appears to be altered in the disease state. Immunostaining for L-ornithine decarboxylase (ODC), an enzyme catalyzing the first committed step of the polyamine synthesis pathway, was found to be elevated in the neocortex of AD patients in one study (69), and ODC activity was increased in the temporal cortex (but reduced in the occipital cortex and unchanged in the hippocampus and putamen) of individuals with AD in another study (70). Concentrations of S-adenosylmethionine (a precursor of spermine and spermidine biosynthesis) are significantly decreased in the CSF of AD patients (71), while levels of spermidine and putrescine were found to be increased by 70% and decreased by 28%, respectively, in the temporal cortex of individuals afflicted by AD (72). Since these findings present evidence of significant alterations of the polyamine pathway in AD, further research into the exact effect of disease conditions on aminoaldehyde production would be warranted.

Indirect evidence of the possible contributions of aminoaldehydes to neurodegeneration can be observed with animal models. Using a trimethyltin rat model of delayed hippocampal neurodegeneration, researchers demonstrated a 50-fold increase in 3-AP levels prior to cell death, and 100% neuroprotection with the aldehyde-sequestering hydroxylamine NBHA but not ascorbic acid (which is inactive against 3-AP–mediated toxicity) (73). As aminoaldehydes are lysosomotropic agents, their role in AD is also indirectly supported by the findings that increased lysosomal activity and dysregulation contribute to AD pathogenesis (74,75).

iii) Formaldehyde and Methylglyoxal

Post-mortem AD patient examinations found that increased amounts of PAO were co-localized with vascular β-amyloid deposits in cerebral blood vessels (76,77). AD brains also show protein aggregate deposition in areas surrounding cerebral vasculature, suggesting a possible interaction between the protein cross-linking abilities of formaldehyde or methylglyoxal and AD pathogenesis (78). Analysis of patient CSF demonstrated a 2-fold increase in free methylglyoxal (8), as well as a propensity for increased methylglyoxal-derived adducts in AD subjects compared to controls (79). Levels of formaldehyde were elevated in the post-mortem hippocampus of AD patients (80), and in the same study the concentration of formaldehyde in urine was increased significantly in individuals with senile dementia and slightly for those with mild cognitive impairment.

Like MDA, formaldehyde and methylglyoxal have been shown to be potent inducers of β-amyloid oligomerization and fibrillogenesis in vitro (56). These data suggest that methylglyoxal and formaldehyde may contribute to AD pathogenesis by enhancing aggregation of toxic β-amyloid oligomers and protofibrils, resulting in exacerbation of amyloidosis seen in patients afflicted by the disease. It has been demonstrated that low-concentration formaldehyde causes in vitro and in vivo neuronal tau protein polymerization and aggregation, presumably by cross-linking of tau protein thiol and amino groups by formaldehyde polymers (81,82). These amyloid-like tau deposits were shown to produce apoptosis in rat hippocampal cells and neurotypic cell lines (83). Formaldehyde is known to increase inflammation, an event that results in subsequent upregulation of PAO expression and increased production of toxic aldehydes (78). Thus, formaldehyde is able to induce a feed-forward cycle in which its initial formation results in increased expression of PAO and production of more formaldehyde.

RELEVANCE TO PARKINSON'S DISEASE

PD is an age-related movement disorder characterized by clinical symptoms of resting tremor, rigidity and bradykinesia. The disease state features selective degeneration of pars compacta substantia nigra dopaminergic neurons and formation of neuronal cytoplasmic Lewy body inclusions containing α-synuclein (84).

As numerous markers of oxidative stress are increased in PD patients (85-87), it is not surprising that augmentation of lipid peroxidation is also suggested to occur in the disease. Increased levels of MDA and HNE were found in patient plasma and CSF (35,88-91). The CSF concentrations

of HNE found in patients was comparable to the range used for induction of toxicity in rat mesencephalic culture dopaminergic neurons (90). Increases in MDA content and HNE-adducts in post-mortem PD brains were found to be selective for substantia nigra tissues (92,93), although another investigation located the presence of HNE-adducts in patient brainstem and cortex Lewy bodies (94). Post-mortem examination of preclinical PD patients exhibiting neuropathological changes without onset of clinical symptoms revealed a significant increase of MDA- and HNE-adducts in the frontal cortex, amygdala and substantia nigra, suggesting that protein modification by lipid peroxidation-derived aldehydes may be an early step in disease development (95). Immunostaining for acrolein demonstrated a 4-fold increase in acrolein content for PD neuromelanin-containing substantia nigra neurons and an 8-fold increase of co-staining for both acrolein and cytoplasmic α-synuclein in this neuronal population when compared to controls (96).

The pathological hallmark of PD is the presence of neuronal cytoplasmic Lewy bodies primarily composed of aggregated and fibrillized α-synuclein protein (97). As in the case of β-amyloid proteins, it appears that the soluble oligomeric forms of α-synuclein are the most cytotoxic (98). Since this protein has an affinity for lipid membranes, there is a high probability of interaction with lipid peroxidation-derived aldehydes. HNE was demonstrated to covalently modify α-synuclein by means of Michael addition (99), producing a conformational change to a highly stable oligomeric structure that does not undergo further fibrillization and is toxic to primary rat ventral mesencephalonic cultures (100). Furthermore, the presence of MDA-modified α-synuclein was found in the substantia nigra of PD patients, as well as in the frontal cortex and substantia nigra of some individuals considered to have pre-clinical PD (101). As mentioned above, acrolein was co-localized with α-synuclein in PD neuromelanin-containing neurons of the substantia nigra. Incubation of acrolein with the peptide revealed a dose-dependent increase of α-synuclein oligomerization (96).

RELEVANCE TO MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease characterized by chronic CNS inflammation, brain and spinal cord axonal damage and demyelination, as well as selective loss of oligodendrocytes (102). Analysis of lipid peroxidation markers in the CSF of MS patients suggests that this process is augmented in the disease (103), but may not be correlated with progression of disability (104). Examination of brain white and gray matter in MS revealed no significant difference in levels of MDA and HNE from controls, although this could be attributed to high variability between samples (102). In contrast, increased MDA content was found to be present in patient CSF (103,105-107), as well as in the cytoplasm of oligodendrocyte-like cells in active and slowly-expanding lesions (108).

Intriguingly, modification of recombinant rat myelin oligodendrocyte glycoprotein (rrMOG) by MDA was shown to alter its structure, increase the efficiency of its uptake by antigen-presenting cells and enhance the antigenic response as measured by expression of several interleukins (IL-12, IL-12R and IL-23) (109). Immunization with the MDA-modified rrMOG produced a more severe phenotype of experimental autoimmune encephalomyelitis (EAE) mouse model of MS (109). Although further investigation is warranted, the results suggest that oligodendrocyte protein modification by aldehydes may be a possible route for exacerbation of the autoimmune response seen in MS pathogenesis. In addition, EAE mice demonstrated a significant increase in spinal cord acrolein-lysine adducts (110). In this model, the aldehyde-scavenging drug hydralazine was associated with decreased spinal cord myelin damage and more favorable behavioural outcomes (110). The authors suggest that acrolein plays an important role in MS pathogenesis by directly damaging proteins and lipids of the myelin sheath, or activating the proteolytic calpain enzymes that contribute to the breakdown of myelin. Acrolein was also shown to cause a loss of action potential conduction and membrane integrity in guinea-pig spinal cord axons (21,111), an event that may contribute to the axonal deterioration seen in MS.

RELEVANCE TO AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a neuromuscular disease characterized by initial death of upper and lower motor neurons, followed by successive wasting of striated skeletal muscles (112). It presents in two forms, i.e. familial

ALS and the more common sporadic ALS. The sporadic form of ALS has been associated with decreased expression and loss of the glial excitatory amino acid transporter-2 (EAAT-2) in the spinal cord (113). Increased lipid peroxidation is observed in ALS as elevated levels of MDA were found in patient plasma (89,114,115), as well as increased immunoreactivity for MDA-modified proteins in spinal cords of both familial and sporadic ALS cases (116). A large study examining lumbar CSF of 186 sporadic ALS patients found a significant increase of HNE levels in comparison to patients afflicted by other neurological diseases including AD, PD and other motor neuron disorders (117). The authors did not observe a similar increase of HNE content for familial ALS, suggesting a differential role of lipid peroxidation in the two forms of the disorder. A more recent investigation confirmed the elevation of HNE levels in sporadic ALS patient sera and CSF, reporting that increased concentrations of HNE were correlated with disease severity but not the rate of disease progression (118). Levels of HNE-protein adducts in the lumbar spinal cord of sporadic ALS patients were increased 2-fold in comparison to controls, with HNE localized to motor neurons of the ventral spinal cord horn (119). In these spinal cord tissue samples, HNE was demonstrated to produce a covalent adduct with the astroglial EAAT-2 glutamate transporter. Given that protein modification by reactive aldehydes often leads to inactivation of the target protein, the interaction of HNE with EAAT-2 may be an important step in the pathogenesis of sporadic ALS. In a follow-up in vitro study using NSC-19 motor neuron cell lines, addition of HNE resulted in a dose-dependent reduction of glutamate and glucose transport, as well as decreased choline acetyltransferase activity prior to induction of apoptosis (120). As both HNE and mutant SOD proteins found in ALS are able to decrease proteasomal activity, the combination of the two was found to synergistically amplify apoptosis in human neuroblastoma cell lines (19). In contrast to high amounts of HNE-protein adducts observed in the cytoplasm of degenerated motor neurons in sporadic (but not familial) ALS spinal cord, acrolein-protein adducts were absent in both sporadic and familial ALS patients (121). This study suggests that acrolein may not play a significant role in ALS pathogenesis, although further investigation is required.

SUMMARY

As reviewed here, reactive aldehydes represent a promising avenue of research in neurodegenerative disorders. These compounds are produced from a variety of endogenous sources including lipid peroxidation, polyamine metabolism and enzymatic reactions of PAO. Multiple in vitro and in vivo studies have demonstrated that reactive aldehydes can exert cytotoxicity by binding or cross-linking vital cellular proteins, destabilizing mitochondrial function and depleting cellular energy levels, de-regulating membrane potential and inhibiting proteasomal function. The accumulation of these aldehydes in the central nervous system and periphery has been established for numerous neurological disorders including AD, PD, MS and ALS. There is some evidence that lipid peroxidation-derived aldehydes may be increased in early AD or PD and prior to onset of significant clinical symptoms, but similar studies have not been carried out for MS and ALS patients. Although there is uncertainty regarding whether these compounds play a central role in disease initiation or are simply the result of other underlying neuropathological changes, the literature suggests that there is a strong contribution of aldehyde toxicity to disease exacerbation. An understanding of the mechanisms involved in reactive aldehyde toxicity specific to each disorder could lead to the development of promising new therapeutics in the fight against neurodegeneration.

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