ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 1 & 2, 2006

Forum Review

The Role of Oxidative Stress in the Dysregulation of Gene Expression and Protein Metabolism in Neurodegenerative Disease

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ABSTRACT

There are few examples for which the genetic basis for neurodegenerative disease has been identified. For the majority of these disorders, the key to their understanding lies in knowledge of the molecular changes that contribute to altered gene expression and the translational modification of the protein products. Environmental factors play a role in the development and chronicity of neurodegenerative disorders. Environmental stimuli such as hypoxia, toxins, or heavy metals, increase production of reactive oxygen species and lower energy reserves. Chronic exposure to oxidative radicals can adversely affect gene expression and proteolysis. This review summarizes what is currently known about some of the changes in gene expression and protein metabolism that occur after oxidative stress which contribute to neurodegeneration, and reveals areas where more research is clearly needed. *Antioxid. Redox Signal.* 8, 144–151.

INTRODUCTION

OXIDATIVE STRESS occurs when the production of reactive oxygen species (ROS), a normal product of cellular metabolism, is greater than the ability of the cell to repair the resulting damage. In neurodegenerative disease, susceptibility to oxidative stress may be genetically influenced but environmentally activated, (i.e., by exposure to toxins, heavy metals, viruses or hypoxia). This review will explore the oxidative mechanisms underlying the dysregulation of gene expression and damage to protein metabolism. These data should be useful in gaining insight into the molecular mechanisms that underlie cell death in neurodegenerative disease.

OXIDATIVE STRESS AND NUCLEIC ACID DAMAGE

Free radical-mediated tissue damage may be caused by endogenous processes such as an inflammatory response or by exogenous irritants. Water, the most abundant molecule in our body, is very sensitive to these processes. Normally water is a stable molecule, but energy bursts from heat or radiation may split one of the shared electron bonds, producing unpaired electrons on a hydrogen ion and a hydroxyl radical. In an attempt to reconstitute water, free radicals try to pair with other hydrogen atoms and in so doing exert oxidant stress on substrates in the vicinity. Nuclear DNA is often not affected by oxidative stress because the nucleus is poorly oxygenated and the DNA is bound by histones that quench radicals. Mitochondrial DNA, however, is very sensitive to oxidative damage because of its proximity to the respiratory chain, absence of protective histones, and limited DNA repair capabilities (57).

One common product of nucleic acid damage by oxidation is 8-hydroxyguanosine (8OHG). Indeed, 8OHG immunoreactivity is widely used as a marker for evaluating the effect of oxidative stress on nucleic acids. This molecule can be induced by various environmental factors and is known to permanently damage cytoplasmic RNA and mitochondrial DNA, thereby contributing to neurodegeneration. For example, in Parkinson's

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disease, there is increased 8OHG immunoreactivity in neurons of the substantia nigra (78). Patients with multiple system atrophy (MSA) and dementia with Lewy bodies (DLB) also show increased 8OHG immunoreactivity in substantia nigra neurons compared to controls, but less than in Parkinson's disease patients (78). In a separate study, an increase in 8OHG was an early event in Alzheimer's disease (50). In this study, oxidative damage decreased with disease progression suggesting that a compensatory change reduced the damage. Even though studies such as this suggest that oxidative stress is a primary cause of neurodegeneration, it remains unclear whether it is a cause or consequence (4). Certainly, neuronal vulnerability to free radical stress is dependent upon a number of factors, either environmental, genetic or both. For example, offspring of maternal victims of PD have pronounced deficits in Complex I that are responsible for increasing ROS (64).

DNA damage cannot always be repaired properly, a situation that can precipitate cell death. An example of this is Cockayne syndrome (CS), which is caused by mutations in the CSA, CSB, or the xeroderma pigmentosum genes (e.g., XPG). The transcription-coupled repair pathway that involves the XPG and CSB proteins repairs 8OHG lesions, and defects in this pathway are the cause of this syndrome (13, 39, 71). Another example of DNA damage and how the lack of repair induces cell death is found in amyotrophic lateral sclerosis (34, 67). Damaged DNA accumulates in familial amyotrophic lateral sclerosis and 8OHG lesions increase in the motor cortex of patients with the sporadic form of the disease (9, 20). Since the accumulation of DNA damage is a signal for apoptosis, such damage may be partially responsible for the death of upper and lower motor neurons in amyotrophic lateral sclerosis. Additional mechanisms of neurodegeneration, such as mitochondrial dysfunction leading to an increase in free radical generation, may also be involved in sporadic forms of the disease (20).

Cytoplasmic RNA is also vulnerable to oxidative damage. In Alzheimer's disease, selective classes of mRNA species are particularly susceptible, and many of the damaged mRNAs encode products that have been implicated in disease pathogenesis (61). When the damaged mRNAs are expressed in cell lines, they are improperly translated, which leads to protein aggregation (61).

Together these studies suggest that modification of nucleic acids by oxidative stress could be an important feature of neurodegenerative disease. In Cockayne syndrome, correction of the defect using gene therapy might be one therapeutic treatment. In Parkinson's and Alzheimer's disease and in amyotrophic lateral sclerosis, which have 8OHG damage, stimulating DNA repair through antioxidants may be beneficial (11).

Even though the evidence is strong that oxidative stress is damaging, limited production of ROS may be benign or even beneficial. A number of studies have proposed that the generation of ROS is required for energy supplies' signals to reach the nucleus from the mitochondria. Under pathological conditions, ROS increase, which may affect not only electron transport within the mitochondria but also the number and permeability of mitochondria themselves. Under a certain level, ROS presumably induce stress responses by altering the expression of specific nuclear genes to uphold energy metabolism in order to rescue the cell. Once beyond a certain threshold, free radicals can damage mitochondrial and nuclear DNA and induce apoptosis by increasing mitochondrial membrane permeability (38).

OXIDATIVE STRESS AND RNA METABOLISM

Gene expression analysis in neurodegenerative diseases

Several studies have used microarray analysis to examine the effect of oxidative stress on gene expression in various models of neurodegenerative disease. Oxidative radicals have been shown to disrupt the regulation of expression of several genes in the nigral dopaminergic cell line SN4741, including those that encode subunits of Complex I, exocytosis and membrane trafficking proteins, oxidoreductases, and regulatory molecules of apoptosis (75). Several of the genes identified in this study have previously been implicated in Parkinson's disease. They include the B8 and B17 subunits of mitochondrial complex I, which were down regulated, and syntaxin 8 and heme oxygenase-1, which were up regulated (75).

In chronic MPTP- and 6-hydroxydopamine-induced parkinsonian rodent models, microarray analyses show that the expression of genes associated with oxidative stress, inflammation, glutamate and neurotrophin pathways, cytoskeleton, cell cycle control, apoptosis, and signal transduction pathways are significantly altered in toxin-treated animals compared to controls (26, 27, 42, 47). When combined, these studies suggest that a dysregulation of gene expression in the substantia nigra of Parkinson's disease models could eventually lead to dopaminergic neuronal death.

An alternative approach to studying gene expression is to use a candidate gene method. Reverse transcriptase-polymerase chain reaction was used by Aksenov et al. (3) to study changes in the expression of key oxidative stress handling genes in Alzheimer's disease. The results indicated that Mn-SOD mRNA normalized to β-actin was unchanged, but Cu/Zn-SOD mRNA was increased in Alzheimer's disease patients compared to controls. These investigators also noted a general decrease in transcription in Alzheimer's disease brains. Together these data suggest that region-specific changes in ROS-mediated injury rather than a decrease in oxidative stress handling genes, contribute to the neurodegeneration observed in Alzheimer's disease brains (3).

From these examples it is clear that microarray studies benefit the study of neurodegenerative disease by characterizing affected genes and identifying molecular probes that may be used as biomarkers for monitoring neurodegeneration or the benefits of drug therapy. To use the candidate gene methods, one must have some prior information about the genetic basis of the disease, which unfortunately limits their utility. Complete identification of gene expression signatures after exposure to oxidative stress, would certainly help in identifying factors important in disease development and progression.

Transcriptional dysregulation

Modification of transcription factors by oxidation or alkylation can affect both protein–protein and protein–DNA

interactions and thereby alter their activity. In particular, many transcription factors have zinc finger domains that require two or four zinc-coordinated cysteine sulfydryl groups that must be in the reduced form. When oxidative stress induces cysteine oxidation within the zinc finger domain, the zinc coordination is lost and the secondary structure is distorted (73). Among zinc finger transcription factors that are induced by persistent oxidative stress, is Sp1. *In vivo*, the hyperoxidative repression of Sp1 transcription from promoters with essential Sp1 binding sites, includes the simian virus 40 early region, glycolytic enzyme, and dihydrofolate reductase genes (74). Zinc finger transcription factors most likely act as redox sensors and thereby mediate some of the transcriptional changes that occur (reviewed in 73). The quantity and availability of intracellular zinc are important factors for determining the oxidative state of zinc finger transcription factors (73).

An interesting twist to the story of how modified transcription factors may lead to neurodegeneration is that of myocyte enhancer factor 2 (MEF2), a transcription factor that plays a role in neuronal survival (43). A recent study showed that oxidative stress induced phosphorylation of MEF2 by Cdk5 kinase, which inhibits the activity of this factor (23). Since MEF2 is required for survival gene expression, the end result of its phosphorylation is neuronal apoptosis. Previous to this work, the deregulation of Cdk5 activity was shown to be important for pathogenesis of Alzheimer's disease and amyotrophic lateral sclerosis (48, 55, 76).

The induction or repression, in expression of various transcription factors, is also likely to play a role in neurodegeneration. For example, oxidative radicals may stimulate protein kinase cell signaling pathways (32, 63). This activation leads to increases in the transcription of some genes including the transcription factors NF-kB, AP-1 and Sp1, which have all been implicated in redox-modulated gene expression (1, 24, reviewed in 16). Metals such as aluminum, zinc, and lead can also trigger oxidant-sensitive transcription factors (reviewed in 54). Aluminum and lead induce oxidative stress by interacting with ROS, affecting membrane rheology and signaling cascades (54). Aluminum has been associated with the etiology of amyotrophic lateral sclerosis, and in Parkinson's and Alzheimer's diseases. Zinc also increases oxidative stress and affects the activity of redox-sensitive transcription factors Erg-1, AP-1, and NF-κB (41, 53, reviewed in 37, 60, 63).

Dysregulation of pre-mRNA processing

The effect of oxidative stress on pre-mRNA editing and splicing has yet to be thoroughly investigated. There are several studies, however, that suggest that regulation of these RNA processing events is disrupted by oxidative stress. Examples include the editing of the GluR2 subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in amyotrophic lateral sclerosis, and in Alzheimer's and Huntington's diseases (2, 65). A glutamine of GluR2 is changed to an arginine residue, thereby altering the calcium conductance of the receptor. In amyotrophic lateral sclerosis, this editing event is reduced substantially in the ventral gray area of the spinal cord, and could be responsible for increased calcium influx, and perhaps, motor neuronal death (65). A similar change in editing was observed in the prefrontal cortex in Alzheimer's disease and in the striatum in Huntington's disease (2).

One study that looked at changes that occur in an ischemic brain indicated that several splicing regulatory factors were translocated from the nucleus to the cytoplasm (14). The result of this redistribution after oxygen deprivation was a change in alternative splice site selection of the interleukin-1β converting enzyme homolog 1, an enzyme that functions in apoptosis. In another study, hypoxia induced a change in alternative splicing of the presenilin 2 gene in which exon 5 was skipped (58). This is the same change in splicing regulation seen in Alzheimer's disease brains. In addition to these examples, there are numerous other neurodegenerative diseases that show changes in the regulation of alternative splicing, which lead to a shift in the normal ratio of one splice variant to another (reviewed in 17, 19, 22, 25).

OXIDATIVE STRESS AND PROTEIN METABOLISM

In the past decade, intracellular aggregation of proteins has become increasingly recognized as an important pathological hallmark of neurodegenerative disease. Such aggregations appear in numerous disorders including Parkinson's disease, DLB, MSA, and in Huntington's and Alzheimer's diseases, and are characterized by common pathological features. The aggregates contain misfolded or post-translationally modified proteins, are primarily located intracellularly in the cytoplasm of neurons or glia, and are associated with high levels of ROS (31, 40). In Huntington's and Alzheimer's diseases, the respective intracellular aggregates of huntingtin and tau are toxic (15, 35). However, recent work by Arrasate *et al.* (5) questions that toxicity. They, like others (8, 62, 66, 70), have raised the possibility that the isolation of toxic proteins into inclusions are a neuron's normal response to the accumulation of abnormal proteins. In Parkinson's disease, the intracellular inclusions are called Lewy bodies and contain α-synuclein. This protein, which also accumulates with huntingtin in Huntington's disease (15), and serves as the precursor of the nonamyloid component of plaques (NACP) in Alzheimer's disease (29), may be toxic when it is in the form of small aggregates called protofibrils (72). Nevertheless, their accumulation in Lewy bodies may not be toxic. Since mature Lewy bodies are found in surviving neurons in Parkinson's disease, they may reflect a cell's defense to the presence of toxic molecules (5, 66). The intermediate steps to inclusion formation, however, may not be so 'cell'-friendly and could increase a neuron's exposure to pathogenic proteins (see below).

Human α-synuclein is a 140 amino acid molecule that has a highly hydrophobic domain involved in amyloid formation (29). This protein has been detected in Lewy bodies in Parkinson's disease and DLB and in aggregates in glia cells in MSA (31). Aggregated α-synuclein generally forms insoluble β sheets (10), but how this natively unfolded molecule is transformed remains unresolved. Nevertheless, some clues can be found in how oxidative stress affects the translation of the protein, as noted earlier, or modifies it post-translationally (51, 56).

Two mouse models induced by toxin exposure—chronic MPTP/probenecid and rotenone—have α-synuclein- and ubiquitin-immunoreactive aggregates in the cytoplasm but not in the nuclei of nigral dopaminergic neurons (7, 46). Various *in vitro* models also show intracellular aggregation of these proteins, especially in the presence of human α-synuclein or iron (12, 52). In all these cases, the aggregations are not organized as Lewy bodies, but rather as small granular and fibrillar structures that are referred to as "Lewy-like" inclusions (45). Nevertheless, the aggregation process may mimic that in Parkinson's disease including the dependence on enhanced ROS production due to mitochondrial damage (reviewed in 40).

Misfolded, unassembled, or damaged proteins are generally degraded in an ubiquitin-dependent manner by a nonlysosomal, ATP-dependent, protein degradation pathway or ubiquitin-proteasomal system (UPS) (6). This pathway may become dysfunctional or overloaded if the cell has a reduced capacity for ATP production, as occurs under conditions of prolonged oxidative stress (45). Since ubiquitin appears to be an important chaperone of α-synuclein, establishing a link between UPS malfunction and increased ubiquitinated complexes in Lewy bodies may shed light on how proteolysis changes in Parkinson's disease (21).

Post-translational modifications of proteins are part of the degenerative process in Alzheimer's, Huntington's and Parkinson's diseases, and may play a role in inclusion formation. In Parkinson's disease, we know that α-synuclein can be nitrated, hyperphosphorylated, or phosphorylated at tyrosine residues; enhanced oxidative stress increases the rate at which tyrosine is modified (56, 59). Such alterations will alter the hydrophobicity and conformation of the protein, thereby enabling polymer aggregation (56). Abnormal protein phosphorylation may also modify the ability of a protein to bind lipids and affect triglyceride turnover (18).

There is good evidence that lysosomes are capable of carrying out limited proteolysis, especially if the UPS is malfunctioning. However, these organelles also contain the major pool of redox-active labile iron within the cell, and in the presence of oxidative radicals, this iron can relocate to the nucleus where it can damage DNA (36). Interestingly, recent studies provide convincing evidence for a link between proteasomal inhibition and lysosomal proteolysis. Impairments in the UPS system increasingly shunt proteins to lysosomal proteolysis. However, elevations in protein oxidation, nitration, or phosphorylation slows protein turnover and can thereby enhance the aggregation of proteins (33). Lipofuscin granules, which are formed in lysosomes by an iron-catalyzed oxidation of protein and/or lipid residues, further sensitize lysosomes to oxidative stress (69). Oxidative radicals, such as hydrogen peroxide, diffuse easily into the granules where they reduce ferrous iron and form peroxidation byproducts, such as protein carbonyls (45). The low pH in the lysosomal compartments produces an environment compatible with these activities. Lipofuscin granules accumulate with age. However, the progressive accretion of indigestible residues, as demonstrated in Alzheimer's and Parkinson's diseases (8, 49), accelerates lipofuscin formation (69). Lipofuscins can interfere with the autophagic process by which most lysosomal contents are normally degraded, suggesting that these granules reflect lysosomal dysfunction and, presumably, a decline in protein degradation (69). Although the increase in these granules is part of the normal aging process, their appearance is dramatically accelerated in various neurodegenerative diseases (44, 49) as well as in dopaminergic neurons in Parkinson's disease (45). Lipofuscin granules are also numerous in brain stem neurons outside of the substantia nigra in Parkinson's disease (8).

In Parkinson's disease, dopaminergic neurons, lipofuscin granules are intimately associated with abundant neuromelanin. Neuromelanin, normally synthesized enzymatically in lysosomes, co-localizes with a large accumulation of iron (77). Although reduction in neuromelanin content is reported in Parkinson's disease, this may be due to the loss of neuromelanin-containing dopaminergic neurons and not to decreased levels in lysosomes of remaining neurons. The cellular content of lipofuscin and neuromelanin may be important for Lewy body formation, since lipofuscin substructure is granular and associated with lipid as early stage Lewy bodies show (30, 45). The high lipid content of lysosomes and Lewy bodies may also play a role in protein accretion and serve as an important source of hydrogen bonds for protein nitration as well as contribute to an increase in the length of protein filaments (21, 28). Overloaded lysosomes with their lipofuscin, iron and lipid contents, may rupture, as they have been shown to do under *in vitro* conditions (79). The contents would then be expelled into the cytoplasm where they would further damage mitochondria and its DNA. Moreover, lipofuscins could form nucleation centers for protein filaments as a first step in the process of Lewy body formation (45).

SUMMARY AND CONCLUSIONS

Significant molecular changes can occur in neurodegenerative disease at every level of gene expression from transcription through post-translation modification of proteins, and each may play an important role in neuronal death. Figure 1 summarizes the prominent pre- and post-translational modifications that are associated with prolonged oxidative stress and lead to neuronal injury and death. Mitochondrial DNA, which is particularly sensitive to oxidative injury (57), contributes significantly to reduced levels of ATP and increased production of ROS when damaged. The incorporation of 8OHG into mitochondrial DNA in neurodegenerative disease is known to elevate oxygen metabolism and contribute to mitochondrial failure. Such damage will ultimately decrease energy supplies and directly impact protein translation and degradation.

Oxidative radicals also impair transcription factor activity. Oxidized cysteine residues on zinc finger domains can disrupt the zinc coordination of transcription (74). Moreover, other metals such as aluminum and lead interfere with transcription by activating transcription factors that can induce cell death (54). When the regulation of pre-mRNA splicing is impaired by oxidative stress, the ratio of splice variants may shift which could increase the production of damaging transcripts. In addition, abnormal RNA editing of the GluR2 subunit of the AMPA receptor has been seen in amyotrophic lateral sclerosis, Huntington's and Alzheimer's diseases, and could contribute to excessive calcium permeability and cell death (2, 65).

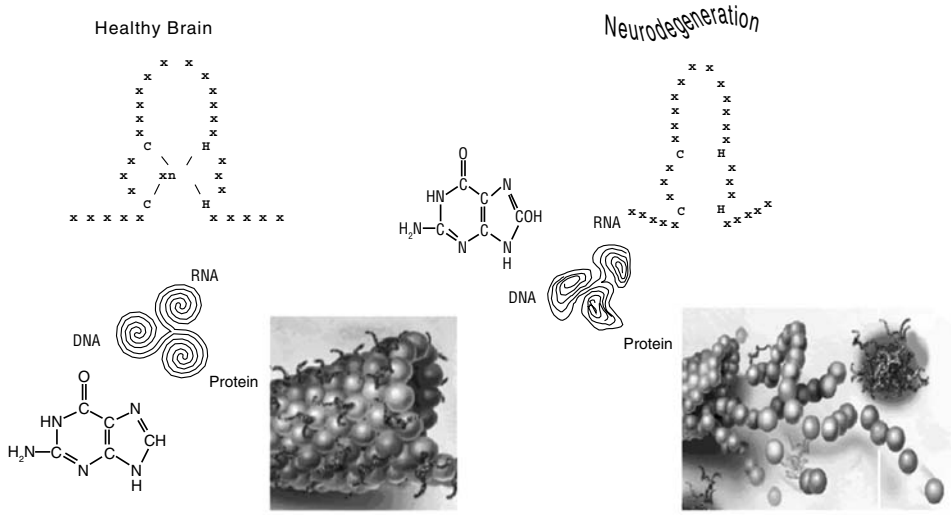

FIG. 1. The 'triskele' of gene expression in a healthy and neurodegenerative brain after exposure to oxidative stress. The triskele symbol represents three legs or branches radiating from a common center. In the case of gene expression, the phenotype of an individual (*the center*) is a product of the state (healthy or defective) of DNA, RNA and proteins (*the branches*). Each leg of expression is dependent on the others, creating an interdependent flow of information. In a healthy brain, nucleic acid damage is repaired, transcription and factors required for post-transcriptional processing function properly, and appropriate protein modifications and interactions are present. Overall, cellular homeostasis is maintained through normal physiological functions. In neurodegeneration, any branch may become distorted, resulting in the three branches of gene expression no longer being interdependent. Nucleic acids are improperly modified, transcription is disrupted, and protein processing spins out of control ultimately leading to the death of the neuron.

Protein metabolism is negatively impacted by oxidative stress. Damage to mitochondria, either through DNA damage or a dysfunctional Complex I will deplete the cell of its energy. The loss of ATP may shift proteolytic functions away from the energy-expensive UPS, to lysosomes, where proteins and their oxidized or nitrated residues accumulate. Increased cellular burdens of abnormal transcriptional or alternatively spliced gene products will only increase the proteinaceous deposits in lysosomes. The rapid accretion of lipid and protein residues into lipofuscin granules in neurodegenerative disease is, therefore, an important part of disease pathology and progression (45, 69). Ultimately, interference with cell homeostasis by oxidative radicals dysregulates gene expression and protein metabolism, and neuronal death ensues when the common upstream molecular processes contribute negatively to an already overburdened proteolytic system.

ACKNOWLEDGMENTS

The authors thank Dr. B.L. Roberts for his critical reading of the manuscript. This work was supported in part by a USPHS grant NS 41799 (GEM), and by a grant (W81XWH-05-1-0580) from United States Army Medical Research and Materiel Command NETRP program.

ABBREVIATIONS

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; cDNA, copy deoxyribonucleic acid; CRE, cyclic AMP response elements; CREB, CRE binding protein; DLB, dementia with Lewy bodies; DNA, deoxyribonucleic acid; MEF2, myocyte enhancer factor 2; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, messenger ribonucleic acid; MSA, multiple system atrophy; NII, neuronal intranuclear inclusions; 8OHG, 8- hydroxyguanosine; polyQ, polyglutamine; RNA, ribonucleic acid; ROS, reactive oxygen species; SOD, superoxide dismutase; UPS, ubiquitin-proteasomal system.

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Received for publication May 25, 2005; accepted July 9, 2005.

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