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Forum Review

Oxidative Damage in Huntington's Disease Pathogenesis

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ABSTRACT

Huntington's disease (HD) is a devastating neurodegenerative disorder characterized by the progressive development of involuntary choreiform movements, cognitive impairment, neuropsychiatric symptoms, and premature death. These phenotypes reflect neuronal dysfunction and ultimately death in selected brain regions, the striatum and cerebral cortex being principal targets. The genetic mutation responsible for the HD phenotype is known, and its protein product, mutant huntingtin (mhtt), identified. HD is one of several "triplet repeat" diseases, in which abnormal expansions in trinucleotide repeat domains lead to elongated polyglutamine stretches in the affected gene's protein product. Mutant htt-mediated toxicity in the brain disrupts a number of vital cellular processes in the course of disease progression, including energy metabolism, gene transcription, clathrin-dependent endocytosis, intraneuronal trafficking, and postsynaptic signaling, but the crucial initiation mechanism induced by mhtt is still unclear. A large body of evidence, however, supports an early and critical involvement of defects in mitochondrial function and CNS energy metabolism in the disease trigger. Thus, downstream death-effector mechanisms, including excitotoxicity, apoptosis, and oxidative damage, have been implicated in the mechanism of selective neuronal damage in HD. Here we review the current evidence supporting a role for oxidative damage in the etiology of neuronal damage and degeneration in HD. *Antioxid. Redox Signal.* 8, 2061–2073.

HUNTINGTON'S DISEASE: GENETIC BACKGROUND

HUNTINGTON'S DISEASE (HD) is considered a relatively rare neurodegenerative disease, with highest prevalence rates of 5–10 per 100,000 found in Europe and the United States. Its autosomal dominant inheritance, however, means it has a devastating impact on the families affected.

HD is caused by a mutation in a gene on chromosome 4p16.3 termed "*huntingtin*" *(HD*) (138). The mutation is an expansion of an unstable CAG repeat region in exon 1 of *HD* that is manifest as an expanded polyglutamine (Q_n) stretch, associated with a proline (P)-rich domain, in the 348-kDa protein product "huntingtin" (htt). In unaffected individuals, htt contains 11–34 Q, variable penetrance is seen with 35–39 Q, whereas the disease shows complete penetrance when the Q stretch exceeds 39 (reviewed in 89). Age at onset is inversely correlated with CAG expansion size, and especially long repeats (>55) confer juvenile onset (43, 89). Disease severity, extent of neuropathologic degeneration, and degree of DNA damage are all positively correlated with triplet repeat length (25, 51). Homozygosity does not alter age at onset, but does appear to increase the severity of disease progression (127). Because of the instability of the CAG repeat, another disease trait is anticipation, which is more pronounced after paternal inheritance (99). The most common repeat lengths of 42–50 generally correspond to HD-symptom onset in adulthood, typically in the fourth and fifth decades of life, although large variances in onset ages occur. Disease duration is generally 15–20 years, before premature death. Genomic studies in HD families have revealed a number of additional genetic loci that may also influence disease course. These include genes for ubiquitination enzymes, the glutamate GluR6 kainate receptor subunit, and apolipoprotein E (41, 44, 70, 100).

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HTT PROTEIN AND DISEASE PATHOGENESIS

Despite identification of the HD gene mutation in 1993 (138), the endogenous functions of both wild-type and mutant htt have still to be definitively elucidated, although current evidence suggests that htt is involved in a number of different cell processes (21,108). Htt is a large protein that takes on multiple conformations within cells. This property has been linked to the presence of multiple HEAT domains throughout the protein, which favor the formation of hydrophobic α helices that can generate elongated superhelices. It also contains multiple cleavage sites, and proteolytic processing of htt appears to be a normal physiologic event (40, 88, 145). Htt interacts with many other cellular proteins, its propensity for binding strengthened by the HEAT superhelices, the amino terminal region of htt, and the polyglutamine/proline tract. It is expressed ubiquitously throughout the body (82), and at the neuronal subcellular level, it is present in multiple compartments, with a largely cytoplasmic distribution in perikarya, axons, dendrites, and terminals. The protein contains a nuclear export signal domain, however, and at any given time, ~5% of the cell's htt is found in the nucleus, suggesting that it shuttles between the nucleus and the cytoplasm (120). A recent report suggests that this nuclear translocation activity is regulated by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in conjunction with the ubiquitin-E3-ligase Siah 1 (6). This study also demonstrated that increasing nuclear localization of mutant htt (mhtt) increased its cytotoxicity, findings that add fuel to the hypothesis that a nuclear action of mhtt is required for it to induce toxicity.

Wild-type htt is involved in developmental apoptosis (46, 110) and potential roles in trafficking, RNA biogenesis, and signaling have been inferred by its propensity for colocalization with synaptic vesicles, microtubules, and the postsynaptic density (39, 60, 140). Mutant htt (mhtt) toxicity is apparently due to gain of a novel function, rather than loss of wild-type htt function, because homozygous mhtt mice still develop normally, whereas expression of a single allele of the mutant gene is sufficient to rescue htt-null mice from death *in utero* (46). Mutant htt is also expressed ubiquitously throughout the body, and its distribution shows no overt selectivity for cerebral regions targeted by the disease process, suggesting that another property of neurons within these regions confers vulnerability to mhtt toxicity. *In vitro* and animal studies imply that polyQ-induced toxicity is exacerbated by protein truncation, suggesting that cleavage of mhtt to generate N-terminal htt fragments encompassing the expanded polyQ region may contribute to toxicity. Furthermore, reports that htt fragments are most abundant in cortical projection neurons (52) have led to the proposition that accumulation of mhtt fragments may contribute to corticostriatal dysfunction in HD pathogenesis.

N-terminal mhtt fragments eventually form proteinaceous aggregates, at rates that are exacerbated by longer CAG repeat lengths. Large, ubiquitinated, sodium dodecyl sulfate (SDS)-resistant aggregates that are visible by light microscopy (referred to as "inclusions") develop in neuronal nuclei (neuronal intranuclear inclusions, NII) and in dystrophic neurites (cytoplasmic inclusions, CI) over the disease course. NII and CI have been identified in HD brain and in the brains of mhtt-expressing mice, but are not restricted to the CNS (116). The cellular localizations of aggregates differ between CNS and somatic cells. In the brain, the bulk of aggregates are neuritic, whereas in skeletal muscle, aggregates are found solely within nuclei. Although inclusion formation is a hallmark of HD, the bulk of current evidence suggests that these large inclusions do not directly contribute to the pathogenic mechanism (5, 17, 60). This does not rule out the possibility that mhtt influences cellular functions via other novel interactions with proteins. A number of proteins show increased propensity to bind with htt when the expanded polyQ domain is present, including proteins involved in endocytosis (143) and trafficking (for example, PACSIN and huntingtin-associated protein-1, HAP-1) (85, 97, 139), a number of transcription factors, repressors, and cofactors [including CREB binding protein (CBP), specificity protein 1 (Sp1), TATA-binding protein-associated factor (TAFII-130), p53, NcoR, and Sin3a (45, 128, 131)], the synaptic scaffold protein PSD-95 (132), GAPDH (6), proapoptotic caspases (120), the calcium sensor protein calmodulin, and transglutaminases (149).

Thus, whereas the precise mechanism whereby the *HD* gene defect leads to progressive, selective neurodegeneration is still a tantalizing question, a number of cellular pathways show alterations during mhtt-mediated toxicity, including endocytosis, intracellular trafficking, transcriptional regulation, mitochondrial function, postsynaptic signaling, apoptotic cascades, and energy metabolism (20, 22, 29, 47). In this review, we concentrate on the evidence of a role for oxidative damage in HD etiology, and in particular, its potential involvement in disrupting some of the disrupted cellular processes listed earlier, over the course of the disease.

OXIDATIVE DAMAGE AND NEURONAL DYSFUNCTION IN HD

HD Neuropathology

The motor and behavioral disturbances in HD result from alterations in specific neurotransmitter systems and degeneration of selective neuronal subpopulations in the brain. The principal neuropathologic feature of HD is progressive caudal to rostral degeneration of the neostriatum (caudate and putamen) (142), which leads to the choreiform movement disorder characteristic of HD. A number of cognitive and psychiatric disturbances are also prevalent features of the disease, including emotional disturbances, mood changes, and depression. These syndromes generally involve dysfunction in the cerebral cortex and the subcortical limbic system, and disruption of GABAergic and glutamatergic neurotransmitter signaling pathways—systems that are also affected by HD pathology (20, 37, 93).

Although HD pathology eventually affects many brain regions, the primary site of degeneration is within the caudate and putamen (neostriatum). The medium spiny projection neurons show greatest susceptibility (141). Spiny neurons containing the inhibitory neurotransmitter γ-aminobutyric

acid (GABA) constitute 80% of striatal neurons and are the principal input and output neurons of the striatum. Subsets of spiny neurons are classified by the colocalization of GABA with enkephalin (ENK), substance P (SP), dynorphin, or calbindin. In HD striatum, ENK-containing spiny neurons that project to the external segment of the globus pallidus (GPe) are involved earliest and most severely, followed by SP-containing neurons projecting to the internal segment (GPi). Because these are important players in corticostriatal-thalamocortical loops that regulate movement and tone, preferential loss of these neuronal populations underlies the characteristic involuntary choreiform movements in HD (1, 24). Aspiny interneurons are relatively spared during disease progression. These include large aspiny interneurons that use acetylcholine (ACh) as their neurotransmitter and medium-sized interneurons typically containing nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d), neuropeptide Y (NPY), somatostatin (SS), and/or nitric oxide synthase (NOS), and sometimes cholecystokinin (CCK) or the calcium-binding protein parvalbumin (11).

Both the selective vulnerability of the neostriatum and the susceptibility of striatal neuron subpopulations have been suggested to reflect an increased risk for glutamate-mediated excitotoxic damage. The striatum receives a substantial glutamatergic input from the cerebral cortex. The spiny neurons most vulnerable to degeneration contain mainly *N*-methyl-D-aspartate (NMDA) glutamate-receptor subtypes (148), predominantly NMDAR-1 and NMDAR-2B subtypes that facilitate Ca^{2+}-mediated excitotoxicity (126), consistent with the possibility that these cells are lost preferentially because of an excitotoxic insult. In contrast, GluR-1 AMPA ionotropic glutamate-receptor subtypes are more prevalent in the relatively preserved aspiny interneurons. Interestingly, a recent study suggests that variations in genes encoding different NMDA-receptor subtypes, expressed primarily in the striatum, influence age at onset in HD patients (4). The majority of HD patients reach Vonsattel grade 3 or 4 by the time of their premature deaths, by which stage only 5–10% of caudate and putamen neurons remain (141). It is therefore difficult to determine exactly which cellular events led to neurodegeneration in lost cells. However, some information can be gained from surviving neurons, assuming that a cohort of the remaining cells is dysfunctional by this stage. Most surviving neurons appear morphologically normal, although some are atrophied; however, postmortem studies have revealed increased levels of the oxidative-damage marker lipofuscin in these cells (24).

The relative resistance of NADPH-d–containing aspiny interneurons in HD has been attributed to their capacity to generate NO. NO synthase (NOS)-positive striatal neurons are resistant to a number of acute excitotoxic insults mediated by nitric oxide (NO), including ischemic insults (77, 95). This resistance may be related to antioxidant properties of these cells, since cultured NO- and NMDA-resistant neurons contain elevated levels of the mitochondrial superoxide radical scavenging enzyme manganese superoxide dismutase (MnSOD, SOD2) (55). The extensive neuronal loss seen in caudate and putamen of the most severely affected HD patients (Vonsattel grade 4) suggests, however, that ultimately all cell types are susceptible to cell death in HD.

Postmortem studies in HD brain

Mutant htt expression is linked with oxidative damage to multiple cellular components, including proteins, DNA, and phospholipids in HD brain postmortem tissue, lymphoblasts, and cerebrospinal spinal fluid (CSF) (24, 49, 54). Studies in postmortem brain show increased levels of DNA strand breaks, DNA oxidative damage products such as 8-hydroxydeoxyguanosine (OH^8dG), 3-nitrotyrosine (3-NT, a product of peroxynitrite-mediated protein nitration), malondialdehyde (MDA, a marker for oxidative damage to lipids), lipofuscin accumulation (a marker of lipid peroxidation), and heme oxygenase (HO, formed during oxidative stress), in HD striatum and cerebral cortex. Further, activated microglia are also found in HD brain from early disease stages, most prominent in areas proximal to the most severely affected areas (115), and inducible NO synthase (iNOS) has been identified in microglia close to degenerating neurons (134).

Striatal neurons in postmortem HD brain show increased incidences of DNA strand breaks, the extent of which positively correlates with CAG repeat length (26, 106), suggestive of both apoptotic and necrotic mechanisms of cell death, and free radical–mediated oxidative damage to DNA. Interestingly, in studies that demonstrated substantial increases in DNA fragmentation in both HD cerebral cortex and striatum, relative to levels in age-matched control brain, we found that mitochondrial DNA (mtDNA) is more susceptible to fragmentation than is nuclear DNA (nDNA) (24). By using HPLC, we also found increased oxidation of DNA bases in HD brain. Oxidation of deoxyguanosine to generate 8-hydroxy-deoxyguanosine (OH^8dG) was increased in nDNA from caudate of HD patients with severe neuropathology (Vonsattel grade 4), relative to age- and sex-matched controls (23). Brain regions relatively spared by HD pathology, including frontal cortex, parietal cortex, and cerebellum, did not show significant alterations in nDNA OH^8dG (23).

Deposition of lipofuscin is associated with peroxidative damage to lipids. This fluorophore is produced by the reaction of aldehyde products of free radical–induced oxidation with amino compounds and accumulates in lysosomes in postmitotic cells, including neurons and cardiac myocytes. Lipofuscin deposition increases with age (137) and under conditions of increased oxidative stress and metabolic rate (98). Lipofuscin deposition is exacerbated in HD brain, and the extent of lipofuscin accumulation in HD striatal neurons increases with the neuropathologic severity of the disease (24).

Immunohistochemical staining in postmortem tissue also demonstrates oxidative damage to lipid, protein, and DNA in HD cerebral cortex and striatum (24, 49). Staining for 3-NT, MDA, OH^8dG, and HO, all showed increased intensity and extent of immunoreactivity in HD brain, with the density of staining increasing with increased pathologic grade (24, 49, 54). In low-grade HD cases (Vonsattel grades 1 and 2) with less extensive cerebral pathology, oxidative damage appears first in dorsal striatum and eventually affects caudal striatum as the disease progresses. By Vonsattel HD grades 3 and 4, striatal cell loss is already severe, and hence immunoreactivities of oxidative damage markers decrease accordingly (24).

Additional, although more indirect, evidence of a role for oxidative stress in HD etiology is the fact that the mitochon-

drial tricarboxylic acid (TCA)-cycle enzyme aconitase is markedly impaired in HD brain. The extreme reduction in aconitase activity observed in the caudate of severely affected HD patients (133) has been attributed to Fe-S clusters within the protein, which make it a prime target for free radical–mediated oxidative damage. Furthermore, the energetic defects seen in HD brain (23, 57) are similar to those induced in cell culture by peroxynitrite, which preferentially inhibits activity of the electron-transport chain enzyme complex II-III and, to a lesser extent, complex IV (16). In addition, inhibition of state 3 respiration induced by expression of expanded polyQ constructs in isolated mitochondria is associated with increased generation of reactive oxygen species (ROS) (107).

Biomarkers in the circulation?

Elevated levels of the DNA damage marker OH^8dG have recently been detected in HD blood plasma (61), and the lipid peroxidation markers MDA and 4-hydroxynonenol are increased in the serum (130) of symptomatic HD patients. These observations are consistent with oxidative DNA damage contributing to HD pathogenesis and suggest that measuring plasma OH^8dG levels holds promise as a peripheral biomarker for tracking disease progression. Furthermore, plasma OH^8dG elevations were ameliorated by administration of creatine, a high-energy phosphate donor that can buffer cellular energy depletion (61), consistent with the hypothesis that oxidative damage in HD is induced by defects in energy metabolism.

Another intriguing recent study suggests that mhtt-induced perturbations of the kynurenine pathway (Fig. 1) may also be detected relatively noninvasively in HD patients' blood (130). This study reports that the ratio of kynurenine to tryptophan is substantially elevated in HD blood, compared with levels in age- and sex-matched control subjects. This implies increased activity of indoleamine dioxygenase (IDO) activity to metabolize tryptophan, which is linked with increased oxidative damage, because superoxide radical ($O_2^{\bullet -}$) is a preferred substrate for IDO. In addition, increased blood levels of lipid peroxidation markers were found in the same HD patients (130). Driving the kynurenine pathway is consistent with increasing generation of the endogenous excitotoxin quinolinic acid (Fig. 1) (67, discussed later), and the generation of metabolites with prooxidant properties, 3-hydroxykynurenine and 3-hydroxyanthranilic acid. Although Stoy and colleagues (130) found that blood quinolinic acid levels were equivocally altered in HD patients, and blood levels of these prooxidant metabolites were unaltered, elevated 3-hydroxykynurenine levels have previously been detected in the putamen and frontal cortex of HD postmortem brain (58, 102). Because this compound is linked with the generation of free radicals and hydrogen peroxide, these observations are therefore suggestive of an increased propensity for oxidative damage in HD brain. Another kynurenine metabolite, kynurenic acid, is an ionotropic glutamate-receptor antagonist with particular efficacy for modulating NMDA-receptor subtype activity via binding at co-agonist glycine sites (13). It is neuroprotective against a number of excitotoxic insults (129) and may therefore act as an endogenous neuroprotectant against mhtt-induced excitotoxicity. Studies of kynurenic acid levels in HD brain, however, show ambiguous results, with some studies reporting increased kynurenic acid levels in brain tissue from symptomatic patients (35, 58) and from a transgenic mouse model of HD (58), whereas others show decreases in HD brain and CSF (9, 62).

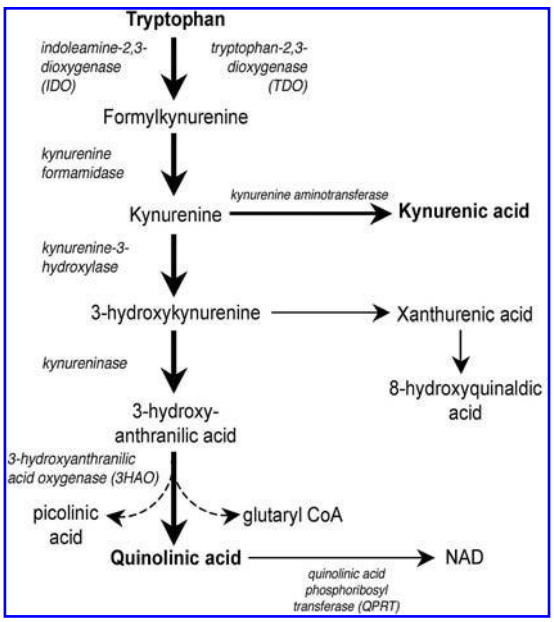

FIG. 1. Tryptophan metabolism and quinolinic acid generation via the kynurenine pathway.

Animal models of HD

Genetic HD models. The generation of genetic mouse models of HD expressing mhtt has provided the unprecedented opportunity to observe the evolution of pathogenic processes in the context of a chronically progressing disease phenotype. It is not, of course, possible to recapitulate all aspects of HD pathology, phenotype, or human gene expression in a mouse, but a number of different mouse models exist that closely simulate some aspects of HD pathogenesis—the nature of the disease phenotype expressed depending on the context in which the mutant gene is expressed (reviewed in 22, 63). In general terms, mice expressing N-terminal fragments of *HD* exon 1 develop a rapidly progressing disease phenotype that recapitulates aspects of the motor defects and weight loss seen in HD, whereas mice expressing full-length human mhtt, or with mutations knocked into the full-length endogenous murine *Hdh* gene, have a more protracted disease course with less-prominent motor defects, but develop selective neuronal degeneration.

The majority of reports of oxidative damage in HD mice are from "fragment" mouse models of HD that express an N-terminal fragment of human mhtt, in particular the R6/2 mouse line (92), because these are the most thoroughly characterized and thus the most commonly used of the models available to date. HPLC studies have revealed increased concentrations of OH^8dG in the urine, plasma, and striatal micro-

dialysates of R6/2 HD mice, and in isolated mouse brain nDNA (14). R6/2 mouse striatum also shows increased immunostaining for OH^8dG (14). These findings were made in symptomatic mice at late stages of the disease process, adding to the argument that although oxidative damage may play a role in the pathogenesis of neuronal degeneration in HD and HD models, it is likely to be secondary to other toxic insults.

It has still to be determined whether oxidative damage occurs before overt neuronal dysfunction in genetic models of HD, which would suggest a causative role in the pathogenetic mechanism. In Fig. 2, however, we present immunohistochemical findings from early disease–stage (8-week-old) R6/2 HD mice demonstrating overt lipid peroxidation in the striatum. At this age, mice show body-weight loss, the onset of tremor and reduced open-field motility, and impaired motor ability (for example, as assessed on a rotarod apparatus). No signs of overt CNS cell loss are seen at this time. The striata of 8-week-old mice show increased immunostaining for three different lipid peroxidation markers, malondialdehyde (MDA), 4-hydroxynonenal (HNE), and the isoprostane 8-iso-prostaglandin (8-isoPGF2a), in comparison with levels in littermate wild-type mice. The intensity of immunoreactivity for these oxidative damage markers increases over time, as shown in 14-week-old animals (Fig. 2), suggesting a progressive accumulation of oxidative damage products in disease-targeted brain regions. By this age, mice are approaching the end of their life spans, the HD-associated phenotypes of motor defects and weight loss are more pronounced, brain weight is reduced, and histochemistry reveals striatal, cortical, and neuronal atrophy (2).

The *HD* mutation also appears to increase susceptibility to metabolic stress in HD mice. We were unable to detect a basal elevation in free radical production in the striatum of symptomatic R6/2 HD mice, by using HPLC analysis of microdialysates to measure the rate of conversion of 4-hydroxybenzoic acid to 3,4-DHBA as a measure of hydroxyl radical generation (15). Administration of the mitochondrial toxin 3-nitropropionic acid (3-NP), however, significantly increased striatal 3,4-DHBA generation concomitant with striatal lesion formation in both wild-type and HD mice, but both free radical generation and lesion volume were exacerbated by mhtt expression in the HD mice (15). Glutathione levels are also elevated in cortical and striatal mitochondria from R6/2 mice, suggesting that HD mitochondria experience an elevated oxidative stress (32).

In another fragment mouse model of HD (the R6/1 line), elevated lipid peroxidation appears to affect vulnerable brain regions specifically (104). In this HD mouse line that expresses a shorter CAG repeat than the associated R6/2 line, and hence develops a more protracted and less severe phenotype than R6/2 mice, the extent of lipid peroxidation within the striatum increases as disease symptoms progress. Peroxidative damage within the cerebral cortex appears to be less

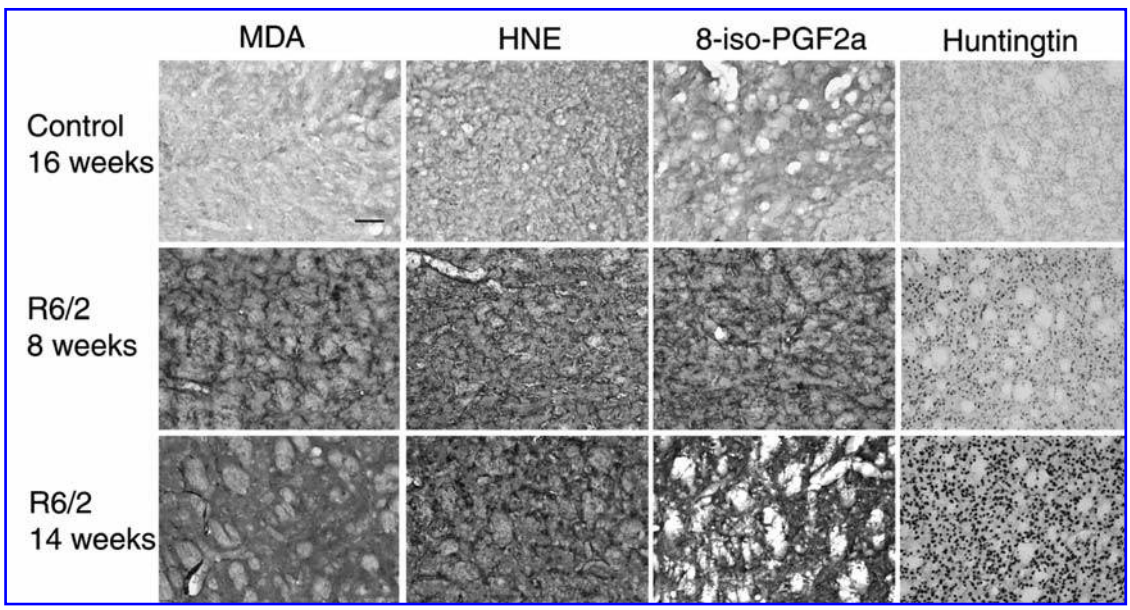

FIG. 2. Increases in lipid peroxidation markers are exacerbated with disease progression in HD transgenic mice. Representative sections through the striatum of R6/2 HD mice at the approximate age of symptom onset (8 weeks), in end-stage morbid mice (14 weeks), and in wild-type littermate control mice. Immunostaining for malondialdehyde (MDA), 4-hydroxynonenal (HNE), and the isoprostane 8-iso-prostaglandin (8-isoPGF2a), demonstrates that all three lipid peroxidation markers are elevated in R6/2 mice around the age of symptom onset, compared with levels in older wild-type mice. The intensity of immunoreactivity for these markers also increases as mice age, concomitant with exacerbated disease phenotypes of motor defects and weight loss in these animals. The normal life span of this HD mouse line is ~14–16 weeks. The right-hand column shows immunostaining for huntingtin (htt; EM48 antibody), demonstrating the progressive deposition of htt-positive aggregates within striatal cells over the disease course.

pronounced than in the striatum, whereas the cerebellum is spared (104).

Additional evidence of a role for oxidative stress in disease pathogenesis in HD mice comes from a recent proteomics study in symptomatic R6/2 mice that has identified increased oxidation of a number of key cellular proteins (105). These include the metabolic enzymes creatine kinase and aconitase, alpha- and gamma-enolase (neuron-specific enolase), heat shock protein 90, and the voltage-dependent anion channel 1, suggesting that oxidative modification of cellular components may contribute to cellular dysfunction and ultimately to disease pathogenesis. Further indirect evidence that oxidative damage participates in the process of degeneration in HD comes from findings that the antioxidant agents lipoic acid and BN-82451 are neuroprotective in HD mice (R6/2 and N171–82Q lines), increasing survival and delaying striatal atrophy in these genetic models of HD (2, 76).

Toxin models of HD

Activity of complex II (succinate ubiquinol oxidoreductase) of the respiratory chain is reduced in severely affected brain regions (caudate and putamen) of symptomatic HD patients (23, 57, 133). Consequently, pharmacologic inhibitors of mitochondrial complex II have been found to induce striatal damage and motor phenotypes in animals that closely resemble those seen in HD patients. Here we discuss observations from studies using mitochondrial complex II toxins (3-NP and malonate) and excitotoxins (quinolinic acid), suggesting that oxidative damage associated with HD-like lesions is linked with mitochondrial energetic dysfunction and excitotoxicity.

3-Nitropropionic acid (3-NP). The mitochondrial toxin 3-nitropropionic acid (3-NP) irreversibly inhibits the activity of the mitochondrial metabolic enzyme succinate dehydrogenase (SDH), which participates in both the tricarboxylic acid (TCA) cycle and in complex II–III of the electron-transport chain. Systemic administration of 3-NP to humans, nonhuman primates, and rodents results in CNS lesions that selectively target medium spiny neurons within the striatum, recapitulating the regional and neuronal specificity of pathologic events in HD (for review, see 19, 21).

In humans, ingestion of 3-NP induces cognitive impairment and motor abnormalities including dystonia, involuntary jerky movements, torsion spasms, and facial grimaces. CT scans show that 3-NP intoxication produces cerebral lesions principally targeting the basal ganglia, localized primarily to the putamen but sometimes extending to the caudate (87). Systemic administration of 3-NP to both rats and primates produces striatal lesions that are strikingly similar to those seen in HD brain, and thus 3-NP has become a widely used experimental tool to model the neuronal susceptibility and motor phenotype characteristic of the disease (19). In primates, prolonged 3-NP administration produces selective striatal lesions involving loss of calbindin neurons but sparing of NADPH-d neurons, concomitant with spontaneous and apomorphine-inducible choreiform movement disorders resembling HD (17).

In rats, 3-NP–induced basal ganglia lesions are associated with elevated lactate levels (94), increased NMDA-receptor binding (146), and can be ameliorated by reducing the glutamatergic innervation of the striatum, via either application of NMDA-receptor antagonists or decortication (73, 122). These observations are consistent with the 3-NP toxicity arising from secondary excitotoxic mechanisms, whereby energy depletion within vulnerable neurons facilitates abnormal activation of NMDA receptors and subsequent Ca^{2+} influx (11, and discussed later). Interestingly, the neurodegenerative sequelae of systemic administration of the toxin are largely restricted to the striatum, despite a relatively uniform reduction in SDH activity throughout the brain (18), highlighting once again the vulnerability of striatal neurons to metabolic stress. Stimulating energy generation by administration of creatine markedly attenuates 3-NP toxicity, ameliorating lesion volume, lactate production, and ATP depletion in the striata of 3-NP–treated rats (94).

Now numerous reports assert that 3-NP toxicity is associated with increased oxidative damage within the CNS. Systemic 3-NP administration to rodents results in elevations in striatal hydroxyl (OH^-) and superoxide ($O_2^{\bullet -}$) free radical generation (72, 73, 123), and in a number of markers of oxidative damage, including OH^8dG, 3-NT (75, 123), the lipid peroxidation marker MDA (111), oxidized hydroethidine (72), and DNA fragmentation (71). Susceptibility to 3-NP–induced oxidative stress is also worsened by aging, demonstrated by increased DNA fragmentation and reduced expression of the DNA repair enzyme apurinic/apyrimidinic endonuclease in older mice (19, 71). The involvement of impairments in intrinsic antioxidant protection pathways after 3-NP is further supported by observations of reduced striatal glutathione (GSH) levels (135). In addition, mice overexpressing the superoxide free radical scavenger Cu/Zn superoxide dismutase (SOD1) are resistant to 3-NP–induced toxicity, developing far smaller striatal lesions and lower levels of oxidative damage markers than do wild-type mice exposed to the same 3-NP treatment regimen (12). In contrast, reducing free radical scavenging capability by eliminating the gene for glutathione peroxidase (GSHPx) in knockout mice exacerbated striatal damage and 3-NT elevations after 3-NP administration (75). Mice with a deficiency in the mitochondrial SOD, manganese superoxide dismutase (MnSOD; $SOD2^{-/+}$ mice), also show enhanced vulnerability to 3-NP (3, 72). Oxidized hydroethidine, 8-hydroxyguanosine, and 3-NT immunoreactivity were found to be increased in $SOD2^{-/+}$ mice compared with wild types after 3-NP administration. Furthermore, increasing CuZnSOD antioxidant activity in $SOD2^{-/+}$ mice by crossing them with SOD1 overexpressing mice attenuated both the DNA fragmentation and striatal lesion formation induced by 3-NP in $SOD2^{-/+}$ mice, suggesting that superoxide production may critically regulate the degree of excitotoxic damage and subsequent oxidative damage induced in the striatum by 3-NP.

More indirect evidence for the critical role of oxidative damage in the pathogenic process initiated by 3-NP is that a number of antioxidants protect against 3-NP toxicity in rodents. Striatal 3-NP lesions are attenuated by free radical spin traps (50, 122, 147), although one study reports exacerbation

of 3-NP neurotoxicity by the spin trap PBN (81). Protective effects are also reported with nitric oxide synthase (NOS) inhibitors (68, 121), the glutathione precursor *N*-acetyl-L-cysteine, NAC (50, 68), the antiinflammatory and antioxidant agent celastrol (34), and by overexpression of the heat shock protein HSP-70 (38).

Increases in lipid peroxidation levels and astrocytic damage have also been reported in the hippocampus of 3-NP–treated rats (111). This hippocampal damage was prevented by treatment with taurine, a semiessential amino acid with both antioxidant and $GABA_A$ agonist activity. Taurine also reversed the impaired prepulse inhibition (PPI) response and locomotor hypoactivity caused by 3-NP in these animals, concomitant with a twofold increase in GABA concentration, increased succinate dehydrogenase activity, as well as having antioxidant effects including reducing striatal MDA and elevating striatal glutathione (GSH) levels (135).

Another line of evidence supporting oxidative damage in the etiology of 3-NP–mediated neuronal damage comes from studies of cerebral matrix metalloproteinase (MMP) levels in response to 3-NP. Abnormal levels of proteases and free radicals activate MMPs, leading ultimately to digestion of the blood–brain barrier (BBB). 3-NP toxicity increases MMP-9 expression in the injured striatum, putatively because of oxidative damage generating elevated levels of oxidized hydroethidine. Increased BBB permeability ensues. MMP inhibition attenuates 3-NP–induced BBB disruption, cerebral swelling, and lesion formation (74). Furthermore, SOD1-overexpressing transgenic mice show decreased lesion size and edema along with decreased immunoreactivity for MMP-9 after 3-NP (74), implying that reducing 3-NP–associated oxidative stress prevents the subsequent activation of MMP-9.

3-NP–mediated neuronal injury also induces antioxidant defense systems. One such mechanism involves activation of a transcription factor, NF-E2 related factor (Nrf2), after 3-NP exposure (27, 125). Nrf2 controls the coordinated expression of critical antioxidant and detoxification genes (phase 2 genes) through a promotor sequence termed the antioxidant response element (ARE) (66). Phase 2 genes work synergistically to produce a pleiotropic cellular defense that scavenges reactive oxygen/nitrogen species (ROS/RNS), detoxifies electrophiles and xenobiotics, and maintains intracellular reducing potential (65, 83). Normally, Nrf2 is sequestered in the cytoplasm by the actin-bound regulatory protein Keap1 (69), which acts as a molecular "switch." In response to electrophiles/ROS, Keap1 undergoes a conformational change that releases Nrf2, allowing it to translocate into the nucleus and activate expression of phase 2 genes (144). Thus, Nrf2 provides an important mechanistic link between oxidative stress and the expression of prosurvival antioxidant genes.

By using transgenic reporter mice, Calkins and colleagues (2005) recently demonstrated that ARE-dependent gene expression occurs in the immediate border of 3-NP–induced striatal lesions, potentially in reactive astrocytes typically found within this region (27). Loss of Nrf2 function in $Nrf2^{-/-}$ mice exacerbated 3-NP–induced motor deficits and striatal lesions, when compared with both wild-type mice and heterozygous knockout animals ($Nrf2^{+/-}$) (125). Preactivation of the Nrf2 response by administration of the small molecule Nrf2 inducer, *tert*-butylhydroquinone (tBHQ) attenuated 3-NP toxicity in $Nrf2^{+/-}$ mice (but not in $Nrf2^{-/-}$, as induction of Nrf2 is necessary for protection). Similarly, overexpression of Nrf2 via viral Nrf2 gene delivery to the striatum before 3-NP insult also reduced 3-NP lesion size. In addition, 3-NP–induced ARE-dependent gene expression in cultured astrocytes could be completely suppressed by overexpression of a dominant-negative form of Nrf2 (125). Thus, 3-NP–mediated toxicity appears to involve free radical damage mechanisms, and this oxidative response activates protective antioxidant gene-expression pathways. It remains to be seen whether similar modulations of protective gene-expression pathways occur in HD. However, an increasing body of evidence suggests that mhtt interferes with gene transcription to modulate numerous cellular pathways in HD brain and in genetic animal models, suggesting that this may be a key step in the mhtt initiation of cellular damage (20, 131).

Malonate. Malonate is another selective inhibitor of succinate dehydrogenase that induces motor impairments and neuronal pathology resembling HD, after intrastriatal administration in rodents (it does not cross the BBB) (56). Similar to 3-NP, malonate produces age-dependent striatal lesions that can be significantly attenuated by NMDA-receptor antagonists. Further indirect evidence that energetic defects contribute to malonate-induced neurodegeneration come from observations that the proenergy and antioxidant compound coenzyme Q_{10} attenuates malonate neurotoxicity in animal models (11, 123). Creatine and cyclocreatine are also neuroprotective against malonate toxicity in mice, via a mechanism whereby increasing metabolic efficiency reduces malonate-induced hydroxyl radical generation (94). Malonate-induced lesion volume can be further reduced by combining creatine treatment with administration of the antioxidant nicotinamide (91).

Malonate-induced increases in the conversion of salicylate to 2,3- and 2,5-dihydroxybenzoic acid, an index of hydroxyl radical generation, are exacerbated in mice lacking the free radical scavenger glutathione peroxidase (GSHPx) (75). Mice lacking the neuronal isoform of NOS (nNOS) gene, and therefore with impaired nitric oxide (NO) generation, also show reductions in the size of malonate-induced striatal lesions (123). Further, 3-NT concentrations are elevated after intrastriatal malonate injection, whereas lesion size is attenuated by free radical spin traps and nitric oxide synthase (NOS) inhibitors (123).

Therefore, substantial evidence indicates that nitric oxide–mediated oxidative damage is involved in cell death processes after energetic disruption induced by both 3-NP and malonate. Because these mitochondrial toxins induce a pattern of cell damage mimicking that seen in HD, by a mechanism that involves interfering with the activity of an oxidative phosphorylation enzyme complex known to be impaired in HD brain, it is therefore tempting to extrapolate a key role for oxidative damage as an execution step in the cell-death pathway initiated by mhtt in HD patients.

Excitotoxin HD models: quinolinic acid. The involvement of excitotoxic processes in striatal vulnerability is inferred by observations that a number of glutamate receptor agonists induce neuronal injury resembling the selective cell

death seen in HD striatum. Intrastriatal injections of the endogenous NMDA-receptor agonist quinolinic acid induce preferential loss of medium spiny neurons but spare NADPH-d and parvalbumin-positive neurons, whereas injection of the non–NMDA-receptor agonists kainate or quisqualate results in loss of both spiny and NADPH-d–positive aspiny neurons (11, 77). NMDA receptor–mediated lesions in primates are associated with an apomorphine-inducible movement disorder resembling the choreic movements in HD. Some (although not all) genetic models of HD also show age-dependent declines in glutamate-receptor densities in striatum and cerebral cortex, altered striatal neuron responses to glutamate agonists, and increased vulnerability to NMDA and quinolinic acid–induced excitotoxic damage (28, 30, 59, 150).

The relevance of excitotoxin models to HD pathogenesis is highlighted by the fact that striatal neurons that are especially vulnerable to injury in HD are anatomically put at risk for excitotoxic insults, because of the large glutamatergic innervation from the cerebral cortex, and by findings of elevated levels of the endogenous excitotoxin quinolinic acid in HD brain (8, 102, 109). Toxicity induced by the kynurenine pathway metabolite quinolinic acid (Fig. 1) involves increases in ROS (84), DNA damage (113), reduced glutathione levels (90), and peroxidative damage that can be rescued by Fe-porphyrin compounds (84, 103). The energy substrate pyruvate is also protective against quinolinic acid toxicity (113). Interestingly, intrastriatal administration of quinolinic acid in rodents has also been shown to increase htt immunoreactivity (136), leading to a suggestion that htt may be induced as a cytoprotective agent after activation of the kynurenine pathway, and again emphasizing the close links between this pathway and HD pathogenesis.

Mutant Htt and oxidative damage

Defects in mitochondrial function and energy metabolism pathways in HD brain. Substantial evidence indicates that defects in cerebral energy metabolism are among the earliest adverse events induced by mhtt. Because metabolic pathways and mitochondrial function are intrinsically linked to a number of cellular systems and processes that are ultimately disrupted during the progression of HD, including the generation and scavenging of free radicals, it appears that oxidative damage in HD is linked with bioenergetic dysfunction. Impairments in energy metabolism in affected brain regions of HD patients have been reviewed extensively elsewhere (22, 119). In brief, classic signs of HD include profound weight loss (42) and skeletal muscle wasting associated with defects in ATP generation (86, 114). Glucose metabolism is reduced in brain regions targeted by the disease by the time patients are symptomatic (48, 79), and for some period before symptom onset (33, 48), indicative of neuronal dysfunction and/or loss principally in the basal ganglia and cerebral cortex. Lactate production is elevated in the basal ganglia and cerebral cortex of symptomatic HD patients, but can be attenuated by treatment with the metabolic co-factor coenzyme Q_{10} (78). Biochemical studies in HD postmortem tissue have revealed selective dysfunction of components of the mitochondrial tricarboxylic acid (TCA) cycle and electron transport chain (ETC) in affected brain regions, in particular complex II, complex IV, and aconitase (23, 57, 133). Further indirect evidence that energetic defects contribute to neurodegeneration in HD is provided by findings that creatine and coenzyme Q_{10} are protective in animal models of HD, putatively through enhancing the efficiency of energy production and delivery in neurons.

Mitochondrial dysfunction is further implicated by morphologic abnormalities in brain and lymphoblast mitochondria from HD patients, and mitochondrial membrane depolarization, Ca^{2+} handling, and ATP generation are also abnormal in HD lymphoblasts. Mutant htt has also been shown to impair oxidative phosphorylation and energy production when expressed in a clonal striatal cell line. STHdh$^{Q111/Q111}$ cells, derived from the striatum of *Hdh* knock-in mice, show reduced cAMP levels (53), increased vulnerability to mitochondrial complex II inhibition by 3-NP (112), and significantly reduced O_2 consumption and ATP production rates relative to wild-type cells, attributed to increased Ca^{2+} influx through NMDA receptors (96, 124).

Excitotoxic processes. Mutant htt expression induces alterations in several components of the glutamate neurotransmitter system in affected brain regions that may render cells vulnerable to glutamate-mediated excitotoxic damage (discussed earlier). The considerable glutamatergic innervation of the neostriatum from the cerebral cortex is postulated to exacerbate the risk of excitotoxic damage to striatal neurons. Studies of glutamate-receptor subtypes in postmortem tissue from late-stage and presymptomatic HD patients show that NMDA receptors are selectively depleted in HD striatum, suggesting preferential loss of neurons bearing these receptors (148), and that excitotoxic stress may occur early in the disease course.

Excitotoxic damage may also occur in circumstances in which extracellular glutamate levels are normal but energy metabolism is impaired, by so-called "secondary excitotoxicity" (11, 22). In conditions of impaired energy metabolism, reduced ATP production may disrupt the maintenance of Na^+/K^+-ATPase pumps regulating ionic and voltage gradients across cell membranes, leading to prolonged or inappropriate opening of voltage-dependent ion channels and partial membrane depolarization. If this is severe enough, then normally inert extracellular levels of glutamate can trigger NMDA-receptor activation resulting in Ca^{2+} influx, nitric oxide synthase (NOS) activation, and free radical production via increased peroxynitrite ($ONOO^-$) formation. $ONOO^-$, produced by the reaction of NO with superoxide radical ($O_2^{\bullet -}$), may then react with CuZn-SOD to form nitronium ion, which nitrates tyrosine residues in proteins (64). The elevated Ca^{2+} influx induced may also result in sequestering of Ca^{2+} in mitochondria, which in turn increases free radical generation by the mitochondria. Free radicals including $O_2^{\bullet -}$ and hydroxyl radicals ($OH^{\bullet -}$) are constantly produced as by-products of aerobic metabolism, but production increases under circumstances of electron transport chain inhibition or molecular defects (24). Ca^{2+} concentrations similar to those induced by neuronal exposure to excitotoxins increase mitochondrial generation of $OH^{\bullet -}$ and carbon-centered radicals (24*)*. An alternative pathway for NO/$ONOO^-$-mediated toxicity is via peroxidative DNA damage, leading to activation

of poly(ADP-ribose) synthetase (PARP). PARP is a nuclear enzyme involved in DNA repair, but excessive PARP activation can exhaust cellular energy supplies, inducing cell death cascades due to energetic dysfunction (36).

Potential functional consequences of oxidative damage to DNA, proteins and lipids include perturbations of DNA transcription and translation, protein synthesis, enzyme activities, neuronal trafficking, endocytosis, abnormal htt/protein interactions, and membrane fluidity, all of which are seen in HD brain or animal models of HD (22, 47, 60, 80, 131). Increased free radical generation that outstrips antioxidant and repair capabilities of mitochondria will therefore lead to a negative cycle of progressively increasing oxidative damage to the mitochondria, ultimately exacerbating cellular injury. The slow, progressive nature of neuronal injury in chronic neurodegenerative disorders such as HD, therefore, may reflect the cycling of free radicals and mitochondrial dysfunction, leading to the gradual buildup of damaged and dysfunctional cell components, until a threshold is reached, above which neuronal dysfunction and death ensue.

CONCLUSIONS

As discussed earlier, compelling evidence indicates that oxidative damage to multiple cellular elements contributes to neuronal dysfunction at some stage of the cell death mechanism induced by mhtt in HD brain. Findings from animal models using either genetic approaches or mitochondrial toxins to replicate aspects of HD pathology, however, suggest that accumulation of oxidative damage markers is a relatively late phenomenon, evident after the onset of symptoms and other pathologic changes associated with HD. Thus, it appears that oxidative damage is most likely an execution step induced secondarily to other mhtt-mediated events. The prime candidates for these defective pathways include bioenergetic and mitochondrial defects, but the exact mechanism whereby mhtt initiates bioenergetic defects still must be elucidated. In this regard, recent evidence suggests that mhtt has the ability to interact with mitochondria, and hence may deleteriously influence mitochondrial function directly (31, 101). Alternatively, another recent and persuasive argument is that mhtt's primary deleterious action within cells may be at the level of gene transcription (6, 20, 45, 128). The resultant downstream modulation of gene regulation would affect many different cellular pathways, but evidence is building that implicates this mechanism as a potential source of the defects in energy metabolism, mitochondrial function, and increased oxidative damage seen in HD brain and *in vivo* models of the disease.

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ABBREVIATIONS

ACh, acetylcholine; ARE, antioxidant response element; BBB, blood–brain barrier; CBP, CREB binding protein; CCK, cholecystokinin; CI, cytoplasmic inclusions; CREB, cAMP-responsive element binding protein; 3,4-DHBA. 3,4-dihydroxybenzoic acid; ENK, enkephalin; GABA, γ-aminobutyric acid; GAPDH, glyceraldehydes 3-phosphate dehydrogenase; GPe, globus pallidus external segment; GPi, globus pallidus internal segment; GSH, glutathione; GSHPx, glutathione peroxidase; HAP-1, huntingtin-associated protein-1; HD, Huntington's disease; *HD,* huntingtin gene; *hdh*, murine huntingtin gene; HO, heme oxygenase; htt, huntingtin protein; IDO, indoleamine dioxygenase; MDA, malondialdehyde; mhtt, mutant huntingtin; MMP, matrix metalloproteinase; NADPH-d, nicotinamide adenine dinucleotide phosphate diaphorase; nDNA, nuclear DNA; NII, neuronal intranuclear inclusions; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; 3-NP, 3-nitropropionic acid; NPY, neuropeptide Y; Nrf2, NF-E2–related factor; 3-NT, 3-nitrotyrosine; $O_2^{\bullet -}$, superoxide radical; OH^-, hydroxyl radical; OH^8dG, 8-hydroxydeoxyguanosine; PARP, poly(ADP-ribose) synthetase; PBN, phenyl-*N*-tert-butylnitrone; Q_n, polyglutamine; RNS, reactive nitrogen species; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SDS, sodium dodecyl sulfate; SP, substance P; SOD1, Cu/Zn superoxide dismutase; SOD2, manganese superoxide dismutase; Sp1, specificity protein 1; SS, somatostatin; TAFII-130, TATA-binding protein-associated factor; tBHQ, *tert*-butylhydroquinone; TCA, tricarboxylic acid.

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