Redox Signaling, Oxidative Stress and Neurodegenerative Diseases

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Redox Signaling, Oxidative Stress and Neurodegenerative Diseases

- **Oxidative stress happens in Neurodegeneration:**
  Cause, Contributor or Consequence
  - Alzheimer’s disease
  - Huntington’s disease
  - Amyotrophic Lateral Sclerosis
  - Parkinson’s disease

- **Parkinson’s disease**
  - Energy/redox metabolism
  - Gene-environment interactions
  - Signaling and Redox modulation
Neurodegenerative diseases

- Neurodegenerative diseases are defined as hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction.

- These disorders are often associated with atrophy of the affected central or peripheral structures of the nervous system and include: Alzheimer's Disease and other dementias, Parkinson's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease), Huntington's Disease, Prion Diseases, and others.

- There is no cure for these diseases.
Main mechanisms associated with neurodegeneration

**Energy and Metabolism dysfunction**
- Oxidative Phosphorylation, Glycolysis
- Impaired ATP-dependent processes (Synaptic transmission, protein quality control mechanisms)
  - ATP is required to maintain antioxidant systems
  - Glucose metabolism regulates the PPP (NADPH), antioxidant precursors and glycative stress

**Mitochondrial dysfunction**
- Energy failure
- Signaling (Calcium, pro-cell death molecules)
  - Increase steady state levels of reactive oxygen species (oxidative damage)

**Dysfunction in Protein Quality Control Mechanisms.**
- Protein Folding
- Protein degradation
  - Proteasome
  - Autophagy
  - Impaired mitochondria turnover and accumulation of oxidized biomolecules
Oxidative stress is a common event in the pathogenesis of neurodegenerative diseases

- **Parkinson's disease (PD)**
  - Mitochondrial toxins, dopamine oxidation
  - Decreased antioxidant levels (GSH)
  - Lipid peroxidation, protein (carbonyls and nitrotyrosines) and nucleic acid oxidation

- **Alzheimer's disease (AD) and mild cognitive impairment.**
  - Increased lipid-peroxidation (CSF), protein (carbonyls and nitrotyrosines) and nucleic acid oxidation
  - Oxidative stress influences Aβ formation and Aβ has pro-oxidant effects

- **Huntington's disease (HD)** – Energy metabolism
### Table II. Diverse molecular modifications observed in Alzheimer’s diseased brains.

<table>
<thead>
<tr>
<th>Modifications in Alzheimer’s disease</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative protein modifications</td>
<td>Increases in protein carbonyls and other protein oxidation products (glutamic and aminoadipic semi-aldehydes), increased levels of methionine sulfoxide oxidized SOD, creatine kinase and glutamine synthetase UCHL1 is heavily oxidized</td>
</tr>
<tr>
<td>Nitrate protein modifications</td>
<td>Increased levels of nitrotyrosine neurofibrillary tangles Other nitrate proteins are β-actin, α-enolase and triosephosphate isomerase</td>
</tr>
<tr>
<td>Lipid peroxidation</td>
<td>Increased levels of HNE</td>
</tr>
<tr>
<td>Oxidative DNA damage</td>
<td>Increases in 8OHdG and other base oxidation products in mitochondria and nucleus</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Decreased activities of complex IV, alpha-ketoglutarate dehydrogenase, pyruvate dehydrogenase</td>
</tr>
<tr>
<td>Proteasome dysfunction</td>
<td>Decreased proteasomal activity, abnormal accumulation of proteins containing polyubiquitin</td>
</tr>
</tbody>
</table>

### Table III. Diverse molecular modifications observed in Parkinson’s diseased brains.

<table>
<thead>
<tr>
<th>Modifications in Parkinson’s disease</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative protein modifications</td>
<td>Increased levels of protein carbonyls in substantia nigra, oxidized SOD1 Increased levels of oxidized dopamine (cysteinyldopamine and cysteinyldopamine)</td>
</tr>
<tr>
<td>Nitrate protein modifications</td>
<td>Increased levels of nitrotyrosine in α-synuclein and Lewy bodies</td>
</tr>
<tr>
<td>Lipid peroxidation</td>
<td>HNE-products in Lewy bodies and increased peroxidases</td>
</tr>
<tr>
<td>Oxidative DNA damage</td>
<td>Increased levels of DNA oxidation product 8OHdG in mitochondrial and total DNA</td>
</tr>
<tr>
<td>Glutathione</td>
<td>Decreased levels of GSH</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Decreased activities of complex I and alpha-ketoglutarate dehydrogenase</td>
</tr>
<tr>
<td>Proteasome dysfunction</td>
<td>Genetic defects in inherited Parkinson’s disease, decreased activities in sporadic Parkinson’s disease, decrease UCHL1 activity</td>
</tr>
<tr>
<td>Oxidized dopamine</td>
<td>Auto-oxidation of free non-vesicle dopamine to quinone</td>
</tr>
</tbody>
</table>
ROS and oxidative stress during the aging process

Exogenous Factors
- environmental conditions
- lifestyle
- stress conditions

Endogenous sources of ROS
- Changes in gene expression
- Modulation of signal transduction pathways

Accumulation of molecular injury: DNA, protein, lipids
- Organelle damage (e.g., mitochondria, peroxisomes)

Cellular responses:
- inflammation, survival, proliferation, death

Systematic responses:
- aging, organ dysfunction, frailty, diseases

Passage of Time

normalization
activation
repair
damage
Alzheimer's disease

- The two core pathological hallmarks of Alzheimer's disease are amyloid plaques and neurofibrillary tangles.
- The amyloid cascade hypothesis suggests that deposition of amyloid β (Aβ) triggers neuronal dysfunction and death in the brain.
- Genetic causes of Alzheimer's disease include mutations of the genes encoding amyloid precursor protein (APP) and presenilin 1 (PSEN1) and PSEN2. PSEN1 and PSEN2 mutations affect concentrations of Aβ_{1-42} because the presenilin proteins form part of γ secretase, which cleaves APP to produce Aβ.
- Many treatable medical conditions are also associated with an increased risk of Alzheimer's disease, including stroke, diabetes (inflammation).
Amyloid beta peptide

A) Amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated as a regulator of synapse formation, neural plasticity and iron export.

Amyloidogenic processing is initiated by β-secretase beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), releasing a shortened sAPPβ. The C99 fragment is a γ-secretase substrate, generating Aβ and AICD (amyloid precursor protein intracellular domain).

B) Soluble Aβ is prone to aggregation. Protofibrils (upper) and annular or pore-like profiles (lower) are intermediate aggregates. Self-association of Aβ monomers into oligomers (right) is dependent on concentration (left IB) and is promoted by oxidizing conditions (lane 2) and divalent metal conditions (lane 3, right IB).
• Tau proteins are proteins that stabilize microtubules. Four repeat sequences (R1-R4) make up the microtubule-binding domain (MBD).

• Normal phosphorylation of tau occurs on serine and threonine residues.

• When followed by proline (P), these amino acids are phosphorylated by glycogen synthase kinase 3 (GSK-3β), cyclin-dependent kinase (cdk5), or mitogen-activated protein kinase (MAPK).

Nonproline-directed kinases phosphorylating tau are Akt, Fyn, protein kinase A (PKA), calcium–calmodulin protein kinase 2 (CaMKII), and microtubule affinity-regulating kinase (MARK).

• Excessive kinase, reduced phosphatase activities, or both cause hyperphosphorylated tau to detach and self-aggregate and to destabilize microtubules.
Alzheimer’s disease and oxidative stress

- Amyloid β shows **peroxidative activity** on cell and organelle membrane lipids yields the mitochondrial toxins hydroxynonenal (HNE) and malondialdehyde.
- Cellular Aβ directly attacks electron transport complex IV (cytochrome c oxidase) and key Krebs-cycle enzymes (α-ketoglutarate and pyruvate dehydrogenase) and damages mitochondrial DNA (mtDNA), leading to fragmentation.
- **Lipid peroxidation products also promote tau phosphorylation** and aggregation, which in turn inhibit complex I.
- **Neuroinflammation and metal-induced ROS**
- Contradictory results have been found with respect to the effect of dietary intake of antioxidants, such as vitamin E in reducing the risk or the rate of progression of Alzheimer's disease.

NEJM Volume 362:329-344
Alzheimer’s disease and RNS

- NMDAR hyperactivation triggers generation of NO and subsequent S-nitrosylation of neuronal proteins, contributing to synaptic damage and eventually neuronal death.

- Soluble oligomers of Aβ oligomers, can facilitate neuronal NO production in both NMDAR-dependent and - independent manners.

- S-Nitrosylation of the fission-inducing protein Drp1 (dynamin-related protein 1, forming SNO-Drp1) can contribute to synaptic damage and neuronal cell death by triggering excessive mitochondrial fission and bioenergetic impairment.
AD and Redox Signaling

S-Nitrosylation-Mediated Redox Transcriptional Switch Modulates Neurogenesis and Neuronal Cell Death

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http://dx.doi.org/10.1016/j.celrep.2014.06.005
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MEF2C (Myocyte Enhancer Factor 2C); S-nitrosocysteine (SNOC); B-cell lymphoma-extra large (Bcl-xL)
Huntington’s disease and oxidative stress

• Huntington disease (HD) is an autosomal dominant neurodegenerative disease.
• HD is caused by a CAG (glutamine) repeat expansion in the first exon of the HTT gene that encodes huntingtin (Htt).
• γ-Aminobutyric acid (GABAergic) medium spiny neurons of the striatum that contain enkephalin or substance P and project to the globus pallidus and substantia nigra are particularly vulnerable in HD.
• Defects in energy metabolism, particularly mitochondrial function, represent a common thread in studies of HD pathogenesis in humans and animal models.
• Impaired oxidative phosphorylation, oxidative stress, impaired mitochondrial calcium handling, abnormal mitochondria trafficking, deregulation of key factors of mitochondrial biogenesis, such as the transcriptional coactivator PPARγ coactivator-1α (PGC-1α), and decreased glycolysis.

<table>
<thead>
<tr>
<th>Repeat count</th>
<th>Classification</th>
<th>Disease status</th>
<th>Risk to offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26</td>
<td>Normal</td>
<td>Will not be affected</td>
<td>None</td>
</tr>
<tr>
<td>27–35</td>
<td>Intermediate</td>
<td>Will not be affected</td>
<td>Elevated but &lt;50%</td>
</tr>
<tr>
<td>36–39</td>
<td>Reduced Penetrance</td>
<td>May or may not be affected</td>
<td>50%</td>
</tr>
<tr>
<td>40+</td>
<td>Full Penetrance</td>
<td>Will be affected</td>
<td>50%</td>
</tr>
</tbody>
</table>
Huntington’s disease and oxidative stress

• Mitochondrial toxins such as malonate and 3-nitropropionic acid (3-NP) inhibit succinate dehydrogenase (SDH), which is part of complex II of the electron transport chain.

• Neuroprotection: Coenzyme Q₁₀ is an electron acceptor from complex I and complex II that also has antioxidant activity. Creatine and triacetyluridine can buffer intracellular energy stores.

Nature Reviews Neuroscience 5, 373-384 (May 2004)
HD and Redox Homeostasis

Cystathionine γ-lyase deficiency mediates neurodegeneration in Huntington’s disease

Bindu D. Paul¹, Juan I. Sbodio¹, Risheng Xu¹-², M. Scott Vandiver¹-², Jiyoung Y. Cha¹, Adele M. Snowman¹ & Solomon H. Snyder¹-²,³

**HD:** Clinical staging with increasing severity of the disease. Specificity protein 1 (Sp1), a known transcription factor for CSE and co-activator transcription initiation factor TFIID subunit 4 (TAF4)

**Diagram:**
- Methionine → S-Adenosylmethionine → S-Adenosylhomocysteine → Homocysteine → CSE → H₂S → Striatum → Cystathionine → CSE → Cysteine → CBS → γ-Glu-Cys → CBS → Glutathione

**Graphs:**
- Relative CSE expression
- Relative cysteine production
- Relative H₂S production

DOI: 10.1038/nature13136
Amyotrophic lateral sclerosis

- Amyotrophic lateral sclerosis (ALS) is a paralytic disorder caused by motor neuron degeneration.

- The causes of most cases of ALS are as yet undefined. Excessive excitatory tone, protein misfolding, impaired energy production, abnormal calcium metabolism, altered axonal transport and activation of proteases and nucleases.

- Several factors are proposed to instigate these phenomena, including latent infections by viral and non-viral agents, toxins (for example, insecticides and pesticides) and autoimmune reactions.

- The protein products of these mutated genes are cytosolic Cu/Zn superoxide dismutase (SOD1), alsin, senataxin (SETX), synaptobrevin/VAMP (vesicle-associated membrane protein)-associated protein B (VAPB) and dynactin have been reported to cause ALS.

- About 20–25% of all familial ALS cases arise because of mutations in SOD1, the protein product of which accounts for 0.1–0.2% of the cellular proteins in the CNS.

- TDP-43 protein (known as TARDBP) accounts for approximately 2-6% of all familial ALS cases and is found aggregated in sporadic cases.
• In the aberrant redox chemistry model, mutant superoxide dismutase 1 (SOD1) is unstable and aberrant chemistry is mediated by promiscuous interaction with non-conventional substrates.
  – Hydrogen peroxide ($\text{H}_2\text{O}_2$) or peroxynitrite (ONOO$^-$) can react with reduced SOD1 (SOD1$^-\text{Cu}^+$).
  – Molecular oxygen ($\text{O}_2$) can react aberrantly with Zn-deficient SOD1 to generate an excess of superoxide anion ($\text{O}_2^-$).
  – The unstable protein can also release free copper and/or zinc, which might be toxic.

• In the protein toxicity (proteotoxic) model, conformationally altered mutant SOD1 forms toxic, proteinaceous deposits.
  – Aggregated SOD1 inhibits chaperone and/or proteasome activity, with subsequent misfolding and insufficient clearance of numerous proteins.
  – Alternatively, these aggregates could sequester, inactivate or enhance the toxicity of other proteins crucial for cellular processes.

Nat Rev Neurosci. 2006 Sep;7(9):710-23.
TDP-43 has been shown to bind both DNA and RNA and have multiple functions in transcriptional repression, pre-mRNA splicing and translational regulation. T-cell intracellular antigen (TIA)-1 and TIA-1-related protein (TIAR) are mRNA-binding proteins that can aggregate within granules under specific stress conditions. Frontotemporal lobar degeneration (FTLD) characterized by TDP-43 pathology (FTLD-TDP).
Multiple sclerosis, Inflammation and oxidative stress

- Multiple sclerosis is a **chronic inflammatory disease of the central nervous system**, associated with demyelination and **neurodegeneration**. The mechanisms of tissue injury are currently poorly understood, but recent data suggest that **mitochondrial injury** may play an important role in this process.

- Both in MS and in neurodegenerative diseases, inflammation initiates microglial activation.

- In MS, inflammation is immune-mediated but in neurodegenerative diseases the primary causes of inflammation remain speculative.

- **Activated microglia produce $O_2^{-\cdot}$ and $\cdot$NO reactive species that combine to induce primary synthesis of peroxynitrite.**

- Peroxynitrite inhibits glutamate transporters and/or activates glutamate receptors causing glutamate overload.

- **Excitotoxicity entails mitochondrial dysfunction, calcium overload.**
Redox control of prion and disease pathogenesis

- The underlying cause of brain pathology in all prion disorders is **PrP-scrapie (PrP(Sc))**, a beta-sheet-rich conformation of a normal glycoprotein, the prion protein (PrP(C)).
- In prion disorders, **imbalance of brain-iron homeostasis is observed before end-stage disease and worsens with disease progression**, implicating iron-induced oxidative stress in disease pathogenesis.
What causes Parkinson’s disease

- Parkinson’s disease (PD) is a **chronic progressive neurodegenerative disorder** that leads to shaking (tremors) and difficulty with walking, movement, and coordination. Parkinson's may lead to a deterioration of all brain functions, and an early death.

- Loss of **dopamine neurons** from the substantia nigra pars compacta leads to deficiency of dopamine in the caudate and putamen (“striatum”).

- Currently, there is no treatment to cure or stop PD progression.

- The exact cause of PD is unknown.
  - Familial (Hereditary) forms of PD (~10%) 
    - α-synuclein, Parkin, DJ-1, PINK1 and LRRK2 genes.
  - Sporadic (Idiopathic) PD 
    - ~5% are linked to genetic alterations
    - Environmental or occupational factors.
Products of PD-associated genes that affect mitochondrial function and oxidative stress

Rare inherited mutations in genes encoding electron transport chain components have been associated with parkinsonism.

- Parkin is partially localized to the outer mitochondrial membrane,
- PINK1 is a mitochondrial serine–threonine kinase that affords protection against oxidative stress and acts with Parkin to regulate the balance of mitochondrial fission and fusion.
- DJ-1 is relocated to mitochondria under conditions of oxidative stress and is thought to be neuroprotective under such conditions.
- The α-synuclein protein has an amino-terminal mitochondrial targeting sequence and, when overexpressed or under conditions of acidification, is at least partially associated with the inner mitochondrial membrane, where it might cause direct damage.
- LRRK2 associates, at least in part, with the outer mitochondrial membrane
- HTRA2 is a mitochondrial serine protease, the release of which might be involved in apoptotic cell death.

*Nature Clinical Practice Neurology (2008) 4, 600-609*
DJ-1 in Parkinson's disease

Chemical Exposure → Oxidative Stress Insult → Loss of function mutation in DJ-1 → Increased sensitivity to oxidative stress → Accelerated death of DA neurons in SNpc → Parkinson's Disease

DJ-1 → SH → Over-oxidation of key cysteine & increase in acidic isoforms → Decreased protective activity
Experimental models of PD

- A single cause for PD is unlikely to emerge. Experimental models address different hallmarks of PD, depending on the question asked...
  - Mitochondrial dysfunction
  - Dopamine metabolism
  - Oxidative Stress
  - Genetic mutations
  - Impairment in protein quality control mechanisms
- There is no experimental PD model that recapitulates all aspects of PD.
- Genetic models induce poor DA loss.
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been used extensively as a model of PD.
- While epidemiological evidence strongly suggests a link between environmental exposures (pesticides, heavy metals), environmental exposures, by themselves, are not the cause of PD.
What makes a dopaminergic neuron the target?

- Dopamine and Iron (pro-oxidant)
- Dopaminergic neurons consume a significant amount of energy due to:
  - Pacemaking activity
  - Vesicle transport
  - Action potential and membrane potential maintenance through the unmyelinated axon

The axonal arbors of single nigrostriatal dopaminergic neurons in rat brain. The image shows axon fibers in the neostriatum. Red and blue lines indicate the axon fibers located in the striosome and matrix compartments of the neostriatum. A single dopamine neuron can influence up to 5% of all neurons in the neostriatum or ~75,000 neurons.

Oxidative stress in substantia nigra

- Using transgenic mice that expressed a redox-sensitive variant of green fluorescent protein targeted to the mitochondrial matrix, it was demonstrated that normal autonomous pacemaking created an oxidant stress that was specific to vulnerable SNc dopaminergic neurons but not in neurons in the ventral tegmental area.

- The oxidant stress engaged induced transient, mild mitochondrial depolarization or uncoupling.

- Knocking out DJ-1 (PARK7), which is a gene associated with an early-onset form of Parkinson's disease, down-regulated the expression of two uncoupling proteins (UCP4 (SLC25A27) and UCP5 (SLC25A14)), compromised Ca2+-induced uncoupling and increased oxidation of matrix proteins specifically in SNc dopaminergic neurons.

*Nature*. 2010 Dec 2;468(7324):696-700
Redox regulation of Parkinson’s Disease

- Redox cycling
- Thiols
  - GSH
  - Cysteine modifications
  - Trx/Prx/Srx
- Oxidative Stress
- Hydrogen sulfide
- Redox regulated transcription factors
- Mitochondria
- Inflammation
Why have antioxidant clinical trials failed?

- Antioxidant supplementation has for the most part failed to achieve meaningful effects in PD.
  - Lack of specificity
  - Administration of antioxidants might not have been given early enough
  - Not all cases arise from the same causes
  - Wrong experimental models
  - Oxidative stress is not the main/single cause in neurodegeneration
Environmental agents and Parkinson’s disease

- Environmental agents linked to increased incidence/risk to develop Parkinson’s disease
  - Pesticides
  - Heavy Metals

- The U.S. is the country as a whole with the world’s highest prevalence of PD.

- For residents of highly agricultural areas, pesticides are environmental risk factors of major public health concern for populations directly working with them or indirectly exposed by residential proximity to crop fields.


- Not a single environmental toxicant can be the cause of sporadic PD.
Mitochondrial Dysfunction: Redox Homeostasis vs Bioenergetics

Redox homeostasis

Bioenergetics
Paraquat toxicity *in vivo*

**A**

PBS

MPTP

**B**

Control

PQ

**C**

TH

PSSG

Merge

PBS

PQ

Antioxid Redox Signal 2012; 17(12):1676-93.
**In vivo** metabolic dysfunction induced by PQ

Anandhan et al., Mol Neurobiol. 2016 (accepted)
Gene-Environment Interactions in PD

The Multi-hit Hypothesis
Gene-Environment Interactions in Parkinson’s Disease

- Parkinson’s disease is a multifactorial disease: ageing, genetics and environment.

- The formation of intracellular aggregates (Lewy bodies) of which a major component is the protein α-synuclein, is a pathological hallmark.

- Mitochondrial dysfunction and energy failure induced by environmental toxicants can lead to α-synuclein misfolding and aggregation by an impairment in protein quality control mechanisms.
α-synuclein Potentiates PQ Toxicity and Metabolic Dysfunction

Anandhan et al., Mol Neurobiol. 2016 (accepted)
α-synuclein Potentiates PQ-induced Metabolic Dysfunction

A

B

C

D

Anandhan et al., Mol Neurobiol. 2016 (accepted)
Glucose metabolism regulates α-synuclein-PQ toxic interaction

A

![Graph A](image)

B

![Graph B](image)

C

![Graph C](image)

D

![Graph D](image)

Anandhan et al., Mol Neurobiol. 2016 (accepted)
Glucose metabolism and PQ + α-synuclein toxic interaction in PD

**Glucose metabolism regulates α-synuclein + PQ toxicity.**
- PQ and α-synuclein impair glucose metabolism.
- PQ increases glucose transport and translocation of glucose transporters.
  - Inhibition of GLUT-like transporters prevents α-synuclein + PQ toxicity.
- Inhibition of PPP protects against α-synuclein + PQ.

**AMPK signaling regulates α-synuclein + PQ toxicity.**
- Activation of AMPK and cell death are mediated by the iNOS.
- AMPK protects against α-synuclein + PQ.
- α-synuclein and impairment of AMPK signaling and induce an overall metabolic dysfunction that enhances PQ toxicity.

Anandhan et al., Mol Neurobiol. 2016 (accepted)
Summary

• Three main mechanisms linked to neurodegeneration.
  – Energy Failure
  – Mitochondrial dysfunction
  – Dysfunction in Protein Quality Control Mechanisms.

• Three major risk factors involved in neurodegeneration: Age, genes and environment.

• Alterations in redox homeostasis in neurodegeneration are not isolated events.
  – Cell signaling
  – Bioenergetics
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