Metabolism and Redox Homeostasis in Brain Function and Disease

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1. Complexity of the CNS
   - Cellular composition and metabolic interactions
   - Redox homeostasis
     • Glial cells (astrocytes)

2. Neurodegenerative Disorders
   - Major causes (including redox imbalances)
   - Examples
     • Alzheimer’s disease
     • Huntington’s disease
     • Amyotrophic Lateral Sclerosis
     • Parkinson’s disease
       - Energy/redox metabolism
       - Gene-environment interactions
       - Signaling and Redox modulation
Complexity of the Nervous System

- The **nervous system** coordinates the actions or organisms by transmitting signals to and from a centralized location. It is defined by the presence of neurons or nerve cell components.
  - Central Nervous System (CNS)
    - Brain and Spinal Cord
  - Peripheral Nervous System (PNS)
    - Nerve fibers or axons
    - Somatic (voluntary), Enteric (gastro-intestinal system), Autonomic (sympathetic or emergency-activated, and parasympathetic or relaxed-activated)

Malfunction of the nervous system can occur as a result of **genetic defects**, **damage due to trauma or toxicity**, **infection** at any stage during development or simply of ageing
Particularities about Neurons

• Highly specialized cells that transduce, store and communicate information. “Functional unit of the brain”, Neuronal doctrine

• Post-mitotic neurons
  – Low capacity of regeneration in adults
doi:10.1038/nature25975, 2018
doi:10.1016/j.stem.2018.03.015, 2018

• Reprogrammed to depend heavily on mitochondrial metabolism as energy source
  • Brain accounts for 20% of overall energy consumption in human body.
  • 80% is directed to the maintenance of excitability: Membrane potential, ionic balance
It is not all about neurons!!

- **Cell types in the nervous system:**
  - **Ependymal cells:** Cerebrospinal fluid.
  - **Oligodendrocytes:** Nerve insulation (myelin).
  - **Astrocytes:** Metabolic regulators
  - **Microglia:** Immune surveillance

- **Infiltration cells and Blood-Brain Barrier**
Communication between brain cells
Mitochondria in Astrocytes

What is their function?

- Astrocytes are highly glycolytic

- Mitochondrial FFA (free fatty acid) oxidation is primarily restricted to astrocytes

Cellular/Molecular

Respiration-Deficient Astrocytes Survive As Glycolytic Cells
In Vivo

SCIENTIFIC REPORTS

OPEN
Astrocytes and oligodendrocytes in grey and white matter regions of the brain metabolize fatty acids
• In contrast to the replenishment of the GSH pool upon oxidative stress (GSH ↔ GSSG), xenobiotic detoxification depletes GSH
• Cysteine is the limiting factor in de novo GSH synthesis.
Mitochondrial Anaplerotic Metabolism and Xenobiotic Defense

A

- Mitochondrial Anaplerotic Metabolism

- Xenobiotic Defense

- Extracellular Lactate Citrate L-glutamate NMR spectra intensity (Fold change)

- Control
- 5 µM NaAsO₂
- 10 µM NaAsO₂
- 20 µM NaAsO₂

- NMR spectra intensity (Fold change) vs. time (min)

B

- Mitochondrion

- Glutamate

- Glutamate

- Lactate

- Pyruvate

- OAA

- Asp

- Mal

- αKG

- OGC

- IDH

- MPC1

- CPT1

- CPT2

- MDH1

- FAO

- Etomoxir

- NaAsO₂

- NaAsO₂ + Etomoxir

- Oxygen Consumption Rate Fold Change vs. time (min)

- ETC ROS

- Mitochondrion

- ATP S

- ADP + P
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.

*Nature Reviews Neuroscience 7, 278-294*
Aging is the primary risk factor for neurodegeneration

Exogenous Factors:
- Environmental conditions
- Lifestyle
- Stress conditions

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

Cellular responses:
- Inflammation, survival, proliferation, death

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

Passage of Time

ROS (Reactive Oxygen Species)

Accumulation of molecular injury:
- DNA, protein, lipids

Organelle damage:
- (e.g., mitochondria, peroxisomes)

Normalization and repair of ROS damage
Inhibition of oxidative stress in cholinergic projection neurons fully rescues aging-associated olfactory circuit degeneration in Drosophila

Ashiq Hussain1, Atefeh Pooryasin2,3†, Mo Zhang4†, Laura F Loschek4, Marco La Fortezza5, Anja B Friedrich1, Catherine-Marie Blais1, Habibe K Üçpunar4, Vicente A Yépez5, Martin Lehmann7, Nicolas Gompel5, Julien Gagneur6, Stephan J Sigrist2,3, Ilona C Grunwald Kadow1,4,8*
Pathology of Neurodegeneration

AD, Alzheimer’s disease; FTD, Frontotemporal dementia; HD, Huntington’s disease; LBD, Lewy Bodie Dementia; PD, Parkinson’s disease; ALS, Amyotrophic Lateral Sclerosis

Molecular Mechanisms Associated with Neurodegeneration

- **Dysfunction in Protein Quality Control Mechanisms.**
  - Protein Folding
  - Protein degradation
    - Proteasome
    - Autophagy

- **Energy Failure**
  - Oxidative Phosphorylation, Glycolysis

- **Mitochondrial dysfunction**
  - Oxidative stress and alterations in redox homeostasis
  - Energy failure
  - Mitochondria quality control
  - Ca$^{2+}$ and cell death

- **Vesicle Transport and Dysfunction**
  - Vesicle Integrity (Lysosomes)
  - Vesicle Trafficking (Neurotransmission)
  - Vesicle Function (Cargo loading)

**Spinocerebellar ataxias.**
1, aggregation; 2, apoptosis; 3, autophagy; 4, Ca$^{2+}$ homeostasis alterations; 5, disruption of axonal transport and vesicle trafficking; 6, excitotoxicity; 7, interference with gene transcription; 8, mitochondrial impairment; 9, oxidative stress; 10, alterations of proteasome degradation; 11, synaptic dysfunction; 12, unfolded protein response (UPR); 13, potassium channel dysfunction;

Ca$^{2+}$, calcium ions; ER, endoplasmic reticulum; Glu, glutamate; K+, potassium ions; Na+, sodium ions; Q, glutamine; Ub, ubiquitin.

http://dx.doi.org/10.1093/brain/awl081
Extrinsic (Non-Neuronal) Factors Associated with Neurodegeneration

- **Non-Neuronal Cells.**
  - Microglia
    - Inflammation
  - Blood Brain Barrier
    - Infiltration of other cells
  - Astrocytes
    - Inflammation and Metabolism

- **Environmental/Occupational Exposures**
  - Stress
  - Toxicants

- **Infections**

- **Microbiome**

*Nature 544, 304–305*
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
Alzheimer’s and the Aβ peptide

- Pathological hallmarks: Aβ senile plaques and neurofibrillary tangles (Tau).
- The amyloid cascade: Deposition of Aβ triggers neuronal dysfunction
- Genetic causes: Mutations in the amyloid precursor protein (APP) and presenilin 1 (PSEN1) and PSEN2, which affect concentrations of Aβ\textsubscript{1-42}.

A. Amyloidogenic processing is initiated by β-secretase (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).

NEJM Volume 362:329-344
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.
Elevated glucose and oligomeric β-amyloid disrupt synapses via a common pathway of aberrant protein S-nitrosylation

Mohd Waseem Akhtar1, Sara Sanz-Blasco1, Nima Dolatabadi1,2, James Parker1,2, Kevin Chon1, Michelle S. Lee1, Walid Soussou1,3, Scott R. McKercher1,2, Rajesh Ambasudhan1,2, Tomohiro Nakamura1,2 & Stuart A. Lipton1,2,4
Huntington’s disease and oxidative stress

- 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.

Classification of the trinucleotide repeat, and resulting disease status, depends on the number of CAG repeats:

<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 ≤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>

HD and Redox Homeostasis

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

Bindu D. Paul1, Juan I. Sbodo1, Risheng Xu1,2, M. Scott Vandiver1,2, Jiyoung Y. Cha3, Adele M. Snowman1 & Solomon H. Snyder1,2,3

Reverse transulfuration

Methionine → S-Adenosylmethionine → S-Adenosylhomocysteine → Homocysteine → CSE → H2S

Serine → CBS → Cystathionine → CSE → Cysteine → γ-Glu-Cys → CSE → H2S

Glutathione → CSE → CBS → H2S

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

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.

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.

In the protein toxicity model, conformationally altered mutant SOD1 forms toxic, proteinaceous deposits.

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).
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%)  
  - \( \alpha \)-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,
- 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.
- 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.

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

Chemical Exposure

Oxidative Stress Insult

Age

Loss of function mutation in DJ-1

Increased sensitivity to oxidative stress

Accelerated death of DA neurons in SNpc

Parkinson’s Disease

Over-oxidation of key cysteine & increase in acidic isoforms

Decreased protective activity
PD-related mutations are found in all brain cells

- Glia account for over 50% of the cells in the brain and can be divided into various subtypes, of which astrocytes are the most populous
- PD-related genes have biological functions in glial cells
  - Inflammation
  - Glutamate homeostasis
  - Neuroprotection
  - Trophic support
  - Mitochondrial function

https://doi.org/10.1016/j.tins.2017.04.001
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 neostraitum 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 (VTA).

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

*Nature*, 2010 Dec 2;468(7324):696-700
Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson’s disease

Lena F. Burbulla, Pingping Song, Joseph R. Mazzulli, Enrico Zampese, Yvette C. Wong, Sohee Jeon, David P. Santos, Judith Blanz, Carolin D. Obermaier, Chelsea Strojny, Jeffrey N. Savas, Evangelos Kiskinis, Xiaoxi Zhuang, Rejko Krüger, D. James Surmeier, Dimitri Kraina
Redox regulation of Parkinson’s Disease

- Redox cycling
- Thiols
  - GSH
  - Cysteine modifications
  - Trx/Prx/Srx
- Oxidative Stress
  - Iron
  - Dopamine content
- 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 linked to increased incidence/risk to develop Parkinson’s disease

- **Pesticides**
- **Heavy Metals**
- **Dietary factors:** Toxicol Sci. 2014, 140:179.

- 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.
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.
In vivo metabolic dysfunction induced by PQ

**Striatum**
- P: 9.39e-04

**Midbrain**
- P: 1.36e-04

**Cortex**
- P: 0.02

<table>
<thead>
<tr>
<th></th>
<th>Striat</th>
<th>Mid</th>
<th>Cereb</th>
<th>Cort</th>
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<tr>
<td>PQ</td>
<td></td>
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<tr>
<td>pAMPK T172</td>
<td>[Image]</td>
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<tr>
<td>AMPK α1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>vs Cont</td>
<td>1 1.9 1 3.5 1 0.6 1 0.7</td>
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<tr>
<td>pACC</td>
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<td>β-actin</td>
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<tr>
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<td>1 1.6 1 5 1 1.2 1 0.9</td>
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</table>
α-synuclein Potentiates PQ Toxicity and Metabolic Dysfunction

A

<table>
<thead>
<tr>
<th>MOI</th>
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<tbody>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
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</table>

B

Cell survival (%)

0 20 40 60 80 100

PQ [μM]

0 50

Empty

α-synuclein

A53T

C

PC1 37.7%

PC2 16.7%

PC3 13.7%

Control

α-syn

PQ

α-syn + PQ

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

**A**

![Bar graph showing relative 13-C NMR intensity](chart)

**B**

![ECAR over time](chart)

**C**

<table>
<thead>
<tr>
<th>PQ [μM]</th>
<th>Empty</th>
<th>α-synuclein</th>
<th>A53T</th>
<th>pAMPK T172</th>
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<td>50</td>
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</table>

**D**

![Cell survival vs Paraquat](chart)
α-synuclein Does Not Modulate Mn Content but Triggers Metabolic Dysfunction

A

Cell Survival (%)

MnCl$_2$ [mM]

B

Mn content (ng/mg protein)

MnCl$_2$ [mM]

C

Mn (ng/mg wet weight)

Cerebellum Cortex Midbrain Striatum

D

Midbrain

E

Cortex

LDA2

LDA1

LDA2

LDA1

p : 0.01

p : 0.36

*
Metabolic Dysfunction Induced by \(\alpha\)-synuclein + Mn

A

![Bar chart showing NMR intensity (% vs Empty) for various metabolites including Glucose, UDP-gluc, Fruct/Fruct 6-P, Fruct 1,6-bisP, Pyruvate, Alanine, Lactate, and Glycine. The bars are differentiated by conditions: Empty, \(\alpha\)-synuclein, Empty + Mn, and \(\alpha\)-synuclein + Mn. Asterisks indicate significant differences.]

B

![Bar chart showing NMR intensity (% vs Empty) for Glucose, Lactate, Alanine, and Pyruvate in the extracellular medium. Asterisks indicate significant differences.]

C

![Line graph showing ECAR (Fold change) over Time (min) for Empty and \(\alpha\)-synuclein conditions. Inset: Metabolite interactions including Glucose, Lactate, Fruct 6-P, Fruct 1,6-BP, Pyruvate, and TCA Cycle (Glut and Citrate).]
α-synuclein Interacts with Aldolase A

A

![Graph showing PDH activity](image)

B

![Immunostaining images](image)

C

![Graph showing PDH activity in response to MgCl₂ and MnCl₂](image)

D

![Bar graph showing ATP content](image)
Gene-Environment Interactions and PD

- α-synuclein impairs glucose metabolism by inhibition of Aldolase activity.
  - This channels carbon flux to the PPP to increase PQ’s redox cycling and ROS formation
  - Facilitates ATP depletion induced by Mn exposure
  - Glucose metabolism has opposite effects

- AMPK signaling exerts a protective effect.
  - Activation of AMPK can be mediated by both ROS and ATP depletion.
  - AMPK protects against the toxicity of gene (α-synuclein)-environment (PQ or Mn) interactions.
Summary

• CNS and Brain is a complex system that integrates different cells and structures
  – Redox metabolism and bioenergetics in the brain is regulated by the interaction between distinct components

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

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

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