Oxidative Stress and Cigarette Smoke

Stephan Gebel
Luxembourg Centre of Systems Biomedicine
University of Luxembourg

sbv IMPROVER Jamboree
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Molecular interactions map on Parkinson’s disease

• CellDesigner (The Systems Biology Institute, Tokyo, Japan)
• SBML (Systems Biology Markup Language)
• based on curated literature and databases (e.g., REACTOME)
• publicly available and freely accessible at http://pdmap.uni.lu
• visualisation and easy navigation by google map design

Oxidative Stress in Parkinson's Disease: A Mechanism of Pathogenic and Therapeutic Significance

CHUN ZHOU¹, YONG HUANG¹, and SERGE PRZEDBORSKI¹,²
¹Department of Neurology, Columbia University, New York, New York 10032
²Departments of Pathology and Cell Biology, Columbia University, New York, New York 10032

Review Article
Mechanism of Oxidative Stress in Neurodegeneration

Sonia Gandhi and Andrey Y. Abramov

Review Article
Role of Redox Signaling in Neuroinflammation and Neurodegenerative Diseases

Hsi-Lung Hsieh¹ and Chuen-Mao Yang²
¹ Department of Nursing, Division of Basic Medical Sciences, Chang Gung University of Science and Technology, Taoyuan, Taiwan
² Department of Physiology and Pharmacology and Health Aging Research Center, College of Medicine, Chang Gung University, 259 Wen-Hwa 1st Road, Kwei-San, Taoyuan, Taiwan
Review Article

Parkinson disease: from pathology to molecular disease mechanisms

David T. Dexter\textsuperscript{a}, Peter Jenner\textsuperscript{b,\textdagger}

\textsuperscript{a} Parkinson’s Disease Research Group, Centre for Neuroinflammation & Neurodegeneration, Division of Brain Sciences, Faculty of Medicine, Imperial College London, Hammersmith Hospital Campus, London, UK
\textsuperscript{b} Neurodegenerative Diseases Research Group, Institute of Pharmaceutical Science, School of Biomedical Sciences, King’s College London, London SE1 9NH, UK
Definition of Oxidative Stress

“A serious imbalance between oxidation and antioxidants”

Wikipedia:
• **Oxidative stress** reflects an **imbalance** between the systemic manifestation of **reactive oxygen species** and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage.
• **Disturbances** in the normal **redox state** of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including **proteins, lipids, and DNA**.
• In humans, oxidative stress is thought to be involved in the development of **cancer, Parkinson's disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction**……
• Reactive oxidative species act as **cellular messengers in redox signaling**. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling.
• Reactive oxygen species can be beneficial, as they are used by the **immune system** as a way to attack and kill pathogens.
Redox Homeostasis

- Oxidative Stress
  - Metabolism
  - Inflammation
  - Mitochondria
  - Protein Modification
    - Lipid Peroxidation
    - DNA Damage

- Anti-Oxidants / Repair Mechanisms
  - Glutathione
  - SOD
  - TRX / GPX
  - Catalase

Disease
Oxidants in Cigarette Smoke


Oxidants in Cigarette Smoke

Barry. B. Halliwell and Henrik. E. Poulsen, Eds
Cigarette Smoke and Oxidative Stress
Springer, Heidelberg, Germany, 2006
16 articles on 407 pages
Cigarette Smoke and Oxidative Stress

- Which compounds in CS are causally involved in the development of CS-related human diseases?
- How is oxidative stress affecting the disease related cellular processes?
- Which compounds in CS are mediating relevant oxidative stress?
Start from Biology

Model system:

*in vitro* cell culture systems

exposure to aqueous extract of cigarette smoke called **smoke-bubbled (sb) PBS.**
glutathione, OH\(^{\cdot}\), SH-reactivity

- pronounced expression of the antioxidant protein heme oxygenase 1 (HMOX1)
- depletion of glutathione (GSH) by 60% after 2 h of exposure
- hydroxyl radical that induces DNA strand breaks in vitro were not responsible for the HMOX1 induction
- addition of cysteine (NAC) rescued glutathione and inhibited of HMOX1 induction

> sulfhydryl reactive activity in aqueous extract of cigarette smoke

peroxynitrite, aldehydes

- **peroxynitrite** which is generated by NO and superoxide is inducing gene expression in sbPBS treated cell

- cigarette smoke-derived **aldehydes** such as acrolein cause glutathione depletion

➢ **peroxynitrite** and **aldehydes** cooperates in the induction of the cellular stress response

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The activity of NF-κB in Swiss 3T3 cells exposed to aqueous extracts of cigarette smoke is dependent on thioredoxin. *Toxicol Sci.* **59**, 75-81.

- **NFκB** activity is transiently inhibited by sbPBS
- this follows the kinetic of glutathione depletion and recovery
- **thioredoxin reductase** expression is induced by sbPBS

➤ **thioredoxin** is responsible for the restoration of NFκB activity after CS-exposure

redox-sensitive transcription factor NFE2L2 (nuclear factor, erythroid 2-like 2)

Modified from Dinkova-Kostova A T et al. PNAS 2002;99:11908-11913
redox-sensitive transcription factor NFE2L2 (nuclear factor, erythroid 2-like 2)

- gene promotor assay identified NFE2L2 binding site (stress response element) in HMOX1 promoter

- siRNA antisense experiments showed that NFE2L2 induces the expression of stress related genes by sbPBS

- transcription factor NFE2L2 mediates the oxidative stress response *in vitre*

component in aqueous extract of CS that generate oxidative stress *in vitro*.

- **hydroxyl radicals** derived from hydrogen peroxide by Fenton reaction induce DNA damage
- sulfhydryl reactive **aldehydes** deplete GSH
- **peroxynitrite** derived from NO and superoxide induce transcriptional activation of oxidative stress genes via activation of NFE2L2
- **superoxide** is generate in CS by redox-cycling of hydrochinonone
- **hydrogen peroxide** is generate in a catalytic reaction from superoxide by superoxide-dismutase (SOD)
CS-response in animal systems

Oxidative Stress Response
• e.g., HMOX-1, NQO1, GCLC, TXNRD1, SRXN, SOD, SLC7A11, GST, GPX2
• adaptation process at low doses
• gradient between nose and lung
• transient expression
• mainly NFE2L2 dependent

Xenobiotic Responses
• e.g., CYP1A1, CYP1B1, ALDH3A1, AKR1C1
• no adaptation
• no gradient between nose and lung

Inflammatory response
• e.g., CXCL1, CCL2, MSR1, SAA3, MMP12
• continuously increasing
• persistent

Redox Homeostasis

- Cigarette Smoke
- Metabolism
- Inflammation
- Mitochondria

Oxidative Stress

Anti-Oxidants

- Glutathione
- TRX /GPX
- Catalase
- SOD
CS-response in human smokers

Effects of cigarette smoke on the human airway epithelial cell transcriptome

- Oxidative Stress Response
  - expression of NQO1, GCLM, GCLC, TXN, TXNRD1, SLC7A11, PRDX1, GPX2
  - increase GSH in epithelial lining fluid

- Xenobiotic Responses
  - expression of CYP1A1, CYP1B1, ALDH3A1, AKR1C1

A. Spira: “Our findings that drug metabolism and antioxidant genes are induced by smoking in airway epithelial cells is consistent with in vitro and in vivo animal studies.”

Main player in CS-induced oxidative stress

Cigarette Smoke → Lipid Peroxidation → aldehydes acrolein 4-HNE → Redox Cycling

superoxide \( O_2^- \) → peroxynitrite \( \text{ONOO}^- \) → nitrite oxide \( \text{NO}^- \) → hydrogen peroxide \( \text{H}_2\text{O}_2 \)

Fenton-Reaction → hydroxyl \( \text{OH}^- \)

Glutathione

- GSR
- GLXR
- GPX
- GST
- Thioredoxin
- TXNRD
- AKR
- ALDH
- SOD
- PRDX
- NQO1
- HMOX1

Anti-Oxidants

- SLC7A11
- GCLM
- GGT

Redox Cycling

benzo-quinone → benzoquinone

Cigarette Smoke:

- Lipid Peroxidation

Oxidative Stress

- aldehydes acrolein 4-HNE
- hydro-quinone
- benzo-quinone
- superoxide \( O_2^- \)
- peroxynitrite \( \text{ONOO}^- \)
- nitrite oxide \( \text{NO}^- \)
- hydrogen peroxide \( \text{H}_2\text{O}_2 \)

Anti-Oxidants:

- GSR
- GLXR
- GPX
- GST
- Thioredoxin
- TXNRD
- AKR
- ALDH
- SOD
- PRDX
- NQO1
- HMOX1

Redox Cycling:

- benzo-quinone
- hydro-quinone

Fenton-Reaction:

- hydroxyl \( \text{OH}^- \)

Oxidative Stress:

- aldehydes acrolein 4-HNE
- lipid peroxidation
decomposition of reactive species

aldehydes
acrolein
4-HNE

Superoxide
$O_2^-$

Hydrogen peroxide
$H_2O_2$

Quinone

Acide
alcohol

Hydro-quinone

H$_2$O
Protein-SH \rightarrow Protein-SO- \rightarrow Protein-SO2- \rightarrow Protein-SO3- \rightarrow proteasome

ROS \rightarrow GST \rightarrow GLXR \rightarrow GSSG \rightarrow GSH \rightarrow NADP(+)

TRX (red) \rightarrow TRX (ox) \rightarrow TXNRD1 \rightarrow NADPH \rightarrow NADP(+)

debris \rightarrow inclusion bodies
causes for glutathione depletion

Glutathione

- aldehydes
- xenobiotics

GS-aldehyde

- GS-conjugates

GST

ROS

Protein-SO-

Protein-NO

Protein-SSG

GPX

RNS

GSSG

GLXR

Glutathione Depletion

new GSH synthesis necessary

NADPH

GR

NADP(+)

new GSH synthesis necessary
Glutathione

Thioredoxin

Mitochondria

Cigarette Smoke

aldehydes
acrolein
4-HNE

superoxide
$O_2$

hydrogen peroxide
$H_2O_2$

nitrite oxide
$NO^-$

hydroxyl
$OH^-$

peroxynitrite
$ONOO^-$

enzymatic degradation of stressors

induced protein synthesis (e.g., via redox sensitive TF NRF2)

first line of defence

second line of defence

ER stress response

proteasome activity

DNA damage response

inhibition of translation

autophagy, mitophagy

cell cycle arrest

recovery/apoptosis

recovery/apoptosis

Inflammation

decision on death or life

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anti-apoptotic properties of thioredoxin
Mitophagy: p62/SQSTM1 (sequestosome)

- Mitophagy is preserving mitochondrial homeostasis by eliminating of damaged mitochondria
- relevant in Parkinson’s Disease
- PINK and PARKIN are sensor of mitochondrial membrane potential and
- P62/SQSTM1 mediates anchoring of damaged mitochondria to membranes that targets the complex to lysosomal degradation
- P62/SQSTM1 is involved in NFE2L2 signalling
- P62/SQSTM1 is induced by CS in vitro and in animal systems
DJ-1/PARK7

- mutant DJ-1 is identified as one cause for familial Parkinson’s Disease
- DJ-1 activity is regulated via oxidation status
- DJ-1 activates NFE2L2 by sequestering its inhibitor KEAP1
- DJ-1 acts as sensor for Oxidative Stress

H. Ariga et al. 2013, Oxidative Medicine and Cellular Longevity

Decline in NRF2-regulated Antioxidants in Chronic Obstructive Pulmonary Disease Lungs Due to Loss of Its Positive Regulator, DJ-1

Deepti Malhotra1, Rajesh Thimmulappa1, Ana Navas-Acien1, Andrew Sandford2, Mark Elliott2, Anju Singh1, Linan Chen3, Xiaoxi Zhuang3, James Hogg2, Peter Pare2, Rubin M. Tudor4,5, and Shyam Biswal1,5,6
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