The Role of Protein Radicals in Neuroinflammation
As a Model of GWI & Therapeutic Strategies

Microglia Activation

Pathogen | Environment | Disease

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Gulf War Illness (GWI)

Known:
★ Devastating multisymptom illness.
★ Symptoms - delayed & persistent.

Unknown:
★ Specific cause(s) unknown.
(But we have some good hypotheses.)
★ Patholobiology - poorly understood.
(But we have some good hypotheses.)
★ Markers & treatments are elusive.

Many Symptoms Linked to Peripheral & Central Inflammation

Headaches & Pain
Memory Deficits
Behavioral Impairments: Hippocampal Volume
Impaired Learning
GI Dysfunction
Chronic Fatigue

Why is the immune perturbation chronic?
Microglia are a Source of Chronic Inflammation and Oxidative Stress

Lessons from a Parkinson’s Disease Model: Inflammation-mediated Neuropathology is **Delayed** & **Progressive**

*Early time points (0-6 m) – Model of chronic neuroinflammation without overt toxicity.*
M1 Polarization & Dysregulated Activation
(The Deleterious Phenotype: Exaggerated & Chronic)

M1 Pro-inflammatory Response
(M1) Pro-inflammatory Response

(M2) Wound Healing/Alternative Response

Impaired Resolution

- NOX2: Common Mechanism of Microglia-Mediated Neurotoxicity

<table>
<thead>
<tr>
<th>Microglia Activator/Toxin</th>
<th>Extracellular Superoxide</th>
<th>Pro-inflammatory Factor Production</th>
<th>References</th>
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<tbody>
<tr>
<td>Lipopolysaccharide</td>
<td>Yes</td>
<td>Yes</td>
<td>Qin et al., JBC, 2004</td>
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<td>Diesel Exhaust Particles</td>
<td>Yes</td>
<td>No</td>
<td>Block et al., FASEB J, 2004; Levesque et al., JNC, 2013</td>
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<tr>
<td>Paraquat</td>
<td>Yes</td>
<td>No</td>
<td>Wu et al., Ant. Red. Sig., 2005</td>
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<td>α Synuclein</td>
<td>Yes</td>
<td>No</td>
<td>Zhang et al., FASEB J 2005</td>
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<td>Substance P</td>
<td>Yes</td>
<td>No</td>
<td>Block et al., FASEB J, 2006</td>
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<tr>
<td>MMP3</td>
<td>Yes</td>
<td>Yes</td>
<td>Kim et al., FASEB J, 2006</td>
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<td>μ Calpain</td>
<td>Yes</td>
<td>No</td>
<td>Levesque et al., Brain, 2010</td>
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Microglial ROS are Detrimental Through Two Mechanisms

Microglial NOX2 Activation

Gulf War-like Exposures?

1

ROS

Neuron Damage or Impaired Function

TNFα  PGE₂

Cytokines

Amplification of Pro-inflammatory Genes

NFkB AP-1

(NOX2 Activation)

Dual Roles of NF-κB p50 in Inflammation

NF-κB Subunits

p50  p52  p65  c-rel  reIB

Initiator (Pro-inflammatory Gene Expression)

Expression

Repessor (Constitutively Bound & Resolution)

Promoter

Pro-inflammatory Gene
The Multiple Hit Hypothesis of GWI: Many Potential Causes/Exposures/Stressors May Act in Synergy for Persistent Impact

- Combustion Products From Tent Heaters
- Kuwaiti Oil Well Fires
- Infectious Diseases (LPS)
- Cholinergic & Related Neurotoxicants (Chlorpyrifos)
- Sand & Particulate Exposures
- Vaccines
- Depleted Uranium

Protein Radicals & the Immune Hypothesis of GWI

- Chronic Peripheral Immune Perturbation
- Chronic CNS M1 Activation & Priming

Multiple Interacting GW Exposures

NOX2 Inhibition

Peripheral & CNS Symptoms

Protein Radical Formation

Peripheral Immune Marker

Chronic ROS/Intermittent Cytokines

Chronic ROS & Cytokines

(NF-κB p50*)
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