The effect of chronic stress on T cell-induced neuroinflammation

Neurobiology of Stress
Paris, June 2014

Alon Monsonego, Ph.D.

The Shraga Segal Department of Microbiology and Immunology and
The National Institute for Biotechnology in the Negev

Ben-Gurion University
Israel
Immunity

Reduced lymphocyte function

Impaired cytokine homeostasis

Disregulation of innate and adaptive immunity

Brain function and repair

Protein aggregation (amyloid beta-peptide, α-synuclein)

Chronic glial activation

 Reactive oxygen species

Glutamate toxicity

Stress hormones

Cognitive Decline/Neurodegeneration

(Immunosenescence/Peripheral Inflammation)
How chronic stress or inflammation impair the immunomodulatory functions of the HPA?

- Aging and Neurodegenerative diseases
- Autoimmunity and autoinflammation
Experimental design:

CVS (chronic variable stress) for 24 days

EAE (experimental autoimmune encephalomyelitis) for 15 days

Behavior
T-cell activation

Cort; body weight

Cort; clinical score; T-cell activation

24 days

15 days
**EAE induction and course**

- **T-cell activation**
- **Acute**
- **Remission**
- **Relapse**

**Disease score**

10-15 Days following MOG immunization

- Aggressive T-cell response
- Regulatory mechanisms
T-cell mediated paralysis in a mouse model of multiple sclerosis:

Mice injected with myelin basic protein and complete Freund's adjuvant develop EAE and are paralyzed.

The disease is mediated by myelin basic protein-specific $T_H^1$ cells.

Disease can be transmitted by transfer of T cells from affected animal.

Figure 13-3 Immunobiology, 6/e. (© Garland Science 2005)
Function of lymphocyte subpopulations in EAE:

**Proinflammatory**
- Microglia activation (phagocytosis)
- Severe brain inflammation/autoreactivity

**Immunoregulatory**
- Chemokines (Leukocyte recruitment)
- Brain antibodies
- Neurotrophic factors
- Neurogenesis/Oligodendrogeneration

**Neuroprotective**
- CD11c+
- IL-17
- Th1, IFN-γ
- Th2, IL-10, IL-4
- Treg, IL-10, TGF-β
EAE induction and course

T-cell activation

Disease score

Acute

Remission

Relapse

Days following MOG immunization

10-15
Male and female C57BL6 mice differentially respond to chronic variable stress
CVS induces impaired CORT response to stimuli

- Non-stressed
- Stressed

CORT levels (ng/ml)

Weeks

Days post MOG immunization

CORT (ng/ml)
Experimental autoimmune encephalomyelitis (EAE) is more severe in male than in female mice.

Days post onset
Clinical score

- Females
- Males

* * * * * * * * * *

Days post onset
Clinical score

Days post onset
CVS exacerbates experimental autoimmune encephalomyelitis in female mice.
T-cell activation does not change in stressed mice

<table>
<thead>
<tr>
<th></th>
<th>IL-2</th>
<th>IFN-γ</th>
<th>IL-17</th>
<th>IL-4</th>
<th>TNF-α</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-stressed</strong></td>
<td>1881 ±52.9</td>
<td>40773 ±3067</td>
<td>1576 ±147</td>
<td>718 ±68</td>
<td>625 ±72</td>
</tr>
<tr>
<td><strong>Stressed</strong></td>
<td>1675 ±226</td>
<td>39560 ±6576</td>
<td>1735 ±214</td>
<td>800 ±52</td>
<td>587 ±79</td>
</tr>
</tbody>
</table>
CVS decreases the sensitivity of Th1 and Th17, but not Th2, effector T cells to the immunosuppressive effects of methylprednisolone (MP).
Stress induces increased Th1/Th2 and Th17/Th2 ratios
CVS decreases the fraction of FoxP3 regulatory cells among CD4 T cells

**p=0.08**
Chronic stress

Homeostatic stress management

Acute inflammation

Corticosterone (CORT)

Anti-inflammatory cytokine

Pro-inflammatory cytokine

Treg

CORT-sensitive Teff

CORT-resistant Teff

Immune regulation

Pathogenic autoimmunity

Corticosterone (CORT)

Harpaz Et al., EJI 2013
Increased effector CD4 T cells in elderly human subjects

Harpaz et al, in preparation
Consequences of Immunosenescence:

- Declined immunity
- ?
- Immune dysregulation: CORT resistance and enhanced T cell-induced inflammation
- ?
- Accelerated Aging and Alzheimer’s disease
Chronic HPA activation

Resistance to steroid treatment  Loss of immune regulation

Cort resistance

Chronic HPA activation

Peripheral blood
Mononuclear cells

Peripheral infection/sepsis

Autoimmune diseases

Stress  Aging/ Neurodegenerative diseases
Diagnostic kit to determine the loss of immune potency and regulation resulting from chronic stress and inflammation

Performed on isolated PBMCS out of 5-10 ml of blood

Clinical assessments:
- Steroid treatment efficacy
- Stress progression and its impact on immune functionality (T cells, monocytes, DCs)
- Disease state and prognosis
Alzheimer’s diseases:
- Protein toxicity
- Chronic glial activation
- Reactive oxygen species
- Cytokine disregulation (TNF-α, IL-1β)
- Demyelination

Repair mechanisms:
- Clearance of damaged proteins
- Neuroprotection
- Neurogenesis
- Remyelination
- Cytokine homeostasis

Clinical symptoms

Stress management    Exercise    Nutrition and supplements

Ageing

Immune modulation

Alzheimer’s diseases:
- Protein toxicity
- Chronic glial activation
- Reactive oxygen species
- Cytokine disregulation (TNF-α, IL-1β)
- Demyelination

Clinical symptoms
Acknowledgments:

**Students and postdocs at the BGU:**

Anna Nemirovski
Rona Baron
Roy Elmaliach
**Idan Harpaz**
Jenny Shapiro
Itai Strominger
Shira Or
Nitzan Levi
Kati Vinogradov
Kate Eremenko
Niva Blum

**The National Institute of biotechnology in the Negev and The Department of Microbiology and Immunology Ben-Gurion University, Israel**

**Collaborations:**

Trevor Owens, Ph.D.
Howard Weiner, M.D.
Irun Cohen, M.D.
Steffen Jung, Ph.D.
Alon Friedman, Ph.D.
Smadar Cohen, Ph.D.
Eitan Rubin, Ph.D.
**Hagit Cohen, Ph.D.**
Ilya Fleidervish, Ph.D.
Bente Finsen, Ph.D.
Tzvi Dwolatzky, MD