The immune system and anxiety disorders

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Agenda

• Introduction to the immune system
  – The immune system and the CNS

• How the immune system can influence psychological symptoms

• Anxiety and immune changes
  – Stress and immune function
  – Anxiety disorders and immune function
Immune system in brief
How does peripheral immune activity influence the CNS?

A. Active transport of cytokines across BBB
B. Activation of vagus nerve
C. Passage of cytokines through porous areas of BBB
D. Direct migration of circulating immune cells
E. All of the above
How the immune system influences psychological symptoms

Immune alterations

Activated microglia

Altered HPA axis functioning

Altered tryptophan metabolism

Direct neuronal/monoaminergic effects

Neuropsychiatric effects
How the immune system influences psychological symptoms

Immune alterations

- Activate microglia
- Altered HPA axis functioning
- Altered tryptophan metabolism
- Direct neuronal/monoaminergic effects

Neuropsychiatric effects
• Physiological levels helpful
  – IL-1β – maintains plasticity and LTP
  – TNF-α – Upregulates AMPA and improves synaptic strength

• High pathological levels
  – IL-1β – inhibits LTP
  – TNF-α – impaired LTP
  – IL-6 – inhibits LTP and glutamate release
Cytokine effects on hippocampus

Synaptic strength / LTP

Increasing IL-1, TNF, IL-6

Correlates with “depression”

Adapted from Khairova 2009
How the immune system influences psychological symptoms

Immune alterations

Activated microglia

Altered HPA axis functioning

Altered tryptophan metabolism

Direct neuronal/monoaminergic effects

Neuropsychiatric effects
Aetiology of IFN-Induced Depression: Trp Metabolism

Diet → Tryptophan → 5-HTP → 5-HT

Tryptophan Metabolic Pathway

Tryptophan hydroxylase

Aromatic amino acid decarboxylase
Aetiology of IFN-Induced Depression: Tryp/5-HT Depletion?

Indoleamine dioxygenase

IFNs

L-Kynurenine

Diet

Tryptophan

Tryptophan hydroxylase

5-HTP

Aromatic amino acid decarboxylase

5-HT

Tryptophan Metabolic Pathway

Change in tryptophan correlates with increasing depression

• Increase in K/Trp ratio (IDO): $p = 0.017$
• Assoc with depression: $R^2 = 0.340$, $p = 0.001$

Christmas in preparation
How the immune system influences psychological symptoms

Immune alterations

- Activated microglia
- Altered HPA axis functioning
- Altered tryptophan metabolism
- Direct neuronal/monoaminergic effects

Neuropsychiatric effects
HPA axis

- Pro-inflammatory cytokines
  - Activate HPA axis
  - May downregulate Glucocorticoid receptors centrally – causes increased cortisol release

- Glucocorticoids normally anti-inflammatory
- But during prolonged stress are pro-inflammatory in CNS – increased IL-1b and TNFα
How the immune system influences psychological symptoms

Immune alterations

Activated microglia → Altered HPA axis functioning → Altered tryptophan metabolism → Direct neuronal/monoaminergic effects → Neuropsychiatric effects
Activated Microglia

• Produce increased:
  – IL-1b, IL-6, TNF-a, MCP-1 (more macrophages)
  – Cause damage through reactive oxygen species
  – Increased IDO expression

• Some mice models lacking Hoxb8
  – Display OCD-like grooming behaviour
Stress and Immune function
Anxiety and immune function – Psychological Stress

![Graph showing IL-6 levels over time in Control and Maltreated groups.](Carpenter et al. Neuropsychopharmacology 2010)
Anxiety and immune system
Immune stressor

Wright Brain Behaviour Immunity 2005
Anxiety and immune response correlate during challenge

\[ A \]

\[ r = 0.60 \]

\[ \Delta \text{Anxiety Level} \]

\[ \text{TNF} \]

Reichenberg Archives of General Psychiatry 2001
Anxiety varies with immune markers in general population

<table>
<thead>
<tr>
<th>Inflammation and coagulation factors, by anxiety status</th>
<th>Spielberger state anxiety inventory (STAI) score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First tertile</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>1.2 ± 0.9</td>
</tr>
<tr>
<td>Tumor necrosis factor-α (mg/dl)</td>
<td>4.8 ± 1.7</td>
</tr>
<tr>
<td>Interleukin-6 (mg/dl)</td>
<td>1.8 ± 0.7</td>
</tr>
<tr>
<td>Homocysteine (μmol/l)</td>
<td>9.7 ± 3.3</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>255 ± 45</td>
</tr>
<tr>
<td>Amyloid-a (mg/dl)</td>
<td>3.4 ± 2.1</td>
</tr>
<tr>
<td>White blood cell (×1000 counts)</td>
<td>6.5 ± 1.3</td>
</tr>
</tbody>
</table>

| **Women**                                               |              |                |               |         |
| C-reactive protein (mg/dl)                             | 1.1 ± 1.1     | 1.6 ± 1.2*     | 2.1 ± 1.0**   | 0.005   |
| Tumor necrosis factor-α (mg/dl)                        | 0.4 ± 1.2     | 7.2 ± 3.9      | 7.9 ± 4.2     | 0.15    |
| Interleukin-6 (mg/dl)                                  | 1.5 ± 0.8     | 2.6 ± 1.7*     | 2.9 ± 1.6*    | 0.02    |
| Homocysteine (μmol/l)                                  | 9.7 ± 2.7     | 10.2 ± 2.1*    | 12.4 ± 2.4*   | 0.03    |
| Fibrinogen (mg/dl)                                     | 277 ± 55      | 340 ± 58*      | 398 ± 42*     | 0.03    |
| Amyloid-a (mg/dl)                                      | 4.1 ± 2.2     | 4.5 ± 1.7      | 5.1 ± 3.4     | 0.24    |
| White blood cell (×1000 counts)                        | 6.2 ± 1.7     | 6.9 ± 1.1*     | 7.2 ± 1.3*    | 0.02    |

* p < 0.05.
** p < 0.01 for the comparison between third or second tertiles vs. first tertile using Bonferroni correction to account for multiple comparisons.
### Table 3. Levels of Basal and Stimulated Cytokines in Studies of PTSD

<table>
<thead>
<tr>
<th>Author(s) (Year)</th>
<th>Sample</th>
<th>Stimulation Method</th>
<th>Findings</th>
<th>Increased Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gill, Vythilingam, and Page (2008)</td>
<td>26 PTSD, 24 TC, and 21 NTC, all women</td>
<td>LPS and PHA and incubated for 48 hr</td>
<td>Higher levels of IL-6 and TNF-α vs. TC and NTC in PTSD. Lower a.m. cortisol and higher a.m.</td>
<td>Yes</td>
</tr>
<tr>
<td>Song, Zhou, Guan, and Wang (2007)</td>
<td>34 earthquake survivors with PTSD, 30 TC and 34 NCT</td>
<td>None</td>
<td>Lower IL-8 in PTSD vs. TC and NTC, lower IL-2 in PTSD and TC vs. NTC, IL-6 correlated with anxiety (.38) and depression symptoms (.41)</td>
<td>No</td>
</tr>
<tr>
<td>De Kloet et al. (2007)</td>
<td>29 male veterans, 29 TC, and 25 NTC (18/29 PTSD, also MDD)</td>
<td>PHA and incubated for 72 hr, or LPS and incubated for 18 hr</td>
<td>Lower TNF-α in PTSD vs. NTC, but not PTSD vs. TC, ND in IFN-γ, or IL-10</td>
<td>No</td>
</tr>
<tr>
<td>Von Kanel et al. (2007)</td>
<td>9 PTSD, 14 NTC</td>
<td>None</td>
<td>Higher TNF-α, ND in IL-6 IL-4, or IL-10</td>
<td>Yes</td>
</tr>
<tr>
<td>Pervanidou et al. (2007)</td>
<td>57 children ages 7-18 following an MVA, 1 and 6 months later, 40 NTC</td>
<td>None</td>
<td>High a.m. IL-6 and p.m. cortisol 24 hr after an MVA predicted PTSD development at 6 months</td>
<td>Yes</td>
</tr>
<tr>
<td>Woods, Page, et al. (2005)</td>
<td>32 abused women with PTSS, 30 TC, 39 NTC</td>
<td>LPS and PHA, incubated for 48 hr</td>
<td>Higher IFN-γ in PTSD compared to TC and NTC</td>
<td>Yes</td>
</tr>
<tr>
<td>Rohleder, Joksimovic, Wolf, and Kirschbaum (2004)</td>
<td>12 male and female refugees and 13 NTC</td>
<td>LPS incubated for 6 hr</td>
<td>Higher IL-6, ND in TNF-α</td>
<td>Yes</td>
</tr>
<tr>
<td>Tucker et al. (2004)</td>
<td>86 PTSD (men and women), 21 TC</td>
<td>None</td>
<td>Higher IL-1β and lower IL-2R at baseline that were correlated. Following treatment IL-1β and IL-2R were similar to TC’s</td>
<td>Yes</td>
</tr>
<tr>
<td>Baker et al. (2001)</td>
<td>11 combat PTSD (men) 8 NTC</td>
<td>None</td>
<td>Higher IL-6 in the CSF collected between 11 a.m. and 5 p.m. ND in ACTH, cortisol, or NE ND in sIL-6r; or CRP correlations; sIL-6r and intrusion score (.26), CRP and intrusion (.16)</td>
<td>Yes</td>
</tr>
<tr>
<td>Millor, Sutherland, Hutchison, and Alexander (2001)</td>
<td>15 PTSD (10 men) 8 TC</td>
<td>None</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>
Immune and HPA changes in PTSD

• Increased proinflammatory cytokines
  – IL-1b, TNFα, IL-6, CRP
  – Increased IL-6 response time of trauma may predict PTSD at 6 months

• HPA dysfunction
  – Reduced CSF CRF
  – Increased circulating cortisol
  – Increased response/sensitivity to Dex
IL-1β reduced in OCD

Brambilla, Biological Psychiatry 1997
Denys, Psychoneuroendocrinology 2006
Summary

• Brain has constituent immune cells
  – Have many homeostatic functions in addition to traditional pathogen removal
• Cross-talk between CNS and peripheral immune systems
• Psychological stressors induce immune responses and vice versa
• Much work is needed to delineate role of immune system in anxiety disorders