Entzündung - Schmerz - Depression

Claudia Sommer
From inflammation to sickness and depression: when the immune system subjugates the brain

The Sickness Response

- Viral or bacterial infection
- Fever
- Hyperalgesia
- Nausea
- No appetite
- No interest
- Tiring easily
- Sleep fragmented
- Depressed and irritable
- Mild cognitive disorders
  - impaired attention
  - difficulties in remembering recent events

Ancher, Michael, "The Sick Girl", 1882, Statens Museum for Kunst, Copenhagen
The Sickness Response

- Normal response to infection
- Endocrine, autonomic, and behavioral changes
- Triggered by soluble mediators that are produced at the site of infection by activated immune cells
  - **pro-inflammatory cytokines**
  - coordinate the local and systemic response to microbial pathogens
  - **may get access to the brain**
Pro- and antiinflammatory cytokines

Pro-inflammatory cytokines

– Interleukin-1β (IL-1β)
– Interleukin-2 (IL-2)
– Interleukin-6 (IL-6)
– Interleukin-17 (IL-17)
– Tumor necrosis factor-alpha (TNF)

Anti-inflammatory cytokines

– Interleukin-4 (IL-4)
– Interleukin-10 (IL-10)
– Interleukin-13 (IL-13)
– Transforming growth factor β1 (TGFβ1)

…..up to interleukin-35 and many chemokines…….
Chronic Inflammation

Cytokines Neurotransmitters

Depression

Pain
Low grade chronic inflammation

- Chronic heart failure
- Cancer
- Cardiovascular disease
- Rheumatoid disorders (not in acute stages)
- Obesity
- Diabetes
- Atherosclerosis
Depression in CHF is associated with impaired NYHA status and daily activities, resulting in enhanced hospitalisation rates and medical costs with a great impact on long-term health.
Chronic heart failure and depression

- Major depression is a common disorder with lifetime prevalence of 13%.

- Depression is even more common in patients with ischemic heart disease, with prevalence rates between 15% and 22%.

- CHF patients with major depression have
  - twice the mortality rate at 3 months (OR = 2.5) and 1 year (OR = 2.23) and
  - increased hospital admission rate (OR = 1.9) at 3 months (OR = 1.9) and 1 year (OR = 3.07) compared with CHF patients who were not depressed.

Musselmann et al. Am J Psychiatry 2001;158:8
Chronic heart failure and cytokines

Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial\textsuperscript{1–3}

Stefanie S Schleithoff, Armin Zittermann, Gero Tenderich, Heiner K Berthold, Peter Stehle, and Reiner Koerfer


The pathophysiologic concept of chronic heart failure has changed from an isolated hemodynamic view to a more complex concept involving neurohormonal overactivation and increased concentrations of proinflammatory cytokines.

The cytokine hypothesis of heart failure proposes that heart failure progresses because the cytokine cascade activated after myocardial injury exerts deleterious effects on the heart and circulation.

(Seta et al. J. Cardiac Failure 1996)
Example: Cancer and cytokines

Some cytokines induce depression

- IFNα late onset
- IL-2 early onset

- therapy interruption
- anti-depressants
- prevention

Early depressive symptoms in cancer patients receiving interleukin-2 and/or interferon alpha-2b therapy

Some cytokines induce pain

- TNF, IL-1β
  - local injection site pain
  - Generalized pain

Cytokines induce pain: Experimental data

Cytokines antagonists attenuate neuropathic pain

Neuropathic hyperalgesia can be attenuated with antibodies to IL-1β

How do cytokines induce pain

1. Locally
   • Sensitization of primary afferent neurons via
     • Induction/release of further algesic mediators
       - NGF
       - Prostaglandins
       - Neuropeptides
     • Direct actions on neuronal excitability
       – Sensitization of TRP-channels
       – Sensitization of ion channels
     • Phenotype switch

2. In the CNS
   • Sensitization of higher order neurons
   • Glia-neuronal interaction on synaptic strength

3. Systemically
   • Modulation of central pain thresholds
Chronic widespread pain and fibromyalgia

- 40 + 15 pts. with CWP, 40 controls
  - Mean age 51±9 y
  - Mean duration of disease 10±7 y

- Analysis of whole blood for cytokine mRNA using quantitative RT-PCR
  - Th1 cytokines: TNF, IL-2 (‘pro-inflammatory’)
  - Th2 cytokines: IL-4, IL-10 (‘anti-inflammatory’)

Üceyler et al. Arthritis Rheum 2006;54:2656-64
Cytokine gene expression in FMS

Üceyler et al. Arthritis Rheum 2006;54:2656-64
Treatment of Fibromyalgia Syndrome

• The best drugs are antidepressants!

Treatment of Fibromyalgia Syndrome With Antidepressants
A Meta-analysis

Winfried Häuser, MD
Kathrin Bernardy, PhD
Nurecan Üçeyler, MD
Claudia Sommer, MD

Context  Fibromyalgia syndrome (FMS) is a chronic pain disorder associated with multiple debilitating symptoms and high disease-related costs. Effective treatment options are needed.

Objectives  To determine the efficacy of antidepressants in the treatment of FMS by performing a meta-analysis of randomized controlled clinical trials.

Conclusion  Antidepressant medications are associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients with FMS.

JAMA. 2009;301(2):198-209

www.jama.com
Cytokines and Pain

- Control
- Injury
- Inflammation

Treatment

- Pro-inflammatory
- Anti-inflammatory
Cytokines and Depression

- Mice or rats injected with
  - LPS systemically
  - TNF or IL-1β in the CNS

- stay in a corner of their home cage in a hunched posture
- show little or no interest in their physical and social environment
- show decreased motor activity
- Social withdrawal
- reduced food and water intake,
- altered cognition
In vivo production of IL-6 in control subjects and depressed patients at baseline and after anti-depressant therapy.

Cytokine production (IL-6) and treatment response in major depression

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Responders</th>
<th>Non-responders</th>
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<tbody>
<tr>
<td>Pre-treatment</td>
<td></td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>40</td>
<td>50</td>
<td>30</td>
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</tbody>
</table>

In vivo production of IL-6 in controls and depressive patients at baseline and after anti-depressant therapy.

Pretreatment of laboratory animals with the tricyclic antidepressant imipramine reduced the intensity of “sickness behavior” (anhedonia, anorexia, and decreased social exploration), induced by cytokine administration.

Can antidepressants similarly attenuate cytokine-induced depression in humans?

Paroxetine for the prevention of depression induced by high-dose interferon alpha

Anti-depressants (TCA, SSRI, SARI) inhibit release of cytokines in vitro

Maes et al. Neuropsychopharmacology 1999;20:370-379
Wichers and Maes J Psychiatry Neurosci 2004; 29:11-7
In vitro effects of three different antidepressant drugs on LPS-stimulated secretion of interferon-gamma and IL-10 in healthy volunteers

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Control</th>
<th>Clomipramine</th>
<th>Sertraline</th>
<th>Trazodone</th>
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</thead>
<tbody>
<tr>
<td>IFNγ (U/mL)</td>
<td>575</td>
<td>465</td>
<td>384</td>
<td>458</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>547</td>
<td>665</td>
<td>680</td>
<td>658</td>
</tr>
<tr>
<td>IFNγ/IL-10 ratio</td>
<td>0.72</td>
<td>-0.12</td>
<td>-48</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

ADs change the ratio to an anti-inflammatory profile
Mechanisms of cytokine induced depression

- Influence on the metabolism of neurotransmitters (serotonin, norepinephrine, dopamine) via IDO
- Influence on serotonin reuptake
- Stimulation of expression and release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH)
- Decreased hippocampal expression of brain derived neurotrophic factor (BDNF) and reduced hippocampal neurogenesis
The role of IDO

- Indoleamin-2,3-dioxygenase

\[
\text{L-tryptophan} \xrightarrow{\text{IDO}} \text{N-formylkynurenine}
\]
L-tryptophan → tryptophan hydroxylase → 5-hydroxytryptophan → aromatic amino acid decarboxylase → 5-hydroxytryptamine (5-HT) → N-acetyltransferase → N-acetyl-5-HT → 5-hydroxyindole-O-methyltransferase → melatonin

Indoleamine 2,3-dioxygenase

→ formamidase → 2-amino-3-(3-oxoprop-1-enyl)-fumaric acid → non-enzymatic cyclization → quinolinate

→ niacin
Inductors of IDO

- IFN $\alpha,\beta,\gamma$
- Tumor necrosis factor-alpha (TNF $\alpha$)
- Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)
- Interleukin (IL)-12, IL-18,
- Lipopolysaccharides
- Amyloid $\beta$ protein
- Tryptophan

- IDO-Inhibitor: IL-4
IDO, 5-HT, cytokines, and Depression

Overstimulation of NMDA receptors, leading to hippocampal damage and oxidative stress

Oxidative stress and apoptosis

5-HT synthesis

QUIN

3-OH-KYN

KYN

KYNA

TRP

KYN

I DO

BBB

IL-4

TRP

Tryptophan

Kynurenine

IL-10

IL-4

Tryptophan

IFN-α

IFN-γ

TNF-α

IL-10

Wichers MC, Maes M. *J Psychiatry Neurosci* 2004; 29:11-7
Reducing 5-HT from two sides

The Proinflammatory Cytokines Interleukin-1beta and Tumor Necrosis Factor-Alpha Activate Serotonin Transporters

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Thank you for your attention!