Inflammation, Depression, and Therapy

Robert Dantzer
MD Anderson Cancer Center
Department of Symptom Research
Houston, TX
rdantzer@mdanderson.org
An emerging concept in psychoneuroimmunology in the late 1980s: The immune system needs the brain

- Like any other physiological system in the body, the immune system needs the brain to do what it has to do and to be regulated.

- This is possible because the brain has an « immunostat » that enables it to perceive and represent what is going on in the immune system, using immune cell communication molecules (cytokines).

![Diagram showing interactions between CNS, immune cells, cytokines, ANS & Neuroendocrine Factors.]

Cytokines: IL-1β, TNFα, IL-6
Theodor Rombouts, 1640, Allegory of the Five Senses
Museum voor Schone Kunsten, Ghent, Belgium
The nervous and immune systems produce a common set of peptide and nonpeptide neurotransmitters and cytokines that act on a common repertoire of receptors in the two systems...This complete biochemical information between neurons and immune cells allows the immune system to function as a sensory organ.

Bacteria, viruses, antigens, tumour cells and other agents that are too small to see or touch, make no noise, have no taste or odour, are "noncognitive stimuli," that "result in transmission of information to the CNS via the aforementioned shared signal molecules to cause a physiological response that is ultimately beneficial to the host and detrimental to the infectious agent."
Sickness behavior as an example of immune-to-brain communication

Biological Basis of the Behavior of Sick Animals

BENJAMIN L. HART
Department of Physiological Sciences, School of Veterinary Medicine
University of California, Davis, CA 95616

Received 1 February 1988
Cytokines induce sickness behavior

Pathogen-associated molecular patterns

Toll-like receptor

Activation of innate immunity (NF-κB, MAP kinases)

Peripheral proinflammatory cytokines (IL-1β, TNFα, IL-6)

Immune-to-brain communication pathways

Neuroendocrine alterations

Metabolic alterations

Behavioral changes
Peripheral administration of IL-1β induces a transient episode of sickness

Operant responding for food (Fixed ratio 10)

Social exploration of a juvenile
The sickness inducing effects of peripheral IL-1 are mediated centrally (Kent et al, 1992; Laye et al, 1994)
Why we feel sick and behave in a sick way when we are ill: inflammation propagates to the brain

Pathogen-associated molecular patterns

Activation of innate immunity

Peripheral proinflammatory cytokines

Immune-to-brain communication pathways

Brain proinflammatory cytokines

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Behavioral changes
MOTIVATIONAL INTERPRETATION OF SICKNESS

Threat $\rightarrow$ Fear $\rightarrow$

Pathogenic microorganisms $\rightarrow$ Sickness $\rightarrow$

- Fear feelings
- Fear behavior
- Visceral arousal
- Malaise
- Sickness behavior
- Visceral arousal
- The brain forms a representation of the peripheral innate immune response. This representation is at the origin of sickness behavior.

- Sickness behavior corresponds to a reorganization of the host’s priorities.

- Sickness behavior is normally fully reversible.

*Georges Canguilhem: « être en bonne santé, c’est pouvoir tomber malade et s’en relever » (To be healthy is to be able to become ill and recover from it…)"
Is depression a form of sickness disorder?

Vincent Van Gogh, *Old Man in Sorrow*, 1890
<table>
<thead>
<tr>
<th>Major depressive disorders (DSM-IV)</th>
<th>Sickness Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Depressed mood</td>
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</tr>
<tr>
<td>• Loss of interest/anhedonia</td>
<td>• Loss of interest/anhedonia</td>
</tr>
<tr>
<td>• Changes in appetite/weight</td>
<td>• Anorexia</td>
</tr>
<tr>
<td>• Insomnia/hypersomnia</td>
<td>• Altered sleep pattern</td>
</tr>
<tr>
<td>• Psychomotor retardation/agitation</td>
<td>• Reduced locomotor activity/apathia</td>
</tr>
<tr>
<td>• Fatigue/anergia</td>
<td>• Lethargy</td>
</tr>
<tr>
<td>• Decreased concentration</td>
<td>• Cognitive disturbances</td>
</tr>
<tr>
<td>• Worthlessness or guilt</td>
<td>• ?</td>
</tr>
<tr>
<td>• Suicidal thoughts</td>
<td>• ?</td>
</tr>
</tbody>
</table>

(Yirmiya, Brain Res, 1996, 711, 163-174)
# Prevalence of Depression in Medically Ill Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>✦ General Population</td>
<td>5-10%</td>
</tr>
<tr>
<td>✦ Cancer</td>
<td>18-39%</td>
</tr>
<tr>
<td>✦ Autoimmune Disorders</td>
<td>15-40%</td>
</tr>
<tr>
<td>✦ Cardiovascular Disease</td>
<td>15-40%</td>
</tr>
<tr>
<td>✦ Chronic illnesses (e.g. irritable bowel syndrome, chronic fatigue syndrome)</td>
<td>15-60%</td>
</tr>
<tr>
<td>✦ Obesity / Metabolic Syndrome</td>
<td>20-30%</td>
</tr>
</tbody>
</table>

Evans et al., *Biol Psychiat*, 2005, 58, 175-89
Depression is more than sickness: immunotherapy-induced depression in cancer patients

Adapted from Capuron et. al. Biol Psychiatry 2004, 56, 819-824
Preclinical approaches to the mechanisms of inflammation-associated depression
Lipopolysaccharide (LPS) and Bacillus Calmette-Guerin (BCG) induce depressive-like behavior in the forced swim test (Moreau et al., 2008, O'Connor et al., 2009)

Assessment of depressive-like behavior after recovery from sickness behavior

**LPS**

**BCG**

**Immobility (sec)**

Saline

Fluoxetine (40 mg/kg, ip)

Desipramine (20 mg/kg, ip)

Sal

LPS (24 h before)

Sal

BCG

**Immobility (sec)**

7 14 21 days

30 cm
How does activation of the immune system translate into depressive disorders?

Depressed mood is specifically associated with decreased plasma tryptophan levels in IFNα-treated cancer patients

(Capuron et al., Mol Psychiat, 2002)
Immune stimuli cause tryptophan starvation by activation of indoleamine 2,3 dioxygenase

This hypothesis was initially formulated in the context of Immunology of Reproduction to account for maternal immunotolerance of the trophoblast (Mellor and Munn, 1999)

IDO = indoleamine 2,3 dioxygenase
Working hypothesis: activation of IDO mediates the transition from sickness to depression.
Working hypothesis: activation of IDO mediates the transition from sickness to depression.

- Neurovegetative symptoms (e.g., sickness, fatigue)
- Mood and cognitive symptoms

Activation of innate immunity

Proinflammatory cytokines

Activation of IDO

Minocycline

Symptom Intensity

Time

Neurovegetative symptoms (e.g., sickness, fatigue)

Mood and cognitive symptoms
Administration of minocycline attenuates LPS-induced expression of brain proinflammatory cytokines and IDO and blocks depressive-like behavior.

(O’Connor et al., Mol Psychiat 2009)
Working hypothesis: activation of IDO mediates the transition from sickness to depression

Pharmacological or genetic inhibition of IDO

Activation of innate immunity

Proinflammatory cytokines

Activation of IDO

Symptom Intensity

Time

Neurovegetative symptoms (e.g., sickness, fatigue)

Mood and cognitive symptoms
Blockade of IDO by 1-MT does not impact LPS-induced brain cytokine expression but abrogates depressive-like behavior

(O’Connor et al., Mol Psychiat 2009)
However, immune stimulation increases brain kynurenine without decreasing brain tryptophan

Raison et al., 2010: Hepatitis C virus-infected patients treated with interferon-alpha

Beenders et al., in preparation: Mice injected with ip LPS
Activation of IDO leading to immunosuppression by tryptophan starvation (Mellor and Munn, 1999)

Meanwhile in immunology

Activation of IDO leading to immunosuppression by paracrine production of kynurenine metabolites by enzymes downstream of IDO. These kynurenine metabolites ultimately induce apoptosis of Th1 cells (Fallarino et al., 2002)
LPS-induced inflammation is associated with formation of cytotoxic kynurenine metabolites produced by activated microglia.
Administration of KYN to IDO-deficient mice restores LPS-induced depressive-like behavior.
Inhibition of KMO in LPS-treated mice abrogates LPS-induced depressive-like behavior

Tryptophan → Kynurenine → 3-OH Kynurenine → Quinolinic acid → NMDA Receptor

Forced Swim Test

Duration of Immobility (s)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ro 61-8048</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sal</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>LPS</td>
<td>180</td>
<td>100</td>
</tr>
</tbody>
</table>

* Indicates significant difference.
KMO-dependent kynurenine metabolites have the potential to act as NMDA receptor agonists.

The depressive-like behavior induced by LPS should be blocked by the NMDA receptor antagonist ketamine.

As ketamine acts by diverting glutamate to AMPA receptors, the AMPA receptor antagonist NBQX should restore LPS-induced depressive like behavior.
Blockade of NMDA receptor by ketamine abrogates LPS-induced decrease in sucrose preference and this effect is restored by AMPA receptor antagonism by NBQX.

(Walker et al., Neuropsychopharmacology, 2013)
We can understand now why we feel sick and behave in a sick way when we are ill: immune activation propagates into the brain and triggers a normally reversible motivational state.

Recruitment of IDO results in the formation of neurotoxic kynurenine metabolites that transform sickness into depression.

Targets for intervention include cytokines, activation of IDO and formation of kynurenine metabolites.
**Bordeaux team:**
Rose-Marie Bluthé
Nathalie Castanon
Jacques Lestage
Maïte Moreau
Lucile Capuron
Sophie Layé
Patricia Parnet
Jan-Pieter Konsman
Robert Dantzer

**Houston Team:**
Robert Dantzer
Adam Walker
Elisabeth Vichaya
Annemieke Kavelaars
Cobi Heijnen

**Utrecht team:**
Annemieke Kavelaars
Cobi Heijnen
Niels Eijkelkamp