Cytokine Actions in the Brain: From Sickness Behavior to Depression

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1. What are the mechanisms of action of cytokines on the brain?
2. How is organized the sickness response to cytokines?
3. How does sickness behavior translate into pathology?

How can peripherally produced cytokines act in the brain?

Peripheral cytokines

Brain targets

HPA axis activation
Fever
Sickness behavior

Peripheral cytokines do not need to get into the brain because they are produced in the brain

Peripheral cytokines

Brain cytokines

Humoral pathway

Neural pathway

Vagotomy abrogates the induction of hypothalamic IL-1β expression and sickness behavior

From Layé, Bluthe et al, 1995

Conclusions

- By their actions on the brain, proinflammatory cytokines produced by activated macrophages and monocytes induce sickness behavior
- The brain forms a molecular and cellular representation of the peripheral immune response
- This representation is mediated by several immune-to-brain communication pathways including a neural pathway that is critical for sickness behavior
1. Why do we feel and behave in a sick way when we are ill?

2. How is organized the sickness response to cytokines?

3. How does sickness behavior translate into pathology?

- 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.)
What does happen when the innate immune system remains activated?

Examples:
- Chronic inflammatory disorders
- Chronic administration of exogenous cytokines
- Cancer
- Aging
- Viral pathologies

Each of these conditions is associated not only with specific signs of the disease but also with non-specific symptoms of an exaggerated sickness response such as fatigue and an increased incidence of affective and cognitive disorders.

Prevalence of Depression in Patients with Immune-based Disorders

<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>
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See for review, Evans et al., Biological Psychiatry, 58, 2005

Temporal Evolution of the Behavioral Symptoms Induced by Chronic Cytokine Therapy

The brain forms a molecular and cellular representation of the activation state of the innate immune system.

This representation organizes the normal response of the host to infection and danger signals.

This representation can lead to the development of disorders of affect and cognition.

Review of sickness behavior evidence

- increased prevalence of clinical depression in physically ill people
- peripheral or central administration of lipopolysaccharide (LPS) or cytokines directly, induces sickness behaviour
- major depressive disorders develop in roughly a third of patients who are treated with the recombinant human cytokines
- some depressed patients have increased peripheral inflammatory markers