Immune adaptation in the central nervous system in response to systemic infections

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Ageing, healthy ageing and risk factors for age-related neurological disease

Common factor: low grade systemic inflammation

How does systemic inflammation impact on the brain?
Outline of talk

Outline of the talk:

• Does the immune system communicate with the brain?
  – Which biological pathways are involved?
  – Which cells and molecules are involved in this communication

• What are the consequences of systemic inflammation in health?

• What are the consequences of (chronic) systemic inflammation during ageing or age-related neurological diseases?
Why do we feel so bad when we are ill?
Feeling ill.....

Bacterial or viral infection

- Feverish and nauseated
- Ignore food and drink
- Lose interest in physical and social environment
- Tired, fragmented sleep
- Feel depressed and irritable
- Mild cognitive disorders, ranging from impaired attention and difficulties in remembering recent events

Sickness is a normal response to infection and is triggered by soluble mediators produced immune cells
The molecular mechanisms by which inflammation communicates with the brain

- **TLR4**
- **Cytokines, Inflammatory mediators** (IL-1β, TNF, IL-6, IL-10, IL1RA)
- **Through sites lacking BBB**
  - Circumventricular organs of choroid plexus.
  - **Vagus nerve**
  - ** Neural activation of brainstem - hypothalamus "depression"
- **Directly across BBB**
  - **Active transport**
  - Cytokines, NO, PGE2
- **HPA axis (fever)**
Systemic challenge with LPS results in release of pro-inflammatory cytokines

Serum

IL-6

PGE2

Brain

TNF-α

IL-6

IL-1β

Typical symptoms after systemic challenge with LPS

- Anhedonia
- Fatigue
- Depression
- Piloerection
- Fever

If pro-inflammatory mediators help us recover, how does this link to age-related diseases?

Teeling et al BBI, 2007, 2010
Microglial priming and phenotype switching without morphological change

Molecular mechanism?? ---Micro-array---

Cunningham J. Neuroscience 2005, 2009
Puentener J Neuroinflammation, 2012
Systemic inflammation and disease progression in Alzheimer disease

Table 1: Period prevalence of systemic inflammatory events at baseline and during the 6-month follow-up period and effect size on cognitive decline

<table>
<thead>
<tr>
<th>Acute systemic inflammatory event</th>
<th>2 mo at or before baseline</th>
<th>6 mo after baseline</th>
<th>Effect size mean difference (SE), pts ADAS-COG change from baseline to 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infection</td>
<td>16 (32.0)</td>
<td>51 (34.0)</td>
<td>2.6 (1.0)</td>
</tr>
<tr>
<td>Genitourinary infection</td>
<td>11 (22.0)</td>
<td>27 (18.0)</td>
<td><strong>5.9 (1.8)</strong></td>
</tr>
<tr>
<td>Accidental trauma</td>
<td>9 (18.0)</td>
<td>32 (21.3)</td>
<td>2.4 (1.0)</td>
</tr>
<tr>
<td>Gastrointestinal infection</td>
<td>8 (16.0)</td>
<td>14 (9.3)</td>
<td><strong>6.0 (2.4)</strong></td>
</tr>
<tr>
<td>Other infections</td>
<td>3 (6.0)</td>
<td>13 (8.6)</td>
<td><strong>5.4 (2.5)</strong></td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>2 (4.0)</td>
<td>11 (7.4)</td>
<td>3.5 (1.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (2.0)</td>
<td>2 (1.4)</td>
<td>4.0 (0.3)</td>
</tr>
</tbody>
</table>

ADAS-COG = Alzheimer’s Disease Assessment Scale-Cognitive subscale.

C. Holmes et al 2009
pro-inflammatory mediators (cytokines, prostaglandins)
Fever and transient behaviour changes
TLR3
TLR4
Humoral transmission (blood vessels)
neuronal transmission (vagus nerve)
Fever and exaggerated behaviour changes and neuronal damage
Disease or aged brain
primed microglia
altered microenvironment
Young, healthy brain
Lack of social interaction
Increased sleep
Fever
Aids recovery
Depression
Fatigue
Cognitive decline
Delays recovery
Most studies use single, high dose of LPS to elicit systemic inflammation
Live bacterial/viral infections, or chronic low grade inflammation are less well described
S. Typhimurium 10x6 CFU

Sickness behaviour
Systemic cytokines
Central cytokines

Young

Young vs Aged

Healthy vs Diseased
S. typhimurium induces long-lasting phenotype changes to vascular endothelial cells and microglia
Phenotype and functional changes to cerebral endothelial cells

Cerebral vasculature?
Long term consequences?
MHCII is up-regulated on microglia following low dose LPS ic: systemic *S. typhimurium* induces priming
Systemic *S. typhimurium* induces impaired memory function
A single systemic infection with *S. typhimurium* results in:

- Long-lasting endothelial cell activation
- MHCII
- Altered BBB permeability
- Microglial activation/priming
- Pro-longed pro-inflammatory cytokine production
- Reduced cognitive function

Chronic, low grade inflammation?
Consequences for neurodegenerative disease onset and progression?
Systemic inflammation in a mouse model of neurodegeneration (ME7)

- ME7 (20 wks) + saline
- ME7 (20 wks) + Salmonella

**CD68**

**MHCII**

Analysis of IL-1β fold increase (RNA):
- 1 week Salmonella
- 4 weeks Salmonella
- 8 weeks Salmonella

Graph showing IL-1β fold increase over time (weeks): 12, 13, 16, 20
CNS leukocyte infiltration: CD3+ T cells

ME7 (20 wks) + Salmonella

Laminin

CD3

CD3+ T cells

no infection
Salmonella

MET 13wks
MET 16wks
MET 20wks
Characterisation of CNS CD3 T cells

- **CD8+ lymphocytes per field**
  - ME7 13wks
  - ME7 16wks

- **Granzyme B**
  - ME7 13wks
  - ME7 16wks

- **PD-1**
  - ME7 13wks
  - ME7 16wks

Legend:
- Open bars: no infection
- Filled bars: Salmonella
conclusions

Low grade systemic infections result in priming of microglia – life long exposure to systemic inflammation may play a role in the pathogenesis of age-related diseases such as AD, PD and AMD.

Possible mechanism include cerebral vessel activation, increased permeability of BBB, extravasation of plasma proteins (IgG)

Neurodegeneration induces priming and individuals respond stronger to systemic inflammation (LPS and real infections)

Increased leukocyte infiltration into diseases CNS following systemic inflammation, but role in diseases progression is unclear
Neuron-Glia interactions keep microglia in a down-regulated state.

Changes in microenvironment = changes in microglia adaptive/maladaptive.

Figure 1: Communication between the CNS and the immune system contributes to homeostasis during systemic infections, resulting in transient, reversible microglial activation, and adaptive behavioural and metabolic changes. Normal ageing and low grade systemic inflammation results in prolonged (primed) microglial activation and symptoms such as mood changes and fatigue can arise. We hypothesize that multiple or chronic systemic inflammation accelerates the normal ageing process, resulting in irreversible pathological changes in the CNS, depression and cognitive decline.
acknowledgement

Katie Lunnun
Ursula Püntener
Steven Booth
Olivia Larsson
Salome Murinello
James Fuller
Adam Hart
Patrick Garland
Roxana Carare

Rob Deacon, Nick Rawlins
Oxford University

Colm Cunningham
Trinity College, Ireland

Martin J. Glennie
Mark Cragg
Andrew Lotery
V. Hugh Perry

Clinical Neurosciences
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