Inflammatory mediators in delirium: Where the neural circuitry of sickness syndrome and dementia meet

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The Maldonado schematic is heroic, but I would argue that Delirium is not a single entity and we need to think about Different routes to (etiologies of) delirium differently.
Systemic inflammation signals to the healthy brain

And can do so across an intact BBB via multiple routes
1) Neural afferents

2) Circumventricular organs

Dantzer et al., Nature reviews Neuroscience, 2008
3) Brain endothelium

Adaptive Sickness Behaviour Response (Rodents)

1) Systemic inflammation
   - Vagus Nerve
   - COX-2, COX-1
   - Brain Endothelium

2) Noradrenergic Nuclei
   - Area Postrema
   - Macrophages
   - IL-1β

3) Brain Endothelium
   - PGE2
   - COX-2
   - COX-1

AMYGDALA
   - Anxiety and Behavioural Suppression

PVN
   - HPA Axis Activation
   - Fever Response

MPO
   - Mild Cognitive Changes
   - and Behavioural Suppression

HIPPOCAMPUS

Also Saper, 2012
Cunningham & MacLullich, BBI, 2013
Sickness behaviour neurocircuitry is very similar in humans
Sickness responses are exaggerated in animals with prior pathology

Hypothermia

IL-1β expression

Combrinck et al., Neuroscience, 2002
Microglial priming

Primed microglial show exaggerated IL-1 responses to Subsequent stimulation with either central or systemic inflammation

Cunningham et al., J. Neurosci, 2005
Perry et al., Nature Rev. Imm, 2007
Microglial Priming

Cunningham et al., J Neuroscience, 2005

Van Gool et al., Lancet, February 2010
Microglial activation

Is increased in delirium versus non-delirium (multiple etiologies)

Van Munster et al., 2011

But would like to understand the role of microglia and of inflammatory mediators in delirium

Need model systems!
Model system 1: mild LPS superimposed upon neurodegenerative disease

Here are some data from our First model of delirium during Dementia

Although LPS induces IL-6 equally in normal animals and those with prior neurodegenerative disease only those with prior degeneration show acute cognitive deficits upon LPS challenge.

This is an important prediction made by the model because this sort of weak association between IL-6 and delirium has frequently been observed in the clinical literature.

Murray et al., Neurobiology of Aging, 2012

Equivalent IL-6 responses, differential cognitive deficits
The prior point is emphasized here: Surgery always induces IL-6 and IL-8 but these are not higher in delirium patients here and are rarely very clearly different in delirium with respect to controls. Therefore I would argue that the prior condition of the brain (IE PREDISPOSITION) is the key factor in whether systemic inflammation induces delirium or not.

<table>
<thead>
<tr>
<th>Inflammatory Marker</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>P-Value*</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>0.38 (1.17)</td>
<td>.86</td>
</tr>
<tr>
<td>No delirium</td>
<td>0.51 (0.91)</td>
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</tr>
<tr>
<td>IL-1β</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>0.40 (0.55)</td>
<td>.57</td>
</tr>
<tr>
<td>No delirium</td>
<td>0.46 (0.61)</td>
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<tr>
<td>Tumor necrosis factor alpha</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>6.12 (9.28)</td>
<td>.54</td>
</tr>
<tr>
<td>No delirium</td>
<td>6.2 (9.96)</td>
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</tr>
<tr>
<td>IL-6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>7.95 (8.59)</td>
<td>.65</td>
</tr>
<tr>
<td>No delirium</td>
<td>8.27 (8.49)</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>9.16 (7.02)</td>
<td>.56</td>
</tr>
<tr>
<td>No delirium</td>
<td>8.6 (6.51)</td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
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</tr>
<tr>
<td>Delirium</td>
<td>1.81 (1.64)</td>
<td>.10</td>
</tr>
<tr>
<td>No delirium</td>
<td>2 (1.37)</td>
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<tr>
<td>Pro-/anti-inflammatory ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>12.44 (9.61)</td>
<td>.18</td>
</tr>
<tr>
<td>No delirium</td>
<td>11.14 (5.71)</td>
<td></td>
</tr>
</tbody>
</table>

Cerejeira et al., JAGS 2012
Association versus Causation

IL-6, IL-8: Biomarkers or predictors of delirium OR just measures of severity of systemic inflammation?

Molecules like IL-1 and TNF-α are more potent

Are systemic or central levels more important?

CSF levels of IL-8 associated with delirium
CSF levels of IL-1 associated with delirium
(MacLullich et al., 2011, Cape et al., in revision)

To establish causation: need model systems

(Systemic inflammation impact on vulnerable brain)
Predisposition is the key determinant

Increasing severity of the predisposing factor (underlying degenerative disease), progressively increases risk of acute cognitive dysfunction upon systemic inflammation.

Griffin et al., J. Neurosci 2013
**Microgliosis**

Increases NBH<12<16w

Disease induces COX-1 in microglia

LPS induces COX-2 at endothelium

Griffin et al., J. Neurosci 2013
COX-1, but not COX-2 inhibition protects against LPS-induced cognitive dysfunction

Griffin et al., J. Neurosci 2013
1) Systemic IL-1RA is protective
2) IL-1β is sufficient
3) Ibuprofen is protective

Griffin et al., J. Neurosci 2013
BAD SYNERGY: IL-1 and prostaglandins

Annals of Delirium, November 2013
This is a discussion/digest of Griffin et al., 2013, Journal of Neuroscience written for clinical researchers not familiar with reading mouse inflammatory and experimental psychology studies.
Model system 2: $p75^{NTR}$-saporin lesion of basal forebrain to produce a hypocholinergic state. THEN challenge with low dose LPS
Systemic LPS (100 µg/kg) induces acute working memory deficits only in animals with prior hypocholinergia

Field et al., J Neurosci 2012
1) T-maze performance is cholinergic dependent
2) Donepezil protects against LPS-induced deficits

Field et al., J Neurosci 2012

Rivastigmine was not protective in ICU delirium but unlikely that those patients had underlying cholinergic deficiency. Once again, we have to be careful about generalising across different delirium etiologies.
So, we can return to our schematic depicting sickness behaviour neurocircuitry and update it to show how many of these aspects are exaggerated during aging and neurodegenerative disease AND to emphasise that key mediators such as IL-1\(\beta\) and prostaglandins are CAUSATIVE both in sickness behaviour and in the acute cognitive deficits that I have shown you in our 2 model systems today.
Summary

• Delirium is not a single entity - need to study routes to dysfunction in multiple etiologies and not over-generalise

• Can separate PREDISPOSING (COX-1, microglia, loss of ACh tone) vs. TRIGGERING factors (acute IL-1β, TNF-α, medication changes)

• The neurocircuitry of sickness behaviour syndrome, and its exaggeration in age/dementia, make useful predictions that should be investigated

• Urgent things to do!
Future directions/urgent needs

There is an urgent need to scale up preclinical models to help elucidate delirium pathophysiology in multiple settings.

There is a need to coordinate/reconcile with the HPA axis changes

Have to refine neuroinflammatory hypotheses and test them

Examination of interaction of these systems with drugs/medications and neurotransmitter systems (ACh work begun but need to think about NE, GABA, Glutamate, DA)

Need to disentangle the impact of systemic inflammation on acute cognitive dysfunction from its effects on long-term sequelae.