Acute evolution of brain damage following stroke – influence of risk factors

Dr Chris McCabe
Chris.McCabe@glasgow.ac.uk
Ischaemic stroke – Time is brain

**Ischaemic Core:**
irreversibly damaged and cells are destined to die.

**Ischaemic Penumbra:**
tissue does not function normally but is still viable and may recover if blood flow is restored or drugs given to support survival

*from Rothwell et al.*
Acute evolution of brain damage following stroke

Permanent MCAO

McCabe et al, J Cereb Blood Flow Metab. In press
Acute evolution of brain damage following stroke – gender differences

Permanent MCAO

ADC Defined Lesion Volume (mm$^3$)

Time after MCAO (mins)

0.5 hr
1 hr
2 hr
3 hr
4 hr
24 hr

3/12 rats died

Slice

2
3
4
5
6
7

Male Sprague Dawley
Female Sprague Dawley

McCabe et al, J Cereb Blood Flow Metab. In press
Acute evolution of brain damage following stroke – influence of hypertension

Permanent MCAO

<table>
<thead>
<tr>
<th>Slice</th>
<th>1 hr</th>
<th>4 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADC Defined lesion Volume (mm$^3$)

- Male WKY
- Male SHRSP
- Male Sprague Dawley
- Female Sprague Dawley

Time after MCAO (mins)

Reid et al, J Cereb Blood Flow Metab. 2012 Sep;32(9):1765-77
Early reperfusion at 60 min can salvage brain tissue...

Transient MCAO

Reid et al, unpublished data
but not in the SHRSP?

Factors involved in worse outcome?
- Poorer collateral flow and perfusion following recanalisation
- Increased oxidative stress
- Inflammation – systemic &/or central

Transient MCAO

Stroke co-morbidities such as age, hypertension, atherosclerosis, obesity & diabetes all have a strong inflammatory component
Systemic inflammation impairs reperfusion

- Inflammation associated with increased risk of stroke and worse outcome following stroke
- Systemic inflammation induced with IL-1 resulted in hypoperfusion following reperfusion and increased infarct volume
- Hypoperfusion was due in part to an upregulation of the vasoconstrictor ET-1

Recanalisation in the presence of stroke co-morbidities (i.e hypertension, age, atherosclerosis) may result in impaired perfusion partly through effects of inflammation on the cerebrovasculature

Murray et al., Stroke. 2014 Nov;45(11):3412-9
Angiotensin(1-7) attenuated the increased expression of iNOS, IL-1a, IL-6, CXCR4 & CD11b 24hr post ET-1 MCAO.

- ↓ NF-κB
- Mas Receptor immunoreactivity present in neurons in rat cerebral cortex and striatum as well as macrophages/microglia.
Does Angiotensin-(1-7) improve outcome following reperfusion?

**MCAO: 90min**

- **Pre-MCAO**
- **Reperfusion**
- **3 days**
- **7 days**

**MRI (DWI) at 30 & 60 min post MCAO**

- Osmotic mini-pump infusion i.c.v
- T<sub>2</sub> MRI scan Brain snap frozen

18 point neurological score & Tail Cuff BP

**C. Stock**

University of Manchester
Ang-(1-7) increases tissue salvage following reperfusion

Arroja M., unpublished data
Questions?

- Temporal changes in Cerebral blood flow – laser doppler/speckle imaging
- Methods of detecting and measuring inflammatory mediators post stroke? Blood samples, brain tissue..
- BBB breakdown, Haemorrhagic transformation

Ongoing & Future studies

- Investigating the role of Ang(1-7) on the acute evolution of brain damage in the presence of stroke co-morbidities (Mariana Arroja, PhD student & Dr Emma Reid)
- Potential of inhaled NO as a therapeutic strategy to improve CBF following stroke (Joachim Biose, PhD student)
- Understanding the role of Alpha 5 Beta1 Integrin on BBB integrity and outcome following stroke (Biav Kittani, PhD student)
Acknowledgements

• Dr Emma Reid
• Ms Mariana Arroja, PhD student
• Prof Mhairi Macrae
• Mrs Lindsay Gallagher
• Dr Tracey Baskerville
• Dr Debbie Dewar
• Dr Ku Mastura Ku Mohd Noor, PhD student
• Dr William Holmes
• Mr Jim Mullin
• Dr Lorraine Work

Translational Medicine Research Collaboration

The Henry Smith Charity
founded in 1628