General Effects of Spinal Cord Stimulation on Activation of M1 And M2 Microglia

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DISCLOSURES

William J. Smith has no conflicts to disclose
Introduction

Microglia release both algesic and analgesic factors

- Isolation of microglia via flow cytometry + RNAseq allows unprecedented detail
- Research in neurodegeneration has revealed diverse spectrum of activation states
- Classic terminology refers to M1 as pro-inflammatory and M2 as neuroprotective

- Imbalance of microglial activation states


Materials and Methods

- Sprague-Dawley rats (n=10-13) per group
- Spared Nerve Injury (SNI) utilized as neuropathic pain model [4]
- Continuous SCS applied for 48 hours
- Collection of the ipsilateral dorsal quadrant of the spinal cord adjacent to lead placement
- RNA sequencing to quantify gene expression
- Previously published datasets for microglia were cross referenced to our data [5,6]
- Pearson correlations measured the treatment effect within each cell type

All procedures approved by the Institutional Animal Care and use Committee at Illinois Wesleyan University
Results

<table>
<thead>
<tr>
<th></th>
<th>Correlation of M1 Gene expression to Naïve profile</th>
<th>Correlation of M2 Gene expression to Naïve profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR SCS</td>
<td>R = 0.43 (p&lt;0.01)</td>
<td>R = 0.44 (p&lt;0.01)</td>
</tr>
<tr>
<td>HR SCS</td>
<td>R = 0.60 (p&lt;0.01)</td>
<td>R = 0.08 (p=0.47)</td>
</tr>
</tbody>
</table>

**M1 Activation Genes**

- Gene Expression After SNI
- Gene Expression after HR-SCS
- Gene Expression After LR-SCS

**M2 Activation Genes**

- Gene Expression after SNI
- Gene Expression after HR-SCS
- Gene Expression After LR-SCS

Correlation of M1 Gene expression to Naïve profile:
- LR SCS: R = 0.43 (p<0.01)
- HR SCS: R = 0.60 (p<0.01)

Correlation of M2 Gene expression to Naïve profile:
- LR SCS: R = 0.44 (p<0.01)
- HR SCS: R = 0.08 (p=0.47)

Graph shows the expression levels of M1 and M2 genes before and after SNI, HR-SCS, and LR-SCS treatments.
Results

<table>
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<tr>
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<th>Downregulated genes modulated towards Naïve</th>
<th>Upregulated genes modulated towards Naïve</th>
<th>Downregulated genes further downregulated</th>
<th>Upregulated genes further upregulated</th>
<th>Total M1 activation genes decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR SCS</td>
<td>20 Genes</td>
<td>23 Genes</td>
<td>9 Genes</td>
<td>9 Genes</td>
<td>32 Genes (52%)</td>
</tr>
<tr>
<td>HR SCS</td>
<td>22 Genes</td>
<td>27 Genes</td>
<td>7 Genes</td>
<td>5 Genes</td>
<td>34 Genes (55%)</td>
</tr>
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</thead>
<tbody>
<tr>
<td>LR SCS</td>
<td>36 Genes</td>
<td>35 Genes</td>
<td>4 Genes</td>
<td>8 Genes</td>
<td>44 Genes (53%)</td>
</tr>
<tr>
<td>HR SCS</td>
<td>32 Genes</td>
<td>34 Genes</td>
<td>8 Genes</td>
<td>9 Genes</td>
<td>41 Genes (49%)</td>
</tr>
</tbody>
</table>
Conclusions

- The M1 Microglial activation transcriptome of HR-SCS and LR-SCS positively correlated with the one for the Naïve state (R=0.60 and R=0.43 respectively)

- Only the M2 Microglial activation transcriptome of LR-SCS correlated with the one for the Naïve state (R=0.44)

- LR-SCS tend to increase the expression of >50% of M2 Microglial activation genes indicating a possible neuroprotective action of SCS

- Both HR-SCS and LR-SCS tend to decrease the expression of >50% of M1 Microglial activation genes after SNI indicating a possible anti-inflammatory action of SCS

- This work demonstrates that SCS may be used to tune microglial activation states towards favorable therapeutic effects.