Psychosocial Influences on Pain and Depression

A. Courtney DeVries, PhD

Departments of Neuroscience and Psychology
Institute of Behavioral Medicine Research
Research Goal

To determine the physiological mechanisms through which psychosocial factors alter the risk of pain and affective disorders after nerve injury.
General Methods

Adult male mice

Spared nerve injury

Ligation, followed by transection and resection, of right sural and common peroneal nerves
General Methods

Mechanical allodynia: von Frey monofilaments
Depressive-like behavior: Forced swim test
**Hypothesis:** Stress Exacerbates Allodynia and Causes Depressive-like Behavior After SNI

**Experimental Design:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Day -14</td>
<td>Stress 2h/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day -1</td>
<td>SNI/SHAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>SNI/SHAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>SNI/SHAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>SNI/SHAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>SNI/SHAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Stress Exacerbates Allodynia and Depressive-like Behavior After SNI

Norman et al., Molecular Psychiatry
Possible Physiological Mechanisms

Serum Corticosterone

Cortical IL-1β
Hypothesis: Corticosterone Mediates the Effects of Stress on SNI-Induced Neuroinflammation and Behavior

Experimental Design:

Day -14

Stress 2h/day + MET or Vehicle

Day -1

SNI

Day 0

Allodynia Testing

Day 1

Allodynia Testing

Day 3

Allodynia Testing

Day 7

Allodynia Testing & Swim Test
Role for Stress-Induced Corticosteroids

Serum Corticosterone

Cortical IL-1β

Metyrapone is a corticosteroid synthesis inhibitor that maintains basal corticosteroid concentrations during stress.
Metyrapone Ameliorates the Effects of Stress on Allodynia & Depressive-like Behavior After SNI
Hypothesis: IL-1ra Will Prevent SNI-Induced Depressive-like Behavior

Experimental Design:

- **Day -14**: Cannulation
- **Day -1**
- **Day 0**: SNI/SHAM
- **Day 1**: Allodynia Testing
- **Day 3**: Allodynia Testing
- **Day 6**: Allodynia Testing & Swim Test
- **Day 7**: IL-1ra 1.8 ug/day
IL-1ra Prevents the Expression of Depressive-like Behavior After SNI

IL-1ra: IL-1 receptor antagonist
Interim Conclusion

Nerve injury causes neuroinflammation which in turn contributes to the development of depressive-like behavior. Both allodynia and depressive-like behavior are exacerbated by prior exposure to stress.
Hypothesis: Affiliative Social Behavior Will Reduce SNI-Induced Depressive-like Behavior

Experimental Design:

Day -7
Housing

Day -1
Allodynia Testing
Pair Housed
With OVX female

Day 0
SNI/SHAM

Day 1
Allodynia Testing
Socially Isolated

Day 3
Allodynia Testing

Day 7
Allodynia Testing & Swim Test
Social Interaction Reduces Allodynia and Eliminates Depressive-like Behavior After SNI
Social Pairing After Nerve Injury Also Is Effective at Reducing SNI-Associated Allodynia
Hypothesis: Social Interaction Reduces the Effect of Stress on Allodynia After SNI

Experimental Design:

Day 7

Stress 1h/day

Day 0

SNI/SHAM

Day 3

Allodynia Testing

Day 7

Allodynia Testing & Swim Test

Day 1

Allodynia Testing

Day -1

Pair Housed

Socially Isolated
Social Interaction Improves SNI-Related Allodynia But Does Not Eliminate The Effects of Stress
Hypothesis: The Protective Effects of Social Interactions on SNI Are Due to the Suppression of IL-1

Experimental Design:

Day 7
Cannulation, and Housing

Day -1
Alloodynia Testing

Day 0
Alloodynia Testing

Day 1
Alloodynia Testing

Day 3
Alloodynia Testing

Day 7
Alloodynia Testing & Swim Test

Pair Housed  Socially Isolated
IL-1 Mediates the Effects of Social Interaction on Allodynia

• Giving IL-1 to paired mice increases allodynia

• Giving IL-1ra to socially isolated mice reduces allodynia
Summary

- SNI causes neuroinflammation which in turn promotes the development of depressive-like behavior
- Stress exacerbates neuroinflammation, allodynia and depressive-like behavior through a corticosteroid mediated pathway
- Social interaction reduces SNI-associated neuroinflammation, allodynia and depressive-like behavior.
Environmental factors that increase neuroinflammation after nerve injury exacerbate allodynia and depressive-like behavior, while environmental factors that decrease neuroinflammation after nerve injury reduce allodynia and depressive-like behavior.
Last Thought: The Same Relationships Among Neuroinflammation, Stress, Depression, and Allodynia May Exist For Other Forms of Neuropathic Pain

CA/CPR: Cardiac Arrest/CPR
Thanks

Collaborators on These Projects:
Greg Norman
Kate Kareлина
Monica Gaudier-Diaz
Adam Hinzey

Phil Popovich & Jessica Alexander

Support provided by NINR R01 to ACD