Utility of animal models for TMJD and orofacial pain

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Chronic orofacial pain is highly prevalent in the US, affecting ≈ 20% of the population.
The uniqueness of TMJD-related pain
<table>
<thead>
<tr>
<th>(Similar to)</th>
<th>DEEP PAIN</th>
<th>CUTANEOUS PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localization</td>
<td>Diffuse</td>
<td>Localized</td>
</tr>
<tr>
<td>Description</td>
<td>Cramping, Aching, Throbbing, Dull</td>
<td>Sharp, Pricking, Stabbing, Shooting</td>
</tr>
<tr>
<td>Noxious St.</td>
<td>Not necessarily tissue damaging</td>
<td>Usually tissue damaging</td>
</tr>
<tr>
<td>Referred Pain</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hyperalgesia/Allodynia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Dual afferent projections

Orofacial injury

Vi/Vc transition

Caudal Vc

Hypoth

Ad

Vagus

Cereb

Olive

PB

Submed

VPM

Po

Autonomic responses

Somatic reflex

Pain modulation

Discriminative pain
Differential gene expression in trigeminal and dorsal root ganglia

Lopes et al. 2017
Preclinical models

Injection of inflammatory/algesic agents

- Freund’s adjuvant/Carrageenan
- Capsaicin
- Formalin
- Serotonin
- NGF
- Hypertonic/acidic saline
- Mustard oil
- Inflammatory soup ...
Nerve injury (Constriction, transection, compression...) 

- Infraorbital nerve
- Mandibular nerve
- Inferior alveolar nerve
- Mental nerve
- Compression of the trigeminal nerve root
- ...

Muscle injury - Myogenic pain 

- Masseter inflammation
- Masseter muscle tendon ligation
Joint loading/TMJ osteoarthritis

- Splint placement
- Mis-placement of dental implant
- Repeated mouth opening
- Disc displacement

Comorbidity conditions

- Masseter inflammation + Stress
Assessing Orofacial Pain in Preclinical Studies
Conditioned place avoidance

Injured side versus uninjured side

Stimulation: Suprathreshold von Frey filament / 15 s

Guo et al., 2016
Facial expression

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not present</td>
<td><img src="image1" alt="Not present image" /></td>
</tr>
<tr>
<td>1</td>
<td>Moderate</td>
<td><img src="image2" alt="Moderate image" /></td>
</tr>
<tr>
<td>2</td>
<td>Severe</td>
<td><img src="image3" alt="Severe image" /></td>
</tr>
</tbody>
</table>

- Orbital tightening
- Nose bulge
- Cheek bulge
- Ear position
- Whisker change

Grooming

A) Forepaw face rubbing

B) Lower lip skin/cheek rubbing against cage surface

C) Hindpaw face scratching

Lanford et al., 2010

Romero-Reyes et al., 2013
Operant behavioral assay

Neubert et al., 2005

Cha et al., 2012
Biting/Eating Behavior
Assessment of incising ethology in the absence and presence of jaw muscle hyperalgesia in a mouse home cage environment

C.G. Widmer, J. Morris-Wiman

Top View

Side View

Water Bottle Access

Mounted Mouse Chow

X axis

Y axis

Nano1.7 multi-axis force/torque sensor

Mounted Mouse Chow
Dolognawmether

Dolan et al., 2010
Effect of masseter tendon injury

Guo et al., 2010
Characterization of BMSCs

Bone marrow

CD90$^+$ CD45$^-$
CD105$^+$ CD11b$^-$
CD73$^+$ CD34$^-$
...
...

2d post-BMSCs

TL - BMSC

TL - Veh

Guo et al. 2019
Effect of bone marrow stromal cells

Guo et al., 2019

Male

Bite force

Female

Bite force

Guo et al., 2019
Perspectives

- Relevance of animal models
- Relevance of study plan
- Incomplete understanding of mechanisms

Balanced Immune Regulation

Reduced Inhibitory Regulation
Balanced Immune Regulation

To homeostasis

Glia

Only killing weeds will be insufficient to make a healthy lawn

Reactivation

Reduced Inhibitory Regulation
Suggestions/Recommendations

- Enhance interactions/collaborations between clinical and basic scientist

- Reversed translational approach to develop models more relevant to TMJD

- Studying pain chronicity, not only acuteness

- Immune homeostasis

- Systematical analyses of big data: -Oomics (RNAs, proteins, epigenetics)
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