Meningeal afferent signaling and the pathophysiology of migraine

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Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Mean rank (95% UI)</th>
<th>% change (95% UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Low back pain</td>
<td>1.1 (1.0 to 1.2)</td>
<td>43 (34 to 53)</td>
</tr>
<tr>
<td>2 Major depressive disorder</td>
<td>1.0 (1.0 to 1.3)</td>
<td>37 (25 to 50)</td>
</tr>
<tr>
<td>3 Iron-deficiency anaemia</td>
<td>3.3 (2.7 to 4.0)</td>
<td>-1 (-3 to 2)</td>
</tr>
<tr>
<td>4 Neck pain</td>
<td>4.3 (3.7 to 4.8)</td>
<td>41 (28 to 55)</td>
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<tr>
<td>5 COPD</td>
<td>5.8 (5.3 to 6.4)</td>
<td>46 (32 to 62)</td>
</tr>
<tr>
<td>6 Other musculoskeletal disorders</td>
<td>5.8 (4.7 to 6.9)</td>
<td>45 (38 to 51)</td>
</tr>
<tr>
<td>7 Anxiety disorders</td>
<td>6.4 (4.9 to 7.9)</td>
<td>37 (25 to 50)</td>
</tr>
<tr>
<td>8 Migraine</td>
<td>8.9 (6.5 to 11.3)</td>
<td>40 (31 to 51)</td>
</tr>
<tr>
<td>9 Diabetes</td>
<td>9.1 (6.5 to 13)</td>
<td>68 (56 to 81)</td>
</tr>
<tr>
<td>10 Falls</td>
<td>10.1 (7.4 to 13)</td>
<td>46 (30 to 64)</td>
</tr>
<tr>
<td>11 Osteoarthritis</td>
<td>12.3 (9.7 to 15)</td>
<td>64 (50 to 79)</td>
</tr>
<tr>
<td>12 Drug use disorders</td>
<td>17.5 (13 to 22)</td>
<td>40 (27 to 54)</td>
</tr>
<tr>
<td>13 Hearing loss</td>
<td>13.5 (7 to 20)</td>
<td>29 (17 to 38)</td>
</tr>
<tr>
<td>14 Asthma</td>
<td>15.3 (10 to 20)</td>
<td>28 (21 to 34)</td>
</tr>
<tr>
<td>15 Alcohol use disorders</td>
<td>15.8 (12 to 21)</td>
<td>32 (15 to 50)</td>
</tr>
<tr>
<td>16 Schizophrenia</td>
<td>16.0 (9 to 22)</td>
<td>48 (37 to 60)</td>
</tr>
<tr>
<td>17 Road injury</td>
<td>16.1 (12 to 20)</td>
<td>30 (13 to 49)</td>
</tr>
<tr>
<td>18 Bipolar disorder</td>
<td>16.6 (9 to 23)</td>
<td>41 (31 to 51)</td>
</tr>
<tr>
<td>19 Dysthymia</td>
<td>18.6 (13 to 26)</td>
<td>41 (34 to 48)</td>
</tr>
<tr>
<td>20 Epilepsy</td>
<td>21.8 (18 to 27)</td>
<td>36 (27 to 47)</td>
</tr>
<tr>
<td>21 Ichaemic heart disease</td>
<td>21.8 (17 to 29)</td>
<td>48 (37 to 57)</td>
</tr>
<tr>
<td>22 Encephalopathy</td>
<td>22.5 (15 to 35)</td>
<td>79 (19 to 39)</td>
</tr>
<tr>
<td>23 Diarrhoea</td>
<td>23.1 (16 to 30)</td>
<td>5 (1 to 11)</td>
</tr>
<tr>
<td>24 Alzheimer’s disease</td>
<td>25.9 (21 to 33)</td>
<td>90 (110 to 88)</td>
</tr>
<tr>
<td>25 BPH</td>
<td>26.3 (20 to 35)</td>
<td>84 (48 to 120)</td>
</tr>
<tr>
<td>26 Tuberculosis</td>
<td>27.0 (20 to 35)</td>
<td></td>
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</tbody>
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Migraine is 2-3 times more common in females

Ferrari et al 2015
Characteristics of Migraine

Before an attack
- Yawning
- Fatigue
- Food cravings
- Drowsiness or depression
- Irritability or tension
- Occurs 24-48 h before attack

During an attack
- Nausea, vomiting
- Sweating or cold hands
- Sensitivity to light and sound
- Scalp tenderness or extracephalic allodynia
- Throbbing, unilateral pain
- Can last from 4-72 h

After an attack
- “Hungover”
- Weakness
- Tiredness
- Mood changes
- Can last for hours to days after attack is over
What is the source of migraine pain?

- The simplest explanation for the head-specific pain of migraine is that trigeminovascular-mediated afferent input is necessary.

- It has been known for over 70 years that the meninges are sensitive to chemical and mechanical stimuli.

- What are the mechanisms by which meningeal afferents respond to these stimuli and what happens in the meninges to initiate nociception?
Modeling Headache in a Rodent

Day 0:
- Surgery
- Recovery

Day 7:
- Dura Injection
  - Allodynia Testing

1h, 5h

Diagram:
- Dummy Cannula
- Cannula
- Skull
- Dura
- Brain
Interleukin 6 (IL-6)

- Released from numerous cell types
- Contributes to a variety of inflammatory pain conditions

- IL-6 can be produced from a variety of cells (dural mast cells, meningeal macrophages, dural fibroblasts)

- **IL-6 levels are elevated in migraine patients** (Fidan et al 2006; Sarchielli et al 2006; Kocer et al 2009; Uzar et al 2011).

- **IL-6 mRNA elevated in the cranial periosteum of chronic migraine patients** (Perry et al 2016).
Prior exposure to IL-6 sensitizes dural afferents to moderate pH changes.
Dural IL-6 sensitizes both males and females

Facial Withdrawal Threshold (g)

Time (h)

IL-6 .1 ng Female
Vehicle Female
IL-6 .1 ng Male
Vehicle Male

pH 7.0
Hindpaw IL-6 does not sensitize hindpaws to pH 7.0
IL-6 primes dural afferents to subthreshold stimuli

How and where does sensitization occur?
Central Projections of Trigeminal Neurons
Peripheral levels of BDNF and NGF in primary headaches

F Blandini1, L Rinaldi3, C Tassorelli2, G Sances2, M Motta3, A Samuele1, R Fancellu1,4, G Nappi2,5 & A Leon3

1Laboratory of Functional Neurochemistry and 2Headache Centre, Neurological Institute 'C. Mondino', Pavia, 3Research & Innovation (R&I) Company, Padova, 4University of Insubria, Varese, and 5Department of Neurology and Otorhinolaryngology, University of Rome 'La Sapienza', Rome, Italy

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Cephalalgia

RAPID COMMUNICATION

Increased serum levels of brain-derived neurotropic factor during migraine attacks: a pilot study

Marco Túlio A. Tanure · Rodrigo S. Gomez · Rubens Carlos L. Hurtado · Antônio L. Teixeira · Renan Barros Domingues

DOI 10.1007/s10194-012-0454-5

ORIGINAL

Brain-derived neurotrophic factor in primary headaches

Marlene Fischer · Georg Wille · Stephanie Klien · Hind Shanib · Dagny Holle · Charly Gaul · Gregor Broessner
Does BDNF contribute to priming?

ANA-12 (BDNF receptor antagonist) 24 hours after IL-6 Systemic injection
Does brainstem BDNF contribute to priming?

TrkB/FC (BDNF sequestering agent) 24 hours after IL-6
TrkB/FC given into the cisterna magna

![Graph showing the effect of TrkB/FC on facial withdrawal threshold over time.
IL-6/Vehicle group compared to IL-6/TrkBfc group.](image-url)
Does brainstem BDNF contribute to priming?

TrkB/FC (BDNF sequestering agent) 24 hours after IL-6
TrkB/FC given into the cisterna magna

Male

Female

Facial Withdrawal Threshold (g)

Time (h)

72 hr BL  3 hr  24 hr  48 hr

- IL-6/Vehicle/pH 7.0
- IL-6/TrkBfc/pH 7.0

Facial Withdrawal Threshold (g)

Time (h)

72 hr BL  3 hr  24 hr  48 hr

- IL-6/Vehicle/pH 7.0
- IL-6/TrkBfc/pH 7.0
Does intracisternal BDNF prime to moderate pH?

1 pg BDNF administered directly into the cisterna magna. pH 7.0 applied to the dura at 72 hours.

BDNF given into the cisterna magna mimics IL-6 on the dura.
1 pg BDNF administered directly into the cisterna magna. Sodium nitroprusside (SNP, 3 mg/kg) given IP at day 16.

BDNF given into the cisterna magna primes to migraine triggers.
Dural IL-6 sensitizes to systemic NO donors

SNP—sodium nitroprusside, 3 mg/kg
Does intracisternal BDNF prime to systemic NO donors?

1 pg BDNF administered directly into the cisterna magna.
Sodium nitroprusside (SNP, 3 mg/kg) given IP at 72 hours.

BDNF given into the cisterna magna primes to migraine triggers
Summary: The dural afferent system is pH/IL-6 sensitive and primed by input from the meninges and BDNF in the brainstem.

Future Questions:
• What is the mechanism of sensitization?
• What is the origin of BDNF?
• Where is sensitization occurring and how long does it last?
• Do other molecules (e.g. CGRP) contribute to priming?
• Can priming be produced by other stimuli than dural IL-6 or IC BDNF?
• Are there unique BDNF-dependent plasticity mechanisms in pain circuits?
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