Tension-type headache
Pathophysiology

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Pathophysiology of Tension-Type Headache

- Peripheral mechanisms
  - Muscular factors
- Central mechanisms
  - Altered central nociception

Episodic Tension-Type Headache
Referred pain from myofascial tissues

Travell and Simons, The Trigger Point Manual 1983

Muscle activity

Jensen et al., Electroenceph. clin. Neurophysiol. 1994
Stress-induced pain and muscle activity in patients with migraine and tension-type headache

Leistad et al., Cephalalgia 2006

Local tenderness scores

- Chronic tension-type headache
- Healthy controls

Bendtsen et al., Arch Neurol 1996
Tenderness induced by static exercise

Patients with frequent ETTH developed significantly more shoulder and neck tenderness in response to static exercise than healthy controls (P=0.04).

Christensen et al., Cephalalgia 2005

Pain induced by infusion of endogenous substances

Patients with frequent ETTH experienced significantly more pain in response to infusion of endogenous substances in trapezius muscle than healthy controls (P≤0.05).

Mork et al., Cephalalgia 2004
Microdialysis
Muscle blood flow during exercise

\[ P = 0.03 \]

- CTTH patients
- Controls

Ashina et al., Brain 2002

Microdialysis
No in vivo signs of muscle ischemia or inflammation

\[ P = 0.38 \]

- CTTH patients
- Controls

Ashina et al., Brain 2002, Cephalalgia 2003
Peripheral factors

• Summary
  – Tenderness and hardness is increased
  – Degree of tenderness is significantly related to headache frequency, intensity and treatment outcome
  – Increased tenderness in response to static exercise
  – Experimental tenderness precedes headache
  – Decreased blood flow during exercise

• Conclusion
  – Muscular factors are probably of primary importance

Suprathreshold pain sensitivity in chronic TTH

Patients have considerably increased pain sensitivity both in skin and muscle and both in cephalic and extracephalic regions (P<0.05).

Ashina et al., Cephalalgia 2006
Central factors in chronic TTH

- The hyperalgesia is generalized (found in all tissues examined) and of comparable degree in all examined locations
- Increased central pain sensitivity in chronic, but not in infrequent episodic, TTH
- Decreased antinociceptive activity in chronic TTH

(Sandrini et al. 2006)

Mirtazapine in chronic tension-type headache

Improvement in AUC

Bendtson and Jensen, Neurology 2004
Tenderness in responders and non-responders to amitriptyline

Bendtsen and Jensen, Cephalalgia 2000

Stimulus-response function, trapezius muscle

Bendtsen et al., Pain 1996
Chronic tension-type headache

Continuous painful input from pericranial myofascial tissues

induce and maintain

central sensitization such that normally innocuous stimuli become painful

Conversion from episodic to chronic tension-type headache

Bendtsen, Cephalalgia 2000

Central sensitization in chronic TTH

- How to test this hypothesis?
Nitric oxide and nociception

Ashina 1999

Increased platelet NOS in CTTH (Sarchielli 2002)

Ashina et al., Brain 2000

Nitric oxide induced headache in CTTH

- Nitrogllycerin
- Placebo

Sensitization of sensory afferents or dilatation
Sensitization of trigeminal nucleus or spinal dorsal horn

Ashina et al., Brain 2000
Treatment with a NOS inhibitor in CTTH
Headache intensity over time

0 15 30 60 90 120 minutes

VAS (%)

L-NMMA
Placebo

Ashina et al., Lancet 1999

Voxel-based morphometry in chronic tension-type headache

MOH vs. controls: no change
Migraine vs controls: no change
MOH vs. migraine: no change

Chronic TTH vs. controls:
Decrease in grey matter in the ant. & post. cingulate cortex, insulae, brainstem, precuneus and parahippocampus

Decrease in grey matter positively correlated to headache duration in years

Most likely a consequence of central sensitization

Schmidt-Wilcke et al., Neurology 2005
Cathcart et al., Cephalalgia 2010

CTTH at baseline P200 5th train

Controls at baseline P200 5th train

Buchgreitz et al., Brain, 2008
Abnormal pain processing in chronic tension-type headache: a high-density EEG brain mapping study

Conclusions

- Lack of reduction in brain activity during tonic muscle pain in patients with chronic TTH may be explained by impaired inhibition of the nociceptive input
- Supraspinal response to muscle pain is abnormal in chronic TTH

Buchgreitz et al., Brain, 2008
Change in Pressure Pain Threshold from 1989 to 2001

- Developed CTTH (N=9)
- Developed FETTH (N=20)
- Developed Coexist H. (N=7)
- Developed Migr. (N=9)
- No headache (N=62)

Buchgreitz et al., Pain 2008

Tenderness and pain sensitivity in relation to development of TTH

- Subjects who developed episodic TTH had increased tenderness but normal pain sensitivity at follow-up
- Subjects who developed chronic TTH had normal pain sensitivity at baseline but developed increased central pain sensitivity at follow-up
- Conclusions
  - Increased central pain sensitivity is not a risk factor but a consequence of frequent headache
  - Central sensitization plays an important role for the chronification of TTH

Buchgreitz et al., Pain 2008
Central factors in chronic TTH
Summary

- The central nervous system is sensitized in chronic, but not in episodic, tension-type headache
- Central sensitization may be induced by prolonged painful input from pericranial myofascial tissues
- Descending pain inhibition may be deficient

**ABERRANT PAIN PROCESSING**

- **Supraspinal structures**
  - Sensory cortex and thalamus
  - Supplementary motor area
  - Limbic system
  - PAG
  - RVM
  - Motor cortex

- **Brain stem/spinal cord**
  - Increased pain transmission
  - Inhibition
  - Facilitation

- **Pericranial myofascial tissues**
  - Sensitized nociceptive second order neurons: V, C2 and C3
  - Motor neurons
  - Stimulation
  - A-delta and C
  - Sensory afferents
  - A-beta
  - Muscle fibres

*Bendtsen, Cephalalgia 2000*
Chronic tension-type headache
Peripheral and central mechanisms

Deficient descending inhibition

Increased activity
Pain transmission
Central sensitization

Release of inflammatory peptides

Conversion of episodic to chronic headache

Jensen et al., 1998
Future perspectives

- Identify source of peripheral nociception to prevent development of central sensitization and thereby conversion of episodic to chronic TTH
- Reduce established central sensitization
- Animal model (Ellrich et al. 2005, 2006)
- Muscular factors
  - Abnormal activation or release of chemical mediators
- Central factors
  - Neuroimaging
  - Reduction of central sensitization, e.g., by nitric oxide inhibitors or NMDA-antagonists