Understanding trigeminal pain pathways: lessons from teeth

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“We do not observe the same violent effect from any other nerve in the body being exposed either by wound or sore, as we do from the exposure of the nerve of a tooth. Perhaps the reason for the intenseness, as well as the quickness of the sense of heat and cold in the teeth, may be owing to their communicating these to the nerve sooner than any other part of the body.”

John Hunter (1770)
Natural History of the Teeth
Aims & Objectives

To review the anatomical and physiological basis of trigeminal pain sensation.

Specifically:

- The properties of nociceptors
- The brainstem trigeminal nuclei and CNS pathways
- Cortical regions involved in pain perception
- Basic science insights into the mechanisms of chronic orofacial pain.
Orofacial pain is common, affecting up to 7% of UK patients (Aggarwal et al. 2006), and about 10% report multiple pains (chronic widespread pain, IBS, chronic fatigue).

Diagnosis and management falls between medical and dental practitioners, and can involve pain specialists, neurologists and dental specialists in secondary care – multi-expert input is needed to avoid patients being labelled as “difficult” or “mad”.

Care for orofacial pain patients is only perceived as successful by 24% of them (Beecroft et al. 2013), requiring on average attendance at 7 healthcare settings, seeing 3 different specialists.
Orofacial Pain: the diagnostic problem

There are numerous causes, with dental pain being the most prevalent, but this type of pain is not usually chronic. The history and examination should enable you to at least narrow down the range of diagnostic possibilities, which will facilitate appropriate further investigations.

- Teeth & periodontal ligament
- TMJ
- Headaches
- Salivary
- Cervical degeneration
- Sinuses, ENT
- Neuralgia (V, IX, BMS)
- Atypical
- CNS pathology (MS, tumours)
Somatosensory innervation

The mouth and face are innervated by the 5th cranial nerve (trigeminal), which emerges from the anterior surface of the pons to traverse the pre-pontine cistern and pass into Meckel’s cave, where its cell bodies are located. It has 3 divisions (opthalmic, maxillary, mandibular) that have distinct innervation territories.

Nociceptors are nerve fibres that respond specifically to noxious stimuli, such as intense pressure or temperature. The tooth-pulp and cornea seem to innervated solely by nociceptors, as pain is the only sensation that can be elicited from these tissues.
Facial nociceptors

Similar to nociceptors elsewhere in the body, several functional sub-groups are recognized, based on conduction velocity and receptor characteristics:

- **C-Polymodal**: unmyelinated axons (< 2.5 m/s), respond to several stimulus modalities (heat, pressure, algogens).

- **High threshold mechanoreceptors**: typically lightly myelinated (5 – 25 m/s) that respond only to strong mechanical stimuli.

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Hu & Sessle, 1988

Beitel & Dubner, 1976
Corneal receptors

The predominant, and possible sole, sensation that can be evoked by stimulation of the cornea is one of pain. There is some evidence that cold stimuli can be differentiated from mechanical/heat stimuli on the basis of the quality of the sensation, but this is always described in terms of pain rather than temperature.

Animal studies have identified several groups of corneal nociceptors:

- Mechanosensory units
- Polymodal units
- Cold units

Some corneal C-fibres are sensitive to hypoxia and metabolites of ischaemia and may function as ‘metaboreceptors’.

McIver & Tanelian, 1991
Belmonte et al. 1991
Gallar et al. 1993
Using teeth as a model system

Pain is the only sensation that can be perceived from dentine, even outer dentine (up to 3mm from pulp).

There is little direct evidence to account for this sensitivity.

Generally, pains evoked by different stimuli (hot, cold, mechanical, osmotic pressure) cannot be differentiated from one another.
Sensory transduction in teeth

Some of the nociceptors that supply the tooth-pulp are activated by a unique transduction system that involves the dentinal tubules acting as hydraulic linkages (Gysi, Branstromm).

All pain-producing stimuli can cause fluid movement through human dentine \textit{in vitro}.

In experimental animals it is possible to record a small outward flow of fluid from exposed dentine under physiological conditions (10-20 pl/s/mm$^2$).
Hydrostatic pressure and dental nerve firing

Pulpal nerve discharge increased as fluid flow velocity through dentine increased, although this is only true for outward flow evoked by negative pressures.

In general, pulpal nerve fibres were insensitive to inward flow evoked by positive pressures, except at the most intense pressures applied (±500 mmHg).
Multi-modal tooth pulp afferents

- Hydrostatic pressure
- Hot & cold
- Probing
- Air jet
Nerve activity & fluid flow

- Cold (5°C)
- Air jet
- Osmotic (4M dextrose)
- Probing
- Hot (55°C)
Sensory transduction in teeth

Pulpal nerve discharge evoked by hydrostatic pressure stimuli increased as the magnitude of the fluid flow through dentine increased.

Experiments using a range of different stimulus modalities suggested that, for some nerve fibres, a common transduction mechanisms involving fluid flow through dentine was involved. Pulpal sensory nerve fibres are more responsive to fluid flow out of the pulp, rather than flow into the pulp.

This process might involve the Piezo2 mechanically-sensitive ion channel that is highly expressed in corneal afferents.

Brom et al. 2014
Central targets: brainstem

The trigeminal nerve enters the brainstem at the level of the pons and splits into 2 bundles. One branch terminates in the main sensory nucleus and the second, thicker branch turns caudally to run the length of the brainstem. This is the descending (or spinal) tract of the trigeminal nerve.

Beneath the spinal tract of the trigeminal nerve is the spinal trigeminal nucleus. This nucleus is divided into 3 subnuclei: caudalis, interpolaris & oralis.

Many nociceptors terminate in subnucleus caudalis, which is laminated like the spinal cord.
Central terminals of tooth-pulp afferents

Tooth-pulp nerve fibres terminate principally in subnucleus caudalis, but project to all regions of the brainstem trigeminal nucleus.

This gives rise to 4 separate topographic maps within the brainstem that represent the whole orofacial region.

Brainstem terminations

Mediolateral Pattern
-2.7 mm

Rostrocaudal Pattern
0-1 mm
2.6-3.5 mm
4.6-5.5 mm

‘Onion skin’ segmentation

Superior
Lateral
Medial
Inferior

Caudal
Brainstem neurons activated by nociceptors

Animal studies have shown that brainstem neurons that receive tooth-pulp input are concentrated at the rostral end of subnucleus caudalis and dorsomedially in subnucleus oralis. Neurons in caudalis respond tend to only to noxious stimuli, whereas those in oralis integrate lots of nociceptive and non-nociceptive inputs. Neurons with input from the cornea are concentrated at the caudalis/interpolaris junction (Pozo & Cervero, 1993).

Boissonade & Oakden, 1996
Hu et al. 1981
Campbell et al. 1985
Are all sub-nuclei equal?

Tooth-pulp fibres project to all regions of the trigeminal nucleus, but are all subnuclei equally important?

Comparative data from the star-nosed mole suggests that different trigeminal brainstem maps can exaggerate different parts of the face.

Sawyer et al. 2014
Brainstem projections

Projections out of the brainstem trigeminal nuclei tend to be arranged into 2 distinct groups:

- A contralateral thalamo-cortical pathway (sensory-discriminative)
- An ipsilateral ponto-amygdaloid pathway (affective-cognitive)

Barnett et al. 1995
Cortical regions that process dental pain

Studied in humans using functional imaging (fMRI) during electrical tooth-pulp stimulation. Activations were observed in both SI and SII somatosensory cortices as well as the anterior insula (thought to represent body awareness/interception) and anterior cingulate cortex. All 4 of these cortical regions are activated during a variety of noxious stimuli, with the cingulate being an integrator of attention, motivation and emotion.

Weigalt et al. 2010
Neuroanatomy summary

Sensory afferents from the orofacial region terminate in the brainstem trigeminal nuclear complex, with individual topographic maps present in each of the 4 trigeminal subnuclei.

Brainstem neurons that process tooth-pulp (noxious) input are concentrated in subnucleus caudalis and oralis.

From the brainstem, ascending pain-related information is either relayed laterally, via a trigemino-thalamo-cortical pathway or medially via a trigemino-ponto-amygdaloid route.

The lateral pathway conveys sensory-discriminative information (location, quality, intensity) whereas the medial pathway is affective-cognitive (unpleasantness, ‘emotional feelings’).
Neurobiology of chronic orofacial pain

TMJ pain: intra-capsular injection of Freund’s adjuvant (Thut et al. 2007); single molar tooth crown that caused occlusal interference (Cao et al. 2009).

Obstructive parotitis: Freund’s adjuvant injected along the parotid duct and papilla sealed (Ogawa et al. 2003).

Neuropathic pain: Ligation/section of various branches of the trigeminal nerve.

Migraine: application of inflammatory mediators to dura (Strassman et al. 1996; Mello-Carillo & Lopez-Avilla, 2013)

Whiplash/cervical degeneration: facet joint distraction (Lee et al. 2004).

Photokeratitis: ocular exposure to UV (Tashiro et al. 2010).
Insights into mechanisms I

In peripheral nerve fibres:

- Persistent spontaneous activity from damaged lingual nerve fibres (Yates et al. 2000)
- Accumulation of sodium channel Nav1.8 in painful human lingual nerve neuromas (Bird et al. 2013)
- Activation of dural nerve fibres by mast cell degranulation (Levy et al. 2007)
In the trigeminal ganglion:

Glial cell activation from inflammation in one tooth affects sensory processing from adjacent teeth (Matsuura et al. 2013)

In the CNS:

Laminar-specific oestrogen-dependence of TMJ-responsive neurons to graded stimulation with chemical algogens (Tashiro et al. 2007)
Basic Science Summary

Noxious orofacial stimuli are detected by specialised nociceptors. Unique sensory transduction mechanisms exist in tooth-pulp and cornea. Multiple sensory maps of the trigeminal innervation territory are found in the brainstem nuclear complex that may be functionally-specified to represent different aspects of orofacial sensation.

Ascending pathways activate a lateral ‘sensory-discriminative’ thalamo-cortical circuit and a medial ‘affective-cognitive’ system, similar to spinal systems. Some models of chronic orofacial pain have been developed which have helped understand mechanisms, but as yet have not provided any translational benefits.