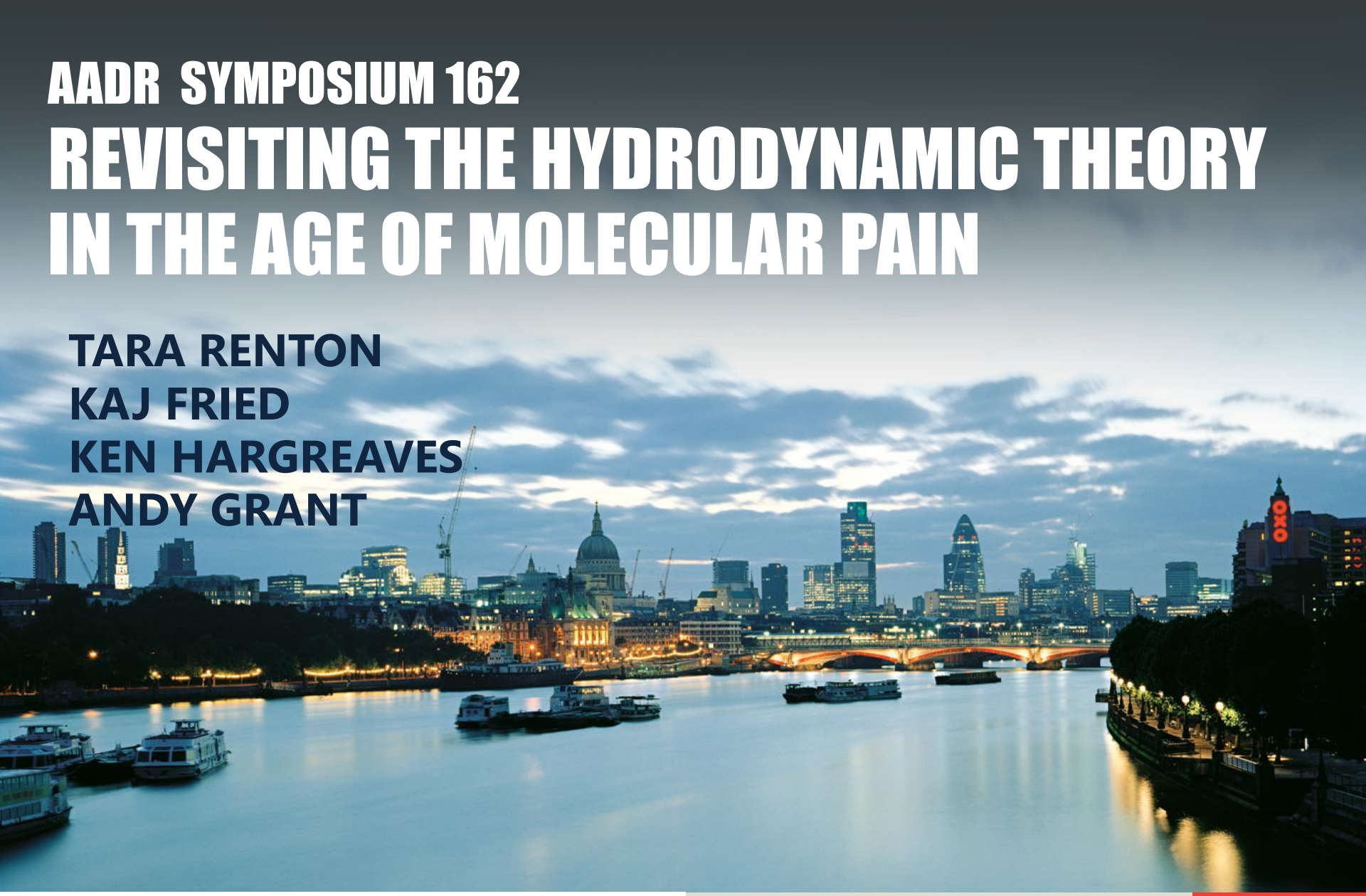
University of London

AADR SYMPOSIUM 162

REVISITING THE HYDRODYNAMIC THEORY IN THE AGE OF MOLECULAR PAIN

TARA RENTON
KAJ FRIED
KEN HARGREAVES
ANDY GRANT



American Association Dental Research
Saturday March 22nd 2014

KING'S College LONDON

AADR Symposium 162

Revisiting the Hydrodynamic Theory in the Age of Molecular Pain

Organizers/Chairs: *T. RENTON and A. GRANT*

8 a.m.**1316** Introduction and Summary of Experimental Evidence for the Hydrodynamic Theory
***T. RENTON**, King's College London Dental Institute, London, UK*

8:20 a.m.**1316** Algoneurons: Aβ Low-Threshold Mechanosensors as Pain Neurons in the Tooth
***K. FRIED**, Karolinska Institute, Stockholm, Sweden*

8:40 a.m.**1316** TRPV1 Expression and Function in Dental Afferents
***K. HARGREAVES**, University of Texas - San Antonio / Health Science Ctr, San Antonio, TX*

9 a.m. **1316** Functional Expression of TRP Channels in Human Odontoblasts ***A. GRANT**, King's College London, London, England*

9:20 a.m. Discussion

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Learning Objectives:

- Understand how recent advances in dental neurophysiology at the cellular and molecular levels relate to dental pain
- Understand the experimental evidence questioning the Hydrodynamic Theory of dental pain

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Introduction and Summary of Experimental Evidence for the Hydrodynamic Theory

Tara Renton
Professor Oral Surgery
Kings College London

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Love conquers all things except poverty and toothache.

Mae West

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IASP definition of pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

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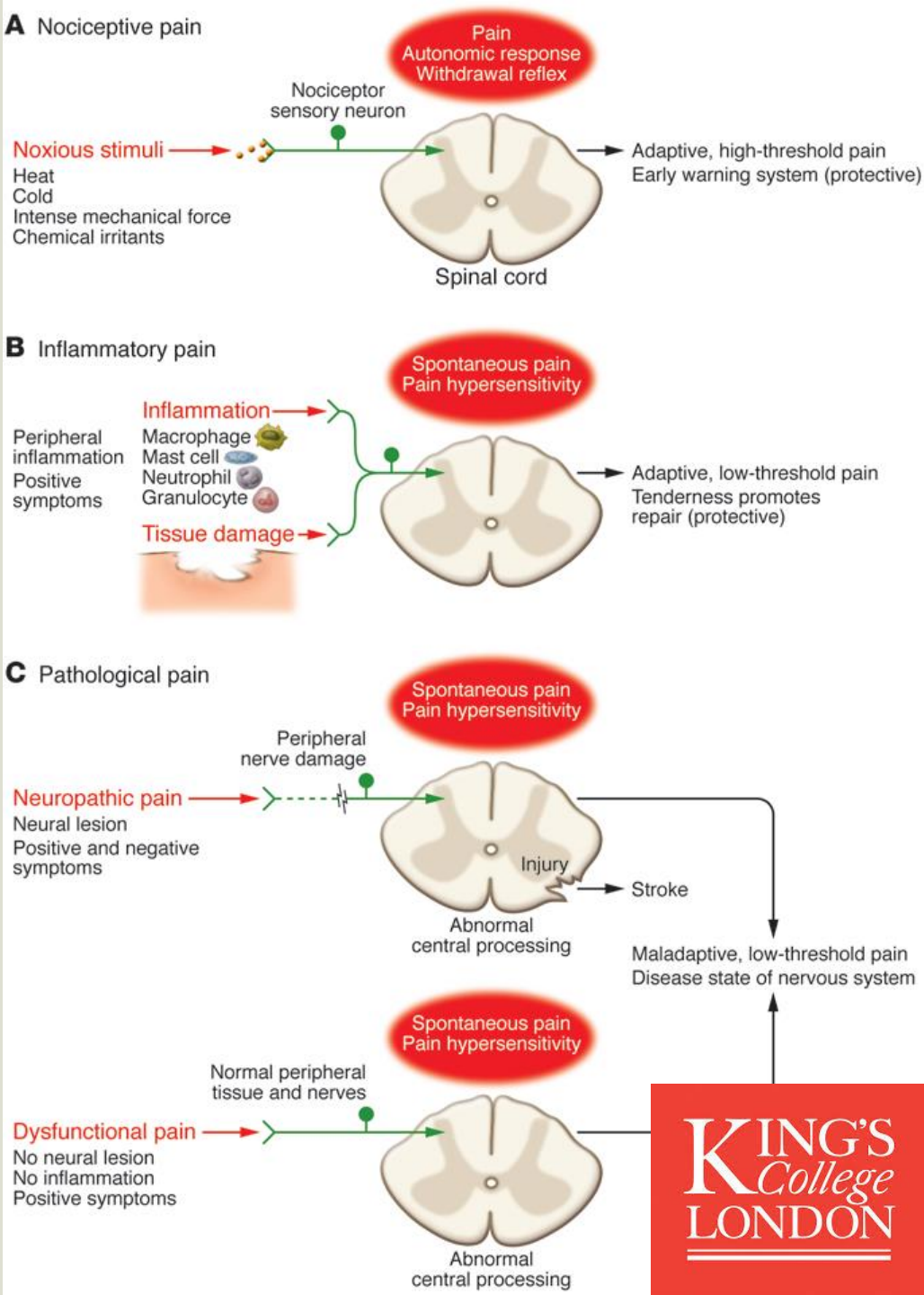
4 types of pain

Nociceptive healthy feeling pain 'pain'

Inflammatory pain health short lived after insult

Neuropathic pains

Dysfunctional pain



Clifford J. Woolf. **What is this thing called pain?** J Clin Invest. Nov 1, 2010; 120(11): 3742–3744.

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Healthy nociceptive pain

Dentine sensitivity

Healthy inflammatory pain/infection/t Trauma

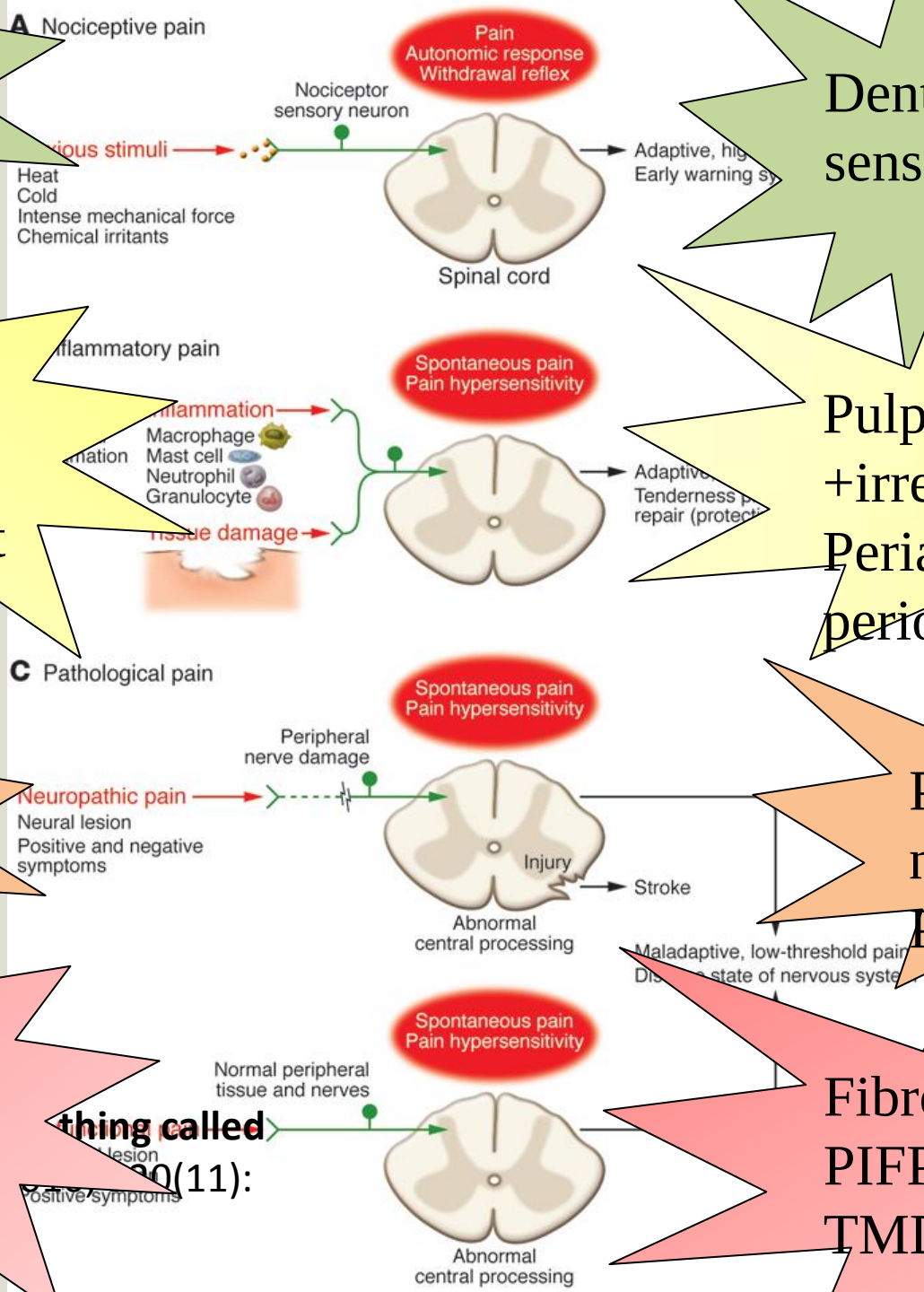
Pulpitis reversible +irreversible Periapical periodontitis

Chronic neuropathi c pain

Posttraumatic neuropathy PDAP/ PHN

Dysfunctional pain

Fibromyalgia PIFP TMD arthromyalg

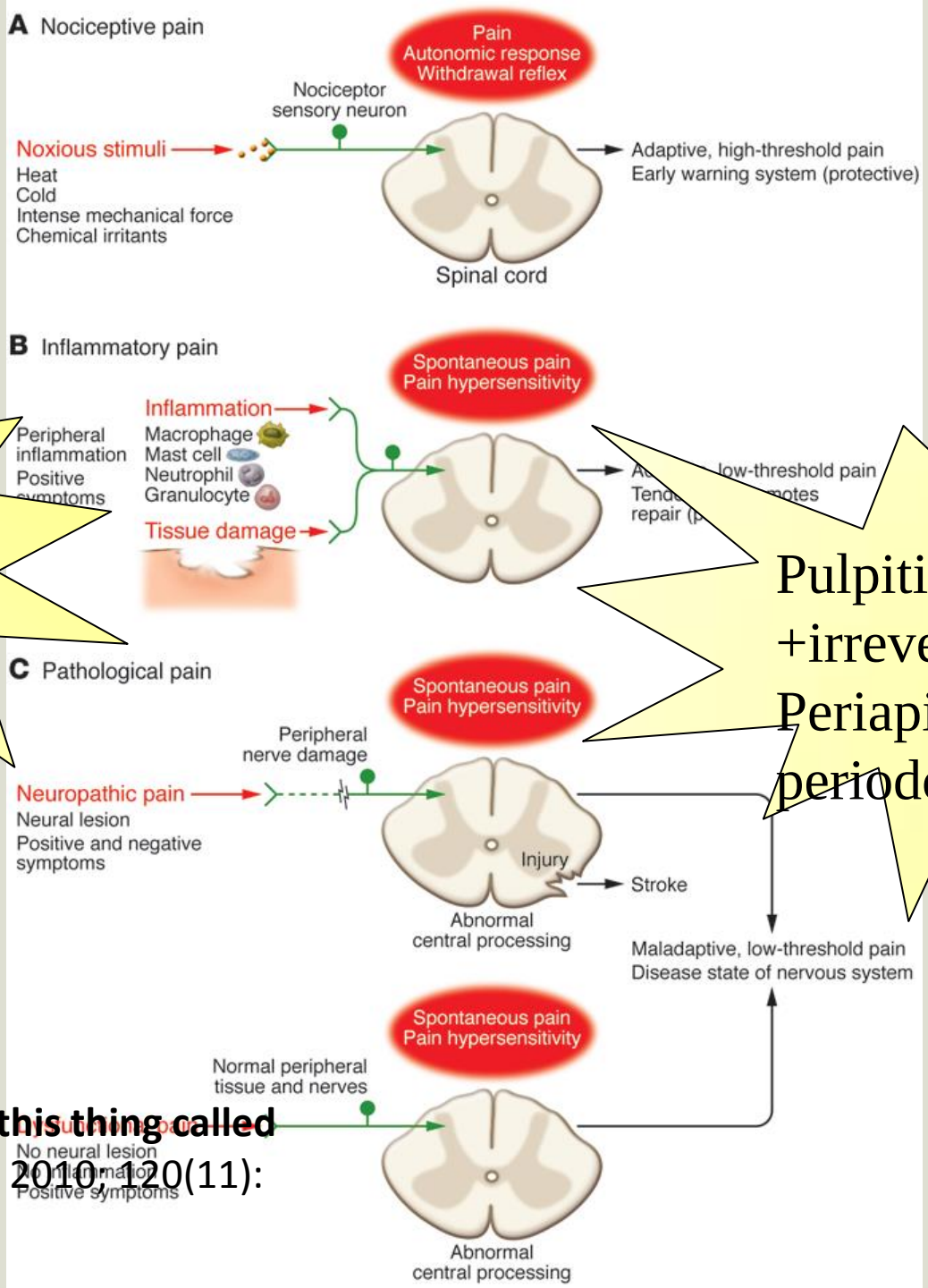


thing called

(11):

3742–

Healthy inflammatory pain/infection/t Trauma



Pulpitis reversible +irreversible Periapical periodontitis

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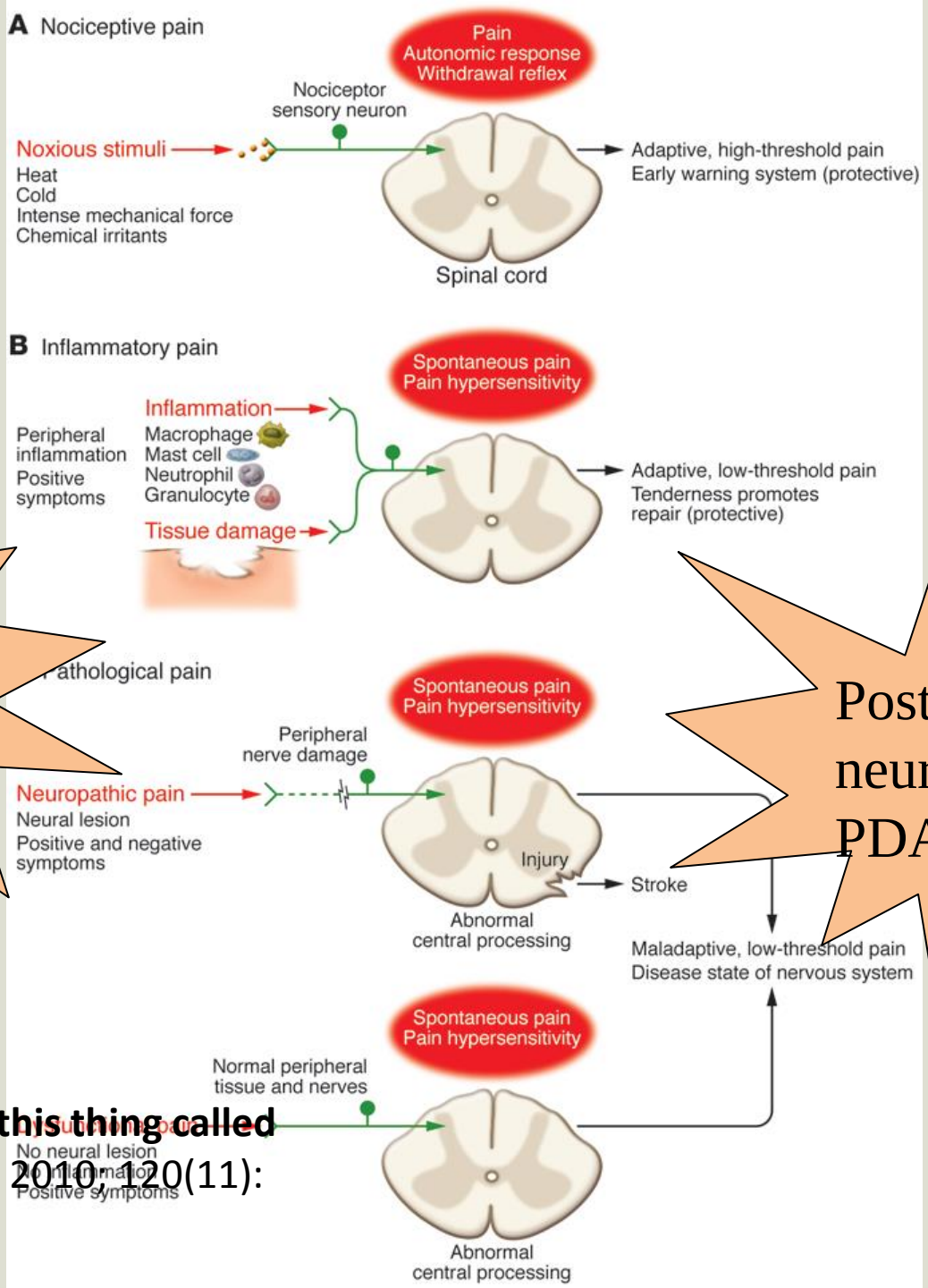

Chronic neuropathic pain

Post traumatic neuropathy PDAP/ PHN

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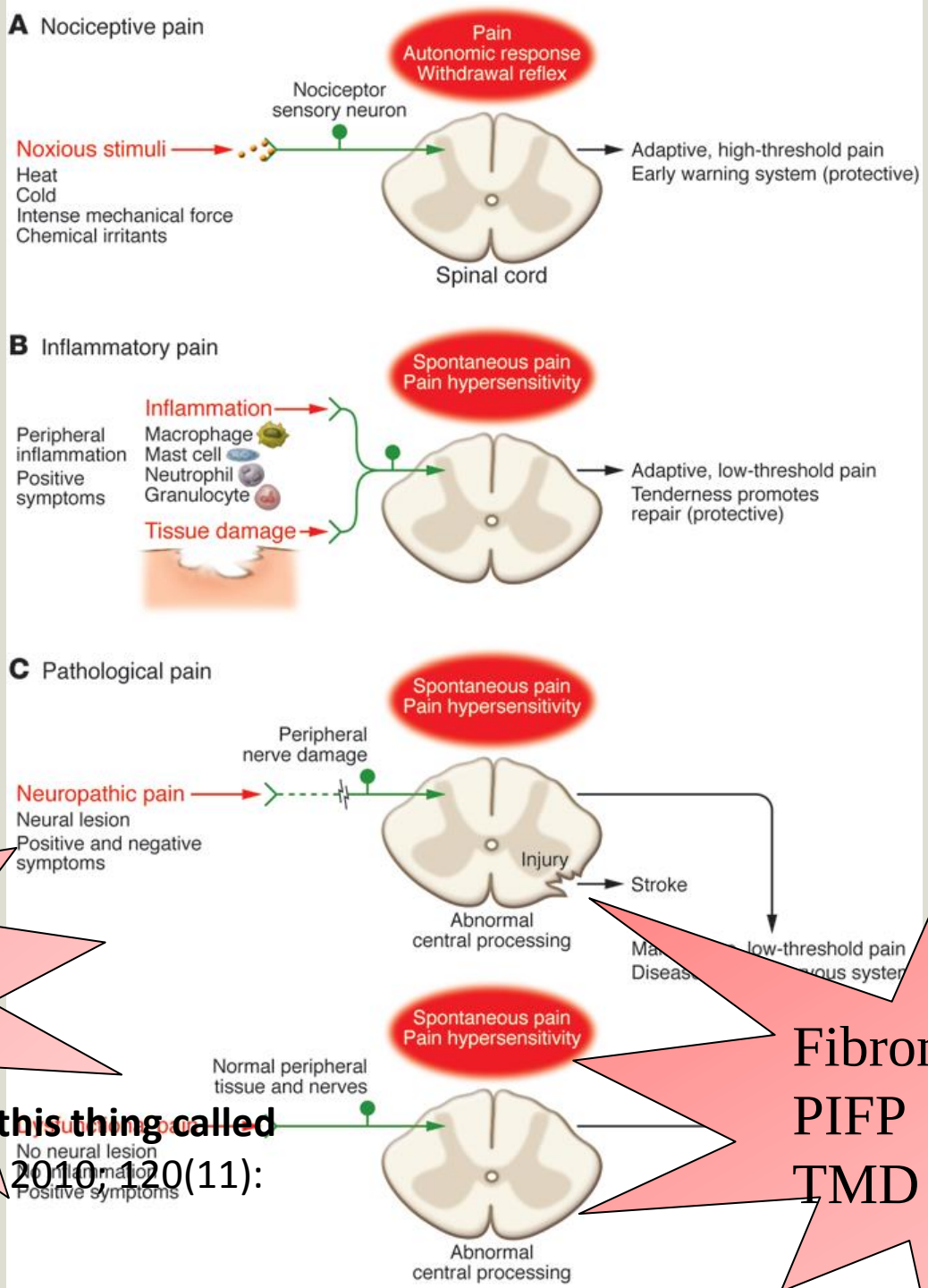


Dysfunctional pain

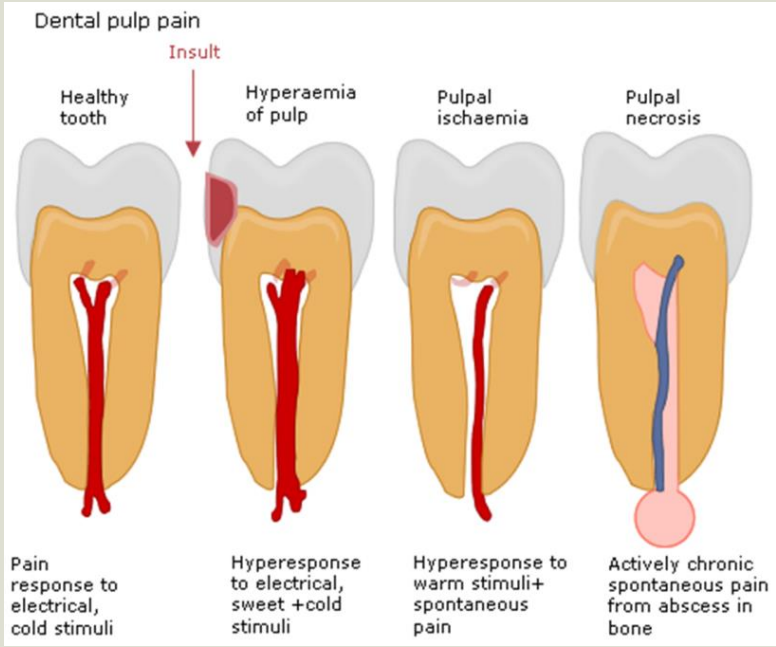
Fibromyalgia
PIFP
TMD arthromyalgia

Clifford J. Woolf. **What is this thing called pain?** J Clin Invest. Nov 1, 2010; 120(11): 3742–3744.

Dental Pain

Odontogenic

- **Healthy**
  - Dentine sensitivity
- **Inflammatory pain**
  - Dental impaction pain model post extraction/ surgical pain
  - Peri dental mucosal inflammation
    - Pericoronitis
  - Toothache –
    - Dental pulpitis
    - Irreversible pulpitis
    - Periapical periodontitis
- **Chronic dental pain-**
  - **Neuropathic dental pain**



Stephen A. Cooper, Models for clinical assessment of oral analgesics **The American Journal of Medicine**. Volume 75, Issue 5, Part 1 , Pages 24-29, 14 November 1983

Dental Pain

Odontogenic

- **Healthy**
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Nociceptive pain

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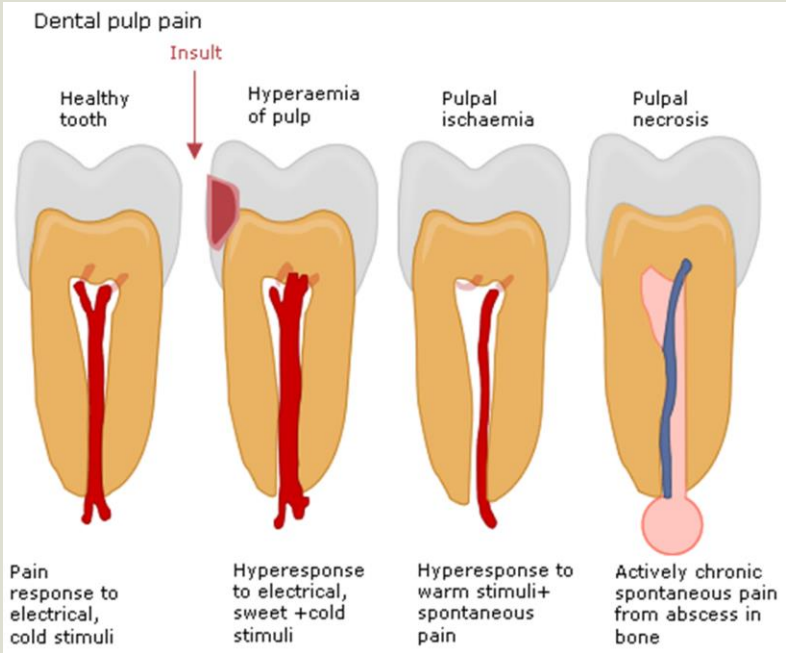

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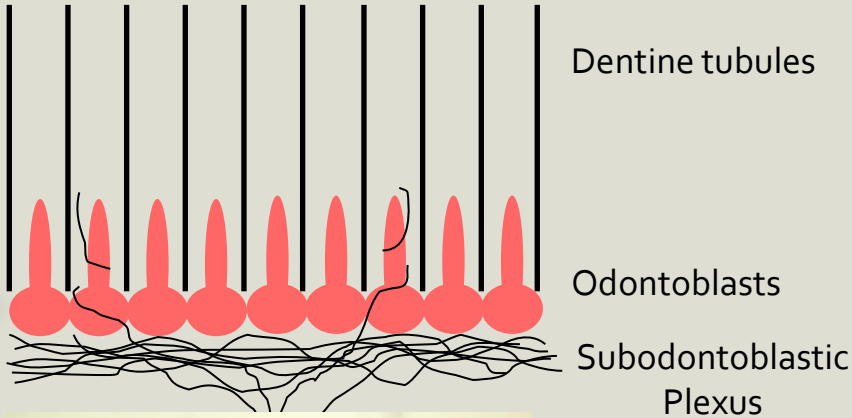
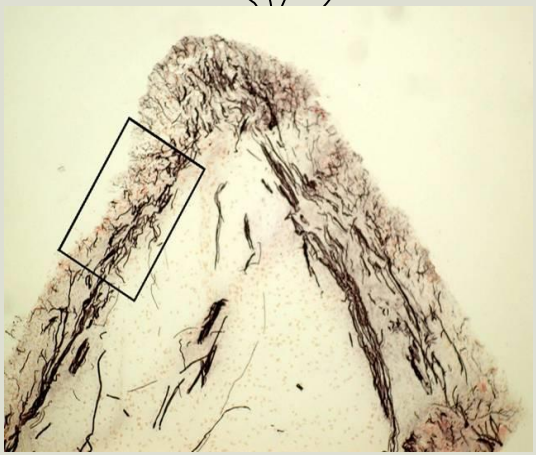
Unique features?

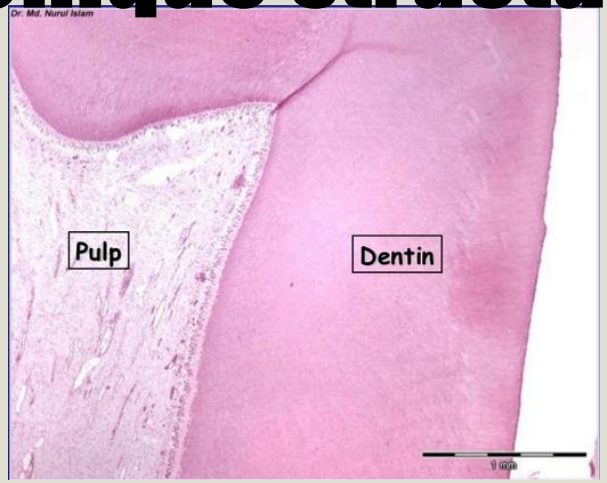
Thermal or mechanical stimulations of dentine /tooth pulp result in a painful sensation unlike that in other tissues in the body (Cook *et al.*, 1997)

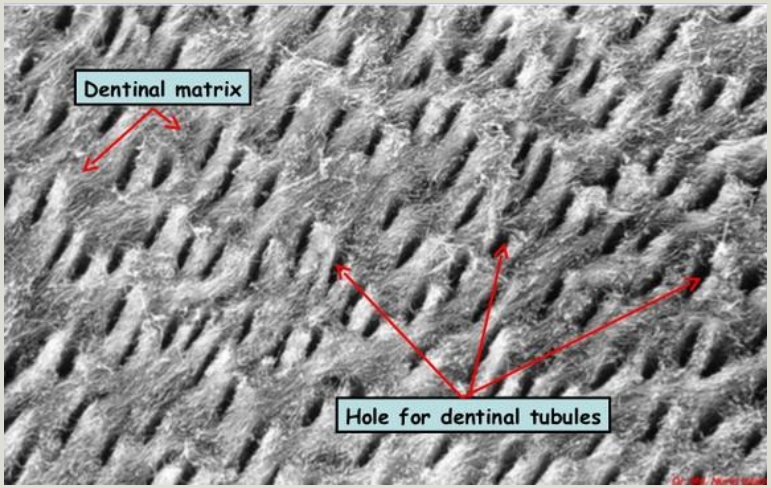




Roughly 57% of adult population affected by dentine hypersensitivity . Peak age: 30 - 39 years – Cummins D, J Clin Dent 2009a; 20(Spec Iss): 1–9. **Still under-reported at present** – Gillian D et al, Dental Update2013 Sep;40(7):514-6, 518-20, 523-4

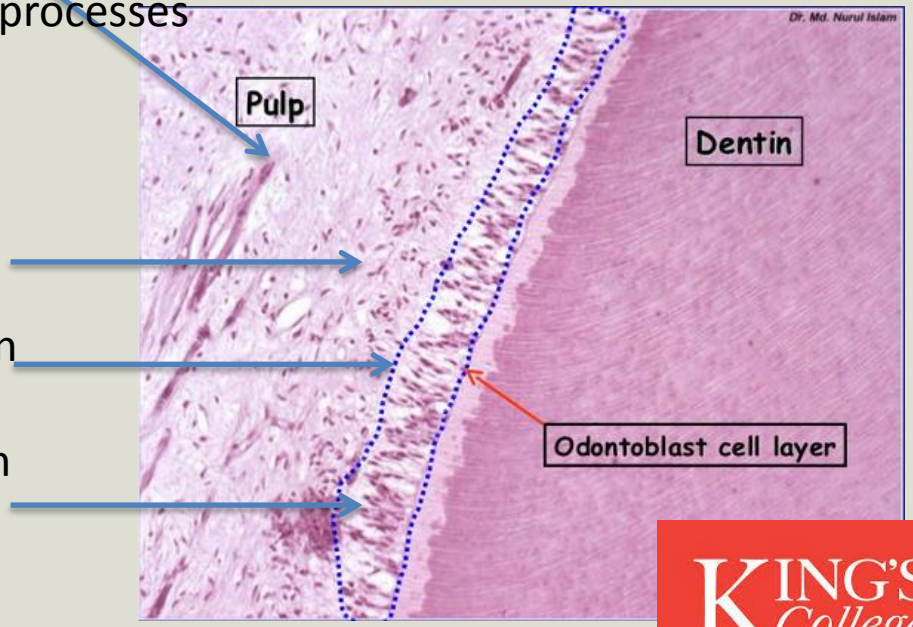
Unique structure





- Pulpal core, which is in the center of the pulp chamber with many cells and an extensive vascular supply; except for its location, it is very similar to the cell-rich zone.
- Cell rich zone; which contains fibroblasts and undifferentiated mesenchymal cells.
- Cell free zone (zone of Weil) which is rich in both capillaries and nerve networks.
- Odontoblastic layer; outermost layer which contains odontoblasts and lies next to the predentin and mature dentin

Most of the dentinal microtubules contain non-myelinated terminal fibrils and odontoblastic processes



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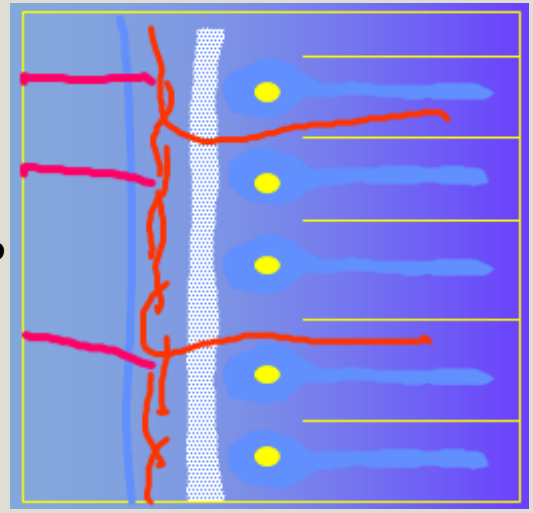
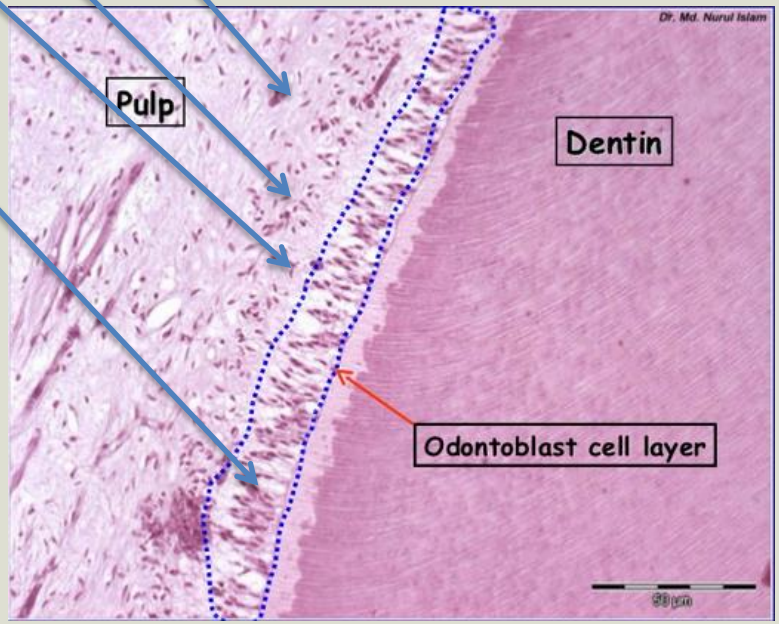


Odontoblast cells lining pulp with processes into the Dentine tubules



Unique innervation

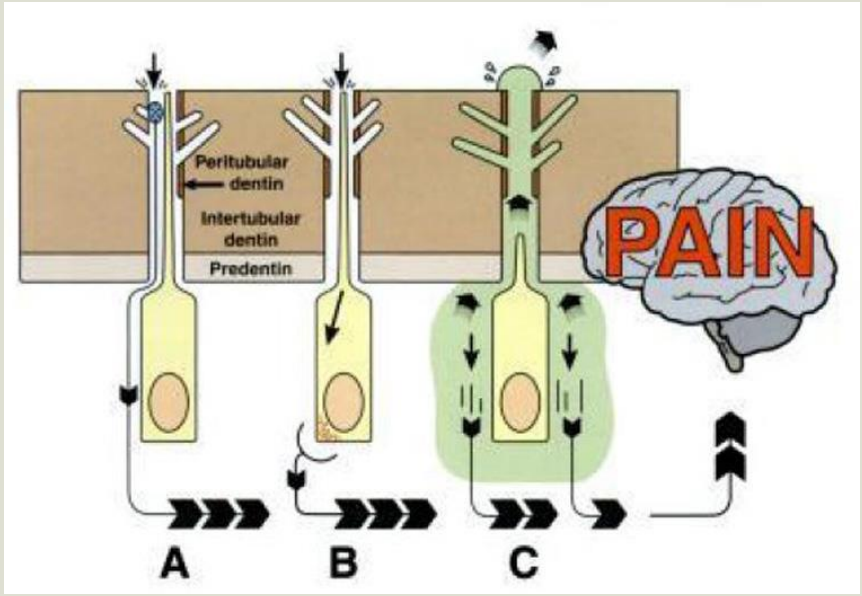
- Nair [1995] concluded that human premolar teeth contain 2300 axons at the apex; 87% of these are unmyelinated, and the remainder are myelinated.
- The nerve terminals are either found in the pulp proper (generally the unmyelinated C fibers) or they can travel through the odontoblast layer and terminate a short distance (150-200 mm) within the dentinal tubule (generally the Aδ or A-β fibers).
- Both myelinated and unmyelinated nerve fibers are present in the pulp. 70-90% of intrapulpal axons consist of unmyelinated C-fibers, which might be involved in slow, dull, drawling dental pain [Azerad J&Woda A.1977; Nair 1995].
- The remaining myelinated intrapulpal fibers are mostly Aδ fibers that are responsible for the rapid, sharp, lancinating, well-localized nociception [Abd-Elmeguid A, Yu DC 2009]

Theories of dental nociceptive pain

1 **Activation** -Direct neural stimulation neural theory, whereby nerve endings that penetrate dentinal tubules directly respond to external stimuli

2 **Transduction**- Odontoblast acting as transducer

3 **Hydrodynamic theory** fluid movements within the dentinal tubules are detected by nerve endings near the dentin



In all theories the activation of dental primary afferents eventuall delivers dental nociception to the central nervous system.

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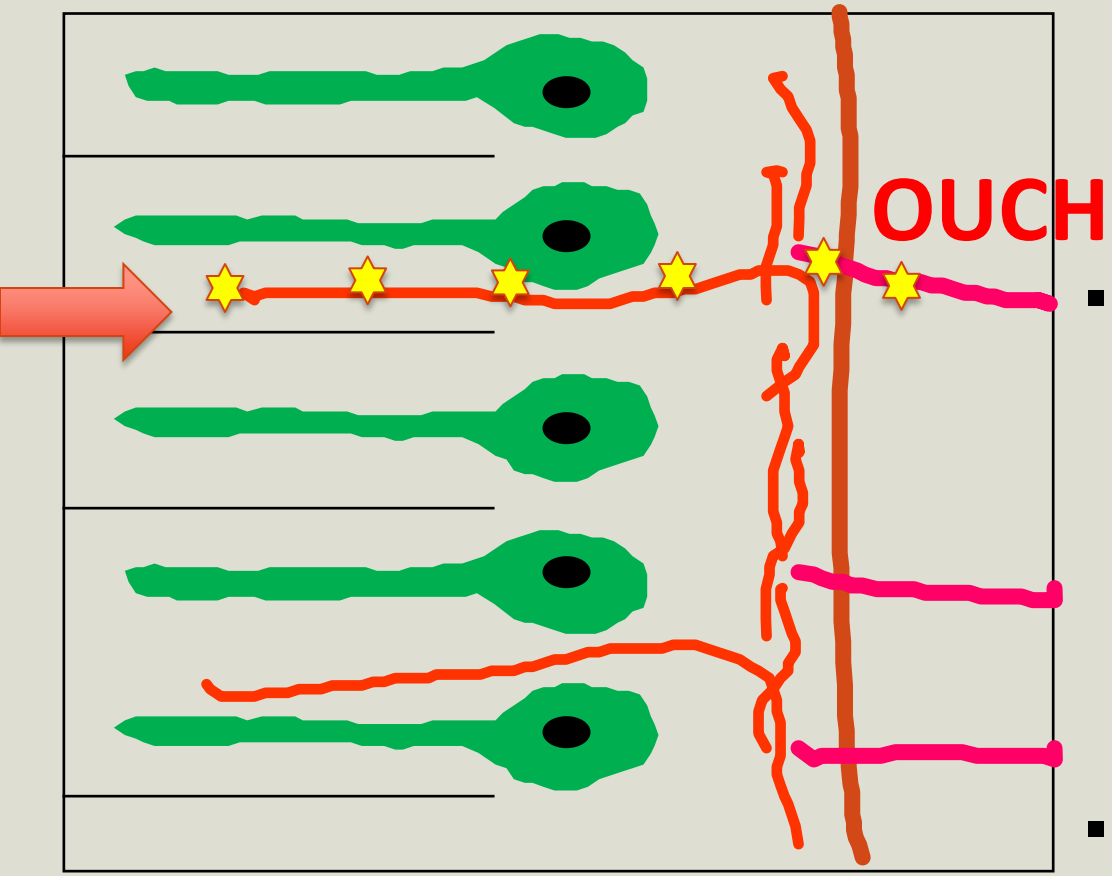
1. **Activation theory-** direct neural activation

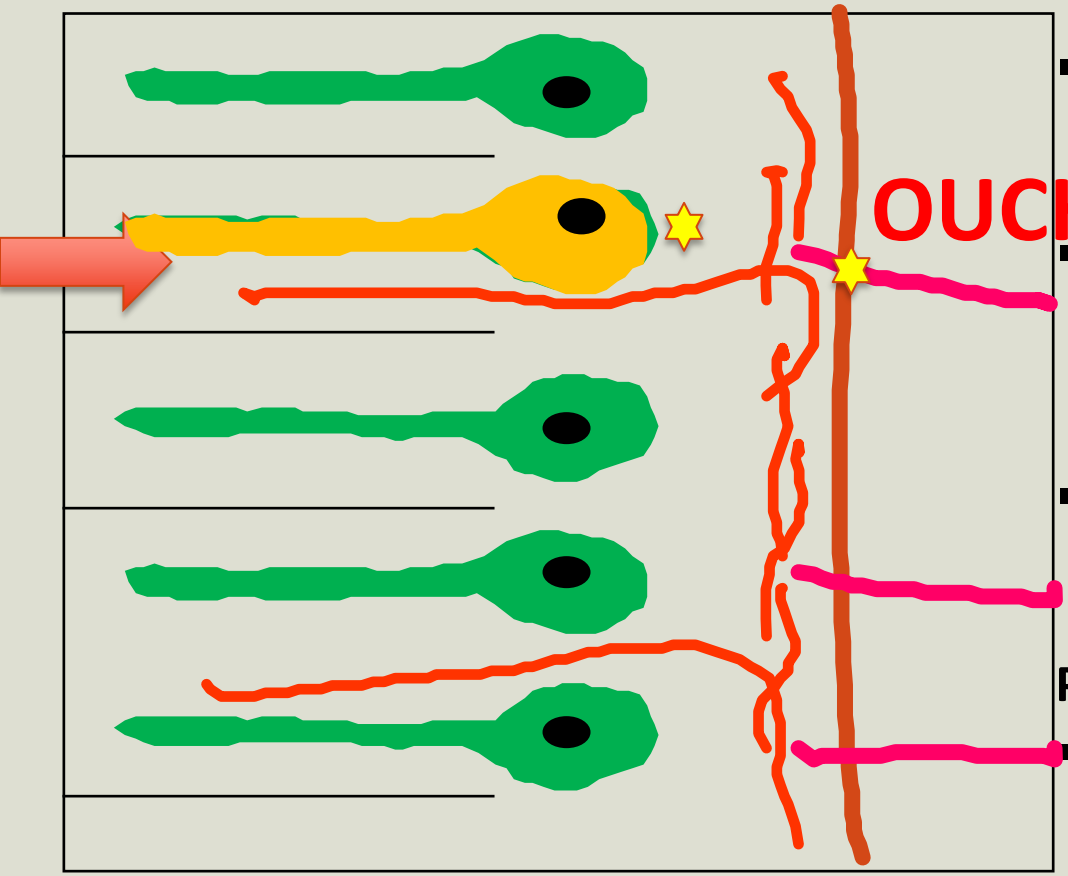


Problems

- 40% of dentinal tubules are innervated in the tip of pulp horns, far fewer tubules are innervated in more apical locations, with less than 1% of tubules innervated in the midradicular region. (**Fearnhead RW. 1957**)
- fibers located in the subodontoblastic plexus pass toward and terminate in the odontoblastic layer as free nerve endings, whereas others terminate in the predentin or enter dentin by way of dentinal tubules where they extend about 100 mm (**Byers MR, Narhi MV. 1999**).
- Most dental afferents are medium-to-large myelinated Aβ-fibers (**Paik *et al*., 2009; Fried *et al*., 2011**)

Application of known noxious stimuli (ATP) do not cause pain

2. **Transduction theory-** odontoblast acting as transducer



'Odontoblasts play a pivotal role'

- **Mechanosensitive** K+ channels and N-type Ca2+ channels in odontoblasts (**Magloire *et al.*, 2010**)
- **Thermosensitive** TRP channels in rat and human odontoblasts **(Chung and Oh, 2013**)
- Cooperation of TRP channels with mechanosensitive K+ channels participated in the perception of temperature (Noël *et al.*, 2009)
- **Primary Cilia** on odontoblasts provide mechanosensory role **(Magloire *et al.*, 2010)**

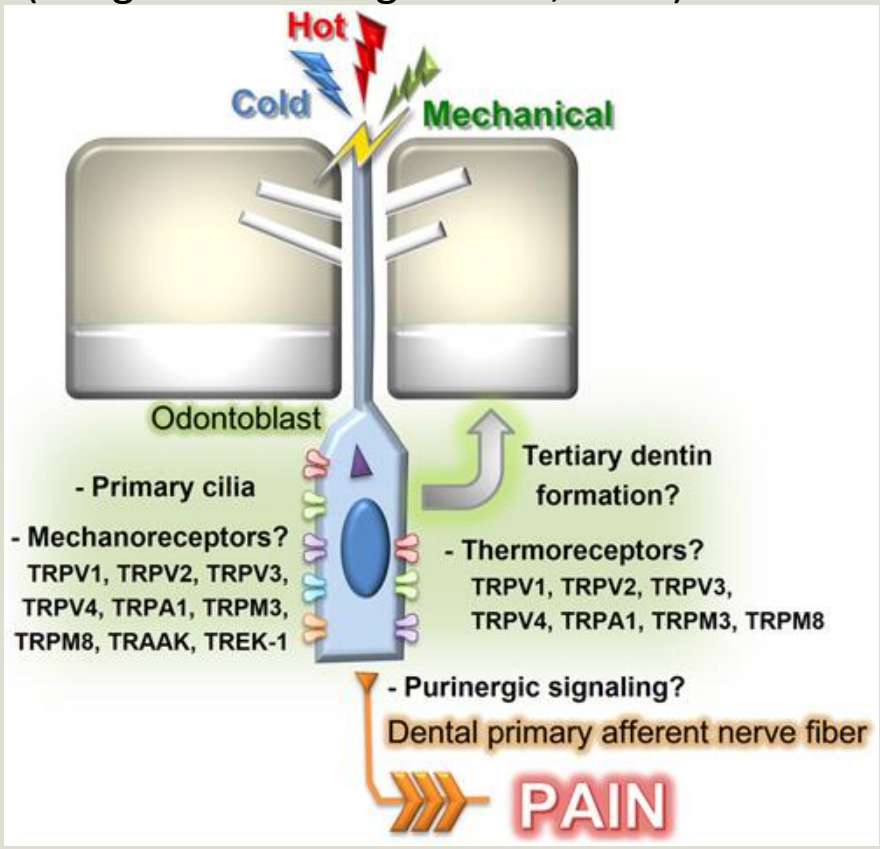
Problems

- BUT mechanism of signalling between odontoblasts and underlying dental primary afferents must be demonstrated to support the sensory role of odontoblasts.

2. **Transduction theory-** odontoblast acting as transducer

(Image from Chung and Oh, 2013)

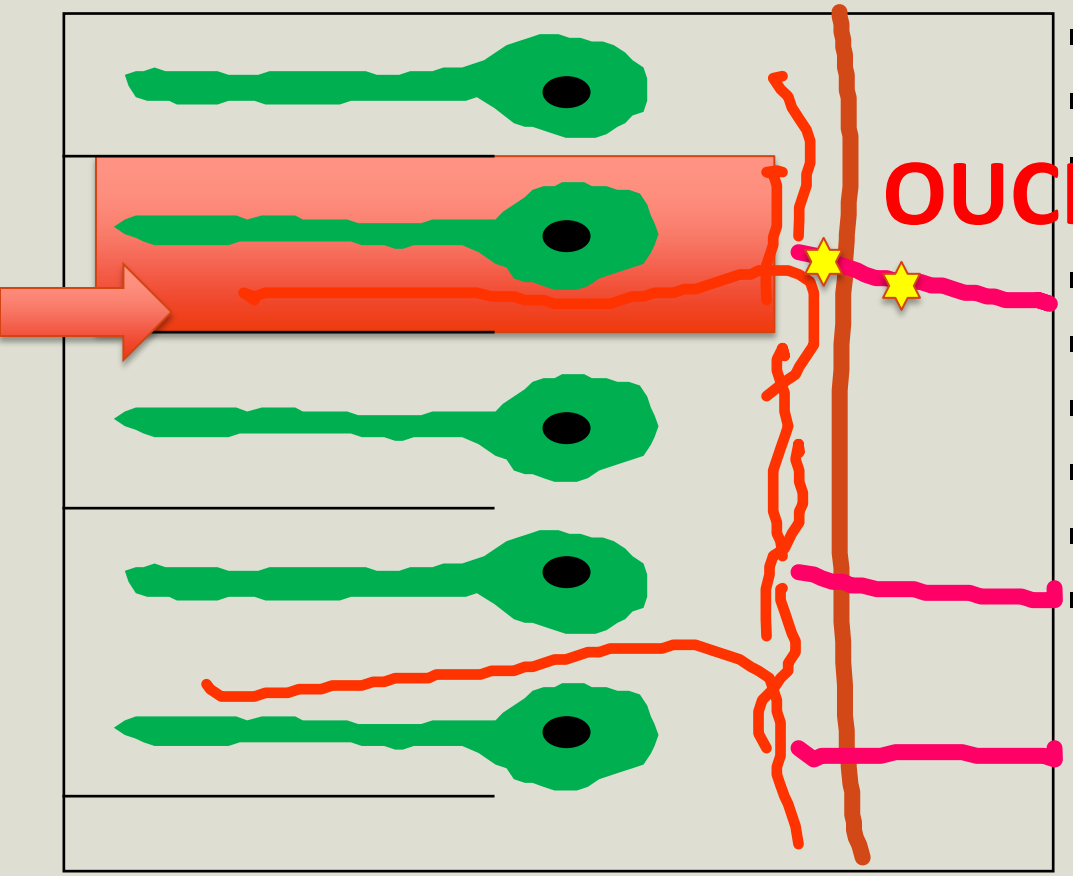
Putative mechanosensitive ion channels revealed by single-cell RT-PCR analysis of dental primary afferent neurons, such as TRPM3, TRPV4, ASIC3, TREK-1, TREK-2, ENaC-α, and ENaC-γ, might therefore also contribute to dental pain (Hermanstyne *et al*., 2008; Vandewauw *et al.*, 2013).



Activation of purinergic P2X receptors in orofacial tissues is sufficient to produce central sensitization in the medullary dorsal horn (Cherkas *et al*., 2012). Expression of P2X3 (Alavi *et al*., 2001) and P2X7 receptors (Itoh *et al.*, 2011) in nociceptive dental primary afferents, together with the intimate relationship of odontoblasts to trigeminal sensory axons (Magloire *et al*., 2010), suggests that ATP could mediate painful signalling between odontoblasts and neurons (Lim and Mitchell, 2012).

3. The hydrondynamic theory

(Hydrostatic pressure /osmolality changes)

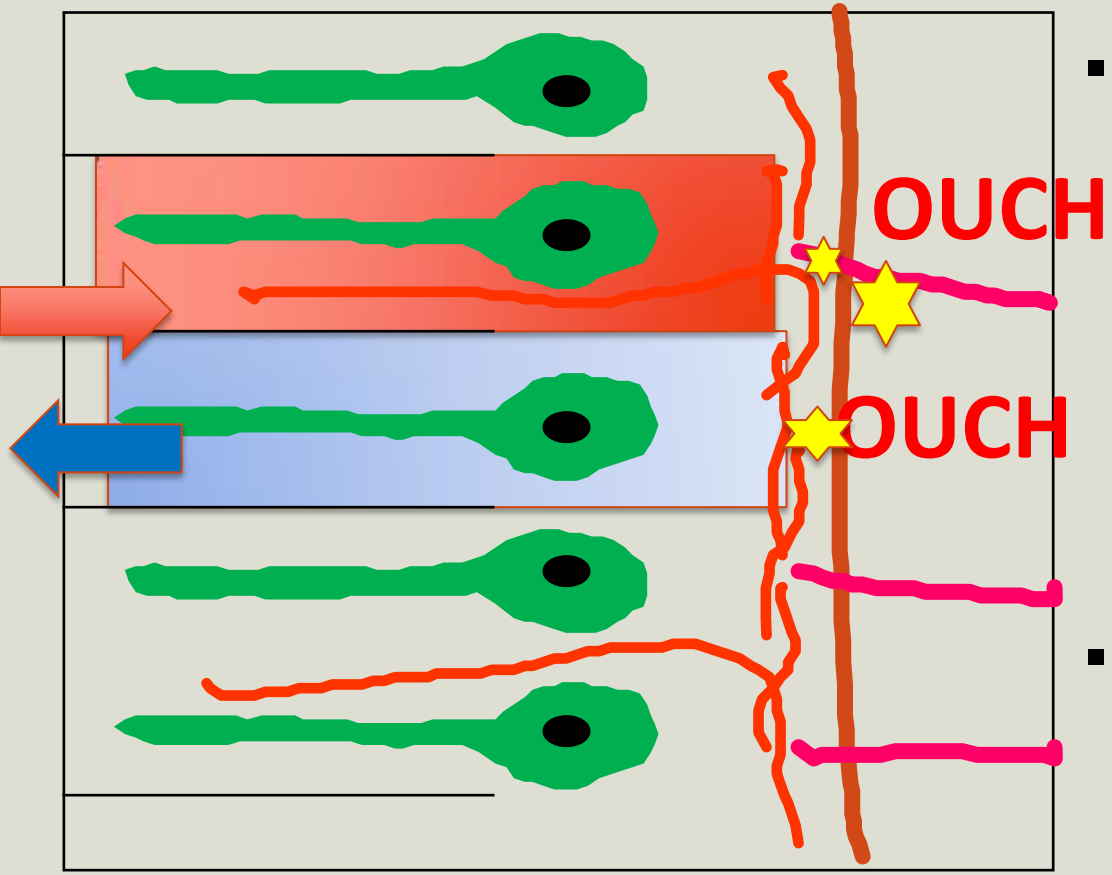


Support

Dentinal tubules have clearly demonstrated a relationship between dentine permeability and sensitivity hat supports the hydrodynamic theory

- *Proposed by Gysi 1900*
- *JD WHite 1955*
- *Brannstrom M, Linden LA, Astrom 1967*
- *Brannstrom M. Astrom A 1972*
- Ahlquist M et al 1994
- Charoenlarp et al 2007 a and b
- Noparatkailas S et al 2009
- Brederson *et al.*, 2013
- Chung and Oh, 2013 propose TRPV1 as a receptor for mechano transduction or detecting hyper-osmolarity as a detector of hypertonicity in dental afferents contributing to the generation of dental pain in response to hyperosmotic conditions such as the consumption of sweet substances.

3. The hydrondynamic theory



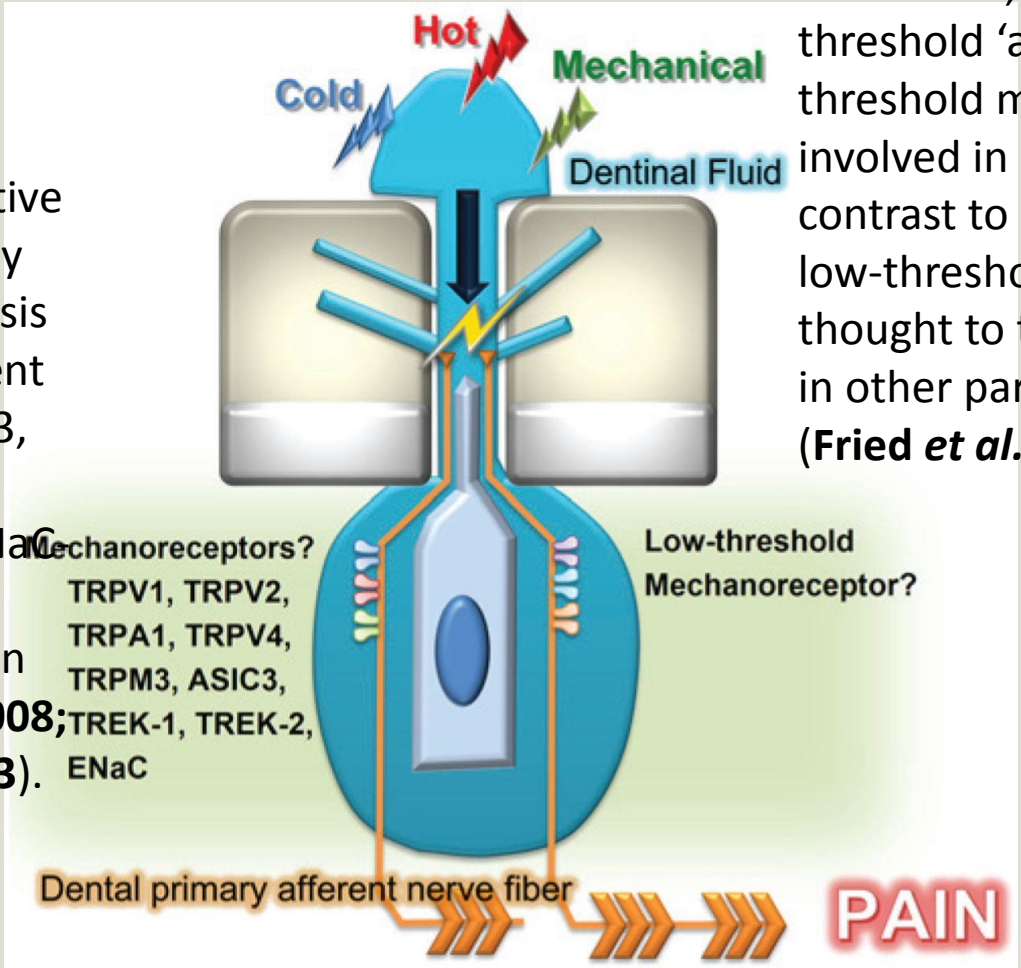
Problems Nerve type and supply
Role Trek? Purinoreceptors activating pulp nerves?

Support

- *in vivo* single nerve fiber recordings of beagle dogs revealed that 75% of mandibular pulpal nerves responded to mechanical stimulation of exposed pulp **(Chung and Oh, 2013)**
- Inward and outward movement of dentinal fluid contributes differentially to dental pain (Lin *et al.*, 2011). Outward movement of the fluid in response to cold stimuli is faster than inward movement by hot stimuli, cold sensation is more readily detected by Aδ fibers in dentinal tubules as sharp pain in early pulpitis. (**Lin *et al.*, 2011).**
- Pulsating pain often described by chronic pulpitis suggests that tooth pain might be induced by hydrostatic pressure applied to inflamed pulp tissue encased within hard dentin structures **(Heyeraas and Berggreen, 1999)**

3. The hydrondynamic theory

Putative mechanosensitive ion channels revealed by single-cell RT-PCR analysis of dental primary afferent neurons, such as TRPM3, TRPV4, ASIC3, TREK-1, TREK-2, ENaC-α, and ENaC-γ, might therefore also contribute to dental pain (**Hermanstyne *et al.*, 2008; Vandewauw *et al.*, 2013**).



(Image from Chung and Oh, 2013)

?

Fried *et al.*, 2011 proposed as low threshold 'algoneurons': low-threshold mechanoreceptors involved in nociception, in contrast to conventional low-threshold mechanoreceptors thought to transduce light touch in other parts of the body (**Fried *et al.*, 2011**)

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So where are we now?

There is a good deal of evidence in support of the theory that dentina sensitivity and hypersensitivity is due to the detection of movement of fluid in dentinal tubules.

Question 1 Does dental pain detection occur by;

- direct activation of pulpal nociceptors or
- the nociceptors being indirectly activated by odontoblasts?

Question 2 What mechanisms of signalling activate the pulpal afferent nociceptors;

- By molecular receptor mediating the mechanical activation?
- By odontoblasts activating underlying dental primary afferents?

The hydro transduction theory?

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