

# Nociception

- Pain and nociception are different
  - Nociception detection of “pain” / noxious stimuli
  - Pain is a personal experience (influenced by other factors)
    - Unpleasant sensory and emotional experience

## Pain Pathway

Detection of stimulus = nociception

Processing of stimulus in cortex = pain experience

### Spino-bulbo-spino loop

- Information conveyed by nociceptor
  - Nociceptors are primary afferent neurons with cell body in dorsal root ganglion
  - Nociceptor one end is in the periphery, while the other end is in the spinal cord
- Message integrated at spinal cord level
- Projection neurons send information from spinal cord to the brain (**ascending pathways**)
  - Send info to the brain via spinothalamic tract
  - Many pathways
- Information processed by cortex
  - Cortex processes pain
- Brain sends info back to spinal cord (**descending pathways**)

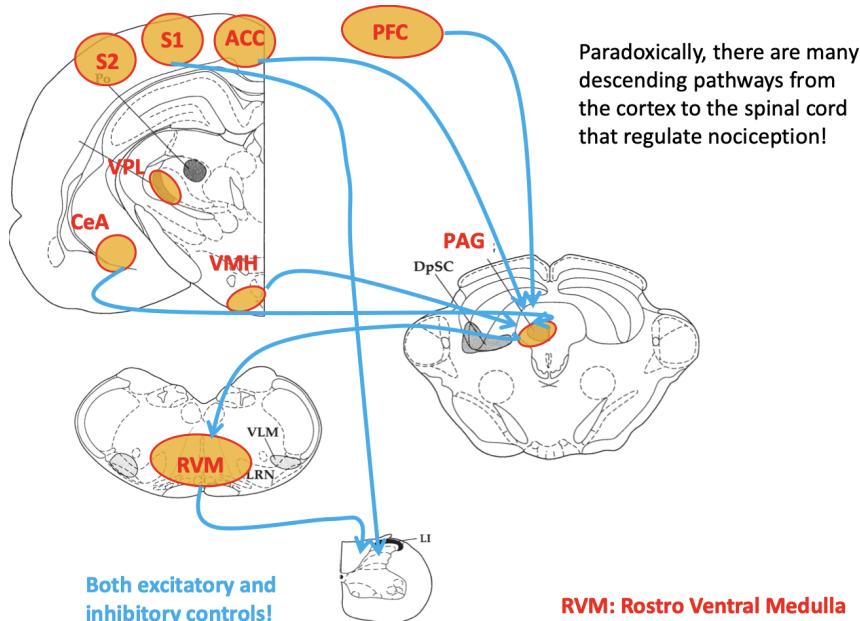
### Ascending pathways

- Interaction between affective brain areas with pain areas → mixture to create the “pain experience”
  - Projection neurons project to parabrachial nucleus (PBN) → alarm centre
  - PBN to periaqueductal grey (PAG)
    - PAG important for coping behaviors, fight or flight, central site of actions of analgesic, allows the body to be able to carry on doing the most important thing despite the pain
  - PBN project to central nucleus of amygdala (CeA)
    - Emotional responses of pain
  - PBN projects to ventromedial nucleus of hypothalamus (VMH)
    - Emotional and autonomic components of pain
  - Projection neurons project to ventral posterolateral thalamic nucleus (VPL)
    - Sensory-discriminative and affective motivational aspects of pain

- VPL projects to ACC (anterior cingulate cortex)
  - Cognitive and motivational-emotional aspects of pain

## Descending pathway

- Prefrontal cortex (PFC) projects to PAG
- CeA, VMH, ACC projects to PAG
- PAG projects to rostroventral medulla (RVM)
  - Both excitatory and inhibitory control
  - Can increase or decrease pain



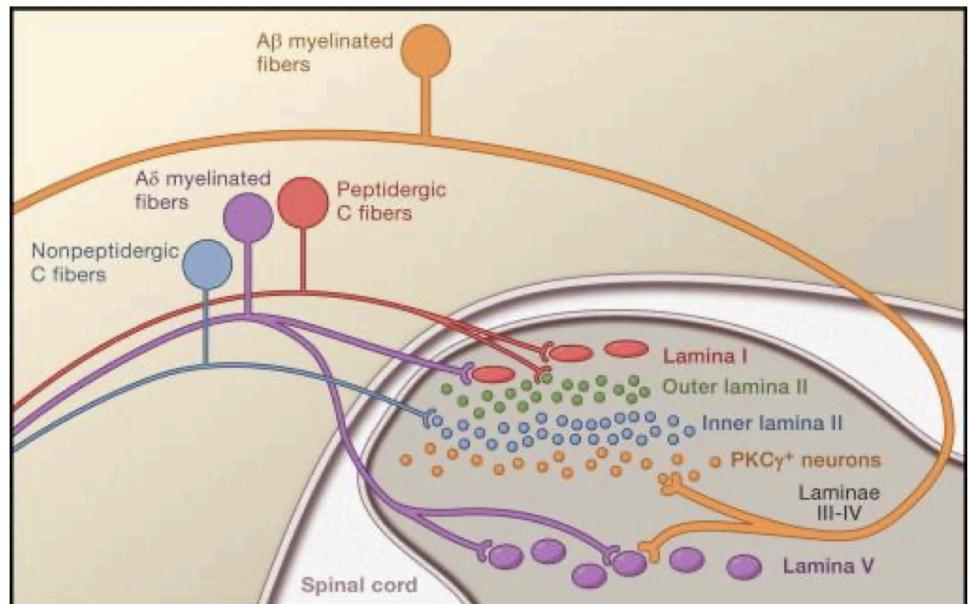
- 

## Primary Afferents

- Primary afferents → neurons that convey any sensory information from the periphery (not just skin) to CNS
  - Some are nociceptors (involved in pain)
  - Classified by:
    - Conduction velocity (size and myelination)
      - C fibers → non-myelinated
        - Slow burning pain
        - Affective effects (e.g. feeling miserable)
        - Trigger autonomic responses
        - **2 subtypes**
          - Peptidergic C-fibres
            - Release substance P / calcitonin gene related peptide in the periphery
            - Promote inflammatory response
            - Neurogenic response → healing after injury

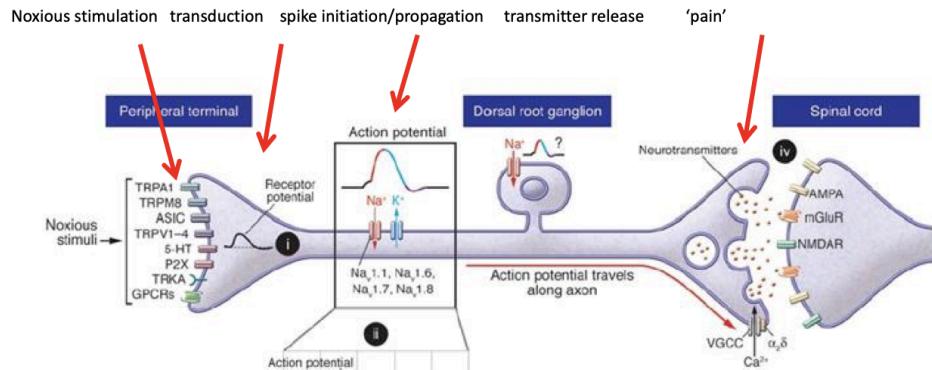
- Non-Peptidergic
- A delta → myelinated (a little bit), faster conduction velocity than C fibre
  - Sharp pricking fast pain
  - Precise localisation of stimulus
  - Reflex withdrawal
- Response properties (sensory modality)
  - Mechanical nociceptors
    - Most A-delta, but some C fibres
    - Appear specialised to signal quickly about contact with sharp objects and provide fast input to trigger protective reflexes
  - Polymodal nociceptors
    - Mostly C, a few A-delta
    - Most numerous sub-class
    - Respond to variety of stimuli
    - Fire to strong pressure, noxious heating, and a range of irritant chemicals and some inflammatory mediators (e.g. bradykinin)
- Terminals: Target tissues
  - Only C-fibres terminate in the epidermis
    - Peptidergic C fibres terminate in the stratum spinosum
    - Non-peptidergic C fibres terminate in stratum granulosum
      - Terminate more deeply into the skin
  - Myelinated A-delta fibres stay in dermis

## Central terminals

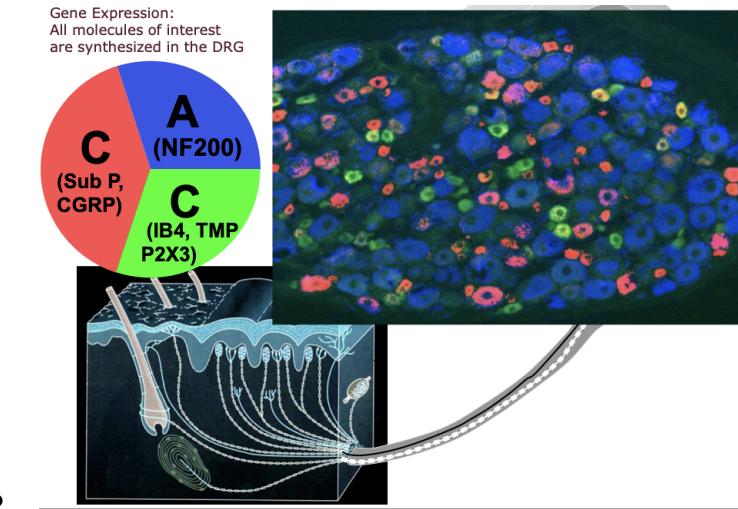


- - Peptidergic C fibers terminates superficially into dorsal horn in lamina 1 and outer lamina II
    - Sometimes synapse directly onto projection neurons
  - A-delta terminates in outer lamina II and V

- Non-peptidergic C fibers terminate in inner lamina II
- Neurochemical phenotypes (molecular signatures)



- No clear marker for myelinated A-delta fibre
  - Marking myelin will also mark other fibres with myelin (e.g. fibers conducting touch not pain)
  - Dissect DRG from mice and section them
  - Very large usually = touch relevant afferents



- - Blue is myelinated
  - Very large might not be nociceptors
  - Green = nonpeptidergic C fibres

## Transduction

- Nociceptors only specific to nociceptive stimuli that are noxious
- Transduction is initiated by membrane depolarisation → generator (receptor) potential
- When the generator potential is of sufficient magnitude, it is transformed into an action potential towards DRG cell bodies
  - Channels specific to nociceptors to conduct AP ( $\text{NaV}1.7$  and  $\text{NaV}1.8$  channels)
    - If pain is in the periphery, if these channels blocked, then pain is blocked

Nav1.7 Channel:

- Voltage gated sodium channels
- Mutations
  - Loss of function mutation → No perception of pain, sensory-discriminative deficit

## TRP Channels

- TRP (transient receptor potential) superfamily of ion channel comprises proteins with 6 transmembrane domains and cytoplasmic N- and C-termini
  - Not all TRP channels are involved in pain, but some are strongly linked with pain and nociception
- TRP proteins assemble as homo or heterotetramers to form cation-permeable ion channels
  - Integration of nociceptive information results in influx of sodium and calcium in nociceptive afferents
  - Generator (receptor) potential is reached

## 3 types of transducers for nociception:

- TRPV1
  - Very strongly linked with pain
  - Responds to noxious heat and capsaicin
  - First TRP channel discovered in mammalian sensory neurons was TRPV1
- TRPA1
  - Responds to cinnamon and mustard
  - Important for detecting noxious cold and injury evoke cold hypersensitivity
  - Often found on TRPV1 expressing nociceptors
- TRPM8
  - Transduces non-noxious stimuli
  - Important for cold sensations
  - Responds to mint
  - If a primary afferent expresses TRPM8 it doesn't mean that it is a nociceptor, because linked to other sensory information

## Experiments:

### TRPV1

- (Caterina et al., 2000)
  - Animal response to hot plate changes after knock-out of TRPV1 → can stay on hot plate for longer, less responsive to acute thermal nociception
- (Davis et al., 2000)
  - Same group, TRPV1 knock-out mice did not differ with wild-type group in their detection of acute heat, however, TRPV1 may be essential for mechanisms leading to thermal hyperalgesia (response to heat stimulus after injury)

- After thermal nociceptive stimuli, wild-type mice with inflammatory response to this heat stimulus reacted much quicker than knock-out animals in response to another heat stimulus

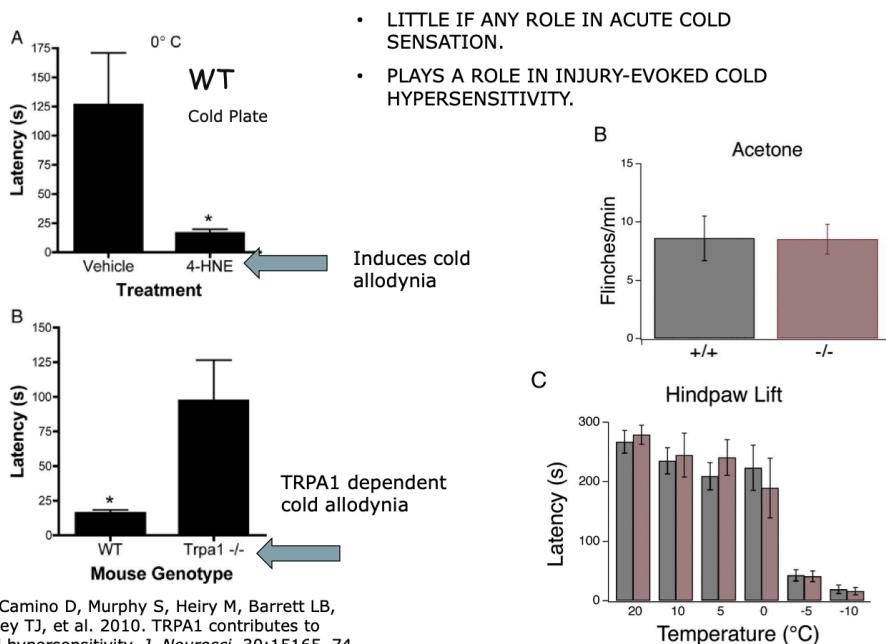
## TRPA1

Acetone (cooling agent) → exact same response to acetone with without TRPA1

- little contribution to normal acute cold sensation

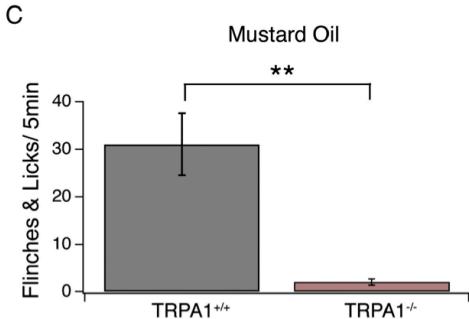
No TRPA1 channels → cannot feel noxious cold as quickly

TRPA1 important for injury evoked cold hypersensitivity, animals with TRPA1 only less sensitive to cold (cold allodynia) after injury, not the case with knock-out mice

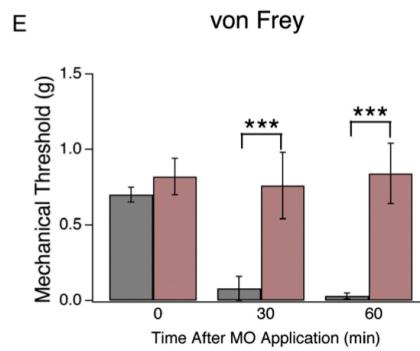
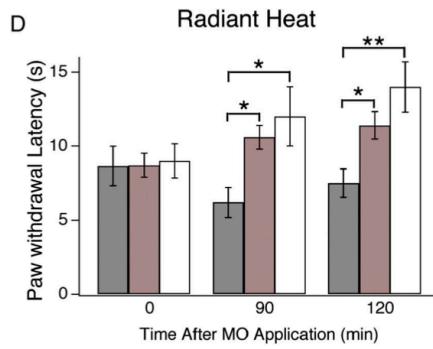


TRPA1 important for detecting chemical irritants (e.g. mustard oil)

- IMPORTANT ROLE IN CHEMONOCCEPTION: DETECT CHEMICAL IRRITANTS



Cell. 2006 Mar 24;124(6):1269-82.  
TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents.  
Bautista DM

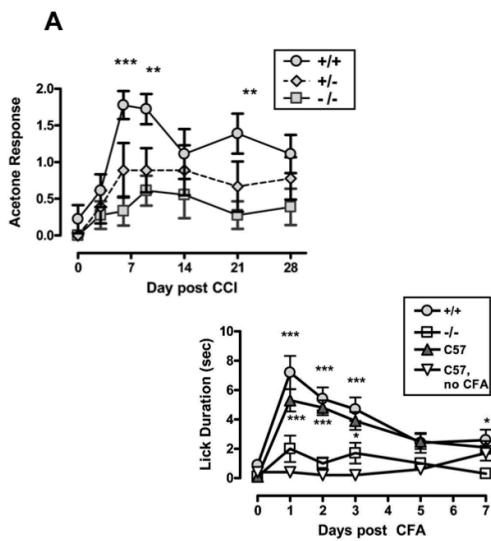


## TRPM8

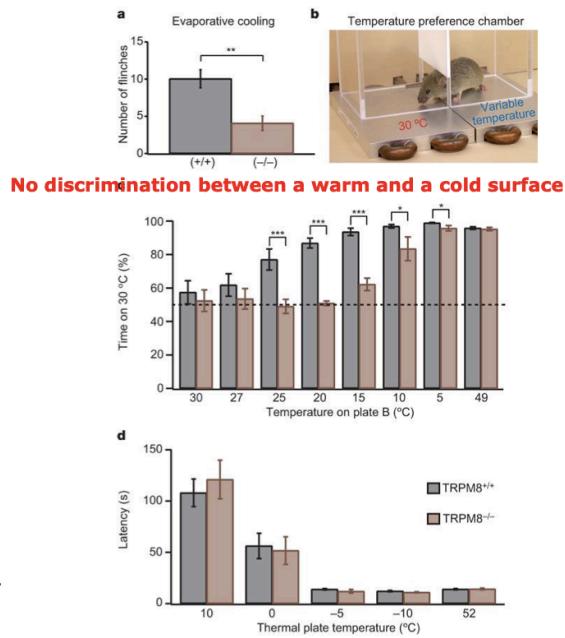
Following nerve injury, animal with TRPM8 gene deleted do not respond to cold pain as much as wild-type

Knock-out mice cannot distinguish normal acute cold sensation

Colburn R et al. Attenuated cold sensitivity in TRPM8 null mice. Neuron 2007 May 3;54(3):379-86.



Bautista DM et al. 2007. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature* 448:204–8



- PROFOUND DEFICIT IN BOTH NORMAL (ACUTE) COLD SENSATION AND INJURY-EVOKED COLD HYPERSENSITIVITY.

## TRP channels and injury

Neurotrophic factors are essential for survival land axon guidanc enduring development

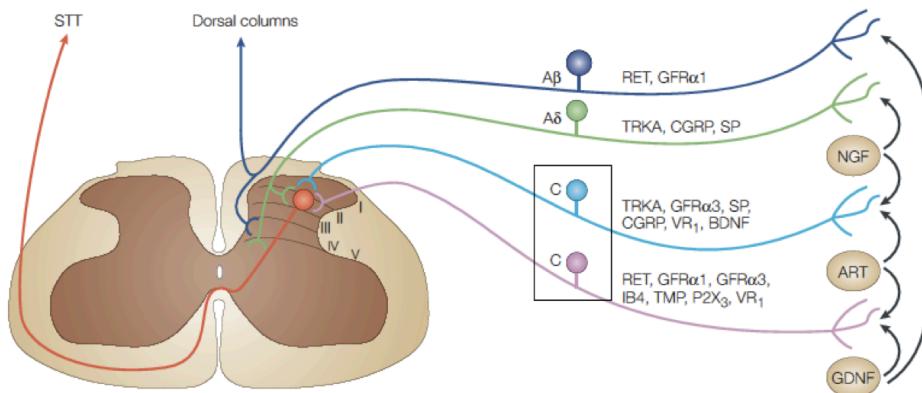
- Important for primary afferents
- Give information of what happened to the primary afferent

Have a key role in maintenance of afferents phenotype and therefore are important for the pain and sensitivity that are associated with tissue injury in adults

2 main classes:

- NGF
  - NGF, BDNF, NT3 and NT4
  - Receptors for NGF are expressed on nociceptors, the factors are not expressed on the nociceptors, they are released by cells in the skin or surrounding tissue
  - Communicate with preferred receptors in primary afferents

### Growth factor receptors differentially expressed on nociceptors



Neurotrophic factors as novel therapeutics for neuropathic pain.

Sah DWY, Ossipov MH and Porreca F.

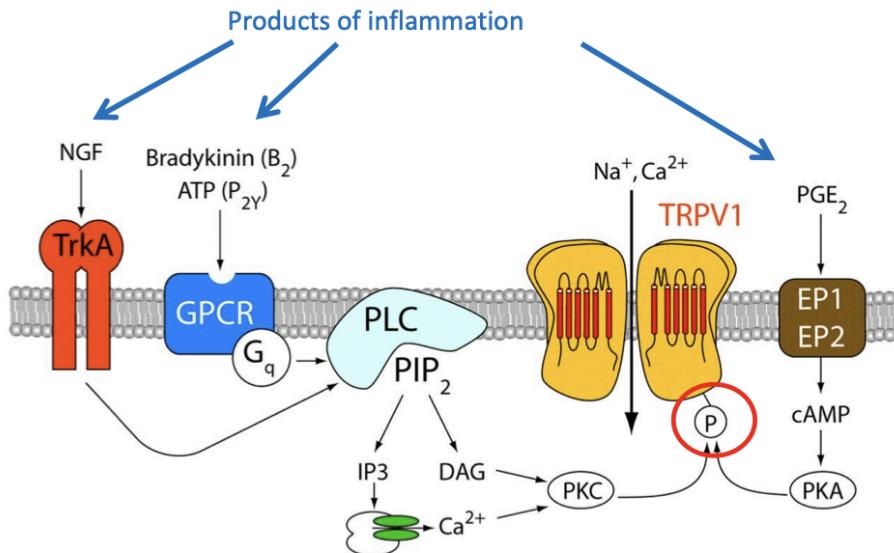
Nat Reviews Drug Discovery 2003 June 2003; 461-472.

- 
- Glial cell line-derived family
  - GDNF

Nociceptors show extraordinary plasticity following inflammation or nerve damage

- Polymodal nociceptors show increased heat and /or pressure responses → sensitised
- Heat nociceptors begin firing to noxious pressure (they get more like polymodal nociceptors)
- Mechanical nociceptors sometimes become more sensitive to pressure and may become heat sensitive, but of the different types of nociceptor this group is least affected by inflammation

## Sensitization of the TRPV1 channel

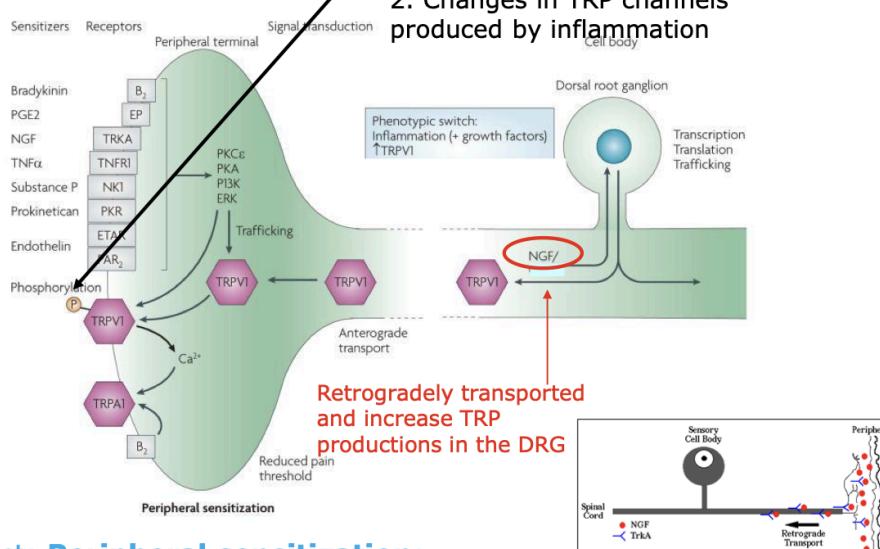


**TRPV1 sensitization depends on channel phosphorylation by protein kinase C (PKC) or protein kinase A (PKA)**

Sensitisation of TRPV1 channel is due to interaction between NGF and TrkA receptors, as well as other products of inflammation

Intracellular pathways alter TRP thresholds, kinetics, and trafficking to the membrane

1. Intracellular pathways alter TRP thresholds, kinetics *and* trafficking to the membrane



**Overall effect: Peripheral sensitization:**  
reduction in the pain threshold at the site of inflamed tissue

Nature reviews Drug Discovery (2009) 8:55p

NGF can travel to dorsal root ganglion

TRPV1 returns to channel (retrograde transport)

## Headache (Primary)

Pain localised in the head = headache

Trigeminal nerve pathway responsible for headache (from trigeminal ganglion, sits below and outside of the brain, in the periphery) → 3 branches that gives sensation to the face

- Ophthalmic
- Maxillary
- Mandibular

Occipital nerve → back of face

International Classification of Headache Disorders		
	IHS code	Classification
Primary headaches		<ol style="list-style-type: none"><li>1. Migraine</li><li>2. Tension-type headache</li><li>3. Trigeminal autonomic cephalgias</li><li>4. Other primary headache disorders</li></ol>
Secondary headaches		<ol style="list-style-type: none"><li>5. Headache attributed to trauma or injury to the head and/or neck</li><li>6. Headache attributed to cranial or cervical vascular disorder</li><li>7. Headache attributed to non-vascular intracranial disorder</li><li>8. Headache attributed to a substance or its withdrawal</li><li>9. Headache attributed to infection</li><li>10. Headache attributed to disorder of homeostasis</li><li>11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structures</li><li>12. Headache attributed to psychiatric disorder</li></ol>
Painful cranial neuropathies, other facial pains and other headaches		<ol style="list-style-type: none"><li>13. Painful lesions of the cranial nerves and other facial pain</li><li>14. Other headache disorders</li></ol>

Primary headache = headache is the focus, actual disease

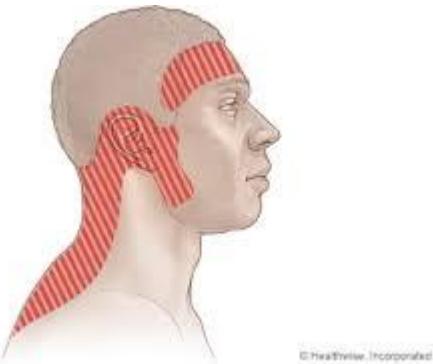
Secondary headache = headache is a symptom to another condition

Facial pain

### Tension Type headache

- Very common
- Pain characteristics:

- Tightness / Pressure
- Mild to moderate
- Not aggravated by movement
- Duration: 30 min to several days
- With or without pericranial tenderness
- No nausea, photophobia and phonophobia
  - You can still move around
- More prevalent in women
- 3% of population has chronic TTH
  - Chronic → goes on about 15 days or more per month
- Pathophysiology
  - Unknown
  - Pericranial and cervical muscle tenderness compared to controls



© Healthwise, Incorporated.

- Absence of pericranial muscle activity or inflammation
- Sensitisation is hypothesised as main cause
  - Episodic TTH → peripheral sensitisation (first order neuron)
  - Chronic TTH → central sensitisation (second order neuron)
    - Chronic TTH cannot pass unless the central second-order neuron calms down

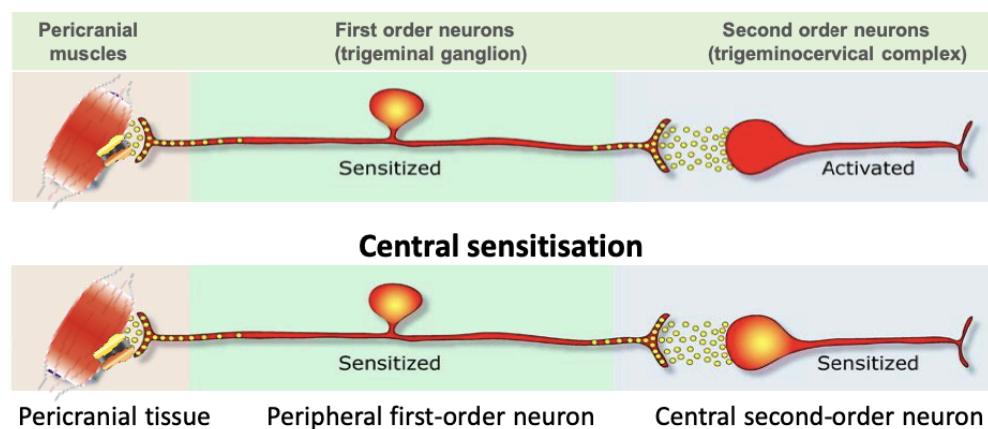


Figure adapted from Levy D, et al. 2004.

- Hyperactivity (more firing) in peripheral primary-order neuron → becomes sensitised
- More activation of second-order neurons, and second-order neuron become sensitized
  - Second-order neuron found within dorsal horn

- Persistent firing keeps activating second-order neuron and sensitises it
- Takes time for sensitised neurons to return to non-sensitised state

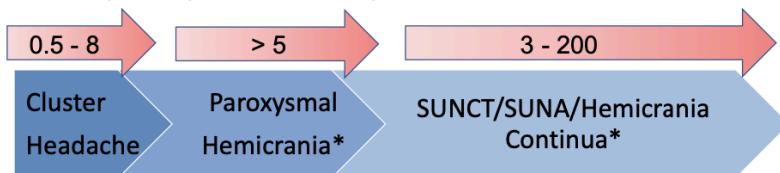
## Trigeminal Autonomic Cephalgias

- Symptoms are similar, but duration of attacks are different

- Duration (min)



- Frequency (attacks/day)



- Hemicrania can be treated with indomethacin (non-steroidal anti-inflammatory) only

- A group of different headaches:

- Cluster headache

- Prevalence greater in men

- But still rare, 0.5% - 1% prevalence
- Past year more women come with cluster headache diagnosis, because they are often misdiagnosed

- Pain characteristics:

- Excruciating orbital/supraorbital/temporal pain
  - Patients cannot stay still, agitated
- Unilateral and same side most of the time
- Stabbing-like
  - Hot poke

- Attack duration: 15min to 3h

- Frequency: 0.5-8 attacks per day

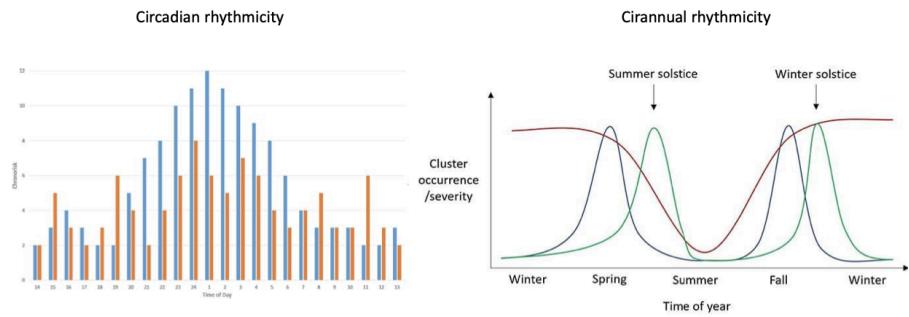
- At least one ipsilateral autonomic feature (on the same side always):

- Conjunctival lacrimation
  - Discharge of tears
- Nasal congestion
- Rhinorrhea
- Eyelid edema (and face swelling)
- Forehead and facial sweating

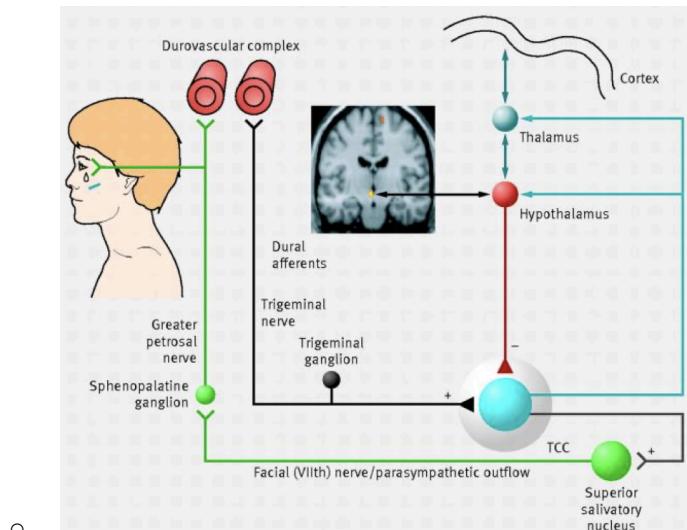
- Remission period between bouts of attacks

- Attacks happen in certain period of year (bouts)

- Most patients get it at the same time of the year



- ○ Light changes (spring or autumn) = gets headache
  - Countries getting more sunlight report less people with cluster headaches
  - Patients with cluster headaches may leave the country during this time of bouts, but they get it immediately after they come back → biological clock is important
  - Headache synchronizes with time (e.g. with circadian rhythm, which is controlled by hypothalamus) → always on the clock
- Outside of bouts patient can function normally, even normal triggers cannot trigger headache
- Pathophysiology
  - Hypothalamic malfunction linked with hypothalamus
    - Brain imaging has demonstrated that there is hypothalamic activity during bouts of attack
    - Deep brain stimulation in hypothalamus works, but very risky
    - Unknown how hypothalamus contributes to headache because lack of understanding of the specific subregion involved
  - Hypothesis: Posterior hypothalamic activation may modulate signaling through the trigeminocervical complex (TCC)
    - **Involvement of the trigeminovascular reflex arc**

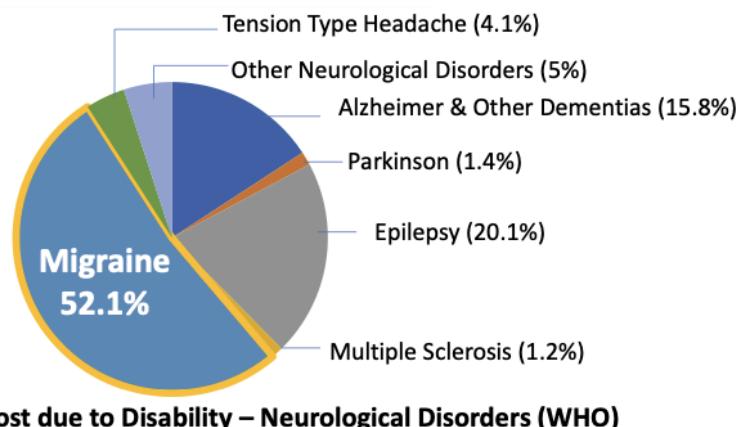


- Trigeminal nerve projects away from TCC

- Hypothalamus can modulate TCC and thus the subsequence projection of trigeminal nerve to other regions
- Trigeminal fibers activated the parasympathetic system through superior salivatory nucleus which in turn activate fibers of greater petrosal nerve through the sphenopalatine ganglion
- Paroxysmal hemicrania
- Short-lasting unilateral neuralgiform headache attacks (SUNCT & SUNA)
- Hemicrania continua
- Probable trigeminal autonomic cephalgias

## Migraine

- Very prevalent condition in the world
- Most disabling neurological disorder

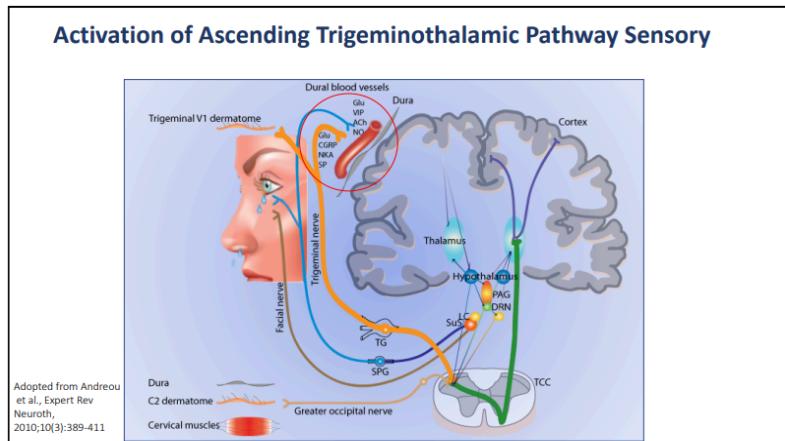


Years Lost due to Disability – Neurological Disorders (WHO)

- 
- Affects young people, declines with age
  - 20-50 years old
- Migraine classification
  - Migraine with aura (doesn't mean patients will always get aura)
  - Migraine without aura
- Strong family history - genetic components
  - Polygenic condition, no single gene contributing to migraine
  - However, there is one type of migraine we know which genes contribute to it...
    - Familial hemiplegic migraine
      - Symptoms: aura + half of body feels weak, mimic stroke symptoms
      - Rare
      - 3 genes involved:
        - FHM1
          - Calcium channel
          - Mutation: increase calcium flux at presynaptic terminal

- FHM2
    - Na<sup>+</sup>/K<sup>+</sup> ATPase
    - Mutation: Re-uptake of potassium glutamate into glia cells
  - FHM3
    - Na<sup>+</sup> channels
    - Mutation: Increase sodium influx
  - Mutations of genes increase excitability of neurons → pain pathway more likely to be activated
  - Genetic predisposition can predict migraine threshold
    - Can manage attacks with lifestyle
- Migraine patients cannot habituate to a stimulus
  - Habituation controlled by balance of excitation and inhibitory pathways
  - Migraines may be caused by increased glutamate availability (has been identified in plasma and CSF in patients)
- Lower threshold for excitation probably due to hyperactivity of excitatory neurotransmission and lower activity of inhibitory transmission
- Pain characteristics:
  - Episodic
  - Unilateral
  - Throbbing
  - Worse with movement
  - Attack duration: 4 to 48 hours
- Additional associated symptoms:
  - Nausea and vomiting
  - Sensory sensitivities (photophobia/phonophobia/osmophobia)
    - Attacks can be triggered (e.g. by stress, sleep disturbances, flashing lights)
- Phases of migraine attack:
  - Premonitory phase
    - Attack has already begun but patient may not realize
    - Symptoms not associated with pain
      - Cravings
      - Yawning
      - Fluid retention
      - Heightened perception
    - Consistent activation of hypothalamus
      - Possible candidates in hypothalamus, all have direct connections with descending pain pathway:
        - Periventricular nucleus
        - A11 nucleus
        - Posterior hypothalamic nucleus
        - Tuberomammillary nucleus
  - Aura phase (for some migraines, but not all)
    - Auras are transient neurological symptoms with a typical behaviour
    - Migraine headaches can be present during or following the aura phase
    - Aura without headache is not uncommon

- Symptoms
  - Visual changes
    - 20% - 30% of patients
  - Speech difficulties
  - Confusion
  - Numbness of fingers and limbs
- Pathology of migraine aura mimics **cortical spreading depression**
  - Slow, self-propagating wave of depolarisation of neurons and glial activation
  - Results in an initial hyperaemic phase followed by an oligaemic phase
    - Blood flow changes → vasodilation as wave reaches an area, then vasoconstriction (may contribute to visual changes such as blind spots)
  - Does not cross cerebral hemispheres or spreads to deeper brain structures
    - Only affects 1 hemisphere most of the time
  - Begins in the occipitocortex
    - Glutamatergic signalling → excitatory
      - Experiment: Fluorescent Ca<sup>2+</sup> influx into neurons demonstrates activation of areas in transgenic mice
    - A depression phase follows wave of excitation
      - Neurons in depression phase cannot be activated until after a long time
      - 1 wave for migraine
  - Headache phase
    - Activation of ascending trigeminothalamic pathway sensory



- Cortex perceives the signal as painful
- Mechaninal sensors in the meninges → interaction with the meninges causes migraine like pain
- Chemicals that do not cross BBB can trigger migraine attack in sufferers
  - Calcitonin-gene related peptide
    - Found in A-delta and C trigeminal fibers
      - Trigeminal nerve types: