

NOCICEPTORS and PERCEPTION of PAIN

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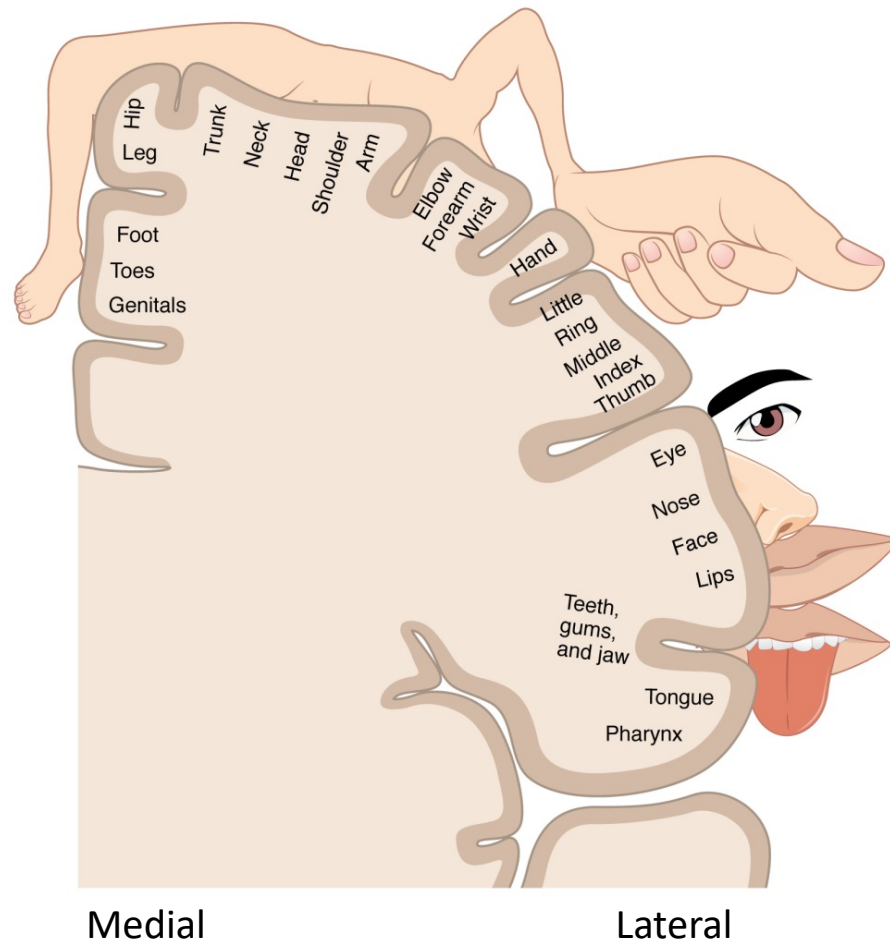
DPMP, Medizinische Universität Innsbruck

Topics of the lecture

- What is nociception vs. pain
- How nociception works and how a nociceptor is defined
- Characteristics of nerve fibers and dorsal root ganglion
- How to test nociception
- Type of pain and pain models
- Pain pathways and important molecular partners
- Specific pain syndromes and pain therapy

Somatotopic map of the body

Sensory
homunculus



Nociception

It comes from Nocere = injure.

It is the physical action of exciting small-caliber primary endings via mechanical, thermal, or chemical stimuli.

Body detection of tissue damage or threat of damage, however there can be tissue damage without pain.

Pain

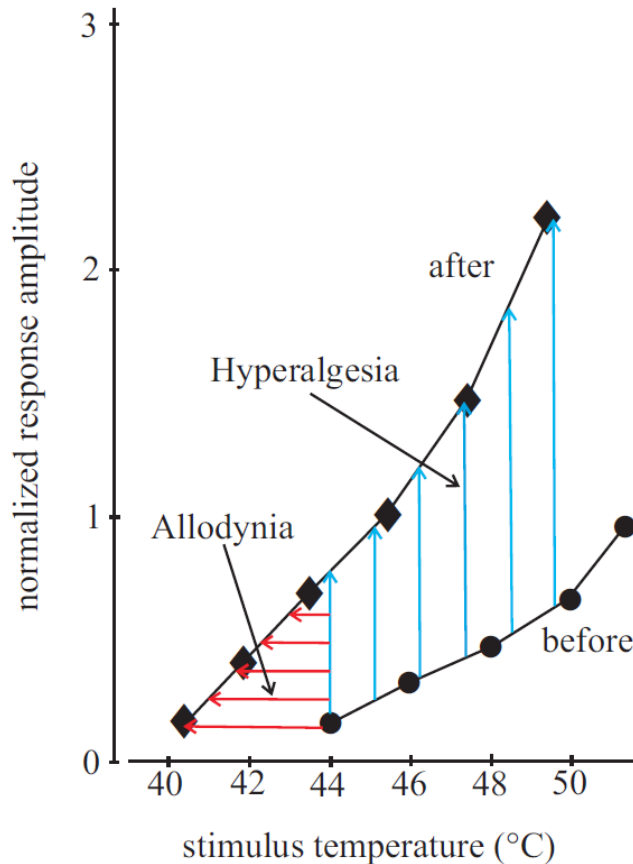
It comes from Poinē = penalty.

Pain is defined as the unpleasant sensory experience normally associated with tissue damage, however there can be pain without tissue damage too.

Allodynia or Hyperalgesia?

ALLODYNIA

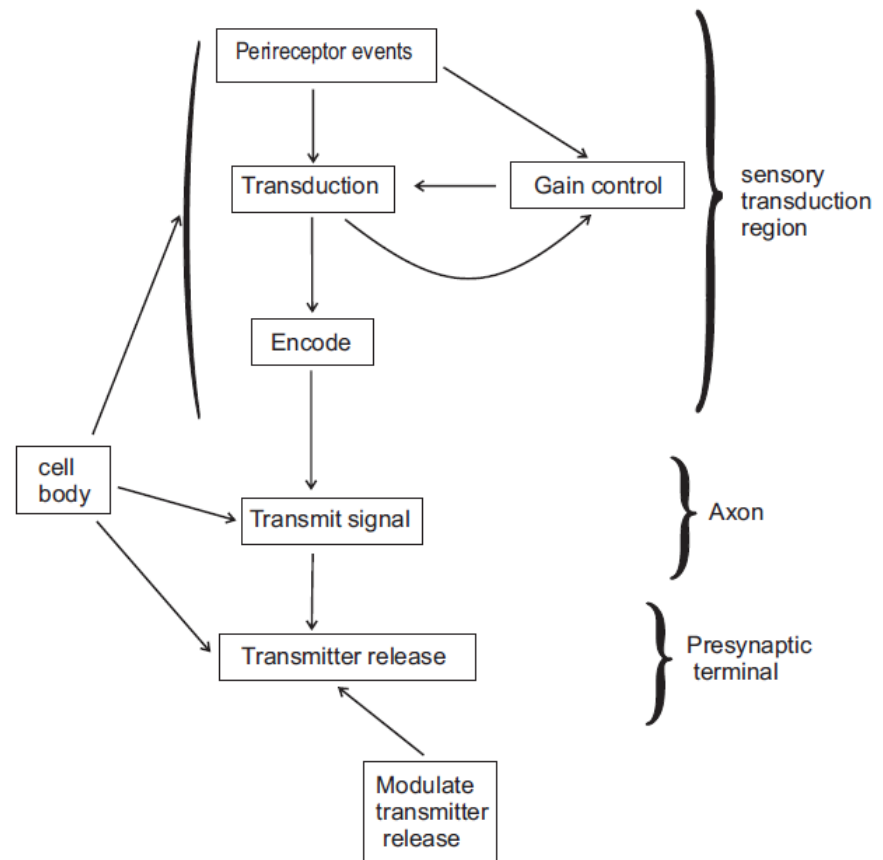
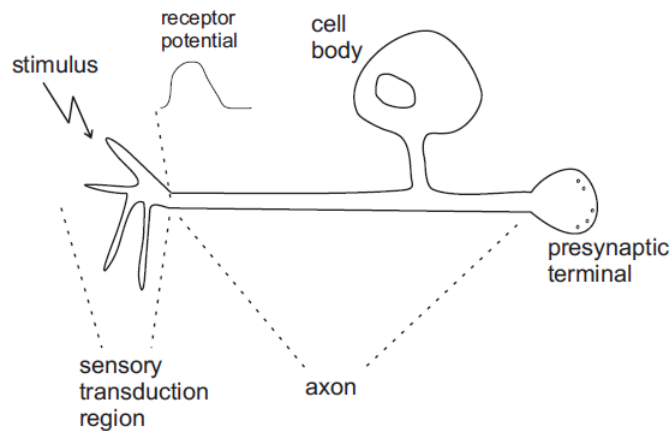
Pain resulting from normally painless stimulus



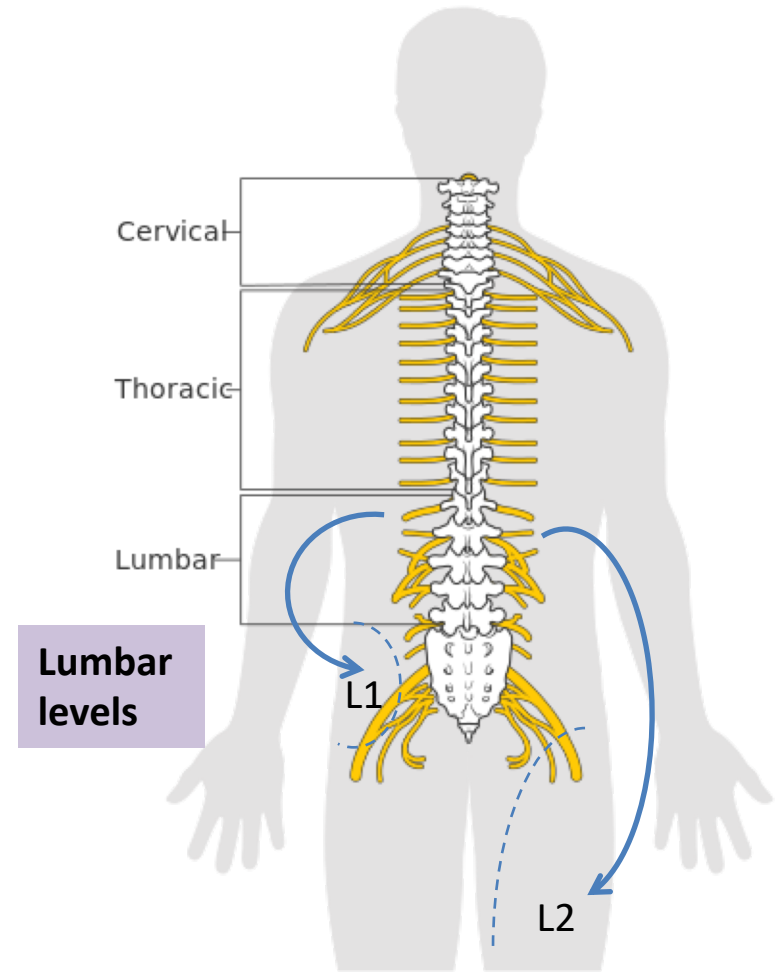
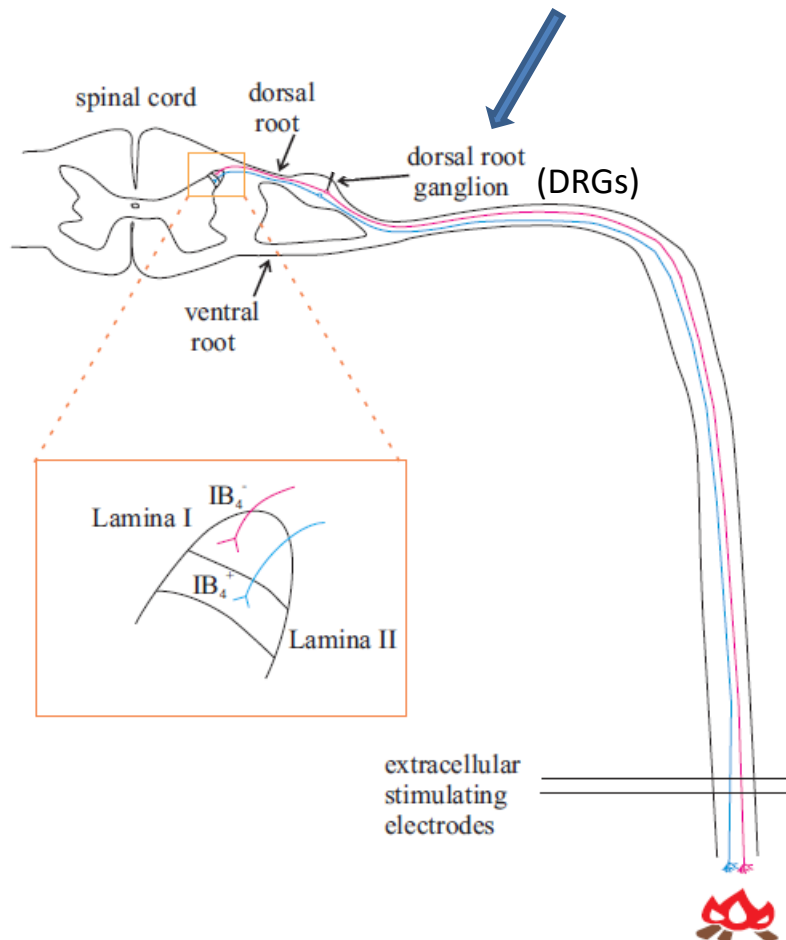
HYPERALGESIA

Excessive response and sense of pain to a normally painful stimulus

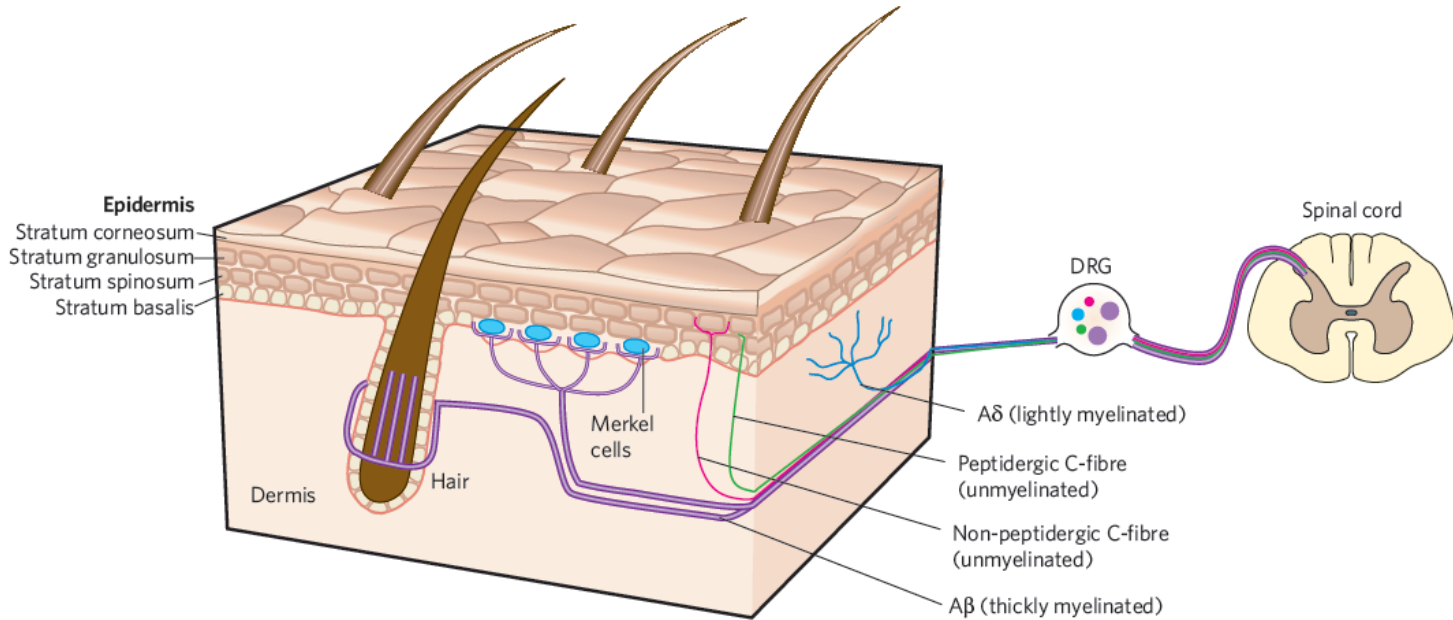
What is a nociceptor and how a nociceptor works?



Where are nociceptors located? (1)



Where are nociceptors located? (2)

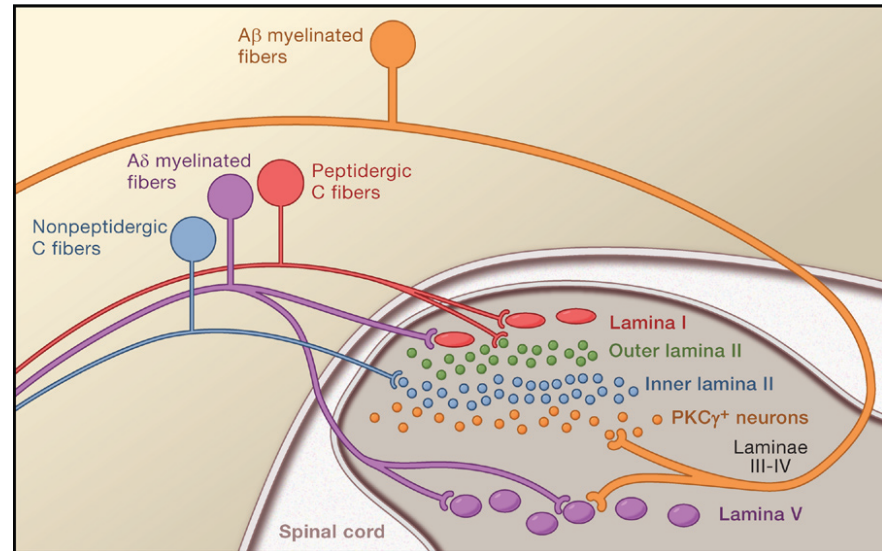
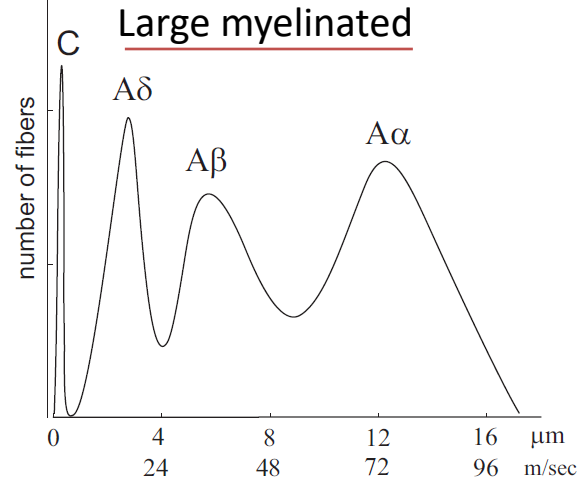


Lumpkin and Caterina, *Nature*; 2007

- Signal is generated in **periphery** at nerve **terminals**
- Receptors translate stimulus into **receptor potential**
- Receptor potential is transformed into **action potential**
- **cell bodies** of **somatosensory** neurons are located in **dorsal root ganglia** (DRG)

Characteristics of nerve fibers

Small unmyel.



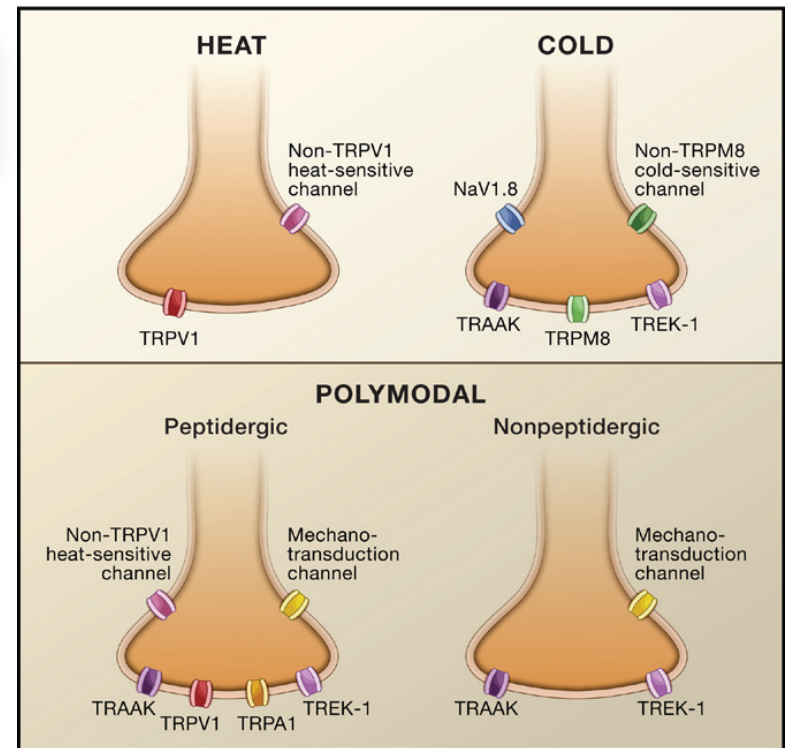
Fein, *Nociceptors and the perception of Pain*; 2012;
Basbaum, *Cell* (139); 2009

NERVE FIBERS	ALPHABETICAL NOMENCLATURE	NUMERICAL NOMENCLATURE	FIBER DIAMETER [μm]	CONDUCTION VELOCITY [m/sec]
Myelinated	A α	Ia	17 ca.	80 – 120
	A α	Ib	16 ca.	80 – 120
	A β	II	8 ca.	35 – 75
	A δ	III	1 – 5	5 – 30
Unmyelinated	C	IV	0.2 – 1.5	0.5 – 2

Classification of nociceptors by noxious stimulus

What is a
Noxious stimulus???

Fibers	Receptor type	Response
A δ	Mechanical	Sharp pricking
A δ	Thermal and mechano-thermal	Slow burning, cold sharp
C	Polymodal	Hot, burning, cold and mechanical stimuli



Basbaum, *Cell* (139); 2009

Subpopulations in DRGs

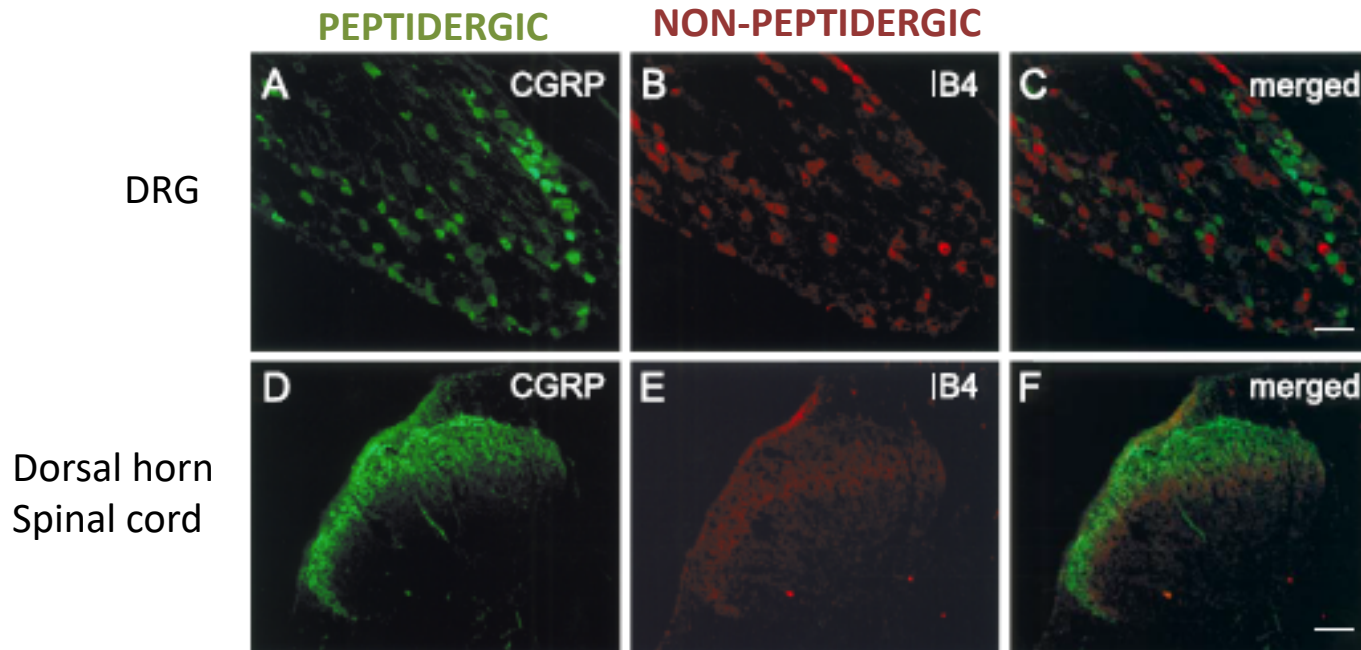
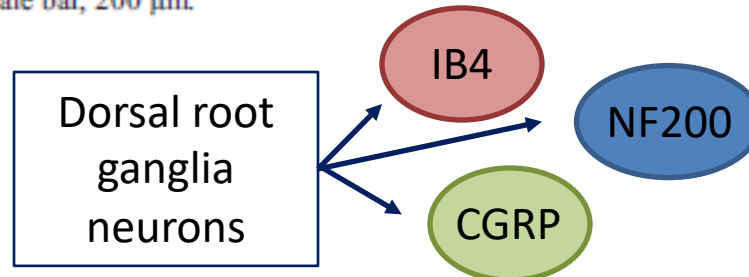


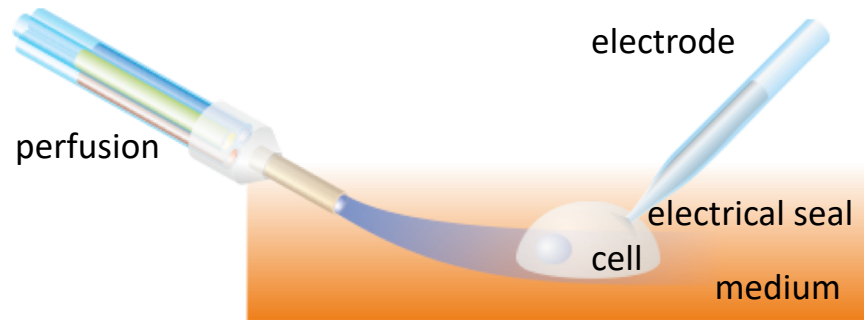
Fig. 1. Fluorescent photomicrograph showing the dorsal root ganglion (DRG) at L2 level (A–C) and dorsal horn (D–F) in naïve rats. Double staining demonstrates minimal colocalization of CGRP (green) with IB4 (red) in DRG neurons and superficial dorsal horn. Scale bar, 200 μ m.



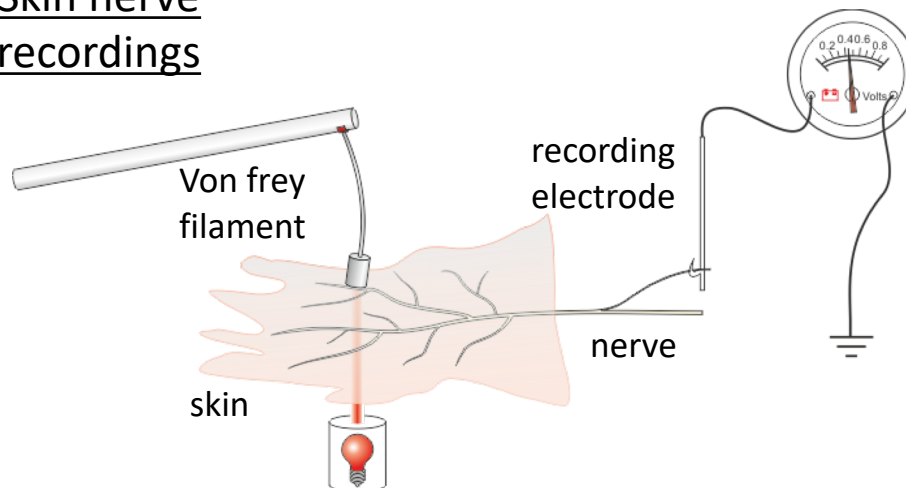
How to test nociception (1)

IN VITRO

Patch-Clamp



Skin nerve recordings

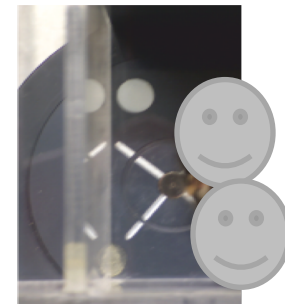


IN VIVO

Mechanical stimuli: Von Frey test



Heat stimuli: Hagreaaves test



How to test nociception (2)

Mechanical stimulation:

- pin-prick;
- pressure;
- Mechanical stimulation of the muscle or the viscera

Pin-prick (Von Frey)

QST pressure pain threshold measurements



→ Mechanical cortical stimulation can be revealed by fMRI

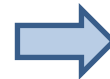
Thermal stimulation:

- Cold stimulation;
- Freeze lesion (-20°C);
- Contact heat;
- Burn injury

Chemical stimulation:

- capsaicin;
- Mustard oil

In vitro studies

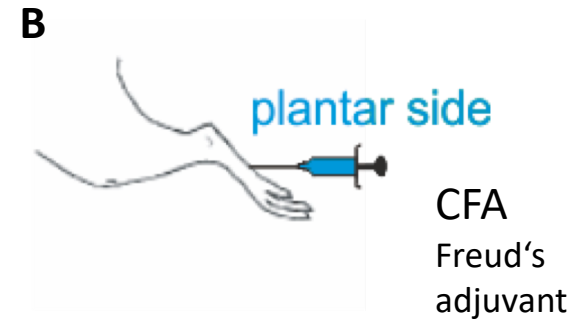
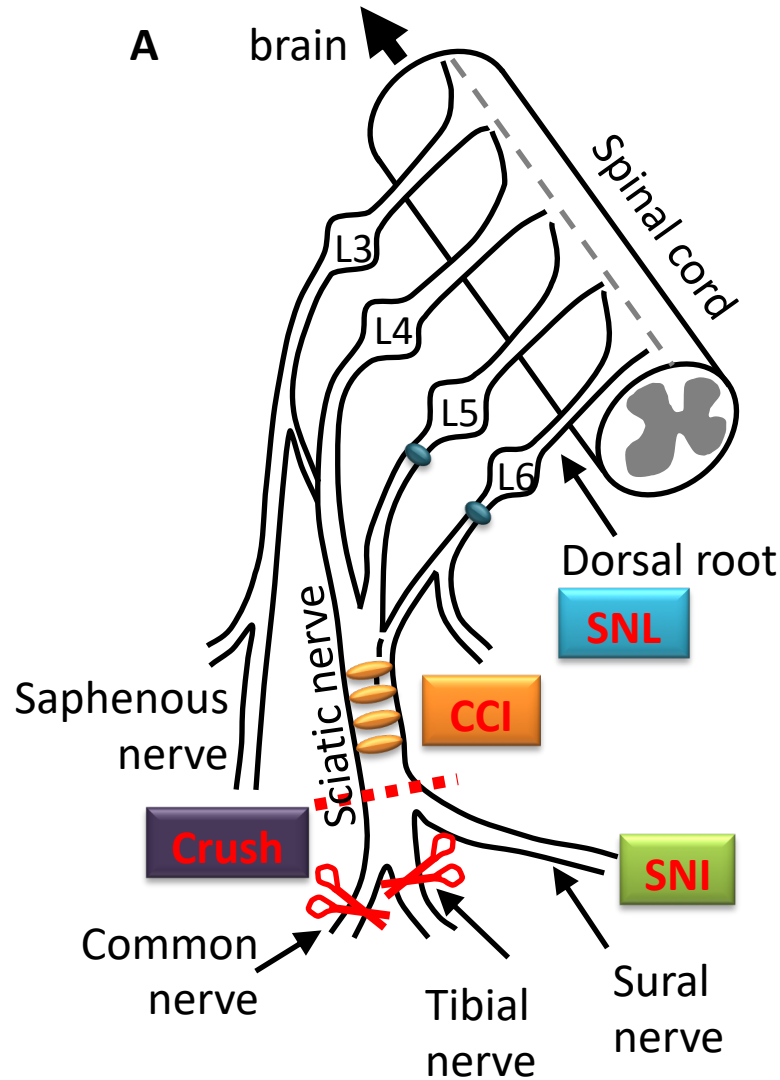


Animal Models



Human studies

Pain models



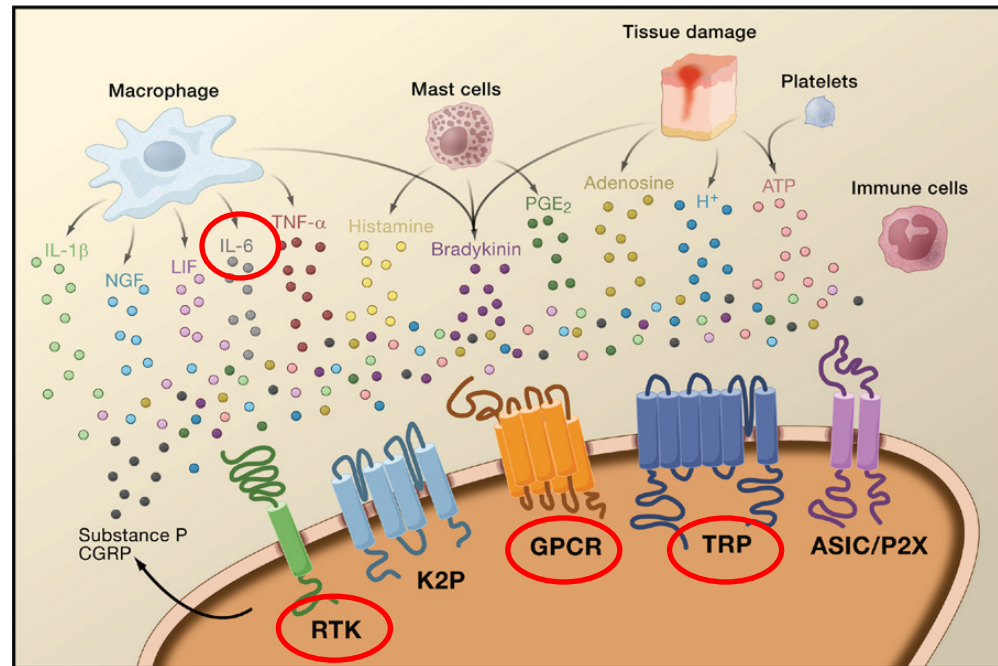
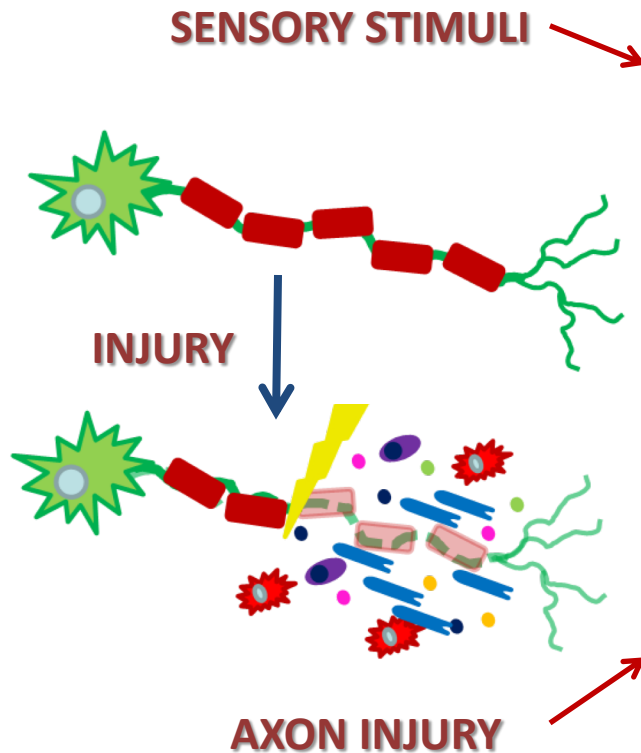
Types of Pain

1. Physiological (related to tissue damage)
2. Inflammatory (immunological)
3. Neuropathic (can be associated with 1 & 2)

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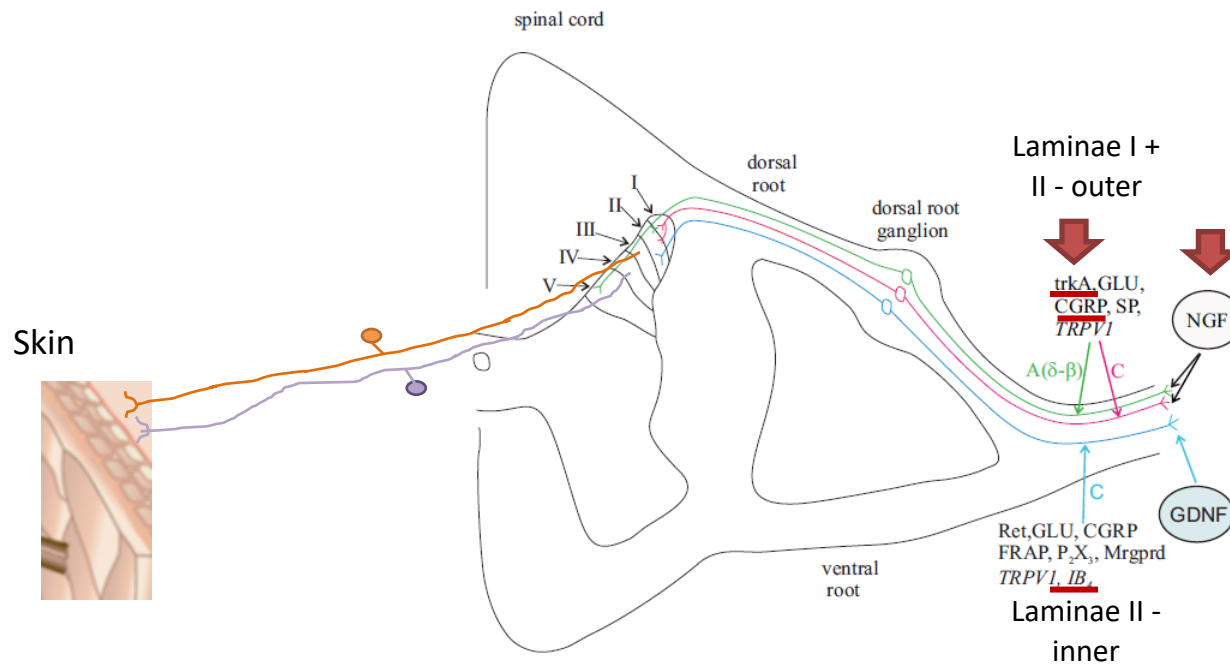
Signal transduction in nociception



nociceptor

Basbaum, *Cell* (139); 2009

Neurotrophins - NGF



Modified from
Fein, *Nociceptors and the perception of Pain*; 2012

Channels (1)

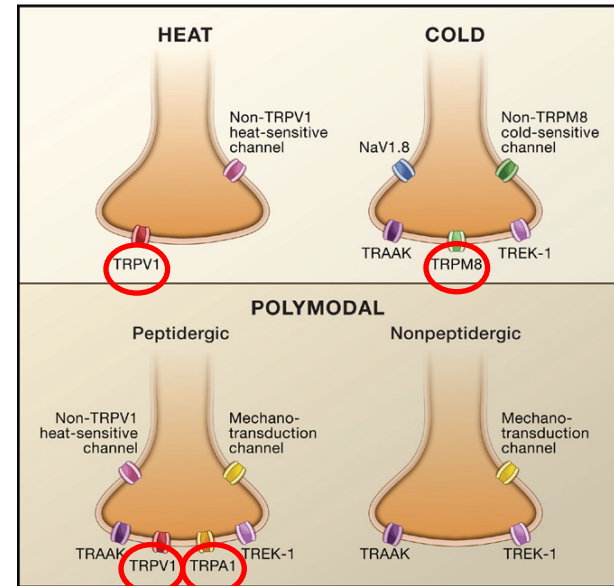
TRP channel family:

- **TRPC** (canonical),
- **TRPV** (Vanilloid), - TRPV1
- **TRPM** (Melastatin), - TRPM8
- TRPP (Polycystin),
- TRPML (Mucolipin),
- **TRPA** (Ankyrin) - TRPA1

Heat stimulus:

TRPV1 – activation 43°C

capsaicin



Heat stimulus (C- and Aδ fibers):

TRPV1 – thermal activation of 43°C

TRPV2, 3, 4 – same range of T°C and very hot (>50°C) and warm (mid 30°C)

Cold stimulus (Aδ fibers) : TRPM8 (30 – 10°C)

TRPA1 (<15°C)

Mechanical stimulus (C- and Aδ fibers):

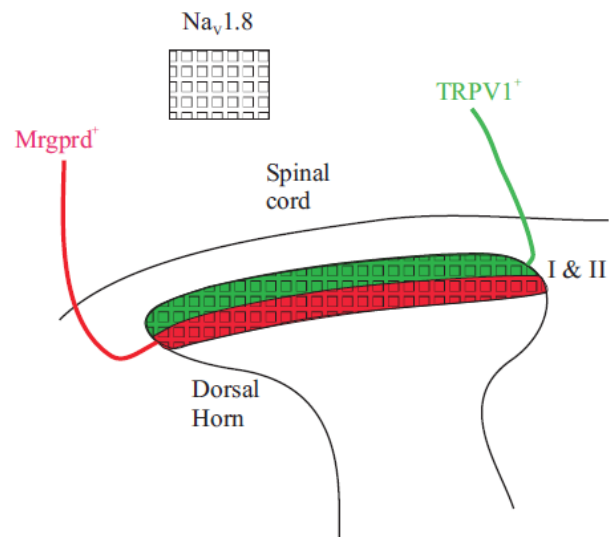
TRPV2 – medium and large diameter Aδ fibers

TRPA1 – mechanical pressure

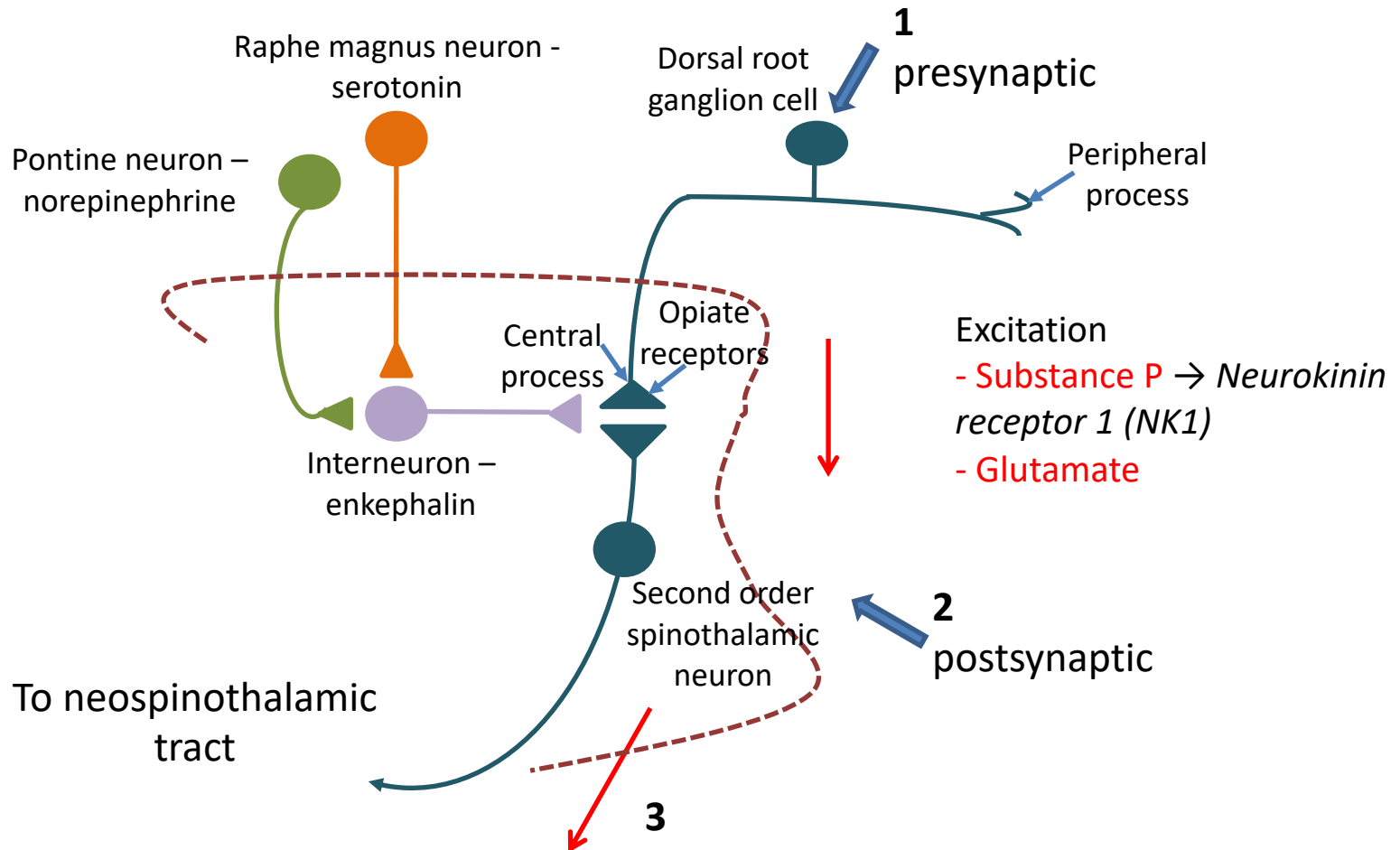
Channels (2)

Voltage –gated **sodium** and potassium channels

- Nav1.8 and Nav1.9 (TTX-resistant) → human pain disorders
- Patients with loss-of-function mutations → unable to detect noxious stimuli → suffer injuries
- Gain-of-function mutations (Nav1.7) leads to hyperexcitability → erythromelalgia and extreme pain disorders, intense burning sensations



Which are the neurotransmitters involved in the pain pathways?



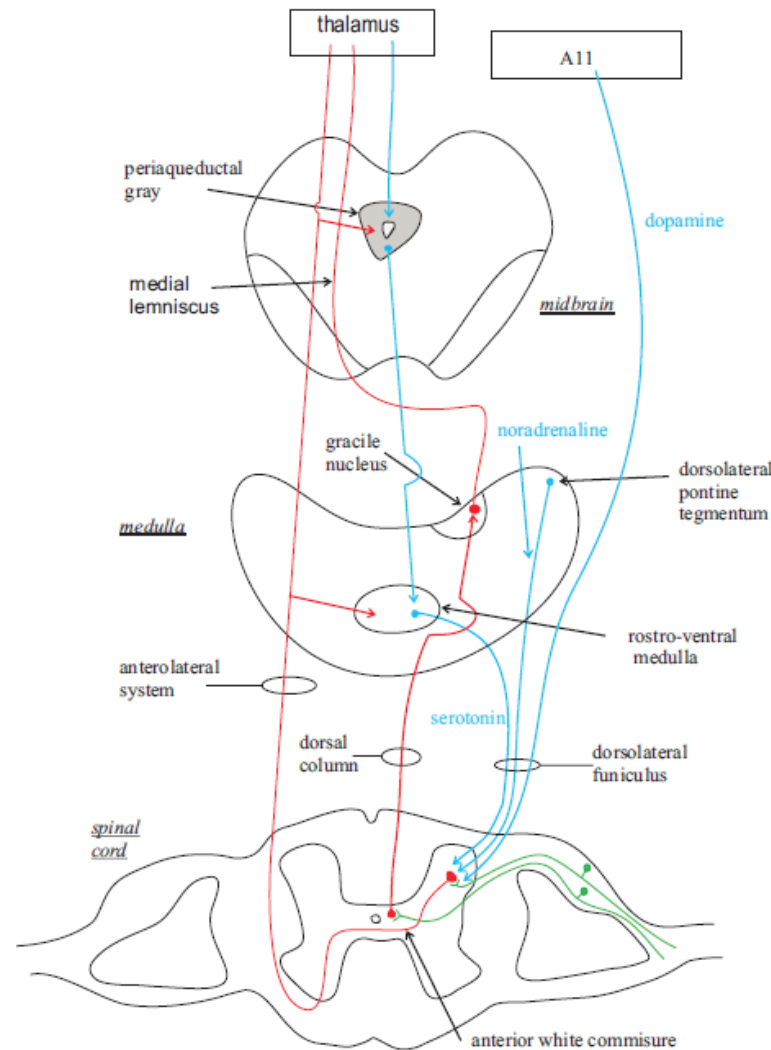
Substance P

- Family of **tachykinins**;
- Undecapeptide (11 aa);
- Endogenous **receptor**: NK1, family GPRCs;
- **Localization**: nerve endings, in synaptic vesicles, in some neurons of dorsal root ganglia
- **Release** : released from nerve endings and in the dorsal horn of the spinal cord. The release is calcium dependent. GABA and glutamic acid may be involved in the release of SP.
- **Functions**: **neurotransmitter** involved in
 - nociception
 - vasodilation in the periphery
 - wound healing

Ascending and descending pathways modulating pain sensory mechanisms

Ascending pathways:
Neospinothalamic tract

To the **thalamus** and
somatosensory **cortex**



Descending pathways

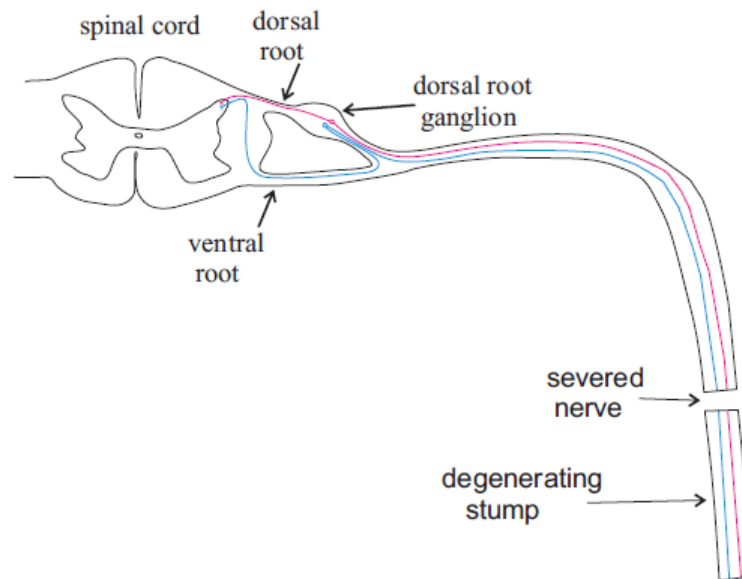
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Neuropathic pain

- Acute or nociceptive pain is a necessary protective mechanism
- In contrast **chronic pain** serves no obvious survival or helpful function
- Neuropathic pain is one type of chronic pain with **evidence of a lesion or damage** to the primary nociceptors (e.g. NOT migraine)




Specific pain syndromes

- **Hyperalgesia:** enhancement sensation of pain, which results from tissue damage. Endogenous substances like prostaglandins, histamine, substance P, serotonin and bradykinin. (usage of ASPIRIN® for therapy)
- **Causalgia** (Sympathetic Dystrophy Syndrome): burning sensation by increased sympathetic efferent activity after peripheral injury
- **Neuralgia:** severe persistent pain in cranial or spinal nerve. E.g. trigeminal neuralgia → interruption of trigeminal nerve or anticonvulsant administration
- **Thalamic pain syndrome:** lesions in the posterior thalamus cause chronic pain → etiology poorly understood
- **Referred pain:** pain arising from deep visceral structures and felt on the surface of the body.
- **Phantom pain:** overactivity of the dorsal horn neurons → false feeling

Pain therapy

- Physical approach
 - Rehabilitation
 - Acupuncture
 - Light therapy
- Psychological approach
 - Hypnosis
 - Cognitive behavioral therapy
- Medications
 - Non-opioid analgesics (Ibuprofen)
 - Opioids analgesics (Morphine)
 - Antidepressants drugs (Gabapentin)
 - Cannabinoids (medical marijuana)
- Interventional procedure



IMPROVED
LIFE QUALITY
of the PATIENTS