Smärtfysiologi


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Kongenital analgesi

As kids, they bit off their tongues and jumped from landings and trees, breaking arms and legs

Paul said he also used to push the swing seat away from him. "I'd let it come back and smash my face. I broke my nose and teeth.“

Paul remembers that he used to put his hand on the top of a stove - "just because I liked the sound of it sizzling."

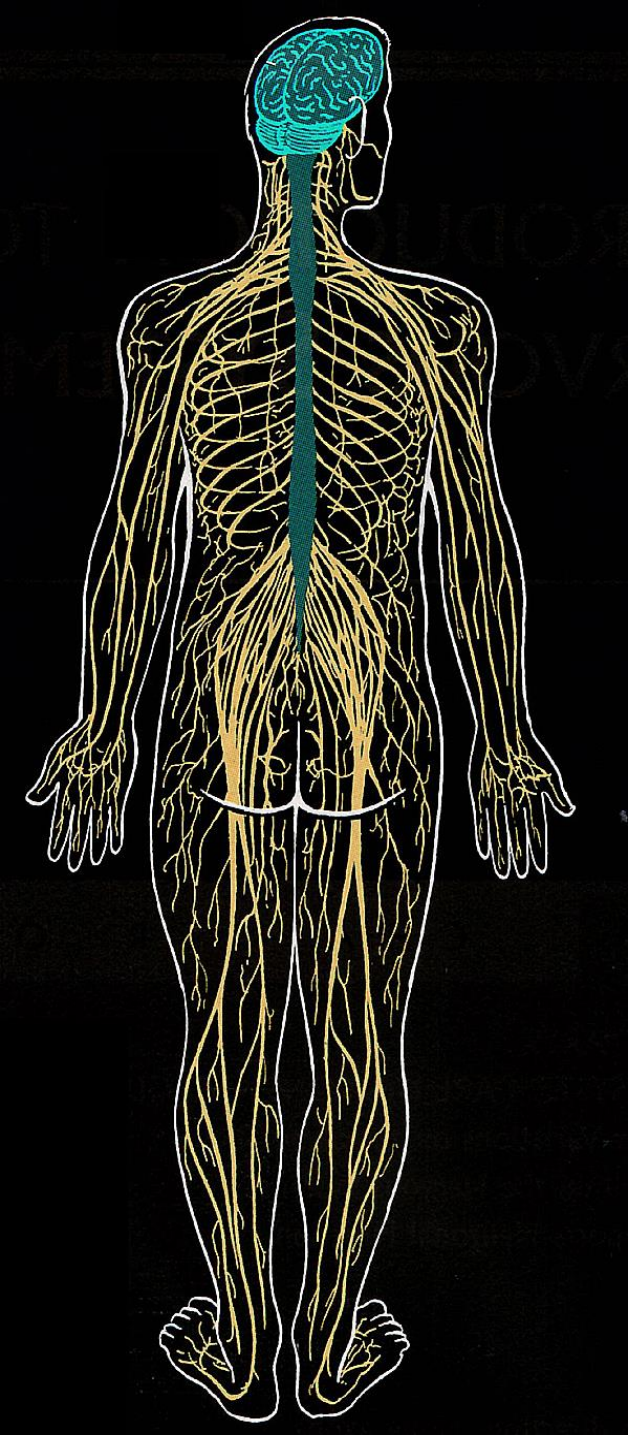
He still has a scar down his back. "I leaned against a radiator." Feeling no pain, "I pushed away and I was stuck. I ripped a chunk of my flesh off."

Paul's baby sister Amanda, who also felt no pain, died of septicemia when she bit off her tongue and contracted an acute bacterial infection.

In the hospital, "He broke his foot, and they didn't discover it until a day and half later. They had no idea when or how it happened.

"Normal people, when they get muscle pain, lactic acid flows in," said Paul. "That causes you to get tired and sore, and you sit down. "We just kept on running or whatever. We played a lot harder, until our bones would physically give out. ... Our muscles have become useless.”

"Because of the way we damaged our joints, we gave ourselves arthritis. I don't want to loose control over my hands. I can barely pick up a cup, and it's only going to get worse.”



Varför skilja på nociception och smärta?

Pain - definition

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- A person's report of an experience as pain should be respected.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain

Nociceptive pain (nociceptiv smärta)
Pain that is due to the activation of nociceptors.

Neuropathic pain
Pain caused by a lesion (skada) or disease of the somatosensory nervous system.

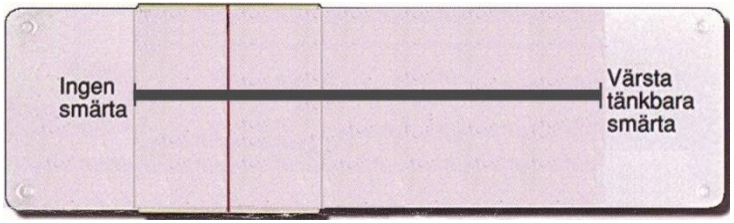
Nociplastic pain
Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

Alltså: Smärta är inte alltid nociceptiv och aktivering av nociceptorer leder inte alltid till smärta.

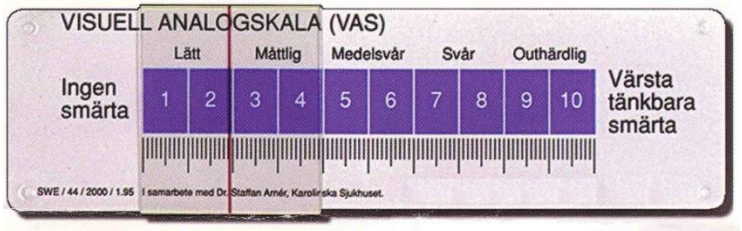
Kvantifiering av smärtupplevelse

VAS = visuell analogskala

Framsida
(patient)



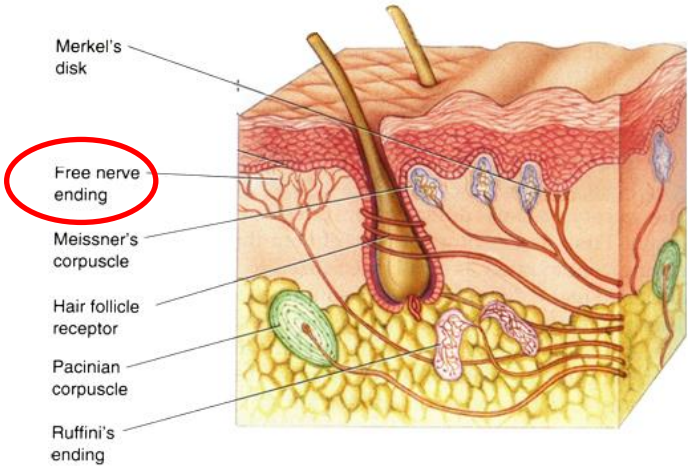
Baksida
(undersökare)



Noxious stimulus (nociceptivt stimulus) (nocere = att skada)
A stimulus that is damaging or threatens damage to normal tissues

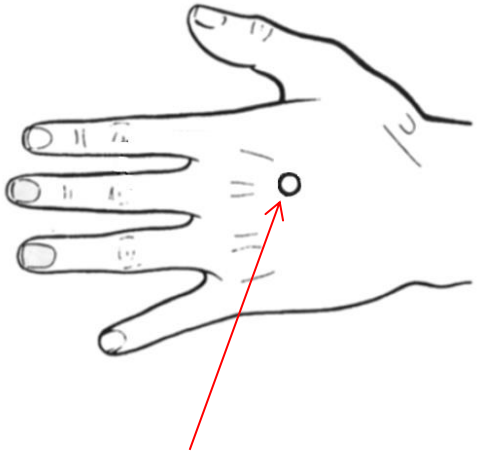
Nociceptor
A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.

Nociception
The neural process of encoding noxious stimuli.



Nociceptorer finns i
Hud, slemhinnor, muskler
bindväv, ligament, ledkapslar
ben, blodkärl, viscera, tänder …

Nociceptorer finns inte i
CNS, ledbrosk



Exempel på receptivt fält

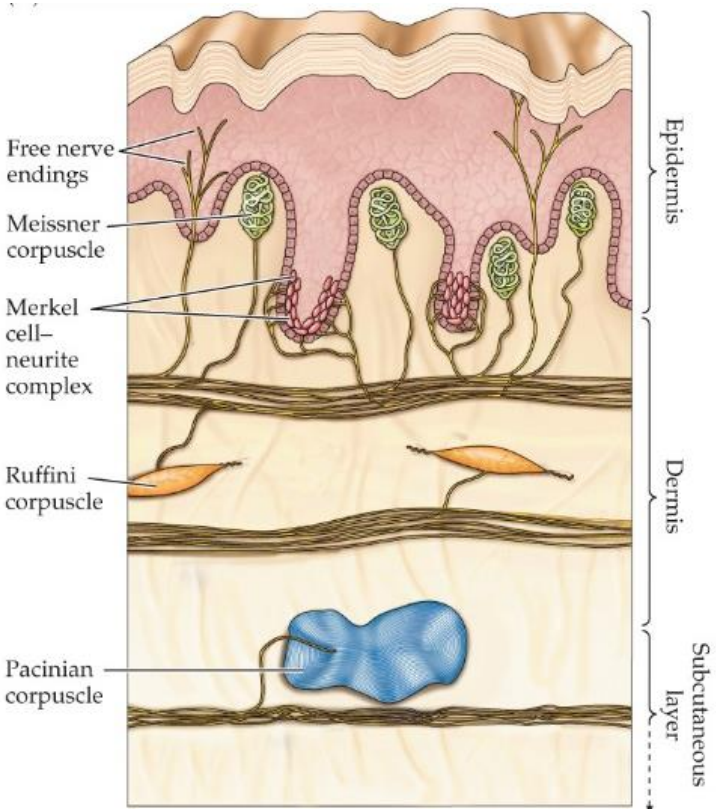
Stimuli

Mekaniskt känsliga

Temperaturkänsliga
(smärtsam hetta/kyla)

”Kemiskt känsliga”

Huden innehåller olika receptorer



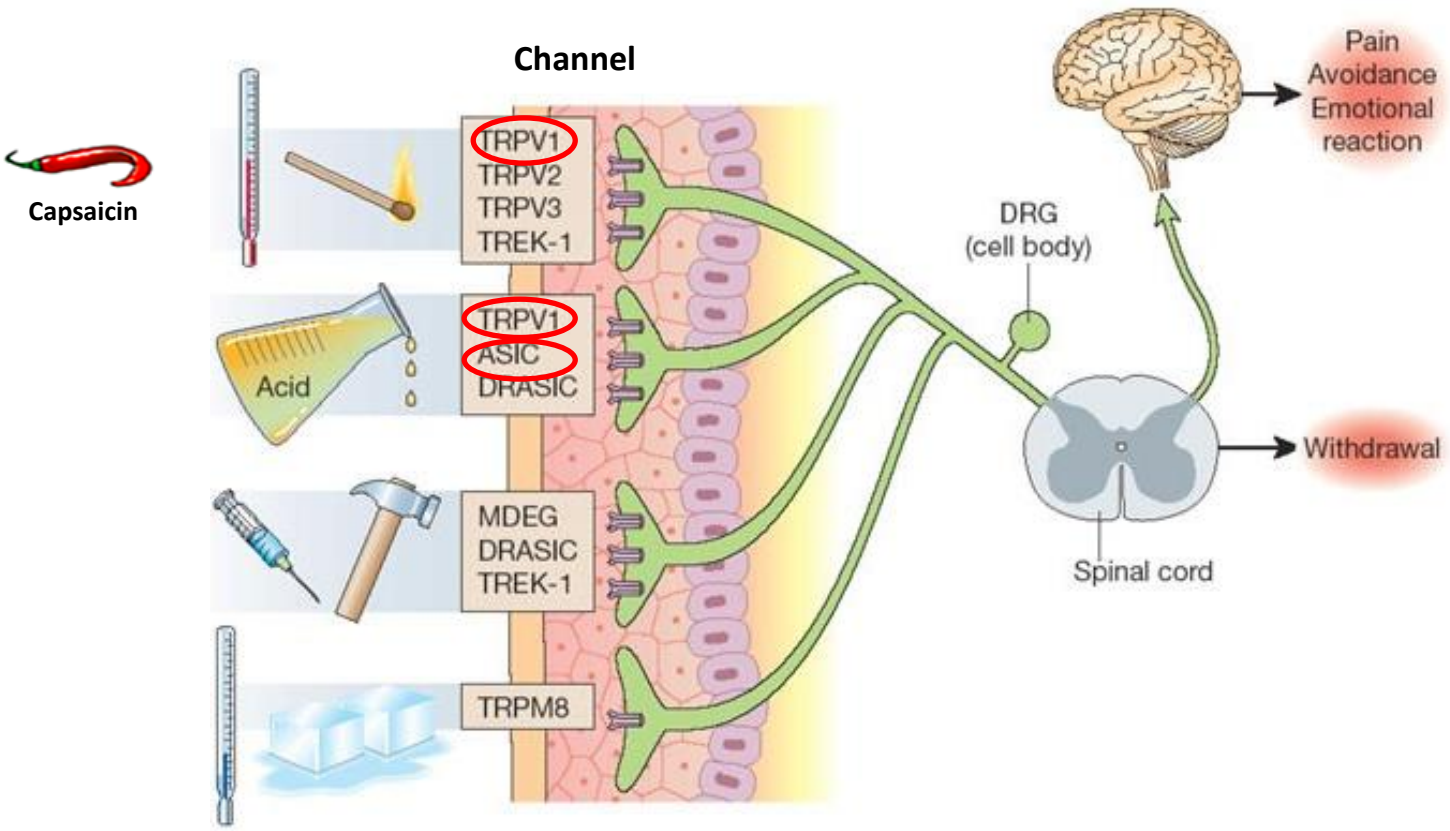
Tjocka myeliniserade (Ab) Beröring

Tunna myeliniserade (Ad) Temperatur
- kyla
- Nociception (smärta)

Omyeliniserade (C)
Temperatur,
-värme
-kyla
-Nociception (smärta, klåda)

- Affektiv beröring (C-taktil, CT)

Jonkanaler och nociceptiv smärta



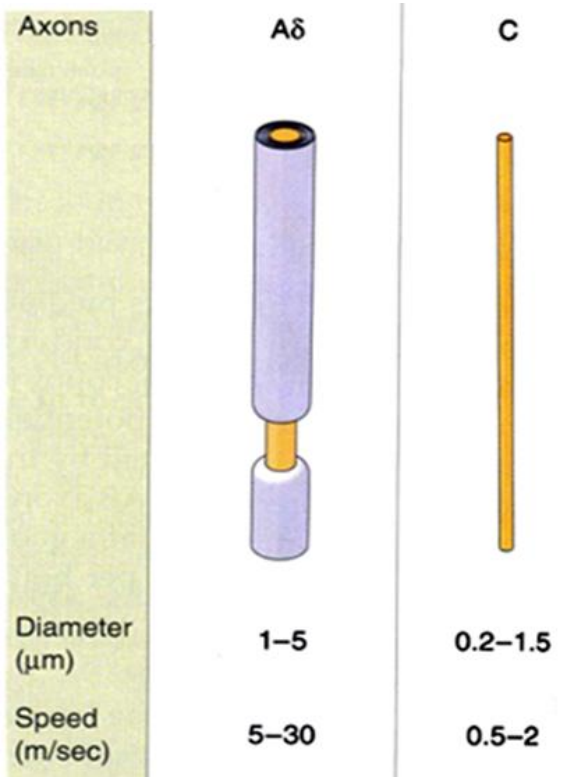
Nociceptorer är utrustade med en mängd olika membranbundna jonkanaler och receptorer, såsom till exempel ”transient receptor potential” (TRP)-kanaler (ex TRPV1), syrakänsliga jonkanaler (ASIC), purinerga receptorer(P2X) samt olika G-proteinkopplade eller kinas-länkade receptorer (t.ex.bradykinin 2-och prostaglandinreceptorer).

TRP – transient receptor potential

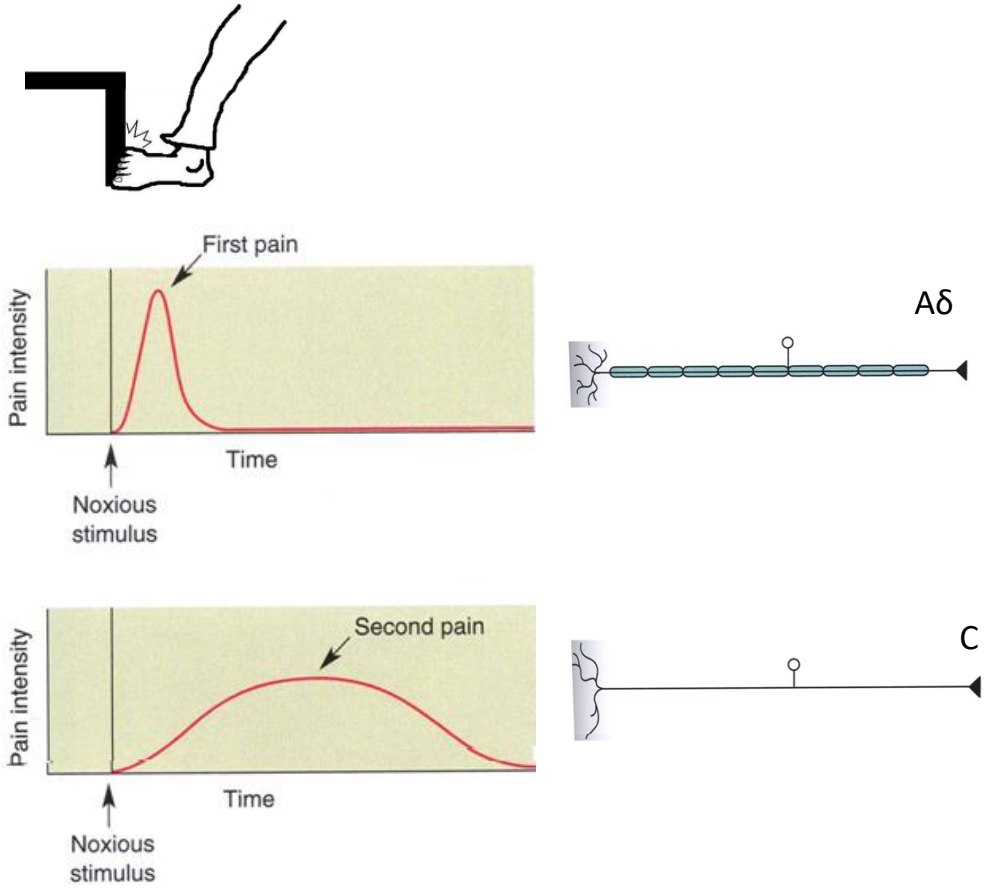
ASIC - acid sensing ion channel

V - Vanilloid

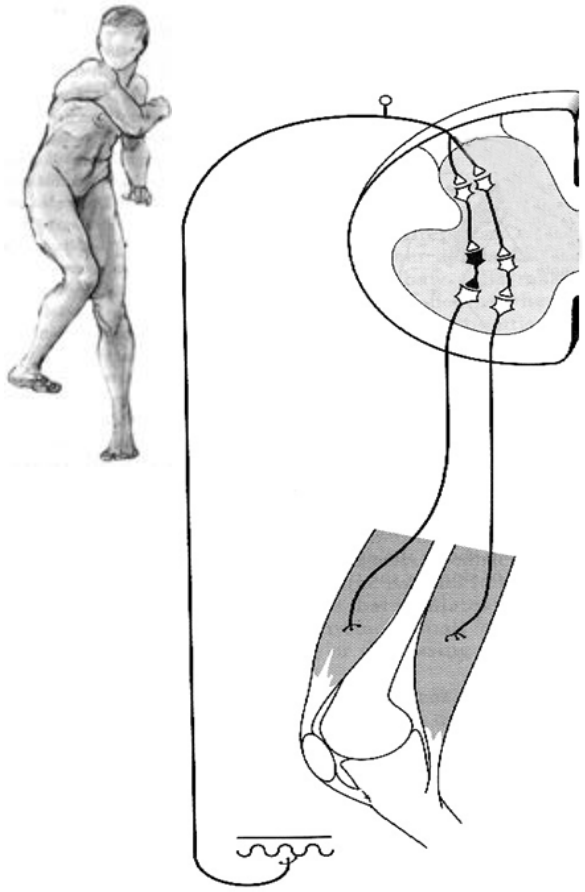
Axoner från nociceptorer

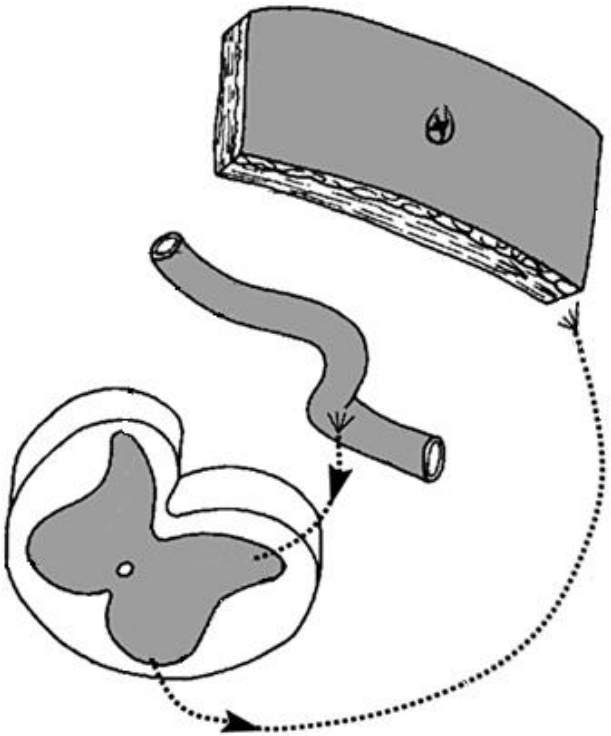


”Dubbla smärtupplevelsen”

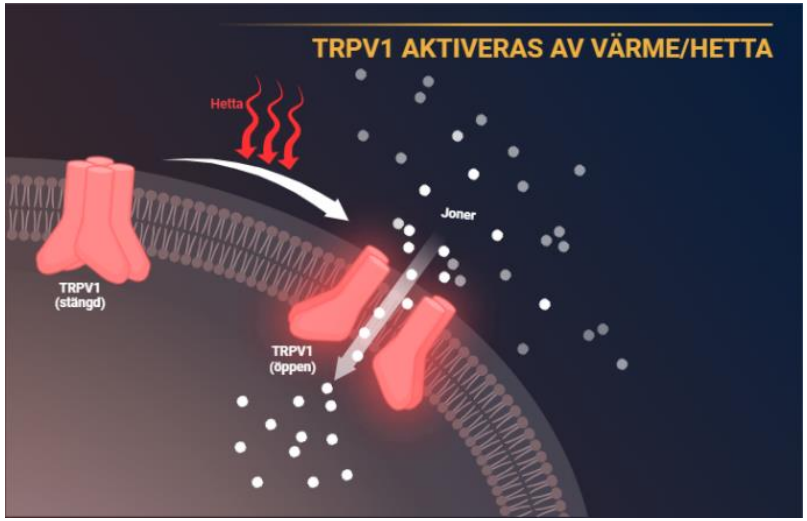


Exempel på nociceptiva reflexer

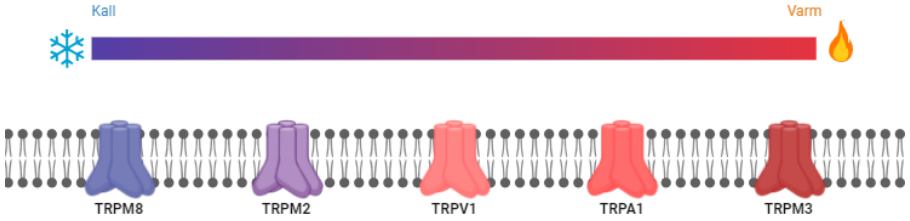




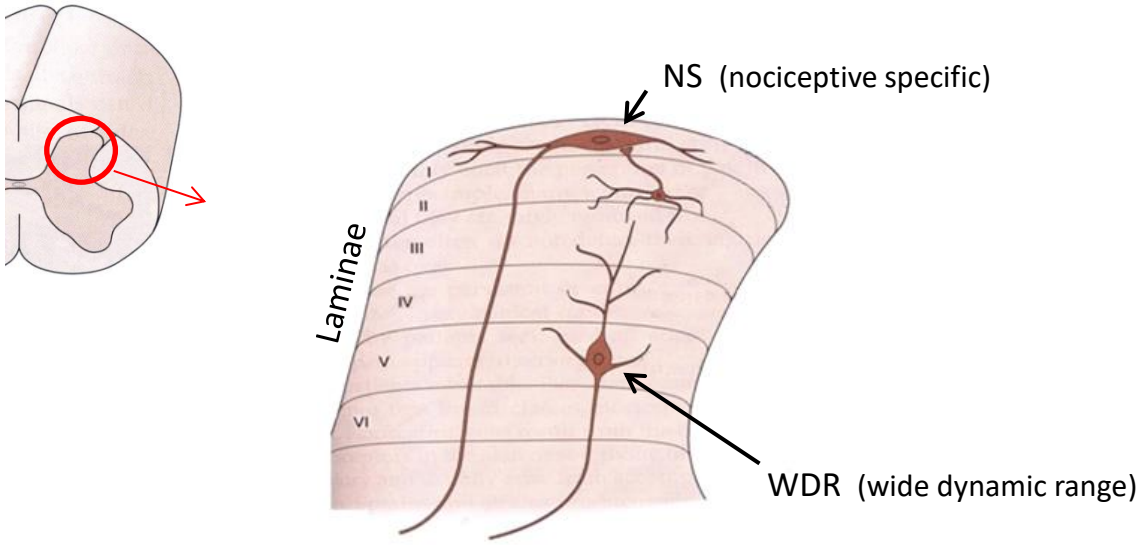
Exempel på jonkanal i nociceptorer
TRPV1 (Vanilloidreceptorn)



- Icke-selektiv katjonskanal (släpper igenom positiva joner)
- *Aktivering:* Capsaicin (chilipeppar), leukotriener, Hetta (>43º), H^+ (pH <6)
- *Sensitisering:* H^+, ATP, Bradykinin, Prostglandiner (sänker temp.tröskeln)

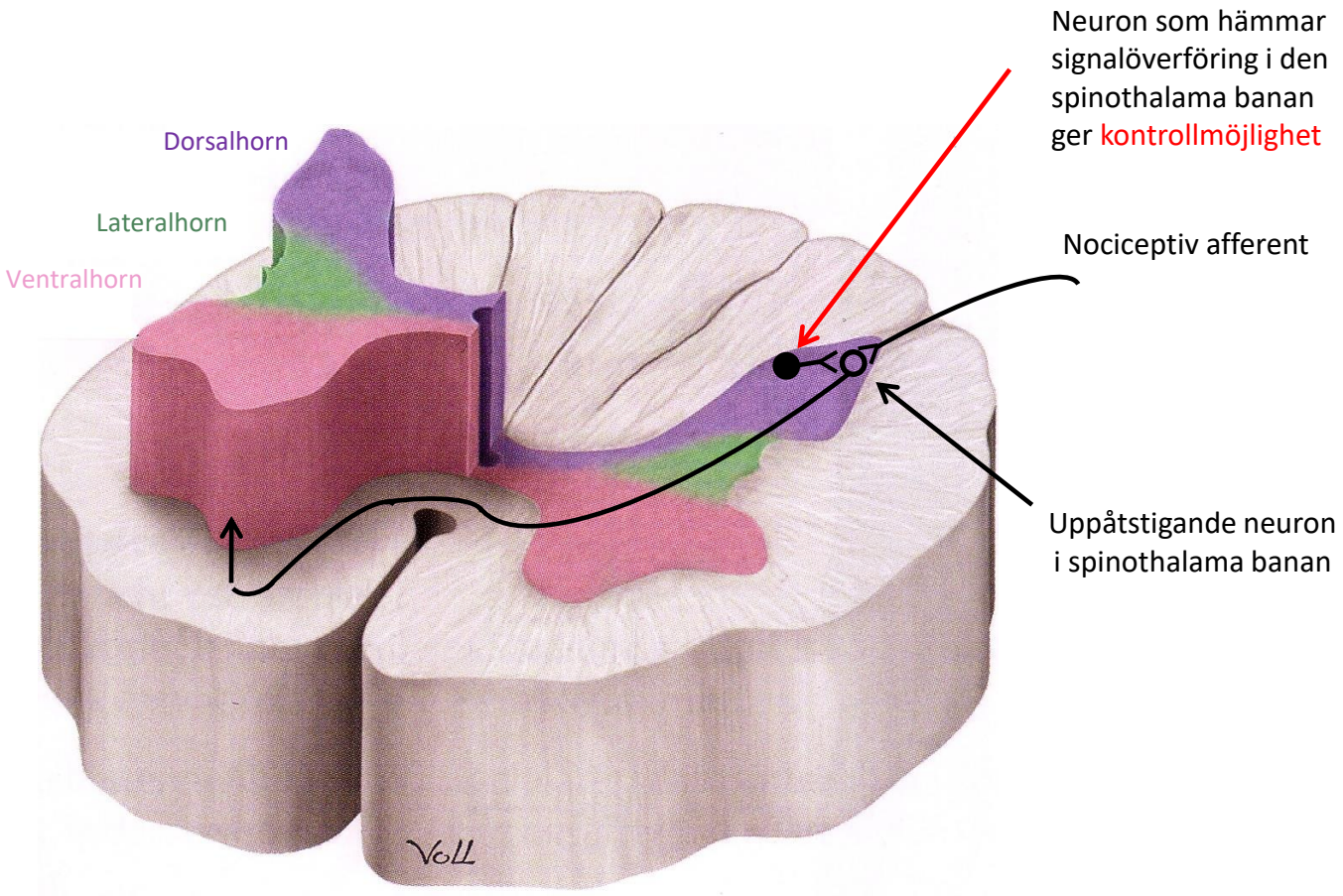


Dorsalhornet



Nociceptivt specifika (NS) **neuron** (Lamina I), små receptiva fält (hud)
Wide dynamic range (WDR) **neuron** (Lamina V), stora receptiva fält (hud), får också inflöde från tryck- och beröringsafferenter (Aβ-fibrer) samt från viscerala smärtafferenter

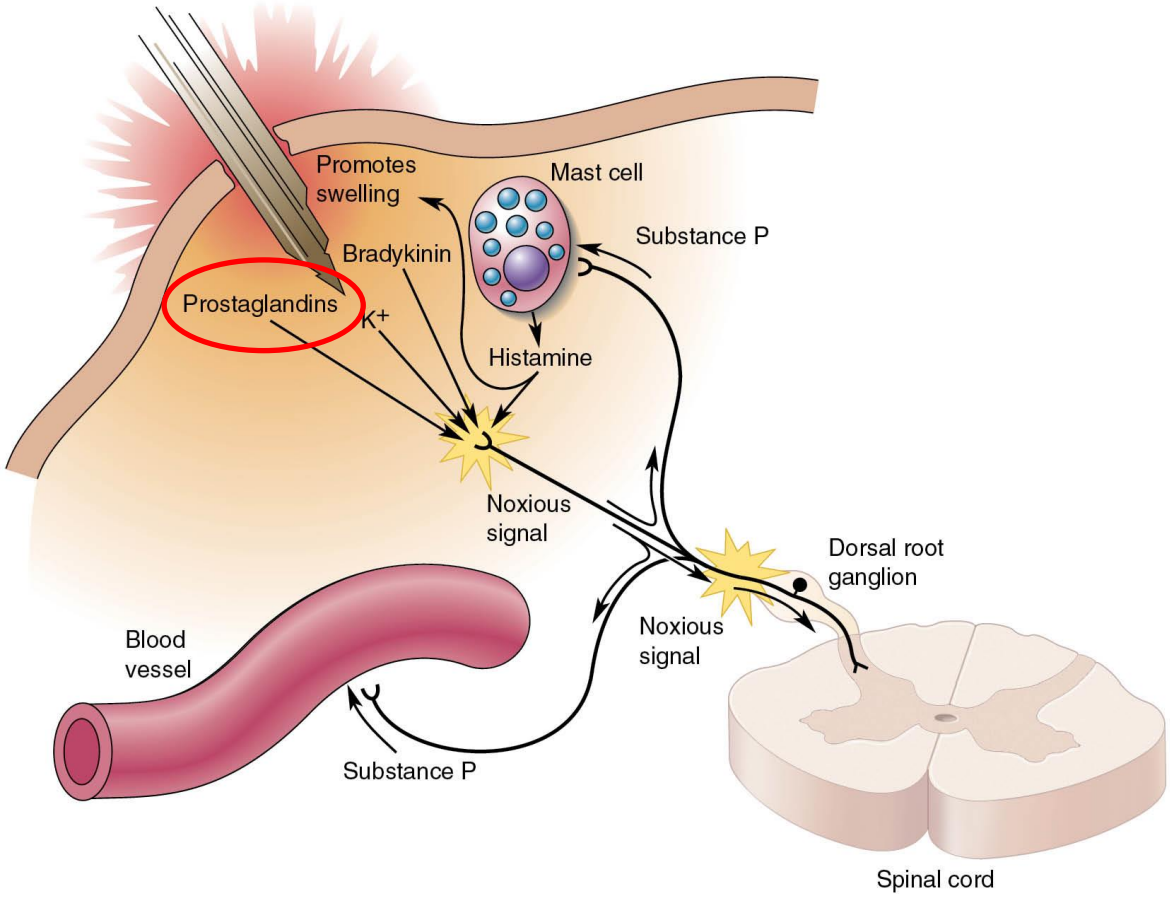
Kontroll av signalöverföring i uppåtstigande banor



Inflammatoriska mediatorer påverkar nociceptorer

Perifer sensitisering

= Increased responsiveness and reduced threshold of nociceptive neurons in the periphery, to the stimulation of their receptive fields.



Inflammatoriska mediatorer påverkar nociceptorer

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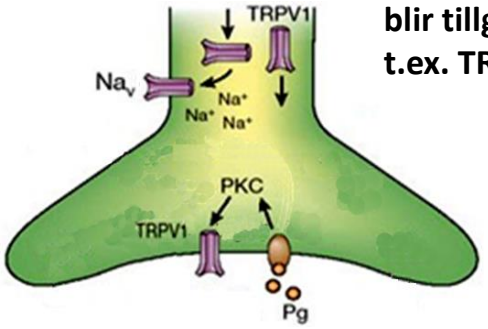
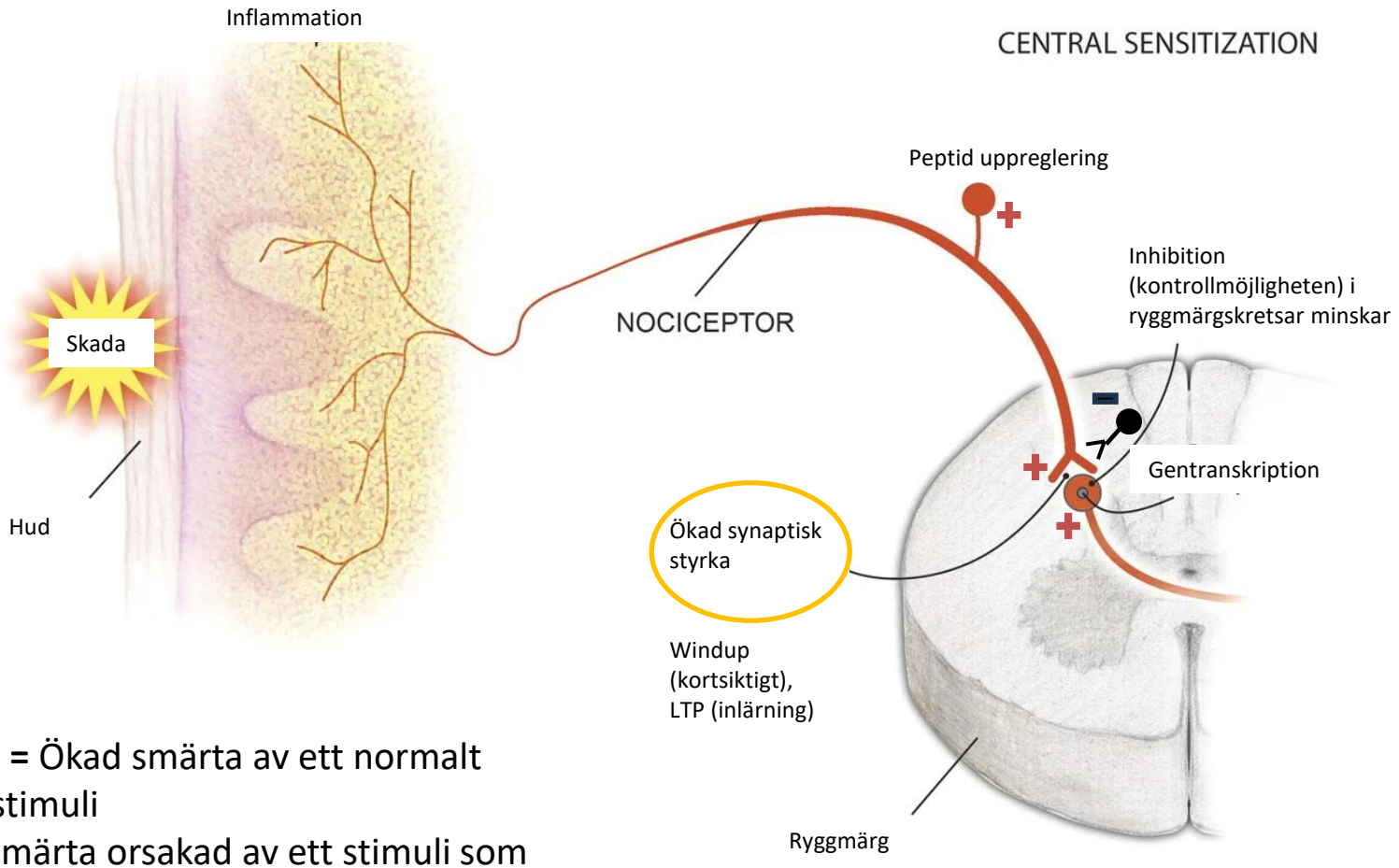
Fler vNa ger sänkt tröskel för aktions-potential



Fler jonkanaler blir tillgängliga, t.ex. TRPV1

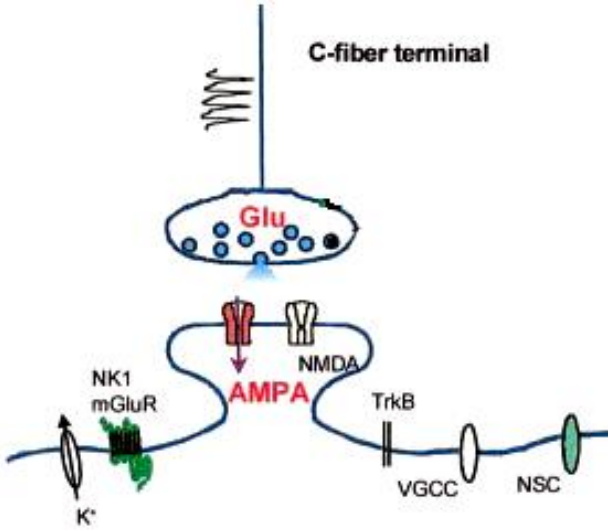
Jonkanaler blir lättare att aktivera

Synaptisk plasticitet i nociceptiva banor: Central sensitisering
(associerat med initiering och bibehållande av långvarig smärta)



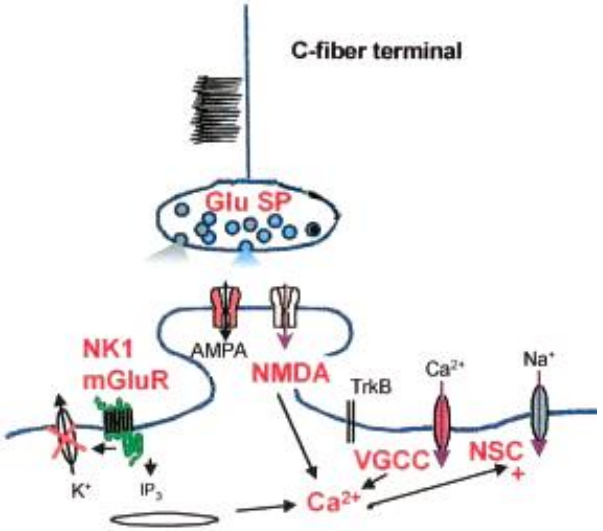
Hyperalgesi = Ökad smärta av ett normalt smärtsamt stimuli

Allodyni = Smärta orsakad av ett stimuli som normalt inte är smärtsamt (t.ex. beröring vid solskada)

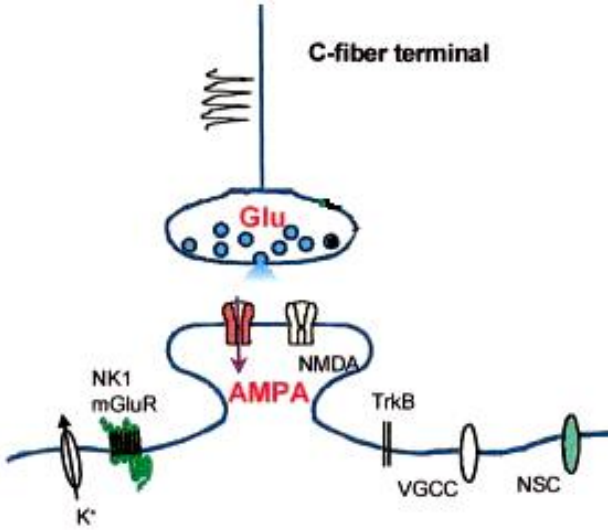


Nociceptivt dorsalhornsneuron

”Wind-up”

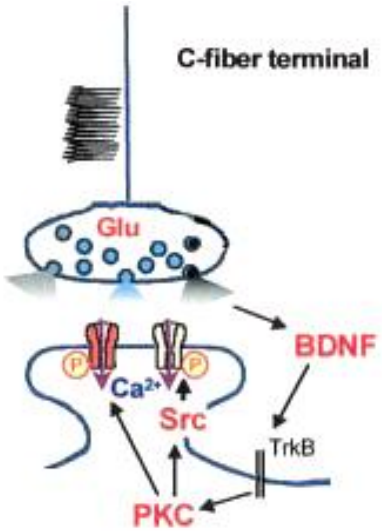


Intensiv aktivering av C-fiberaxonen → Frisättning av SP (substance P) som binds till NK1 receptorer, samt ökat glutamat ”spill over” med inbindning till mGluR (extra-synaptiska metabotropa glutamatreceptorer) → Stängning av kaliumkanaler → Ökad depolarisering → Öppning av spänningskänsliga Ca-kanaler (VGCC) samt öppning av NMDA kanaler. Den ökade Ca-koncentrationen öppnar NSC (non selective cation channels) → inflöde av Na-joner som ytterligare ökar depolarisationen. Nettoeffekt: Ökad fyrningsfrekvens i de nociceptiva dorsalhornsneuronen. En form av korttidsplasticitet.



Nociceptivt dorsalhornsneuron

Central sensitisering



Intensiv aktivering av C-fiberaxonet → Frisättning av BDNF (brain derived neurotrophic factor) som binds till TrkB (tyrosinkinasreceptor B) → Aktivering av PKC → Fosforylering av AMPA/NMDA-kanaler. Långtidsplasticitet

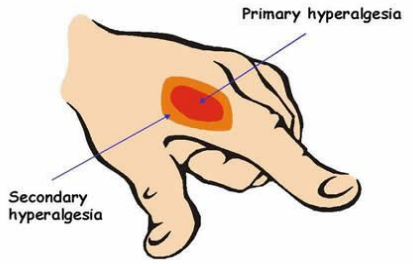
Detta initieras och/eller underlättas av flera olika extracellulära mediatormolekyler, varav många frisätts av gliaceller (astrocyter och mikroglia).

Konsekvenser av sensitisering

Hyperalgesi

- ökad smärta av en normalt smärtsam retning (increased pain from a stimulus that normally provokes pain)

- primär - i skadat område
- sekundär - i närliggande intakt vävnad



Allodyni

= smärta orsakad av en normalt inte smärtsam retning (pain due to a stimulus that does not normally provoke pain) t.ex.

- palpation av t.ex. inflammerad sena
- beröring av solskadad hud
- matintag vid inflammerad munslemhinna (infektion, brännskada)

Experimentell sensitisering

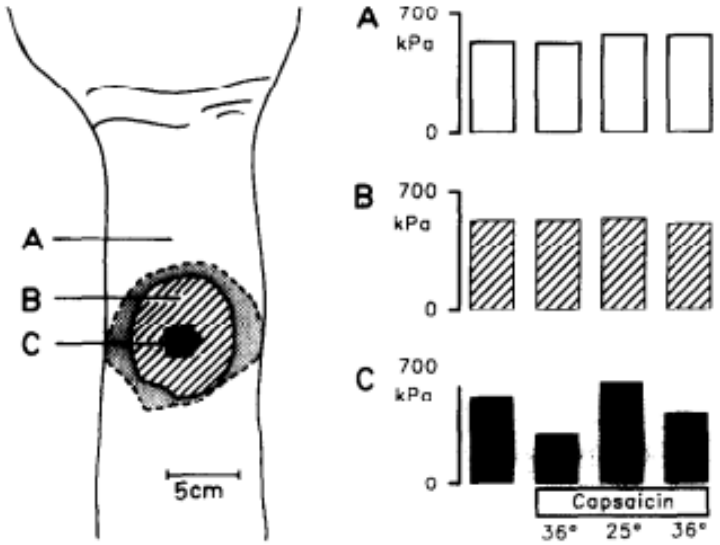


Fig. 3. Illustration of the spatial extension of mechanical hyperalgesia after 30 min of topical capsaicin application to the volar side of the forearm in 1 participant. The black area marks the skin exposed to capsaicin, and hatched and punctated regions illustrate the extension of mechanical hyperalgesia tested with cotton swabs or punctate stimuli. A, B and C mark the spots where pressure pain thresholds were tested, and the panel on the right side shows the corresponding values. Pressure pain thresholds drop only inside the skin area treated with capsaicin, and this effect is temperature dependent.

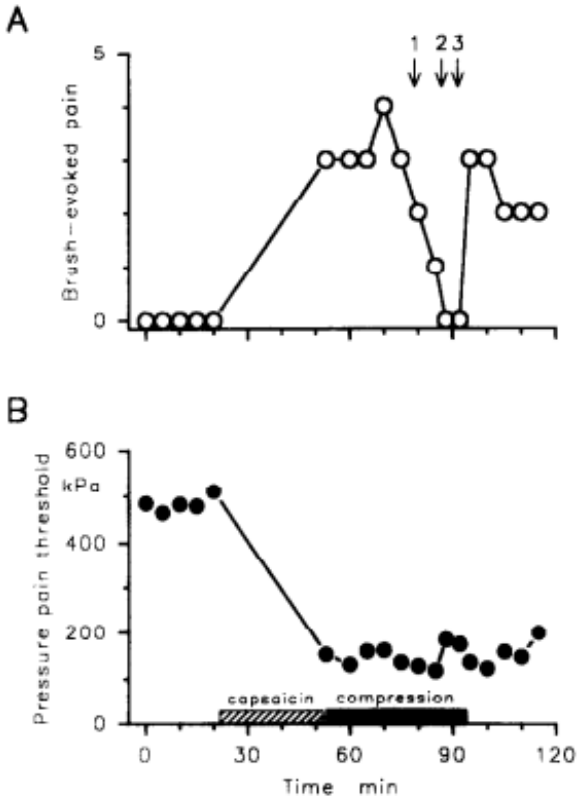
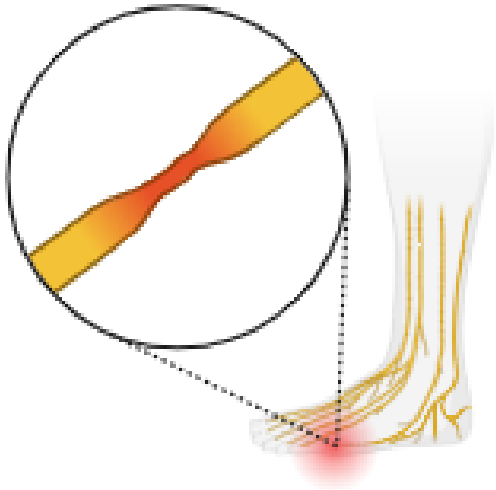


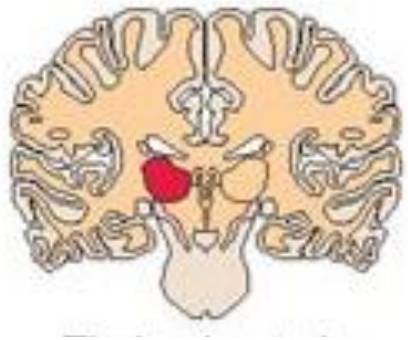
Fig. 6. Illustration of a nerve compression block experiment in 1 participant after application of 1% capsaicin solution for 30 min to the dorsum of the hand. Nerve compression started immediately after the first score of brush-evoked pain (A) and pressure pain threshold (B) had been obtained. Numbers in A indicate the stages of the nerve block in the surroundings of the capsaicin application site: 1 = sensation of touch starts to fade; 2 = sensation of touch eliminated; and 3 = loss of cold sensations.

Koltzenburg et al, Pain 1992

Neuropatisk smärta

(smärta orsakad av sjukdom i somatosensoriska nervsystemet)



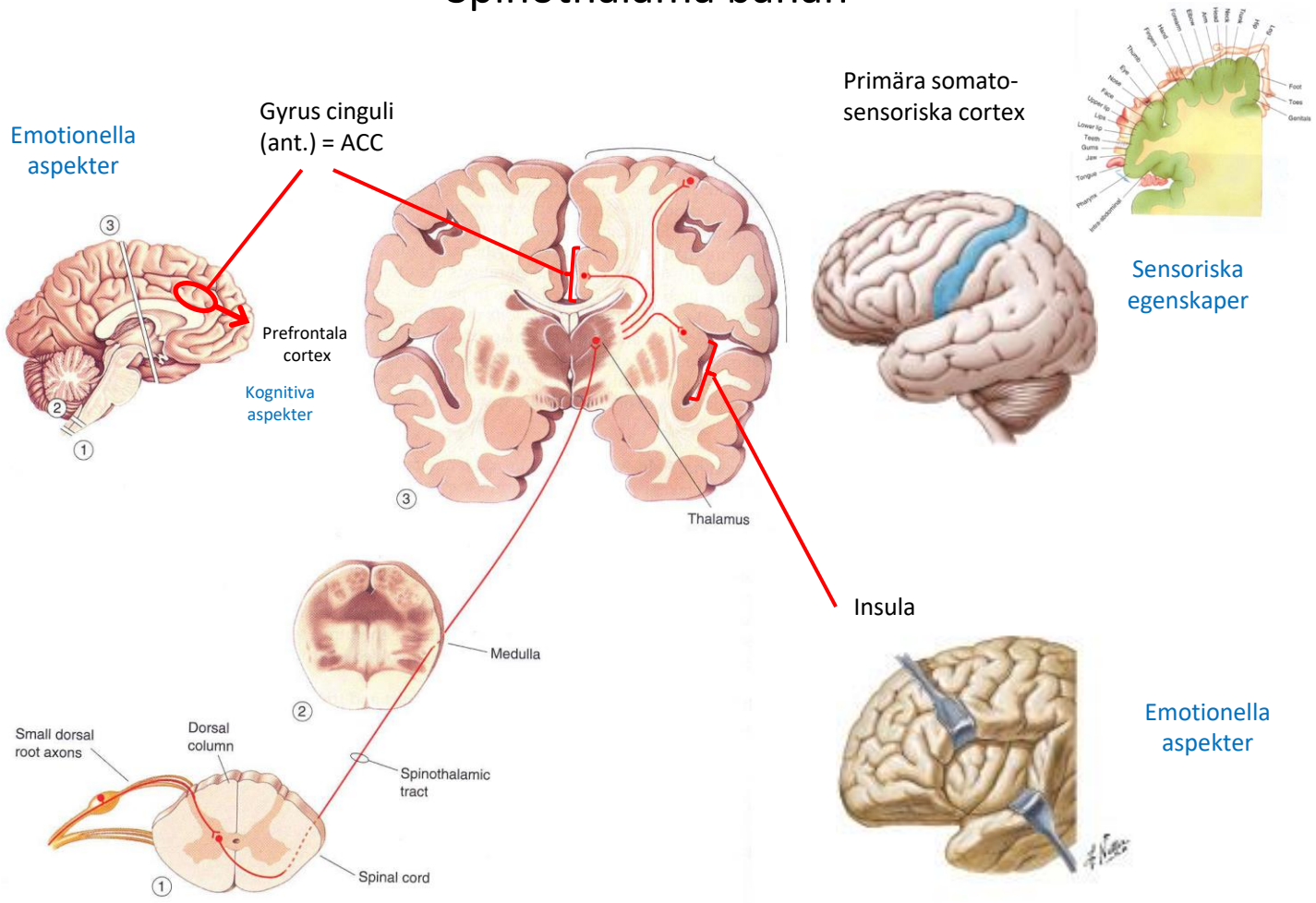


Thalamus stroke

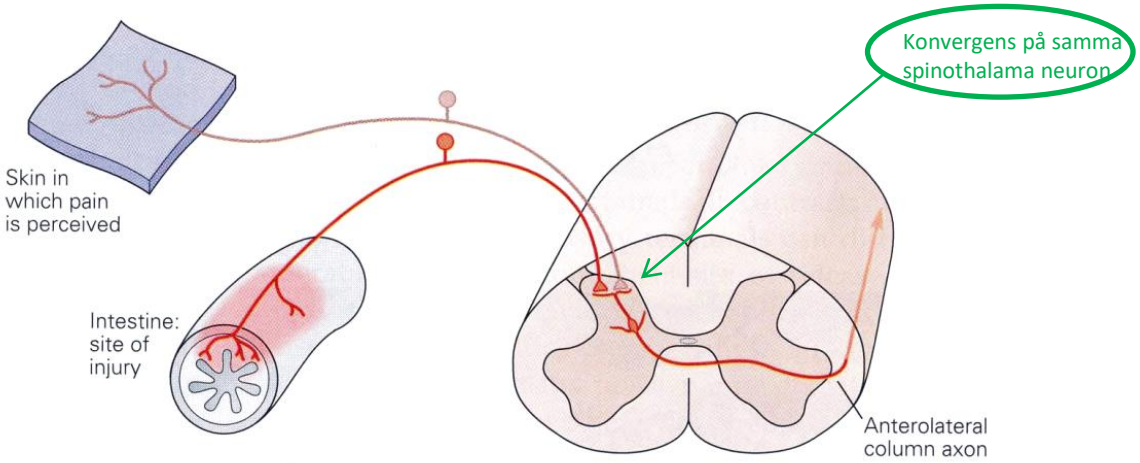
Hyperalgesi och allodyni är vanligt förekommande vid neuropatisk smärta

Smärtlindring exempel:
Antidepressiva (vissa sorter)
Antiepileptika
Na kanal blockerare
NMDA receptor antagonister
(Opioider)

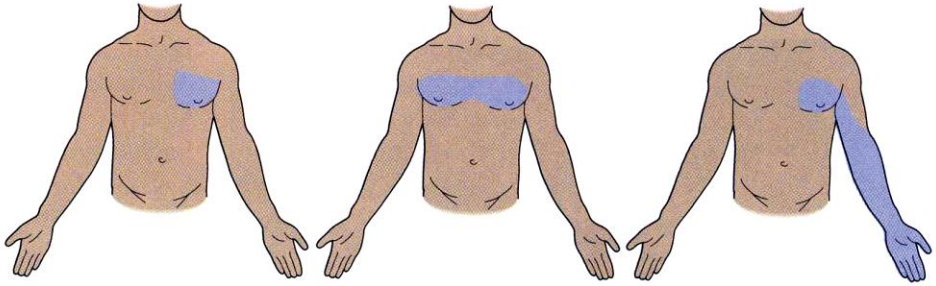
Spinothalama banan



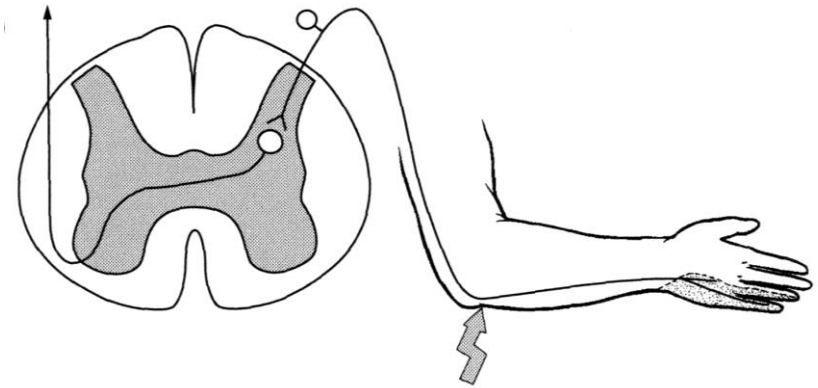
Refererad smärta



Ex ”kärlkramp” (angina pectoris)



Parestesi och projicerad smärta

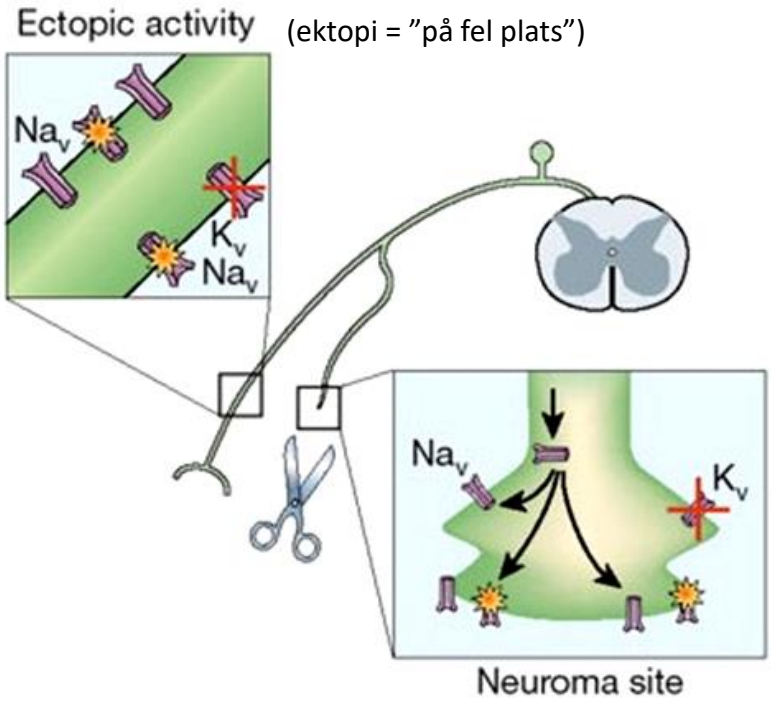


Aktivitet i ”hudnervsaxon” tolkas alltid av CNS som att receptorerna stimulerats dvs upplevelsen ”projiceras till” axonets innervationsområde.

Detta gäller även när aktionspotentialerna inte uppstår genom receptor-aktivering t.ex. vid elektrisk stimulering av axonet eller vid s.k. ”änkestöt”.

- Projicerad smärta (exempel på icke nociceptiv smärta)
- Parestesi = onormal känselupplevelse
- Fantomsmärta

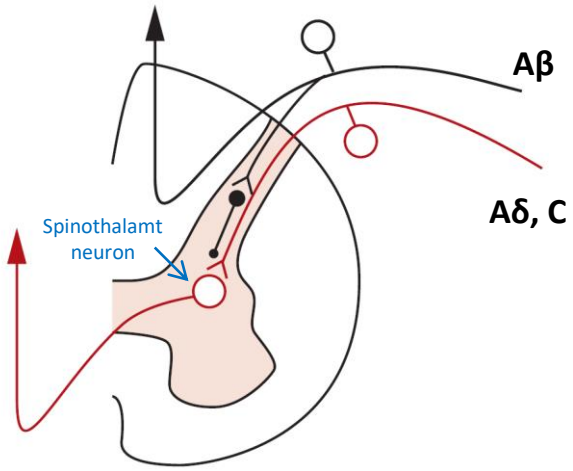
Neurom



Perifera nervskador kan resultera i mycket ”lättretade” s.k. neurom

Rekrytering av spänningskänsliga Na^+-kanaler

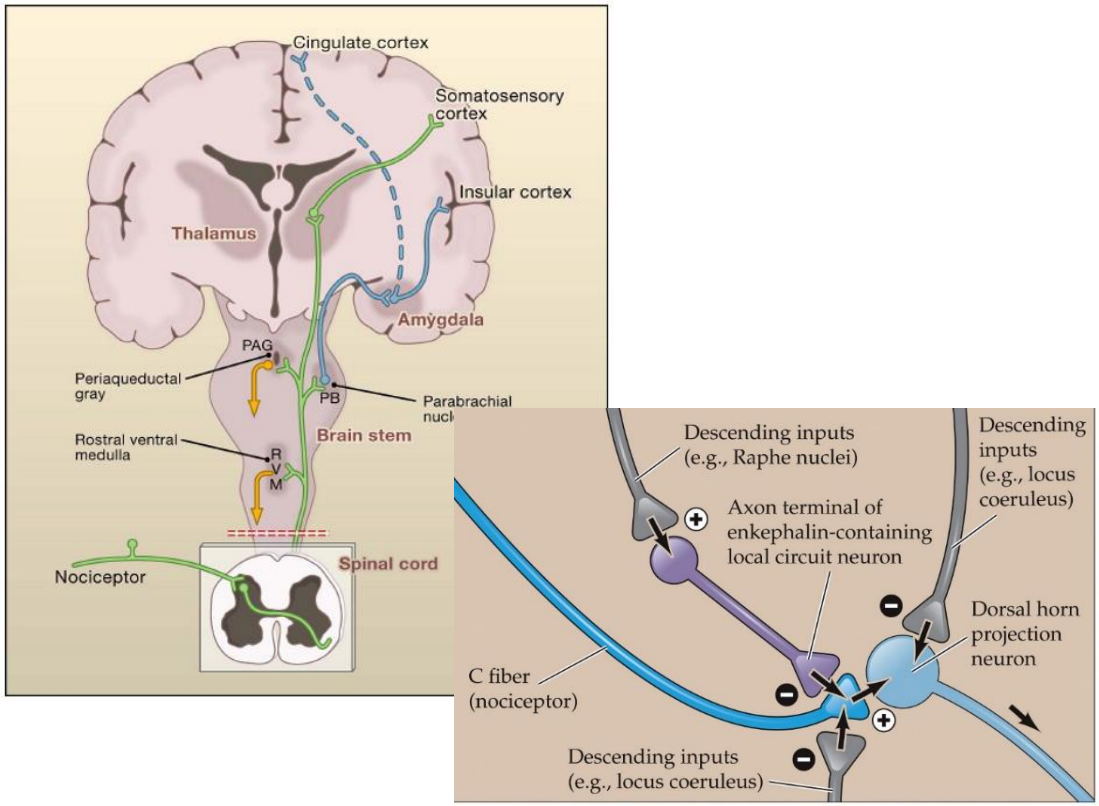
”Gate-kontroll” lokalt i dorsalhornet



Det spinothalama neuronet exciteras av smärtafferenter (Aδ-, C-fibrer). **Interneuronet** inhiberar det spinothalama neuronet vilket minskar smärtintensiteten. Interneuronet exciteras av **beröringsafferenter (Aβ)**. Balansen mellan dessa bestämmer interneuronets aktivitet och därmed inhibitionen av det spinothalama neuronet.

Exempel; att blåsa på brännskadad hud. Finns fler exempel på ”port mekanismer” i dorsalhornet, t.ex. nociceptorer hämmar klåda.

Kontroll från nedåtstigande banor



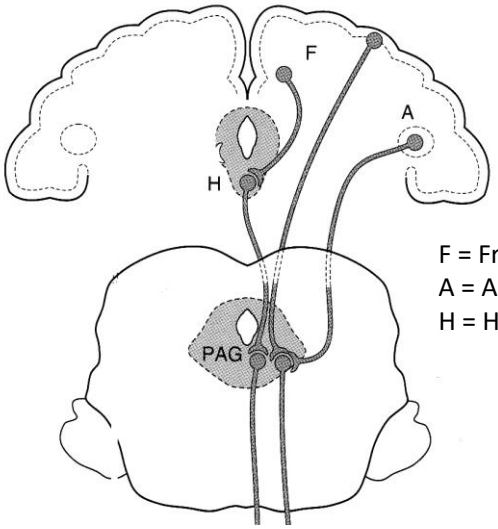
Serotonerga neuron i raphe-kärnorna aktiverar opioida (enkefalin) interneuron i dorsalhornet

Elektrisk stimulering i **PAG** (periaqueductal gray matter) i hjärnstammen ger smärthämning (djurförsök)

Aktiverar ett nedåtgående bansystem som i dorsalhornet hämmar överföring i spino-thalama banan. Neuronen i PAG projicerar först till raphe-kärnorna medialt i hjärn-stammen där de har kontakt med serotoninerga neuron. Neuronen i raphekärnorna projicerar sedan ner till ryggmärgen och aktiverar där opioida inhibitoriska neuron, som hämmar överföringen i den spinothalama banan.

Hur aktiveras PAG ?

Nedåtstigande banor



F = Frontal cortex
A = Amygdala
H = Hypothalamus

Opioider (peptider)
β-endorfin
Dynorfin
Enkefalin

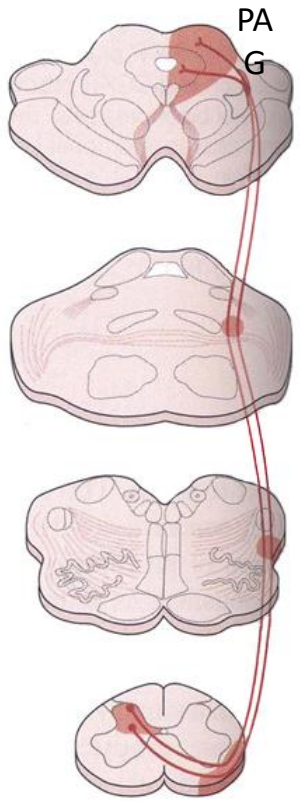
Förväntan och inlärning
– effekt på
smärtupplevelsen

PLACEBO – ”jag skall behaga”

NOCEBO – ”jag skall skada”

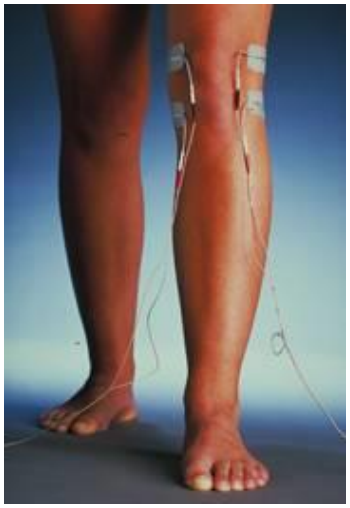
Hur aktiveras PAG ?

Spino-mesencephala banor



Afferent aktivitet från ergoreceptorer (en typ av muskel-receptorer) under muskelarbete

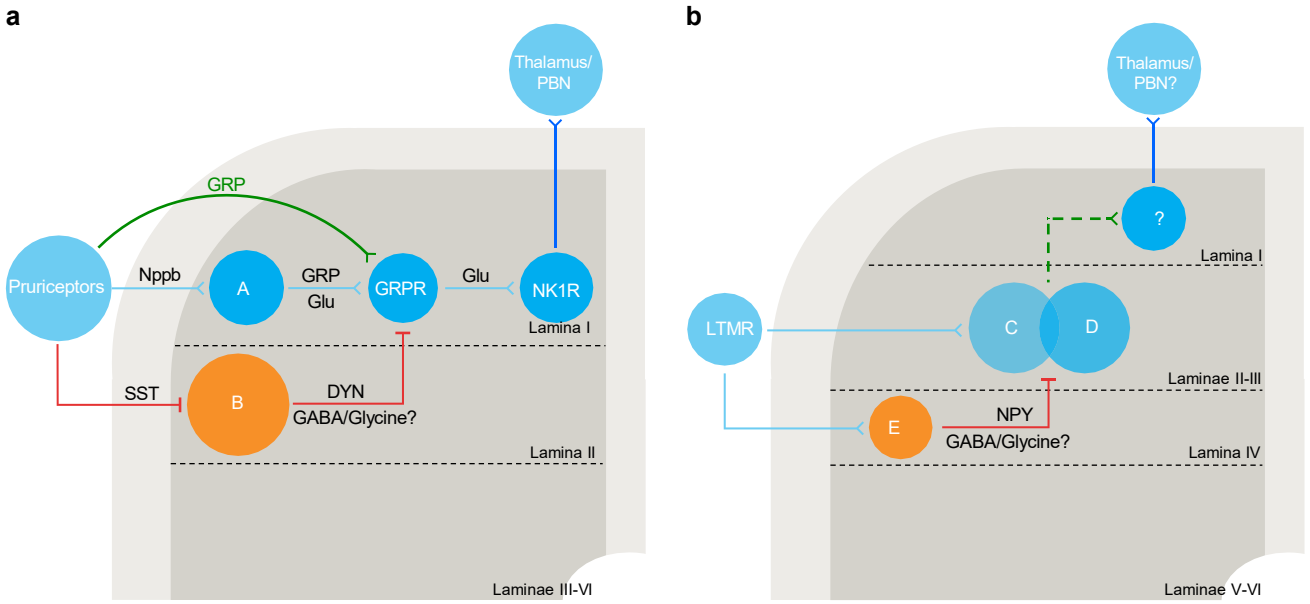
TENS – Transkutan elektrisk nervstimulering



1) Lågfrekvent stimulering med högre stimuleringsstyrka som aktiverar muskler för att genom muskelkontraktionerna aktivera ergoreceptorer (”simulerat muskelarbete”)

2) Högfrekvent stimulering med lägre stimuleringsstyrka som aktiverar beröringsafferenter. (”Gate control hypothesis”?)

Kretsar för klåda i dorsalhornet



Chemical itch

Mechanical itch

Fig. 1 Model of spinal circuits for chemical and mechanical itch. a When activated by chemical itch stimuli, the peripheral pruriceptors send the itch signals to spinal neurons via Nppb, a primary itch transmitter. The secondary sensory neurons then activate GRPR$^+$ neurons by releasing GRP, after which the itch signals are conveyed to the spinal projection neurons before reaching the thalamus or PBN for further processing.

b Light touch stimuli activate LTMRs to evoke mechanical itch, and the mechanical itch information is transmitted to spinal neurons, a subset of which are gated by spinal inhibitory neurons. PN projection neuron, LTMR low-threshold mechanoreceptor, Glu glutamate.

Sammanfattningsvis finns ett antal olika kretsar identifierade för både klåda och olika sorters smärta.

Kretsar för klåda i hjärnan

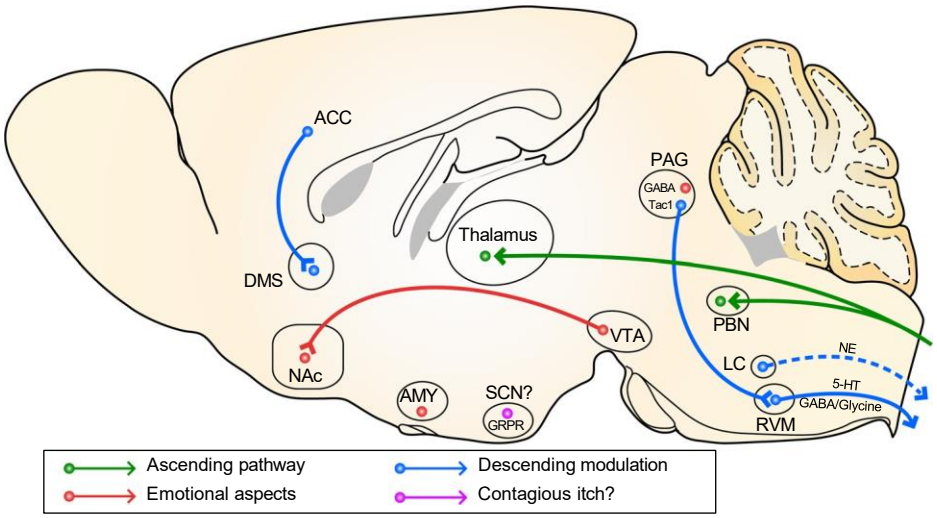
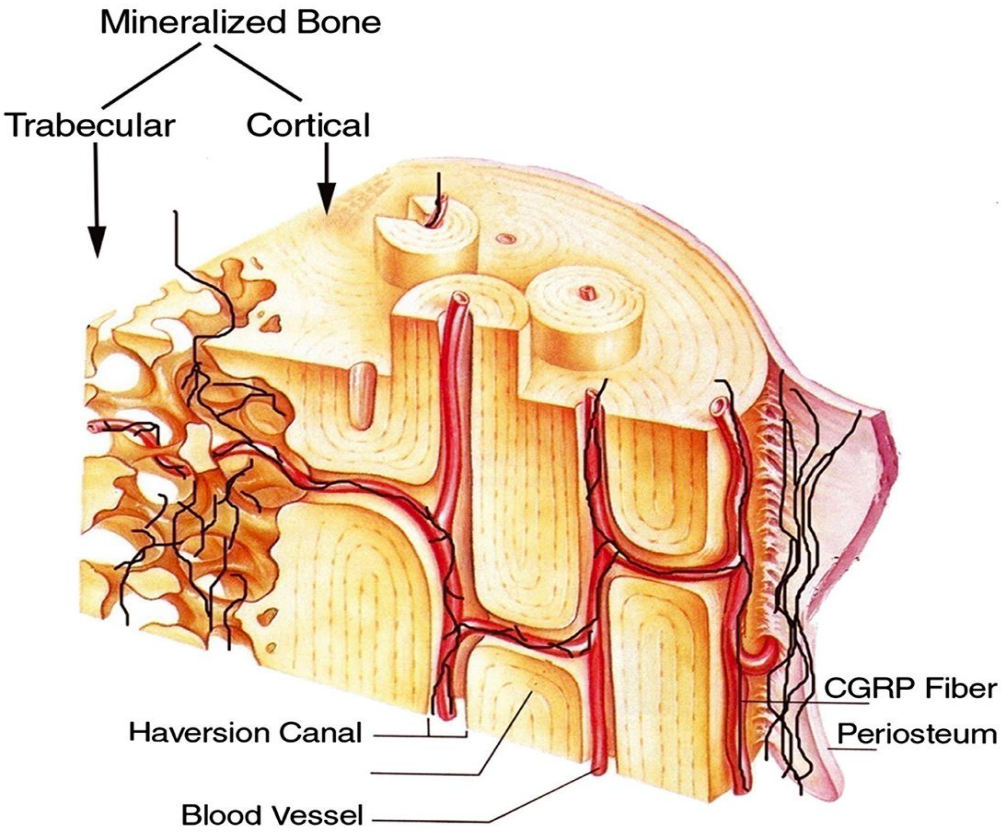


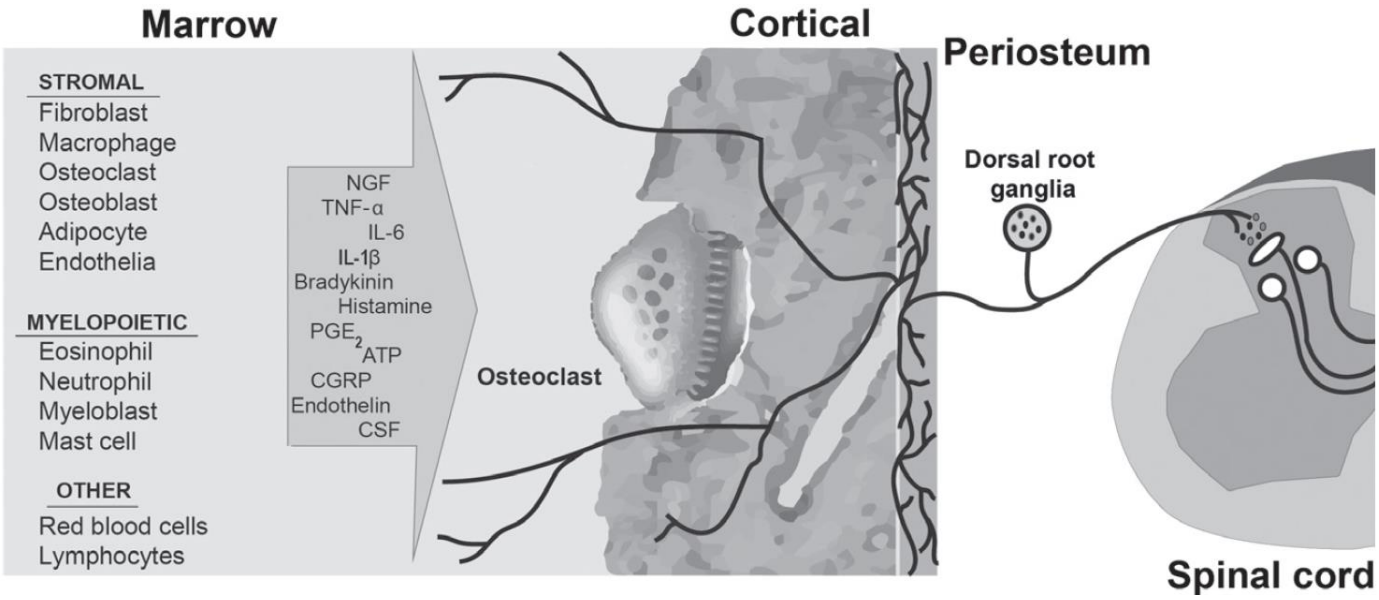
Fig. 2 Brain circuits for itch signal processing and modulation. The chemical itch signals are first relayed to the PBN and thalamus by spinal projection neurons, while visually contagious itch in mice is proposed to be mediated by the SCN GRPR^{+} neurons in the hypothalamus. The emotional components of itch sensation may be encoded by the amygdala, GABAergic neurons in the PAG, and different neuronal populations in the VTA. The PAG^{Tac1}-RVM circuit is involved in the descending modulation of itch signal processing, and brain-derived neuromodulators such as 5-HT and noradrenaline can also substantially modulate spinal itch circuits in a feedback manner. Projections from the ACC to the DMS selectively modulate histamine-dependent itch. AMY amygdala, LC locus coeruleus, NE noradrenaline.

Nociception i ben

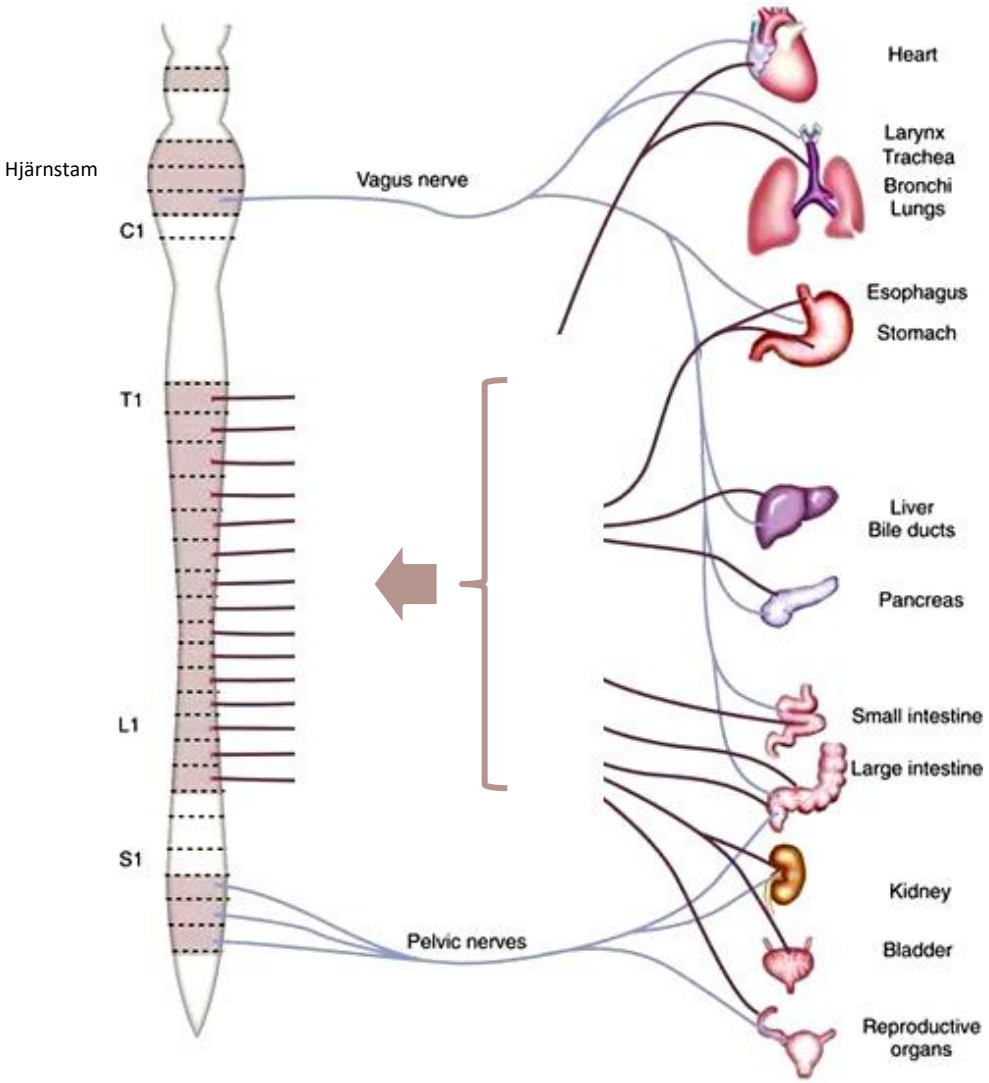


Adapted from Marieb and Mallet Human Anatomy, 1994

Perifer sensitisering i benvävnad



Fria nervändslut i inre organ (viscera)
- <u>delvis</u> nociceptiv funktion



The Bane of Pain Is Plainly in the Brain. (by Allan Basbaum)

Pain is an intricate potion, Of sensations, cognitions, emotions,
Acute pain may be terrible But it's persistent pain that's unbearable;
And rarely responds to mere lotions.

Though pain may not be easy to bear, There's often a reason for pain being there. It's critical to know, Lest a cancer unbeknownst grow. Pain signals a need for repair.

You learned of children with Congenital Insensitivity to Pain. They're unaware when they have fractures or sprains. These children are rare, But they need constant care. Or their injuries will not be contained.

You see, A deltas and C's are essential, To establish the painful potential.
But shake your hand or vibrate, And you may close Melzack and Wall's Spinal Gate
So that the pain is no longer sequential.

In fact, there are myriad ways to control pain, Which is perhaps why cordotomy's on the wane.
Find out what the morphine dose is, Even consider hypnosis. Remember pain's not a stimulus; it's a perception of the brain.

In this regard, find a pregnant woman and ask her, Is LaMaze merely a ploy to distract her? Or when labor pain Is not "perceived" by the brain, Are the endorphins a relevant factor?

Speaking of endogenous opioids—there are numerous classes. Some reportedly are as potent as grass is.
So, if you're in pain
Just depend on your brain
Because the endorphins are the true opiates of the masses.