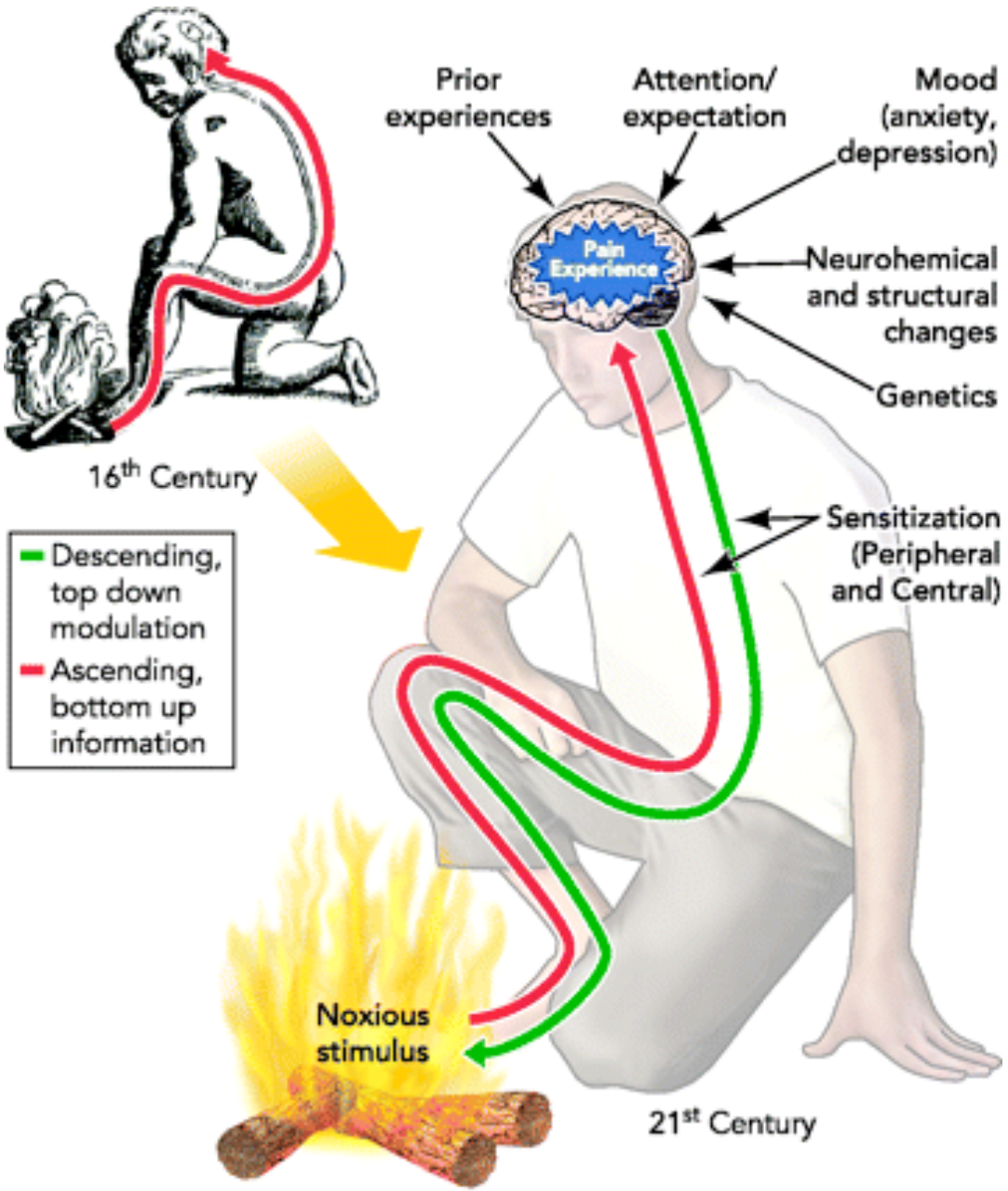
DOLORE

Galata morente, Musei Capitolini, Roma

FISIOLOGIA E TRATTAMENTO



Pain perception: ancient and current concepts

Left: Cartesian view of pain. According to the classical Cartesian view, pain was considered to be a hard-wired system in which noxious input was passively transmitted along sensory channels to the brain.

Right: 21st century view of pain. Pain is acknowledged to represent a multidimensional experience that is influenced by both bottom-up and top-down modulatory influences.

Pain has the distinction of being the **commonest symptom** for which a person approaches medical care

Various Definitions of Pain

- *Aristotle did not include a sense of pain when he enumerated the five senses; he, like Plato before him, saw pain and pleasure not as sensations but as emotions.*
- "*An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage*".
- *"A complex experience consisting of a physiological (bodily) response to a noxious stimulus followed by an affective (emotional) response to that event. Pain is a warning mechanism that helps to protect an organism by influencing it to withdraw from harmful stimuli. It is primarily associated with injury or the threat of injury, to bodily tissues".*
- *"A perception, not really a sensation, in the same way that vision and hearing are. It involves sensitivity to chemical changes in the tissues and then interpretation that such changes are harmful. This perception is real, whether or not harm has occurred or is occurring. Cognition is involved in the formulation of this perception. There are emotional consequences and behavioral responses to the cognitive and emotional aspects of pain".*

Evolutionary and behavioral role

Pain is part of the body's defense system, producing a reflexive retraction from the painful stimulus, and tendencies to protect the affected body part while it heals, and avoid that harmful situation in the future. It is an important part of animal life, vital to healthy survival.
People with congenital insensitivity to pain have reduced life expectancy.

PAIN BY OUTLIVING ITS USEFULNESS AS A WARNING SYSTEM MAY BECOME CHRONIC AND DEBILITATING

PAIN:

-definition of pain: an unpleasant sensory or emotional experience

-perception of pain is a product of brain's abstraction and elaboration of sensory input.

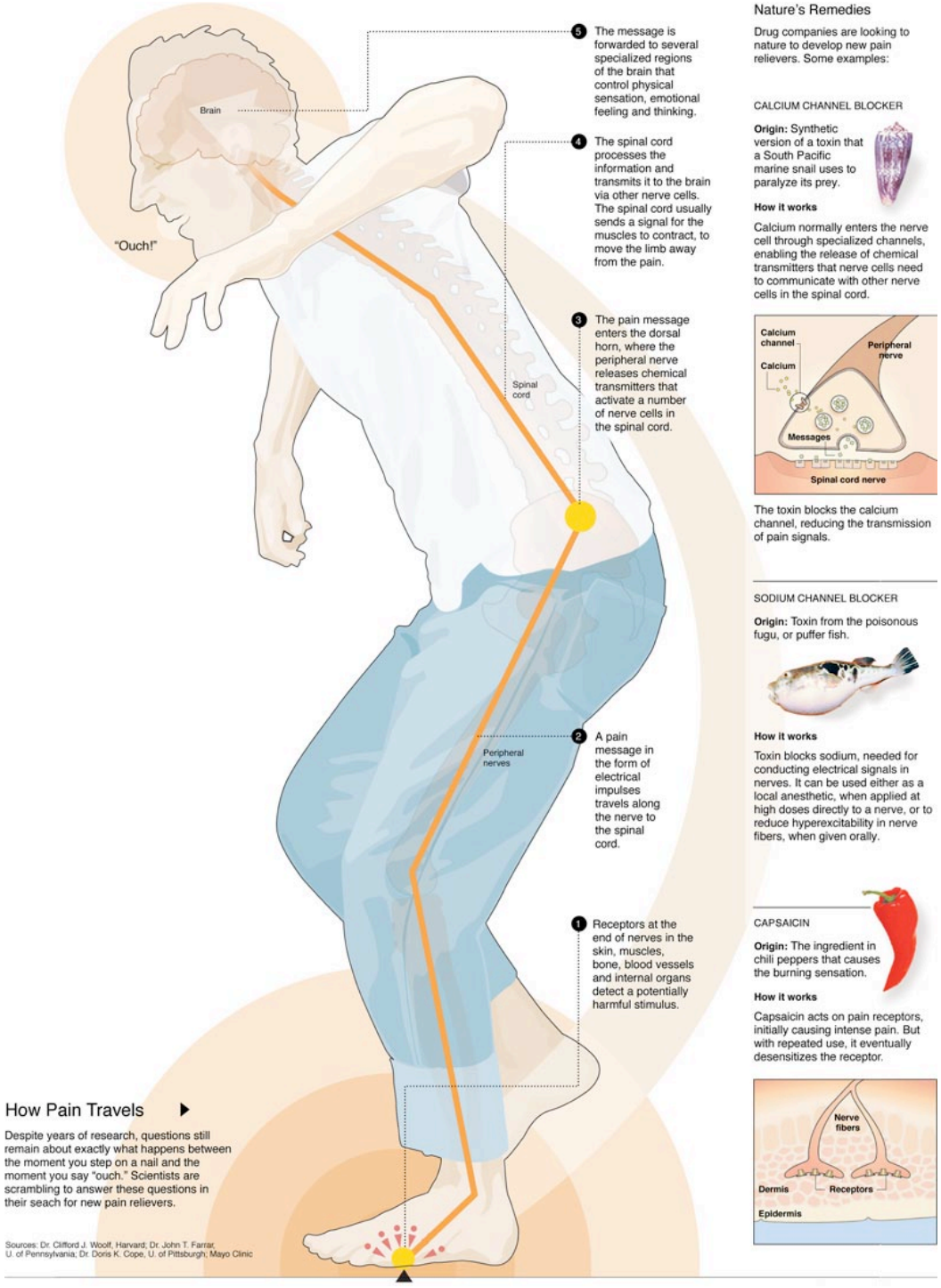
-perception of pain varies with individuals and circumstances (soldier injured)

-activation of nociceptors does not necessarily lead to experience of pain (**Pain asymbolia**, also called pain dissociation, is a condition in which pain is perceived, but does not cause suffering. This results from injury to the brain, lobotomy, cingulotomy or morphine analgesia. Preexisting lesions of the insula may abolish the aversive quality of painful stimuli while preserving the location and intensity aspects. Typically, patients report that they have pain but are not bothered by it, they recognize the sensation of pain but are mostly or completely immune to suffering from it)

-pain can be perceived without activation of nociceptors (phantom limb pain, thalamic pain syndrome)

-important for survival, protect from damage: congenital and acquired insensitivity (diabetic neuropathy, neurosyphilis) to pain can lead to permanent damage

-pain reflexes can be stopped if not appropriate (step on nail near precipice, burn hands while holding a baby. Pain can be suppressed if not needed for survival (soldier…).



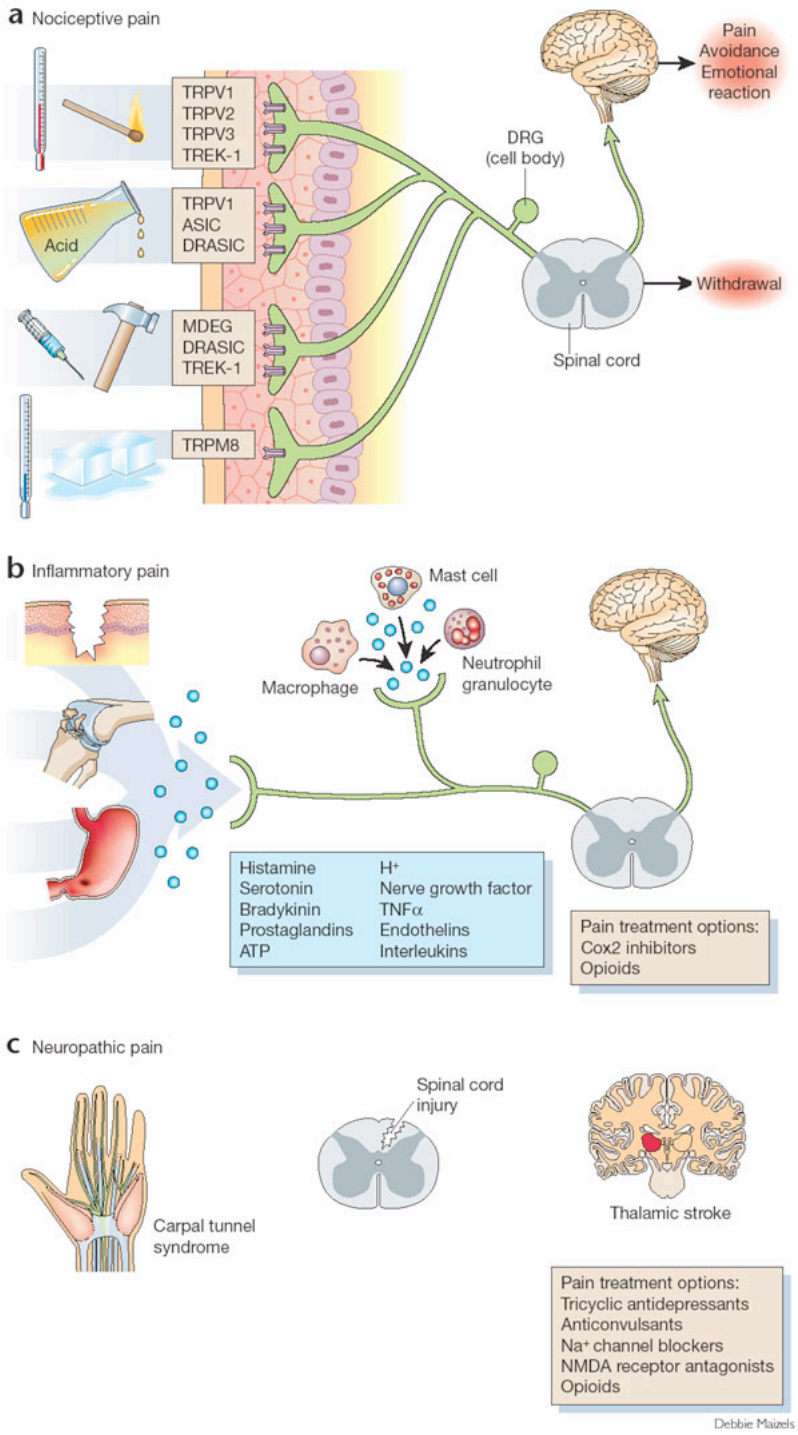
Despite years of research, questions still remain about exactly what happens between the moment you step on a nail and the moment you say.

Pain pathway

There are four processes in the pain pathway

1. transduction
   - Noxious stimuli translated into electrical activity at sensory nerve endings
2. Transmission
   - Propagation of impulses along spinothalamic pathway.
3. Modulation
   - Transmission is modified
4. Perception
   - Affective / motivational aspect

Each of these processes present a potential target for analgesic therapy



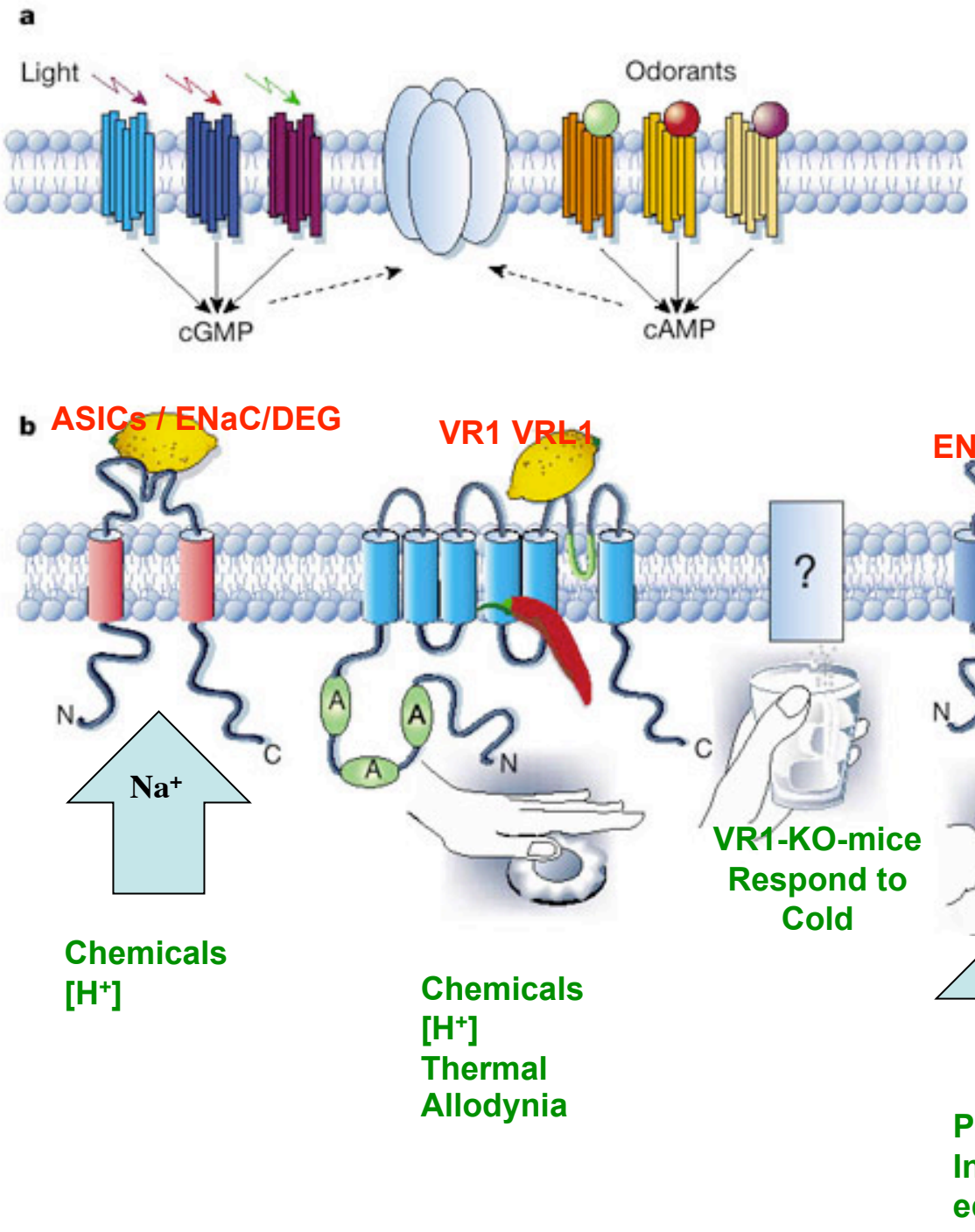
DIFFERENT PAIN MECHANISMS

Nociceptive, inflammatory and neuropathic pain.

(a) Noxious stimuli are transduced into electrical activity at the peripheral terminals of unmyelinated C-fiber and thinly myelinated A-fiber nociceptors by specific receptors or ion channels sensitive to heat, mechanical stimuli, protons and cold. This activity is conducted to the spinal cord and, after transmission in central pathways, to the cortex, where the sensation of pain is experienced.

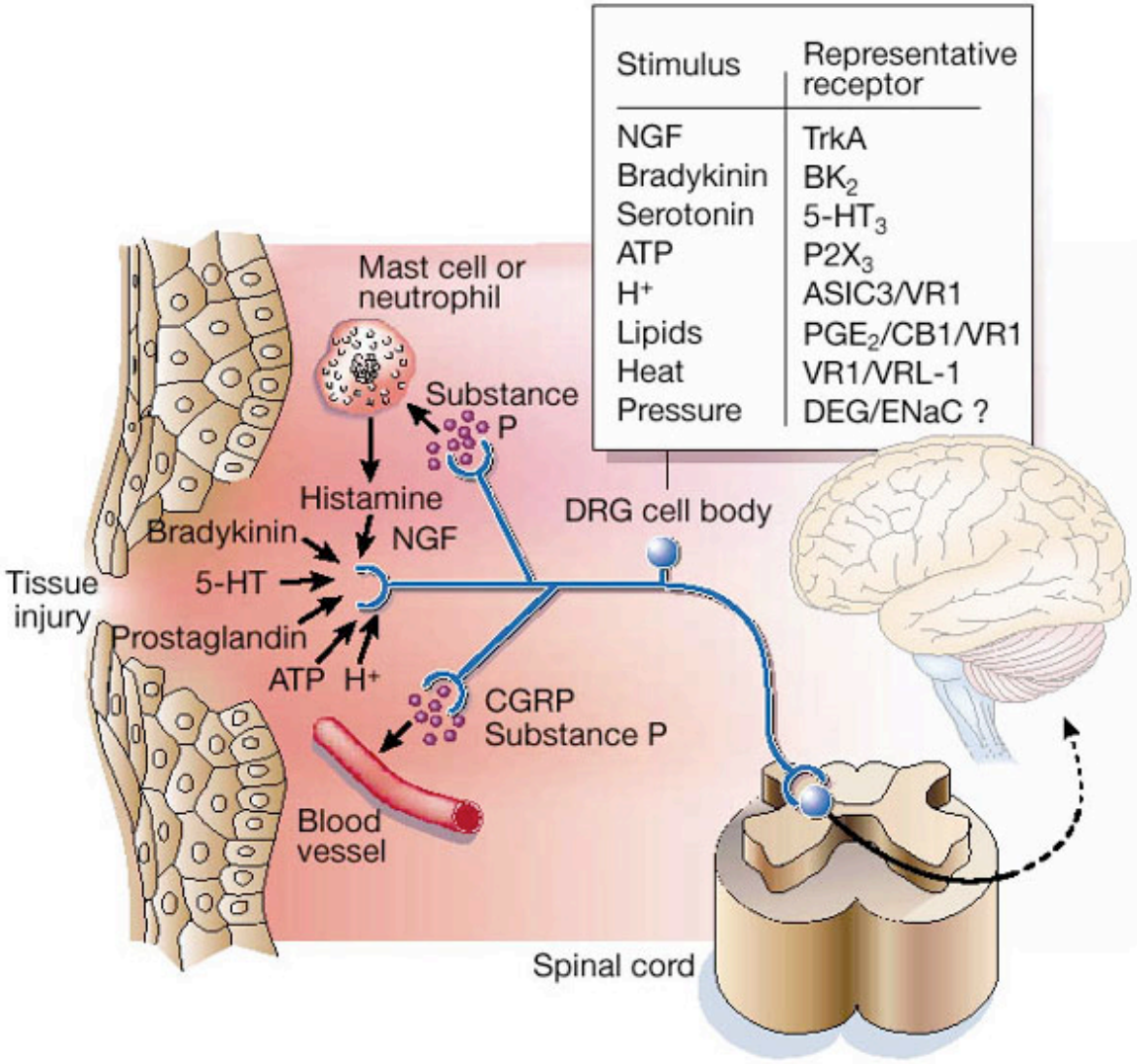
(b) Damaged tissue, inflammatory and tumor cells release chemical mediators creating an 'inflammatory soup' that activates or modifies the stimulus response properties of nociceptor afferents. This, in turn, sets up changes in the responsiveness of neurons in the CNS.

(c) Neuropathic pain arises from lesions to or dysfunction of the nervous system. Conditions affecting the peripheral nervous system, as in carpal tunnel syndrome, the spinal cord after traumatic injuries or the brain after stroke, can all cause neuropathic pain, which is characterized by a combination of neurological deficits and pain.



a, Light or odorants are detected by a convergent signalling pathway in which GPCR modulate the production of cGMP or cAMP, which then activate a single type of cation channel.
b, Nociceptors use different signal-transduction mechanisms to detect physical and chemical stimuli. TRP-channel family members (VR1 and VRL-1) detect noxious heat, and that ENaC/DEG-channel family detect mechanical stimuli. Molecular transducers for noxious cold remain enigmatic. Noxious chemicals, such as capsaicin or acid may be detected through a common transducer (VR1). At the same time, a single type of stimulus can interact with multiple detectors, (H^+ activate VR1 and ASICs (ENaC/DEG)

Nociceptor function is modified in response to tissue damage



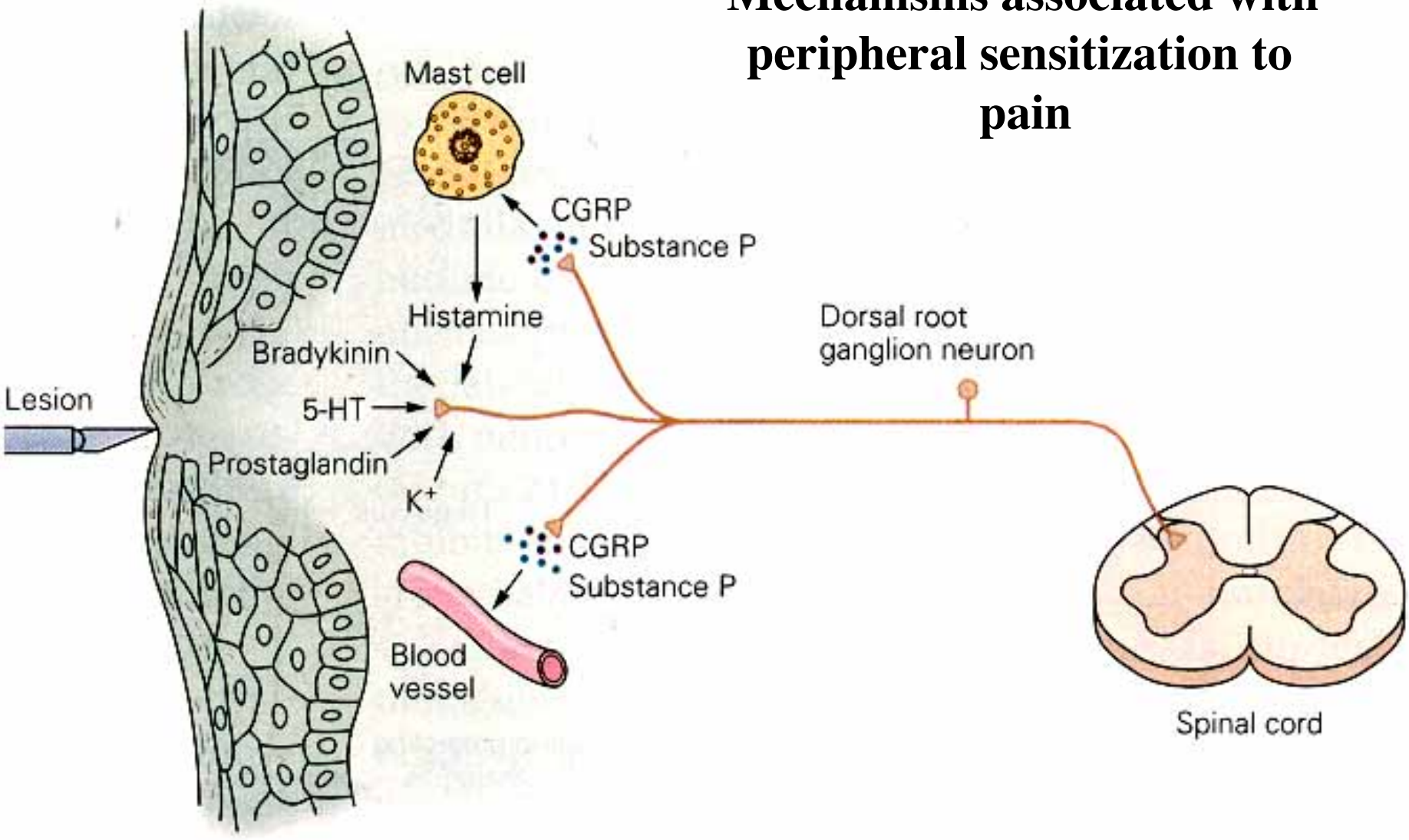
Components of the 'inflammatory soup' include peptides (bradykinin), lipids (prostaglandins), neurotransmitters (5-HT, HA and ATP) and neurotrophins (NGF).

They a) sensitize (lower the threshold) or b) excite the terminals of the nociceptor by interacting with cell-surface receptors expressed by these neurons.

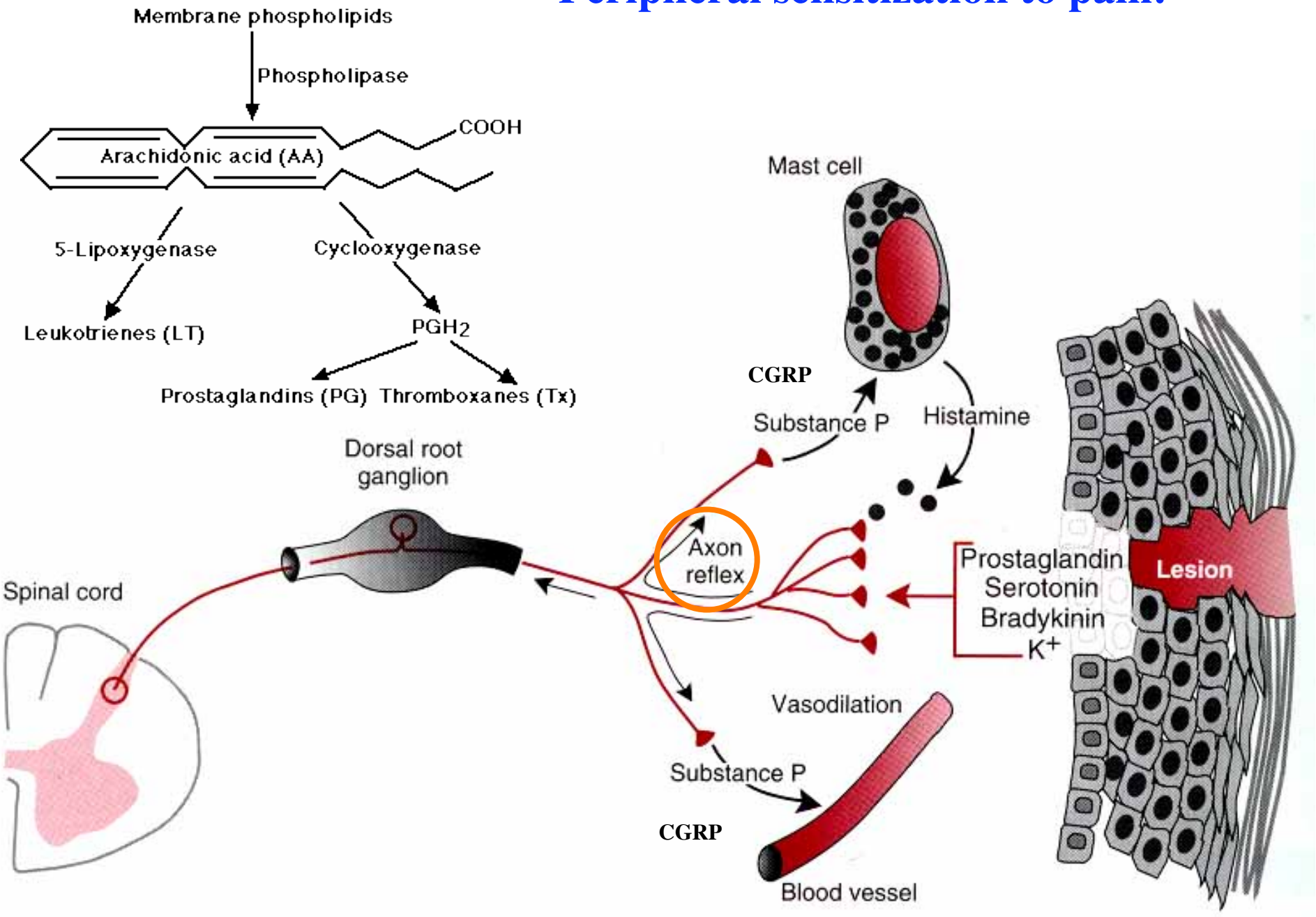
Activation of the nociceptor not only transmits afferent messages to the spinal cord dorsal horn but also initiates the process of neurogenic inflammation.

This is an efferent function of the nociceptor whereby release of neurotransmitters, notably substance P and calcitonin gene related peptide (CGRP), from the peripheral terminal induces vasodilation and plasma extravasation (leakage of proteins and fluid from postcapillary venules), as well as activation of many non-neuronal cells, including mast cells and neutrophils. These cells in turn contribute additional elements to the inflammatory soup.

Mechanisms associated with peripheral sensitization to pain



Peripheral sensitization to pain:



Agents that Activate or Sensitize Nociceptors:

Cell injury → arachidonic acid → prostaglandins → +> vasc. permeability
(cyclo-oxygenase) → sensitizes nociceptor

Cell injury → arachidonic acid → leukotrienes → +> sensitizes nociceptor

Cell injury → +> tissue acidity → +> kallikrein → +> bradykinin → +> vasc. permeability
→ activates nociceptors

Substance P (released by free nerve endings) → sensitize nociceptors

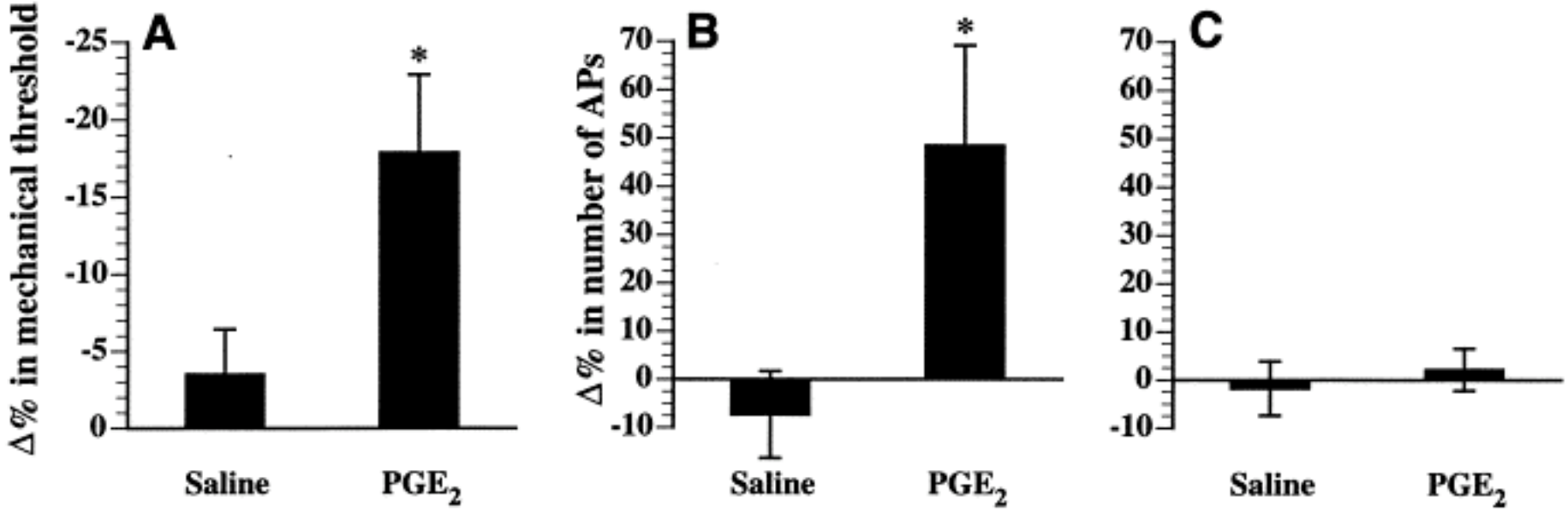
Mast cells +> release histamine → activates nociceptors

Calcitonin gene related peptide (free nerve endings) → dilation of peripheral capillaries

Serotonin (released from platelets & damaged endothelial cells) → activates nociceptors

Cell injury → potassium → activates nociceptors

Effect of intradermal injection of PGE_2 on mechanically-sensitive cutaneous C-fiber nociceptors.



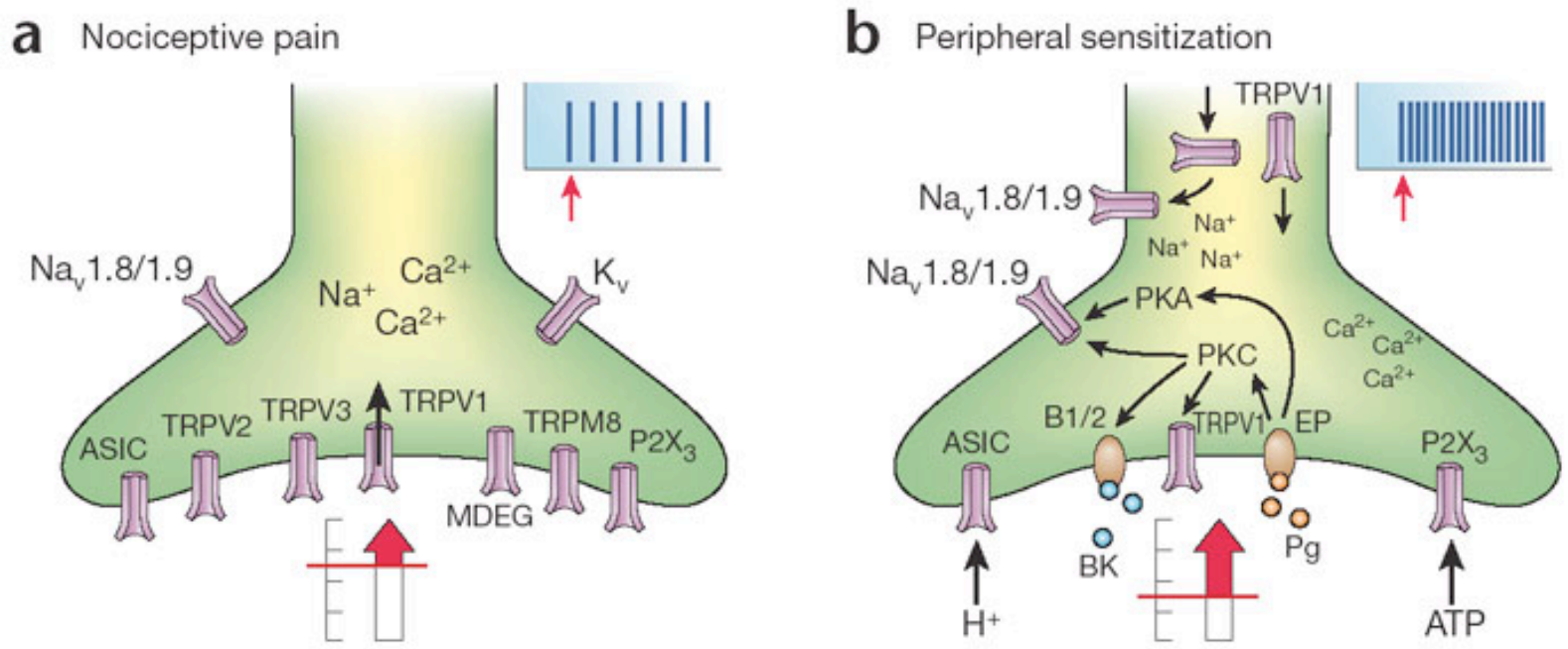
(A) %change of mechanical threshold after saline and PGE_2 was -3.5±2.9 and -17.9±5.0, respectively. The change in the mechanical threshold after PGE_2 was statistically significant (P*<0.01).**

(B) % change of number of action potentials (APs) evoked by sustained threshold stimulus after saline and PGE_2 was −7.4±9.01 and 48.5±20.7, respectively. Number of APs was significantly increased after PGE_2 (P*<0.01).**

(

C) The percentage change of number of APs evoked by non-threshold stimulus after saline and PGE_2 was −1.8±5.6 and 2.1±4.4, respectively. Number of APs did not significantly change after saline and PGE_2 (*P*=ns).

Data are expressed as mean±SEM.

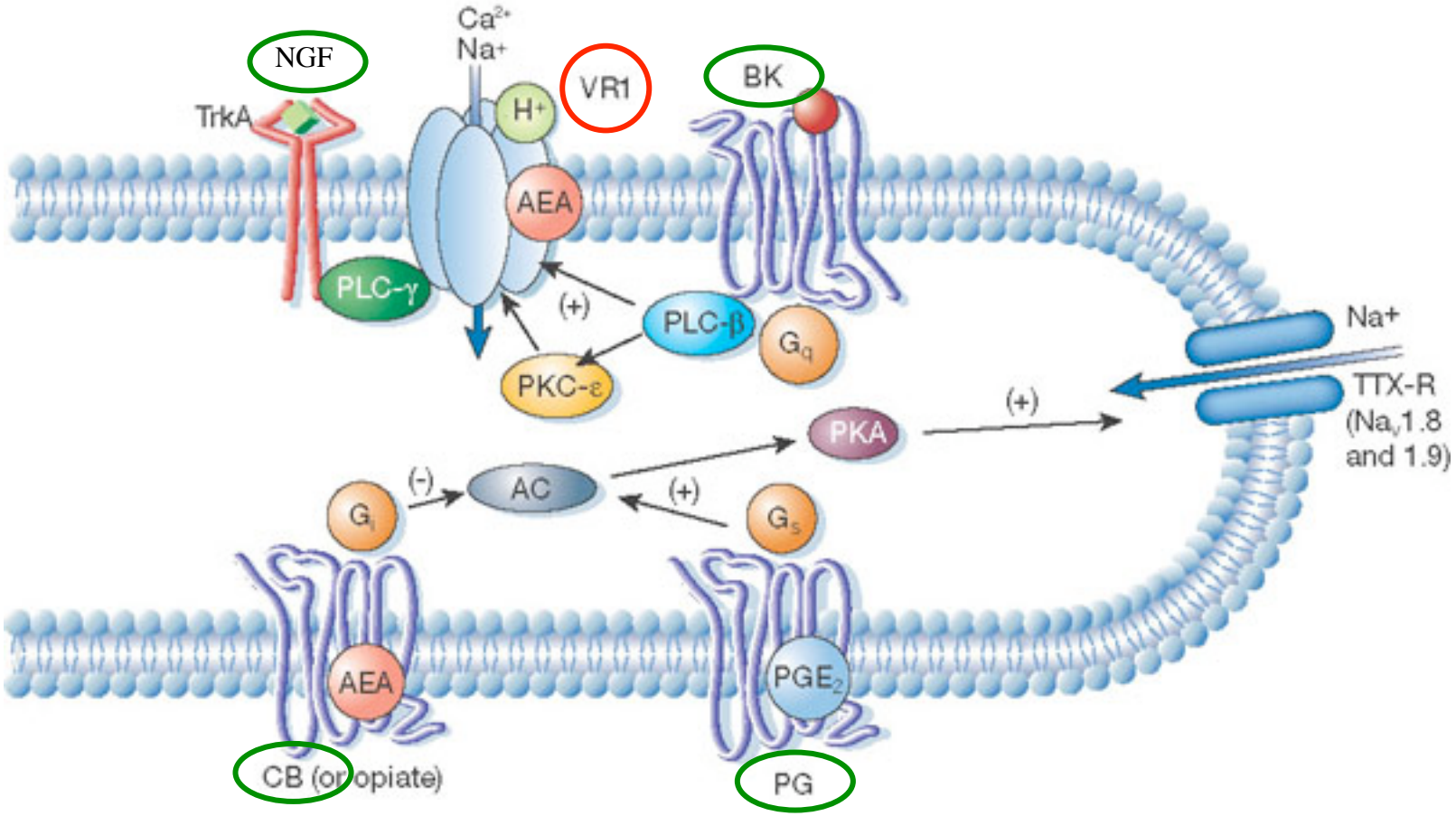


Nociceptor-mediated pain is driven by activation of peripheral nociceptor sensory fibers

(a) Nociceptive pain is produced by noxious stimuli acting on high-threshold nociceptors.

(b) Components of the 'inflammatory soup', such as bradykinin or PGs, bind to G-protein-coupled receptors and induce activation of PKA and PKC in nociceptor peripheral terminals, which then phosphorylate ion channels and receptors. As a result, the threshold of activation of transducer receptors such as TRPV1 is reduced, and the excitability of the peripheral terminal membrane increases, producing a state of heightened sensitivity, termed 'peripheral sensitization'.

Mechanisms to make pain worse, analgesia by COX inhibitors and cannabinoids

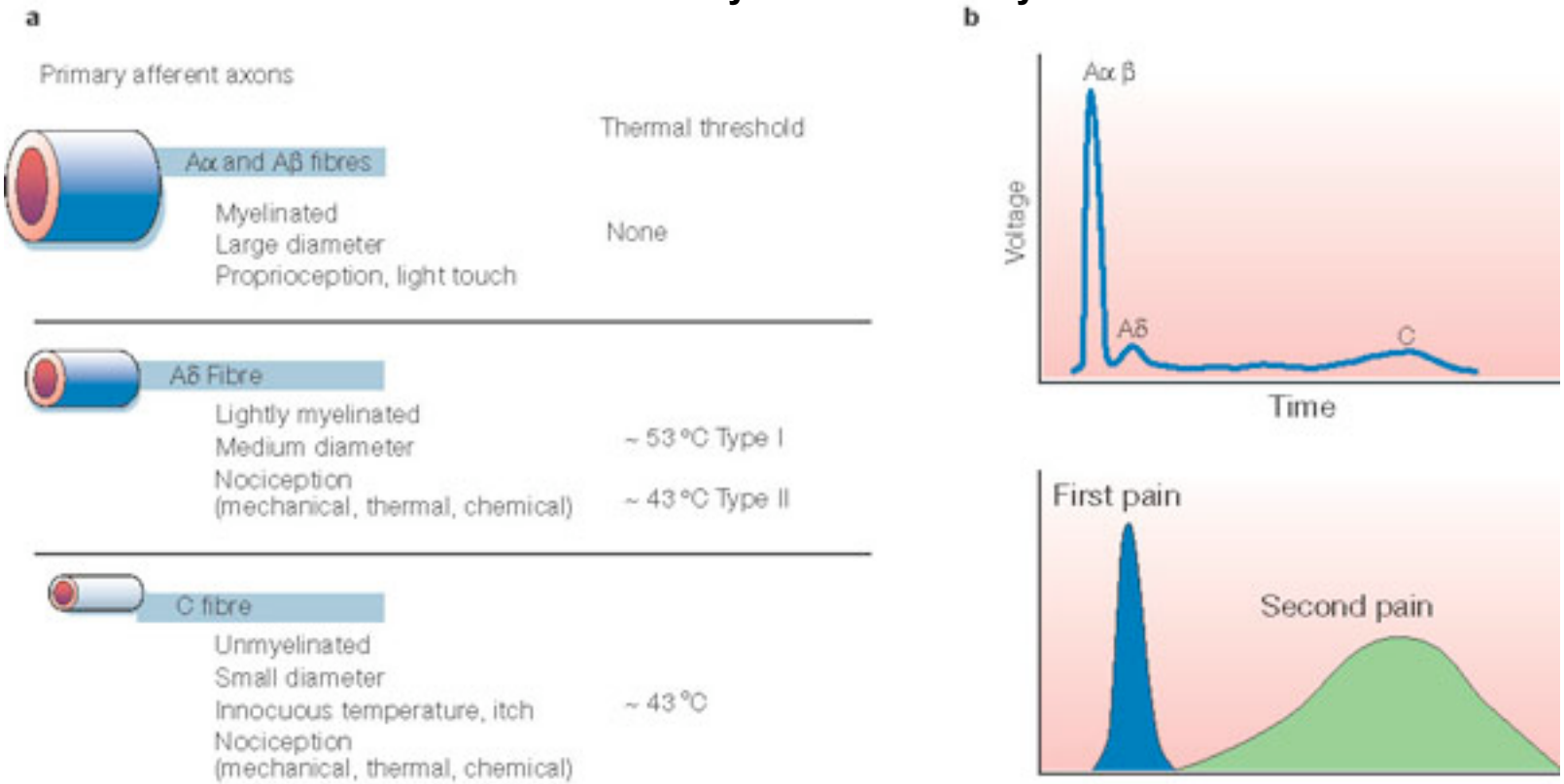


❑**VR1 and tetrodotoxin-resistant (TTX-R) voltage-gated sodium channels are downstream targets of modulation. Responses of VR1 to heat can be potentiated by direct interaction of the channel with extracellular H^+ or lipid metabolites, such as anandamide (AEA). VR1 activity can also be heightened by NGF or bradykinin, which bind to TrkA and BK, respectively, to stimulate PLCs signalling pathways. These actions potentiate VR1 function.**

❑**PGE_2 activating adenylyl cyclase (AC) also enhance nociceptor excitability. This occurs by a cAMP-dependent PKA-phosphorylation of $Na_v1.8$ and/or $Na_v1.9$.**

❑**By activating G_i-coupled receptors, opiates and cannabinoids can counteract these increases in excitability of the nociceptor, and produce a peripherally mediated analgesia.**

Fibers that innervate head & body arising from N.trigeminus and DRG can be divided into 3 groups anatomically and functionally



a, Peripheral nerves include small-diameter and medium- to large-diameter myelinated afferent fibres, as well as small-diameter unmyelinated afferent fibres.
b, The fact that conduction velocity is directly related to fibre diameter is highlighted in the compound action potential recording from a peripheral nerve. Most nociceptors are either A or C fibres, and their different conduction velocities (6–25 and 1.0 m s^{-1}, respectively) account for the first (fast) and second (slow) pain responses to injury.

Tissue specificity: cornea, pain also from innocuos tactile stimuli; teeth, all is painful; intestine distension no damage request; ischemia, sensitivity to H^+

Transduction - A delta fibres and C fibres

A-Delta fibres	**C- fibres**
myelinated	unmyelinated
fast (first) pain -conduct at 5-35m/sec	Slow (second) pain – conduct at 0.5-2.0m/ sec
Associated with Sharp, brief, prinking pain	Associated with dull,burning, aching, prolonged pain
Well localised	More diffuse
Elicited by mechanical or thermal stimuli	Elicited mainly by chemical stimuli or persisting mechanical or thermal stimuli

To summarize peripheral sensitization to pain:

-Sensitization results from the release of various chemicals by the damaged cells and tissues (bradykinin, prostaglandins, leukotrienes…). These chemicals alter the type and number of membrane receptors on free nerve endings, lowering the threshold for nociceptive stimuli.

-The depolarized nociceptive sensory endings release substance P and CGRP along their branches (**axon reflex**), thus contributing to the spread of edema by producing vasodilation, increase in vascular permeability and plasma transvasation, and the spread of hyperalgesia by leading to the release of histamine from mast cells.

-Aspirin and NSAID block the formation of prostaglandins by inhibiting the enzyme cyclooxygenase.

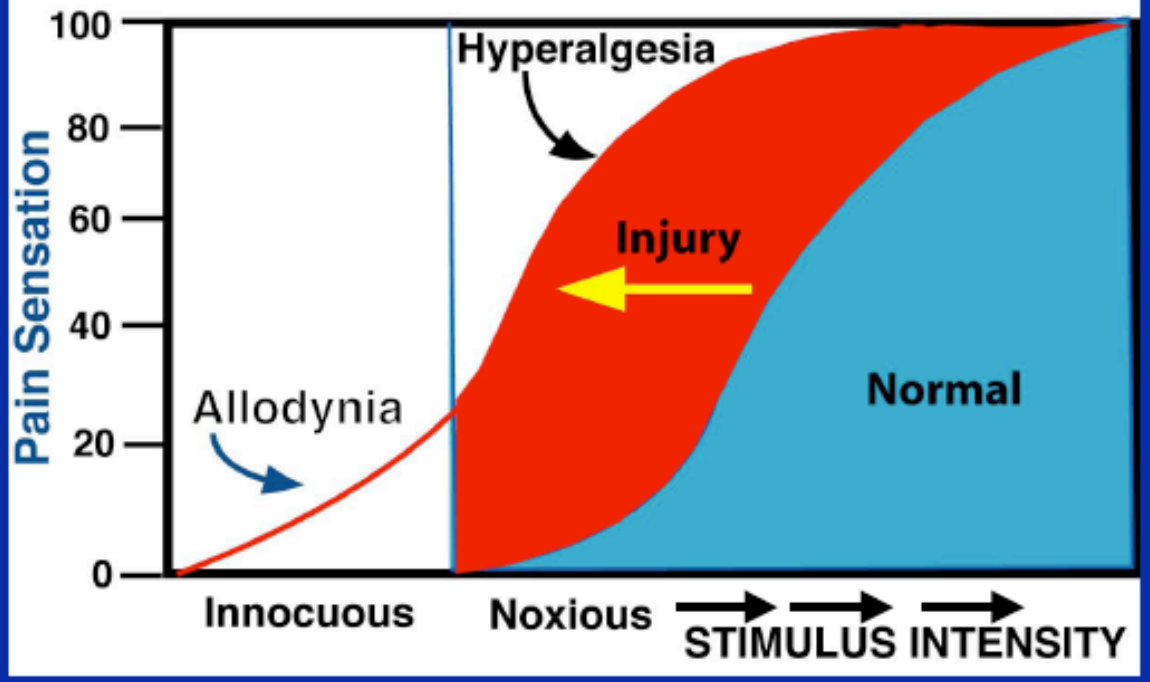
-Local anesthetic preferentially blocks C fiber conduction, cold decreases firing of C fibers, ischemia blocks first the large myelinated fibers.

E. Algesic—pain producing vs. **Analgesic**—pain preventing

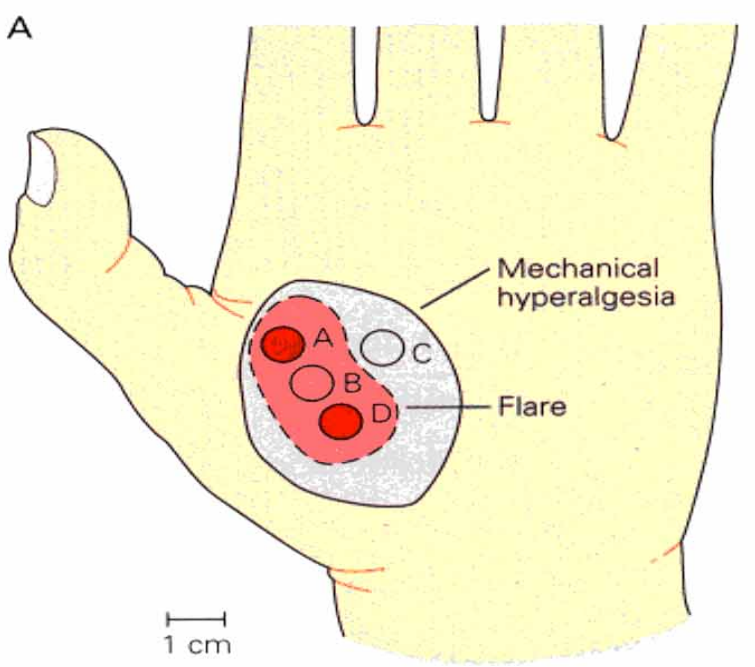
F. Hyperalgesia—increased pain sensation elicited by a noxious stimulus

G. Allodynia—a pathological condition in which pain is produced by a stimulus that is normally innocuous (sunburn).

Graph showing normal pain sensation (blue); hyperalgesia (red) & allodynia



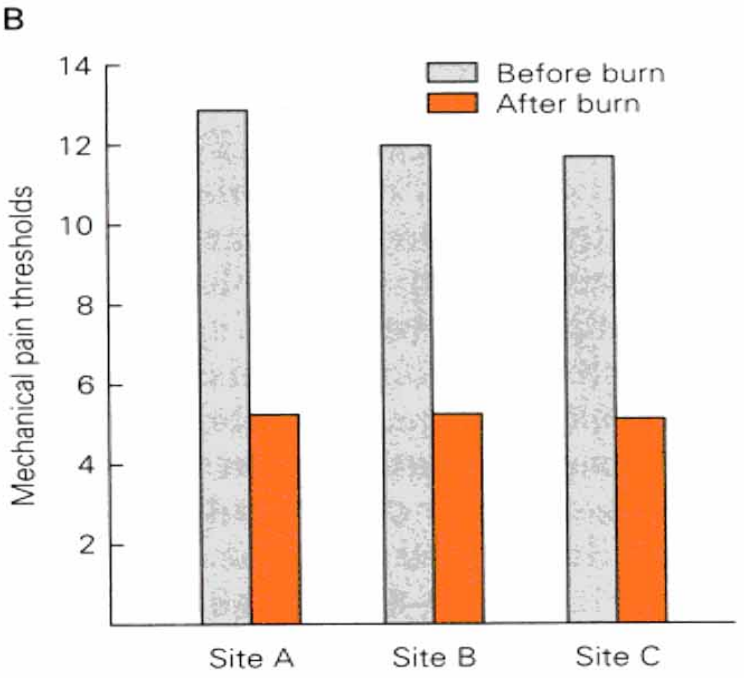
Peripheral sensitization to pain:

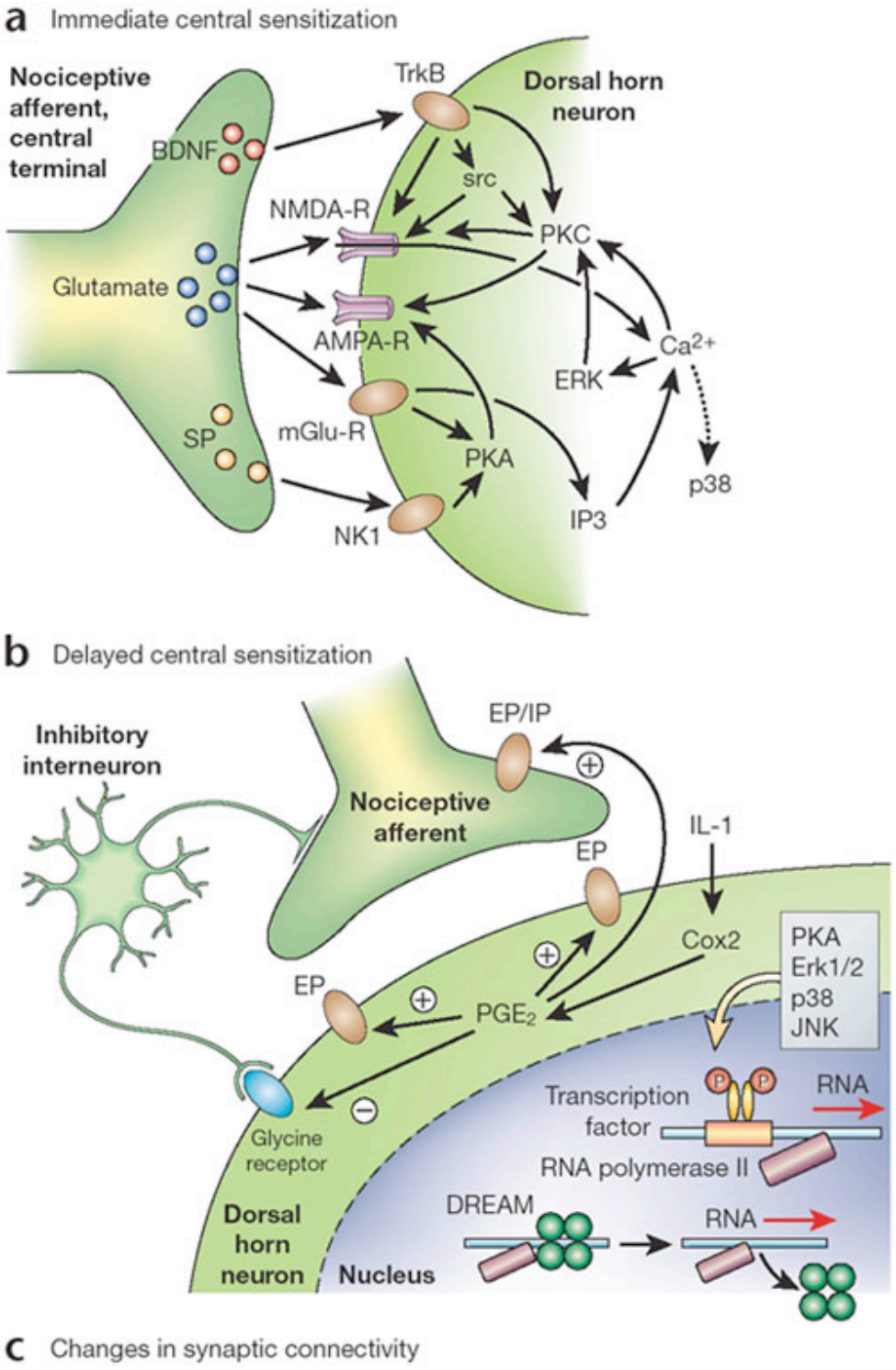


Some definitions:

Hyperalgesia→ increased sensitivity to an already painful stimulus

Allodynia→ normally non painful stimuli are felt as painful (i.e .light touch of a sun-burned skin)

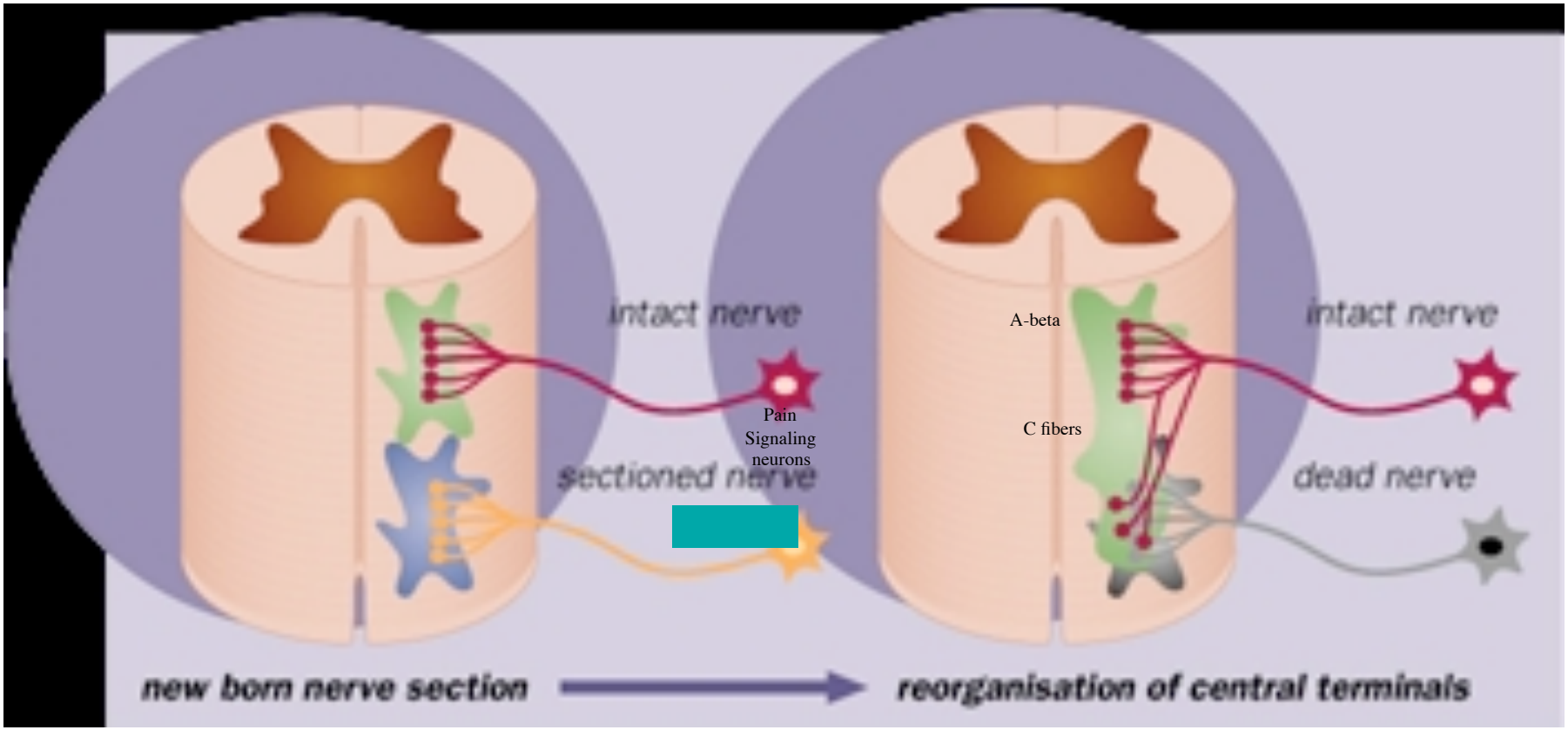




Non-nociceptor-mediated pain is generated by sensory inputs that would normally produce an innocuous sensation, and reflects a change in the functioning of central neurons.

(a) Activity-dependent central sensitization. An immediate and relatively short-lasting increase in the excitability and responsiveness of pain transmission dorsal horn neurons, which is due to phosphorylation of ion channels and receptors and follows nociceptor-driven transmitter release and activation of intracellular kinases. Eventually, the response to normally subthreshold inputs is increased.

(b) Transcription-dependent central sensitization. Enhanced gene expression due to the activation of transcription factors, as well as the removal of repressors like DREAM, results in long-lasting changes in the function of dorsal horn neurons. Cox2 induction leads to PGE_2 production, which acts pre- and postsynaptically to facilitate excitatory and reduce inhibitory transmission.



Neuropathic pain:

N

When peripheral or central NS is damaged (trauma, cancer, infections (H.zoster), diabetes (neuropathy)

→ Following peripheral nerve injury, nonpainful stimuli become painful (allodynia) sensory deficits (cold or heat perception) decrease and hyperalgesia. Greater loss of small fibers than large diameter fibers. Axons of surviving A-beta fibers sprout new branches and make connection to neurons vacated by the lost C fibers.

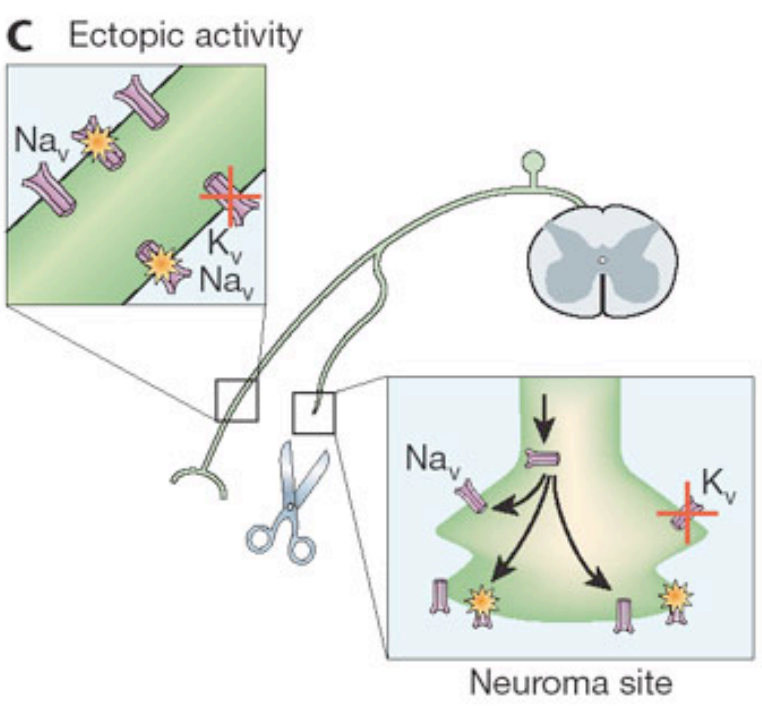
→Thalamic pain syndrome: usually following stroke in the ventral basal thalamus. Rearrangement of local circuit leads to excruciating pain.

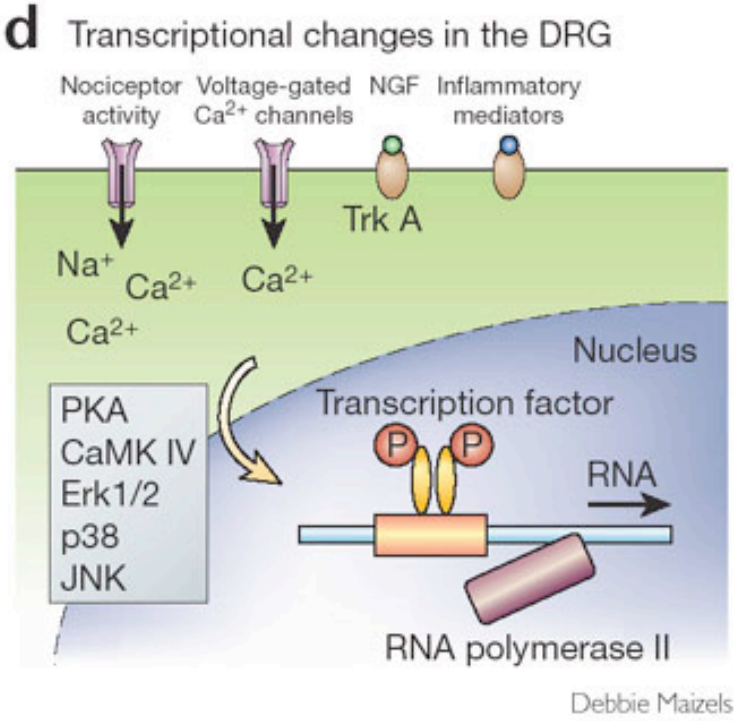
→Phantom limb pain:

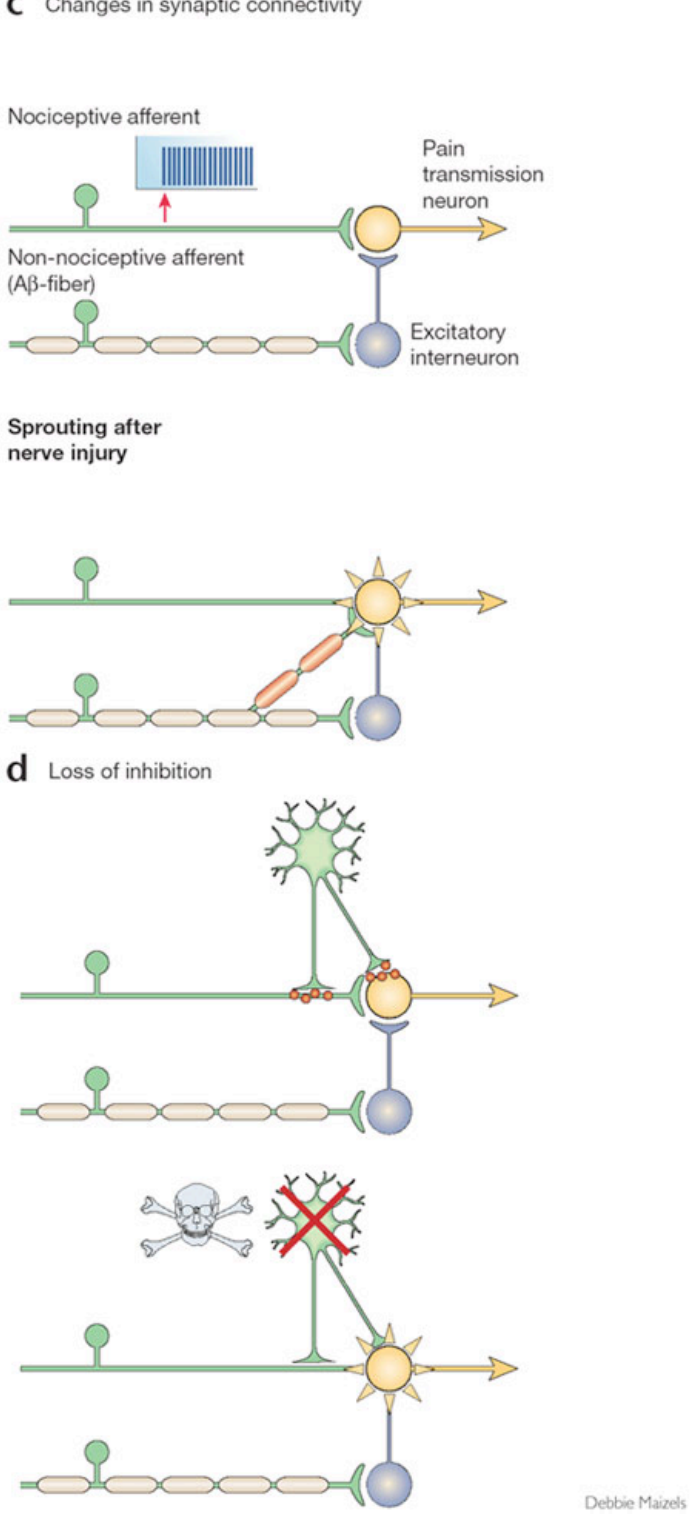
Nociceptor-mediated pain is driven by activation of peripheral nociceptor sensory fibers

(c) After injury to nociceptor neurons, increases in transcription or altered trafficking of sodium channels as well as a reduction in potassium channels increases membrane excitability sufficiently so that action potentials are generated spontaneously (ectopic activity).

(d) Activity-dependent signal transduction cascades and signaling pathways downstream to receptors bound by cytokines and growth factors act to modify transcription in nociceptor neurons. Altered production of numerous proteins modifies the phenotype of the neurons, changing their transduction, conduction and transmission properties.

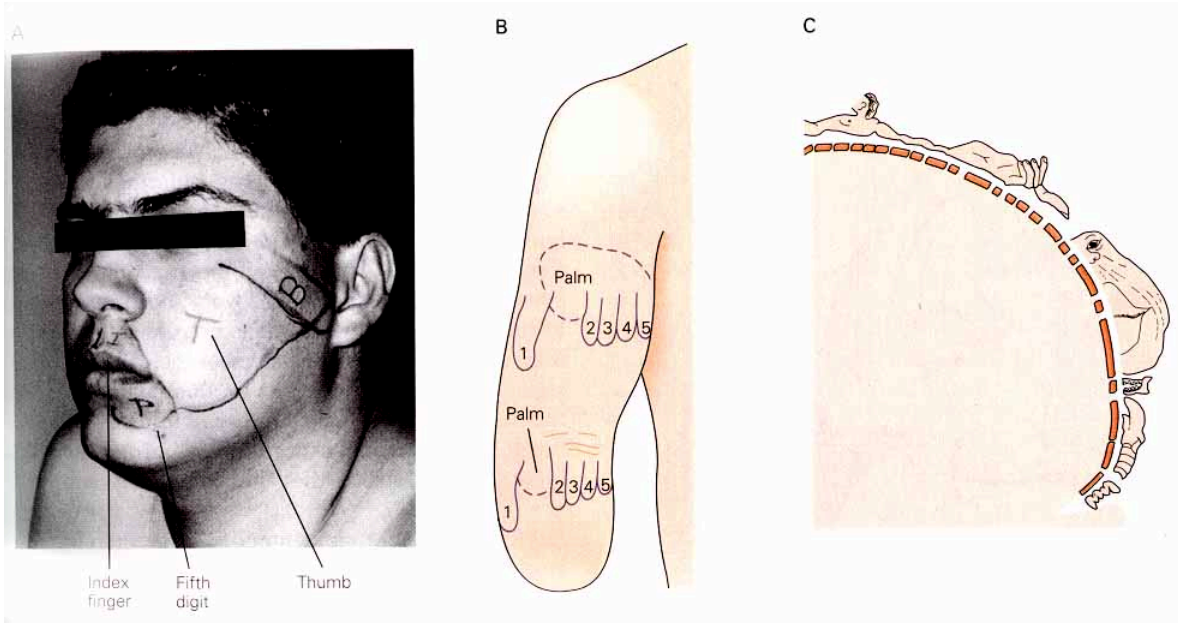




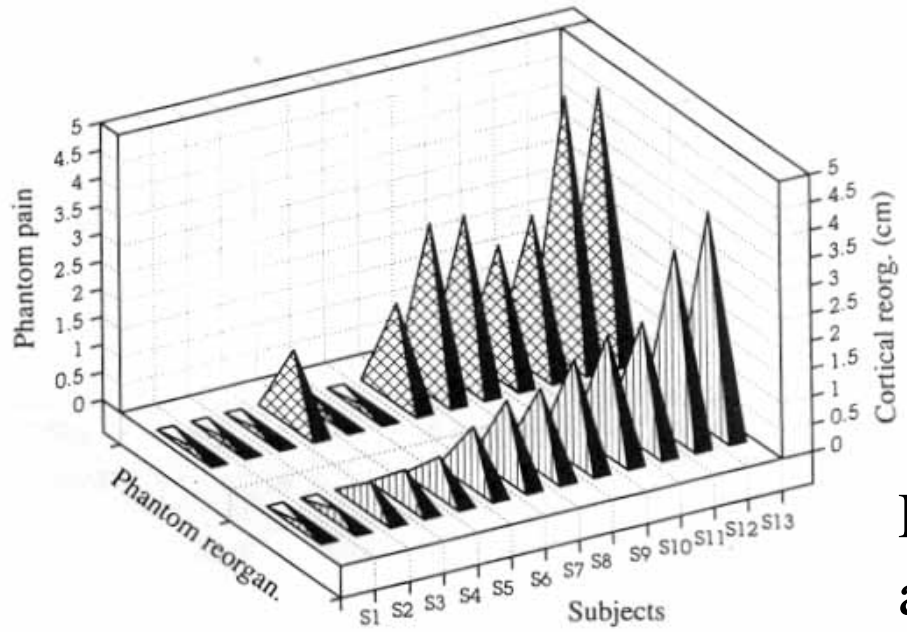


c) After peripheral nerve injury, the central terminals of myelinated non-nociceptive A-afferents sprout in the dorsal horn and form new connections with nociceptive neurons in laminae I and II. This re-wiring of the circuitry of the spinal cord may contribute to persistent pain hypersensitivity.

(d) Disinhibition. Normal sensory inflow is actively controlled by inhibitory interneurons. Reduced synthesis of the inhibitory neurotransmitters GABA and glycine or loss of these inhibitory interneurons after excessive release of the excitotoxic amino acid glutamate following peripheral nerve injury increases the excitability of pain transmission neurons such that they begin to respond to normally innocuous inputs.

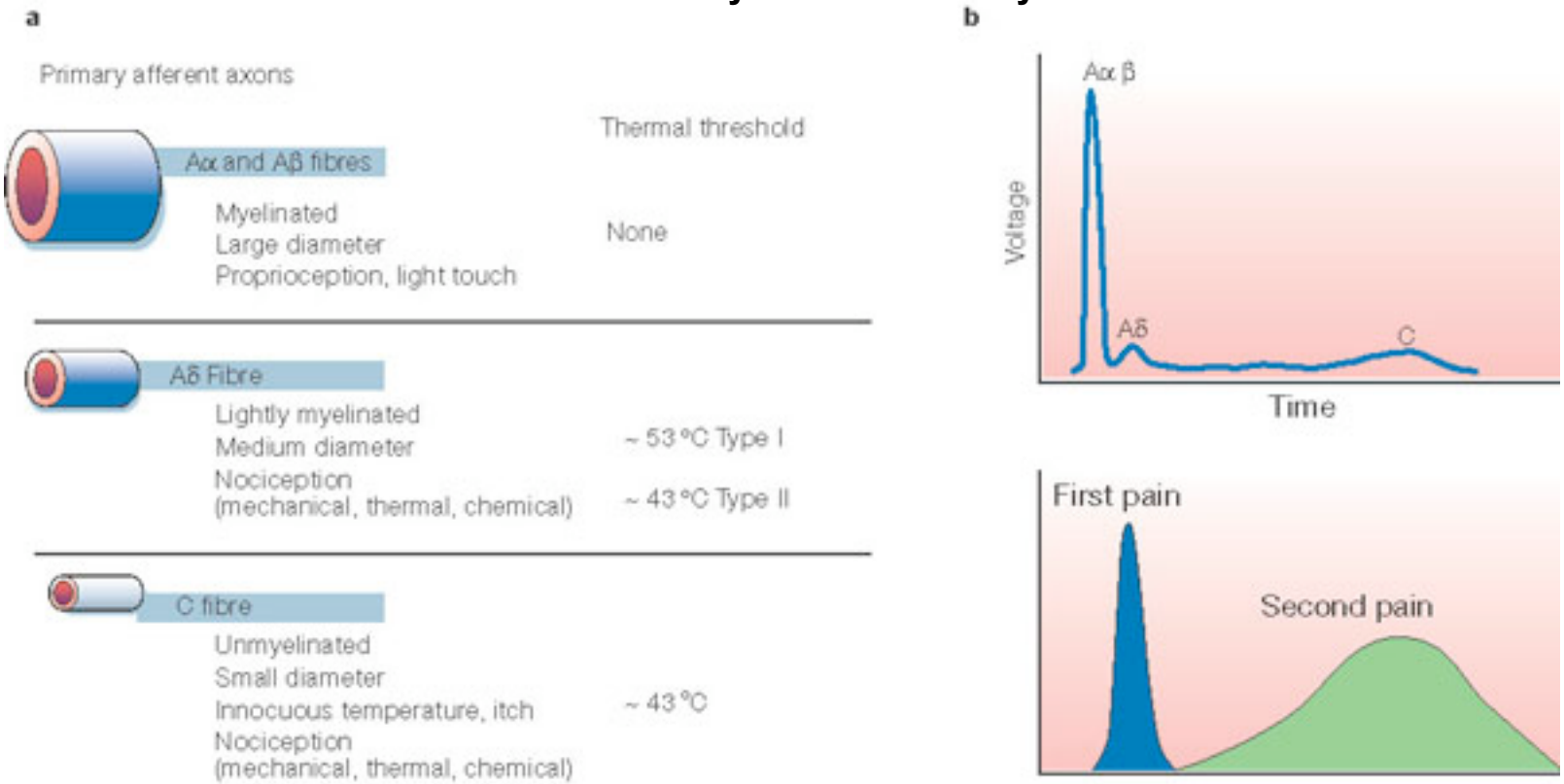


→Phantom limb pain:
during amputation under general anesthesia the spinal cord can still "experience" the insult produced by the surgical procedure and central sensitization occurs. To try to prevent it, local infiltration of anesthetics in the site of surgery. But studies show also rearrangement of cortical circuits (cortical region of the missing limb receives afferents from other site of the skin)



Phantom Pain intensity as a function of Cortical Reorganization.

Fibers that innervate head & body arising from N.trigeminus and DRG can be divided into 3 groups anatomically and functionally



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Tissue specificity: cornea, pain also from innocuos tactile stimuli; teeth, all is painful; intestine distension no damage request; ischemia, sensitivity to H^+

Pain input to the spinal cord:

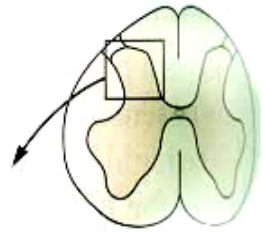
-Projecting neurons in lamina I receive A-delta and C fibers info.

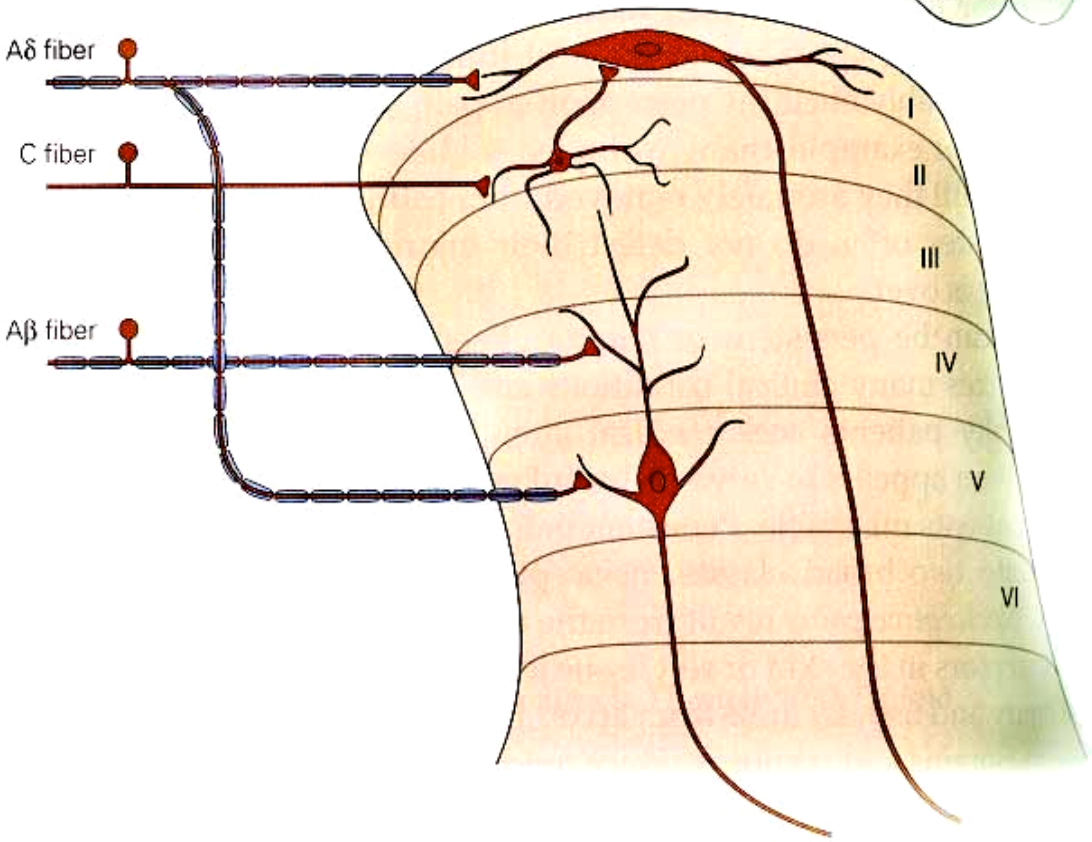
-Neurons in lamina II receive input from C fibers and relay it to other laminae.

-Projecting neurons in lamina V (**wide-dynamic range neurons**) receive A-delta, C and A-beta (low threshold mechanoceptors) fibers information.

How is pain info sent to the brain: hypotheses → pain is signaled by lamina I and V neurons acting together. If lamina I cells are not active, the info about type and location of a stimulus provided by lamina V neurons is interpreted as innocuous. If lamina I cells are active then it is pain.

Thus: lamina V cells→ details about the stimulus, and lamina I cells→ whether it is painful or not





-A-delta and C fibers release glutamate and peptides on dorsal horn neurons.

-Substance P (SP) is co-released with glutamate and enhances and prolongs the actions of glutamate.

-Glutamate action is confined to nearby neurons but SP can diffuse and affect other populations of neurons because there is no specific reuptake.

SYNAPSE IN SUBSTANTIA GELATINOSA

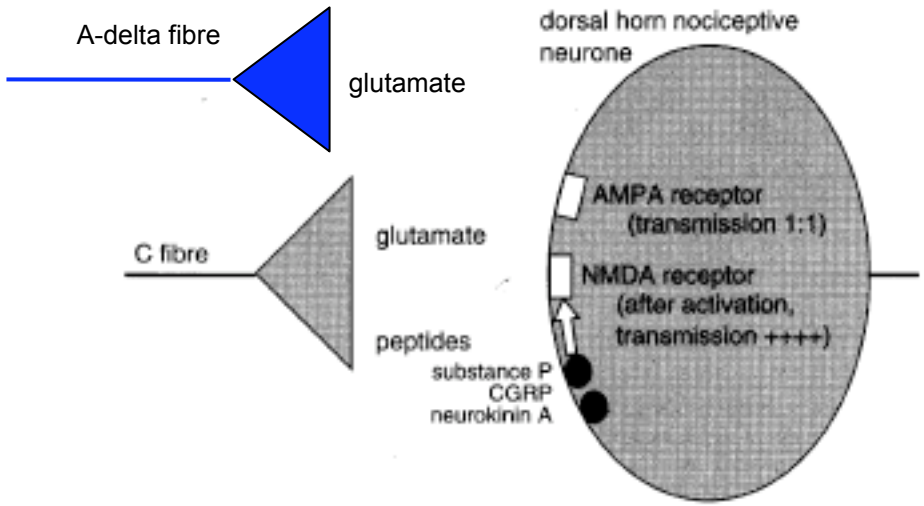


Figure 3.2 Diagram of synapse in substantia gelatinosa, illustrating some transmitters and receptors: peptides activate the NMDA receptor which amplifies the response to incoming nociceptive stimuli. (After Dickenson, 1996, with kind permission of the publishers.)

Triple labelling of the same sections for glutamate, calcitonin gene-related peptide and substance P revealed that glutamate was often co-localized with either of the two neuropeptides in the same terminals. There is an abundant glutamate immunoreactivity in the superficial layers of the rat dorsal horn.

SYNAPSE IN SUBSTANTIA GELATINOSA (SP)

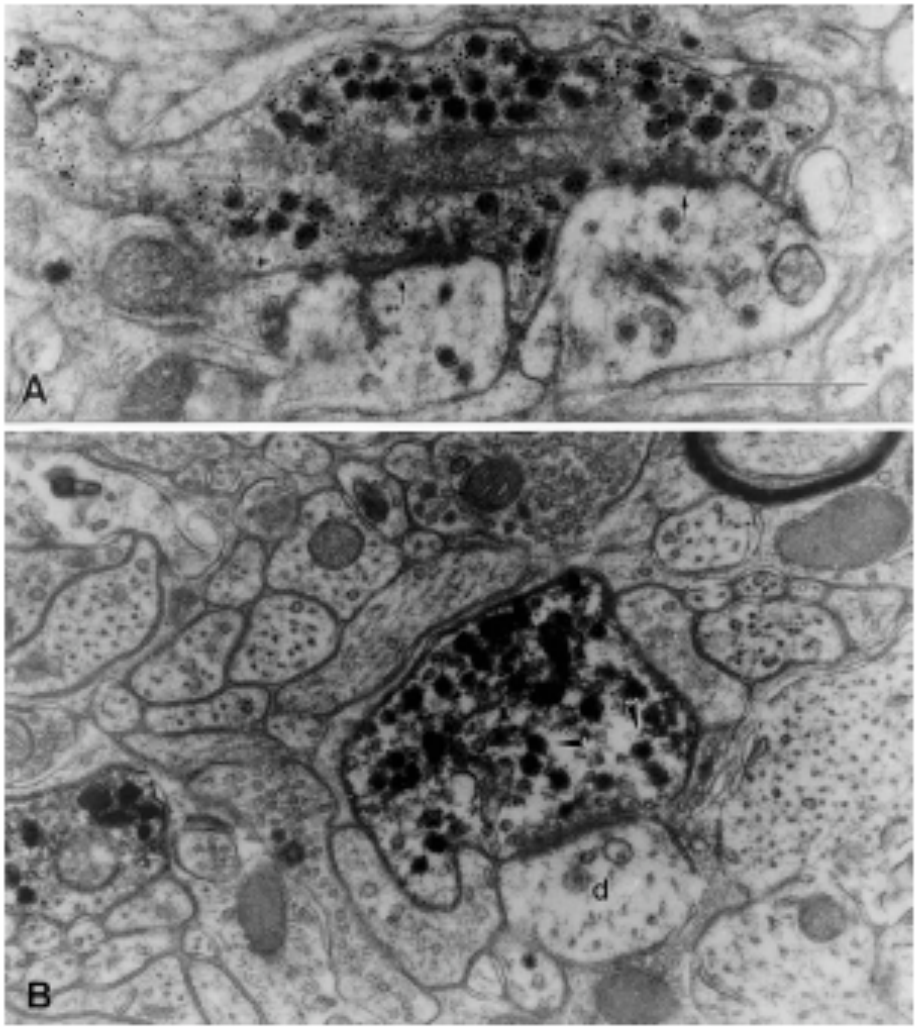
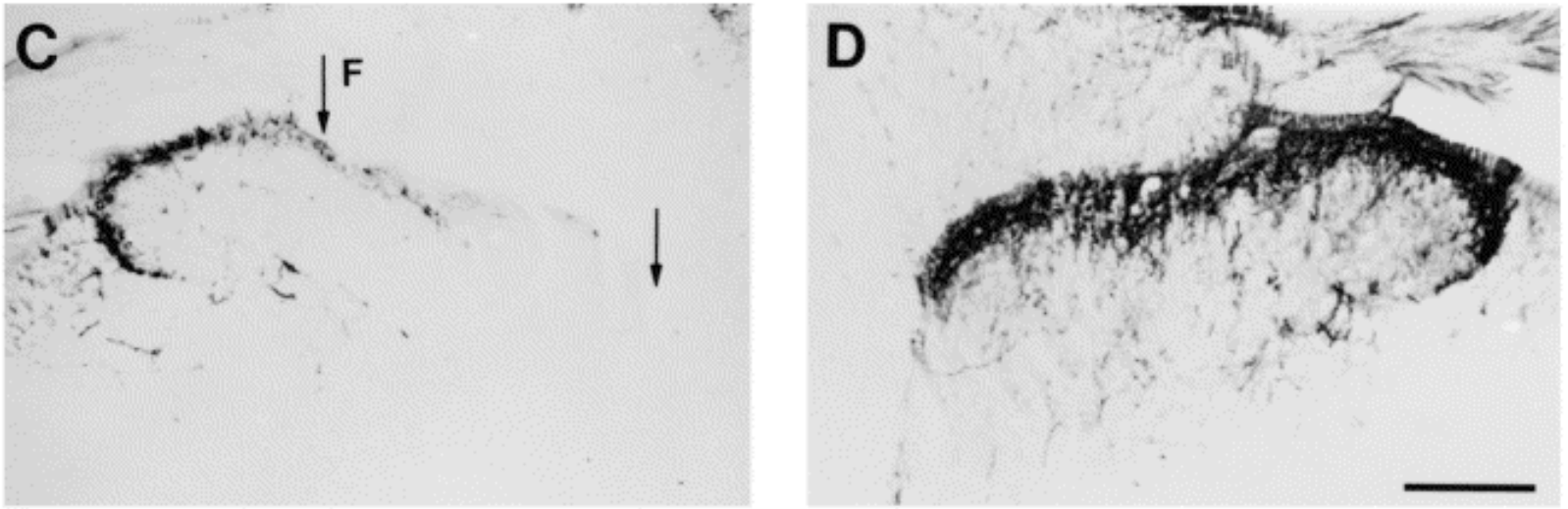


FIGURE 30.4 Peptide content of dense core vesicles in primary afferent synaptic terminals in the superficial dorsal horn of a monkey spinal cord. The electron micrograph in **A** illustrates a synaptic ending that was shown to be immunoreactive for substance P, using the immunogold staining technique. The gold particles are in close relationship to dense core vesicles. The arrows indicate synaptic contacts made by this ending on dendrites in the neuropil of the superficial dorsal horn. The scale is 1 μm. (From Alvarez *et al.*, 1993.) The electron micrograph in **B** shows an axodendritic synapse in the dorsal horn of a monkey. In this case the dense core vesicles in the terminal were stained for calcitonin gene–related peptide using the immunoperoxidase technique. (From Carlton *et al.*, 1988.)

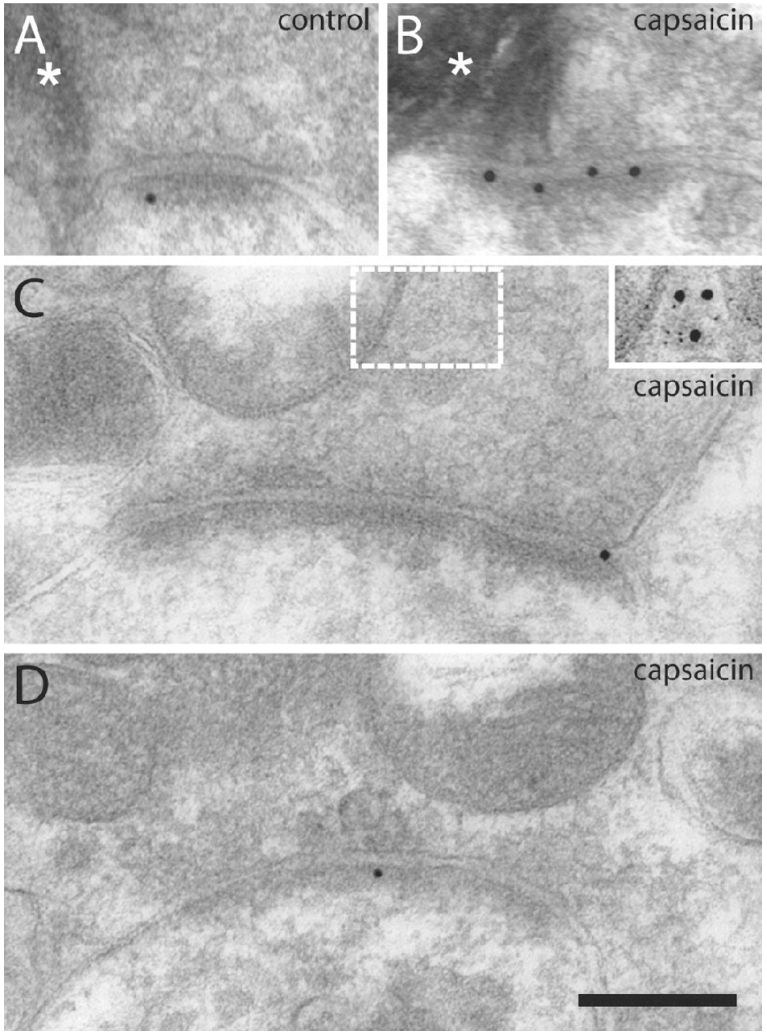
Extent of Laminae I and II in the spinal cord shown by staining CGRP found in small fibre primary afferents



Photomicrographs illustrating calcitonin gene-related peptide (CGRP) immunolabeling in the dorsal horn of the C7 segment after C4–T2 rhizotomy. C: Ipsilateral to the rhizotomy, D: contralateral. Note the absence of staining in the medial part of C7 segment when seven consecutive roots are cut. Calibration bar equals 200 microm.

From Catherine Abbadie et al., Brain Research 930 (2002) 150–162

Examples of GluR1 postembedding immunogold labeling at identified primary afferent synapses after cutaneous capsaicin injection.



Examples of GluR1 postembedding immunogold labeling at identified primary afferent synapses after cutaneous capsaicin injection.
A, B, Electron micrographs of immunolabeled synapses formed by peroxidase+, nonpeptidergic C-fiber terminals in the dorsal horn of controls (A) and after capsaicin stimulation (B). Asterisks indicate peroxidase reaction product.
C, Synapse formed by a SP+/CGRP+ terminal in dorsal horn ipsilateral to capsaicin injection. The white frame indicates the corresponding area of the adjacent section labeled for SP (5 nm gold) and CGRP (15 nm gold) that is shown in the inset.
D, Immunolabeled synapse formed by a presumed LTM fiber in dorsal horn ipsilateral to capsaicin-stimulated skin. Scale bar (in D): 200 nm, valid for A–D.

The Journal of Neuroscience

Larsson M , Broman J J. Neurosci. 2008;28:7084-7090

SYNAPSE IN SUBSTANTIA GELATINOSA

Centrally mediated hyperalgesia:

→Under conditions of persistent injury, C fibers fire repetitively and the response of dorsal horn neurons increase progressively ("wind-up" phenomenon). This is due to activation of the N-methyl-D-aspartate (NMDA)-type glutamate receptor and diffusion of substance P that sensitizes adjacent neurons. Blocking NMDA receptors can block the wind-up.

→Noxious stimulation can produce these long-term changes in dorsal neurons excitability (central sensitization) which constitute a memory of the C fiber input. Can lead to spontaneous pain and decreases in the threshold for the production of pain.

→Carpal tunnel syndrome: median nerve frequently injured at the flexor retinaculum. Pain ends up affecting the entire arm. (rat model → partial ligature of sciatic nerve or nerve wrapped with irritant solution)

Mechanisms of early-onset central sensitization:

Windup→homosynaptic activity-dependent plasticity characterized by a progressive increase in firing from dorsal horn neurons during a train of repeated low-frequency C-fiber or nociceptor stimulation.

During stimulation, glutamate + substance P + CGRP elicit slow synaptic potentials lasting several-hundred milliseconds. Windup results from the summation of these slow synaptic potentials. This produces a cumulative depolarization that leads to removal of the voltage-dependent Mg2+ channel blockade in NMDA receptors and entry of Ca2+. Increasing glutamate action progressively increases the firing-response to each individual stimulus (behavioral correlate: repeated mechanical or noxious heat are perceived as more and more painful even if the stimulus intensity does not change.

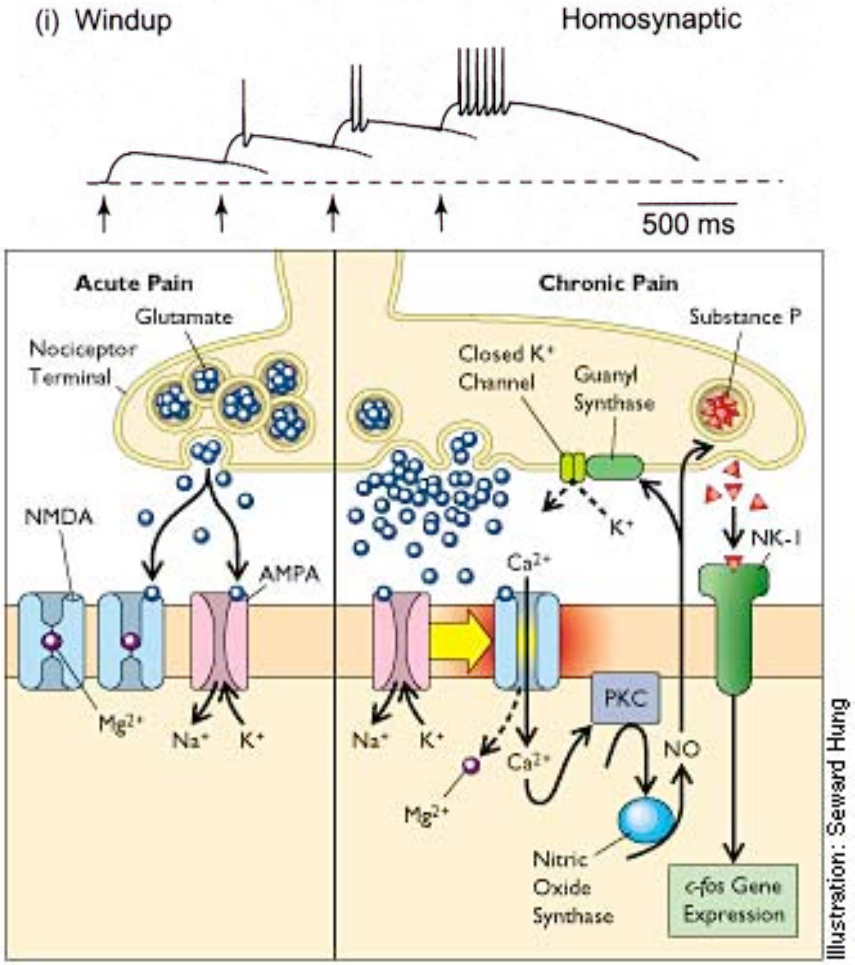
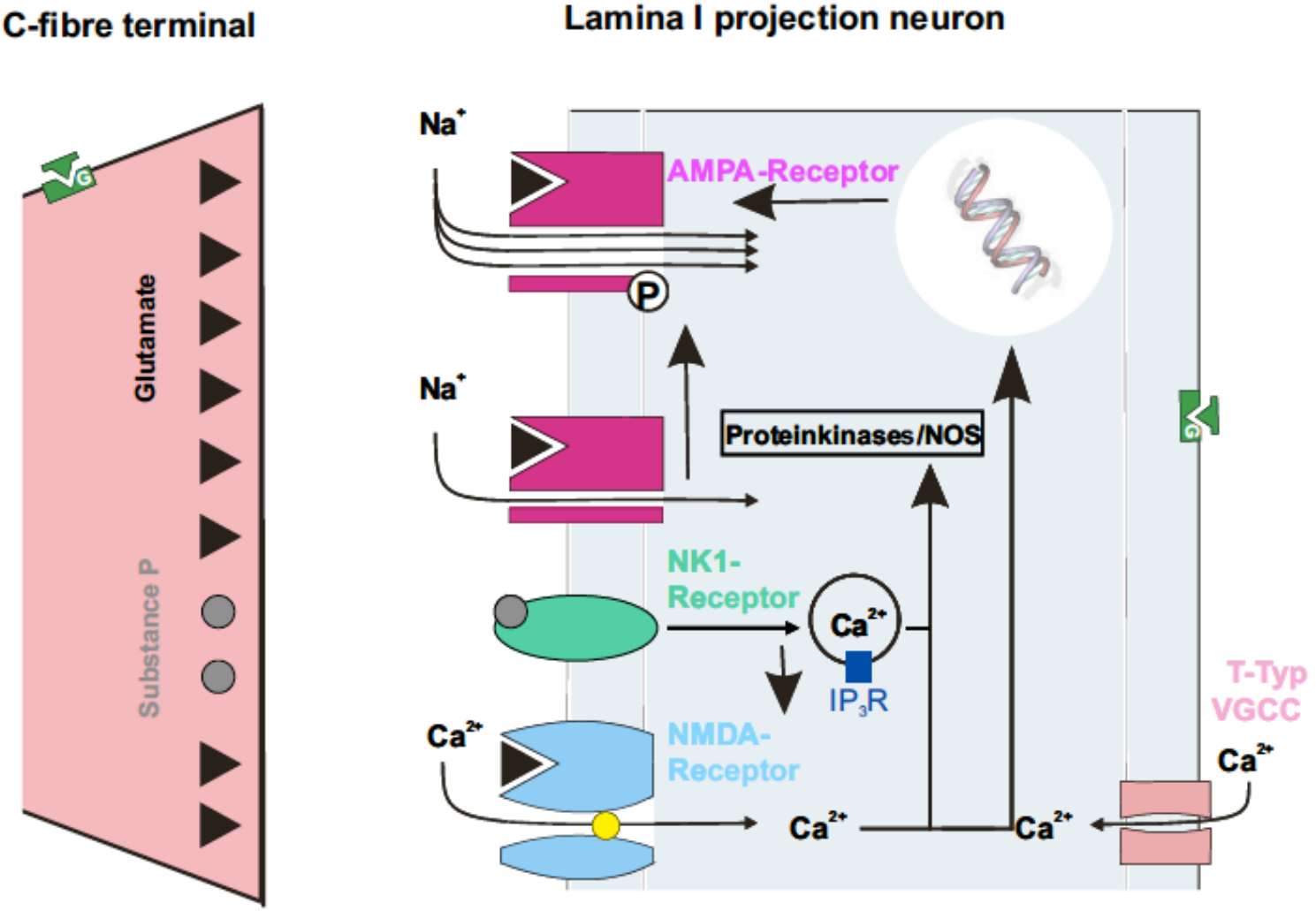
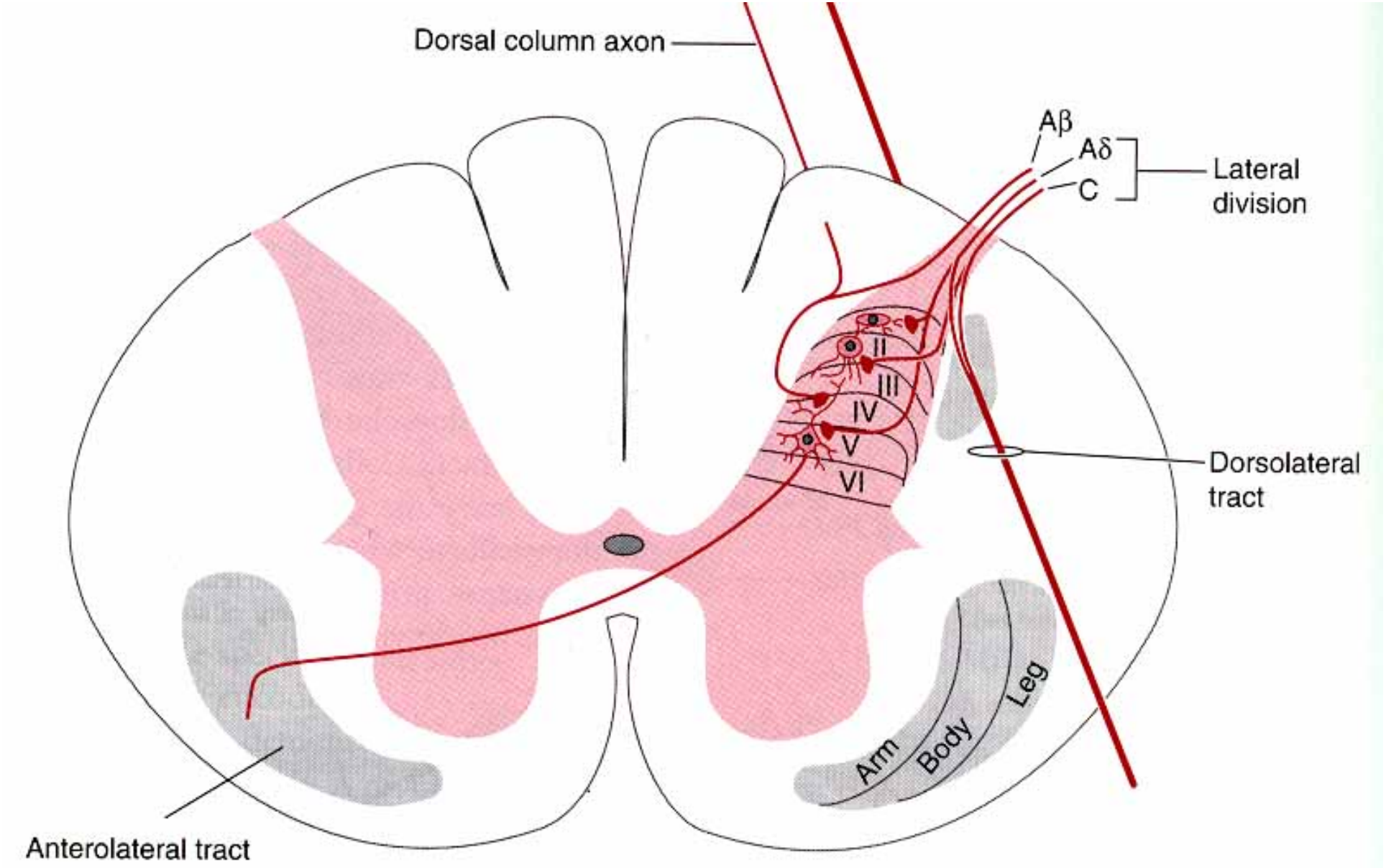


Figure 3. Incoming pain signals trigger the release of glutamate into the synaptic cleft between nociceptors and dorsal horn cells. In acute pain, glutamate activates AMPA receptors on Na^+, K^+ channels. With prolonged activation, the polarization of the membrane changes; the Mg^{2+} plug in the Ca^{2+} channels is removed; and NMDA receptors in the channel complex are primed for glutamate activation. Ca^{2+} flowing into the cell activates protein kinase C, the enzyme needed for NO synthase production of NO. NO diffuses through the dorsal cell membrane and synaptic cleft into the nociceptor and stimulates guanyl synthase-induced closure of K^+ channels. Since endorphins and enkephalins inhibit pain by opening these channels, closure induces opiate resistance. NO also stimulates the release of substance P, which, by binding to NK-1 receptors in the dorsal horn membrane, triggers *c-fos* gene expression and promotes neural remodeling and hypersensitization.



Potential mechanisms of potentiation and de-potentiation at synapses between C-fibres and spinal cord projection neurons. Conditioning electrical nerve stimulation or natural noxious stimulation triggers release of GLU and SP which causes opening of NMDA receptor channels and T-type voltage-gated Ca^{2+} channel and Ca^{2+} release from intracellular stores. This activates Ca^{2+}-dependent signal transduction pathways including PKs and transcription factors. Synaptic strength is probably increased by phosphorylation of synaptic proteins including AMPA receptor channels, altered trafficking of synaptic proteins, e.g. increased insertion of AMPA receptors into the sub-synaptic membrane and de-novo protein synthesis. According to this model, LTP can be prevented if release of GLU and/or SP is inhibited, for example by activation of pre-synaptic, G-protein-coupled μ-opioid receptors, or if opening of voltage sensitive and Ca2+ permeable ion channels is blocked, e.g. via postsynaptic inhibition by an opioid. Depotentiation could result from de-phosphorylation of synaptic proteins, changes in receptors trafficking and degradation of synaptic proteins.

Gate Control Theory of Pain:



Gate Control Hypothesis:

Wall & Melzack 1965

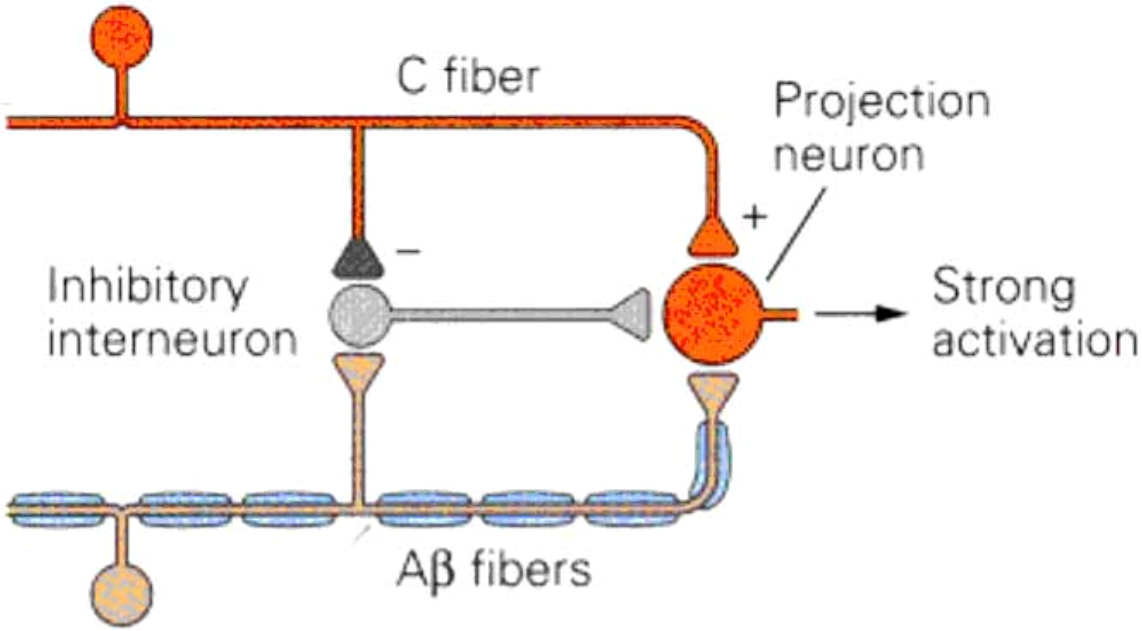
→Hypothesized interneurons activated by A-beta fibers act as a gate, controlling primarily the transmission of pain stimuli conveyed by C fibers to higher centers.

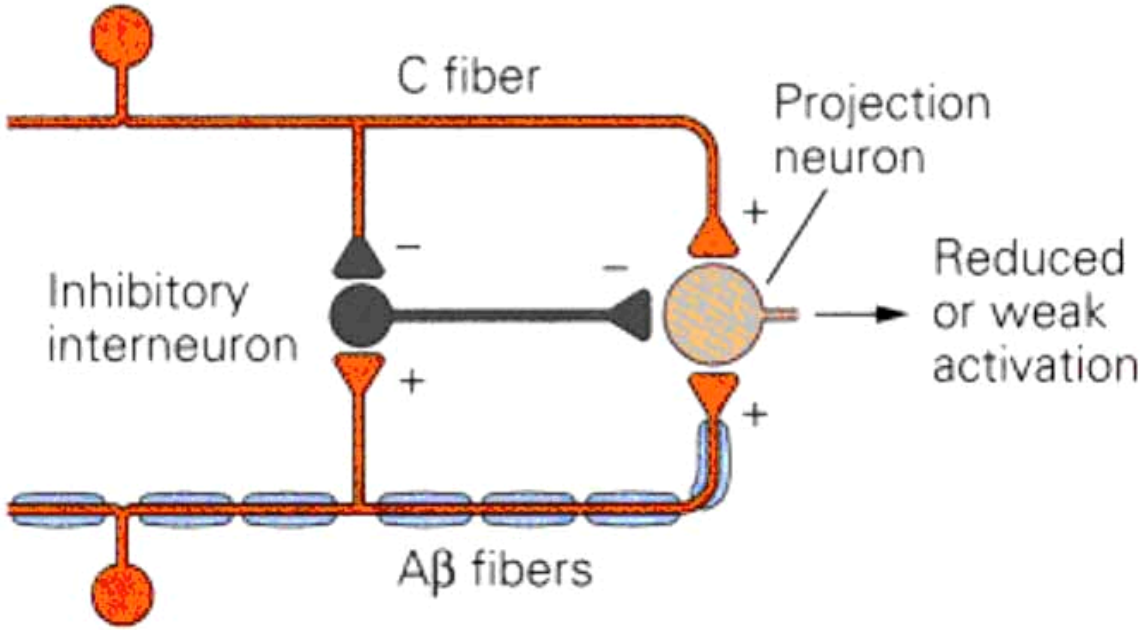
→i.e. rubbing the skin near the site of injury to feel better.

→i.e. Transcutaneous electrical nerve stimulation (TENS).

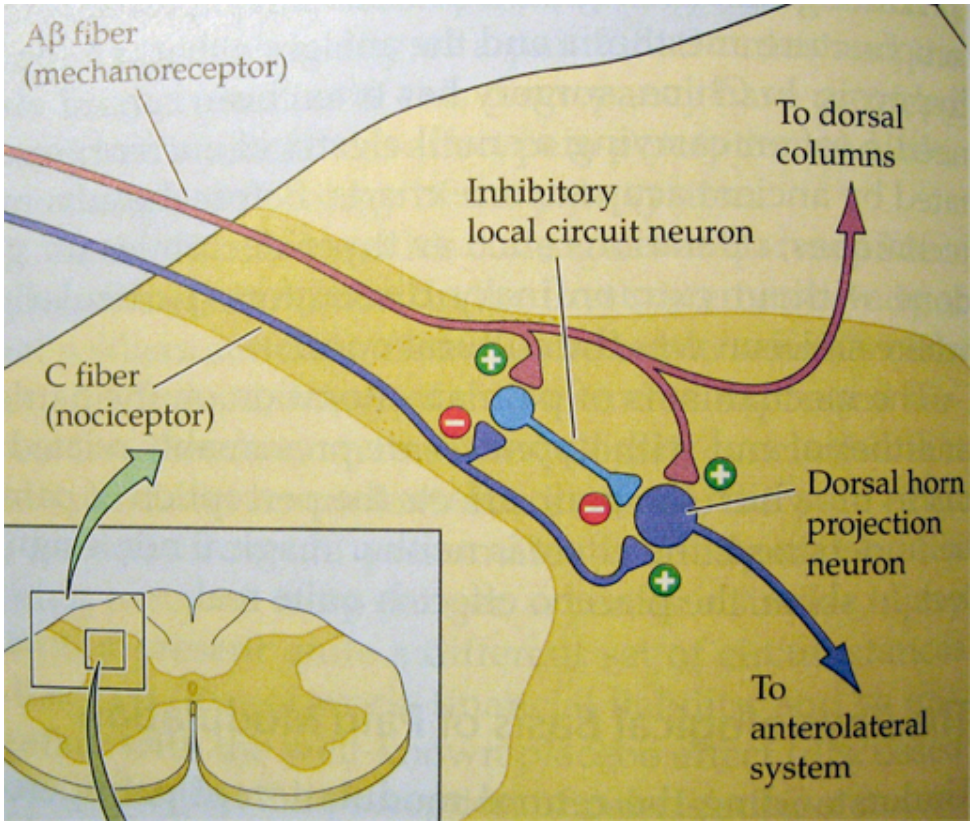
→i.e. dorsal column stim.

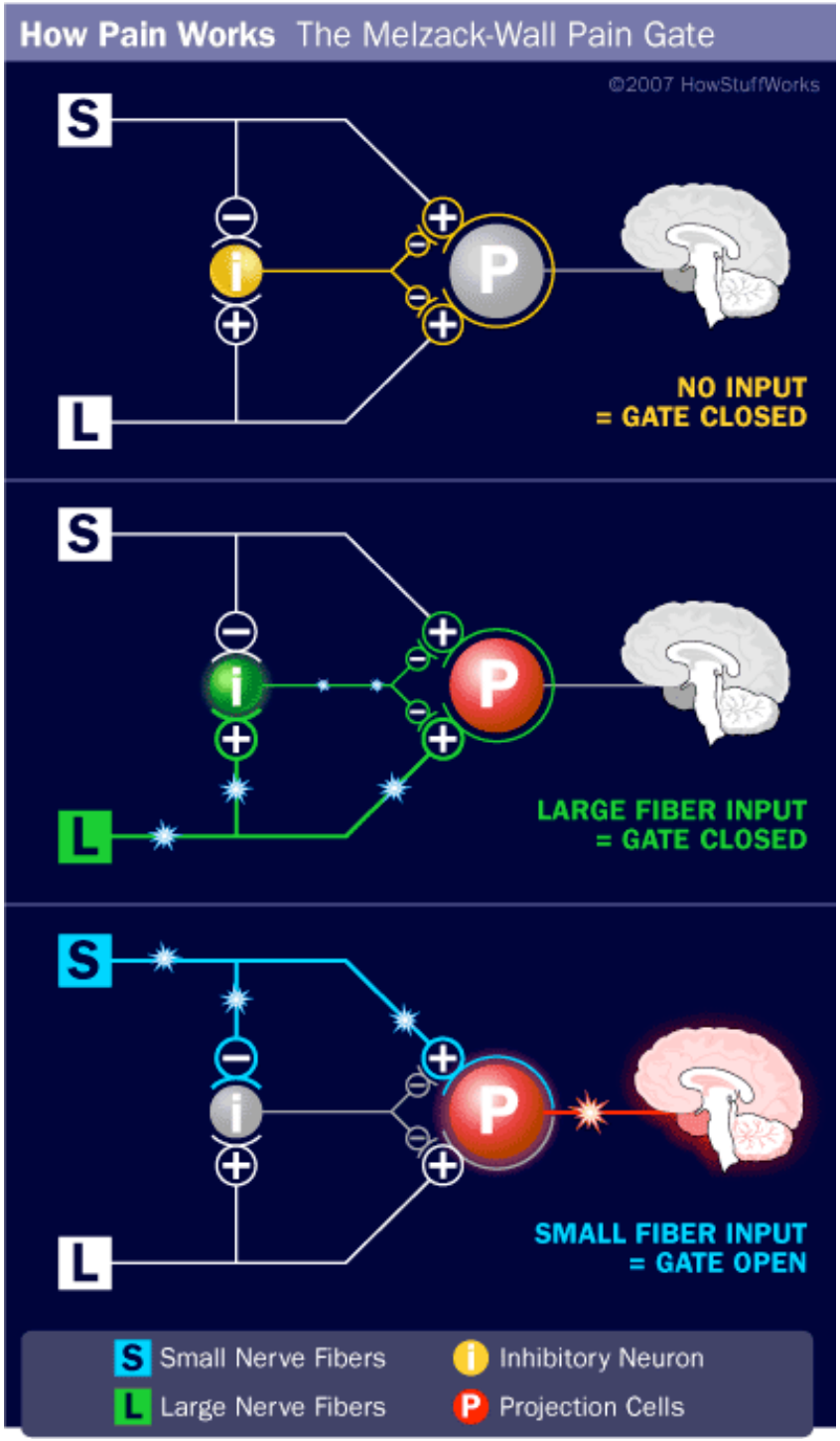
→i.e. Acupuncture



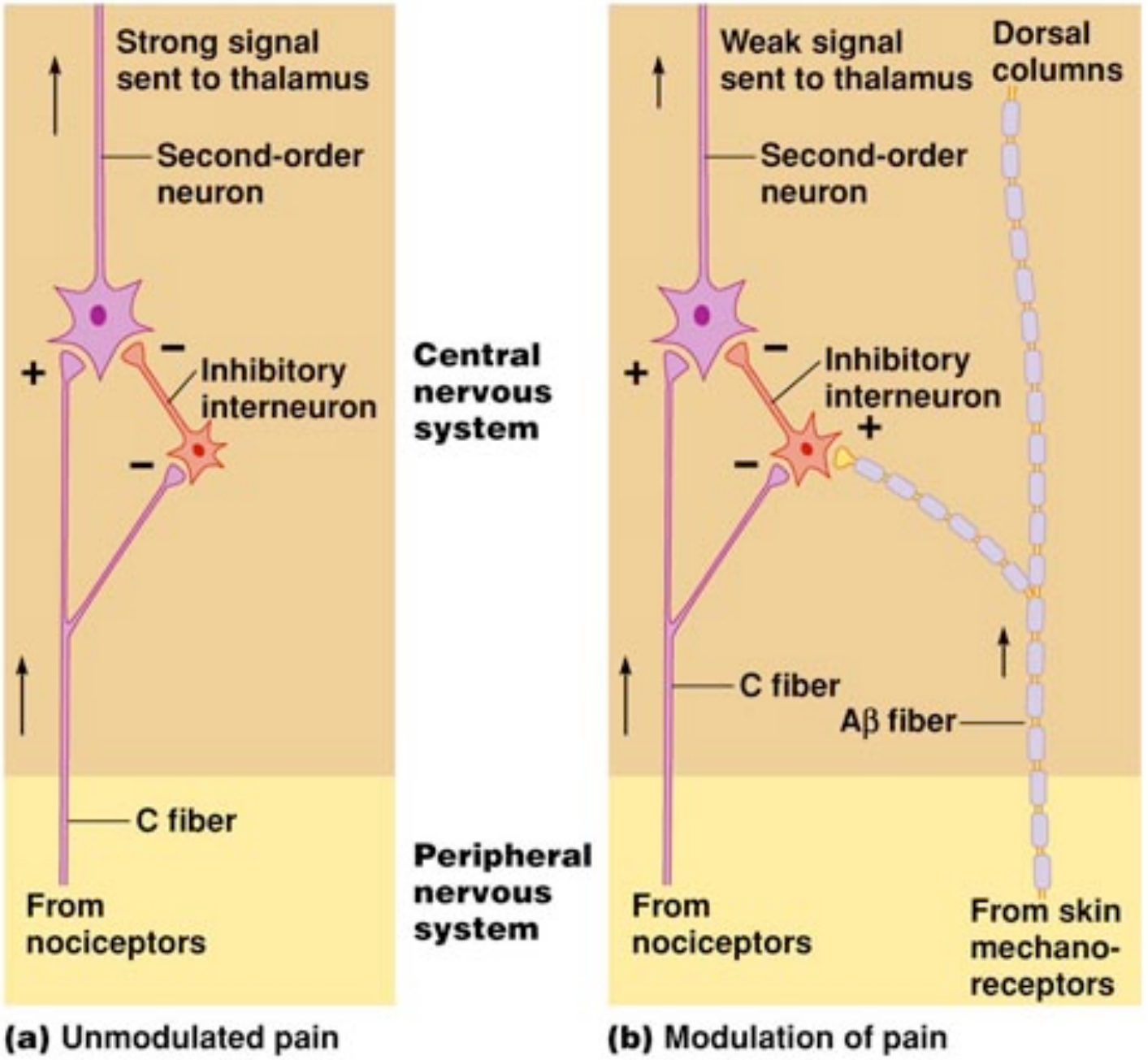


Gate Control Hypothesis





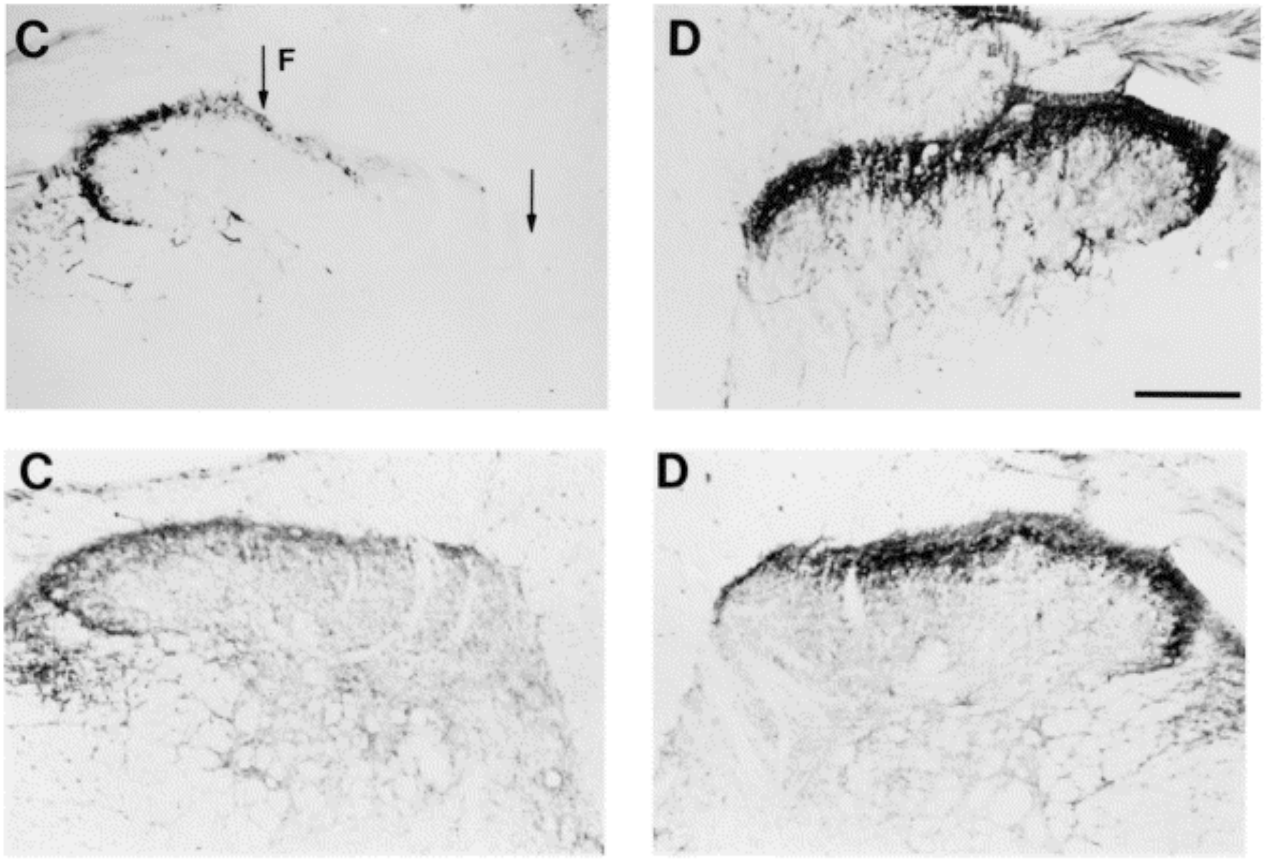
THE ROLE OF INHIBITORY INTERNEURONS



(a) Unmodulated pain

(b) Modulation of pain

Distribution of endogenous opiate receptor compared with CGRP in rat cord



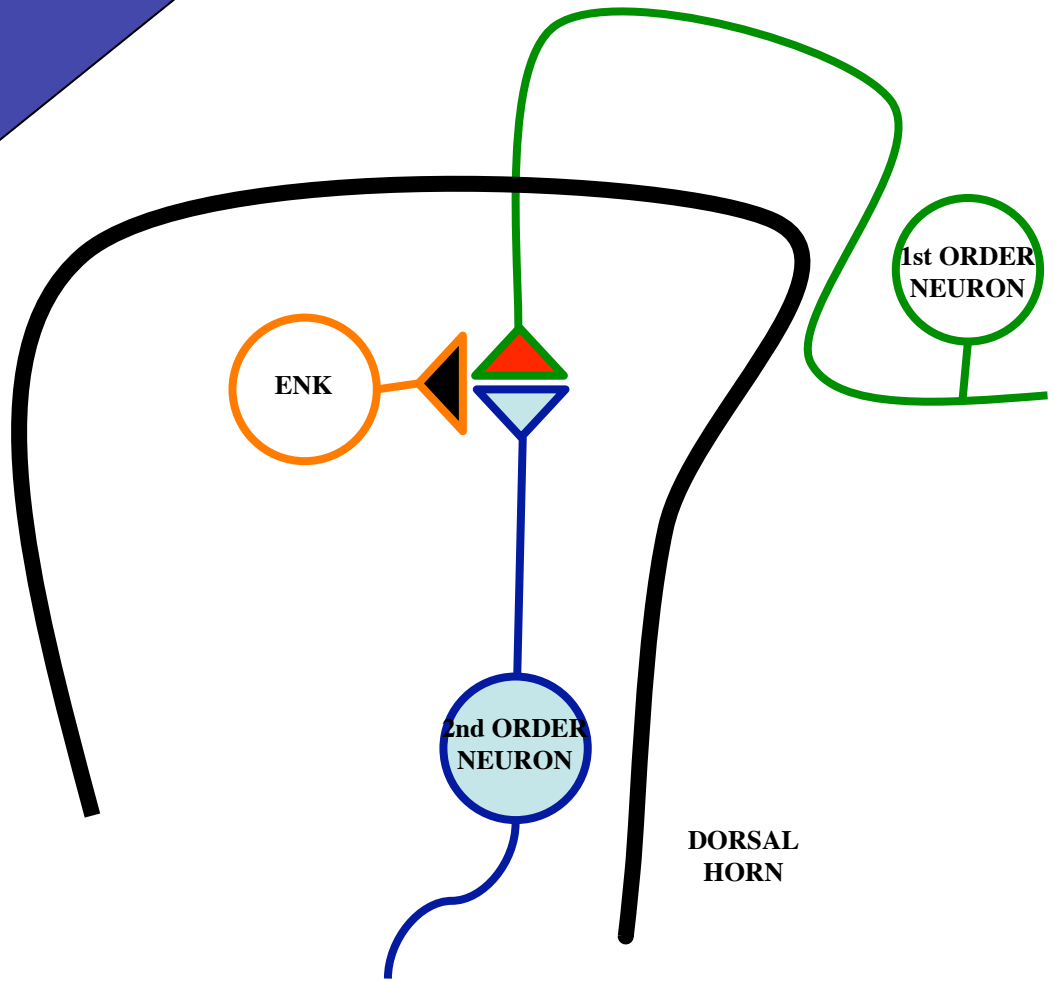
Staining for CGRP as in previous slide. Calibration bar equals 200 microm.

Staining for the delta opiate receptor

Photomicrographs of the C7 segment after C4–T2 rhizotomy. C: Ipsilateral to the rhizotomy, D: contralateral. Note (1) the staining is very similar for both markers, i.e. delta opiate receptors are mostly in laminae I and II and (2) marked reduction of staining on the rhizotomy side for the delta receptor indicating that a lot of the receptors are on the terminals of primary afferents.

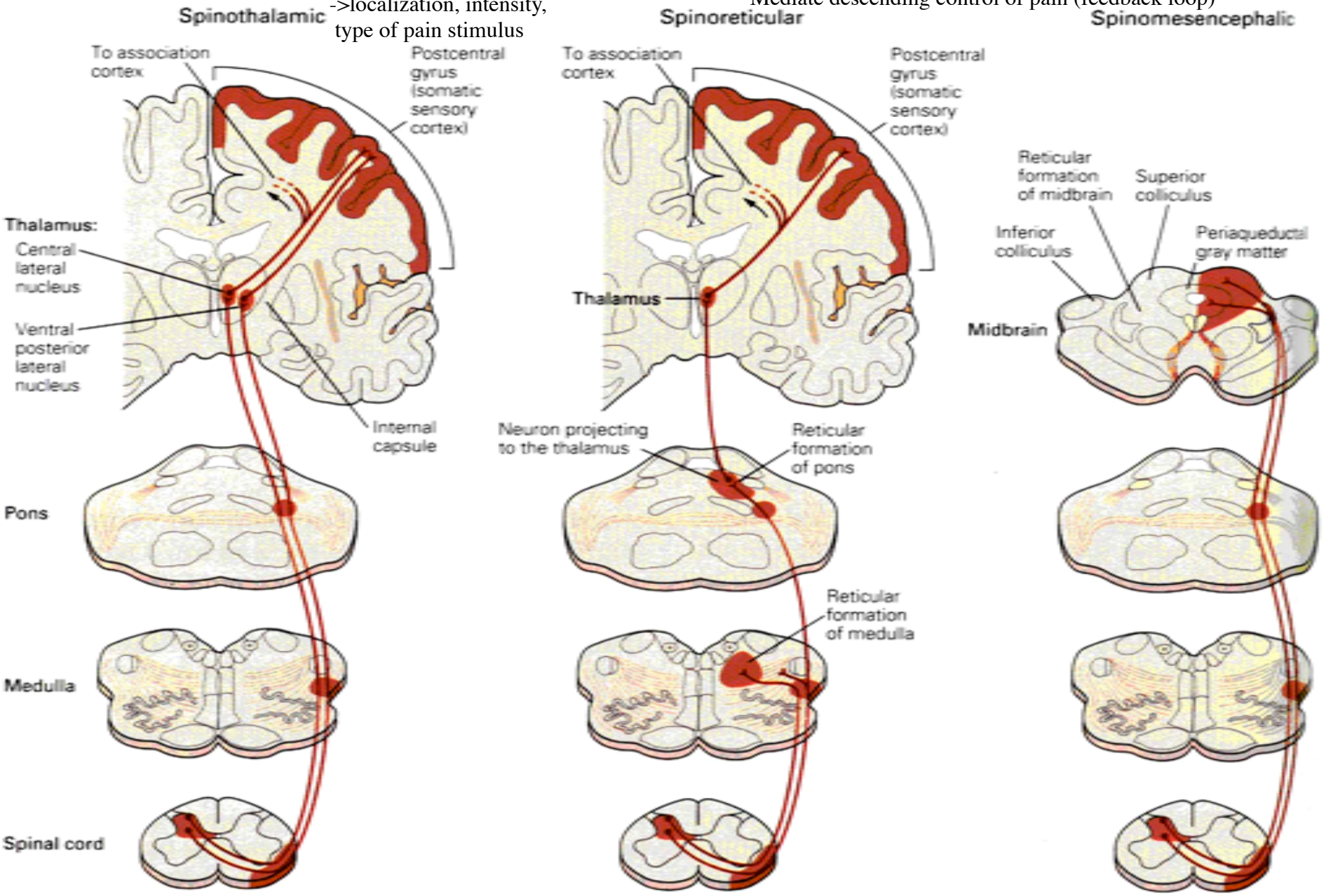
From Catherine Abbadie et al., Brain Research 930 (2002) 150–162

Gate Control Hypothesis: ENKEPHALNERGIC INTERNEURONS

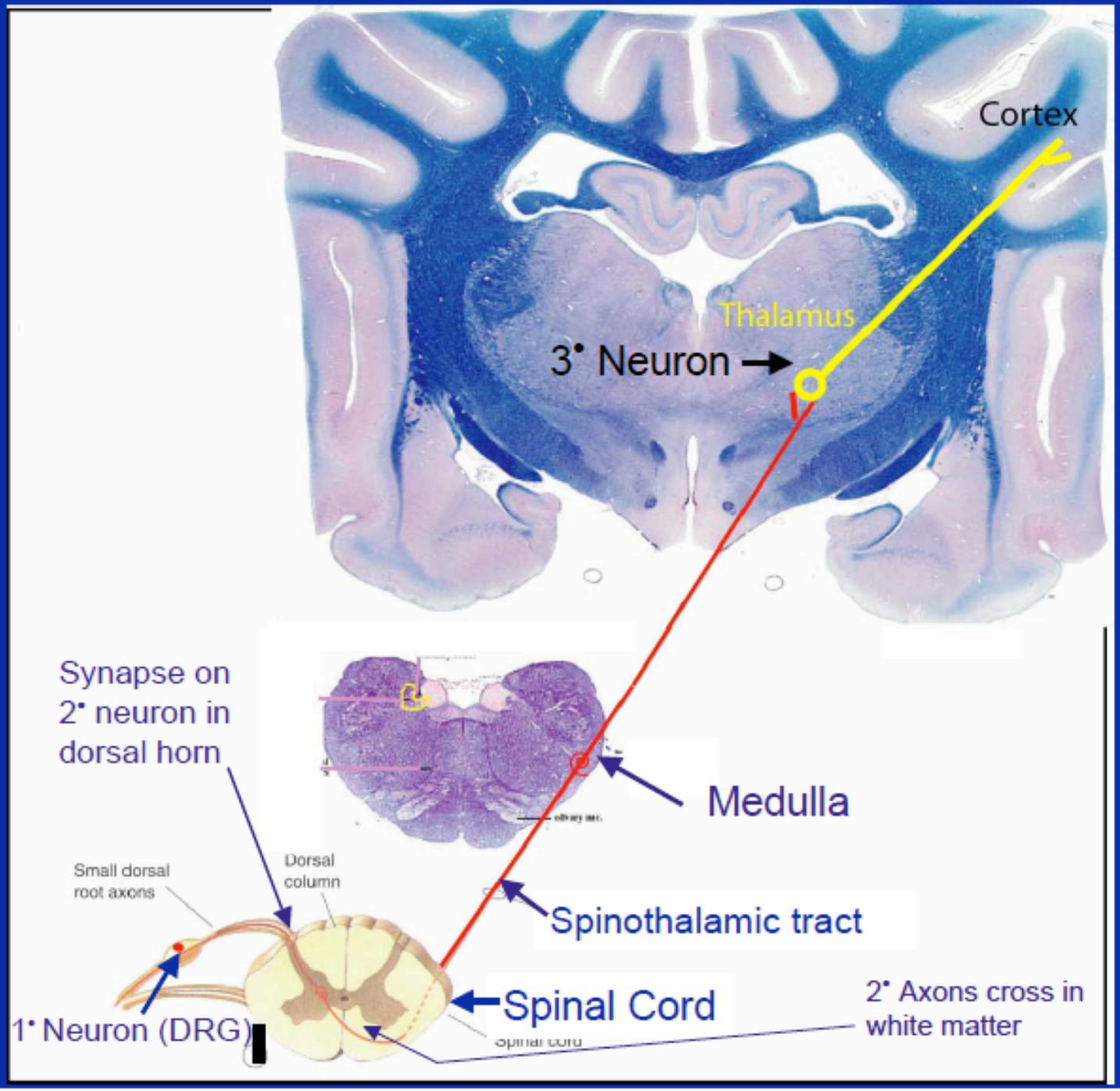


Ascending Pathways:

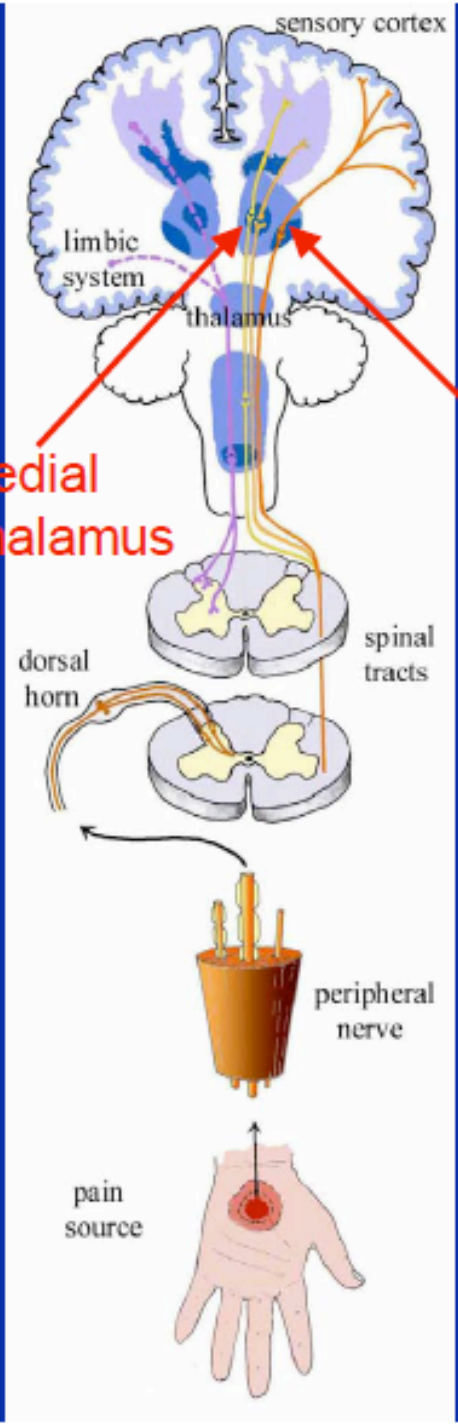
->arousal, emotion; involves limbic system, amygdala, insula, cingulate cortex, hypothalamus. Mediate descending control of pain (feedback loop)



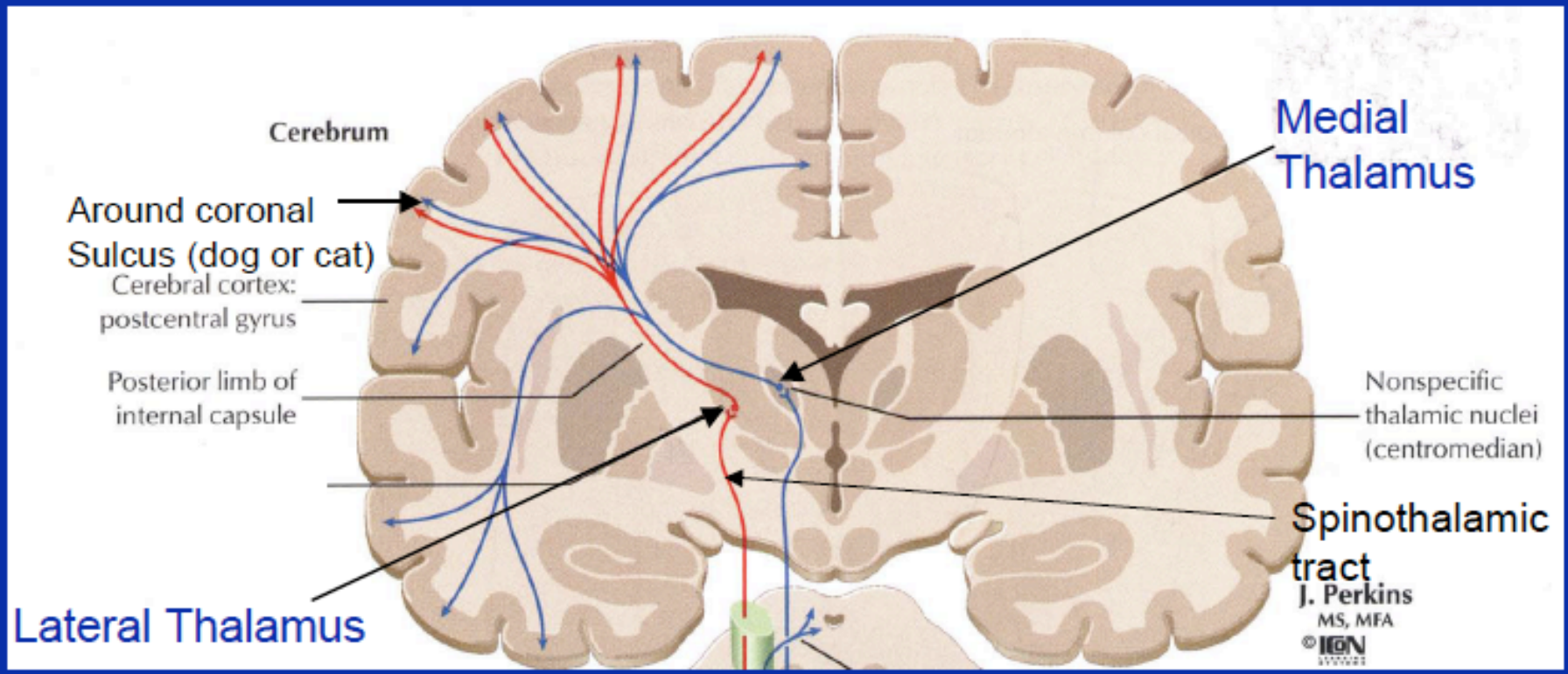
Pain Pathways: Spino-thalamic tract



(C). The axons of 2nd order neurons synapse on 3rd order neurons in the thalamus. The **Thalamus** is the crucial relay for the reception and processing of nociceptive information in route to the cortex. Axons terminating in the **lateral thalamus** mediate discrimative aspects of pain. Axons terminating in the **medial thalamus** mediate the motivational-affective aspects of pain (emotional aspects of pain; attention to and memory of pain).

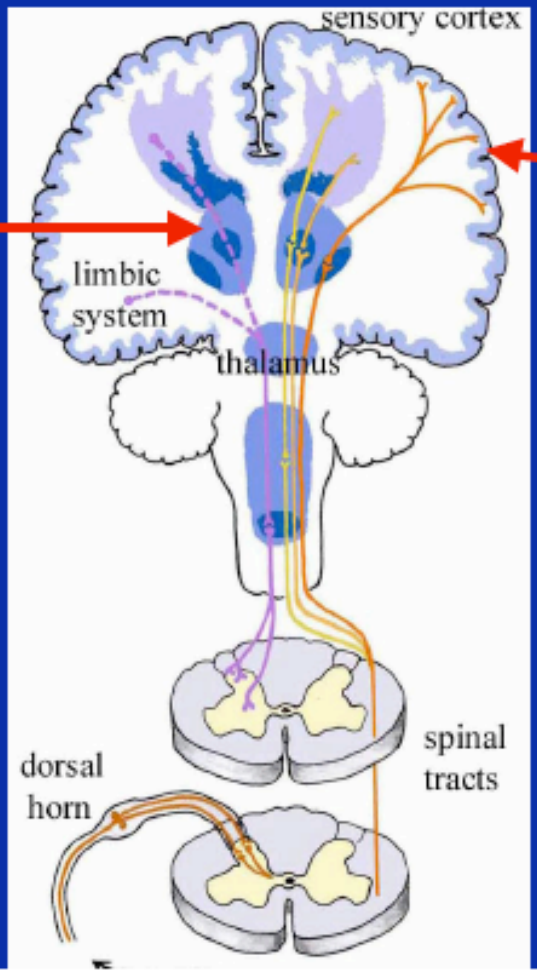


(D) These 3rd order neurons in the thalamus in turn send their axons to the **cerebral cortex.** Note: neurons in the lateral thalamus (for discrimination) project to the somatosensory cortex. Neurons in the medial thalamus (for affective aspects of pain project to other areas of cortex (prefrontal, insular and cingulate gyrus).



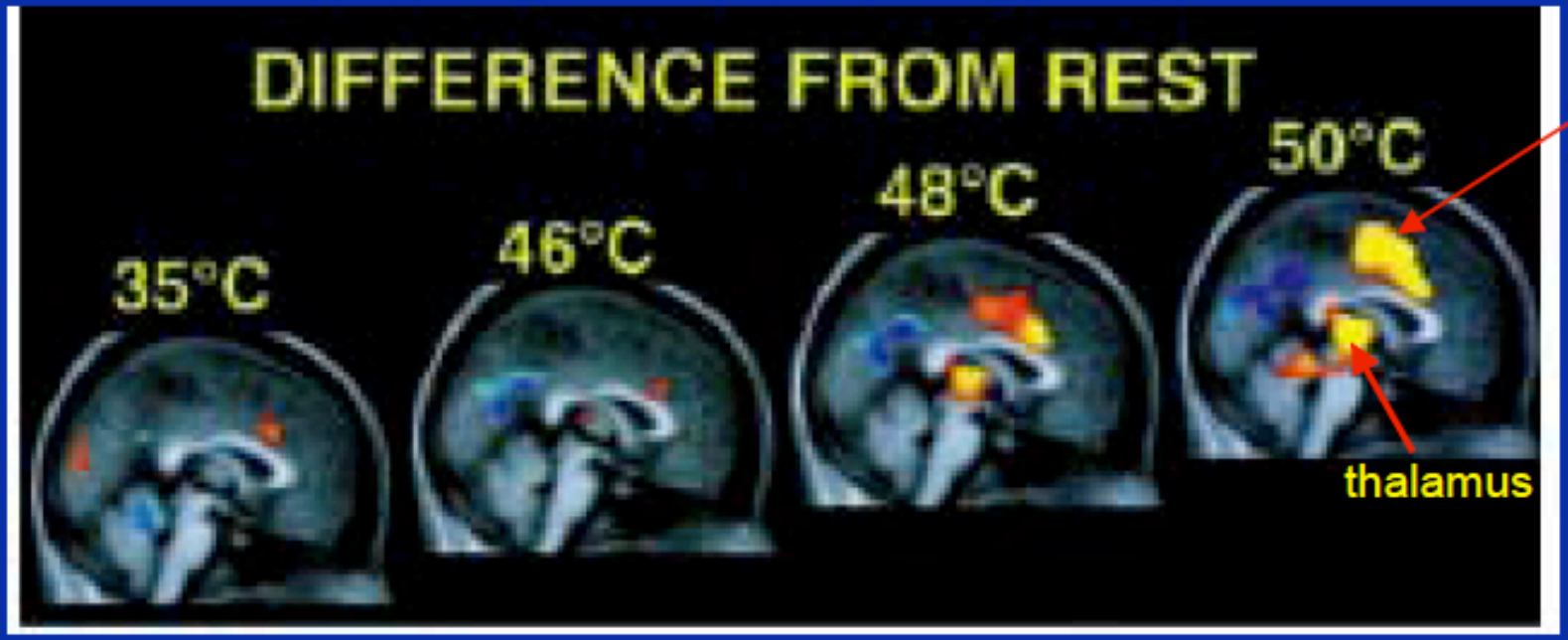
Note: An animal becomes aware of painful stimuli at the level of the thalamus, the cerebral cortex is required for localization of the pain to a specific body region. It should also be noted that in addition to pain the spinothalamic pathway conveys temperature sensation.

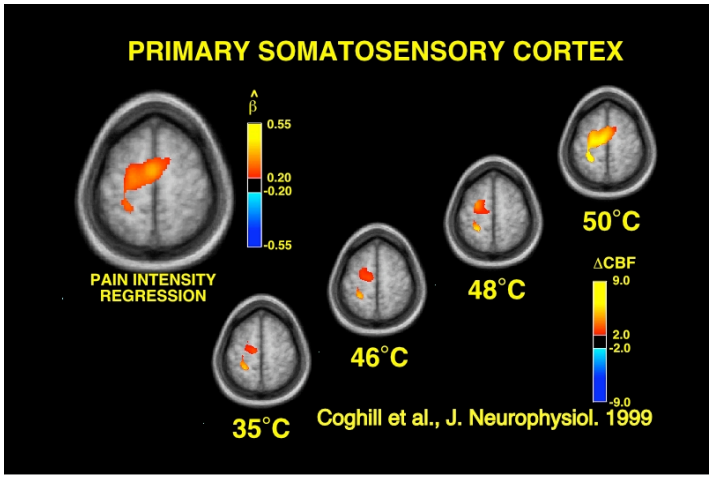
Thalamus: Aware of pain

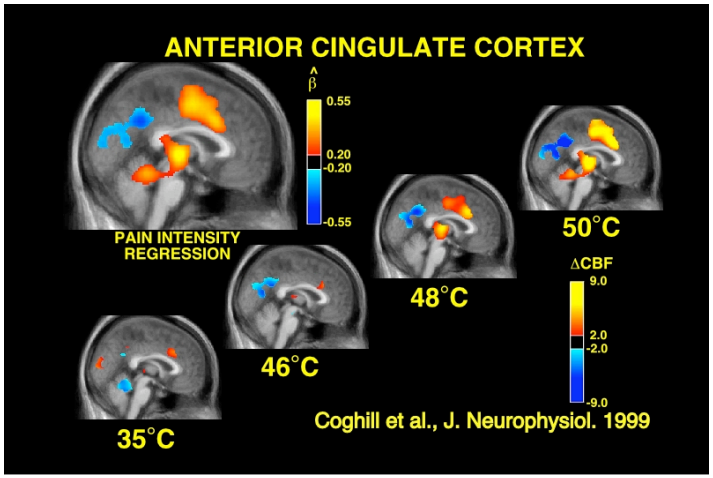


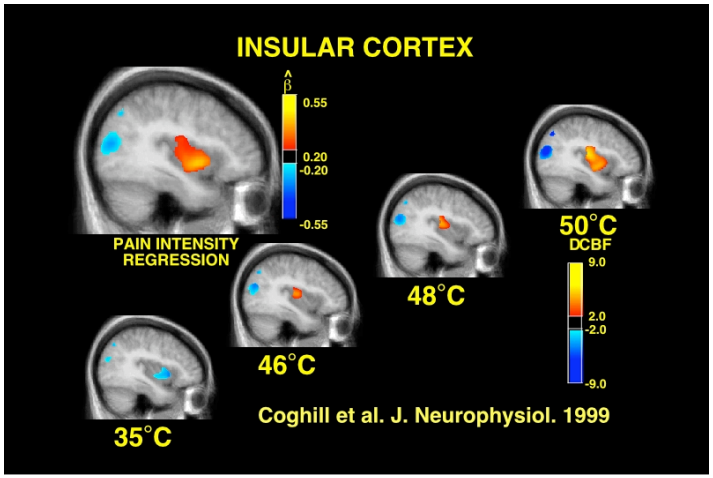
Somatosensory Cortex: required for localization of pain.

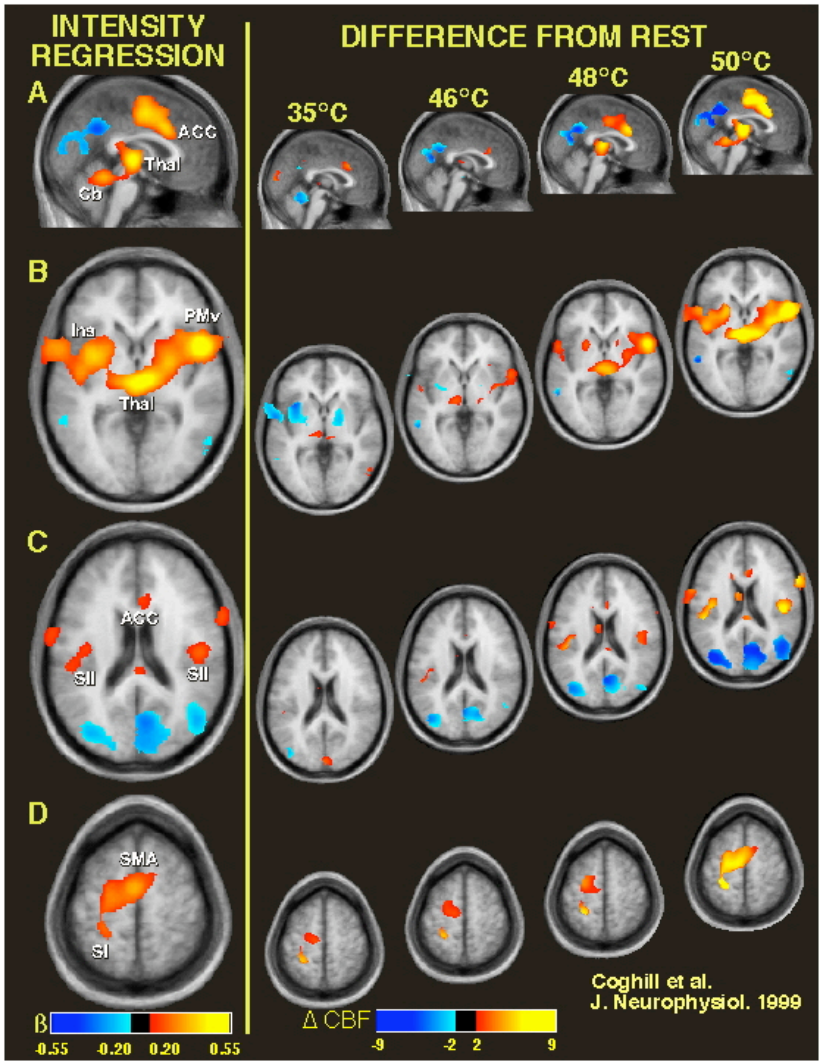
Human brain activity related to pain intensity during acute unilateral noxious heat stimulation. Increases in cerebral blood flow are found in the **thalamus and anterior cingulate cortex** as stimulus temperature increases.









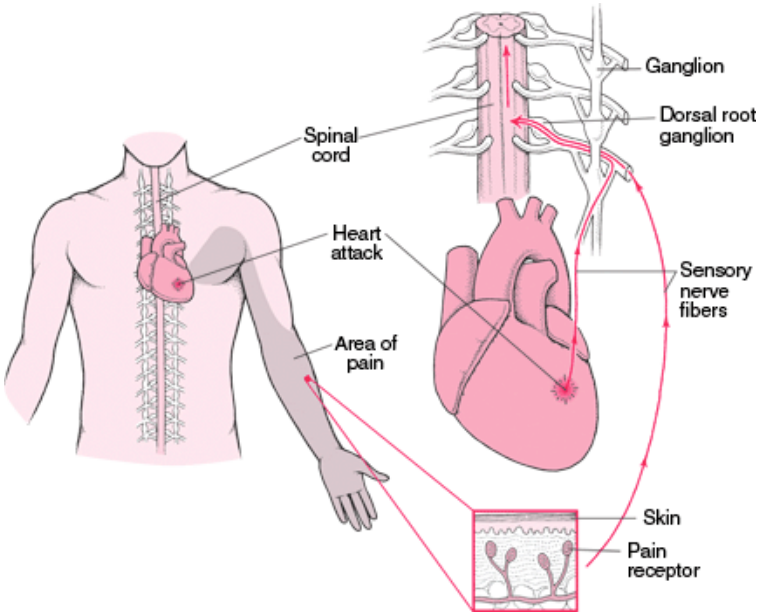


Multiple regression analysis (left panel) of positron emission tomography data revealed statistically reliable relationships between perceived pain intensity and activation of a functionally diverse group of brain regions, including those important in sensation, motor control, affect, and attention. Pain intensity-related activation occurred bilaterally in the cerebellum (CB), putamen, thalamus (Thal), insula, anterior cingulate cortex (ACC), and secondary somatosensory cortex (SII), contralaterally in the primary somatosensory cortex (SI) and supplementary motor area (SMA), and ipsilaterally in the frontal operculum (PMv).

Referred pain

- Pain experienced at a point distant to its point of origin
- Area of referred pain is supplied by same spinal segment as actual site of pain
- Brain misinterprets signals as coming from somatic regions
- Knowledge of different types of referred pain is important in clinical diagnosis because in many visceral ailments the only clinical signs is referred pain.

Referred Pain: pain being felt in an area away from the actual source of the pain.



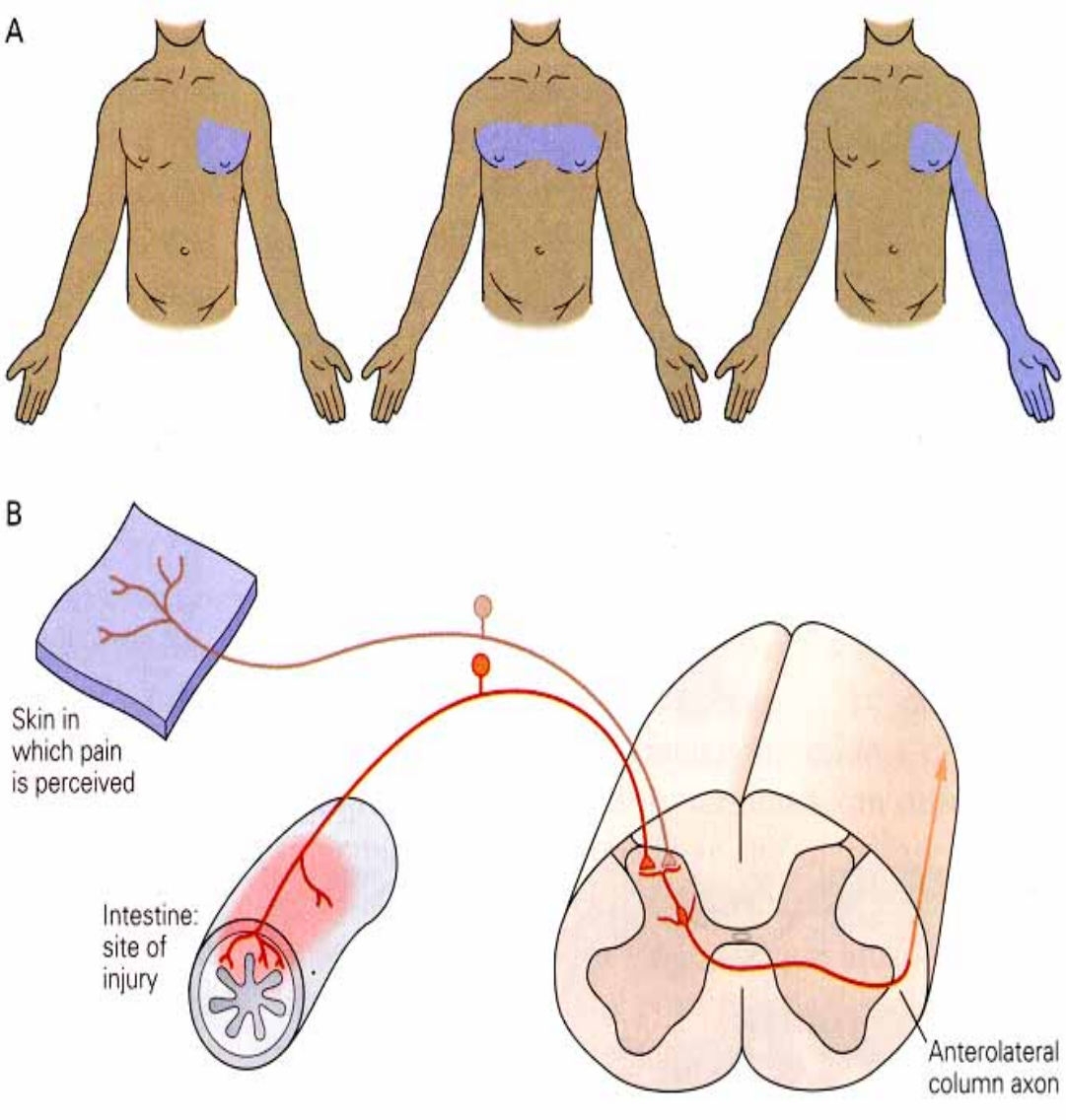
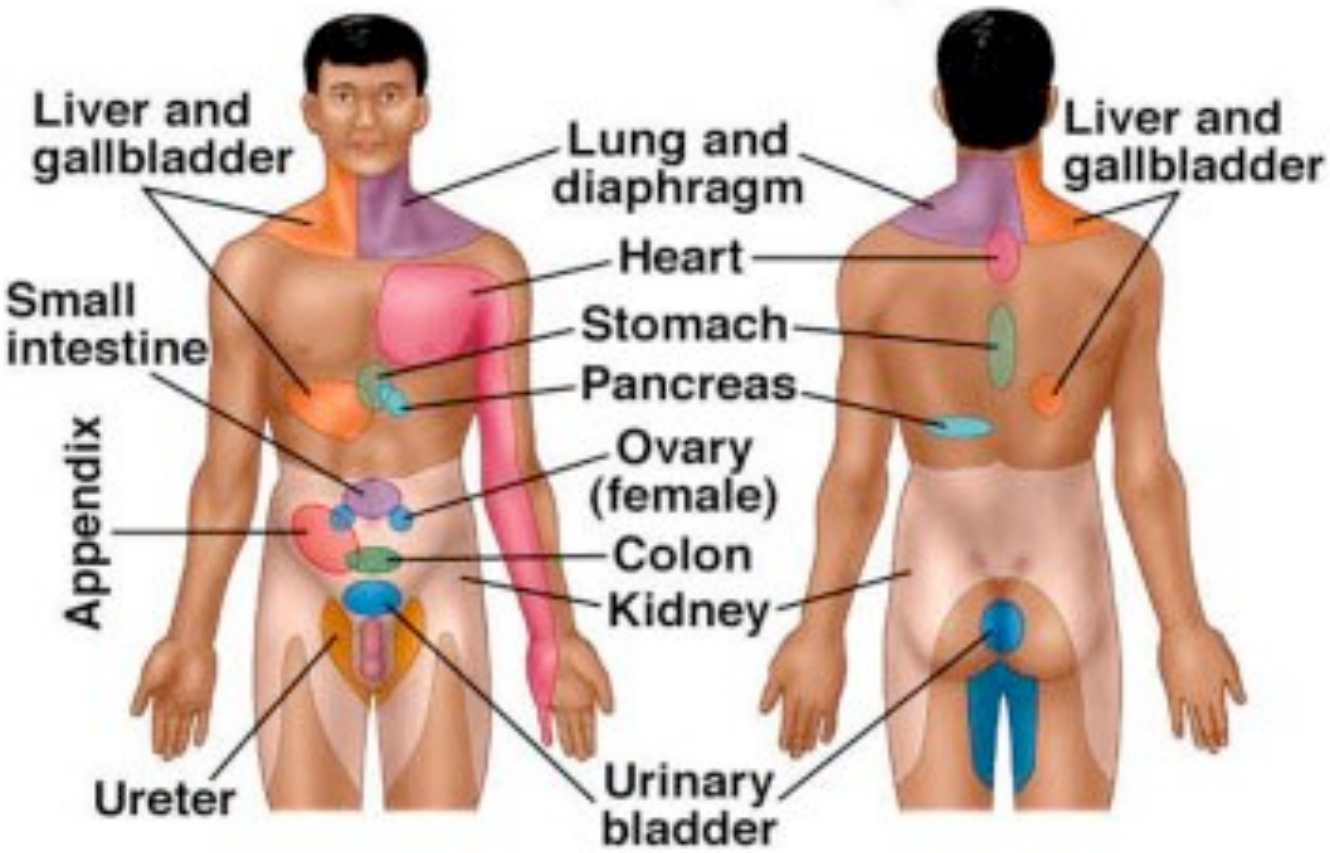


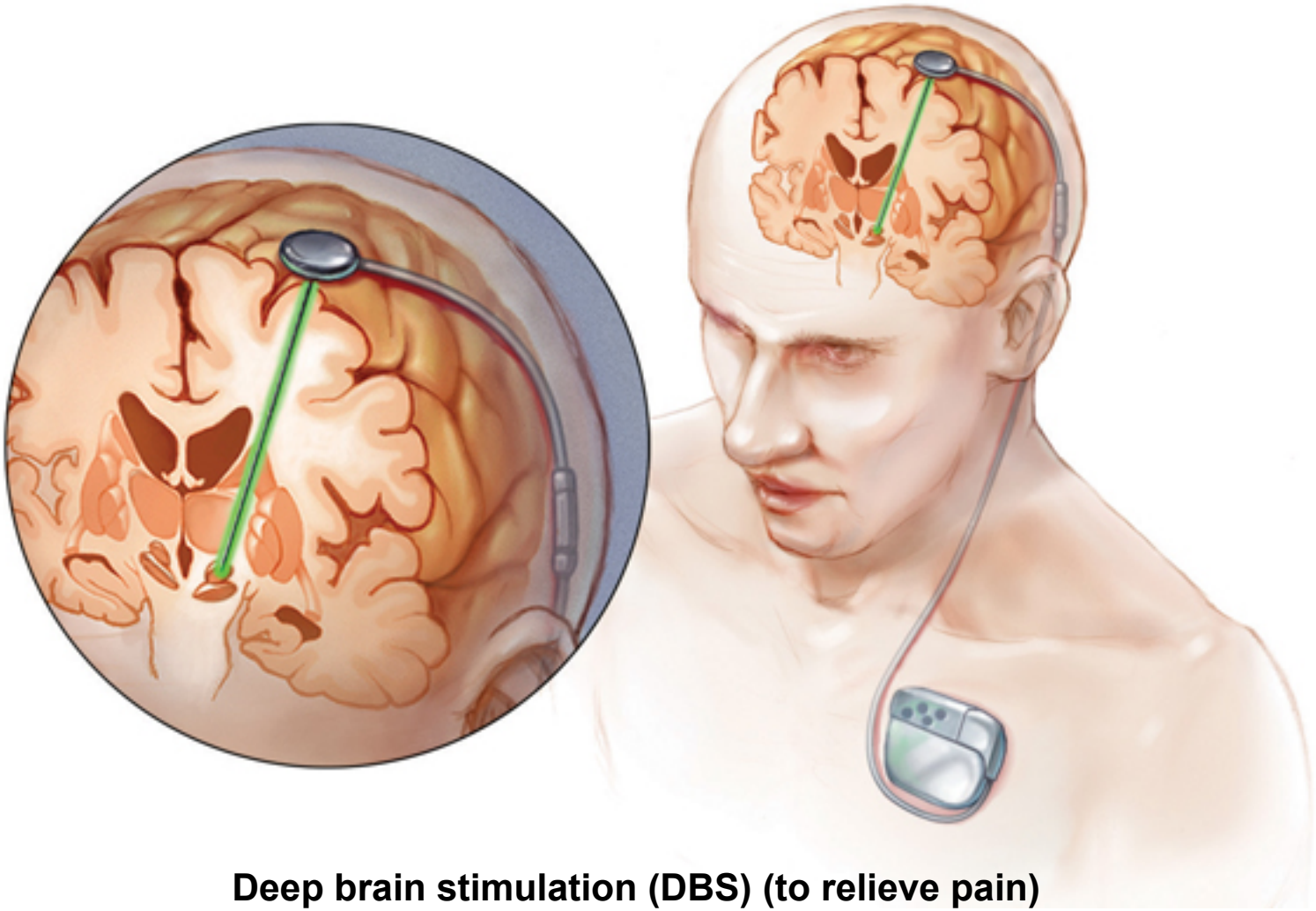
Table 10-8 Typical Patterns of Referred Pain

Organ damaged	Dermatomes in which pain may be felt
Diaphragm	C3–C4
Heart	T1–T4 (mainly left)
Stomach	T6–T9 (mainly left)
Gallbladder	T7–T8 (right)
Duodenum	T9–T10
Appendix	T10 (right)
Reproductive organs	T10–T12
Kidney, ureter	L1–L2

Referred Pain: pain being felt in an area away from the actual source of the pain



Descending pathways regulating the transmission of pain: Electrode implantation and pulse generator



Deep brain stimulation (DBS) (to relieve pain)

A) suppress the activity in nociceptive pathway but

B) B) does not affect touch, pressure and normal temperature sensation.

Descending pathways regulating the transmission of pain information:

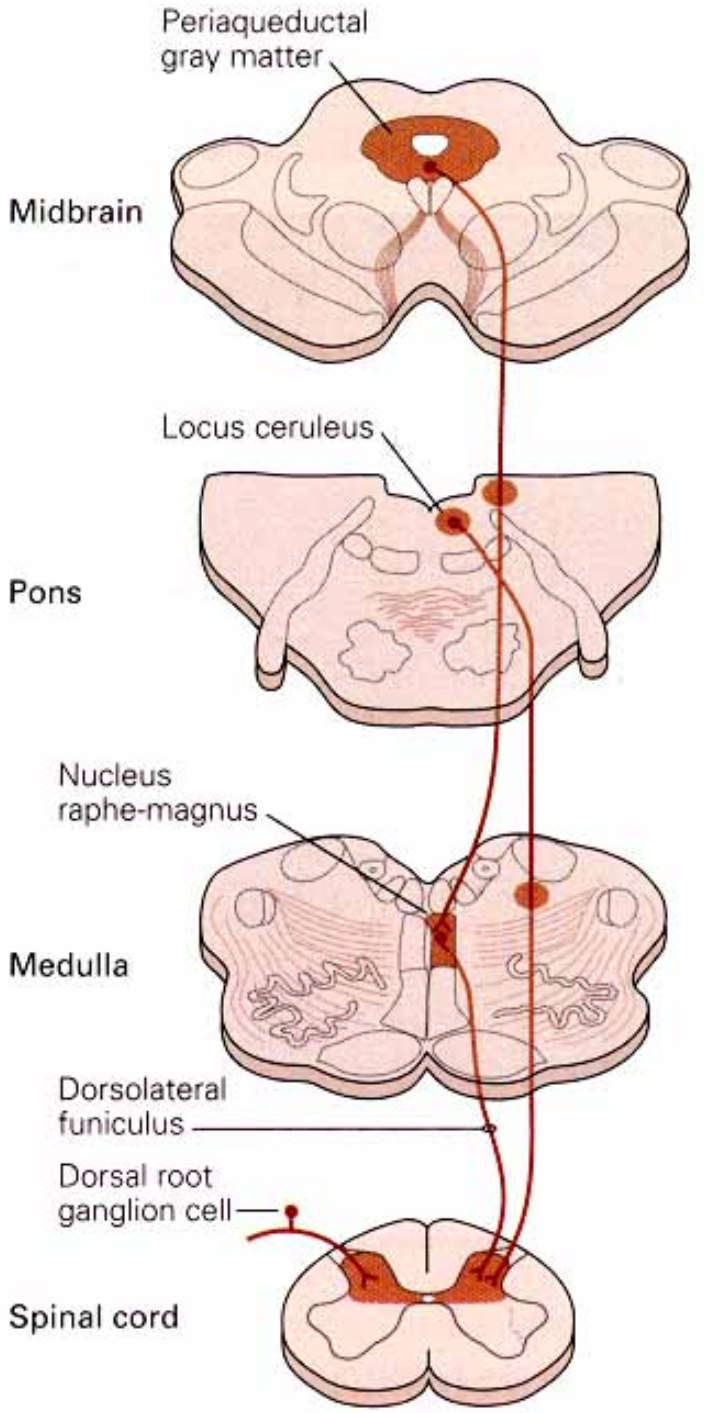
→intensity of pain varies among individuals and depends on circumstances (i.e. soldier wounded, athlete injured, during stress).

→Stimulation of PAG causes analgesia so profound that surgery can be performed.

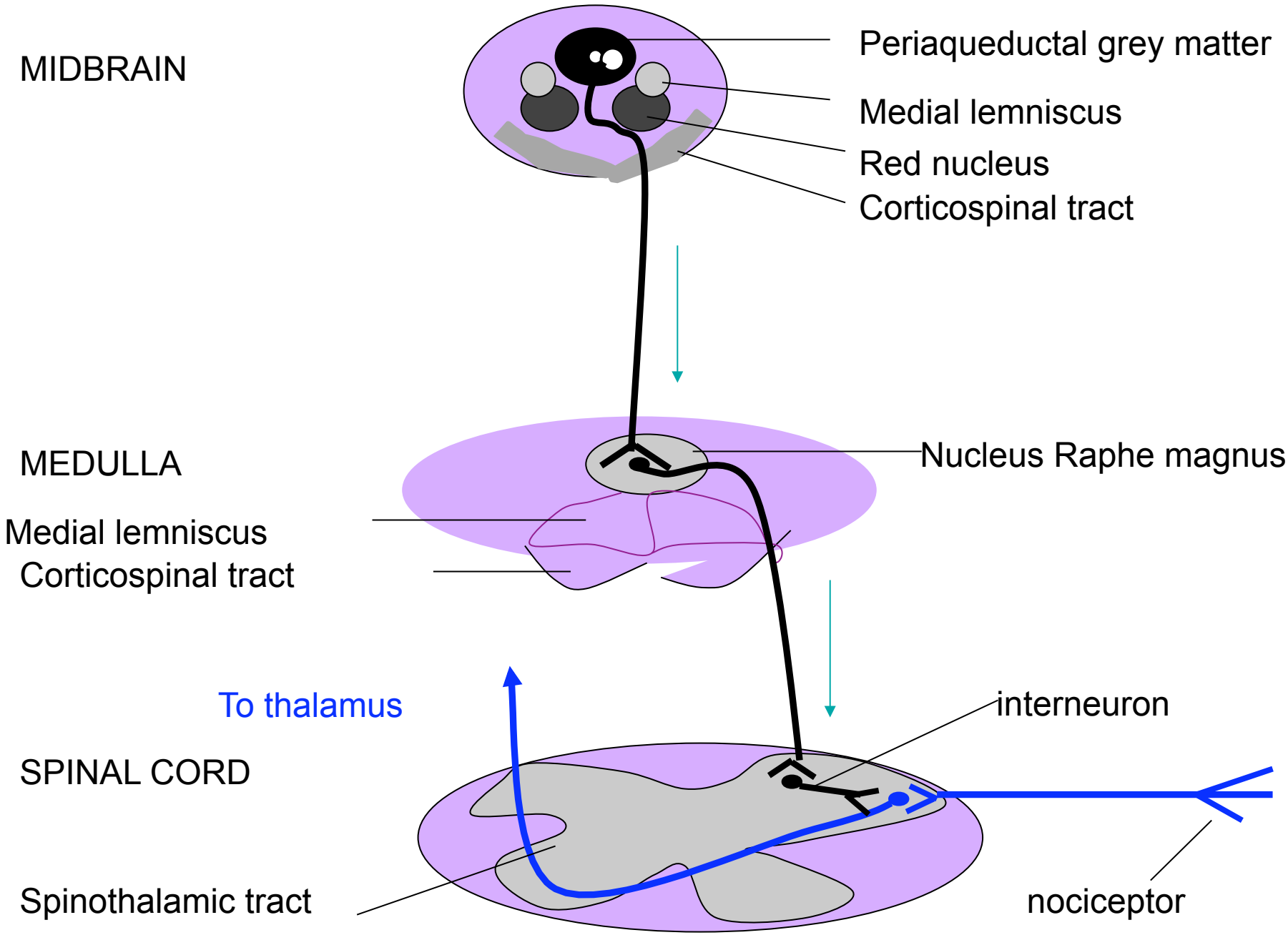
→PAG stimulation can ameliorate intractable pain.

PAG receives pain information via the spinomesencephalic tract and inputs from cortex and hypothalamus related to behavioral states and to whether to activate the pain control system.

PAG acts on raphe & locus ceruleus to inhibit dorsal horn neurons via interneurons and morphine receptors.



Pain modulation – descending pathway



Pain modulation – descending pathway

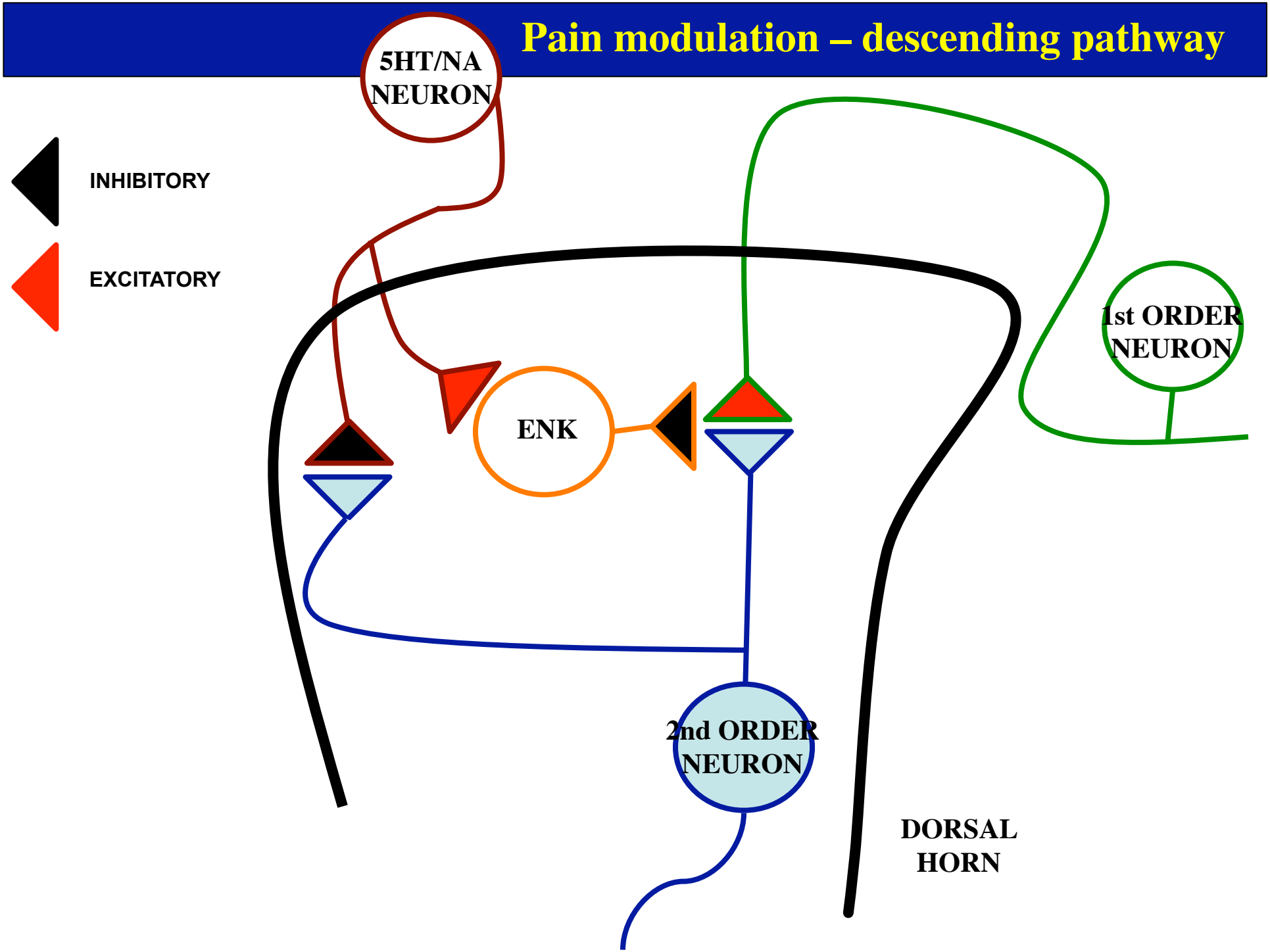
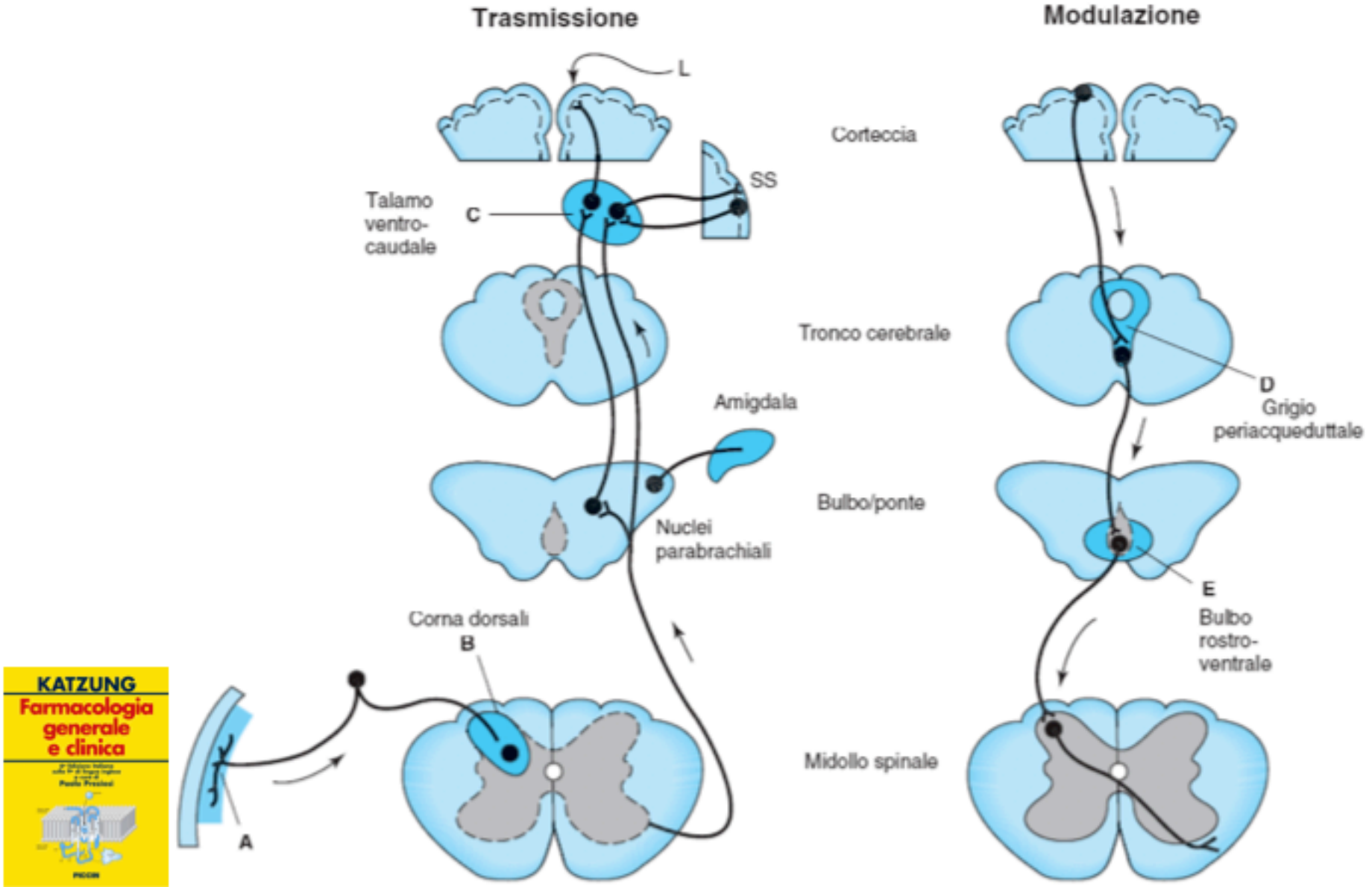


Figura 31-3. Siti putativi di azione degli oppioidi analgesici (aree più scure).



Dal Volume: Farmacologia generale e clinica

Animal models of chronic pain:

Central pain models: 1) weight drop or contusion; 2) photochemical SCI; 3) excitotoxic SCI

Peripheral nerve injury models: 1) nerve transection; 2) chronic constriction injury (Bennett); 3) partial sciatic nerve ligation (Seltzer); 4) L5/L6 spinal nerve ligation; 5) L5 spinal nerve ligation; 6) sciatic cryoneurolysis; 7) inferior caudal trunk resection; 8) sciatic inflammatory neuritis.

Peripheral neuropathy induced by diseases: 1) postherpetic neuralgia; 2) diabetic neuropathic

Cancer pain models: 1) chemotherapy-induced peripheral neuropathy; 2) vincristine-induced peripheral neuropathy; 3) taxol-induced peripheral neuropathy; 4) cisplatin-induced peripheral neuropathy; 5) cancer invasion; 6) bone cancer; 7) mouse femur bone cancer; 8) mouse calcaneus bone cancer; 9) rat tibia bone cancer.

Molecular tools in Pain research:

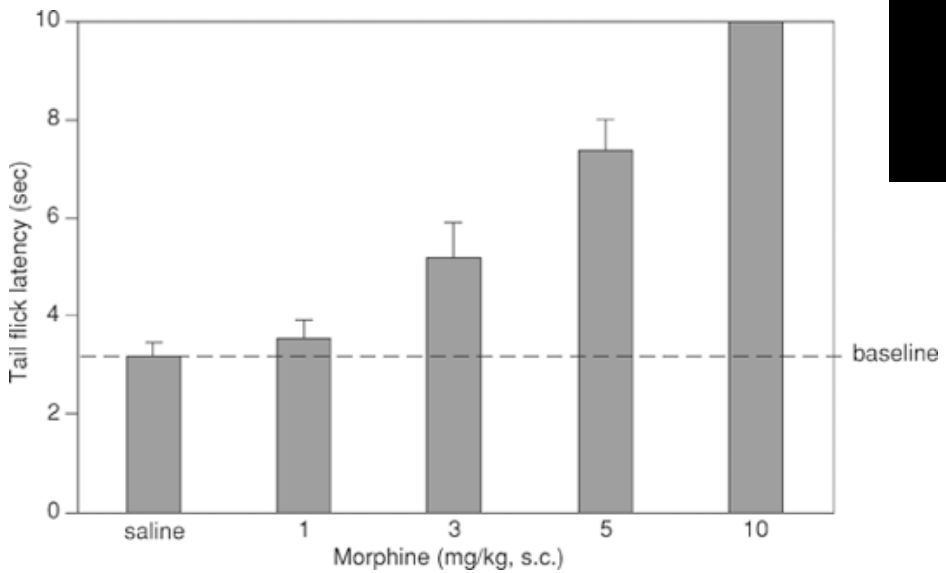
"Toxin to kill targeted cells": to use receptor-mediated endocytosis to selectively deliver cytotoxins to specific types of neurons. The effector toxin of choice is the ribosome inactivating protein (RIP), saporin (SAP). i.e. SAP combined with substance P to kill neurons expressing neurokinin-1 (NK-1) receptor.

"Antisense oligonucleotide (ASO)-mediated knockdown": an ASO, typically 15-25 nucleotides in length, is designed to bind a complementary sequence on the target RNA. As a consequence, the protein product coded by that particular RNA is not synthesized. i.e. knock down of PSD-93/chapsin-110

"Knockout/transgenic mice": create mice that either overexpress or do not express presumably pain-related proteins. i.e. mice lacking the capsaicin receptor; mice lacking PKC-gamma; mice lacking neurokinin-1 (NK-1) receptor…(others→NGF, TrkA, p75, interleukin-6, interferon-gamma, prostaglandin receptors, bradykinin receptor, substance P, PPT-A, neurokinin-1, adenosine-2a, B-endorphin, enkephalin, u-opioid receptors, delta-opioid receptors, kappa-opioid receptors, orphaninFQ/nociceptin receptor, adrenergic receptors, serotonin receptors, PKA-RIB, PKC-gamma, nitrix oxyde, Go, NR1-NMDA…

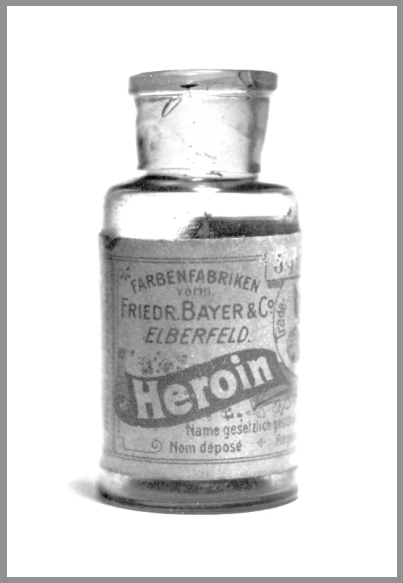
"Fusion molecule": i.e. use recombinant techniques to couple the extracellular domain of trkA receptor to the Fc portion of human immunoblobin G, to produce a fusion protein that binds and neutralize the effects of NGF.

HOT PLATE TEST



TAIL FLICK TEST

Opioids



Pharmacology

OPIATES

- **OPIUM COMES FROM THE POPPY PLANT - PAPAVER SOMNIFERUM**
  - **An erect herbaceous annual or biennial which grows in 3 major areas of the world: Southeast Asia, Middle East, and Latin and South America**
    - **50 to 150 cm tall**
    - **Stems are slightly branched**
    - **Leaves are large, erect, and oblong**
    - **Petals are 4 - 8 cm in length**
    - **Petal colors are white, pink, purple and violet**

PROCESS OF DERIVING OPIUM FROM POPPIES

After flowering, the petals drop in a few days leaving bulbous green capsules atop the stalks. These are the seed pods.

Incisions are made in the pods and the milky fluid that oozes out is air dried. This must be done while the pods are still green.

CONTENTS OF THE POPPY POD FLUID:

- Morphine 4 - 21 %
- Codeine 1 - 25%

There are at least 20 other alkaloids, such as Thebaine, in the fluid

DEFINITIONS

Papaver Somniferum
“Poppy Plant”

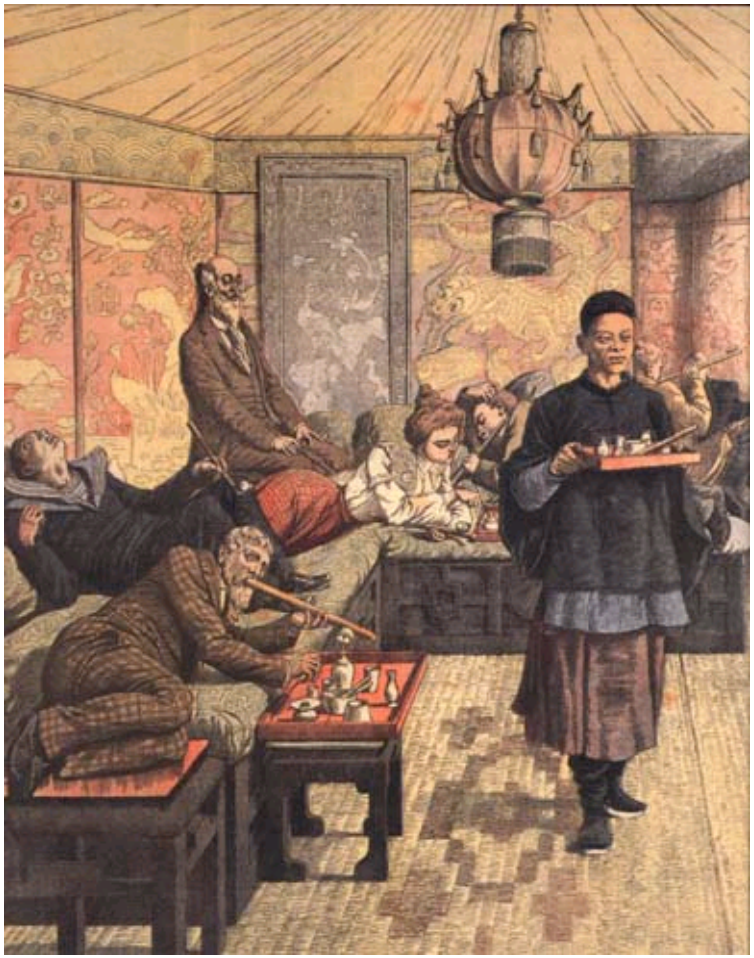
- Opium
  - Fluid obtained from the poppy plant
- Opiate
  - a substance derived from opium
- Opioid
  - substance with morphine-like actions, but not derived directly from the poppy plant

OPIUM HISTORY

- **4000 – 2000 BC:** Opium believed to be discovered in the Mediterranean area.
- **1500 BC:** Egyptian papyri list opium as one of 7000 remedies.
- **1st century AD:** Opium poisoning described.
- **1655:** Portuguese physician, Acosta, wrote of withdrawal sickness.
- **1701:** British physician, John Jones, advocated moderation in the use of the drug in order to avoid the discomforts with its continued use.
- **1805:** Morphine isolated as the main active ingredient in **opium.**

OPIUM HISTORY

- 1850 – 1865 thousands of Chinese laborers immigrated to the US and brought the habit of opium smoking with them (Opium Den shown on right)
- Civil war soldiers became opioid dependent through medical treatment – referred to as “army disease” or “soldier’s disease”
- It was estimated that the total number of opium users in the U.S. in 1868 was 100,000
- Heroin was first synthesized in 1874 by the chemist, C.R. Alder Wright
  - First commercial production in 1898 by the Bayer Pharmaceutical Company
  - 1898: Heinrich Dreser announced that tests confirmed heroin was ideal for treating bronchitis, emphysema, asthma, tuberculosis, and was a cure for opium and morphine dependence

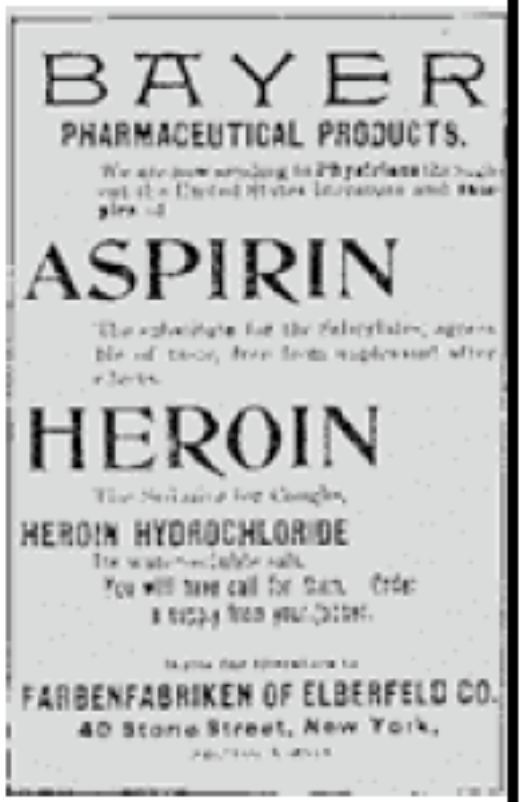


Chemical investigations

- 1804/5 Séquin / Serturner isolated morphine
  - Hypodermic syringe invented in 1853
- 1874 diacetyl morphine (heroin, diamorphine)
- 1897 heroin marketed by Bayer
  - (addictive nature not appreciated)
- 1923 Structure proposed (Gulland and Robinson)
- 1952 Morphine synthesised
- 1975 Hughes and Kosterlitz

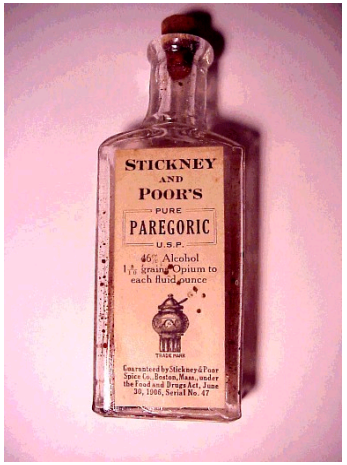
  → enkephalins (Gk. Kephale = head)
- Thousands of opioid analogues synthesised

Goal = potent, non-addictive analgesic



1897 Bayer advertisement
ASPIRIN
The Substitute for Salicylates
HEROIN
The Sedative for Coughs

HISTORICAL OPIATE PRODUCTS



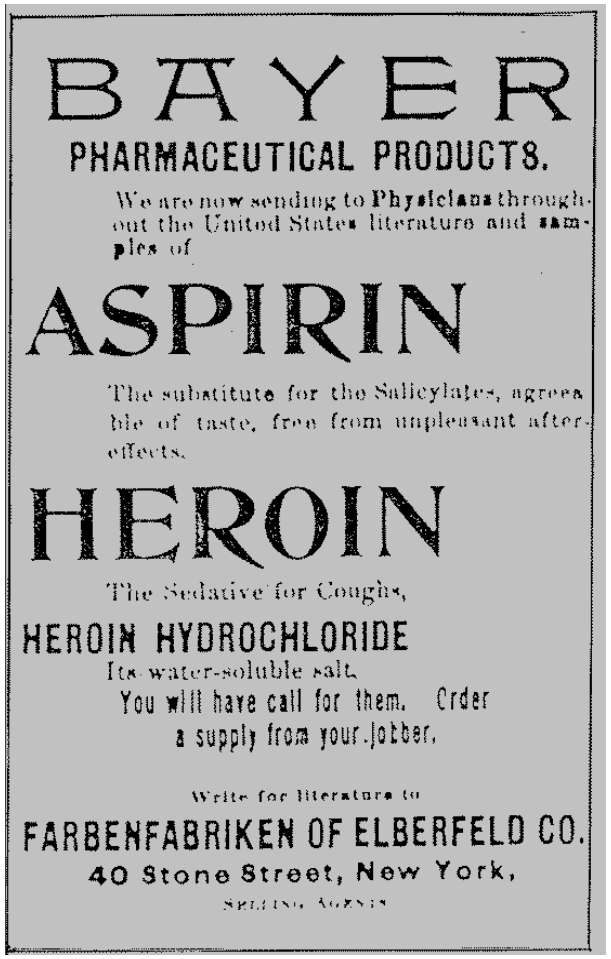
- **This bottle of Stickney and Poor's paregoric was distributed much like the spices for which the company is better known.**
- **McCormick also manufactured and sold paregoric, which is a mixture of opium and alcohol.**
- **Doses for infants, children, and adults are given on the bottle. At 46% alcohol, this product is 92 proof which is pretty potent in itself.**

HISTORICAL OPIATE PRODUCTS

- **Many products, marketed for adults and children, were sold for pain and cough relief. They all contained opium**.

HISTORICAL OPIATE PRODUCTS

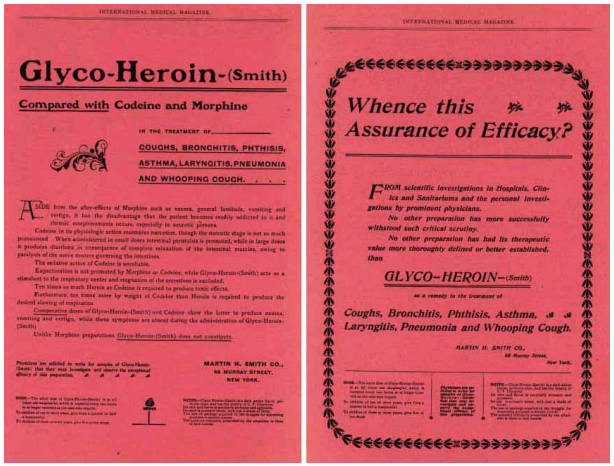
- **There were ads in papers and journals for Bayer's many products, including aspirin and heroin.**



HISTORICAL OPIATE PRODUCTS

- **These heroin tablets, manufactured by the Fraser Tablet Company, were marketed for the relief of asthma.**

1903 ADS



Glyco-Heroin-(Smith)

Compared with Codeine and Morphine

IN THE TREATMENT OF

COUGHS, BRONCHITIS, PHTHISIS, ASTHMA, LARYNGITIS, PNEUMONIA AND WHOOPING COUGH.

Aside from the after-effects of Morphine such as nausea, general lassitude, vomiting and vertigo, it has the disadvantage that the patient becomes readily addicted to it and chronic morphinomania occurs, especially in neurotic persons.

Codeine in its physiologic action resembles narcotine, though the narcotic stage is not so much pronounced. When administered in small doses intestinal peristalsis is promoted, while in large doses it produces diarrhœa in consequence of complete relaxation of the intestinal muscles, owing to paralysis of the nerve centers governing the intestines.

The sedative action of Codeine is unreliable.

Expectoration is not promoted by Morphine or Codeine, while Glyco-Heroin-(Smith) acts as a stimulant to the respiratory center and stagnation of the secretions is excluded.

Ten times as much Heroin as Codeine is required to produce toxic effects.

Furthermore, ten times more by weight of Codeine than Heroin is required to produce the desired slowing of respiration.

Comparative doses of Glyco-Heroin-(Smith) and Codeine show the latter to produce nausea, vomiting and vertigo, while these symptoms are absent during the administration of Glyco-Heroin-(Smith).

Unlike Morphine preparations Glyco-Heroin-(Smith) does not constipate.

Physicians are solicited to write for samples of Glyco-Heroin-(Smith) that they may investigate and observe the exceptional effects of this preparation.

MARTIN H. SMITH CO., 80 MURRAY STREET, NEW YORK.

Whence this Assurance of Efficacy?

FROM scientific investigations in Hospitals, Clinics and Sanitariums and the personal investigations by prominent physicians.

No other preparation has more successfully withstood such critical scrutiny.

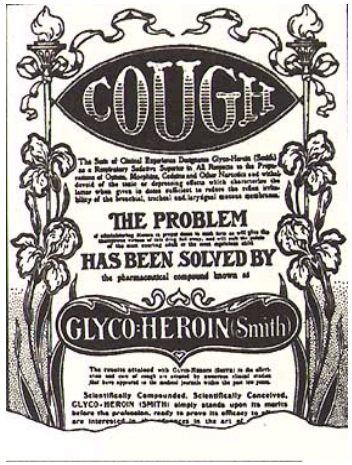
No other preparation has had its therapeutic value more thoroughly defined or better established, than

GLYCO-HEROIN-(Smith)

as a remedy in the treatment of

Coughs, Bronchitis, Phthisis, Asthma, Laryngitis, Pneumonia and Whooping Cough.

MARTIN H. SMITH CO., 80 Murray Street, New York.



COUGH

The Sum of Clinical Experience Designates Glyco-Heroin (Smith) as a Respiratory Sedative Superior to All Narcotics in the Properties of Opium, Morphine, Codeine and Other Narcotics and which, devoid of the toxic or depressing effects which characterize the latter when given in doses sufficient to relieve the reflex irritability of the bronchial, tracheal and laryngeal mucous membranes.

THE PROBLEM

HAS BEEN SOLVED BY

the pharmaceutical compound known as

GLYCO-HEROIN (Smith)

The results attained with Glyco-Heroin (Smith) in the affections and care of cough are secured by numerous clinical studies that have appealed to the medical profession within the past few years.

Scientifically Compounded. Scientifically Conceived. GLYCO-HEROIN (SMITH) simply stands upon its merits before the profession, ready to prove its efficacy to [illegible] are interested in [illegible] in the art of

These magazine advertisements are for Glyco-Heroin manufactured by Martin H. Smith Company (NY).

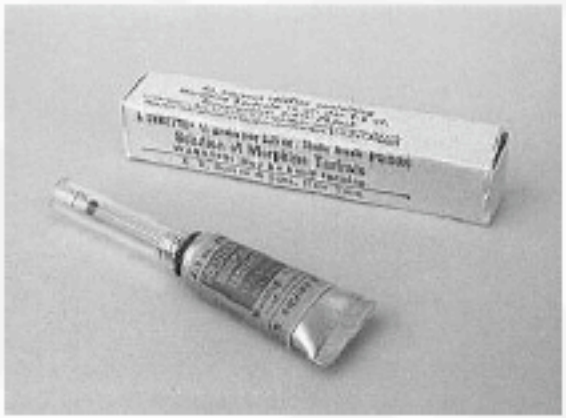
Heroin was widely used not only as an analgesic, but also as a remedy for asthma, coughs, and pneumonia.

Mixing heroin with glycerin (and often adding sugar or spices) made the bitter-tasting opiate more palatable for oral consumption.

Opioid Analgesics

Opiates:

- Alkaloids derives from *Papaver somniferum*
- Already used 4000 B.C. (*opius* greek: "little juice")
- 1805: Morphine isolated (*morpheus:* Greek god of dreams)
- 1874: synthesis of heroin (introduced in 1898 by Bayer as a cough medicine)
- Opium tincture heavily used during civil war
- Opiates freely available in the US until 1914
- 1914: Harrison Act
  Prevented physicians from maintaining addiction



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