

Elementi di fisiopatologia, semeiotica e farmacologia del dolore

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Definizione di Dolore



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.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- 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.

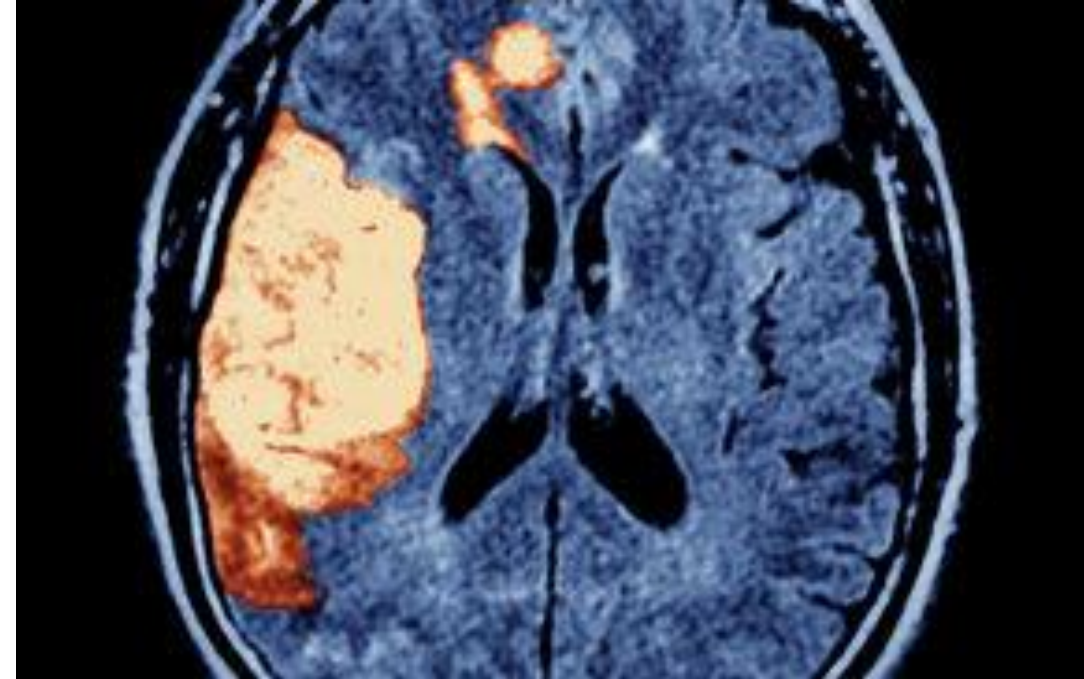
Dolore nocicettivo

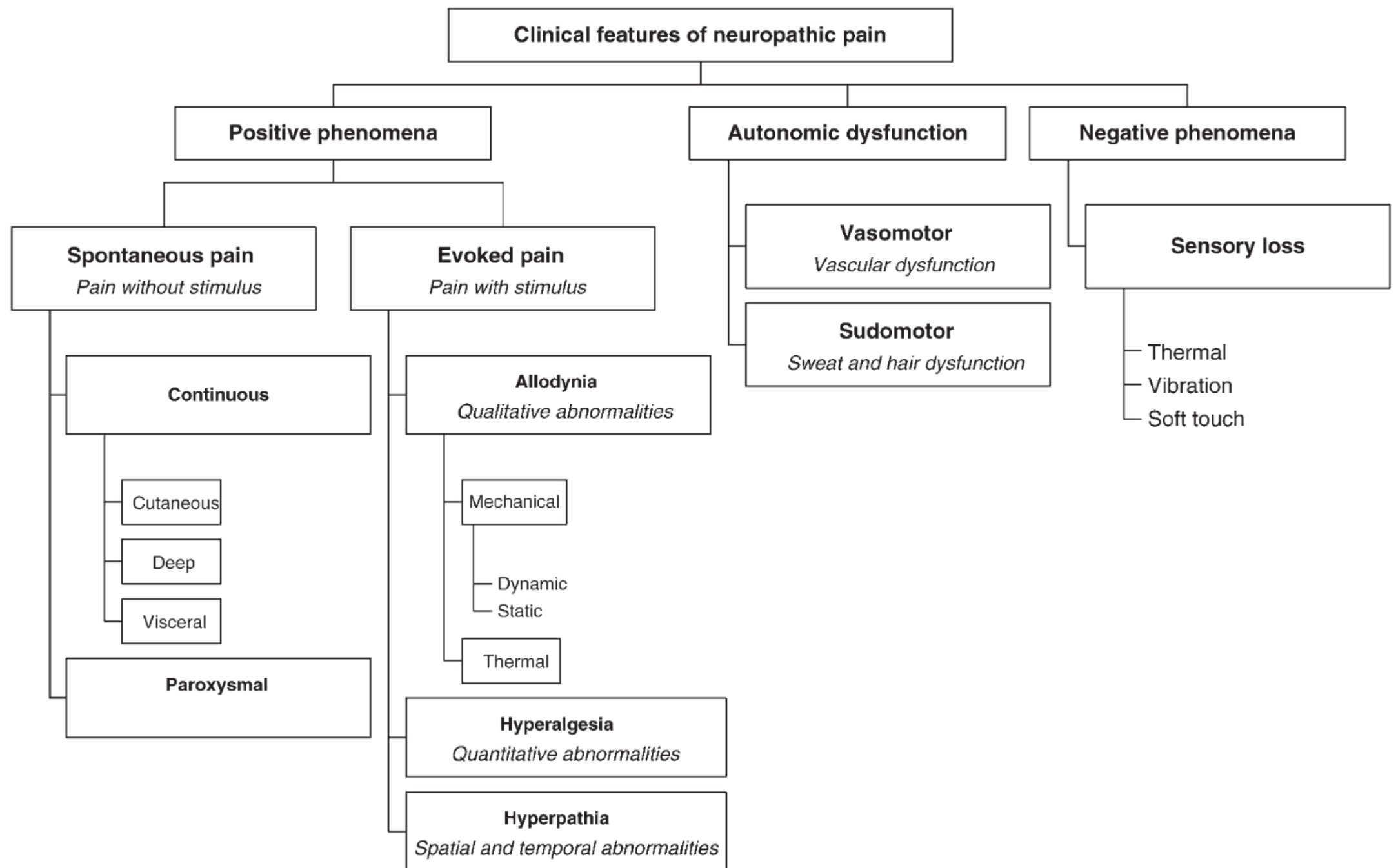


Dolore neuropatico

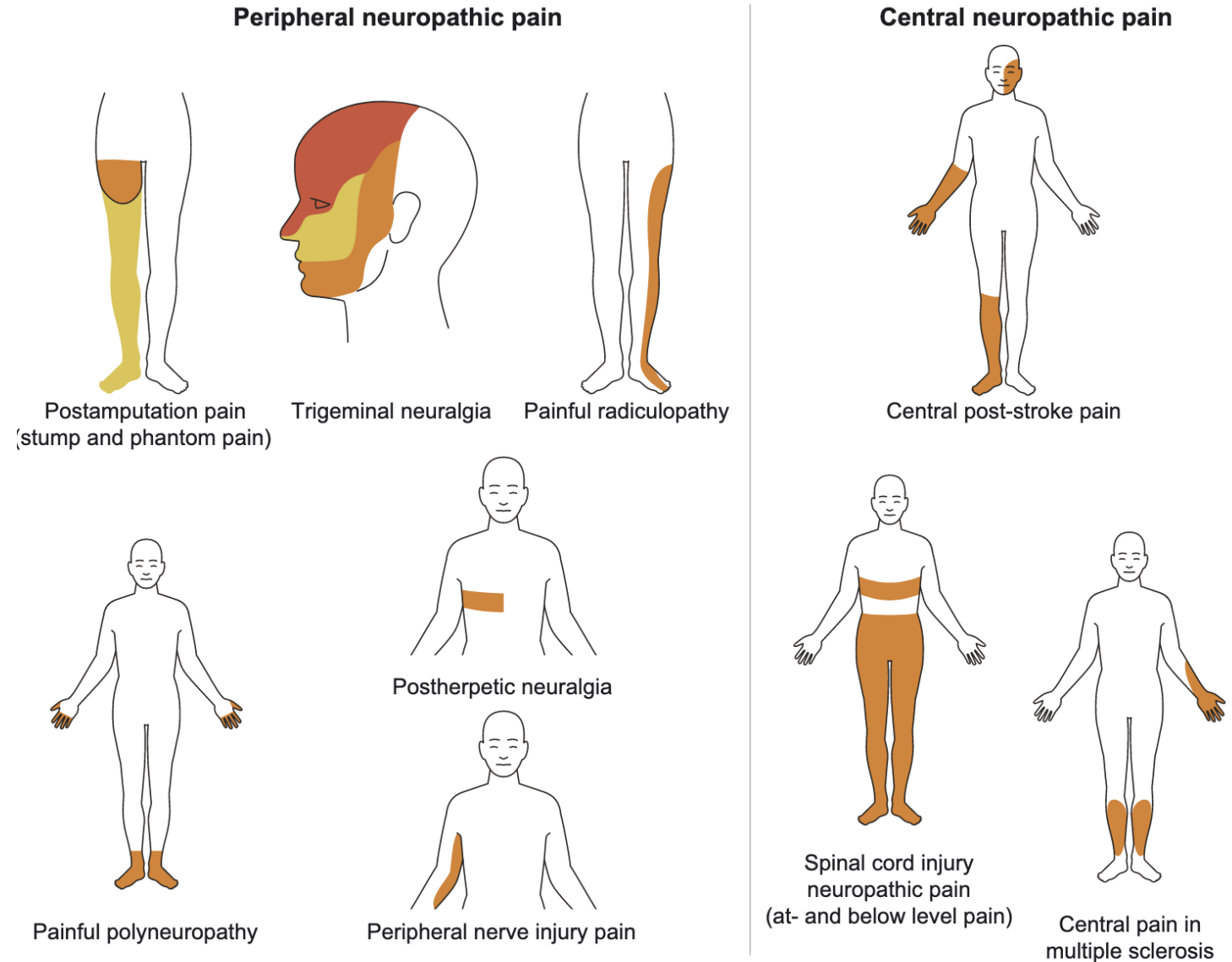
Pain caused by a **lesion** or disease of the **somatosensory** nervous system.

Note: Neuropathic pain is a clinical description (and not a diagnosis) which **requires a demonstrable lesion or a disease** that satisfies established neurological diagnostic criteria.





Dolore neuropatico



Finnerup NB, Kuner R, Jensen TS. Neuropathic Pain: From Mechanisms to Treatment. *Physiological Reviews*. 2021;101(1):259-301.
doi:10.1152/physrev.00045.2019

FIGURE 4. Classification of neuropathic pain and examples of the neuroanatomical distribution of pain and sensory abnormalities [139].

Dolore nociplastico

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.

Note: Patients can have a combination of nociceptive and nociplastic pain

Dolore nociplastico

Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397(10289):2098-2110. doi:10.1016/S0140-6736(21)00392-5

Features of nociplastic pain conditions

- Combined peripheral and central pain sensitisation
- Hyper-responsiveness to painful and non-painful sensory stimuli
- Associated features
 - Fatigue
 - Sleep disturbance
 - Cognitive disturbances
 - Hypersensitivity to environmental stimuli
 - Anxiety and depressed mood

Supraspinal mechanisms

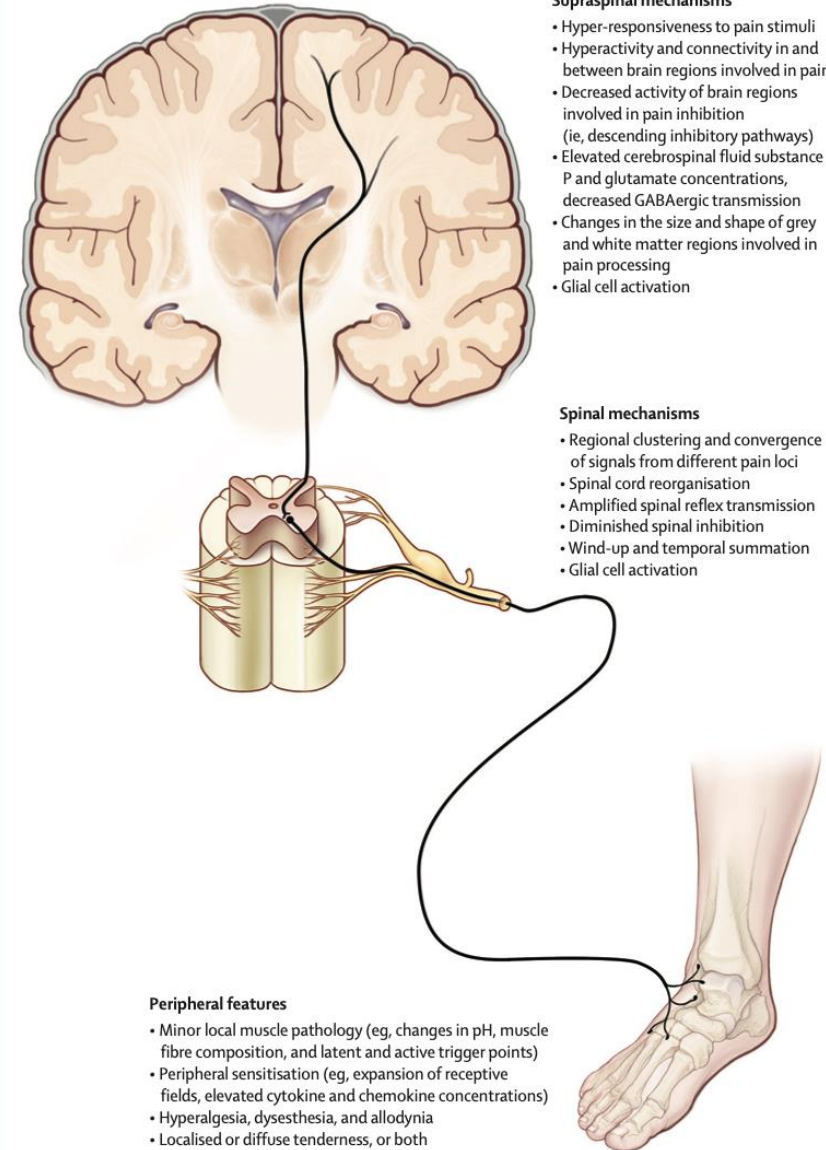
- Hyper-responsiveness to pain stimuli
- Hyperactivity and connectivity in and between brain regions involved in pain
- Decreased activity of brain regions involved in pain inhibition (ie, descending inhibitory pathways)
- Elevated cerebrospinal fluid substance P and glutamate concentrations, decreased GABAergic transmission
- Changes in the size and shape of grey and white matter regions involved in pain processing
- Glial cell activation

Spinal mechanisms

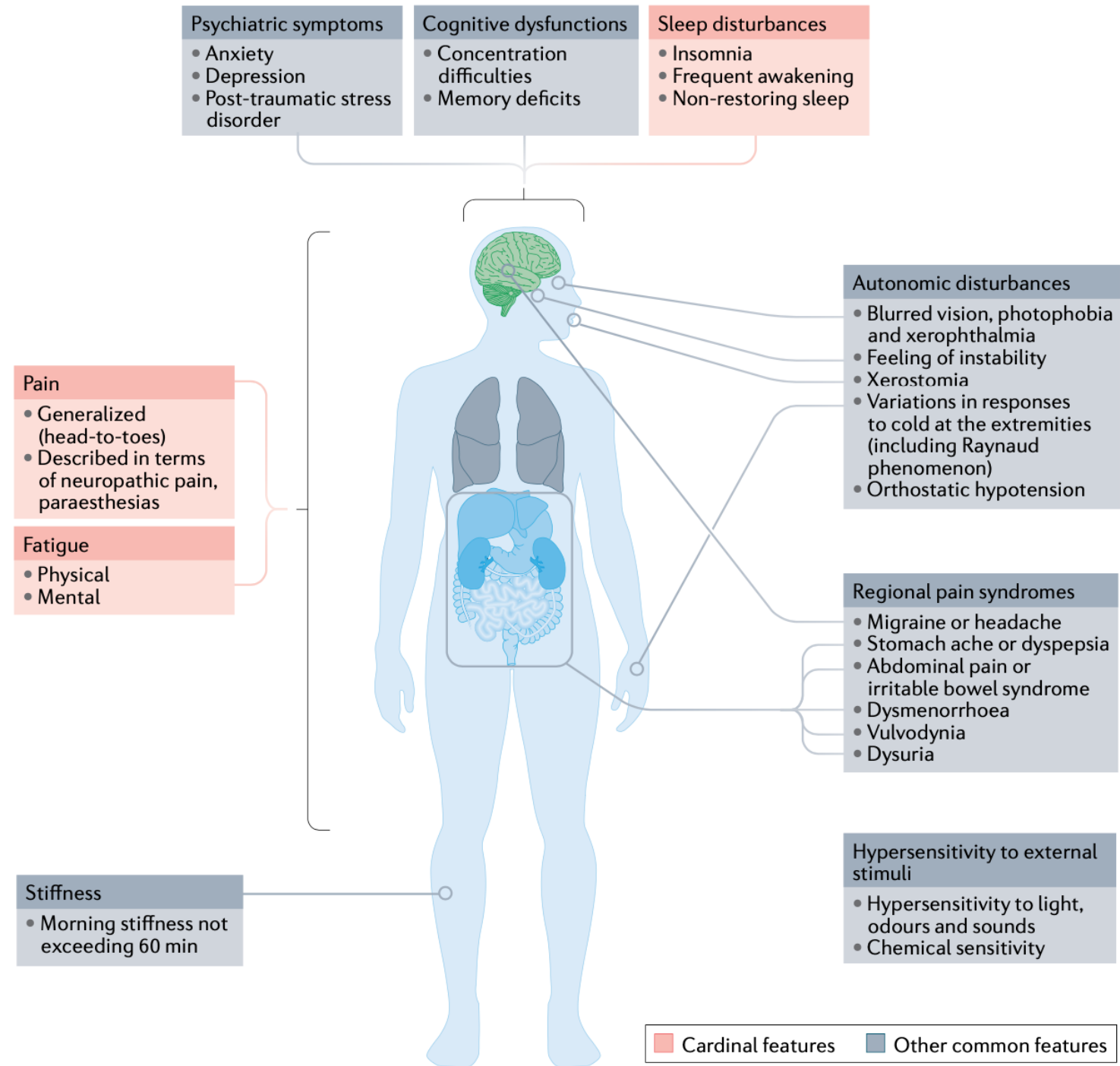
- Regional clustering and convergence of signals from different pain loci
- Spinal cord reorganisation
- Amplified spinal reflex transmission
- Diminished spinal inhibition
- Wind-up and temporal summation
- Glial cell activation

Peripheral features

- Minor local muscle pathology (eg, changes in pH, muscle fibre composition, and latent and active trigger points)
- Peripheral sensitisation (eg, expansion of receptive fields, elevated cytokine and chemokine concentrations)
- Hyperalgesia, dysesthesia, and allodynia
- Localised or diffuse tenderness, or both



Fibromialgia



Dolore secondario

Dolore primario

Origina dall'azione dei nocicettori dove è applicato lo stimolo

Dolore riferito

Convergenza sugli stessi neuroni secondari di afferenze da tessuti viscerali e somatici diversi

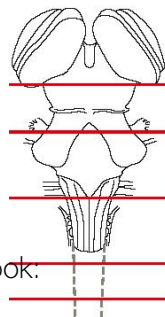
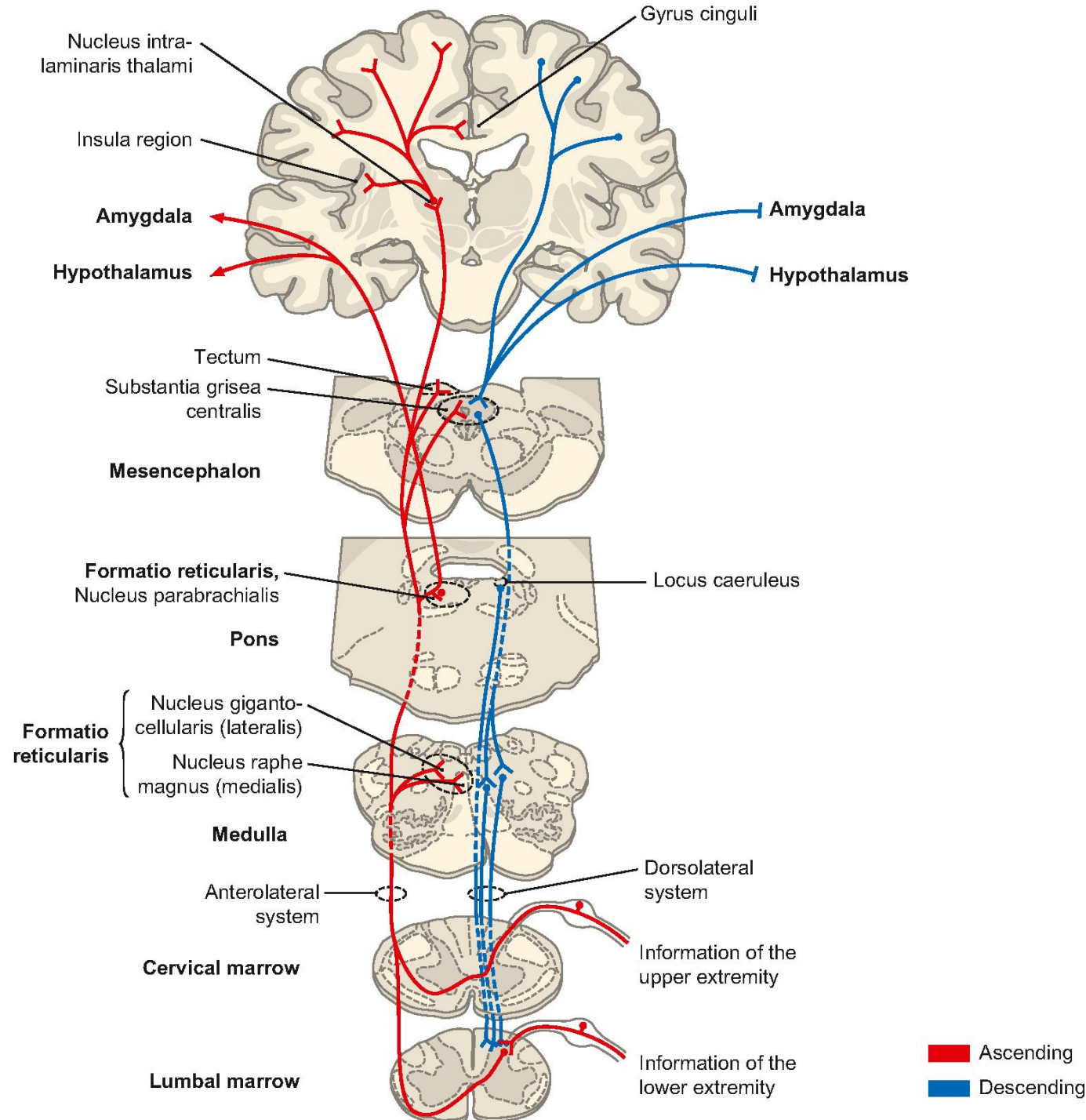
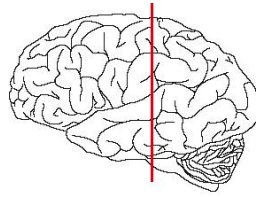
Dolore riflesso

Nocicezione in un viscere induce spasmo di un muscolo metamericamente correlato

Dolore di proiezione

Dolore neuropatico in cui l'attività patologica delle strutture nervose viene interpretata come dolore nella mappa corporea delle aree innervate da tali strutture

Sistema nocicettivo



CLASSIFICATION AND PHYSIOLOGIC CHARACTERISTICS OF PERIPHERAL NERVE FIBERS

Class	A α	A β	A γ	A δ	B	C
Function	Motor	Touch/Pressure	Proprioception/ Motor Tone	Pain/Temperature	Preganglionic autonomic	Pain/temperature
Myelin*	+++	+++	++	++	+	–
Diameter (μm)	12–20	5–12	1–4	1–4	1–3	0.5–1
Conduction speed (m/sec)	70–120	30–70	10–30	12–30	10–15	0.5–1.2
Local anesthetic Sensitivity**	++	++	+++	+++	++	+ [†]
* +++ , heavily myelinated; ++ , moderately myelinated; + , lightly myelinated; – , nonmyelinated; ** +++ , most susceptible to impulse blockade; and [†] least susceptible.						

Nocicettore

- **Recettore sensoriale** responsivo agli stimoli nocivi o potenzialmente nocivi e **che può contribuire alla percezione del dolore**
- Termine applicato inizialmente al terminale periferico e, per estensione, a tutte le componenti del primo neurone
- Variano per densità e rappresentazione nei tessuti
- A livello viscerale nocicettori a bassa soglia meccanica
- Nocicettori «**silenti**» o *mechanically insensitive nociceptors* possono essere reclutati e sensibilizzati agli stimoli meccanici da stimoli chimici
- Nocicettori generalmente **fibre A δ** e **fibre C**

La cute presenta la più vasta gamma di nocicettori

Fibra Peptidergica esprime
Substance P o
calcitonin gene-related peptide

Mas1-related G protein-coupled
receptor D (MrgprD)

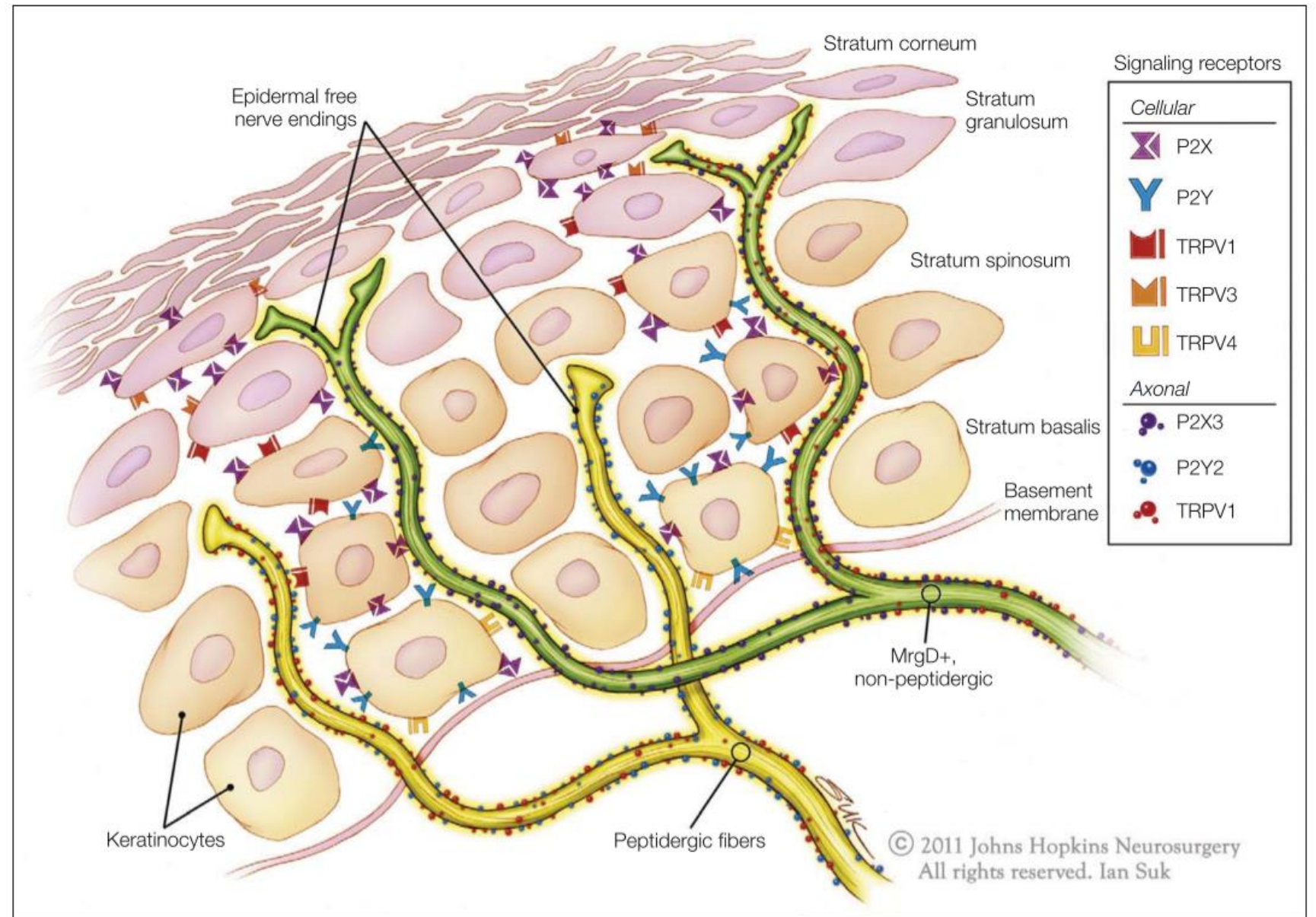


Figure 1-4. Schematic illustration of unmyelinated fiber terminations in the epidermis. Non-peptidergic, MrgD⁺ neurons terminate as free nerve endings in the most superficial layers of the epidermis. Peptidergic neurons terminate in deep layers of the epidermis. Some of the signaling receptors found on keratinocytes and free nerve endings are also illustrated. (Artwork by Ian Suk, Johns Hopkins University; adapted from Dussor G, Koerber HR, Oaklander AL, et al 2009 Nucleotide signaling and cutaneous mechanisms of pain transduction. *Brain Research Reviews* 60:24–35.)

Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.

Stephen McMahon FMSFSB, Martin Koltzenburg MDF, Tracey I, Turk DC. *Wall & Melzack's Textbook of Pain: Expert Consult - Online and Print*. Elsevier Health Sciences; 2013.

Classificazione microneurografica

- A δ -mechanonociceptors ($AM_{[mechano]}$; sharp pain)
- A-mechanoheat (AMH)
- C-polymodal nociceptors ($CM_{[mechano]}H_{[heat]}$; dull, burning [heat] pain)
- C-mechanonociceptors (CM)
- C-heat (CH)
- C-mechano- and heat-insensitive (CMiHi, or sleeping nociceptors)
- C-mechanoinsensitive-histamine responsive (CMiHis+, or itch fibers)
- Group IV muscle nociceptors (cramping pain)

Table 1-1 Comparison of Type I and Type II A-Fiber Nociceptors

CHARACTERISTIC	TYPE I	TYPE II
Heat threshold to short stimuli	High	Low
Heat threshold to long stimuli	Low	Low
Response to intense heat	Slowly increasing	Adapting
Response latency to intense heat	Long	Short
Peak latency to intense heat	Late	Early
Mechanical threshold	Most are MSAs	Most are MIAs
Conduction velocity	A δ and A β fibers	A δ fibers
Sensitization to heat injury	Yes	No
Location	Hairy and glabrous skin	Hairy skin

MIAs, mechanically insensitive afferents; MSAs, mechanically sensitive afferents.

Table 3 Characterization of human C-fibre nociceptors using microneurography

Nociceptor afferents and subpopulations	Response characteristics	Neurophysiological properties	Receptive fields
C-mechanosensitive ('polymodal')	Mean mechanical response ~30 mN (range 3.4–750 mN). Majority respond in 10–300 mN range Weak and transient response to algogens ^a Respond to cowhage and histamine	ADS: Low latency changes during low-frequency stimulation e.g. <2% during 5 min 0.25-Hz stimulation High (> 10%) latency changes during 2-Hz stimulation CV ~1 m/s 10 mA activation threshold ^b	100 mm ² (10–363 mm ²) Uniform shape, some irregular; size varies depending on body site
C-mechano-heat	Mean temperature response ~40°C; > 45°C linear response between stimulus temperature and firing frequency		
C-mechano-heat-cold	Also respond to cold <20°C		
C-high threshold mechanoreceptors	Only respond to mechanical stimuli; no thermal response		
C-mechanoinsensitive	Unresponsive or very strong mechanical stimulus > 750 mN Thermal response at > 48°C Strong and sustained response to algogens (unresponsive to endo-thelin 1)	ADS: High latency changes during low-frequency stimulation e.g. > 5% during 0.25-Hz stimulation High (> 10%) latency changes during 2-Hz stimulation CV ~ 0.8 m/s > 30 mA activation threshold ^b	500 mm ² , discontinuous patches, irregular in shape, heterogeneous physiological response properties across receptive field
C-mechanoinsensitive-heat-insensitive ('silent')	Unresponsive to mechanical/thermal stimulus; can be sensitized after algogen (mustard oil/capsaicin) application		
C-mechanoinsensitive-histamine-positive ('pruriceptors', C-itch afferents)	Very sensitive to histamine, no response to cowhage		

The Action Potential

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Meccanotrasduzione

1. transient receptor potential vanilloid type 4 (TRPV4)
2. acid-sensing ion channel type 3 (ASIC-3)
3. low-threshold voltage-gated calcium channel (VGCC) CaV3.2

Termotrasduzione

freddo “nocivo” → TRPA1, ankyrin type 1

fresco → TRPM8, melastatin type 8

Caldo → TRPV4

Molto caldo → TRPV1

Chemotrasduzione

Acidosi → TRPV1, ASIC-3

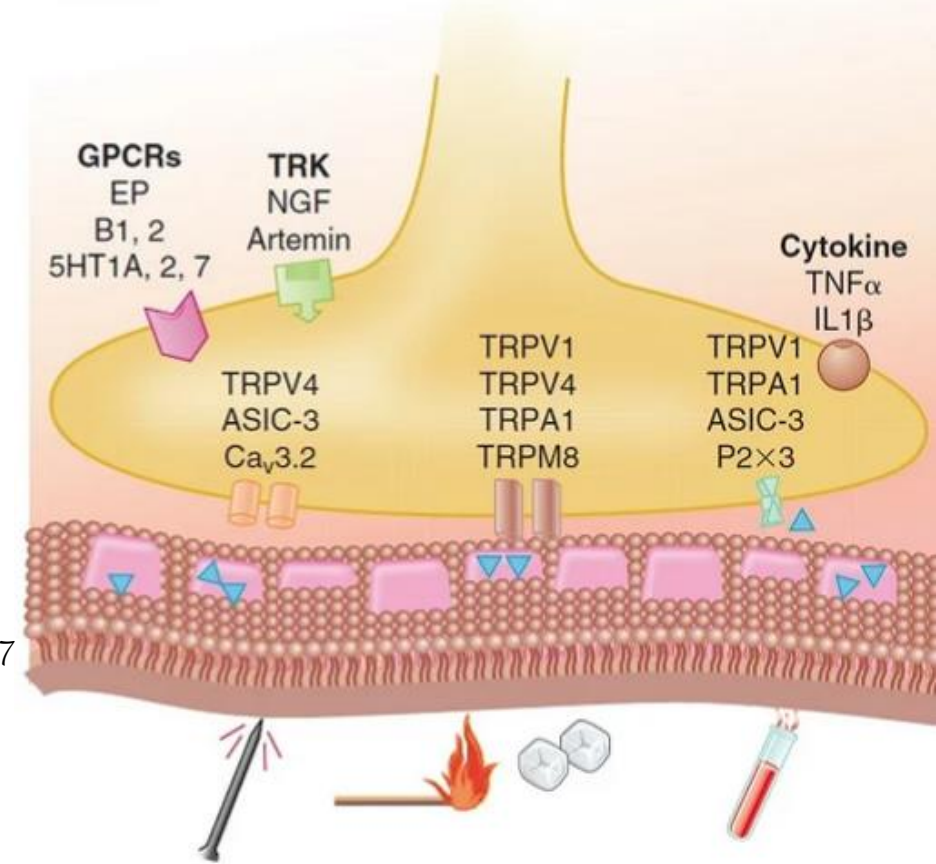
Composti organici (aldeidi) → TRPA1

Molecole endogene

1. ATP → recettore P2X3
2. H⁺ → ASIC 1, ASIC2, TRVP1
3. Bradichinina → B1, B2
4. Serotonina → 5HT_{1A}, 5HT₂, 5HT₇
5. PGE2 → EP2
6. NGF, artemina → tyrosine kinase receptor A (TrkA)
7. IL-6, TNF-α

Transduction

Naive



Histamine
ATP/NGF



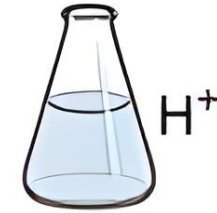
Cold



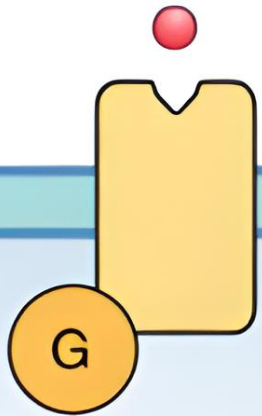
Heat



Protons



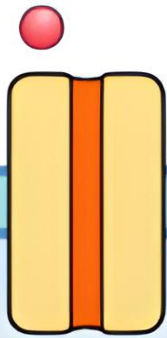
Mechanical
force



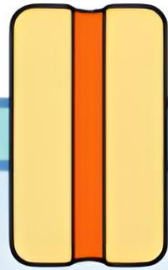
GPCRs



Tyrosine
kinases



Purino-
ceptors



TRPMs



TRPVs



ASICs/
TRPV1



?ASICs
?TRPV4
?TREK-1

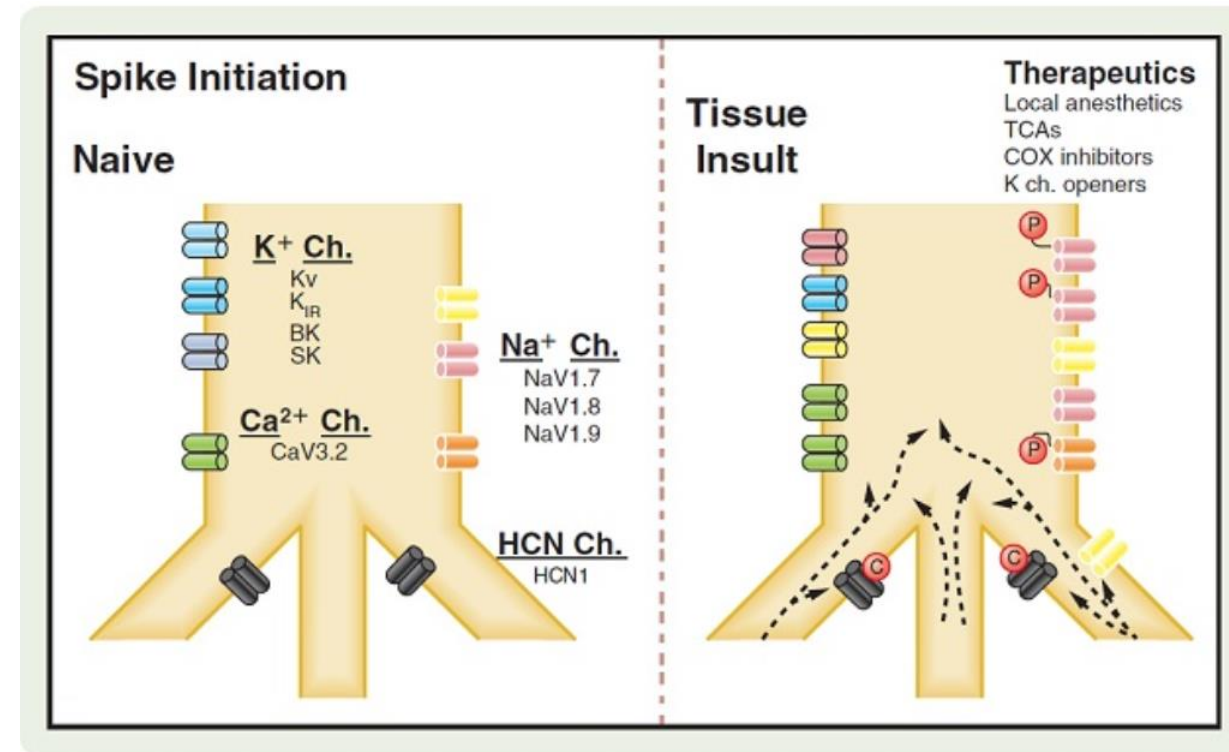
La soglia per la regolazione del potenziale d'azione è regolata da **Sensibilizzazione**

1. voltage-gated K⁺ channels (KV)
2. inward rectifying K⁺ channels (KIR)
3. two-pore K⁺ channels (K2P)
4. large-conductance calcium-modulated K⁺ channels (BK)
5. small conductance calcium-dependent K⁺ channels (SK)
6. nonselective inward rectifying cation channel (HCN)
7. voltage-gated sodium channel (VGSC) NaV1.9

Upstroke del PdA

1. NaV1.7
2. NaV1.8

- ↓ densità canali/corrente K⁺
- ↑ densità canali/corrente/attività CaV3.2, HCN, NaV



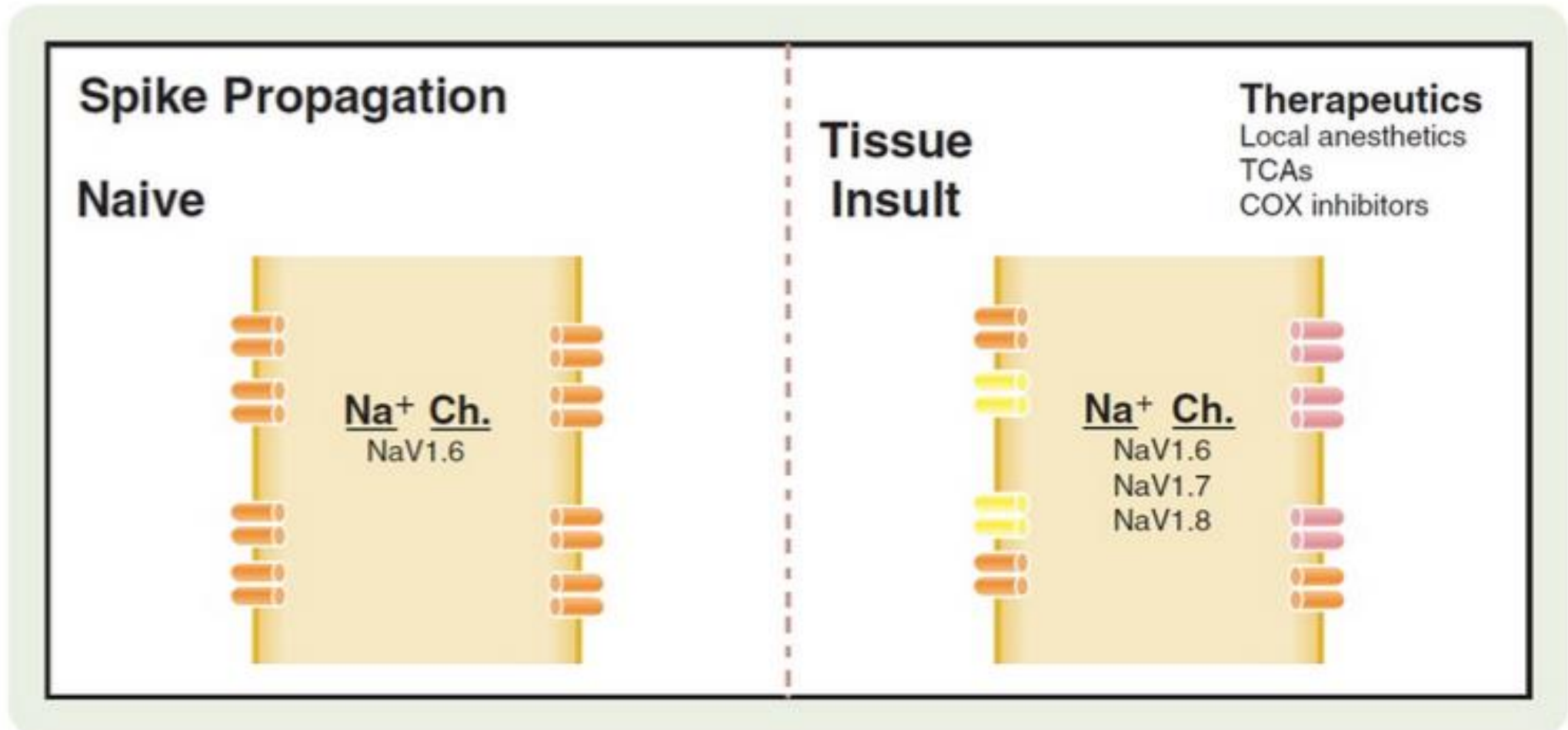
Trasduzione del segnale

VGSC NaV1.6

Dopo stimolo nocivo

→ NaV1.7

→ NaV1.8



Danno nervoso

→ Cambiamento del soma e dell'assone prossimale

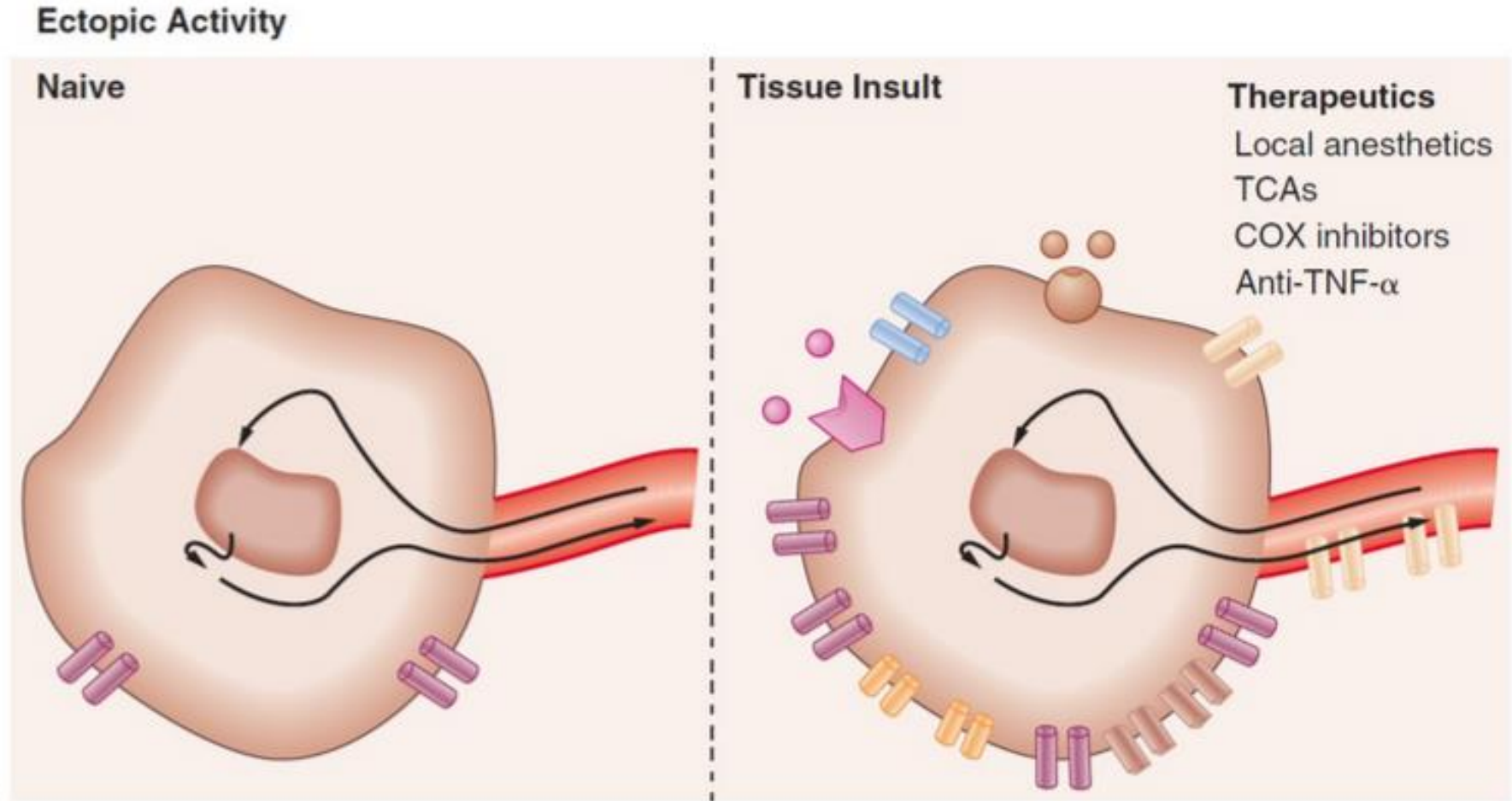
↑ Proteine di trasduzione

→ Responsività a stimoli meccanici, termici, chimici

↑ canali sodio

→ Instabilità di membrana

→ **Attività ectopica**



Rilascio del neurotrasmettitore

Ca²⁺ dipendente

Ingresso Ca²⁺ via high-threshold VGCCs

1. N-type channels (CaV2.2) ← principale, modulato da oppioidi e α-agonisti
2. P/Q-type (CaV2.1)
3. L-type (CaV1.3)

Vescicole

- Glutamato
- SP, CGRP

Recettori ionotropici facilitatori

- P2X3
- TRPV1

Recettori metabotropici facilitatori

- EP prostanoide
- β1, β2

Inibizione tramite recettore presinaptico

GABA

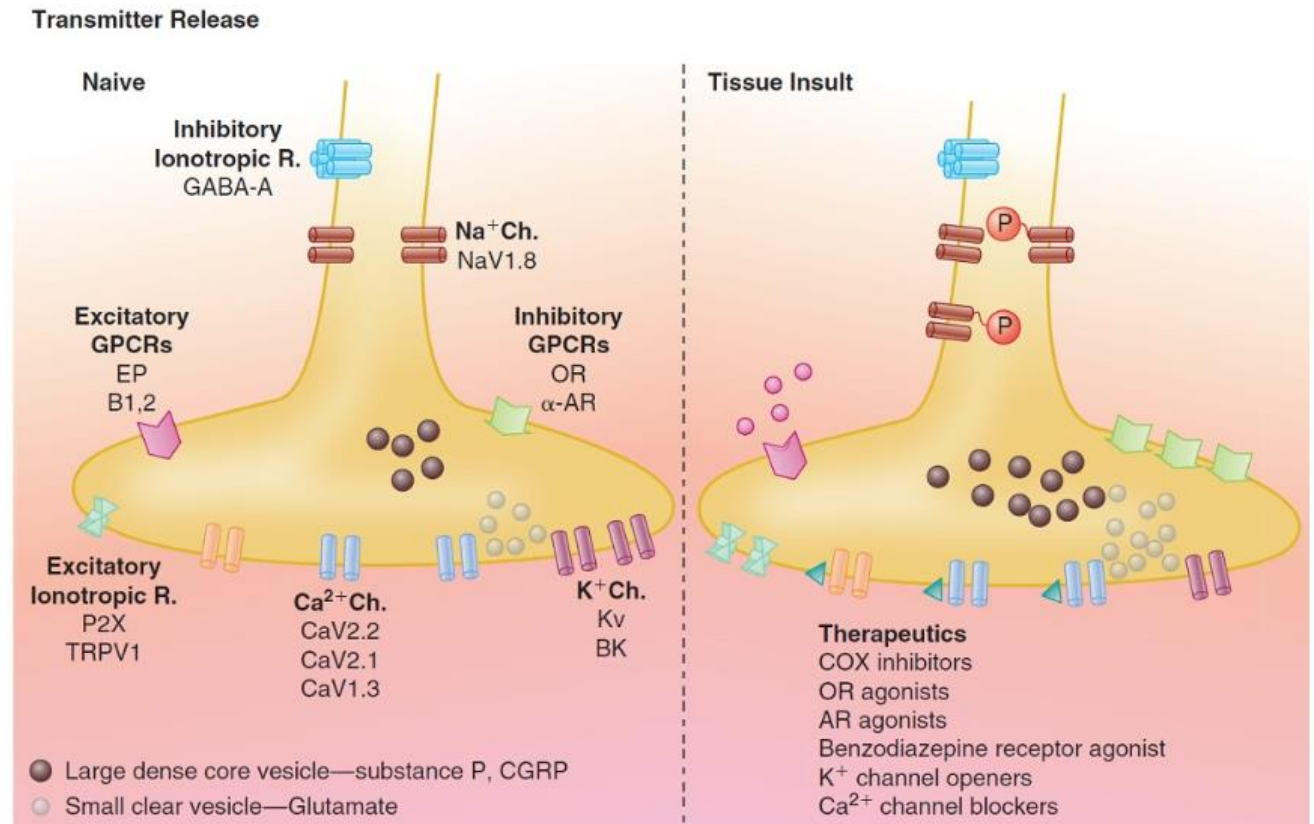
Canale della corrente eccitatoria

Nav1.8

Canali delle correnti inibitorie

- voltage-gated (KV) K⁺
- calcium-modulated (BK) K⁺

Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.



Midollo spinale – 2° neurone

L'individuazione delle strutture spinali e sovraspinali correlate alla nocicezione è molto complessa e si basa su diverse tecniche

- Iniezione intra-neuronale di coloranti
- Attivazione retrograda per via assonale
- Immunoistochimica
- Marcatori di risposta espressione geni c-fos e pERK

Neuroni 2° ordine

Maggioranza riceve afferenze sensoriali non-nocicettive

Minoranza esclusivamente nocicettivi

Afferenze dei neuroni 2° ordine

1. Primaria (nocicettore)
2. Interneuroni segmentali
3. Propriospinali (spinali non segmentali)
4. Sovraspinali

Afferenze inibitorie possono rendere maggiormente selettiva la trasmissione nocicettiva dei neuroni non esclusivamente nocicettivi

Classificazione funzionale dei nocicettori

Distinzione in base alla risposta a stimoli non-nocicettivi e nocicettivi

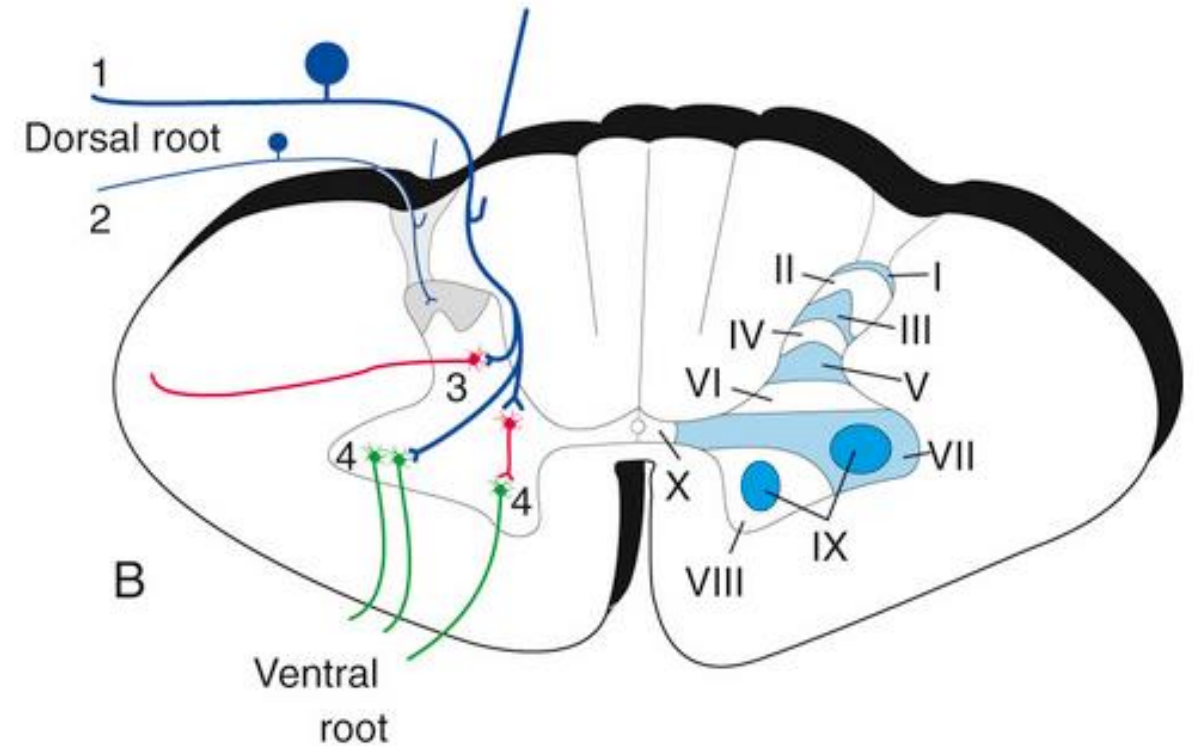
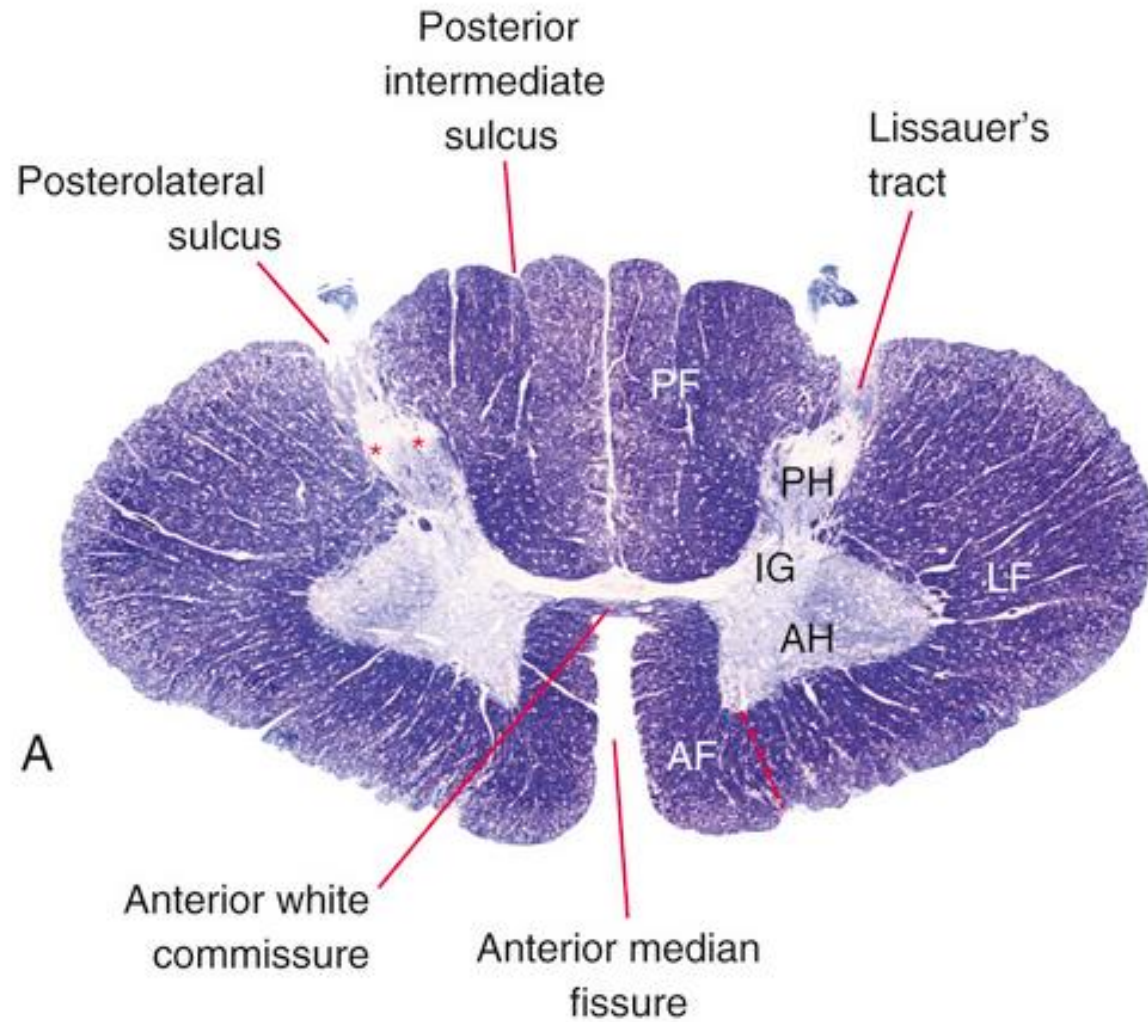
Classe I ↔ esclusivamente **non-nocicettivi** ↔ **low threshold**

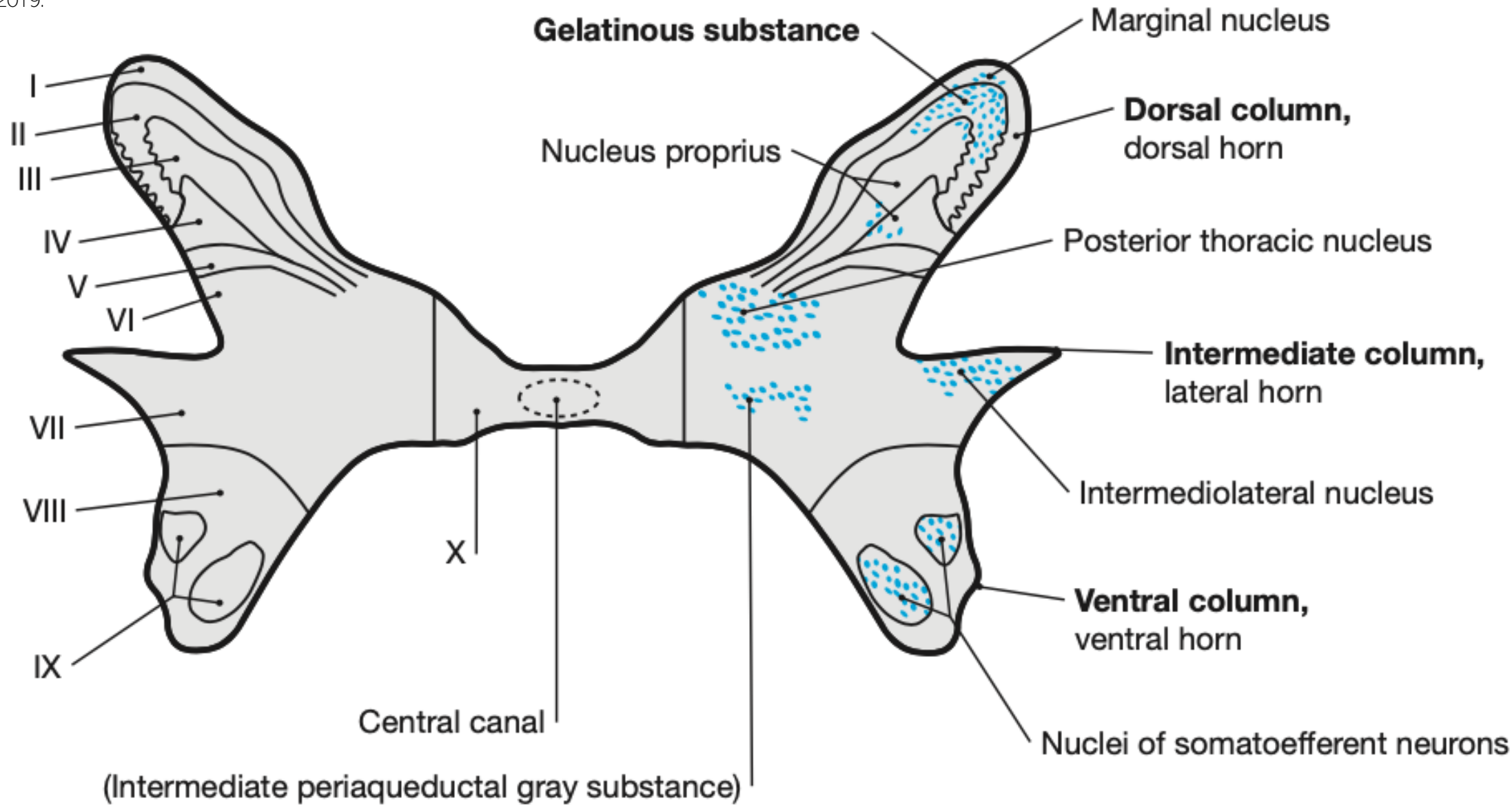
Classe II ↔ sia non-nocicettivi sia nocicettivi ↔ **wide-dynamic-range**
/ convergent ← rispondono a diffuse noxious inhibitory controls
(DNIC)

Classe III ↔ esclusivamente nocicettivi ↔ **high threshold**

Classe IV ↔ non responsivi sia a stimoli non-nocicettivi sia nocicettivi

Organizzazione della sostanza grigia





Lamina I

Zona marginale

Insieme alla Lamina II ricevono afferenti nocicettivi (SP+++, CGRP +++)

Fos, pERK +++ ↔ double-labeling proencefalina, dinorfina, glutammato, NDMA-R, GABA, glicine, GABA-B R, NK-1 R, calbindin, recettori glucocorticoidi, recettore estrogeni $\alpha.1$

Lamina II

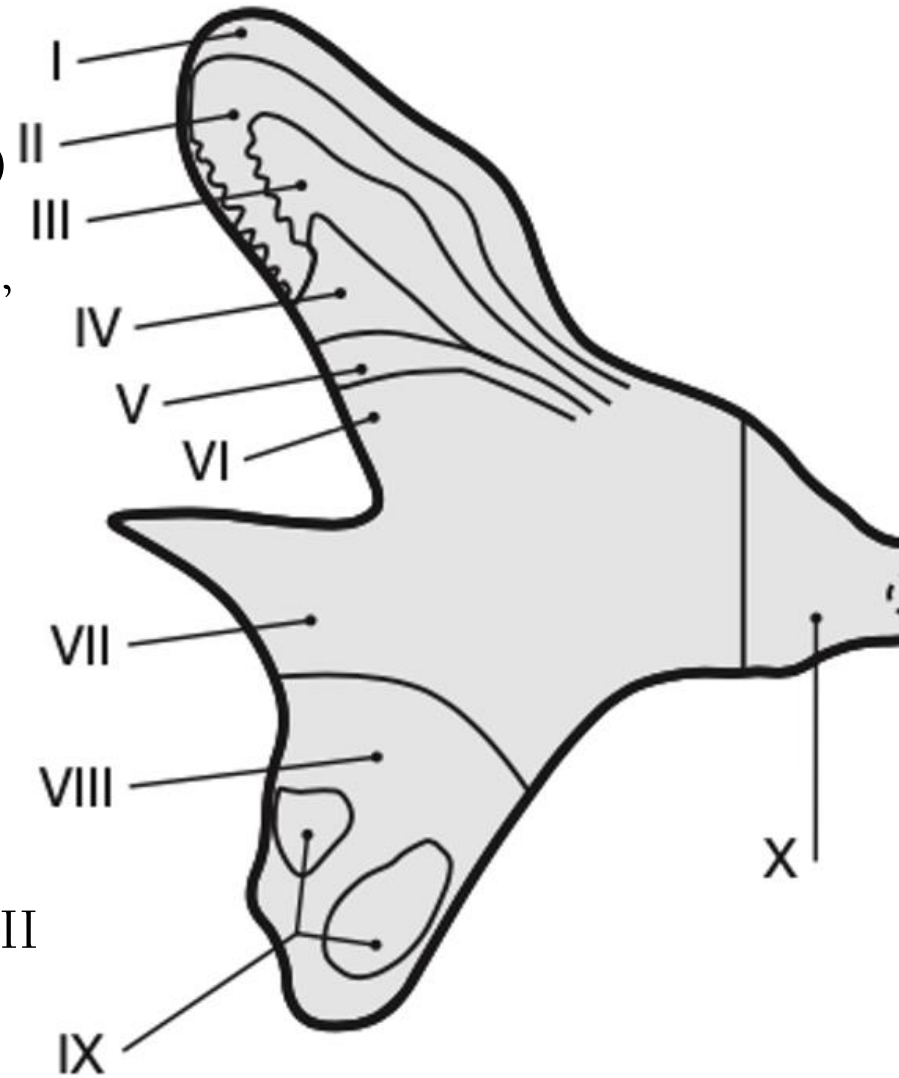
substantia gelatinosa

cellule peduncolate esterne → assoni-sinapsi alla Lamina I e dendriti centrali

cellule insulari → interneuroni inibitori GABA/enkefalina → diffuse arborizzazioni assionali e dendritiche → varie sinapsi estese alla Lamina II

input sia nocicettivi sia non-nocicettivi

target di vie discendenti serotoninergiche e noradrenergiche



Paulsen F, Waschke J, Hombach-Klonisch S, Klonisch T, Peeler J. Sobotta Clinical Atlas of Human Anatomy, One Volume, English. Elsevier Health Sciences; 2019.

Lamina III-IV

nucleus proprius

riceve afferenze mielinizzate a bassa soglia incluse propriocettive

sottopopolazione di grandi neuroni i cui dendriti si connettono alle zone superficiali

alcuni neuroni contribuiscono al sistema delle colonna dorsali altri al tratto spinotalamico

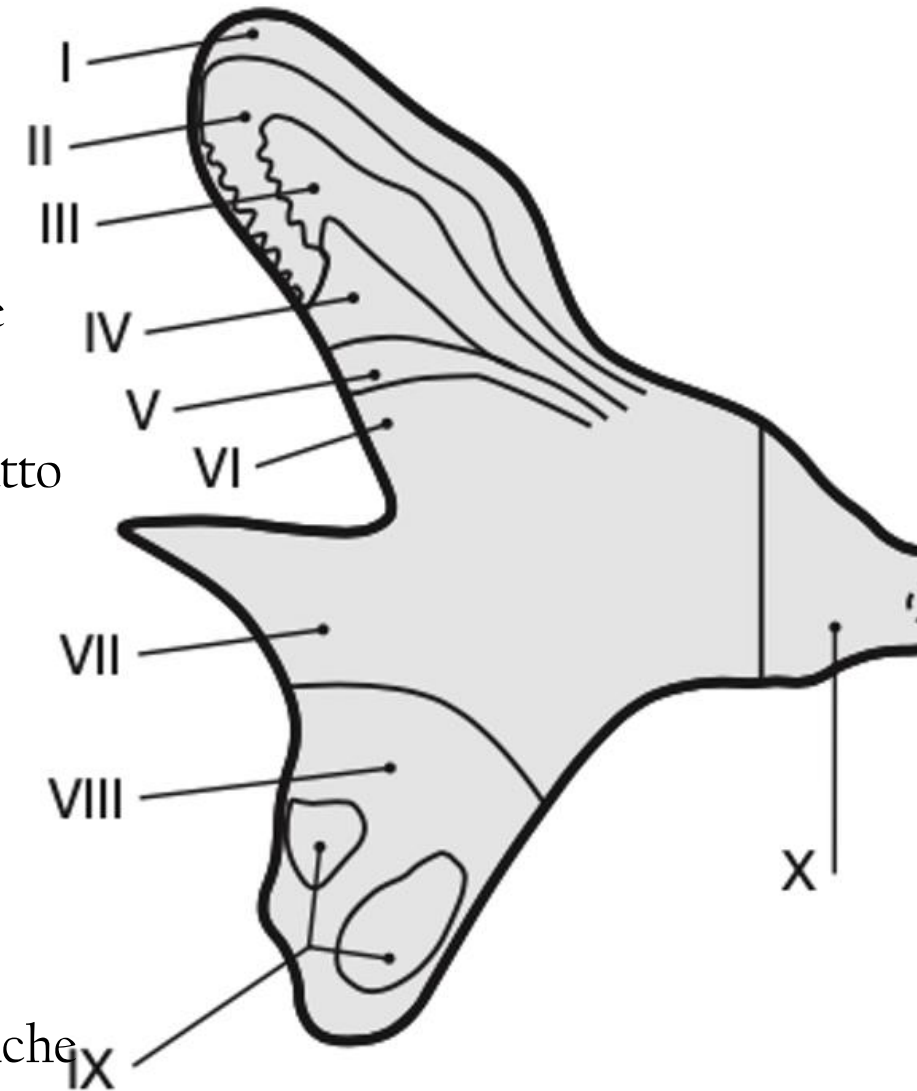
Lamina V

Afferenze dei nocicettori A δ e C

Afferenze mielinizzate a bassa soglia

Una parte di neuroni raggiunge Laminae I-II con arborizzazioni dendritiche

Ricevono afferenze somatiche, muscolari, viscerali



Paulsen F, Waschke J, Hombach-Klonisch S, Klonisch T, Peeler J. Sobotta Clinical Atlas of Human Anatomy, One Volume, English. Elsevier Health Sciences; 2019.

Lamina VI

Piccoli neuroni presenti nelle entumescenze cervicali e lombari

Afferenze a bassa soglia muscolari

Afferenze sia bassa sia alta soglia dalla cute

Lamina X

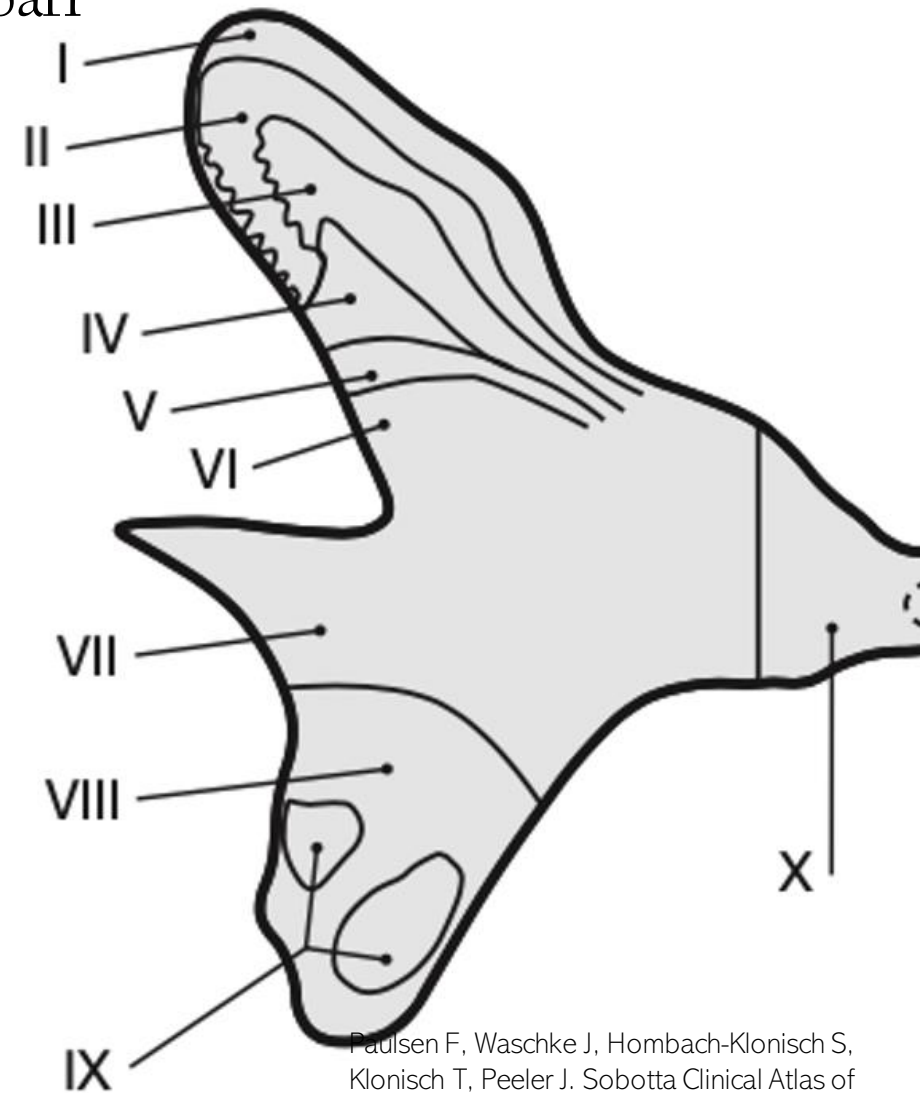
Attorno al canale centrale

Ricevono afferenze bilaterali di tutti i tipi

Alcuni neuroni proiettano tramite colonna dorsali al bulbo

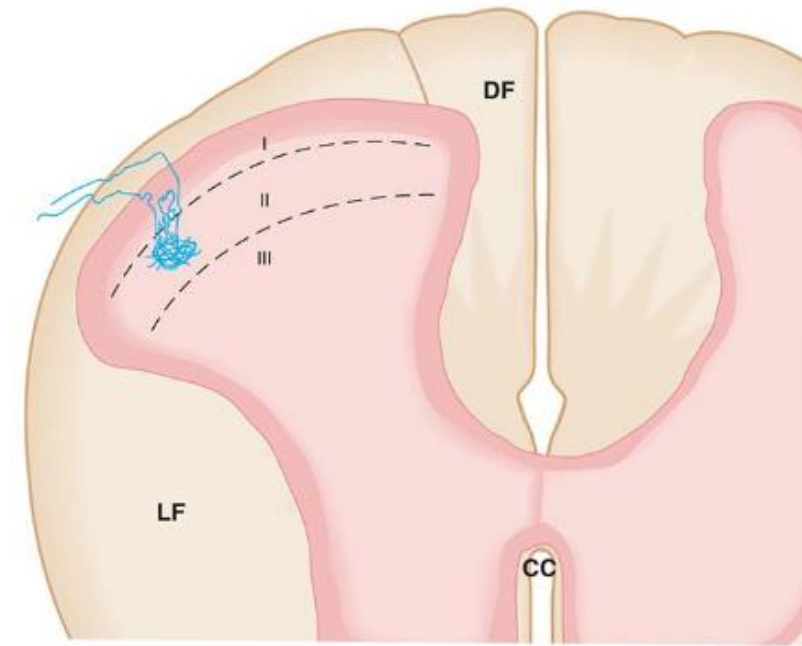
Estesi input peptidergici, noradrenergici e serotoninergici

Interneuroni inibitori (GABA, glicina)



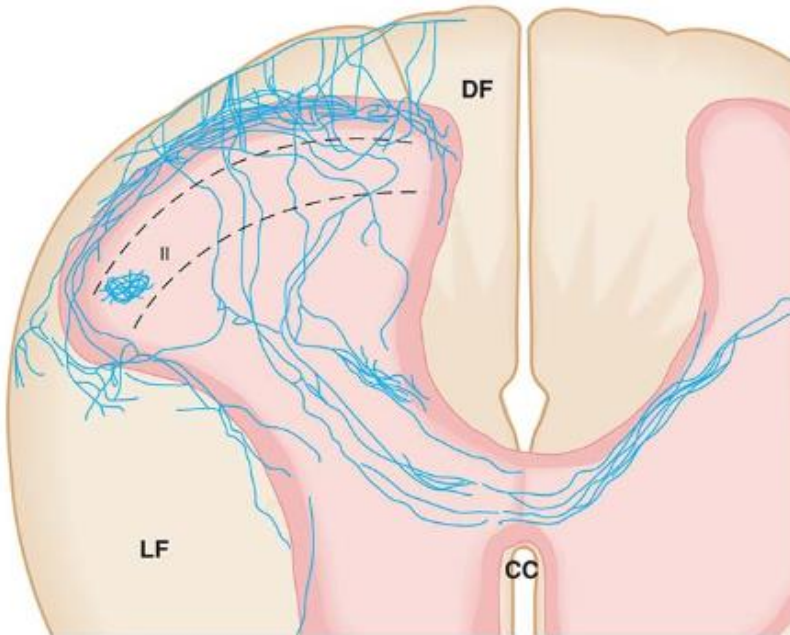
Paulsen F, Waschke J, Hombach-Klonisch S, Klonisch T, Peeler J. Sobotta Clinical Atlas of Human Anatomy, One Volume, English. Elsevier Health Sciences; 2019.

Afferenza fibra C
somatica



A

Afferenza fibra C
viscerale

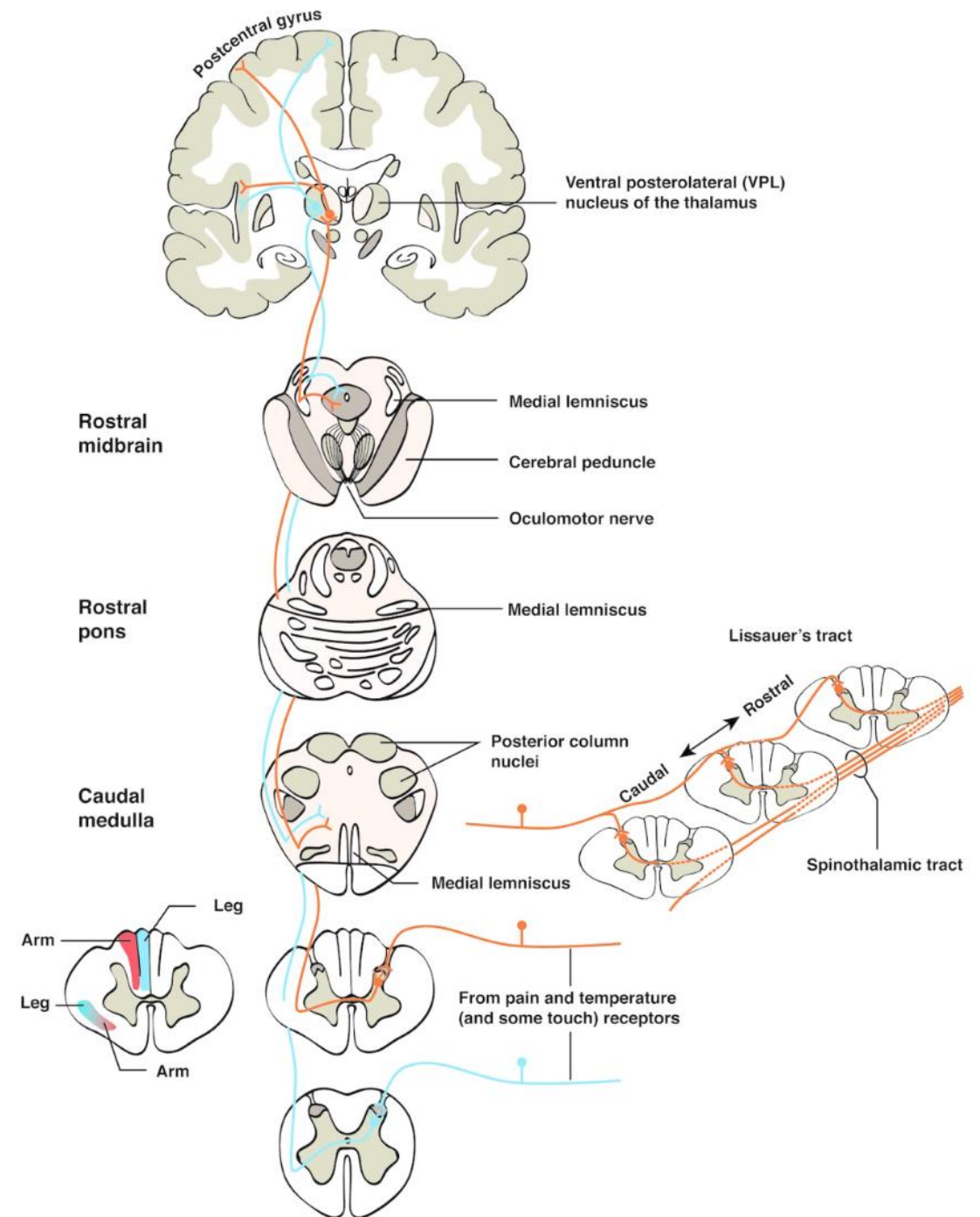


B

Proiezioni

I neuroni nocicettivi spinali proiettano verso

1. Altri segmenti spinali
2. Talamo
3. Ipotalamo
4. Mesencefalo
5. Ponte
6. Bulbo



Khalid S, Tubbs RS. Neuroanatomy and Neuropsychology of Pain. Cureus. 9(10):e1754.

doi:10.7759/cureus.1754

Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.

Maggioranza degli assoni decorrono nei fasci di sostanza bianca

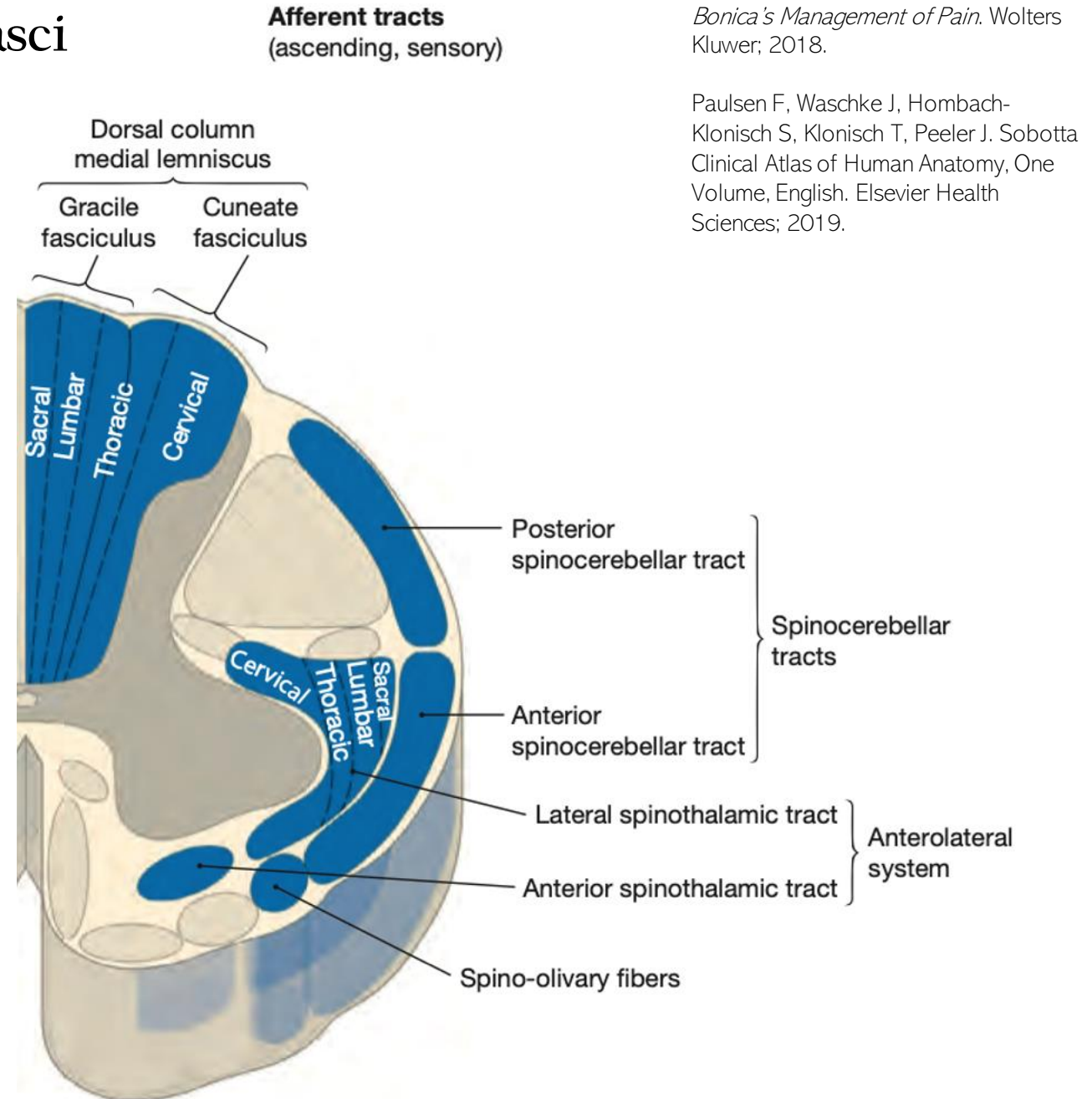
1. Quadranti ventrolaterali
2. Sistema mediano dorsale
3. Funicolo dorsolaterale (minoranza)

Decussano in gran parte le fibre verso

- Talamo
- Tronco encefalico

NON decussano la maggioranza verso

- Nuclei della sostanza reticolare



Ballantyne JC, Fishman S, Rathmell JP.
Bonica's Management of Pain. Wolters
Kluwer; 2018.

Paulsen F, Waschke J, Hombach-
Klonisch S, Klonisch T, Peeler J. Sobotta
*Clinical Atlas of Human Anatomy, One
Volume*, English. Elsevier Health
Sciences; 2019.

Tratto spinotalamico

Tratto neo-spinotalamico

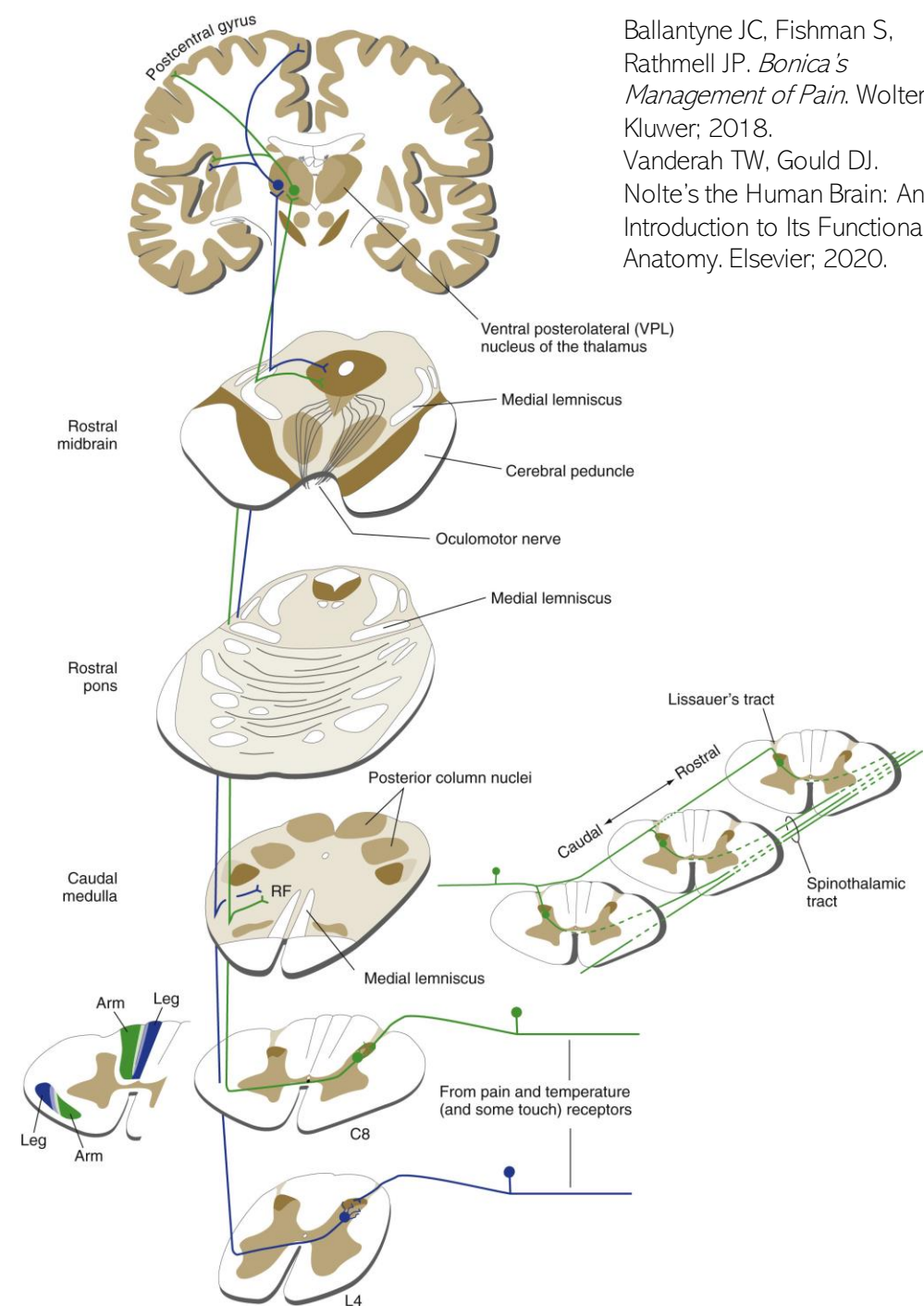
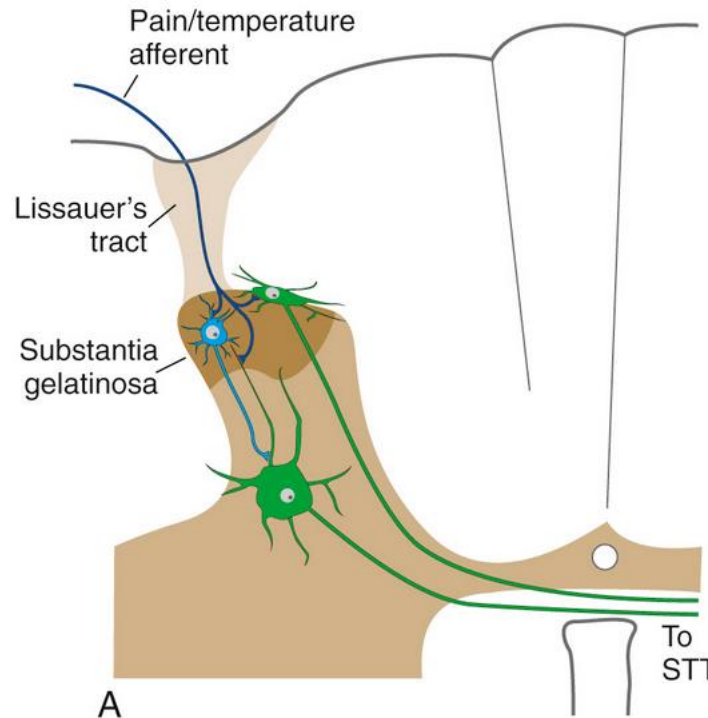
- Diretto al gruppo ventrobasale del Talamo controlaterale
(decussazione via fascio di Lissauer)
 - Talamo → Corteccia somatosensitiva
- Localizzazione
- Intensità

Tratto paleo-spinotalamico

Numerose biforcazioni assionali

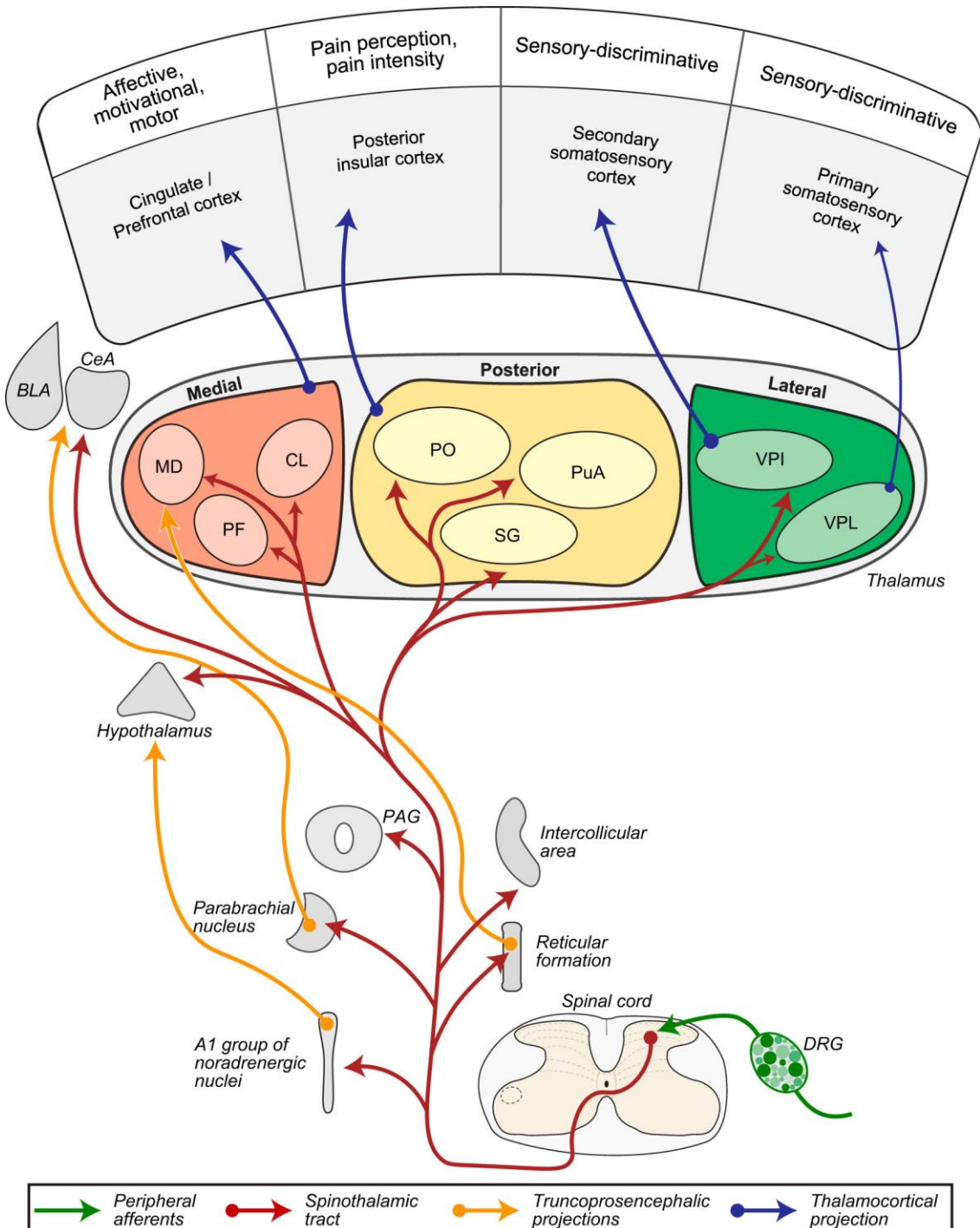
- Bulbo
- Ponte
- Mesencefalo
- Talamo mediale
- Ipotalamo
- Strutture limbiche

→ Aspetti emotivi e motivazionali del dolore



Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.
Vanderah TW, Gould DJ. *Nolte's the Human Brain: An Introduction to Its Functional Anatomy*. Elsevier; 2020.

FIGURE 1. Scheme depicting spinothalamic tract signaling to thalamus and cortex. *Bottom:* the peripheral sensory inputs, the spinothalamic tract, and its terminations in the brain stem, including pain-relevant projections of brain stem nuclei to prosencephalic areas. *Middle:* the thalamic targets of the spinothalamic tract and connections to the amygdala. Only thalamic nuclei relaying spinothalamic tract inputs are shown. The trigeminothalamic tract and ventral posterior medial thalamic nucleus (VPM) are not shown for clarity. *Top:* the thalamic relay to cortex and functional modalities. CL, centrolateral nucleus; MD, mediodorsal nucleus; PF, parafascicular nucleus; PO, posterior nucleus; PuA, anterior pulvinar nucleus; SG, supragenicular nucleus; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus.



Tratti SpinoReticolare e SpinoMesencefalico

Proiezioni dei neuroni di 2° ordine che NON raggiungono il Talamo

Tratto SpinoReticolare

Tratto SpinoMesencefalico

Maggioranza NON decussa e il Tratto SpinoMesencefalico invia fibre anche alle colonna dorsali

Neuroni SpinoReticolari

- SpinoBulbari
- SpinoPontini
- SpinoOlivari
- SpinoSolitari
- SpinoRafe
- SpinoParabrachiali

Tratto SpinoReticolare

Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.

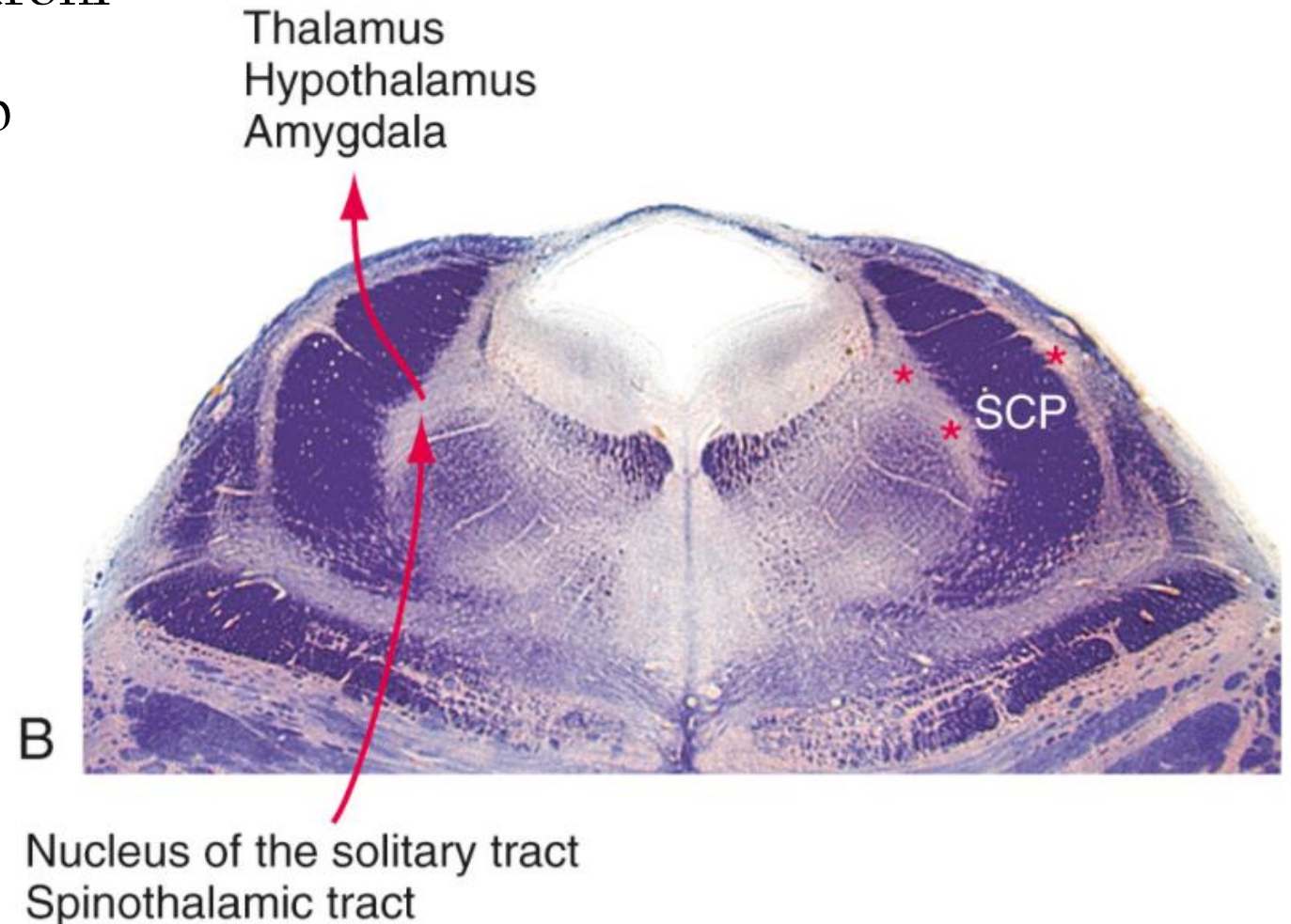
Vanderah TW, Gould DJ. *Nolte's the Human Brain: An Introduction to Its Functional Anatomy*. Elsevier; 2020.

Localizzazione e caratteristiche dei neuroni SpinoReticolari uguali ai neuroni SpinoTalamici che proiettano al Talamo Mediale

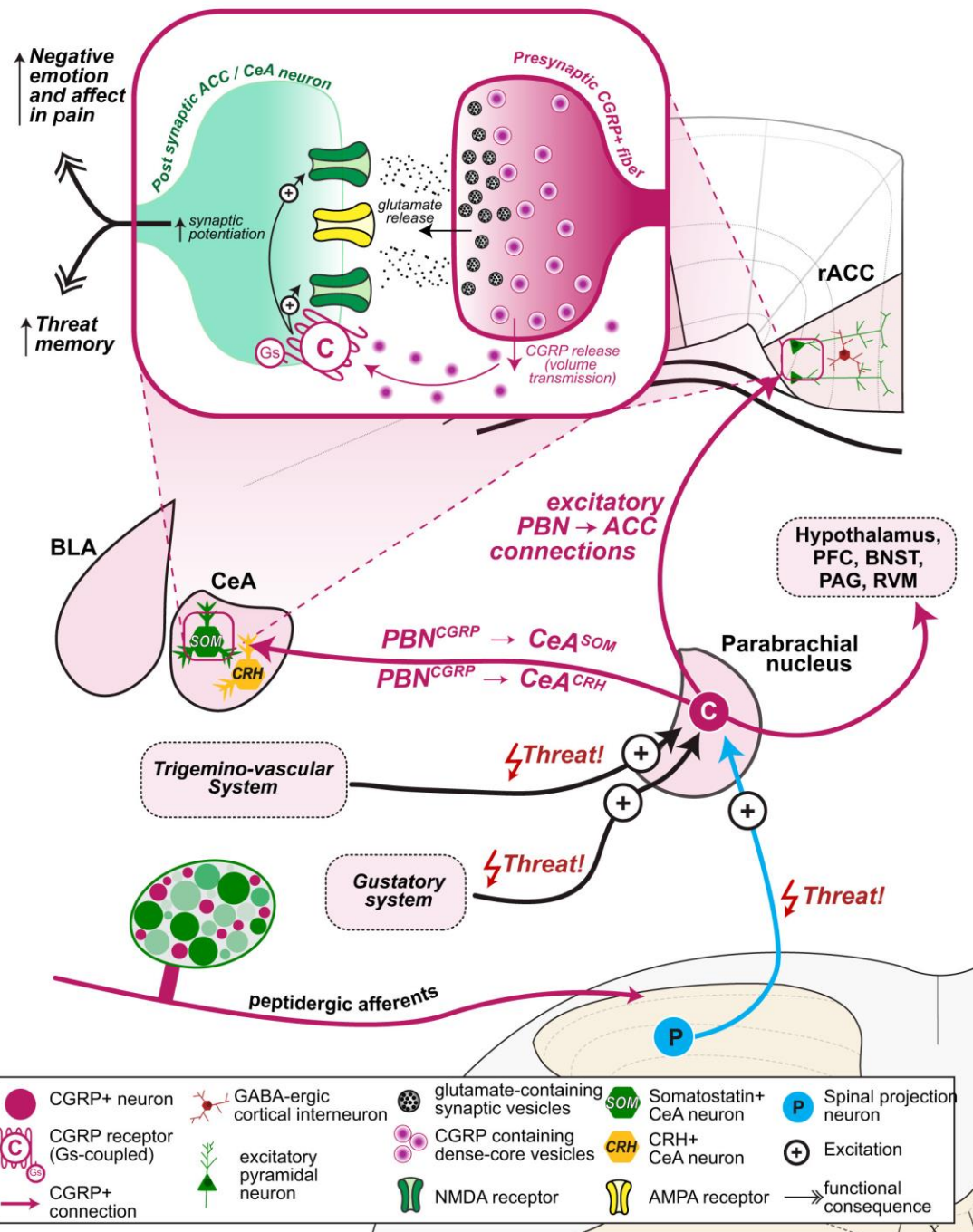
- Lamine profonde
- Tipo Nocicettori esclusivi o Wide-Dynamic-Range

Target

- Nuclei Sistema Nervoso Autonomo
- Regolazione della nocicezione
- Nucleo Parabrachiale del Ponte → Strutture limbiche sottocorticali (e.g. Amigdala)



Detail view of CGRP+ fiber action on ACC/ CeA neurons



Nucleo Parabrachiale

→ Proiezioni peptidergiche [calcitonin gene-related peptide (CGRP)]

→ Sinapsi eccitatorie

→ Amigdala

→ Corteccia cingolata

→ Memoria della minaccia

→ Reazione avversiva

Kuner R, Kuner T.
Cellular Circuits in the
Brain and Their
Modulation in Acute and
Chronic Pain. *Physiol
Rev.* 2021;101(1):213-
258.
doi:10.1152/physrev.00
040.2019

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; CRH, corticotropin releasing hormone; DRG, dorsal root ganglion; NMDA, N-methyl-d-aspartate receptor; PAG, periaqueductal grey; PBN, parabrachial nucleus; rACC, rostral anterior cingulate cortex; RVM, rostral-ventral medulla oblongata; SOM, somatostatin.

Tratto SpinoMesencefalico

Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.

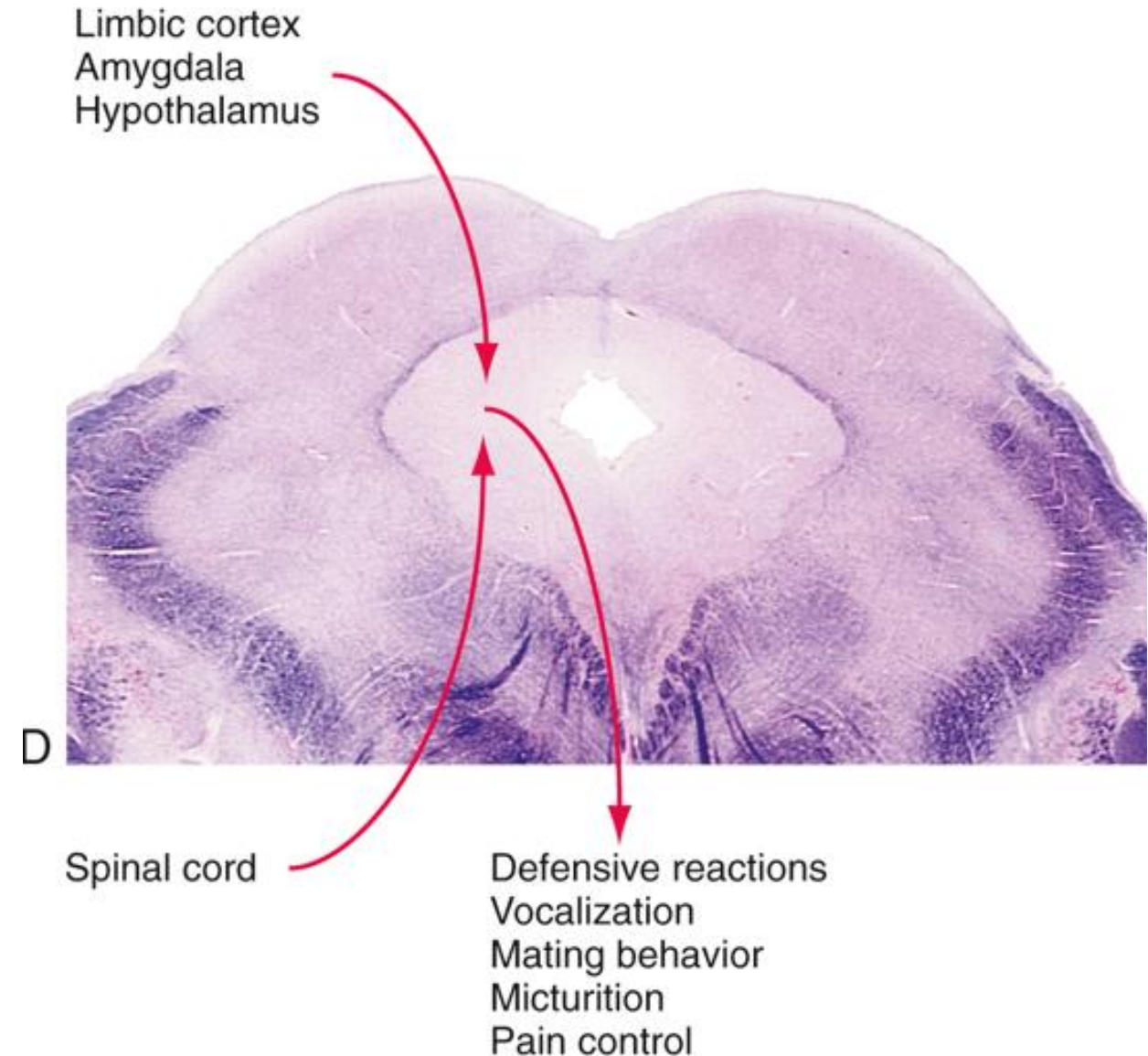
Vanderah TW, Gould DJ. *Nolte's the Human Brain: An Introduction to Its Functional Anatomy*. Elsevier; 2020.

Localizzazione e caratteristiche dei neuroni SpinoMesencefalici simili ai neuroni SpinoTalamici che proiettano al Talamo Laterale

- Laminae I e V
- Predominanza di Nocicettori esclusivi

Target

- Grigio Periacqueduttale
- Nucleo Collicolare
- Nucleo Cuneiforme



Postsynaptic Dorsal Column Neurons

Postsynaptic Dorsal Column Neurons

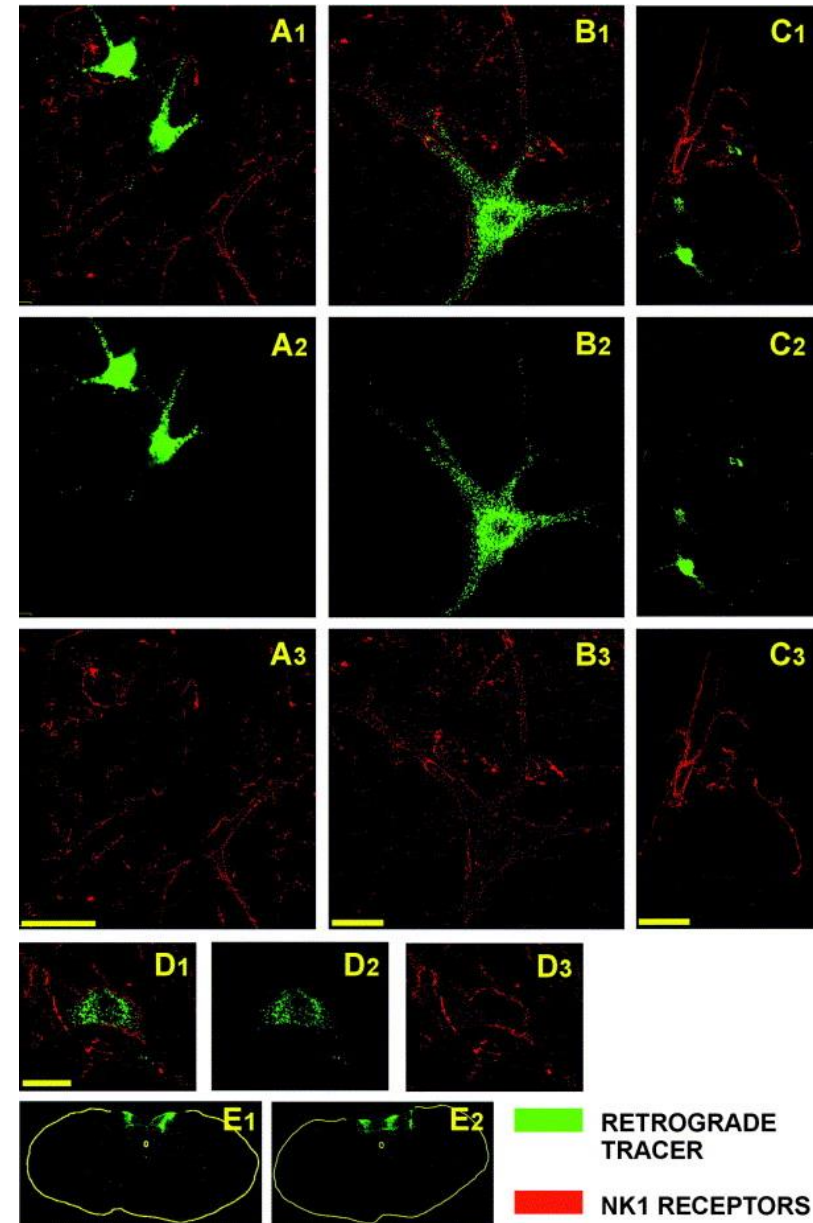
Sistema di proiezione localizzato nella linea mediana

Nocicezione dei tessuti profondi (colon, vescica, utero)

- Laminae III, IV, X
- Neuroni Nocicettivi e WDR
- → Talamo VentroBasale

Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.

Palecek J, Paleckova V, Willis WD. Postsynaptic dorsal column neurons express NK1 receptors following colon inflammation. *Neuroscience*. 2003;116(2):565-572. doi:10.1016/s0306-4522(02)00660-7



Modulazione della nocicezione

- Meccanismi spinali
- Meccanismi sovraspinali

Modulazione segmentaria acuta: gate control theory

Attivazione delle fibre $A\beta$ inibisce la trasmissione delle fibre $A\delta$ e C

Inibizione presinaptica

Attivazione di interneuroni GABA- e/o glicinerfici della sostanza gelatinosa

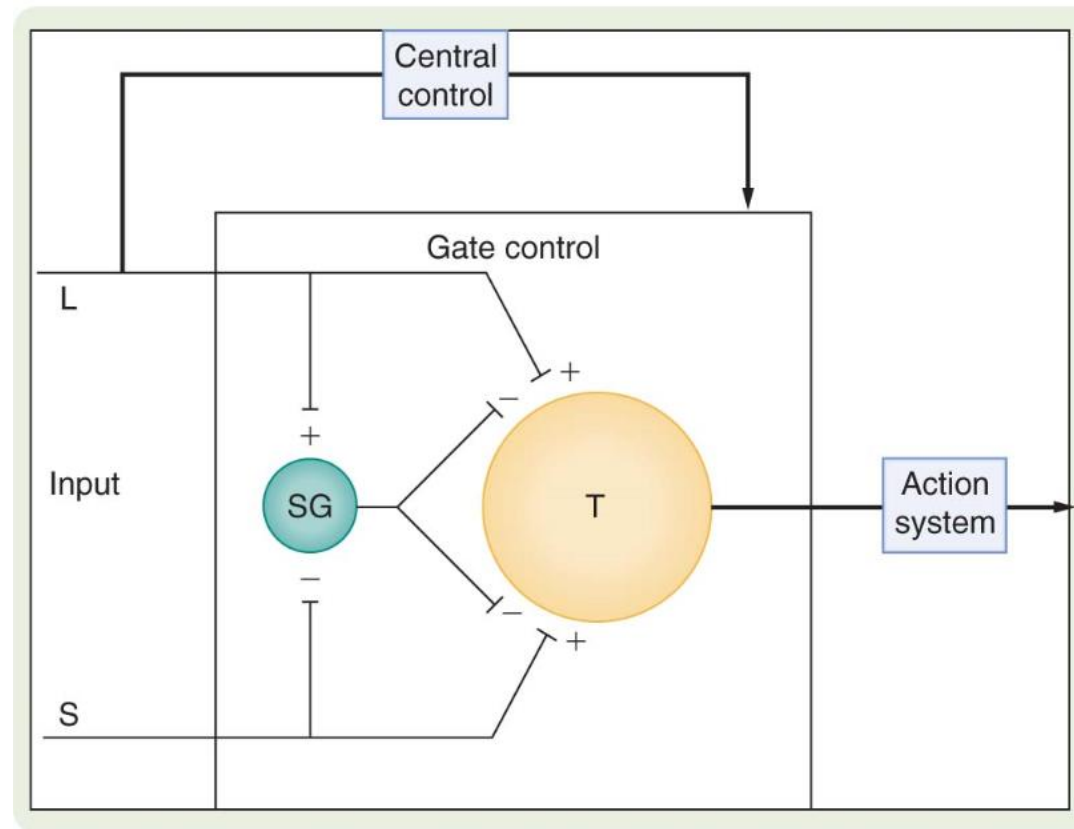


TABLE 5.1 Central Nervous System (CNS) Sites Modulating Nociceptive Transmission (NT)

CNS Site	Direct Projection to Spinal Segments	Possible Relay Sites	Facilitation NTs	Inhibition NTs
<i>Spinal Cord</i>				
Segmental	NA	Multisegmental	GLUT	GABA, glycine
Propriospinal	Many	Multisegmental	GLUT	GABA, glycine, opioid, ACh
Heterosegmental	Many	Multisegmental-RVM-DRt	GLUT	Opioid, 5-HT, NE, GABA

Strutture sovraspinali della modulazione del dolore

- Grigio Periacqueduttale PAG – Mesencefalo
- Bulbo Rostrale Ventrale RVM
- Nucleo del Rafe Magno – Bulbo
- Nucleo Gigantocellulare NGC - Bulbo
- Nucleus Reticularis Gigantocellularis pars alpha NGC α - Bulbo e Ponte caudale
- Nucleo paragigantocellulare NpGC – Tegmento Pontino
- Formazione reticolare del Mesencefalo
- Locus coeruleus gruppi cellulari A6 e A5 - Ponte
- Nucleo reticolare laterale - Bulbo
- Nucleo Parabrachiale – Ponte
- Nucleo del Tratto Solitario – Tronco caudale
- Corteccia cingolata anteriore
- Amigdala
- Ipotalamo

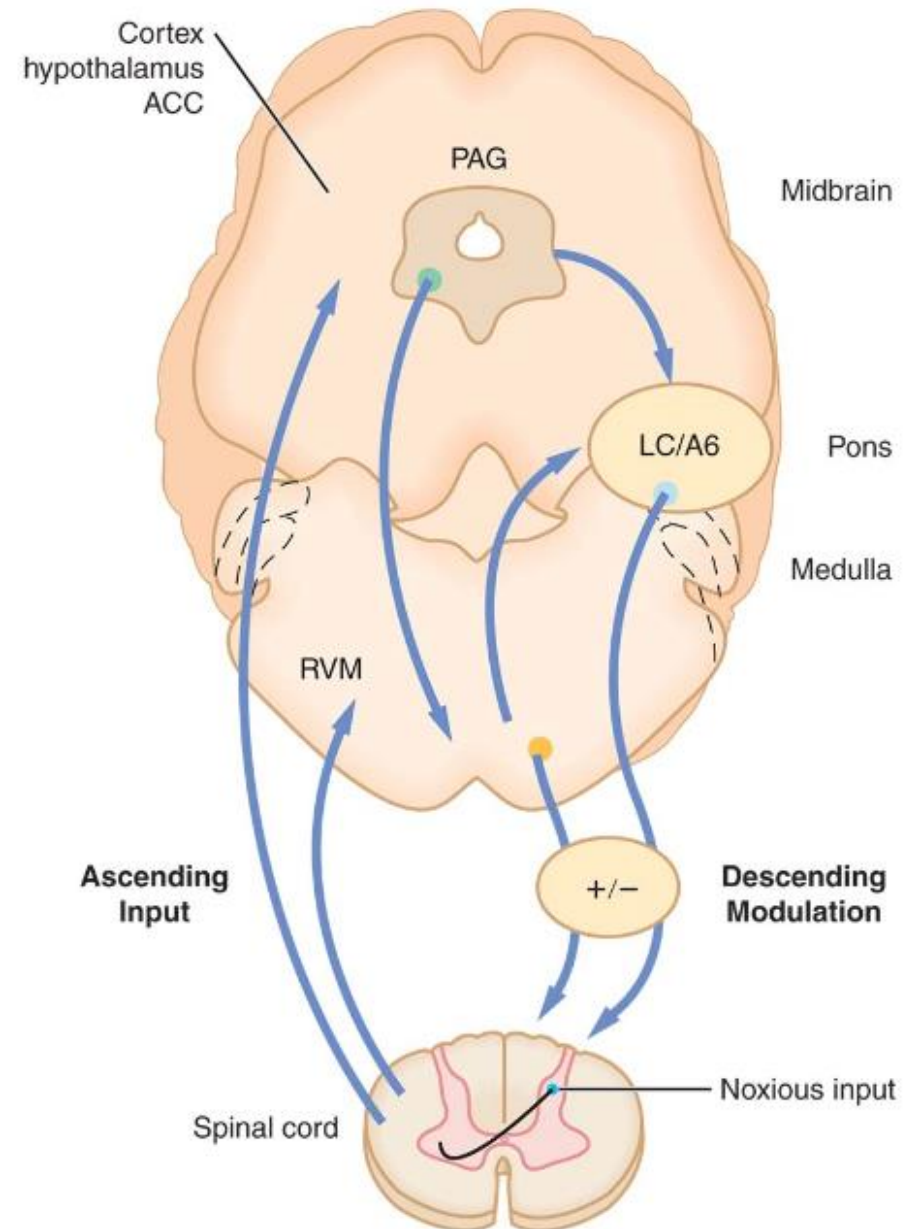
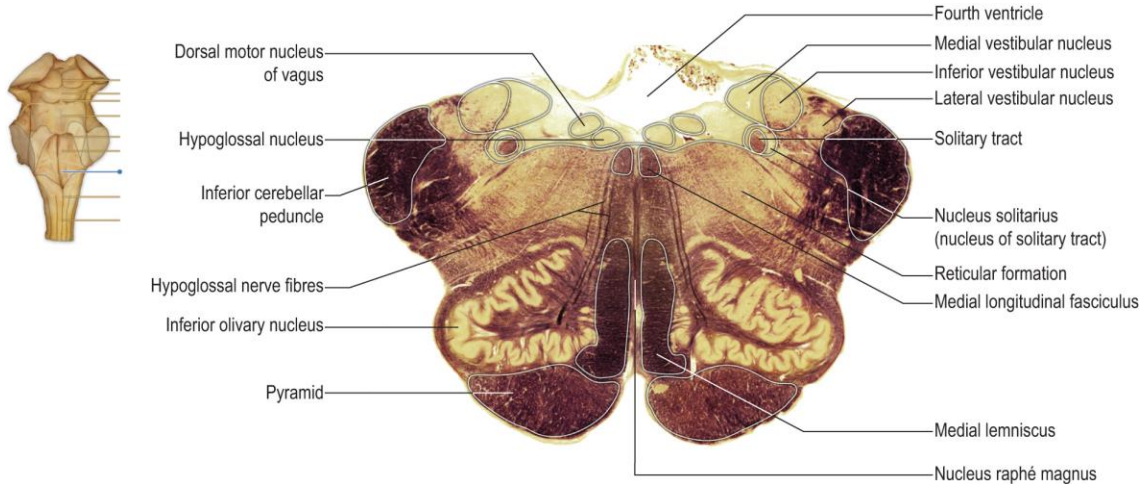


TABLE 5.1 Central Nervous System (CNS) Sites Modulating Nociceptive Transmission (NT)

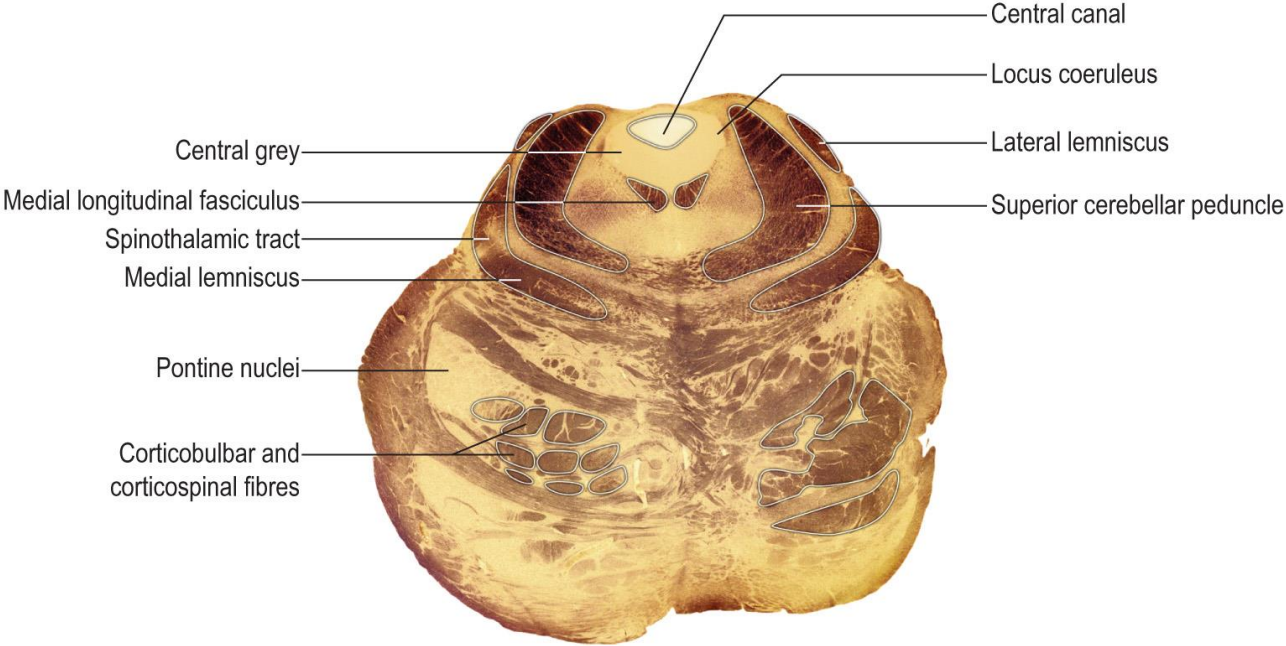
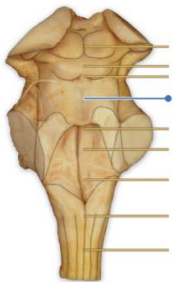
CNS Site	Direct Projection to Spinal Segments	Possible Relay Sites	Facilitation NTs	Inhibition NTs
Medulla				
NTS	Few	RVM, LC, PAG, A5, cortex	GLUT	NE and 5-HT together
RVM (region)	Many		5-HT2, 5-HT3, NE (α 1), GLUT, ACh	5-HT1A, 5-HT1B, 5-HT1D, 5-HT7, opioid, NE (α 2), ACh, GABA, glycine
NRM	Many		5-HT2, 5-HT3	5-HT, opioid, ACh, GABA
NGC, NGC α , NpGC	Many	LC	GLUT, 5-HT, CCK-B, NE (α 1)	5-HT, NE(α 2)
LRN	Some	LC, RVM, A5		NE (α 2)
A1	Few		NE (α 1)	NE (α 2)
DRt	Many		GLUT	



Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.
Crossman AR, Neary D. *Neuroanatomy E-Book: An Illustrated Colour Text*. Elsevier Health Sciences; 2018

TABLE 5.1 Central Nervous System (CNS) Sites Modulating Nociceptive Transmission (NT)

CNS Site	Direct Projection to Spinal Segments	Possible Relay Sites	Facilitation NTs	Inhibition NTs
Pons				
LC/A6/A5	Many		NE (α 1)	NE (α 2)
PBN/A7	Many/few	PAG, RVM	NE (α 1)	NE (α 2), oxytocin?



Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.
Crossman AR, Neary D. *Neuroanatomy E-Book: An Illustrated Colour Text*. Elsevier Health Sciences; 2018.

TABLE 5.1 Central Nervous System (CNS) Sites Modulating Nociceptive Transmission (NT)

CNS Site	Direct Projection to Spinal Segments	Possible Relay Sites	Facilitation NTs	Inhibition NTs
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Mesencephalon

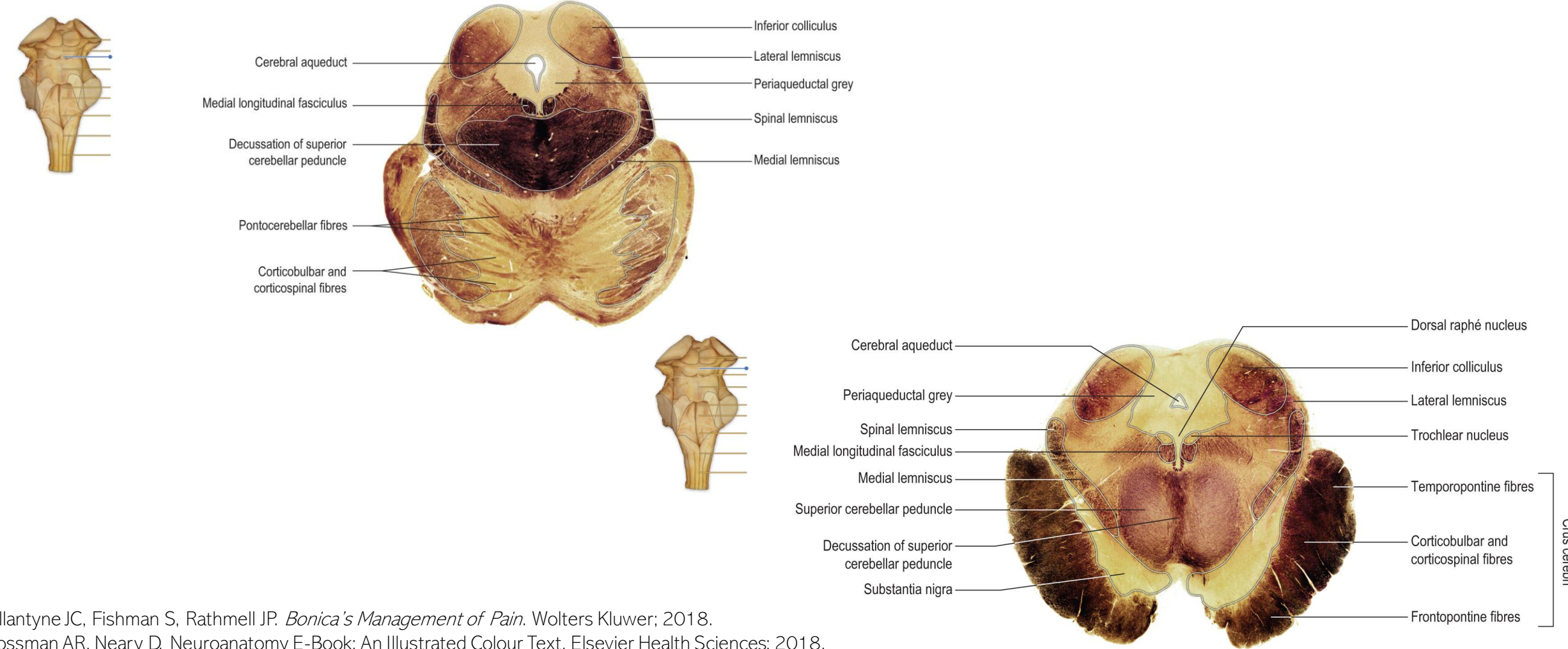
PAG

Few

RVM, LC

NE (α1), 5-HT

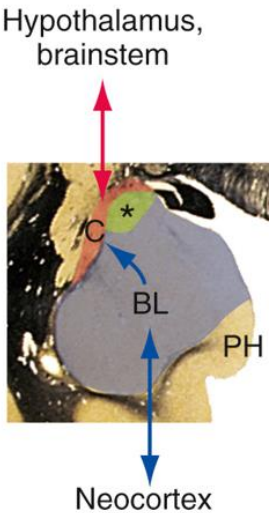
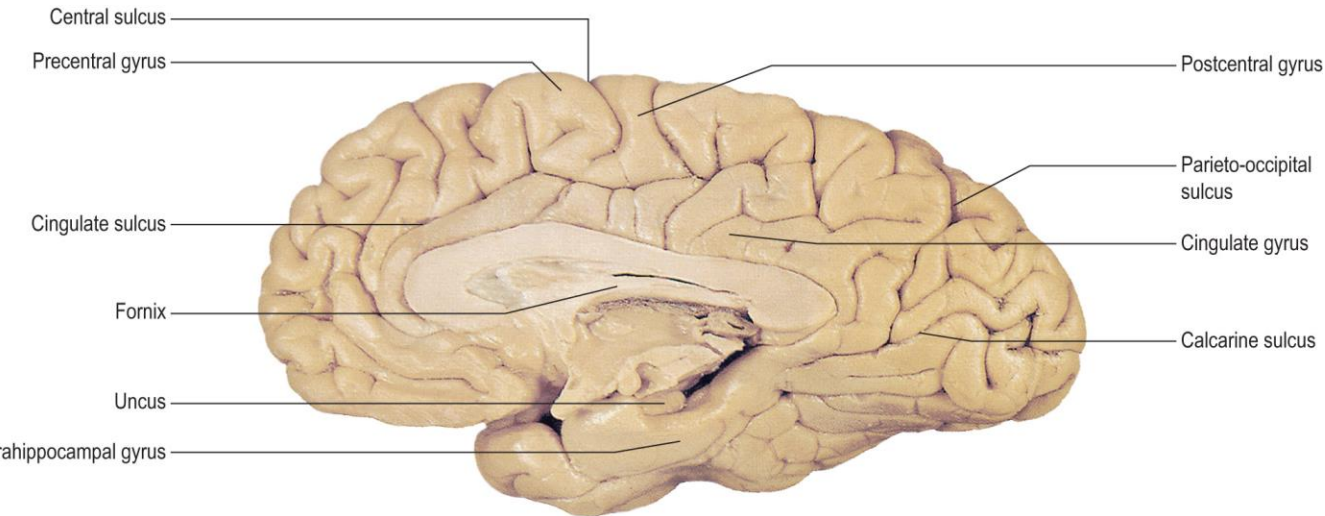
5-HT, NE (α2), opioid, ACh



Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.
Crossman AR, Neary D. *Neuroanatomy E-Book: An Illustrated Colour Text*. Elsevier Health Sciences; 2018.

TABLE 5.1 Central Nervous System (CNS) Sites Modulating Nociceptive Transmission (NT)

CNS Site	Direct Projection to Spinal Segments	Possible Relay Sites	Facilitation NTs	Inhibition NTs
Diencephalon Cortex				
Hypothalamus	Some	RVM, PAG	GLUT	5-HT, NE(α 2), DA
Amygdala	Some	PAG, PBN	GLUT, oxytocin? CRF-related?	NE(α 2), oxytocin? CRF related?
ACC	Few	RVM, PAG	GLUT, 5-HT	
Sensory cortex	Few	RVM	GLUT	5-HT, NE(α 2), opioid
Sensory cortex	Few	?	GLUT	5-HT, NE(α 2), opioid
VLO	Few	RVM, PAG	GLUT	5-HT, NE(α 2), opioid



Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.
Crossman AR, Neary D. *Neuroanatomy E-Book: An Illustrated Colour Text*. Elsevier Health Sciences; 2018.

La via pontospinale noradrenergica

Corteccia Prefrontale

Amigdala

Ipotalamo-Nucleo paraventricolare

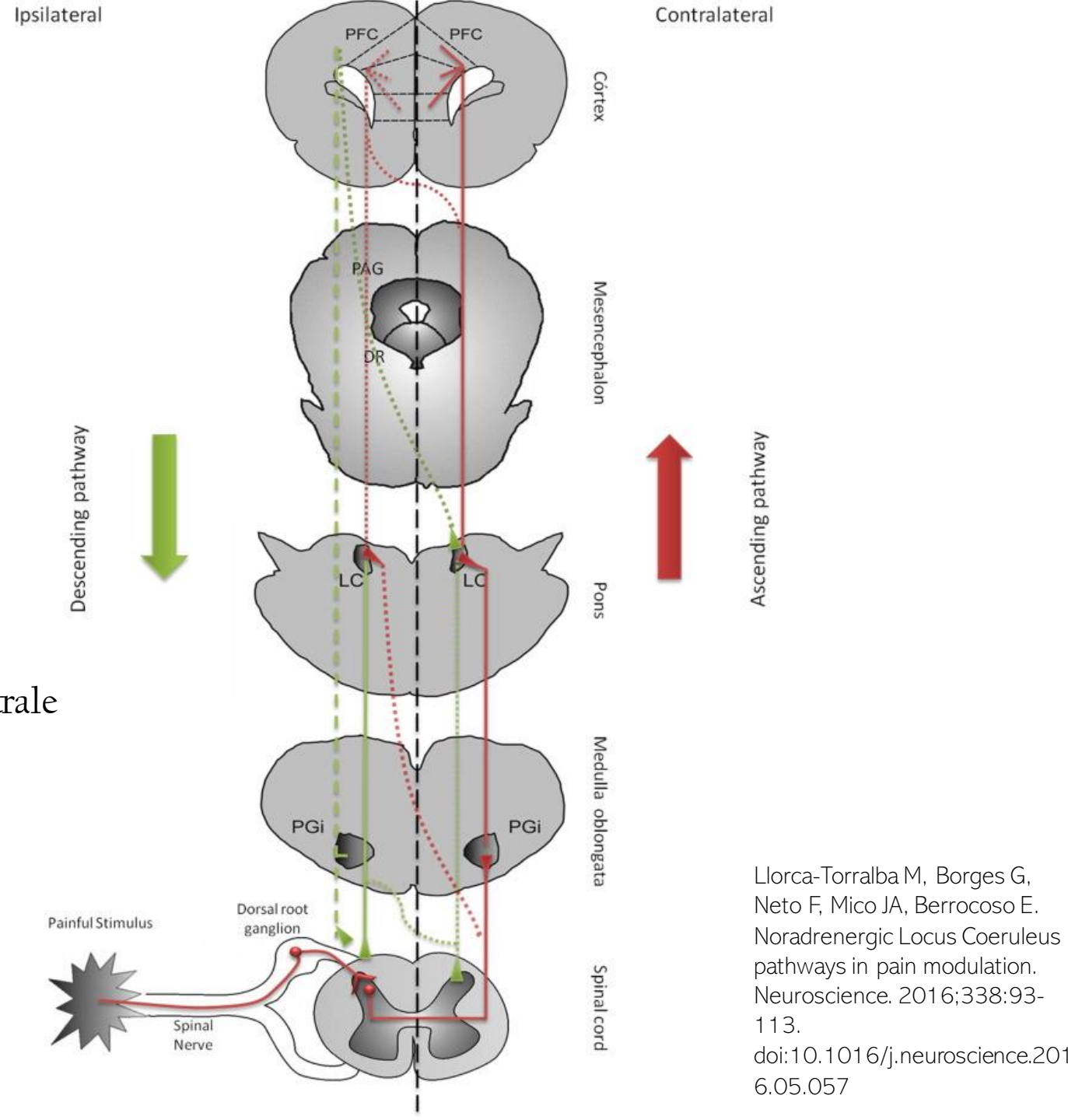
↑
Ponte-Locus cœruleus

↑
Bulbo- Paragigantocellularis nucleus

↑
Decussazione (fascio di Lissauer)

↓
Corno dorsale
Laminae VII, VIII, IX, X

Funicolo ventrale
ipsilaterale



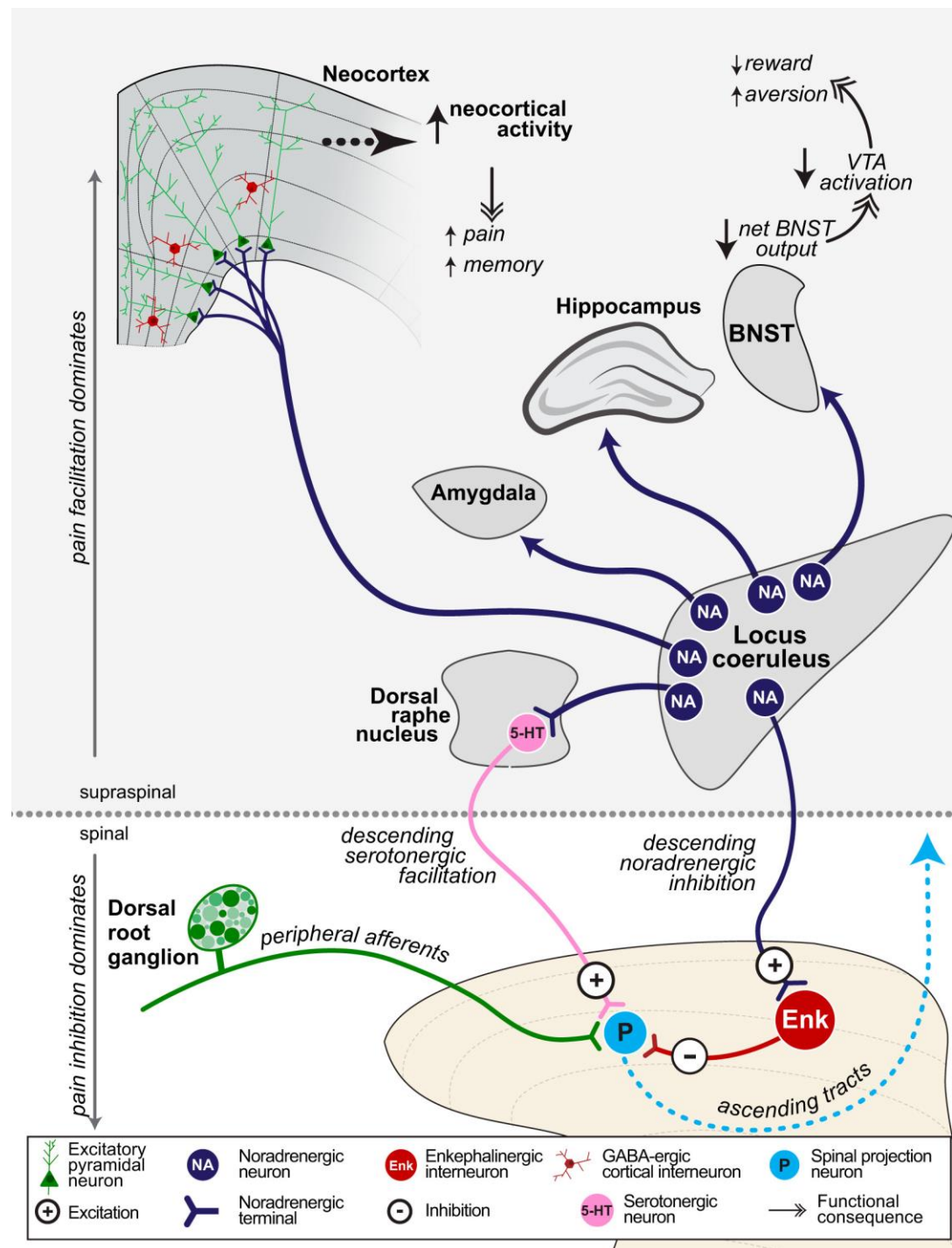
Llorca-Torralba M, Borges G, Neto F, Mico JA, Berrocoso E. Noradrenergic Locus Coeruleus pathways in pain modulation. Neuroscience. 2016;338:93-113. doi:10.1016/j.neuroscience.2016.05.057

Modulazione sovraspinale: via noradrenergica

Locus coeruleus
principale nucleo
noradrenergico

LC **ventrale** →
proiezioni spinali →
antinocicezione

LC **dorsale** →
proiezioni cerebrali
e.g. Corteccia
Prefrontale →
pronocicezione



Kuner R, Kuner T.
Cellular Circuits in the
Brain and Their
Modulation in Acute and
Chronic Pain. *Physiol
Rev.* 2021;101 (1):213-
258.
doi:10.1152/physrev.00
040.2019

Modulazione sovraspinale: via serotoninergica

Bulbo rostrale ventrale

Gruppi neuronali classificati in base alla frequenza di scarica rispetto alla risposta motoria (movimento della coda) allo stimolo nocivo (calore) nell'animale sedato

ON cells ↑ firing poco prima del movimento della coda

OFF cells ↓ firing

NEUTRAL = firing

Morfina →

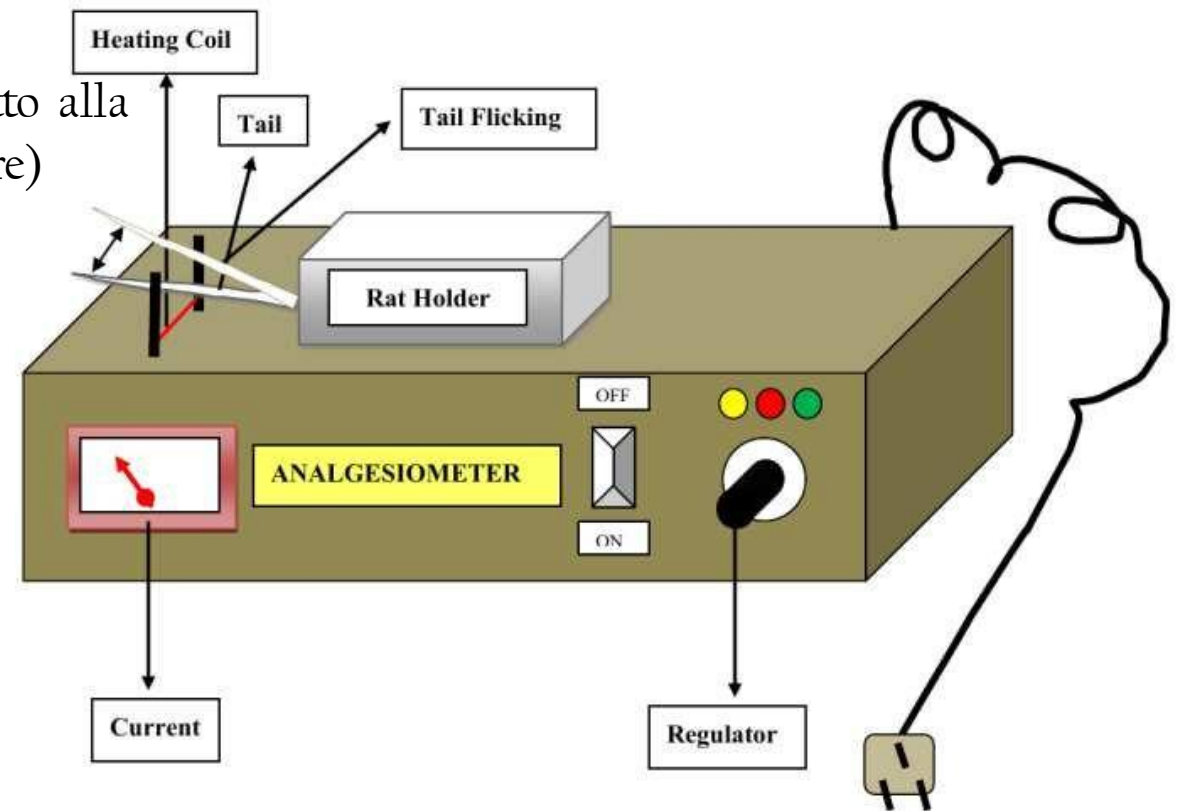
→ Soppressione del movimento della coda

→ OFF cells continuamente attive

→ ON cells ↓ attività

→ **OFF cells ANTinocicezione**

→ **ON cells PROnocicezione**



Ballantyne JC, Fishman S, Rathmell JP. *Bonica's Management of Pain*. Wolters Kluwer; 2018.

<https://www.sciencepublishinggroup.com/journal/paperinfo?journalid=391&doi=10.11648/j.ijnpt.20160206.11>

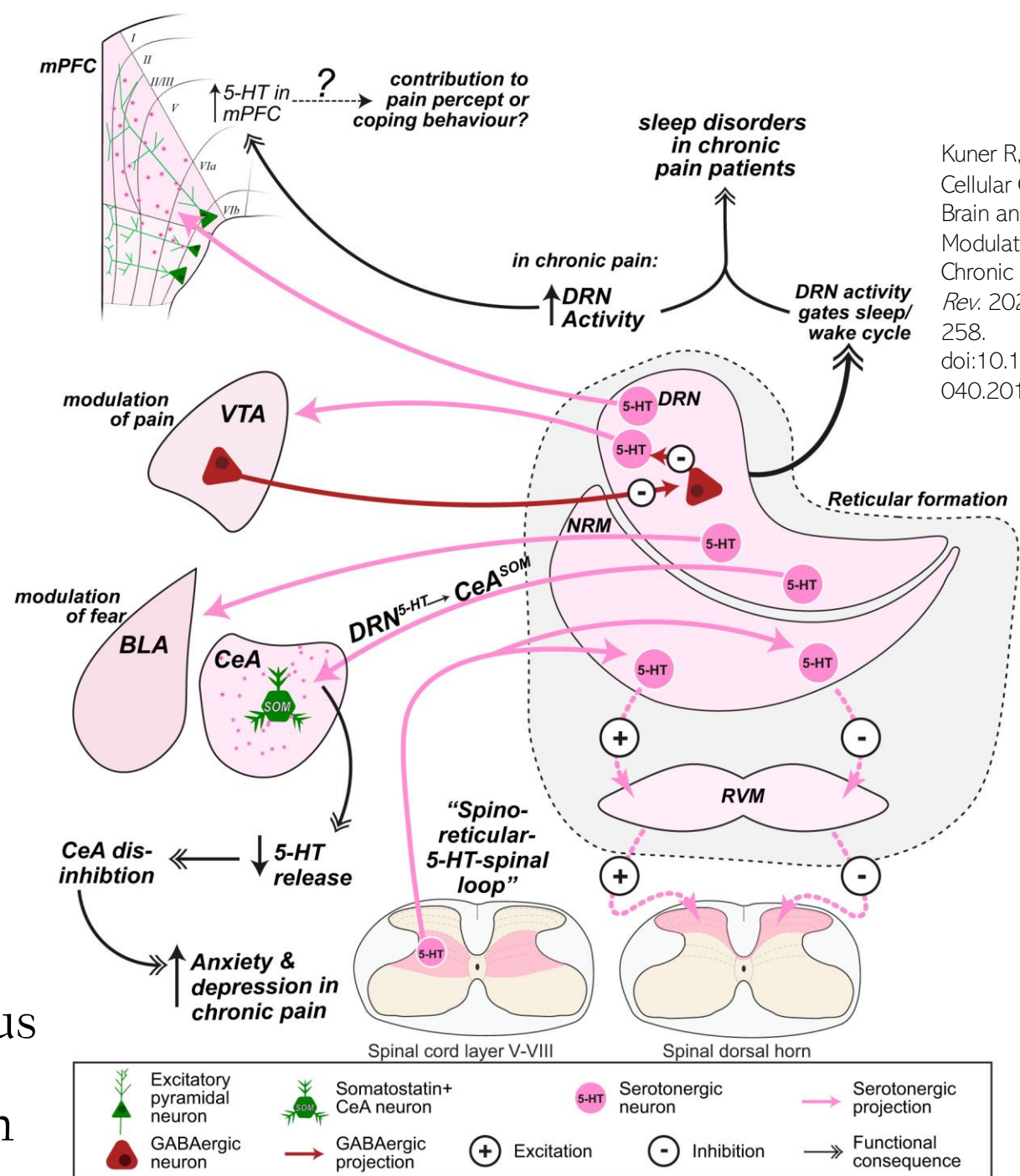
Proiezioni discendenti

- Midollo spinale
- Ruolo **inibitorio** e **facilitatorio** (dominante nel dolore cronico)

Proiezioni ascendenti

- Comportamenti ansioso-depressivi nel dolore cronico
- Disturbi del sonno nel dolore cronico

CeA, central amygdala; DRN, dorsal raphe nucleus; 5-HT, 5-hydroxytryptamine/serotonin; mPFC, medial prefrontal cortex; NRM, nucleus raphe magnus; RVM, rostral-ventral medulla oblongata; SOM, somatostatin



Kuner R, Kuner T.
Cellular Circuits in the
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Chronic Pain. *Physiol
Rev.* 2021;101(1):213-
258.
doi:10.1152/physrev.00
040.2019

Sensibilizzazione

Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs.

Note: Sensitization can include a drop in threshold and an increase in suprathreshold response. Spontaneous discharges and increases in receptive field size may also occur.

Clinically, sensitization may only be inferred indirectly from phenomena such as hyperalgesia or allodynia.

Wind up

Impulsi ripetitivi o prolungati ad alta intensità dagli afferenti C

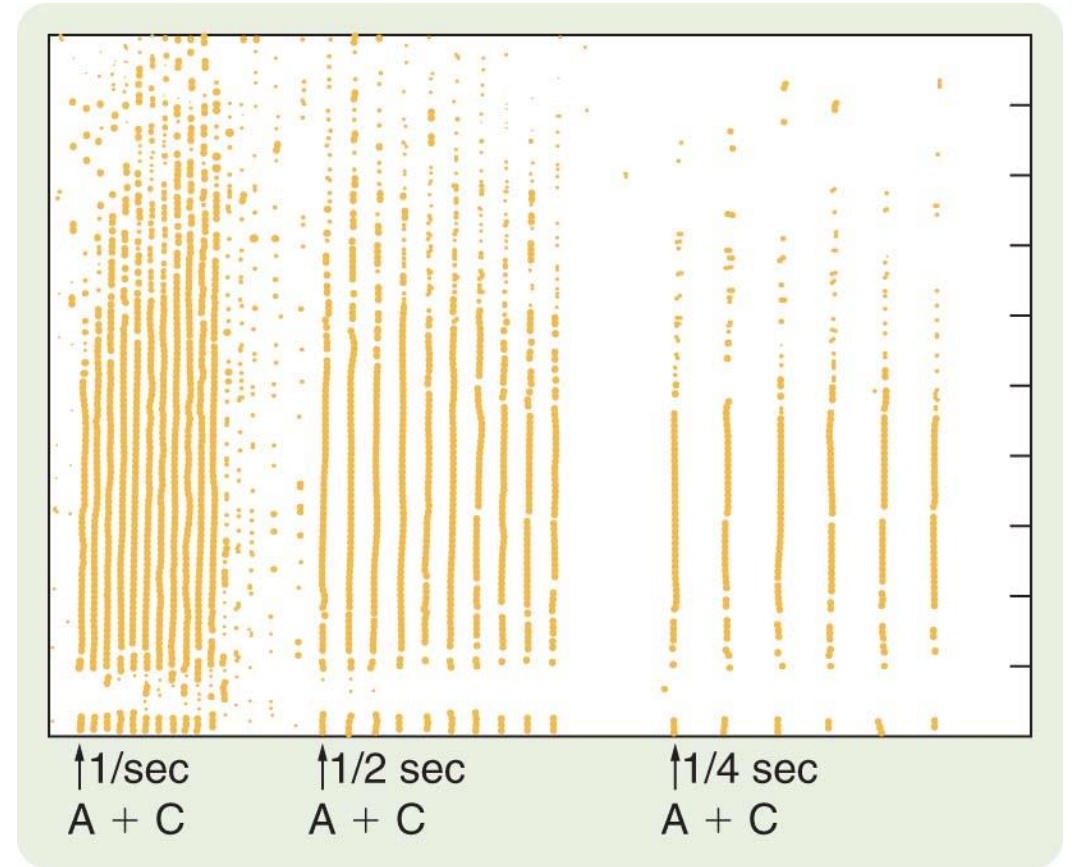
→ Aumento eccitabilità del 2° neurone

Attivazione ≥ 1 Hz delle fibre C

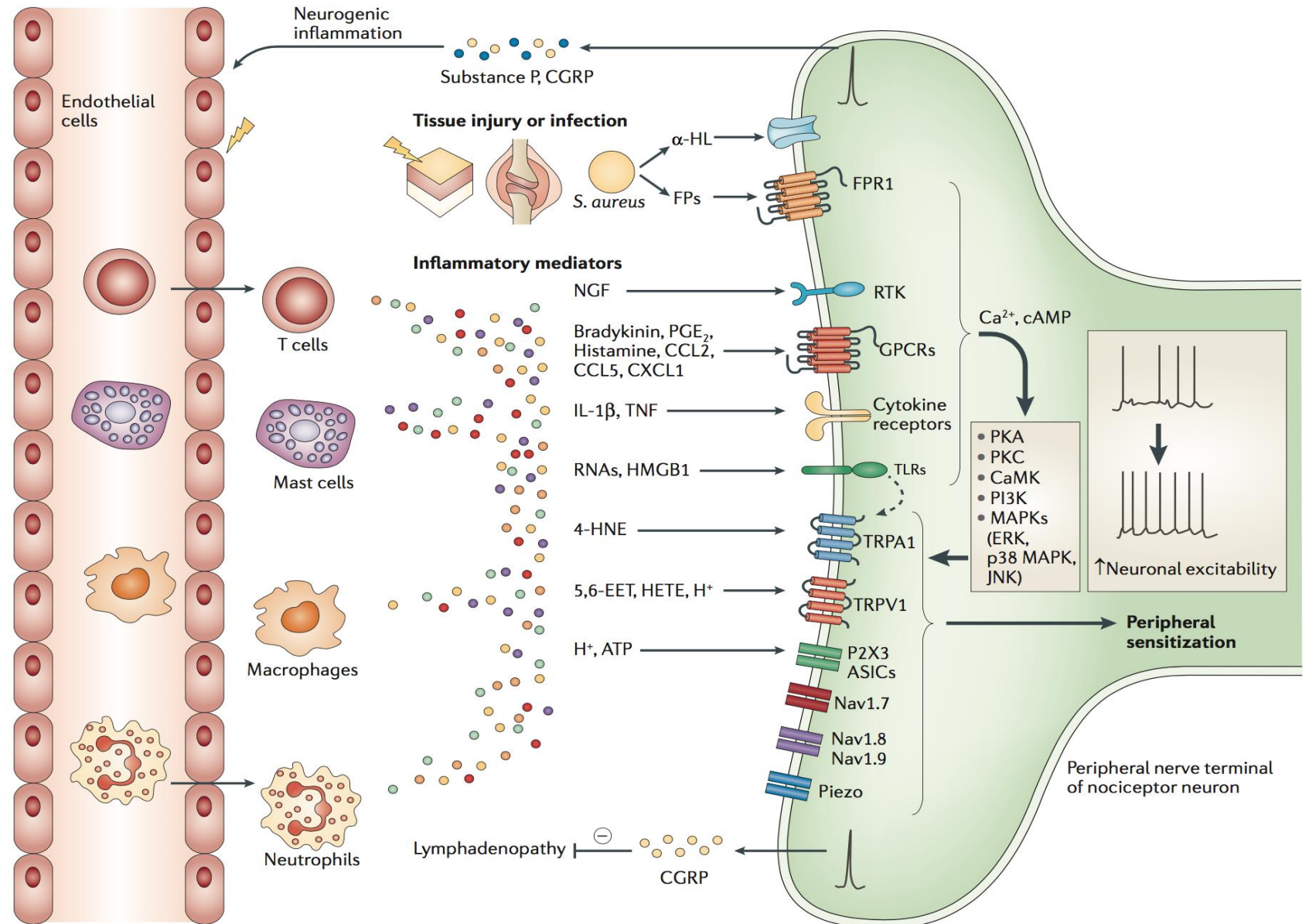
→ Incremento sequenziale del numero di potenziali di azione evocati a ogni stimolo

Recettore NMDA sembra critico per il wind up

Effetto scompare in pochi secondi alla cessazione dello stimolo



Infiammazione e sensibilizzazione periferica



Inflammation e sensibilizzazione periferica

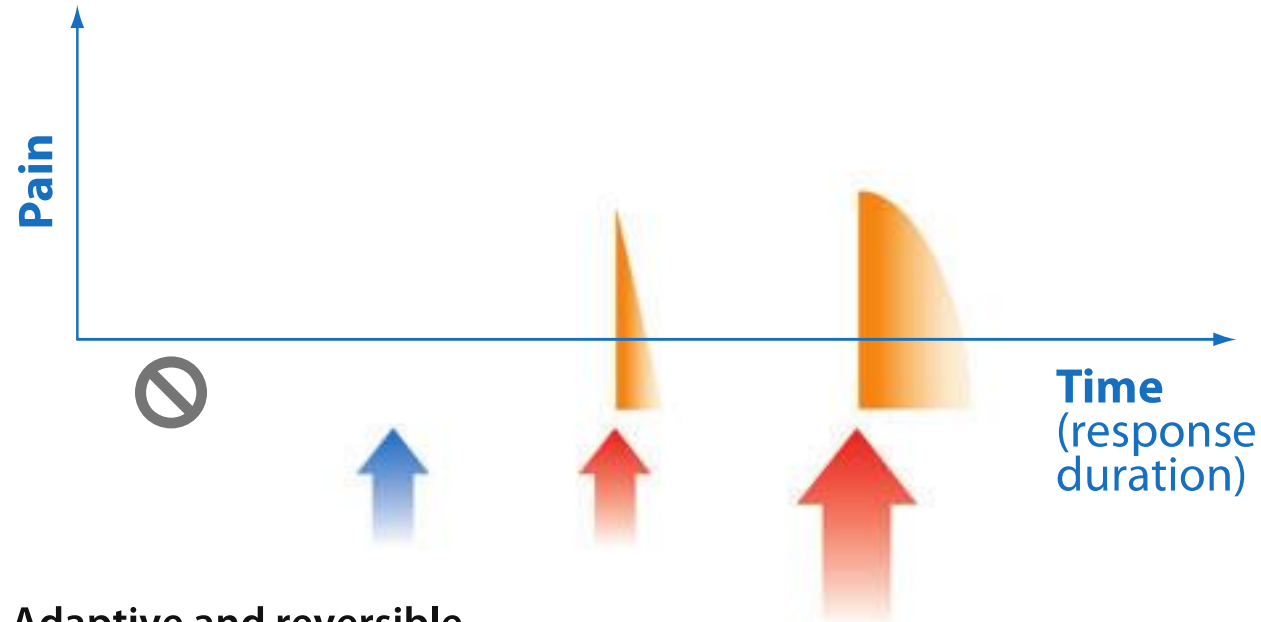
Inflammatory pain

Active inflammation

Spontaneous and stimulus-dependent pain

Sensory amplification

Evoked by low- and high-intensity stimuli



Adaptive and reversible

Protects by producing pain hypersensitivity during healing

Semeiotica



Iperalgesia al caldo 🔥



Heat allodynia

Normally non-painful heat stimuli evoke pain

Touch skin with objects of 40 °C (metal roller, glass of water)
Control: touch skin with objects of skin temperature

Painful burning temperature sensation in the area of affected (damaged or sensitized) primary afferent nerve endings (primary zone)

Sensibilizzazione centrale

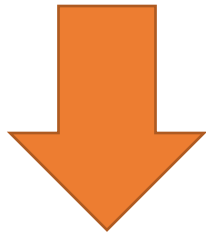


Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.

Note: See note for sensitization and nociceptive neuron above. This may include increased responsiveness due to dysfunction of endogenous pain control systems. Peripheral neurons are functioning normally; changes in function occur in central neurons only.

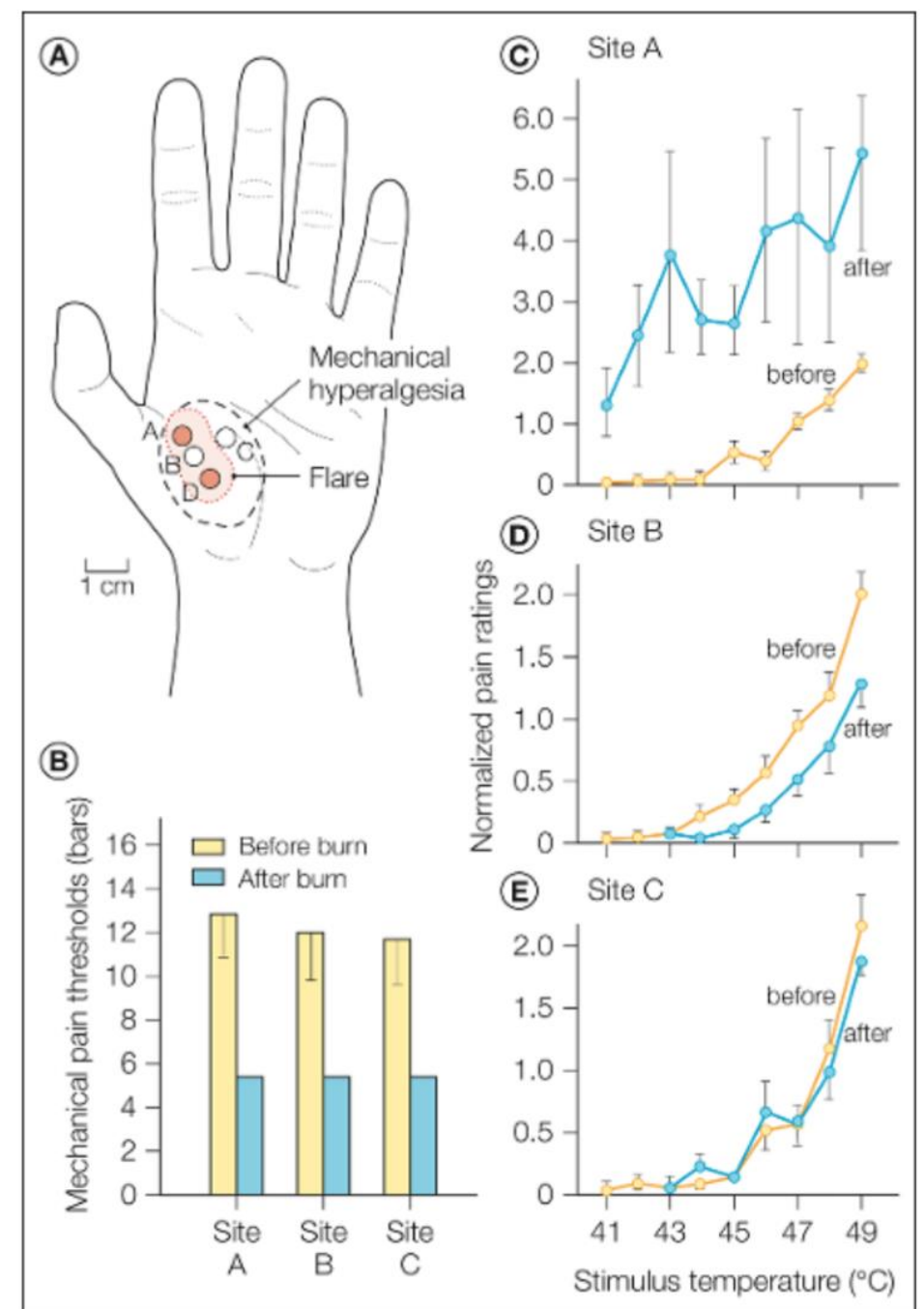
Sensibilizzazione centrale: Neurofisiologia

Iniezione di capsaicina intradermica

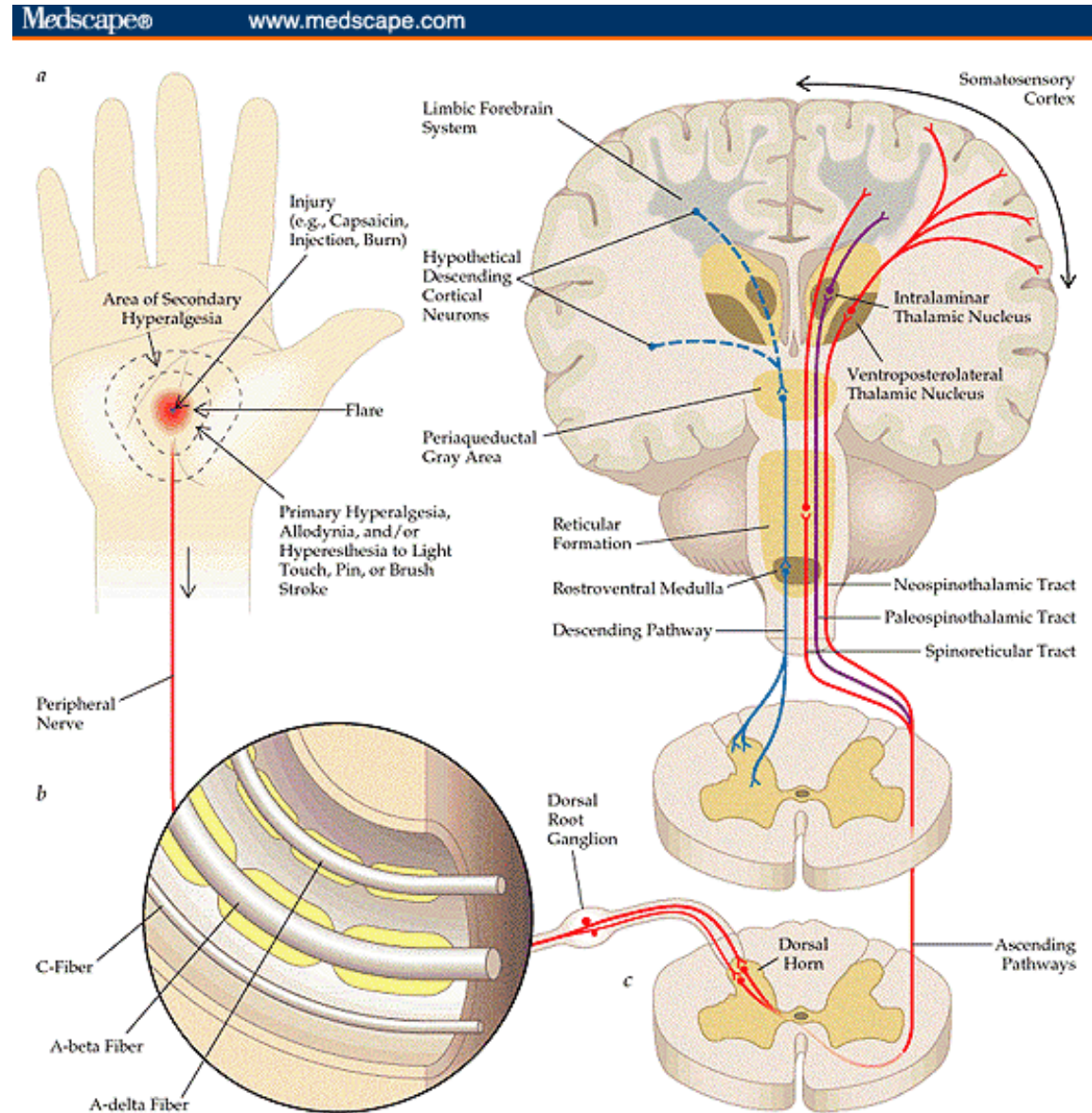


3 aree di iperalgesia:

- 1) piccola area di iperalgesia al caldo vicino al sito di iniezione (1-2 h)
- 2) area di **allodinia dinamica** (diverse ore)
- 3) vasta area di **iperalgesia puntata** (fino a 24 h)



Sensibilizzazione centrale: Neurofisiologia



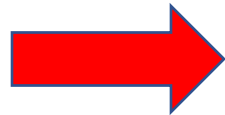
Fibra Afferente Nocicettiva

Rilascio ATP e chemochine (CCL2, CCL21, CX3CL1), Matrix MetalloProtein-9, NeuRegulin-1, Calcitonin-Related-Gene-Peptide



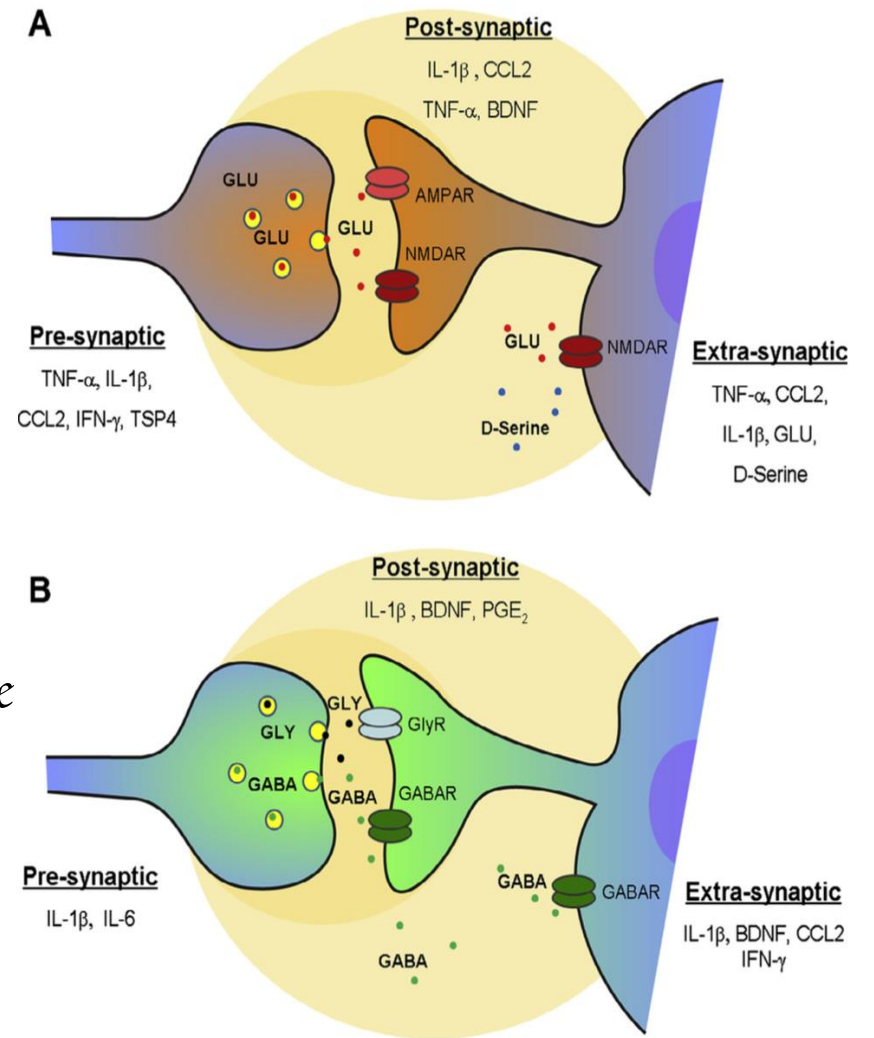
Microglia

- fosforilazione p38 e ERK
- rilascio citochine (TNF- α , IL-1b, IL-18) e Brain-derived neurotrophic factor



Astrociti

- fosforilazione JNK e P-ERK
- rilascio chemochine (CCL2), citochine (IL-1b)
- Rilascio ATP e Glutammato
- Riduzione uptake Glu da danno della fibra nervosa



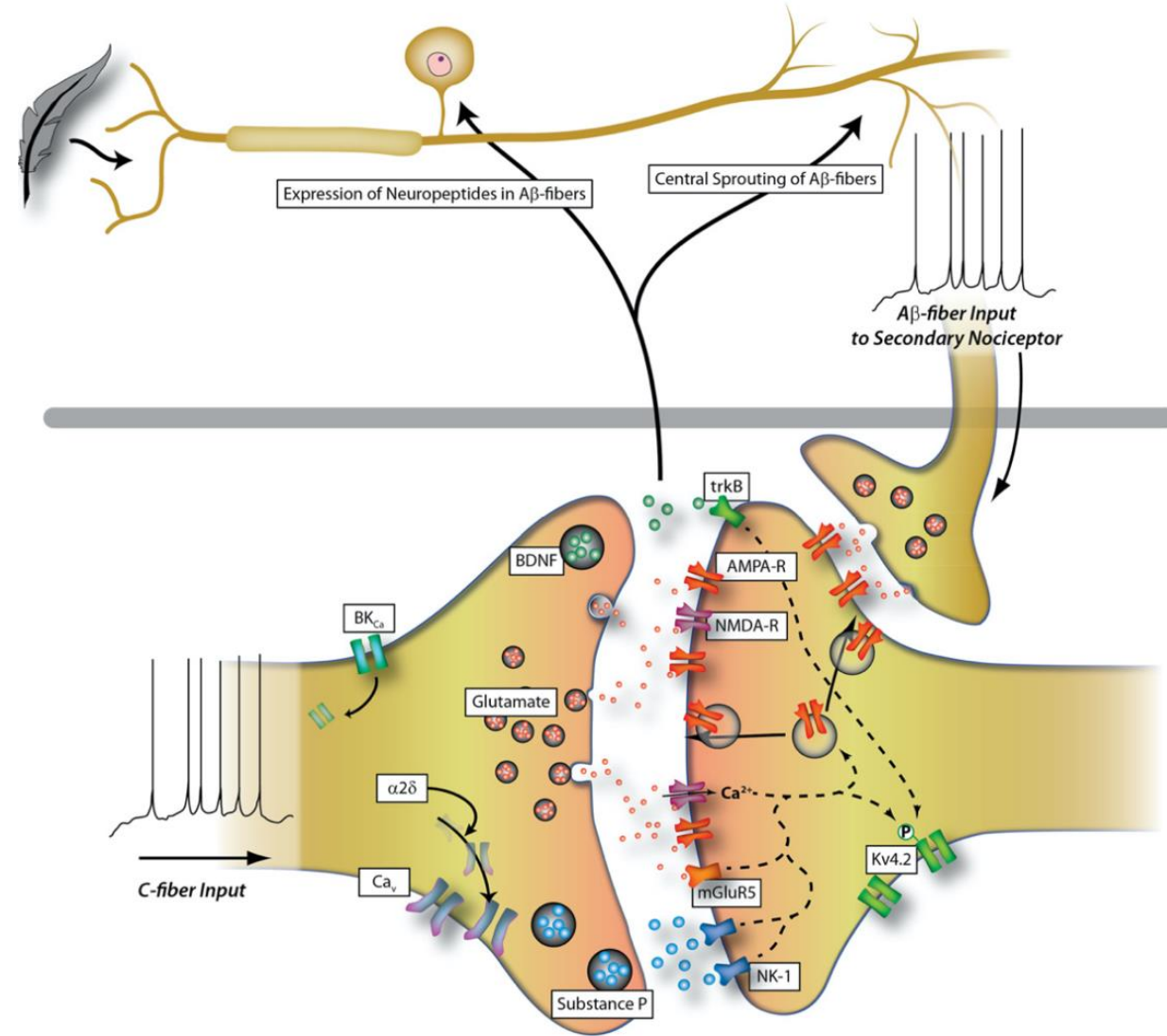
**SENSIBILIZZAZIONE NEURONI DEL CORNO DORSALE
ATTIVAZIONE DELLA MICROGLIA**

Sensibilizzazione centrale: riorganizzazione delle sinapsi spinali

- 1) Rinforzo omosinaptico (fibre C ad alta soglia)
- 2) Rinforzo eterosinaptico (fibre A β e C a bassa soglia \rightarrow neuroni nocicettivi)

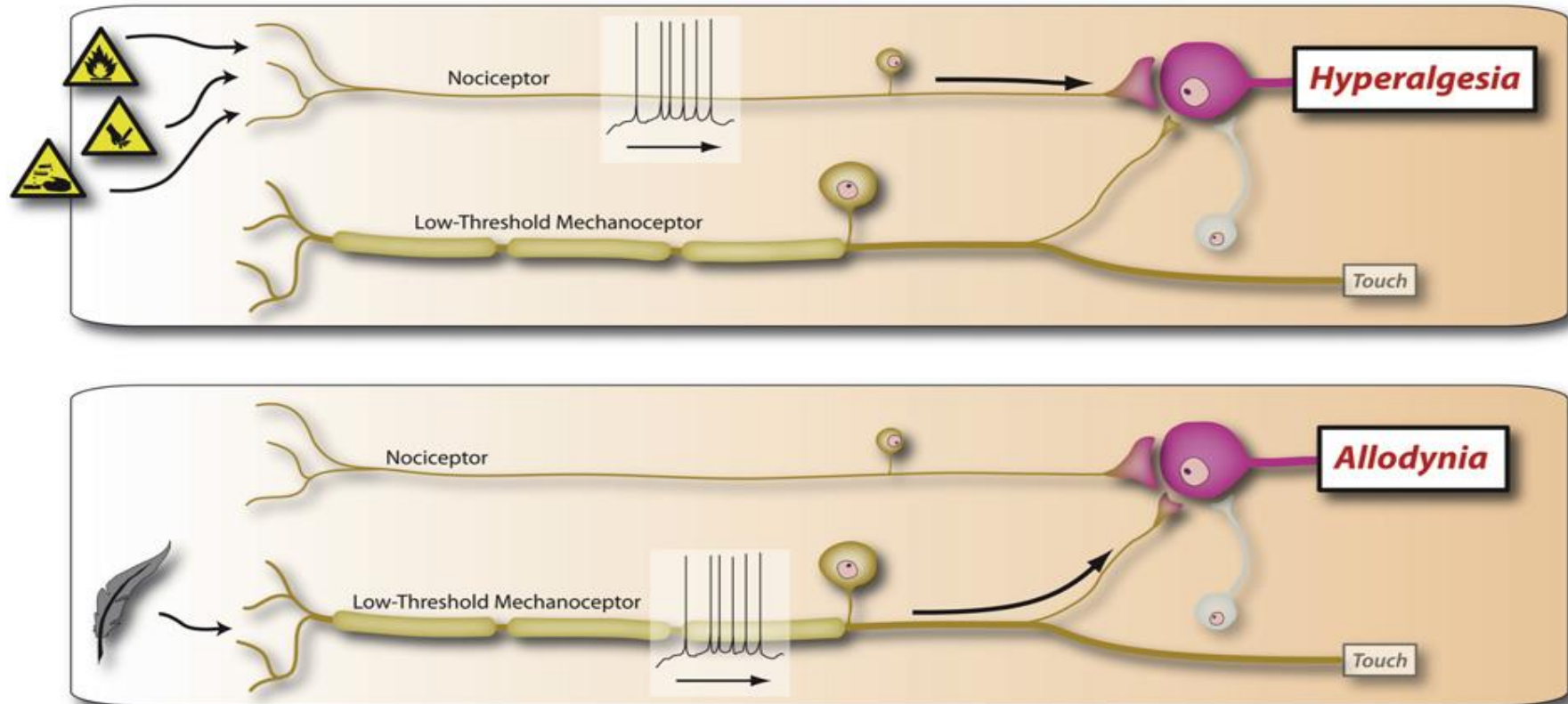


- \downarrow soglia di scarica dei nocicettori
- \uparrow campi recettivi
- alterazione dinamica temporale di scarica

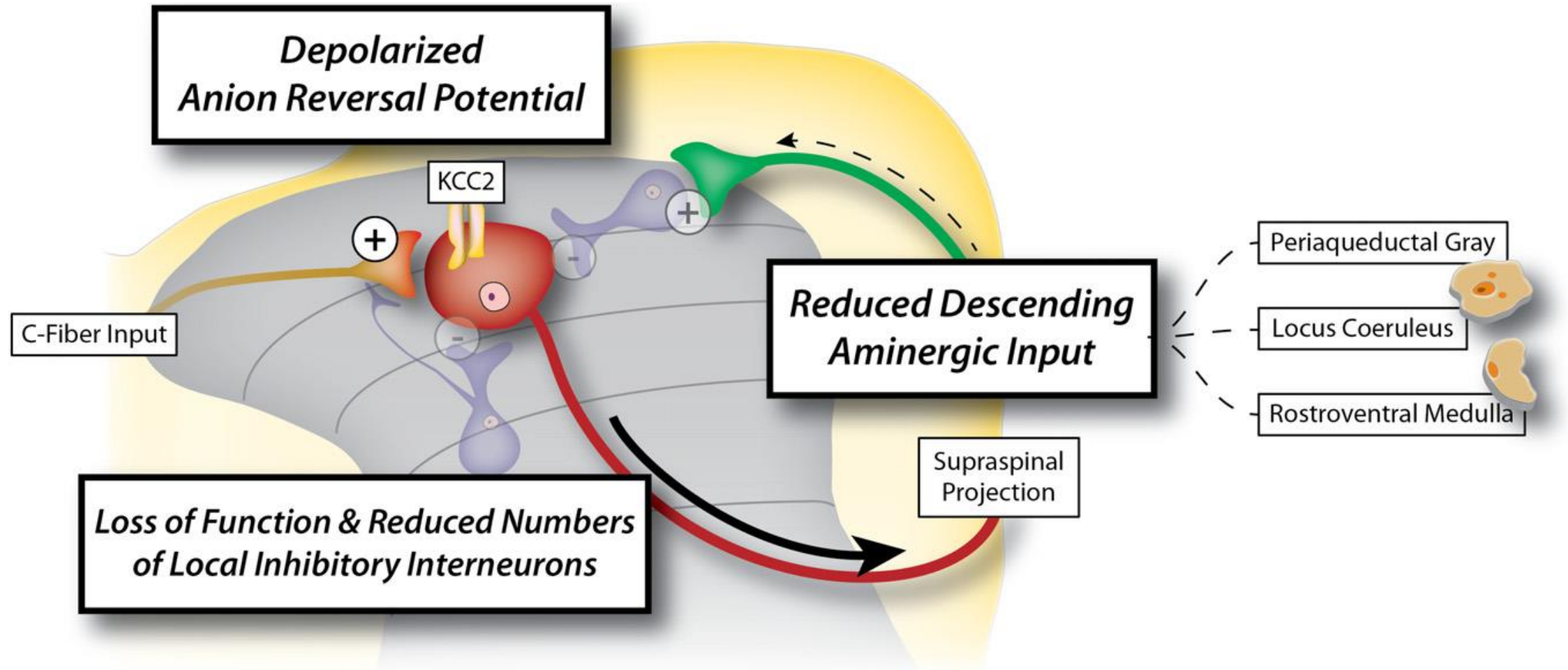


Sensibilizzazione centrale

Central Sensitization

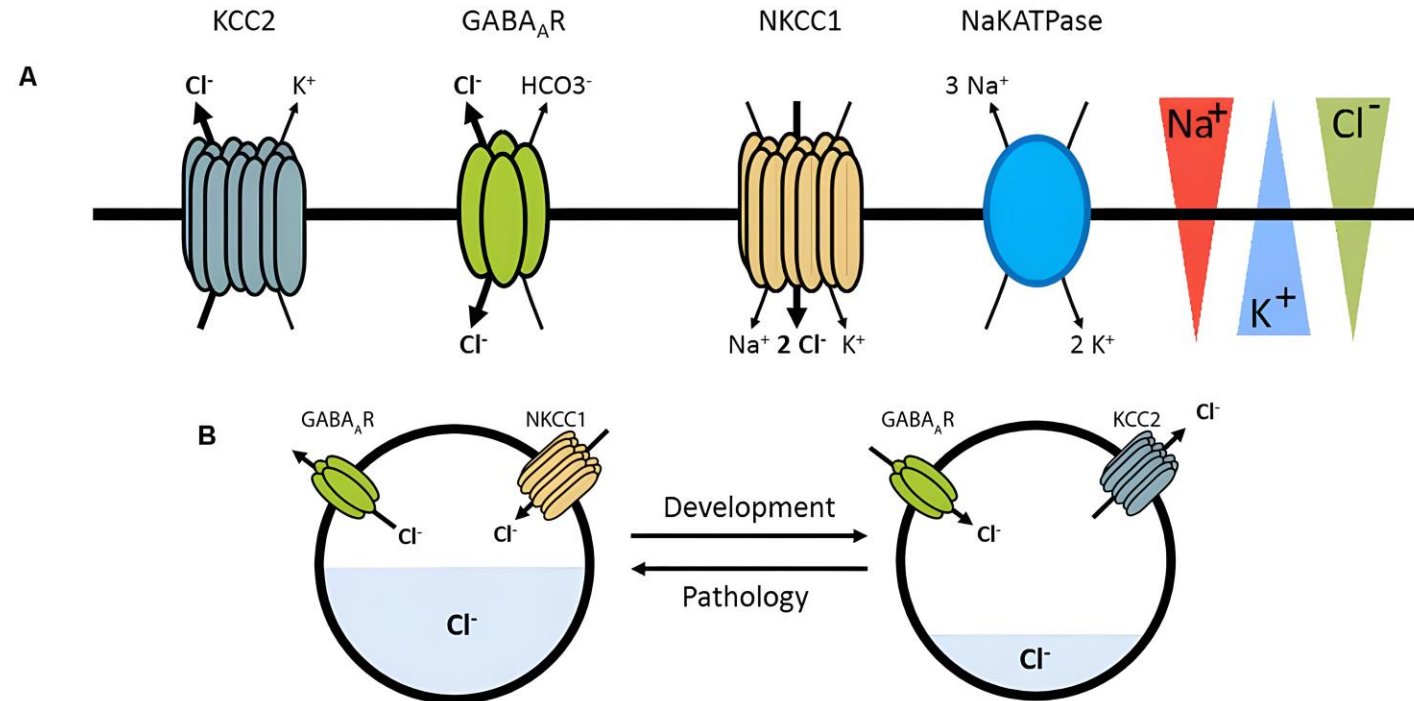


Sensibilizzazione centrale: neuroplasticità maladattativa



GABA-A e omeostasi del cloro

La normale inibizione sinaptica da parte di GABA e glicina dipende in modo critico dalle attività coordinate di due cotrasportatori di cationi-cloruro funzionalmente distinti: $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotrasportatore-1 (**NKCC1**) e $\text{K}^+ - \text{Cl}^-$ cotrasportatore-2 (**KCC2**). Il KCC2, codificato da Slc12a5, è il meccanismo dominante di estrusione del Cl^- a livello neuronale, mentre l'NKCC1 normalmente innalza i livelli intracellulari di Cl^- oltre l'equilibrio e si oppone all'azione del KCC2.

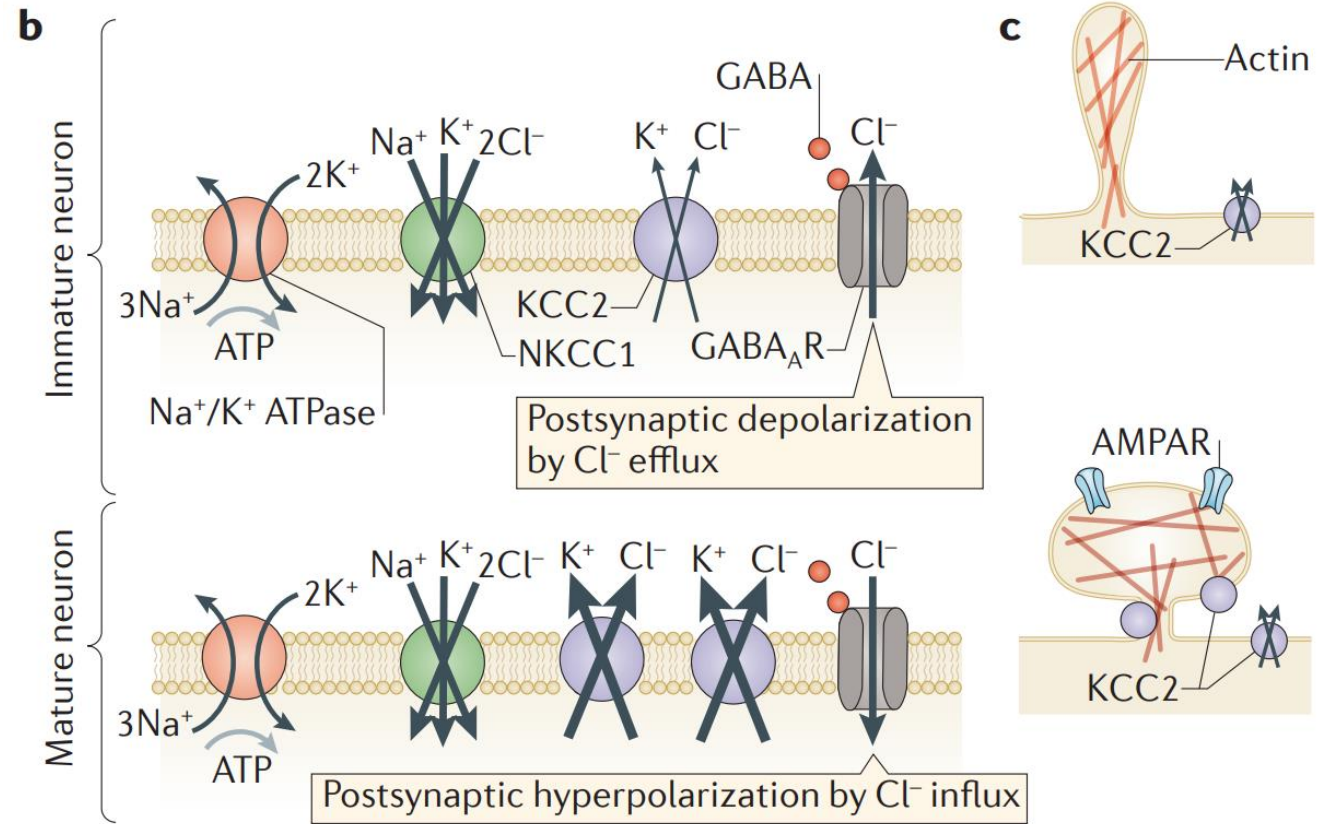


K. Kaila, T. J. Price, J. A. Payne, M. Puskarjov, J. Voipio, Cation-chloride cotransporters in neuronal development, plasticity and disease. *Nat Rev Neurosci* 15, 637–654 (2014).
E. Côme, M. Heubl, E. J. Schwartz, J. C. Poncer, S. Lévi, Reciprocal Regulation of KCC2 Trafficking and Synaptic Activity. *Front. Cell. Neurosci.* 13 (2019).

GABA-A e omeostasi del cloro

La concentrazione di cloruro intracellulare influisce sul gating dei recettori GABAA, modulando la funzione del recettore e influenzando il potenziale di inversione delle risposte GABAergiche.

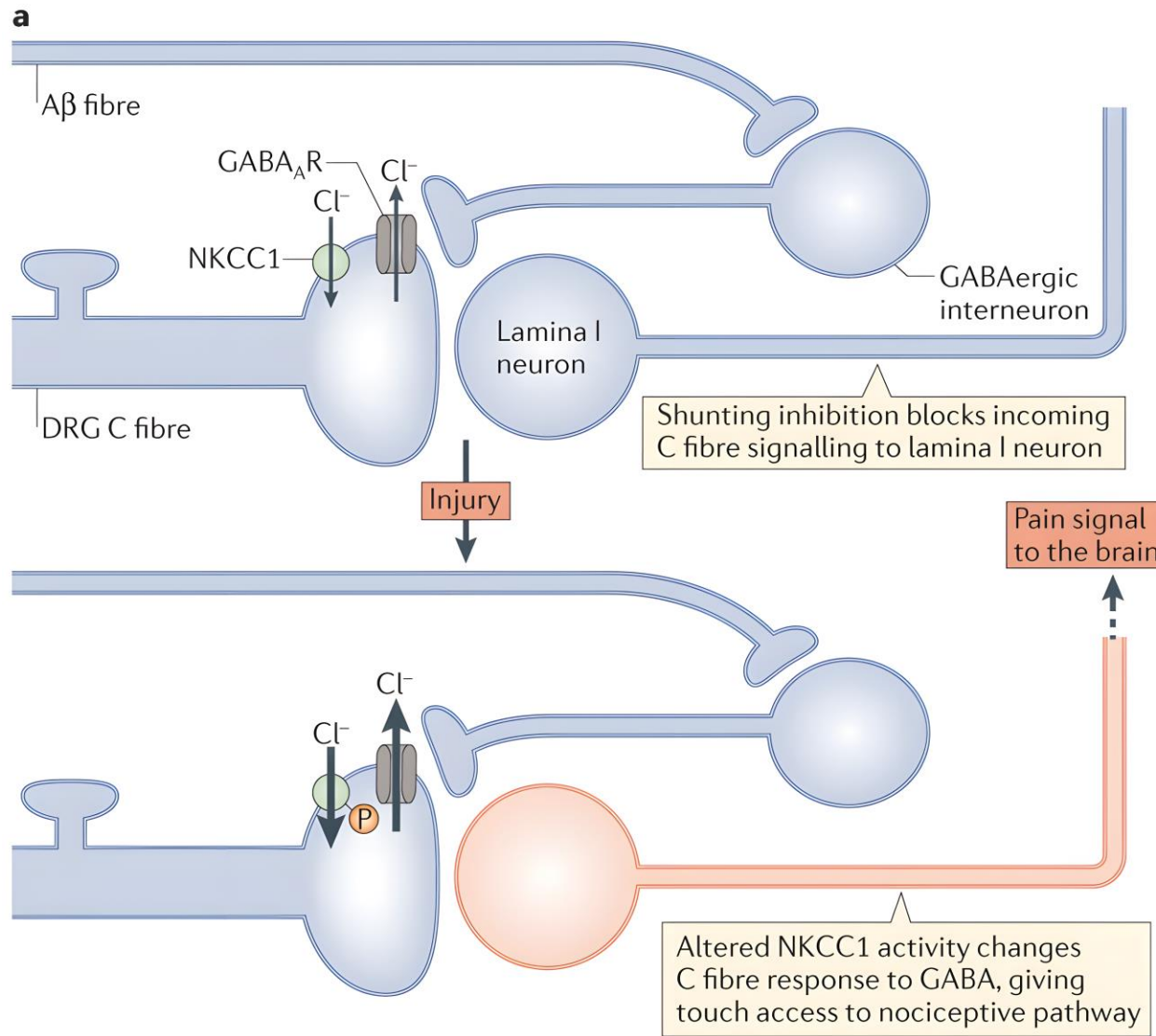
- In un cervello immaturo, alti livelli di cloruro intracellulare, regolati dai co-trasportatori $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ (NKCC1), portano a risposte GABA depolarizzanti. Questa depolarizzazione può portare all'eccitazione, promuovendo l'attivazione dei canali del calcio voltaggio-dipendenti del potenziale d'azione del sodio e generando potenziali depolarizzanti.
- D'altra parte, nel cervello adulto, i bassi livelli intracellulari di cloruro stabiliti da KCC2 determinano correnti GABAergiche inibitorie.



GABA-A e omeostasi del cloro

Il potenziale di equilibrio dei recettori GABAA (EGABA) è determinato dal gradiente di cloruro transmembrana, che determina la forza trainante del flusso di cloruro attraverso questi recettori. Pertanto, le variazioni della concentrazione intracellulare di cloruro hanno un impatto significativo sulle proprietà funzionali delle sinapsi inibitorie mediate dai recettori GABAA, influenzando l'eccitabilità neuronale e la trasmissione sinaptica.

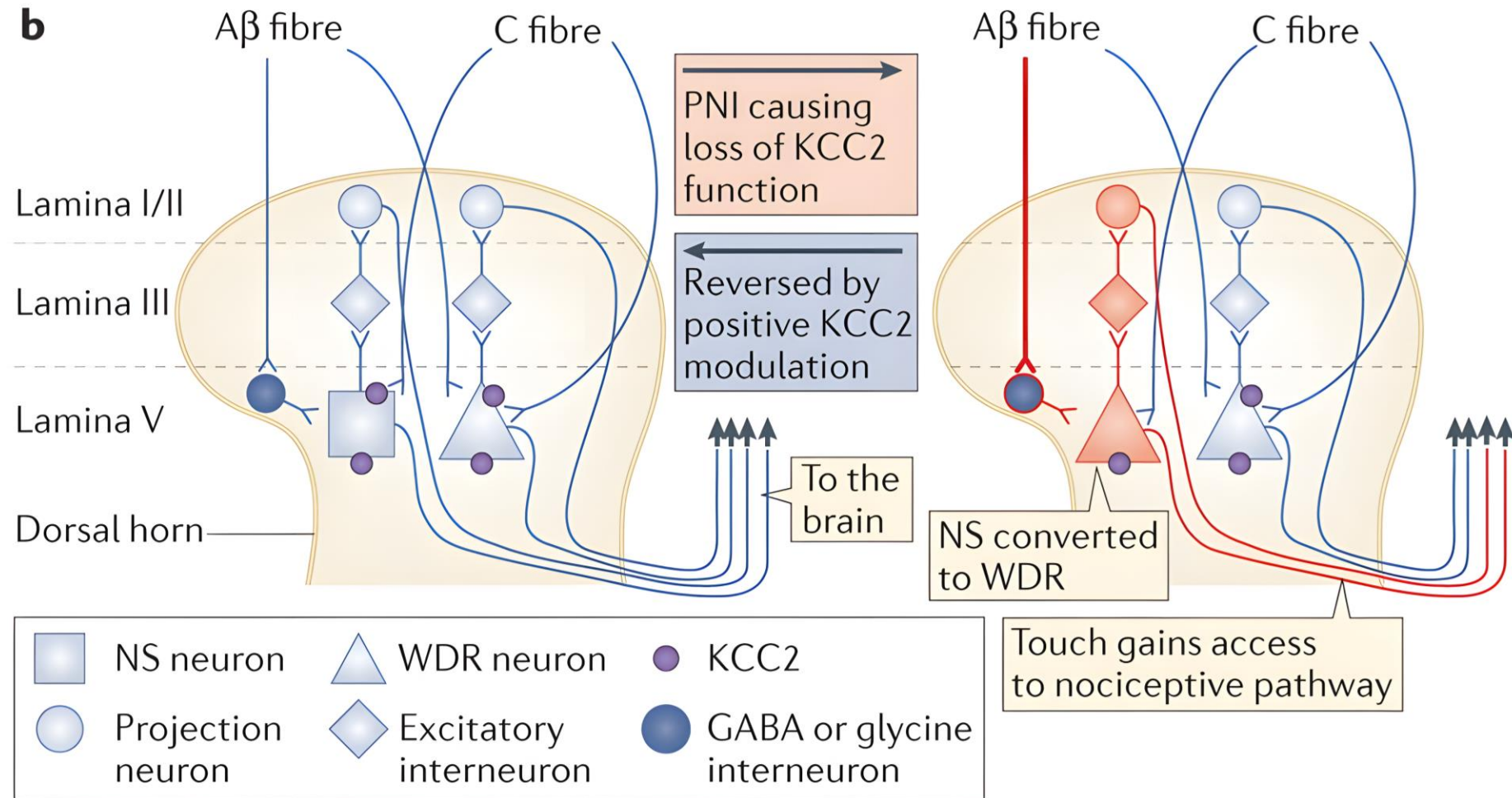
GABA-A e omeostasi del cloro



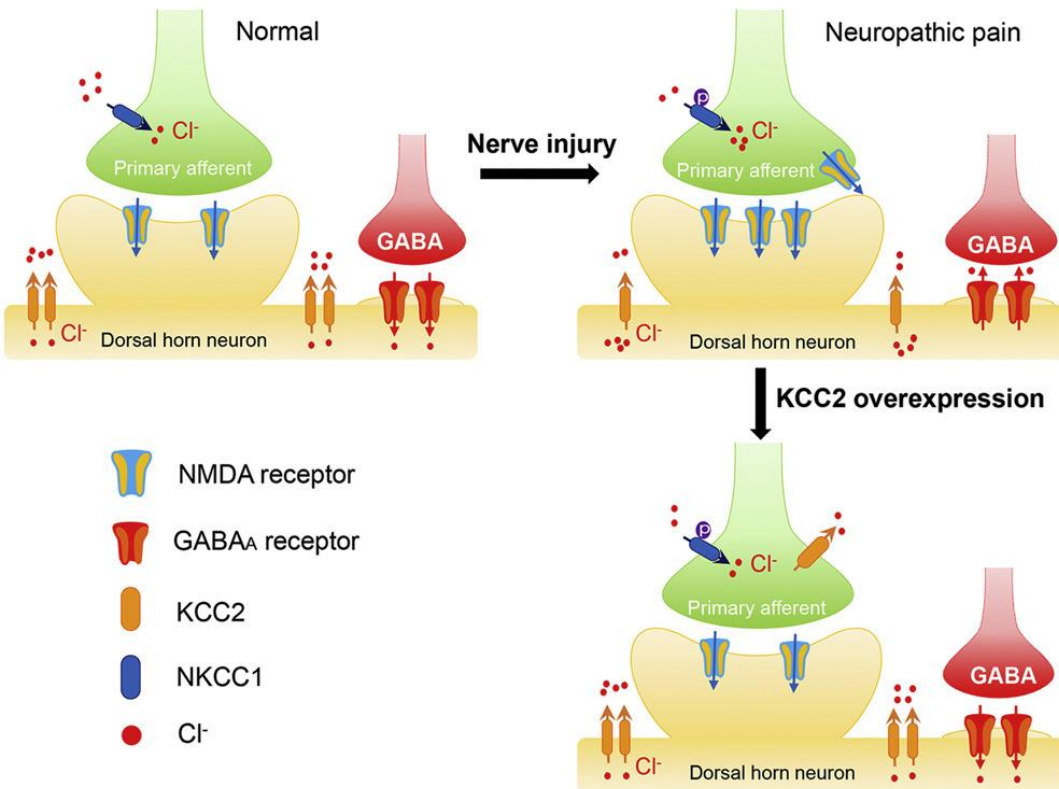
Shunting inhibition

Suppression of postsynaptic excitation that results from an increase in neuronal membrane conductance that is caused by activation of GABA_A receptors or glycine receptors.

GABA-A e omeostasi del cloro



GABA-A e omeostasi del cloro



Highlights

- Intrathecal delivery of KCC2 in lentiviral vectors eliminates neuropathic pain
- KCC2 gene transfer restores spinal cord KCC2 function impaired by nerve injury
- KCC2 ectopic expression counteracts NKCC1 activity in primary sensory neurons
- Restoring Cl⁻ homeostasis normalizes spinal cord synaptic NMDA receptor activity

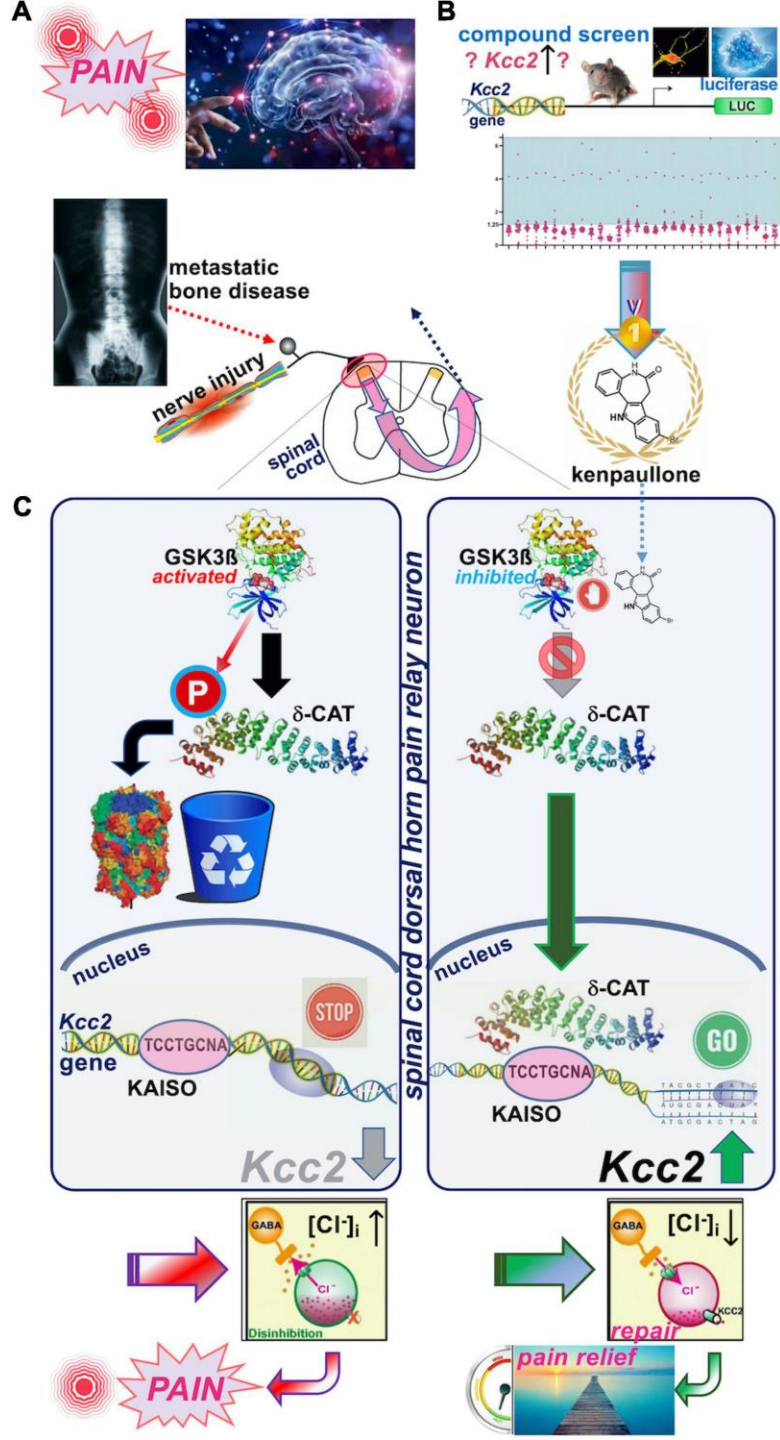


FIGURE 2 | Schematic overview of the recent discovery of kenpaullone as *Kcc2* gene expression-enhancing compound. **(A)** Upper left. Nerve injury pain and bone cancer pain are serious and pressing unmet medical needs. Preclinical models were used to test kenpaullone, which proved highly effective in both. **(B)** Upper right. “Junkyard of cancer” drugs were screened for their potency to enhance *Kcc2* gene expression, using primary neurons derived from newborn mice cerebral cortexes. The *Kcc2* promoter, in these neurons, was driving luciferase (LUC), so that LUC could serve as a primary screening read-out. Kenpaullone was identified as a “winner,” capable of switching on the *Kcc2* gene, which previous research predicted to be beneficial for chronic pain. **(C)** Middle panels, left-hand: Nerve injury by constriction or cancer cells populating a bone activates GSK3β, an enzyme that tags other proteins with phosphate. In nerve cells dedicated to pain relay in the spinal cord, GSK3β tags delta-catenin (δ-CAT), which routes δ-CAT to the cellular garbage bin. Without δ-CAT in the cells’ nucleus, the *Kcc2* gene remains switched off. This in turn makes the pain relay neurons run full of chloride, which makes them electrically more jittery, with chronic “refractory” pain as a result. Right-hand panel: Treatment with kenpaullone inhibits GSK3β’s phosphate-tagging capability, so that δ-CAT becomes untagged, which clears the way to the nerve cells’ nucleus. There it binds to the DNA region of the *Kcc2* gene critical for switch-on or switch-off, the promoter. By binding there, δ-CAT reverts the switch-off to switch-on and the *Kcc2* gene runs again, making KCC2 protein. KCC2 in turn pumps chloride ions out of the pain-relay nerve cells, making them electrically more stable. This leads to circuit repair and pain relief, based on resetting of the genetic switches. Instead of Kenpaullone, δ-CAT can serve as payload of a gene therapy approach that directs expression of δ-CAT and hence KCC2 to pain relay nerve cells in the spinal cord.

Semeiotica



Allodinia meccanica dinamica

Mechanical dynamic allodynia	Normally non-painful light-pressure moving stimuli on skin evoke pain	Stroking skin with painter's brush, cotton swab or gauze	Sharp burning superficial pain in the primary affected zone, spreading into unaffected skin areas (secondary zone)
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Gold Standard: Quantitative Sensory Testing

Iperalgesia puntata/ Temporal summation

Mechanical punctate or pinprick hyperalgesia	Normally stinging-but-not-painful stimuli evoke pain	Manual pricking of the skin with a safety pin, sharp stick or stiff von Frey hair	Sharp superficial pain in the primary affected zone, spreading into unaffected skin areas (secondary zone)
Temporal summation	Repetitive application of identical single noxious stimuli is perceived as increasing pain sensation (wind-up-like pain)	Pricking the skin with safety pin at <3 s intervals for 30 s	Sharp superficial pain of increasing intensity





painDETECT[®] SCHMERZ-FRAGEBOGEN

Datum: _____ Patient: Name: _____ Vorname: _____

Wie würden Sie Ihren Schmerz **jetzt** im Augenblick einschätzen?

0 1 2 3 4 5 6 7 8 9 10
kein _____ max

Wie stark war der **stärkste** Schmerz in den letzten 4 Wochen?

0 1 2 3 4 5 6 7 8 9 10
kein _____ max

Wie stark war der Schmerz in den letzten 4 Wochen im **Durchschnitt**?

0 1 2 3 4 5 6 7 8 9 10
kein _____ max

Kreuzen Sie das Bild an, welches Ihren Schmerzverlauf am besten beschreibt:

☐ Dauerschmerzen mit leichten Schwankungen

☐ Dauerschmerzen mit Schmerzattacken

☐ Schmerzattacken dazwischen schmerzfrei

☐ Schmerzattacken dazwischen Schmerzen

Bitte kennzeichnen Sie Ihren **Hauptschmerzbereich**

Strahlt Ihr Schmerz in weitere Körperregionen aus? ja ☐ nein ☐

wenn ja, dann zeichnen Sie bitte die Richtung ein, wohin der Schmerz ausstrahlt.

Leiden Sie in den eingezeichneten Bereichen an einem Brenngefühl (z.B. Brennesseln)?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

Haben Sie im Bereich Ihrer Schmerzen ein Kribbel- oder Prickelgefühl (wie Ameisenlaufen, Stromkribbeln)?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

Ist leichte Berührung (Kleidung, Bettdecke) in diesem Bereich schmerzhaft?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

Haben Sie im Bereich Ihrer Schmerzen blitzartige, elektrisierende Schmerzattacken?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

Ist Kälte oder Wärme (Badewannenwasser) in diesem Bereich gelegentlich schmerzhaft?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

Leiden Sie in den von Ihnen eingezeichneten Bereichen unter Taubheitsgefühl?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

Löst ein leichter Druck z.B. mit dem Finger in diesem Bereich Schmerzen aus?

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

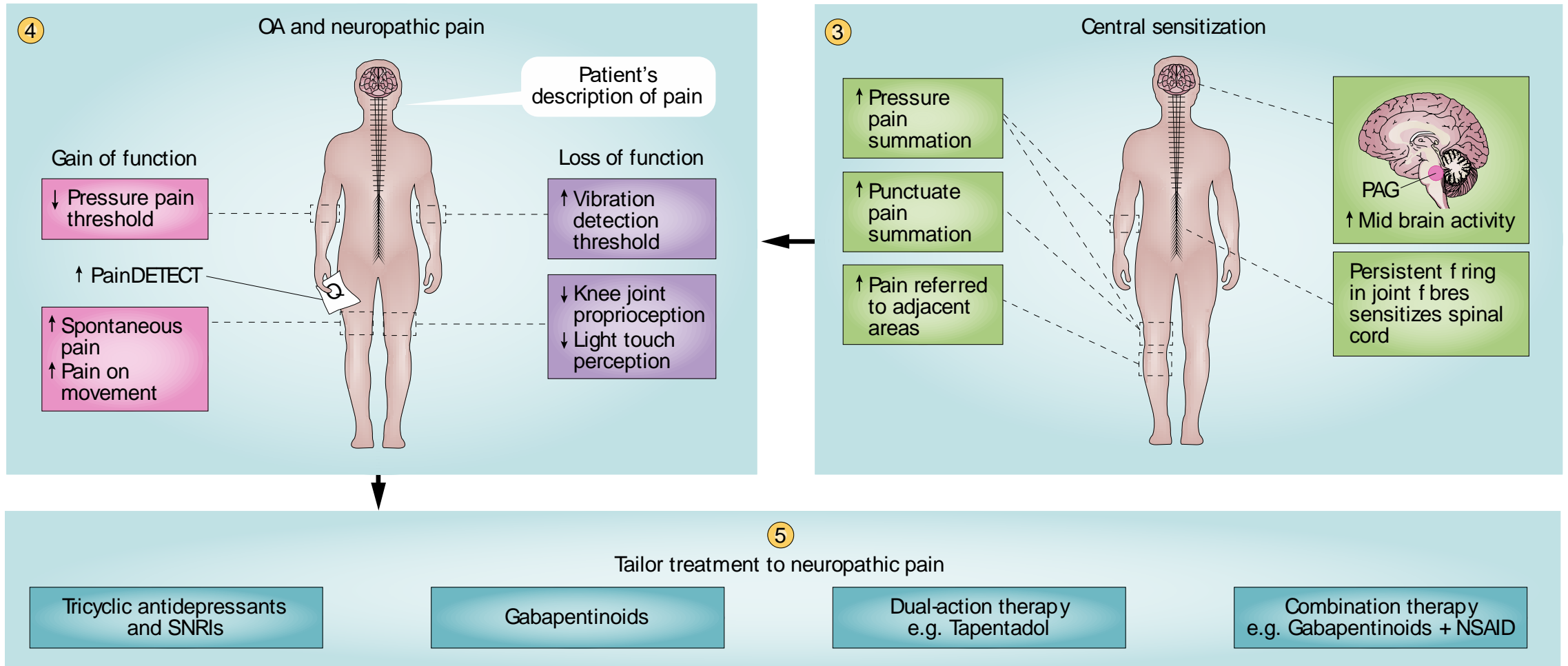
(vom Arzt auszufüllen)

nie ☐ kaum ☐ gering ☐ mittel ☐ stark ☐ sehr stark ☐

x 0 = 0 x 1 = x 2 = x 3 = x 4 = x 5 =

Score-Gesamtsumme von 35

Dolore neuropatico vs sensibilizzazione centrale



Sensibilizzazione centrale nel Low Back Pain

Model parameters for criteria in the final ‘central sensitisation pain’ model.

Criteria	Regression coefficient	SD	95% CI lower	95% CI upper	OR	OR 95% CI lower	OR 95% CI upper
4 Pain disproportionate to injury	2.72	0.63	1.48	3.96	15.19	4.39	52.48
13 Disproportionate aggs/eases	3.42	0.66	2.13	4.72	30.69	8.41	112.03
25 Psychosocial symptoms	2.03	0.79	0.49	3.58	7.65	1.64	35.79
33 Diffuse palpation	3.32	0.75	1.84	4.80	27.57	6.28	121.09

According to the final model, ‘*Disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors*’ was the strongest predictor of CSP. A distortion in the stimulus–response relationship between movement/mechanical stimuli and pain has been suggested as a possible clinical indicator associated with a dominance of CSP (Butler, 2000). Distortions in this relationship may reflect those alterations in the functional, chemical or structural properties of a widely distributed network of CNS neurones that may lead to excessive neuronal excitability and enable nociceptive inputs to become magnified (hyperalgesia) and/or non-noxious stimuli to initiate or augment nociceptive transmission (allodynia) (Woolf and Salter, 2006; Dickenson, 2007). This symptom could represent one example of the ways in which these phenomena may manifest clinically.

Componenti neuropatiche in Low back pain

Model parameters for criteria in the final ‘peripheral neuropathic pain’ model.

Criteria	Regression coefficient	SD	95% CI lower	95% CI upper	OR	OR 95% CI lower	OR 95% CI upper
3 History of nerve injury	2.54	0.64	1.29	3.80	12.64	3.59	44.49
9 Dermatomal distribution	3.19	0.69	1.85	4.53	24.29	6.33	93.18
29 Nerve movement tests	2.68	0.49	1.72	3.65	14.64	5.59	38.37

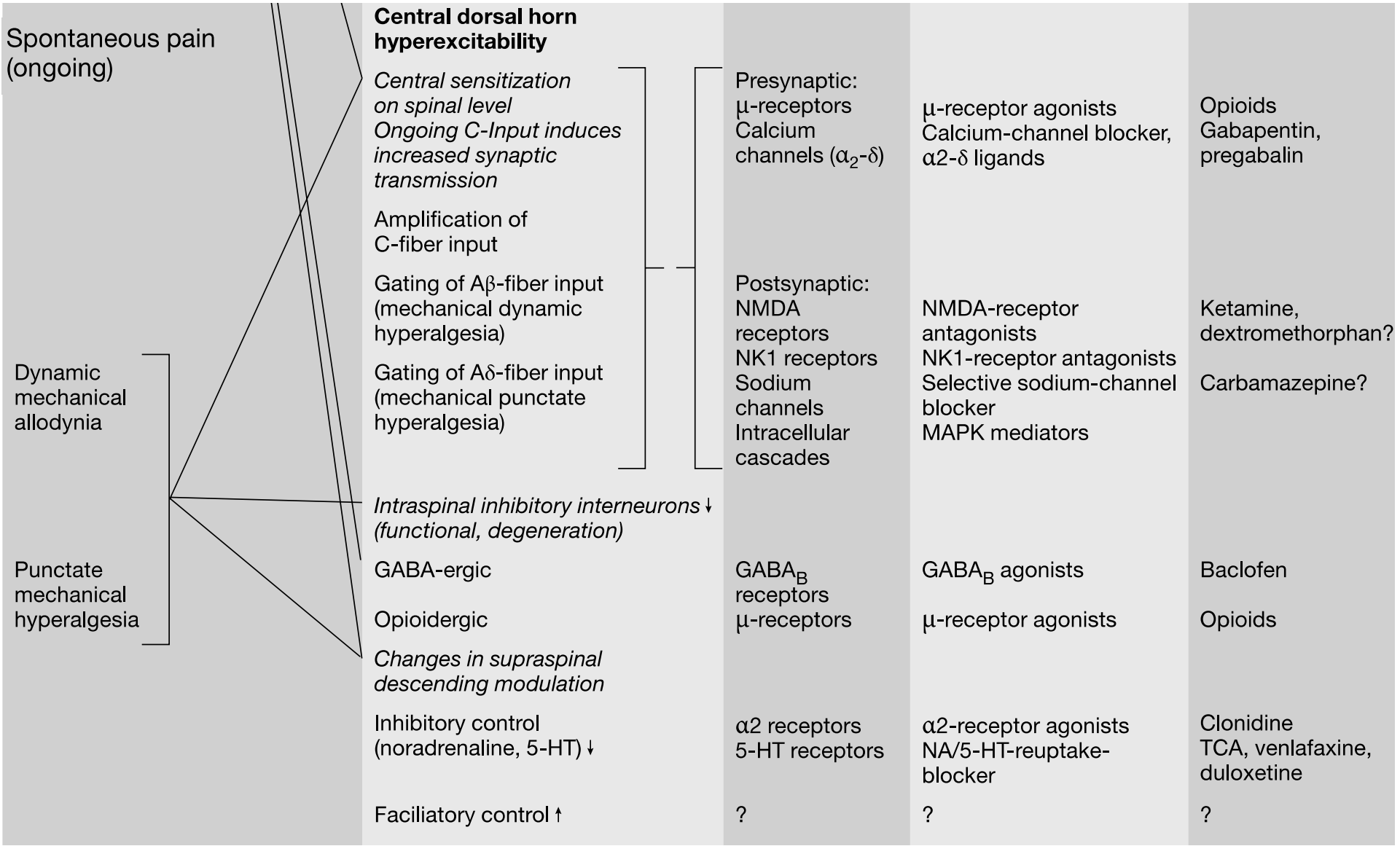
Abbreviations: SD-Standard deviation, 95% CI-95% confidence interval, OR-Odds ratio.

According to the final model, ‘Pain referred in a dermatomal or cutaneous distribution’, was the strongest predictor of PNP. Patho-physiologically, dermatomal/radicular pain is thought to arise from ectopic discharges from the dorsal root or its ganglion ([Bogduk, 2009](#)), a mechanism entirely consistent with those thought to underlie PNP ([Costigan et al., 2009](#)).

Segni di Sensibilizzazione Centrale da ricercare

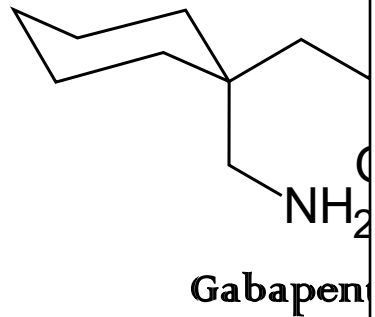
- ❖ Dynamic allodynia: use a gauze, a brush, cotton
- ❖ Punctate hyperalgesia: gentle pricking
- ❖ Temporal summation: frequent multiple pricks (eg 10 in <30s)
- ❖ Loss of proportionality between stimulus and clinical response
- ❖ Widespread pain
- ❖ Maladaptive “pain behavior”

Sensibilizzazione centrale: mechanism-oriented therapy

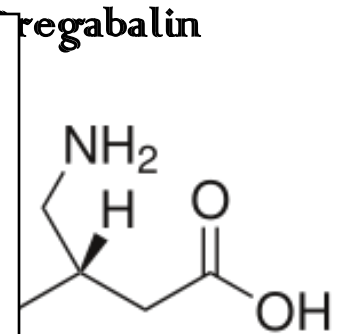
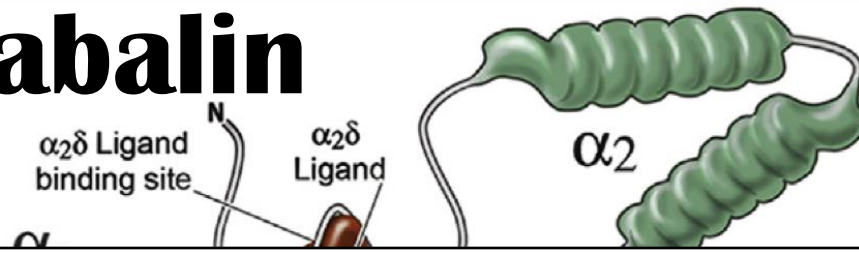


Baron R. Mechanisms of disease: neuropathic pain--a clinical perspective. Nat Clin Pract Neurol. 2006;2(2):95-106. doi:10.1038/ncpneuro0113

Gabapentin e pregabalin



«Point mutation of arginine 217 in **$\alpha 2\delta$ -1** or genetic ablation of **$\alpha 2\delta$ -1** completely abolishes the antinociceptive effects of pregabalin in neuropathic mice (Field et al. 2006; Patel et al. 2013).»



Gabapentin e pregabalin

Subunità $\alpha_2\delta$

- Trafficking dei canali Ca^{2+} nelle zone attive della sinapsi
- Controllo dell'influsso di Ca^{2+}
- Controllo del rilascio di neurotrasmettitore

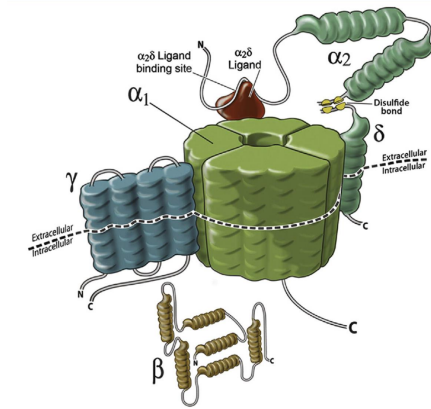
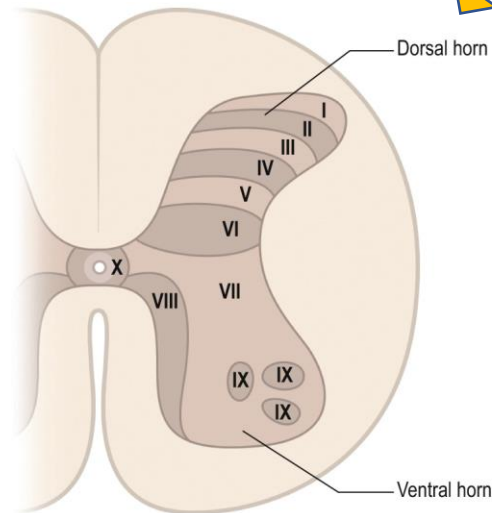
Midollo spinale

Presinaptico

Lamine superficiali corno dorsale-
fibre C

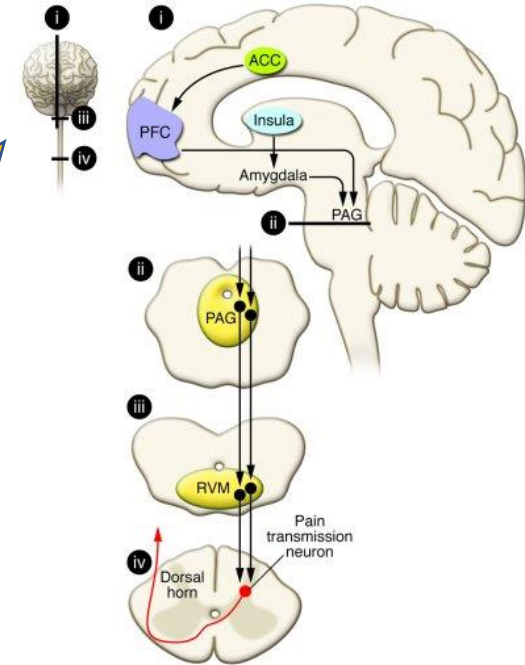
Postsinaptico

Neuroni lamine più profonde




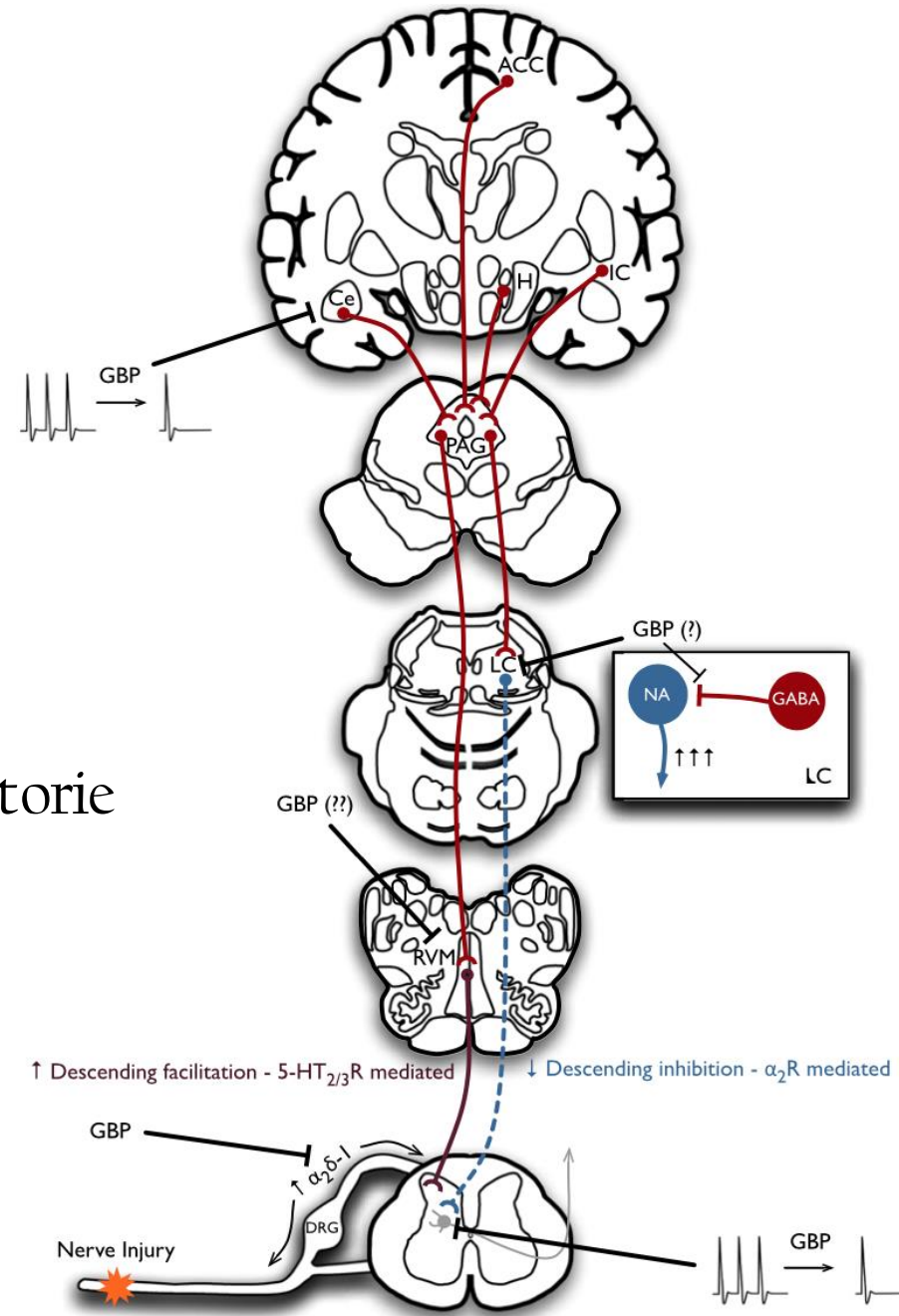
Encefalo

- Rafe dorsale
- Grigio periacqueduttale
- Locus coeruleus
- Amigdala



Gabapentin e pregabalin

- ↓ Trafficking dei canali Ca^{2+} DRG → 
- terminali corno dorsale
- analgesia solo se ↑ vie discendenti facilitatorie pronocicettive



Gabapentin e pregabalin

Table 1. Main pharmacokinetic parameters of gabapentinoids.

	Gabapentin	Pregabalin	Mirogabalin
T_{\max}	≈ 3 h	≤ 1 h	≈ 1 h
Bioavailability (%)	Dose-dependent	≥ 90	N/A
PP binding (%)	$< 1\%$	$< 1\%$	25%
V_d	0.8 L/kg	0.5 L/kg	N/A
Cl_r	125 mL/min	70 mL/min	218 mL/min
$T_{1/2}$	5–6 h	5.5–6.7 h	N/A

Cl_r : Renal clearance; N/A: not available; PP: plasma proteins; $T_{1/2}$: elimination half-life; T_{\max} : time to reach maximal blood concentration after oral administration; V_d : apparent volume of distribution.

Gabapentin

- Assorbimento intestinale attivo tramite low-capacity amino acid transporter (LAT) saturabile

Non desiderabile

- Biodisponibilità orale variabile: 80% 100 mg TID vs 27% 1600 mg TID

Non desiderabile

- Trasporto attivo tramite barriera ematoencefalica tramite LAT

- Eliminazione renale

- Dosaggi 900-3600 mg/die divisi in 3 somministrazioni

Non desiderabile

Pregabalin

- Assorbimento intestinale attivo tramite meccanismi

multipli: cinetica lineare indipendente dalla dose

Desiderabile

- Biodisponibilità orale 90%

Desiderabile

- Eliminazione renale con riassorbimento tubulare
- Dosaggi 150-600 mg/die divisi in 2 somministrazioni

Gabapentinoidi: effetti avversi

Summary of findings 3. Gabapentin compared with placebo for neuropathic pain (all conditions pooled): adverse events and withdrawals

Gabapentin compared with placebo for neuropathic pain (all conditions pooled): adverse events and withdrawals						
Patient or population: adults with neuropathic pain						
Settings: community						
Intervention: gabapentin 1800 mg to 3600 mg daily (gabapentin encarbil 1200 mg to 3600 mg daily)						
Comparison: placebo						
Outcome	Probable outcome with gabapentin	Probable outcome with placebo	RR and NNH (95% CI)	Number of studies, participants	Certainty of the evidence (GRADE)	Comments
Participants experiencing at least one adverse event	630 per 1000	490 per 1000	RR 1.3 (1.2 to 1.4) NNH 7.5 (6.1 to 9.6)	18 studies 4279 participants	Moderate	Many events. Unlikely new research would change this finding
Adverse event withdrawals	110 in 1000	82 in 1000	RR 1.4 (1.1 to 1.7) NNH 30 (20 to 66)	22 studies 4346 participants	High	Unlikely new research would change this finding
Serious adverse events	32 in 1000	28 in 1000	RR 1.2 (0.83 to 1.7) NNH not calculated	19 studies 3948 participants	Moderate	Small number of events but no suggestion of difference
Death	3 in max 3603 exposed	5 in max 2377 exposed	Not calculated	Not calculated	Very low	Few events, relatively short duration for drug possibly taken over periods of years

CI: confidence interval; NNH: number needed to treat for an additional harmful outcome; RR: risk ratio

Gabapentinoidi: effetti avversi

Particular adverse events

Somnolence, drowsiness, or sedation was reported as an adverse event in 20 studies with 4288 participants, and it occurred in 14% of participants with gabapentin at doses of 1200 mg daily or more, and in 5.2% with placebo ([Analysis 3.3](#)). The risk ratio was 2.8 (2.3 to 3.5), and the NNH was 11 (9.4 to 14).

Dizziness was reported as an adverse event in 21 studies with 4739 participants, and it occurred in 19% of participants with gabapentin at doses of 1200 mg daily or more, and in 6.6% with placebo ([Analysis 3.4](#)). The risk ratio was 2.9 (2.4 to 3.4), and the NNH was 8.0 (7.0 to 9.4).

Peripheral oedema was reported as an adverse event in 12 studies with 3325 participants, and it occurred in 6.7% of participants with gabapentin at doses of 1200 mg daily or more, and in 1.7% with placebo ([Analysis 3.5](#)). The risk ratio was 4.1 (2.7 to 6.4), and the NNH was 20 (16 to 27).

We assessed the quality of evidence for these outcomes as moderate. While there was a reasonable number of events, definitions of adverse events and reporting was not consistent.

Ataxia or gait disturbance was reported as an adverse event in four studies with 510 participants. It occurred in 14% of participants with gabapentin at doses of 1200 mg daily or more, and in 2.6% with placebo ([Analysis 3.6](#)). The risk ratio was 5.5 (2.5 to 12), and the NNH was 8.5 (6.1 to 14).

We assessed the quality of evidence for ataxia as low. There was a small number of studies and events.

Gabapentinoidi e abuso

Gabapentinoid abuse appears to be far more prevalent among current or past opioid abusers (one study identified a 1.1 and 0.5% rate of gabapentin and pregabalin abuse, respectively, among the general population aged 16–59 years in the UK, whereas studies of patients with opioid use disorders demonstrated much higher gabapentin (15–22%) and pregabalin (3–68%) abuses rates).

Gabapentinoid abuse typically involves supratherapeutic doses, often in clear excess of the recommended max dose, in order to achieve euphoric effects.

La via pontospinale noradrenergica

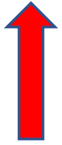
Corteccia Prefrontale

Amigdala

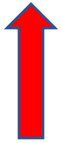
Ipotalamo-Nucleo paraventricolare



Ponte-Locus coeruleus



Bulbo- Paragigantocellularis nucleus



Decussazione (fascio di Lissauer)

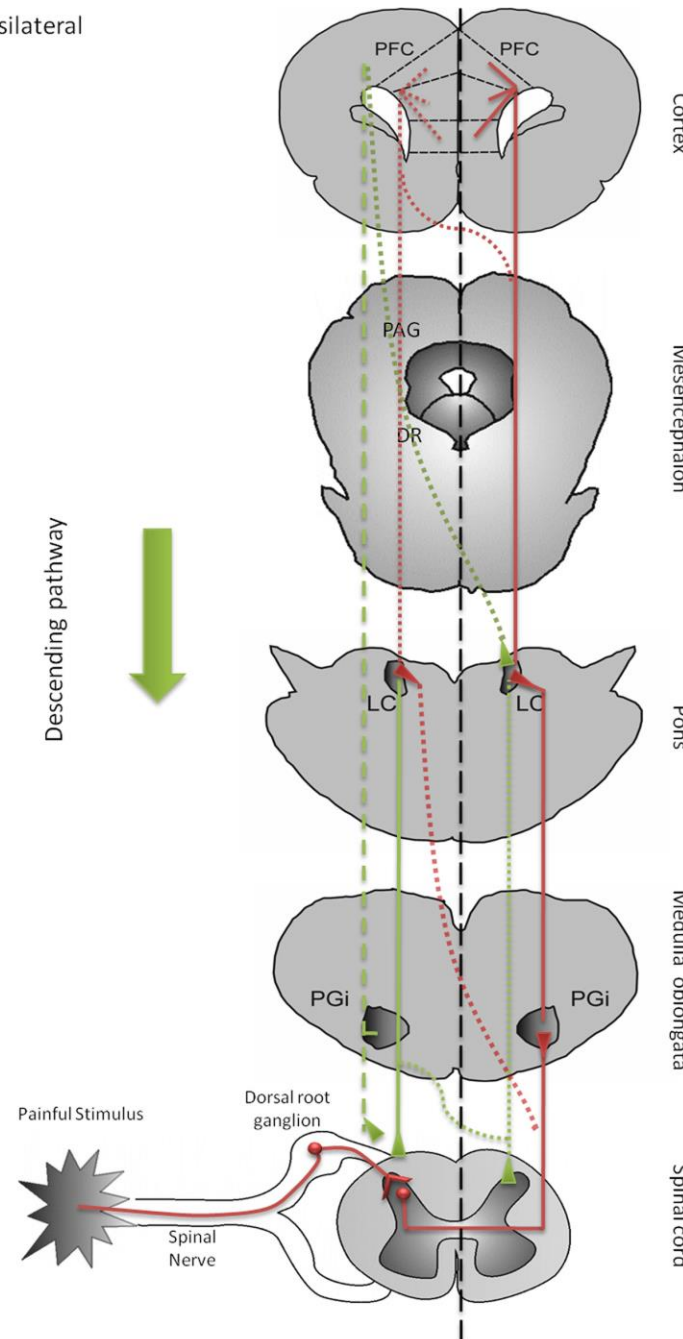


Corno dorsale

Danno reale/potenziale-Nocicezione

Ipsilateral

Descending pathway



Contralateral

Cortex

Mesencephalon

Pons

Medulla oblongata

Spinal cord

Ascending pathway

Llorca-Torralba M, Borges G, Neto F, Mico JA, Berrocoso E. Noradrenergic Locus Coeruleus pathways in pain modulation. Neuroscience. 2016;338:93-113. doi:10.1016/j.neuroscience.2016.05.057

La via discendente serotoninergica: *friend AND foe*

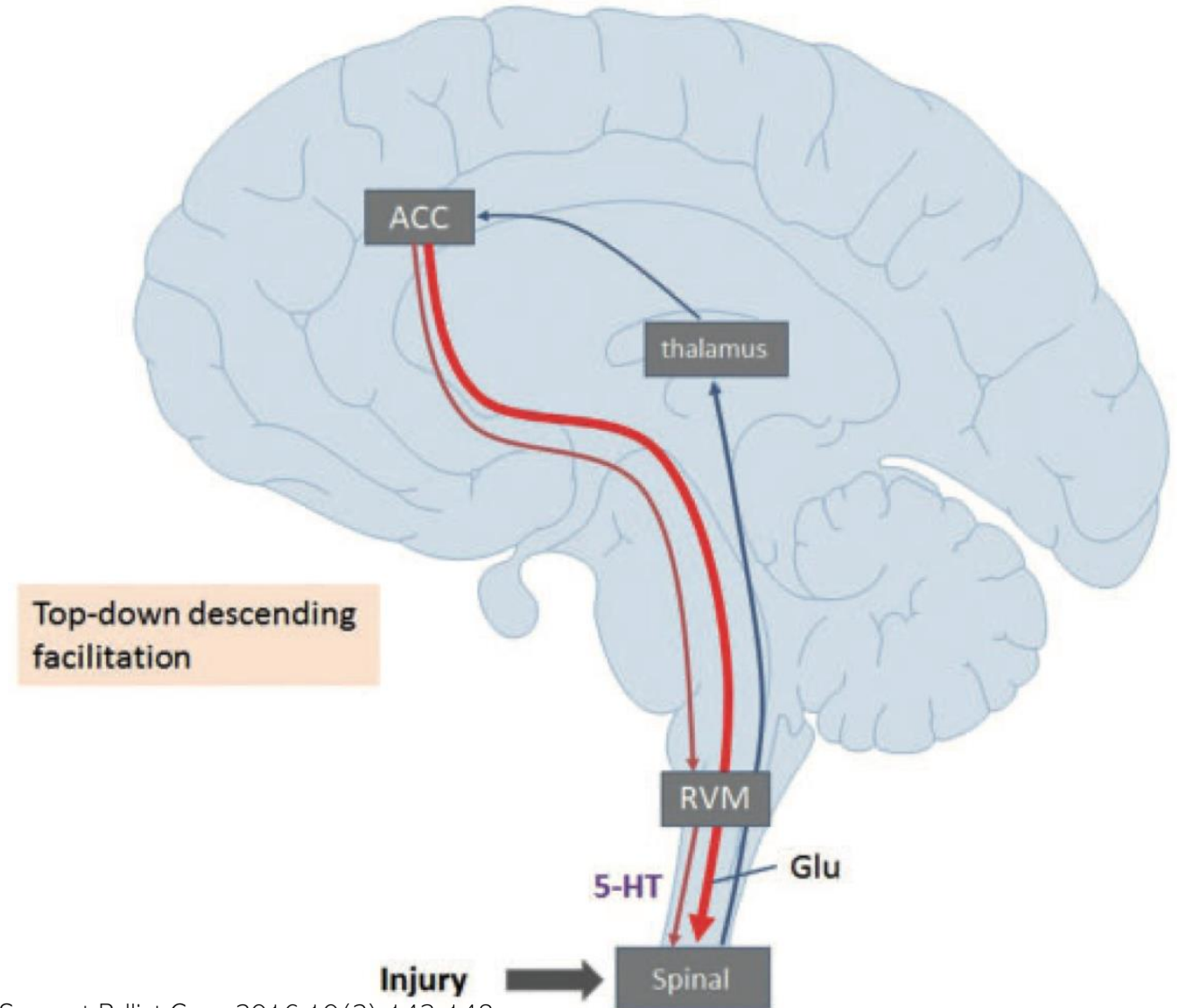
Recettori

5-HT₂ and 5-

HT₃ FACILITAZIONE

5-HT₇ and 5-

HT_{2A} INIBIZIONE



Bannister K, Dickenson AH. What do monoamines do in pain modulation? *Curr Opin Support Palliat Care*. 2016;10(2):143-148.

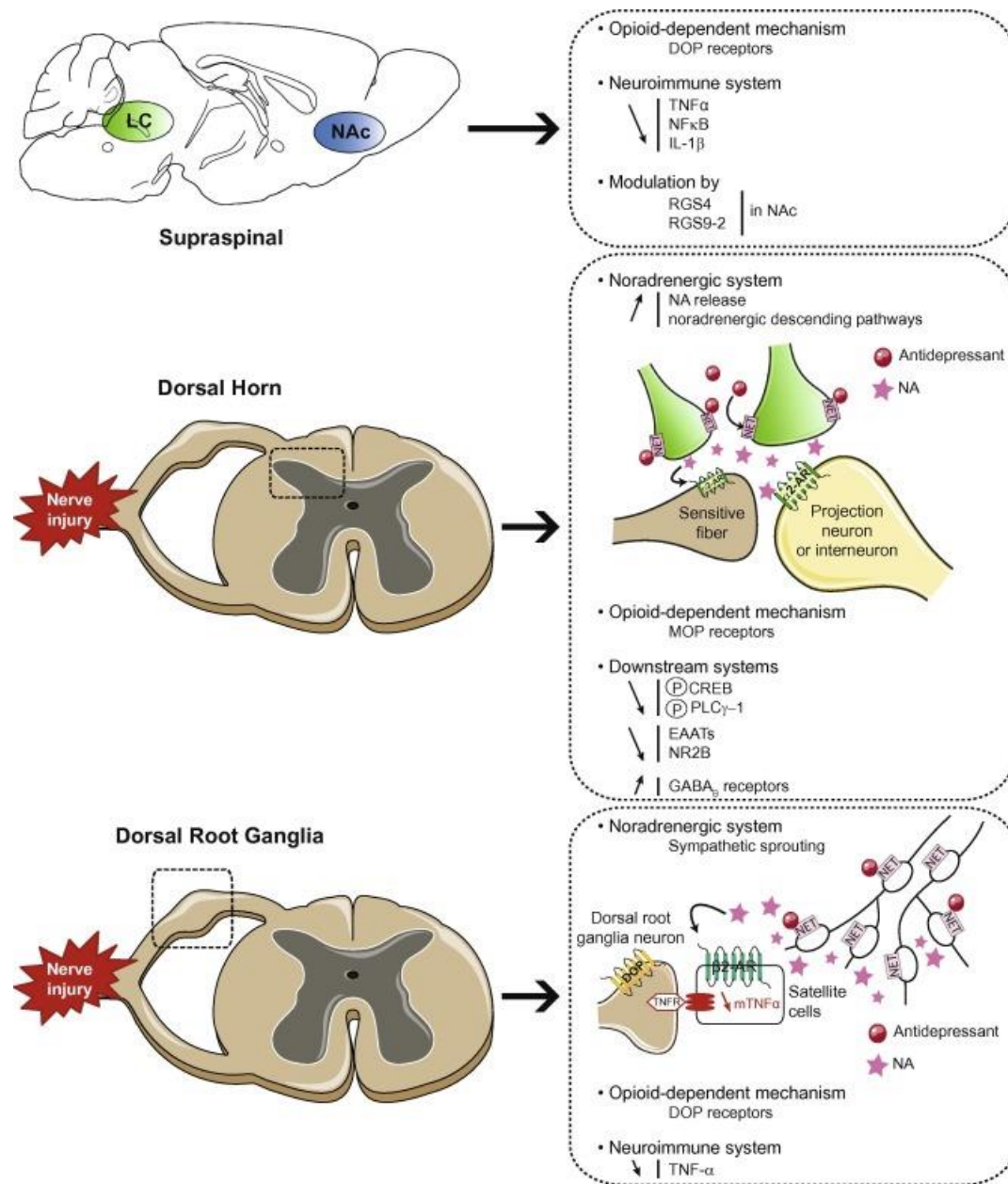
doi:10.1097/SPC.0000000000000207

Zhuo M. Descending facilitation. *Mol Pain*. 2017;13:1744806917699212. doi:10.1177/1744806917699212

Antidepressivi e analgesia

- Meccanismo centrale
(recettori α_{2A} , MOR, DOR)
- Meccanismo periferico
(recettori β_2 , DOR, modulazione via $\text{TNF}\alpha \rightarrow \text{NF-}\kappa\text{B}$)

⚠ *Analgesia \neq effetto antidepressivo*



Pharmacological profile of antidepressant drugs tried in neuropathic pain.

		TCA		SNRI	DNRI	SSRI
		Amitriptyline Imipramine Clomipramine	Nortriptyline Desipramine Maprotiline	Venlafaxine Duloxetine	Bupropion	Fluoxetine Paroxetine Citalopram
Reuptake inhibition	Serotonin	+	–/(+)	+	–	+
	Noradrenaline	+	+	+	+	–
	Dopamine	–	–	–	+	–
Receptor blockade	α-Adrenergic	+	+	–	–	–
	H1-histaminergic	+	+	–	–	–
	Musc. cholinergic	+	+	–	–	–
	NMDA	+	+	–	?	–
Ion channel blockade	Sodium	+	+	(+)/–	?	(+)/–/?
	Calcium	+	+	?	?	?

TCA=tricyclic antidepressants, SNRI=serotonin noradrenaline reuptake inhibitors, DNRI=dopamine noradrenaline reuptake inhibitors, SSRI=selective serotonin reuptake inhibitors.

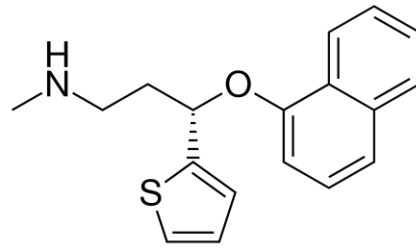
+: action present.

(+): action weak.

–: action not present.

?: not known.

Duloxetina



Serotonin-noradrenaline
reuptake inhibitors
duloxetine or venlafaxine*

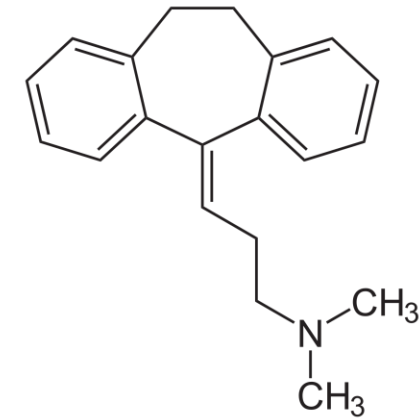
60–120 mg, once a day (duloxetine);
150–225 mg, once a day (venlafaxine extended
release)

Tricyclic antidepressants

25–150 mg, once a day or in two divided doses

- ⊘ CrCl <30 mL/min
- ⚠ non dializzabile
- ⊘ insufficienza epatica

Triciclici (es. Amitriptilina)



- ⚠ anziano dosaggio >75 mg/die
(effetti anticolinergici e ↑ cadute)
- ⚠ > 100 mg/die ↑ rischio di morte
cardiaca improvvisa
- ⊘ QTc lungo
- ⚠ cardiopatia ischemica
- ⚠ <24 aa (↑ suicidalità)
- ⚠ glaucoma angolo chiuso

Duloxetina: effetti avversi (dosaggio 60-120 mg)

- nausea (37%)
- xerostomia (32%)
- vertigini (22%)
- sonnolenza (20%)
- insonnia (20%)
- diarrea (14%)
- sudorazione 6.5% - 9.3%
- tremori 3.3% - 10.2%

Adverse events were very common in these trials but were, in general, mild. The rates of any adverse event and adverse events leading to cessation of treatment were significantly greater with duloxetine than with placebo at the 60 mg and 120 mg doses, which are the doses used in clinical practice. However, withdrawals because of adverse events were relatively few (duloxetine, all doses combined, 12.6% versus placebo 5.8% (RR 1.99, 95% CI 1.67 to 2.37)). The NNTH for cessation of treatment was 17 (95% CI 13 to 26). These figures are in line with the retrospective analysis

Triciclici: effetti avversi

Anti-Colinergico

- Diplopia
- Costipazione
- Vertigini
- Xerostomia
- Confusione
- Ritenzione urinaria
- Tachicardia

Anti- α 1

Ipotensione ortostatica

Anti-H1

Sedazione

Aumento del peso

Confusione

↑QTc

↑ Aritmie ventricolari

↑ Morte cardiaca improvvisa

↓Soglia epilettogena

↑ Suicidalità

Teratogenicità

Paracetamolo

Meccanismi **centrali** di analgesia

- Inibizione **Perossido-dipendente** dell'enzima COX (perossido↓ a livello cerebrale)
- Attivazione vie discendenti **serotoninergiche**
- Inibizione del reuptake degli **endocannabinoidi** (anandamide) tramite metabolita N-arachidonoylphenolamine (AM404)

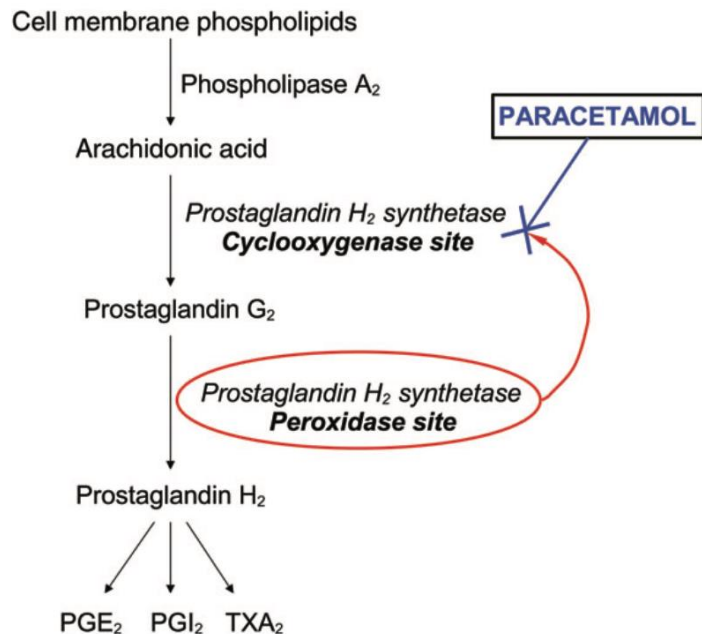


Fig 1 Role of paracetamol in inhibition of prostaglandin production.

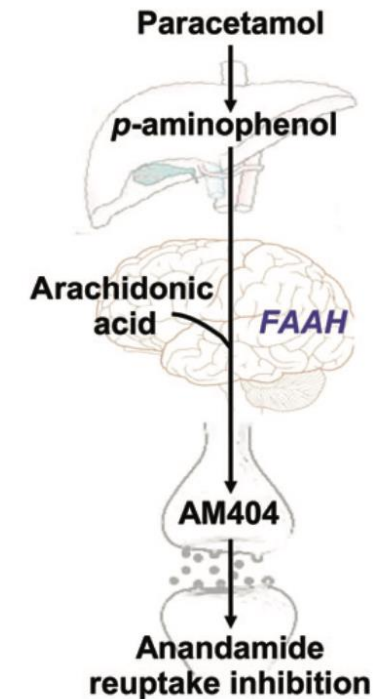
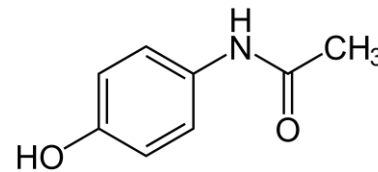


Fig 2 Conversion of paracetamol to AM404, an endocannabinoid reuptake inhibitor.

Fino a **4000 mg/die**

Pediatrico: fino a 80 mg/kg/die



Abuso di alcol

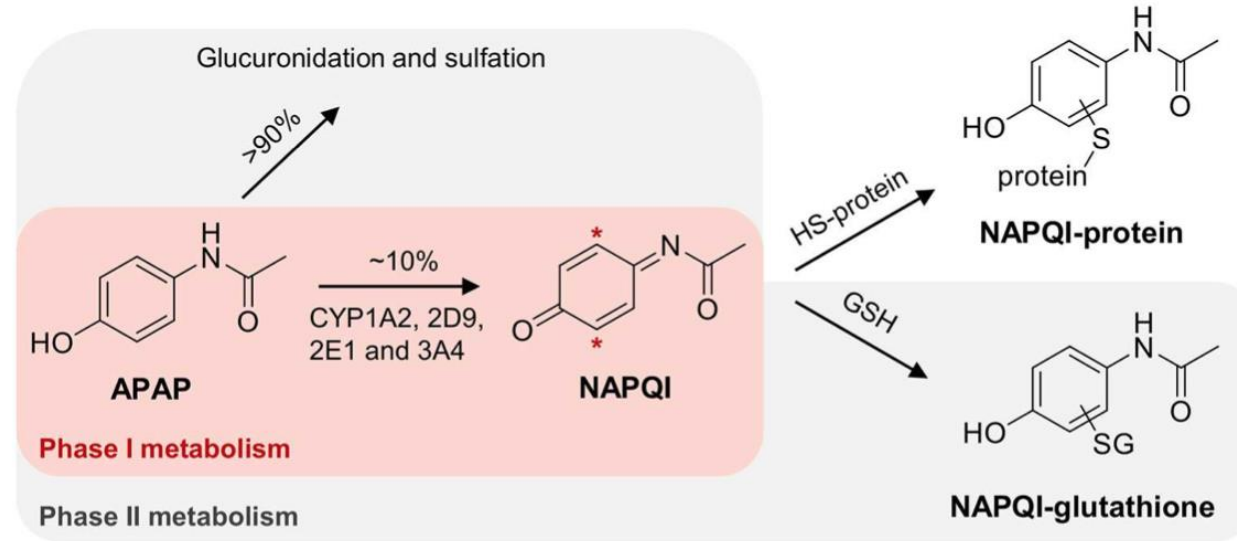


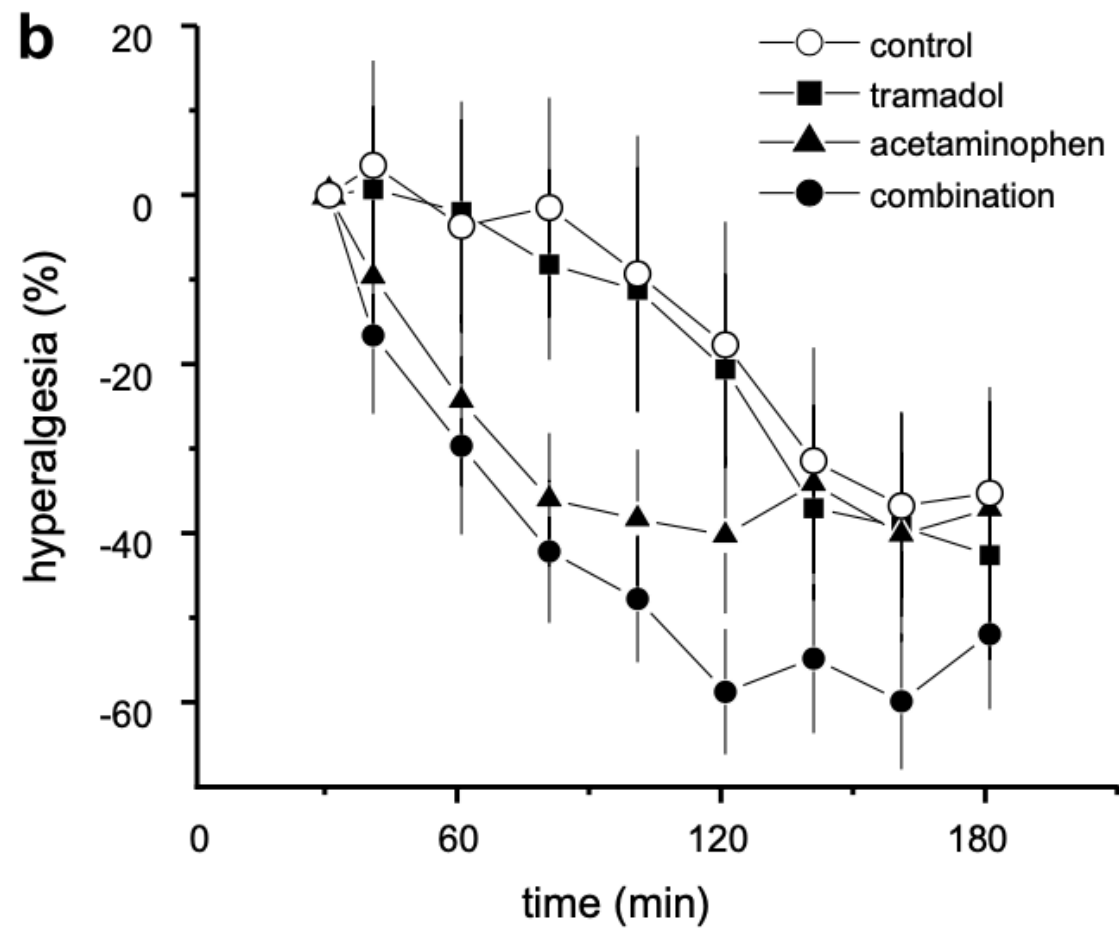
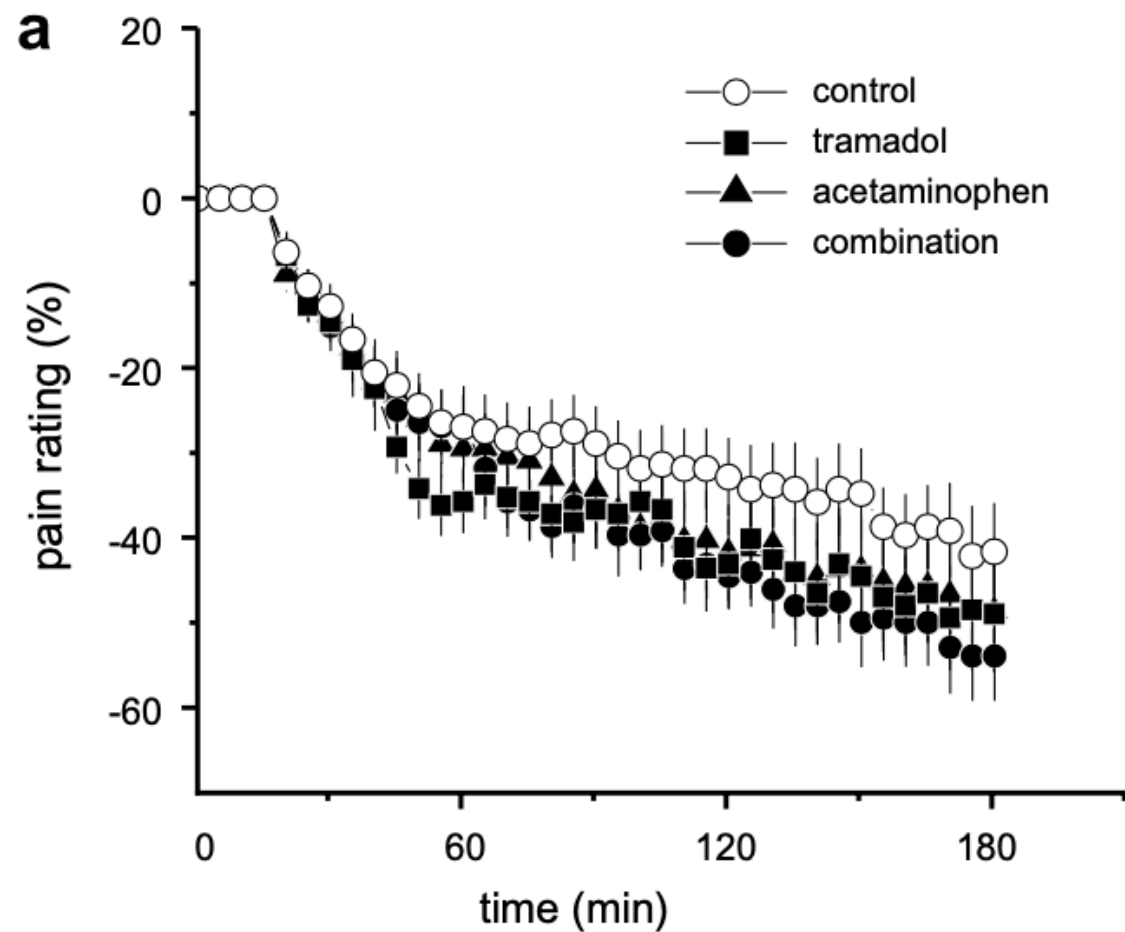
FIGURE 1 | Simplified scheme of APAP metabolism, leading to the formation of NAPQI with subsequent GSH conjugation. Hepatotoxicity of NAPQI is linked to protein binding to cysteine sites.

Table 2

Theoretical and experimental ED₅₀ values with 95% CL and ratios for combinations of NSAIDs with paracetamol (PARA) in the writhing test of mice

Combinations	ED ₅₀ (95% CL) mg/kg i.p.		Ratio NSAID:PARA
	Theoretical	Experimental	
Naproxen/paracetamol	47.9 (35.3–64.9)	13.9* (9.9–18.3)	1:1.06
Metamizol/paracetamol	38.9 (30.7–49.3)	13.8* (10.3–18.8)	1:1.73
Piroxicam/paracetamol	28.9 (21.4–39.0)	11.9* (8.8–17.1)	1:5.81
Diclofenac/paracetamol	28.8 (20.6–40.1)	7.4* (4.4–15.4)	1:6.03
Nimesulide/paracetamol	28.5 (20.8–38.9)	7.4* (4.4–10.6)	1:6.50
Meloxicam/paracetamol	27.9 (20.8–37.5)	11.4* (8.3–16.5)	1:7.60
Parecoxib/paracetamol	26.5 (19.2–33.8)	12.2* (10.0–14.8)	1:30.1
Ketoprofen/paracetamol	39.3 (33.5–47.4)	20.4* (15.8–25.6)	1:31.6
Ibuprofen/paracetamol	25.1 (19.2–32.8)	9.6* (8.3–11.1)	1:58.1
Combinations	ED ₅₀ (95% CL) mg/kg p.o.		Ratio NSAID:PARA
	Theoretical	Experimental	
Diclofenac/paracetamol	72.6 (63.3–83.1)	32.3* (21.6–53.3)	1:7.11

* $P < 0.05$.



NSAIDs

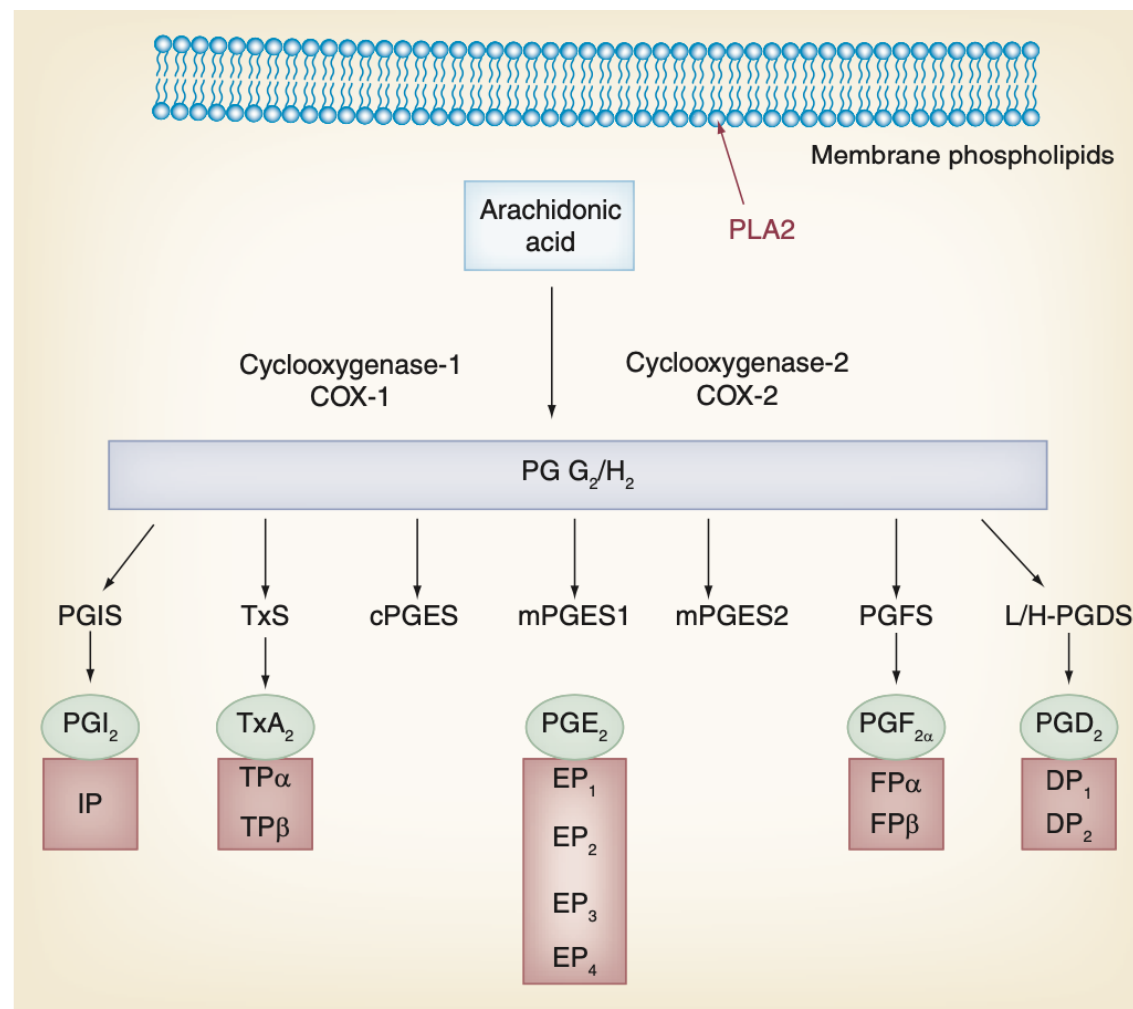
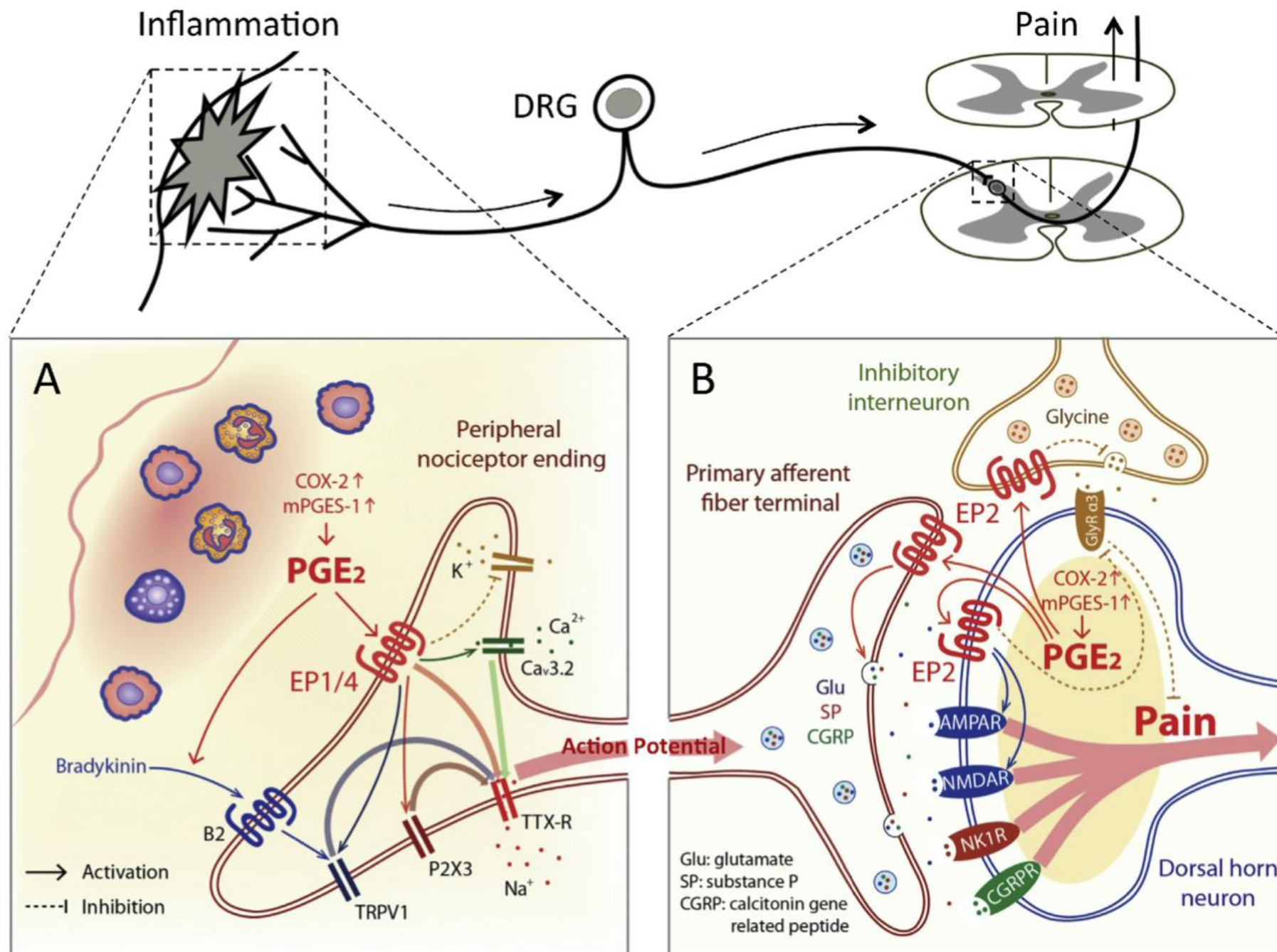
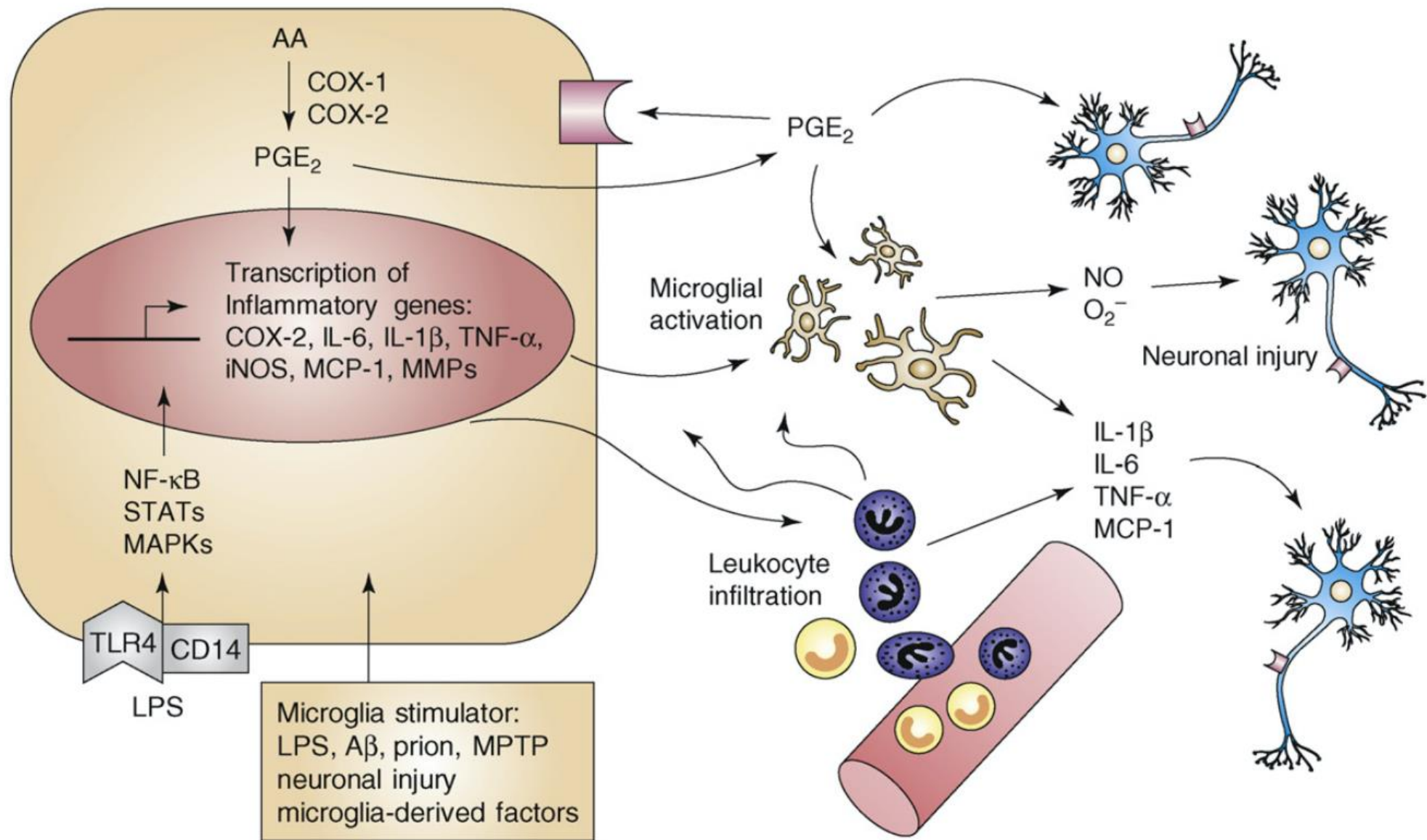


Figure 1. Cyclooxygenase pathways of arachidonic acid metabolism. Prostanoids are generated from arachidonic acid stored within the cell membrane and esterified to glycerol in phospholipids. A receptor-dependent event initiates phospholipid hydrolysis, mainly through the activity of phospholipase A₂. Once released, intracellular free arachidonic acid is transformed to prostaglandin H₂ by the activity of prostaglandin H synthases (named COX-1 and COX-2). Prostaglandin H₂ is metabolized to the prostanoids by different synthases expressed in a tissue-specific manner.

COX: Cyclooxygenase; DP: Prostaglandin D receptor; EP: Prostaglandin E receptor; FP: Prostaglandin F receptor; IP: Prostacyclin receptor; PG: Prostaglandin; PGI₂: Prostacyclin; PLA₂: Phospholipase A₂; TP: Thromboxane A₂ receptor; TxA₂: Thromboxane A₂.





TRENDS in Pharmacological Sciences

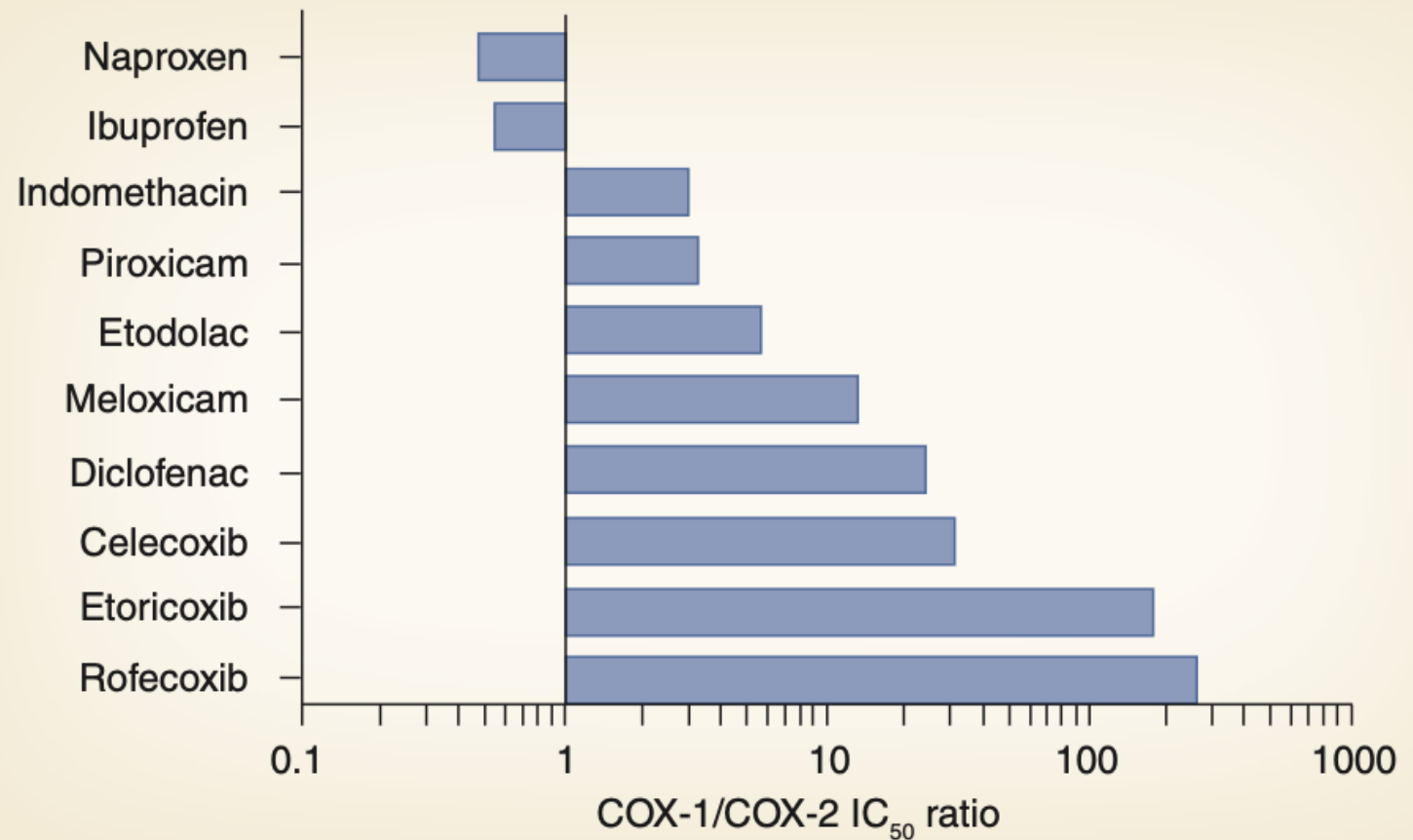
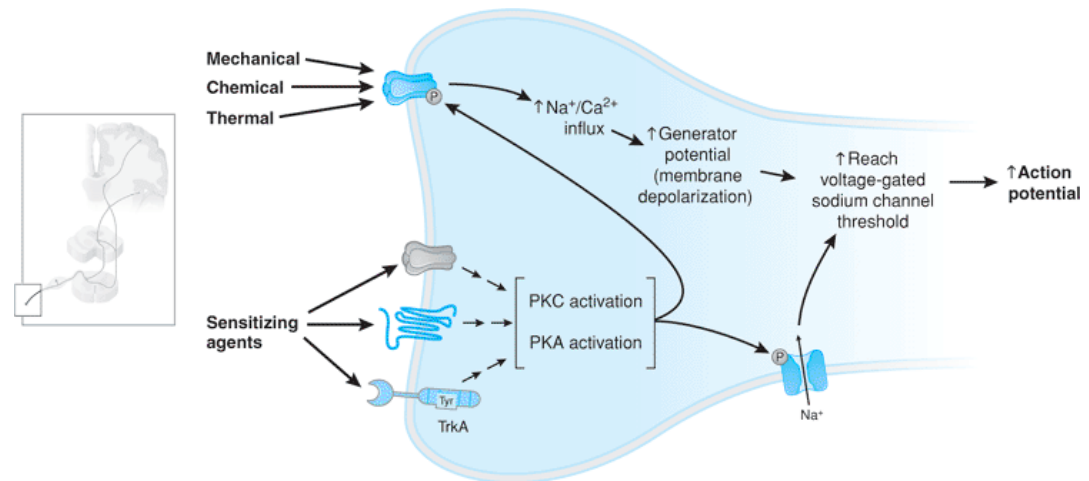
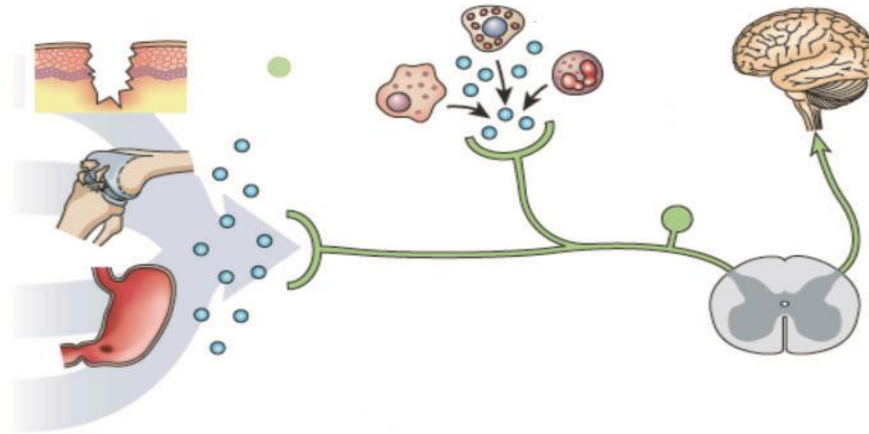
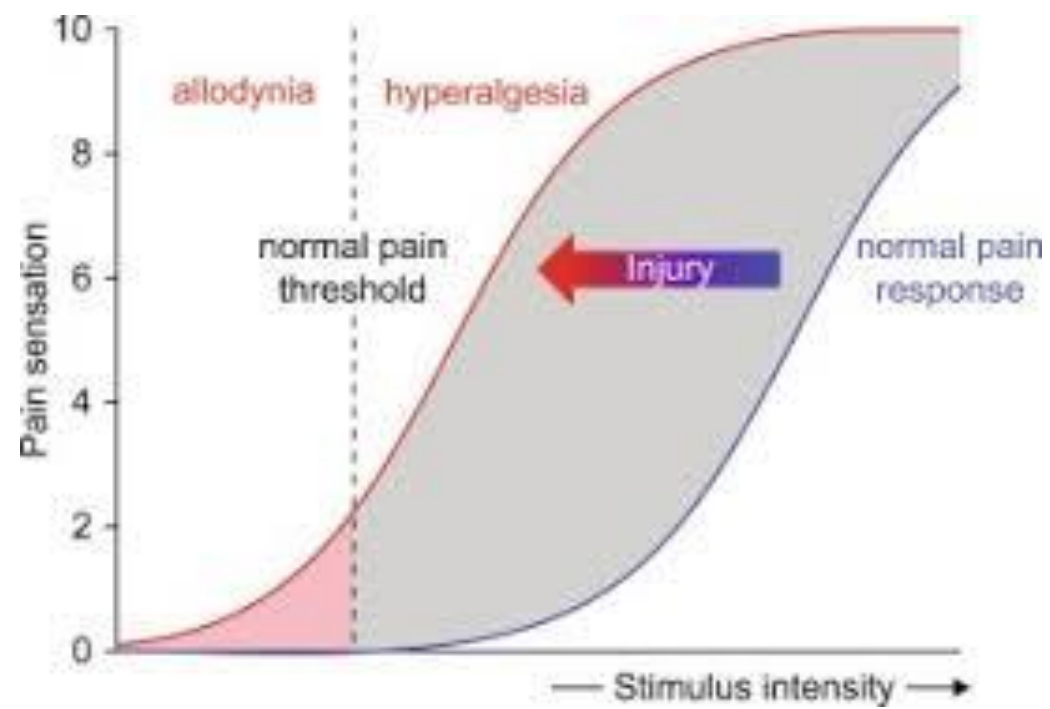
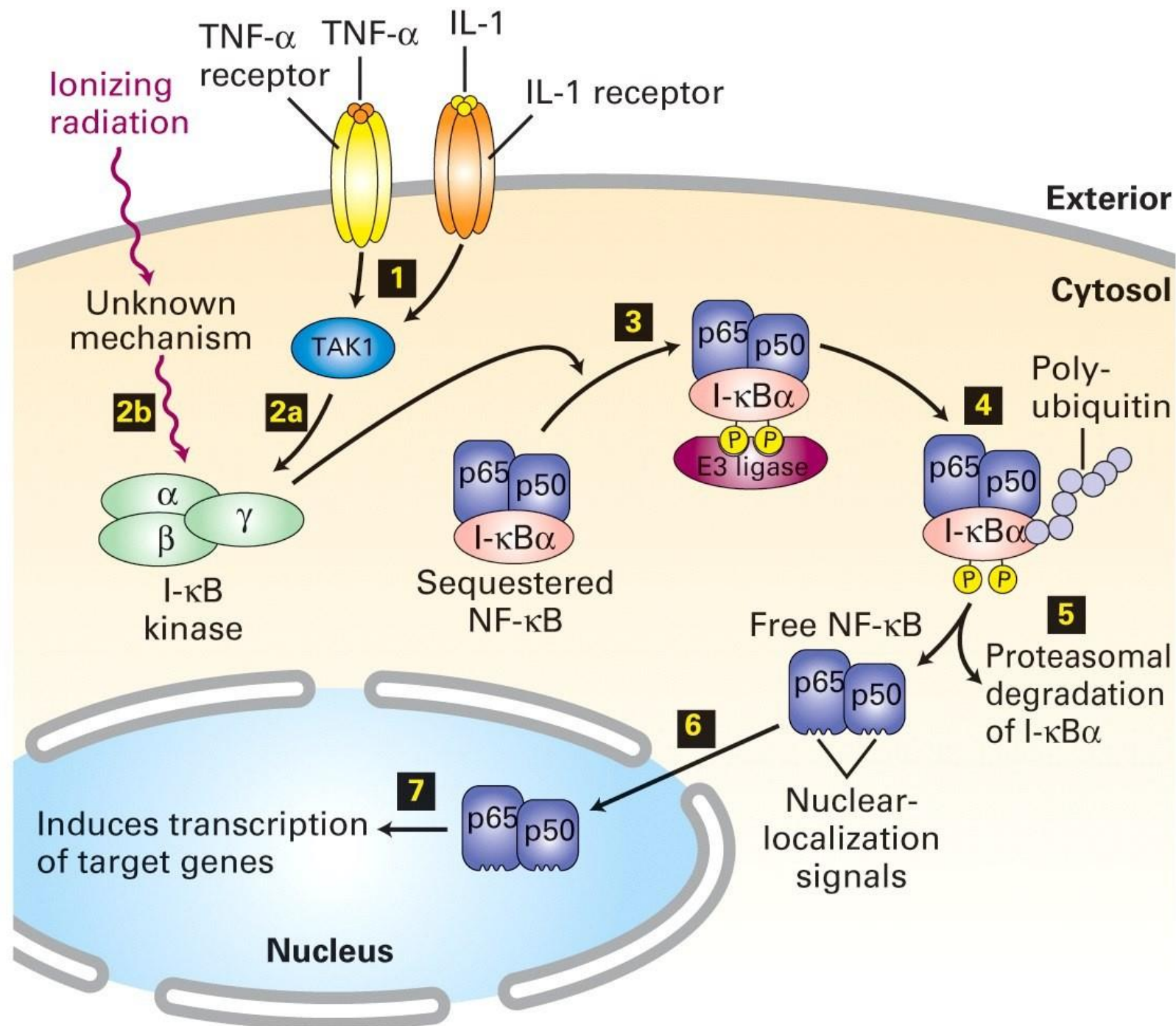


Figure 2. Degree of selectivity for COX-2 by the different NSAIDs *in vitro* expressed as ratio of IC₅₀ values for COX-1 and COX-2. The degree of COX selectivity of NSAIDs, defined by their potency to inhibit by 50% COX-1 and COX-2 activities *in vitro*. Higher values of COX-1/COX-2 IC₅₀ ratio (>1) mirror higher selectivity versus COX-2. Lower values (<1) mirror higher selectivity for COX-1. IC₅₀ is the concentration of the drug required to inhibit the activity of COX-1 and COX-2 by 50%. COX: Cyclooxygenase; IC₅₀: 50% inhibitory concentration.

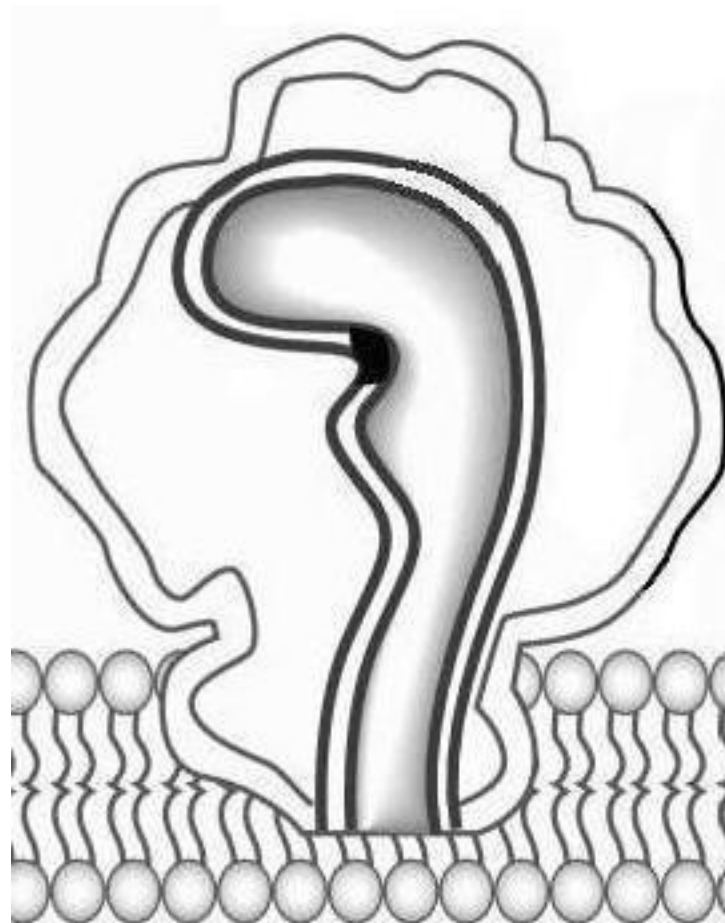
SENSIBILIZZAZIONE PERIFERICA





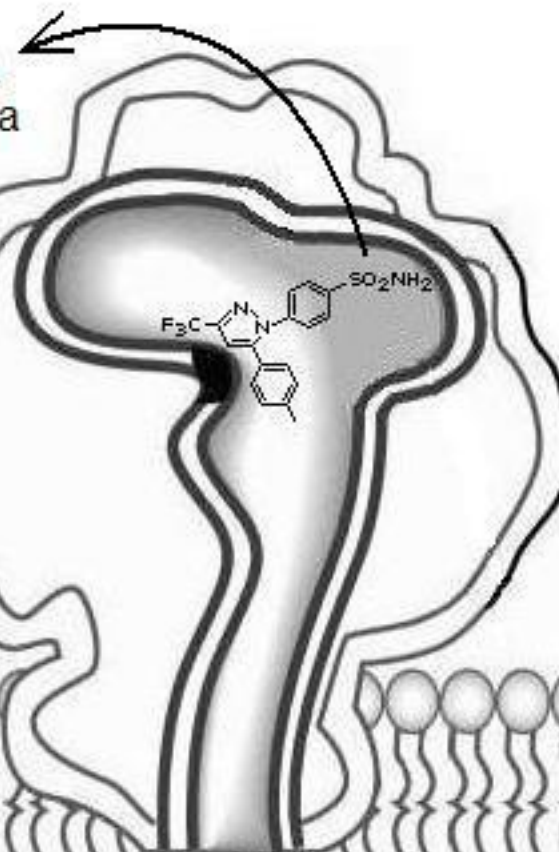


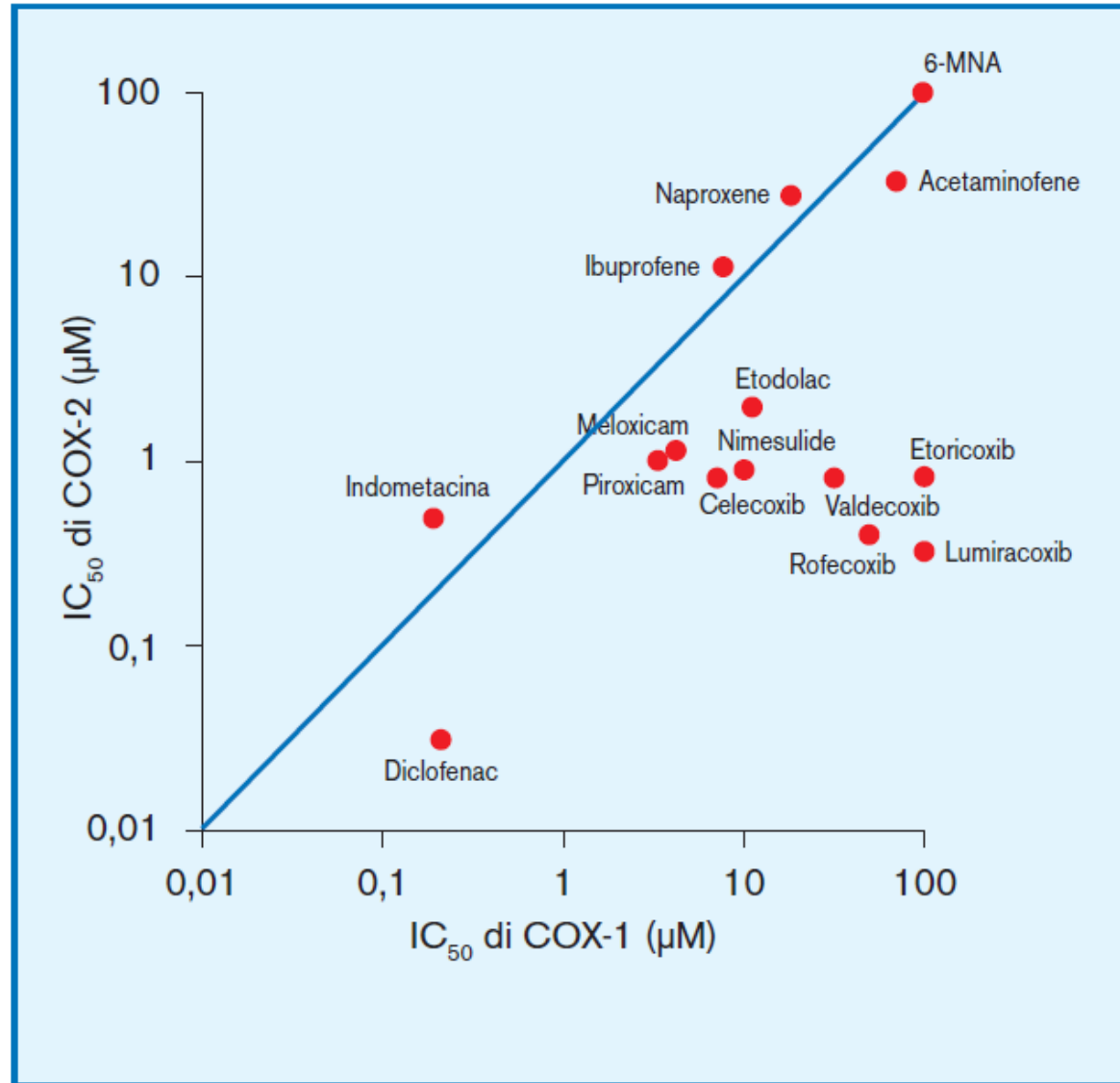
COX-1



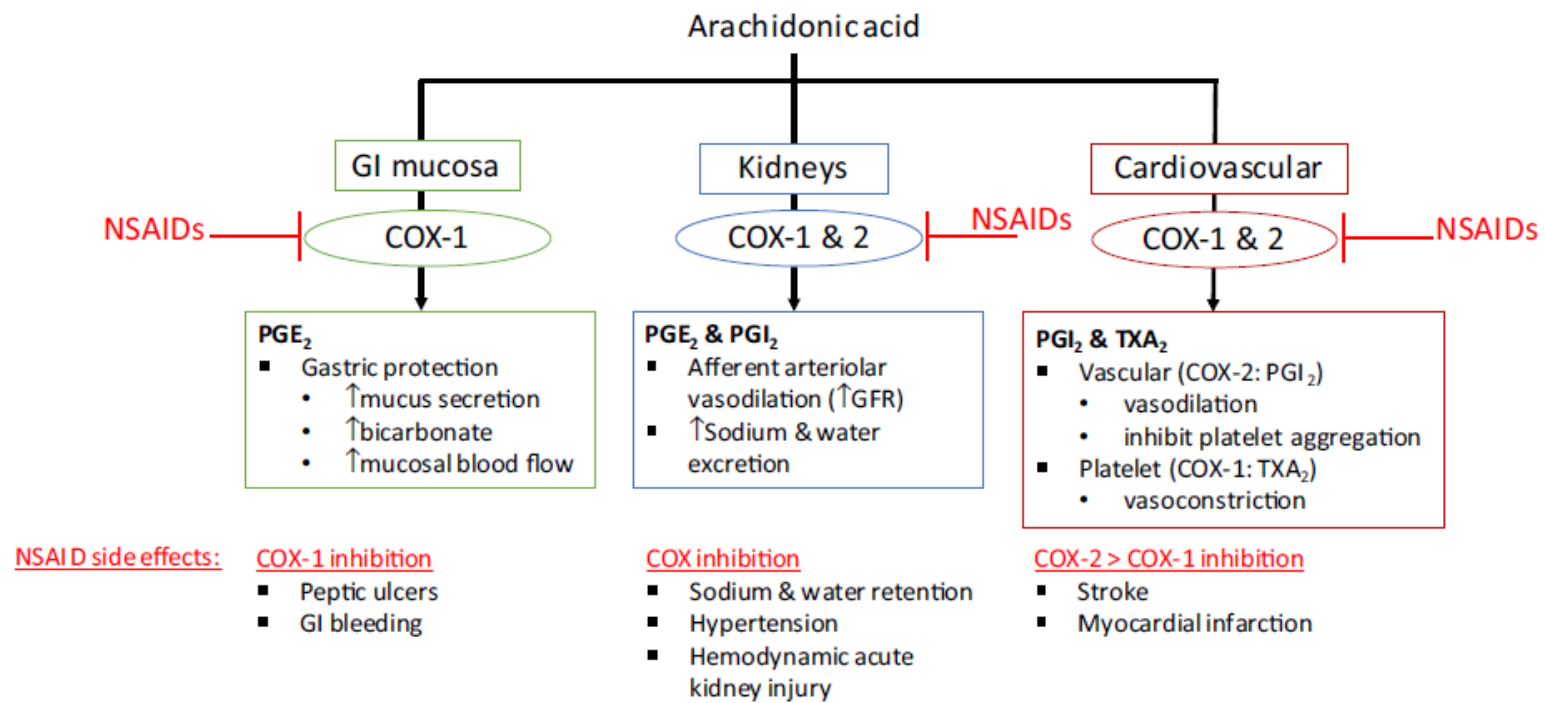
COX-2

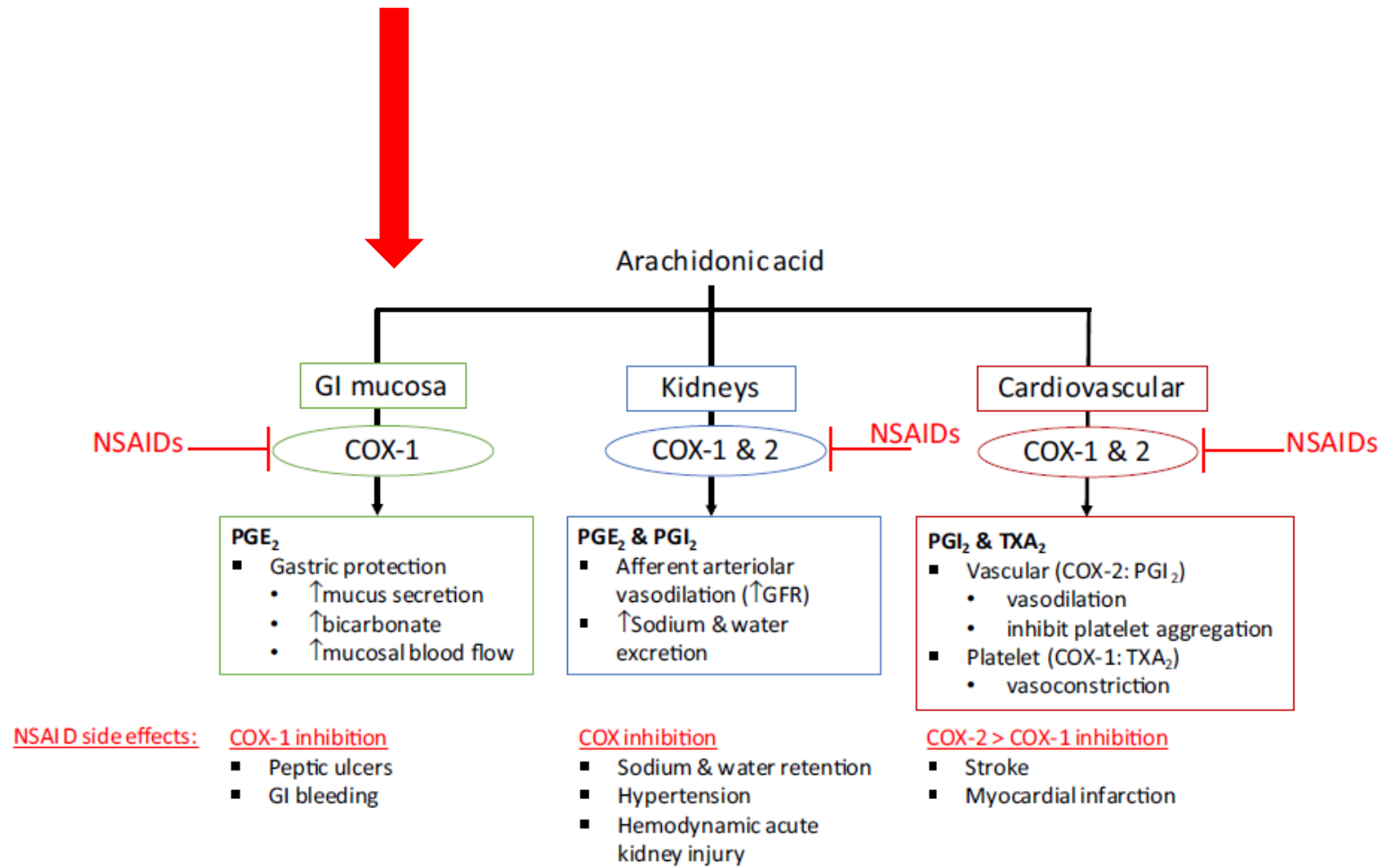
tasca
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secondaria





modificata da Patrignani et al., BBA 2015





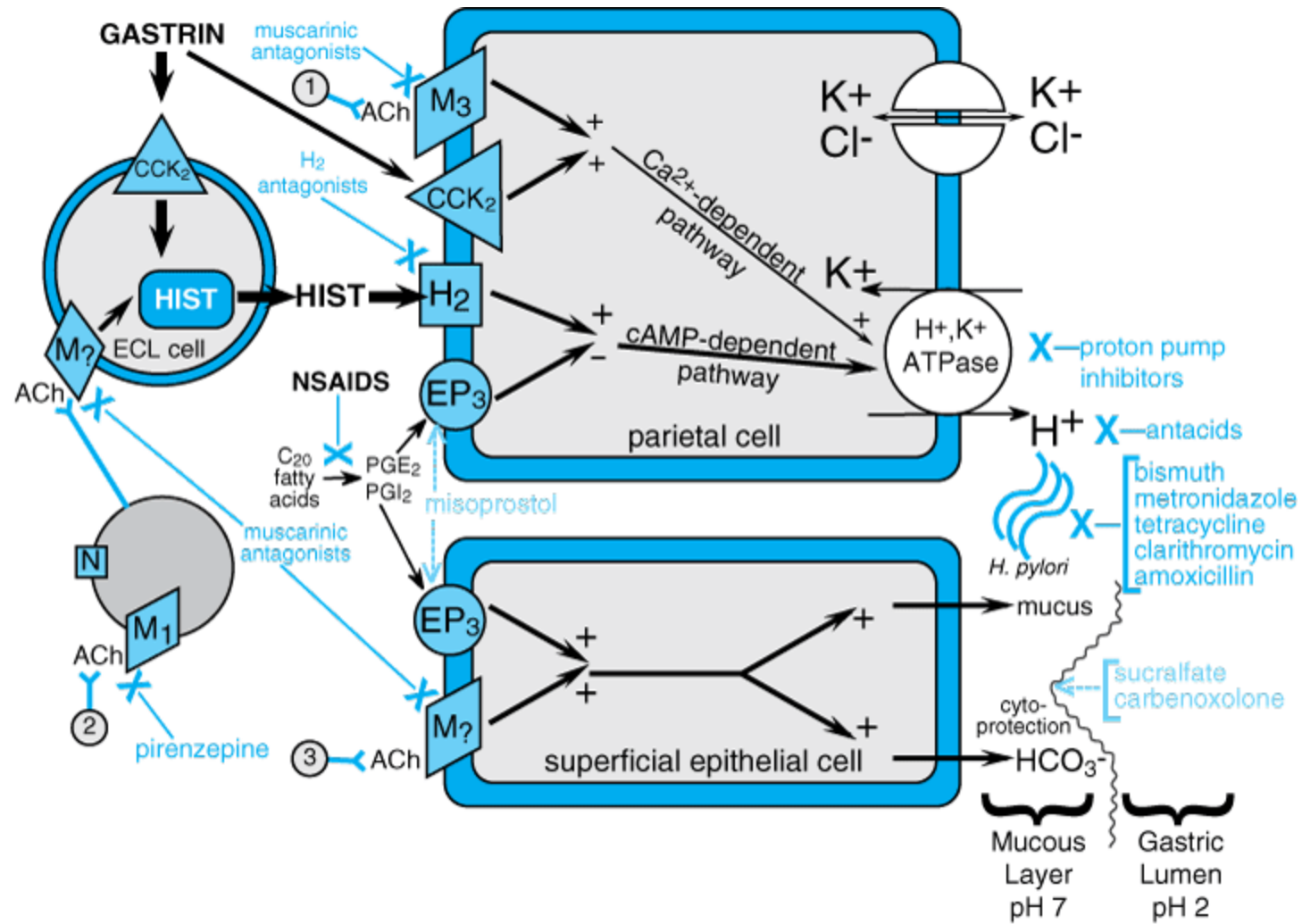
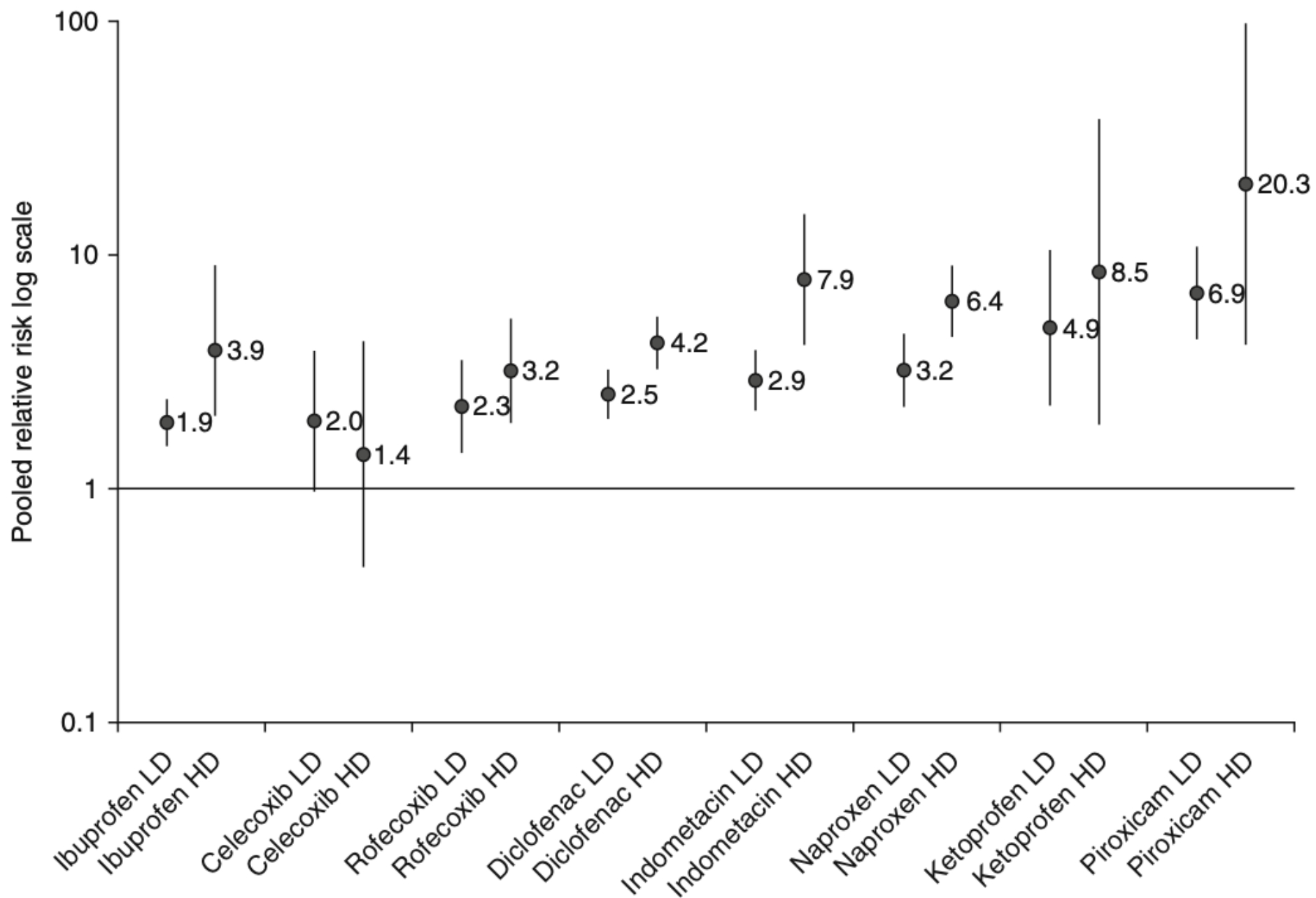
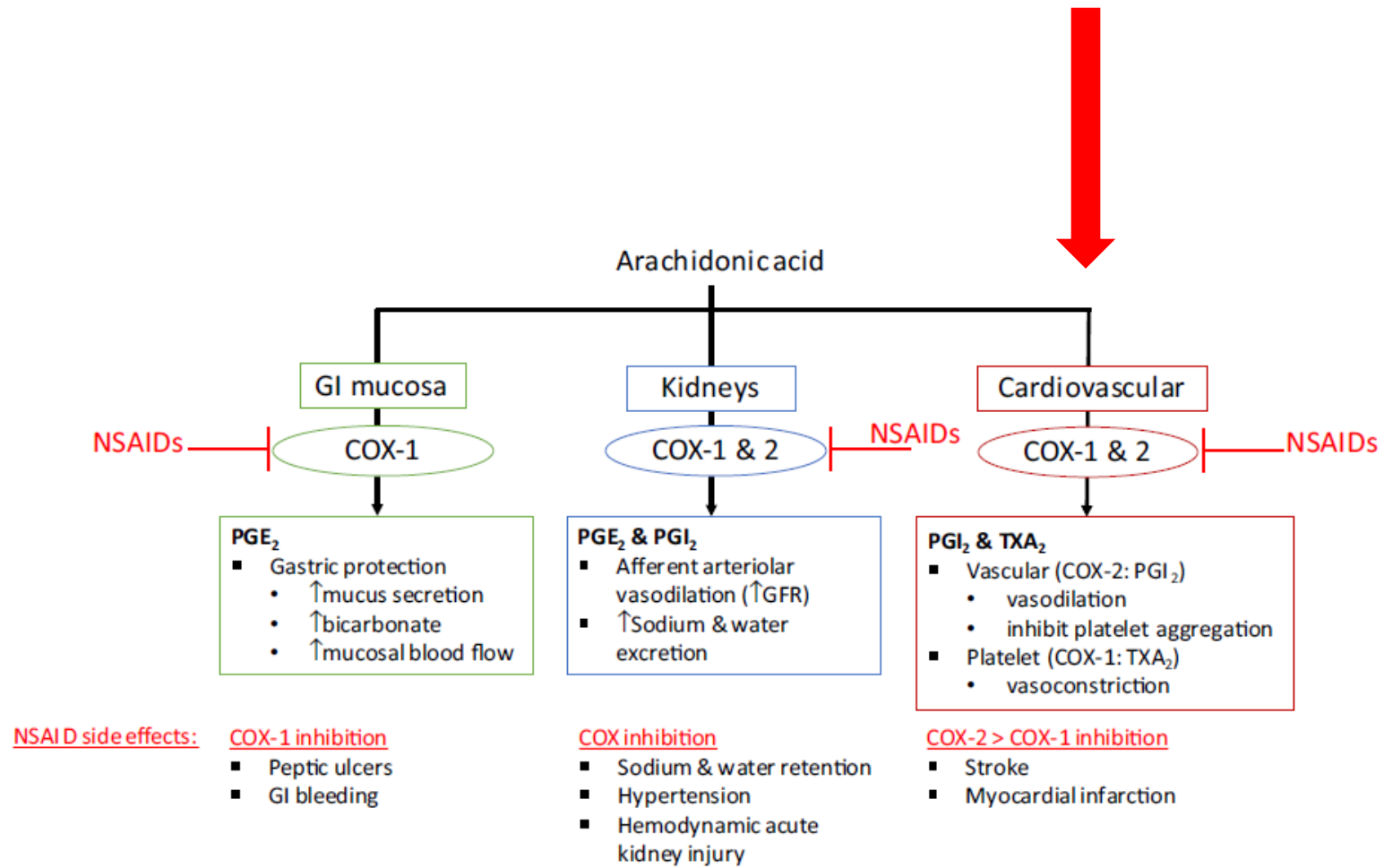


Table 1 Risk factors for GI complications associated with NSAID use

Risk factors
<ul style="list-style-type: none">• Age 60 years and above• Dyspepsia history• Current high dose of NSAID• Multiple NSAID therapy• Concomitant use of ASA• Uncomplicated peptic ulcer history• Concomitant use of corticosteroids• Concomitant use of oral anticoagulants• Peptic ulcer bleeding• <i>Helicobacter pylori</i> infection• Cigarette smoking• Alcohol use• Chronic debilitating disorders, especially cardiovascular disease





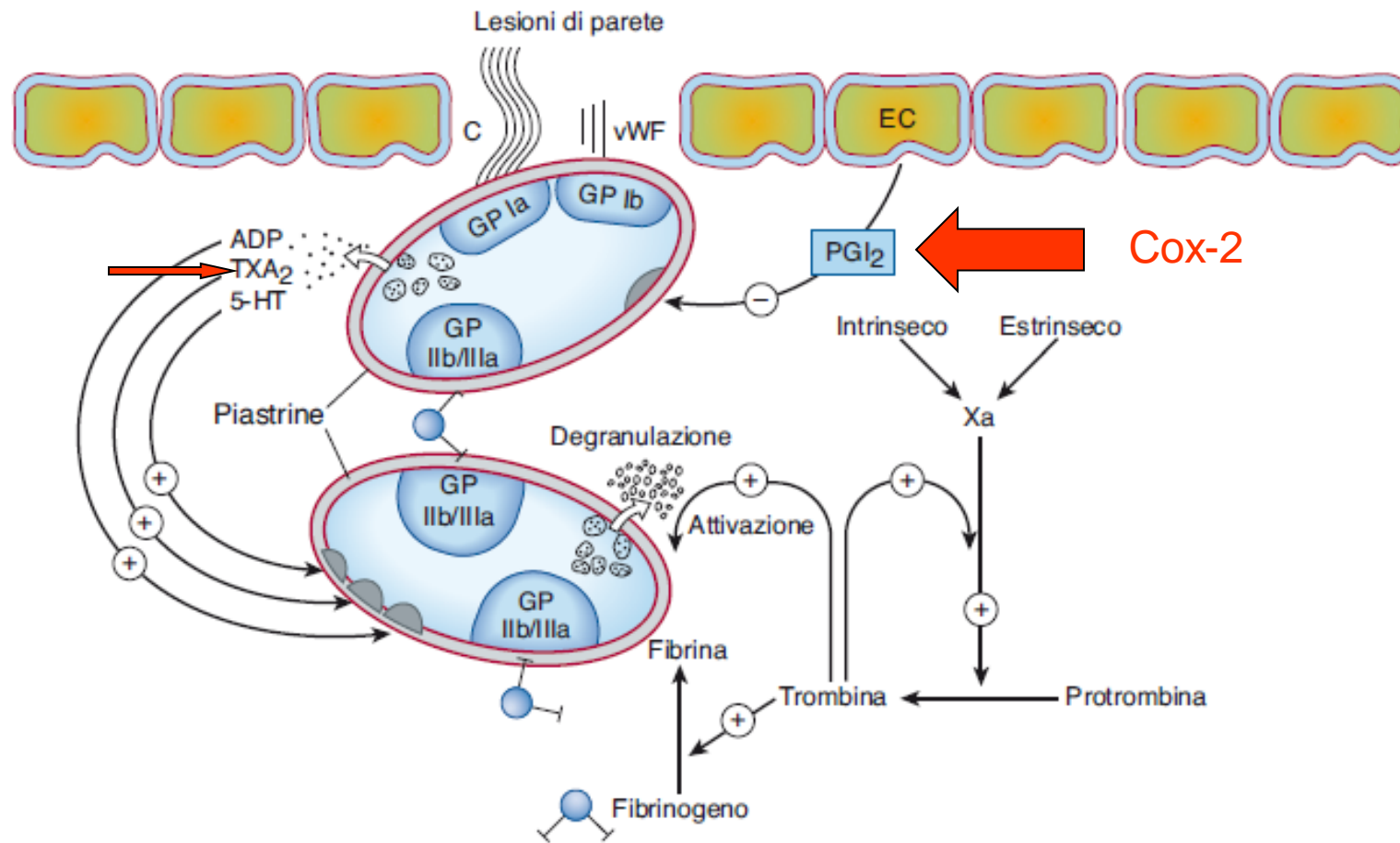
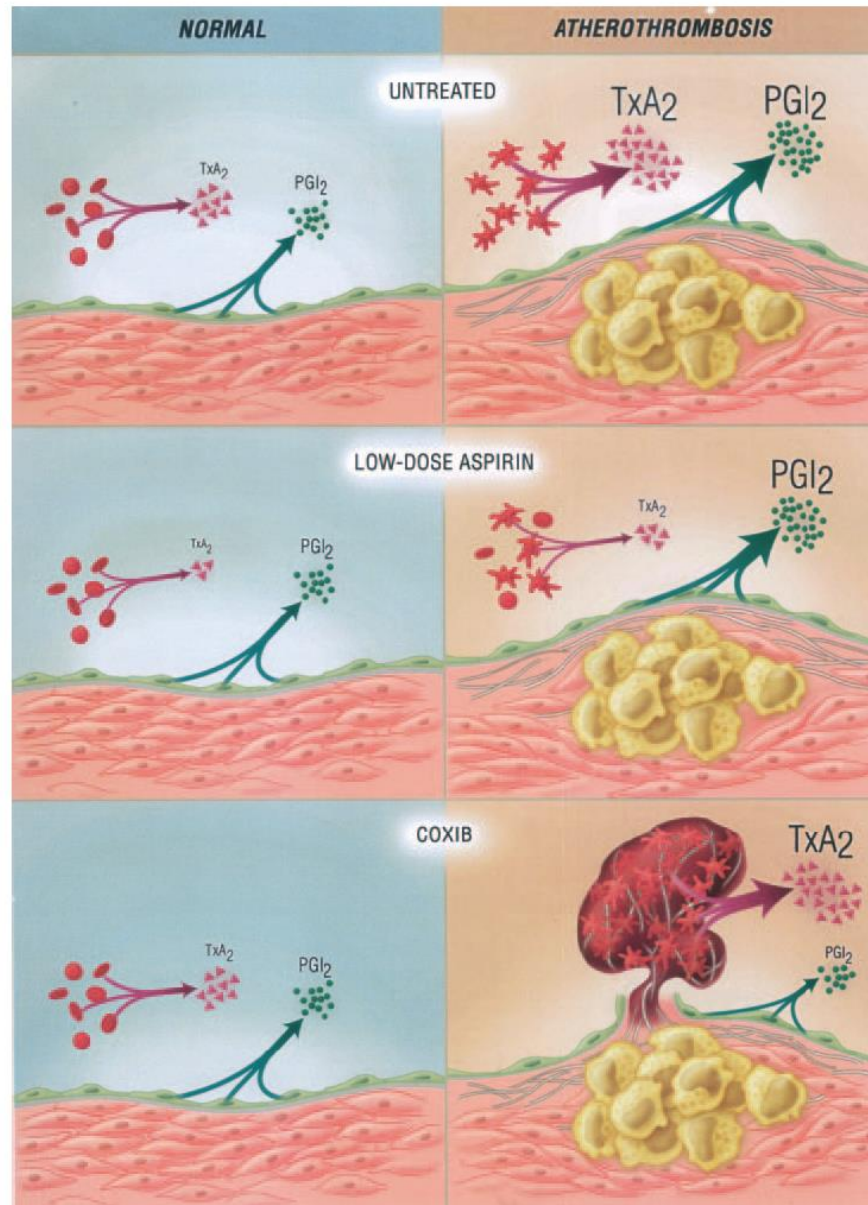
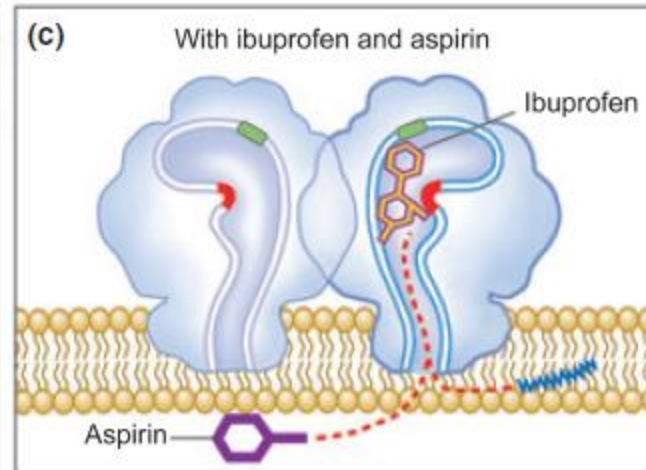
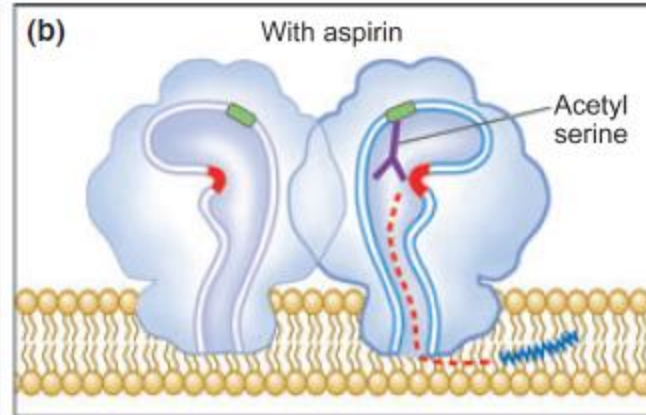
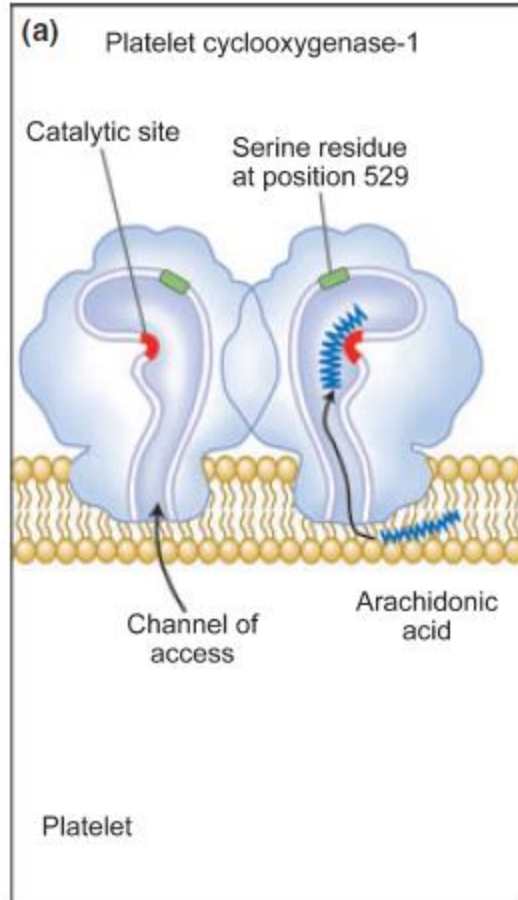


Figura 34-1. Formazione del trombo in sede di parete vasale danneggiata (EC, cellula endoteliale) e ruolo delle piastrine e dei fattori della coagulazione. Tra i recettori di membrana piastrinici vi sono il recettore glicoproteico (GP) Ia che lega il collagene (C), Ib che lega il fattore von Willebrand (vWF) e IIb/IIIa che lega il fibrinogeno ed altre macromolecole. La prostaciclina (PGI₂), ad azione antiaggregante piastrinica, viene rilasciata dall'endotelio. Tra le sostanze aggreganti rilasciate a seguito della degranulazione piastrinica vi sono l'ADP, il TXA₂ e la 5-HT. La formazione del fattore Xa è esemplificata nella fig. 34-2. (Ridisegnata e riprodotta, previo consenso, da Simoons ML, Decker JW: New directions in anticoagulant and antiplatelet treatment [Editorial], *Br Heart J* 1995; 74:337).



B.G. KATZUNG
S.B. MASTERS
A.J. TREVOR
**FARMACOLOGIA
GENERALE E CLINICA**





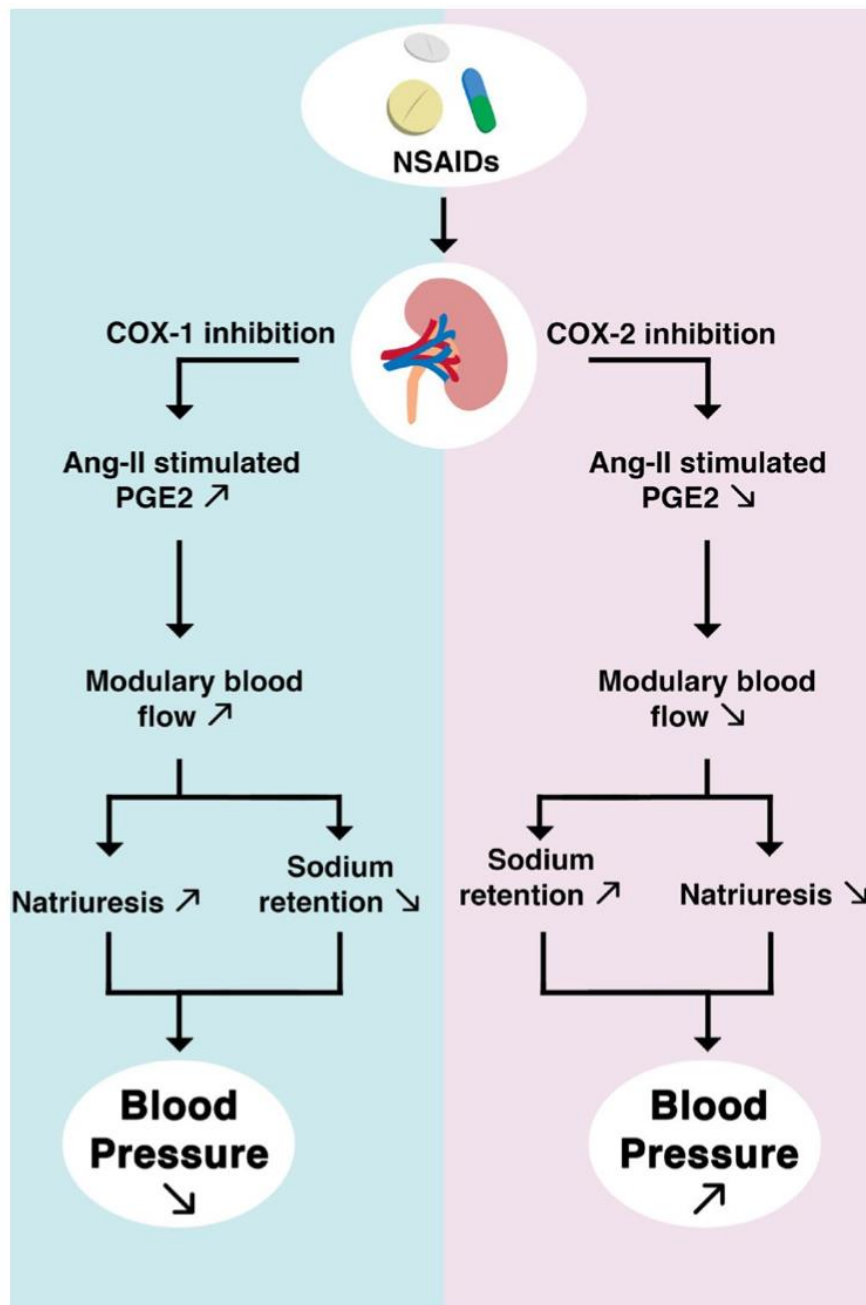


Table III. Selected risk factors for NSAIDs-induced acute nephrotoxicity.

Perinatal age

- Multiple pregnancies (especially monochorionic twin pregnancies)
- Prolonged and cumulative doses
- Short term between treatment and delivery
- Genetic factors
- Low birthweight
- Concomitant drugs (aminoglycosides, glycopeptides, diuretics)

Pediatric age

- Dehydration
- Hypovolemia
- Haemorrhage
- Congestive heart failure
- Liver failure
- Pre-existing renal problems
- Urinary tract malformations
- Recurrent urinary tract infections
- NSAIDs multitherapy
- Concomitant drugs (beta-blockers, ACE inhibitors, diuretics, aminoglycosides)
- Alcohol consumption
- Cystic fibrosis

Adult age

- Elderly
- Renal disease
- NSAIDs multitherapy
- Concomitant drugs (inotropes, calcium channel blockers, diuretics)
- Prolonged therapy

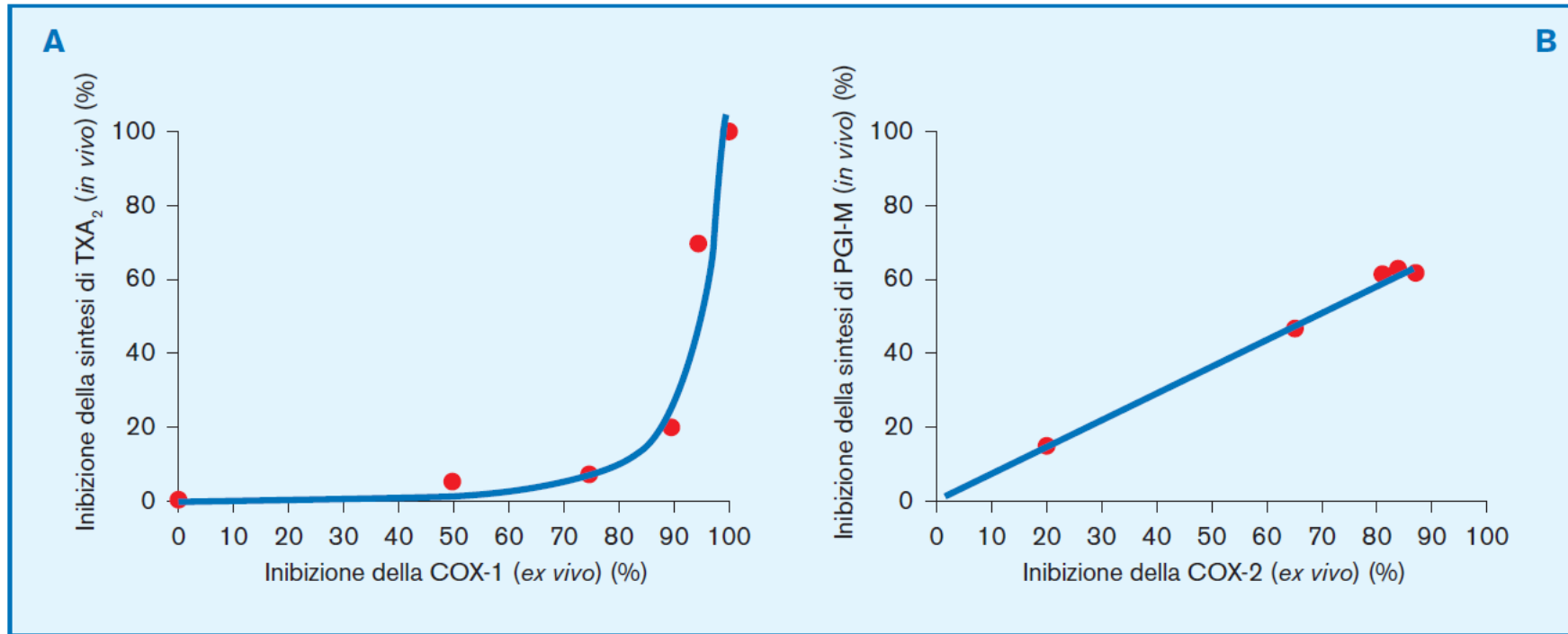
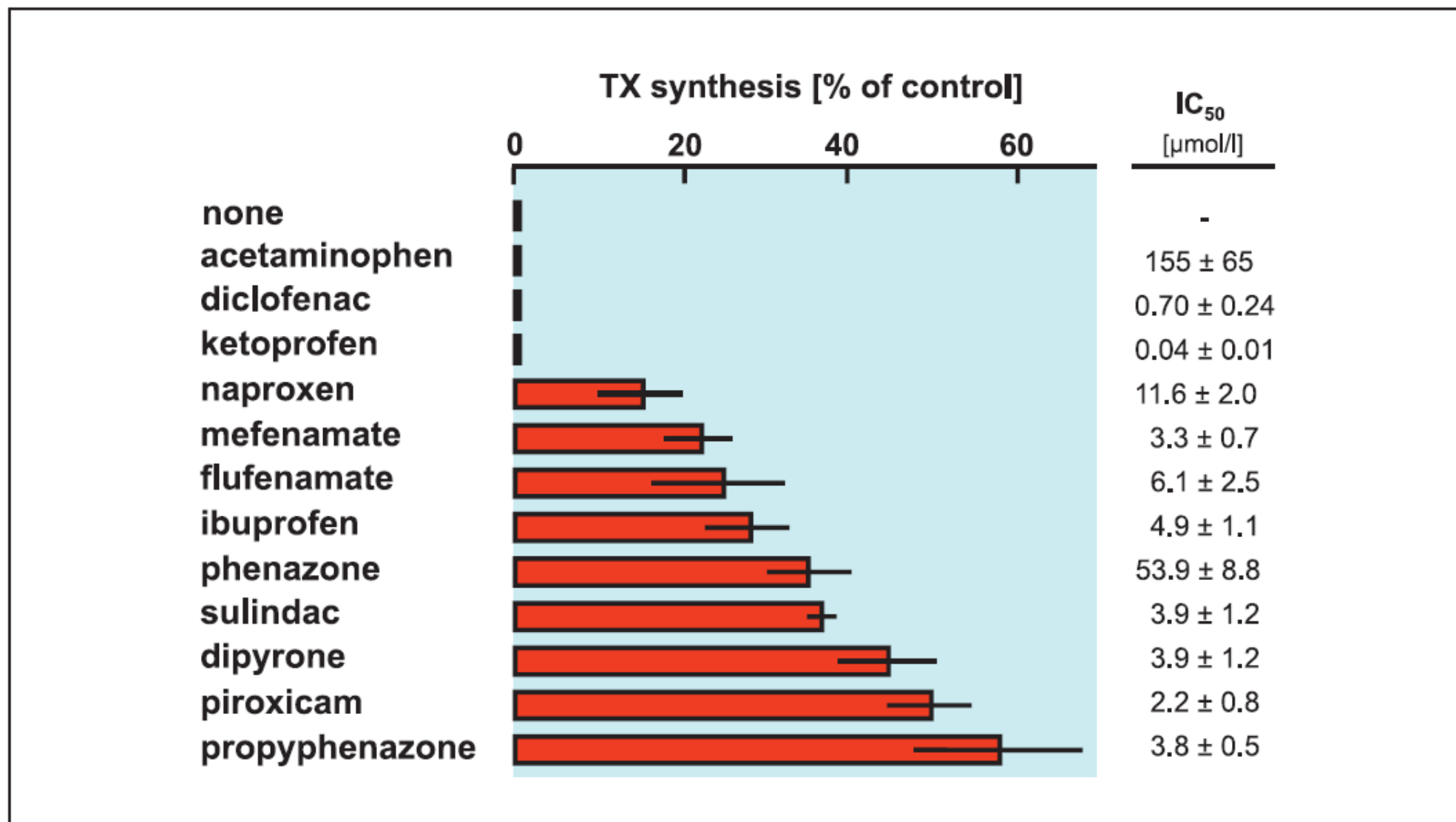


Figura 3. Relazione tra la percentuale di inibizione delle COX-1 e delle COX-2 misurata su sangue intero e gli effetti anti-trombotici (**A**) e antinfiammatori (**B**) in vivo, misurati come inibizione della sintesi di tromboxano (TXA_2) e prostaciclina (PGI) (modificata da [8]). PGI-M, metabolita della prostaciclina

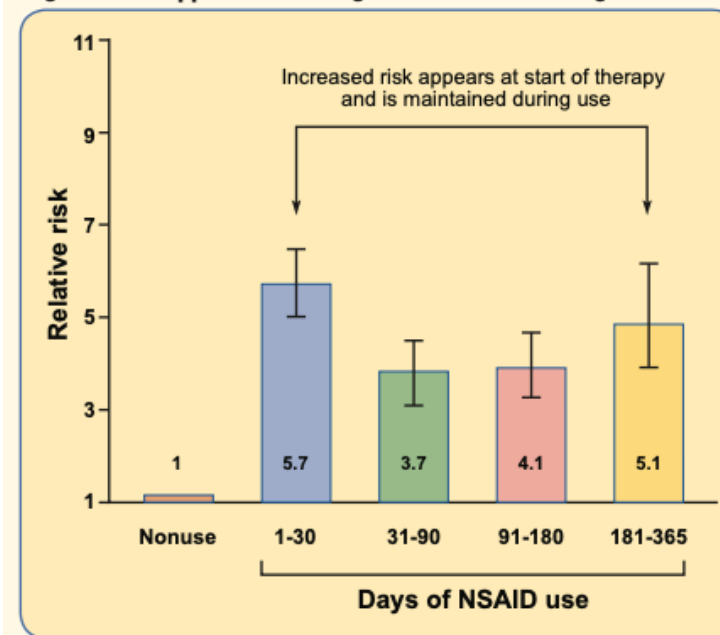
modificata da Brune et al. J Pain Res, 2015



Renal Event

- Three studies were identified evaluating the temporal relationship between use of NSAIDs and acute renal failure; one study evaluated acute tubular interstitial nephritis.
- Acute administration of diclofenac has a rapid, profound, negative impact on renal function in patients with heart failure, specifically, significant decrease in glomerular filtration rate, urine flow, and excretion rates of sodium and potassium in patients with congestive heart failure treated with an ACE inhibitor ($P < 0.05$).¹⁶
- Celecoxib and rofecoxib have a relatively short median time to onset of adverse renal events from the start of therapy: 18 days and 10 days, respectively.⁵
- The risk of acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted rate ratio, 2.05; 95% CI, 1.61-2.60) and receded thereafter. There was a twofold increase in the risk of acute renal failure with any NSAID within 1 month of a first prescription; this risk decreased after at least 30 days without an NSAID prescription (Table 3).¹⁹

Figure 2.
High Risk of Upper GI Bleeding is Maintained During NSAID Use



Source: Hernandez-Diaz et al., 2000.¹⁴

CV Event

- Six studies were included in the CV assessment: four retrospective studies, one randomized clinical trial (occurrence of CV adverse events was a secondary endpoint), and one prospective survey.
- Even short-term use of NSAIDs was associated with increased risk of death from MI (Figure 3), specifically a statistically significant increased risk starting early in and persisting throughout the treatment.²
- The risk of developing CV adverse events was greater in patients with a history of ischemic heart disease.^{8,9}
- The risk of first myocardial infarction was more evident early in the treatment period and remained elevated for up to a week after the last prescription.^{13,17}
- Only one study¹⁷ assessed the time to CV event in a specific number of days, finding that events occurred a median of 9 days from first time prescription (rofecoxib). Risk remained elevated for the first 7 days after discontinuation and returned to baseline between days 8 and 30.

Ketamina

- Miscela racemica o enantiomero S-ketamina
- S-ketamina 3-4x potenza R-ketamina
- **Elevato metabolismo** epatico di **primo passaggio** → biodisponibilità orale 8–24 %
- Metabolismo ossidativo epatico
- Norketamina $\frac{1}{5}$ potenza analgesica – C_{\max} a 30 min da bolo iv
- Clearance sistemica 60–147 L/h/70 kg = perfusione epatica

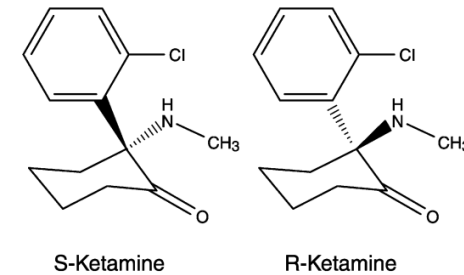
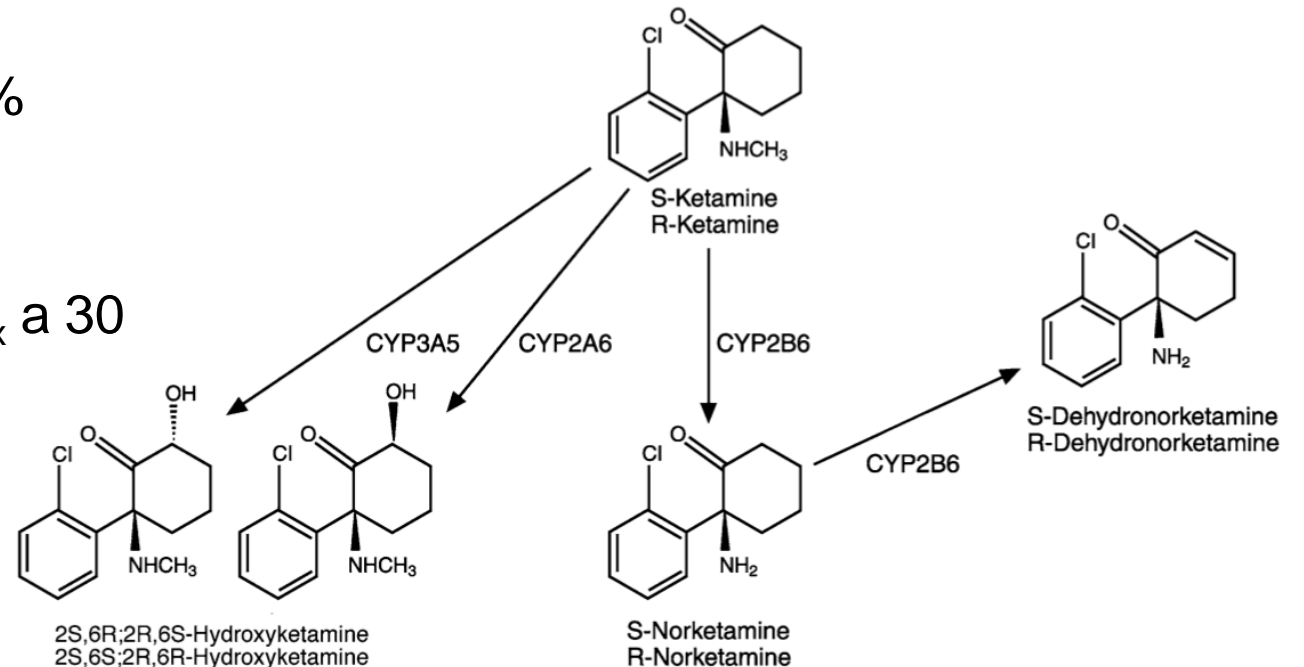
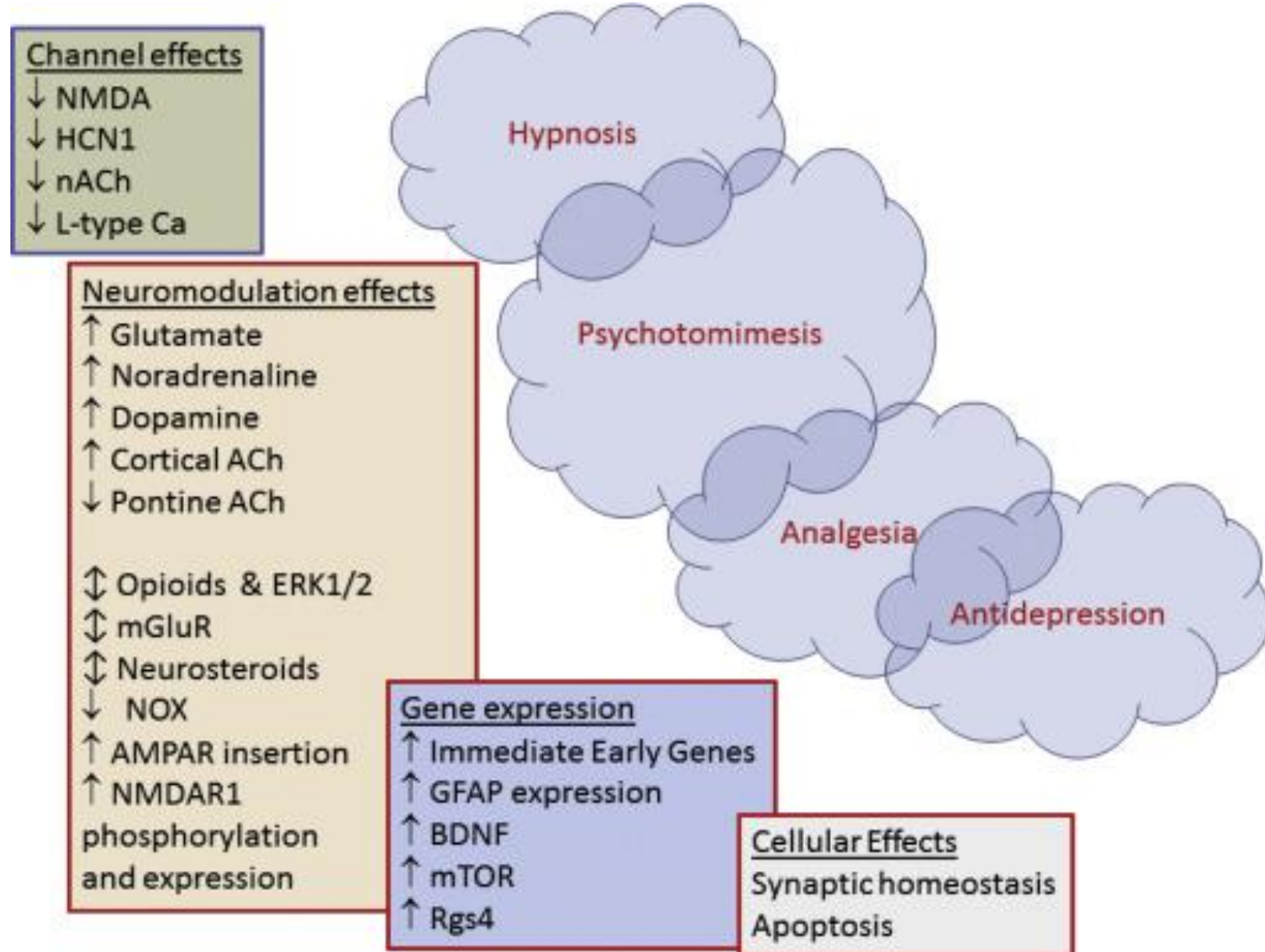


Fig. 1 Chemical structures of the *N*-methyl-D-aspartate receptor antagonist ketamine. An asymmetric carbon atom in the C2 position creates a chiral structure, resulting in two optical isomers



Ketamina



Sleigh J, Harvey M, Voss L, Denny B. Ketamine – More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care. 2014;4(2):76-81. doi:10.1016/j.tacc.2014.03.002

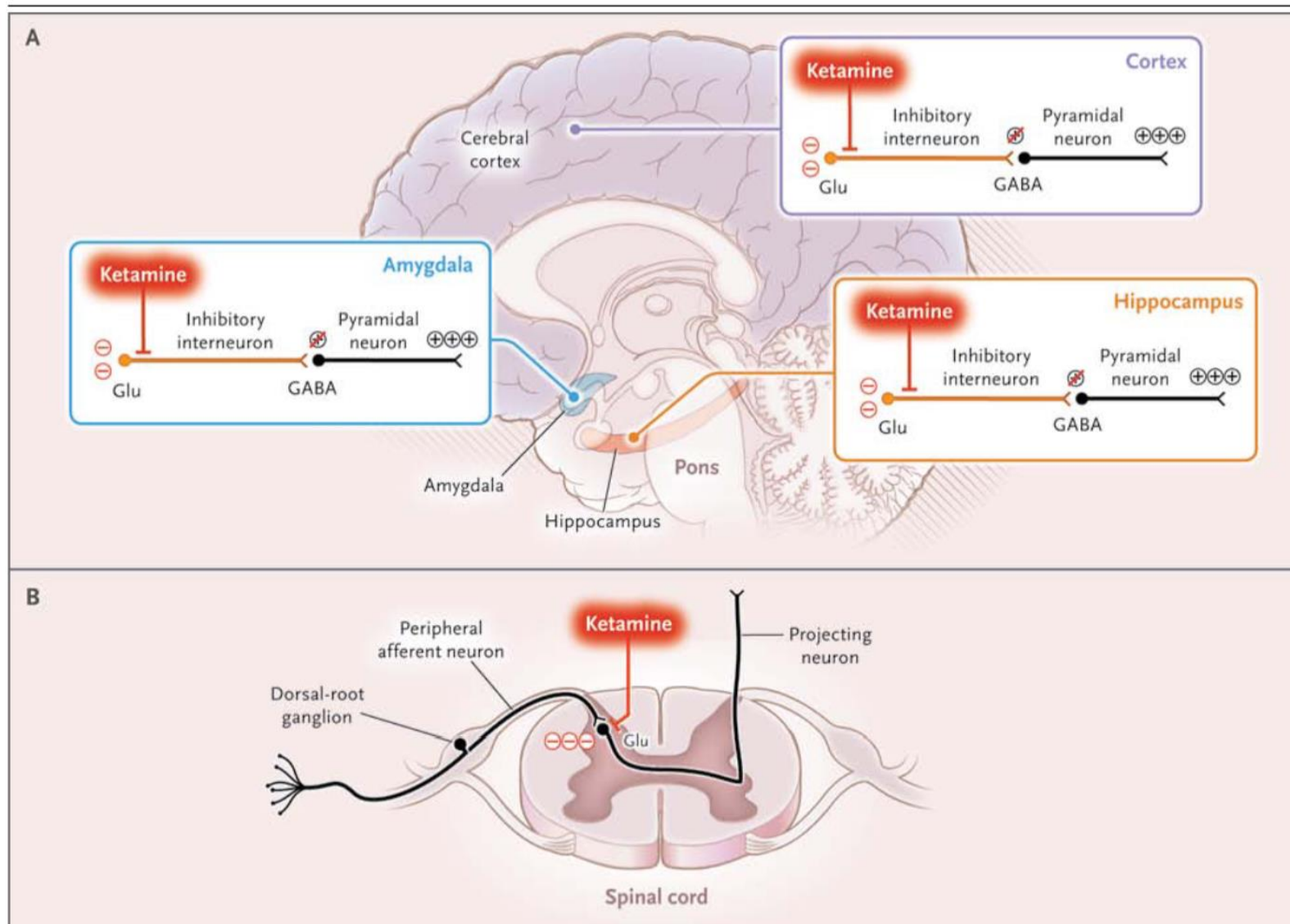
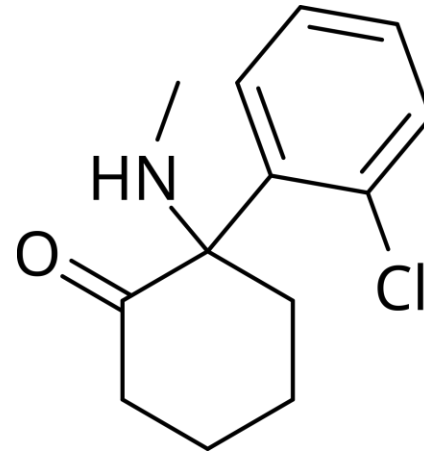


Figure 4. Unconsciousness and Active Brain States.

Ketamine binds preferentially to *N*-methyl-D-aspartate (NMDA) receptors on inhibitory interneurons in the cortex, limbic system (amygdala), and hippocampus, promoting an uncoordinated increase in neural activity, an active electroencephalographic pattern, and unconsciousness, as shown in Panel A. In the spinal cord, ketamine decreases arousal by blocking NMDA glutamate (Glu)–mediated nociceptive signals from peripheral afferent neurons in the dorsal-root ganglion to projecting neurons, as shown in Panel B.



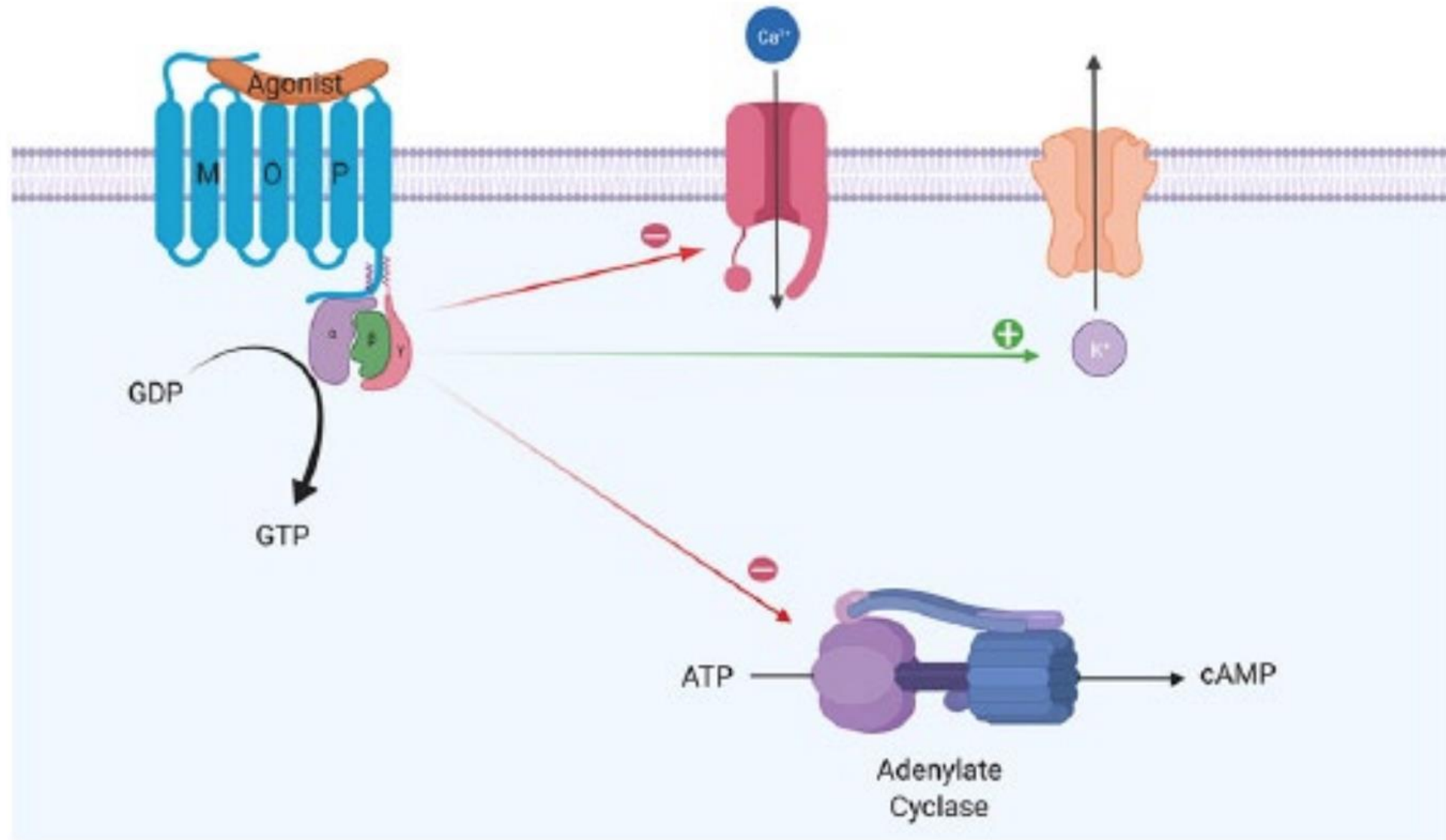
Oppioidi



Gropper MA, Eriksson LI, M.D LAF, et al. Miller's Anesthesia. Elsevier; 2019.

TABLE 24.2 Pharmacologic Actions of Opioids and Opioid Receptors in Animal Models

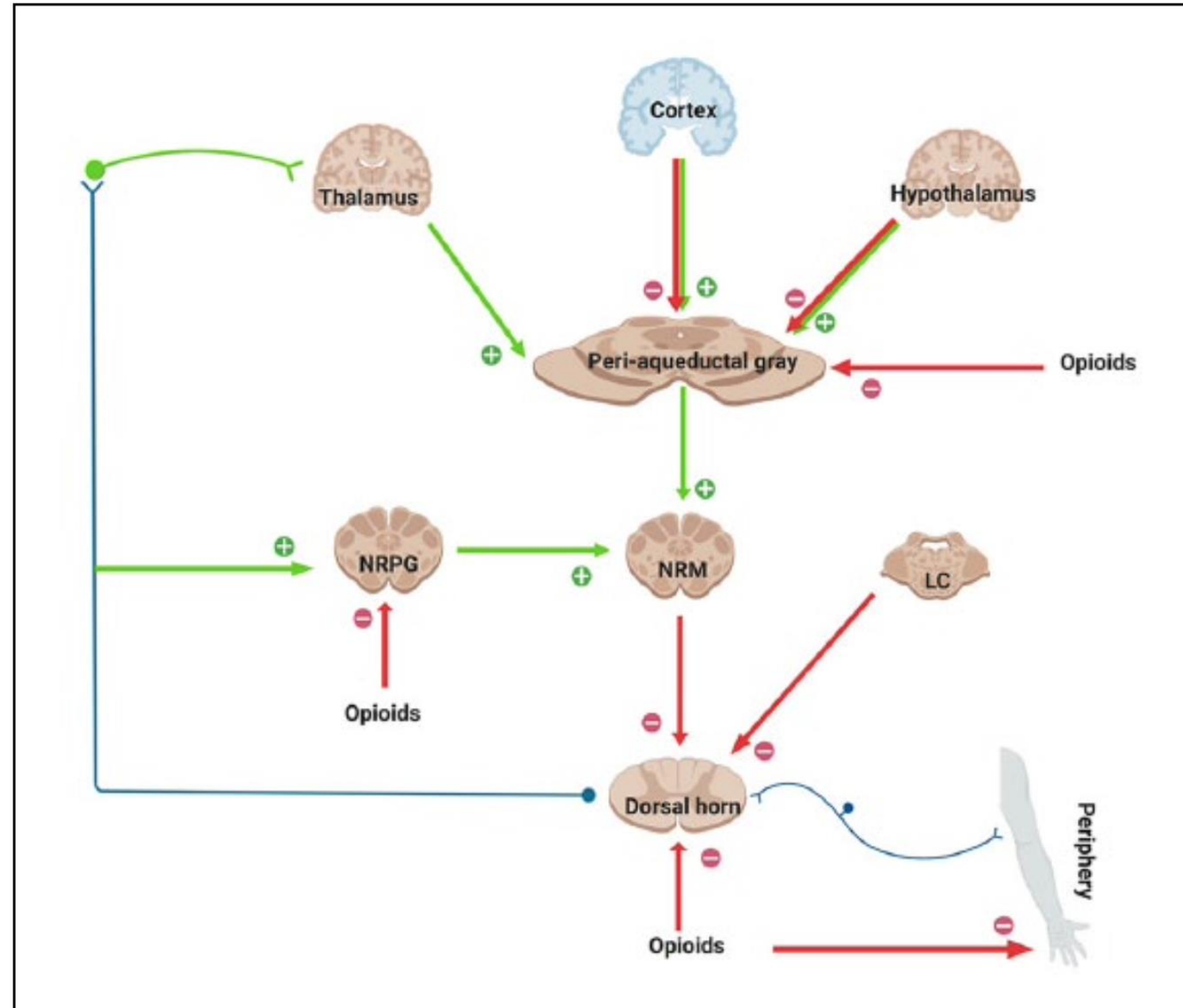
ACTIONS OF			
	Receptor	Agonists	Antagonists
ANALGESIA			
Supraspinal	μ, δ, κ	Analgesic	No effect
Spinal	μ, δ, κ	Analgesic	No effect
Respiratory function	μ	Decrease	No effect
Gastrointestinal tract	μ, κ	Decrease transit	No effect
Psychotomimesis	κ	Increase	No effect
Feeding	μ, δ, κ	Increase feeding	Decrease feeding
Sedation	μ, κ	Increase	No effect
Diuresis	κ	Increase	
HORMONE SECRETION			
Prolactin	μ	Increase release	Decrease release
Growth hormone	μ and/or δ	Increase release	Decrease release
NEUROTRANSMITTER RELEASE			
Acetylcholine	μ	Inhibit	
Dopamine	δ	Inhibit	

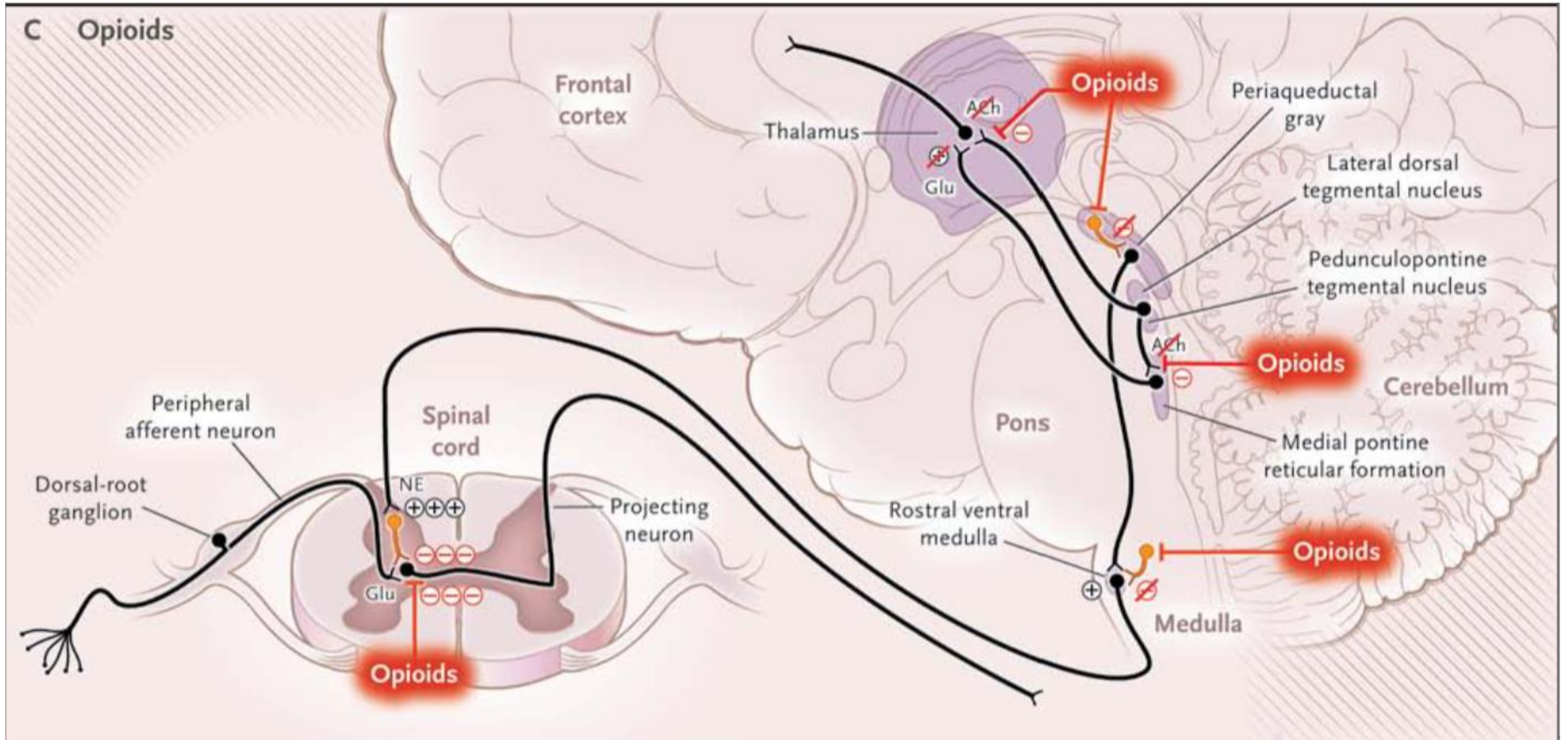


Stimolo vie discendenti

- Grigio periacqueduttale PAG e *nucleus reticularis paragigantocellularis* (NRPG)
- Attivazione dei neuroni discendenti inibitori
- ↑Attività nucleo del rafe magno (NRM)
- ↑ Output serotoninergico ed encefalinergico sulla sostanza gelatinosa del corno dorsale

Effetto diretto inibitorio sui neuroni nocicettivi della sostanza gelatinosa del midollo spinale

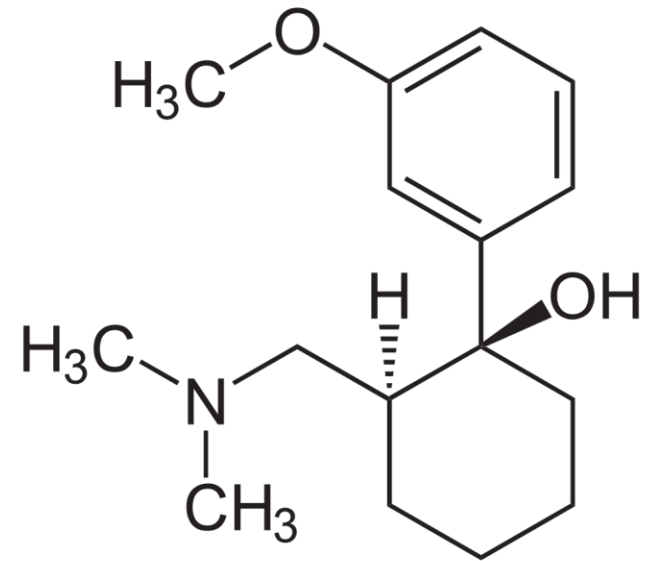
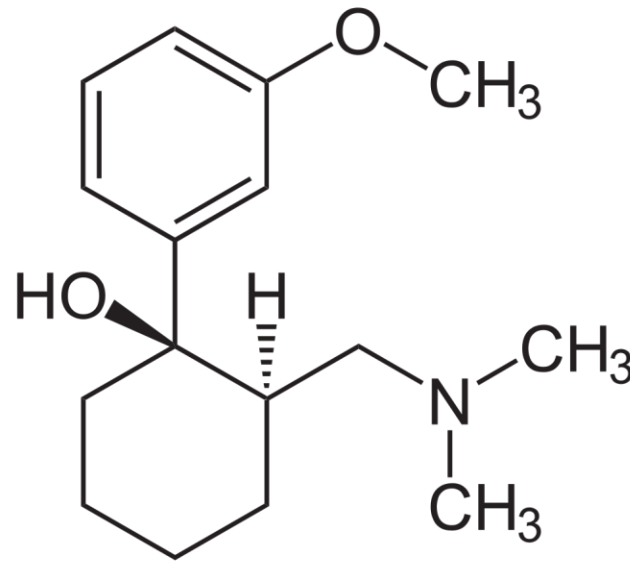




	Morphine	Fentanyl	Alfentanil
Potency (vs morphine)	1	100	10–20
pK _a	8.0	8.4	6.5
Plasma protein bound (%)	30–35	84	90
Volume of distribution (litre kg ⁻¹)	2–4	3–5	0.4–1.0
Blood–brain equilibration rate (min)	120–180	6	1
Terminal half life (h)	2–3	3.5	1.6
Relative hydrophobicity	1	580	90
Time to relative onset (min)	6	2	1
t _{1/2ke0} (min)	100	6	1
Time to maximum concentration (min)	19	4	2
Relative duration of action (min)	78–96	7	2
Benefits	Long-lasting duration of analgesia; cheapest opioid	Short time to efficacy; better benefit/risk ratio in the elderly	Very short time to efficacy
Disadvantages	Long time to action; peak effect and adverse events may occur 40–60 min after the last administration	Short duration of action; increased risk of accumulation in the obese patient	Very short duration of action

Tramadolo

- (+)-Tramadolo agonista **MOR** e inibitore reuptake di **serotonina**
- (+)-O- desmethyl-tramadol (M1) agonista **MOR** Potenza 6x
- (-)-Tramadolo inibitore reuptake di **noradrenalina**



Attraversa BBE 10 min dopo assunzione orale

Escrezione **renale** 90%

Massima dose 400 mg/die

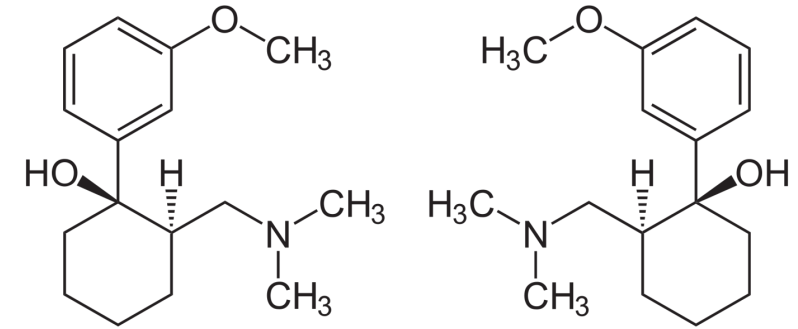


- ultra-rapid metabolizer CYP450 2D6
→ depressione respiratoria
- Interazione SSRI / SNRI / Triciclici
→ **Sindrome serotoninergica**



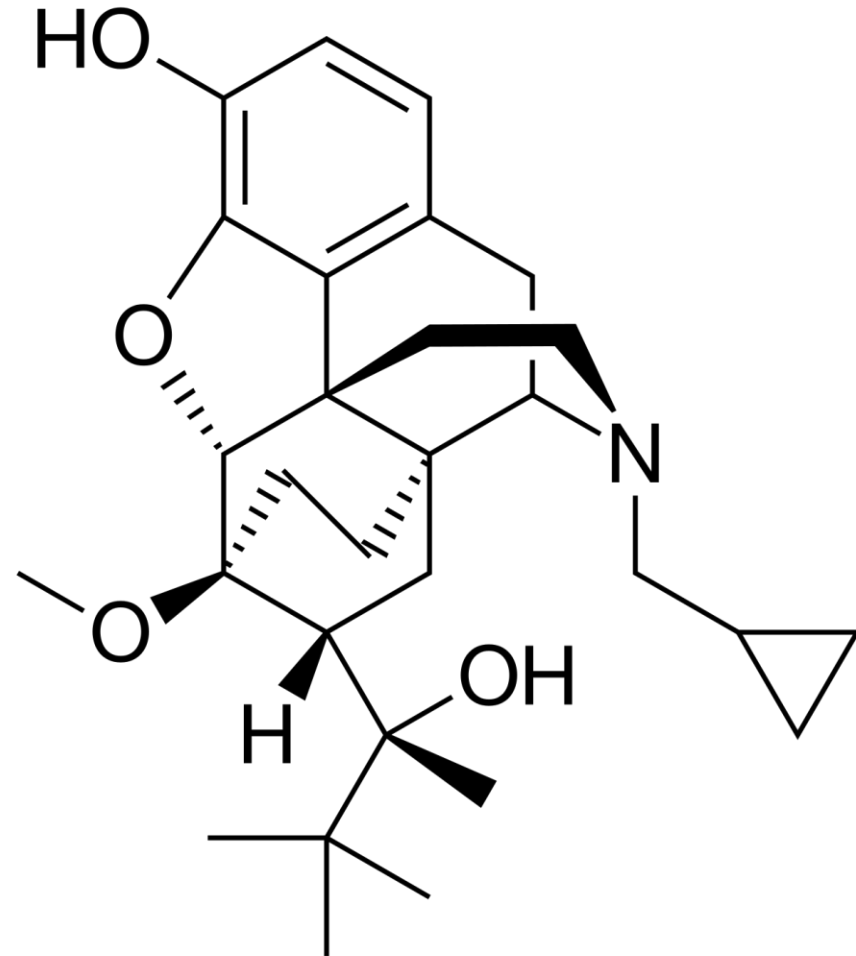
1–10% Caucasici
3–4% Afro-American
1–2% Asiatici

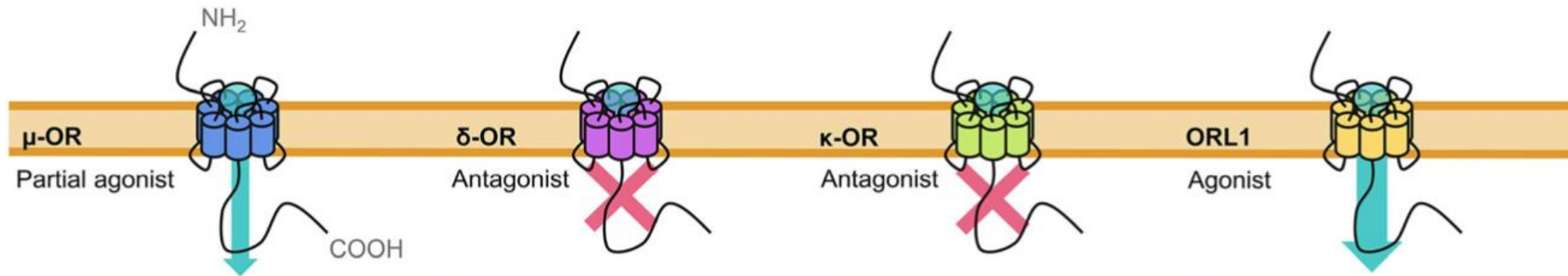
Più elevata in popolazioni
medio-orientali e Ebrei
Ashkenazi



Buprenorfina

Buprenorphine is a Schedule III opioid analgesic with unique pharmacodynamic and pharmacokinetic properties that may be preferable to those of Schedule II full μ -opioid receptor agonists. The structure of buprenorphine allows for multimechanistic interactions with opioid receptors μ , δ , κ , and opioid receptor-like 1. Buprenorphine is considered a partial agonist with very high binding affinity for the μ -opioid receptor, an antagonist with high binding affinity for the δ - and κ -opioid receptors, and an agonist with low binding affinity for the opioid receptor-like 1 receptor. Partial agonism at the μ -opioid receptor does not provide partial analgesia, but rather analgesia equivalent to that of full μ -opioid receptor agonists. In addition, unlike full μ -opioid





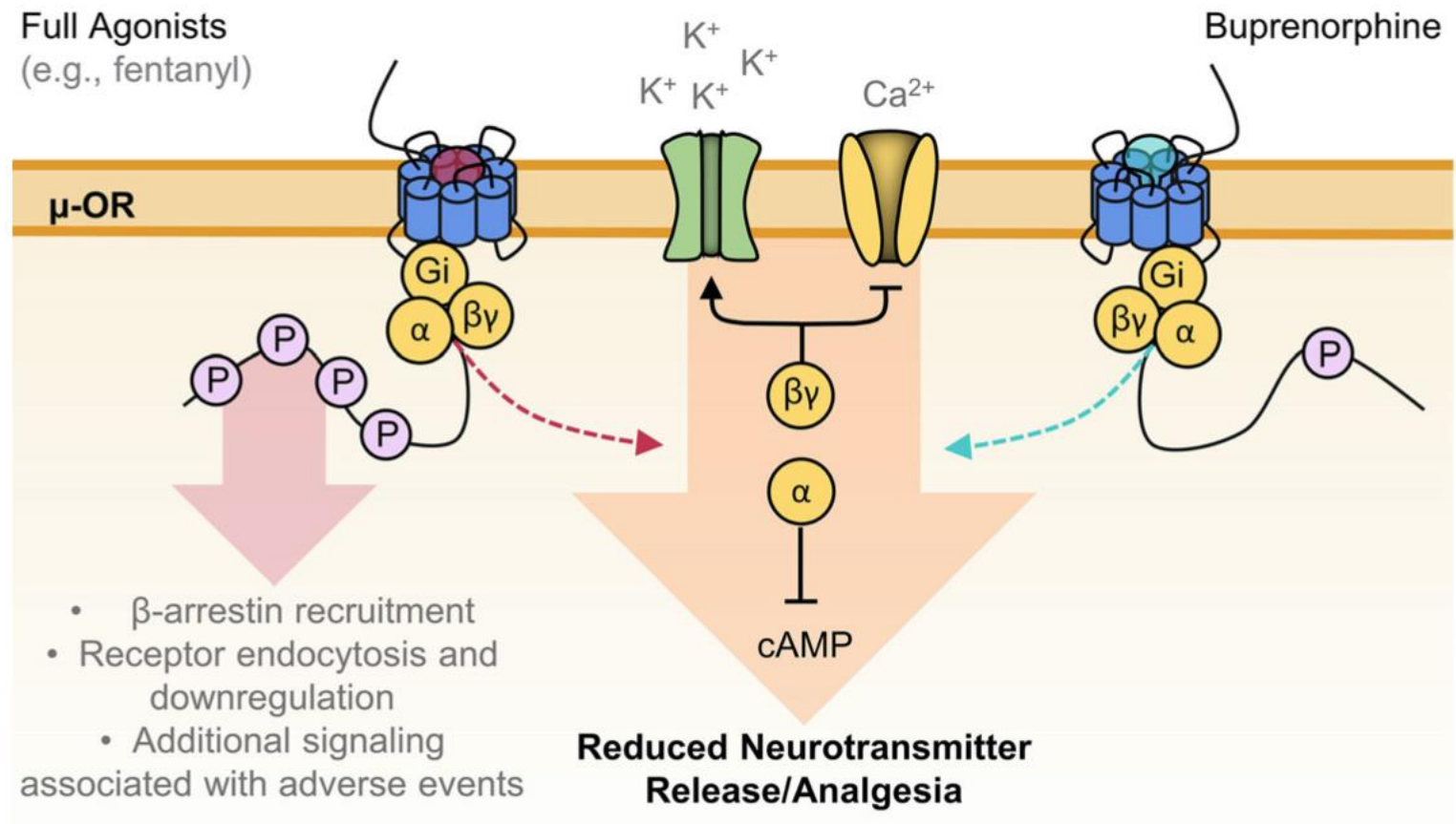
- Potent analgesia
- Ceiling on respiratory depression and euphoria
- Limited impact on GI motility
- Limited physical dependence, abuse potential, and withdrawal symptoms
- Reduced immunosuppression and impact on the HPA axis
- Reduction in suicidal thoughts, anxiety, and depression
- Limited dysphoria

- Anti-opioid effects
- Myocardial protection
- Limited impact on GI motility*
- Limited respiratory depression*

- Reduced depression, dysphoria, suicidal tendencies, anxiety, and hostility
- Limited potential for addiction* and tolerance
- Reduced immunosuppression

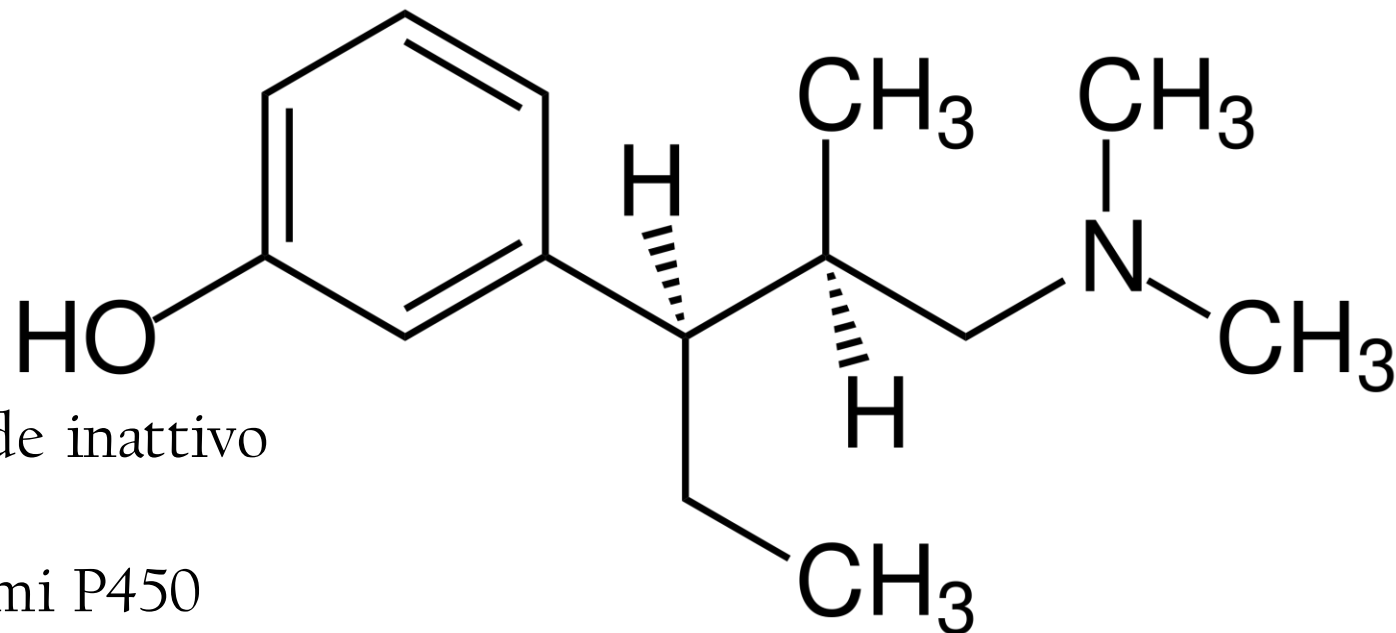
- Enhanced spinal analgesia
- Reduced supraspinal analgesia
- Diminished opioid-rewarding effects
- Limited potential for tolerance

Buprenorphine also demonstrates a **ceiling effect on serine 375 phosphorylation**, whereas full μ -opioid receptor agonists show continuously elevated phosphorylation levels with increasing doses, consistent with the known dose **ceiling effect of buprenorphine on respiratory depression** [36, 37, 39, 40]. This unique μ -



Tapentadolo

- Agonista **MOR** + inibitore **reuptake della noradrenalina**
- Effetto opioid sparing
- Forte analgesia e **basso “μ-load”**
- Metabolita tapentadolo-O-glucuronide inattivo
- Non significativa interazione su enzimi P450



Analgesia in pediatrics

Lago et al.

Guidelines for procedural pain in the newborn

Analgesics	Minimum age Germany ^a	Minimum age US ^b
Morphine ^c	Neonates	Not approved ⁹⁶
Hydromorphone	1 year	Not approved ⁹⁷
Fentanyl	2 years	2 years ^{98,99}
Oxycodone	12 years	11 years ¹⁰⁰
Tapentadol	2 years	Not approved
Tramadol	1 year	^d 12 years ⁹⁵
Metamizole	3 months	Not approved ⁹³
Paracetamol	Term neonates	Neonates ¹⁰¹
Ibuprofen	3 months	6 months ¹⁰²
Diclofenac	6 years	Not approved ¹⁰³
Aspirin	12 years	Not approved ¹⁰⁴
Combination products		
Codeine/paracetamol	12 years	^d 12 years ⁹⁴
Dihydrocodeine/ aspirin/caffeine	Not available	^d 12 years ¹⁰⁵
Butalbital/paraceta- mol/caffeine	Not available	12 years ¹⁰⁶

Table 3 Analgesic and anaesthetic drugs used in newborn

Drug	Dose	Safety considerations
Local anaesthetic		
EMLA lidocaine–prilocaine 5% cream	0.5–1 g under non-adhesive occlusive dressing 60 min before procedure	Check for any local reactions (hyperaemia, flushing, vaso-constriction) every 15 min
Liposomal lidocaine 4% cream	1 g under occlusive dressing 30 min before procedure	
Lidocaine 1%	2–4 mg/kg buffered with sodium bicarbonate 1:10	Maximum dosage 5 mg/kg
Oxybuprocaine 0.4% and tetracaine 1% eye drops	1 drop per eye	
Systemic analgesic		
	Bolus dose	Infusion dose
Morphine	50–100 mcg/kg i.v. in 60 min	10–40 mcg/kg/h
Fentanyl	0.5–3 mcg/kg i.v. in 30 min	0.5–3 mcg/kg/h
Acetaminophen or paracetamol	10–15 mg/kg i.v. in 15 min every 6–8 h (i.v.–oral)	
General anaesthetic		
Ketamine	0.5–2 mg/kg i.v.	0.5–1 mg/kg/h
Thiopental	2–6 mg/kg i.v.	
Propofol	2.5 mg/kg	0.5–4 mg/kg/h
Muscle relaxants		
Vecuronium	0.1 mg/kg i.v.	0.05–0.1 mg/kg/h
Mivacurium	0.2–0.3 mg/kg i.v.	
Epidural anaesthetic		
Bupivacaine 0.08–0.1%		0.25 mg/kg/h for max 24–36 h
Ropivacaine	0.9 mg/kg	0.2 mg/kg/h
Levobupivacaine 0.25%	2.5 mg/kg	0.25–0.75 mg/kg/h

Lago P, Garetti E, Merazzi D, et al. Guidelines for procedural pain in the newborn. *Acta Paediatr.* 2009;98(6):932-939. doi:10.1111/j.1651-2227.2009.01291.x

Eerdeken M, Beuter C, Lefeber C, van den Anker J. The challenge of developing pain medications for children: therapeutic needs and future perspectives. *J Pain Res.* 2019;12:1649-1664. doi:10.2147/JPR.S195788