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FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG
MEDIZINISCHE FAKULTÄT

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Endogenous pain inhibitory mechanisms

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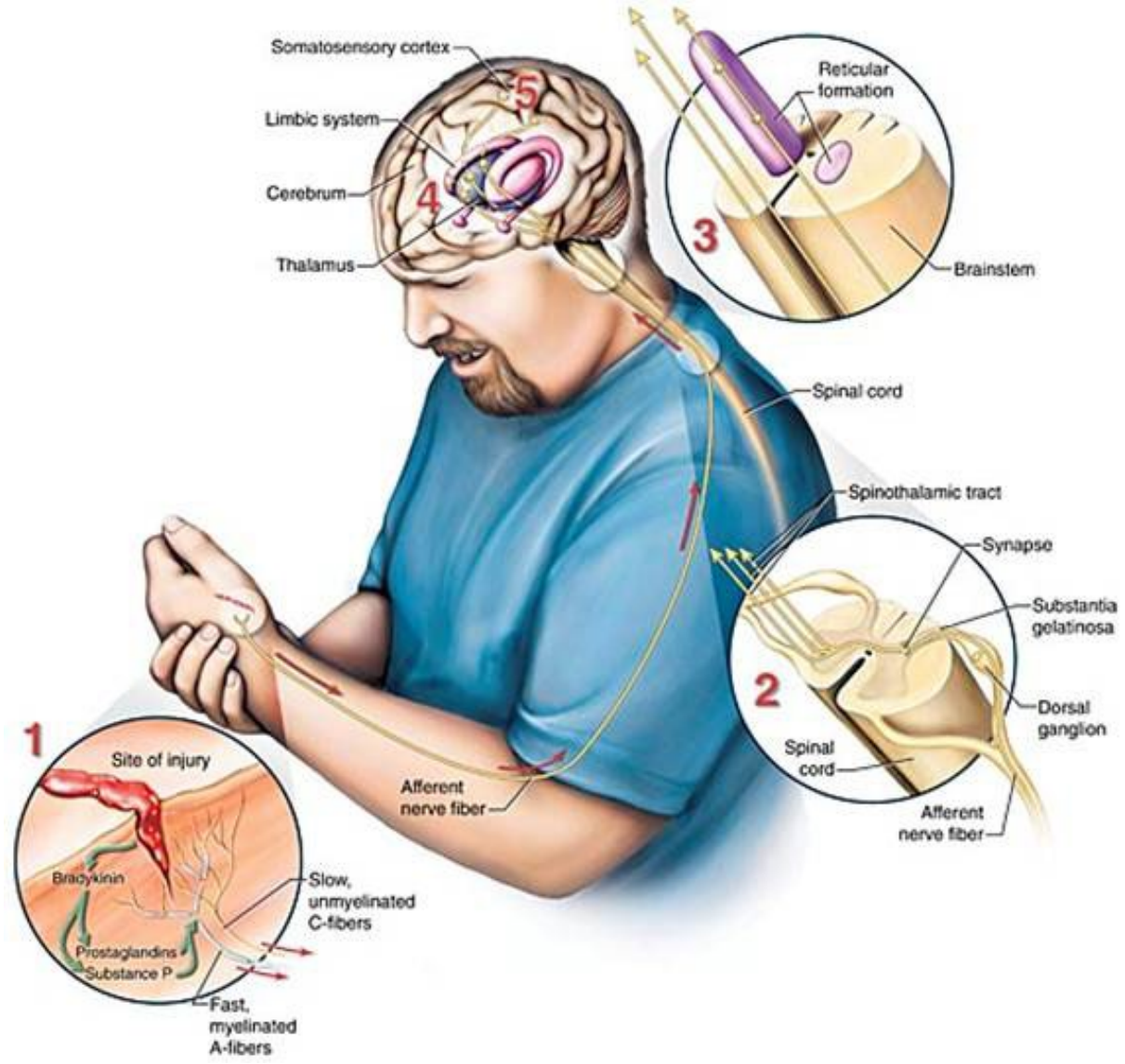
Definition of pain and nociception



„Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

International Association for the Study of Pain, 1979

Nociception: all peripheral and central neuronal processes that can lead to pain

Pain: sensation, perception, cognition, experience; pain requires consciousness

Adressed topics

- **Retrospection:** Basic organization of ascending and descending pain modulating pathways
- **Recollection:** Molecular mechanisms of nociceptive transmission and central sensitization
- **Controlling spinal nociception:** Interneurons and molecular antinociceptive mechanisms
- **Descending pathways:** On and Off cells in the rostral ventromedial medulla
- **Supraspinal antinociceptive mechanisms:** Diffuse inhibitory control systems (DNIC)
- **Central pain inhibition:** Stress- and exercise-induced hypoalgesia and acupuncture

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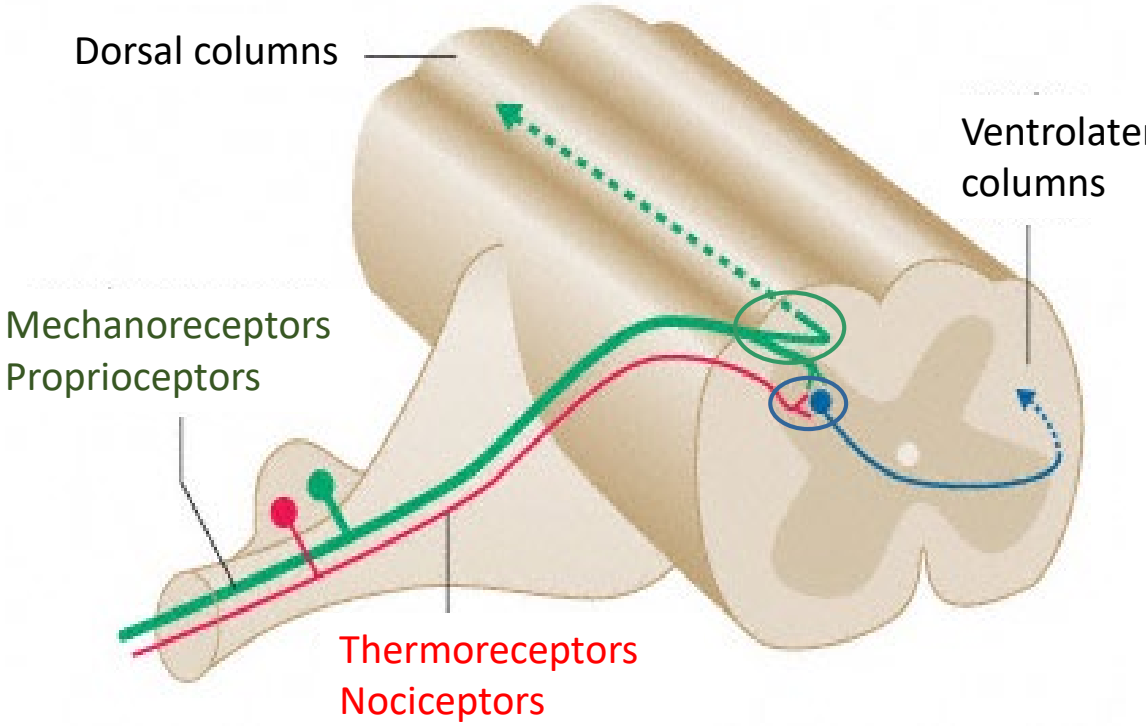
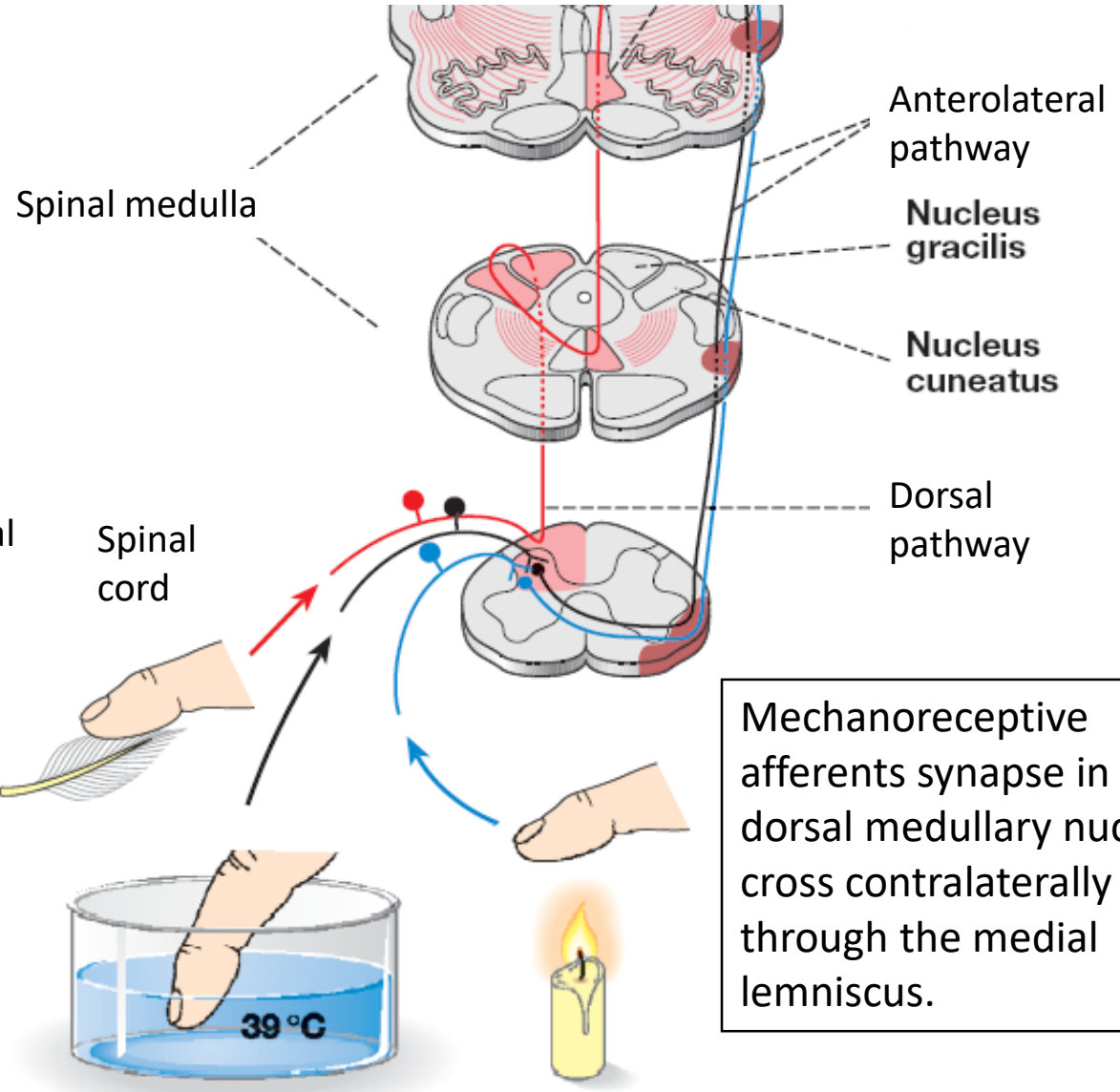
Ascending sensory spinal pathways

Mechanoreceptive afferents (Aβ fibers) send collaterals into the dorsal horn; the main pathways ascent in the ipsilateral dorsal columns. Nociceptive and thermoreceptive afferents (Aδ and C fibers) synapse in the dorsal horn on second order neurons, which ascend in the antero-lateral columns.



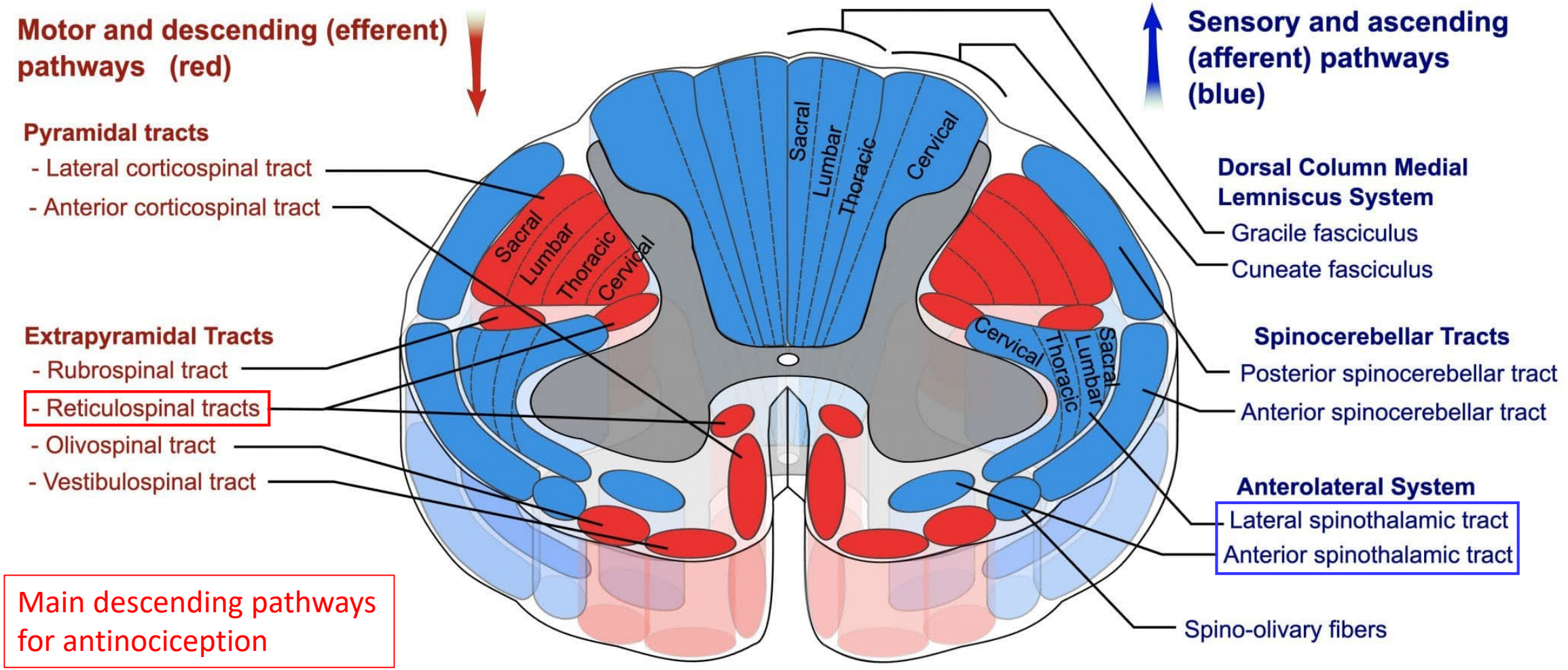
Schmidt/Unsicker Teil B Abb. 10-6



Mechanoreceptive afferents synapse in the dorsal medullary nuclei cross contralaterally through the medial lemniscus.

Deetjen/Speckmann/Hescheler Abb. 3-1

Descending and ascending spinal pathways



Main descending pathways for antinociception

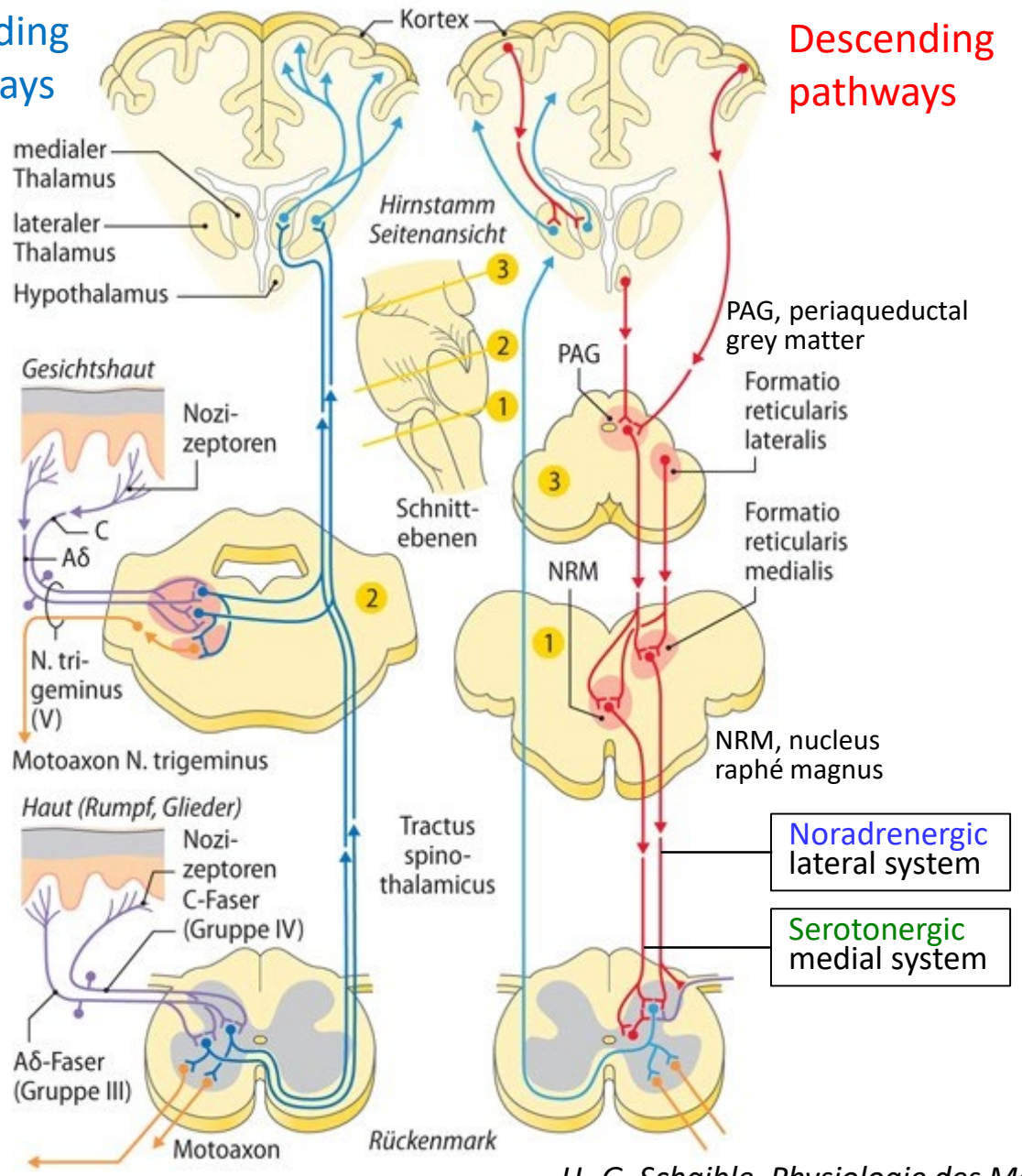
Main ascending pathways for nociception

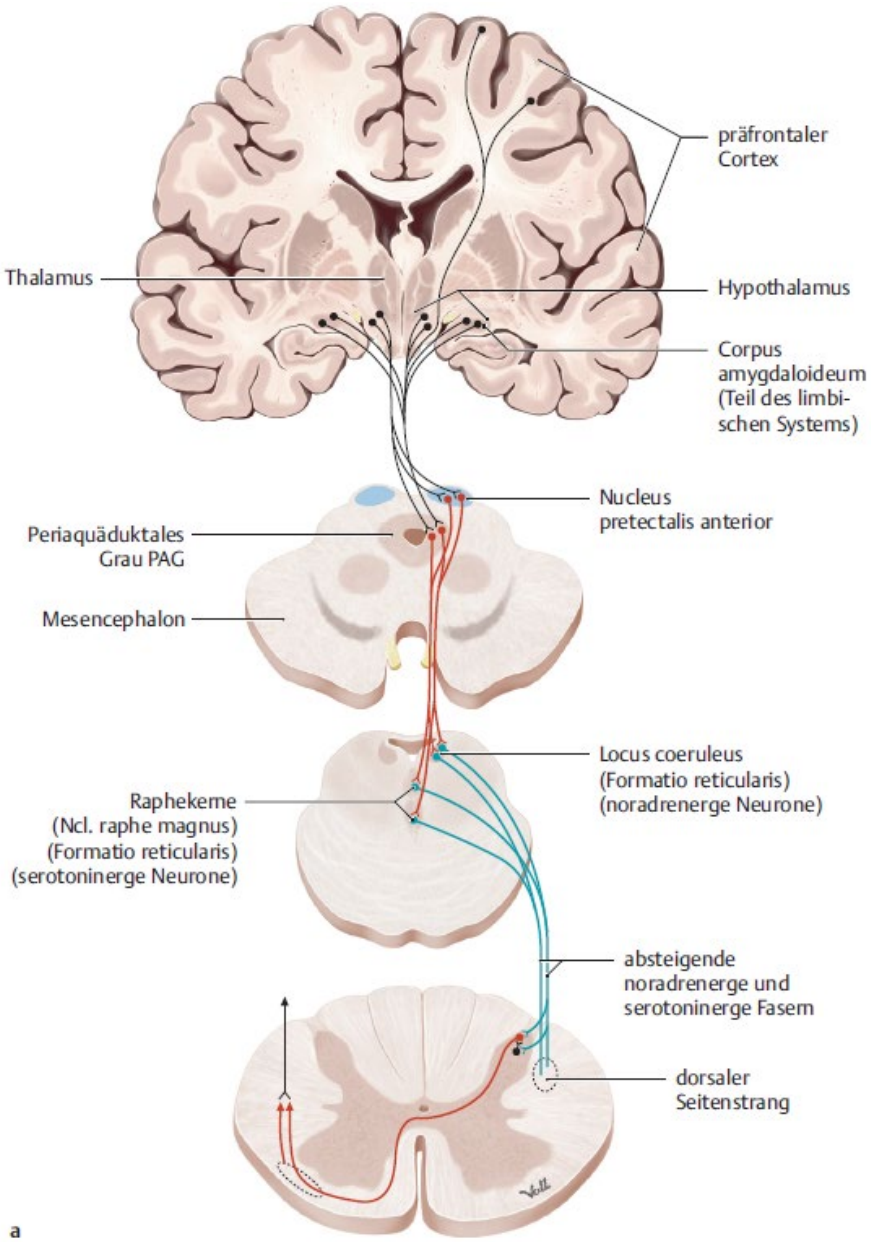
https://geekymedics.com/the-descending-tracts-of-the-central-nervous-system/

Ascending and descending spinal pathways

Ascending pathways

Descending pathways

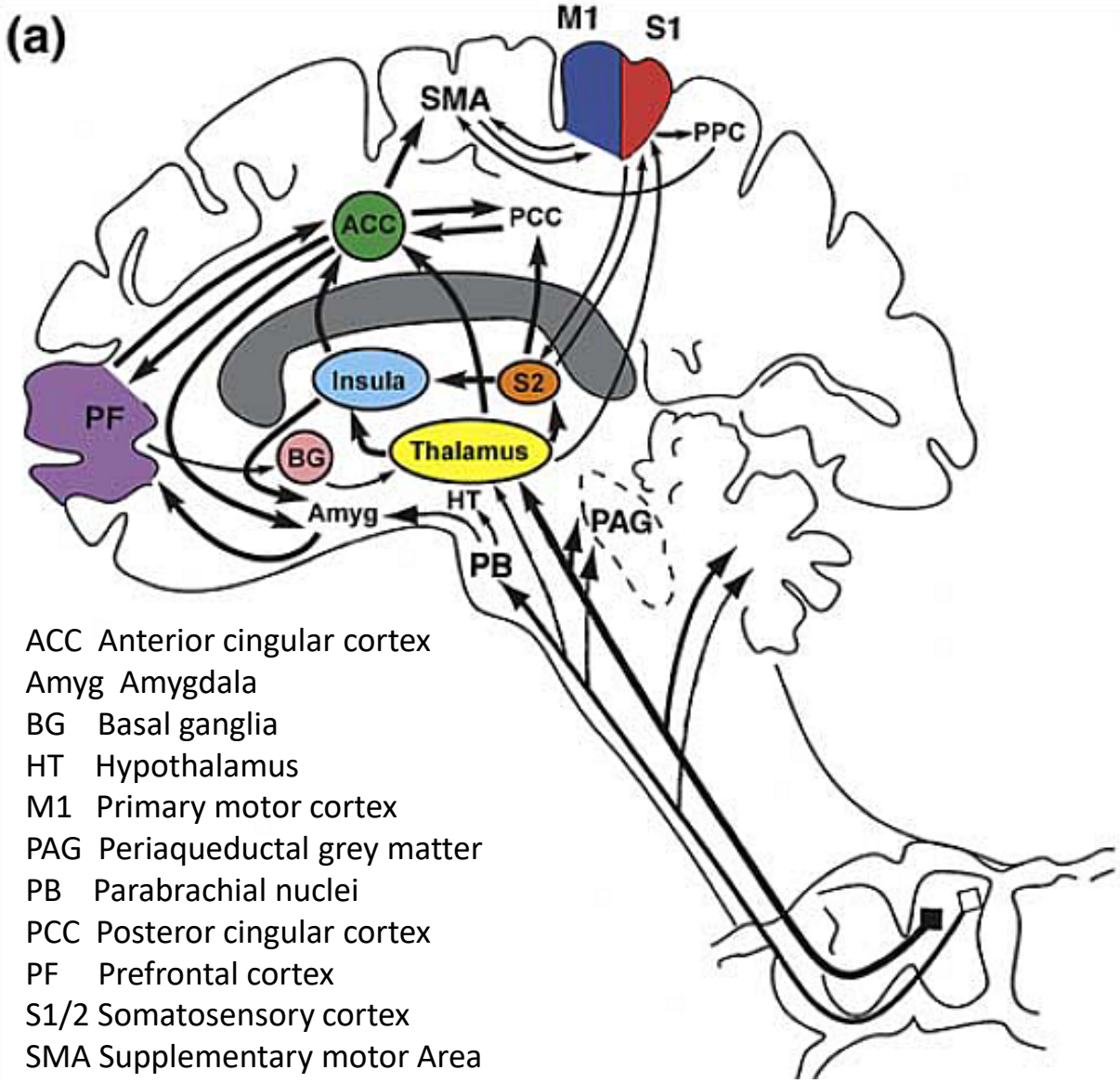




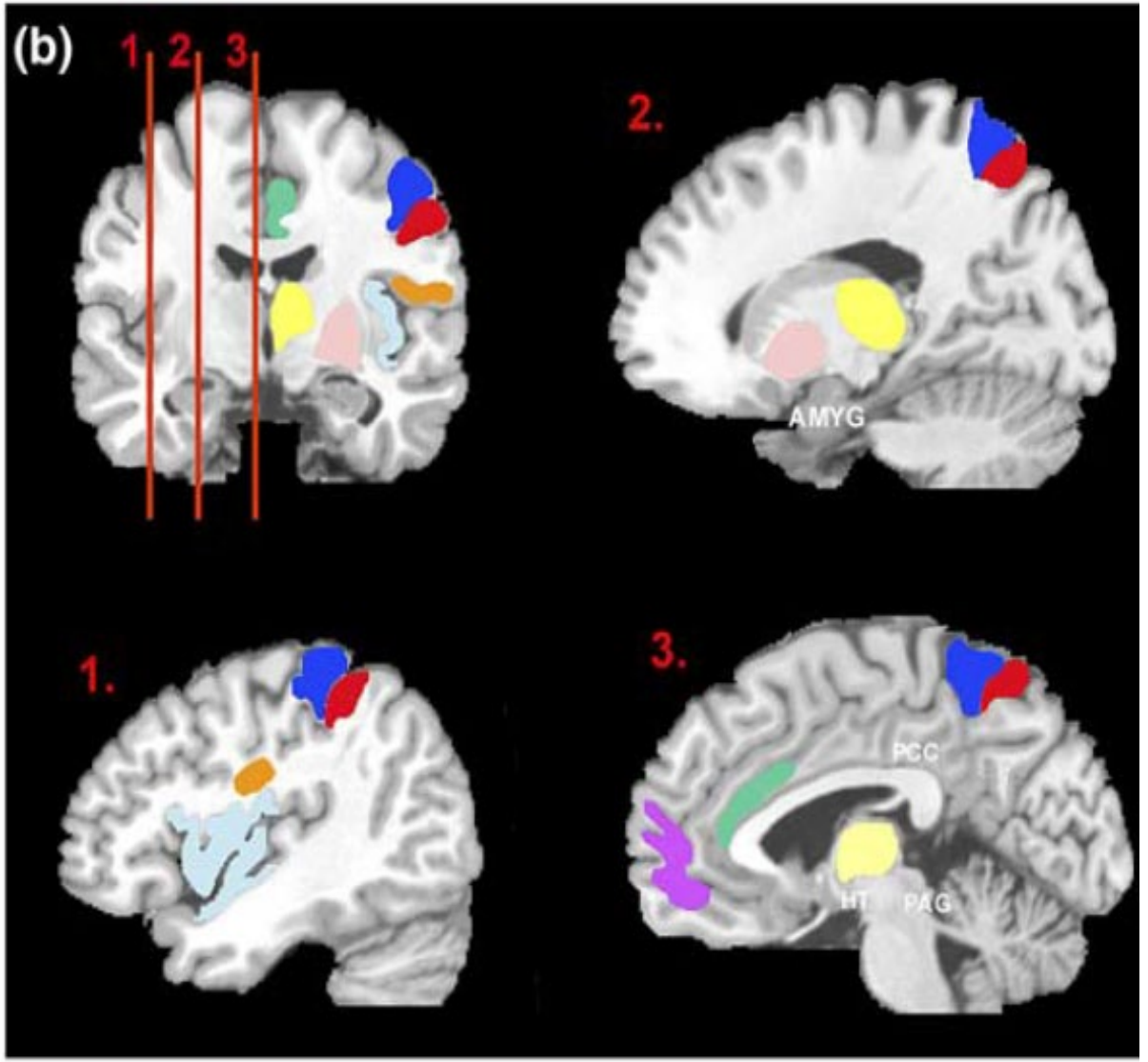
H.-G. Schaible, Physiologie des Menschen, Springer

Schünke et al. Prometheus, Thieme 2012

Ascending pathways and cerebral areas for pain processing

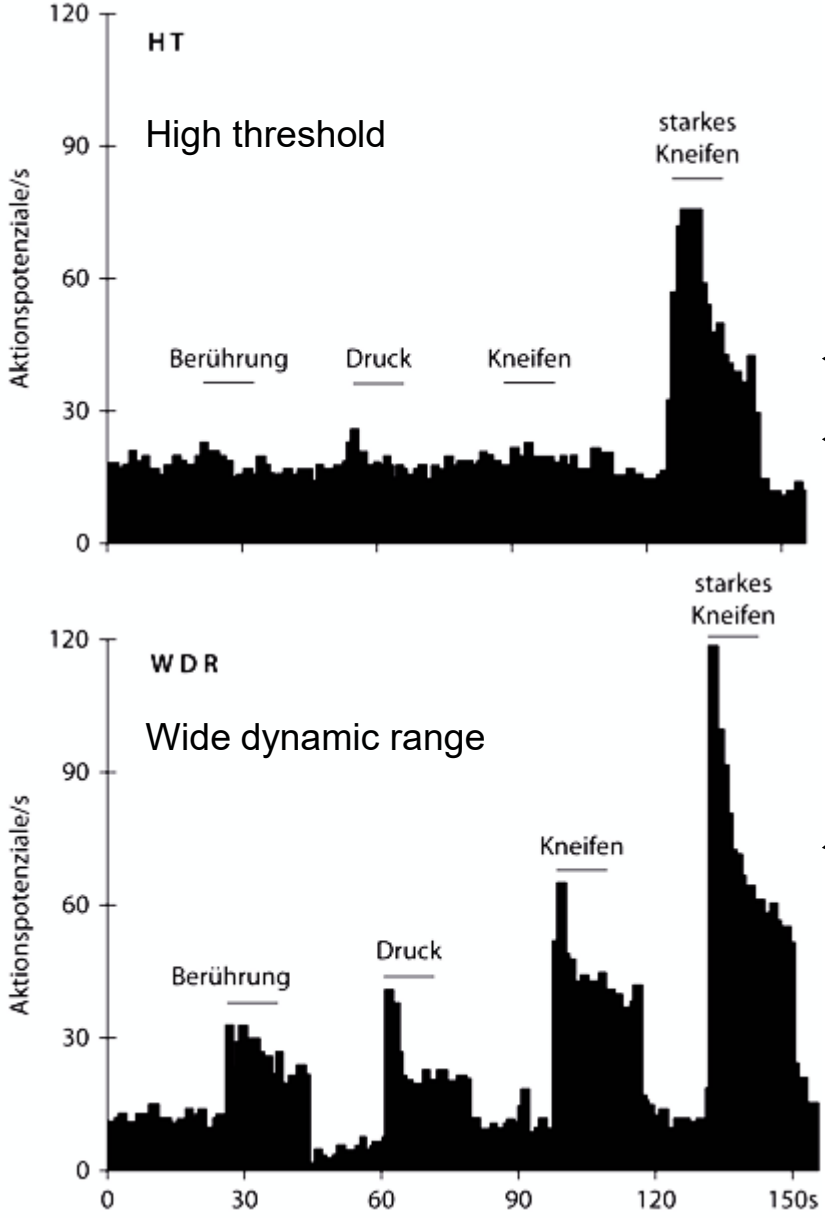


ACC Anterior cingular cortex
Amyg Amygdala
BG Basal ganglia
HT Hypothalamus
M1 Primary motor cortex
PAG Periaqueductal grey matter
PB Parabrachial nuclei
PCC Posteror cingular cortex
PF Prefrontal cortex
S1/2 Somatosensory cortex
SMA Supplementary motor Area

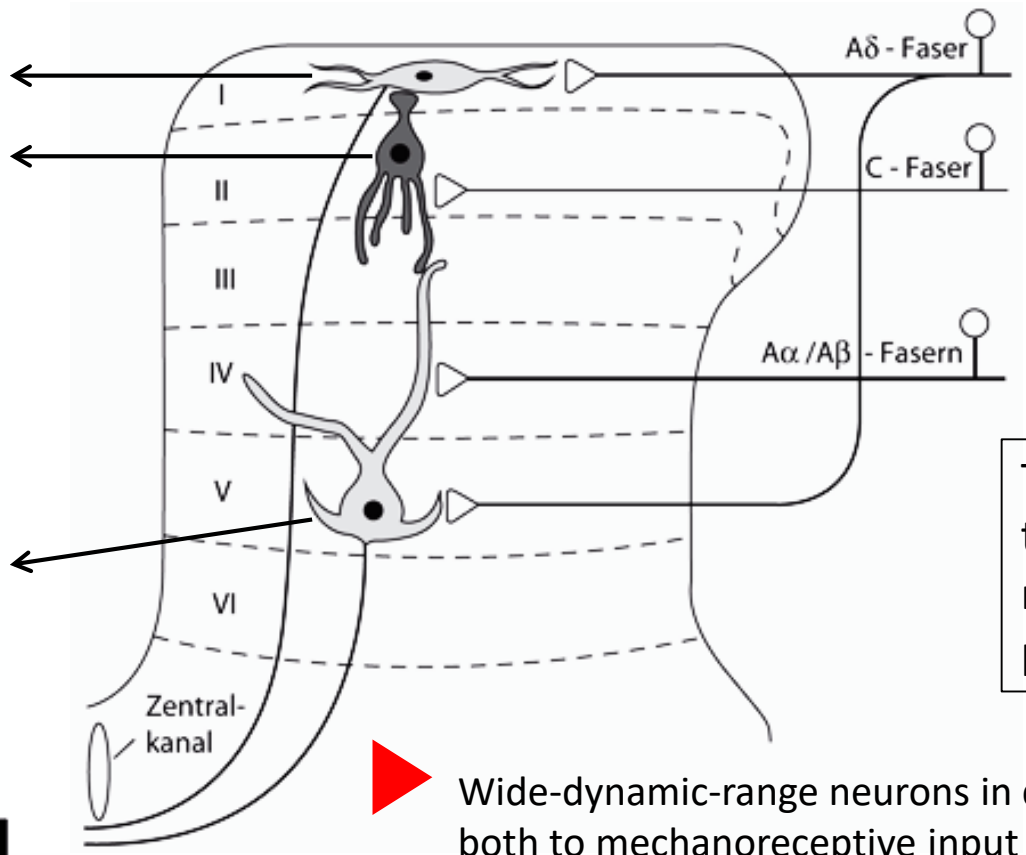


A.V. Apkarian et al, Eur J Pain 2005; 9: 463

Basic types of nociceptive neurons in the spinal dorsal horn



Nociception-specific neurons in the superficial laminae resdponsd specifically to nociceptive input from afferent C- and Aδ-fibers.

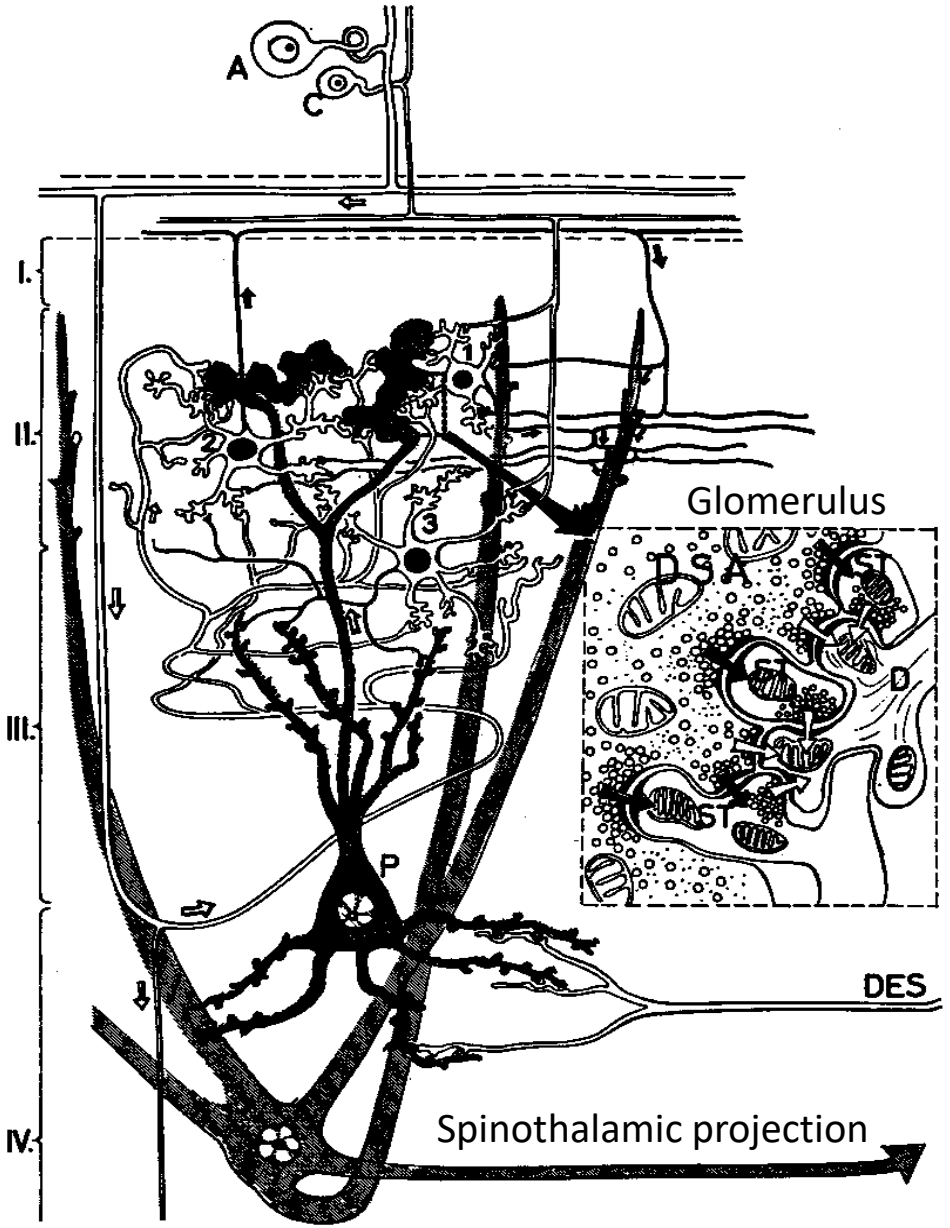


The WDR neurons are the decisive target neurons for endogenous pain control.

Wide-dynamic-range neurons in deep laminae respond both to mechanoreceptive input from afferent A-fibers as well as to nociceptive input from Aδ-fibers.

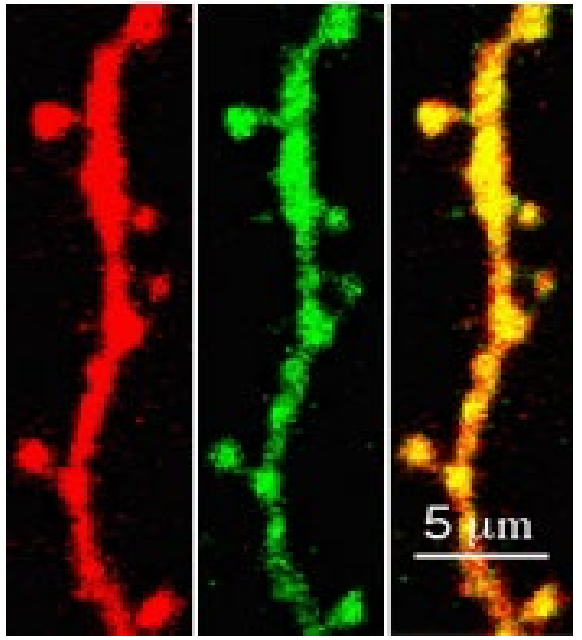
Magerl & Treede, Physiologie von Nozizeption und Schmerz, Springer 2011

Afferent wiring in the spinal dorsal horn and synaptic spines



Willis & Coggeshall 1991

- The synaptic wiring in the dorsal horn is very complex. Deep laminae neurons are connected to superficial laminae by their dendrites. Synaptic contacts can be reciprocal with both pre- and postsynaptic zones. The functional properties of these glomeruli are only rudimentally known.



- Spinothalamic projection neurons are preferably in lamina IV. Descending projections (DES) are indirectly connected with projection neurons through interneurons.

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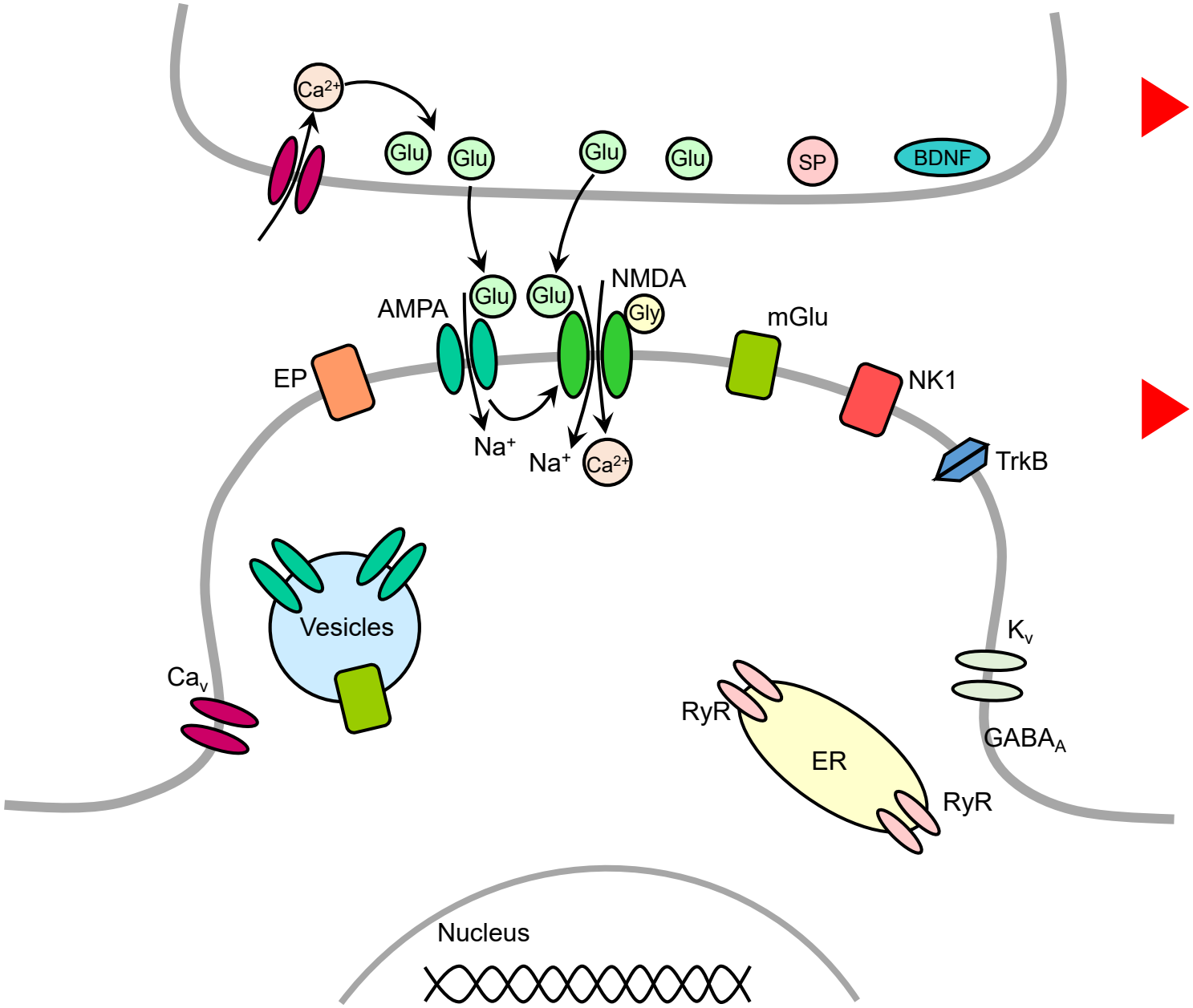
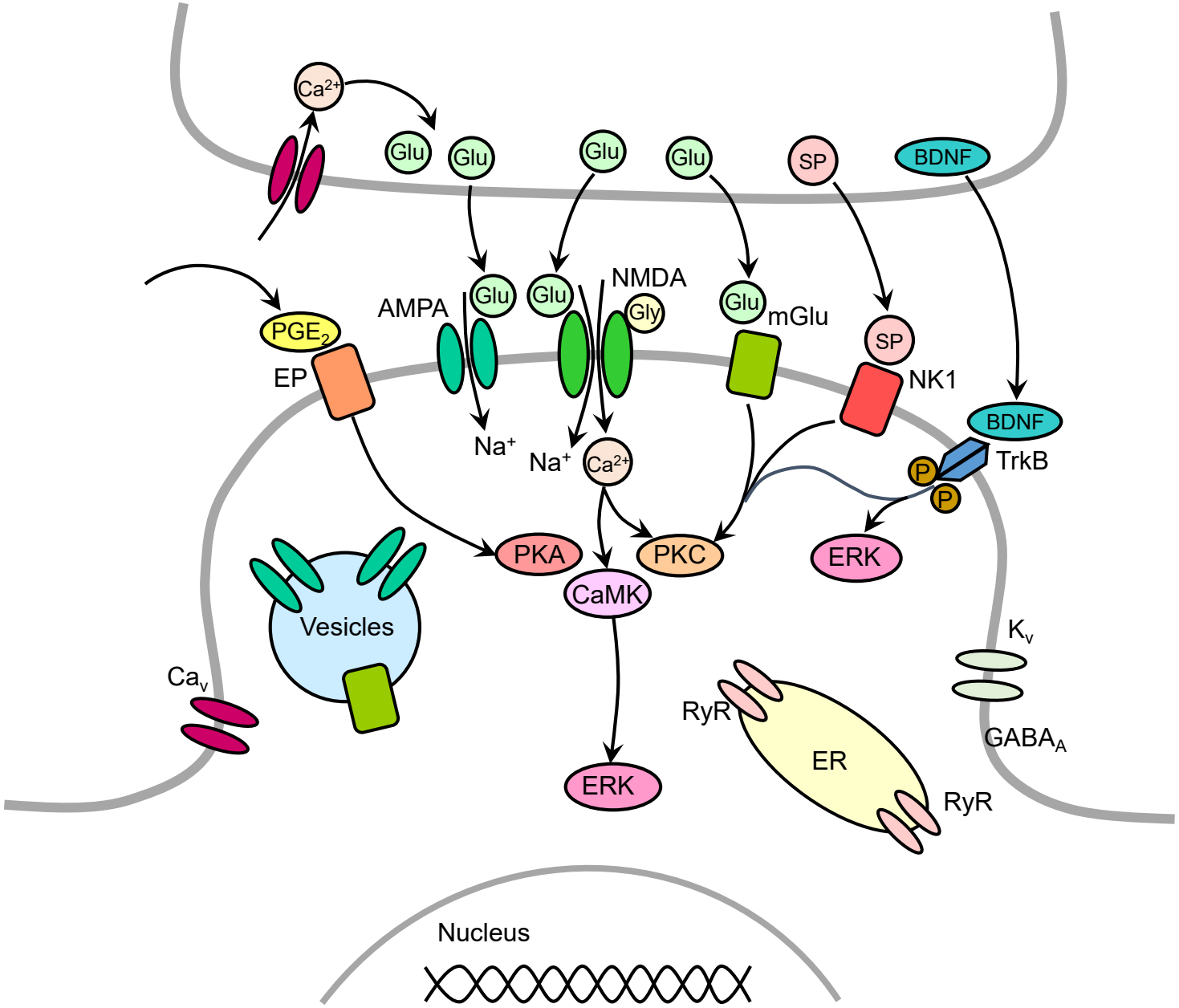
Central sensitization step 1: Activation of glutamate receptors



- Neurotransmitter (glutamate) release from presynaptic terminals is activated by calcium influx through voltage-dependent calcium channels.
- Glutamate is activating different types of glutamate receptor channels of the postsynaptic neuron leading to sodium influx and hence postsynaptic potential as well as calcium inflow through N-methyl-D-aspartate channels.

Central sensitization step 2: Activation of G-protein-coupled receptors

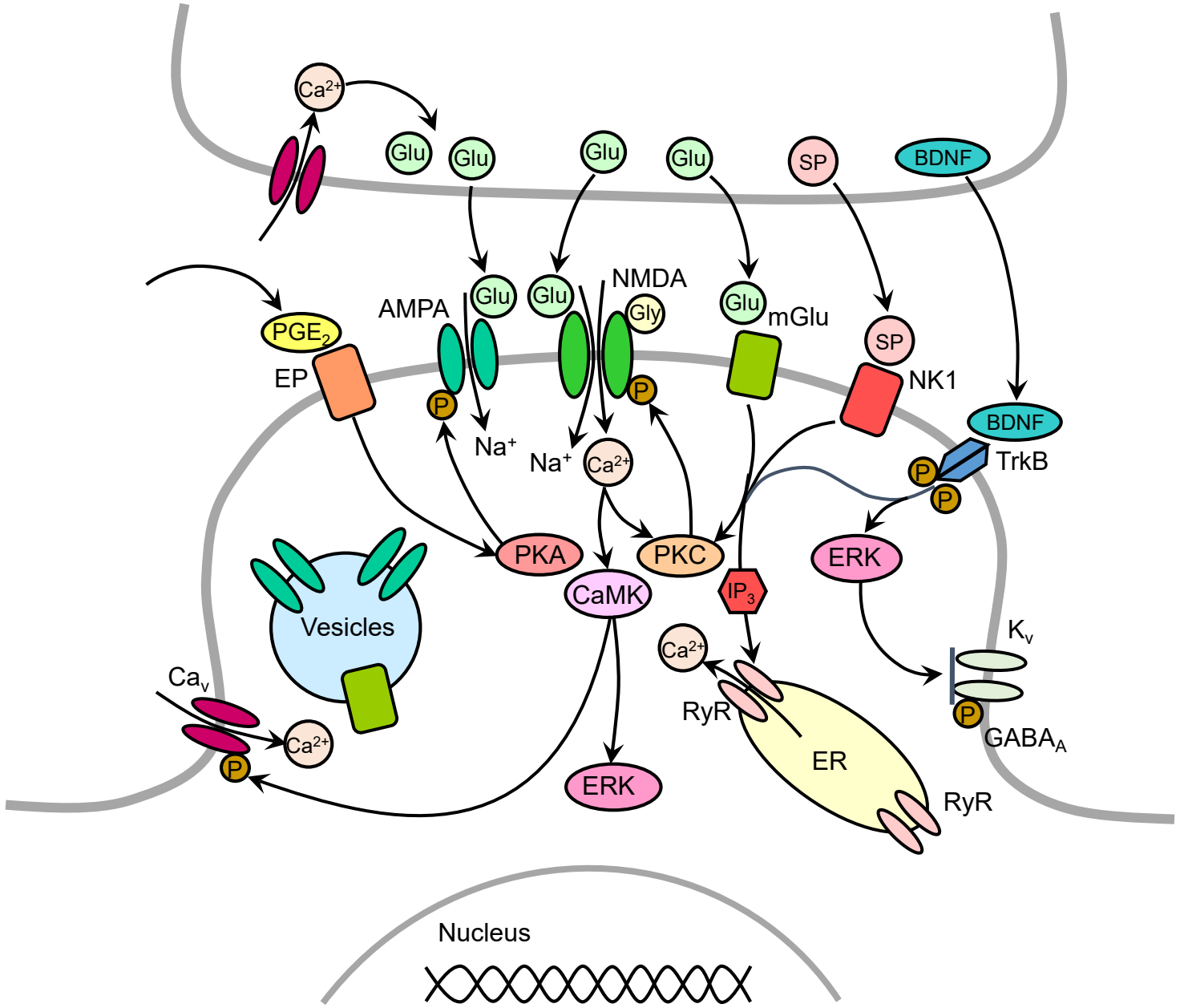


- Postsynaptic metabotropic receptors like prostaglandin receptors (EP), metabotropic glutamate receptors or neurokinin-1 receptors (binding substance P) are G-protein-coupled; through metabolic cascades, they activate different kinds of protein kinases.

Brain-derived neurotrophic factor (BDNF) activates the tyrosine receptor kinase B (TrkB), an autophosphorylating receptor.

All cascades can end up with the activation of the extracellularly regulated kinase (ERK).

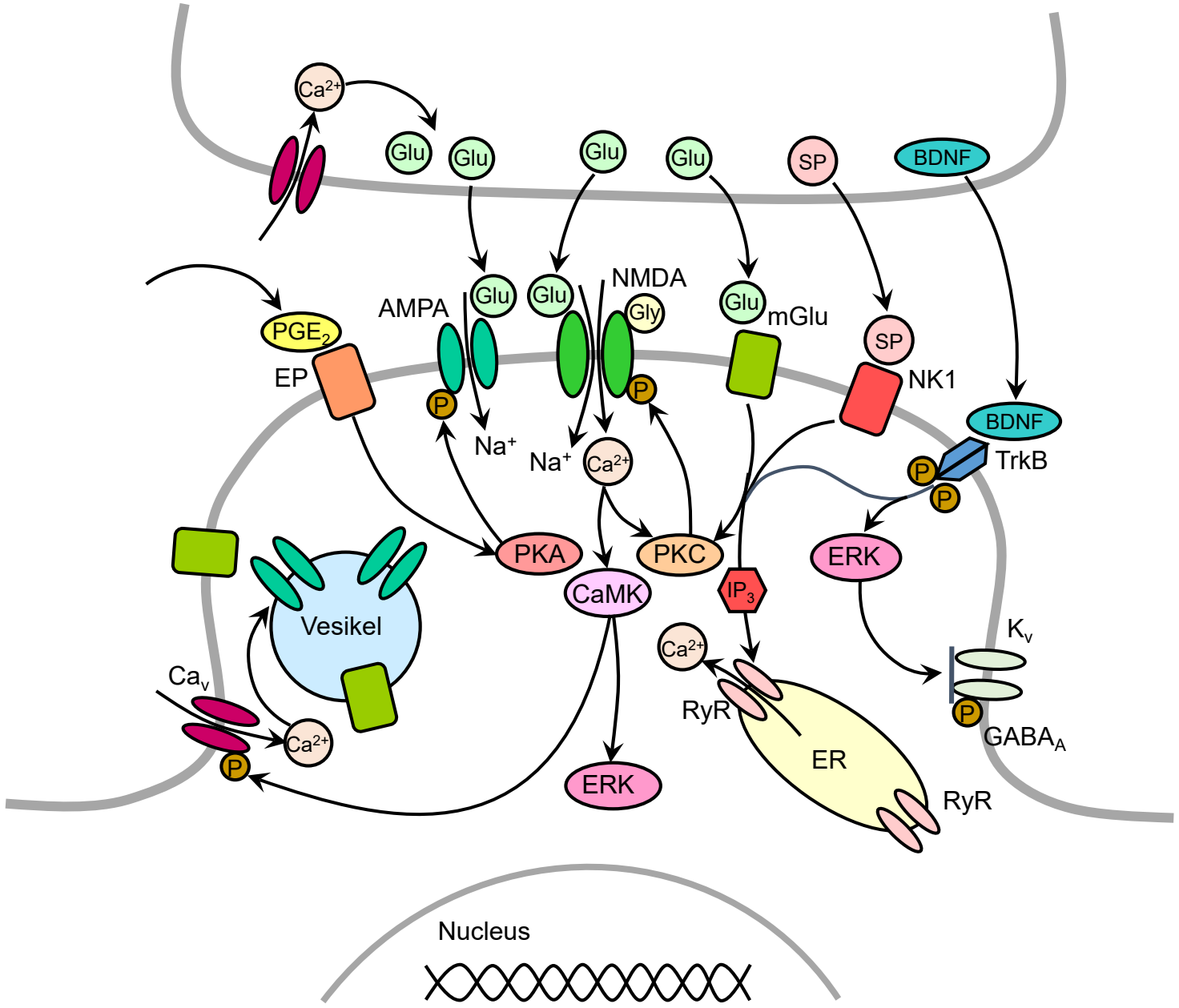
Central sensitization step 3: Metabolic cascades and action of protein kinases



- The activated protein kinases (PKA, PKC, CaMK) phosphorylate receptor channels and voltage-dependent ion channels, which changes the ion conduction and leads *summa summarum* to the facilitation of postsynaptic activation.

Intracellular increases in intracellular calcium by opening of voltage-dependent calcium channels or ryanodin receptor channels in the endoplasmic reticulum foster calcium-dependent processes.

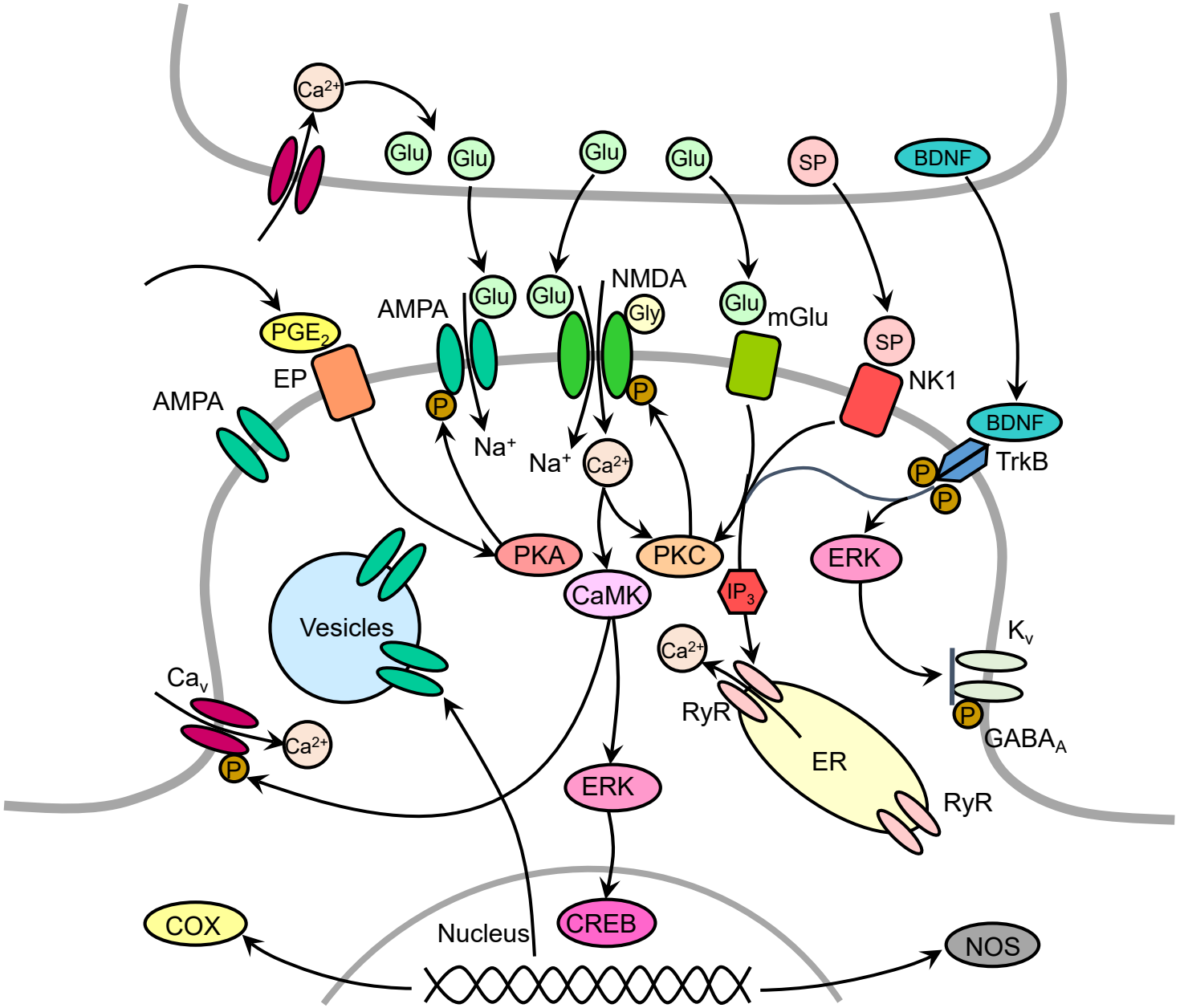
Central sensitization step 4: Recruitment of channels and receptors



- Long-lasting increase in calcium levels induce the integration of ion channels and receptors of different kinds (particularly glutamate receptor/channels) into the postsynaptic membrane increasing the postsynaptic responses to transmitter release.

This is the first plastic change increasing synaptic function for a long time.

Central sensitization step 5: *De novo* expression of channels and enzymes

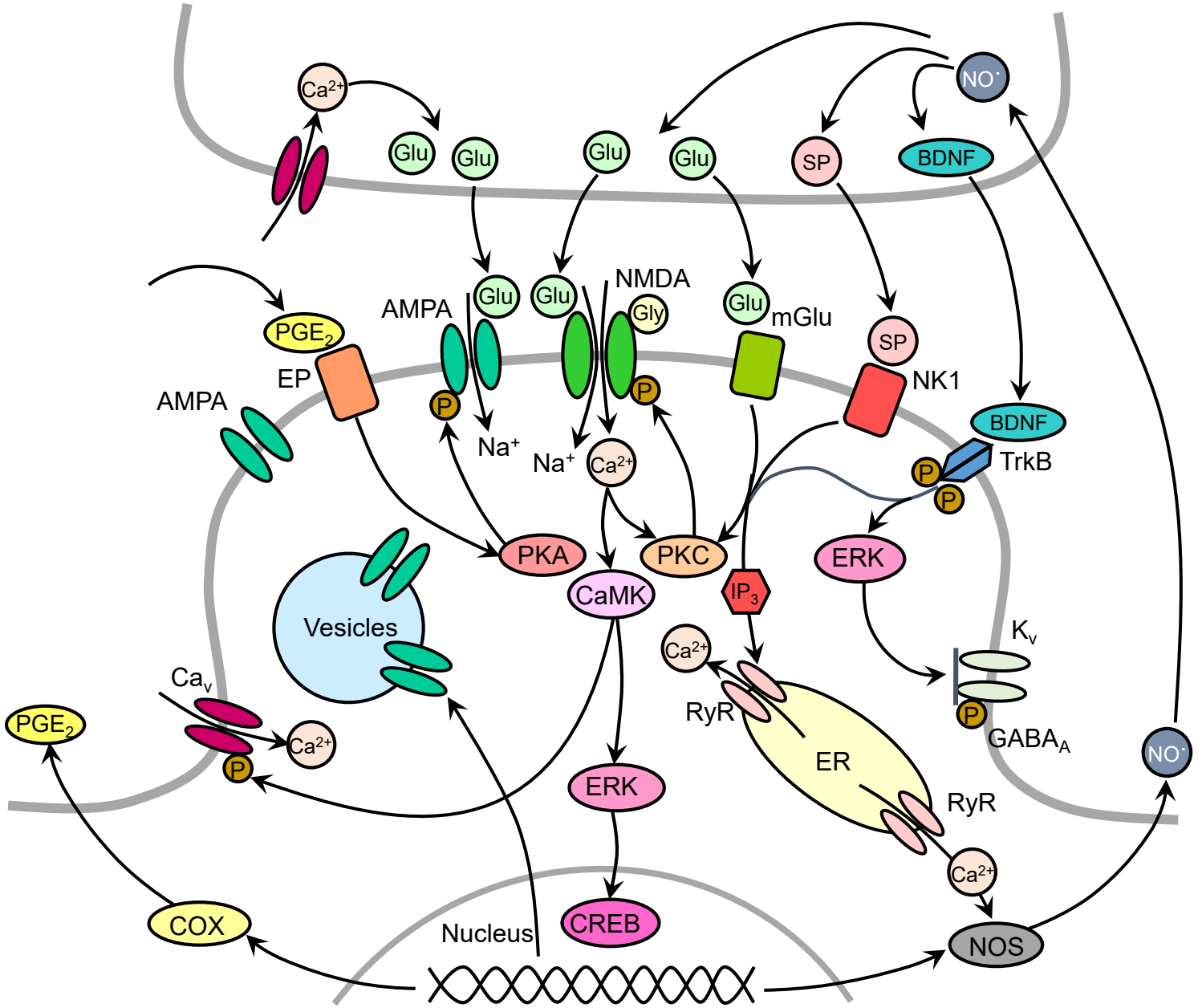


- Long-lasting increase in calcium levels induce also the activation of the extracellularly regulated kinase (ERK), which leads to the production of transcription factors like the cAMP response element binding protein (CREB).

The CREB induces transcription of genes encoding proteins for new channels and receptors that are stored in vesicles.

This is another important step of postsynaptic plasticity, which cannot be reversed immediately.

Central sensitization step 6: Production of nociceptive mediators and „retrograde transmitters“

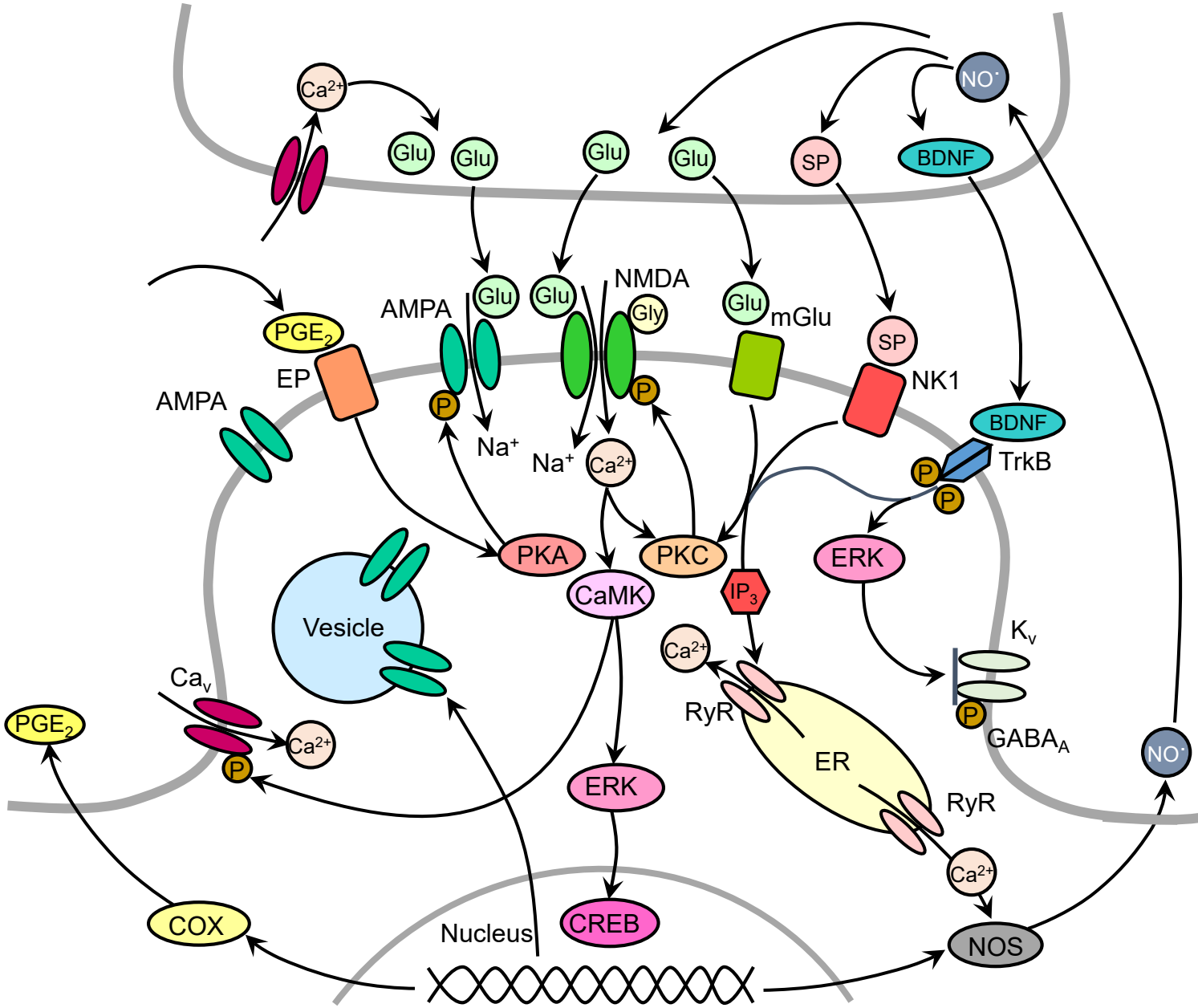


- Gene expression includes also transcription of enzymes, which give rise to the production of nociceptive mediators like protaglandins (PGE_2) and „retrograde transmitters“ like nitric oxide (NO).

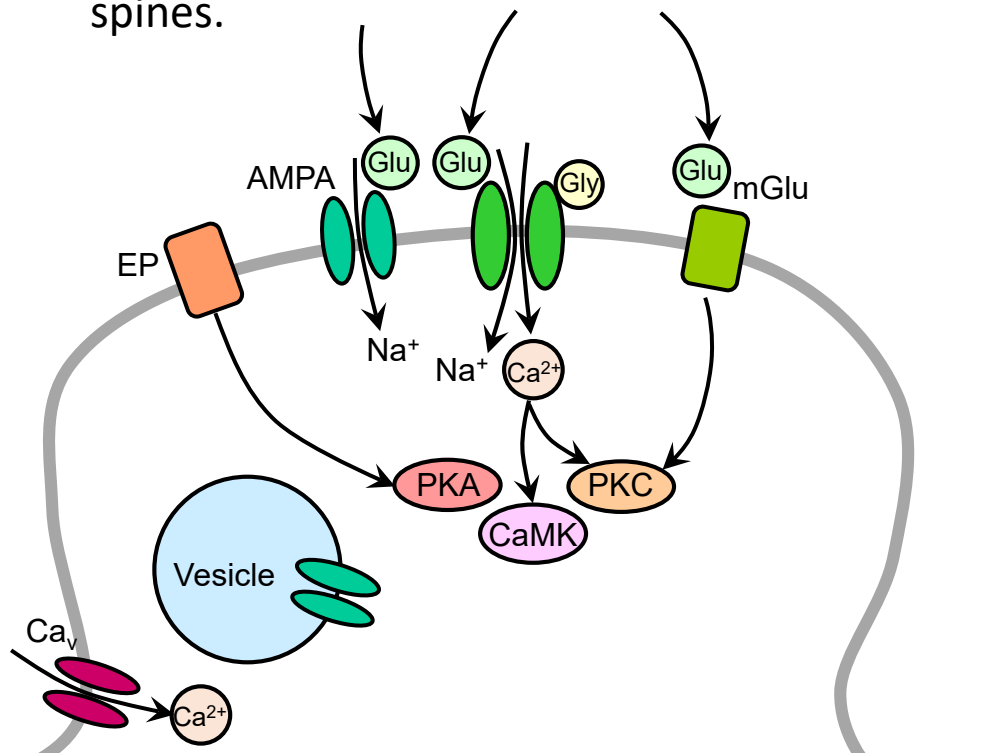
NO is rapidly diffusing through cell membranes, reaches the presynaptic terminals and may facilitate the production and release of neurotransmitters.

PGE_2 can contribute to reciprocal sensitization of neurons. Glial cells may be other targets of these mediators.

Central sensitization step 7 (final): Formation of new postsynaptic spines – plasticity of synapes

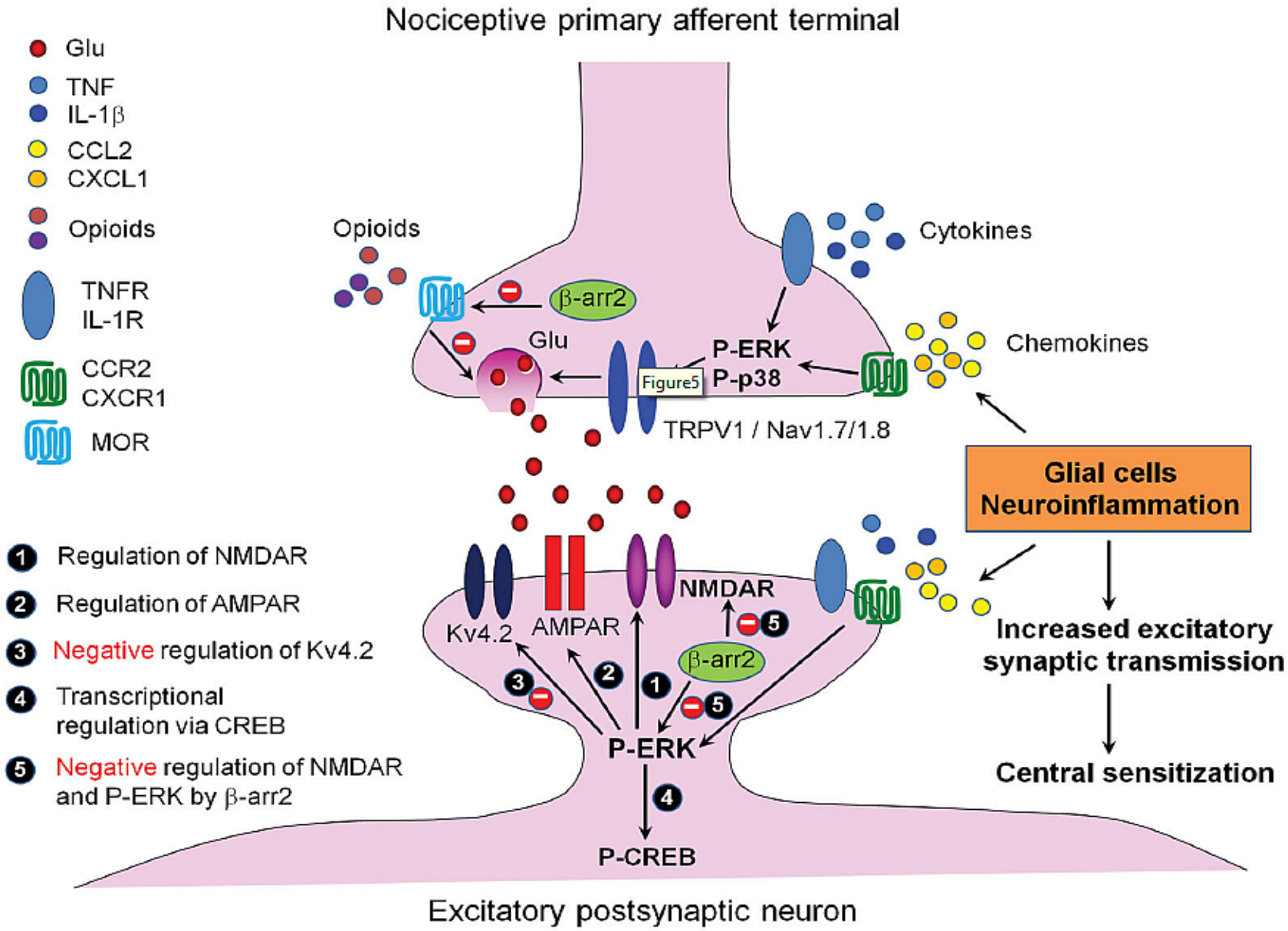


The final step of neuronal plasticity is growth of postsynaptic membranes and generation of new postsynaptic spines.



Receptor proteins and ion channels are integrated into the new membranes.

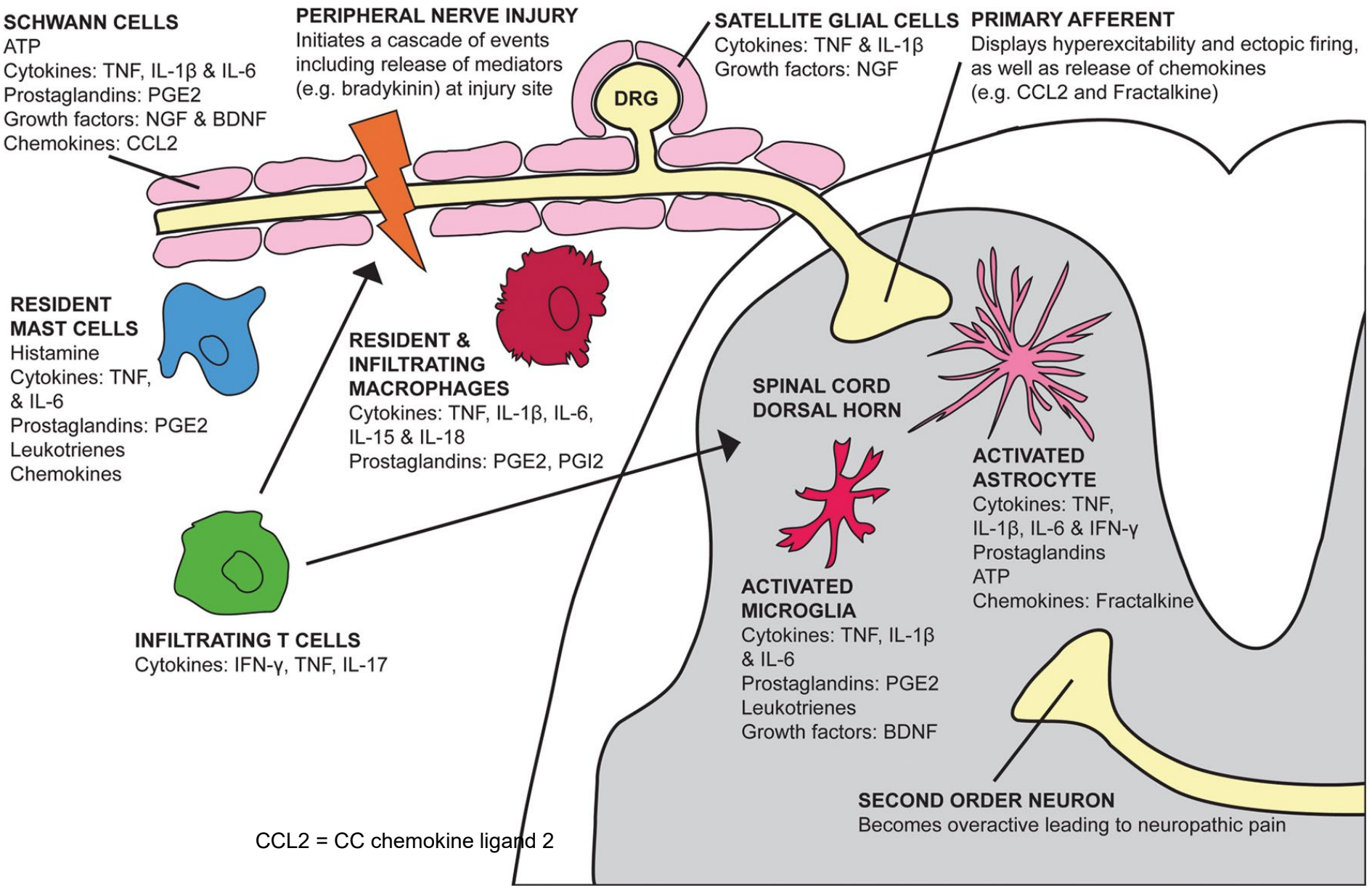
Neuroinflammation and central sensitization involving glial cells (microglia, astrocytes)



- Glial cells involved in neuroinflammation can produce different kinds of chemokines (cytokines) that act both pre- and postsynaptically on central neurons by regulating ion channels and G-protein-coupled receptors.

R. Ji al et W. Maixner, Anesthesiology 2018; 129: 343-66

Central sensitization mechanisms in neuropathic pain



CCL2 = CC chemokine ligand 2

- Several types of glial cells in the dorsal horn and infiltrating mononuclear cells can produce cytokines and other mediators under pathological conditions thereby contributing to central sensitization.

Neuropathic Pain, ed. Cory Toth and Dwight E. Moulin. Cambridge University Press 2013

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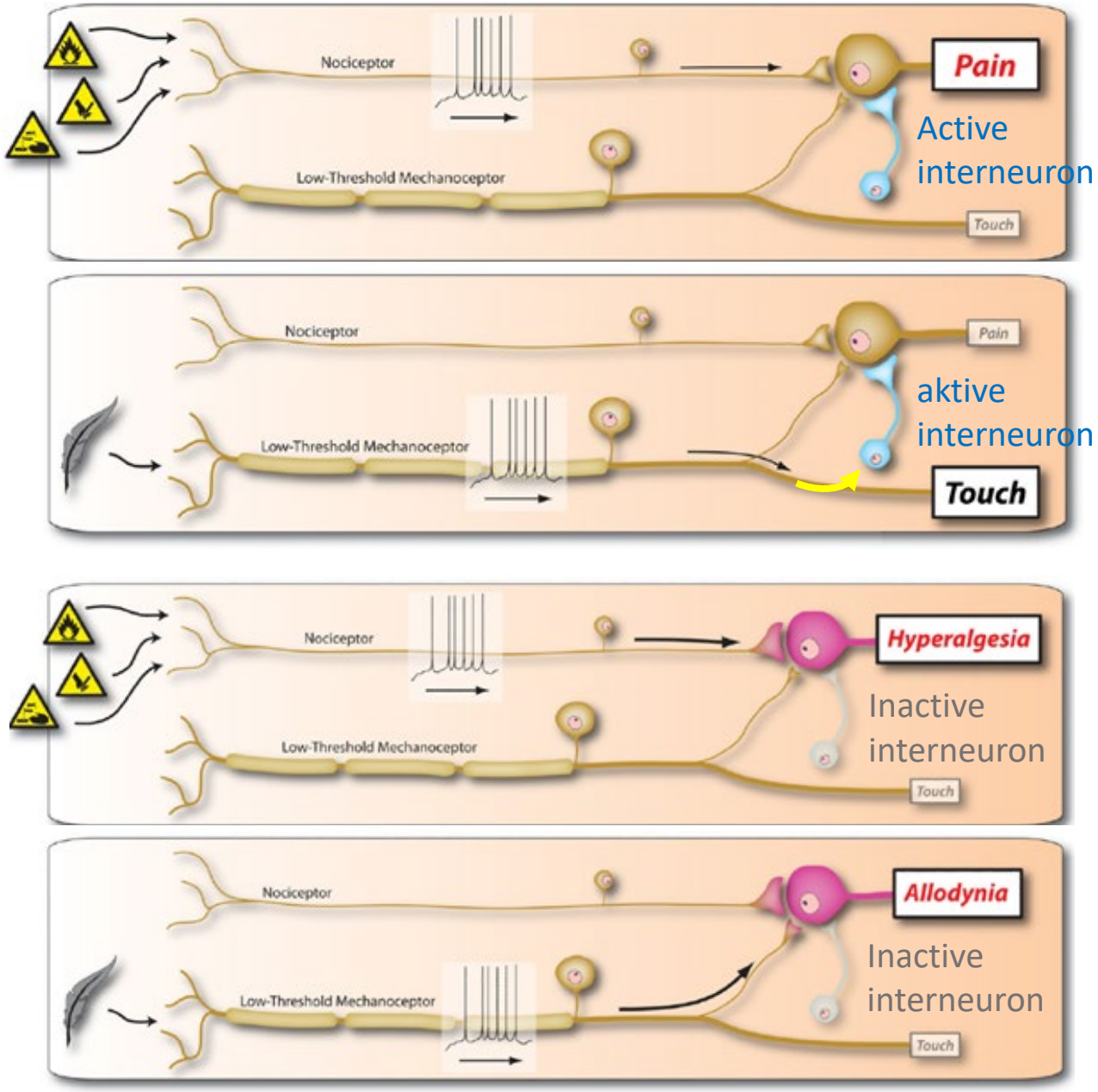
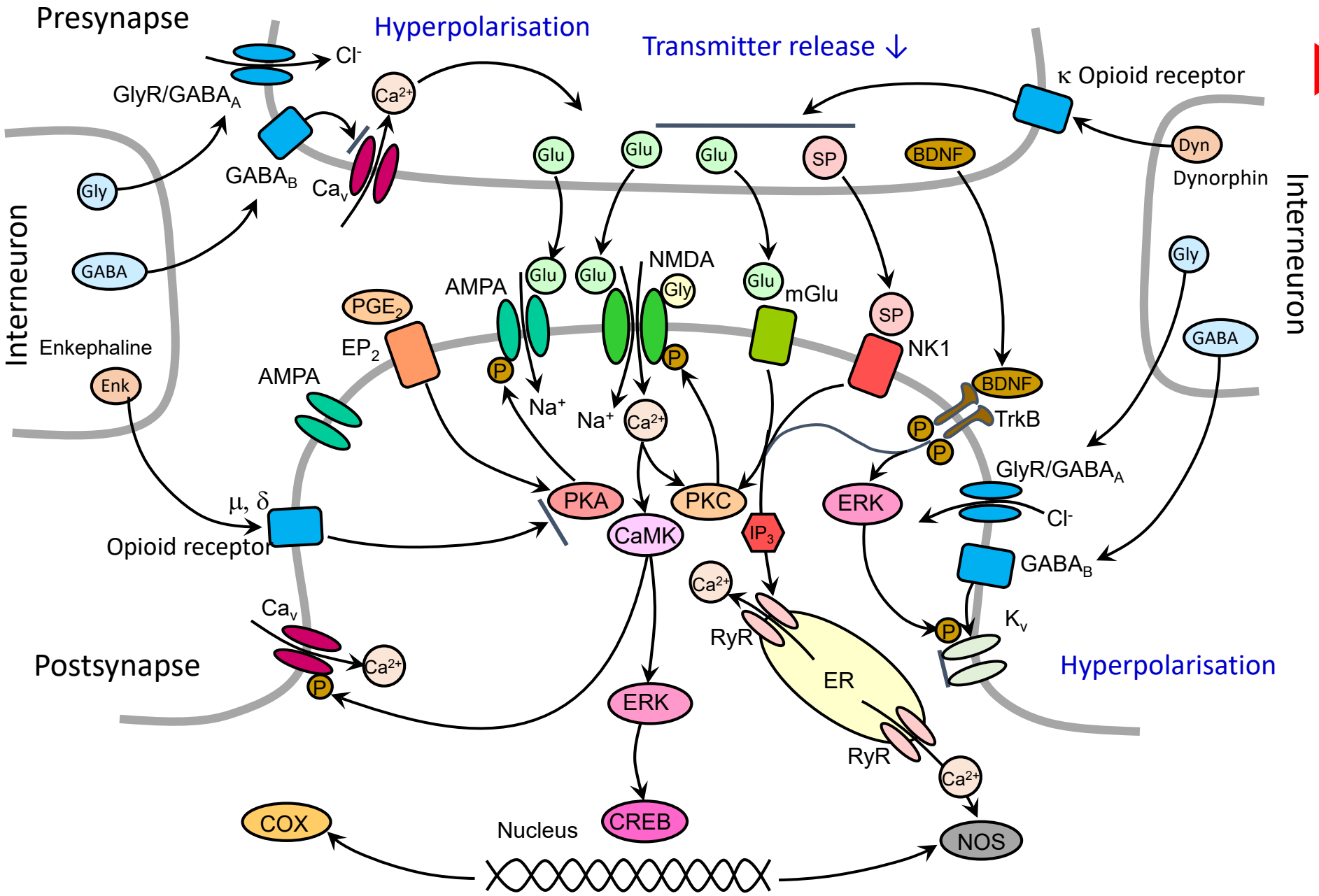
Spinal mechanoreceptive and nociceptive projection to second order neurons



- WDR second order neurons receive input from both nociceptive and mechanoreceptive afferents. Inhibitory interneurons can modulate the activity of WDR neurons.
- Activated mechanoreceptive afferents (Aβ) can modulate the activity of WDR neurons through (inhibitory) interneurons („gate control“). The exact mechanism is not clear.
- Chronic pain syndromes like hyperalgesia and allodynia can significantly depend on the inactivation of inhibitory interneurons.

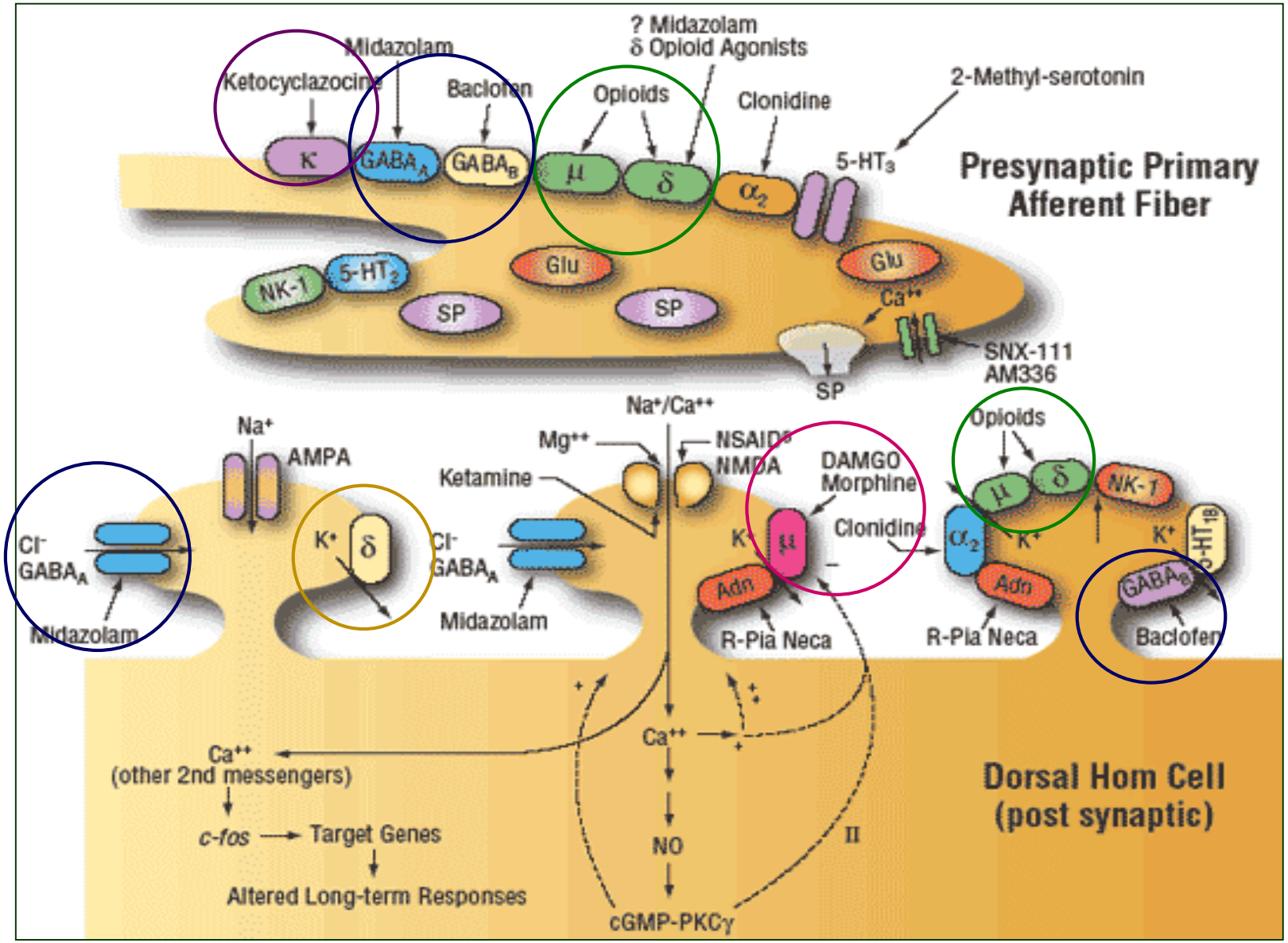
Clifford Woolf, Pain 2011; 152 (Suppl 3): S2-15

Inhibitory neurotransmitter actions at spinal neurons



Inhibitory neurons in the spinal dorsal horn operate with neurotransmitters, which bind pre- or postsynaptically to inhibitory receptors like GABA, glycin or opioid receptors. On principle they counteract the excitatory mechanisms, i.e., they increase the membrane potential (hyperpolarisation) through inflow of Cl^- or outflow of K^+, inhibit voltage-dependent Ca^{2+} channels and reduce the activity of sensitizing protein kinases.

Inhibitory receptor systems in the dorsal horn



www.medscape.com

- Besides the classical inhibitory neurotransmitters and receptors (GABA, glycin) three types of opioid receptors (μ, δ and κ) are involved in the pre- and postsynaptic inhibitory mechanisms.

Multiple receptor systems can contribute to the synaptic transmission in the spinal dorsal horn.

Endogenous opioids, opioid receptors and effects

Endogenous opioids	Receptors	Production sites
Endorphins (β-Endorphin)	μ	Hypothalamus, Hypophysis
Enkephalins (Met-, Leu-Enkephalin)	μ, δ	CNS, Adrenal gland, Gut
Dynorphins (Dynorphin A, B)	κ	CNS, Gut

Receptors	Expression sites	Effects
μ_1	Brain	Analgesia, Bradykardia, Hypotonia
μ_2	Brain, Spinal cord, Peripheral organs	Analgesie, Constipation, Euphoria, Respiratory depression
κ	Brain, Spinal cord	Analgesia, Sedation, Dysphoria
δ	Brain, Spinal cord, Peripheral organs	Analgesia, Constipation
?		Miosis, Nausea

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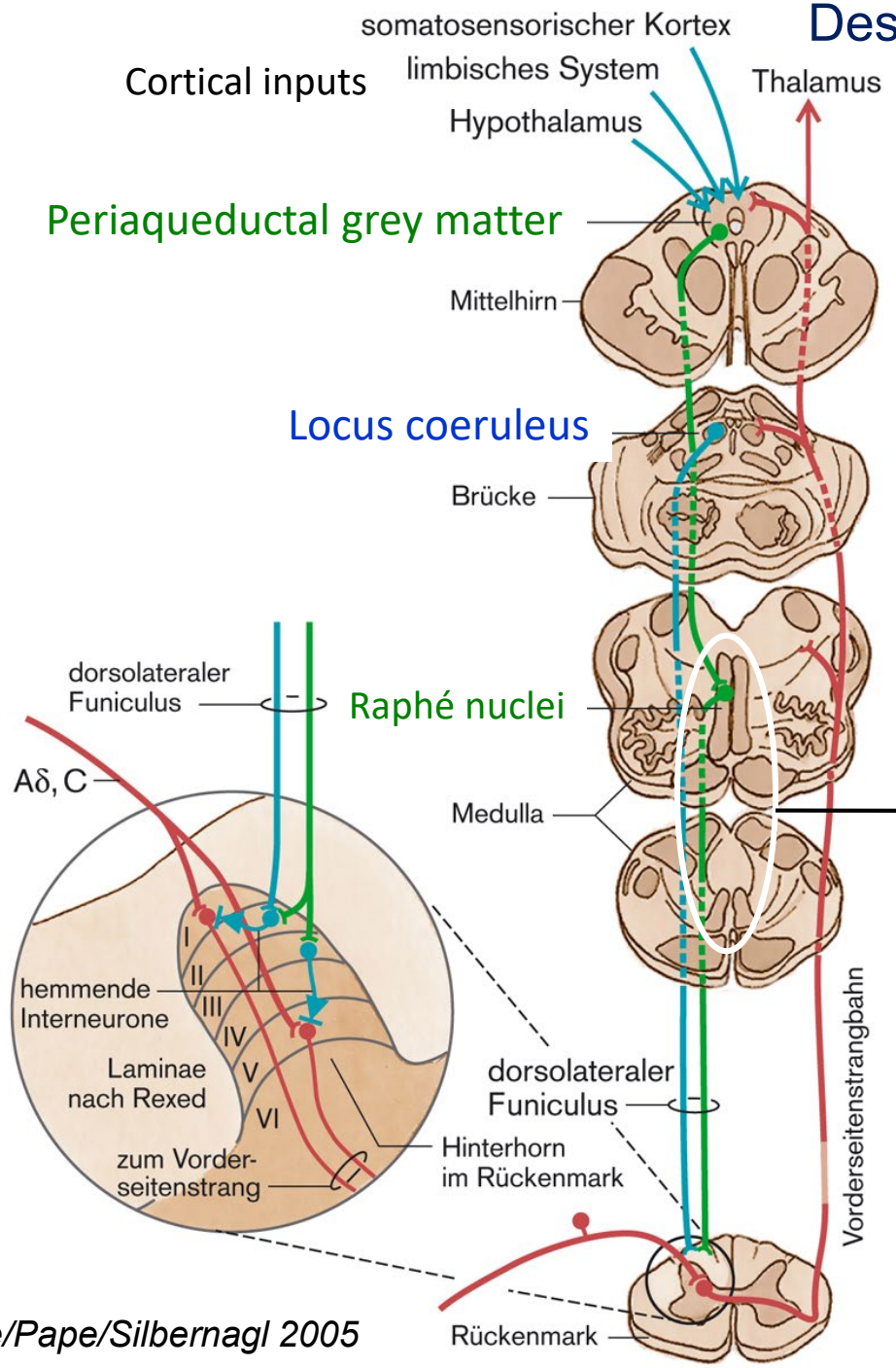
Descending antinociceptive systems



Hypothalamic system

β-Endorphin

Lateral inhibitory system

Noradrenalin (Norepinephrine)

Medial inhibitory system

Serotonin (5-HT)

Rostral ventromedial medulla (RVM)

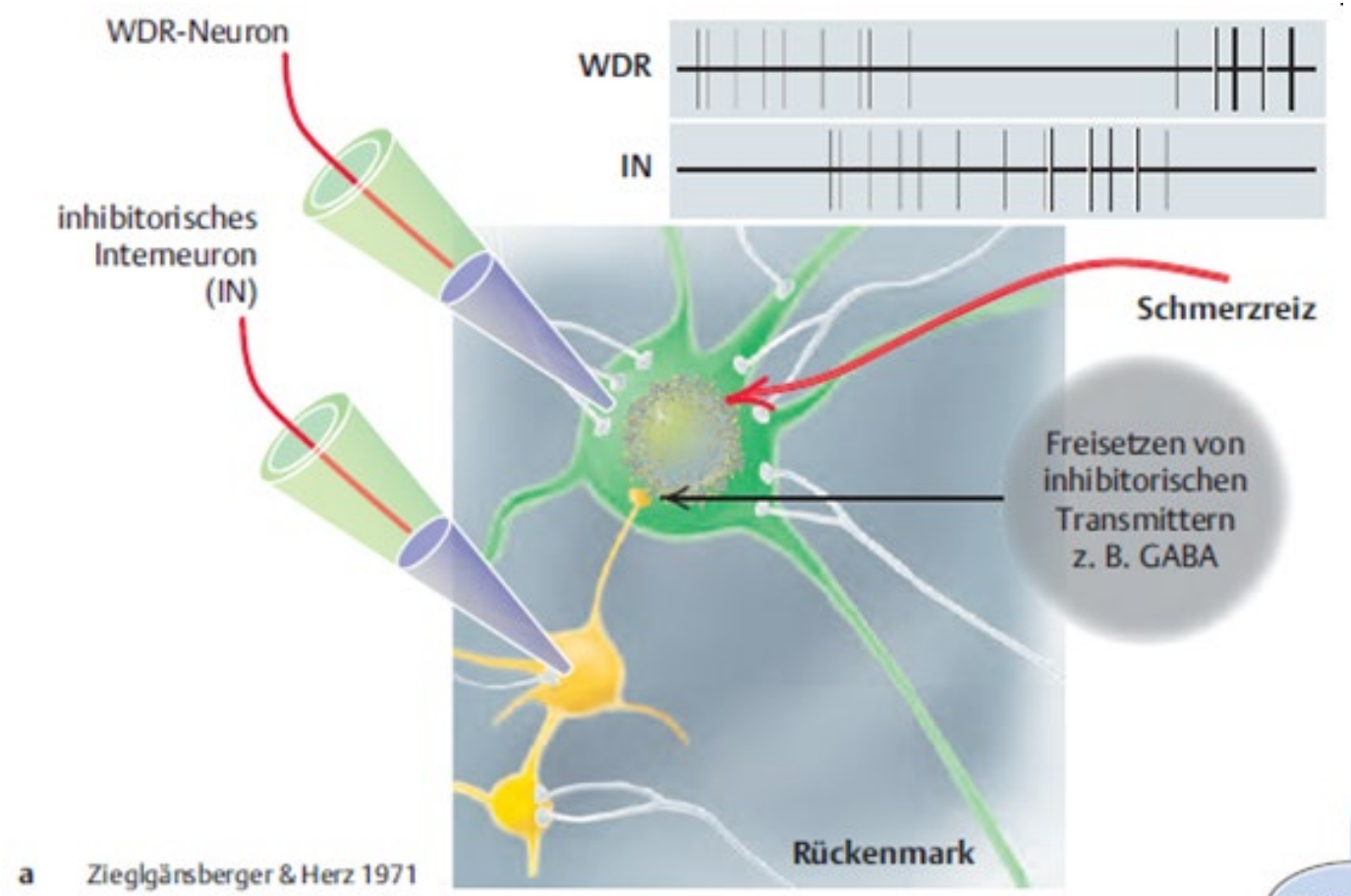
Spinal interneurons

Dynorphin
Enkephalin

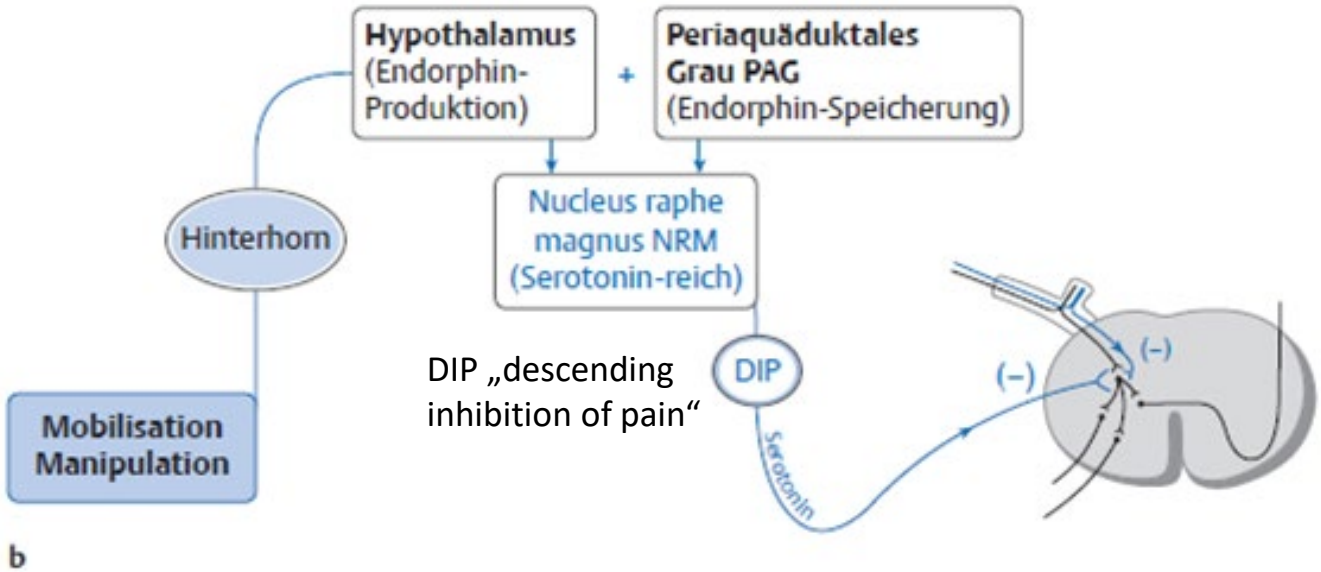
The descending pain modulating systems are classically devided into a more laterally descending noradrenergic system and a more medially descending serotonergic system. Both systems interact with neurons in the rostral ventromediasl medulla (RVM). The descending axons synapse to spinal interneurons, many of which operate with opioids as neuromodulators. Opioids are also released from the hypothalamus, operating as hormones.

Klinke/Pape/Silbernagl 2005

Basic principle of spinal WDR neuron inhibition in the dorsal horn

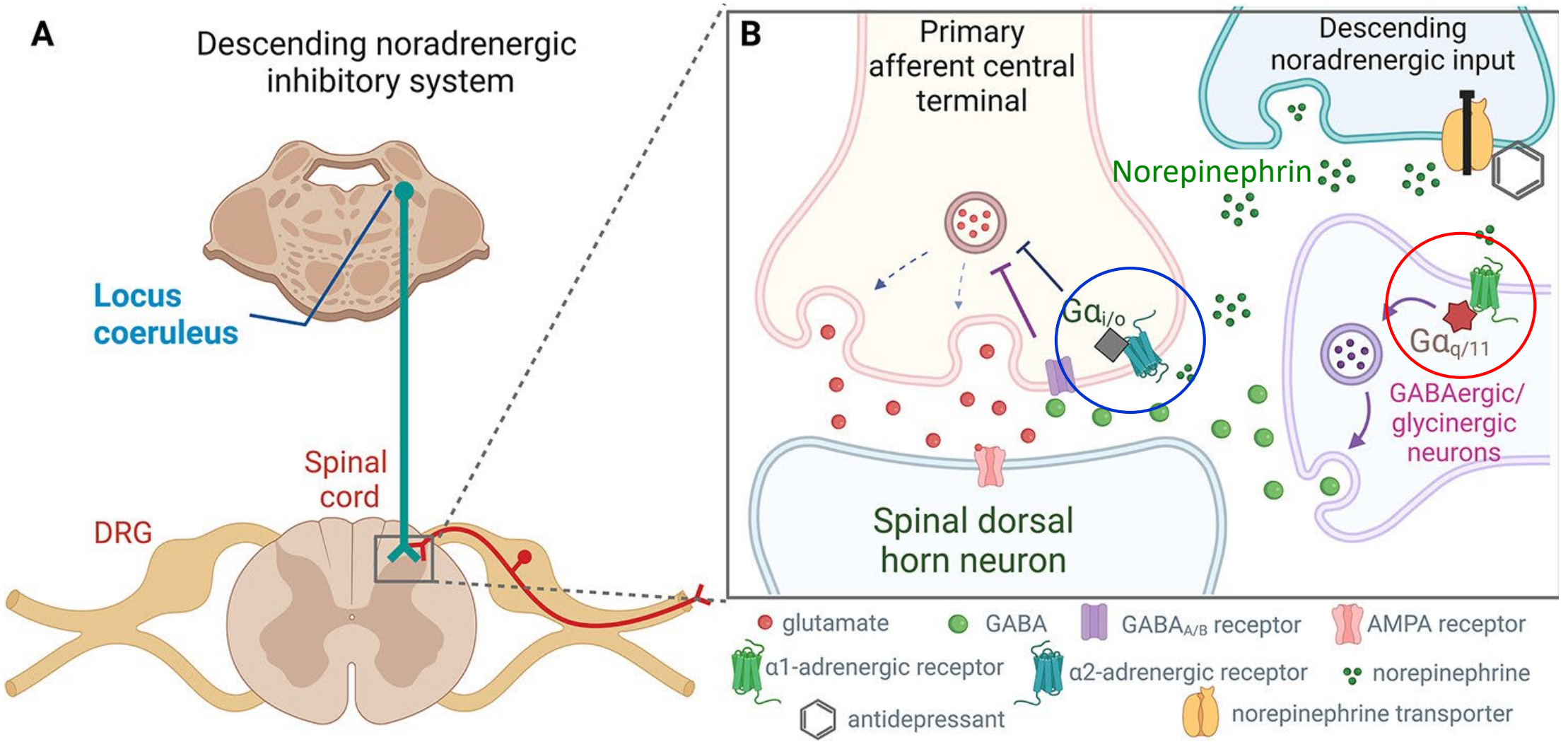


- Inhibition of spinal dorsal horn WDR neurons is managed by interneurons releasing inhibitory neurotransmitters (mainly GABA). Interneurons are activated by descending neurons, e.g. serotonergic neurons from the raphé nuclei in the midbrain, which receive descending input from the hypothamaus and the periaquaeductal grey matter (PAG).



U. Böhni & H. Locher, Manuelle Medizin 1, Thieme

Transmission effects of the descending noradrenergic system

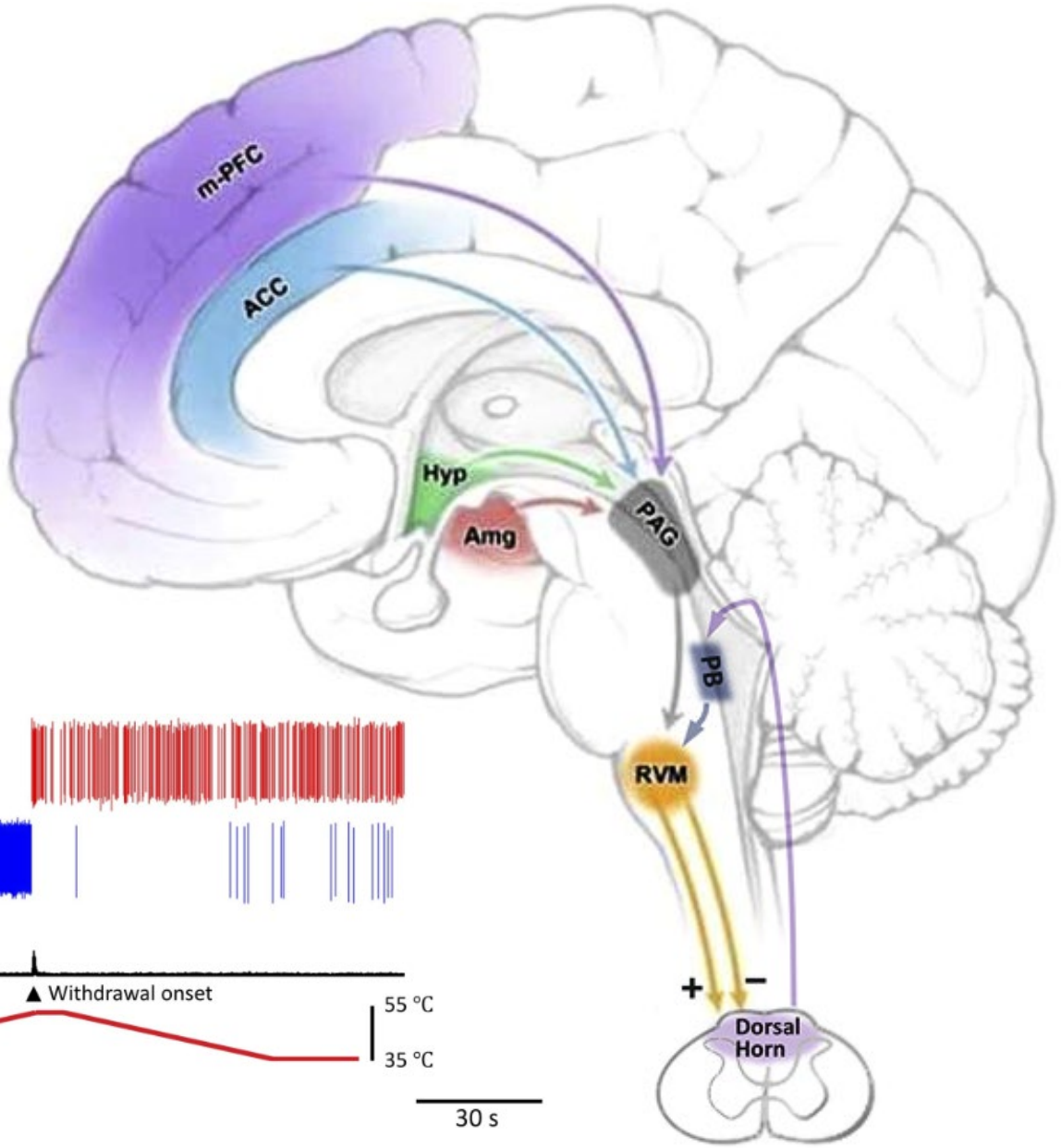


Norepinephrin released from descending noradrenergic neurons activates α-receptors coupled with inhibitory G-proteins on primary afferent terminals (presynaptic) decreasing nurotransmitter release and α-receptors coupled with excitatory G-proteins on inhibitory interneurons causing increase in GABA and glycin release.

Huang et al, ACS Chem. Neurosci. 2023, 14, 7, 1261–1277

Cortical inputs to the descending control system

ACC, anterior cingular cortex
Amg, Amygdala
Hyp, Hypothalamus
m-PFC, medial prefrontal cortex
PAG, periaqueductal grey matter
PB, parabrachial nuclei
RVM, rostral ventromedial medulla

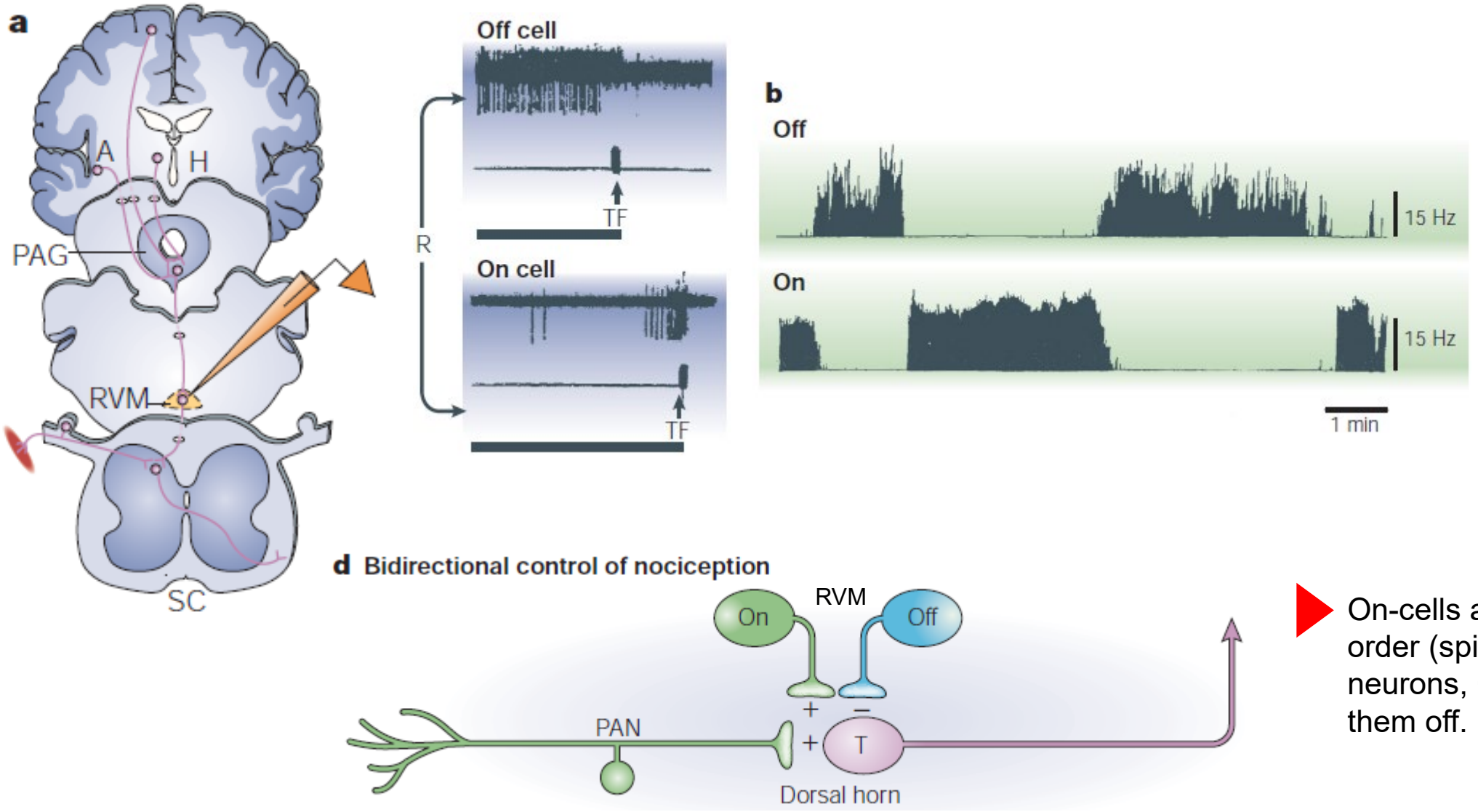


The rostral ventromedial medulla (RVM) contains a network of activating and inhibitory neurons which project to the spinal dorsal horn. Via the periaqueductal grey matter (PAG) the RVM receives cortical input from different areas processing *rational* (m-PFC), *emotional* (ACC) *autonomic* (Hyp) and *affective* information (Amg).

This means that descending control can be influenced by conscious, emotional and autonomic motivs.

Q. Chen & M.M. Heinricher, Front. Pain Res. 2022; 3:932476

On- and Off-cells in the Rostral Ventromedial Medulla (RVM) and their impact on dorsal horn neurons

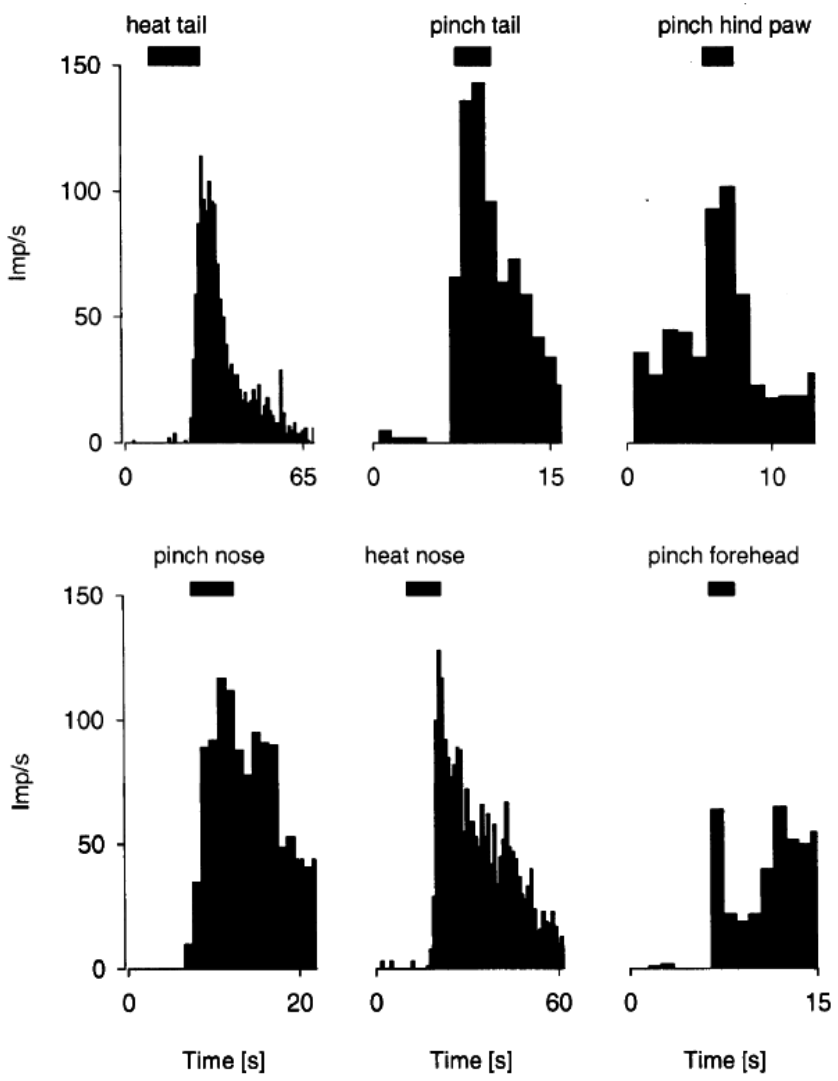


On-cells activate second order (spinothalamic) neurons, Off-cells switch them off.

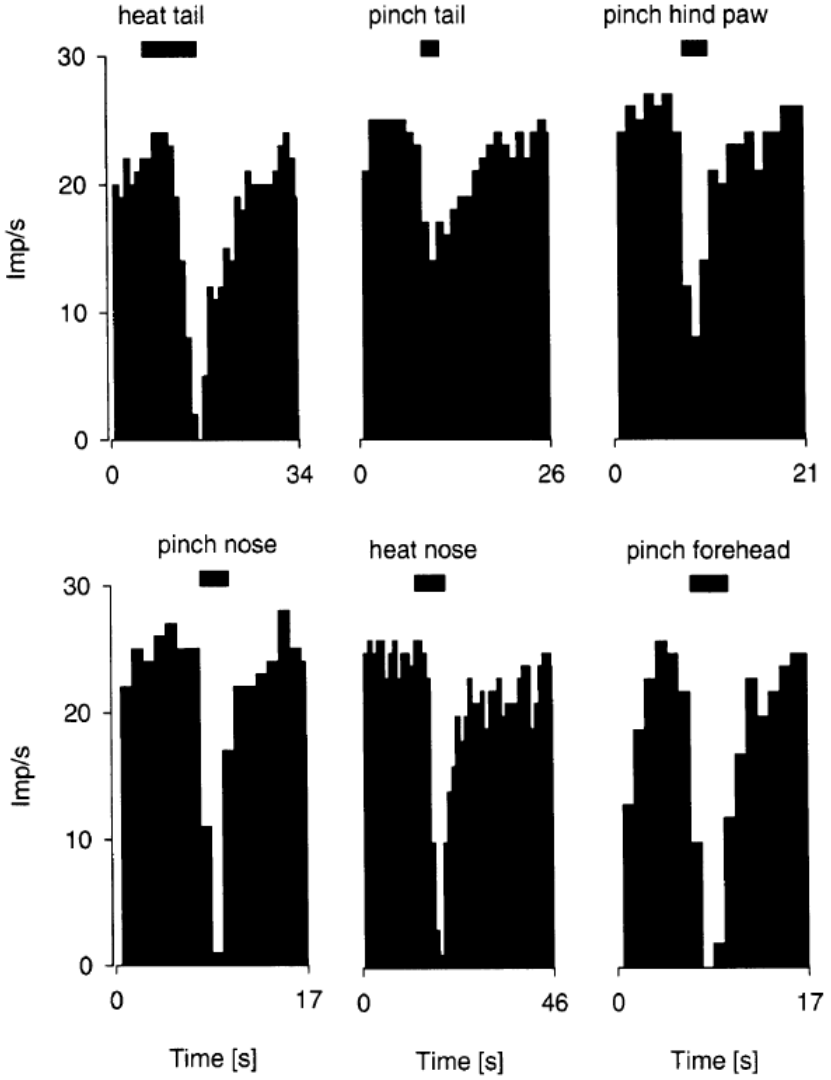
H. Fields, Nat. Rev. Neurosci. 2004; 5: 565-75.

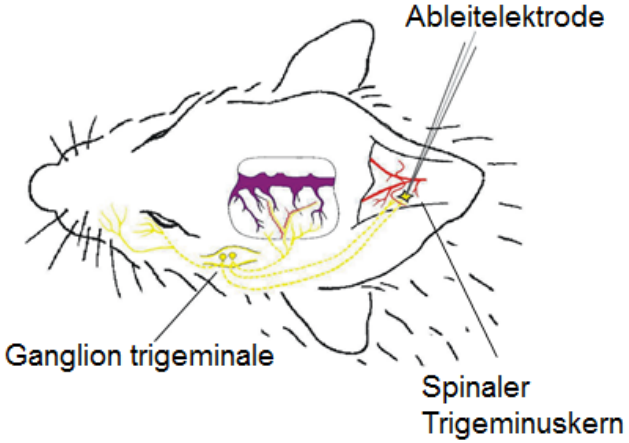
Activity of On- and Off-cells in der RVM during different noxious stimuli

On-cell



Off-cell



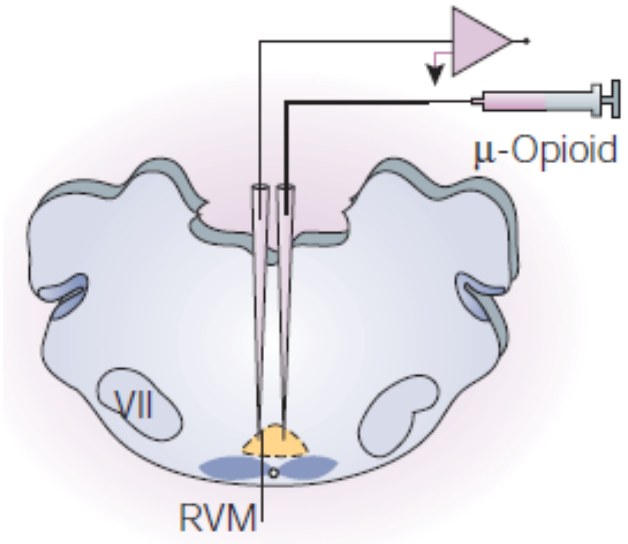


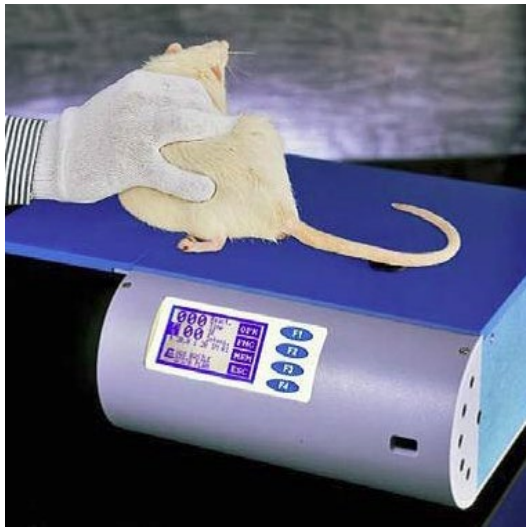
- On-cells show usually no ongoing activity but are activated during noxious stimulation of nearly all body areas. Off-cells are spontaneously active and are silenced upon noxious stimulation.

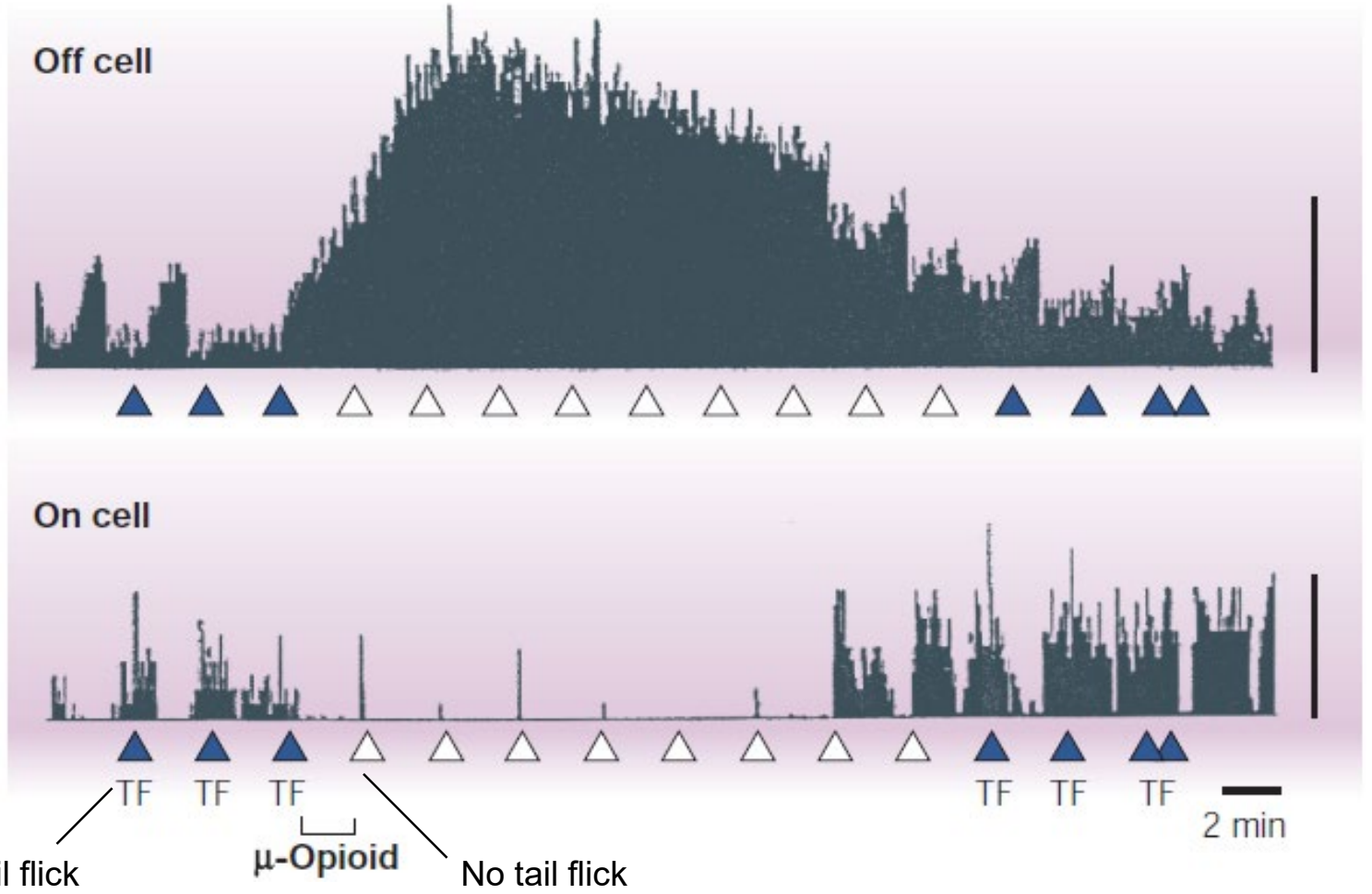
J. Ellrich et al., Pain 90 (2001)

Morphin activates Off-cells and inhibits On-cells in the RVM

c



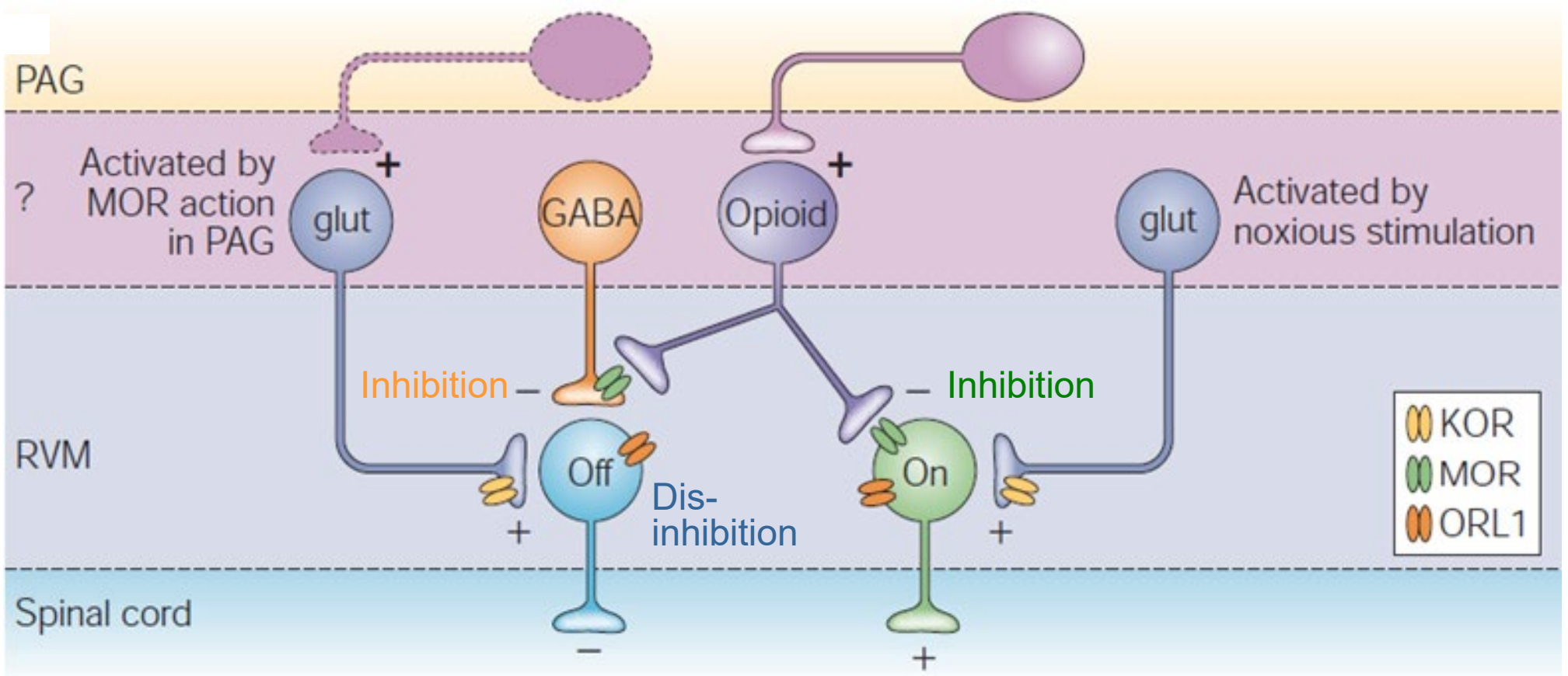




http://www.youtube.com/watch?v=5h3NqjizHU0

H. Fields, Nat. Rev. Neurosci. 2004; 5: 565-75.

Effects of opioids on On- and Off-cells in the rostral ventromedial medulla



K-Opioid-R.

μ-Opioid-R.

Opioid-like R.

On-cells in the RVM are activated by nociceptive input and can be inhibited by opioids directly (postsynaptic mechanisms).

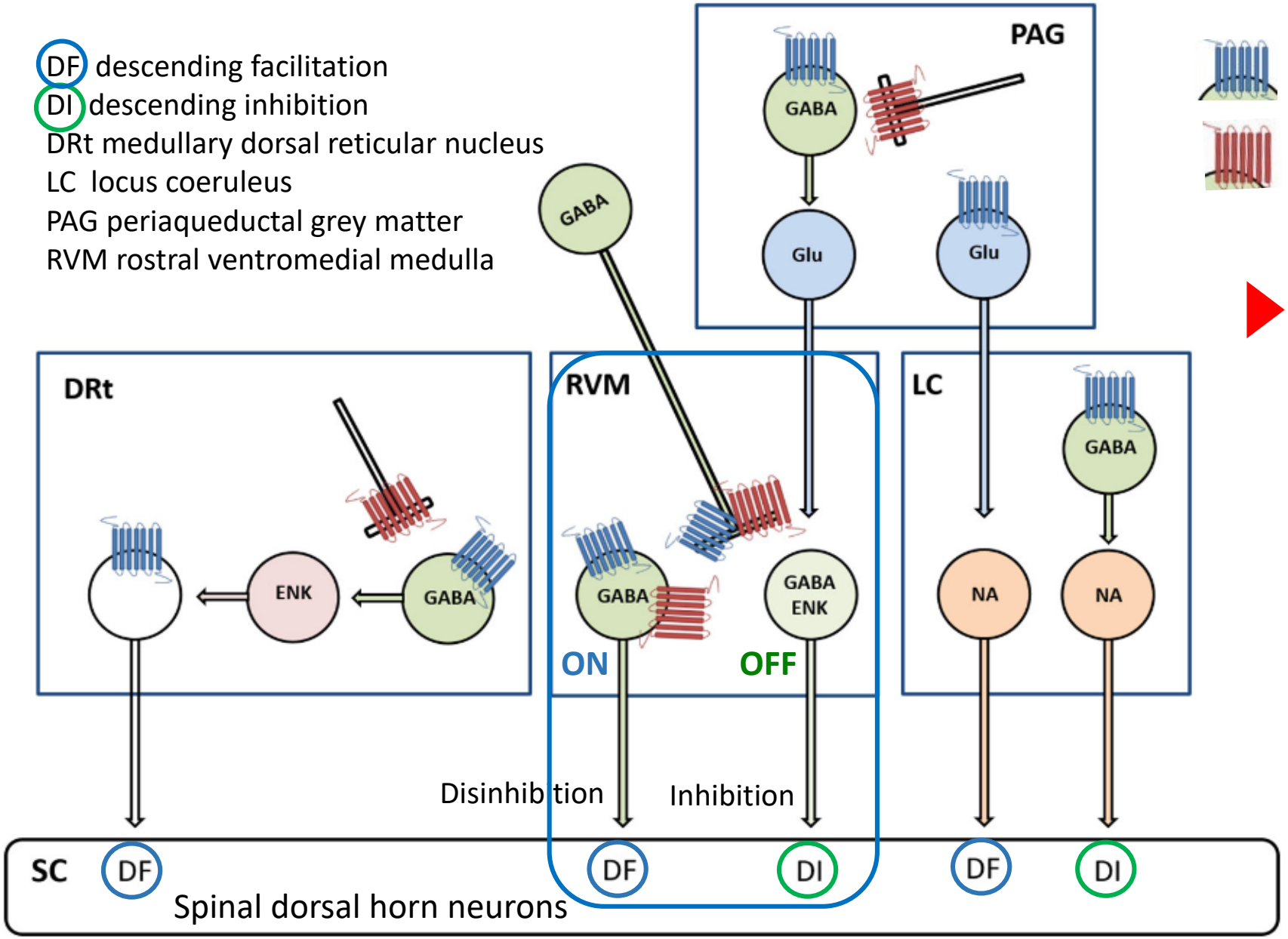
Off-cells in the RVM are under GABAergic inhibitory control and are disinhibited by opioidergic neurons (presynaptic inhibition of GABAergic neurons).

The On- and Off-cell system may explain immediate pain control by modulating the activity of spinothalamic neurons.

H. Fields, Nat. Rev. Neurosci. 2004; 5: 565-75.

Complexity of the descending neuromodulatory system

DF descending facilitation
DI descending inhibition
DRt medullary dorsal reticular nucleus
LC locus coeruleus
PAG periaqueductal grey matter
RVM rostral ventromedial medulla



μ-opioid receptor

δ-opioid receptor

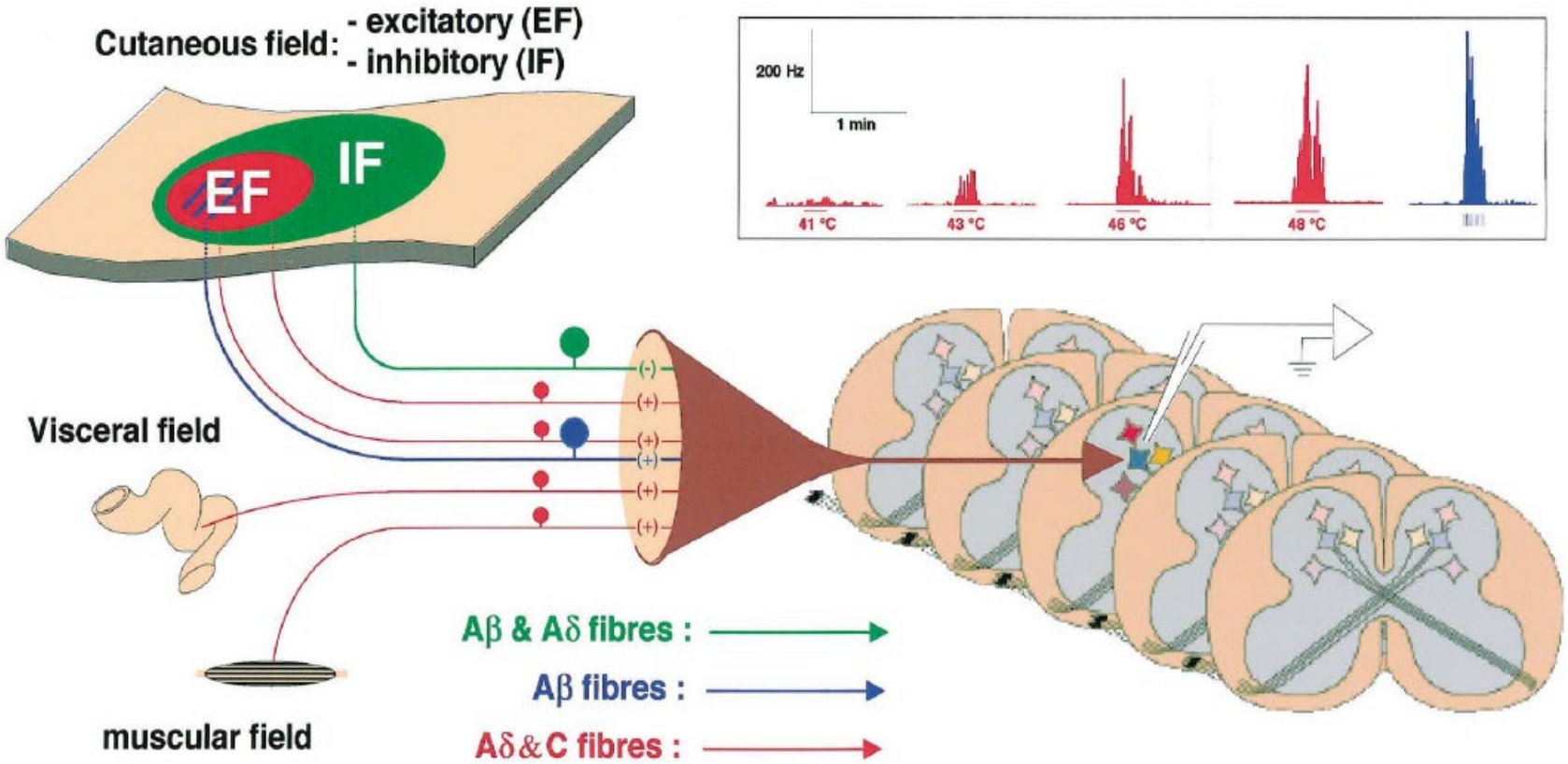
The On- and Off-cell system in the rostral ventromedial medulla (RVM) ist only part of the whole descending neuromodulatory systems, which can have both facilitating and inhibitory effects on the neurons in the spinal dorsal horn (SC). Other contributions come from the dorsal reticular nucleus (Drt) and the locus coeruleus (LC).

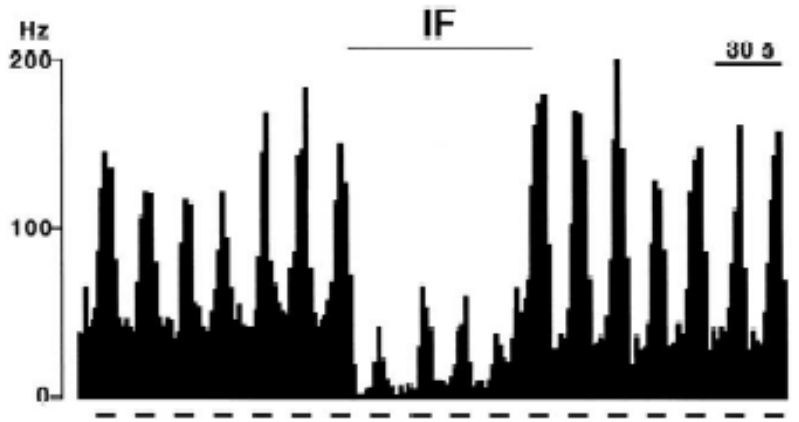
I. Tavares et al, Front. Pain Res 2021;2:696515

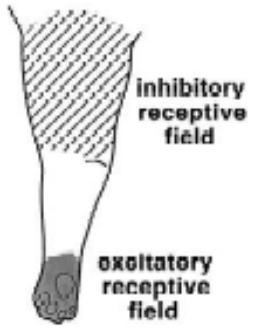
Adressed topics

- **Retrospection:** Basic organization of ascending and descending pain modulating pathways
- **Recollection:** Molecular mechanisms of nociceptive transmission and central sensitization
- **Controlling spinal nociception:** Interneurons and molecular antinociceptive mechanisms
- **Descending pathways:** On and Off cells in the rostral ventromedial medulla
- **Supraspinal antinociceptive mechanisms:** Diffuse inhibitory control systems (DNIC)
- **Central pain inhibition:** Stress- and exercise-induced hypoalgesia and acupuncture

Multireceptive neurons in the Ncl. dorsalis reticularis



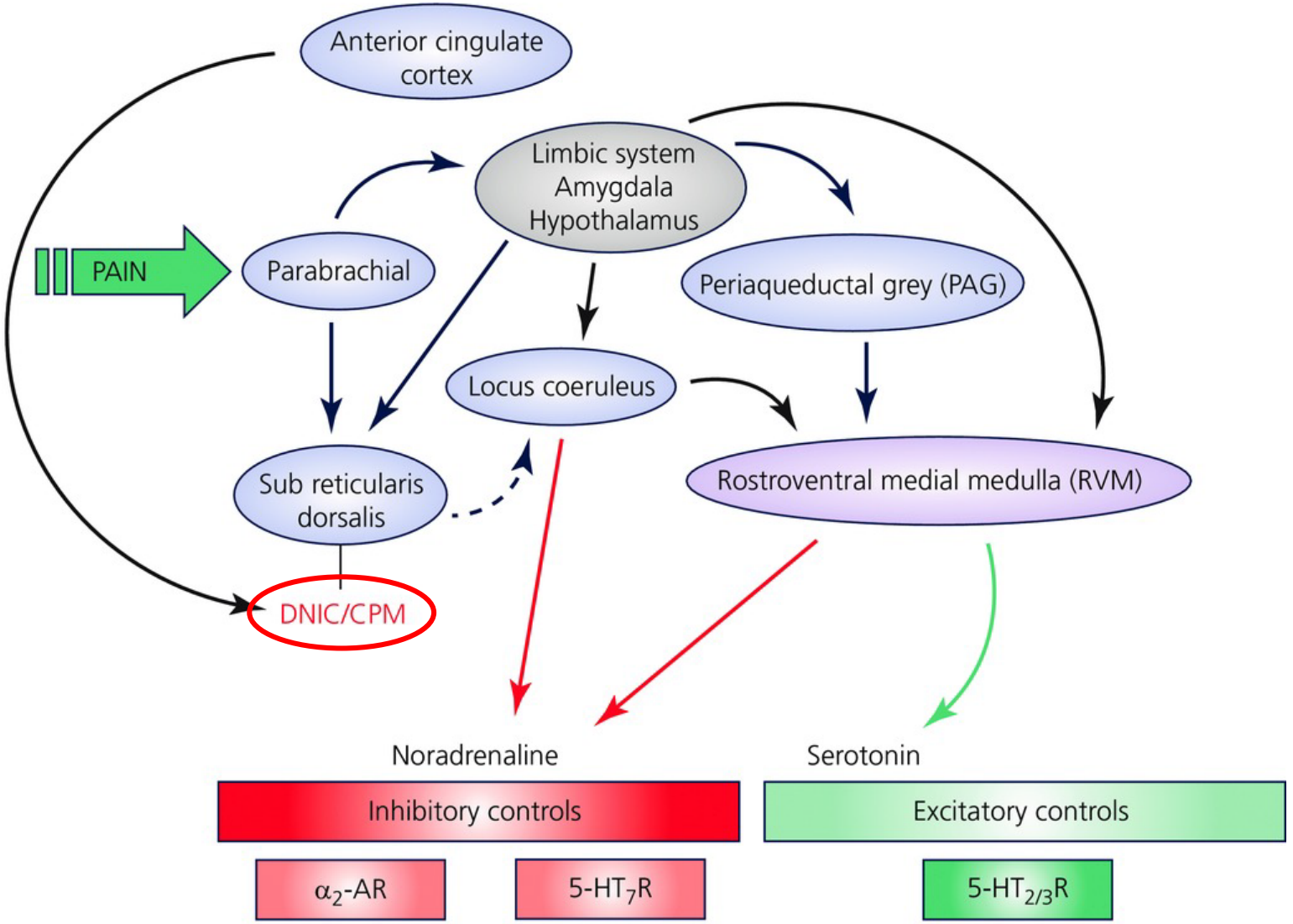




Multireceptive neurons in the spinal dorsal horn receive input from low- and high-threshold afferents of the skin, the deep tissues and the viscera. Their cutaneous receptive fields have a inhibitory periphery. They are inhibited by noxious stimuli of many different regions of the body. The dorsal reticular nucleus in the caudal medulla is involved in the “diffuse noxious inhibitory controls” (DNIC) activated by Aδ- and C-fibers.

D. Le Bars, Brain Res Rev 2002; 40: 29-44.

Descending pain modulatory system

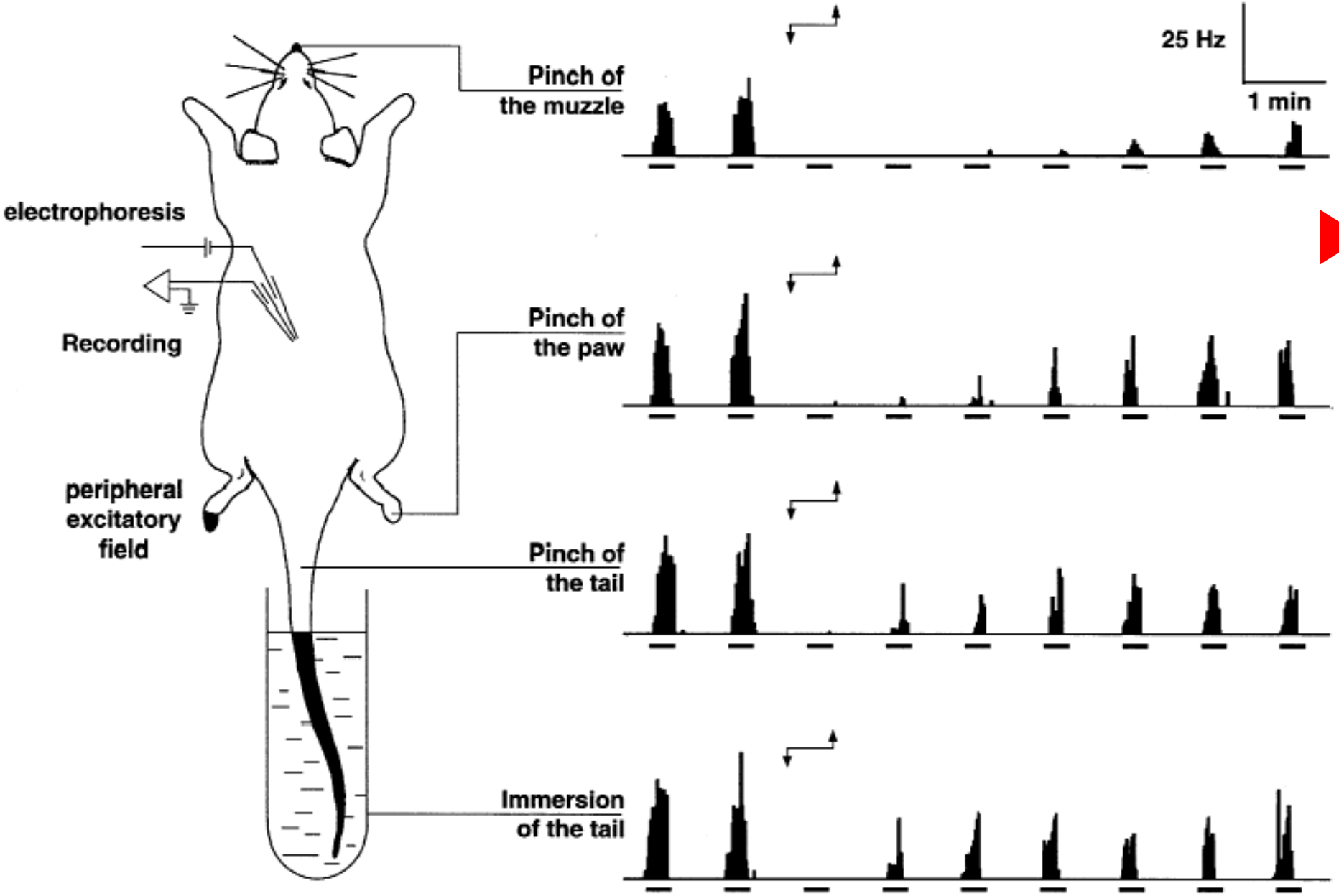


The descending pain modulating systems operate with inhibitory (α_2 adenergic receptors) and excitatory mechanisms (5-HT$_2$ receptors) in the RVM. Both can have antinociceptive effects. The subreticular nucleus is involved in the **Diffuse Noxious Inhibitory Controls (DNIC)** phenomenon clinically visible as **Conditioned Pain Modulation (CPM).**

The Journal of Physiology

Bannister & Dickenson, J Physiol 595 (2017)

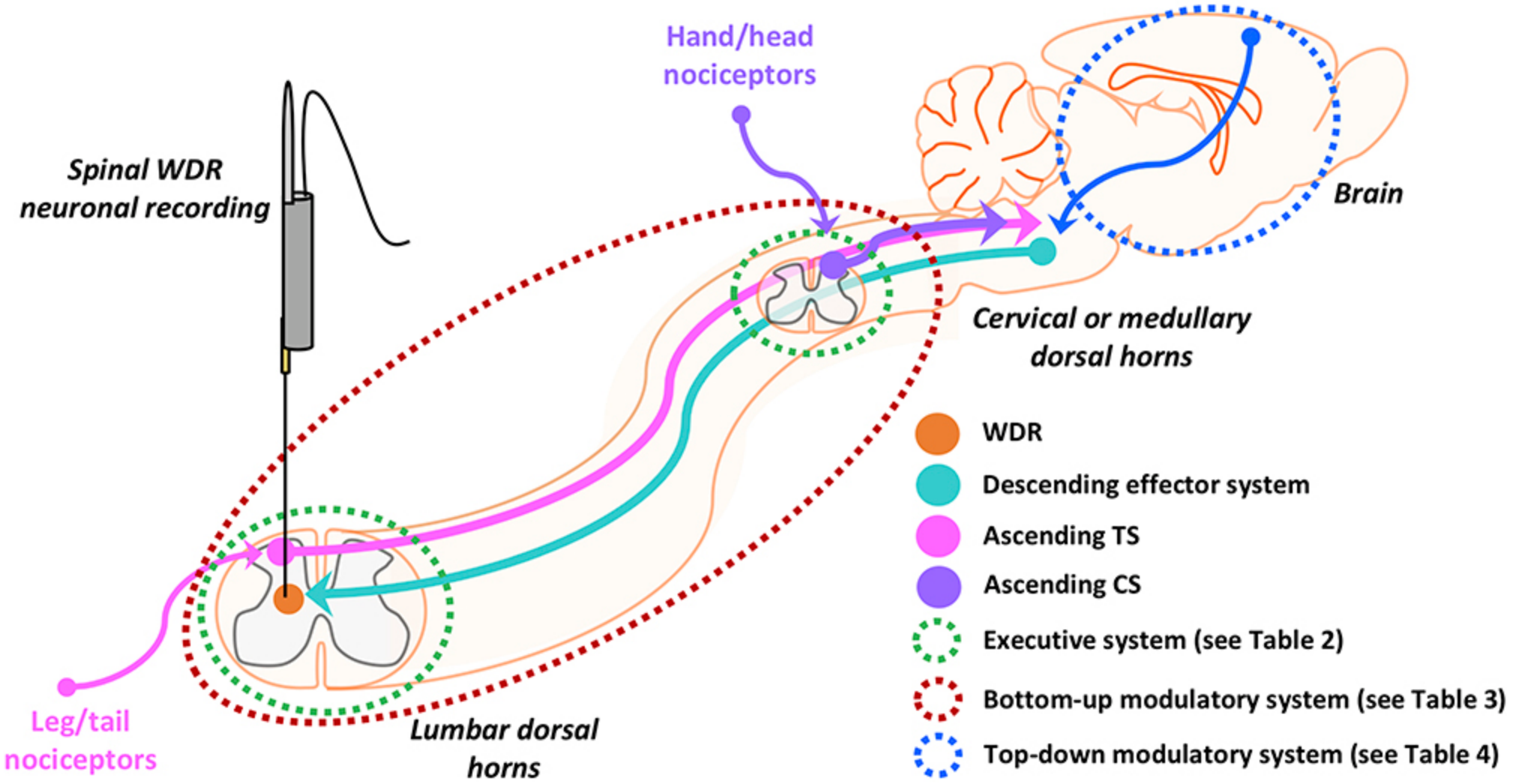
Multireceptive neurons in the Ncl. dorsalis reticularis respond to DNIC



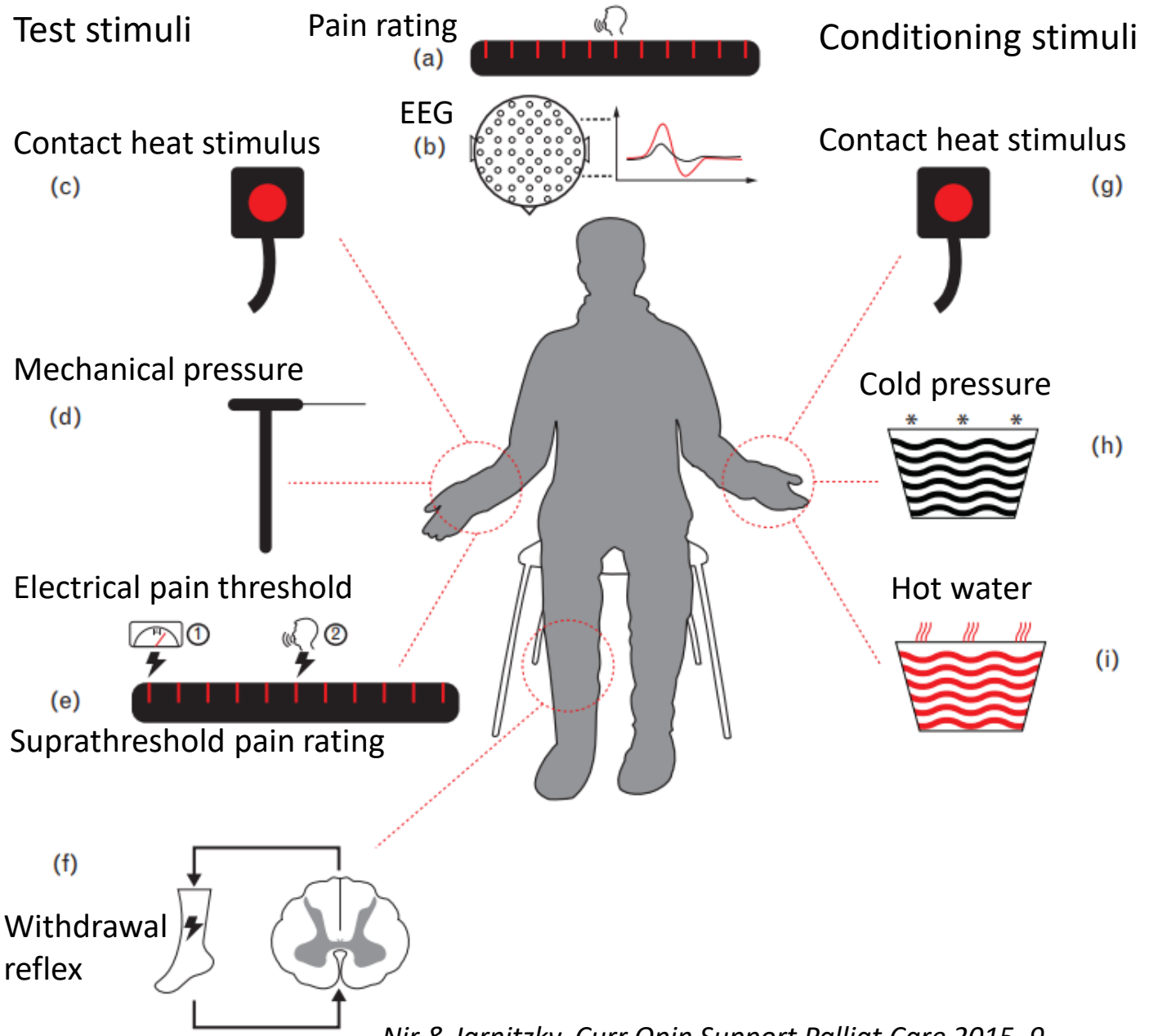
D. Le Bars, Brain Res. Rev. 40 (2002)

Multireceptive neurons in the dorsal horn are silenced by short noxious stimulation of multiple areas (Aδ- and C-fibers input) for *many minutes*. The dorsal reticular nucleus in the caudal medulla is involved in the "diffuse noxious inhibitory controls" (DNIC).

Hypothetic system of diffuse noxious inhibitory controls (DNIC)



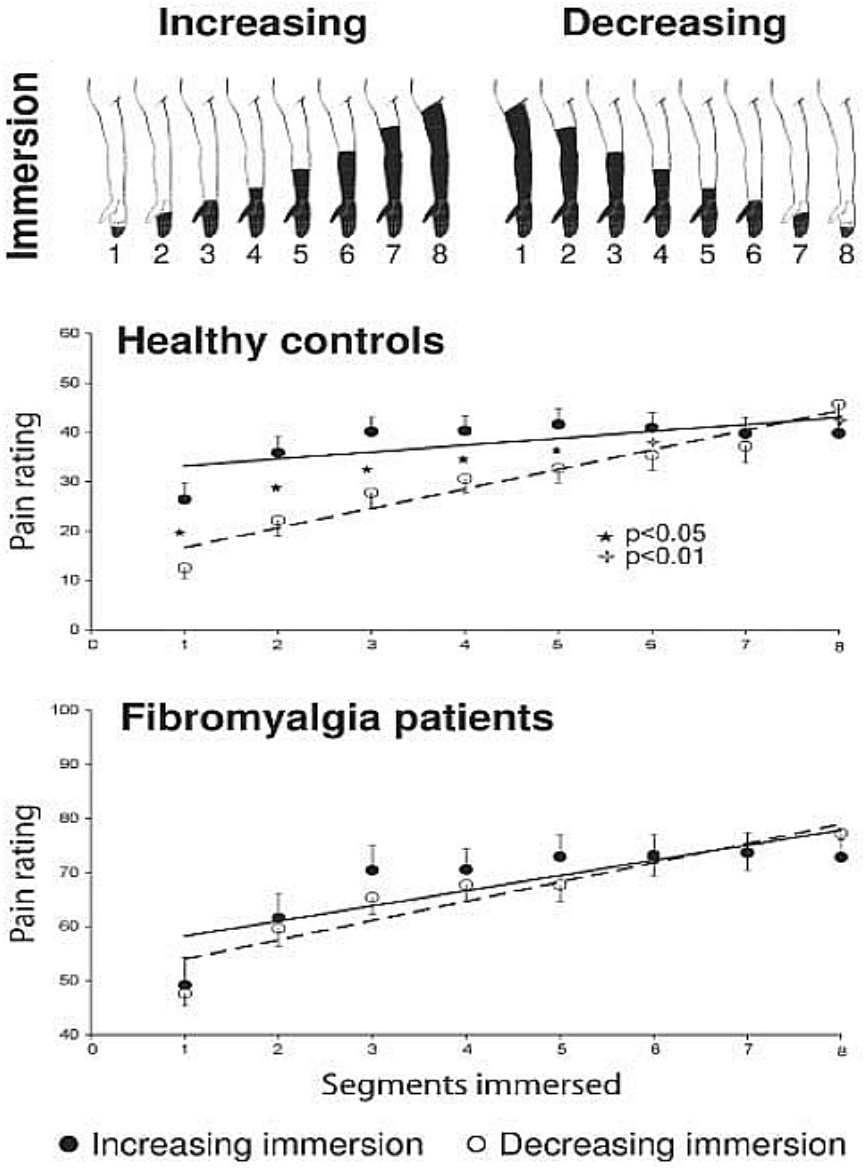
Conditioned pain modulation testing DNIC in humans



Nir & Jarnitzky, Curr Opin Support Palliat Care 2015, 9

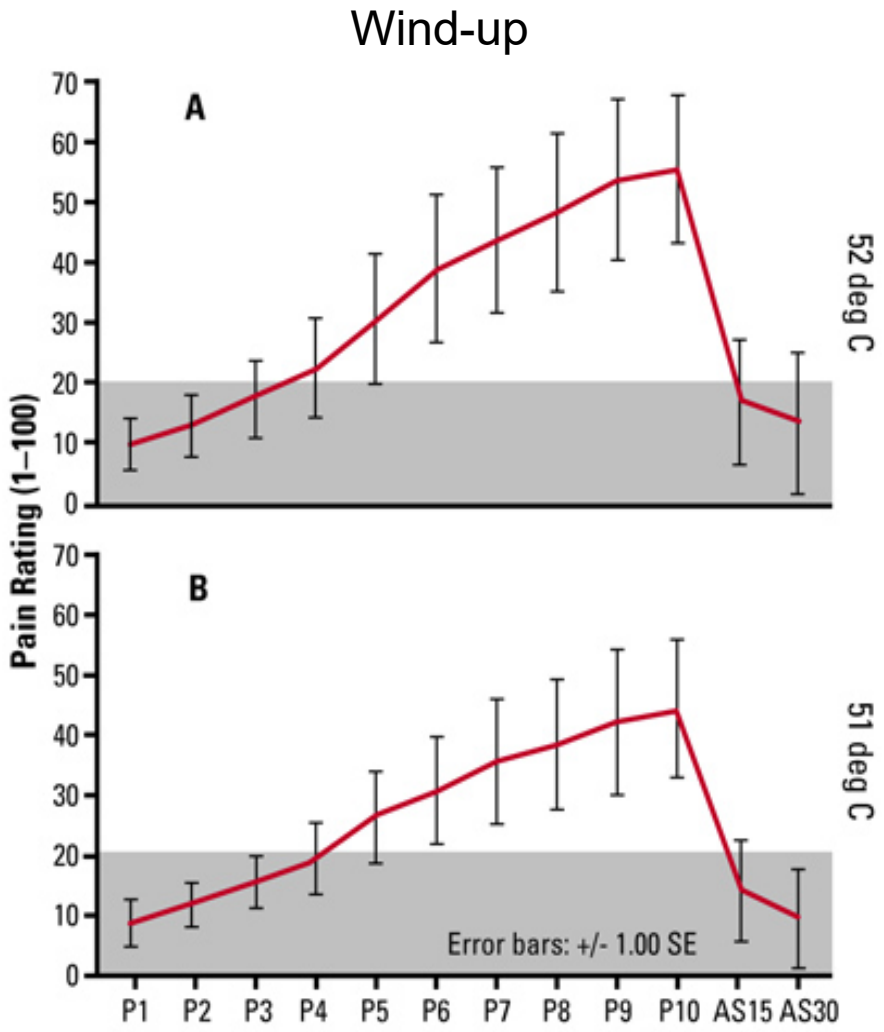
- Conditioned pain modulation tests are appropriate for testing the effect of DNIC in humans. Thereby, pain rating or objective parameters of pain (EEG) to noxious thermal, mechanical or electrical stimuli are assessed before and after a *homo- or heterotopic* conditioning stimulus. Decreased responses to test stimuli indicate DNIC.

Pathological DNIC and wind-up phenomenon of pain ratings in fibromyalgia patients



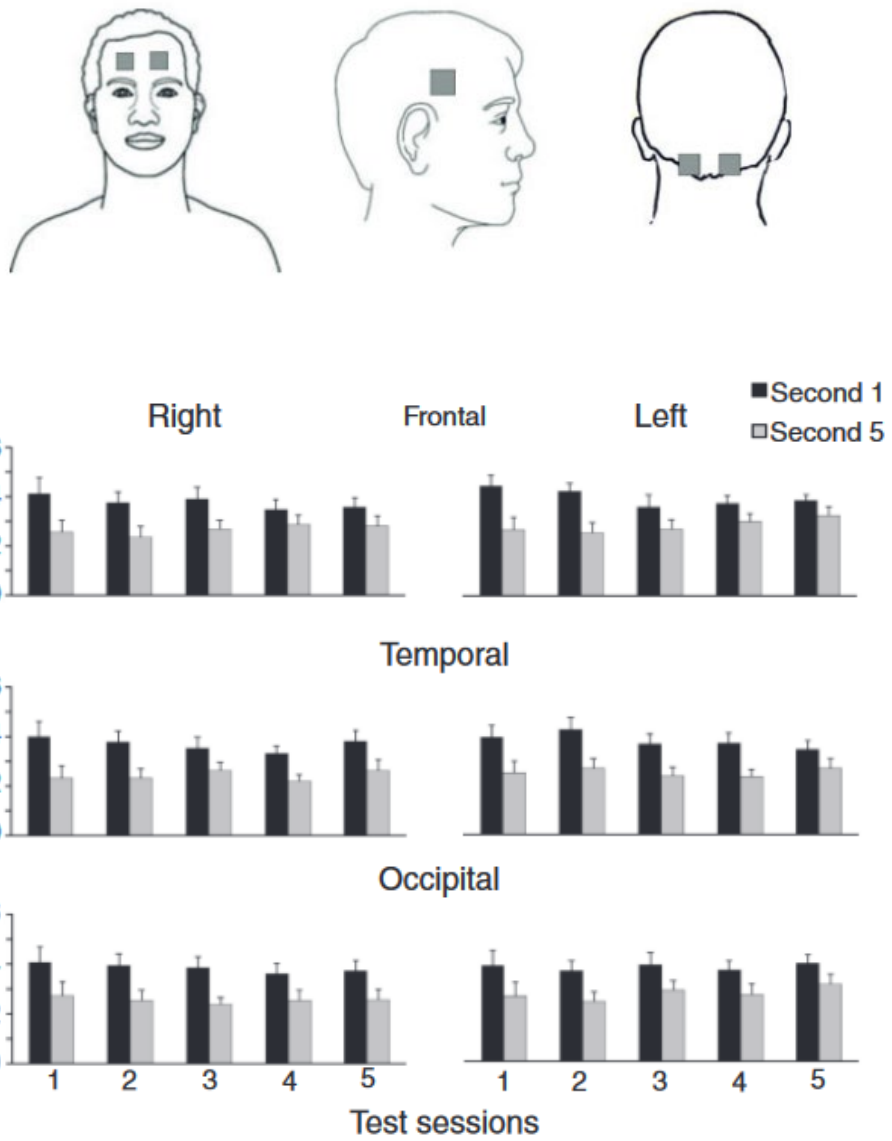
- Noxious stimulation (heat) of an increasing followed by a decreasing area is usually followed by less pain rating (habituation).
  This habituation is lacking in patients with fibromyalgia.

- Repetitive noxious stimulation (heat) at same intensity causes an increase in pain rating („wind-up“ phenomenon) in fibromylagia patients.

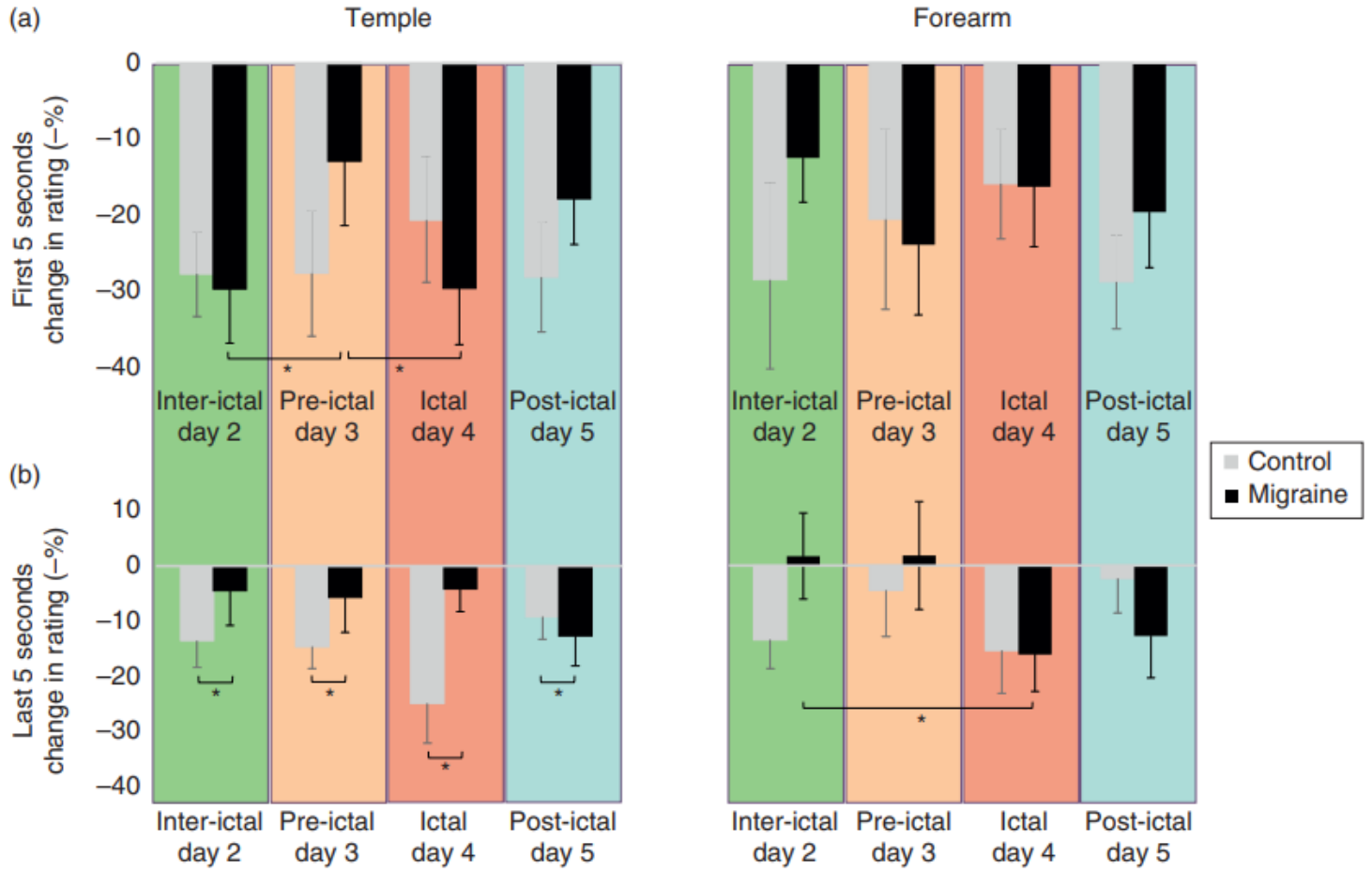


Julien et al., Pain 114 (2005)

DNIC may underlie habituation to painful stimuli – habituation deficit in migraine



Periodic painful electrical stimulation is experienced as less painful after stimulation of some seconds (habituation). This phenomenon is disturbed in migraine patients (habituation deficit), particularly in the ictal phase.



Strupf et al, Cephalalgia 2019;39:585–596

*Helfenstein et al, Cephalalgia 2022;*42:1148–1159

Adressed topics

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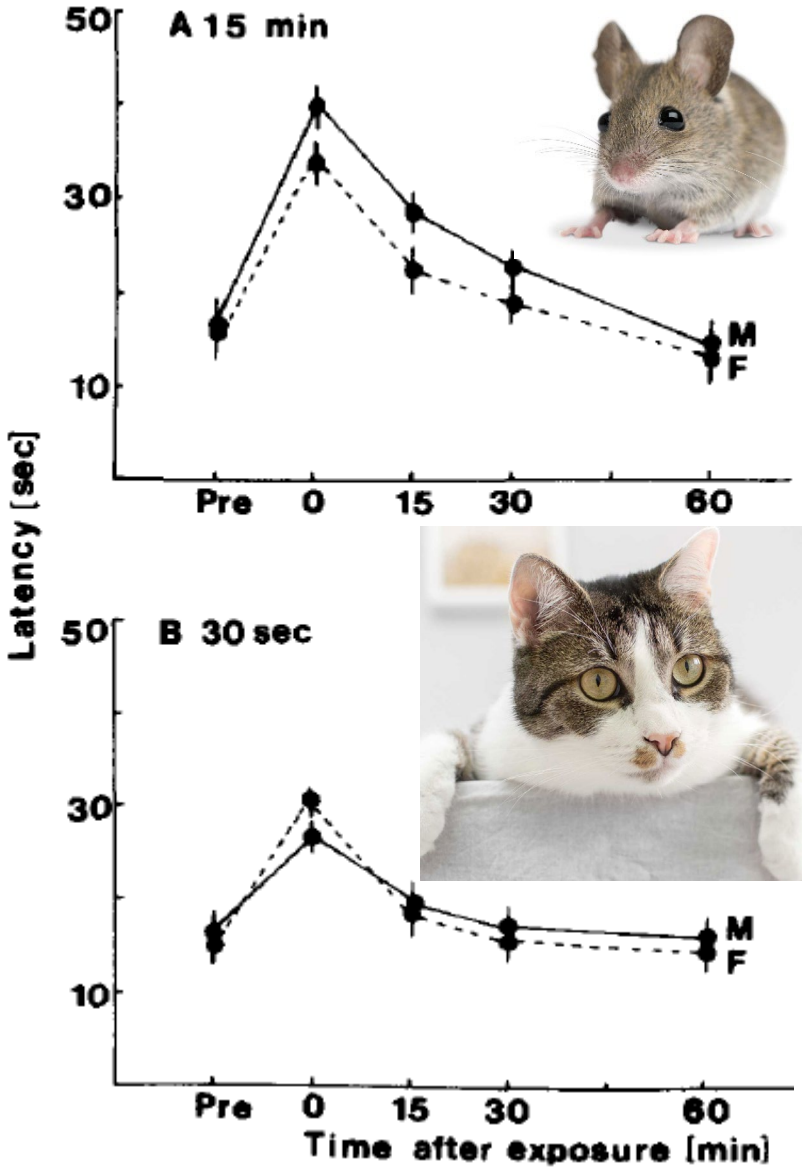
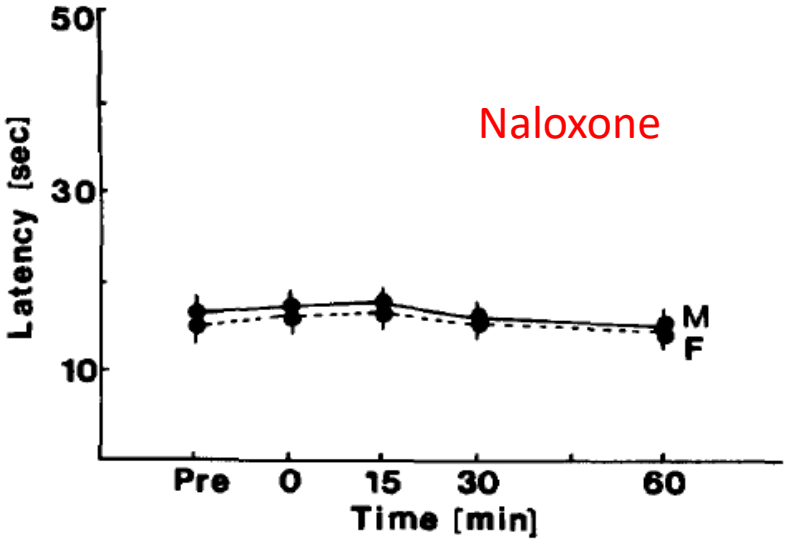
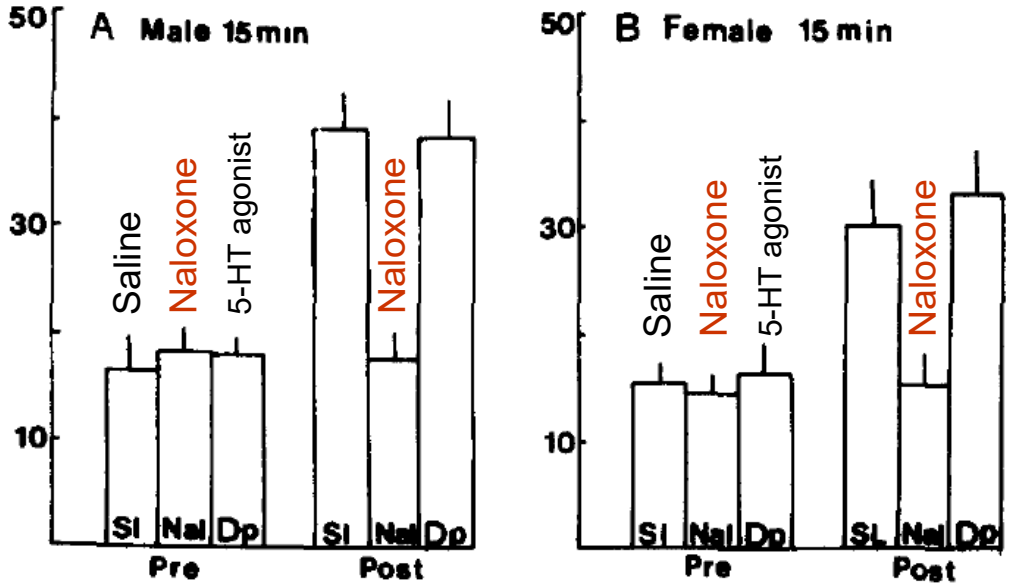
Predator-induced opioid-dependent analgesia in mice

Latency to heat (50°C) for licking behavior





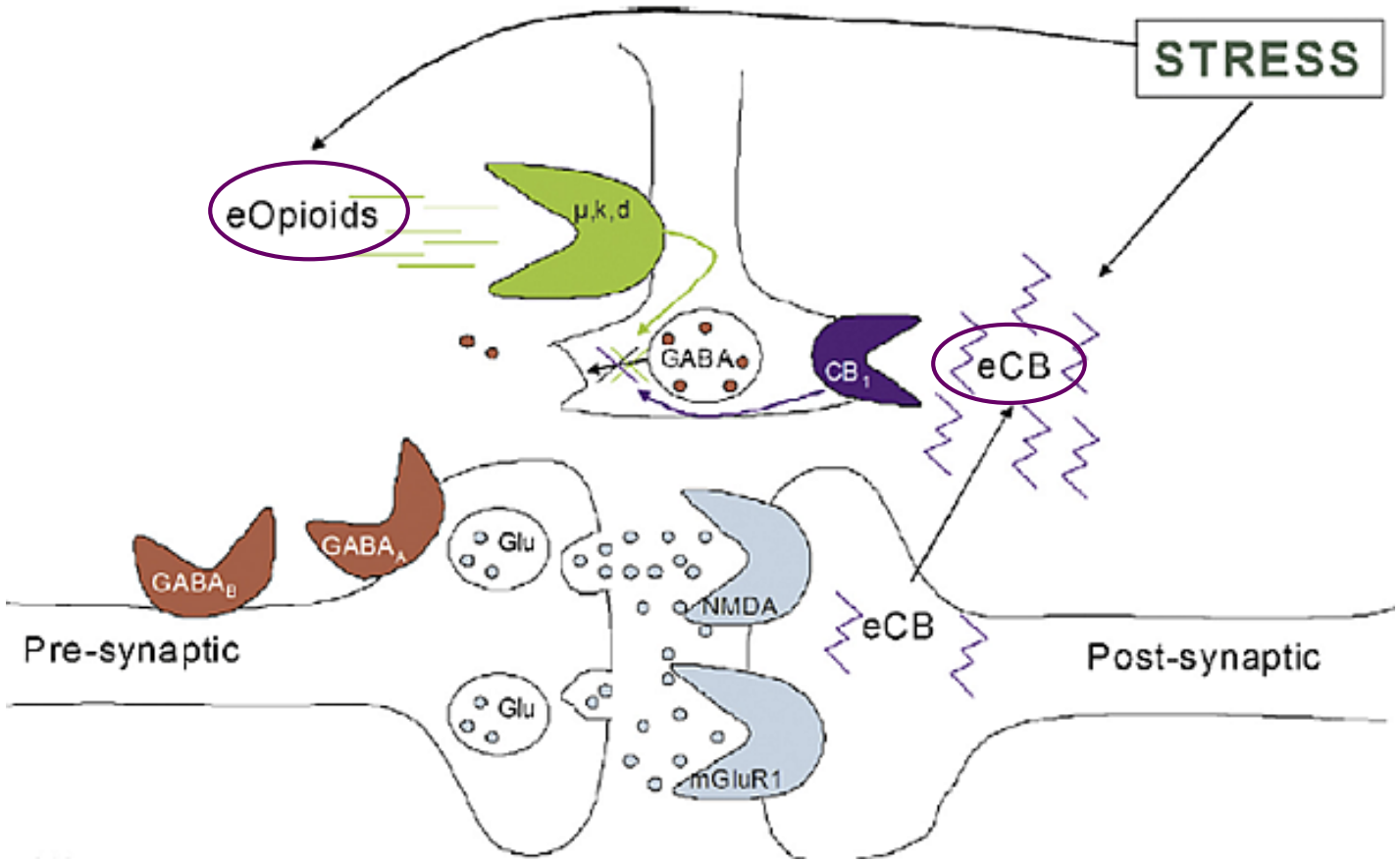
- Seeing a predator decreases licking behavior as a response to heat stimuli in mice. This analgesic effect is abolished by the opioid antagonist naloxone (opoid antagonist) showing the involvement of opioidergic mechanisms.

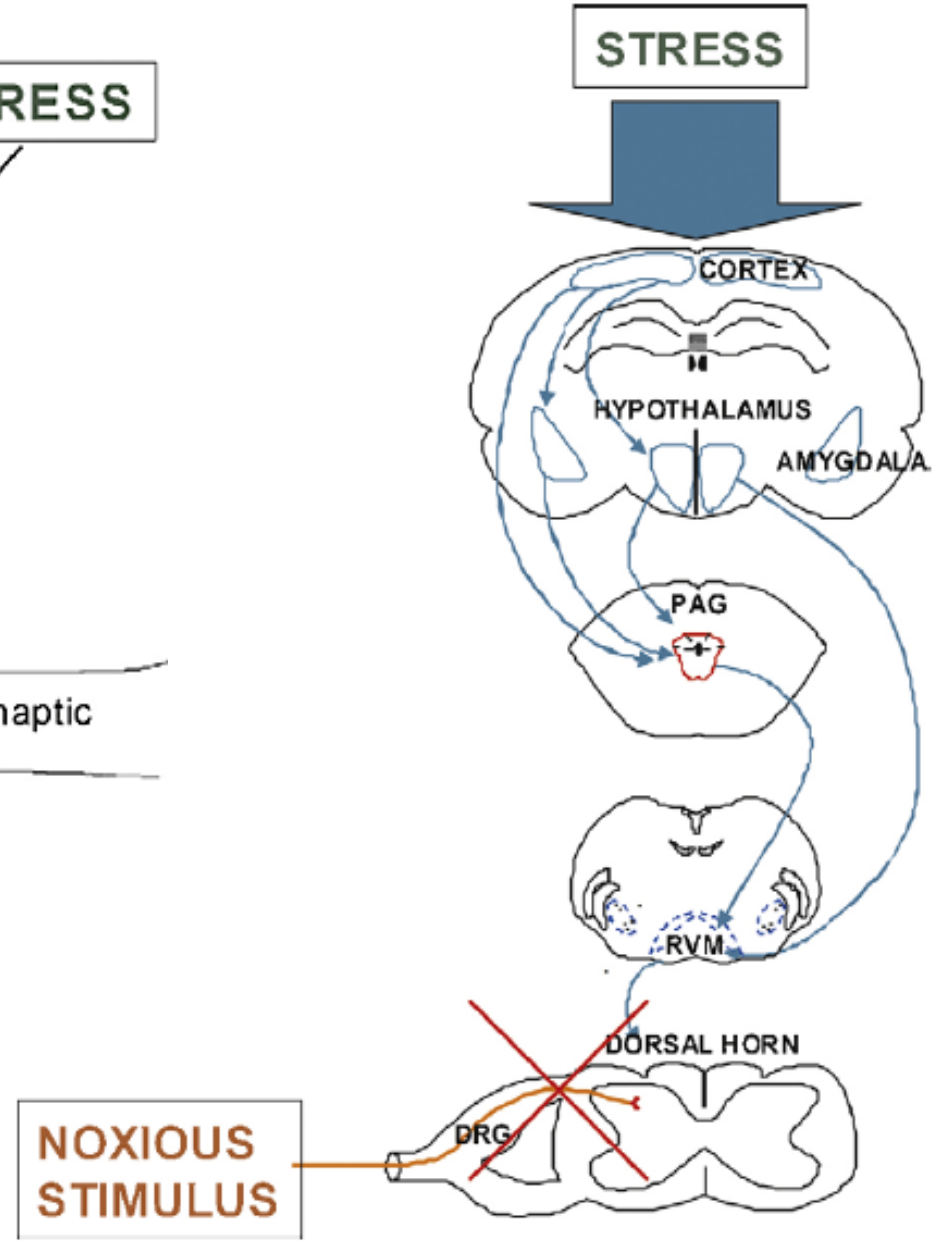


Stress-induced analgesia can be explained by central opioid mechanisms.

Kavaliers & Colwell, Brain Res. 568 (1991)

Proposed presynaptic mechanism of stress-induced analgesia



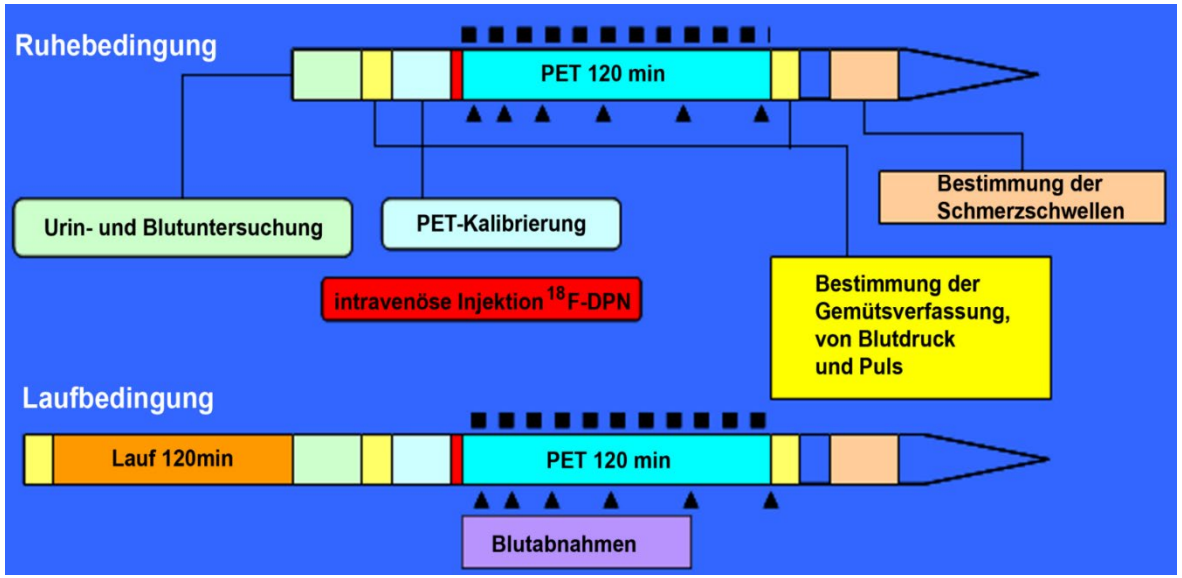


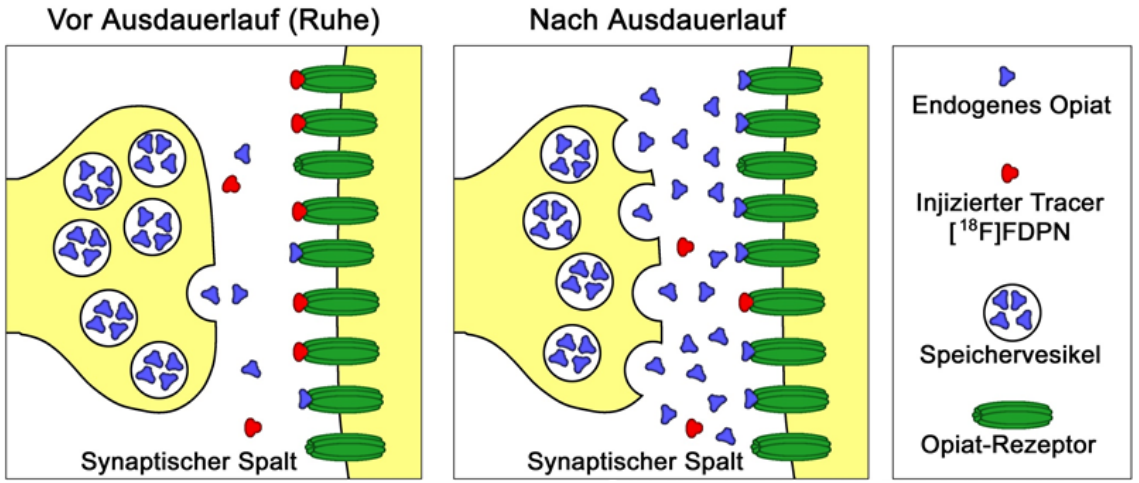
- Acute stress may cause secretion of endogenous opioids and endocannabinoids causing spinal analgesia.

Butler & Finn, Progr. Neurobiol. 88 (2009)

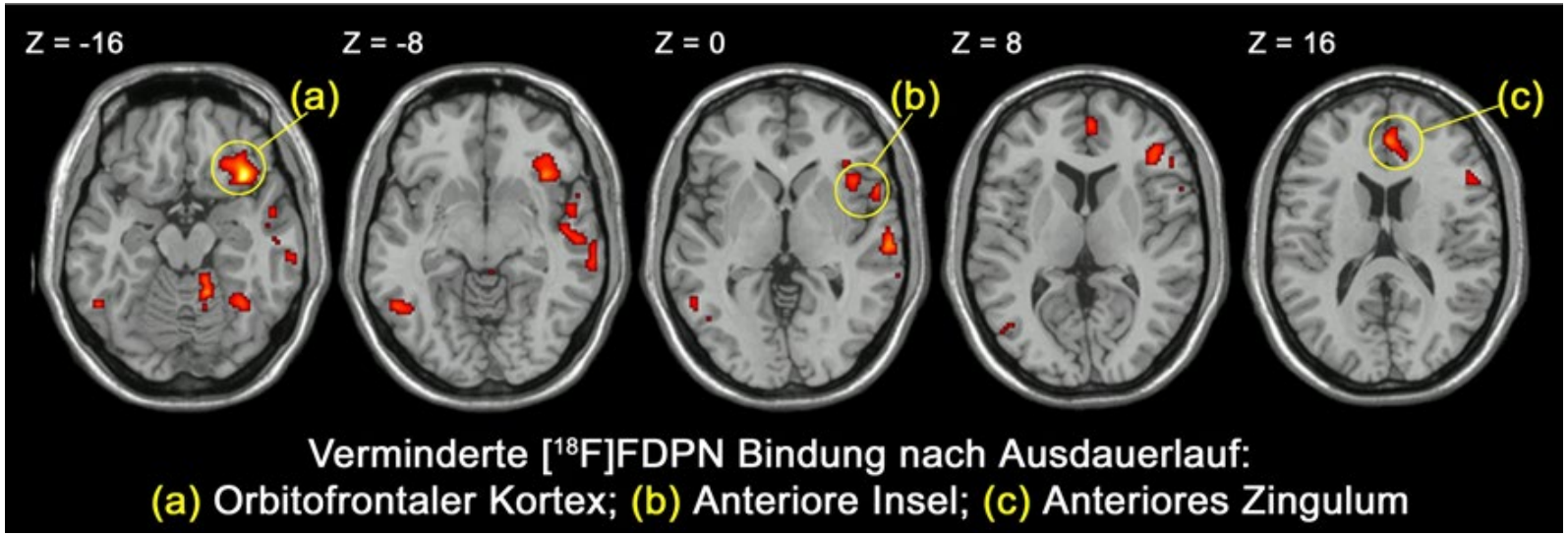
Opioid release in long-distant runners („runners high“)

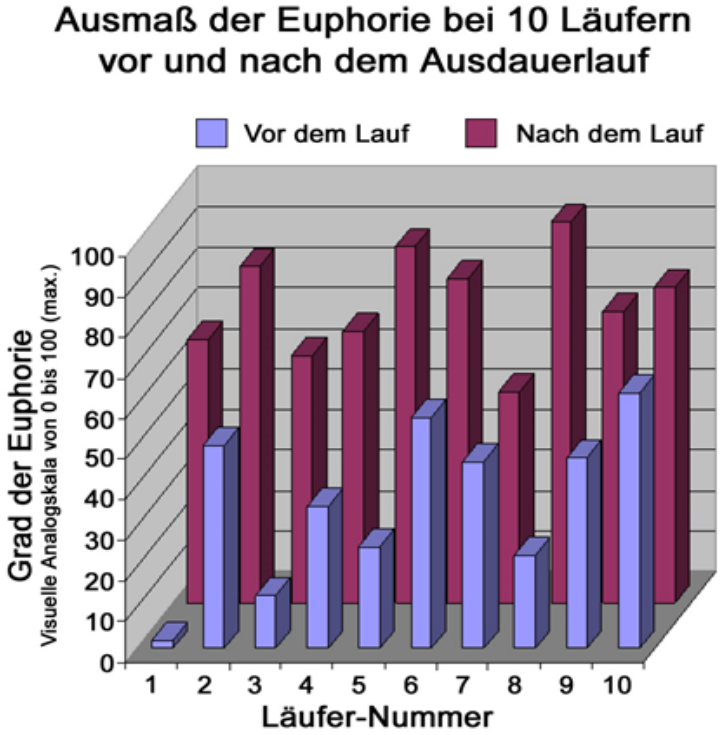
Versuchsablauf





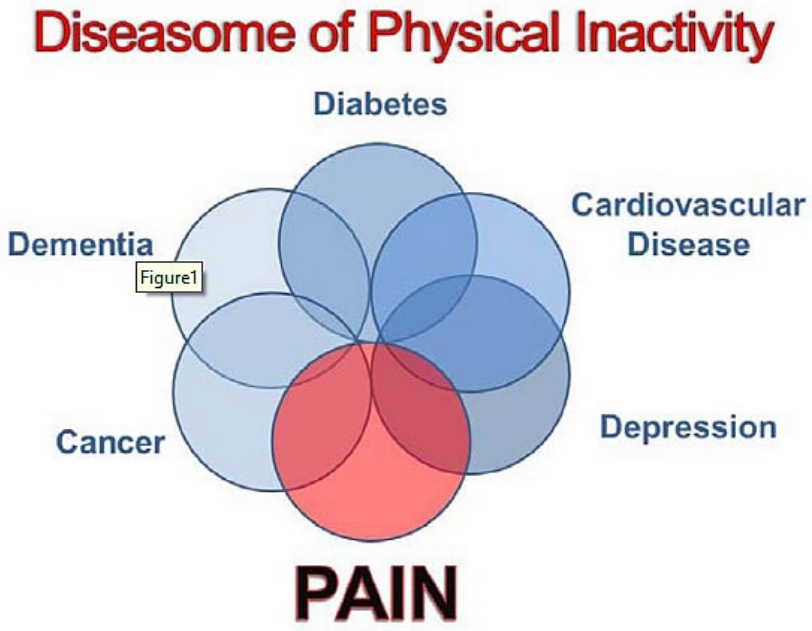
^{18}F-DPN = Fluor-markiertes Diprenorphin



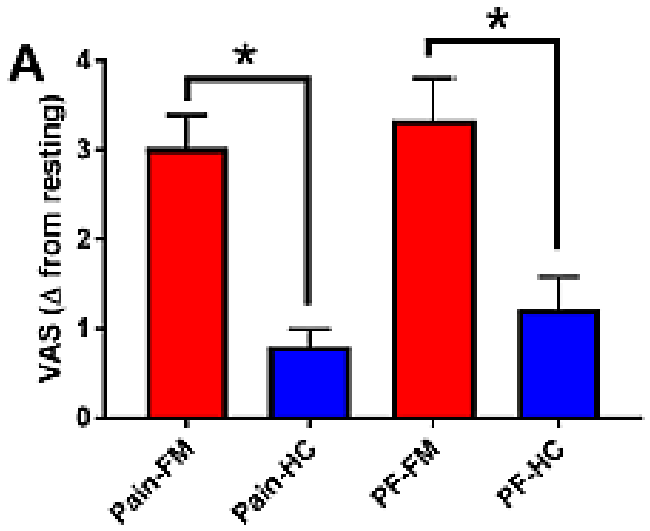


H. Boecker et al, Cereb Cortex 2008; 18: 2523-31; Methods 2008; 45: 307-318

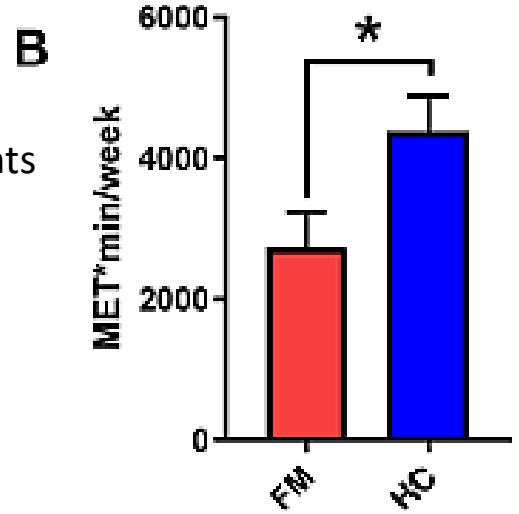
Pain, fatugue and excercise in fibromyalgia



Pain and fatigue



Physical activity



FM = fibromyalgia patients
HC = healthy controls
MET = activity measure
PF = physical fatigue
VAS = visual analog scale

A. In fibromyalgia patients both pain (measured on a visual analog scale) and physical fatigue are significantly increased.

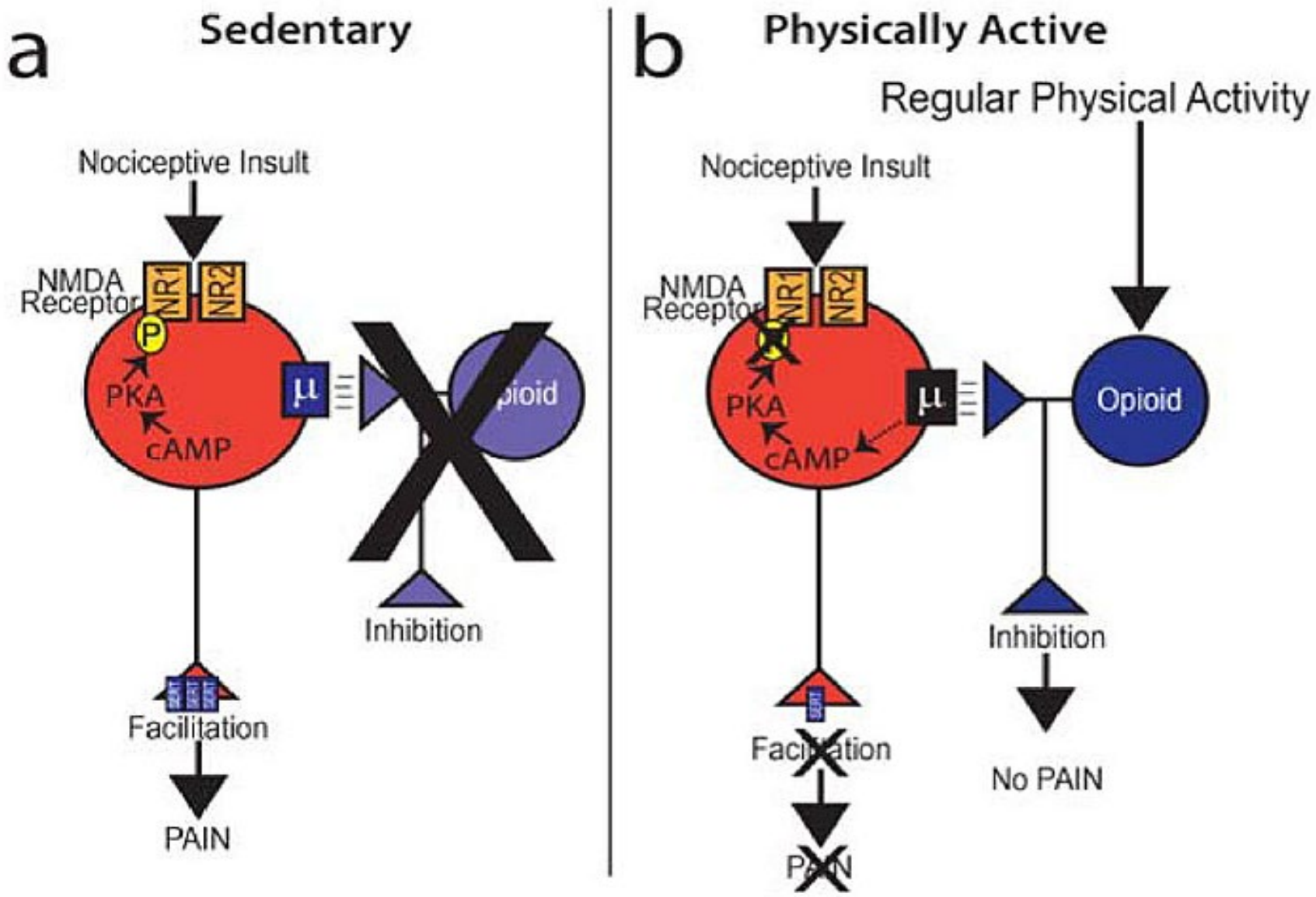
B. This is the main reason why fibromyalgia patients are significantly less active than healthy controls.

Chronic painful diseases like fibromyalgia are frequently accompanied by decreased activity, which finally increases the pain.

Therefore, light exercise is essential for these pain patients.

K. Sluka et al, Pain 2018; 159 (Suppl 1): S91-97

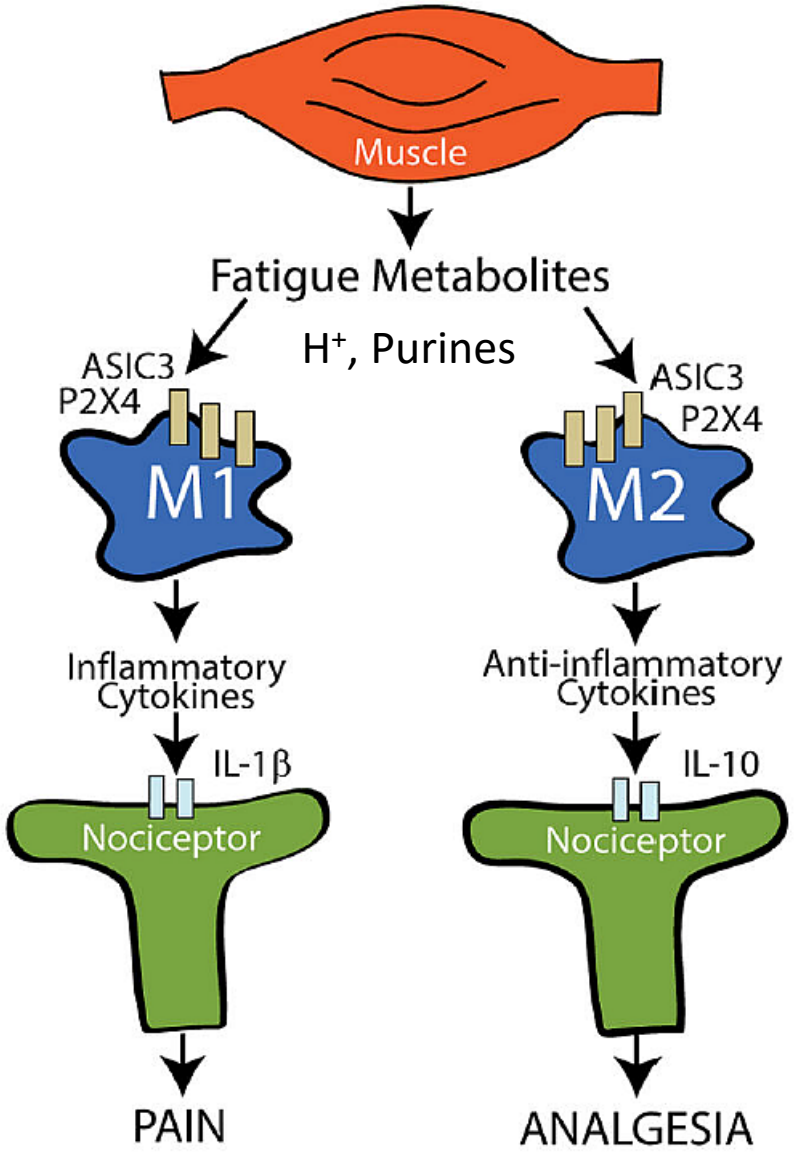
Changes in spinal neurotransmission and activity of macrophages



- Sedentary behavior facilitates nociceptive transmission in the dorsal horn at NMDA receptors and suppresses the antinociceptive activity of opioidergic interneurons, while physical activity increases opioidergic effects.

K. Sluka et al, Pain 2018; 159 (Suppl 1): S91-97

Changes in spinal neurotransmission and activity of macrophages



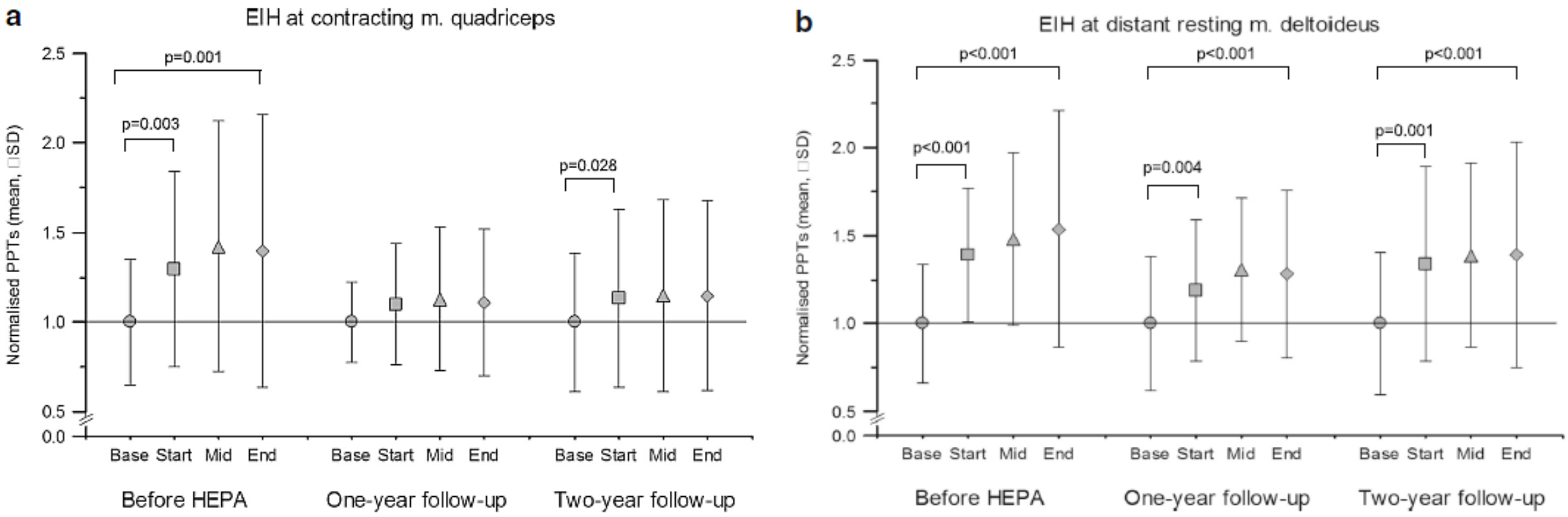
- Fatigue muscles release metabolites like protons and purines, which induce the formation of type-1-macrophages that secrete inflammatory and noxious cytokines like IL-1b.

Light exercise causes formation of type-2-macrophages with anti-inflammatory and anti-nocicpetive cytokines like IL-10.

Muscle activity can significantly contribute to pain therapy due to its anti-inflammatory effect.

K. Sluka et al, Pain 2018; 159 (Suppl 1): S91-97

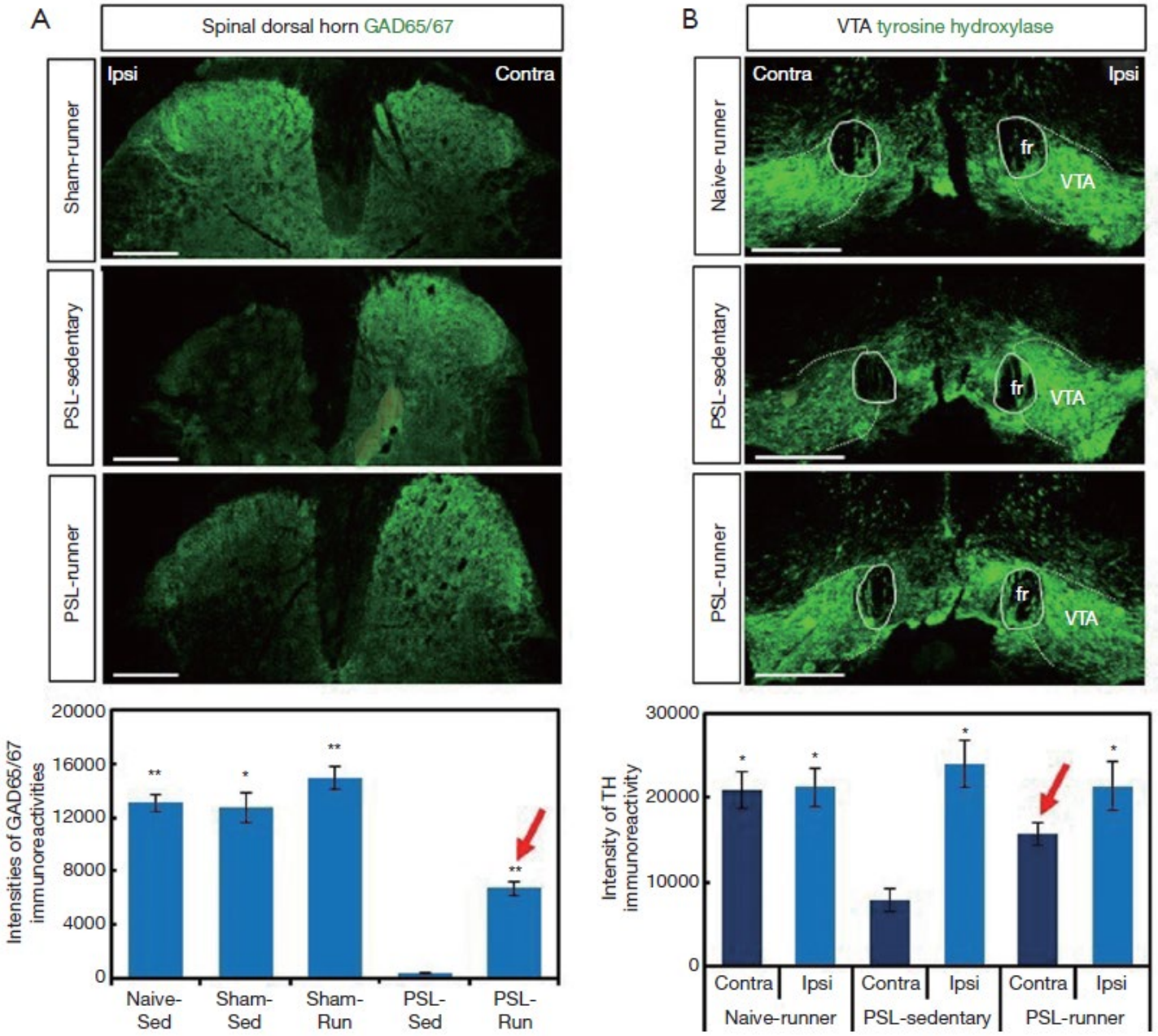
Impact of physical activity on pain sensation in patients with rheumatoid arthritis



In patients with rheumatoid arthritis after physical training and moderate aerobic (HEPA) the pain pressure thresholds (PPTs) increase (i.e., the pain decreases). This seen both at the trained muscle (M. quadriceps, **a**) as well as at not trained muscles (M. deltoideus, **b**). This indicates multisegmental improvement of the pain symptomatics.

M. Löfgren et al, Arthritis Research & Therapy 2018

Impact of physical activity on the production of GABA and dopamine

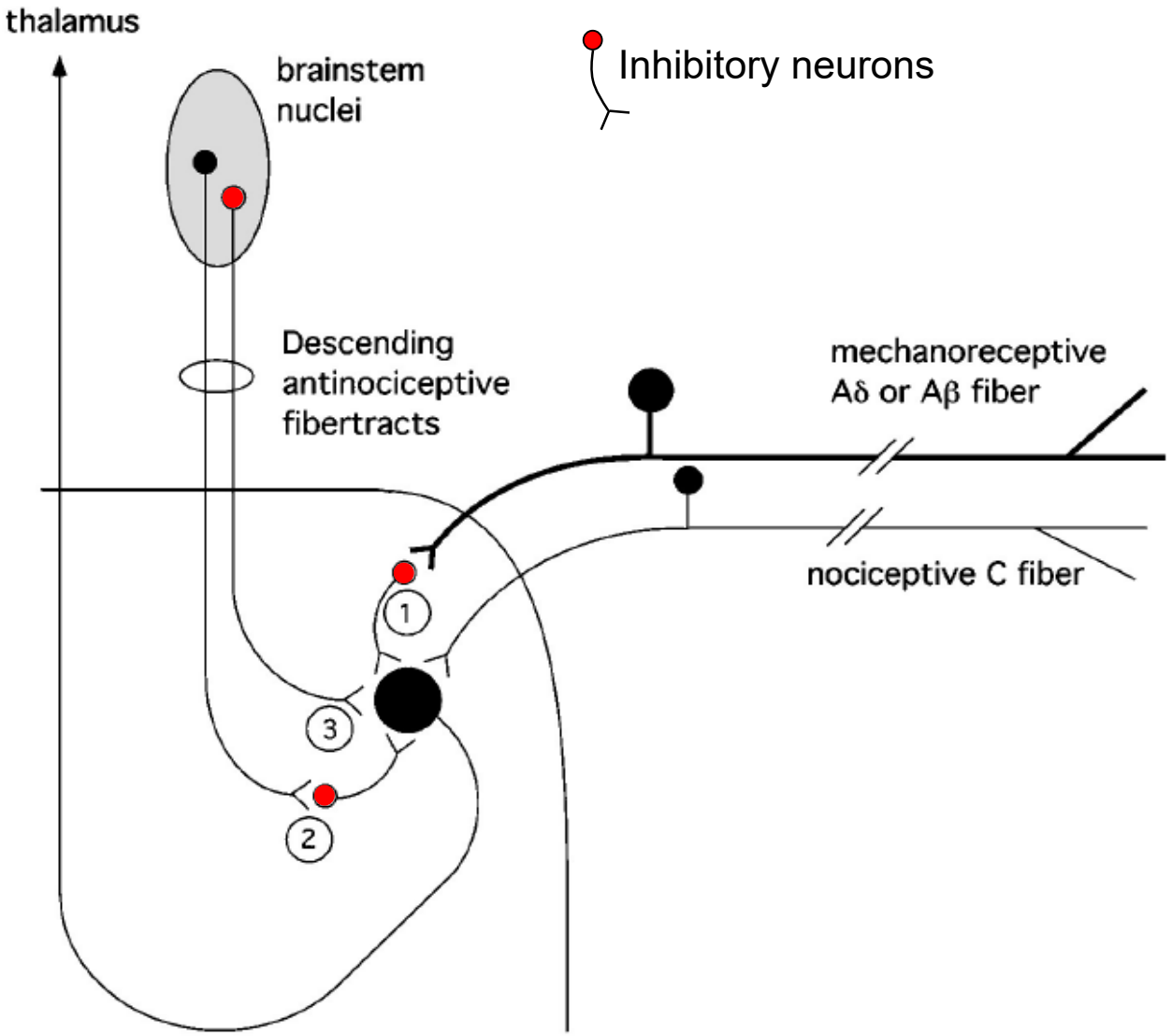


After partial ligature of the sciatic nerve (N. ischiadicus) as a model of neuropathic pain, GAD65/67 (glutamate decarboxylase, a marker for GABA production) in the ipsilateral dorsal horn and tyrosine hydroxylase (a marker for dopamine synthesis) in the contralateral ventral tegmentum are decreased. Following physical activity (running wheel) this loss of GABA and dopamine is partly compensated (red arrows) and the pain thresholds are normalized.

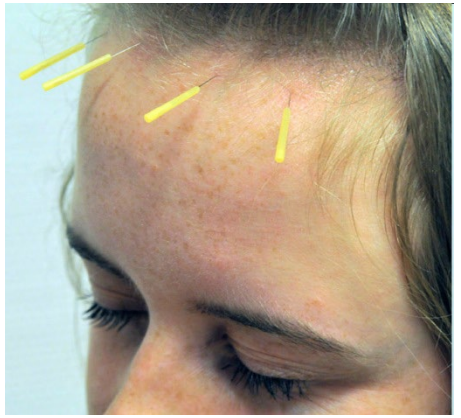
Neuropathic pain, which is partly due to the loss of GABAergic inhibition in the dorsal horn and the anti-depressive dopamine production in the tegmental area, can be alleviated through physical activity, which partly compensates this loss.

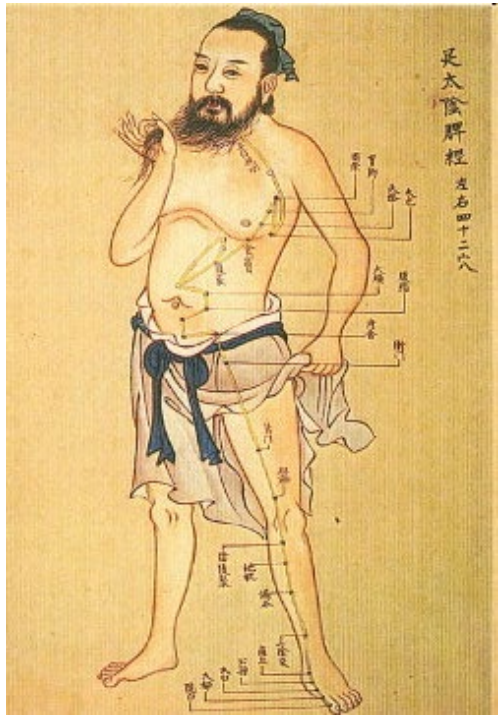
M. Löfgren et al, Arthritis Research & Therapy 2018

Principles of descending and segmental inhibitory systems in the dorsal horn



Zeilhofer, Cell. Mol. Life Sci. 2005



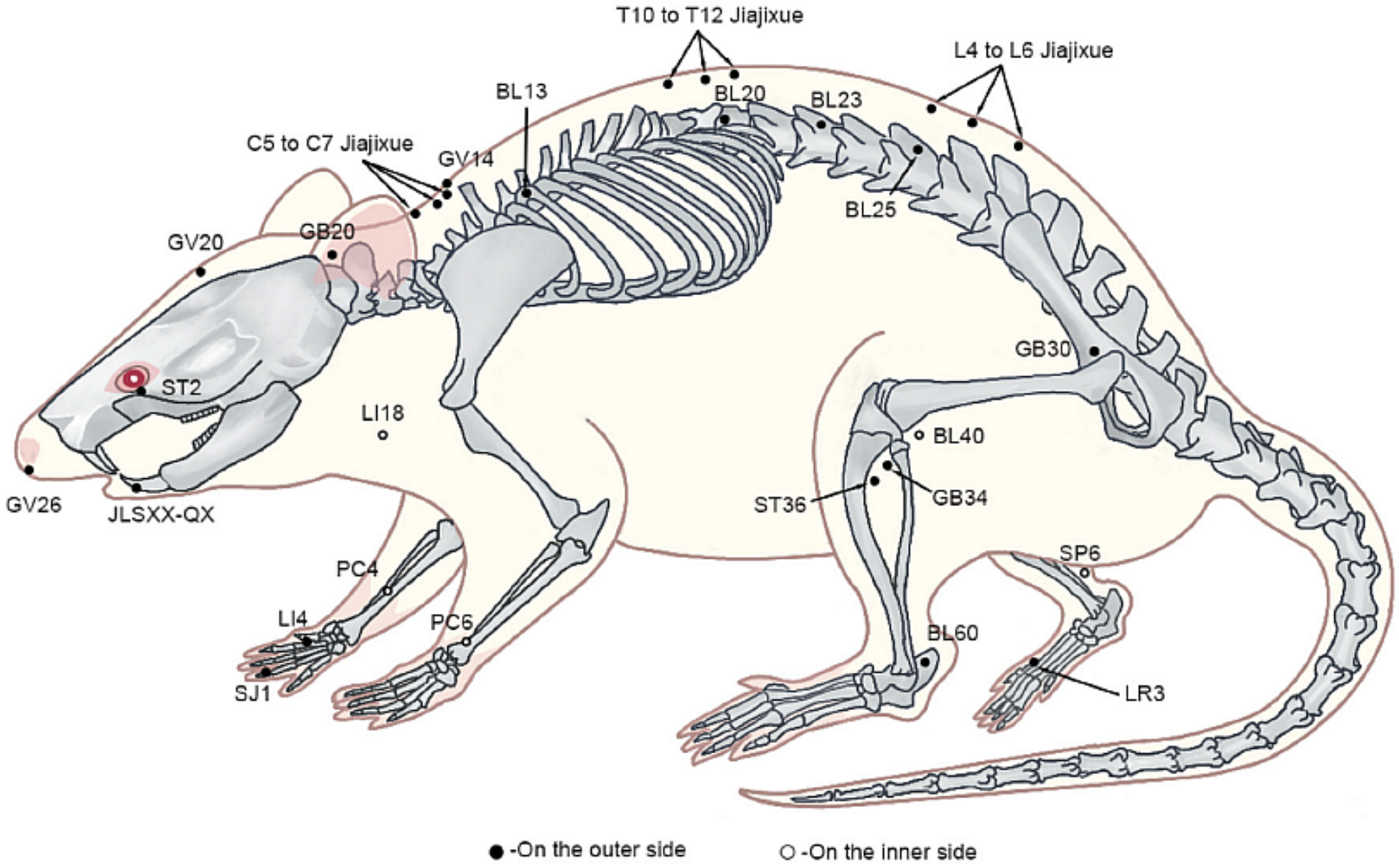


① Inhibitory interneuron, activated by mechanoreceptive afferent pathway

② Inhibitory interneuron, activated by descending efferent pathway

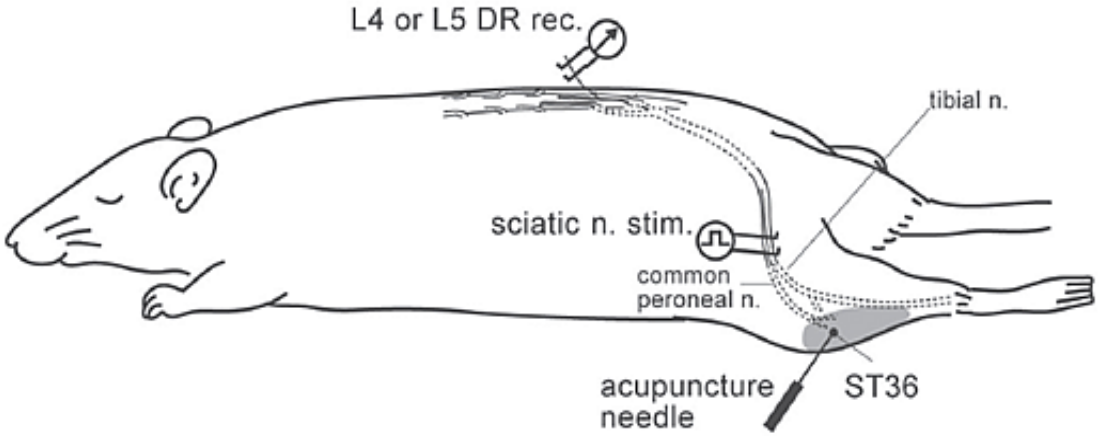
③ Directly inhibitory, descending pathway

Acupuncture points in the rat

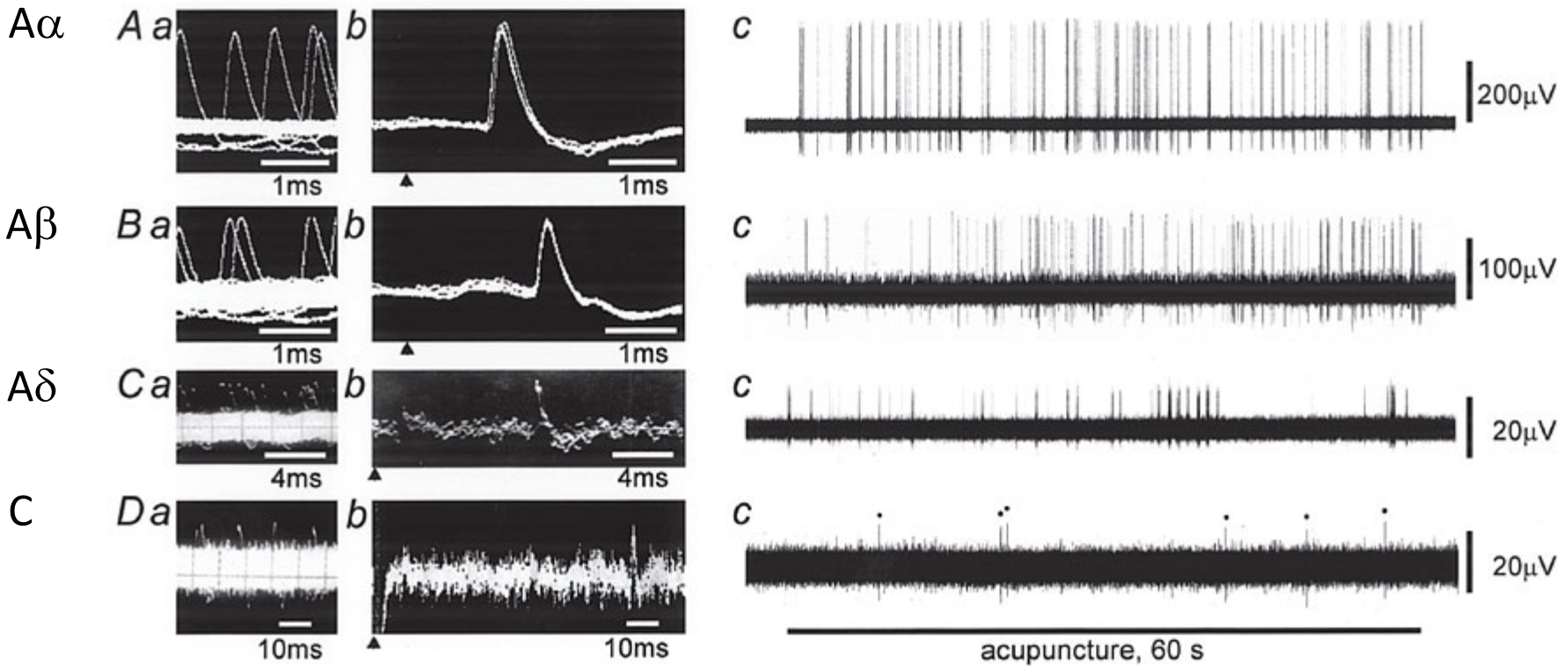


Y. Chen et al., Front Neurology 2023; 14: 1093849

Activation of afferent fibers of all groups through acupuncture



- Recordings from single afferent fibers in the lumbar dorsal roots show activation of all fibers during acupuncture.

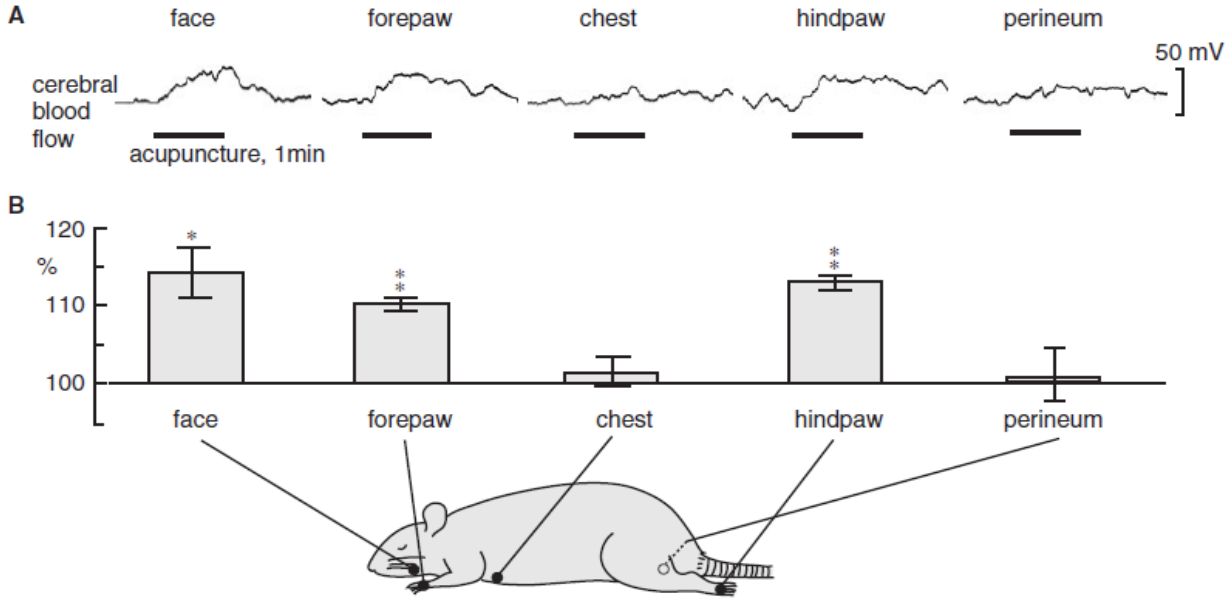


Acupuncture activates both low- and high-threshold (nociceptive) afferents. The pain inhibitory effect of acupuncture may (at least partly) depend on counter-irritation.

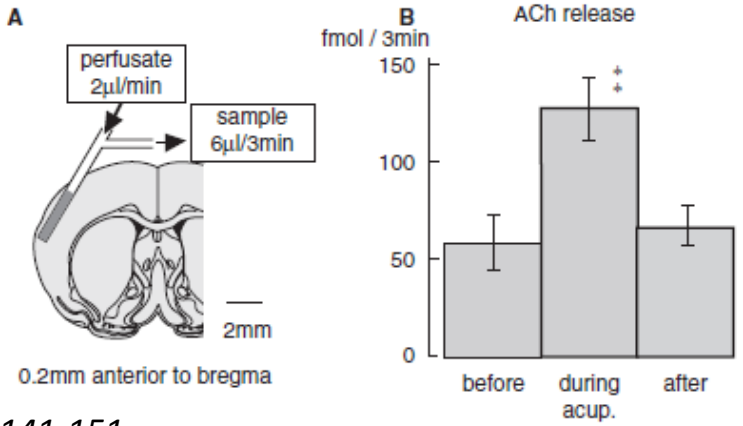
Kagitani et al., Jap. J. Physiol. 55 (2005)

Effects of local „acupuncture“ and „acupressure“ in animals

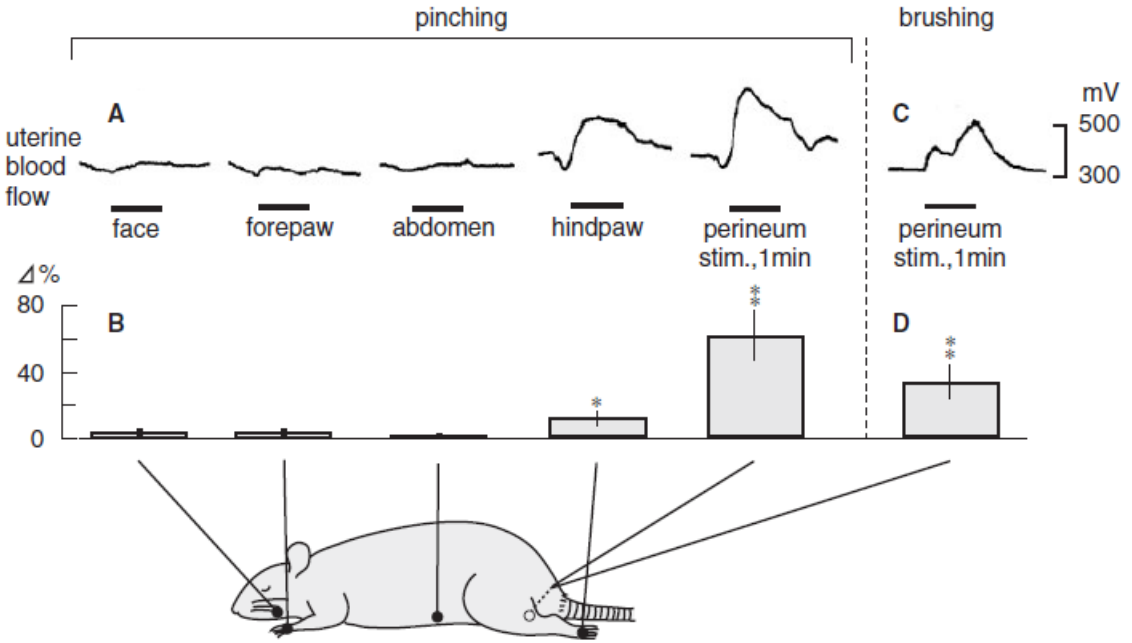
Central effect: Experimental acupuncture in the face as well for- and hindlegs increases **cerebral blood flow** and the relase of acetyl choline in the parietal cortex.

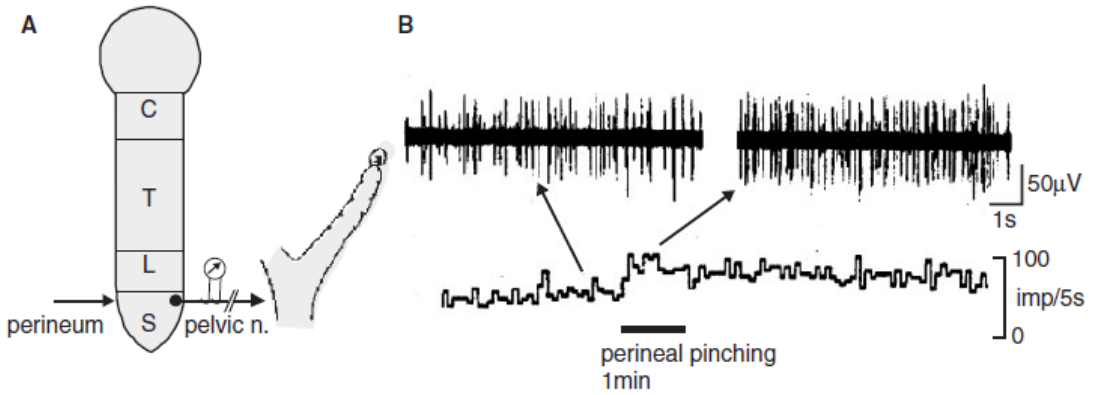


„Acupuncture“ and „acupressure“ have central and peripheral autonomic effects.



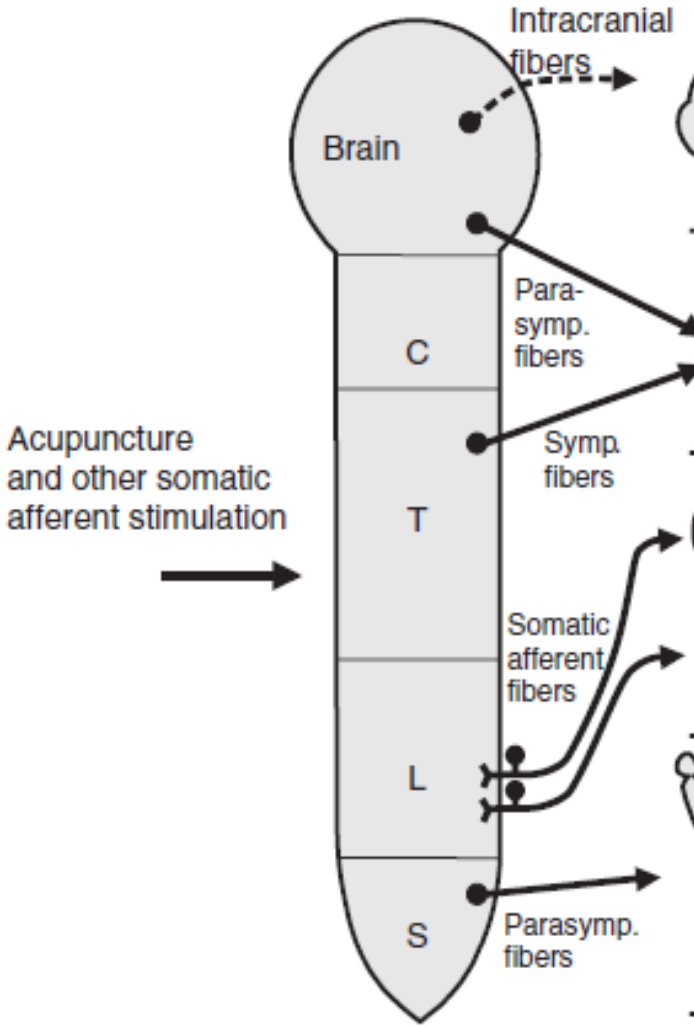
Segmental effect: noxious and non-noxious stimulation of hind foot and tail increases the **uterine blood flow** and the neuronal activity of the pelvic nerve.





S. Uchida & H. Hotta, aCAM 2008; 5: 141-151

Effects of local „acupuncture“ and „acupressure“ in animals



Organs	*Blood flow response*	*Efferent nerve path way*	*Neurotransmitters*	*References*
Cerebral cortex	Increase	Intracranical fibers	Acetylcholine	19
Eyeball	Increase	Parasympathetic fibers	Nitric oxide	31
	Decrease	Sympathetic fibers	Noradrenaline	
Peripheral nerve	Increase	Somatic afferent fibers	CGRP	32
Skeletal muscle	Increase	Somatic afferent fibers	CGRP	27
Uterus	Increase	Parasympathetic fibers	Acetylcholine	23

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Effects of acupuncture on nociceptive functions during acupuncture of rodents

References	Pain model	Species	Intervention methods	Acupoints	Acupuncture parameter	Pain-related behavior	Test site	Biochemical measurements
Wang et al. (31)	SNI	Rat	EA	ST36/SP6	2 Hz, 0.5–1.5–2 mA, 30 min	PWL	Lateral hypothalamus	c-Fos-Positive Orexin Neurons↑
Zhu et al. (32)	SNI	Mouse	EA	ST36/SP6	2 Hz, 0.1 mA, 30 min	PWT	Brains	rACC Glu -vlPAG↓
Xia et al. (33)	SNI	Rat	EA	ST36/SP6	2 Hz, 1–2–3 mA, 30 min	PWT	L4–L6 spinal cord	HMGB1↓, TLR4↓, MyD88↓, NF-κB p65↓, CD11b↓
Ali et al. (34)	SNL	Rat	EA	ST36/SP6	2 Hz, 2–3 mA, 20 min	PWT	Spinal microglial	IL-10↑, β-endorphin↑
Wei et al. (35)	SNL	Rat	EA	GB30/GB34	2 Hz, 1–2–3 mA, 30 min	PWT	L5 DRGs	p-AXL↓, AXL↓
Zheng et al. (36)	SNL	Rat	EA	ST36/BL60	2/100 Hz, 1.5 mA, 30 min	MWT and TWL	L4–6 spinal cords	Iba-1↓, BDNF↓, P2X4↓, GABAAγ2↑
Liang et al. (37)	SNL	Rat	EA	ST36/BL60	2 Hz, 0.5–1.0–1.5 mA, 30 min	PWT and PFD	L4 DRG	P2X3R↓
Wu et al. (38)	SNL	Rat	EA	ST36/BL60	2 Hz, 1.5 mA, 30 min	MWT and TWL	L4–6 DRG	P2X7R↓, p-p38↓, Iba1↓ BDNF↓, IL-1β↓, IL-6↓, TNF-α↓, IL-10↑
Wang et al. (39)	SCI	Rat	EA	PC5/PC6	2 Hz, 2 mA, 20 min	PWT and PWL	L4–6 spinal dorsal horn	p-mTOR↓, p-S6K1↓, p-4E-BP1↓, SP↓, CGRP↓
Ji et al. (40)	SCI	Rat	EA	EX-B 2/BL25/BL40/BL60	1–2–3 mA, 2/100 Hz, 20 min	TWL	L4–L6 spinal cord	COX 2↓
Hou et al. (41)	BPAI	Rat	EA	T10–T12 Jiajixue	2/15 Hz, 30 min	TWL	SC, MC, Cpu, DLT	Metabolic alterations of brain↑
Xu et al. (42)	BPAI	Rat	EA	C5–C7 Jiajixue	2/15 Hz, 1.5 mA, 30 min	MWT and TWL	Spleen and lymph nodes	CD4+ T cells↑, β-endorphin↑, IL-17A↑, p-p65 NF-κB↑
Fei et al. (43)	DNP	Rat	EA	ST36/BL60	1 mA and 2 Hz	PWT and PWL	L4–6 DRGs	P2X3R↓
He et al. (44)	DNP	Rat	EA	ST36/BL60	2/100 Hz, 1–2 mA, 30 min	PWL	L4–L6 DRGs	P2X3 receptors↓, CGRP↓
Tang et al. (45)	DNP	Rat	MA	BL14/BL21/BL24	20 min	MWT and TWL	L4–6 DRG	P2X4↓, OX42↓
							Serum	CXCR3↓, TNF-α↓, IL-1β↓, IL-6↓, GSP↓, lipid metabolisms↓
Zhou et al. (46)	DNP	Rat	EA	ST36/BL60	2 Hz, 1 mA, 15 min	PWT	L4–L6 DRGs	P2X3R↓, p-PKC↓
Li et al. (47)	PHN	Rat	EA	GB30/GB34	2 Hz, 1 mA, 30 min	MWT	L4–L6 DRGs	Netrin-1↓, DCC↓, UNC5H2↑
Gao et al. (48)	Neck-incision pain model	Rat	EA	LI18, LI4-PC6, or ST36-GB34	2/100 Hz, 1 mA, 30 min	PT	C2–C5 dorsal cervicospinal cord	ATP↑, P2X7R↑, fractalkine↓, CX3CR1↓
Qiao et al. (49)	Neck-incision pain model	Rat	EA	LI18, LI4-PC6, or ST36-GB34	2/100 Hz, 1 mA, 30 min	PT	C3–C6 DRG	SP↓, CGRP↓, GAD67↑
Qiao et al. (50)	Neck-incision pain model	Rat	EA	LI18/LI4-PC6/ST36-GB34	2/100 Hz, 1 mA, 30 min	PT	C3–6 DRGs	SP↓, GFAP↓, GABA A α2R↑, GABA B R1↑

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The multiple effects comprise inhibitory actions on the transduction (downregulation of TRPV1, HCN), decrease in neuropeptide release (substance P, CGRP) and pro-nociceptive cytokines (TNF-α, IL-1β), inhibition of spinal transmission (NMDA receptors, BDNF) and neuroinflammation (JAK2/STAT3) as well as strengthening of inhibitory transmission (GABA receptors, SOM) and the descending inhibition (β-endorphin, μ-receptors).

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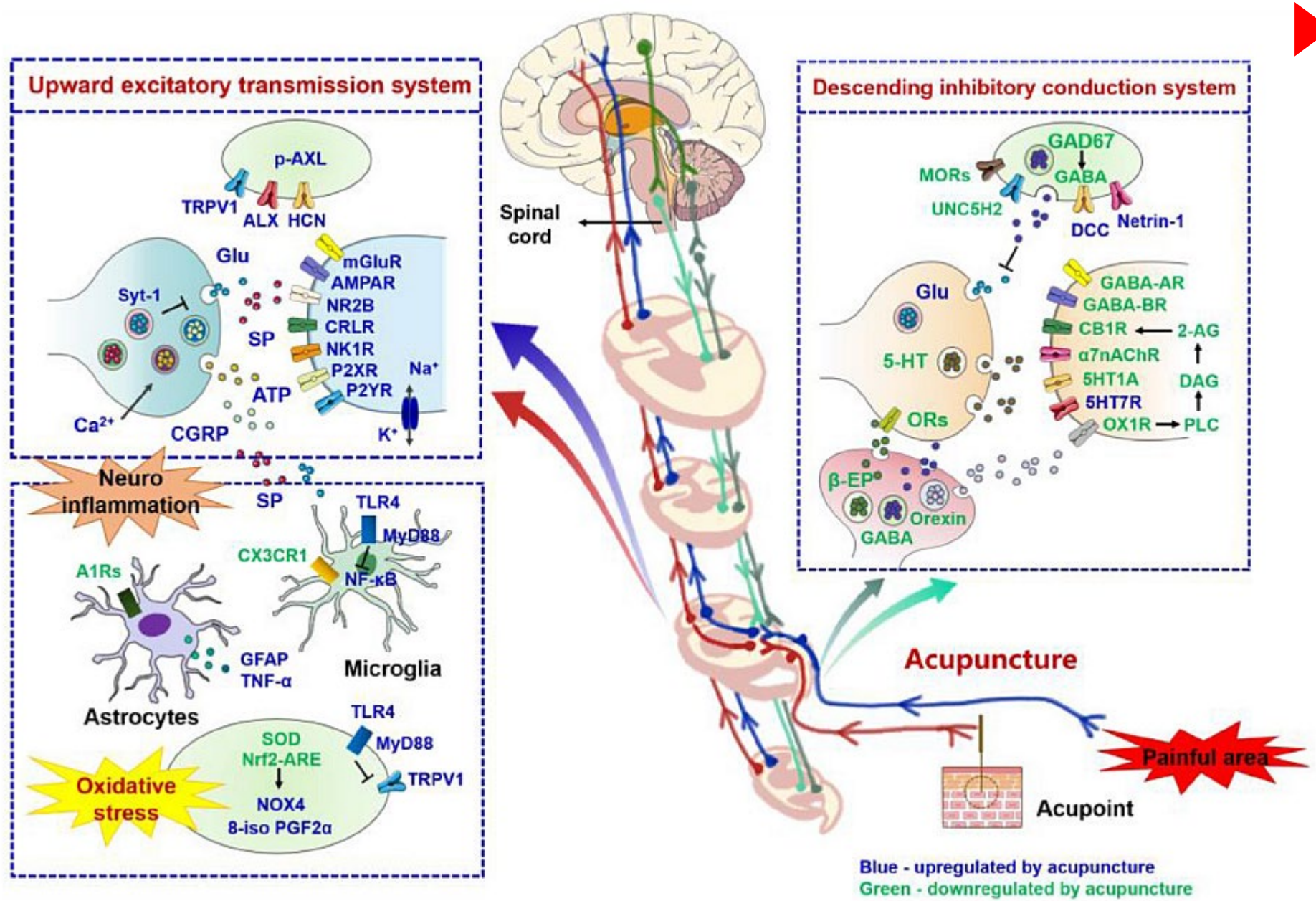

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Thank you for your patience