pharmazentrum frankfurt

Institut für Klinische Pharmakologie

Graduiertenkolleg Biologicals 1172

Chemical Mediators and Pain

Ellen Niederberger

PAIN

"An unpleasant, subjective, sensory and emotional experience associated with actual or potential tissue damage"

(IASP, 1979)

→ A universal experience that can span from mild discomfort to excruciating agony.

→ Alters quality of life

Nociception

measurable neurophysiological event of a type usually associated with pain; activity in nerve pathways, objective

Nociceptor

A receptor (free nerve ending) preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.

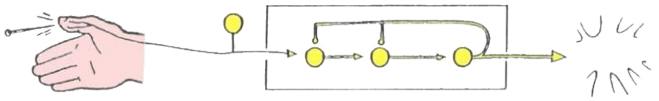
Noxious Stimulus

A stimulus which damages normal tissues.

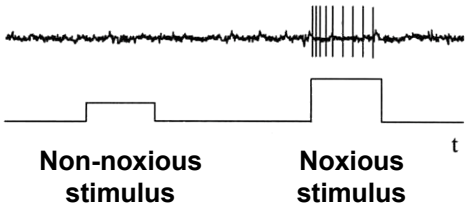
Pain types

Physiological nociceptive pain

e.g.
pin prick

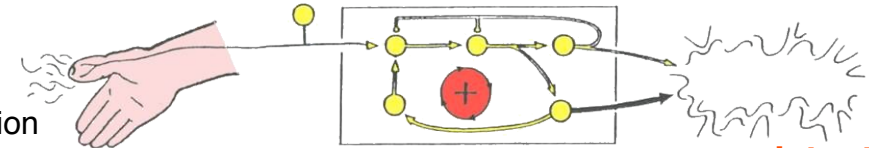


Acute pain

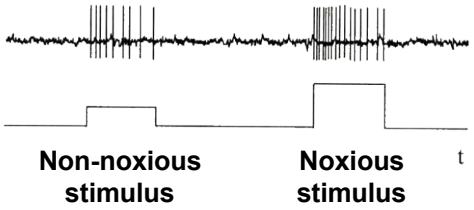


Pathophysiological nociceptive pain

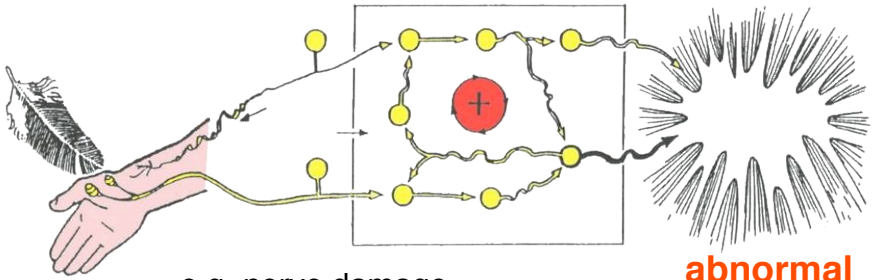
e.g.
inflammation



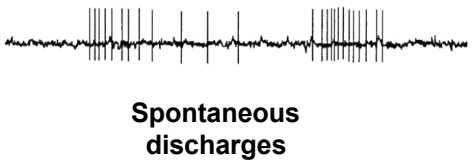
persistent pain



Neuropathic pain



abnormal pain



Pain qualities

- **Somatic pain** (skin, muscles, joints,connective tissue)

- *surficial pain*, acute, easy to localize, short pain

- *deep pain* dull pain, e.g. headache

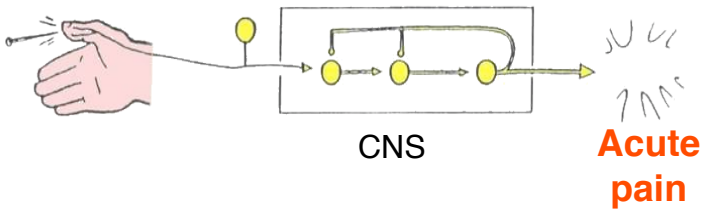
- **Visceral pain** (inner organs)

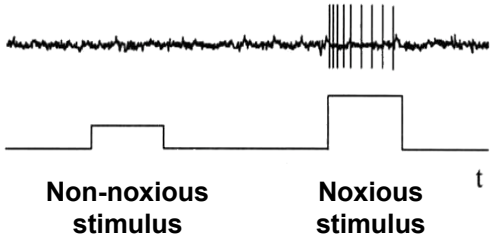
- dull pain

Physiological pain

Physiological nociceptive pain

e.g.
pin prick



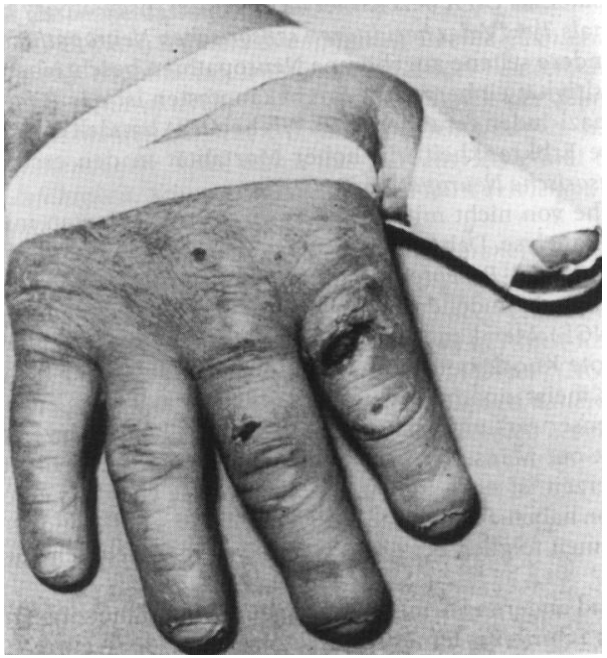


- high threshold
- short duration

Physiological pain

Functions

- body defence mechanism
- protects us from external harm
- prevents further damage
- prevents activity while the body heals

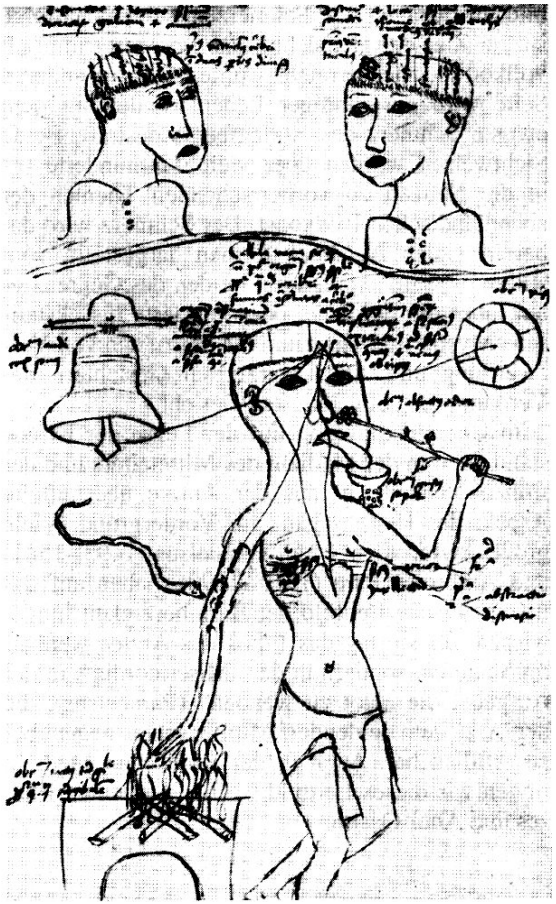


- pain indifference
- pain insensitivity

Acute pain

- Associated with an obvious cause.
- Triggers protective responses: avoidance, reduced mobility to assist healing.
- Rapid onset
- Varies in intensity
- Transient, Intermittent or persistent

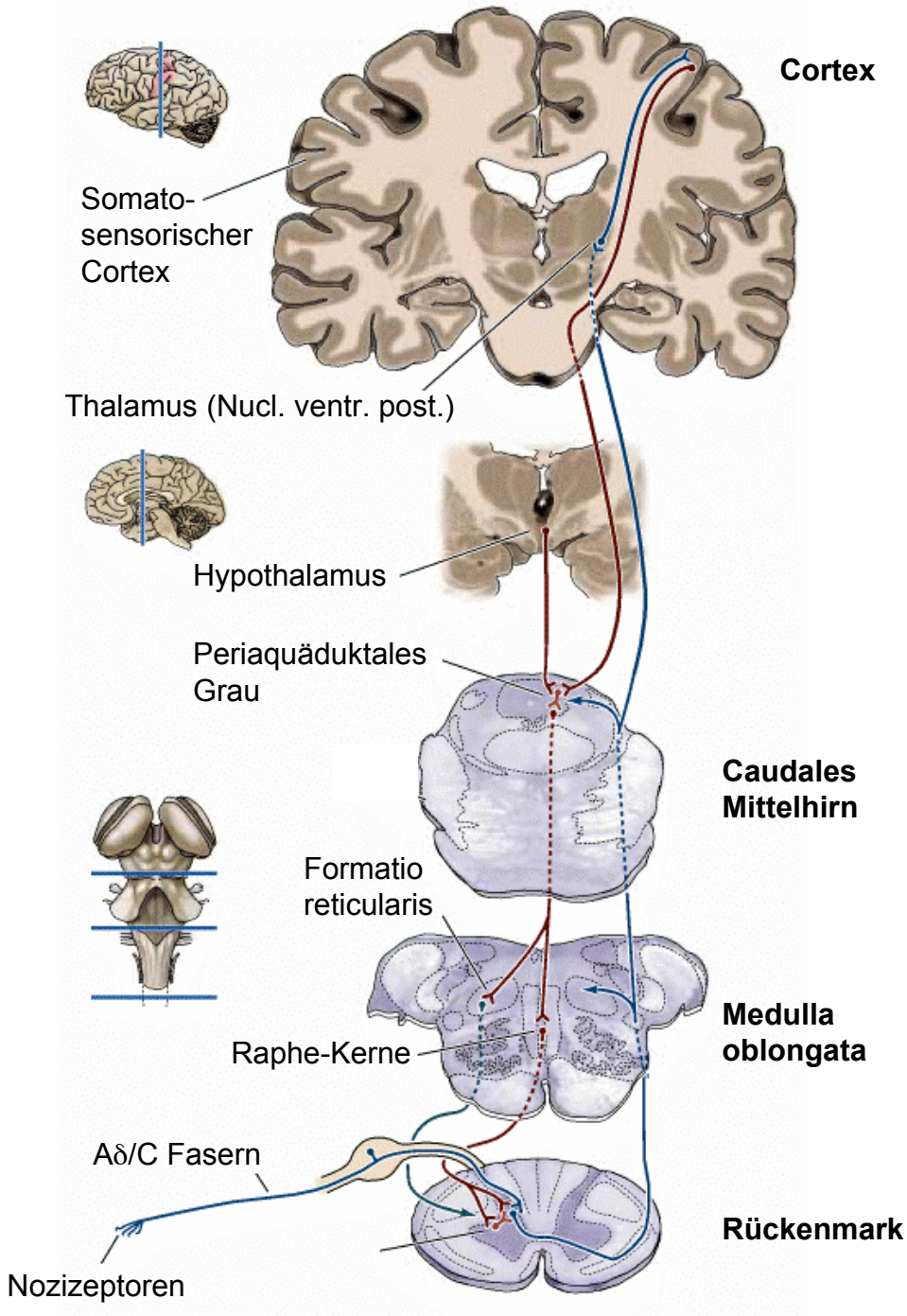
Pain transmission (historical view)



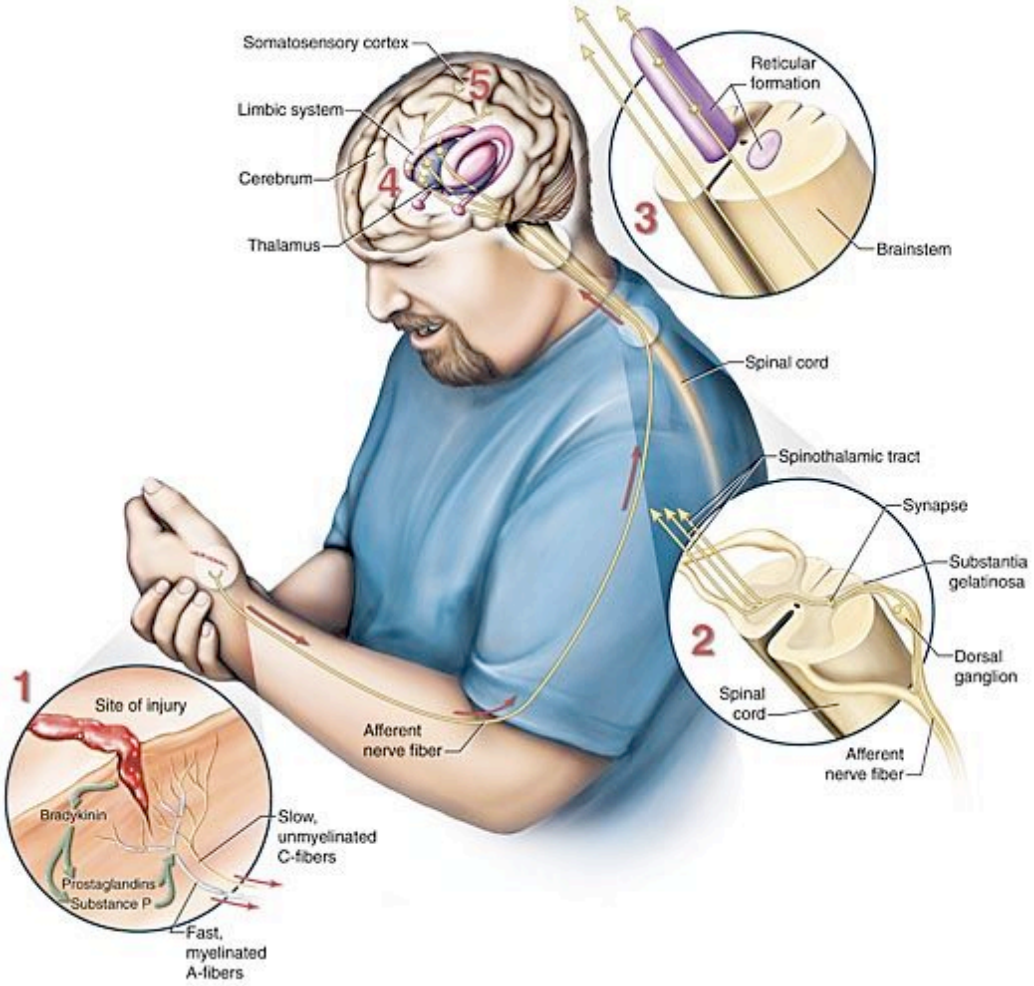
Gerard de Harderwyck 1496

René Descartes 1664

Ascending nociceptive and descending antinociceptive system



Nociceptive Transmission

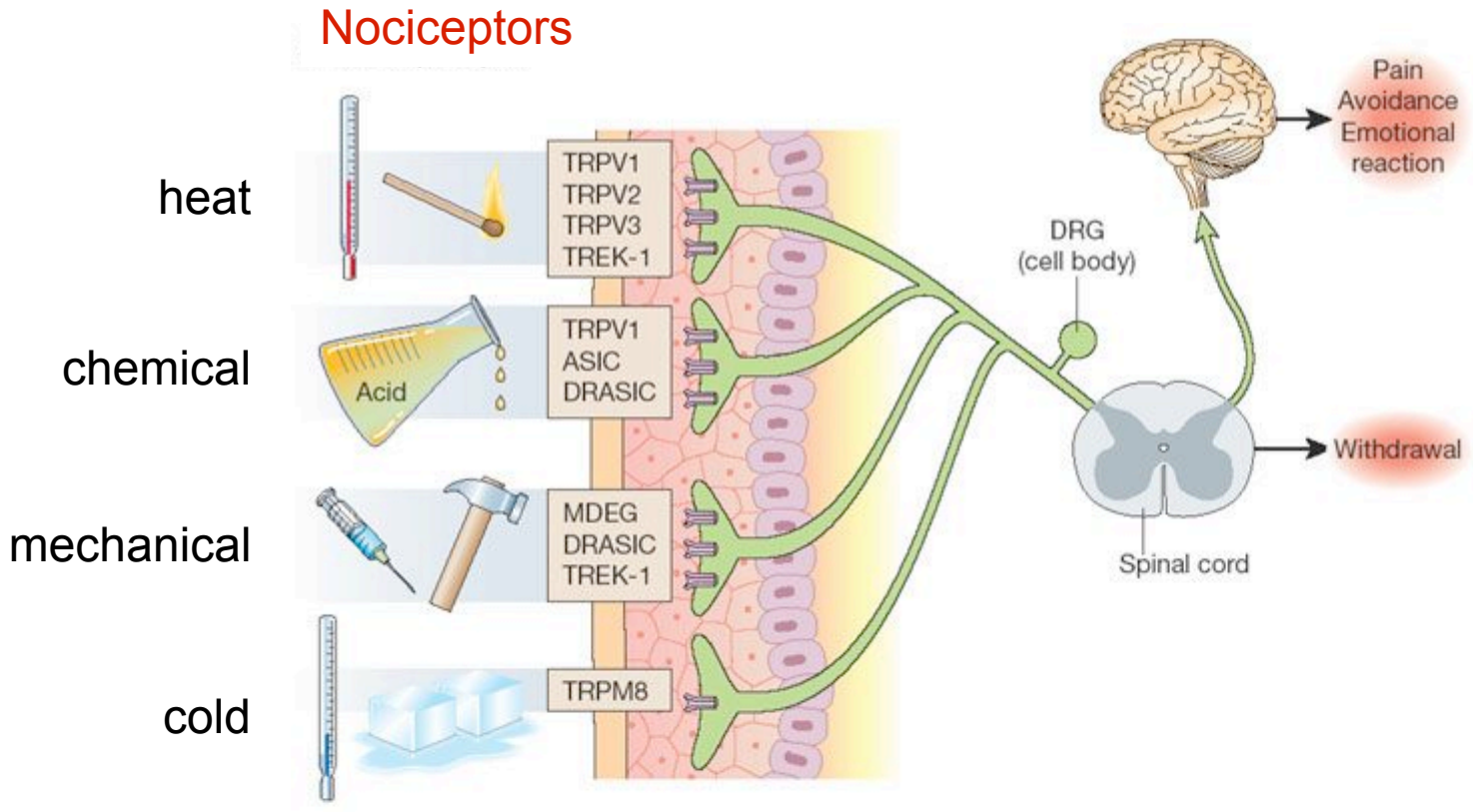


1 Periphery

2 Spinal Cord

3 Brain

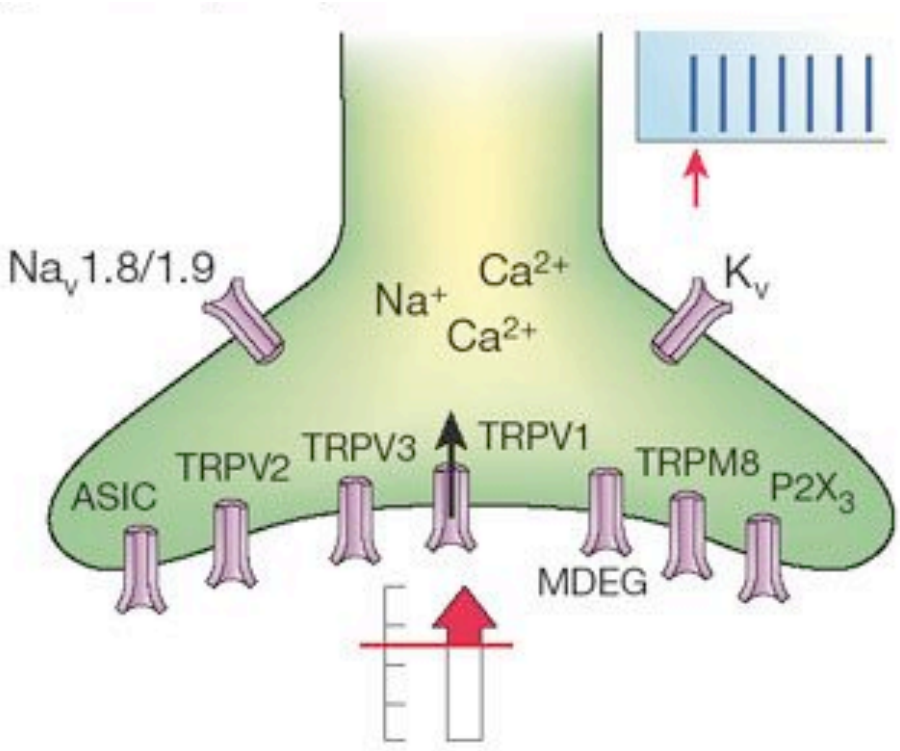
Nociceptive Transmission (Periphery)



Tissue-specific nociceptors

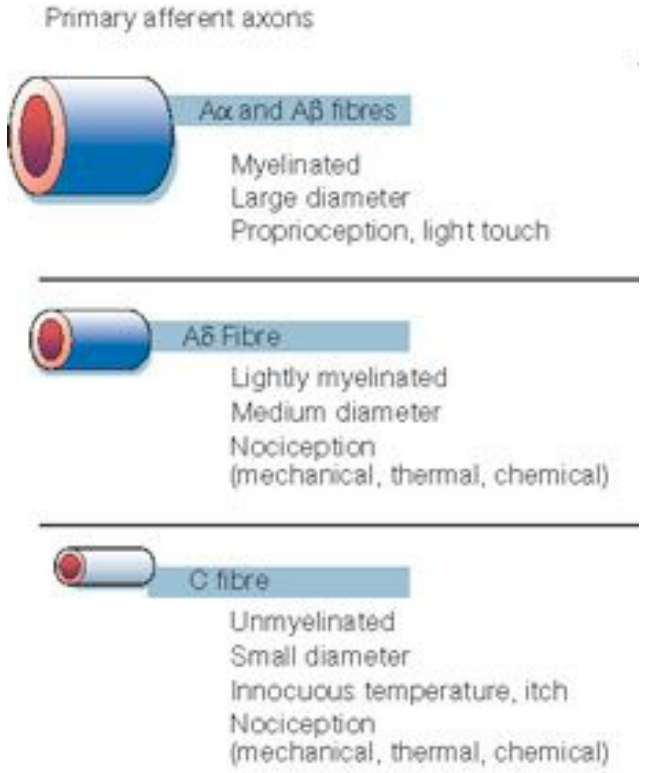
- **Skin nociceptors**
- **nociceptor in the musculoskeletal system**
- **Visceral nociceptors**
- **Trigeminal nociceptors**
- **(Irritation sensors** e.g. reflexes, itching)

Chemical mediators in the primary afferent

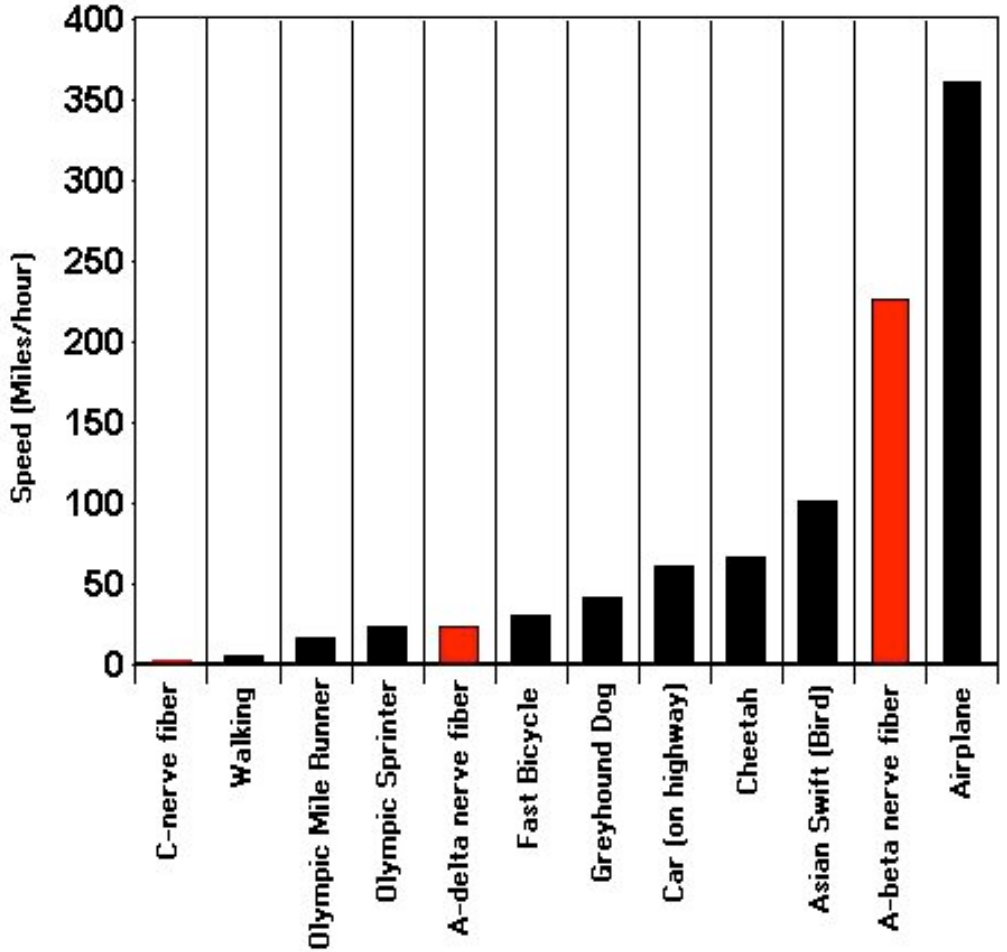


Functional properties of primary afferents

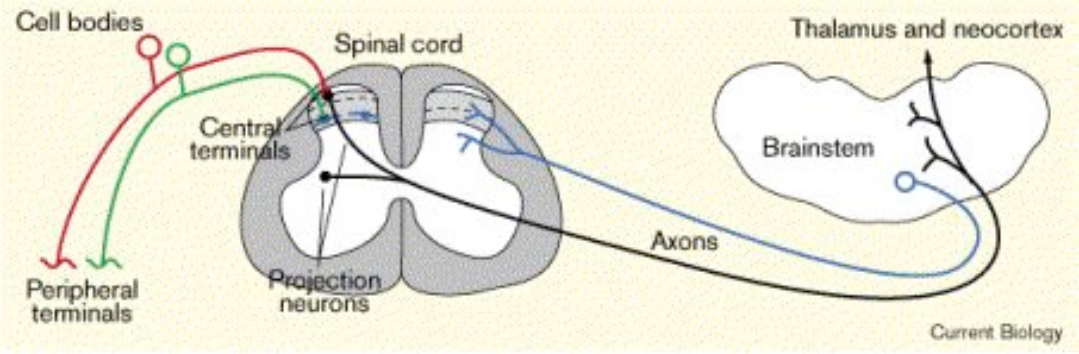
- Aα– and Aβ-fibres (Ø 15 µm, myelinated, conduction velocity 30-120m/sec) non-nociceptive
- A_δ-fibres (Ø 2-3 µm, thinly myelinated, conduction velocity 2-40m/sec) nociceptive
- C-fibres (Ø 0,5-1 µm, unmyelinated, conduction velocity <2m/sec) nociceptive



Functional properties of primary afferents

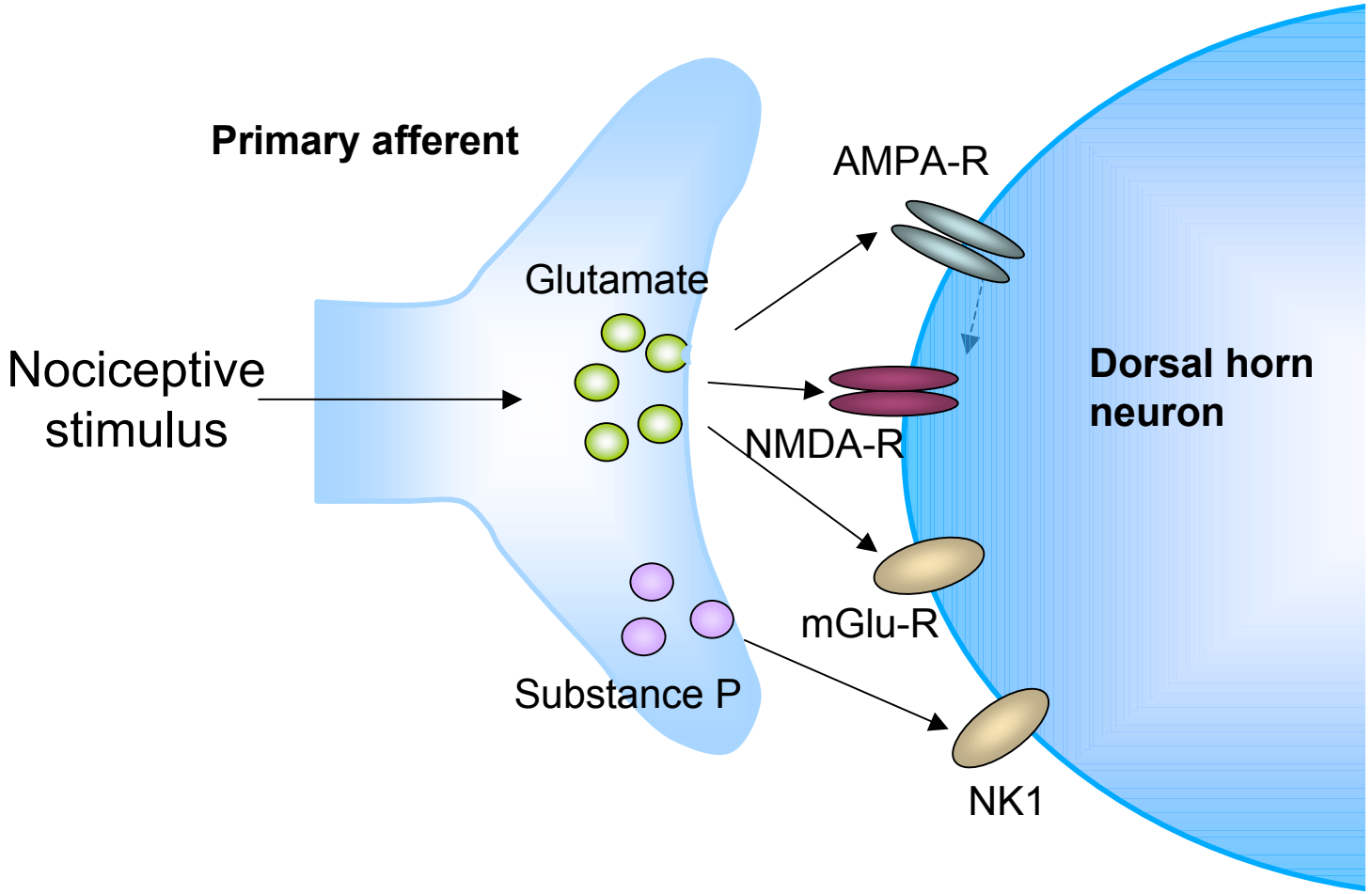


Nociceptive transmission in the spinal cord



→ Transmission from primary to secondary nociceptive neurons (projection neurons) in the dorsal horn of the spinal cord by excitatory amino acids and neuropeptides

Nociceptive transmission in the spinal cord

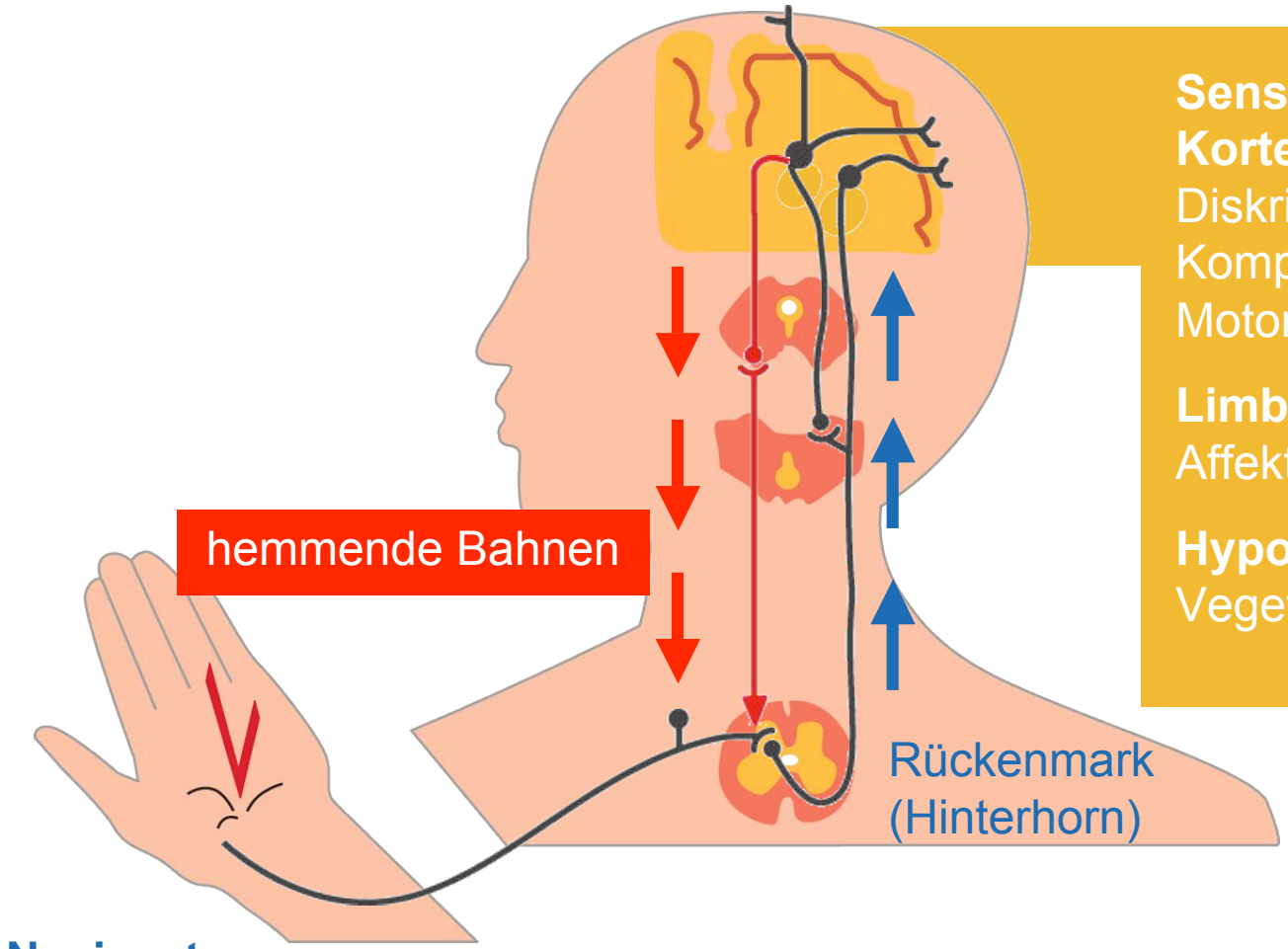


Nociceptive neurons in the spinal cord

- **class 1 neurons** (low threshold, without nociceptive activity)
- **class 2 neurons** (wide dynamic range)
- **class 3 neurons** (high threshold, specifically nociceptive)

- Expression of „immediate early genes“
- Ascending tracts ➠ *Tractus spinothalamicus*

Schmerzbahnen



Sensomotorischer Kortex
Diskriminatorische Komponente +
Motorische Komponente

Limbisches System
Affektive Komponente

Hypothalamus
Vegetative Komponente

Nozizeptor
sensorische Komponente

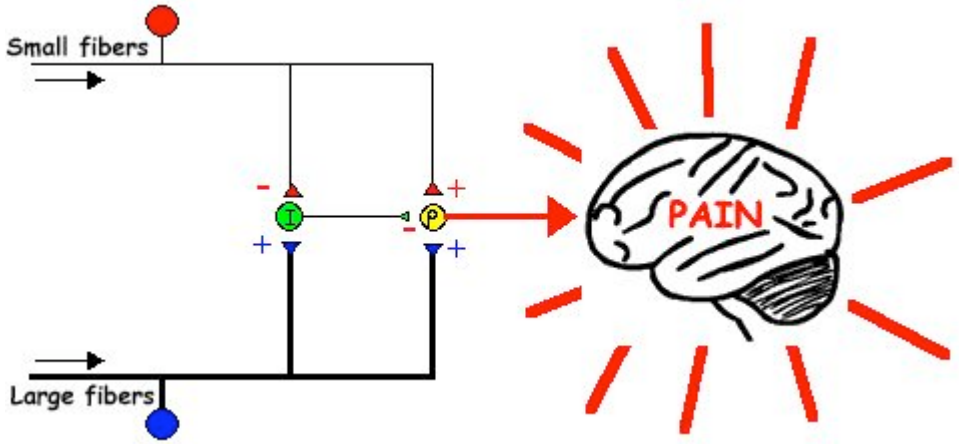
Endogenous antinociceptive system

- Inhibitory Synapses
- <u>Transmitter:</u>

-Endorphine and Enkephaline

-Adenosine

-GABA



Gate control theory, Wall and Melzack, 1965 , Science

Adjustment of central nociceptive threshold

- Segmental spinale and supraspinal inhibition
- Gate-control-hypothesis

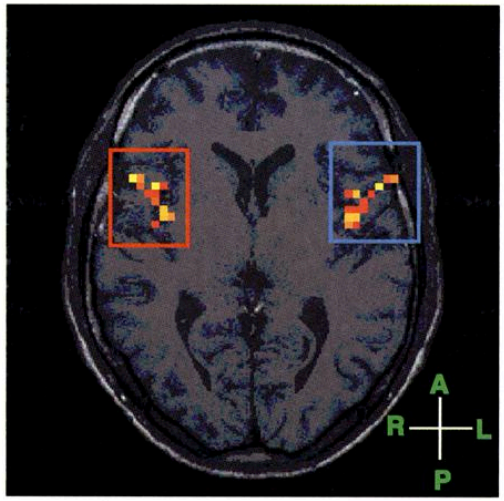
Brain regions

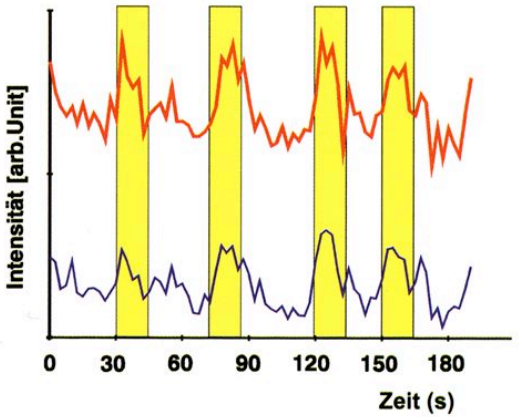
„Pain centres“

- Lateral system (sensory discriminating)
- Medial system (affective)

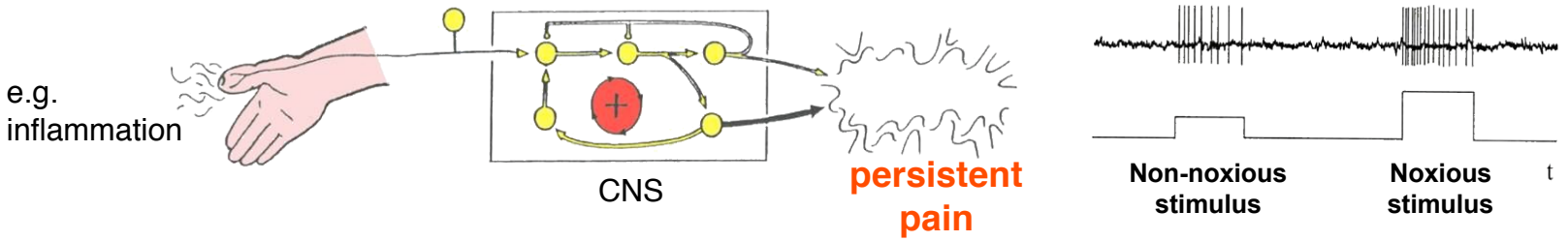
Examinations

- Electrophysiological recordings
- Recording of evoked potentials
- Positron emission tomography (regional changes in blood circulation)
- Magnetic resonance imaging (regional changes in oxygen concentration)





Pathophysiological nociceptive pain



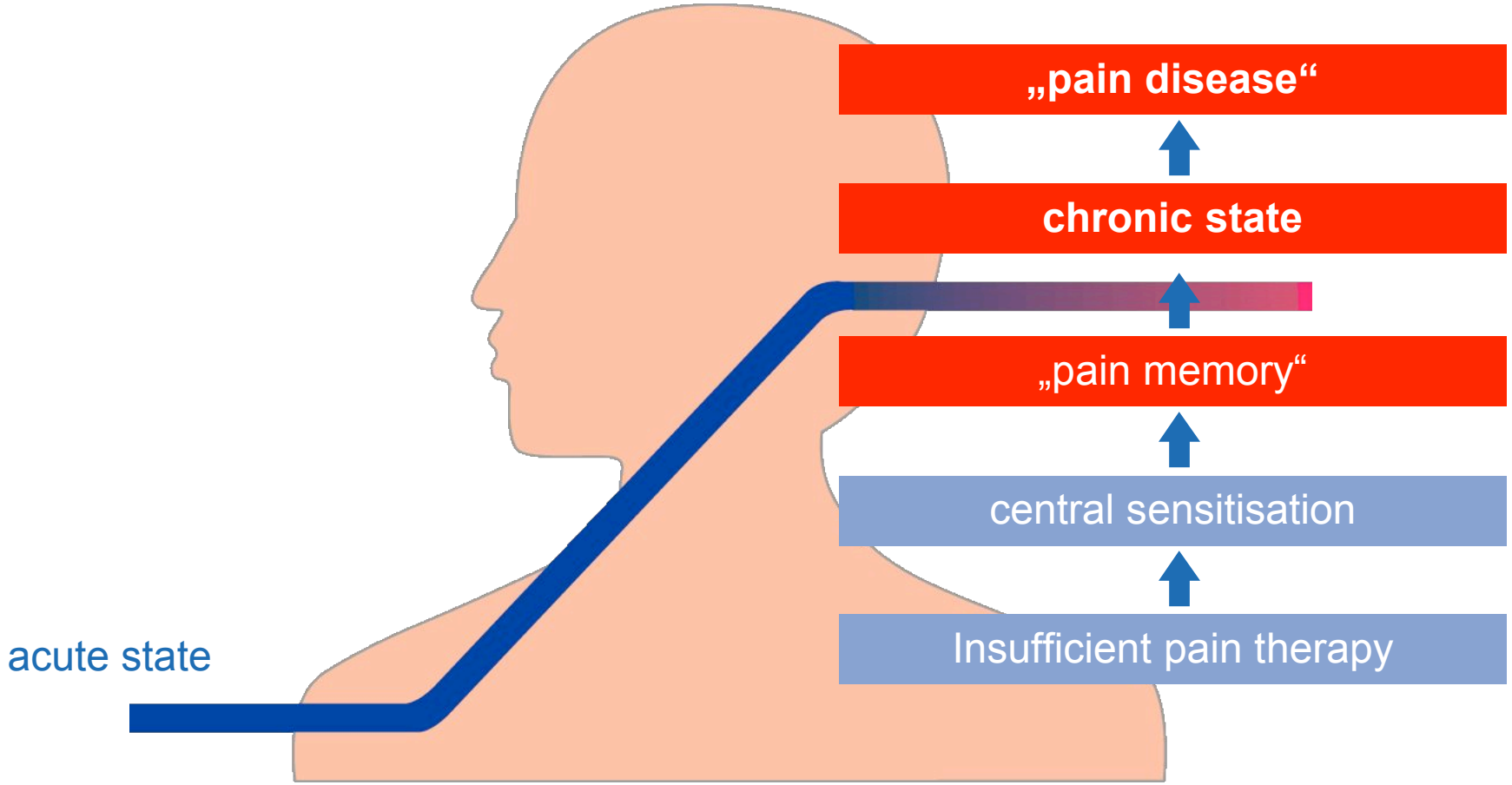
- synaptic plasticity
- low threshold

⇨ *Hyperalgesia:* Increased response to a noxious stimulus

⇨ *Allodynia:* Pain due to a stimulus which does not normally provoke pain.

⇨ Persistent pain

Chronification of pain



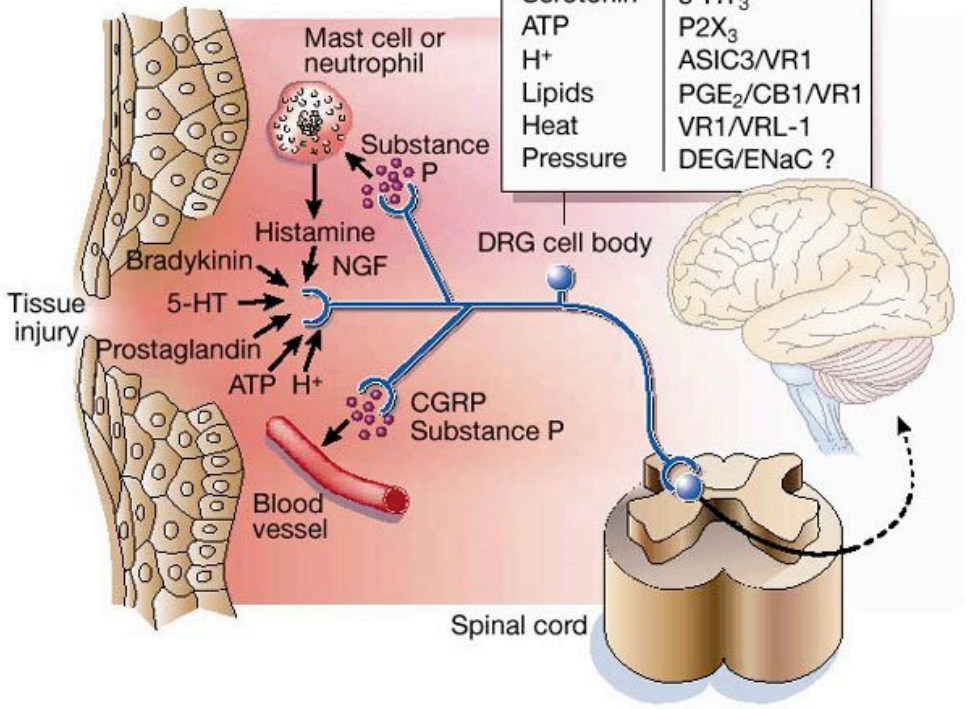
Chronification of pain

- Chronic pain = Pain that lasts longer than 3 months
- „Pain disease“
- Pain remains after the initial injury has resolved.
- Pain can be a result of injury, disease or inflammation
- Peripheral or central disorder
- Peripheral and central sensitization

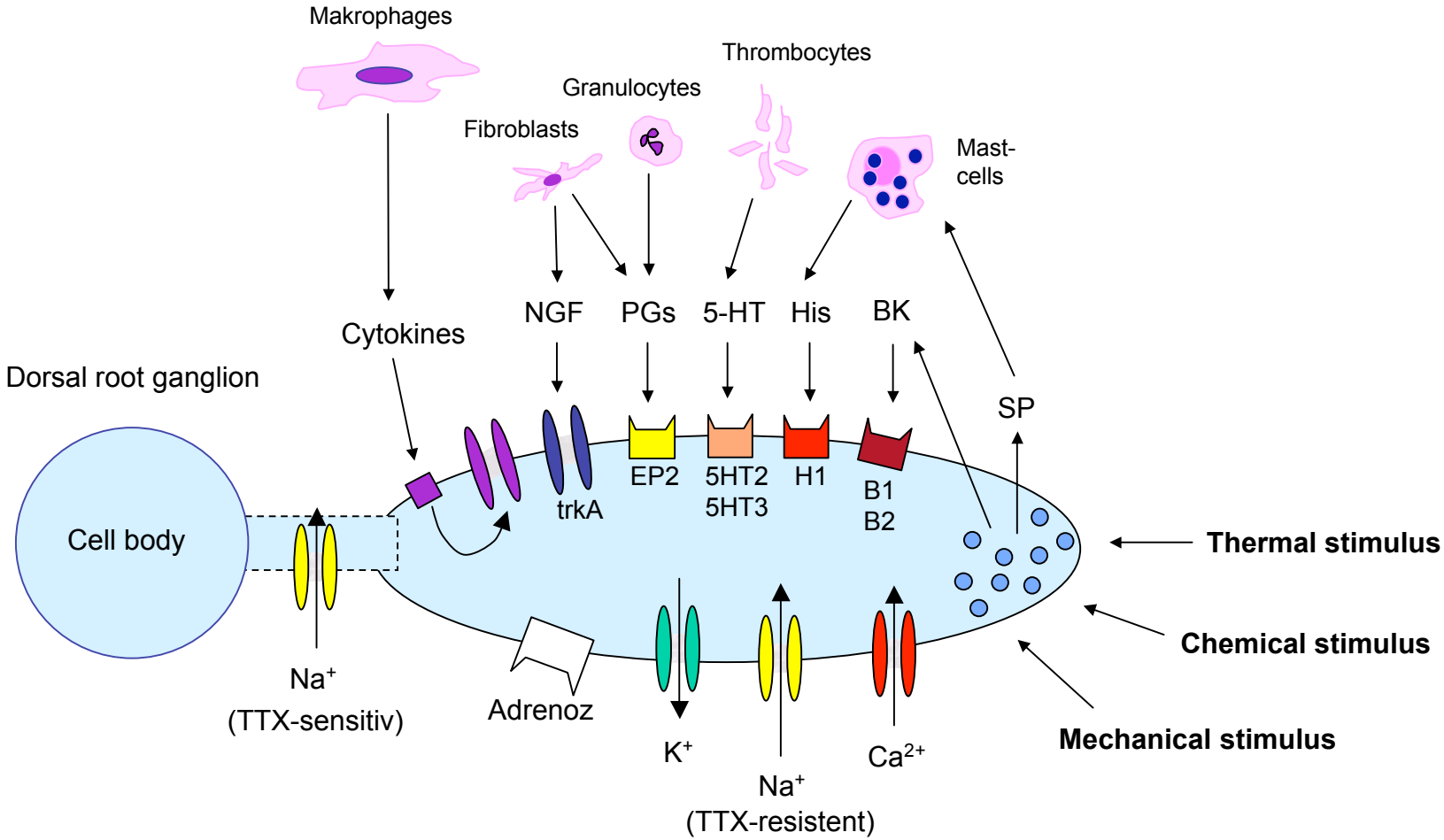
Mediators of inflammation (Periphery)

„Inflammatory soup“

Stimulus	Representative receptor
NGF	TrkA
Bradykinin	BK_2
Serotonin	$5\text{-}HT_3$
ATP	$P2X_3$
H^+	ASIC3/VR1
Lipids	PGE_2/CB1/VR1
Heat	VR1/VRL-1
Pressure	DEG/ENaC ?



Chemical mediators in the primary afferent



Chemical mediators

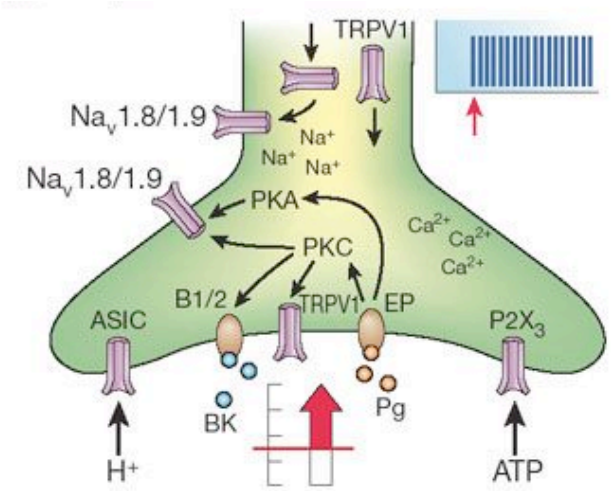
→ Activation of G-protein coupled receptors or tyrosine kínase receptors on nociceptive terminals

→ Phosphorylation of receptors and ion channels in the nociceptive terminals

→ Expressional changes

→ Change of thresholds and kinetics

⇨ Peripheral Sensitization



Changes in the periphery

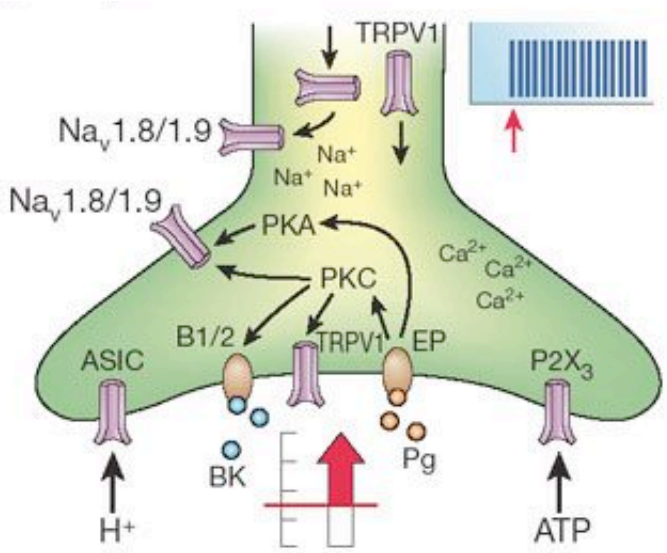
Peripheral

Transduction
TRPV1, TRPV2, TRPV3, TRPM8
ASIC, DRASIC
MDEG, TREK-1
BK_1, BK_2
$P2X_3$

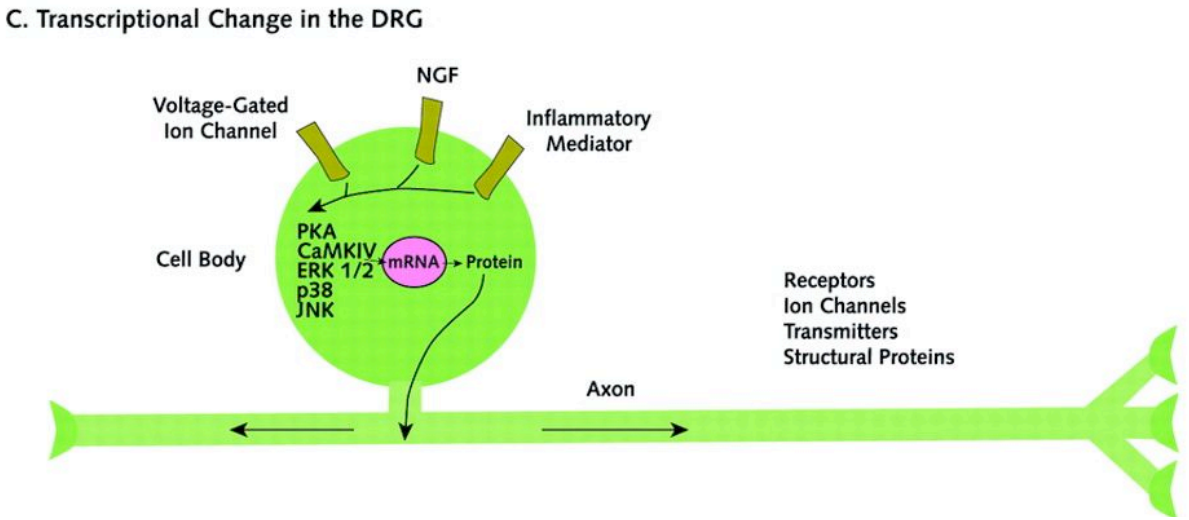
Peripheral sensitization
NGF, TrkA
TRPV1
$Na_v1.8$
PKA, PKC isoforms, CaMK IV
Erk1/2, p38, JNK
IL-1β, $cPLA_2$, COX2, EP1, EP3, EP4
TNFα

Membrane excitability of primary afferents
$Na_v1.8$, $Na_v1.9$
K^+ channel

Synaptic transmission
***Pre*synaptic**
VGCC
Adenosine-R
(mGlu-R)



Processing in the DRG



Woolf, C. J. Ann Intern Med 2004;140:441-451

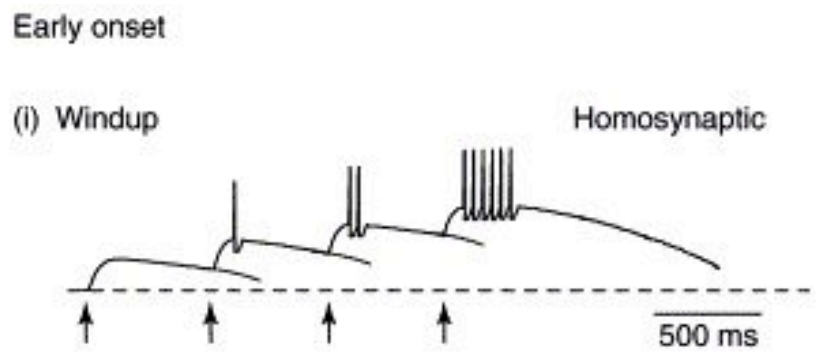
Central sensitization

⇨ Increase of excitability of nociceptive neurons in the dorsal horn of the spinal cord

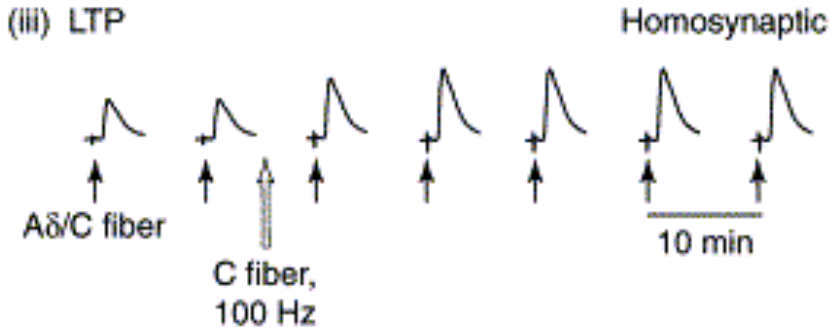
- „Wind up“
- Long-term-potentiation (LTP)
- Inhibition of inhibitory neurons
- Increase in intracellular Ca^{2+}
- Activation of immediate early genes (IEGs)

⇨ Persistent pain, secondary hyperalgesia

Central sensitization



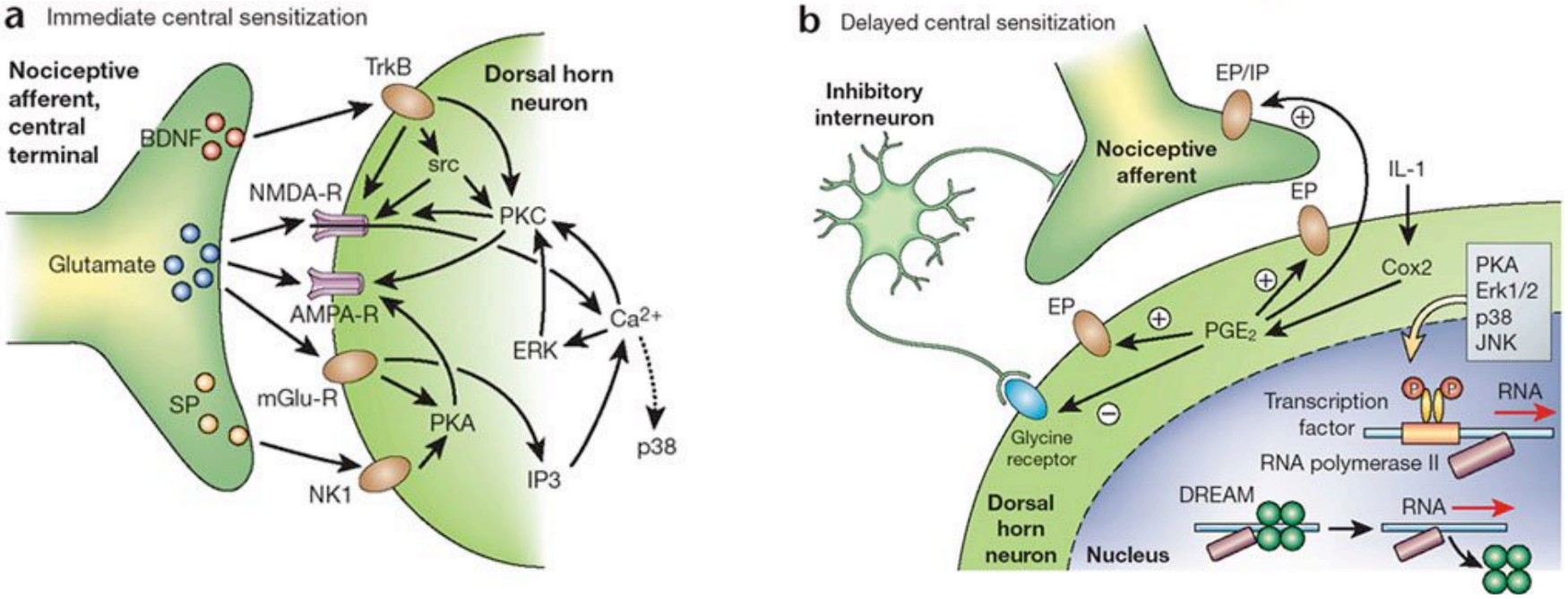
- Repetitive nociceptive stimulation
- „Accumulation“ of response



- High-frequency stimulation
- Increased longterm response (postsynaptic potential, postsynaptic current)

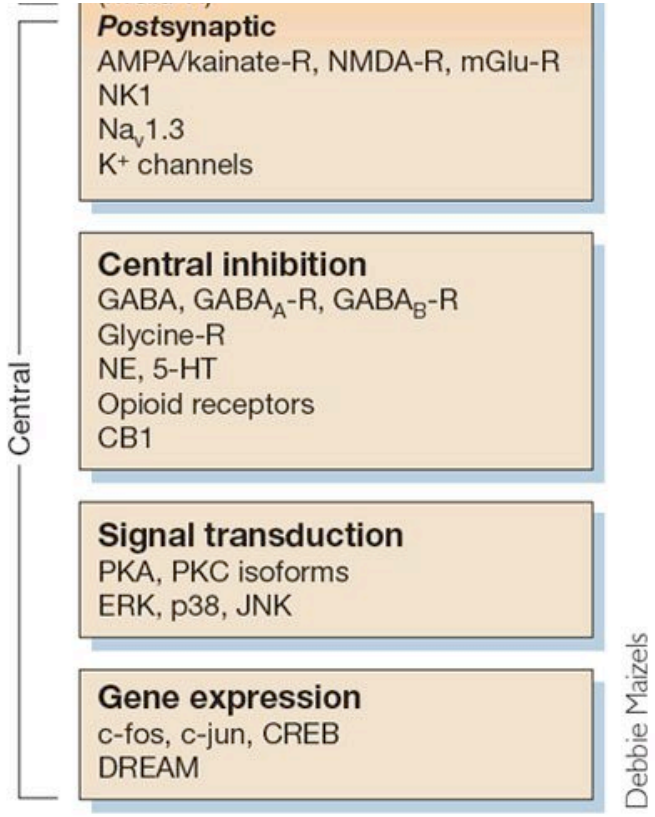
Ji R.R. et al., TRENDS in Neuroscience, 2003, (26), 696

Central sensitization



J. Scholz and C.J. Woolf, Nature Neuroscience 2002

Changes in the CNS



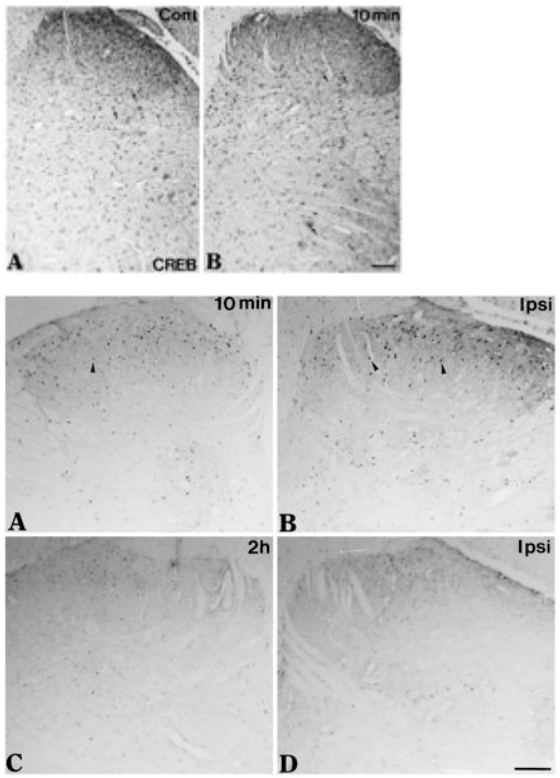
Spinal plasticity

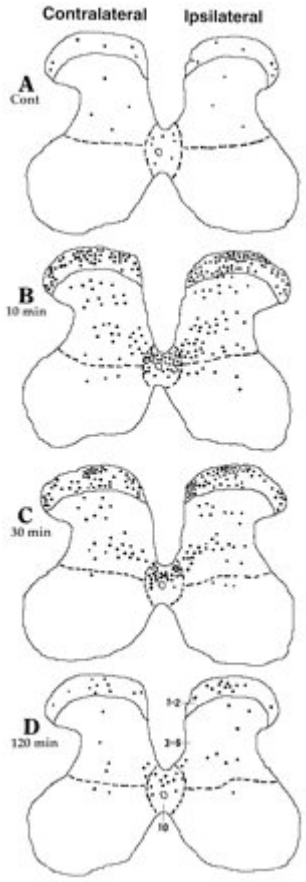
(after formalin injection into one hindpaw)

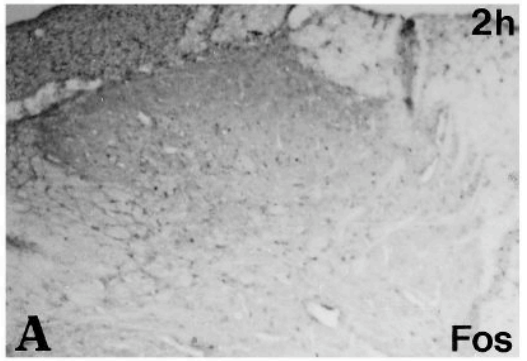
CREB

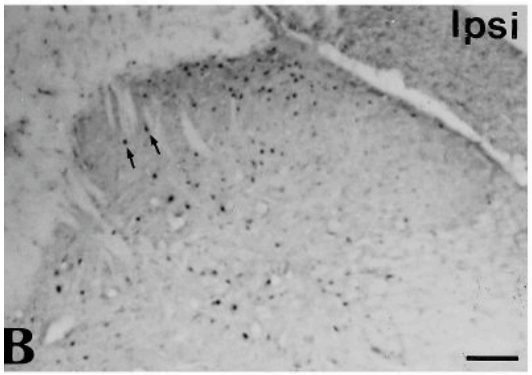
c-Fos

phospho-CREB

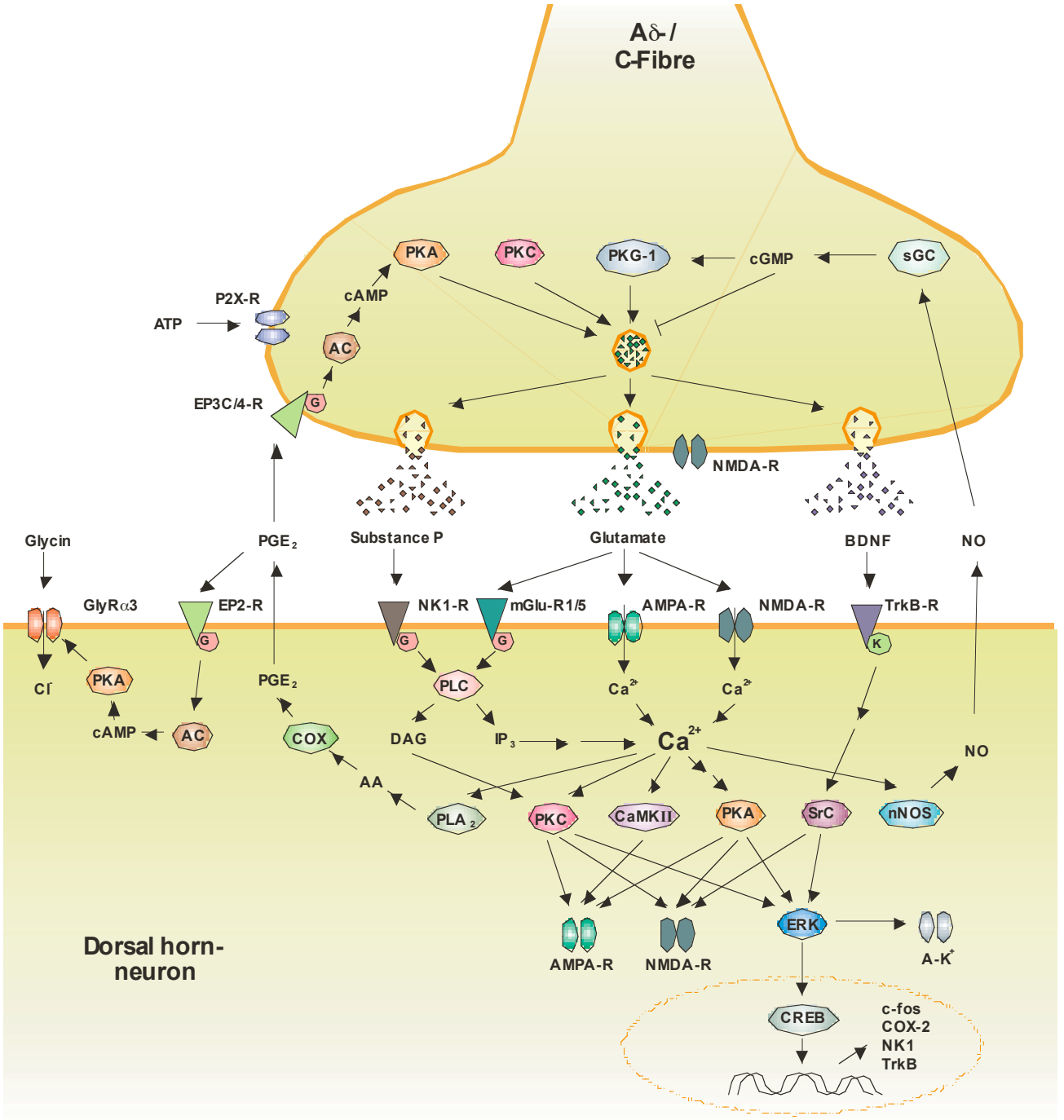




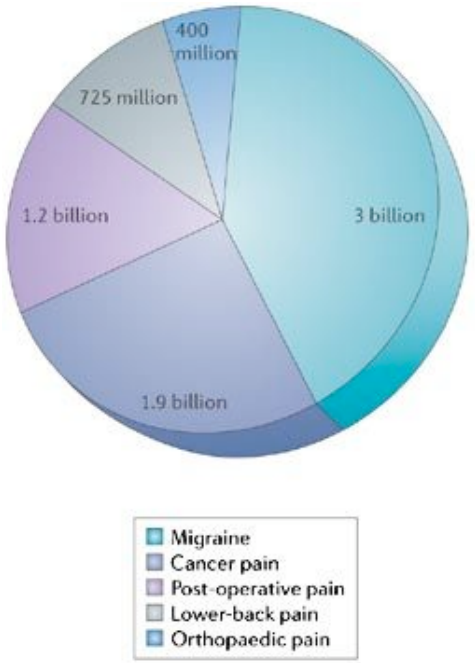




Ji and Rupp, J. Neuroscience,1997



Pharmacotherapy of pain and inflammation



Estimated worlwide size of pain submarkets
Total market for pain drugs: 7.25 billion US$

Gershell and Goater *Nature Reviews Drug Discovery* **5**, 889–890 (November 2006) | doi:10.1038/nrd2179

Prevalence of chronic pain

<25 years of age 17.3 %

>65 years of age 42 %

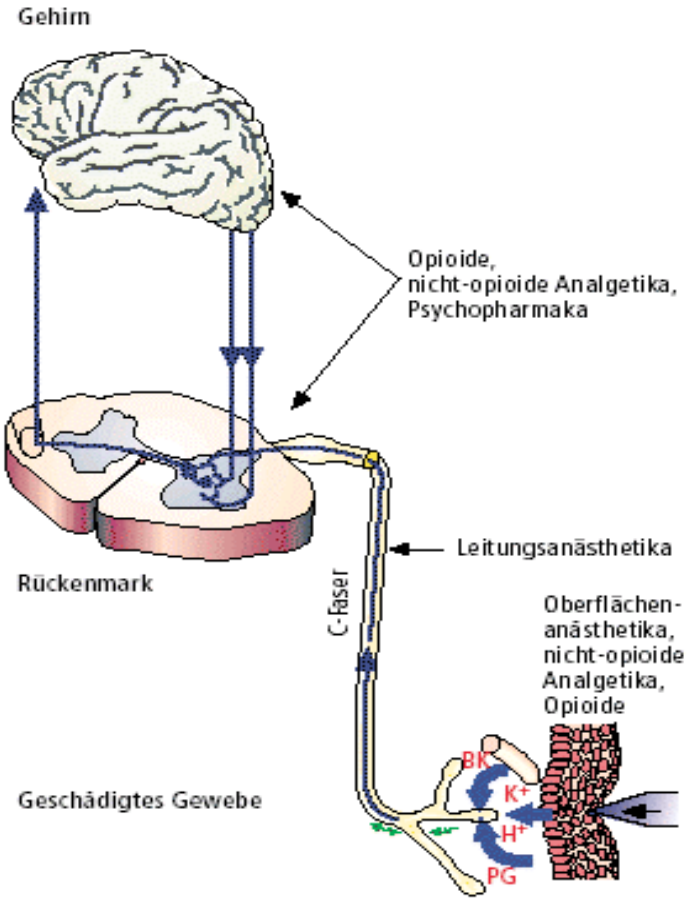
Analgesics

Non-Opioid-Analgesics

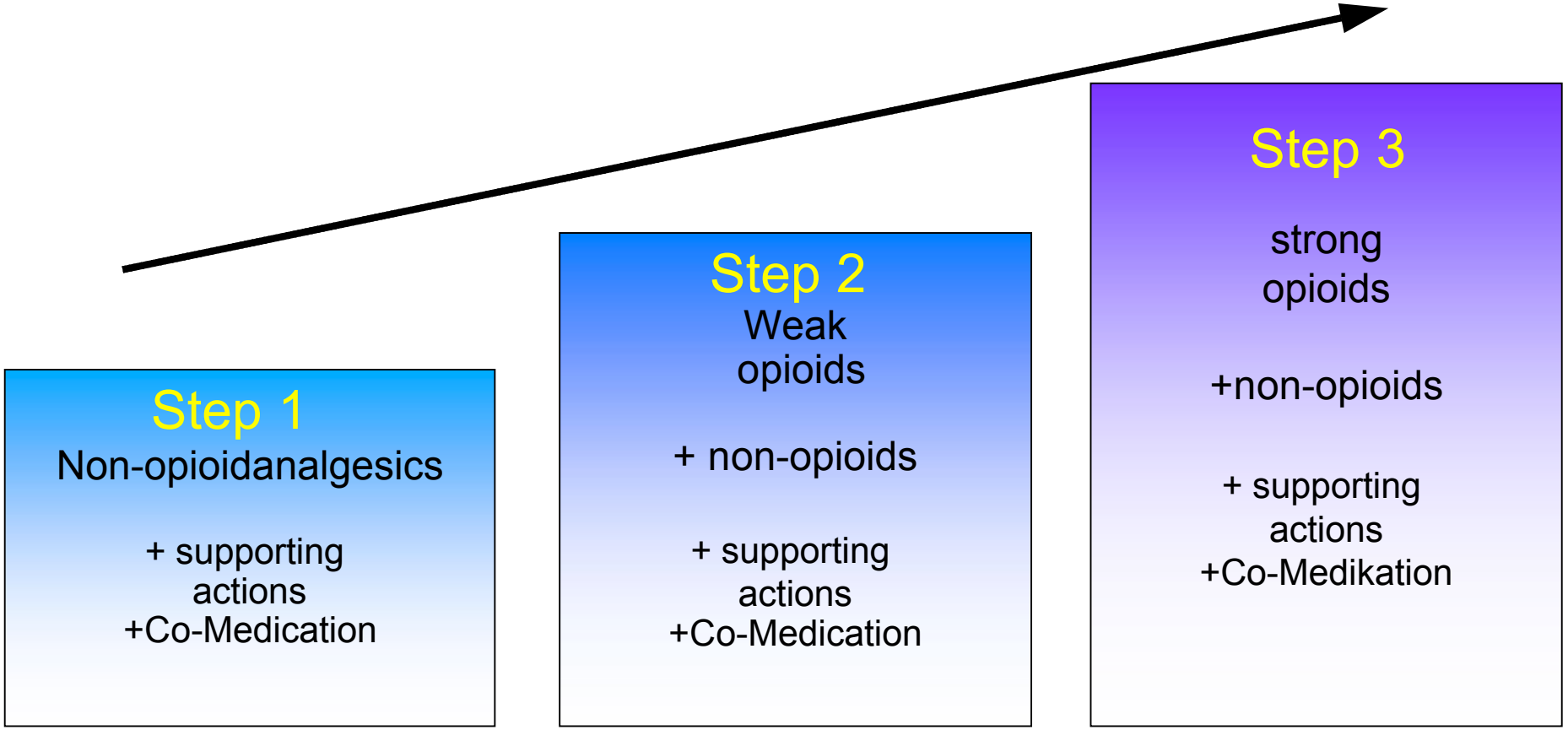
central and peripheral effects

Opiod-Analgesics

mainly central effects



WHO-analgesics ladder

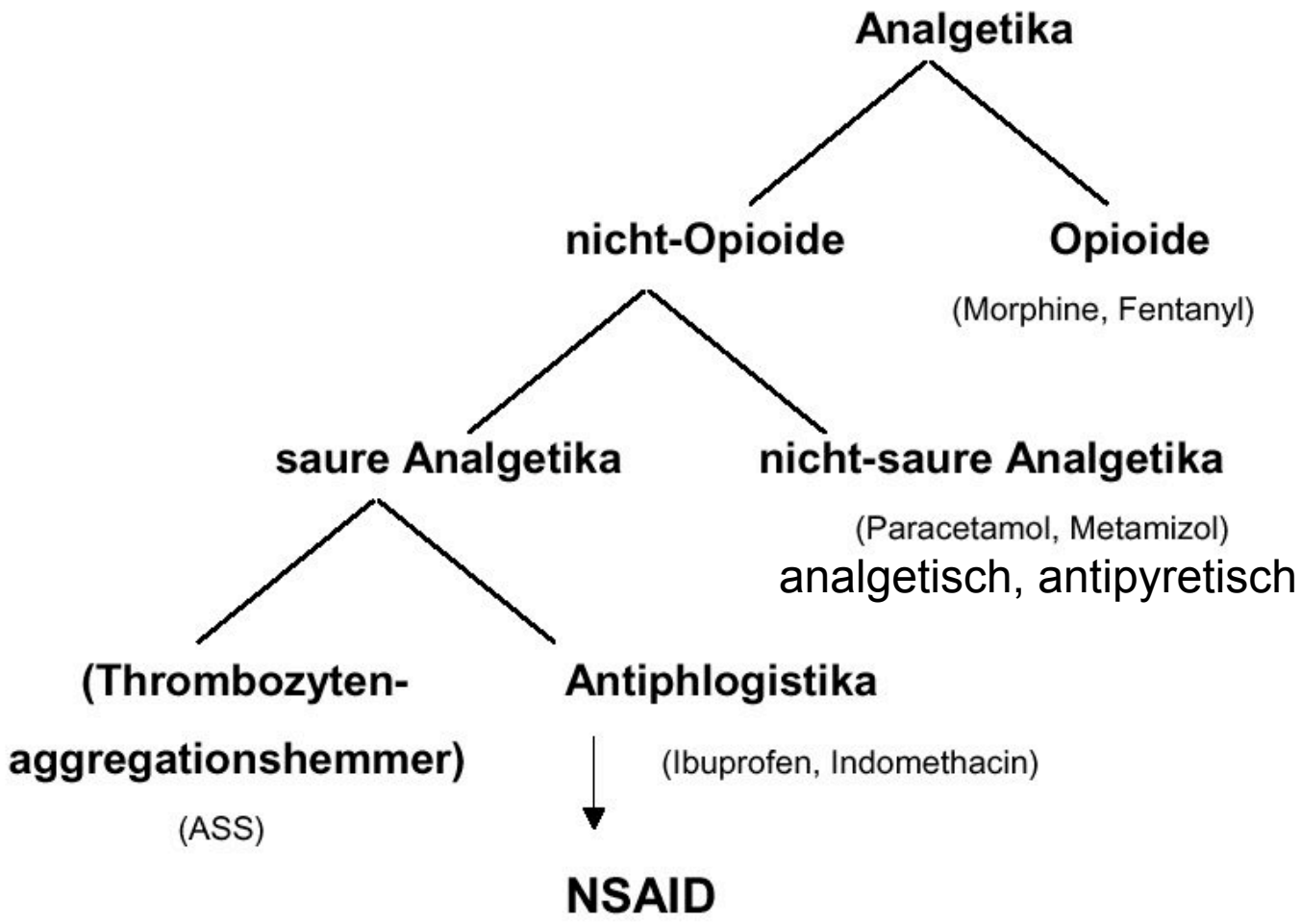


Pain rating

- difficult, since subjective
- quantitative rating using a visual analog scale
- Worst imaginable pain
- No pain

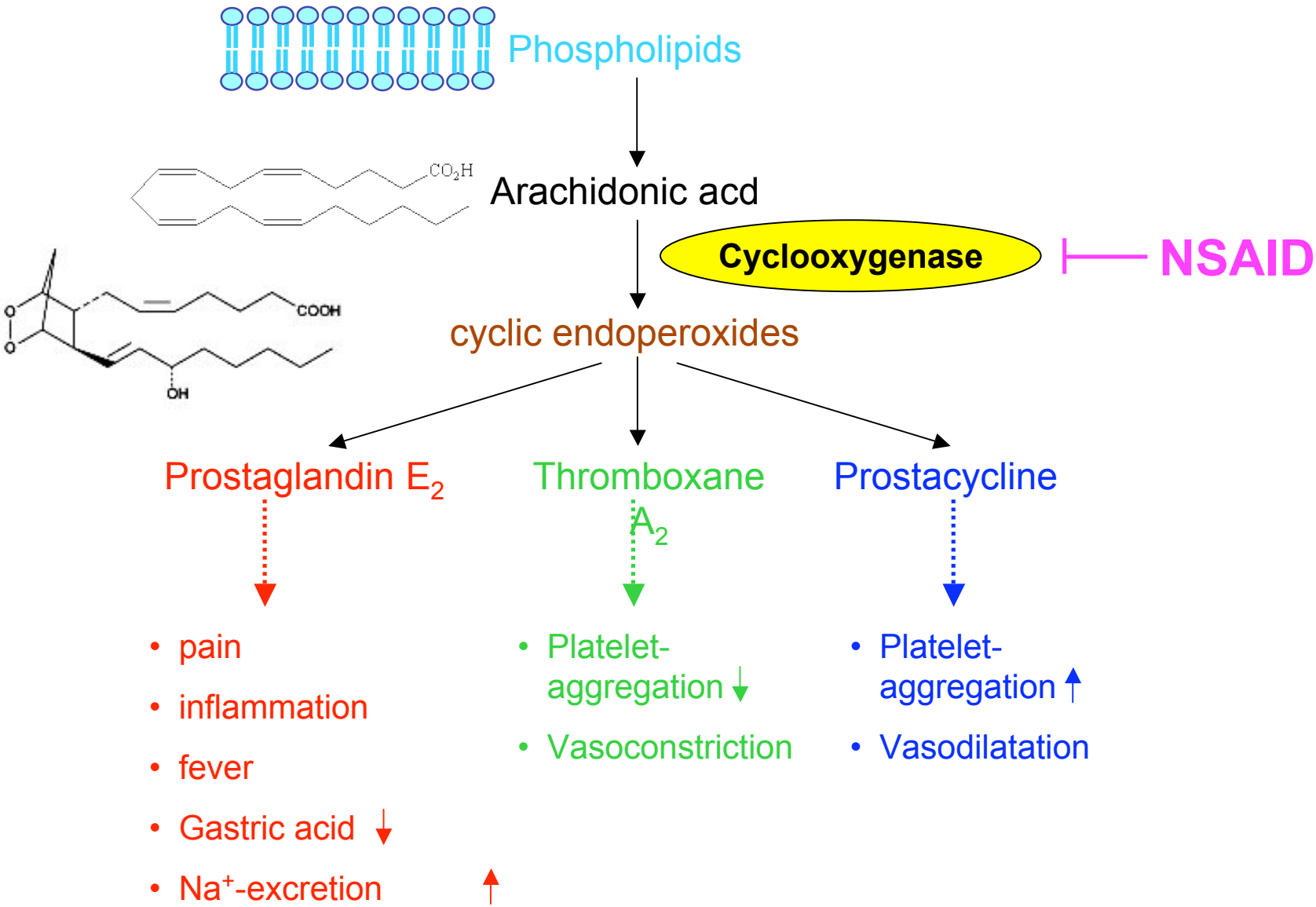
Numerische Rating-Skala (klinischer Alltag und Verlaufskontrolle)

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst pain



Non-**s**teroidal **a**nti-**i**nflammatory **d**rugs

Arachidonic acid-cascade



Non-steroidal anti-inflammatory drugs (NSAIDs)

Traditional NSAIDs

- Acetylsalicylsäure
- Ibuprofen
- Diclofenac

- Inhibition of Cyclooxygenase (COX) 1 + 2
- analgesic, antipyretic and antiphlogistic

Physiolog. Stimulus

Physiolog. Adaptation

Inflamm. Stimulus

-

„Coxibs“

-

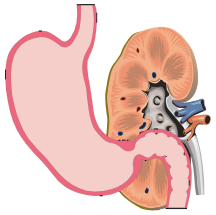
COX-1
constitutive

COX-2
constitutive and inducible

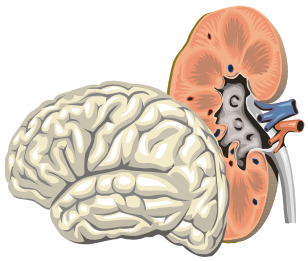
COX-2
inducible

platelets
($TX A_2$)

stomage, kidney
(PGE_2)



Endothelium
(PGI_2)



PGE_2

inflammation, pain

Non-steroidal anti-inflammatory drugs (NSAIDs)

Traditional NSAIDs

- Acetylsalicylsäure
- Ibuprofen
- Diclofenac

- Inhibition of Cyclooxygenase (COX) 1 + 2
- analgesic, antipyretic and antiphlogistic

Coxibs

- Celecoxib
- Etoricoxib

- selektive inhibition of COX 2

⇨ less gastrointestinal side effects

2004 bzw. 2005: withdrawal of Rofecoxib (Vioxx®) and Valdecoxib

Because of: increased incidence of cardiovascular diseases

Non-steroidal anti-inflammatory drugs (NSAIDs)

Indications

- pain
  - headache, tooth pain
  - Migraine
  - Rheumatic pain
- fever
- inflammation

Side effects

- gastrointestinal

(less in case of COX-2 selective)

- kidney disturbaces
- Cardiovascular (Coxibs)

Non-steroidal anti-inflammatory drugs (NSAIDs)

effective analgesics, but:

From 1000 patients an average of

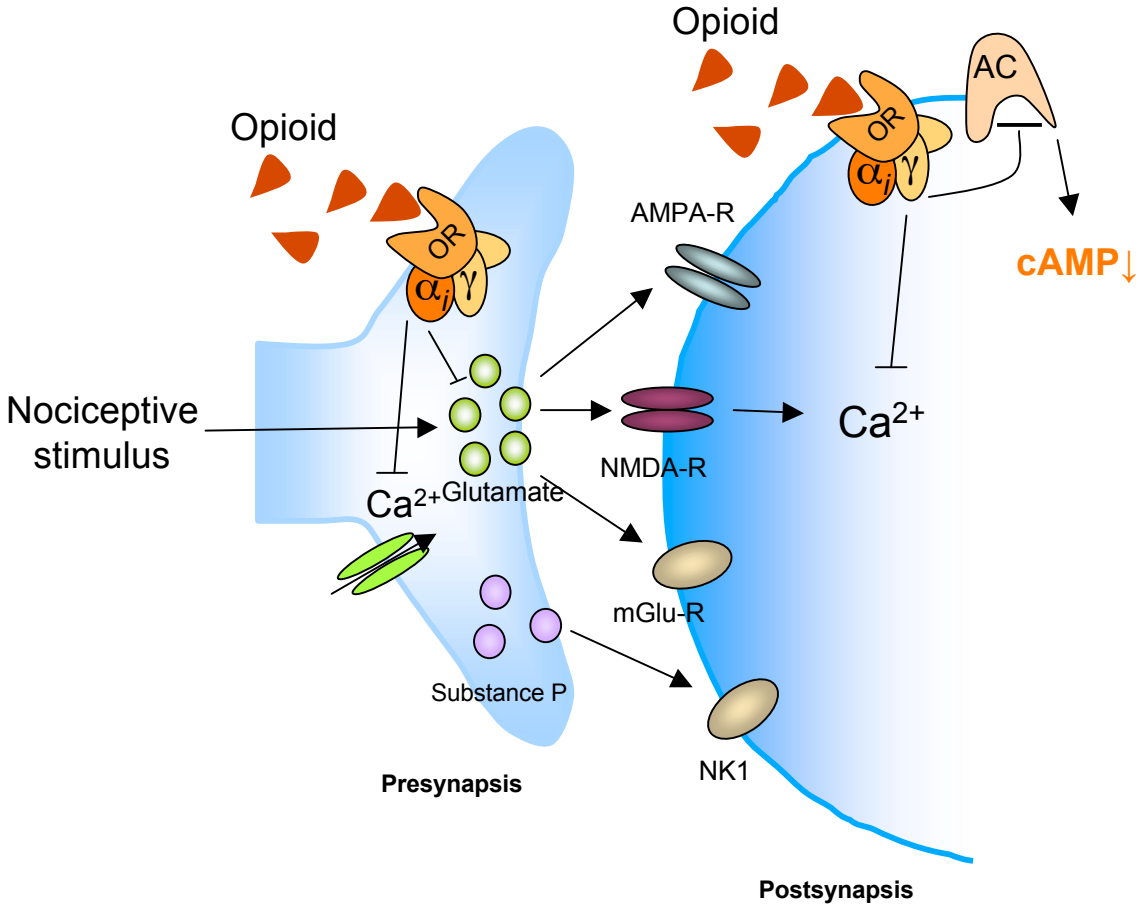
- 100 patients develop ulcera
- 10 patients develop stomage bleeding
- 1 patient dies

Singh G., Am. J. Med. 1998, 105 (Suppl. 1B) 325-385

Opiod-analgesics

- Agonists of μ, κ, δ-opiod-receptors

- Activation of the endogenous antinociceptive system
- cAMP intracellular↓
- Inhibition of transmitter release



Indications

- Severe and worst pain
  - Postsurgical
  - Traumatic
  - Tumor pain

- Morphine
- Tramadol (Tramal®) weak μ-agonist
- Codein (cough)

Effects of Opioid-Analgesics

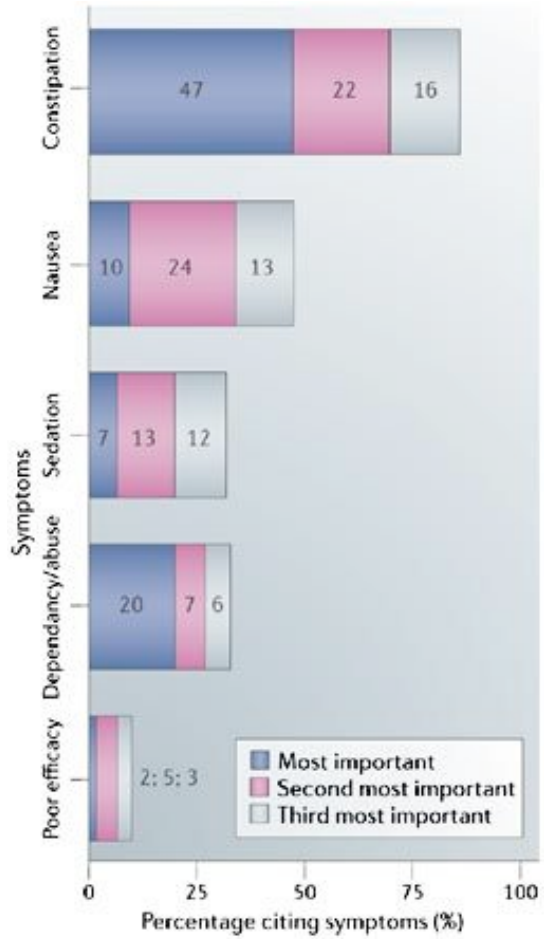
central

- Analgesia
- Sedation
- sickness, emesis
- Euphoria
- Respiratory depression *(in case of pain minor)*
- Decreased cough
- itching
- Decreased blood pressure
- Tolerance
- addiction

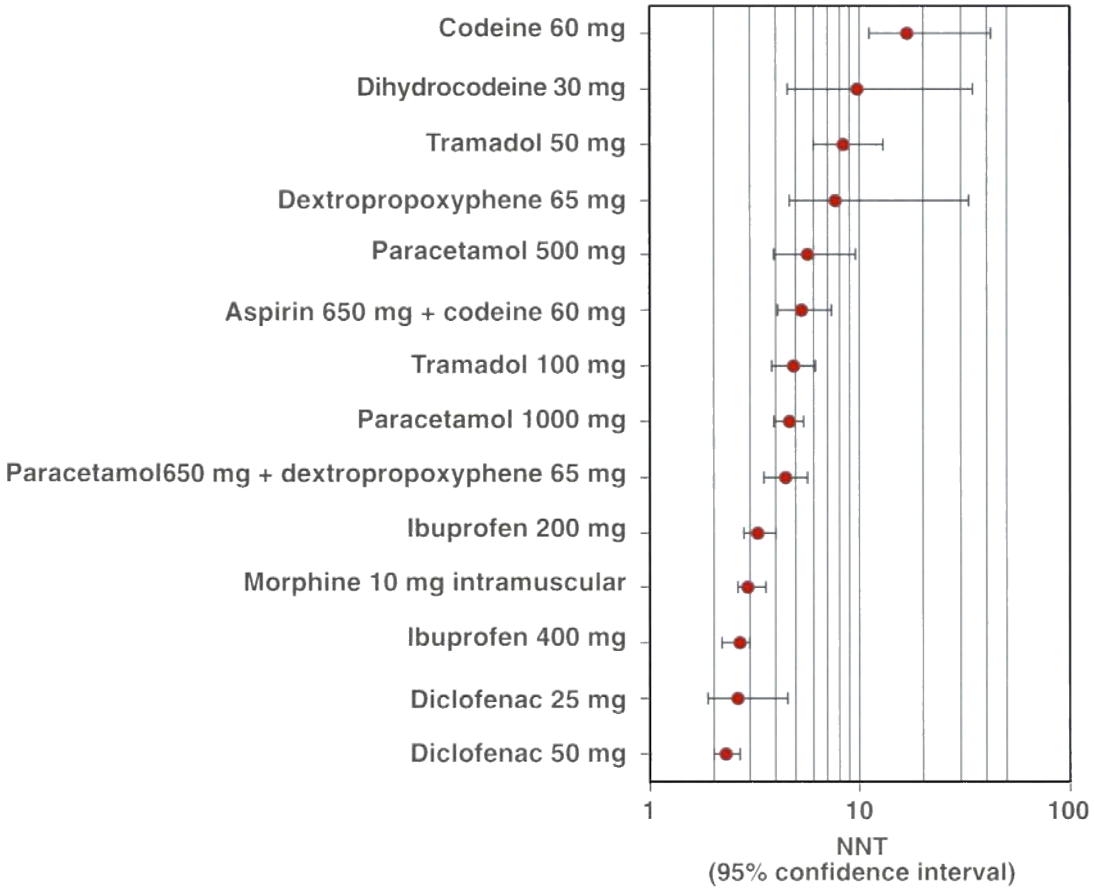
peripheral

- Analgesia
- Obstipation
- Inhibition of bile flow
- anuresis
- Release of histamin, itching

Most Opioids are under control of the **Narcotics law (BtMG)**, to avoid abuse



Gershell and Goater *Nature Reviews Drug Discovery* **5**, 889–890 (November 2006) | doi:10.1038/nrd2179



Wirksamkeitskriterium NNT= „ **N**umber **N**eeded to **T**reat“:

Number of patients needed to treat to reach analgesia in at least 50% of the patients

McQuai, 1999

Pain research-necessary?

- ~ 5-8 Mio patients suffering from chronic pain in germany
  ⇨ Analgesics = most common pharmaceutics
  (93 Mio prescriptions 2003)
- Long-term use of analgesic is particularly associated with severe side effects
- A number of patients is not sufficiently treated with the currently available drugs

Urgent need of analgesics with new and altenative mechanism of action

in vitro models

Animal models

Nociceptive animal models

Species: In most cases rats and mice

General principle: *motoric reaction* to a stimulus as a parameter for the extentof nociception

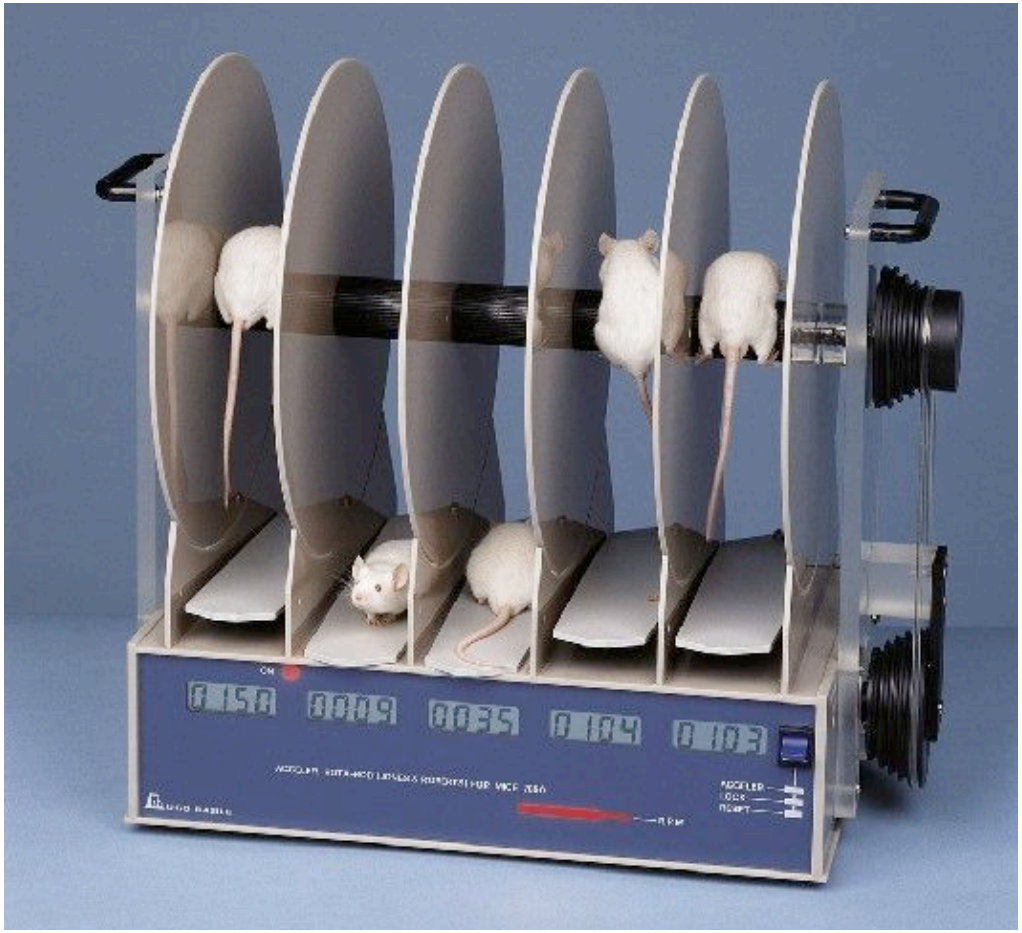
Stimuli:

- thermal
- mechanical
- chemical

⇨ More than one method necessary to increase significance

Motorical testing:
Rotarod-Test

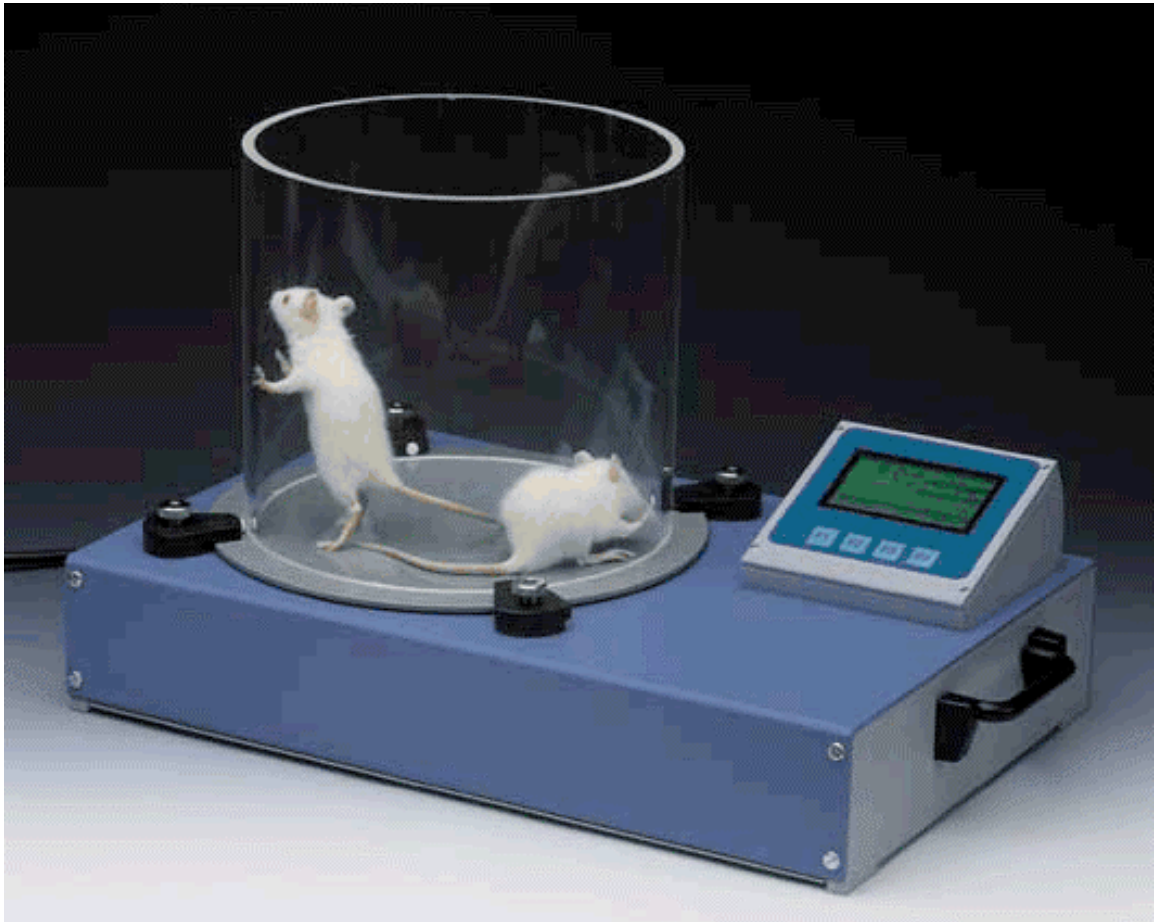
- Animals are placed onto a rotating rod
- Latency until the animals fall from the rod



Measurement of acute thermal nociception

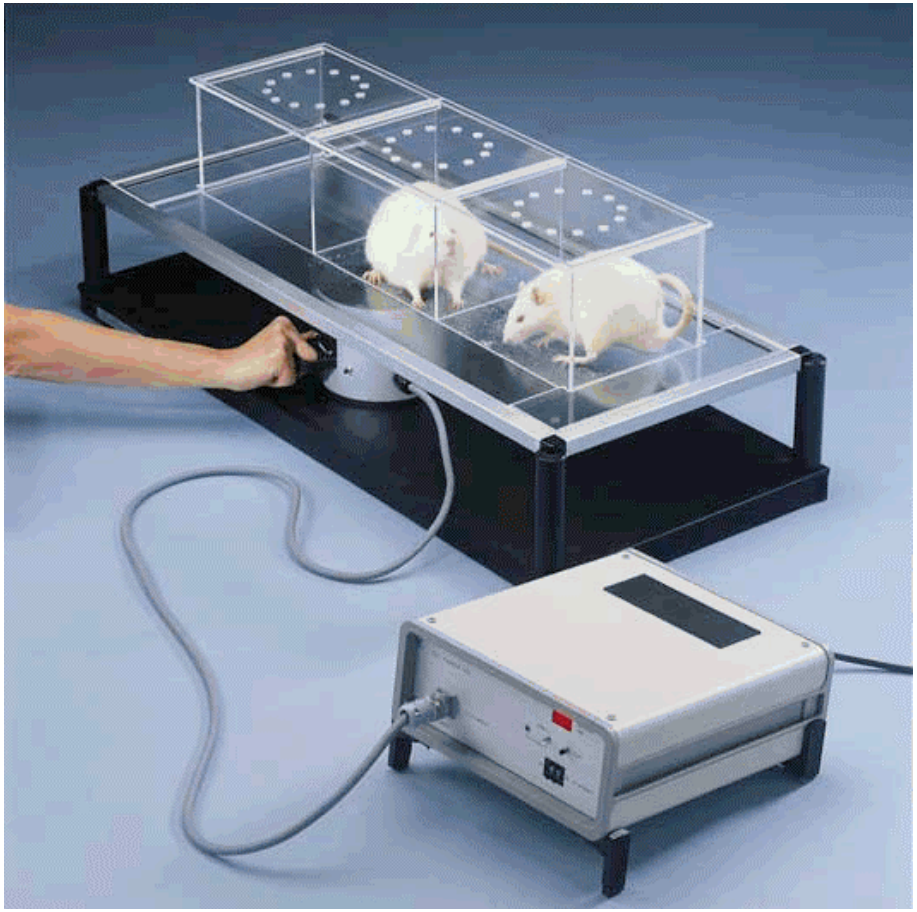
Hot Plate-Test

- Animals are placed onto a 52°C warm Plate
- Latency until licking the paw/jumping



Measurement of thermal Hyperalgesia:
Hargreaves-Test

- Induction of paw inflammation by injection of zymosan
- Stimulation of the inflamed paw by a thermal stimulus
- Paw withdrawal latency

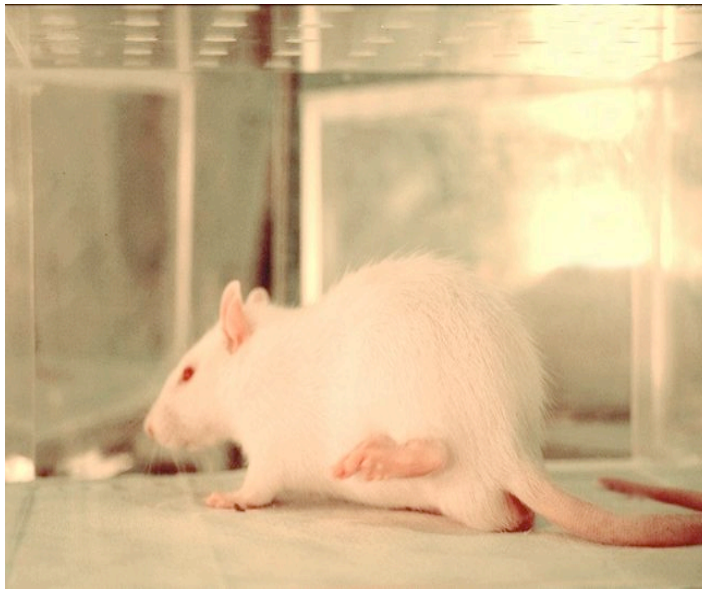


Measurement of mechanical Hyperalgesia
Dynamic Plantar-Test

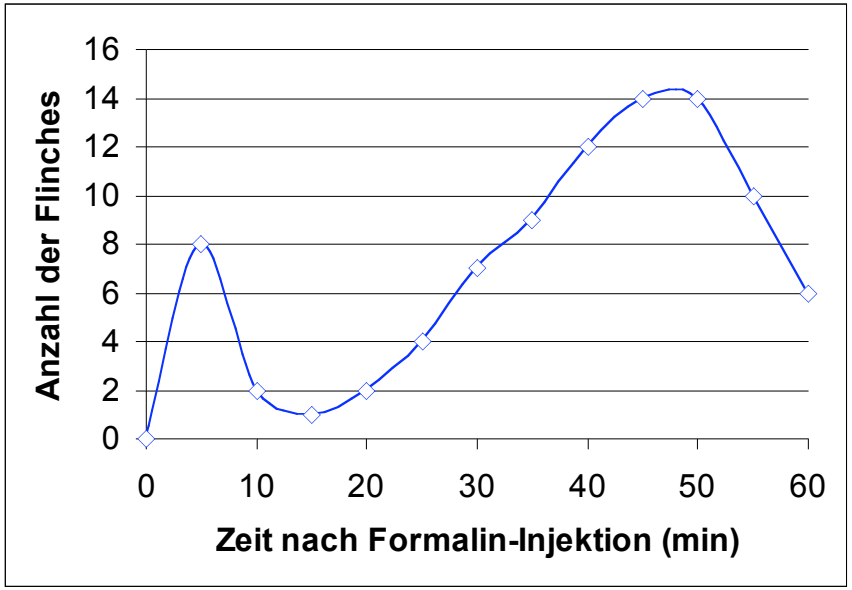
- Induction of paw inflammation by injection of zymosan
- Stimulation of the inflamed paw by a steel rod
- Paw withdrawal latency

Measurement of tonic pain :
Formalin-Test

- Injection of Formalin into one hind paw
  ⇨ “Flinches” (rats)
  licking (mice)
- Counting Flinches / licking over 60 min or 45 min, respectively



- Nociceptive respnse in 2 phases

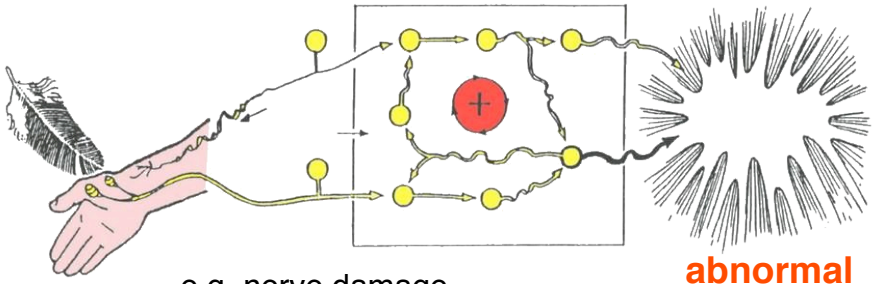


Phase 1 (0 - 10 min): *acute pain*

Phase 2 (11 – 60 min): *tonic pain*

Neuropathic pain

Neuropathic pain



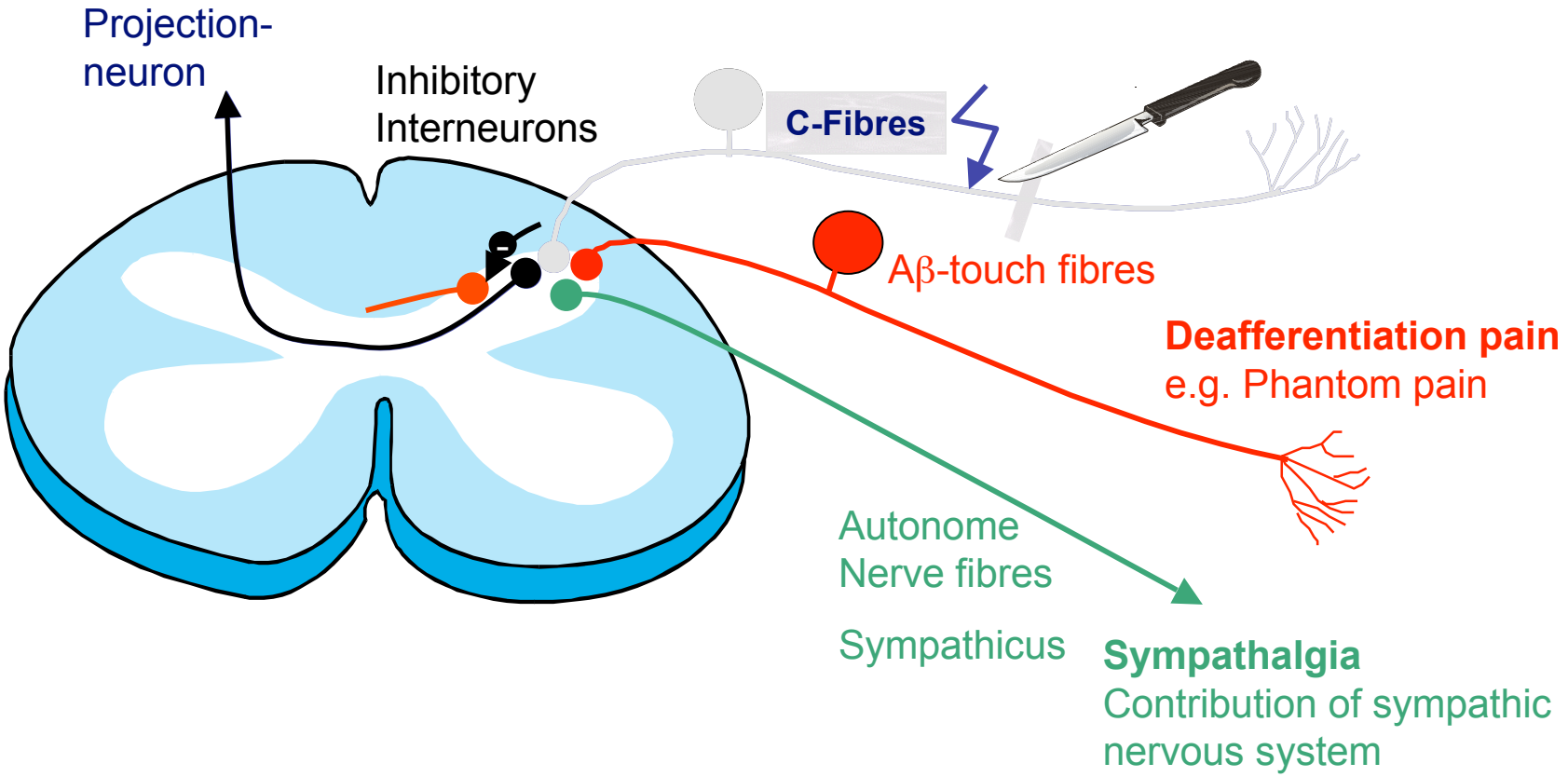
e.g. nerve damage

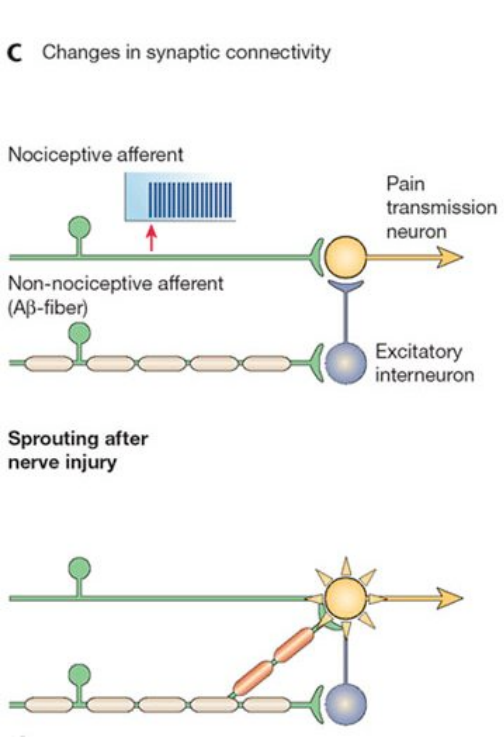
abnormal pain

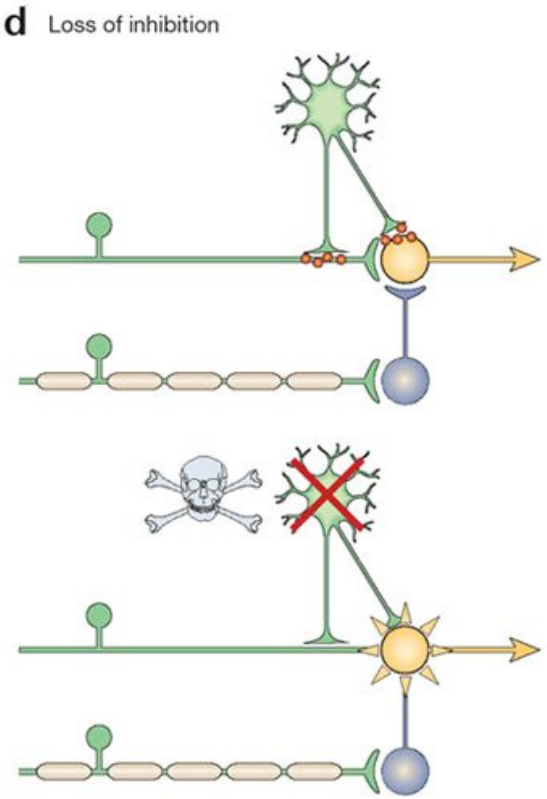
Spontaneous discharges

Pain

caused by damage of peripheral nerves







Loss of inhibition

J. Scholz and C.J. Woolf, Nature Neuroscience 2002

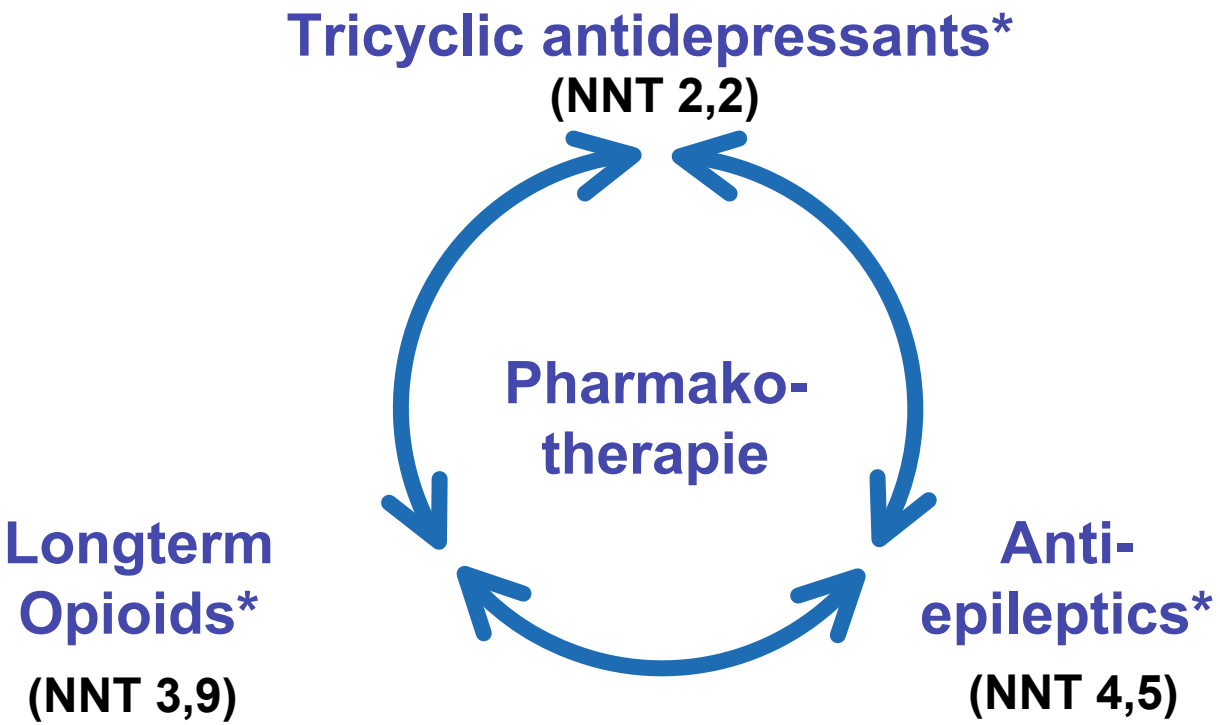
Decsending tracks from the brain stem inhibit activity of nociceptive neurons in the spinal dorsal horn by release of Noradrenalin und Serotonin

GABAergic interneurons are responsible for tonic inhibition in the dorsal horn.

- ~ 300.000 Menschen suffer from severe neuropathic pain

Causes:

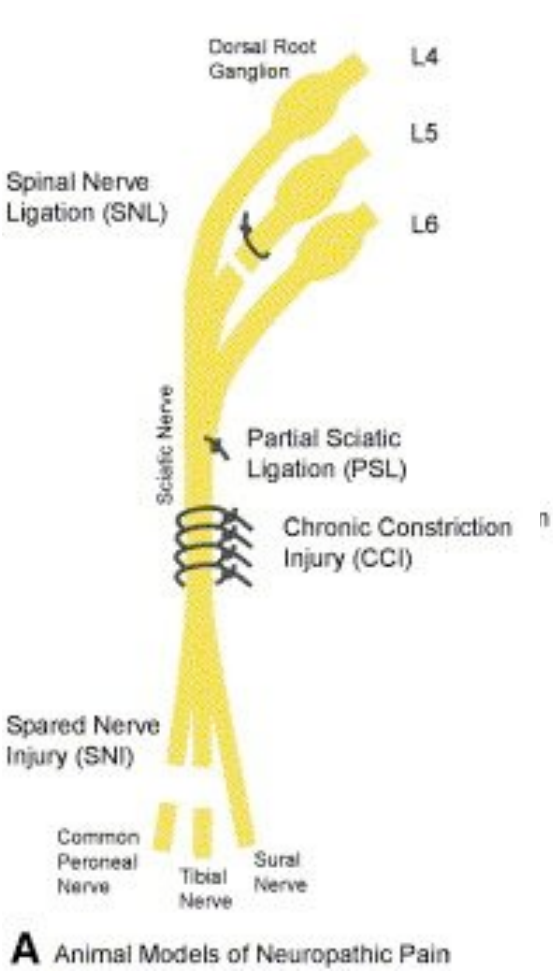
- Herpes zoster
- Diabetes
- Mechanical nerve damage (amputation, herniated disk, accident)
- Alcohol



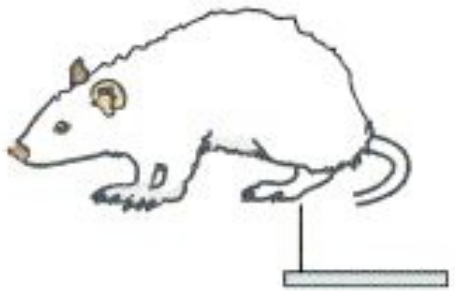
* (in Mono- or combinatorial therapie)

Freynhagen, R., Baron, R.: Kompendium Neuropathischer Schmerz, 2003
Beniczky et al., J. Neural Trans., 2005

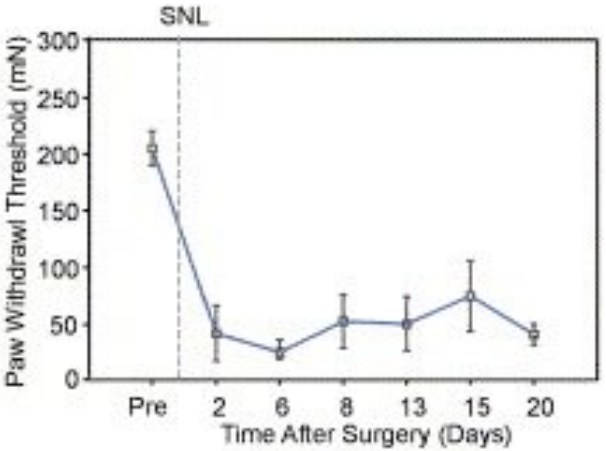
Animal models of neuropathic pain

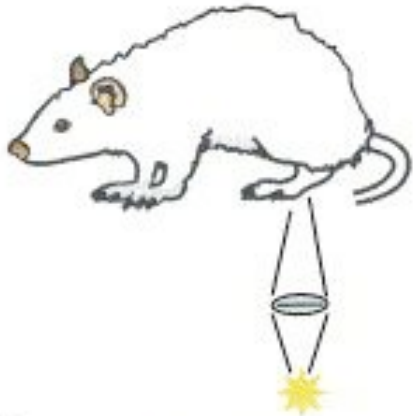


A Animal Models of Neuropathic Pain

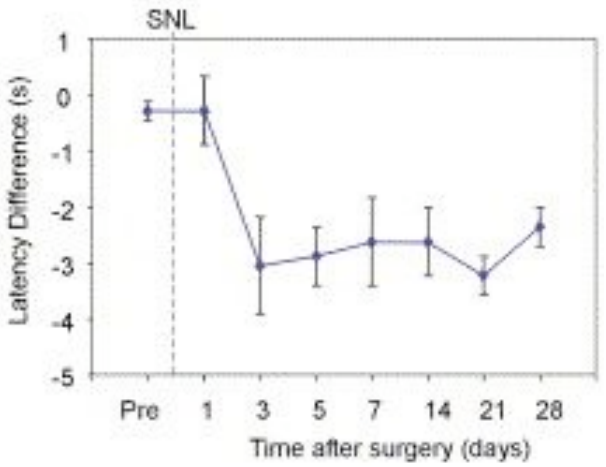


B Von Frey Test of Mechanical Threshold





C Radiant Heat Test of Thermal Sensitivity



Summary

Physiological Pain

Protection and warning, high threshold

Pathophysiological Pain

- Inflammatory pain ⇨ Hyperalgesia, Allodynia

→ Treatment is necessary to avoid „pain memory“: Opioids, non-Opiods

- Neuropathic Pain ⇨ Allodynia

→ Treatment is insufficient: Opioids, TCA, AE

Research for new analgesics is important

Traditional analgesics exhihibit a number of side effects

Some patients cannot be sufficiently treated