Pathological Physiology of Nervous System: Neuro 1 - Pain

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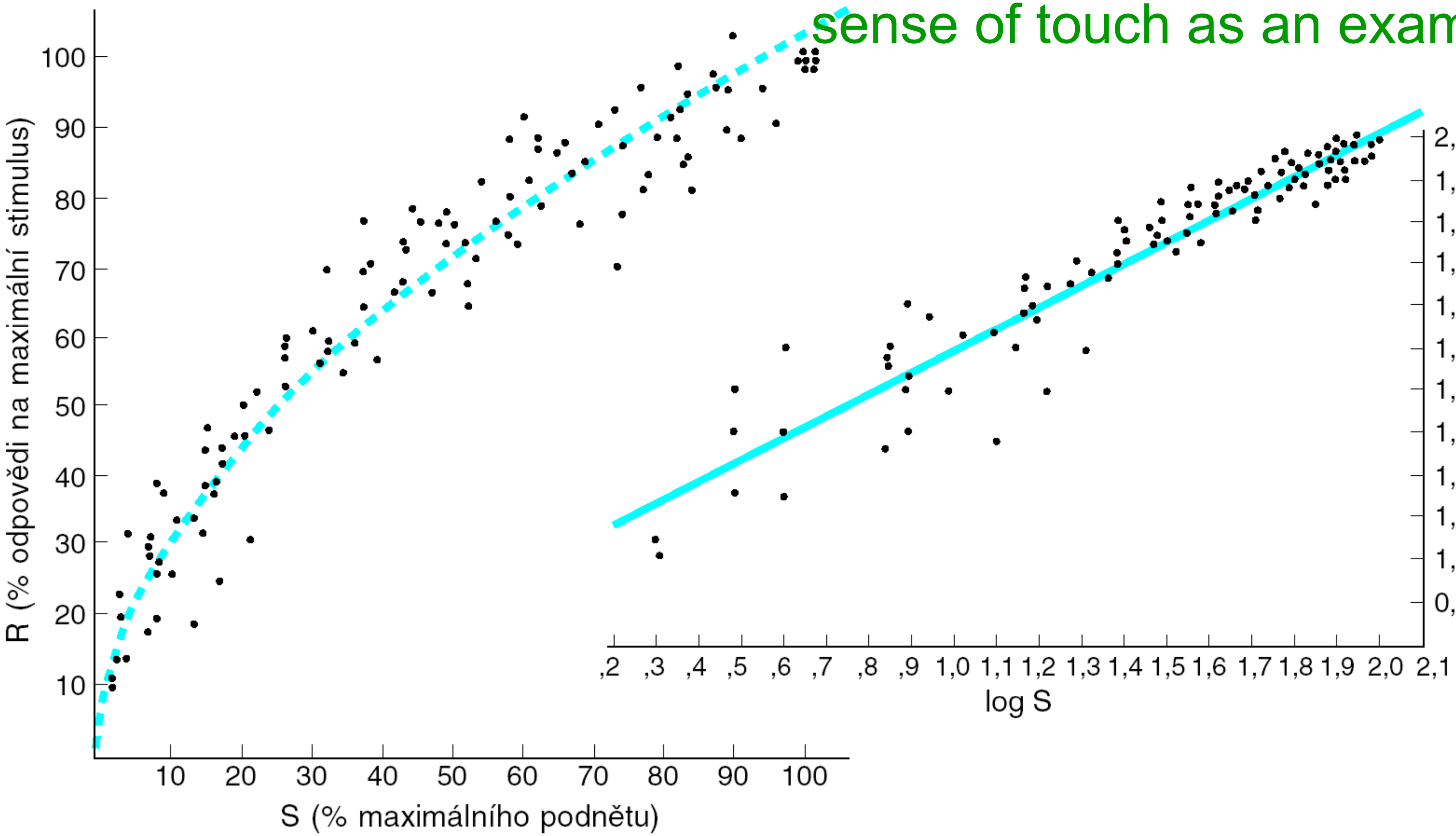
Outline

- An Attempt To Describe Pain Objectively: Psychophysics
- Biological and Pharmacological approach to pain

Response (R) is function of stimulus intensity (S), R=f(S), sense of touch as an example



Obr. 5-5. Vztah mezi intenzitou dotykového podnětu (S) a frekvencí akčních potenciálů v senzorických nervových vláknech (R). Tečky znázorňují jednotlivé hodnoty u koček; jsou vyneseny do souřadnic lineárních **(vlevo)** a logaritmických **(vpravo)**. Rovnice vyjadřuje vypočítaný exponenciální vztah mezi R a S. (Reprodukováno se souhlasem z WERNER, G., MOUNTCASTLE, VB. *Neural activity in mechanoreceptive cutaneous afferents. Stimulus-response relations, Weber functions, and information transmission*. J Neurophysiol, 1965, 28, 359.)

Design of Experiments to Measure Hotness, Construction of the Scoville Scale of Hot Chili Peppers…

Wilbur Lincoln Scoville, american pharmacist, (1865 – 1942)

Scoville ratings of chemicals (Scoville heat units)	substance examples
16,000,000,000	Resiniferatoxin
5,300,000,000	Tinyatoxin
16,000,000	Capsaicin
15,000,000	Dihydrocapsaicin
9,200,000	Nonivamide
9,100,000	Nordihydrocapsaicin
8,600,000	Homocapsaicin
160,000	Shogaol (dehydr. ginger oil)
100,000	Piperine (black pepper alkaloid)
60,000	Gingerol (ginger oil)
16,000	Capsiate

Scoville ratings of hot peppers **examples**

3 000 000-6 000 000	Pepper spray
2 000 000	Trinidad Moruga Scorpion
1 850 000	Chocolate 7-Pot
1 600 000	Dorset Naga
1 450 000	Trinidad Scorpion Butch Taylor
1 200 000	Naga Viper, Trinidad 7 Pot Jonah
1 200 000	Satan's Strain Trinidad Scorpion Moruga
1 100 000	Naga Morich, Infinity Chili
1 050 000	Bhut Jolokia
850 000	Trinidad 7 Pot CARDI Strain
350 000 – 580 000	Red Savina Habanero
100 000 – 350 000	Habanero
50 000 – 100 000	Pepper Birds Eye, Piri Piri
30 000 – 50 000	Tabasco pepper
5 000 – 23 000	Serrano
5 000 – 10 000	Chipotle
2 500 – 8 000	Jalapeño, Tabasco sauce
1 000 – 2 000	Poblano
100 – 500	Pimento

Psychophysics = describes, how subjective response depends on magnitude of physical, or chemical stimulation

R - (response) subjective intensity
S - (stimulus) physical intensity

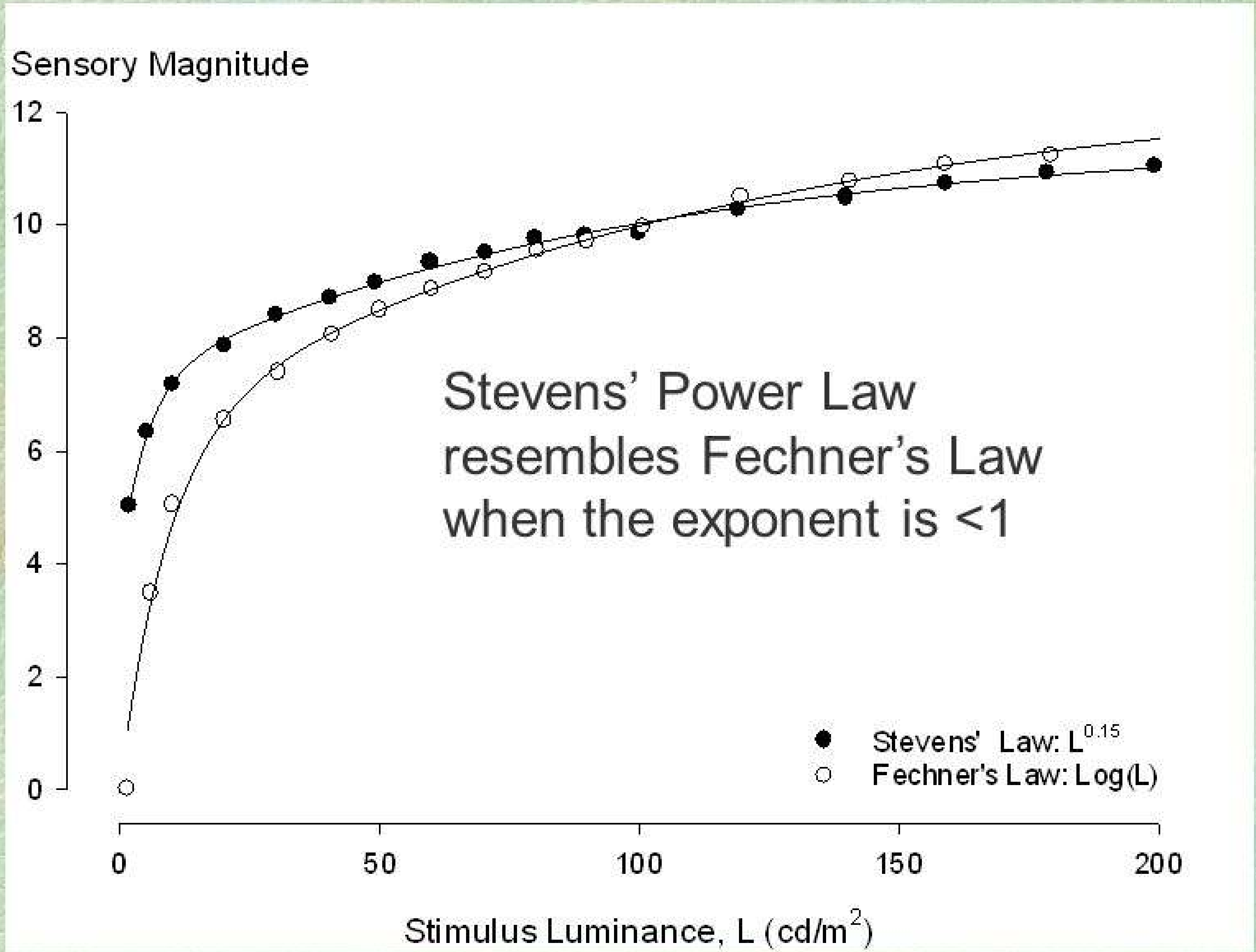
Examples:
Chili pepper hotness: S... active or dry substance concentration, R... hotness

Pain: S… damage intensity (pain modality typology is better corresponding to R),
R... pain

Various curves can be fitted to given datapoints (linear dependence, logarithm, power function, etc.)

Comparing Fechner's Law with Stevens' Power Law

Fig. 3.6



Psychophysical laws

R - (response) subjective intensity
S - (stimulus) physical intensity
S_0 - threshold stimulus intensity
A - constant of proportion
N - exponent

Weber – Fechner (logarithmic) law

$$R = A\log\left(S / S_0\right)$$

Stevens (power) law

$$R = A\left(S - S_0\right)^N$$

Exponents in the Stevens (power) law

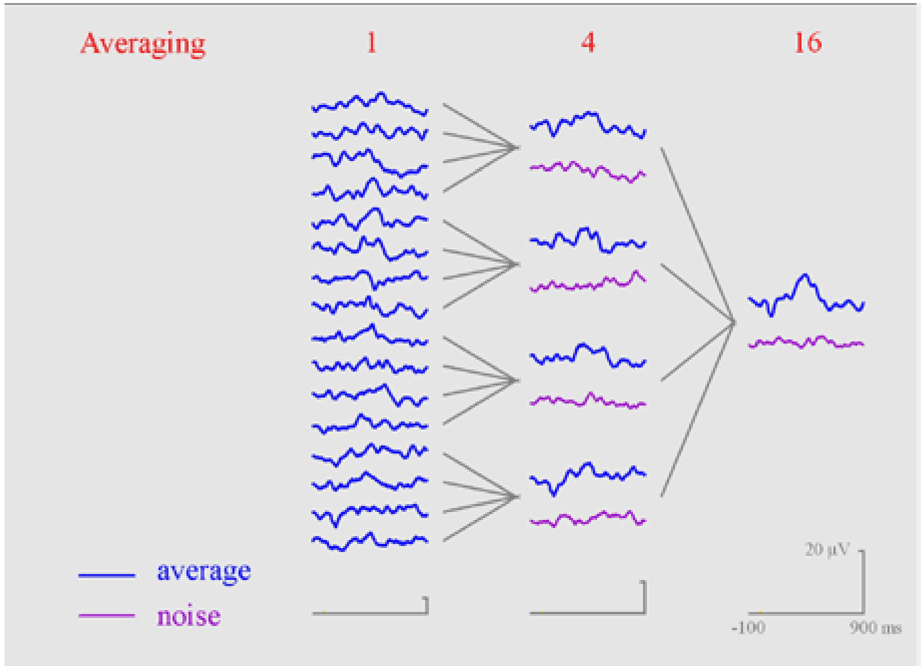
Table 18-1. Representative exponents of power functions relating psychophysical magnitude to stimulus magnitude on prothetic continua*

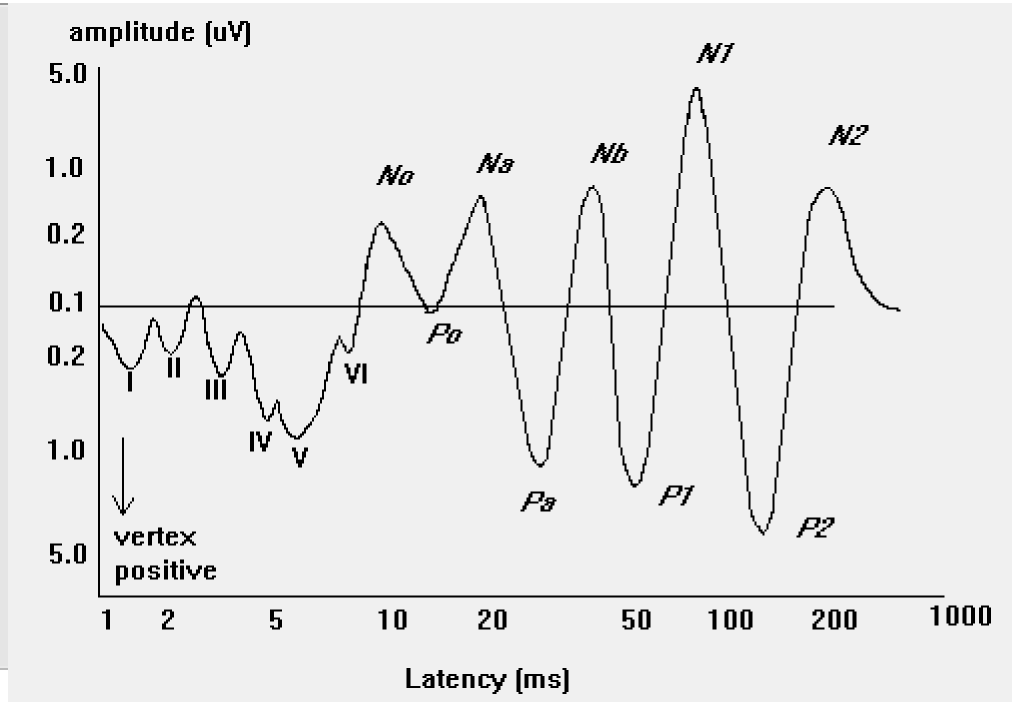
Continuum	Exponent	Stimulus conditions
Loudness	0.60	Binaural
Loudness	0.54	Monaural
Brightness	0.33	5° target—dark-adapted eye
Brightness	0.50	Point source—dark-adapted eye
Lightness	1.20	Reflectance of gray papers
Smell	0.55	Coffee odor
Smell	0.60	Heptane
Taste	0.80	Saccharine
Taste	1.30	Sucrose
Taste	1.30	Salt
Temperature	1.00	Cold—on arm
Temperature	1.60	Warmth—on arm
Vibration	0.95	60 Hz—on finger
Vibration	0.60	250 Hz—on finger
Duration	1.10	White-noise stimulus
Repetition rate	1.00	Light, sound, touch, and shocks
Finger span	1.30	Thickness of wood blocks
Pressure on palm	1.10	Static force on skin
Heaviness	1.45	Lifted weights
Force of hand-grip	1.70	Precision hand dynamometer
Autophonic level	1.10	Sound pressure of vocalization
Electric shock	3.50	60 Hz, through fingers

*From Stevens.[37a]

... other ways of objective investigation of sensory perception, including somatosensation and pain...

Evoked potentials

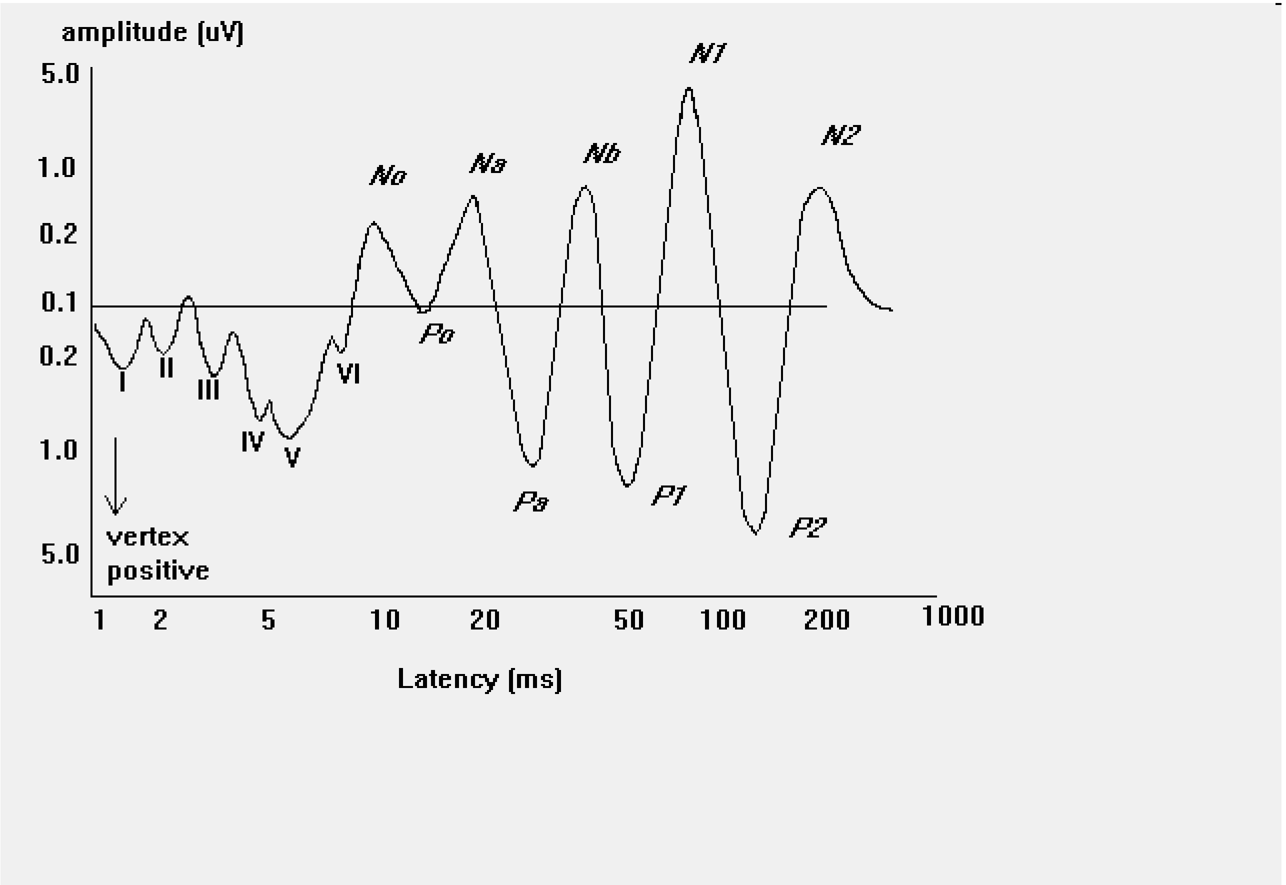




Measurement principle: repeated EEG response to stimulus is summed up (averaged)
The sensory response is a result

Example: evoked potentials of different parts of the auditory pathway

Evoked potentials – auditory as example



Objective Audiometry:
Brainstem or cortical evoked response audiometry BERA (CERA, CZ),
Auditory Brainstem Response (ABR)

Somatosensoric EP (SEP) – mechanical or electrical stimulation

- stimulus duration 2 - 300 ms, repetition rate up to 3 Hz
- recorded from various locations in correspondence to stimulations
- typical sequence (positive and negative EEG waves)

P1	N1	P2	N2	P3	N3
16 ms	20 ms	28 ms	33 ms	43 ms	50 ms

typical use:

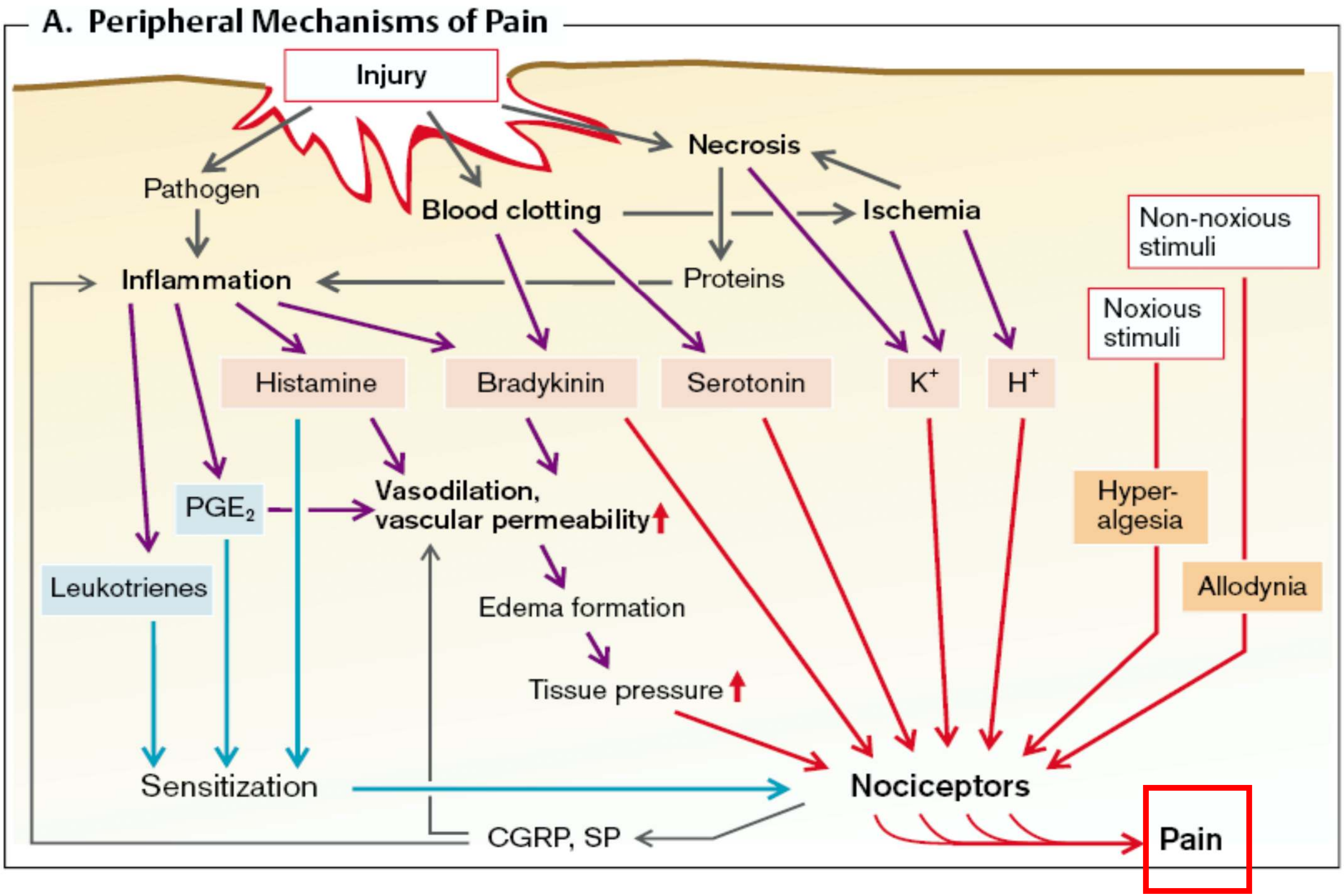
- during spinal cord surgery – continuous checkup of CNS conditions
- prolonged latency in multiple sclerosis

Only experimental: is maping of pain using functional magnetic resonance imaging, fMRI; differentiation between painful and neutral stimulation in somatosensation

In practice only specialized centers dispose with the avanced methods

How is diagnosis and fighting with pain in medical practice?...

Biological and Pharmacological Approach to Pain



CGRP (Calcitonin-gene related peptide), SP (Peptide substance)

Tissue injury leads to painful sensation

Pain:

1 is a warning that something goes wrong

2 helpful to diagnostics and localization pathologies

3 can be pathologic, anoying beyond the purpose

Psychological pain components

Algothymic component is its emotional context

Algognostic component says, where, what and how much it gets wrong

Pains, which lose the warning purpose are **…neuralgic pains**

neurologic investigation shows no deviation from norm.

Psychophysics: - no relation between stimulus intensity and percept intensity

- there is continuous transition between various touch and pain sensations

tickling, sharp point touch, warm, cold vs.

itching, puncture, scalding (opaření), congelation

what itches, we scrub (scrape) (?), [Fenistil – antihistaminic, antipruriginous drug]

Pain is modified by…

- previous experience, expectations
- instruction, suggestion
- emotions, especially fear and anxiety
- concurrent activation of other sensory inputs
- diversion/ redirection of attention

Pain leads to activation of…

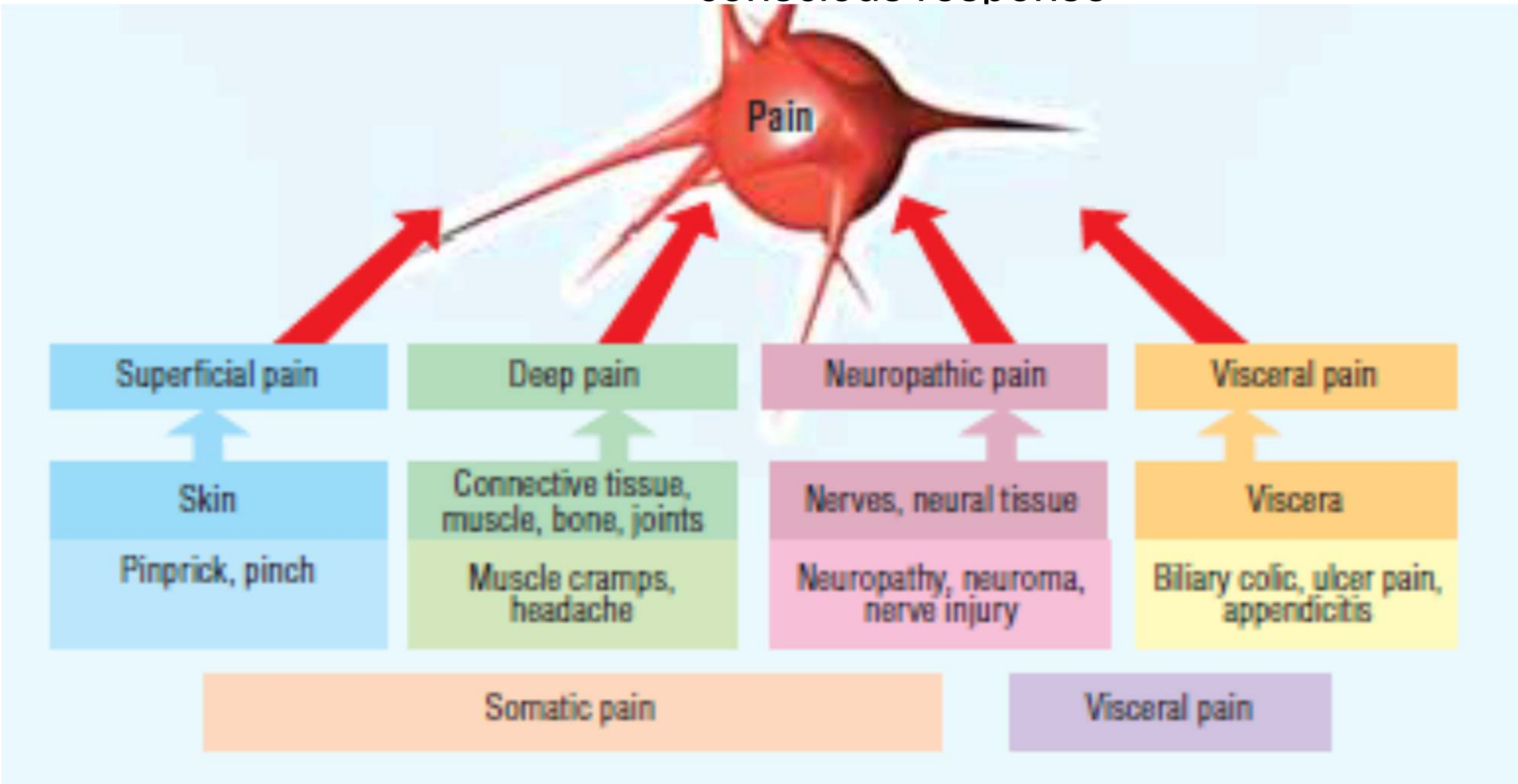
- sympathetic n.s.

vasoconstriction, hypertension, tachycardia, sweating, paleness, goose flesh, mydriasis

- parasympathetic n.s.

hypotension, bradycardia, nausea/ vomiting

- motor response
- conscious response



Types of pain, phenomenology

Patho-genetic classification of pain

•receptive (nociceptive)

•peripheral neurogenous (neuropathy)

•central neurogenous

•originating in autonomous nervous system (Sympathetic n.s.)

•visceral

•pain of psychical origin

Acute pain

-cause can be identified

-short term

-disappears when the original cause is cured

-usually does not recurr

Chronic pain

-longer than 6 months

-cause may not be identified

-intensity higher than expected to known stimulus

-causes high physical and psychical stress

-annoying in daily life

Mechanoreception – receptor organs (long list ☹)

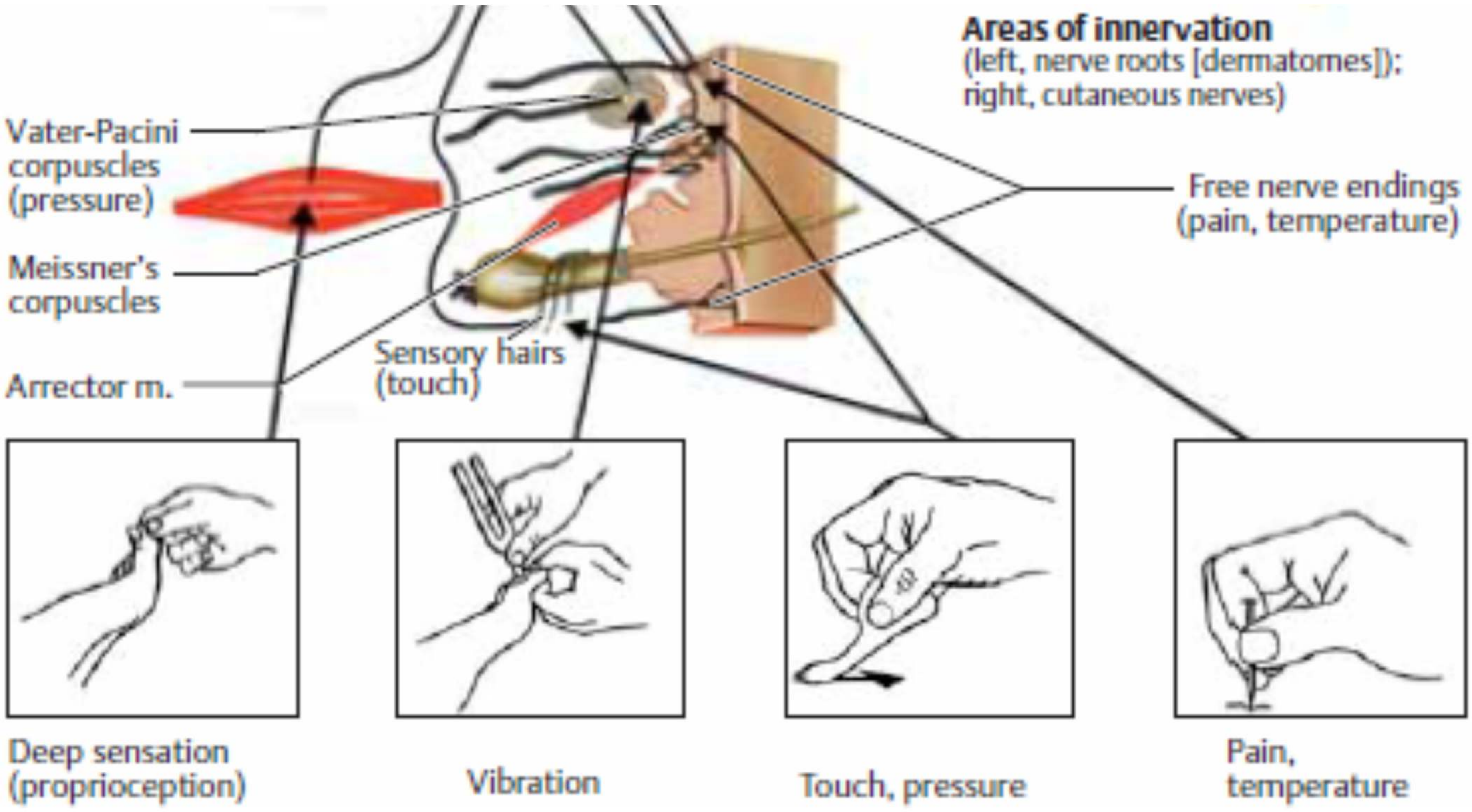
I. Mechanoreceptors
Skin tactile sensibilities (epidermis and dermis)
Free nerve endings
Expanded tip endings
Merkel's discs
~~Plus several other variants~~
Spray endings
Ruffini's endings
Encapsulated endings
Meissner's corpuscles
Krause's corpuscles
Hair end-organs
(Deep tissue sensibilities, Free nerve endings, Expanded tip endings, Spray endings, Ruffini's endings, Encapsulated endings)
Pacinian corpuscles
Plus a few other variants

Muscle endings
Muscle spindles
Golgi tendon receptors
~~Hearing~~
~~Sound receptors of cochlea~~
~~Equilibrium~~
~~Vestibular receptors~~
~~Arterial pressure~~
~~Baroreceptors of carotid sinuses and aorta~~

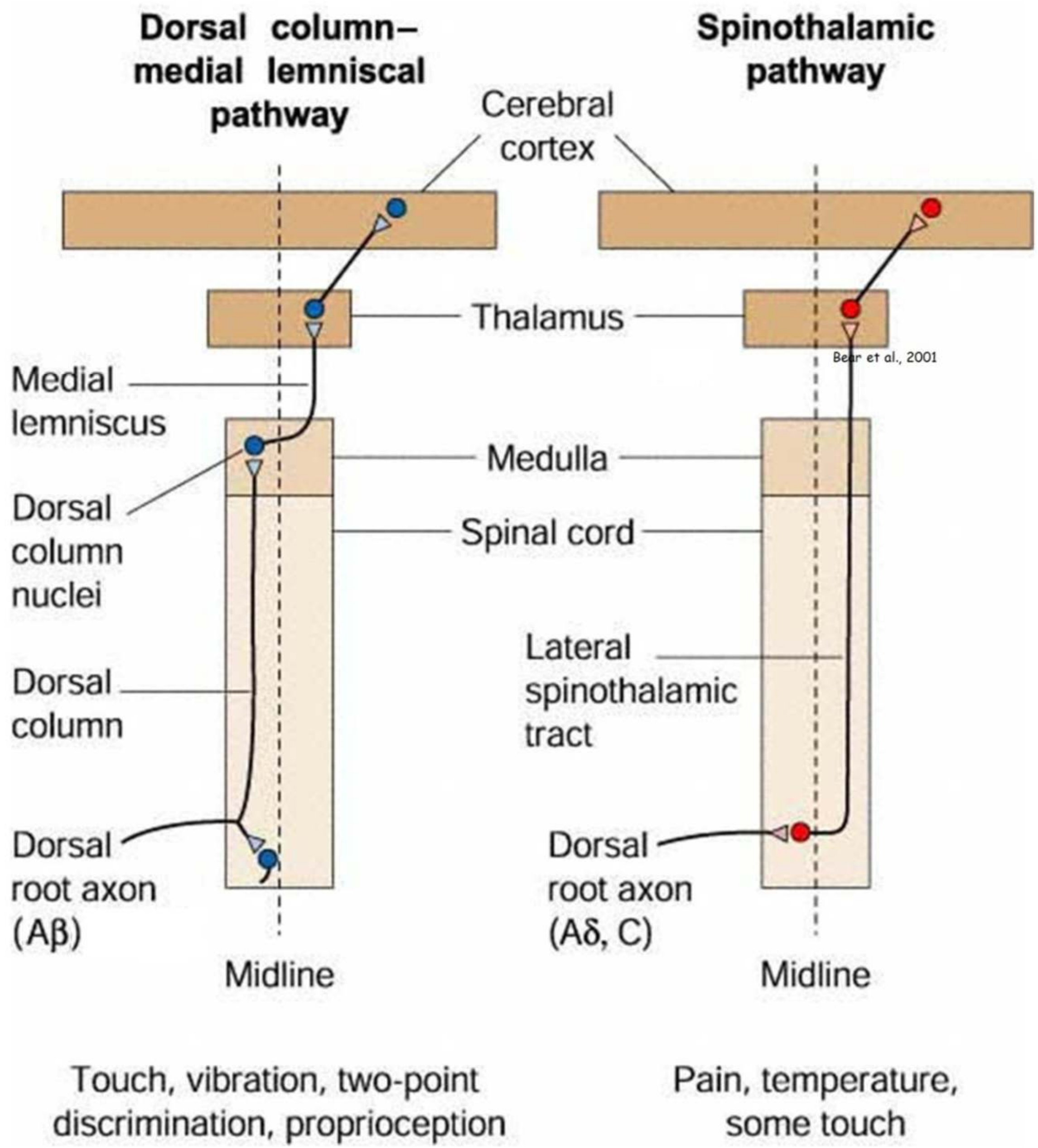
II. Thermoreceptors
Cold
Cold receptors
Warmth
Warm receptors

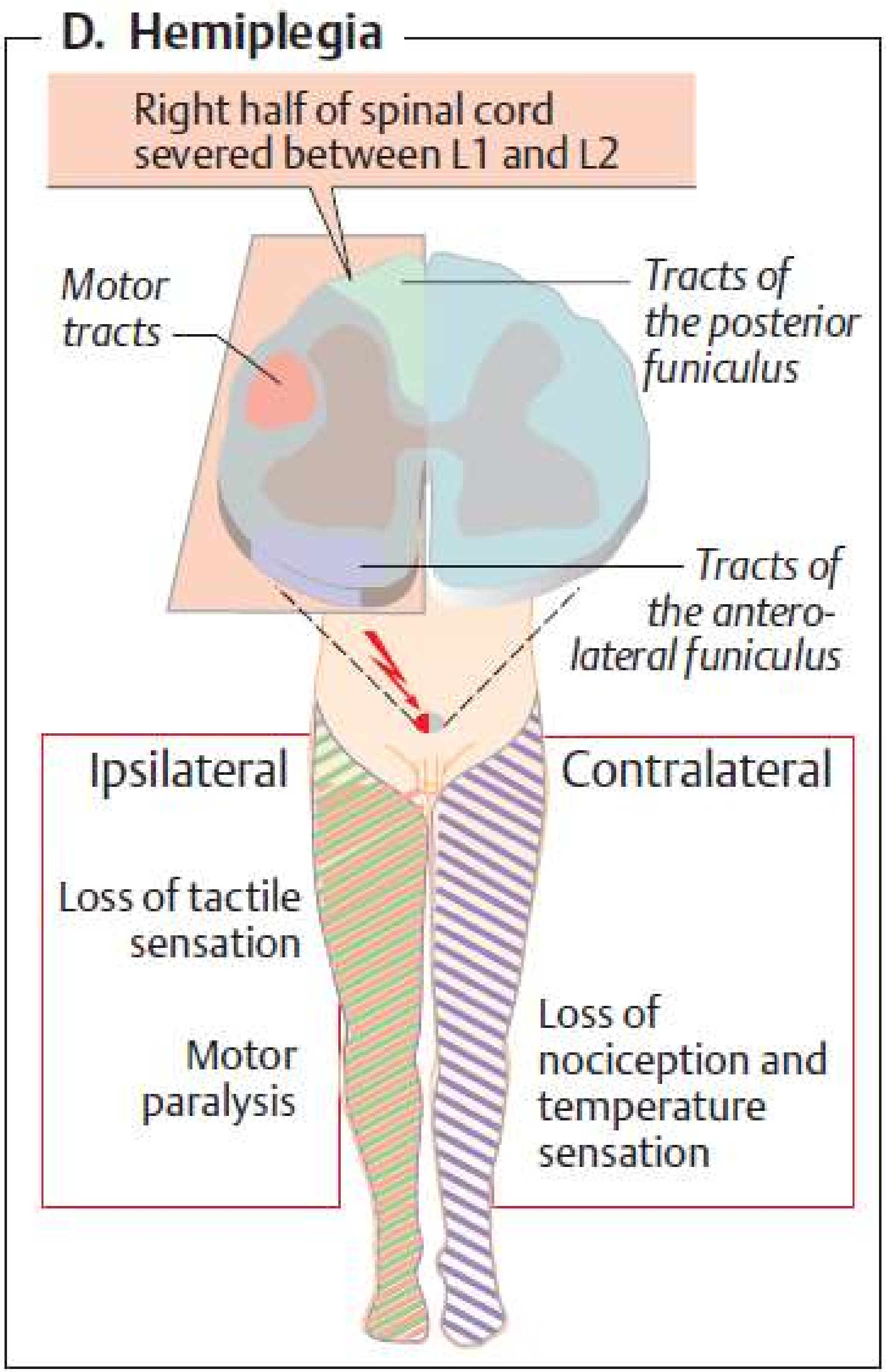
III. Nociceptors
Pain
Free nerve endings

Four major touch modalities



Schematic crossings of spinal cord somatosensory pathways





Dissociation of somatosensory modalities in the unilateral spinal cord lesion

One set of the somatosensory pathways crosses in the appropriate spinal cord segment and the other set crosses as a whole in medulla oblongata

This is a condition of Brown-Sequard syndrome

Fibres conducting nociceptive stimuli

- **C-fibres** – without myelin sheets, action potentials are convected slowly, fibres convect deep, nonaccurate localized, diffuse pain

- **Aδ-fibres** – with thin myelin sheet, fibres mediate fast conduction of sharp, accurate localized pain

- **Aα/Aβ-fibres** – large myelinated. Fibres do not convect nociceptive stimuli, they mediate tactile stimuli

- Afferent fibres enter dorsal spinal roots. In this region exist excitatory and inhibitory interneurons. Inhibitory interneurons gate the passage of information into thalamus and cortex.

Nociceptors, pain receptors = dedicated receptors, ion channels and free nerve endings

- They are sensitive on the **pH changes** (pH in acute abscess, phlegmona reaches 5,8 = pain, pH in chronic abscess is normal, without pain)

- Nociceptors register the **ratio K^+:Ca^{2+}** (treshold for pain is lower in the lower Ca^{2+} level in ECV)
- evoking inflammation are (permeability of vessel wall, oedema) histamin, bradykinin, serotonin

- direct influence of free-nerve endings: potassium, histamin, bradykinin serotonin

- sensitisation of nociceptors: prostaglandins, esp. PgE_2, interleukin-1, interleukin-6, cyclooxygenases (COX-1, COX-2)

- From activated free nerve endings P-substance is released. It influences vessel wall (vasodilation, permeability of vessel wall, oedema) and mast cells (release of histamin after degranulation).

Painful stimuli

-chemical

-endogenous inflammation mediators (bradykinin, prostaglandins, serotonin, histamin, K+, H+, Il-1)

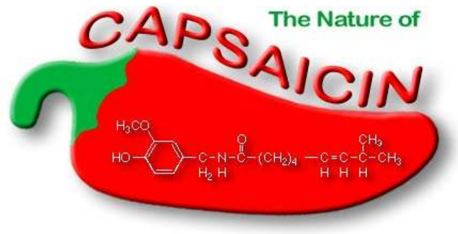
-exogenous substances (capsaicin, formalin = formaldehyde)

-low/ high temperatures

-temperature above 42°C is damaging

-mechanical

During painful stimuli…



- are activated tetrodotoxin resistant (TTX-R) channels
- ATP is relased from damaged cells and acts as pain mediator. ATP receptors are purin receptors (P_2X)
- vaniloid receptors (VR_1), are receptors for capsaicin, also activated above 42°C, pH < 6.5
- activated acid sensing ion channels (ASIC), when pH < 6.5
- Up-regulation of post-synaptic receptors of excitation neuro-transmitters - glutamate (NMDA) and substance P (NK_1)

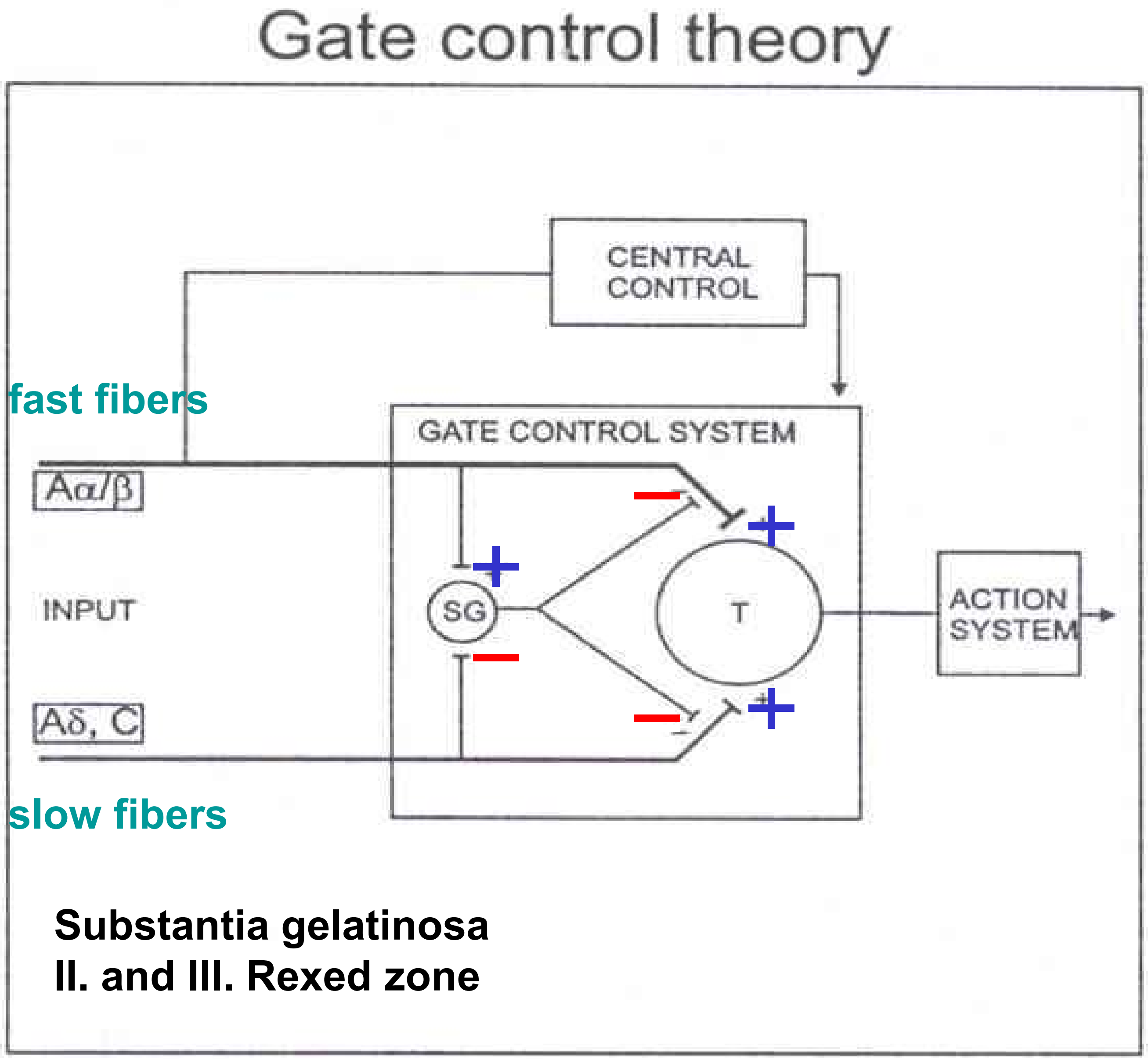
Vaniloid Receptors and Pain

Birds versus mammals...

(Versus insects...)

Eating hot peppers can be beneficial to rise the individual pain threshold…

Pain gating control – spinal cord



Substantia gelatinosa
II. and III. Rexed zone

Opioid system and others

- nigro-striatal and meso-limbic, dopaminergic
  - motor systems and reward pathways
- hypothalamo-hypophyseous
  - central hormone modulation
- ascendent and descendent pathways
  - modulation
  - ascendent – spinal cord, talamus
  - descendent – peri-aquaeductal grey, nuclei raphe

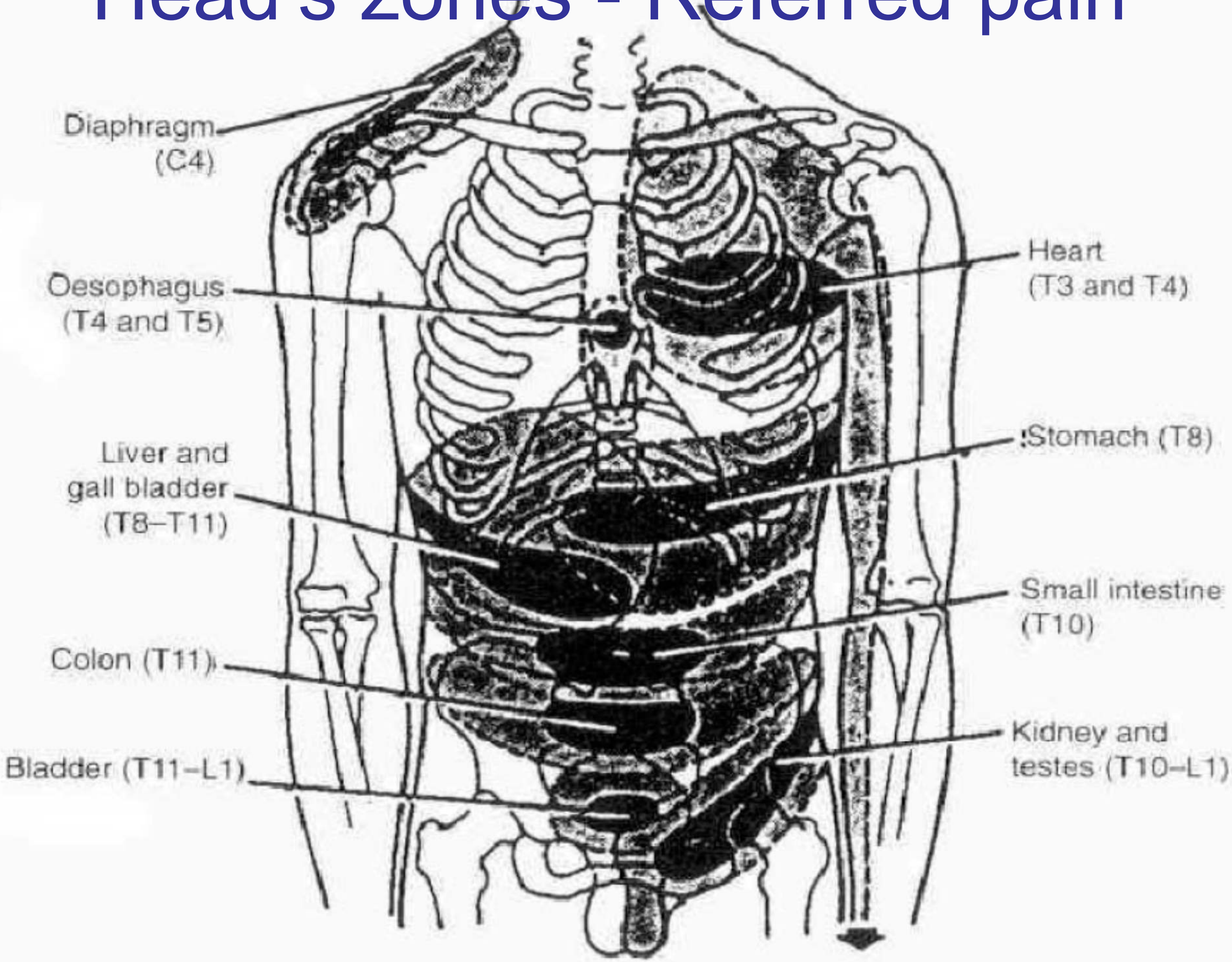
Endogenous opioids

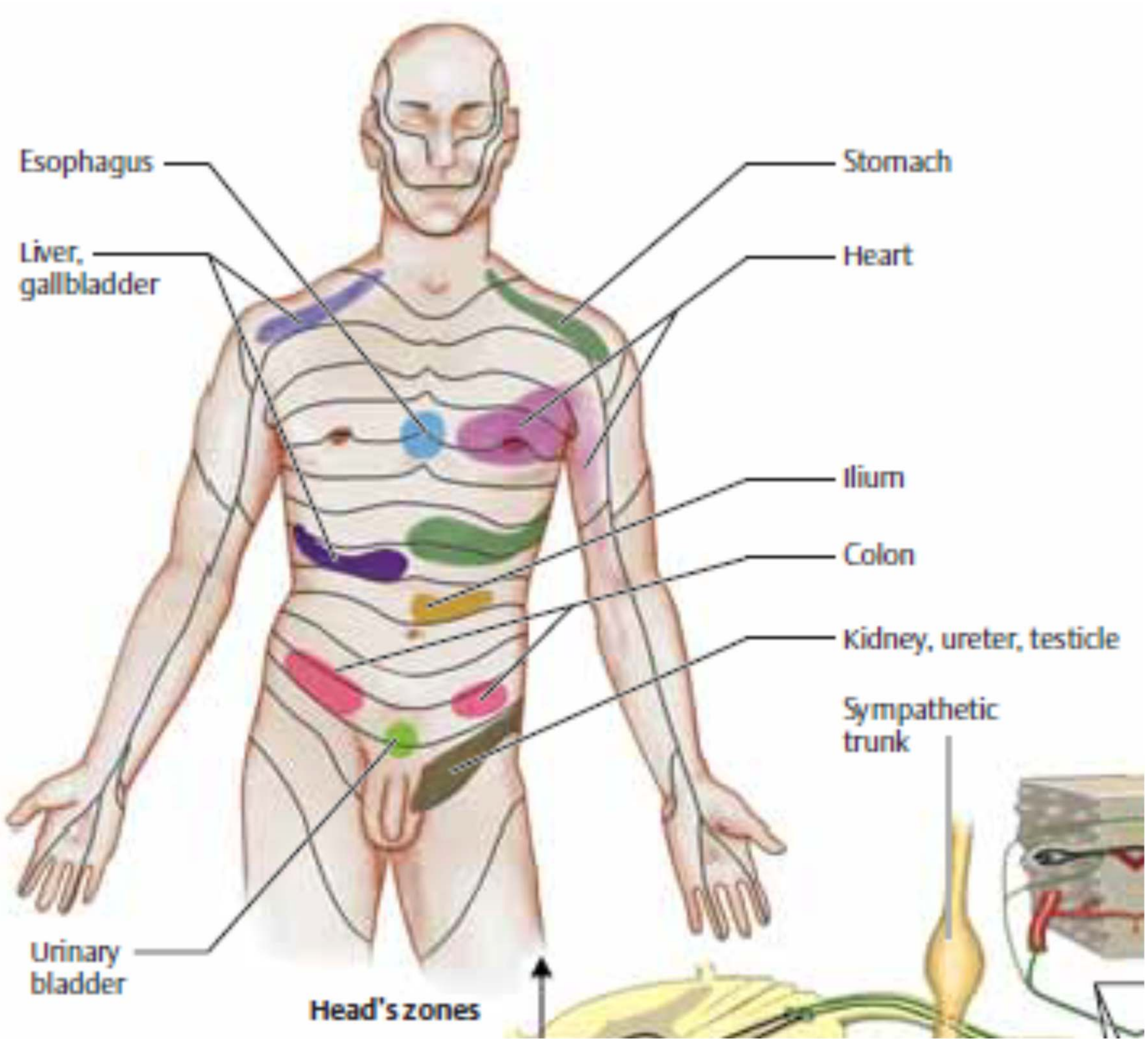
- β-endorphine (31 AA) - μ
- Endomorphine (4 AA) - μ
- Leu-enkefalin (5 AA) - δ
- Met-enkefalin (5 AA) - δ
- Dynorphine(A:AA 1-8, B:AA1-17) - κ
- nociceptin/ orphanin
- nocistatin
- pre-synaptic receptors
  - Inhibiting neuro-transmitter release
  - ⇓ Ca^{2+}
- post-synaptic receptors
  - ⇑ K^{+} conductance – hyperpolarization

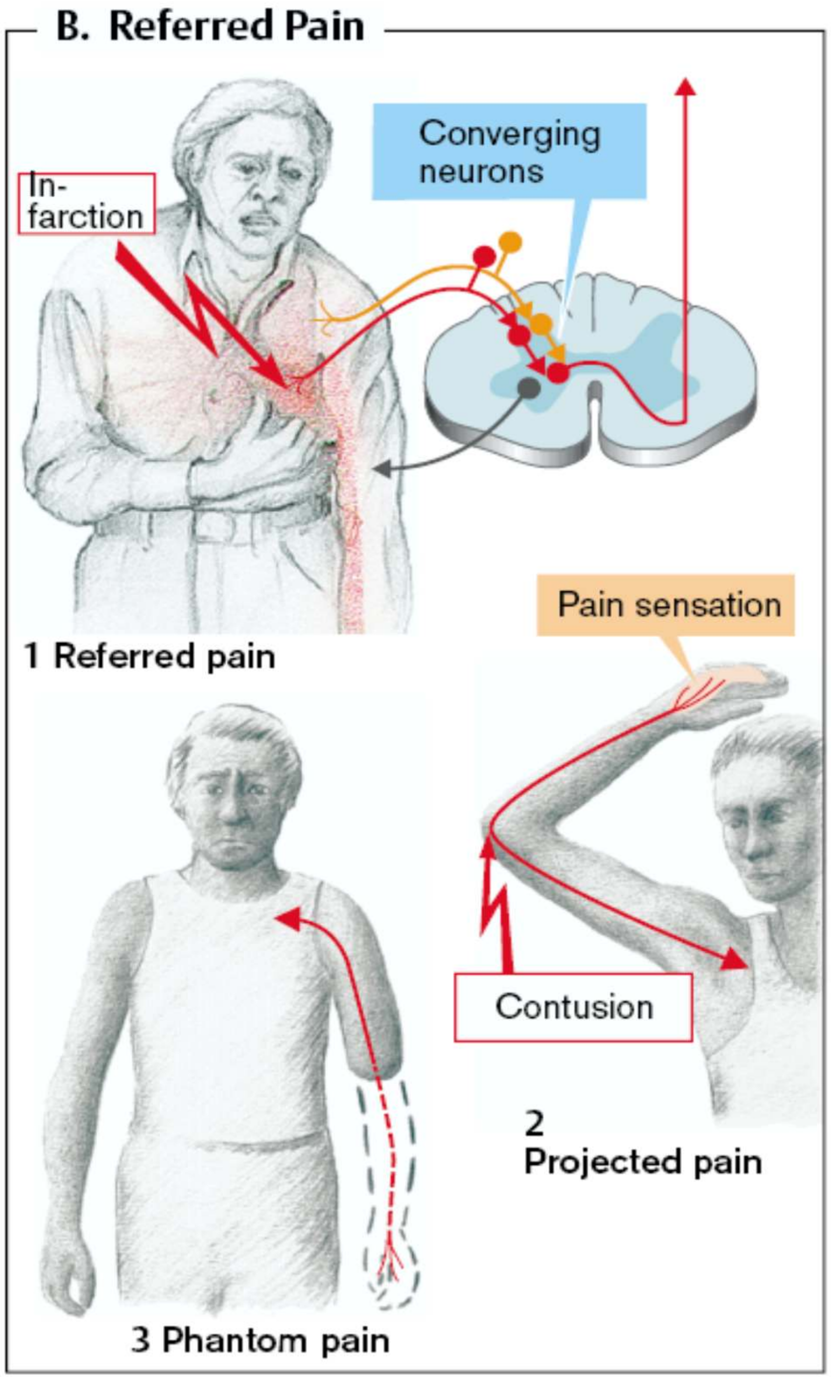
Endogenous cannabinoids

- amids and esthers of fatty acids
- anandamid
- palmitoyl-etanolamid (PEA)
- receptors CB1 a CB2
- CB1 in PAG and RVM,
  sensory neuron
- CB2 in structures of
  immune system
- FAAH – hydrolasis of FA amids
- In the inner ear and auditory pathway as well

Head's zones - Referred pain

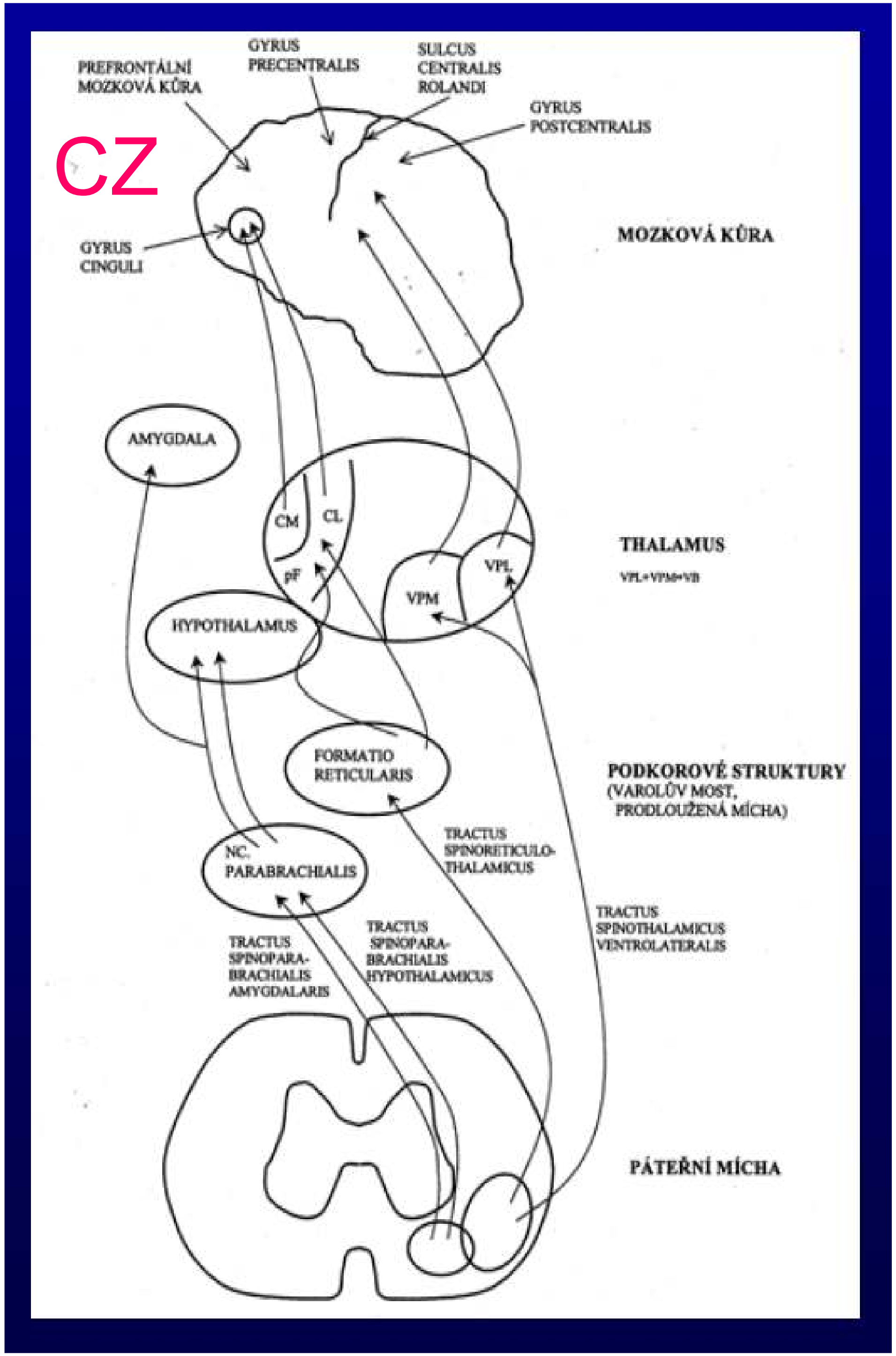



Esophagus
Liver, gallbladder
Stomach
Heart
Ilium
Colon
Kidney, ureter, testicle
Sympathetic trunk
Urinary bladder
Head's zones



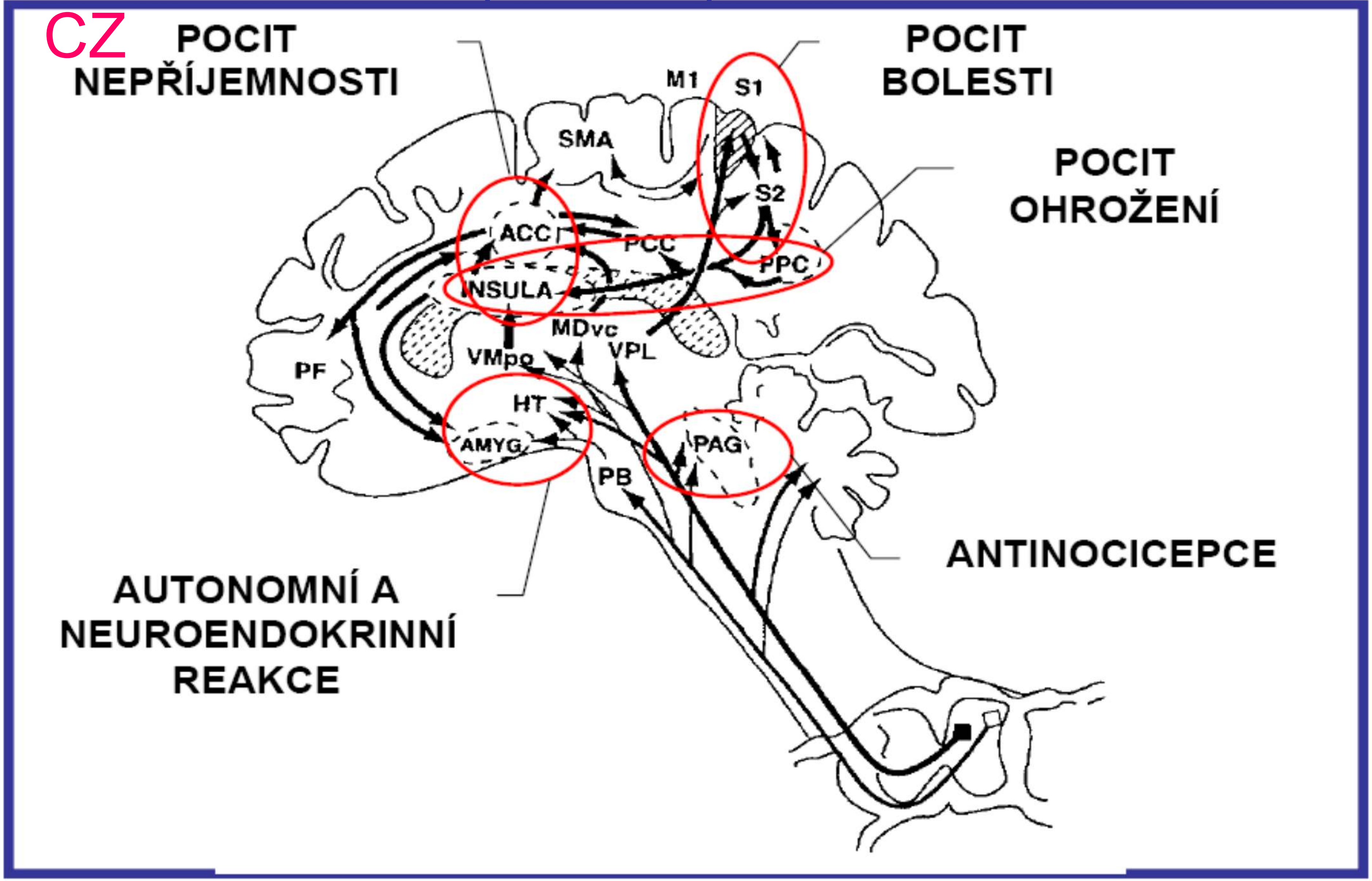
Referred and pathologic pain

Other pathologic painful sensations:
…,
headache,
n. trigeminus,
Migraine,…

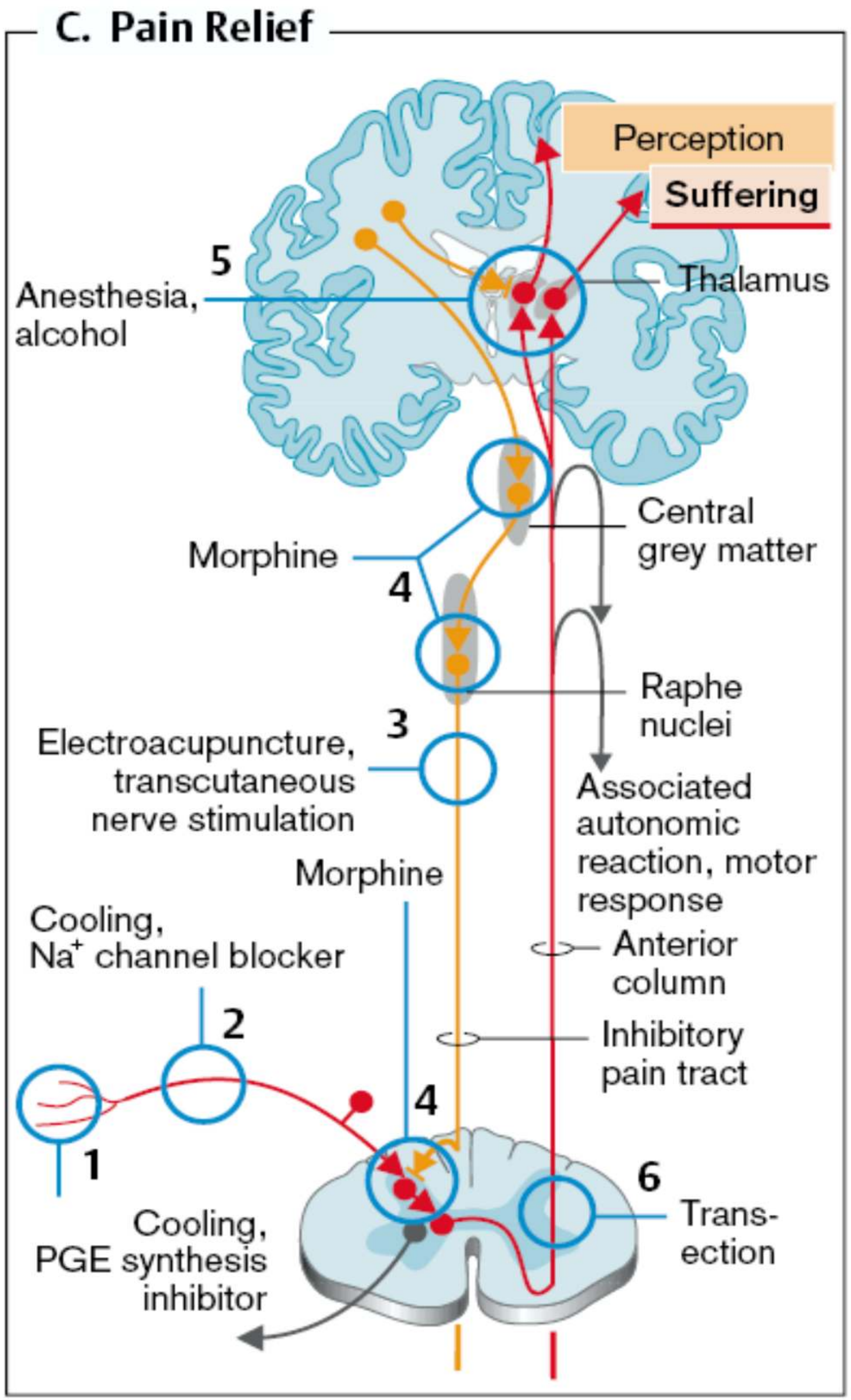


Localization of CNS pain pathways

Localization of sensory, affective and cognitive pain components



Pain Relief


C. Pain Relief
Perception
Suffering
Thalamus
5
Anesthesia, alcohol
Central grey matter
Morphine
4
Raphe nuclei
3
Electroacupuncture, transcutaneous nerve stimulation
Associated autonomic reaction, motor response
Morphine
Cooling, Na+ channel blocker
Anterior column
2
Inhibitory pain tract
4
1
6
Trans-ection
Cooling, PGE synthesis inhibitor

END
OF THE LECTURE

Thanks for your attention

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