Pathofyziology of nerve system II

Intracranial hypertension

Epilepsy

Pain

Intracranial hypertension

Epilepsy

Pain

Intracranial Pressure and Cerebral Perfusion Pressure

Brain is enclosed in the skull…

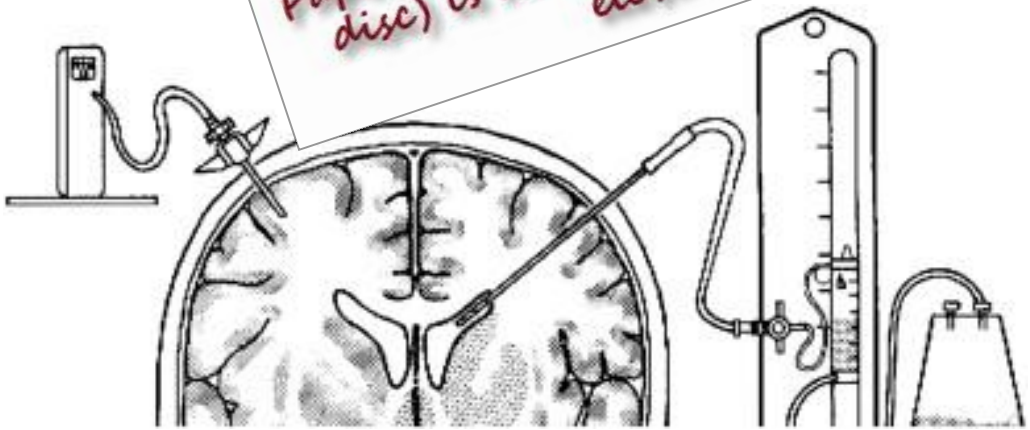
… an advantage before trouble occurs…

… big problem after trouble occurs.

Intracranial pressure (ICP) is pressure inside the skull

Physiological values
ICP: 7 - 15 mmHg
CPP: 70 - 90 mmHg

Papilledema (swelling of the optic disc) is reliable sign that ICP is elevated



http://ars.els-cdn.com

Intracranial compartments

- Brain
- Cerebrospinal fluid (CSF)
- Blood

Cerebral perfusion pressure

- The pressure gradient through which blood flows to the brain

$$\textbf{CPP} = \textbf{MAP} - \textbf{ICP}$$

Cerebral perfusion pressure

Mean arterial pressure

Intracranial pressure

Cerebral perfusion pressure

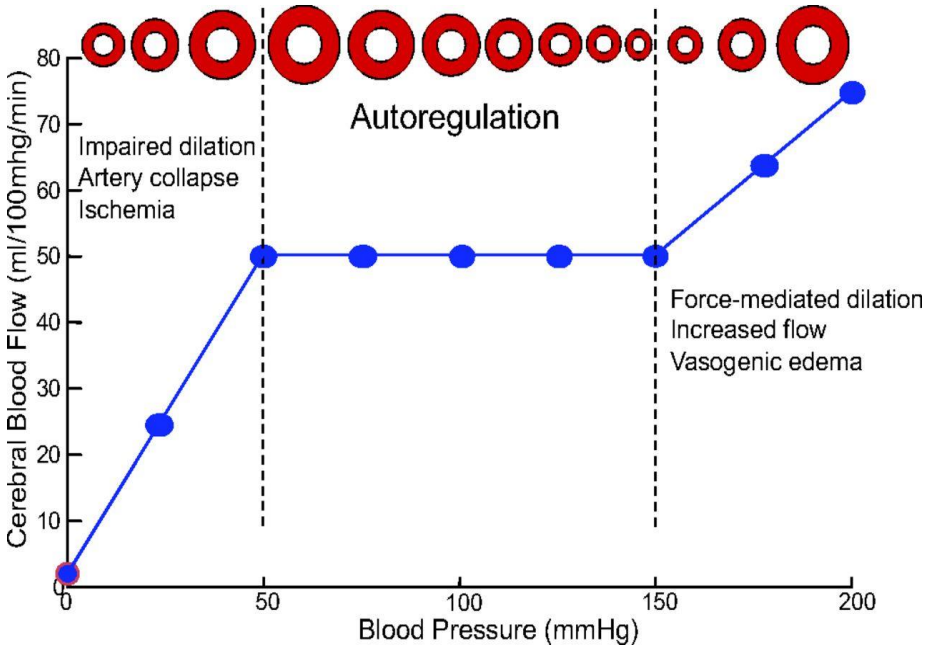
CPP = MAP - ICP

Cerebral perfusion pressure

Mean arterial pressure

Intracranial pressure

CPP is a crucial parameter determining **CBF (cerebral blood flow)**



normal cerebral perfusion pressure (CPP) = 70-100mmHg

safe CPP> 50 mmHg

CPP 30-50 mm Hg leads to a reversible functional disorder

CPP <30mm Hg leads to irreversible changes

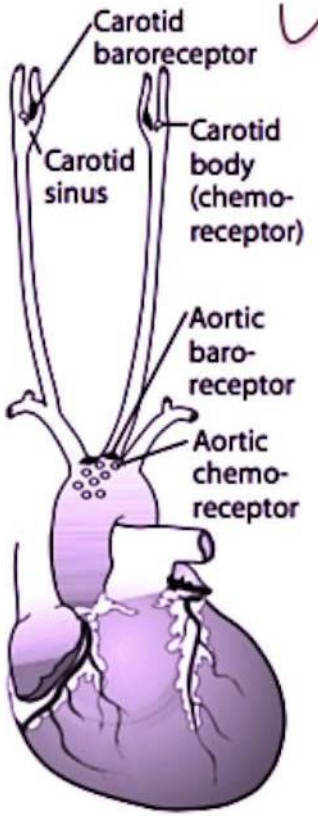
Cerebral perfusion pressure

CPP = MAP - ICP

Cerebral perfusion pressure

Mean arterial pressure

Intracranial pressure



Receptors:

1. Aortic arch transmits via vagus nerve to medulla (responds **only** to ↑ BP)
2. Carotid sinus transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

Baroreceptors:

1. Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
2. Carotid massage—↑ pressure on carotid artery → ↑ stretch → ↑ afferent baroreceptor firing → ↓ HR.

Chemoreceptors:

1. Peripheral—carotid and aortic bodies respond to ↓ P_{O_2} (< 60 mmHg), ↑ P_{CO_2}, and ↓ pH of blood.
2. Central—respond to changes in pH and P_{CO_2} of brain interstitial fluid, which in turn are influenced by arterial CO_2. Do not directly respond to P_{O_2}. Responsible for Cushing reaction— ↑ intracranial pressure constricts arterioles → cerebral ischemia → hypertension (sympathetic response) → reflex bradycardia. Note: Cushing triad = hypertension, bradycardia, respiratory depression.

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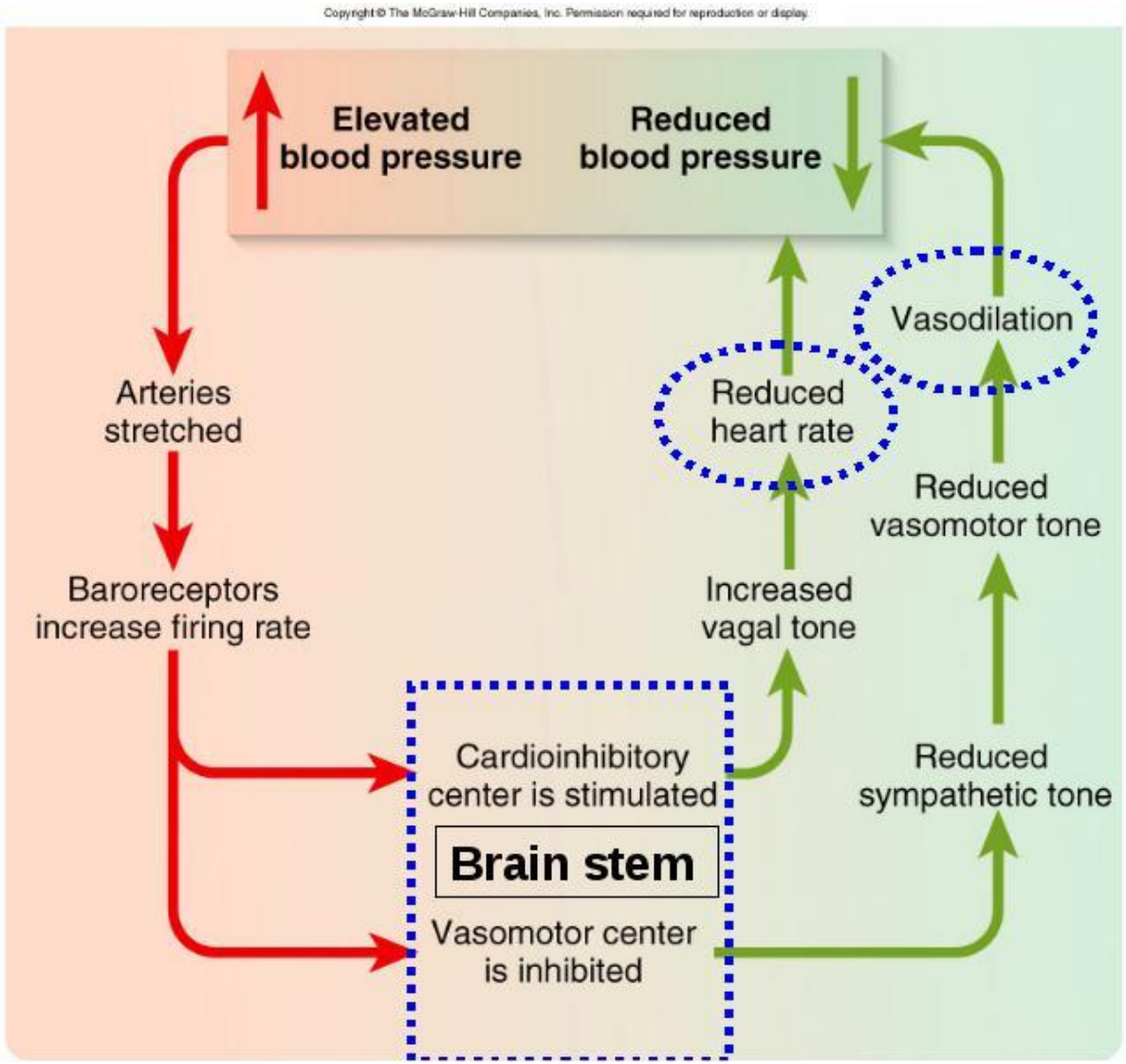
Baroreflex



http://www.azkurs.org/chapter-20-blood-vessels--circulation.html

Cerebral perfusion pressure

CPP = MAP - ICP

Cerebral perfusion pressure

Mean arterial pressure

Intracranial pressure

Intracranial pressure (ICP)

- Normal 7-15mmHg
- Tolerable till 25 mmHg
- Loss of consciousness 40-50 mmHg
- Over 50 mmHg ischemia of brain

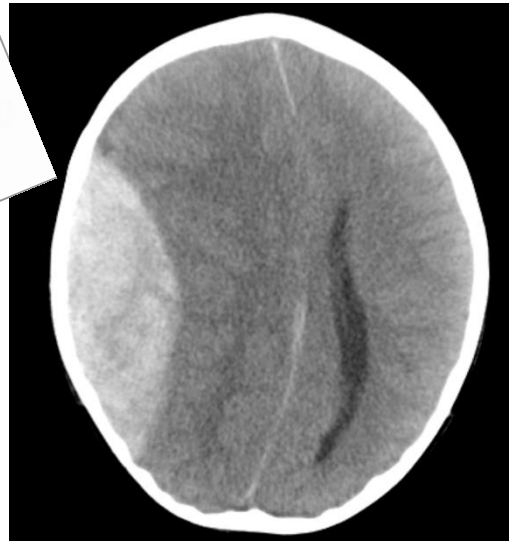
Fast onsetof ICP (e.g. bleeding) X Slow onset ICP (e.g. Tumor growth)

Causes of Intracranial Hypertension

Brain compartment

- Edema
- Tumor
- Hemorrhage
- Infection

Dynamic of development is an important factor.

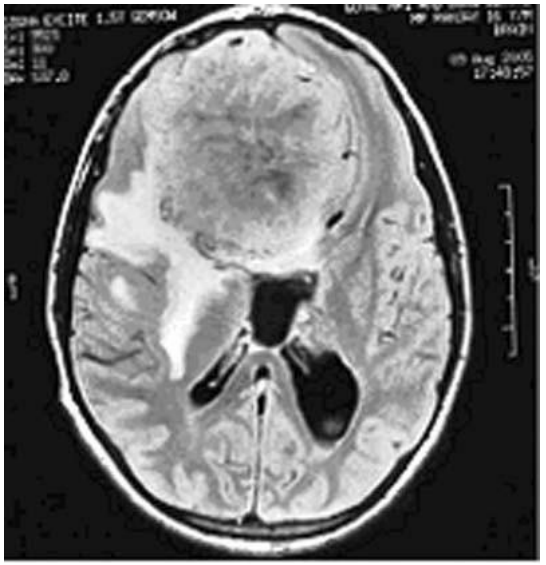


CSF compartment

- Hydrocephalus

Compartment of blood

- Venous sinus thrombosis
- Acidosis - ischemia



Lumbar puncture should not be performed if there is intracranial hypertension. Cerebral herniation may occur in such a case.

Causes of Intracranial Hypertension
Brain Edema

Cytotoxic (intracellular)

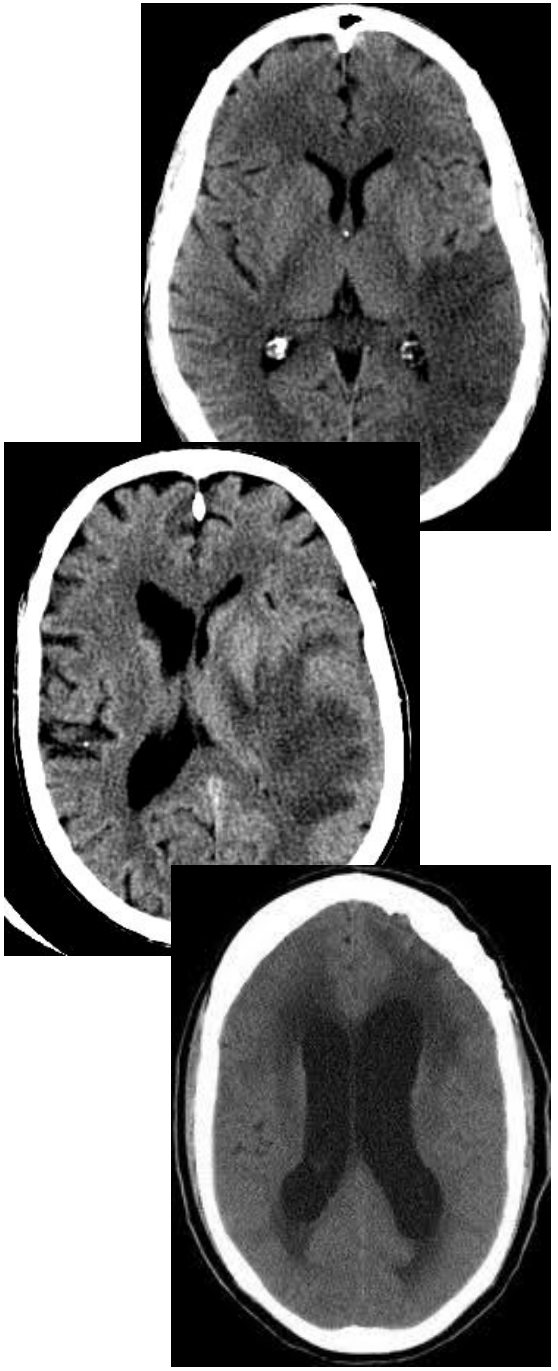
- Na/K ATPase failure
- Na or Ca influx
- H_2O
- Mainly occurs in first 24 h. following insult

Vazogenic (extracellular)

- Damage of endothelial cells and Blood – Brain barrier
- Extravasation of proteins and electrolytes into Interstitial space
- Mainly occurs at 24 h. after insult and later

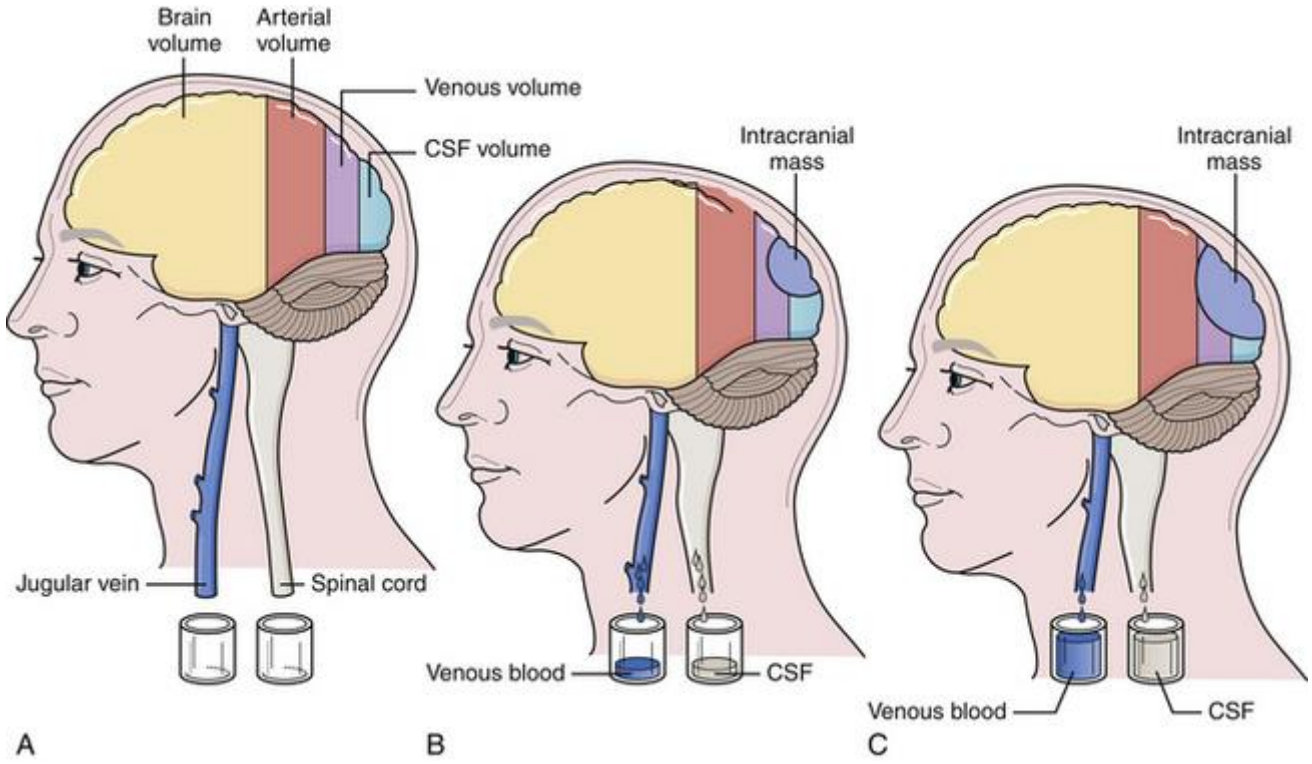
Interstitial

- Obstruction of CSF circulation
- Mechanical damage of CSF- brain barrier
- Infiltration of CSF into intersticial space



Compensation - (slow) increase of ICP

- Limitation: of cerebrospinal fluid volume (CSF) and venous reserve



https://clinicalgate.com/intracranial-hypertension/

Compensation/de-compensation - (fast) increase of ICP

CPP = MAP - ICP

Cerebral perfusion pressure

Mean arterial pressure

Intracranial pressure

↑ ICP → **↓ CPP** → **↓ CBF** → **↑ MAP**

Compensation/de-compensation - (fast) increase of ICP

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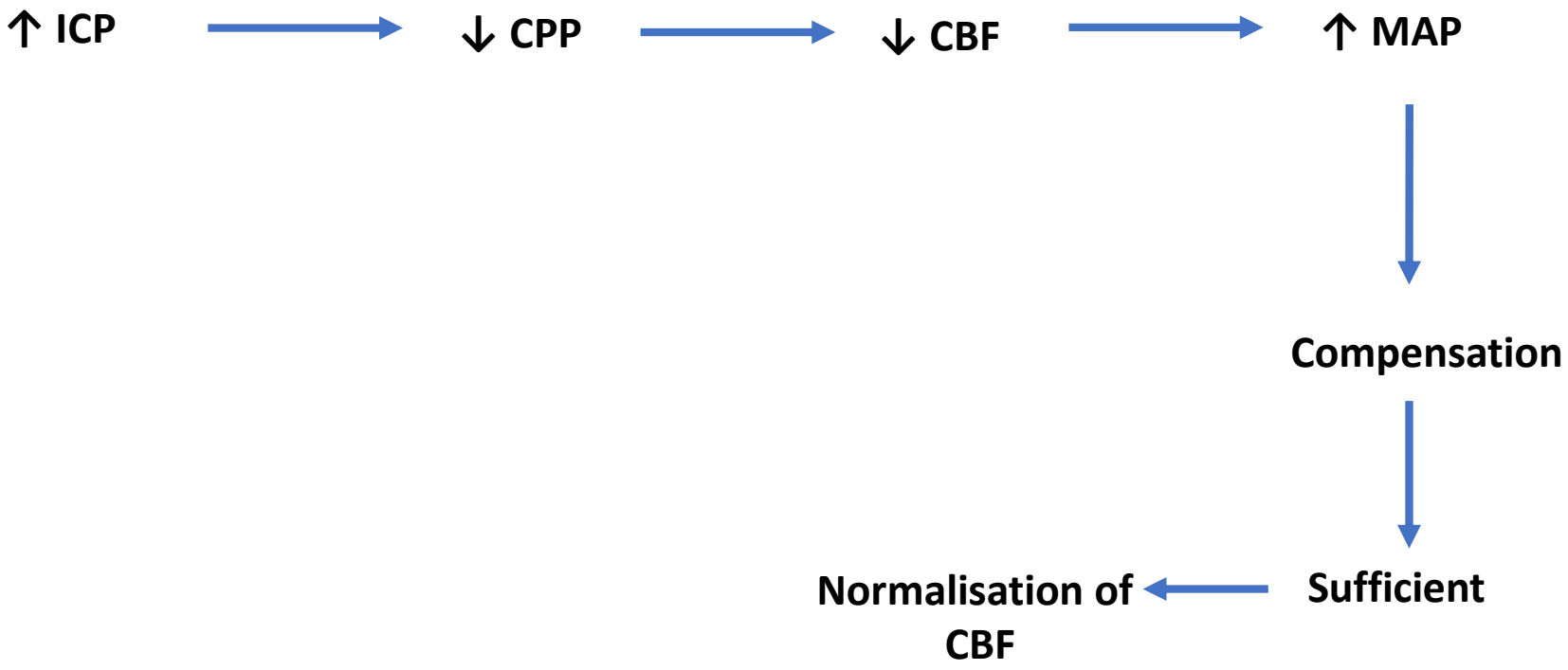
- CPP: Cerebral perfusion pressure
- MAP: Mean arterial pressure
- ICP: Intracranial pressure



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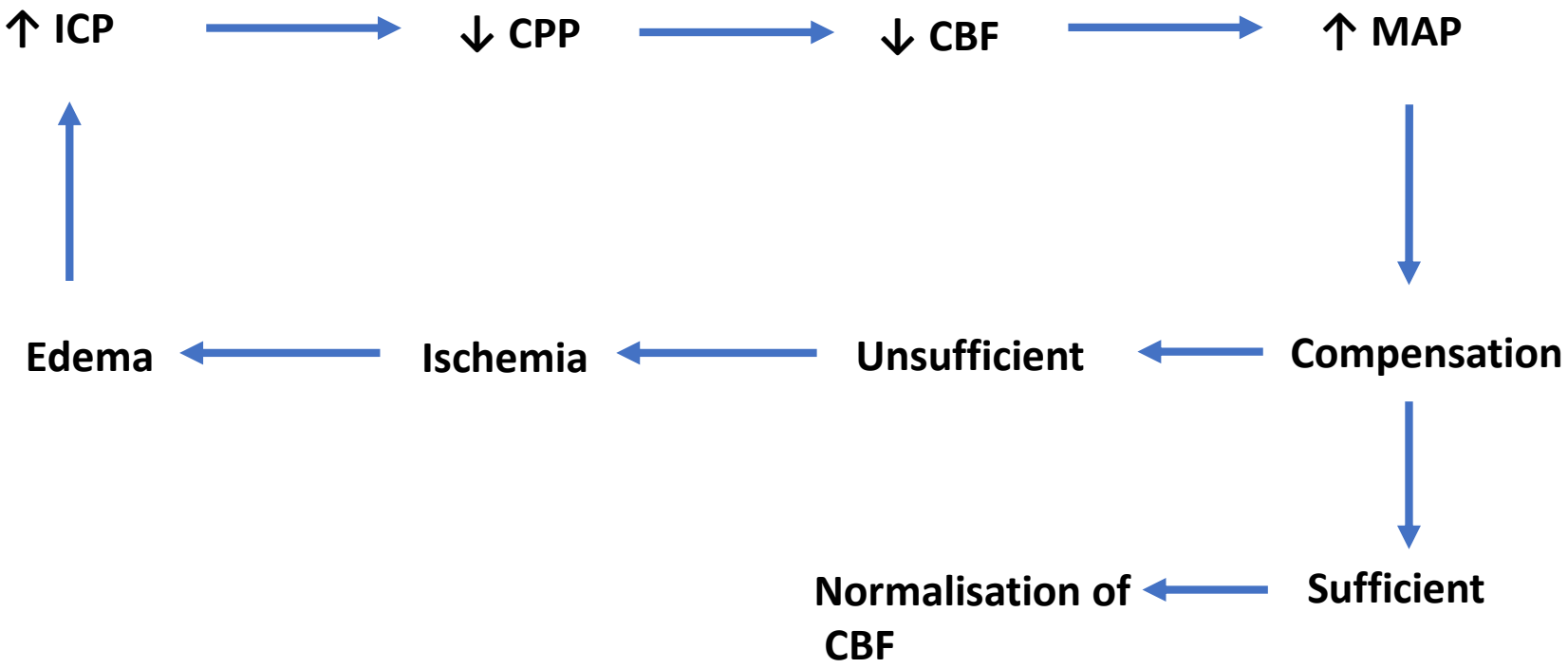
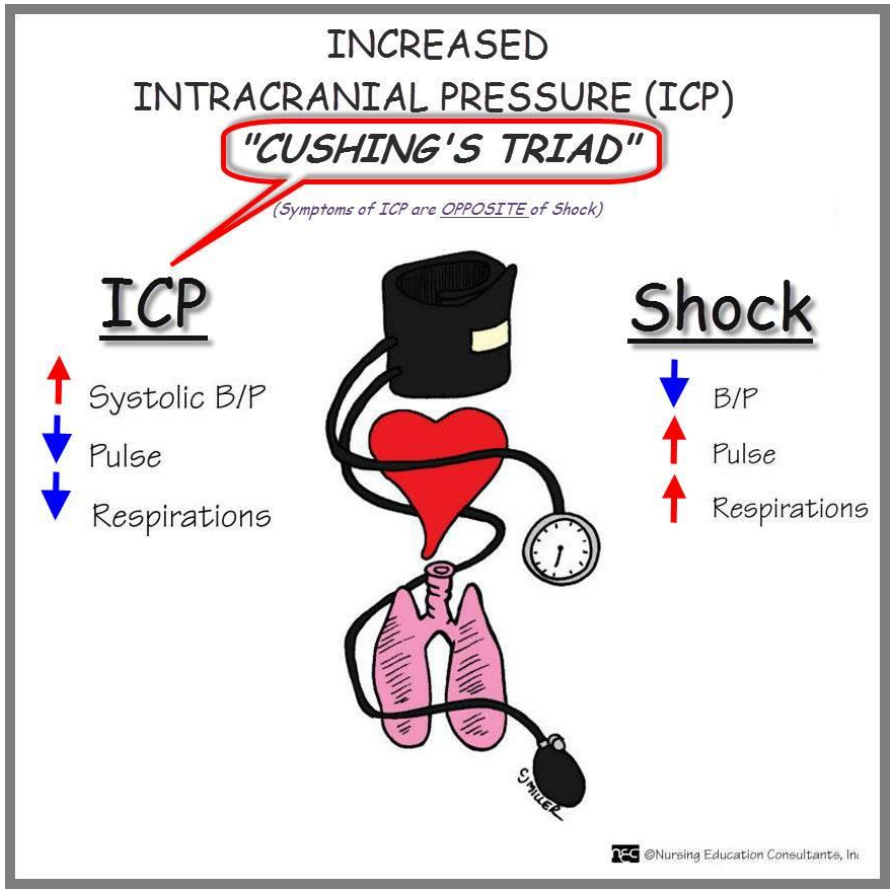


Cushing´s triad



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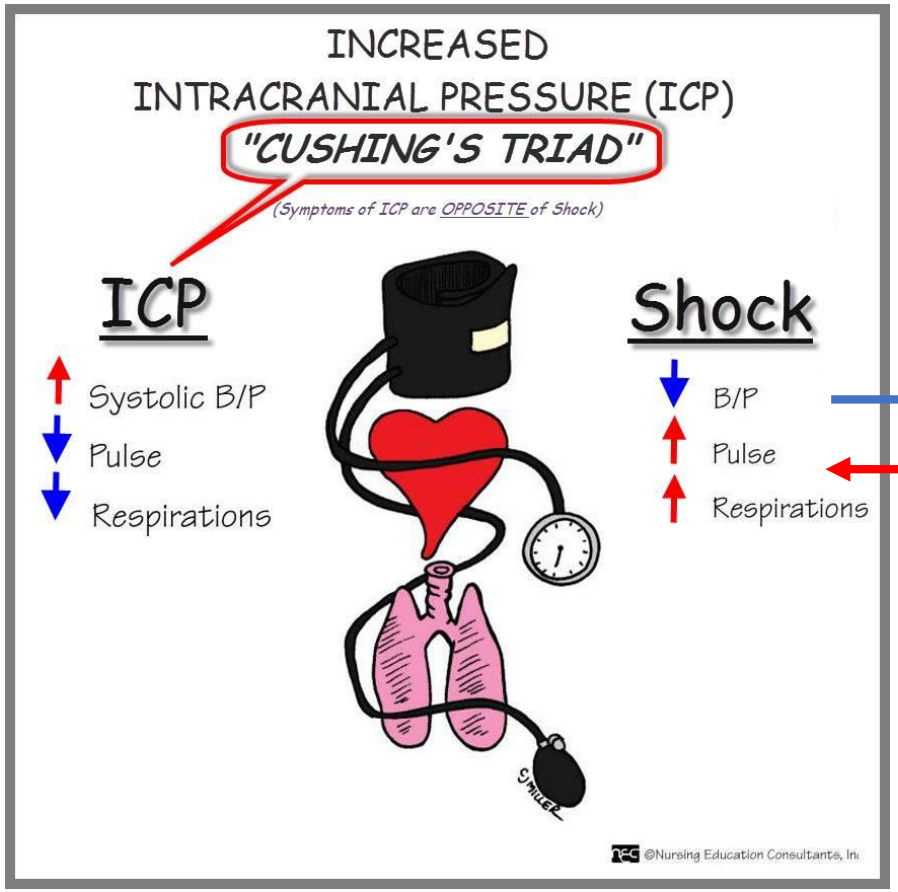

Sympathetic activation

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Cushingova triáda

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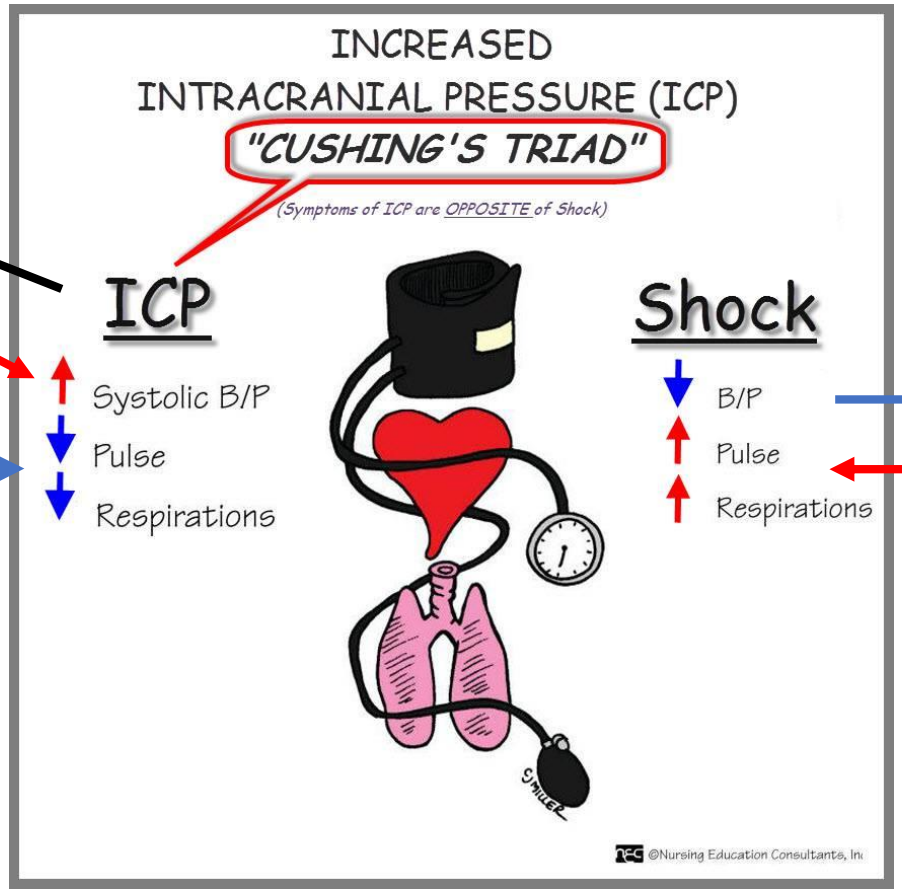


Sympathetic activation

Unclear mechanism

Probably rebound co-activation of parasympathetic system (simultaneous increase of sympathetic tone and parasympathetic tone)

Perhaps also pressure on the brain stem

https://it.pinterest.com/pin/395753885990152490/

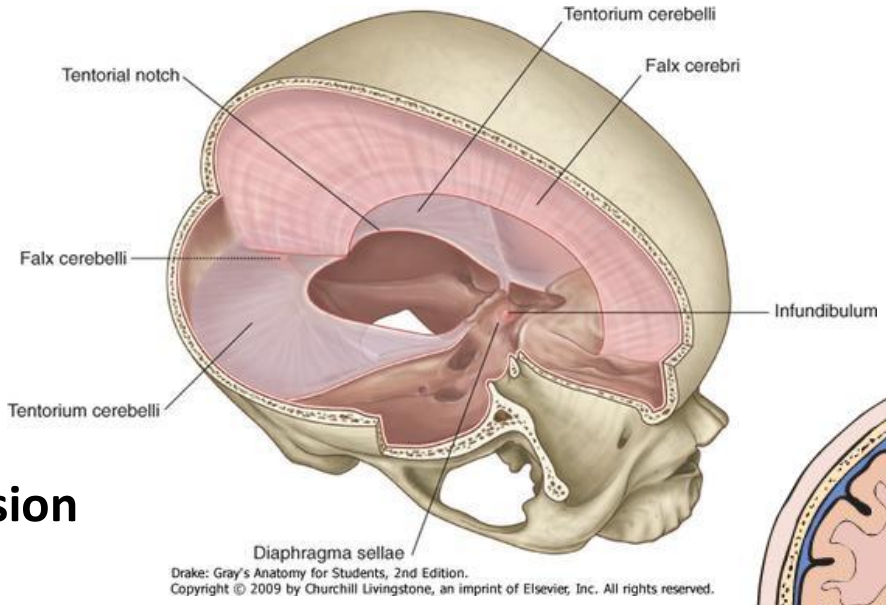
Consequences of Intracranial Hypertension

Compression

of adjacent tissue

Infratentorial lesions

- Allvays acute
- **Risk of brain**
- **stem compression**



http://edutoolanatomy.wikispaces.com

Cerebral herniation

- Subfalcine
- Transtentorial
- Tonsillar
- Central

✓ Permanent damage of brain

✓ Risk of brain stem compression

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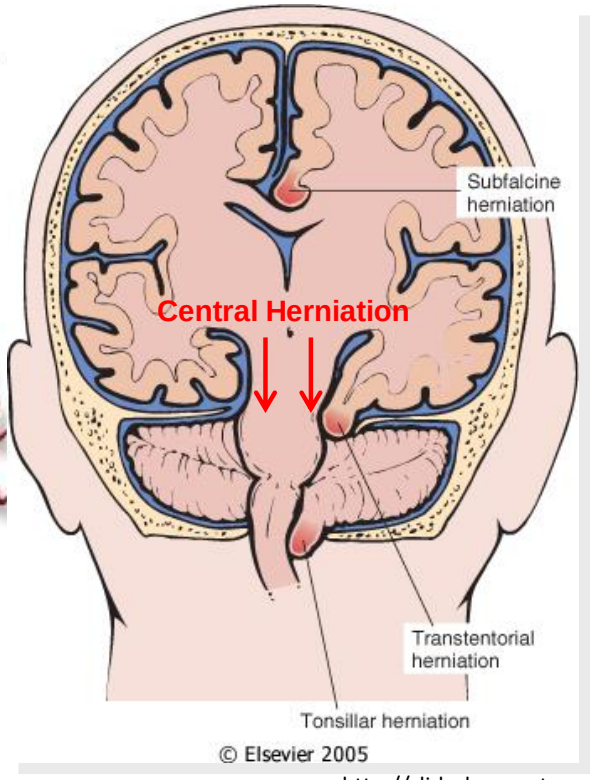

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Intracranial hypertension

Epilepsy

Pain

Epilepsy

- One of the most common neurological diseases
- About 50 million people suffer from epilepsy worldwide
- Approx. 80% of patients live in developing countries (birth trauma, infection)

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- Epileptic seizure
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    - ✓ Consciousness
    - ✓ Perception
    - ✓ Behavior
    - ✓ Motor functions
    - ✓ Sensitivity
  - The basis is excessive and synchronous neuronal activity

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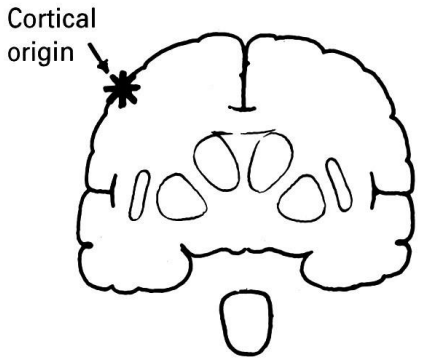
✓ Parcial
✓ Generalized
✓ Non-classifiable

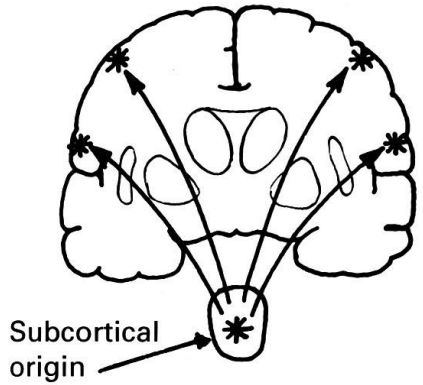
Epilepsy - Classification

- Focal seizures – *account for 80% of adult epilepsies*
- Simple partial seizures
- Complex partial seizures
- Partial seizures secondarilly generalised



- Generalised seizures

- Unclassified seizures



Seizure terms

- Ictal= seizure
- Post-ictal= confusion following seizure
- Aura= abnormal sensation preceding loc
- Automatisms= nonsensical involuntary movements
- Tonic= tonic contraction producing extension and arching
- Clonic= alternating muscle contraction-relaxation
- Complex= consciousness impaired
- Simple= consciousness unimpaired
- Partial= focal region involved
- Generalized= whole brain
- Convulsions= shaking
- Grand mal and petite mal="street terms" for convulsive and non-convulsive seizure respectively

Causes of epilepsy

- Structural changes of the cortex
  - ✓ Focal pathology
  - ✓ Congenital (malformations of the cerebral cortex)
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- Autoimmune disorders
- Genetic etiology
  - Great importance is assumed, but the information is sketchy
- Unknown etiology

Partial epileptic seizures

- based on a part of the cerebral cortex from one hemisphere, motor manifestations are one-sided

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- Partial simplex
  - No presence of consciousness disorder

  ✓ With motor symptoms (muscle twitching)
  ✓ With somatosensitive / sensory manifestations (sensitivity / sensory disorders)
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- Partial to generalized
  - arise as partial and then spread throughout the brain

Generalized epileptic seizures

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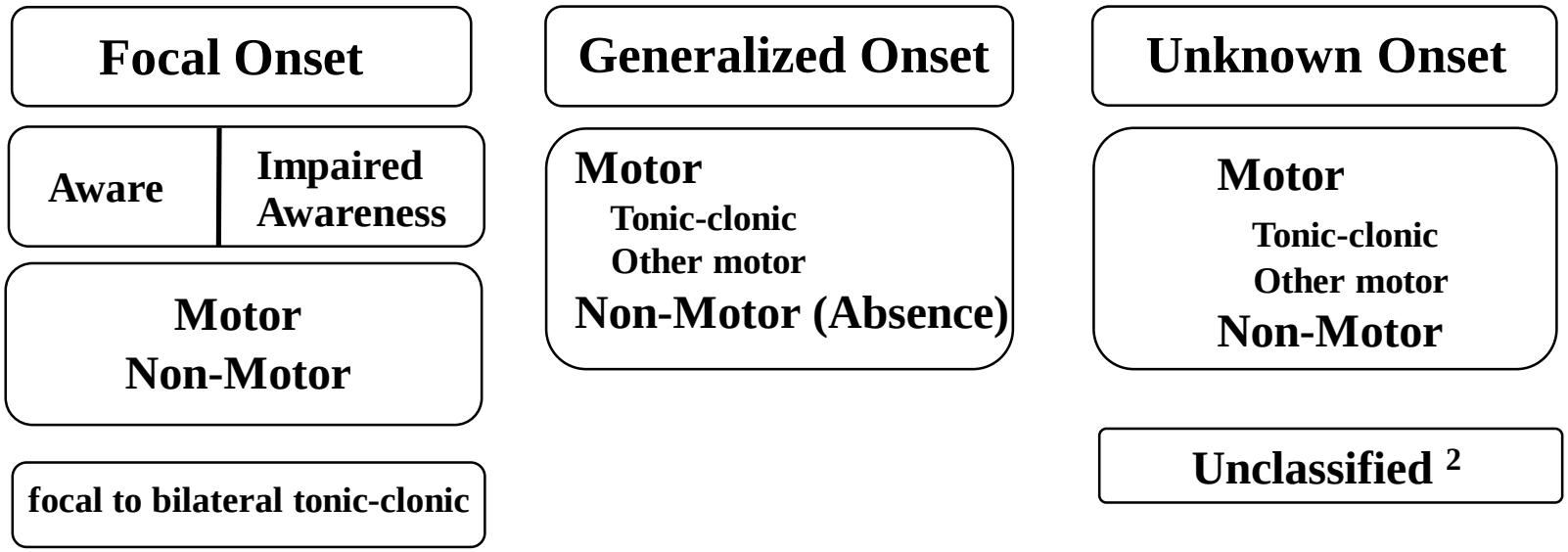
- ✓ **Atonic** (sudden drop in muscle tone leading to fall)

ILAE 2017 Classification of Seizure Types Basic Version [1]



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

[2] Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

ILAE 2017 Classification of Seizure Types Expanded Version[1]

Focal Onset

Aware	Impaired Awareness

Motor Onset
- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified[3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

2 These could be focal or generalized, with or without alteration of awareness

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Status epilepticus

- A protracted seizure
- Life-threatening condition

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- ✓ Grand mal - a seizure longer than 15 minutes
  (Grand mal usually resolve spontaneously over 5-10 minutes)
- ✓ Petit mal - hours to days
  (can be difficult to diagnose)

- Untreated status epilepticus leads to energy collapse, brain edema and death
- The possibility of failure of basic vital functions due to CNS disruption

Intracranial hypertension

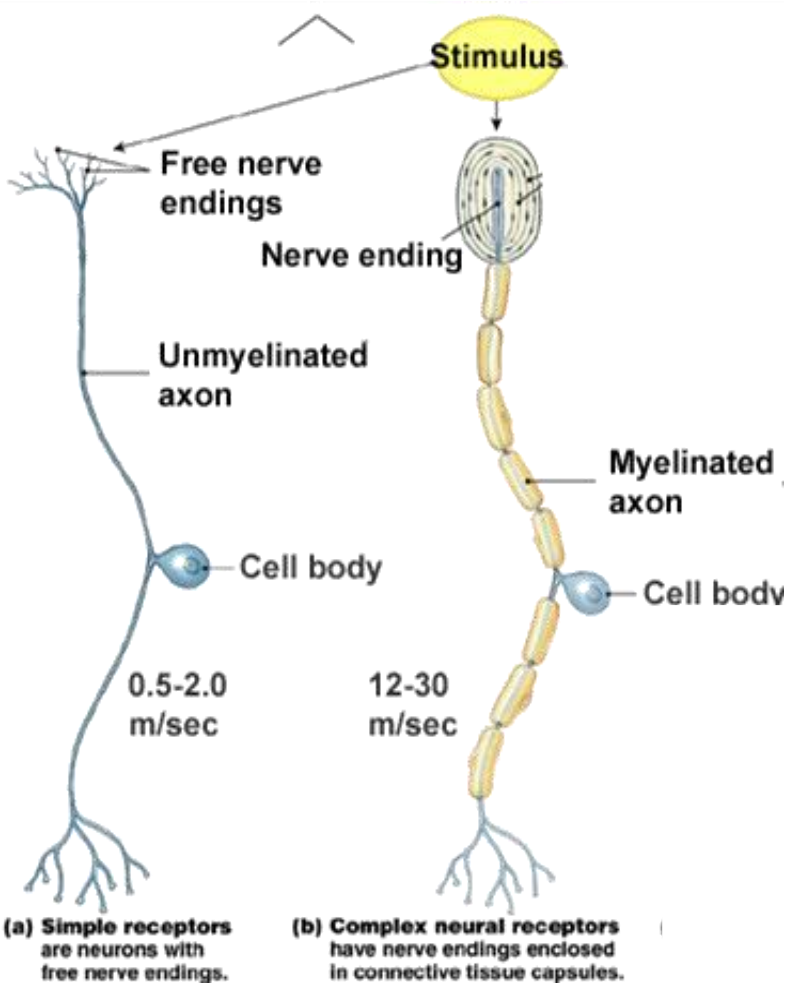
Epilepsy

Pain

Free nerve endings

- Unsialized nerve endings
- Polymodal
  - Nociception
  - Thermoreception
  - Mechanoreception

- A delta fibers
- C fibers



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Nociceptors

- Free nerve endings responding to very intense stimuli

- The nature of the stimulus
  - Mechnaical
    - Big pressure
    - Sharp object
  - Thermal
    - Upper limit approx. 45 dg. Celsius
    - Lower limit - variable
  - Chemical
    - pH
    - Inflammatory mediators, etc.

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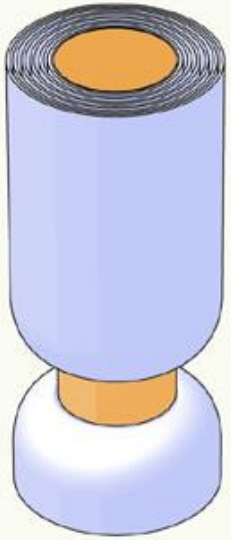
A delta fibers
– sharp, localized pain

C fibers
– dull, poorly localized pain

Nerve fibers

Axons from skin	Aα	Aβ	Aδ	C
Axons from muscles	Group I	II	III	IV
				
Diameter (μm)	13–20	6–12	1–5	0.2–1.5
Speed (m/sec)	80–120	35–75	5–30	0.5–2
Sensory receptors	Proprioceptors of skeletal muscle	Mechanoreceptors of skin	Pain, temperature	Temperature, pain, itch

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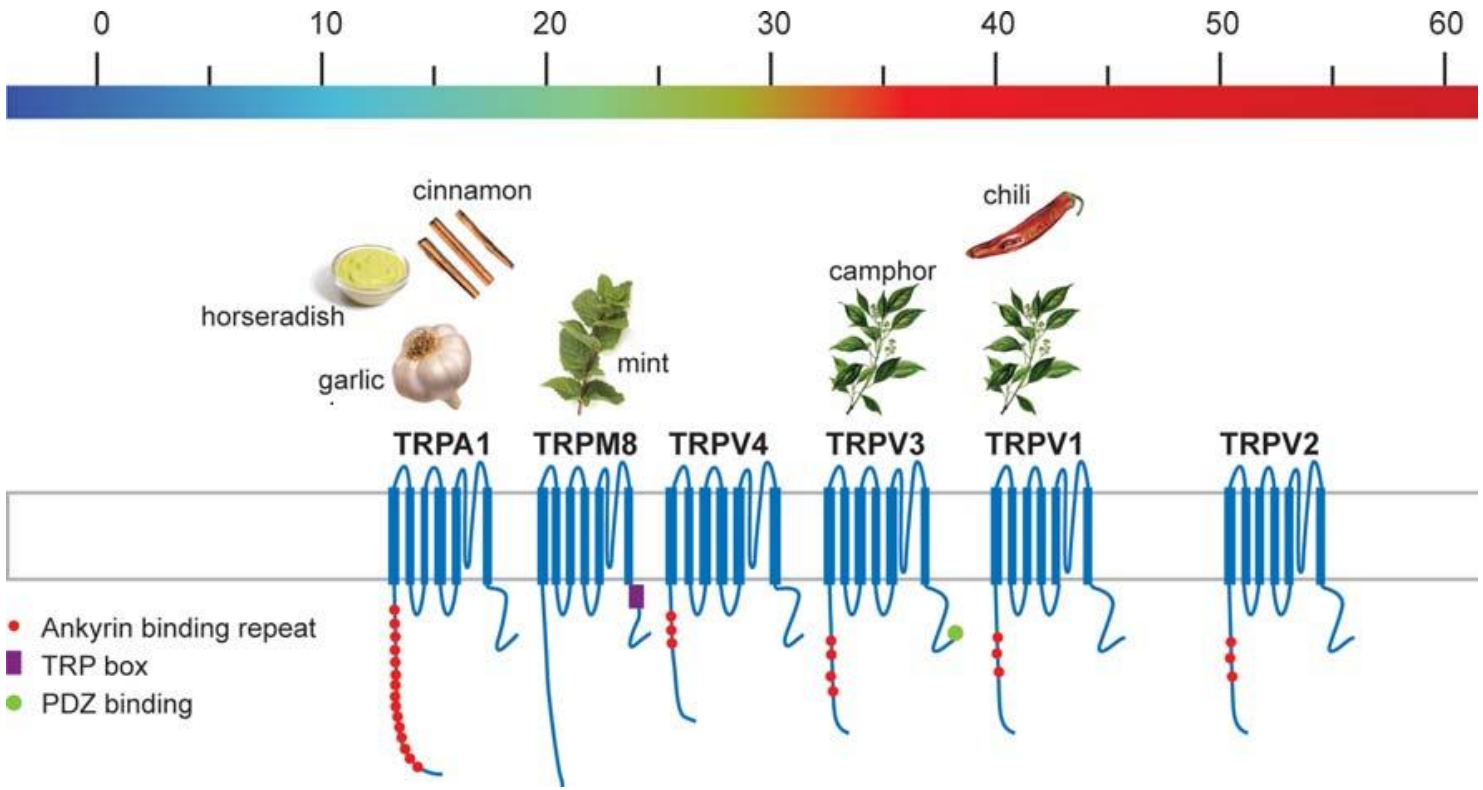
Reception component

- algoreceptors, nociceptors are free nerve endings (specialized chemoreceptors)
- localization: skin, tendon shrouds, ligaments, muscles, hollow organs
- receptors do not adapt, density fluctuates: fingertips> dentin> back skin> not in parenchyma of liver, spleen, lung, brain, cartilage
- the force of irritation translates into the pulse frequency in the periphery
- nociceptive fibers may be irritated throughout their course

Termoreceptors

- Free nerve endings sensitive to heat
- TRP channels (transient receptor potential)
- Each TRP channel subtype is sensitive to a particular temperature and chemical substance



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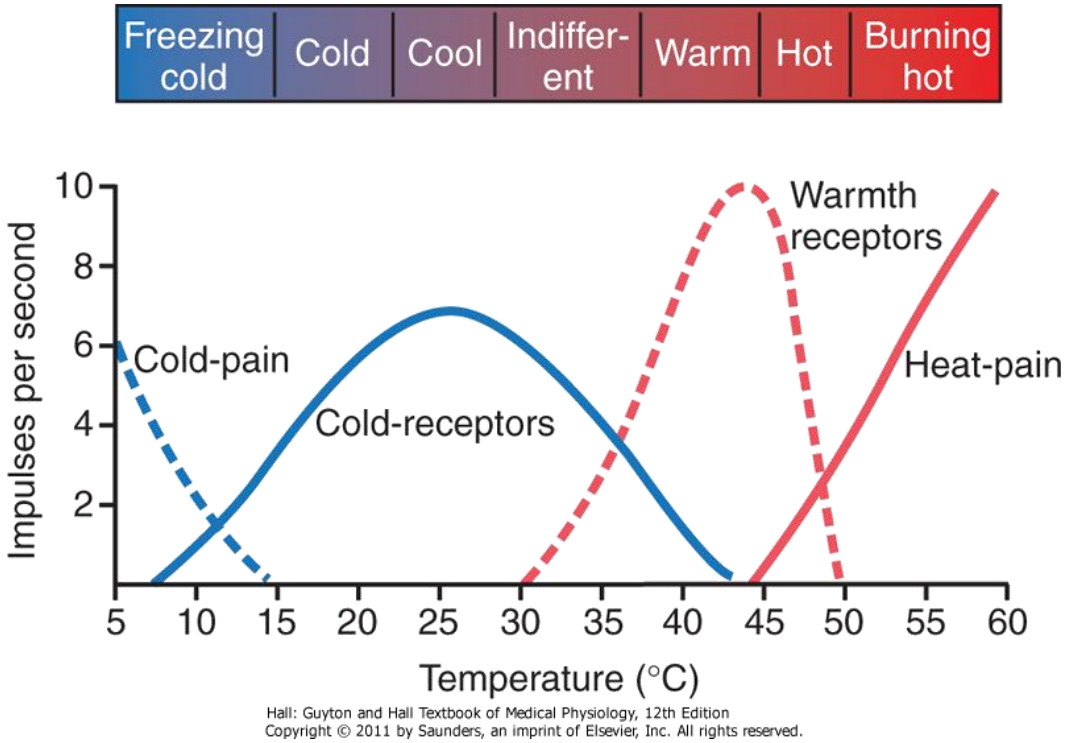
Termoreceptors

- Temperature perception is determined by the activity ratio of different thermoreceptors



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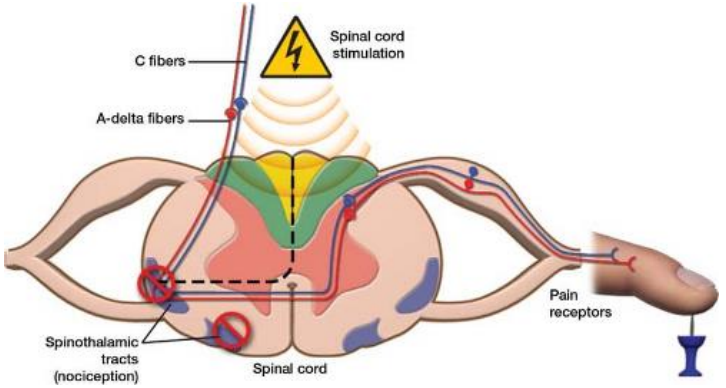
Conduction of painful sensations

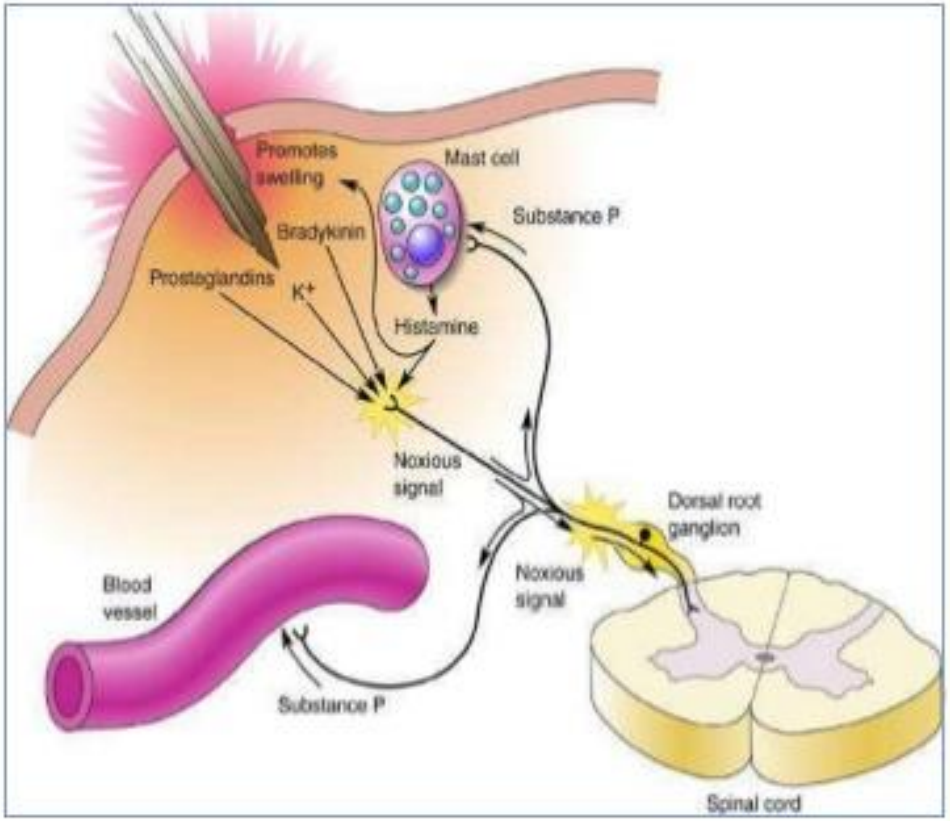
- 2 types of fibers - form half of all back spinal cord fibers

1. **strong myelinated fibers, type Aδ -** superficial pain, respond to strong mechanical stimuli
2. **thin non-myelinated fibers of type C -** deep pain, polymodal: mechanically, chemically, by heat, by cold, by anoxia



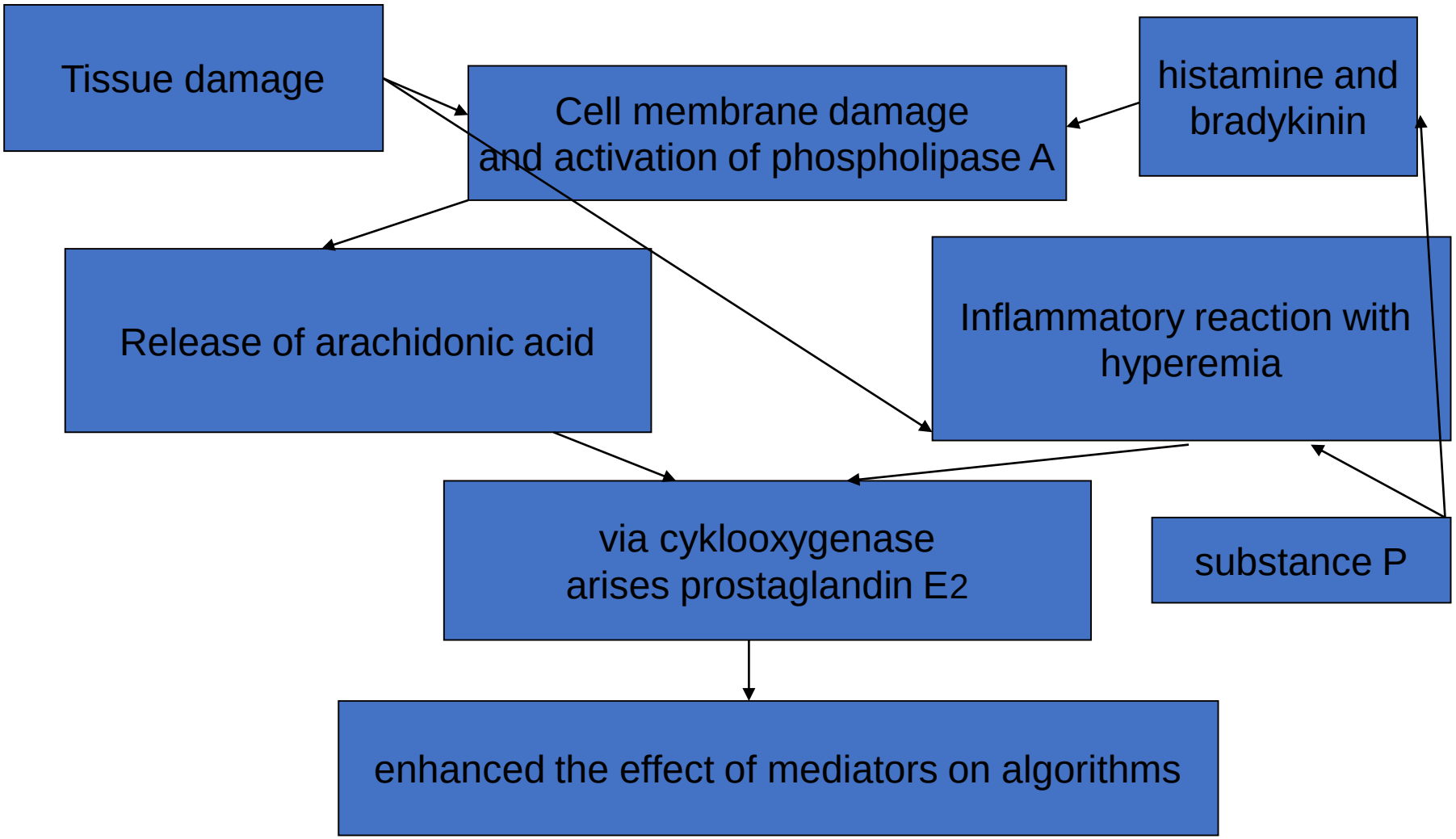
- bradykinin
- potassium release from damaged cells
- Histamine
- Serotonin
- drop of pH in the tissue
- calcitonin gene related peptide, vasointestinal peptide, ATP

- **Transduction:** Translation of a (chemical) pain stimulus into electrical activity on nerve level.

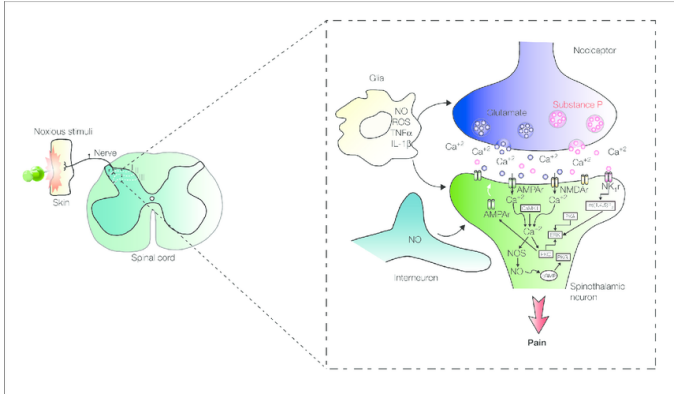


https://www.slideshare.net/muhammadakhan754365/pain-anatomy-and-physiology

Mechanism of algoreceptors activation



First neuron fibers

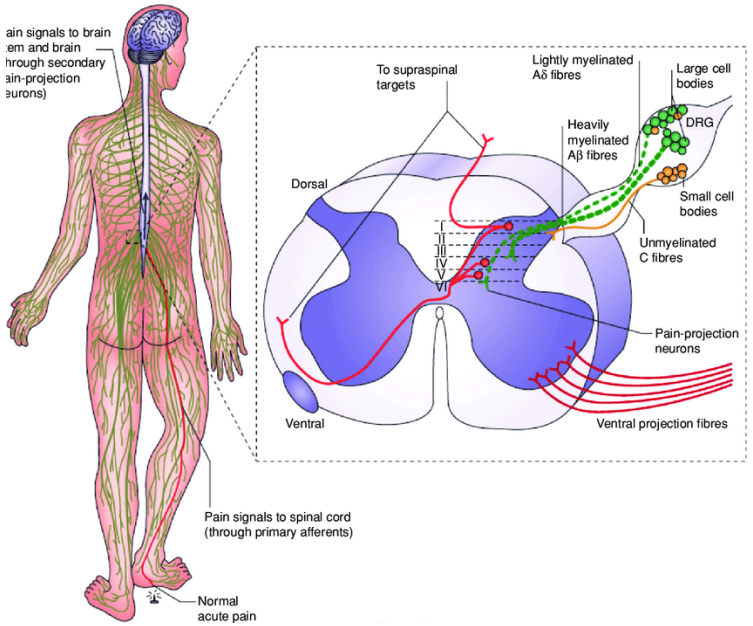


- switched in the posterior spinal horn in ncl. proprius
  the synapse mediator is substance P
- substance P is the second peripheral nociceptive sensitizer
- substantia gelatinosa Rolandi - an inhibitory region in the posterior spinal horns

  → mediator - enkephalin

- back horn area is damped from CNS

  → tractus reticulospinalis



https://www.researchgate.net/figure/Nociception-Normal-pain-signalling-in-the-body-is-transmitted-to-the-spinal-cord-dorsal_fig1_316130682

Conduction of painful sensations

Aδ fibers – from the skin, well localized pain, so-called primary pain

→ **tractus spinothalamicus** - 3 neuronal phylogenetically newer pathway

C fibers – poorly localized, secondary pain from deeper parts of the skin and deeper lokalised organs

→ **tractus spinoretikulothalamicus** – an older polysynaptic system, impulses are transmitted to higher centers through short axon pathways

vegetative response: change in pressure, tachypnea, mydriasis, sweating, increased muscle tone,…

Somatosensory pathways

- Three systems

- (Archispinothalamic)
  - Interconnection of adjacent segments (tr. Spinospinalis)

- Paleospinothalamic
  - tr. Spinoreticularis, tr. Spinotectalis…

- Neospinothalamic
  - tr. Spinothalamicus

- Dorsal column system
  - tr. Spinobulbaris

Somatosensory pathways

- Three systems
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  - Interconnectic
- Paleospinot
  - tr. Spinoret
- Neospinothala
  - tr. Spinothala
- Dorsal column sy
  - tr. Spinobulbaris

EVOLUTION….

Evolutionary old structures have not been replaced by new ones during evolution, but the old has been kept and the new added

Somatosensory pathways

- Paleospinothalamic
  - Low resolution – dull, diffuse pain („slow pain“)
- Neospinothalamic
  - High resolution – sharp, localized pain („fast pain“), temperature
  - Low resolution – touch
- Dorsal column system
  - High resolution – touch, proprioception

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Immediate survival

Long-term survival

Somatosenzory pathways

Table I
The Sensory Modalities Represented by the Somatosensory Systems

Modality	Sub Modality	Sub-Sub Modality	Somatosensory Pathway (Body)	Somatosensory Pathway (Face)
Pain	sharp cutting pain		Neospinothalamic	Spinal Trigeminal
	dull burning pain		Paleospinothalamic	
	deep aching pain		Archispinothalamic	
Temperature	warm/hot		Paleospinothalamic	
	cool/cold		Neospinothalamic	
Touch	itch/tickle & crude touch		Paleospinothalamic	
	discriminative touch	touch	Medial Lemniscal	Main Sensory Trigeminal
		pressure		
		flutter		
		vibration		
Proprioception	Position: Static Forces	muscle length		
		muscle tension		
		joint pressure		
	Movement: Dynamic Forces	muscle length		
		muscle tension		
		joint pressure		
		joint angle		

http://neuroscience.uth.tmc.edu/s2/chapter02.html

Paleospinothalamic system

- Tr. Spinoreticularis, spinotectalis…

Paleospinothalamic system

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- Evolved before neocortex

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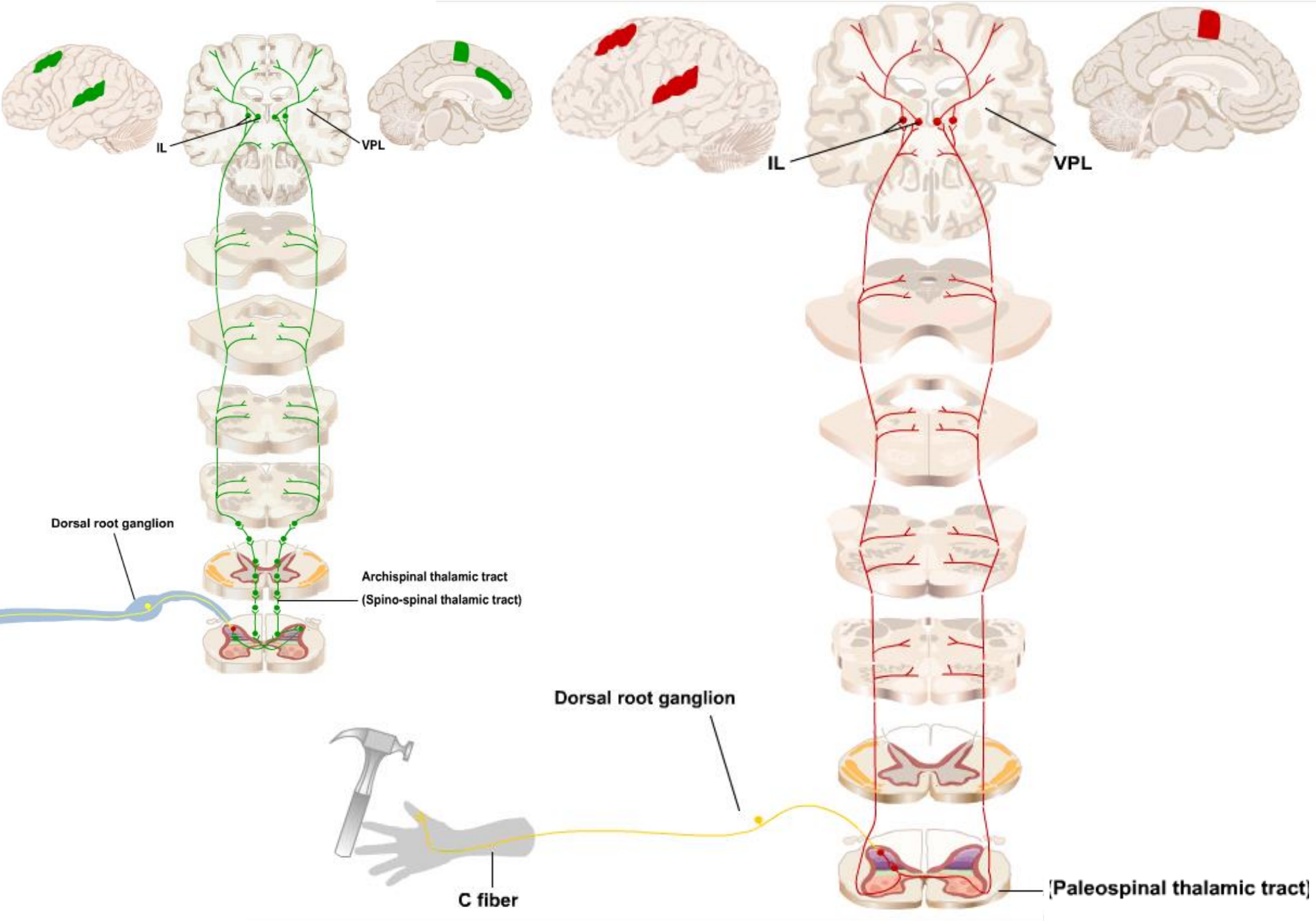
- This tract is not designed for „such a powerful processor as neocortex“
- Approximately half of the fibers cross the midline


IL
VPL
Dorsal root ganglion
Archispinal thalamic tract
(Spino-spinal thalamic tract)
IL
VPL
Dorsal root ganglion
C fiber
Paleospinal thalamic tract

Neospinothalamic system

- Tr. Spinothalamicus

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- Younger structure primarily connected to neocortex
- „High capacity/resolution“

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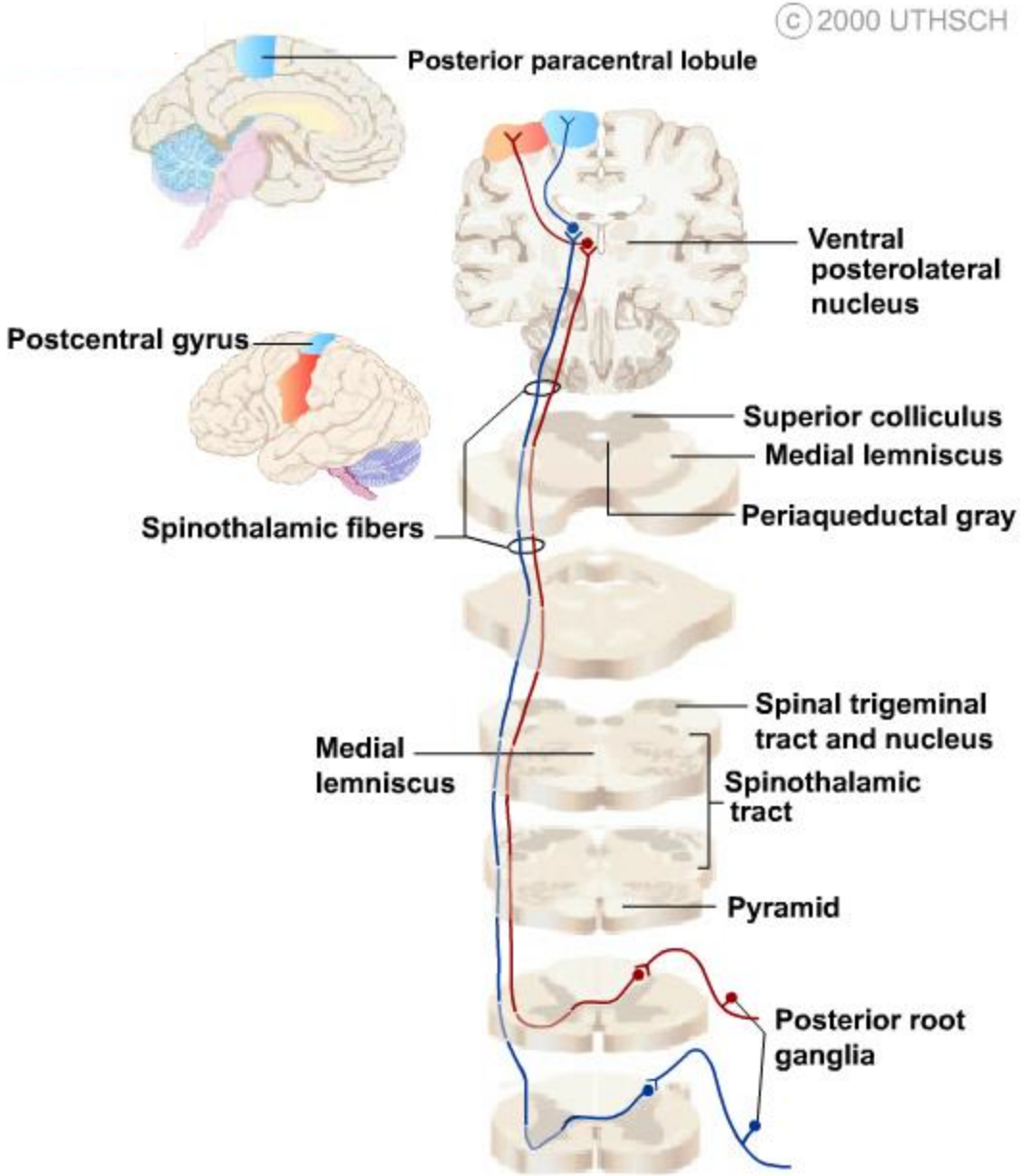
- The fibers cross midline at the level of entry segment



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Dorsal column system

- Tr. Spinobulbaris

Dorsal column system

- Tr. Spinobulbaris
- The youngest system
- High capacity

Dorsal column system

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- Vibration
- Proprioception

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- Better object recognition
- Adaptive value

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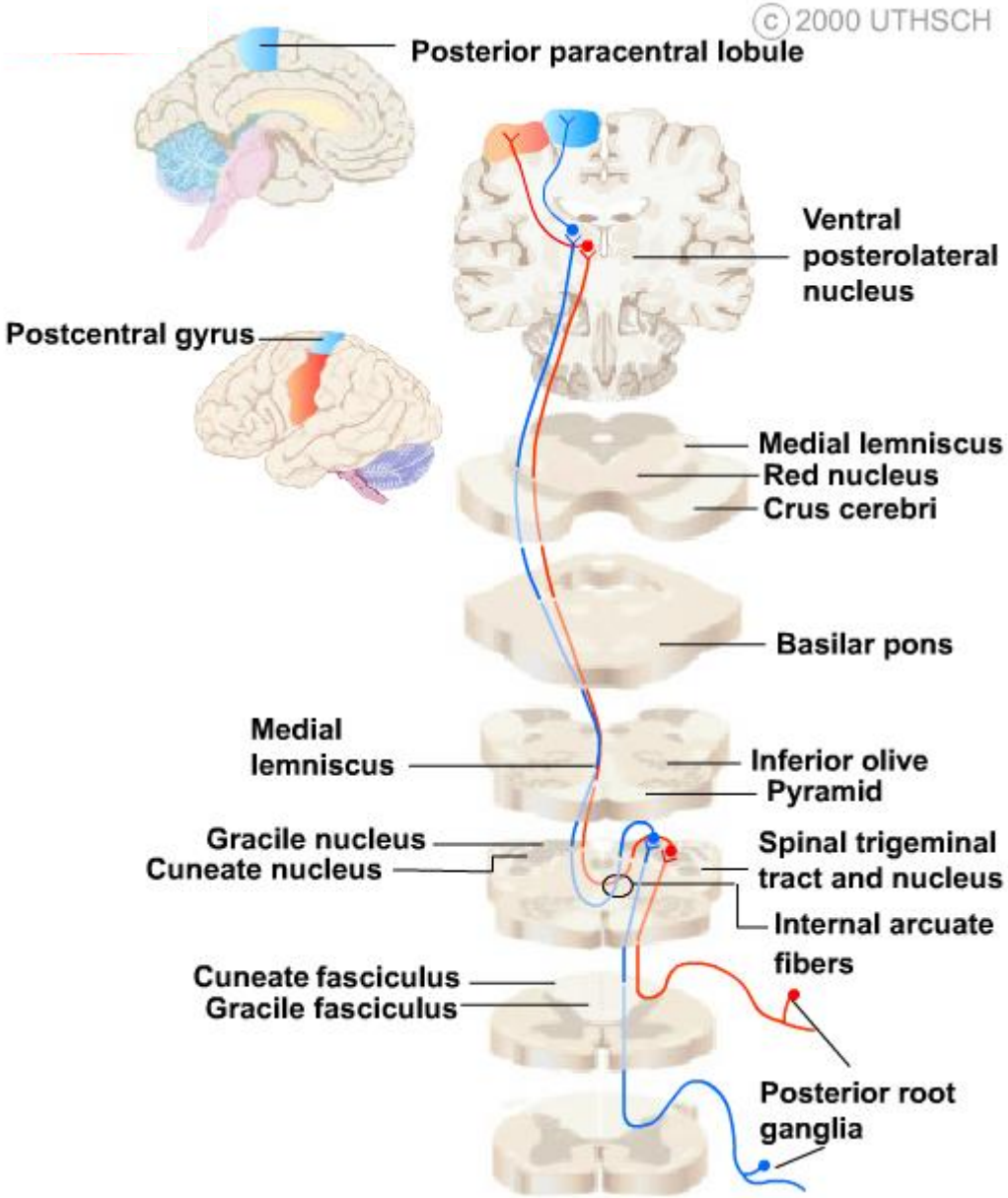
- Tr. Spinobulbaris
- The youngest system
- High capacity
- Tactile sensation
- Vibration
- Proprioception
- Fine motor control
- Better object recognition
- Adaptive value
- The fibers cross midline at the level of medulla oblongata



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Gate theory

CHARACTERISTICS	A DELTA FIBRES	C-FIBRES
MYLENATION	MYELINATED LARGE DIAMETER	NON-MYLENATED SMALL DIAMETER
CONDUCTION SPEED	FAST(70-120 m/sec)	SLOW(0.2-2 m/sec)
ONSET	FIRST FAST PAIN	SECOND SLOW PAIN
DURATION	BRIEF	LONG
RECEPTIVE FIELD	SMALL	LARGE
LOCALIZATION	PRECISE	DIFFUSE
SENSORY QUALITY	SHARP,PRICKING	ACHING,DULL, BURNING
CNS RESPONSE	RELFEX,ANALYSIS	EMOTIONAL, SUFFERING

- **Melzack and Wall 1965**
- Stimulation of A fibers – closes
- Stimulation of C fibers – opens

- substantia gelatinosa Rolandi neurons with inhibitory function modulate the input of pulses from A and C fibers into T effector neurons

- T cells are actively inhibited by substantia gelatinosa neurons at rest
- the resulting impression is determined by the ratio of nociceptive, modulating and feedback mechanisms

Gate theory

- **mechanisms**:

  1. substantia gelatinosa Rolandi
  2. descendent inhibitory system

- **descendent inhibitory system** :

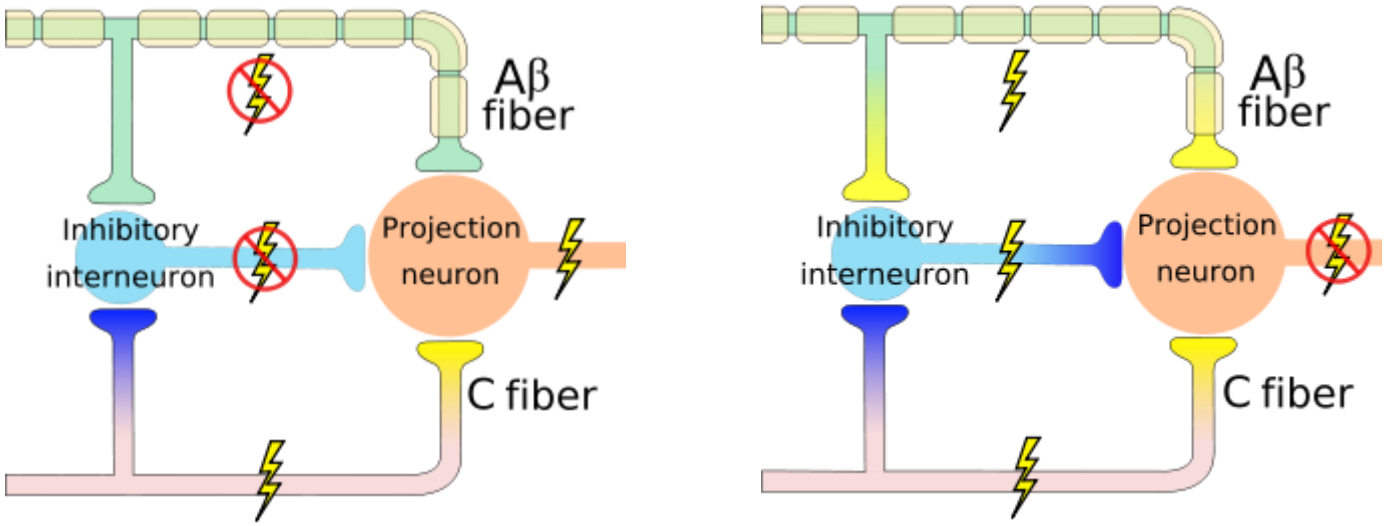
a/ **opioid system**: comes from the cortex, thalamus, limbic-hypothalamic structures periakveductal gray and reticular formation

b/ **adrenergic system**: from locus coeruleus

c/ **serotoninergic system**: comes from the nuclei of the brain stem (nucleus raphae magnus, nucleus reticularis gigantocelularis)

Pain modulation on the spinal level

Gate control theory of pain



https://en.wikipedia.org/wiki/Gate_control_theory

Algogenní efekt	Analgetický efekt
substance P, neurokiny, neurotenzin, neuropeptid Y	endorfiny, enkefaliny, dynorfiny
noradrenalin	noradrenalin
serotonin	serotonin
GABA	GABA
serin, glycin, glutamát	somatostatin
N-metyl-D-aspartát, NO	kalcitonin
prostaglandiny	a další

Processing of painful information

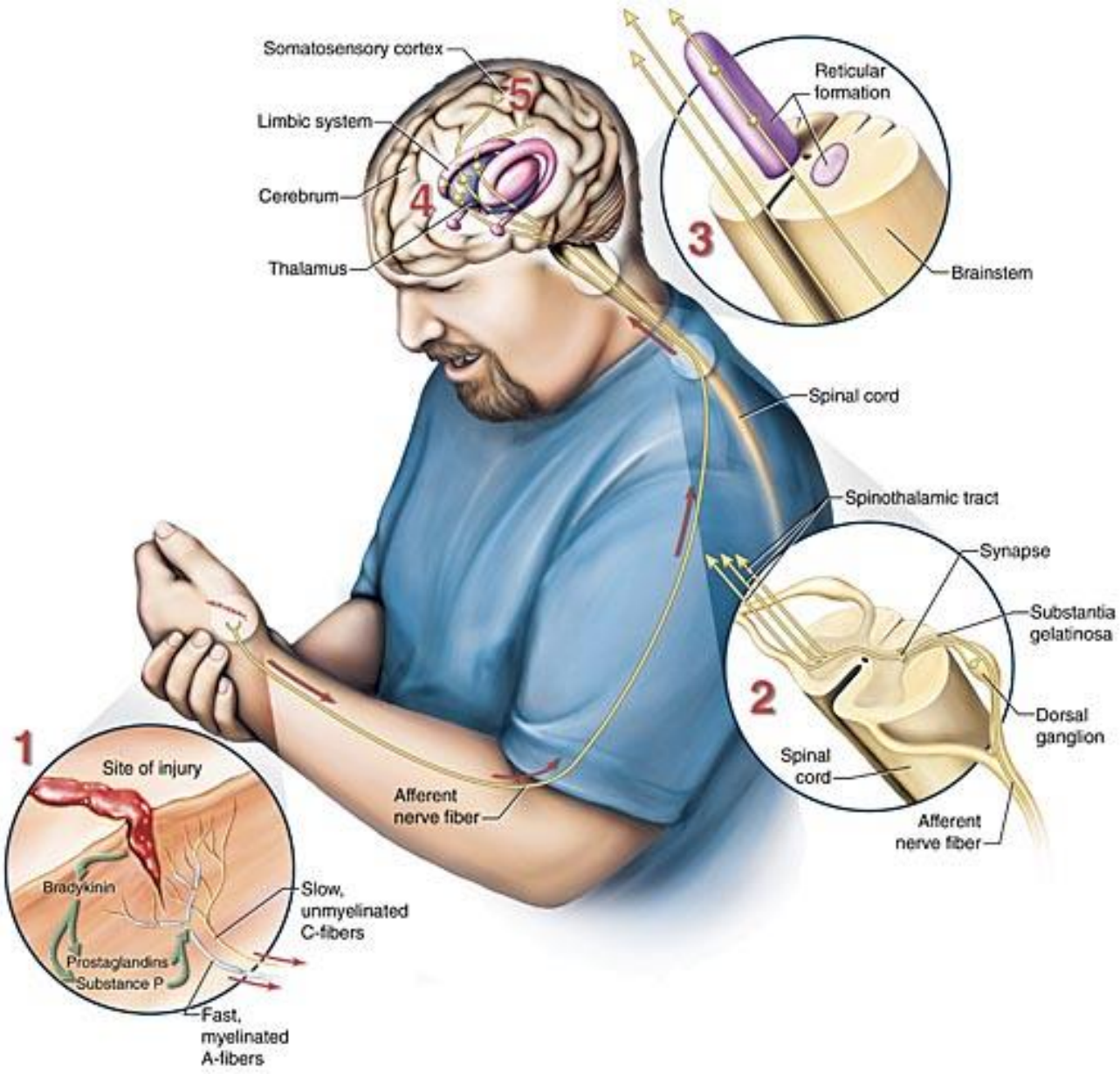
neocortex - cognitive processing

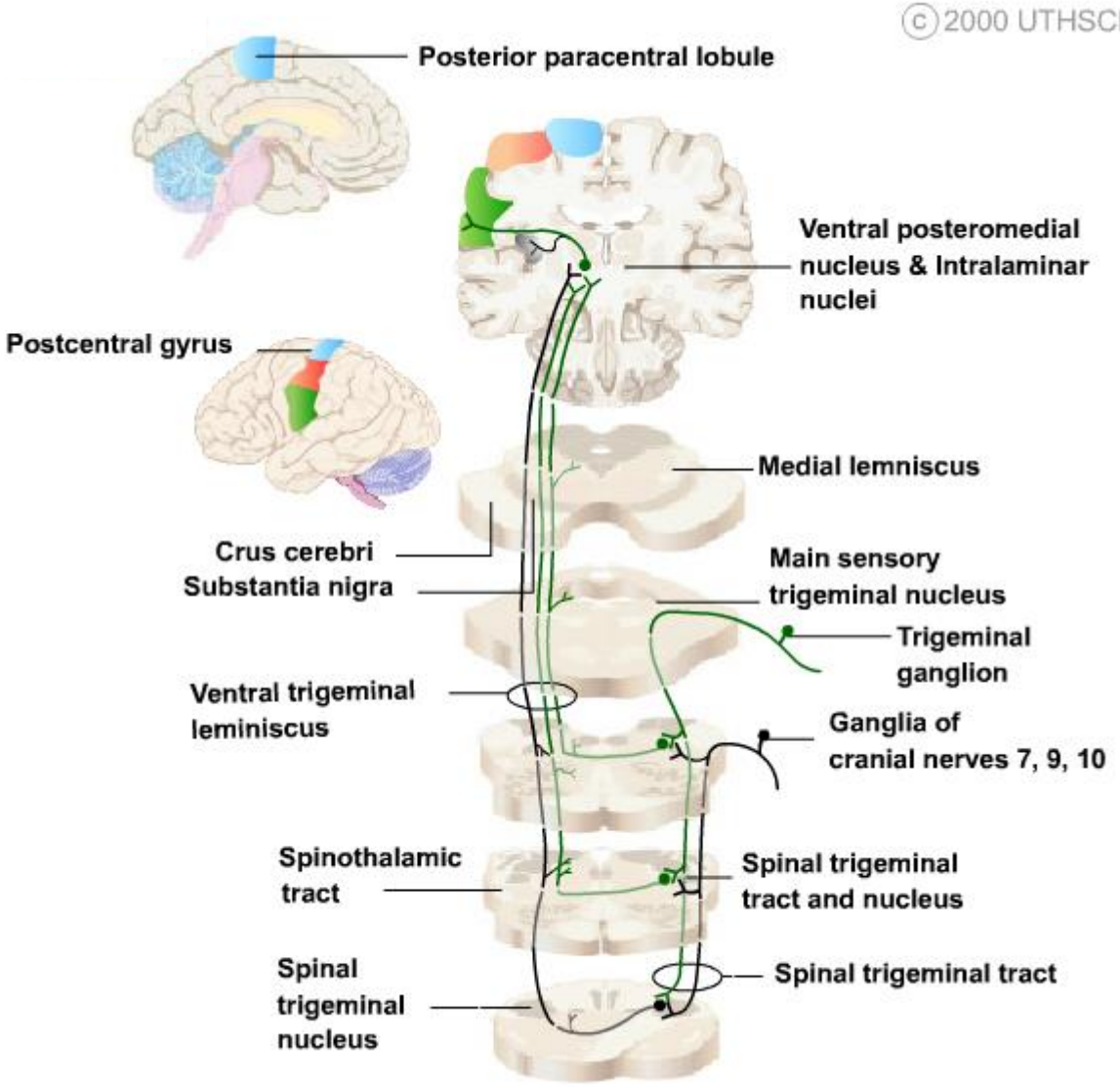
limbic system - affective processing

hypothalamus - release of hormones, endorphins

brain stem - control of breathing and circulation, reticular activation system

spinal cord - motor and sympathetic reflexes


Somatosensory cortex
5
Limbic system
Cerebrum
4
Thalamus
Reticular formation
3
Brainstem
Spinal cord
Spinothalamic tract
Synapse
Substantia gelatinosa
2
Dorsal ganglion
Spinal cord
Afferent nerve fiber
Afferent nerve fiber
1
Site of injury
Bradykinin
Prostaglandins
Substance P
Slow, unmyelinated C-fibers
Fast, myelinated A-fibers



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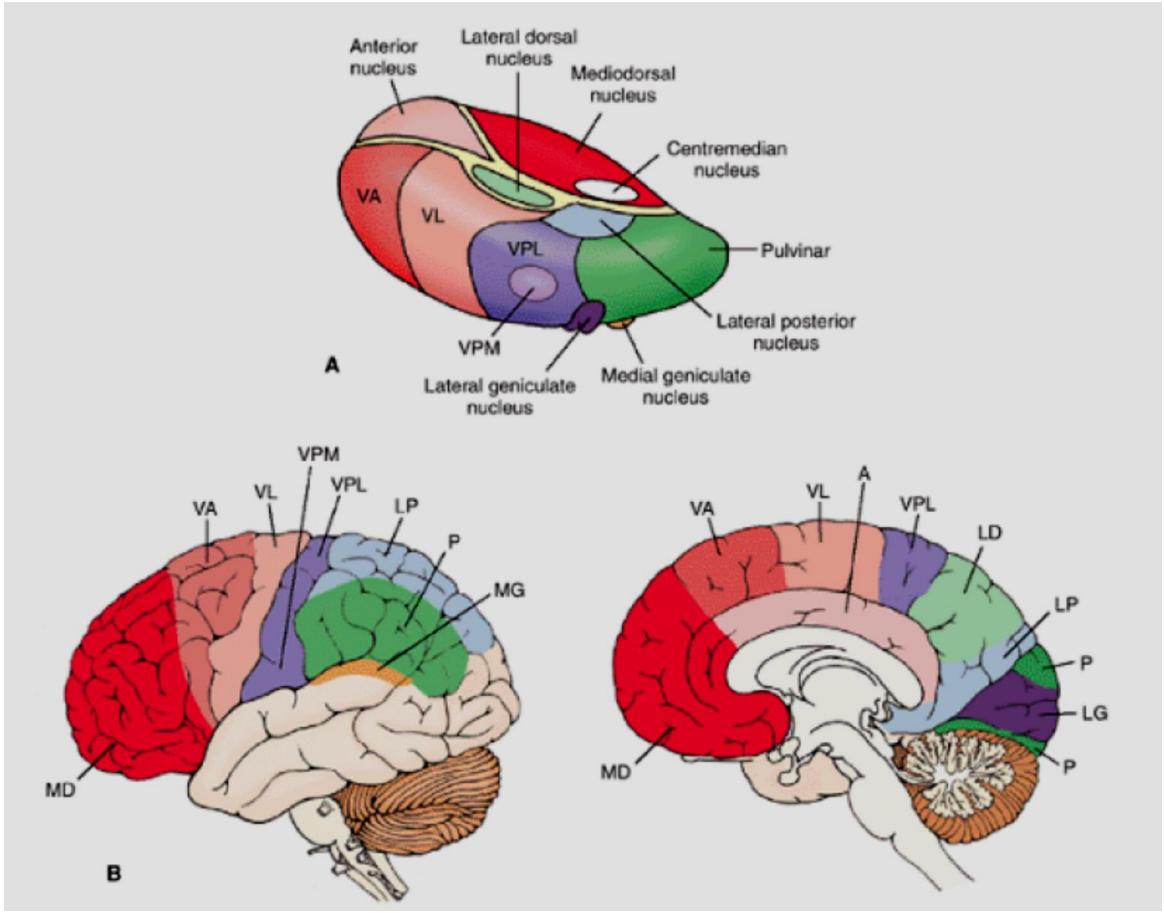
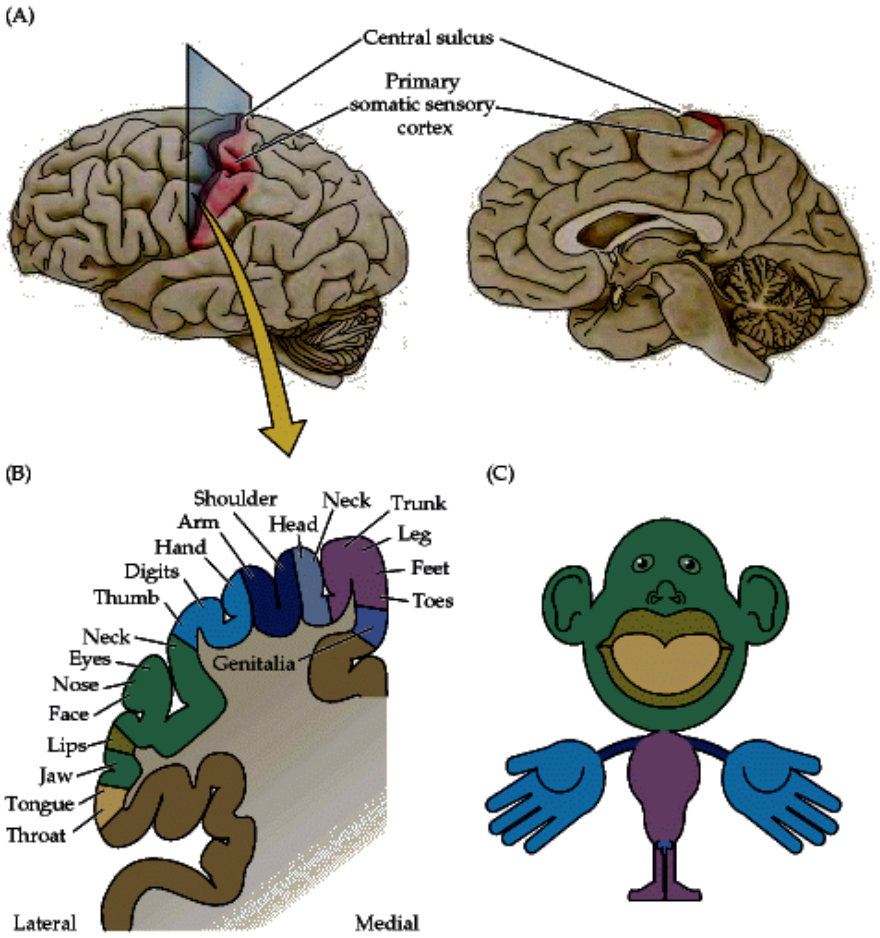
Thalamus a neocortex

- Almost all the afferent information gated in the thalamus
- Olfaction is an exception
- Bilateral connections between neocortex and thalamus



http://www.slideshare.net/drpsdeb/presentations

Neokortex



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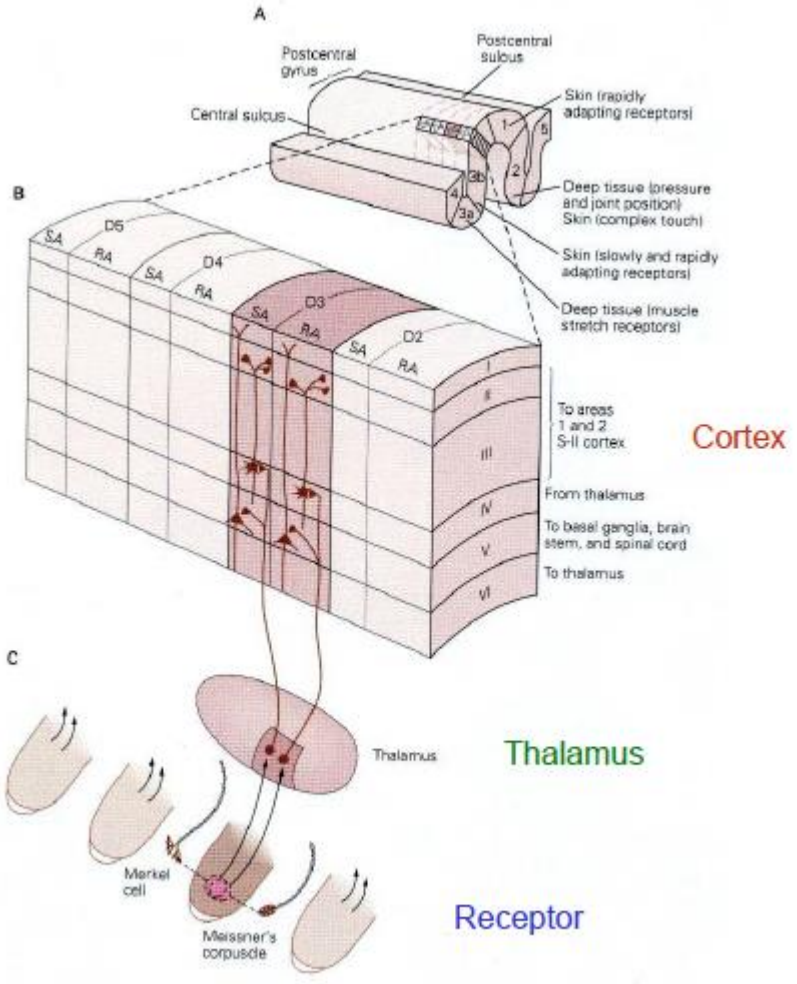
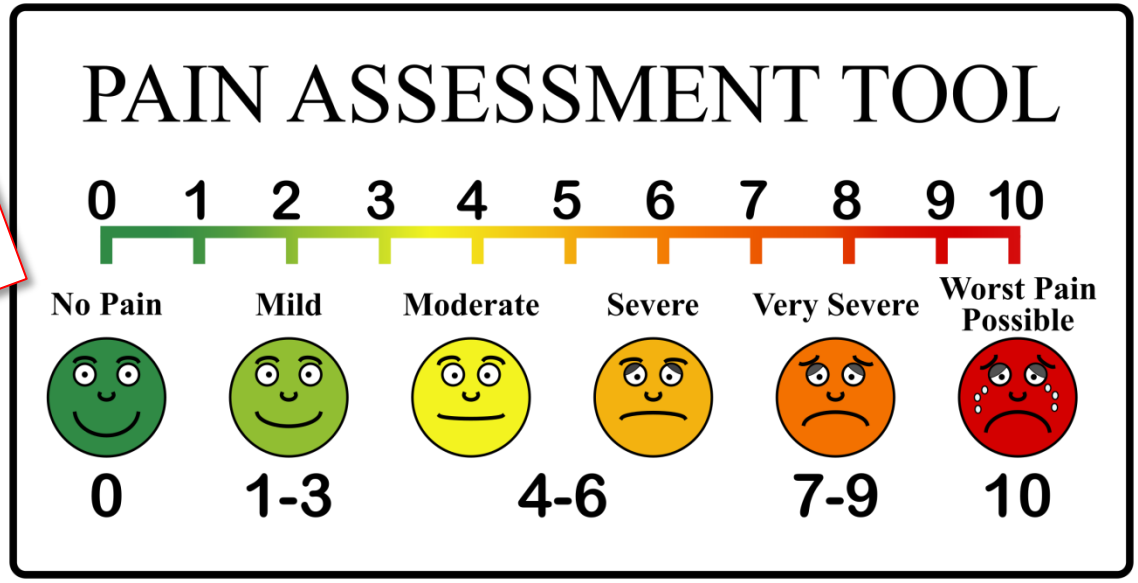


http://www.shadmehrlab.org/Courses/physfound_files/wang_5.pdf

Pain

- Distressing feeling associated with real or potential tissue damage
- Sensor x psychological component
- Physiological x pathological pain
- Acute (up to 6months) x chronic (more than 6 months)

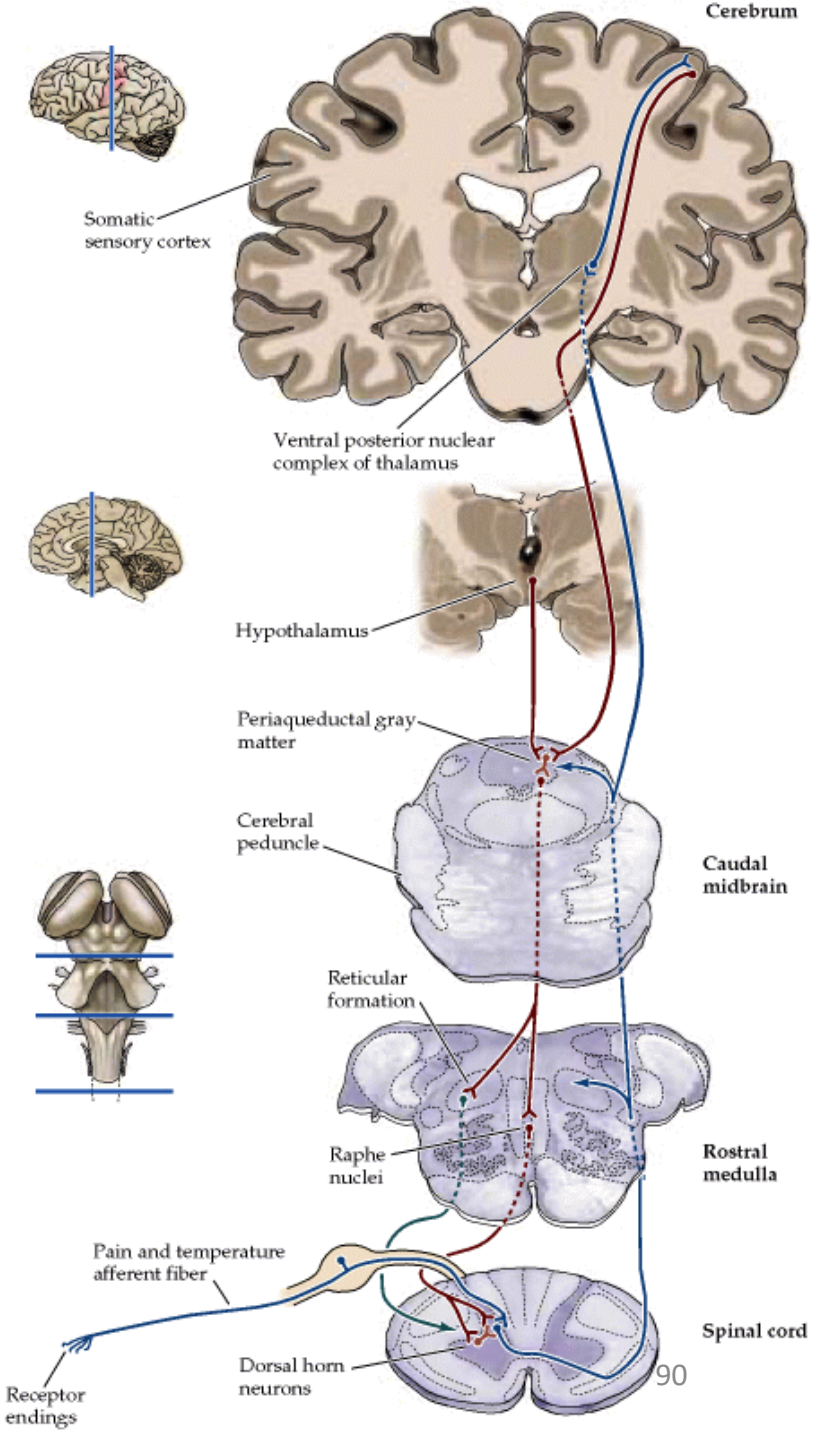
Subjective character



https://www.cheatography.com/uploads/davidpol_1460561912_Pain_Scale__Arvin61r58.png

Descendent pathways modulating pain

- Somatosemcoric cortex
- Hypotalamus
- Periaquaeductal gray
- Nuclei raphe



Bolest

Fyziologická

- Aktivace nociceptorů
- Informace o (potenciálním) nebezpečí/poškození

Patologická

- Není vázána na nociceptory
- Poškození struktur zapojenných do vedení nebo zpracování bolestivého podnětu
  - Nerv (neuropatie)
  - Plexus (plexopatie)
  - Kořen (radikulopatie)
  - Míšní dráha (myelopatie)
  - Mozek (např. thalamus)
- Mechanismus
  - Např. tlak, krvácení, metabolické postižení

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Akutní

- Do 6 měsíců
- Většinou odeznění po odstranění příčiny
- Vegetativní odpověď
  - Aktivace sympatiku
- Psychologická komponenta
  - Úzkost

Chronická

- Nad 6 měsíců
- Obtížně léčitelná
- Vegetativní odpověď chybí
- Psychologická komponenta
  - Deprese, podráždění

Visceral organ pain

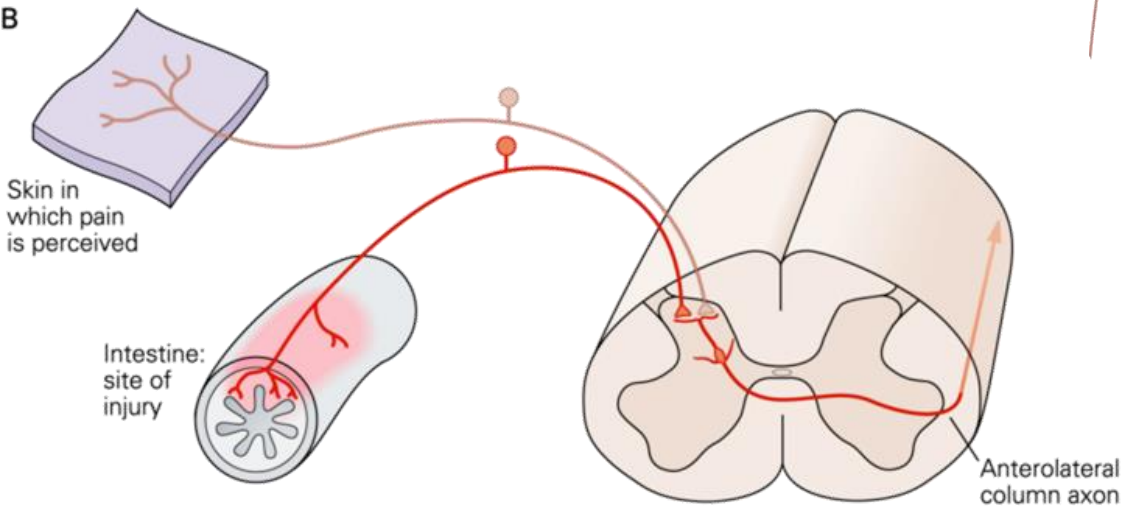
- it is transmitted to typical skin ranges →

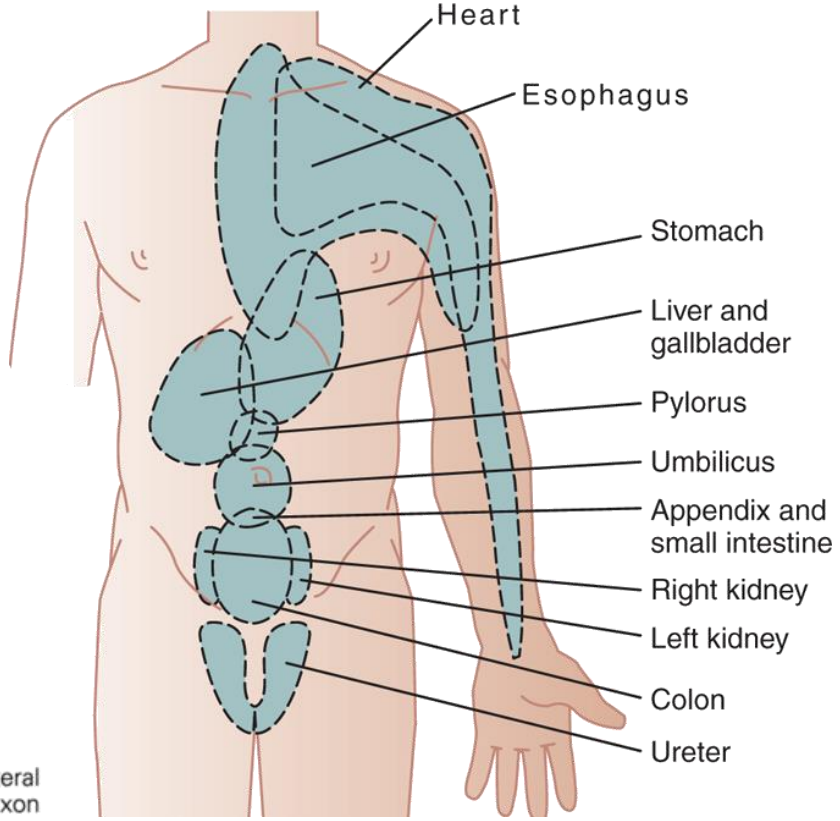
Head zones corresponding to the projection of the affected organ →

localy observed increased sensitivity to other modalities and enhancement of vegetative symptoms :

vasomotor, sudomotor, dermographism + increased muscle tone to defense musculaire

Referred pain





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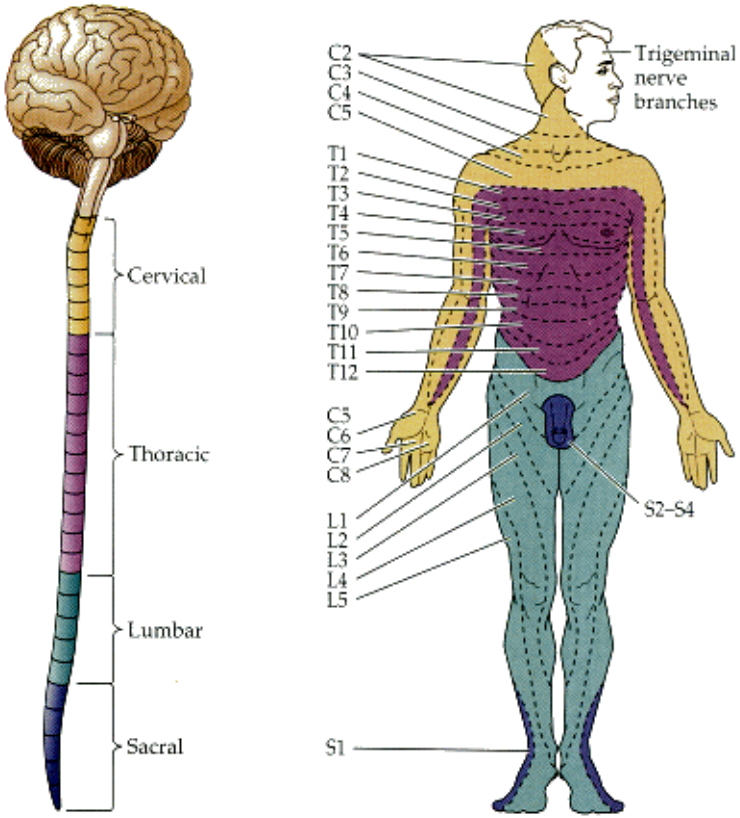
Dermatomy



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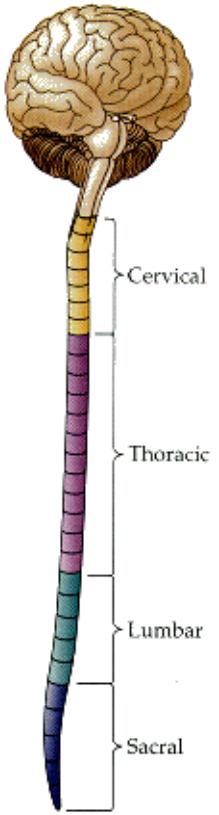

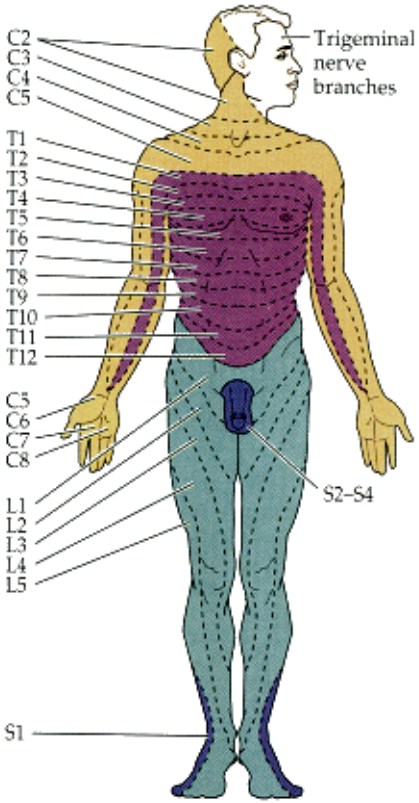

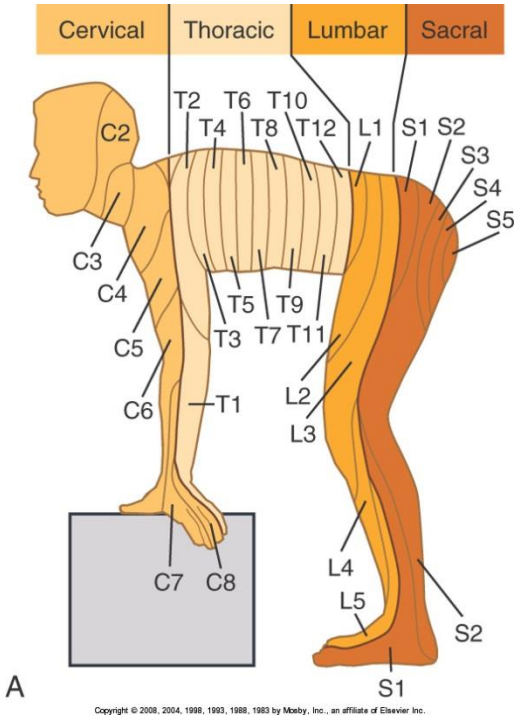

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http://www.slideshare.net/CsillaEgri/presentations

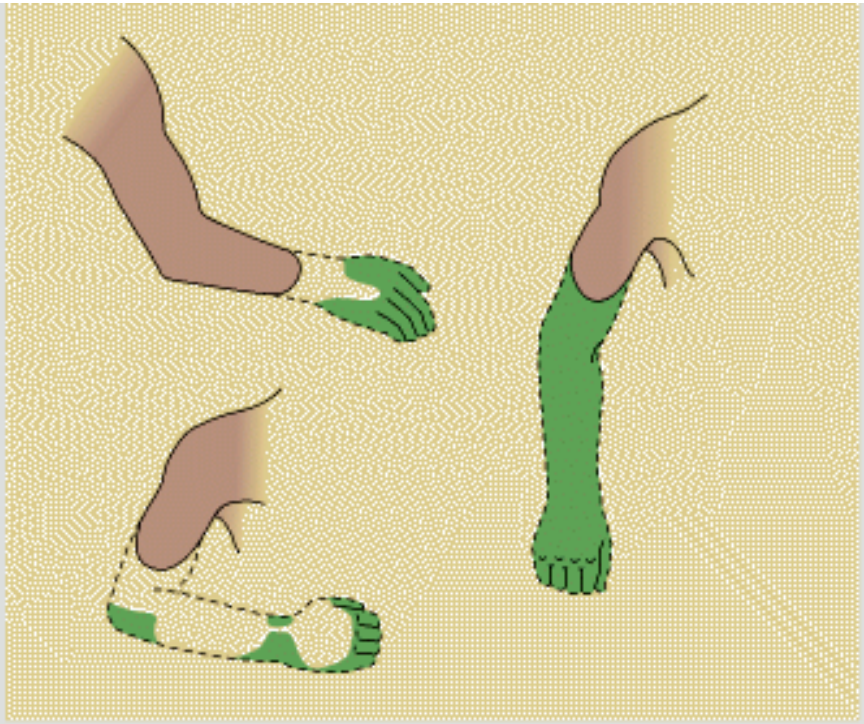
Special types of pain

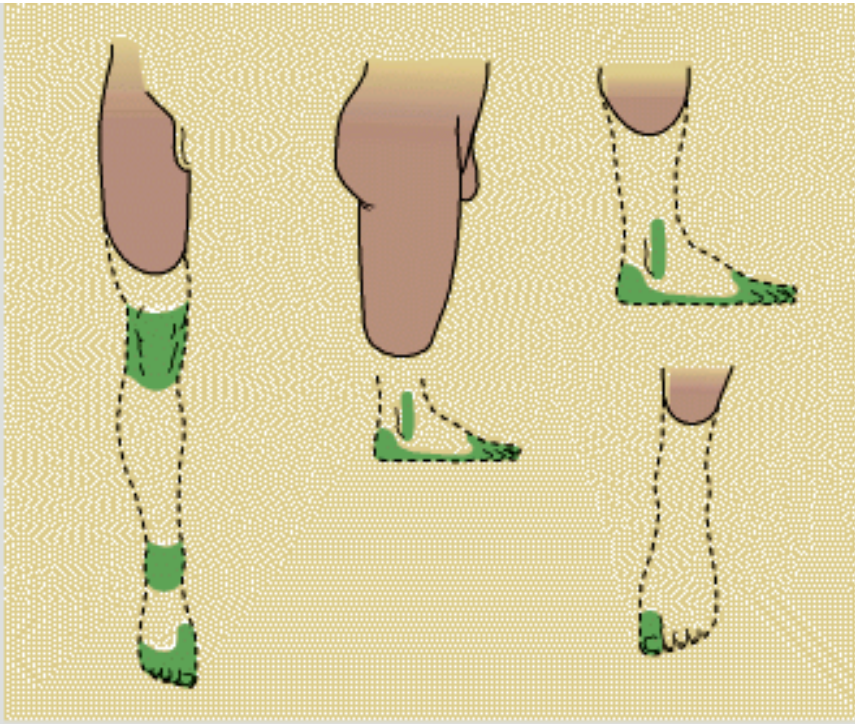
- **neuralgia**

  sharp, seizure, affects peripheral or cranial nerves (often trigeminus, facialis) →
  after traumatic injury, oppression, viral disease, mainly herpetic, metabolic (DM)

- pain in chronic compression of peripheral nerves and nerve roots
  intervertebral disk hernia, nerve depression in bone channel →
  pain + paraesthesia, mechanoreceptors (tactile) are discontinued from long term pressure action, painful afferentation remains intact
- →
  burning pain

Phantom pain





http://www.slideshare.net/drpsdeb/presentations

Special types of pain

- **phantom pain**
  after limb amputation, after losing other parts of the body, after tooth extraction →
  the impression of the presence of a removed body part, a smaller percentage (about 30%) of pain (patients with long-term pain before amputation) → substantia gelatinosa deaferentation or brain irritation

Special types of pain

- **ischemic pain**
  it is a result of a defect in blood flow to the myocardium, smooth or skeletal muscle →
  release of substance P, histamine, serotonin, potassium from cells, ↓ pH

  migraine pain
  migraine is characterized by pulsating, predominantly unilateral headaches typically lasting 4-72 hours with nausea, eventual vomiting, photophobia and phonophobia, suffering from 12% of the adult population

Migraine

- the spread of blood flow down the cortex is secondary to decreased neuronal function (metabolic depression)

  epiphenomenon of so-called Lea's cortical depression spontaneous electrical activity

  Depression begins at the occipital pole and spreads forward on the lateral, medial and ventral sides of the brain

  a transient ionic and metabolic disturbance at the front of the wave that triggers changes in blood flow and focal symptoms

  vessel blood flow decreases by 20-30%, usually for 2-6 hours

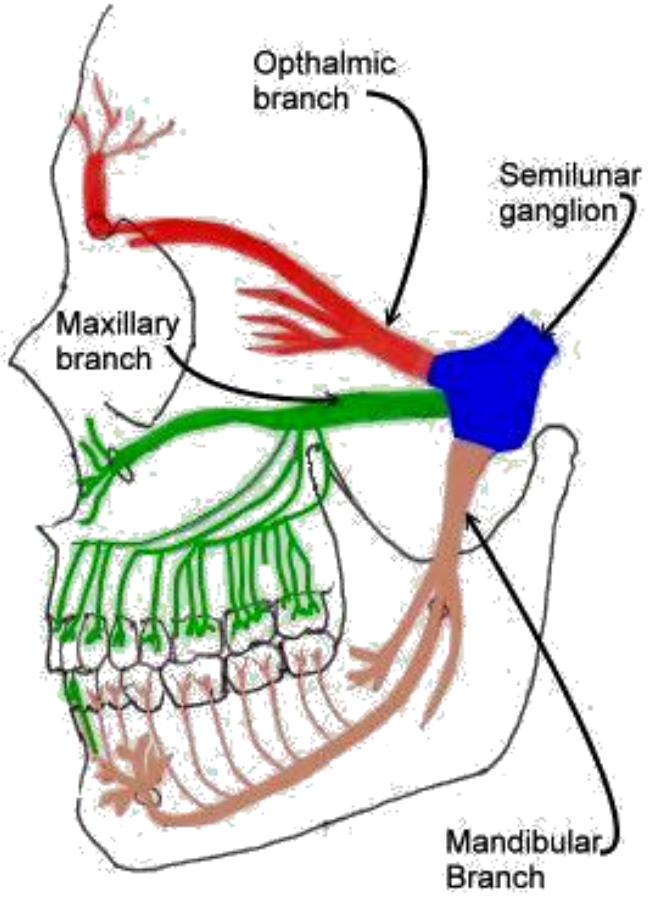
Migraine

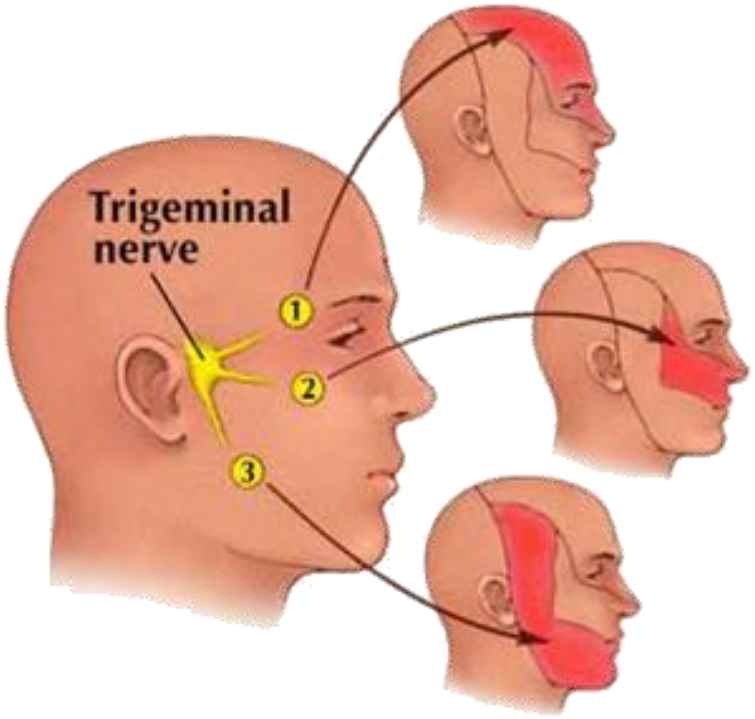
- the so-called trigeminovascular system mediates pain perception

  when depolarizing the fibers of the trigeminovascular system, substance P is released from the nerve endings into the wall of the cerebral vessels and also transmits nociceptive signals to the CNS

  Substance P potentiates pain mechanisms by increasing vascular permeability, degranulates mast cells with subsequent release of histamine, serotonin, and dopamine, and stimulates prostaglandin synthesis.
  → These substances surround the artery with painful sterile inflammation.

Trigeminal system





Parestézie = Spontánně vyvolané subjektivní kožní vjemy, které jsou nebolestivé a nejsou vyvolány stimulací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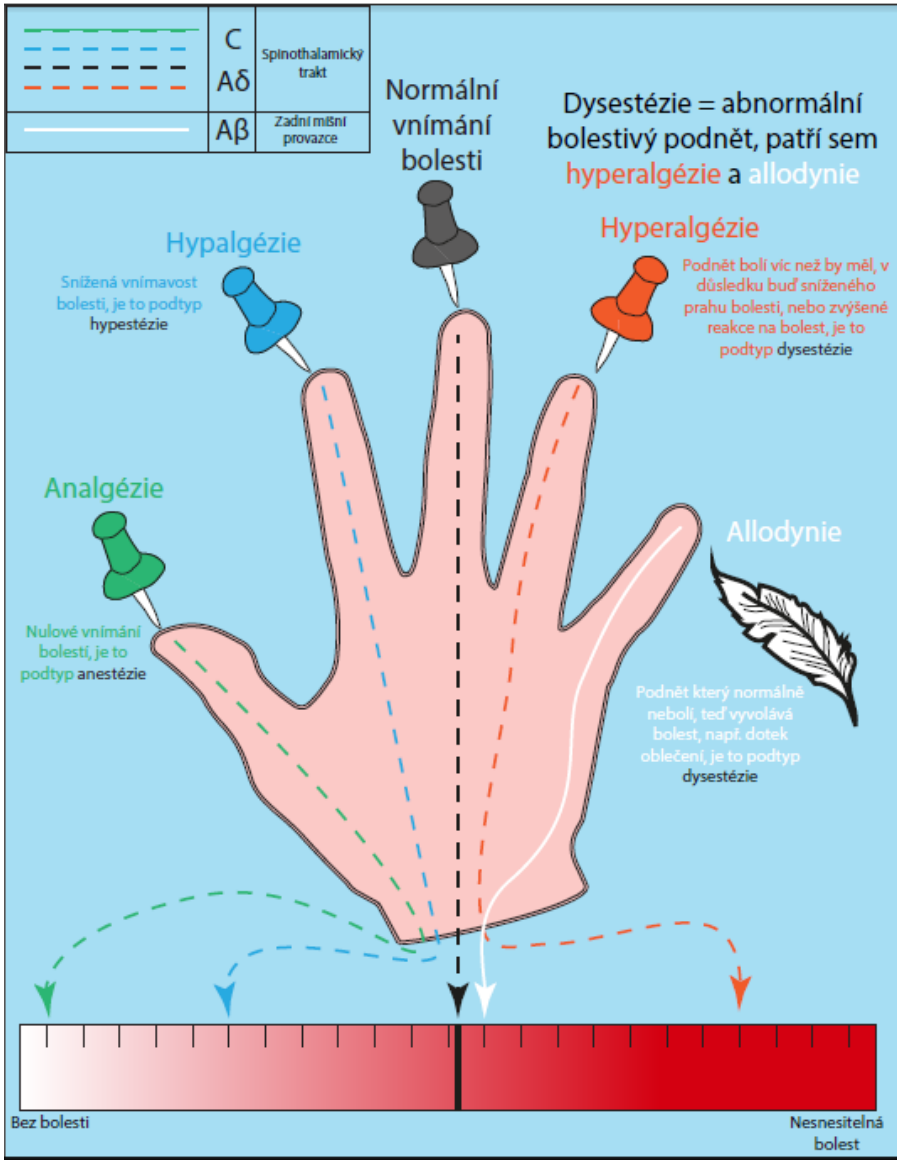
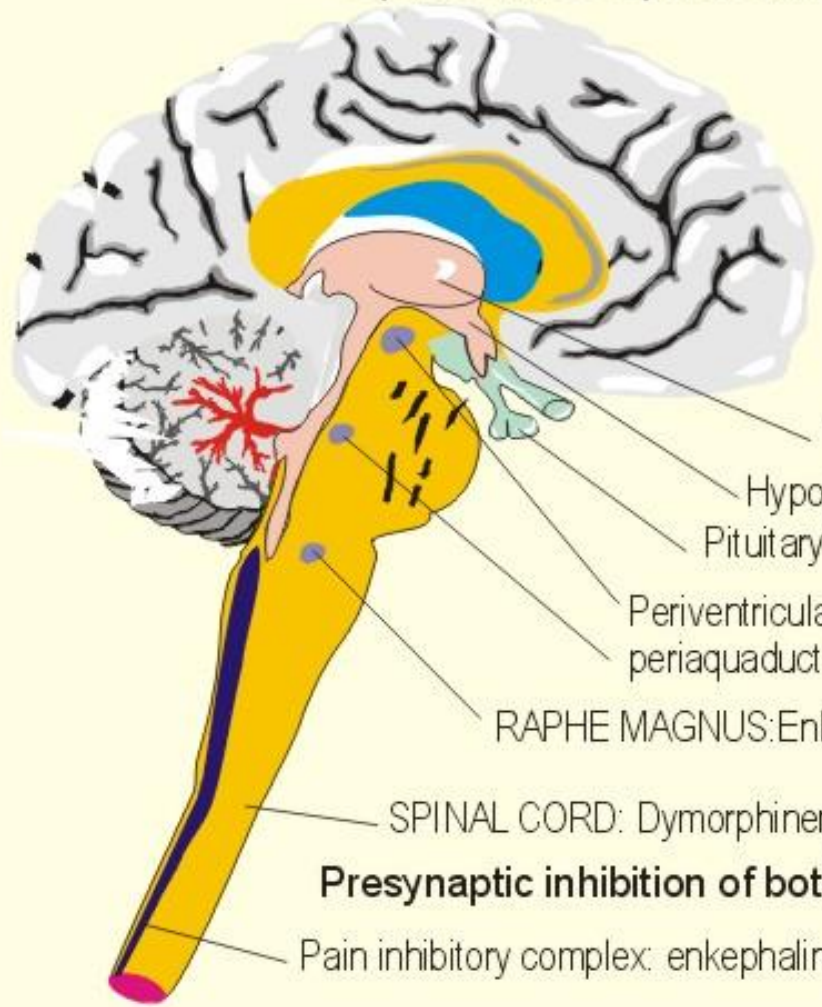
Brnění
Píchání
Pálení
Mravenčení
Svědění


C
Aδ
Aβ
Spinothalamický trakt
Zadní míšní provazce
Normální vnímání bolesti
Dysestézie = abnormální bolestivý podnět, patří sem hyperalgézie a allodynie
Hypalgézie
Snížená vnímavost bolesti, je to podtyp hypestézie
Hyperalgézie
Podnět bolí víc než by měl, v důsledku buď sníženého prahu bolesti, nebo zvýšené reakce na bolest, je to podtyp dysestézie
Analgézie
Nulové vnímání bolesti, je to podtyp anestézie
Allodynie
Podnět který normálně neboli, teď vyvolává bolest, např. dotek oblečení, je to podtyp dysestézie
Bez bolesti
Nesnesitelná bolest

Opiate Receptors In The CNS



Thalamus

Hypothalamus

Pituitary glands

} β - endorphin (μ- & δ)

Periventricular nuclei
periaquaductal grey

} Morphine
Dynorphin (μ)

RAPHE MAGNUS:Enkephalin (δ)

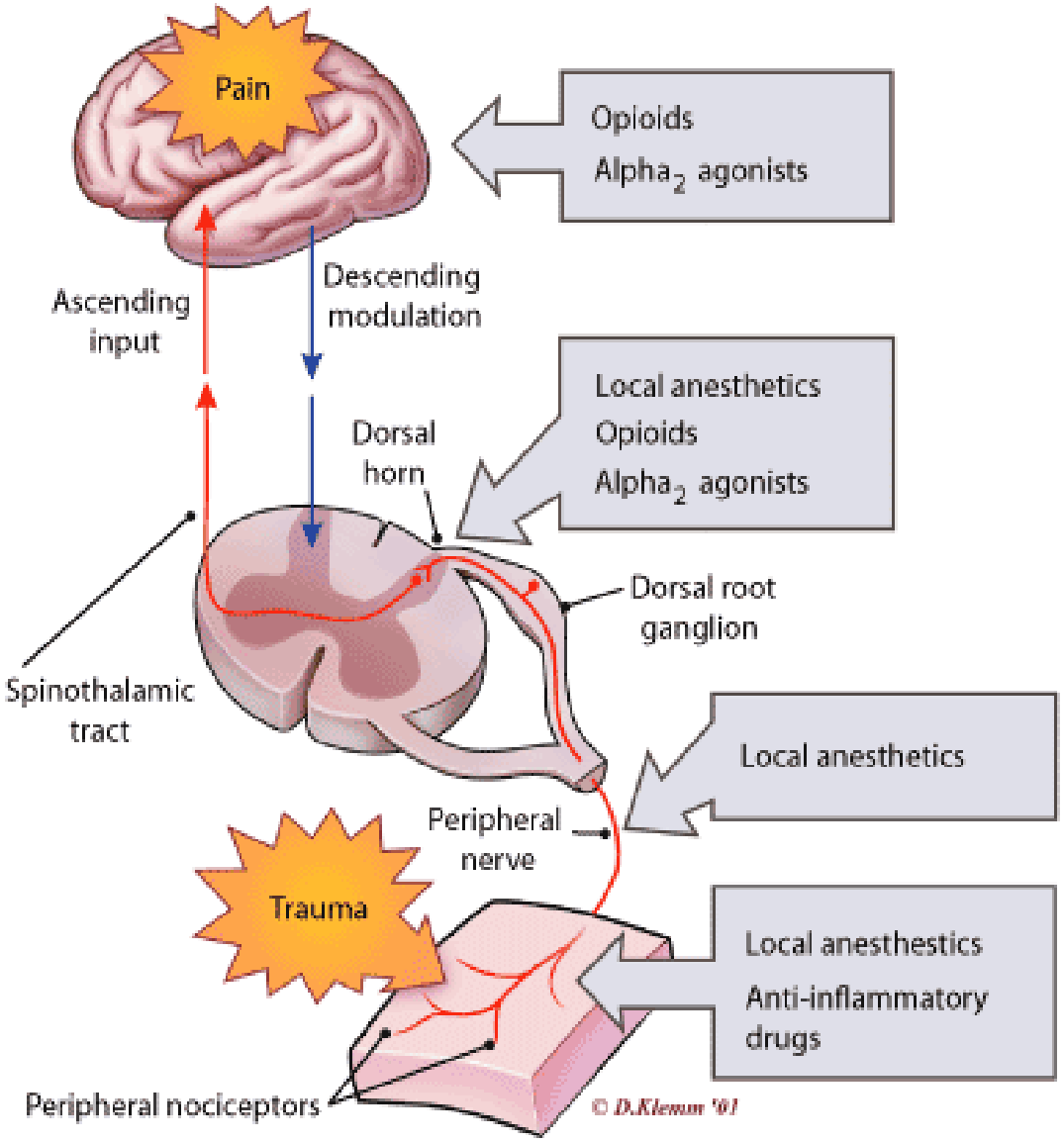
SPINAL CORD: Dymorphinergic neuron with κ-receptors

Presynaptic inhibition of both III and IV fibres by enkephalins

Pain inhibitory complex: enkephalin (δ)

Fig. 3-10

KMc


Pain
Opioids
Alpha$_2$ agonists
Ascending input
Descending modulation
Local anesthetics
Opioids
Alpha$_2$ agonists
Dorsal horn
Dorsal root ganglion
Spinothalamic tract
Local anesthetics
Peripheral nerve
Trauma
Local anesthetics
Anti-inflammatory drugs
Peripheral nociceptors
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Thanks