mechsense

Pain physiology
Rundt om thorax, Kolding 2017

Christina Brock

Cand med vet, PhD

Mech-Sense

- Medical gastroenterology, Aalborg Hospital
- Pain and neurophysiology of visceral origin
- 45 publications/year
- 1 professors
- 8 post docs
- 6 PhD students
- Masterstudents, etc

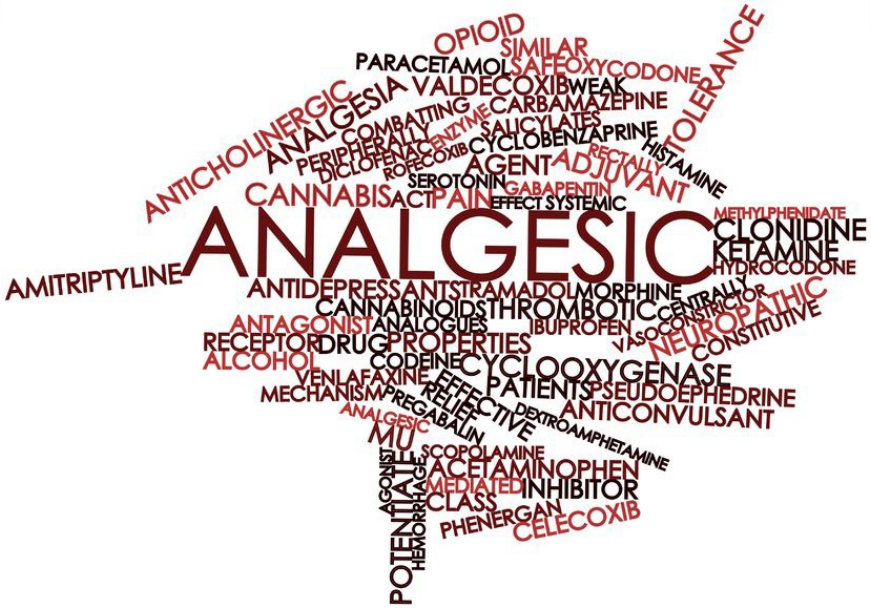
Pain pathway

- Transduction
  - Noxious stimuli translated to electrical stimuli at sensory nerve endings
- Transmission
  - Propagation of impulses along spinothalamic tract
- Modulation
  - Transmission is modified
- Perception
  - Affective and emotional aspects
- Interpretation and behavior

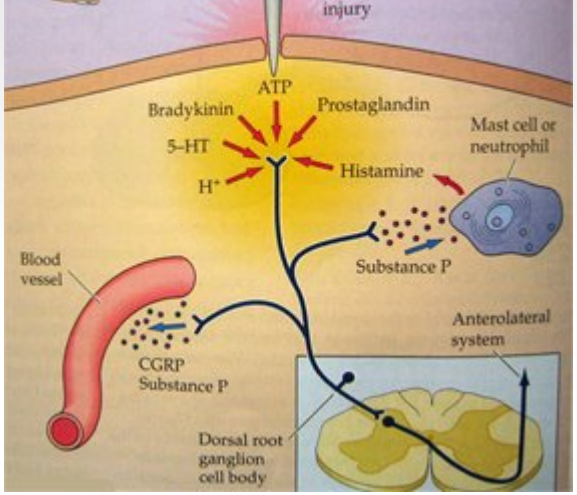
EACH OF THESE PROCESSES PRESENT A POTENTIAL TARGET FOR ANALGESIC TREATMENT

Introduction to pain and analgesics

- Transduction
  - Peripheral receptor
  - Peripheral sensitization
- Tranmission
  - Synnapse
  - Central sensitization
- Modulation
  - Descending inhibition /descending fascilitation
- Perception
  - Personality/stress/anxiety/coping/placebo-effect



Transduction



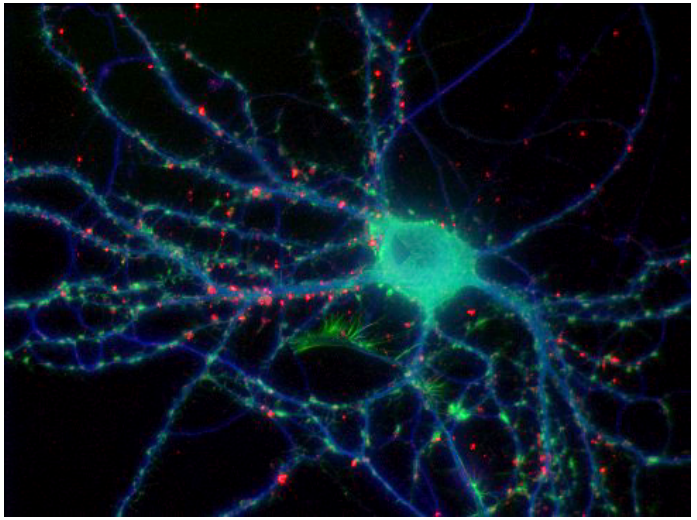
Noxious stimuli translated to electrical stimuli at sensory nerve endings

Physiological way:
"A specialized cell or group of nerve endings that responds to sensory stimuli".

Biochemical way:
"A molecular structure or site on the surface or interior of a cell that binds with substances such as hormones, antigens, drugs, or neurotransmitters".

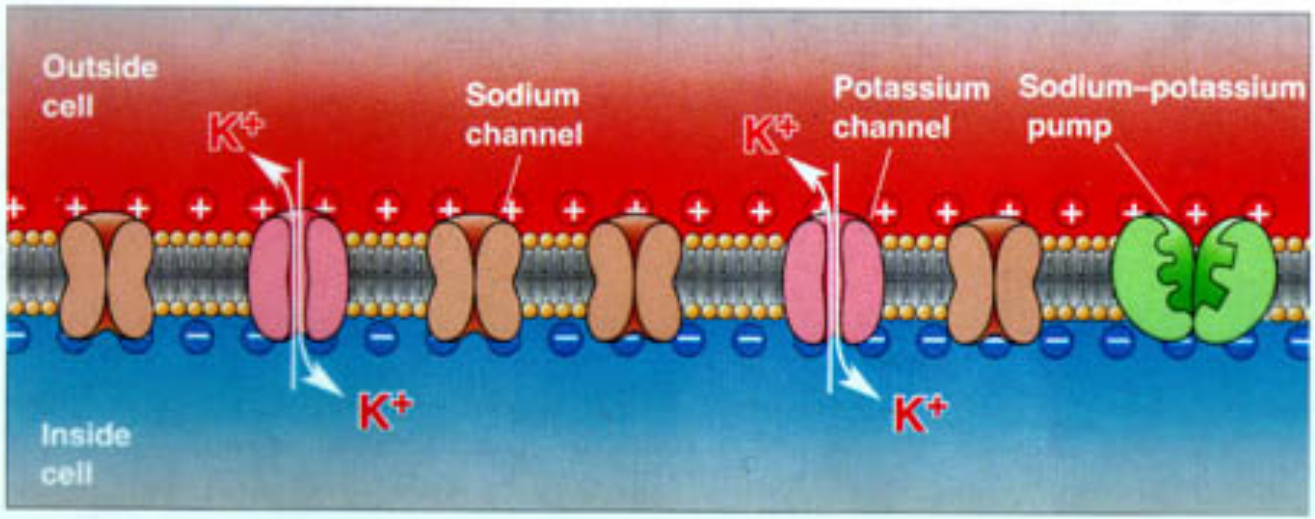
Action potential

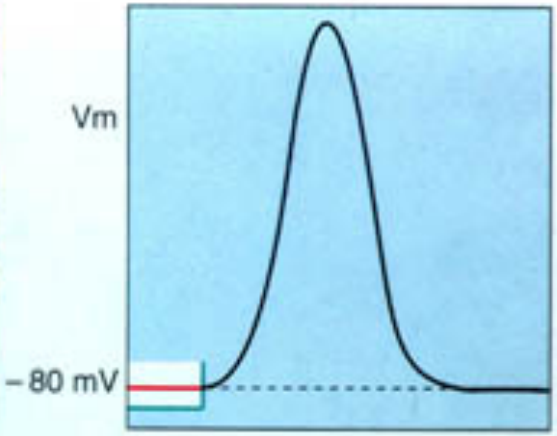
- Change in the electrical membran potential in the neuron
- Duration 2-5 msec
- Absolute/relative refractory periode.
- Targets can either be a hormon producing cell, a neuro secretory cell e.g. in the hypothalamus or a muscle celle
- 4 phases:
  - Resting potential
  - Depolarization
  - Repolarization
  - Recovery/refractory



Resting potential

- The negative resting potential of -70-80mV
- Negative charged ions e.g. proteins indside the cell
- Positive charged potassium ions, moves passively from outside the cell to the indside, untill equilibrition.

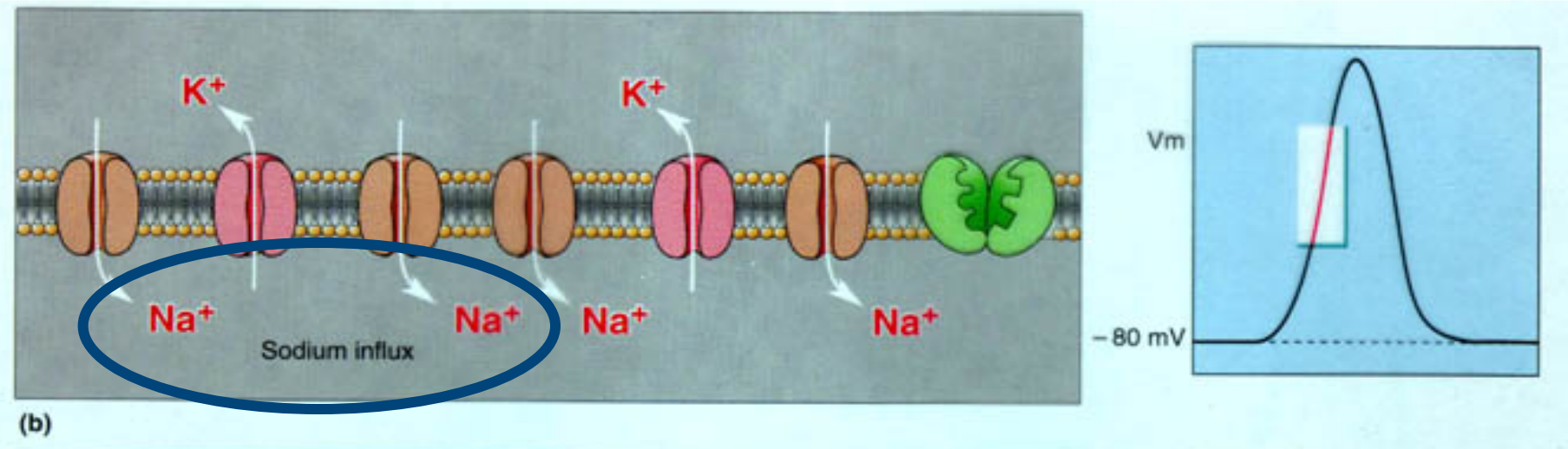




(a)

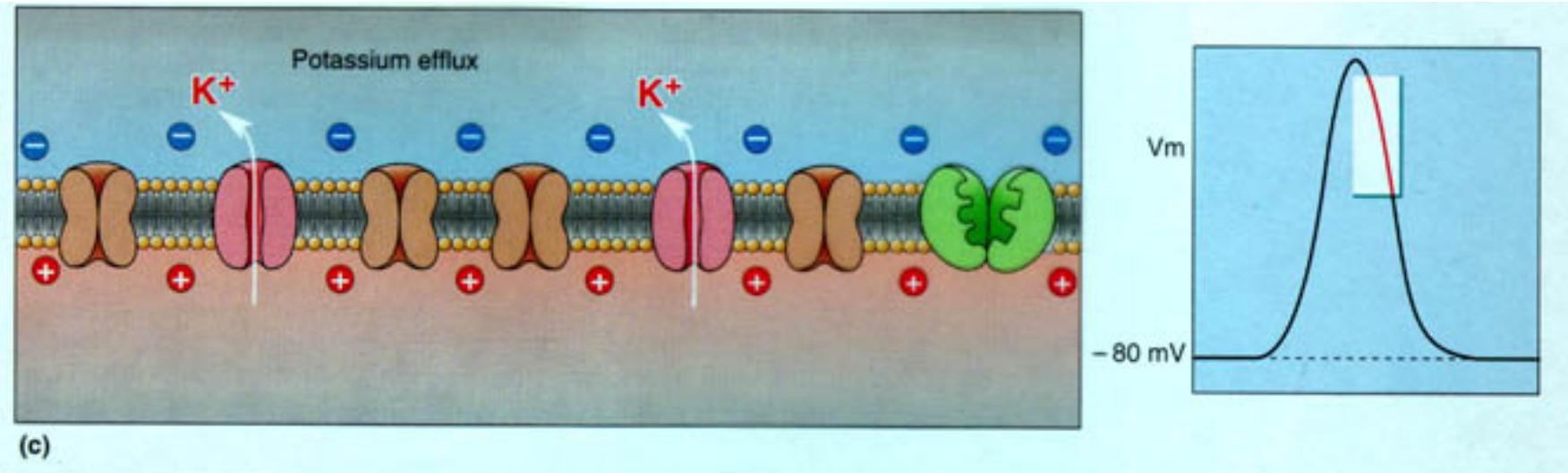
Depolarization

- Following stimulus, sodium gated channel proteins open and sodium ions rush (*fascilitated Na+ diffusion*) from the outside of the axomembrane to the inside.
- Polarity change across the neuron from -65mV to +40mV.
- The axoplasm is now positively charged compared to the outside of the neuron.



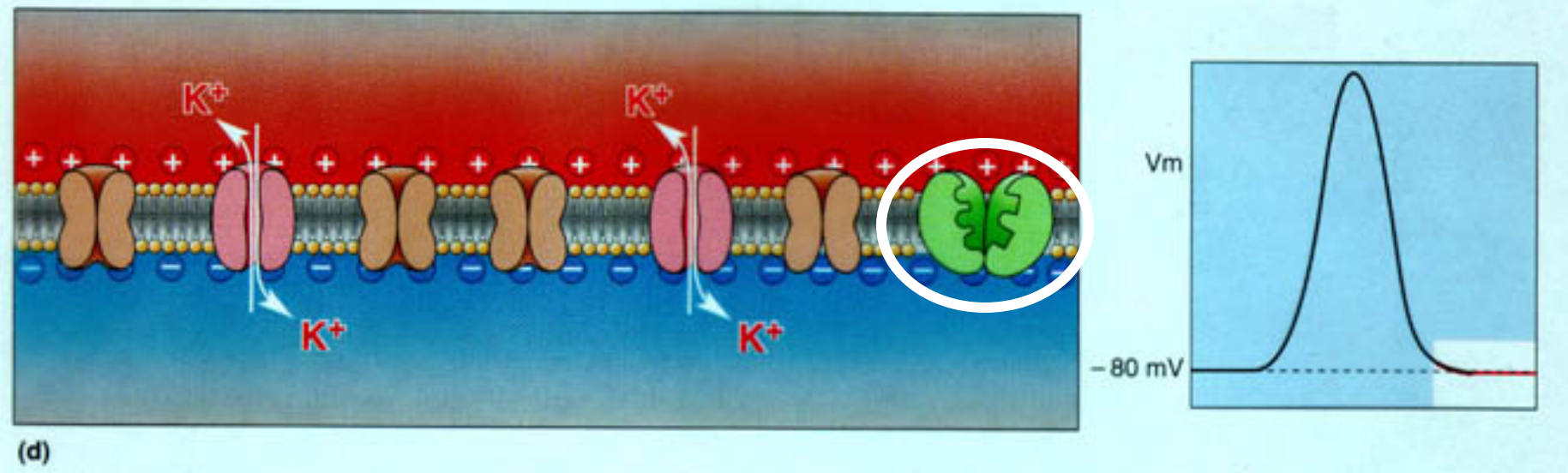
Repolarization

- Sodium influx opens potassium gated channels and potassium ions rush *(facilitated K+ diffusion)* to the outside of the axomembrane.
- Outside of the membrane positively charged The potential across the membrane returns from +40mV back to -65mV.

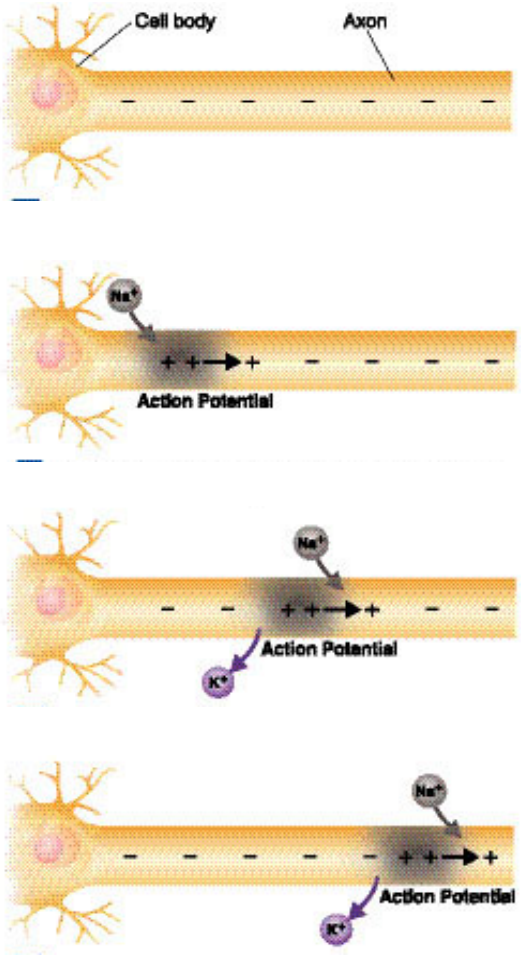


Recovery/Refractory Period

- Recovery periode no generation of action potential
- The active transport of sodium and potassium (*energy dependent Na+/K+ pump)* is re-establishing the resting potential by pumping sodium ions out and potassium ions back in through the axomembrane.



Nerve conductivity

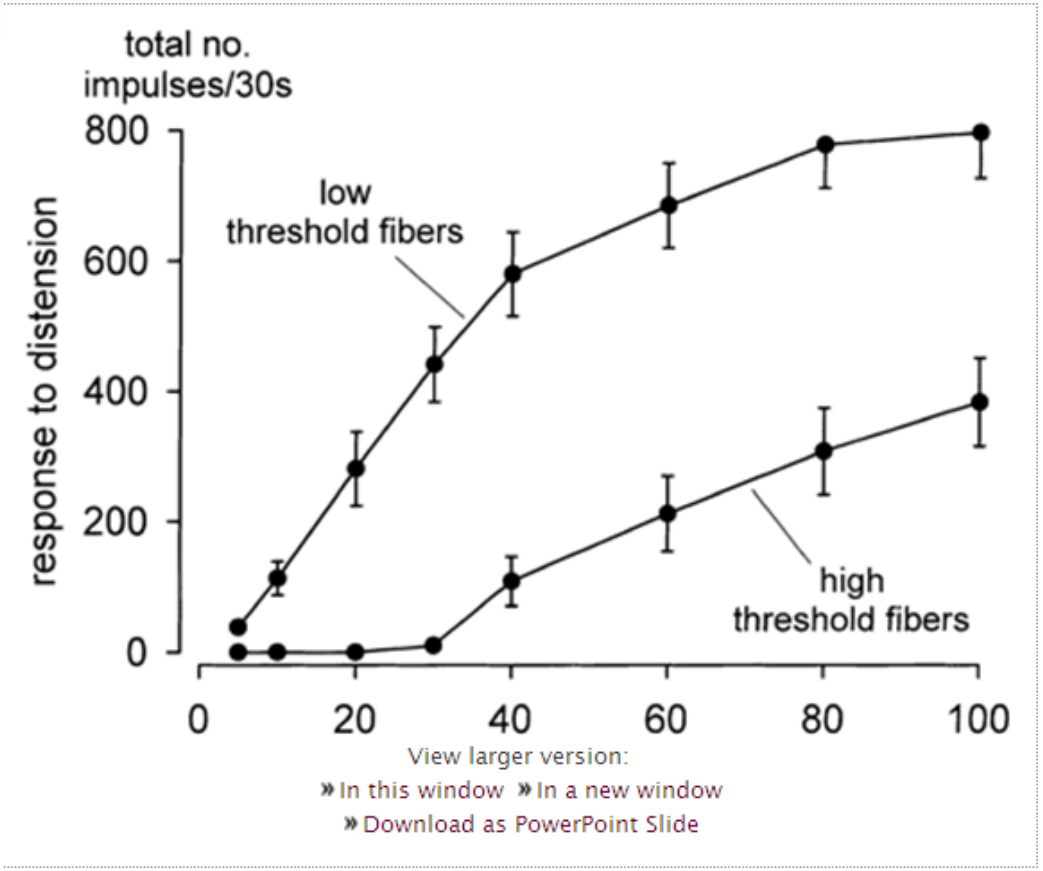


Peripheral sensitization

- Neurotransmitters are upregulated
- LT and HT fibres are activated
- NGF: retrograd transport to the celle nucleus in the paravertebral ganglion.

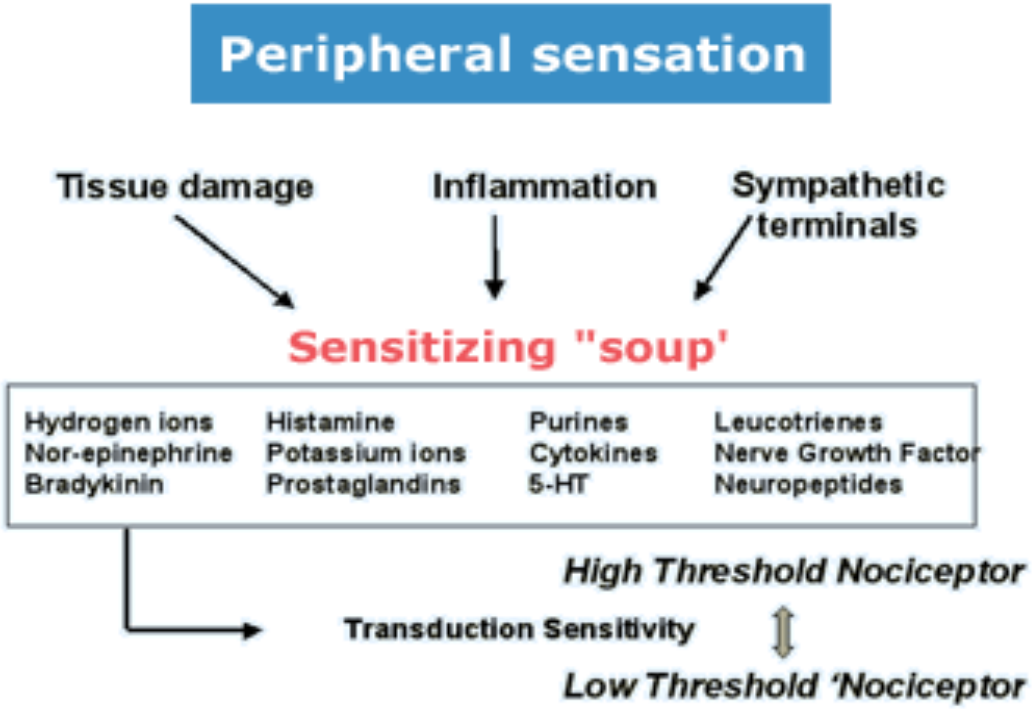
  - enhances the peptid formation,
  - upregulats the number of ion-channels
  - upregulates the number of receptors
- Silent fibres?

Low Threshold and High Threshold fibres

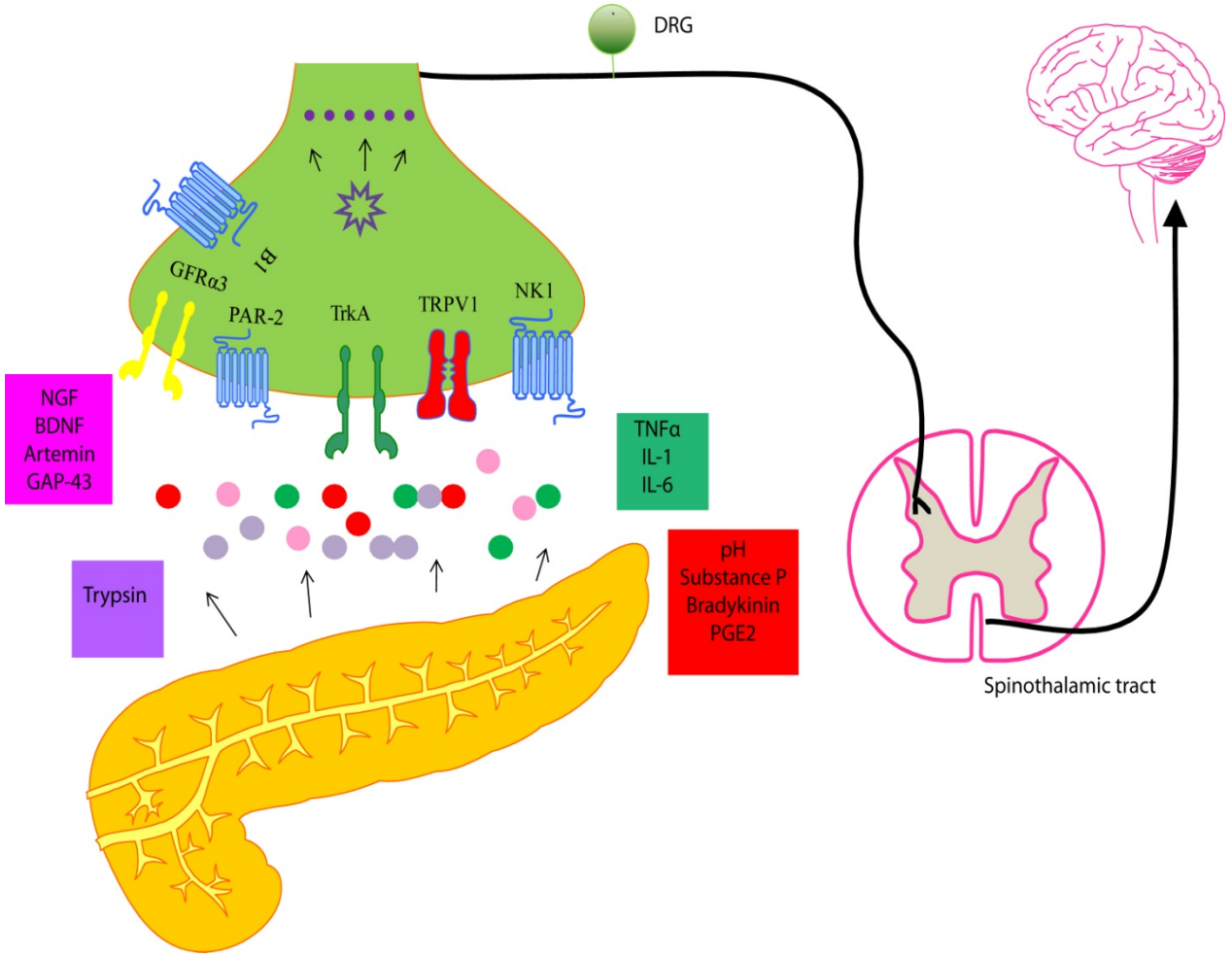


What activates HT to LT?

Inflammatory soup



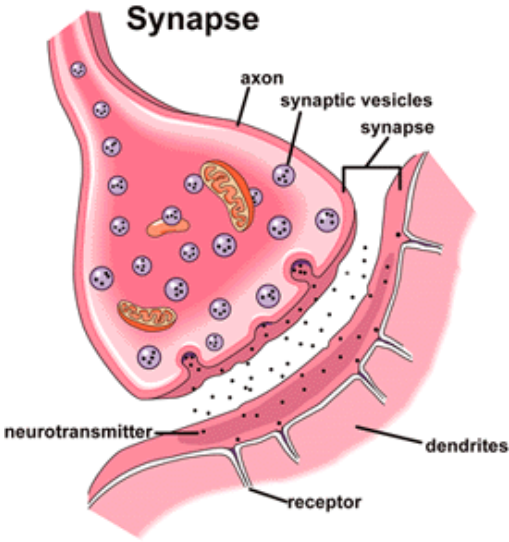
Chronic pancreatitis



Transmission & transmitters

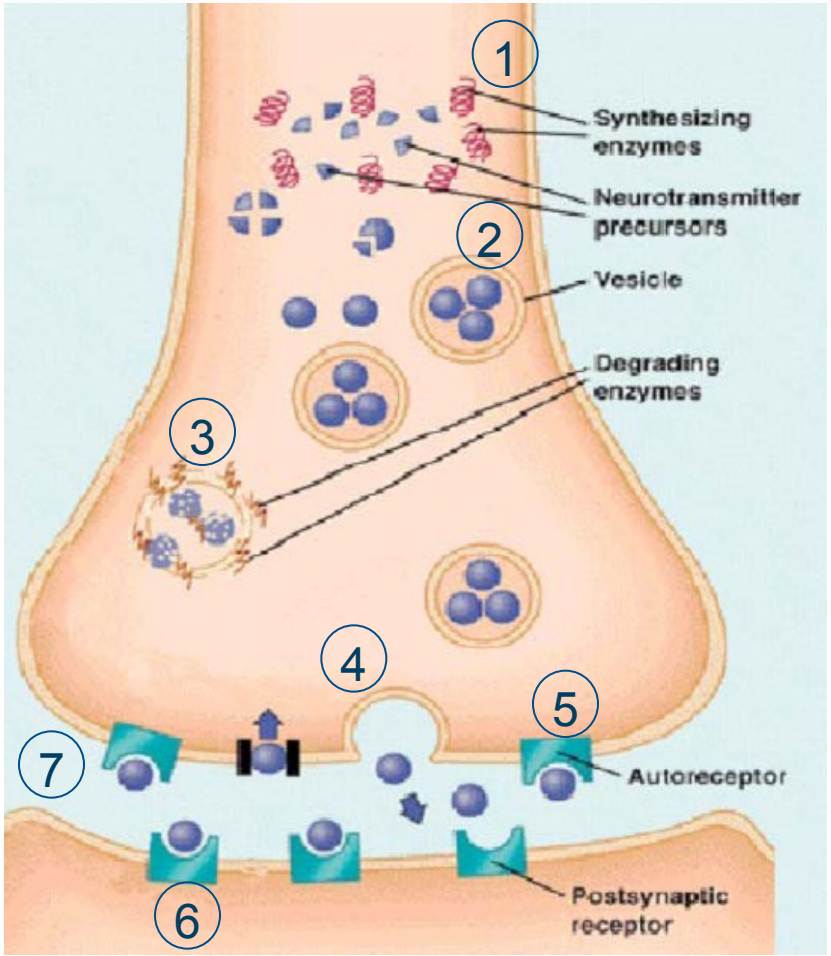
- Pre-synaptic part (bouton), presynaptic membrane
- Synaptic cleft
- Post-synaptic membrane

- Vesicles in the boutons, chemical transmitters bind to specific receptors, and influence on the membrane´s ionchannels
- *Excitatory transmitters* will enhance
- Na+ ion channels
- *Inhibitory transmitters* will enhance
- Cl- ion channels.



Neurotransmitters

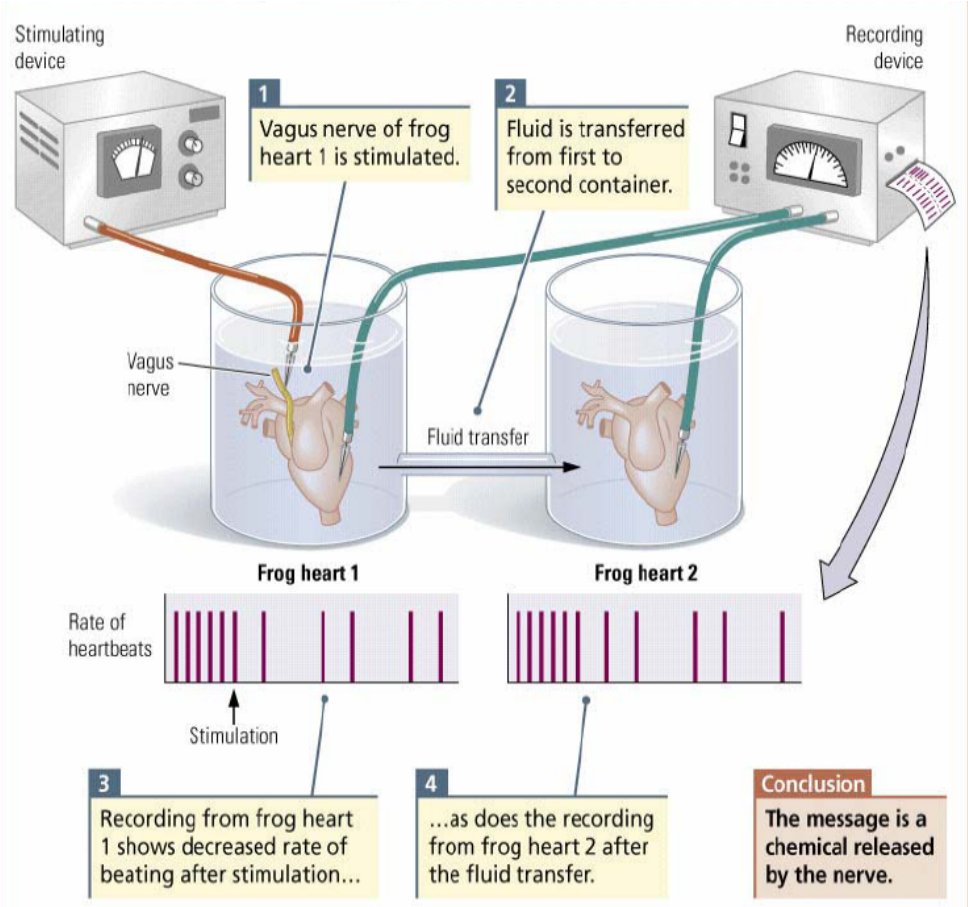
1. Neurotransmitters (NT) are synthesized
2. NT stored in vesicles
3. NT that leak from vesicles are destroyed by enzymes
4. Action potentials cause vesicles to fuse with membrane and release NT into the synapse.
5. Released NT bind to autoreceptors and inhibit further synthesis and release.
6. Released NT bind to postsynaptic receptors.
7. Released NT are removed by reuptake or enzymatic degradation.



Transmitter substances

- *1) Neuropeptides: Acetyl cholin* acting on cholinerge celles: Neuro-muscular junction of striated musculature and Autonomic ganglion, both sympathetic and parasympathetic. It is inactivated by ACh-E.
- *2) Monoamines: Adrenalin, Noradrenalin and dopamin (serotonin & histamin)* acting on adrenerge celles: Sympathetic ganglions. (F,F&F)
- 3)*Glutamate* most common excitatory substance in CNS
- *4) GABA, m*ost important inhibiting transmitter in the spine.
- 5) *Glycin*, inhibitory transmitter in the spine and brainstem.
- 6) Endorfin and enkefalin binding to opioid receptors causing anaesthesia.

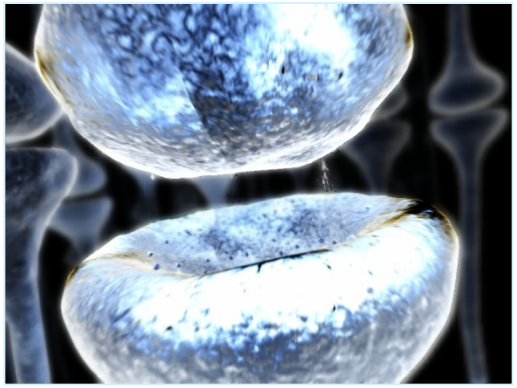
Chemical Neurotransmission



- Stimulated vagus nerve from frog
- Transferred bath from stimulated heart to second heart
- Both hearts decreased heart rate!

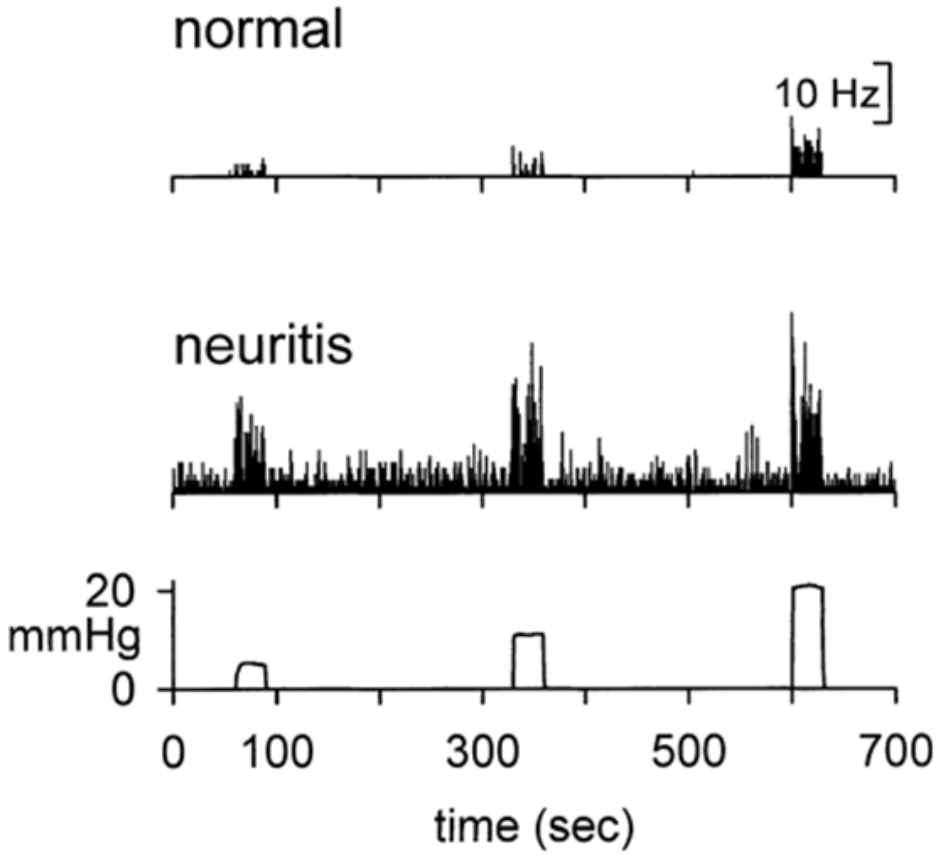
Central sensitization

- Hyper-excitation of dorsal horn neurons
- NMDA
- Convergence
    - decrease activation threshold
    - enhanced response
    - increased firing

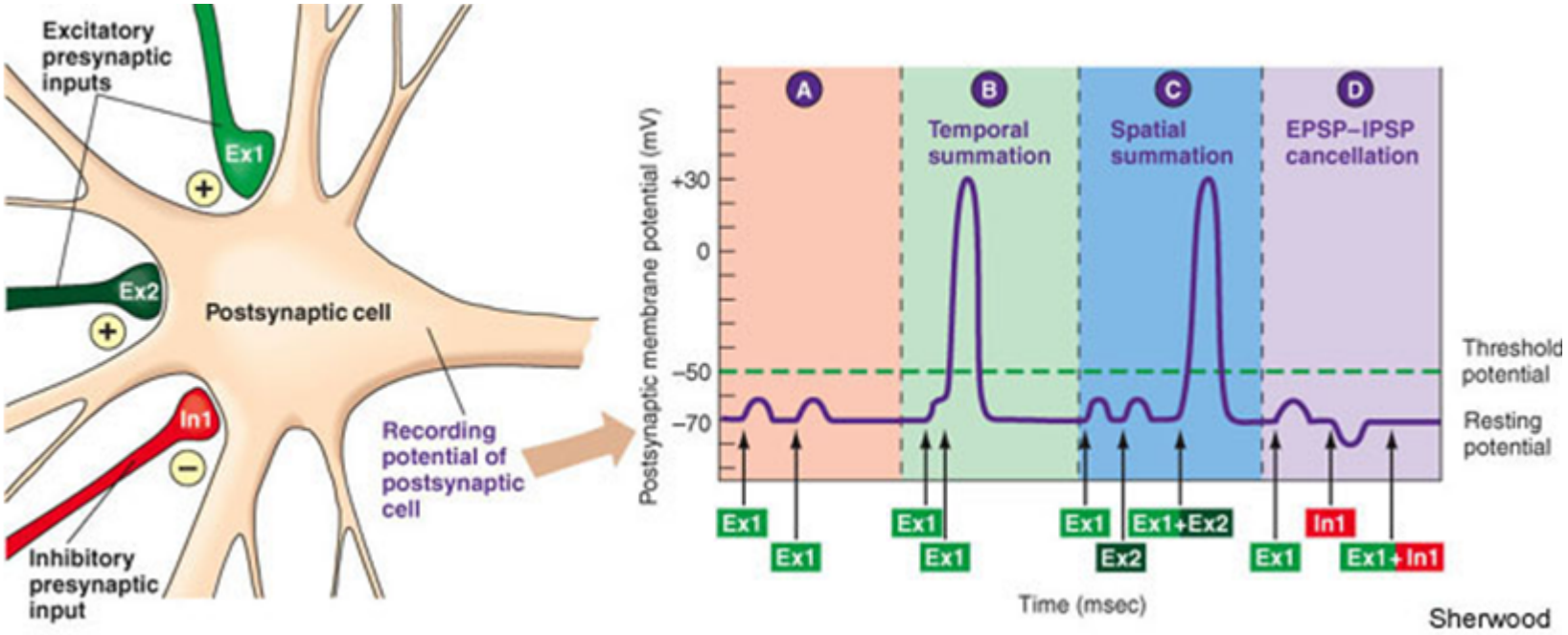


Hyper excitability

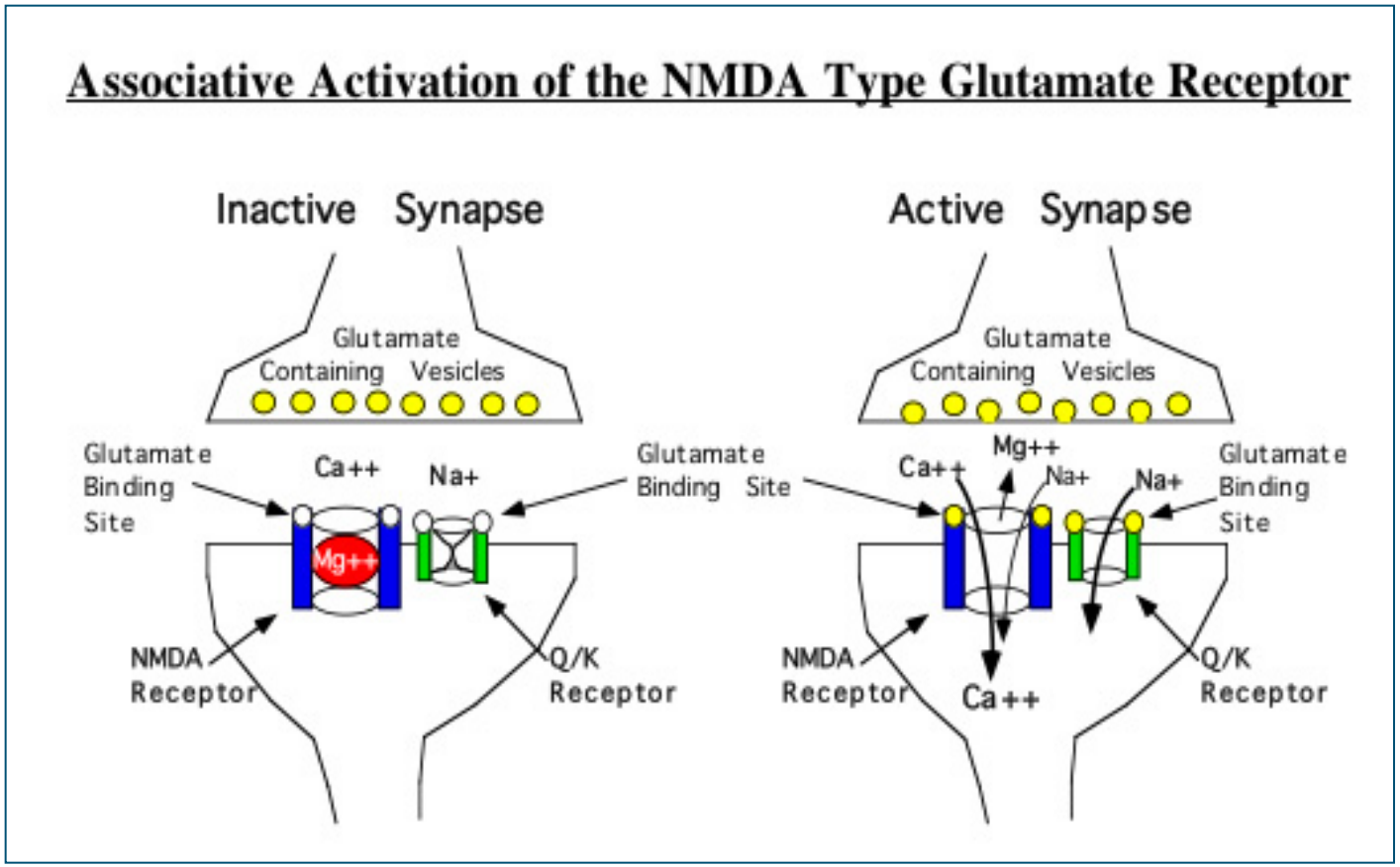
- Same stimulus results in increased nerve activity



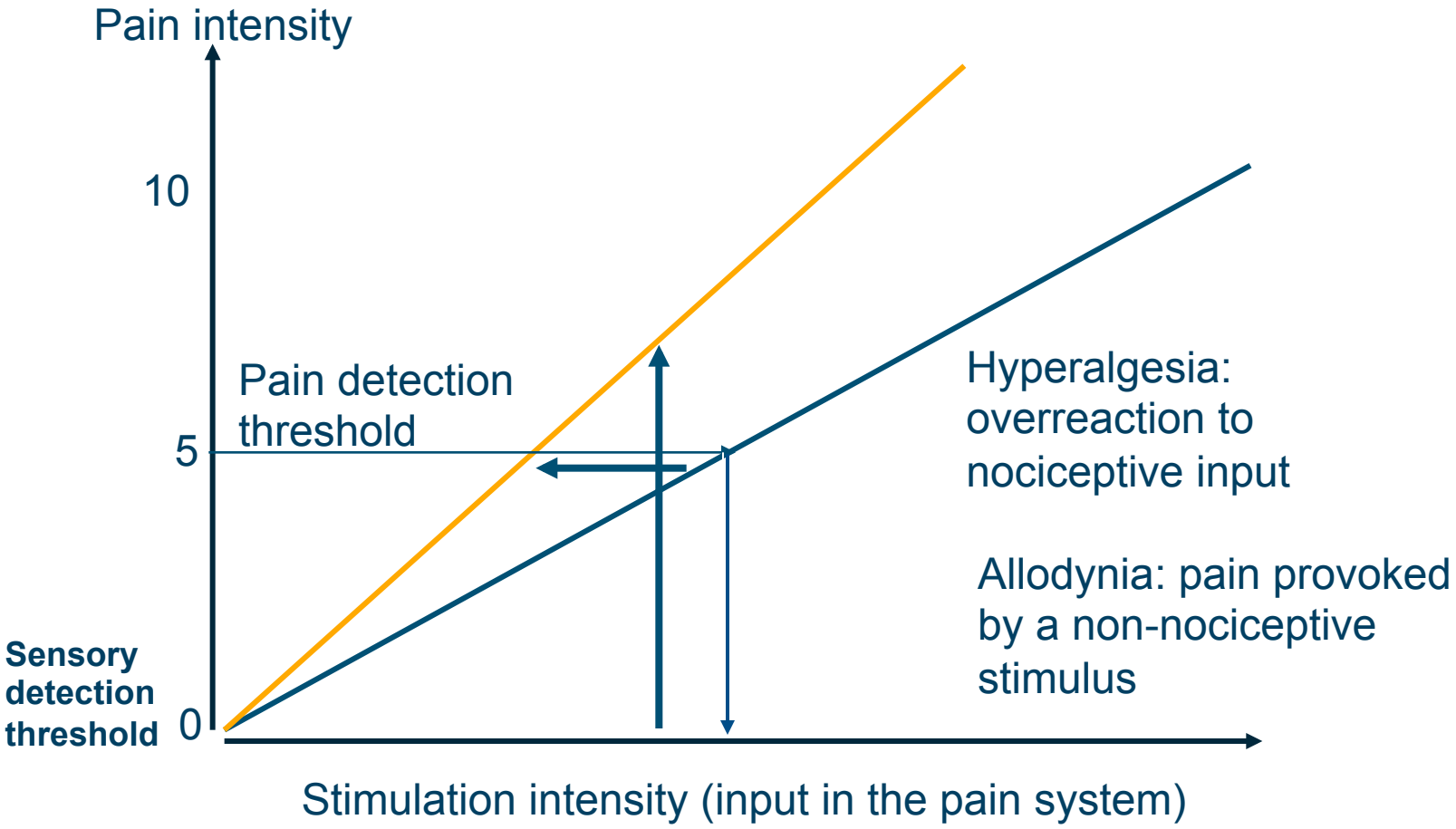
Temporal summation



Spinal level: NMDA receptor



Hyperalgesia and Allodynia



Ascending transmission

Transmission through brainstem,medulla obl., pons, midbrain, to thalamus

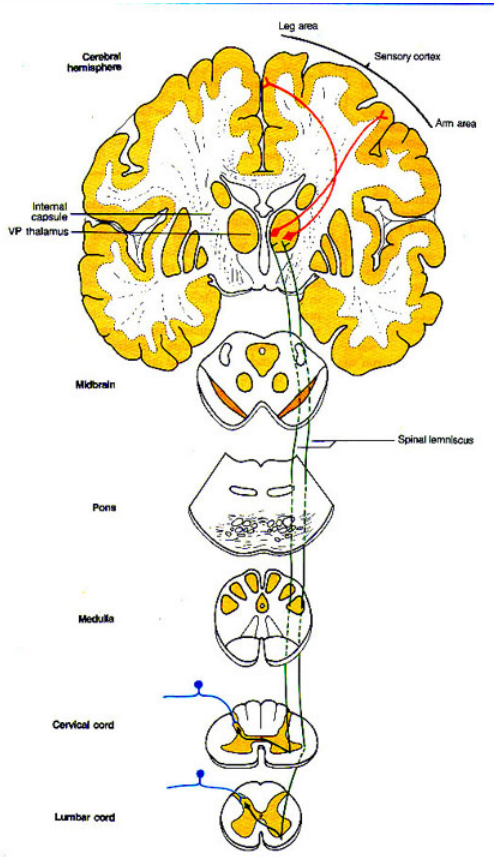
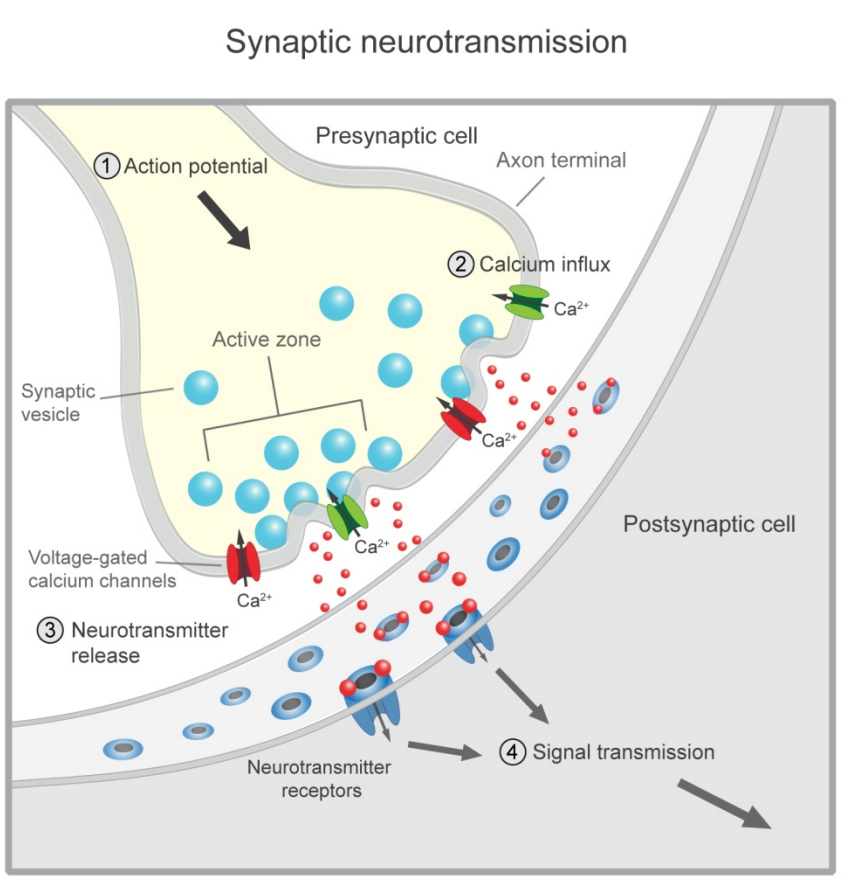


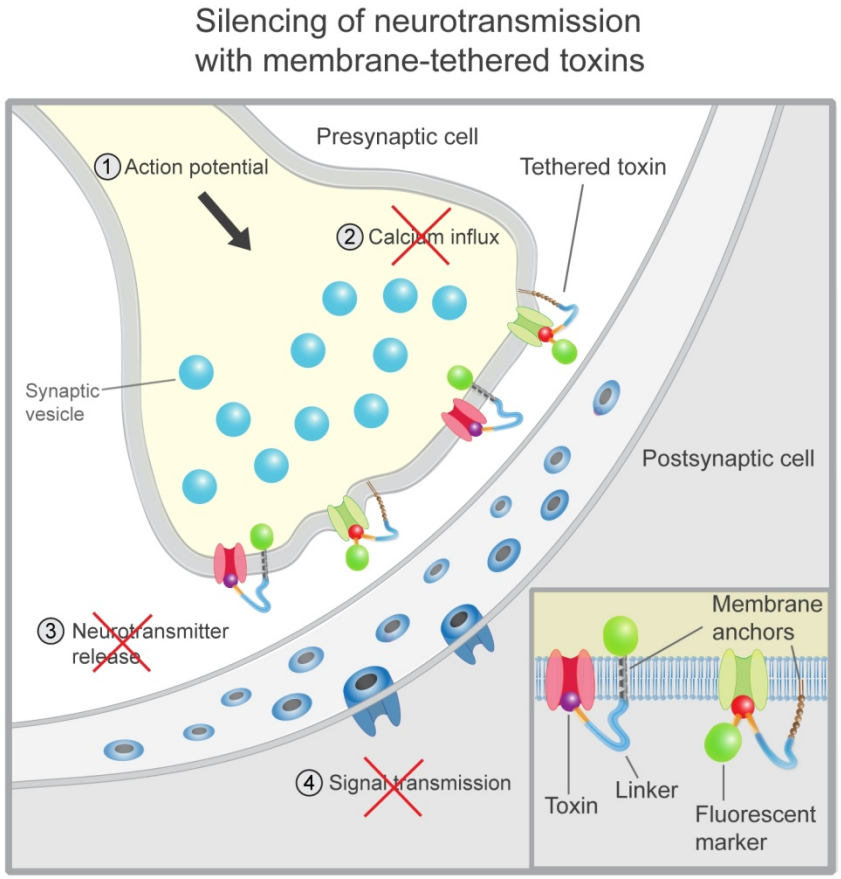
Fig. 5.15 **The spinothalamic tract system.**
The central pathways for pain, temperature, touch and pressure are illustrated.

Pain modulation

Synaptic
Descending inhibition
Descending fascilitation
Supraspinal

Synaptic transmission





Pain inhibition

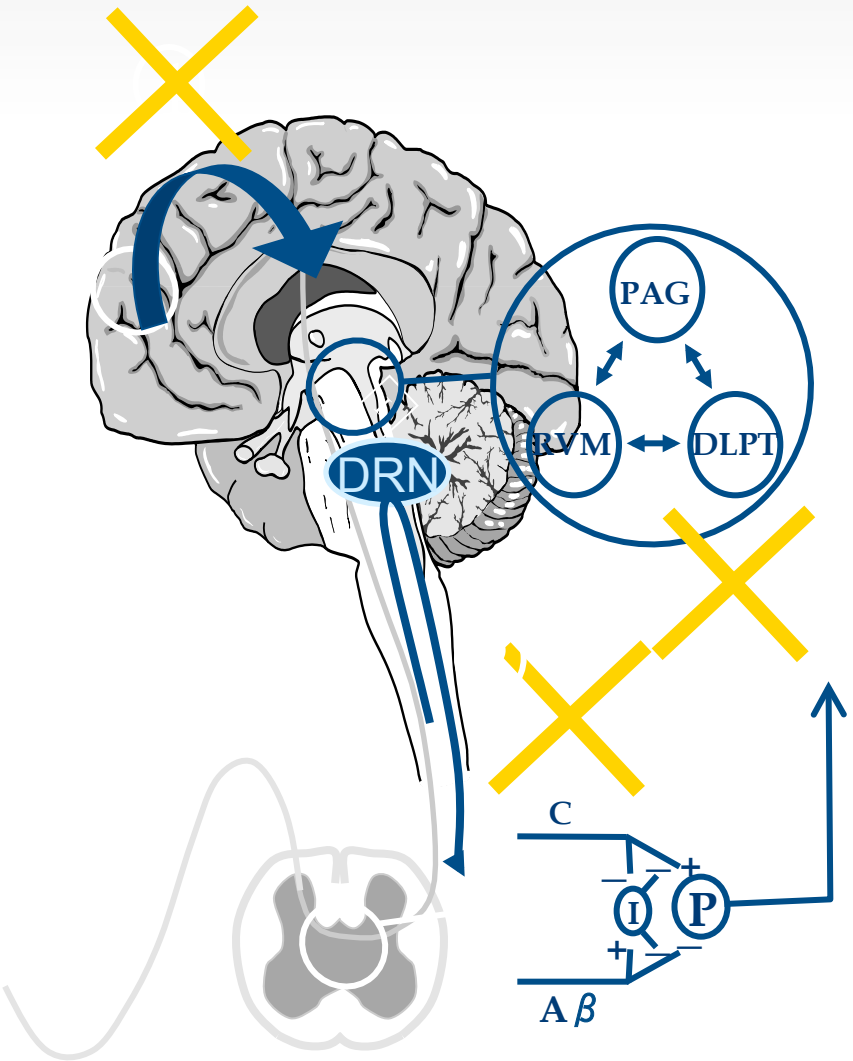
1 SEGMENTAL INHIBITION

2 DNIC

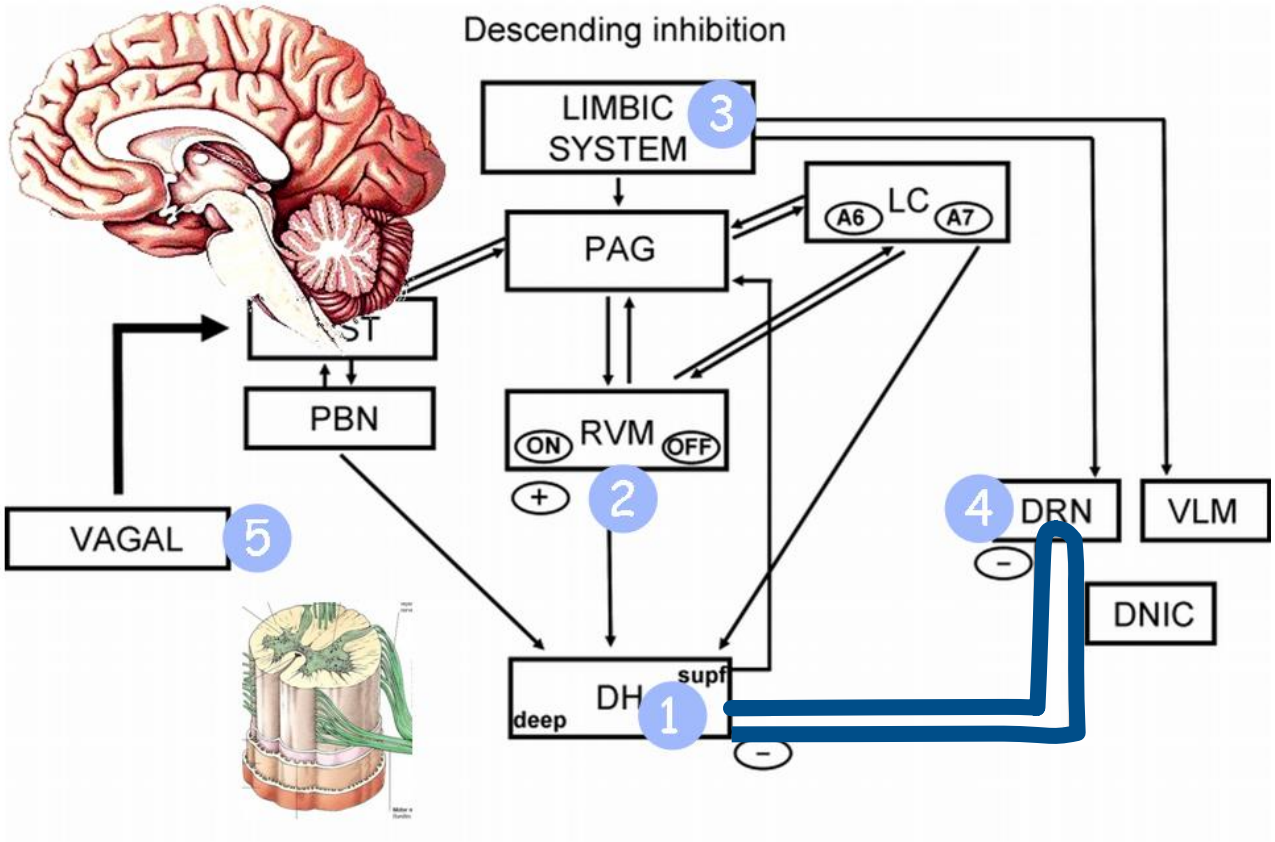
3 ON/OFF CELLS

4 TOP-DOWN CONTROL

FRONTAL-
CORTICO-
LIMBIC-
BRAINSTEM
TOP DOWN



Inhibitory pathways



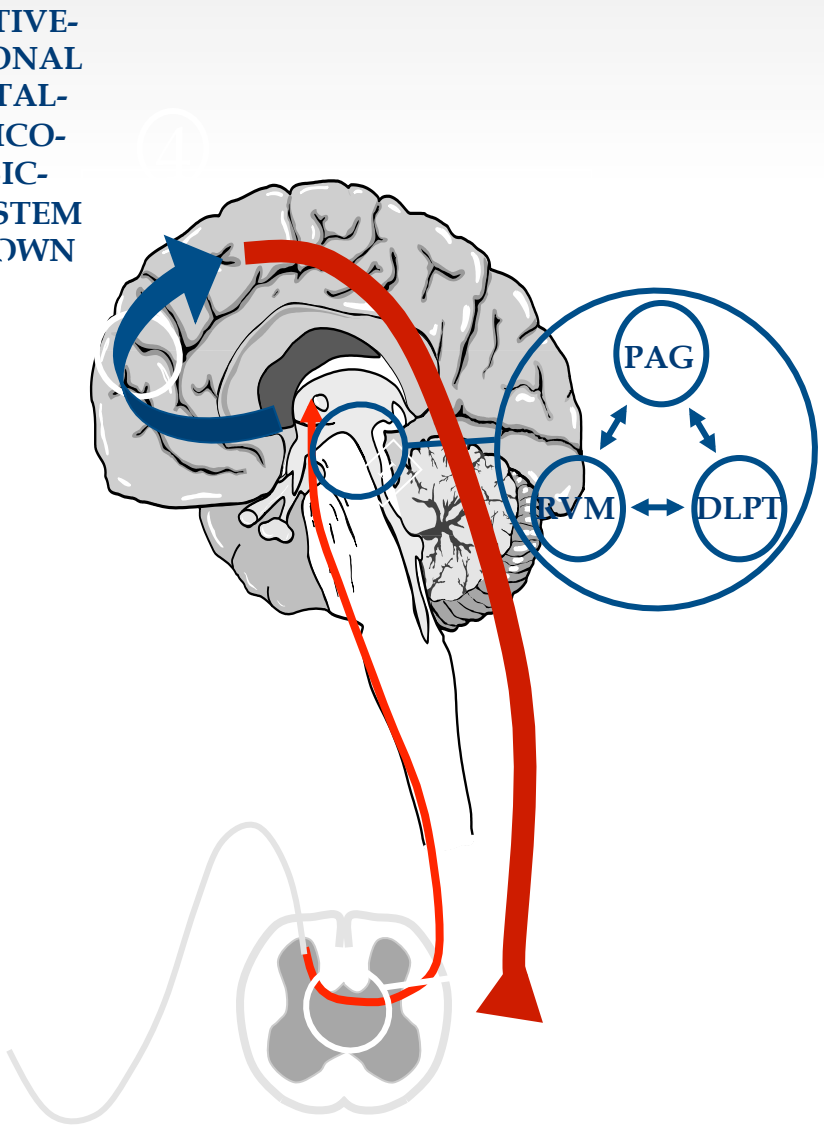
Pain fascilitation

1 ANXIETY

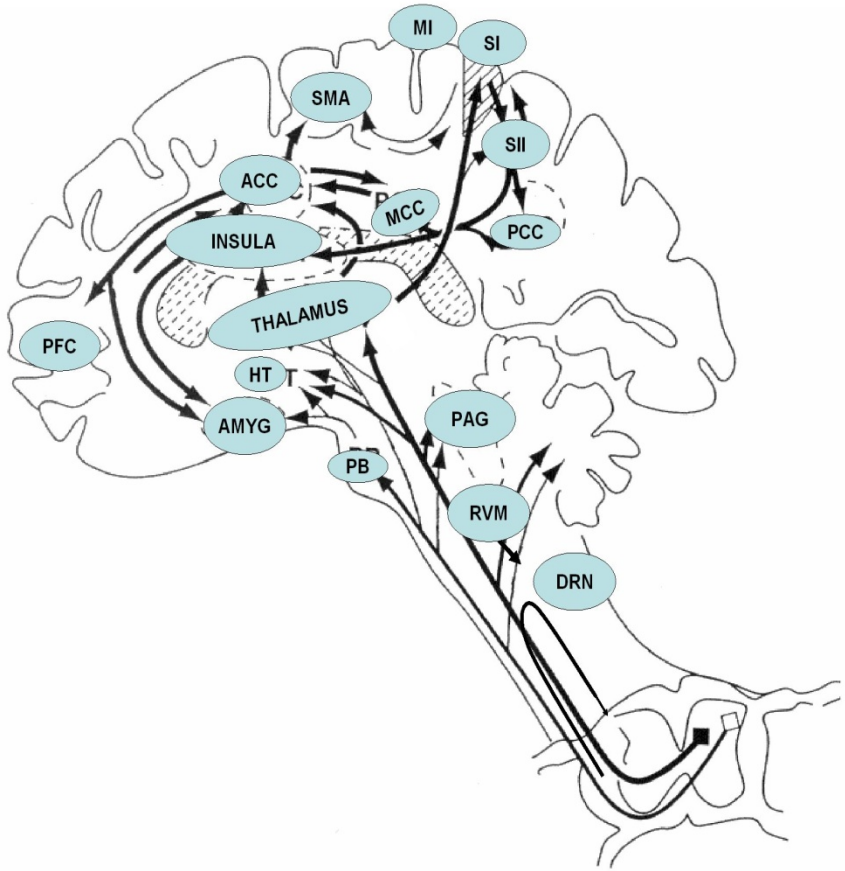
2 NEUROTICISM

3 CATASTROPHIZING

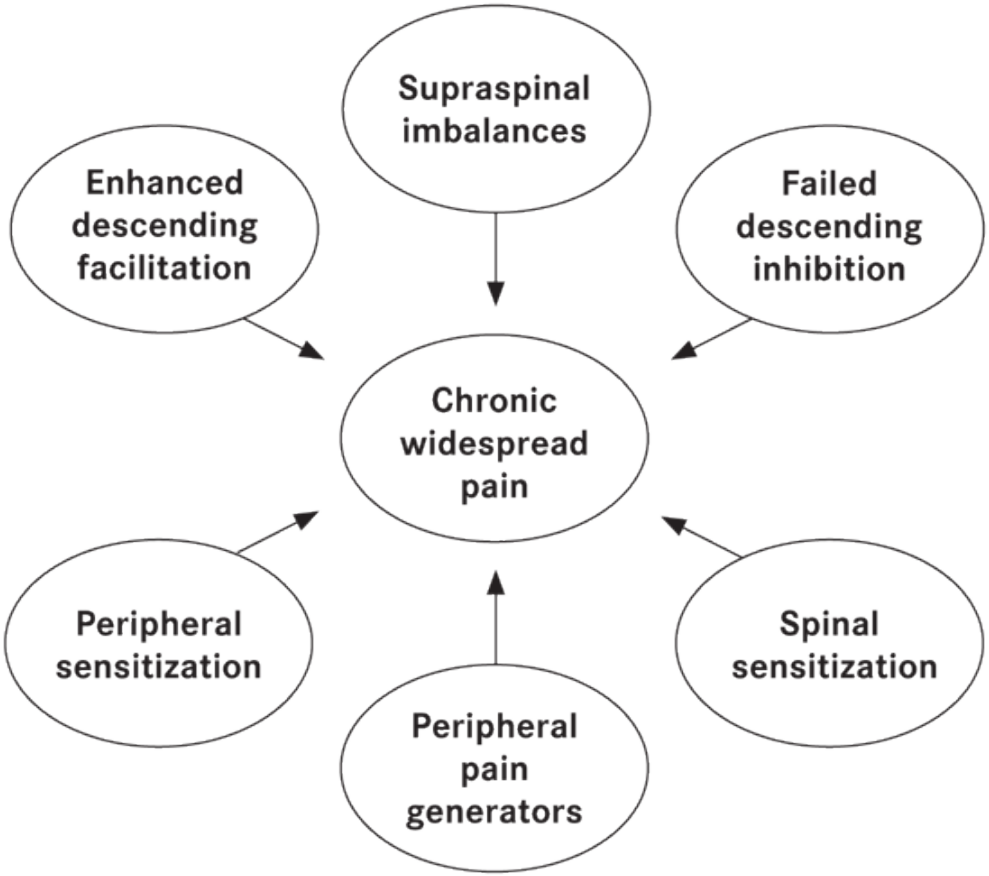
4 COPING STRATEGIES



Perception



Development of chronic pain



Todays agenda

- Characterize and relate location, quality and referral of visceral pain to underlying pathology.
- Explain general characteristics of visceral pain, pain character, duration and involved triggering events.
- Distinguish pain of visceral or peritoneal/pleural origin.

Todays agenda

- **Characterize and relate location, quality and referral of visceral pain to underlying pathology.**
- Explain general characteristics of abdominal pain, like pain character and duration and involved triggering events.
- Distinguish pain of visceral or peritoneal origin.
- Conduct an appropriate examination of an individual in abdominal pain.

Characterize abdominal pain
Underlying pathophysiology

- Nociception vs. Pain
- Frequency of abdominal pain
- Somatic vs visceral pain
- Autonomous system
- Characterize symptoms

What is nociception?

- Nociception is the unconscious sensory process, peripheral or central, through an activation of sensory transducers
- Examples: homeostatic regulations sensation of e.g. satiety and fullness.

What is pain?

- Pain is the unpleasant, sensory and emotional experience, in relation to direct or potential tissue injury.
- It involves cognitive and affective components.
- “No brain- no pain”

Frequency of abdominal pain

Table 2. Leading Gastrointestinal Symptoms Prompting an Outpatient Clinic Visit in the United States, 2000

Symptom	Estimated no. of visits[a]
Abdominal pain, cramps, spasms	12,275,373
Diarrhea	[illegible]
Nausea	3,316,009
Vomiting	2,884,373
Heartburn and indigestion (dyspepsia)	1,824,043
Constipation	1,327,156
Anal/rectal bleeding	1,260,644
Blood in stool (melena)	1,179,224
Other, unspecified gastrointestinal symptoms	957,866
Decreased appetite	715,737
Difficulty swallowing (dysphagia)	676,421
Anal/rectal pain	514,896
Other symptoms or changes in bowel function	466,803
Jaundice	431,410
Abdominal distension, fullness, or swelling	384,877
Abdominal mass or tumor	247,850
Gastrointestinal bleeding	229,729
Anal/rectal swelling or mass	224,093
Flatulence	209,434

NOTE. Source: National Ambulatory Medical Care Survey 2000 (http://www.cdc.gov/nchs/nhcs.htm).
[a]The total number of outpatient visits was estimated from a random sample of 27,369 patient visits to 1388 physicians participating in the National Ambulatory Medical Care Survey 2000.

12.275.373

GASTROENTEROLOGY 2004;126:1448–1453

Digestive and Liver Diseases Statistics, 2004

MARK W. RUSSO, JEFFREY T. WEI, MICHELLE T. THINY, LISA M. GANGAROSA, ALPHONSO BROWN, YEHUDA RINGEL, NICHOLAS J. SHAHEEN, and ROBERT S. SANDLER
Division of Gastroenterology and Hepatology, Department of Medicine, and the Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, North Carolina

Background & Aims: **Digestive and liver diseases are associated with substantial morbidity and mortality in the United States. Statistics about the incidence, prevalence, mortality, and resource utilization of digestive and liver diseases in the United States may be cumbersome to obtain because they are scattered in multiple sources. These data may be useful for policy makers, grant applicants, and authors.** ***Methods:*** **Data on the most common gastrointestinal and liver diseases were collected from large publicly available national databases. Information was collected on inpatient and outpatient gastrointestinal complaints and diagnoses, gastrointestinal cancers, and deaths from common liver diseases.** ***Results:*** **The leading gastrointestinal complaint prompting an outpatient visit is abdominal pain, with 12.2 million annual visits, followed by diarrhea, nausea, and vomiting. Abdominal pain is the leading outpatient gastrointestinal diagnosis, accounting for 5.2 million visits annually, followed by gastroesophageal reflux disease, with 4.5 million visits. Gallstone disease is the most common inpatient diagnosis, with 262,411 hospitalizations and a median inpatient charge of $11,584. Colorectal cancer is the most common gastrointestinal cause of death and is the most common gastrointestinal cancer, with an incidence of 54 per 100,000. Among gastrointestinal cancers, primary liver cancer had the highest increase in incidence from 1992 to 2000.** ***Conclusions:*** **Gastrointestinal and liver diseases are associated with significant outpatient and inpatient healthcare utilization. Following trends in utilization is important for determining allocation of resources for health care and research.**

Digestive and liver diseases are common in the United States. They affect large numbers of individuals and exact a considerable financial and social burden. These diseases are associated with frequent physician visits and hospitalizations and are sometimes fatal.

Although data on digestive and liver conditions are collected on a regular basis, they are sometimes difficult to locate. Moreover, previous compilations of statistics on digestive diseases are lengthy or do not provide data on outpatients.[1,2] The American Gastroenterological Association publication, *The Burden of Gastrointestinal Diseases*, is a comprehensive report, but it is lengthy and has not been recently updated.[1] Herein, we provide a concise description of frequently used statistics displayed in tables comparing common gastrointestinal diagnoses. A publication on selected digestive diseases in the United States focused mostly on costs and does not provide data on symptoms and diagnoses for outpatient visits or on the incidence and prevalence of gastrointestinal cancers.[2]

Our goals were to collect and report the most recent statistics on deaths, symptoms, physician visits, and hospitalizations for common digestive and liver diseases. These data are unique because they are population based and are gathered from large national databases. This information should be a valuable reference for authors, grant applicants, funding agencies, and policy makers. Importantly, the data are likely to raise questions and lead to future research.

Materials and Methods

Gastrointestinal Causes of Death

Data on the leading causes of death were obtained from mortality tables from the Division of Vital Statistics, National Center for Health Statistics (Table 1). A total of 2,403,351 deaths in the United States were reported during the year 2000. Causes of death were reported on the basis of the 10th revision of the International Classification of Diseases (ICD-10; 1992). In constructing these tables, the underlying cause of death is ascertained from death certificate data and then coded according to the most recent revision of ICD-10 codes. ICD-10 codes were published by the World Health Organization in 1992 and have been used for coding and classifying causes of death since 1999. ICD-10 codes differ from ICD-9 codes in some ways, although the overall content is similar. ICD-10 has alphanumeric categories rather than numeric categories and

Abbreviations used in this paper: ICD, International Classification of Diseases; NAMCS, National Ambulatory Medical Care Survey; NIS, Nationwide Inpatient Sample; SEER, Surveillance, Epidemiology, and End Results.

0016-5085/04/$30.00
doi:10.1053/j.gastro.2004.01.025

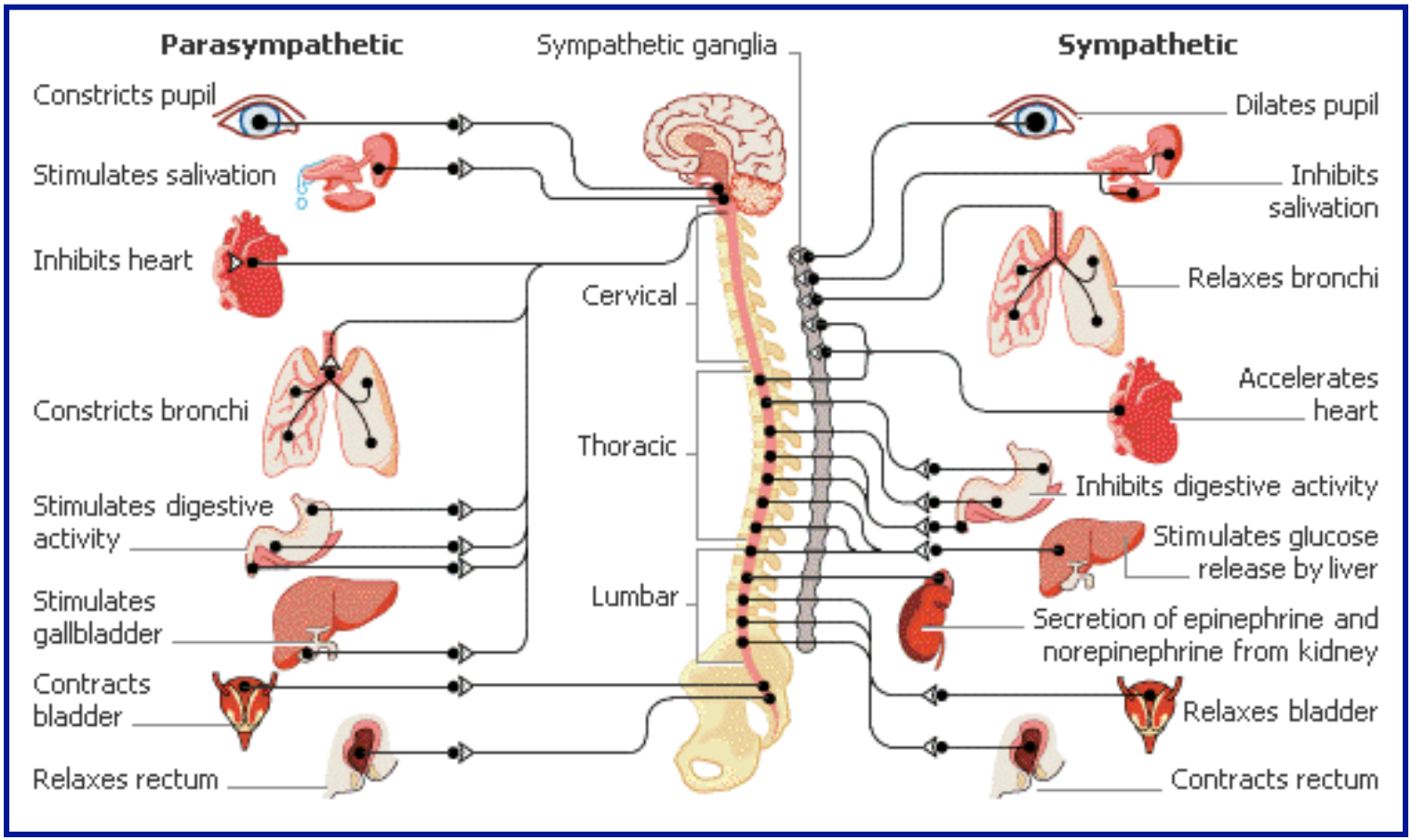
mechsense

Somatic vs. Visceral pain

- Pain can be felt all over the body
- Localisation of the stimulus is exact
- The feeling of pain is related to the nature of the stimulus (pricking, warm, etc.)
- Intensity related to extent of lesion
- Withdrawal reflexes and pain behaviour

- Pain does not arise in all viscera
- Stimuli are not always painful
- The feeling of pain is non-specific
- Diffuse localisation of pain
- Referred pain to somatic areas
- Accompanied by greater autonomic, emotional and motor responses

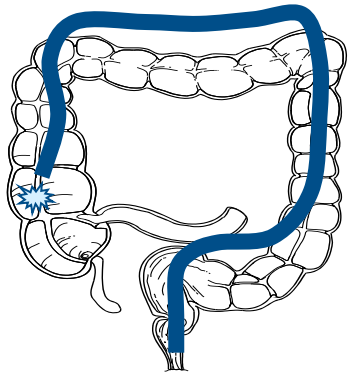
Parasympathetic & sympathetic Innervation

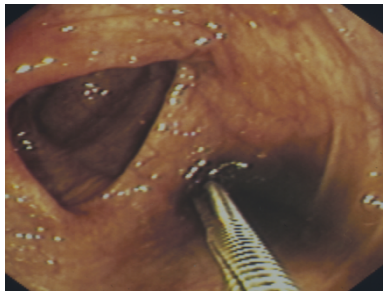


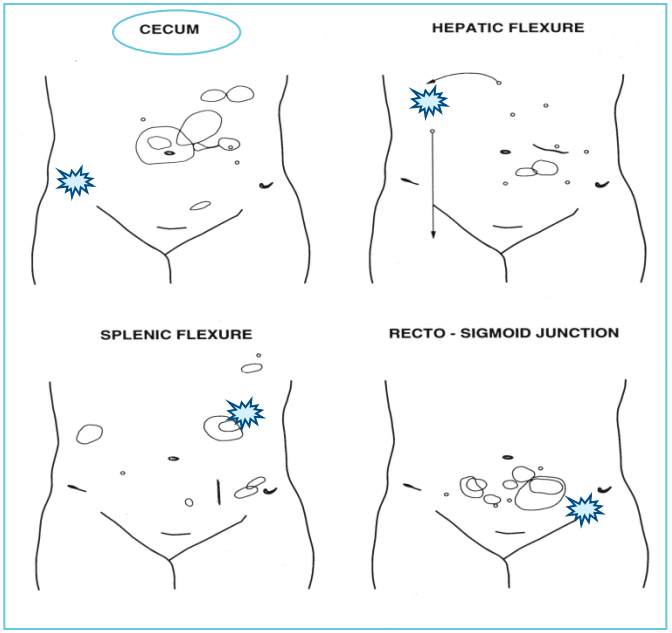
Location

- Complexity i neural structures explain differences in clinical pictures.
- Classical example is acute appendicitis:
  - Initial diffuse location in midline (primary visceral afferents)
  - Activation of autonomous system and ENS: nausea, sweat etc.
  - More localised pain (silent fibres) and muscle fibres
  - Cutaneous hyperalgesia
  - Transmural affection of peritoneum
  - Mc Burneys point

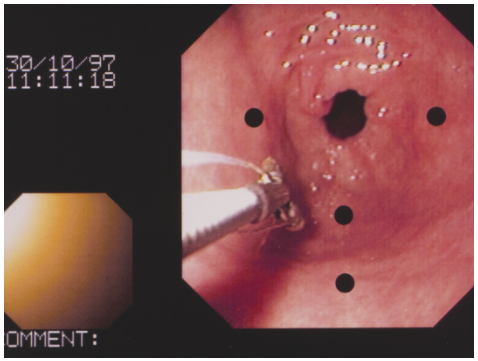
Location

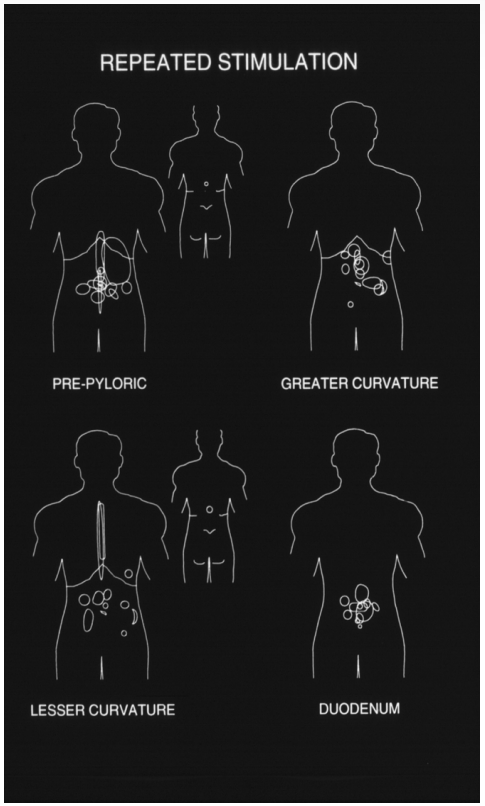





CECUM
HEPATIC FLEXURE
SPLENIC FLEXURE
RECTO - SIGMOID JUNCTION

Location





The symptoms in strictly localised diseases of the stomach (such as peptic ulcers) have great inter-individual variation. The clinician should be aware of the many clinical pictures and perform an endoscopy despite atypical pain referral.

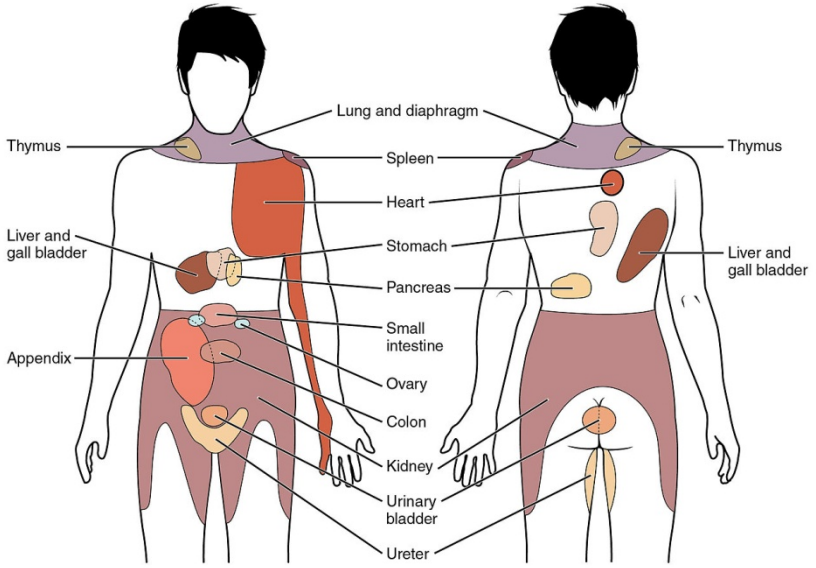
This is also valid for diseases in the small and large intestine

Pain referral

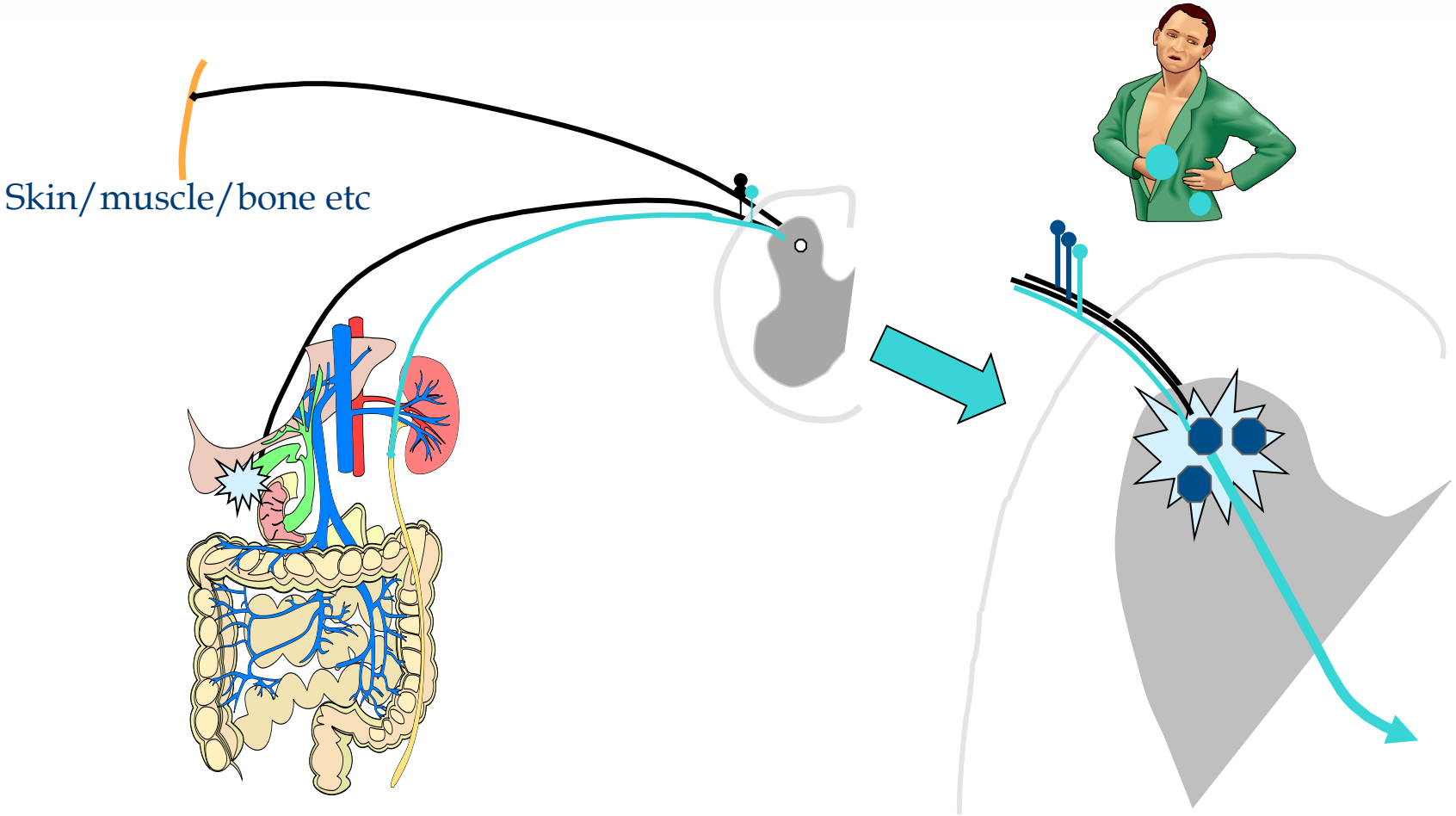
- Animal models
- Experimental human models
- Head 1893, described viscerotomes
- Example is pain in left arm due to heart ischemia

Viscero-somatic referrals

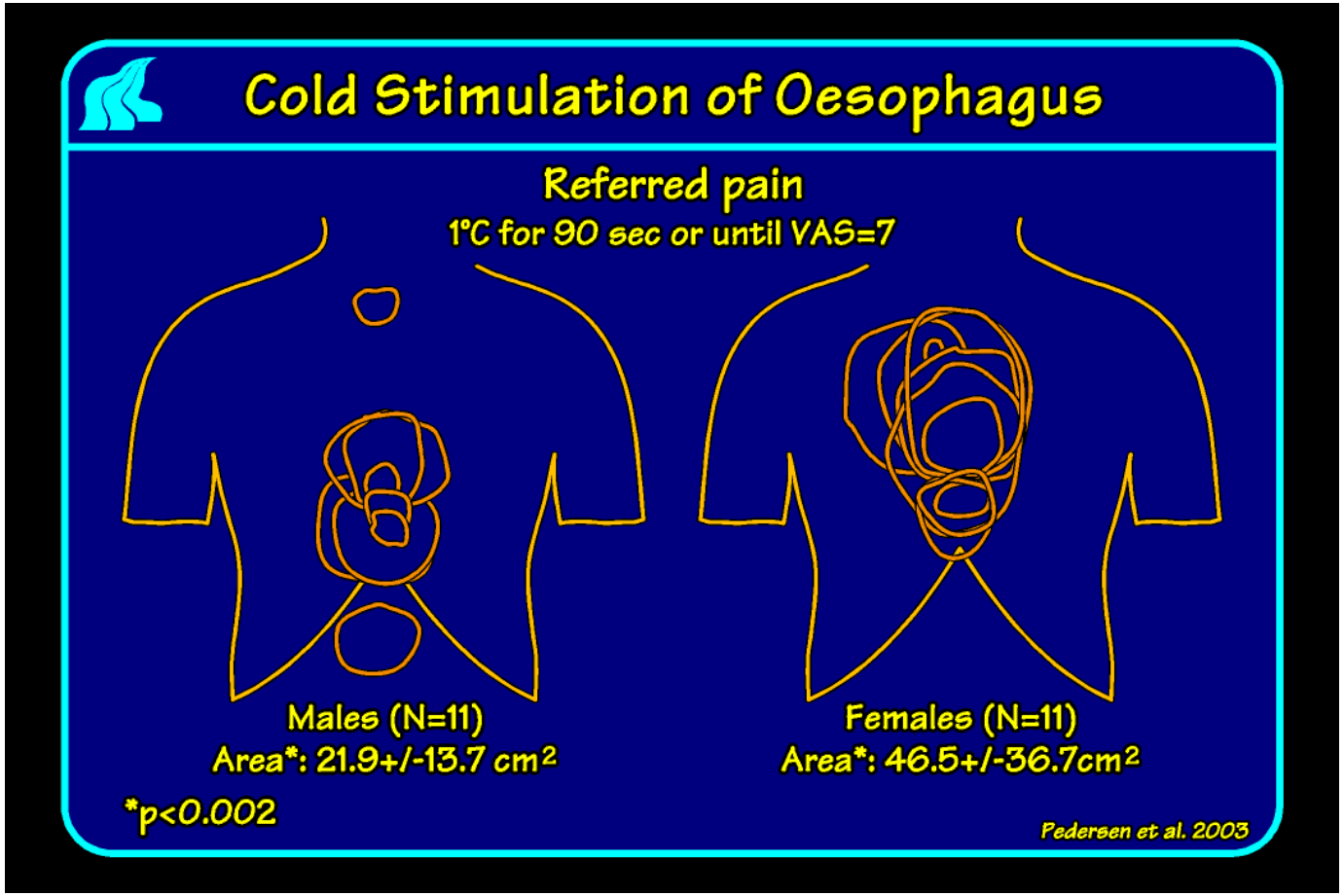
- Pharynx — Ear
- Heart — Left shoulder, arm
- Esophagus — Substernal
- Gallbladder — Shoulder
- Pancreas — Mid back



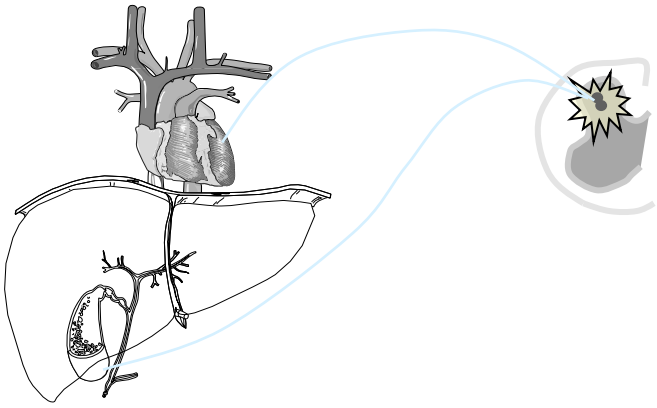
Schematic - pain referral

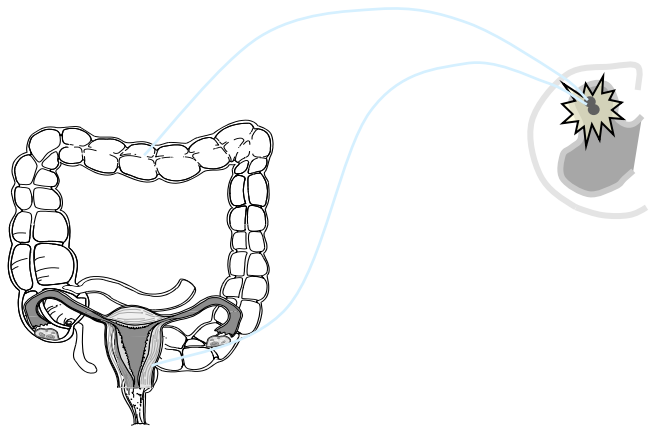


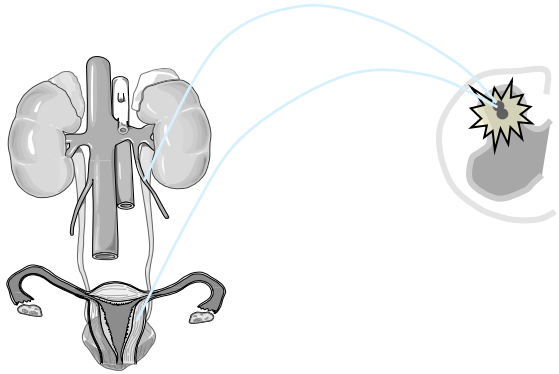
Viscero-somatic referral

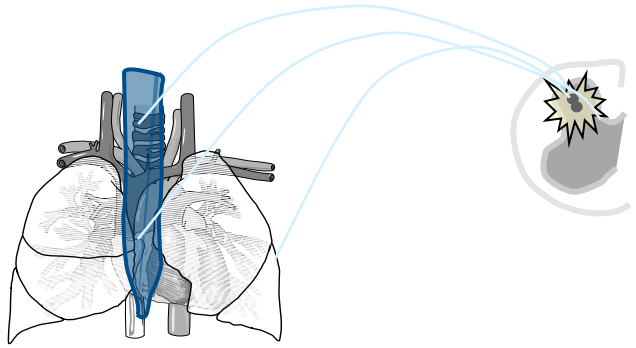


Viscero-visceral referral







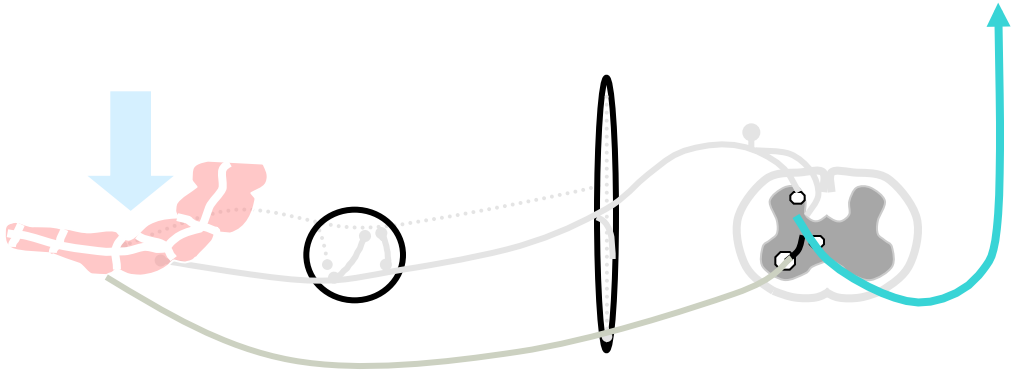


Todays agenda

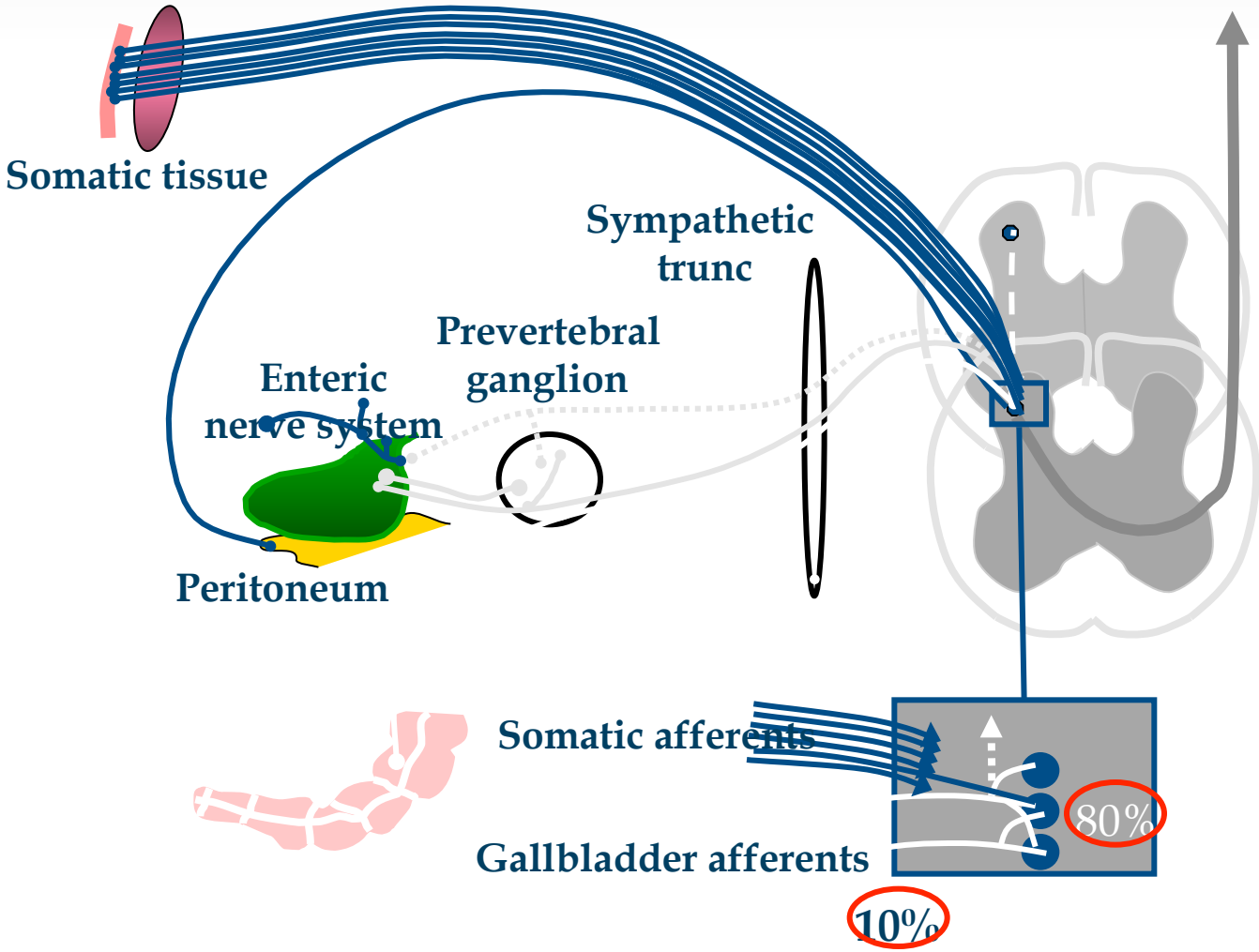
- Characterize and relate location, quality and referral of abdominal pain to underlying pathology.
- **Explain general characteristics of abdominal pain, like pain character and duration and involved triggering events.**
- Distinguish pain of visceral or peritoneal origin.
- Conduct an appropriate examination of an individual in abdominal pain.

Gut-brain Axis

- Peripheral level
  - Peripheral sensitization
- Spinal level
  - Hyperalgesia
  - Central sensitization
  - NMDA receptor
- Supraspinal level
  - Cortical plasticity



Primary afferents



Ascending transmission

Transmission through brainstem,medulla obl., pons, midbrain, to thalamus

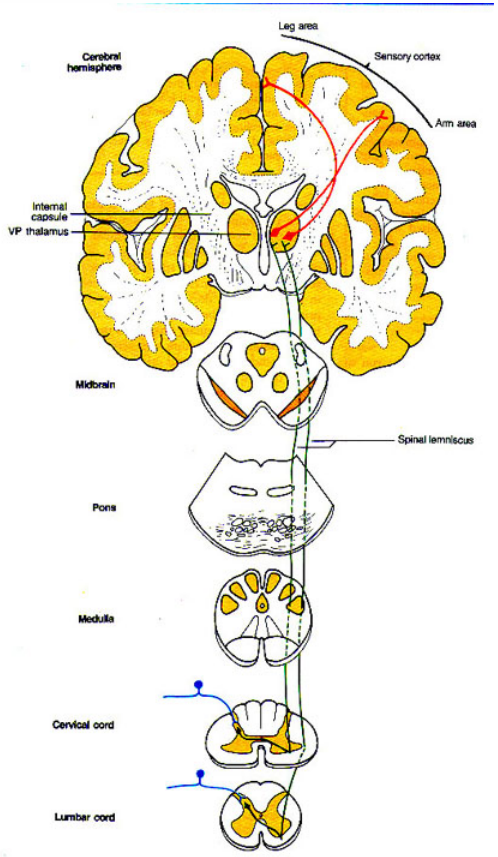
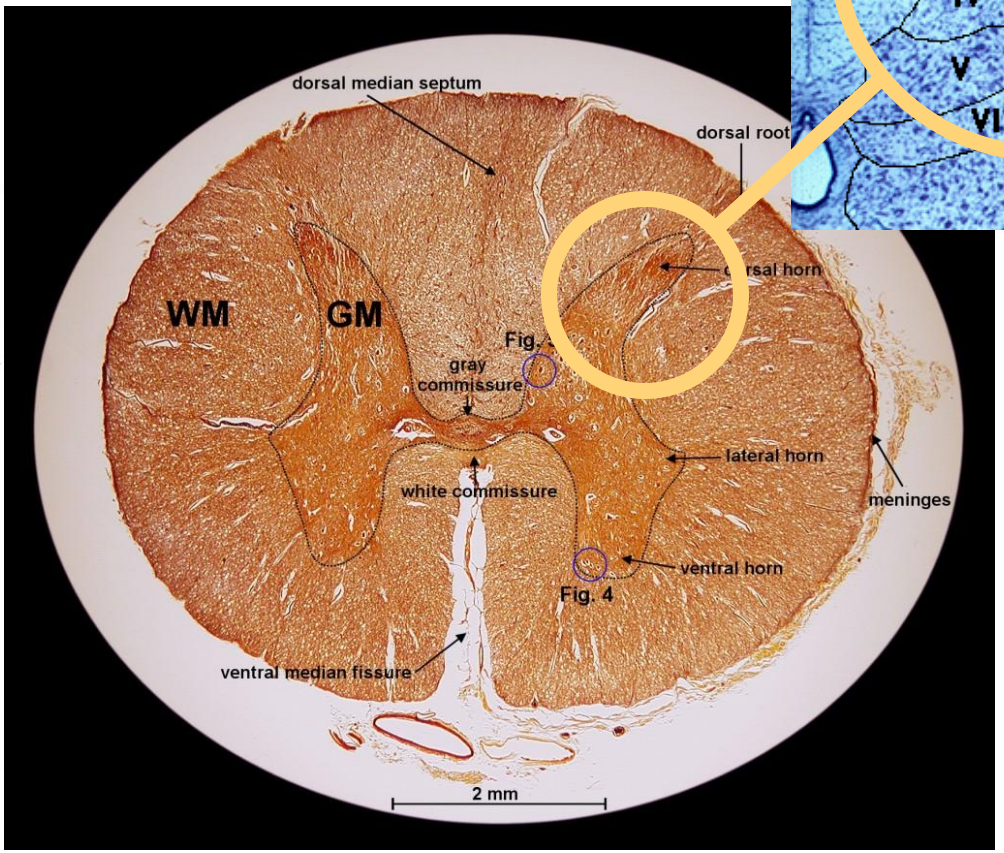
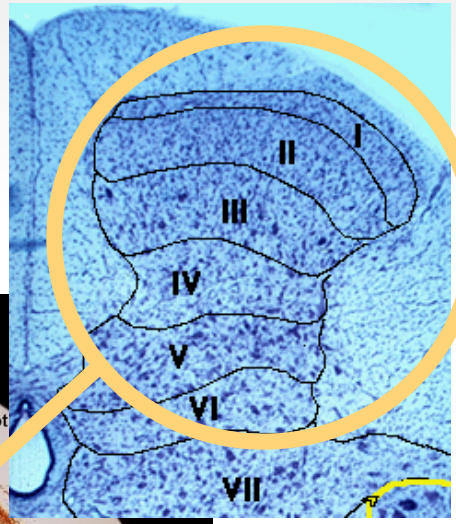


Fig. 5.15 **The spinothalamic tract system.**
The central pathways for pain, temperature, touch and pressure are illustrated.

The spinal level



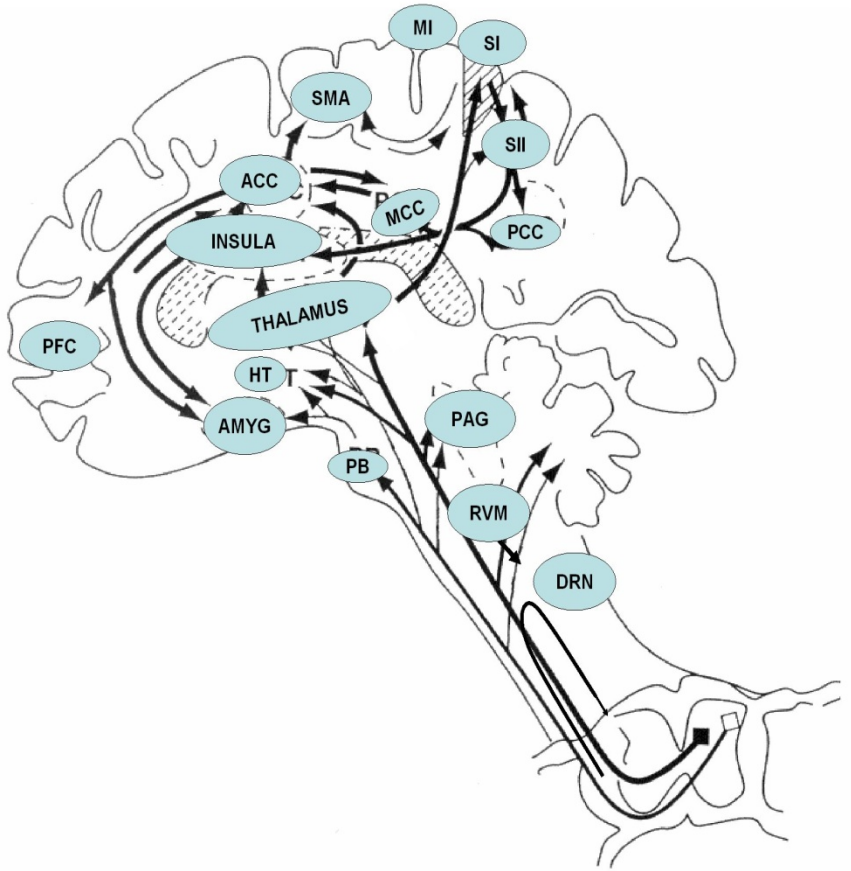


II: Nociceptive-specific neurons

V: Wide-dynamic neurons

mechsense

The supraspinal level



mechsense

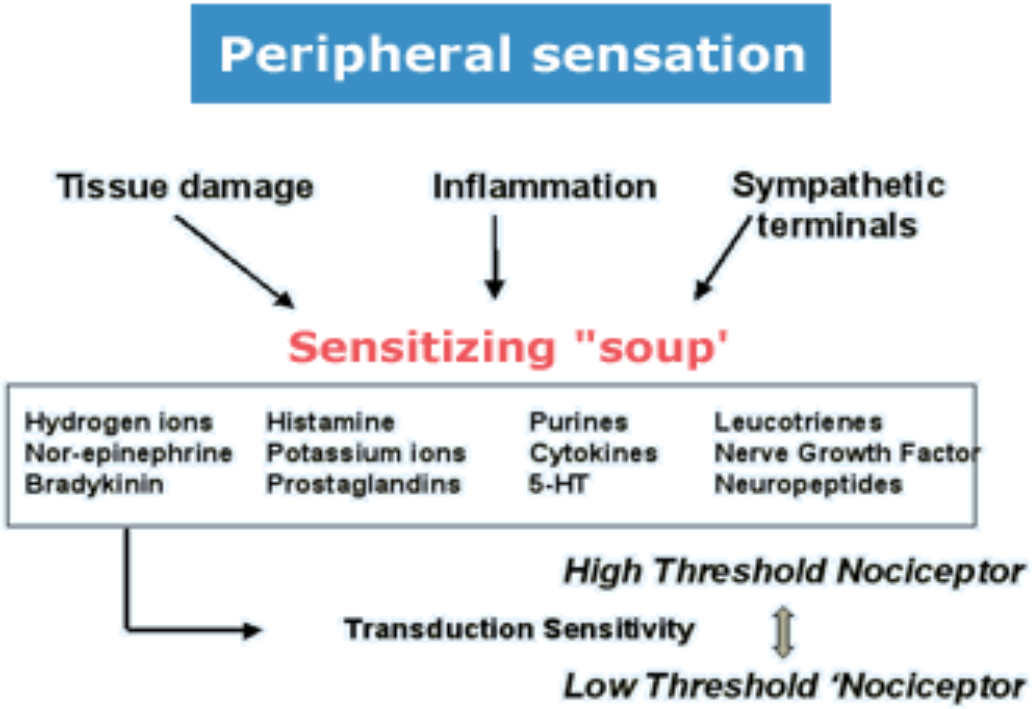
The Somatosensory Cortex

Peripheral sensitization

- Neurotransmitters are upregulated.
- LT and HT fibres are activated
- NGF: retrograd transport to the celle nucleus in the paravertebral ganglion.

  - It enhances the peptid formation,
  - Increases the number of ion-channels
  - Increases the number of receptors
- Silent fibres?

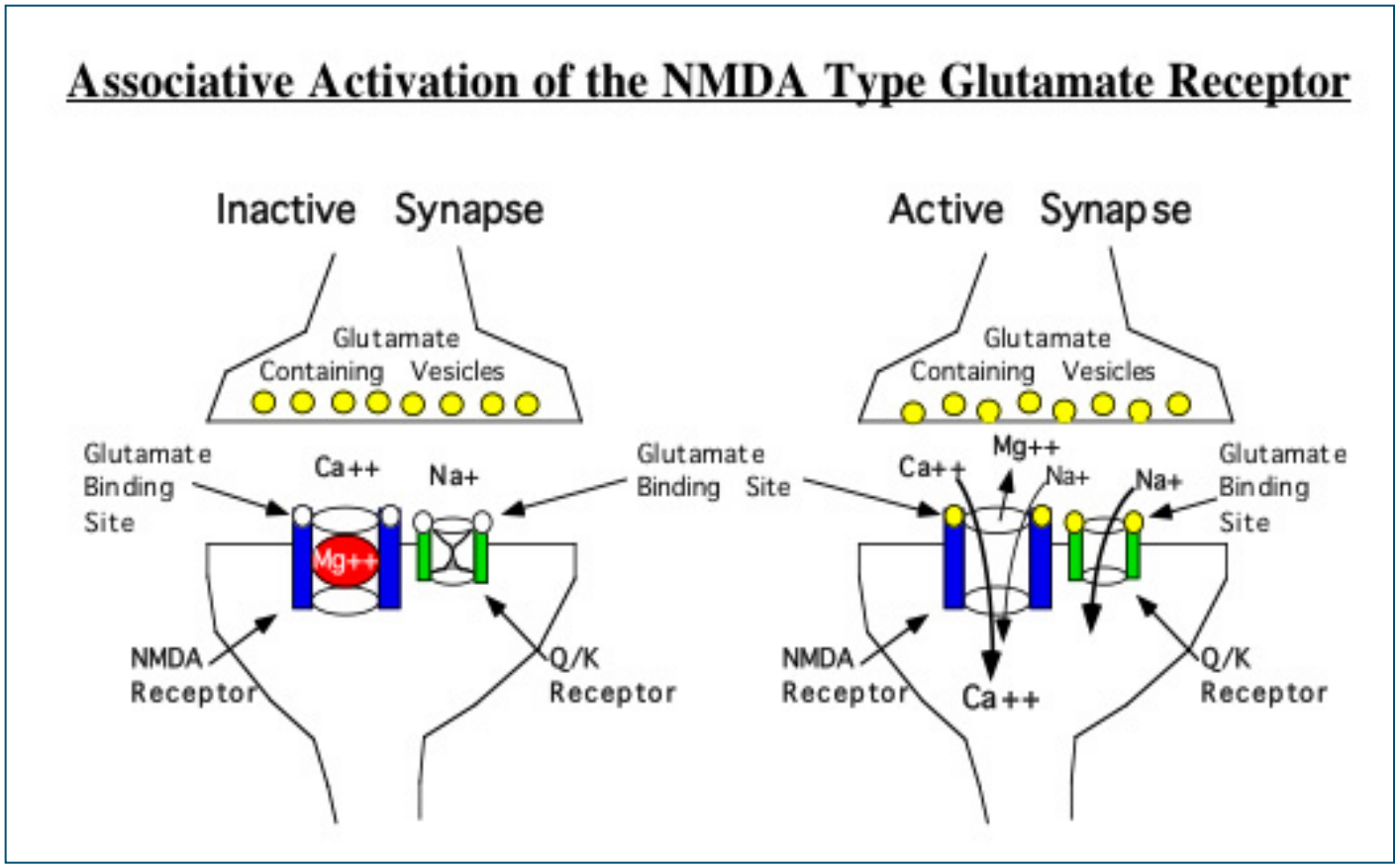
Inflammatory soup



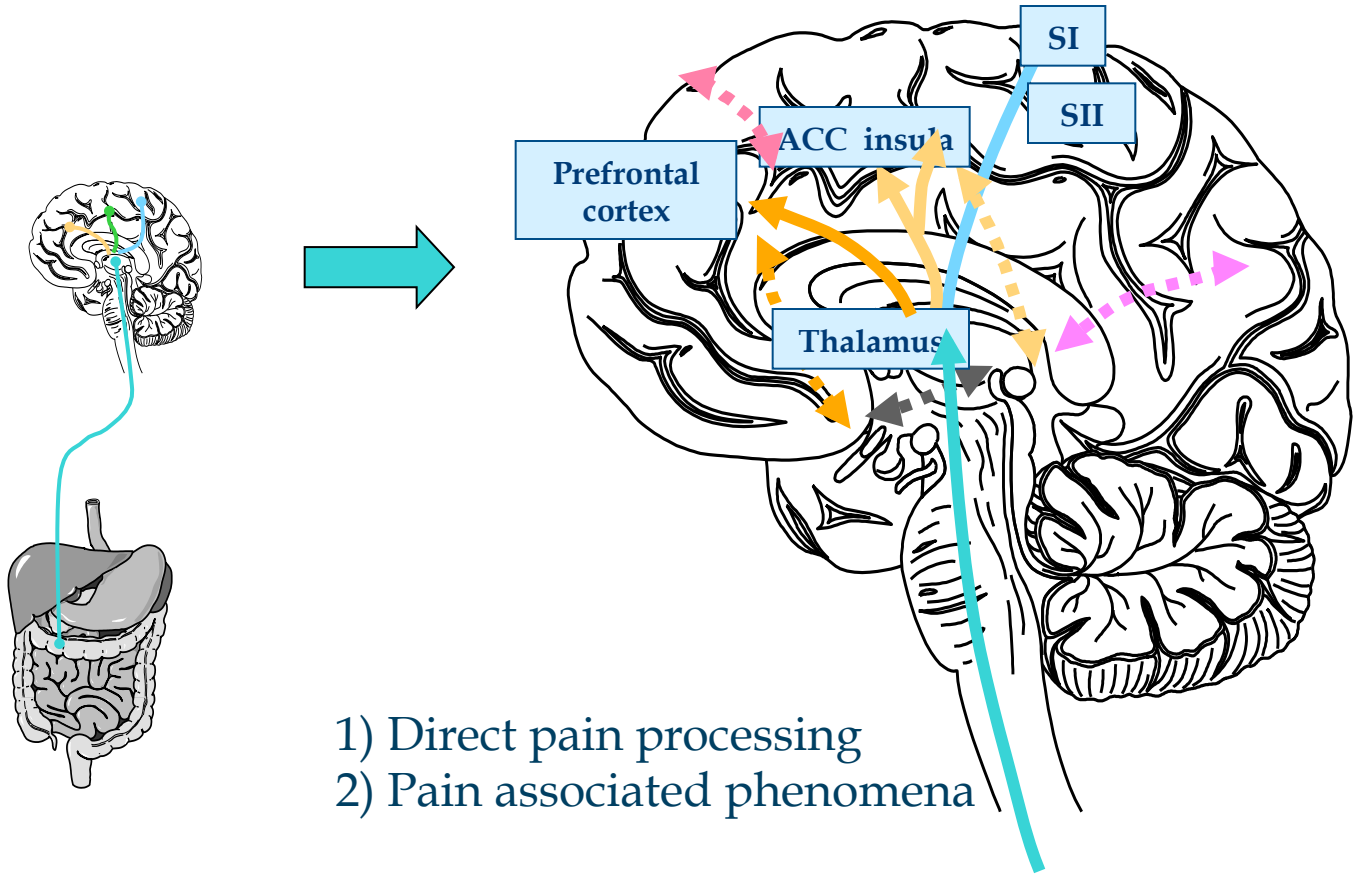
Central sensitization

- Substance P are released from the nerve fibres, creating a faster excitatory potential, and thus polarisation of the post synaptic cell
- Neurokinin 1 is activated through chronic pain, especially pain of neurogenic origin
- NMDA receptor is blocked by a Mg^{++} ion, but through stimulation, this is released, resulting in an open channel
- PKA (protein kinase A), PKC (protein kinase C), NOS(Nitrogenoxid synthease)
- Loss of inhibating interneurones, loss of GABA

Spinal level: NMDA receptor



Cortical level



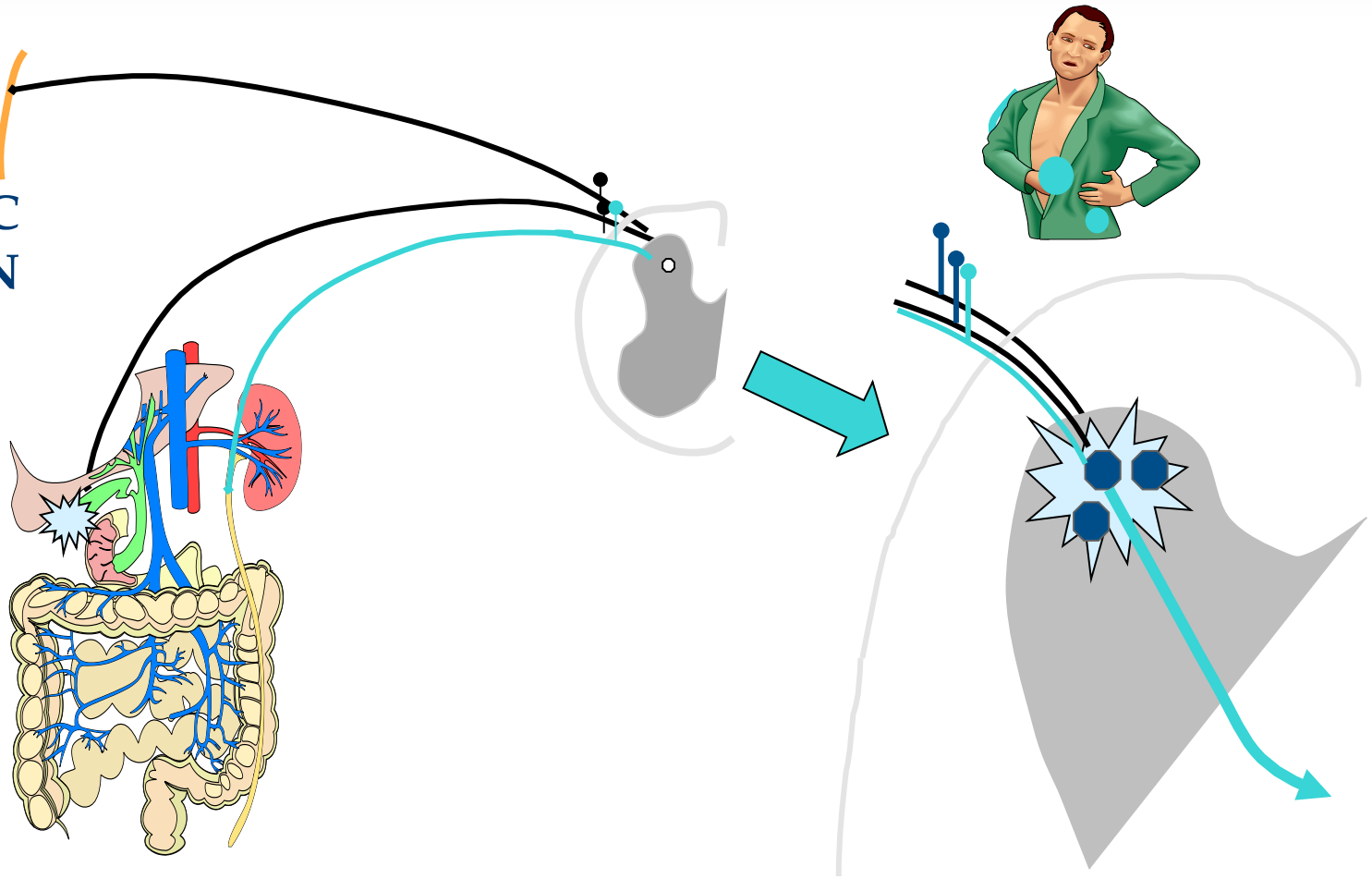
1) Direct pain processing
2) Pain associated phenomena

Todays agenda

- Characterize and relate location, quality and referral of abdominal pain to underlying pathology.
- Explain general characteristics of abdominal pain, like pain character and duration and involved triggering events.
- **Distinguish pain of visceral or peritoneal origin.**
- Conduct an appropriate examination of an individual in abdominal pain.

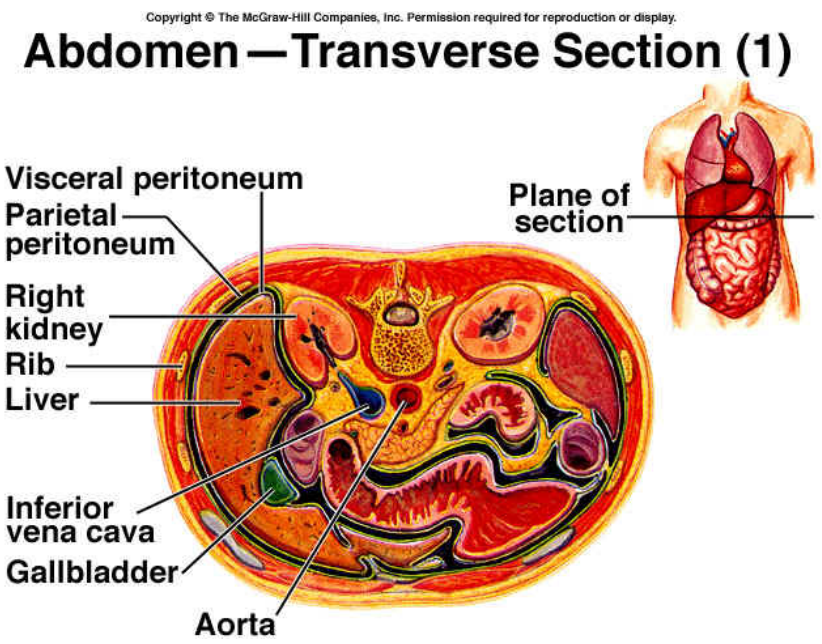
Distinguish pain from peritoneum

PERITONEUM
SOMATC
INNERVATION
ORGANOTOPIC
LOCALISATION



Peritoneum parietale (somatic innervation)

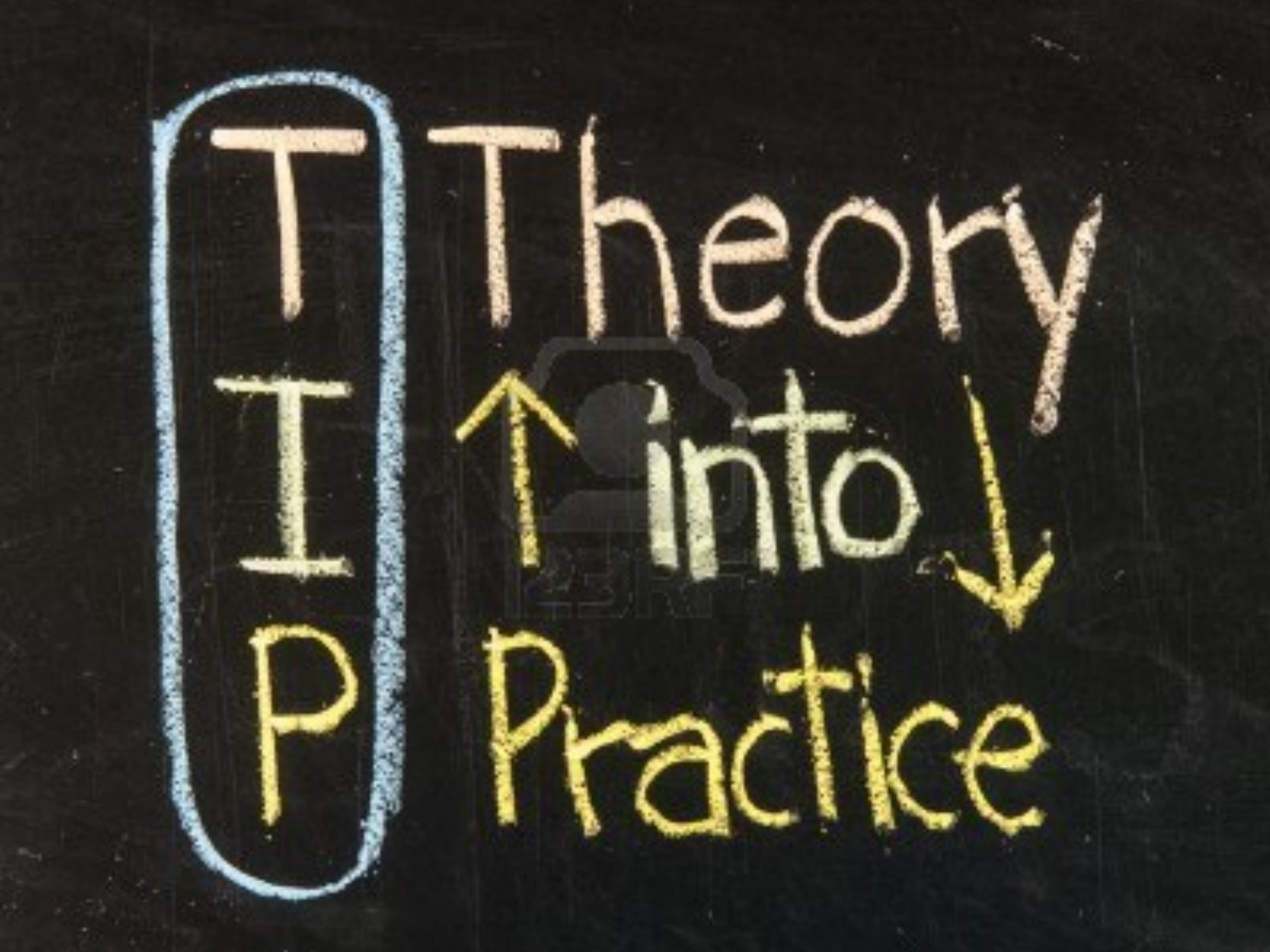
- Peritoneum parietale
- Embryology mesoderm
- Peritoneum precise localisation
- Covers liver capsula (metastasis)



Take home messages

- Visceral pain differs from somatic pain
- Involvement of autonomus nervous system
- Poor organotopic localisation
- Pain referrals
- Segmental overlap
- Peritoneum/pleura parietale receives somatic innervation

Pharmacological options???

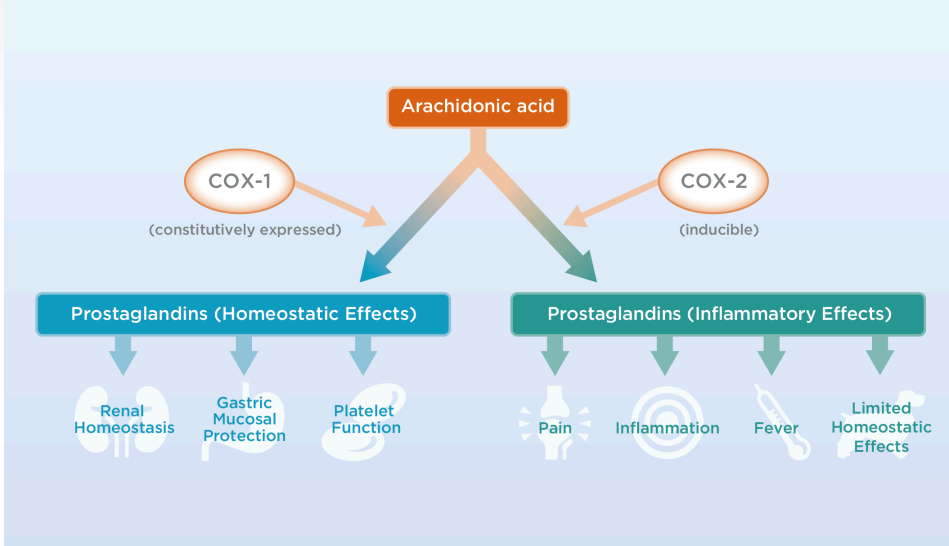

T
I
P
Theory
into
Practice

Analgesics in the periphery

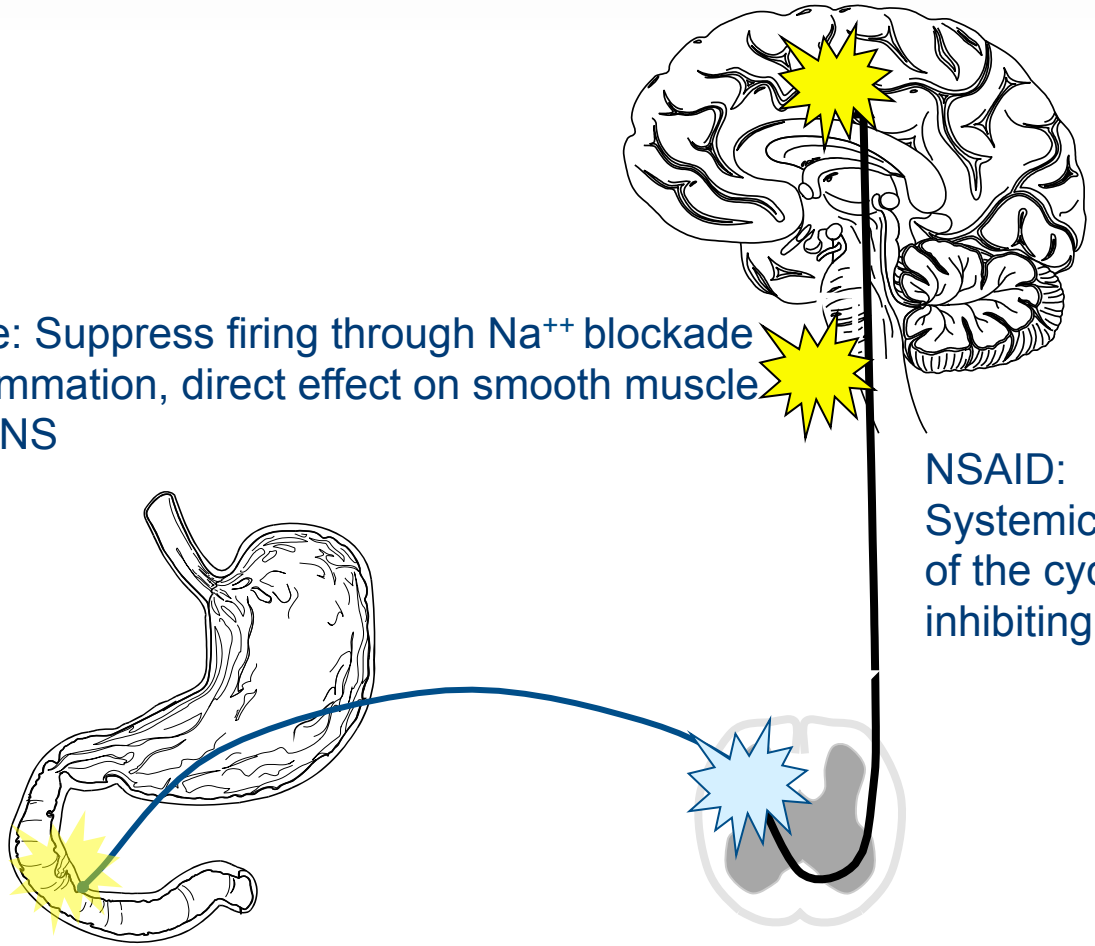
- Lidocain
- Bupivacaine
- Paracetamol
- NSAIDS
- Opioids
- Specific antagonists (TRPV, Nk, NGF, Glutamate)

NSAIDS

- COX inhibition
  - Finadyne: *Flunixine*
  - Equipalazone: *Phenylbutazone*
  - Metacam*: Meloxicam*
  - Rimadyl: *Carprofen*
- COX 2 inhibition:
  - Equioxx: *Firocoxib*
  - Previcox*: Firocoxib*



Lidocaine and NSAIDs



Lidocaine: Suppress firing through Na^{++} blockade
Anti-inflammation, direct effect on smooth muscle cells in ENS

NSAID:
Systemic (incl CNS) inhibition of the cyclooxygenase inhibiting formation of prostaglandins

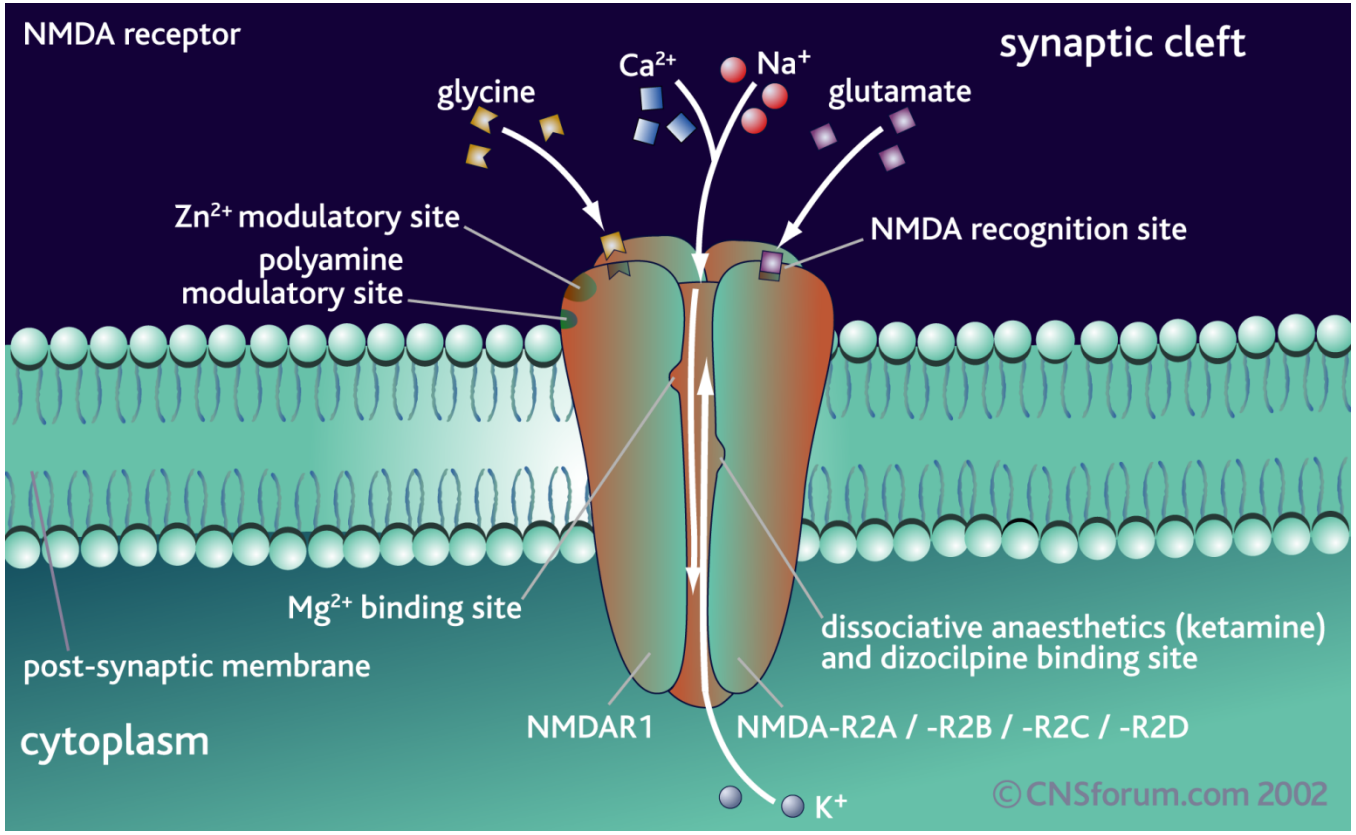
Peripheral effects

Equine medicine:
Malone 2006
Brianceau 2002
Merck Vet Journal

Analgesics in the spinal cord

- NSAID
- NMDA- antagonist
- Opioids
- Noradrenergics
- Gabapentin/pregabalin

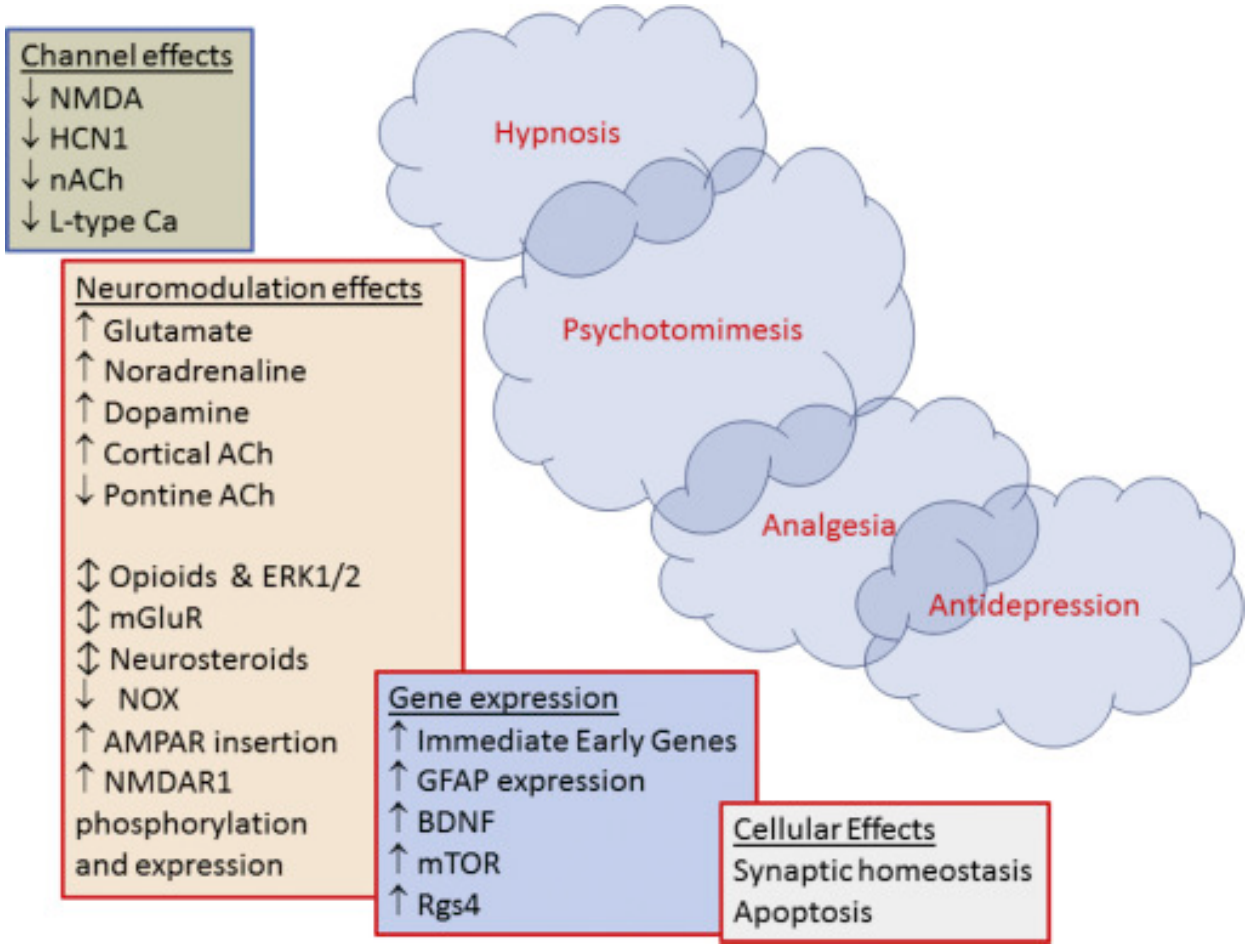
NMDA receptor



NMDA-antagonism

- NMDA-antagonist
  - Ketalar: *Ketamine*
  - Zoletil: *Tiletamine + zolazepam*
  - Methadone
  - Dextrometorphane

Multiple mechanisms of ketamine

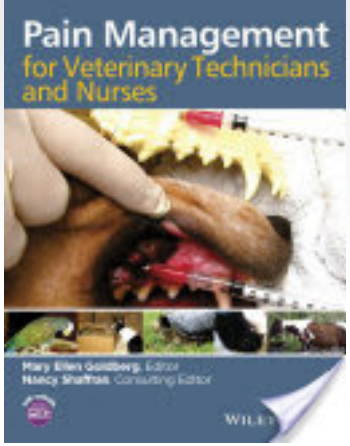


Sleigh 2014

Analgesics and descending inhibition

- Opioids
- SSRI/NSRI
- adrenergics
- gabapentin/pregabalin

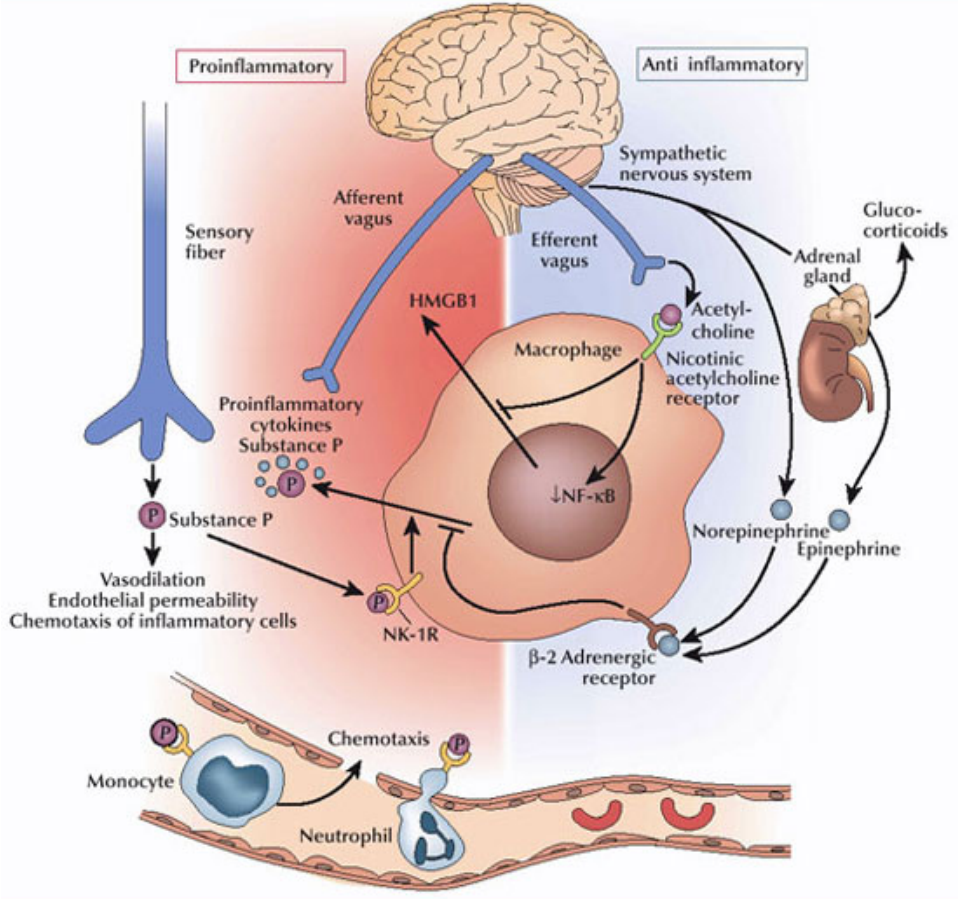
α-2-adrenergic receptor agonists



- α-2 adrenergics
  - Domitor: *Medetomidine*
  - Domosedan: *Demetodine*
  - Rompun: *Xylazine*
  - Clonidine

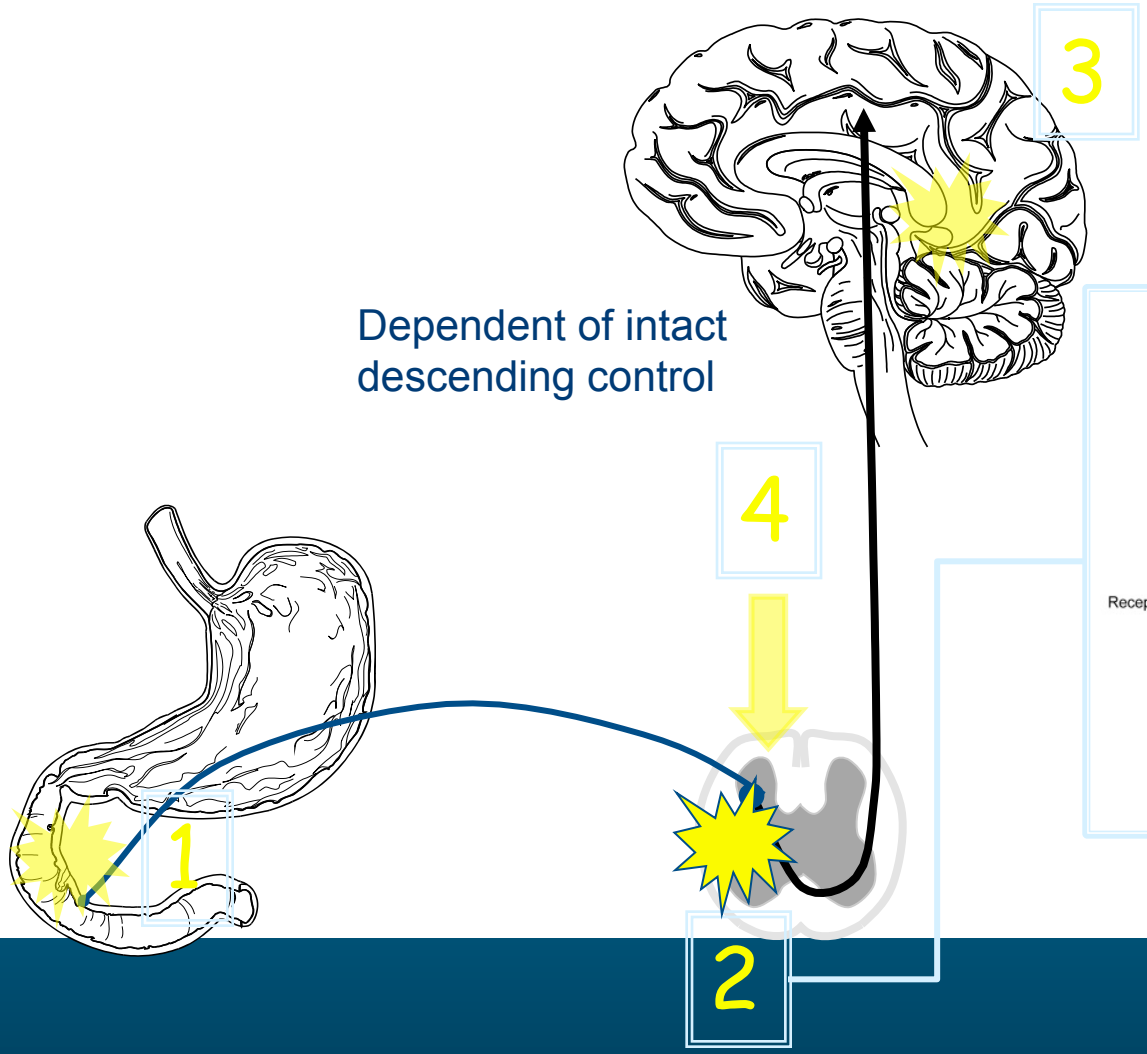
Antagonised with revivon, antisedan, temgesic

Neuroinflammation

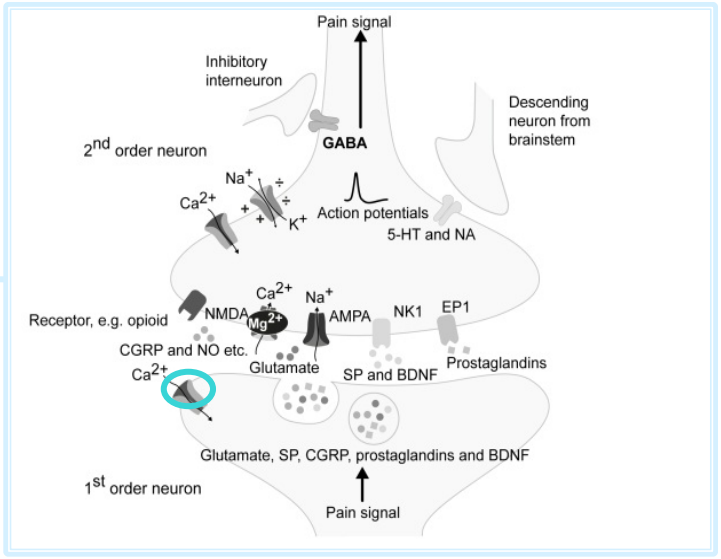


Gabapentinoids
Noradrenergics
Cannabinoids

Anticonvulsants (gabapentinoids)



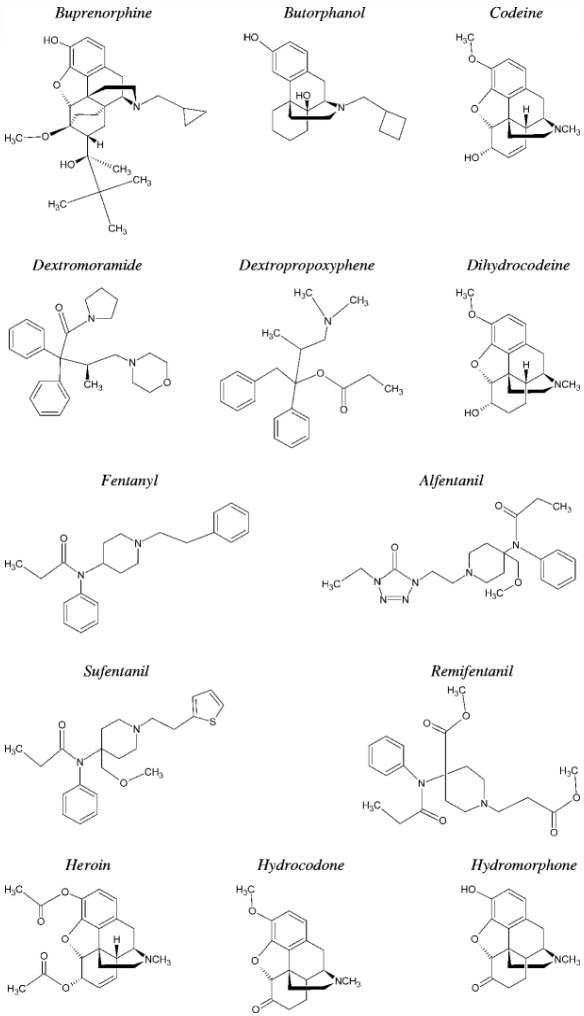
Dependent of intact descending control

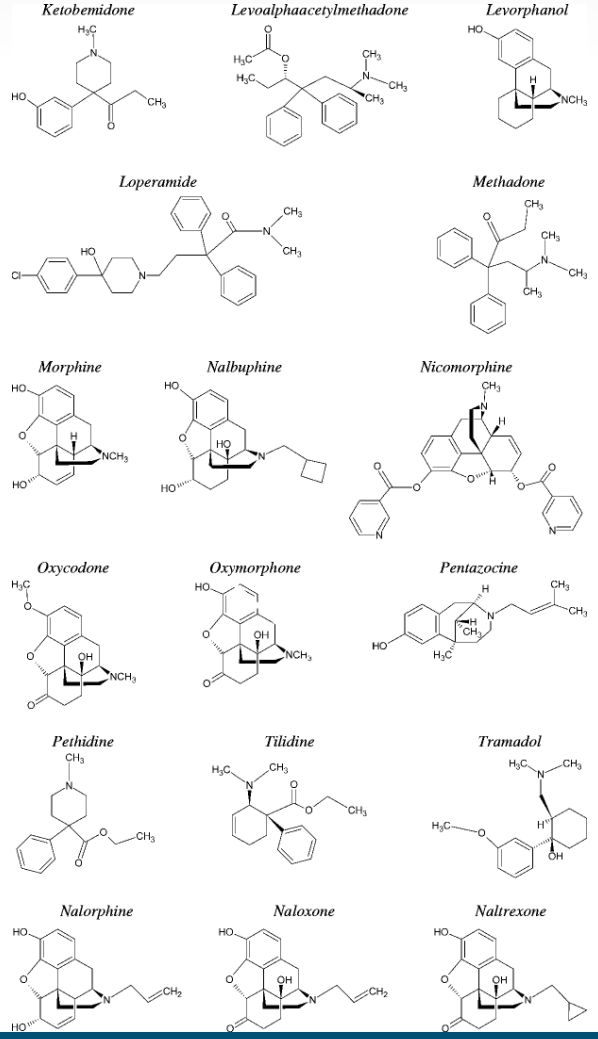


Inhibit calcium channels

mechsense

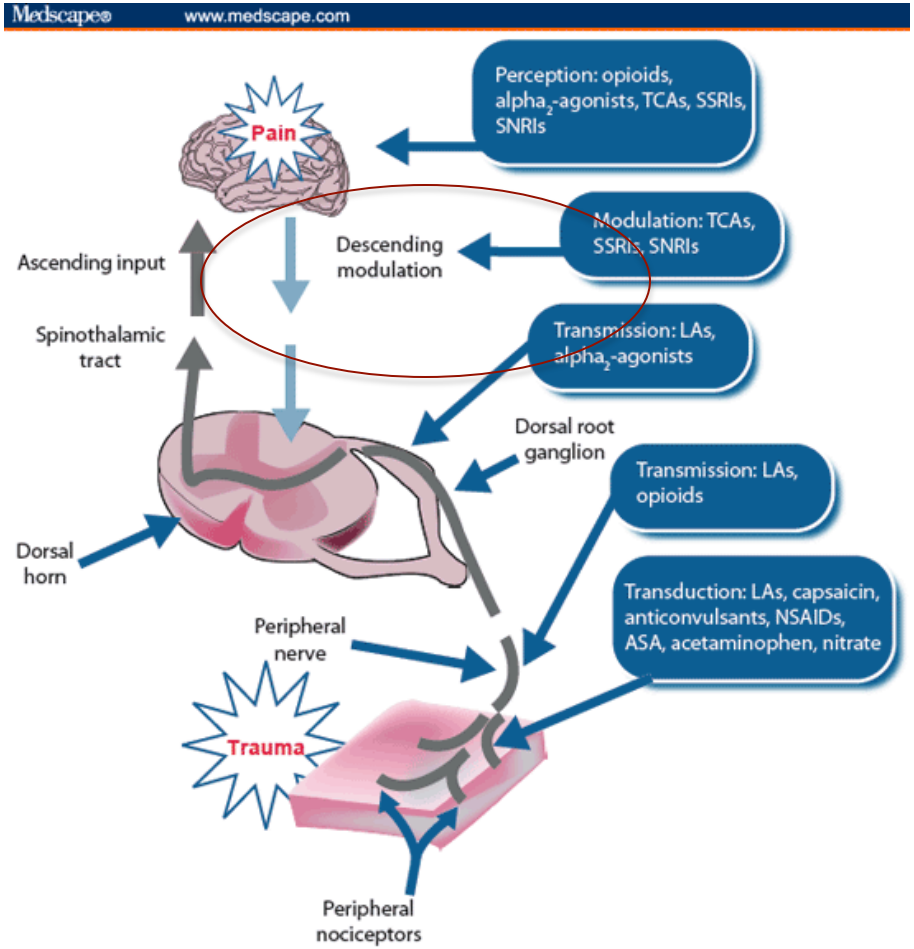
Opioids



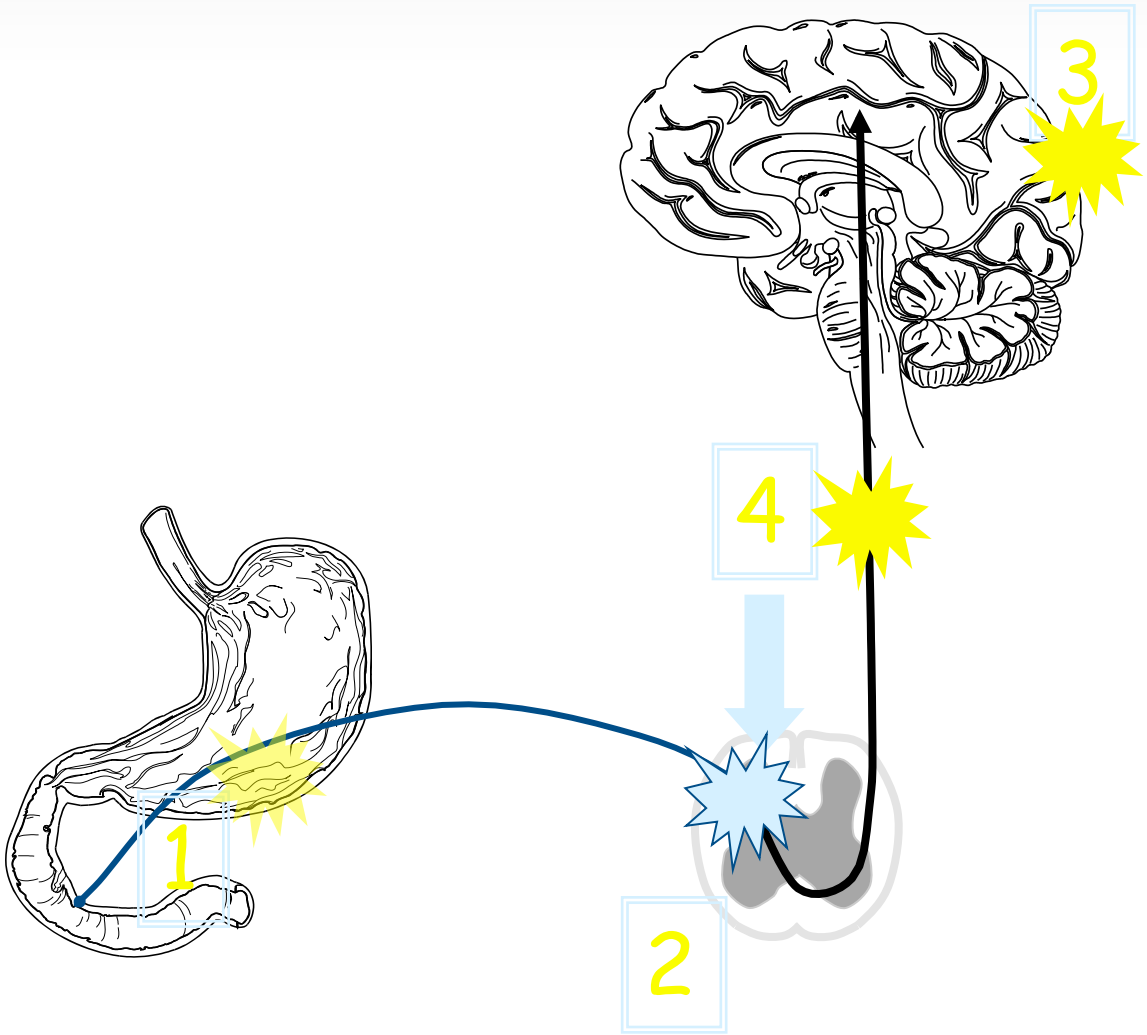


mechsense

Mechanisms of opioids



Opioids

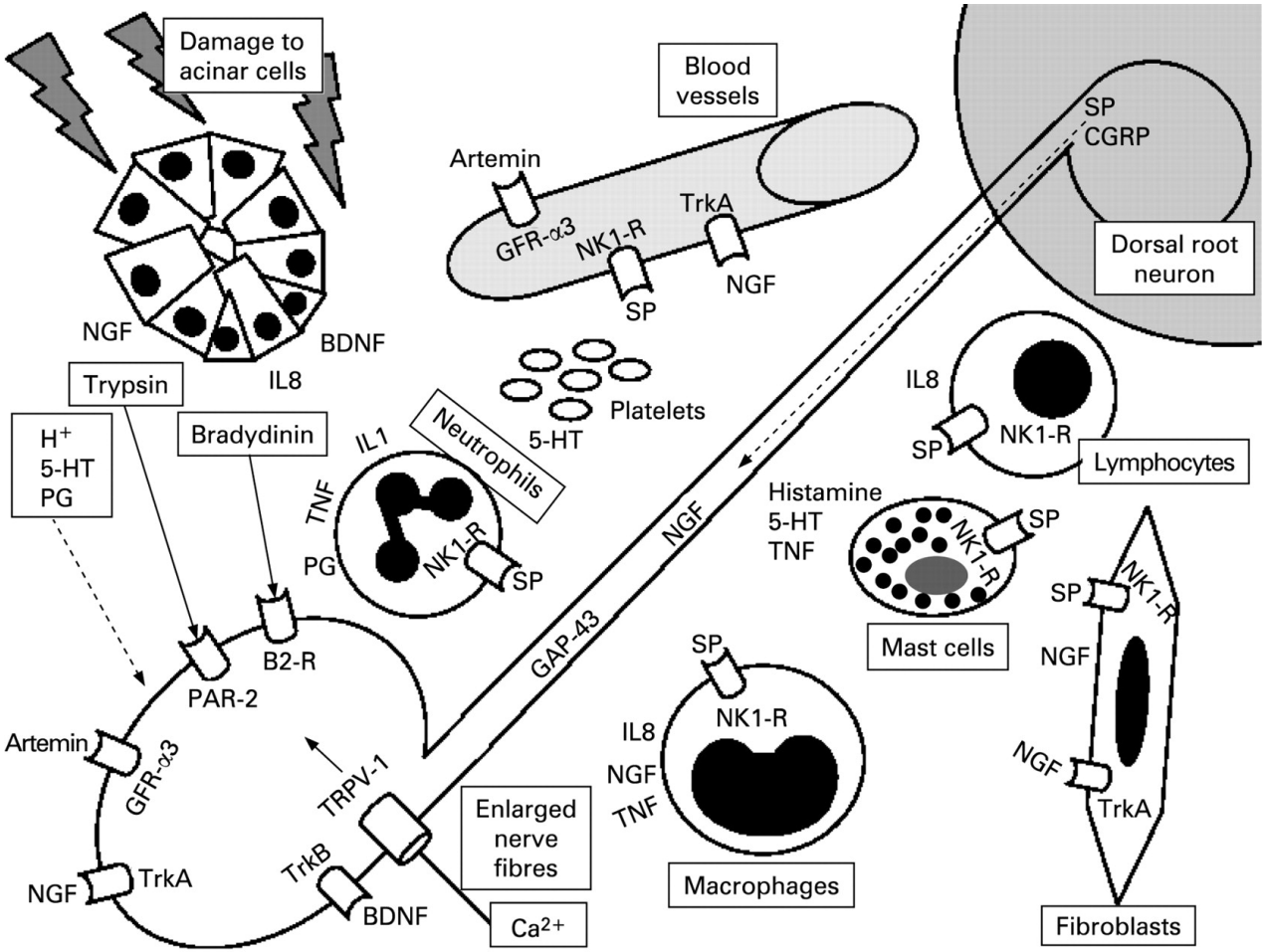


Staahl et al. Basic Clin Pharmacol Toxicol 2011
Lelic et al. J Clin Neurophysiol 2011

Analgesics and the brain

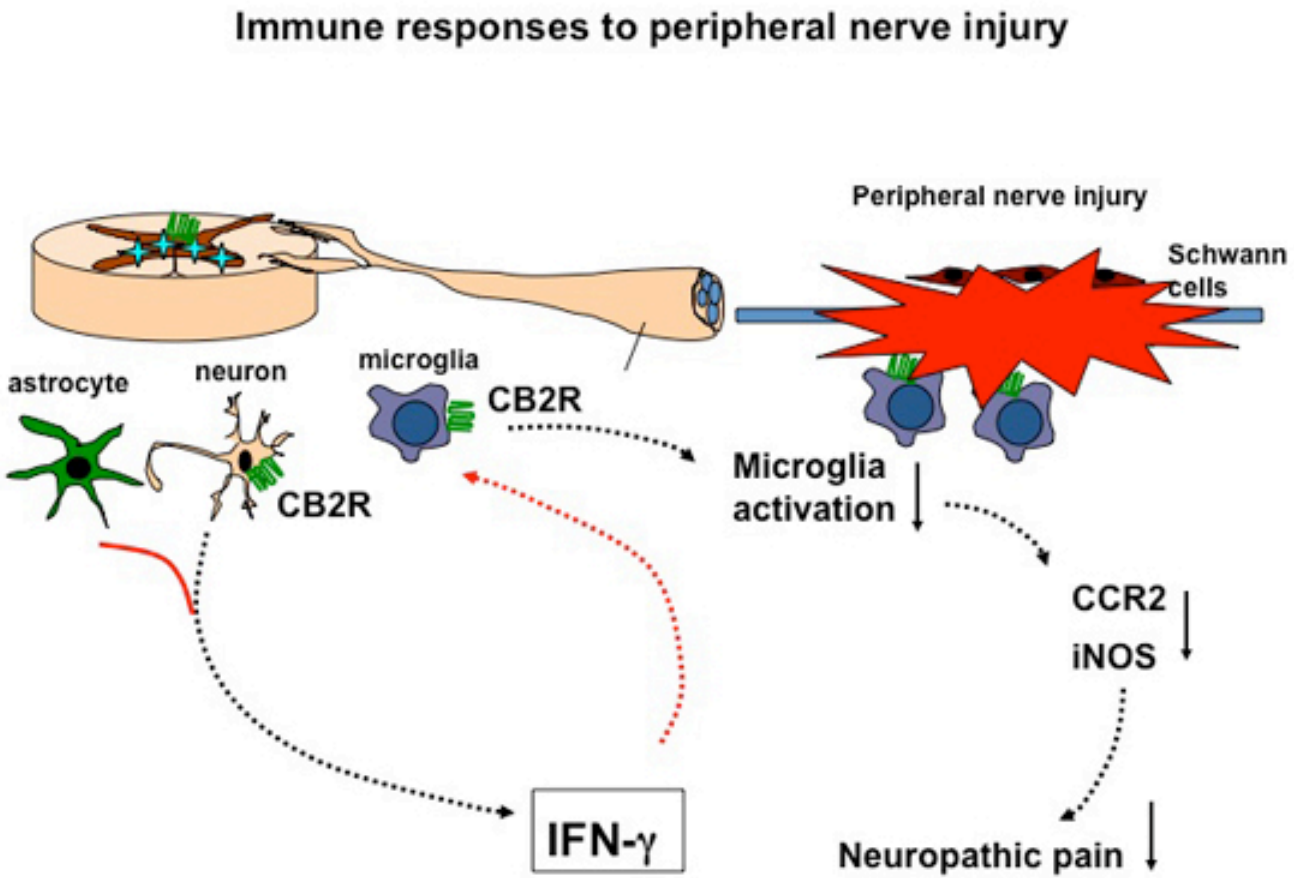
- NSAID
- Paracetamol
- Opioids
- SSRI/SNRI/TCA
- Pregabalin/gabapentin
- Cannabinoids

Neuropathic pain

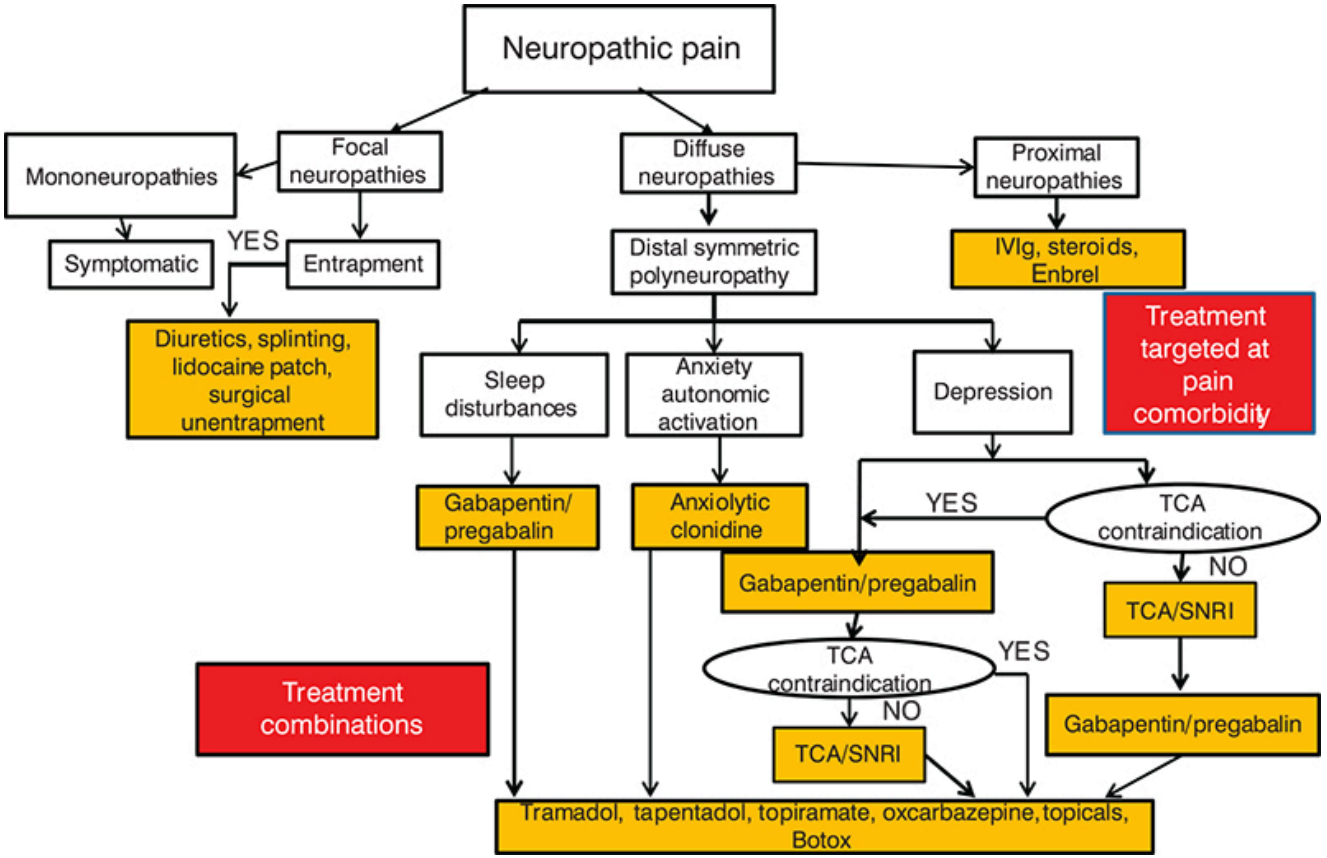


Drewes et al. 2010

The role of microglia

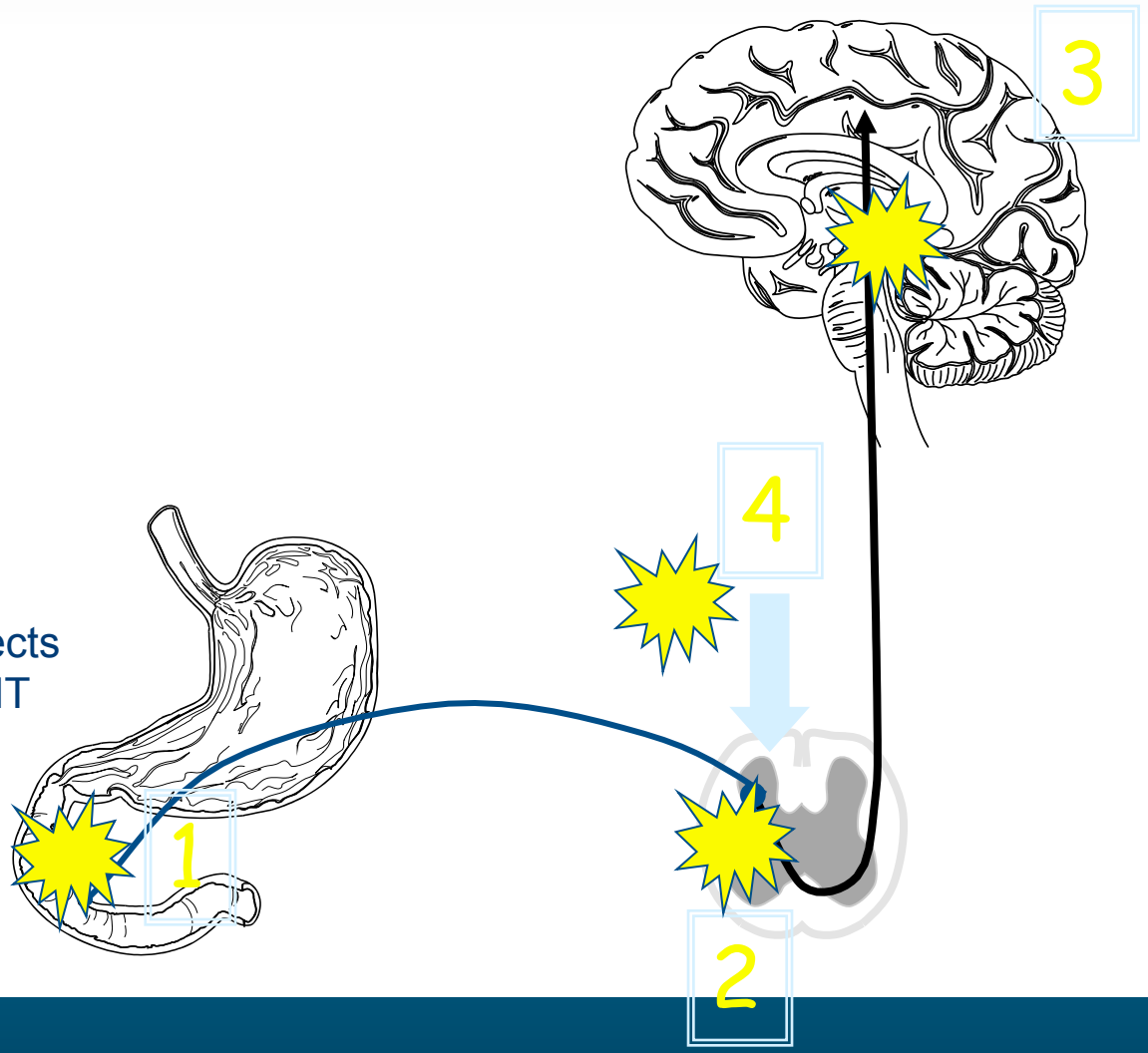


Treatment of neuropathic pain

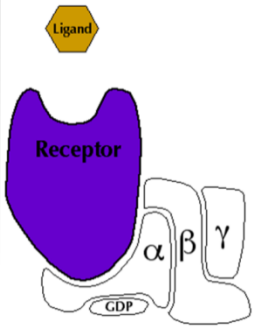


Tricyclic antidepressants and SSRI/SNRI

Peripheral effects
adenosine, 5HT



mechsense



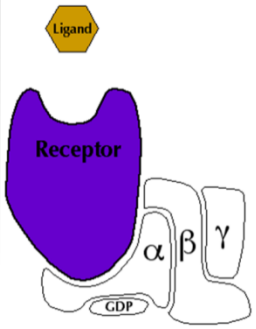
Receptor profile

	Neurotransmitter reuptake blockade						Receptor blockade		
	5-HT	Norepinephrine	Dopamine	α_1	α_2	H_1	Ach	5-HT_{1A}	5-HT_2
Tricyclic antidepressants									
Amitriptyline	+++++	+++	−	+++	+	++++	+++	+	+++
Imipramine	++++	+++++	−	++	+	++++	++	++	++
Desipramine	+++	+++++	−	++	+	++	++	−	−
Clomipramine	+++++	+++	−	++		+++	++	−	−
SSRIs									
Fluoxetine	+++++	++	−	−	−	−	−	−	−
Paroxetine	+++++	+++	+−		−	0	++	−	−
Sertraline	+++++	+	+++	++	+	0	+	−	−
Citalopram	+++++	−	0	+	+	+	0	−	−
SNRIs									
Venlafaxine	++++	+	−	0	0	0	0	0	0
Duloxetine	+++++	++++	+	−	−	−	−	−	−
Atypical agents									
Bupropion	0	+	+	−	−	−	0	−	−
Nefazodone	++	++	++	+++	−	++	−		+++
Mirtazapine[a]	−	0	0	+		++++	+		+++
Azapirones									
Buspirone	0	0	0	0	0	0	0	++	0

Camilleri et al. Gastroenterol 2006;130:1421-34

Anti-depressants

- SSRI / SNRI
- Prozac: *Fluoxetine*
- Venlafaxine
- TCA
- Clomipramine: *Clomicalm*

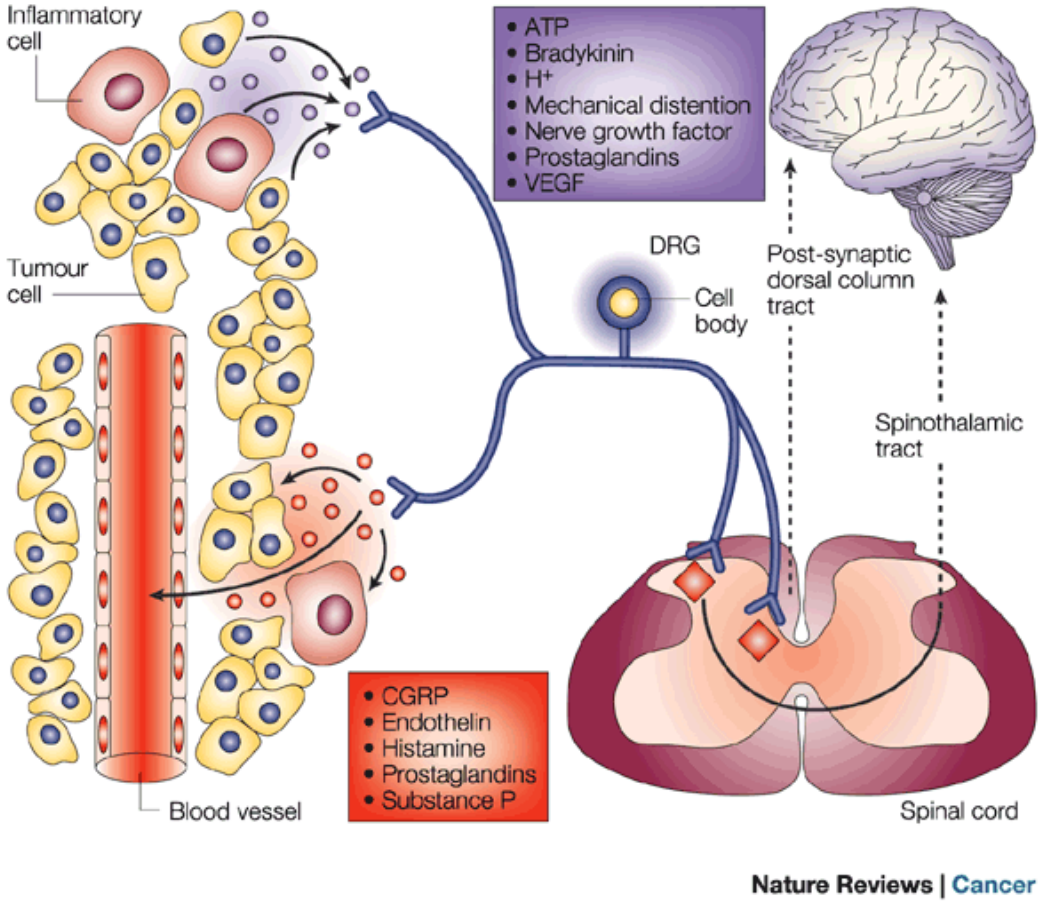


Receptor profile

	Neurotransmitter reuptake blockade						Receptor blockade		
	5-HT	Norepinephrine	Dopamine	α_1	α_2	H_1	Ach	5-HT_{1A}	5-HT_2
Tricyclic antidepressants									
Amitriptyline	+++++	+++	−	+++	+	++++	+++	+	+++
Imipramine	++++	+++++	−	++	+	++++	++	++	++
Desipramine	+++	+++++	−	++	+	++	++	−	−
Clomipramine	+++++	+++	−	++		+++	++	−	−
SSRIs									
Fluoxetine	+++++	++	−	−	−	−	−	−	−
Paroxetine	+++++	+++	+−		−	0	++	−	−
Sertraline	+++++	+	+++	++	+	0	+	−	−
Citalopram	+++++	−	0	+	+	+	0	−	−
SNRIs									
Venlafaxine	++++	+	−	0	0	0	0	0	0
Duloxetine	+++++	++++	+	−	−	−	−	−	−
Atypical agents									
Bupropion	0	+	+	−	−	−	0	−	−
Nefazodone	++	++	++	+++	−	++	−		+++
Mirtazapine[a]	−	0	0	+		++++	+		+++
Azapirones									
Buspirone	0	0	0	0	0	0	0	++	0

Camilleri et al. Gastroenterol 2006;130:1421-34

Cancer pain overview



Summarize…..

- Pain can be modulated at all levels
- Combination therapy are strategic
- Mechanism based undertanding of the different analgesics favor the proffessional pain management

Questions

Questions