Pijnmedicatie & Farmacologie

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UZA
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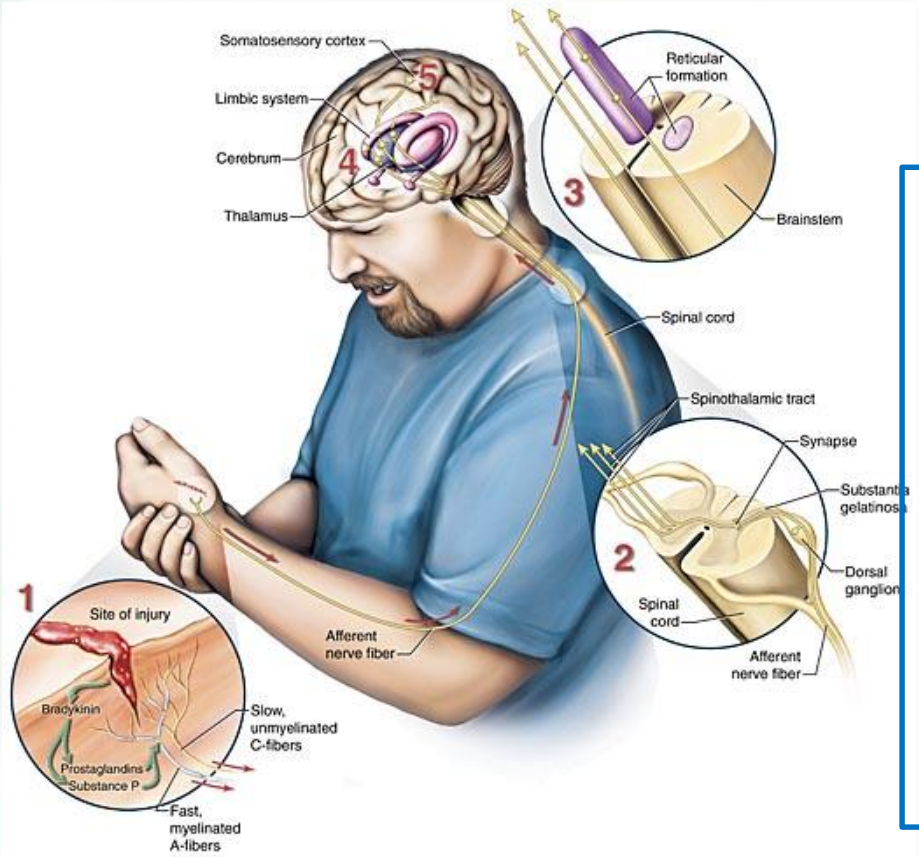
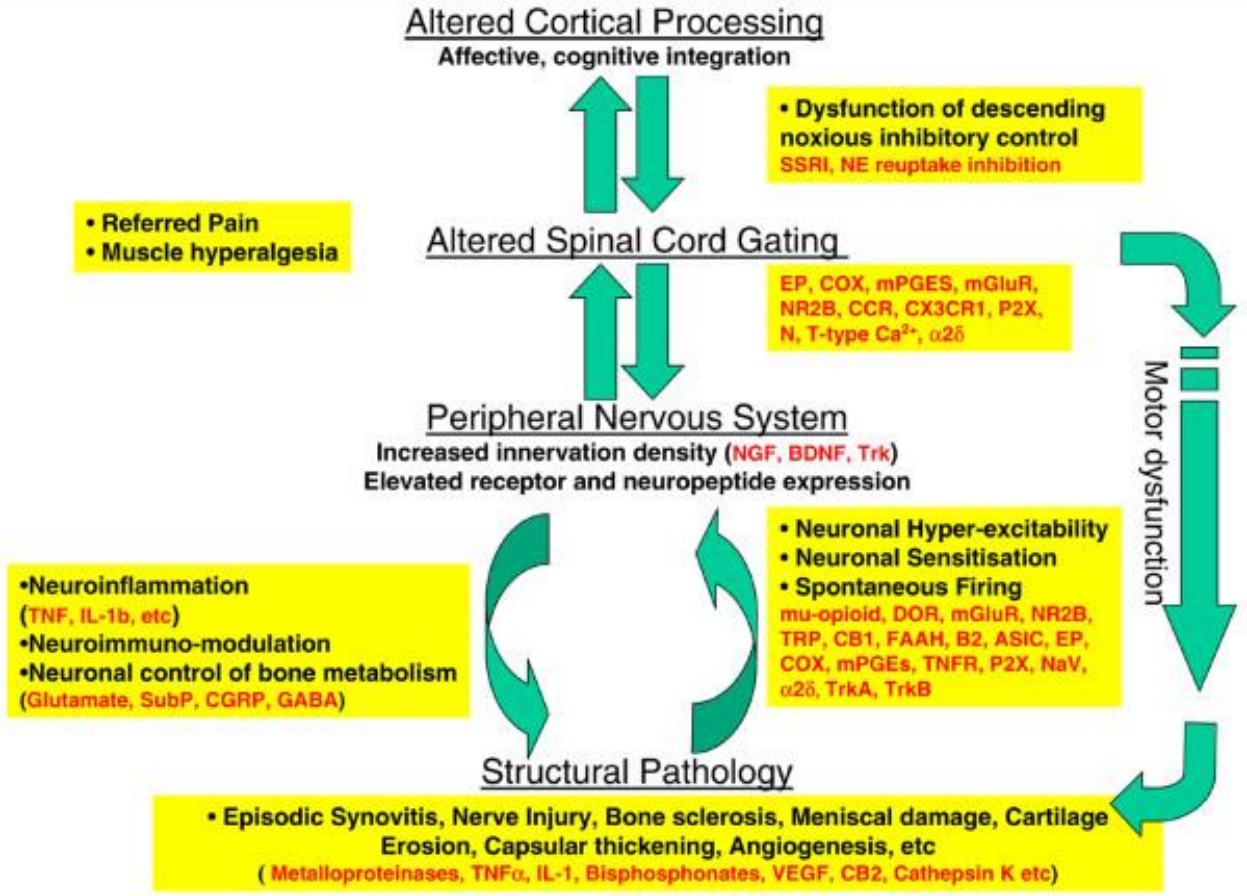
Fysiologische pijn

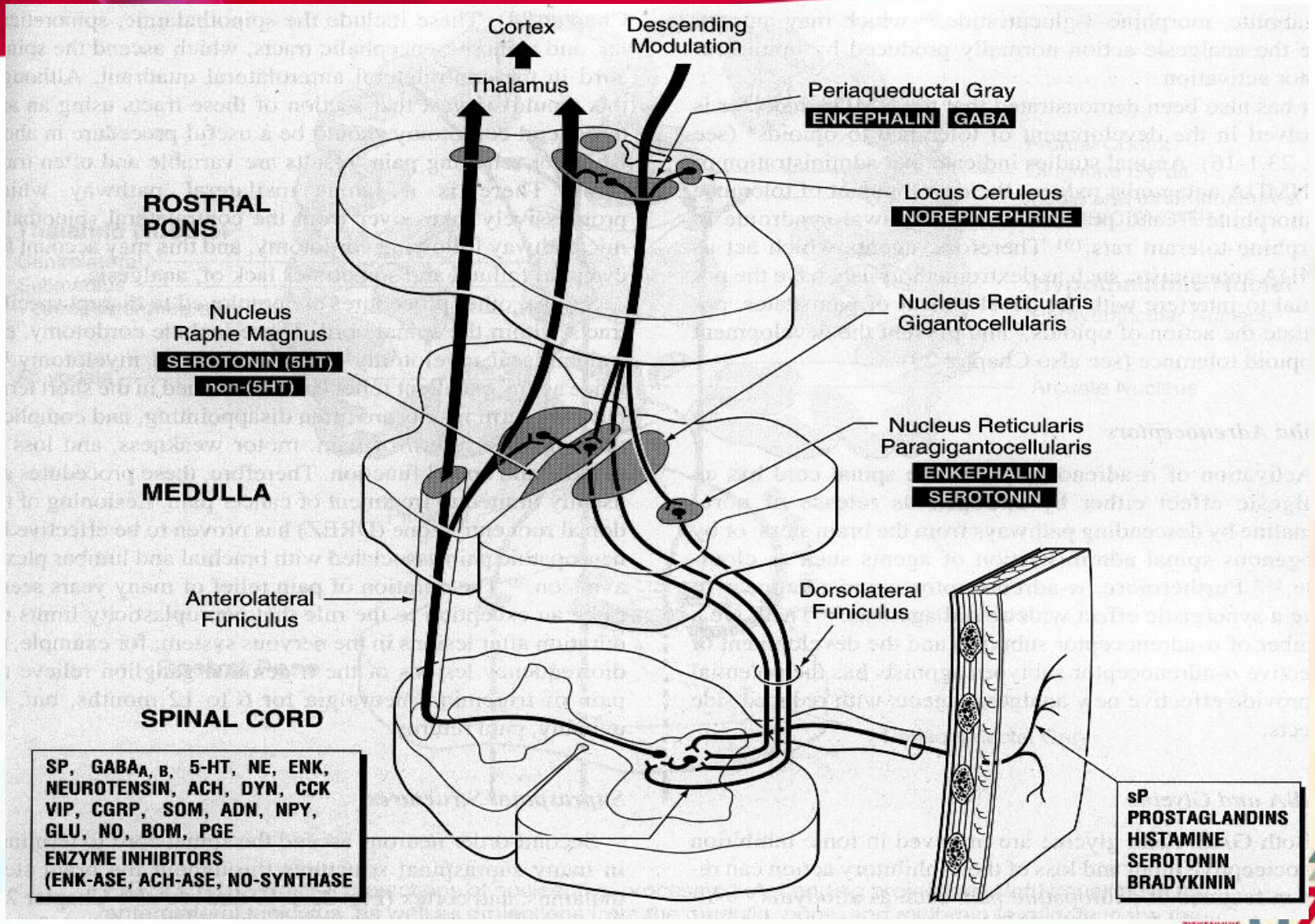


- Transductie
  - **Activatie Nociceptoren**
  - **Nociceptieve stimuli**
- Transmissie
  - **Voortgeleiding impulsen**
    - Dorsale hoorn
    - Hersenen
- Modulatie
  - **↓↓ of ↑↑↑ nociceptieve impulsen (dorsale hoorn)**
- Perceptie

Therapeutische aanpak



Afferent and Descending Pathways



Treatment
'Step by Step'

Analgetische Ladder of Lift

3. 'Strong' Opioid Analgesics
Plus Non-Opioid Analgesics
Plus Adjuvant Drugs

Morphine
Oxycodone
Methadone
Piritramide
(TTS-)Fentanyl
Tapentadol

2. 'Weak' Opioid Analgesics
Plus Non-Opioid Analgesics
Plus Adjuvant Drugs

Codeine
~~D-propoxyfeen~~
Hydrocodeine
Tramadol
Nefopam
Buprenorfine ?

1. Non-Opioid Analgesics
Plus Adjuvant Drugs

Aspirin
Paracetamol
NSAIDs

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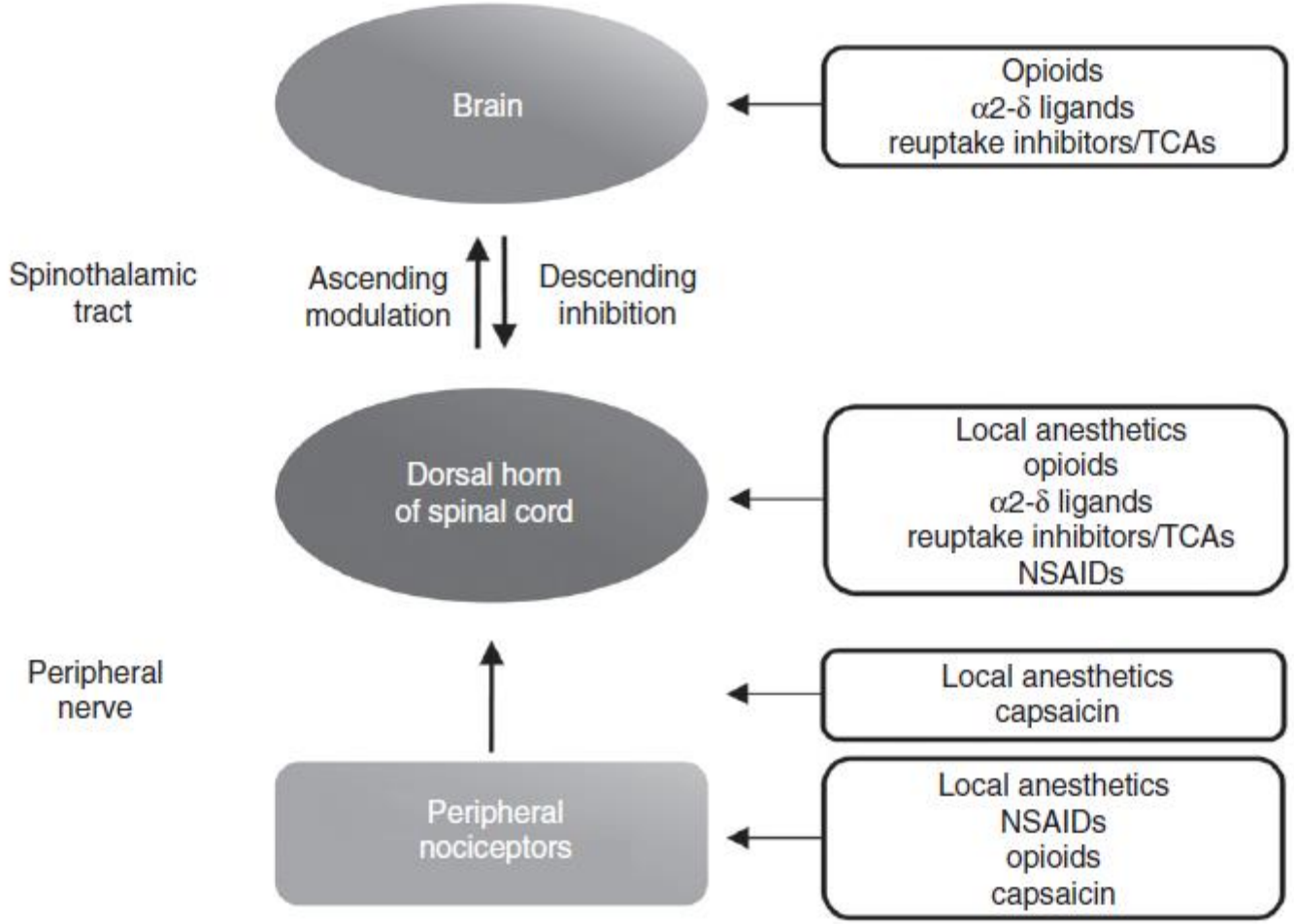
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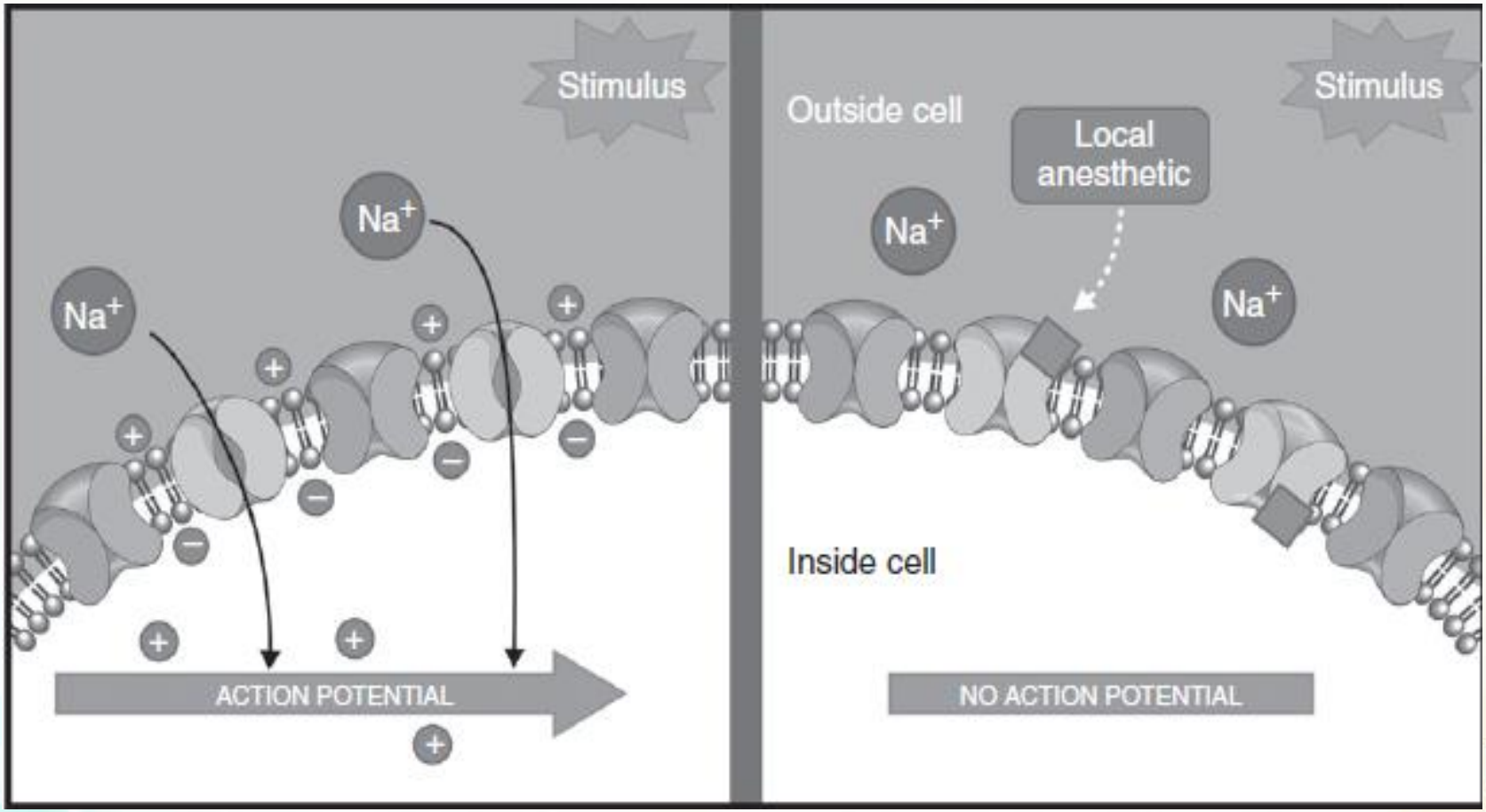
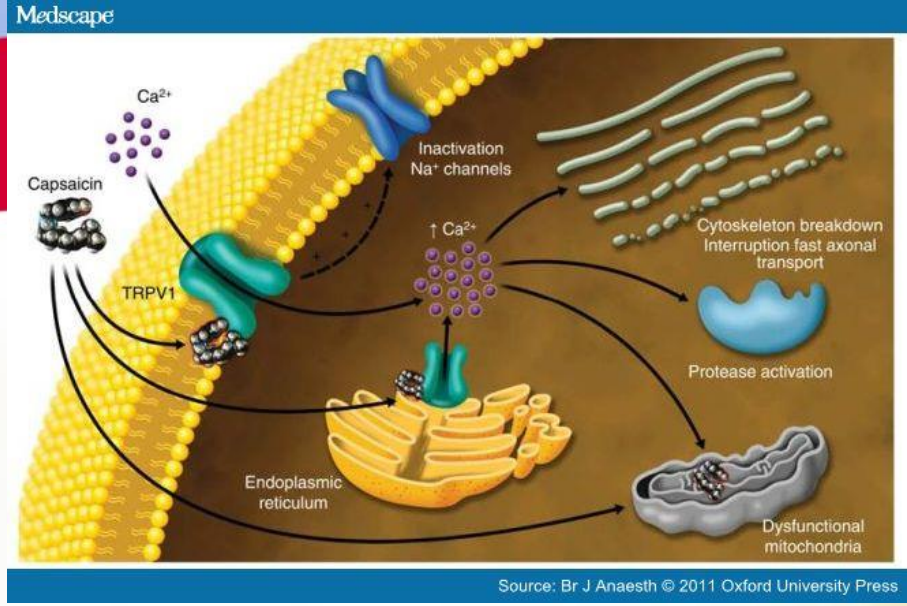
Perifeer Zenuwstelsel (1)

- Locale anesthetica
  - **Blokkade Na^+-kanalen in neuronale membranen**



Perifeer Zenuwstelsel (2)



- Capsaicine (Qutenza®)
  - **Perifere neuropathie**
  - **Applicatie 30 – 60 min**
  - **3 maanden analgesie**
  - **Geen lange-termijn effecten**
    - Neurodegeneratieve veranderingen (perifeer + centraal)
      - ↓ efficaciteit synaptische transmissie dorsale hoorn

- NSAID
  - **Inhibitie van cyclooxygenase enzyme**
    - ↓↓ vrijzetting inflammatoire mediatoren (PG)
  - **Neveneffecten !!**
  - **Topicale applicatie … ?**

TCA's ?

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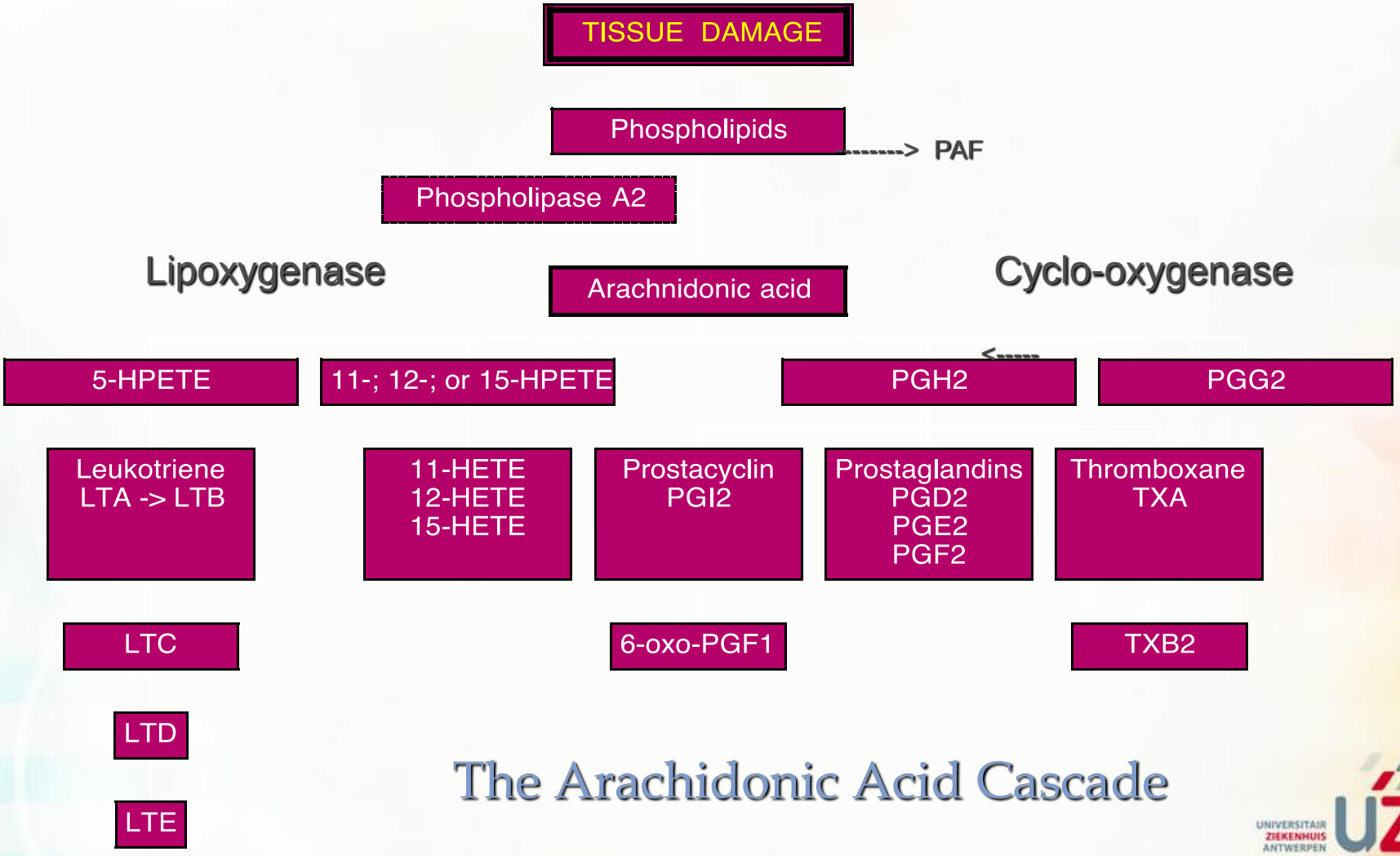
Peripheral Antinociceptive Modulation by NSAIDs (1)



The Arachidonic Acid Cascade

Peripheral Antinociceptive Modulation by NSAIDs (2)

- Inhibition of *Cyclo-Oxygenase*
  - **(at least) 3 distinct categories of inhibitors**
    - Reversible competitive inhibition
      - Ibuprofen; piroxicam
    - Reversible non-competitive inhibition
      - Paracetamol
    - Irreversible inactivation
      - Aspirin, indomethacin

Peripheral Antinociceptive Modulation by NSAIDs (3)

- Inhibition of *Lipoxygenase*
  - **LTB and 12-HETE present in inflammation**
    - Chemotactic action on leucocytes
      - Lower firing threshold of pain fibers
      - Stimulate nociceptors
    - Diclofenac; Indomethacin
- *Non-prostaglandin* Inhibitory Actions
  - **Interference with cell membrane processes**
    - Piroxicam; Indomethacin

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Central Antinociceptive Modulation by NSAIDs (1)

- *Central Prostaglandin Synthesis*
  - **Reduction of Prostaglandins E and F in CNS**
    - Diclofenac; indomethacin; naproxen, PCT
- *Opioid* Mechanisms
  - **Central opioid mechanism of action**
    - Diclofenac; ketorolac; lysine acetylsalicylate
      - Reversal by naloxone
    - Reduce heroin withdrawal syndrome

Central Antinociceptive Modulation by NSAIDs (2)

- *Serotonergic* Mechanisms
  - **Brain stem and spinal cord**
    - Serotonin and 5-hydroxyindoleacetic acid
    - Diclofenac
  - **Activation of descending serotonin pathways**
    - Probably through 5-HT_2 receptor system
- *NMDA* Mechanisms
  - **Reduction of hyperalgesia induced by**
    - Spinal glutamate or substance P receptors
    - Aspirin; ibuprofen; ketorolac

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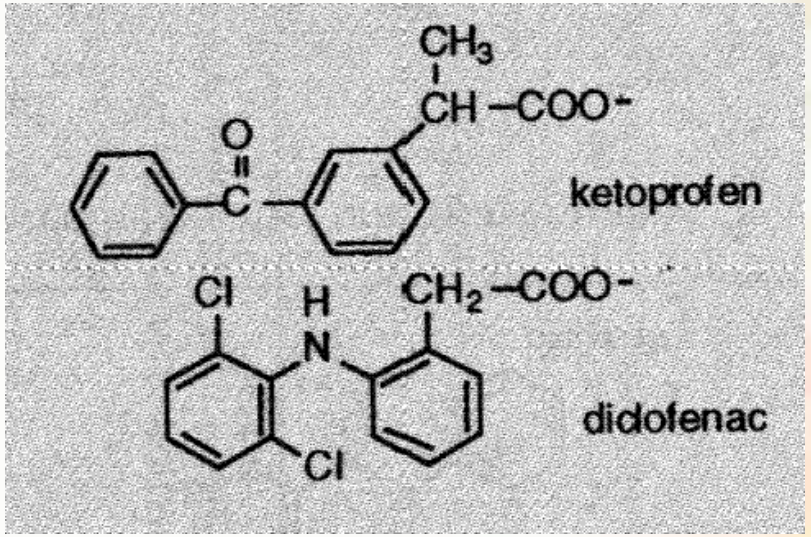
High Potency - Fast Elimination

- Arylpropionic : Ketoprofen
  - Rofenid®; Rofenid Enteric®; Rofenid Long Acting®; Rofenid Retard®
  - 0.5-2h T*max*, 1.1-4h T*1/2*
  - 200mg (-300mg) daily dose
- Arylacetic acids
  - 0.5-2h T*max*, 4-10h T*1/2*
  - **Diclofenac (Voltaren,Cataflam®)**
    - Dissolve in stomach
    - Short half-life of 1 - 2 h
    - Daily dose:100 - 150 mg
  - **Ketorolac (Taradayl®)**
    - 100% bio-availability IM/PO
    - 10 - 30mg every 6-8 hours
    - 60 (elderly) to 90 mg daily dose
    - IM/IV max 2 days

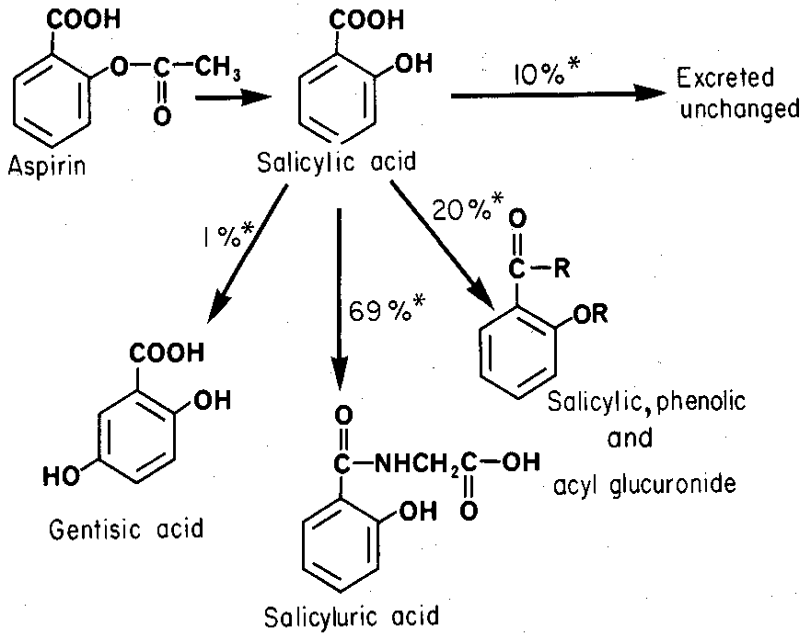


No combination with other NSAIDs

Not during labor and delivery

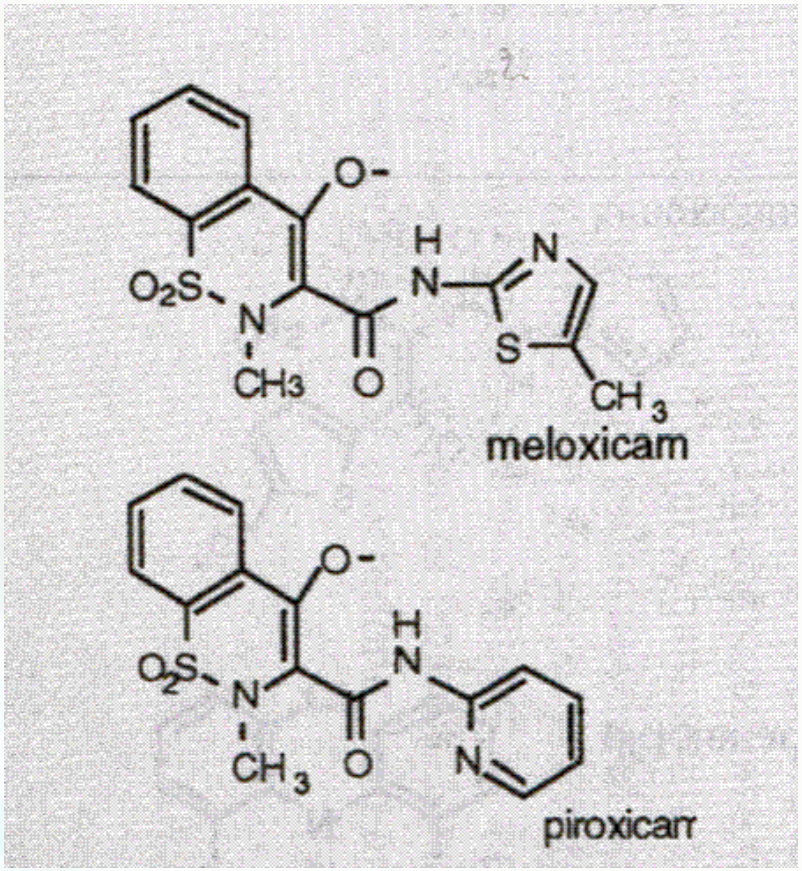
Low Potency - Fast Elimination

- **Salicylates**
  - +/- 0.25h T*max*
  - +/- 20min T*1/2*
  - **Low dose (500mg, 2x/d)**
    - Analgesic & antipyretic effect
  - **High dose (1000mg, 3x/d)**
    - Anti-inflammatory effect
  - **Individual variation in absorption**
    - Dosage not predictable



- **Lysin - acetylsalicylic acid (Aspegic®)**
  - **water soluble salt, sodium free**
  - **1.8g aspegic = 1.0g aspirin**
  - **fast absorption**
  - **500 - 1000mg, 2 to 3 x/day**

High Potency - Slow Elimination



- Oxicams
  - **Piroxicam (Feldene®)**
    - 3-5h T*max*, 35-70h T*1/2*
    - 20mg-40mg, daily dose
    - Lyotabs equal Tmax, T1/2
    - Elevated aminotransferase levels in 15
      - Monitor liver enzymes first 8 wk
  - **Tenoxicam (Tilcotil®)**
    - 100% bio-availability PO
    - 3-5h T*max*, 42-98h T*1/2*
    - 20mg-40mg daily dose
    - Inhibitor of metalloproteinase
      - Degenerative bone diseases!

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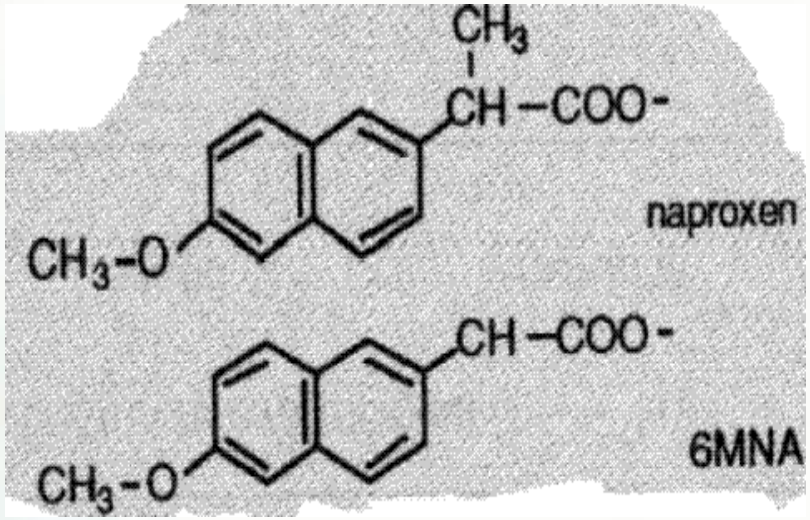
Intermediate Potency
Intermediate Elimination



- Arylpropionic acids
  - **Naproxen EG®; Naprosyne®**
    - 2-4h T*max*
    - 12-15u T*1/2*
    - 500 - 1000mg daily dose
    - Extremely good penetration
      - Synovia
      - Inflammatory tissues
  - **Apranax®** ***(natriumnaproxen)***
    - < 1h T*max*
    - 12 – 15u T*1/2*
    - 550 mg, 2 x day

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Cyclo-oxygenase

- Physiological stimulus
  - Constitutive expressed enzyme

COX-1

Platelets, stomach, intestine, kidney

  - Normal cell functions "house keeping"

- Tissue damage
  - Inducible enzyme
  - Not constitutive ??

COX-2

Macrophages, synoviocytes

  - Inflammation, regulation electrolyte balance

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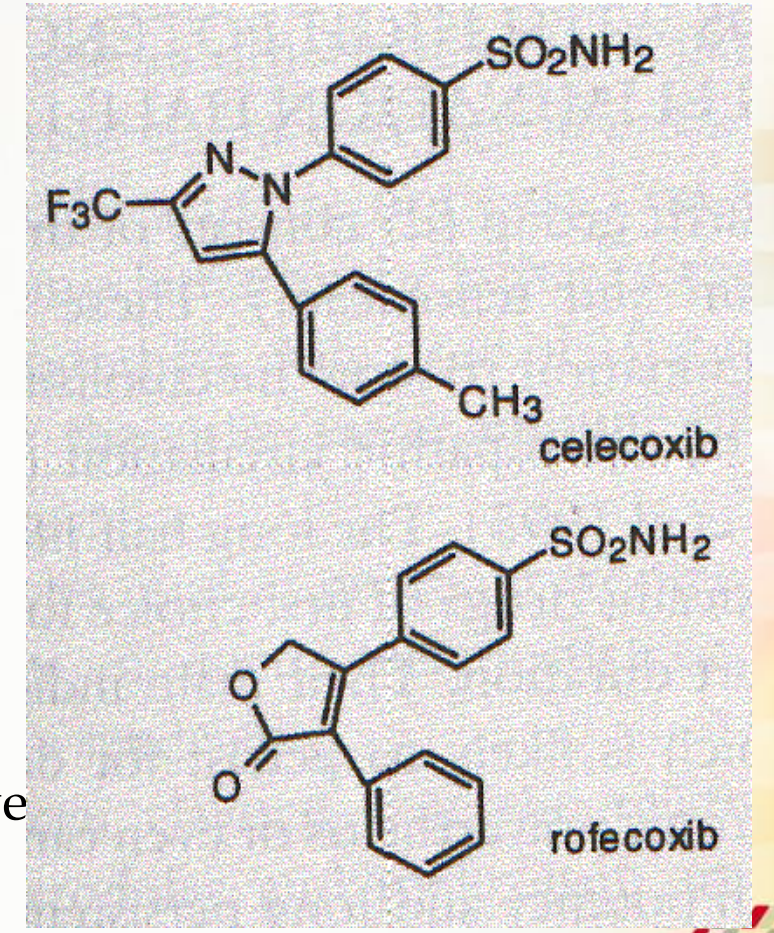
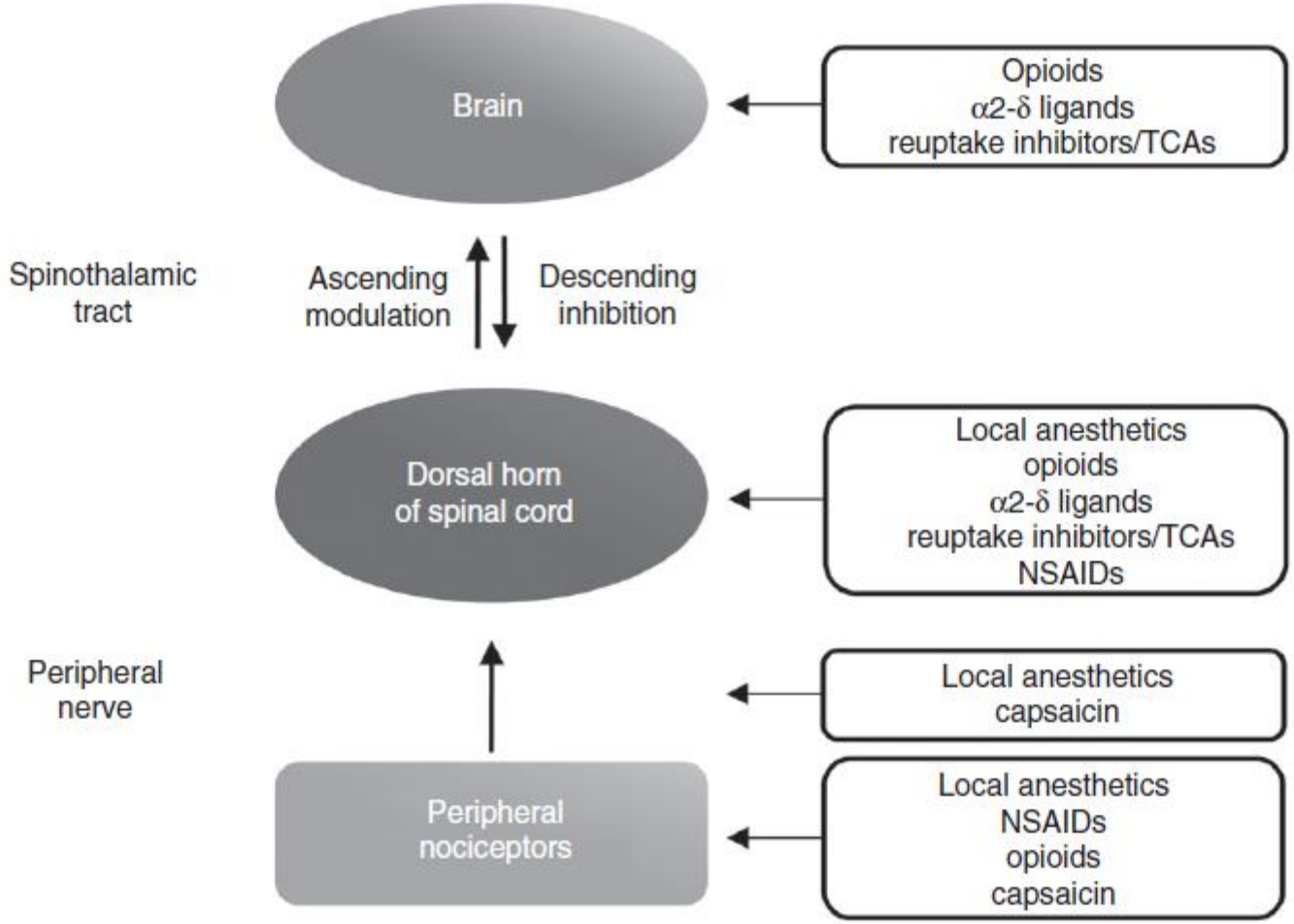
Selective COX-2 Inhibitors

- Celecoxib (Celebrex®)
  - 2-4 h T*max*, 9-15 h T*1/2*
  - 400mg max daily dose
- Valdecoxib (Bextra®)
  - 20mg max daily dose
  - no dose adjustments in elderly
- Etoricoxib (Arcoxia®)
  - faster effect
  - long-term effect (once daily)
  - no information on side effects ye

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Paracetamol (1)

- **Non-acidic antipyretic analgesic**

  (Dafalgan®, Perdolan Mono®; Efferalgan, Dolprone...)

  - **Very weak inhibitor cyclooxygenase (central, indirect ?)**
  - **Strong *antipyretic* effect**
  - **Lacks significant anti-inflammatory property**
  - **Maximum analgesic effect at 1000 mg**
    - Central action (synthesis of prostaglandins)
    - Importance of high and quick peak plasma concentration
    - Dose-effect correlation in CNS
    - Ceiling of analgesic effect at 1g PO, and this 3 x day
    - Better than 60 mg Codeine and Tramadol 100 mg
    - Combinations remain possible !

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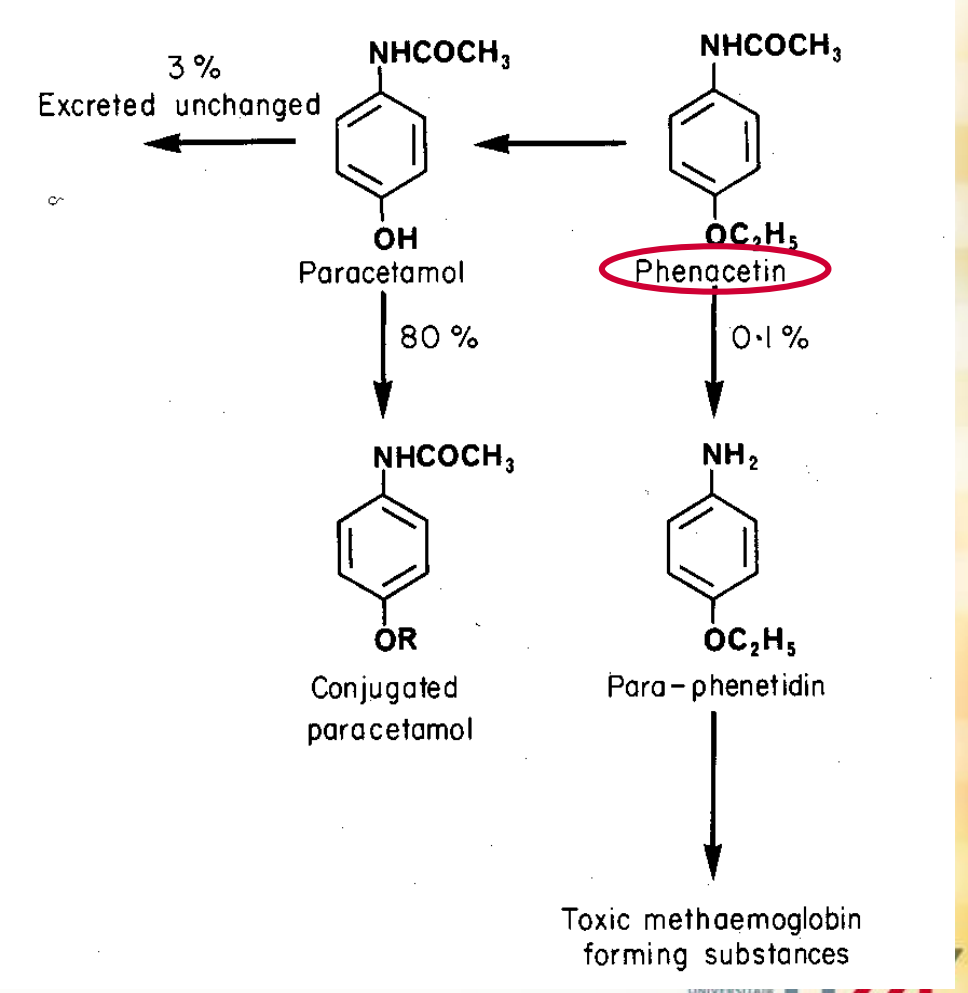
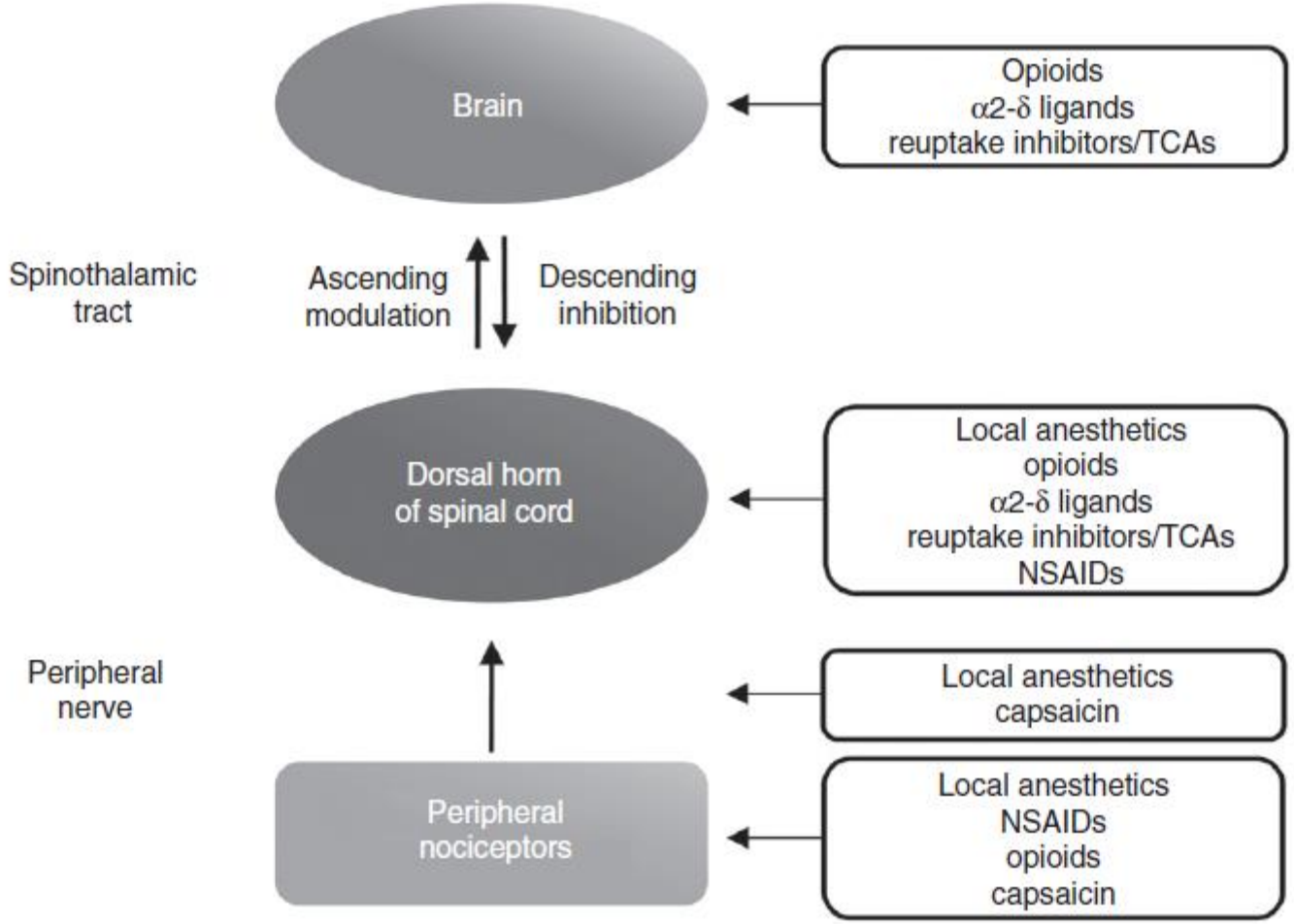
Paracetamol (2)

- Short term use
  - **< 4 gm / day**
- Long term use
  - **< 3.2 gm / day**
  - **< 2.4 gm / day**
    - Elderly
    - Debilitated persons
    - Alcohol intake
    - Malnutrition



Paracetamol (3)

- Perfusalgan (IV)
  - **Different from previous Pro-Dafalgan !!**
    - Pro-drug: 2:1 conversion , Mannitol
  - **Concentration of 10 mg/ml**
  - **Water soluble form of paracetamol**
  - **1:1 ratio**
  - **Faster onset of action**
  - **More efficacious**
  - **First day : 6g ?, 2g better than 1g ?**
  - **Longer duration of action**
  - **Slow administration (!) otherwise possible hypotension**
  - **Good local tolerance**
    - Osmolarity and pH close to human plasma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Tramadol Hydrochloride (1)

- Synthetic, *centrally* acting analgesic

(Contramal®, Dolzam®,Tradonal®; Tramium®; ...)

- **Dual mechanism of action:**
  - Specific selectivity and low affinity for μ-opioid receptor
    - » 6000 times less than morphine
  - Interaction with neurotransmitter transmission
    - » Stimulation neuronal serotonin release
    - » Inhibition pre-synaptic reuptake NA and serotonin

- **Analgesic effect of <u>each</u> component is modest**
  - Low incidence of certain opioid-like adverse effects
  - Low tolerance and dependence potential
- **RESPONDERS and NON-RESPONDERS ?**

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Tramadol Hydrochloride (2)

- No respiratory depression in therapeutic range
- Almost no risk of constipation
- Nausea/vomiting; somnolence; transpiration
- No euphoria
- Low plasma protein binding (20%)
  - **No interference other drugs (except MAO-I, 5-HT antagonisten)**
  - **Combination with NSAIDs allowed**
- Not a non-steroidal anti-inflammatory drug
  - **No anti-inflammatory activity**
  - **No prostaglandines side effects**

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Tramadol Hydrochloride (3)

- Conversion in liver to active M_1 metabolite
  - **Excretion as unaltered drug and metabolites in urine**
  - **Low-affinity of parent compound + high-affinity binding of M1 metabolite to μ-opioid receptor**

- Risk of seizures
  - **Doses above recommended range**
  - **Decreasing seizure threshold**
    - Tricyclic antidepressants
    - SSRI's
    - MAO-inhibitors

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Tramadol Hydrochloride (4)

- Potency:
  - **IV: 100mg tramadol = 10mg morphine**
  - **PO: 50mg tramadol = 10mg morphine**
    - Bio-availability: tramadol 70% vs. morphine 20-25%
- Duration of 3 - 6 h ,T*max* PO 1 - 2 h; Parenteral 45 min
- Max daily dose **400mg**
  - **No changes in elderly (<75 years)**
  - **Increase interval**
    - Liver failure
      - Higher levels tramadol
      - Decreased levels of M1
    - Renal failure
      - Creatinine clearance < 30mL/min
        - » 50-100mg every 12h

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Tramadol + … : fixed combinations

- Combination analgesic (Zaldiar®, …)
  - **Paracetamol (325mg) + Tramadol hydrochl. (37.5mg)**
  - **The rationale for combining complementary analgesics acting by different pathways is an improved benefit/risk ratio through enhancement of analgesia (synergim or addition) and/or reduction of side effects**
- No undesirable interactions when the two analgesics are given in combination as either single or repeated doses
- The time to achieve maximal plasma concentrations is about 30-60 minutes for paracetamol and 2 hours for tramadol
- Both drugs are metabolised via the liver, but each compound is broken down along separate metabolic pathways
- Cave: long-acting combinations !?

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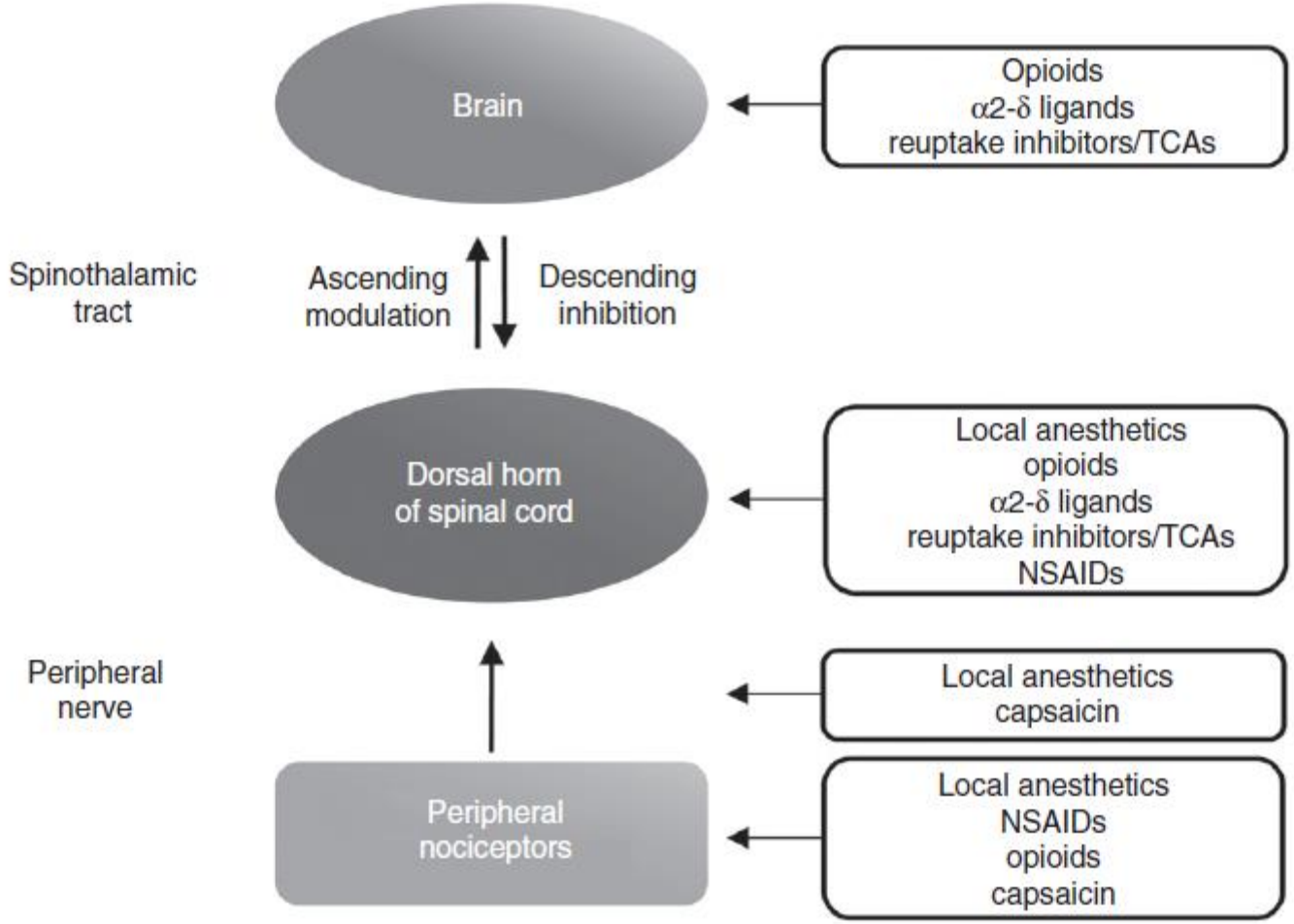
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Classification of strong Opioids

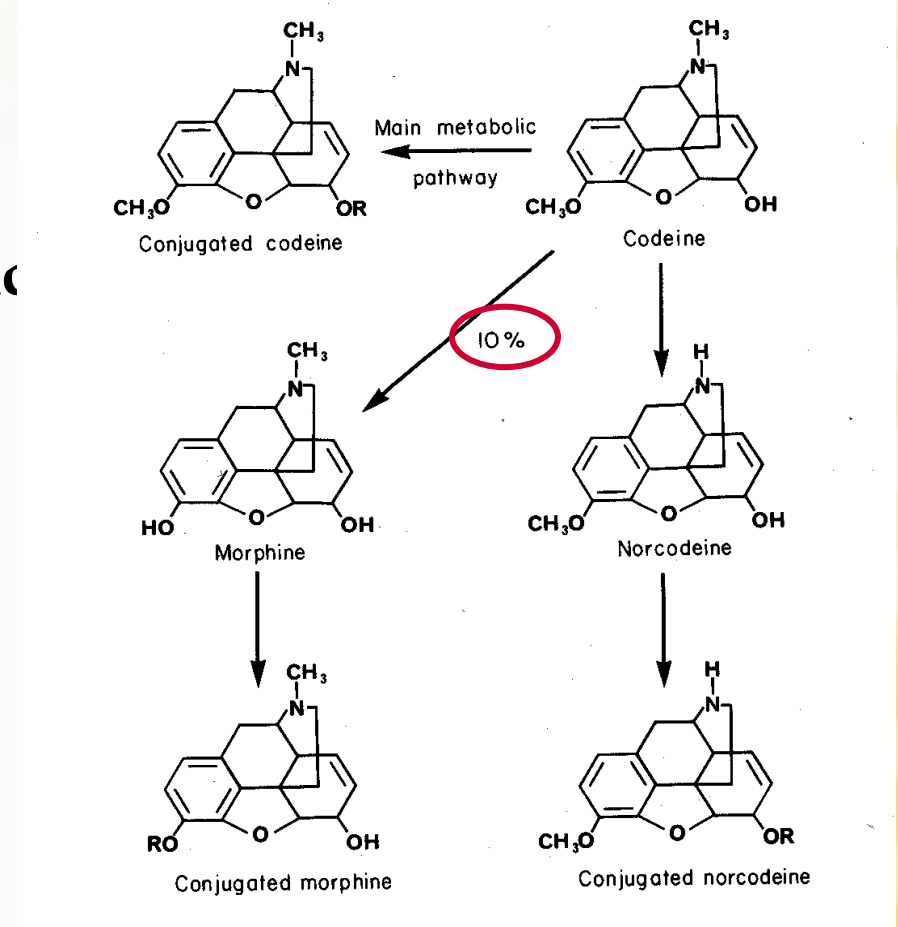
Full Agonists	Partial Agonists	Mixed Agonist-Antagonists
Codeine	Buprenorphine	*Nalbuphine*
Fentanyl		*Butorphanol*
Sufentanil		*Dezocine*
Hydrocodon		*Pentazocine*
Meperidine		Tilidine
Methadone		
Morphine		
Oxycodone		
Propoxyphene		

Neveneffecten van opioiden

- Dysforie, euforie
- Sedatie
- AH depressie
- Nausea, braken
- Miosis
- Sfinter contractie
- Onderdrukken van maag-darm en blaasfunktie
- Jeuk
- Convulsies
- Tolerantie, afhankelijkheid

Full agonist : Codeine

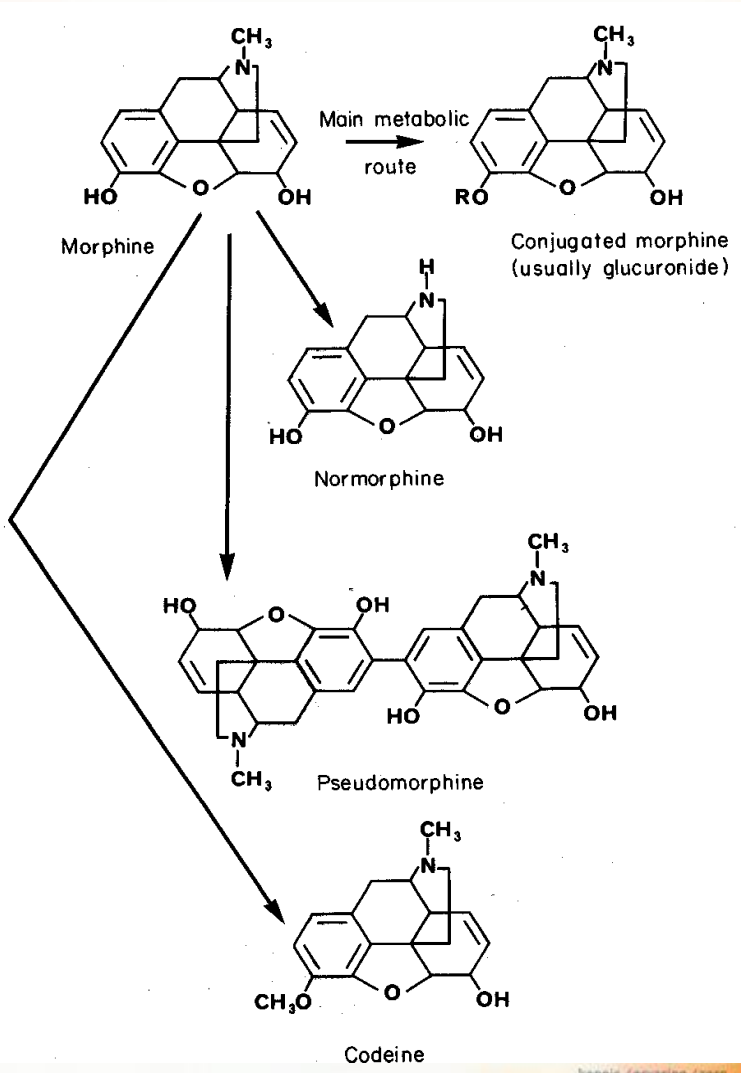
- Alkaloid of opium
  - **Analgesic effect 5-10x <M+**
  - **Duration of action: 5 hrs**
  - **Also anti-tussivum, -diaretic**
  - **Weak resp. depression**
- Associations !
  - **With paracetamol**
    - Dafalgan codeine, Perdolan
    - Panadol codeine, Lonarid N
  - **With aspirin**
    - Dolviran
  - **Codeine derivates**
    - Dihydrocodeine (Codicontin), with longer duration (up to 12 h)



Full Agonist : Morphine

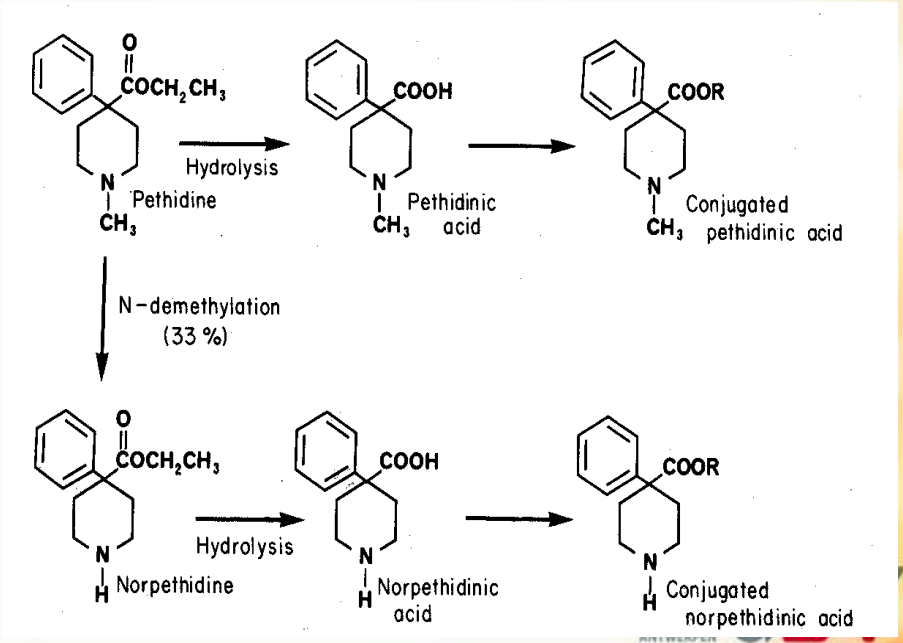
- Principal and…. most *active* alkaloid of opium
- Many routes (versatile)
- Immediate-release
- Sustained-release
- 25-35% first-pass
- SC / IM: 10 mg / 70 kg
- IV: 2 - 10 mg / 70 kg
- Oral : bioavailability 20%

Parenteral Dose: 5 - 10 mg every 3-6 h



Full Agonist : pethidine

- Pethidine / meperidine (Dolantine® - nu Pethisom®)
  - **Weaker analgesic effect than morphine**
    - 100mg Dolantine = 10mg Morphine
    - Least potent of synthetic opioids
  - **Shorter duration of action than morphine (2 - 4 h)**
  - **Onset (IM) : 20-30 min**
  - ***Spasmolytique* activity**
  - **Side effects:**
    - Less respiratory depression
    - CV-depressive action
    - Never during labor



Labor : max fetal concentr after 140 min.
T1/2 : mother 3h, fetus 23h

Full Agonists : Piritramide

IM: 0.2 - 0.3 mg/kg (20mg) every 6 h
(max daily of 80 mg)

- Piritramide (Dipidolor®)
  - **Derived from 3,3-difenylpropylamine**
  - **Less potent than morphine (15-20mg=10mg M+)**
  - ***Special clinical profile***
    - Less nausea; constipation; resp. depression
    - More sedation
    - Few cardiovascular effects
  - **Onset after IM injection: 15 to 20 min**
  - **Duration: 4 to 6 hours**
  - **IV ? : 2-4mg/bolus …. (no official indication)**

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Full Agonists : Methadone

- 100% synthetic substance (L-isomer)
- *High protein binding in tissue*
- Low plasma concentration
  - **Low tolerance**
  - **Longlasting suppression of heroine withdrawal**
  - **N-demethylation**
  - **Anti-tussive but**
    - actually better substances with
    - Less dependency

Full (synthetic) Agonists

- Fentanyl and Sufentanil
  - **More potent than morphine (F50µg = 10mg M+)**
  - **Sufentanil = Fentanyl x 4-6**
  - ***Special clinical profile***
    - More sedation
    - Few cardiovascular effects
  - **Onset after IV injection: <5min.**
  - **Duration: 2 to 6 hours**
  - **Transdermal (Durogesic) as main chronic therapy**
  - **Effective as breakthrough pain**
    - Transmucosal, intranasal, transbucal, ….

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Partial Agonist Opioid

- Buprenorphine (Temgesic®; Transtec®, ….)
  - **Semisynthetic derivate of morphine alkaloid thebaine**
  - **Partial agonist effect at μ-opioid receptor in CNS**
    - High affinity at μ-opioid receptors
    - Low intrinsic activity at μ-opioid receptors
    - Relaxation of Oddi Sphinter
  - **Sublingual administration:**
    - 50% biological availability
    - Peak clinical effect within 1 to 4 hours
    - Elimination half-life between 24 to 37 hours
    - Metabolism in liver (glucuronide conjugation + N-dealkylation)
      - Principally excreted in faeces and urine
  - **High lipid solubilty, very high protein binding**
    - Remaining in tissues for several days

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Brand Name		Daily Dose of Buprenorphine	Duration of Use per Patch
TRANSTEC 35 µg/h		0.8 mg	3 days
TRANSTEC 52,5 µg/h		1.2 mg	3 days
TRANSTEC 70 µg/h		1.6 mg	3 days

- *Transdermal*
- 3 different doses
  - **35 µg/h (total dose of 20 mg buprenorphine)**
  - **52.5 µg/h (total dose of 30 mg)**
  - **70 µg/h (total dose of 40 mg)**
- Weekly doses no longer available in Belgium (1/2020)
- Active during 72 hours
- Matrix technology
  - **No leakage ! (1/2 patch possible)**
  - **No substance abuse possible !**

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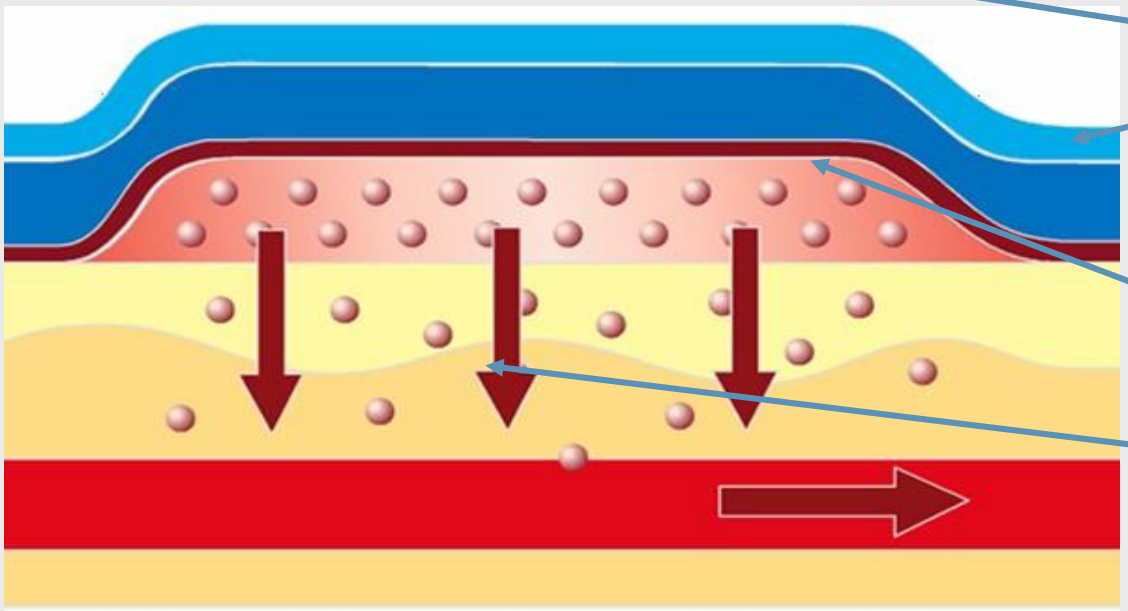
Matrixsysteem

Grote reserve
72u werking!



Partial Agonist or Ag-Antag ?

- Pentazocine (Fortal®), derivate from Phenazocine
  - **Synthetic opioid, too weak antagonistic effect**
  - **Related to kappa-opioid receptor stimulation**
  - **Weak antagonist μ-opioid activity**
    - Deliberately produced to decrease drug abuse
  - **30 mg (60mg better ?) pentazocine = 10 mg M+**
  - **Duration of action : 3-6h**
  - **Metabolised in liver, excreted by the kidneys**
  - **IV administration increases systemic vascular resistance, and systemic, pulmonary arterial pressure**
  - **No repeated injections into the skin (fibrosis!)**
  - **Psychotomimetic reactions**
  - **Antagonised by nalloxone only.**

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Agonist + Antagonist (2)

- Tilidine (Valoron) + Naloxone (Valtran®)
  - **100mg = 10mg morphine**
  - **Analgesic effect 10 - 20 minutes after PO**
  - **Duration: 4 to 6 hours**
  - **No cough depression, no cardiovasc. Effects**
  - **Naloxone < 8mg no clinical effect (analgesia!)**
    - First-pass effect of naloxone
  - **Overdosage : fear for resp. depression**
    - Antagonistic effect proportional to dose

PO Dose: 10 - 20 drops every 6-8 h
Max dose of 4 x 40 drops

ZIEKENHUIS ANTWERPEN
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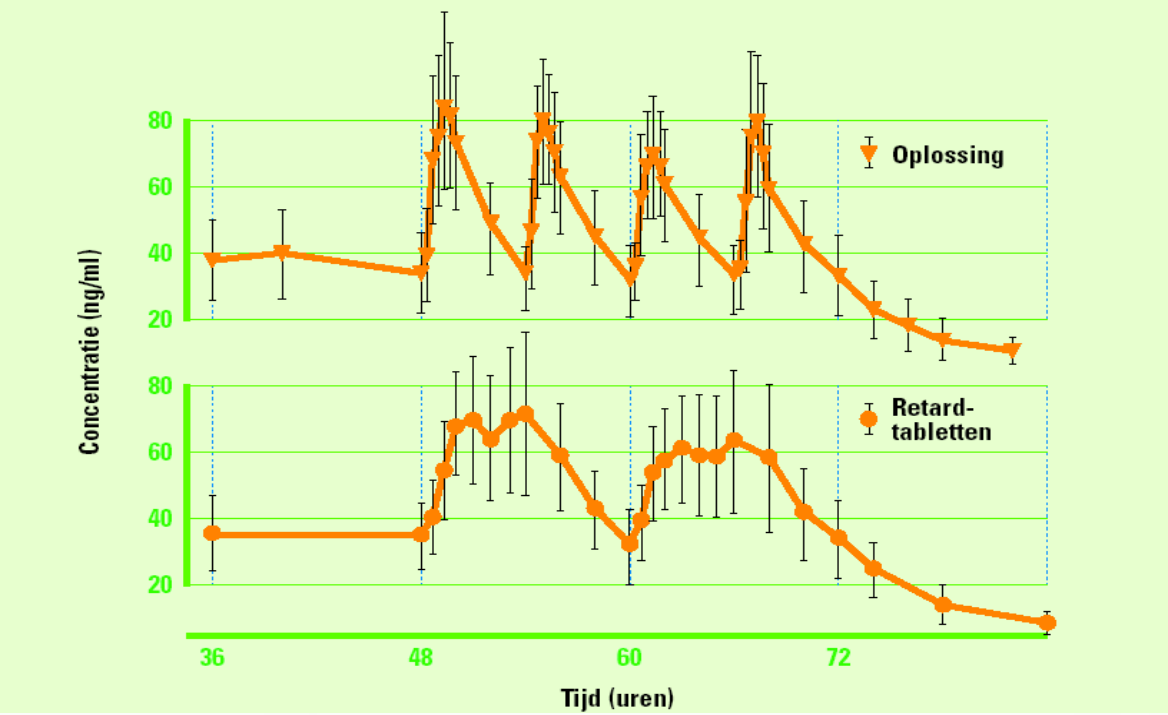
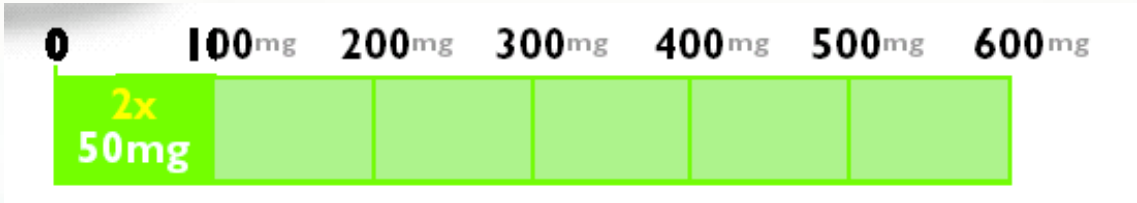
Agonist + Antagonist

- Long-acting form (Valtran Retard®)

Verlengde werking : 12 uren ⇨ 2 x per dag





Agonist + Antagonist (3)

- Oxycodone + Naloxone (Targinact)
  - **Idential analgesic effect compared to oxycodone**
  - **Less gastro-intestinal side effects (obstipation)**
    - Scientific evidence very weak

- Many more such combinations to expect in the (near) future, focusing on the obstipation induced by opioids…

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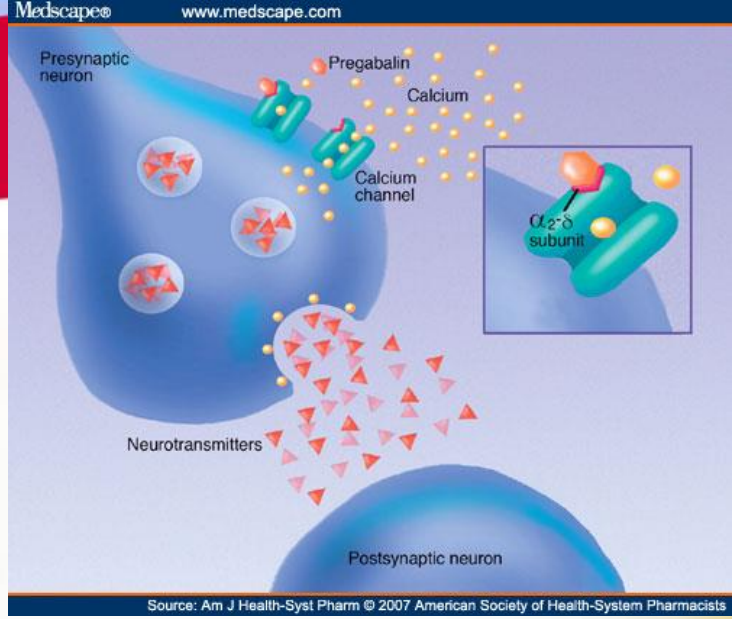
Adjuvantia

- Farmaca die strictu sensu geen analgetica zijn, kunnen in bepaalde omstandigheden toch een (belangrijk) analgetisch effect induceren
  - **Vb. Neuropathische pijn**

- Werkzaam op specifieke plaatsen in de pijngeleidingsbanen
  - **Vaak werkzaam via mechanismen die niet geactiveerd worden door “klassieke” analgetica**

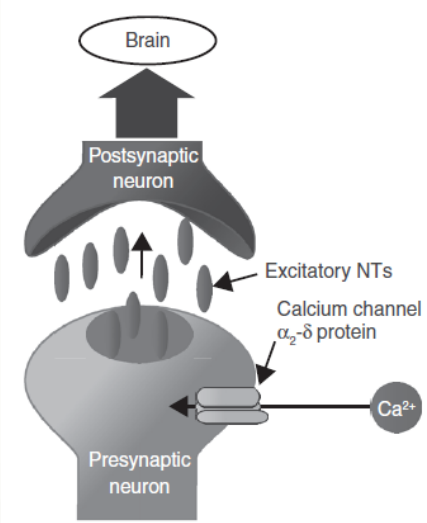
$\alpha_2\delta$ ligands (Ca^{2+})

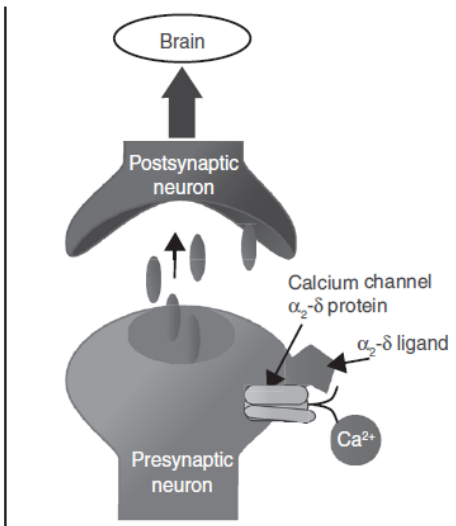


- Binding subeenheid van voltage-afhankelijke Ca^{2+} kanalen op neuronale membranen
  - ↓↓ **excitatoire neurotransmitters**

- Activatie descenderende inhiberende banen
  - ↑ **NA concentratie spinaal**

- Gabapentine, Pregabaline



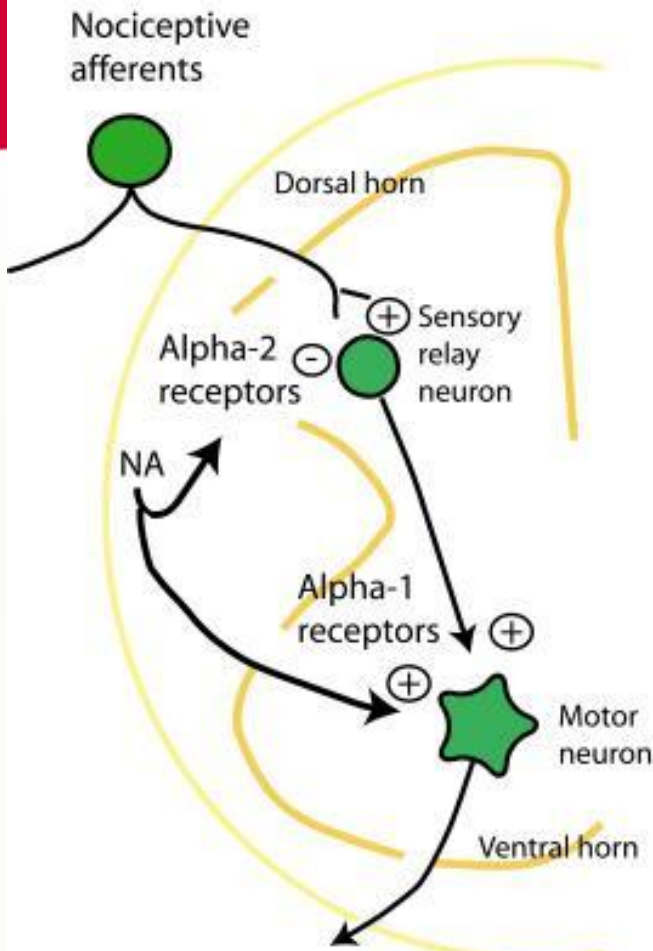


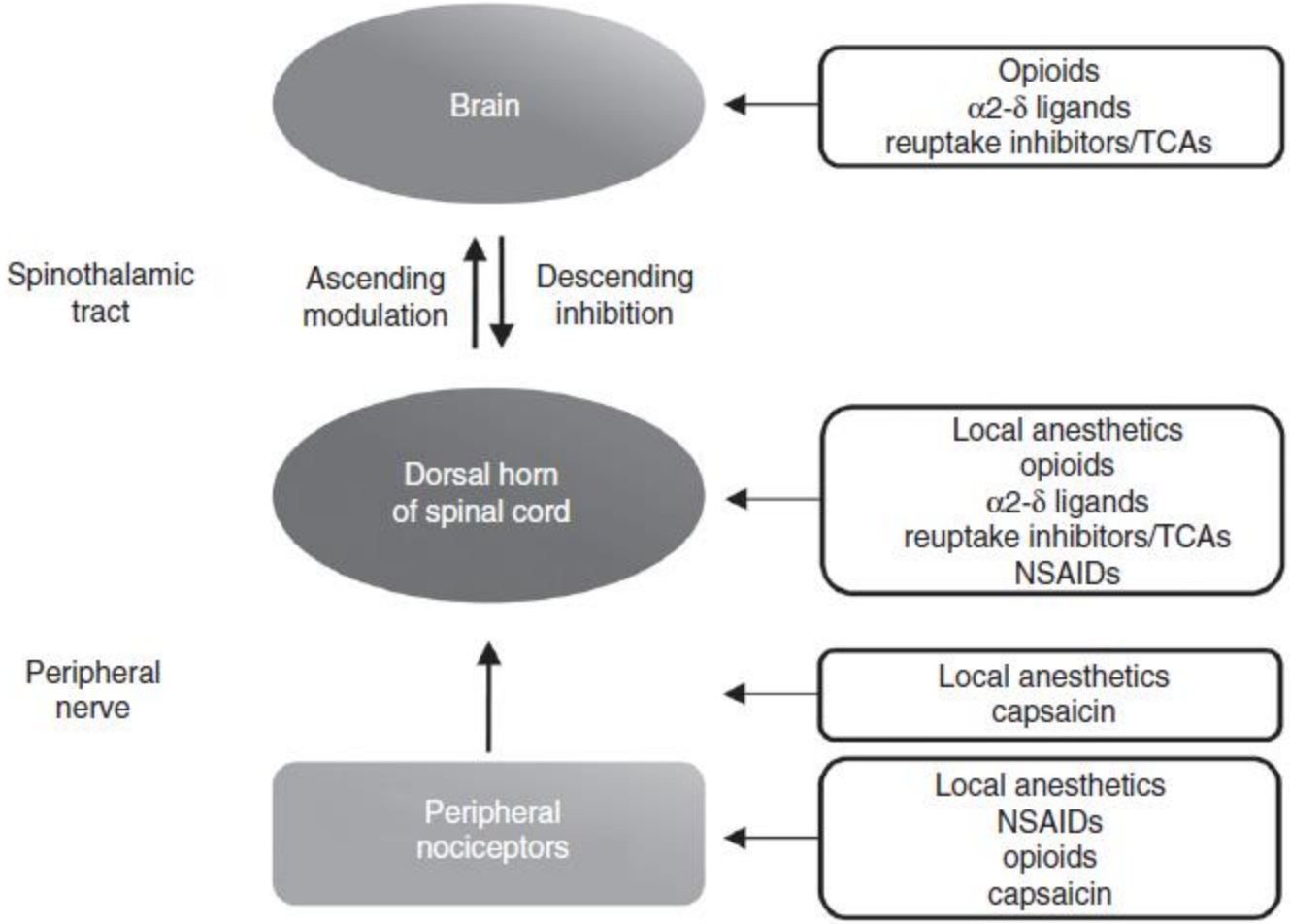
Descenderende inhibitie

- **α2(A)-adrenoreceptor** agonisten
  - Clonidine
  - Dexmedetomidine
    - Grotere selectiviteit 1620:1 (vs. 300:1)
    - $T_{1/2}$: 2 à 3 uur

- Essentiële rol in
  descenderende pijnmodulatie

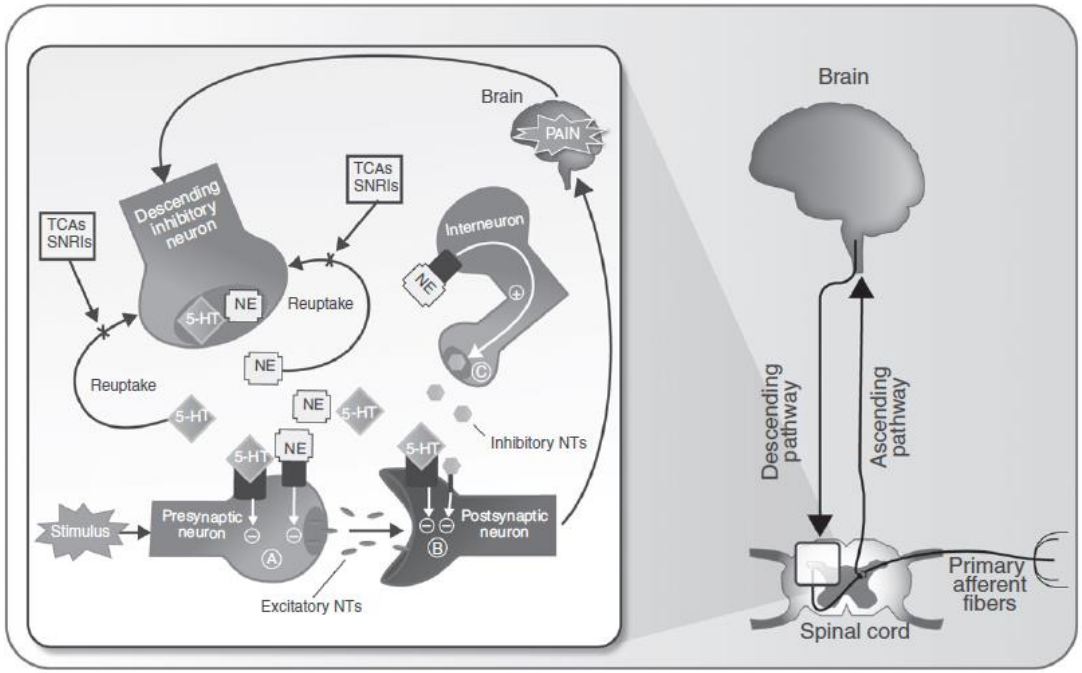
  - Stimulatie ⇒ **veralgemeende analgesie**
    - Locus coeruleus
    - Parabrachiale nucleus in medulla
  - G-proteïne gemedieerde K^+ kanalen




Brain
Opioids
α2-δ ligands
reuptake inhibitors/TCAs
Spinothalamic tract
Ascending modulation
Descending inhibition
Dorsal horn of spinal cord
Local anesthetics
opioids
α2-δ ligands
reuptake inhibitors/TCAs
NSAIDs
Peripheral nerve
Local anesthetics
capsaicin
Peripheral nociceptors
Local anesthetics
NSAIDs
opioids
capsaicin

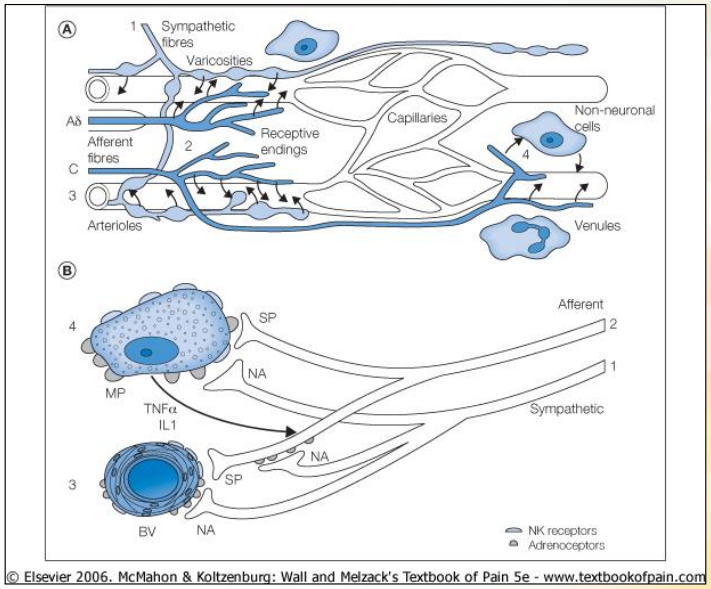
“Corticale” Sensitizatie

- TCA’s
  - “7 farmaca in één”
    - Serotonin reuptake inhibitoren
    - Norepinephrine reuptake inhibitoren
    - Anticholinerge-antimuscarine farmaca
    - Alpha-1 adrenerge antagonisten
    - Antihistaminica
    - Opioid-achtige effecten
    - Locale anesthetica
- (SSRI’s)
- SNRI’s
  - Venlafaxine (Efexor®)
  - Duloxetine (Cymbalta®)



Autonome Dysregulatie

- Complex Regionaal Pijnsyndroom (CRPS)
  - **Farmacologische behandelingsmogelijkheden**
  - **Interventionele R/ thv. sympathische ganglia**
    - Locale anaesthetica thv. sympathetische paravertebrale ganglia
    - Regionale intraveneuze behandeling (sympathicolysis)
      - Guanethidine (beschikbaarheid!?)
      - Locale anaesthetica
  - **Heelkundige sympathectomie**
    - Zeer beperkte evidentie !
      - Risico op uitgesproken oedeem
        - » Blijvende overgevoeligheid
  - **Fysiotherapie (beweging)**
    - Uitermate belangrijk !
    - Aangetoond effect op lange-termijn
      - ↓ pijn en ↑ *actieve* mobilisatie
        - » Lymfe-drainage: géén voordeel
  - **Psychologische behandeling (± fysiotherapie)**
    - Langdurige ↓↓ symptomatologie



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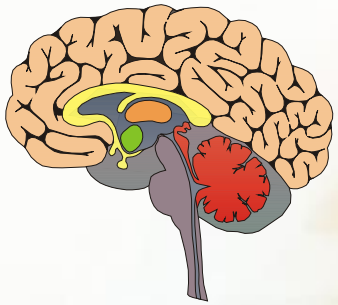
Multimodal Analgesia

5. Perception

Opioids, Paracetamol,
Clonidine, Ketamine,
Gabapentin, Tricyclics



6. CNS Responses

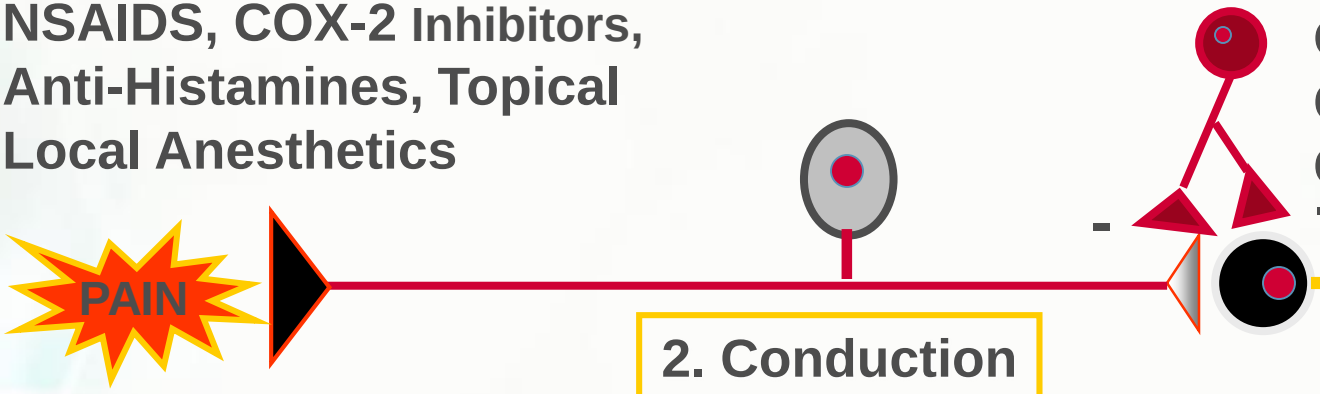
Muscle Relaxants,
Beta Blockers

1. Transduction

NSAIDS, COX-2 Inhibitors,
Anti-Histamines, Topical
Local Anesthetics

4. Modulation

Opioids,
Clonidine,
COX-2 Inhibitors



2. Conduction

Peripheral Nerve Block
Local Anesthetics

3. Transmission

Epidural Block
Local Anesthetics

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