Antiparkinson drugs,
Opioid analgetics

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Extrapyramidal movement disorders

<u>akinetic/hypokinetic rigid syndromes</u>

Parkinson's disease,

<u>hyperkinetic rigid syndromes</u>

chorea, tic, athetosis, ballismus

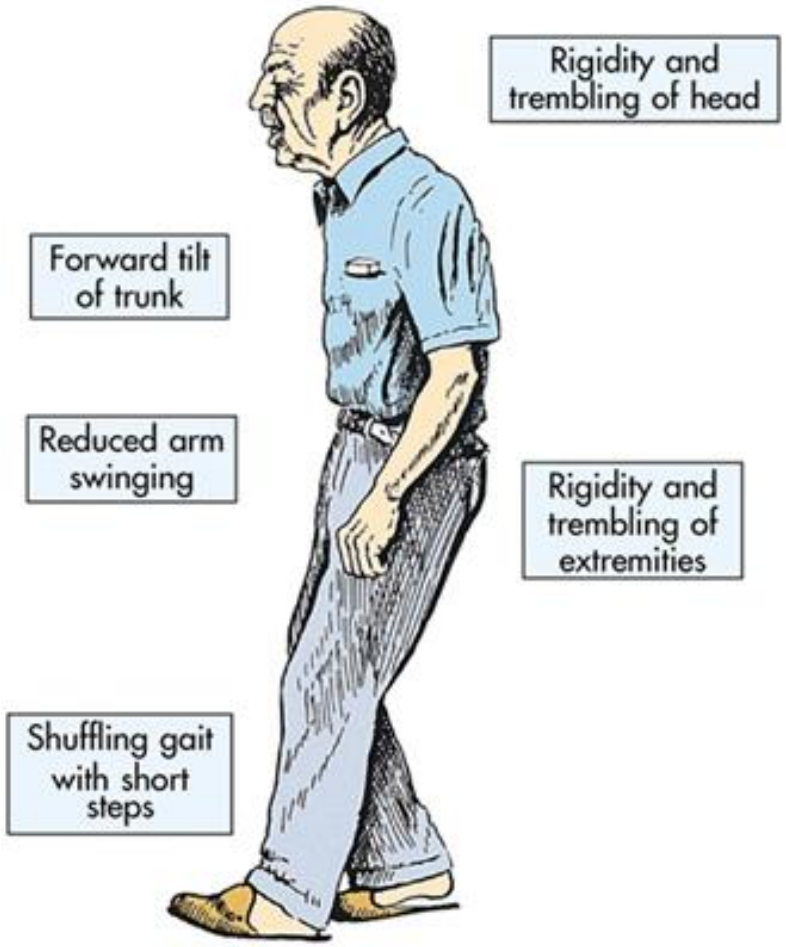
<u>Parkinsonism:</u>

- Etiology:
  - dopamine depletion of nigrostriatal dopaminergic pathway→disbalance of dopamin/ACh
  - uncontrolled function of GABAergic neurons (c.striatum→ s.nigra, g.pallidus, cortex)
  - background:
    - exogenous:
      - MPTP (meperidine derivative)→MPP+ (selective destruction) → new age in therapy, role of MAO inhibitors
      - drugs: dopamin receptor antagonists (antipsychotic drugs-butyrophenone/phenotiazine), reserpine (depletes dopamine stores)
    - endogenous:
      - neurotoxins
      - mutation of α-synuclein, LRRK2

Parkinson's disease

Symptoms:

- impaired motorium
  - hypo/bradykinesis
    - starting hezitation, freezing
    - mogigraphia
  - rigor
  - tremor
- impaired cognitive functions
  - cognitive slowing
  - dementia
  - aphasia
- autonomic symptoms
  - hypersalivation
  - obstipation
  - hypotension



Parkinson’s disease

Pharmacological ways

1. dopamine substitution:
   - levodopa

2. dopamine R agonism:
   - bromocriptin
   - pergolide
   - pramipexole - ropinirole
   - apomorphine
   - rotigotine

3. MAO/COMT inhibition:
   - selegilin
   - tolcapone/entacapone

4. acetylcoline blocking drugs:
   - benztropine mesylate
   - biperiden

Dopamine substitution

- levodopa (Dopaflex®)
  - metabolic precursor of dopamine
  - active form in CNS by DOPA decarboxylase
  - rapidly absorbed from small intestine
  - half-time:1-3 hours
  - 3% of administered levodopa enters CNS (first pass metab., peripheral decarb.)
  - peripheral dopa decarboxylase inhibitor
    - carbidopa (1:10)-(1:4)
    - benserazid
  - adverse effects:
    - vomiting, nausea (area postrema D2R agonism)
    - cardiac arrhytmias (tachycardia, VES), hypotension
    - dykinesias (choreoathetosis)
    - hallucinations, nightmares, euphoria (th.:clozapine)
    - fluctuation in response
      - end of dose - wearing off
      - on/off phenomenon (unrelated to timing of doses)
  - clinical use
    - levodopa (100 mg) + carbidopa/benserazid – sinement/madopar
    - levodopa+carbidopa+COMT inhibitor (entacapone)
    - tolerance in 3-4 years
    - decrease gradually! (abrupt cessation may cause akinetic state)
  - CI
    - psychotic patients
    - patients taking MAO-A inhibitor

Dopamine R agonism

- bromocriptine
  - ergot derivative
  - D_2R agonist
  - a.e.:nausea, vomiting
  - th.: akinetic crisis, hyperprolactinaemia
  - therapeutic dose: 7,5 - 30 mg
- pergolide
  - ergot derivative
  - D_1R and D_2R
  - more effective, than bromcriptine (combination therapy/refractory cases)
  - a.e.: cardiac valvulopathy, cardiac arrhythmias
- pramipexole - ropinirole
  - D_3R agonism (not ergot derivative)
  - monotherapy – first line drug in management of early PD
  - alternative route at levodopa th. fluctuation
- apomorhine
  - D_2R agonism
  - temporary relief of „off phenomenon”, akinetic crisis
  - a.e.:nausea, dykinesias, drowsiness
  - th.: 3-6 mg / max. 10 mg subcutaneous injection
- rotigotine
  - skin patch
  - early treatment of Parkinson’s disease

MAO inhibition

- selegiline (Deprenyl®)
  - irreversible inhibitor of MAO-B
    (at higher dose: MAO-A)
  - adjunctive therapy
    - prolonged effect/reduced dose of levodopa
    - reduce on/off, end of dose phenomenon
  - th. dose: 2x5mg/day
  - a.e.: insomnia

- rasagiline
  - more potent (1mg/day)
  - CI: SSRI, tricyclic antidepressants
    → serotonin syndrome

- MAO-A
  - norepinehrine, serotonin, dopamine
- MAO-B
  - dopamine, serotonin

COMT inhibition

- compensatory activation of COMT (due to inhib. of DOPA decarb.)
  - 3-OMD ↑, competition with levodopa (tp. in intestinal mucosa and BBB)
- tolcapone, entacapone
  - selective COMT inhibitors
  - rapidly absorbed
  - half-life: 2 hours
  - th.:
    - prolong „on” period
    - reduced levodopa dose
  - a.e.:
    - abdominal pain
    - dyskinesias
    - diarrhea
    - hepatotoxicity (tolcapone)
  - th. dose:
    - entacapone 3x200mg/day
    - tocapone 5x100 mg/day

Amantadine (Viregyt®)

- antiviral agent
- pharmacodynamic effects:
  - facilitating dopamine synthesis, release
  - antagonism on $A_{2A}R$ → potentiating dopaminergic function
  - Blocks NMDA (glutamate) R
  - Anticholinergic property
- clinical use:
  - acute application
  - beneficial eff. in rigor, tremor, akinesia
  - 2x100mg/day p.o.
- adverse effects:
  - depression, irritability, insomnia, agitation, confusion
  - acute toxic psychosis
- CI:
  - seizures
  - heart failure

Ach blocking drugs

- central acting antimuscarinic preparations
  - benztropine mesylate
  - biperiden
  - orphenadrine
  - procyclidine
  - trihexyphenidyl

- antimuscarinic effect (blocking M_1R, M_3R)

- a.e.:
  - tachycardia
  - mydriasis
  - dry mouth/skin
  - obstipation
  - agitation/agression

Emergency

Akinetic crisis:

- akinesis
- insuff. swallowing, insuff. respiration
- exsiccosis

- th::
  - bromocriptine (5-10mg), pergolide
  - amantadine inf. (2-3x 200mg) in mild cases
  - apomorhine inf. in severe cases
  - supportive th.:
    - antibiotics
    - anticoagulants
    - fluid/electrolyte supplementation

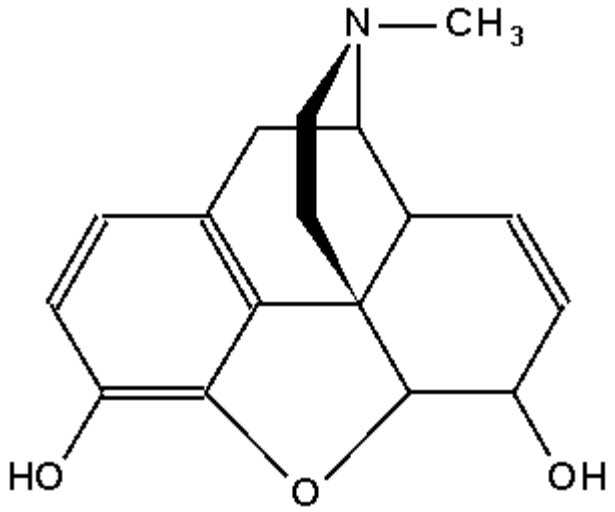
Major (Opioid) analgetics

History:

- opium (opos:"juice"), opiate, opioid
- obtained from"opium poppy" (Papaver somniferum)
- white substance→brown gum = OPIUM
- OPIUM contains alkaloids e.g.: morphine, narcotine, papaverine, etc.

Chemical structure:

- phenantrene derivative
- termed after Morpheus (God of dreams)
- two planar and two aliphatic rings
- N connected substitutive groups



morphine

Classification

- endogenous opioids
  - endorphins
  - enkephalins
  - dynorphins
- naturally occuring (morphine, codein, narcotin)
- semisynthetic (heroin, hydromorphone, oxycodone)
- synthetic (fentanyl, meperidine, methadon)

- based on chemical structure
  - phenantrenes
    - morphine, codeine, oxycodone
  - phenylheptylamines
    - methadone
  - phenylpiperidines
    - diphenoxylate, loperamide
    - fentanyl

Opioid receptors

μ R (MOR)
- cortex
- ventral/caudal thalamus
- medulla oblongata
- spinal cord (dorsal horn)
- peripherial tissue
- periaqueductal grey
- locus coruleus
- GIT

→ inhibition of resp., sedation, GIT effect, modul. of NT release

κ R (KOR)
- spinal cord
- hyppocampus, limbic area
- GIT

→ psychotomimetic effects, GIT effect

δ R (DOR)
- cortex
- brain stem
- peripherial tissues

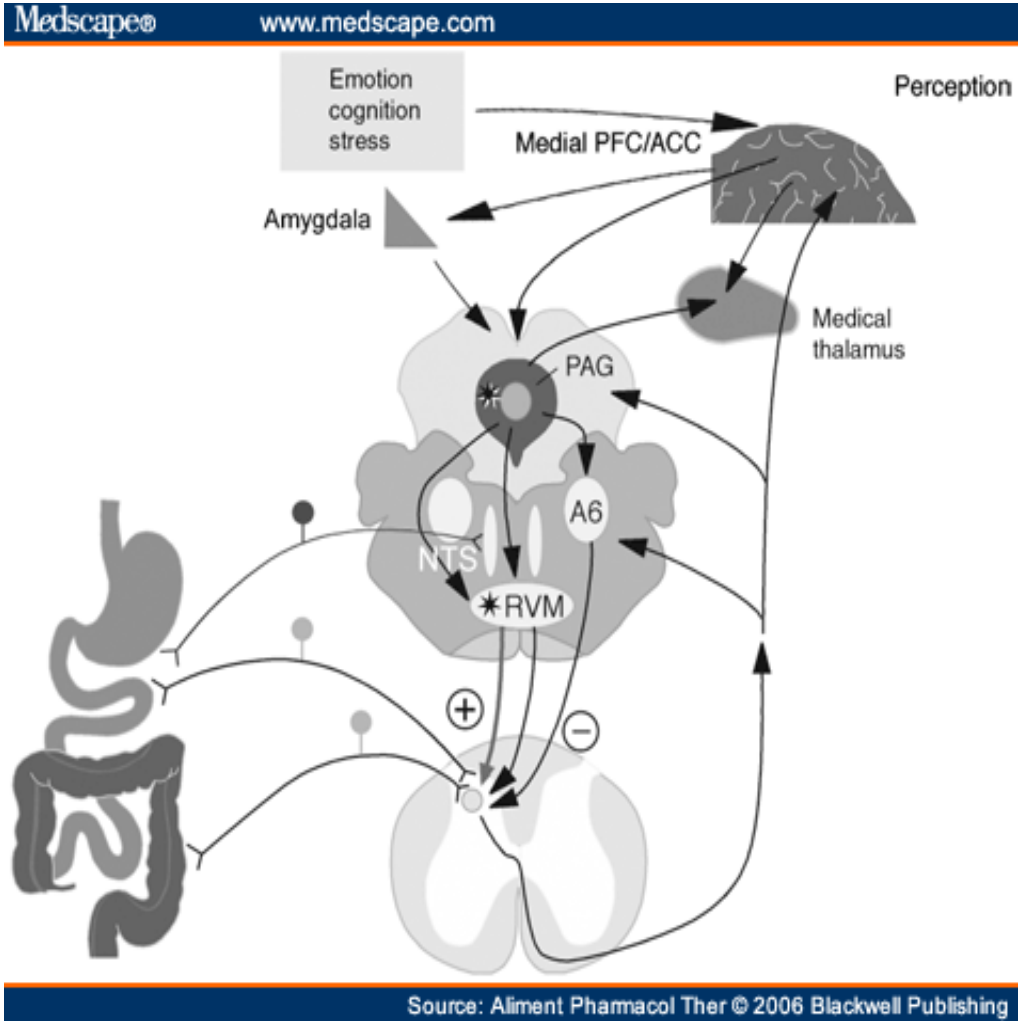
→ modul. of hormone and NT release

Novel opioid receptors:
ORL1:
orphanin opioid-receptor like subtype 1
endogenous ligand:
nociceptin (dynorphin like peptide)

Cellular actions:

- G protein coupled action→ blocking AC→cAMP↓
  - blocking VG Ca2+ channels on presynaptic nerve terminals (↓NT release)
  - opening K+ channels on postsynaptic neurons (hyperpolarization)

Nociceptive pathways



<u>ascending pathway:</u>

peripherial tissue
dorsal horn
spinothalamic tract
thalamus
cortex (area postcentralis)

<u>descending (modulatory) pathway:</u>

periaqueductal grey, raphe nucleus
NTs: serortonine, endogene opioids

locus coruleus
NTs: NA, A, D, Ach

inhibited by GABAerg interneurons
(tonic inhibitory effect)

Opioid analgetics (especially morphine)

Pharmacokinetic features:

- modest absorption from GIT
- ineffective per os
  - hydrophilic structures are absorbed poorly
  - high first-pass metabolism (except codein, oxycodone)
- highest concentrations in highly perfused organs
- metabolized in liver
  - M_3G, effect on GABAerg R→↑cc.→seizures
  - M_6G (10% of morphine degr.) 4-6x potency comp. to morphine
    - metabolite of codeine (pediatric application?)

Opioid analgetics

CNS effects:

- analgesia
  - reduce sensory and emotional (affective) components of pain
- euphoria
  - pleasent floating sensation with lessened anxiety and distress
- sedation
  - drowsiness
  - clouding of mentation
- respiratory depression
  - depressed response to CO_2 challenge→Pa_{CO2}↑
  - dose-related
  - dangerous in ICP, COPD, asthma
- cough supression
  - supression of cough reflex
  - airway obstruction!
- miosis
  - no tolerance develops (see later)→diagnostical symp. in opioid intoxication
- truncal rigidity
  - spinal cord action, failure in ventillation
- nausea and vomiting
  - area postrema-chemoreceptor trigger-zone
- hyperthermia
  - anterior hypothalamus – μR agonism

Opioid analgetics

Extracranial effects:

- Cardiovascular system
  - hypotension
    - central depression of vasomotor system
    - release of histamin
  - tachycardia
    - meperidine (pethidine)
  - Pa_{CO2}↑→cerebral vasodilation→ICP↑
- GIT
  - spastic obstipation
    - tonic (persistent contraction)↑
    - motility (rhythmic contr. and relax.)↓
- Biliary tract
  - contraction of biliary smooth muscle
  - contraction of Oddi sphincter
- Renal
  - antidiuretic effect, RBF↓
- Uterus
  - reduce uterine tone
  - labour prolongation

Opioid analgetics

Therapeutical application:

- Analgesia
  - severe, constant pain (cancer, terminal illnesses)
  - fentanyl transdermal system (fentanyl patch, Durogesic®)
  - PCA vs. fixed interval administr.
- Acute pulmonary oedema (ALVF)
  - preload↓
  - afterload↓
  - reduce anxiety, generalised sympatic tone↓
  - decreases hyperventillation, resp. panic
  - ACS
- Anaesthesia
  - sedative, anxiolytic, analgesic properties
  - premedication, ET intubation: 100µg Inj. Fentanyl
  - epidural/subarachnoideal administration
- Supression of cough (antitussive agents)
  - codeine, oxycodone
- Diarrhea
  - never if diarrhea is associated with infection

Opioid analgetics

Alternative routes of administration

- i.v. application
  - rapid effect
  - respiratory depression
- rectal suppositories
  - morphine, hydromorphone
- transdermal patch
  - fentanyl TTS
- intranasal application
  - avoiding first pass metabolism
  - butorphanol
- PCA
  - demanded application of preprogrammed dose
- i.m. injection

Endogenous opioids:

- endorfins
  - hypophysis: POMC→ACTH + α-MsH + β endorphin
    - μR affinity↑
    - supraspinal/spinal analgesia, sedation, inhibition of respiration
- dynorphins
  - dynorphin A, dynorphin B
    - κR affinity↑
    - supraspinal/spinal analgesia, slowed GIT motility
- enkephalins
  - met-enkephalin, leu-enkephalin
    - δR affinity↑
    - supraspinal/spinal analgesia, slowed GIT motility
    - modulation of hormone and neurotransmitter release

Opioid analgetics

- diamorphine (heroin)
  - diacetyl derivative of morphine (lipophylic structure!!!)
  - rapid crossing of blood-brain barrier→rush↑
  - less emetic
  - dependence!
- codeine
  - IA: 20% (analgesic potency)
  - no euphoria, no addiction
  - antitussive activity
  - active metabolite: M6G
  - combined with paracetamol, acetaminpohen
- methadone
  - bioavailability↑→oral application
  - long term acting
  - potent analgesic effect
    - μR agonism
    - blocking NMDA R
    - blocking monoamine reuptake system
  - lower euphoriac effect
  - used treating morphine/diamorphine addiction

Opioid analgetics

- pethidine (meperidine):
  - no sedative effects (restlessness)
  - antimuscarinic action
  - hallucinogenic, convulsant effect (active metabolite-normeperidine)
  - no uterus relaxation (analgesia during labor)
  - a.e.: Serotonin syndrome
    (co-application with MAO-inhibitors)

- fentanyl, sufentanyl
  - 100x analgesic effect
  - anaesthesia practice
  - PCA, patch

- tramadol
  - weak μR agonist
  - less potent (analgesia)
  - no resp. depressive effect
  - nausea, vomitus!

- buprenorphine
  - partial μR agonism, κR antagonism
  - long-term action
  - detoxification of heroine abusers
  - respiratory depression!

Opioid analgetics

- diphenoxylate, diphenoxin, loperamide
  - peripherial effect, no pass to CNS
  - dipehenoxylate + atropin= Reasec®
  - obstipation

- Opioid antagonists
  - μR, δR, κR antagonism
  - ANTIDOTUM!
  - naloxone
    - 0,1mg-0,4mg i.v.
    - short half-life (intox. relapse)
    - „over-shoot" effect (rebound NA, ACh release)
    - 10 mg naloxone : 25 mg heroin
  - naltrexone
    - half-life: 10 hours → prolonged effect
    - oral application

Opioid analgetics

1. tolerance
   - 2-3 weeks at therapeutic dose
   - background: persistent activation of opioid receptors
     - up regulation of cAMP system
     - receptor recycling
       - receptor endocytosis
     - receptor uncoupling
       - structural dysfunction in opioid receptors
   - tolerance to euphoriac effect, analgesic effect, anxiolytic effect
   - no tolerance to respiratory depression, miosis!!!!!

2. physical dependence
   - withdrawal/abstinence syndrome (lasting days)
     - autonomic: rhinorrhea, lacrimation, mydriasis, diarrhea, vomitting, piloerection
     - seizures, myoclonus
     - hyperthermia

3. psychologic dependence
   - compulsive use/craving (drug seeking behaviour)
   - elevated incidence at MD's!!!

Opioid analgetics

- Detoxication methods
  - supportive therapy
    - fluid/electrolyte suppl.
    - anticonvulsive agents: BZD
    - antipsychotics
    - antihypertensive:
      - clonidin (α_2R agonism)-central acting sympatholytic drug
      - βR blockers
  - methadon substitution
    - long acting μR agonist
    - less euphoriac effect
    - receptor occupancy – no effect when morphine/heroin applied
    - dose reduction
  - naltrexon therapy
    - long acting μR, δR, κR antagonism
    - p.o.
    - application after withdrawal symptoms
  - Ultra short opioid detoxification
    - i.v. naloxone/naltrexone
    - massive withdrawal symptoms
    - supportive therapy !!!!