Uterotonics, tocolytics, smooth muscle relaxants

Vasoactive peptides

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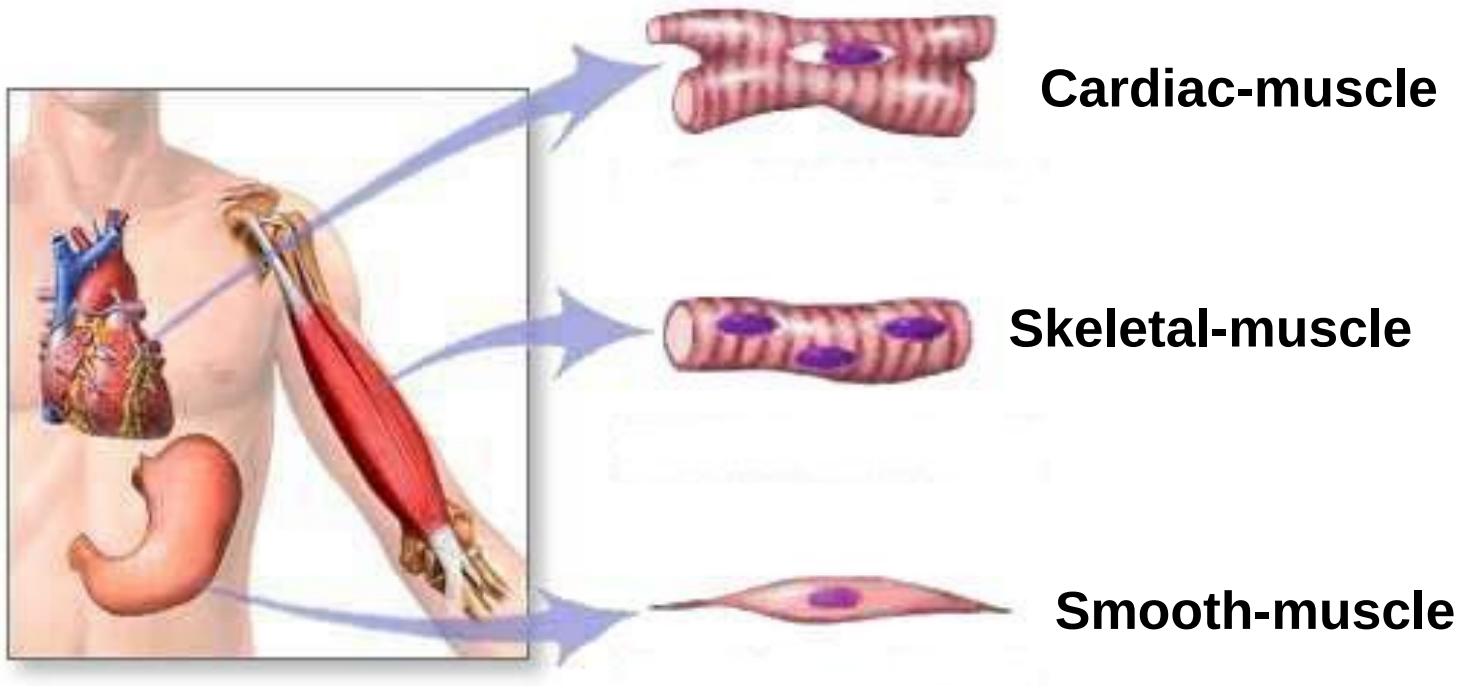
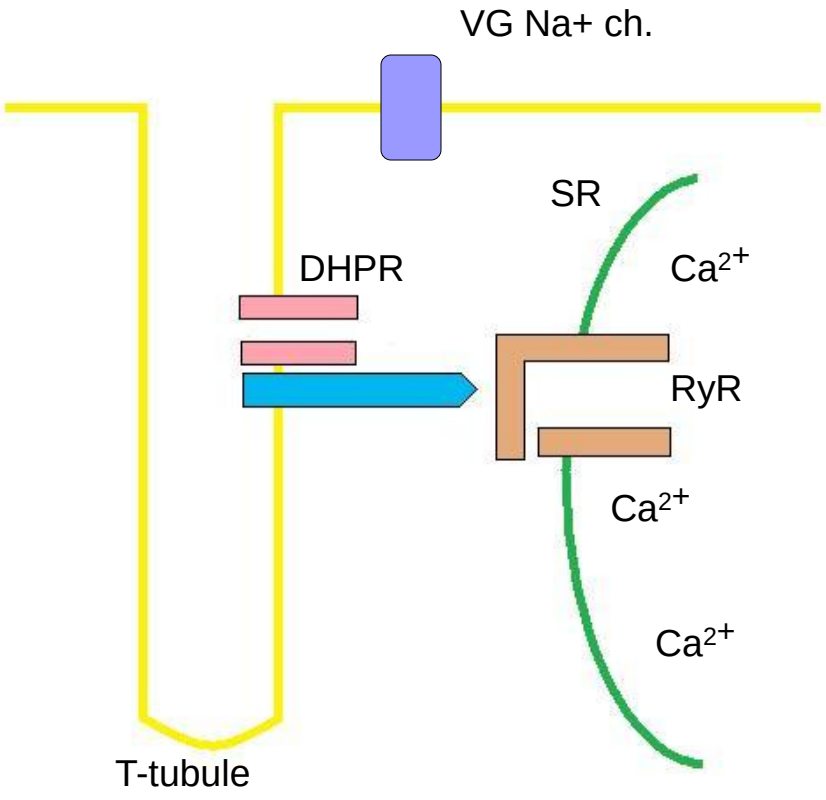
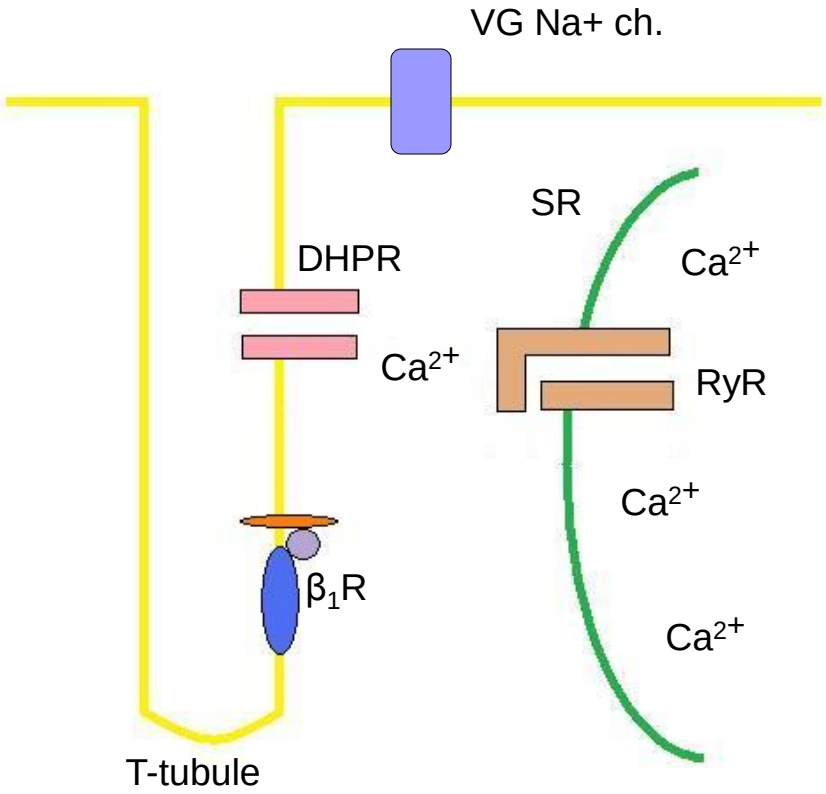


Length?
Neural regulation?
Spontaneous activity?
Response?
Receptor-profile?

Skeletal muscle



Cardiac muscle

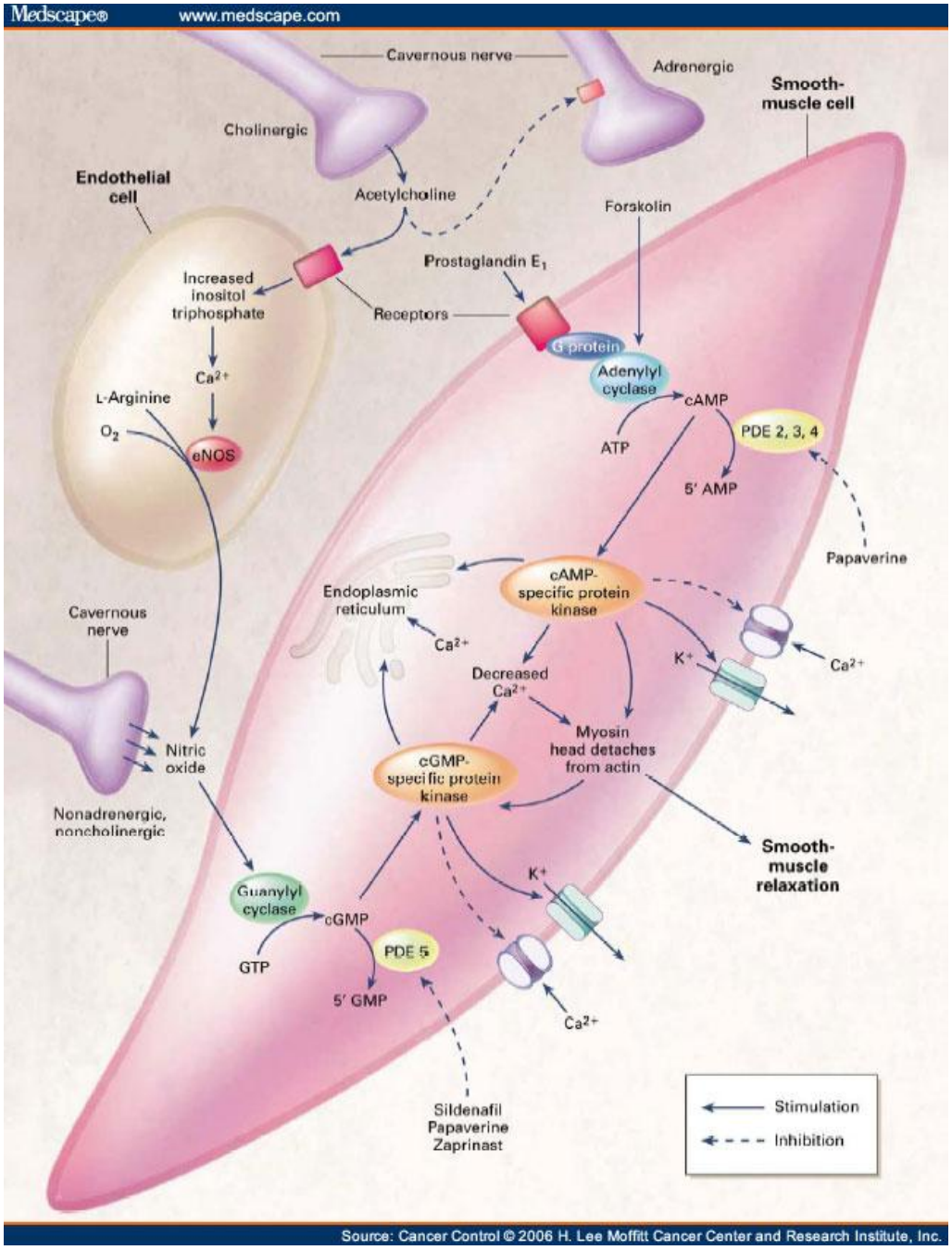


Pharmakologic targets:

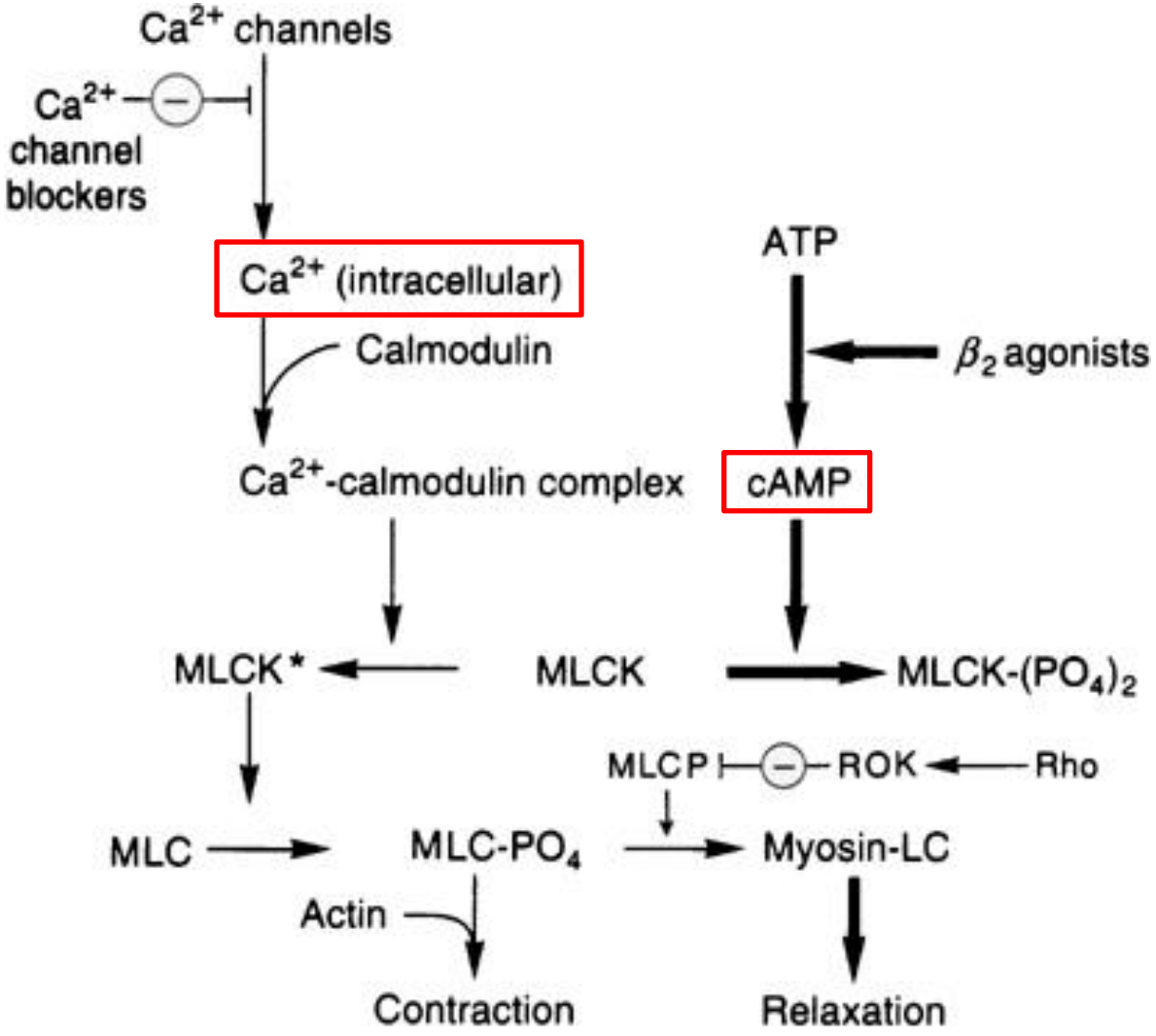
- mAch (M_1R, M_3R)
- adrenoceptors (α, β)
- L-type Ca^{2+} channels
- PG receptors
- 5HT receptors
- K^+ channels (+) chromokalin
- Histamin receptors
- AT receptors
- NO (vessels) – sGC!
- ANF receptors – GC!
- PDE-inhibitors – inodil.!

Σ:

- contraction
  - cAMP↓, Ca2+↑
- relaxation
  - cAMP↑, cGMP ↑



Contraction – Relaxation (sm)



Physiologic, neuroendocrine regulation of the uterinal tone

- pacemaker cells - fundus (myometrium)
- regular, rhythmic, coordinated, spontaneous myometrium contractions (fundus→cervix)
- associated with menstrual cycle! (pregnancy)
  - oestrogen
  - progesteron
  - oxytocin
  - prostaglandines
  - uterinal adrenerg system
- labor
  - (fetal) cortisol↑ → oestrogen/progesteron↑ (placenta)

Endocrine regulation of the uterinal tone (motility)

<u>Oestrogen</u>

- membrane depolarisation (myometrium)
- oxytocin R ↑
- αR sensitivity ↑
- endogenous PG synthesis ↑ in decidual cells
- gap junction ↑

<u>Progesteron</u>

- membrane-stabilising effect (myometrium)
- oxytocin R ↓
- βR ↑ sensitivity ↑
- endogenous PG synthesis↓

Endocrine regulation of the uterinal tone

- Prostaglandines - $PGF_{2\alpha}$, PGE_2, PGI_2-(prostacyclin)
  - endogenous prostaglandin-synthesis
  - endometrium-myometrium
  - 2. phase of menstrual cycle (luteal phase)

- uterinal tone (motility) frequency↑, amplitude↑, cervix dilation
  - in every period of gestation!
  - before terminus: placenta

- PG synthesis can be…..:

stimulated:

- Ca2+
- platelet activating faktor (PAF)
- β-agonists
- oestrogene
- TGF-α
- cortisol
- EGF
- IL-1 (α és β)
- lipopolisacharides
- TNF
- CRH, ACTH

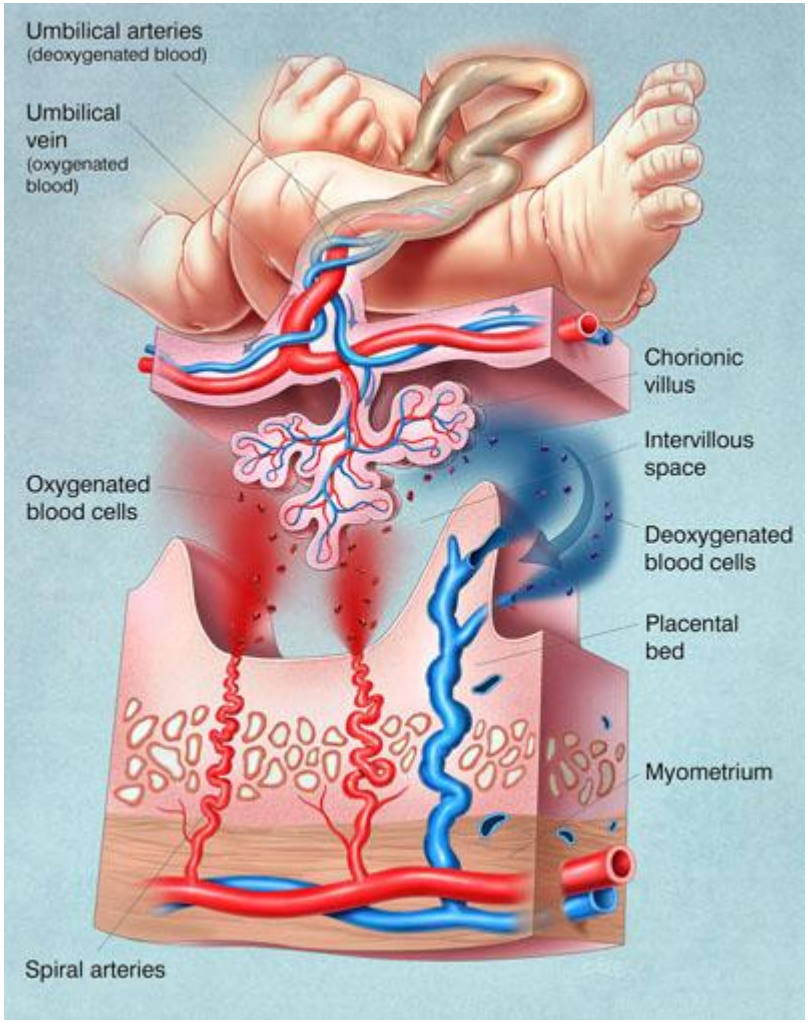
inhibited:

- lipocortin
- progesterone
- interferon α
- chorial phospholipase A2 inhibitor (lipokortinVII)

Drugs acting on uterus

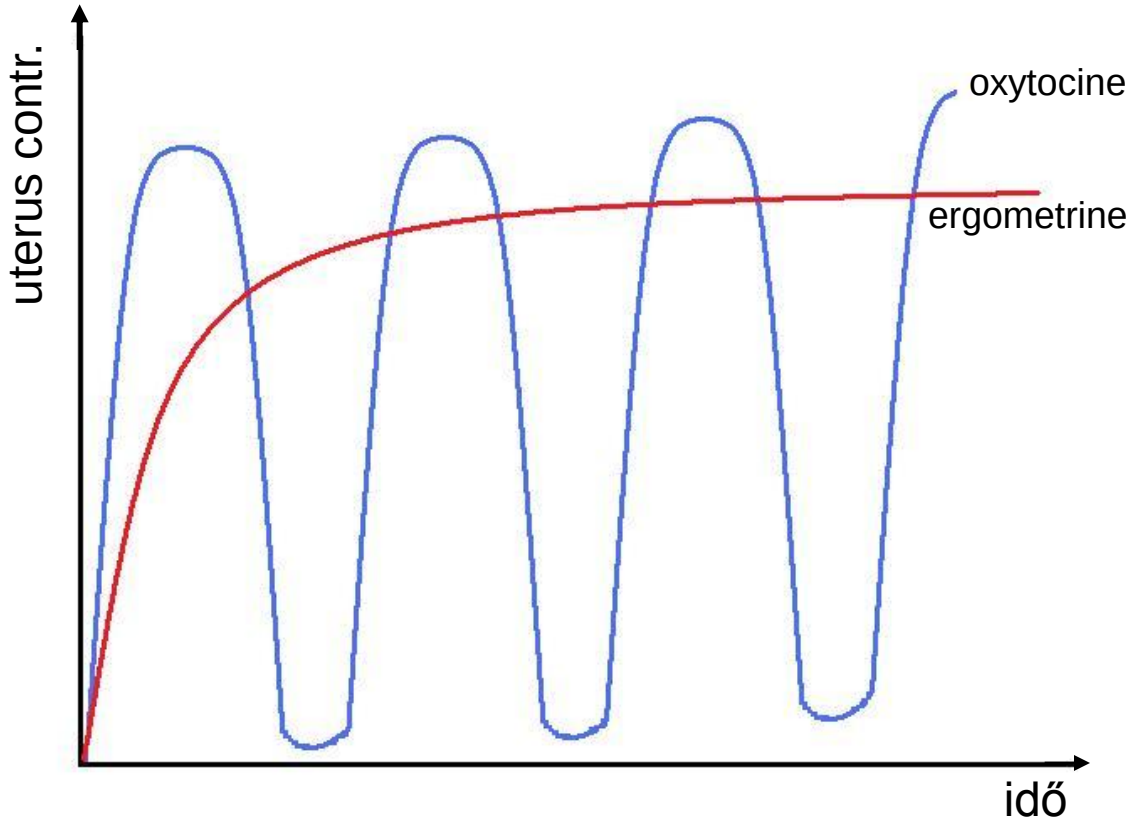
- Uterotonics:
  - Labor induction (delivery, abortus)
  - Labor stimulation, enhancement (inertia uteri)
  - 3rd (placentar) stage induction
  - Prevention and therapy of postpartum haemorrhage (tonic cc.)
    - i.v. application
    - monitoring! (CTG)
  - KI:
    - rupture of uterus
    - placenta praevia
    - abruption of placenta

Uteroplacentar unit



- phases of labor:
  - 1st stage (cervix<10 cm)
    - early labor phase
    - active labor phase
    - transient phase
  - 2nd stage (pushing phase)
  - 3rd stage (placentar phase)
- phasic or tonic contraction ???

oxytocin vs. ergometrin



tonic or rhythmic uterus contraction?

Uterotonics

- oxytocin
  - synthesis, storage:
    - hypothalamus (nucleus supraopticus/paraventricularis)
    - neurohypophysis
    - ADH (Leu→Arg; Arg→IsoLeu)- structural resemblence!!!
    - $t_{1/2}$: 5 min
  - effect:
    - Oxytocin R (ic. Ca2+↑)
    - uterus contraction↑
    - myoepthelial cell contraction↑ („milk let down”)
    - clinical use: 500ml dextrose – 5NE oxytocin (10NE/l)
    - in high doses – tonic uterus contraction
  - th.: 2-3 IU (1IU=0,5 mg)
    - stimulating/augmenting labor
    - 1st, 2nd stage
    - dgn.: estimating placentar reserve – HR (before terminus)
  - th.: 5-10 NE
    - 3rd stage
    - prevent postpartum haemorrhage
  - a.e.:
    - hypotension, tachycardia (CAVE: halothan - RR↓)
    - rupture of uterus
    - electrolyte disturbances (ADH-resembl.!)

Uterotonics

- ergot-alkaloids
  - Claviceps purpurea – alkaloids – 5HTR, αR-es, DR-es
  - ergotism
    - gangraena
    - abortus
    - psychotic dysfunctions (hallucination)
  - effect:
    - KIR:
      - hallucinogene ($5HT_2R$ agonism)
      - extrapyramidal effect (D_2R agonism)
      - migraine th. (5HTR)
    - CV
      - RR↑ (αR, DR)
    - uterus
      - in low doses – rhytmic, regular, phasic uteruscontr..↑
      - in large doses – TONIC, CONSTANT uteruscontr..↑
  - adverse effects:
    - tachycardia, angina pectoris
    - necrosis in extremities
  - clinical application:
    - ergotamine- (Ergam) - 0,15-0,6 mg i.m. v. 3x20 drops p.o.
    - methylergometrine (Methergin)– 0,2 mg i.m./.i.v.

Uterotonics

Ergot alkaloide	$5HT_1R$	Dopamine receptor	α adrenoceptor	Uterus cc.
Ergotamin	0	–	(PA)	++
Dihydroergotamin	0	–	–	+
Ergometrin	(PA)	(PA)	(PA)	+++
Bromocriptin	–	A	(PA)	–
Methysergid	(PA)	–	–	–

Uterotonics

- Prostaglandines
  - uterinal tone frequency↑, amplitude↑, cervix dilation↑
    - in every phase of gestation
    - N.B.: misoprostol (Cytotec) – therapy of gasric ulcer
  - th.: stimulating /induction of labor, induction of abortus
  - clinical use
    - local– gel (Prepidil-PGE2), ProstinE2 (dinoprostone)
    - Prostin E2 – PGE_2 analogue (dinoproston) injection
    - sulproston (Nalodor) injection - postpartum haemorrhagia
  - a.e..:
    - headache
    - GIT (nausea, vomitus)
    - bronchospasm, chest pain
  - CI.:
    - asthma bronchiale
    - epilepsy

Drugs acting on uterus

- Tocolysis: inhibition of uterinal motility (tone)
  - delaying premature birth (25%)
  - in emergency
    - acute fetal distress
    - placenta praevia
    - rupture of uterus
  - Main purpose: maturing fetal lungs - distress↓(app.48-72 hours)
  - CI:
    - haemorrhage
    - maternal disease: DM, arrhythmia
    - fetal disease (infection, abortus, dead fetus)

Tocolytic drugs

- β sympathomimetics
  - th.: asthma bronchiale.! – selective β_2 agonists
  - fenoterol
  - salbutamol (Brycanil) -10 μgramm/min i.v. (8-12h)
  - a.e:
    - tachycardia – ECG monitor!
    - hypotension
    - hyperglycaemia – BG controll!
- atosiban
  - oxytocine receptor antagonist
  - 6,75 mg i.v.

Tocolytic drugs

- $MgSO_4$
  - mechanism of action:
    - bivalent cation (MIMR????)
    - β sensitivity↑
  - th.:
    - 4-6 g/15-20 min i.v. bolus , 2-4g/h i.v.
    - clinical use: VT (torsade de pointes)
    - ANTIDOTE: Ca^{2+} gluconate
    - a.e.:.:
      - AV-block, bradycardia
      - dizziness

- NSAIDs
  - mechanism of action:
    - COX inhibition ($PGF_{2\alpha}$, PGE_2, PGI_2 ↓)
  - significant tocolytic effect
  - reversible vs. irreversible
  - irreversible: aspirin (postpartum haemorrhage)
  - indometacin: 50-75mg/day p.o.
  - th.: only before 28. gestation week N.B.: closure of arterious duct. (Botallo)

Tocolytic drugs

- Ca2+ channel blockers
  - mechanism of action:
    - blocking L type Ca2+ channels - DHP (nifedipin)
  - efficacy↑
  - a.e.:
    - „flushing”, headache
  - th.: not recommended (fetal distress, pulmonaryedema)
- metilxanthines
  - aminophylline
  - cAMP PDE-inhibition
  - th.: temporary effect
  - side effect profile↑
- ethanol
  - hypophyseal oxytocin release↓
  - direct relaxing effect
- anxiolytic drugs
  - sedative, anxiolytic effect
  - diazepame, promethazine

What/When should I administer….?

Uterotonic agent

- Labor induction
- Labor „augmentation”
- Postplacentar phase
- Postpartum haemorrhage

Tocolytic agent

- Premature birth
  - prevention
  - prolongation
- Emergency
  - acut fetal distress
  - placenta praevia
  - prolapse of umbilical cord
  - threatening rupture of uterus

Drugs acting on smooth muscle

- Spastics
  - cholinomimetics
    - pilocarpin, muskarin
    - neostigmin, organo-phosphates
  - ergot-alkaloids, 5HTR agonists
    - ergometrin
  - oxytocine
  - prostaglandines
- Spasmolytics
  - cholinolytics
    - atropin, homatropin, ipratropium-bromid
  - sympathomimetics
    - selective βR agonists
      - fenoterol, salbutamol
  - smooth muscle relaxants
    - papaverin, drotaverin

Spasmolytics

- papaverine
  - Papaverinium chloratum
  - opium (morfine, codein, narcotin, papaverine)
  - blocking VG Ca^{2+} channels/ inhibiting PDE II, III, IV
  - Smooth muscle relaxing effect
    - GIT, biliary tract
    - Urogenital tract
    - Respiratory system
  - CV
    - (-) chronotrop effect
    - ectopic focus↑
    - vasodilatation (RR↓)
    - a. pulmonalis, cerebral art. dilation (pulm. emb., migrain th.)
  - analgetic, sedative effect (high doses)
  - PPB↑
  - 50-100 mg i.v, i.m. (CAVE: bradycardia, AV-block, ES, VF)
  - p.o.: slow absorption→ethaverin, moxaverin

Spasmolytics

- drotaverine (No-Spa®)
  - izokinolon derivative
  - drotaverine > papaverine (potency)
  - oral bioavailab.↑
  - p.o., i.m., i.v.
  - th.: 40-120 mg
  - co-application
    - ibuprofen/diclofenac + drotaverine

Spasmolytics

- caroverine, mebeverine
  - effect:
    - VG Ca^{2+} channel blockade
    - 10x (papaverine)
  - p.o., absorption↑
  - GIT, biliary tract
  - th.:
    - caroverine: 20-40mg
    - mebeverine: 150-200 mg

- trimebutine
  - effect
    - peripheral agonist of μ κ δ R
    - th.: IBS

Spasmolytics

- pinaverin
  - pinaverium bromide
  - smooth relaxing effect
    - blocking of VG Ca2+ channels
    - cholinolytic effect
      - ↓CV side effect profile
  - th.:
    - GIT, biliary tract
    - urogenital tract
    - PMS, dymenorrhea
- AchR blocking drugs
  - no primer – solitaer application
    - broad side effect profile! – atropin intox!
    - coapplication (+NSAID) – synergism
      - Troparinum combinatum (homatropine + papaverine)
      - Meristin (papaverine + phenobarbitale)
      - Steralgin (methylhomatropine + drotaverine)
      - Reasec (atropine + diphenoxylate)