Pharmacologic targets:

- mAch (M1R, M3R)
- adrenoceptors (α, β)
- PG receptors
- 5HT receptors
- Histamin receptors

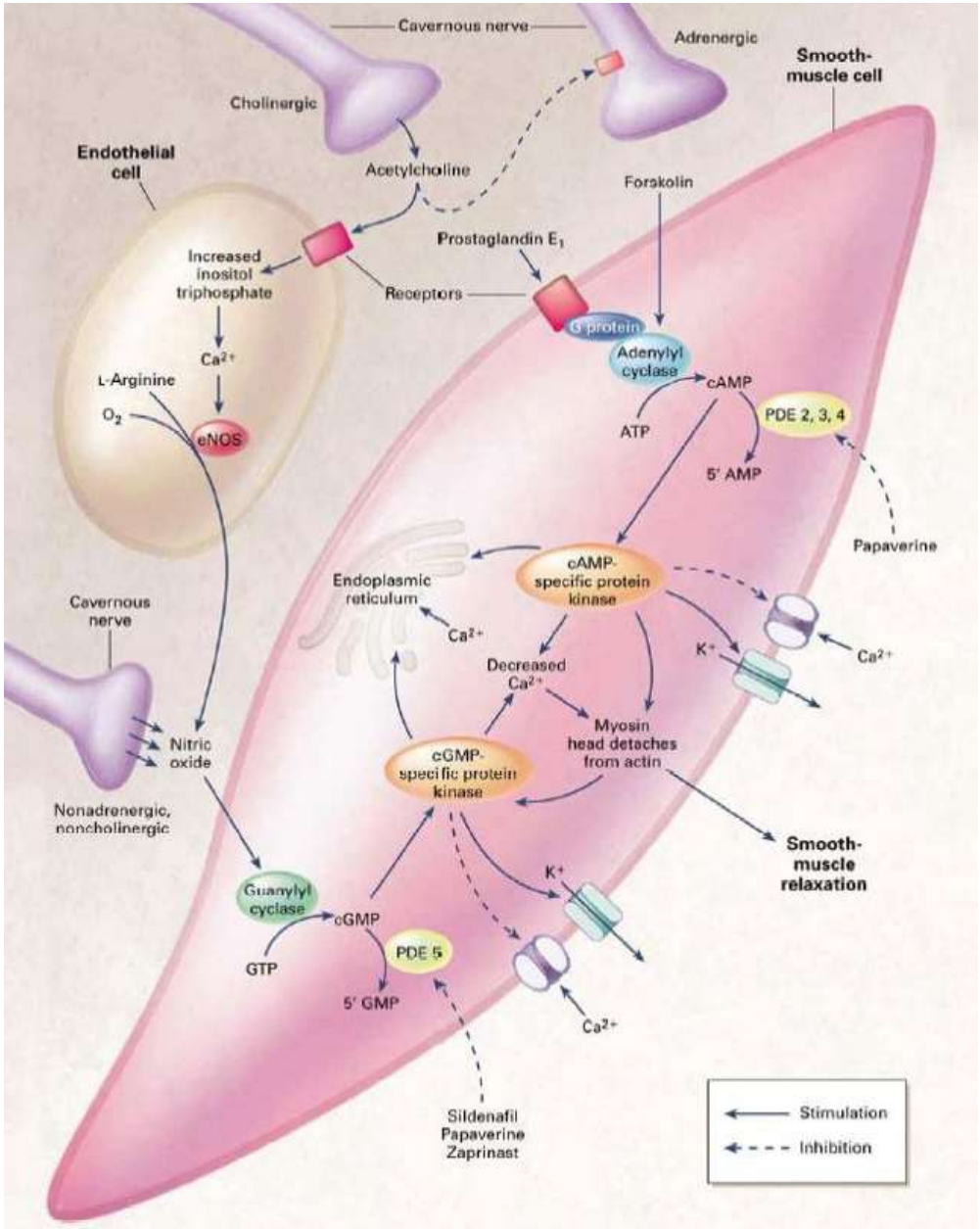
- L-type Ca^{2+} channels
- K^+channels

- AT receptors
- ANF receptors – GC!

- NO (vessels) – sGC!
- PDE-inhibitors

Σ:

- contraction
  - cAMP↓, Ca^{2+}↑
- relaxation
  - cAMP↑, cGMP↑



Physiologic neuroendocrine regulation of the uterinal tone

- pacemaker cells - fundus (myometrium)
- regular, rhythmic, coordinated, spontaneous myometrium contractions (fundus ⟶ cervix)

- changes during the menstrual cycle and pregnancy!
- endocrine and autonomic control
  - estrogen
  - progesteron
  - oxytocin
  - prostaglandins
  - uterinal adrenerg system – β_2 (relax) and α (contract)
- menstrual cycle
  - weak ⟶ stronger
- pregnancy
  - early: estrogen + progesterone ⟶ hyperpolarization
  - labor: (fetal) cortisol↑ ⟶ estrogen/progesterone↑ (placenta) / oxytocin ?

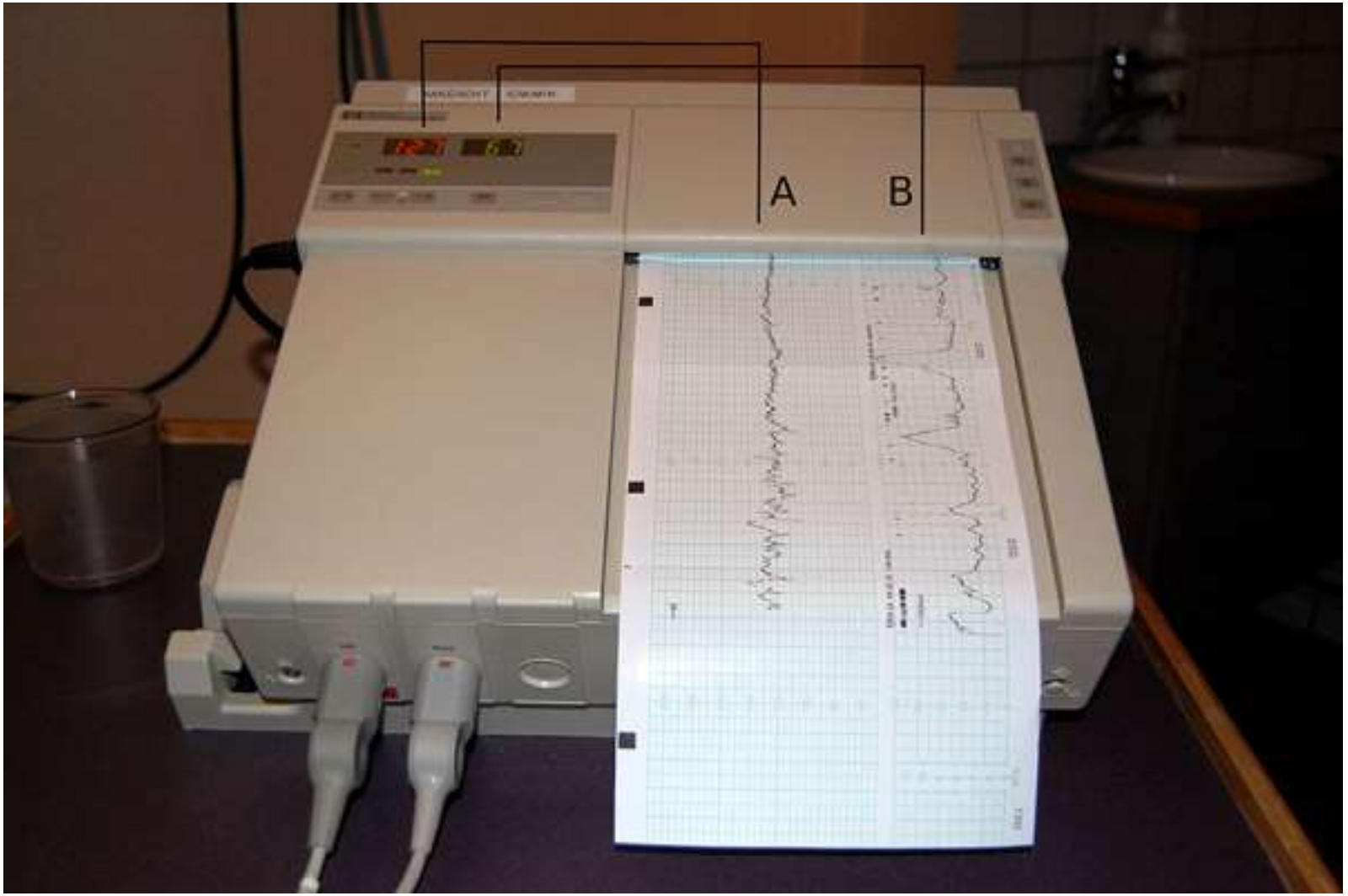
Endocrine regulation of uterinal tone (motility) in pregnancy

Estrogen

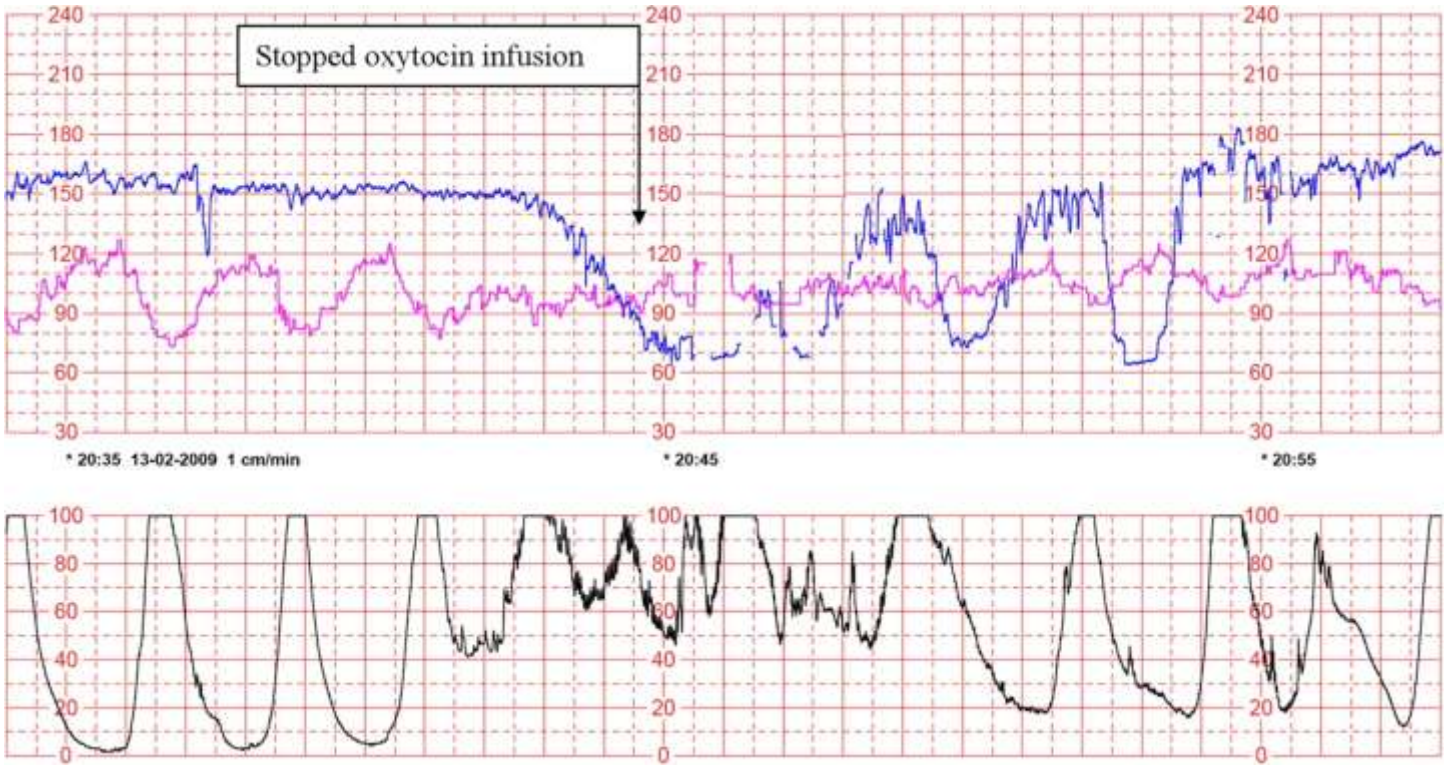
- membrane depolarisation (myometrium)
- oxytocin R ↑
- αR sensitivity ↑
- endogenous PG synthesis ↑ in decidual cells
- gap junction ↑

Progesterone

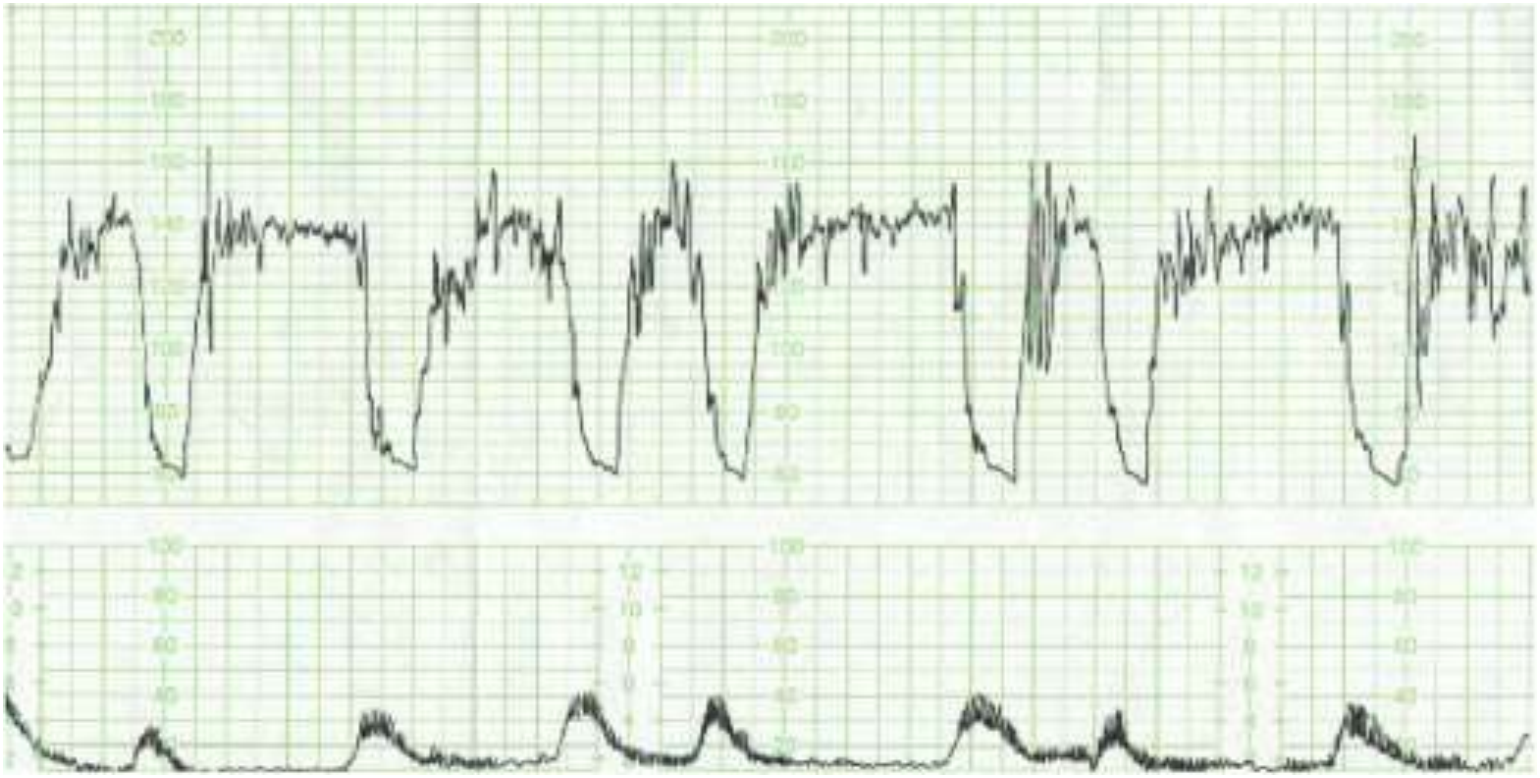
- membrane-stabilising effect (myometrium)
- oxytocin R ↓
- βR number ↑ and sensitivity ↑
- endogenous PG synthesis ↓


A
B

Cardiotocography recording - oxytocin



Cardiotocography of a case of oxytocin-induced uterine hyperstimulation. **Hypertonic uterine contractions resulted in fetal bradycardia.** After stopping the oxytocin infusion for 9 mins, the fetal bradycardia recovered.



Drugs that stimulate the uterus (uterotonics)

- **oxytocin**
  - natural peptide hormone (9 AA – nonapeptide)
- **ergometrin** / ergotamin
  - ergot alkaloids (origin: fungus - *Claviceps purpurea*)
- **prostaglandins**
  - $PGF_{2\alpha}$, PGE_2, PGI_2

Clinical use of uterotonics

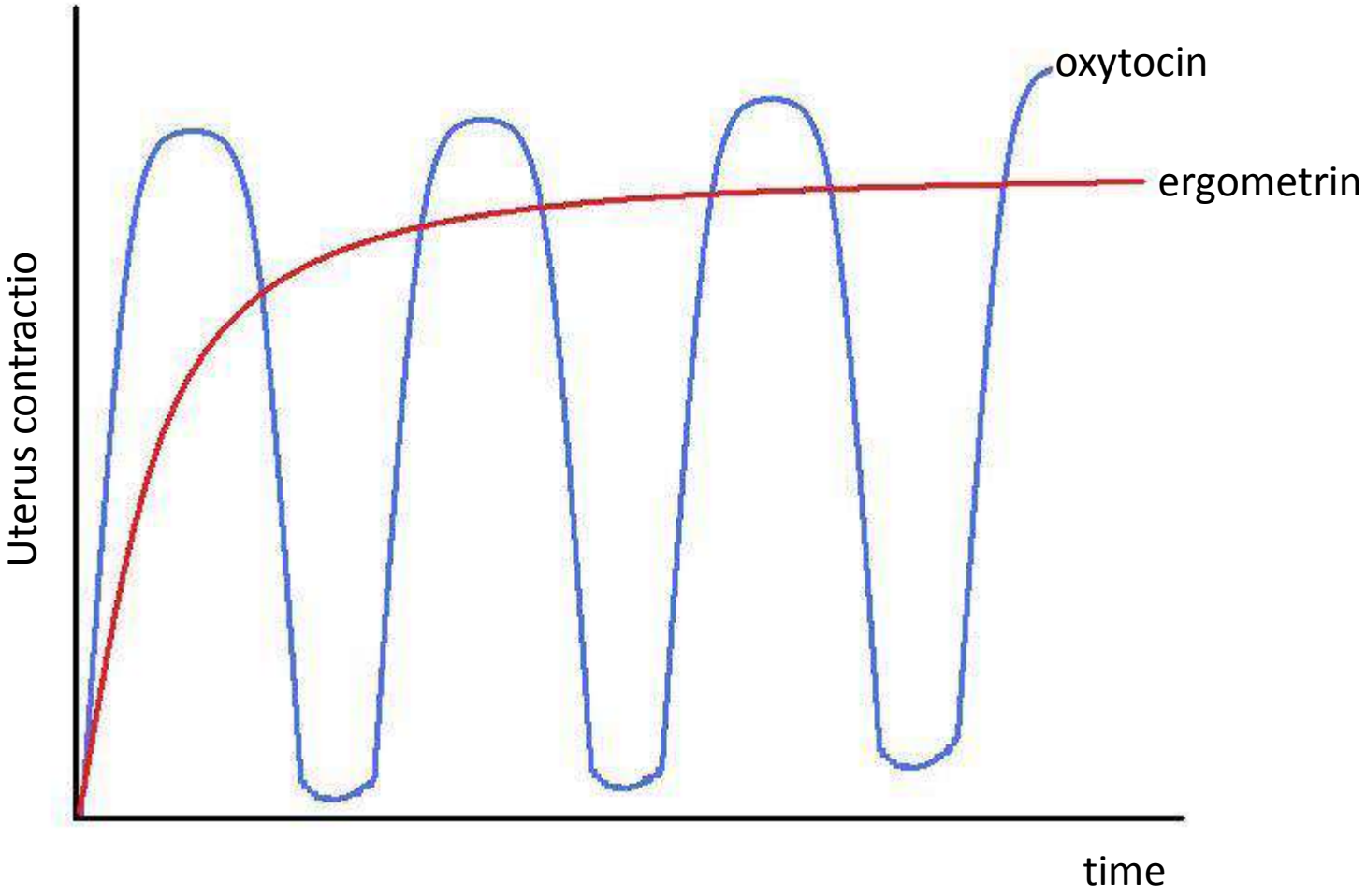
Indications:

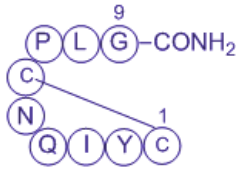
- labor induction (delivery, abortus)
- labor stimulation, enhancement (inertia uteri)
- 3rd (placentar) stage induction
- prevention and therapy of postpartum haemorrhage (tonic)
  - i.v. application
  - monitoring! (CTG)

Contraindications:

- rupture of uterus
- placenta praevia
- abruption of placenta

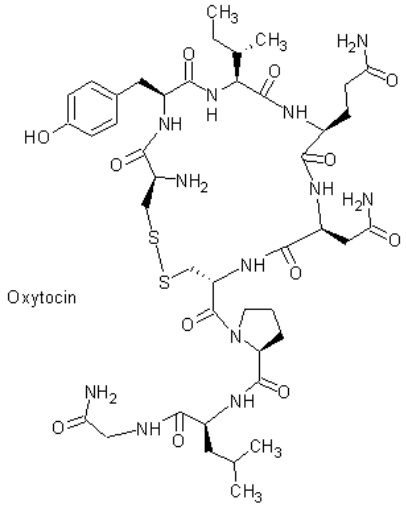
Difference in action between oxytocin and ergometrin

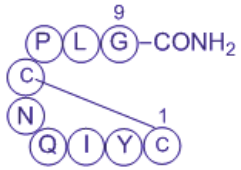




Oxytocin

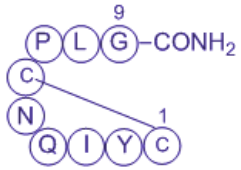
- Οχνσ τοκοσ ≈ sharp childbirth / sudden delivery
- Synthesis, storage
  - hypothalamus (supraoptic/paraventricular nucleus)
  - neurohypophysis
- Structure
  - 9 AA, (6 circular)
  - ADH (Leu→Arg; Arg→IsoLeu)
    - structural resemblence!!!
- Pharmacokinetics
  - iv. infusion
  - $t_{1/2}$ ≈ 5 min





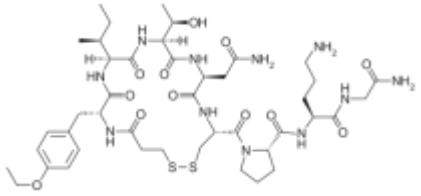
Oxytocin

- Effect
  - Oxytocin R (ic. Ca^{2+}↑) ⟶ uterus contraction↑
  - myoepithelial cell contraction↑ („milk let down”)
  - role in mating and parenting benavior
- Clinical use
    - 500ml dextrose + 5IU oxytocin (10IU/l)
    - in high doses ⟶ tonic uterus contraction
  - Th: **stimulating/augmenting labor** – 1st, 2nd stage
    - 2-3 IU (1IU=0,5 mg)
  - Dg.: estimating placentar reserve – HR (before terminus)
  - Th.: 3rd stage / prevent postpartum haemorrhage
    - 5-10 IU



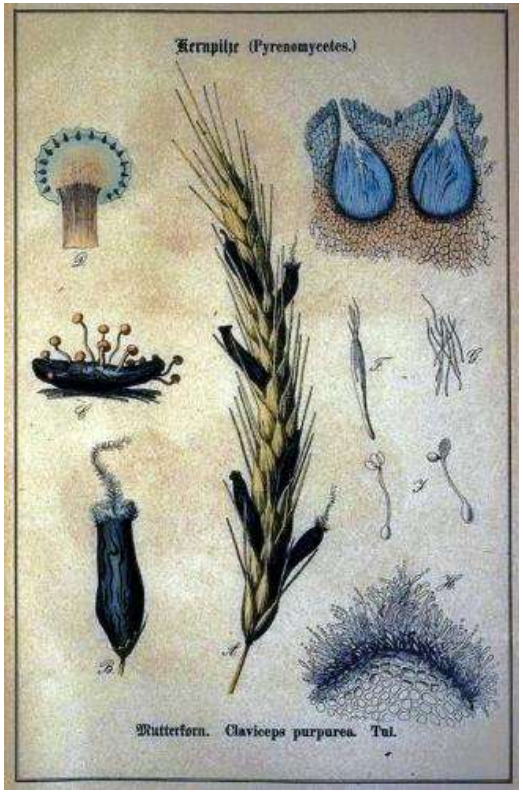
Oxytocin

- adverse effects:
  - hypotension, tachycardia (CAVE: halothane - RR↓)
  - rupture of uterus
  - electrolyte disturbances (ADH-resembl.!)
    - water retention
- oxytocin receptor antagonists
  - atosiban (Tractocile, Antocin)
    - for tocolysis
  - eppelsiban
    - in development
    - for prevention of premature ejaculation in man)



Ergot alkaloids

- several alkaloids (*Claviceps purpurea*)
  - ergotism: gangraena, abortus, psychosis (hallucination)
  - 5-HT, α, D receptors



St Anthony's fire

Ergot alkaloids (ergometrin)

- uterus contraction / vasoconstriction
  - in low doses: ↑ rhytmic, regular, phasic
  - in large doses: ↑ **TONIC, CONSTANT**
- action depends on the contractile state
  - contracted (normal after delivery) → little effect
  - relaxed → strong contraction → reduced bleeding
- clinical indication: postpartum hemorrhage
  - ergometrin - (Methergin) – 0.2 mg im./iv.
  - ergotamin (Ergam) – 3x20 drops po. / 0.15-0.6 mg im.

Ergot alkaloids (ergometrin)

- adverse effects
  - nausea, vomiting (D_2 – CTZ)
  - vasoconstriction and ↑ blood pressure
    - headache, blurred vison
    - angina pectoris
    - necrosis in extremities (with overdose)

Prostaglandins

- $PGF_{2\alpha}$, PGE_2, PGI_2 (prostacyclin)
  - endogenous prostaglandin-synthesis
  - endometrium-myometrium
    - 2nd phase of menstrual cycle (luteal phase)
    - uterinal tone (motility): frequency↑, amplitude↑, cervix dilation
  - in every period of gestation!
    - sensitivity is increasing
    - before terminus: placenta

Prostaglandin synthesis can be …

stimulated:

- Ca^{2+}
- platelet activating faktor (PAF)
- **β-agonists**
- **estrogene**
- TGF-α
- cortisol
- EGF
- IL-1 (αés β)
- lipopolisacharides
- TNF
- CRH, ACTH

inhibited:

- lipocortin
- **progesterone**
- interferon α
- chorial phospholipase A2 inhibitor (lipocortin VII)

Prostaglandins

- uterinal tone frequency↑, amplitude↑, cervix dilation↑
  - in every phase of gestation
  - misoprostol (Cytotec 200) as abortive (see therapy of gasric ulcer)
- th.: stimulating /induction of labor, induction of abortus
- clinical use
  - local–gel (Prepidil-PGE_2), ProstinE_2 (**dinoprostone**)
  - Prostin E_2 –PGE_2analogue (dinoprostone) injection
  - **sulprosto**n (Nalador) injection - postpartum haemorrhagia
- adverse effects
  - headache
  - GIT (nausea, vomitus)
  - bronchospasm, chest pain
- contraindication
  - asthma bronchiale
  - epilepsy

Tocolytics

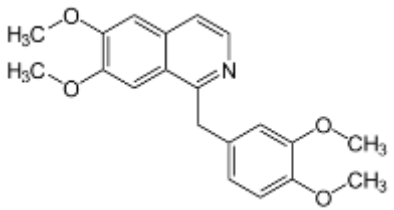
- β-sympathomimetics
  - salbutamol (Brycanil) - 10 µg/min iv. (8-12h / max 48 h)
  - terbutaline
  - ritodrine
  - prevent premature labour (22-33 weeks)
  - delay delivery → glucocorticoid → ↓ RDS
- atosiban (Tractocile, Antosin)
  - oxytocin receptor antagonist

- $MgSO_4$
  - MoA: bivalent cation
    - β-sensitivity ↑
  - th.:
    - 4-6 g/15-20 min i.v. bolus , 2-5 g/h i.v.
  - clinical use: VT (torsade de pointes)
  - antidote: Ca^{2+} gluconate
- NSAIDs
  - indometacin: 50-75mg/day p.o.
  - th.: only before 28. gestation week
  - N.B.: early closure of ductus arteriosus (Botallo)
- Minor use:
  - Ca2+ channel blockers
  - Metilxanthines
  - Anxiolytics
  - Ethanol

Tocolytics

- Ca^{2+} channel blockers
  - mechanism of action:
  - blocking L-type Ca^{2+} channels-DHP (nifedipin)
  - efficacy↑
  - a.e.: „flushing”, headache, tachycardia
  - th.: not recommended (fetal distress, pulmonary edema)
- methylxanthines
  - aminophylline
  - cAMP PDE-inhibition
  - th.: temporary effect
  - side effect profile ↑
- ethanol
  - hypophyseal oxytocin release ↓
  - direct relaxing effect
- anxiolytic drugs
  - sedative, anxiolytic effect
  - diazepam, promethazine

Smooth muscle relaxants



- papaverine
  - opium alkaloid (but isoquinoline ring structure)
  - blocking VGCC, inhibiting PDE II, III, IV
  - smooth muscle effect in
    - GIT, biliary tract
    - urogenital tract
    - respiratory system
  - cardiovascular effect
    - (-) chronotrop effect
    - ectopic focus↑
    - vasodilatation (RR↓)
    - a. pulmonalis, cerebral art. dilation (pulm. emb., migrain)
  - analgetic, sedative effect (high doses)
  - PPB↑
  - 50-100 mg i.v, i.m. (CAVE: bradycardia, AV-block, ES, VF)
  - p.o.: (8 cg) slow absorption → ethaverin, moxaverin

Smooth muscle relaxants

- drotaverine (No-Spa)
  - higher potency than papaverine
  - higher oral bioavail.
  - 4-12 cg
  - Combinations: diclophenac, ibuprofen
- pinaverine (Dicetel)
  - VGCC blocker
  - GIT, urogenital specific

Other GI spasmolytics

- caroverine, mebeverine (Duspatalin® caps. – OTC)
  - effect:
    - VG Ca^{2+}-channel blockade + others
  - p.o., good absorption
  - GIT, biliary tract
  - th.:
    - caroverine: 20-40mg
    - mebeverine: 150-200 mg

- trimebutine
  - effect
    - antimuscarine + peripheral agonist of μ, κ and δ receptors
    - th.: IBS

General characteristics

- **peptides** with effects on
  - vascular smooth muscle
  - other cells/tissues (neurotransmission, kidney etc.)
- classification
  - **vasoconstrictors**
    - angiotensin, endothelins, NPY, vasopressin
  - **vasodilators**
    - bradykinin, ANP, BNP, CGRP, VIP
  - **mixed**
    - substance P

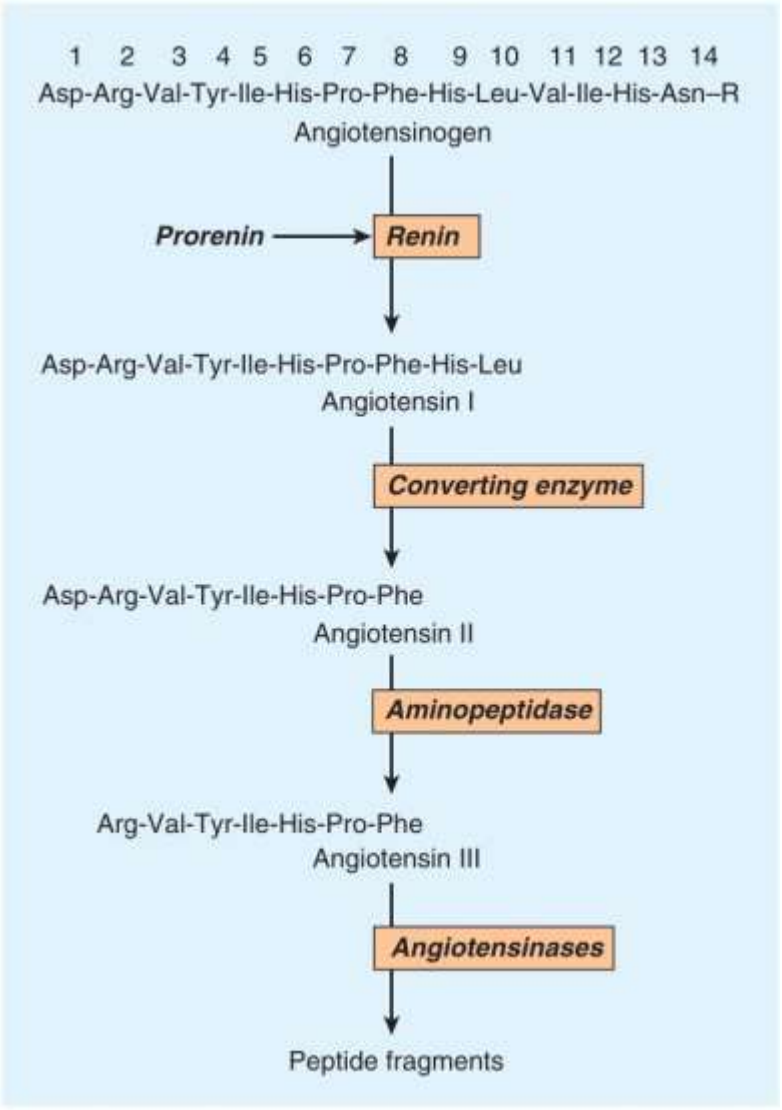
General characteristics

- cell surface receptors, mostly G-protein coupled
- parenteral adminstration (sc.)
- variable clinical significance
  - e.g. angiotensin system ↔ endothelins, CGRP

Peptide	Properties
Angiotensin II (ANGII)	↑ IP_3, DAG via AT_1 G protein-coupled receptors. Constricts arterioles, increases aldosterone secretion
Bradykinin	↑ IP_3, DAG, cAMP, NO. Dilates arterioles, increases capillary permeability, stimulates sensory nerve endings
Natriuretic peptides (ANP, BNP)	↑ cGMP via ANP_A receptors. Dilate vessels, inhibit aldosterone secretion and effects, increase glomerular filtration
Calcitonin gene-related peptide (CGRP)	An extremely potent vasodilator; causes hypotension and reflex tachycardia
Endothelins	↑ IP_3, DAG via G protein-coupled ET_A and ET_B receptors. Synthesized in vascular endothelium. Constrict most vessels and contract other smooth muscle
Neuropeptide Y	Causes vasoconstriction and stimulates the heart. Effects mediated in part by IP_3
Substance P, neurokinins	Act on neurokinin receptors (NK_1, NK_2, NK_3). Dilate arterioles, contract veins and intestinal and bronchial smooth muscle, cause diuresis; substance P is a transmitter in sensory pain neurons
Vasoactive intestinal peptide (VIP)	↑ cAMP via G protein-coupled receptors VPAC1 and VPAC2. Dilates vessels, relaxes bronchi and intestinal smooth muscle

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; DAG, diacylglycerol; IP_3, inositol trisphosphate.

Angiotensin and its antagonists

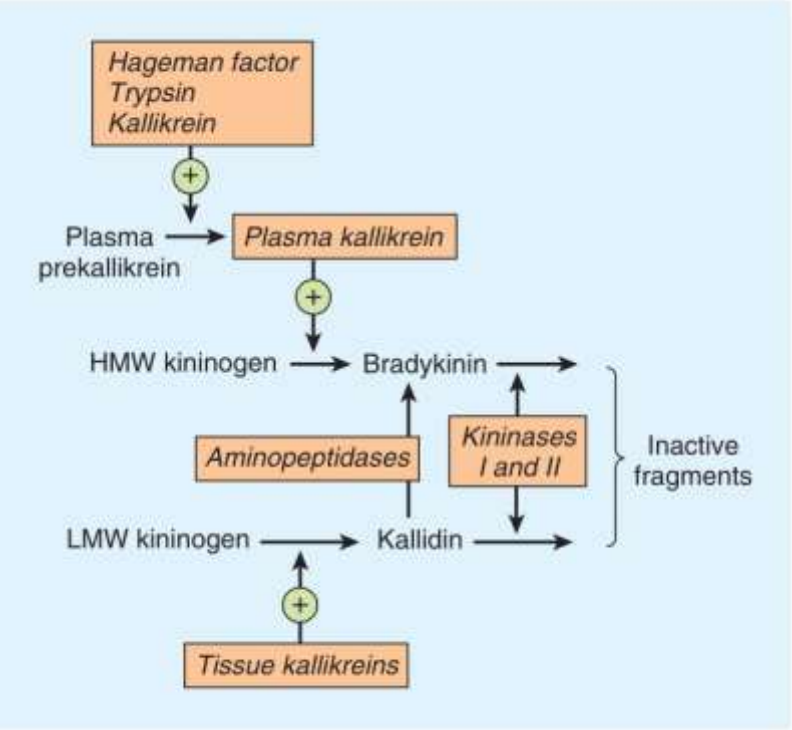


- effects
  - arteriolar vasoncontriction
  - aldosterone ↑
  - norepinephrine release ↑ (AT_1R)
  - cardiac remodeling
- clinical use: **antagonists**
  - ACE inhibitors (e.g. captopril, enalapril etc.)
  - ATR blockers (e.g. losartan, valsartan etc.)
  - renin inhibitor (aliskiren)
  - inhibitors of renin release (β-blockers)

Vasopeptidase inhibitors

- blocks neutral endopeptidase 24.11 and ACE
  - natriuretic peptides ↑
  - angiotensin II ↓
- effects
  - vasodilation, ↓ vasoconstr, Na excretion ↑ → TPR ↓, blood pressure ↓
- **omapatrilat**
- **no clinical approval**
  - agioedema, cough

Bradykinin



- B_1 and B_2 receptors
- potent vasodilator
- role in
  - inflamm., edema, pain, salivation
- no clinical use but
  - see ACE inhibitors
  - hereditary angioedema
    - **ecallantide**
      - kallikrein inhibitor
    - **icatibant**
      - B_2 receptor antagonist

Natriuretic peptides

- ANP, **BNP** (atria), *CNP*
- effects
  - guanylyl cyclase ↑ → cGMP↑ → vasodil.
  - GFR ↑ / ↓ Na reabs. / renin ↓
- clinical role
  - congestive heart failure
    - BNP plasma cc. ≈ severity
  - **nesiritide** – recombinant BNP
    - **used in: acute heart failure iv. inf.**
    - toxicity: hypotension, renal damage

Endothelins

- produced by endothelial cells
  - autocrin / paracrin
  - variations: ET-1 / ET-2 / ET-3 – receptors: **ET_A** / ET_B
  - long lasting **vasoconstriction**
- clinical relevance
  - ET receptor antagonists
  - bosentan (nonsel) / ambrisentan (ET_A)
    - **pulmonary hypertension** (oral / in mild cases)

Neurokinins (substance P)

- NK_1 and NK_2 receptors – CNS and periphery
- mixed vascular effect
  - arteriolar dilation ↔ vein contraction (GI and airway too)
- other roles
  - local hormone in GI
  - pain
    - capsaicin – depletes substance P
      - approved for: topical use arthritic joints, post-herpetic neuralgia
  - nausea, vomiting
    - aprepitant – NK1 antagonist
    - delayed emesis associated with cancer chemotherapy

Vasopressin (ADH)

- V_1 and V_2 receptors
  - V_{1a} – vasoconstriction / V_{1b} - release of ACTH
  - V_2 – antidiuretic effects (aquaporin channels)
- agonist
  - desmopressin (V_2)
  - clinical use: pituitary diabetes insipidus / von Willebrand disease (extrarenal V_2 → release of factor ↑)
- antagonists
  - conivaptan - V_{1a} and V_2
  - tolvaptan – V_2
  - used in hyponatremia
  - older: demeclocycline, also see lithium

VIP, CGRP, NPY

- **no current clinical role**
- VIP
  - in CNS and PNS and GI / neurotransmitter
  - vasodilation
- CGRP
  - thyroid, smooth muscle
  - cotransmitter
  - vasodilation → hypotension → reflex tachycardia
  - role in migraine ?
    - oral antagonist would be nice
- NPY
  - vasoconstrictor, cotransmitter
  - CNS: hypotension, hypothermia, feeding ↑