DRUGS AFFECTING SMOOTH MUSCLES

Topic A34: Smooth muscle relaxants used for relief gastrointestinal (GI) and urogenital (UG) spasms. Drugs influencing uterus function

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Smooth muscle function is controlled by the autonomic nervous system, hormones and other chemicals

- eyes
- airways
- gastrointestinal (GI) system
- blood vessels
- urinary bladder
- uterus
- prostate

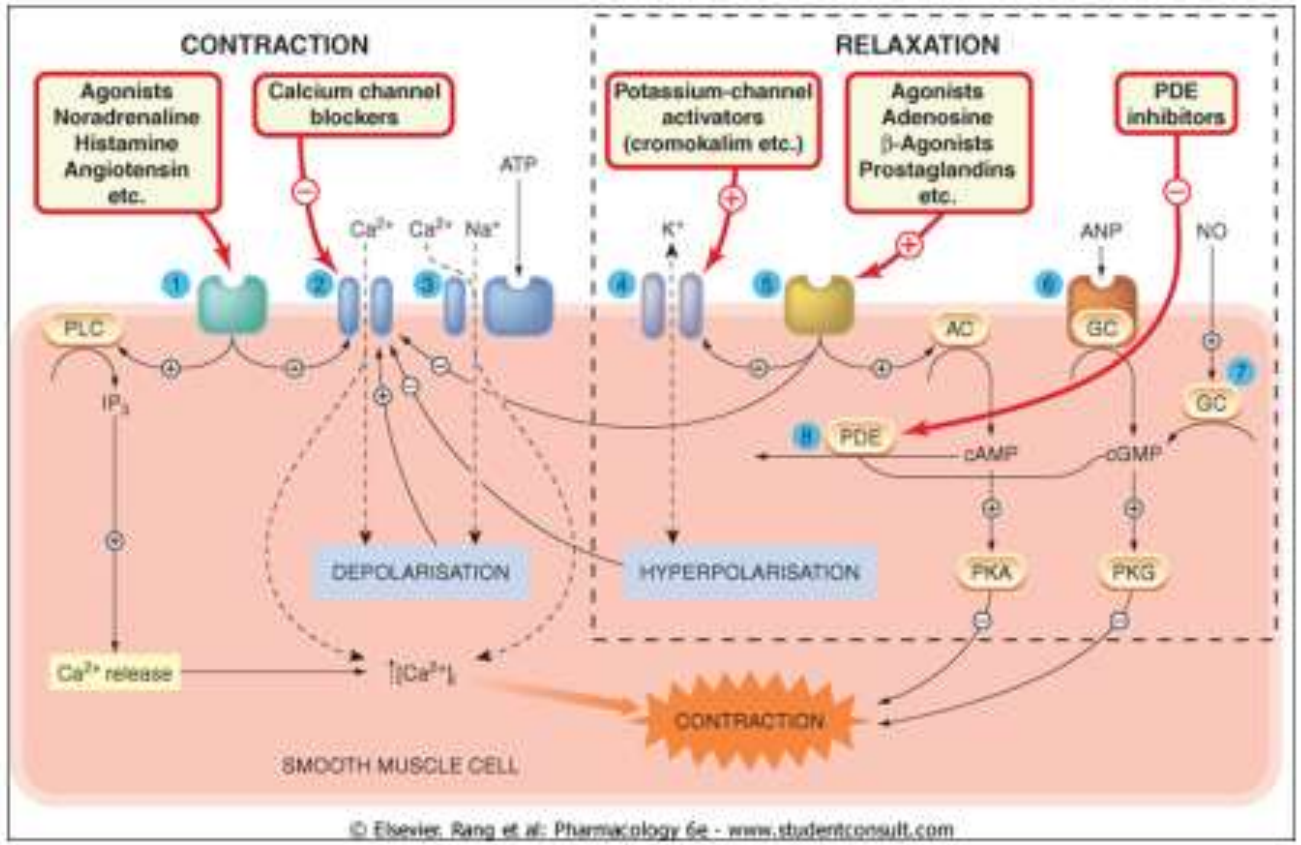
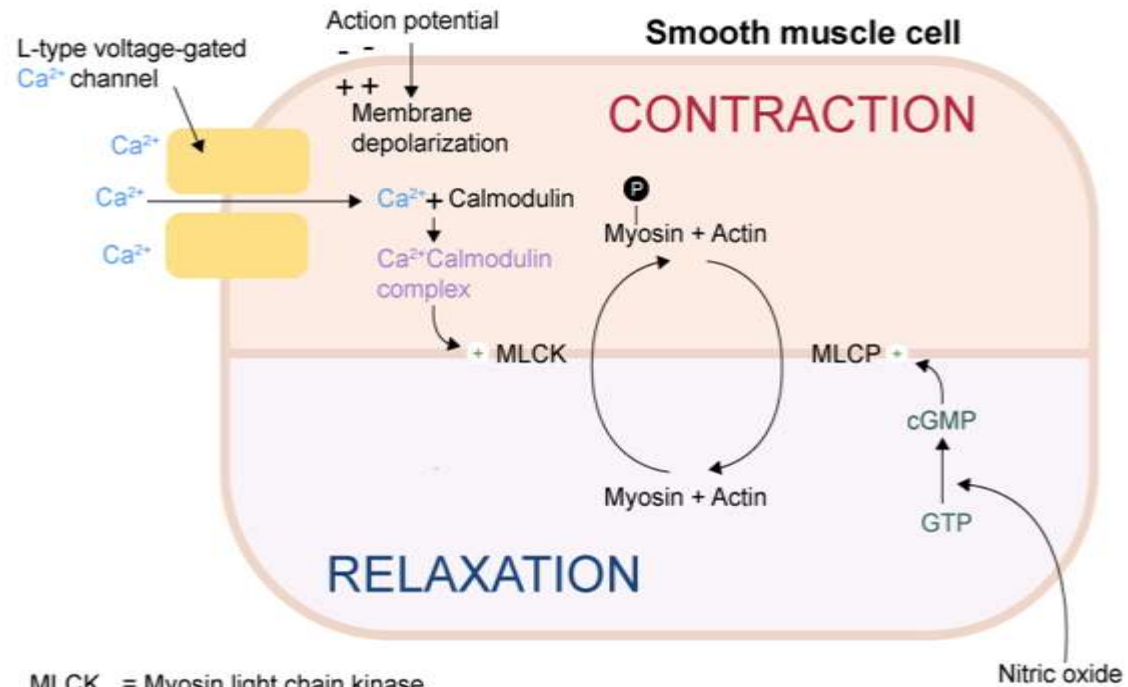


Figure 4-10 Mechanisms controlling smooth muscle contraction and relaxation. 1. G-protein-coupled receptors for excitatory agonists, mainly regulating inositol trisphosphate formation and calcium channel function. 2. Voltage-gated calcium channels. 3. Ligand-gated cation channels (the P2X receptor for ATP is the main example). 4. Potassium channels. 5. G-protein-coupled receptors for inhibitory agonists, mainly regulating cAMP formation and potassium and calcium channel function. 6. Receptor for atrial natriuretic peptide (ANP); coupled directly to guanylate cyclase (GC). 7. Soluble guanylate cyclase, activated by nitric oxide (NO). 8. Phosphodiesterase (PDE), the main route of inactivation of cAMP and cGMP. AC, adenylate cyclase; PKA, protein kinase A; PKG, protein kinase G; PLC, phospholipase C.



MLCK = Myosin light chain kinase
MLCP = Myosin light chain phosphatase
GTP = Guanosine triphosphate
cGMP = Cyclic guanosine monophosphate

Endogenous compounds *contracting* smooth muscle

ACh
Biogenic amines (E, NE, 5-HT, histamine)
Lipids (prostanoids [PG, TXA_2], leukotrienes)
Polypeptides (oxytocine, AngII, endothelins)
Neuropeptides (SP, NK, NPY)
ATP and derivatives

Endogenous compounds *relaxing* smooth muscle

Ach (NO)
Biogenic amines (E, histamine)
NO
ATP and derivatives
Neuropeptides
    VIP, PACAP (pituitary adenylate cyclase-activating peptide)
CGRP
Bradykinin

Drugs acting in the eye

- myotic agents: parasympathomimetics – **Pilocarpine**. Indicated for the treatment of glaucoma as eye drop: ciliary muscle contraction - ↑aqueous humor outflow - ↓intraocular pressure

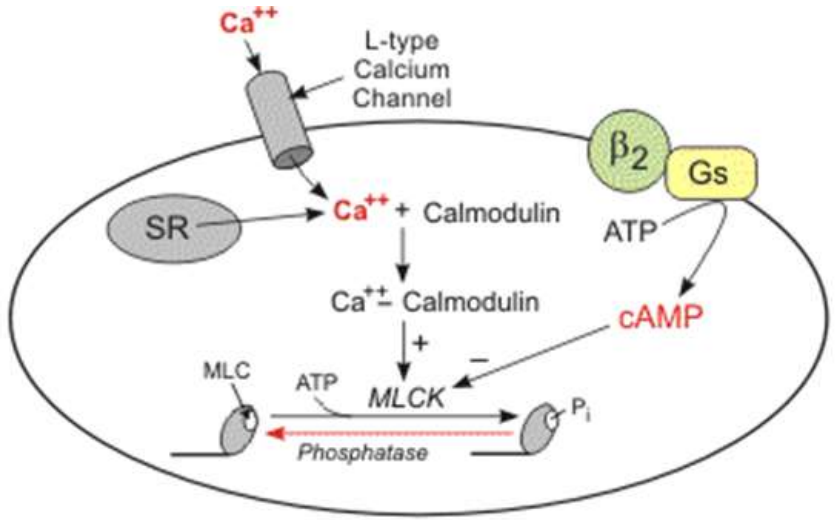
- mydriatic agents: - parasympatholytics – **Cyclopentolate**, **Tropicamide** – for retina investigation in ophtalmology.
  - sympathomimetics (sympathetic discharge, α-agonists)

Drugs acting on the bronchi- bronchodilators

- β_2 receptor agonists- e.g. **Terbutaline, Fenoterol, Salmeterol, Formoterol**- bronchodilators
- phosphodiesterase inhibitors (PDE) – e.g. Theophylline- bronchodilator
- parasympatholytics – e.g. **Ipratropium**, **Tiotropium** – bronchodilators
- leukotriene antagonist – **Montelukast**
- (5- lipoxigenase inhibitor – Zileuton)

Drugs acting on the bronchi- bronchoconstrictors

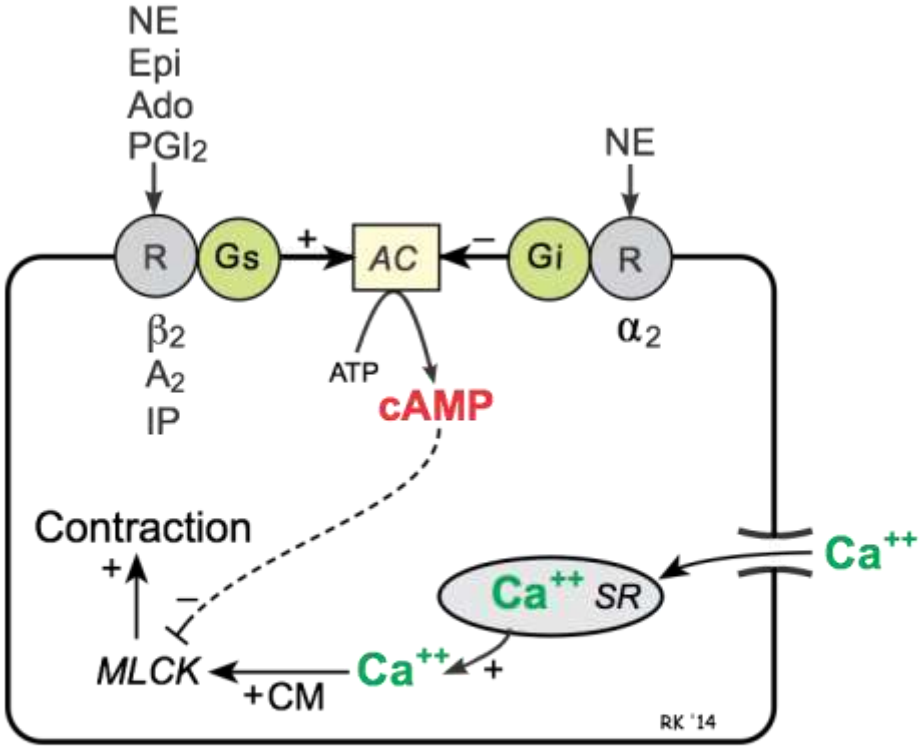
- parasympathomimetics, histamine



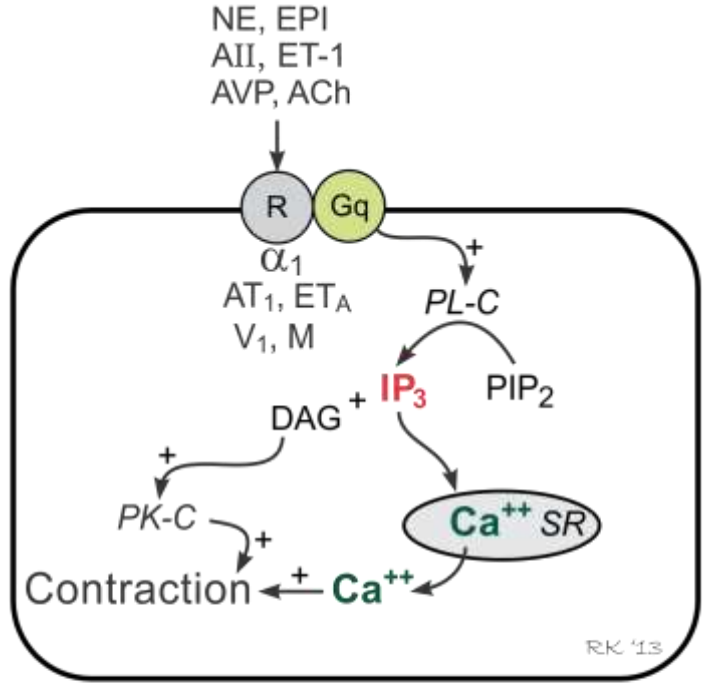
Abbreviations: SR, sarcoplasmic reticulum; Gq, Gs-protein; MLC, myosin light chain; MLCK, myosin light chain kinase; Pi, myosin phosphorylation

Drugs acting on the vascular smooth muscles

- β_2 AR stimulation, α_1 AR inhibition - vasodilation, α_1 AR stimulation-contraction
- Ca^{++} channel inhibitors, nitrates, direct vasodilators (…)



R, receptor; Gs, stimulatory G-protein; AC, adenylyl cyclase; CM, calmodulin; MLCK, myosin light chain kinase; SR, sarcoplasmic reticulum; NE, norepinephrine; Epi, epinephrine; Ado, adenosine; PGI , prostacyclin; β_2, beta-2-adrenoceptor; α_2, alpha-2-adrenoceptor; A_2, adenosine receptor; IP, prostacyclin receptor.



R, receptor; Gq, phospholipase C-coupled Gq-protein; PL-C, phopholipase C; PIP_2, phosphatidylinositol biphosphate; IP_3, inositol triphosphate; DAG, diacylglycerol; PK-C, protein kinase C; SR, sarcoplasmic reticulum; NE, norepinephrine; AII, angiotensin II; ET-1, endothelin-1; AVP, arginine vasopressin; ACh, acetylcholine; α_1, alpha$_1$-adrenoceptor; AT_1, type 1 angiotensin receptor; ET_A, type A endothelin receptor; V_1, vasopressin type 1 receptor; M, muscarinic receptor.

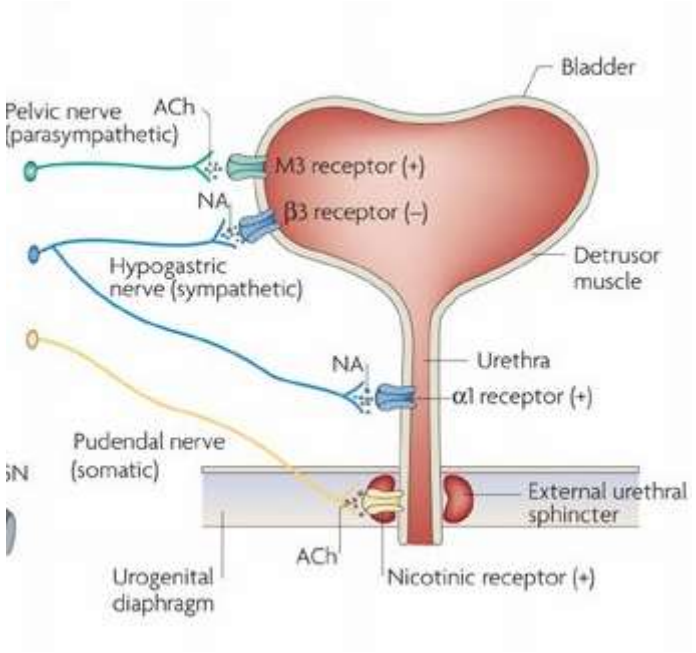
Drugs acting on GI and UG tract

- <u>smooth muscle constrictors</u>: parasympathomimetics - **Betanechol** (di), **Neostigmine** (indi), are indicated in postoperative ileus (if there is no mechanical obstruction) and urinary retention

- <u>smooth muscle relaxants</u>:
  - parasympatholytics
    - **Atropine, Scopolamine, Butylscopolamine**, **Homatropine methylbromide** - indicated in GI spasm. They help to relief smooth muscle cramp caused by gallstones or kidney stones.

    - **Oxybutinin** - bladder spasm following urologic surgery. Avaialble as oral or transdermal form. Similar to Oxybutinin is Trospium

    - **Darifenacin**, **Solifenacin**, **Tolterodine**, Fesoterodine- for urinary incontinance.



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Side effects: dry mouth, constipation, urinary retention, blurred vision
Contraindications: glaucoma, paralytic ileus

Drugs acting on GI and UG tract

- smooth muscle relaxants:
    - Ca^{++} channel blockers
        - **Pinaverin** - indicated in GI dysmotility, Dumping syndrome. Weak absorbtion from the GI tract, mainly local effect
        - **Nifedipine**- indicated in sphincter Oddi spasm, ureteral spasm

- non-specific smooth muscle relaxants, spasmodics:
    - **Papaverine, Drotaverine**
    - **Mebeverine**

Drugs acting on GI and UG tract

Papaverine

- MOA: Ca^{++} channel blocker and PDE inhibitor
- Pharmakokinetics: oral, parenteral administration (im, iv)
- Adverse effects: negative inotropic, hypotension, arrhytmias, liver toxicity, GI, prolonged erection
- Indications: GI and UG spasm

Drotaverine

- spasmolytic, structurally similar to Papaverine
- available as an oral or parenteral preparation

Agents relaxing (pregnant) uterus - tocolytics

The aim of their use:

- to delay premature labor
- to prolong intrauterine period in order to initiate fetal lung surfactant production with glucocorticoids
- (…)

Drugs:

- **Atosiban**, oxytocine receptor antagonist, effective from the 24th week of pregnancy
- β_2 receptor agonists: - **Terbutaline**, Fenoterol, Salbutamol- from the 16th week of pregnancy. Effective mainly for short term, at a long term use tolerance develops. SE: tachycardia, tremor
- **Magnesium sulfate**, in infusion
- Ca^{++} channel blockers, e.g. **Nifedipine**, their use is limited by their cardiovascular side effects
- Progesterone
- Ethanol

Agents relaxing the NON-pregnant uterus

Indicated in:

- dysmenorrhoea

Drugs:

- NSAIDs, e.g. **Naproxen**, **Ibuprofen**

Agents contracting the pregnant uterus

Drugs:

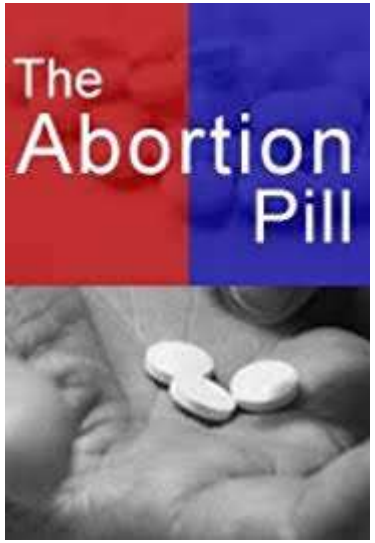
- **Oxytocine**, indicated for induction of labor and postpartum uterine bleeding (in high doses, tonic contraction). Administration: iv, im, or intranasaly (to initiate lactation)

- **Ergot alcaloids**, Ergonovine - indicated in postpartum hemorrhage if oxytocine is not effective

Agents contracting the pregnant uterus

Drugs:

- **Prostaglandins:**
  - **Dinoprostone,** synthetic PGE_2- vaginal gel or tabs. for oxytocic use. Approved for inducing abortion, ripening of the cervix for induction of labor
  - **Misoprostol**, synthetic PGE_1 analog in combination with Mifepristone – to produce early abortion (*the abortion pill*)
  - **Carboprost**, $PGF_{2\alpha}$ analog, to induce second-trimester abortion, to control postpartum hemorrhage if conventional methods are not effective



Agents acting on male reproductive system

Drugs:

- **Alprostadil,** PGE_1 analog, intracavernosal or urethral suppository – 2nd line treatment for erectile dysfunction

- **Sildenafil**, Tadalafil, Vardenafil- PDE-5 inhibitors, indicated for erectile dysfunction

- **Alfuzosin**, **Tamsulosin**. α_{1A} antagonists, indicated in benign prostatic hyperplasia