What are vasodilators?

- dilate blood vessels
  - Which vessels? – arteries, arterioles, venules and veins
  - How? – smooth muscle relaxation (direct/indirect)

Why are they used?

- control blood pressure / blood flow
  - systemic / local (e.g. pulmonary, coronary, peripheral)
- ↓ the work of the heart (thus O_2 need)
  - heart failure / angina

- Vasodilators are used
  - to **antagonize increased vascular tone**
    - systemically or
    - locally
  - thus improve the efficacy of circulation under pathological conditions

A vast array of various mediators is responsible for the control of vascular tone

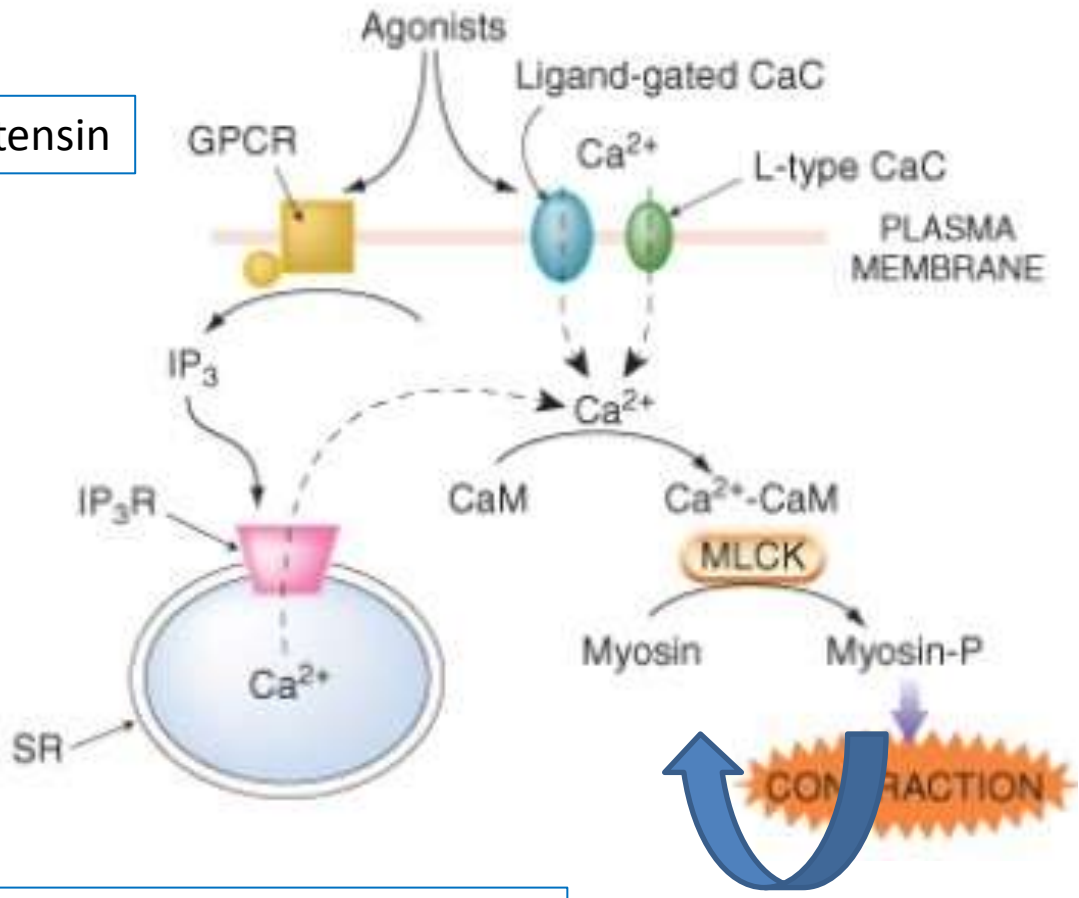
Sources of mediators controlling vascular smooth muscle tone

- secreted by autonomic (sympathetic) nerves
  - e.g. NAdr+, ATP+
- secreted by endothelium
  - e.g. endothelin+, prostacyclin (PGI_2)-, NO-
- circulating hormones
  - e.g. angiotensin+
- other
  - e.g. thromboxane (TXA_2)+, 5-HT+/-, natriuretic peptides-

+ : constriction / - : dilation

Excitation - contraction coupling in smooth muscle

eg. NAdr / angiotensin

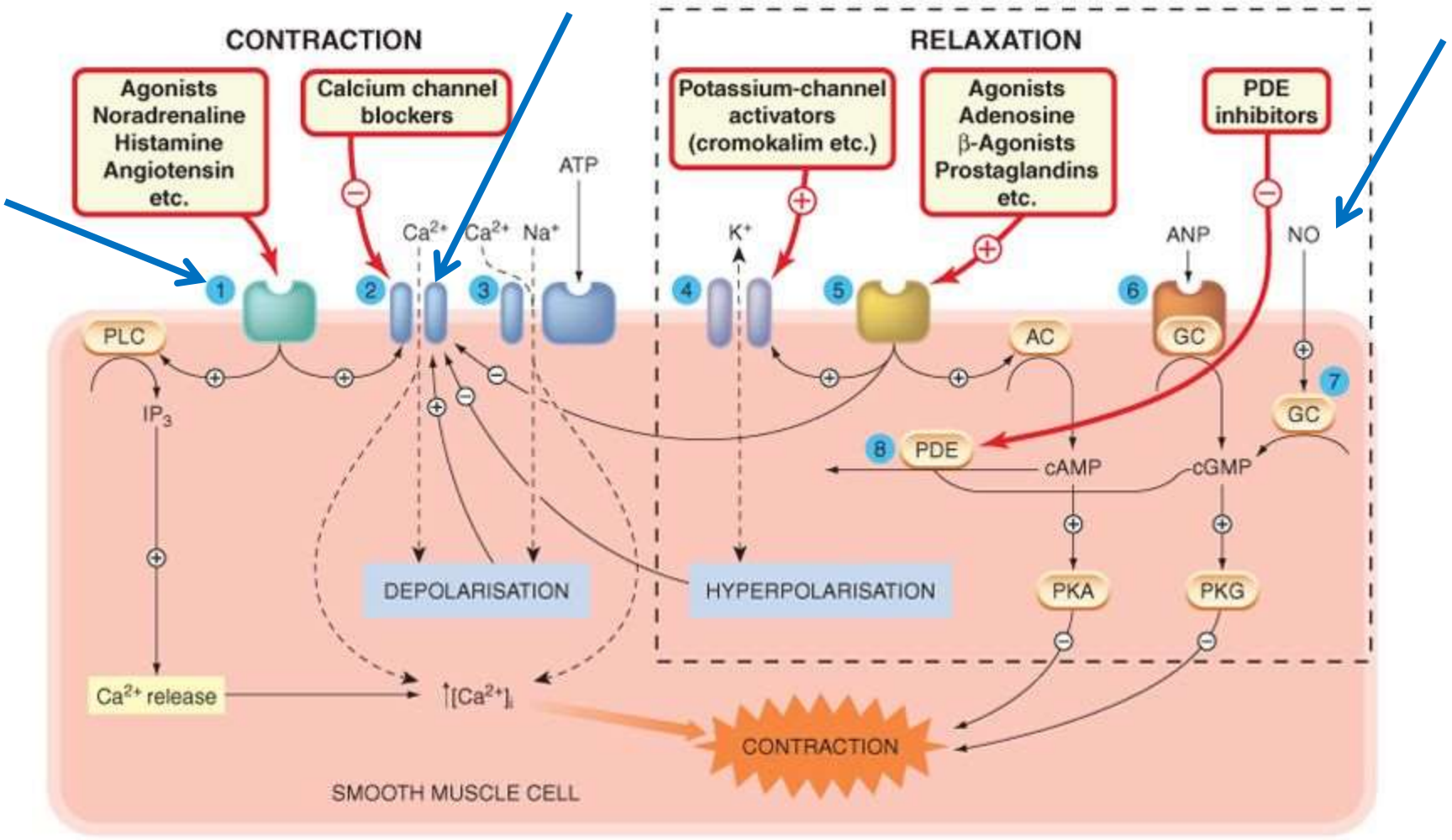


- *ic. Ca is central*
- *but depol. and EC Ca is not absolute req.*

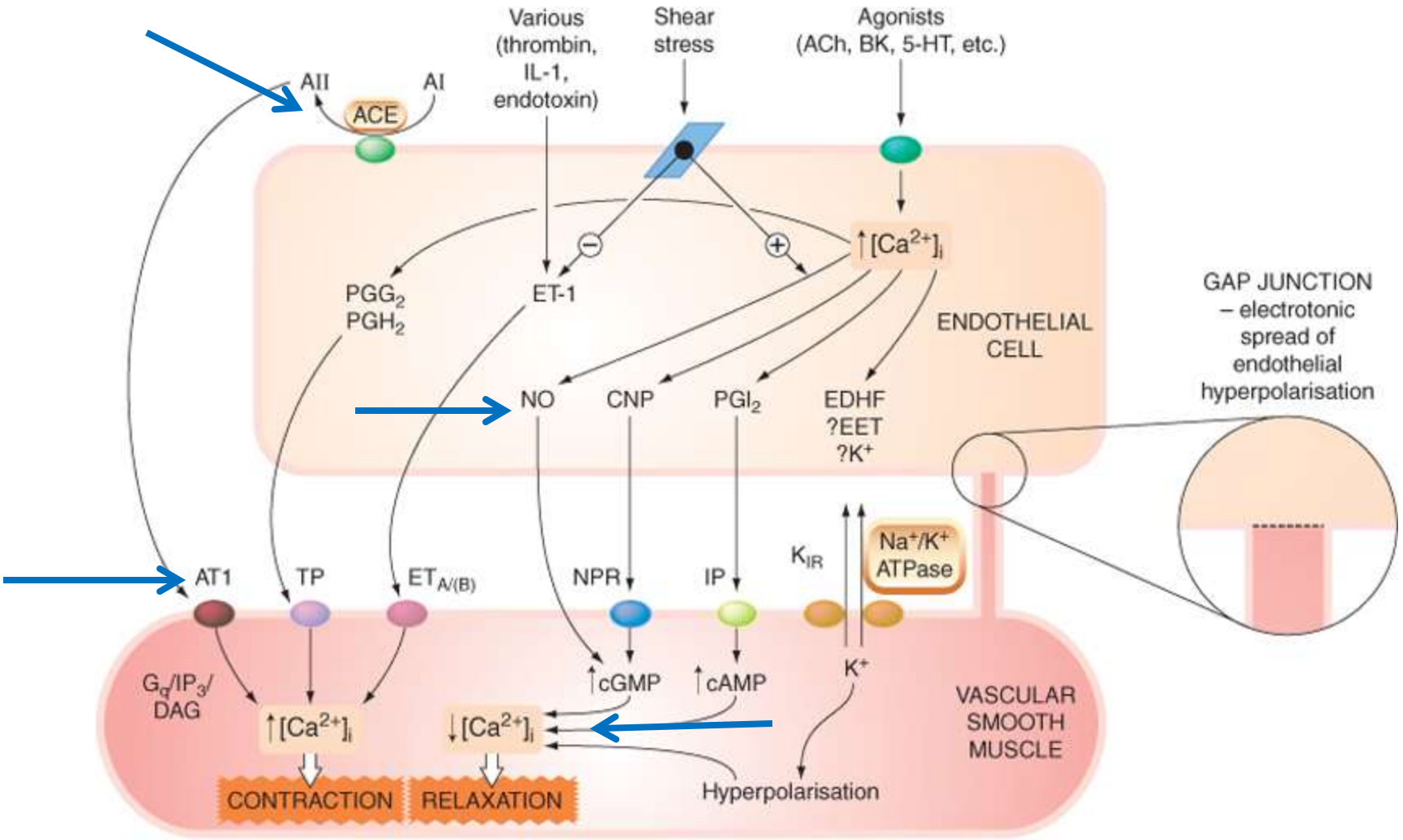
myosin phosphatase

vascular smooth muscle tension → diameter → blood pressure / flow

Control of smooth muscle contraction and relaxation



Role of endothelium in controlling vascular smooth muscle



some are tonically active: e.g. NAdr, NO, endothelin

Endothelium derived mediators controlling vascular smooth muscle tension

- prostanoids
  - relax.: PGI2, PGE2
  - constr.: PGG2, PGH2
- nitric oxide
- peptides
  - relax.: CNP, adrenomedulin
  - constr.: **angiotensin II**, endothelin
- endothelium derived hyperpolarizing factor(s)
  - NO and PG independent vasodilation
  - identity ?

Classification of vasodilators according to their mechanism of action

- ***directly acting vasodilators***
  - calcium channel blockers – e.g. nifedipine
  - K_{ATP} channel activators – e.g. minoxidil
  - drugs that increase cytoplasmic cyclic nucleotide concentrations
    - cyclase activators – e.g. nitrates, β_2 agonists
    - PDE inhibitors – e.g. methylxantines, sildenafil
- ***indirectly acting vasodilators***
  - drugs that interfere with the sympathetic nervous system
    - e.g. α_1 blockers
  - **RAS blockers** (aliskiren, captopril, losartan …)
  - drugs that stimulate endothelial NO release – e.g. ACh, BK
  - drugs that block the endothelin system
    - bosentan, ambrisentan - used in pulmonary hypertension
- *other (unknown) mechanism of action*
  - hydralazine/dihydralazine, ethanol, propofol

Directly acting vasodilators

- *calcium channel blockers* (L-type voltage dependent)
  - dihydropyridines - e.g. **nifedipine**
  - verapamil
  - diltiazem
- *K_{ATP} channel activators*
  - **minoxidil,** diazoxide, nicorandil, levosimendan
- *cAMP/ cGMP level increasing drugs*
  - increased adenylyl cyclase activity
    - prostacyclin (PGI_2 / epoprostenol), β_2 agonists, fenoldopam
  - increased guanylyl cyclase activity
    - **organic nitrates** (nitroglycerine, nitroprusside), NO, natriuretic peptides
  - phosphodiesterase inhibitors
    - **sildenafil** + others – erectile dysfunction
    - papaverin, theophylline, milrinone, inamrinone – not used as vasodilators

Classification according to clinical use

- *hypertension*
  - calcium channel blockers - both outpatient and emergency
  - oral vasodilators: hydralazine and minoxidil - long-term outpatient therapy of severe hypertension
  - parenteral vasodilators: nitroprusside, diazoxide and fenoldopam - hypertensive emergencies
- *angina pectoris*
  - organic nitrates - for immediate relief
  - calcium channel blockers - especially for prophylaxis
- *heart failure (mainly acute severe form)*
  - several may improve symptoms (nitroprusside, phentolamine, nitrates)
  - hydralazine + isosorbide dinitrate
  - RAS blockers

Ca^{2+} channel blockers

- „use dependent” blockade
- heart > vascular: verapamil > diltiazem > nifedipine
  - no reflex tachycardia with verapamil
- arteriolar dilation
  - decreased blood pressure
  - coronaries – variant (Prinzmetal) angina
  - nimodipine – cerebral vessels – subarachnoid hemorrhage
- other smooth muscles
  - not significant – e.g. verapamil – constipation
- adverse effects
  - ankle edema
  - bradycardia, negative inotropy (verapamil)

K^+ channel activators

- hyperpolarization – voltage dependent Ca^{2+} channel ↓
- **minoxidil**
  - arteriolar, long duration, oral, severe hypertension, in combination
  - hirsutism (see Rogaine solution)
- diazoxide
  - iv., arteriolar dilator, long duration of action (4-12 hours)
  - now rarely used (and only for short periods)
  - tox: hypotension, inhibits insulin release – used in insulinoma
- nicorandil
  - NO donor too
  - arteriolar and venous effects
  - angina, currently approved for use in Europe and Japan
- levosimendan
  - see heart failure – Ca sensitizers
  - in acute heart failure in Europe, noninferiority against dobutamine

Cyclase activators

- cGMP
  - nitrates – e.g. nitroglycerin, Na-nitroprusside
  - NO
  - nesiritide – BNP
- cAMP
  - fenoldopam / dopamine
  - β_2 agonists – not used as vasodilators / see asthma
  - prostacyclin (PGI2 / epoprostenol)

Nitrates / nitrites

- NO release
  - enzyme reaction: organic nitrates (e.g. nitroglycerine)
    - mitochondrial aldehyde dehydrogenase
  - **"direct release"** (e.g. Na-nitroprusside / molsidomine)
- **nitroglycerine** (glyceryl trinitrate)
  - acute angina – **sublingual** (peak ~ 4 min, $t_{1/2}$ ~ 1-3 min)
    - amyl nitrite is obsolete for angina (short duration / unpleasant odor)
  - preferentially **venodilation** + epicardial coronaries + atherosclerotic stenosis + collateral vessels (no "coronary steal")
  - inhibiton of thrombocyte aggregation
  - long term administration deleterious ? (e.g. Nakamura et al. 1999)
- isosorbid dinitrate / isosorbid-5-mononitrate (oral F ≈ 100%)
- Na-nitroprusside
  - i.v. infusion, light sensitive, cyanide release
  - arterial effects ≈ venous effects

Nitrates / nitrites

- **tolerance**
  - mechanism ?
    - neurohumoral activation, SH depletion, free radicals, inactivation of mitochondrial aldehyde reductase ...
  - to avoid/decrease: **intermittent dosing**
- **adverse effects**
  - orthostatic hypotension
  - tachycardia
  - throbbing headache
  - ↑ intracranial pressure (in case of overdose)

Inhaled NO gas

- selective dilation of pulmonary vasculature
  - because rapid reaction of NO by hemoglobin
- ↓ pulmonary pressure, ↑ oxygenation
- FDA: newborns with persistent **pulmonary hypertension**
- questions – long term outcome???
  - ARDS
  - primary pulmonary hypertension
  - pulmonary embolism
  - lung transplantation

Nesiritide

- synthetic BNP (B-type natriuretic peptide)
- effects
  - ↑cGMP → smooth muscle relax.
  - diuresis
- clinical use
  - iv. infusion
  - **acute heart failure**
- toxicity
  - excessive hypotension
  - renal damage ? / mortality ?

Fenoldopam

- selective D_1 receptor agonist (cAMP ↑)
  - vasodilation
    - afferent and efferent arterioles in kidney
    - mesenteric arteries
  - natriuresis
- clinical use
  - short term iv. infusion in severe hypertension
- toxicity
  - due to vasodilation: tachycardia, headache, flushing
  - glaucoma

Prostacyclin (PGI_2 , epoprostenol)

- effects
  - cAMP ↑
  - potent vasodilator
  - inhibitor of platelet aggregation
- use
  - iv. infusion ($t_{1/2}$ ≈ 2-3 min)
    - analogs with longer half life
      - iloprost ($t_{1/2}$ ≈ 30 min) – inhaled / iv.
      - treprostinil ($t_{1/2}$ ≈ 4 h) – sc. / iv.
  - pulmonary hypertension
- toxicity
  - headache, flushing, hypotension
  - diarrhea

Vasodilators in pulmonary hypertension

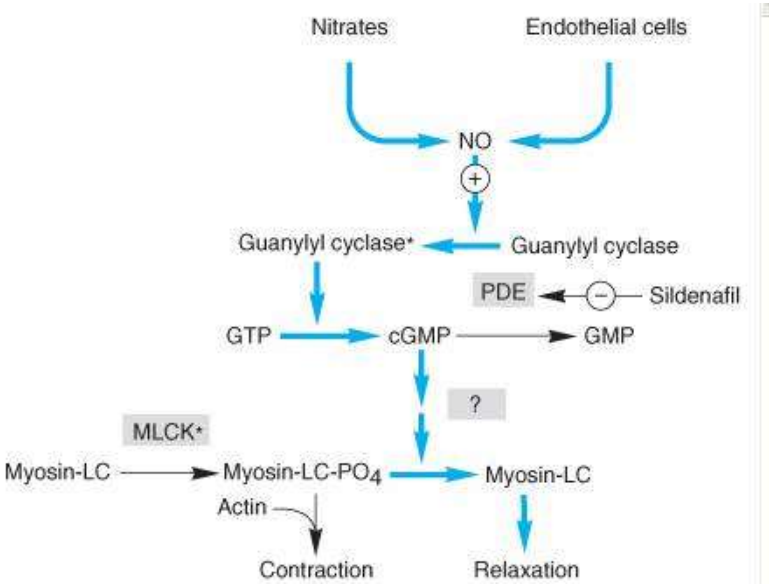
- endothelin receptor antagonists
  - bosentan, ambrisentan
  - oral / in mild cases
- prostanoid analogs
  - iloprost (inhal.), treprostinil (sc), beraprost
  - parenteral / in severe cases
- epoprostenol
  - long term iv. infusion
- NO inhalation
  - in newborn babies
- sildenafil
- Ca channel blockers

PDE inhibitors

- theophylline
  - used in asthma / not only PDE inhibitor (adenosine antag.)
- papaverin
  - Ca channel block too
  - GI smooth muscle relaxation
- milrinone, inamrinone
  - PDE3 inhibitors, see positive inotropic drugs
  - ↑ contractility and vasodilation
- cilostazol
  - PDE3 inhibitor
  - used in intermittent claudication
- sildenafil
  - PDE5 inhibitor
  - used in erectile dysfunction / pulmonary hypertension

Interaction of nitrates with PDE5 inhibitors

- risk factors for erectile dysfunction ≈ coronary artery disease
- PDE5 inhibitors: sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra)
- profound cGMP ↑ → severely reduced BP



Hydralazine / dihydralazine

- unknown mechanism of action
  - NO release ? (not K channels)
  - selective for arterioles
- orally administered
- clinical use
  - hypertension
    - hypertensive crisis during pregnancy – short term only
  - heart failure
    - in combination with nitrates (esp. African American)
- toxicity
  - headache, flushing, reflex tachycardia → angina
  - reversible lupus like syndrome
    - primarily in “slow acetylators”