Peripheral circulation I: Physiology of vascular wall

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Lecture slides

Regulation of regional blood flow

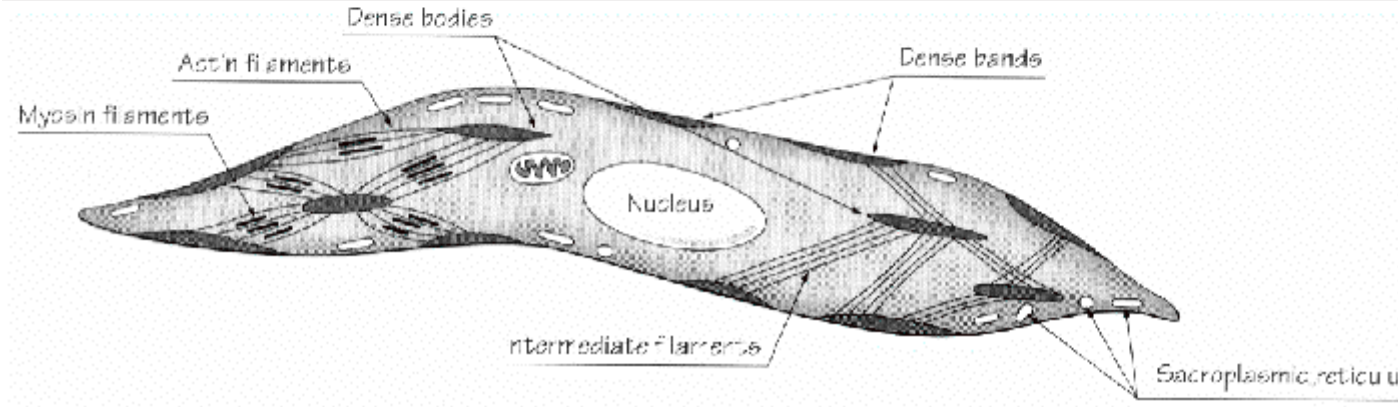
- Resistance vessels (arterioles): changes in diameter
  - Vasodilation
  - Vasoconstriction

Prerequisite: basal tone
- nerve-independent
- sympathetic tone

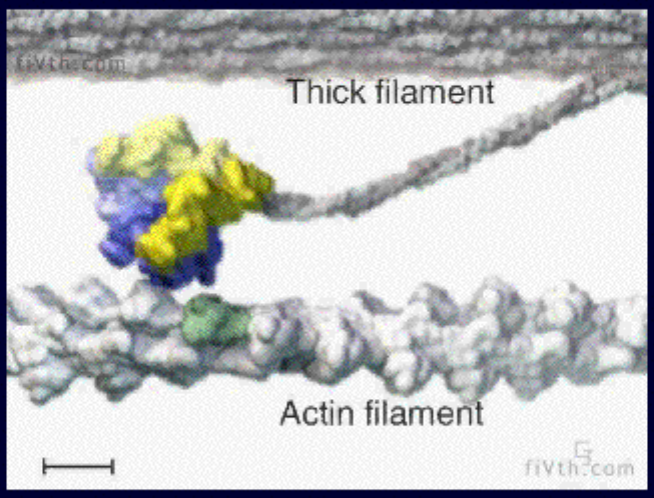
- Changes in the diameter of open vessels
- Changes in the number of open vessels („recruitment")

Vascular smooth muscle contraction

- Actin (thin filaments)
  - attached to *dense bodies* made of α-actin (in cytoplasm & inner side of membrane)
- Myosin (thick filaments)
  - hexamere of 2 heavy & 2 different pais of light chains



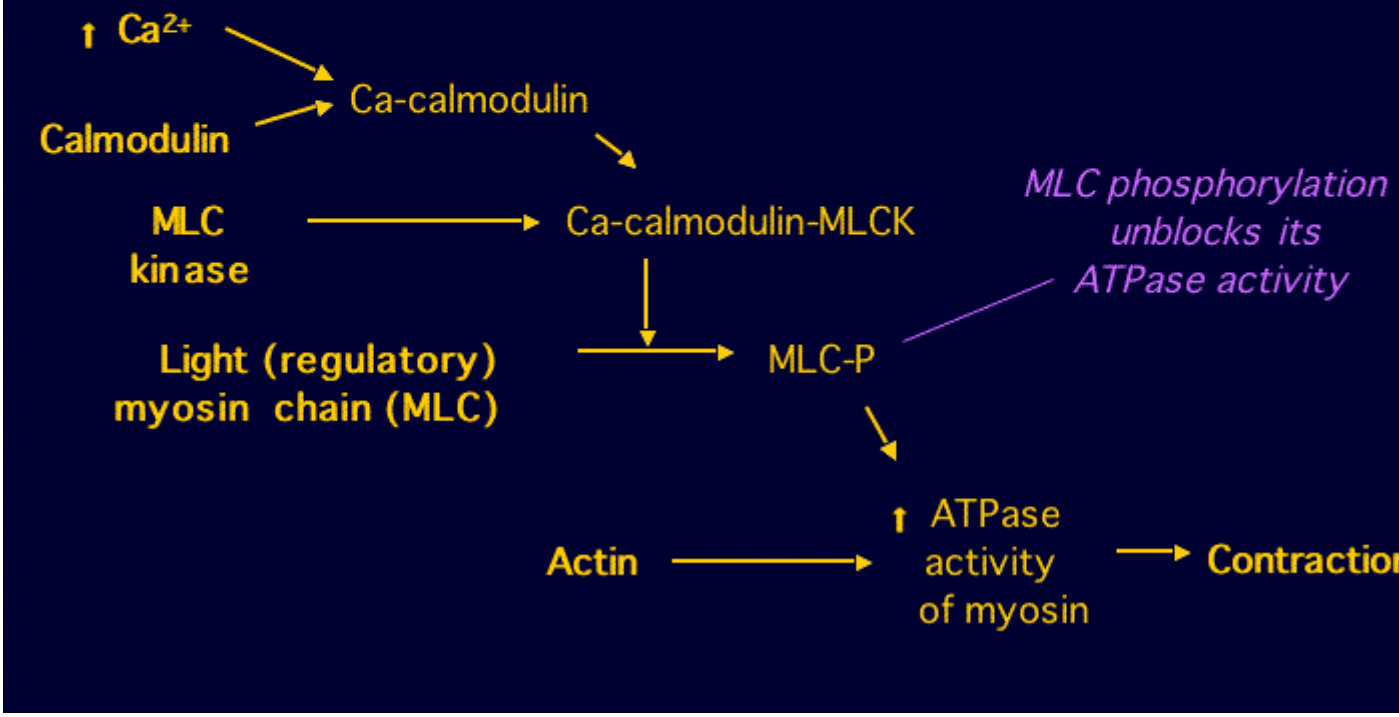
Vascular smooth muscle (VSM) contraction



VSM contraction

- Slow
- Strong
- Lasting
  - w/o ATP, the N-terminal (catalytic) myosin head is attached to actin filament (maintains tone with minimal energy)
- Intercellular communication via gap junctions

Activation of VSM contractile apparatus



VSM inactivation

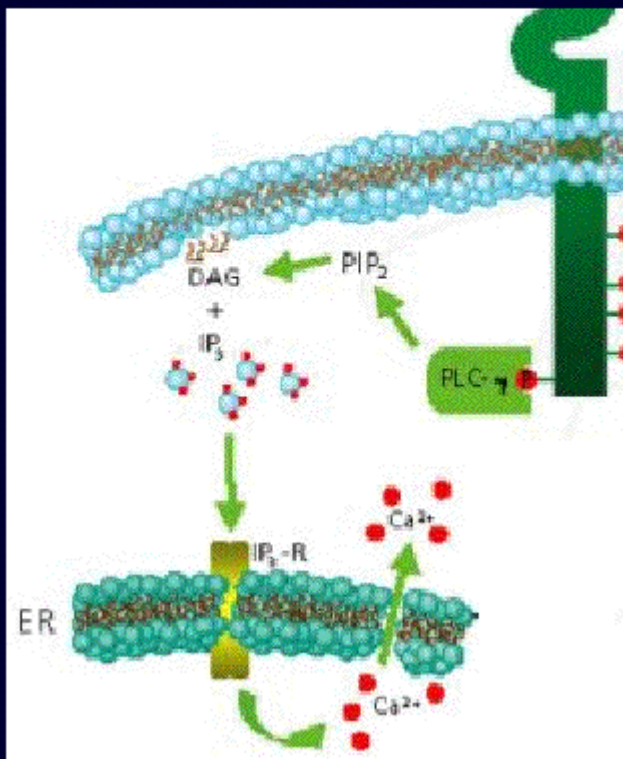
- ↓ $[Ca^{2+}]_i$
  - ↓ influx
  - pumping outside
    - Ca^{2+} ATPase
    - Na/Ca antiport
  - pumping to reticulum (SERCA)
- Ca^{2+}-independent MLC phosphatase prevails over MLCK → ↓ MLC phosphorylation (→ activity)

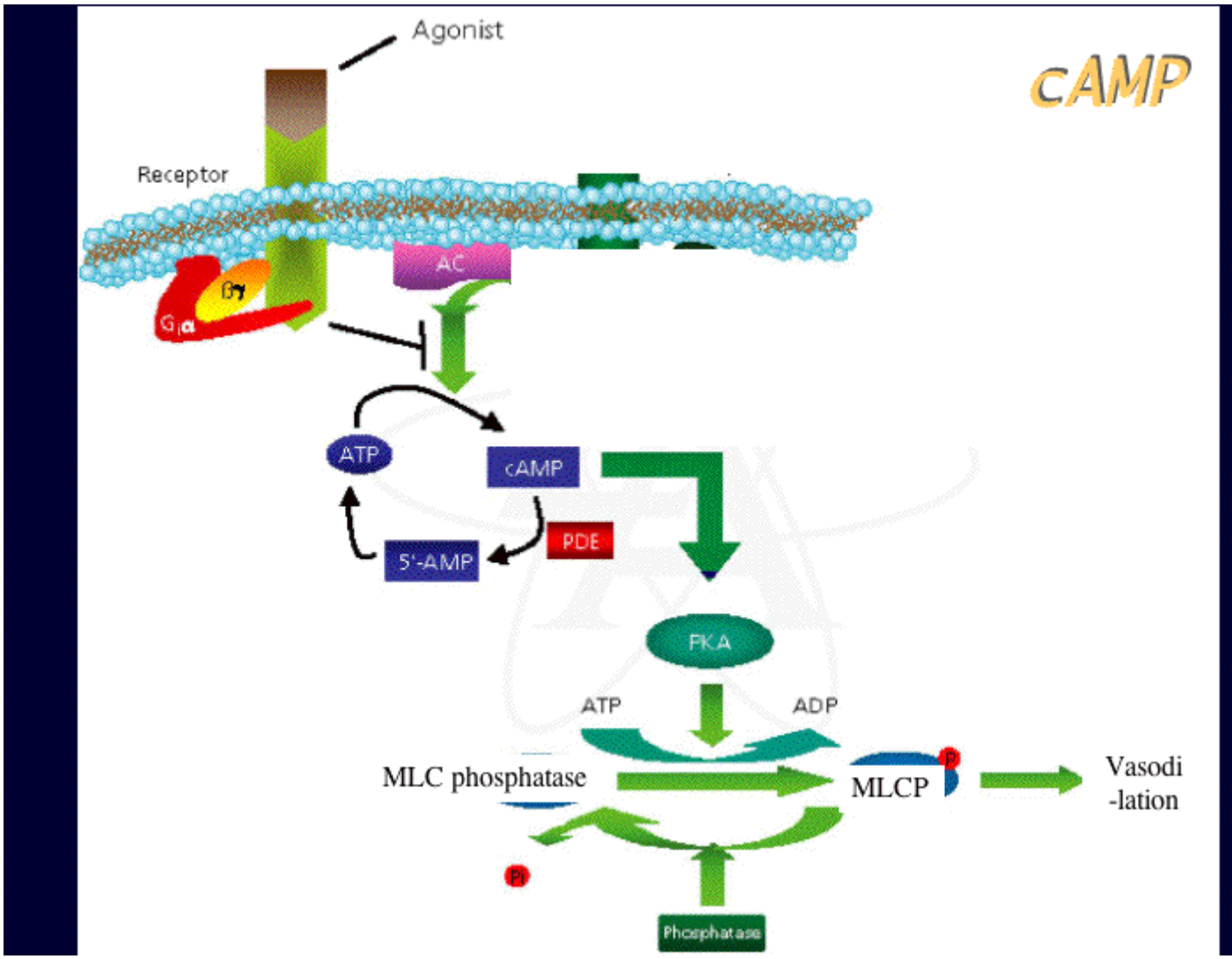
Excitation-contraction coupling

- Electromechanical
  - voltage-gated Ca^{2+} channels (VOC)
- **Pharmacomechanical**
  - receptor-operated Ca^{2+} channels (ROC)
  - Ca^{2+} from sarcoplasmic reticulum
  - Sensitization
    - Rho kinase → MLC phosphorylation
    - A, C, G kinases → MLC phosphatase inhibition

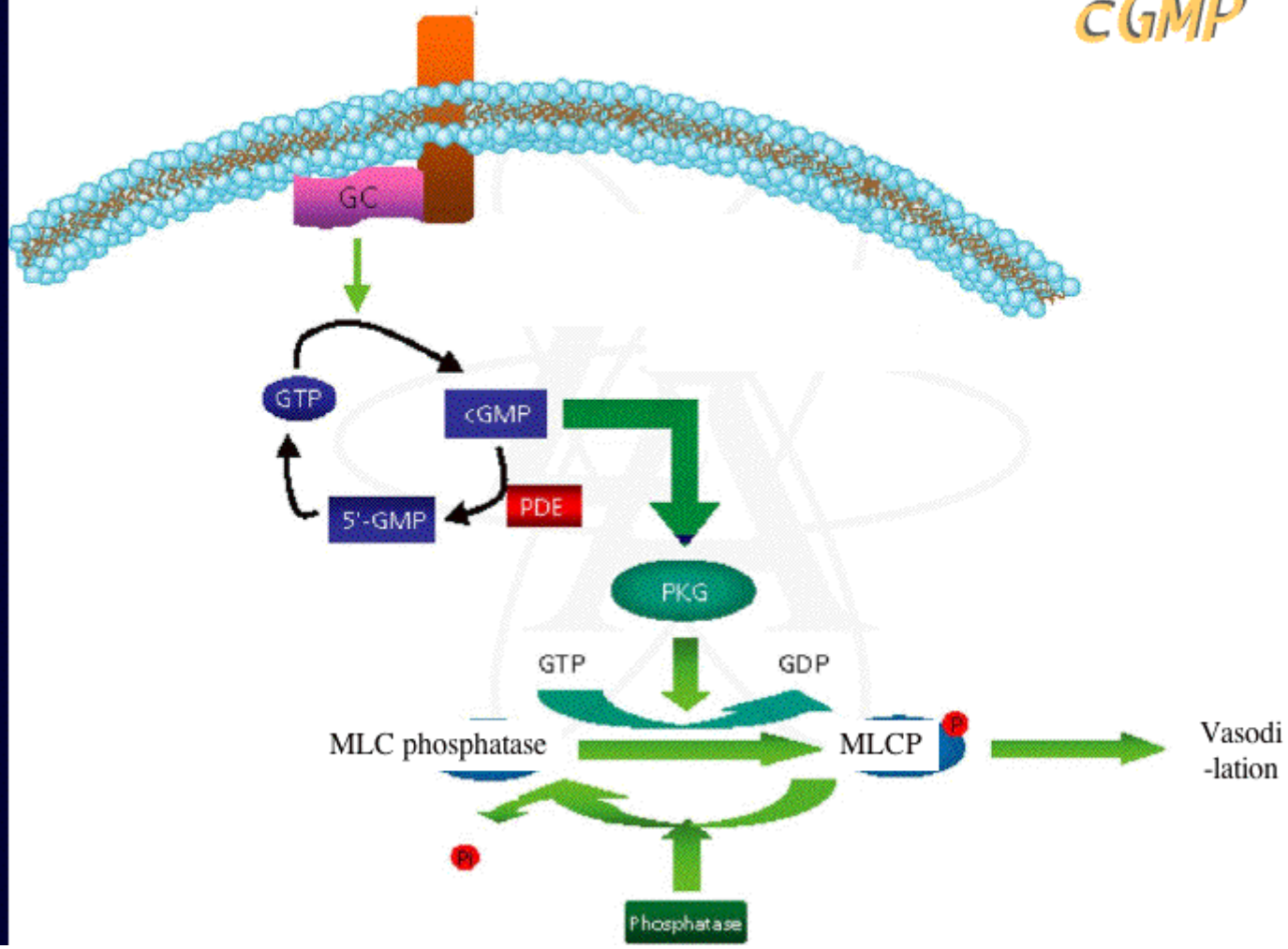
Phospholipase C → IP_3 + DAG

- from membrane phospholipids
- IP_3 activates Ca channel of endoplasmic reticulum
  - DAG ↑↑ PKC affinity to Ca




cAMP
Agonist
Receptor
AC
βγ
Gα
ATP
cAMP
PDE
5'-AMP
PKA
ATP
ADP
MLC phosphatase
MLCP
P
Vasodi
-lation
Pi
Phosphatase

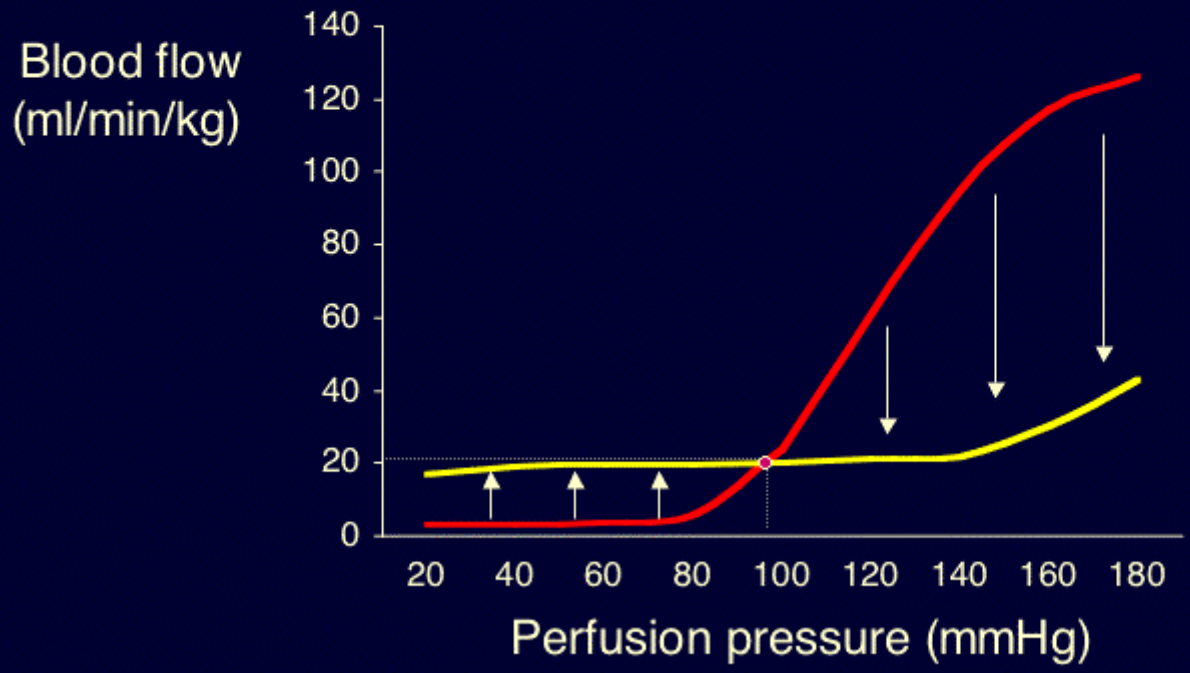
cGMP


GC
GTP
cGMP
5'-GMP
PDE
PKG
GTP
GDP
MLC phosphatase
MLCP
P
Vasodi
-lation
Pi
Phosphatase

Vascular tone regulation

- Local (mainly ♥, brain, kidney): autoregulation of blood flow
- Neural (mainly skin, GIT): inter-organ distribution
  - important where local flow can be reduced for the sake of the whole body (blood pressure maintenance)
  - almost not at all in brain & ♥
- Humoral - total PVR, not distribution

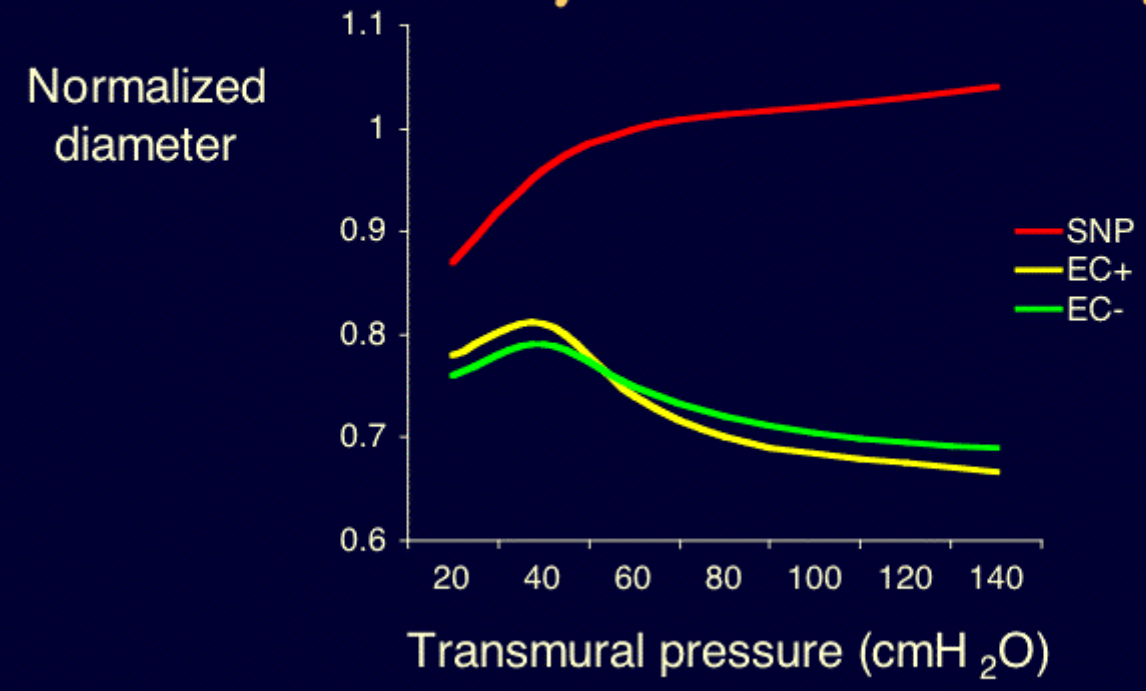
Local autoregulation of blood flow



Blood flow autoregulation

- Importance:
  - Adjusts perfusion to metabolic needs
  - Constant flow during pressure alterations
  - Rises towards periphery
- Mechanisms:
  - Myogenic response
  - Metabolic regulation

Myogenic response to pressure changes



Flow = 0

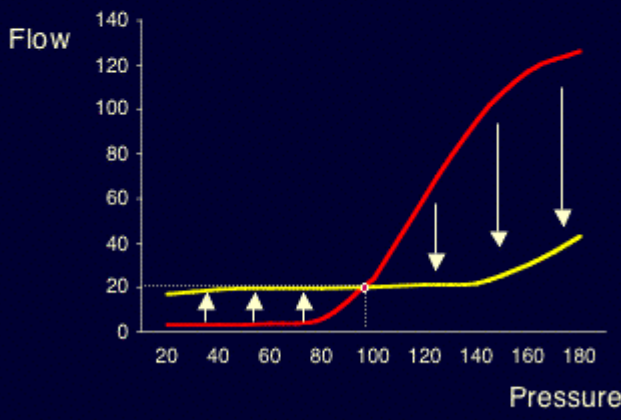
Myogenic response

- Mechanisms unclear
  - Stretch-activated cation channel
  - Ca^{2+} influx
- Important e.g. for orthostasis
  - upright → ↑ transmural pressure in legs
  - myogenic vasoconstriction prevents excessive redistribution of blood to legs & edema

Metabolic regulation

Candidates (complement each other):

- O_2
- CO_2
- H^+
- lactate
- K^+
- adenosine



(probably also ↓ NE release from SNS terminals)

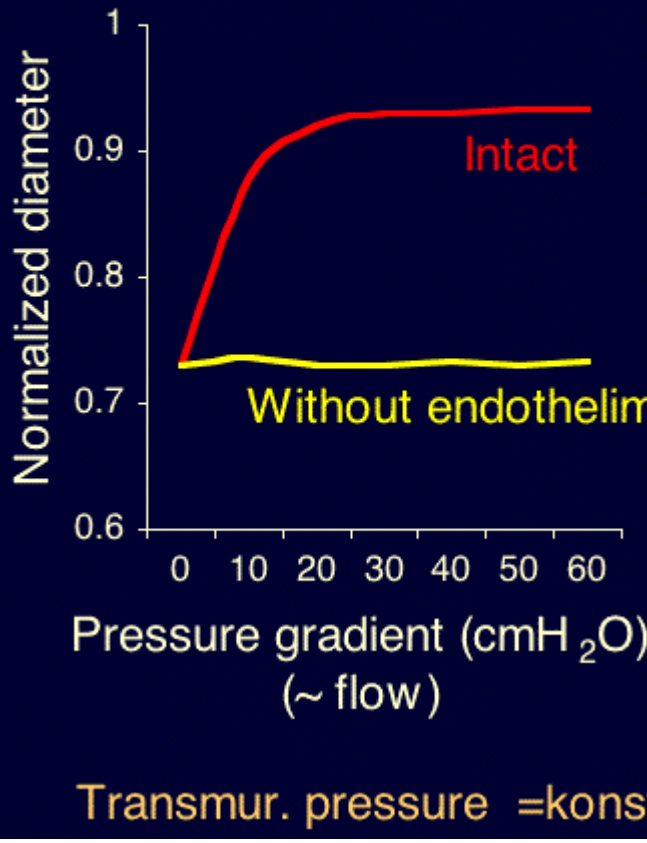
Organs without autoregulation (skin, …)

- Metabolic component minimal due to low metabolism
- Myogenic component suppressed by NO
  - NO inhibition unmasks skin myogenic autoregulation

Coordination of arterial & arteriolar dilation

- Vasodilation of peripheral arterioles accelerates flow in larger feeding arteries
- Shear stress ↑
- NOS activation
- Arterial relaxation

- NO in this situation indispensable



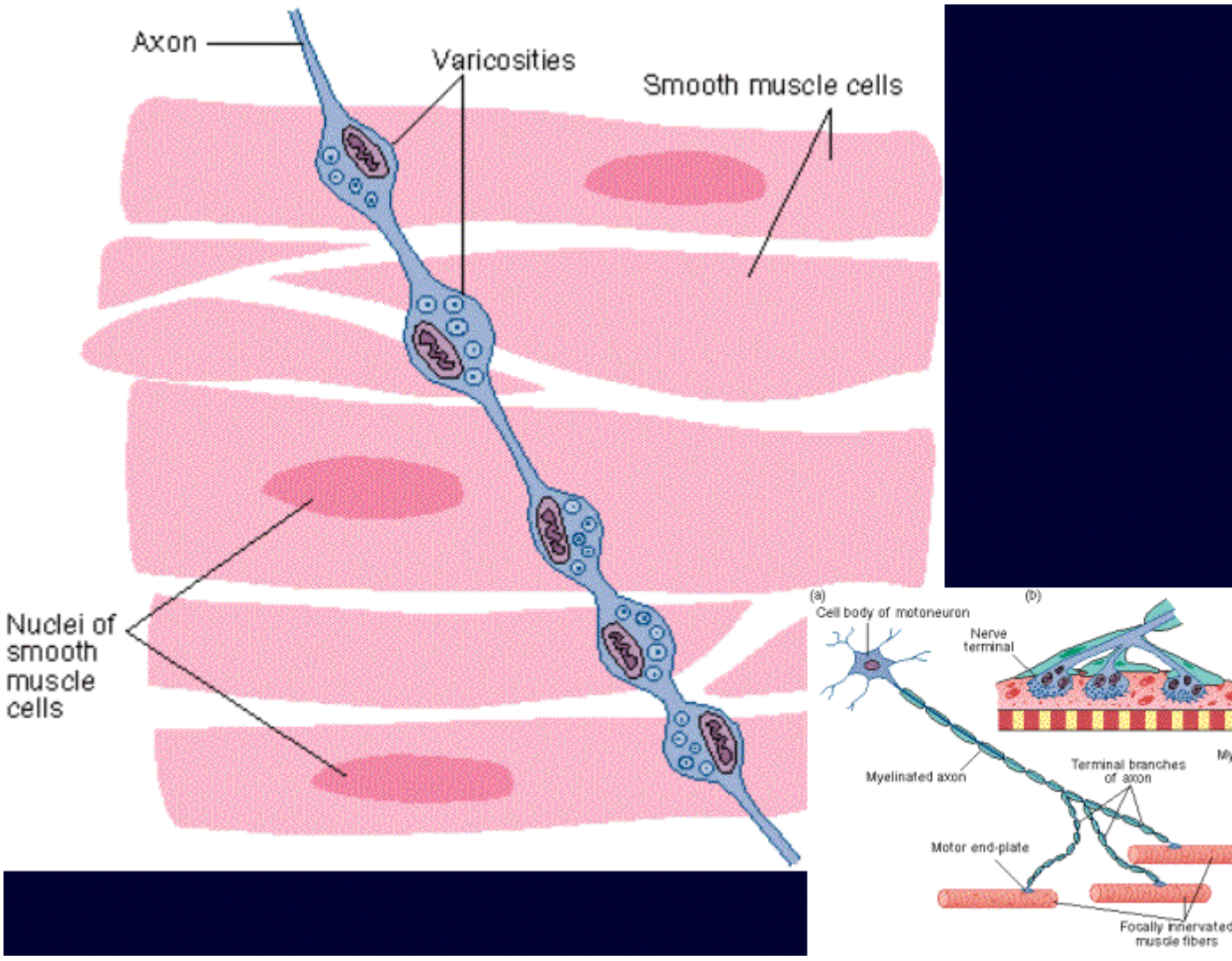
Transmur. pressure =kons

Endothelium

- Nitric oxide (NO)
  - vasodilation via cGMP → G kinase
- Prostacyclin (PGI_2)
  - vasodilation via cAMP → A kinase
- Endothelin (mainly ET-1, also -2 a -3)
  - 21 amino acids from pro-ET-1 (38 AA) by endothelin converting enzyme
  - receptors via G-proteins:
    - ET_A on VSM (mainly intracellular Ca^{2+})
    - ET_B releases NO & PGI_2 from endothelium
- Angiotensin conversion

Neural regulation of vascular tone

- Essentially only **sympathicus**
  - Mostly adrenergic
  - Mainly vasoconstriction
- Parasympathicus only a bit in face, colon, bladder & genital (erection)
  - Cholinergic
  - Vasodilation
- From pressoric & depressoric area of the cardiovascular center in medulla


Axon
Varicosities
Smooth muscle cells
Nuclei of smooth muscle cells
(a)
(b)
Cell body of motoneuron
Nerve terminal
Myelinated axon
Terminal branches of axon
Motor end-plate
Focally innervated muscle fibers

Sympathicus: NA terminals

- α receptors - vasoconstriction
  - more sensitive to NA from nerve terminals than to circulating adrenaline
  - predominant in skin, kidney,...
- β receptors - vasodilation
  - more sensitive to circulating adrenaline than to NA
  - predominant in skeletal muscle
  - similar expression of α a β in coronary & GIT vessels

    flow redistribution to muscle during exercise
- Some SNS terminals in vessels are cholinergic
  - vasodilation
  - skeletal muscle
  - importance ?? (↑ muscle flow when exercise anticipated ?)

Sympathetic regulation of vascular tone

- Capacitance vessels (veins) more sensitive (& have ↓↓ basal tone)
  - (↑ CO before ↓ tissue perfusion)
- SNS lowers filtration to tissues (↓ filtration pressure)

Baroreceptors

- Carotid sinus (more sensitive) & aortic arch
- Activation by stretch
  - Via glossopharyngeal nerve to medulla (nucleus tractus solitarius)
  - Sympathetic tone ↓
- Sensitivity ↓ in hypertension (stiffer carotid sinus)
- Sometimes hypersensitivity → hypotension & fainting because of tight collar

Chemoreceptors

- Peripheral (O_2 in carotid & aortic bodies): only small, supportive role
- Central (CO_2/pH in hypothalamus): massive vasoconstriction (protects CNS from ischemia)

Humoral regulation of VSM: circulating hormones

- **Adrenaline**: (importance < NA from SNS)
  - Skeletal muscles: β vasodilation @ low dose, α vasoconstriction @ high dose
  - Skin & other organs: only α vasoconstriction
- Angiotensin II:
  - ACE from A-I, A-I from angiotensinogen by renin (released from kidny in hypotension or ↓ volume)
  - mainly AT_1 receptors
  - AT_2 opposite effects, but little AT_2 in vessels
    - (their activation can ↑ during AT_1 inhibition because of feed-back ↑ A II - therapeutic significance)

Humoral regulation of VSM: circulating hormones

- ANP:
  - atrial distention
  - natriuresis, vasodilation via cGMP
- Endogenous ouabain (Na-K ATPase inhibitor)
  - Na/K ATPase is electrogenic (3 Na out, 2 K in) → its inhibition depolarizes
    - but ↑ natriuresis by inhibition of Na pumping from primary urine → ↑ volume → ↑ pressure
- Adrenomedullin (peptide from adrenal medulla)
  - ↑ cAMP in VSM
  - ↑ NO in endothelium