université PARIS-SACLAY | GRADUATE SCHOOL Health and Drug Sciences

Vascular tone

Boris MANOURY

October 29th, 2024

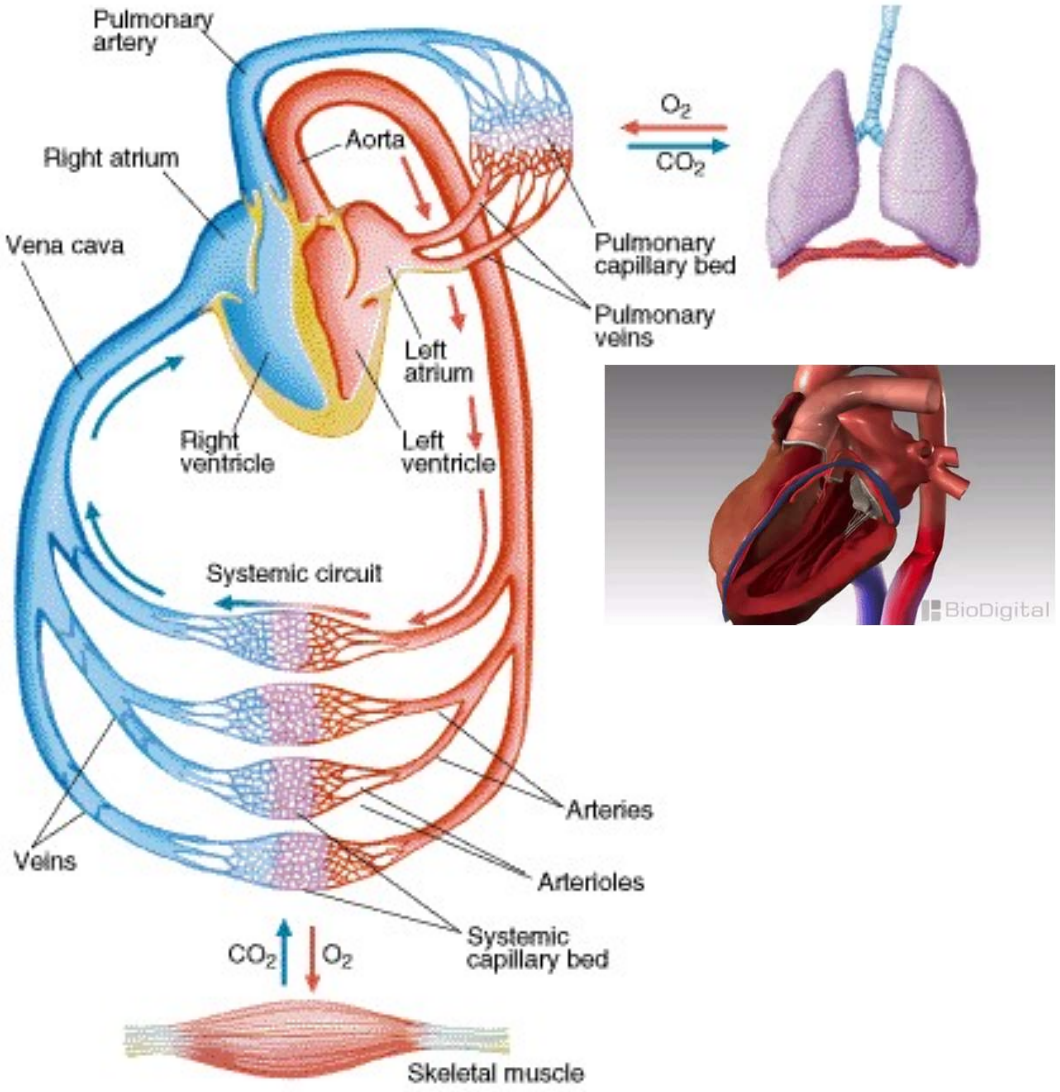
Master 1 D2HP, TU03

« Resistance is the first step to change »

L. Hay

I. Vascular smooth muscle cells (VSMC) : a cell type among others in blood vessels

Organ perfusion is driven by ARTERIAL BLOOD PRESSURE (ΔP_A)



VSMCs in the blood vessel

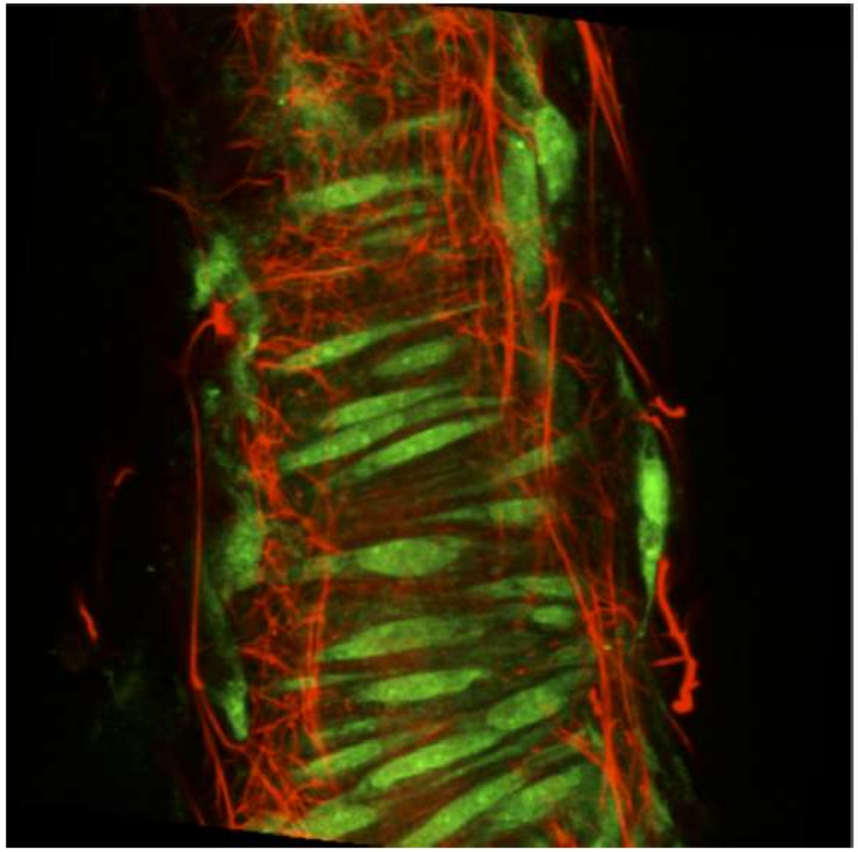


Fig. 2. Confocal image of a longitudinal section of a first-order (1A) arteriole from the cremaster muscle. Smooth muscle cells (SMCs) are organized circumferentially in the vessel wall. The fine fibers visible on the lateral borders are part of the adventitia. The pressurized arteriole was incubated with Alexa fluor 633 hydrazide (red) to visualize the extracellular matrix (ECM) and Yo-Pro (propridium iodide, green) to visualize SMCs. [Courtesy of S. R. Ella, P. S. Clifford, G. A. Meininger, and M. A. Hill.]

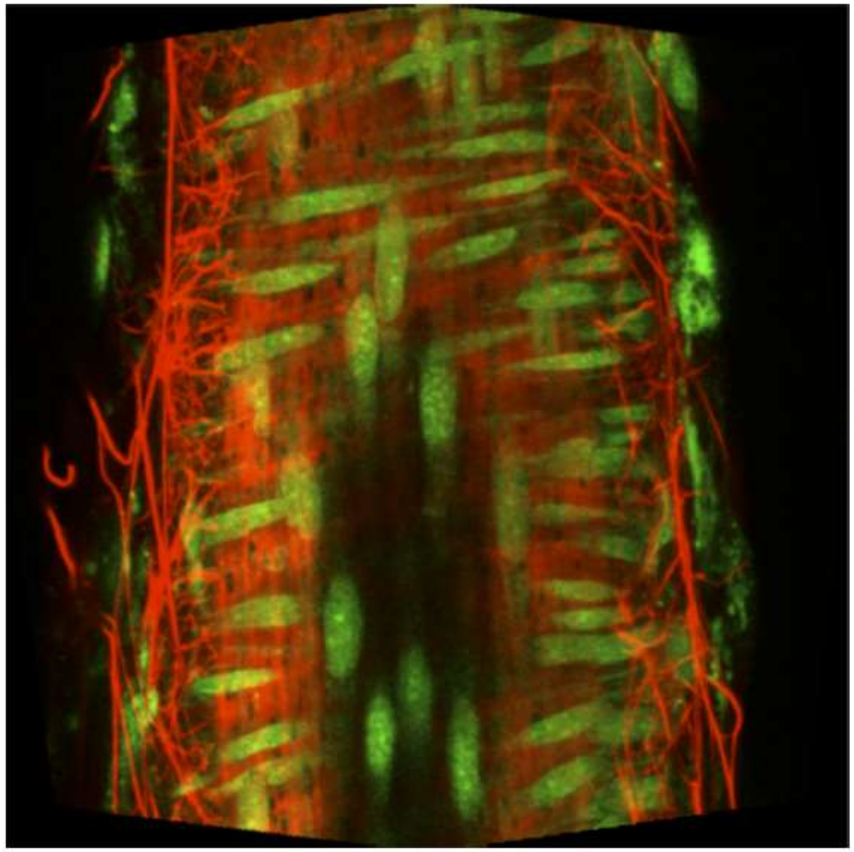
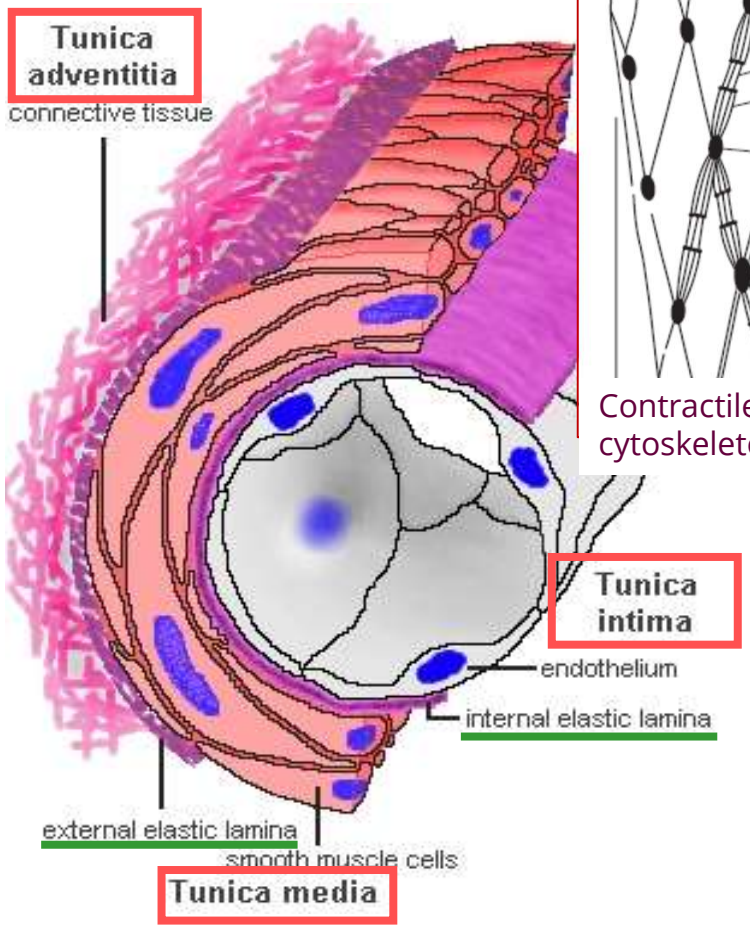


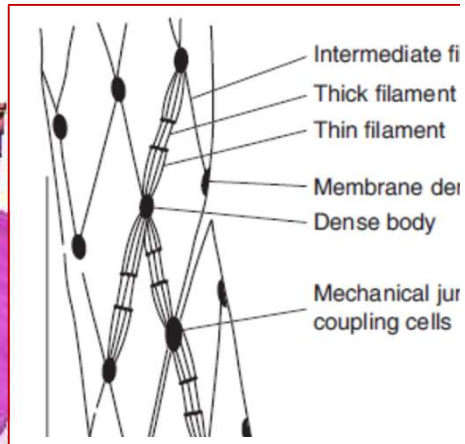
Fig. 3. Confocal image of a longitudinal section of a 1A arteriole from the cremaster muscle. The longitudinal orientation of endothelial cells (ECs) in the vessel wall is in contrast to the circumferential orientation of SMCs. The fine fibers visible on the lateral borders are part of the adventitia. The pressurized arteriole was incubated with Alexa fluor 633 hydrazide (red) to visualize the ECM and Yo-Pro (propridium iodide, green) to visualize ECs and SMCs. [Courtesy of S. R. Ella, P. S. Clifford, G. A. Meininger, and M. A. Hill.]

Clifford, 2011 Adv Physiol Educ

Vascular tissue



Cross-section of an artery



Contractile apparatus and cytoskeleton in VSMCs

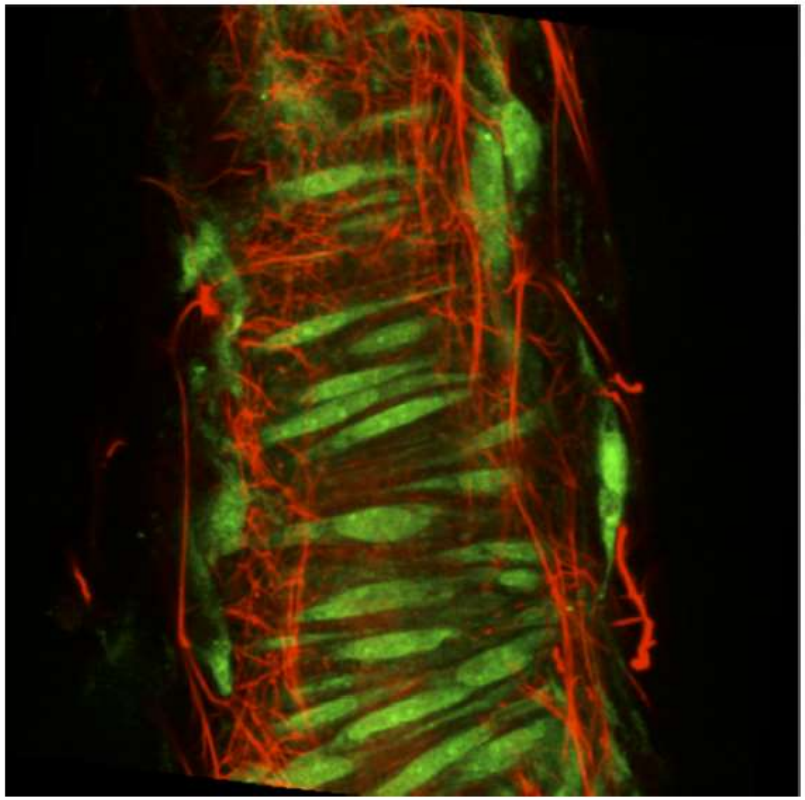
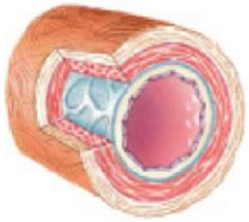


Fig. 2. Confocal image of a longitudinal section of a first-order (1A) arteriole from the cremaster muscle. Smooth muscle cells (SMCs) are organized circumferentially in the vessel wall. The fine fibers visible on the lateral borders are part of the adventitia. The pressurized arteriole was incubated with Alexa fluor 633 hydrazide (red) to visualize the extracellular matrix (ECM) and Yo-Pro (propridium iodide, green) to visualize SMCs. [Courtesy of S. R. Ella, P. S. Clifford, G. A. Meininger, and M. A. Hill.]

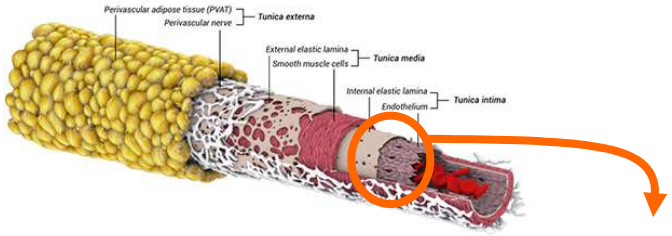
Clifford, 2011 Adv Physiol Educ; Seeney and Hammers Cold Spring Harb Perspect Biol 2018

Various sizes for various functions

		Wall features	function
Conducting system Diameter 1-25 mm		**-intima : endothelium + connective tissue** **-media :** **thick, with elastic fibers +++ for large arteries** - **Smooth muscle +++ for smaller arteries**	- **Blood conduction** - **Pressure reserve : pulsatile energy transmission**
Resistance system Diameter 5 – 500 µM		- **Intima : endothelium** - **Thin media enriched with smooth muscle**	- **Vascular tone : control of blood perfusion** - **Regulation of peripheral resistance**
Capillary Diameter 5 µm		**- Intima only**	**-control of local flow** **Capillary exchanges (gas, nutrients)**

Functions of vascular cells

Perivascular adipose tissue



platelets

hemostasis coagulation

Endothelial cells

proliferation, angiogenesis

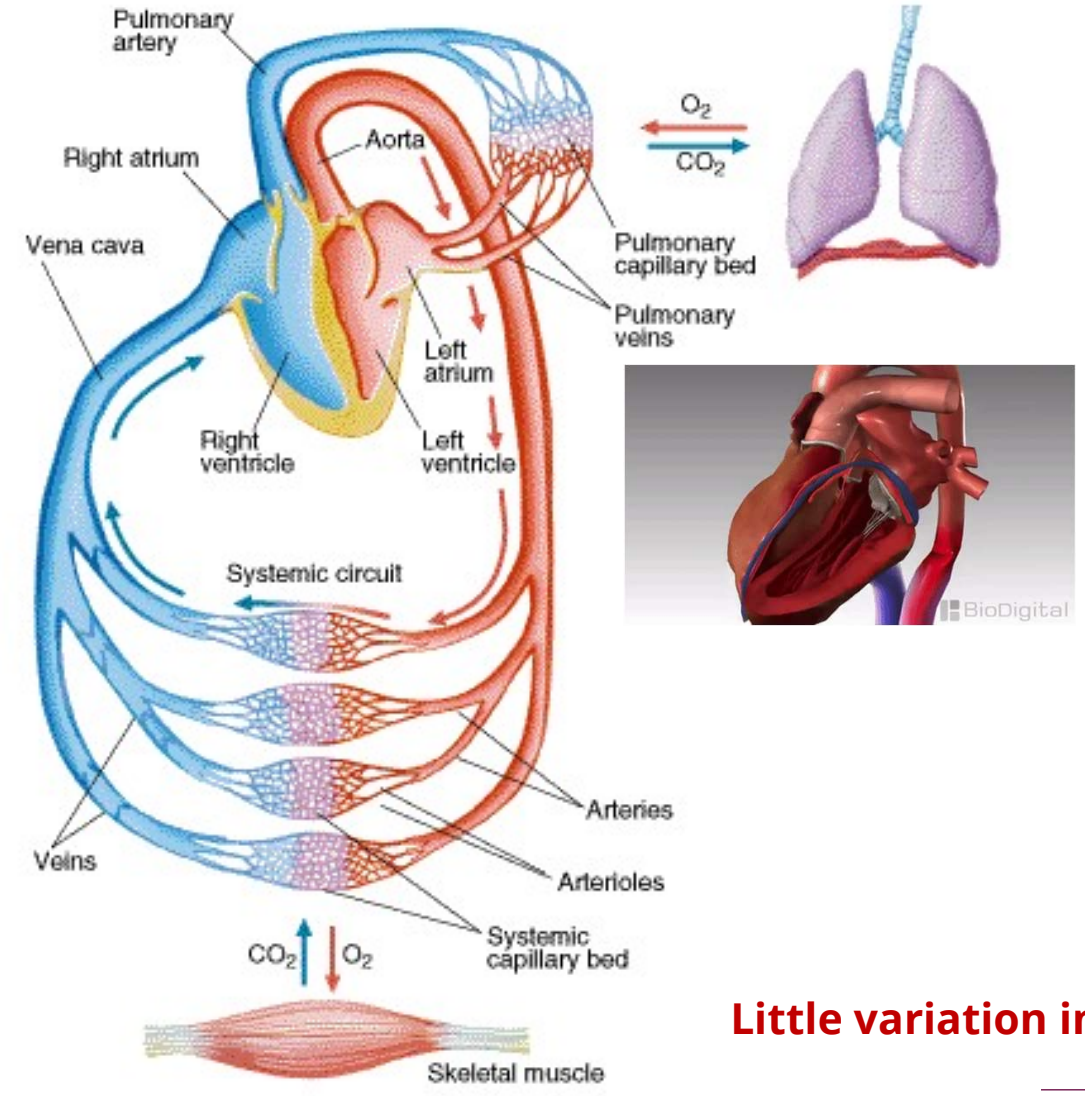
Vascular permeability

vascular tone

proliferation migration

VSMCs

Organ perfusion is driven by ARTERIAL BLOOD PRESSURE (ΔP_A)



Poiseuille's Law

$$\Delta P = Qc \,.\, PVR$$

$$Qc = HR \,.\, Vs$$

ΔP: pressure gradient between both ends of the vessel

Qc : cardiac output (L/min) (laminar flow)

PVR : peripheral vascular resistances

HR : heart rate

V_S: systole ejection volume

$$\mathbf{PVR} = \frac{8\eta L}{\pi r^4}$$

η: viscosity

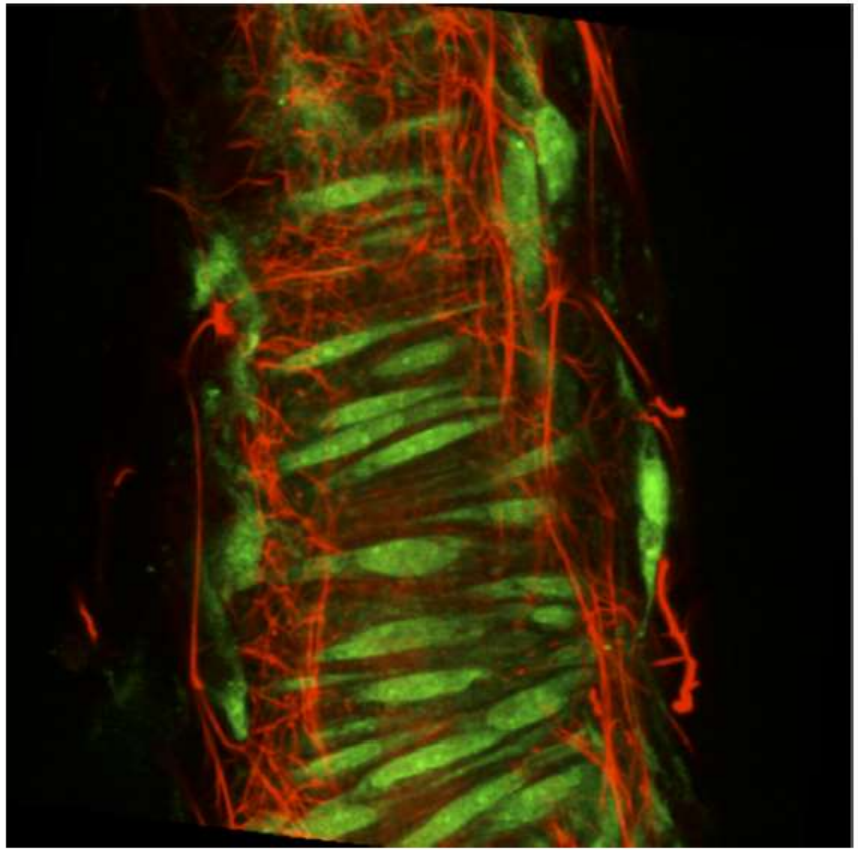
r: radius of the vessel

L: length of the vessel

Little variation in radius => big change in resistance

II. Smooth muscle cell (SMC) contraction

Vascular tone



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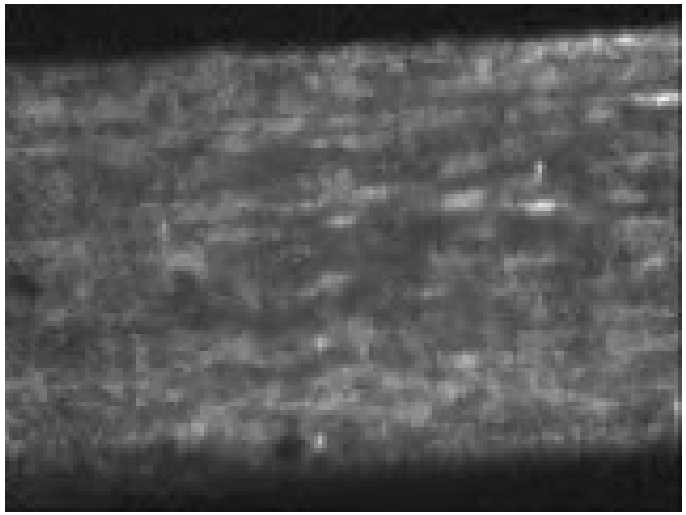


Asynchronous intracellular and synchronized intercellular Ca oscillations associated with vasoconstriction/vasomotion evoked by phenylephrine in mesenteric artery myocytes
Mesenteric artery was stimulated by 10 µM phenylephrine.

Clifford, 2011 Adv Physiol Educ, Borisova et al., 2009 Circ Res

Organisation of the contractile apparatus in SMC

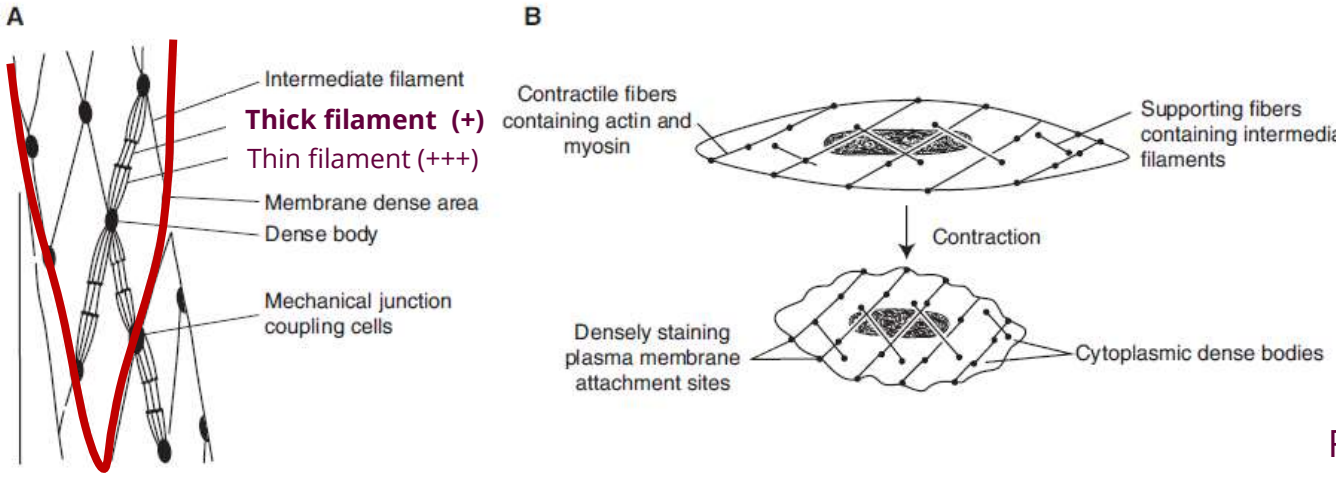
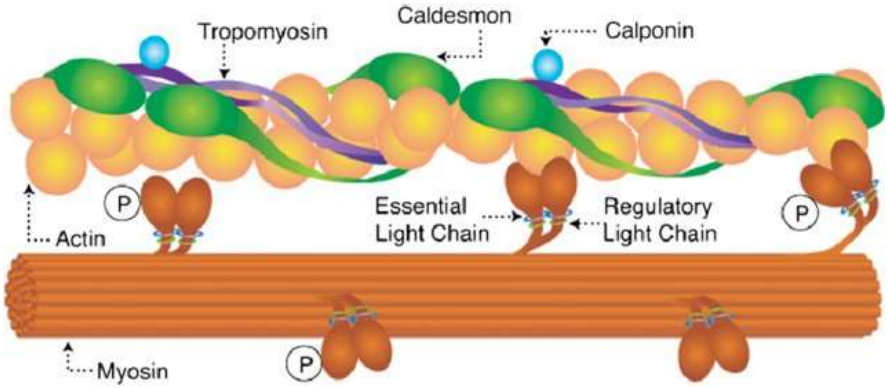


Figure 4. The contractile apparatus of smooth muscle. (*A*) Schematic of the key components of the force-generating protein network in mammalian smooth muscle. (*B*) The organization and rearrangements of the smooth muscle cell cytoskeleton during contraction.

Freshly isolated rat mesenteric artery smooth muscle cells
(B Manoury)



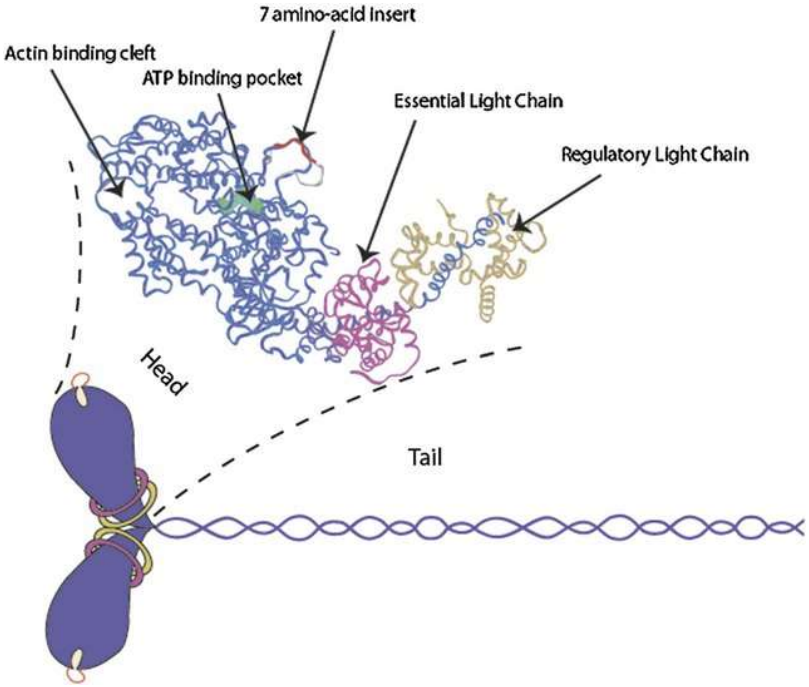
Thin filament : **actin (α-SM actin)**, tropomysosin, caldesmon, calponin (NO TROPONIN in SMC)

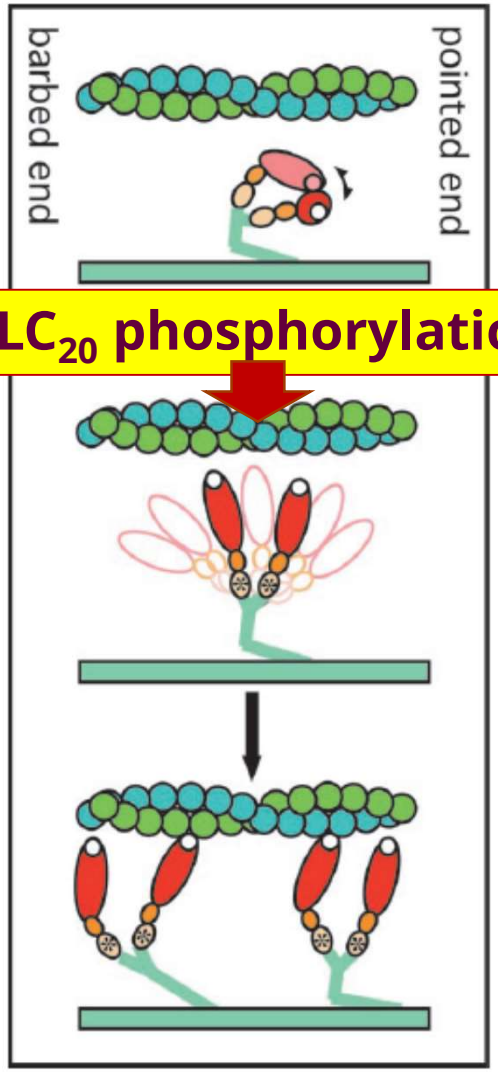
Thick filament (+) :
smooth muscle myosin II dimers

Sweeney and Hammers 2018 Cold Spring Harb Perspect Biol,

Leguillette and Lauzon 2008 Proc Am Thor Soc

Contractile apparatus in SMC : smooth muscle myosin II





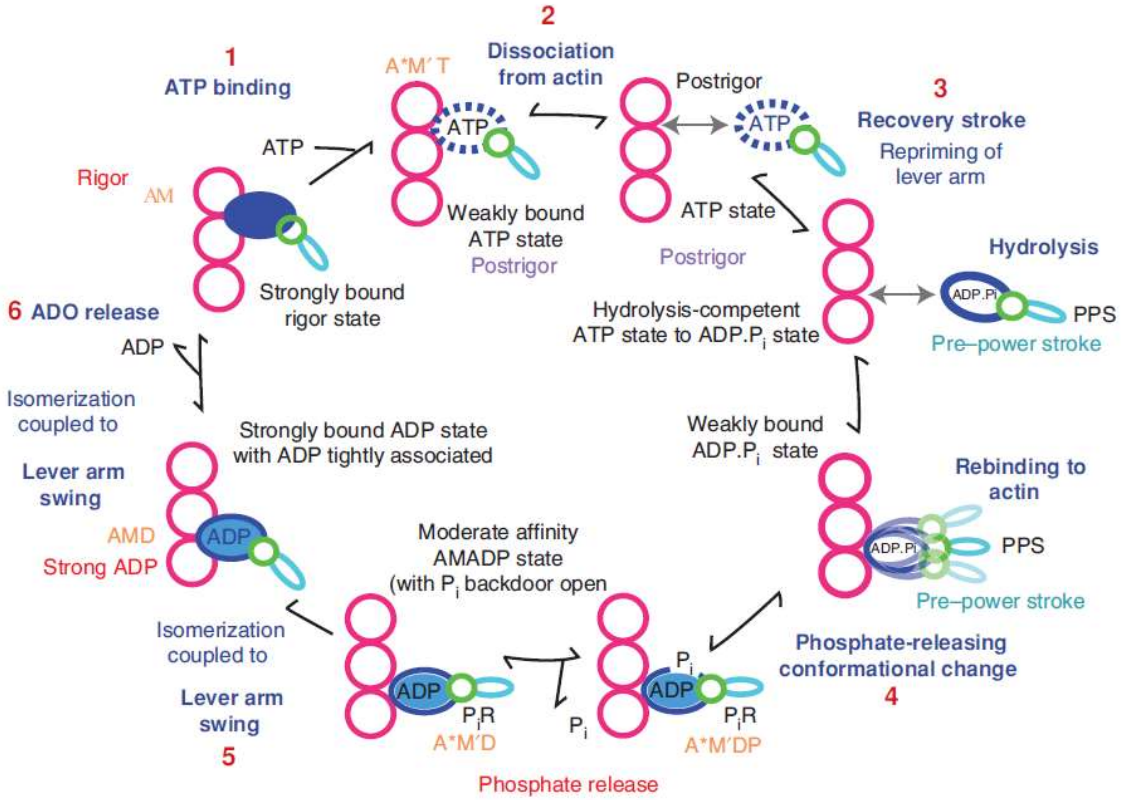
- **2 heavy chains (200 kDa)**
  - **ATPase activity in myosin heads**
- 2 pairs of light chain :
  - 17kDa essential
  - **20 kDa : regulatory (or myosin) / light chain (LC_{20}):**
    phosphorylation at ser-19 => ↑↑ cross bridge cycling

Sweeney and Hammers 2018 Cold Spring Harb Perspect Biol,;

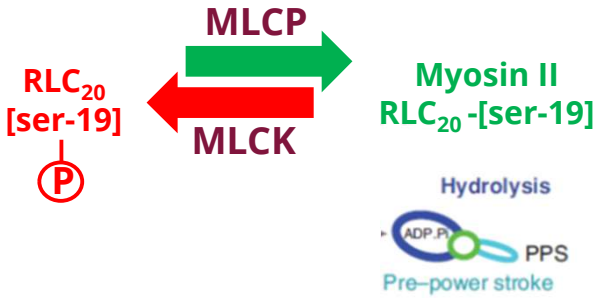
Wendt et al., 2001 PNAS ; Cole and Welsh 2011 Arch Biochem Biophys;

actin –myosin cross bridges cycling

contraction



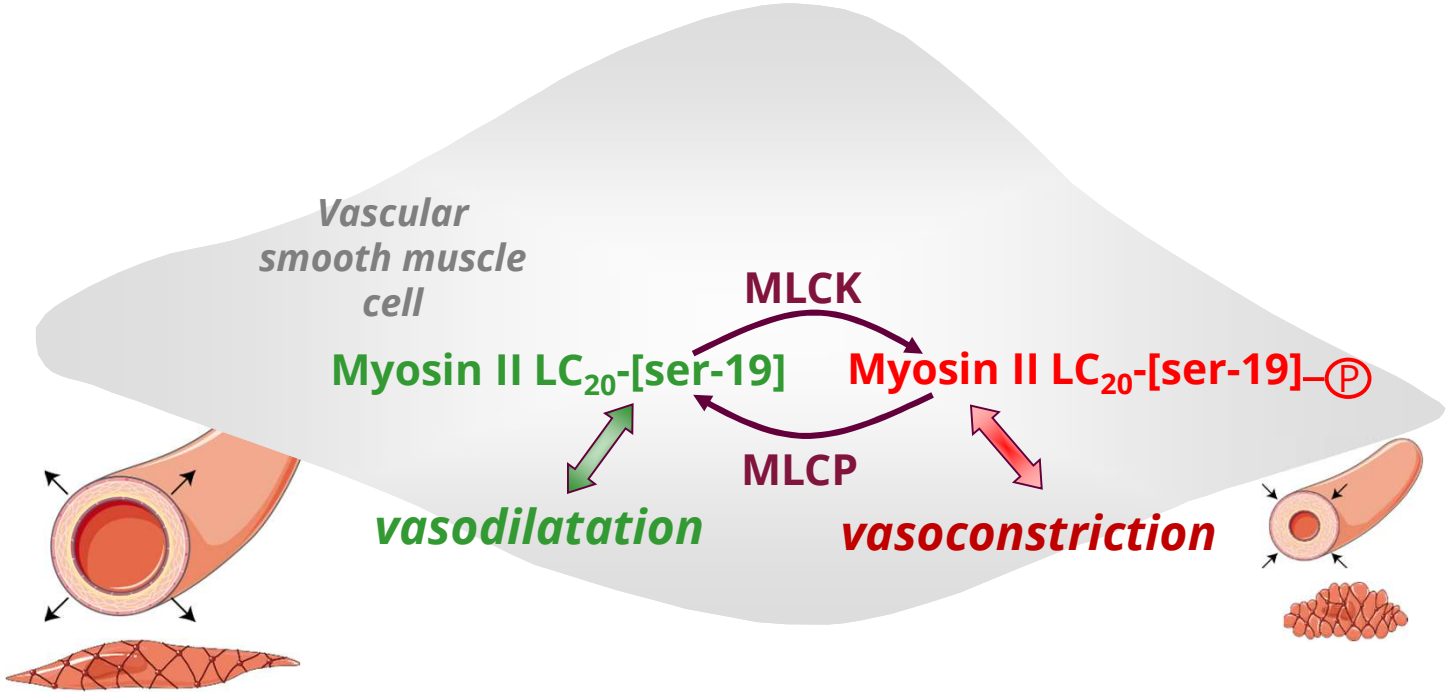
relaxation



- **Mechanism similar as in striated skeletal muscle**
- **ATP hydrolyzed while actin and myosin are detached from another**
- **Myosin cross-bridges attach to actin**
- **Energy of ATP hydrolysis is converted into force during release of the phosphate (Pi) and ADP.**

Sweeney and Hammers 2018 Cold Spring Harb Perspect Biol,;

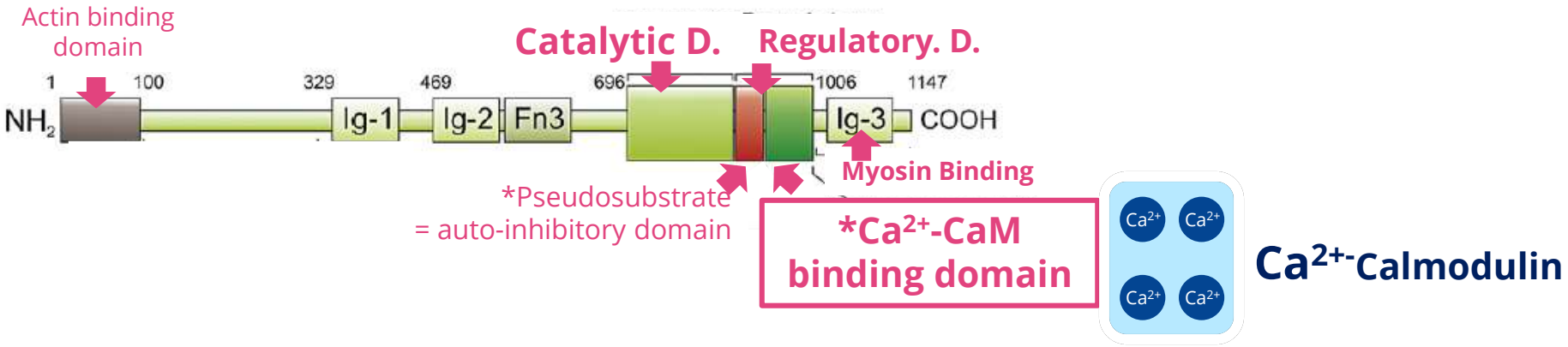
Role of MLCK and MLCP



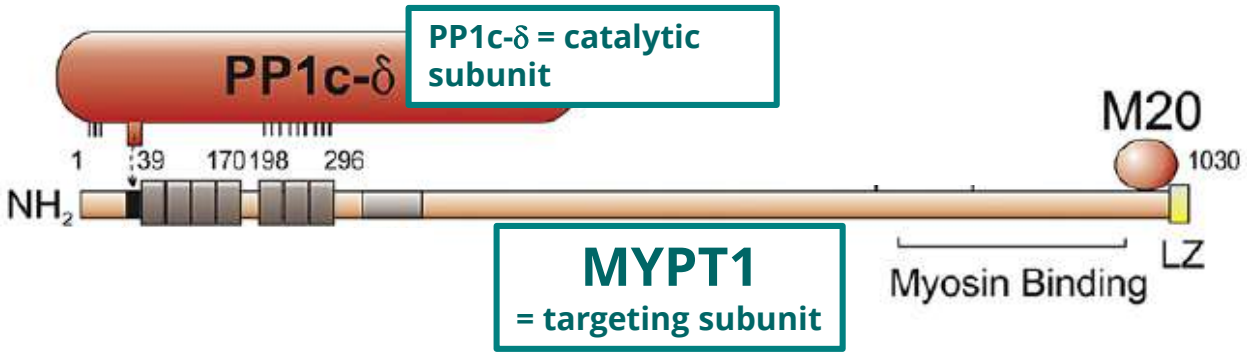
Borisova et al., 2009 Circ Res

MLCK and MLCP

MLCK : myosin light chain kinase



MLCP : myosin light chain



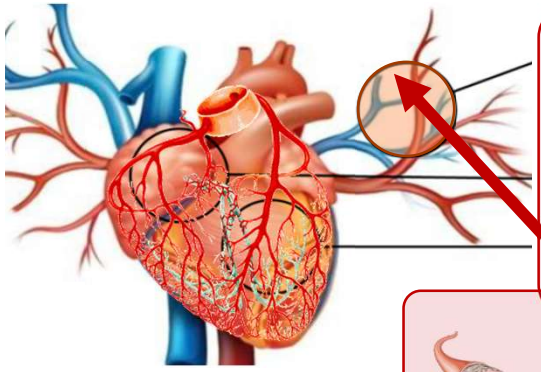
PP1c: catalytic subunit of type1 protein phosphatase

MYPT1 : myosin light chain phosphatase targeting subunit 1

M20 : non catalytic 20kDa subunit

Cole and Welsh 2011 Arch Biochem Biophys

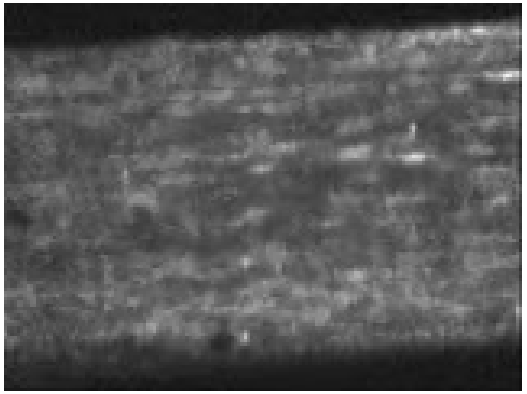
The L-type Calcium channel : role in vascular tone



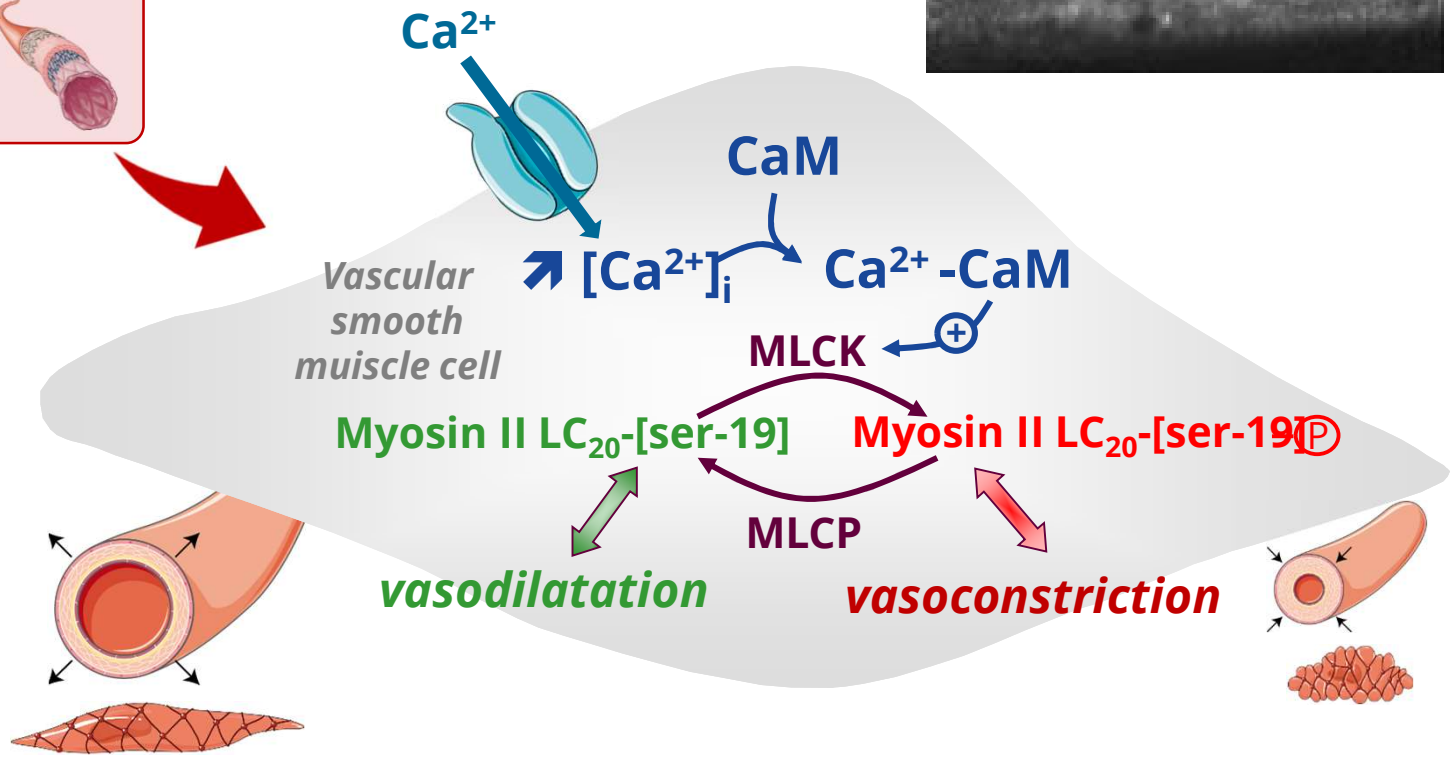
Vascular smooth muscle cell

I(Ca, L) : Ca^{2+} *inward current*

$Ca_V1.2$: vasoconstriction



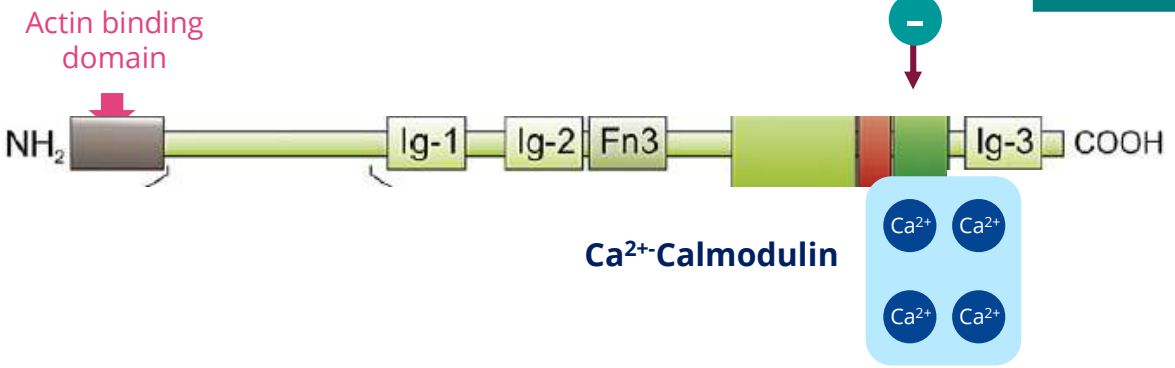
CaM : calmodulin



Borisova et al., 2009 Circ Res

Regulation of MLCK and MLCP activities

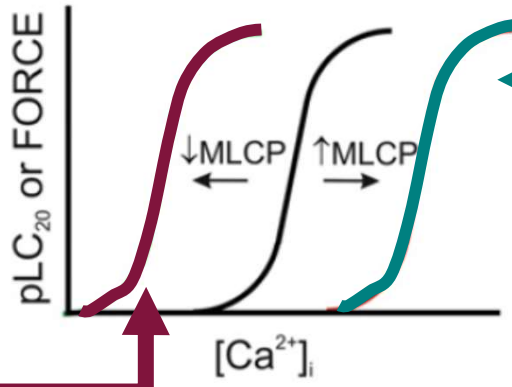
MLCK : myosin light chain kinase



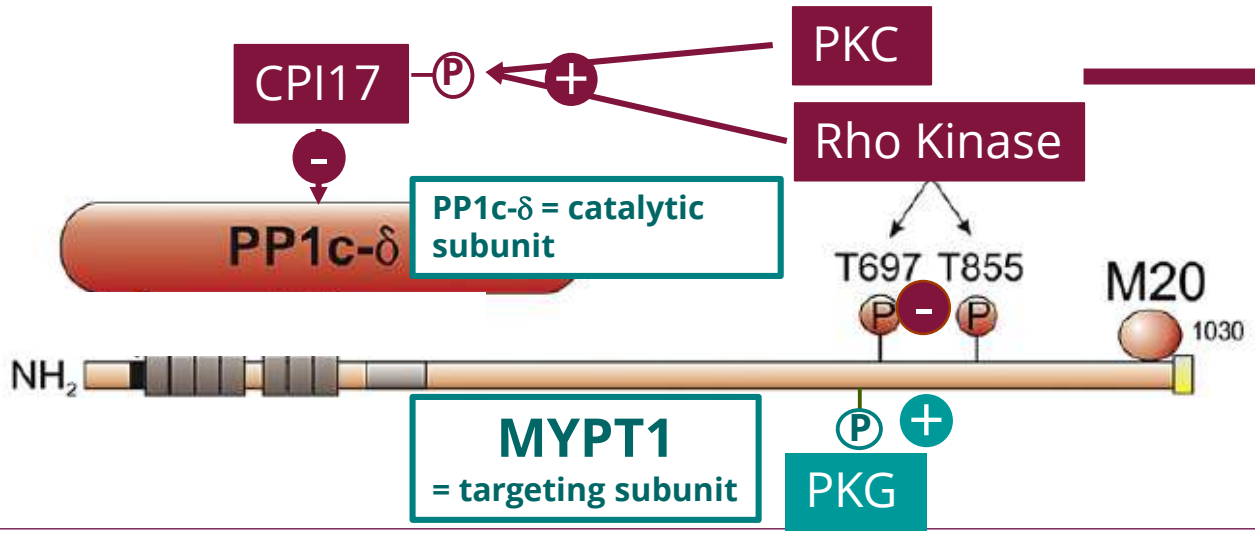
Ca²⁺-Calmodulin

PKA

MLCP activated =>
« Ca²⁺Desensitization »



MLCP : myosin light chain

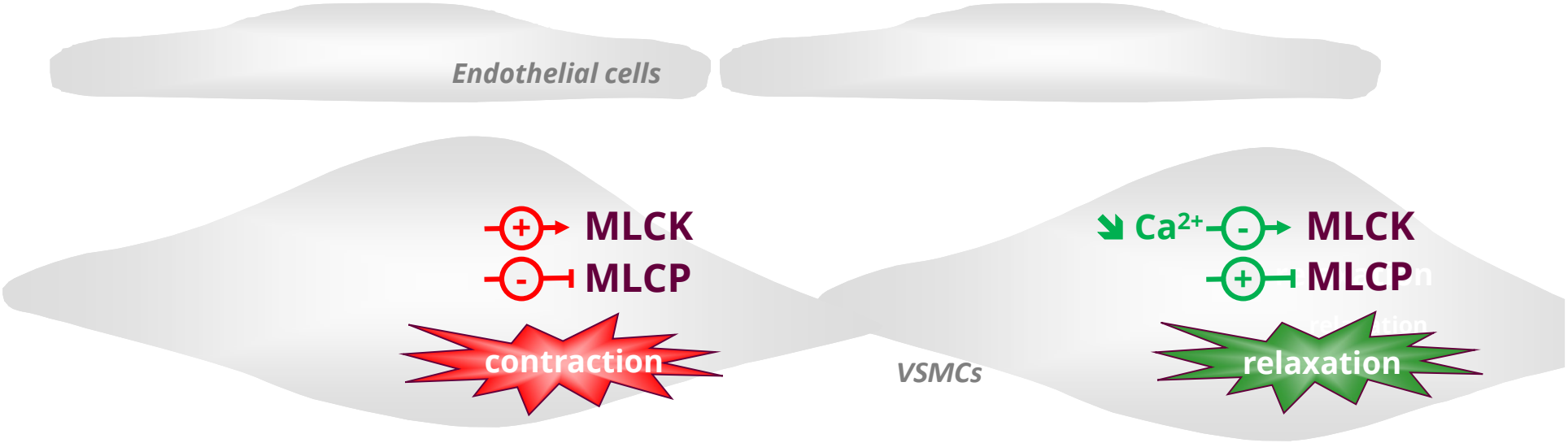


MLCP inhibited =>
« Ca²⁺ Sensitization »...

Cole and Welsh 2011 Arch Biochem Biophys

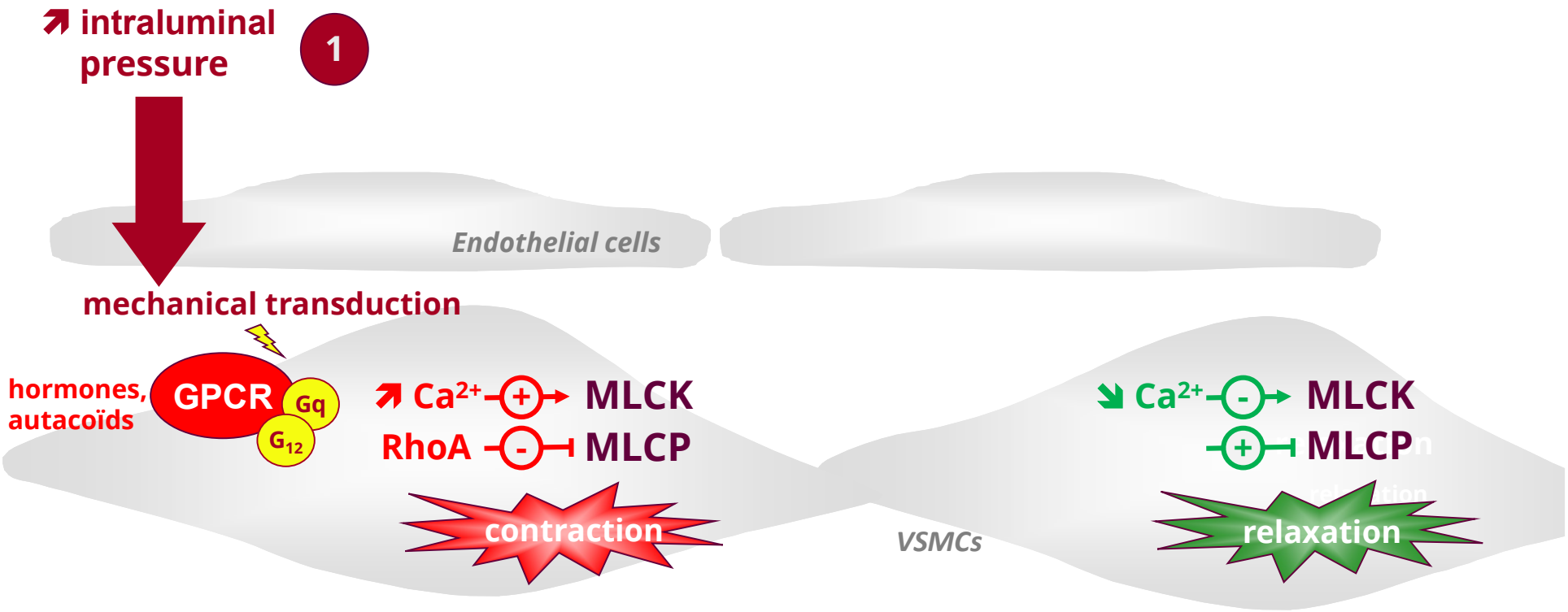
III. Regulation of vascular smooth muscle cell (SMC) contraction

Determinants of vascular tone



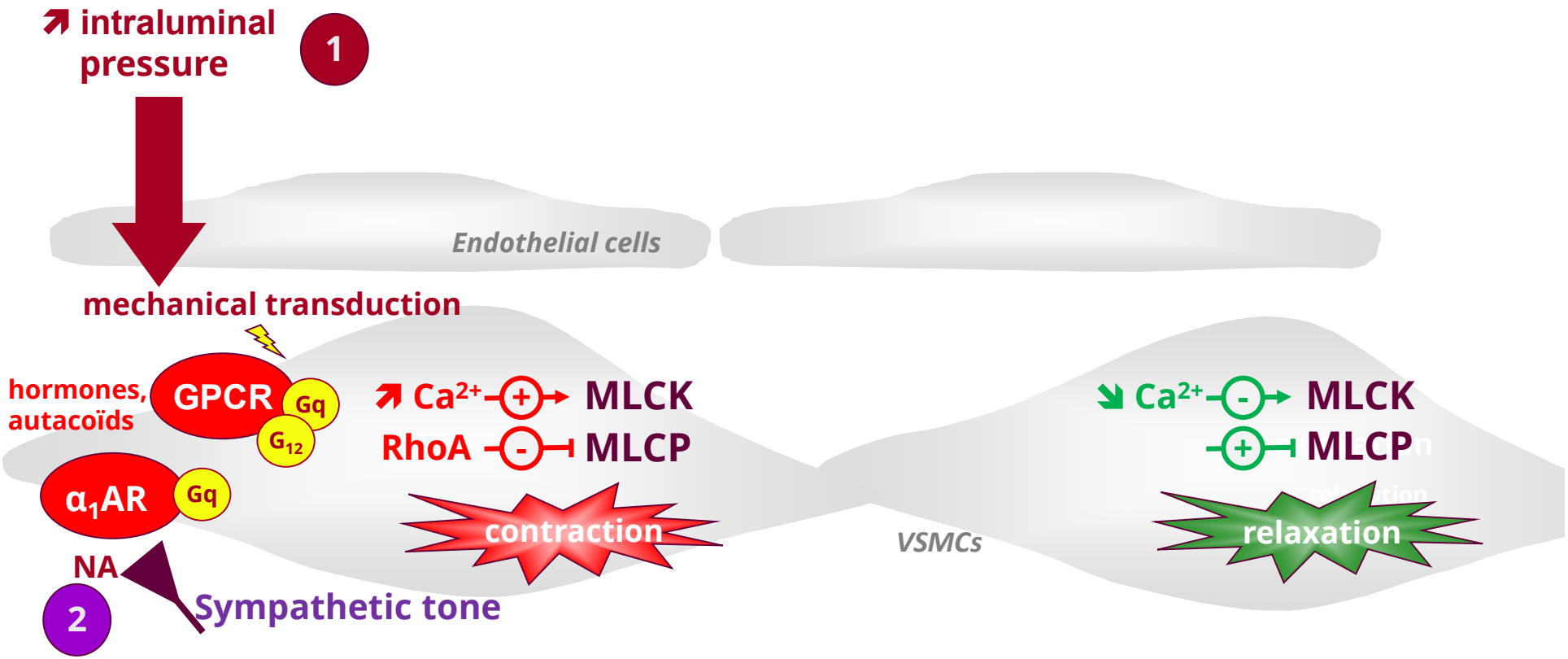
1.
2.
3.
4.

Determinants of vascular tone



1. **myogenic tone :** maintain small arteries in a mid-contracted state
2.
3.
4.

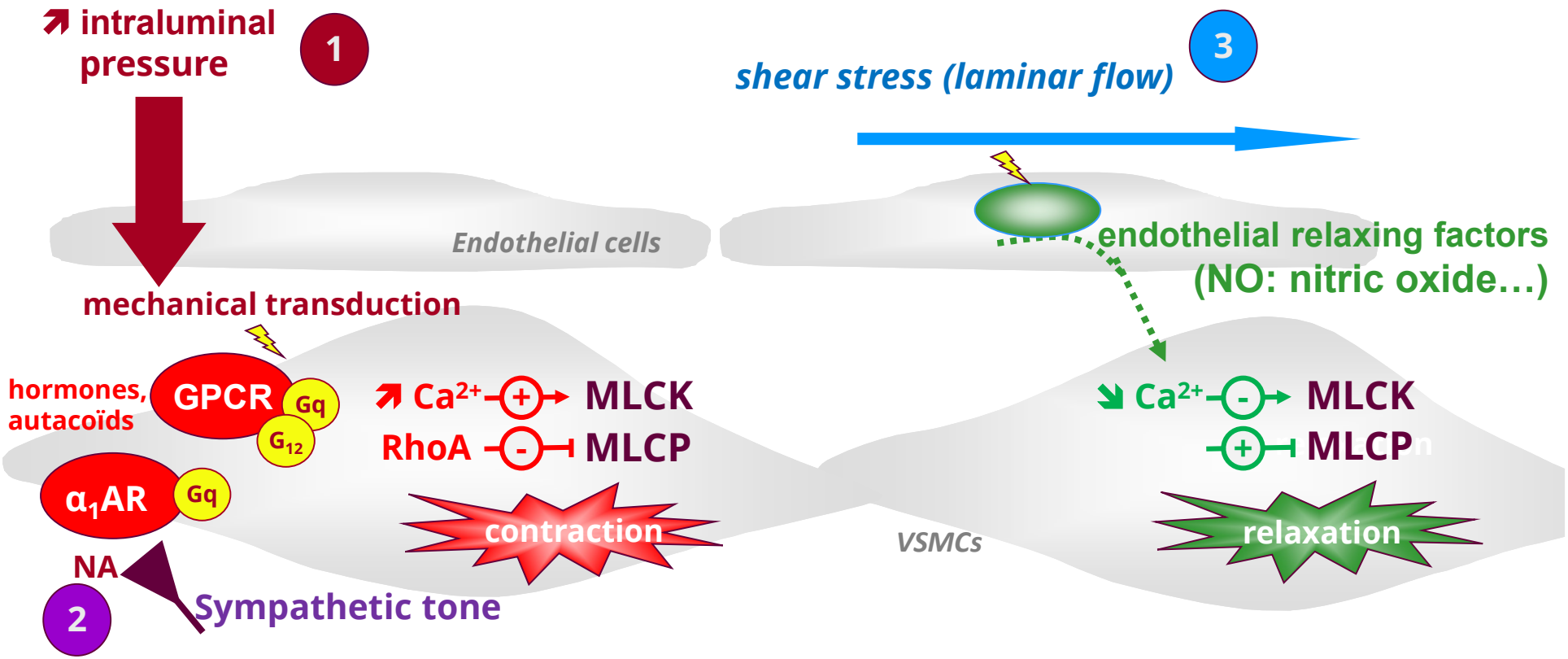
Determinants of vascular tone



1. **myogenic tone :** maintain small arteries in a mid-contracted state
2. **receptor-mediated vasoconstriction:** NA, AngII, ET1...
3.
4.

α_1AR: alpha(1) adrénergic receptor;

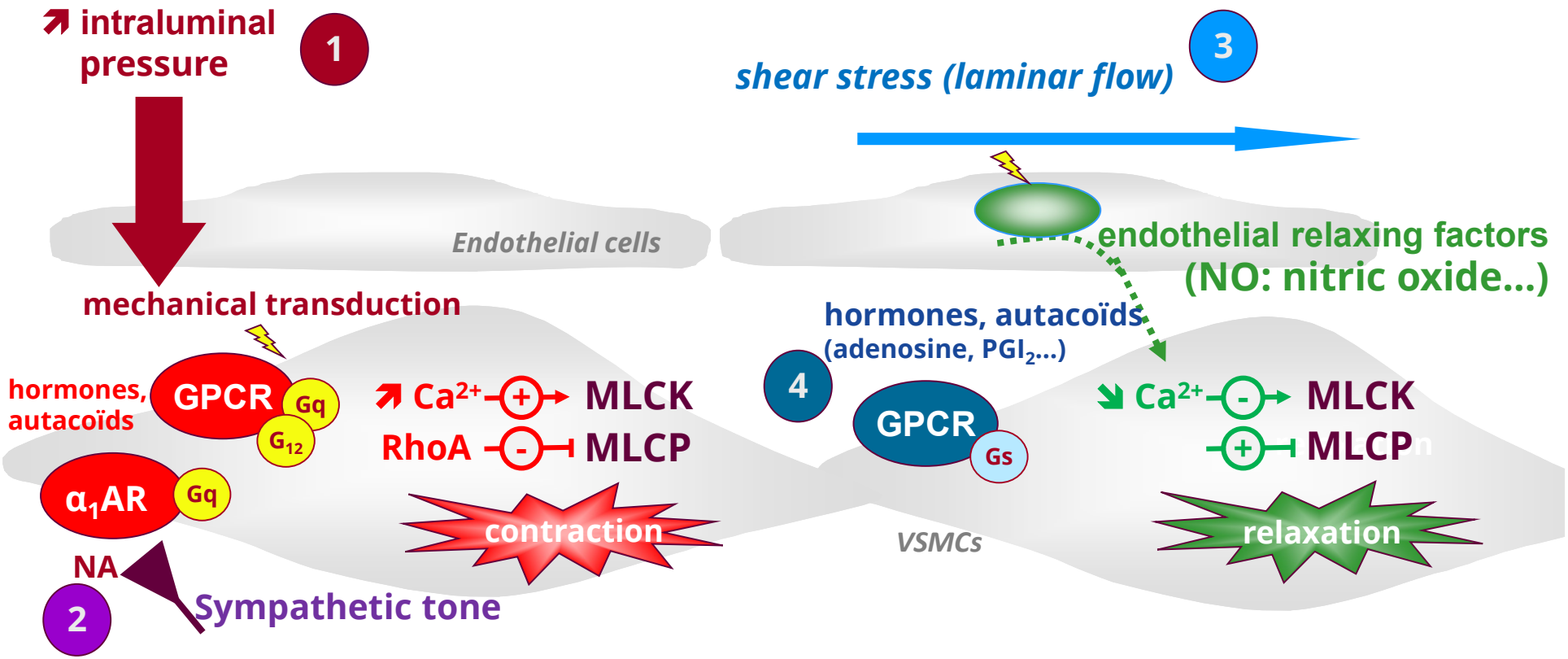
Determinants of vascular tone



1. **myogenic tone : maintain small arteries in a mid-contracted state**
2. **receptor-mediated vasoconstriction: NA, AngII, ET1…**
3. **flow -mediated vasodilatation: release of NO, EDHF…**
4.

α_1AR: alpha(1) adrénergic receptor; EDHF: *endothelium-derived hyperpolarising factor;*
NA: noradrenaline; NO: *nitric oxide*

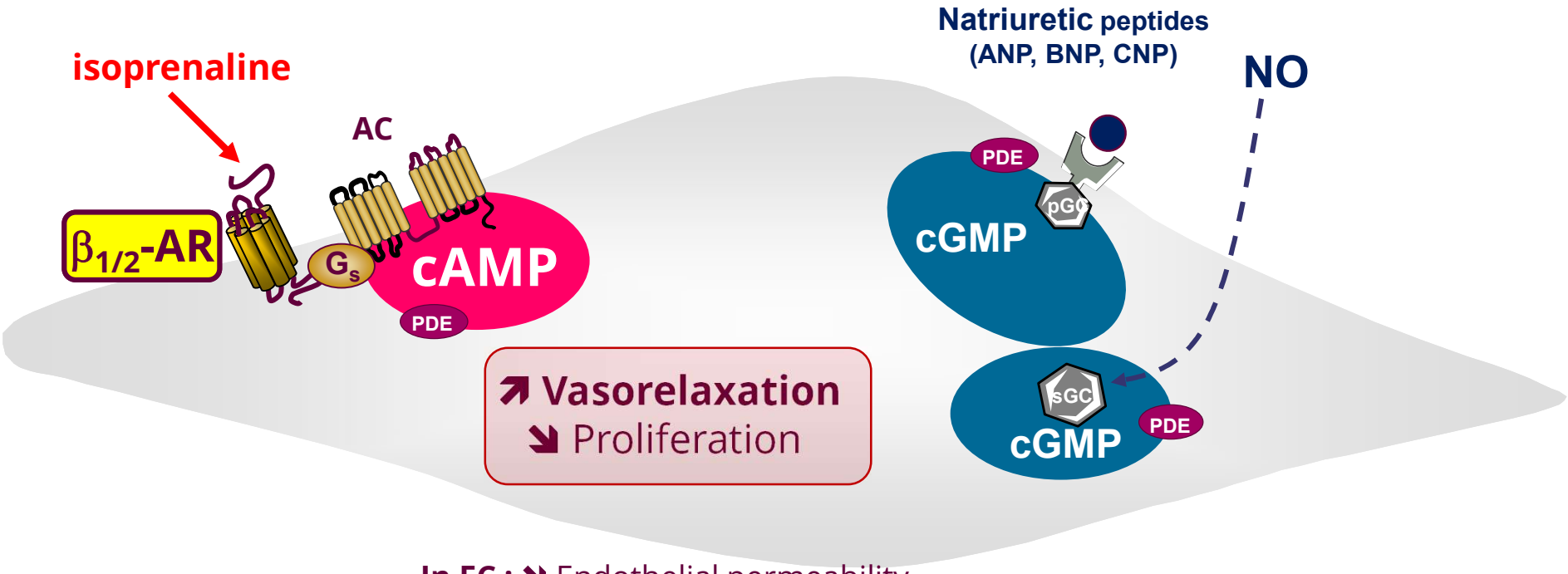
Determinants of vascular tone



1. **myogenic tone :** maintain small arteries in a mid-contracted state
2. **receptor-mediated vasoconstriction:** NA, AngII, ET1...
3. **flow -mediated vasodilatation:** release of NO, EDHF...
4. **receptor-mediated vasodilatation:** PGI_2, adenosine, adrenaline, CGRP

α_1AR: alpha(1) adrénergic receptor; CGRP: calcitonin gene-related peptide; EDHF: *endothelium-derived hyperpolarising factor ;* NA: noradrenaline; NO: *nitric oxide*

Cyclic nucleotides in vasculature: cAMP and cGMP



AC: adenylyl cyclase

cAMP: 3', 5' cyclic adenosine monophosphate

cGMP: 3', 5' cyclic guanosine monophosphate

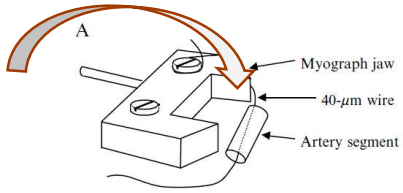
NO: nitric oxide

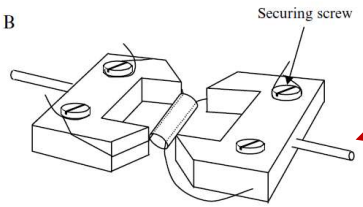
PDE: cyclic nucleotide phosphodiesterase

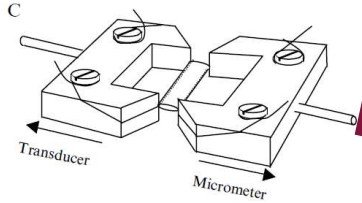
pGC: particulate guanylate cyclase (natriuretic peptide receptor)

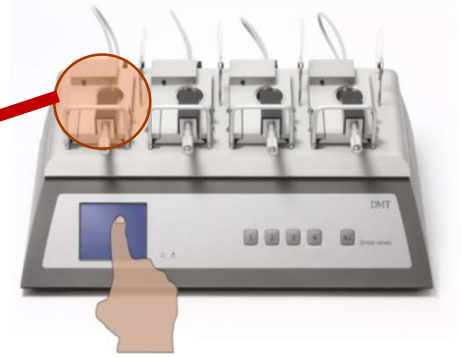
sGC: soluble guanylate cyclase

Myography: a method for studying vascular reactivity





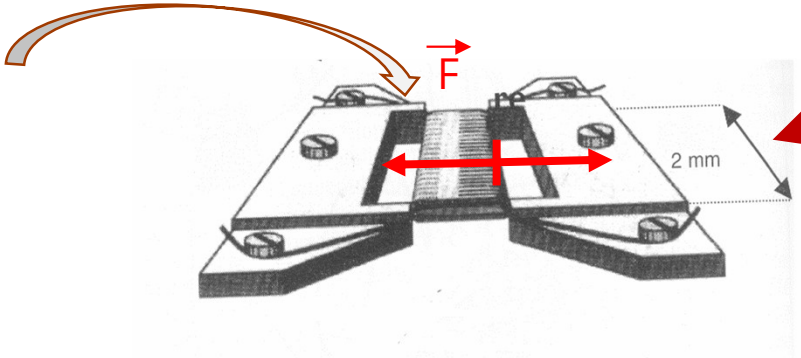


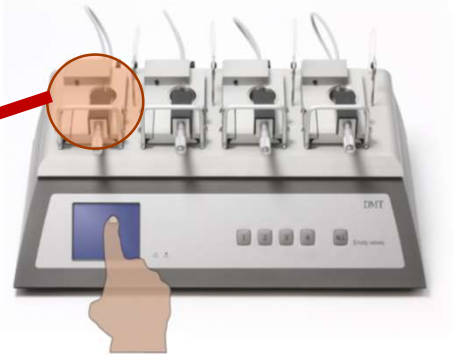


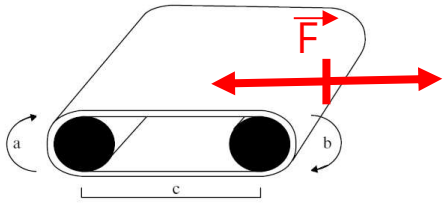
connected to a force transducer

Ward & Snetkov, 2004 Meth Enzymol ; ***Mulvany and Halpern, 1977, Circ Res***

Myography : a method for studying vascular reactivity





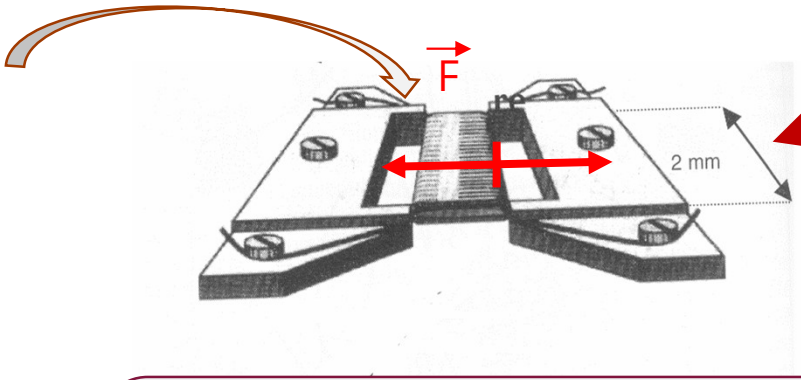


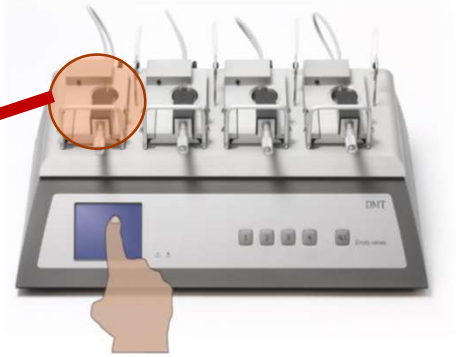
- **artery (diameter : 0,2 – 2 mm)**
- ***ex vivo* recording :** ***tissue in physiological solution, 37°C, pH=7,4, bubbled***
- **<u>isometric tension recording</u> :**
  - ***tissue is stretched under a resting tension;***
  - ***muscle exerts a force (pulling on the transducer) when contracting***

force $\vec{F}$ → force transducer (convert mechanical signal to analogic (voltage-coded) signal) → Data Acquisition device (convert into digital signal) → software

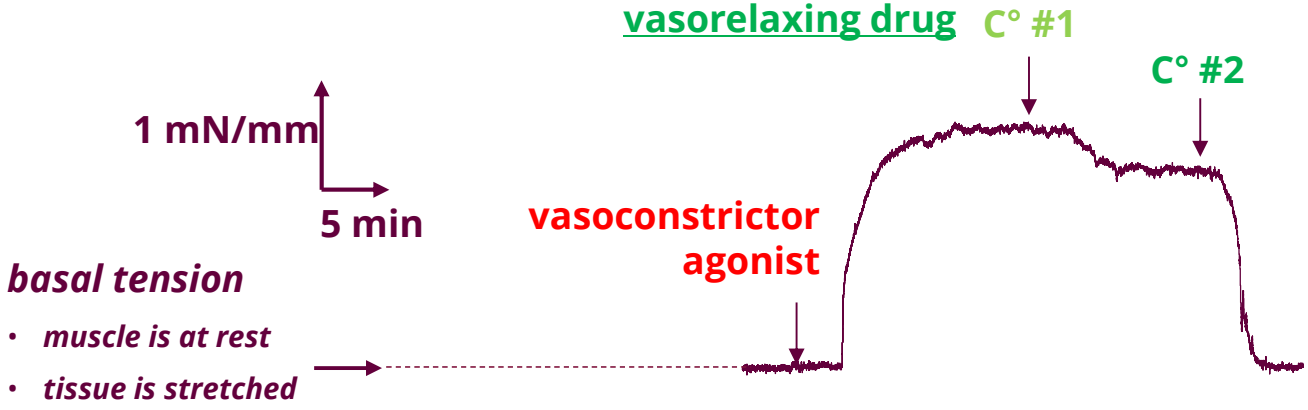
Ward & Snetkov, 2004 Meth Enzymol ; ***Mulvany and Halpern, 1977, Circ Res***

Myography : a method for studying vascular reactivity





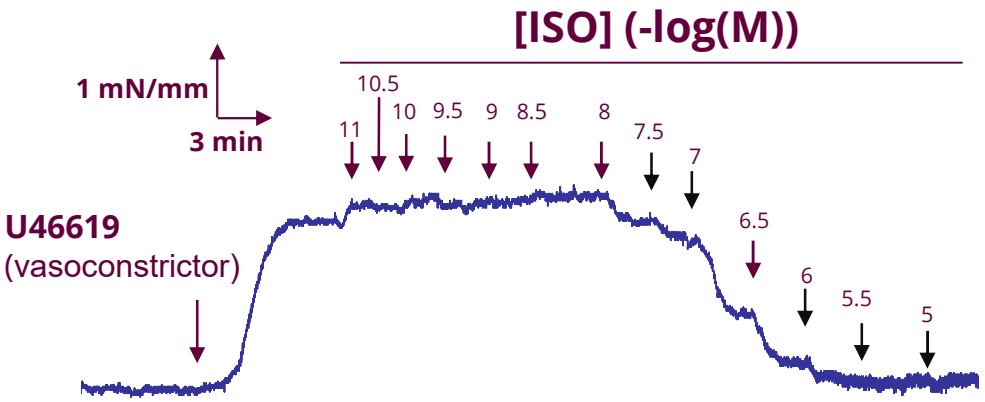
- **Addition of various compounds or solutions**
  - **vasoconstrictors: phenylephrine, thromboxane A2, PGF2α, 5-HT…**
  - **depolarising solution: high K^+ solution**
  - **vasorelaxing drugs: isoprenaline, acetylcholine, NO donor…**

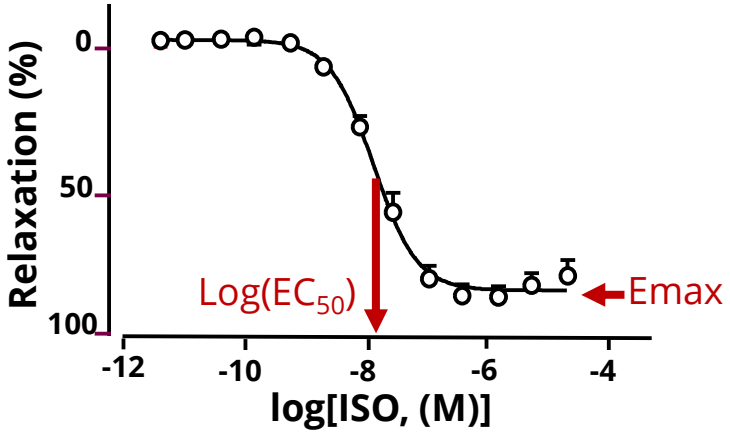


Ward & Snetkov, 2004 Meth Enzymol ; ***Mulvany and Halpern, 1977, Circ Res***

Example: β-adrenergic receptor (β-AR) stimulation

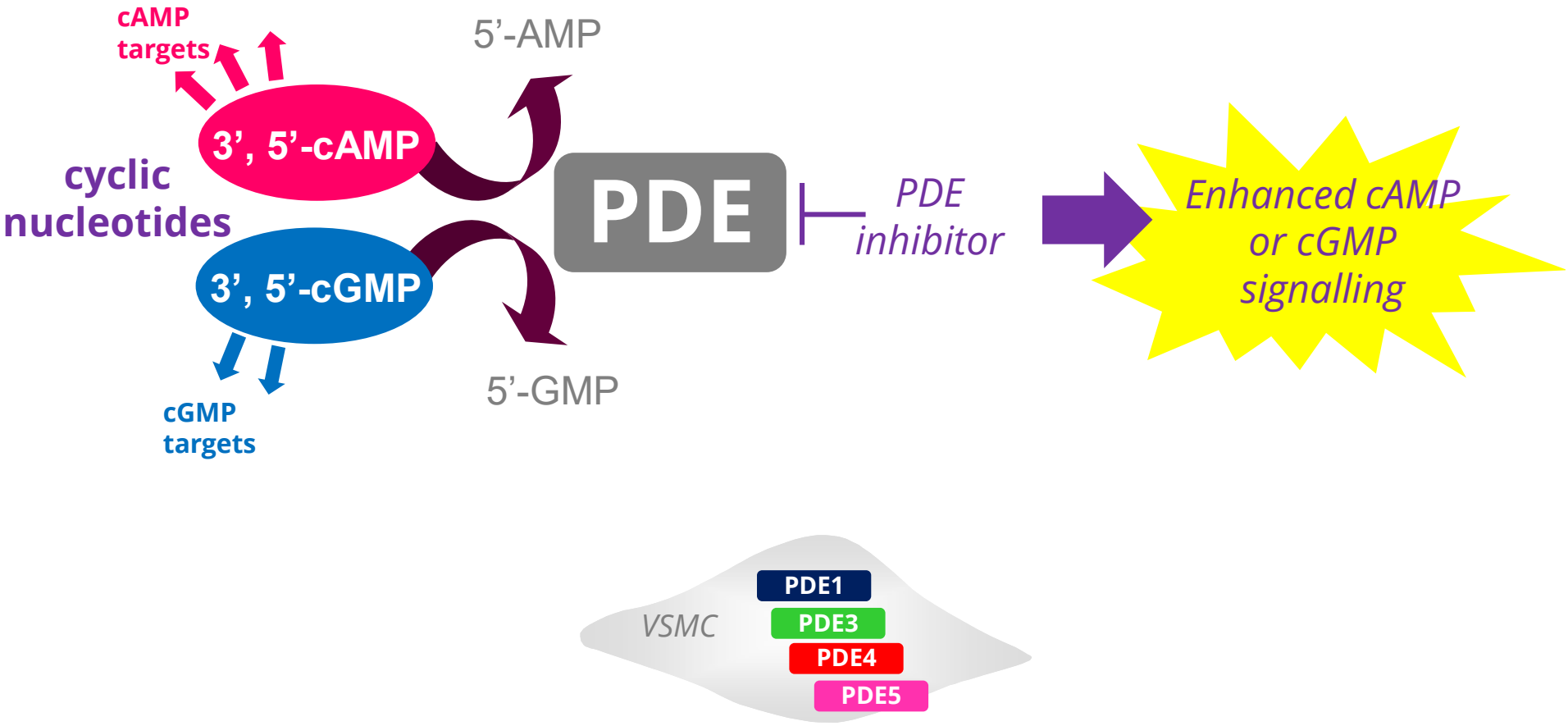
- Rat coronary artery (diameter : 0,3 - 0,5 mm)
- Pre-contraction with a vasoconstrictor (U46619)
- Cumulative addition of β-AR agonist : isoprenaline



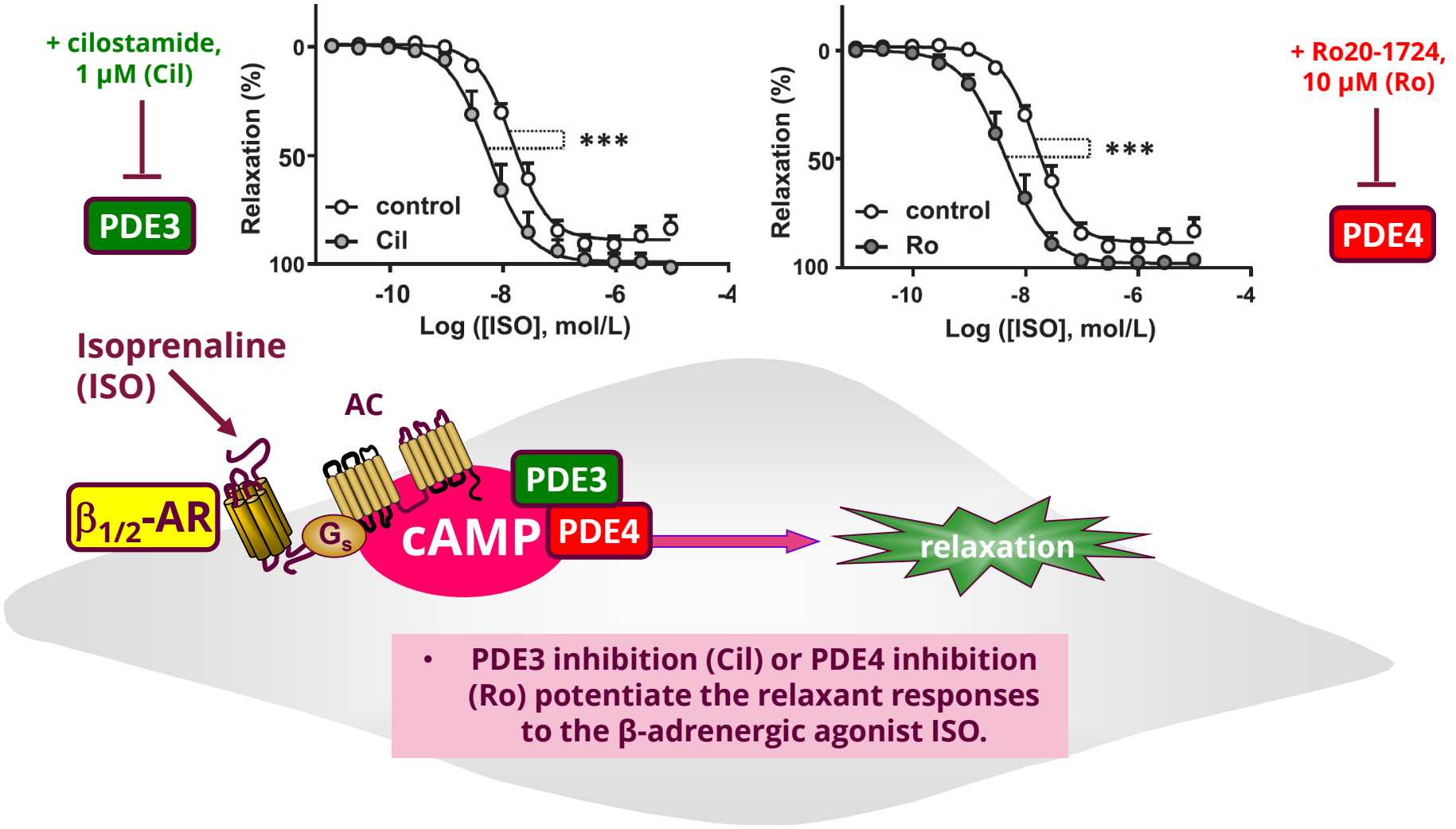


- β-AR agonist : isoprenaline produces a concentration-dependent relaxation of rat coronary artery.
- Max effect : ≈ 90 %
- $EC_{50} \approx 10^{-8}$ M

Cyclic nucleotide phosphodiesterases (PDEs)



Cyclic nucleotides in vasculature: cAMP and cGMP



- **PDE3 inhibition (Cil) or PDE4 inhibition (Ro) potentiate the relaxant responses to the β-adrenergic agonist ISO.**

Idres et al., 2019 Cardiovasc Res

Conclusion : what do I need to know?

- Why is arterial diameter important for determining blood flow and blood pressure?
- What mechanisms make the vascular smooth muscle cell contract?
- What mechanisms make the vascular smooth muscle cell relax?
- Which method can be used to monitor arterial tone ex vivo? What is the principle?