université PARIS-SACLAY | GRADUATE SCHOOL Health and Drug Sciences

Introduction to Cardiovascular Pharmacology

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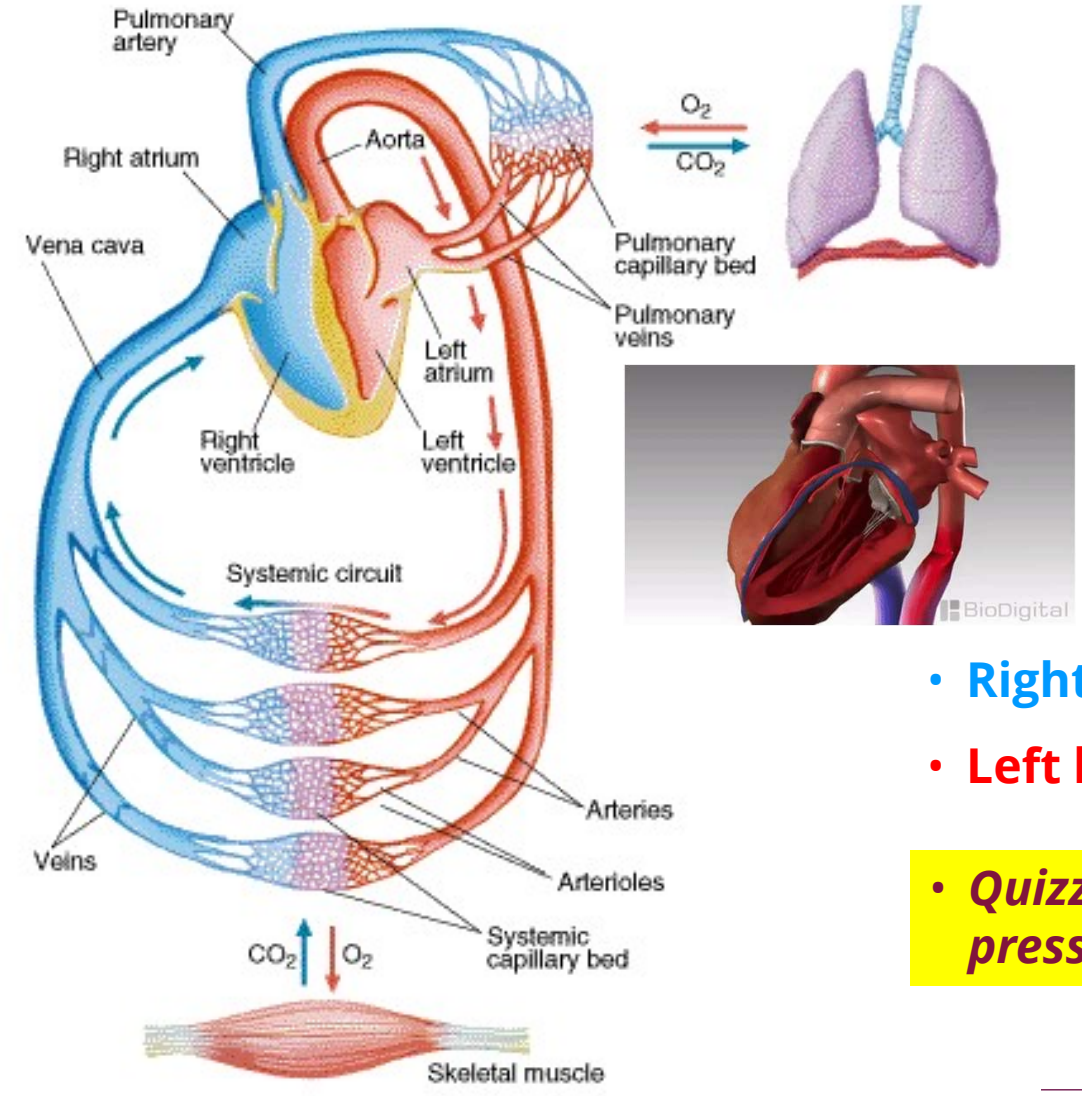
Master 1 D2HP, TU03

Acting on molecular targets to treat cardiovascular disorders

I. Reminder on the neuro-hormonal regulation of the cardiovascular system

Organ perfusion is driven by ARTERIAL BLOOD PRESSURE (ΔP_A)



$$\Delta P_A = Q_c \cdot PVR$$

$$Q_c = HR \times V_s$$

Q_c : cardiac output (L/min)

PVR : peripheral vascular resistances

HR : heart rate

V_s: systole ejection volume

- **Right heart** : low pressure system
- **Left heart :** high pressure system

- ***Quizz : how to treat high blood pressure (arterial hypertension?)***

Neurohormonal stimulation

Sympathetic nervous system

Renin – Angiotensin – aldosterone system

Autonomous nervous system

sympathetic | parasympathetic

NA

α_1 adrenergic receptor

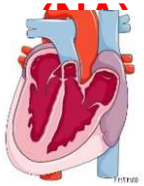
Vasonstriction

(vascular smooth muscle contraction)

↓

↗ **Peripheral Vascular Resistance**

Noradrenaline (NA)



cardiac β_1 adrenergic receptor

inotrope, chronotrope, lusitrope, dromotrope → positive

↓

↗ **Cardiac output**

↗ **Blood Pressure**

hypervolemia ←

NA

renal β_1 adrenergic receptor

↓

renin secretion

↓

Angiotensine I

↓ ***conversion enzyme***

Angiotensine II

AT_1 receptor

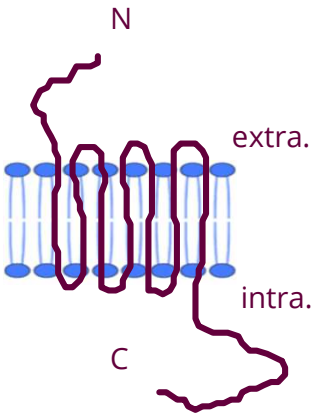
↓

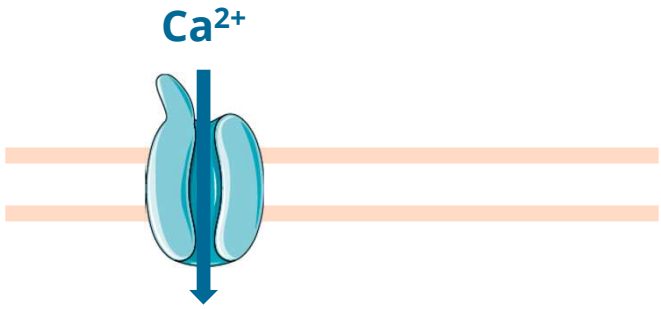
Aldostérone

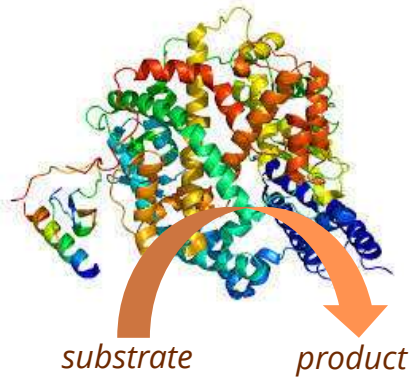
↓

↘ **Diueresis**

II. Some key pharmacological targets to treat cardiovascular diseases





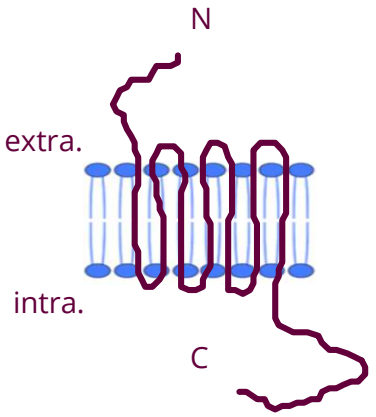


Adrenergic system

Heart failure,
Coronary artery disease
Hypertension

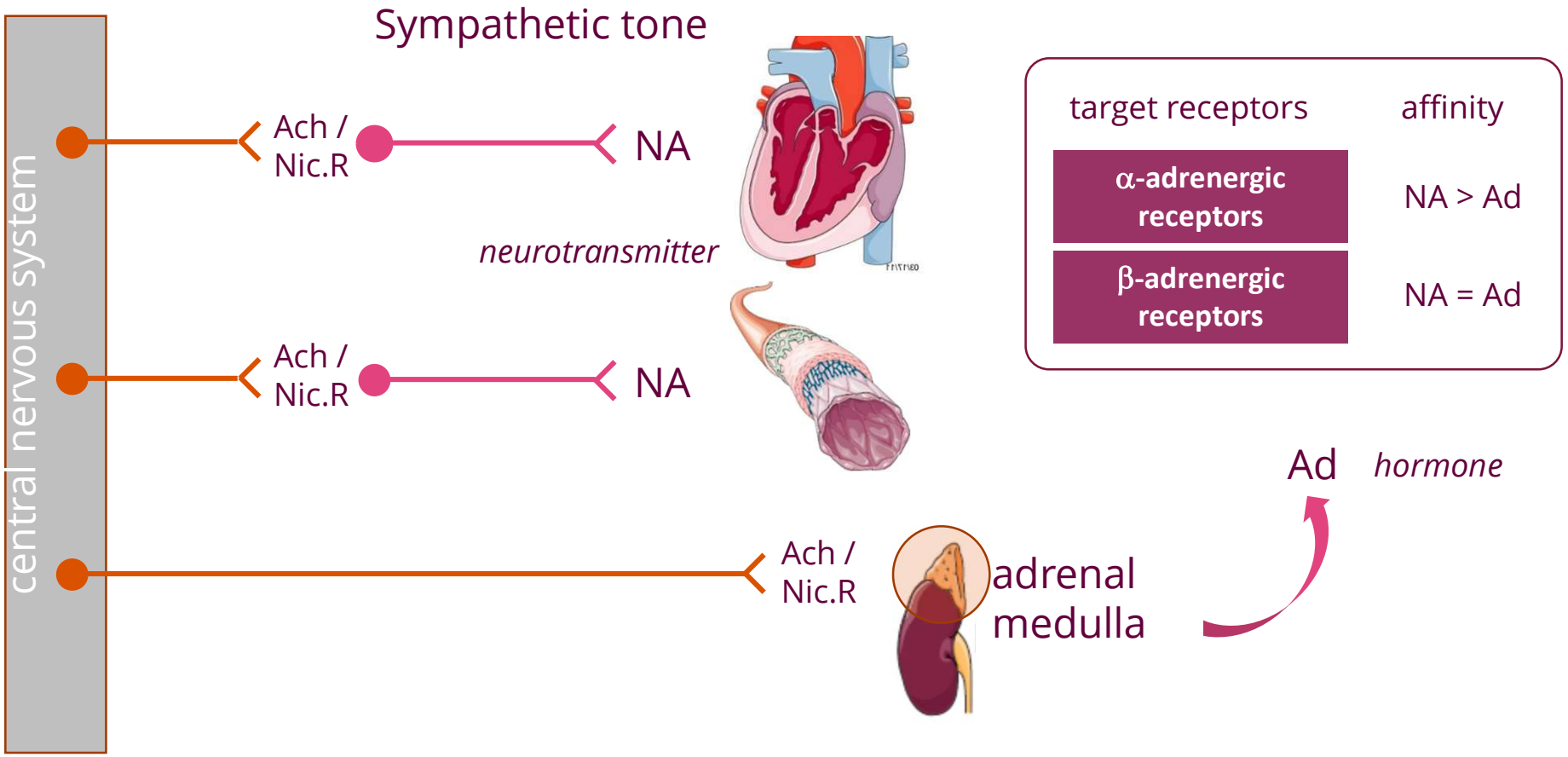
Arrhythmia

Anxiety
…



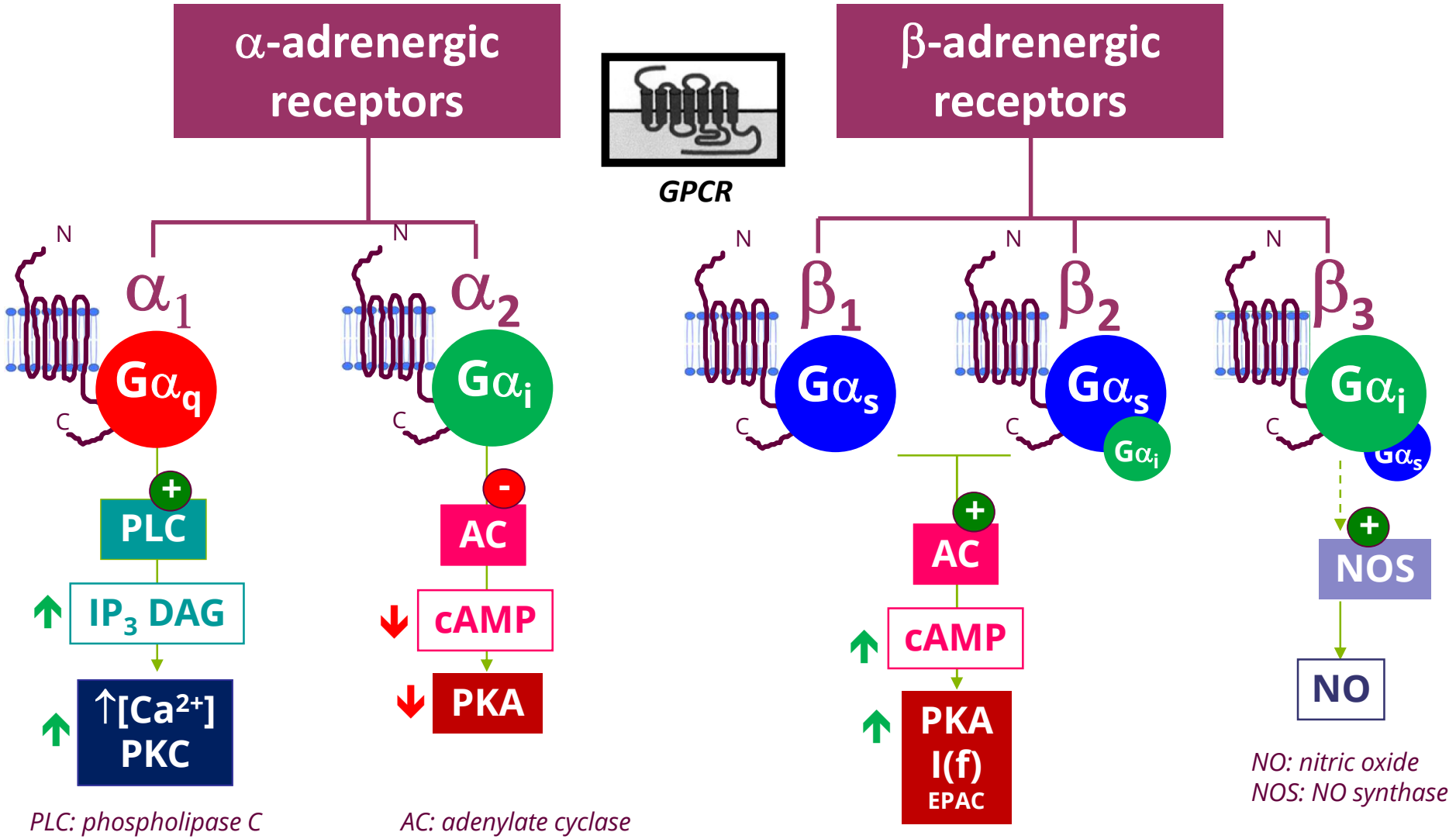
Noradrenaline (NA), adrenaline (Ad) :
mediators of the sympathetic system

Sympathetic Nervous system



target receptors	affinity
α-adrenergic receptors	NA > Ad
β-adrenergic receptors	NA = Ad

α and β adrenergic receptors: coupling

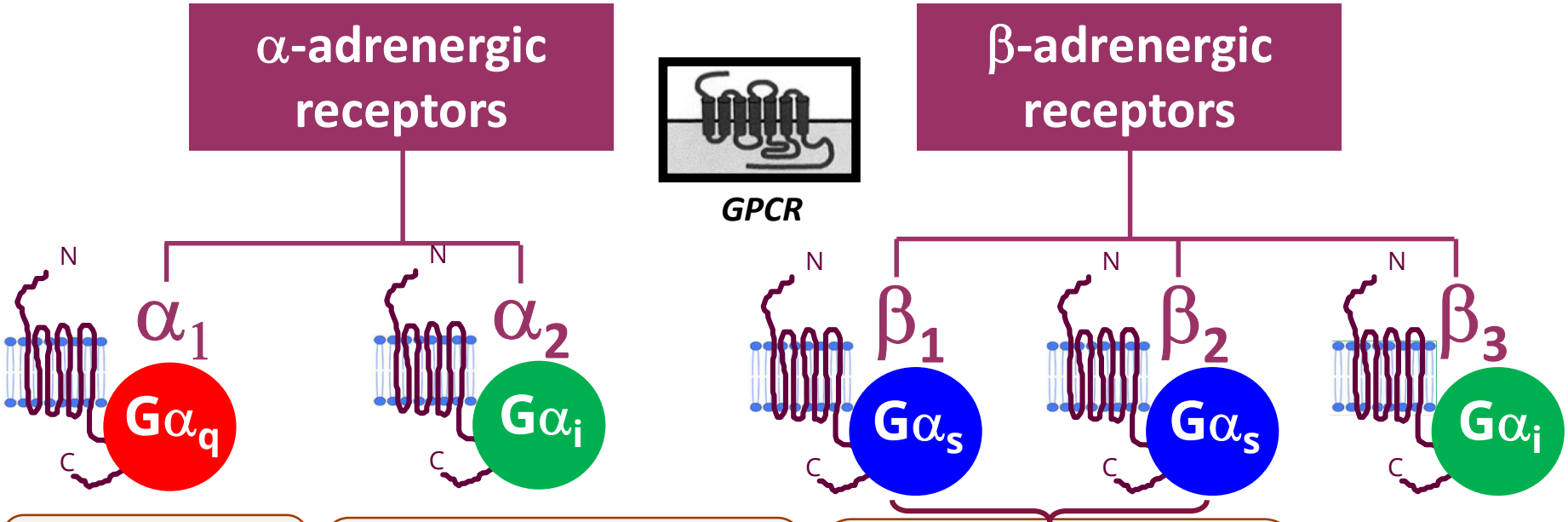


NO: nitric oxide
NOS: NO synthase

PLC: phospholipase C
IP_3: inositol 1,4,5-triphosphate
DAG: diacylglycerol
PKC: proteine kinase C

AC: adenylate cyclase
AMPc: adenosine 3',5'-monophosphate cyclique
PKA: proteine kinase A

α and β adrenergic receptors: cardiovascular effects



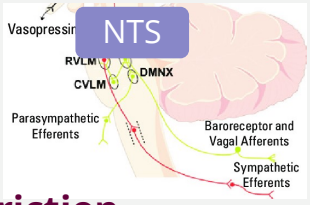
- Vascular smooth muscle cell (VSMC):

vasoconstriction

- **Central control** of BP:

↓ sympathetic

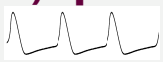
↑ parasympathetic



- VSMC:

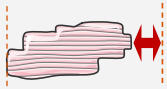
vasoconstriction

- Sinus Node (β_1 +++): **↑ HR**



- Cardiac myocyte (β_1+++):

↑ inotropism



- VSMC:

Vasodilatation

- Kidney

β_1: renin secretion

- Cardiac myoc.:

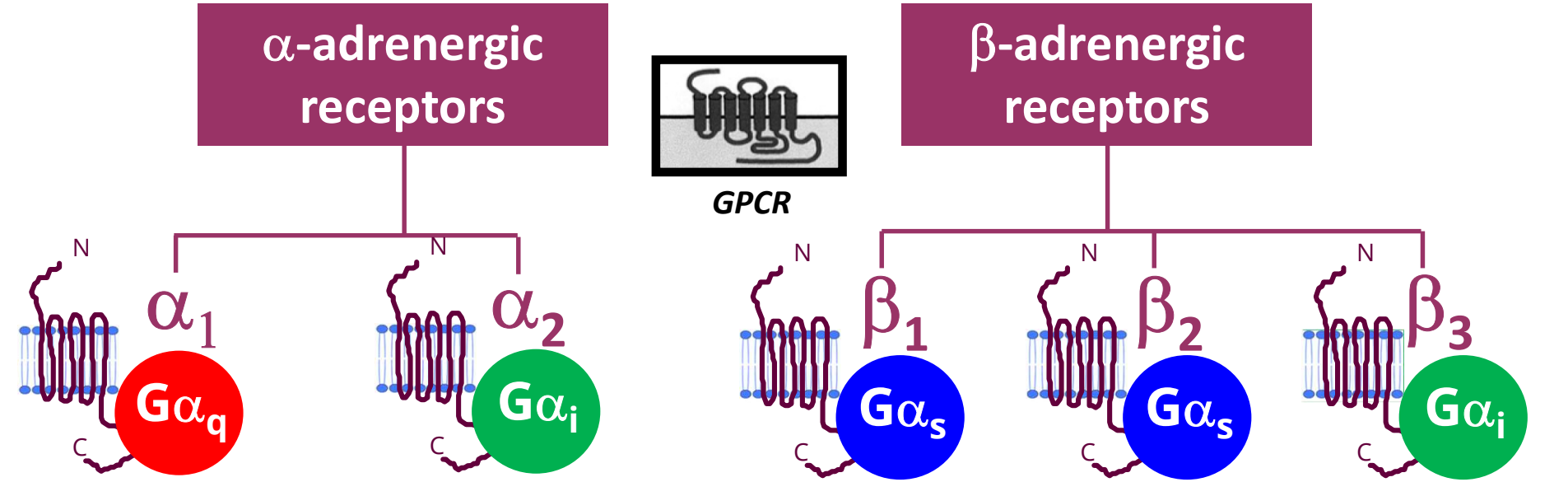
↓ inotropism

- VSMC:

vasodilatation

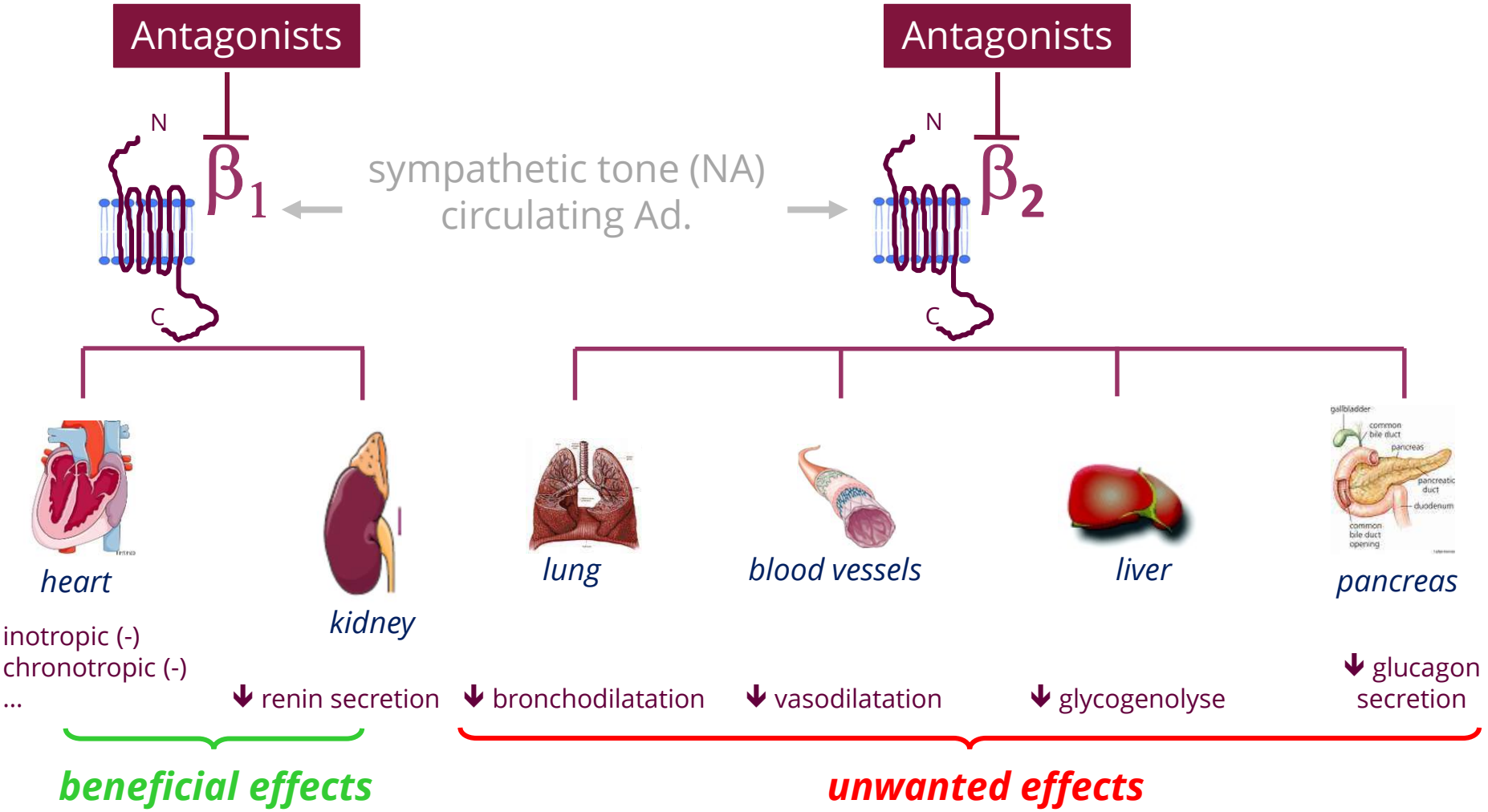
NTS: nucleus tractus solitarii (solitary nucleus) ; HR: heart rate

α and β adrenergic receptors: agonists and antagonists



Agonists			isoprenaline	
phenylephrine		clonidine	dobutamine	salbutamol	(nebivolol)
Antagonists			propranolol, carvedilol, ...	
prazosine		yohimbine	atenolol bisoprolol nebivolol ...	

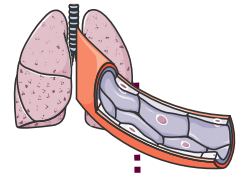
α and β adrenergic receptors: side effects of modulators



=> Relevance of β1 selective antagonists to treat CV disorders.

renin – angiotensin – aldosterone system (RAAS)

Hypertension,
Heart failure,
Acute coronary syndrome,
Cardiovascular prevention…



(pulmonary…) endothelium

angiotensinogen

renin

angiotensin I

Conversion enzyme ACE1

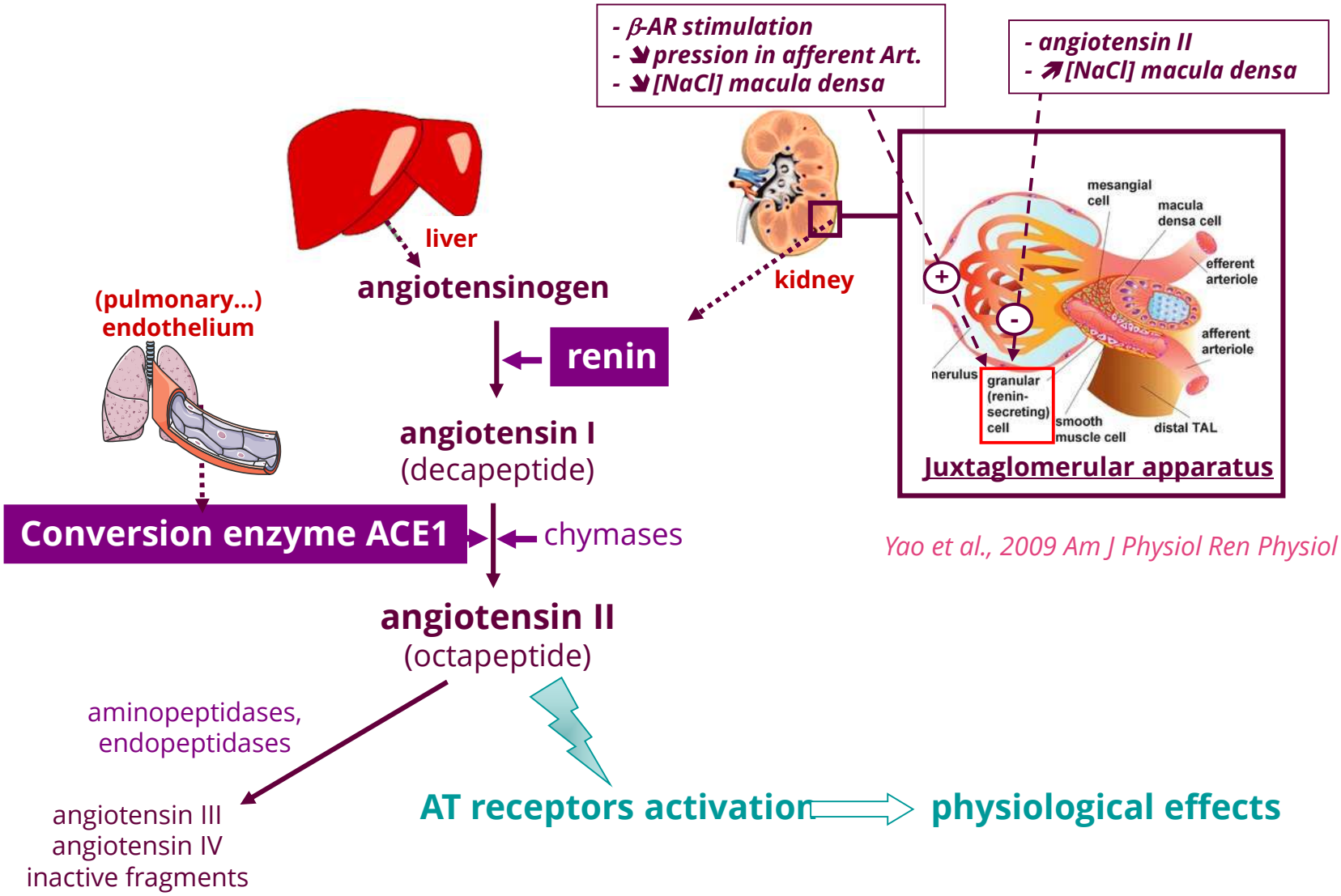
angiotensin II

kidney

adrenal gland
zona glomerulosa, adrenal cortex

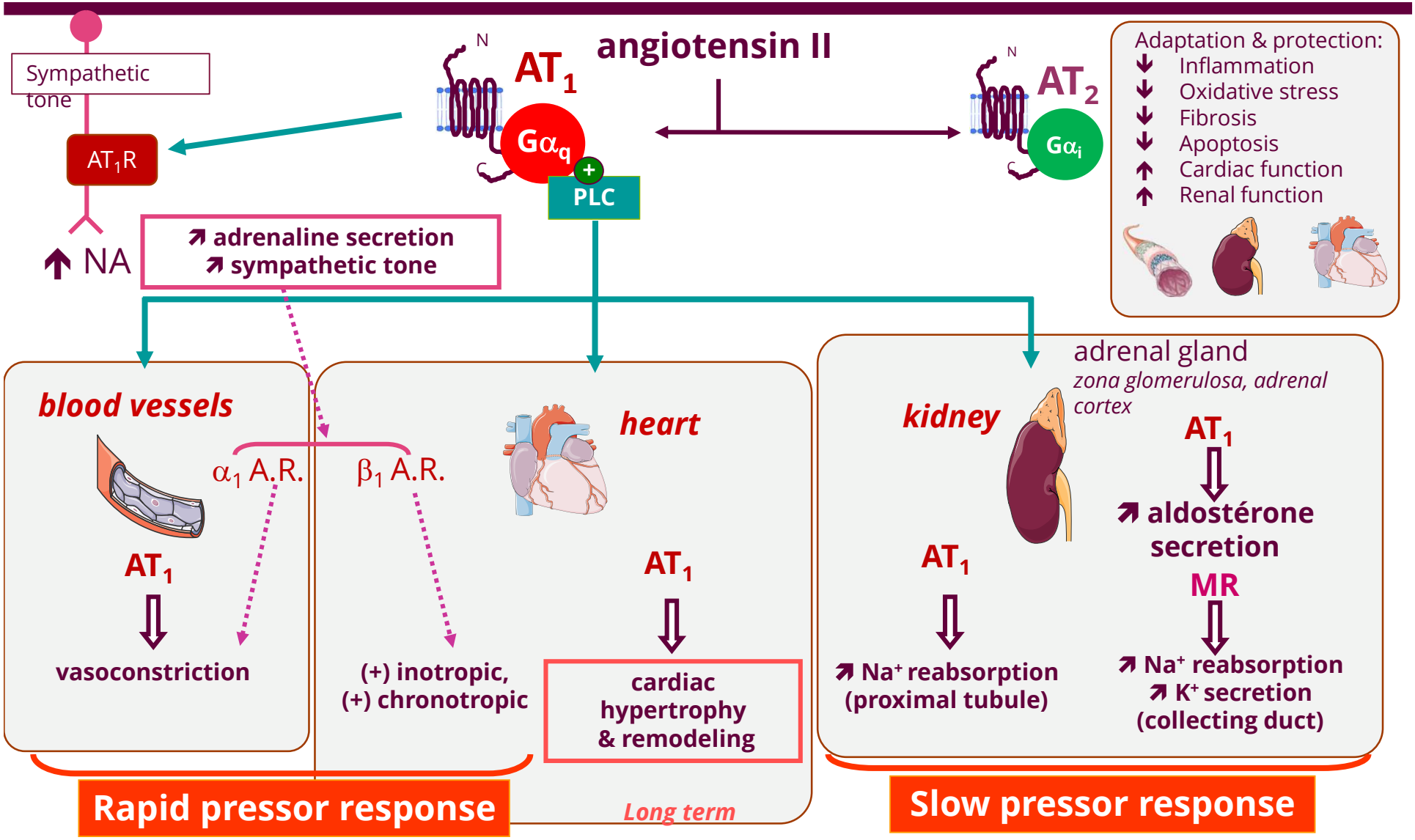
aldosterone

renin – angiotensin – aldosterone system (RAAS)



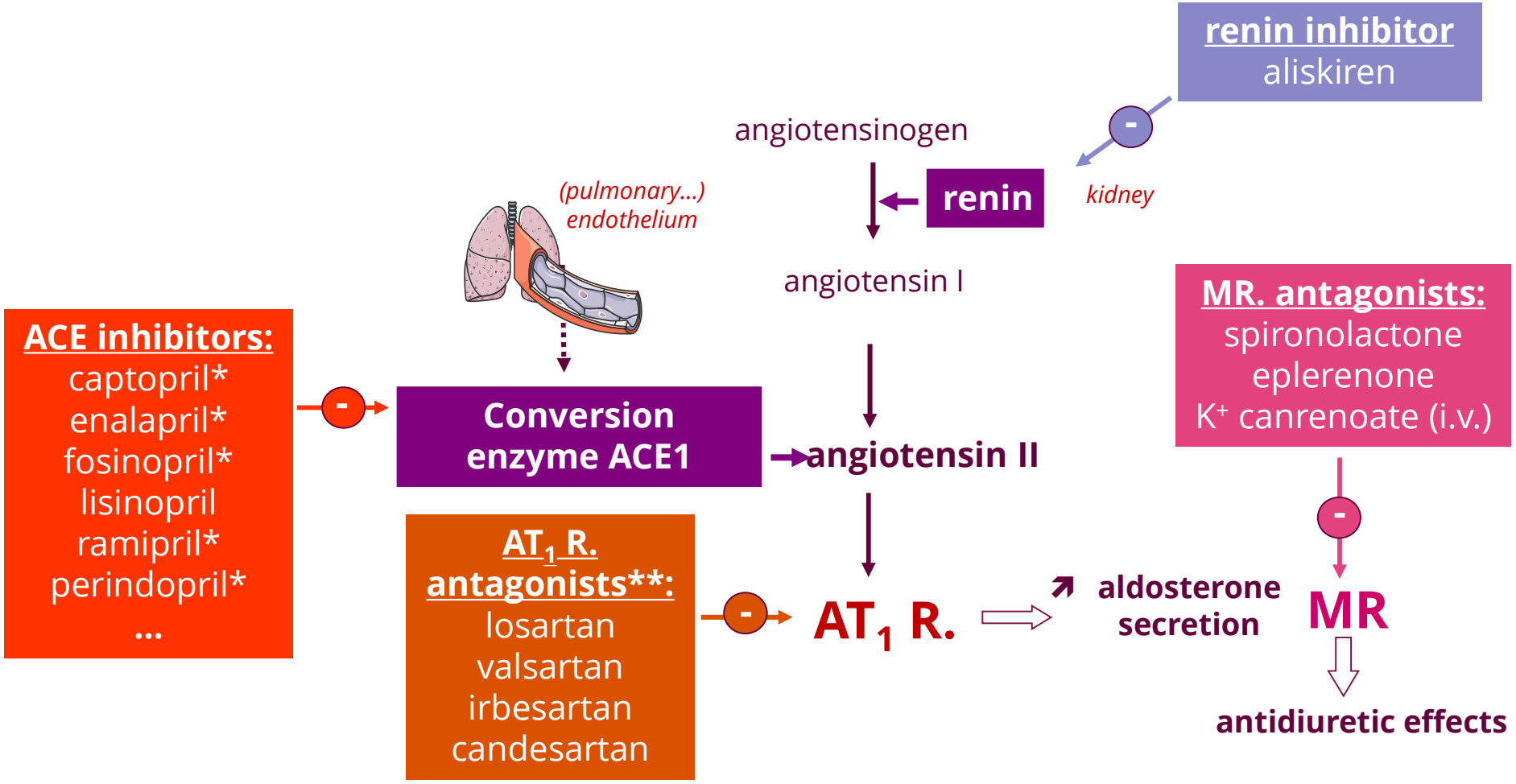
Yao et al., 2009 Am J Physiol Ren Physiol

renin – angiotensin – aldosterone system



MR : mineralocorticoïd receptor

RAAS: pharmacological modulators



*: prodrugs : inactive ester forms => de-esterification => release of active form.
**: competitive reversible antagoniste, selective for AT_1 .R

RAAS : secondary pharmacodynamics of modulators

liver

angiotensinogen

renin inhibitor

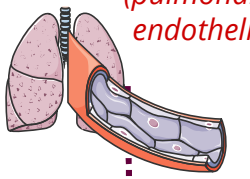
kidney

renin

kininogen

kallicreins

(pulmonary...) endothelium



angiotensin I

MR. antagonists

↗ bradykinin

B_2 R.

Conversion enzyme ACE1

angiotensin II

↗ aldostérone secretion

MR.

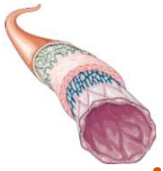
inactive peptide

ACE inhibitors

AT_1 R.

↘ K^+ secretion

hyperkaliemia



↗ *vasodilatation* ☺

↗ *cough* ☹

↗ *Angioneurotic edema (rare)*

AT_1 R. antagonists**:

hypotension ☹

↘ glomerular filtr.

*Acute kidney failure** ☹

*: angiotensin constrict renal efferent arteriole => stabilizes glomerular filtration rate (GFR): decrease AT1 R. activity leads to ↘ decrease GFR. If stenosis of renal arteries => kidney failure,

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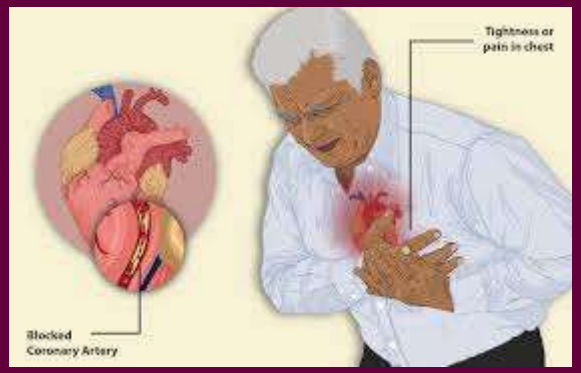
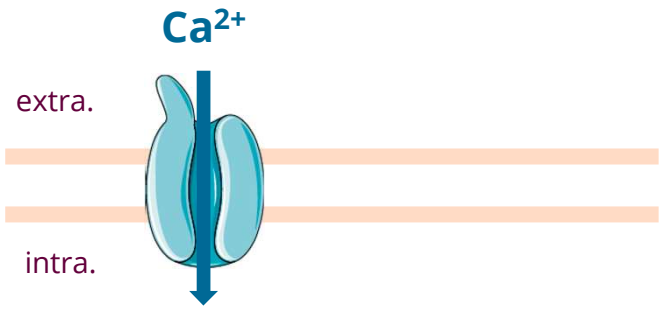
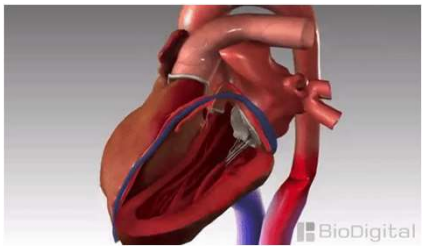
L-type calcium channel



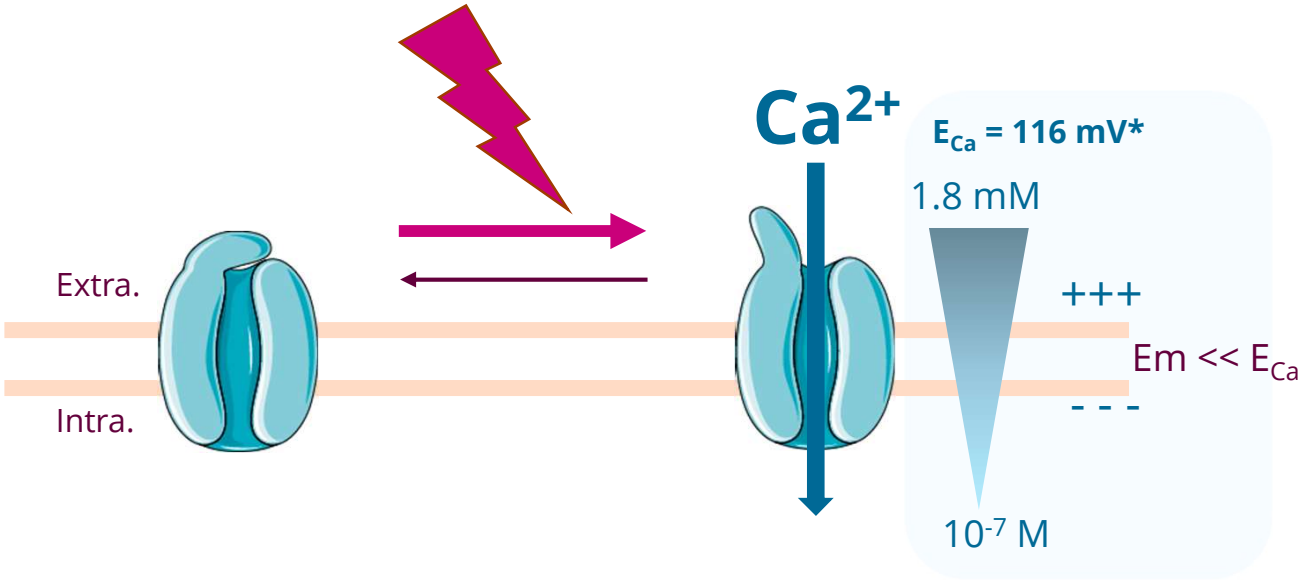
Stable angina,
Hypertension,
…

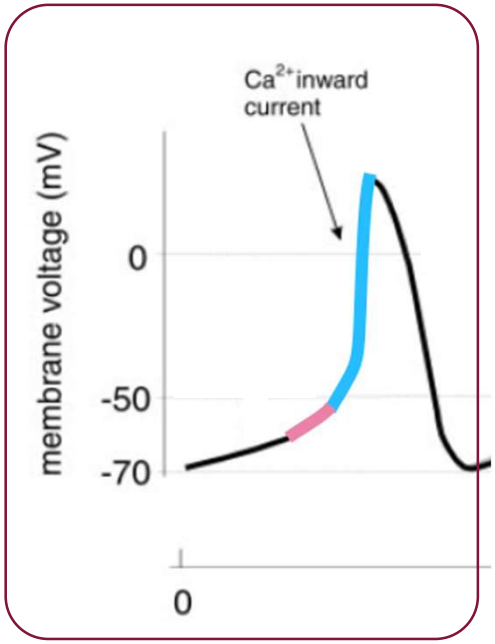


The L-type Calcium channel in the cardiovascular system



Depolarisation
(Em > -40mV)

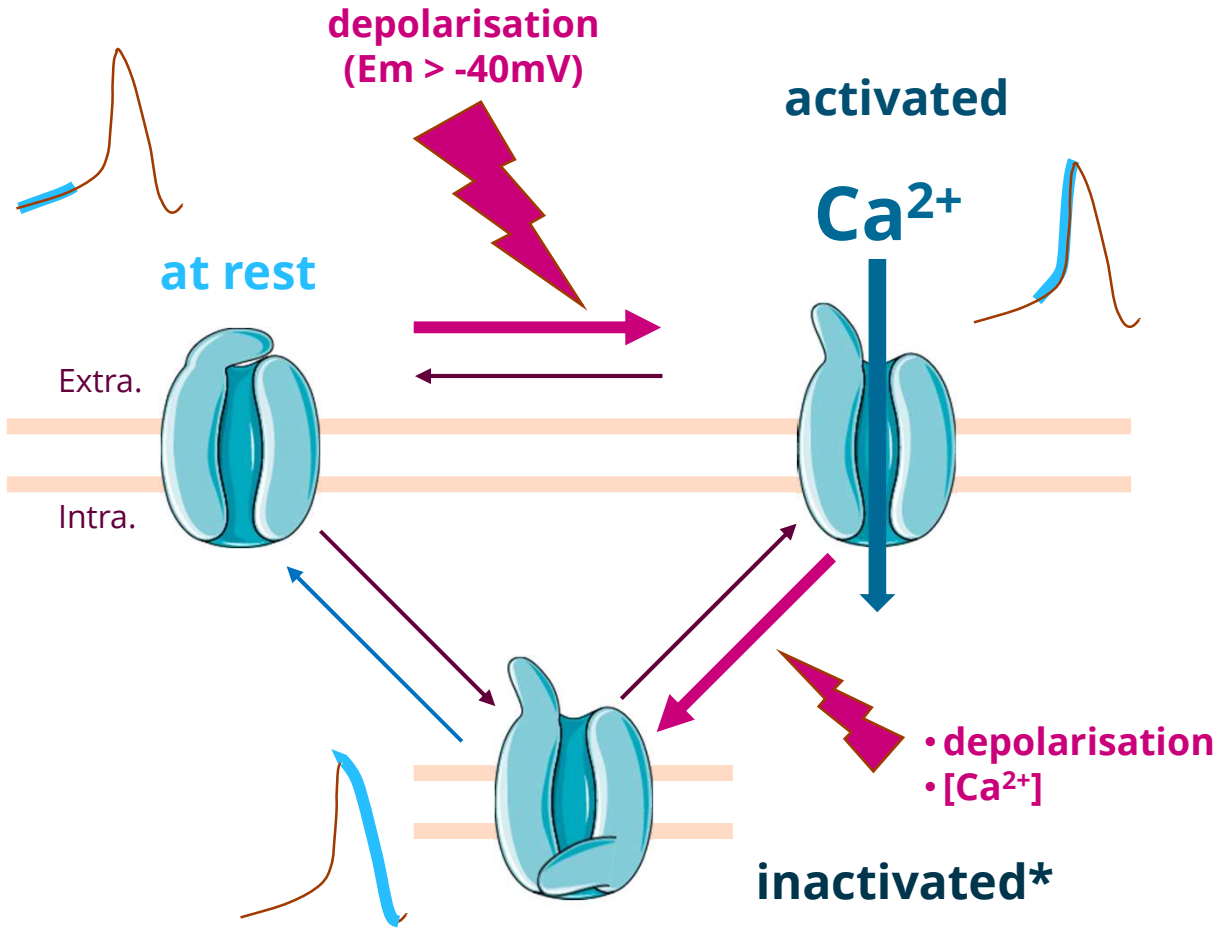




I_{Ca} ➡
- *depolarisation*
- ↑ $[Ca^{2+}]_i$

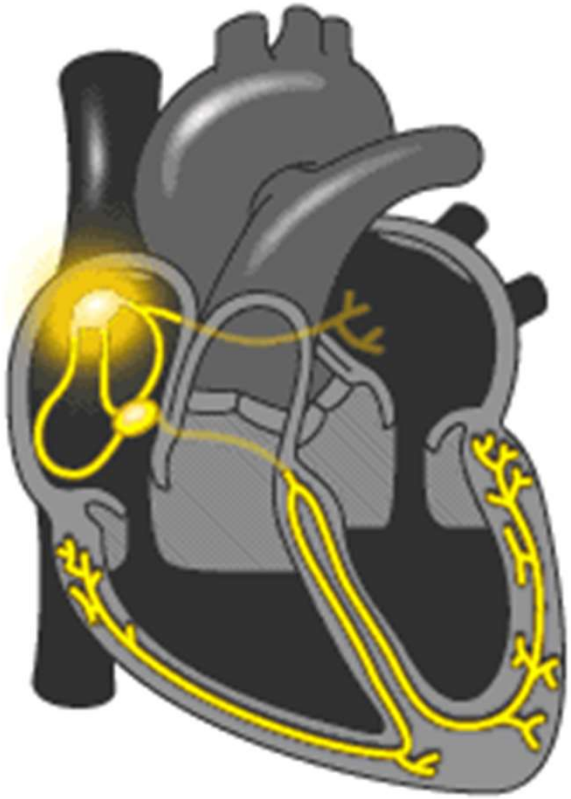
*: E_{Ca} = Ca^{2+} equilibrium potential (Nernst equation) : membrane potential that would oppose net diffusion of Ca2+ across the membrane : $E_{Ca} = RT/ZF \cdot \ln([Ca^{2+}]_{ext} / ([Ca^{2+}]_{int})$

The L-type Calcium channel in the cardiovascular system



*: for I(Ca, L) : L = *long lasting current* = slow inactivation

The L-type Calcium channel : role in the cardiac action potentials (1)



The L-type Calcium channel : role in the cardiac action potentials (1)

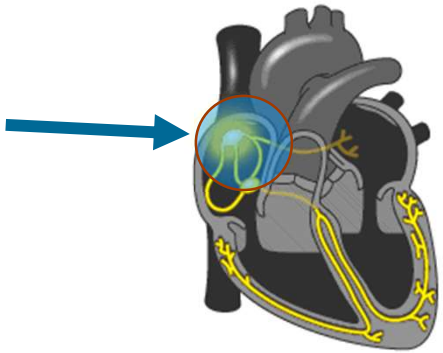
Sinoatrial node (pacemaker cells):

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

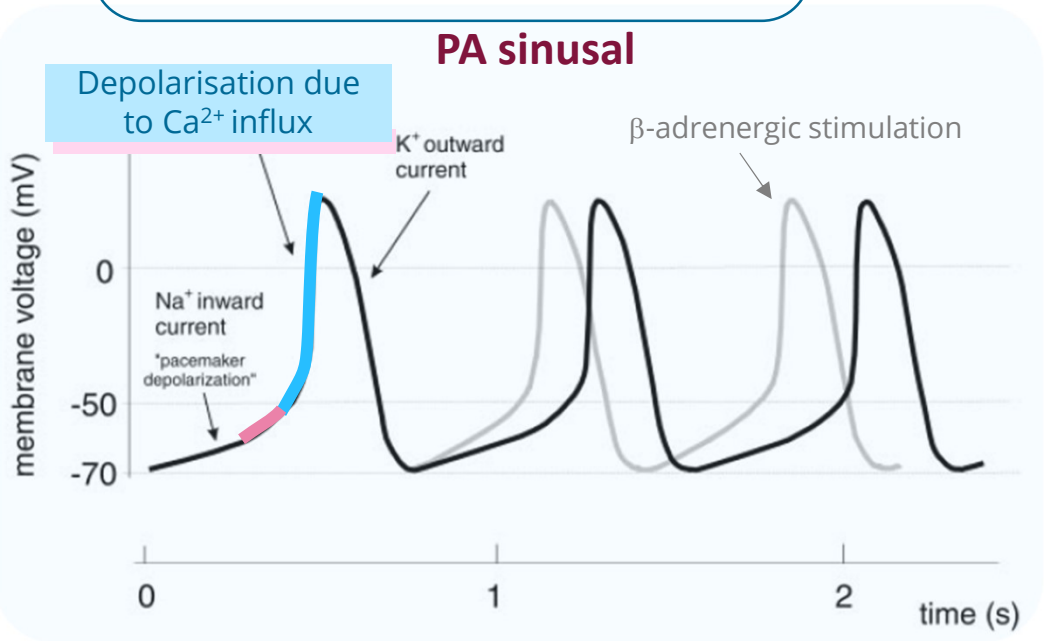
$Ca_V1.3$: pacemaker

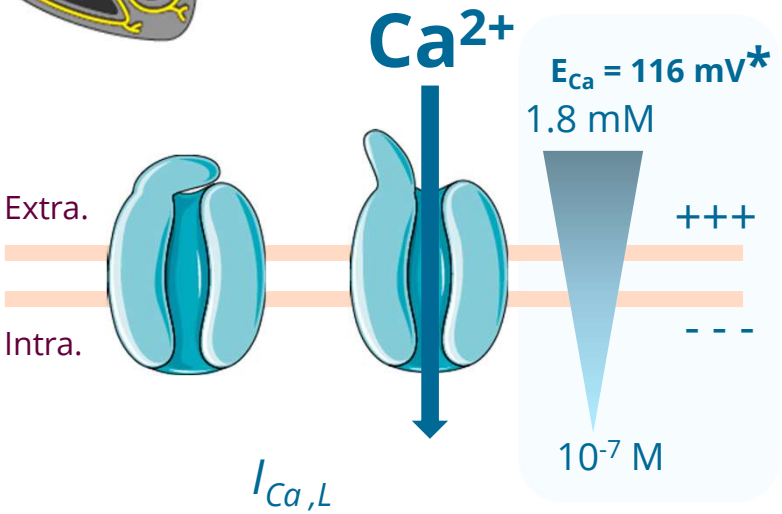
$Ca_V1.2$: ascending phase of the AP

Other depolarising currents : I(f) (Na^+/K^+)
I(Ca, T)



PA sinusal





$I_{Ca,L}$
depolarising

Kaup and Siefert 2001 Annu. Rev. Physiol. Zamponi et al., 2015 Pharmacol Rev

The L-type Calcium channel : role in the cardiac action potentials (2)

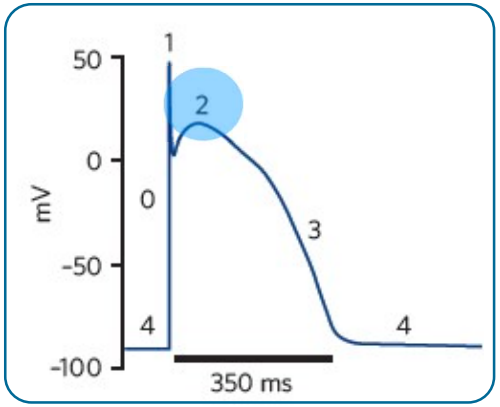
PA in nodes :

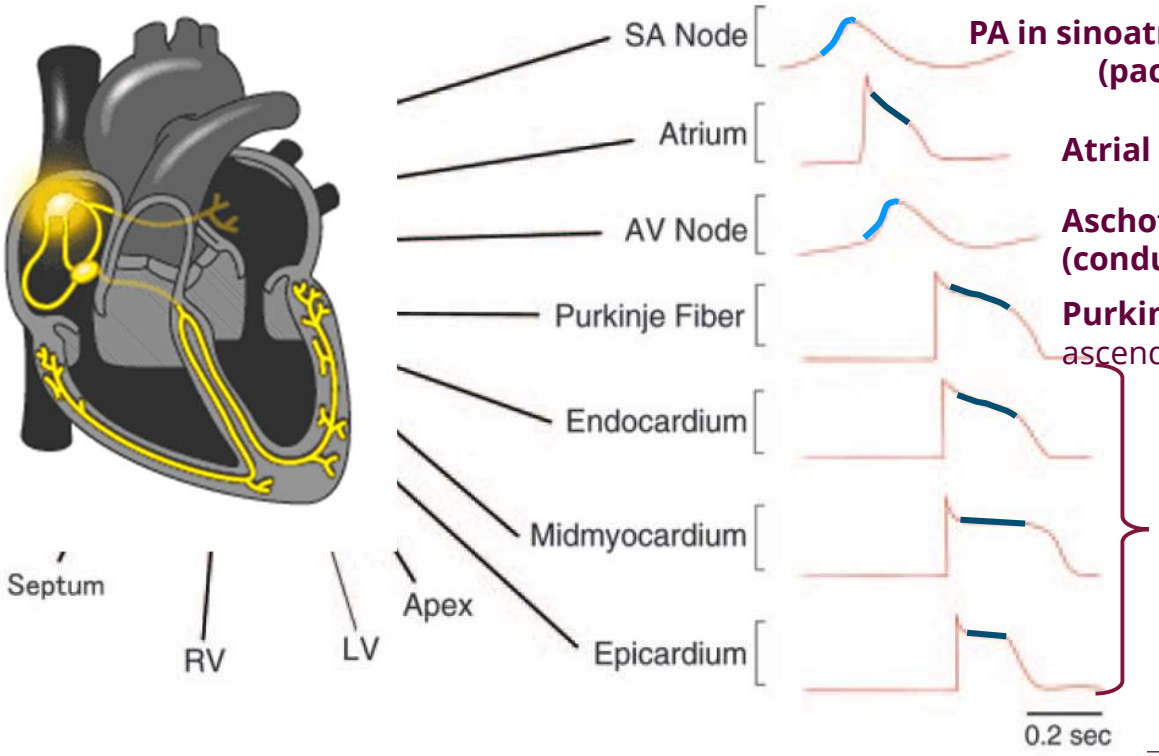
I(Ca, L), ascending phase of AP

PA in atria; conduction system, ventricle:

I(Ca, L) : « plateau » (phase 2)

Balance between calcium influx (depolarising) and K^+ efflux (repolarising)





PA in sinoatrial node (pacemaker)

Atrial myocyte

Aschoff-Tawara (AV) node (conduction)

Purkinje fiber: phase ascendante

ventricular myocyte (contraction)

= action potential (AP) phases when LTCC activity is important

Nerbonne et Kass 2005 Physiol Rev

The L-type Calcium channel : role in the cardiac action potentials (2)

PA in nodes :

I(Ca, L), ascending phase of AP

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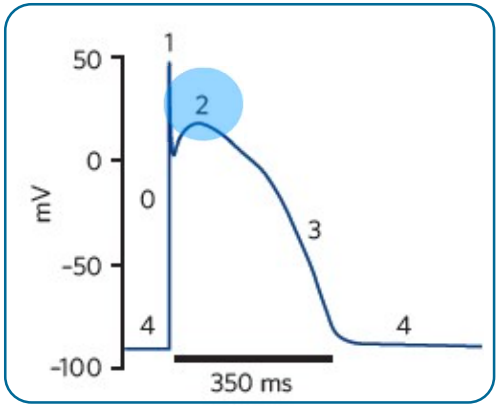
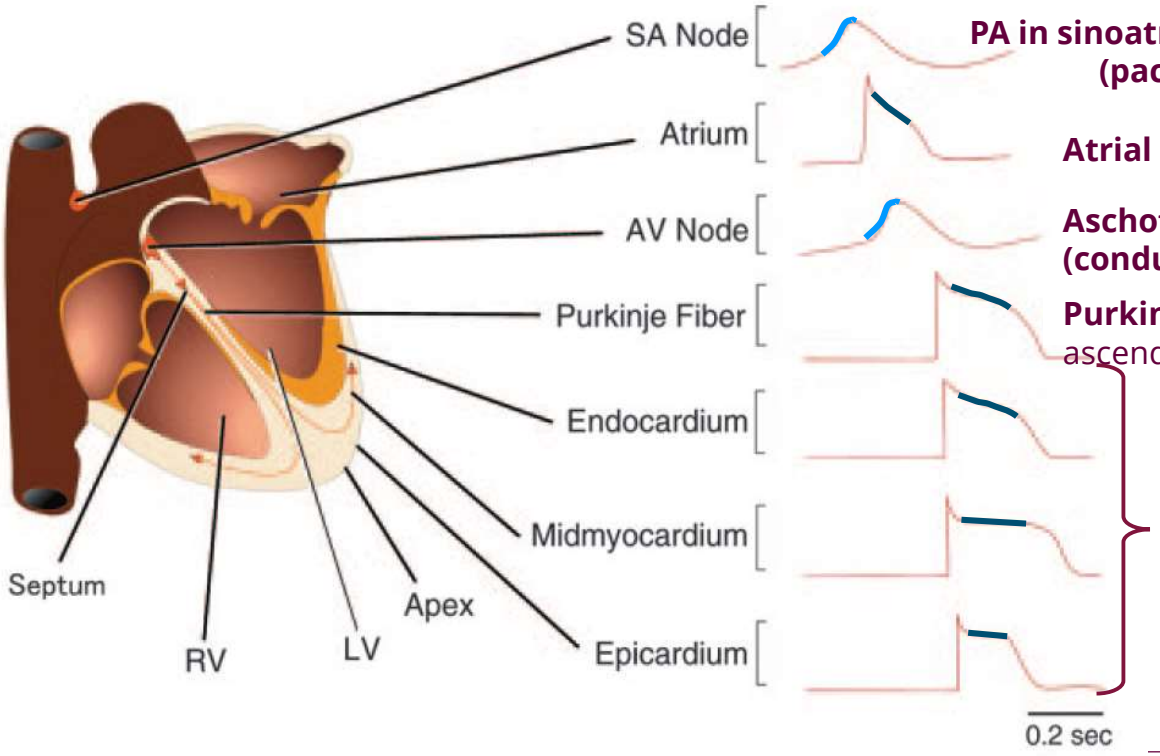




PA in sinoatrial node (pacemaker)

Atrial myocyte

Aschoff-Tawara (AV) node (conduction)

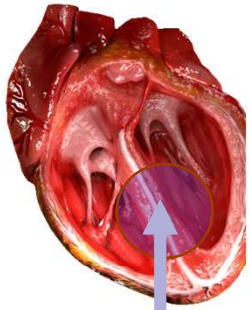
Purkinje fiber: phase ascendante

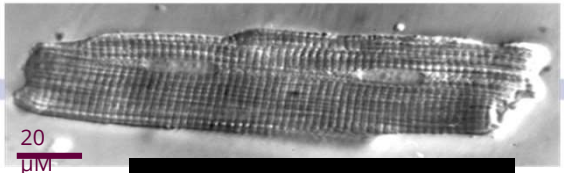
ventricular myocyte (contraction)

= action potential (AP) phases when LTCC activity is important

Nerbonne et Kass 2005 Physiol Rev

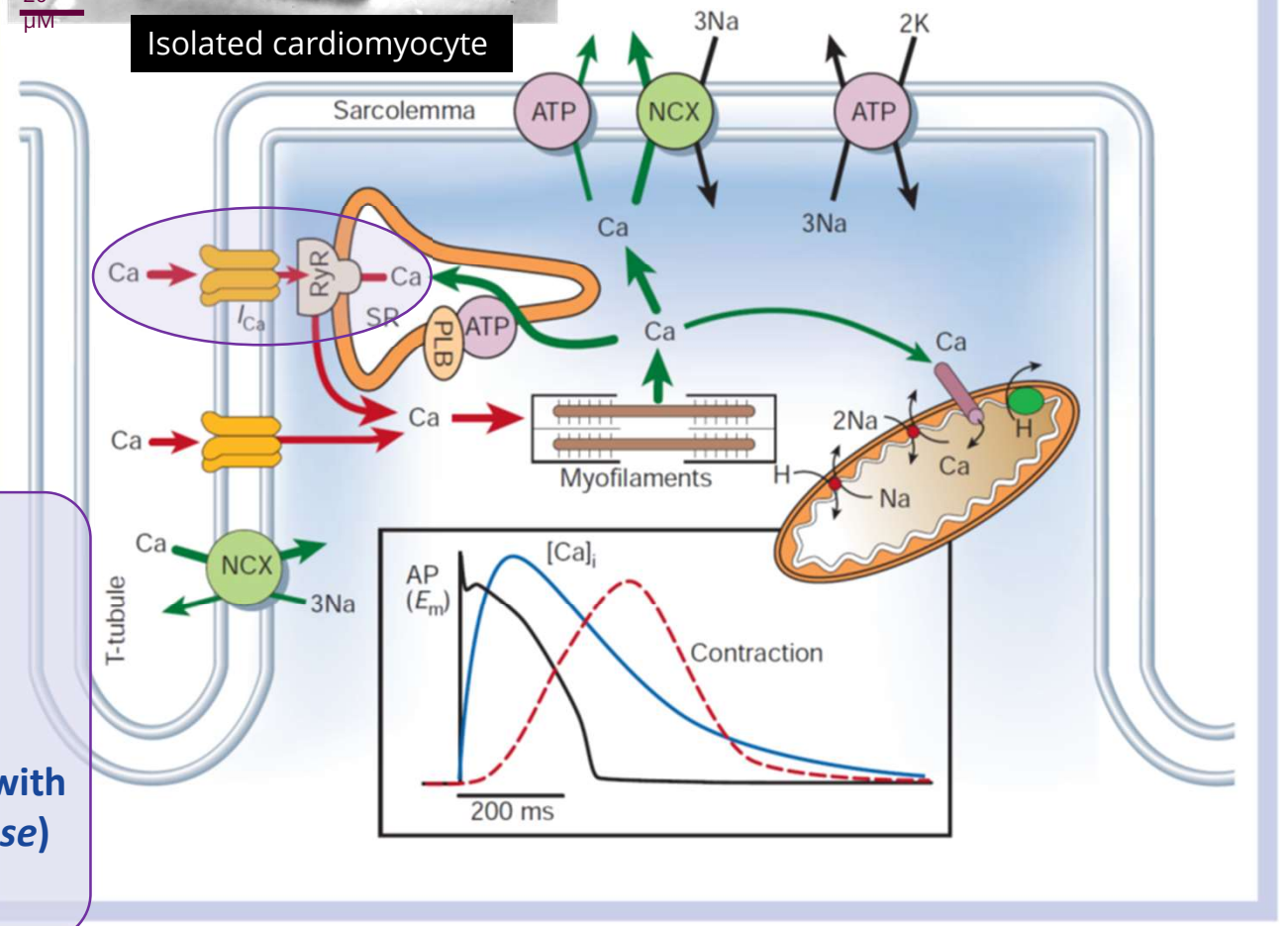
The L-type Calcium channel: role in excitation-contraction coupling





Isolated cardiomyocyte

Figure 1 Ca^{2+} transport in ventricular myocytes. Inset shows the time course of an action potential, Ca^{2+} transient and contraction measured in a rabbit ventricular myocyte at 37 °C. NCX, Na^+/Ca^{2+} exchange; ATP, ATPase; PLB, phospholamban; SR, sarcoplasmic reticulum.



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

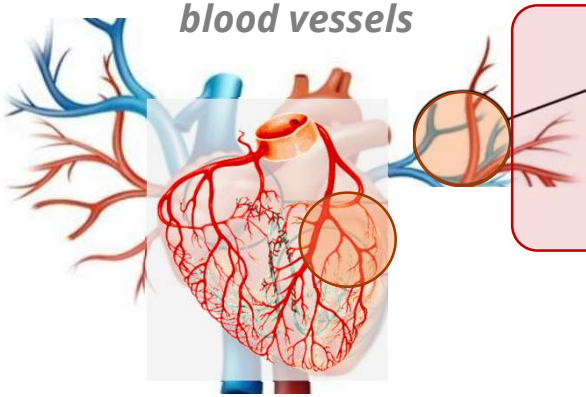
$Ca_V1.2$: - phase 2 of the AP

- ↗ [Ca^{2+}], coupling with RyR2 (*Ca^{2+}-induced Ca^{2+} release*)

Cav1.3 : atrial excitability

Bers et al., 2002 Nature ; Zamponi et al., 2015 Pharmacol Rev

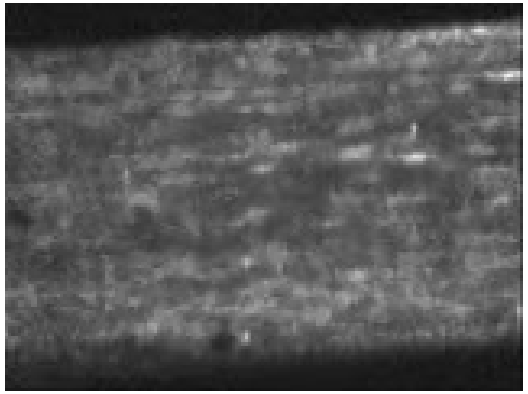
The L-type Calcium channel : role in vascular tone

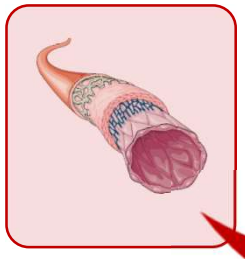


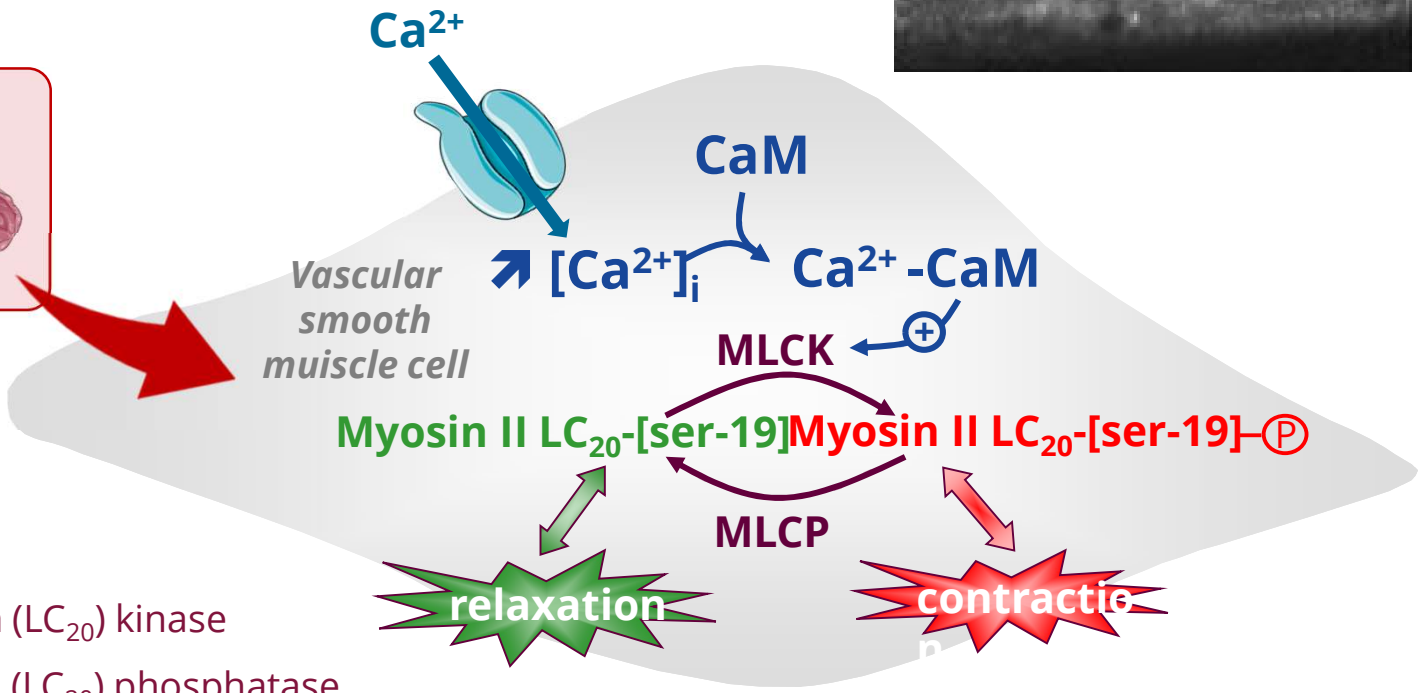
Vascular smooth muscle cell

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

$Ca_V1.2$: vasoconstriction







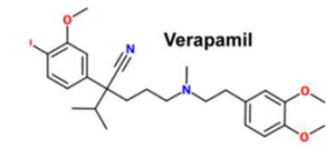
CaM : calmodulin

MLCK : myosin light chain (LC_{20}) kinase

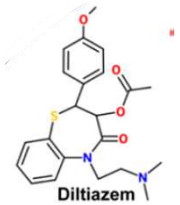
MLCP : myosin light chain (LC_{20}) phosphatase

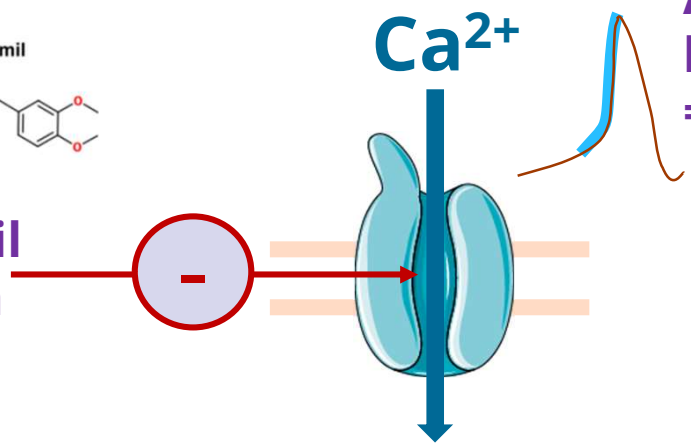
Borisova et al., 2009 Circ Res

$Ca_V1.2$ channel inhibitors /blockers

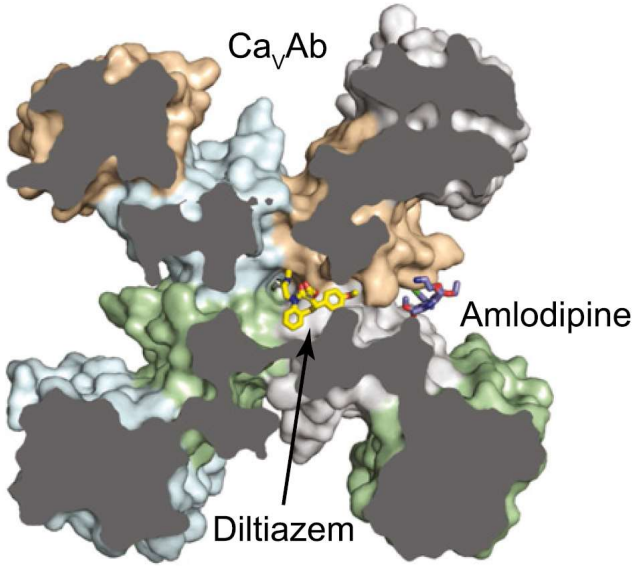


verapamil
diltiazem

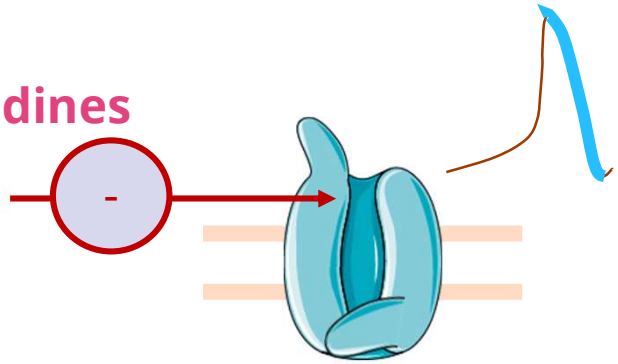




Access to the binding site is facilitated by channel at <u>open</u> state
=> « rate-dependent block »



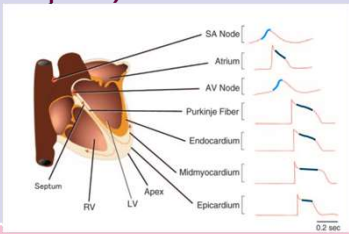
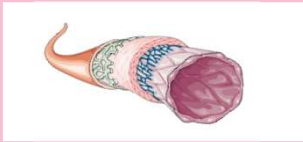
dihydropyridines



Affinity +++ for the channel in the <u>inactivated</u> state
=> « voltage-dependent block »

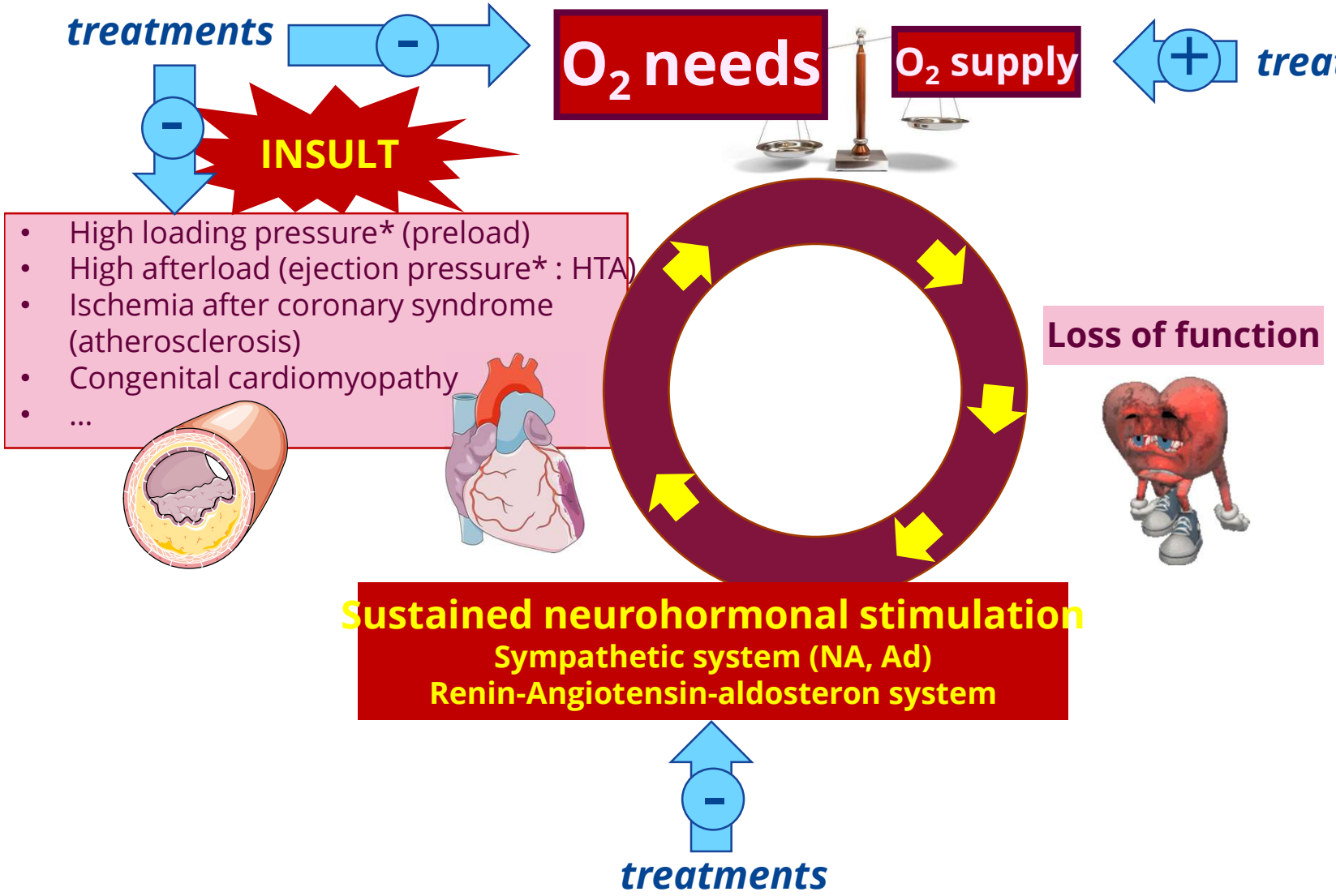
Tang et al. 2016 Nature; Tang et al., 2019 Mol Pharmacol; Zamponi et al., 2015 Pharmacol Rev

$Ca_V1.2$ channel inhibitors /blockers

Pharmacological class	Example of compounds	Binding properties	tissue selectivity of action	Pharmaco-dynamics
phenylalkylamines	**verapamil**	Access to the binding site is facilitated by channel at open state => « rate-dependent block »	**cardiac +** (Em very negative at rest, short depol.) 	**chronotropic (-)** **inotropic (-)** dromotropic (-) bathmotropic (-)
benzothiazepines	**diltiazem**			
1, 4- dihydropyridines (DHP)	**nifédipine** **felodipine** **amlodipine…**	Affinity +++ for the channel in the inactivated state => « voltage-dependent block »	**Vascular smooth muscle ++** (Em less negative at rest, long depolarisations) 	**vasodilatory** (and reflex tachycardia)

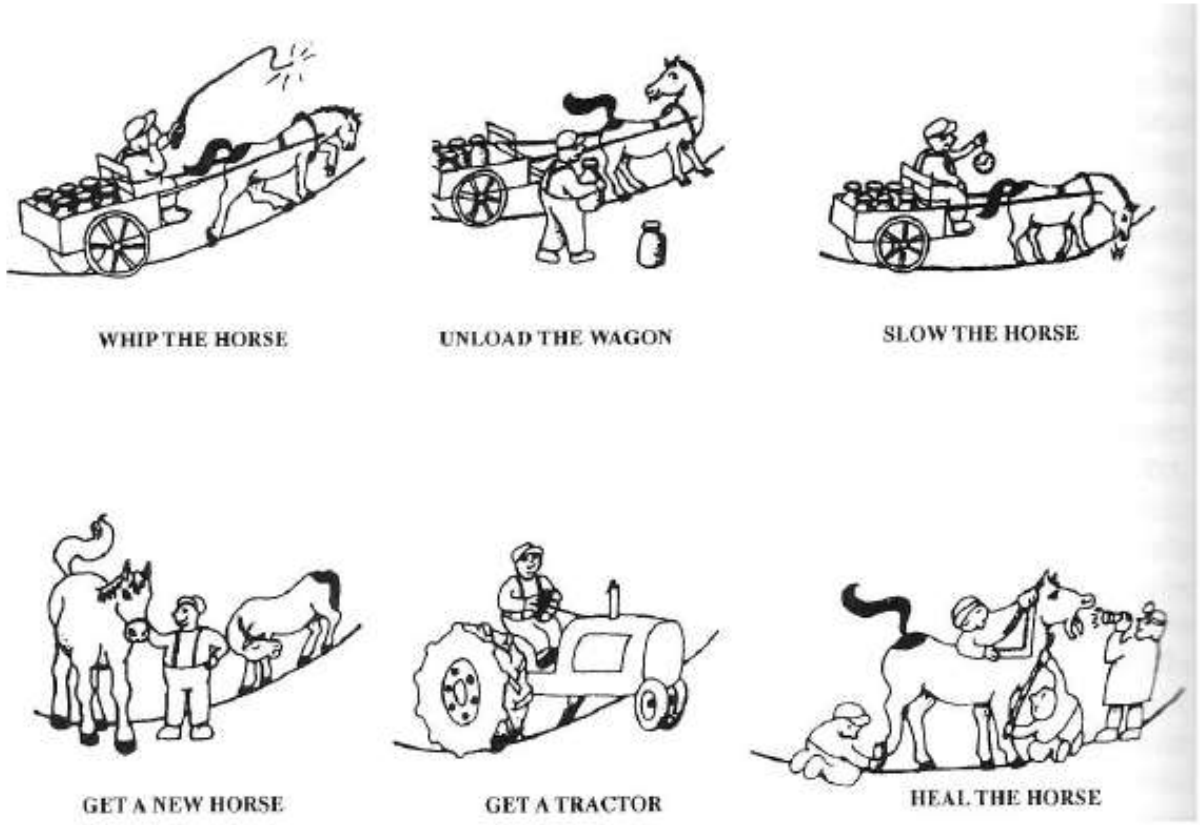
III. Beneficial effects of these medications on CV physiology

Deleterious neurohormal activation fuels maladaptive mechanisms



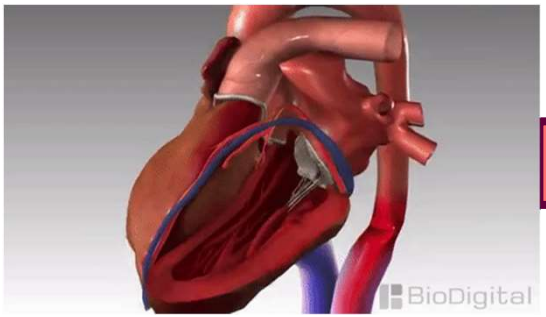
* : ↑ ventricular pressure => ↑ wall tension (Laplace's law) => ↑ O_2 demand

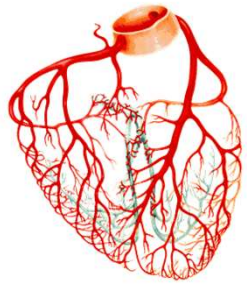
Rational for various treatment strategies



Katz, 2000 Heart Failure

Which strategy would you suggest to improve heart function?





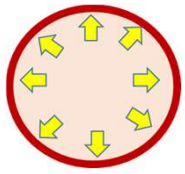
Important concepts **#1 : determinants of O_2 demand?**

↑ heart rate

↑ contractility

↑ wall tension

↑ O_2 needs



↑ diastolic pressure

ex:

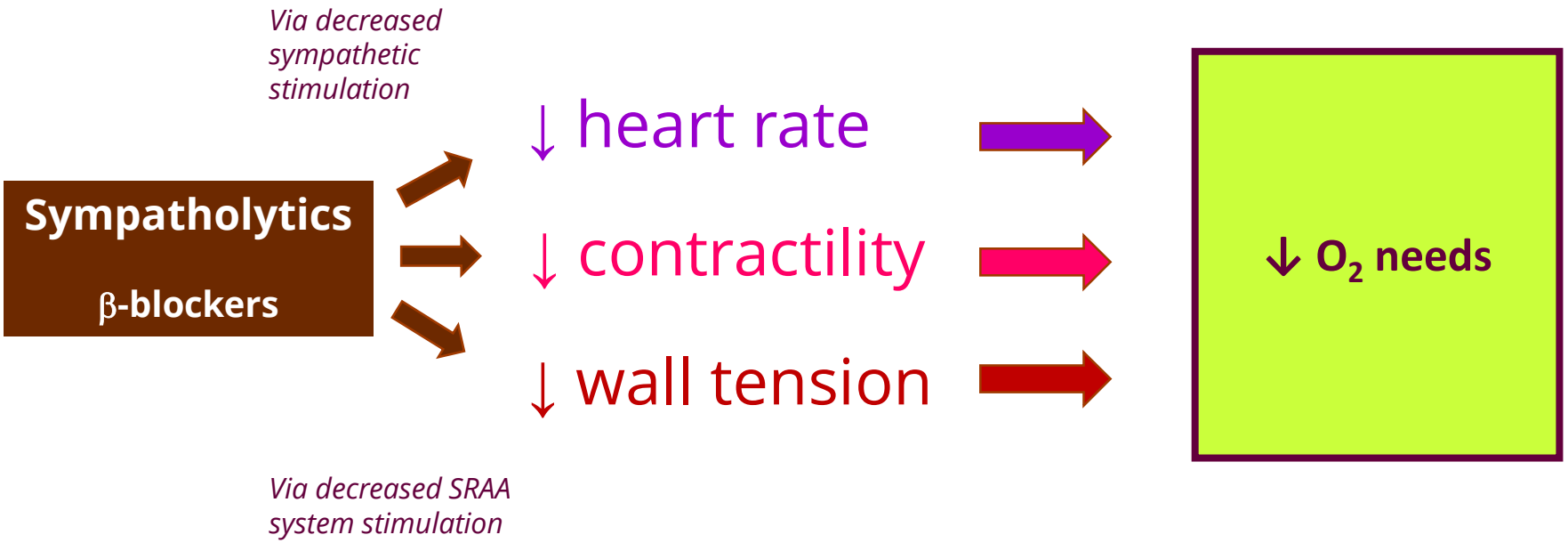
- stiffer myocardium;
- increased end-diastolic volume

↑ systolic pressure

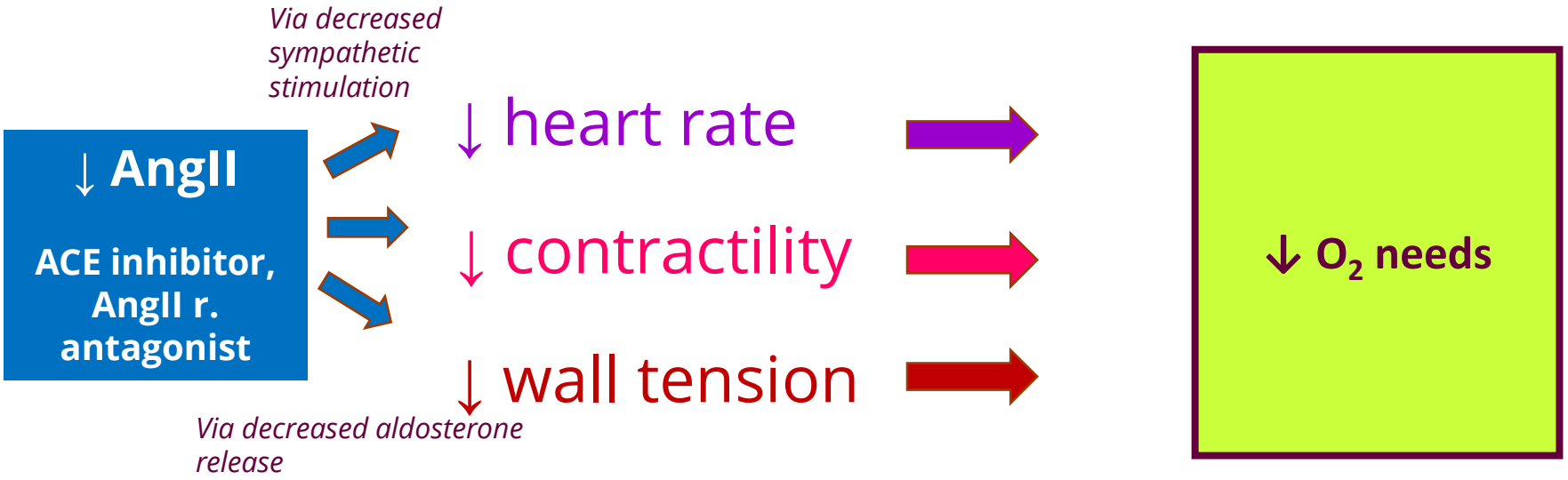
ex:

- increased afterload : peripheral vasoconstriction, arterial hypertension…

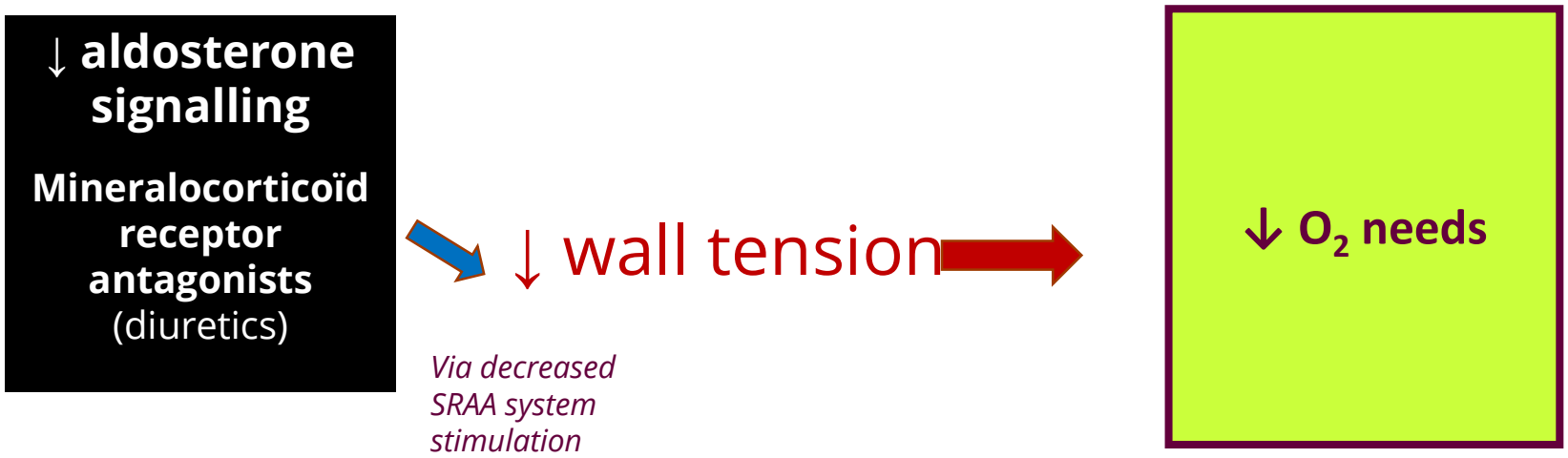
Which drug to…. decrease O_2 needs?



Which drug to…. decrease O_2 needs?



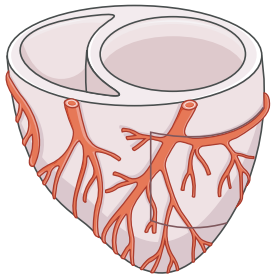
Which drug to…. decrease O_2 needs?

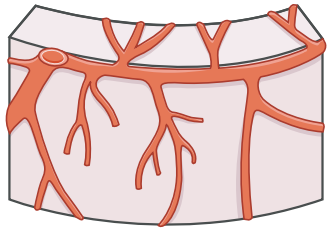


Important concepts **#2**

Indirect benefits from slowing the heart…

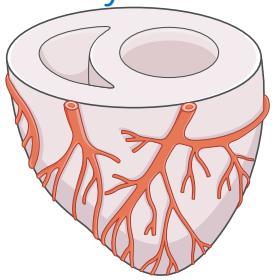
Diastole

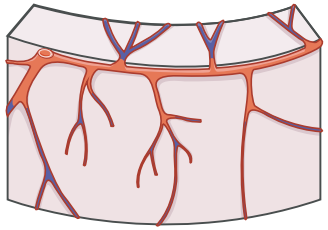




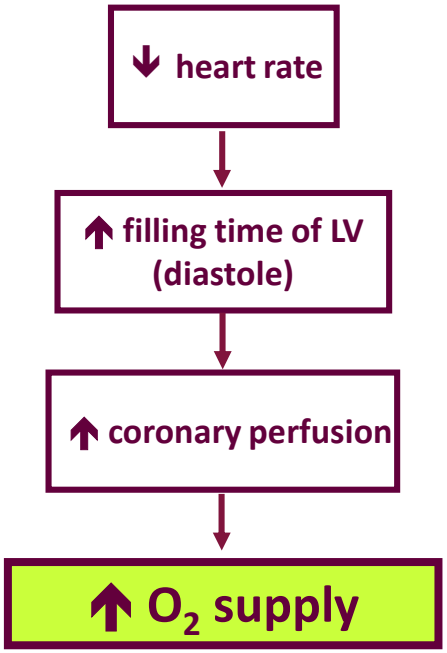
Good coronary perfusion

Systole





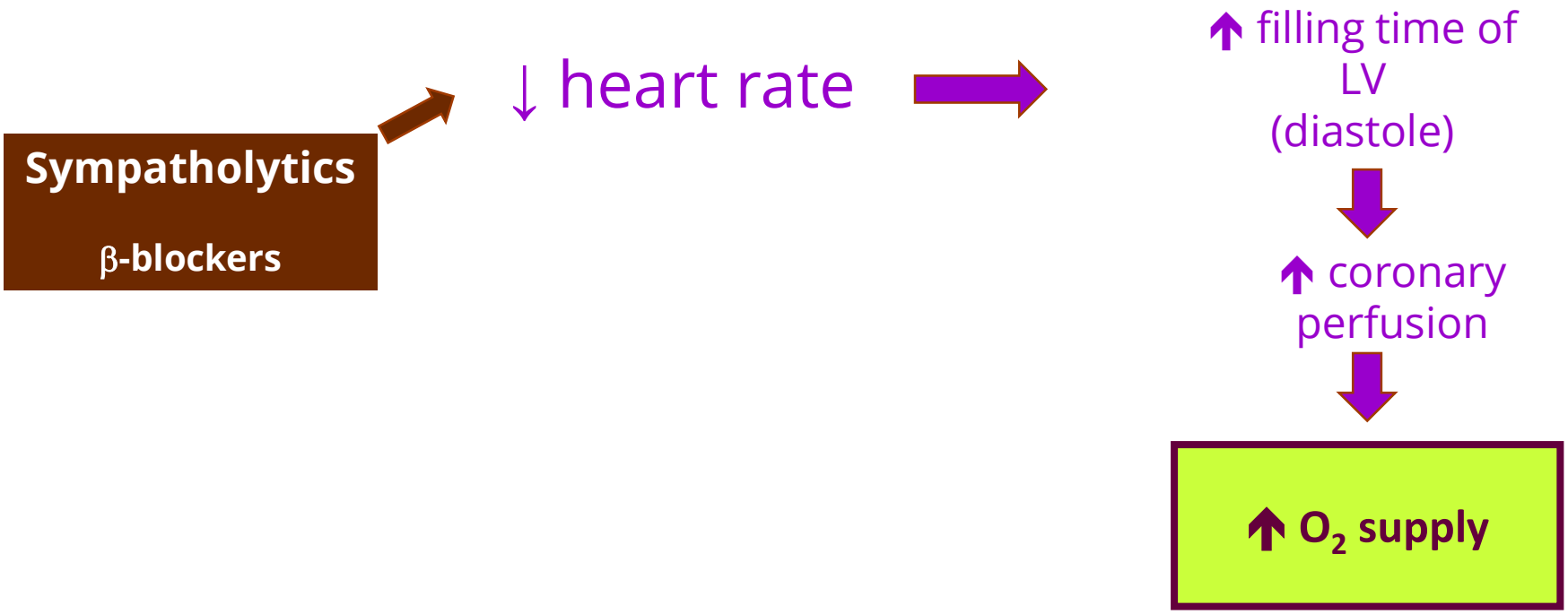
Poor coronary perfusion



Due to extra-vascular compressive forces (high during systole), coronary flux occurs mainly during diastole

Important concepts **#2**

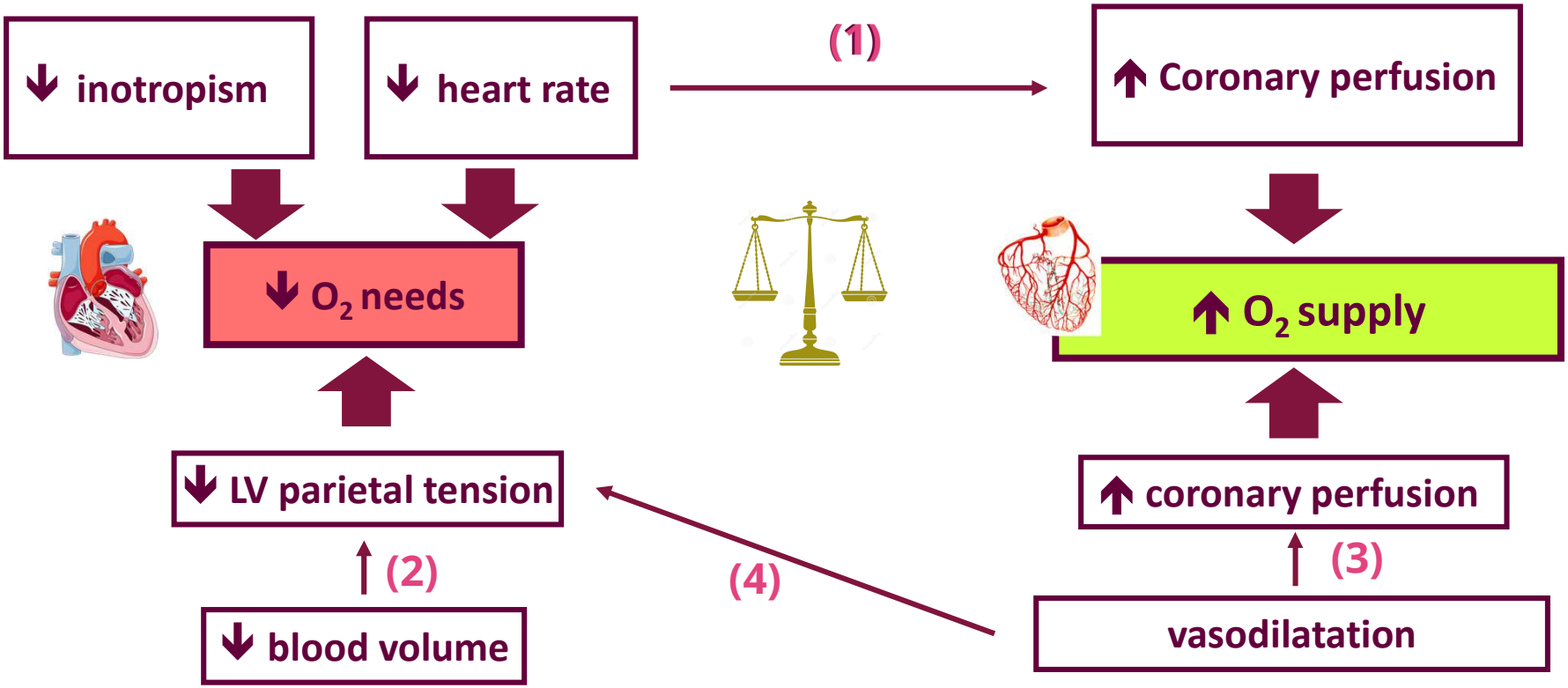
Indirect benefits from slowing the heart…



Examples of pharmacological interventions to treat the CV system

β-A.R. antagonists | (ACE inhibitor, ARA)

« cardiac » CCB: verapamil, diltiazem



MR antagonists (diuretics)

ACE inhibitor, ARA | β-A.R. antagonists

dihydropyridines (+++)

verapamil (++) | diltiazem (+)

Conclusion : what do I need to know?

- Which are the therapeutic targets and the action mechanisms of drugs…
  - Acting on the sympathetic nervous system
  - Acting on the RAA system
  - Acting on the calcium channels in the heart and vessels
- Which are the mechanisms that would…
  - Decrease BP
  - Increase O_2 supply to the myocardium?
  - Diminish O_2 needs of the myocardium?