Microcirculation

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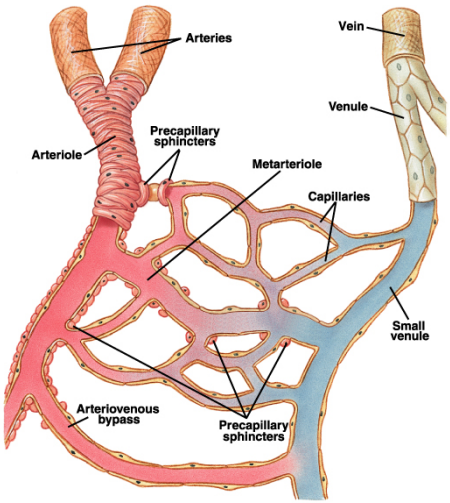


Microcirculation

Microcirculation is a term used to describe the small vessels in the vasculature which are embedded within organs;

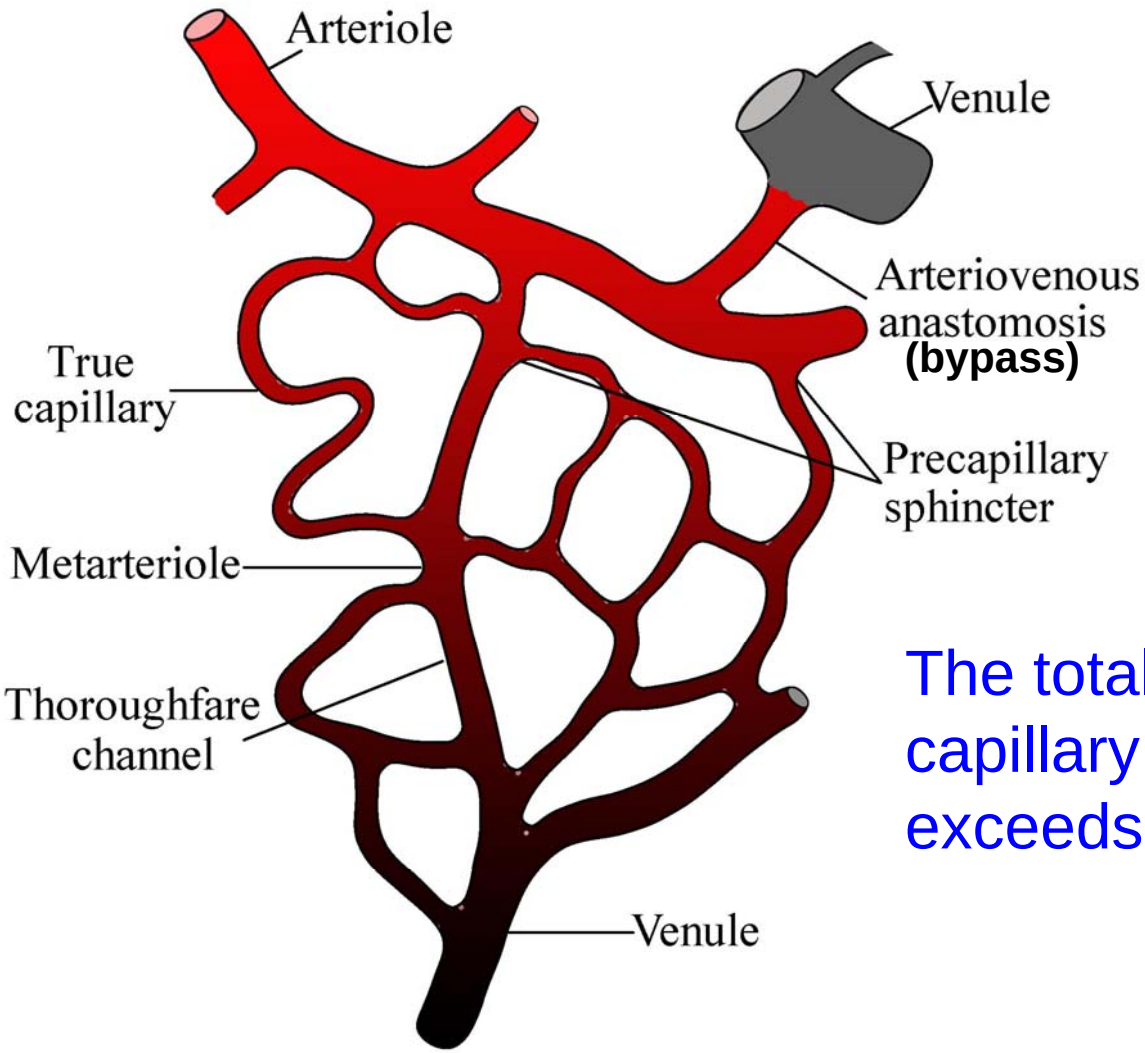
are responsible for the distribution of blood within tissues; as opposed to larger vessels in the **macrocirculation** which transport blood to and from the organs.

The circulation between arteriole and venule.

CAPILLARIES

- Exist in every organ except for cartilage, cornea, hair & dental enamel
- Only 5% of the blood is in capillaries
- Exchange of gases, nutrients, and wastes except in the brain (6-9 um)
- Flow is slow and continuous (1-2s)
- Transcapillary movement occurs by diffusion.

Blood travels from artery to arteriole to capillary to venule to vein typically



The total area of all the capillary walls in the body exceeds 1000 m^2 in the adult!

Thoroughfare channel (always open):

To ensure adequate venous return

Arterioveous anastomosis (rarely open):

To participate in body temperature regulation

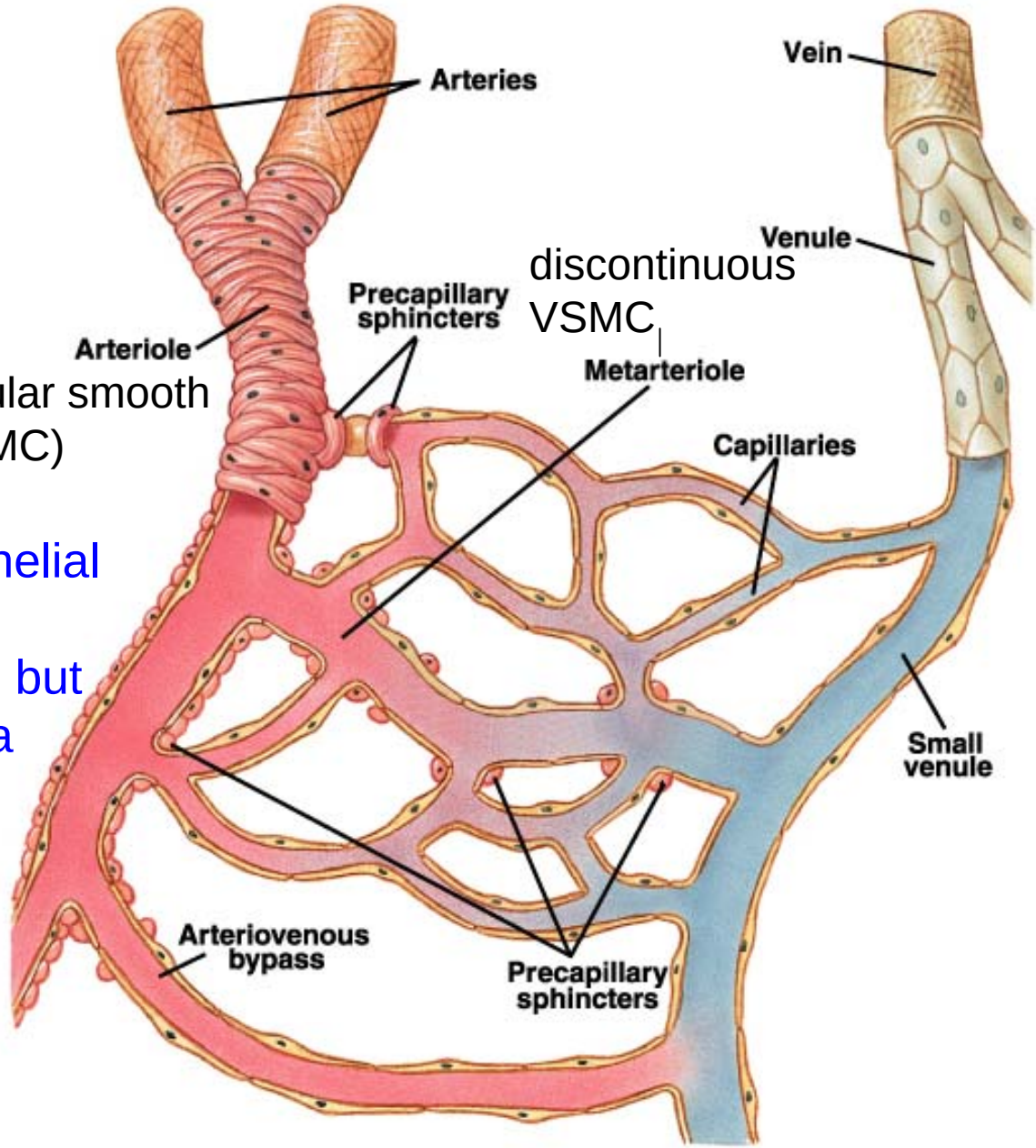
Capillaries (circuitous channel) (open in turn):

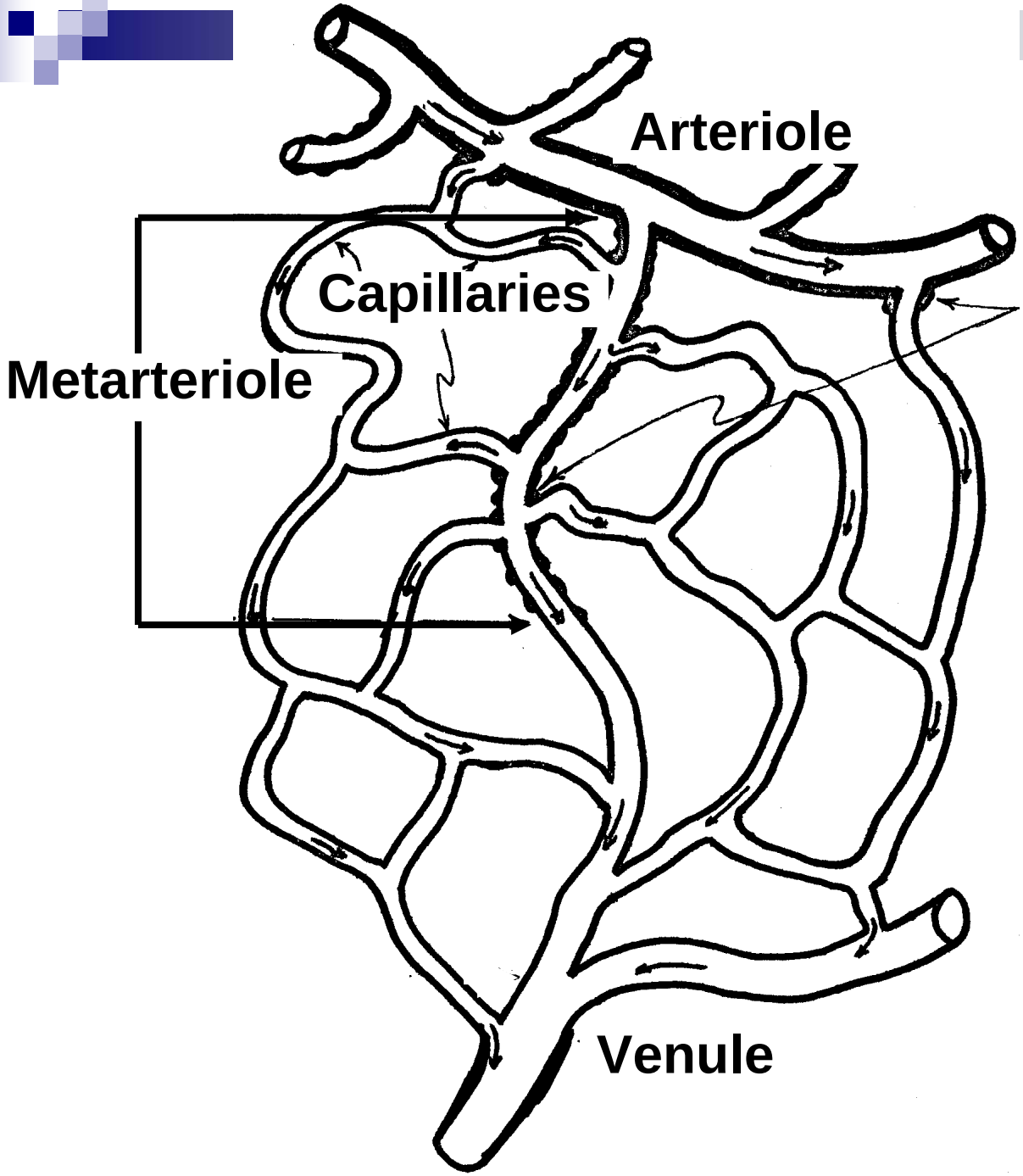
Exchange

Continuous vascular smooth muscle cells (VSMC)

discontinuous VSMC

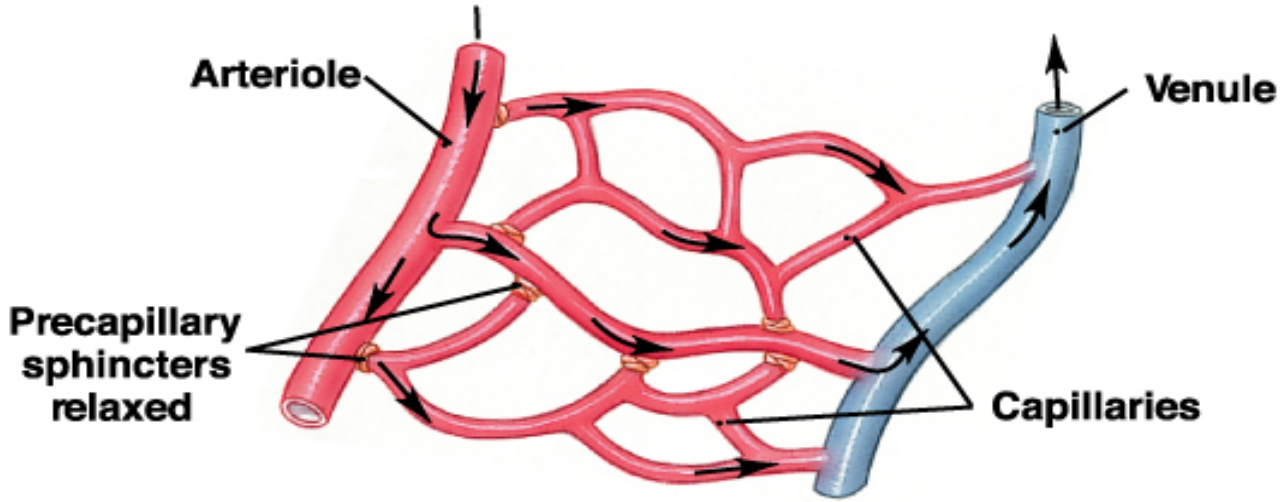
Capillary: single layer of endothelial cells,
Permeable to most substances but not large molecules like plasma protein albumin





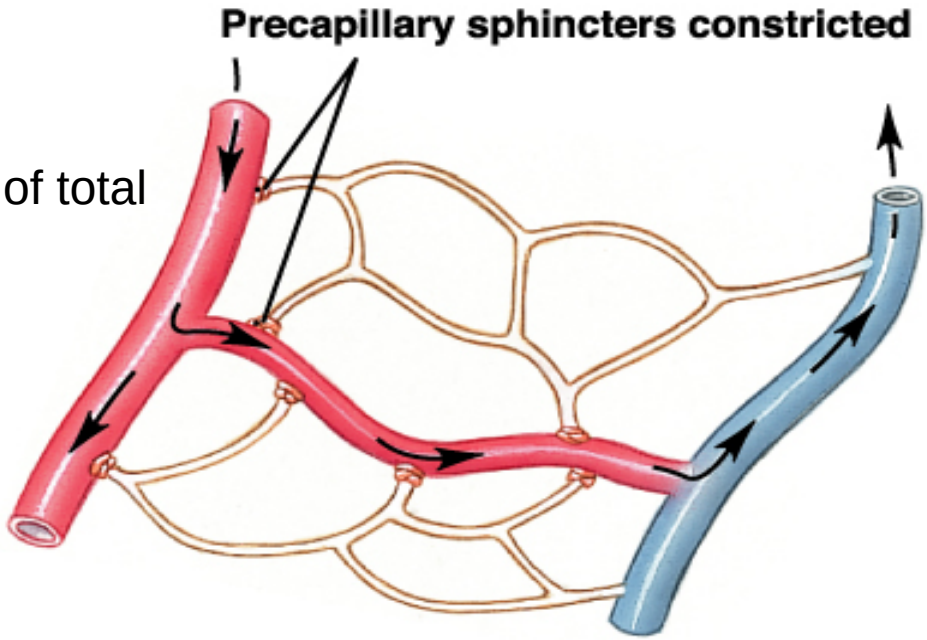
- The arterioles are the major site of the resistance to blood flow, innervated by nor-adrenergic nerve fibers.

- Metarterioles and capillaries are not innervated, respond to local or circulating vasoconstrictor substances.



Precapillary sphincters respond to local or circulating vasoconstrictor/ vasodilator

Inactive capillary: 80% of total



VASOMOTION = Intermittent flow due to constriction-relaxation cycles of metarteriolar smooth muscle & precapillary shpincters (5 - 10/min)

AUTOREGULATION OF VASOMOTION
(Local! In cycles!)

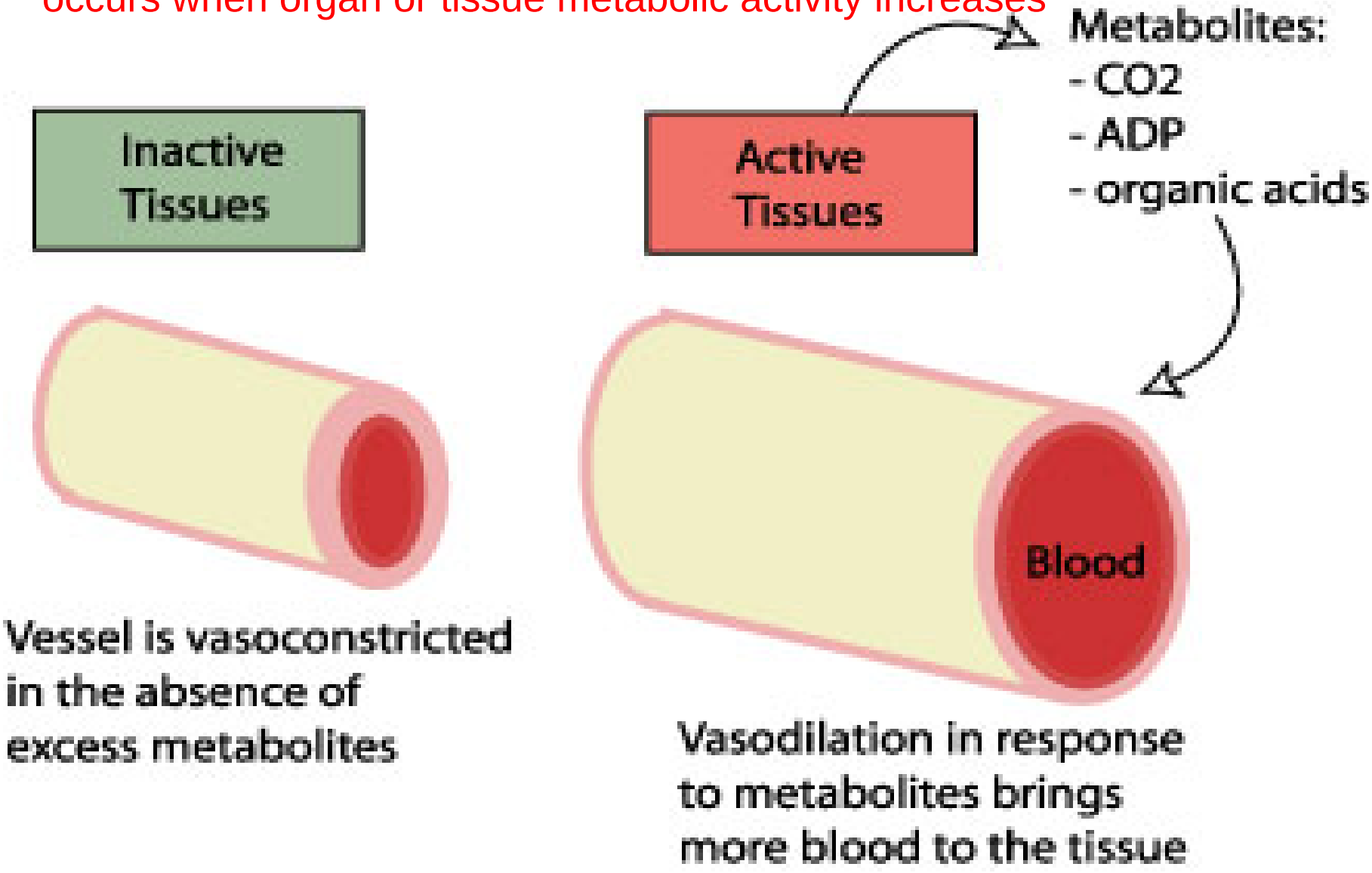
Vasodilator substances produced ← (↓ O2)

e.g. Adenosine → Heart

CO_2 → Brain

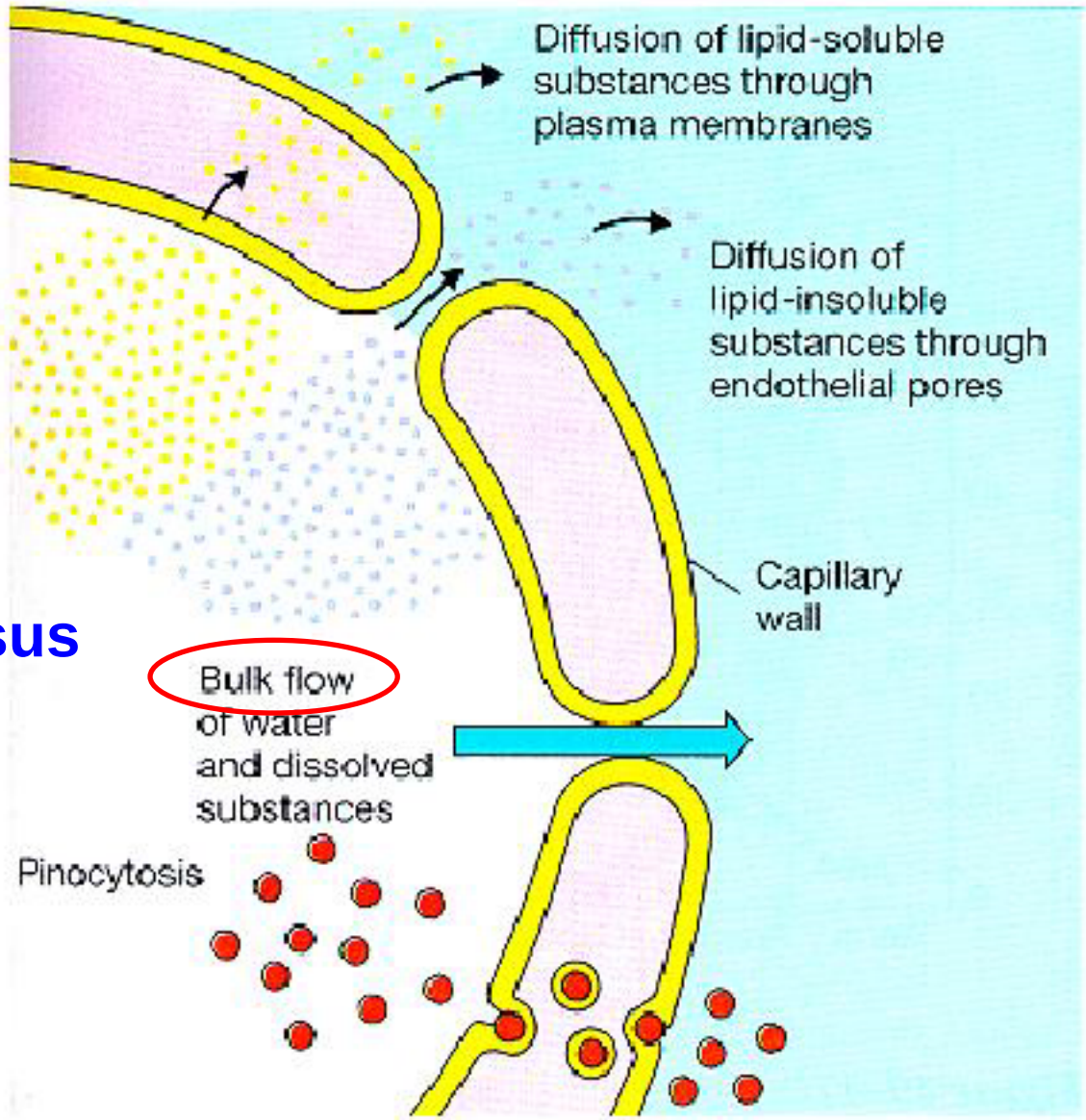
Lactate, H^+, K^+ → Skeletal Muscle

•Hyperemia is an increase in organ blood flow that occurs when organ or tissue metabolic activity increases



Materials exchange by capillaries

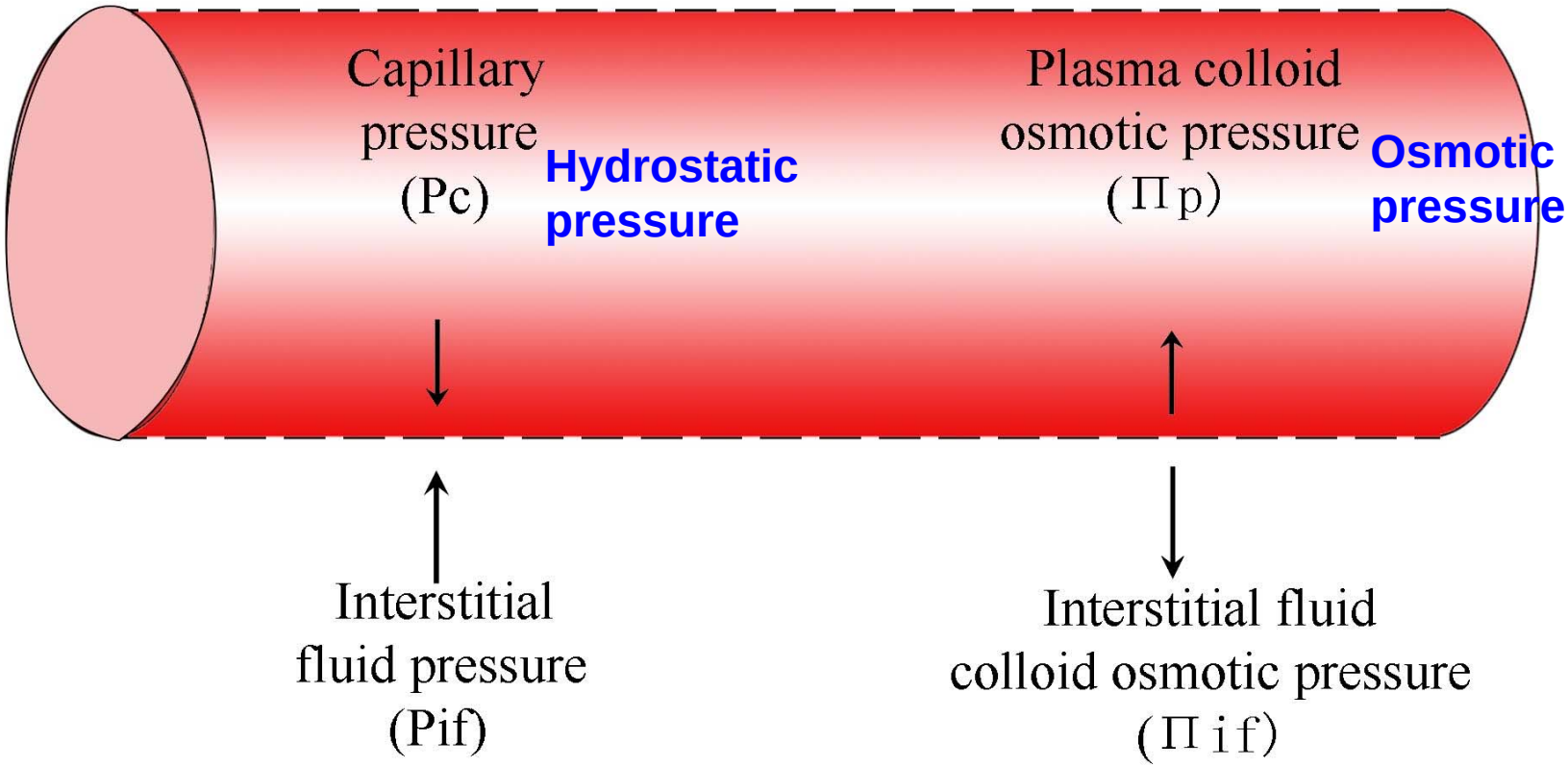
Filtration versus reabsorption

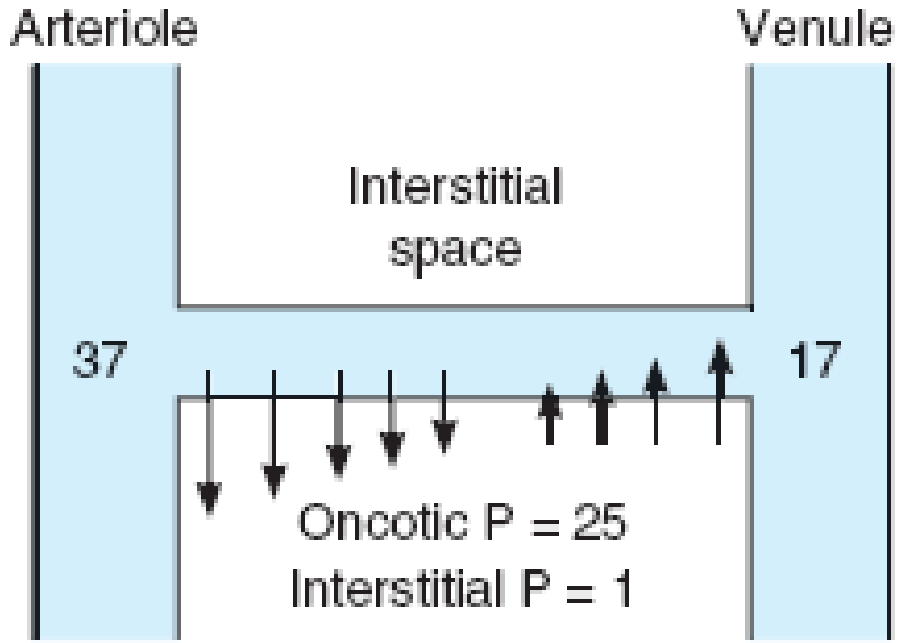


Equilibration with interstitial fluid

EFP (effective filtration pressure)

$= K[(P_c+\pi_{if})-(P_{if}+\pi_c)]$





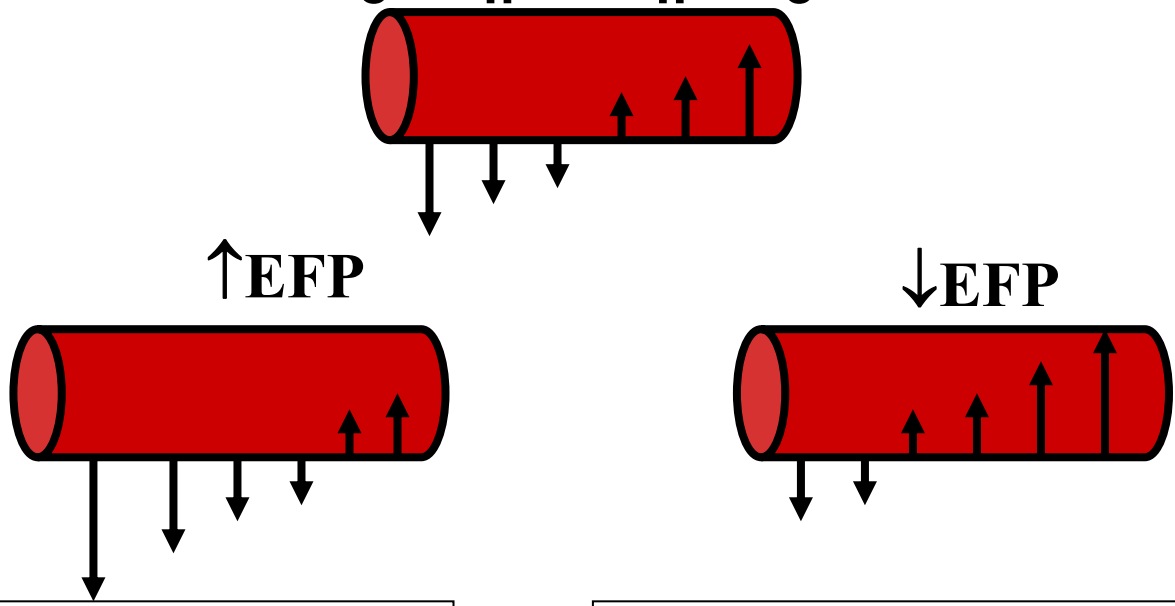
Arteriolar end of capillary: net filtration

Venular end of capillary: net reabsorption

In this example,the pressure differential at the arteriolar end of the capillary is 11 mm Hg ([37 – 1] – 25) outward;
at the opposite end, it is -9 mm Hg (25 – [17 – 1]) inward.

CAPILLARY FLUID SHIFT

$(P_c+\pi_{if})-(P_{if}+\pi_c)$



FAVORS FILTRATION

FAVORS REABSORPTION

RENAL CIRCULATION

PULMONARY CIRCULATION

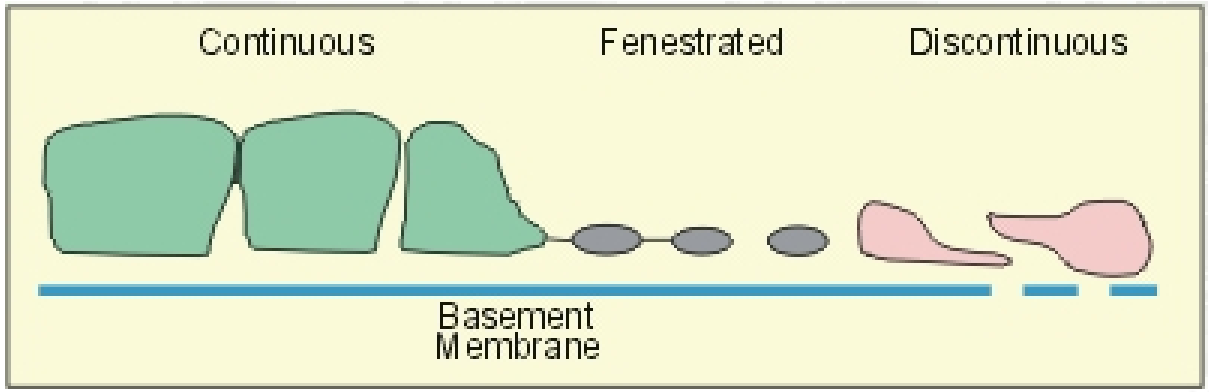
- Fluid moves out of almost the entire length of capillary in the renal glomeruli
- Pulmonary capillary pressure is normally less than osmotic pressure, fluid is always drawn into the blood.

K (capillary filtration coefficient)

Hydraulic conductivity (permeability) of capillaries in various tissues

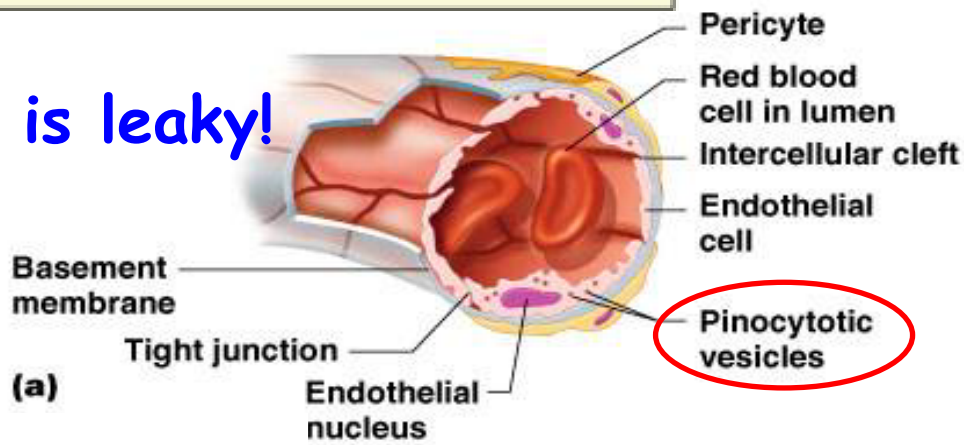
Organ	Conductivity[a]	Type of Endothelium
Brain (excluding circumventricular organs)	3	
Skin	100	Continuous
Skeletal muscle	250	
Lung	340	
Heart	860	
Gastrointestinal tract (intestinal mucosa)	13,000	Fenestrated
Glomerulus in kidney	15,000	

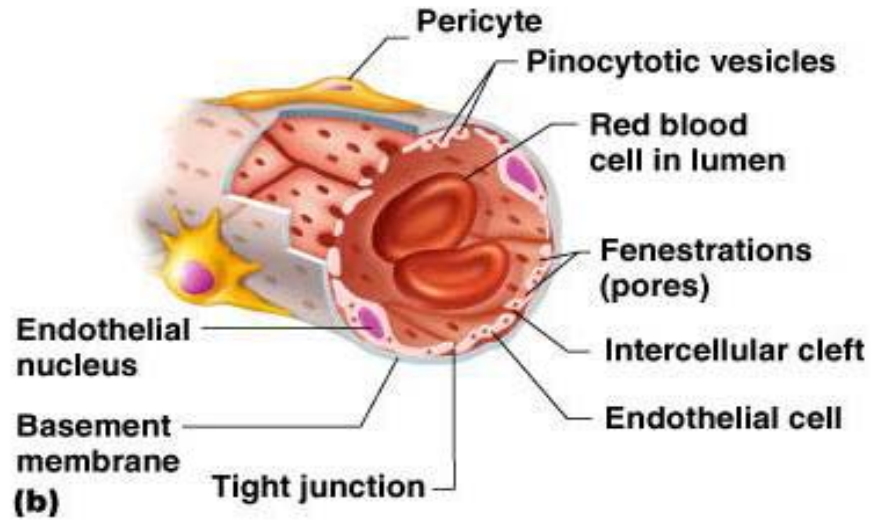
[a]Units of conductivity are 10^{-13} cm^3 s^{-1} $dyne^{-1}$.

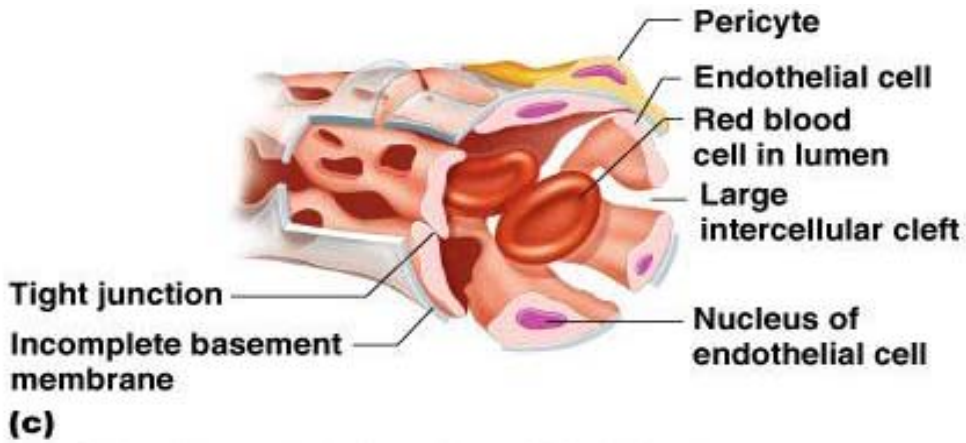


Endothelial cells

The capillary wall is leaky!

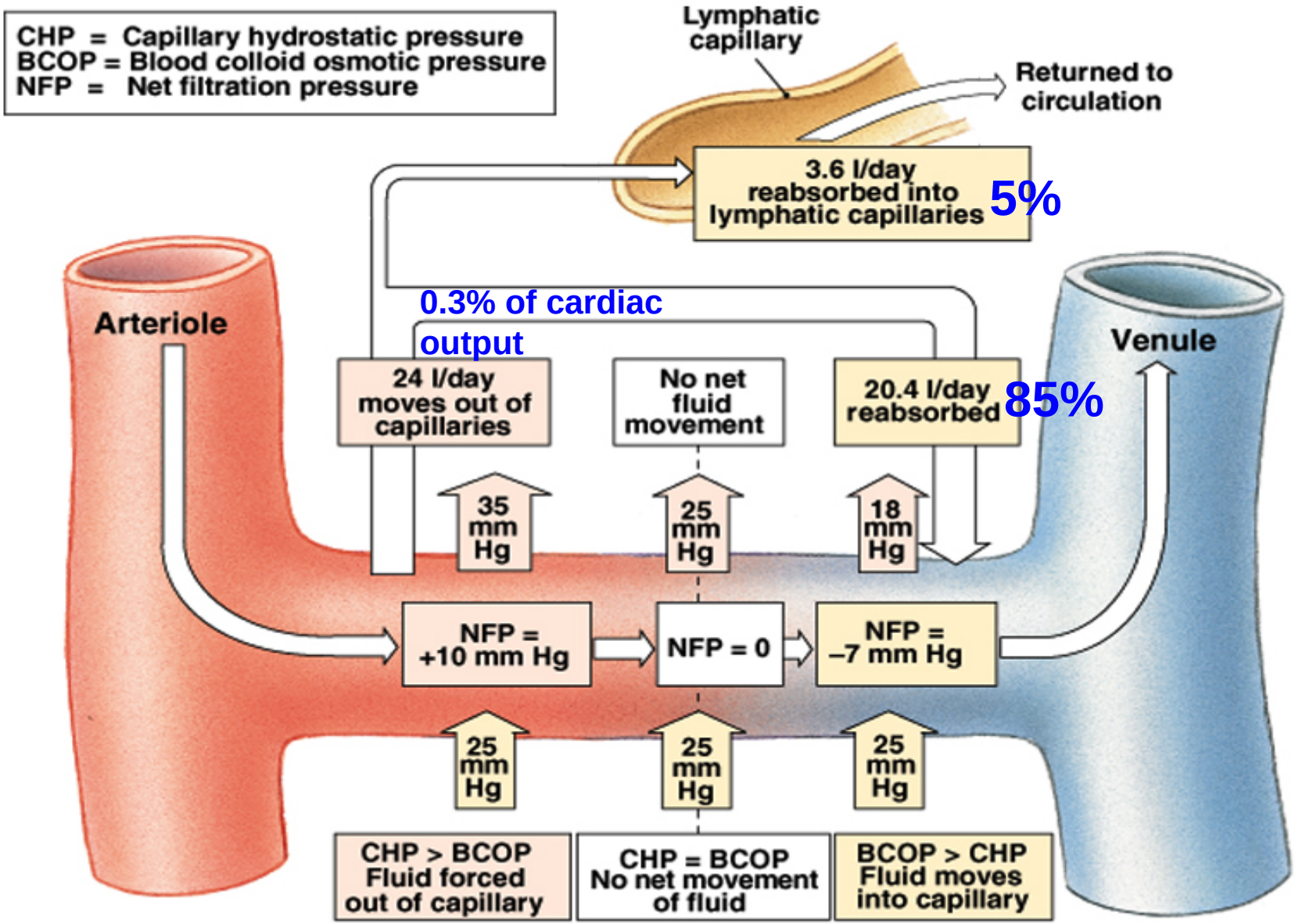






	Continuous capillary	Fenestrated capillary	Discontinuous (sinusoid) capillary
Endothelial cells	Continuous Tight junction	Fenestrated	Fenestrated Large cleft
Basement membrane	Continuous	Continuous	Discontinuous /none
Distribution	Connective tissues Muscles Lung Brain	Gastrointestine Endocrine gland Kidney	Liver Spleen Bone marrow
Permeability	Low	Middle	High

Capillary Exchange - ECF turnover

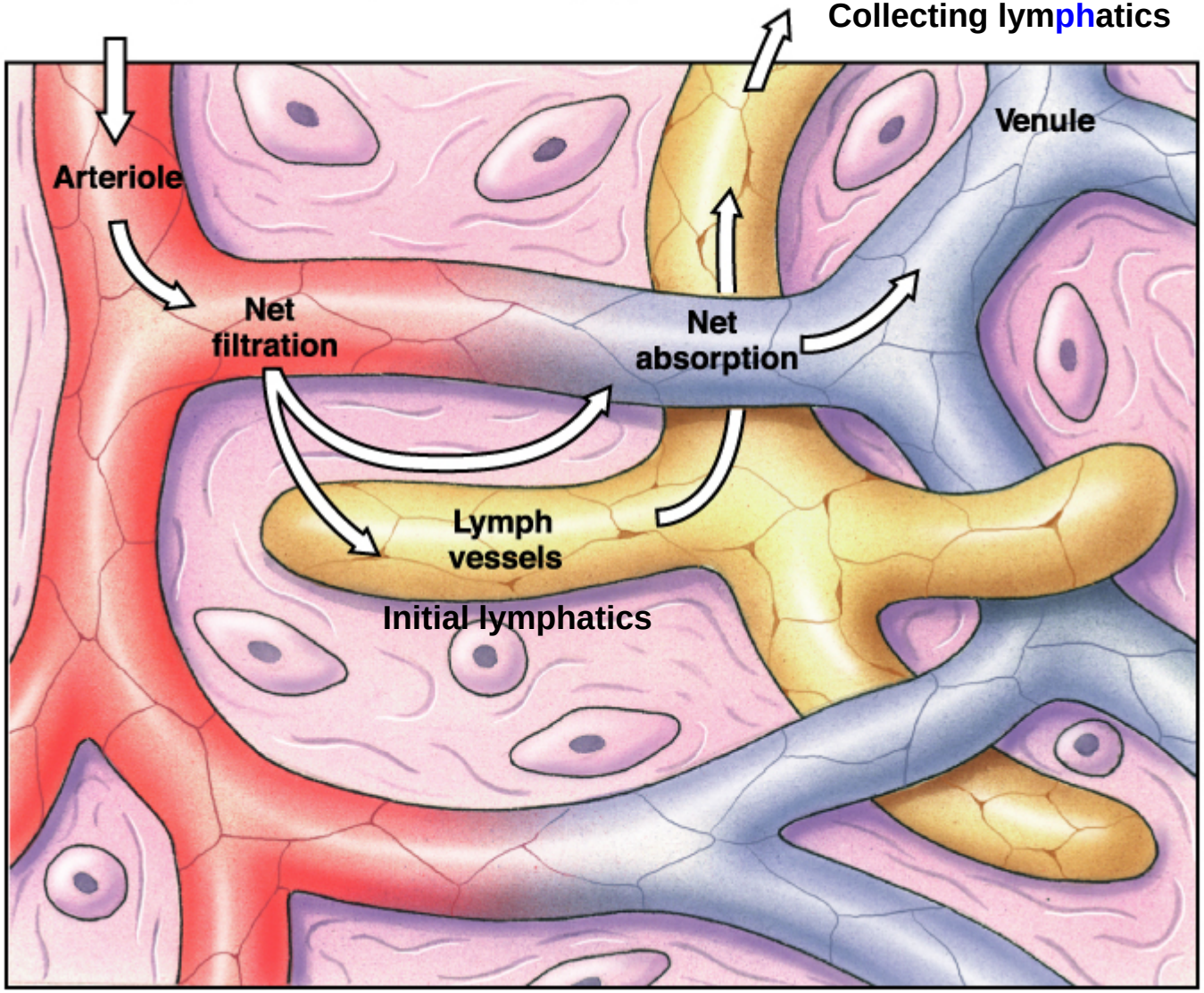


Lymphatic circulation

Right lymphatic duct
Ductus thoracicus

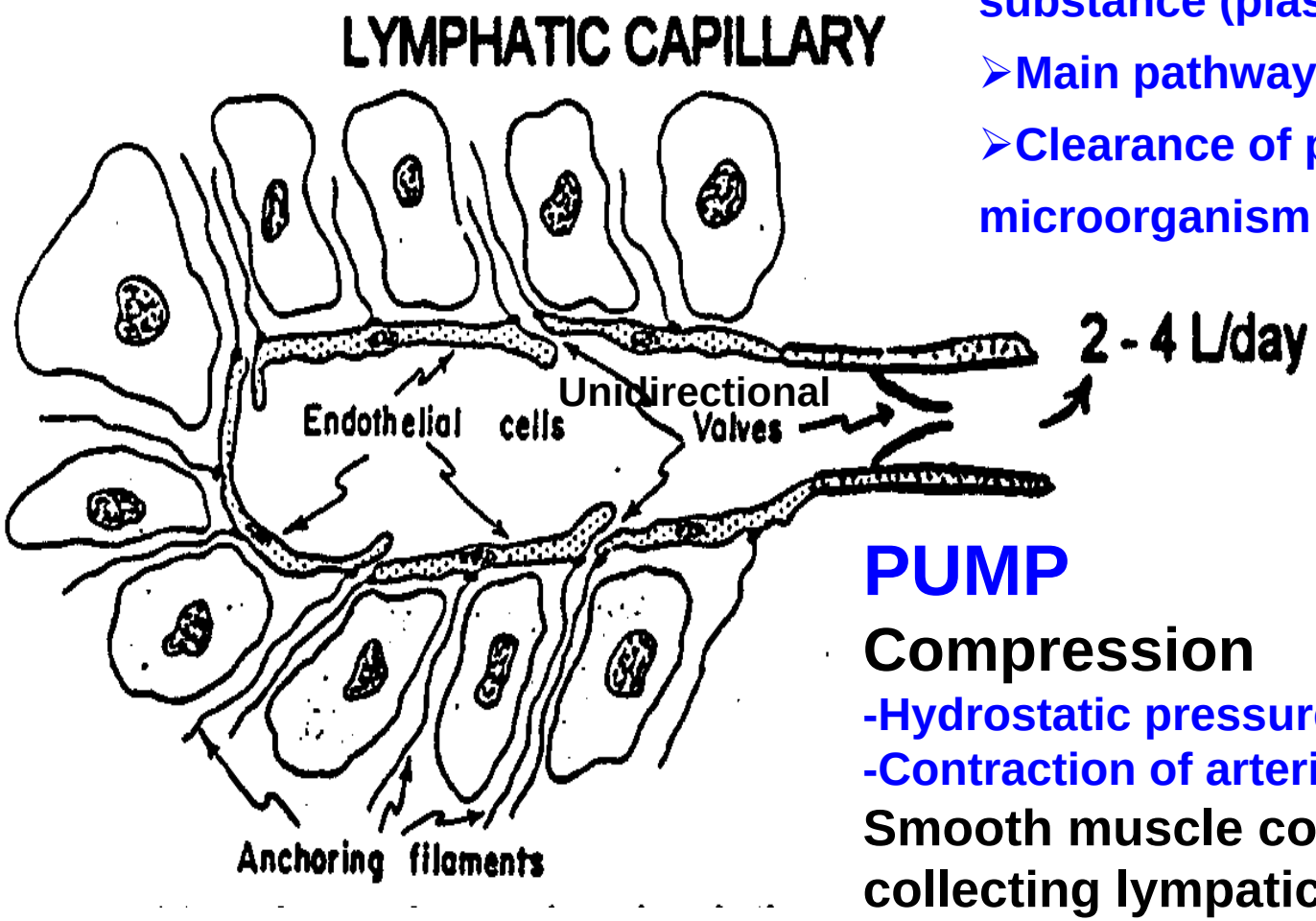
Vein

Close Relationship between capillaries and lymph vessels



Lymphatic Capillary

2 - 4 L/Day (≈ 125 ml/hr)



- Reabsorption of osmotically active substance (plasma protein)
- Main pathway for lipid absorption
- Clearance of pathogenic microorganism

PUMP

Compression

-Hydrostatic pressure

-Contraction of arterioles and venules

Smooth muscle contraction in collecting lympatics

Interstitial fluid volume is dependent on

- capillary hydrostatic pressure
- interstitial fluid hydrostatic pressure
- Capillary osmotic pressure
- Capillary filtration coefficient
- Number of active capillaries
- Lymph flow
- Total extracellular fluid volume (blood volume)

Causes of increased interstitial fluid volume and edema

Increased filtration pressure
Arteriolar dilation
Venular constriction
Increased venous pressure (heart failure, incompetent valves, venous obstruction, increased total ECF volume, effect of gravity, etc)
Decreased osmotic pressure gradient across capillary
Decreased plasma protein level
Accumulation of osmotically active substances in interstitial space
Increased capillary permeability
Substance P
Histamine and related substances
Kinins, etc
Inadequate lymph flow

Why edema occurs when one stands still for long periods?

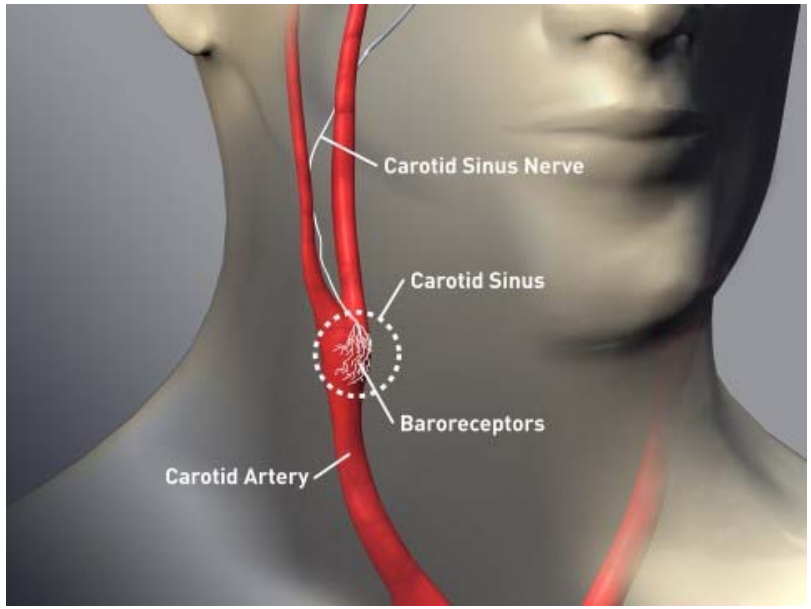
Effects of gravity!

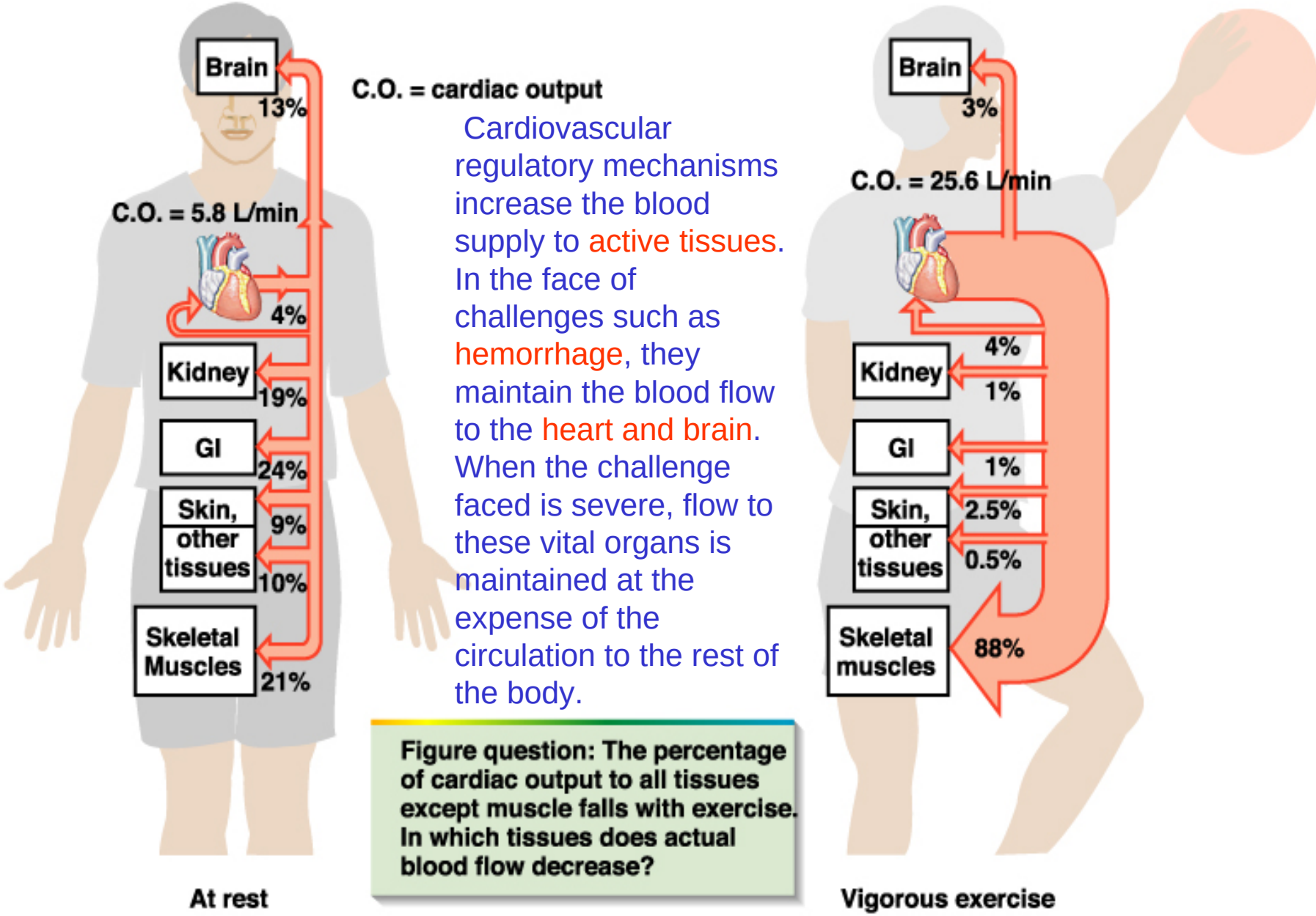
In the upright position

- High arterial pressure is attenuated by arterioles
- High venous pressure is transmitted by venules
- Muscle pump does not work

  •Skeletal muscle contraction keep the venous pressure low by pumping blood toward the heart when the individuals moves about

Cardiovascular Regulatory Mechanisms





Cardiovascular regulatory mechanisms increase the blood supply to active tissues. In the face of challenges such as hemorrhage, they maintain the blood flow to the heart and brain. When the challenge faced is severe, flow to these vital organs is maintained at the expense of the circulation to the rest of the body.

Figure question: The percentage of cardiac output to all tissues except muscle falls with exercise. In which tissues does actual blood flow decrease?

Section outline

·Neural regulation

- Innervation of heart and blood vessels
- Cardiovascular center
- Cardiovascular reflex

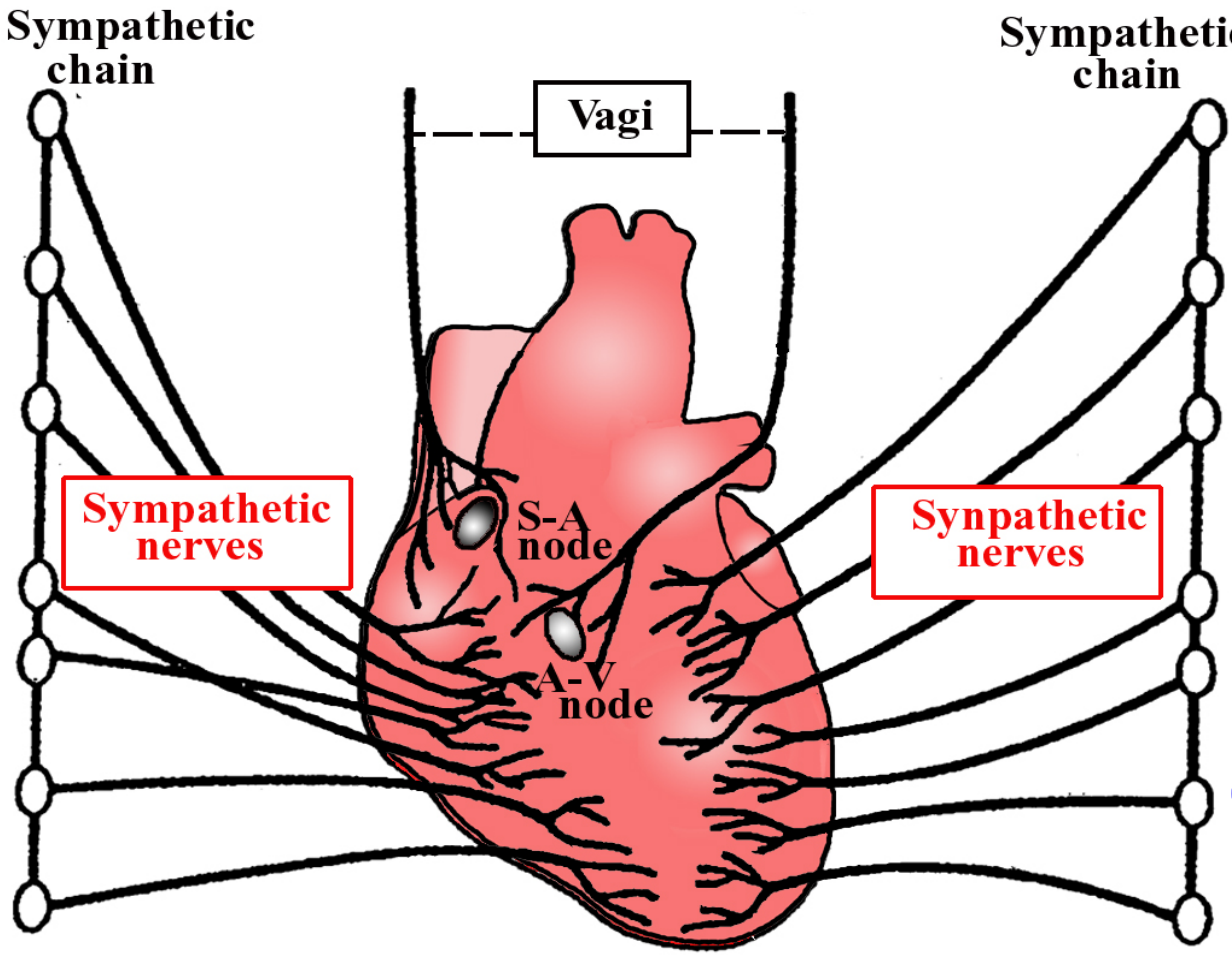
·Humoral regulation

- Epinephrine & Norepinephrine
- Renin-angiotensin-aldosterone system
- Arginine vasopressin
- atrial natriuretic peptide

Neural Regulation

- **Innervation of heart and blood vessels**
- **Cardiovascular center**
- **Cardiovascular reflex**

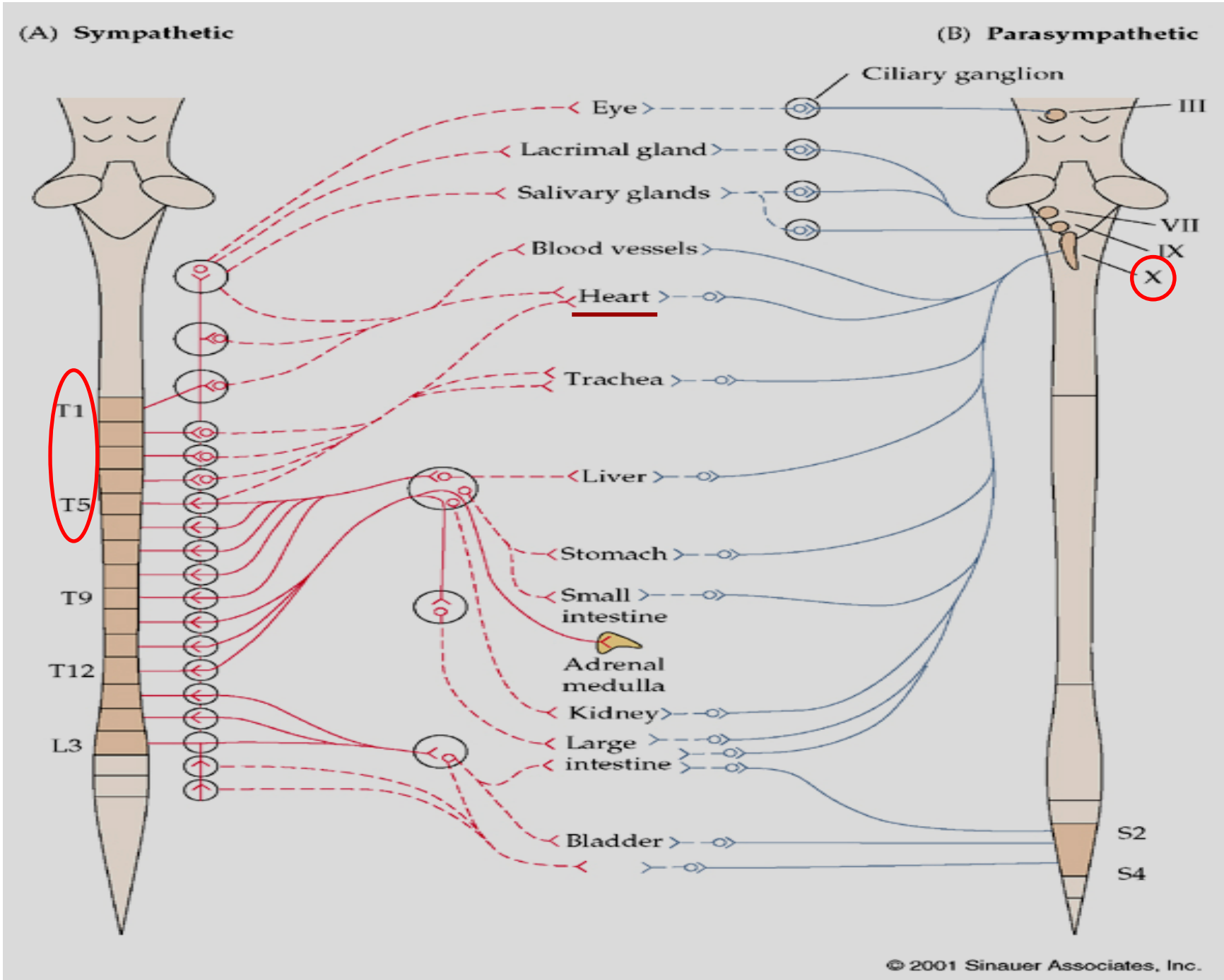
Cardiac Innervation



- Sinoatrial node
- Atrioventricular node
- Bundle of His
- Atrium myocardium
- Ventricle myocardium

(less vagal innervation)

Cardiac innervation	Origin	Transmitter	Effects
Sympathetic cardiac nerves	T(thoracic)1-T5 (Intermediolateral gray column, IML) → middle cervical / stellate ganglia → postganglion fibers	Noradrenergic, NE → β_1 receptors	Tonic sympathetic discharge, positive chronotropic, Inotropic, dromotropic effect.
Vagal cardiac fibers	Nucleus ambiguus (NA)/ Dorsal motor nucleus of vagus (DMV) →endocardial ganglia → postganglion fibers	Cholinergic Ach→ M_2 receptors	•vagal tone negative chronotropic, Inotropic, dromotropic effect.


(A) Sympathetic
(B) Parasympathetic
Ciliary ganglion
Eye
Lacrimal gland
Salivary glands
Blood vessels
Heart
Trachea
Liver
Stomach
Small intestine
Adrenal medulla
Kidney
Large intestine
Bladder
T1
T5
T9
T12
L3
III
VII
IX
X
S2
S4
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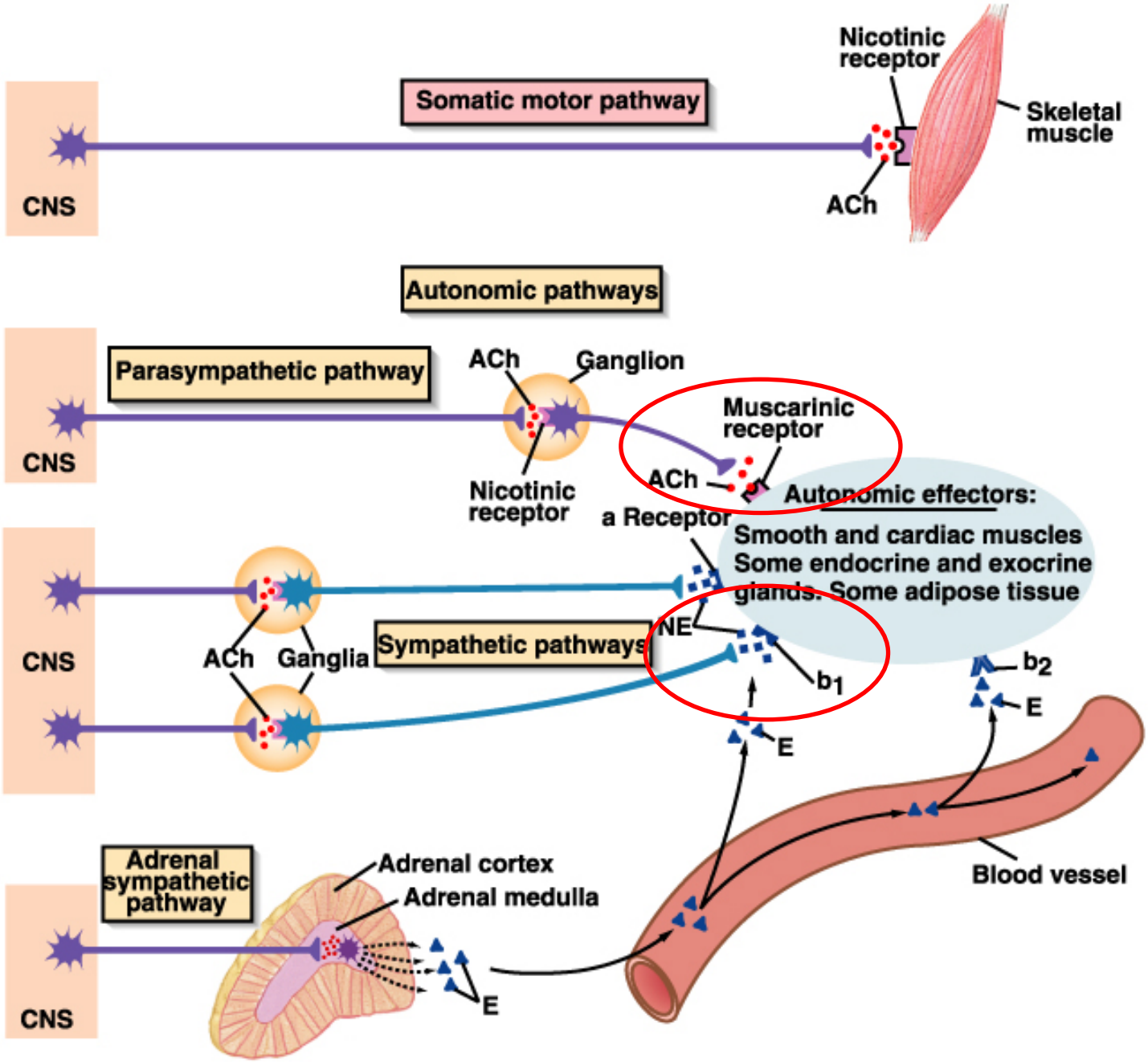
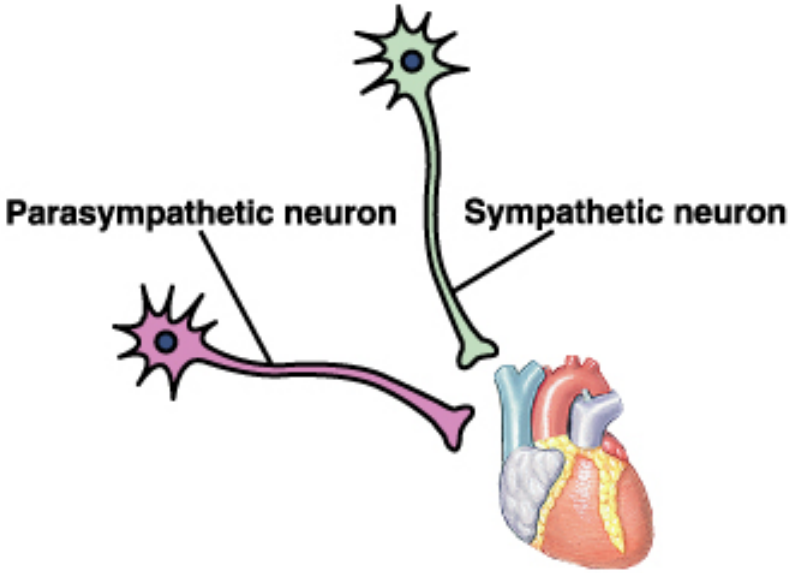
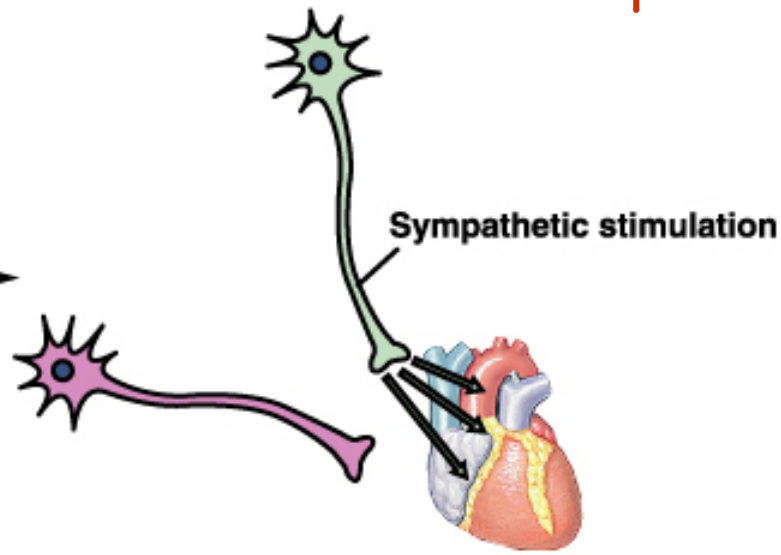
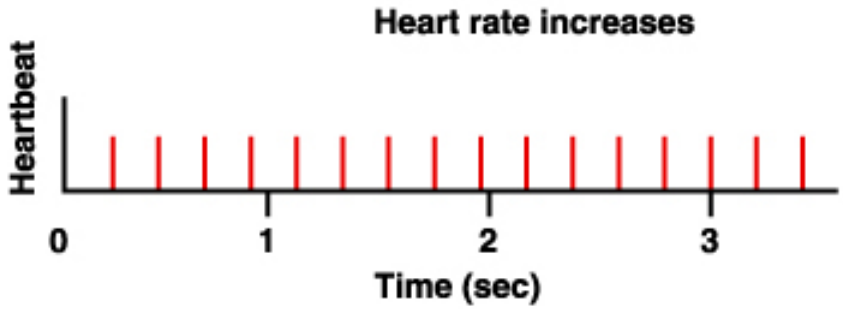
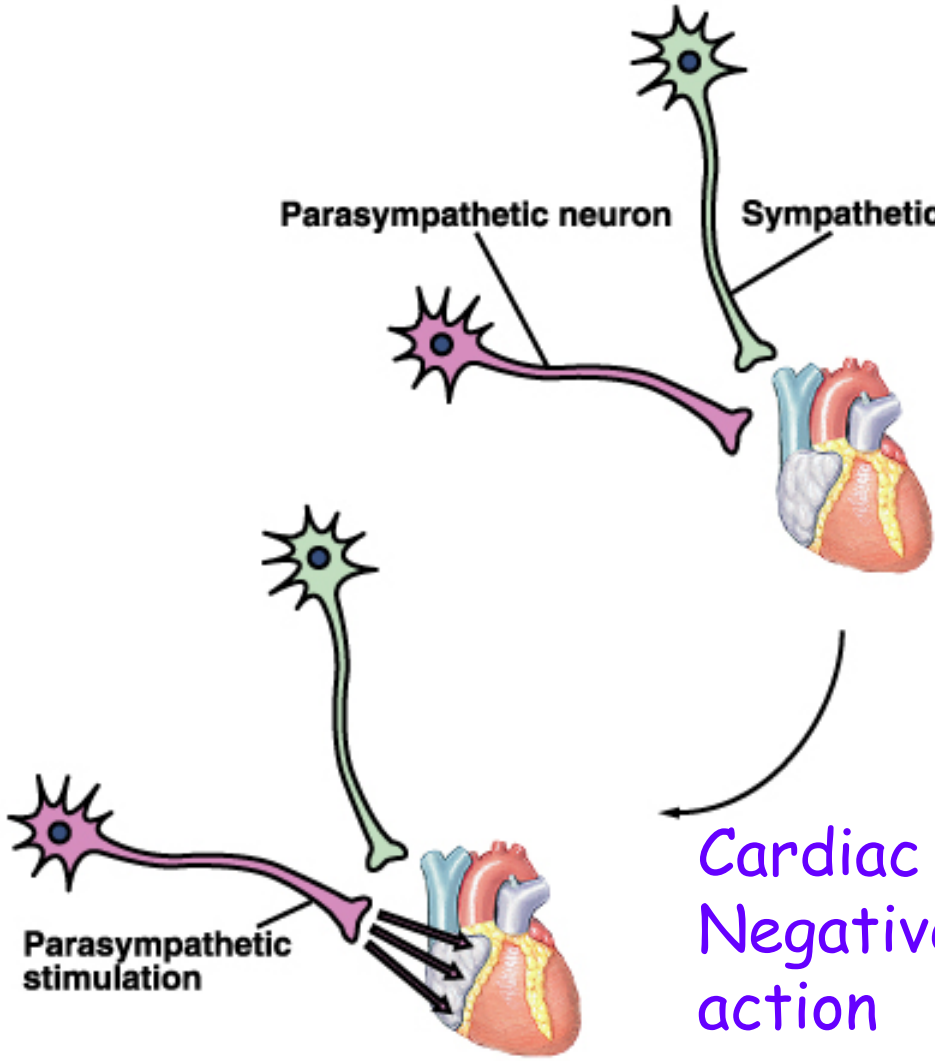

Somatic motor pathway
CNS
Nicotinic receptor
Skeletal muscle
ACh
Autonomic pathways
Parasympathetic pathway
CNS
ACh
Ganglion
Nicotinic receptor
Muscarinic receptor
ACh
Autonomic effectors:
Smooth and cardiac muscles
Some endocrine and exocrine glands. Some adipose tissue
a Receptor
CNS
ACh
Ganglia
Sympathetic pathways
NE
b1
E
b2
E
Adrenal sympathetic pathway
CNS
Adrenal cortex
Adrenal medulla
E
Blood vessel



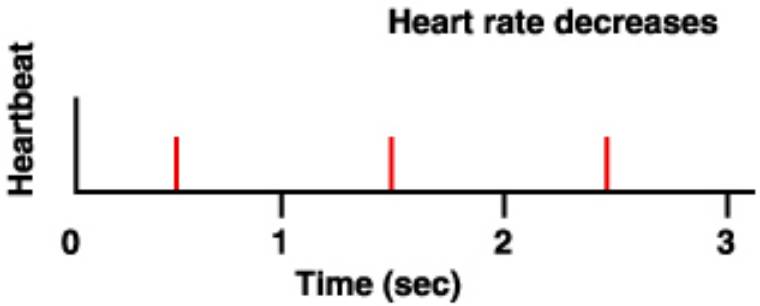
Cardiac sympathetic tone
Positive chronotropic action





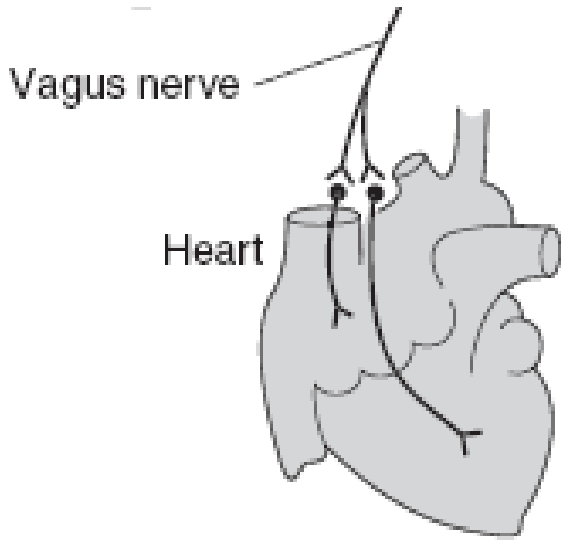


Cardiac vagal tone
Negative chronotropic action

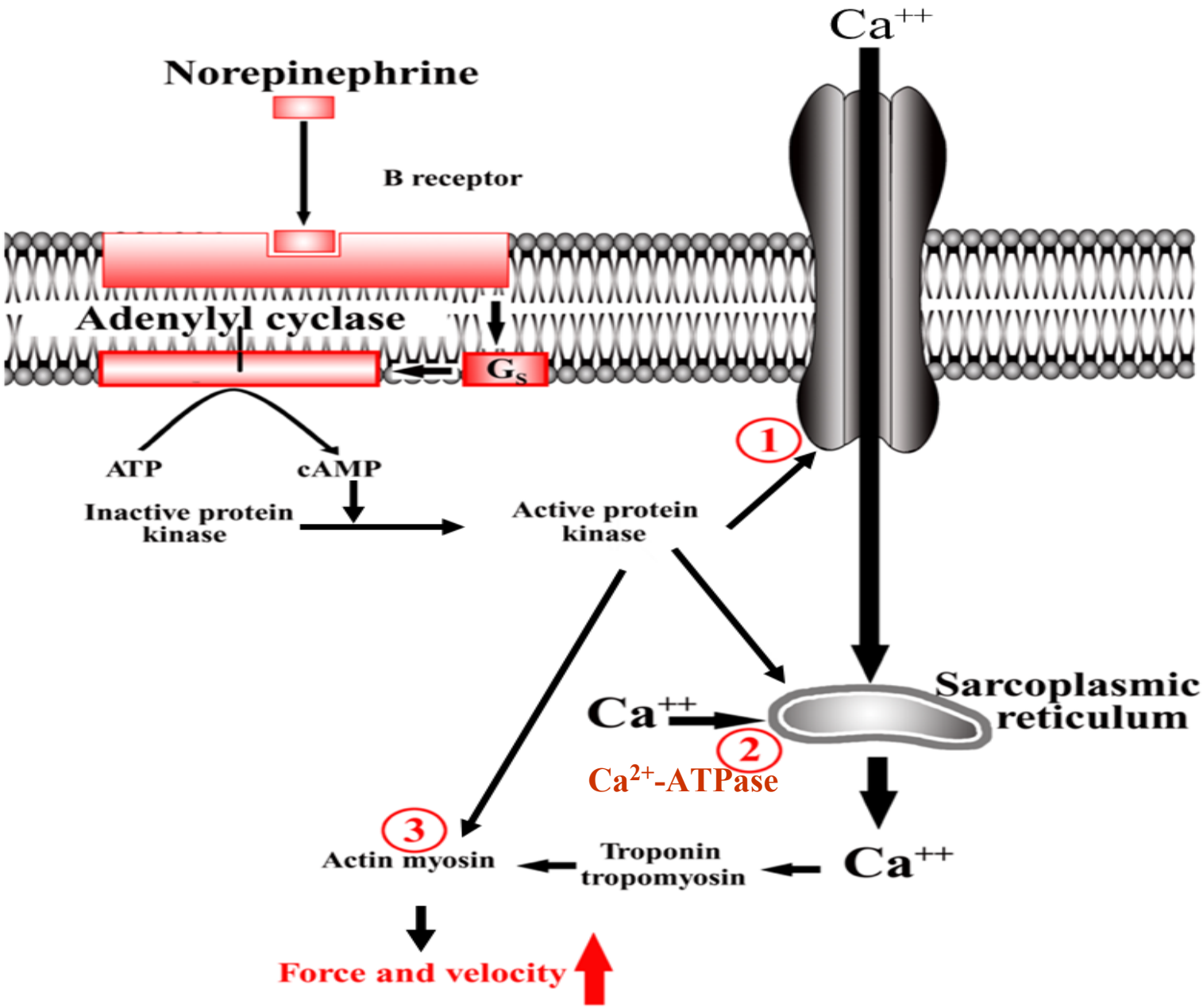


Vagal tone:

more amount of tonic vagal than sympathetic discharge at rest in humans.



In humans in whom both noradrenergic and cholinergic systems are blocked, the heart rate is approximately 100, whose normal resting value is 70.

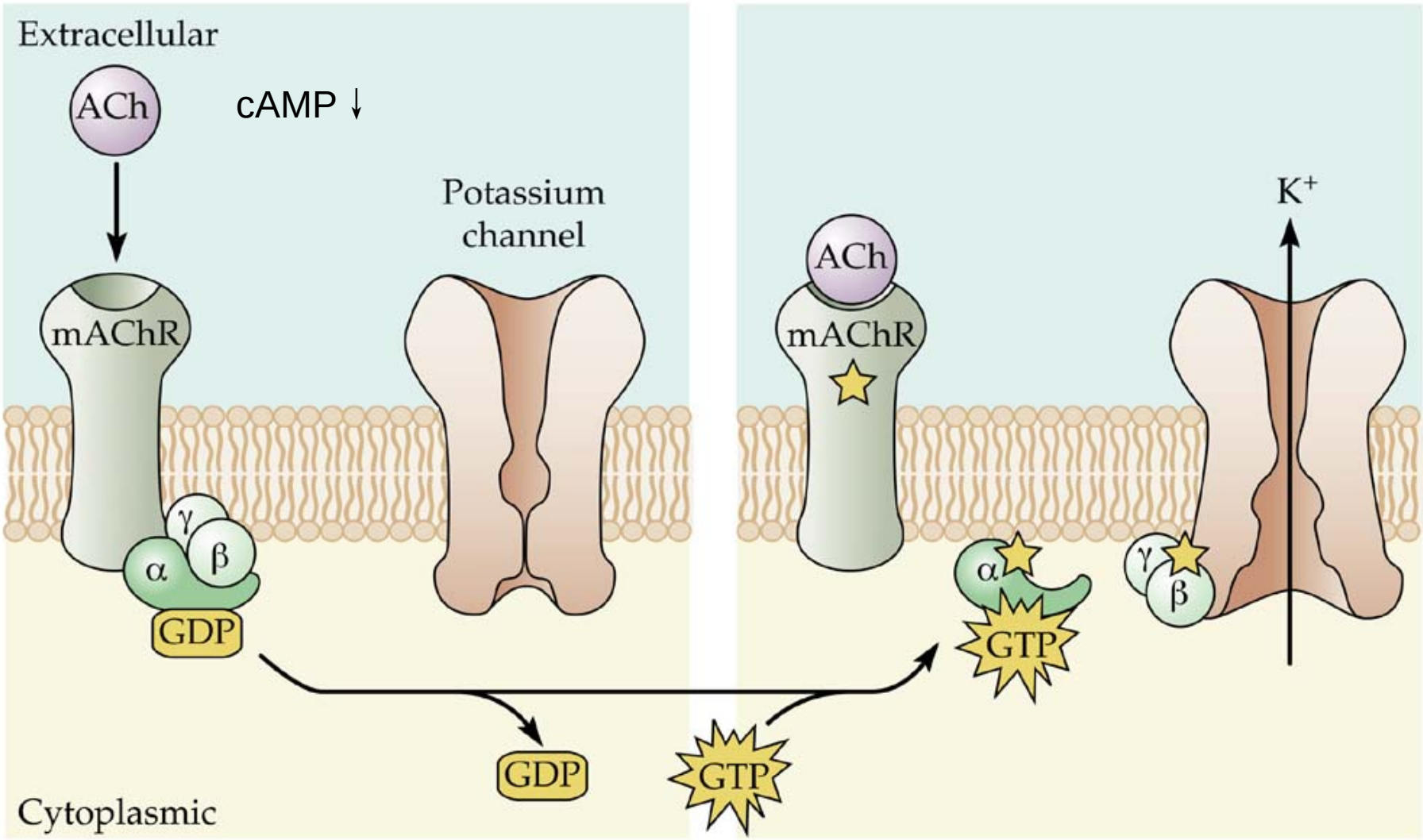


Positive inotropic/chronotropic action

Sir James Black with his Nobel prize medal, awarded to him for his work on drug development, namely his invention of the beta-blocker drug propranolol (1962).

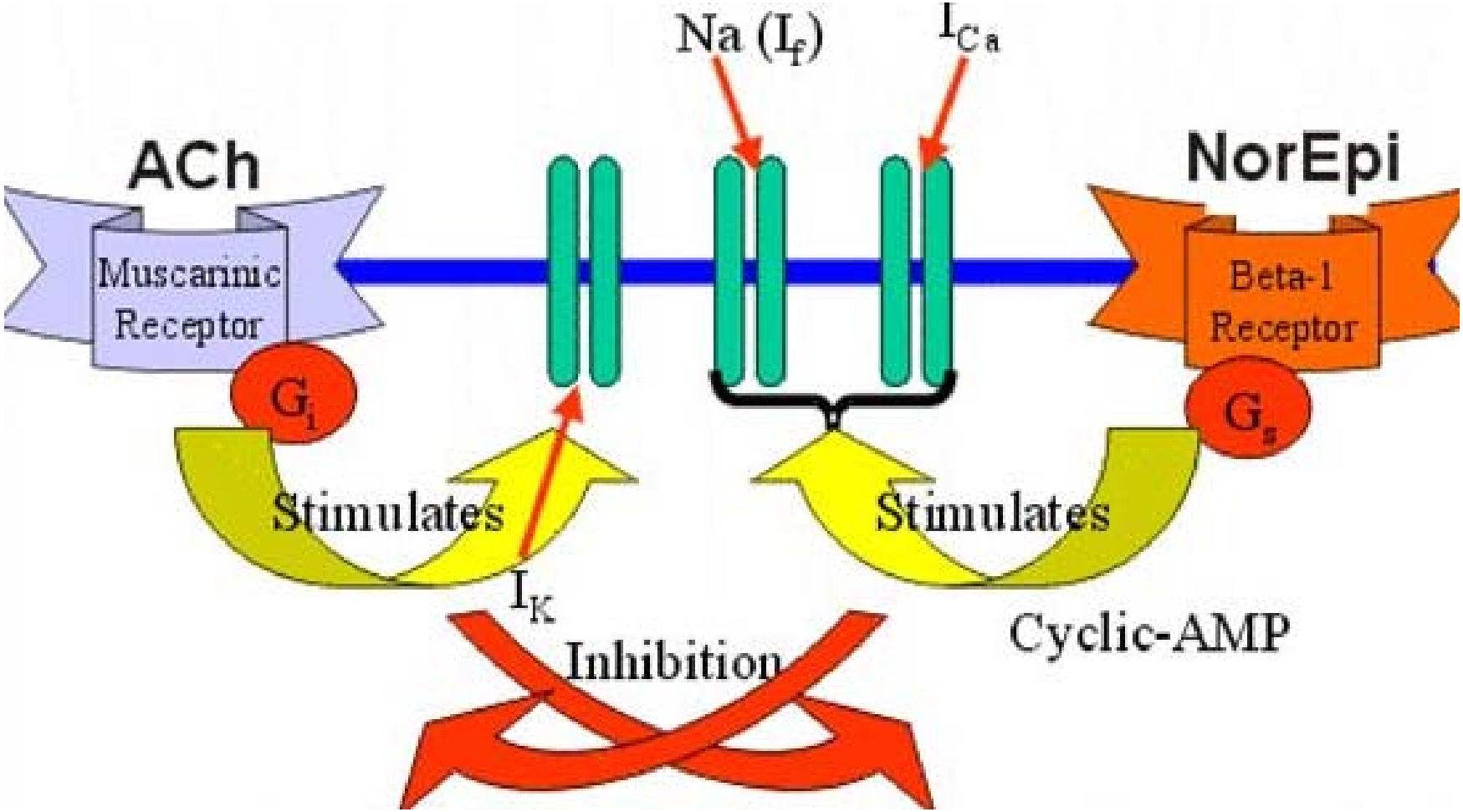
NOBEL prize-winning scientist(1988) Sir James Black has died at the age of 85 (March 23, 2010)

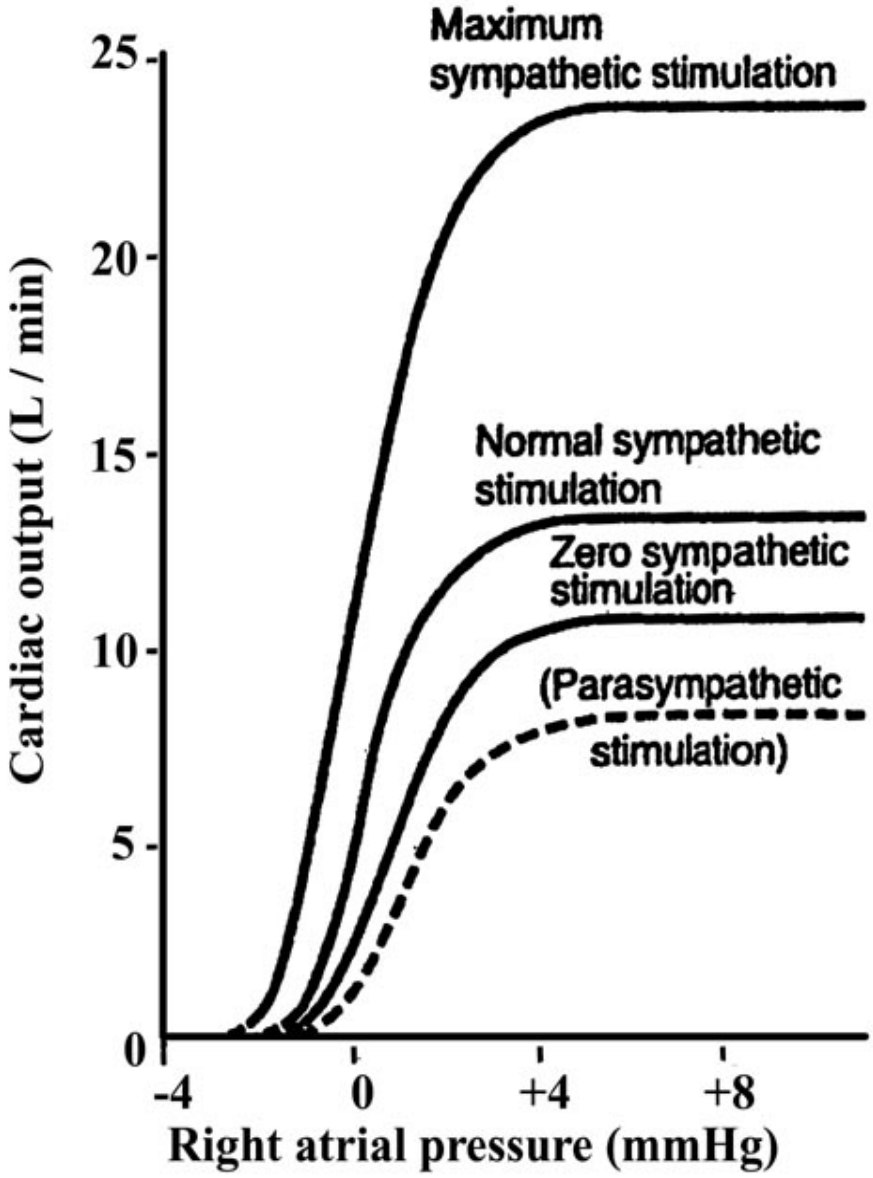
Acetylcholine



Autorhythmic cells

Phase 4 spontaneous depolarization



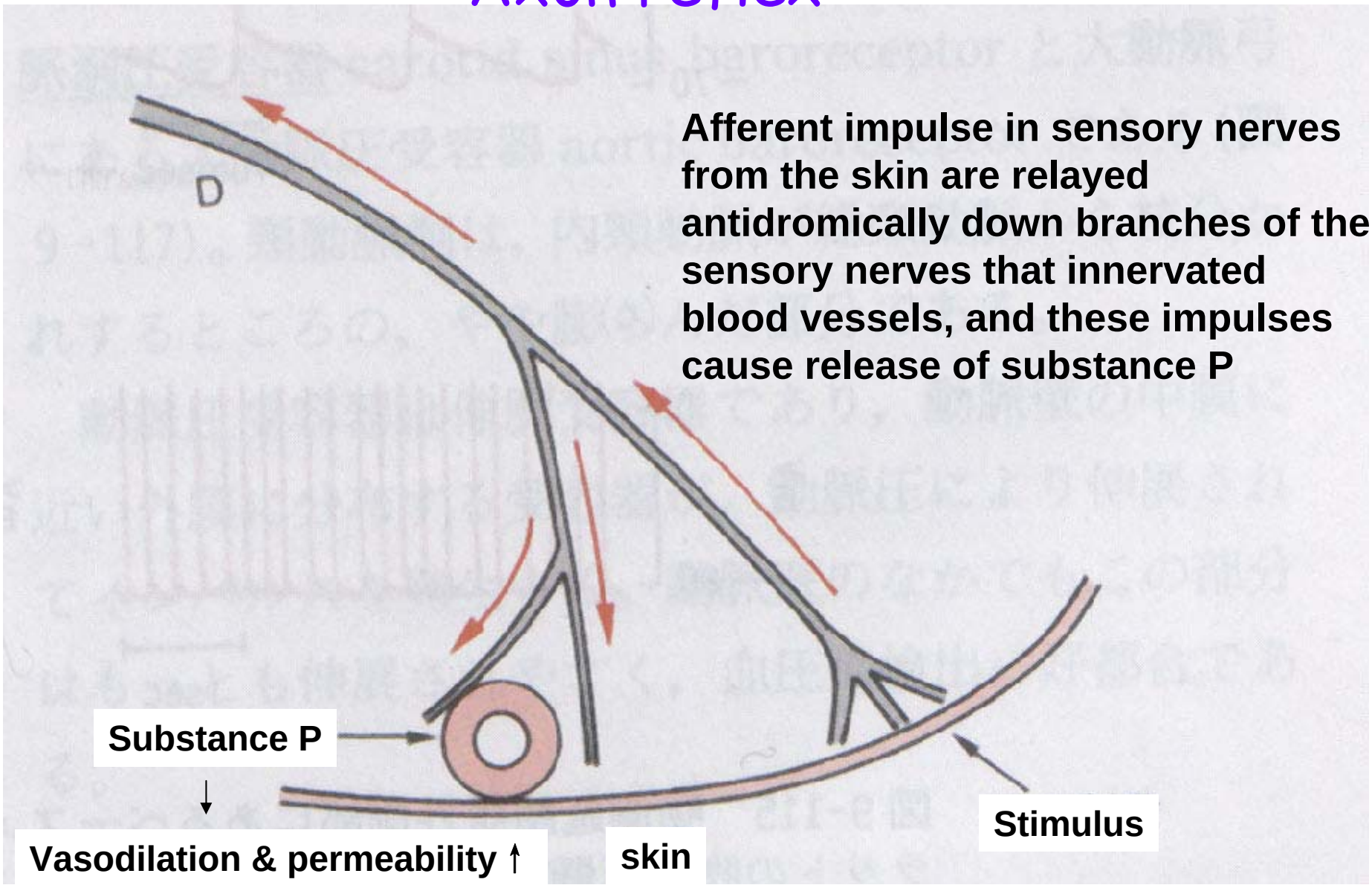

Maximum
sympathetic stimulation
Normal sympathetic
stimulation
Zero sympathetic
stimulation
(Parasympathetic
stimulation)
Cardiac output (L / min)
25
20
15
10
5
0
-4
0
+4
+8
Right atrial pressure (mmHg)

Innervation of the Blood Vessels	Transmitter	Characteristics	Targets
Sympathetic vasoconstrictor fibers	Noradrenergic NE α1>β2 receptors	Tonic activity	to most vascular beds
Sympathetic vasodilator fibers	Cholinergic, Ach M receptor	No tonic activity No participation in BP control. Preganglionic fiber	skeletal muscles, heart,lungs,uterus, kidneys，sweat glands
Parasympathetic vasodilator fibers	Cholinergic, Ach M receptor	No tonic activity No participation in BP control Regulates regional blood flow	blood vessels in salivary & GI gland, liver, external genitalia.

Innervation of the Blood Vessels	Transmitter	Characteristics	Targets
Spinal dorsal vasodilator fiber*	Histamine ATP Substance P	Axon reflex	Skin flush
Nerve fibers containing polypeptide	Vasoactive intestinal peptide	Producing vasodilation Co-existence with acetylcholine	Salivary Glandular Secretion

*Afferent impulse in sensory nerves from the skin are relayed antidromically down branches of the sensory nerves that innervated blood vessels, and these impulses cause release of substance P

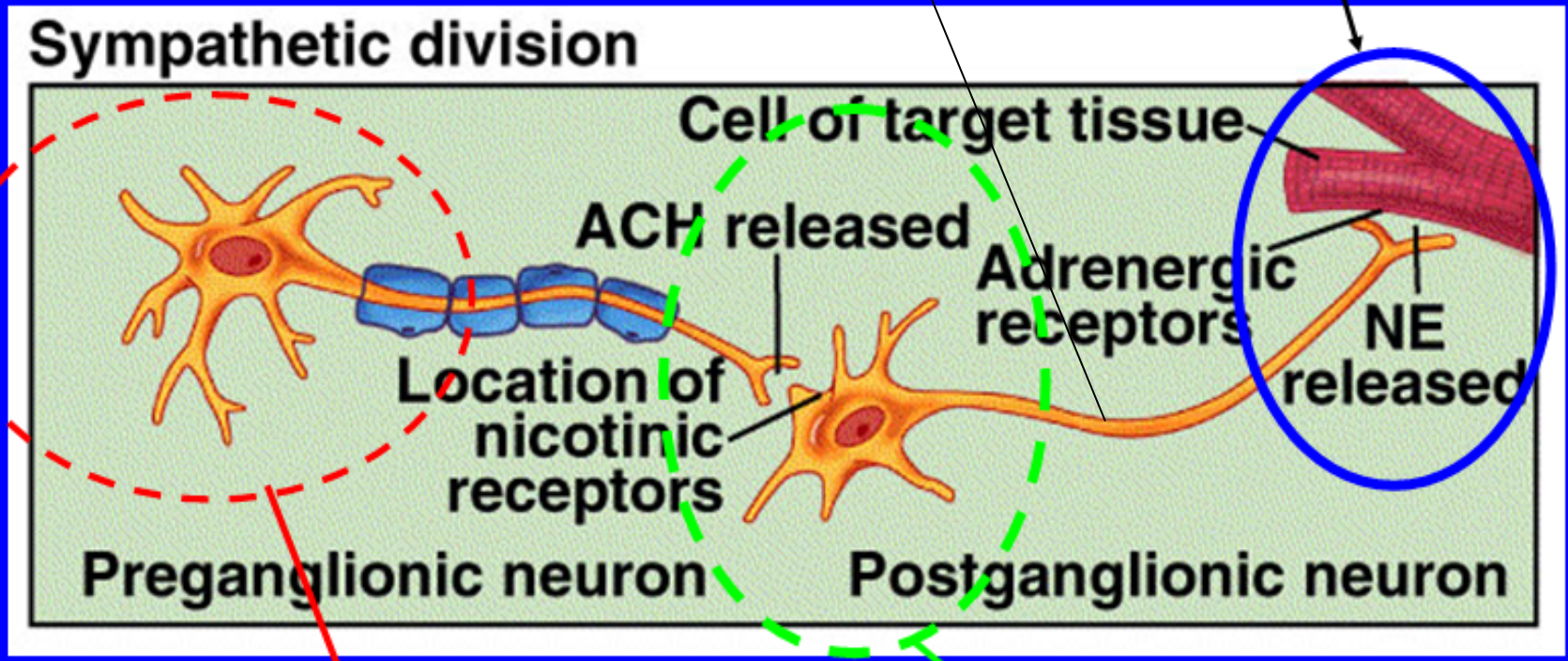
Axon reflex



Afferent impulse in sensory nerves from the skin are relayed antidromically down branches of the sensory nerves that innervated blood vessels, and these impulses cause release of substance P

Sympathetic vasoconstrictor fibers

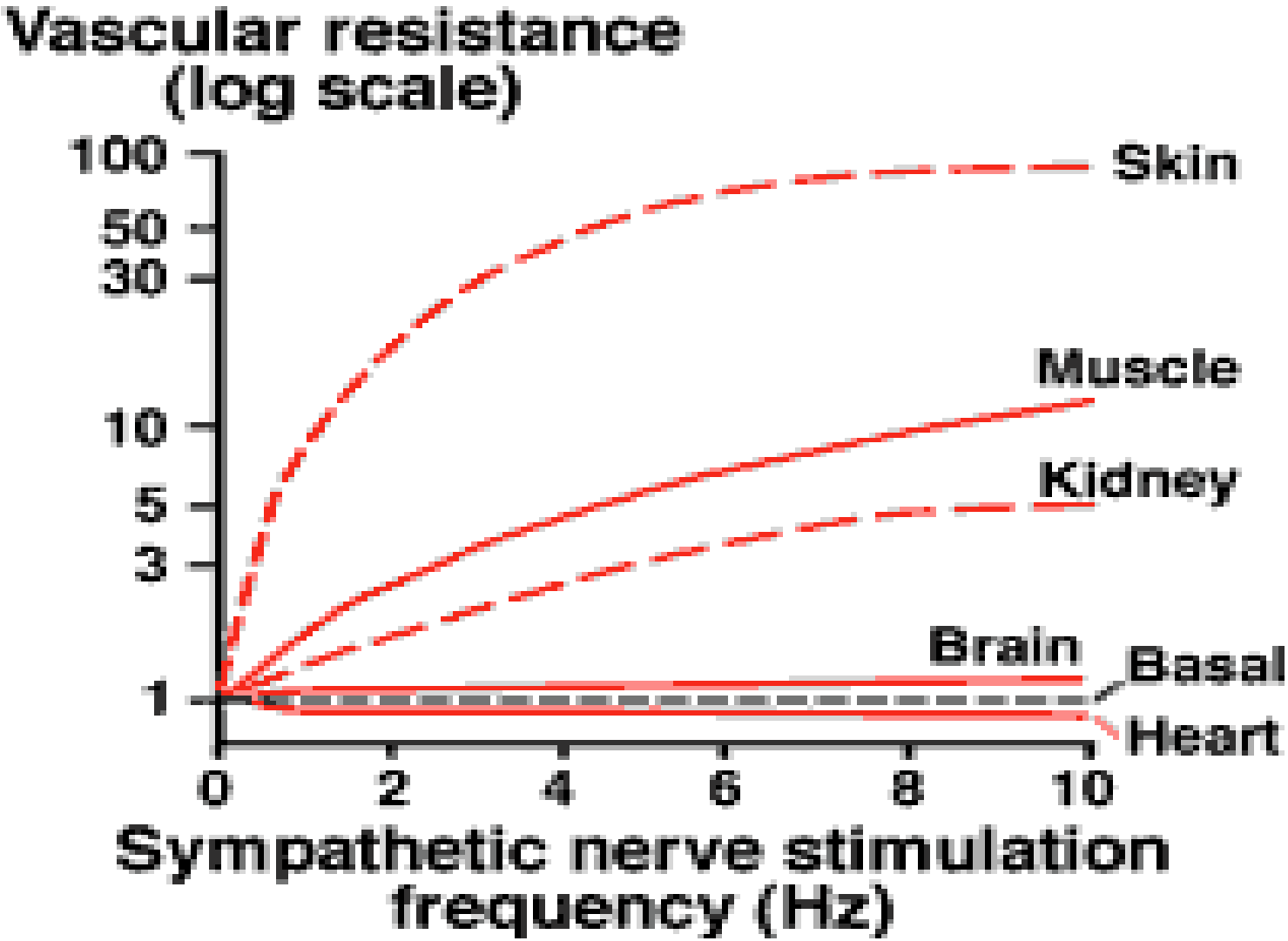
Focus on this synapse



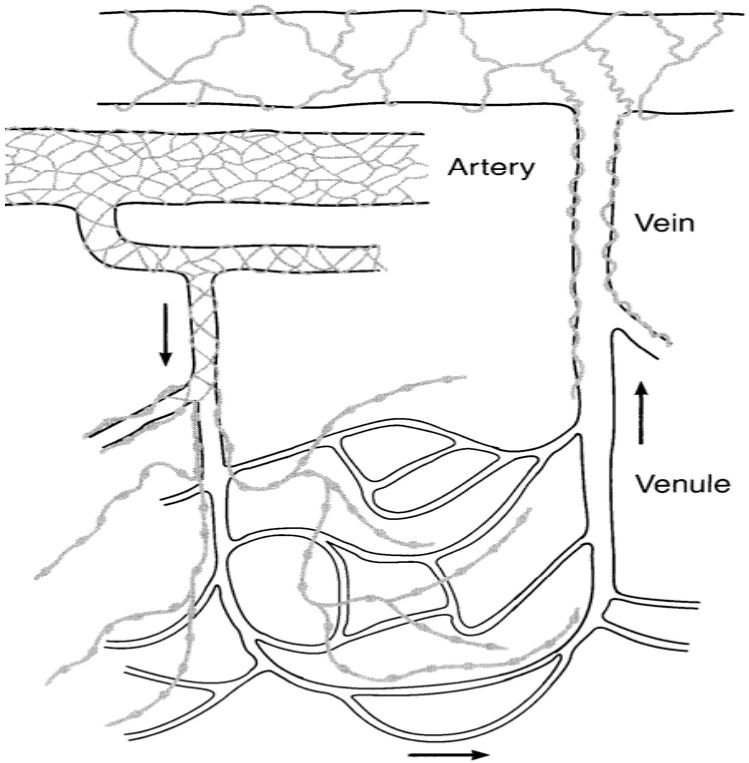
autonomic ganglion

Cell body in spinal cord

Sympathetic vasoconstrictor fibers in various organs



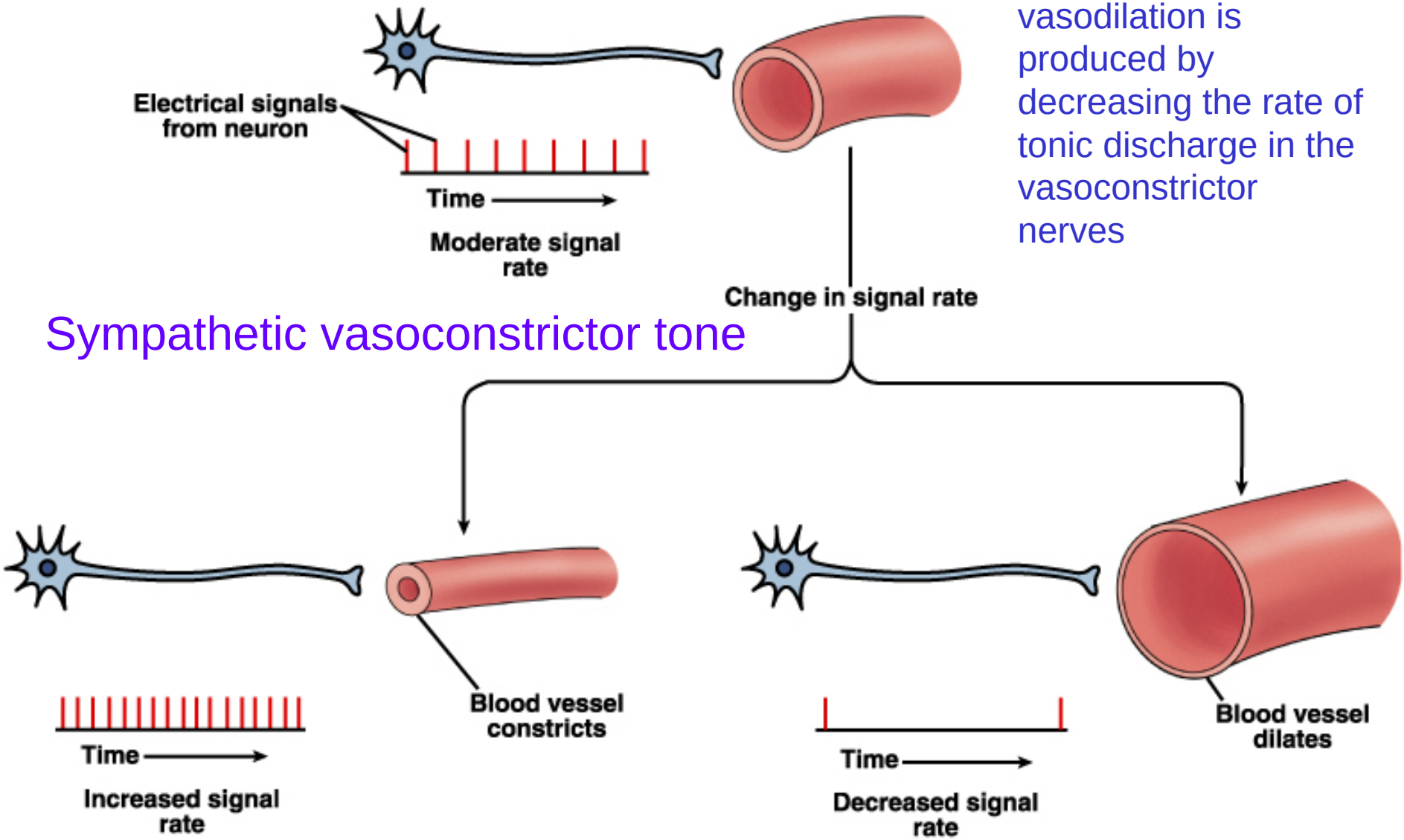
Sympathetic vasoconstrictor fibers in one organ



- The arterioles are most densely innervated
- All blood vessels except capillaries and venules contain smooth muscle, receive sympathetic fibers, regulating tissue blood flow and arterial pressure.
- The fibers to the venous capacitance vessels vary the volume of blood “stored” in the veins.

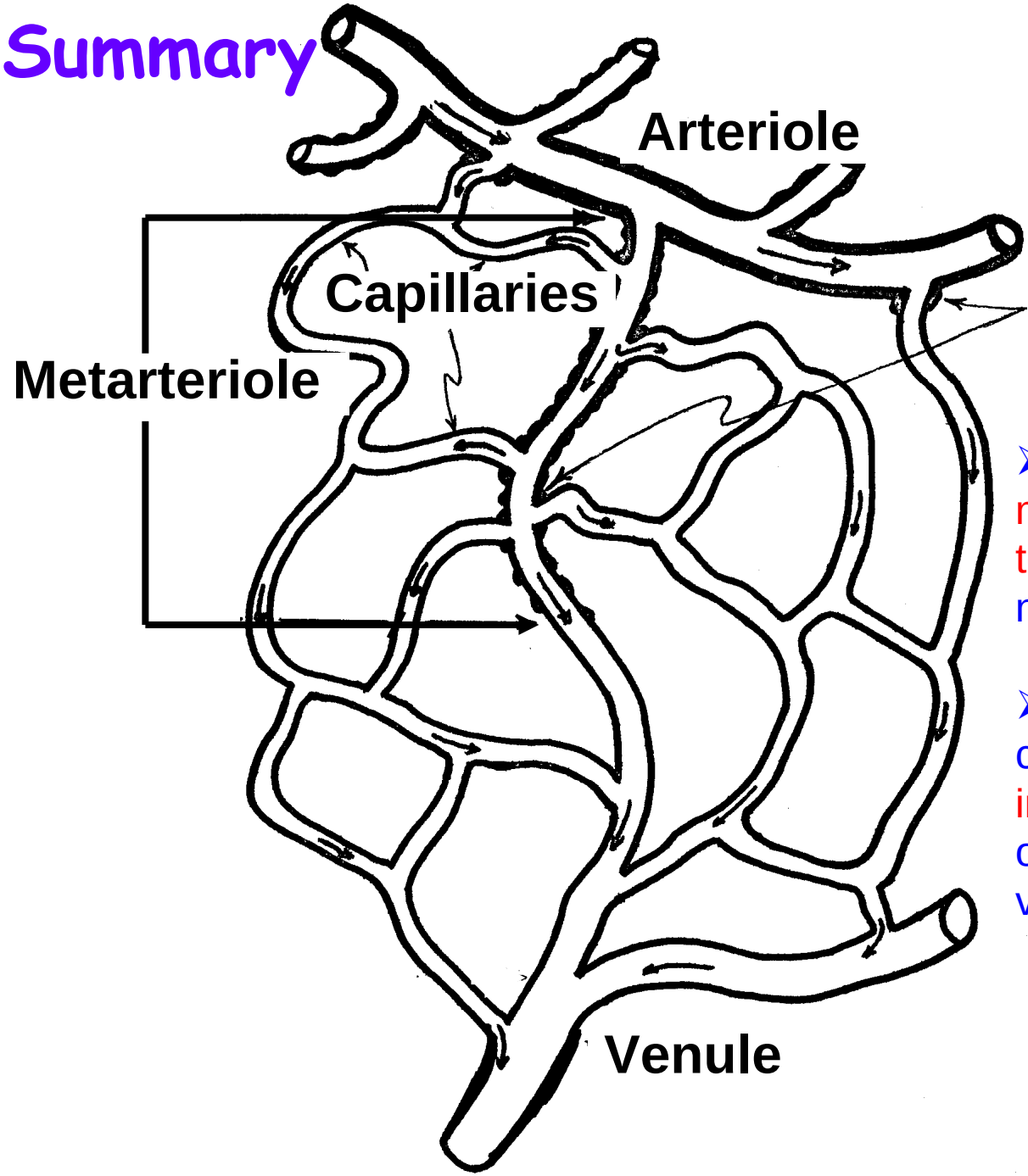
In most tissues, vasodilation is produced by decreasing the rate of tonic discharge in the vasoconstrictor nerves

Sympathetic vasoconstrictor tone



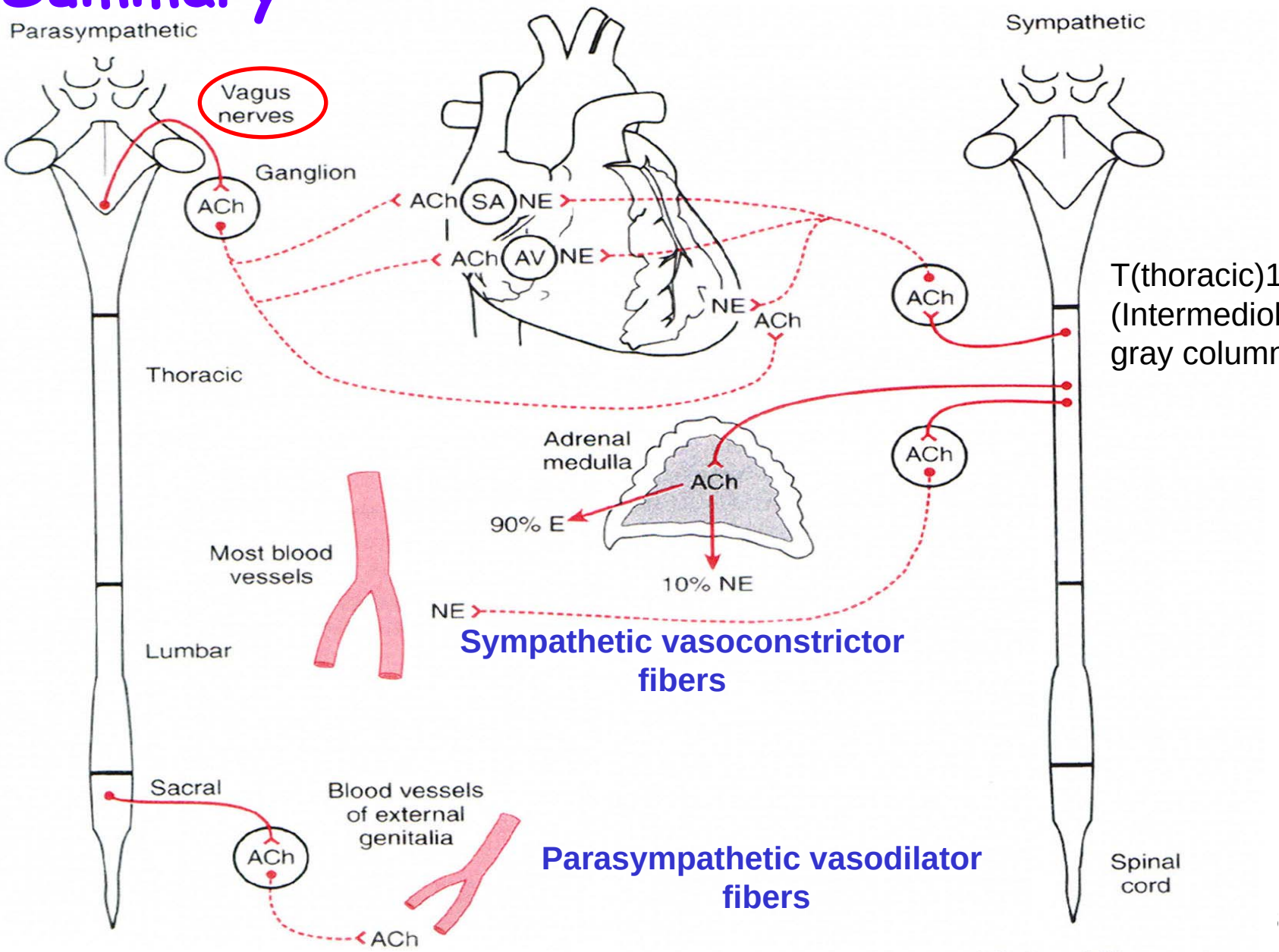
An increase in the storage of blood in the venous reservoirs

Summary



- The arterioles are the major site of the resistance to blood flow, innervated by nor-adrenergic nerve fibers.
- Metarterioles and capillaries are not innervated, respond to local or circulating vasoconstrictor substances.

Summary



T(thoracic)1-T5 (Intermediolateral gray column, IML)

Medullary cardiovascular center

- Pressor area (vasomotor area)

Rostral ventrolateral medulla (RVLM)

- Depressor area

Caudal ventrolateral medulla (CVLM)

- Relay nucleus

the nucleus of tractus solitarius (NTS)

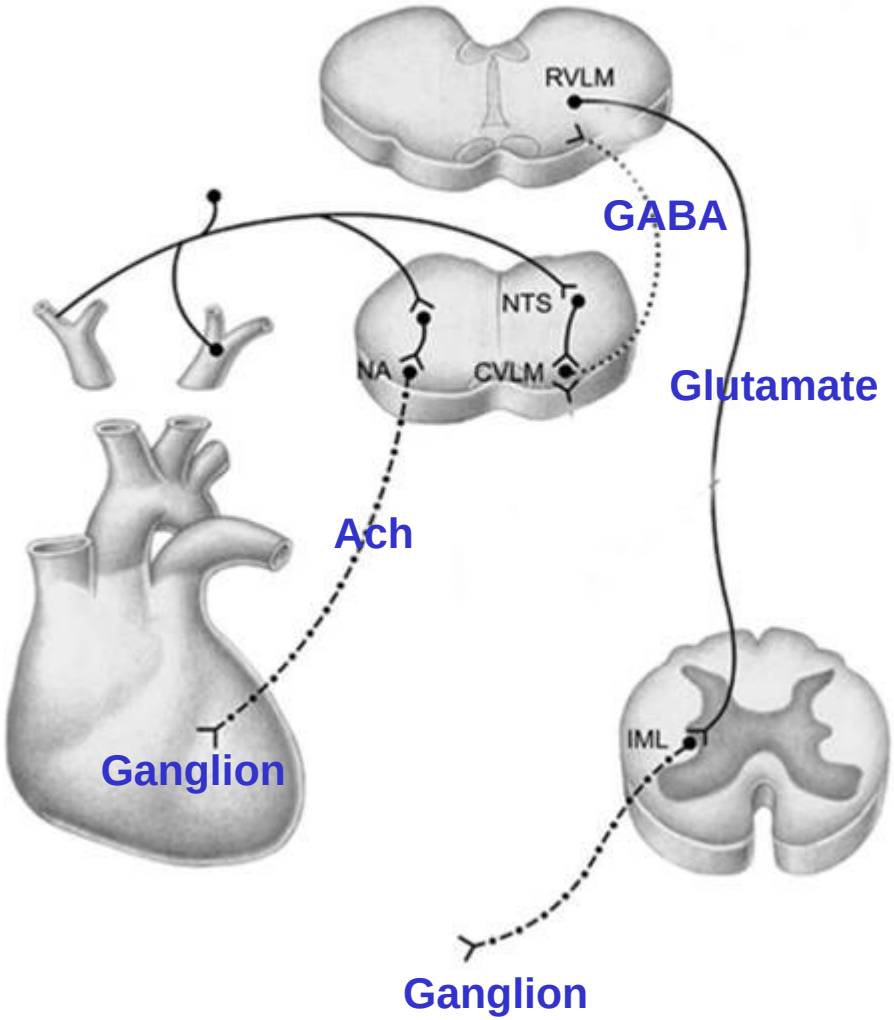
- Cardioinhibitory center

Nucleus ambiguus (NA)/ Dorsal motor nucleus of vagus (DMV)

Medullary Cardiovascular Center

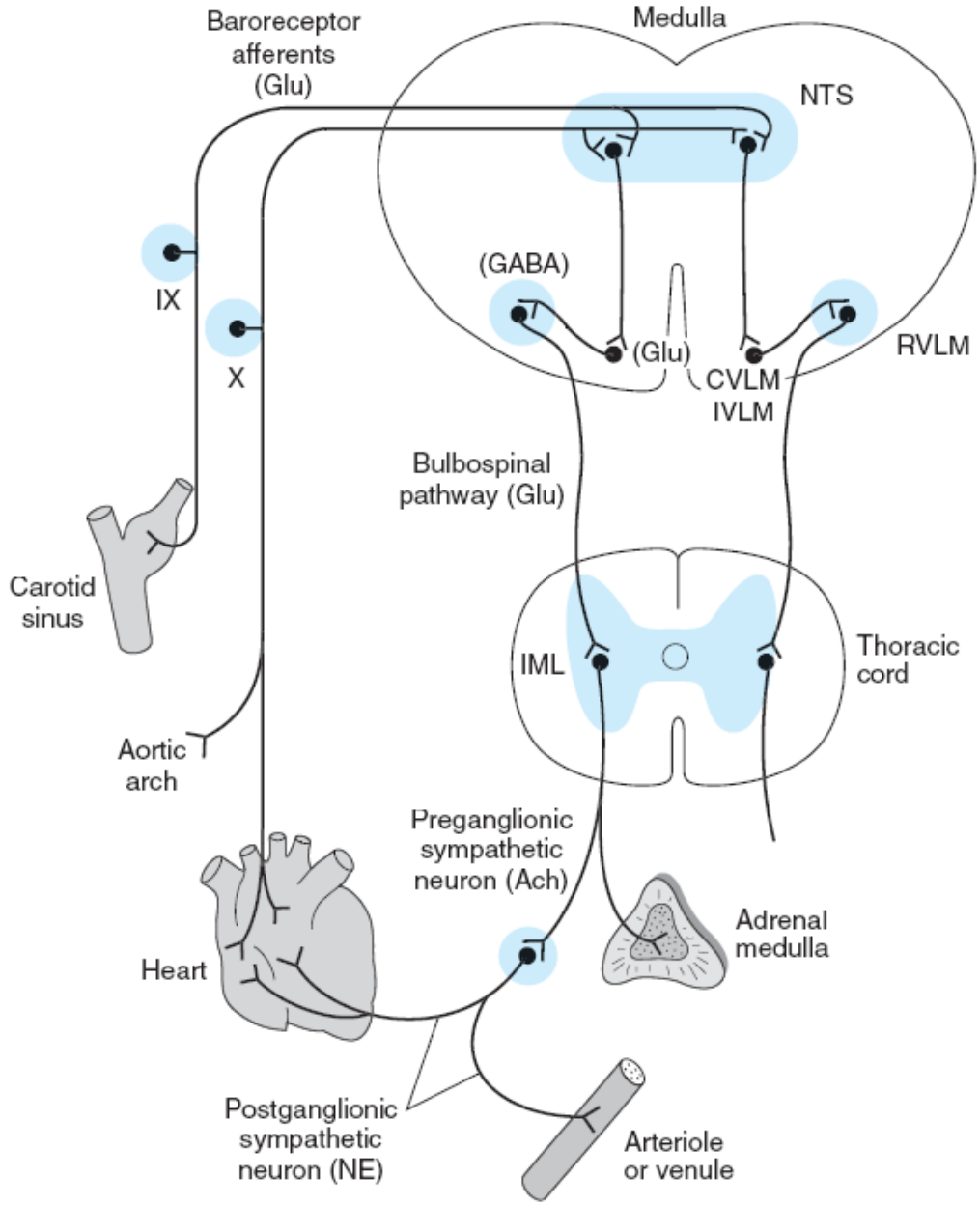
RVLM (center for cardiac sympathetic tone & vaso constrictive tone)	•Inhibited by CVLM	• Sympathetic tonic outputs, projecting to IML(T1-L3) • Promotes vasoconstriction • Important for sympathetic activation in response to **hypotension**
CVLM	•Excited by NTS	Inhibit RVLM, no descending fibers to IML
NA/DMV (center for Cardiac vagal tone)	•Excited by NTS	NA/DMV →vagal tone↑ →bradycardia
NTS	where the afferents end	•Project to CVLM •Project to NA/DMV

Neurotransmitters



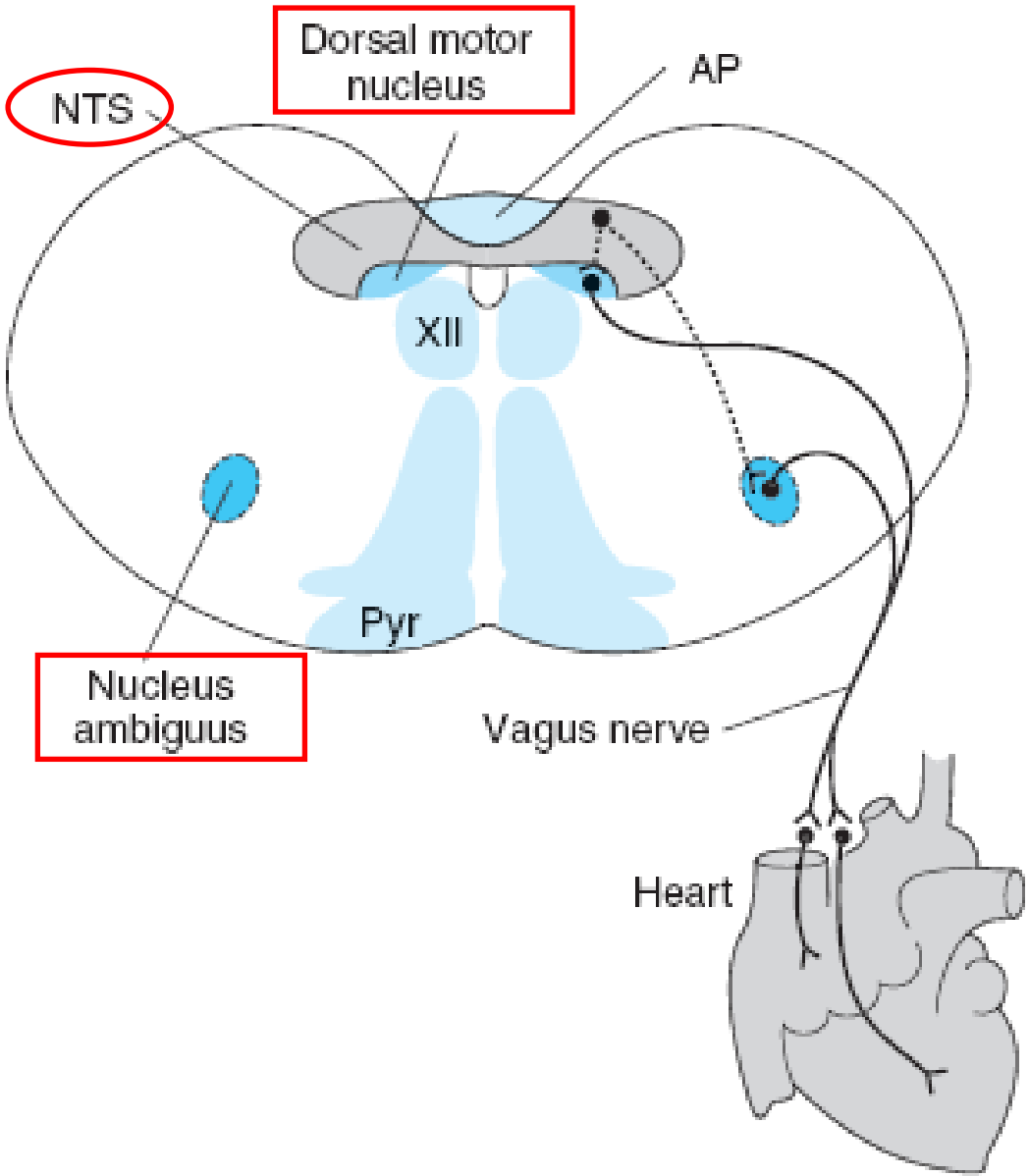
- Continuous line = Glutamatergic projection
- Dotted line GABAergic projection
- dash-dot line = cholinergic projections

Basal pathway involved in the medullary control of cardiac activities

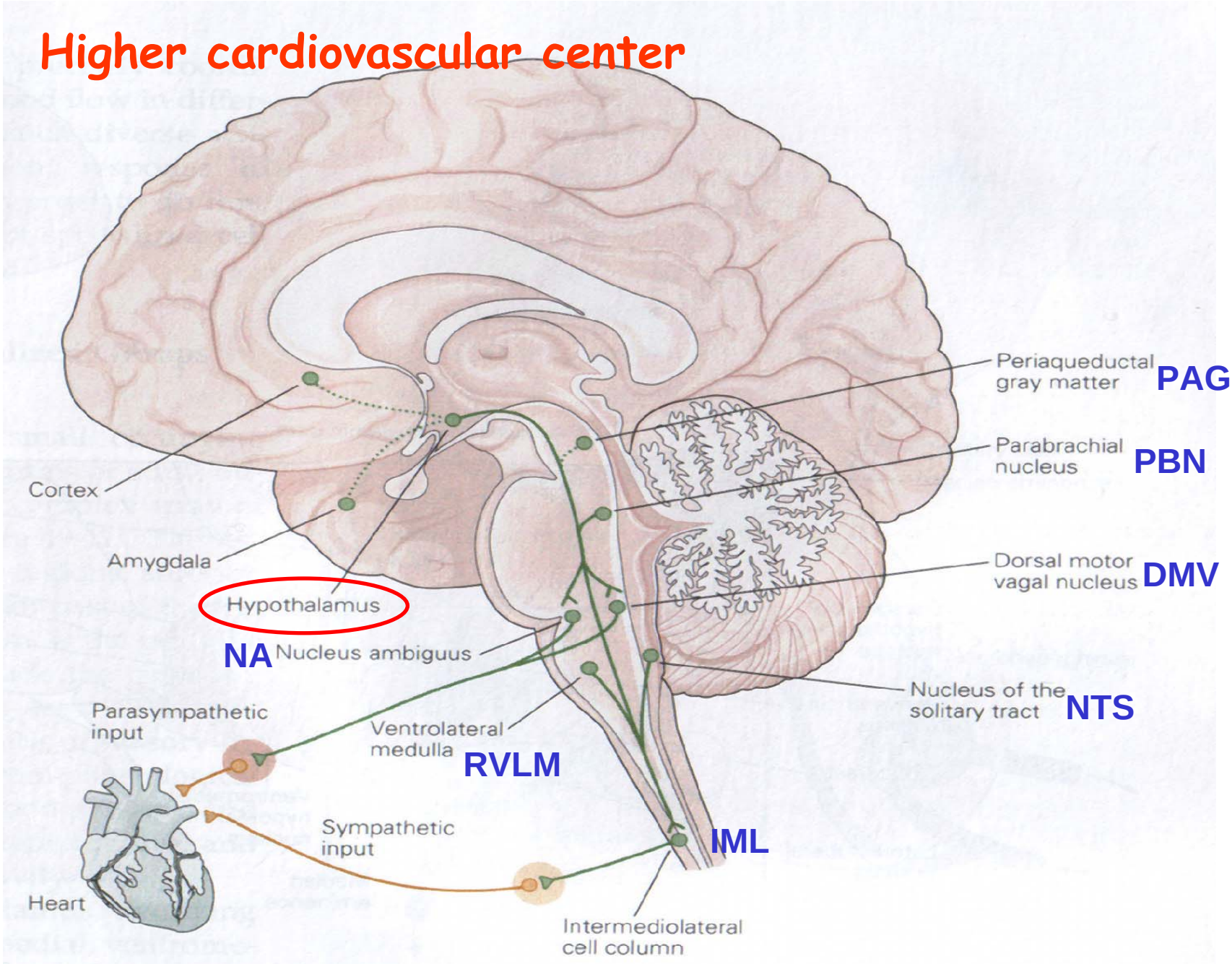


Intermediolateral gray column

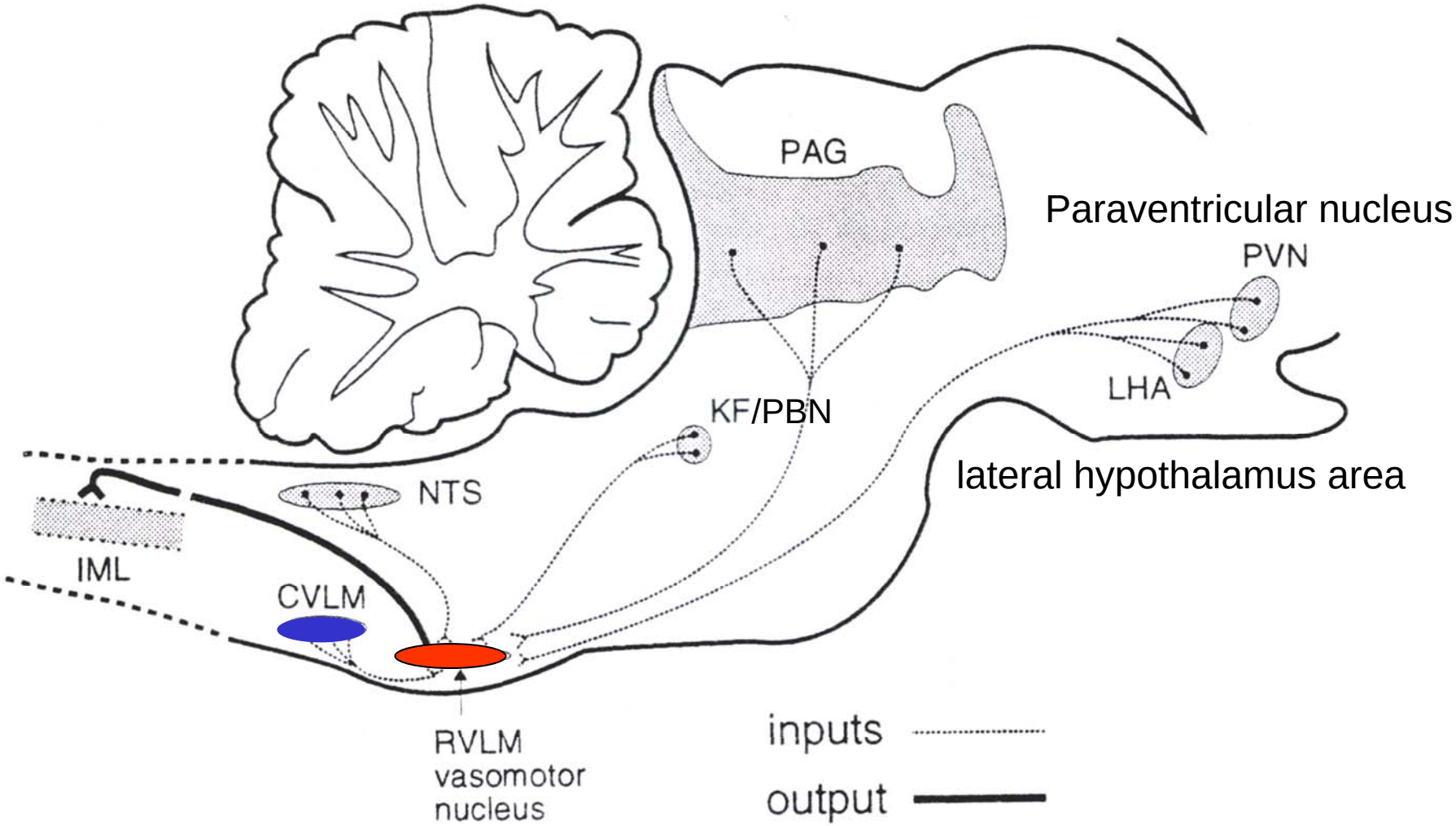
Basal pathway involved in the medullary control of cardiac activities



Higher cardiovascular center



There are descending tracts to the vasomotor area from the cerebral cortex (particularly the limbic cortex) that relay in the hypothalamus. These fibers are responsible for the blood pressure rise and tachycardia produced by **emotions**.
The connections between the hypothalamus and the vasomotor area are **reciprocal**.



Cardiovascular reflex

- **Baroreceptor reflex (depressor reflex)**

Carotid sinus & aortic arch

- **Chemoreceptor reflex**

Carotid body & aortic body

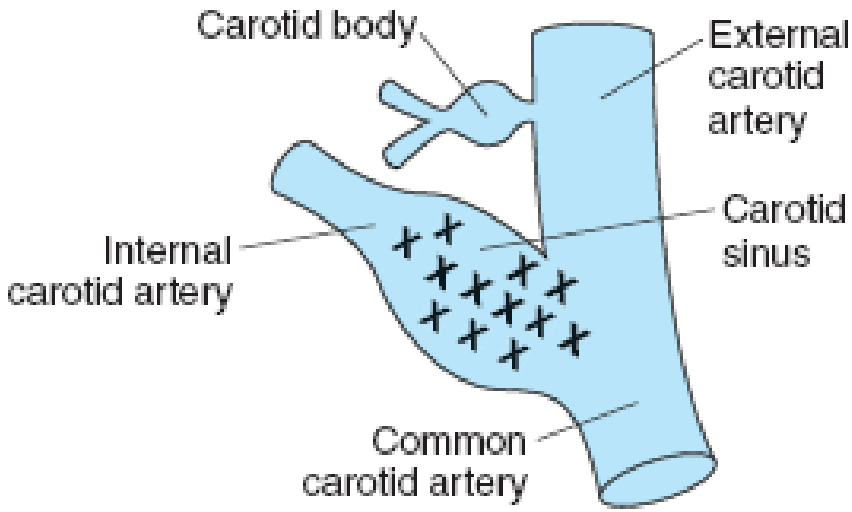
- **Cardiopulmonary receptor reflex**

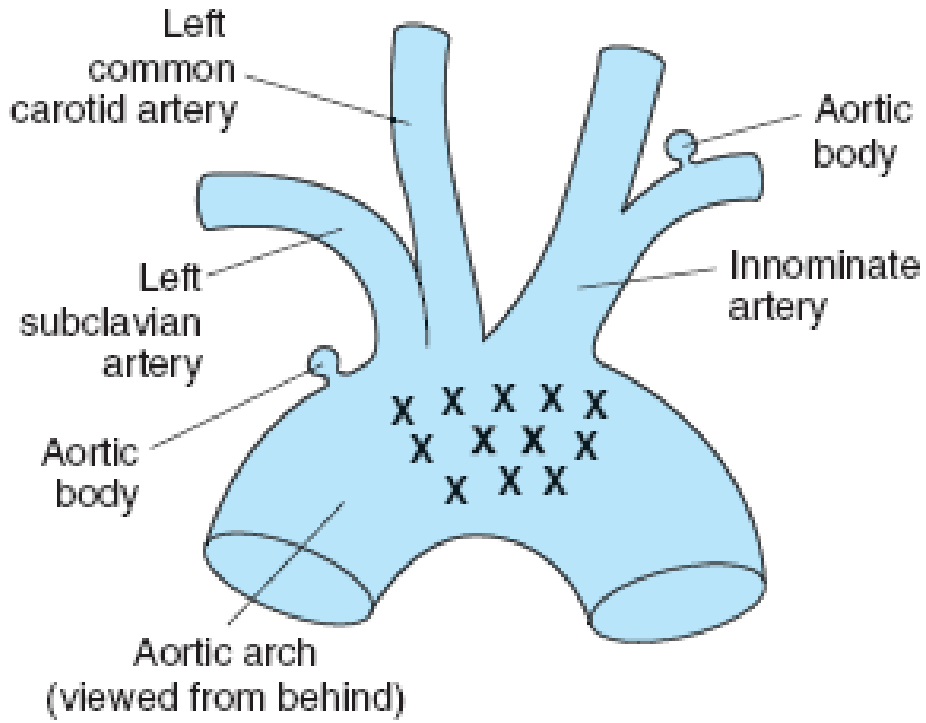
Baroreceptors Reflex
Depressor reflex

Baro-Rs location

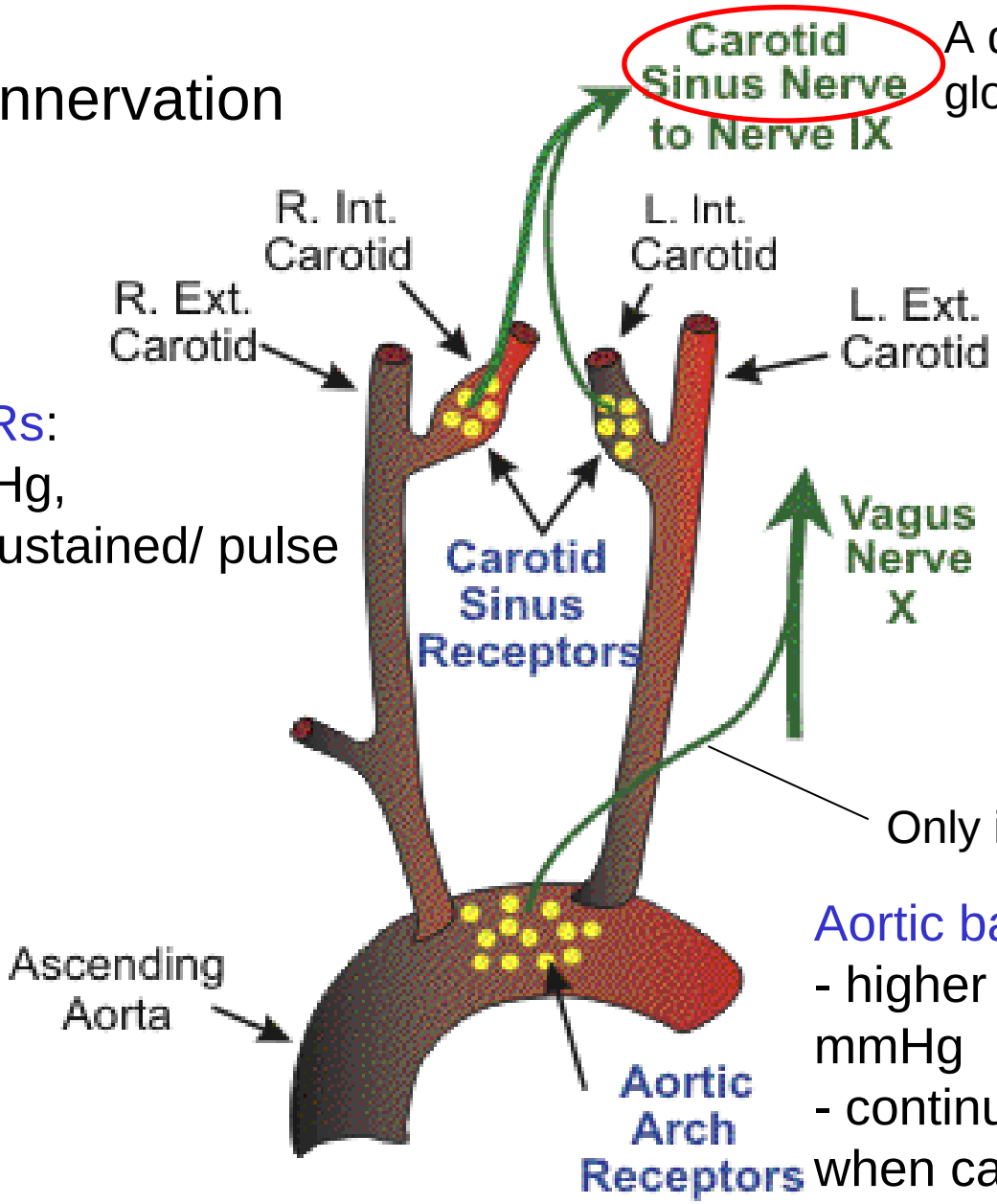
In both carotid sinus and aortic arch:

- branched-coiled bare ends located in the adventitia of the vessels.
- Stretch-sensitive.





Baro-Rs innervation



A distinct branch of glossopharyngeal N

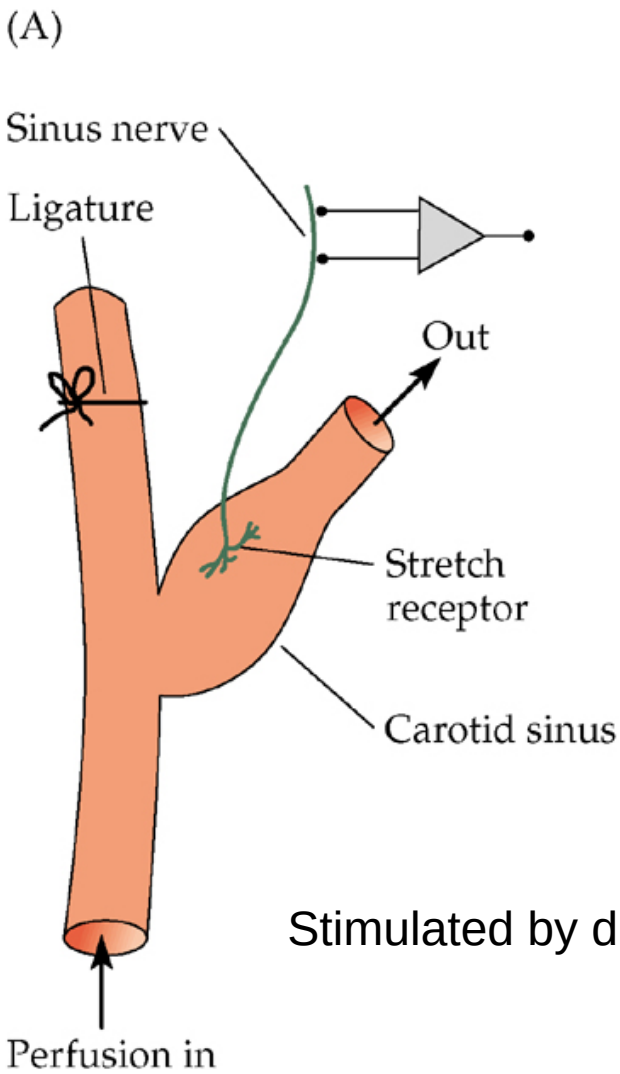
Buffer nerves

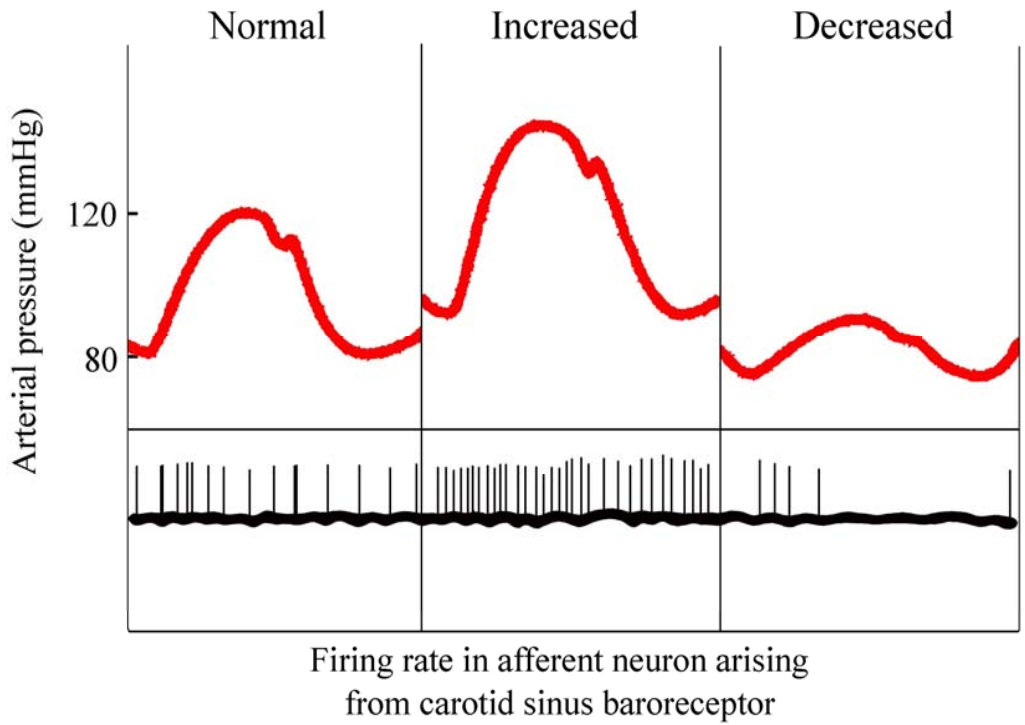
Carotid baro-Rs:
- 50-200 mm Hg,
- respond to sustained/ pulse pressure.

Only in rabbit

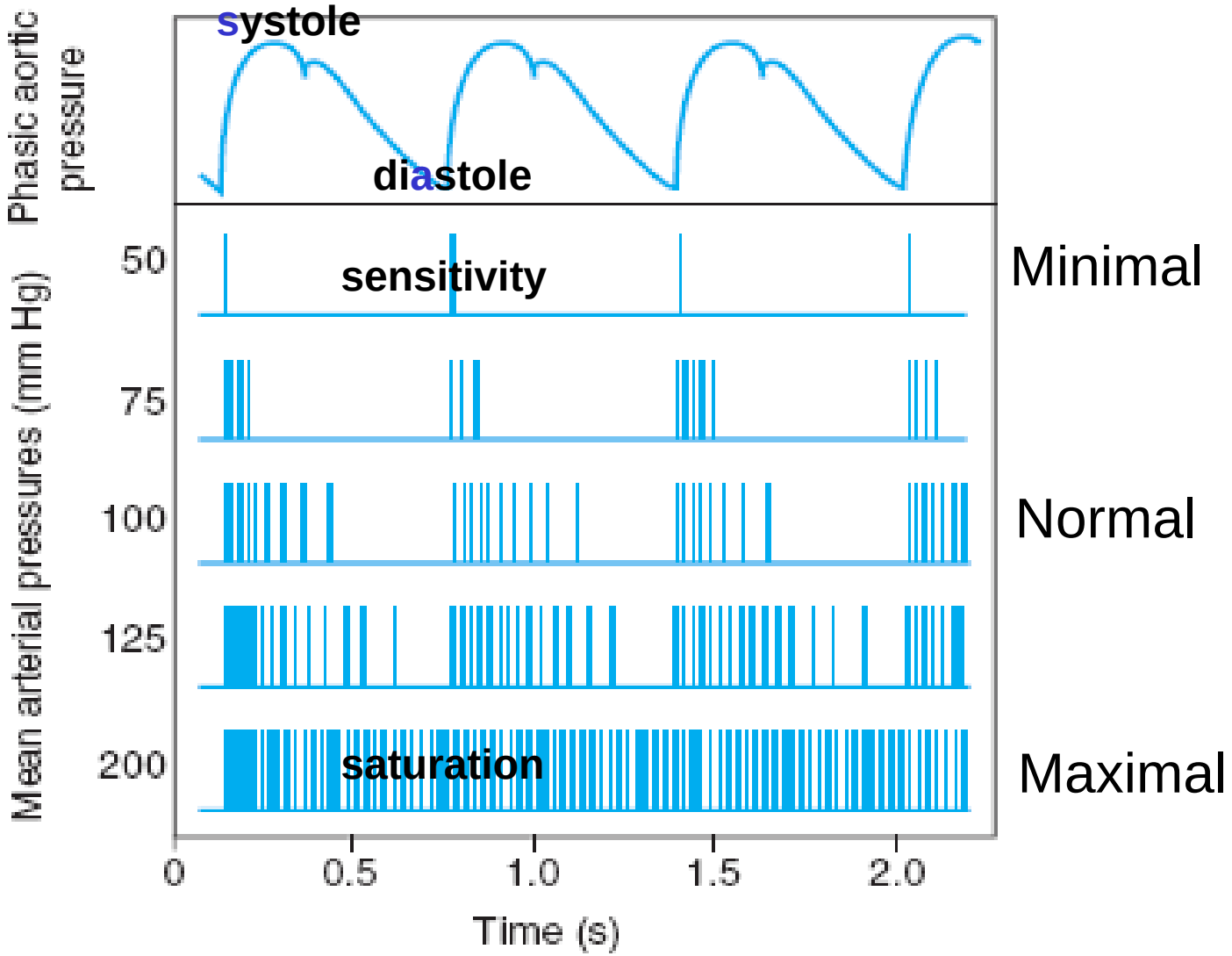
Aortic baro-Rs:
- higher threshold,-110 mmHg
- continues responding to AP when carotid-Rs has already saturated

Baroreceptors are **stretch** but not pressure receptors!



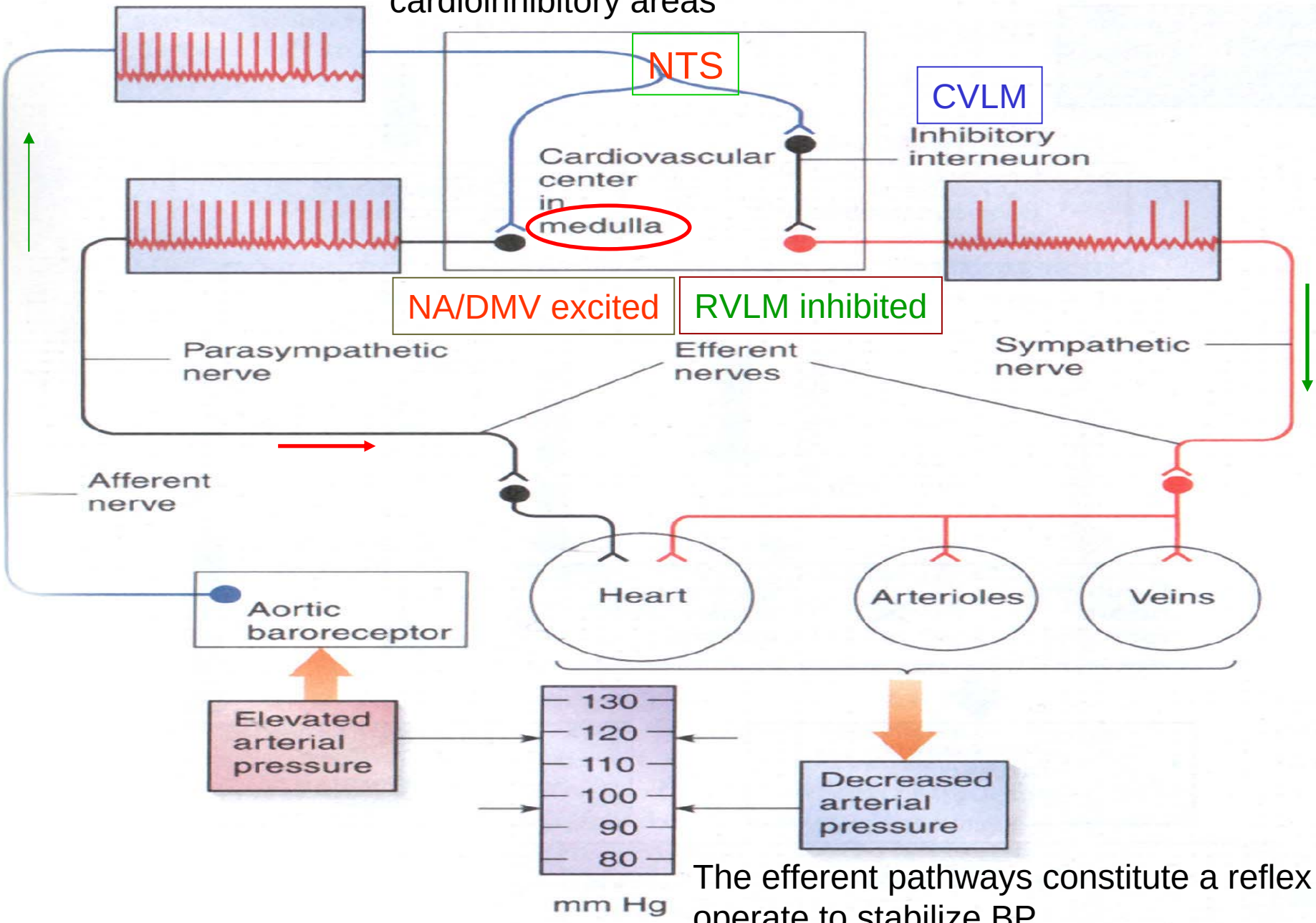


Stimulated by distension of the structures in which they are located



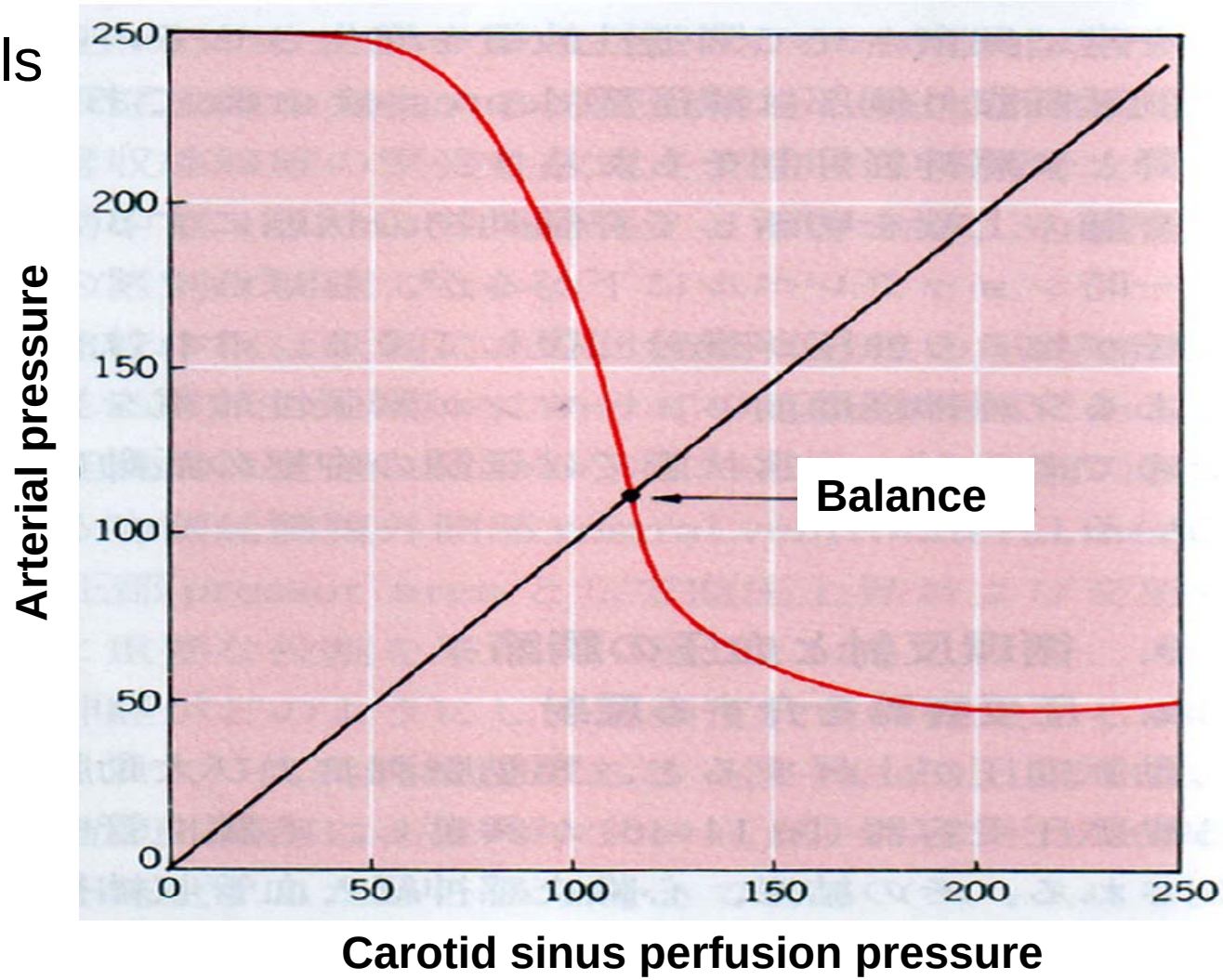
Discharges (vertical lines) in a single afferent nerve fiber from the carotid sinus at various arterial pressures.

Afferent connections up to the vasomotor and cardioinhibitory areas

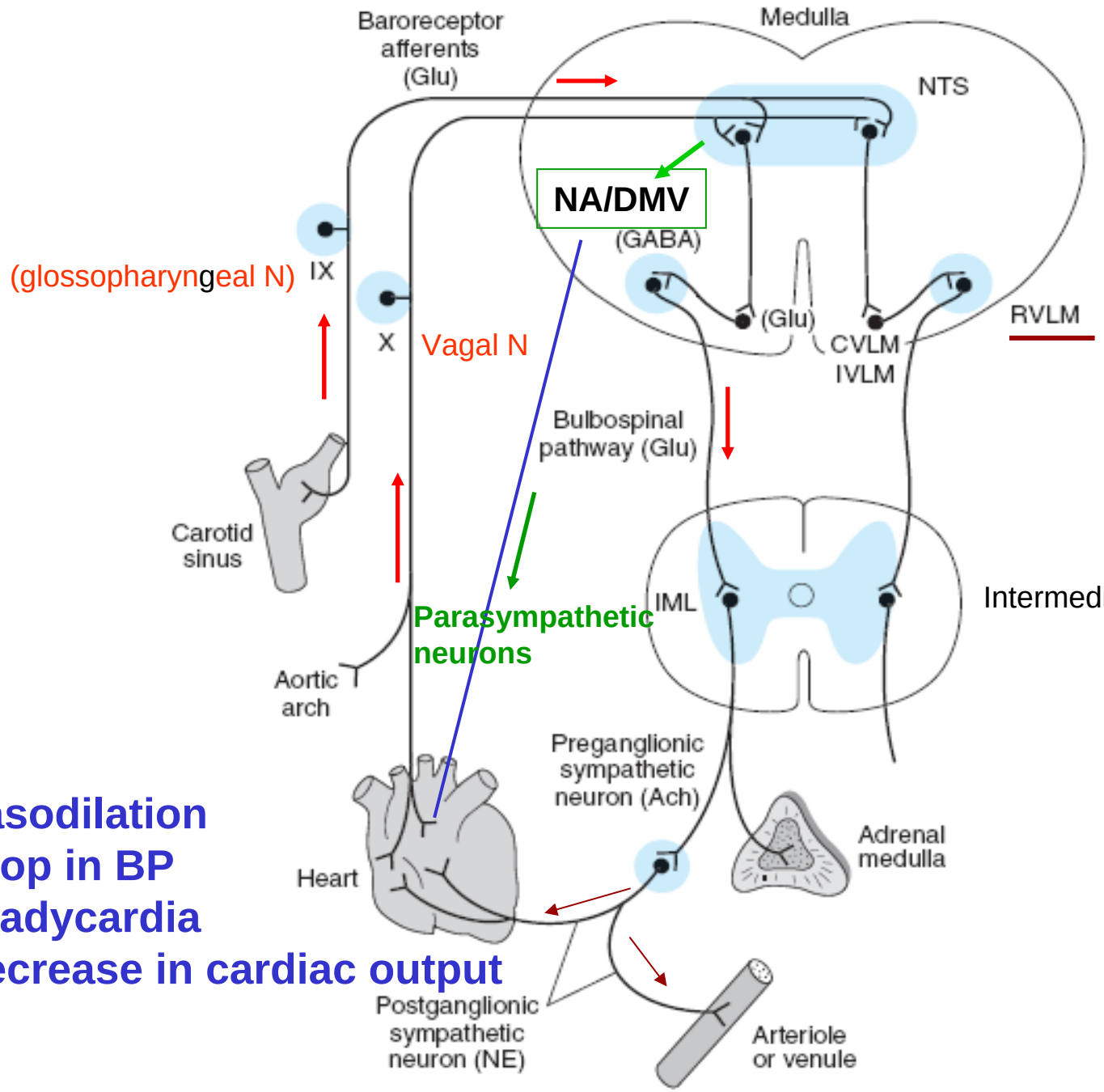


The efferent pathways constitute a reflex operate to stabilize BP

Animal models



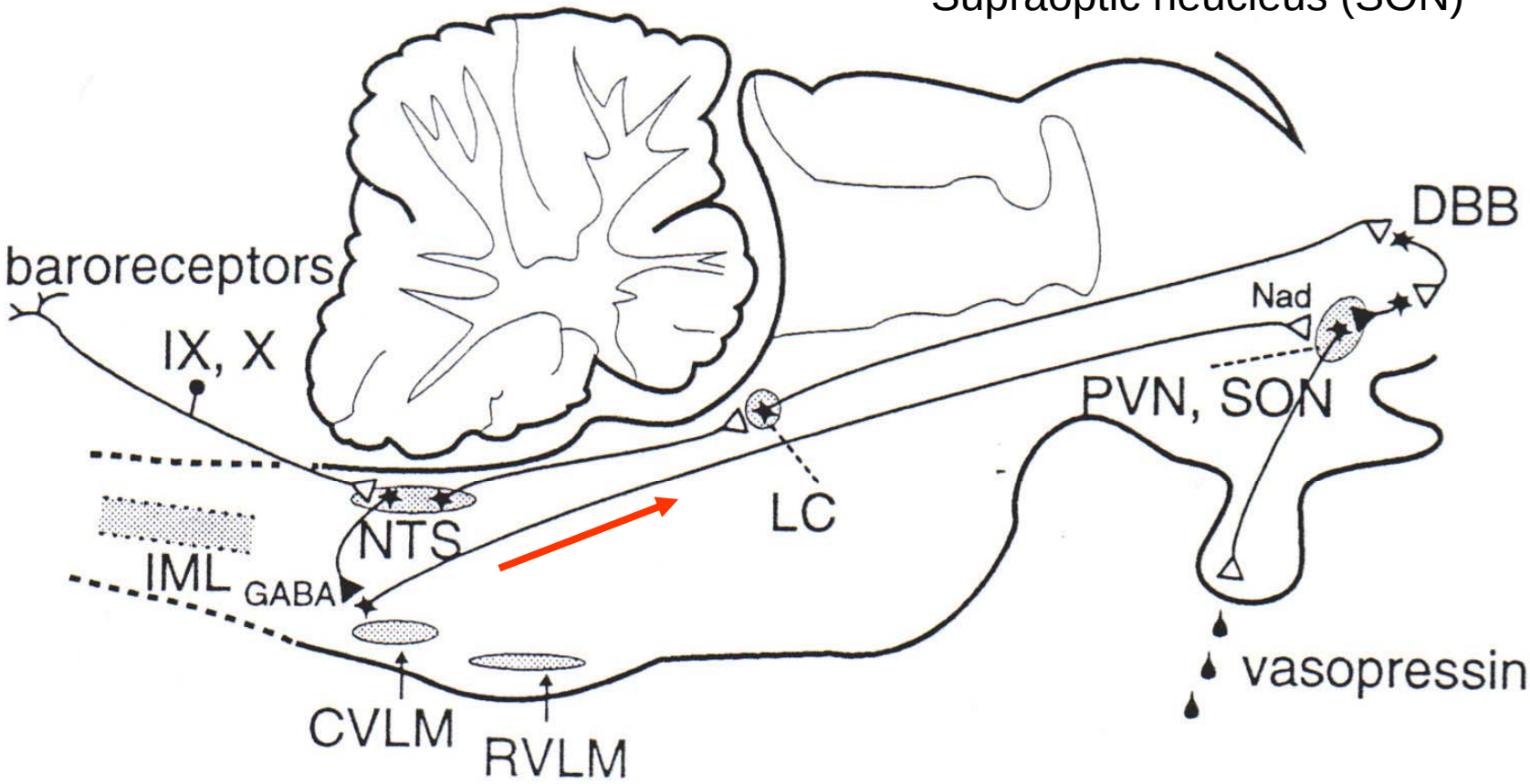
- When one carotid sinus is isolated and perfused, the relation between the perfusion pressure and the arterial pressure is essentially linear at perfusion pressures of 80–120 mm Hg
- There is no discharge and no regulation with the perfusion pressure is below 50 mm Hg.
- At perfusion pressures above 200 mm Hg, there is no further increase in response



- **Vasodilation**
- **Drop in BP**
- **Bradycardia**
- **Decrease in cardiac output**

Paraventricular nucleus (PVN)

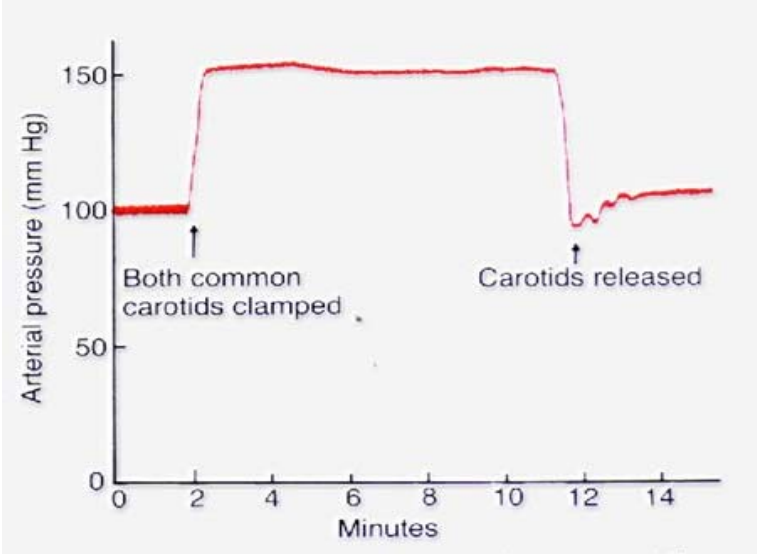
Supraoptic neucleus (SON)



Blood pressure ↑ → Baro-R → CVLM → PVN VP ↓ → Urine formation ↑

inhibitory inputs

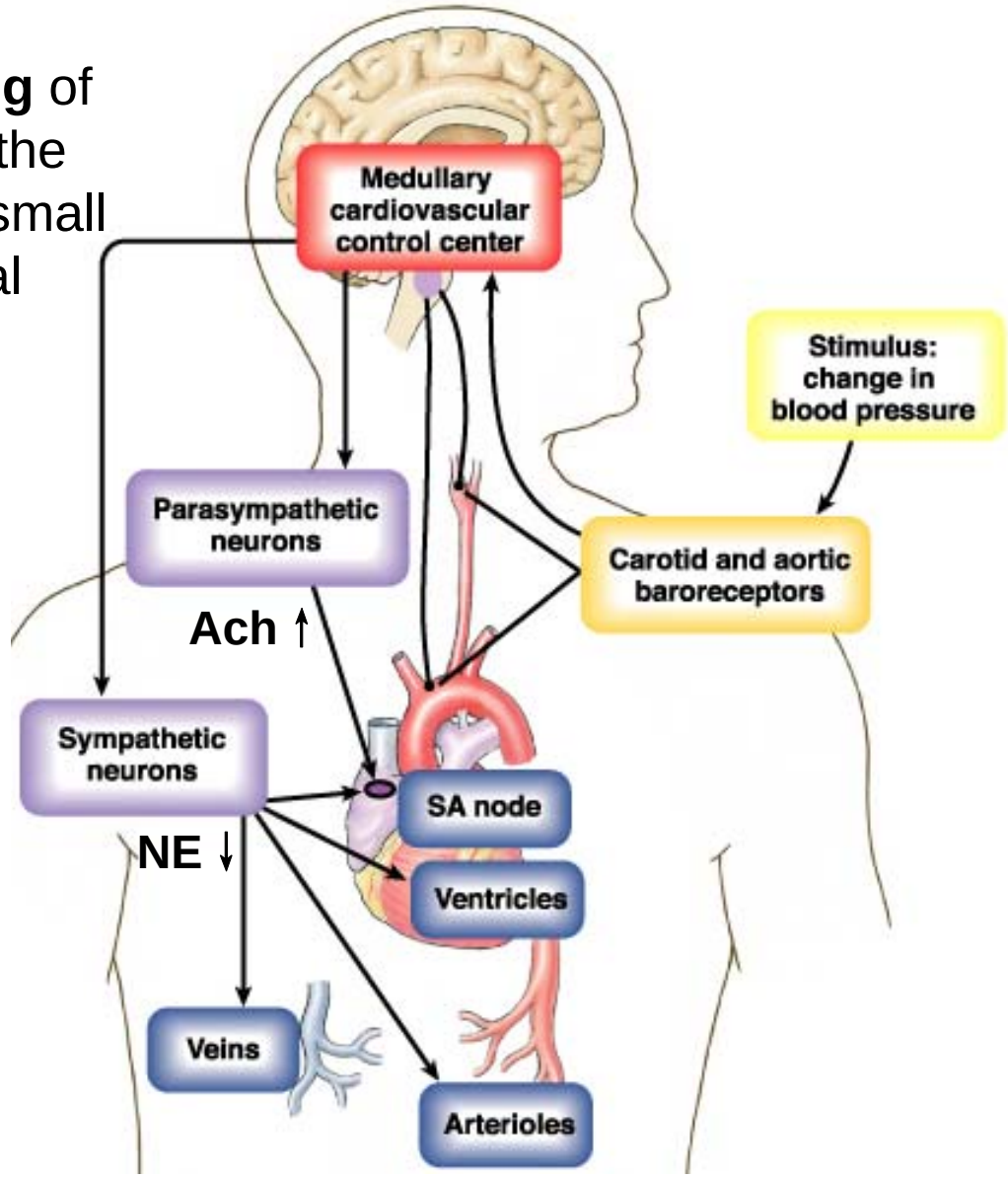
excitatory inputs

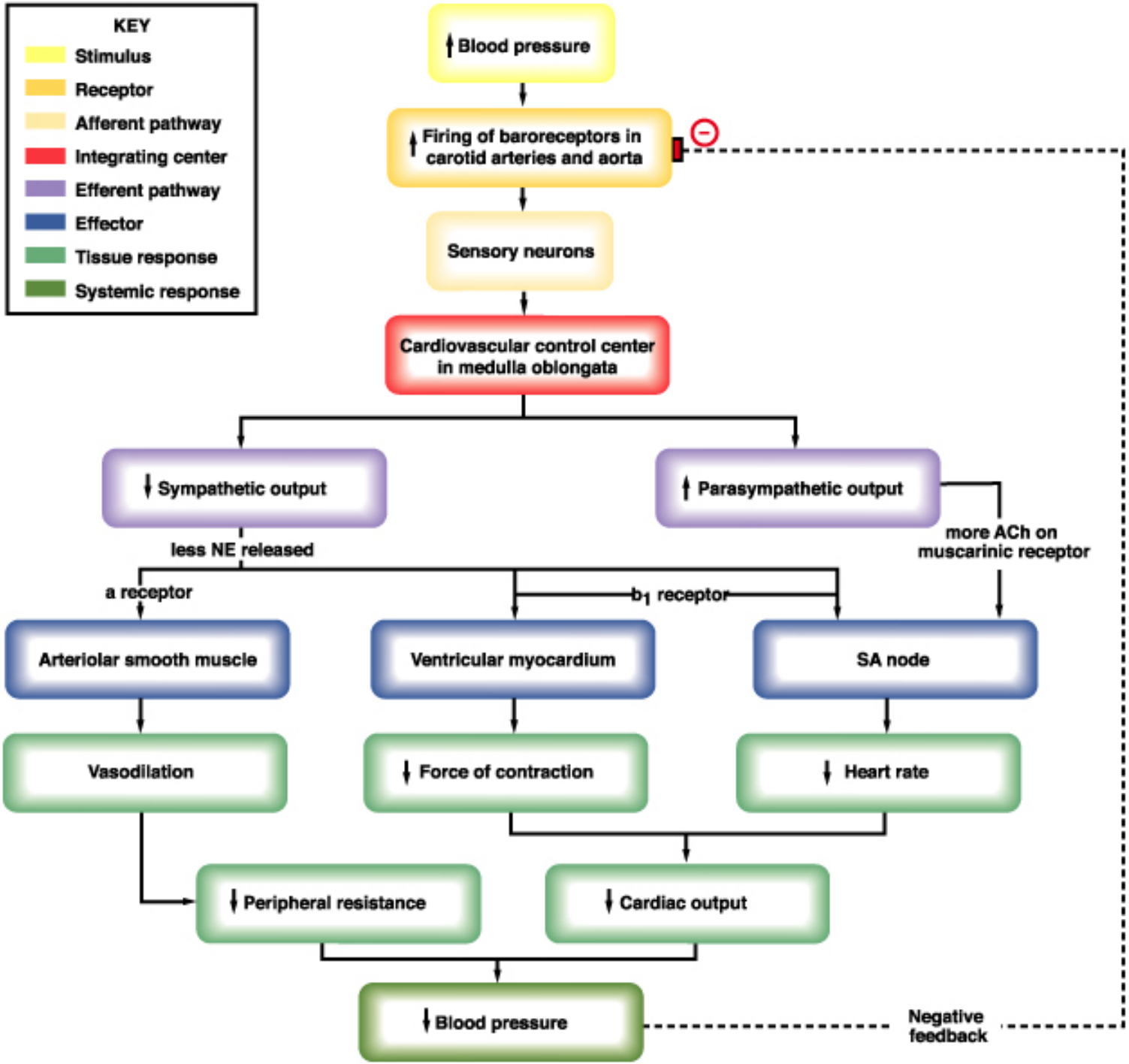


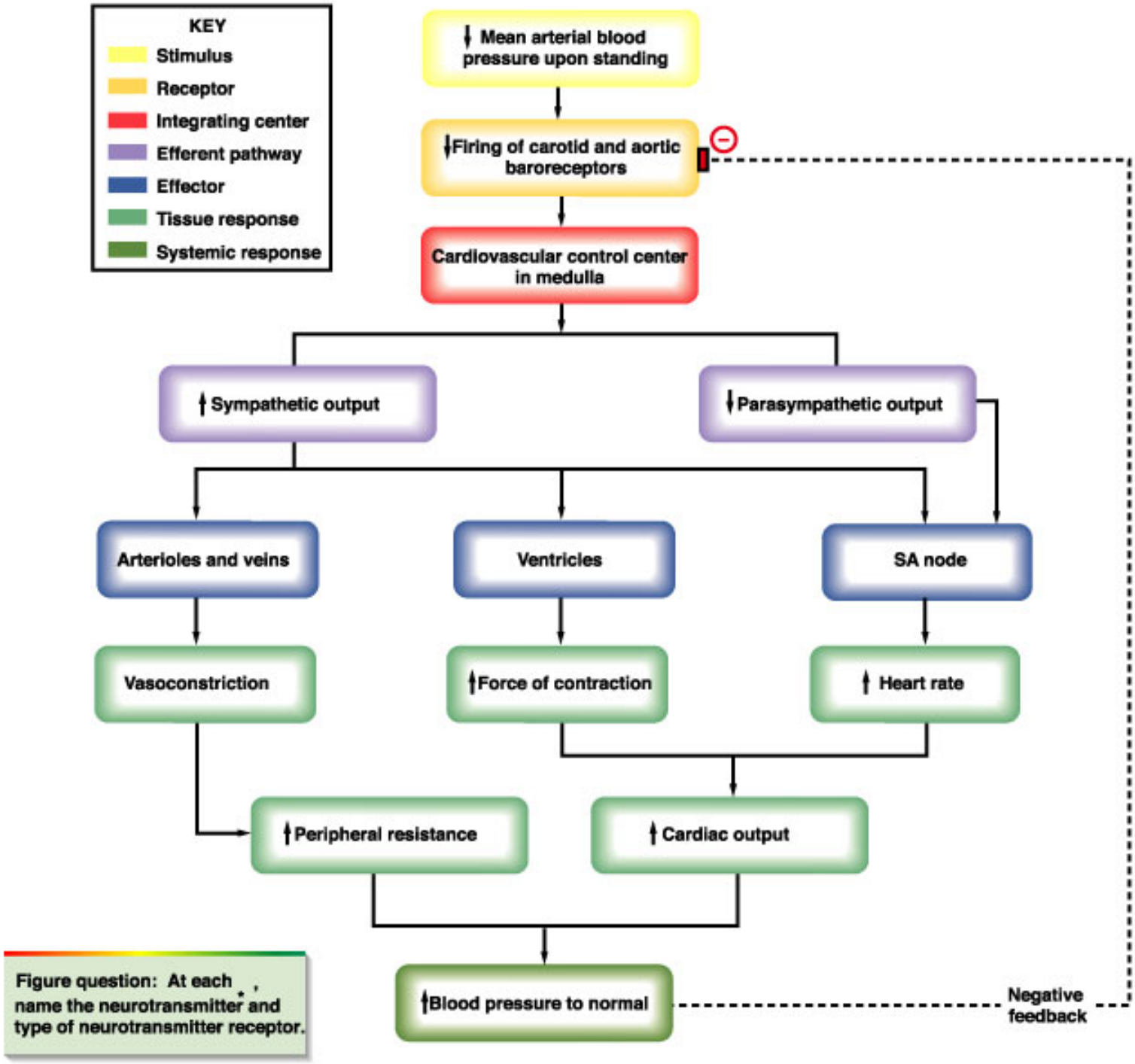
- Bilateral clamping of the carotid arteries proximal to the carotid sinuses elevates the BP because the procedure lowers the pressure in the sinuses.
- Cutting the carotid sinus nerves on each side has the same effect.
- The pressor response following these two procedures is moderate, because the aortic baroreceptors are still functioning normally, and they buffer the rise.
- If baroreceptor afferents in the vagi are also interrupted, BP rises to 300/200 mm Hg or higher and is unstable.
- Bilateral lesions of the NTS, cause lethal **neurogenic hypertension.**

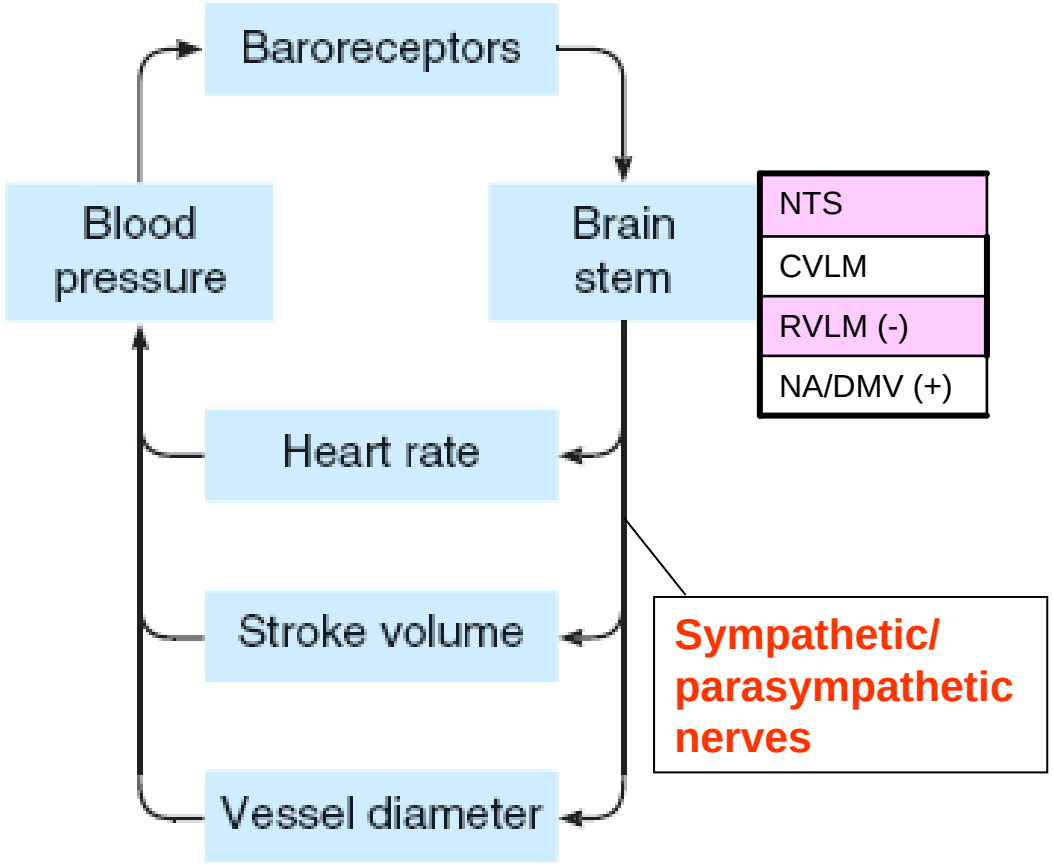
Significance

At the **very beginning** of systemic circulation, the receptors sense the small fluctuations of arterial pressure.



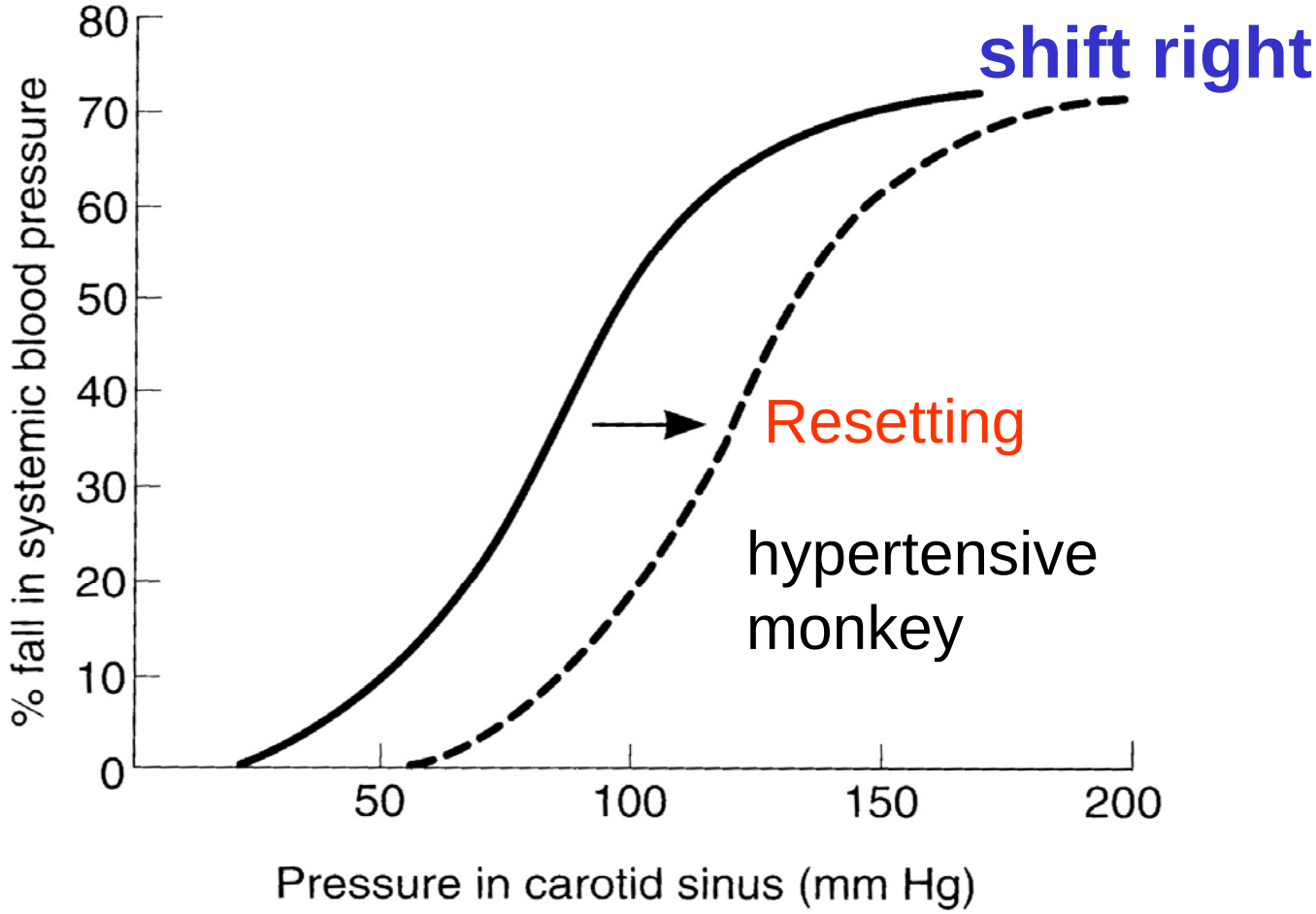

KEY
Stimulus
Receptor
Afferent pathway
Integrating center
Efferent pathway
Effector
Tissue response
Systemic response
Blood pressure
Firing of baroreceptors in carotid arteries and aorta
Sensory neurons
Cardiovascular control center in medulla oblongata
Sympathetic output
Parasympathetic output
less NE released
more ACh on muscarinic receptor
a receptor
b1 receptor
Arteriolar smooth muscle
Ventricular myocardium
SA node
Vasodilation
Force of contraction
Heart rate
Peripheral resistance
Cardiac output
Blood pressure
Negative feedback


KEY
Stimulus
Receptor
Integrating center
Efferent pathway
Effector
Tissue response
Systemic response
Mean arterial blood pressure upon standing
Firing of carotid and aortic baroreceptors
Cardiovascular control center in medulla
Sympathetic output
Parasympathetic output
Arterioles and veins
Ventricles
SA node
Vasoconstriction
Force of contraction
Heart rate
Peripheral resistance
Cardiac output
Blood pressure to normal
Negative feedback
Figure question: At each , name the neurotransmitter and type of neurotransmitter receptor.



- Any drop in systemic arterial pressure decreases the inhibitory discharge in the buffer nerves, and there is a compensatory rise in blood pressure and cardiac output.

- Any rise in pressure increases the inhibitory discharge in the buffer nerves, produces dilation of the arterioles and decreases cardiac output until the blood pressure returns to its previous normal level.


shift right
Resetting
hypertensive
monkey
% fall in systemic blood pressure
0
10
20
30
40
50
60
70
80
50
100
150
200
Pressure in carotid sinus (mm Hg)

Cardiopulmonary receptors

(low-pressure baroreceptor)

Opposite to the high-pressure baroreceptor in the exit from the aorta

Baroreceptors located in the walls of

- the right and left atria (especially referred volume receptor)
- the entrance of the superior and inferior vena **cavae**
- Pulmonary circulation

These receptors in the low-pressure part of circulation are referred to collectively as the cardiopulmonary receptors

- Caused bradycardia & vasodilation when stimulated

Chemoreceptor Reflex

Corneille Heymans

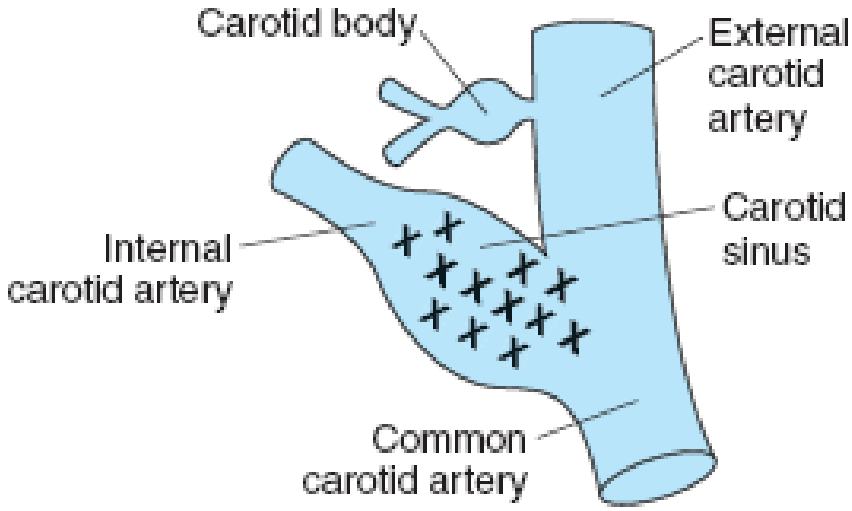
(1892–1968)

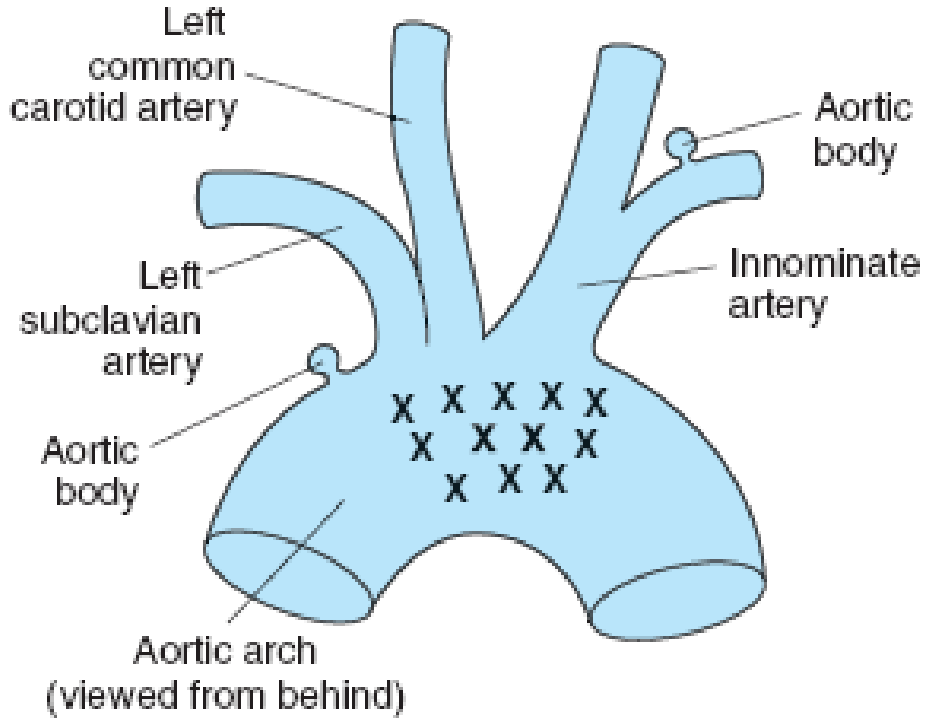
Chemo-Rs location

In both carotid body and aortic body:

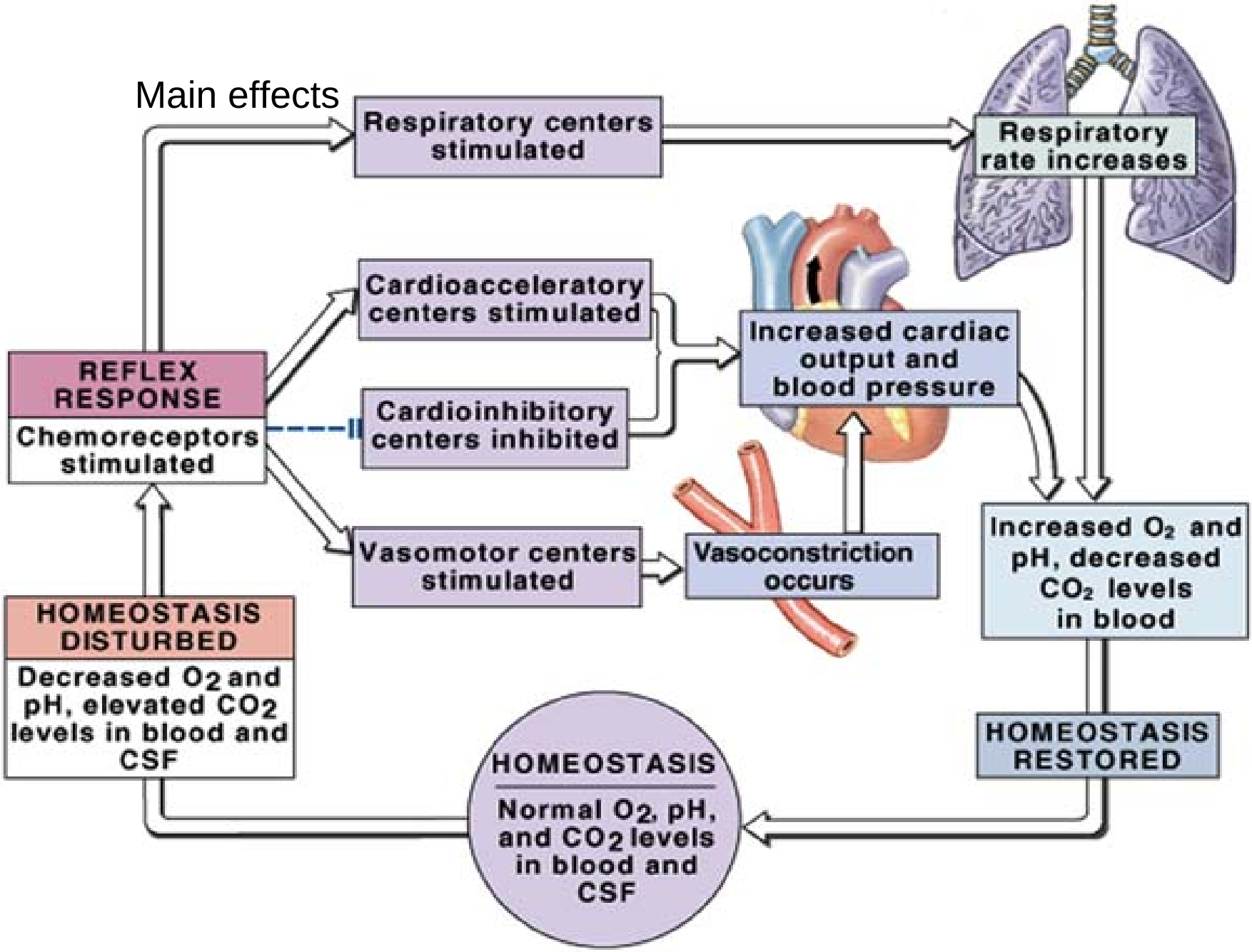
➢Chemo-sensitive: P_{O2}, P_{CO2}, pH

Nobel Prize in 1938





Main effects

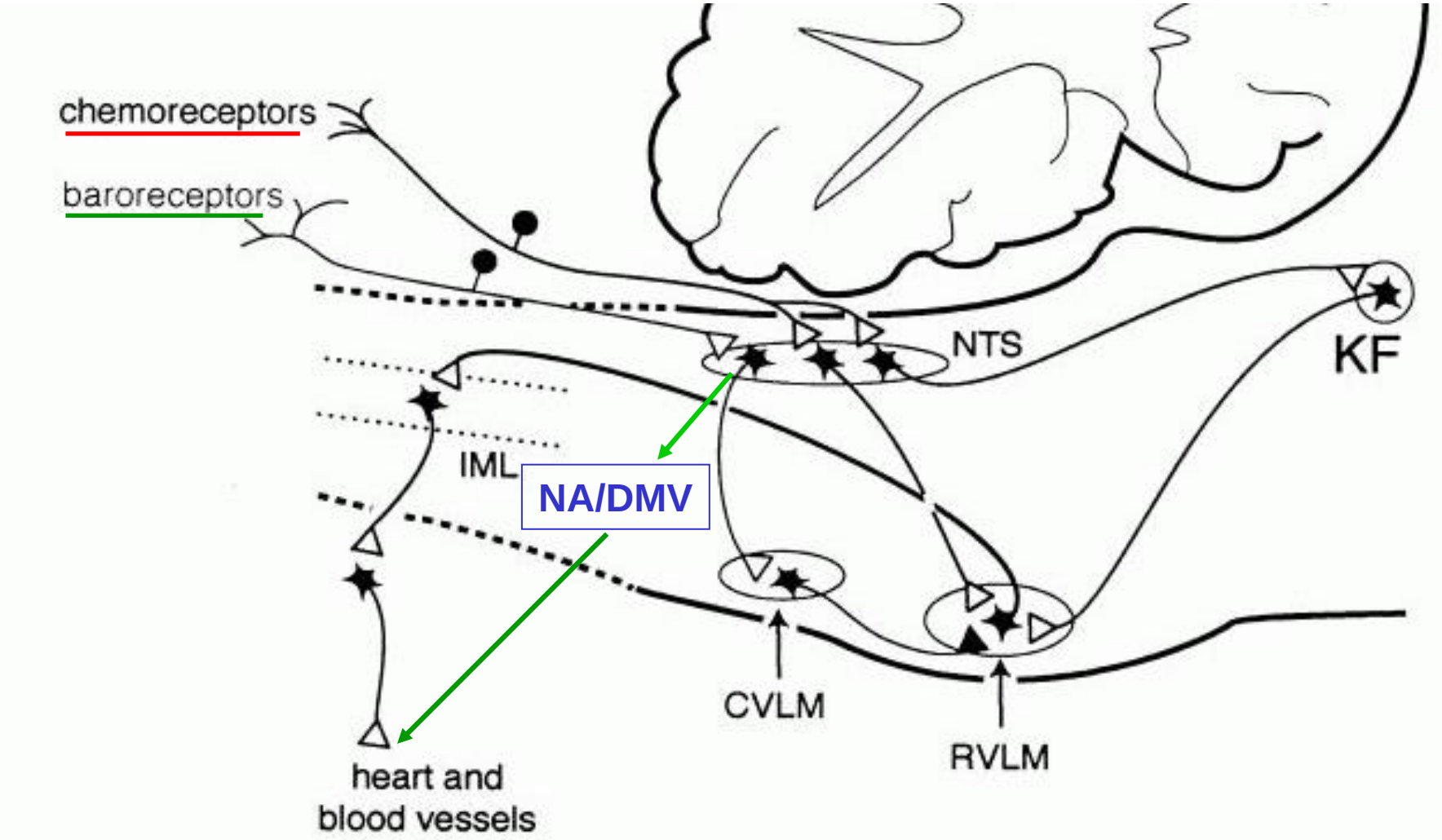


Excitatory inputs

From carotid and aortic chemoreceptors

Inhibitory inputs

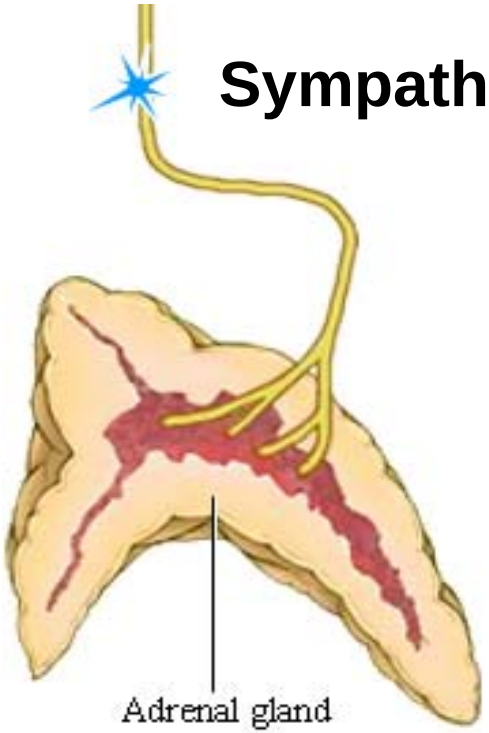
From carotid, aortic, and cardiopulmonary baroreceptors



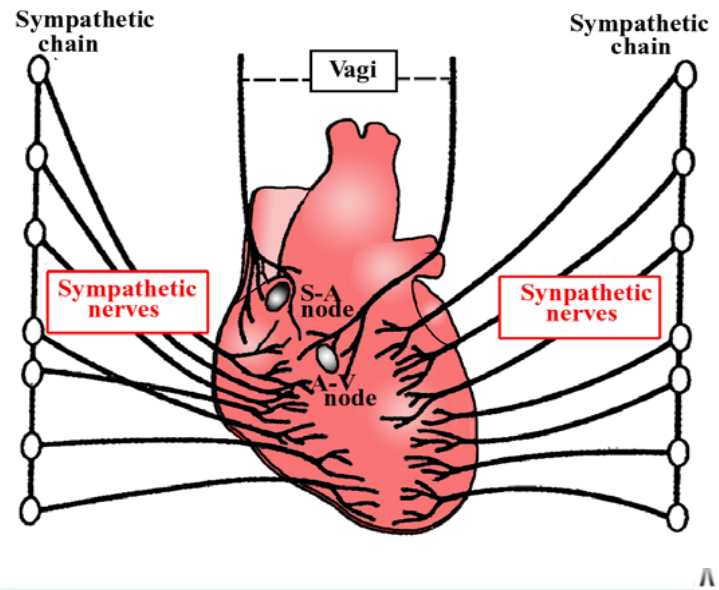
Hormonal Regulation

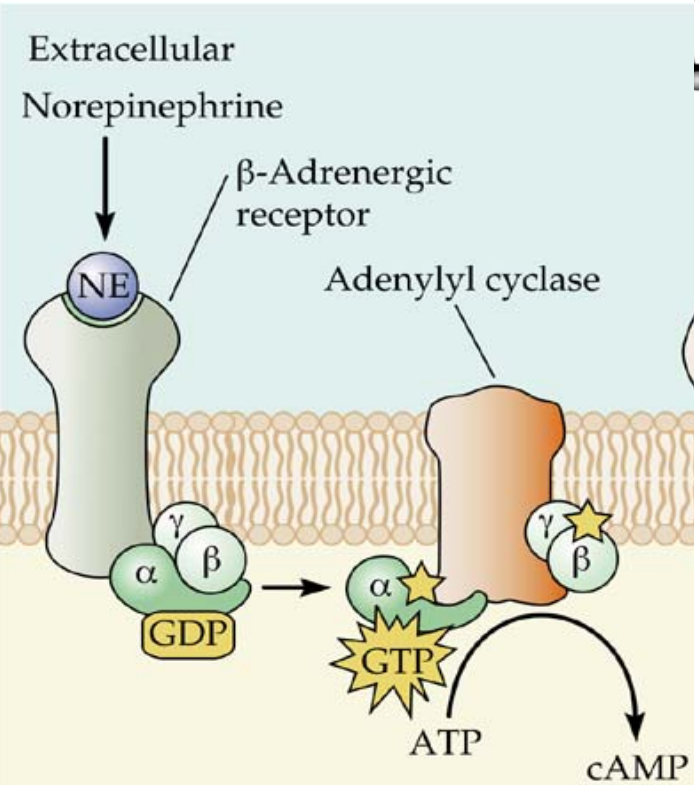
- Epinephrine & Norepinephrine
  - From the adrenal medulla
- Renin-angiotensin-aldosterone system
  - Renin from kidney
  - Angiotensin, a plasma protein
  - Aldosterone from adrenal cortex
- Arginine vasopressin (Antidiuretic Hormone-ADH)
  - ADH from the posterior pituitary (Neurohypophysis)

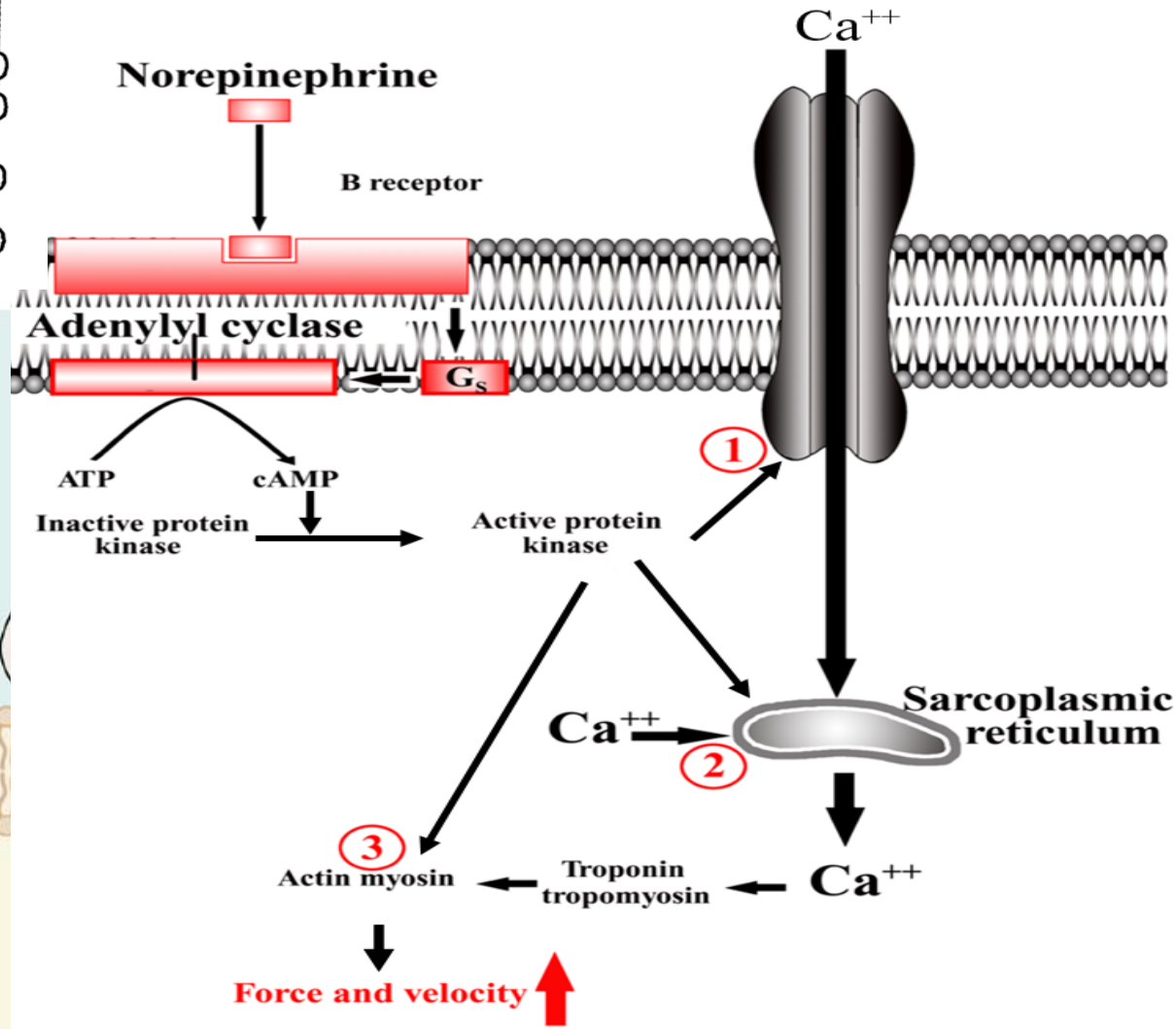
•Epinephrine & Norepinephrine

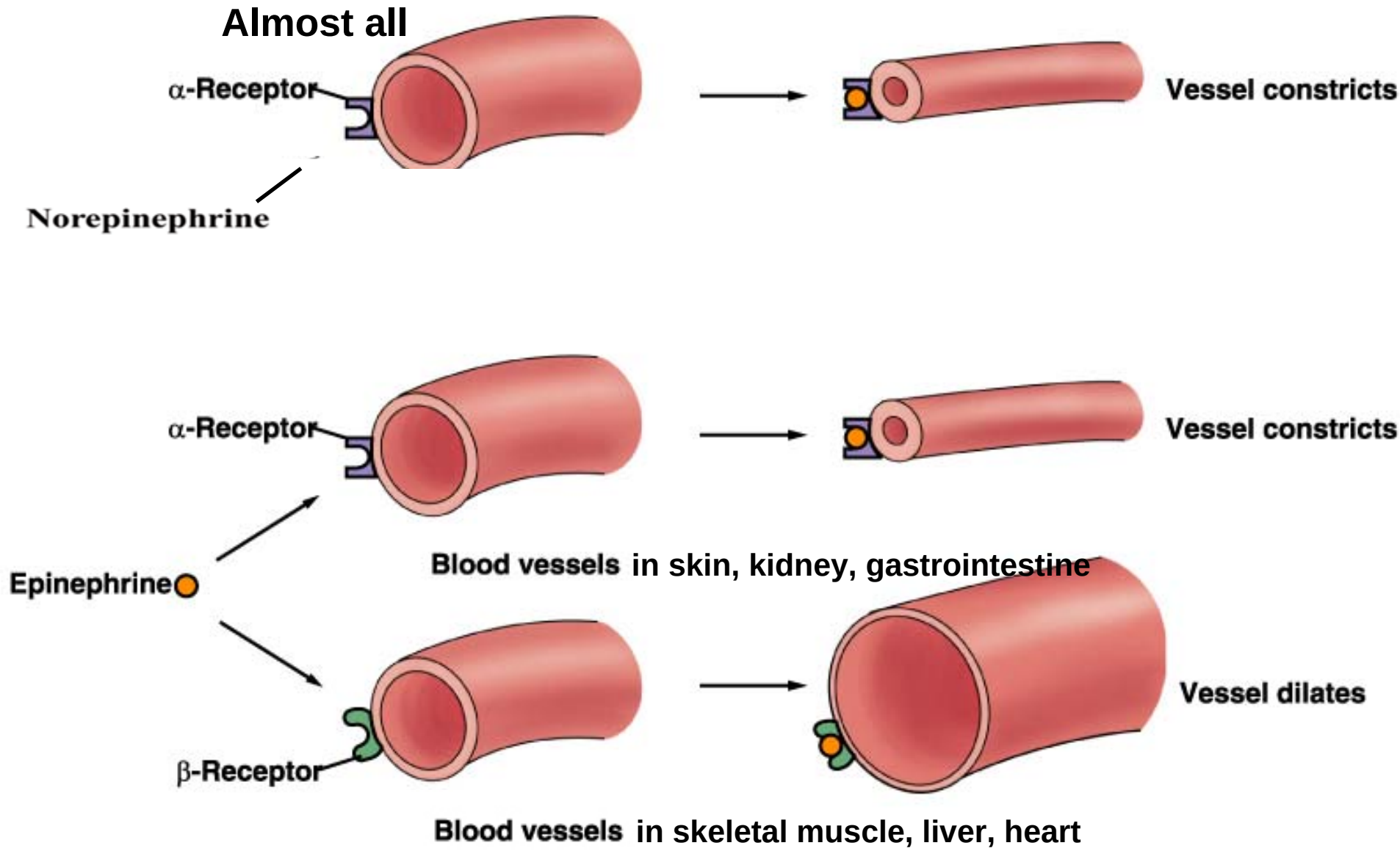


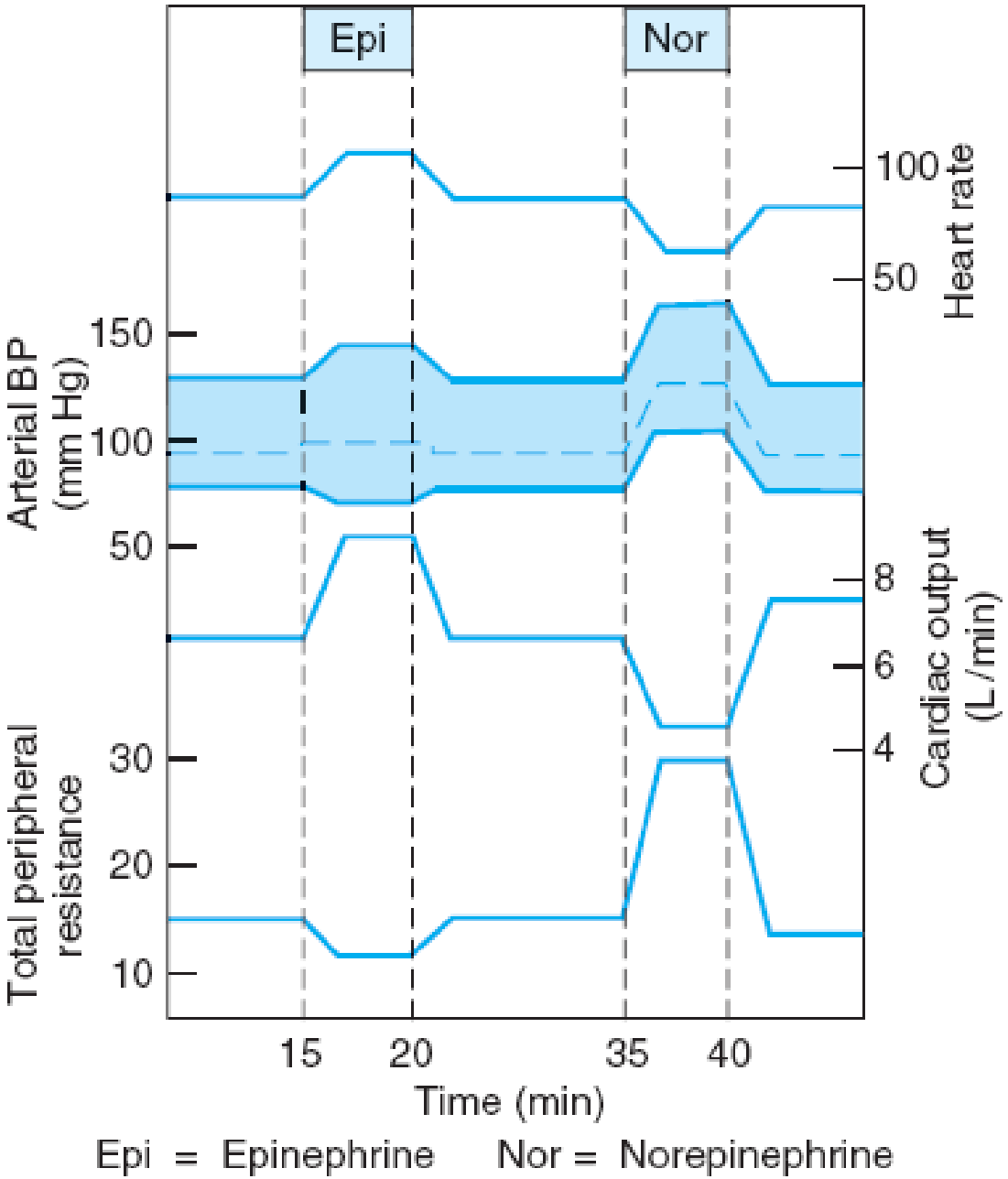
In circulation
Epinephrine (E,80%)
Norepinephrine (NE, 20%)

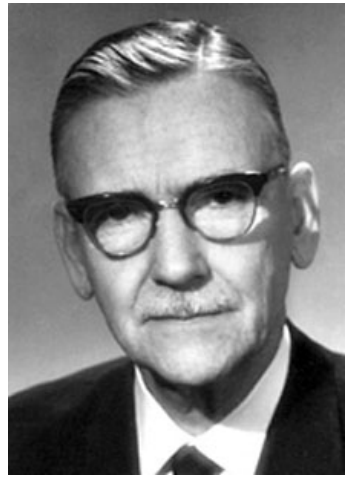

Sympathetic chain
Vagi
Sympathetic chain
Sympathetic nerves
S-A node
A-V node
Synpathetic nerves


Extracellular
Norepinephrine
β-Adrenergic receptor
Adenylyl cyclase
NE
γ
α
β
GDP
GTP
ATP
cAMP


Ca++
Norepinephrine
B receptor
Adenylyl cyclase
Gs
ATP
cAMP
Inactive protein kinase
Active protein kinase
1
Ca++
Sarcoplasmic reticulum
2
3
Actin myosin
Troponin tropomyosin
Ca++
Force and velocity


Almost all
α-Receptor
Norepinephrine
Vessel constricts
α-Receptor
Vessel constricts
Epinephrine
Blood vessels in skin, kidney, gastrointestine
β-Receptor
Vessel dilates
Blood vessels in skeletal muscle, liver, heart

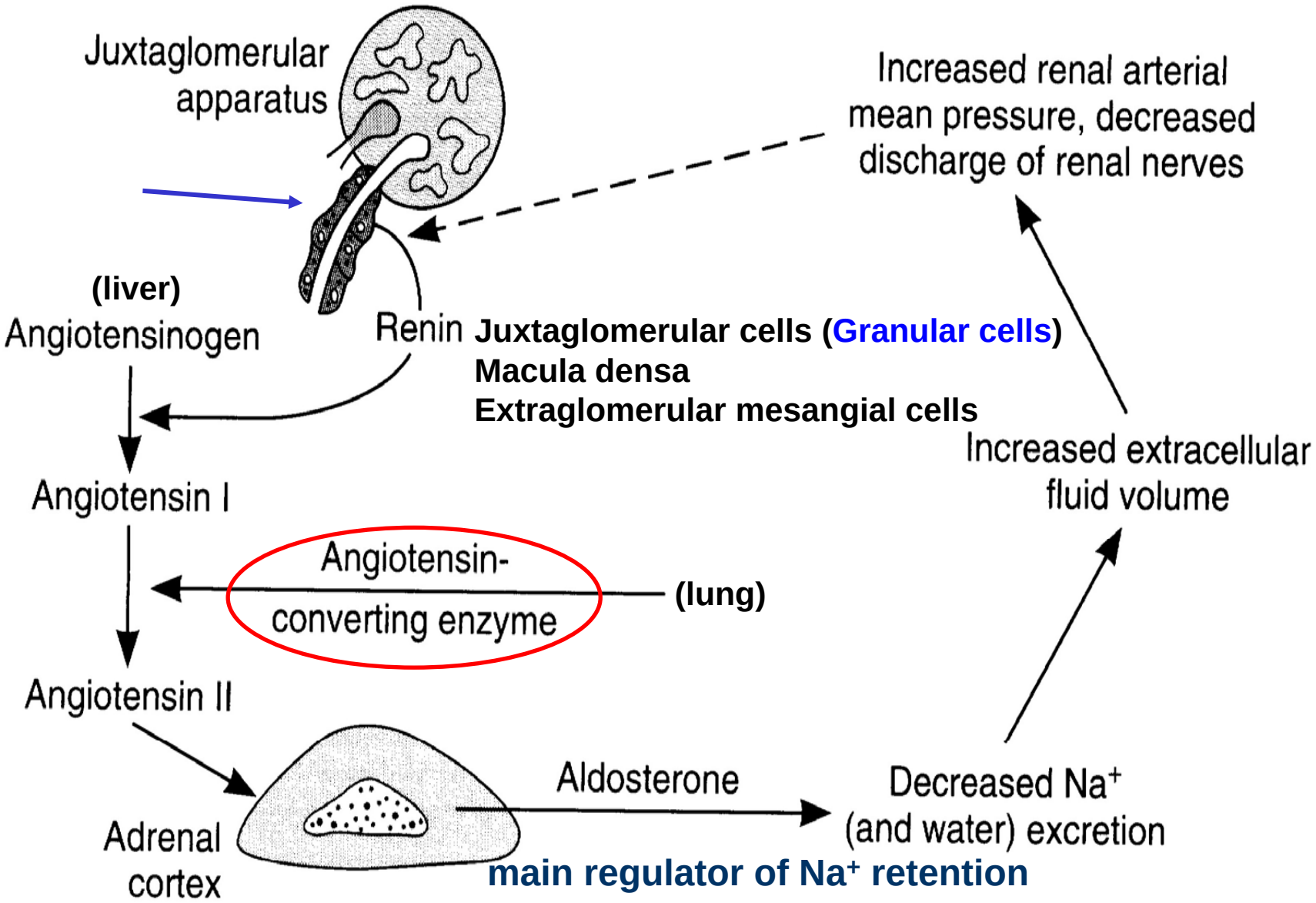




•**Ulf von Euler** (1970, Nobel laureates) discovered NE & E

•**Circulatory changes produced in humans by the slow intravenous infusion of Epi and Nor.**

•Renin-angiotensin aldosterone system, RAAS



- **Renin secretion**

Glomerular capillary pressure ↓
Renal nerve (sympathetic) ↑ → β receptor
Na^+ ↓ in tubular fluid

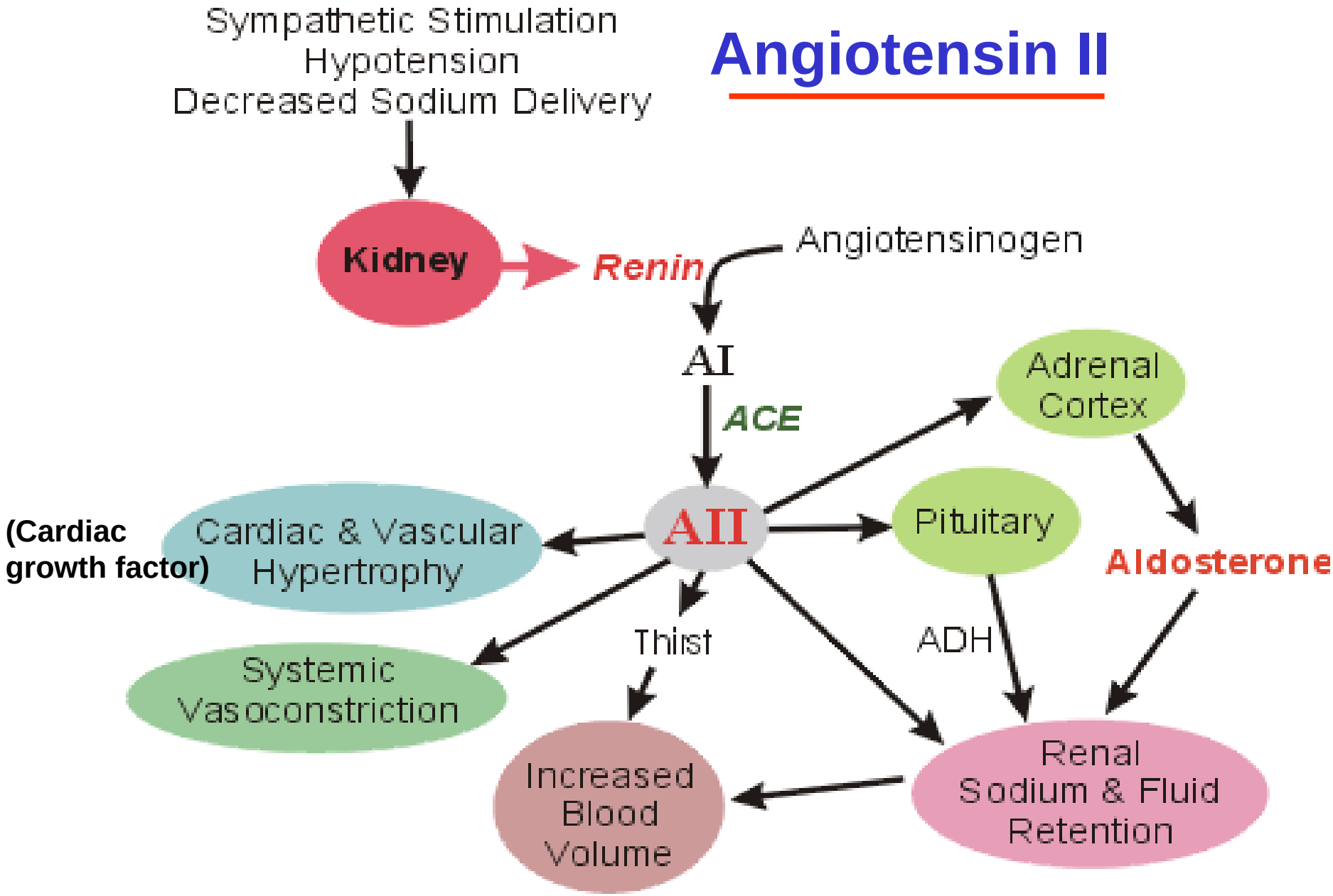
↓

++ Juxtaglomerular apparatus
(considered baroreceptors)

↓

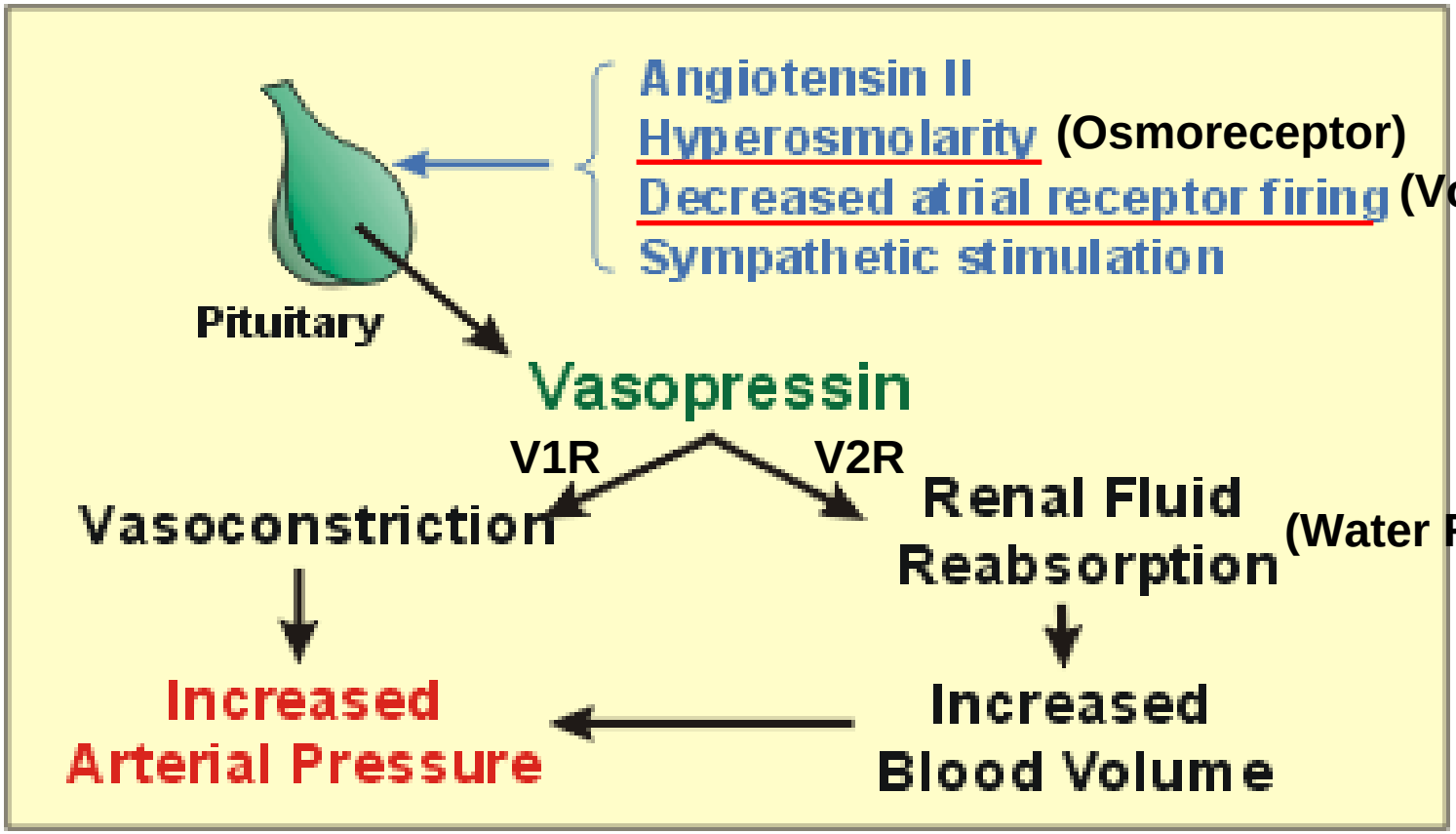
Renin↑

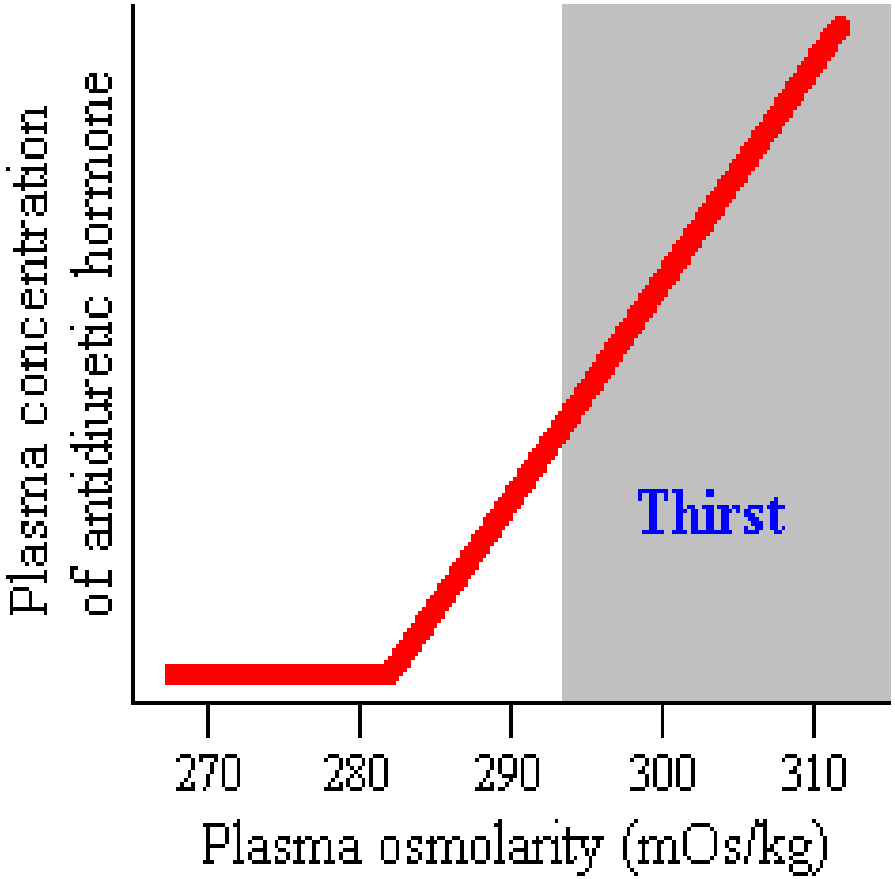
Angiotensin II



•(Arginine) vasopressin

Synthesized by supraoptic & paraventricular nucleus in neurohypophysis

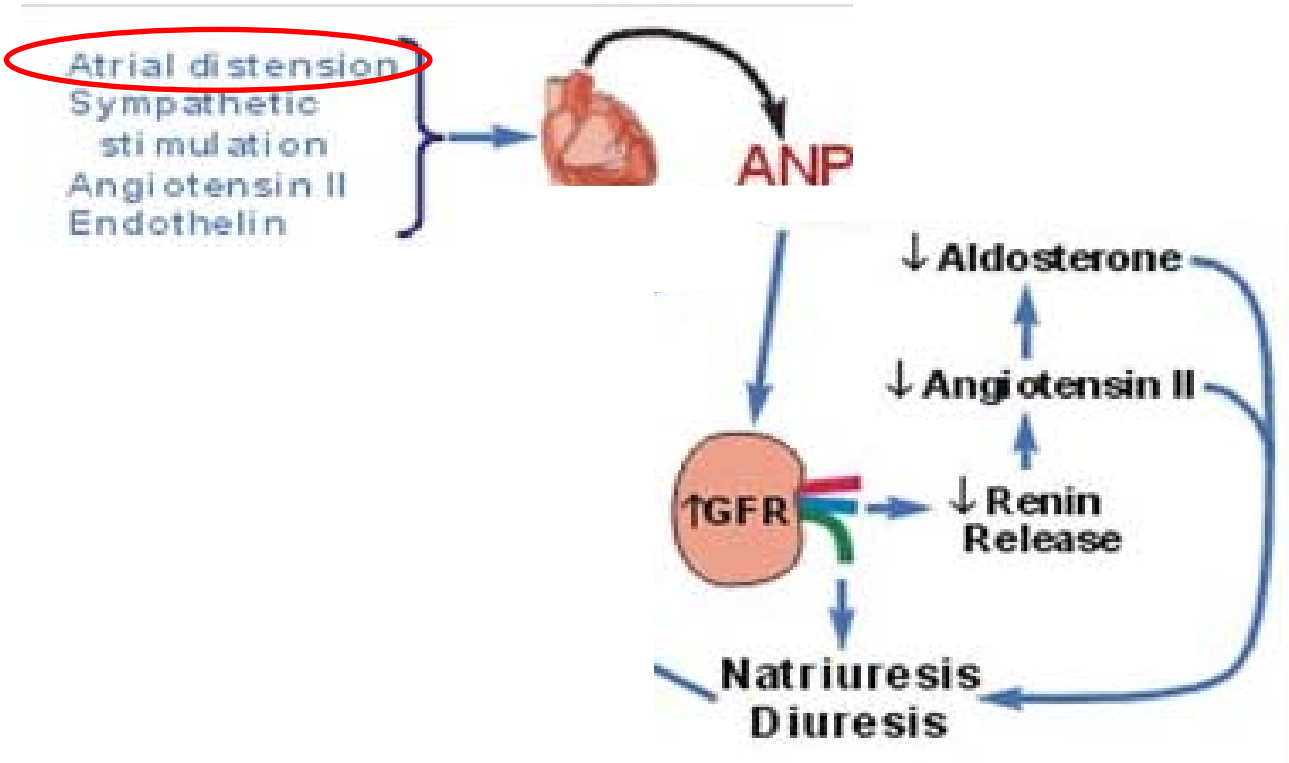


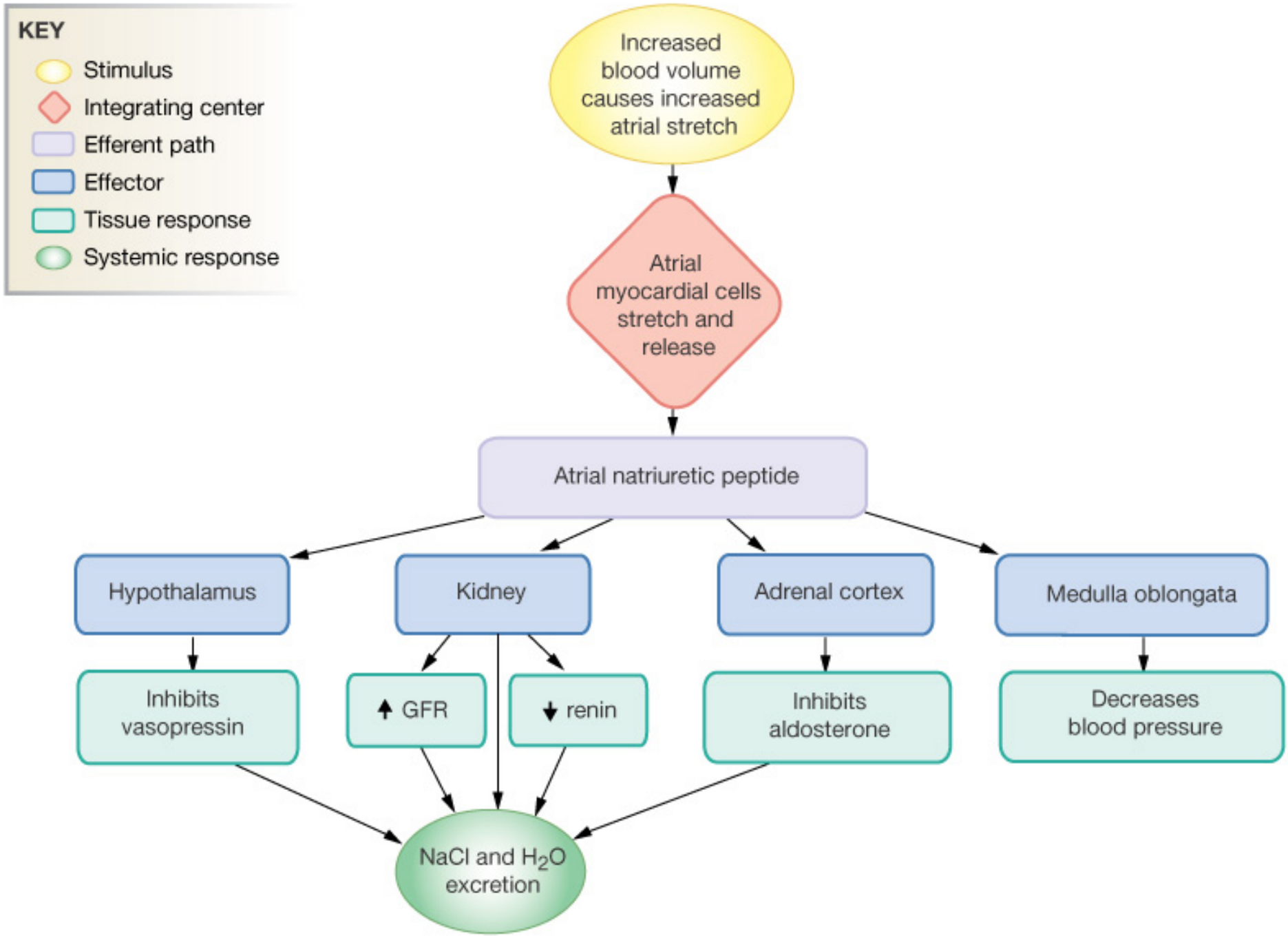

Plasma concentration of antidiuretic hormone
Thirst
270
280
290
300
310
Plasma osmolarity (mOs/kg)


Thank goodness we have ADH

•Atrial natriuretic peptide, ANP

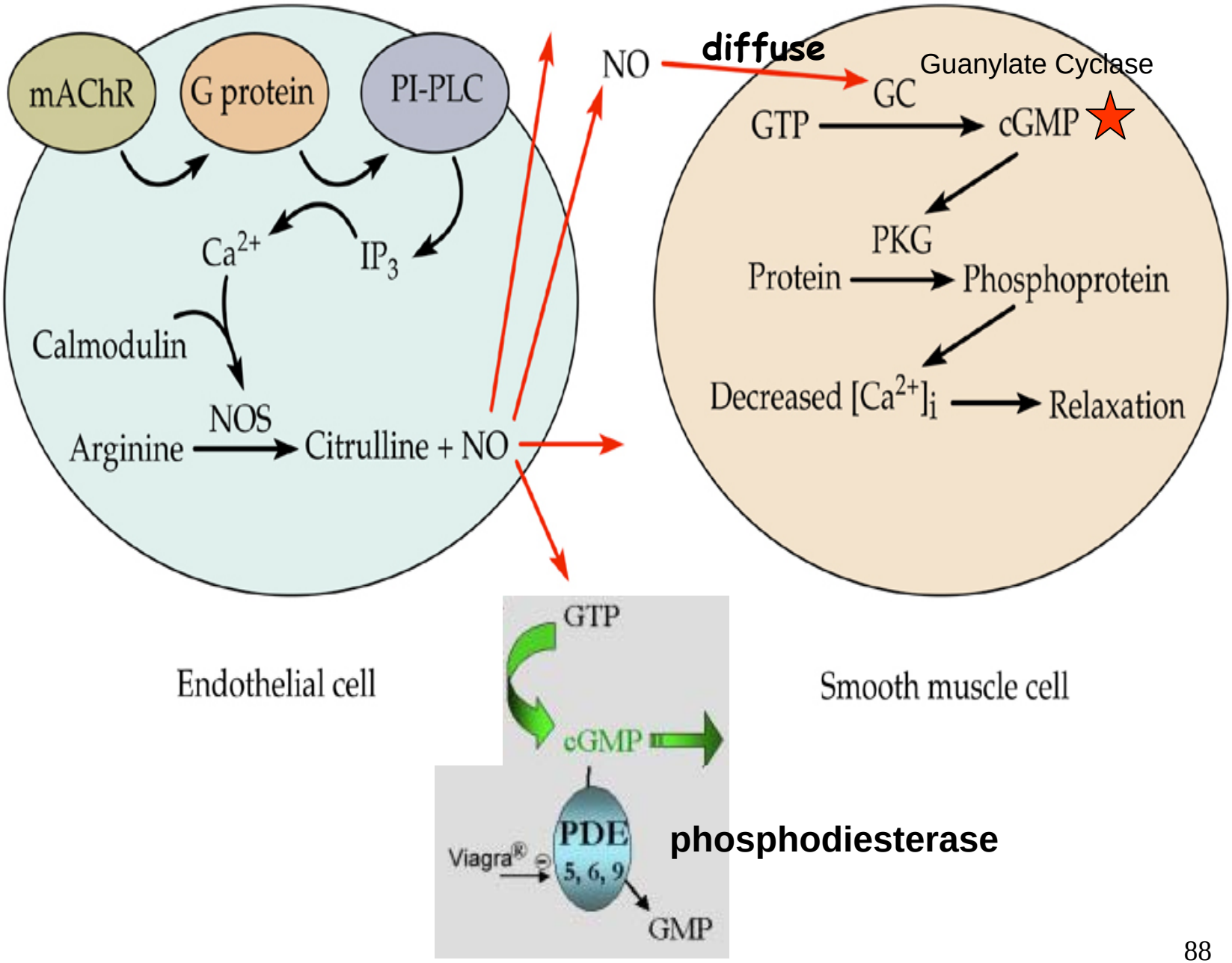
Synthesized by atrium myocardium
Mainly target kidney




KEY
Stimulus
Integrating center
Efferent path
Effector
Tissue response
Systemic response
Increased blood volume causes increased atrial stretch
Atrial myocardial cells stretch and release
Atrial natriuretic peptide
Hypothalamus
Kidney
Adrenal cortex
Medulla oblongata
Inhibits vasopressin
↑ GFR
↓ renin
Inhibits aldosterone
Decreases blood pressure
NaCl and H_2O excretion

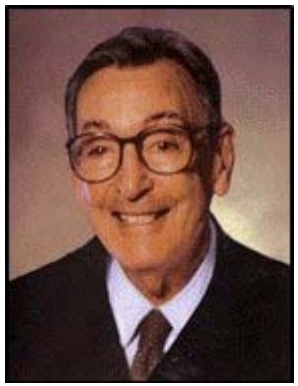
Endothelial chemicals mediating vasoconstriction and Vasodilation

	Source	Effects
Endothelin Endothelium derived vasoconstrictor factor (EDCF)	Endothelial cells	Vasoconstriction
Nitric oxide (NO) Endothelium derived relaxing factor (EDRF)	Endothelial cells	Vasodilation
Prostacyclin	Endothelial cells	Vasodilation

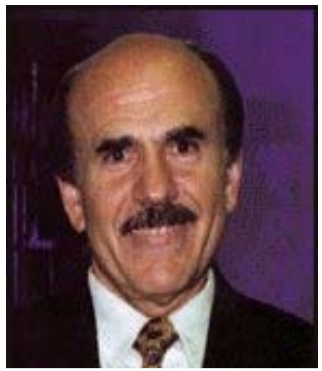

mAChR
G protein
PI-PLC
Ca^{2+}
IP_3
Calmodulin
NOS
Arginine → Citrulline + NO
NO
diffuse
Guanylate Cyclase
GC
GTP → cGMP
PKG
Protein → Phosphoprotein
Decreased $[Ca^{2+}]_i$ → Relaxation
Endothelial cell
Smooth muscle cell
GTP
cGMP
PDE
5, 6, 9
Viagra®
GMP
phosphodiesterase

NO Signaling: 1998 Nobel Prize

- For their discoveries concerning NO as a signaling in cardiovascular system



R.F.Furchgot



L.J. Ignarro

F.Murad

Autoregulation

The capacity of tissues to regulate their own blood flow is referred to as autoregultion

Myogenic mechanisms
Metabolic mechanisms

- Arteries and arterioles are response to perfusion pressure. Increase pressure and the accompanying stretch of VSMCs elicit vasoconstriction, whereas decreased P. elicits vasodilation.

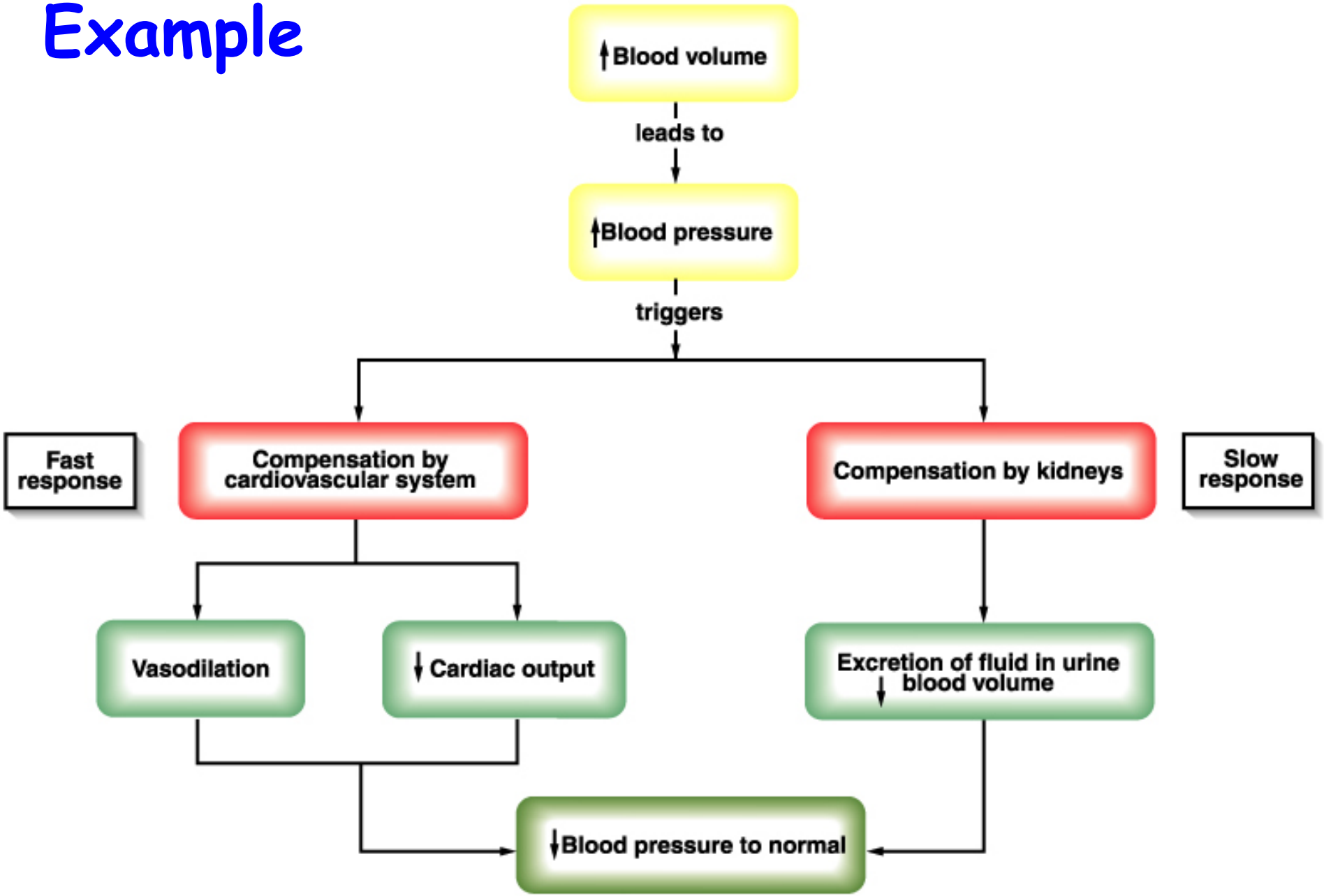
  well developed in the kidneys

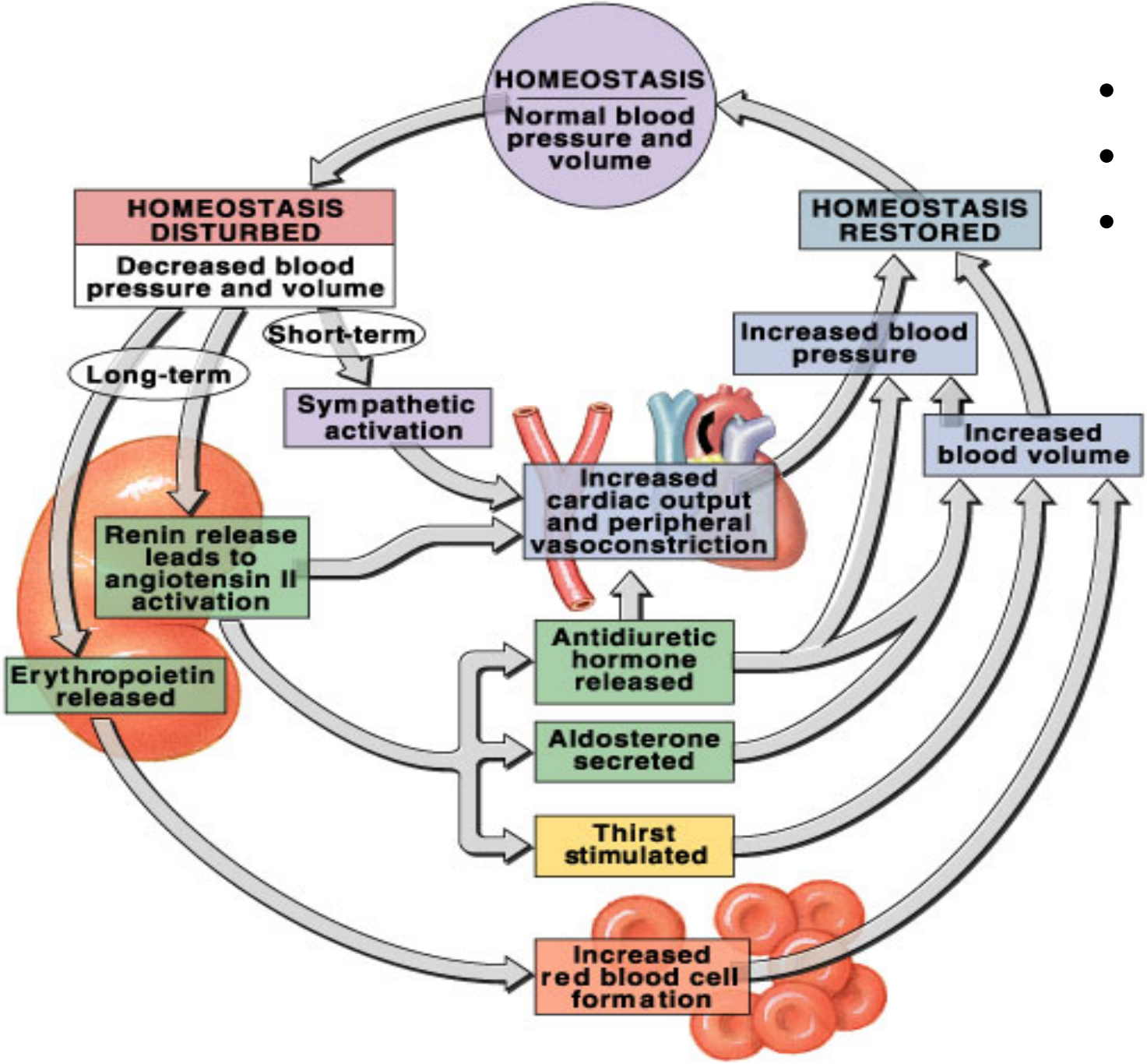
- P_{O2} ↓ or pH ↓ or P_{CO2} ↑ causes vaso-dilation

Long- Term Regulation of AP

- On a time scale of hours or days-occurs via pathways that target the blood vessels, kidneys, in their control of ECF.

Example


↑Blood volume
leads to
↑Blood pressure
triggers
Fast response
Compensation by cardiovascular system
Compensation by kidneys
Slow response
Vasodilation
↓Cardiac output
Excretion of fluid in urine
↓ blood volume
↓Blood pressure to normal



- **Output**
- **Diameter**
- **amount**