Chapter 4.

Circulation System

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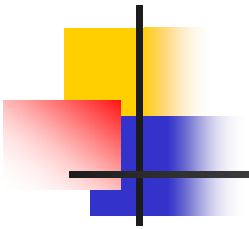
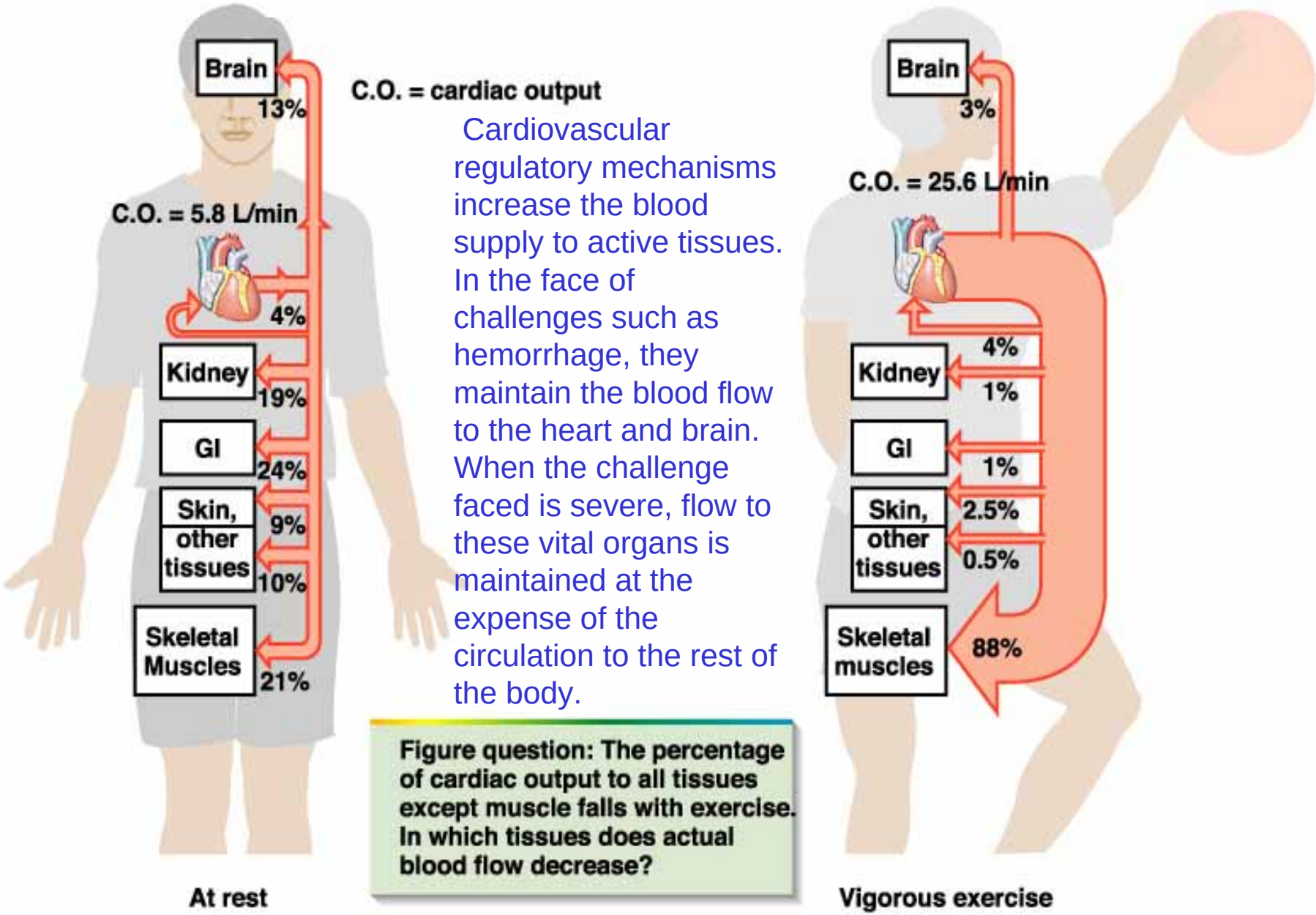


Section 4
Cardiovascular Regulatory Mechanisms

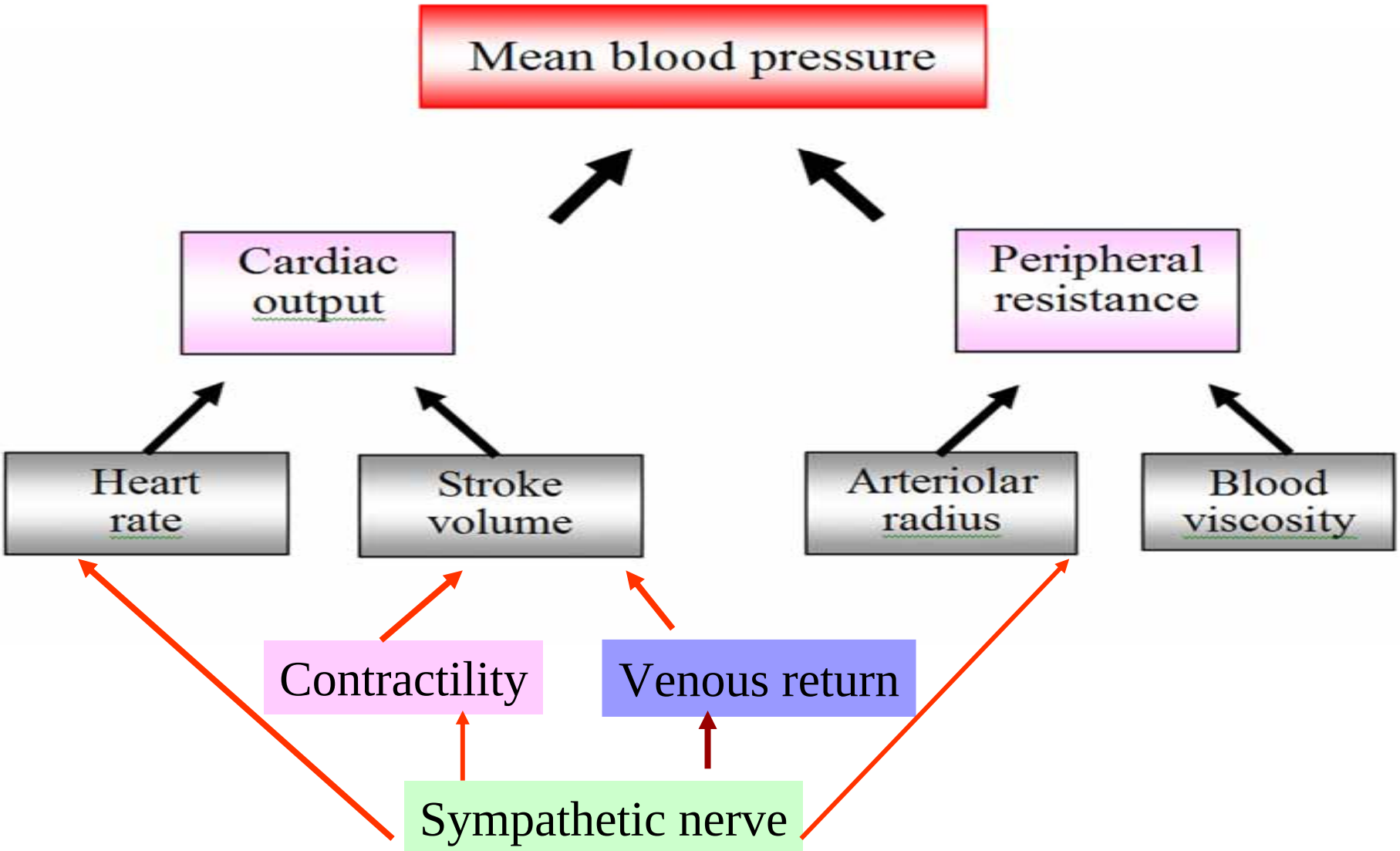


Cardiovascular regulatory mechanisms increase the blood supply to active tissues. In the face of challenges such as hemorrhage, they maintain the blood flow to the heart and brain. When the challenge faced is severe, flow to these vital organs is maintained at the expense of the circulation to the rest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

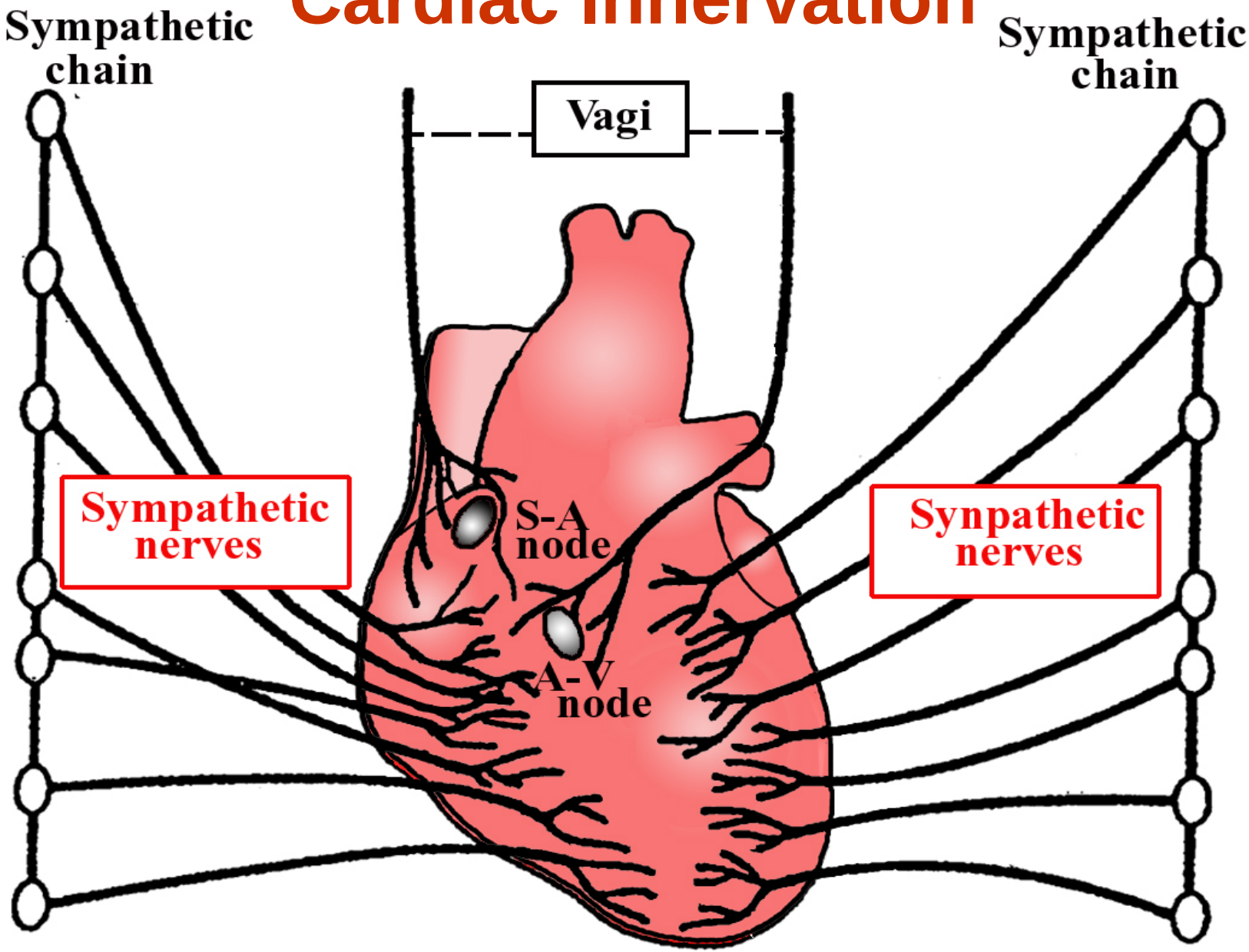
Figure question: The percentage of cardiac output to all tissues except muscle falls with exercise. In which tissues does actual blood flow decrease?

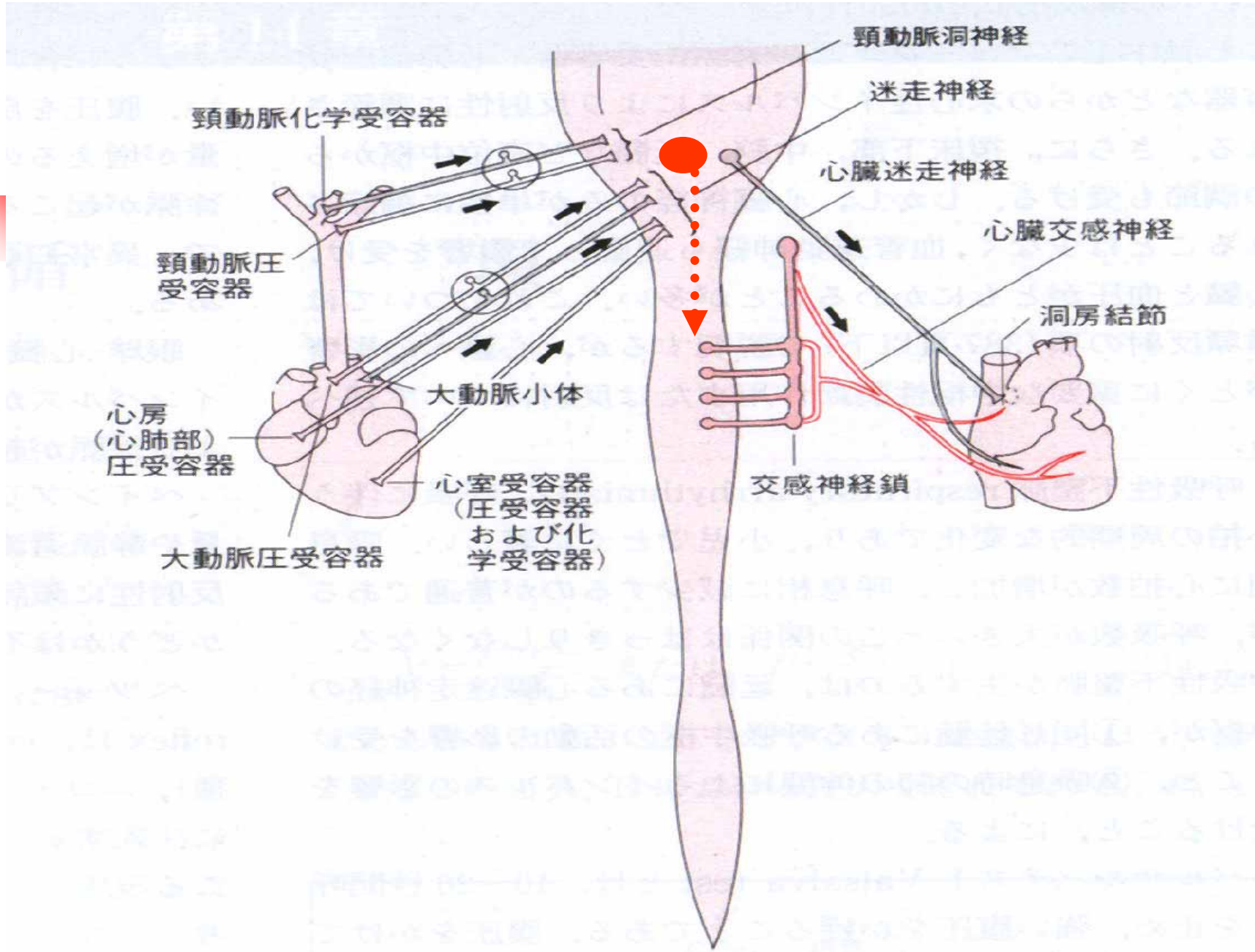
Regulation of Arterial Pressure & Cardiac output

- Adequate blood pressure: necessary for proper organ perfusion.
- Short-term regulation of AP: on a time scale of seconds to minutes ,occurs via neural pathways, targets the heart, vessels, adrenal medulla.


Mean blood pressure
Cardiac output
Peripheral resistance
Heart rate
Stroke volume
Arteriolar radius
Blood viscosity
Contractility
Venous return
Sympathetic nerve

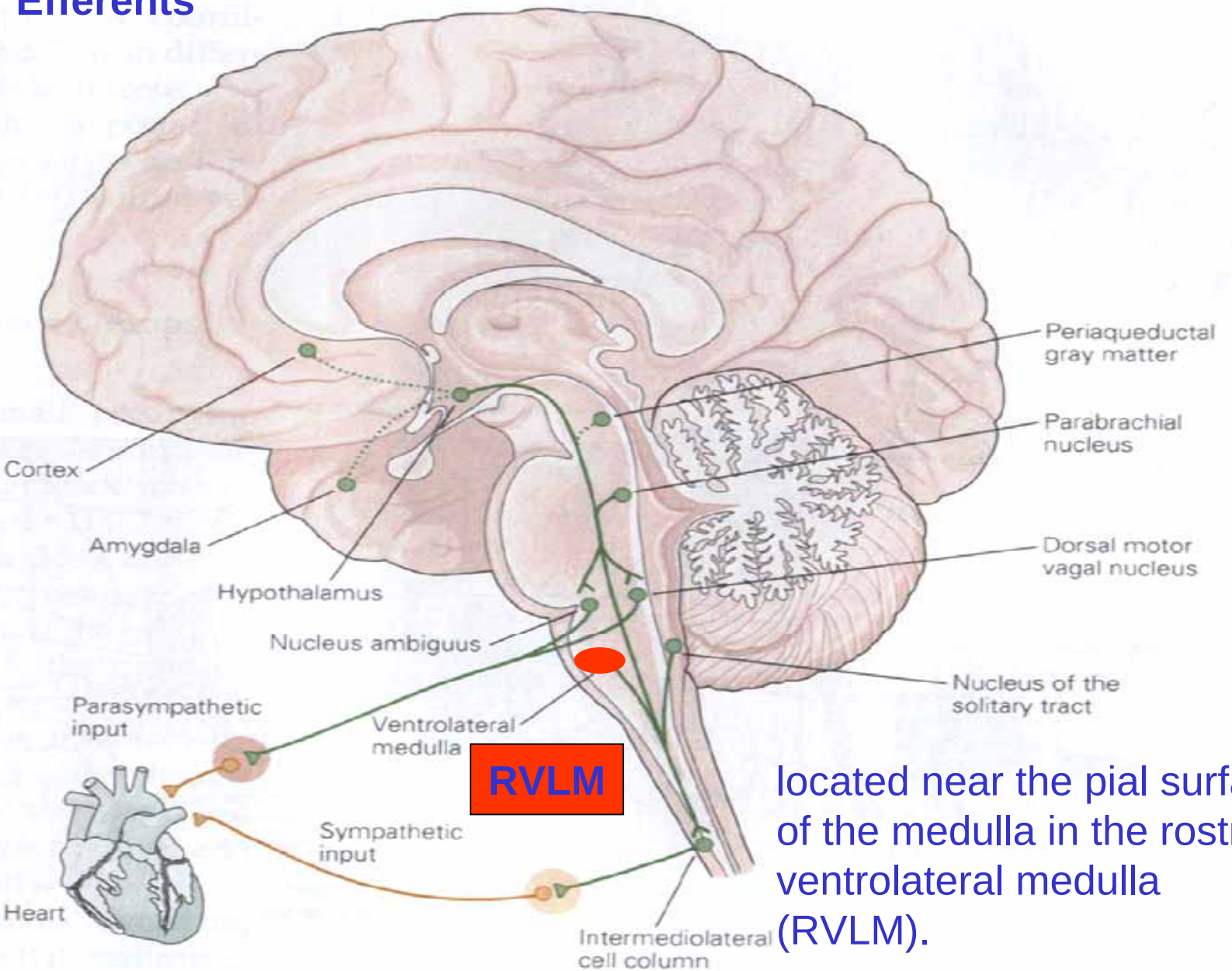
Cardiac Innervation



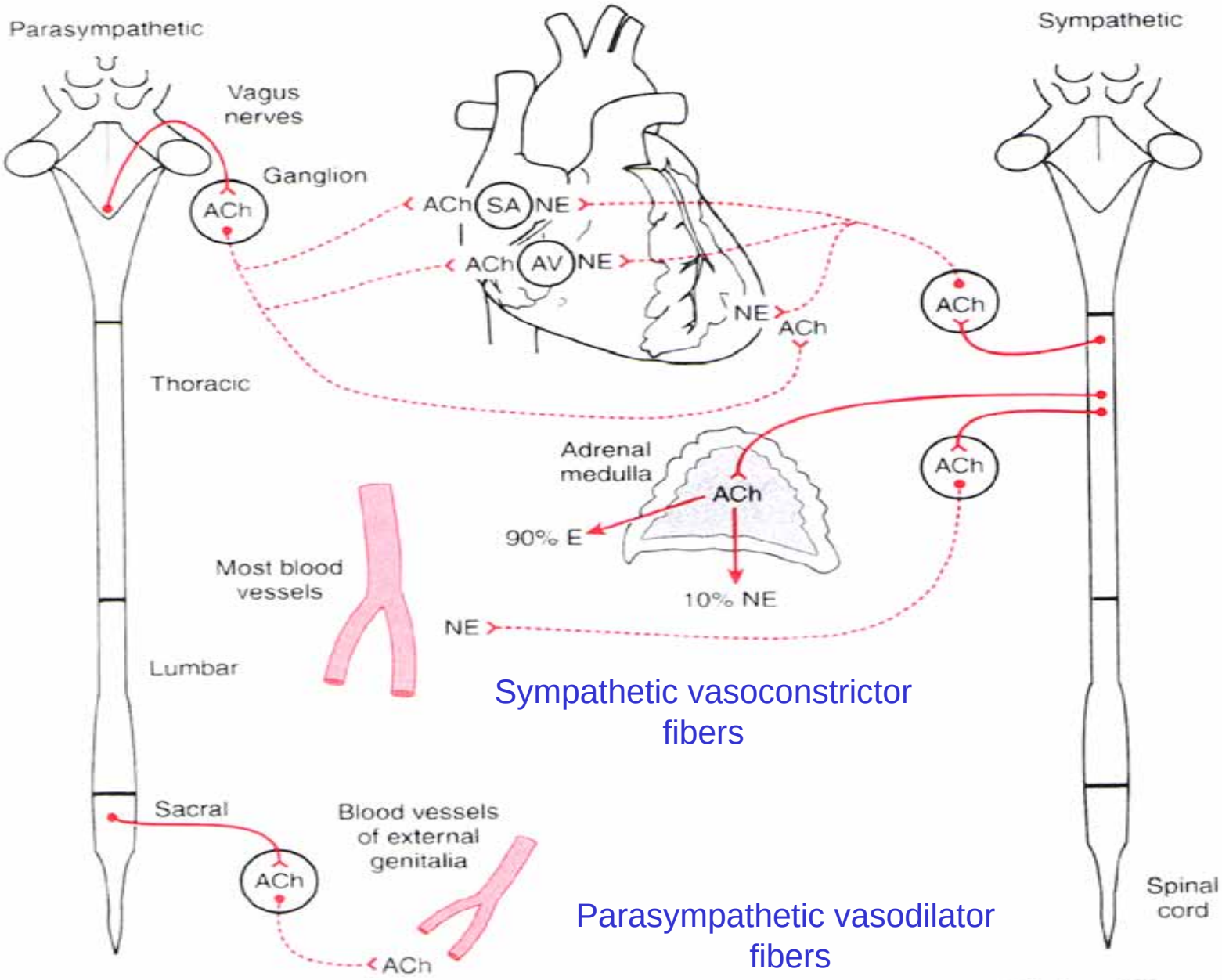

頸動脈洞神経
迷走神経
頸動脈化学受容器
心臓迷走神経
心臓交感神経
頸動脈圧
受容器
洞房結節
大動脈小体
心房
(心肺部)
圧受容器
心室受容器
(圧受容器
および化
学受容器)
交感神経鎖
大動脈圧受容器

Cardiac innervation	Origin	Transmitter	Effects
Sympathetic cardiac nerves	T1-T5(IML) → middle cervical / stellate ganglia → SA node, ventricle muscle.	Noradrenergic, NE → β_1 receptors	Tonic sympathetic discharge, positive chronotropic, inotropic effect.
Vagal cardiac fibers	Nucleus ambiguus(NA) , Dorsa motor nucleus of vagus (DMV)	Cholinergic Ach→ M_2 receptor	▪vagal tone negative chronotropic effect

Efferents

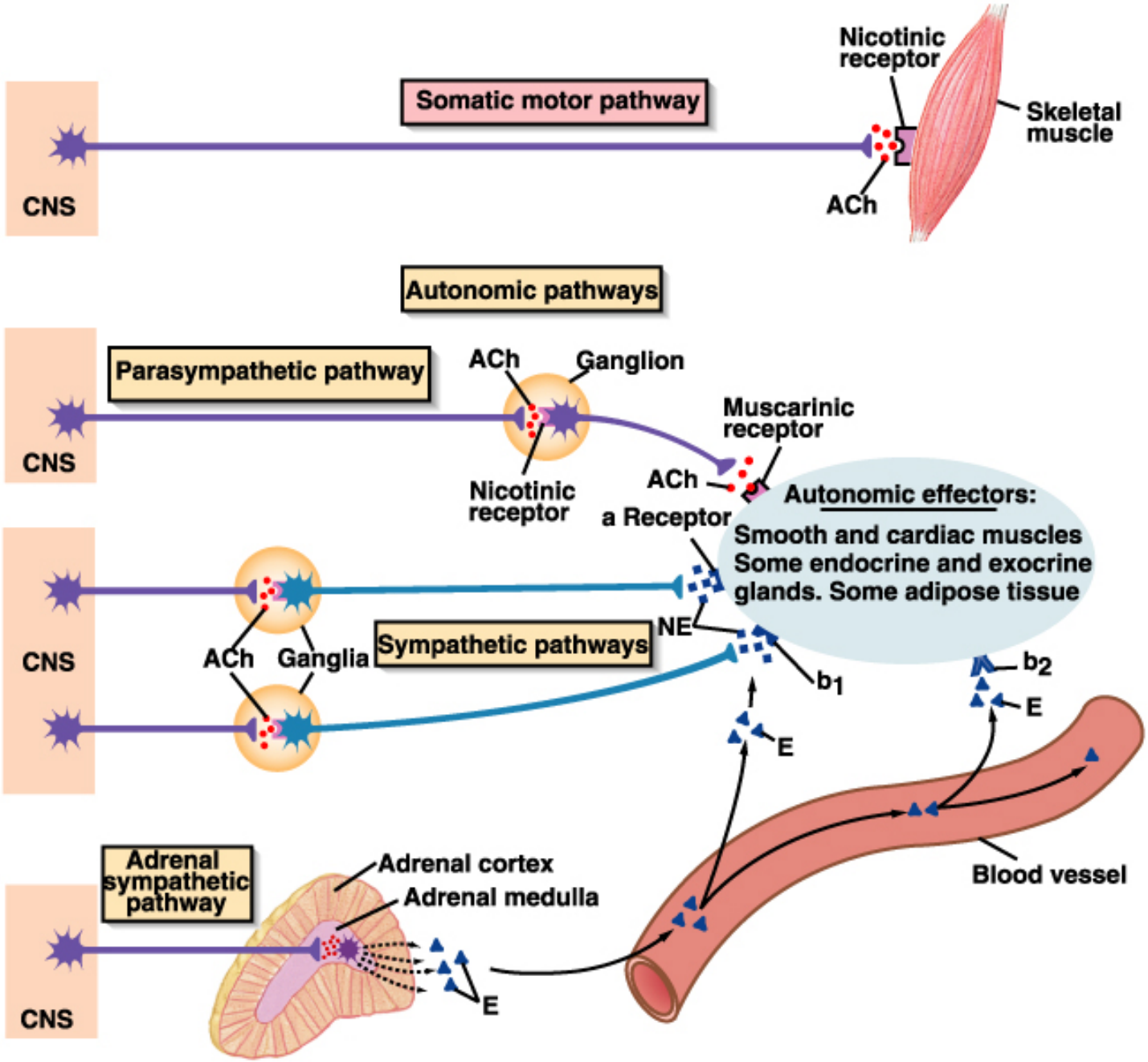


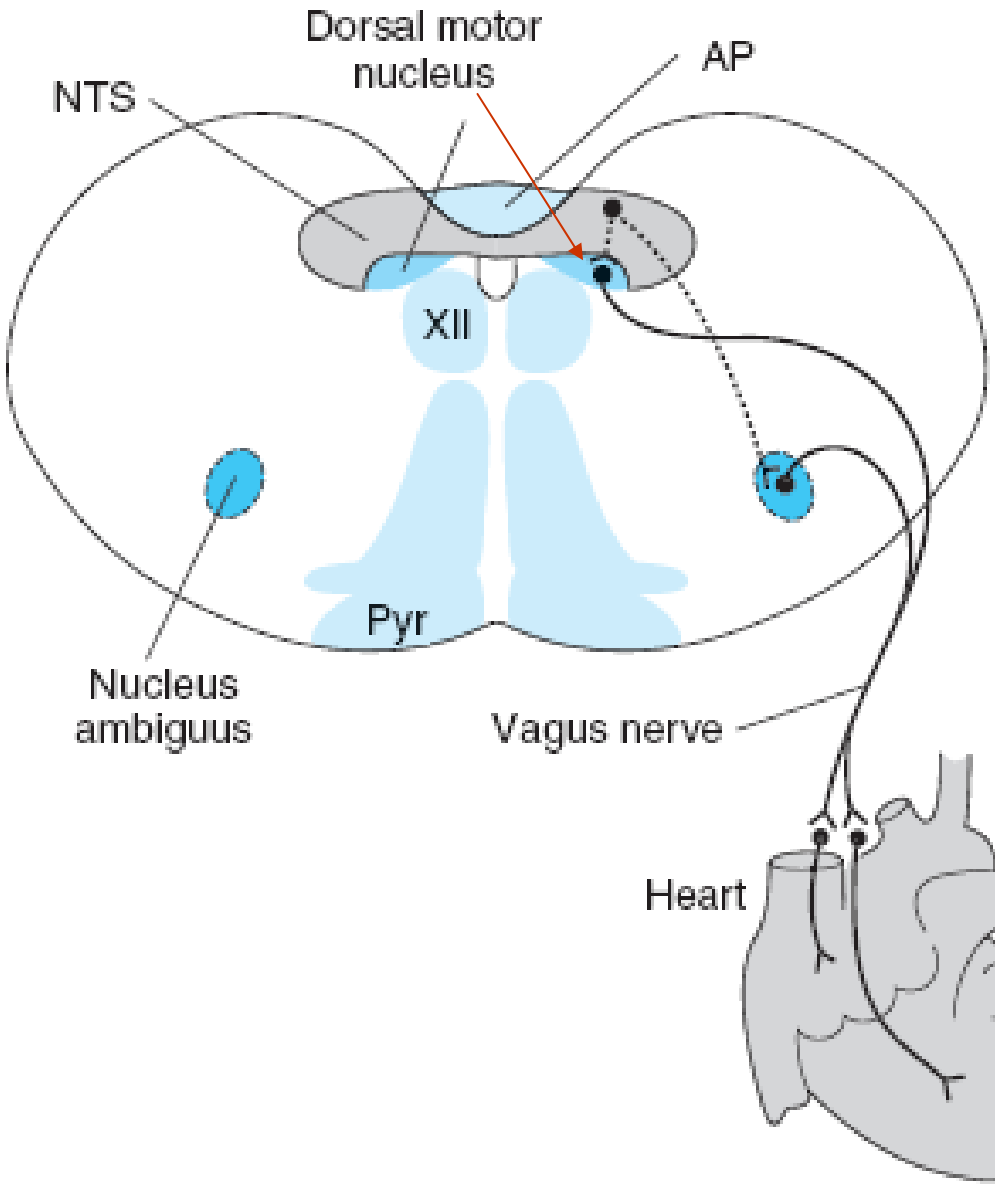
located near the pial surface of the medulla in the rostral ventrolateral medulla (RVLM).



Sympathetic vasoconstrictor fibers

Parasympathetic vasodilator fibers

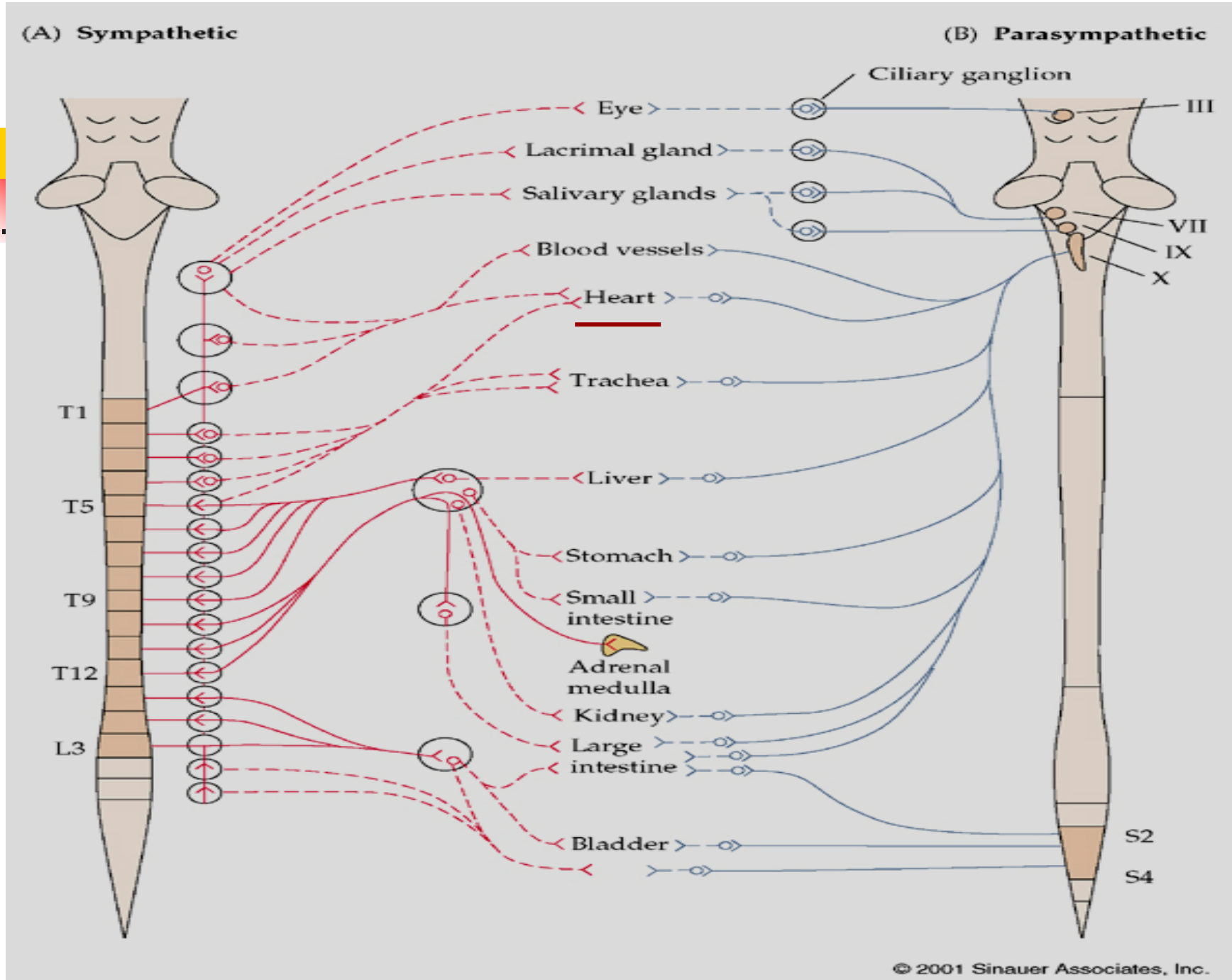

Somatic motor pathway
CNS
Nicotinic receptor
Skeletal muscle
ACh
Autonomic pathways
Parasympathetic pathway
CNS
ACh
Ganglion
Muscarinic receptor
Nicotinic receptor
ACh
a Receptor
Autonomic effectors:
Smooth and cardiac muscles
Some endocrine and exocrine glands. Some adipose tissue
CNS
ACh
Ganglia
Sympathetic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



Vagal Cardiac Nerve

Ach, M_2 receptor. Negative chronotropic effects.

Vagal tone: moderate amount of tonic vagal discharge at rest.


(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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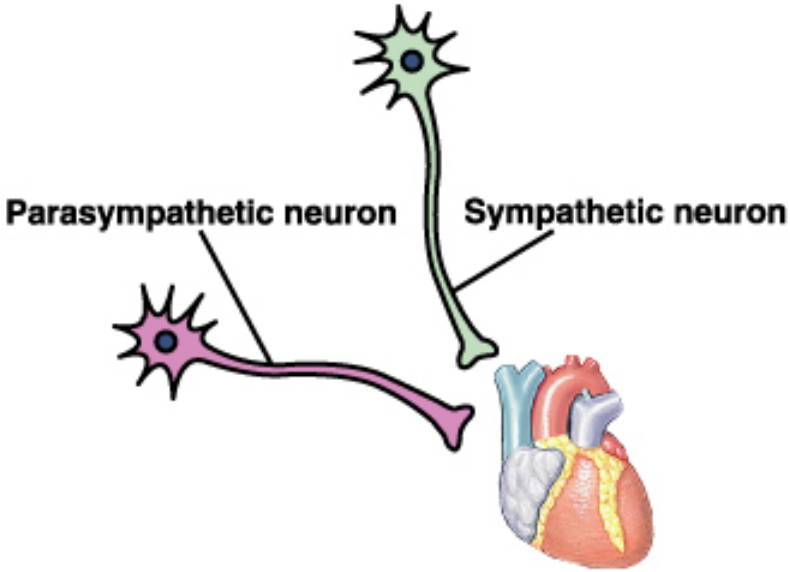
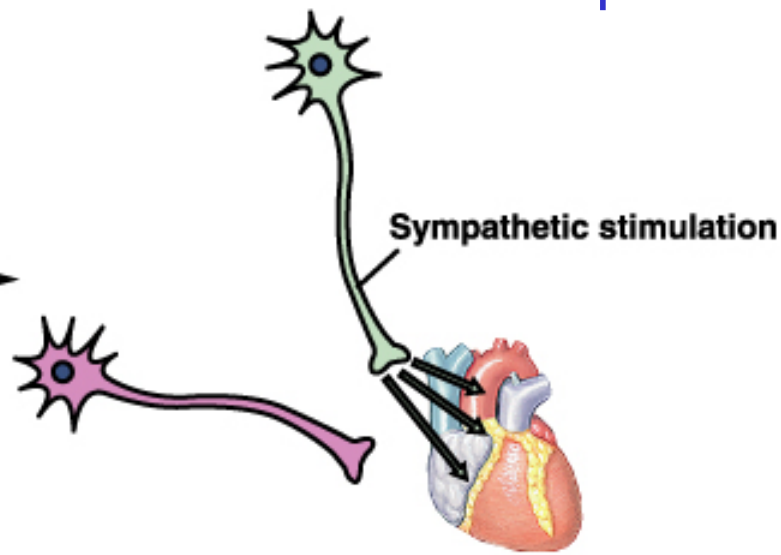
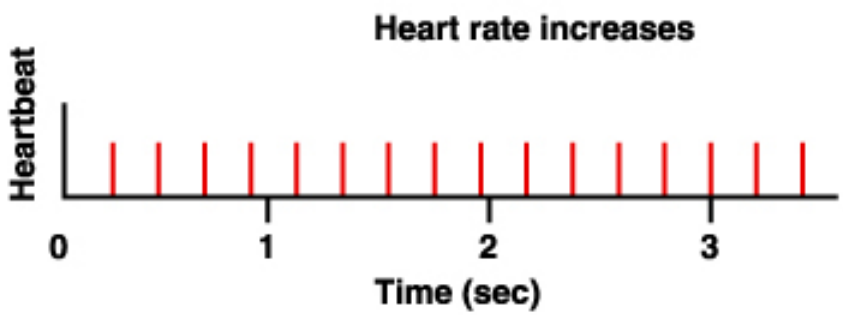
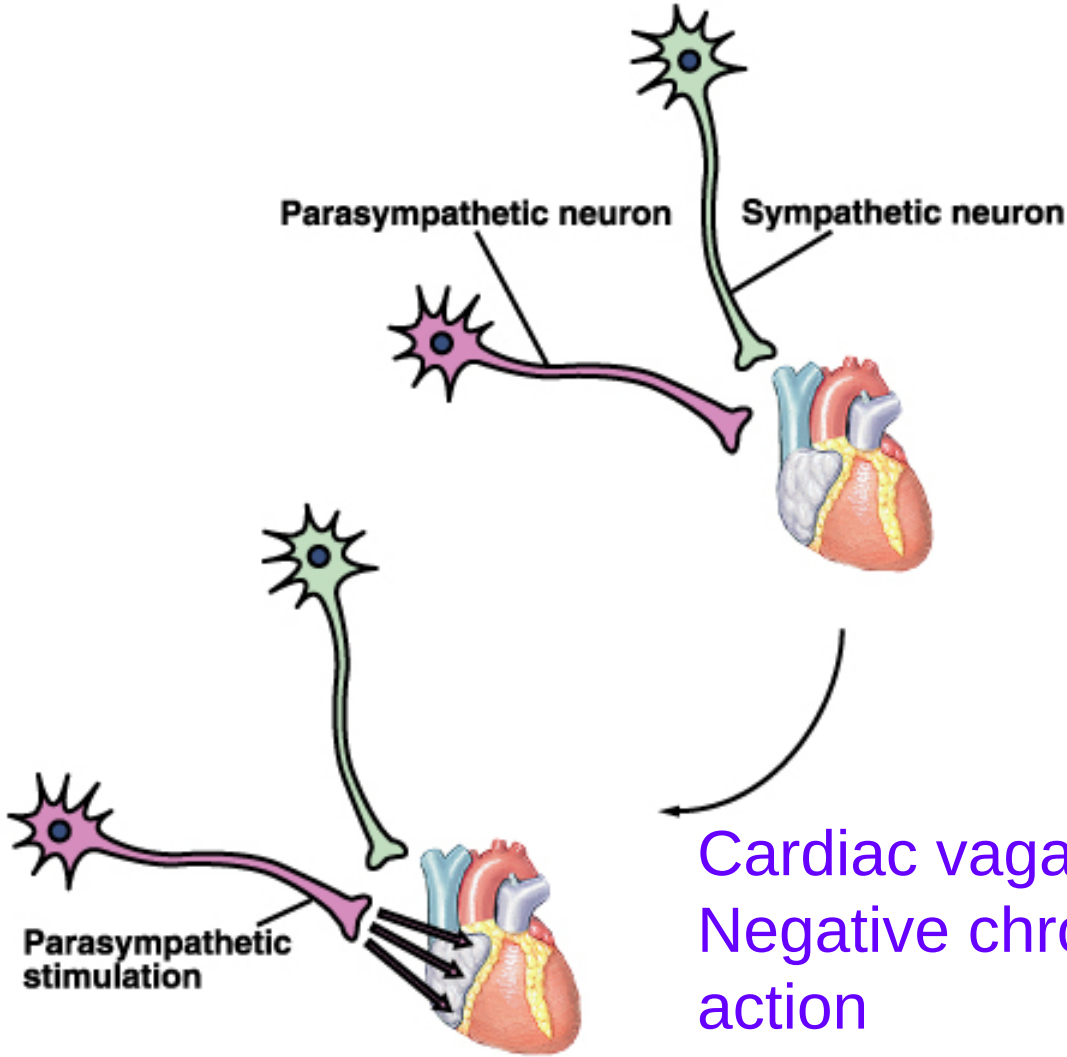


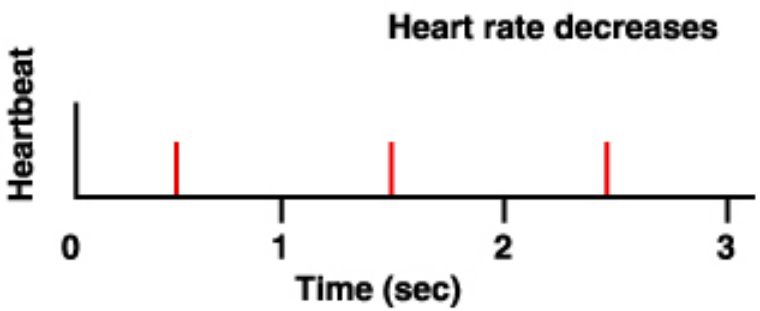
Cardiac sympathetic tone
Positive chronotropic action

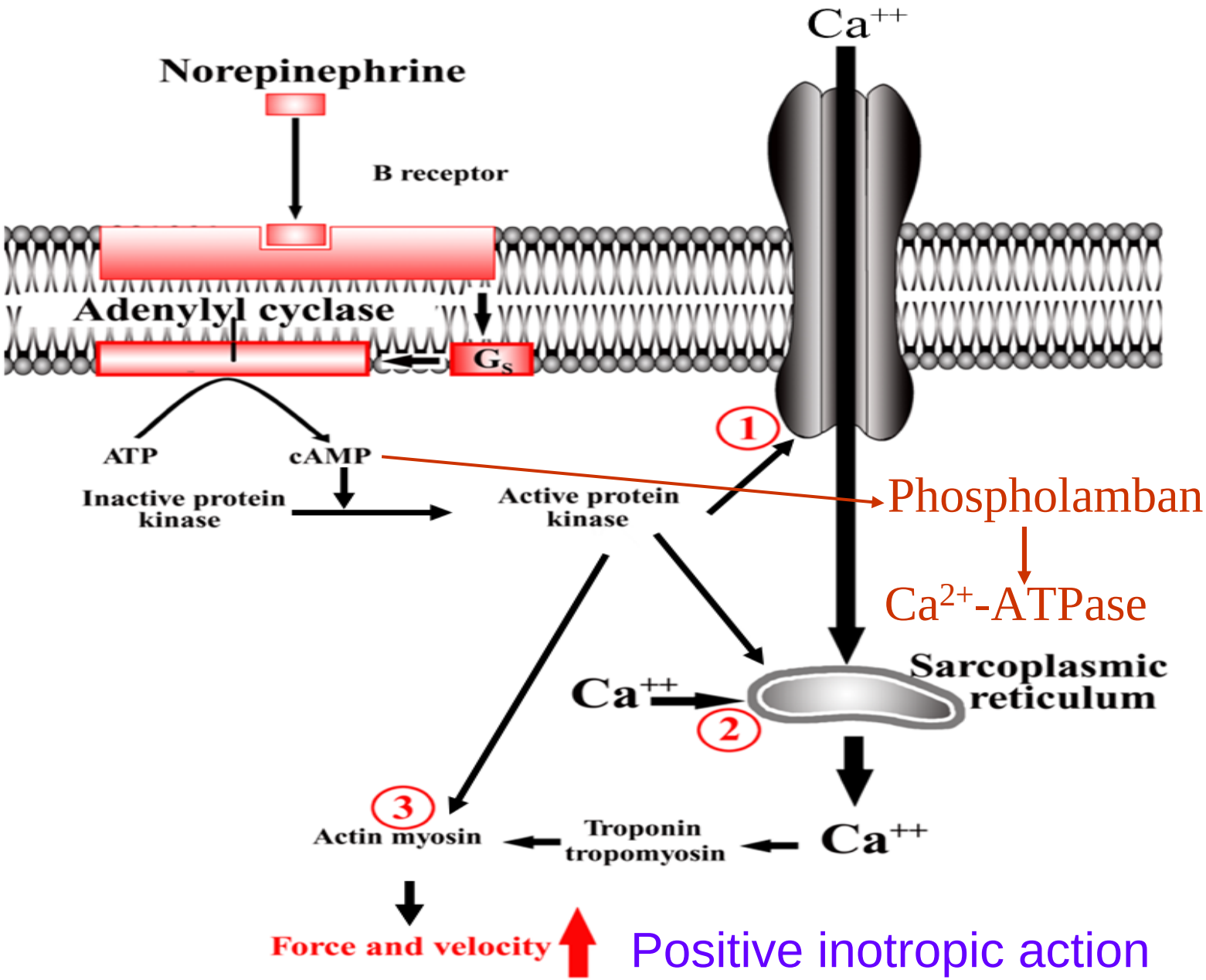


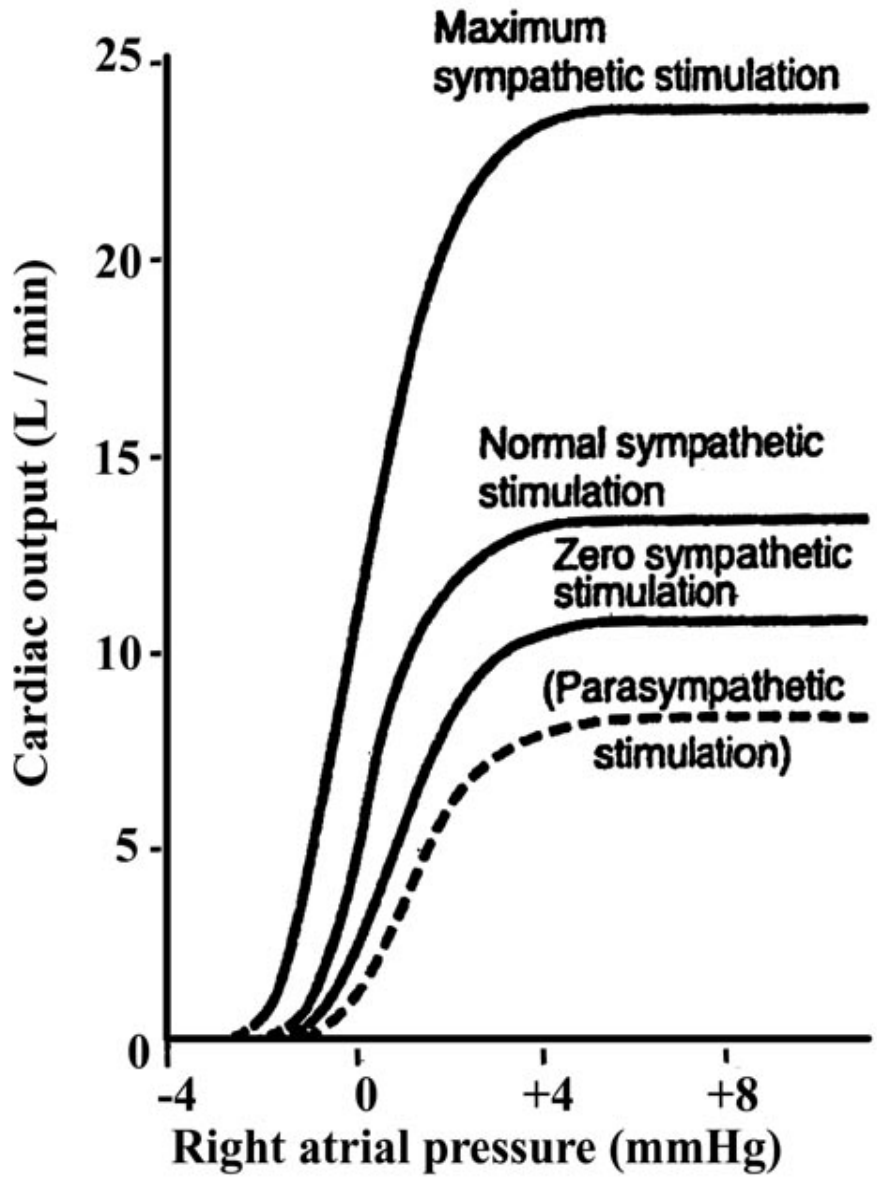




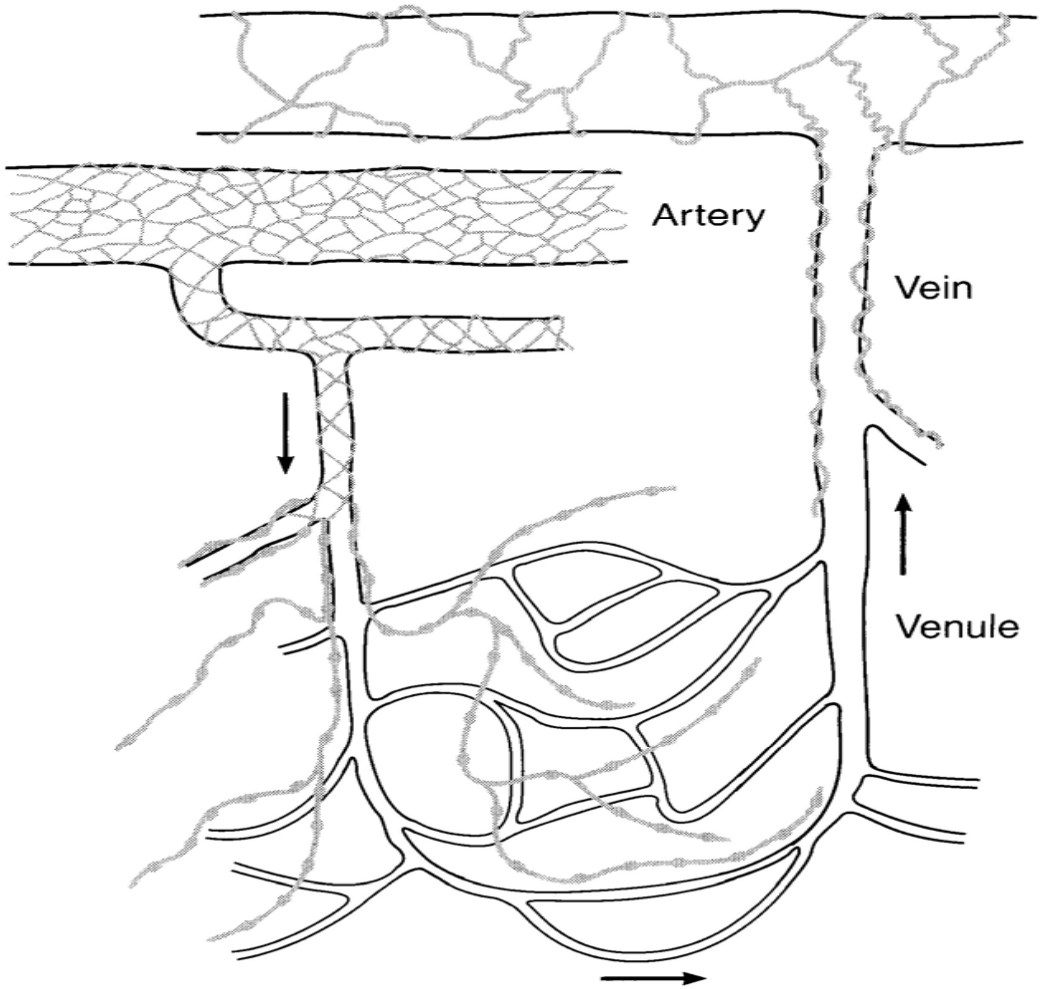
Cardiac vagal tone
Negative chronotropic action




Ca++
Norepinephrine
B receptor
Adenylyl cyclase
Gs
ATP
cAMP
Inactive protein kinase
Active protein kinase
1
Phospholamban
Ca2+-ATPase
Ca++
Sarcoplasmic reticulum
2
3
Actin myosin
Troponin tropomyosin
Ca++
Force and velocity
Positive inotropic action


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(交感缩血管纤维)	Noradrenergic NE α, β receptors	tonic discharge	to most vascular beds
Sympathetic vasodilator fibers(交感舒血管纤维)	Cholinergic, Ach M_2 receptor	no tonic discharge, do no participate in BP control. Preganglionic fiber	skeletal muscles, heart,lungs,uterus, kidneys，sweat glands
Parasympathetic vasodilator fibers(副交感舒血管纤维)	Cholinergic, Ach M receptor	no tonic activity, regulates regional blood flow.	blood vessels in salivary & GI gland, liver, external genitalia.



- The arterioles： most densely innervated,
- All blood vessels except capillaries and venules contain smooth muscle and receive the 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.

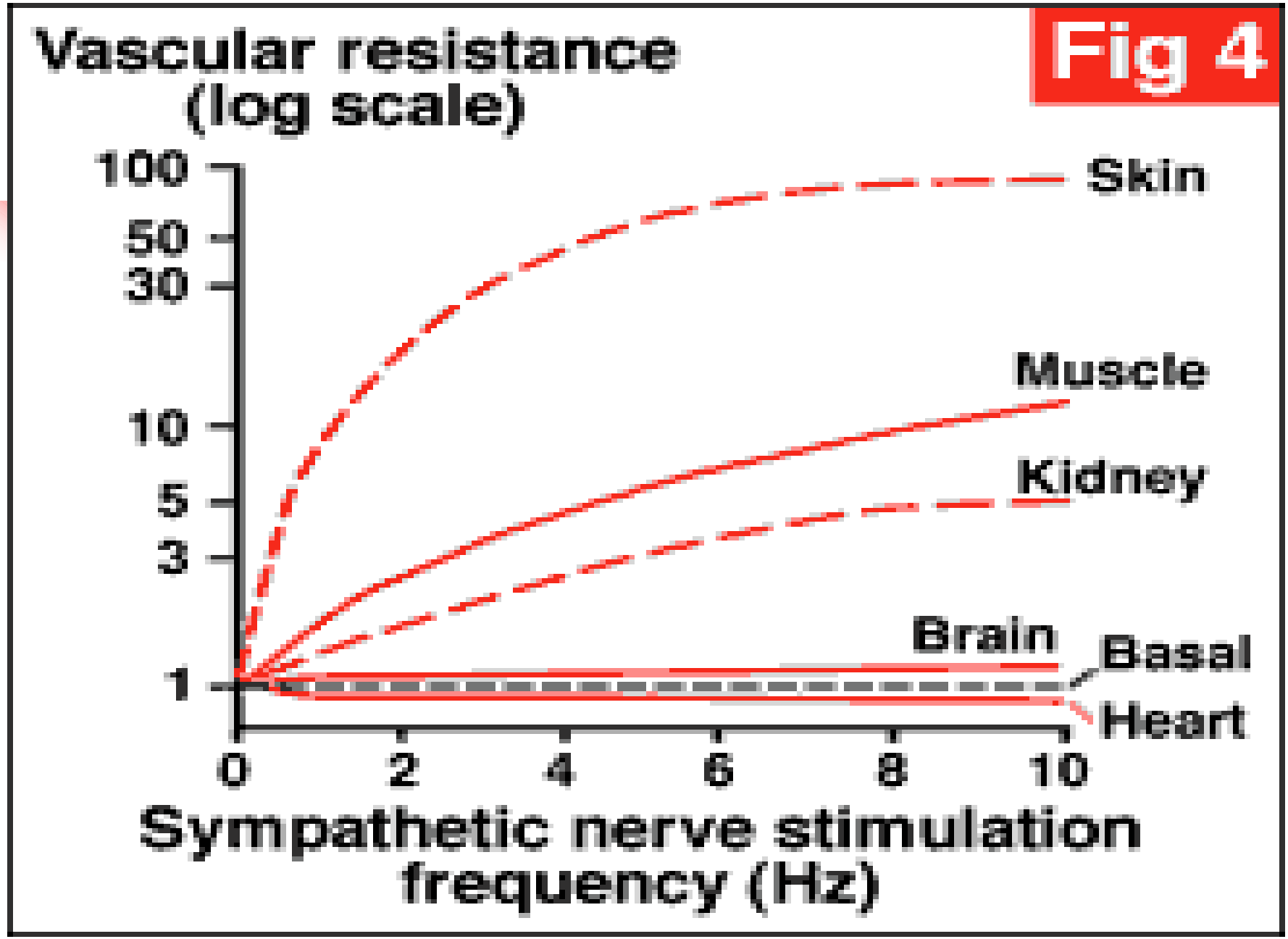
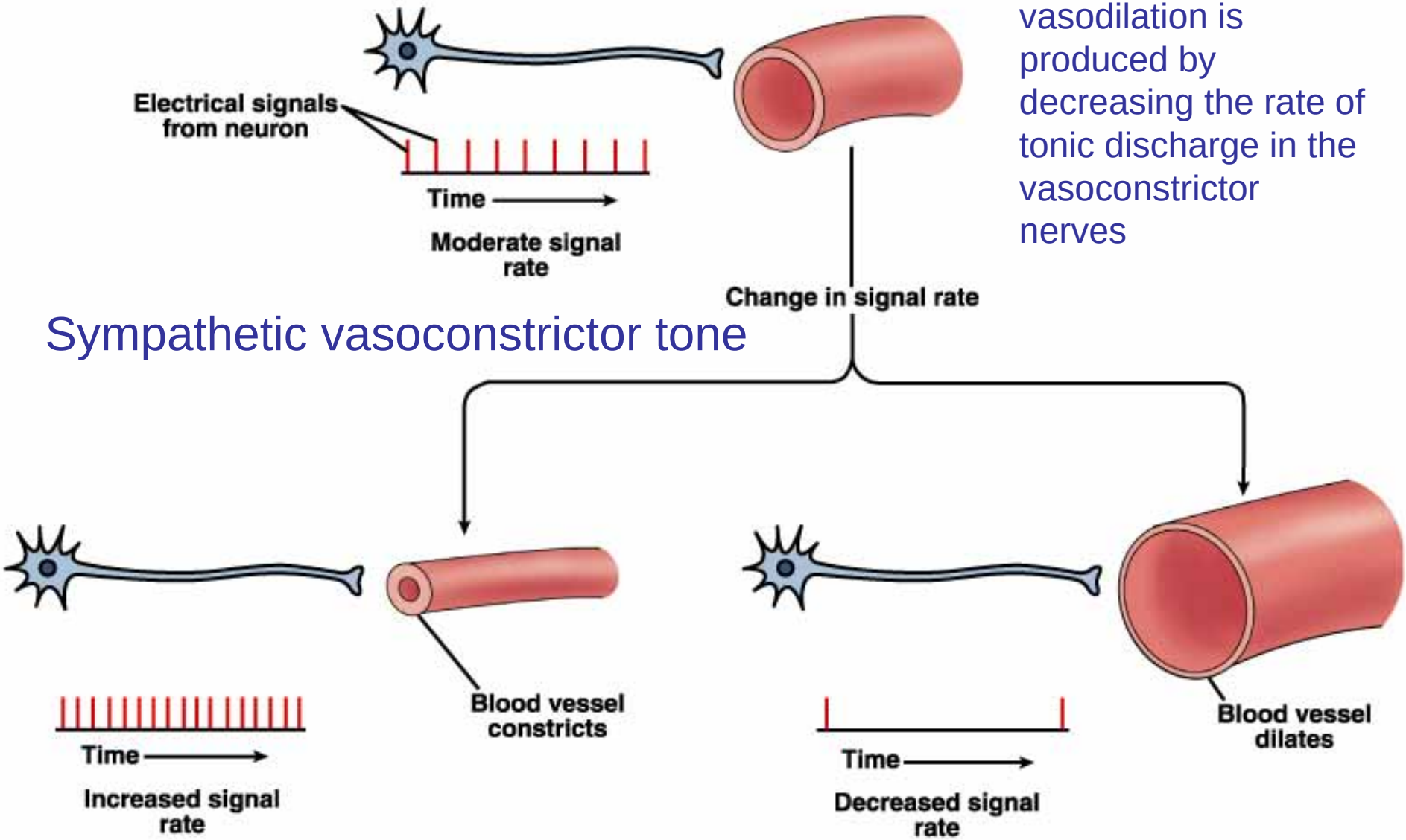


Fig 4
Vascular resistance
(log scale)
100
50
30
10
5
3
1
Skin
Muscle
Kidney
Brain
Basal
Heart
0
2
4
6
8
10
Sympathetic nerve stimulation
frequency (Hz)

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

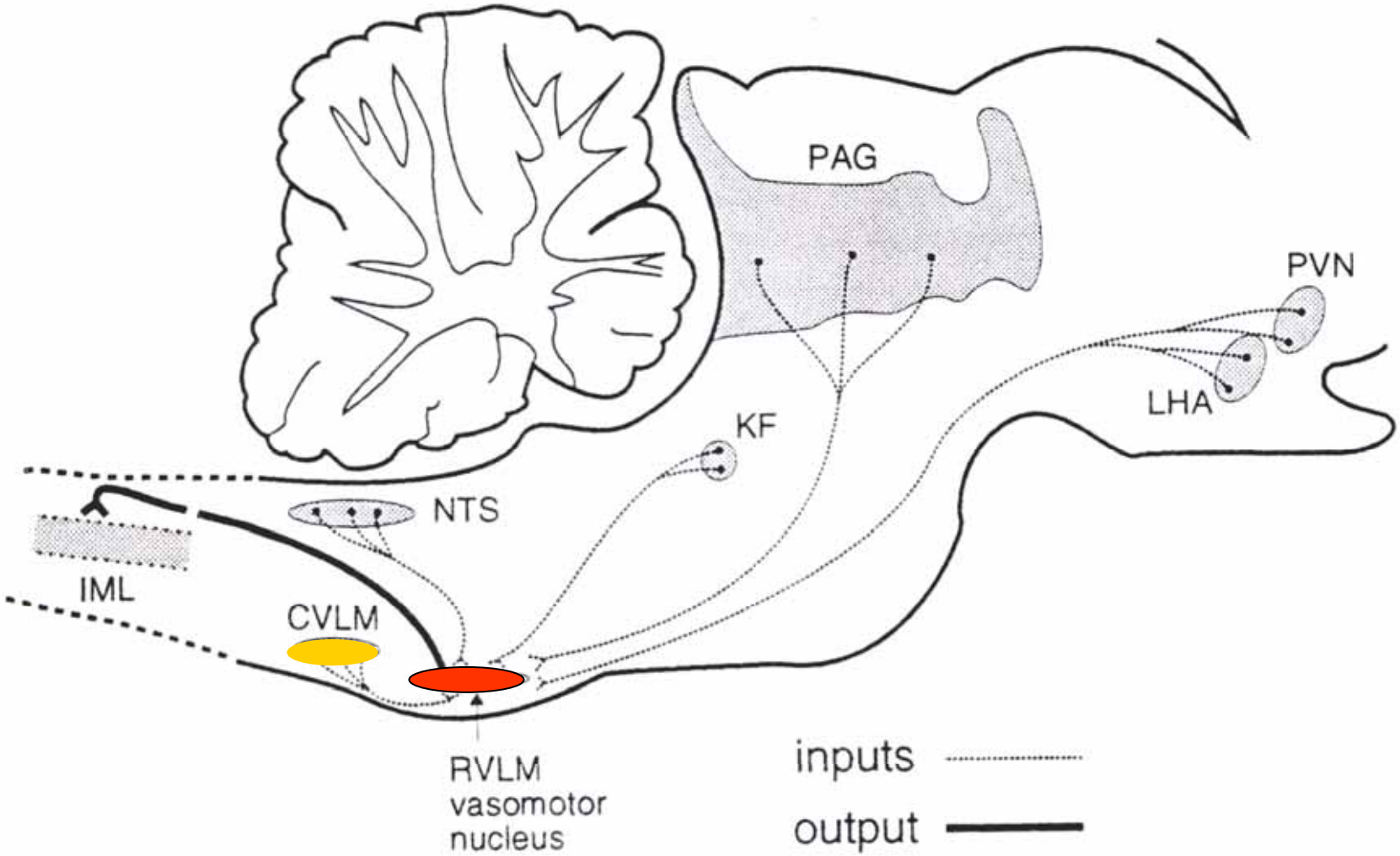
Sympathetic vasoconstrictor tone

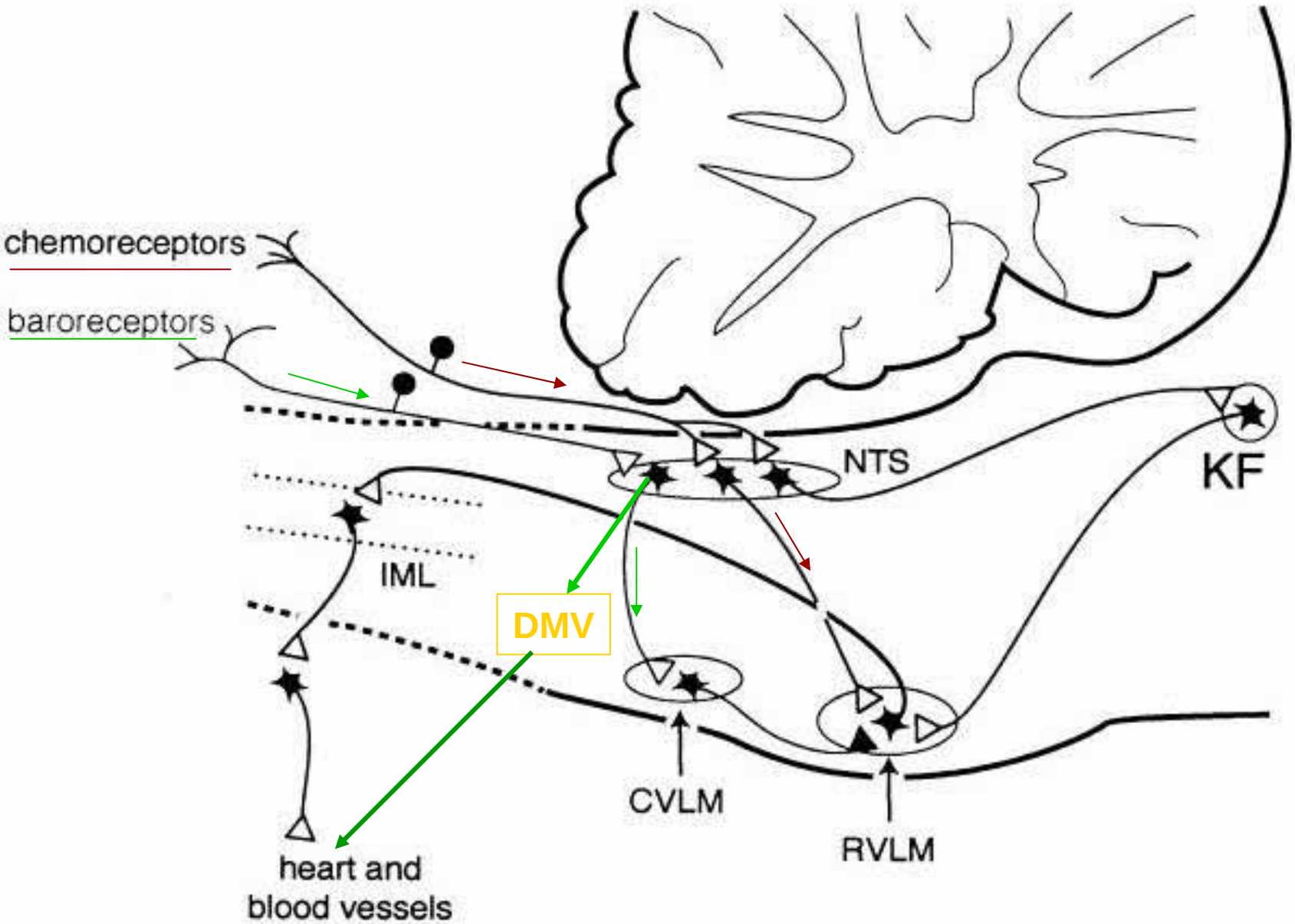


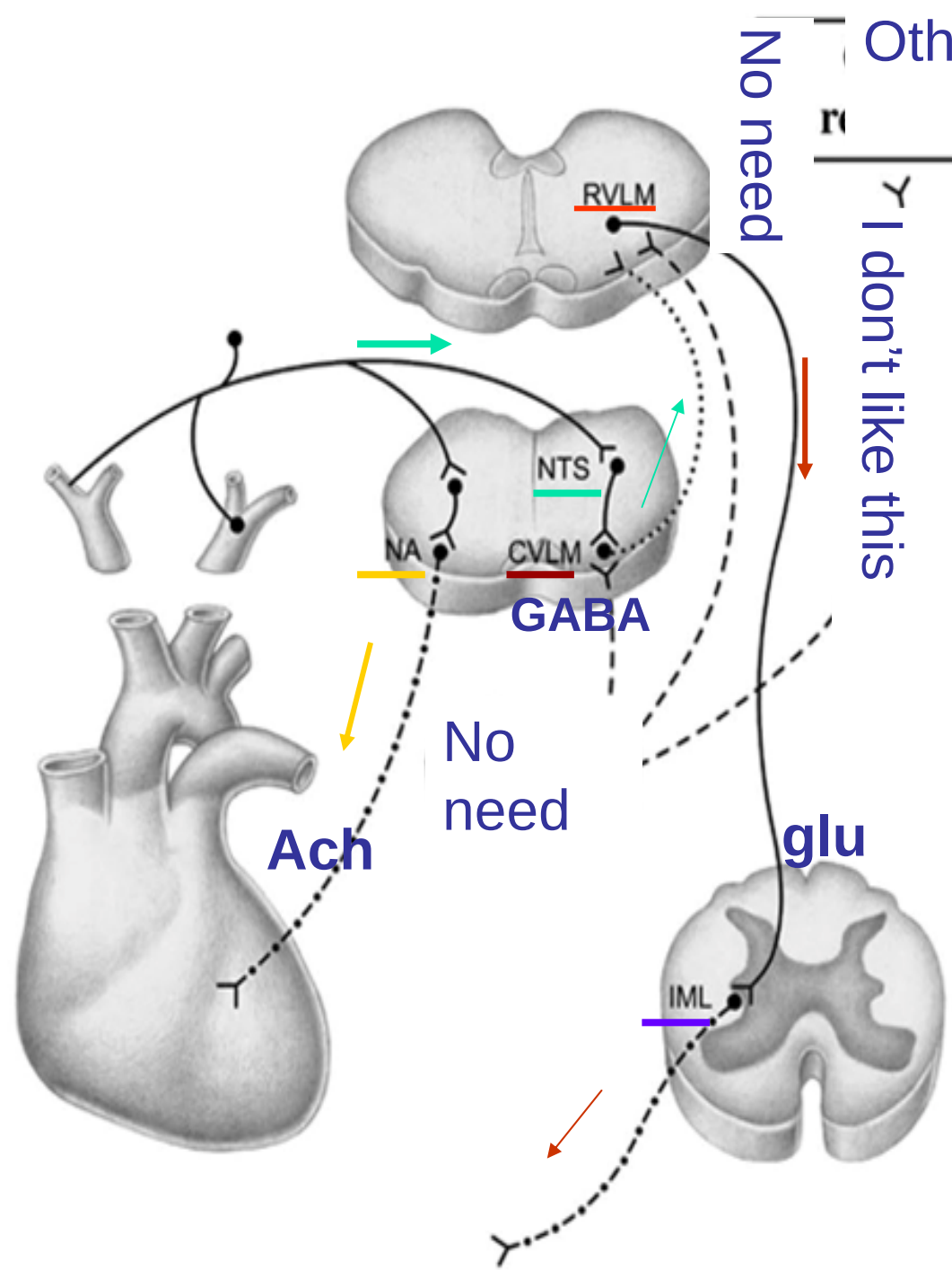
Medullary Cardiovascular Center

RVLM rostral ventro-lateral medulla C1 group, vasomotor area	▪Tonic outputs, always active, projecting to IML(T1-L3) ▪ important for sympathetic activation in response to **hypotension**	▪Promotes vasoconstriction ▪Inhibited by baro-Rs activation & CVLM ▪NTS inhibitory inter-neurons inhibits RVLM, GABA-ergic
CVLM Caudal ventro-lateral medulla A1 group	▪ Project to PVN, mediate vasopressin response to **hypovolemia** ▪ No descending fibers to IML	
Cardio-inhibitory area	DMV, ambiguus	NTS excitatory inter-neurons→DMV →vagal tone↑ →bradycardia
NTS(nucleus of the tractus solitarius)	where the afferents end	Glu.,substance P

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.



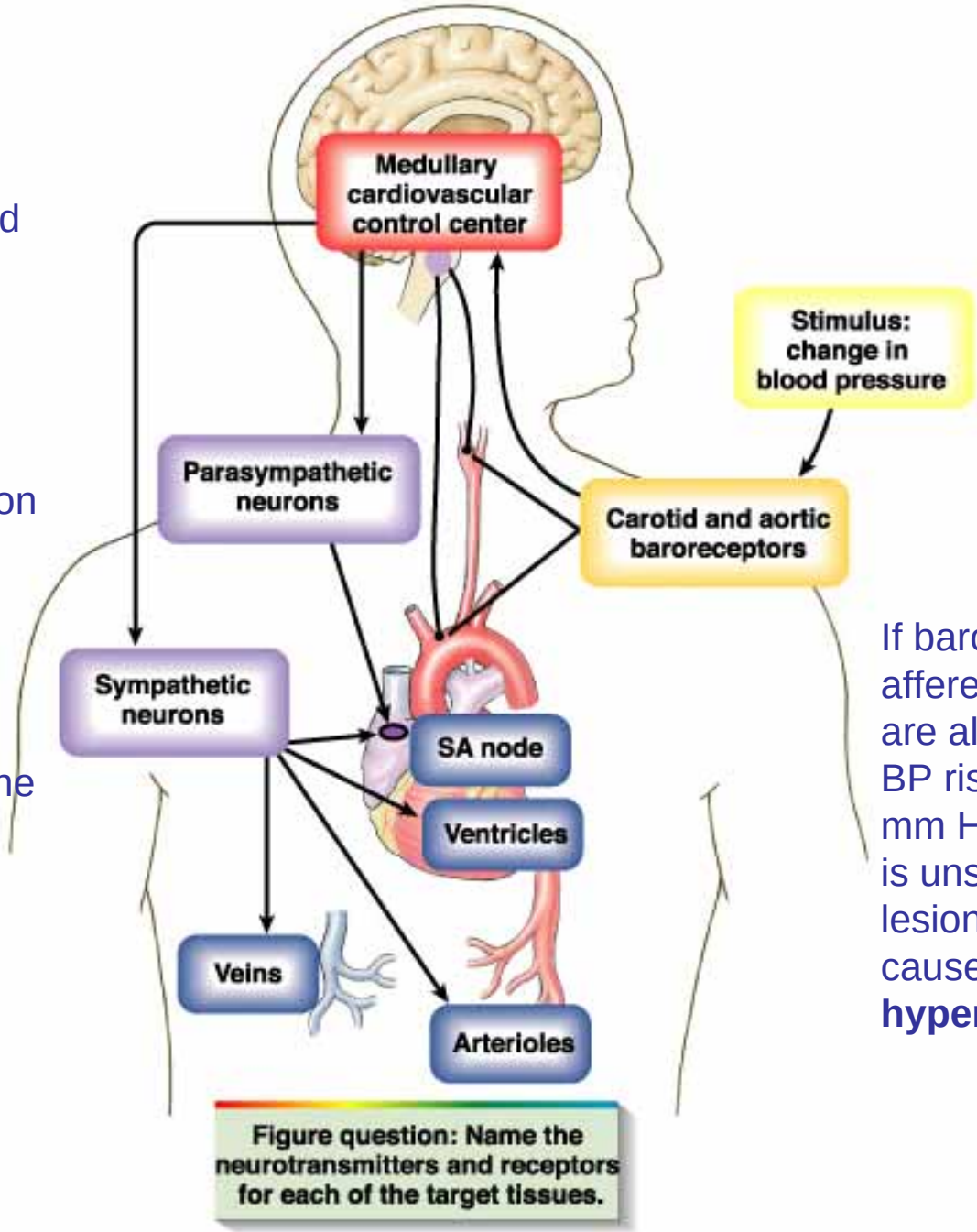

chemoreceptors
baroreceptors
NTS
KF
IML
DMV
CVLM
RVLM
heart and
blood vessels



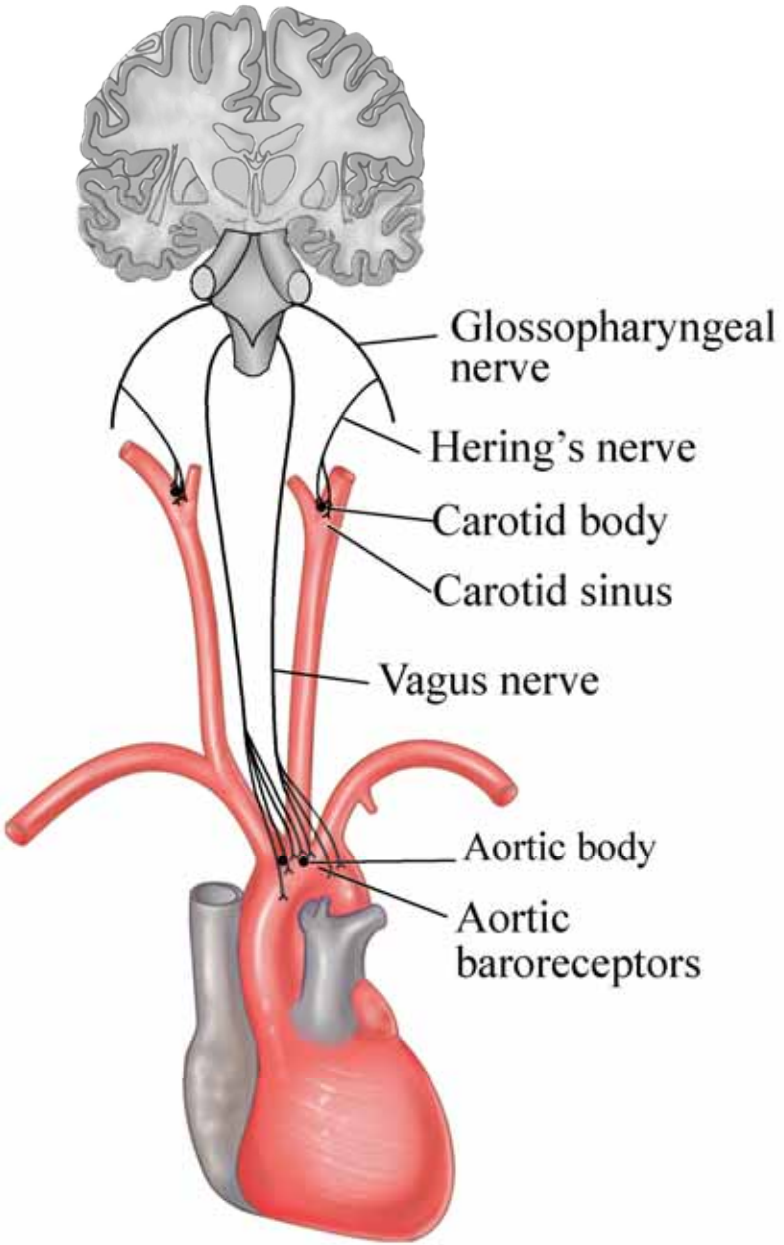
- NA = nucleus ambiguus.
- Dotted line = GABAergic projection;
continuous line = glutamatergic projection;

- dashed line = modulatory projections;
- dash-dot line = cholinergic projections.

Bilateral clamping of the carotid arteries proximal to the carotid sinuses elevates the BP and HR 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.

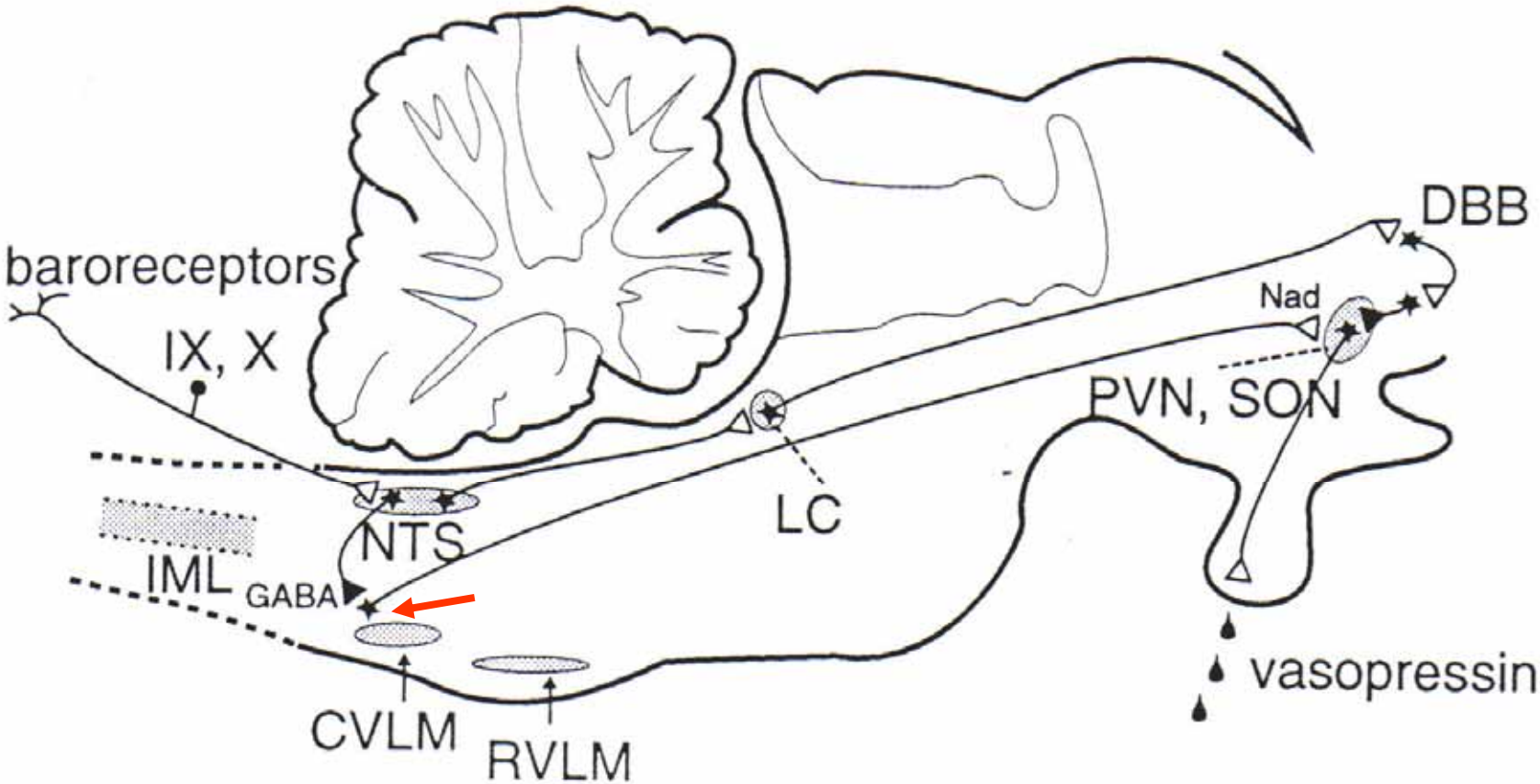


If baroreceptor afferents in the vagi are also interrupted, BP rises to 300/200 mm Hg or higher and is unstable. Bilateral lesions of the NTS, cause **neurogenic hypertension.**



- 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.

- 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.



Blood pressure ↓ → Baro-R → A1 group → VP neuron → Urine output ↓

VP ↑

inhibitory inputs

excitatory inputs

Factors affecting the activity of the vasomotor area in the medulla.

Direct stimulation

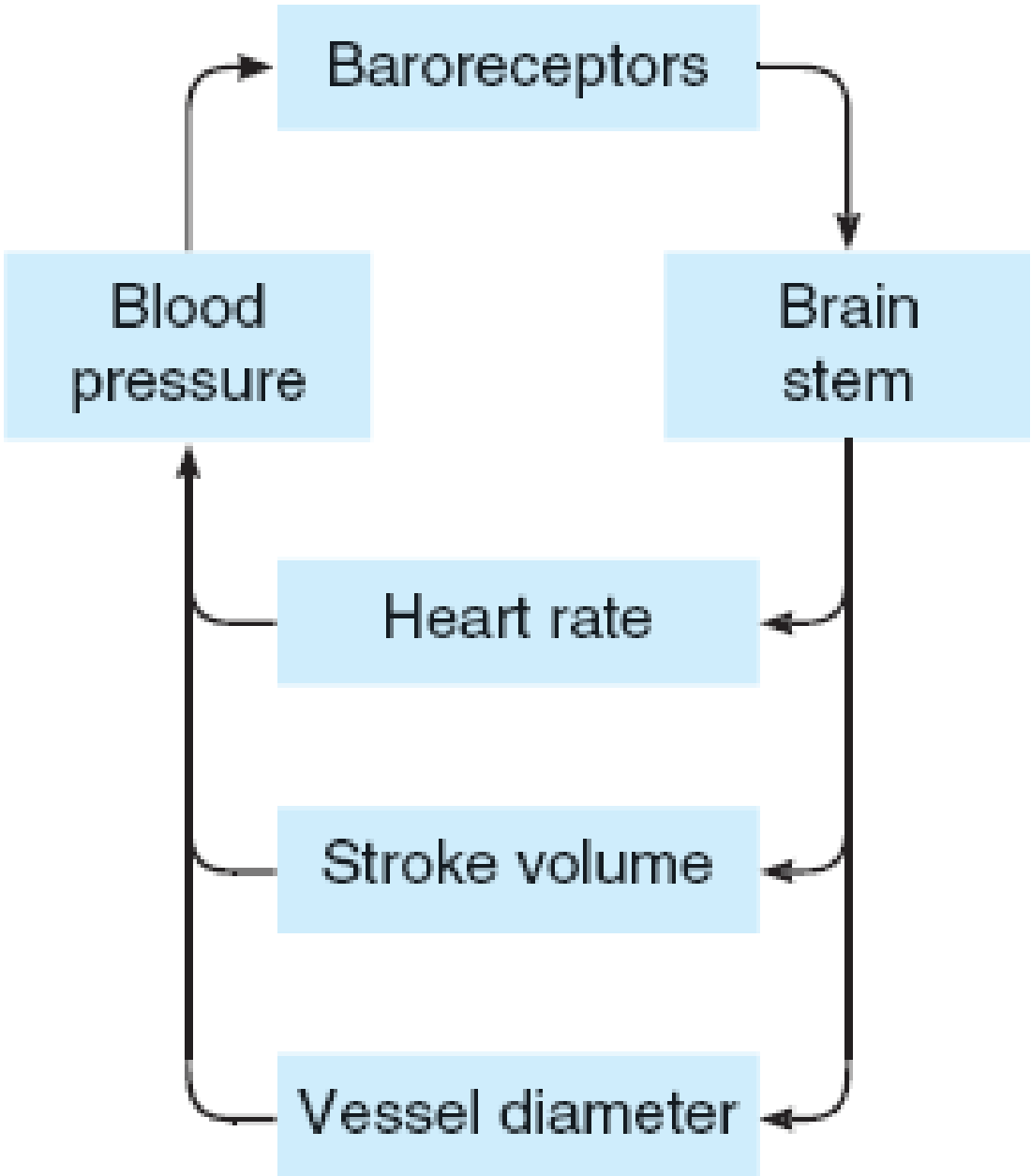
- CO_2
- Hypoxia

Excitatory inputs

- From cortex via hypothalamus
- From pain pathways and muscles
- From carotid and aortic chemoreceptors

Inhibitory inputs

- From cortex via hypothalamus
- From lungs
- From carotid, aortic, and cardiopulmonary baroreceptors



Baroreceptors Reflex Depressor reflex

Baro-Rs in both carotid sinus and aortic arch: branched-coiled bare ends. Stretch-sensitive. Crotid baro-Rs: AP 50-200 mm Hg, respond to sustained/pulse pressure.

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

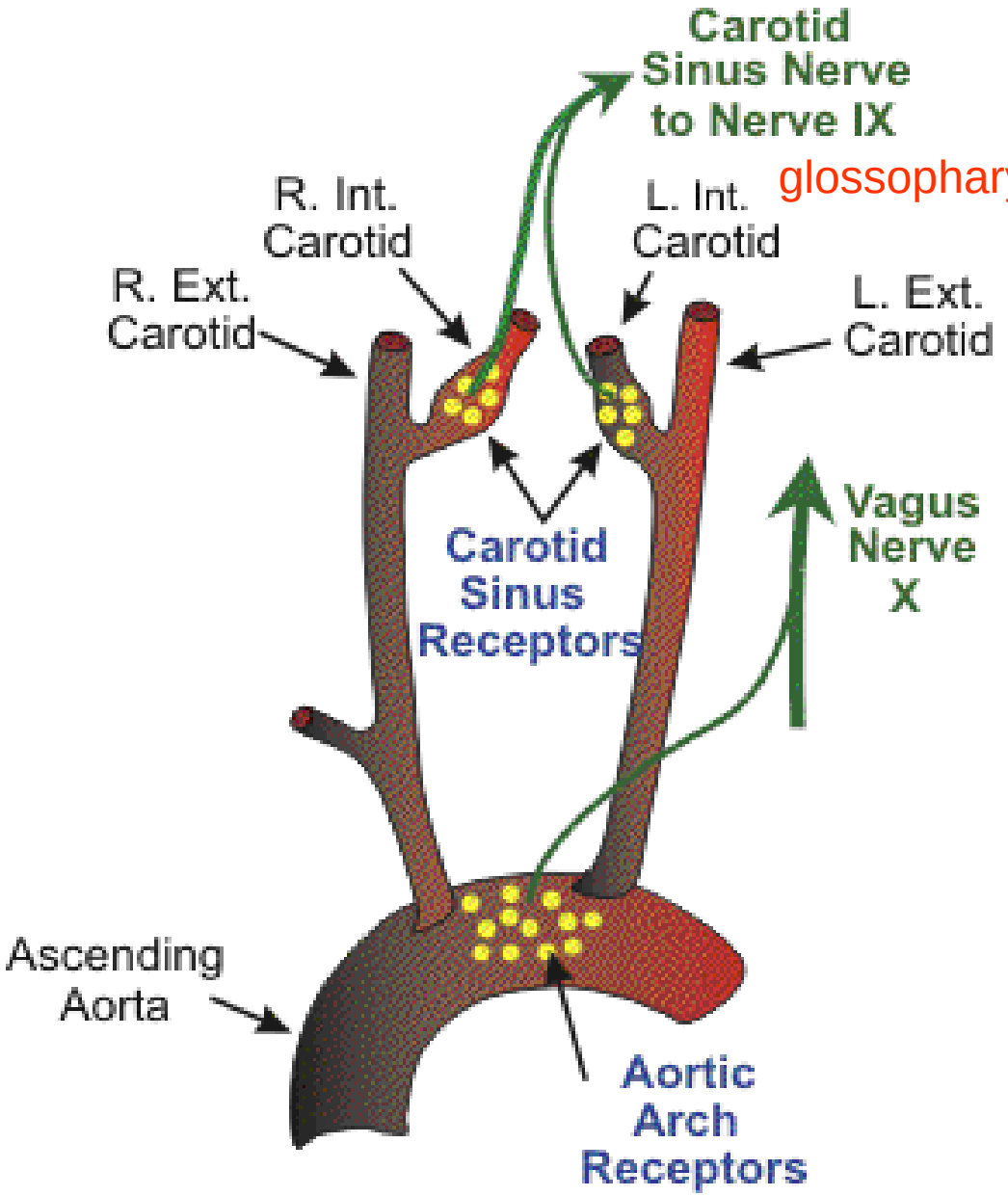


Figure 1. Location and innervation of arterial baroreceptors.

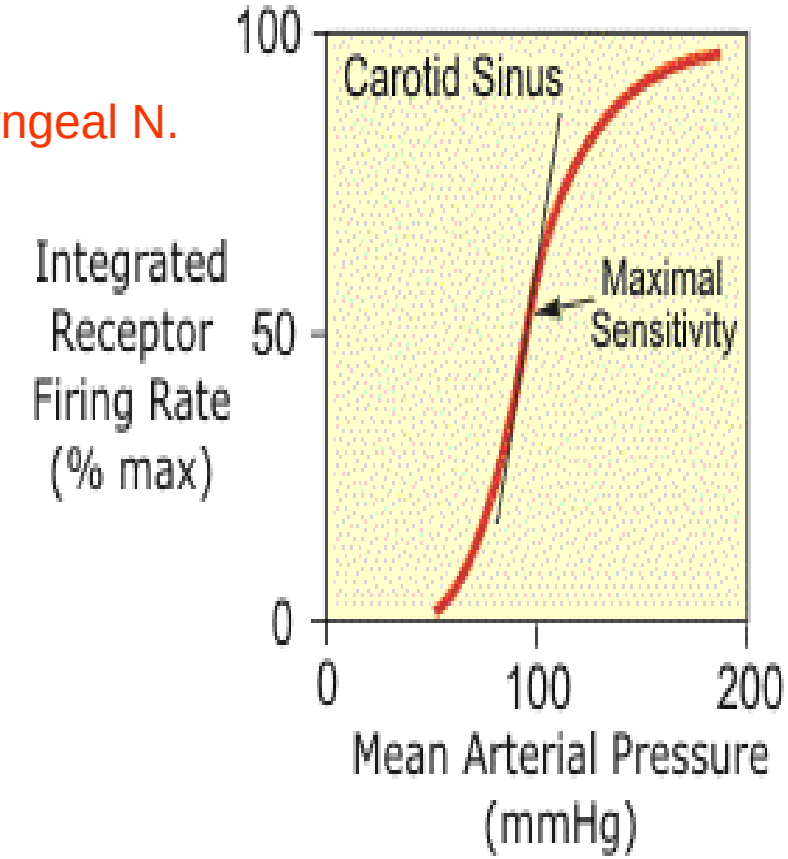
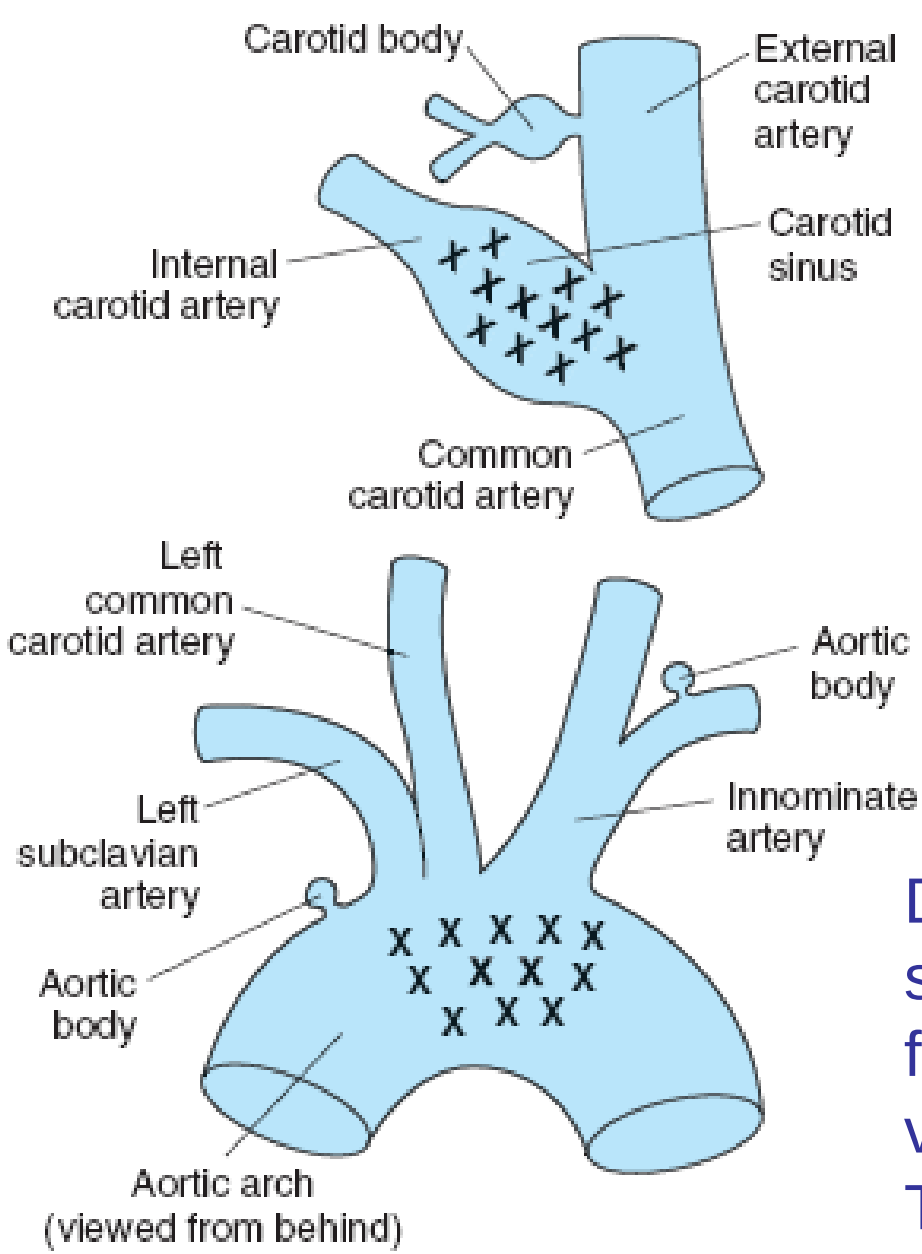
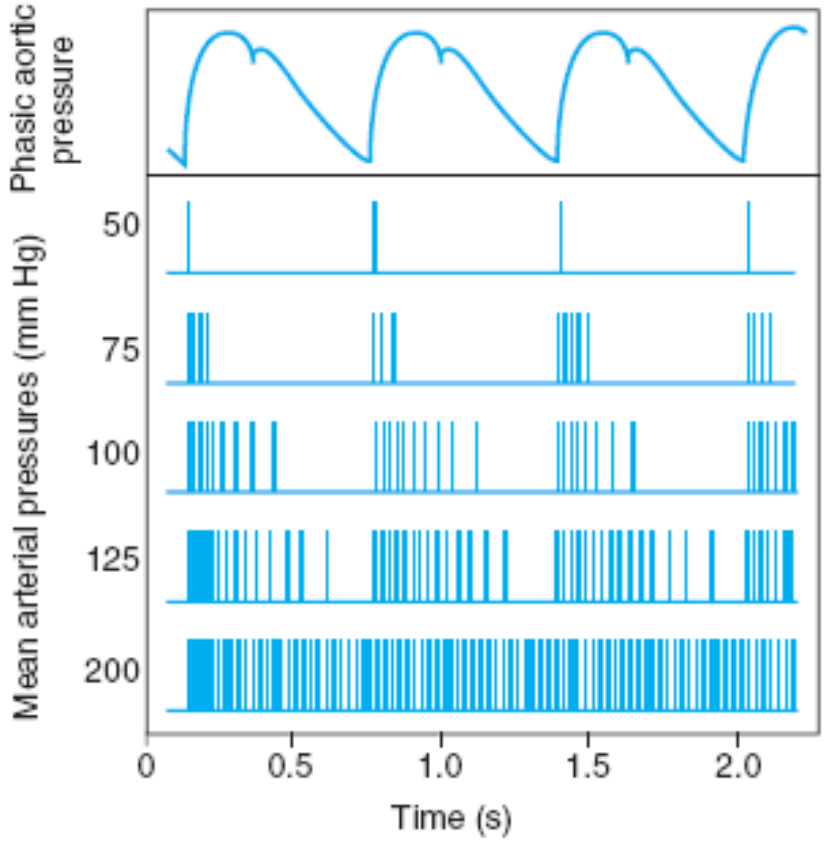
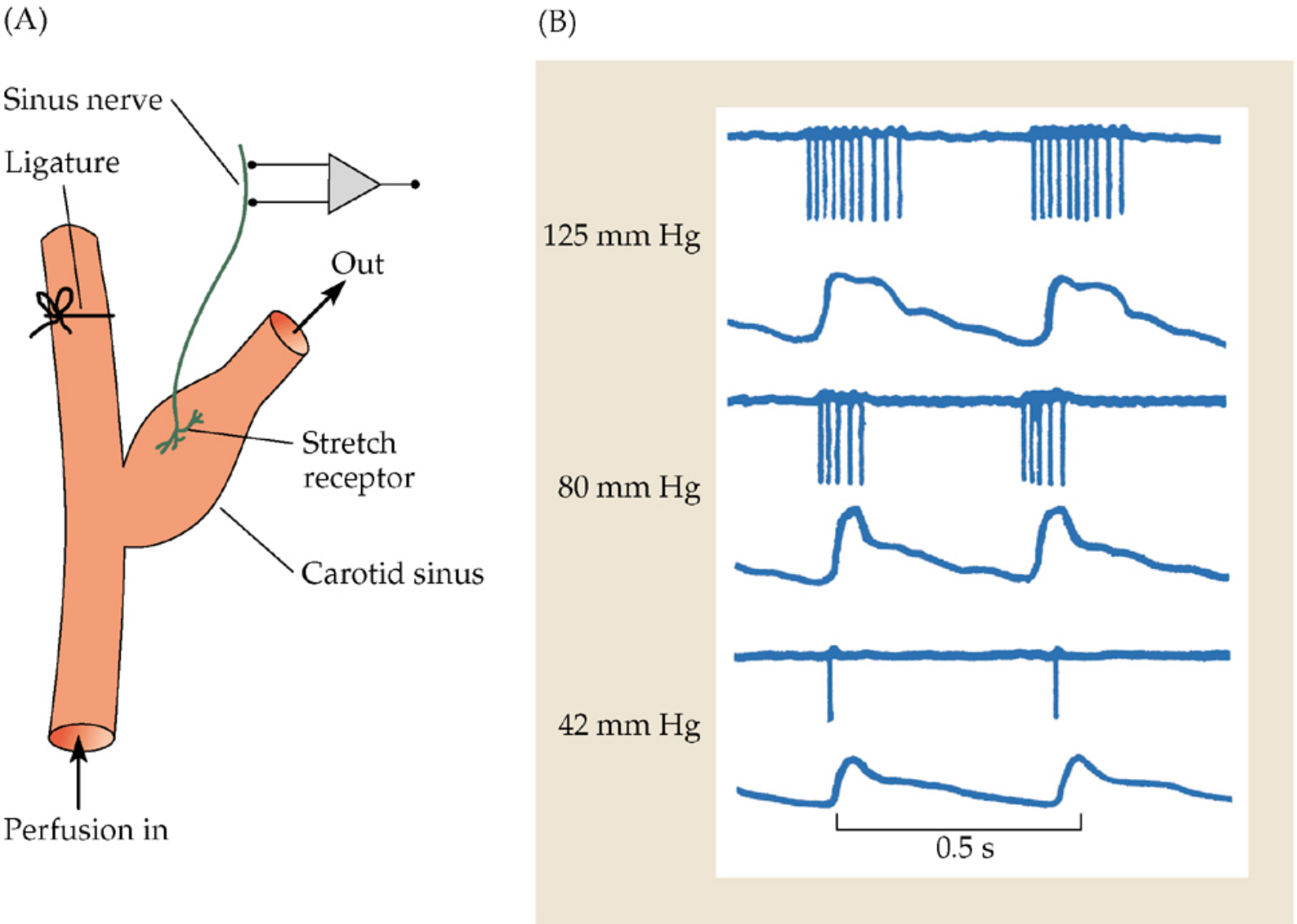


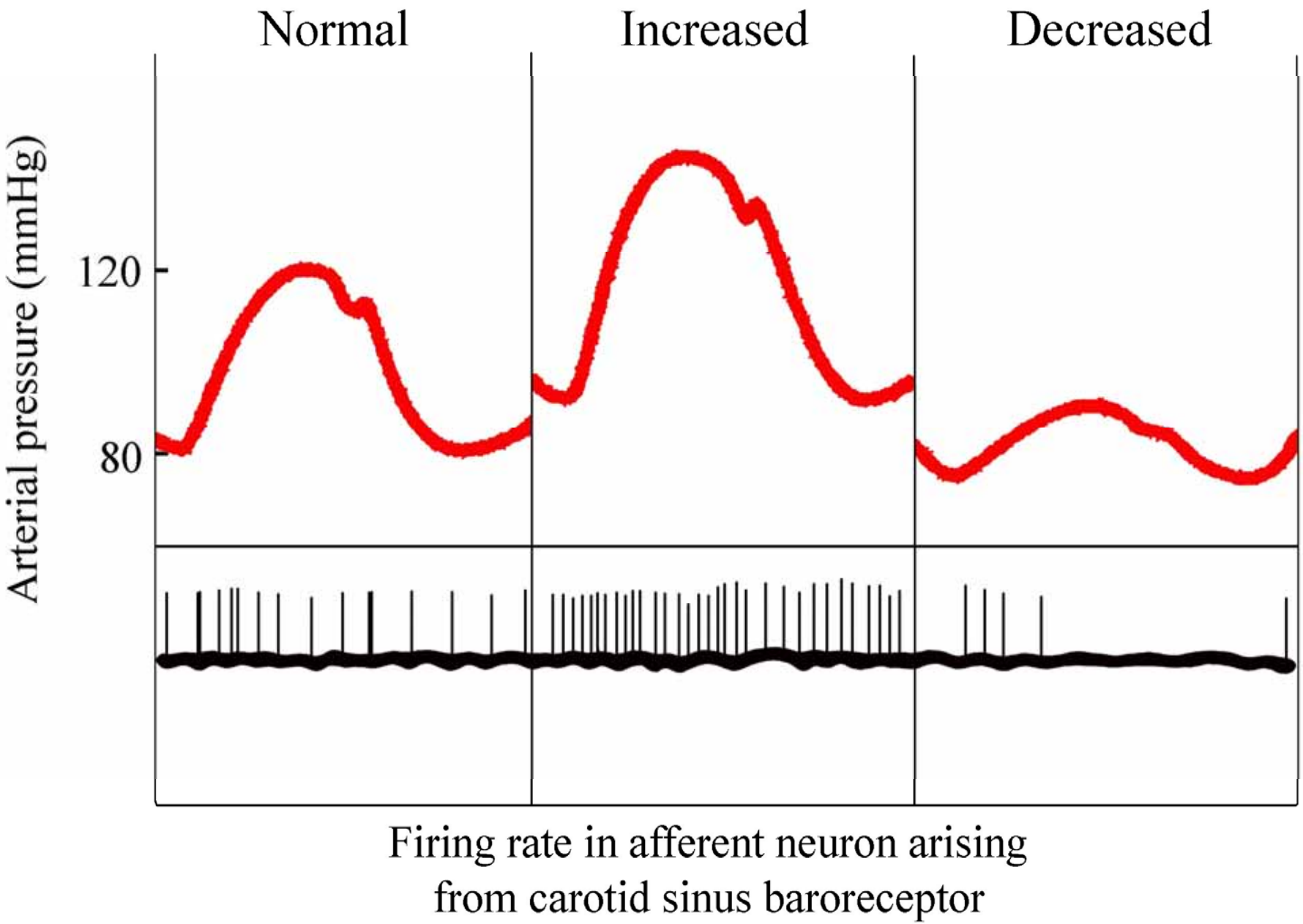
Figure 2. Effects of arterial pressure on carotid sinus firing rate. Increasing arterial pressure increases carotid sinus firing rate. Maximal baroreceptor sensitivity occurs near normal mean arterial pressure.



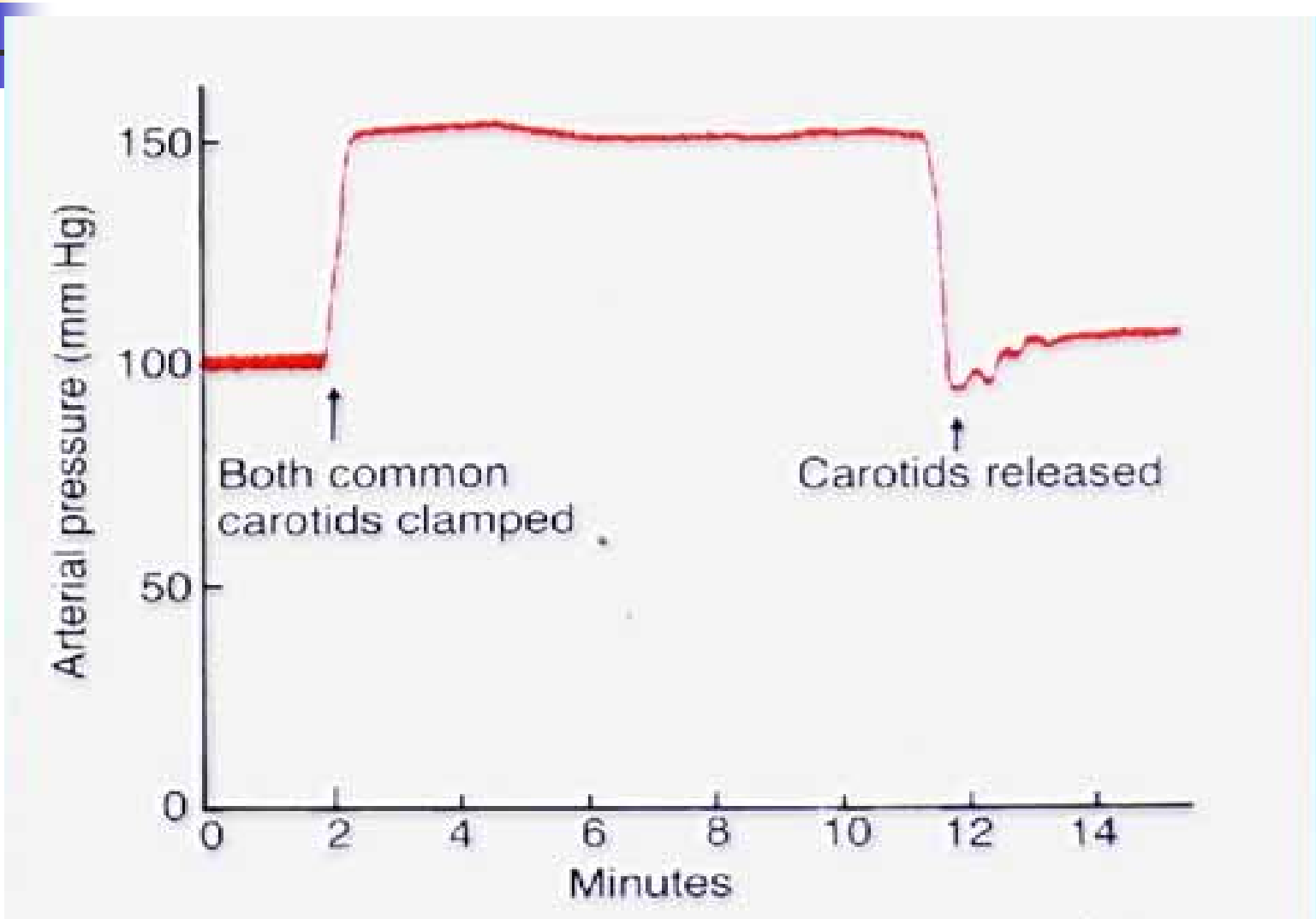


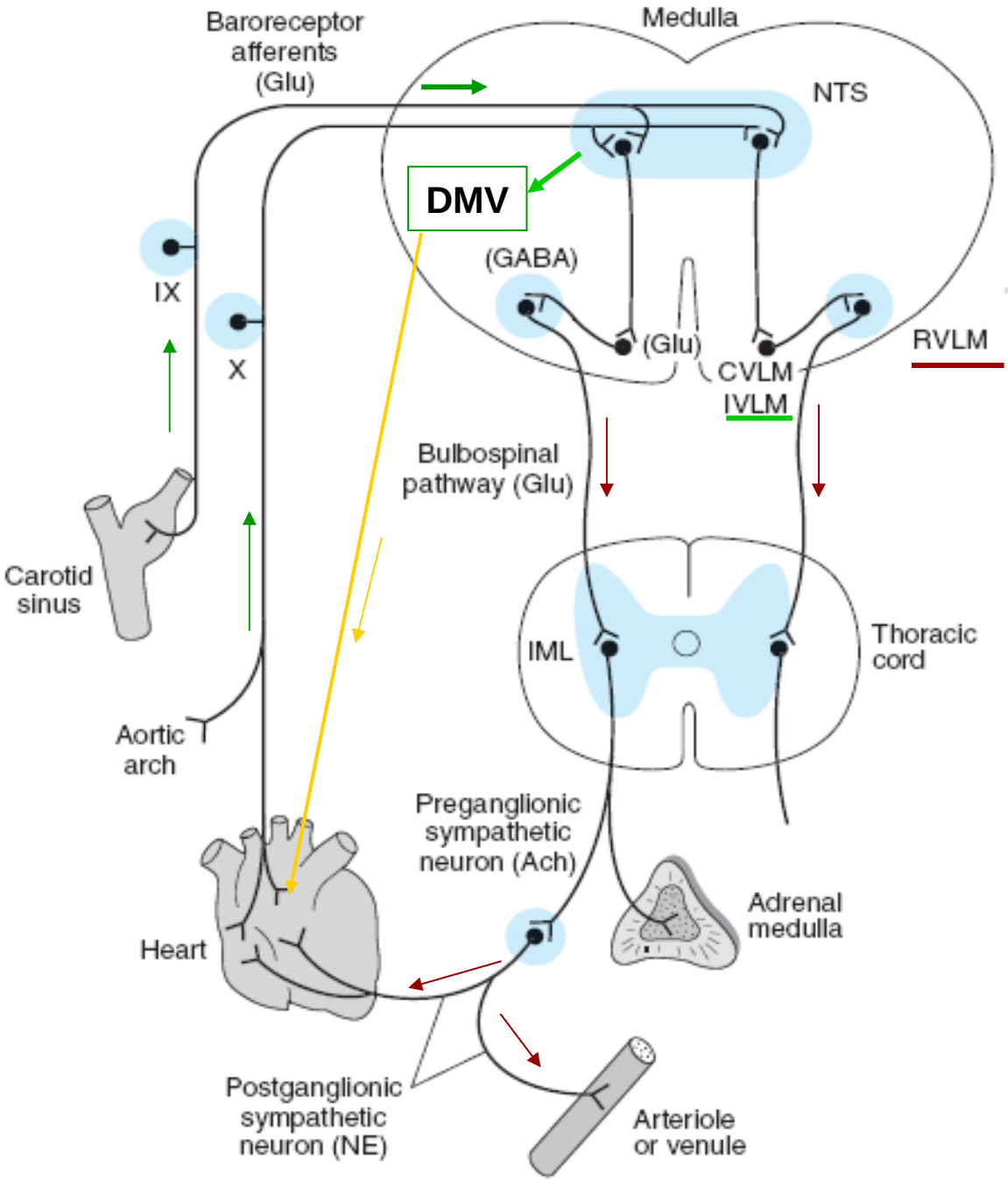
Discharges (vertical lines) in a single afferent nerve fiber from the carotid sinus at various arterial pressures. The receptors are located in the adventitia of the vessels.

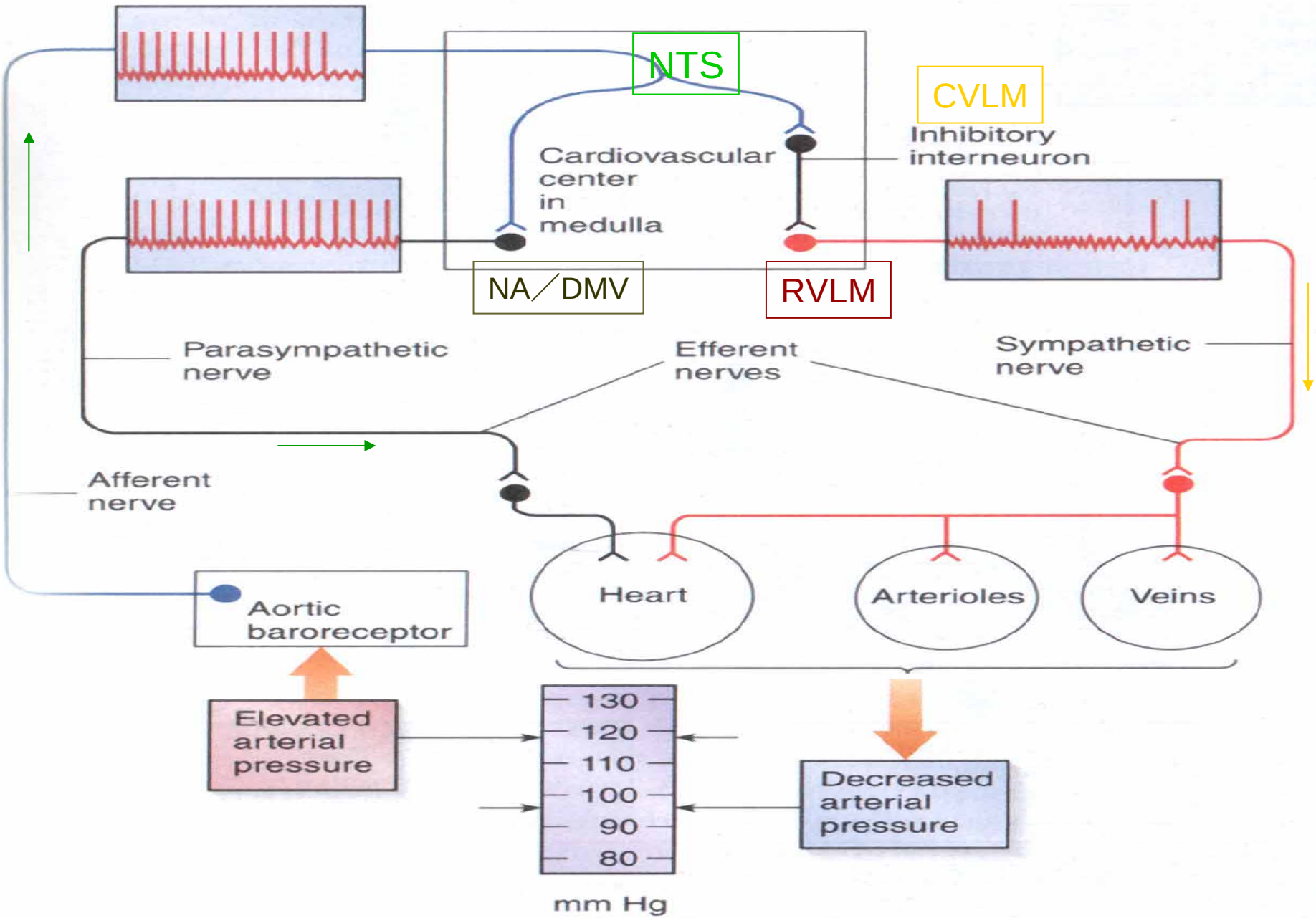


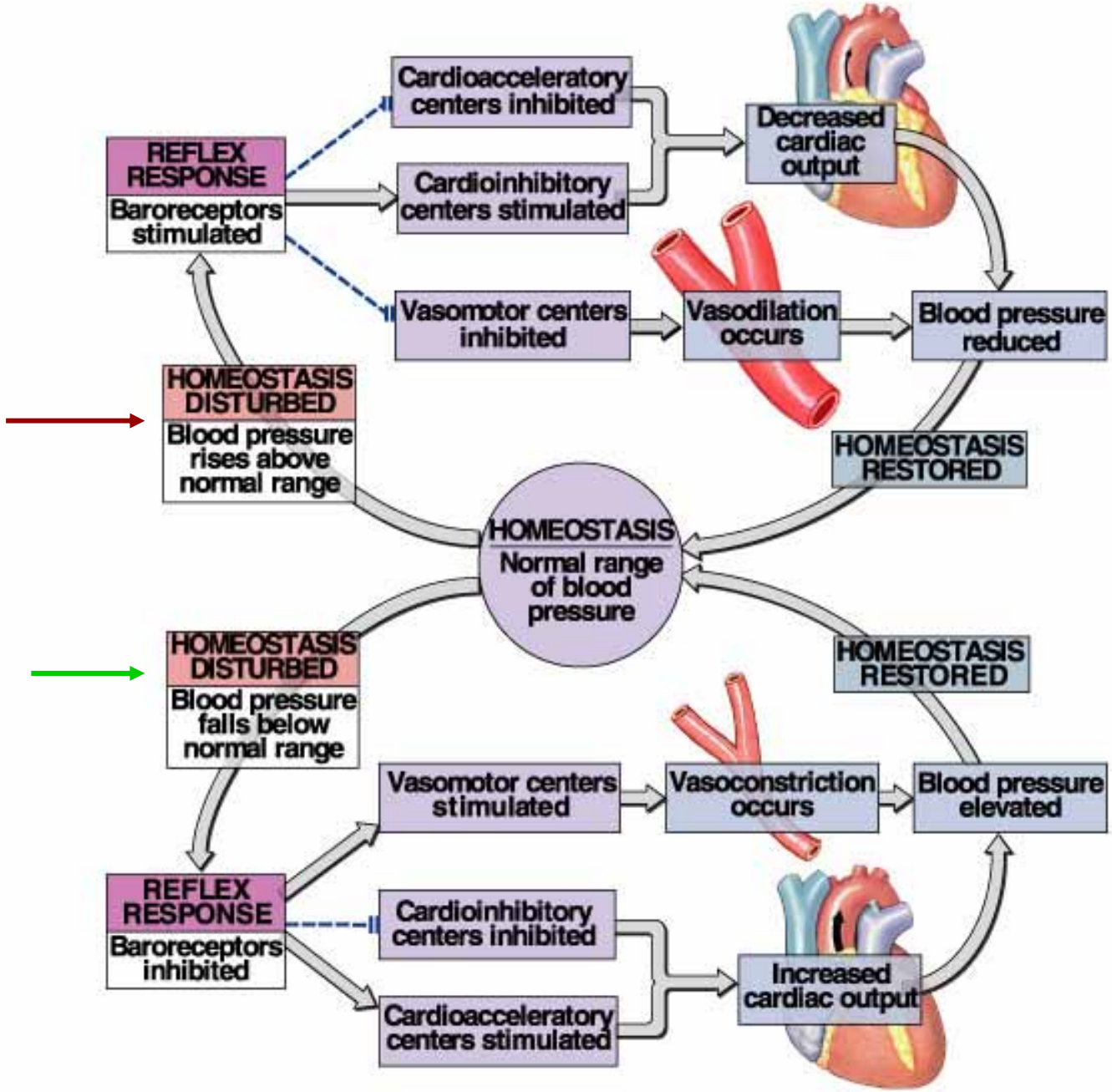

Normal
Increased
Decreased
Arterial pressure (mmHg)
120
80
Firing rate in afferent neuron arising
from carotid sinus baroreceptor

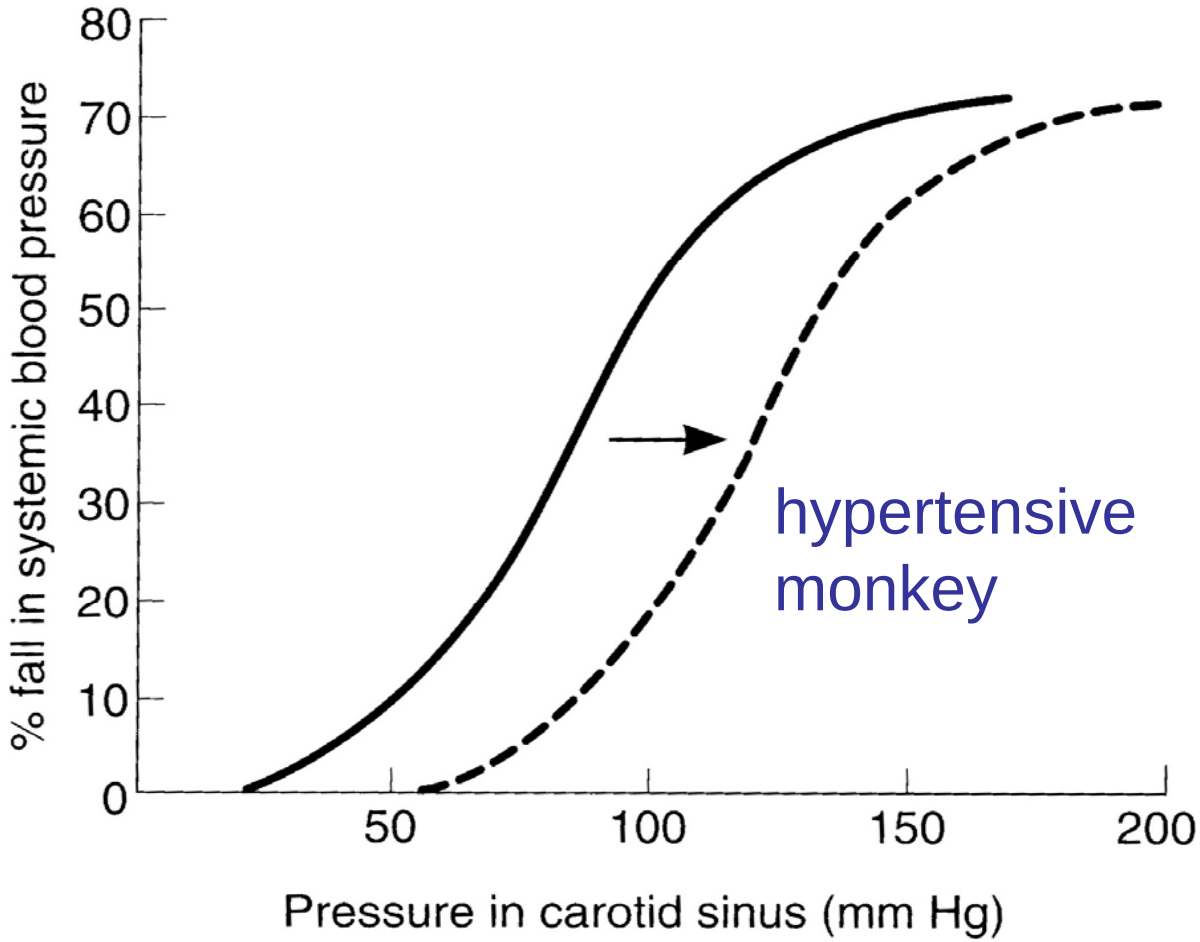
Common carotid clamped




Baroreceptor afferents (Glu)
Medulla
NTS
DMV
(GABA)
IX
X
(Glu)
RVLM
CVLM
IVLM
Bulbospinal pathway (Glu)
Carotid sinus
IML
Thoracic cord
Aortic arch
Preganglionic sympathetic neuron (Ach)
Adrenal medulla
Heart
Postganglionic sympathetic neuron (NE)
Arteriole or venule

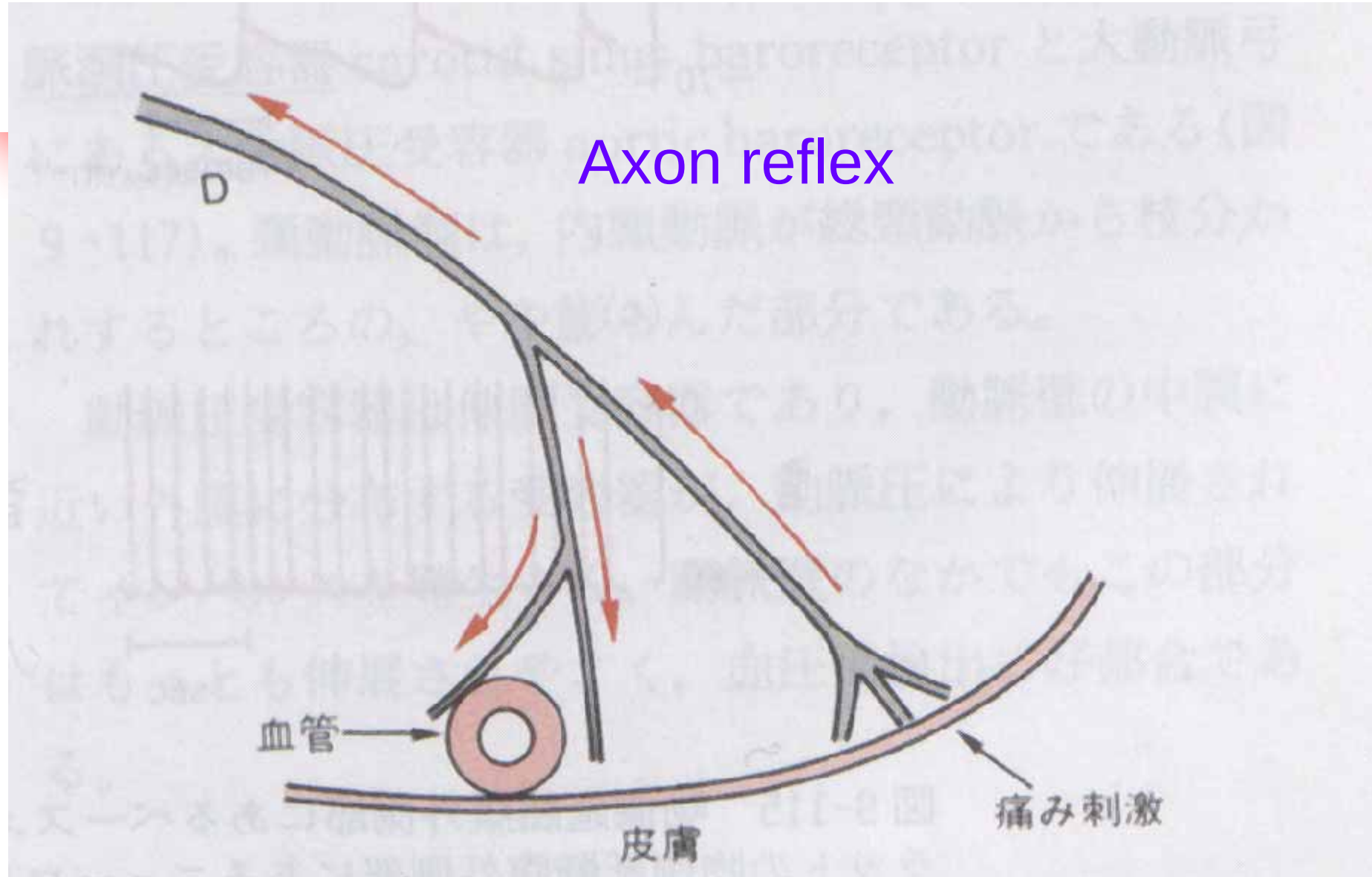

NTS
CVLM
Inhibitory interneuron
Cardiovascular center in medulla
NA／DMV
RVLM
Parasympathetic nerve
Efferent nerves
Sympathetic nerve
Afferent nerve
Heart
Arterioles
Veins
Aortic baroreceptor
Elevated arterial pressure
Decreased arterial pressure
130
120
110
100
90
80
mm Hg


Cardioacceleratory centers inhibited
REFLEX RESPONSE
Baroreceptors stimulated
Cardioinhibitory centers stimulated
Decreased cardiac output
Vasomotor centers inhibited
Vasodilation occurs
Blood pressure reduced
HOMEOSTASIS DISTURBED
Blood pressure rises above normal range
HOMEOSTASIS RESTORED
HOMEOSTASIS
Normal range of blood pressure
HOMEOSTASIS DISTURBED
Blood pressure falls below normal range
HOMEOSTASIS RESTORED
Vasomotor centers stimulated
Vasoconstriction occurs
Blood pressure elevated
REFLEX RESPONSE
Baroreceptors inhibited
Cardioinhibitory centers inhibited
Cardioacceleratory centers stimulated
Increased cardiac output

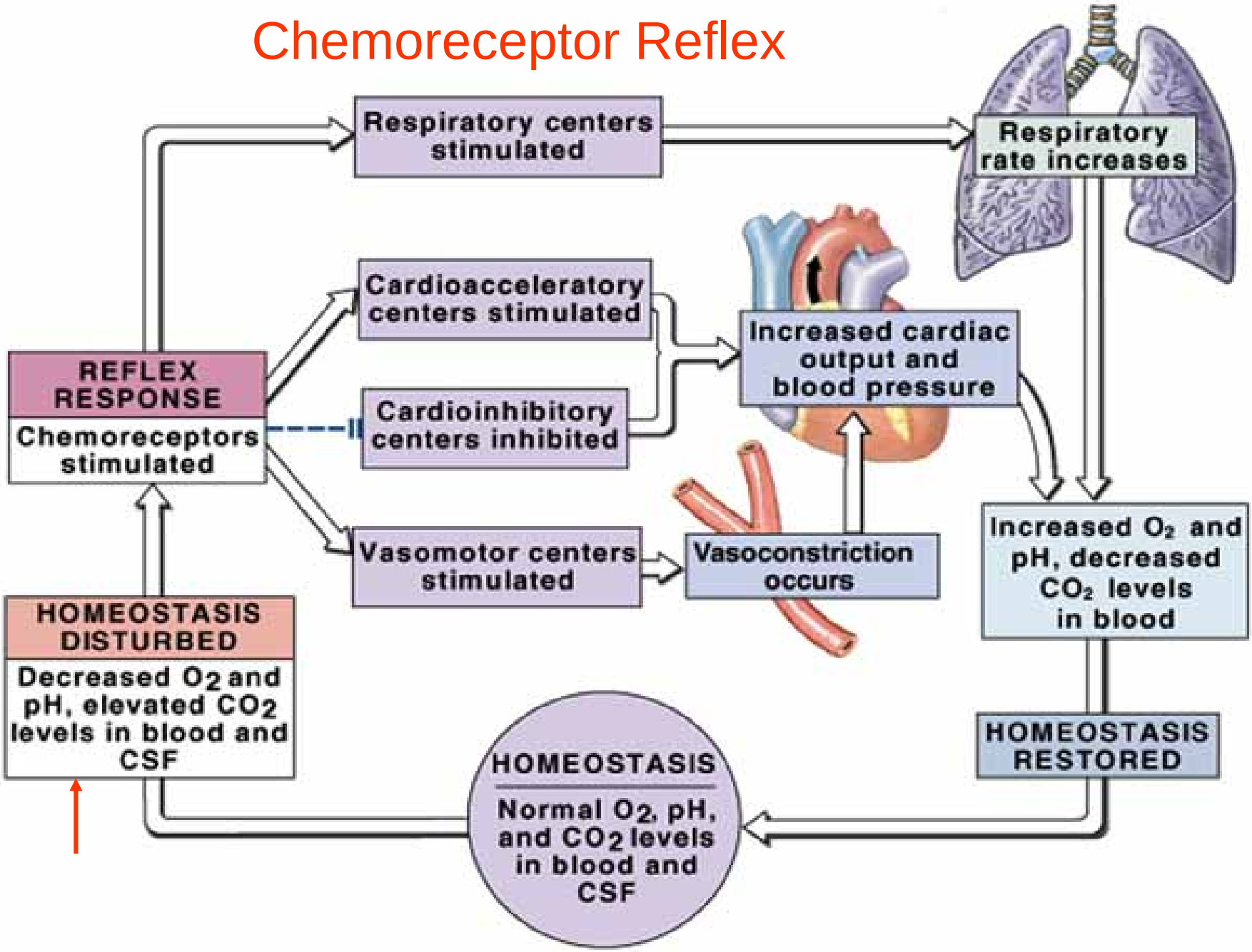


When one carotid sinus of a monkey is isolated and perfused and the other baroreceptors are denervated, there is no discharge in the afferent fibers from the perfused sinus and no drop in the animal's arterial pressure or heart rate when the perfusion pressure is below 30 mm Hg. At perfusion pressures of 70–110 mm Hg, the relation between the perfusion pressure and the fall in blood pressure and heart rate produced in the monkey is essentially linear. At perfusion pressures above 150 mm Hg there is no further increase in response

Axon reflex



Chemoreceptor Reflex

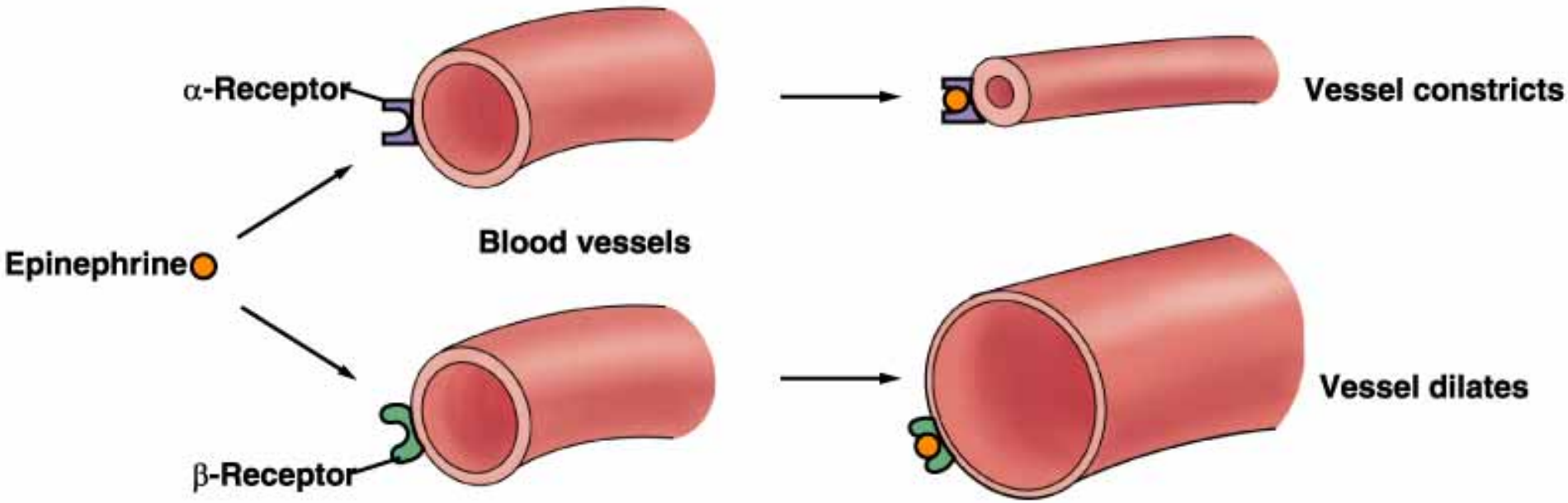


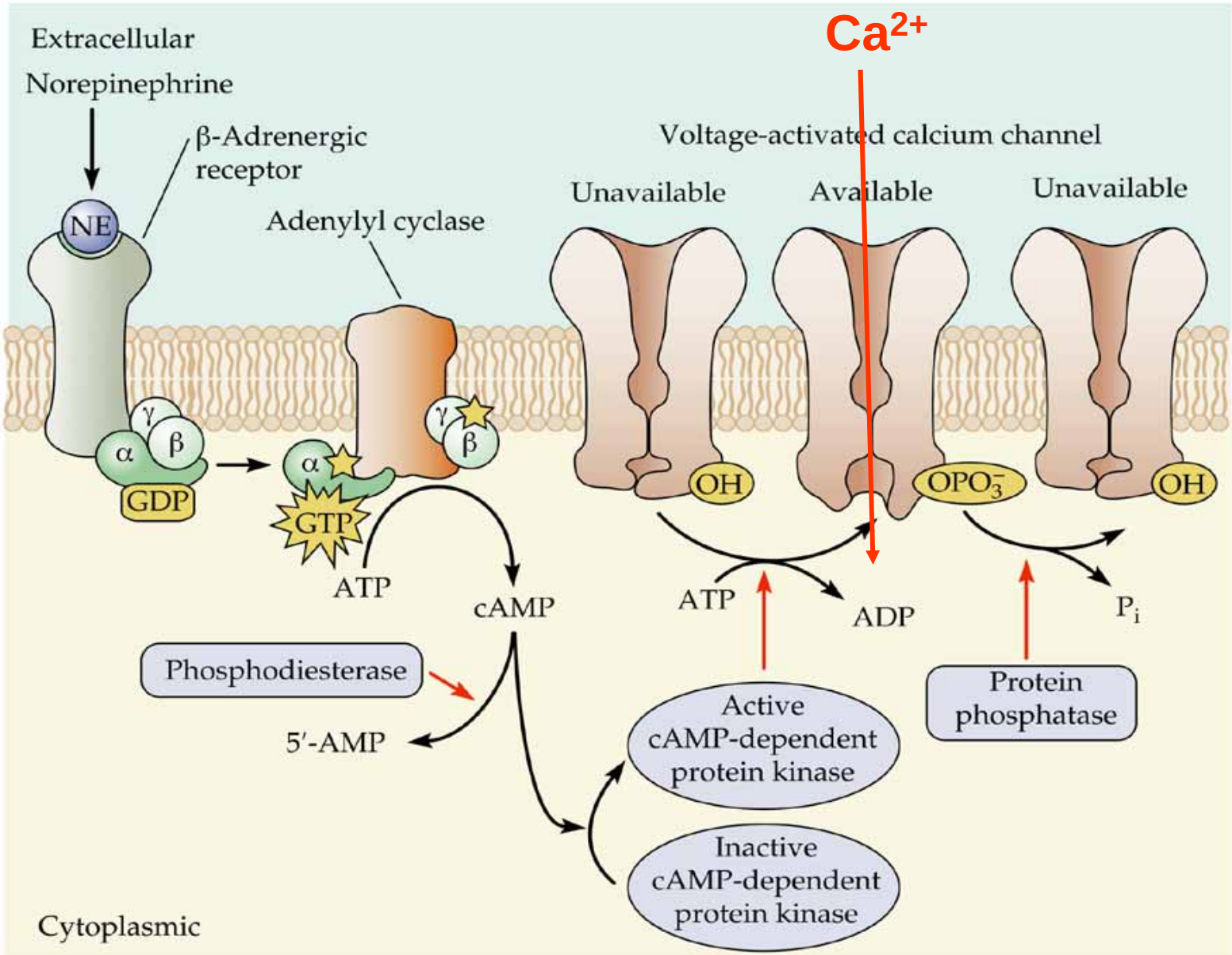
Hormonal regulation

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

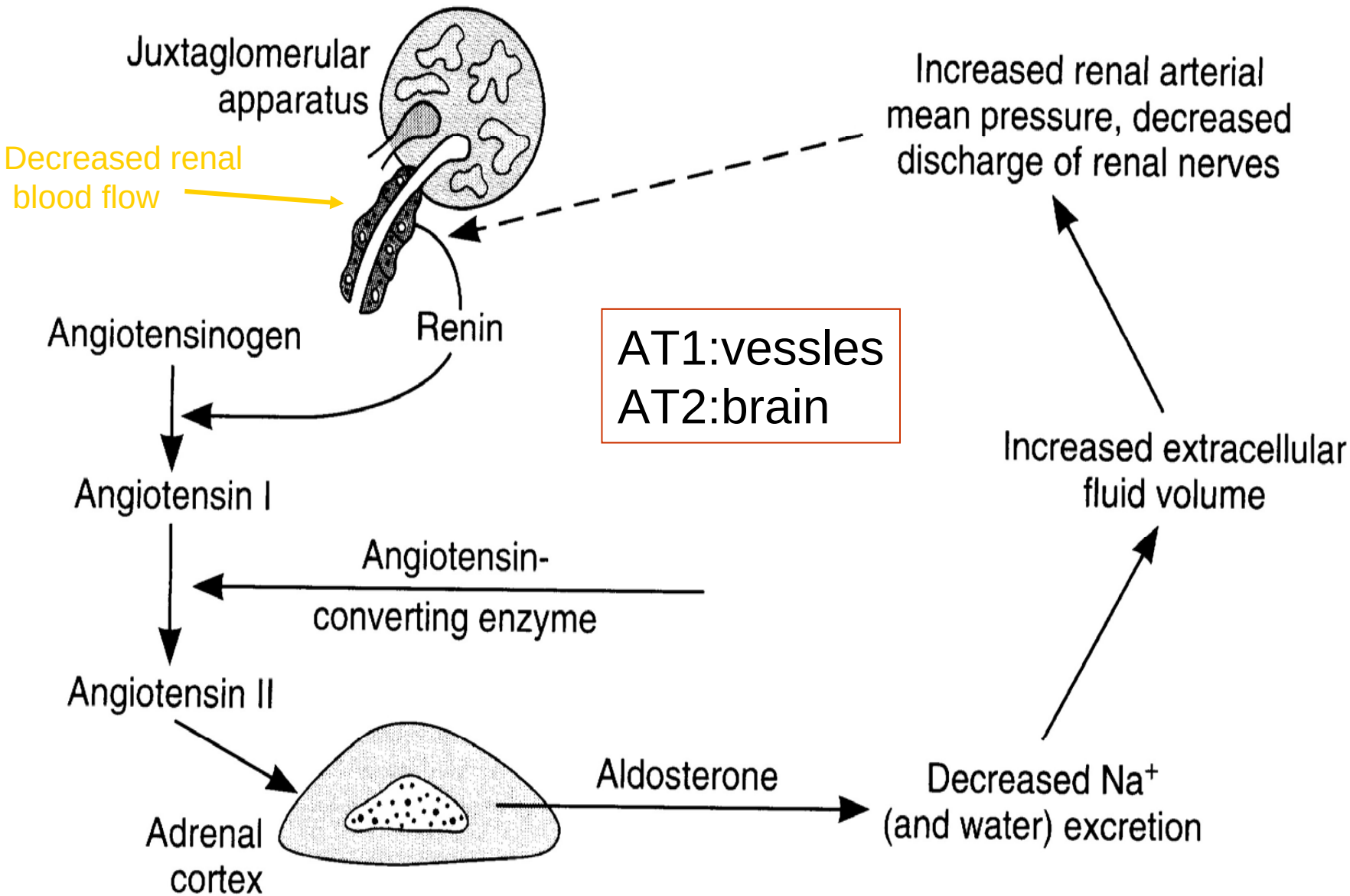
Mechanisms control regional blood flow

- Neural mechanisms: ANS, particular sympathetic division.
- Myogenic mechanisms
- Metabolic mechanisms
- Endothelial mechanisms

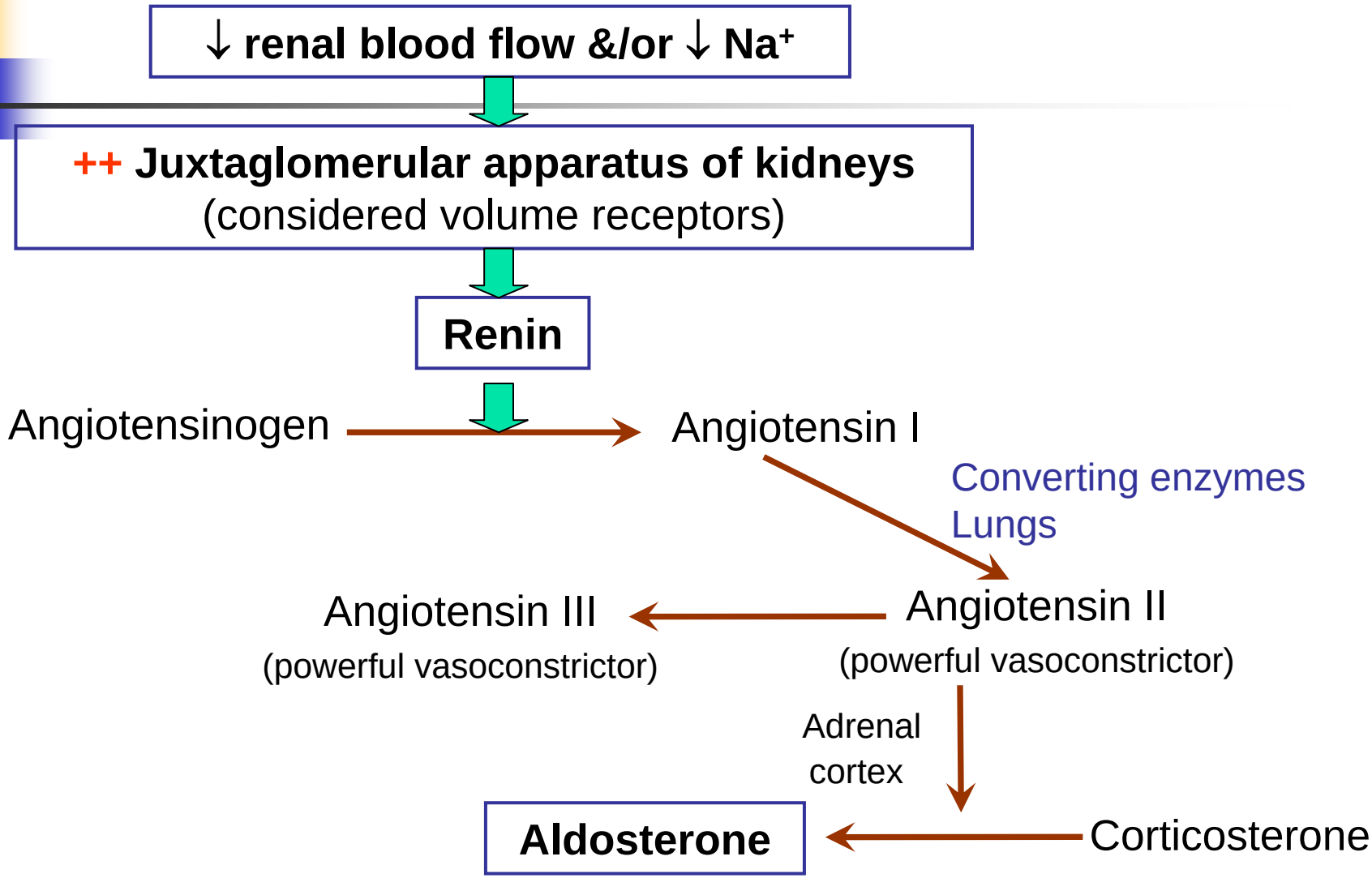

α-Receptor
Epinephrine
Blood vessels
β-Receptor
Vessel constricts
Vessel dilates



Renin-angiotensin aldosterone system, RAAS

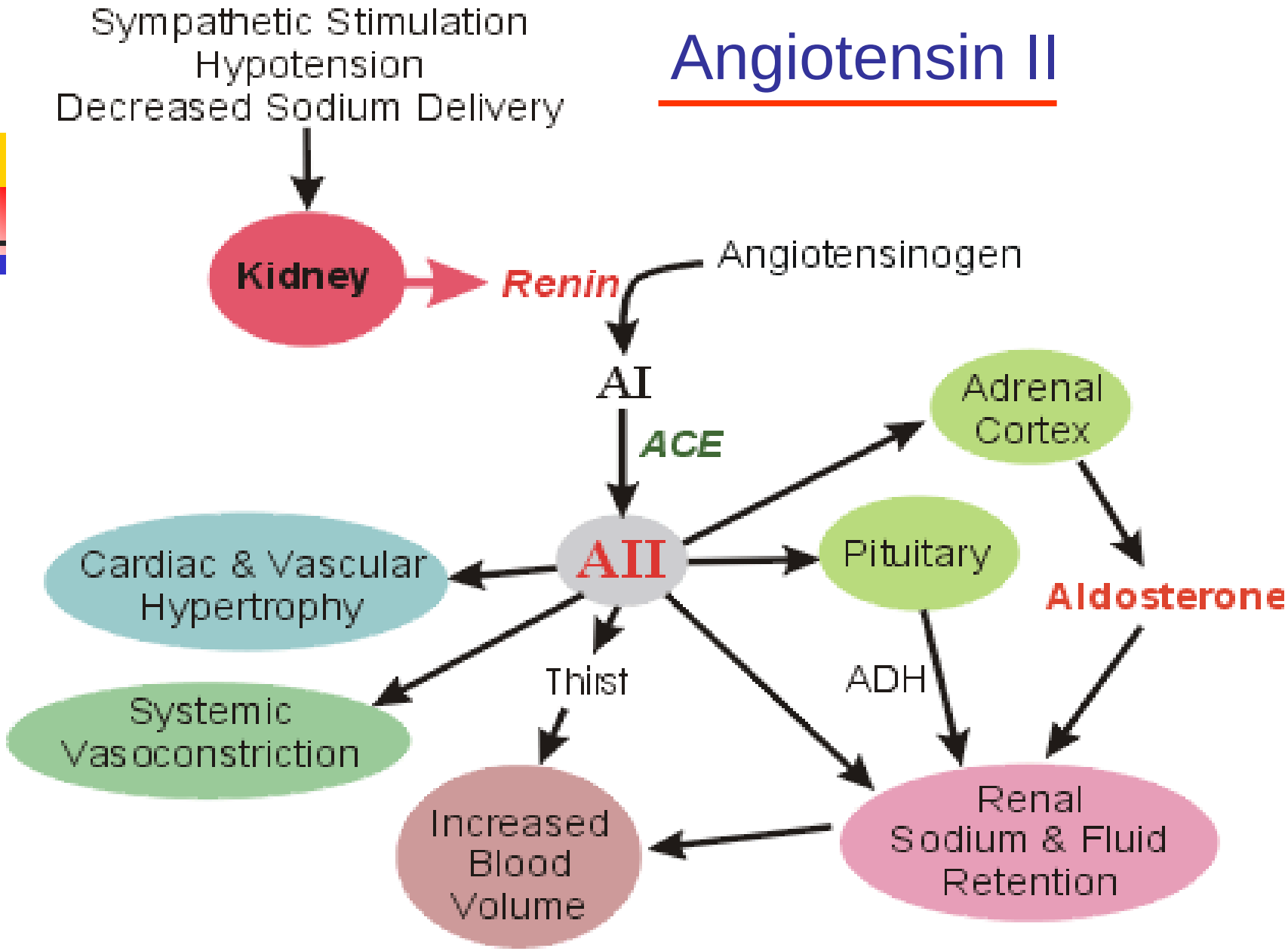


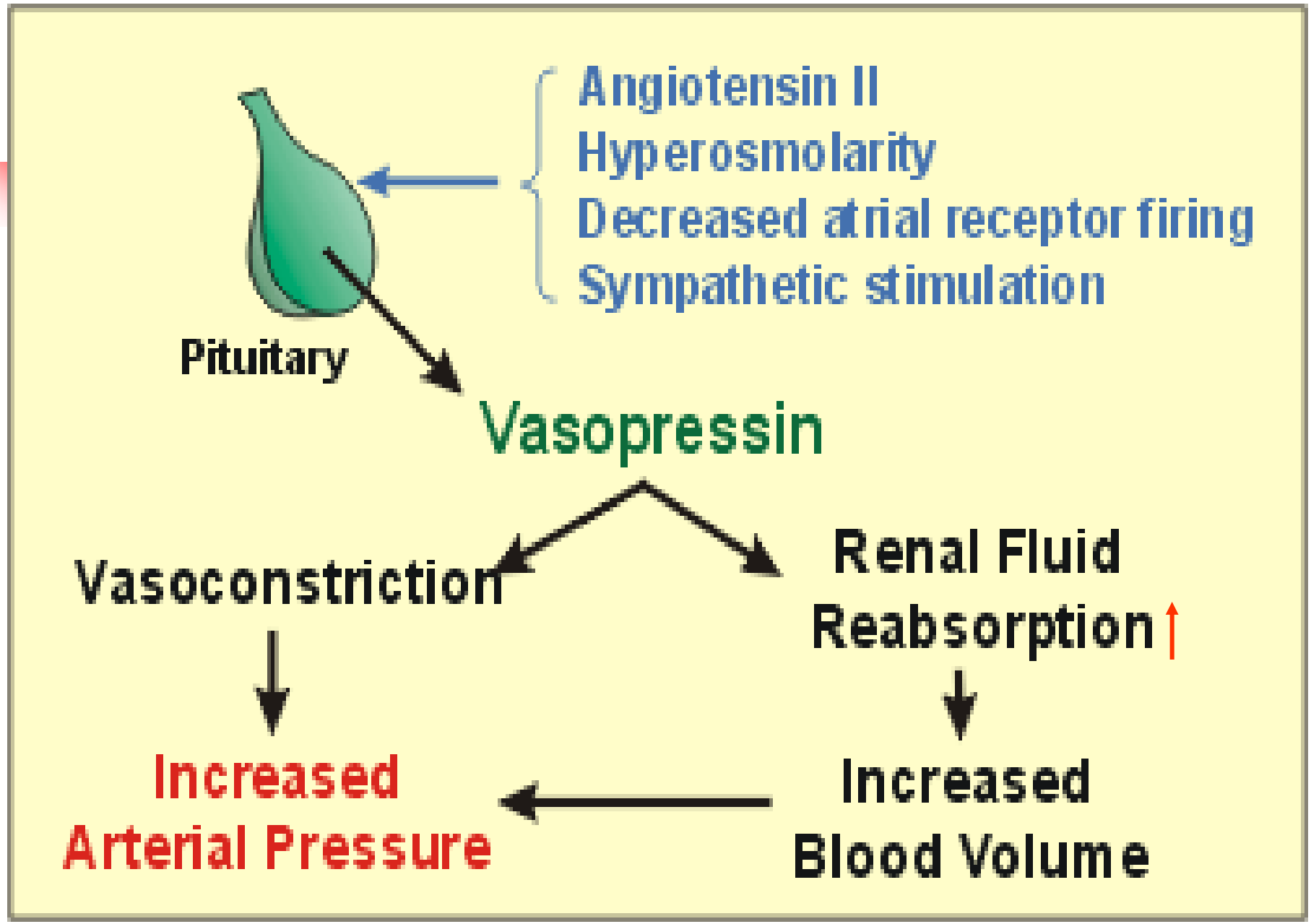
• Renin-Angiotensin Aldosterone System:



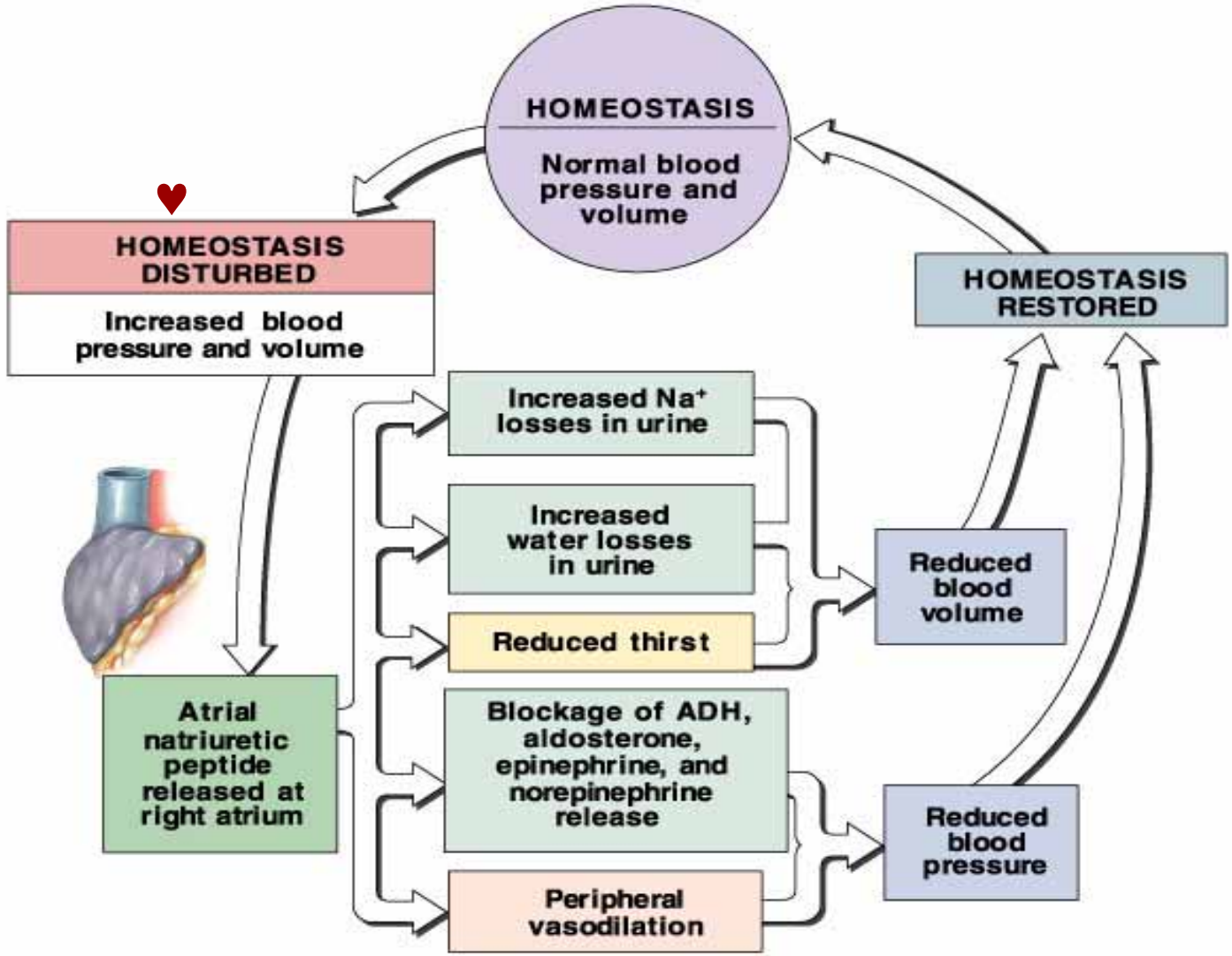
❑**N.B. Aldosterone is the main regulator of Na^+ retention.**

Angiotensin II

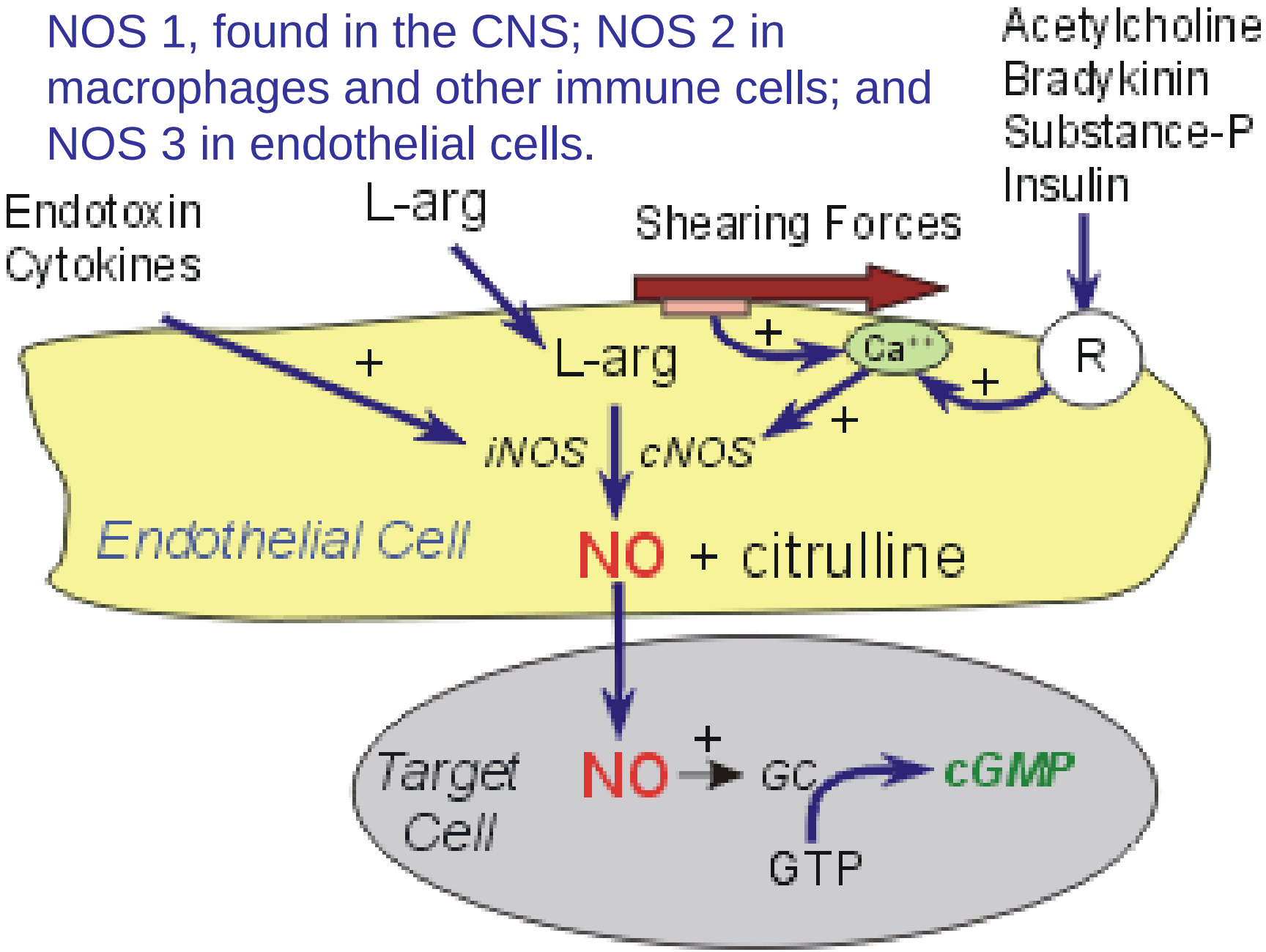


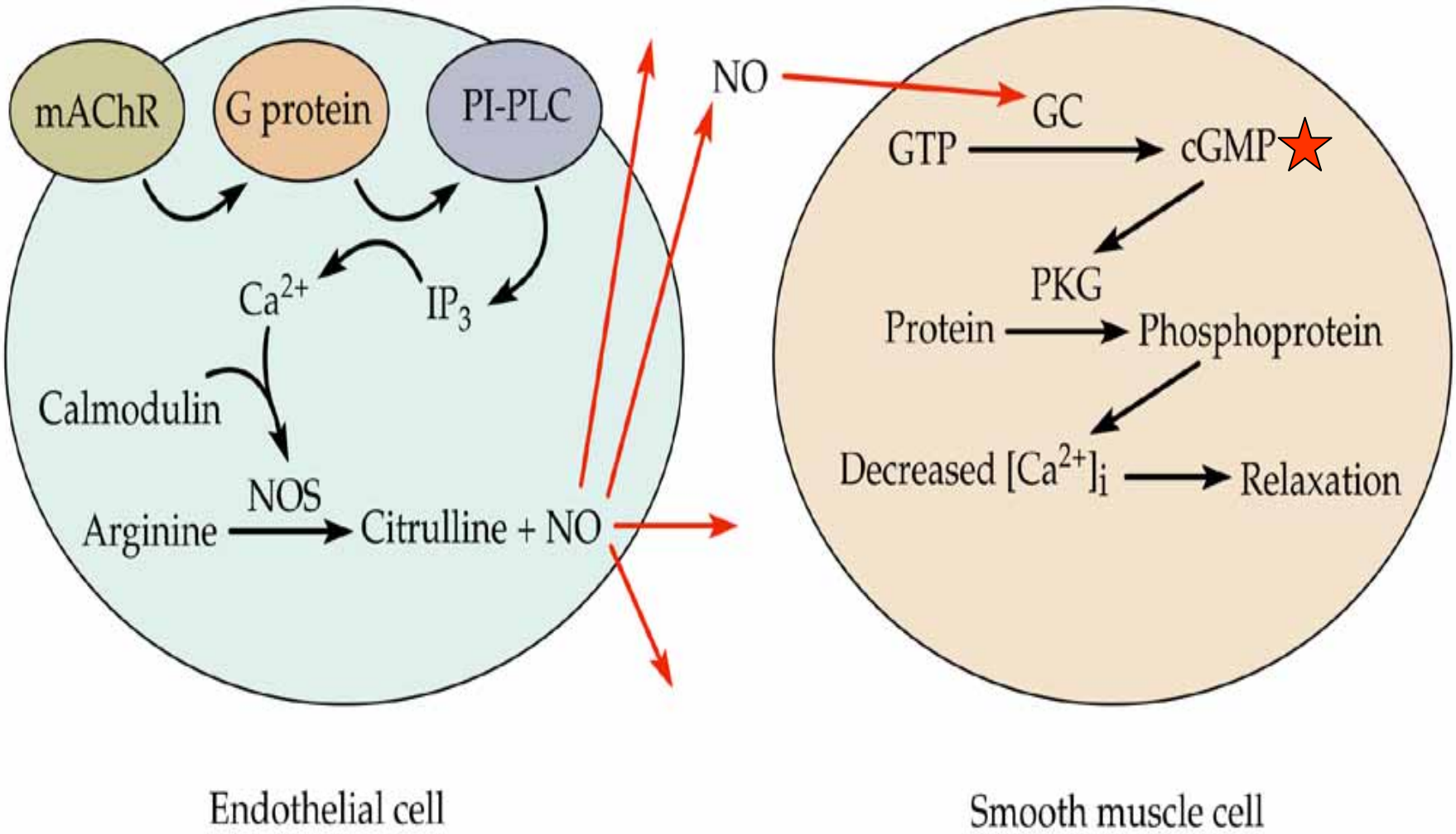

Angiotensin II
Hyperosmolarity
Decreased atrial receptor firing
Sympathetic stimulation
Pituitary
Vasopressin
Vasoconstriction
Renal Fluid Reabsorption
Increased Arterial Pressure
Increased Blood Volume

Increased Blood Pressure：Response

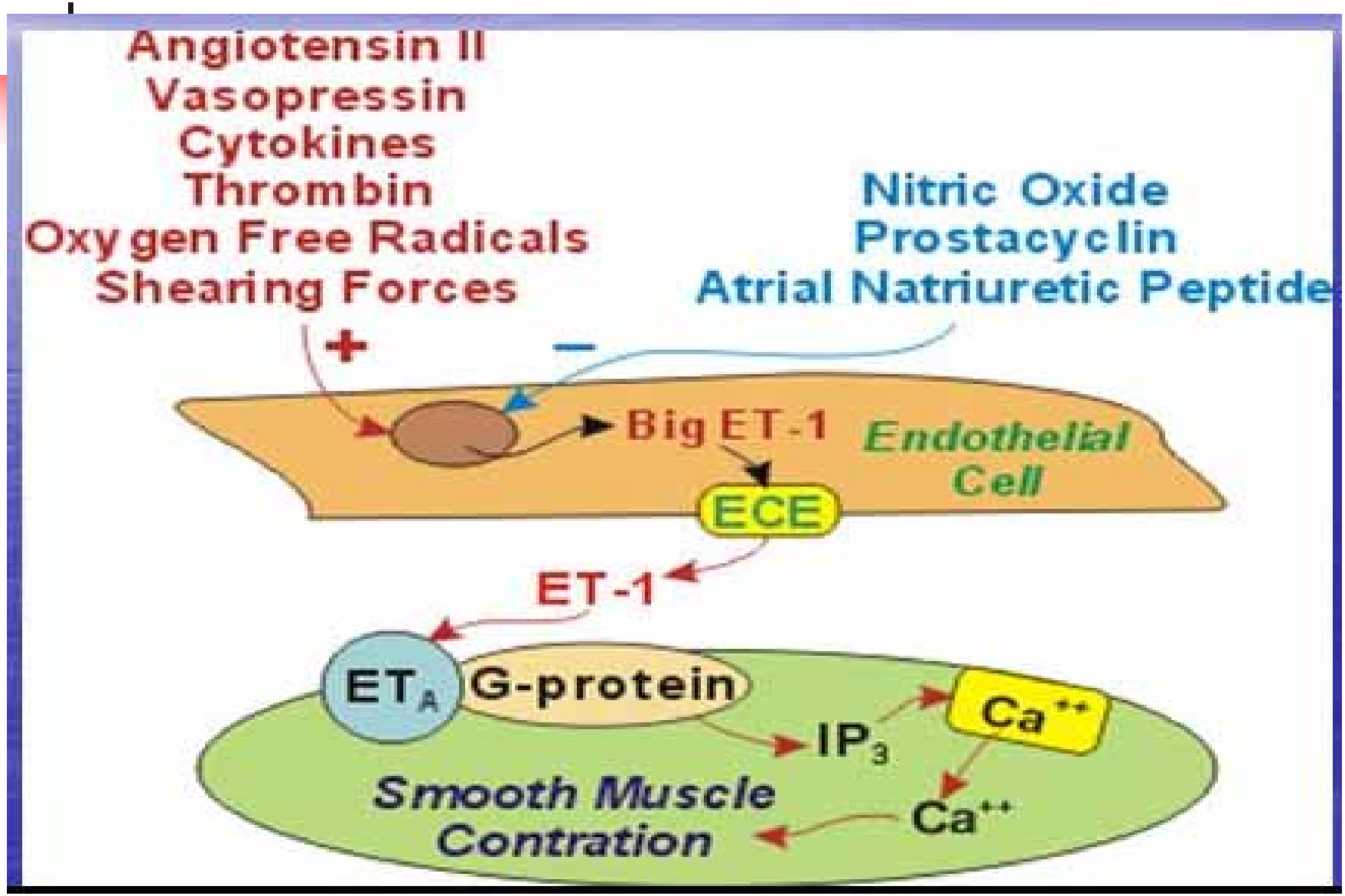


NOS 1, found in the CNS; NOS 2 in macrophages and other immune cells; and NOS 3 in endothelial cells.





Vasoconstrictor factor: endothelin



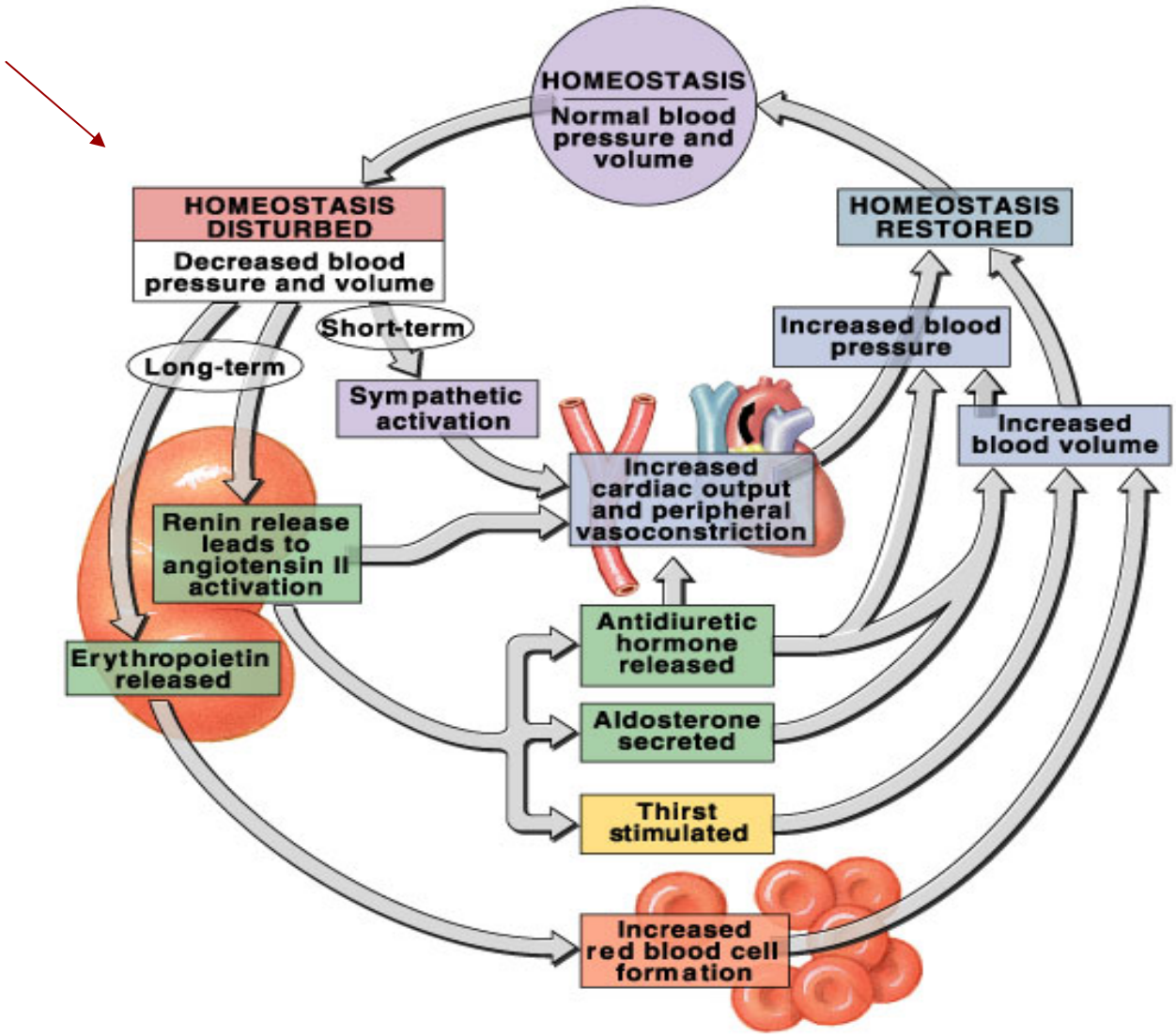
Myogenic and metabolic mechanisms

- Arteries and arterioles are response to change in transmural pressure. Increase pressure and the accompanying stretch of VSMCs elicit vasoconstriction, whereas decreased P. elicits vasodilation.
- A decrease in PO_2 or PH causes vaso-dilation

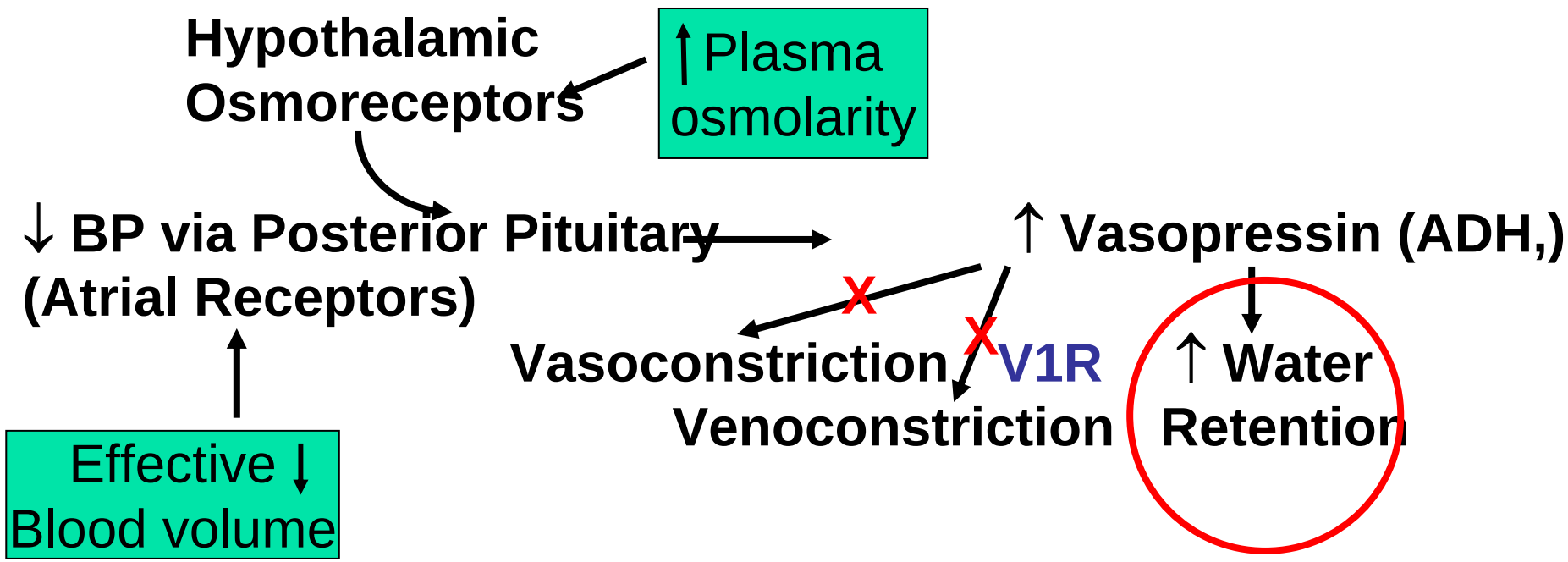
Long- Term Regulation of AP

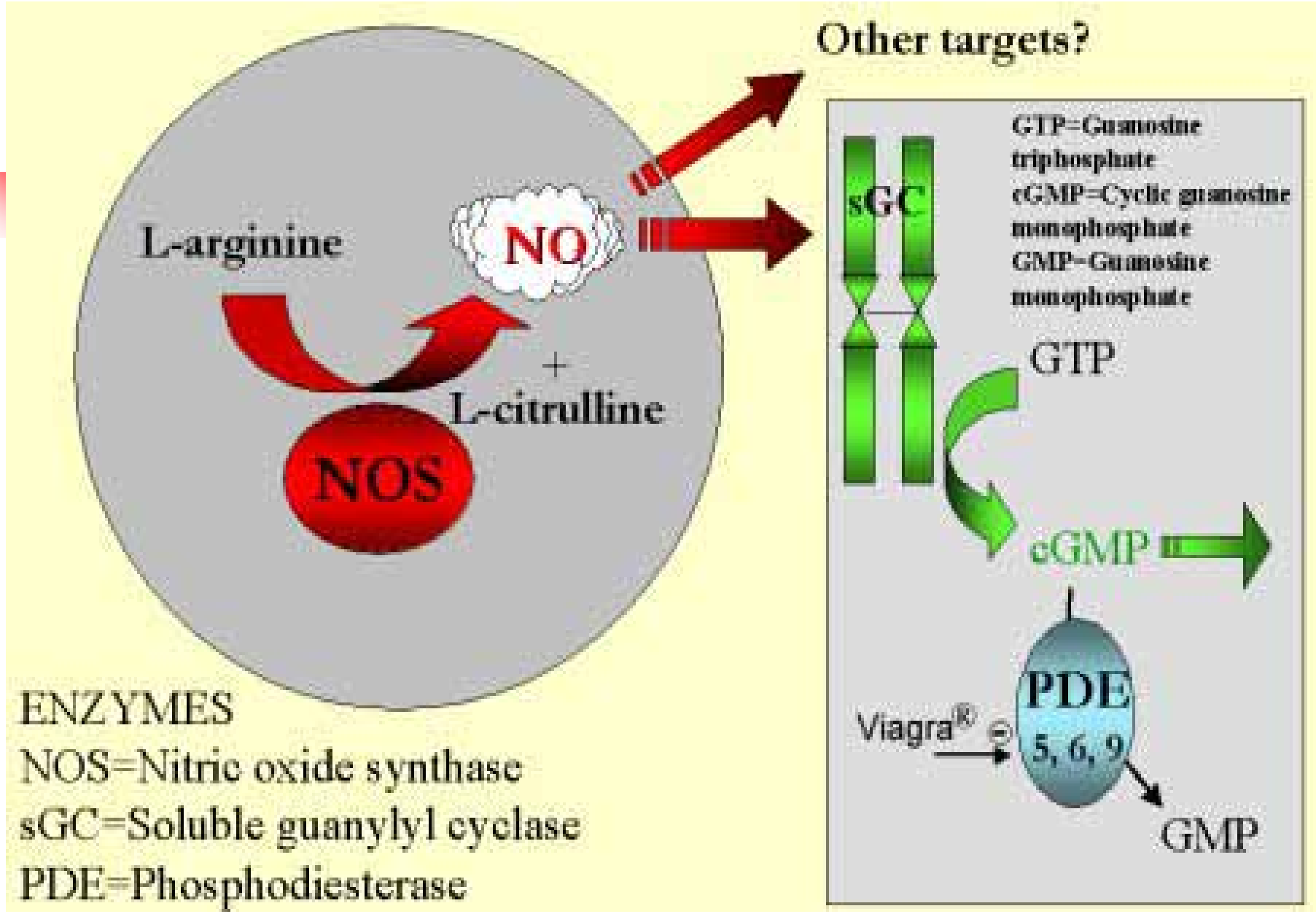
- On a time scale of hours or days- occurs via pathways that target the blood vessels, kidneys, in their control of ECF.
- Mean arterial pressure (MAP) is the principal variable that cadiovasscular system controls, all organs receive same MAP, controls by resistance ↑↓

Decreased Blood Pressure Response



Vasopressin (Antidiuretic hormone)




Other targets?
L-arginine
NO
+
L-citrulline
NOS
GTP=Guanosine triphosphate
cGMP=Cyclic guanosine monophosphate
GMP=Guanosine monophosphate
sGC
GTP
cGMP
PDE
5, 6, 9
Viagra®
GMP
ENZYMES
NOS=Nitric oxide synthase
sGC=Soluble guanylyl cyclase
PDE=Phosphodiesterase

Treatment for erectile dysfunction

- Viagra was approved by the FDA in 1998 and was the first drug for the treatment of erectile dysfunction
- Originally studied for the use in people with high blood pressure and cardiac problems the drug was found to have a very interesting side effect. Viagra increases the blood flow to the penis and enables a man to maintain an erection for at least 4 hours
- One billion dollars in sales were made in Viagra's first year of production.