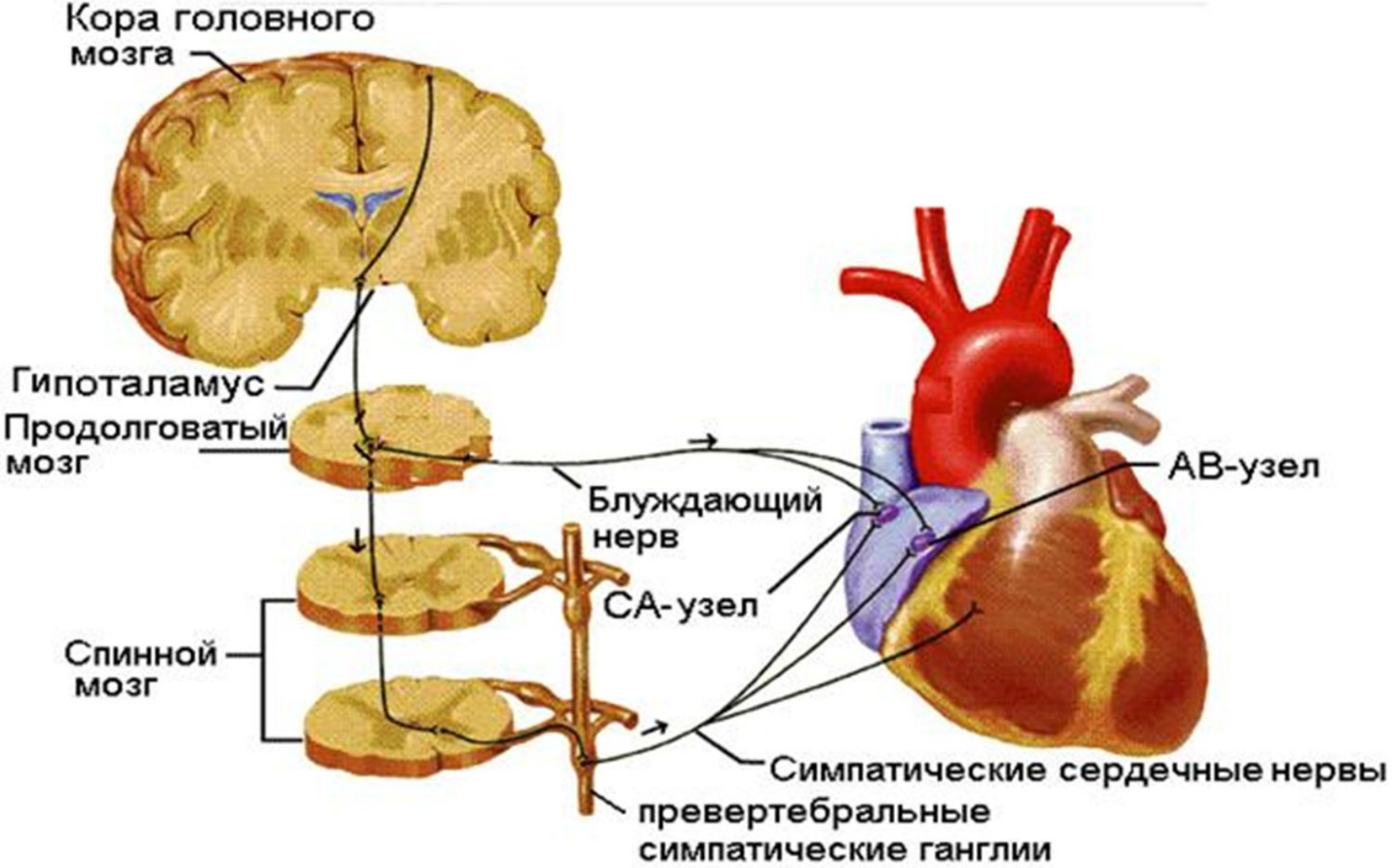
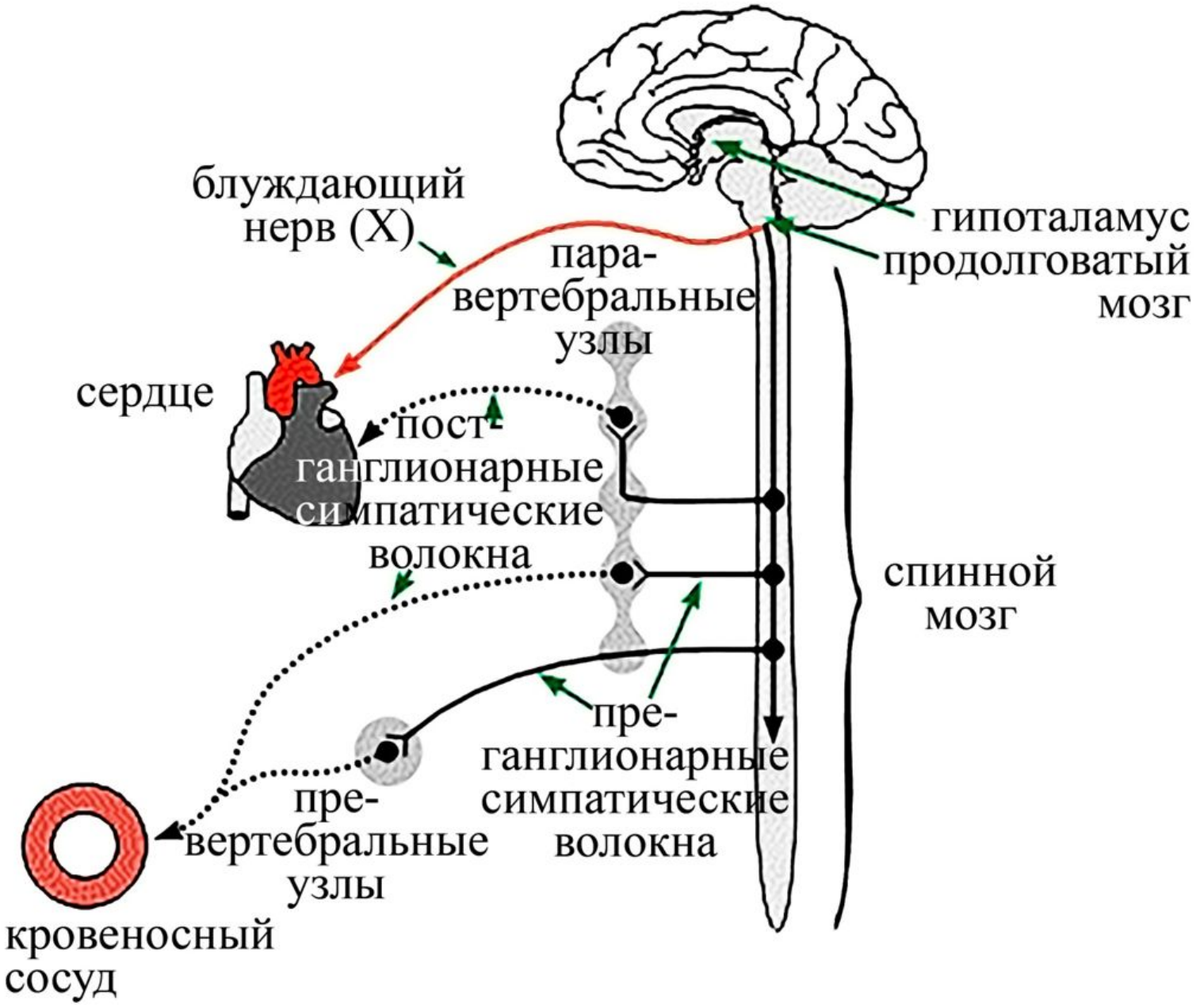
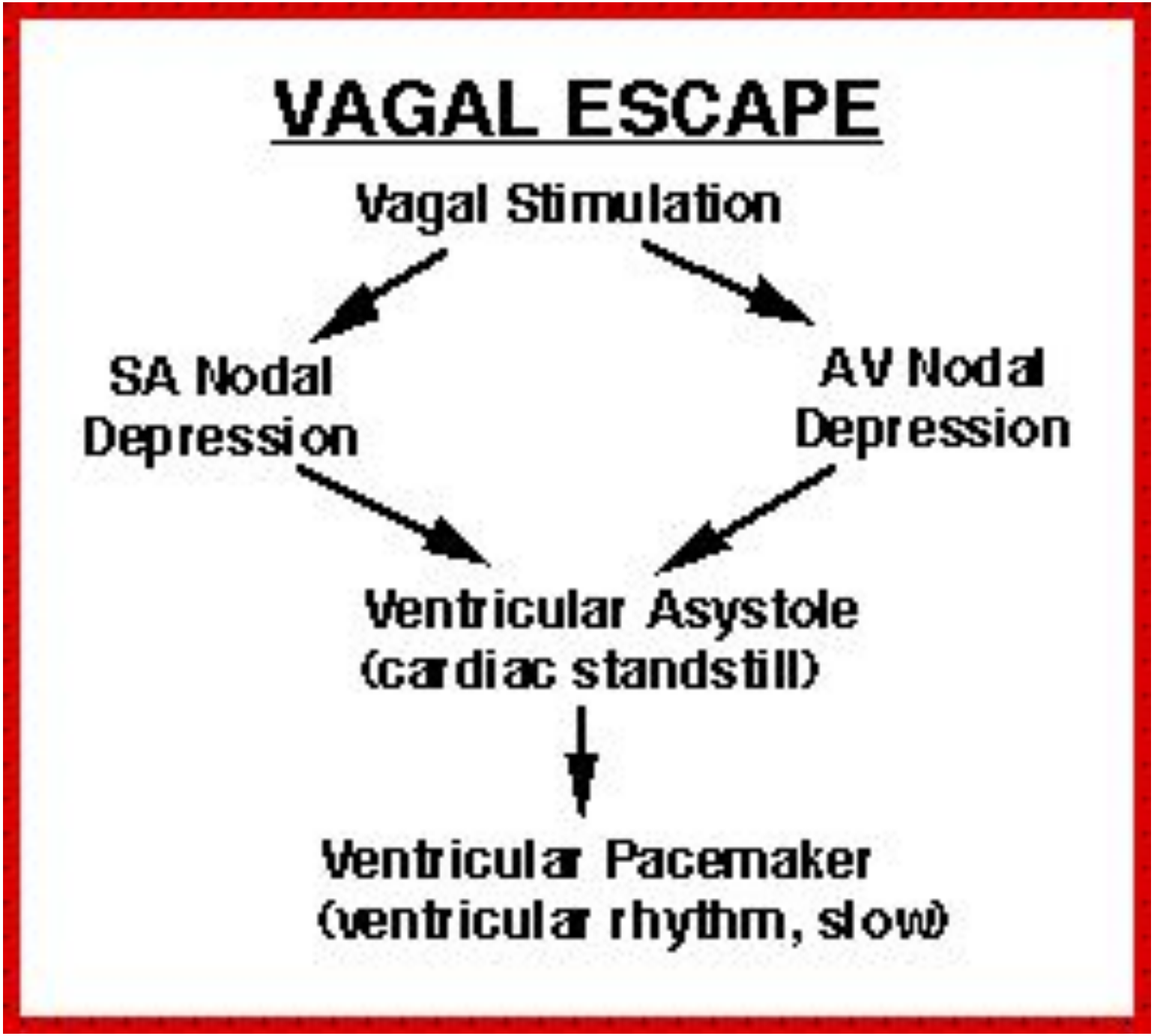
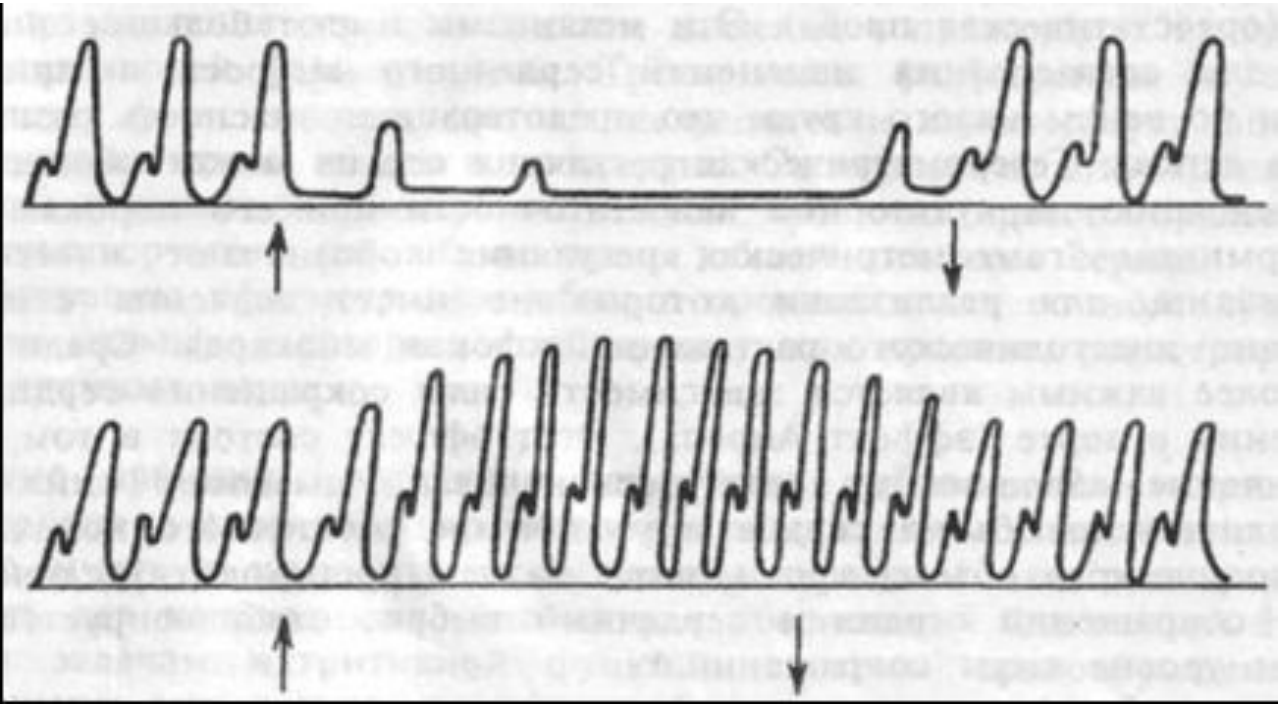
Нейрогуморальная регуляция сердца и сосудов


Кора головного мозга
Гипоталамус
Продолговатый мозг
Спинной мозг
Блуждающий нерв
СА-узел
АВ-узел
Симпатические сердечные нервы
превертебральные симпатические ганглии

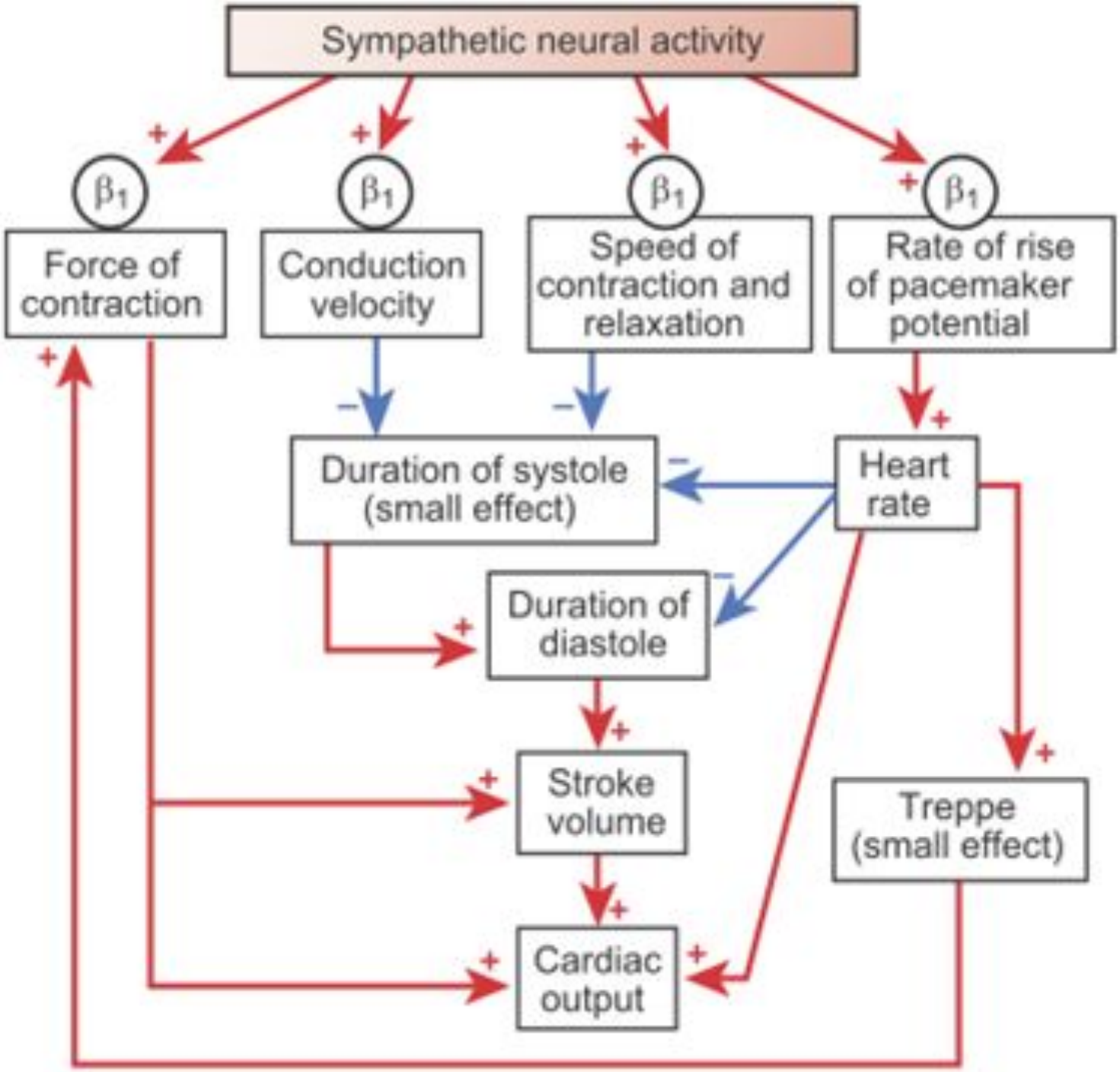

блуждающий
нерв (X)
гипоталамус
продолговатый
мозг
пара-
вертебральные
узлы
сердце
пост-
ганглионарные
симпатические
волокна
спинной
мозг
пре-
ганглионарные
симпатические
волокна
пре-
вертебральные
узлы
кровеносный
сосуд

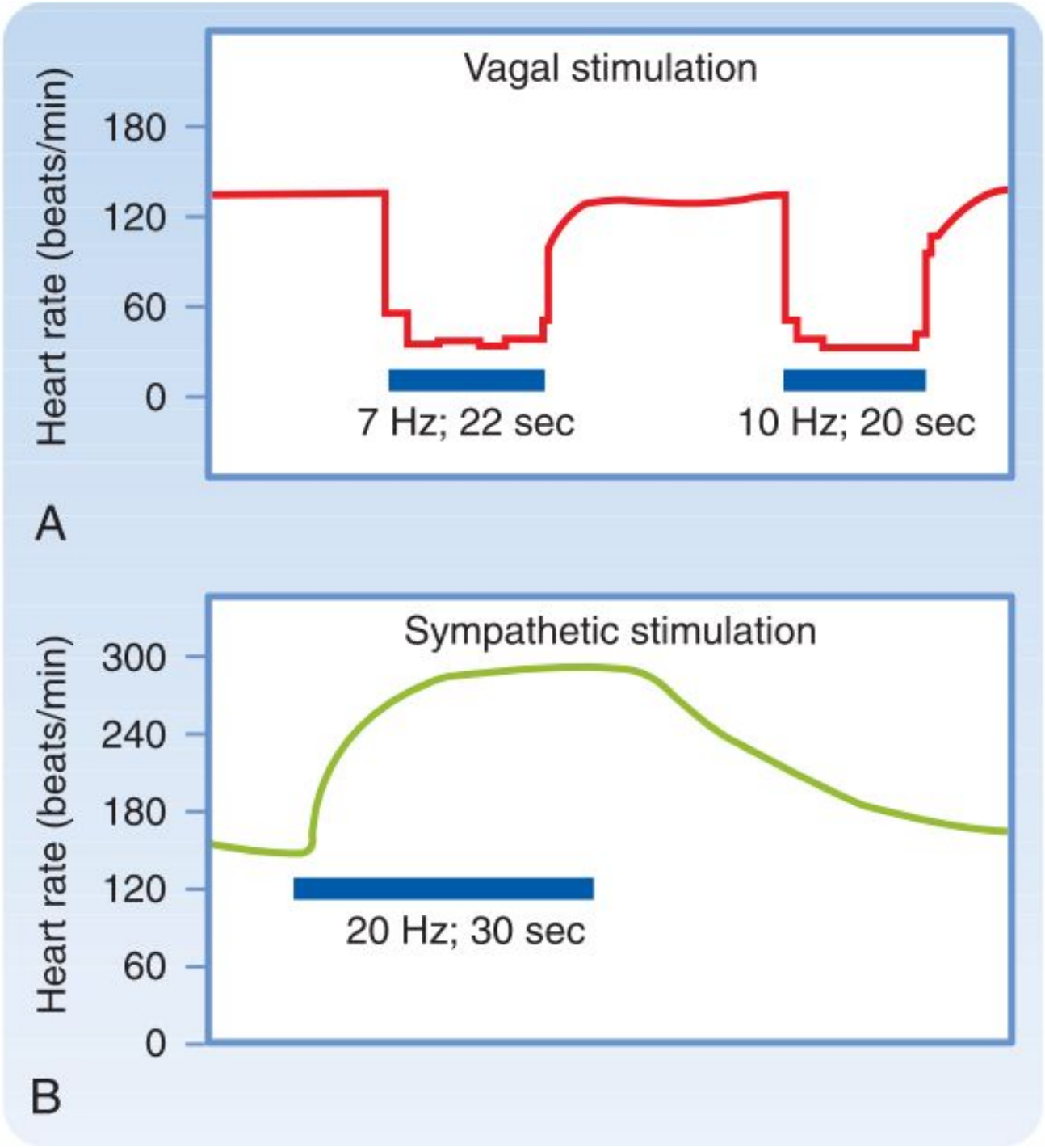

VAGAL ESCAPE
Vagal Stimulation
SA Nodal Depression
AV Nodal Depression
Ventricular Asystole (cardiac standstill)
Ventricular Pacemaker (ventricular rhythm, slow)

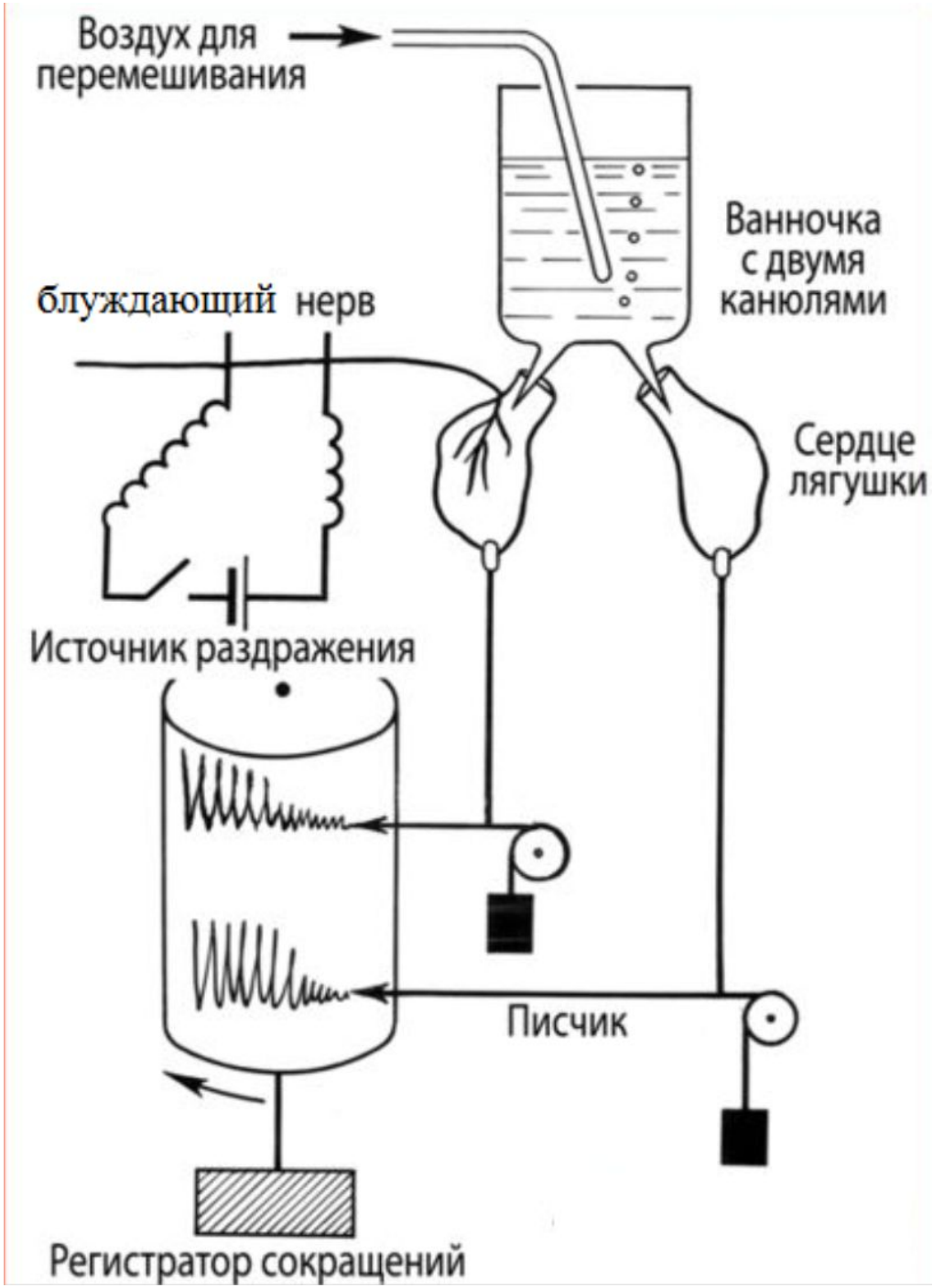


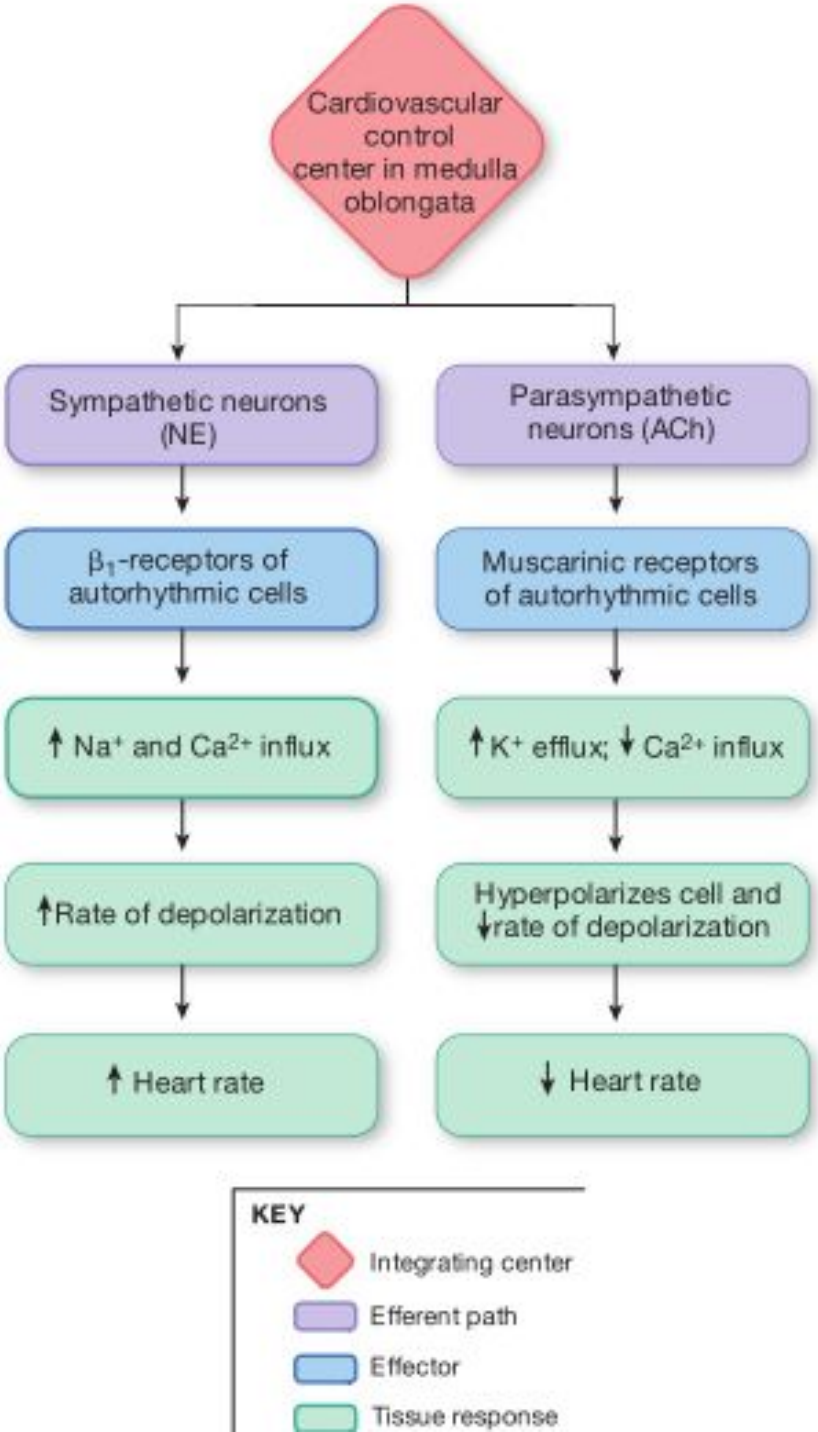
блуждающий нерв

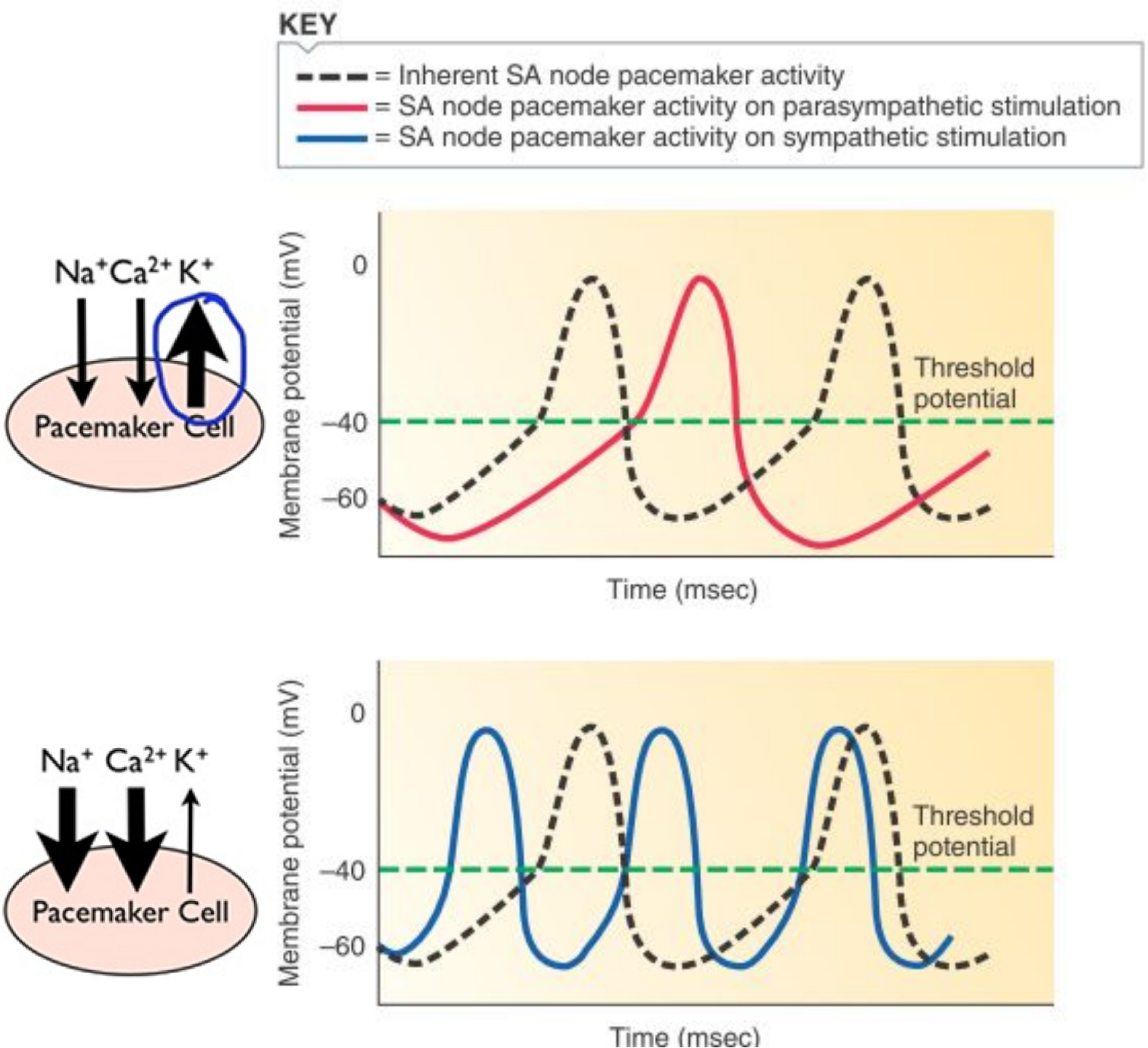
симпатические нервы

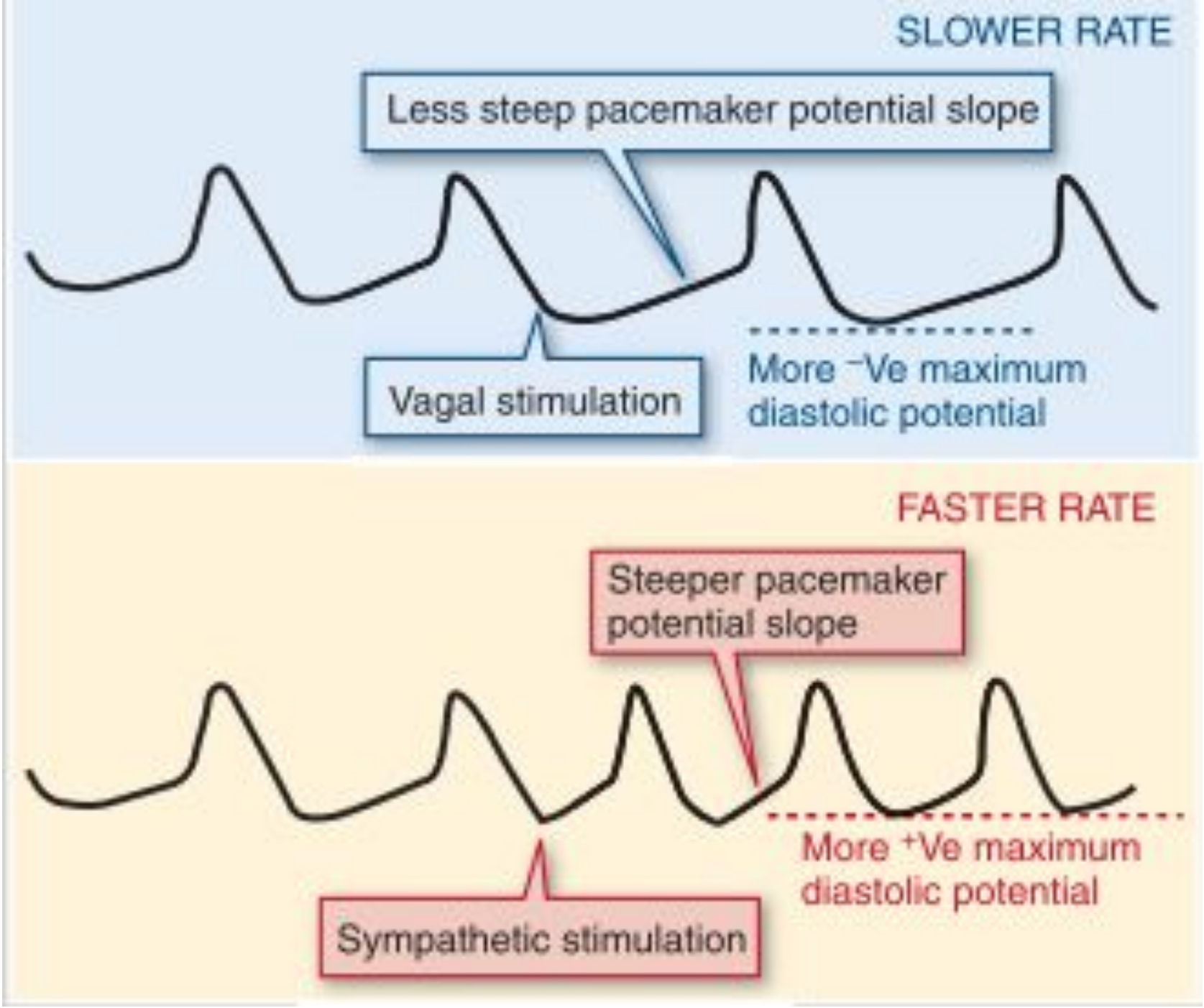

Sympathetic neural activity
β1
β1
β1
β1
Force of contraction
Conduction velocity
Speed of contraction and relaxation
Rate of rise of pacemaker potential
Duration of systole (small effect)
Heart rate
Duration of diastole
Stroke volume
Treppe (small effect)
Cardiac output


Vagal stimulation
Heart rate (beats/min)
180
120
60
0
7 Hz; 22 sec
10 Hz; 20 sec
A
Sympathetic stimulation
Heart rate (beats/min)
300
240
180
120
60
0
20 Hz; 30 sec
B


Воздух для перемешивания
Ванночка с двумя канюлями
блуждающий нерв
Сердце лягушки
Источник раздражения
Писчик
Регистратор сокращений

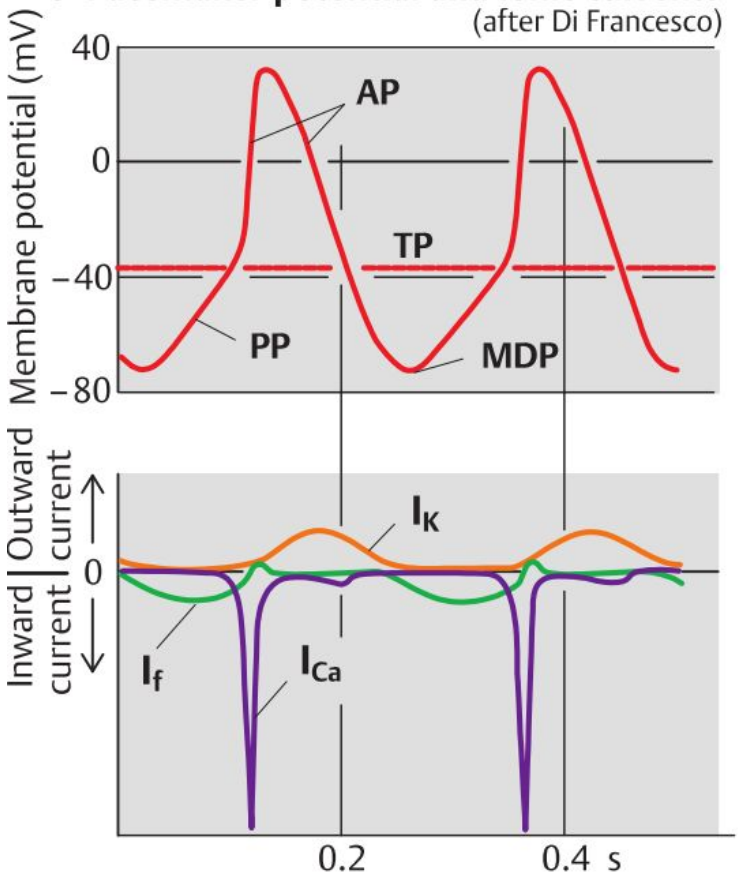

Cardiovascular control center in medulla oblongata
Sympathetic neurons (NE)
Parasympathetic neurons (ACh)
β_1-receptors of autorhythmic cells
Muscarinic receptors of autorhythmic cells
↑ Na^+ and Ca^{2+} influx
↑ K^+ efflux; ↓ Ca^{2+} influx
↑Rate of depolarization
Hyperpolarizes cell and ↓rate of depolarization
↑ Heart rate
↓ Heart rate
KEY
Integrating center
Efferent path
Effector
Tissue response


KEY
= Inherent SA node pacemaker activity
= SA node pacemaker activity on parasympathetic stimulation
= SA node pacemaker activity on sympathetic stimulation
Na+ Ca2+ K+
Pacemaker Cell
Membrane potential (mV)
0
–40
–60
Threshold potential
Time (msec)
Na+ Ca2+ K+
Pacemaker Cell
Membrane potential (mV)
0
–40
–60
Threshold potential
Time (msec)


SLOWER RATE
Less steep pacemaker potential slope
Vagal stimulation
More ⁻Ve maximum diastolic potential
FASTER RATE
Steeper pacemaker potential slope
More ⁺Ve maximum diastolic potential
Sympathetic stimulation

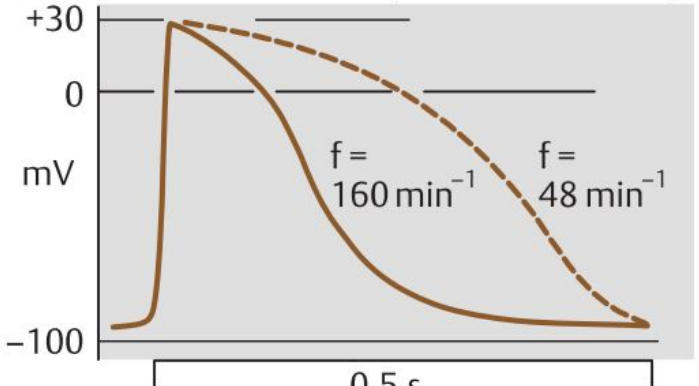
1 Pacemaker potential and ionic currents

(after Di Francesco)

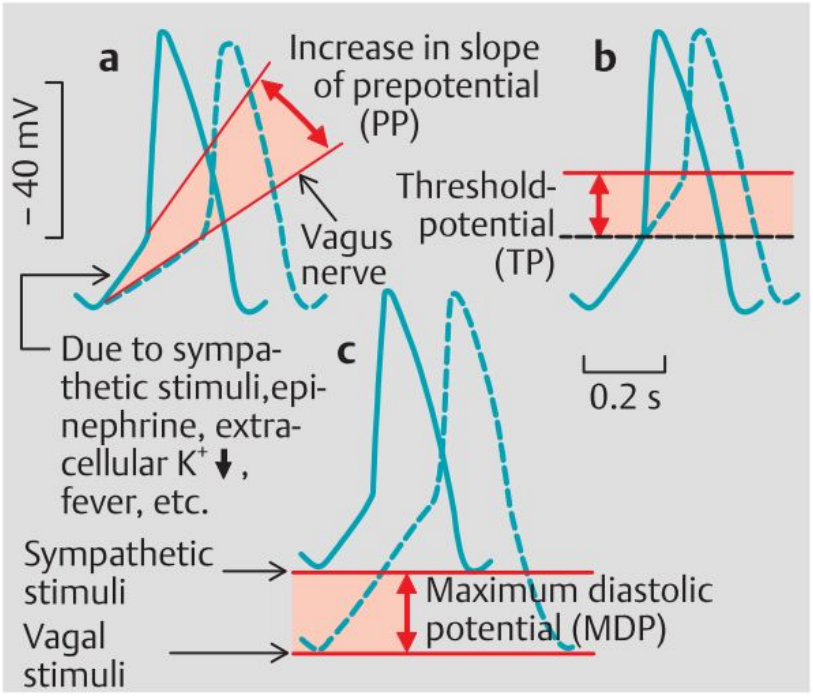


2 Duration of myocardial action potential is dependent on heart rate (f)

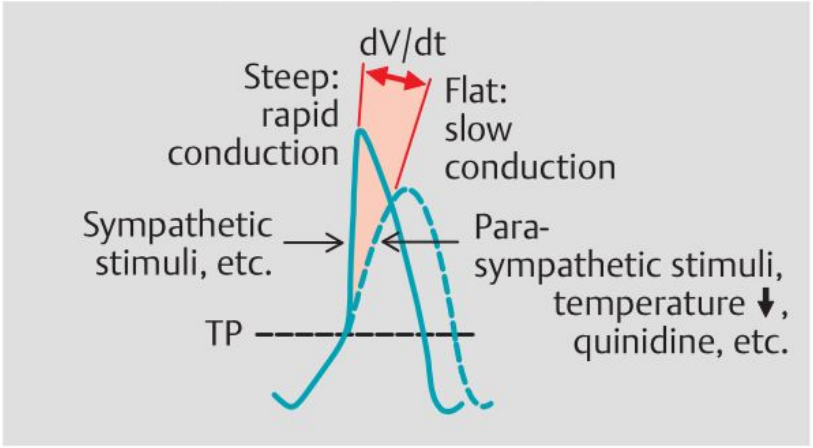
(after Trautwein et al.)

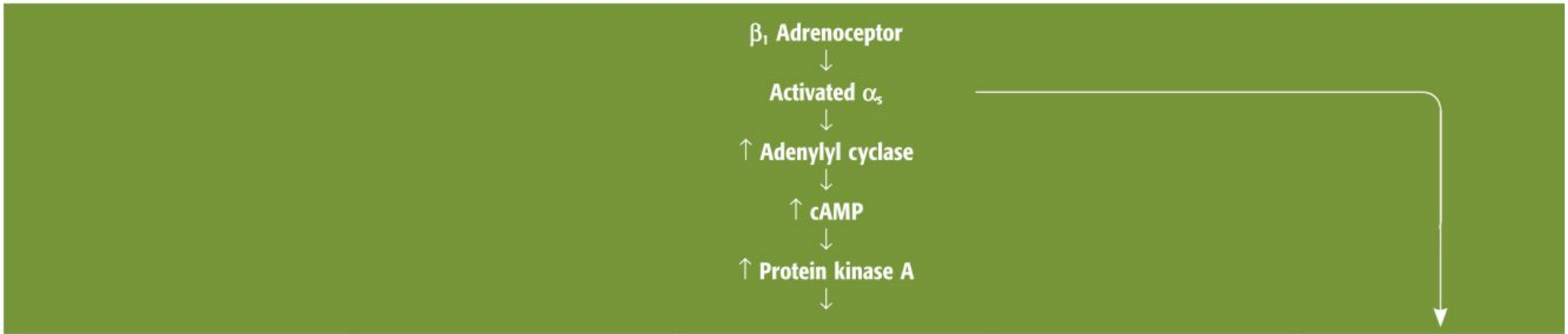


3 Changes in heart rate due to changes in pacemaker potential

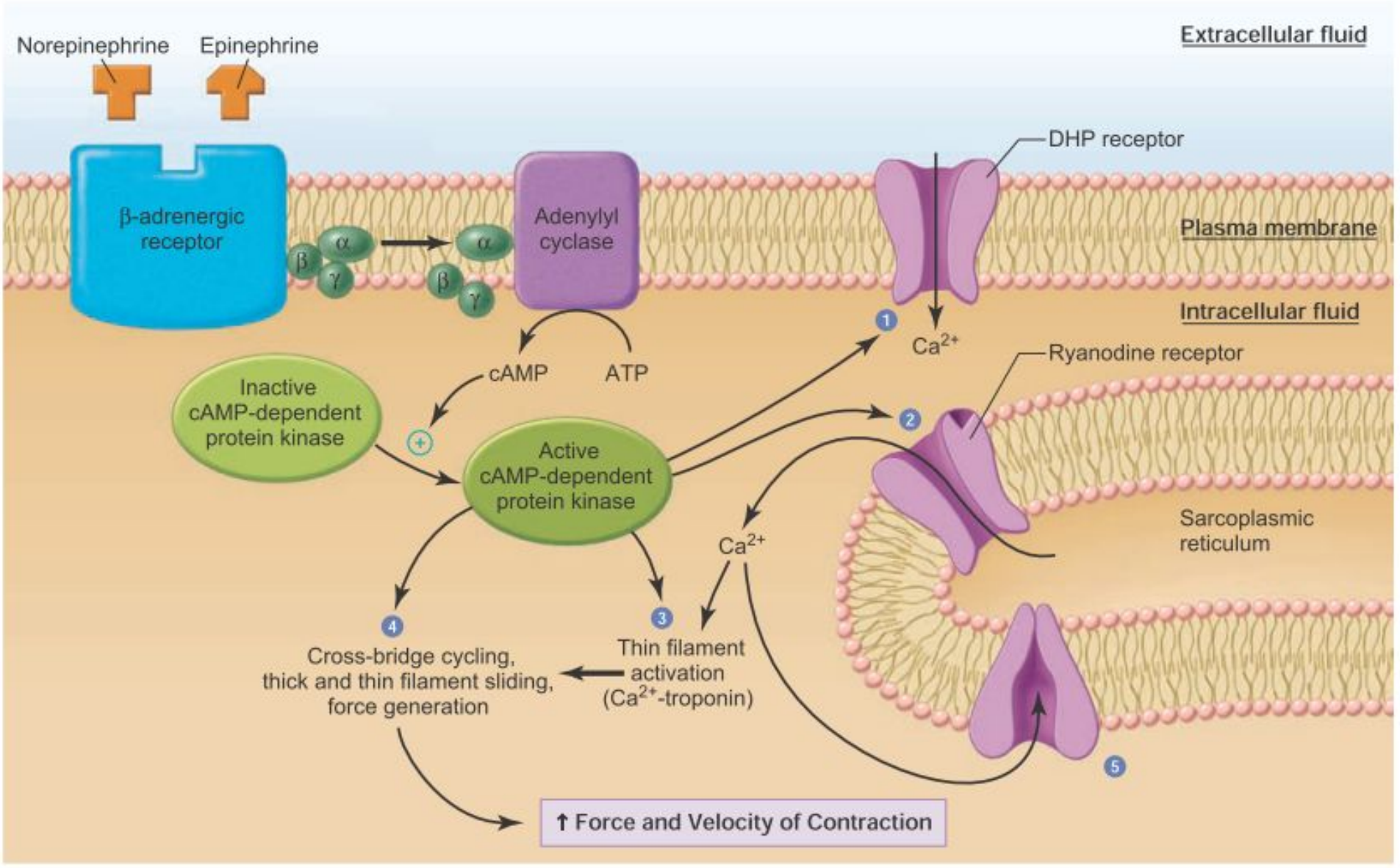


4 Factors that affect the conduction of action potentials (AV node)

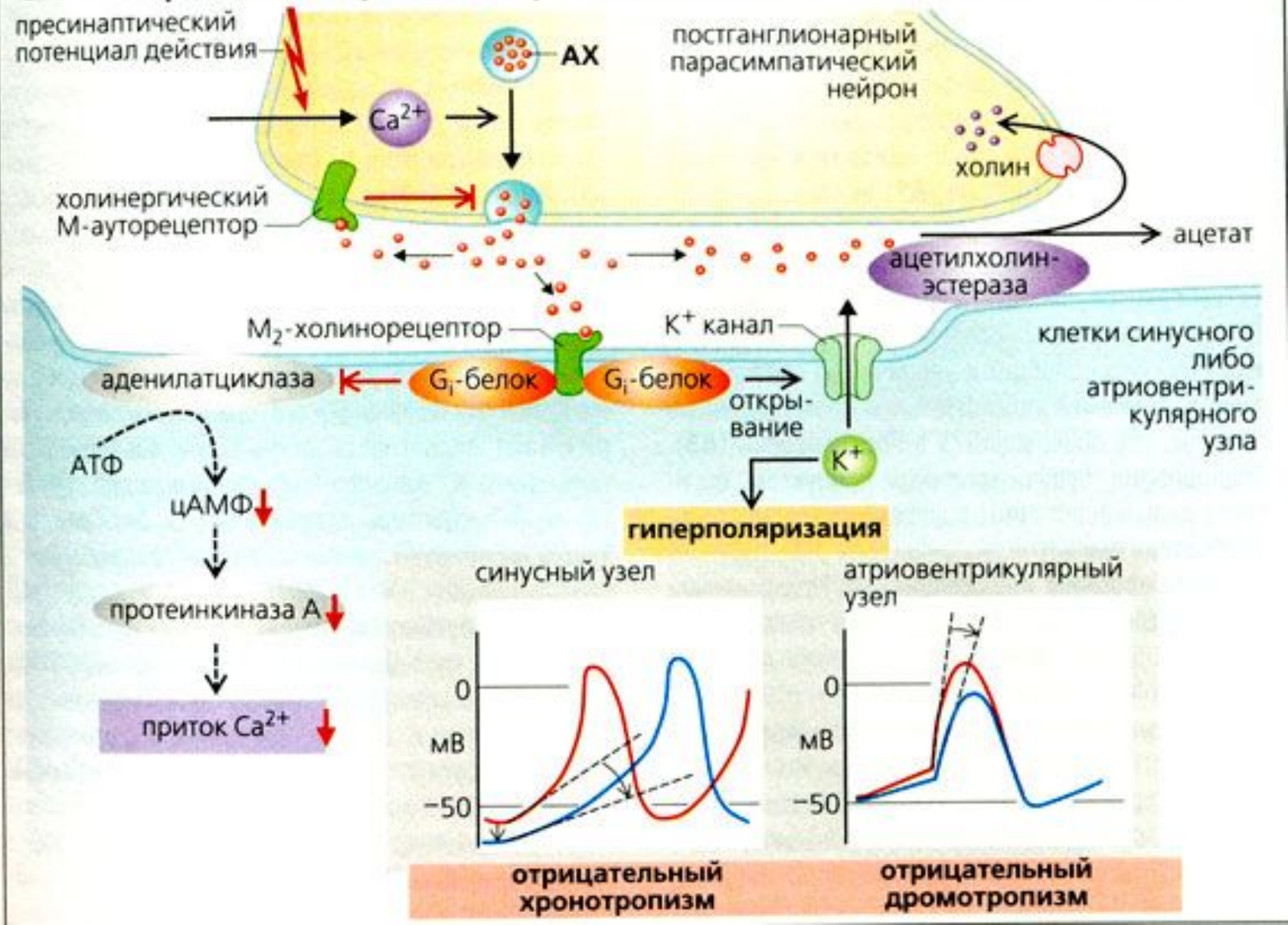




Phosphorylation of L-type Ca^{2+} channels, Cav1.2	Phosphorylation of ryanodine receptor RYR2	Phosphorylation of phospholamban (PLN)	Phosphorylation of troponin I (TNNI3)	Interaction of α_s with Cav1.2
↑Open probability of Cav1.2	Dissociation of FKBP12.6 (calstabin 2) from RYR2-FKBP12.6 complex	↑SR Ca^{2+} pump (SERCA2a)	↑Off-rate of Ca^{2+} from Ca^{2+}-TNNC1 complex	↑Open probability of Cav1.2
↑Ca^{2+} influx	↑Open probability of RYR2	↑Ca^{2+} reuptake into SR ↑Ca^{2+} stores	↑Speed of relaxation (lusitropic)	↑Ca^{2+} influx
↑$[Ca^{2+}]_i$	↑Ca^{2+} release by SR	↑Speed of relaxation (lusitropic effect)	↓Duration of contraction	↑$[Ca^{2+}]_i$
↑Ca^{2+}-induced Ca^{2+} release from the SR (CICR)	↑$[Ca^{2+}]_i$	↓Duration of contraction		↑Ca^{2+}-induced Ca^{2+} release from the SR (CICR)
↑Contractility	↑Contractility			↑Contractility

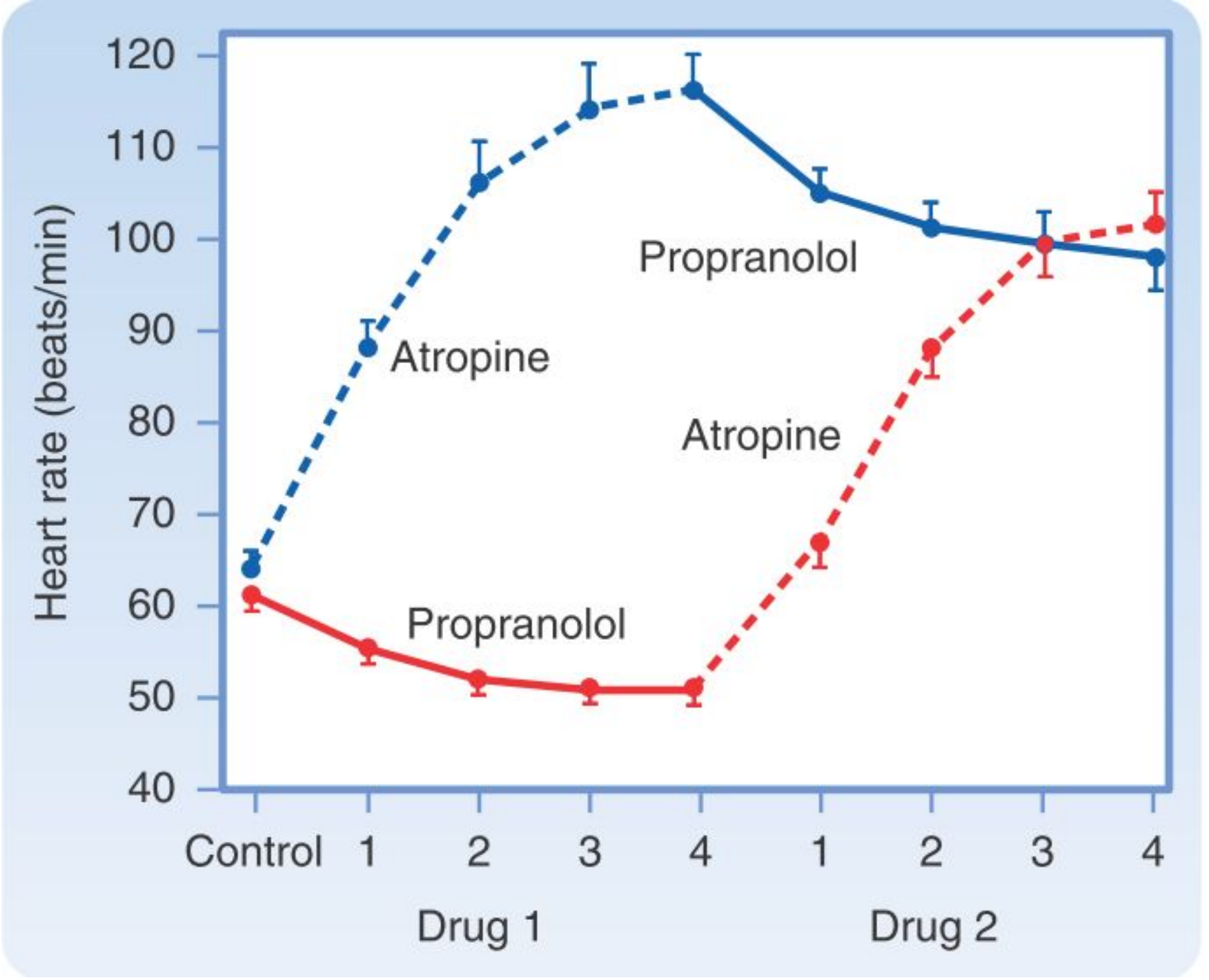

Norepinephrine
Epinephrine
Extracellular fluid
β-adrenergic receptor
α
β
γ
α
β
γ
Adenylyl cyclase
DHP receptor
Plasma membrane
Intracellular fluid
1
Ca2+
Ryanodine receptor
cAMP
ATP
Inactive cAMP-dependent protein kinase
+
Active cAMP-dependent protein kinase
2
Sarcoplasmic reticulum
Ca2+
4
3
Cross-bridge cycling, thick and thin filament sliding, force generation
Thin filament activation (Ca2+-troponin)
5
↑ Force and Velocity of Contraction

Б. Холинергическая передача в сердце



EFFECTOR RESPONSE	ANATOMIC PATHWAY	NEUROTRANSMITTER	RECEPTOR	G PROTEIN	ENZYME OR PROTEIN	2nd Messenger
Tachycardia	Sympathetic	NE	β_1 on cardiac pacemaker	$G\alpha_s$	↑ AC	↑ $[cAMP]_i$
Bradycardia	Parasympathetic	ACh	M_2 on cardiac pacemaker	Direct action of dimeric $G_{\beta\gamma}$	GIRK1 K^+ channels	ΔV_m
Increase cardiac contractility	Sympathetic	NE	β_1 on cardiac myocyte	$G\alpha_s$ Direct action of $G\alpha_s$ on Cav1.2	↑ AC	↑ $[cAMP]_i$
Decrease cardiac contractility	Parasympathetic	ACh	M_2 on cardiac myocyte	$G\alpha_i$	↓ AC	↓ $[cAMP]_i$
			Presynaptic M_2 receptor on noradrenergic neuron	$G\alpha_i$	↓ AC	↓ $[cAMP]_i$ in neuron
			M_3 receptor on cardiac myocyte	$G\alpha_q$	↑ PLC → ↑ $[Ca^{2+}]_i$ → ↑ NOS → ↑ GC	↑ $[cGMP]_i$ → ↓ Cav1.2
Vasoconstriction in most blood vessels (e.g., skin)	Sympathetic	NE	α_1 on VSMC	$G\alpha_q$	↑ PLC	↑ $[Ca^{2+}]_i$
Vasoconstriction in some blood vessels	Sympathetic	NE	α_2 on VSMC	$G\alpha_{i/o}$	↓ AC	↓ $[cAMP]_i$
Vasodilation in most blood vessels (e.g., muscle)	Adrenal medulla	Epi	β_2 on VSMC	$G\alpha_s$	↑ AC	↑ $[cAMP]_i$
Vasodilation in erectile blood vessels	Parasympathetic	ACh	Presynaptic M_2 receptor on noradrenergic neurons	$G\alpha_i$	↓ AC	↓ $[cAMP]_i$ in neuron
		ACh	M_3 on endothelial cell	$G\alpha_q$	↑ PLC → ↑ $[Ca^{2+}]_i$ → ↑ NOS	NO diffuses to VSMC
		NO	NO receptor (i.e., GC) inside VSMC	—	↑ GC	↑ $[cGMP]_i$
		VIP	VIP receptor on VSMC	$G\alpha_s$	↑ AC	↑ $[cAMP]_i$
Vasodilation in blood vessels of salivary gland	Parasympathetic	ACh	M_3 receptor on gland cell	$G\alpha_q$	↑ Kallikrein	↑ Kinins
Vasodilation in blood vessels of muscle in fight-or-flight response	Sympathetic	ACh	Presynaptic M_2 receptor on noradrenergic neurons	$G\alpha_i$	↓ AC	↓ $[cAMP]_i$ in neuron
		NANC	Receptor on VSMC			

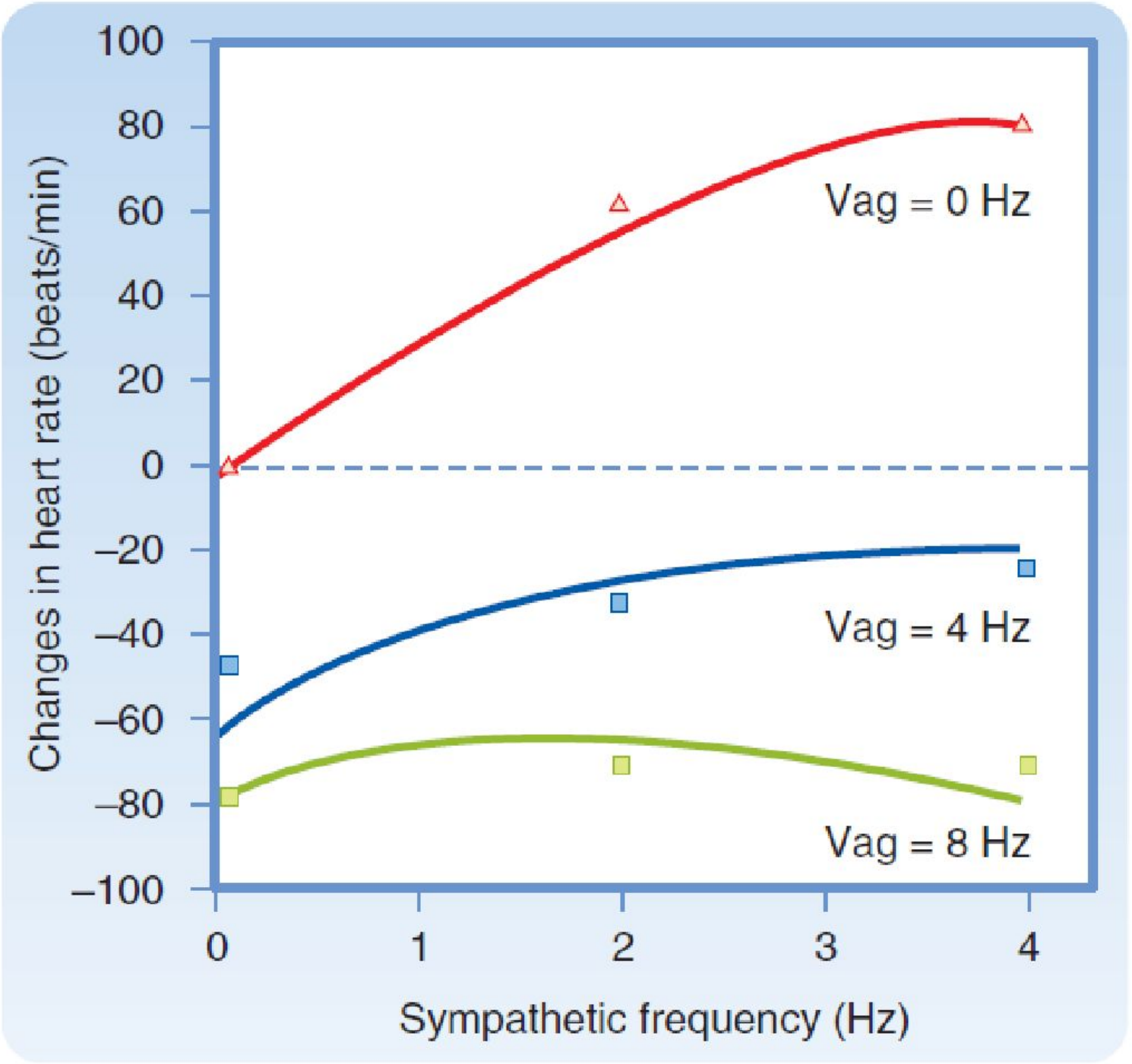
AC, adenylyl cyclase; Epi, epinephrine; GC, guanylyl cyclase; NANC, nonadrenergic, noncholinergic; NE, norepinephrine; PLC, phospholipase C; VIP, vasoactive intestinal peptide; V_m, membrane potential.


Heart rate (beats/min)
120
110
100
90
80
70
60
50
40
Propranolol
Atropine
Atropine
Propranolol
Control
1
2
3
4
1
2
3
4
Drug 1
Drug 2

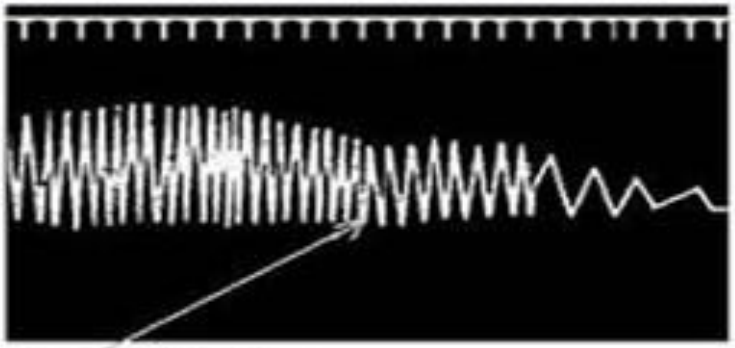
50

Intrinsic Rate (100-110 bpm)

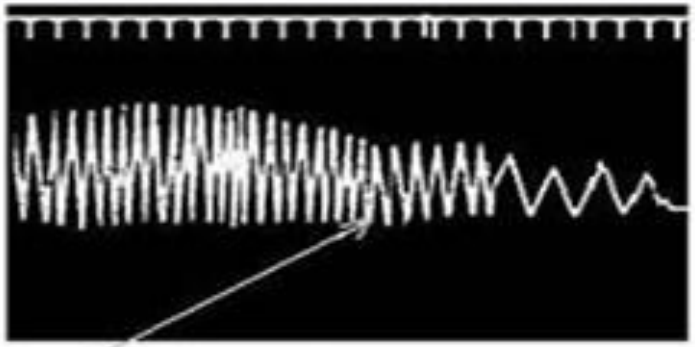
200 bpm


100
80
60
40
20
0
–20
–40
–60
–80
–100
Changes in heart rate (beats/min)
Vag = 0 Hz
Vag = 4 Hz
Vag = 8 Hz
0
1
2
3
4
Sympathetic frequency (Hz)

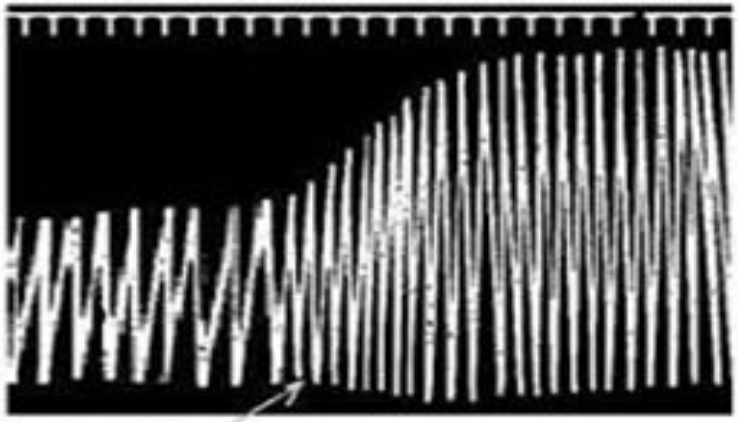
Effects of adrenaline, acetylcholine, potassium and calcium on the isolated heart.



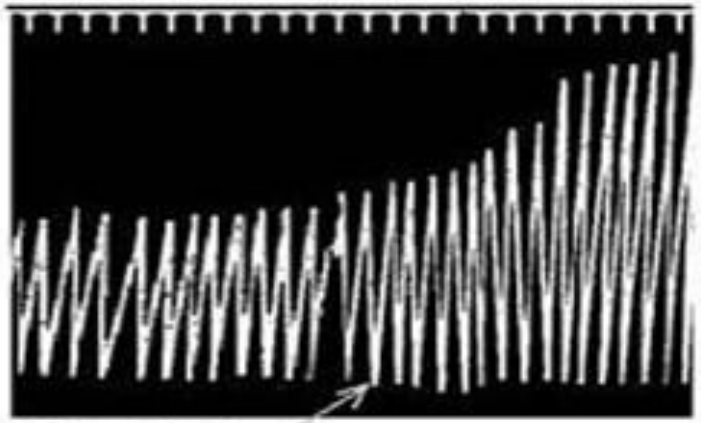
Acetylcholin



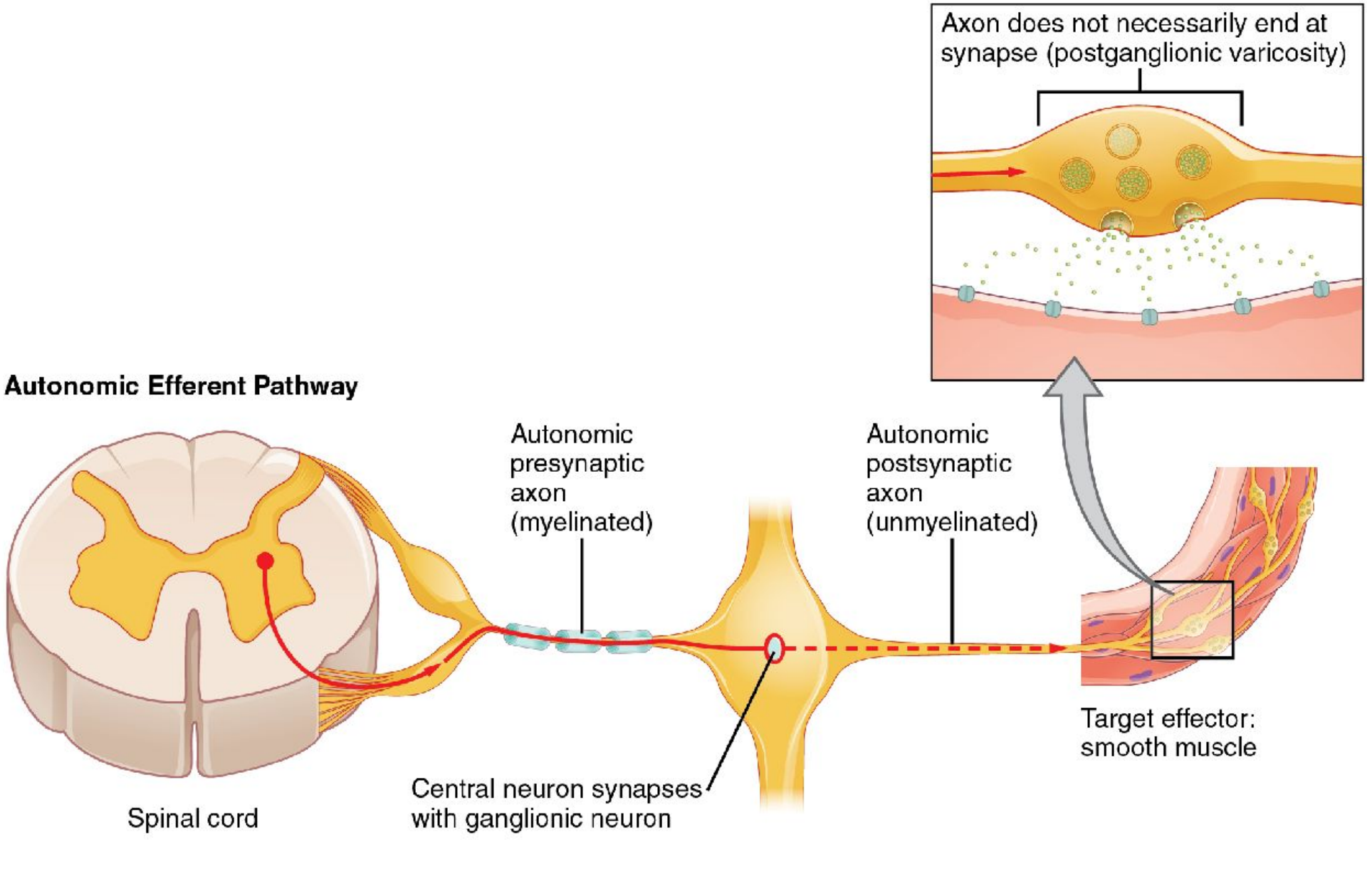
5 % KCl

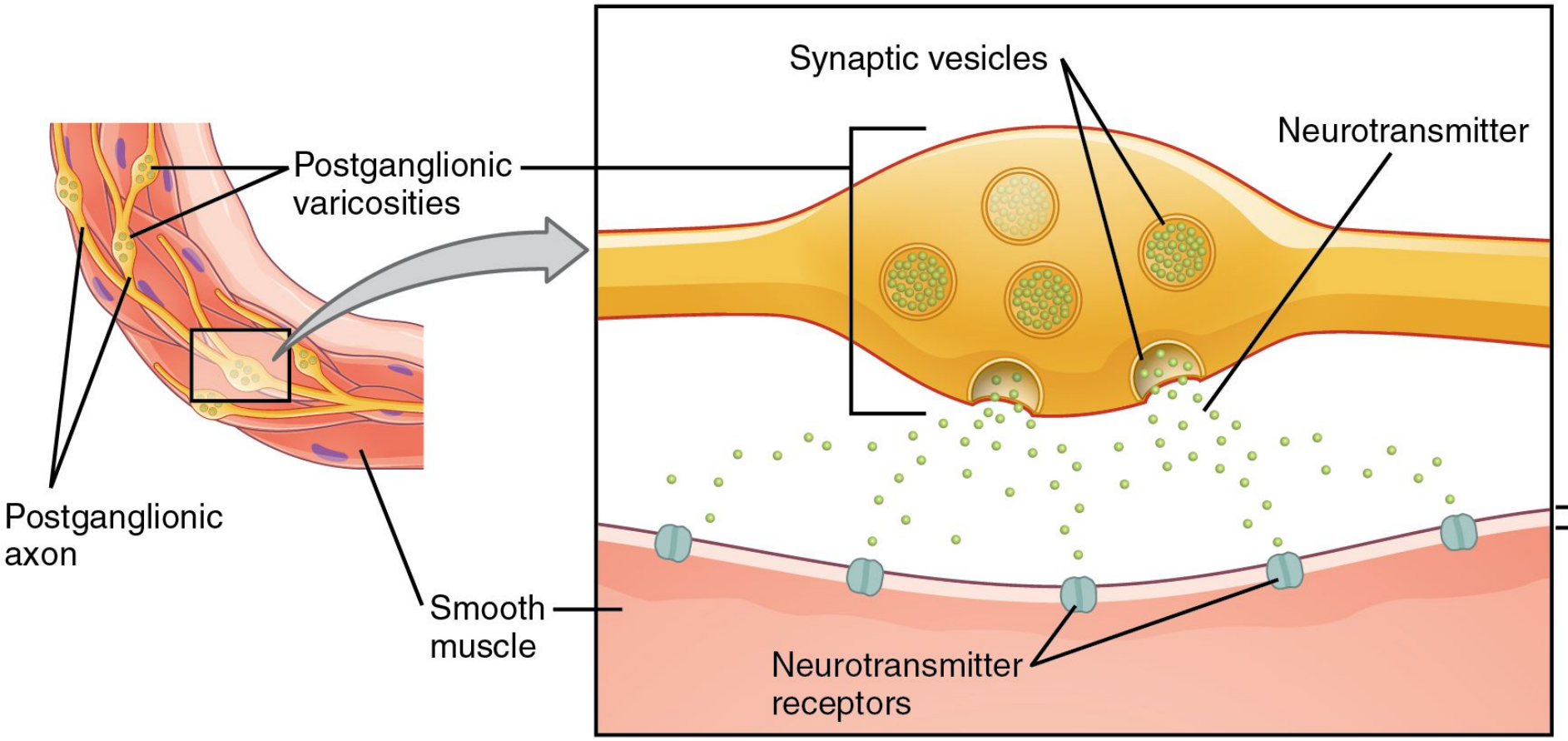


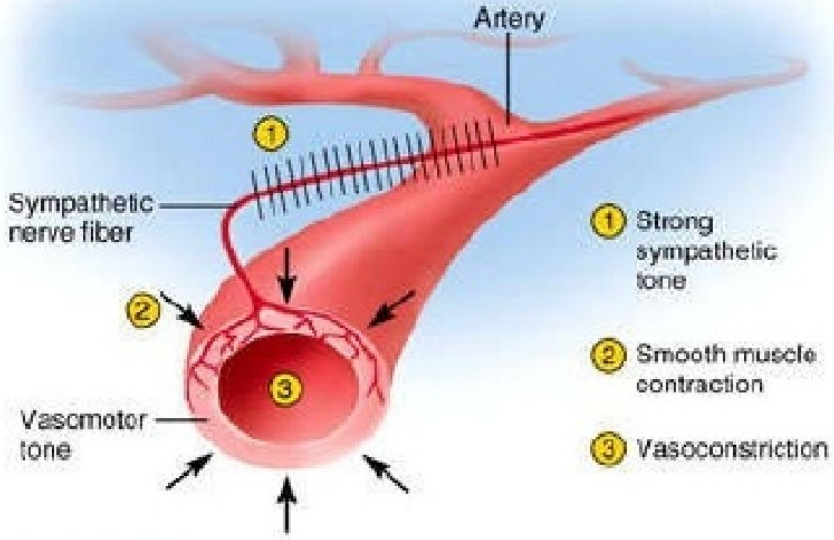
Adrenalin



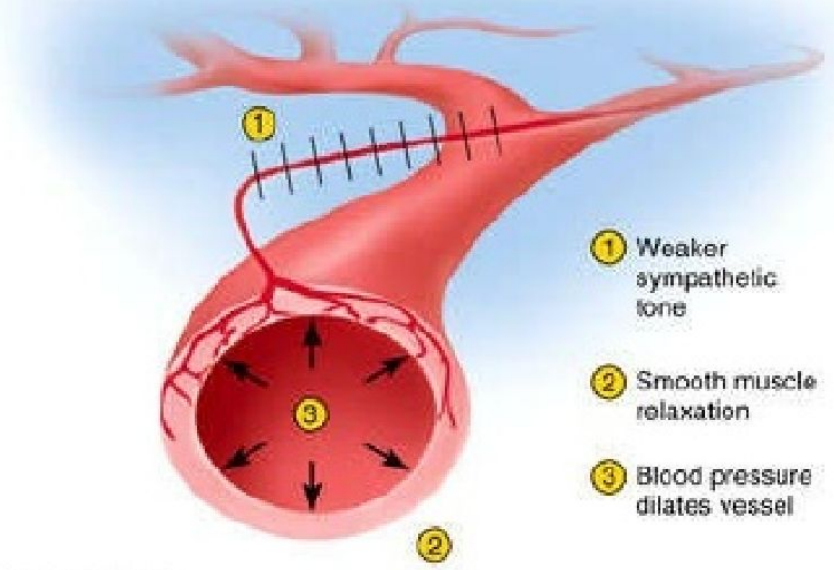
5 % $CaCl_2$


Axon does not necessarily end at synapse (postganglionic varicosity)
Autonomic Efferent Pathway
Autonomic presynaptic axon (myelinated)
Autonomic postsynaptic axon (unmyelinated)
Target effector: smooth muscle
Spinal cord
Central neuron synapses with ganglionic neuron

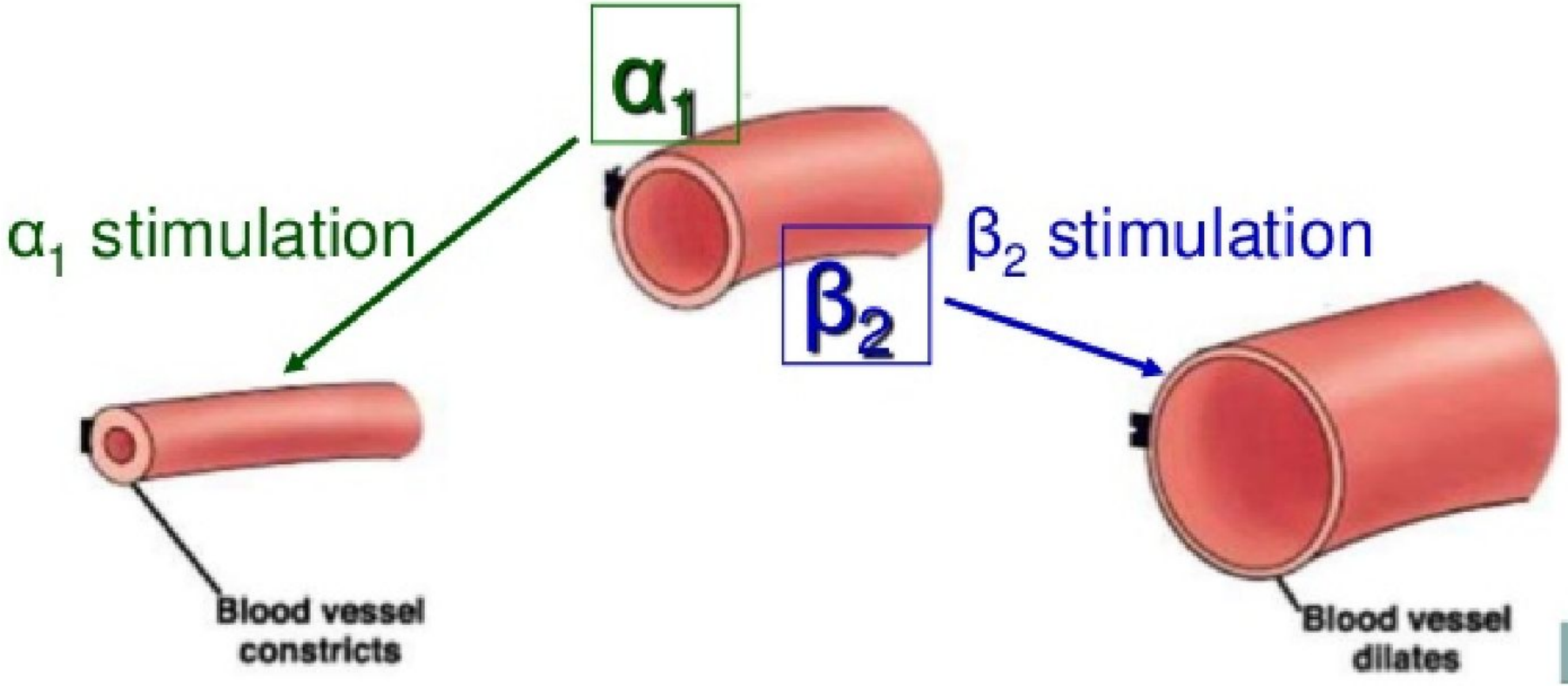

Synaptic vesicles
Neurotransmitter
Postganglionic varicosities
Postganglionic axon
Smooth muscle
Neurotransmitter receptors

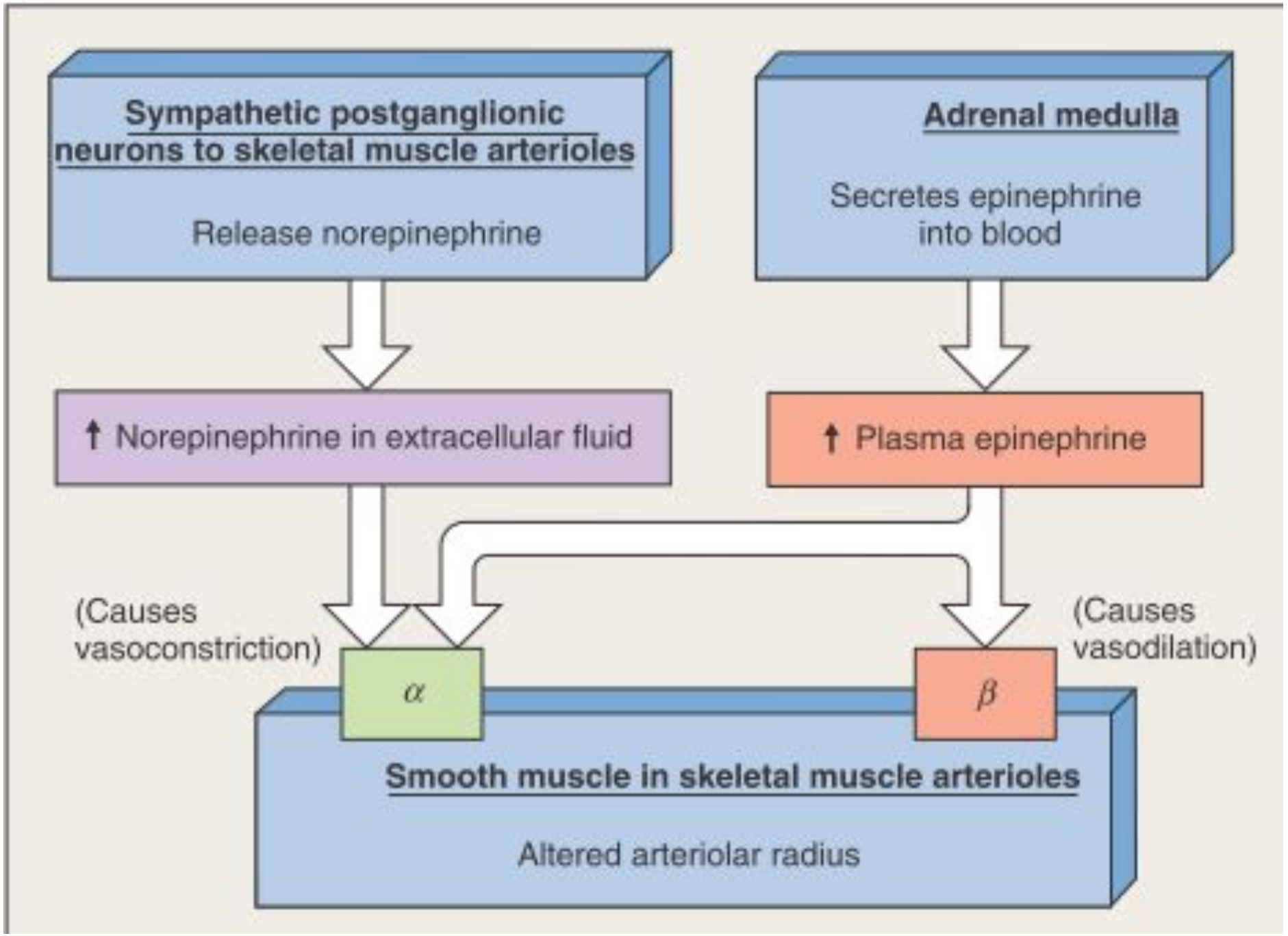


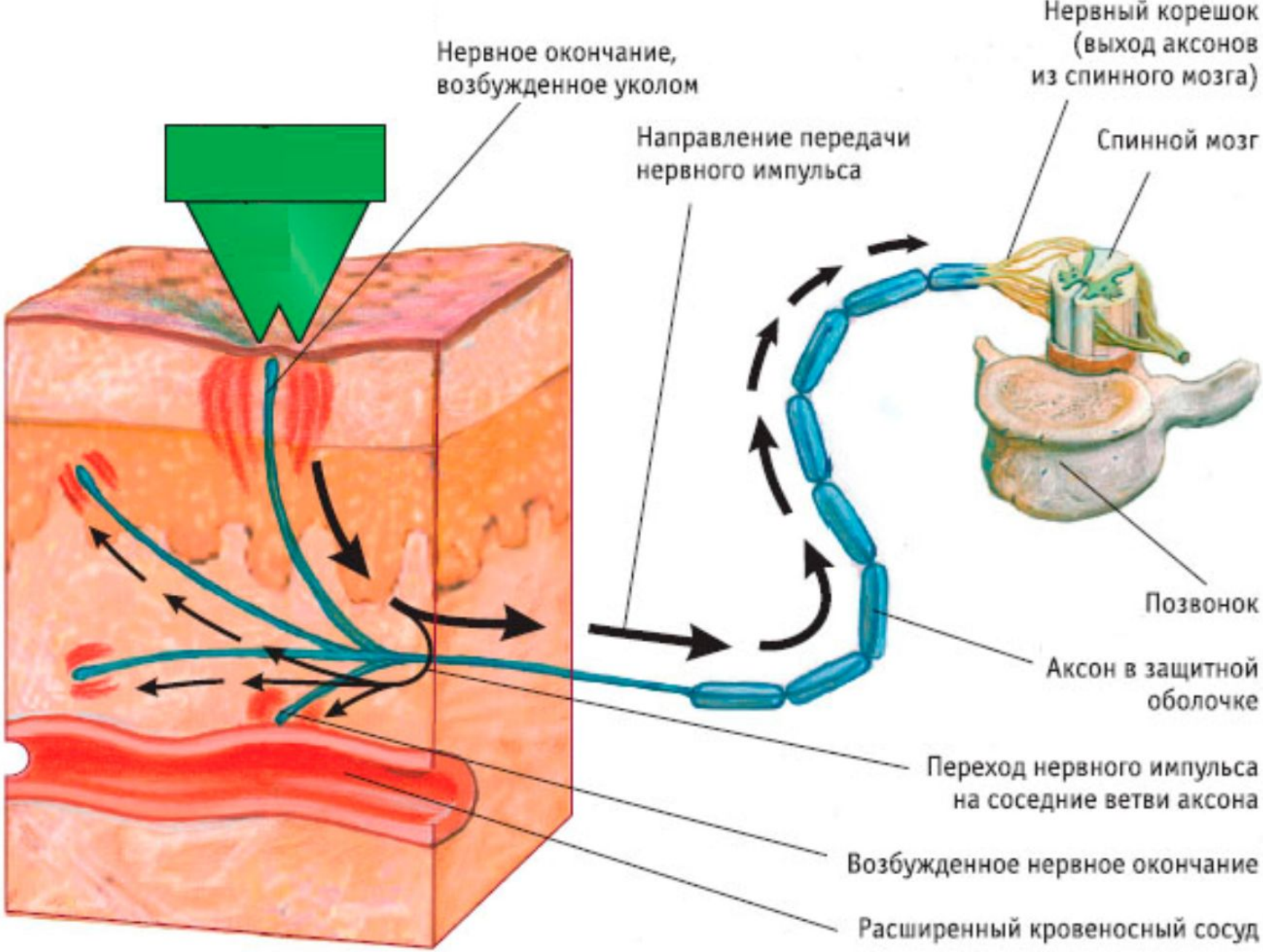
(a) Vasoconstriction



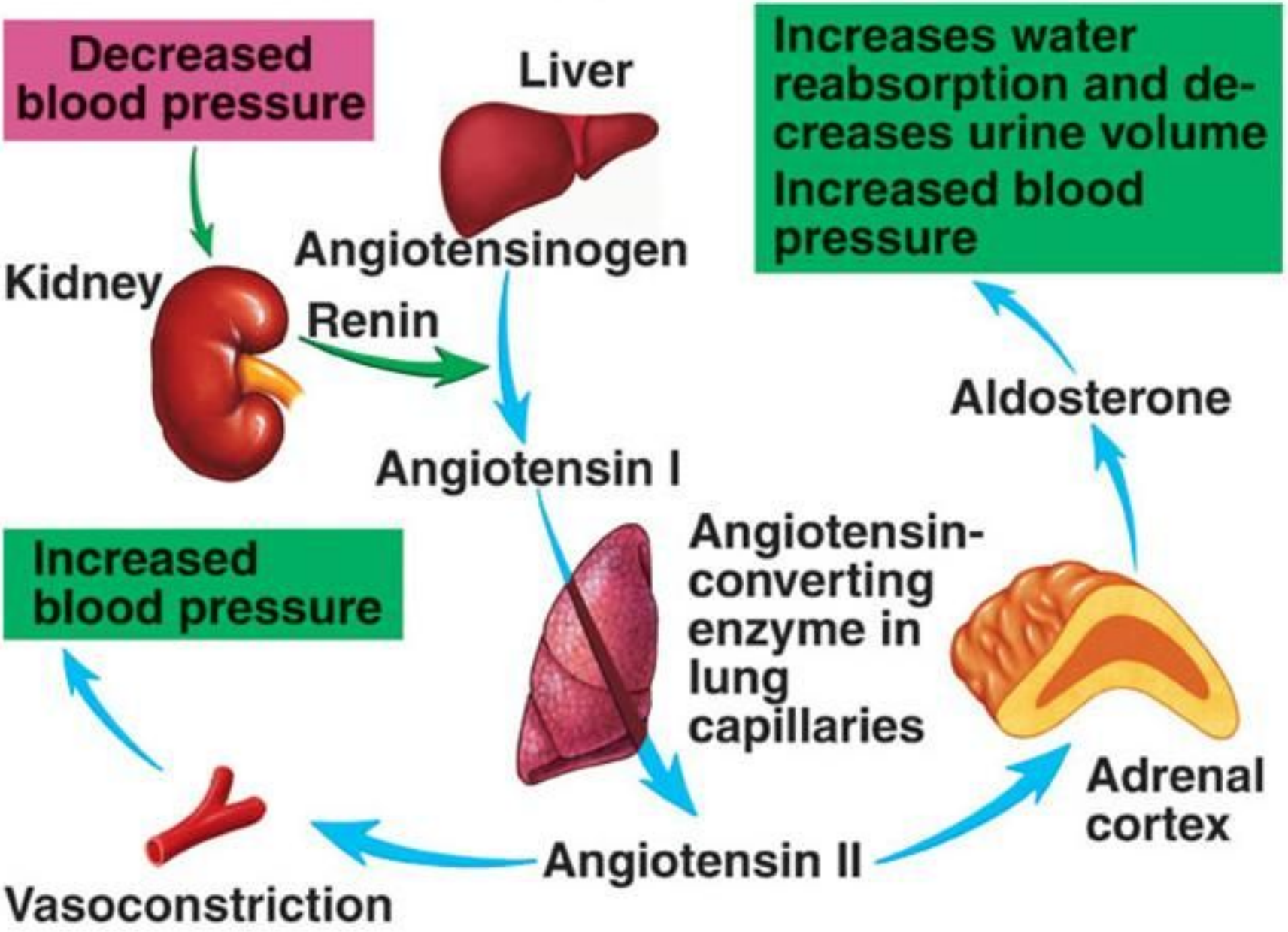
(b) Vasodilation

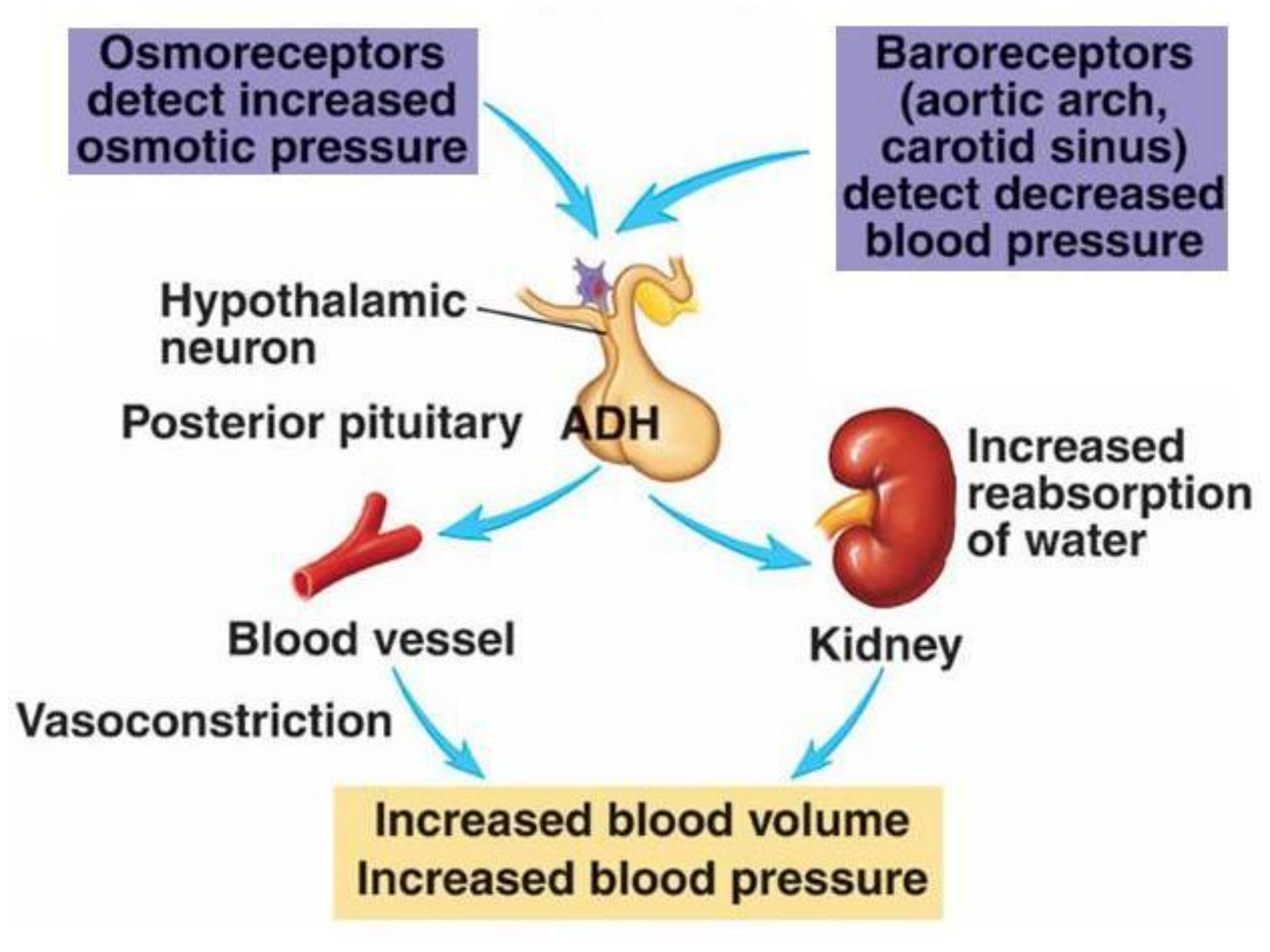

α1
α1 stimulation
β2
β2 stimulation
Blood vessel constricts
Blood vessel dilates


Sympathetic postganglionic neurons to skeletal muscle arterioles
Release norepinephrine
Adrenal medulla
Secretes epinephrine into blood
↑ Norepinephrine in extracellular fluid
↑ Plasma epinephrine
(Causes vasoconstriction)
(Causes vasodilation)
α
β
Smooth muscle in skeletal muscle arterioles
Altered arteriolar radius



Аксон-рефлекс


Decreased blood pressure
Liver
Increases water reabsorption and decreases urine volume
Increased blood pressure
Angiotensinogen
Kidney
Renin
Aldosterone
Angiotensin I
Angiotensin-converting enzyme in lung capillaries
Increased blood pressure
Adrenal cortex
Angiotensin II
Vasoconstriction


Osmoreceptors detect increased osmotic pressure
Baroreceptors (aortic arch, carotid sinus) detect decreased blood pressure
Hypothalamic neuron
Posterior pituitary
ADH
Increased reabsorption of water
Blood vessel
Kidney
Vasoconstriction
Increased blood volume
Increased blood pressure

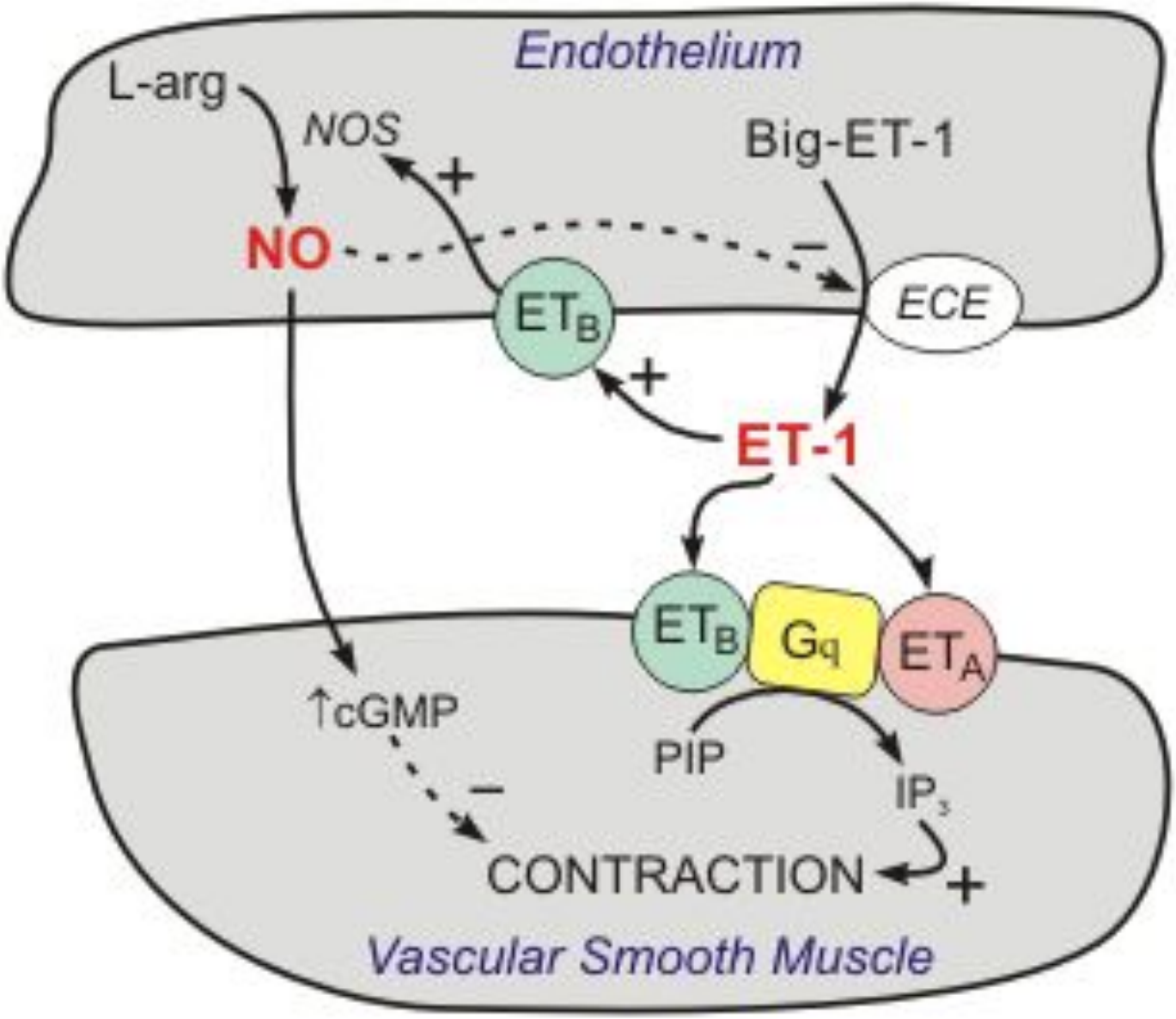
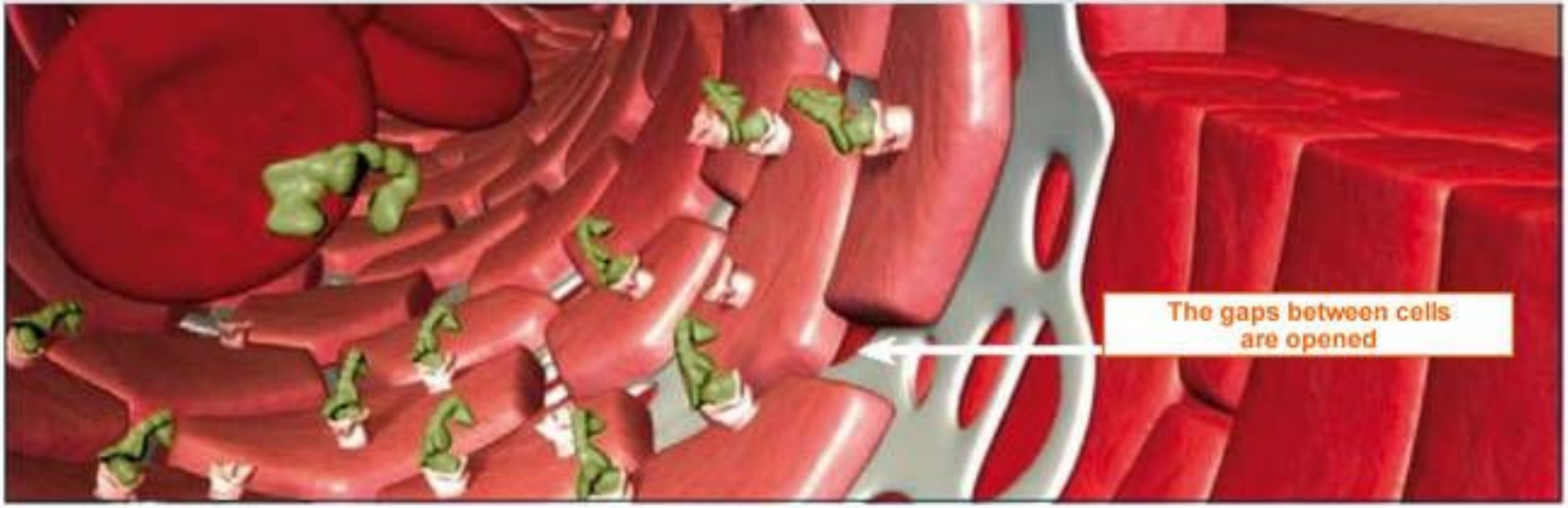
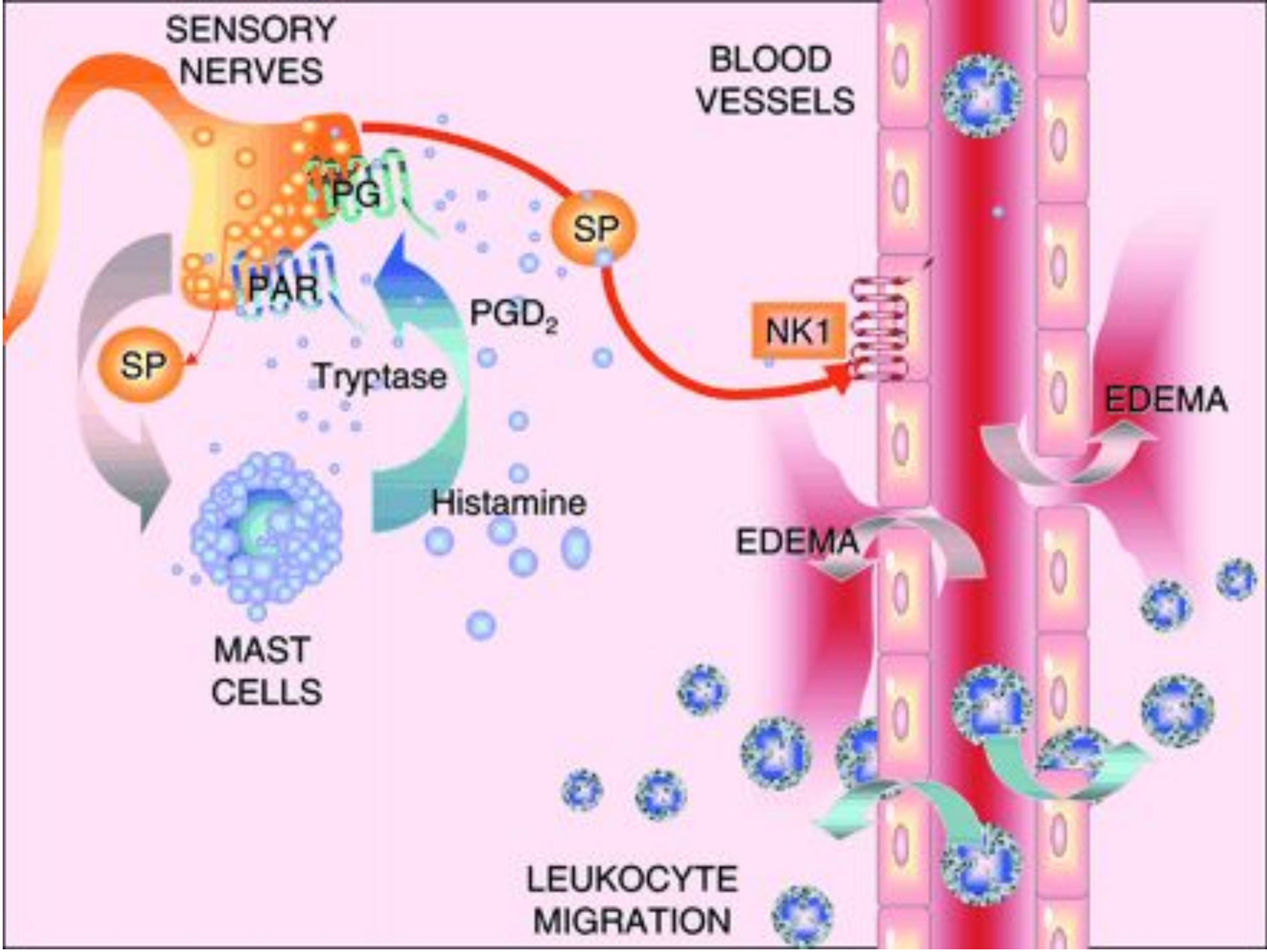


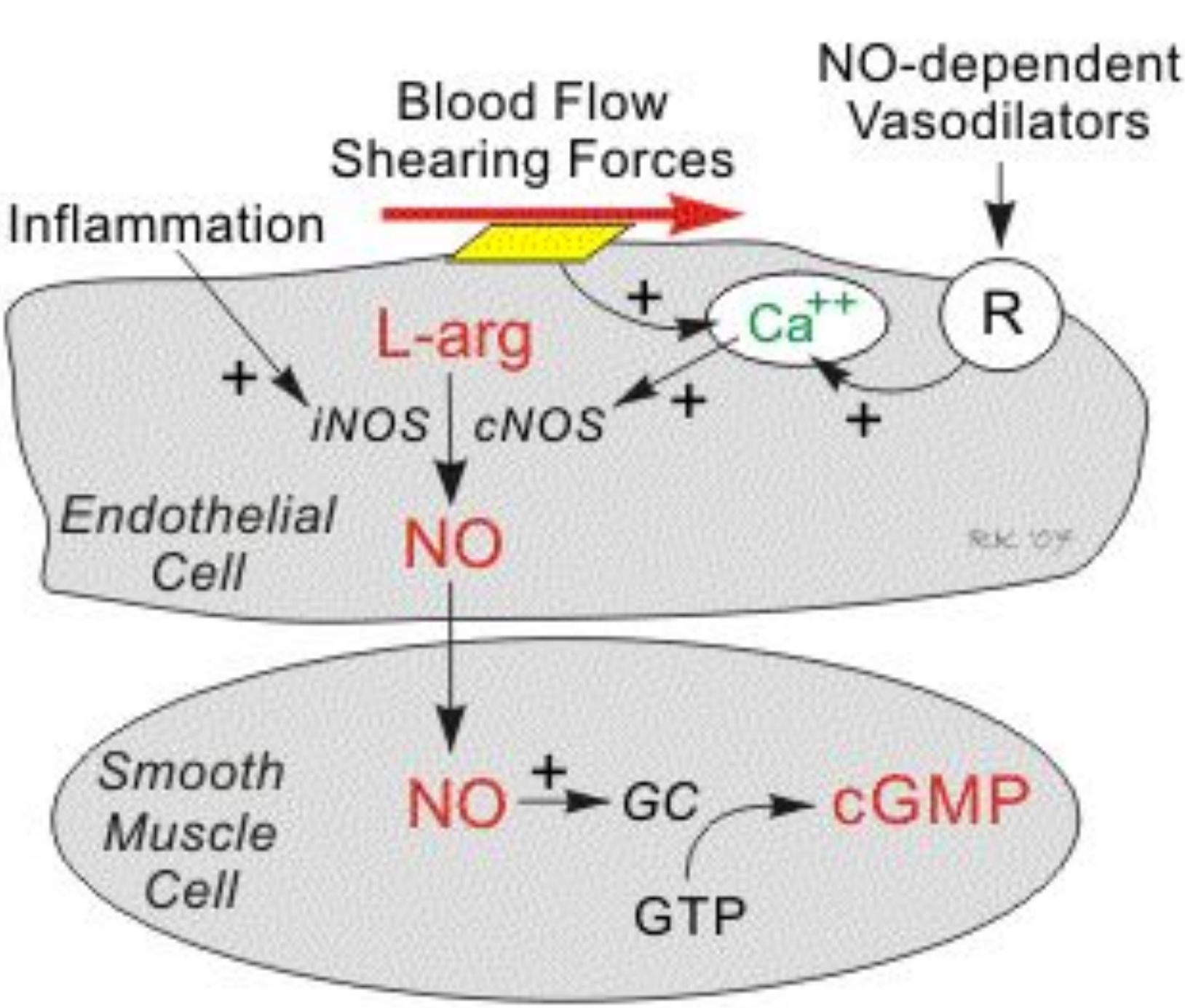
Figure 2. Endothelin receptors and interactions with nitric oxide.

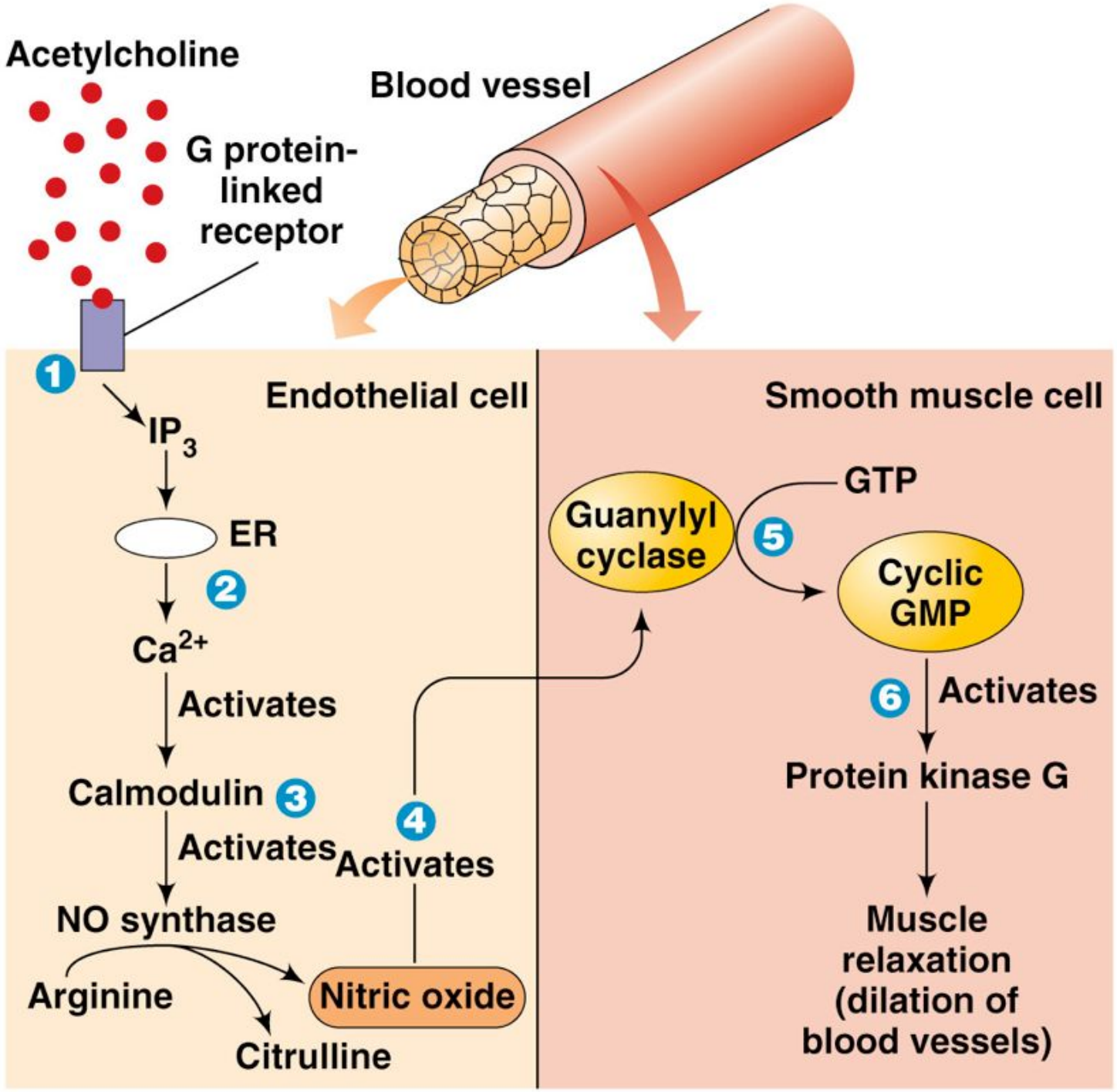
Blood vessel during a bradykinin-mediated swelling attack



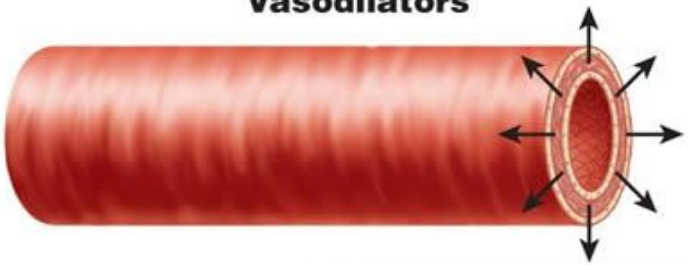
- The increased bradykinin concentration leads to dilation (widening) of the blood vessel and increases the permeability of the vascular wall by binding to the bradykinin B2 receptor.
- The increased permeability permits increased outflow of fluid from the blood vessel, leading to swelling of the surrounding tissue.


SENSORY NERVES
BLOOD VESSELS
PG
SP
PAR
PGD2
NK1
SP
Tryptase
EDEMA
Histamine
EDEMA
MAST CELLS
LEUKOCYTE MIGRATION


NO-dependent
Vasodilators
Blood Flow
Shearing Forces
Inflammation
R
+
Ca++
L-arg
+
+
+
iNOS
cNOS
Endothelial
Cell
NO
Smooth
Muscle
Cell
NO
+
GC
cGMP
GTP


Acetylcholine
G protein-linked receptor
Blood vessel
1
Endothelial cell
Smooth muscle cell
IP3
ER
2
Ca2+
Activates
Calmodulin
3
Activates
NO synthase
Arginine
Citrulline
Nitric oxide
4
Activates
GTP
Guanylyl cyclase
5
Cyclic GMP
6
Activates
Protein kinase G
Muscle relaxation (dilation of blood vessels)

Vasodilators



Metabolic
- ↓ O_2
- ↑ CO_2
- ↑ H^+
- ↑ K^+
- Prostaglandins
- Adenosine
- Nitric oxide

Neuronal
- ↓ Sympathetic tone

Hormonal
- Atrial natriuretic peptide

Intrinsic mechanisms (autoregulation)
- Metabolic or myogenic controls
- Distribute blood flow to individual organs and tissues as needed

Extrinsic mechanisms
- Neuronal or hormonal controls
- Maintain mean arterial pressure (MAP)
- Redistribute blood during exercise and thermoregulation

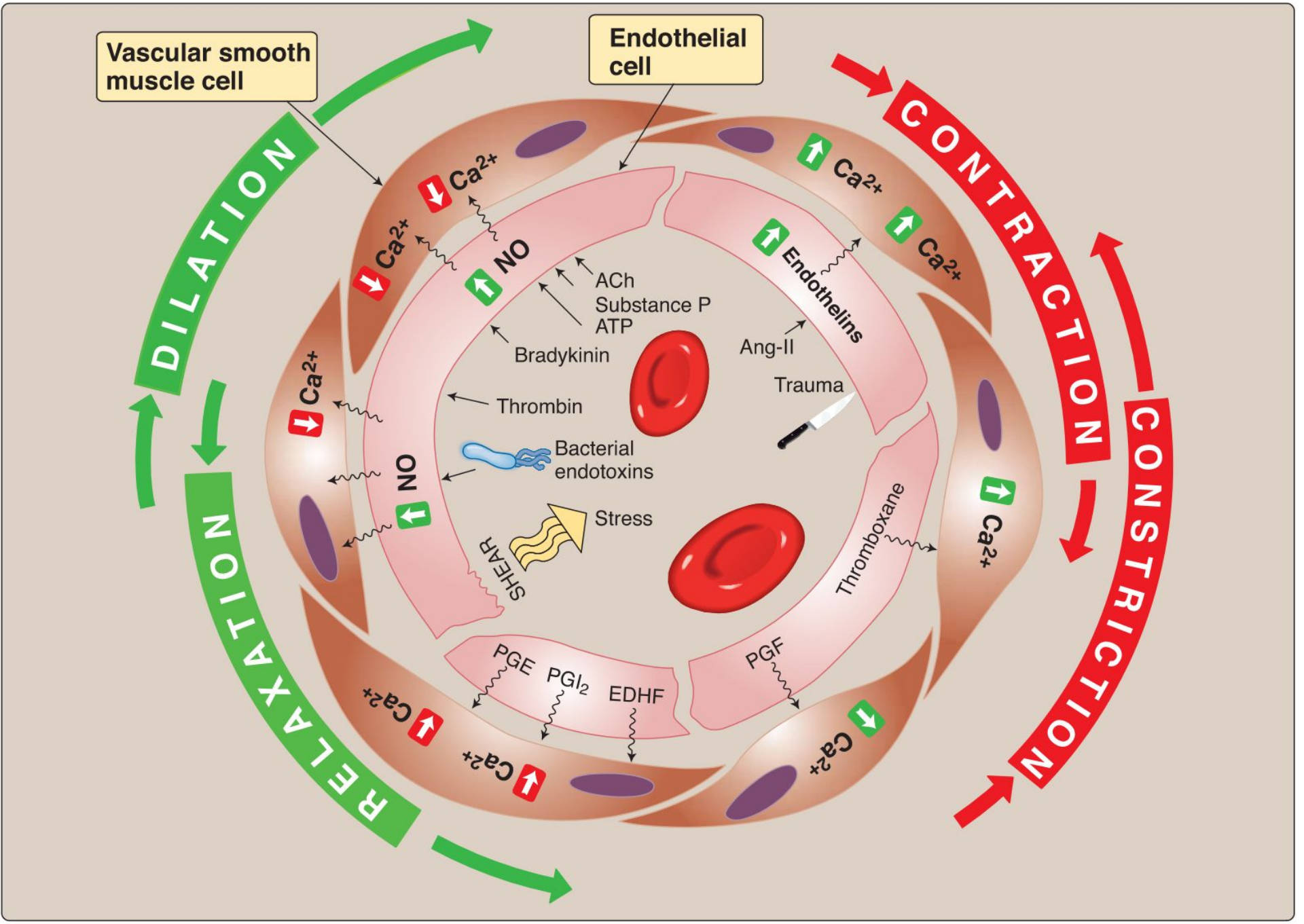
Vasoconstrictors

Myogenic
- Stretch

Metabolic
- Endothelins

Neuronal
- ↑ Sympathetic tone

Hormonal
- Angiotensin II
- Antidiuretic hormone
- Epinephrine
- Norepinephrine


Vascular smooth muscle cell
Endothelial cell
DILATION
CONTRACTION
RELAXATION
CONSTRICTION
Ca2+
NO
ACh
Substance P
ATP
Bradykinin
Endothelins
Ang-II
Trauma
Thrombin
Bacterial endotoxins
Stress
SHEAR
Thromboxane
PGE
PGI2
EDHF
PGF

B. Vasoconstriction and vasodilatation