Антигипертензивные средства

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2013 г.

1

Сэр Стефен Хейлс, 1677-1761

1723

AN

ACCOUNT

OF SOME

HYDRAULIC and HYDROSTATICAL

EXPERIMENTS

MADE ON THE

BLOOD and BLOOD-VESSELS

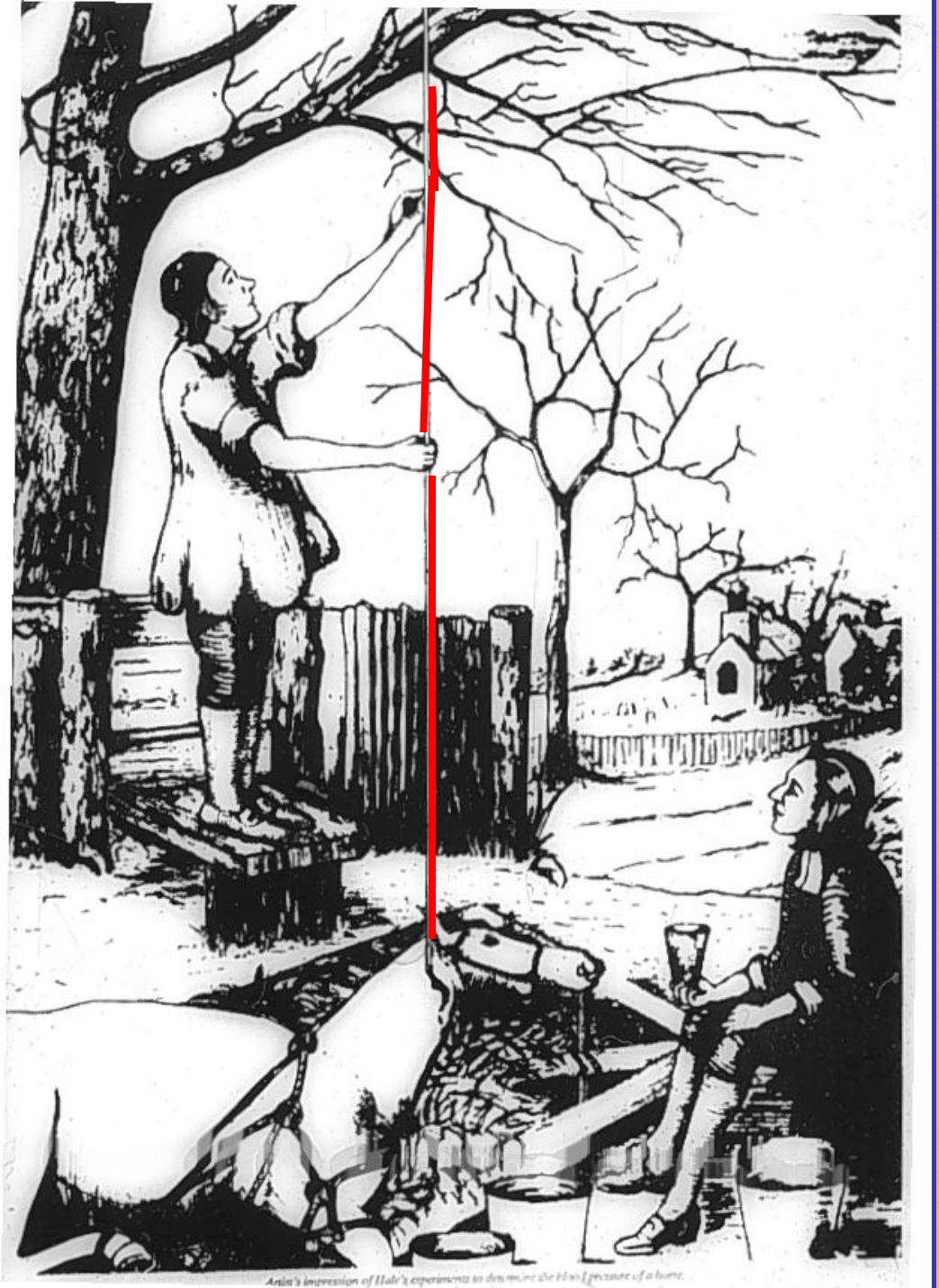
OF

ANIMALS.

EXPERIMENT I.

1. IN December I cauſed a *mare* to be tied down alive on her back; ſhe was 14 hands high, and about 14 years of age, had a fiſtula on her withers, was neither very lean nor yet luſty: having laid open the left crural artery about 3 inches from her belly, I inſerted into it a braſs pipe whoſe bore was $\frac{1}{6}$ of an inch in diameter; and to

that,



Artist's impression of Hale's experiments to determine the blood pressure of a horse

that, by means of another braſs pipe which was fitly adapted to it, I fixed a glaſs tube, of nearly the ſame diameter, which was 9 feet in length: then untying the ligature on the artery, the blood roſe in the tube 8 feet 3 inches perpendicular above the level of the left ventricle of the heart: but it did not attain to its full height at once; it ruſhed up about half way in an inſtant, and afterwards gradually at each pulſe 12, 8, 6, 4, 2, and ſometimes 1 inch: when it was at its full height, it would riſe and fall at and after each pulſe 2, 3, or 4 inches; and ſometimes it would fall 12 or 14 inches, and have there for a time the ſame vibrations up and down, at and after each pulſe, as it had, when it was at its full height; to which it would riſe again, after forty or fifty pulſes.

2. The pulſe of a horſe that is well, and not terrified, nor in any pain, is about 36 beats in a minute, which is nearly half as faſt as the pulſe of a man in health: this *mare*'s pulſe beat about 55 times in a minute, and ſometimes 60 or a 100, ſhe being in pain.

3. Then I took away the glaſs tube, and

Метод определения систолического арт. давления по Рива-Роччи – 1896 г.

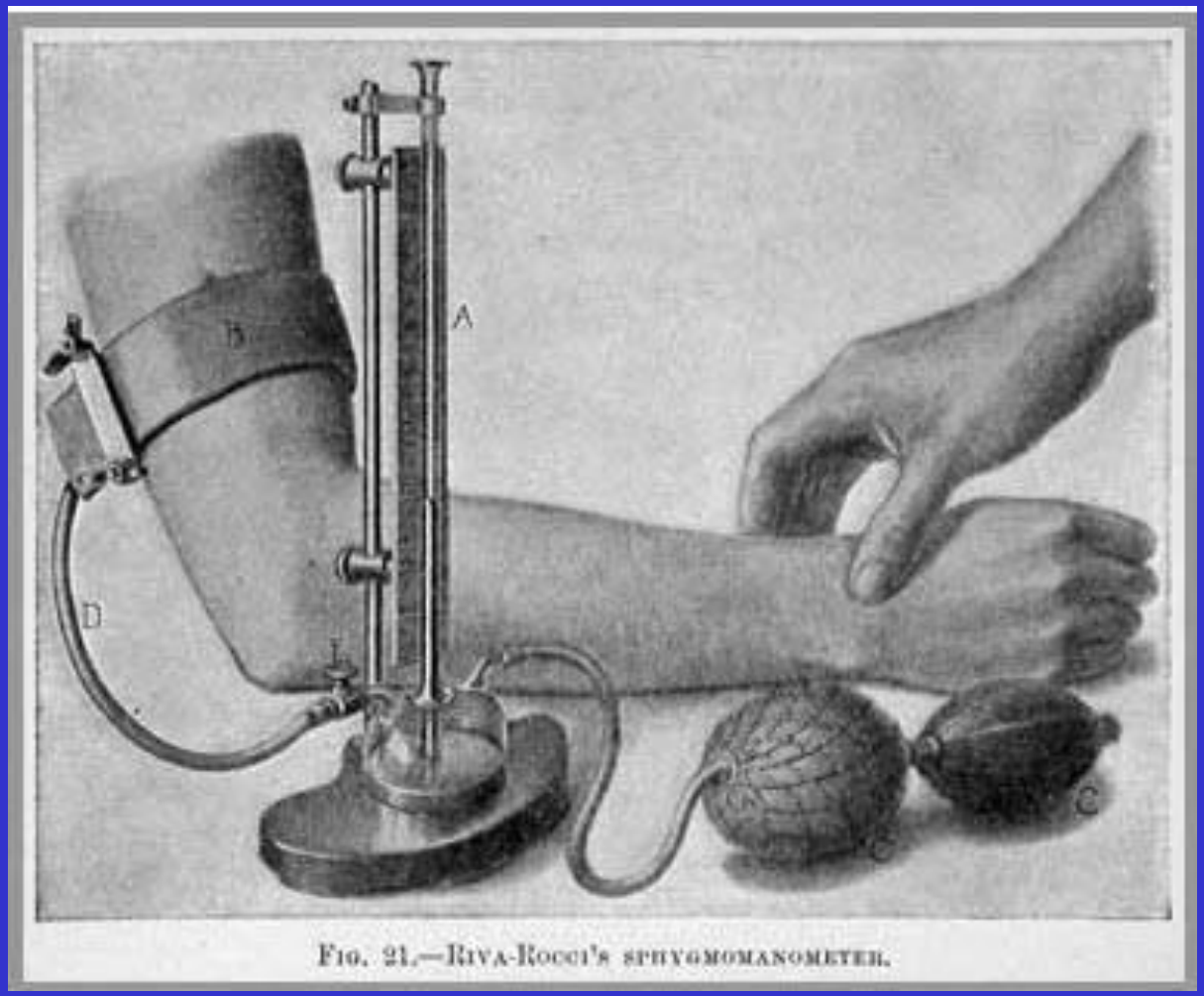


Fig. 21.—Riva-Rocci's sphygmomanometer.

Николай Сергеевич

КОРОТКОВ

(1874–1920)

Выпускник медицинского ф-та Московского университета 1898 года

Др. *Н. С. Коротковъ*. Къ вопросу о методахъ изслѣдованія кровянаго давленія (изъ клиники проф. С. П. Ѳедорова).

На основаніи своихъ наблюденій докладчикъ пришелъ къ тому заключенію, что вполнѣ сжатая артерія при нормальныхъ условіяхъ не даетъ никакихъ звуковъ. Воспользовавшись этимъ явленіемъ онъ предлагаетъ звуковой методъ опредѣленія кровянаго давленія на людяхъ. Рукавъ Rivva-Rocci накладывается на среднюю $^1/_2$ плеча; давленіе въ рукавѣ быстро повышается до полнаго прекращенія кровообращенія ниже рукава. Затѣмъ, предоставивъ ртути манометра падать, дѣтскимъ стетоскопомъ выслушиваютъ артерію тотчасъ ниже рукава. Сперва не слышно никакихъ звуковъ. При паденіи ртути манометра до извѣстной высоты появляются первые короткіе тоны, появленіе которыхъ указываетъ на прохожденіе части пульсовой волны подъ рукавомъ. Слѣдов., цифры манометра, при которыхъ появился первый тонъ соотвѣтствуютъ максимальному давленію. При дальнѣйшемъ паденіи ртути въ манометрѣ слышатся систолическіе компрессіонные шумы, которые переходятъ снова въ тоны (вторые). Наконецъ, всѣ звуки исчезаютъ. Время исчезновенія звуковъ указываетъ на свободную проходимость пульсовой волны; другими словами, въ моментъ исчезанія звуковъ минимальное кровяное давленіе въ артеріи превысило давленіе въ рукавѣ. Слѣд., цифры манометра въ это время соотвѣтствуютъ минимальному кровяному давленію. Опыты на животныхъ дали положительные результаты. Первые звуки-тоны появляются (на 10—12 mm.) раньше, нежели пульсъ, для ощущенія котораго (r. av. radialis) требуется прорывъ большей части пульсовой волны.

Известия Императорской Военно-медицинской академии, 1905, декабрь, № 4, т. XI, с.365

Гипертоническая болезнь -

Хроническое заболевание, основным клиническим признаком которого является длительное и стойкое повышение артериального давления (гипертензия).

Классификация артериальной гипертензии

Категория	АД сист., мм рт. ст.	АД диаст., мм рт. ст.
Оптимальное АД	<120	<80
Нормальное АД	<130	<85
Высокое нормальное АД	130-139	85-89
АГ I степени	140-159	90-99
АГ II степени	160-179	100-109
АГ III степени	≥ 180	≥110

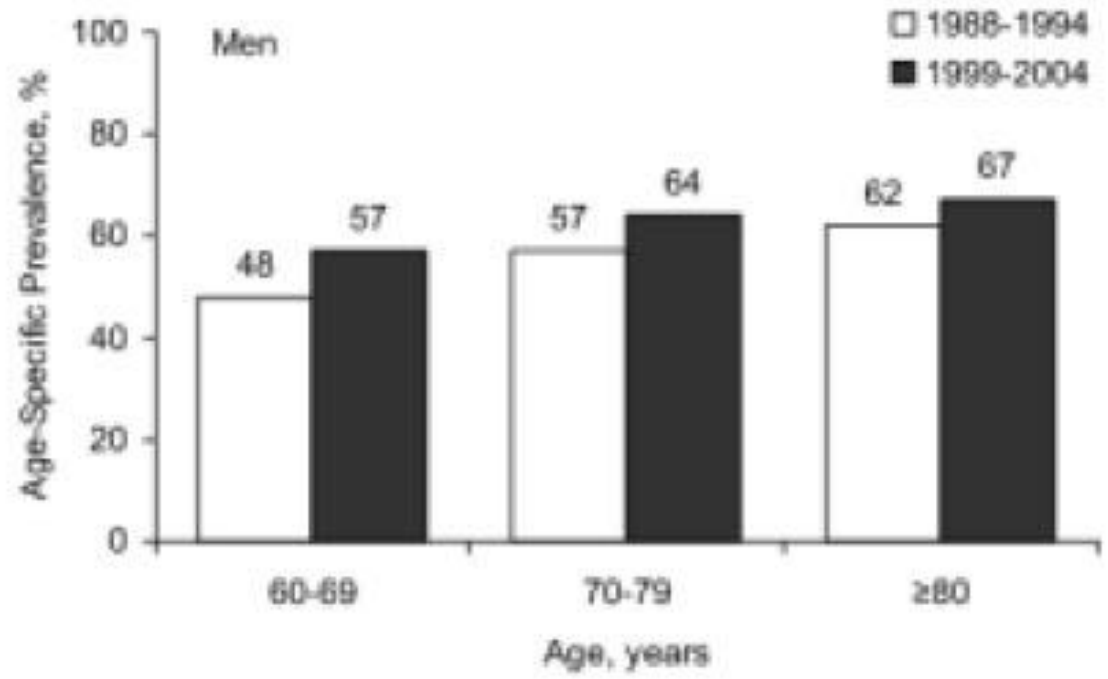
Примечание: если систолическое и диастолическое АД находятся в разных категориях, присваивается более высокая категория артериальной гипертензии

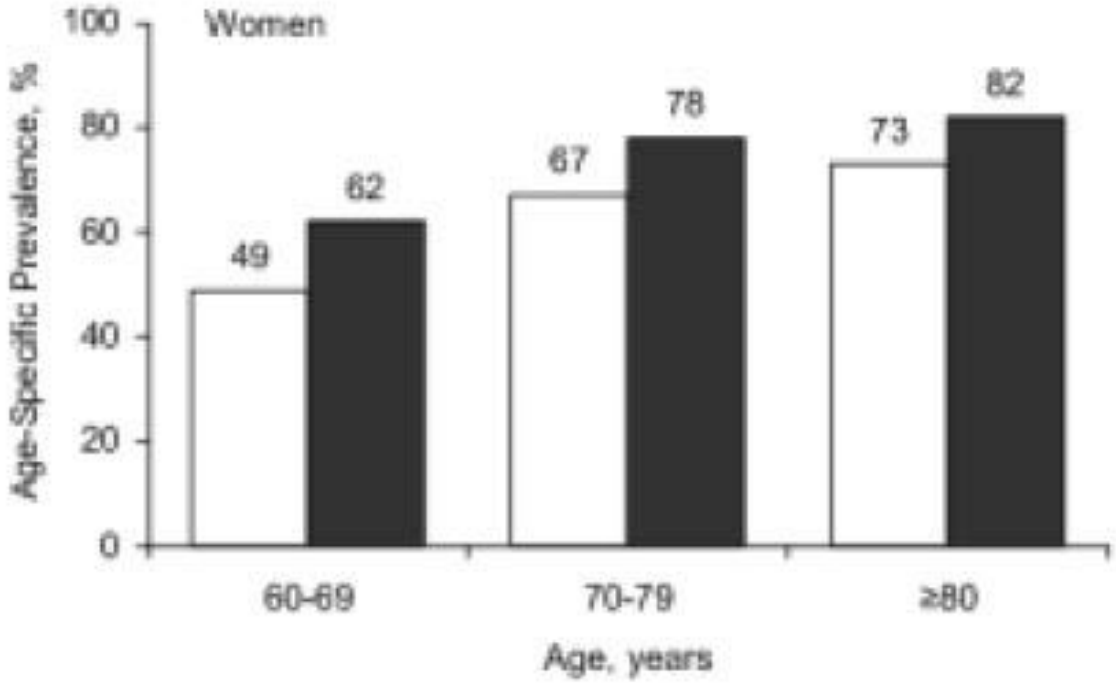
*** Профилактика, диагностика и лечение артериальной гипертонии в Российской Федерации. Кардиология.-2000.-№11**

Классификация артериальной гипертензии JNC VII

Категория	АД сист., мм рт. ст.	АД диаст., мм рт. ст.
Нормальное АД	<120	<80
Предгипертензия	120-139	80-89
АГ I степени	140-159	90-99
АГ II степени	>=160	>=100
Примечание: если систолическое и диастолическое АД находятся в разных категориях, присваивается более высокая категория артериальной гипертензии		

* **Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure**. *The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)*// **NIH Publication № 03-5233. May, 2003.**





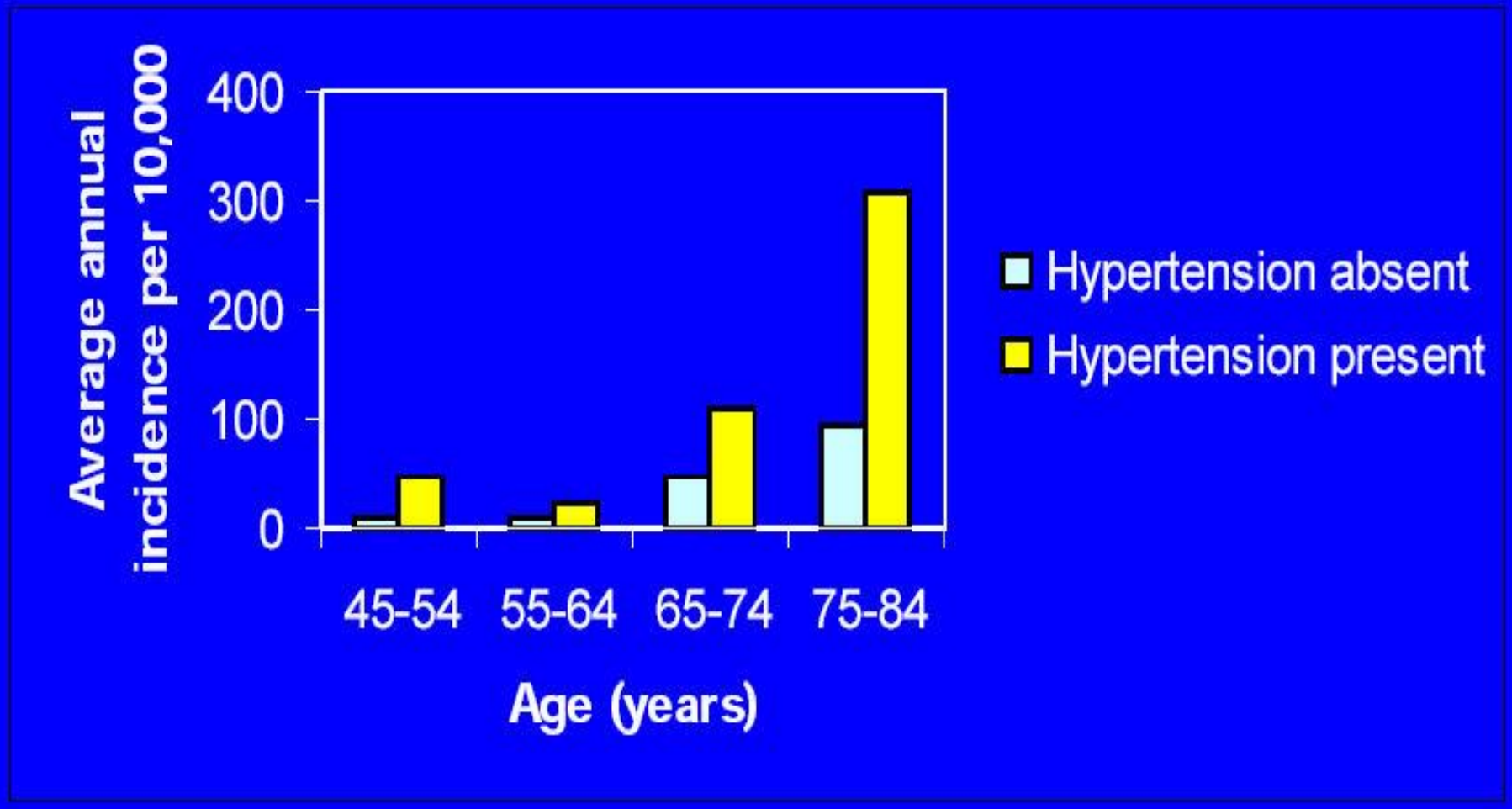
Тенденции к повышению АД с возрастом и со временем

Эпидемиология АГ

	мужчины	женщины
Распространённость АГ, %	**39,9**	**41,1**
Осведомлённость пациентов о наличии у них АГ, %	**37,1**	**58,9**
Лечатся, %	**21,6**	**45,7**
Эффективно лечатся, %	**5,7**	**17,5**

Кобалава Ж.Д., 2001

Stroke + systolic hypertension: men



Athero-thrombotic stroke (Framingham) J Cardiovasc Pharmacol 1993;21:527

Table 7. Identifiable causes of hypertension

Chronic kidney disease

Coarctation of the aorta

Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy

Drug induced or drug related (see table 18)

Obstructive uropathy

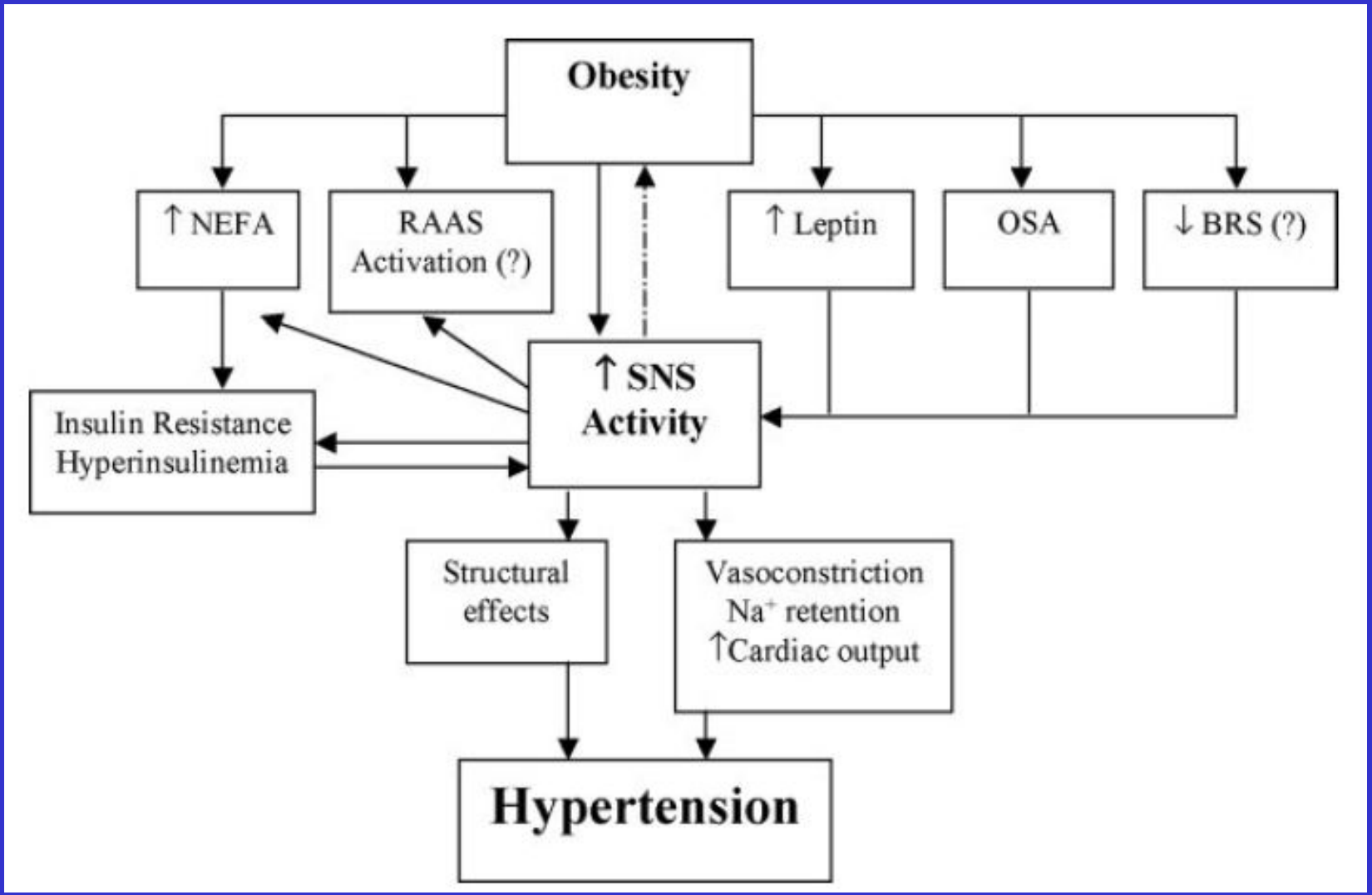
Pheochromocytoma

Primary aldosteronism and other mineralocorticoid excess states

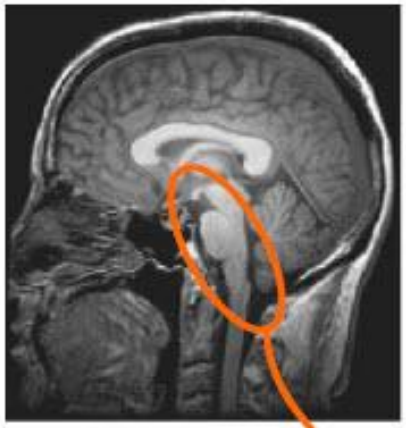
Renovascular hypertension

Sleep apnea

Thyroid or parathyroid disease

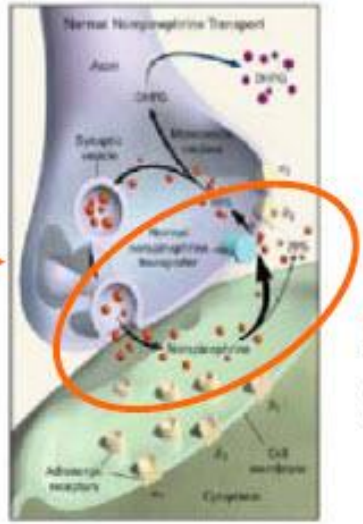


M.Esler et al., Hypertension 2006; 48; 787-796



Quantifying human sympathetic nervous system activity

Sympathetic Nerve Traffic



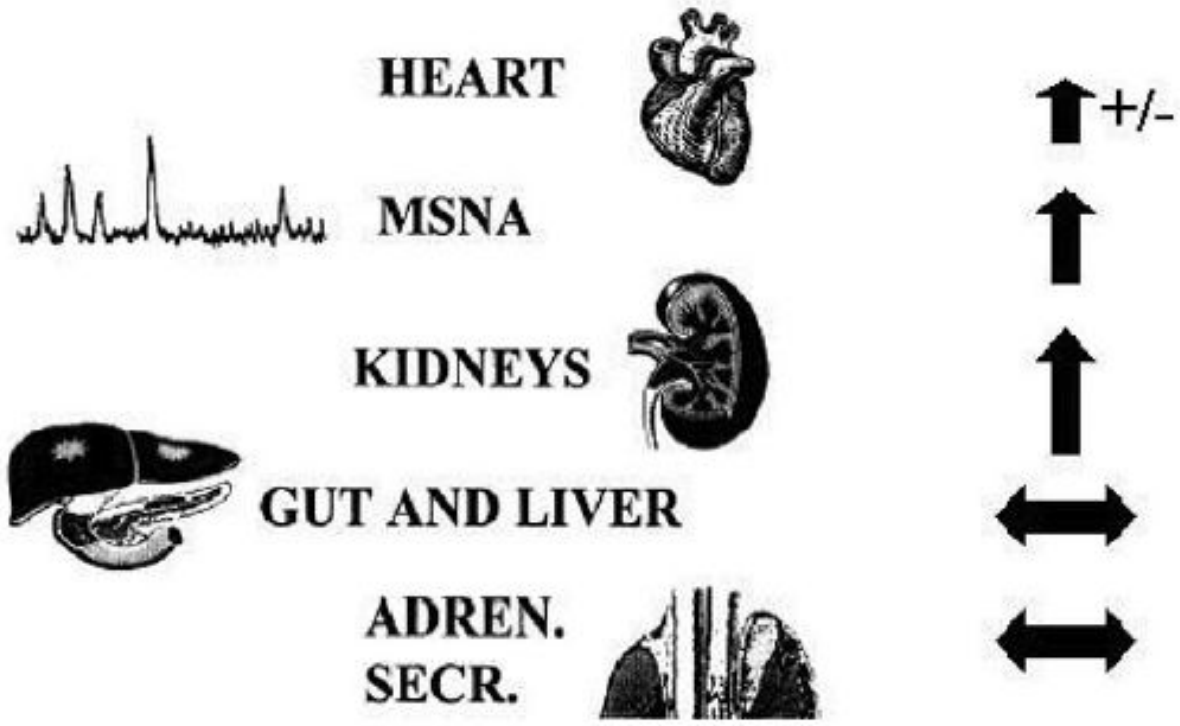
Norepinephrine Spillover

Testing is best done by recording postganglionic nerve traffic (clinical microneurography) and measuring transmitter release from sympathetic nerves to plasma (norepinephrine "spillover")

Murrey Esler, J Appl Physiol 108: 227–237, 2010.

Obesity-Related Hypertension

A Neurogenic Hypertension Variant



M.Esler et al., Hypertension 2006; 48; 787-796

Снижение риска появления основных осложнений ГБ- Hypertension Optimal Treatment (HOT) Study, 1998 (19000 пациентов в 26 странах; 3,8 года)

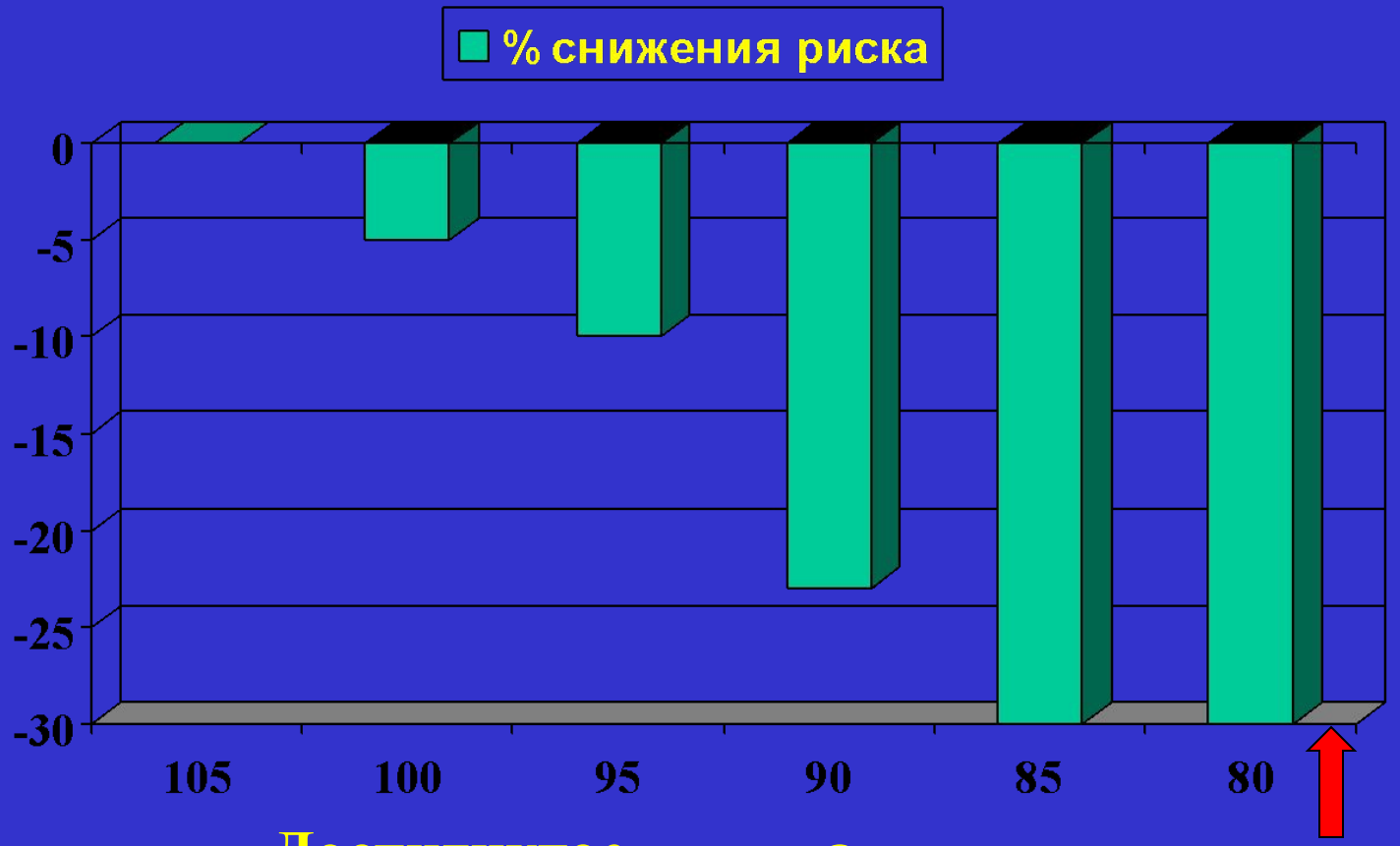
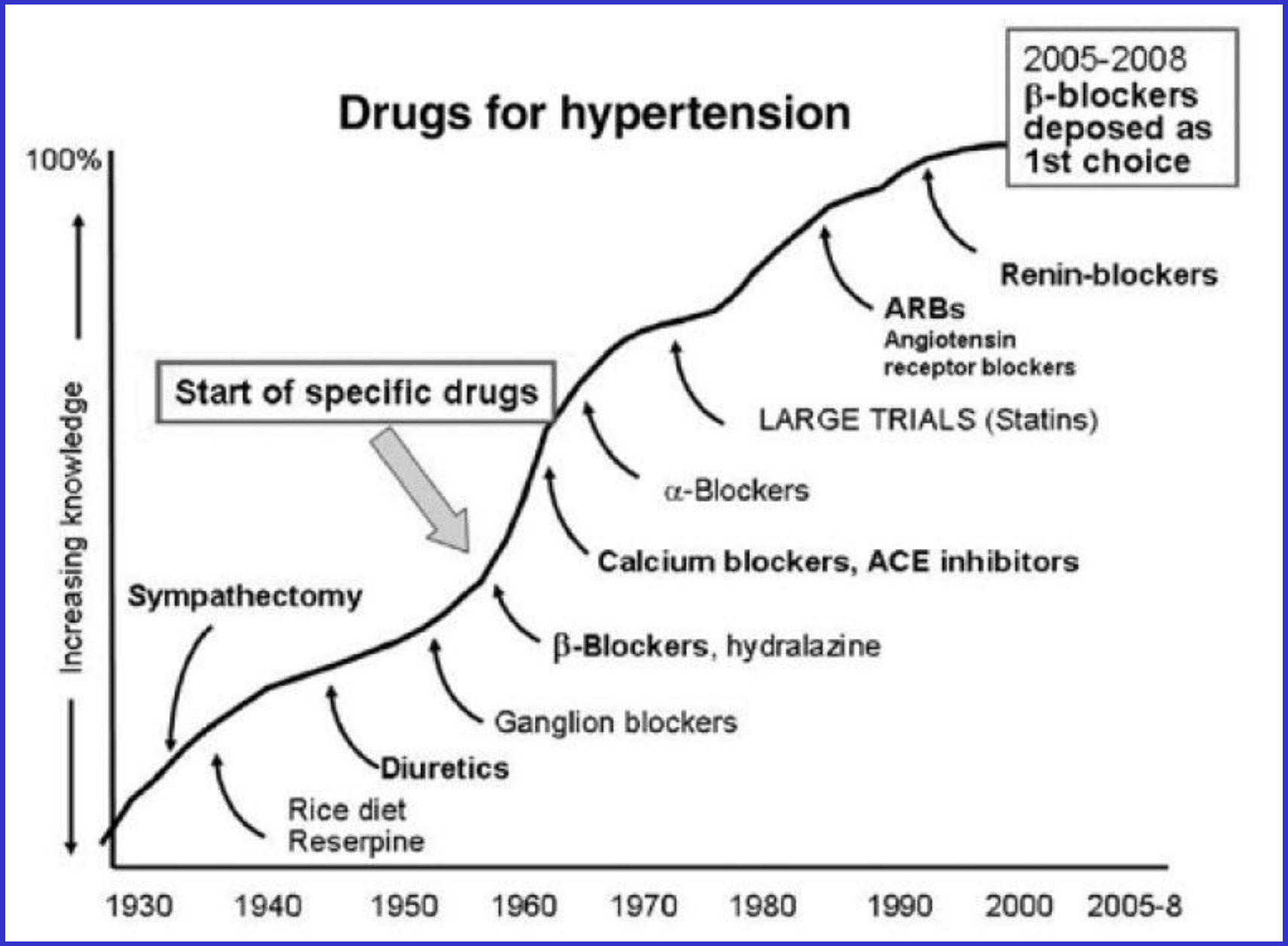


Table 9. Lifestyle modifications to prevent and manage hypertension*

Modification	Recommendation	Approximate SBP Reduction (Range)†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m²).	5–20 mmHg/10kg[92,93]
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg[94,95]
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg[94-96]
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg[97-98]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons.	2–4 mmHg[99]



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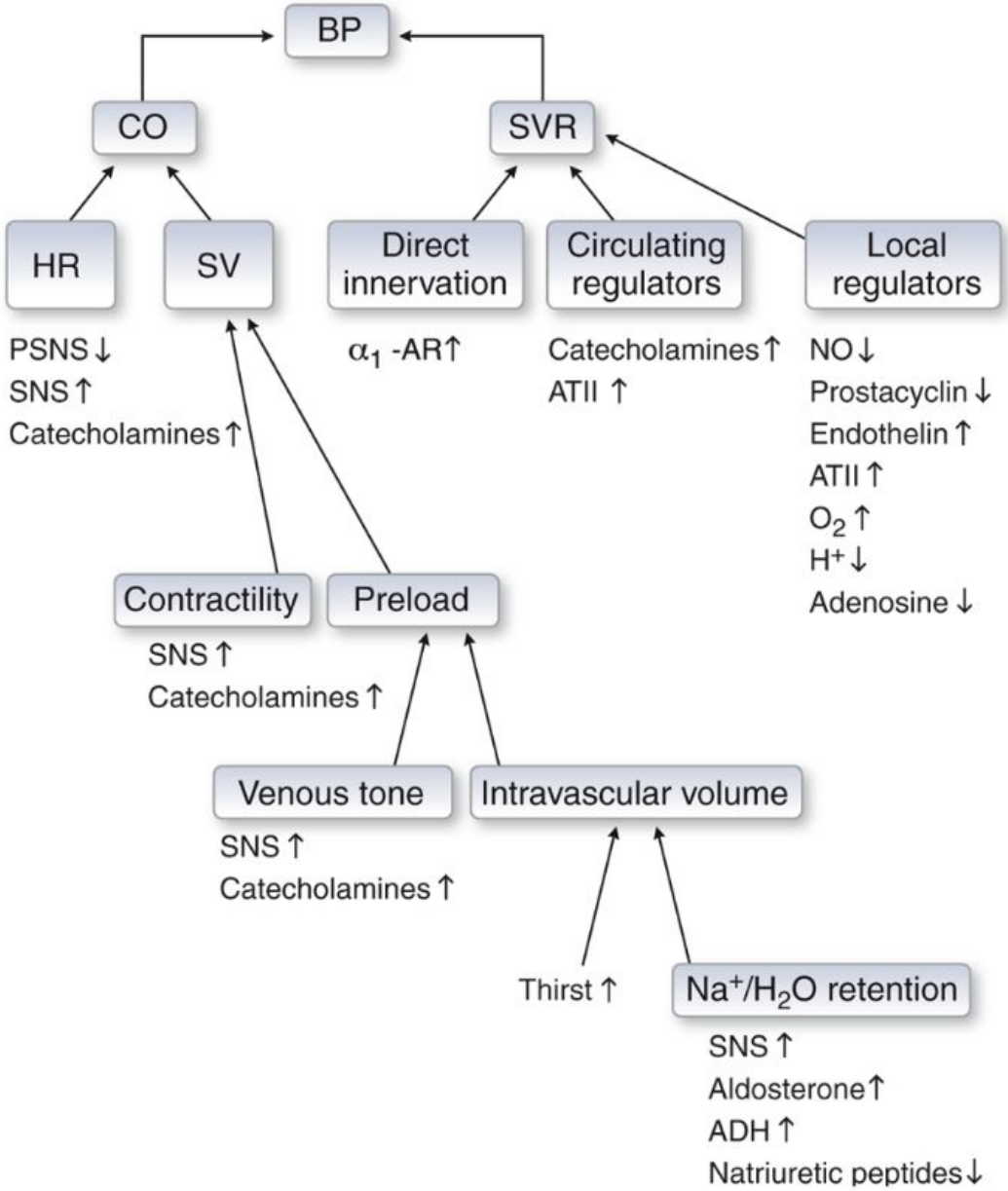
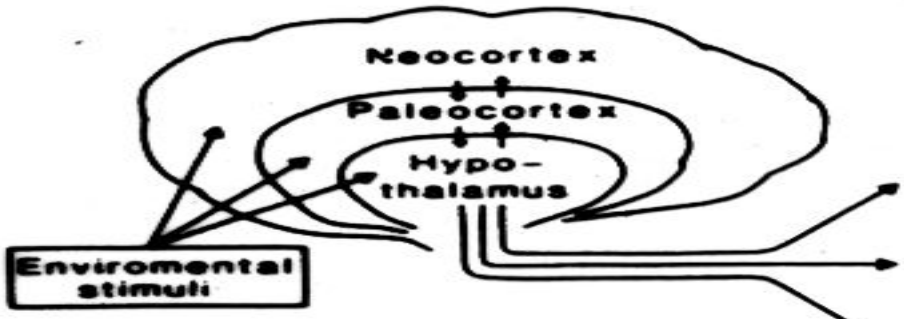


Figure 25-1: Determinants of systemic blood pressure. Blood pressure (*BP*) is the pr...



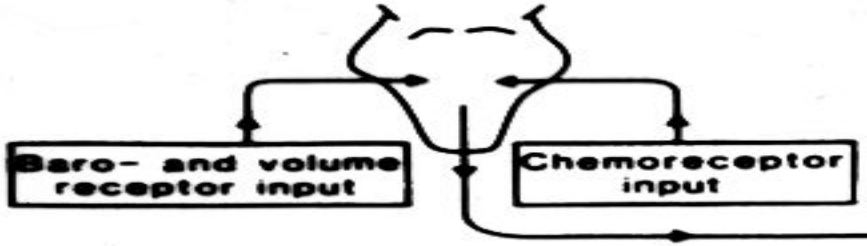
Various integrated patterns based on 3 links:

A. SOMATOMOTOR
(behaviour)

B. VISCEROMOTOR
(circulation, digestion etc.)

C. HORMONAL
(metabolism, electrolytes etc.)

2. BULBAR CONTROL LEVEL



NEURO-HORMONAL CARDIOVASCULAR ADJUSTMENTS
(of output, resistance, flow distr., volume etc.)

3. LOCAL CONTROL LEVEL

Heart Resistance vessels

MYOGENIC ACTIVITY
(controlled by local neg. and pos. feedbacks)

FIGURE 1. Schematic outline of the three major levels of cardiovascular regulation, illustrating principal differences between their respective

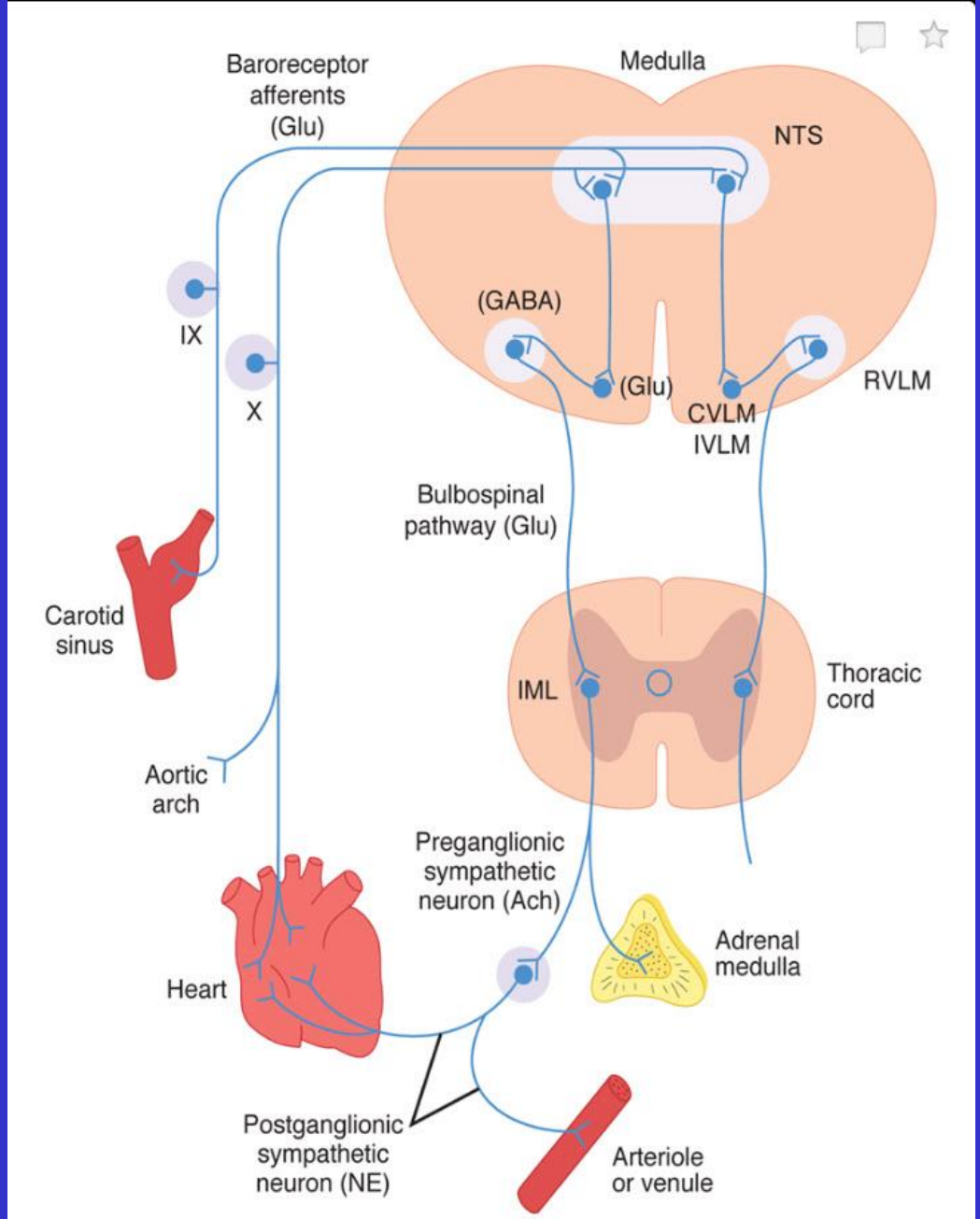
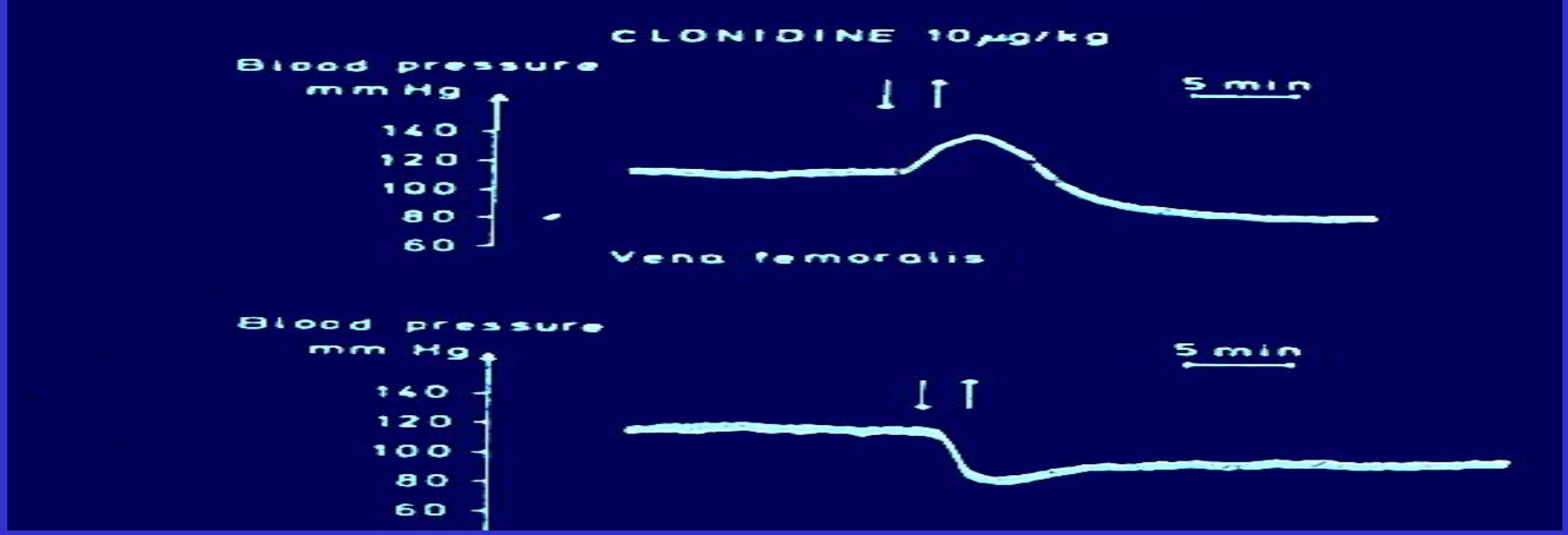


Figure 33-2: Basic pathways involved in the medullary control of blood pressure. Th...



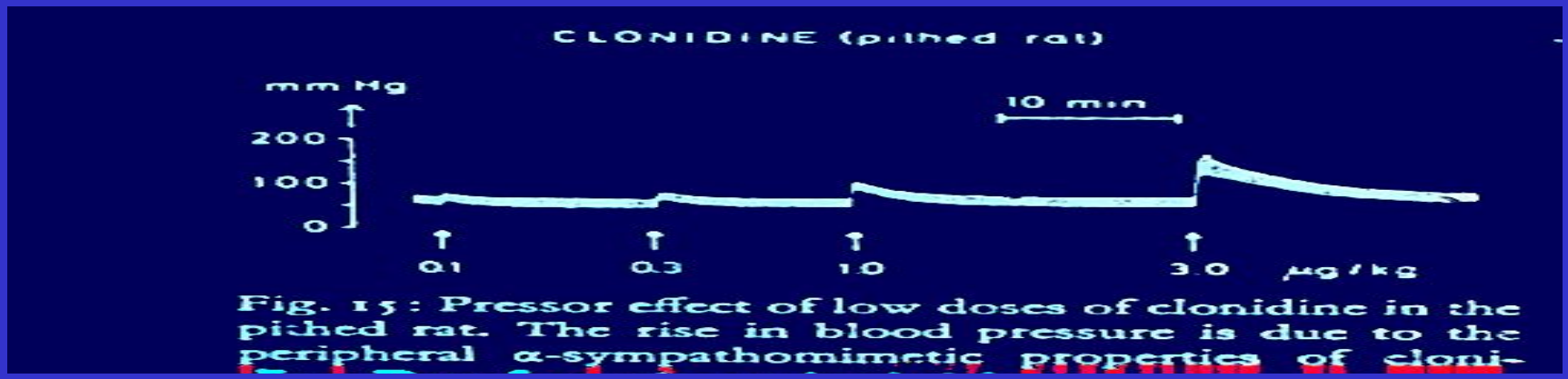
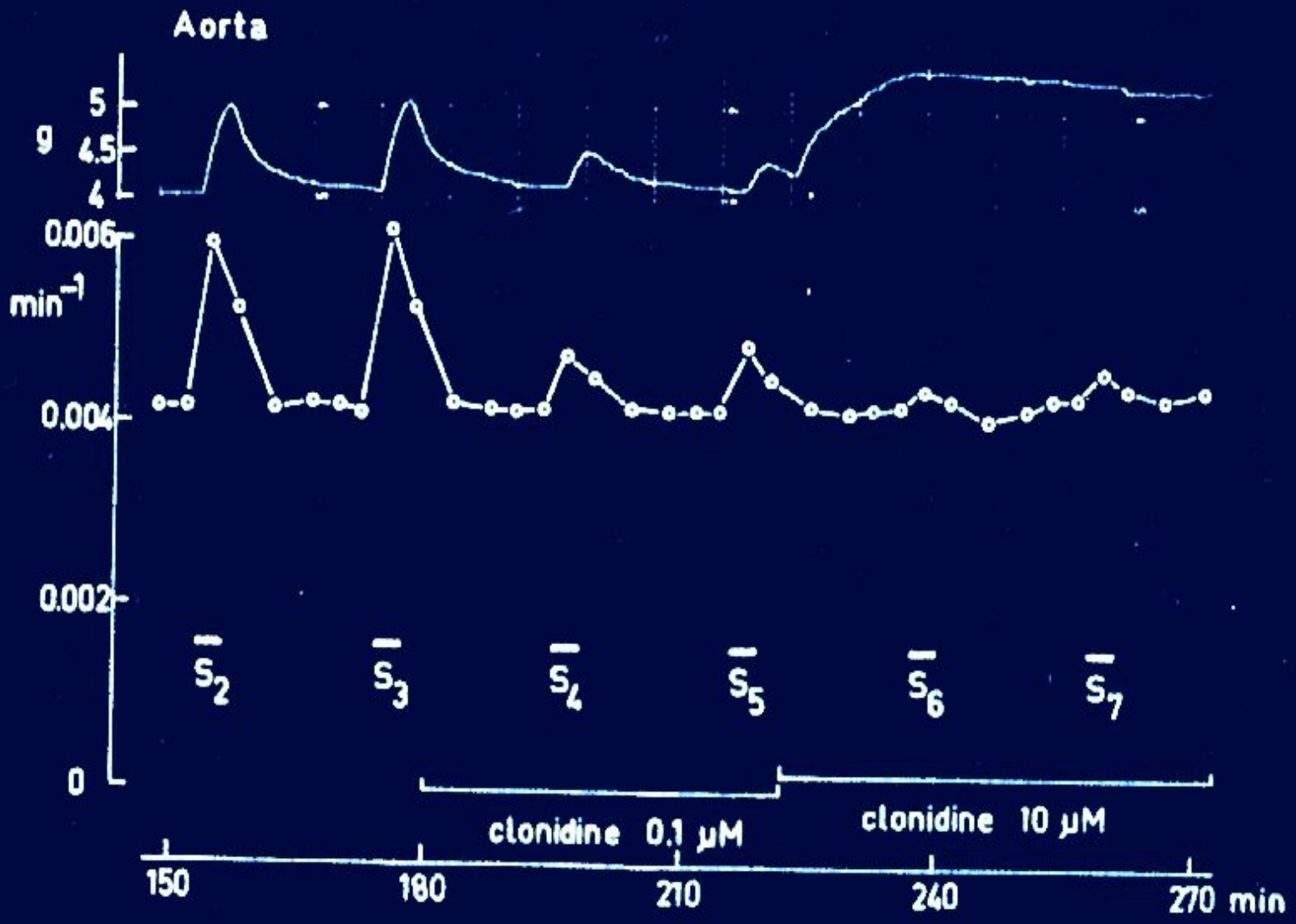
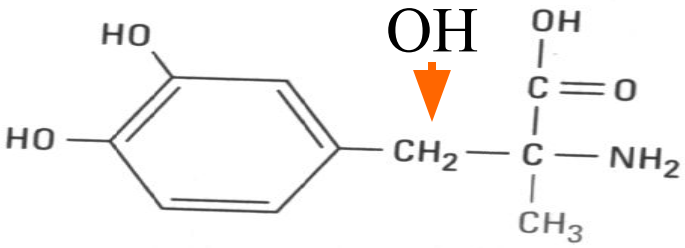


Fig. 15: Pressor effect of low doses of clonidine in the pithed rat. The rise in blood pressure is due to the peripheral α-sympathomimetic properties of clonidine


Aorta
g
5
4.5
4
0.006
min⁻¹
0.004
0.002
0
S2
S3
S4
S5
S6
S7
clonidine 0.1 µM
clonidine 10 µM
150
180
210
240
270 min

Гипотензивные средства центрального действия



α-Methyldopa
(α-methyl group in color)

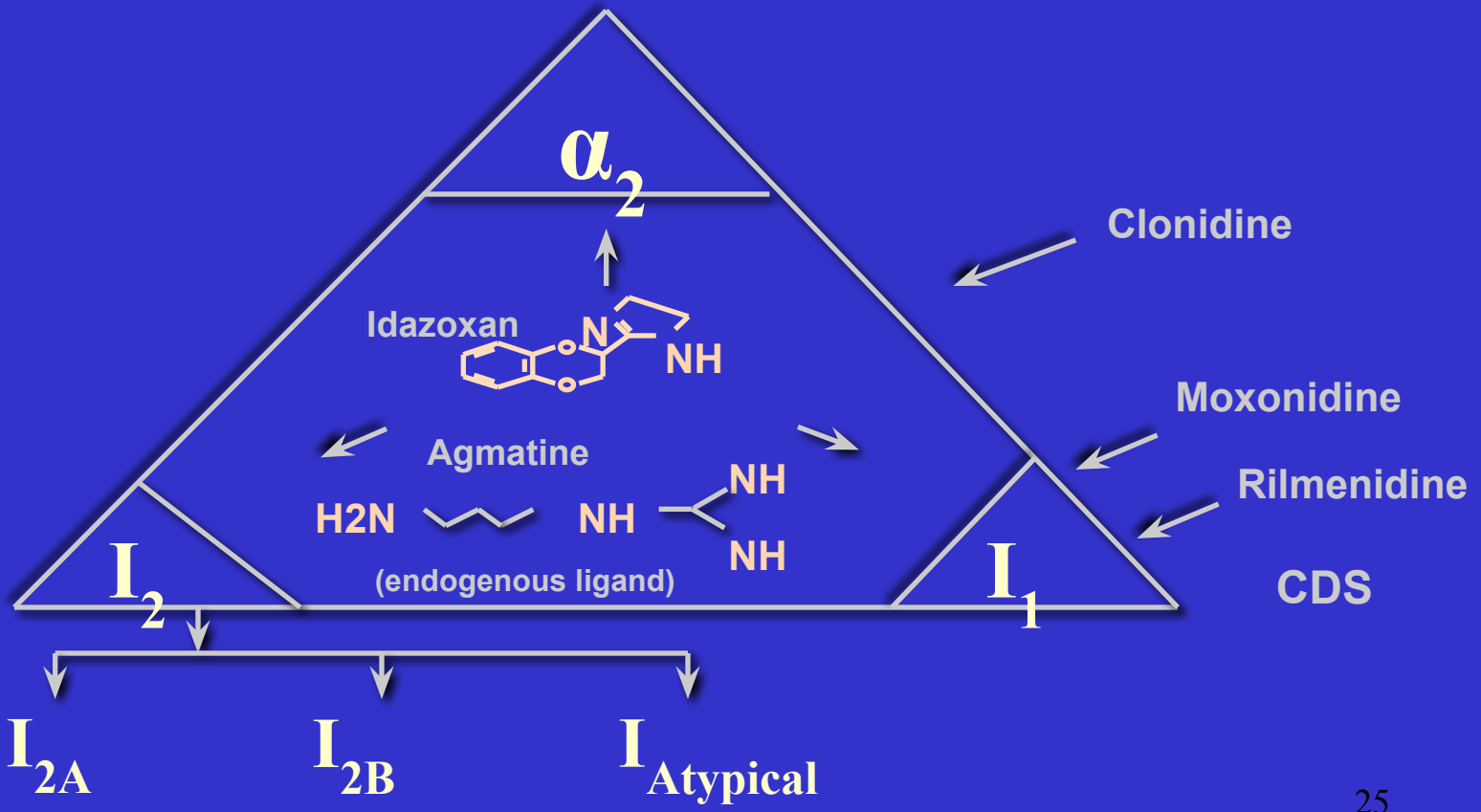
Clonidine

Moxonidine

Rilmenidine

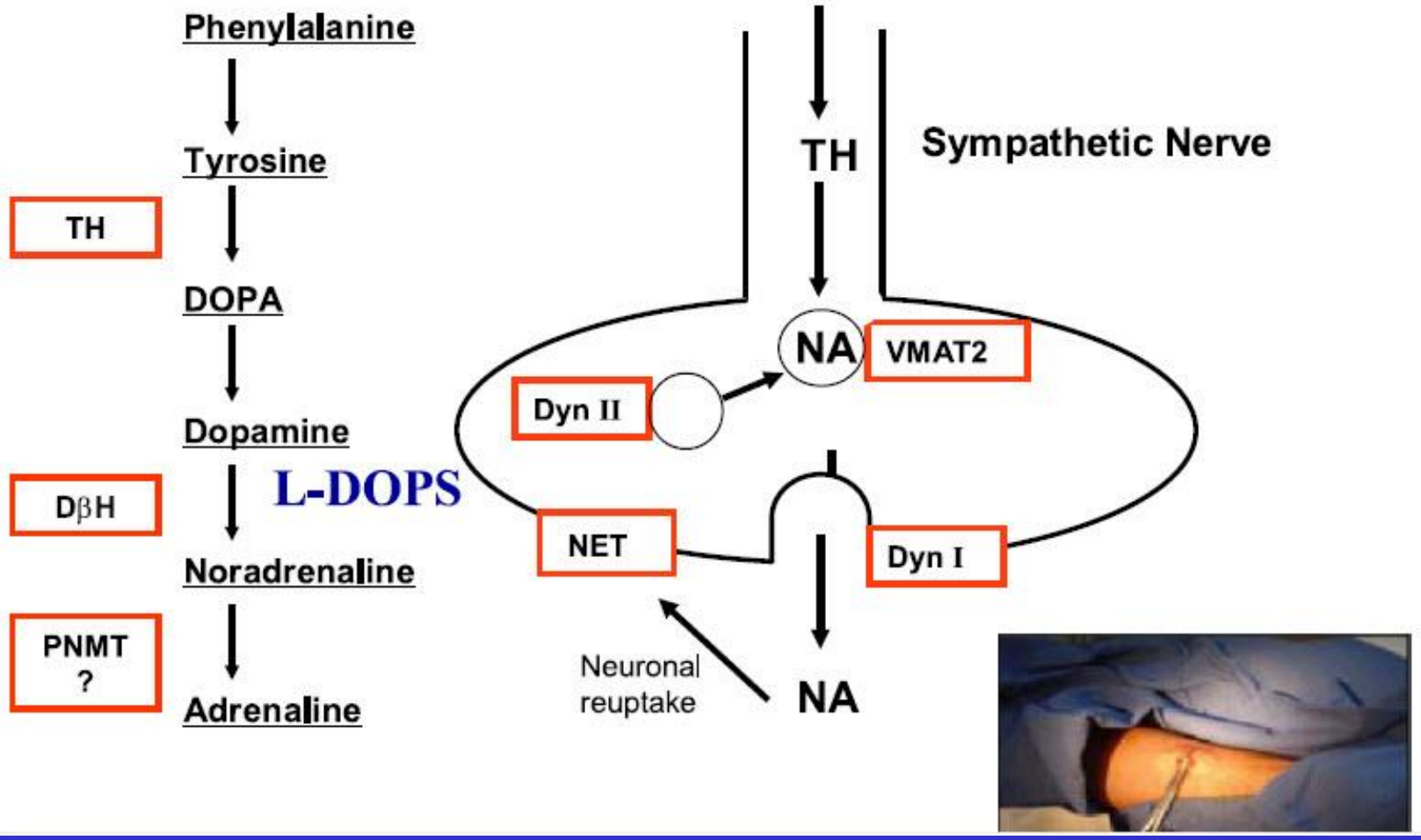
Central alpha-2 agonists and other centrally acting drugs	clonidine (Catapres†)	0.1–0.8	2
	clonidine patch (Catapres-TTS)	0.1–0.3	1 wkly
	methyldopa (Aldomet†)	250–1,000	2
	reserpine (generic)	0.1–0.25	1
	guanfacine (Tenex†)	0.5–2	1

Схема фармакологических взаимоотношений между а $_2$-адренорецепторами, I_1- и I_2-рецепторами

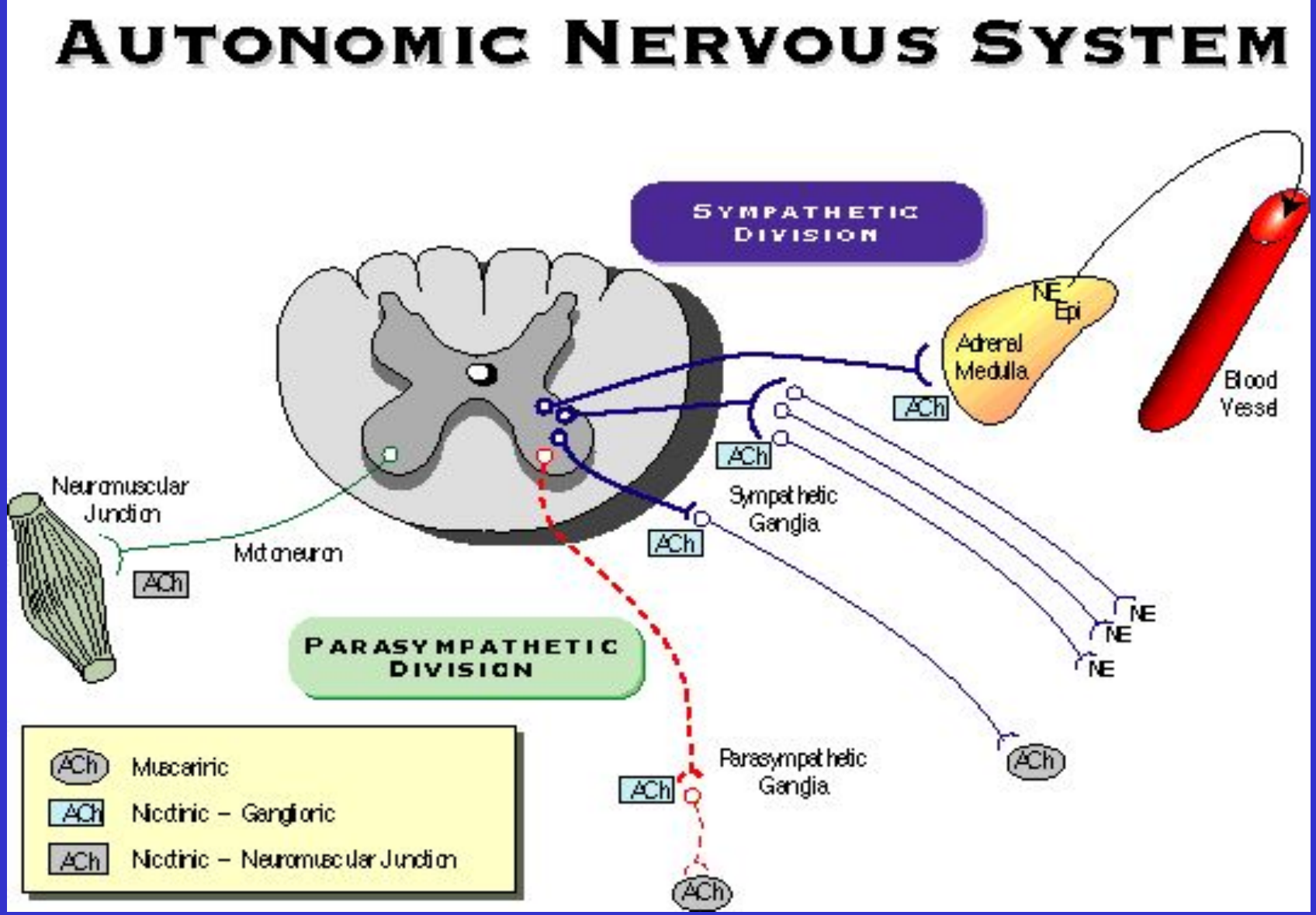


Nutt et al., Annals New York Academy of Sciences, 1995

Sympathetic Nerve Proteins Accessed with Subcutaneous Forearm Vein Biopsy



Murray Esler, J Appl Physiol 108: 227–237, 2010.



1. Ганглиоблокаторы (бензогексоний, азаметоний, триметафан)
2. Симпатолитики (гуанетидин, резерпин)

SITE	PREDOMINANT TONE	EFFECTS OF GANGLIONIC BLOCKADE
Arterioles	Sympathetic (adrenergic)	Vasodilation; ↑ peripheral blood flow; hypotension
Veins	Sympathetic (adrenergic)	Vasodilation; pooling of blood; ↓ venous return; ↓ cardiac output
Heart	Parasympathetic (cholinergic)	Tachycardia
Iris	Parasympathetic (cholinergic)	Mydriasis (pupil dilation)
Ciliary muscle	Parasympathetic (cholinergic)	Cycloplegia (focused to far vision)
Gastrointestinal tract	Parasympathetic (cholinergic)	↓ Tone and motility; constipation; ↓ secretions
Urinary bladder	Parasympathetic (cholinergic)	Urinary retention
Salivary glands	Parasympathetic (cholinergic)	Xerostomia (dry mouth)
Sweat glands	Sympathetic (cholinergic)	Anhidrosis (absence of sweating)

Table 9-2: Effects of Autonomic Ganglionic Blockade on Tissues

Ганлиоблокаторы:

Гексаметоний
Азаметоний
} 2,5 – 3 ч

Триметафан 10-15’

Побочные эффекты

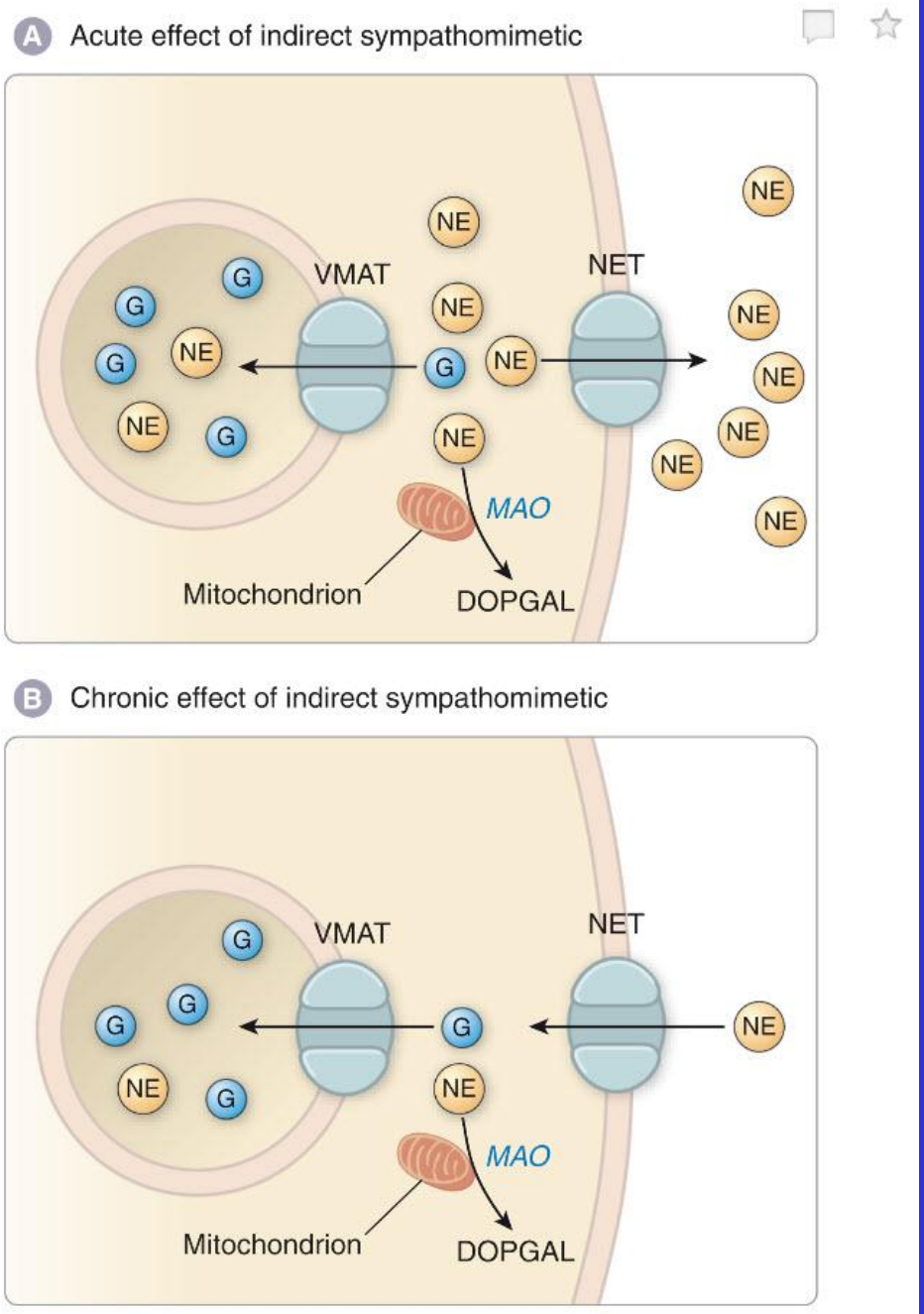
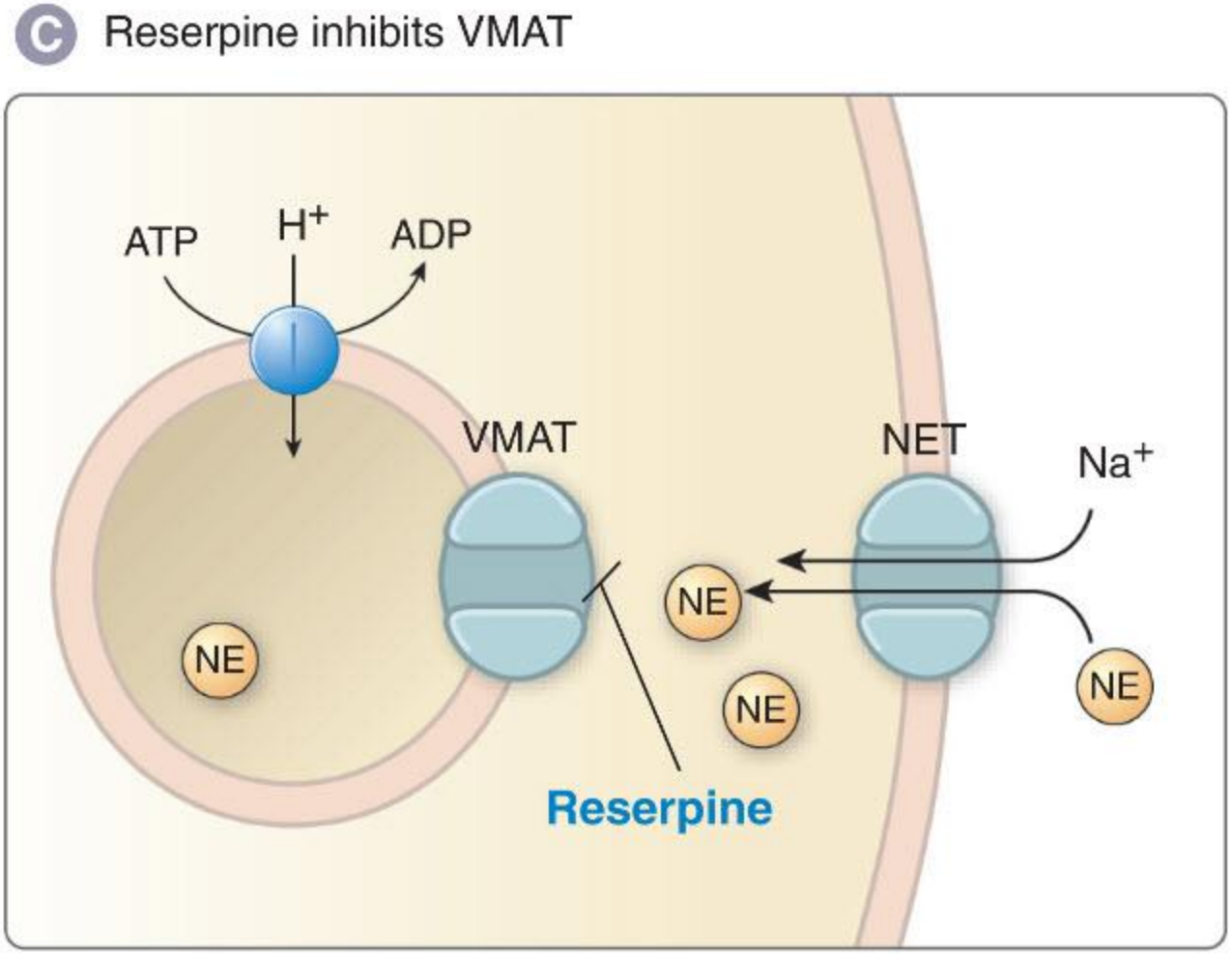


Figure 10-4: Acute and chronic effects of indirect sympathomimetics. Indirect symp...

Механизм действия гуанетидина

Механизм действия резерпина



C. Reserpine inhibits the vesicular monoamine transporter, preventing the refilling of synaptic vesicles with NE and eventually depleting the adrenergic terminal of neurotransmitter. By this mechanism, reserpine inhibits neurotransmission at adrenergic synapses.

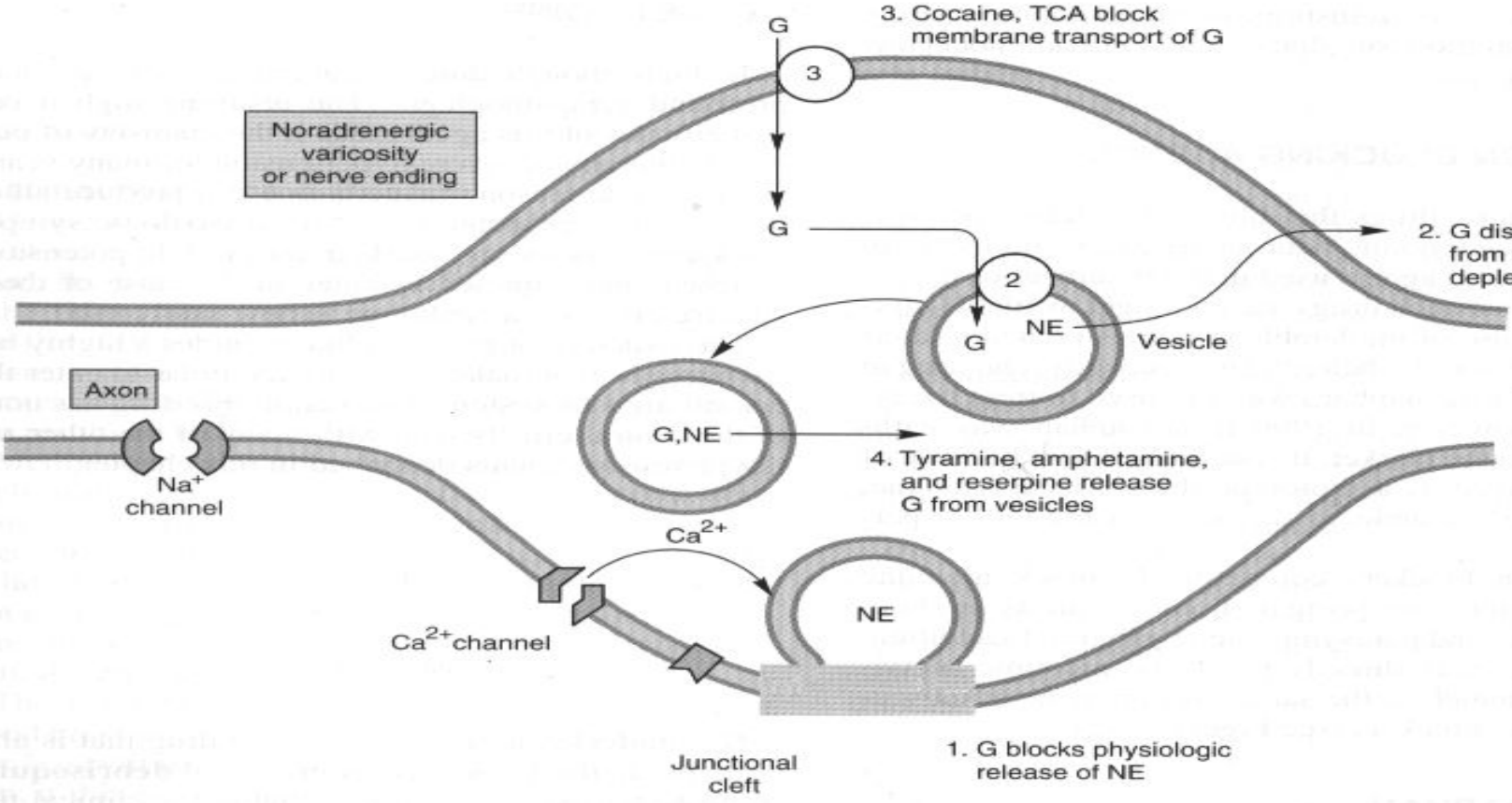
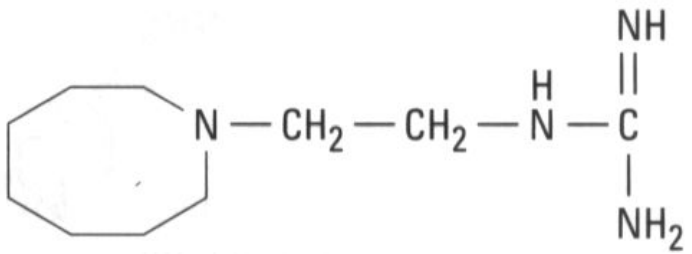
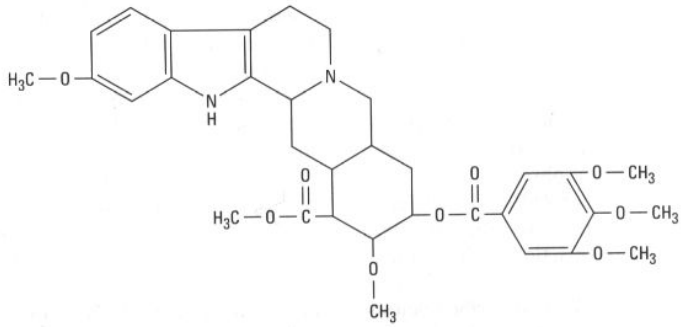


Figure 11–4. Guanethidine actions and drug interactions involving the adrenergic neuron. (G, guanethidine; NE, norepinephrine; TCA, tricyclic antidepressants.)



Guanethidine



Reserpine

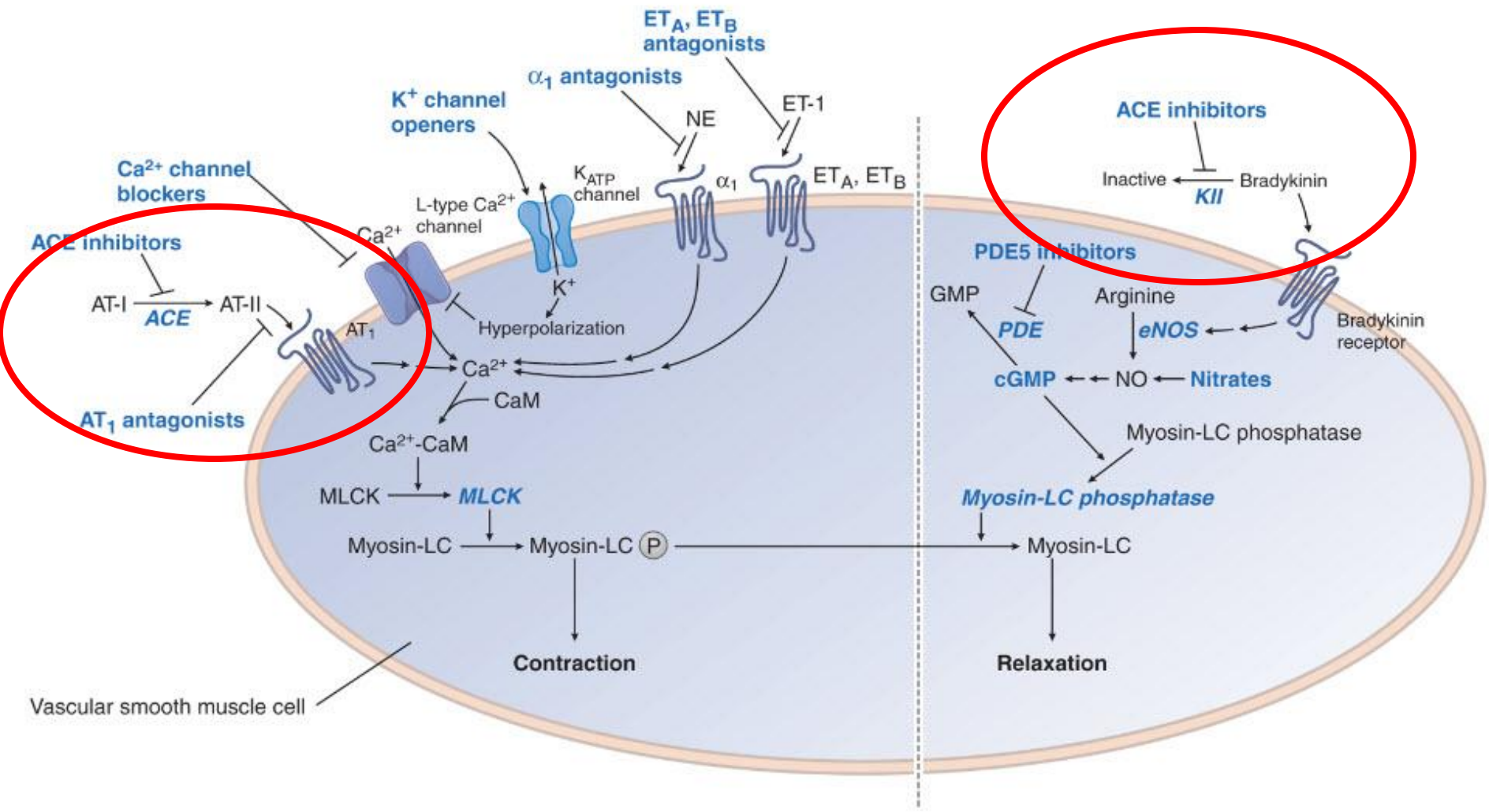
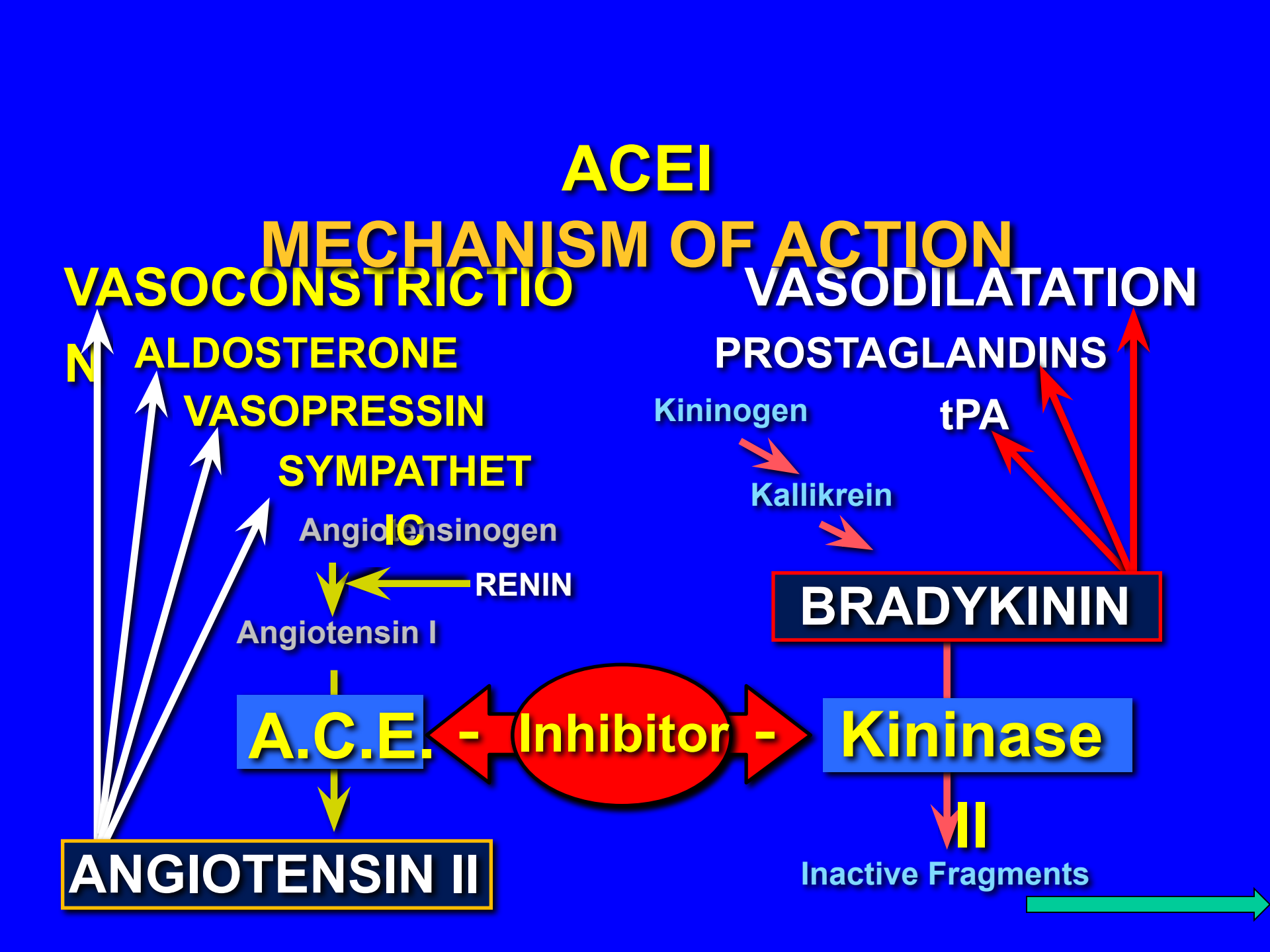


Figure 21-6: Sites of action of vasodilators. Vasodilators act at several sites in the vascular smooth muscle cell. **Left pa...**


ACEI
MECHANISM OF ACTION
VASOCONSTRICTIO
N
ALDOSTERONE
VASOPRESSIN
SYMPATHET
IC
VASODILATATION
PROSTAGLANDINS
Kininogen
tPA
Kallikrein
Angiotensinogen
RENIN
BRADYKININ
Angiotensin I
A.C.E.
Inhibitor
Kininase
II
ANGIOTENSIN II
Inactive Fragments

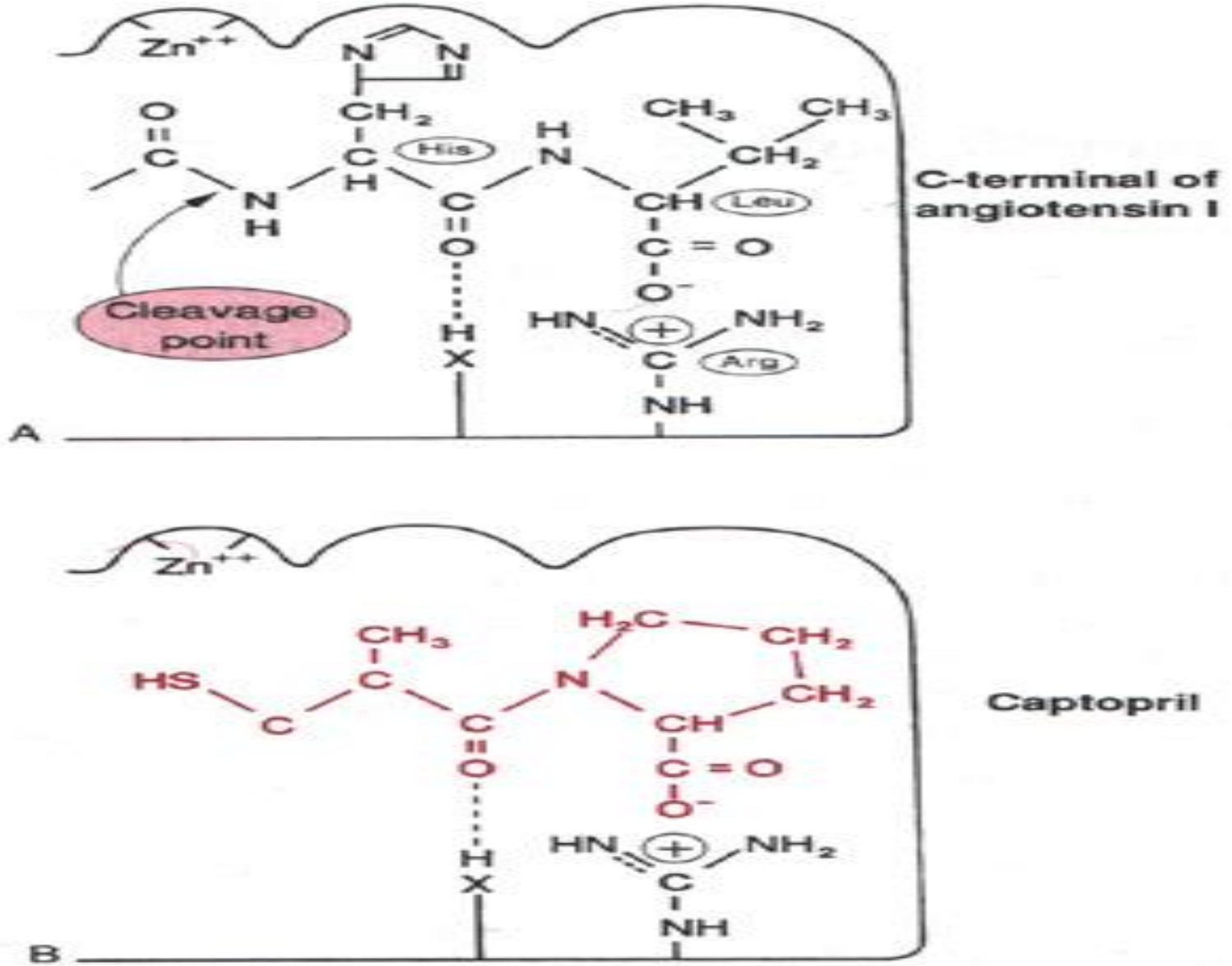
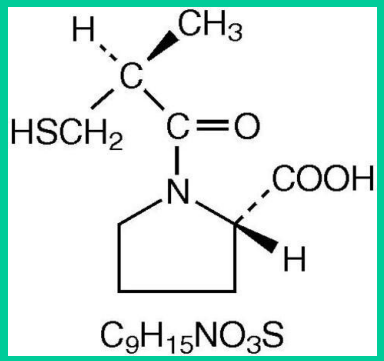


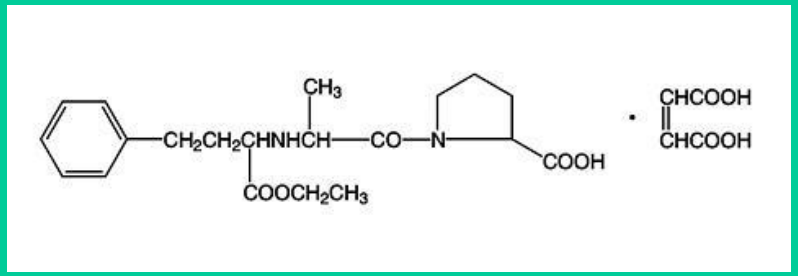
Fig. 14.6 The active site of angiotensin-converting enzyme. **A.** Binding of angiotensin I. **B.** Binding of the inhibitor, captopril, which is an analogue of the terminal dipeptide of angiotensin I.

- Ингибиторы ангиотензин-превращающего фермента



- каптоприл

- Эналаприл



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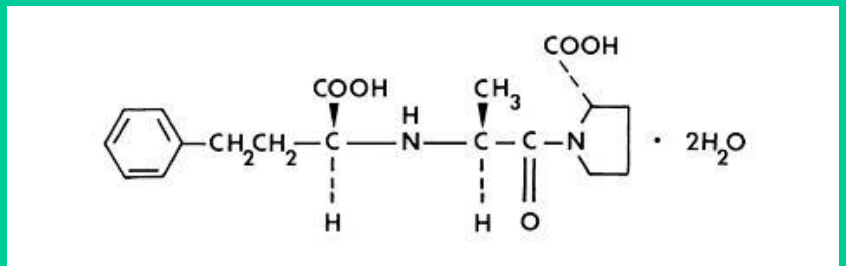
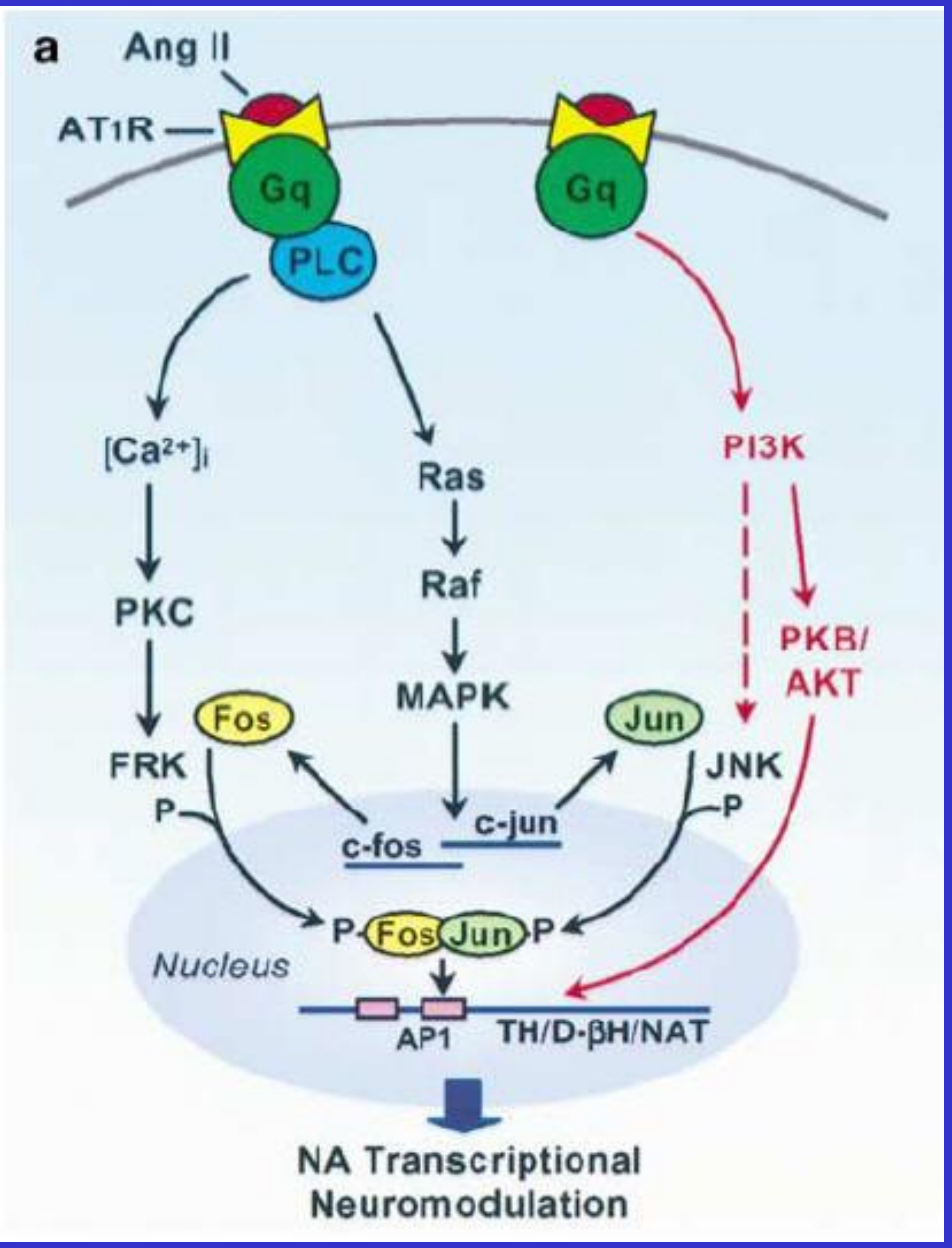
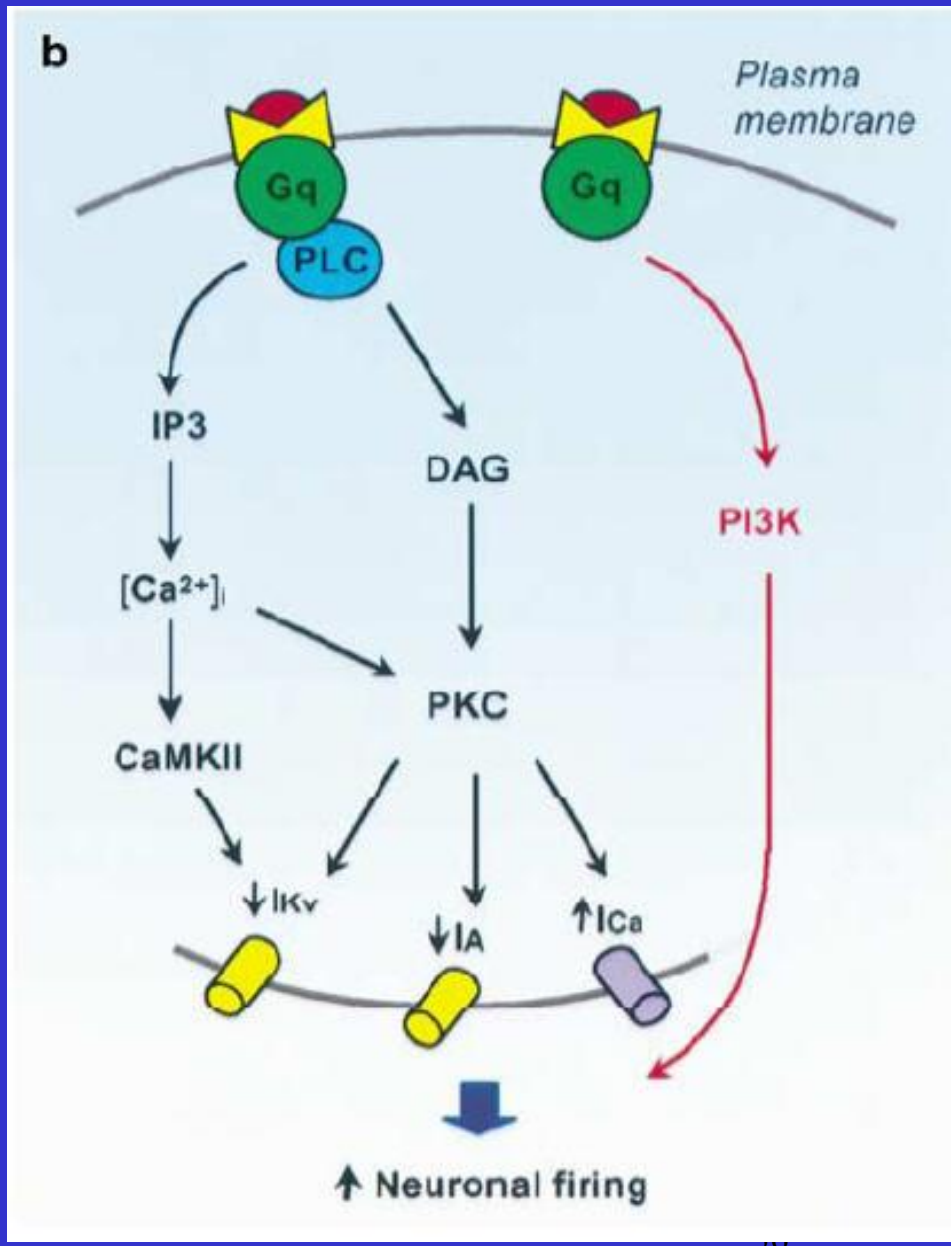


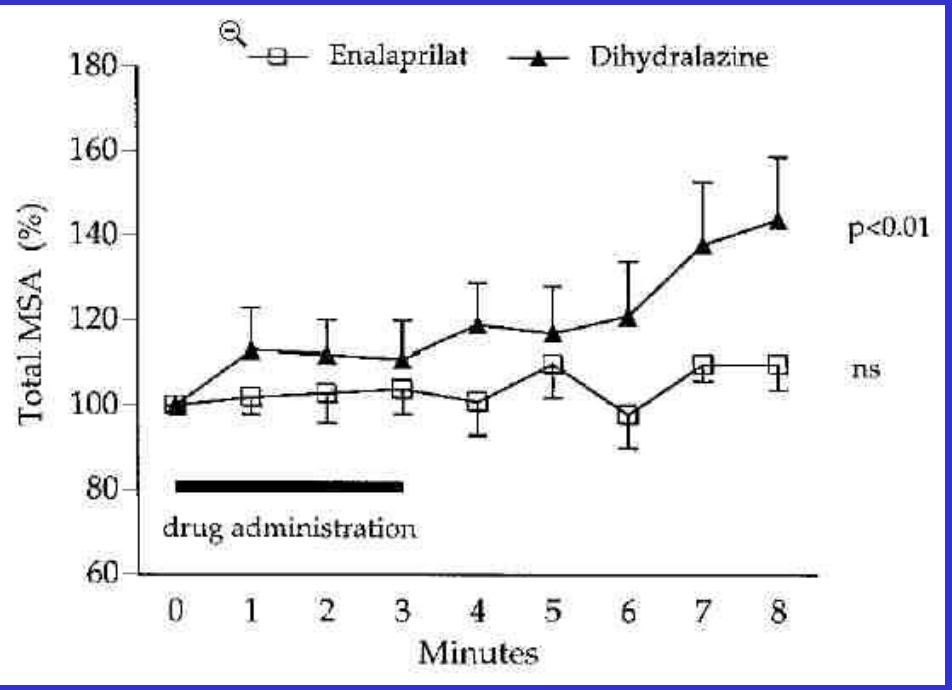
Ренин-анг система мозга



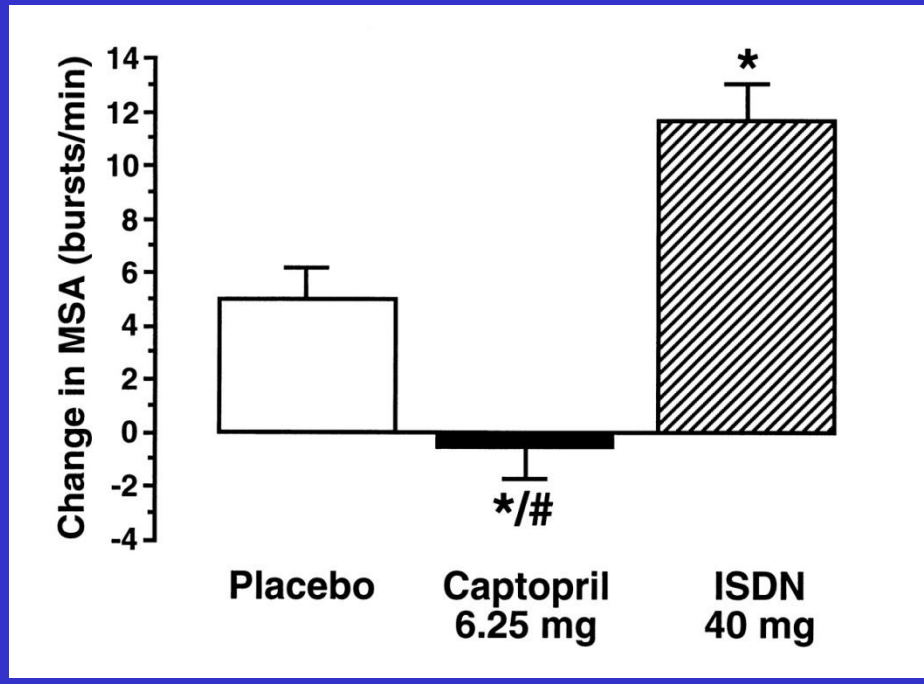


British Journal of Pharmacology (2003) 139, 191–202

Способность ингибиторов АПФ подавлять симпатическую активность у человека



(Johanson et al., 2000)



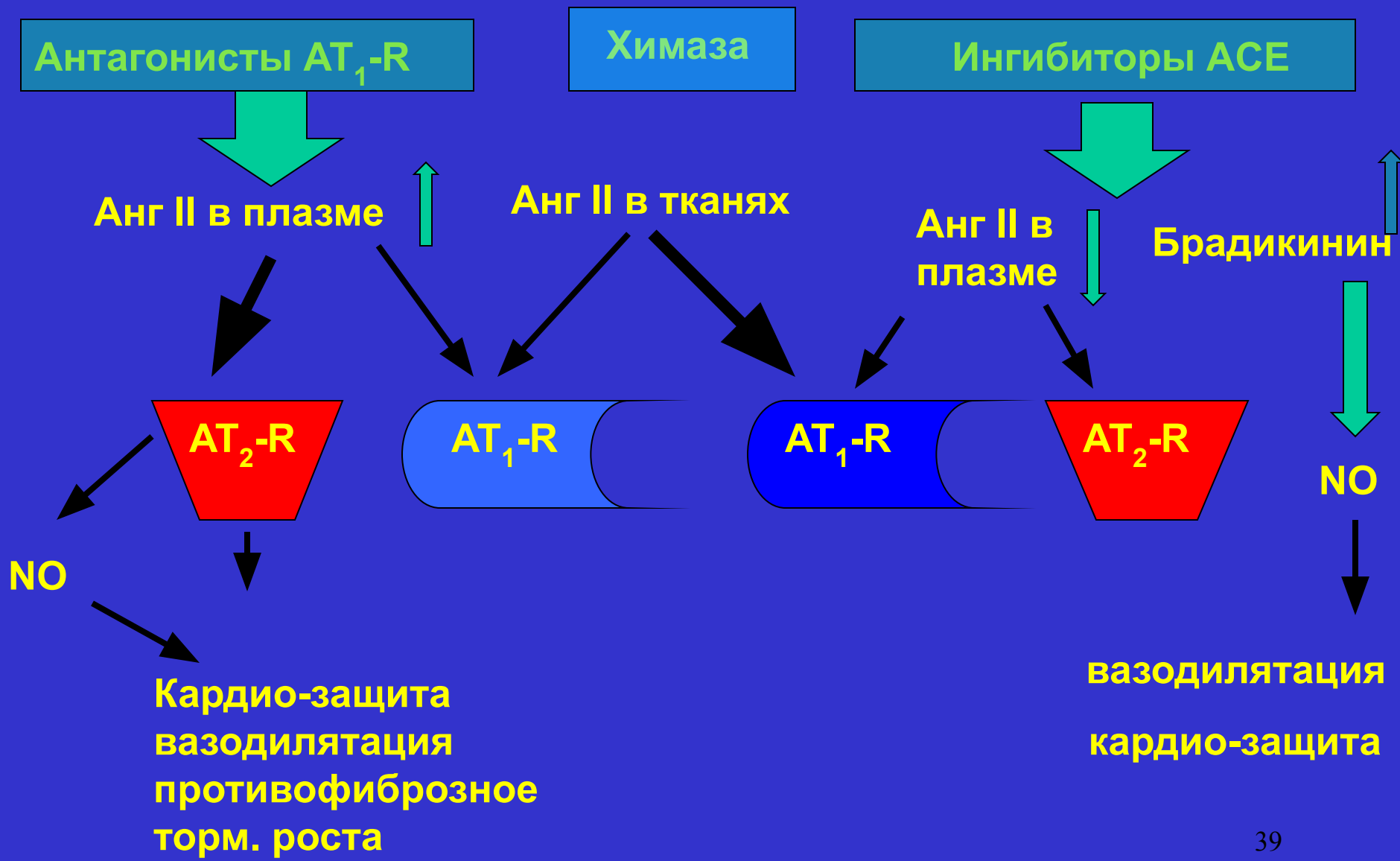
(Corti et al., 2000)

Ангиотензин II- рецепторы

	AT_1-R	AT_2-R
Распределение	Артерии, печень, почки, надпочечники, сердце, мозг(глия)	Плод, мозг (нейроны), миометрий, почки, легкие, сердце
Лиганды	Лозартан, валзартан, ирбезартан	PD123319
Кол-во аминокислот	359	363
Ген в хромосоме	3	X
Передача сигнала в клетку	G_q/G_i белки, активация PLC (Ca^{2+}/IP3)	G_i белок, активация фосфо-тирозин фосфатазы (PTP)
Функция	Вазоконстрикция, секреция альдостерона, гипертрофия, рост клеток, выброс КА	Активация потенциал-зависимых K^+-каналов, ингибирование Ca^{2+}-каналов Т-типа, торможение роста, активация апоптоза, вазодилятация

Обзор H. Matsubara, Circ. Res. 1998;83:1182-1191)

Различие эффектов ингибиторов АСЕ и блокаторов AT_1-рецепторов



Блокаторы Анг II (AT_1) рецепторов

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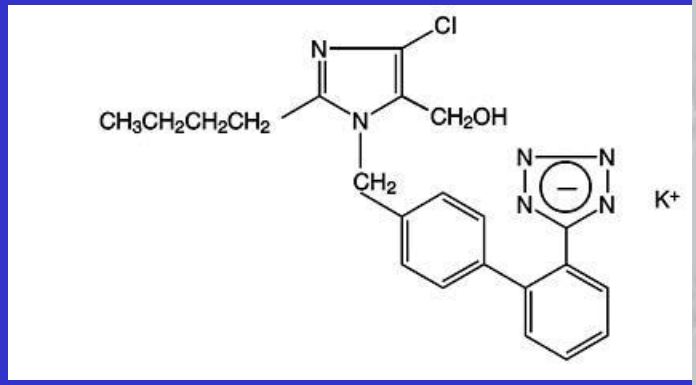
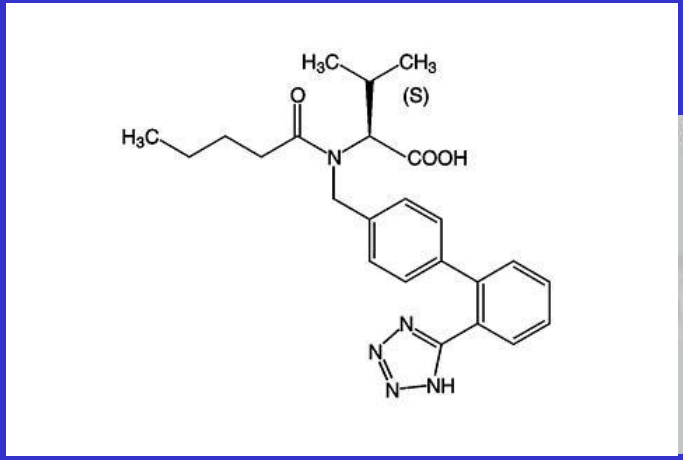


- **Валзартан**



Блокаторы Анг I рецепторов не увеличивают симпатическую активность

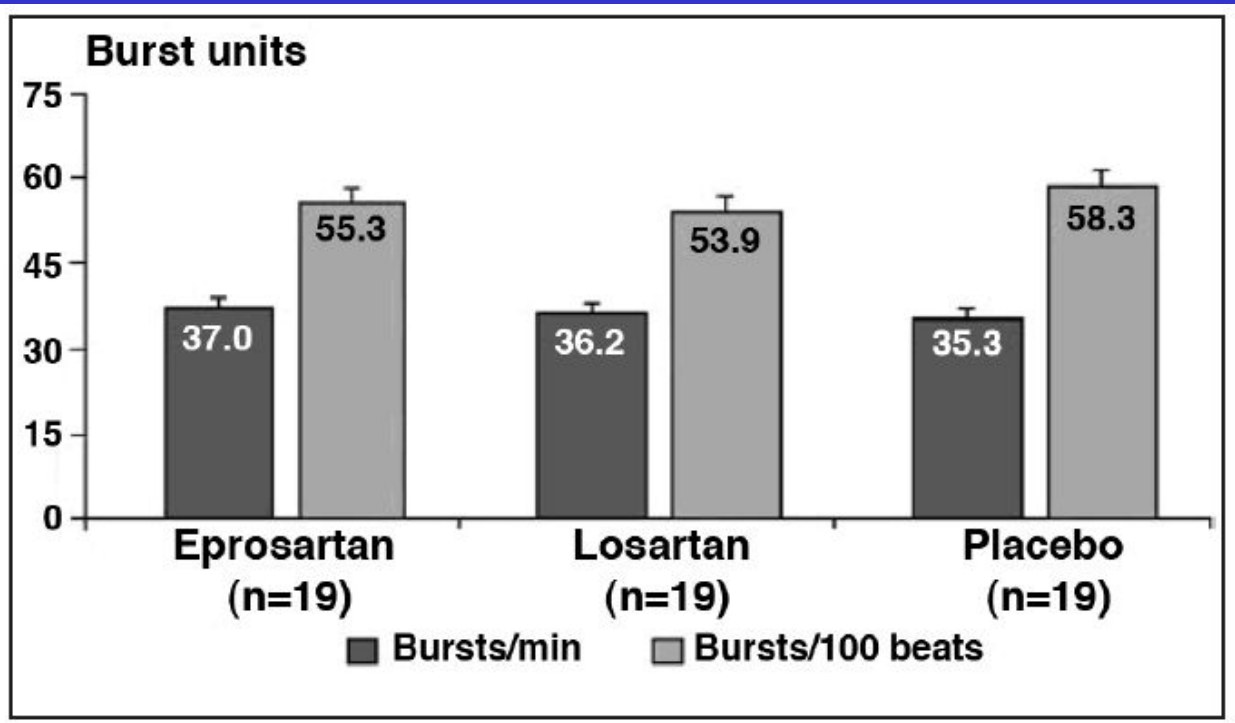


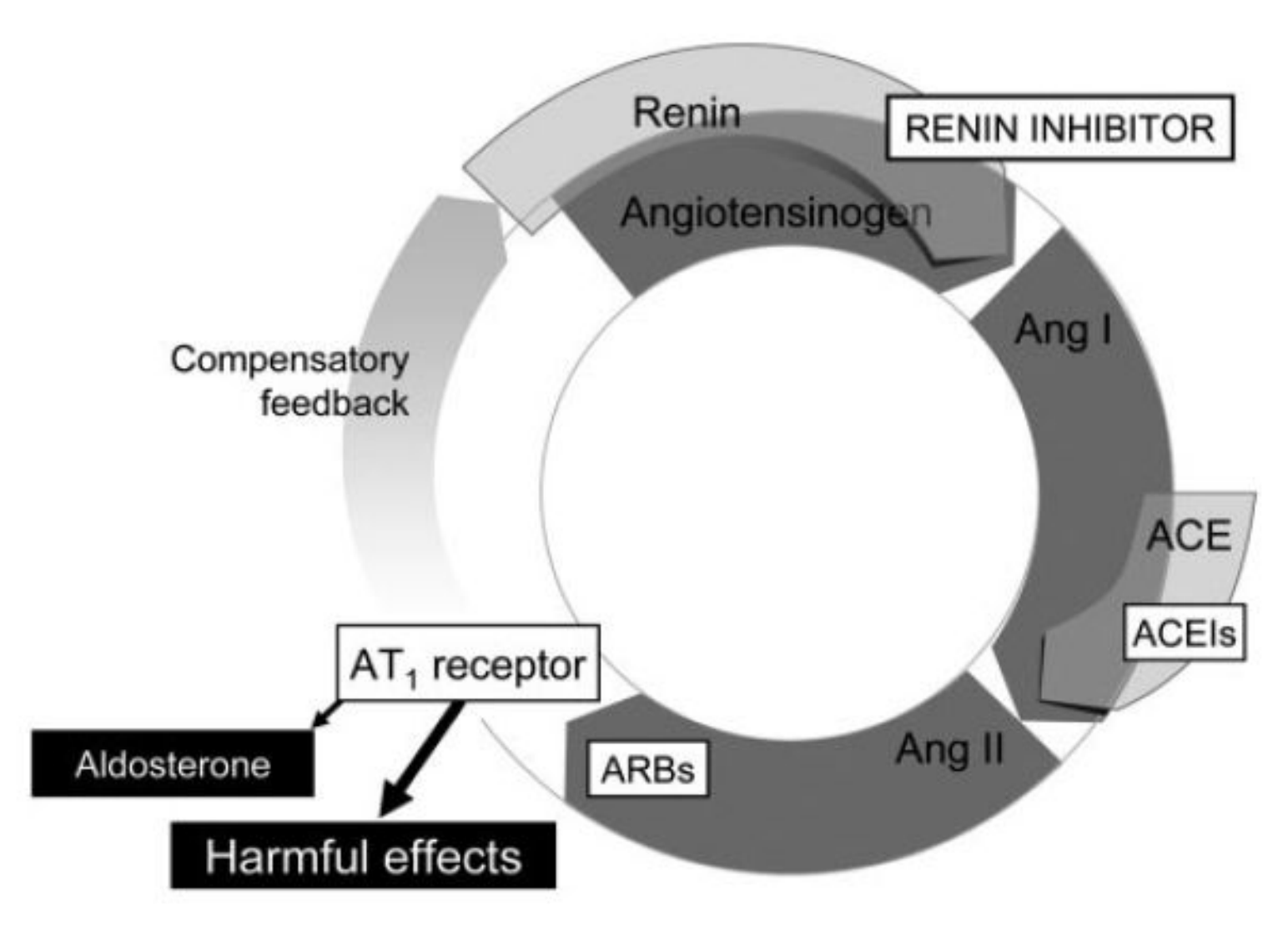
Figure 2. Microneurographic assessment of efferent sympathetic nerve traffic to the skeletal muscle vasculature (muscle sympathetic nerve activity), indicative of central sympathetic outflow, assessed as bursts/minute and bursts/100 beats after 4-week therapy with eprosartan, losartan, or placebo. Data are presented as mean ± SD. Reproduced with permission from Am J Physiol Heart Circ Physiol. *2006;290:H1706–H1712.*[2]

Новое в механизме действия ингибиторов ренин-ангиотензиновой системы

1. Стимулируют адипогенез
2. Стимулируют появление мелких адипоцитов
3. Стимулируют появление инсулин-чувствительных адипоцитов

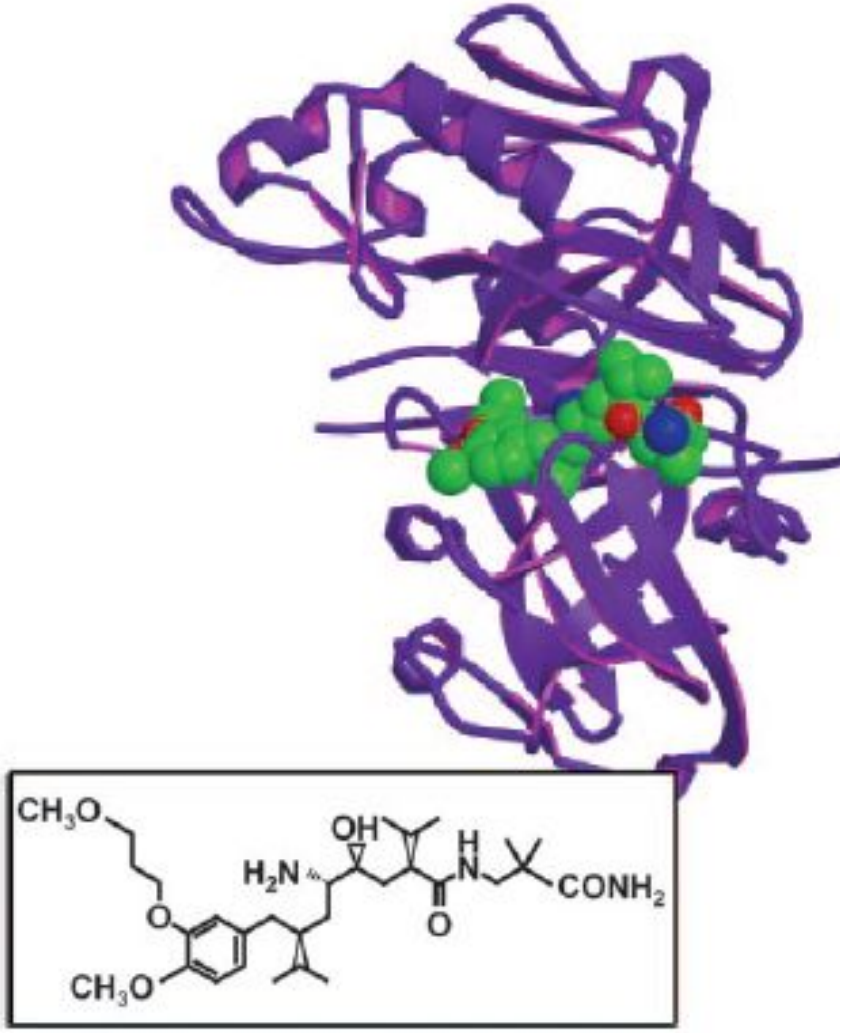
M.Esler et al., Hypertension 2006; 48; 787-796

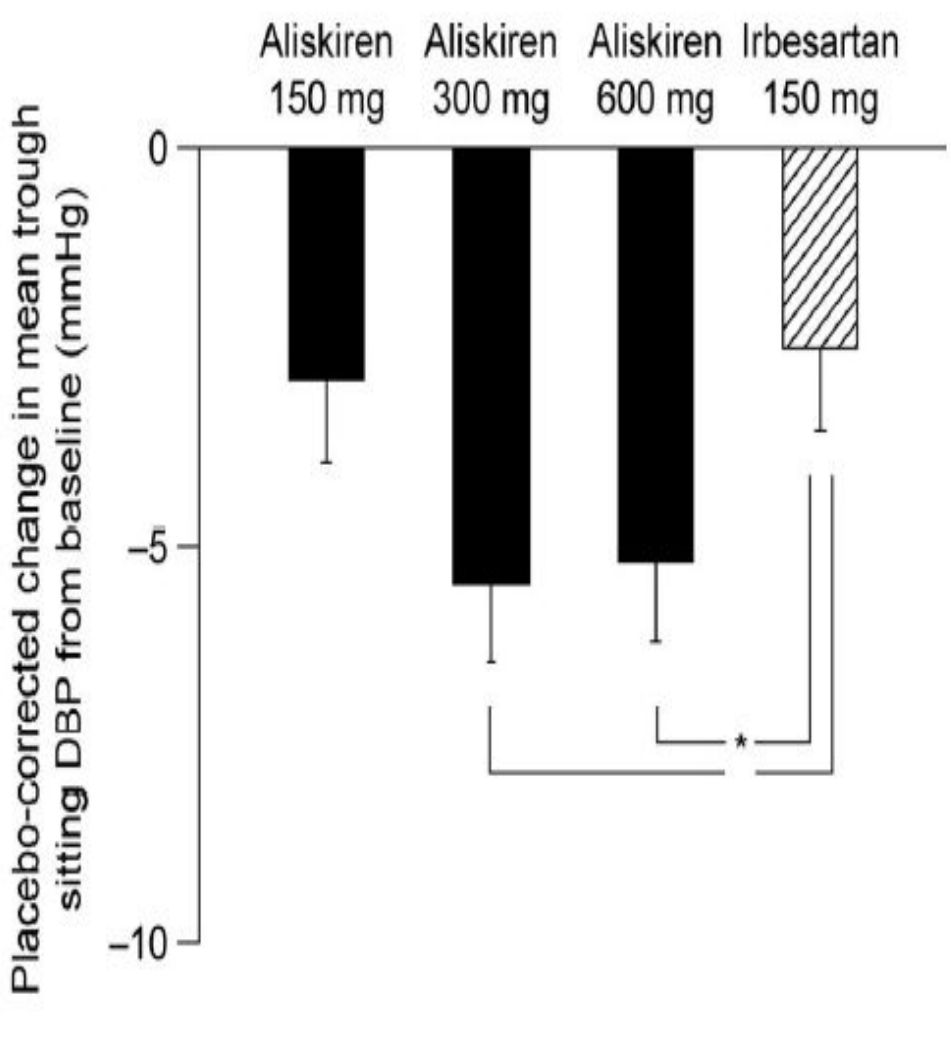
Ингибиторы ренина



Clin J Am Soc Nephrol 1: 221–228, 2006.

Aliskiren – первый пероральный ингибитор ренина





Clin J Am Soc Nephrol 1: 221–228, 2006.

Сосудорасширяющие средства

Блокаторы кальциевых каналов

Активаторы калиевых каналов

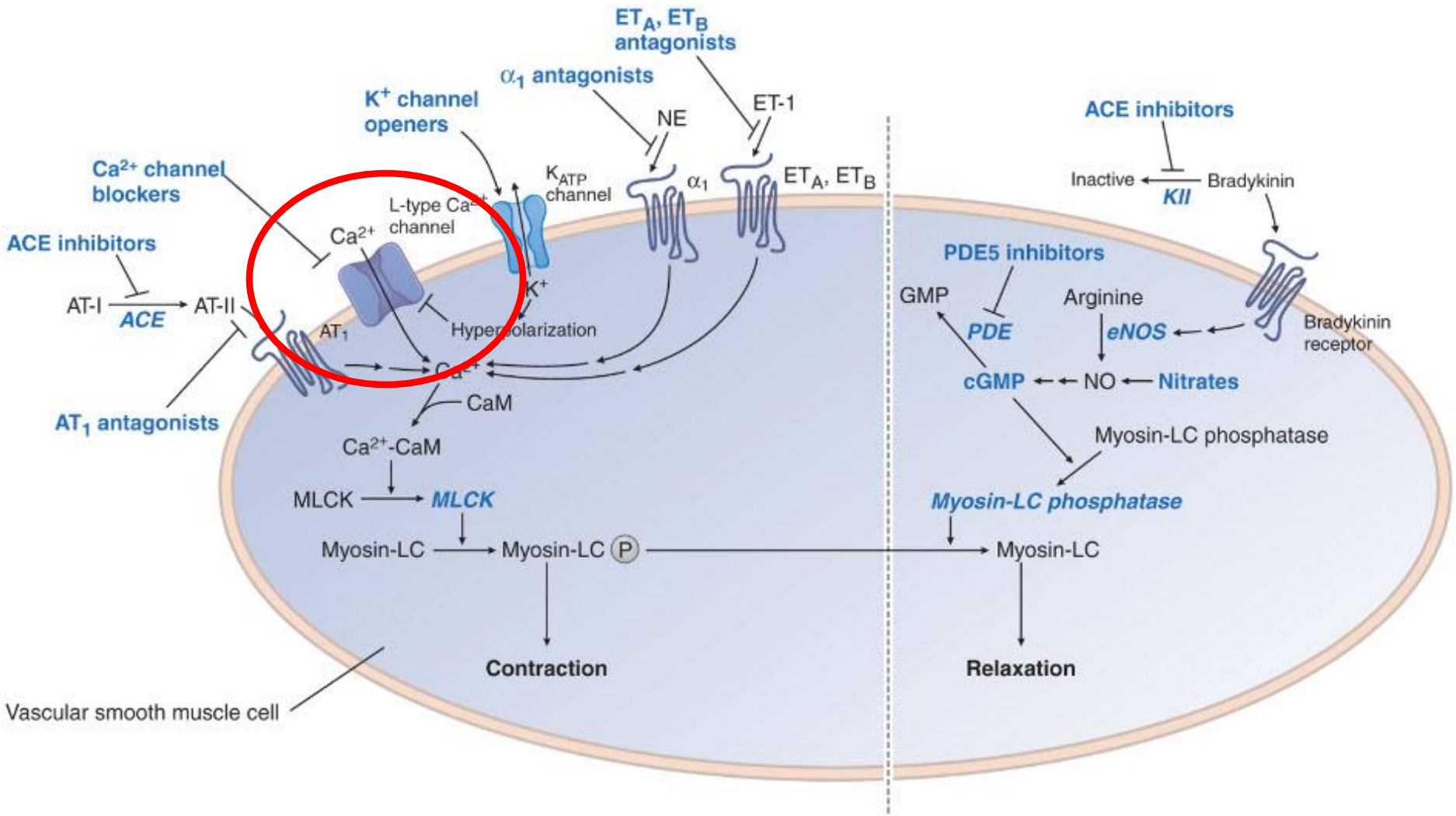
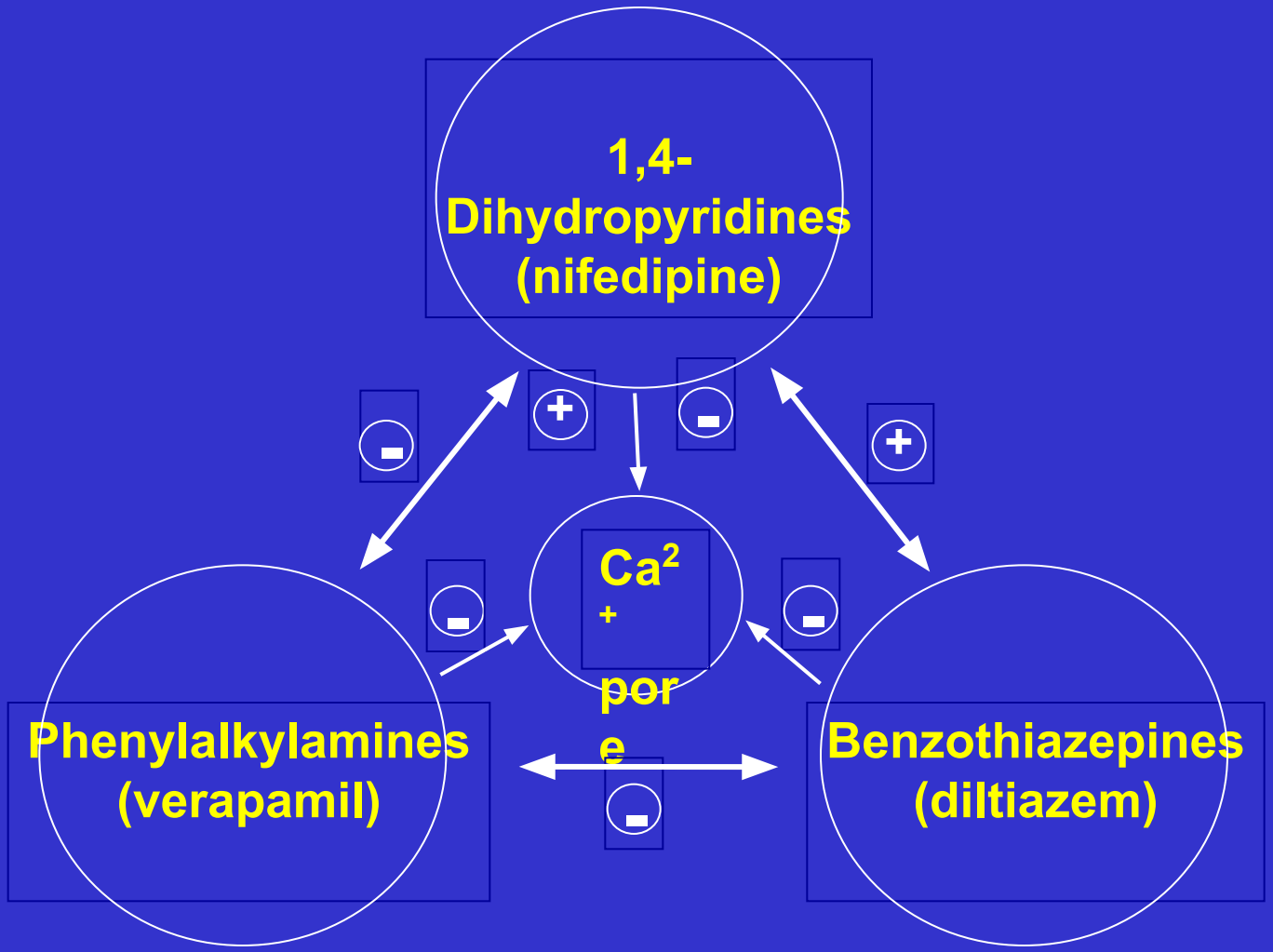


Figure 21-6: Sites of action of vasodilators. Vasodilators act at several sites in the vascular smooth muscle cell. **Left pa...**

Три класса блокаторов кальциевых каналов

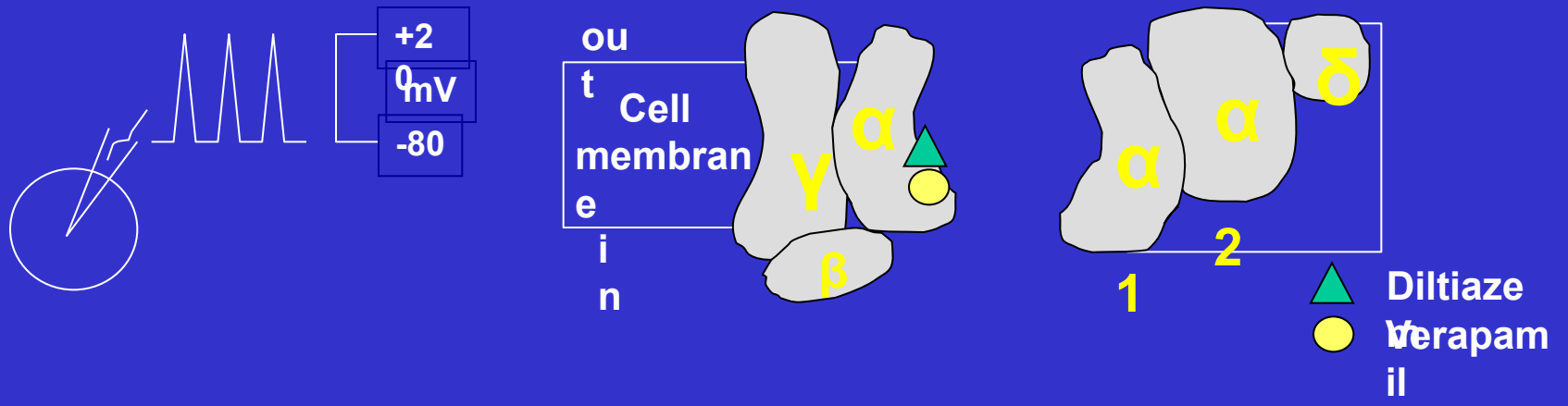
Chemical Type	Chemical Names	Brand Names
Фенилалкиламины Phenylalkylamines	verapamil	Calan, Calna SR, Isoptin SR, Verelan
Бензотиазепины Benzothiazepines	diltiazem	Cardizem CD, Dilacor XR
Дигидропиридины 1,4-Dihydropyridines	Nifedipine nicardipine isradipine felodipine Amlodipine Lercanidipine	Adalat CC, Procardia XL Cardene DynaCirc Plendil Norvasc Zanidip

The Three Classes of CCBs Bind to Different Sites

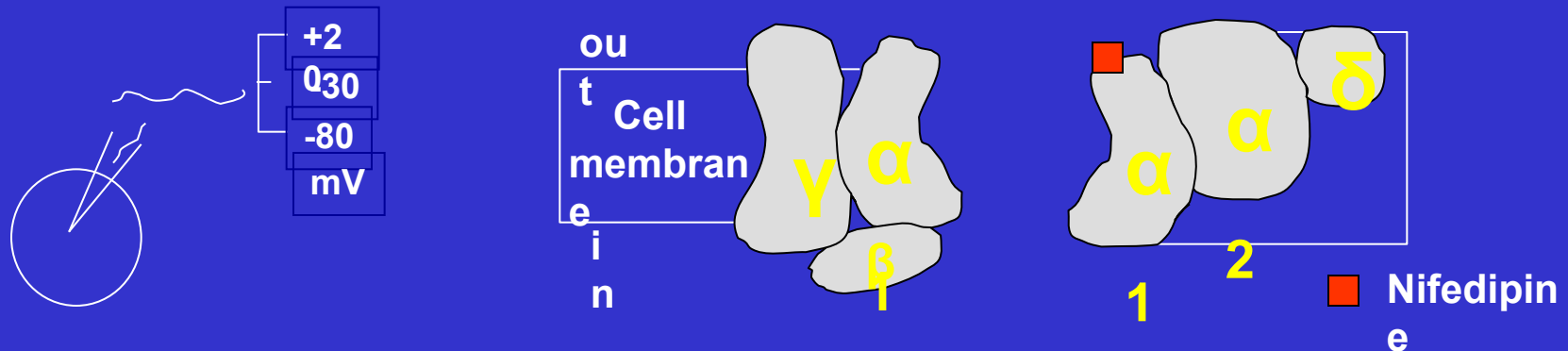


Различие в местах связывания определяет различие в фармакологических эффектах

Use-dependent binding (targets cardiac cells)



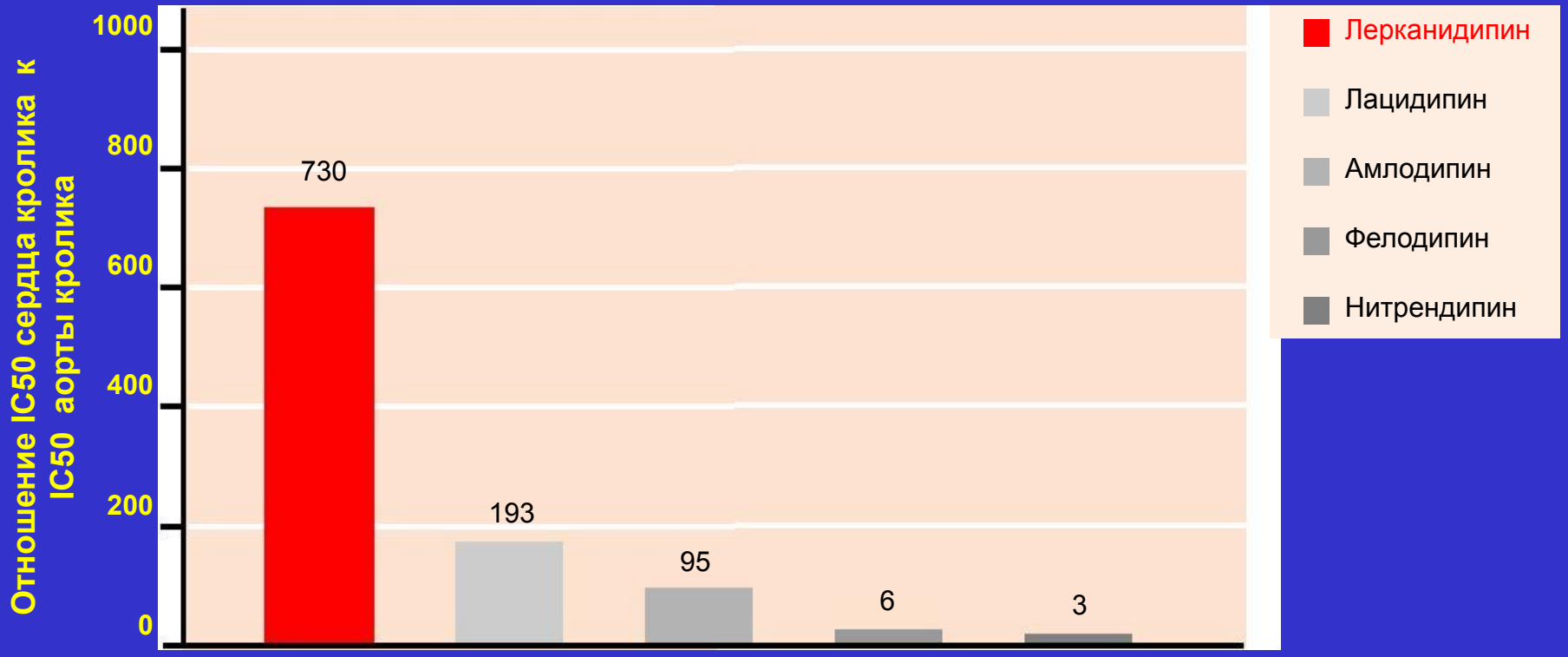
Voltage-dependent binding (targets smooth muscle)



	VASODILATION (PERIPHERAL ARTERIOLES AND CORONARY ARTERIES)	DEPRESSION OF CARDIAC CONTRACTILITY	DEPRESSION OF AUTOMATICITY (SA NODE)	DEPRESSION OF CONDUCTION (AV NODE)
Nifedipine	5	1	1	0
Diltiazem	3	2	5	4
Verapamil	4	4	5	5

The effects of the three different classes of Ca^{2+} channel blockers on vascular tone, cardiac contractility, heart rate, and AV nodal conduction are graded from 0 to 5. 0 = no effect; 5 = significant effect. Note that nifedipine is the most selective drug for peripheral vasodilation, while diltiazem and verapamil have more selective effects on the heart.

Индекс вазоселективности



Angelico P et al, J Pharm Pharmacol 51, 709-714 (1998)

Table 12–5. Pharmacokinetics of some calcium channel blocking drugs.

Drug	Oral Bioavailability	Onset of Action (route)	Plasma Half-Life (hours)	Disposition
Dihydropyridines				
Amlodipine	65–90%	No data available	30–50	> 90% bound to plasma proteins; extensively metabolized.
Felodipine	15–20%	2–5 hours (oral)	11–16	> 99% bound to plasma proteins; extensively metabolized.
Isradipine	15–25%	2 hours (oral)	8	95% bound to plasma protein; extensively metabolized.
Nicardipine	35%	20 minutes (oral)	2–4	95% bound; extensively metabolized in the liver.
Nifedipine	45–70%	< 1 minute (IV); 5–20 minutes (sublingual or oral)	4	About 90% bound to plasma protein; metabolized to an acid lactate. 80% of the drug and metabolites excreted in urine.
Nimodipine	13%	No data available	1–2	Extensively metabolized.
Nisoldipine	< 10%	No data available	2–6	Extensively metabolized.
Nitrendipine	10–30%	4 hours (oral)	5–12	98% bound; extensively metabolized.
Miscellaneous				
Bepridil	60%	60 minutes (oral)	24–40	> 99% bound to plasma proteins; extensively metabolized.
Diltiazem	40–65%	< 3 minutes (IV), > 30 minutes (oral)	3–4	70–80% bound to plasma protein; extensively deacylated. Drug and metabolites excreted in feces.
Verapamil	20–35%	< 1.5 minutes (IV), 30 minutes (oral)	6	About 90% bound to plasma protein. 70% eliminated by kidney; 15% by gastrointestinal tract.

Блокаторы кальциевых каналов – механизмы действия

- Возрастает время закрытого состояния канала
- Расслабляются гладкие мышцы артерий, но не вен
- Значительное снижение постнагрузки, но не преднагрузки

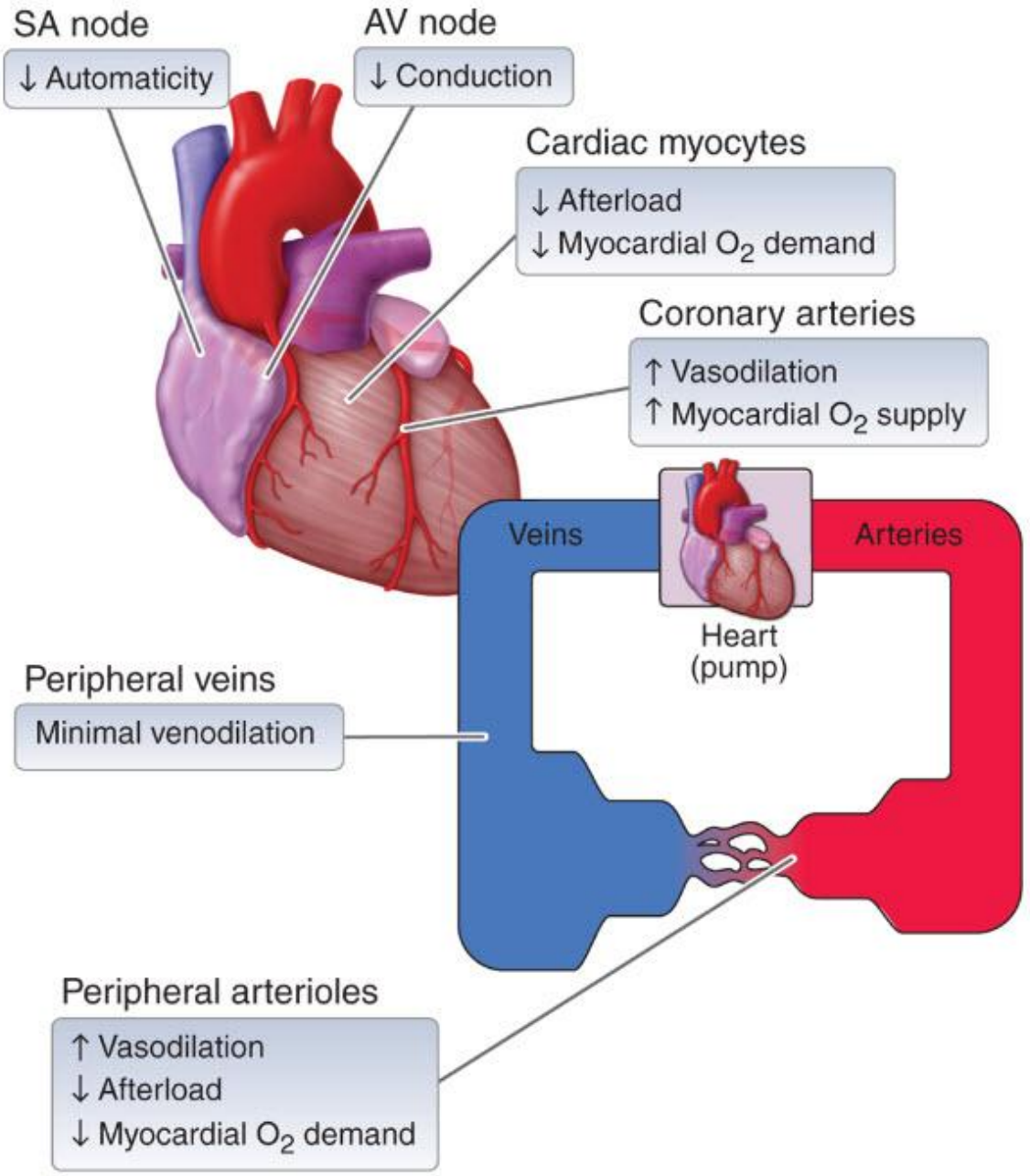


Figure 21-11: Sites of action of Ca^{2+} channel blockers. Ca^{2+} channel blockers dilate coronary arteries and peripheral arte...

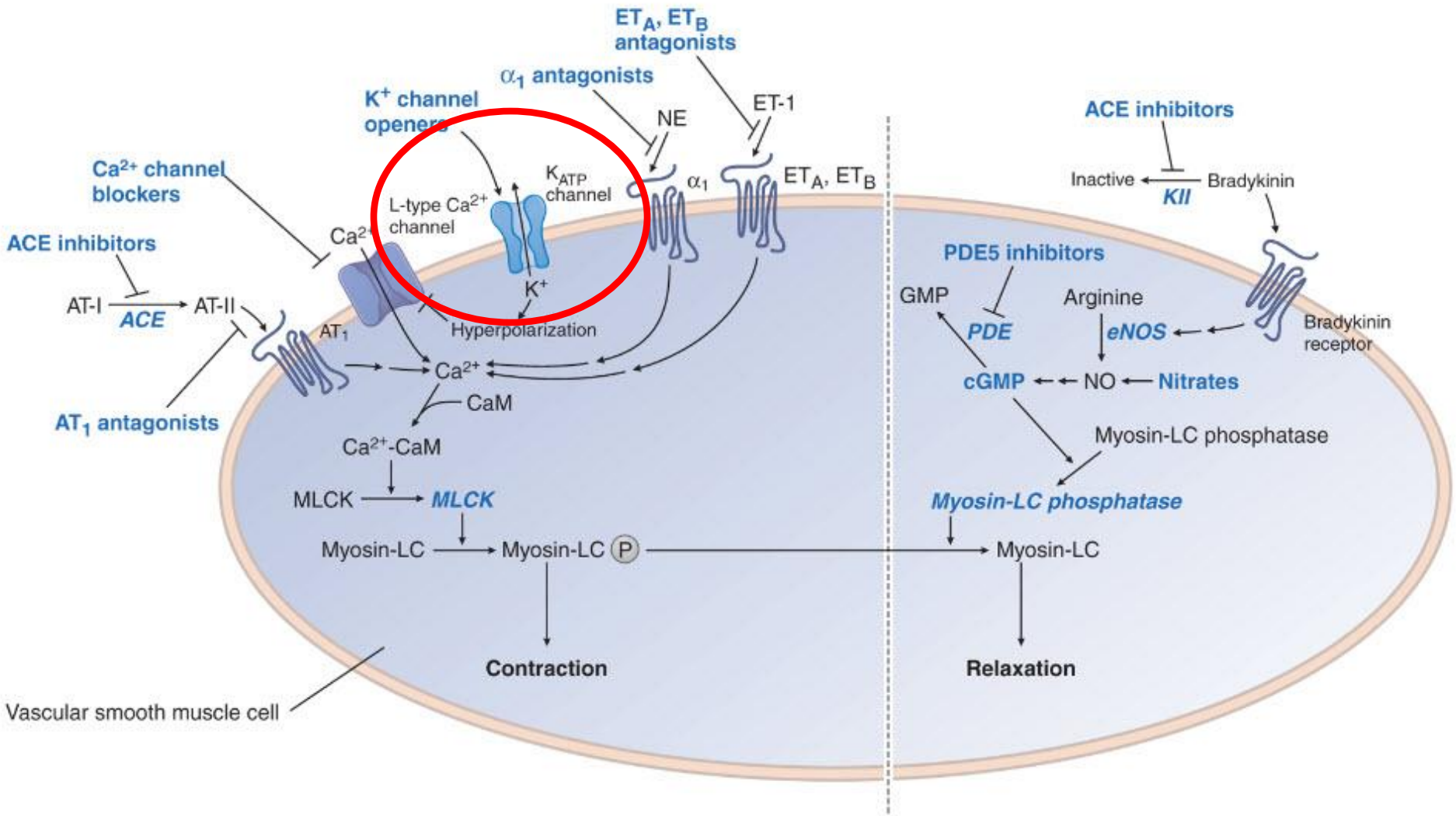
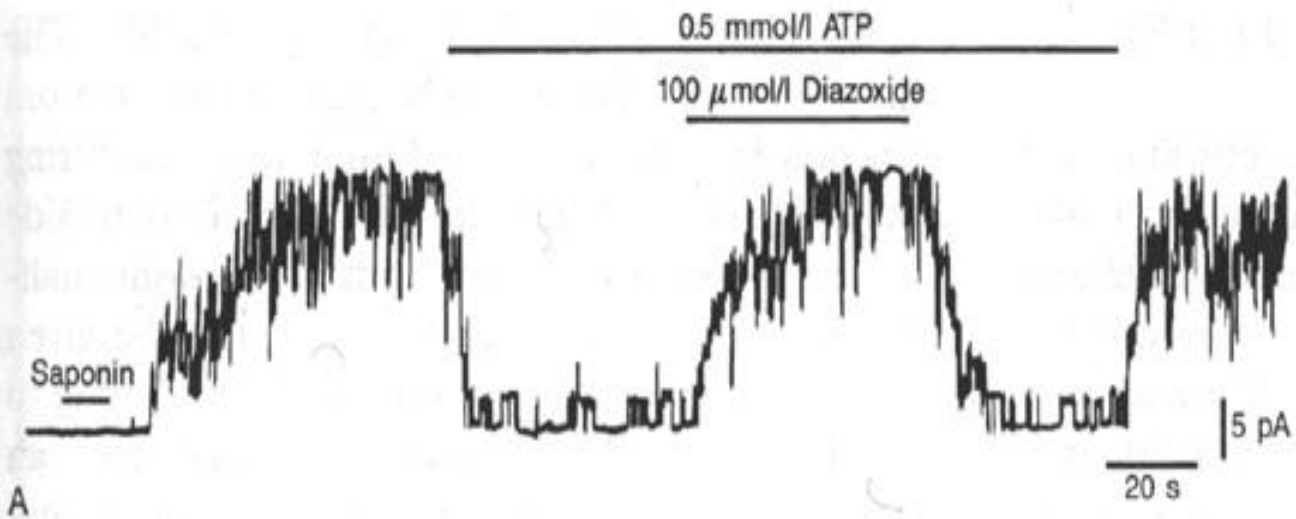


Figure 21-6: Sites of action of vasodilators. Vasodilators act at several sites in the vascular smooth muscle cell. **Left pa...**



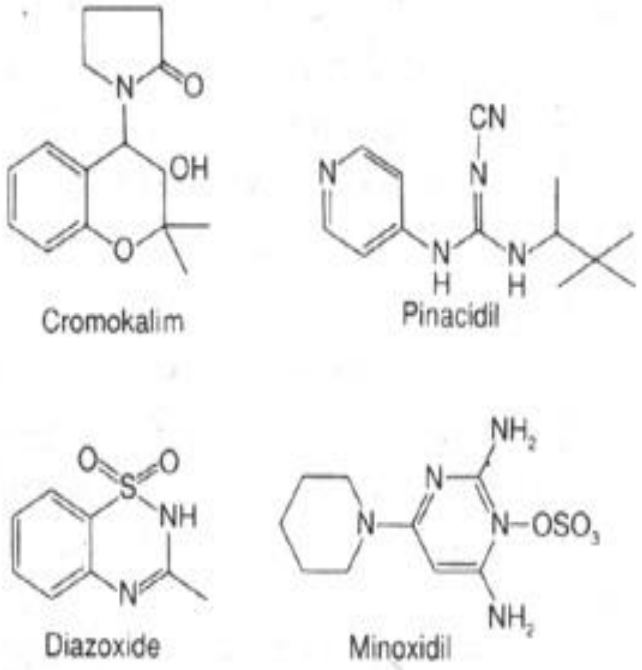
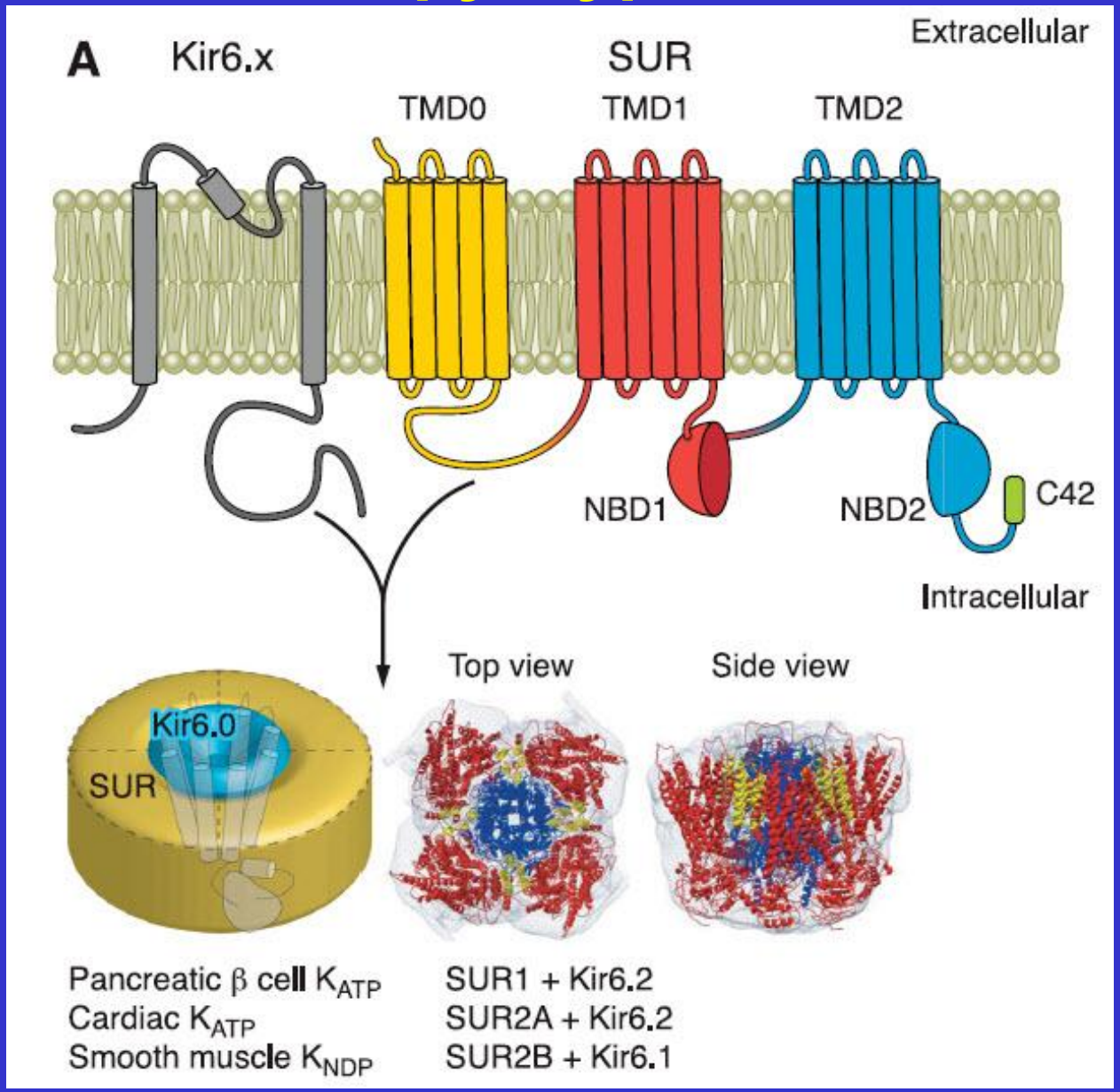
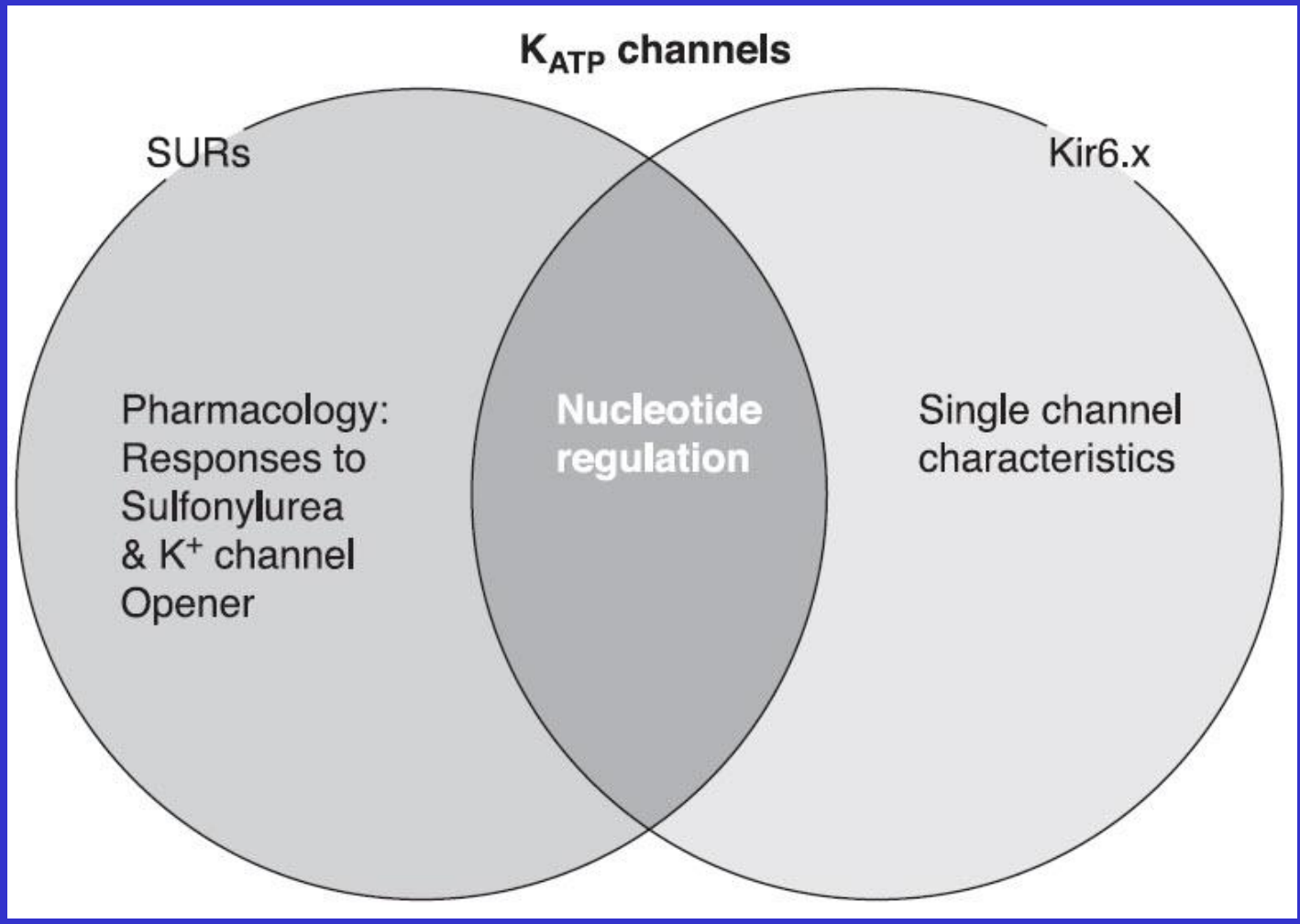


Fig. 14.4 Drugs that act at ATP-sensitive K^+ channels. **A.** K^+ channels opened by diazoxide. The records were obtained from insulin-secreting cells in culture by the patch-clamp technique (Ch. 2). Saponin caused permeabilization of the cell, with loss of intracellular ATP, causing the channels to open (upward deflection) until they were inhibited by ATP. Addition of diazoxide, a vasodilator drug (which also inhibits insulin secretion; see text) causes opening of the channels. In an intact smooth muscle cell, this causes hyperpolarization and relaxation. **B.** Structures of compounds that activate or block ATP-sensitive K^+ channels. (From: (A) Dunne et al. 1990 Br J Pharmacol 99: 169)

Структура К-канала



HIBINO ET AL.
Physiol Rev • VOL 90 • JANUARY 2010



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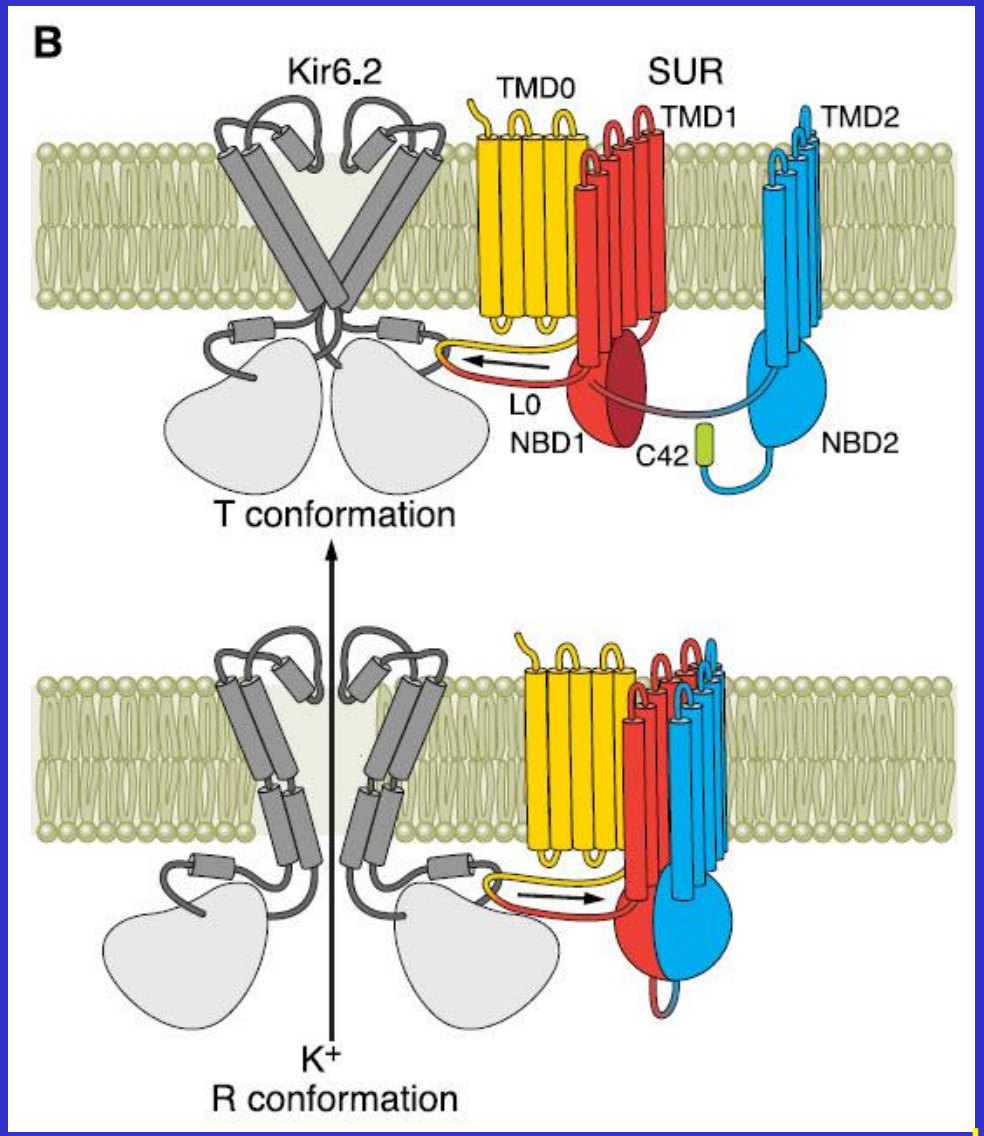
Механизм открытия К-канала



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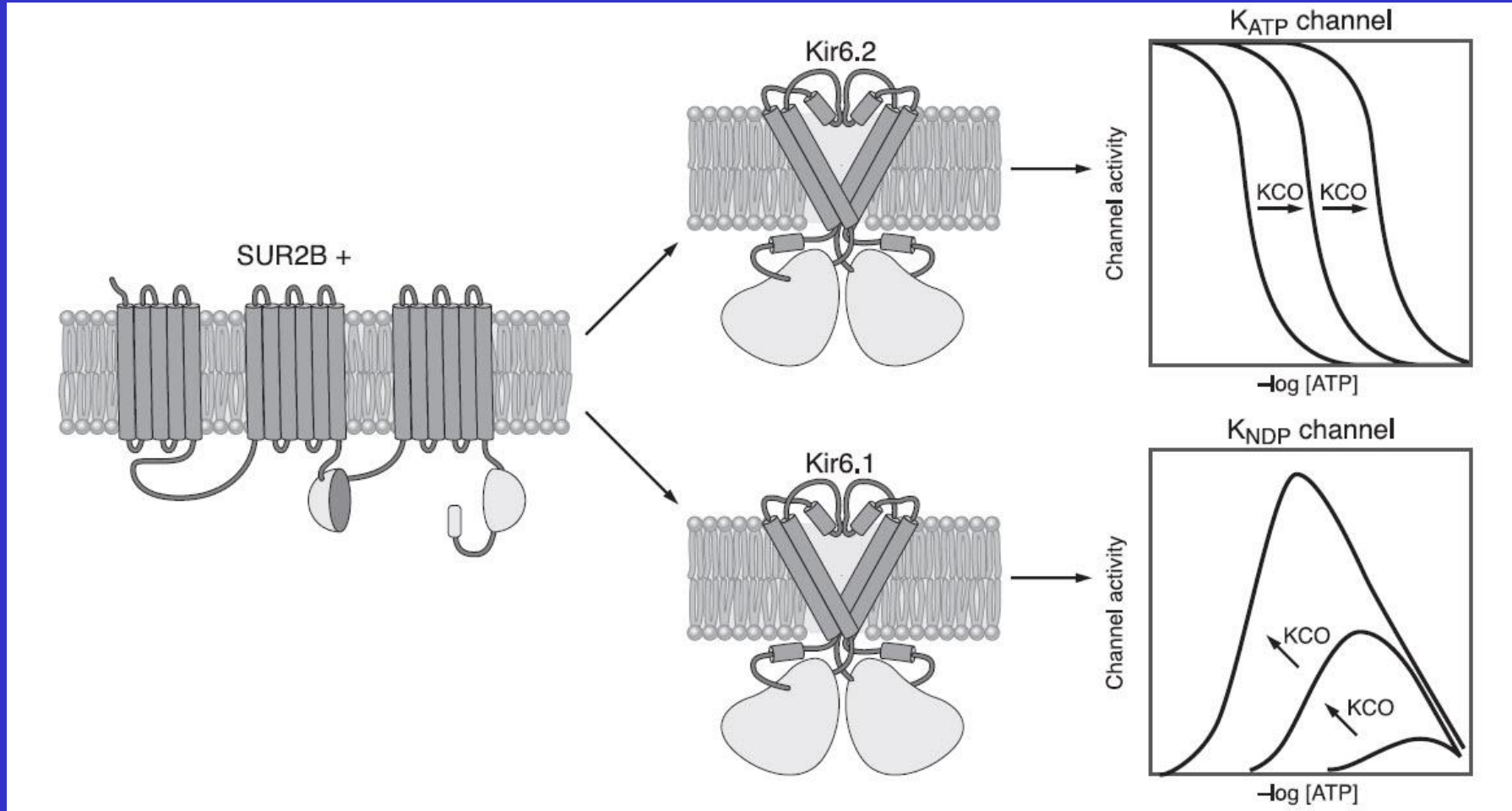

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Профиль активности

	Бета-клетки	Сердце	Сосуды
Diazoxide	+++	-	+++
Cromakalim	-	++	+++
Nicorandil	-	++	+++

Nicorandil + выделяет NO

Minoxidil + стимулирует рост волос

Применение

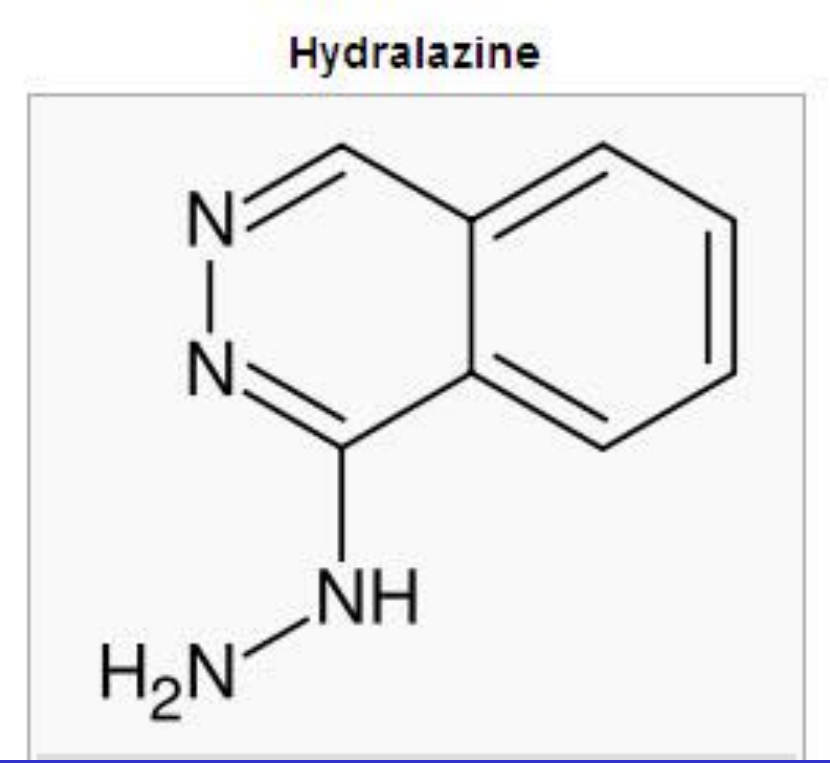
Артериальная гипертония

Стенокардия

Сердечная недостаточность

При риске преждевременных родов

Гидралазин



- Повышает содержание GMP
- Уменьшает выброс Ca^{++} из саркоплазматического ретикулюма
- Выделяет NO

Сосудорасширяющие средства для купирования гипертонического криза

Table 23. Parenteral drugs for treatment of hypertensive emergencies*

Drug	Dose	Onset of Action	Duration of Action	Adverse Effects†	Special Indications
Vasodilators					
Sodium nitroprusside	0.25–10 μg/kg/min as IV infusion‡	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocynate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5–15 mg/h IV	5–10 min	15–30 min, may exceed 4 hrs	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 μg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 μg/min as IV infusion‡	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 hrs IV	15–30 min	6–12 hrs	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV 10–40 mg IM	10–20 min IV 20–30 min IM	1–4 hrs IV 4–6 hrs IM	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia

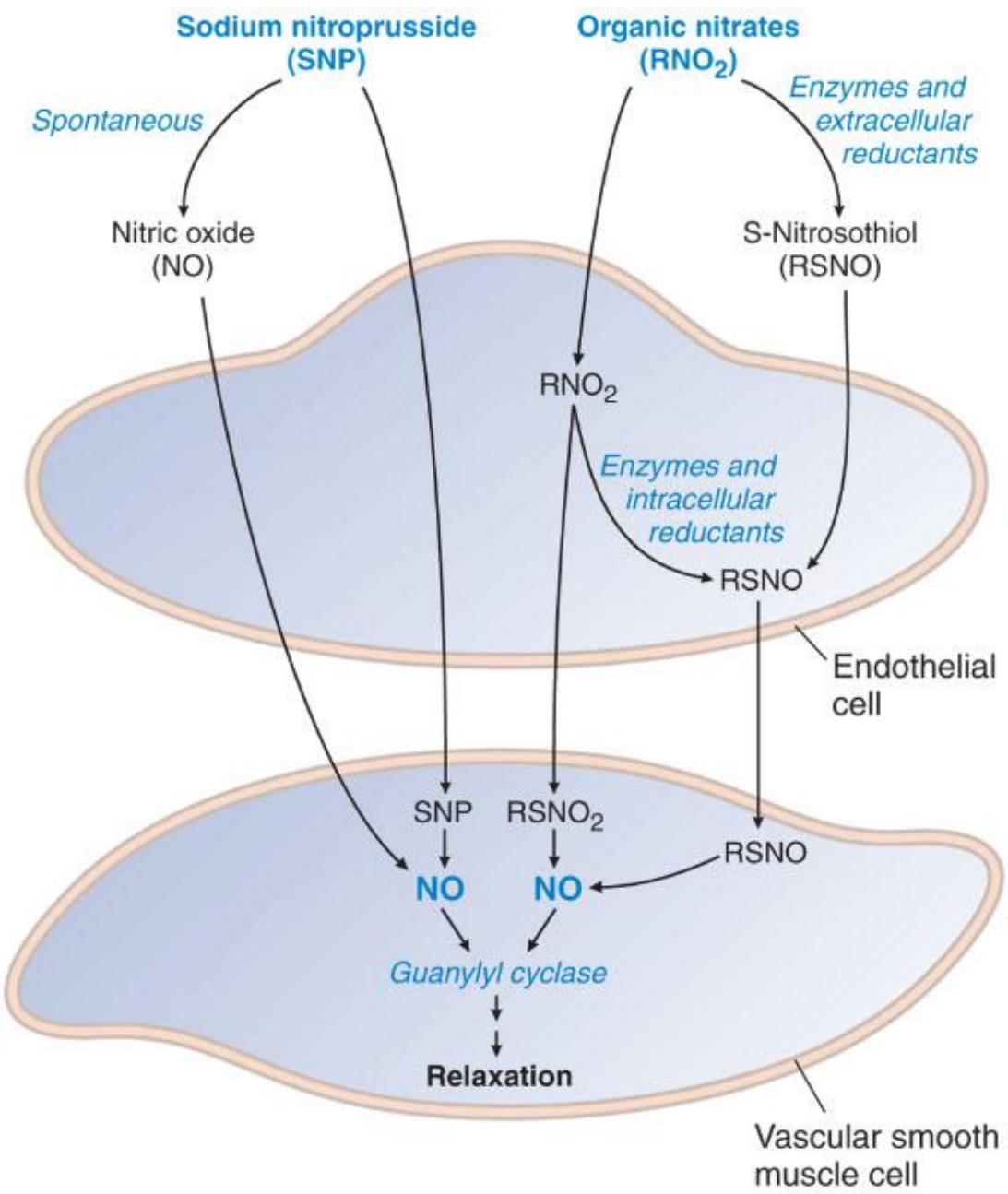


Figure 21-7: Biotransformation of organic nitrates and sodium nitroprusside. Organic nitrates and sodium nitroprussid...

Адреноблокаторы для купирования гипертонического криза

Adrenergic Inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min 0.5–2.0 mg/min IV infusion	5–10 min	3–6 hrs	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 µg/kg/min IV bolus, then 50–100 µg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 µg/min	1–2 min	10–30 min	Hypotension, nausea, asthma, first degree heart block, heart failure	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

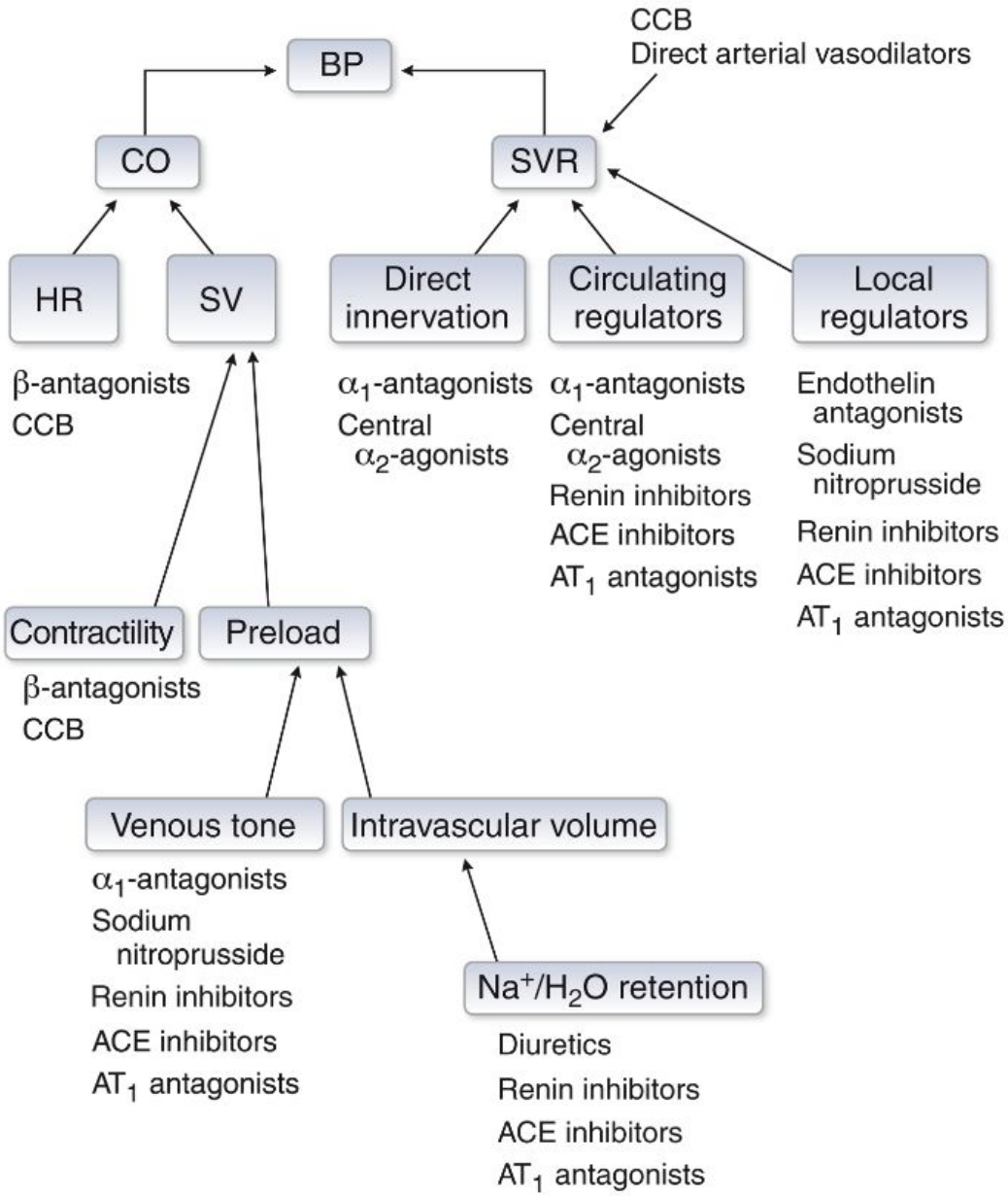


Figure 25-2: Pharmacologic effects of commonly used antihypertensive agents. Ant...

Table 14.5 Commonly used antihypertensive drugs

Mode of action	Drugs	Adverse effects: Postural hypotension	Adverse effects: Impotence	Adverse effects: Other	Special features
Reduction of blood volume/indirect vasodilatation	Thiazide diuretics*	–	++	Urinary frequency, gout, glucose intolerance, hypokalemia, hyponatremia, thrombocytopenia	Reduce stroke in clinical trials, inexpensive
Block of β-adrenoceptors†	Propranolol Atenolol Metoprolol	–	±	Fatigue, cold peripheries	Reduce stroke in clinical trials, inexpensive, additional benefit after M Contraindications: asthma, heart failure, heart block, peripheral vascular disease
ACE inhibition	Captopril Enalapril	–	±	First dose hypotension, dry cough, reversible renal failure in patients with bilateral renal artery stenosis	Additional benefit in insulin-dependent diabetics with proteinuria, following MI, and in patients with heart failure; cause regression of left ventricular hypertrophy
Arteriolar vasodilatation	Ca^{2+} antagonists, e.g. nifedipine, amlodipine nicardipine	–	±	Flushing, headache, ankle edema	
Block of α_1-adrenoceptors†	Prazosin Terazosin Doxazosin	+	±	First dose hypotension	Longer-acting drugs (e.g. terazosin, doxazosin) better tolerated than prazosin. Improve plasma lipids. Useful addition to other drugs when two drugs needed

MI = myocardial infarction, * see Ch. 18, † see Ch. 7

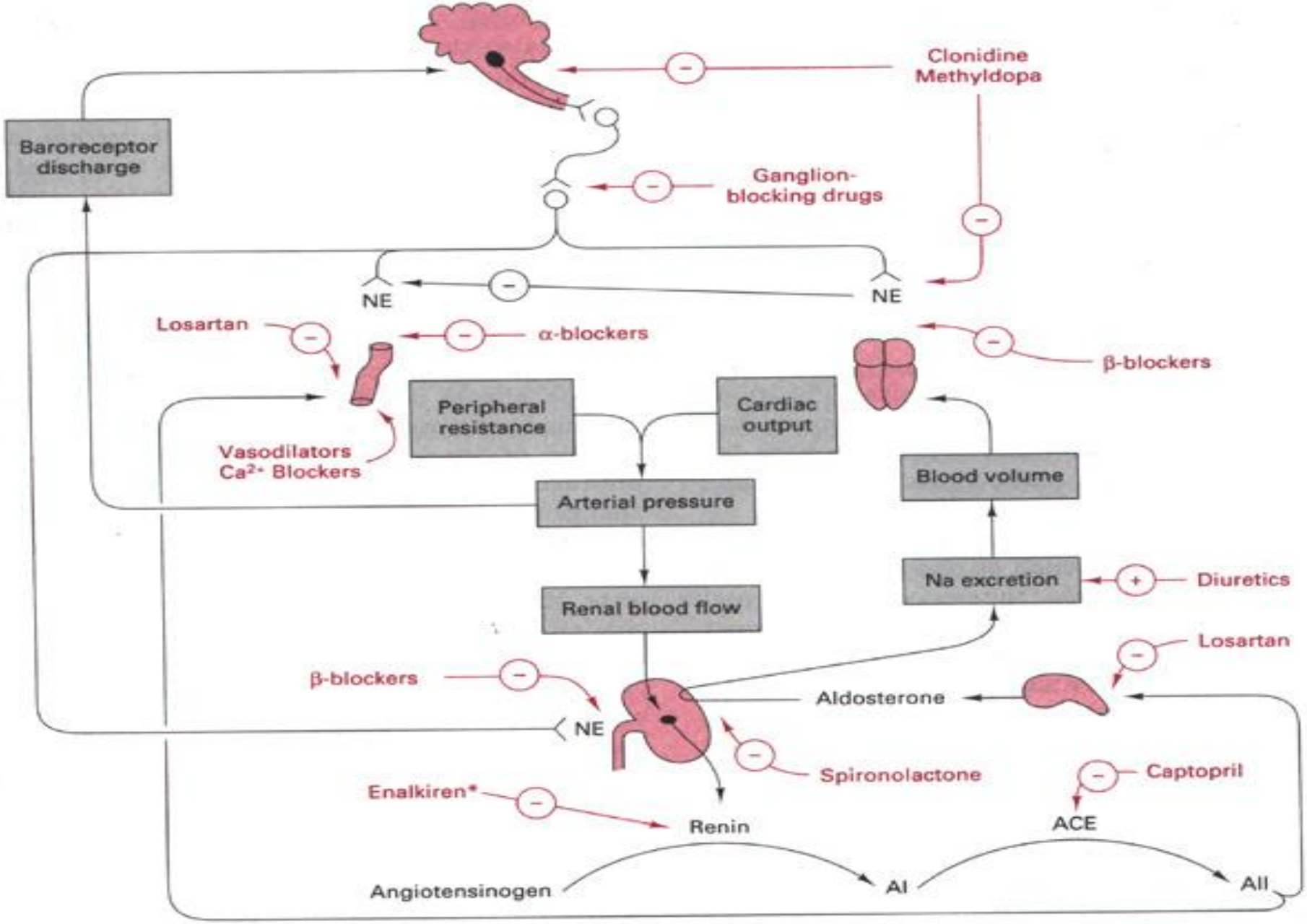
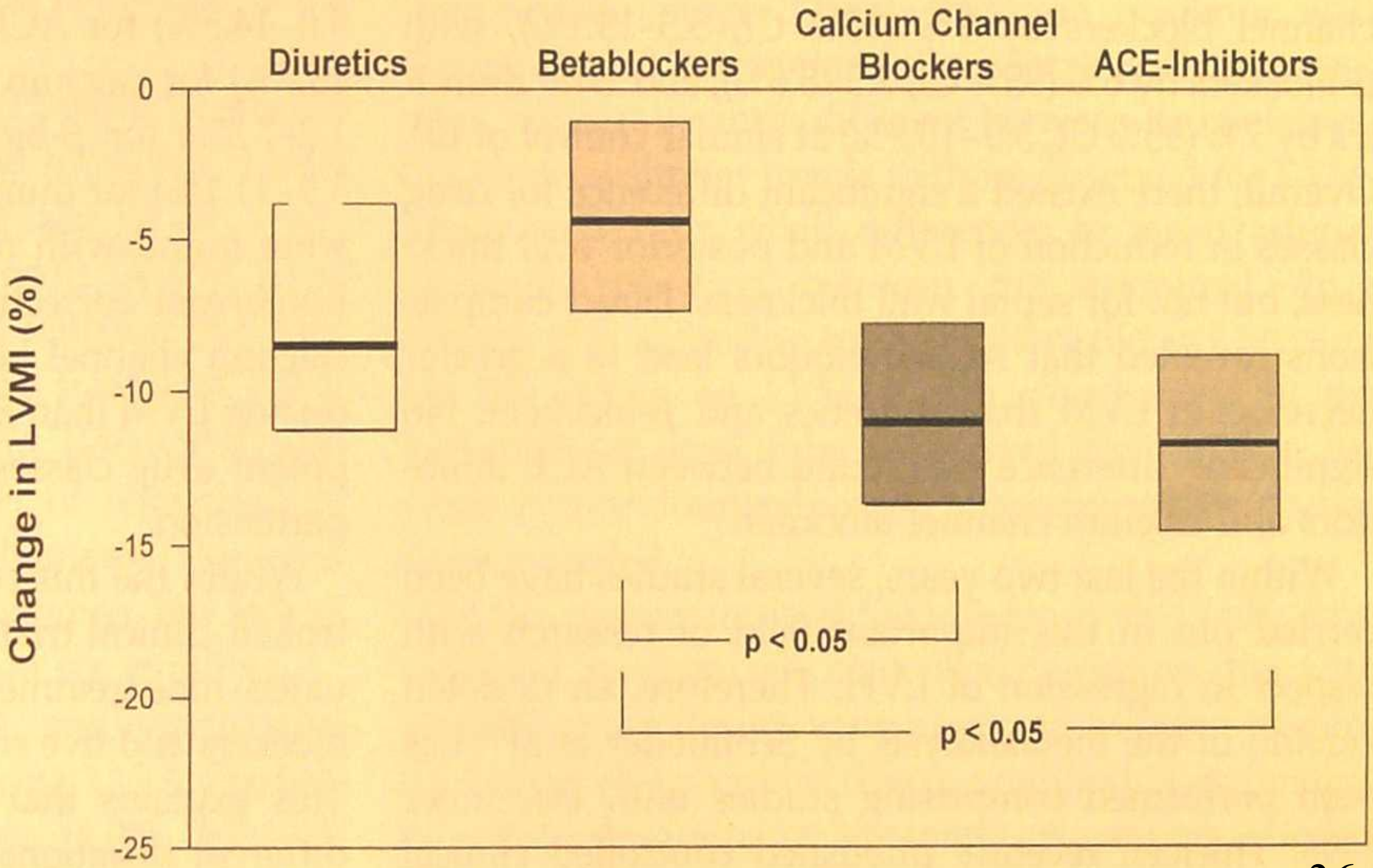


Fig. 14.8 Diagram showing the main mechanisms involved in arterial blood pressure regulation (black lines), ar the sites of action of antihypertensive drugs (red lines). NE = norepinephrine, AI = angiotensin I, AII = angiotensin II, ACE = angiotensin-converting enzyme.



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Schlaich&Schmieder Am.J.Hypertension, 1998,11:1394

Table 3: Adverse effects of drugs: percentage of people with one or more symptoms attributable to treatment*, according to category of drug and dose, in randomised trials [9, 20]

		Percent (95%CI) with symptoms (treated minus placebo)†		
Drug class	No. of trials	1/2 standard dose	Standard dose	Twice standard dose
Thiazides	59	2.0 [-2.2 to 6.3]	9.9 [6.6 to 13.2]	17.8 [11.5 to 24.2]
BBs	62	5.5 [0.3 to 10.7]	7.5 [4.0 to 10.9]	9.4 [3.6 to 15.2]
ACEi	96	3.9 [-3.7 to 11.6]	3.9 [-0.5 to 8.3]	3.9 [-0.2 to 8.0]
ARBs	44	-1.8 [-10.2 to 6.5]	0 [-5.4 to 5.4]	1.9 [-5.6 to 9.3]
CCBs	96	1.6 [-3.5 to 6.7]	8.3 [4.8 to 11.8]	14.9 [9.8 to 20.1]

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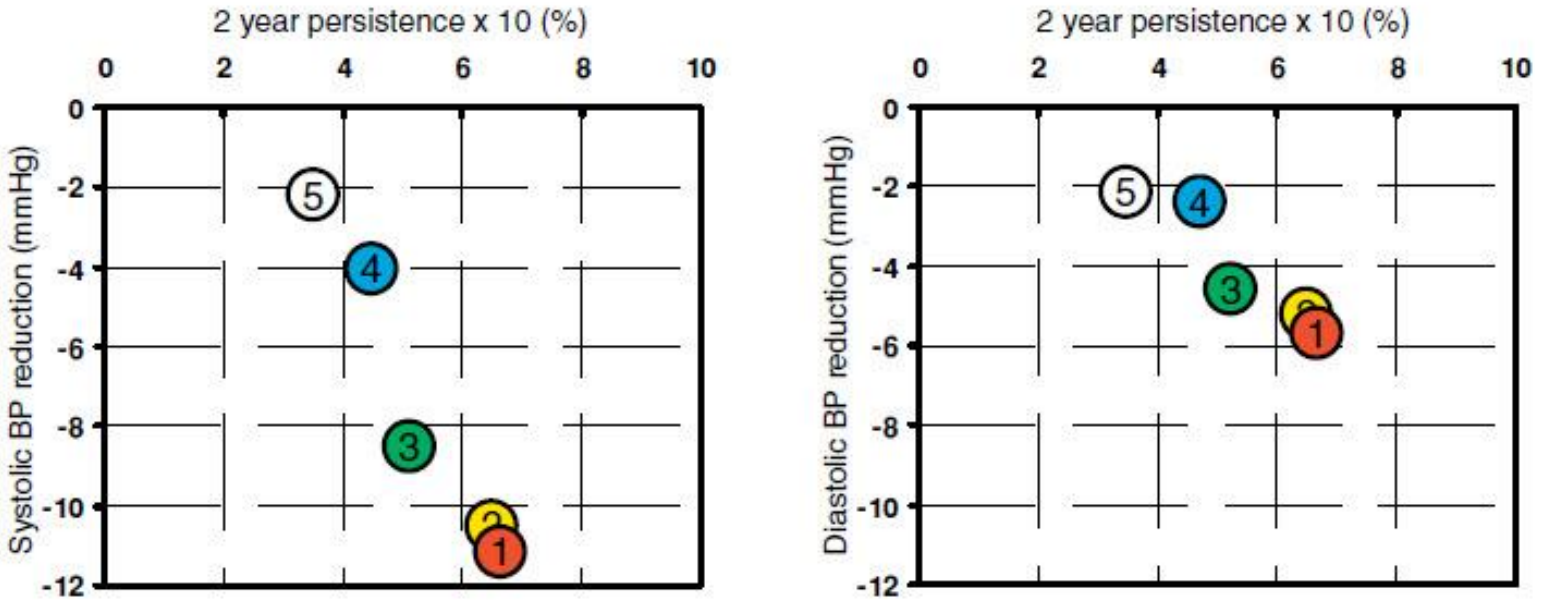
DRUG CLASS	INDICATIONS	CONTRAINDICATIONS
Diuretics	Heart failure Systolic hypertension	Gout
β-Antagonists	Coronary artery disease Heart failure Migraine Tachyarrhythmias	Asthma Heart block
α-Antagonists	Prostatic hypertrophy	Heart failure
Calcium channel blockers	Systolic hypertension	Heart block
ACE inhibitors	Diabetic or other nephropathy Heart failure Previous myocardial infarction	Bilateral renal artery stenosis Hyperkalemia Pregnancy
AT_1 antagonists	ACE inhibitor-associated cough Diabetic or other nephropathy Heart failure	Bilateral renal artery stenosis Hyperkalemia Pregnancy

Table 25-4: Relative Indications and Contraindications for Antihypertensive Agents



1 ARBs: P 68.5%; BP -11.2 / -5.8 mmHg

2 ACEi: P 64.5%; BP -10.5 / -5.1 mmHg

3 CCBs: P 51.6%; BP -8.5 / -4.6 mmHg

4 BBs: P 44.8%; BP -4.0 / -2.3 mmHg

5 Diu: P 34.4%; BP -2.3 / -2.1 mmHg

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Benefits, risks, costs (2)

Chronic HTN	**$ per month**
hydralazine	$8.40
minoxidil	$1.20
amlodipine	$39.90
diltiazem	$40.20
captopril	$16.20
losartan	$38.10

The Medical Letter 2001;43:17-22

Annual average drug costs per patient for different antihypertensives according to the pattern of persistence

Antihypertensive	Continuers [95%CI]
Diuretics	€ 65.09 [58.67–71.52]
Beta-blockers	€ 109.29 [102.46–116.12]
Calcium-channel blockers	€ 234.63 [224.78–244.47]
ACE inhibitors	€ 196.28 [189.69–202.86]
Angiotensin II antagonists	€ 326.16 [313.05–339.27]
Total	**€ 171.73 [167.43–176.04]**

CI, confidence interval.

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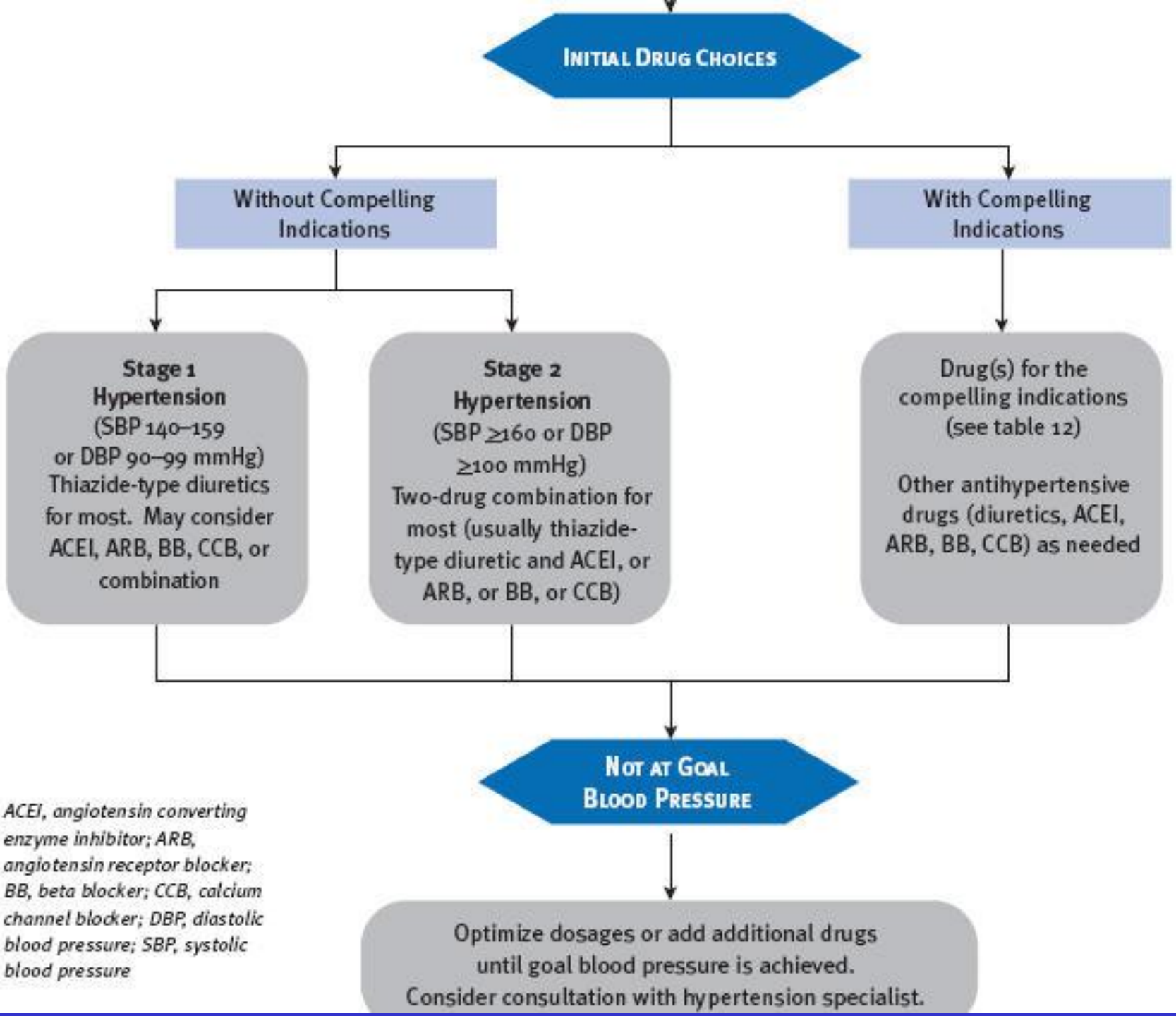

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 12. Clinical trial and guideline basis for compelling indications for individual drug classes

Compelling Indication*	Recommended Drugs						Clinical Trial Basis†
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT	
Heart failure	●	●	●	●		●	ACC/AHA Heart Failure Guideline,[132] MERIT-HF,[133] COPERNICUS,[134] CIBIS,[135] SOLVD,[136] AIRE,[137] TRACE,[138] ValHEFT,[139] RALES,[140] CHARM[141]
Postmyocardial infarction		●	●			●	ACC/AHA Post-MI Guideline,[142] BHAT,[143] SAVE,[144] Capricorn,[145] EPHESUS[146]
High coronary disease risk	●	●	●		●		ALLHAT,[109] HOPE,[110] ANBP2,[112] LIFE,[102] CONVINCE,[101] EUROPA,[114] INVEST[147]
Diabetes	●	●	●	●	●		NKF-ADA Guideline,[88,89] UKPDS,[148] ALLHAT[109]
Chronic kidney disease			●	●			NKF Guideline,[89] Captopril Trial,[149] RENAAL,[150] IDNT,[151] REIN,[152] AASK[153]
Recurrent stroke prevention	●		●				PROGRESS[111]

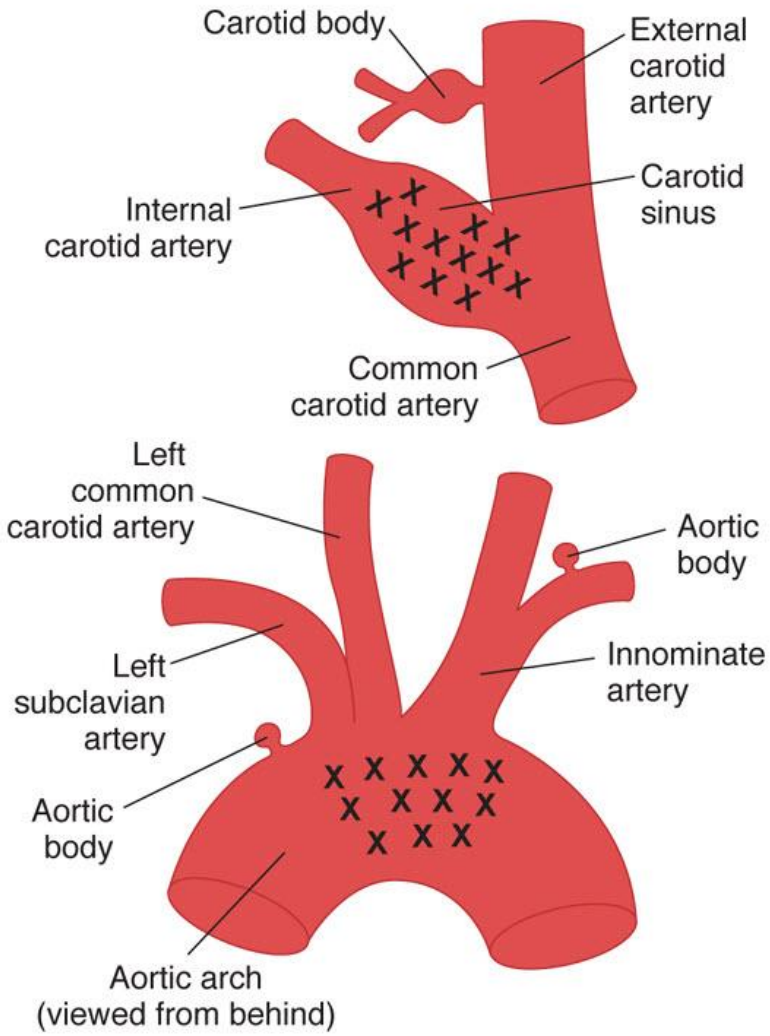

Figure 33-4: Baroreceptor areas in the carotid sinus and aortic arch. X, sites where receptors are located. The carotid and aortic bodies, which contain chemoreceptors, are also shown.

DRUG	DURATION OF ACTION (HOURS)
Thiazide Diuretics	
Chlorothiazide	6–12
Chlorthalidone	48–72
Hydrochlorothiazide	16–24
Indapamide	24
Metolazone	24
Loop Diuretics	
Bumetanide	4–5
Ethacrynic acid	4–5
Furosemide	4–5
Torsemide	6–8
Potassium-Sparing Diuretics	
Amiloride	6–24
Eplerenone	24
Spironolactone	72–96
Triamterene	8–12