# 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.

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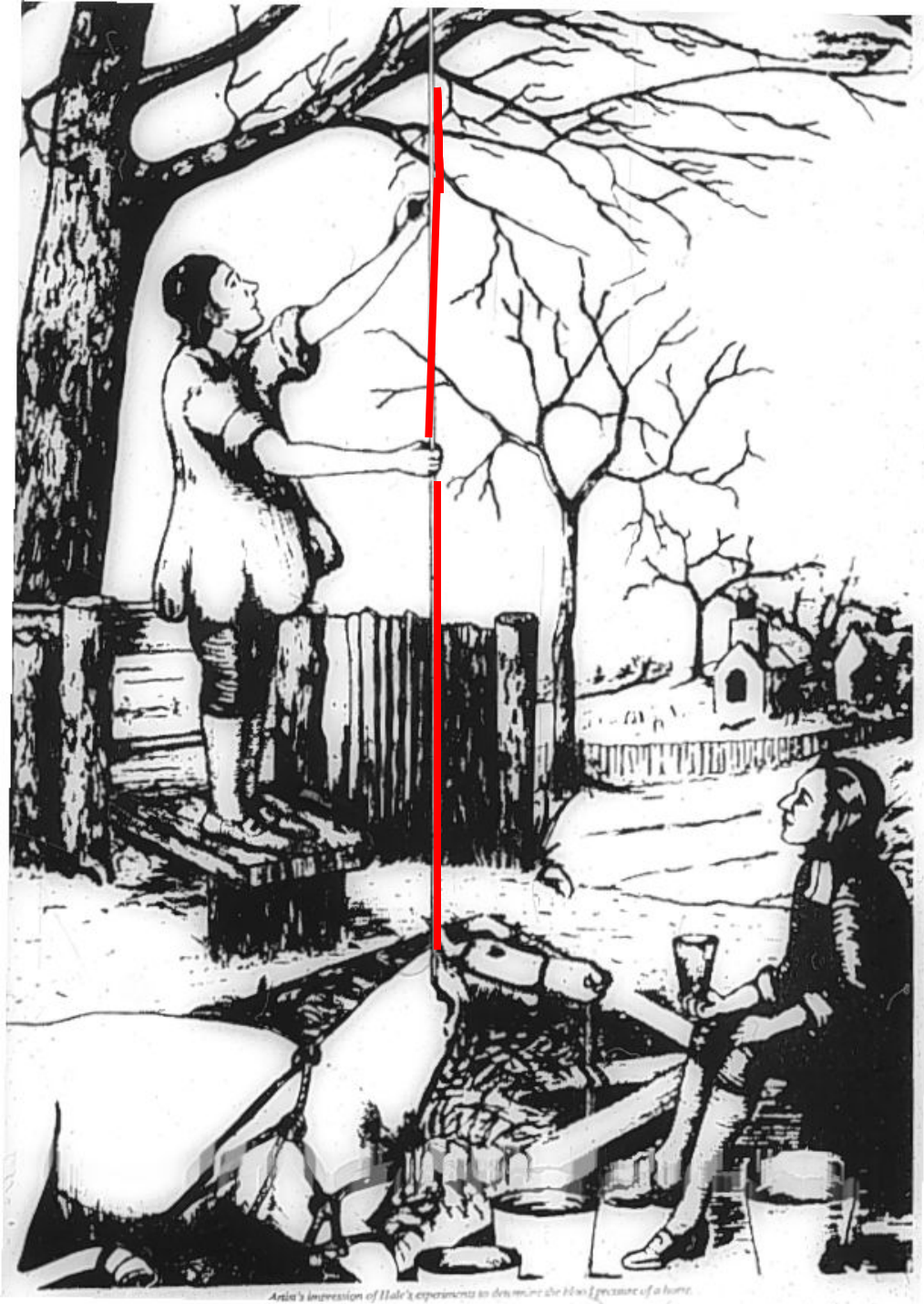
## EXPERIMENT I.

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

B that,



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



that, by means of another brafs pipe which was fitly adapted to it, I fixed a glafs tube, of nearly the fame diameter, which was 9 feet in length: then untying the ligature on the artery, the blood rofe 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 rufhed up about half way in an inftant, and afterwards gradually at each pulfe 12, 8, 6, 4, 2, and fometimes 1 inch: when it was at its full height, it would rife and fall at and after each pulfe 2, 3, or 4 inches; and fometimes it would fall 12 or 14 inches, and have there for a time the fame vibrations up and down, at and after each pulfe, as it had, when it was at its full height; to which it would rife again, after forty or fifty pulfes.

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

3. Then I took away the glafs tube, and let the blood from the artery mount up in

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

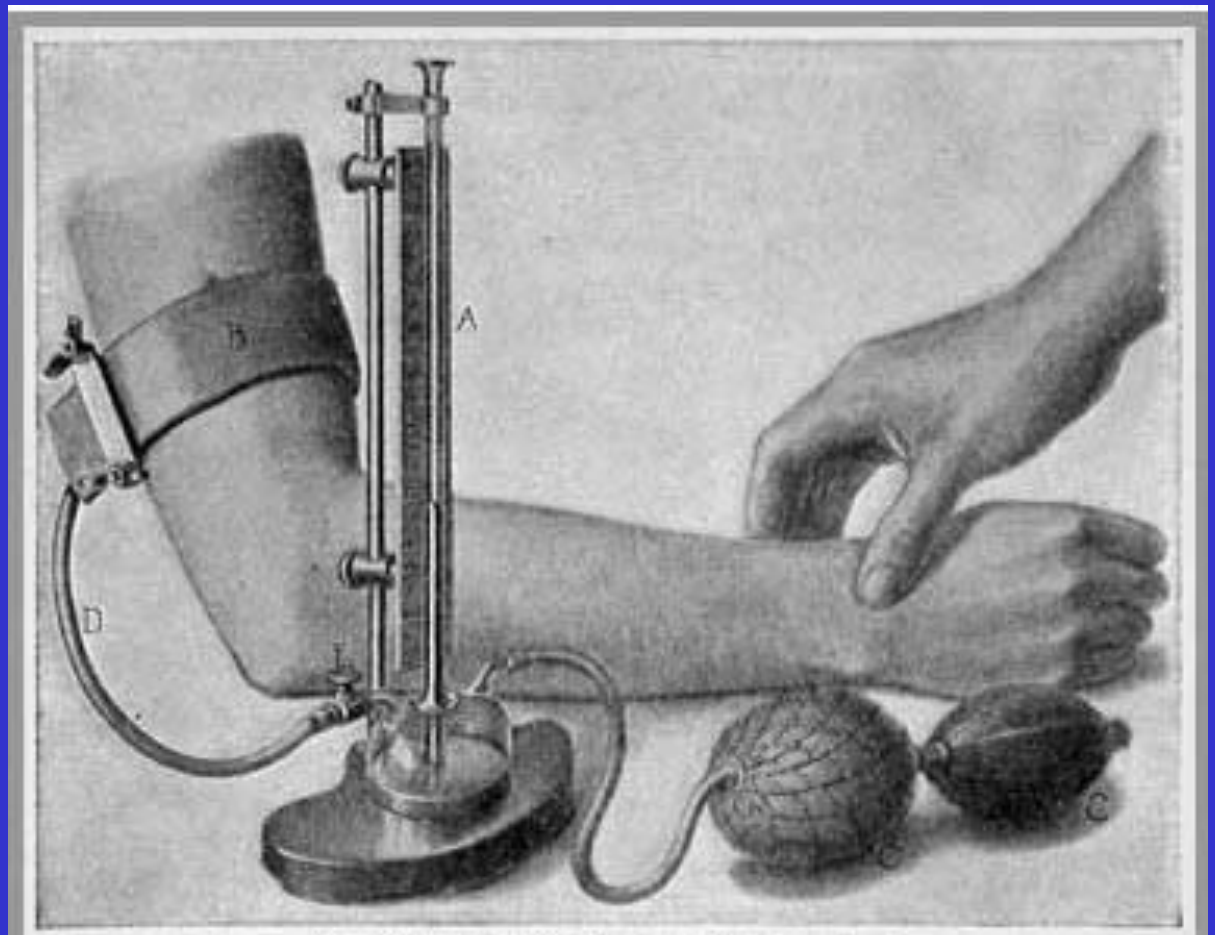



Fig. 21.—Riva-Rocci's sphygmomanometer.

Николай Сергеевич
КОРОТКОВ
(1874–1920)

**Выпускник медицинского ф-та Московского университета 1898 года**

Др. *Н. С. Коротковъ*. Къ вопросу о методахъ изслѣдованія кровяного 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 кровяного 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

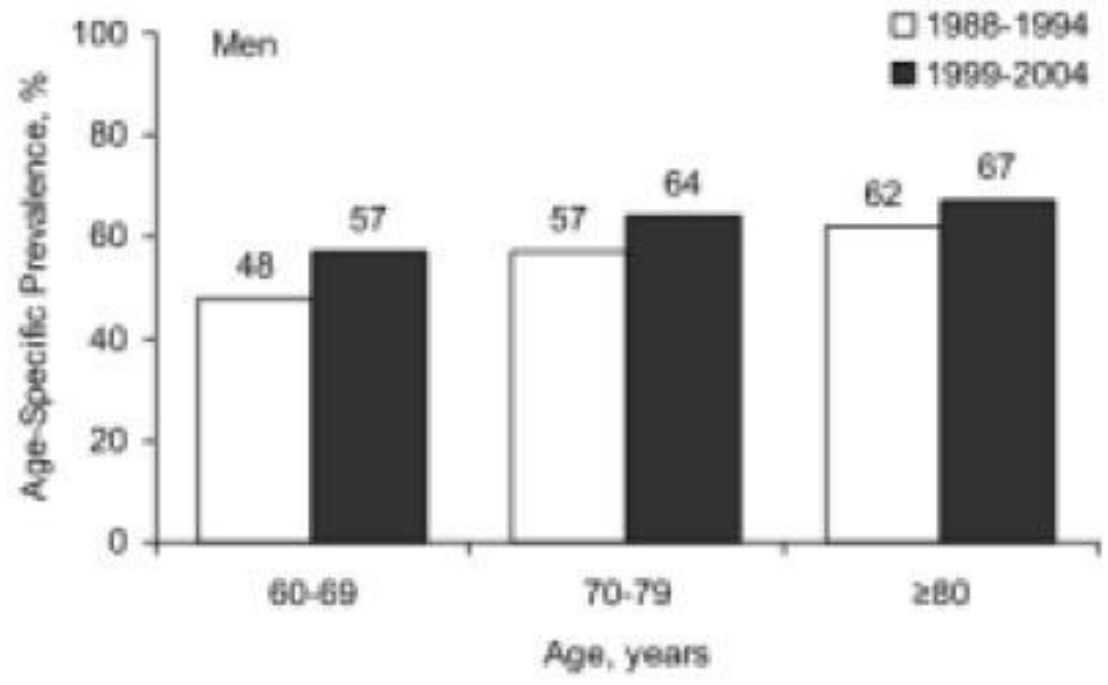
| Категория | АД сист., мм рт. ст. | АД диаст., мм рт. ст. |
|---|---|---|
| Оптимальное АД | <120 | <80 |
| Нормальное АД | <130 | <85 |
| Высокое нормальное АД | 130-139 | 85-89 |
| АГ I степени | 140-159 | 90-99 |
| АГ II степени | 160-179 | 100-109 |
| АГ III степени | ≥ 180 | ≥110 |
| Примечание: если систолическое и диастолическое АД находятся в разных категориях, присваивается более высокая категория артериальной гипертензии | | |

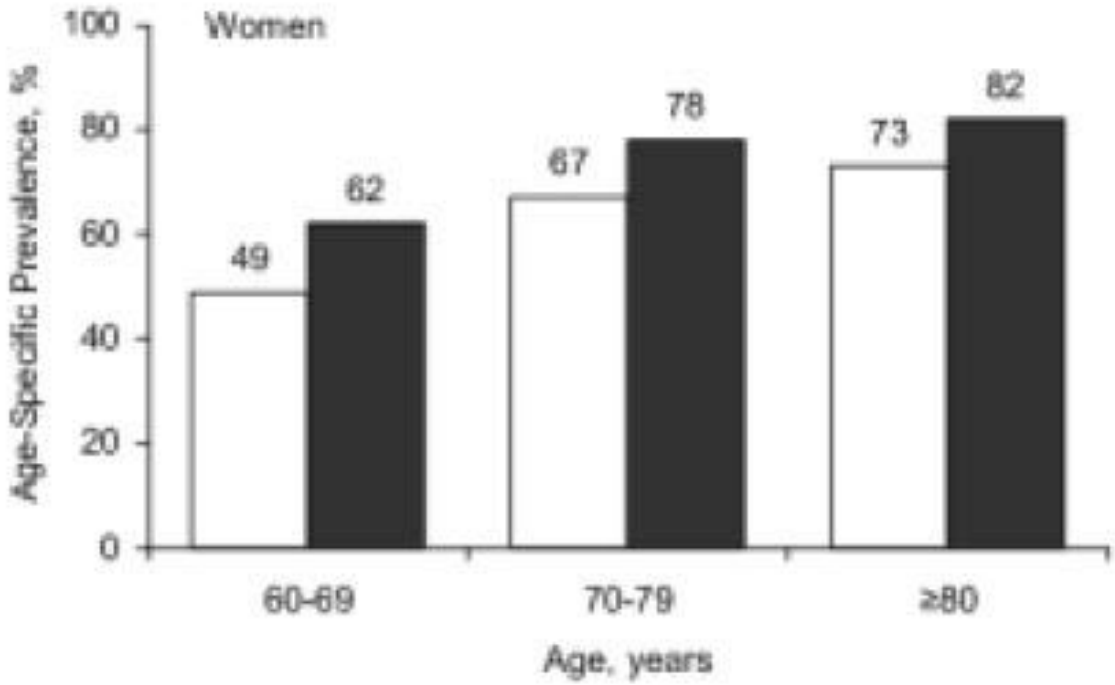
* Профилактика, диагностика и лечение артериальной гипертонии в Российской Федерации. Кардиология.-2000.-№11

# 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

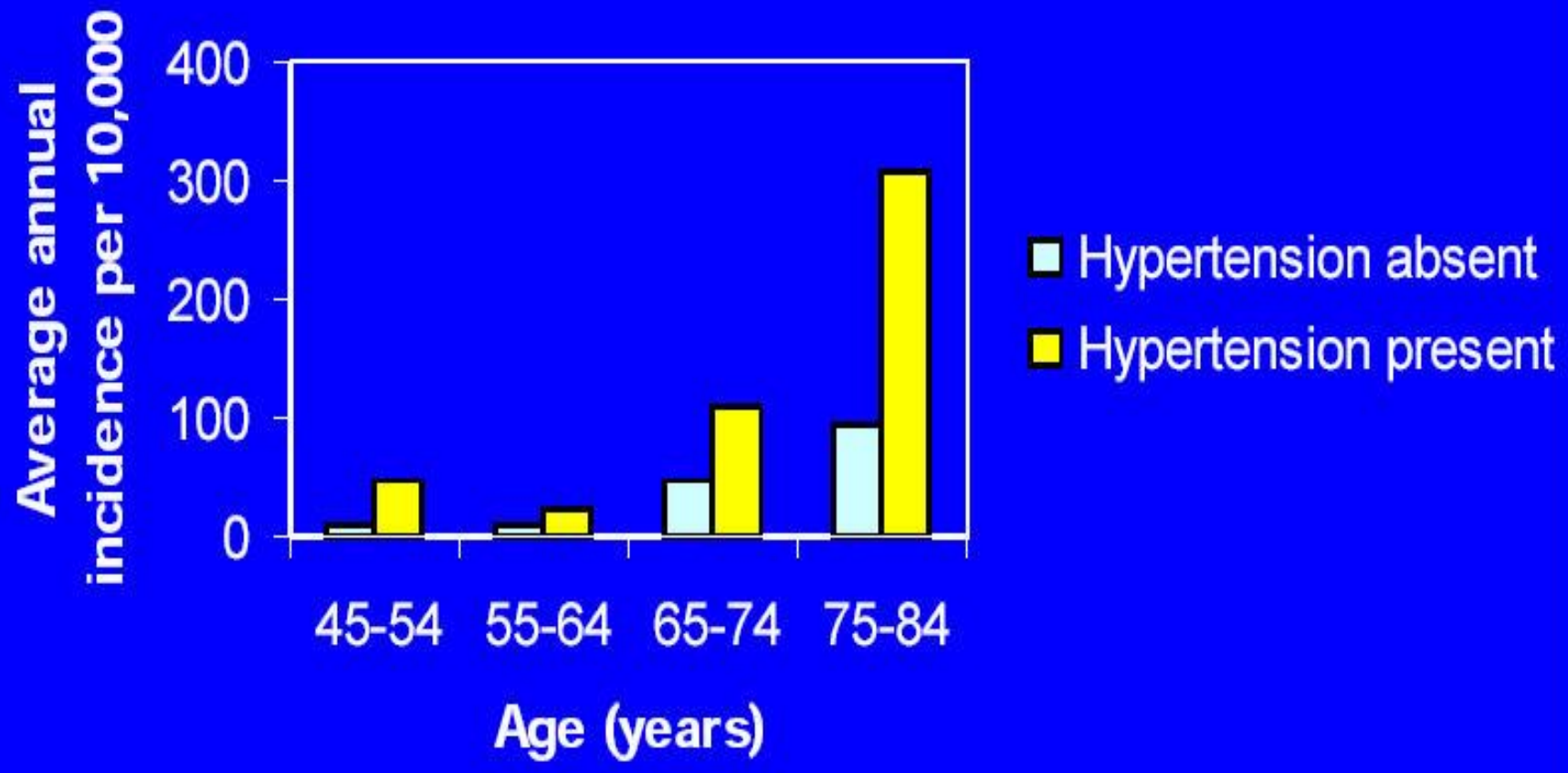
## Эпидемиология АГ

| | 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

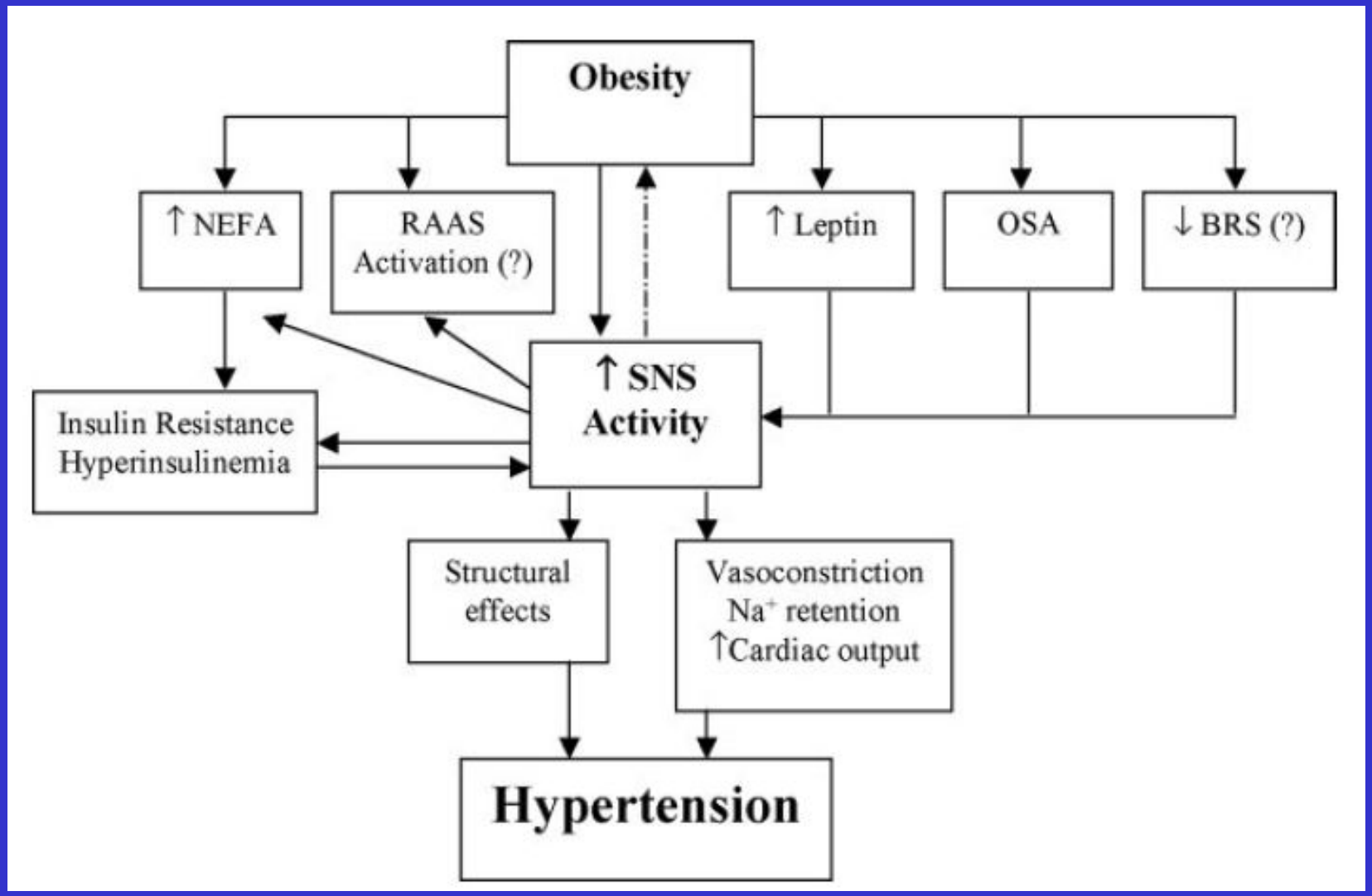
Pheochromocytoma

Primary aldosteronism and other mineralocorticoid excess states

Renovascular hypertension

Sleep apnea

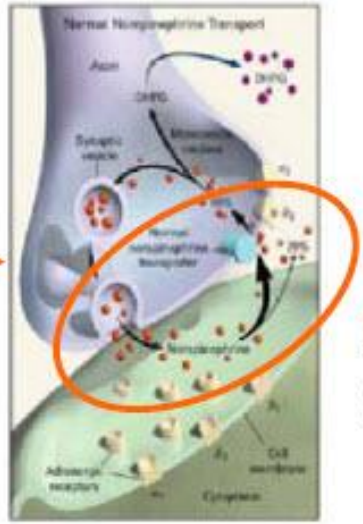
Thyroid or parathyroid disease




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

# Quantifying human sympathetic nervous system activity

**Sympathetic Nerve Traffic**



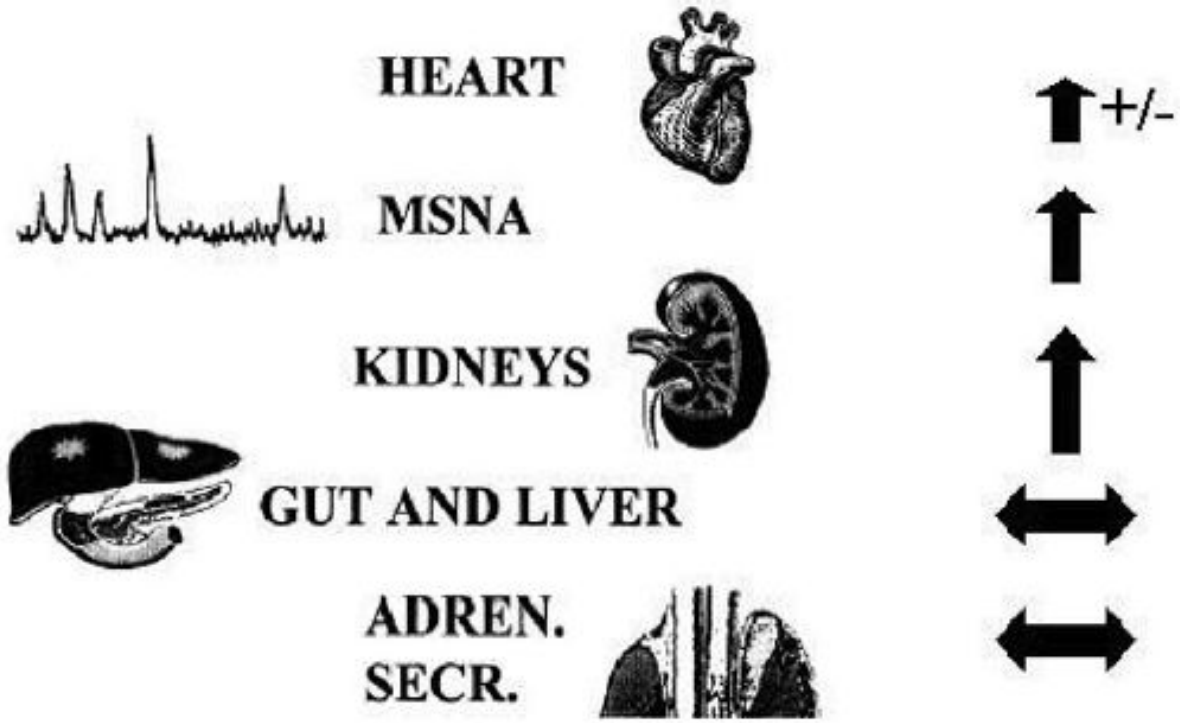
**Norepinephrine Spillover**

**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.

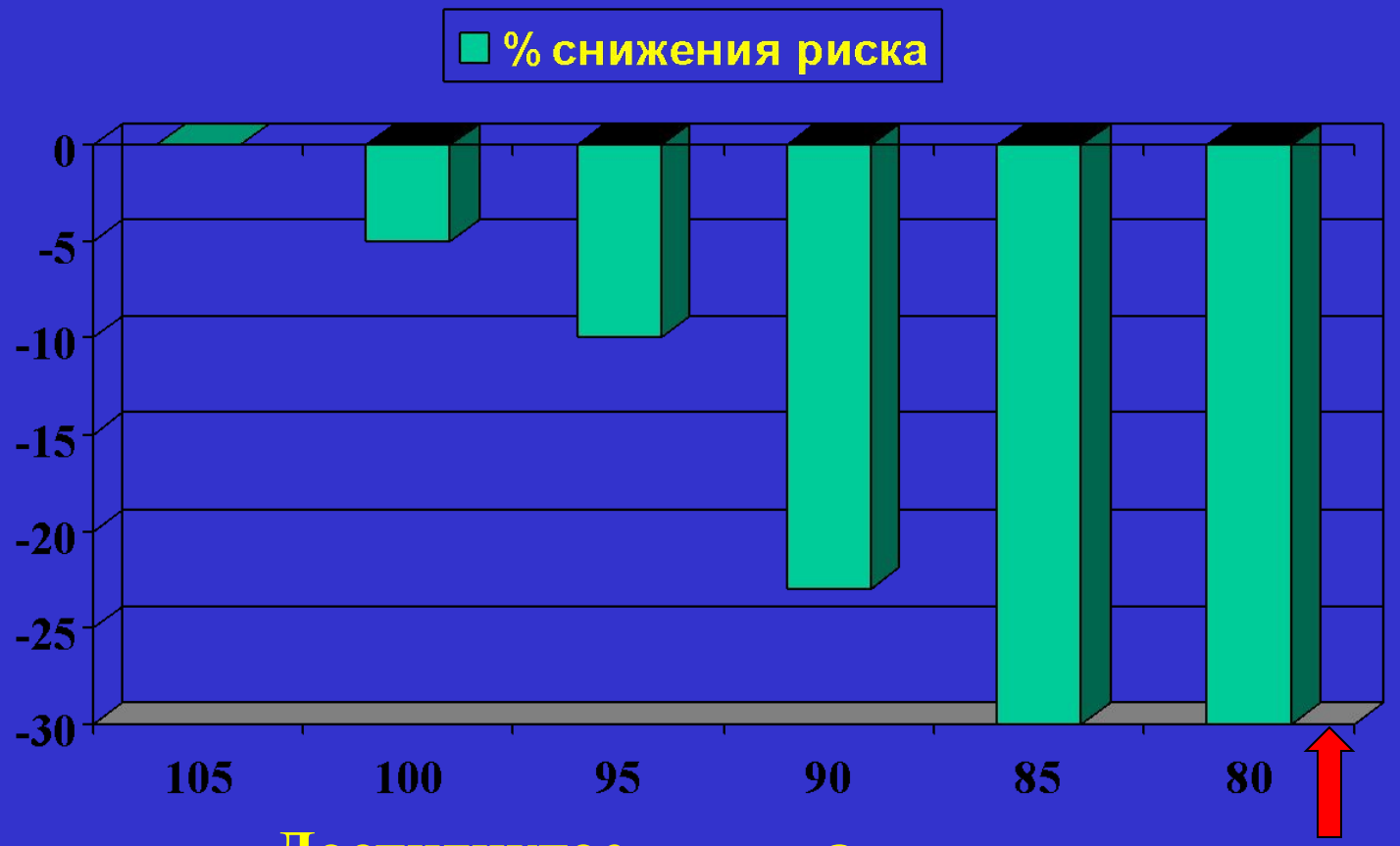
# Obesity-Related Hypertension

## 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)

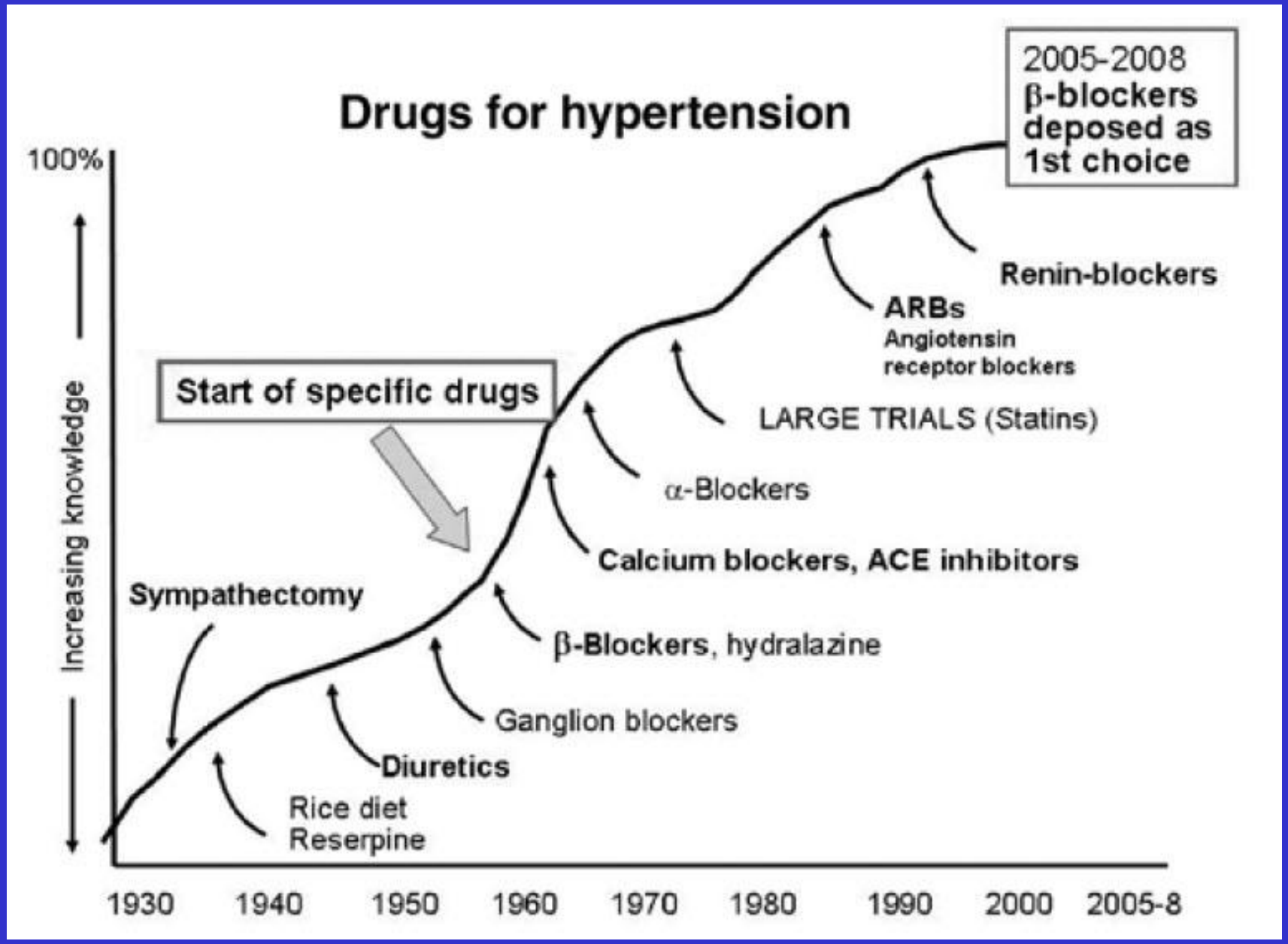



Достигнутое АД диаст.

Оптимальное снижение АД в HOT исследовании- 83 mm Hg

**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] |




CARDIOVASCULAR JOURNAL OF AFRICA • Vol 20, No 1, January/52 February 2009

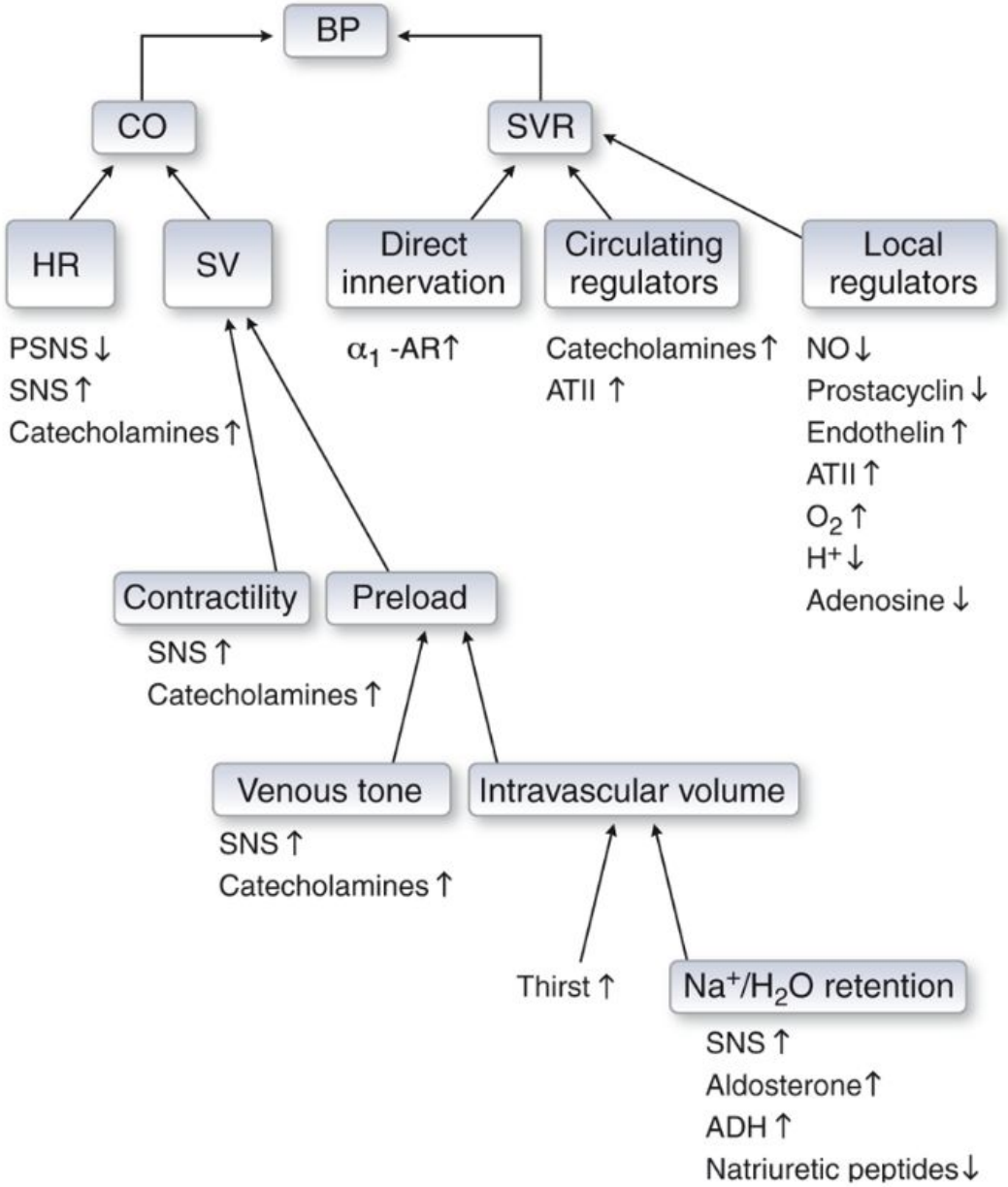



**Figure 25-1**: Determinants of systemic blood pressure. Blood pressure (*BP*) is the pr...

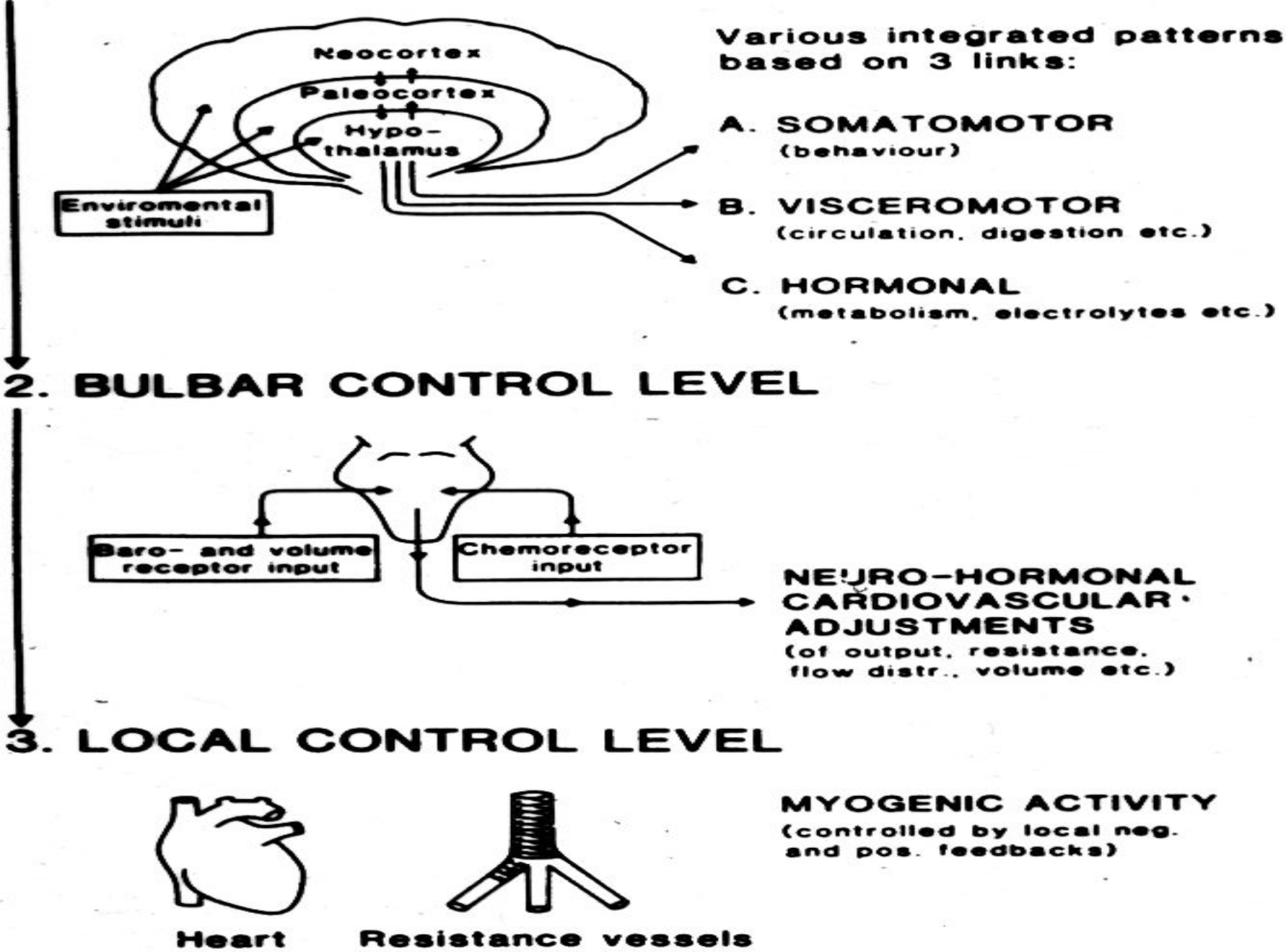



**FIGURE 1.** Schematic outline of the three major levels of cardiovascular regulation, illustrating principal differences between their respective

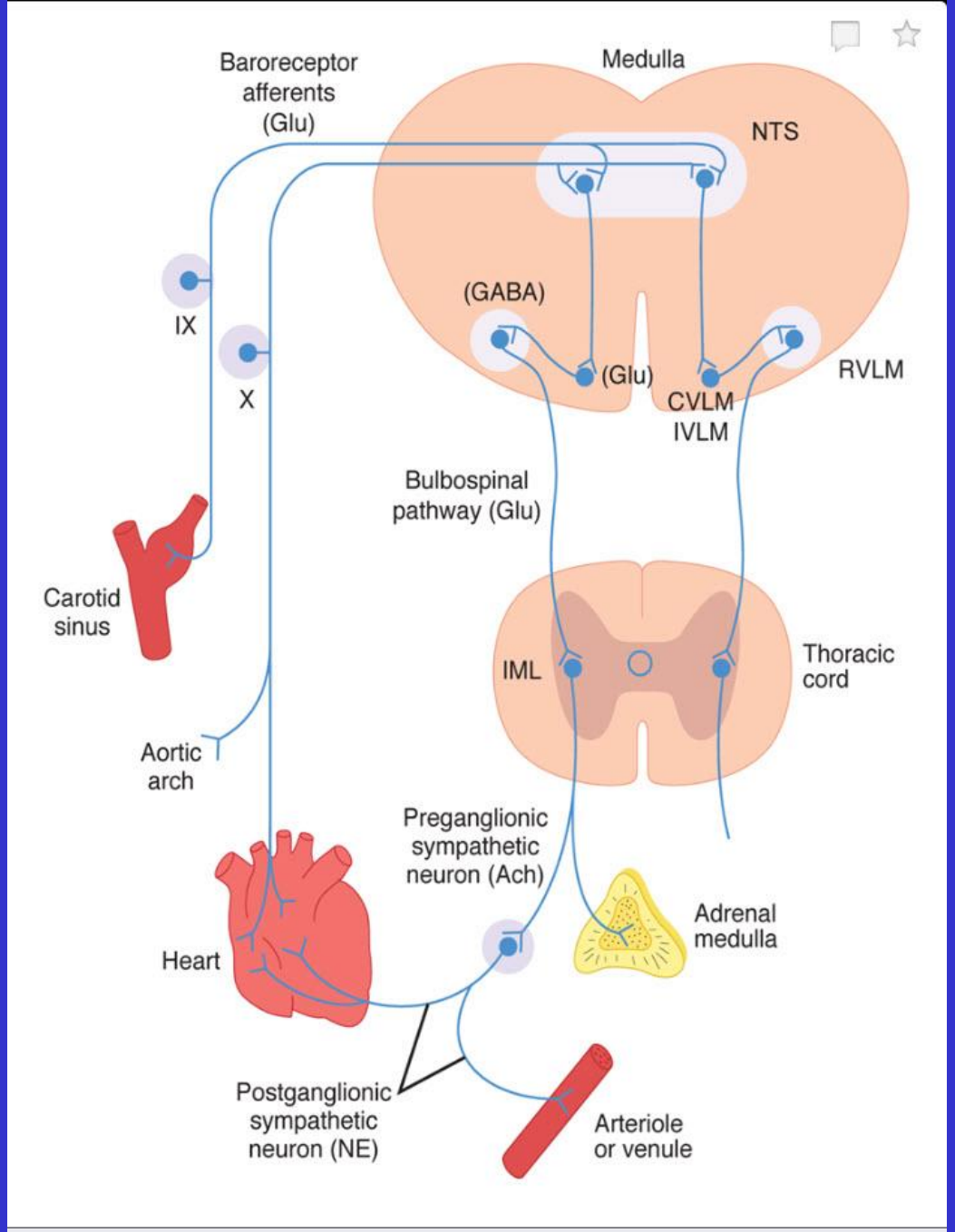



**Figure 33-2**: Basic pathways involved in the medullary control of blood pressure. Th...

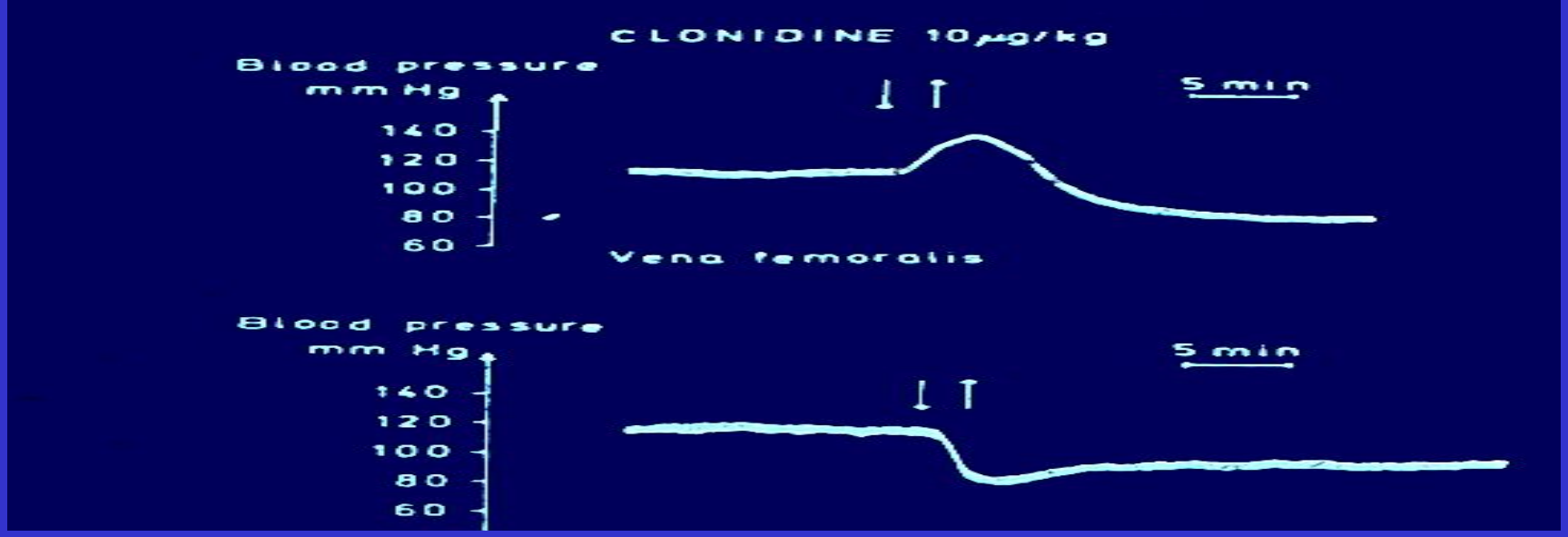
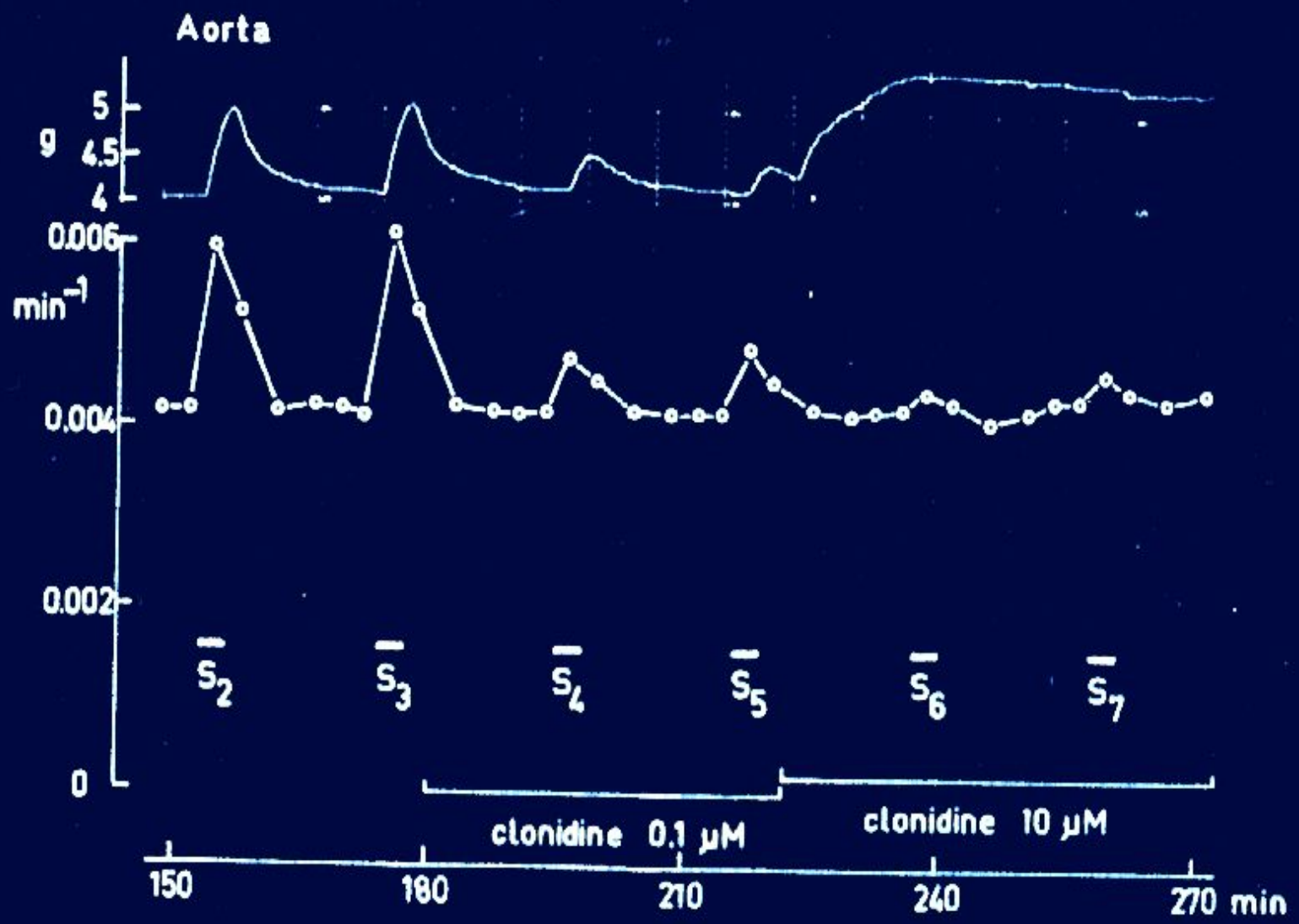
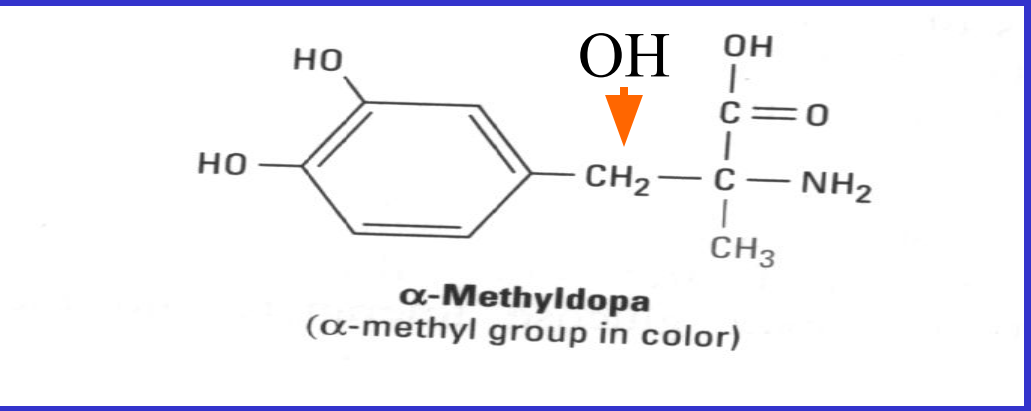


Fig. 15: Pressor effect of low doses of clonidine in the pithed rat. The rise in blood pressure is due to the peripheral α-sympathomimetic properties of clonidine

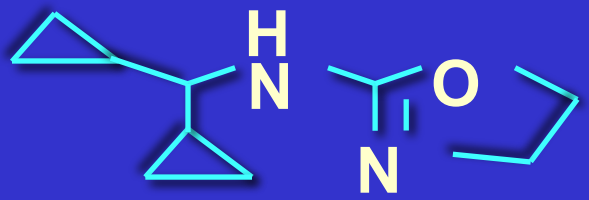

Aorta
g
5
4.5
4
0.006
min⁻¹
0.004
0.002
0
$\bar{S}_2$
$\bar{S}_3$
$\bar{S}_4$
$\bar{S}_5$
$\bar{S}_6$
$\bar{S}_7$
clonidine 0.1 μM
clonidine 10 μM
150
180
210
240
270 min

# Гипотензивные средства центрального действия



Clonidine

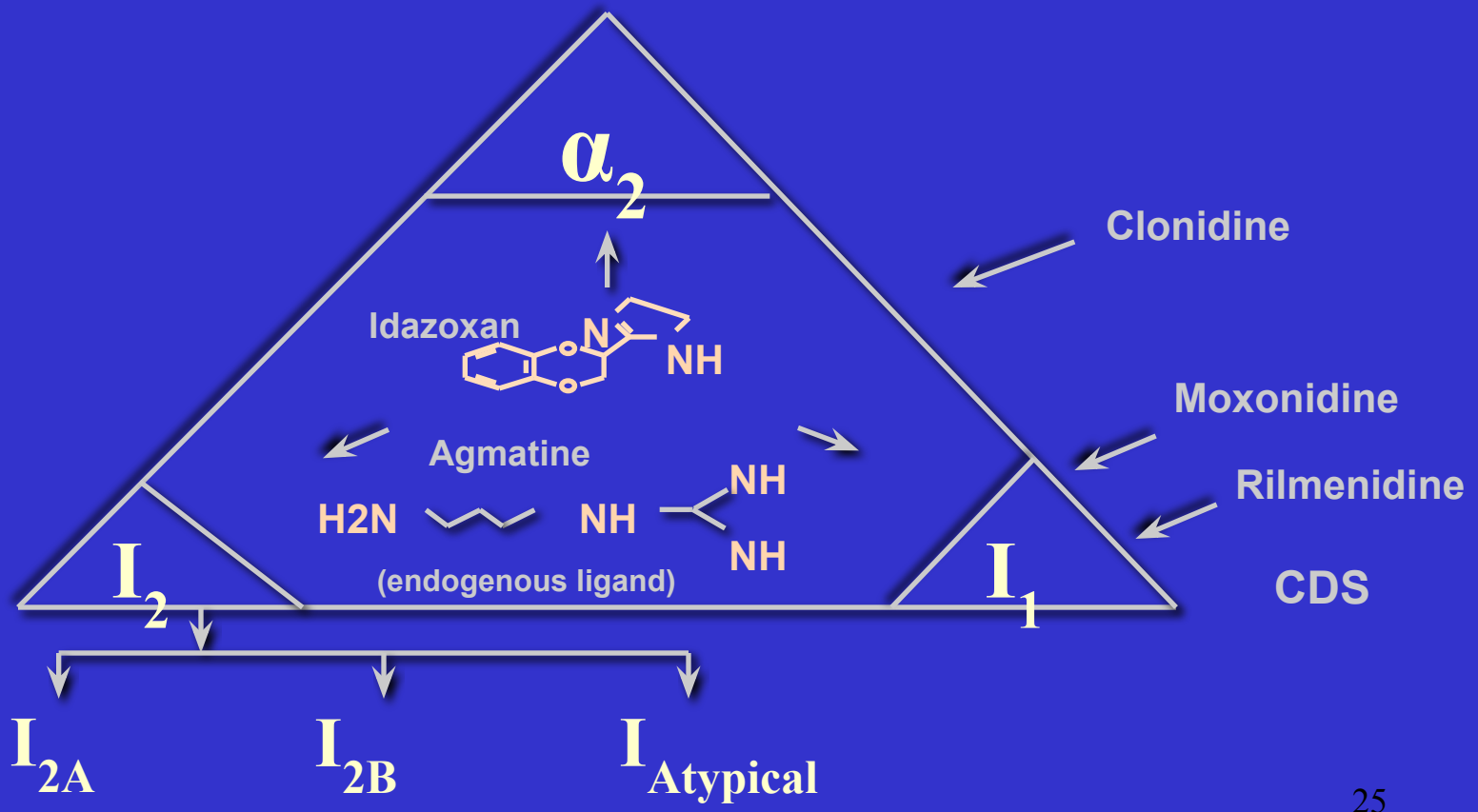
Moxonidine




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 |

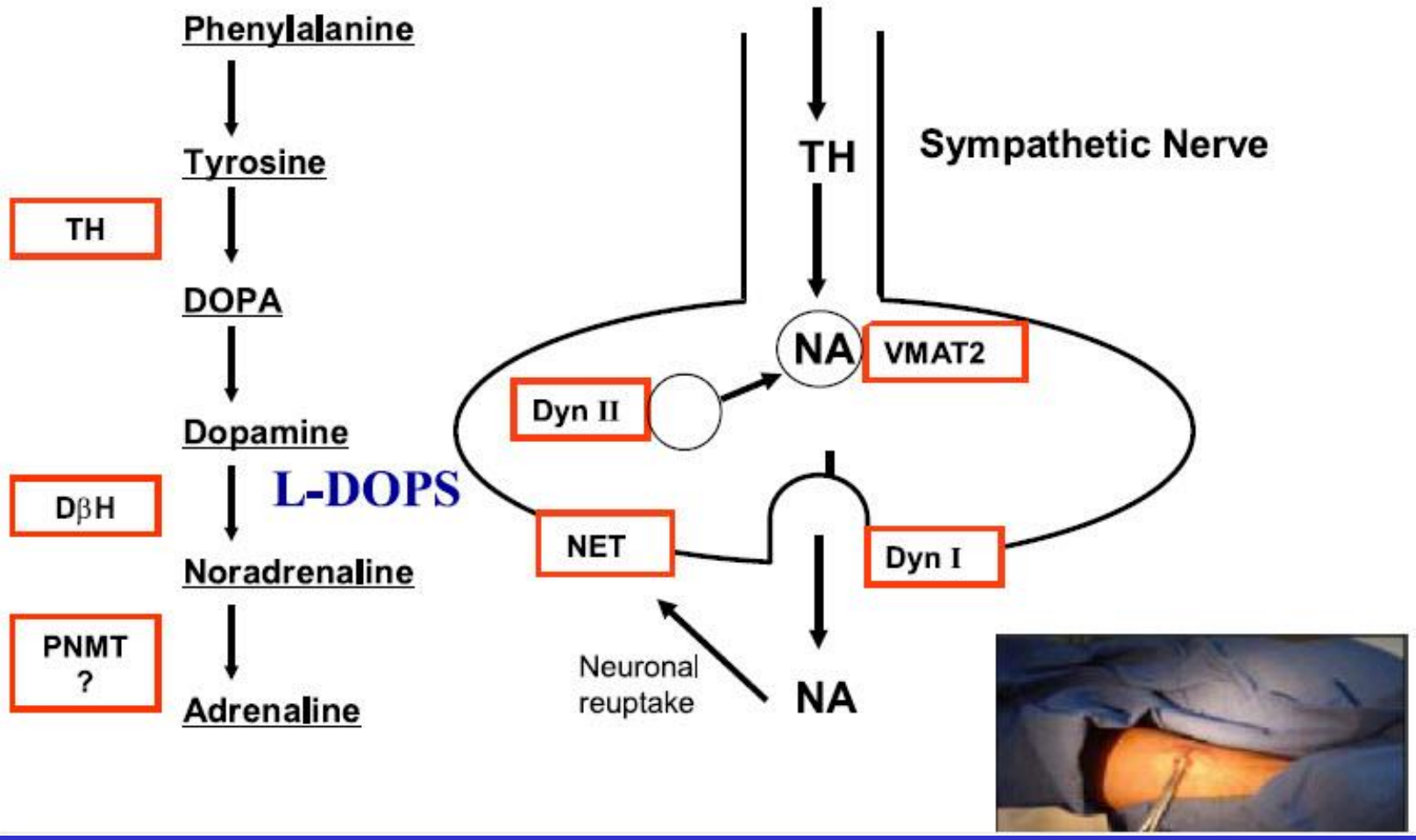
# Схема фармакологических взаимоотношений между а $_2$-адренорецепторами, $I_1$- и $I_2$-рецепторами



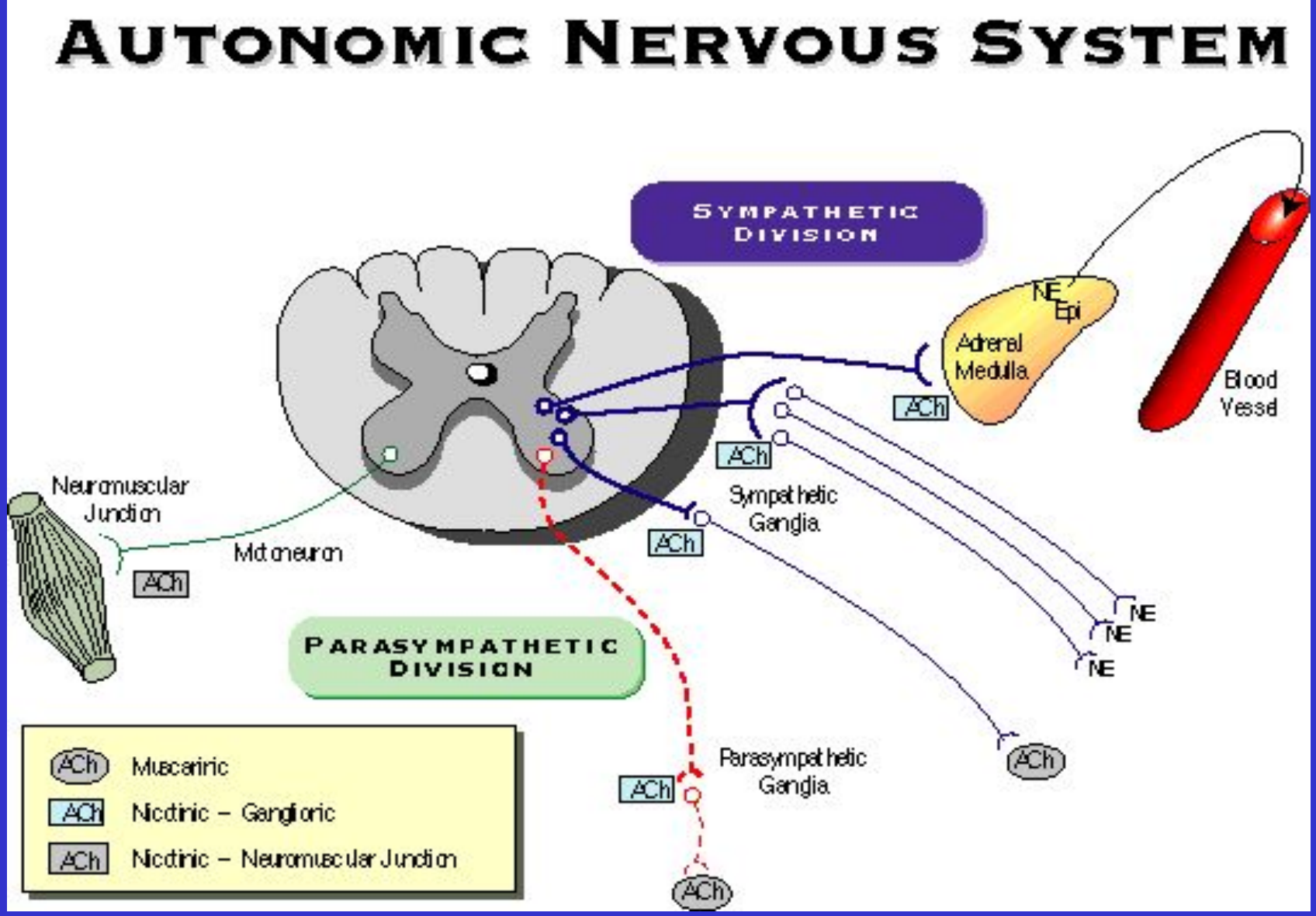



*Nutt et al., Annals New York Academy of Sciences, 1995*

# 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**

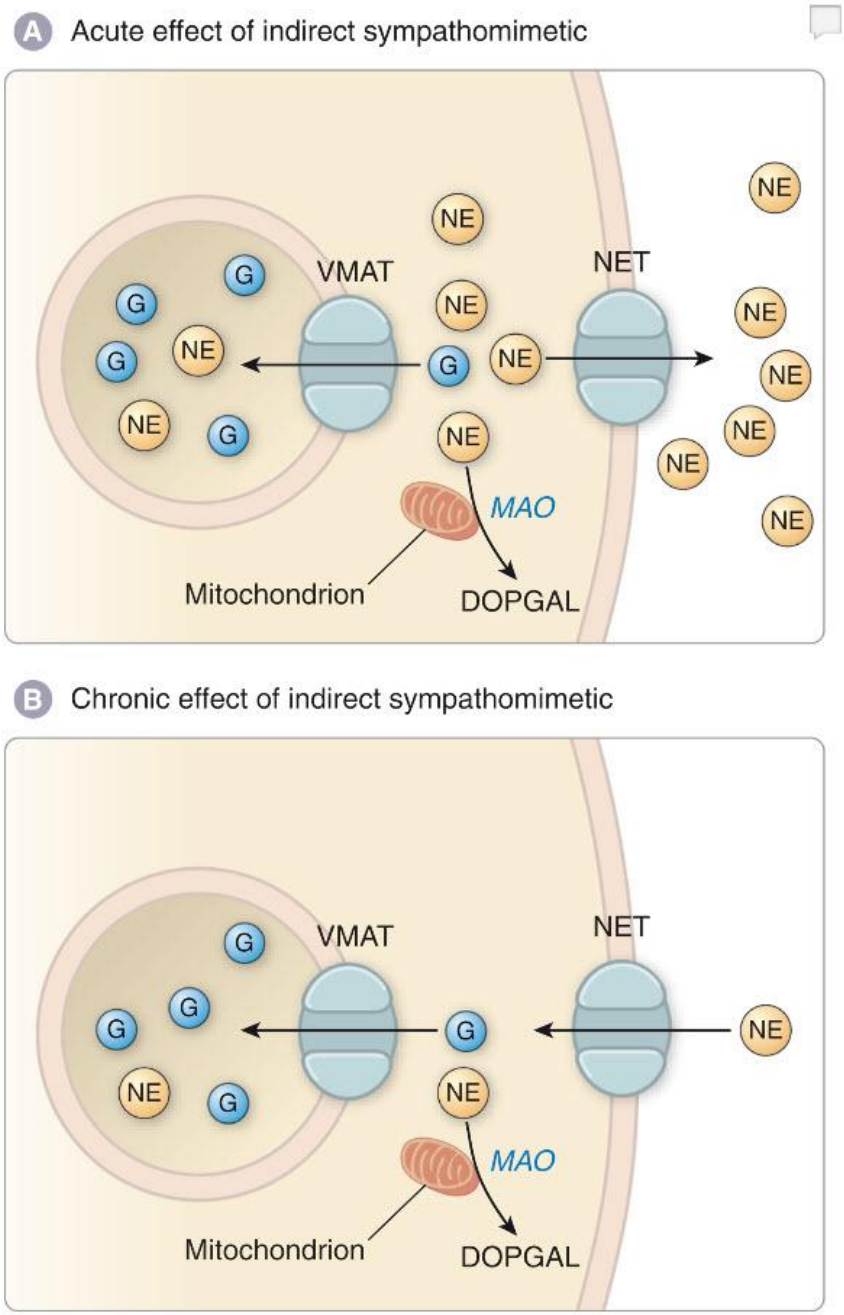
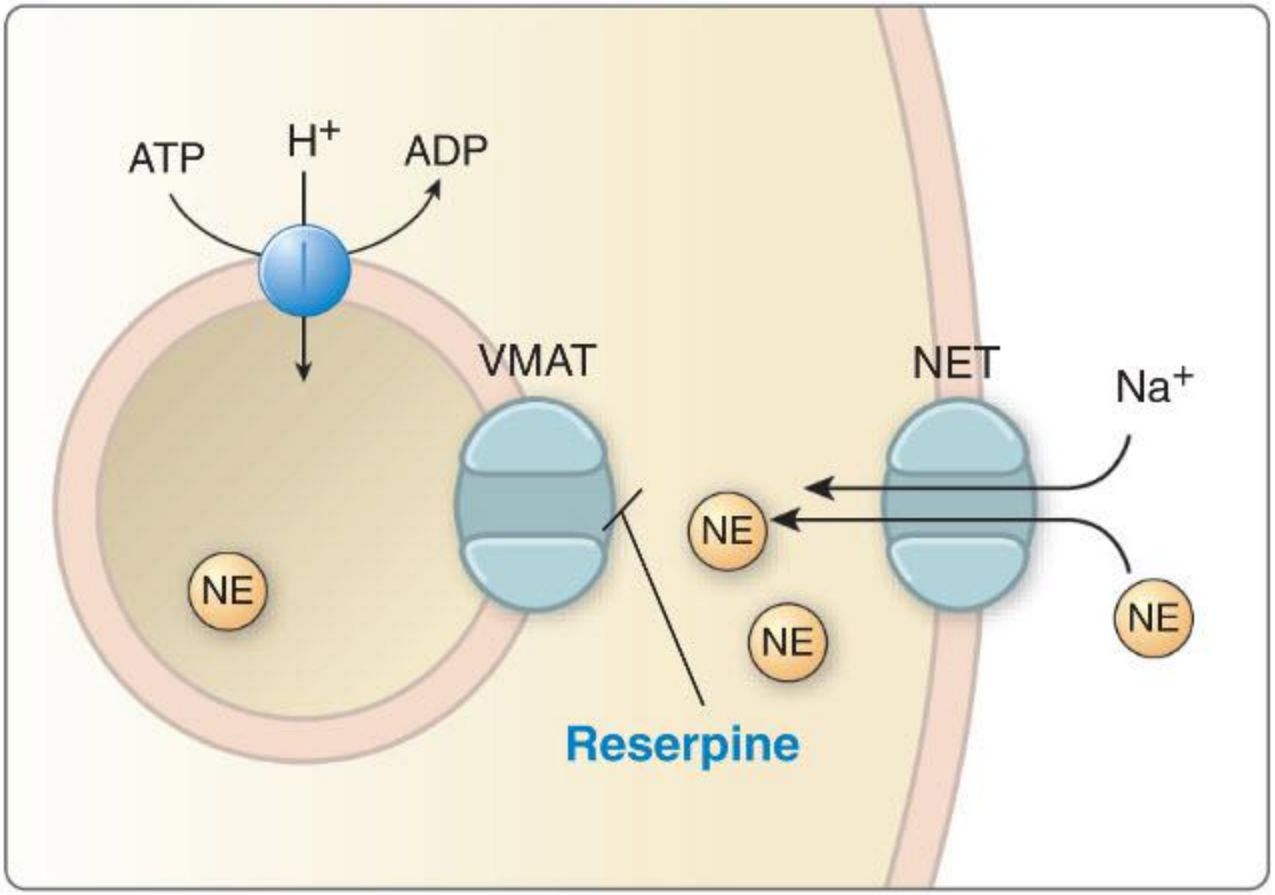



**Figure 10-4**: Acute and chronic effects of indirect sympathomimetics. Indirect symp...

# 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.

3. Cocaine, TCA block membrane transport of G

Noradrenergic varicosity or nerve ending

2. G displaces NE from vesicles and depletes stores

Vesicle

Axon

$Na^+$ channel

4. Tyramine, amphetamine, and reserpine release G from vesicles

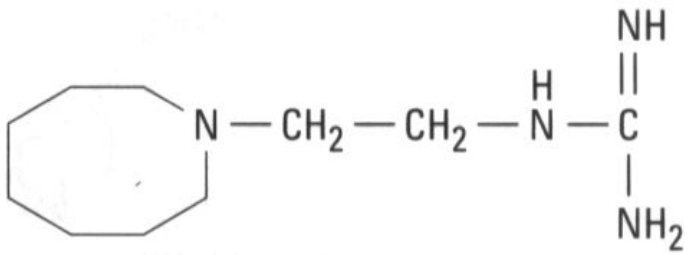
$Ca^{2+}$

$Ca^{2+}$ channel

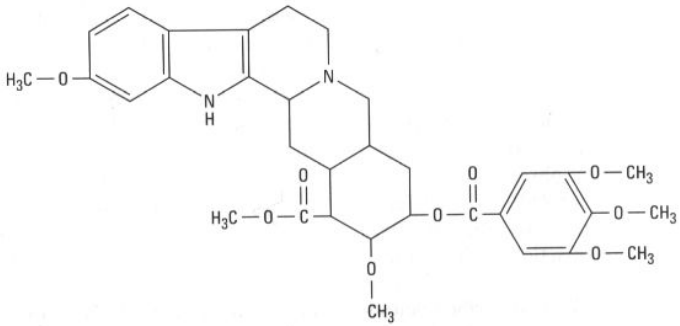
Junctional cleft

1. G blocks physiologic release of NE

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



**Guanethidine**



**Reserpine**

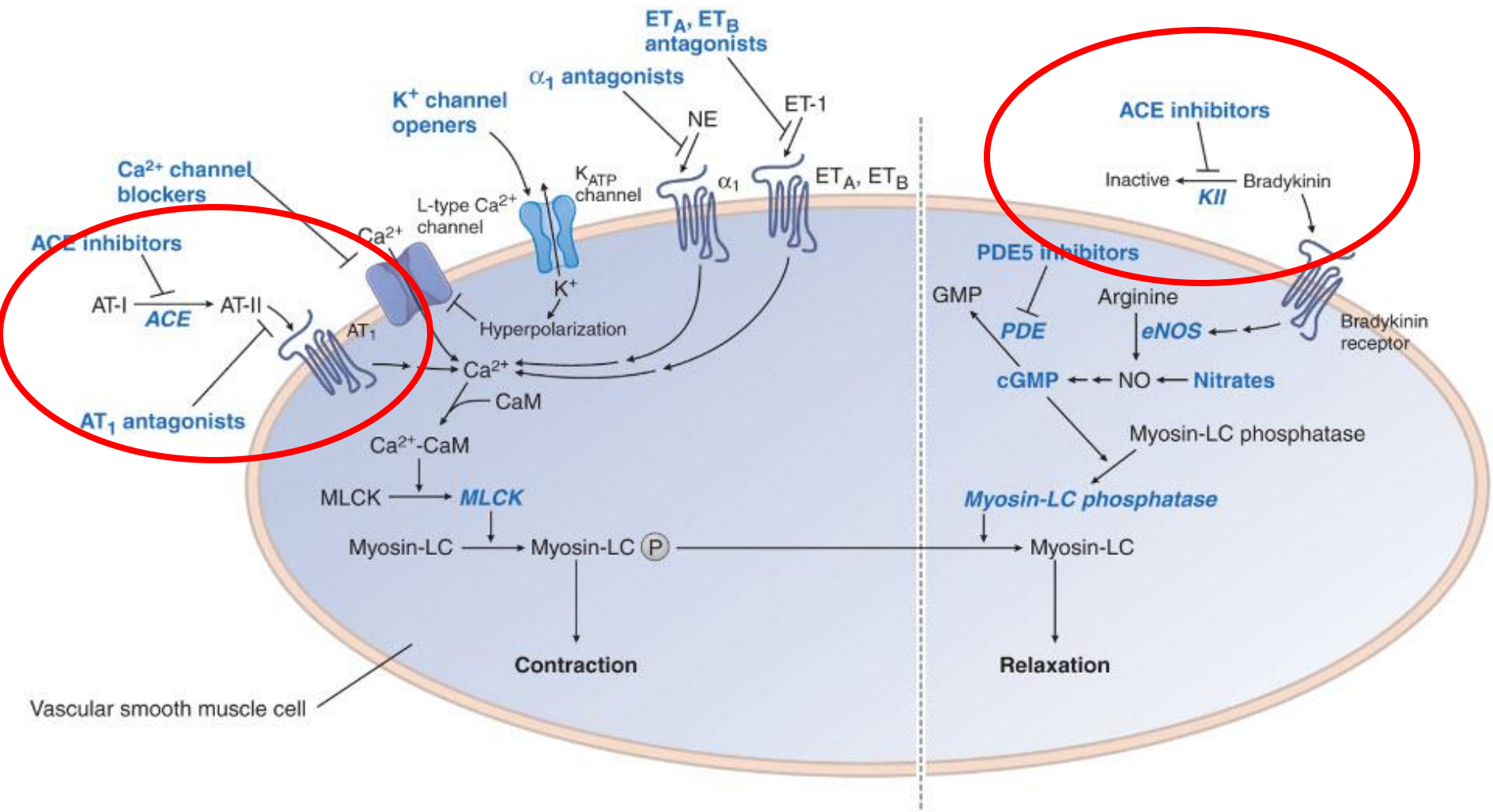
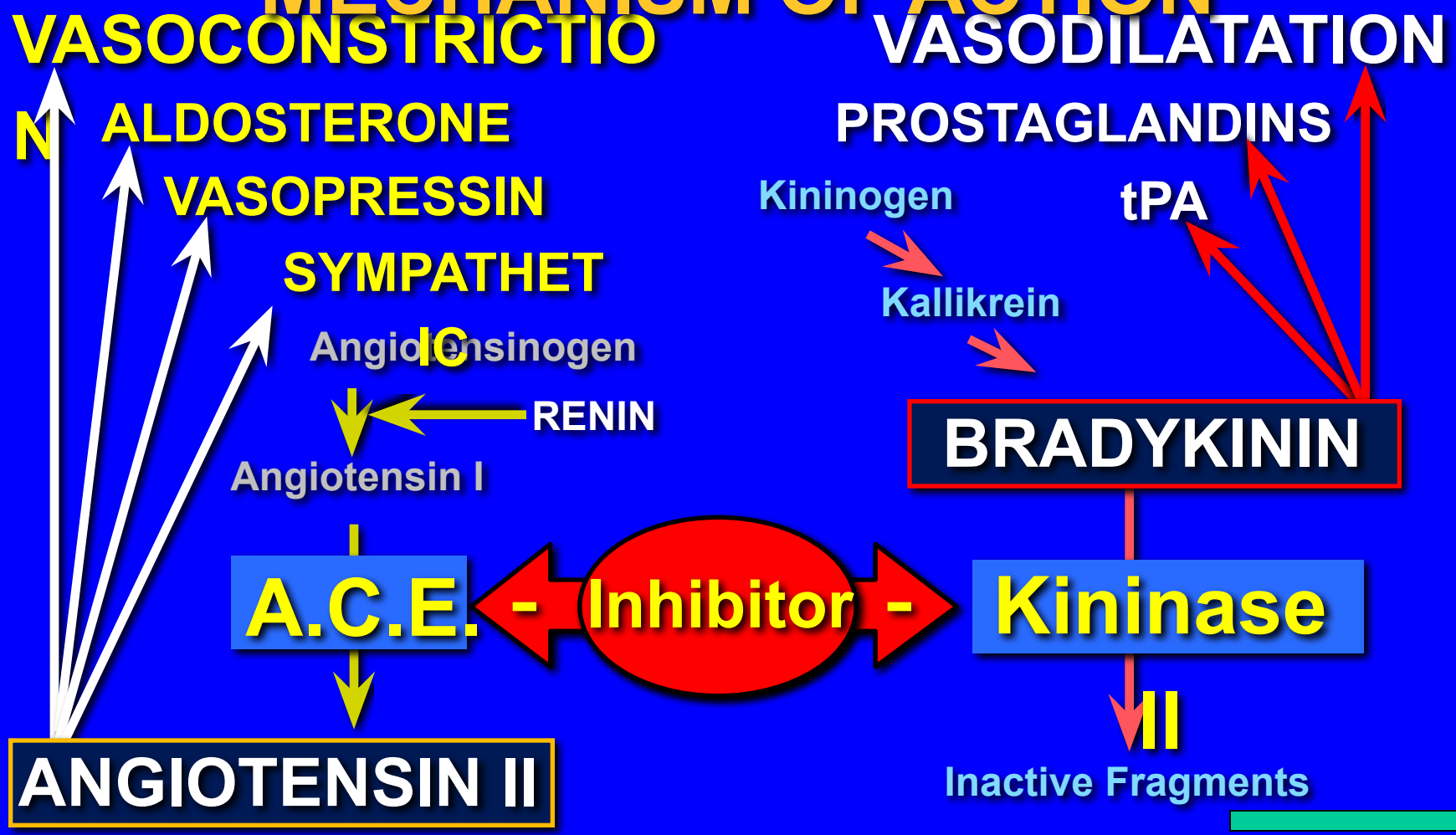



**Figure 21-6**: Sites of action of vasodilators. Vasodilators act at several sites in the vascular smooth muscle cell. **Left pa...**

# ACEI

## MECHANISM OF ACTION



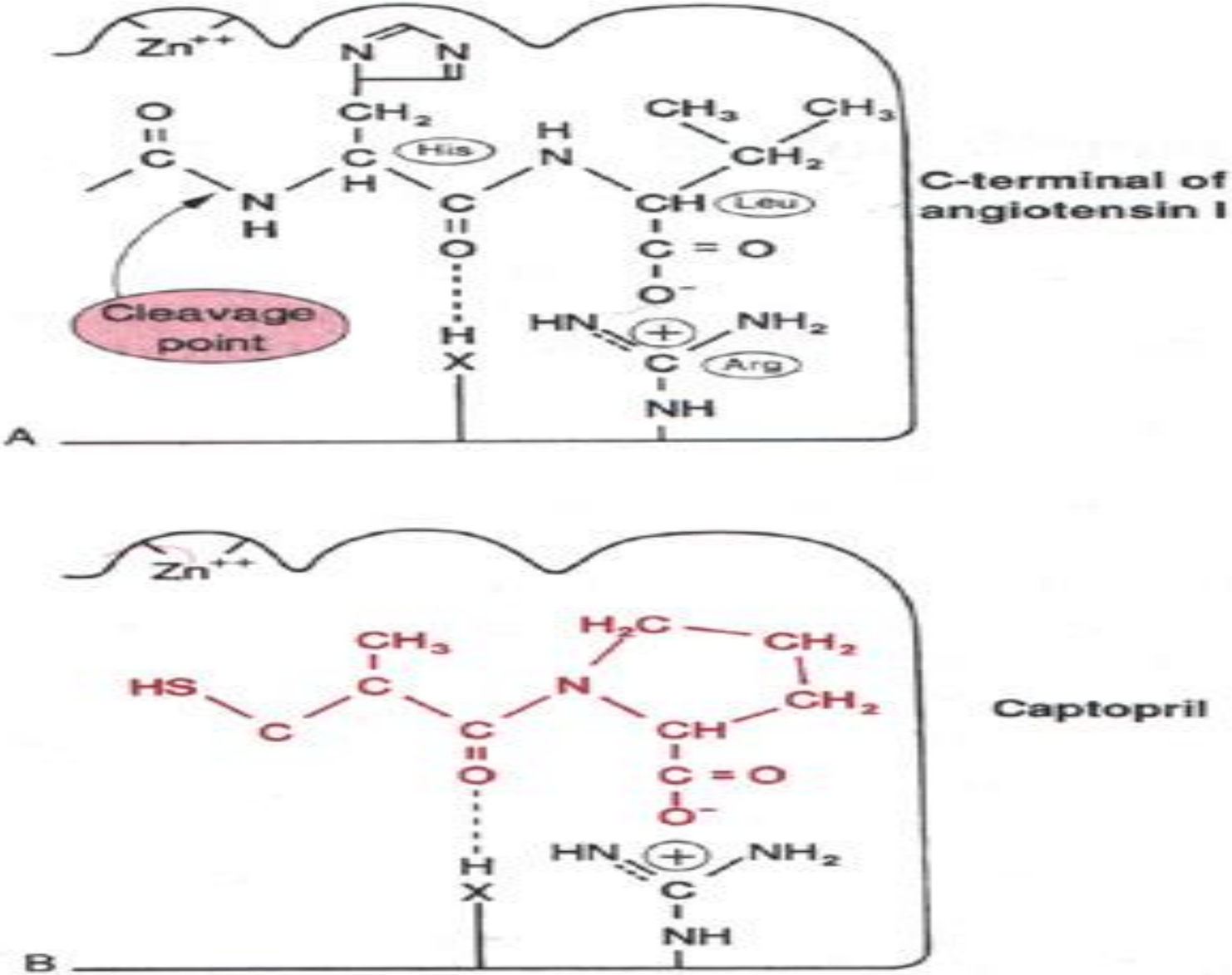
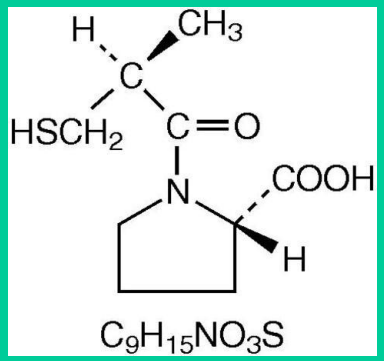


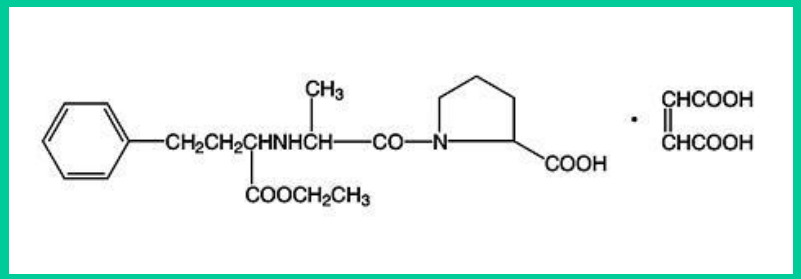

**Fig. 14.6 The active site of angiotensin-converting enzyme. A.** Binding of angiotensin I. **B.** Binding of the inhibitor, captopril, which is an analogue of the terminal dipeptide of angiotensin I.

- Ингибиторы ангиотензин-превращающего фермента

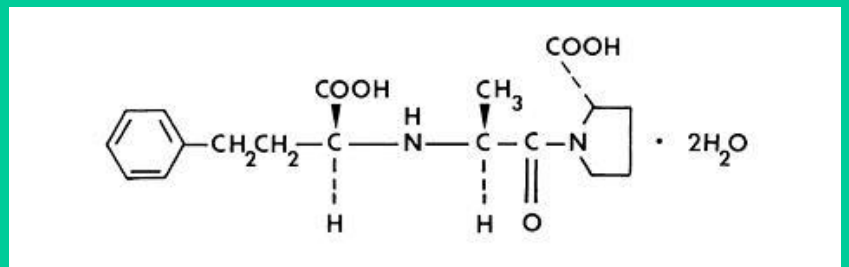



- каптоприл

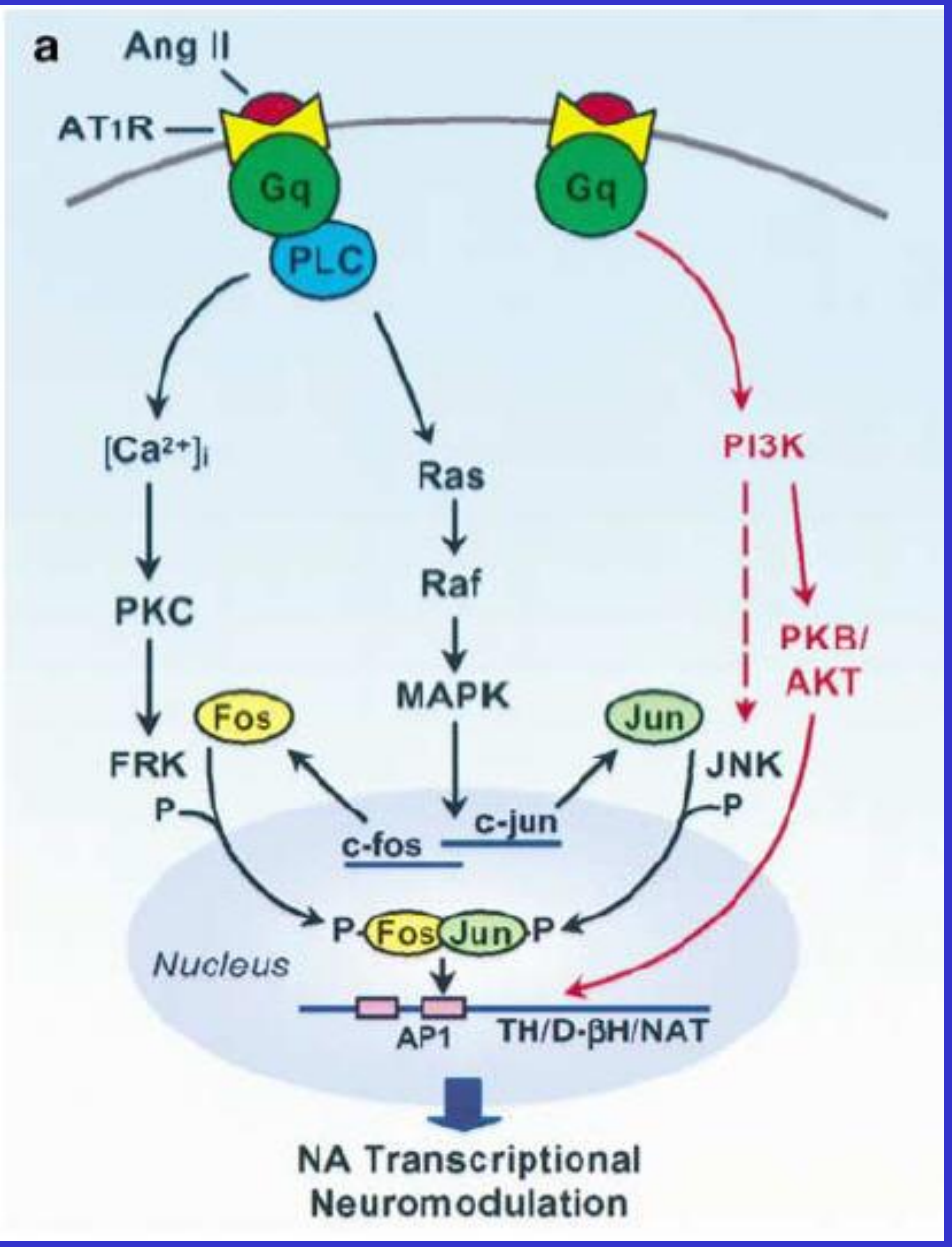
- Эналаприл

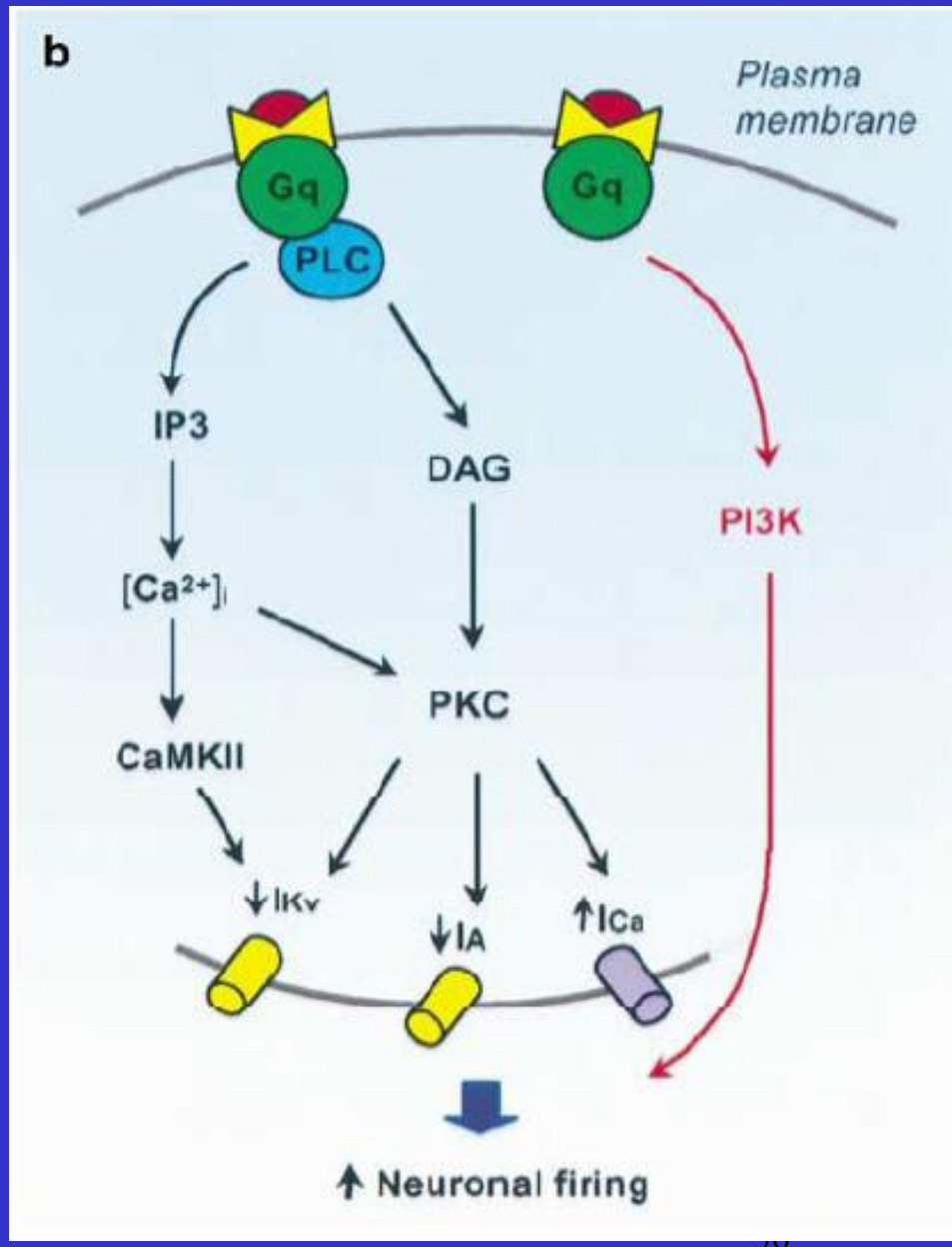


Эналаприлат



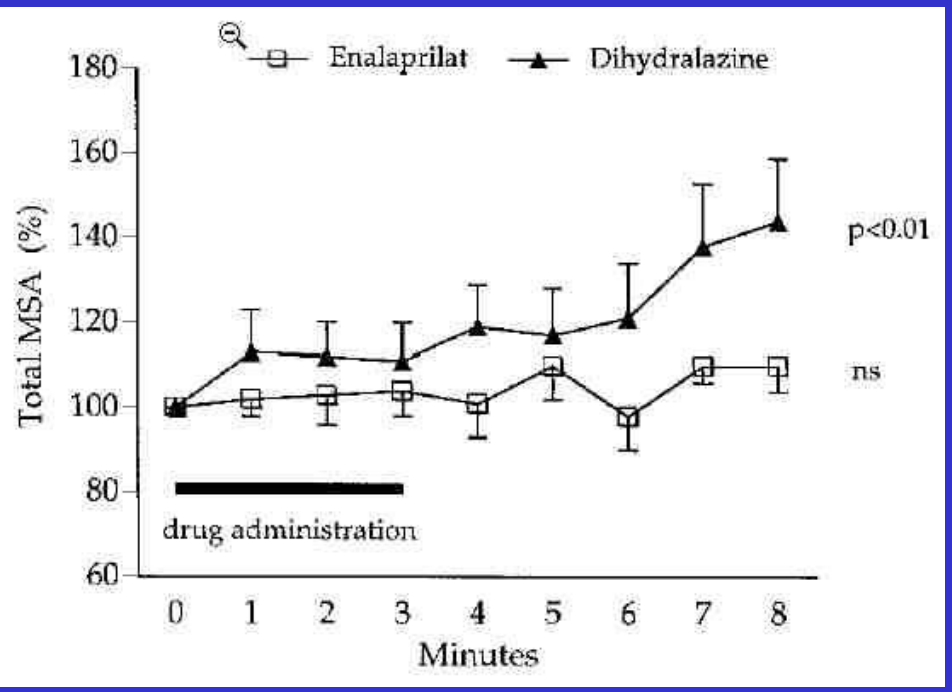
# Ренин-анг система мозга

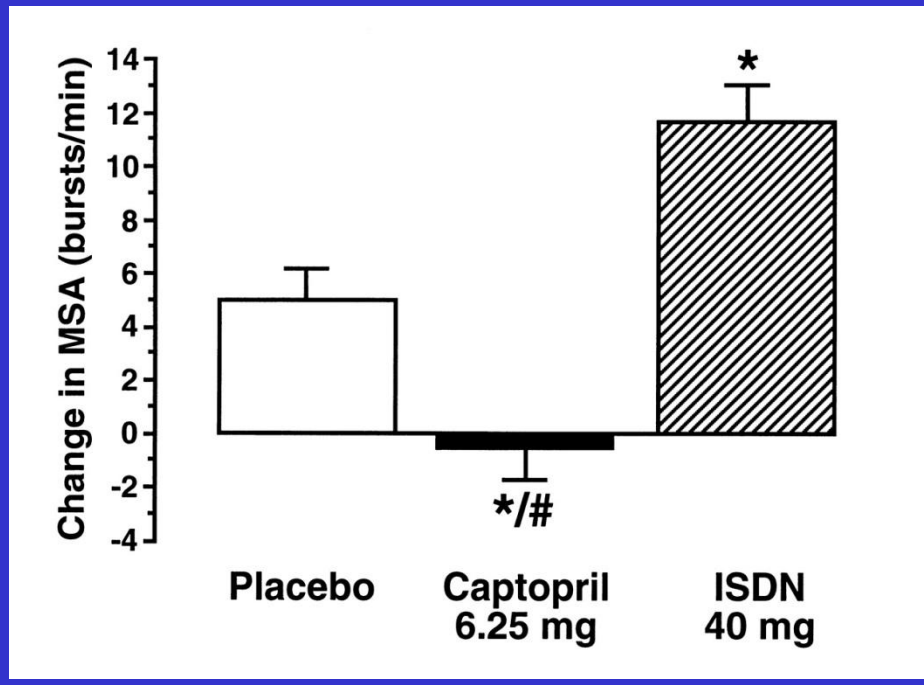



British Journal of Pharmacology (2003) 139, 191–202

# Способность ингибиторов АПФ подавлять симпатическую активность у человека




(Johanson et al., 2000)

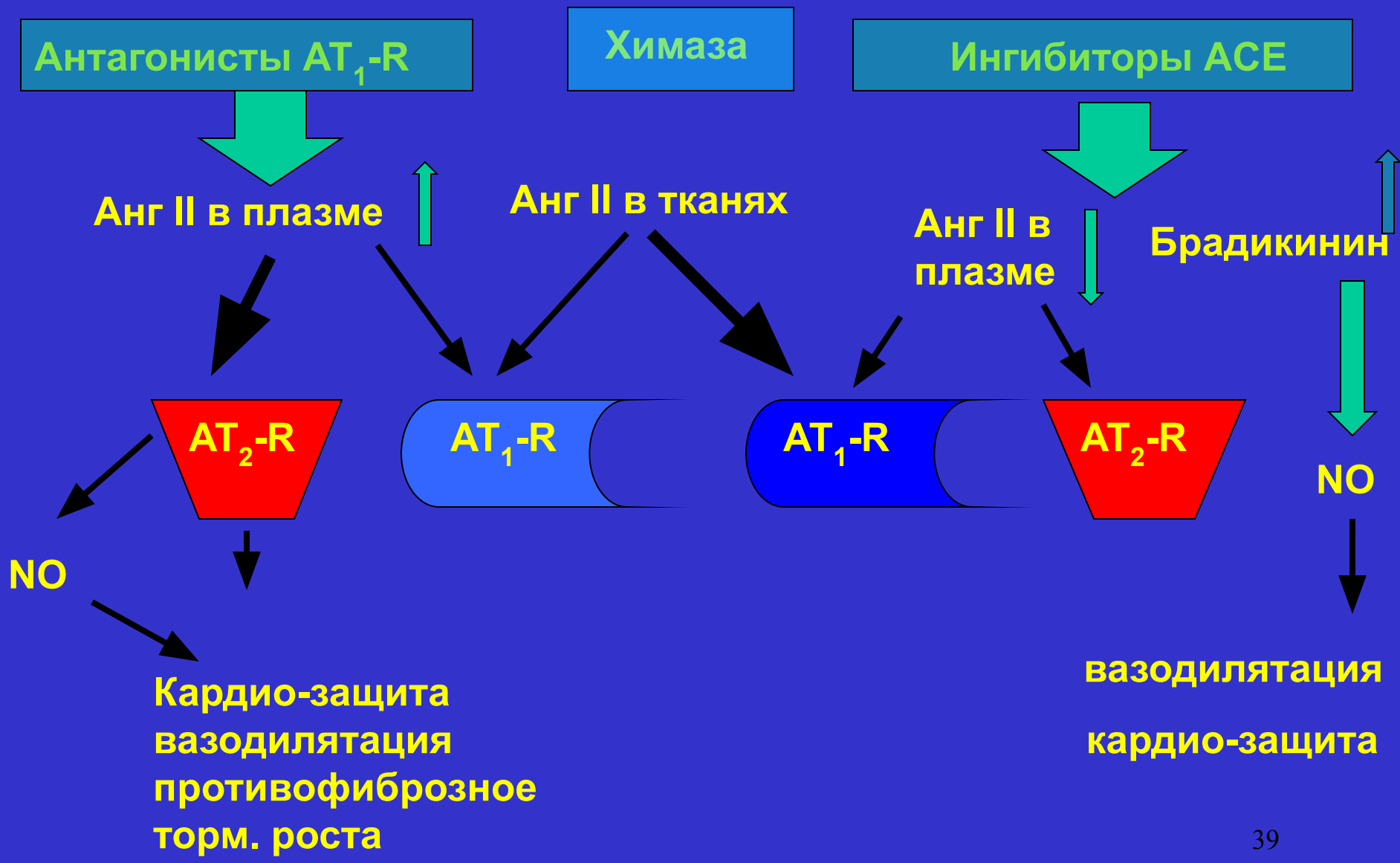
(Corti et al., 2000)

## 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 |

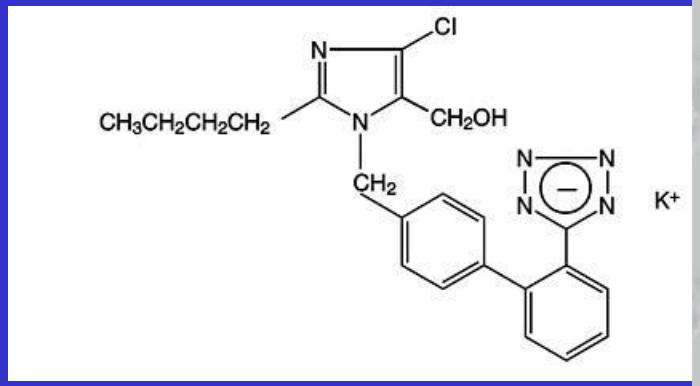
**Обзор H. Matsubara, Circ. Res. 1998;83:1182-1191)**

# Различие эффектов ингибиторов ACE и блокаторов $AT_1$-рецепторов

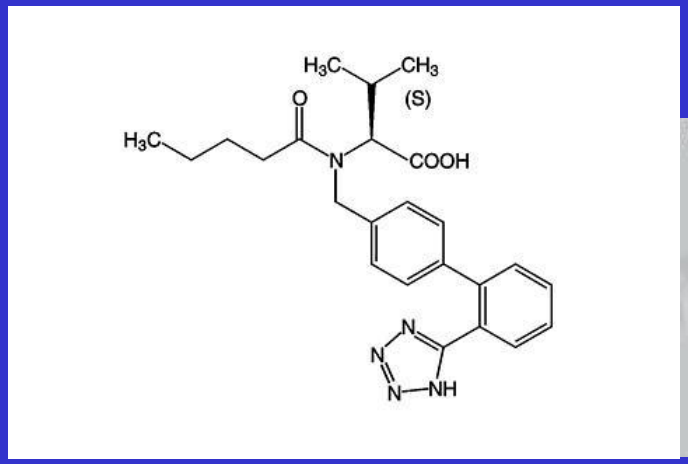


# Блокаторы Анг II ($AT_1$) рецепторов

- Лозартан



- Валзартан



# Блокаторы Анг I рецепторов не увеличивают симпатическую активность

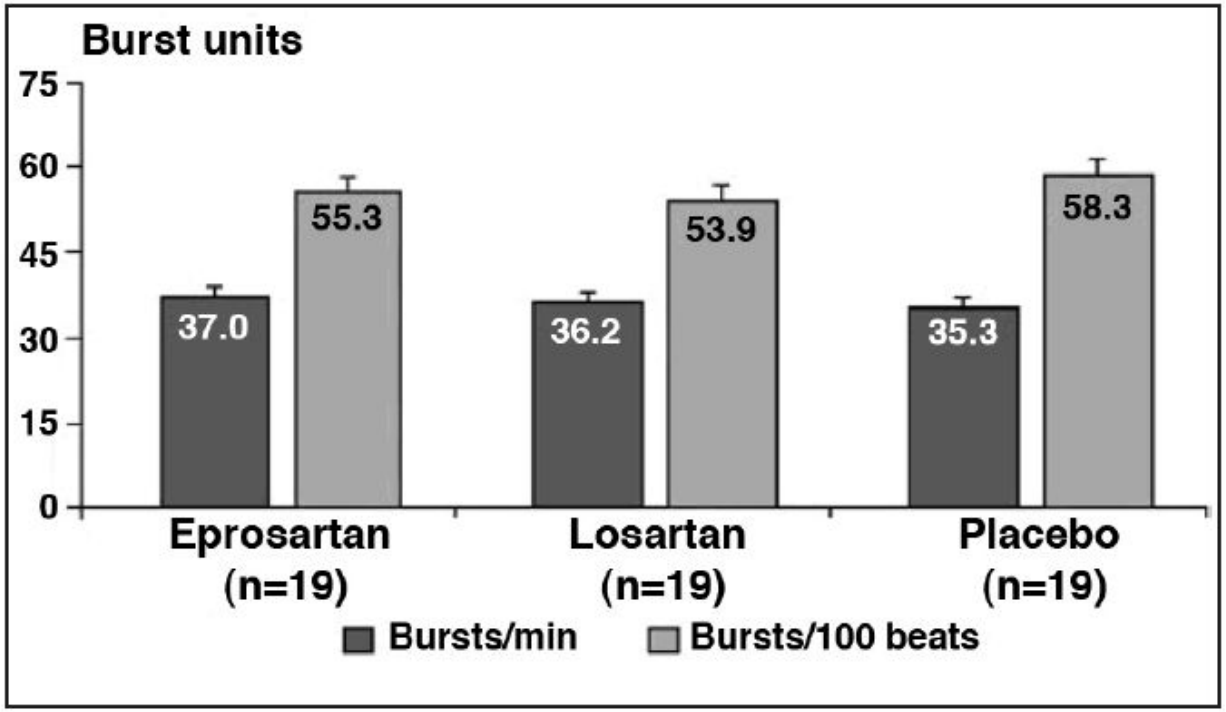


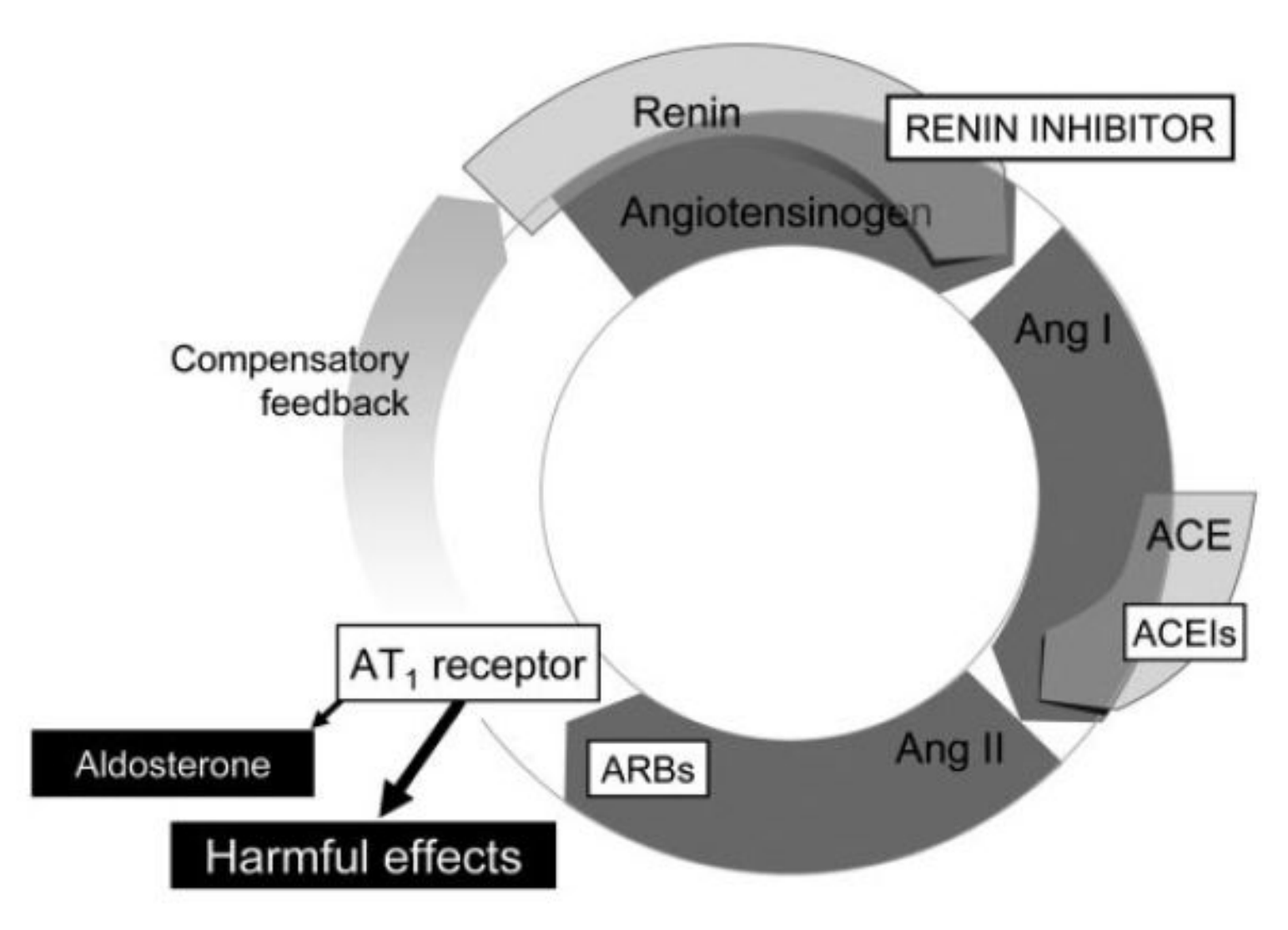

*Figure 2. Microneurographic assessment of efferent sympathetic nerve traffic to the skeletal muscle vasculature (muscle sympathetic nerve activity), indicative of central sympathetic outflow, assessed as bursts/minute and bursts/100 beats after 4-week therapy with eprosartan, losartan, or placebo. Data 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

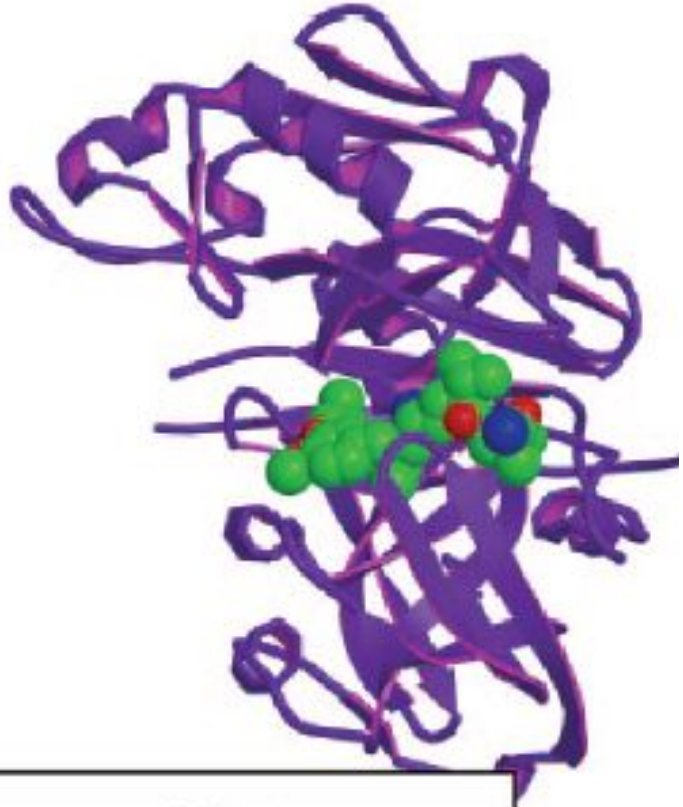
*M.Esler et al., Hypertension 2006; 48; 787-796*

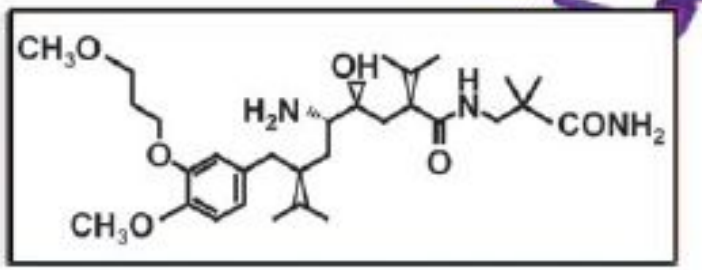
# Ингибиторы ренина

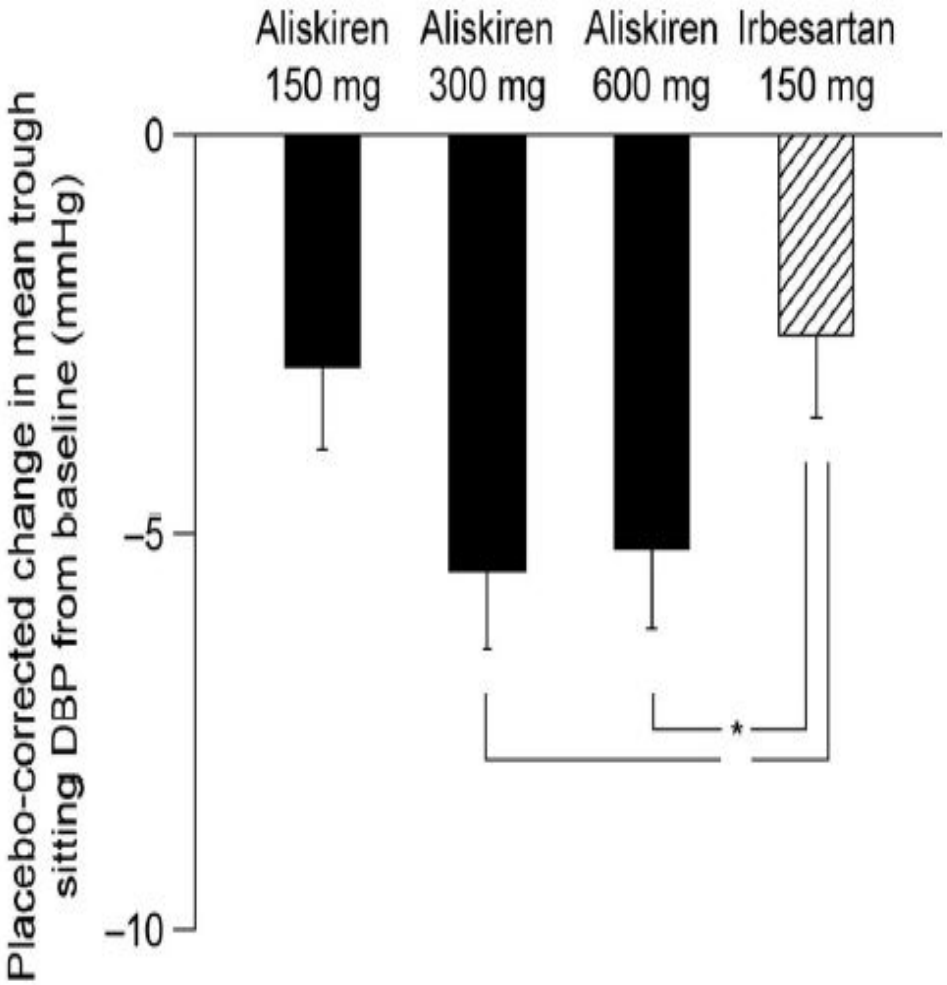



*Clin J Am Soc Nephrol 1: 221–228, 2006.*

# Aliskiren – первый пероральный ингибитор ренина






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

# Сосудорасширяющие средства

Блокаторы кальциевых каналов

Активаторы калиевых каналов

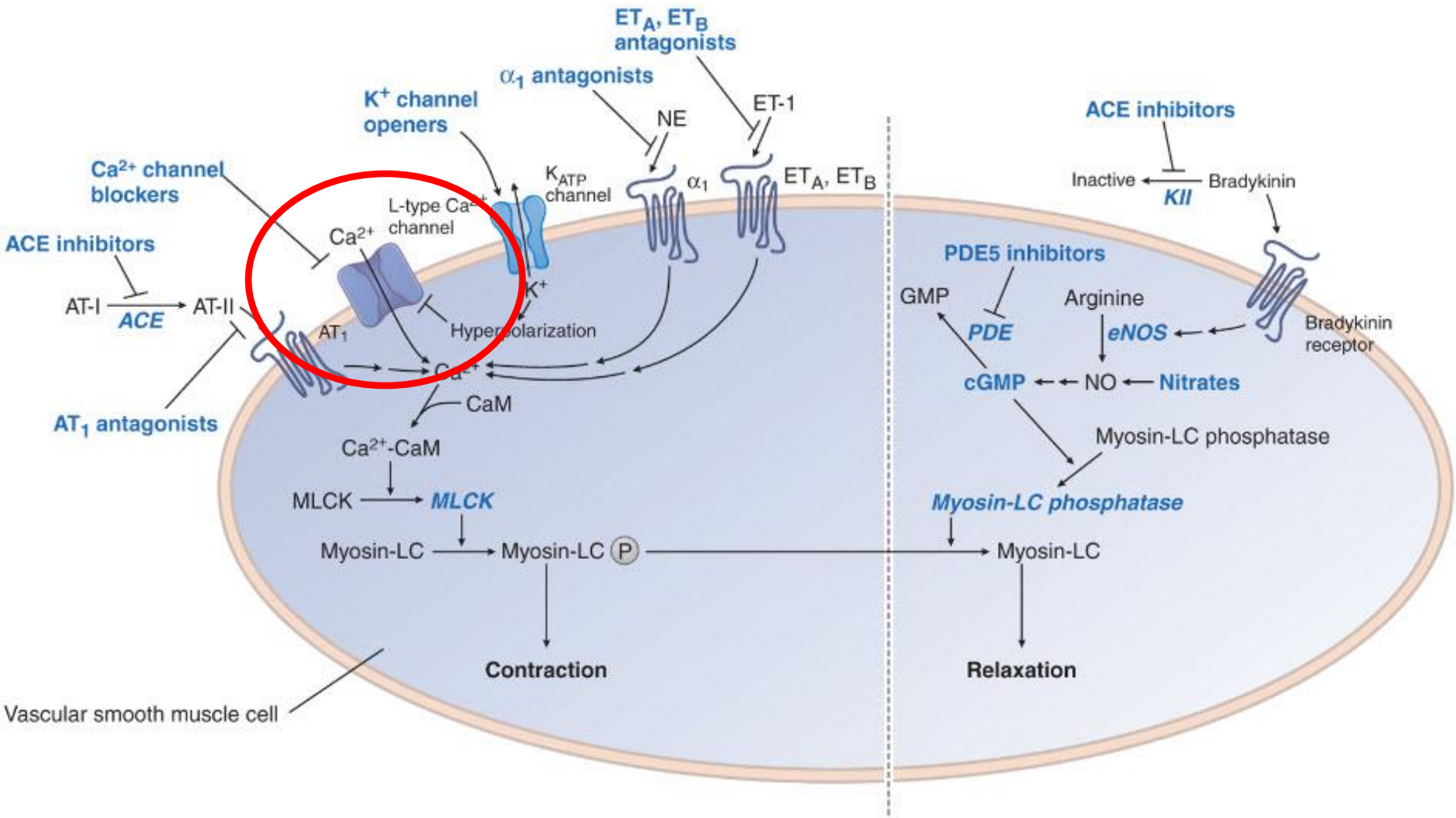
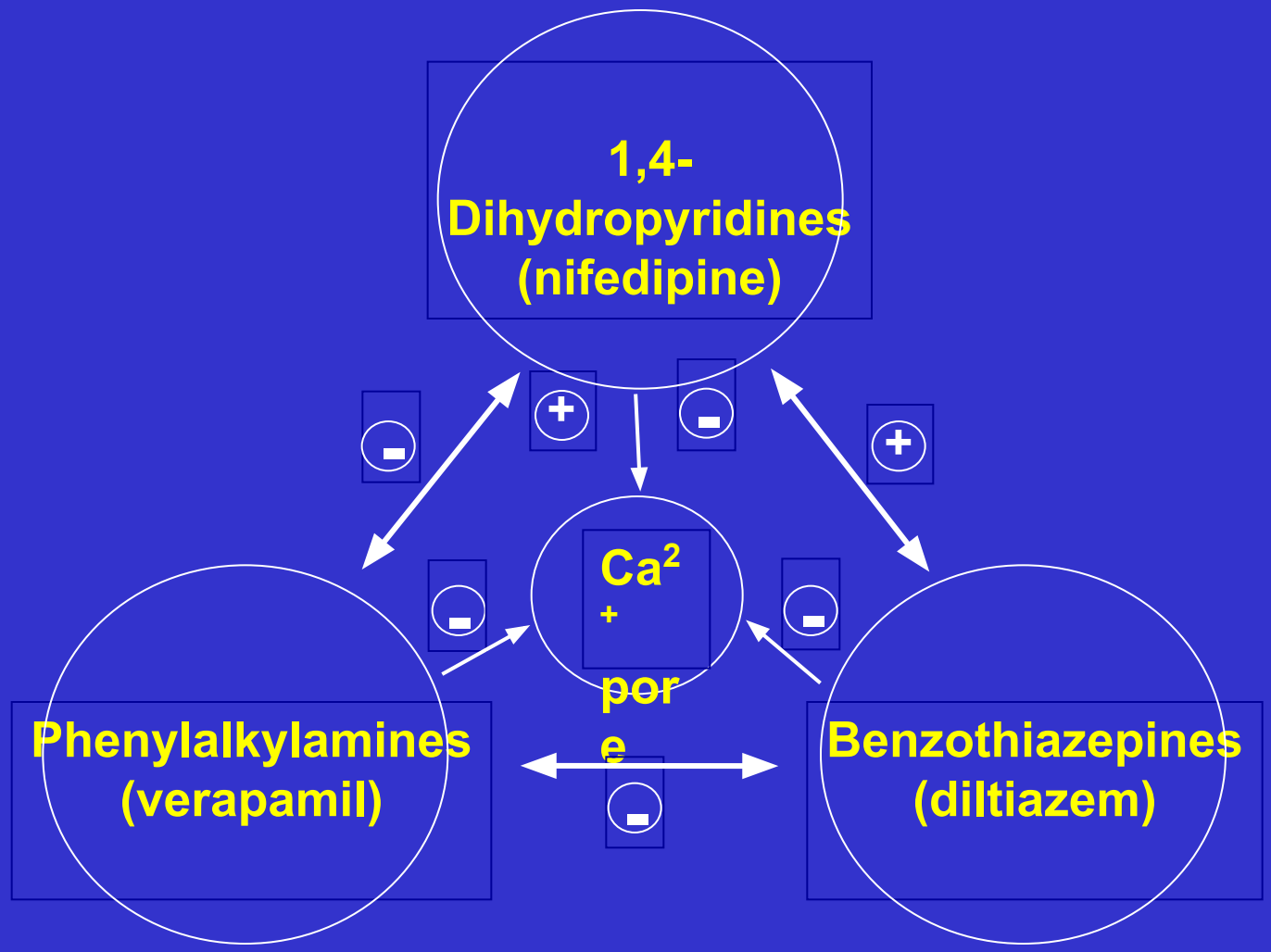



**Figure 21-6**: Sites of action of vasodilators. Vasodilators act at several sites in the vascular smooth muscle cell. **Left pa...**

# Три класса блокаторов кальциевых каналов

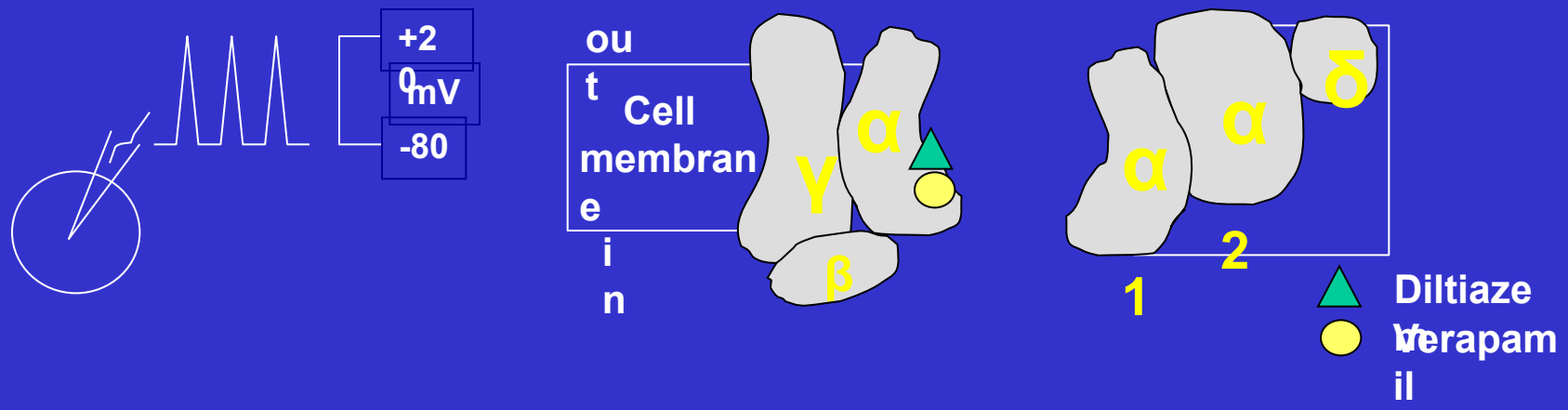
| Chemical Type | Chemical Names | Brand Names |
|---|---|---|
| Фенилалкиламины<br><br>Phenylalkylamines | verapamil | Calan,<br>Calna SR,<br>Isoptin SR,<br>Verelan |
| Бензотиазепины<br><br>Benzothiazepines | diltiazem | Cardizem CD,<br>Dilacor XR |
| Дигидропиридины<br><br>1,4-Dihydropyridines | Nifedipine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

# The Three Classes of CCBs Bind to Different Sites

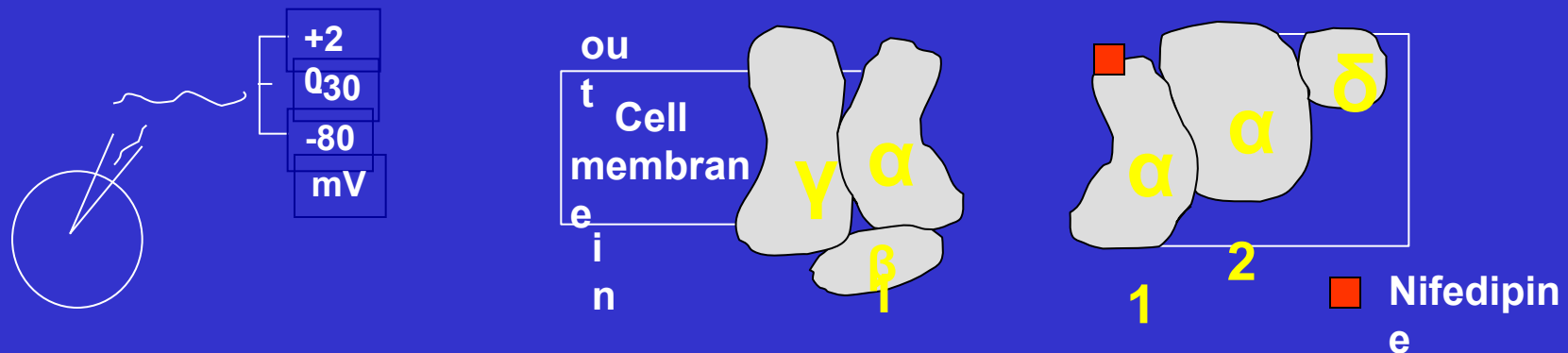


# Различие в местах связывания определяет различие в фармакологических эффектах

## Use-dependent binding (targets cardiac cells)



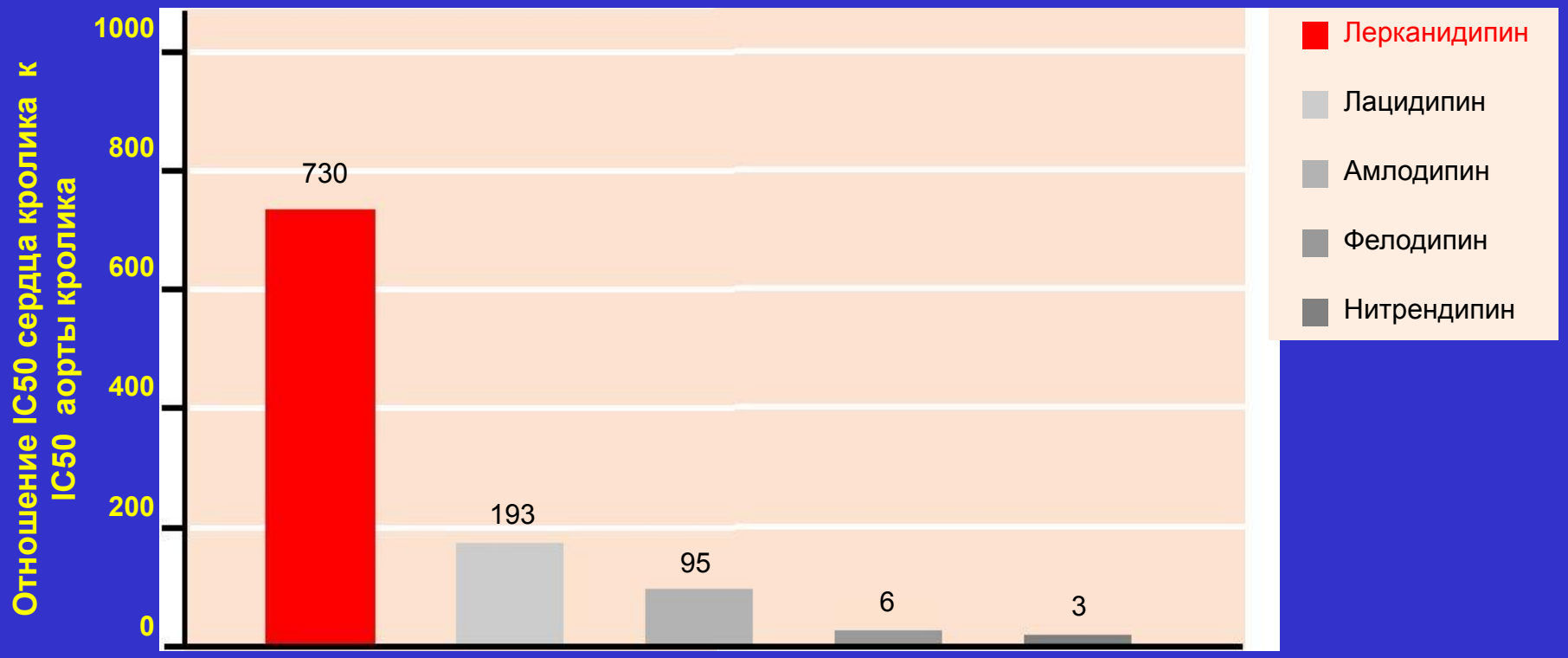

## Voltage-dependent binding (targets smooth muscle)



| | 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

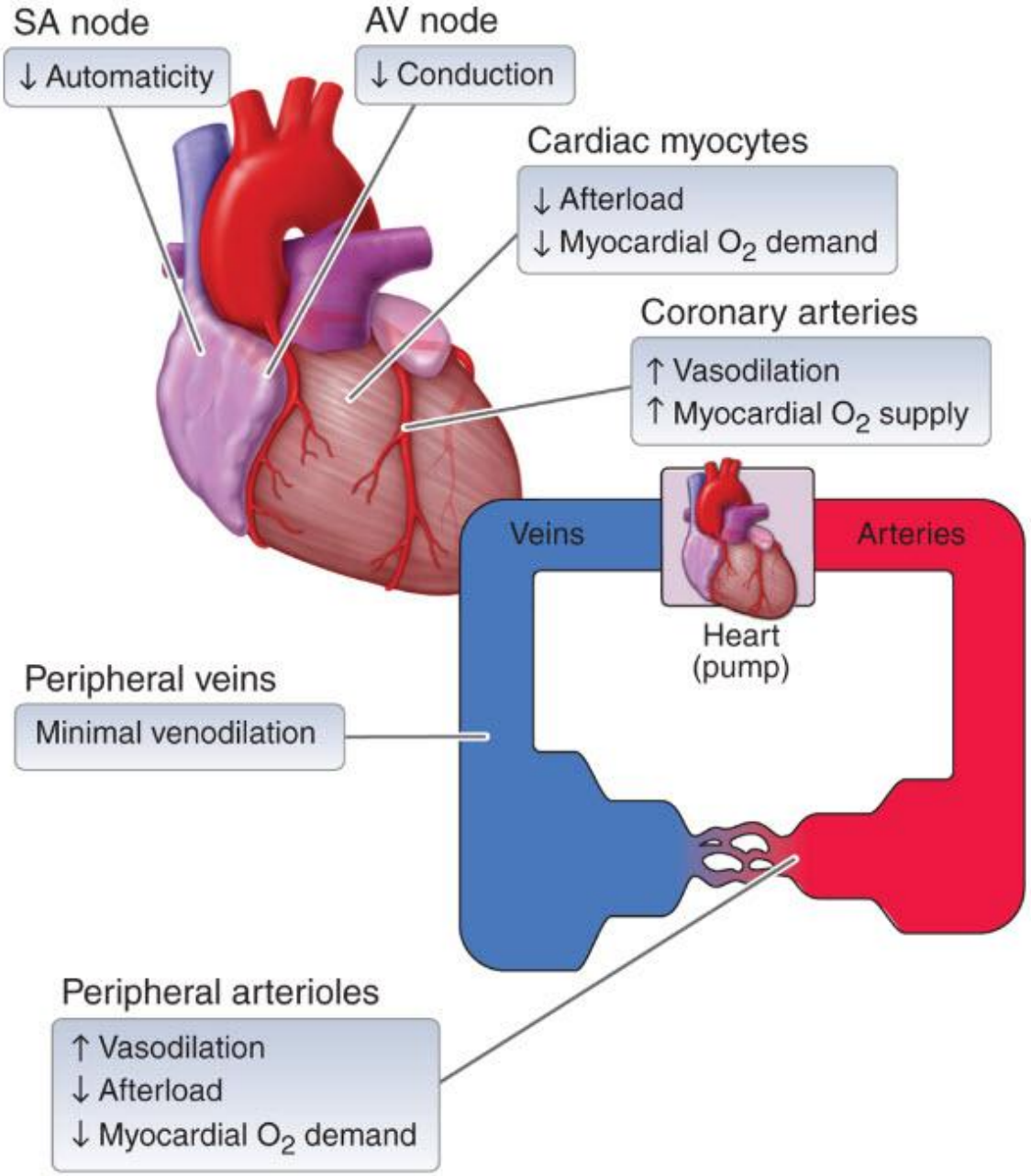



**Figure 21-11**: Sites of action of $Ca^{2+}$ channel blockers. $Ca^{2+}$ channel blockers dilate coronary arteries and peripheral arte...

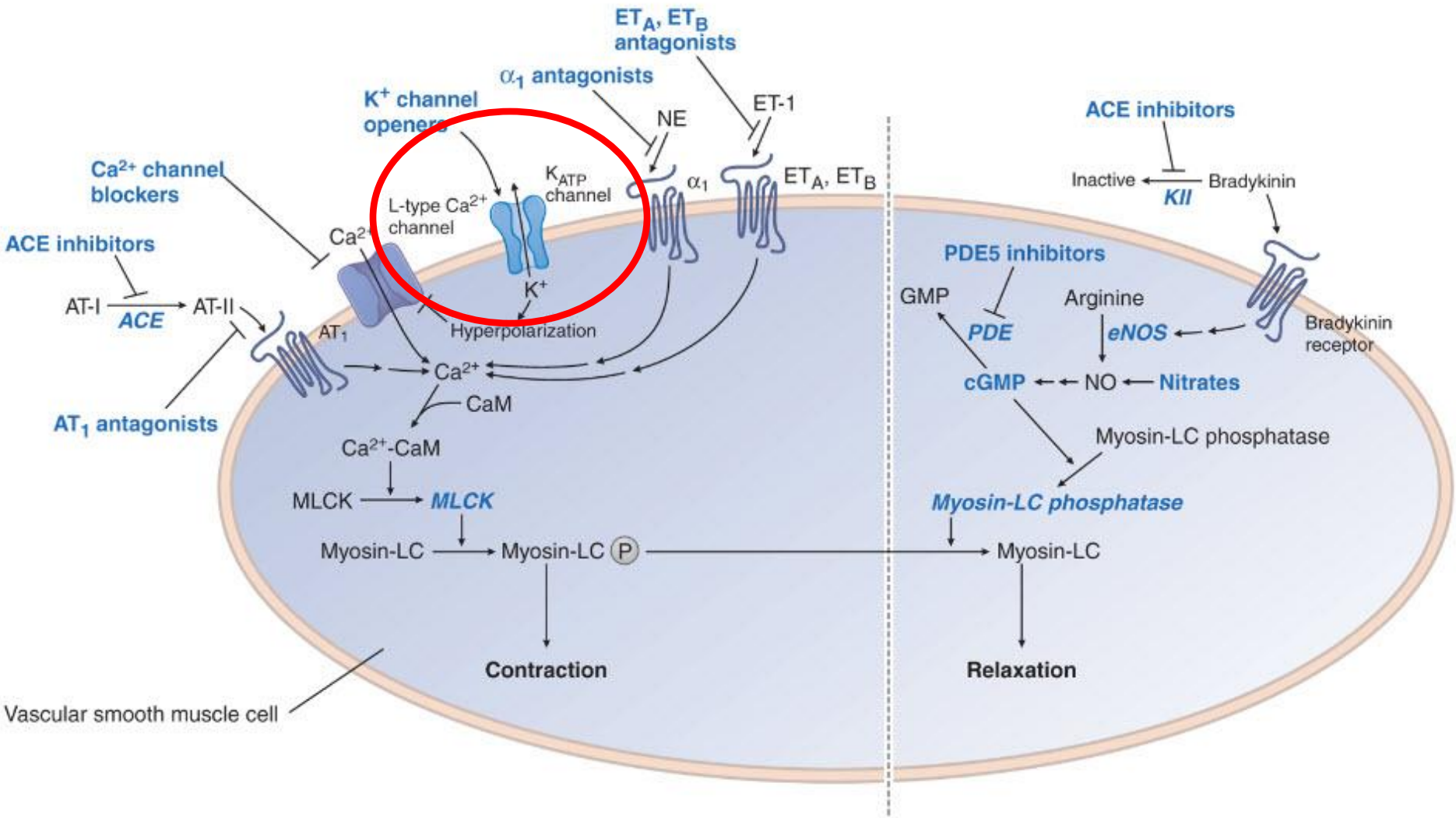
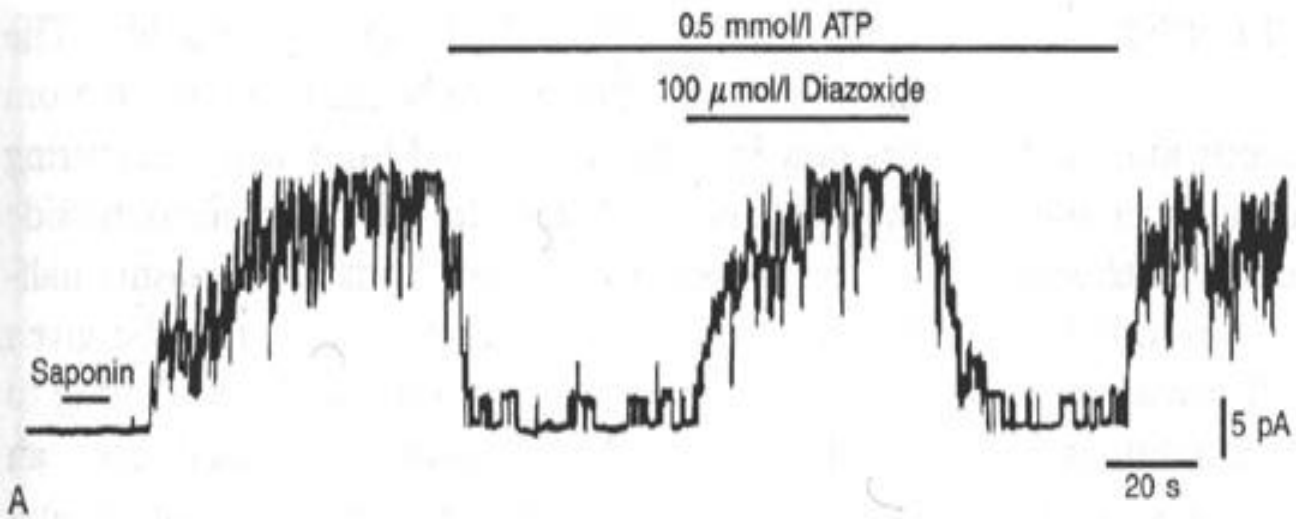



**Figure 21-6**: Sites of action of vasodilators. Vasodilators act at several sites in the vascular smooth muscle cell. **Left pa...**



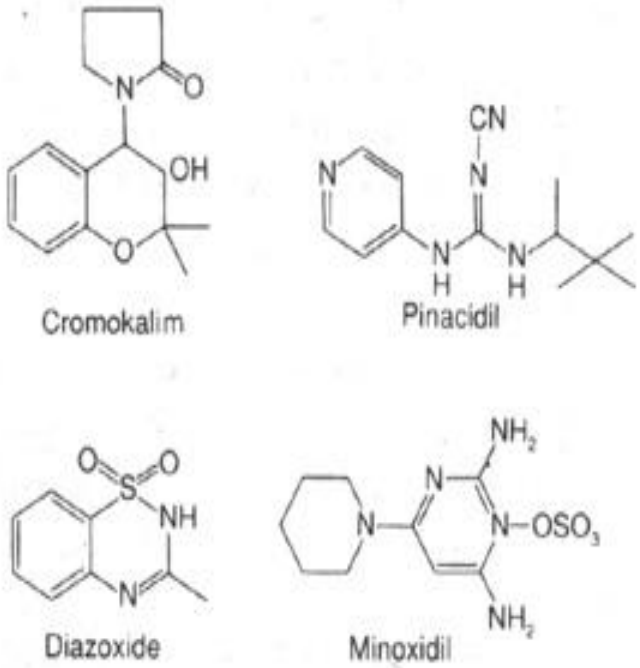
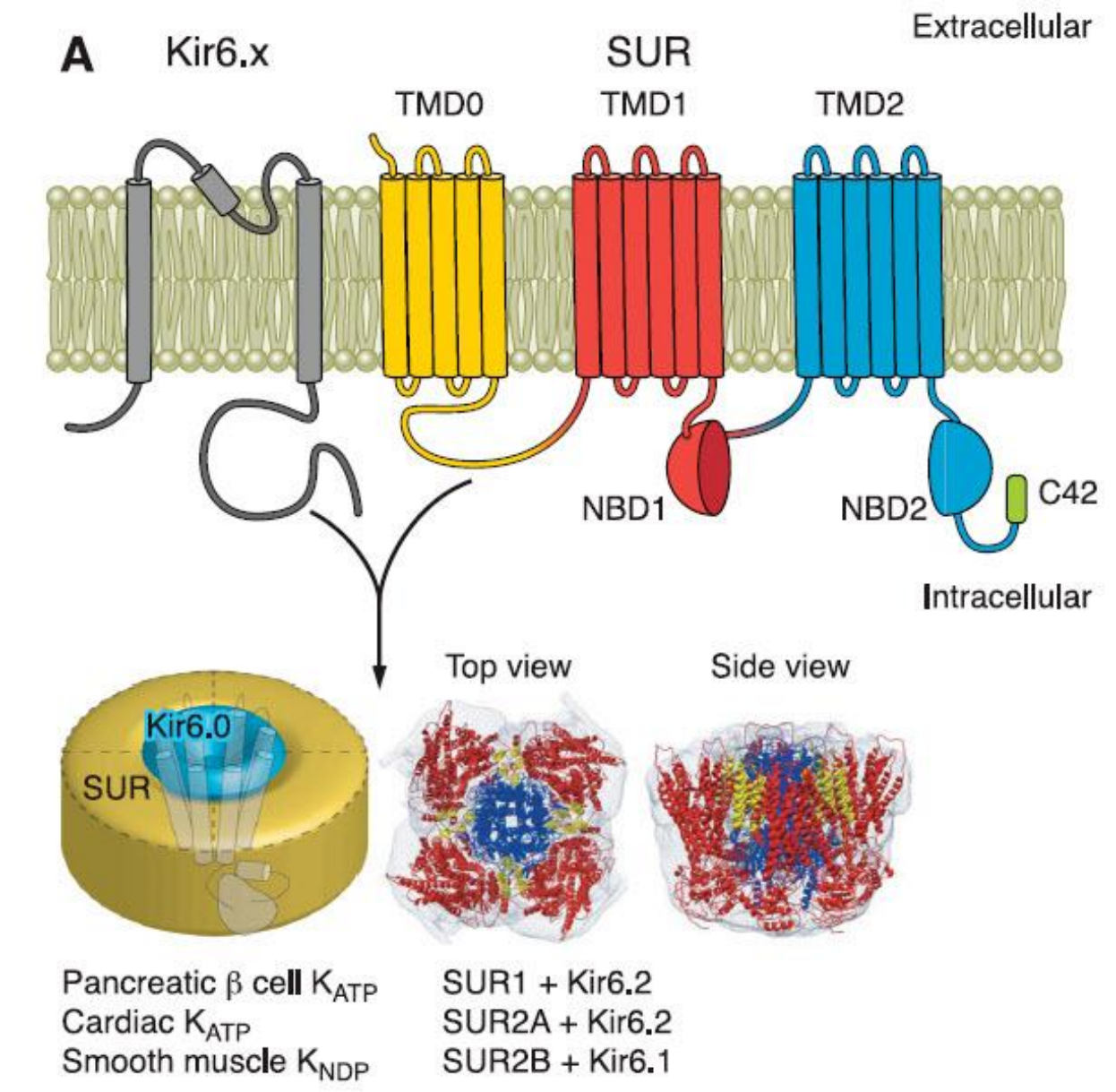




**Fig. 14.4 Drugs that act at ATP-sensitive $K^+$ channels.** **A.** $K^+$ channels opened by diazoxide. The records were obtained from insulin-secreting cells in culture by the patch-clamp technique (Ch. 2). Saponin caused permeabilization of the cell, with loss of intracellular ATP, causing the channels 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

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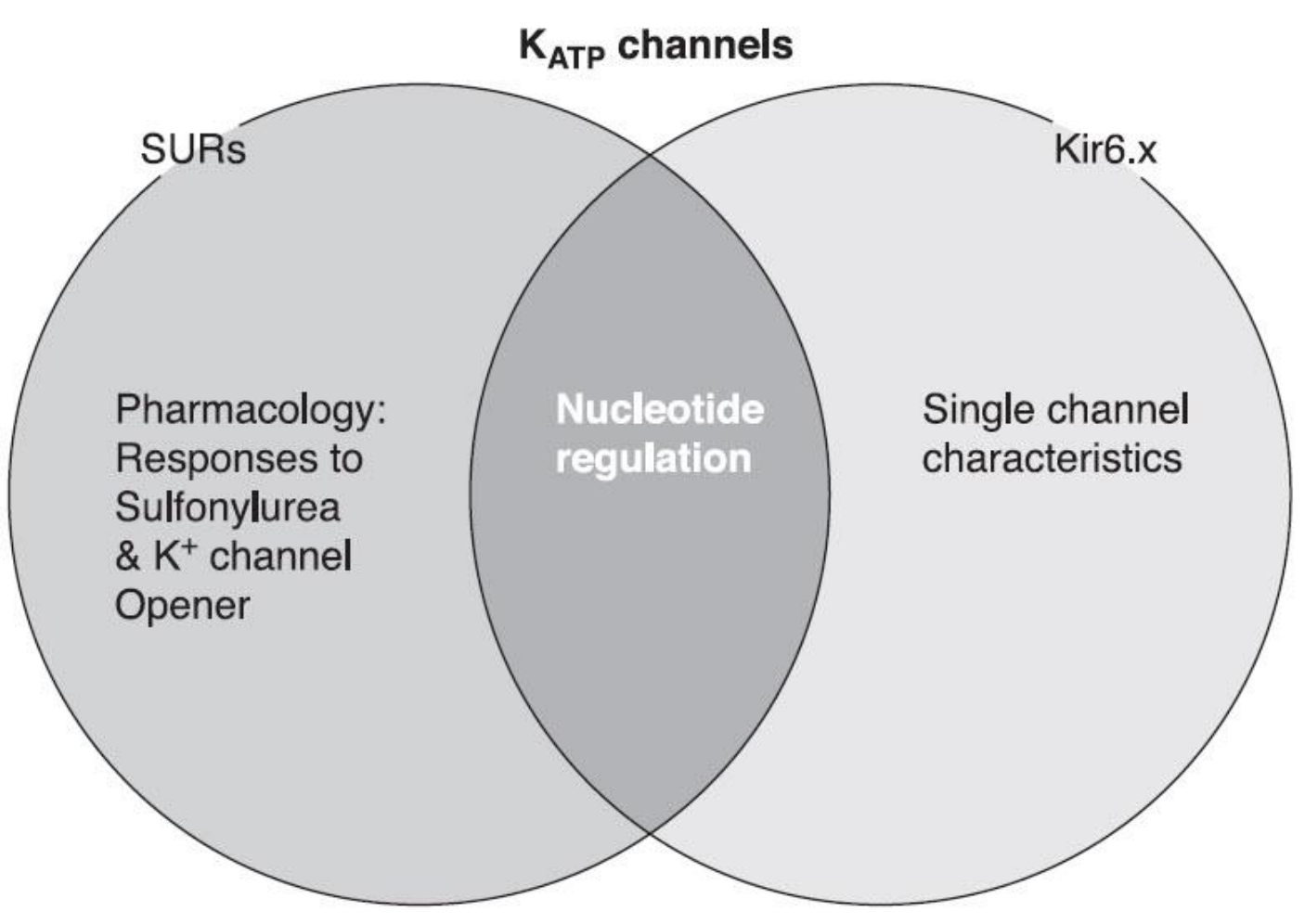
Physiol Rev • VOL 90 • JANUARY 2010

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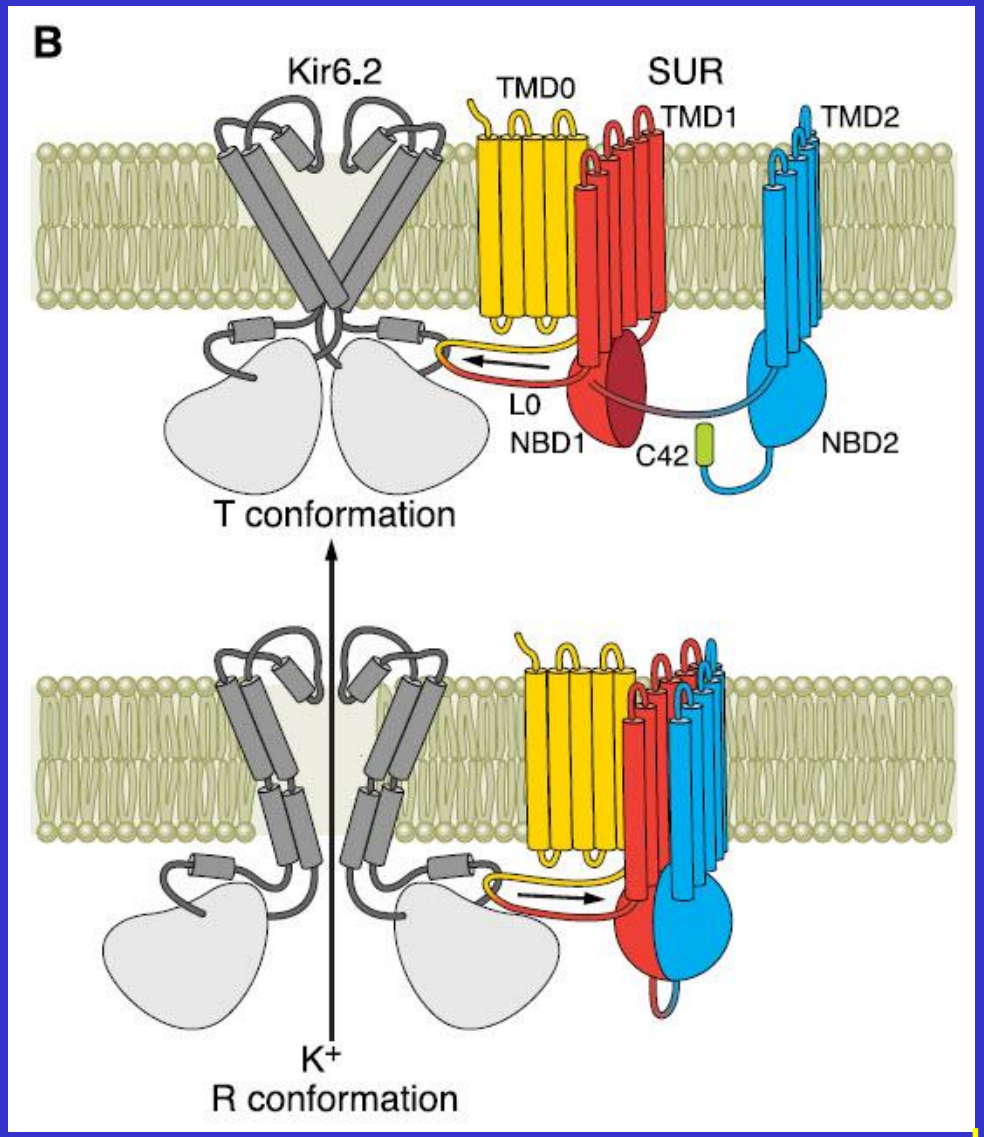
# Механизм открытия К-канала

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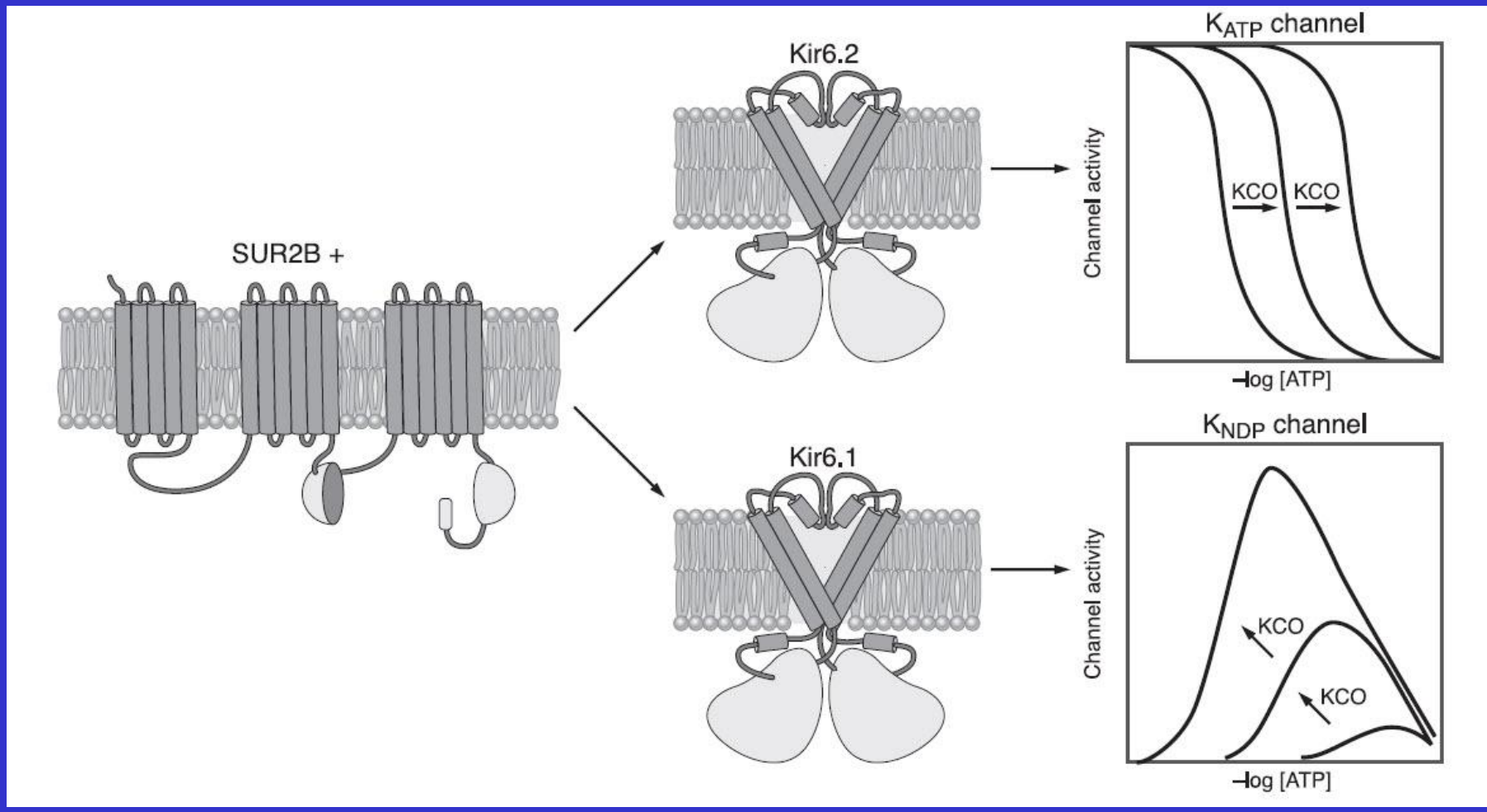


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# Профиль активности

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

Nicorandil + выделяет NO

Minoxidil + стимулирует рост волос

## Применение

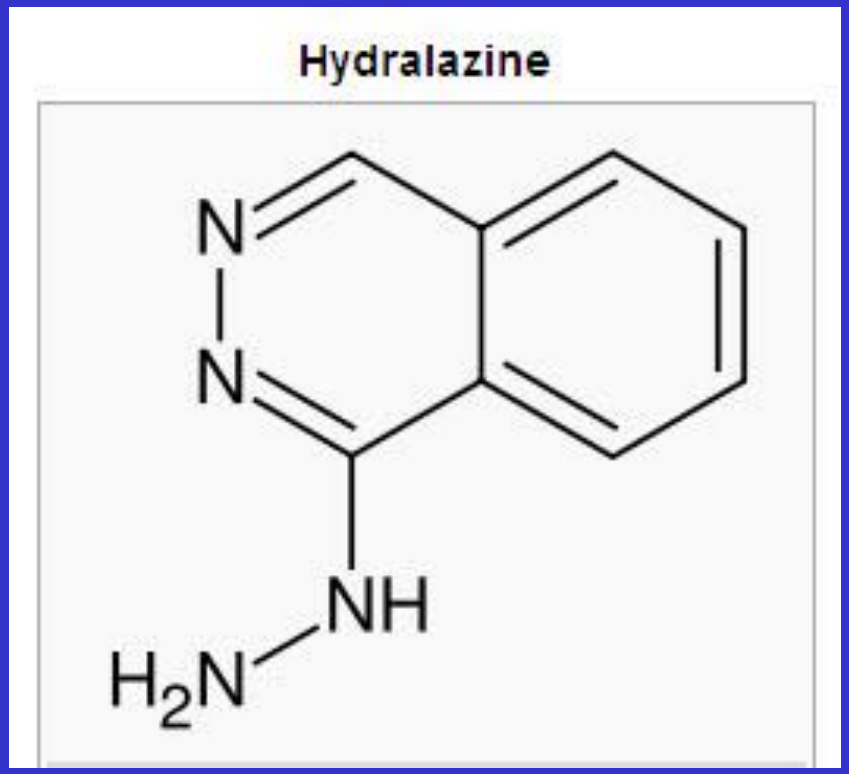
Артериальная гипертония

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<br>10–40 mg IM | 10–20 min IV<br>20–30 min IM | 1–4 hrs IV<br>4–6 hrs IM | Tachycardia, flushing, headache, vomiting, aggravation of angina | Eclampsia |

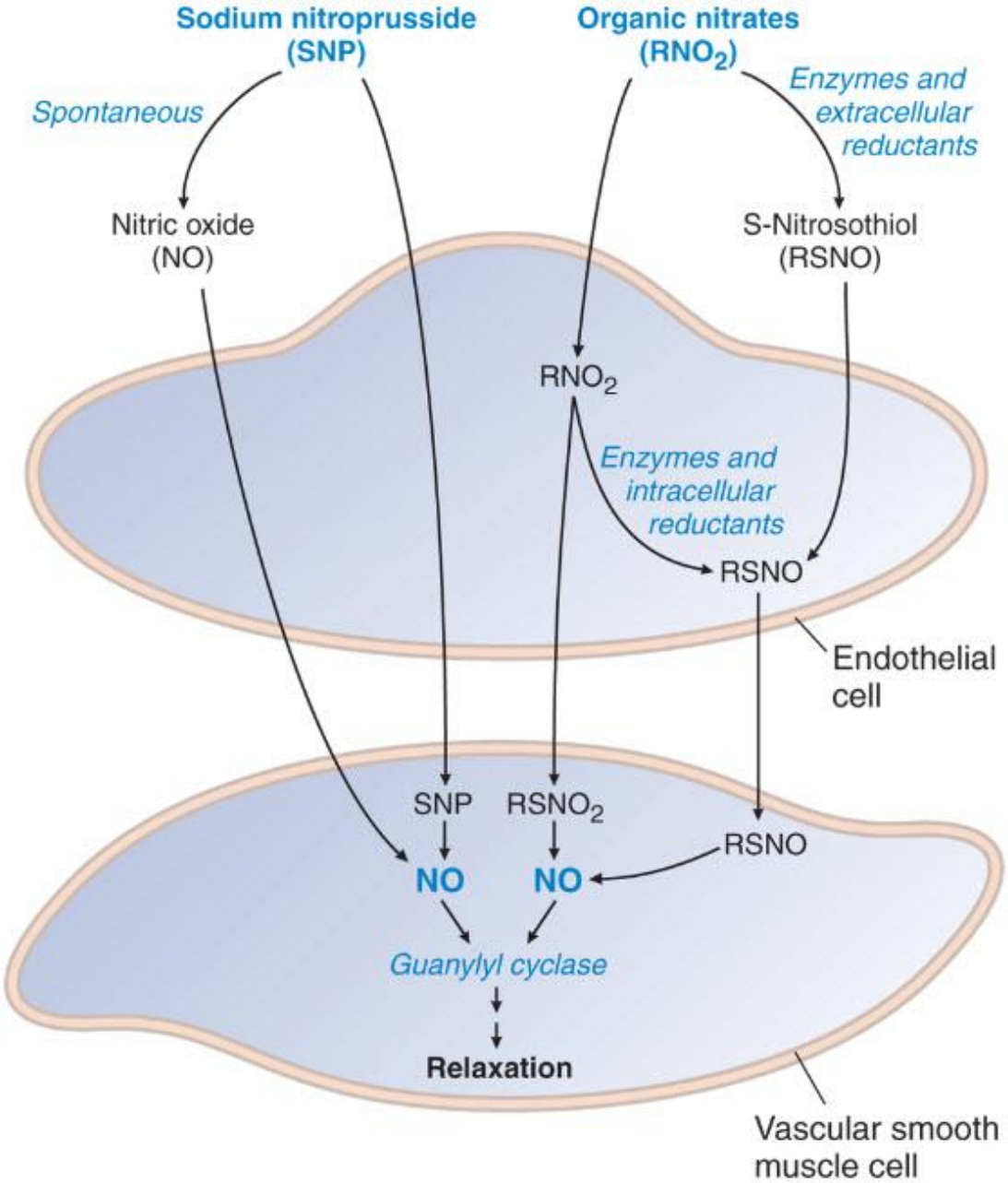



**Figure 21-7**: Biotransformation of organic nitrates and sodium nitroprusside. Organic nitrates and sodium nitroprussid...

# 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 |

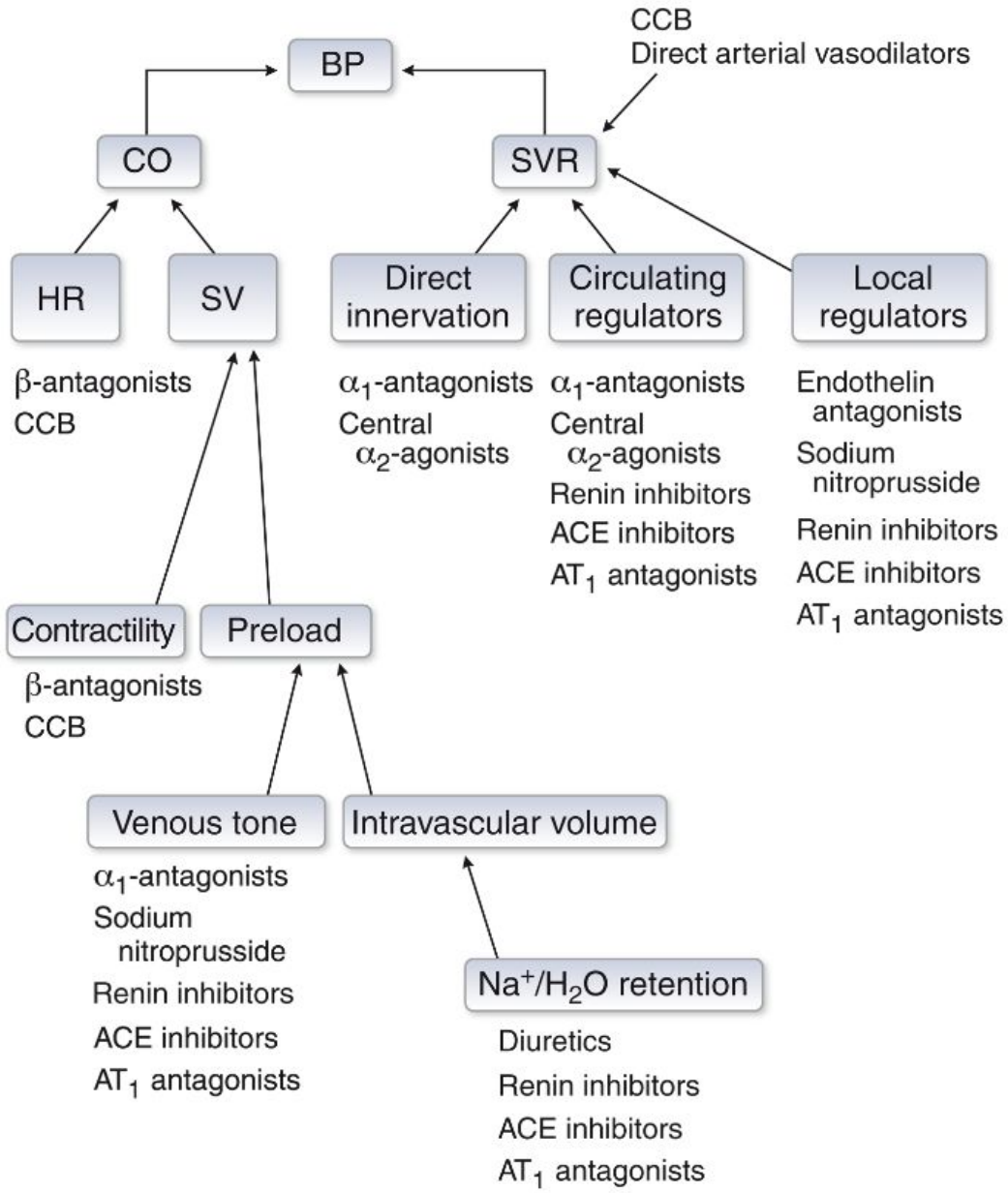



**Figure 25-2**: Pharmacologic effects of commonly used antihypertensive agents. Ant...

**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<br>Atenolol<br>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<br>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 $\alpha_1$-adrenoceptors† | Prazosin<br>Terazosin<br>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

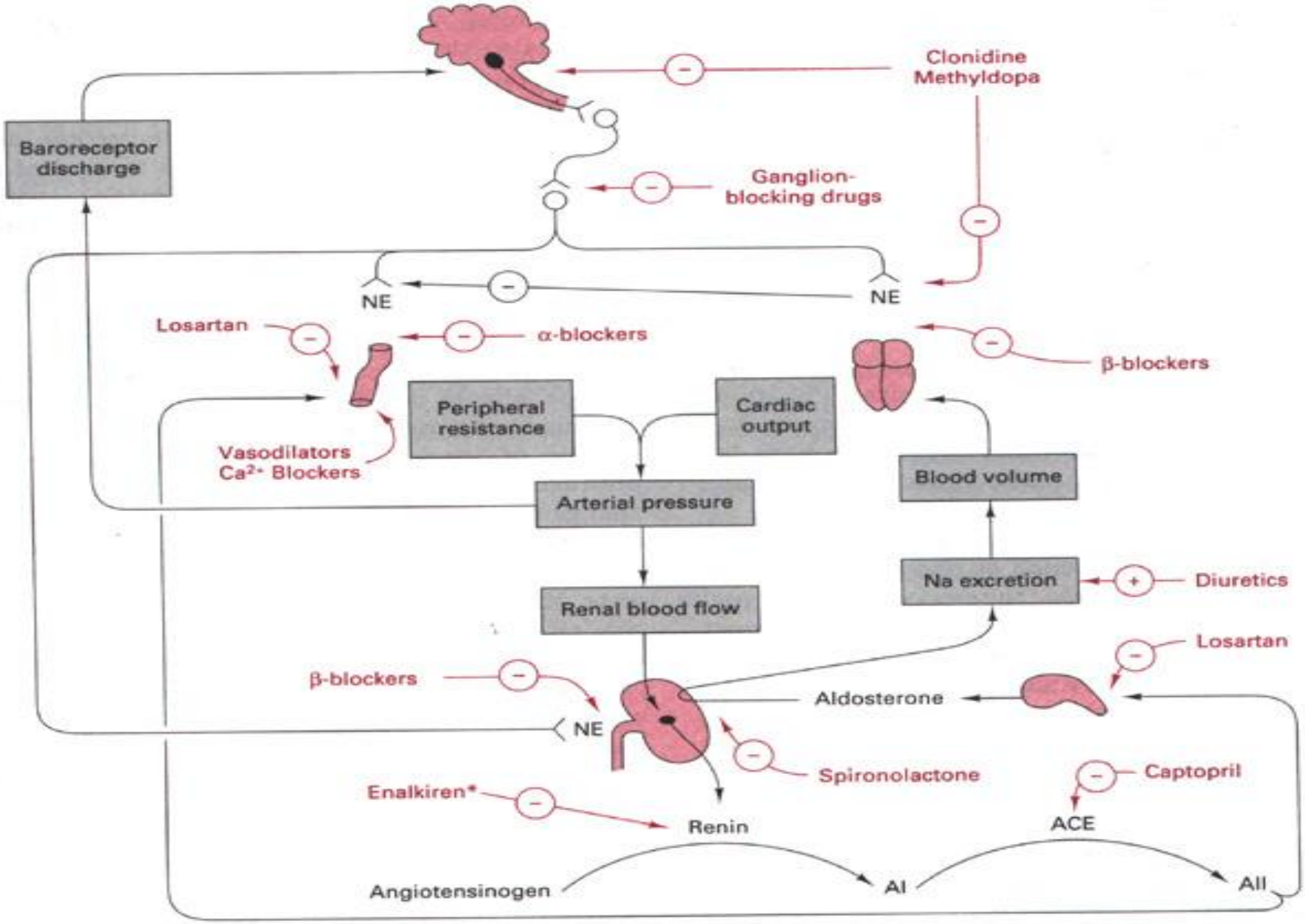
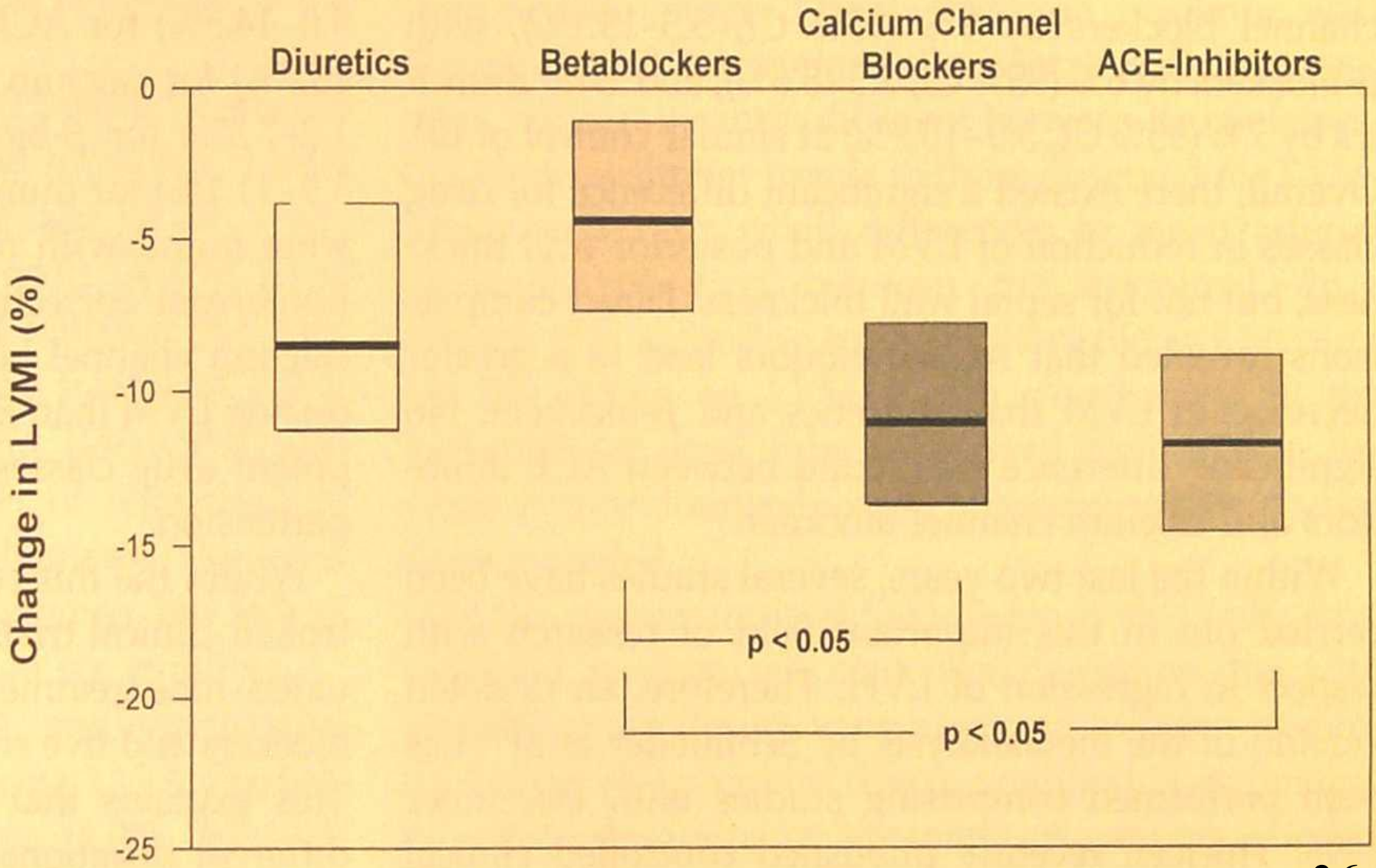



**Fig. 14.8 Diagram showing the main mechanisms involved in arterial blood pressure regulation (black lines), an the sites of action of antihypertensive drugs (red lines).** NE = norepinephrine, AI = angiotensin I, AII = angiotensin II, ACE = angiotensin-converting enzyme.




36

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

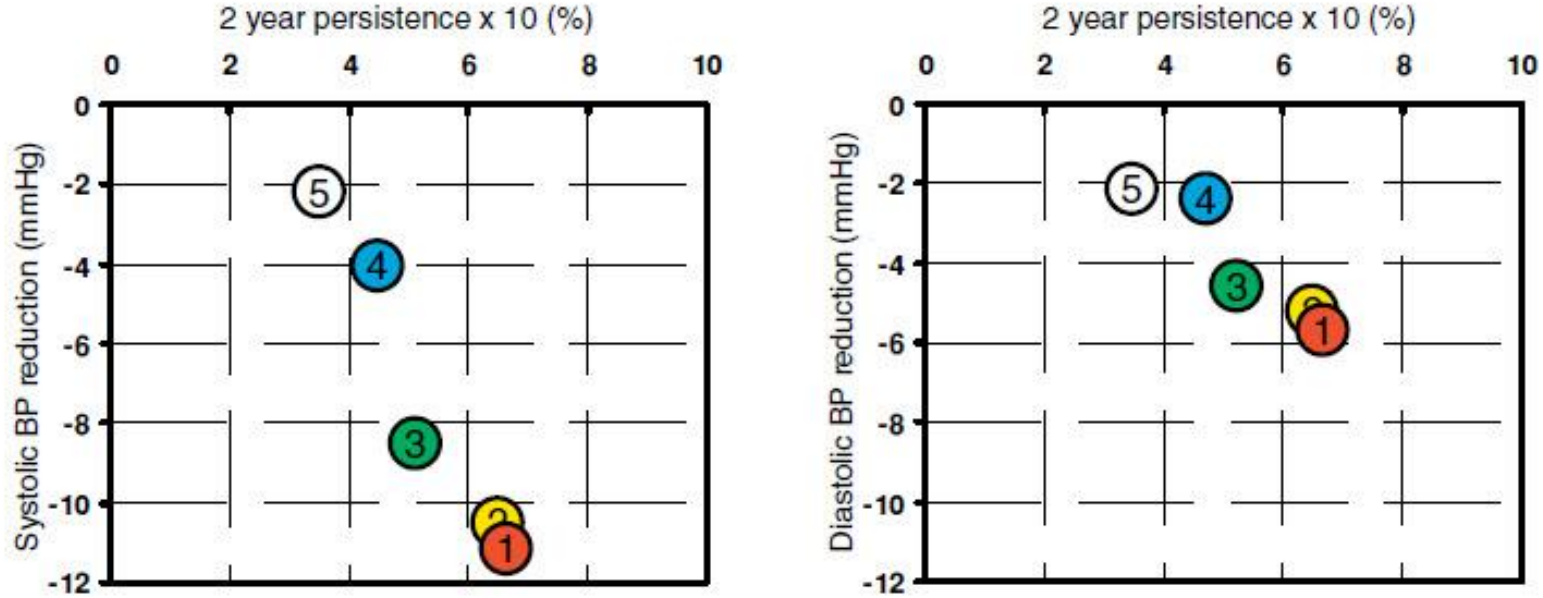
Table 3: Adverse effects of drugs: percentage of people with one or more symptoms attributable to treatment*, according to category of drug and dose, in randomised trials [9, 20]

| | | 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] |

Cardiovascular Diabetology 2009, 8:18

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

Cardiovascular Diabetology 2009, 8:18

# 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 |

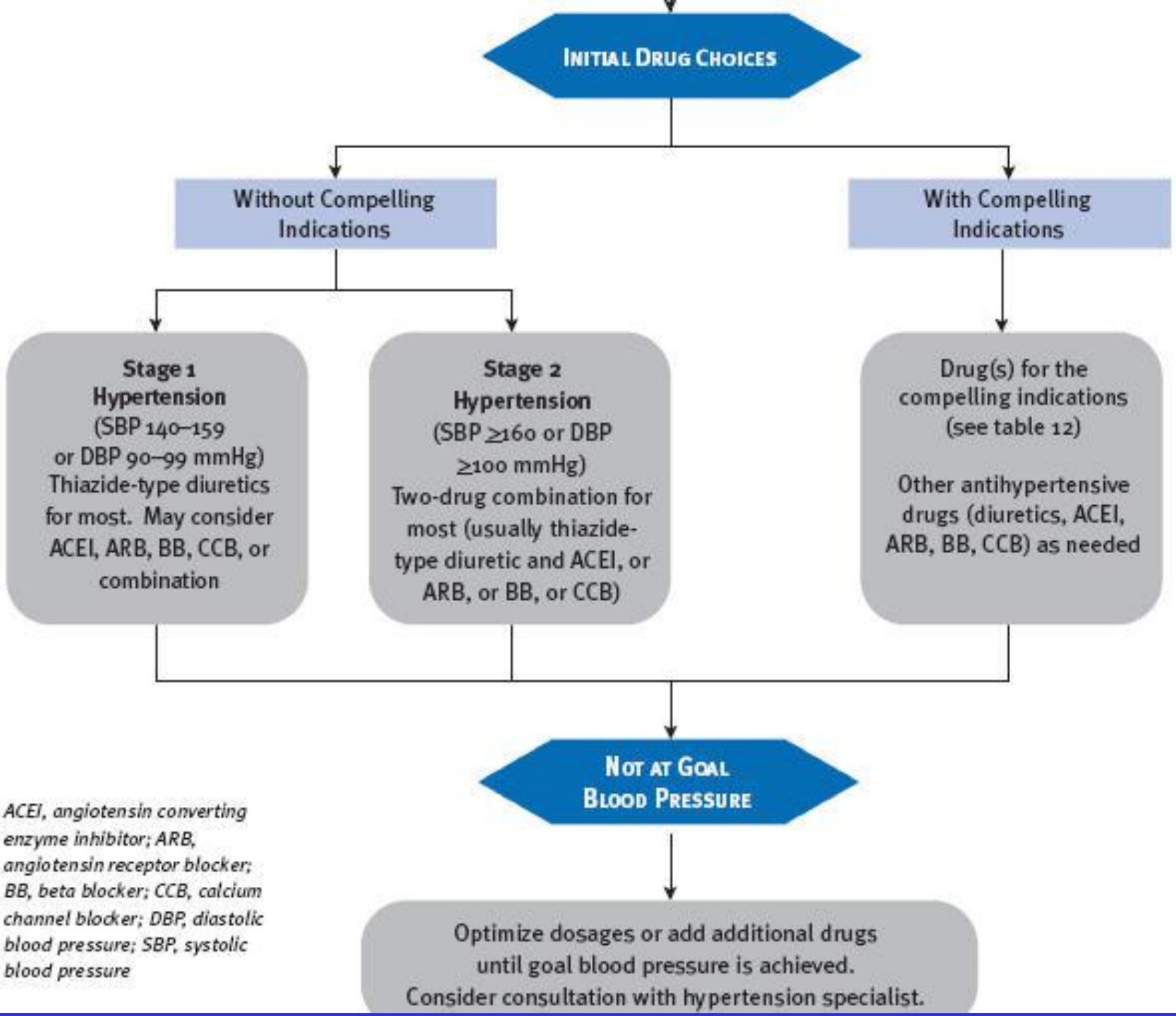
The Medical Letter 2001;43:17-22

# 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.

**Cardiovascular Diabetology 2009, 8:18**




*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] |

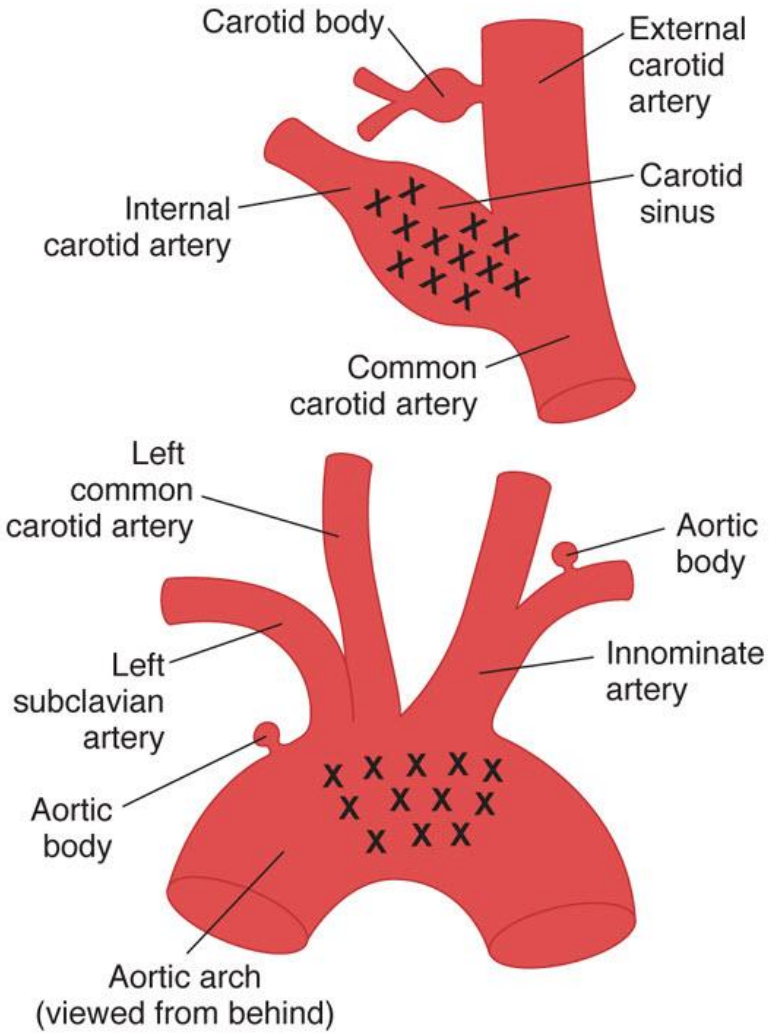



**Figure 33-4**: Baroreceptor areas in the carotid sinus and aortic arch. X, sites where receptors are located. The carotid and aortic bodies, which contain chemoreceptors, are also shown.

| 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 |