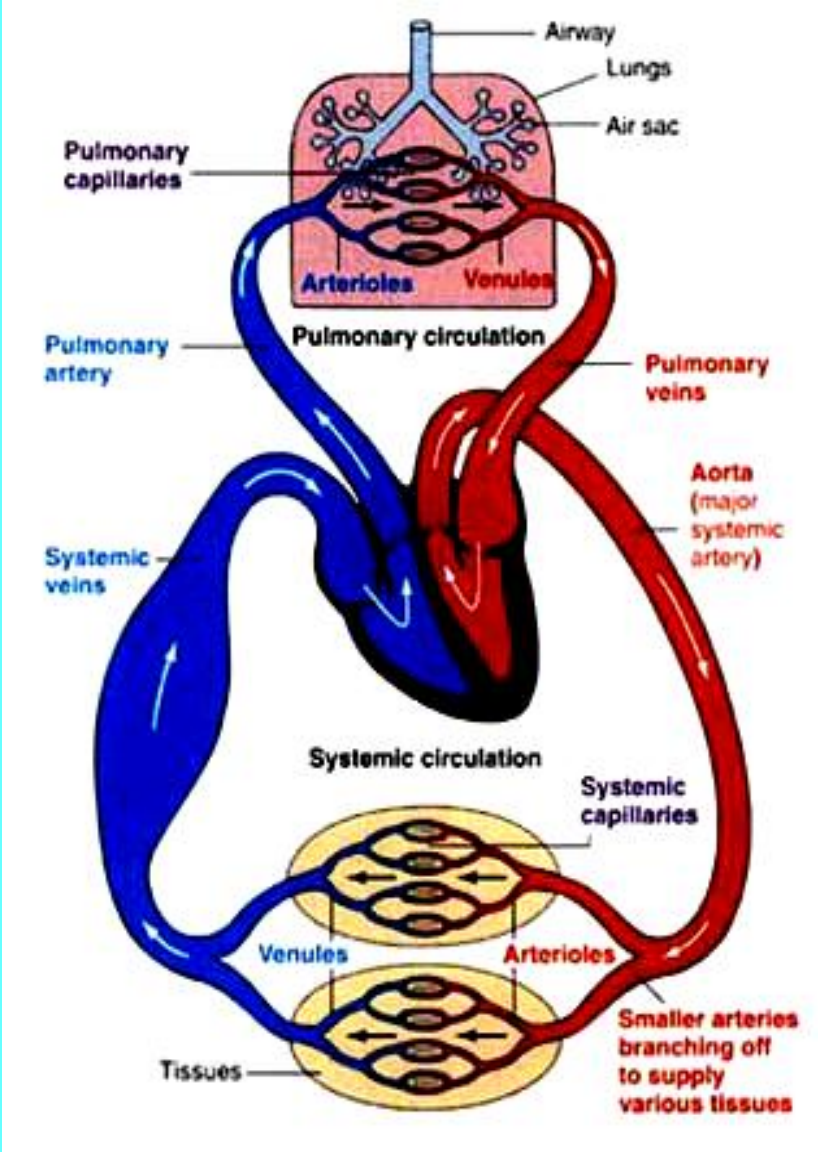
Section 3.

Circulatory System



Chapter 6.

Drugs acting on cardiovascular system(CVS)

Part 1. Drugs Acting Ion Channels in CVS(作用心血管离子通道的药物)

Part 2. Antiarrhythmic Drugs(抗心律失常药)

Part 3. Drugs for Treatment of Congestive Heart Failure

Part 4. Antianginal Drugs(抗心绞痛药)

Part 5. Antiatheroscleotic drugs(抗动脉粥样硬化药)

Part 6. Antihypertensive Drugs(抗高血压药)

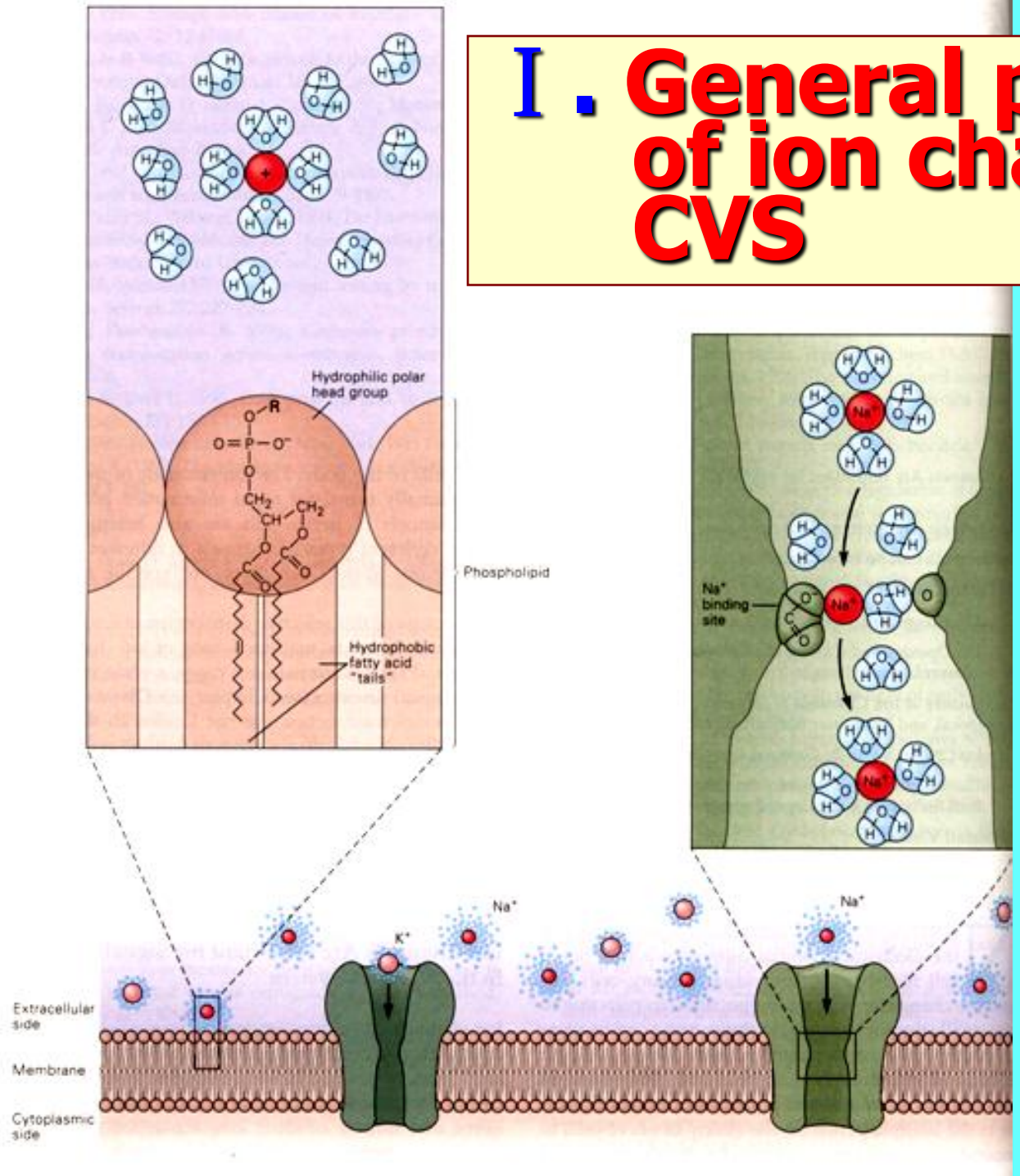
Part 1
Drugs Acting Ion Channels in CVS(作用于心血管系统离子通道的药物)

Contents

Ⅰ. General properties of ion channels in CVS(心血管系统离子通道的特征)

Ⅱ. Drugs affecting ion channels in CVS(作用于心血管系统离子通道的药物)

Ⅰ. General properties of ion channels in CVS



Ion trans-membrane transport

Ⅰ. General properties of ion channels in CVS

1. Properties of ion channels

(1)Permeation(通透性)

(2)Selectivity(选择性)

(3)Gating(门控)

Ⅰ. General properties of ion channels in CVS

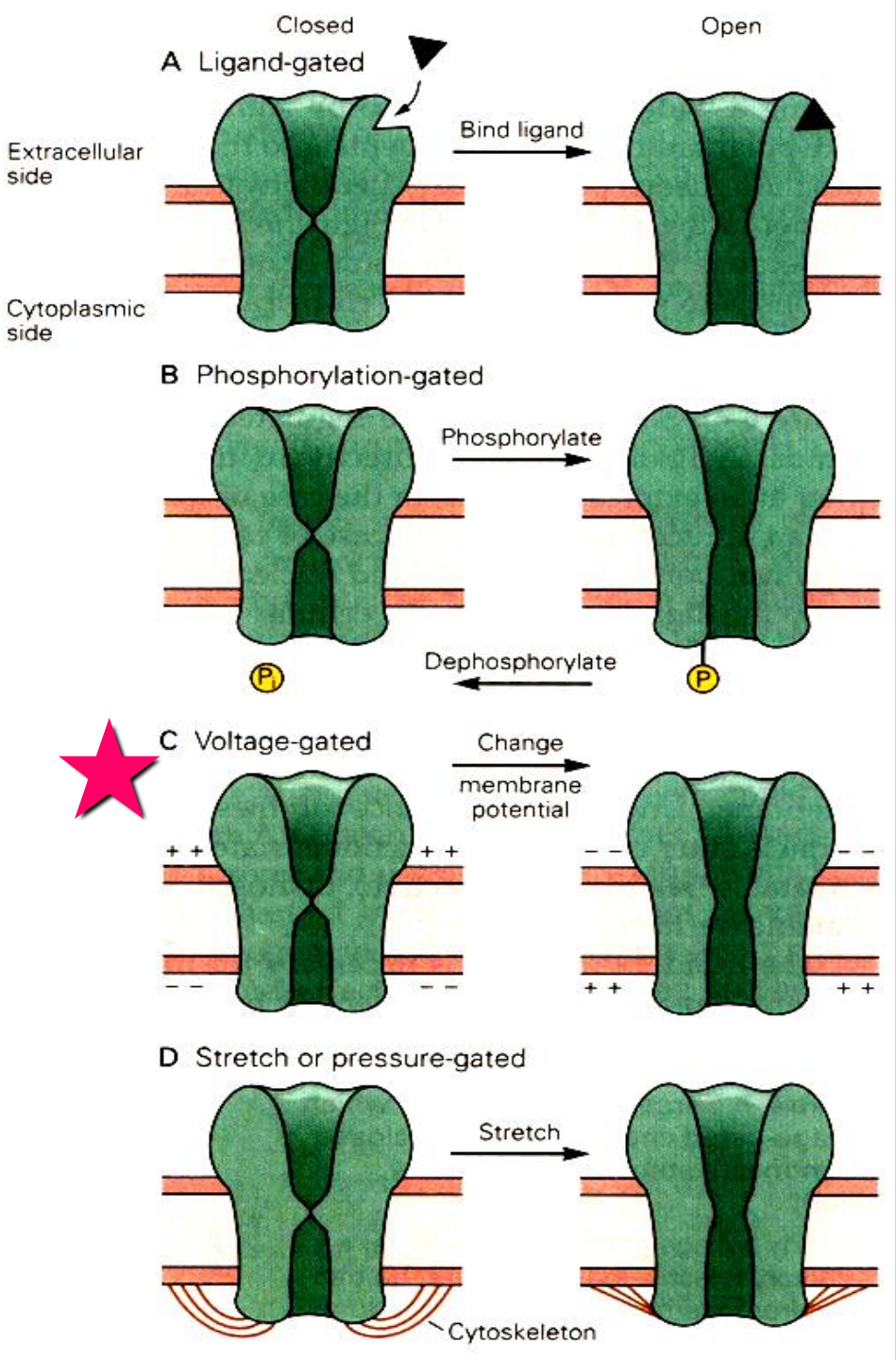
2. Pattern of ion channels

(1)ligand-gated channels

(2)phospharylation-gated channels

(3)voltage-gated channels

(4)mechanosensitive-gated channels (stretch or pressure-gated channels)

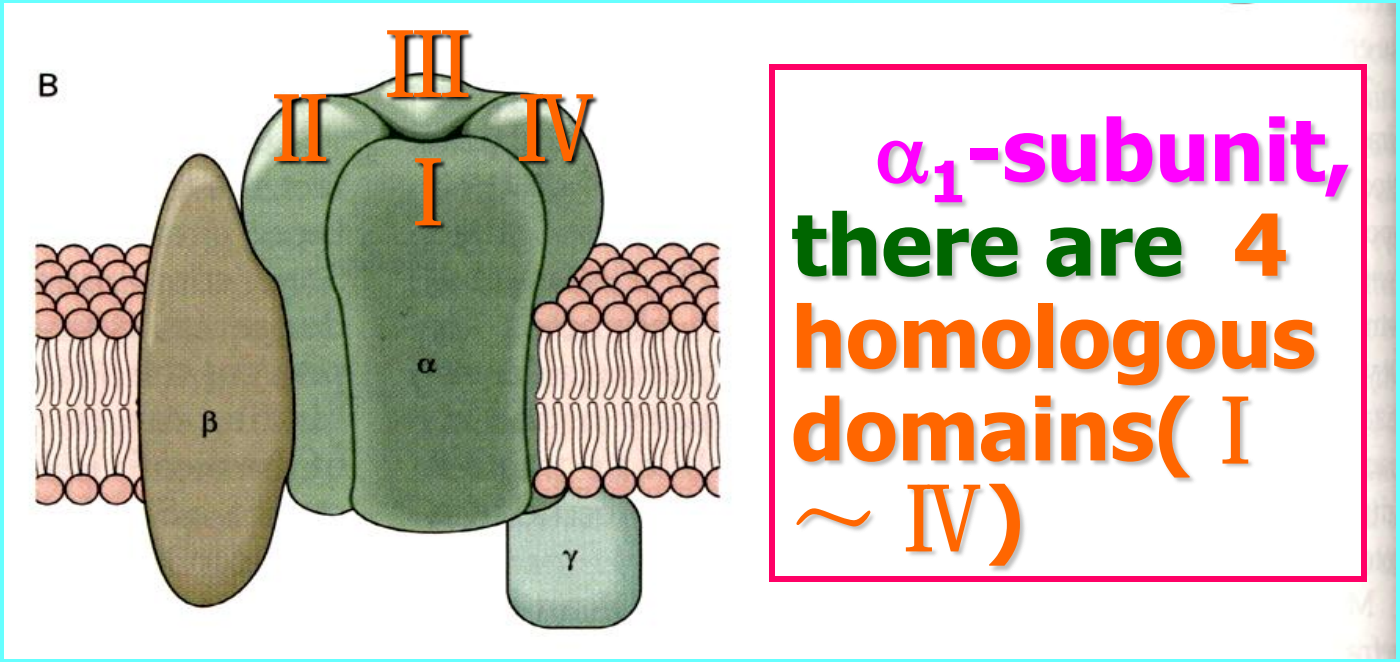


Gating mechanisms of ion channels

The structures of ion channels

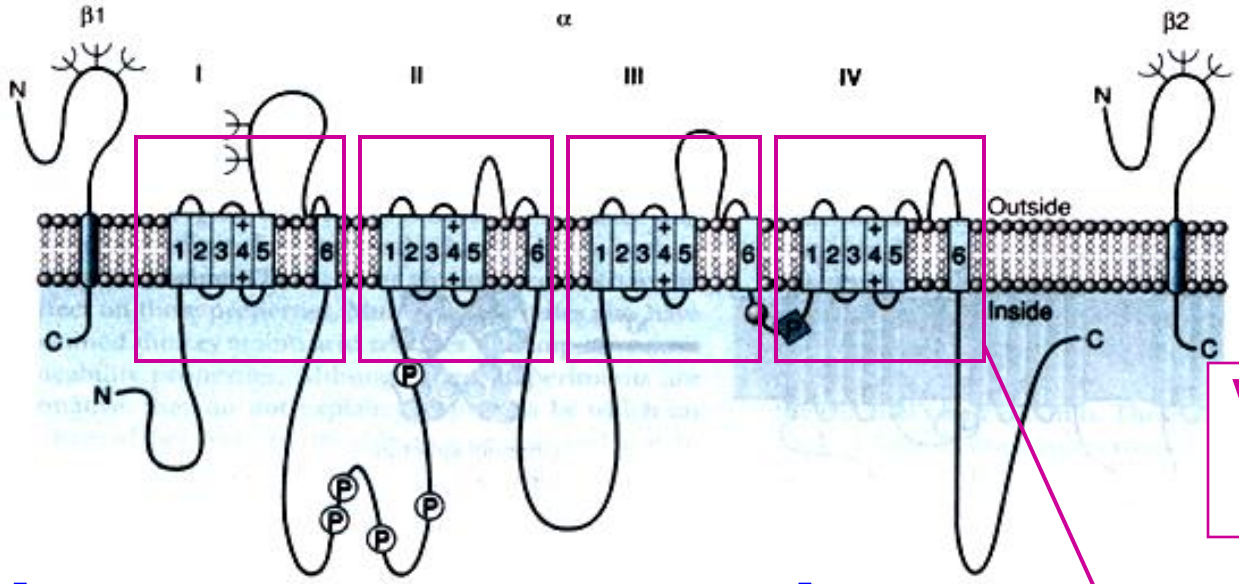
The structures of voltage-gated calcium channels:

There are 5 subunits: α_1, α_2, β, γ, δ.

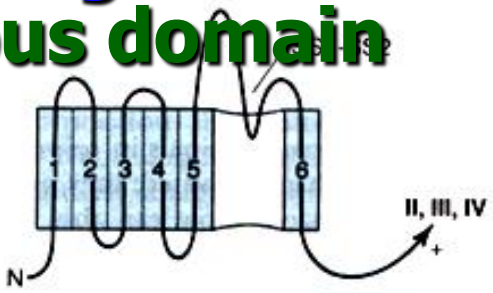


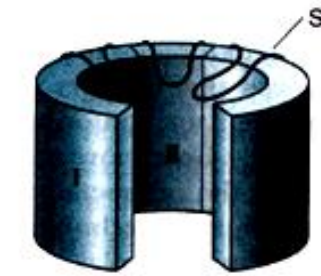
α_1-subunit, there are 4 homologous domains(Ⅰ ～ Ⅳ)

Structure of α-subunit



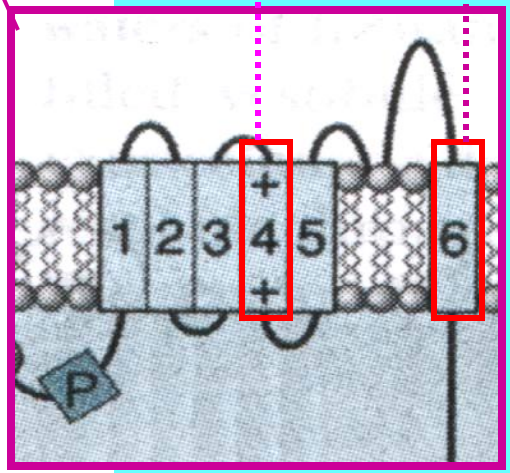
There are 6 transmembrane-spanning segments in each homologous domain

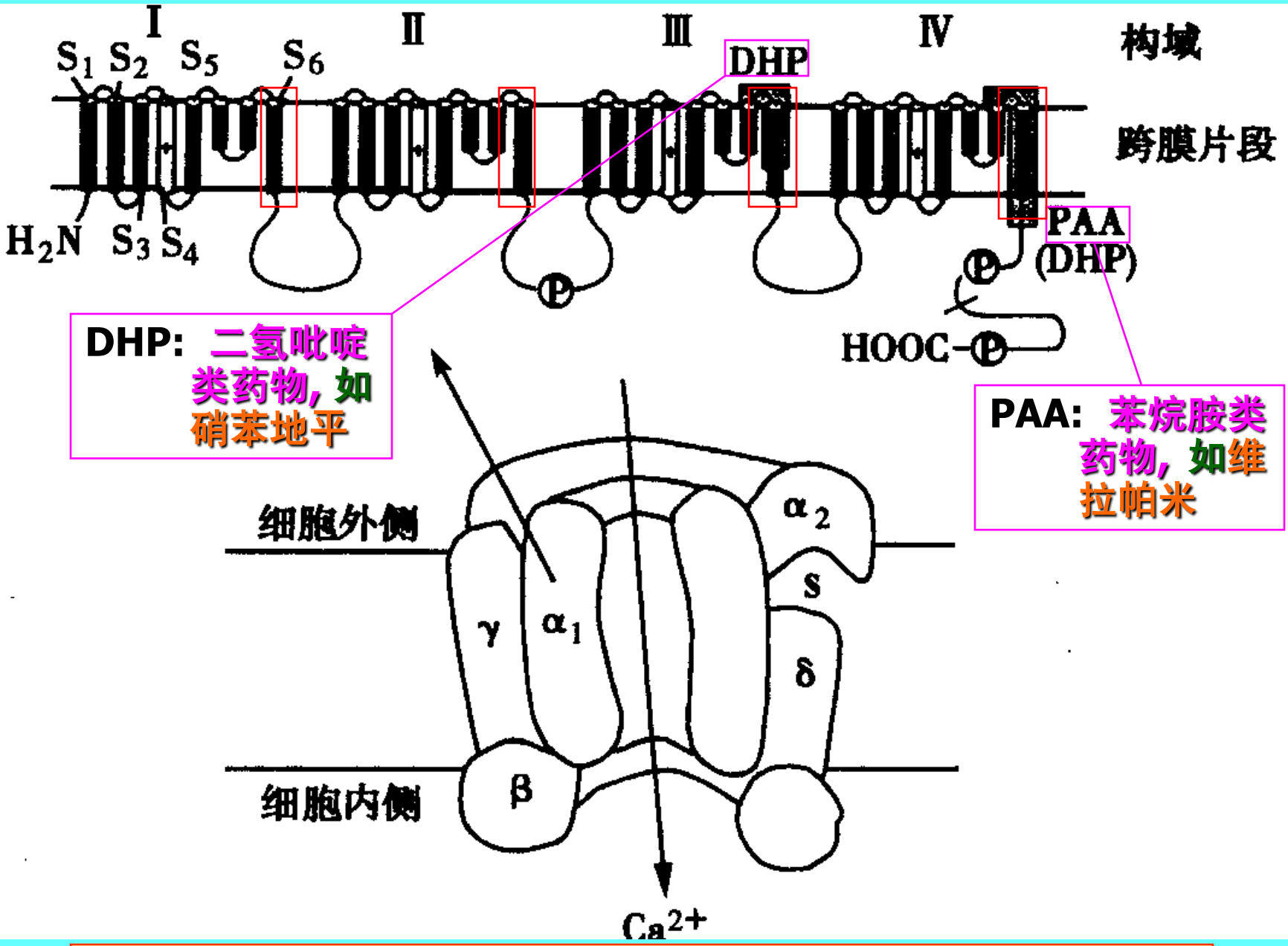




Site of drug binding

Voltage sensor





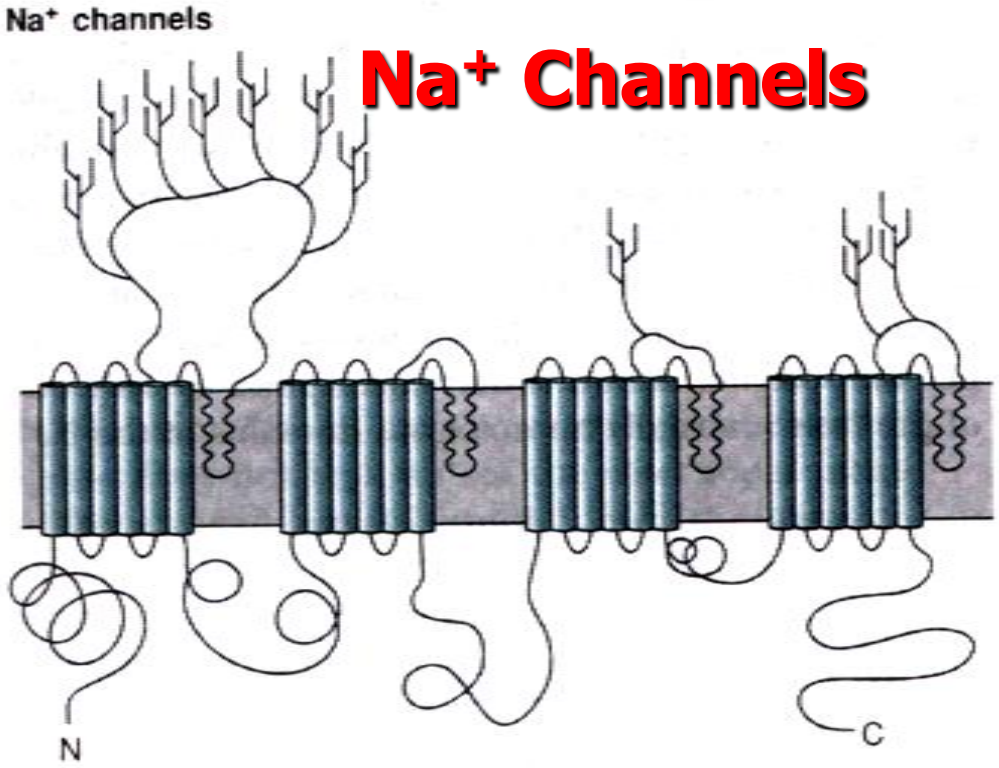
voltage-gated calcium channel

Ⅰ. General properties of ion channels in CVS

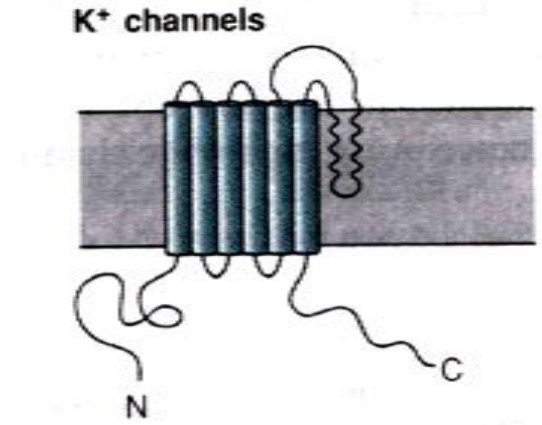
Voltage-gated ion channels

- Na^+ channels
- Ca^{2+} channels
- K^+ channels

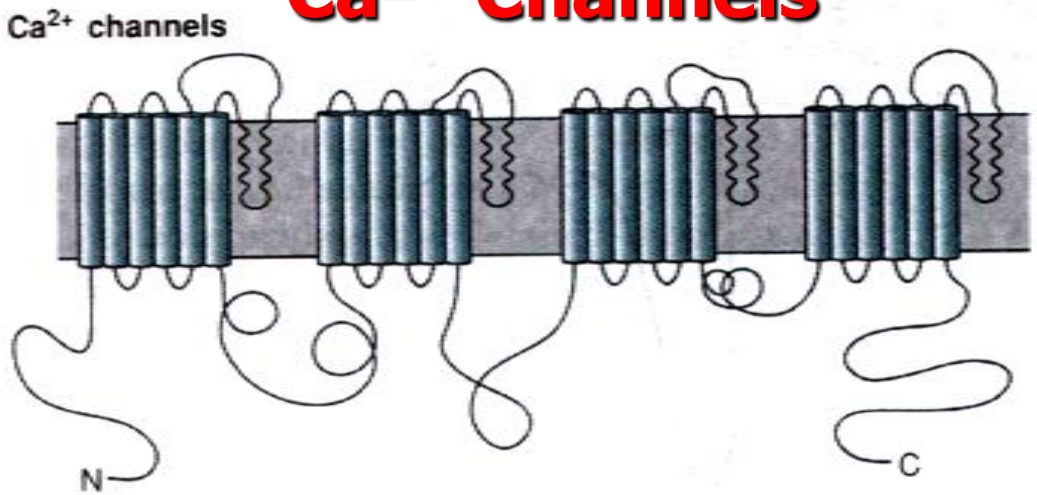
Na^+ Channels

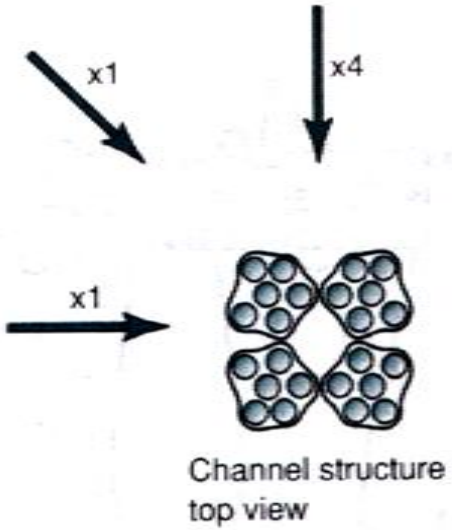


K^+ Channels



Ca^{2+} Channels





Ⅰ. General properties of ion channels in CVS

- **Functional regulation of voltage-gated ion channels**
  - ▲ **Activation —— channel open**
  - ▲ **Inactivation —— channel close**

Ⅰ. General properties of ion channels in CVS

When calcium channel open:

→ **Ca^{2+} inward flow ↑.**

Voltage-gated calcium channel:

L, T, N, P, Q, R types

Properties of L and T types voltage-gated calcium channels

L-type calcium channels

Long lasting opening;

Activated at -10 mV, inactivated at - 60～ - 90 mV;

Distributed in myocardial and vascular smooth muscle.

T-type calcium channels

Transient opening;

Activated at -70 mV, inactivated at -100～ - 60 mV;

Distributed mainly in heart conduction system(S-A node), arterial walls, *etc.*

Ⅱ. Drugs affecting ion channels in CVS

A. Calcium channel blockers

B. Potassium channel modulators

Ⅱ. Drugs affecting ion channels in CVS

A. Calcium channel blockers

A. Calcium channel blockers

1. Classification of calcium channel blockers

(1)Classification according to chemical structure

Phenylalkylamines(苯烷胺类, PAA):
verapamil(维拉帕米) 1st generation

Dihydropyridines(二氢吡啶类, DHP):
nifedipine(硝苯地平) 1st generation
nimoldipine(尼莫地平) 2nd generation
amlodipine(氨氯地平) 3rd generation

Benzothiazepines(苯硫卓类, BZ):
diltiazem(地尔硫卓) 1st generation

A. Calcium channel blockers

(2)Generations of calcium channel blockers

①First generation:
verapamil(维拉帕米),
nifedipine(硝苯地平),
diltiazem(地尔硫卓)

②Second generation: 对血管选择性高.
nimoldipine(尼莫地平),
felodipine(非洛地平)

③Third generation: 同上, 并且 $t_{1/2}$长.
pranidipine(普拉地平),
amlodipine(氨氯地平)

A. Calcium channel blockers

2. Pharmacological effects

(1)Cardiac effects

①Negative inotropic effect:

↓ excitation-contraction discoupling.

②Negative chronotropic and slowing conduction action:

↓ spontaneous depolarization of phase 4 and phase 0 of slow response autonomic cells.

③Protective effect on cardiac ischemia

A. Calcium channel blockers

(2)Effects on smooth muscles

①Vascular smooth muscle:

relaxing the arterial smooth muscles, → ↓ blood pressure(BP),

especially relaxing the coronary artery, increasing blood supply to cardiac muscle.

②Others:

smooth muscle of bronchus, gastro-intestinal tract, ureter(输尿管), uterus(子宫).

A. Calcium channel blockers

(3)Anti-atherosclerosis

①Alleviating Ca^{2+} overload;

②Inhibiting proliferation of smooth muscle cells and protein synthesis of arterial matrix;

③Inhibiting lipid peroxidation;

④Decrease cholesterol level.

A. Calcium channel blockers

(4)Hemodynamic effects

①Improving membrane stability of erythrocytes;

②Inhibiting platelet aggregation.

(5)Others

①Kidney:

Increase the blood flow of kidney.

②Endocrine:

inhibiting the release of ACTH, TSH, insulin, *etc.*

A. Calcium channel blockers

4. Clinical uses

(1)Angina pectoris

①Variant angina: nifedipine

②Stable angina:
verapamil, diltiazem

③Unstable angina:
verapamil, diltiazem,
nifedipine + β receptor blockers

A. Calcium channel blockers

(2)Arrhythmias

①Supraventricular tachycardia;

②Arrhythmias induced by triggered activity following afterdepolarization.

—— verapamil, diltiazem

A. Calcium channel blockers

(3)Hypertension

①Severe: nifedipine

②Mild to moderate:
verapamil, diltiazem

③Complicated with:
coronary heart disease
myocardial ischemia,
peripheral vascular diseases,
bronchial asthma,
chronic obstructive pulmonary diseases(CPOD), *etc.*

A. Calcium channel blockers

(4)Cerebrovascular diseases

transient ischemic attack;
cerebral thrombosis;
subarachnoid hemorrhage.

(5)Others

peripheral vascular spasmodic diseases;
arteriosclerosis;
etc.

A. Calcium channel blockers

5. Adverse effects

(1)peripheral edema:
nifedipine >verapamil >diltiazem

(2)symptoms of sympathetic excitation(→ heart rate ↑):
nifedipine;

(3)heart rate reduced:
verapamil, diltiazem;

(4)hypotension: nifedipine.

A. Calcium channel blockers

6. Contraindications:

nifedipine:

hypotension;

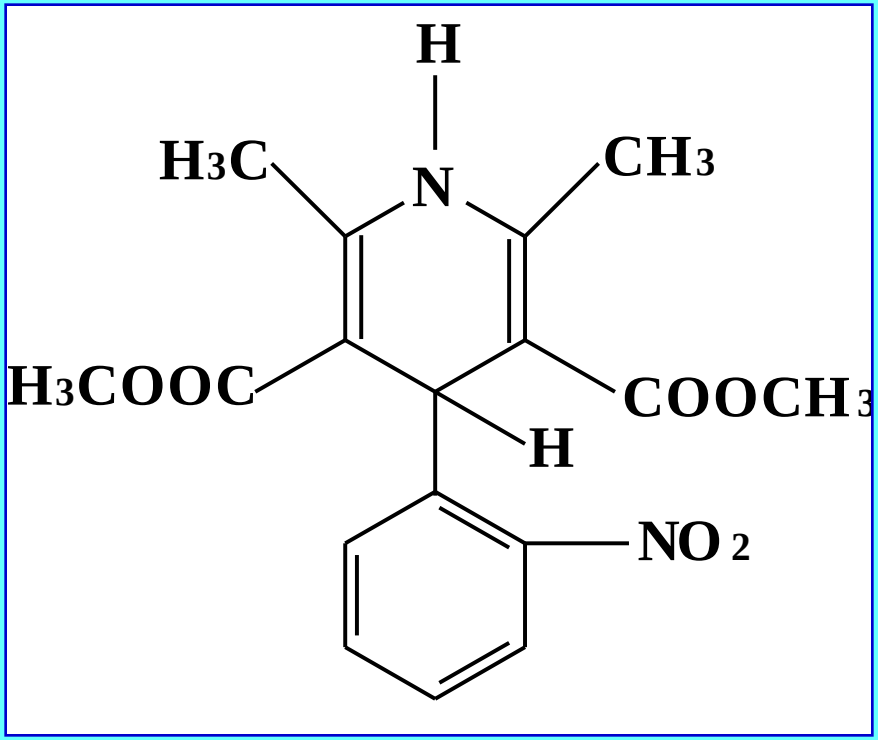
verapamil and diltiazem:

severe heart failure,
sinus bradycardia,
atrioventricular conduction block.

A. Calcium channel blockers

7. Special agents

Nifedipine(硝苯地平)



Nifedipine

(1)Pharmacological effects

①Vessels: vasodilatation, → BP↓, → increase of cardiac output.

②Heart: reflex increase of heart rate, the direct inhibiting effects is weaker.

(2)Clinical uses

①Angina pectoris; ②hypertension;
③peripheral vascular diseases; *etc.*

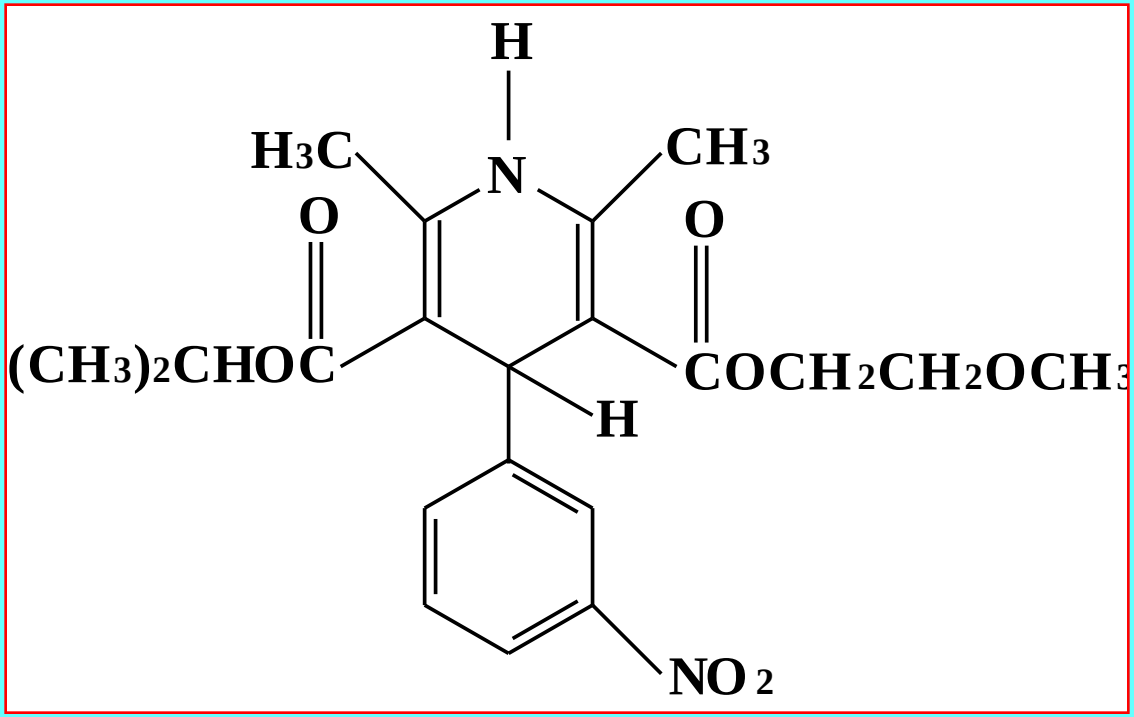
Slow releasing forms(缓释剂型):
↓ADR; ↑action duration.

(3)Adverse effects

Hypotension; tachycardia; edema; headache, flushing, *etc.*

A. Calcium channel blockers

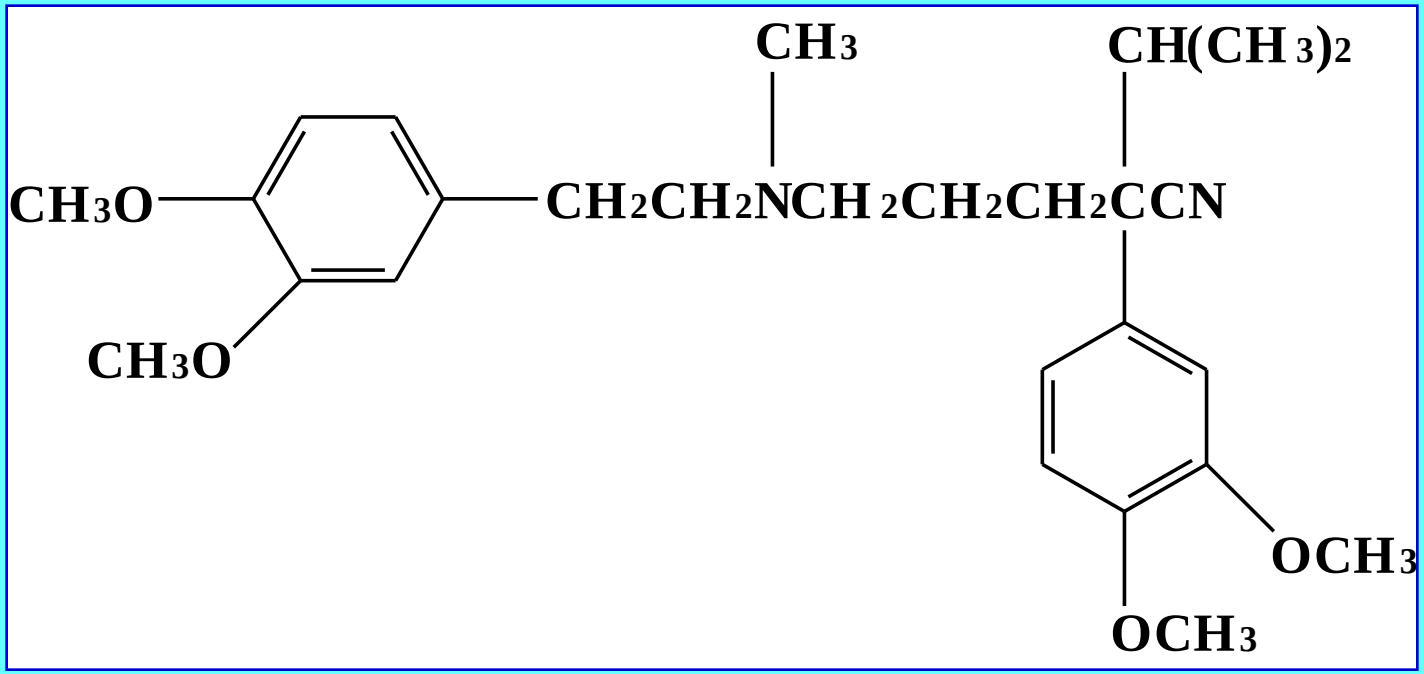
Nimodipine(尼莫地平)



Selectively acting on cerebral vasculature

A. Calcium channel blockers

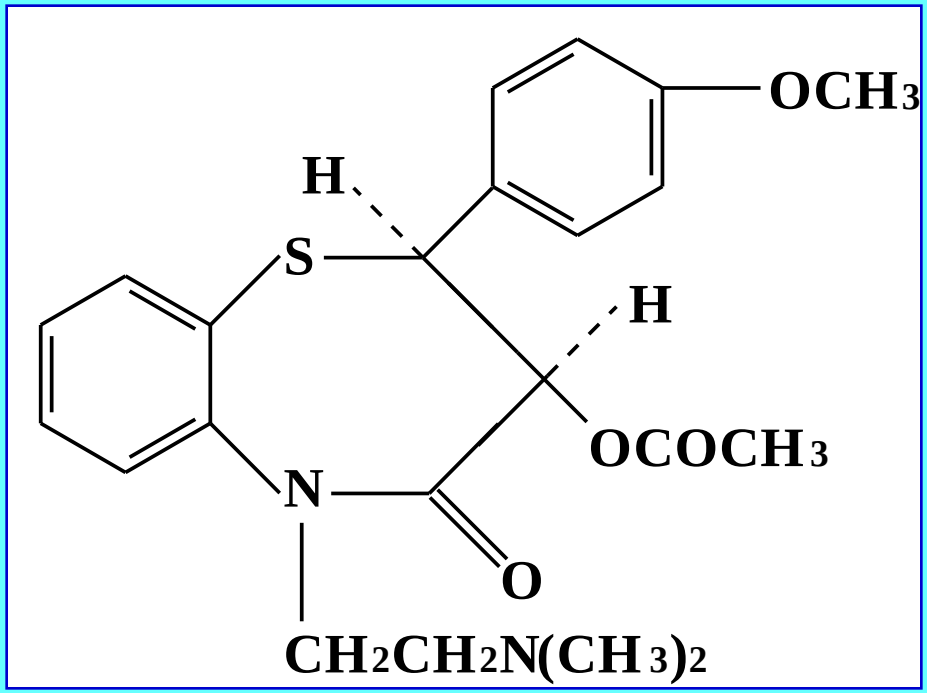
Verapamil(维拉帕米)



Potent efficacy on the heart, and weaker on the vessels

A. Calcium channel blockers

Diltiazem(地尔硫卓)



Potent efficacy on the heart and the vessels

A. Calcium channel blockers

表 21-1　三种钙拮抗药对心血管作用的比较

	硝苯地平	维拉帕米	地尔硫䓬
冠脉张力	- - -	- -	- -
冠脉流量	+++	++	++
扩张外周血管	+++	+	++
心率	0, ++	-	-
心收缩力	0, +	0, -	0, -
房室结传导	0	-	-
房室结 ERP	0	-	-

注：+ 增加，- 减少，0 无影响

Ⅱ. Drugs affecting ion channels in CVS

B. Potassium channel modulators

Potassium channel blockers(PCBs):

Sulfonylureas(磺酰脲类)

for treatment of diabetes(糖尿病)

Amiodarone(胺碘酮)

anti-arrhythmic drugs —— class Ⅲ

Many other drugs under research.

Potassium channel openners(PCOs):

Effects are similar to calcium channel blockers.

A lot of drugs under research.

Class is over !