CALCIUM CHANNEL BLOCKING DRUGS

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Physiological regulatory role of CALCIUM at cellular level

- **Electrical excitability**

  Contraction of
  - sceletal muscle
  - smooth muscle
  - and cardiac cells

- **Release of chemical mediators**

  Exocytosis
  - Secretion in nerve endings

- **Cell death** apoptosis
  necrosis

- **Second messenger especially in immune system**

Extracellularly 1.5 mol/l Ca^{2+} **intracellularly 10^{-7} mol/l free Ca^{2+}**

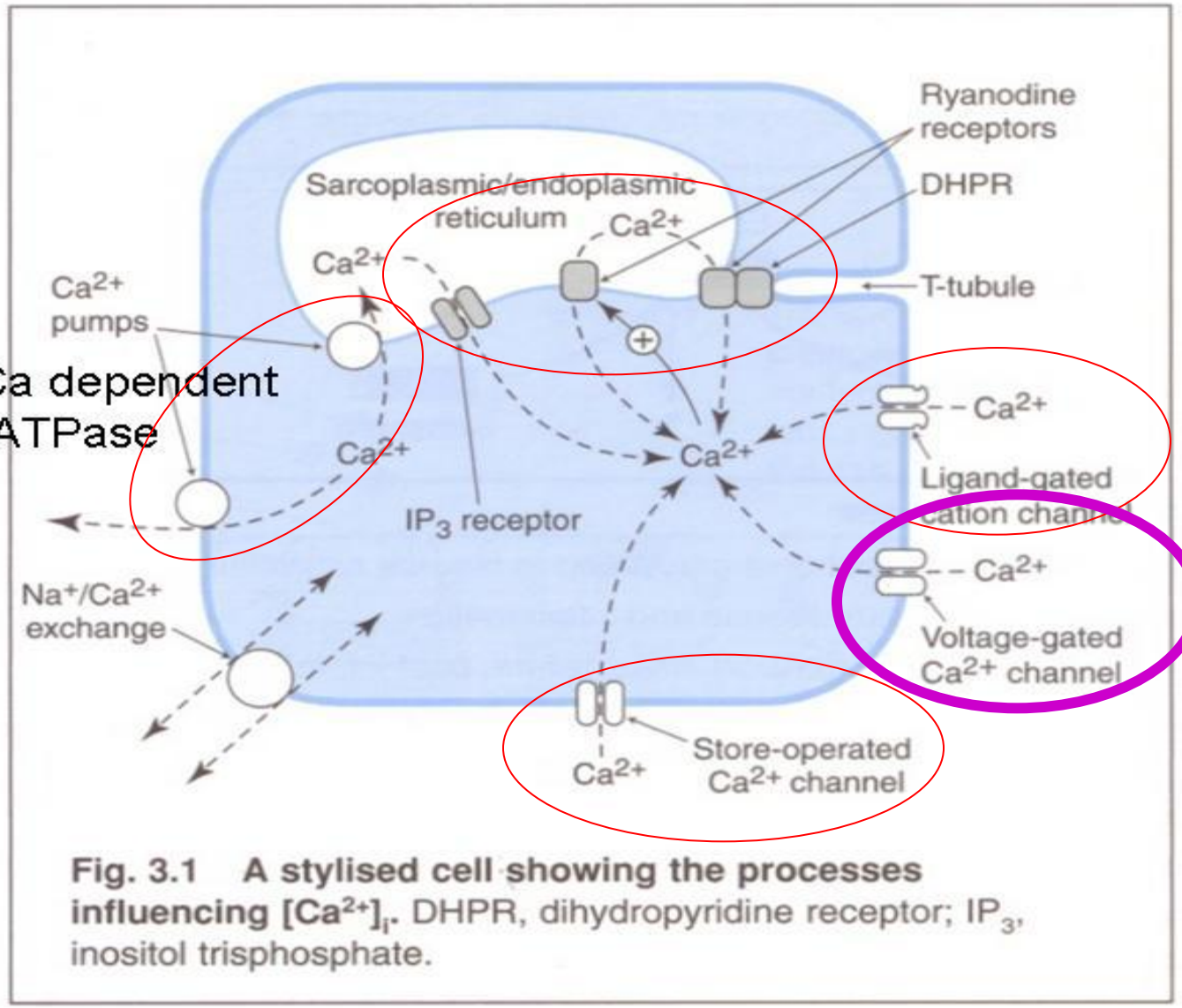


Fig. 3.1 A stylised cell showing the processes influencing $[Ca^{2+}]_i$. DHPR, dihydropyridine receptor; IP_3, inositol trisphosphate.

LIGAND-GATED Ca channels

NMDA glutamate receptors have high affinity to Ca ,

too much stimulation may result in even EXCITOTOXICITY

P2 receptor mediated Ca entry in smooth muscle cells

STORE-OPERATED Ca channels (SOC)

sensitize ER Ca depletion

...peptides of several recognized voltage-activated calcium channels.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_V1.1$–$Ca_V1.3$	Cardiac, skeletal, smooth muscle, neurons ($Ca_V1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, ω-aga-IIIA
T	$Ca_V3.1$–$Ca_V3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+}, mibefradil[1]
N	$Ca_V2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] gabapentin,[4] ω-CTX-GVIA, ω-aga-IIIA, Cd^{2+}
P/Q	$Ca_V2.1$	Neurons	Long, high threshold	ω-CTX-MVIIC, ω-aga-IVA
R	$Ca_V2.3$	Neurons, sperm[2]	Pacemaking	SNX-482, ω-aga-IIIA

Ethosuccimide, valproic acid

[1] Antianginal drug withdrawn from market.

[2] Channel types associated with sperm flagellar activity may be of the Catsper1–4 variety.

[3] Synthetic snail peptide analgesic (see Chapter 31).

[4] Antiseizure agent (see Chapter 24).

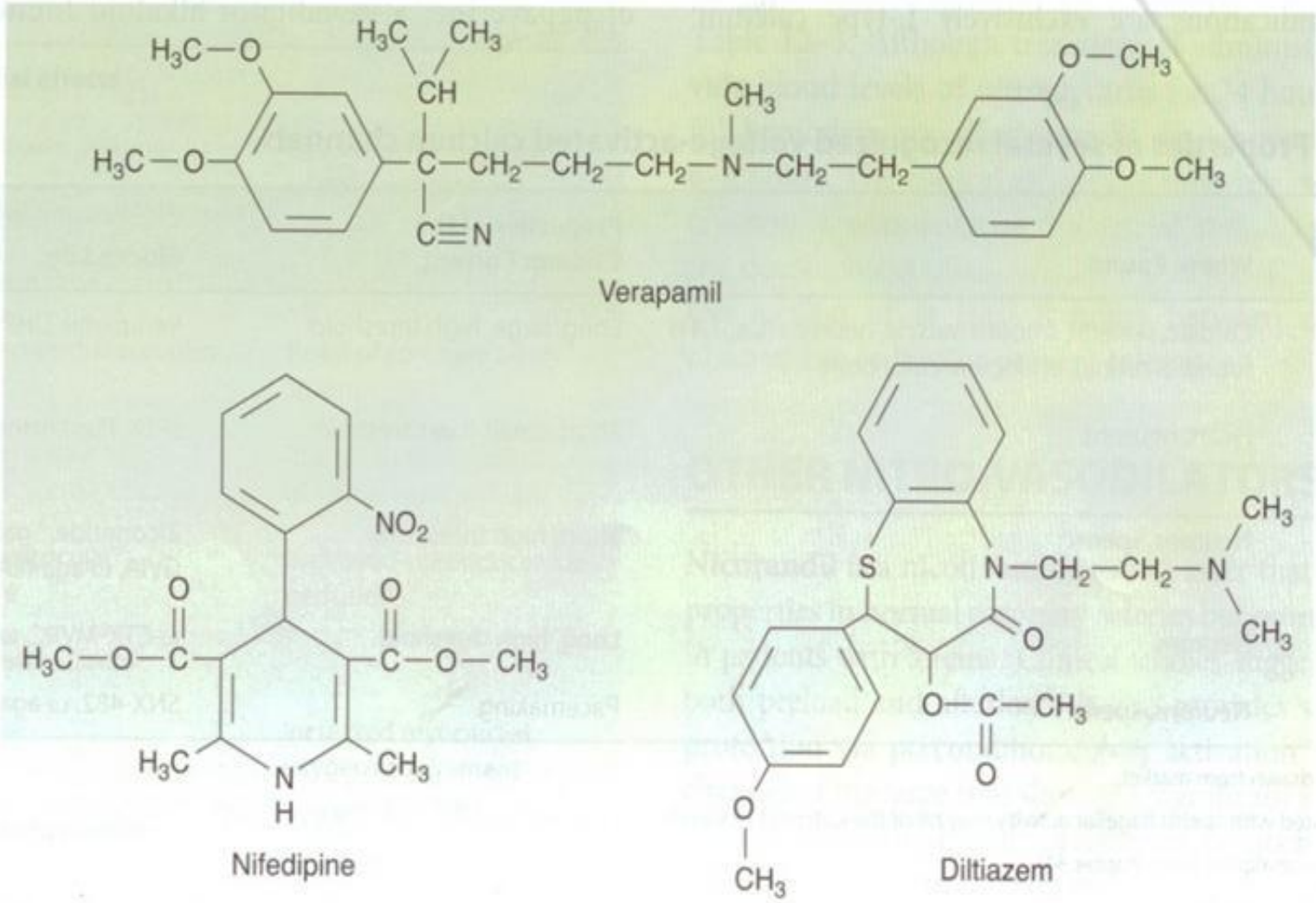
DHPs, dihydropyridines (eg, nifedipine); sFTX, synthetic funnel web spider toxin; ω-CTX, conotoxins extracted from several marine snails of the genus *Conus*; ω-aga-IIIA and ω-aga-IVA, toxins of the funnel web spider, *Agelenopsis aperta*; SNX-482, a toxin of the African tarantula, *Hysterocrates gigas*.

Katzung et al. Basic and Clinical Pharmacology textbook

Calcium channel blocking drugs

used in cardiovascular system

• Groups	prototype
• Phenylalkilamines	verapamil
• Benzothiazepines	diltiazem
• Dihydropiridines	nifedipin



GURE 12–4 Chemical structures of several calcium channel-blocking drugs.

Use of Calcium channel blocking drugs in clinical practice

associated with cardiovascular system

- Antiarrhythmic drugs (class IV)
- Antianginal drugs
- Antihypertensive drugs

Alfa-1 subunit

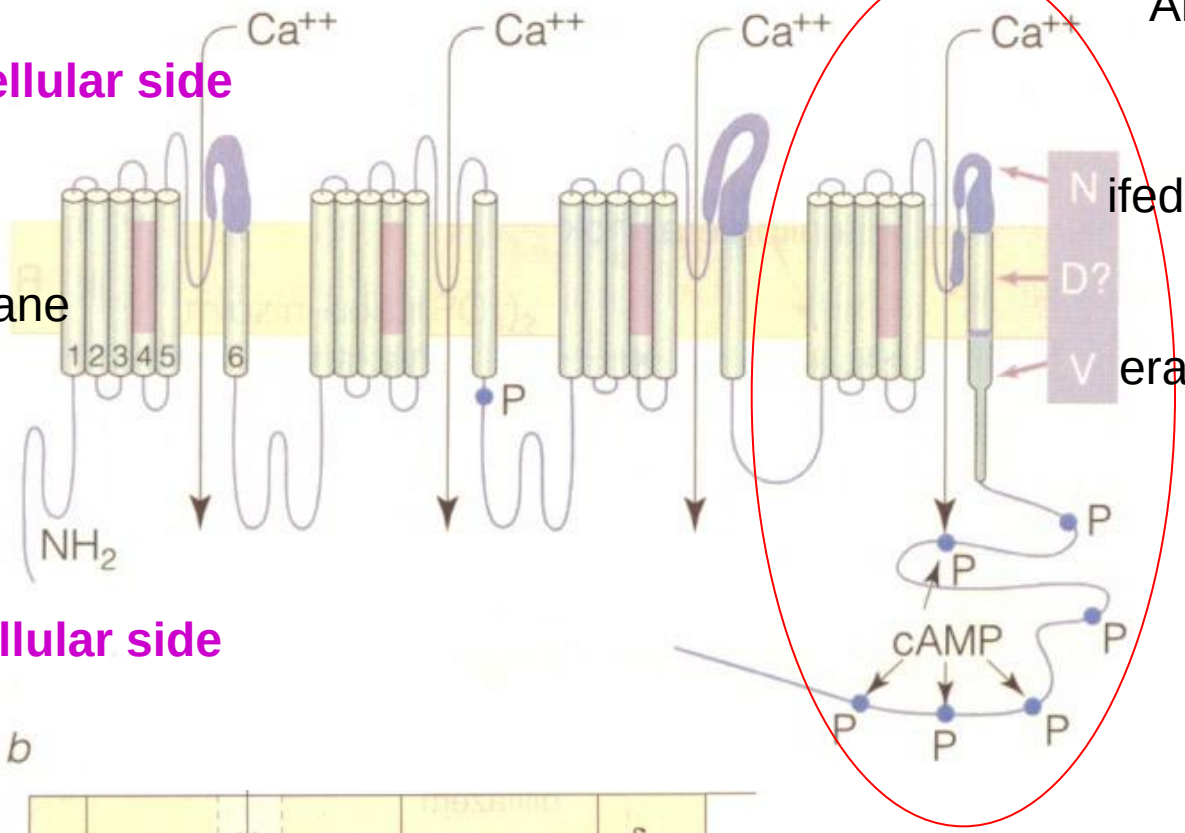
extracellular side

Cell membrane

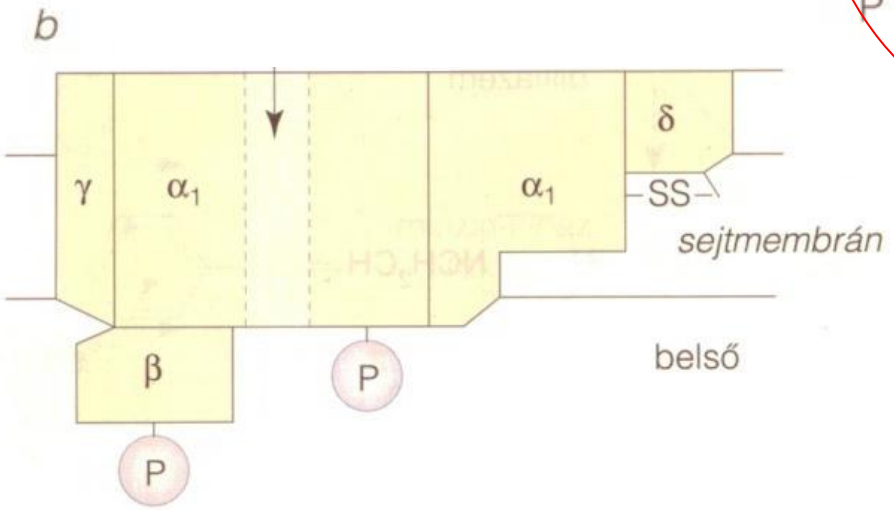
N ifedipine **Dihidropiridines**

D?

V erapamil **Fenylalkilamines**



Intracellular side



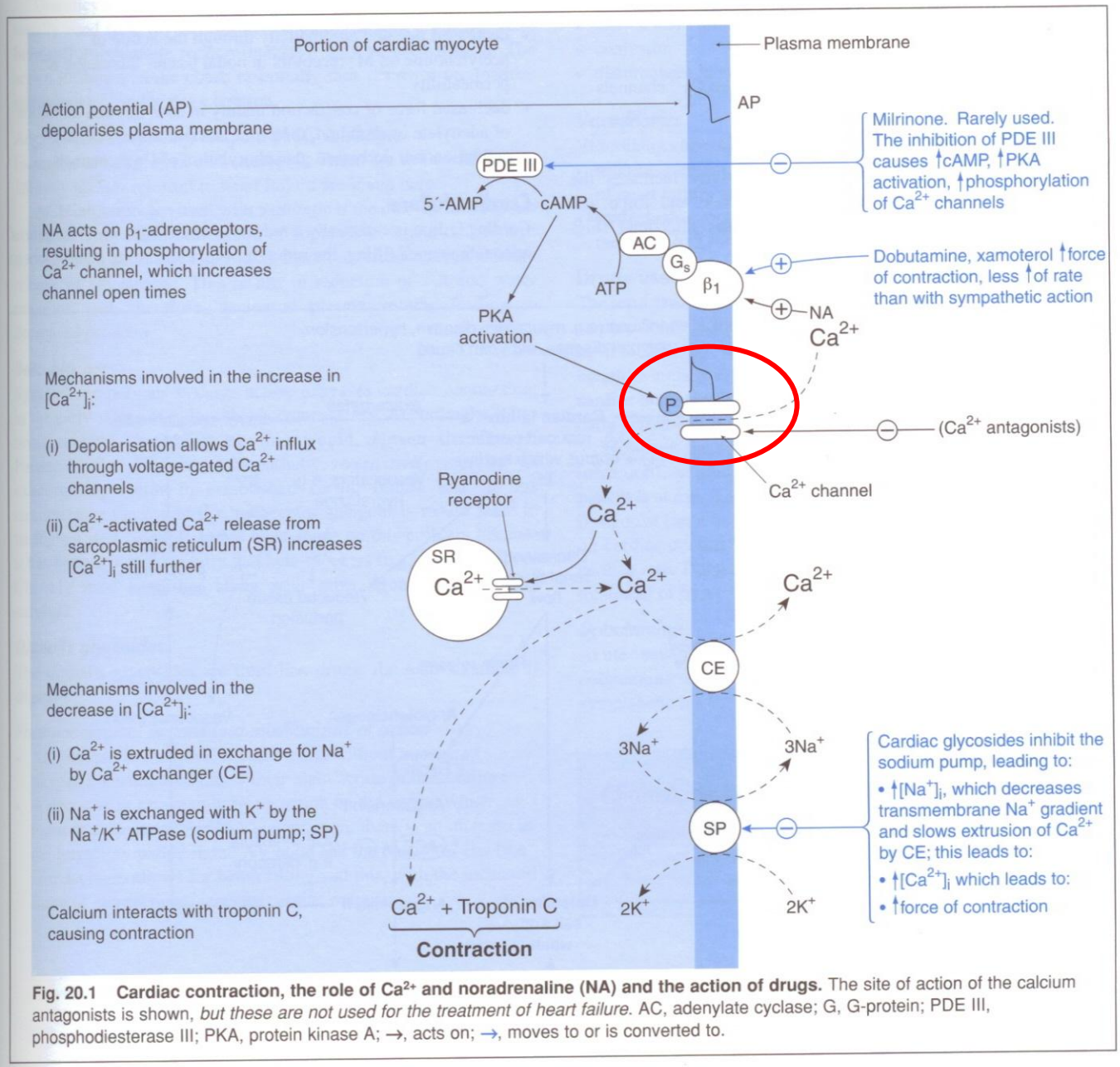
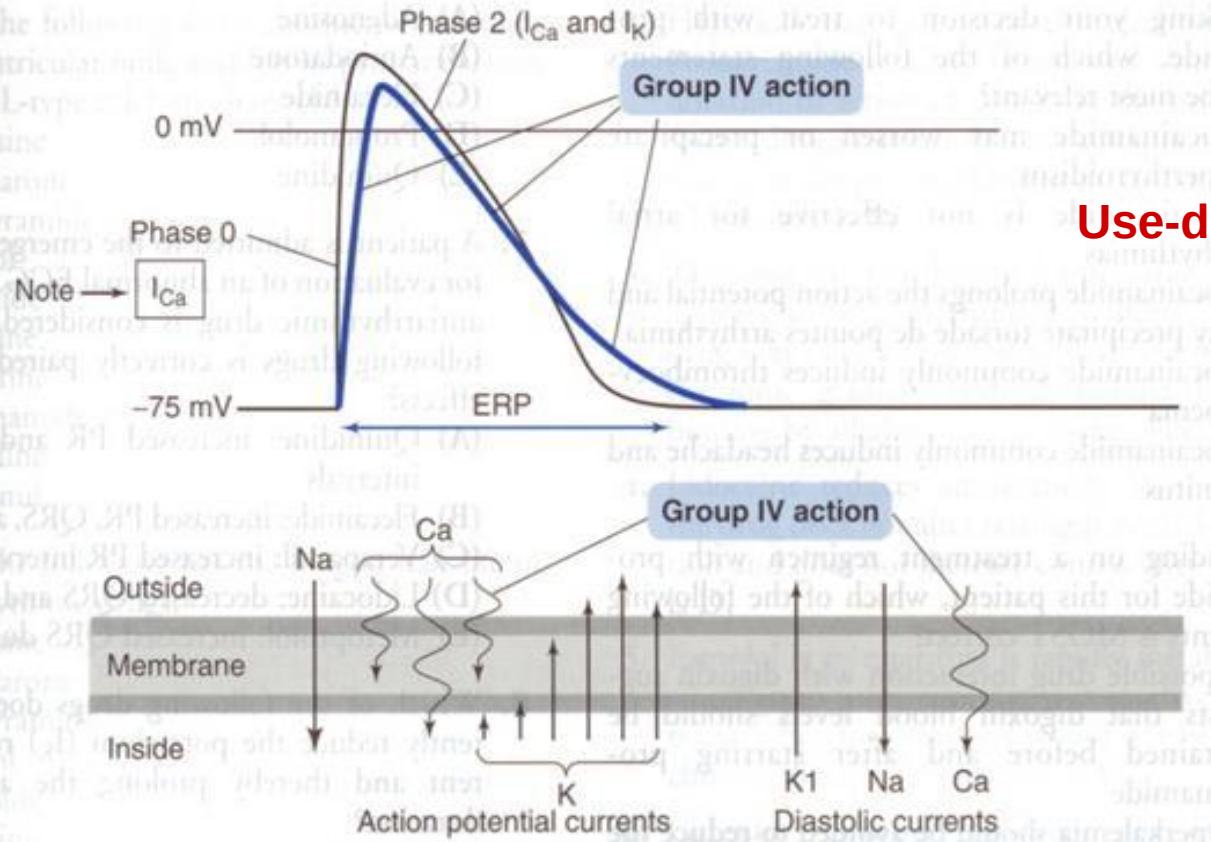


Fig. 20.1 Cardiac contraction, the role of Ca^{2+} and noradrenaline (NA) and the action of drugs. The site of action of the calcium antagonists is shown, *but these are not used for the treatment of heart failure*. AC, adenylate cyclase; G, G-protein; PDE III, phosphodiesterase III; PKA, protein kinase A; →, acts on; →, moves to or is converted to.



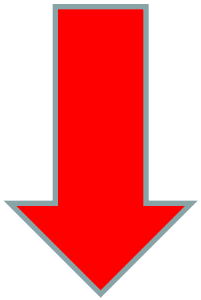
Use-dependent effect

Figure 14–6. Schematic diagram of the effects of class IV drugs in a calcium-dependent cardiac cell in the AV node (note that the AP upstroke in this figure is due mainly to calcium current). Class IV drugs reduce inward calcium current during the AP and during phase 4 (wavy lines). As a result, conduction velocity is slowed in the AV node and refractoriness is prolonged. Pacemaker depolarization during phase 4 is slowed as well if caused by excessive calcium current.

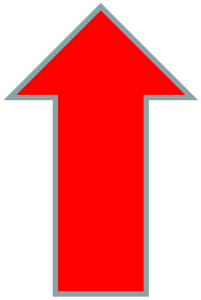
Effect of Ca channel blocking drugs on heart rate

fenylalkilamines | **benzothiazepines** | **dihydropiridines**

Verapamil | **diltiazem** | **nifedipine**



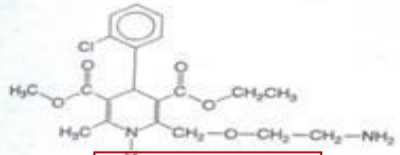
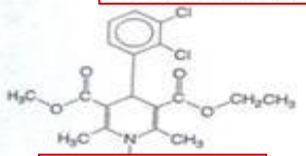
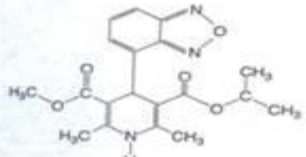
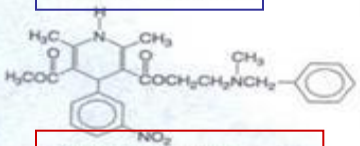
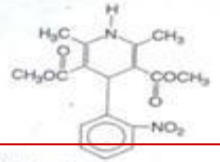
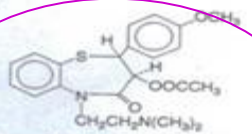
NO CHANGE



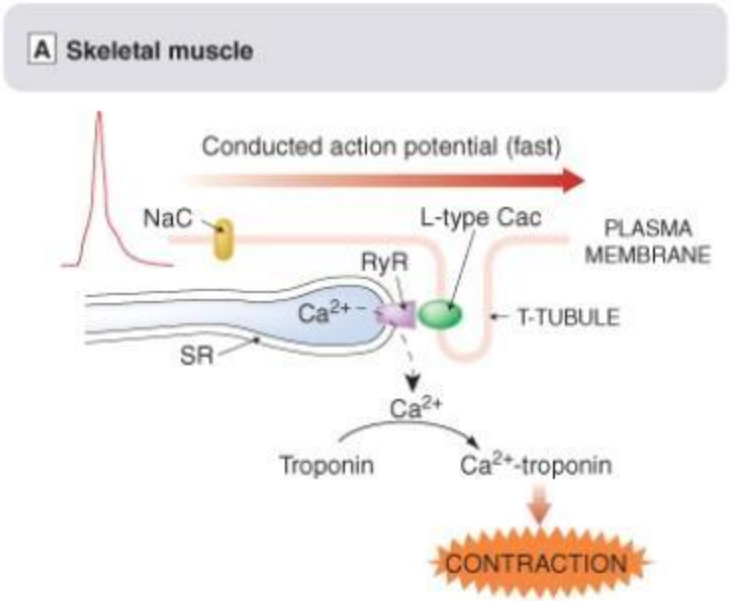
Pulse rate is slowing
by their actions
on conducting tissues

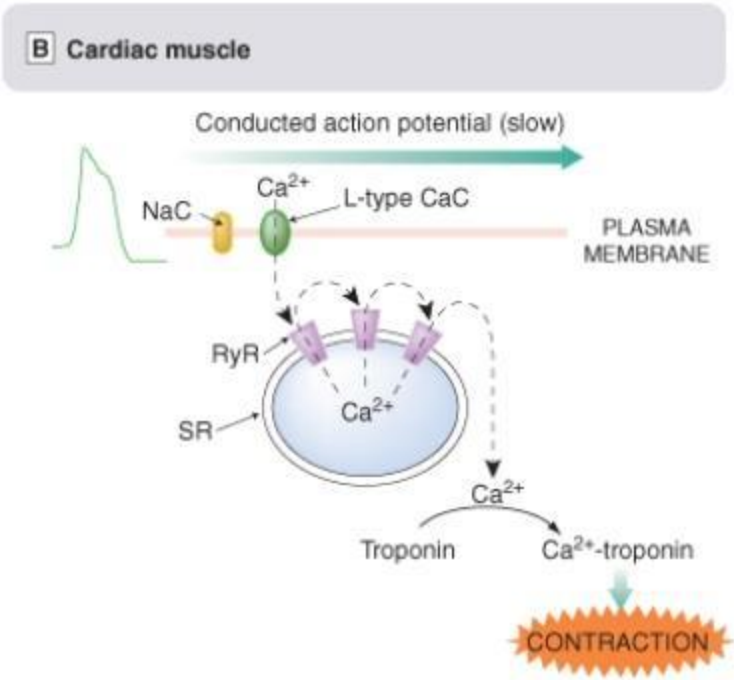
but this is offset of
reflex tachycardia
secondary to vasodilation

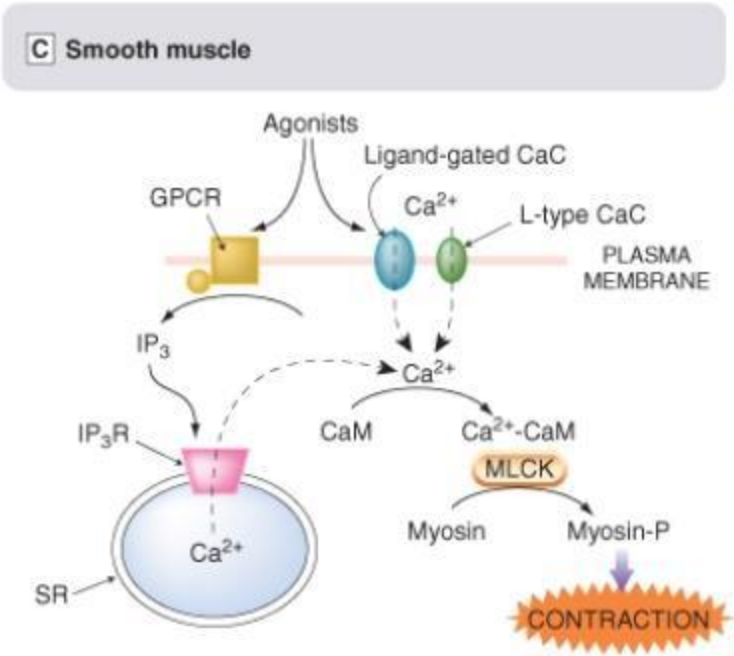
Table 31–2
*Ca^{2+} Channel Blockers: Chemical Structures and Some Relative Cardiovascular Effects**

CHEMICAL STRUCTURE (NONPROPRIETARY AND TRADE NAMES)	VASODILATION (CORONARY FLOW)	SUPPRESSION OF CARDIAC CONTRACTILITY	SUPPRESSION OF AUTOMATICITY (SA NODE)	SUPPRESSION OF CONDUCTION (AV NODE)
 Amlodipine (NORVASC)	5	1	1	0
 Felodipine (PLENDIL)	5	1	1	0
 Isradipine (DYNACIRC)	NR	NR	NR	NR
 Nicardipine (CARDENE, others)	5	0	1	0
 Nifedipine (ADALAT, PROCARDIA)	5	1	1	0
 Diltiazem (CARDIZEM, DILACOR-XR, others)	3	2	5	4
+ Verapamil	4	4	5	5

(Continued)



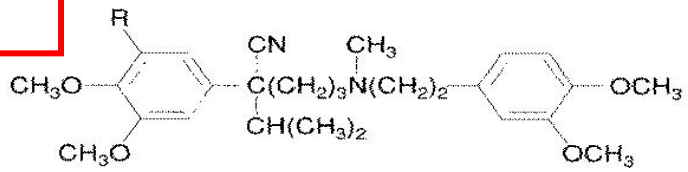




Selectivity of DHPs to vascular smooth muscle cells based on their high affinity to inactive Ca channels

Resting potential of smooth muscle cells is lower than in cardiac muscle cells

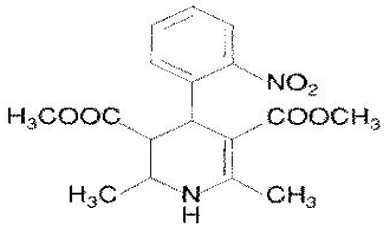
fenilalkilaminok



Negative inotropic and chronotropic effect

R = H verapamil
R = CH_3O gallopamil (D600)

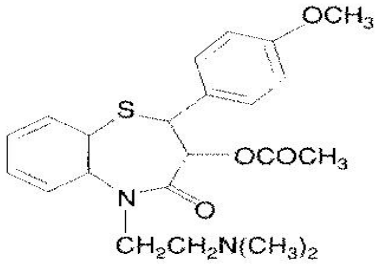
dihidropiridinek



Vasodilation
Stimulation of sympathetic nerve reflexes
No negative inotropic effect

nifedipin

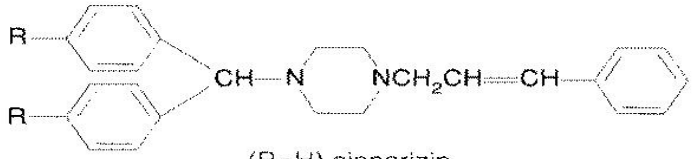
benzothiazepinek



Negative inotropic and chronotropic effect

diltiazem

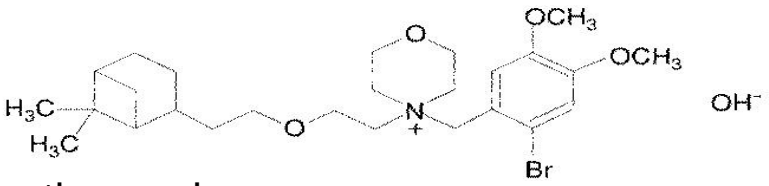
difenilpiperazinok



For migraine prophylaxis

(R=H) cinnarizin
(R=F) flunarizin

egyéb szerkezetűek



Selective inhibition on gastrointestinal smooth muscle

pinaverin

Drug		Oral Bioavailability (%)	Half-life (hours)	Indication
Dihydropyridines				
Amlodipine	Norvasc	65–90	30–50	Angina, hypertension
Felodipine	Felodipin Plendil	15–20	11–16	Hypertension, Raynaud's phenomenon
Isradipine	Lomir	15–25	8	Hypertension
Nicardipine		35	2–4	Angina, hypertension
Nifedipine	Adalat Corinfar	45–70	4	Angina, hypertension, Raynaud's phenomenon
Nimodipine	Nimotop	13	1–2	Subarachnoid hemorrhage
Nisoldipine		< 10	6–12	Hypertension
Nitrendipine	Baypress	10–30	5–12	Investigational
Miscellaneous				
Diltiazem	Dilzem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	Isoptin Chinopamil	20–35	6	Angina, hypertension, arrhythmias, migraine

Table 12–6. Vascular selectivity and clinical properties of some calcium channel-blocking drugs.

Drug	Vascular Selectivity[1]	Indications	Usual Dosage	Toxicity
Dihydropyridines				
Amlodipine	++	Angina, hypertension	5–10 mg orally once daily	Headache, peripheral edema
Felodipine	5.4	Hypertension, Raynaud's phenomenon, congestive heart failure	5–10 mg orally once daily	Dizziness, headache
Isradipine	7.4	Hypertension	2.5–10 mg orally every 12 hours	Headache, fatigue
Nicardipine	17.0	Angina, hypertension, congestive heart failure	20–40 mg orally every 8 hours	Peripheral edema, dizziness, headache, flushing
Nifedipine	3.1	Angina, hypertension, migraine, cardiomyopathy, Raynaud's phenomenon	3–10 µg/kg IV; 20–40 mg orally every 8 hours	Hypotension, dizziness, flushing, nausea, constipation, dependent edema
Nimodipine	++	Subarachnoid hemorrhage, migraine	60 mg orally every 4 hours	Headache, diarrhea
Nisoldipine	++	Hypertension	20–40 mg orally once daily	Probably similar to nifedipine
Nitrendipine	14.4	Investigational for angina, hypertension	20 mg orally once or twice daily	Probably similar to nifedipine
Miscellaneous				
Bepridil	–	Angina	200–400 mg orally once daily	Arrhythmias, dizziness, nausea

Goodman Gilman's The Pharmacological Basis of Therapeutics

1. **Short-acting DHPs:** **nifedipine, nimodipine**

2. **Medium – acting DHPs:** **isradipine, felodipine, nisoldipine**

3. **Long-acting DHPs:** **amlodipine, lacidipine**

For hypertonia with artherosclerotic vessels:

Lacidipine	**long lasting effect controlled by cholesterine**
Israpidine	**increases HDL**

In cerebral ischemia

Nimodipine	**some selectivity for cerebral vessels**

Side effects

Flush, dizziness
Ankle oedema
Fatigue
Constipation

Rarely: **hepatitis, cataracta, cerebral ischemia, depression, gynecomastia agranulocytosis**

ABCD and FACET clinical studies showed increased cardiovascular mortality in the case of the short-acting DHPs

Acute toxicity in overdosage:

AV block
Negative inotropic effect with reduced cardiac output
Hypotension

Therapy: **Ca iv. 2-10 g ! But it has little effect on nodal block**

glucagon, vasopressin, epinephrine

high dose insulin plus glucose supplementation

Mibefradil inhibits T type Ca channels

is a glycoprotein, which was used as antihypertensive and antianginal drug, withdrawn from te market because of severe drug interactions with:

digoxin
other Ca channel blockers
beta blocking drugs
simvastatin
cyclosporine
tacrolimus

Background:

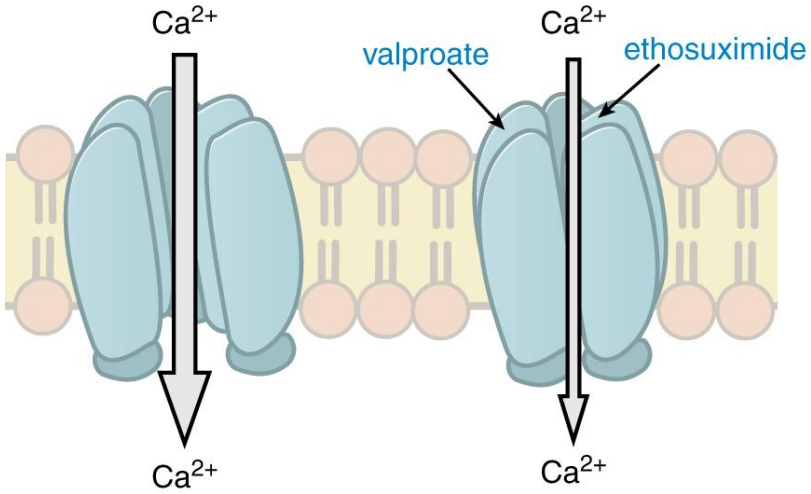
inhibition of P glycoprotein transport/ expump systems, MDR

inhibition CYP3A

ANTIEPILEPTIC DRUGS

Target: T type Ca channels in thalamus

Valproic acid and ethosuccimide



Target: N type Ca channels

Gabapentin and pregabalin

ZICONOTIDE

Special N-type Ca channel blocker

Derivative of the snail omega-conotoxin

Poor bioavailability

Low therapeutic index

Administration only by intrathecally for relieving severe chronic pain