CALCIUM csatorna BLOKKOLÓK

Dr. Benkő Ilona
egyetemi docens

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

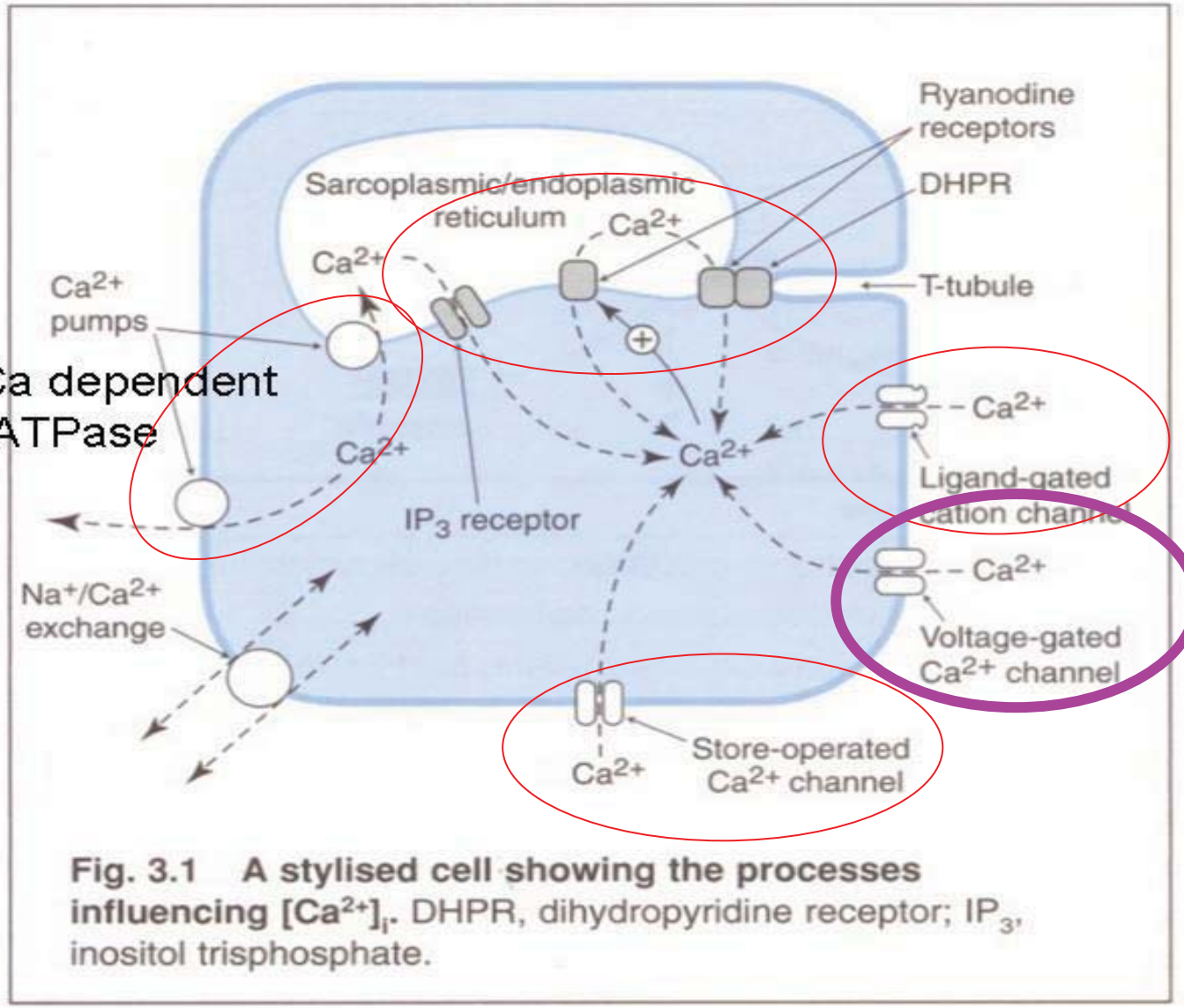


Fig. 3.1 A stylised cell showing the processes influencing $[Ca^{2+}]_i$. DHPR, dihydropyridine receptor; IP_3, inositol trisphosphate.

L type

Ca channel

12

Dale and Haylett: Pharmacology Condensed

A kálcium fiziológiás szabályozó szerepe celluláris szinten

Elektromos excitabilitás

kontrakció — a harántcsikolt vázizom

a simaizom

és a szivizom — sejtekben

Exocitózis

Kémiai mediátorok felszabadulása az idegvégződésekben

Sejthalál — Apoptozis

Second messenger

immunrendszerben
sok sejtben a VDR expresszióját bef.

...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[1] Antianginal drug withdrawn from market.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.

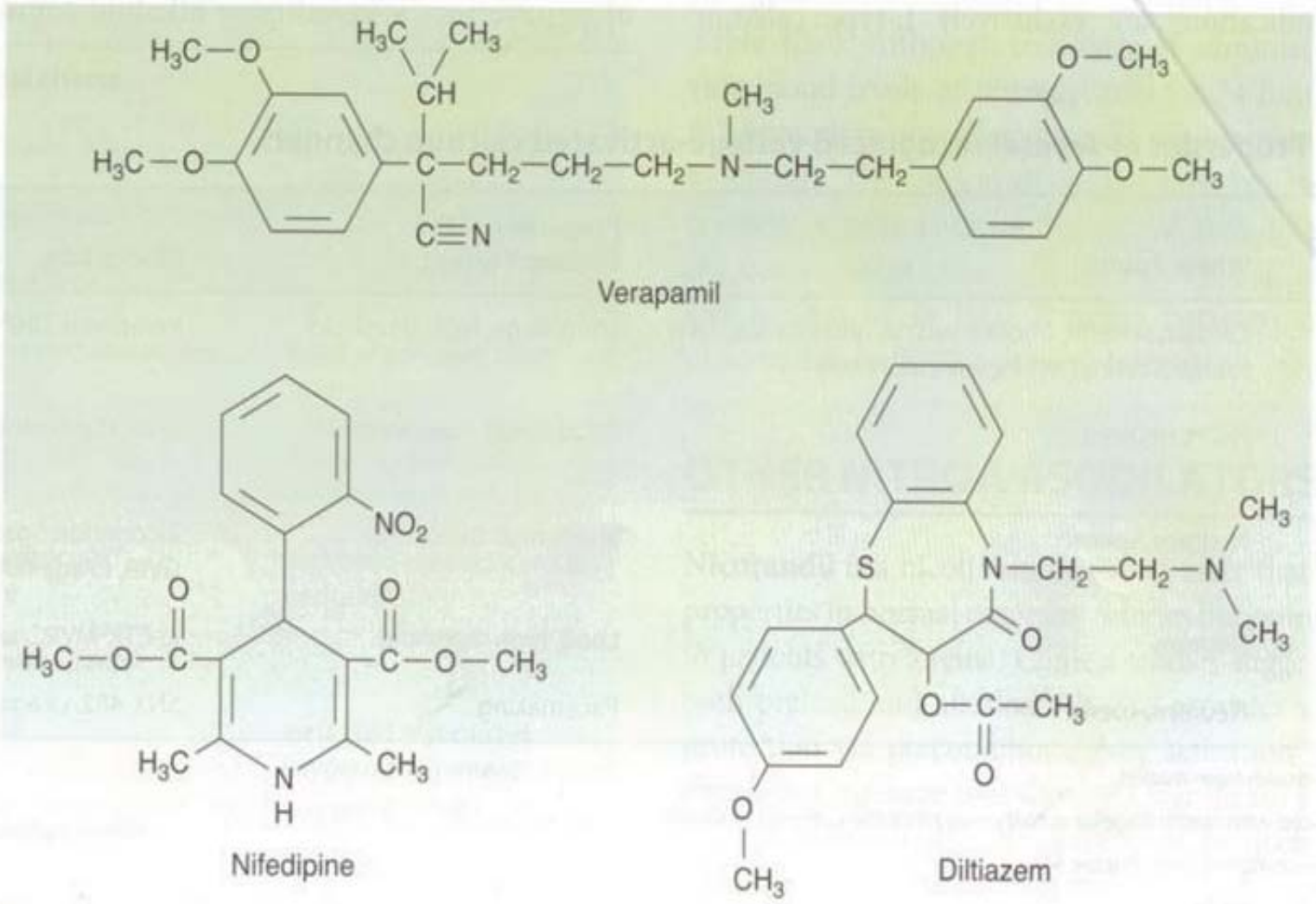
[3] Synthetic snail peptide analgesic (see Chapter 31).

[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*.

A cardiovasculáris rendszerrel kapcsolatos betegségekben használt kálcium csatorna blokkolók

Gyógyszercsoportok	prototipusok
Fenilalkilaminok	verapamil
Benzotiazepinek	diltiazem
Dihidropiridinek DHP	nifedipin



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

A cardiovasculáris rendszerrel kapcsolatos betegségekben használt kálcium csatorna blokkolók terápiás indikációs területei

Antiaritmiás hatás
(az antiaritmiás szerek IV. csoportját alkotják)

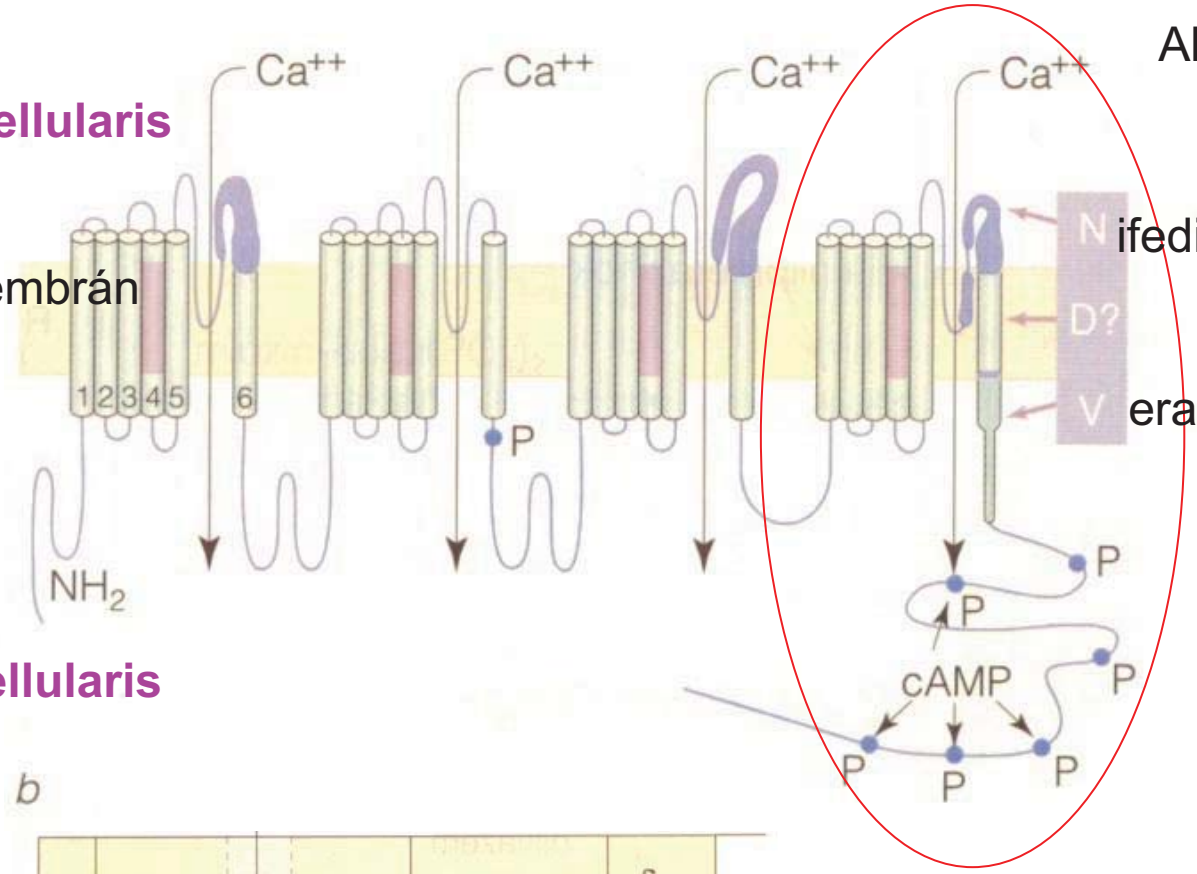
Antianginás hatás

Antihipertenziv hatás

extracellularis

sejt membrán

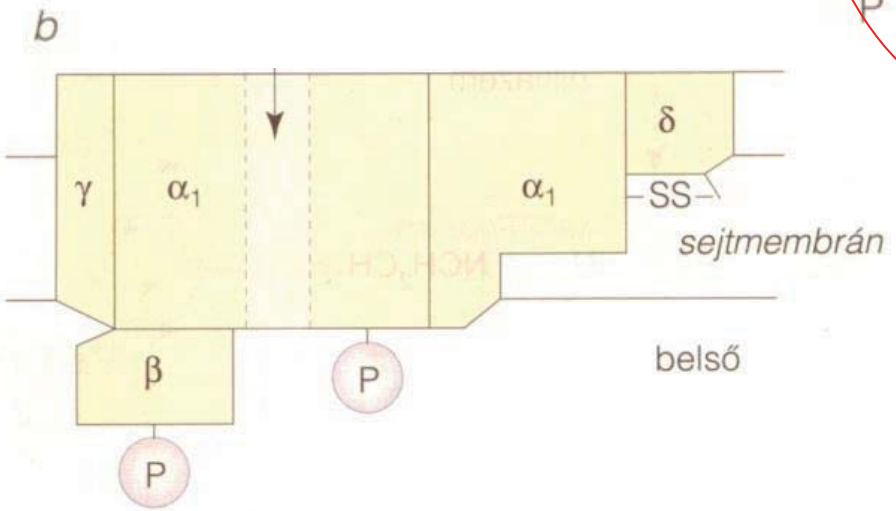
Intracellularis



Alfa-1 subunit

ifedipine **Dihidropiridinek**

erapamil **Fenylalkilaminok**



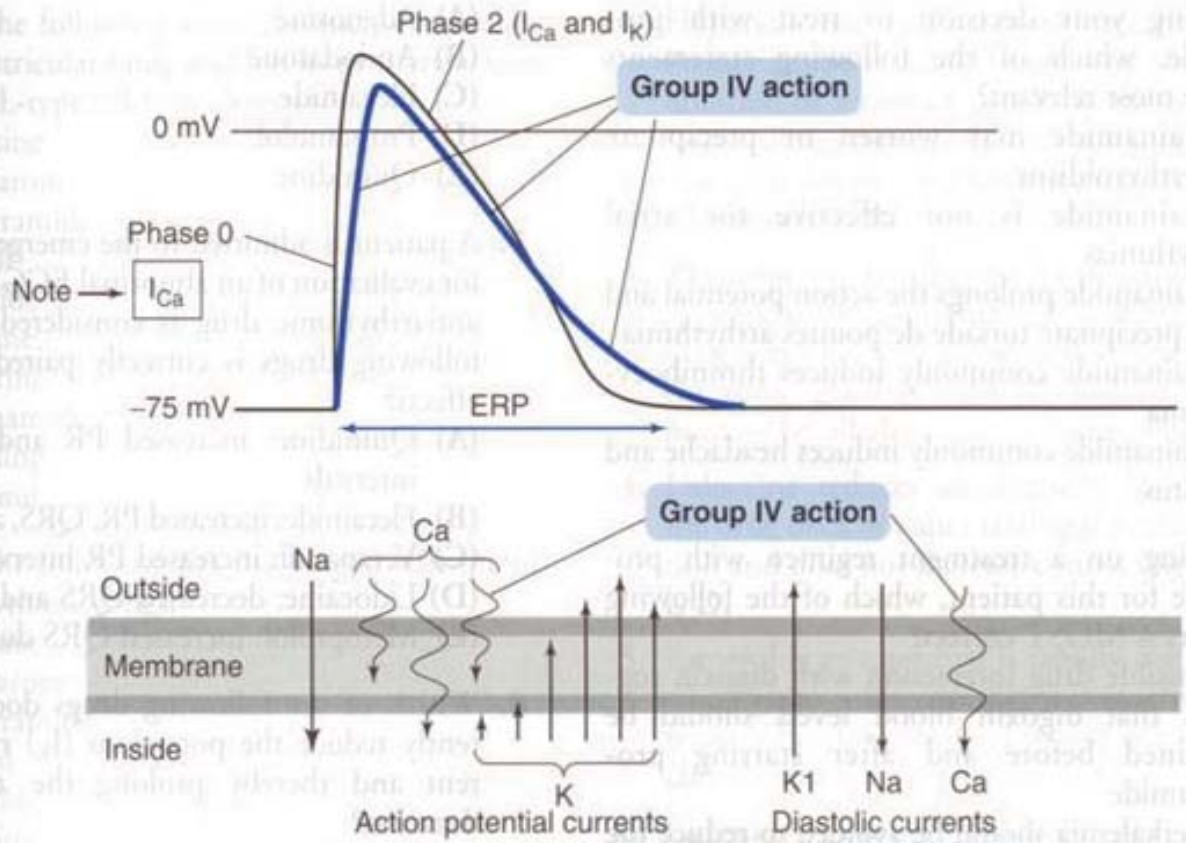


Figure 14–6. Schematic diagram of the effects of class IV drugs in a calcium-dependent cardiac cell in the AV node (note that the AP upstroke in this figure is due mainly to calcium current). Class IV drugs reduce inward calcium current during the AP and during phase 4 (wavy lines). As a result, conduction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

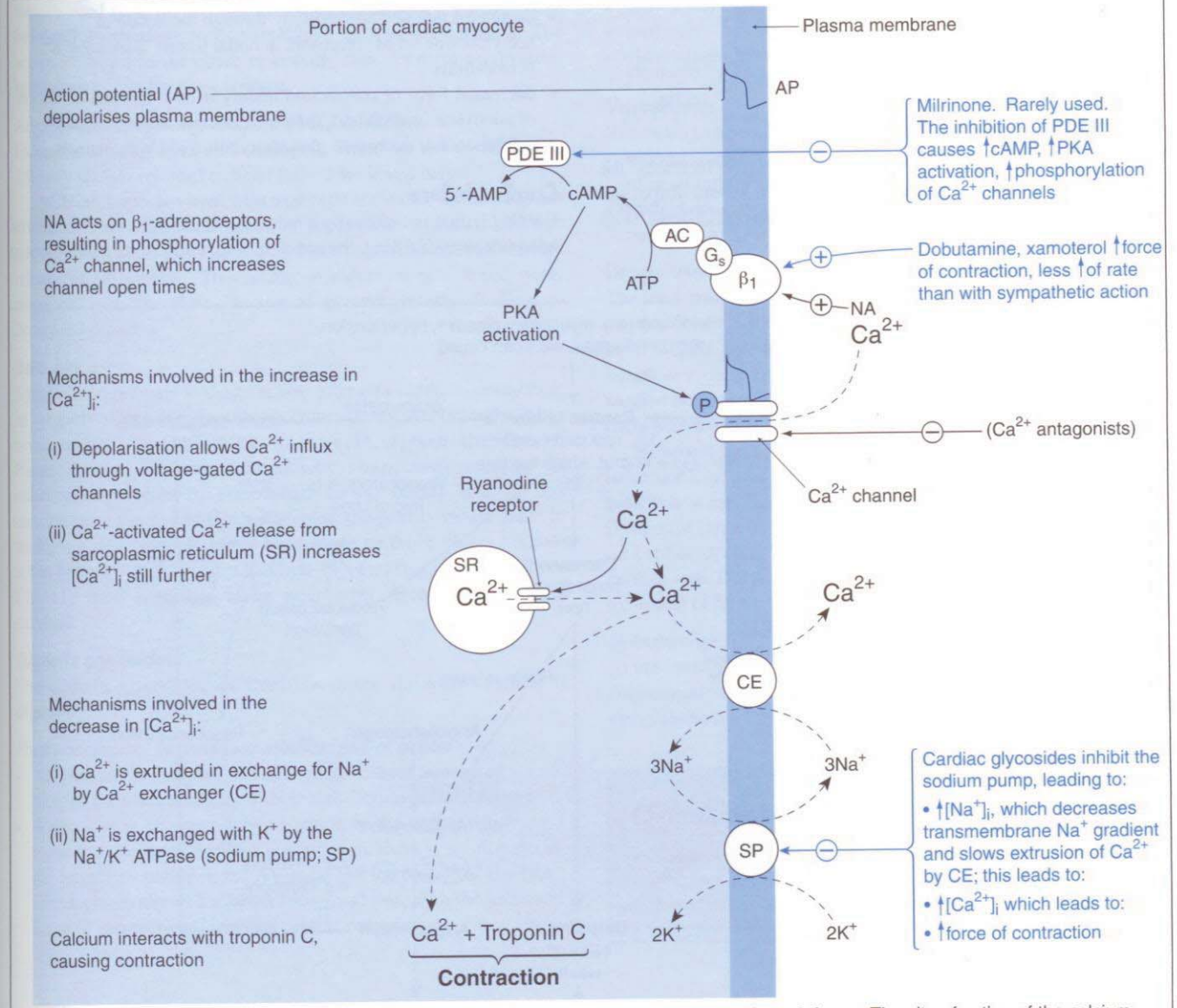
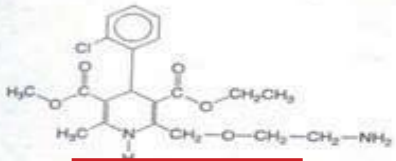
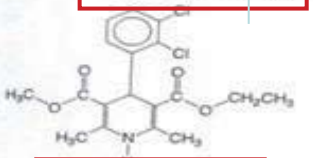
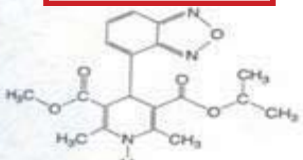
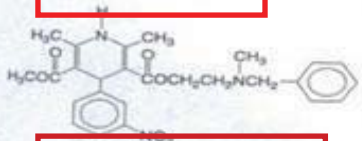
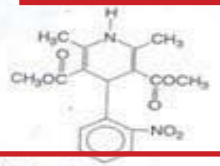
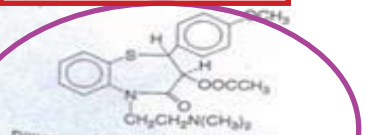
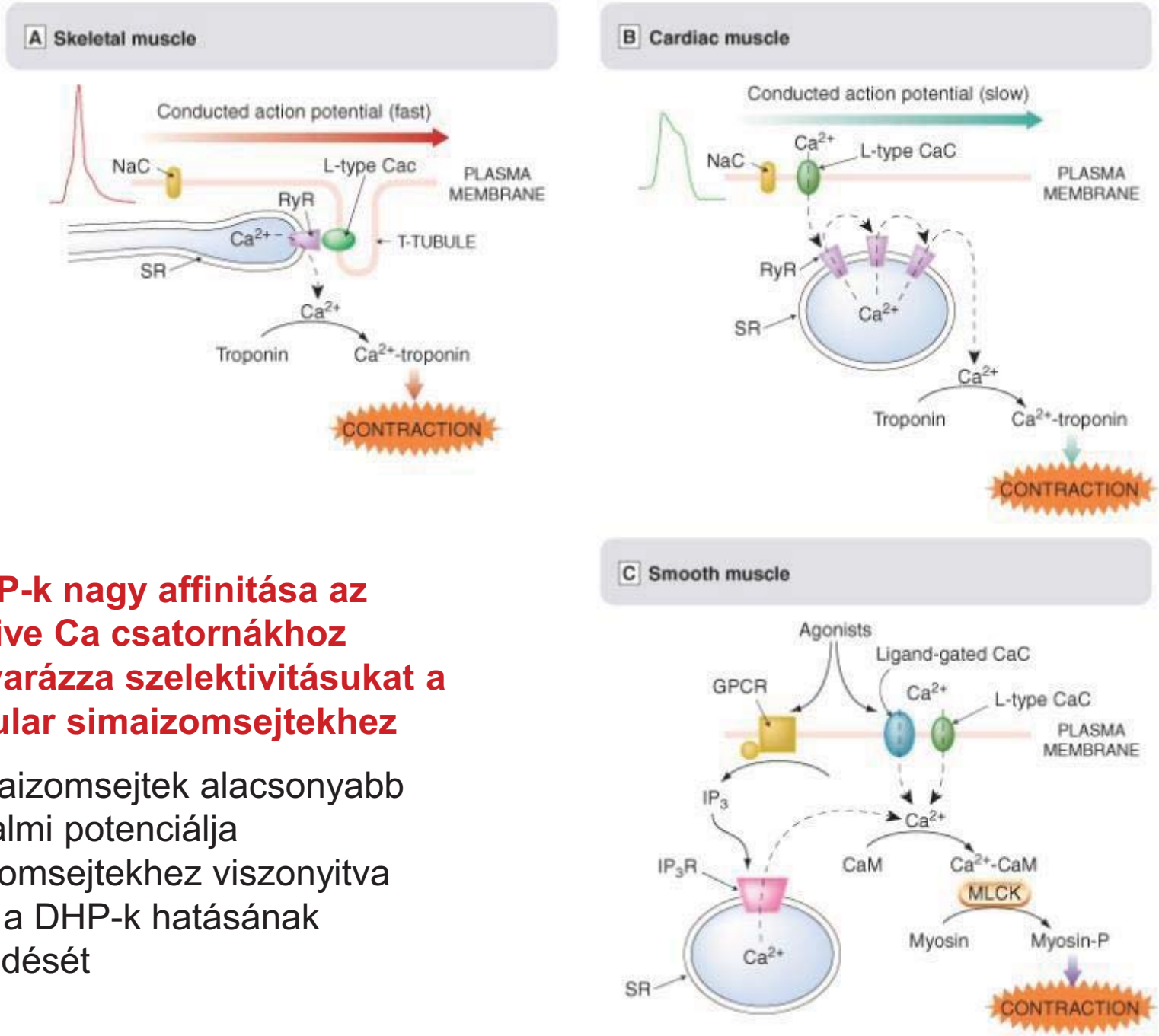


Fig. 20.1 Cardiac contraction, the role of Ca^{2+} and noradrenaline (NA) and the action of drugs. The site of action of the calcium antagonists is shown, *but these are not used for the treatment of heart failure.* AC, adenylate cyclase; G, G-protein; PDE III, phosphodiesterase III; PKA, protein kinase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

*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

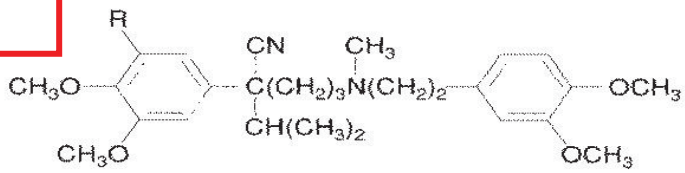
(Continued)



A DHP-k nagy affinitása az inactive Ca csatornákhoz magyarázza szelektivitásukat a vascular simaizomsejtekhez

A simaizomsejtek alacsonyabb nyugalmi potenciálja szivizomsejtekhez viszonyitva segiti a DHP-k hatásának kifejlődését

fenilalkilaminok



Negativ inotrop és chronotrop hatás

R = H verapamil
R = CH_3O gallopamil (D600)

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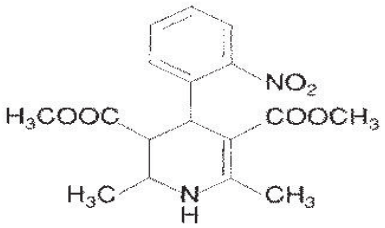
dihidropiridinek



Vasodilatio
a sympatikus idegrendszeri reflexek stimulációja miatt NINCS negativ chronotrop hatás

nifedipin

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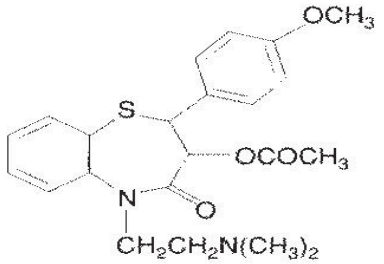
benzothiazepinek



Negativ inotrop és chronotrop hatás

diltiazem

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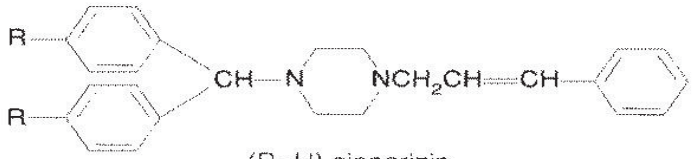
difenilpiperazinok



migraine prophylaxis

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

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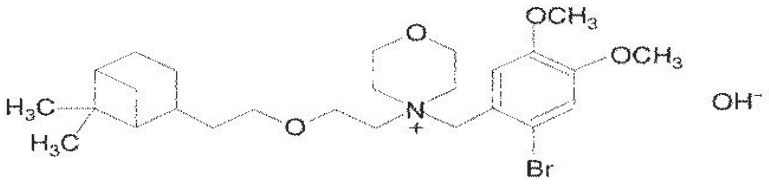
egyéb szerkezetűek

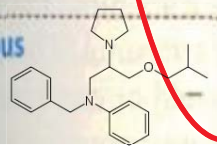


Szelektiv a gastrointestinalis simaizomra

pinaverin

Katzung et al Basic and Clinical Pharmacology textbook

Drug	Vascular Selectivity	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	ventricular Arrhythmias, dizziness, nausea



Vérnyomáscsökkentő /cardiodepressziv dózis

Rövid hatástartamú dihidropiridinek (DHP)				
Nifedipin	1/10	6	2–4×10–20 mg sublingualisan 10 mg/60 spray	hypertonia, angina érszűkület
Nicardipin	1/300	4	3×20–40 mg	angina, hypertonia
Nimodipin	1/30	5	iv. 1 mg/h	subarachno idealis vérzés
Közepes hatástartamú DHP				
Isradipin	1/15	8	2–3×5–7,5 mg	angina, hypertonia, arteriosclerosis
Felopidin	1/118	8	2–3×5–10 mg	angina, hypertonia
Nisoldipin	1/1000	8–11	1–2×5–10 mg	angina, hypertonia
Nitrendipin	1/80	7–8	1–2×10–20 mg	angina, hypertonia
Hosszú hatású DHP				
Amlodipin	1/10	35–50	2,5–10 mg	angina, hypertonia
Lacidipin	1/54	7–8	4–6 mg	angina, hypertonia, arteriosclerosis

Antihipertenziv hatás atherosclerotikus ereken is:

Lacidipin	hosszú hatástartam koleszterintartalomtól függő hatás
Israpidin	increases HDL

cerebralis ischemiában

Nimodipin	fokozott szelektivitás az agyi erekhez

Mellékhatások

Hypotonia, Flush, szédülés, zavartság
Negativ inotrop, fáradékonyság (vázizmokon is gátol kismértékben)
boka oedema
székrekedés

Ritka mellékhatások:
hepatitis, cataracta, cerebral ischemia, depressio, gynecomastia, agranulocytosis

ABCD és FACET klinikai tanulmányok szerint megn9vekedett a cardiovascular mortalitás a short-acting (rövid hatástartamú) DHP-ek esetében

Akut toxicitás túladagolás esetén:

AV block
Negative inotrop hatás csökkent cardiac output !
Súlyos hypotensio

Therapia: Ca iv. 2-10 g ! Kicsi a hatása az AV blokkra

glucagon, vasopressin, epinephrin

ma: **magasdózisú inzulin kezelés + glükóz inf.**

Mibefradil az *L tipusú + T tipusú* Ca csatornák blokkolója

Glikoprotein antihipertenziv és antianginás hatásai miatt használták

KIVONTÁK a forgalomból

Súlyos gyógyszerinterakciók miatt:

DIGOXIN
más Ca csat blokkolók
beta blokkolók
simvastatin
cyclosporin
tacrolimus

Ok: gátolta a P glikoprotein expump MDR transzport rendszert
gátolta a CYP3A

Ziconotid szelektiv N tipusú Ca csat. Blokkoló

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-
Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH2

Kúpos csiga Omega-conotoxin származék

Rossz biológiai hasznosulás

Kicsi terápiás index
mellékhatások: nausea, fejfájás, szédülés, confusio
hypertonia, ataxia, somnolentia, depresszió

Nonopioid, de a kábitó fájdalomcsillapitókhoz hasonló effektivitás !

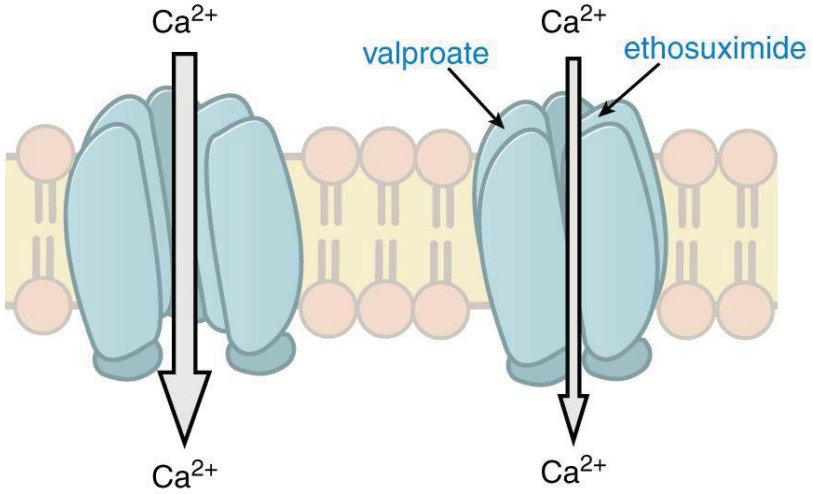
Felhasználás:

intratecalisan súlyos krónikus fájdalmak kezelésére

ANTIEPILEPTIKUMOK

Target: T tipusú Ca csatornák a thalamusban

Valproinsav és etoszukcimid



Target: N tipusú Ca csatornák

Gabapentin és pregabalin

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	6–12	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.

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