Outline

Part One Antianginal drugs

Part Two Antiarrihythmic drugs

Part One Antianginal drugs

I. Review-Angina pectoris (primary symptom of ischemic heart disease)

II. Major antianginal drug classes

I. Review-Angina pectoris (primary symptom of ischemic heart disease)

A. Case study

Case study (Foye's) "MM, a white male, is celebrating his 65th birthday. His two children are visiting from California for the party. Sitting around the birthday table, MM's son reminiscences about the one-on-one basketball games they used to have out in the driveway. On a whim, MM and son decide to give it a go for old time's sake. Of course, MM's son lets dad win the game and not long after coming back into the house MM begins to experience what he describes as a crushing pain beneath his sternum that radiates to his left shoulder and down the inside of his left arm. After sitting quietly for a while, the pain subsided but when MM attempted to climb the stairs to his bedroom, the pain returned. MM was taken to the emergency room of your hospital and admitted for overnight observation and evaluation. Upon exercise stress testing, MM demonstrated an ischemic ECG response along with dyspnea and chest pain at about 70% of maximal heart rate."

A. Case studies

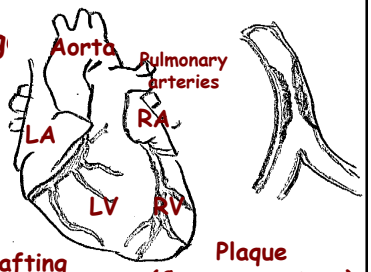
a. What is his diagnosis

b. What are the common causes of angina?

- ❑ Exertion
- ❑ Emotional stress
- ❑ Eating a heavy meal
- ❑ Extreme temperatures (hot or cold)

C. What about this patient?

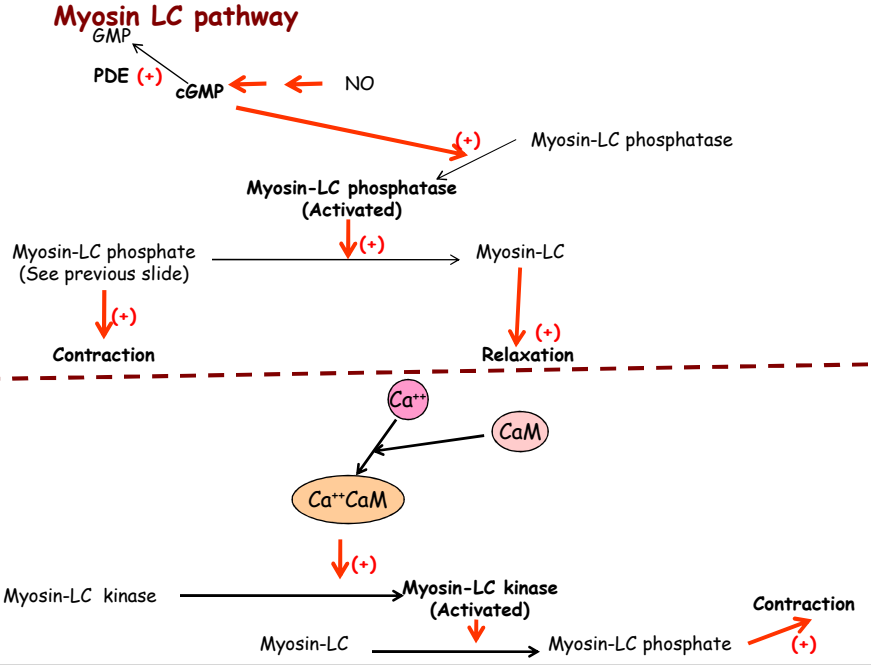
c. Summary of pathological chang

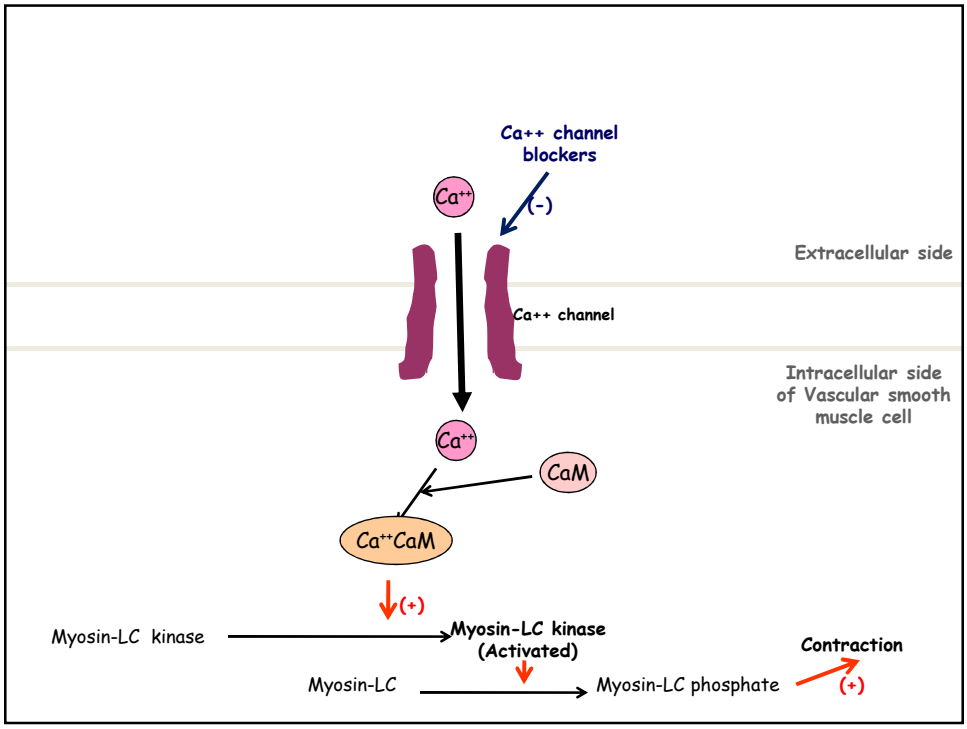


Coronary artery bypass grafting

Plaque (Coronary artery)

d. Control of contraction/relaxation of arterial smooth muscles- Myosin LC pathway



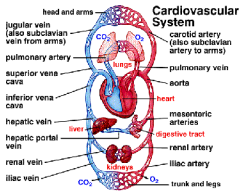


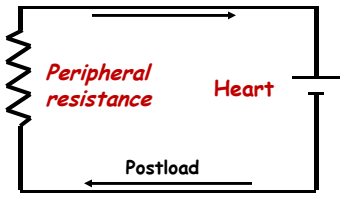
II. Major antianginal drugs

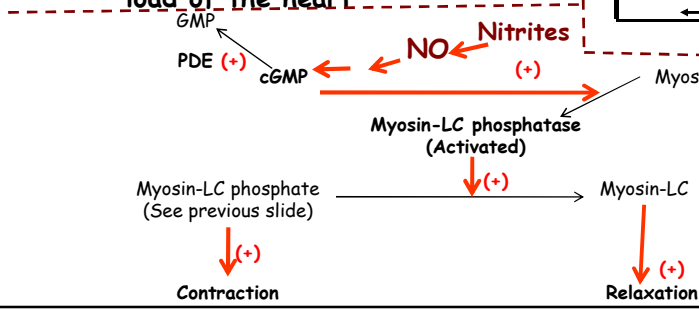
- A. Nitrates and nitrites
- B. Nitric oxide donors
- C. Calcium channel blockers
- D. β-adrenergic blocking agents
- E. Modulators of myocardial metabolism
- F. Miscellaneous coronary vasodilators

A. Nitrates and nitrites

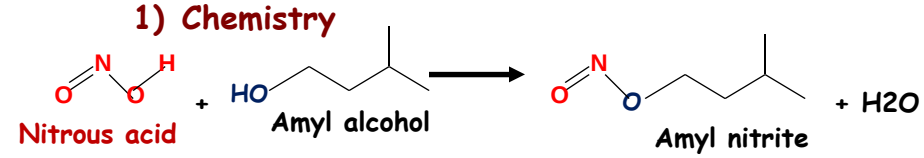
- Pharmacological sources of nitric oxide (NO). But the mechanism is unknown
- Pharmacological effects of NO
  - Relaxation of vascular smooth muscle
    - ↑ Blood supplies and oxygen to myocardial tissues.
    - Peripheral resistance and post load of the heart

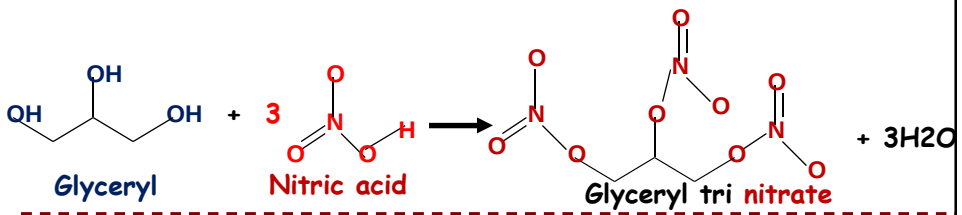


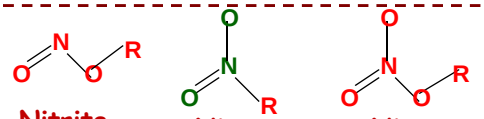


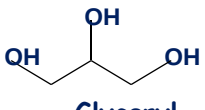


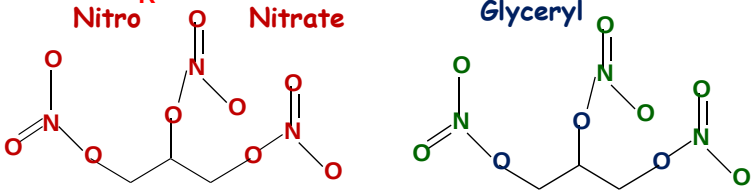
1) Chemistry







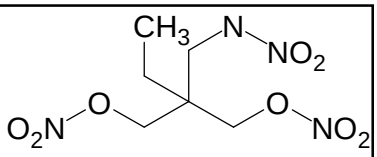




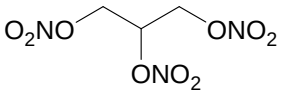
Glyceryltrinitrate or Nitroglycerin (Nitro glycerol)?

2) Commonly used drugs

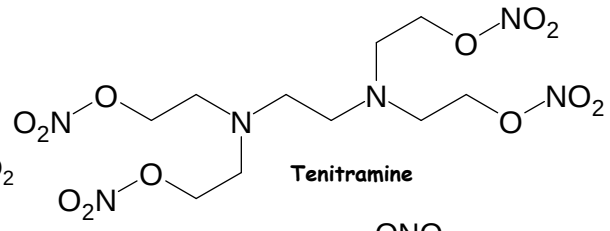
- Active drug moieties
- Why are multiple drugs are developed



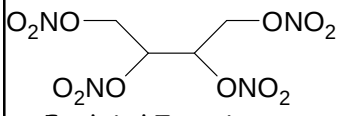
Propatyl nitrate



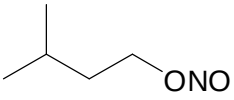
Glyceryl Trinitrate



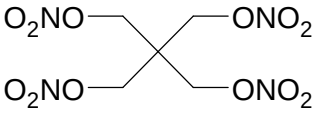
Tenitramine



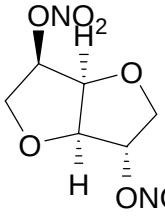
Erythrityl Tetranitrate



Amyl Nitrite

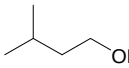
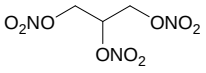
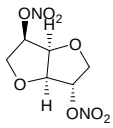
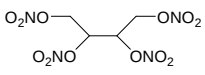
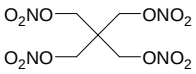


Pentaerythritol Tetranitrate



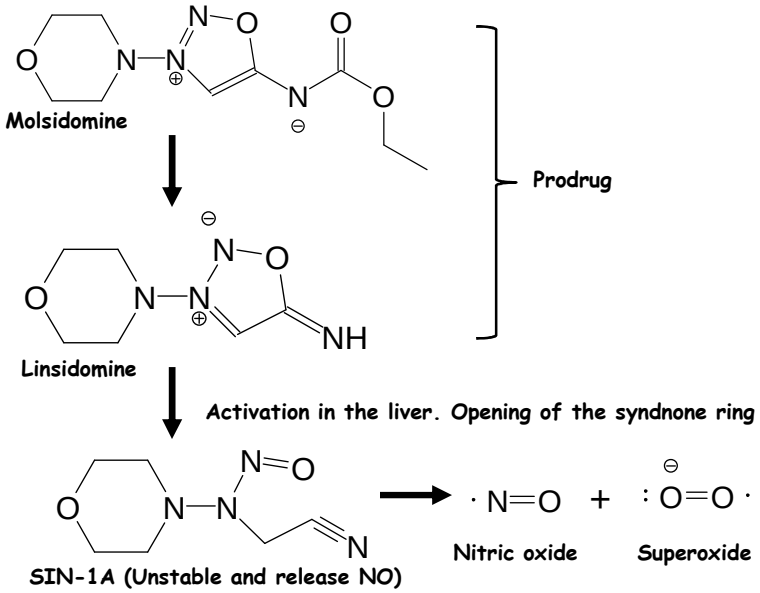
Isosorbide dinitrate

3) Structure/pharmaceutical properties relationships

Structure	Name	On-set time (min)	Peak time (min)	Duration (min)
	Amyl nitrite	0.25	0.5	1
	Glyceroltrinitrate	2	8	30
	Isosorbide dinitrate	3	15	60
	Erythrityl tetranitrate	15	32	180
	Pentaerythritol tetranitrate	20	70	330

B. Nitric oxide donor

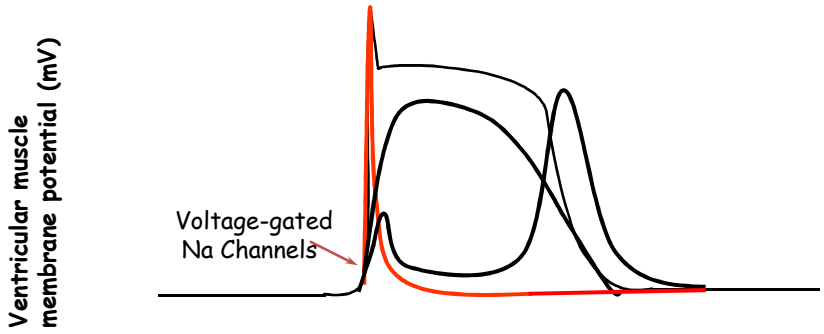
Molsidomine metabolism to nitric oxide



Part Two: Antiarrhythmic drugs
(Classes I-IV, Classification based on MOA)

A. Class I-Na^+ channel blockage
B. Class II-β-adrenergic blockage
C. Class III-K^+ channel blockage
D. Class IV-Ca^{++} channel blockage

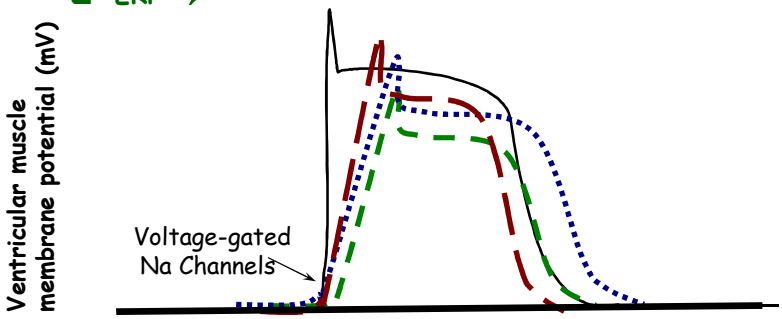
I Class I-Na^+ channel blockage



Ion channels and membrane potential on the myocardiac membrane

Subclasses of Class I antiarrhythmic drugs

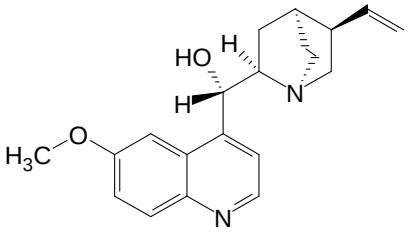
- Class Ia e.g. Quinidine
  - Moderate Na+-channel blockade
  - Effective refractory period (ERP)↑
- Class Ib e.g. Lidocaine
  - Weak Na+-channel blockade
  - ERP↓
- Class Ic e.g. Flecainide
  - Strong Na+-channel blockade
  - ERP →



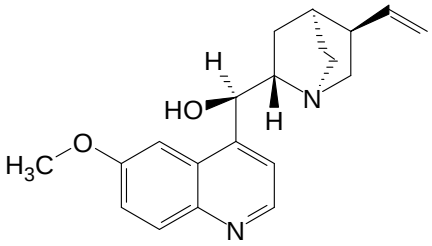
Ion channels and membrane potential on the myocardiac membrane

A. Class Ia: Quinidine

- An alkaloid found in cinchona bark
- Diastereomer of quinine (An anti-malarial, anti-pyretic, and anti-periodic drug)
- Compete P-gp with cardiac glycosides



Quinidine



Quinine

Problem Set #1

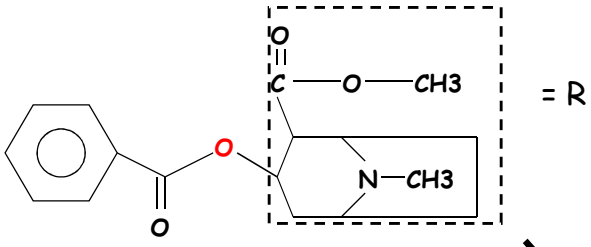
Problem B

Discuss the possible pharmacological/pharmaceutical consequences when a drug has more than one stereoisomer

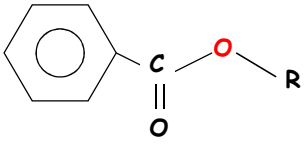
Pharmacological effect	↑	↓	→
Side effect	↑	↓	→
New pharmacological effect	Yes	No	
New side effect	Yes	No	
Changes in pharmaceutical properties	Yes	No	
	Combination		

B. Class Ib: Lidocaine

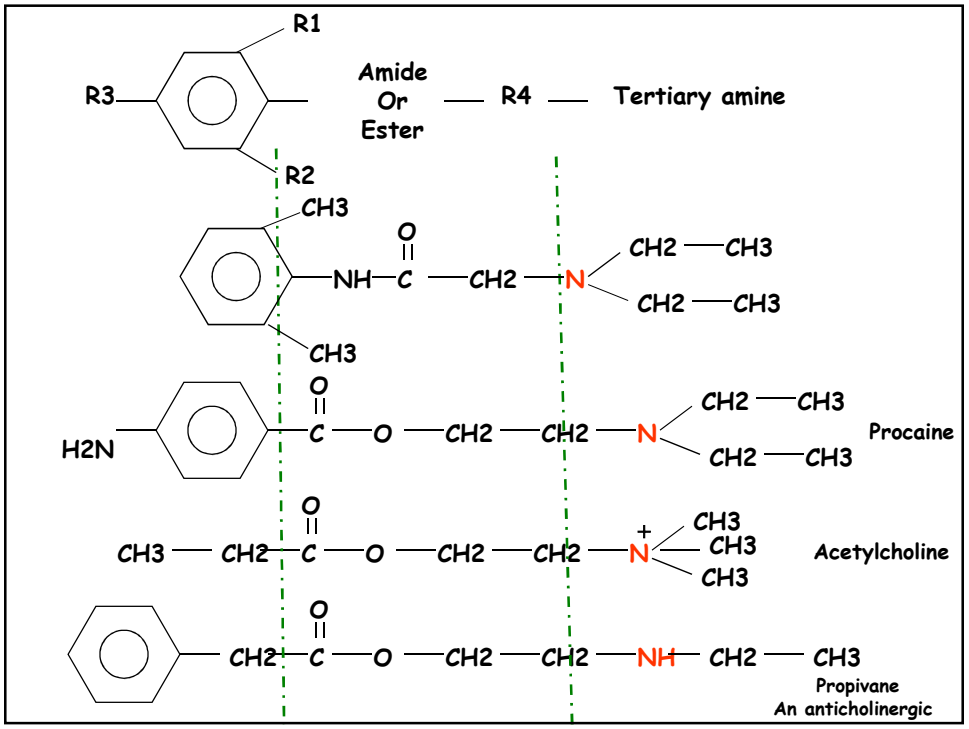
- A synthetic anesthetic derived from cocaine

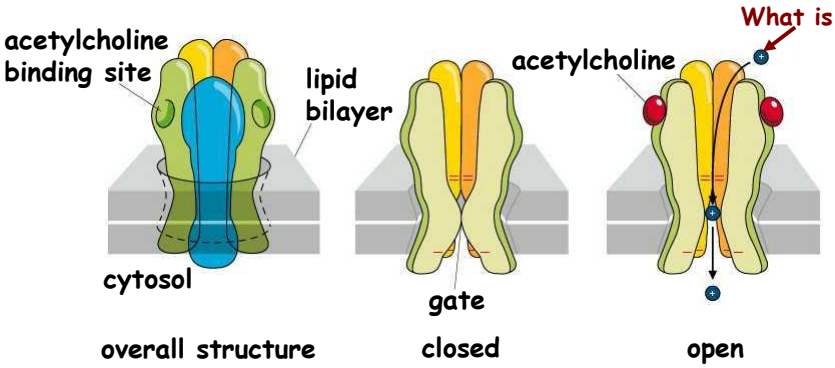


Cocaine



Cocaine, an ester compound, was the lead

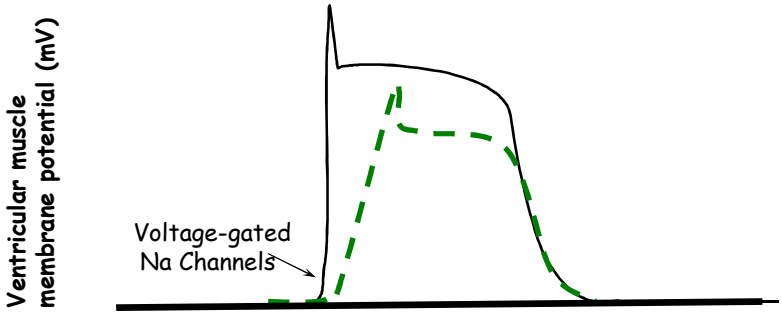




Adapted from ECB Fig 12-18

C. Class Ic.

- MOA
  - Strong Na+-channel blockade
  - But ERP does not change significantly
- Representative drugs
  - Flecainide



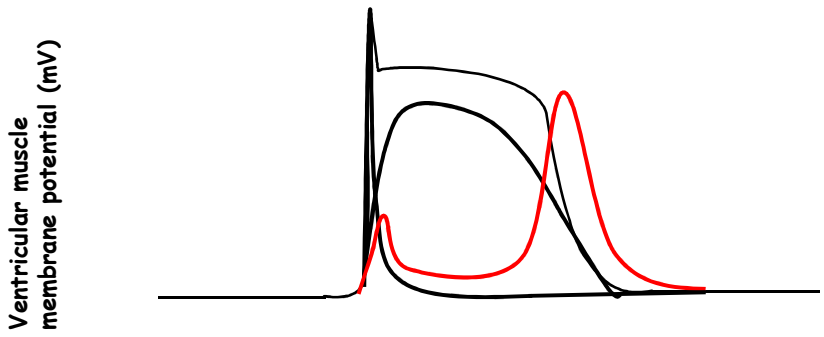
Ion channels and membrane potential on the myocardiac membrane

II. Class II-β-adrenergic blockage

- β-adrenergic blocking agents (Non selective; e.g, Propranolol)
  - Therapeutic uses
    - Antihypertensive
    - Antiarrhythmic
  - Will be discussed tomorrow

III. Class III-K^+ channel blockage

Bretylium tosylate



Ion channels and membrane potential on the myocardiac membrane

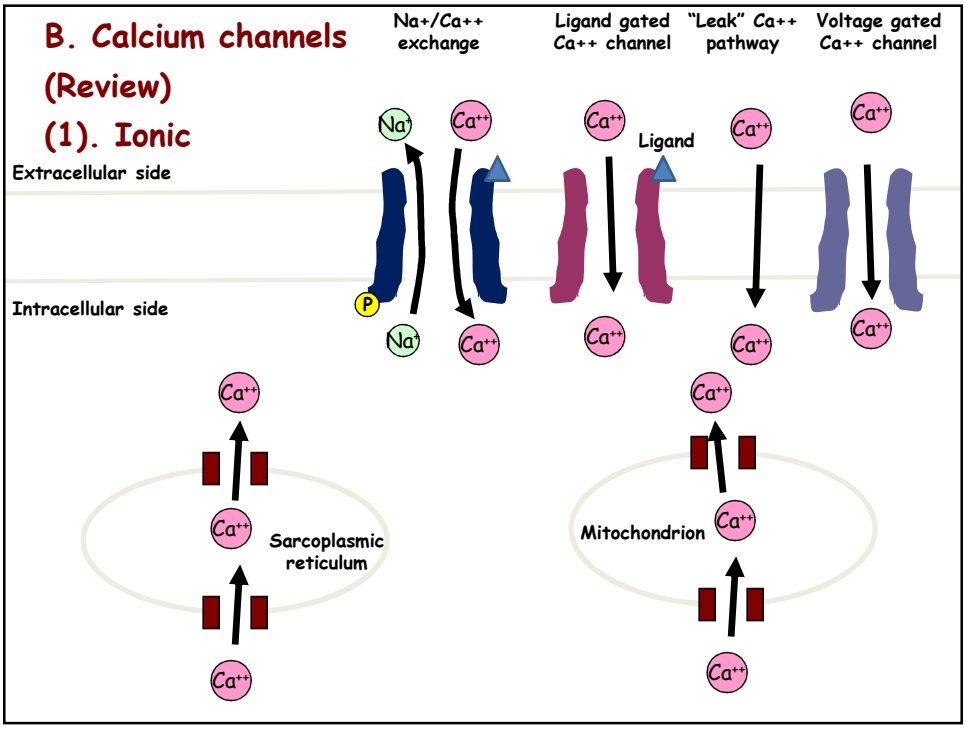
IV. Class IV: Calcium channel blockers

A. Therapeutic uses

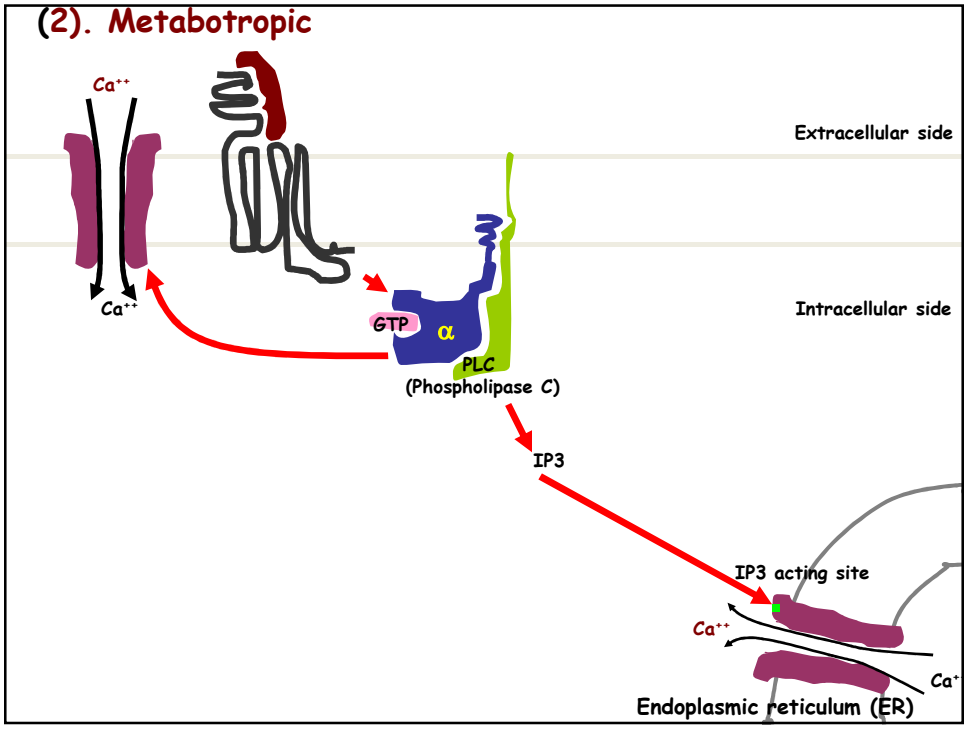
- ❑ Anti-hypertensive
- ❑ Anti-anginal
- ❑ Anti-arrhythmic

B. Calcium channels (Review)

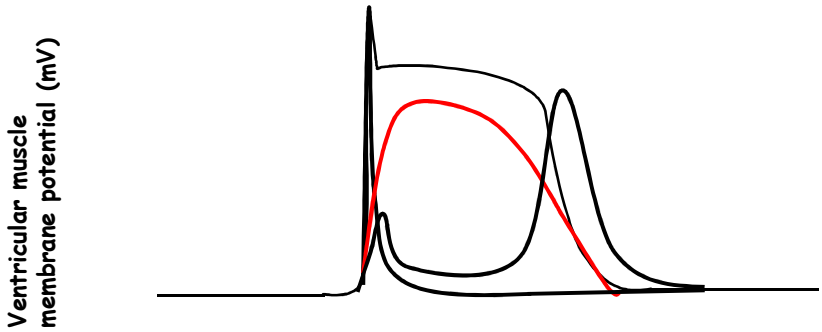
(1). Ionic



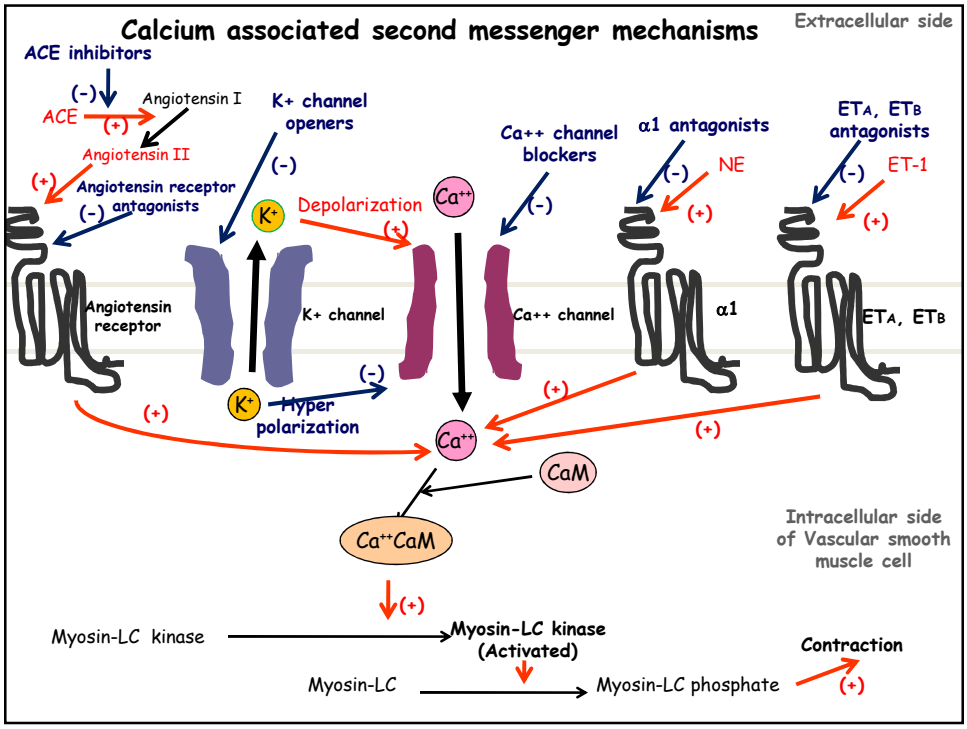
(2). Metabotropic



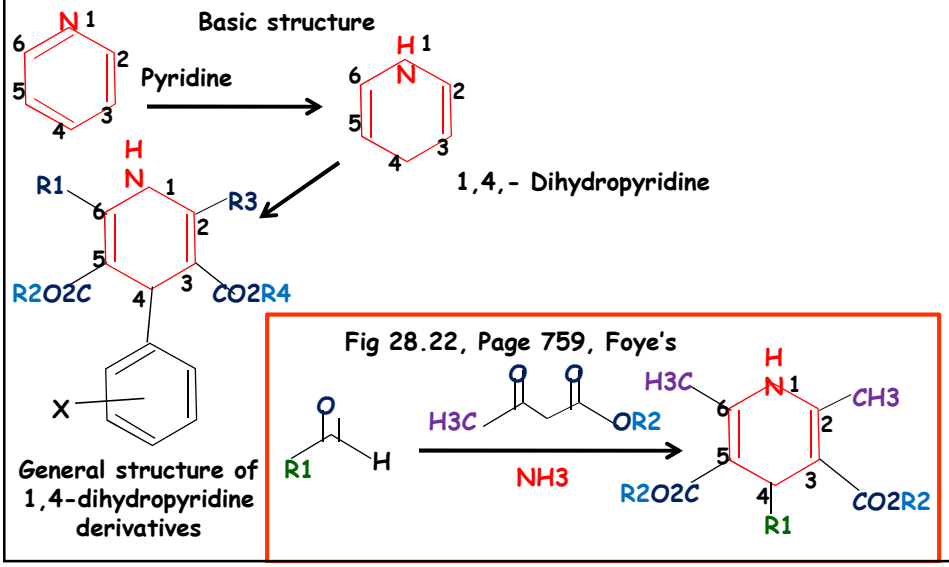
C. Mechanism of action

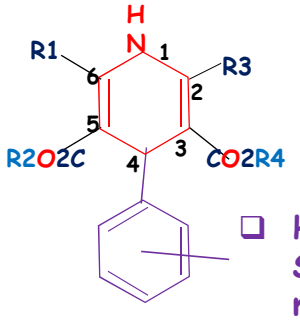


Ion channels and membrane potential on the myocardiac membrane



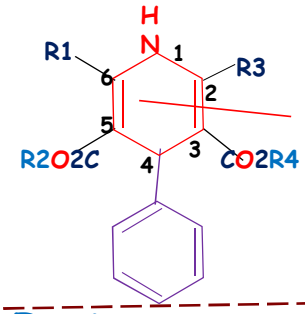
D. SAR of calcium channel blockers (Chapter 28) (Dihydropyridine derivatives)





General structure of 1,4-dihydropyridine derivatives

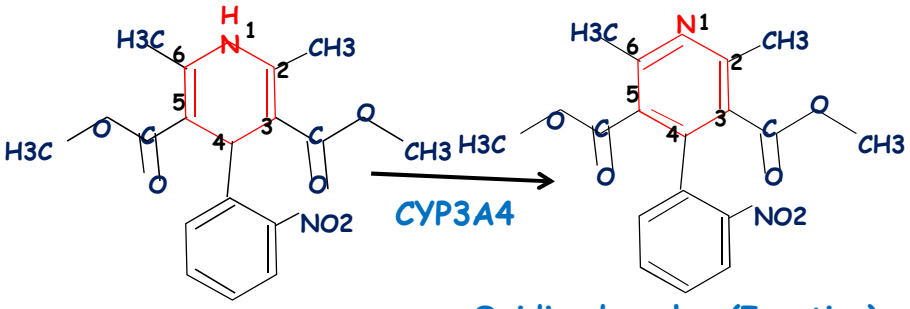
- Heteroaromatic rings and activity↑. Size and position (e.g. phenol ring) is more important than electronic nature
- Small nonplanar alkyl or cycloalkyl group and activity↓



a. Substitution at N1 or the use of oxidized or reduced ring systems decreases or abolishes the activity (WHAT ARE THE OXIDIZED AND REDUCED DIHYDROPYRIDINES?)

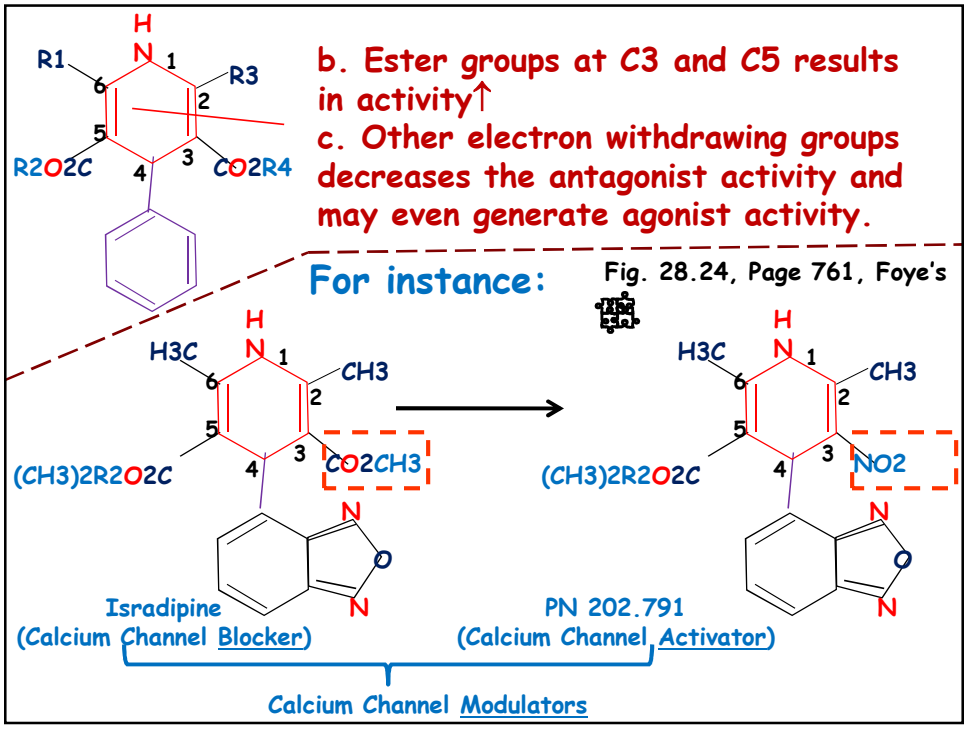
For instance:

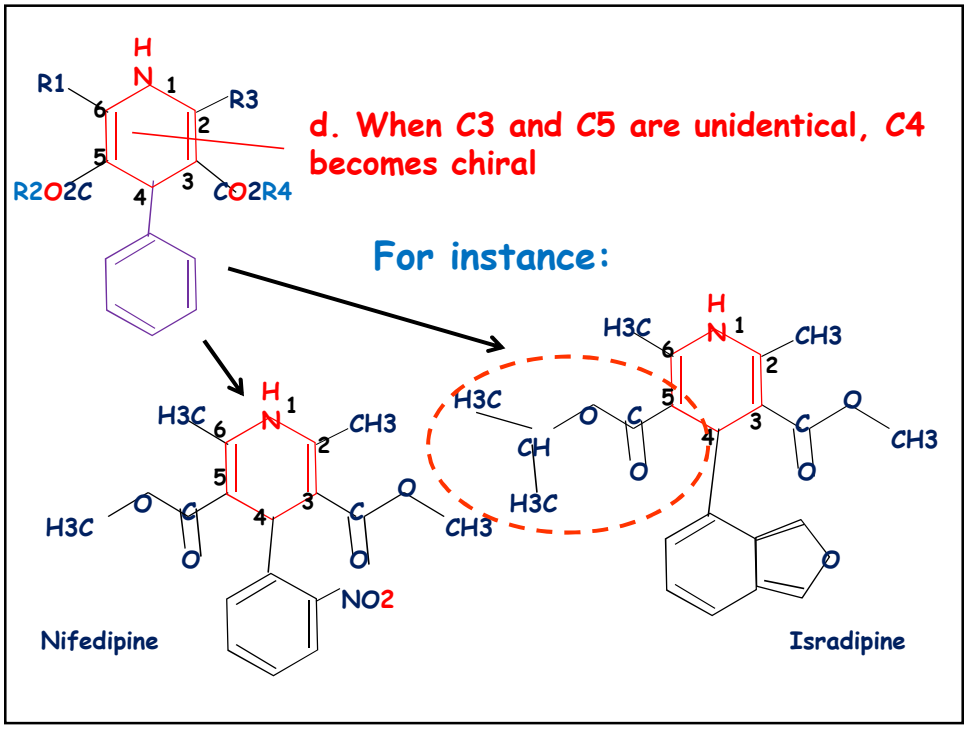
Fig. 28.26, Page 761, Foye's

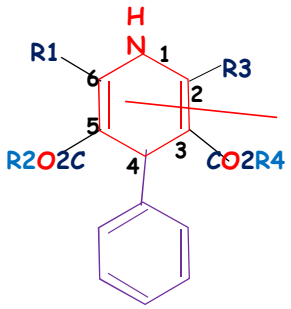


Nifedipine (Active)

Oxidized analog (Inactive)


b. Ester groups at C3 and C5 results in activity↑
c. Other electron withdrawing groups decreases the antagonist activity and may even generate agonist activity.
For instance:
Fig. 28.24, Page 761, Foye's
Isradipine
(Calcium Channel Blocker)
PN 202.791
(Calcium Channel Activator)
Calcium Channel Modulators


d. When C3 and C5 are unidentical, C4 becomes chiral
For instance:
Nifedipine
Isradipine



e. Methyl groups at C2 and C6. These positions can be further modified.