CARDIOVASCULAR PHARMACOLOGY

CALCIUM CHANNEL BLOCKERS

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Calcium Channel Blockers | Mechanism of Action, Indications, Adverse Reactions, Contraindications

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OUTLINE

I) INTORDUCTION

- Two types of Calcium Channel Blockers (CCBs):
  - Dihydropyridines
    - Amlodipine
    - Nicardipine
    - Nimodipine
    - Nifedipine
  - Non-dihydropyridines
    - Verapamil
    - Diltiazem

II) MECHANISM OF ACTION

(A) NON-DIHYDROPYRIDINES

- Act Mainly on the heart
- Verapamil affects primarily on the Cardiac Tissues
- Diltiazem has effects on
  - Cardiac Tissues
  - Vascular Smooth Muscle (Minor)

Mechanism of Action on the Heart:

- Intrinsic Conduction System
  - SA node → AV node → Bundle of hiss → Bundle branches → Purkinje System
- Effect on Pacemaker cells:
  - Inhibit the generation of Action potential from SA node→↓HR (Heart Rate)
  - Block the AV Node→ Inhibit the AV conduction (conduction of the Action potentials from atria to ventricles) → Important in certain Arrythmias
- Effect on Non-Pacemaker Cells (Contractile Unit)
  - ↓ Contractility

(B) DIHYDROPYRIDINES

- Act mainly on Vascular Smooth Muscle
- Effect on Smooth Muscle cells of the Tunica Media (which controls the tone of the smooth muscle) → Relax →Vasodilation
- Vasodilation
  - ↓TPR →↓Afterload
  - ↓TPR →↓ BP

(C) CELLULAR LEVEL MOA

Pacemaker Cell:

- Funny Sodium Channels let Na^+ in and make the pacemaker cell a little positive → T-type Voltage gated Calcium Channels Open → more positive inside of the cell → Activate L-type Calcium Channels → Ca^{2+} rushes in → make inside of the cell SUPER Positive → Initiate Action Potential → propagated to other Pacemaker and Non-pacemaker cells

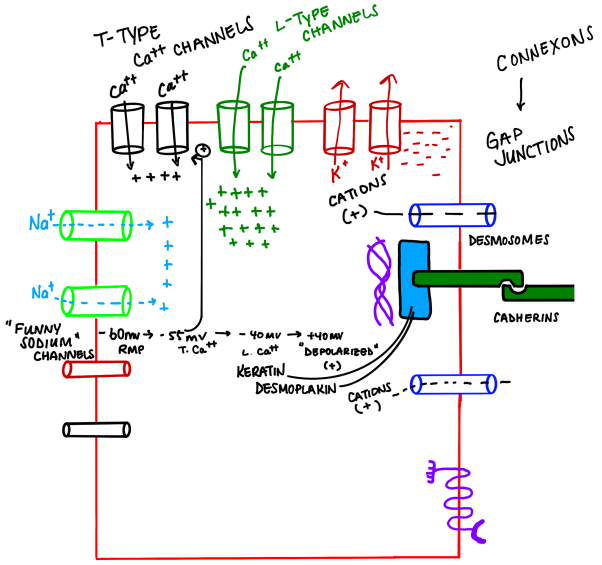

Figure 1. Pacemaker Cell.

Non-Pacemaker Cell

- Some of the Positive Ions flow from the Pacemaker Cell through Gap Junctions to the Non-Pacemaker cell→ make inside of the cell more positive → activate Voltage gated Sodium Channels → Na^+ Flushes in → Super Positive inside of the cell → Action Potentials carried down the Sarcolemma → Activate L-Type Calcium Channels → Ca^{2+} rushes in → Activate Myosin → bind to Actin → Contraction

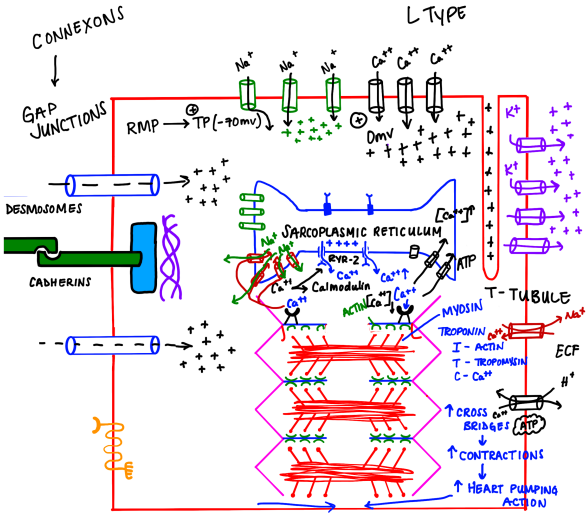

Figure 2. Non-Pacemaker Cell.

- **CCBs** block the L-Type Calcium Channels on the Pacemaker cell → Less positive charge in the cell →↓ Action Potentials → Less Positive Ions go through gap junction to the Pacemaker and Non-Pacemaker Cells →

↓ Na^+ → ↓ Ca^{2+} Influx → also, CCB block the L-Type Calcium Channels on the Non-Pacemaker cell →↓↓↓ Ca^{2+} Influx→ ↓Contraction

Vascular Smooth Muscle Cell

- Smooth muscle cells of the tunica media→ L-type Calcium Channels → When Ca^{2+} flushes in the cell during depolarization → binds to Calmodulin → Activate CAM-Kinase → Phosphorylation of MLCK (Myosin Light Chain Kinase) → Phosphorylation of Myosin → Cross Bridge Formation → Muscle Contraction

- **CCBs** Blocks the L-type Calcium Channels → ↓Ca^{2+} → ↓Ca^{2+} +Calmodulin →↓CAM-Kinase → No activation of MLCK → ↓Contraction

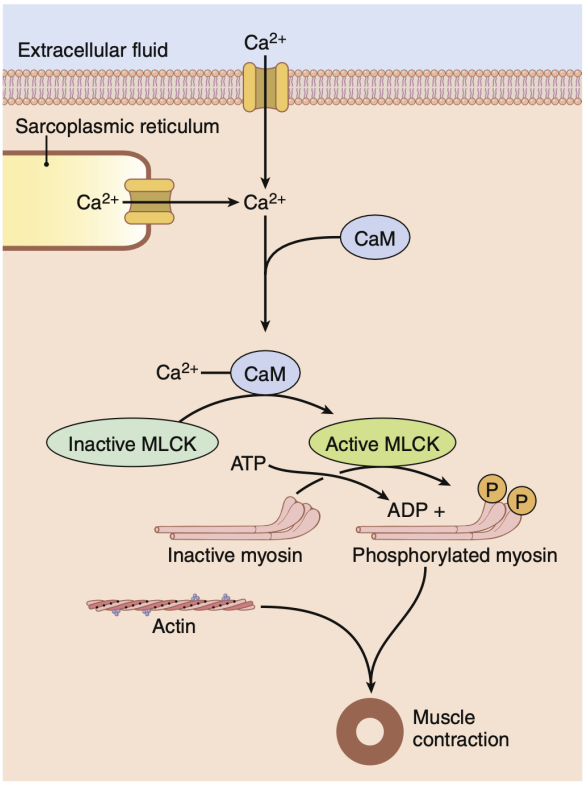

Figure 3. Smooth Muscle Contraction. [Hall & Hall, 2020]

III) INDICATIONS

↓HR and ↓AV conduction

- Supraventricular Arrythmias
  - Supraventricular Tachycardias (SVTs)
  - Atrial Fibrillation
  - Atrial Flutter
- Pre-Mature Atrial Contractions (PACs)

Supraventricular premature beats are atrial contractions triggered by ectopic foci rather than the sinoatrial node. They arise within the atria (atrial premature beats) or, through retrograde conduction, in the atrioventricular node (junctional premature beats). Premature beats may be found in healthy individuals as well as patients with underlying heart disease. Certain triggers, e.g., alcohol, smoking or electrolyte imbalances, may also contribute to the condition. Premature beats do not significantly impair cardiac output on their own; however, they may lead to more severe forms of arrhythmia such as atrial fibrillation. Unless patients exhibit severe symptoms (e.g., tachycardia), those experiencing premature beats do not require treatment. [AMBOSS,2021]

↓Contractility

- ↓CO →↓BP
- ↓Oxygen Demand

- **Angina Pectoris** (Not for Acute coronary Symptoms)
  - Stable Angina
  - For patients who cannot tolerate Beta Blockers or are not responsive to them
- **Prinzmetal Angina** (Vasospastic Angina)
  - Beta Blockers should be avoided
- **Hypertension**
- **Hypertensive Emergencies**
  - SBP≥180, DBP≥120 with end organ damage
- **Hypertension in Pregnancy**
  - Nifedipine

Vasodilation

- ↓BP
- ↓Afterload→ ↓Stress on the heart

- **Hypertension**
- **Raynaud Phenomenon**
- **Subarachnoid hemorrhage SAH** → vasospasm

Raynaud Phenomenon [UpToDate, 2021]

Raynaud phenomenon (RP) is an exaggerated vascular response to cold temperature or emotional stress. The phenomenon is manifested clinically by sharply demarcated color changes of the skin of the digits. The underlying problem is thought to be abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses.
RP is considered primary if these symptoms occur alone without evidence of any associated disorder. By comparison, secondary RP refers to the presence of the disorder in association with a related illness, such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc; scleroderma).

Diseases commonly associated with RP include autoimmune rheumatic diseases such as systemic sclerosis (SSc; scleroderma), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome, and dermatomyositis/polymyositis.

Subarachnoid hemorrhage (SAH) [AMBOSS, 2021]

Subarachnoid hemorrhage (SAH) refers to bleeding into the subarachnoid space. While SAH is often caused by trauma, 5–10% of cases are nontraumatic or spontaneous, in which case they are often due to the rupture of an aneurysm involving the circle of Willis (aneurysmal SAH). Nontraumatic SAH typically manifests with sudden and severe headache, which may be accompanied by nausea, vomiting, signs of meningism, and/or acute loss of consciousness.

Others

- Cluster Headache

Cluster Headache [AMBOSS, 2021]

Cluster headache (CH) is a type of primary headache that mostly affects adult men. Patients present with recurrent, fifteen-minute up to three-hour attacks of agonizing, strictly unilateral headaches in the periorbital and forehead region (areas innervated by the trigeminal nerve). These attacks are associated with ipsilateral symptoms of increased cranial autonomic activity, e.g., lacrimation, conjunctival injection, rhinorrhea, or partial Horner syndrome. Cluster headaches tend to occur in episodic patterns ("cluster bouts") followed by months of remission but are considered chronic if remission between bouts lasts less than one month. Diagnosis is based on the patient's history, in particular on the exact description and timing of the headaches. **Acute episodes are treated with 100% oxygen or triptans, while verapamil is used for preventative treatment.**

- Achalasia
  - Effect on the Smooth Muscles of the GI track → Relaxation
  - Achalasia → Lower esophageal Sphincter is tight → CCB relax the muscle→ help move the food bolus to the stomach
  - Symptoms of Achalasia: Dysphagia, regurgitation

IV) SIDE EFFECTS

Cardiac Adverse effects

Mostly caused by Non-DHPs:

- Bradycardia
  - ↓HR
- Heart Block
  - ↓HR
  - ↓ blood flow to the brain and may cause Syncope
- Hypotension
  - ↓Contractility→↓CO → ↓BP →Hypotension

Vasculature system Adverse Effects

Mostly caused by DHPs

- Reflex Tachycardia
  - Relax the smooth muscle → Vasodilation → Drop BP → Stimulate Carotid Sinus and aortic Sinus (Baroreceptors) → cardiac acceleratory center → activate SNS → ↑HR
- Hypotension
  - Orthostatic Hypotension
- Edema
  - Vasodilation→ ↑Capillary permeability → ↑Fluid in the interstitial space → peripheral Edema
- Flushing
  - Vasodilation of the vessels on the skin

Other Adverse Effects

- Gingival Hyperplasia
  - Thickening of the Gingiva because of ↑Epithelial tissues production
  - Amlodipine
- Constipation
  - ↓GI motility
- **Hyperprolactinemia**
  - Verapamil
  - Hypothalamus → Dopamine producing neurons → Dopamine Inhibits lactotroph that produce prolactin →↓ Prolactin
  - Verapamil inhibits dopamine release → ↑Prolactin
    - Male
      - Gynecomastia
    - Female
      - Galactorrhea
      - Menstrual irregularities

V) CONTRAINDICATIONS

- Wolff-Parkinson-White Syndrome
  - CCBs →↓AV Conduction→ Exacerbate W.P.W.S
  - Can Lead to VTACH or VFIB

Wolff-Parkinson-White pattern

In the normal heart, the atria and the ventricles are electrically isolated, with conduction of electrical impulses from the atria to the ventricles normally occurring via the AV node and the His-Purkinje system. Patients with a preexcitation syndrome have an additional pathway, known as an accessory pathway (also called **bundle of Kent**), which directly connects the atria and ventricles, thereby allowing electrical activity to bypass the AV node, leading to "preexcitation" or earlier than usual activation of the His-Purkinje system. Tissue in the accessory pathways, which are congenital in origin and result from failure of resorption of the myocardial syncytium at the annulus fibrosis of the AV valves during fetal development, typically conducts electrical impulses more quickly than the AV node, resulting in the shorter PR interval seen on the surface ECG [UpToDate, 2021]

- Combination with Beta blockers
  - Because of ↓AV Conduction, ↓HR effect of CCBs.
- Heart Block
- Decompensated heart failure (Weak Heart)
  - CCBs →↓Contractility→ ↓O2 Demand
- Aortic Stenosis
  - Less blood flow goes through aorta to the brain →Syncope
  - Less blood flow to the coronary vessels → Angina
- Hypotensive Patients

VI) POISONING

- One of the treatments in CCBs overdose is Calcium Salts:
  - Calcium gluconate
  - Calcium Chloride
  - They remove the CCBs from the receptor and bind the Calcium Channels

The diagnosis of calcium channel blocker (CCB) poisoning is made clinically on the basis of the history and clinical findings. Typically, there is a history of overdose combined with hypotension. **Overdose with dihydropyridine CCBs (eg, nifedipine) causes hypotension coupled with reflex tachycardia,** although severe toxicity may result in hypotension and bradycardia. **Overdose with verapamil or diltiazem causes the dangerous combination of hypotension and bradycardia.** [UpToDate, 2021]

Good to Know:

- Chronotropy: Any influence on Heart Rate [AMBOSS,2021]
  - Positive Chronotropic action
    - ↑HR
  - Negative Chronotropic action
    - ↓HR
- Inotropy: Any influence on Myocardial contraction [AMBOSS,2021]
  - Positive Inotropic action
    - ↑Contractility
  - Negative Inotropic action
    - ↓ Contractility

VII) REVIEW QUESTIONS

1) A 62-year-old man has developed worsening hypertension despite therapy. His physician wants to prescribe an additional medication that will dilate his blood vessels to help lower his blood pressure. Which of the following is a calcium channel blocker that works primarily on vascular smooth muscle? [Zaslau, 2013]
   a. Amlodipine
   b. Diltiazem
   c. Losartan
   d. Nitroprusside
   e. Verapamil

2) Which one of the following is characteristic of nifedipine treatment in patients with essential hypertension? [Trevor et al, 2018]
   a. Competitively blocks angiotensin II at its receptor
   b. Decreases calcium efflux from skeletal muscle
   c. Decreases renin concentration in the blood
   d. Decreases calcium influx into smooth muscle
   e. Increases calcium excretion in the urine

CHECK YOUR ANSWERS

VIII) REFRENCES

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