Drugs used to treat Congestive Heart Failure (CHF)

BY

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Postive Inotropic Agents.

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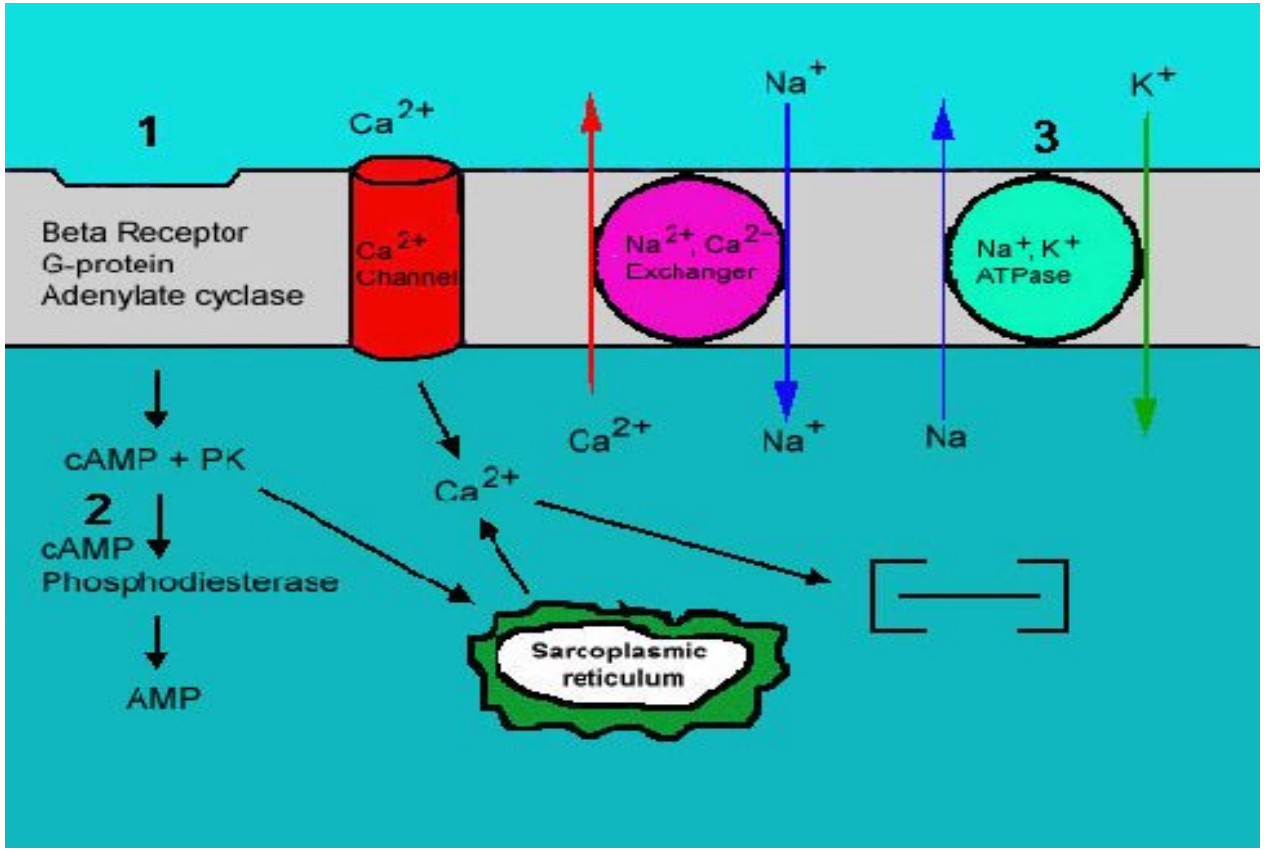
  1. Beta Receptor Agonists e.g. Dopamine..
  2. Phosphodiesterase inhibitors e.g. Milrinone
  3. Na+,K+-ATPase Inhibitors e.g. digoxin.

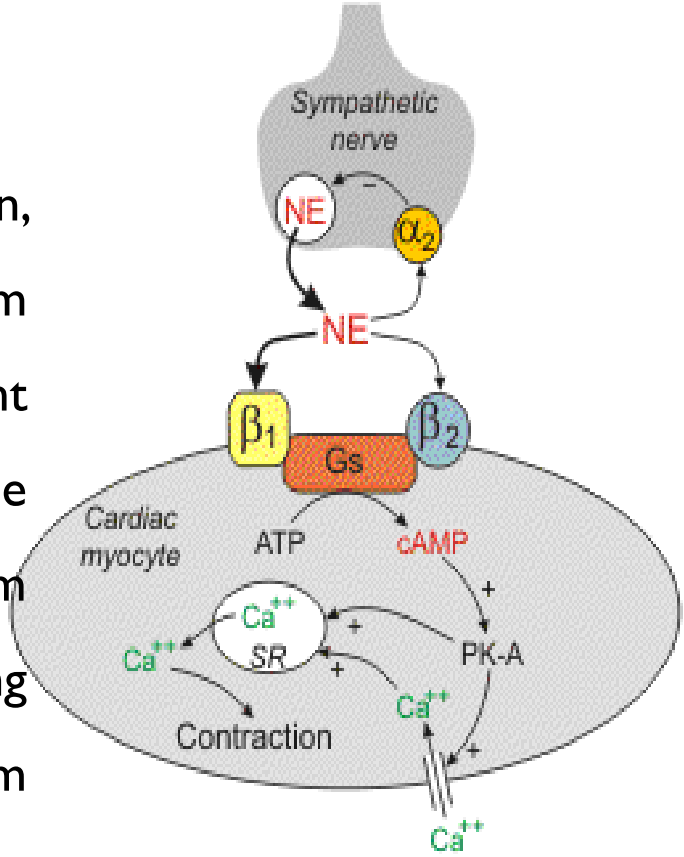


Beta Receptor Agonists.

Example:

- Dopamine and Dobutamine.

- Beta-adrenoceptors are coupled to a Gs- protein, which activate adenylyl cyclase to form cAMP from ATP. Increased cAMP activates a cAMP-dependent protein kinase (PK-A) that phosphorylates L-type calcium channels, which causes increased calcium entry into the cells. Increased calcium entry during action potentials leads to enhanced release of calcium by the sarcoplasmic reticulum in the heart; these actions increase inotropy (contractility).



Abbreviations: NE, norepinephrine; Gs, G-stimulatory protein; PK-A, cAMP-dependent protein kinase; SR, sarcoplasmic reticulum

Mechanism of action of Beta Receptor Agonists.

B agonist

B adrenoceptor

Activbation of Gs - proteins

ATP

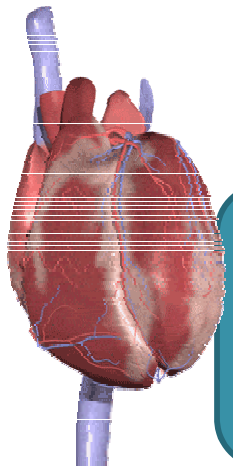
cAMP

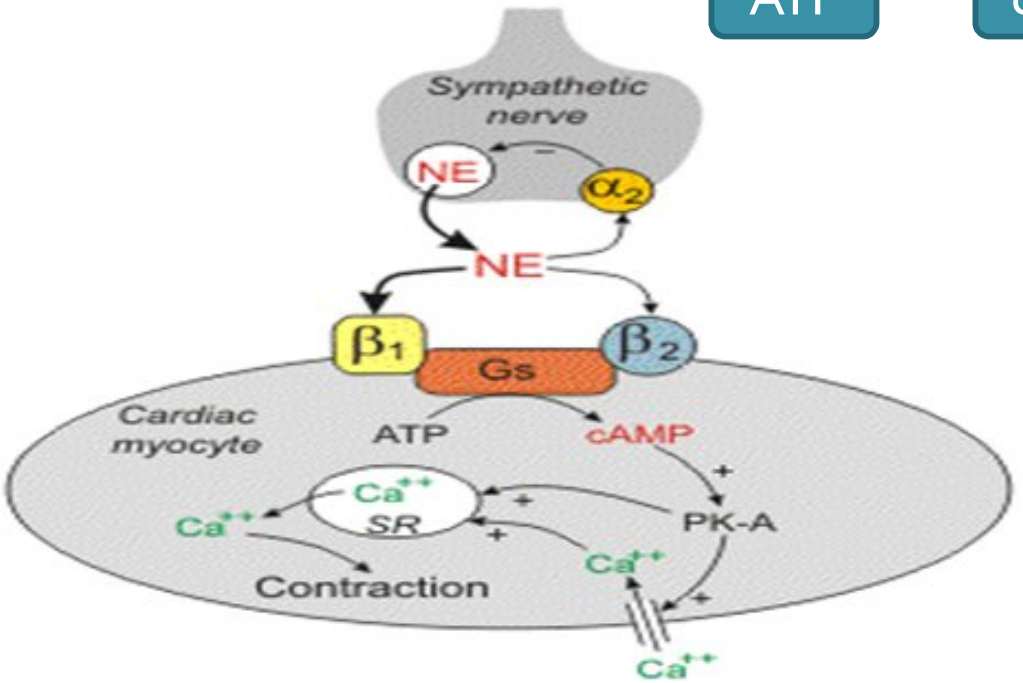
Activation protein - kinase

phosphorylate s L-type calcium channels

Enhanced release of calcium

Increase contractility





B - AGONIST

- They are given by IV infusion in the management of decompensated heart failure. A noteworthy point is that dobutamine can decrease peripheral vascular resistance while dopamine does not have this effect. In the setting of decompensated heart failure, this could lead to an increase in cardiac output

- Because of their short plasma half lives, these drugs must be given by intravenous infusion. As a consequence, the $beta_1$ receptors can be further down-regulated by infusion with these agonists.

- Recall that there is a concern of inducing arrhythmias with these drugs. This concern is even greater in the setting of a damaged, poorly perfused heart.

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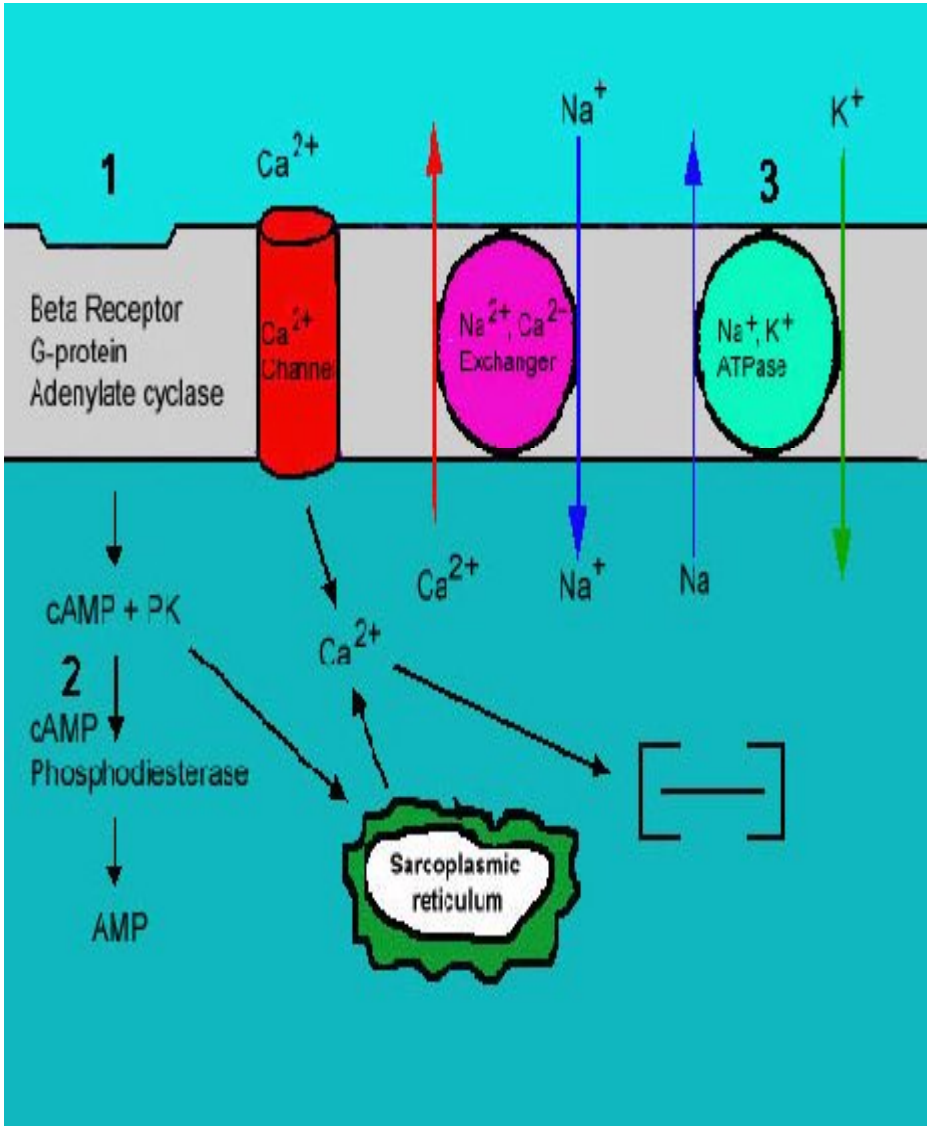
Phosphodiesterase inhibitors

e.g. Milrinone

- These compounds are orally active inhibitors of cAMP phosphodiesterase.

- This enzyme breaks down cAMP thus terminating its actions. The cardiovascular effects of increasing intracellular cAMP are similar to those seen following activation of $beta_1$ and $beta_2$ receptors.



Phosphodiesterase inhibitors

- PDE inhibitors were designed to replace cardiac glycosides as orally active positive inotropic agents for the treatment of congestive heart failure. These PDE inhibitors were shown to increase cardiac output and decrease peripheral vascular resistance.

- However, clinical trials showed oral dosing with these agents were not effective in decreasing the morbidity and mortality in heart failure.

- These drugs are second line agents reserved for the intravenous treatment of decompensated heart failure

Phosphodiesterase inhibitors

Cardiovascular Actions

- There are isoforms of cAMP phosphodiesterase. Inamrinone and milrinone inhibit the cAMP phosphodiesterase isoform that is present in the heart and blood vessels.
- Inhibition of cardiac PDE results in an increased force of contraction and cardiac output.
- Inhibition of vascular PDE produces vasodilation and a decrease in peripheral vascular resistance.
- These agents have the potential to induce arrhythmias.
- Tolerance does not develop to the cardiovascular actions of PDE inhibitors

Side effects of Phosphodiesterase inhibitors:

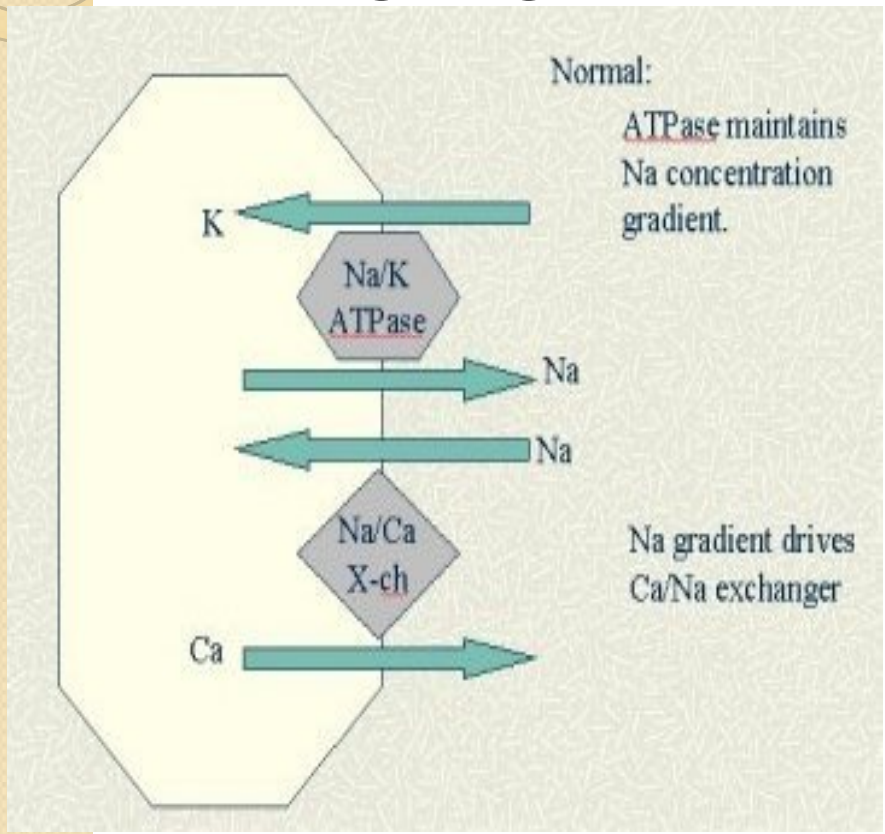
- Arrhythmias
- Thrombocytopenia
- Gastrointestinal-nausea, vomiting, etc
- Less toxicity with milrinone when compared to Inamrinone

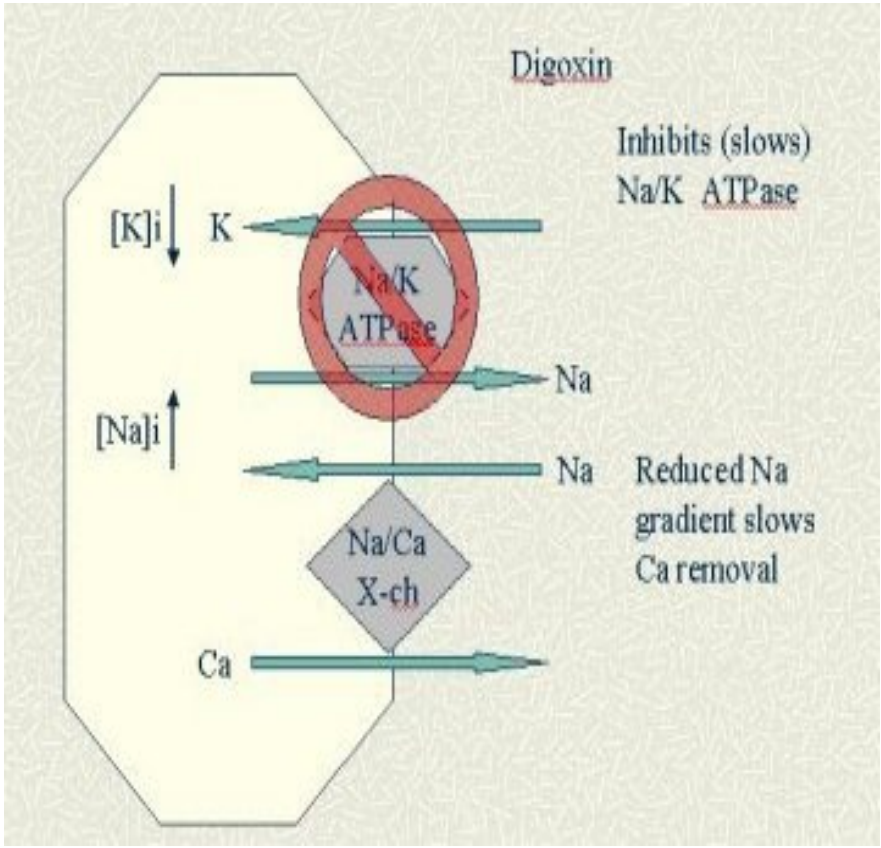
Status in Cardiovascular Medicine

- These agents are reserved for the short term treatment of congestive heart failure.
- These agents are given by intravenous infusion and are used in patients who have not responded well to other positive inotropic agents.
- As more patients are receiving beta blockers for the chronic treatment of heart failure, this makes treatment of decompensated heart failure more problematic. Thus, PDE inhibitors could be particularly effective in this setting.

Na+,K+-ATPase Inhibitors

- e.g. digoxin.





MECHANISM OF ACTION

Mechanism 1:

1. Cardiac glycosides inhibit the myocardial cell Na^+, K^+, ATPase.

2. This enzyme is responsible for maintaining the ionic gradient of the myocardial cell.

3. The inhibition of the Na^+, K^+, ATPase results in an increase in intracellular Na^+. The decrease in the Na^+ gradient diminishes the exchange of Na^+ for Ca^{2+}

4. The increase in intracellular Ca^{2+} is responsible for the positive inotropic action

MECHANISM OF ACTION

2- Negative Chronotropic Effect of Digoxin

- **Stimulates vagus centrally:**

Increases refractoriness of AV node

- Decreases ventricular response to atrial rate
- Controls heart rate in atrial fibrillation

Slows depolarization rate of SA node

- Decreases sinus rate
- Decreases heart rate in Sinus Tachycardia.

Side Effects:

- Narrow therapeutic to toxic ratio

- Non cardiac manifestations

  Anorexia,

  Nausea, vomiting,

  Headache,

  Xanthopsia sotoma,

  Disorientation

Special Considerations that Can Alter the Therapeutic Response to Cardiac Glycosides

1. Renal disease - decreased renal clearance of digoxin

2. Drug Interactions that:

   a) Decrease bioavailability

   Cholestyramine

   b) Decrease renal clearance

   Amiodarone

   Verapamil

   Quinidine

3. Hypokalemia and Electrolytes:

Hypokalemia increases the likelihood of toxicity. Alterations in potassium levels could be exacerbated by co-administration of diuretics.

4. Age

The elderly are more sensitive to cardiac glycosides

5. Hypoxia

Hypoxia increases the likelihood of toxicity

Preparations & routes :

1) Digoxin Tab. for oral use .
2) Digoxin solution in caps. for oral use (lanoxi caps) with 100% bioavailability .
3) Digoxin elixir .
4) Digoxin solution for slow I.V. injection .

Qustions


Thank You