Cardiovascular Drugs
Beta Blockers

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β Adrenergic Receptors

- **β_1:** Positive inotropic and chronotropic effects on the heart.
- **β_2:** Relaxes vascular, bronchial, gastrointestinal and genitourinary
  smooth muscle; stimulates glyconenolysis and gluconeogenesis
  in the liver.
- **β_3:** Lipolysis in adipose tissue.

β Adrenergic Receptors

- β receptors differ in their location and sensitivity to Epinephrine and Norepinephrine (simplified!):

β1	Myocardium	E=NE
β2	Smooth muscle	E (essentially no affinity for NE)
β3	Adipose tissue	NE>E

  i.e. tissue response to agonist is governed by expression of receptor subtypes and ligand present

- *All three* β adrenergic receptors function through a major class of signal transducer: G-proteins

- G-proteins couple β adrenergic receptors to adenylyl cyclase:

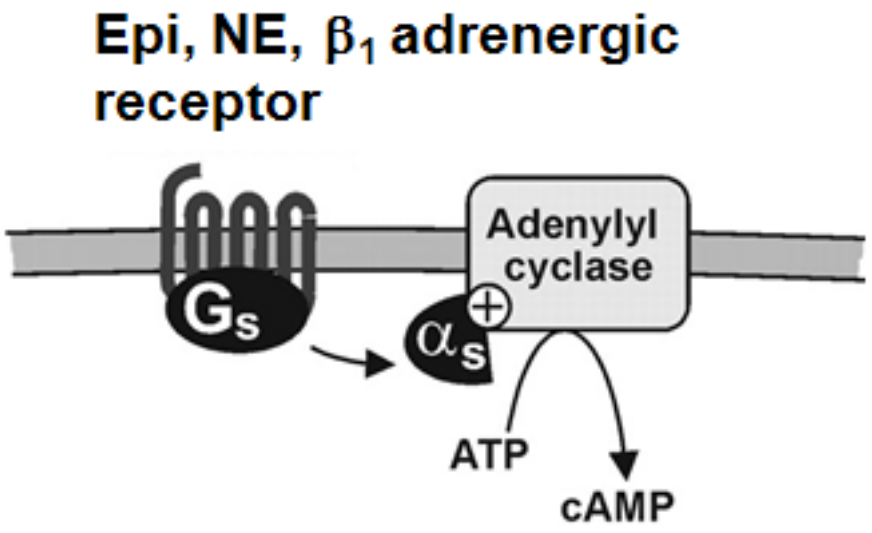
  β agonists *increase* intracellular cyclic AMP levels and protein kinase A activity, which in turn regulate downstream effectors

β Adrenergic Receptors

- β_1 Receptors
  - **$G_{s\ (stimulatory\ G\ protein)}$**: Activation of adenylyl cyclase and increased cAMP levels.
  - Positive inotropic and chronotropic effects on the heart; speeds conduction across the AV node.

  - Agonist: Dobutamine
  - Antagonist: Atenolol

β1 adrenergic receptors function through G_s to stimulate the effector adenylyl cyclase to produce the 2nd messenger cyclic AMP



Activated G_s:

- stimulates adenylyl cyclase to produce cAMP
- enhances activation of voltage gated Ca^{2+} channels in the plasma membrane

cAMP:

- activates protein kinase A, which directly phosphorylates proteins (e.g. troponin I) essential for cardiac muscle contraction
- stimulates sodium/potassium influx which opens voltage-gated Ca^{2+} channels
- inhibits uptake of Ca^{2+} into cellular stores
- cAMP hydrolyzed by phosphodiesterases

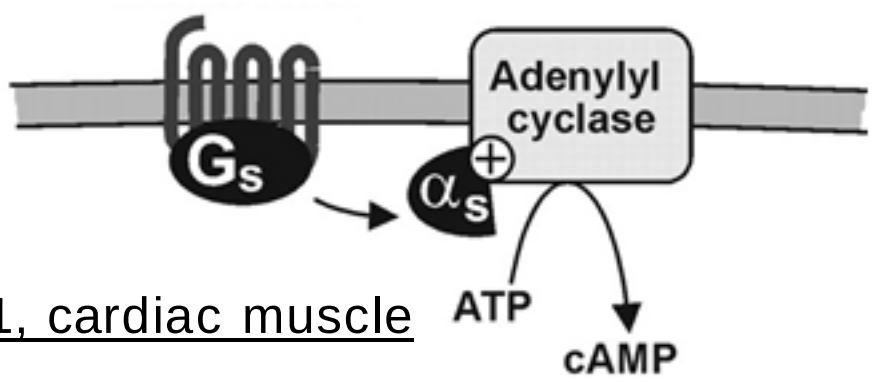
Overall effect: increased intracellular Ca^{2+} concentration and phosphorylation of contractile proteins. Result: cardiac muscle cells expressing β1 receptors contract in response to epinephrine or norepinephrine.

β Adrenergic Receptors

- β_2 Receptors
  - G_s: Activation of adenylyl cyclase and increased cAMP levels.
  - Relaxes vascular, bronchial, gastrointestinal and genitourinary smooth muscle, stimulates the uptake of potassium into skeletal muscle, stimulates glycogenolysis and gluconeogenesis in the liver.
  - Agonist: Terbutaline
  - Antagonist: Propranolol

Why does β1 stimulation cause contraction in cardiac muscle while β2 stimulation causes relaxation of smooth muscle – both elevate cAMP?

Different downstream effectors: different responses



EPI, β1, cardiac muscle

EPI, β2, smooth muscle

↓

protein kinase A

↙ ↘

Phosphorylation of contractile machinery proteins: e.g. Troponin I

Troponin I absent from smooth muscle. PKA phosphorylation of a different target, myosin light chain kinase, inhibits myosin function.

↓ ↘

CONTRACTION

RELAXATION

β Adrenergic Receptors

- **β_3 Receptors**
  - Activate Gs protein, stimulates adenylate cyclase and increases cAMP levels. cAMP activates PKA which stimulates the lipase activity i.e. another context-specific effector
  - Adipose tissue: Lipolysis.

β Adrenergic Receptors

Summary

- **β Receptors**
  - β1, β2 and β3 ALL activate G_s which stimulates adenylyl cyclase and increases cAMP levels.
  - cAMP activates protein kinase A

Outcome depends on what PKA phosphorylates: e.g.

- **Troponin in cardiac muscle (contraction);**
- **MLCK(myosin light chain kinase in smooth muscle (relaxation);**
- **lipase in adipose tissue**

Pharmacology of β Adrenergic Receptor Blocker Drugs

- A number of drugs that block β receptors are widly used in the treatment of many diseases including **hypertension, cardiac arrhythmias, angina pectoris, open-angel glaucoma and to protect against migraine headaches.**

  Variation in pharmacologic and pharmacokinetic properties influence their therapeutic application, side effects and toxicity.

Pharmacology of β Adrenergic Receptor Blocker Drugs

Drug	Adrenergic receptor blocking activity	Membrane stabilizing activity	Intrinsic sympathomimetic activity	Lipid solubility	Half-life (hr)	Elimination
Acebutolol	B_1	+	+	Low	3–4	Hepatic, renal, bile
Atenolol	B_1	0	0	Low	6–9	Unchanged (50%)
Betaxolol	B_1	+	0	Low	14–22	Hepatic
Bisoprolol	B_1	0	0	Low	9–12	Unchanged (50%)
Esmolol	B_1	0	0	Low	0.15	Esterases in RBCs
Metoprolol	B_1	0	0	Moderate	3–7	Hepatic, renal
Carteolol	B_1, B_2	0	++	Low	6	Unchanged (50–70%)
Nadolol	B_1, B_2	0	0	Low	20–24	Unchanged
Penbutolol	B_1, B_2	0	+	High	5	Hepatic
Pindolol	B_1, B_2	+	+++	Moderate	3–4	Renal, unchanged
Propranolol	B_1, B_2	++	0	High	3–5	Hepatic
Sotolol	B_1, B_2	0	0	Low	12	Unchanged
Timolol	B_1, B_2	0	0	Low to moderate	4	Hepatic
Labetalol	B_1, B_2	0	0	Moderate	5.5–8	Hepatic, unchanged

Mechanism of toxicity of β Blockers

- **Toxic effects of acute overdose** with beta blockers result from the drug binding to and inhibiting β-adrenergic receptors throughout the body. The manifestations of poisoning are bradycardia and hypotention.

- In overdose, membrane stabilizing action of some β-blockers predominate causing severe myocardial depressant actions leading to heart block and possibly CNS effects, such as sedation and seizures.

- High doses of β-blockers with intrinsic sympathmimetic activity (e.g., acebutolol) can cause tachycardia and hypertension as a result of their partial agonist effect.

Mechanism of toxicity of β Blockers

- Oral doses of β-blockers are absorbed rapidly and distribute readily throughout the body and undergo first-pass effect.
- High lipid solubility accounts for the CNS effects.
- In overdose pharmacokinetic parameters may changed severely due to decreased cardiac output with subsequently reduced hepatic and renal flow. As a result, high drug concentrations and **extended plasma half life** are expected.
- Obvious toxicity may appear 20 min post ingestion, but usually not observed until 1 to 2 hours. Clinical symptoms persist beyond the drug half life. Blood level alone not reliable for assessing overdose, prognosis and predicting therapy.

Signs and Symptoms of β Blockers Poisoning

Clinical manifestations of beta-adrenergic blocker toxicity

Cardiac	CNS	Other
Arrhythmias	Sleepiness	Bronchospasm
Bradycardia	Dizziness	Pulmonary edema
Atrioventricular block	Unconsciousness	Hypoglycemia
Hypotension	Coma	Hyperkalemia
Tachycardia	Seizures	
Shock	Respiratory depression	

Underlying pathology may influence the toxicity of β-blockers, e.g., bronchospasm and pulmonary edema may be more prominent in patients with chronic obstructive pulmonary disease.

Signs and Symptoms of β Blockers Poisoning

- Electrocardiographic changes are:

- First degree AV block (prolonged PR interval)
- Widening of the QRS complex
- Absence of P waves
- Prolongation of the QT interval

Cardiac changes are not reported uniformly in all β-blocker poisonings. They do occur most frequently with drugs that have membrane stabilizing action or (quinidine-like action).

- CNS effects may involve seizures.

Seizure activity results from hypoglycemia, cerebral hypoxia, or from membrane stabilizing action.

Management of Poisoning with β Blockers

1. Gastric lavage is usually more than emesis because of the possibility of β-blocker- induced seizures.

2. Activated charcoal can be given repeatedly during the first 24 hours to minimize enterohepatic cycling.

3. Administration of glucose for hypoglycemia, Diazepam for convulsions, and monitoring potassium levels.

Management of Poisoning with β Blockers

The major importance in management of toxicity with β-blockers will be to minimize cardiovascular effects.

- If the patient is compromised hemodynamically, **Atropine** may be given. If vagal blockade is unsuccessful, **Isoproterenol**, a specific β_1 agonist can be given cautiously.

- Pressor agents , such as **Dopamine**, **Dobutamine** or **Norepinephrine**, may be useful.

Management of Poisoning with β Blockers

- If the patient is compromised hemodynamically, the treatment of choice is **Glucagon**, which can produces positive inotropic and chronotropic activity and improves AV conduction by binding to **glucagon-specific receptors** in the myocardium and activating the adenyl cyclase system, results in ↑CAMP which gives the action similar to β- receptor stimulation by catecholamines, except that beneficial activity continues despite the presence of β- blockers.

Management of Poisoning with β Blockers

- Phosphodiesterase inhibitors, such as **Theophylline** can increase ↑CAMP

  And give a synergistic effect with glucagon. However, benefit from such therapy has not yet been evaluated.

- Hemoperfusion or hemodialysis may be considered in cases involving Nadolol or Atenolol, especially if there are signs of renal failure. In case of other β- blockers, dialysis not indicated because of their high protein binding and large volume of distribution.