Pharmacology/Therapeutics I Block IV Lectures

2012-2013

38. Drugs to Treat Hyperlipidemia I – Clipstone

39. Drugs to Treat Hyperlipidemia II – Clipstone

40. Pharmacology of Nitric Oxide – Fareed

41. Pharmacology of Vasoactive Peptides - Fareed

42. Diuretics – Byron

43. Antihypertensive Drugs I – Scrogin

44. Antihypertensive Drugs II – Scrogin

45. Antianginal Drugs – Samarel

46. Drugs to Treat Congestive Heart Failure – Samarel

47. Antiarrhythmic Drugs I – Majetschak (To be Posted Later)

48. Antiarrhythmic Drugs II – Majetschak (To be Posted Later)

Drugs used to treat Hyperlipidemia I & II

Date: Wednesday, November 7th, 2012 – 9:30 am – 11:30am

Relevant reading:

Pharmacology: Examination & Board Review. **A.J. Trevor, 9th Edition, p307-314**
Basic and Clinical Pharmacology. B.G. Katzung, 12th Edition, p605-617

Key Concepts and Learning Objectives

1. Recognize that hyperlipidemia represents the presence of elevated/abnormal levels of lipids (i.e. cholesterol and triglycerides) and/or lipoproteins (e.g. LDL & VLDL) in the blood.

2. Recognize that elevated serum LDL-cholesterol is strongly associated with a significantly increased risk of developing atherosclerosis and cardiovascular disease, and that increased triglycerides levels and decreased levels of HDL-cholesterol represent independent risk factors.

3. Learn the presently accepted values for desirable serum LDL-cholesterol, HDL and triglyceride levels, and what levels correspond to borderline high, high and very high.

4. Understand that hyperlipidemia can result from primary genetic defects (e.g. LDL-R), lifestyle factors (e.g. high fat diet), or a combination of genetics, lifestyle and secondary causes.

5. Understand the mechanism of action of the clinically useful anti-hyperlipidemic drugs:
   a) STATINS
   b) Bile acid-binding resins
   c) Cholesterol absorption inhibitors
   d) Niacin
   e) Fibrates
   f) Omega-3 fatty acids

7. Understand the principal therapeutic effects of each of the classes of anti-hyperlipidemic drugs on specific plasma lipid and lipoprotein levels (i.e. LDL, VLDL & HDL).

8. List the clinical indications and major adverse effects of the anti-hyperlipidemic drugs.

9. Recognize the clinically relevant drug interactions of the major anti-hyperlipidemic drugs

10. Understand the treatment options and relevant drug therapies for the treatment of hypercholesterolemia, hypertriglyceridemia, and combined hyperlipidemia.

11. Understand how anti-hyperlipidemic drugs can be combined effectively in the treatment of dyslipidemia.

Drugs to be covered in this lecture:

1. The STATINS

Atorvastatin (Lipitor®)
Fluvastatin (Lescol®)
Lovastatin (Mevacor®)
Simvastatin (Zocor®)
Pravastatin (Pravachol®)
Rosuvastatin (Crestor®)

2. Bile Acid-binding resins

Cholestyramine (Questran®)
Colestipol (Colestid®)
Colesevelam (Welchol®)

3. Cholesterol Absorption Inhibitor

Ezetimibe (Zetia®)

4. Niacin

5. The Fibrates

Fenofibrate (Tricor®, Lofibra®)
Gemfibrozil (Lopid®)

6. omega-3 fatty acids

Eicosapentaenoic acid: Docosahexaenoic acid (Lorvaza®)

Drugs in the treatment of hyperlipidemia I& II

(A) Background

A1. ATHEROSCLEROSIS & HYPERLIPIDEMIA/HYPERLIPOPROTEINEMIA

a) Atherosclerosis is strongly associated with hyperlipidemia: the presence of elevated/abnormal levels of lipids (i.e. cholesterol and triglycerides) and/or lipoproteins (e.g. LDL & VLDL) in the blood

b) The most important risk factor in the development of atherosclerosis is an elevated level of Low Density Lipoproteins (LDL)-a class of lipoprotein that is rich in cholesterol- the so called "bad cholesterol".

c) Elevated serum triglycerides levels are an independent risk factor for atherosclerosis and cardiovascular disease, as well as being a risk factor for pancreatitis

d) Decreased levels of HDL-cholesterol ("good cholesterol") is an independent risk factor for the development of cardiovascular disease

Classification of serum lipid levels by ATP III of NCEP

	LDL-C	HDL-C	Triglyceride
Optimal/desirable	< 100 mg/dL	>40 mg/dL	< 150 mg/dL
Near/above optimal	100-129 mg/dL		
Borderline high	130-159 mg/dL		150-199 mg/dL
High	160-189 mg/dL		200-499 mg/dL
Very high	> 190 mg/dL		>500 mg/dL

Modified from the NCEP ATP III panel guidelines by N.A.C

A2. Causes of Hyperlipoproteinemia

a) Genetics: Either Monogenic (e.g. defective LDL receptor in Familial Hypercholesterolemia) or polygenic (e.g. Familial Combined Hyperlipoproteinemia)

b) Lifestyle (e.g. high fat diet) and other secondary causes (e.g. type-2 diabetes, lipodystrophy & hypothyroidism)

c) Combination of genetics, lifestyle and secondary causes.

A3. The Primary Hyperlipoproteinemias (The Fredricskon Classification)

	Synonyms	Frequency	Defect	Effects on Lipoproteins	Athero-sclerois
Type I	Familial Hyperchylomicronemia	Very rare	LPL deficiency/ ApoCII deficiency	↑ chylomicrons	-
Type IIa	Familial Hypercholesterolemia Familial apoB100 defect Polygenic Hypercholesterolemia	0.2% 0.1% Relatively common	LDL receptor defect ↓Binding of LDL to LDLR Unknown defects result in impaired clearance of LDLs	↑ LDL	+++
Type IIb	Familial Combined Hyperlipidemia	0.5%	Unknown (polygenic): Overproduction of B100 & triglycerides (VLDL) and decreased clearance of LDL	↑ VLDL + ↑ LDL	+++ Obesity Insulin resistance often present
Type III	Familial Dysbetalipoproteinemia	0.02%	Mutant ApoE: Increased production/ decreased clearance of VLDL remnants	↑ IDL	+++
Type IV	Familial Hypertriglyceridemia	1%	Unknown: Overproduction/decreased clearance of VLDL	↑ VLDL	-/+
Type V	Familial Mixed Hypertriglyceridemia	Rare 1/1,000,000	Unknown: Overproduction/decreased clearance of VLDL & chylomicrons	↑ VLDL + ↑ Chylomicrons	-/+

A4. Secondary causes of hyperlipoproteinemias

Hypertriglyceridemia	Hypercholesterolemia
Obesity & overweight	Dietary excess: Cholesterol & sat. Fats
Physical inactivity	Nephrotic syndrome
Cigarette smoking	Hypothyroidism
Excess alcohol intake	Hypopituitarism
High carbohydrate diet (>60%)	Type-2 diabetes
Stress	Anorexia Nervosa
Pregnancy	Acute intermittent porphyria
Certain Diseases:	Biliary cirrhosis
type-2 diabetes	Corticosteroid treatment
Nephrosis	Antiviral protease therapy
Hypopituitarism	
Lipodystrophy	
Certain Drugs:	
Estrogens	
Corticosteroid excess	
Oral contraceptives	
Antiviral protease therapy	

2004 NCEP Treatment Goals

Risk	Cardiovascular Risk Factors	LDL Goal	Initiate lifestyle change if LDL is:	Consider drug therapy if LDL is:
Very High Risk	Current CHD + other factors	<70 mg/dl	>100 mg/dl	<100 mg/dl
High Risk	a) Previous CHD b) Diabetes c) > 2 risk factors	<100 mg/dl (optional <70)	>100 mg/dl	>100 mg/dl
Moderately High Risk	>2 risk factors 10-20% 10yr risk	<130 mg/dl (optional <100)	>130 mg/dl	>130 mg/dl
Moderate Risk	>2 risk factors <10% 10yr risk	<130 mg/dl	>130 mg/dl	>160 mg/dl
Lower Risk	0-1 risk factors	<160mg/dl	>160 mg/dl	>190 mg/dl

Modified from the 2004 NCEP ATP III panel guidelines

A5. Treatment options for Hyperliproteinemia

A5.1 Hypercholesterolemia (elevated LDL-C)

The treatment for hypercholesterolemia is dependent upon the degree of LDL-cholesterol elevation and the calculated cardiovascular risk (see Table).

a) For moderate hyperlipidemia with low cardiovascular risk factors lifestyle changes maybe sufficient to normalize lipoprotein levels.
   (i) Dietary reduction of cholesterol intake
   (ii) Exercise- improves lipoprotein metabolism
   (iii) Weight reduction- improves lipoprotein metabolism

b) For patients with more severe hypercholesterolemia and/or with a high cardiovascular risk, drug therapy should be initiated. The initial drug of choice is a **STATIN** (see below).

A5.2 Hypertriglyceridemia (elevated triglycerides)

a) Lifestyle change: very low fat diet and exercise
b) If necessary (i.e. TG> 500mg/ml), triglyceride-lowering drugs such as a fibrate or niacin can be initiated (see below).

N.B. Drug therapy needs to be continued indefinitely as withdrawal of drug will result in rebound of abnormal lipid profile

(B) Drugs used in the treatment of Hypercholesterolemia

B1. HMG-CoA reductase inhibitors ("STATINS")

Atorvastatin (Lipitor®), Fluvastatin (Lescol®), Lovastatin (Mevacor®), Simvastatin (Zocor®), Pravastatin (Pravachol®), & Rosuvastatin (Crestor®)

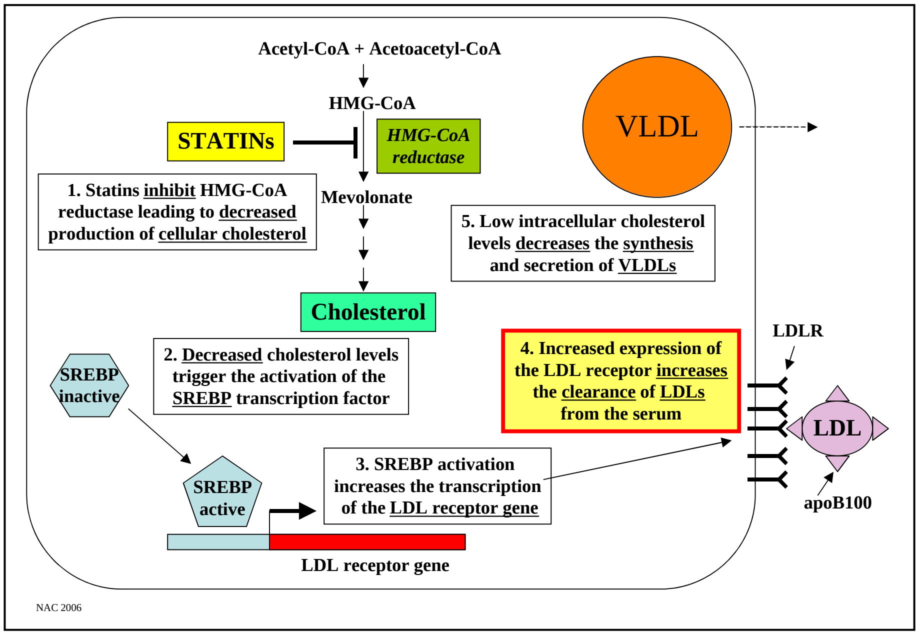
B1.1 Primary clinical effect

- Significant reduction in LDLs (20-60%- dose and drug specific)
- Modest reduction in triglycerides (10-20%)
- Modest 5-10% increase in HDLs

B1.2 Mechanism of Action

a) Inhibition of HMG-CoA reductase

- The statins are analogs of 3 hydroxy-3 methylglutarate, a key metabolite of cholesterol biosynthesis and inhibit HMG-CoA reductase- the rate limiting step in cholesterol biosynthesis, thereby inhibiting endogenous cholesterol synthesis and the production of VLDLs.



b) Increased expression of LDL receptors

- Inhibition of HMG-CoA reductase results in the depletion of intracellular cholesterol, which activates the SREBP transcription factor resulting in the increased transcription of the gene encoding the LDL receptor.

- Increased LDL receptor expression at the plasma membrane results in the uptake of additional LDL from the circulation and the overall reduction of plasma LDL-cholesterol levels

c) Other properties of Statins that contribute towards their beneficial effects in the treatment of atherosclerosis

(i) Inhibit the adhesion of monocytes to the endothelium and migration to the arterial wall
(ii) Inhibit monocyte proliferation
(iii) Inhibit the expression of adhesion molecules expressed on the endothelium
(iv) Inhibit the oxidation of LDL to ox-LDL
(v) Inhibit SMC proliferation
(vi) Inhibit immune and inflammatory responses
(vii) Stabilize the endothelium making atherosclerotic plaques less likely to rupture

<u>B1.3 Therapeutic Uses</u>

a) Drug of choice for treating patients with increased plasma LDL-C levels in all types of hyperlipidemia

b) The dose response relationship of STATIN drugs is non-linear: Doubling the STATIN dose only results in a 5-6% further decrease in LDL-C, while increasing potential toxicity.

c) Patients with Familial hypercholesterolemia benefit much less because of defect in LDL receptor.

d) Drug of choice for patients with high risk of cardiovascular disease irrespective of plasma cholesterol levels.

Numerous clinical trials have demonstrated that the use of either Atorvastatin (Lipitor®) or Simvastatin (Zocor®) in patients with a high cardiovascular risk (i.e. previous history of coronary heart disease, high blood pressure + smoking or type-2 diabetes) can significantly decrease (25-30%) their risk of future cardiovascular events (i.e. heart attack and stroke) and death due to CHD no matter what their initial baseline serum LDL-cholesterol levels.

<u>B1.4 Pharmacokinetics</u>

a) Statins are directly taken up into the liver by a specific anion transporter OATP2
b) There is extensive 1st pass extraction in the liver- consequently these drugs primarily exhibit their dominant effect in the liver
c) Lovastatin (Mevacor®), Simvastatin (Zocor®) & Atorvastatin (Lipitor®) are metabolized by <u>**CYP3A4**</u> mechanisms
d) Fluvastatin (Lescol®) and Rosuvastatin (Crestor®) are metabolized by <u>**CYP2C9**</u> mechanisms
e) Pravastatin (Pravachol®) is <u>**not**</u> metabolized via the cytochrome <u>**P450**</u> pathway
f) Half-lives for Lovastatin (Mevacor®), Simvastatin (Zocor®), Pravastatin (Pravachol®) & Fluvastatin (Lescol®) are ~ 1.5- 2hrs
g) Half-life for Atorvastatin (Lipitor®) is 14hrs and for Rosuvastatin (Crestor®) is 19 hrs
h) All Statin drugs are glucoronidated in the liver: enhances metabolism and secretion

<u>B1.5 Adverse Effects</u>

a) Generally well tolerated- patients that can tolerate one statin can generally tolerate another
b) mild GI disturbances, headache or rash may occur
c) Myalgia (muscle pain; 2-11%) and Myopathy (muscle weakness) are common and increase with <u>increasing dose of drug</u>
d) Rhabdomyolysis (muscle disintegration), although reported, is rare (0.1%) and occurs primarily at <u>**high doses**</u> of drug – can lead to renal failure and even death (8% of cases)

<u>Symptoms</u>: fever, malaise, diffuse myalgia and/or tenderness, marked elevation of serum creatine kinase and myoglobin present in the urine

- More common in patients with either acute/chronic renal failure, obstructive liver disease, or hypothyroidism
- Can be observed with drug interaction especially inhibitors of CYP3A4 e.g. cyclosporin, tacrolimus, gemfibrozil, ketaconazole and HIV Protease inhibitors (see below)
- Fewer muscle effects are observed with <u>Pravastatin</u> (Pravachol**®**)

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e) Biochemical abnormalities in liver function have also been reported (1-2%)

B1.6 Drug interactions.

a) **All** statins with the **exception** of **Pravastatin (Pravachol®)** are metabolized in the liver by the cytochrome P450 system

b) Drugs that inhibit cytochrome P450 enzymes will **increase** the concentrations of statins leading to increased risk of adverse effects such as myopathy and Rhabdomyolysis

- CYP3A4 inhibitors lead to elevated levels of Lovastatin (Mevacor®), Simvastatin (Zocor®) & Atorvastatin (Lipitor®)

CYP3A4 inhibitors associated with increased risk of Rhabdomyolysis
Immunosuppressants: cyclosporin & tacroliminus
Macrolide antibiotics: erythromycin, clarithromycin (Biaxin)
Calcium channel blockers: diltiazem, verapamil
Anti-arrhthymia drugs: amiodrone
Azole anti-fungal agents: itraconazole (Sporanox), ketoconazole (Nizoral),
HIV anti-retrovirals: amprenavir, indinavir, neflinavir & ritonavir
Anti-coagulants: warfarin

- Inhibitors of CYP2C9 increase the plasma concentration of Fluvastatin (Lescol®) and Rosuvastatin (Crestor®)
  e.g. ketoconazole, itraconazole, metronidazole, sulfinpyrazone,

c) Grapefruit juice in large amounts (>1 liter/day) may also increase the plasma concentrations of Lovastatin, Simvastatin & Atorvastatin via inhibition of CYP3A

d) Drugs such as phenytoin, griseofulvin, barbiturates, rifampin and thiazolidnediones that **increase** expression of CYP3A4 can **reduce** plasma concentrations of Lovastatin (Mevacor®), Simvastatin (Zocor®) & Atorvastatin (Lipitor®).

e) Pravastatin (Pravachol®) is **not** metabolized by the cytochrome P450 system and is therefore the drug of choice for use with verapamil, the ketoconazole group of fungal agents and macrolide antibiotics.

f) Gemfibrozil (a fibrate -see below) inhibits the metabolism of **ALL** statin drugs (including pravastatin) by inhibiting statin glucoronidation, which is involved in the metabolism of all Statin drugs, thereby acting to increase statin drug concentrations and increasing the risk of myopathy and rhabdomyolysis. Gemfibrozil also affect Statin drug concentrations by inhibiting the OATP2 transporter-mediated uptake of Statins into the liver.

B1.7 Contraindications.

a) Pregnancy and Nursing Mothers- statins have been shown to induce birth defects
b) Patients with Liver disease
c) Patients taking Gemfibrozil have an increased risk of myopathy and rhabdomyolysis.

B2. Bile acid-binding resins

Cholestyramine (Questran®), colestipol (Colestid®), colesevelam (Welchol®)

B2.1 Primary clinical effect

- Modest 10-25% reduction in LDLs (less effective than statins)
- can potentially cause a small increase in serum triglycerides

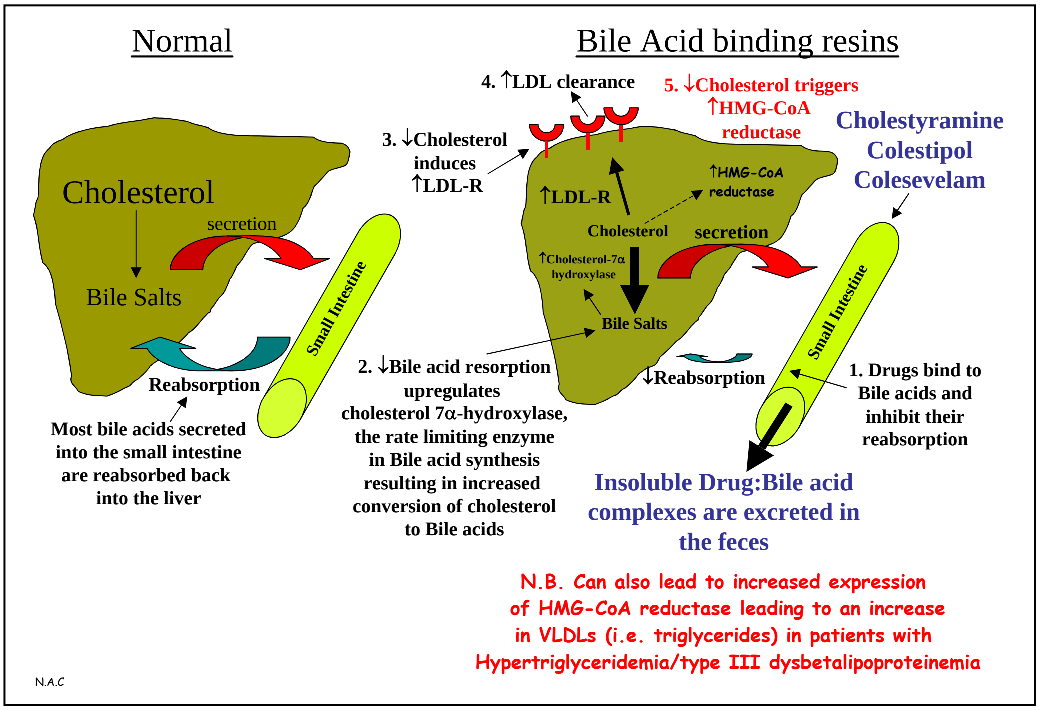
B2.2 Mechanism of Action.

a) Bile acid-binding resins are cationic polymers that act as anion exchangers that bind to negatively charged bile acids/salts and prevent their reabsorption in the small intestine

b) Resin/Bile acid complexes are excreted in the feces (~10-fold increase in excretion)

c) The decreased concentration of re-circulating bile acids up regulates the expression of cholesterol 7-α hydroxylase (rate limiting enzyme in the synthesis of bile acids) thereby promoting the enhanced hepatic conversion of cholesterol into additional bile acids, this lowers the concentration of hepatic cholesterol thereby increasing expression of LDL receptors (via activation of SREBP-see above), which promotes the hepatic uptake of LDL from the plasma, resulting in an overall decrease in the plasma LDL concentration

d) N.B. the decrease in hepatic cholesterol can **also** lead to the **increased** expression of HMG-CoA reductase, resulting in **increased** hepatic cholesterol synthesis and the generation of additional VLDLs- this can actually **increase** serum triglyceride levels in patients with **type III dyslipoproteinemia**.



B2.3 Therapeutic Use.

a) Because of the clinical efficacy of statins, bile acid-binding resins have largely been relegated to second line drugs that are mainly used for the treatment of primary hyperlipidemias in the young (<25 yrs) and in patients for whom statins do not effectively lower plasma LDL-cholesterol

b) Resins can be used together with low dose STATIN in combination therapy to aggressively reduce serum LDL-C concentrations (~50% lower than a statin alone)- allows aggressive reduction of LDL-C without increasing STATIN dose where toxicity may occur.

c) Resins can also be used to relieve pruritus (itching) caused by accumulation of bile acids in patients with biliary obstruction

d) Drug of choice for treating hypercholesterolemia in children and women of child bearing age who are lactating, pregnant, or could become pregnant.

B2.4 Pharmacokinetics

a) Not absorbed or metabolically altered by the intestine
b) Totally excreted in the feces

B2.5 Adverse Effects

a) Since these agents are not absorbed or metabolized they are very safe with few side effects
b) GI disturbances are the most common side effects e.g. constipation, bloating, nausea and flatulence
c) At high concentrations Cholestyramine (Questran®) and colestipol (Colestid®), **but not** colesevelam (Welchol®) can impair the absorbtion of the fat soluble vitamins A, D, E and K – decreased Vitamin K can result in bleeding.

B2.6 Drug interactions.

a) Cholestyramine (Questran®) and colestipol (Colestid®), **but not** colesevelam (Welchol®), interferes with the intestinal absorption of **many drugs** e.g. tetracycline, Phenobarbital, digoxin, warfarin, paravatatin, fluvastatin, aspirin and thiazide diuretics. - These Drugs should be taken either 1-2 hrs before or 4-6 hrs after bile acid-binding resins

B2.7 Contraindications

a) Dysbetalipoproteineimia and Raised Triglycerides (>400 mg/dL) due to risk of further increasing triglyceride levels

B3. Inhibitors of intestinal sterol absorption.

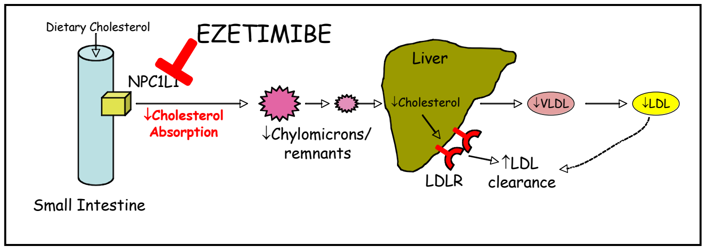
Ezetimibe (Zetia®)

B3.1 Primary clinical effect

- Reduces LDL levels by ~18%
- Minimal effect on HDL and triglycerides

B3.2 Mechanism of action

a) Ezetimibe (Zetia®) inhibits the action of the Niemann-Pick C1-like protein (NPC1L1) involved in the absorption of both dietary and biliary cholesterol in the small intestine



b) This decreases the delivery of dietary cholesterol to the liver, thereby reducing the production of VLDLs. Since VLDLs are the precursors of LDLs, this also leads to a reduction in the serum concentration of LDL-cholesterol.

c) In addition, the reduction in hepatic cholesterol will also result in an increase in the expression of LDL receptors, thereby promoting increased LDL clearance.

B3.3 Therapeutic uses.

a) Reduces LDL levels in patients with primary hypercholesterolemia
b) Significant LDL lowering effects when combined with a STATIN- a further 25% decrease in LDL versus STATIN-treatment alone.
c) The combination of Ezetimibe (Zetia®) together with a STATIN allows the use of a lower dose of the STATIN drug, thereby avoiding potential STATIN-associated adverse effects (e.g. Rhabdomyolysis).

B3.4 Pharmacokinetics

a) Rapidly absorbed by the enterocytes
b) Recirculates enterohepatically several time/day. This acts to continuously re-circulate the drug back to its site of action and limits systemic exposure.

B3.5 Adverse effects

a) Generally well tolerated
b) Flatulence is most common effect
c) Diarrhea and myalgia can occur
d) Low incidence of impaired liver function (reversible)

B3.6 Drug interactions.

a) Cyclosporin increases concentration of Ezetimibe (Zetia®)
b) Bile acid resins interfere with the absorption of Ezetimibe (Zetia®), and if used concurrently should be taken several hours apart

B3.7 Contraindications.

a) Hypersensitivity to Ezetimibe (Zetia®)
b) Patients with mild to severe hepatitis
c) Pregnant women- due to insufficient studies

(C) Drugs used in the treatment of Hypertriglyceridemia

Treatment Options for hypertriglyceridemia

1. When serum triglyceride levels are borderline high (150-199 mg/dL) a lifestyle change is indicated including a low fat diet, exercise and cessation of smoking/alcohol

2. When serum triglyceride levels are high (200-499 mg/dL) initial emphasis should be on reducing non-HDL cholesterol (i.e. LDL-C and VLDL) using a LDL-C lowering drug such as a STATIN or the addition of niacin or a fibrate- ie. To reduce the risk of atherosclerosis

3. When serum triglyceride levels are very high (>500 mg/dL) the initial goal should be to reduce triglyceride levels with either niacin or a fibrate to reduce the risk of pancreatitis. Once triglyceride levels are below 500 mg/dL then LDL-C goals should be addressed

C1. Niacin

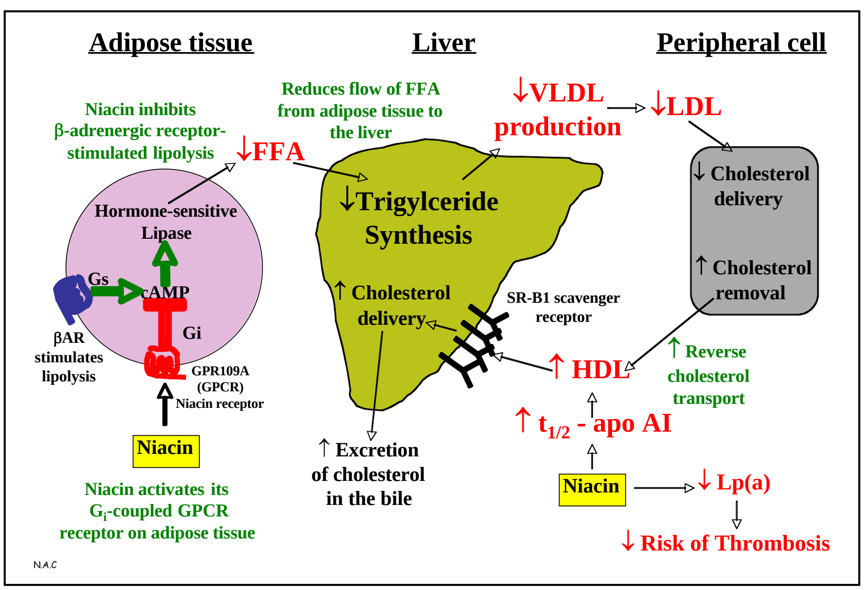
Niacin (nicotinic acid/vitamin B3) is a water-soluble vitamin that, at physiological concentrations is used in the synthesis of NAD & NADP, both important co-factors in intermediary metabolism. The pharmacological effects of niacin require large doses (1,500- 3,000 mg/day) and are independent of conversion to NAD & NADP.

C1.1 Primary clinical effect

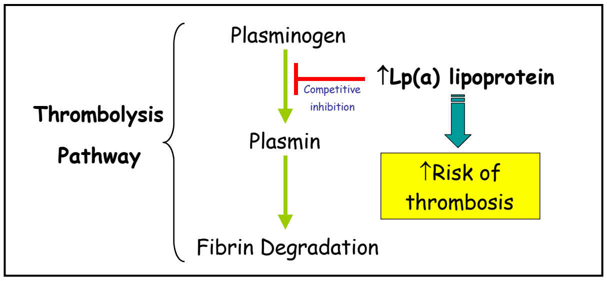
- 30-80% reduction in triglycerides
- 10-20% reduction in LDLs
- 10-30% increase in HDLs-most effective drug at reducing HDL

C1.2 Mechanism of Action

a) Niacin improves virtually all lipid parameters resulting in decreased free fatty acids (FFA), VLDL & LDL and increased HDL
b) Niacin acts via its Gi-coupled GPCR (GPR109A) expressed in adipose tissue to inhibit cAMP-induced lipolysis (stimulated via the Gs-coupled beta-adrenergic receptor.
c) The reduce levels of lipolysis reduce the release of free FFA to the liver
d) Decreased FFA to the liver causes a reduction in the synthesis of triglycerides that in turn reduces production of VLDLs
e) Reduced VLDLs in turn reduce the production of LDL-C
f) Niacin also increases the half-life of apoAI, the major apolipoprotein present in HDL, which in turn increases the plasma concentration of HDL and promotes reverse cholesterol transport (the HDL-mediated transport of cholesterol from the peripheral tissues to the liver where it can be excreted).



g) Niacin also significantly reduces the levels of Lp(a) lipoprotein, which is a modified form of LDL that is covalently coupled to the Lp(a) protein. The Lp(a) protein is homologous to plasminogen and is found in atherosclerotic plaques, where it is thought to contribute towards atherosclerosis by antagonizing the activation of plasminogene thereby inhibiting thrombolysis. Niacin is the only lipid lowering drug to significantly reduce the levels of Lp(a) lipoprotein.



C1.3 Therapeutic Uses

a) Lowers both plasma cholesterol and triglycerides
b) Particularly useful in the treatment of familial combined hyperlipidemias and familial dysbetalipoproteinemia (elevation of both triglycerides and cholesterol)
c) Most effective agent at elevating HDL levels.
d) Often combined with another lipid lowering drug such as a statin or a resin
e) Niacin has been shown to reduce the incidence of myocardial reinfarctions and overall mortality in patients with a history of previous MI
f) The use of Niacin is often limited by poor tolerability (see below).

C1.4 Pharmacokinetics

a) Administered orally
b) Is converted in the body to nicotinamide and is incorporated into NAD+
c) Excreted in the urine unmodified and as several metabolites

C1.5 Adverse effects.

a) Most patients experience skin flushing, itching (pruritis) and a sensation of warmth – this prostaglandin-mediated effect can be diminished by prior treatment with Aspirin or Ibuprofen

b) Some patients experience GI distress, nausea and abdominal pain.

c) Niacin inhibits tubular secretion of uric acid and therefore predisposes to **hyperuricemia** and **gout** (20% of patients)

d) Can cause insulin resistance (generally reversible) and hyperglycemia may be worsened in susceptible patients i.e. Type-2 diabetes

e) Hepatic toxicity has been reported

f) Niacin can exacerbate **peptic ulcer** and is therefore contraindicated in patients with severe peptic disease

g) Poor tolerability often limits the use of the drug

C1.6 Contraindications

a) Peptic Ulcer disease
b) Patients with a history of Gout

c) Caution should be observed in diabetics
d) Caution should be observed in patients with impaired liver function

C2. Fibrates.

Fenofibrate (Tricor®, Lofibra®), Gemfibrozil (Lopid®)

C2.1 Primary clinical effect

- 40-60% reduction in triglycerides
- mild (10-20%) reduction in LDL
- 10-20% increase in HDL

C2.2 Mechanism of action

a) Fibrates are derivatives of fibric acid and act as ligands for the nuclear hormone transcription factor peroxisome proliferator-activated receptors alpha (PPARα)

b) Fibrates activate PPARα, which then binds to its responsive element in the promoters of numerous genes involved in lipoprotein structure and function

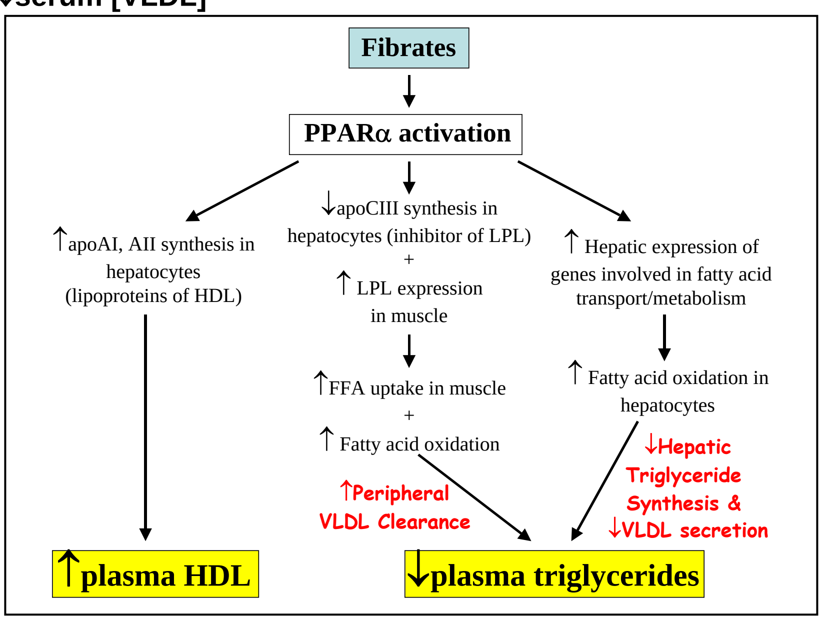
c) PPARα activation acts to decrease plasma triglyceride concentrations by:

(i) increasing the expression of lipoprotein lipase in muscle, thereby resulting in increased muscle lipolysis leading to enhanced uptake and catabolism of triglyceride-rich lipoproteins.

(ii) decreasing the hepatic expression of apolipoprotein CIII (a known inhibitor of lipoprotein lipase), which acts to enhance overall lipoprotein lipase activity, thereby increasing the catabolism of triglyceride-rich lipoproteins.

(iii) increasing the expression of genes involved in fatty acid transport and fatty acid oxidation in hepatocytes, which results in increased fatty acid catabolism, thereby reducing hepatocyte triglyceride synthesis and decreasing the hepatic production of VLDLs

Overall effect: Increased peripheral VLDL clearance and decreased hepatic TG production = **↓serum [VLDL]**



d) PPARα activation increases the plasma concentration of HDLs by increasing the synthesis of apoAI and apoAII, the major apolipoproteins found in HDL. This promotes reverse cholesterol transport.

e) PPARα activation also induces the upregulation of the SR-B1 scavenger receptor in hepatocytes, which binds to HDL and promotes increased transfer of cholesterol from HDLs to hepatocytes, thereby leading to increased secretion of cholesterol into the bile duct. This can lead to increased risk of gallstone formation (see below).

C2.3 Therapeutic Uses

a) Effective at decreasing serum triglyceride levels
b) Useful for increasing concentration of serum HDL-C levels
c) Used in the treatment of hypertriglyceridemias, especially in patients with severe hypertriglyceridemia at risk of pancreatitis and in hypertriglyceridemia with low HDL-C
d) Therapy of choice for patients with Familial dysbetaliporoteinemia (Type III hyperlipoproteinemia: increased plasma triglycerides and lipoprotein remnants)
e) Long-term fibrate usage has been clinically proven to reduce the incidence of coronary events (22%), stroke (25%), and transient ischemia events (59%).

C2.4 Pharmacokinetics

a) Both drugs are completely absorbed after oral administration
b) Drugs are distributed widely and are bound to serum proteins
c) Both drugs undergo extrahepatic circulation
d) Half-life for gemfibrozil is 1.5 hrs and for fenofibrate is 20 hrs

C2.5 Adverse effects

a) Generally well tolerated
b) most common side effects are mild GI disturbances
c) Predisposition to gallstone formation due to increased cholesterol excretion in the bile. Fibrates inhibit expression of cholesterol 7alpha-hydroxylase (the rate-limiting enzyme in Bile acid production), thereby decreasing Bile acid production resulting in increased secretion of free cholesterol, which can result in the formation of gallstones
d) Myopathy and rhabdomyolysis have been reported (esp. Gemfibrozil: increased risk when given with a STATIN)
e) Hepatitis

C2.6 Drug interactions

a) Both drugs are strong protein binders and can therefore displace other protein-bound drugs from albumin resulting in an increased serum drug concentration.

    - potentiates the effects of oral anti-coagulants (e.g. warfarin) leading to increased risk of bleeding. Anticoagulant drug concentrations should be reduced by 30% when given together with a STATIN

- enhances hypoglycemic effects of sulfonylureas

b) Gemfibrozil increases the serum concentration of STATINS leading to increased risk of STATIN-induced adverse effects such as myopathy and rhabdomyolysis

- Gemfibrozil inhibits the transporter responsible for hepatic uptake of STATINs
- Gemfibrozil inhibits STATIN glucoronidation that is involved in the metabolism and excretion of all STATINs

c) Fenofibrate does not affect STATIN metabolism and is therefore the drug of choice for use with a STATIN in combination therapy.

d) Because both drugs are renally excreted, drug concentrations are elevated in patients with renal insufficiency, thereby increasing the risk of drug interactions.

C2.7 Contraindications

a) Pregnant/lactating women

b) Patients with severe hepatic dysfunction-due to increased risk of hepatic damage

c) Patients with severe renal dysfunction-since both drugs renally secreted

d) Patients with pre-existing gallbladder disease

e) Caution should be observed in patients taking a STATIN because of increased risk of Rhabdomyolysis

C3. Fish Oils: Omega-3 long chain polyunsaturated fatty acids

A mixture of Eicosapentaenoic acid and Docosahexanoic acis (Omacor/Lorvaza)

C3.1. Primary clinical effect

- Lowers serum triglyceride levels by 50%
- Minor increase in HDL
- Can increase LDLs in some individuals

C3.2. Mechanism of Action.

- Unclear, but appears to involve the inhibition of hepatic triglyceride synthesis and the increased triglyceride clearance

C3.3. Therapeutic Uses

- Currently approved only as an adjunct to diet and lifestyle interventions in the treatment of hypertryglyceridemia in patients with TG levels >500 mg/dl

C3.4. Adverse Effects

a) Fishy after taste
b) GI: nausea, bloating, diarrhea, flatulence

c) reduces serum concentrations of vitamin E

C3.5. Drug Interactions

a) None
b) Unlike fibrates, fish oils are not associate with an increased risk of Rhabdomyolysis when given together with a STATIN

D. Combination drug therapy.

Combined drug therapy is useful when:

a) LDL-cholesterol levels are not sufficiently reduced in high-risk patients even with the highest dose of STATIN
   - A STATIN + either a Resin, Ezetimibe or Niacin
     Synergistic reduction of LDL-cholesterol with drug combination

b) Both LDL and VLDL levels are elevated (e.g. combined hyperlipoproteinemia)
   - STATIN + Niacin – more effective than either agent alone
   - STATIN + fibrate - in cases where TG and LDL are very high- however should be used with caution as increased risk of myopathy especially with Gemfibrozil (Fenofibrate is preferred drug in this case)

c) When LDL or VLDL levels are not normalized with a single drug regime

d) When HDL deficiency co-exists with other hyperlipidemias
   - Either Niacin or a fibrate is added to increase HDL

e) When VLDL levels are increased during treatment of hypercholesterolemia with a bile acid-binding resin
   - Niacin is added to control elevated VLDL levels

Review of lipid-lowering drug effects

Drug	Effect on LDL	Effect on Triglycerides	Effect on HDL
Statins	↓↓↓↓	↓↓	↑↑
Fibrates	↓	↓↓↓↓	↑↑↑
Niacin	↓↓	↓↓↓	↑↑↑↑
Bile acid Binding resins	↓↓↓	Minimal/ slight increase	↑
Cholesterol Absorption inhibitors	↓	Minimal Effect	Minimal Effect

N.A.C. 2006

Summary of drugs used to treat hyperlipidemia

Drug class	Indications	Mechanism of action	Effect on serum lipids	Adverse effects/ Contraindications	Drug Interactions
Statins Lovastatin Simavastatin Atorvastatin Fluvastatin Rosuvastatin Pravastatin	High LDL	Inhibits HMG-CoA Reductase & triggers SREBP transcription factor leading to: ↑ LDL-R expression ⇒ **↑ LDL clearance**	↓LDL (20-60%) ↓TG (10-20%) ↑ HDL (5-10%)	a) Muscle myalgia/myopathy **b) ***Rhabdomyolysis***** c) Hepatitis Contraindicated in Severe liver disease	**a) CYP3A4 inhibitors (↑[L,S,A])** *INCREASED RISK of ADVERSE EFFECTS* *e.g. erythromycin, cyclosporin, ketaconazole* *HIV prot inhibs & grapefruit juice* **b) CYP3A4 inducers (↓[L,S,A])** *DECREASED CLINICAL EFFICACY* *e.g. phenytoin,phenpbarbital, rifampin* **c) CYP2C9 inhibitors (↑[F,R])** *e.g. ketoconazole/metronidazole* **d) Gemfibrozil** *↓OATP2/↓Glucoronidation ⇒↑[all Statins]*
Bile Acid binding resins Cholestryramine Colestipol Colesevelam	High LDL	Binds bile acids and prevents reabsorption ⇒ ↑Chol 7α-hydroxylase ⇒ ↓ Cholesterol ⇒↑LDLR ⇒ **↑ LDL clearance**	↓LDL (10-25%)	**Can increase TG levels in hypertriglyceridemia** Contraindicated TG > 400 mg/dL	Cholestyramine/Colestipol Interfere with absorption of a number of drugs e.g. Warfarin, Phenobarbital Digoxin & Tetracycline
Ezetimibe	High LDL	Inhibits intestinal absorption of cholesterol (via NPCL1) **⇒↓hepatic cholesterol** ↑ LDL-R expression ⇒**↑ LDL clearance**	↓LDL (~18%)		• Bile acid resins interfere with Ezetimibe absorption
Niacin	High VLDL High LDL Low HDL	a) Acts via GPCR GPR109A to ↓lipolysis in adipocytes **⇒↓[FFA] ⇒↓VLDL** b) ↑apoAI expression **⇒↑HDL production** c)**↓Lp(a) ⇒↓Thrombosis**	↓TG (30-80%) ↓LDL (10-20%) ↑ HDL (10-30%)	**a) Skin flushing (Tx-NSAID)** **b) Risk of Gout** **c) Exacerbates peptic ulcers** d) Risk of hyperglycemia **e)** Hepatitis	
Fibrates Gemfibrozil Fenofibrate	High VLDL Low HDL	Ligands for PPARalpha TF a)↓Apo C3/ ↑LPL expression ↑ Fatty acid oxidation **⇒ ↓ VLDL synthesis** **⇒ ↑ VLDL clearance** b) ↑apoAI expression **⇒↑ HDL production**	↓TG (40-60%) ↓LDL (10-20%) ↑ HDL (10-20%)	**a) Increased gallstones** b) Hepatitis c) Myopathy d) **Rhabdomyolysis** (more common with gemfibrozil) Contraindicated in Severe Renal/hepatic disease	a) Strong protein binders ↑Warfarin ⇒↑risk of bleeding ↑Sulfonylureas ⇒↑hypoglycemia b) STATIN interaction Inhibit OATP2/glucoronidation ↑[Statins] ⇒↑Rhabdomyolysis esp. gemfibrozil

PHARMACOLOGY OF NITRIC OXIDE

Date: November 8, 2012-8:30 am
Reading Assignment: Katzung 12th Ed. Pp. 331-337.
Trevor, Katzung and Master's Pharmacology, Examination & Board Review. 9th Ed., pp. 175-178.

KEY CONCEPTS & LEARNING OBJECTIVES

1. To understand that the originally described endothelium derived relaxing factor (EDRF) is now established to be nitric oxide.
2. To describe the physiologic process which can generate endogenous nitric oxide.
3. To know that arginine is the main endogenous source of nitric oxide.
4. To know the isoforms of the enzymes responsible for the synthesis of nitric oxide.
5. List some of the beneficial effects of nitric oxide.
6. List some of the toxic effects of nitric oxide.
7. What are some of the drugs which can increase the levels of endogenous nitric oxide.
8. List two drugs that spontaneously or enzymatically breakdown in the body to release NO.
9. What are some of the therapeutic uses of nitrates.
10. Describe the term nitric oxide donor.

LIST OF DRUGS COVERED IN LECTURE

1. Nitroglycerine
2. Iso-sorbide dinitrite
3. Amyl nitrate
4. Nitroprusside
5. Hydralazine (vasodilator)
6. Nitric oxide (INOmax)
7. Furoxans (Furazolidone, antiprotozoal)
8. L-Arginine
9. Sildenafil

PHARMACOLOGY OF NITRIC OXIDE

I. INTRODUCTION

Nitric oxide, a gaseous signaling molecule that diffuses vascular and cellular sites and regulates a wide range of physiologic and pathological processes including cardiovascular, cerebrovascular, inflammatory, immune and neuronal pathways.

Nitric oxide produces profound pharmacologic actions, some of which are listed below.

1. Smooth muscle

   - relaxation

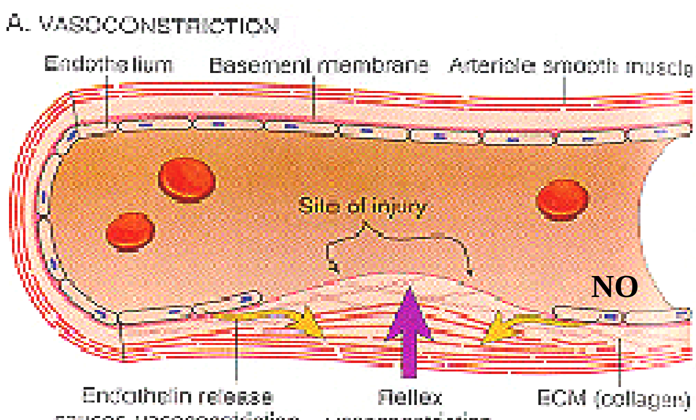
2. Cell adhesion

   - decreased adhesion

3. Inflammatory response

II. DISCOVERY OF NITRIC OXIDE

1. Endogenous nitric oxide (NO) is generated from the oxidation of the guanidine group of arginine. Exposure to bacterial lipopolysaccharide result in the generation of NO in the macrophage. Infection of bacterial endotoxin to animals also increases the NO levels.
2. Upon stimulation with acetylcholine and carbochol, the vascular endothelium release a vasodilatory substance known as the endothelin derived growth factor (EDRF). This EDRF was later characterized to be NO.



III. BIOLOGIC SYNTHESIS AND THE INACTIVATION OF NITRIC OXIDE

1. Synthesis of Nitric Oxide

Nitric oxide designated as NO or simply NO, is a highly diffusible gas composed of one atom of nitrogen and oxygen each. Nitric oxide is synthesized by a family of enzymes collectively termed as nitric oxide synthase (EC.1.14.13.49). Three isoforms of these enzymes have been identified and are summarized in the following table.

Table 19–1. Properties of the three isoforms of nitric oxide synthase (NOS).

	Isoform Names		
Property	NOS-1	NOS-2	NOS-3
Other names	nNOS (neuronal NOS)	iNOS (inducible NOS)	eNOS (endothelial NOS)
Tissue	Neuronal, epithelial cells	Macrophages, smooth muscle cells	Endothelial cells
Expression	Constitutive	Transcriptional induction	Constitutive
Calcium requirement	Yes	No	Yes
Chromosome	12	17	7
Approximate mass	150–160 kDa	125–135 kDa	133 kDa

Katzung 10th Ed. Pp.310.

These isoforms are heme containing flavoproteins employing L-arginine as a substrate and requiring NADPH, Flavin ademine dinucleotide and tetrahydrobiopterin as cofactors.

The conversion of L-arginine to L-citrulline is inhibited by several arginine analogues such as N-monomethyl-L arginine.

Some nitric oxide donors such as oxygenated nitroprusside, spontaneously generates NO, whereas others such as the furoxan and organic nitrates and nitrites such as nitroglycerin require the presence of a thiol compound such as cysteine. Once generated NO interacts with the heme moiety of soluble guanyl cyclase in the cytoplasma of the cell. Upon activation this enzyme converts GTP to cyclic GMP.

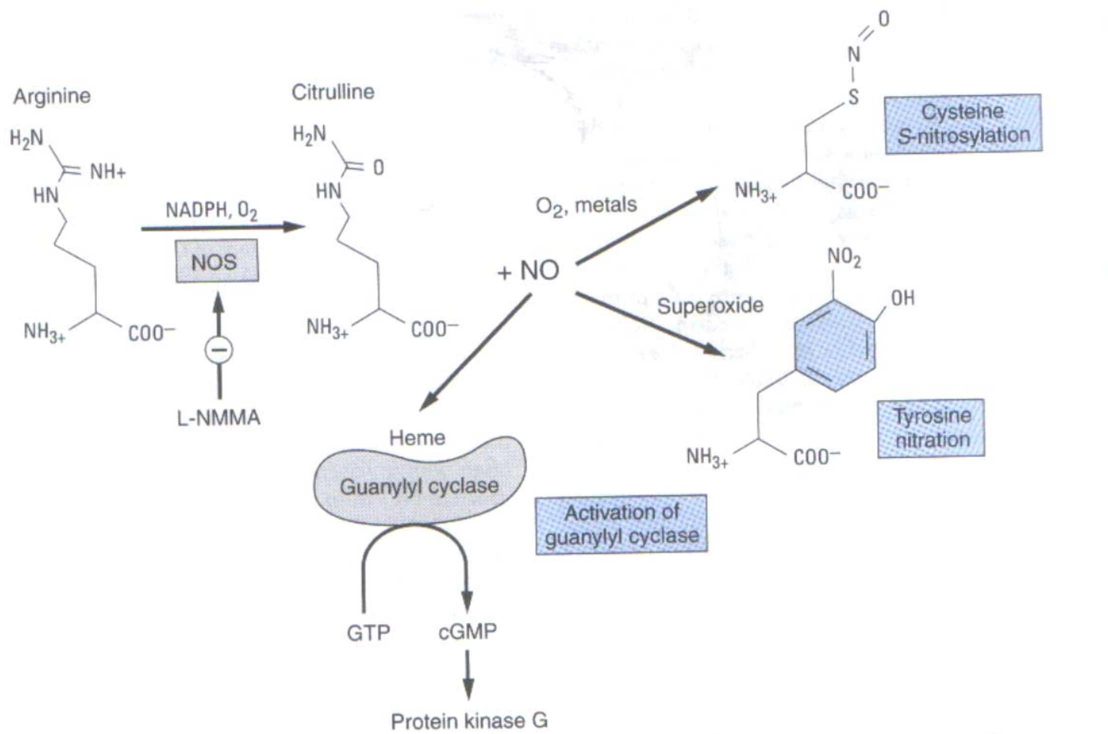


Figure 19–1. Nitric oxide generation from L-arginine and nitric oxide donors and the formation of cGMP. L-NMMA inhibits nitric oxide synthase. Some of the nitric oxide donors such as furoxans and organic nitrates and nitrites require a thiol cofactor such as cysteine or glutathione to form nitric oxide.

Katzung 10th Ed. Pp.310.

Nitric oxide undergoes both oxidative and reductive reactions resulting in the formation of a variety of oxides of nitrogen. These are described in the following table.

Table 19–2. Oxides of nitrogen.

Name	Symbol	Known Function
Nitric oxide	$NO^{\cdot}$	Vasodilator, platelet inhibitor, immune regulator, neurotransmitter
Nitroxyl anion	NO^{-}	Smooth muscle relaxant
Nitrogen dioxide	$NO_2^{\cdot}$	Free radical, nitrosating agent, lung irritant
Nitrous oxide	N_2O	Anesthetic
Dinitrogen trioxide	N_2O_3	Nitrosating agent
Dinitrogen tetraoxide	N_2O_4	Nitrosating agent
Nitrite	NO_2^{-}	Produce $NO^{\cdot}$ at acidic pH
Nitrate	NO_3^{-}	Stable oxidation product of $NO^{\cdot}$

Katzung 10th Ed. Pp.311.

2. Inactivation of Endogenous Nitric Oxide

NO is inactivated by heme and by free radicals superoxide. The scavenger of superoxide such as the enzyme superoxide dismutase may protect nitric oxide and augment it's potency and duration of action. On the other hand, superoxide may interact with NO to generate peroxynitrite ($ONOO^{-}$) which complexes with the sulfhydral groups of several key enzymes. The effects of peroxynitrile are regulated by glutathione. Nitrosoglutathione is a more stable form of cytosolic NO. In cardiovascular diseases and diabetes cellular levels of glutathione are reduced and contribute to the vascular pathology.

IV. INHIBITORS OF NITRIC OXIDE

Several approaches can be used to reduce endogenous nitric oxide levels and thus inhibit its effects. These include:

1. L-arginine derivatives (L-NMMA, L-NAME)
2. Inhibitors of nitric oxide synthase synthesis
3. Inhibitor of binding of arginine to NOs

4. Scavengers of NO

Most of the inhibitors are substrate analogues. Heme is a scavenger for NO. In sepsis and other inflammatory conditions, NOS-2 is induced and results in an increased production of NO. Excess production of NO results in the generation of peroxynitrite which is toxic to cells. Thus, NO inhibitors may be helpful in the treatment of sepsis related disorders.

Table 19–3. Some inhibitors of nitric oxide synthesis or action.

Inhibitor	Mechanism	Comment
N^G–Monomethyl–L–arginine (L–NMMA)	NOS inhibition	May act as substrate in some tissues
N^G–Nitro–L–arginine methyl ester (L–NAME)	NOS inhibition	Less selective NOS inhibitor
7–Nitroindazole	NOS inhibition	Markedly selective for NOS–1 in vivo
S–Methylthiocitrulline	NOS inhibition	Partially selective for NOS–1
Heme	Nitric oxide scavenger	
Protein inhibitor of NOS	Unknown mechanism	Endogenous inhibitor found in brain

NOS, nitric oxide synthase.

Katzung 10th Ed. Pp.313.

V. EFFECTS OF NITRIC OXIDE

NO's major effects are mediated by the activation of guanyl cyclase resulting in the generation of cyclic GMP. NO can also generate several reactive nitrogen derivatives by interacting with molecular oxygen and superoxide radicals.

These oxides of nitrogen are highly reactive and unstable, interact with numerous proteins, lipids, nucleic acids and metabolize. Thus, these reactive species alter the physiologic disposition of cells and tissues and mediate several physiologic and pathologic effects. The beneficial effects include smooth muscle relaxation, vasodilation, immune regulation, anesthetic and anti-athlerosclerotic responses. The pathologic responses include free radical formation, nitrosation and irritant effects.

1. Vascular Effects

NO is involved in the regulation of normal vascular tone. Decreased NO levels in blood vessels may result in an increase in blood pressure.

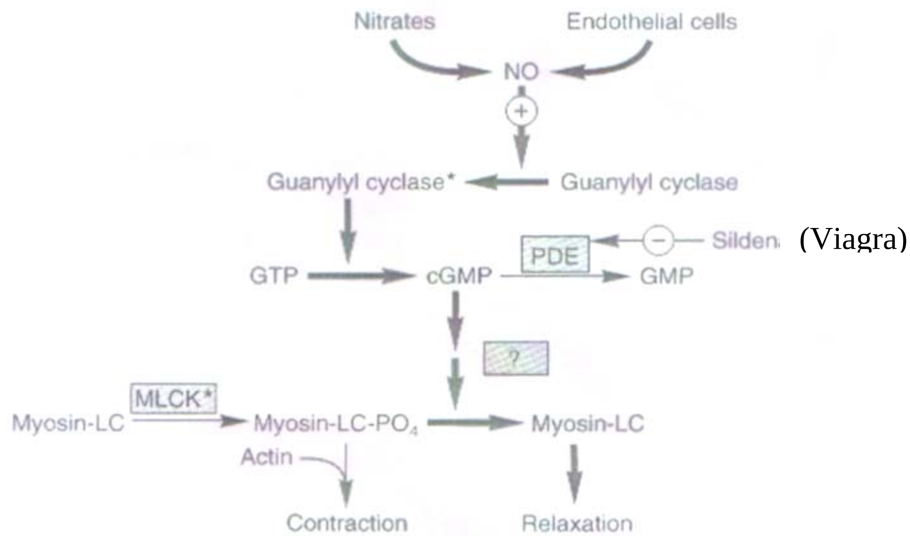


Figure 12–2. Mechanism of action of nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in smooth muscle cells. (MLCK*, activated myosin light chain kinase [see Figure 12–1]; guanylyl cyclase*, activated guanylyl cyclase; ?, unknown intermediate steps. Steps leading to relaxation are shown with heavy arrows.)

Katzung 10th Ed. Pp.185.

NO is also a potent inhibitor of the white cells adhesion to the endothelial surface. It decreases the release of adhesion molecules such as the E-Selectin on the endothelial surface. NO has been shown to protect against ischemic and reperfusion injury.

2. Respiratory Effects

Nitric oxide improves cardiopulmonary function in adults with pulmonary hypertension and is approved for this indication (INOmax). It is administered by inhalation. It is also used in children with acute respiratory distress syndrome (ARDS). Nitric oxide also relaxes airway smooth muscle and acts as a bronchodilator.

3. Septic Shock

Bacterial infection and lipopolysaccharide B activate inducible nitric oxide synthase (NOs-2) resulting in hypotension, shock and possible death. This effect is reversed by NO inhibitors such as the L-NMMA.

4. Atherosclerosis

Vascular plaque and endothelial damage in atherosclerosis results in impaired nitric oxide formation. Decreased release of NO results in vascular defects and increased cellular proliferation. L-arginine and nitric oxide donors are useful in the treatment of atherosclerotic disorders.

5. Platelets

Nitric oxide is a potent inhibitor of platelet adhesion, activation and aggregation and regulates the release of serotonin, growth factors and thromboxane from platelets. Platelets also contain the constitutive and inducible NOs. Cyclic GMP plays an important role in platelet protection. NO also indirectly enhances fibrinolysis by inhibiting the release of antiplasmin for the platelets.

6. Organ Transplantation

Accelerated graft atherosclerosis following organ transplantation is a chronic condition and is a major cause of graft failure. Platelet activation results in the generation of growth factors such as the PDGF. Cellular proliferation causes ischemic and reperfusion injury. <u>Nitric oxide acts as a cytoprotective agent and prevents cellular and</u>

platelet adhesion. Dietary L-arginine increases plasma NO levels has been shown to reduce the graft atherosclerosis. In some cases excessive production of NO may be harmful and promote graft rejection.

7. The Central Nervous System

NO is known to play a major role in the CNS as a neurotransmitter, as a modulator of receptors and the release of other transmitters. NO is implicated in neurmodulatory process and has impact on stroke and vascular dementia. NO has multiple roles in the CNS which are beyond the scope of this discussion.

8. Peripheral Nervous System

Nonadrenergic, noncholinergic (NANC) are widely distributed peripheral tissues. Some NANC neurons release nitric oxide. Erectile responses are thought to be caused by the release of NO from NANC neurons. Nitric oxide donors may be useful in impotence. Such agents as nitroglycerine ointment and nitroglycerin patches have been used. Another approach is to inhibit CGMP degradation by phosphodiesterase 5 with such drugs as Sildenafil (Viagra). Potent interactions between NO donors and Viagra have been reported resulting in hypotension.

9. Inflammation

Nitric oxide has a role in both the acute and chronic inflammation. NOs-3 is involved in the vasodilation associated with acute inflammation. Nitric oxide promotes edema and vascular permeability. In inflammatory bowel disease, arthritis and other diseases of inflammation, NOs-3 is elevated and generates excessive NO levels.

VI. NITRATES AS NO DONORS

Nitrates represent the most widely used donors of nitric oxide (NO). Denitration of such drugs as the nitroglycerin result in the formation of NO which is responsible for the smooth muscle relaxation.

1. Classification and pharmacokinetics

   a. Nitroglycerine

   b. Isosorbide dinitrate (sublingual/oral)

   c. Amyl nitrates (volatile rapid acting)
   Rarely prescribed

2. Pharmacokinetics

Type	Example	Duration of action
Ultra short	Inhaled amyl nitrate	3-5 minutes
Short	Sublingual nitroglycerin iso-sorbide dinitrate	10-30 minutes
Intermediary	Oral or sustained release nitroglycerine or iso-sorbide dinitrate	4-8 hours
Long	Transdermal nitroglycerine	8-10 hours

3. Mechanism of action

   Primarily produce smooth muscle relaxation by releasing endogenous NO which produces the following effects.

   a. Stimulates guanyl cyclase

   b. Increased production of cGMP

   c. Dephosphorylation of myosin

VII. THERAPEUTIC AND DIAGNOSTIC USE OF NITRIC OXIDE.

1. Methods of Administration

   Commercial NO systems are available which can accurately deliver inspired NO concentrations between 0.1 and 80 ppm and simultaneously measure NO and NO_2

concentrations. A consistent inspired level of NO is maintained by administering NO in nitrogen to the inspired limb of the ventilator circuit as intermittent or continuous delivery. NO can be administered via a closely fitted mask. It is administered mostly in the management of primary pulmonary hypertension. After the administration, NO should be gradually discontinued to avoid complications such as rebound

2. Therapeutic Use of Nitric Oxide

   a. Selective pulmonary vasodilation

   b. Treatment of newborn with persistent pulmonary hypotension (improves oxygenation)

   c. Beneficial effects in cardiopulmonary bypass in adults, congestive heart disease, primary pulmonary hypertension, pulmonary edema, lung transplantation and sickle cell crisis.

3. Diagnostic use of Nitric Oxide.

   Inhaled NO is used in Several Diagnostic Procedures.

   a. Can be used during cardiac catherization to evaluate the pulmonary vasodilating capacity of patients with heart failure and pediatric patients with congenital heart disease.

   b. Inhaled NO can also be used to measure the diffusion capacity across the alvelor-capillary unit (better than CO_2 because of greater affinity to hemoglobin and increased water solubility).

   c. Measurement of exhaled NO (nasal and pulmonary) is useful in the diagnosis of respiratory disease.

PHARMACOLOGY OF VASOACTIVE PEPTIDE

Date: November 9, 2012-10:30am
Reading Assignment: Katzung 12th Ed. Pp. 295-312
Trevor, Katzung and Master's Pharmacology, Examination & Board Review 9th Ed., pp. 161-165.

KEY CONCEPTS & LEARNING OBJECTIVES

1. Know the enzyme responsible for the conversion of angiotensinogen to angiotensin I.
2. Know the effects of angiotensin converting enzyme (ACE).
3. Know two of the drugs which are known as angiotensin converting enzyme inhibitors (ACE Inhibitors).
4. What are some of the pharmacologic actions of bradykinin.
5. What are some of the major actions of Atrial Natriuretic Peptide
6. Describe the actions of kallikreins
7. List four of the potent vasoactive peptide
8. Know the actions of endothelins
9. Describe the functions of vasoactive intestinal peptide (VIP), substance P and calcitonin gene-related peptide (CGRP).
10. Know the effect of desmopressin on endothelial cells
11. Know the effects of aprotonin on the actions of kallikrein

LIST OF DRUGS COVERED IN LECTURE

1. Captopril (ACE inhibitor)
2. Enalapril (ACE inhibitor)
3. Losartan (Angiotensin receptor inhibitor)
4. Valsartan (Angiotensin receptor inhibitor)
5. Icatibant (Bradykinin receptor inhibitor)
6. Aprotonin (Kallikrein inhibitor)
7. Desmopressin (Vasopressin analogues, release vW factor)
8. Bosentan (ET_A-ET_B receptor inhibitor)

PHARMACOLOGY OF VASOACTIVE PEPTIDE

A. PHARMACOLOGY OF VASOACTIVE PEPTIDES

Vasoactive peptides are comprised of a wide group of polypeptides of endogenous origin that function as local and plasmatic hormones and neurotransmitters. Of these peptides the angiotensin, the kinins, endothelins and vasopressin play an important role in the overall regulation of hemodynamics and its pathogenesis. Some of these peptides are listed below.

1. Angiotensins (I, II and III)
2. Bradykinin and related kinins
3. Vasopressin
4. Atrial natriuretic peptides and related peptides
5. Endothelins
6. Vasoactive intestinal peptides and related peptides
7. Substance P
8. Neurotensins
9. Calcitonin gene-related peptide
10. Adrenomodulin
11. Neuropeptide Y
12. Urotensin

Mechanisms of Actions

These peptides all act on cell surface receptors. Most act via G protein-coupled receptors and cause the production of second messengers, some may open ion channels.

B. ANGIOTENSIN AND RELATED PEPTIDES

Angiotensin

Angiotensin is formed by the action of renin on angiotensinogen releasing angiotensin I, a decapeptide. Angiotensin I is converted to angiotensin II , an octapeptide by the action of converting enzyme. Angiotensin II is degraded into inactive peptide by the action of angiotensinases. Of these angiotensin I, angiotensin II and angiotensin III, only angiotensin II is active and produces profound vasoconstriction and other pharmacologic responses.

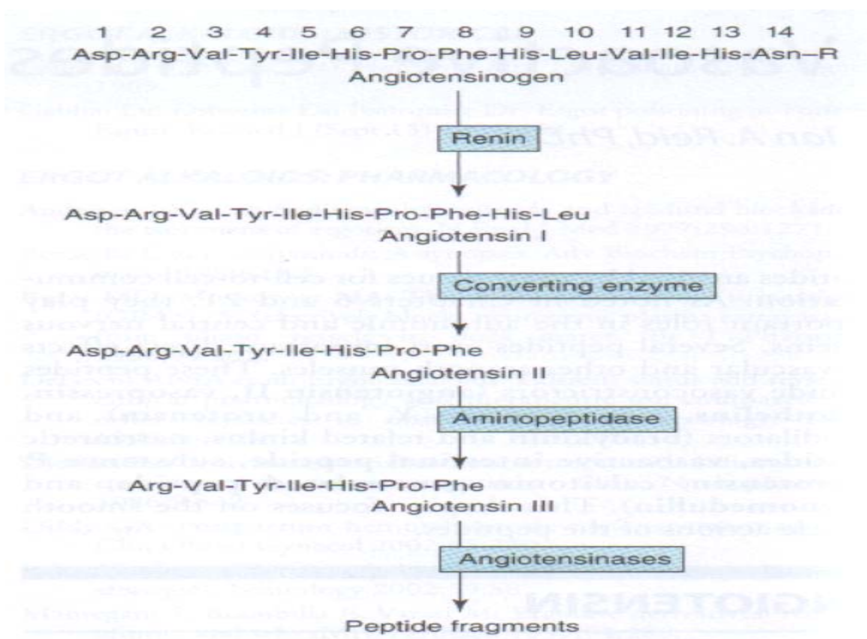


Figure 17–1. Chemistry of the renin-angiotensin system. The amino acid sequence of the amino terminal of human angiotensinogen is shown. R denotes the remainder of the protein molecule.

1. Angiotensinogen

A circulating protein from which renin cleaves angiotensin I. It is a glycoprotein.

Angiotensin production is increased by a variety of drugs including corticosteroids, estrogens, thyroid hormones and Angiotensin II. The plasma levels of angiotensinogen are also increased in pregnancy related hypertension.

2. Angiotensin I

A decapepetide with virtually no biologic activity. It must be converted to the octapeptide, angiotensin II by the action of angiotensin converting enzyme (ACE). Plasma or tissue aminopeptides convert angiotensin II into angiotensin III.

-	Angiotensin I	Decapeptide	(inactive)
-	Angiotensin II	Octapeptide	(active)
-	Angiotensin III	Heptapeptide	(inactive)
-	Angiotensin III fragment	<Tetrapeptides	(inactive)

3. Angiotensin Converting Enzyme

Angiotensin converting enzyme is also known as

- Peptidyl dipeptidase
- Kininase II

It catalyzes the cleavage of dipeptide from the carboxyl terminal of angiotensin I (decapapetide) into angiotensin II (octapeptide). This enzyme is widely distributed in the vasculature mostly located on the luminal structure of the endothelial cells. It has been the primary target to develop antihypertensive drugs.

4. Angiotensinase

A group of peptidases which hydrolyze angiotensin II and angiotensin III into smaller fragments. These peptide fragments are inactive.

5. Pharmacologic Actions of Angiotensin II

Short plasmatic half life (15-60 secs.). This peptide exerts profound effects in the regulation of vascular tone, fluid and electrolyte balance. Excessive production of this peptide results in hypertension and disorders of hemodynamics. On a molar basis, it is 40 times more potent than nor-epinephrine, stimulates autonomic ganglion, increases the release of epinephrine and nor-epinephrine from the adrenal medulla and facilitates autonomic transmissions. It stimulates aldosterone production from the adrenal cortex. At higher concentrations it produces glucocorticoid biosynthesis. Angiotensin is a potent mitogenic agent for the vascular and cardiovascular muscle cells and may contribute to cardiac hypertrophy. Angiotensin converting enzyme inhibitors inhibit the mitogenic responses of angiotensin II.

6. Inhibitors of Angiotensin

   Numerous drugs are now available that block the formation of the action of angiotensin II. These include drugs blocking the rennin secretion and action, conversion of angiotensin I to angiotensin II and block angiotensin receptors.

C. CONVERTING ENZYME INHIBITORS

ACE inhibitors not only block the conversion of angiotensin I to angiotensin II but also inhibit the degradation of other vasopeptides such as the bradykinin, substance P and enkephalin. The action of ACE inhibition to block bradykinin metabolism contributes significantly to the observed hypotensive effect and has been reported to cause severe side effects including cough, angioedema and hypotensive shock.

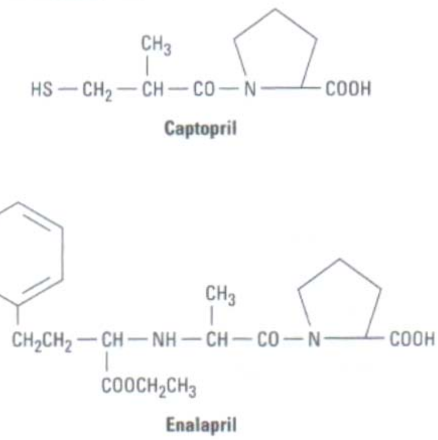


Figure 17–2. Two orally active converting enzyme inhibitors. Enalapril is a prodrug ethyl ester that is hydrolyzed in the body.

D. ANGIOTENSIN ANTAGONISTS

Substitution of certain amino acids such as sarcosine for the phenylalanine in position 8 of the angiotensin II is responsible in the formation of potent peptides antagonist of the action of angiotensin II. The best known of these is antagonists is saralasin. Another class includes the nonapeptide antagonists such as the losartan and valsartan. Clinical benefits of the angiotensin receptor antagonists and ACE are almost the same.

Questions.

1. Do the angiotensin antagonists have any effect on the actions on ACE?
2. Can these angiotensin antagonists be given to a hypertensive patient with sepsis?

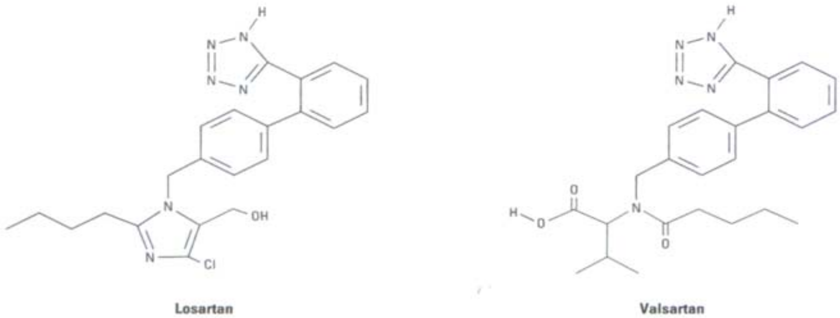


Figure 17–3. Structures of two angiotensin AT_1 receptor antagonists.

E. BRADYKININS AND RELATED PEPTIDES –KININS

Kinins represent one of the most potent groups of vasodilators peptides produced by the endogenous actions of enzymes known as kallikreins or kininogenases. These enzymes act on plasma proteins known as kinongenases.

Kinins can also be generated by insect bites. Wasps and other related insects can release kinin generating enzymes leading to pain, edema, swelling and other inflammatory responses.

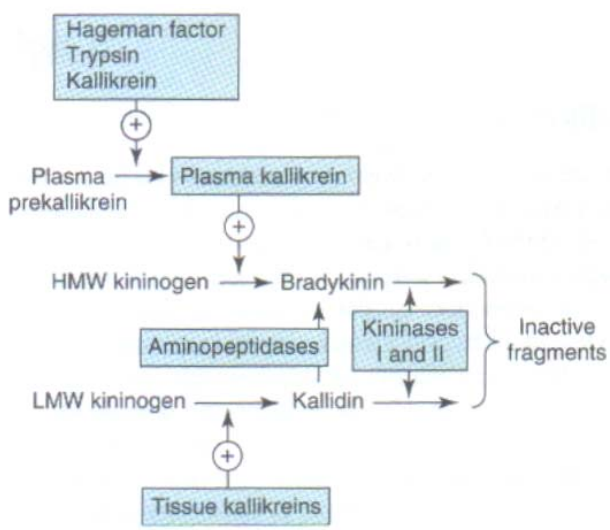


Figure 17–4. The kallikrein-kinin system. Kininase II is identical to converting enzyme peptidyl dipeptidase.

1. Kallikreins

   Kallikreins are glycoprotein enzymes produced in the liver as prekallikreins and are present in plasma and several tissues including kidney, pancreas, gastrointestinal tract, sweat glands and salivary glands. Plasmatic prekallikrein is also known as Fletcher factor and promotes coagulation process via intrinsic system. Plasma prekallikrein can be activated by factor XIIa (Hageman factor).

   Pancreatic kallikrein can be activated by trypsin. The active kallikrein can generate kinins and exert profound action on hemodynamics (hypotension). Many of the patients with consumption coagulopathies (DIC) develop hypotension due to increased kallikrein production.

2. Kininogen

   Kininogens represent plasma lymph and interstitial protein substrates for the kallikreins. Two different types of kininogens are present in plasma. A low molecular weight kininogen (LMWK) and a high molecular weight kininogen (HMWK). The HMWK is also known as the Fitzgeald factor and is involved in the promotion of coagulation process in the intrinsic pathway. Plasma kallikrein cleaves the HMWK to generate bradykinin.

3. Formation of Kinins in Plasma and Tissues

   Three different types of kinins are found in mammalian systems. Each kinin is formed by the action of different enzymes on kininogen. 1.) Bradykinin is released by plasma kallikrein; 2.) Lysyl bradykinin (kallikrein) is released by glandular kallikrein (pancreas kidney) and 3.) Meth-lysylbradykinin is released by pepsin and pepsin like enzymes. All of theses three kinins are found in plasma and urine. In most pathologic conditions related to hypotensive shock. Bradykinin is the predominant peptide.

Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg
1 2 3 4 5 6 7 8 9

Bradykinin

Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

Lysylbradykinin (kallidin; Lys-bradykinin)

Met-Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg

Methionyllysylbradykinin (Met-Lys-bradykinin)

4. Actions of Kinins

    a. Hemodynamic effects

    Marked vasodilation in several vascular beds, including the heart, liver, kidney, intestine, skeletal muscles and liver. These agents are 10 times more potent than histamine. Kinins stimulate the release of nitric oxide and prostaglandins PGE_2 and PGI_2. Kinins promote water and solution passage from the blood to extracellular fluid resulting in edema.

    b. Effect on Endocrine and Exocrine Gland

    Kinins produced in the pancreas, kidney and glandular site may enter the blood circulation and contribute to the localized hypotensive and inflammatory responses.

    c. Role in Inflammation and Pain

    Kinins promote redness, local heat, swelling and pain. Kinins are potent algesic agents. They produce pain by nociceptive afferents in the skin and viscera.

5. Mechanisms of Action of Kinins

   The biologic actions of kinins are mediated by specific receptors localized on the membranes of the target tissues. Two types of receptors are identified, namely the B_1 and B_2 on the basic agonists potencies. B_1 receptors are the predominant receptors for the mediation of the biologic responses of kinins. Thus, drugs to block the actions of bradykinin target B_2 receptors.

6. Metabolism of Kinins

   Kinins are metabolized rapidly (half life 15 seconds) by non-specific kininases. Two plasma kininases have been well characterized namely kinanase I and kininase II. Kinanse II is the same enzyme as the <u>angiotensin converting enzyme</u> and is capable of inactivation the bradykinin and it also converts angiotensin I into angiotensin II. Angiotensin converting enzyme inhibitors such as captopril therefore can inhibit the generation of angiotensin II simultaneously bradykinin levels may increase resulting in hypotension.

Case Report

An elderly hypertensive hospitalized patient was treated with an ACE inhibitor, namely captopril. During hospitalization she became septic due to an infection. Soon after she went into severe hypotensive shock.

What is the likely cause of the hypotensive shock in this patient?

7. Drugs Effecting the Kallkrein Kinin System

   At this time a specific antagonist of the action of kinins is not available. Several inhibitors of both the B_1 and B_2 receptors have been designed and used in animal models, and human trials have been proven useful. Icatibant is a second generation B_2 receptor inhibitor which has undergone limited clinical trials in pain and inflammation. Icatibant is approved in EU and the US for the management of angio-neurotic edema in combination with C_1 estrase inhibitor. Several other B_2 antagonists are available only for experimental purposes. β_2 receptor inhibitors may be useful for the treatment of hypotension and myocardial hypertrophy. The generation of kallikreins can be inhibited with a kallkrein inhibitors, aprotonin. Thus, the bradykinin generated is blocked.

Aspirin is also known to block the algesic effects of prostaglandins generated by bradykinin. On the other hand, the action of kinin can be augmented by ACE inhibitors, which block the degradation of this peptide.

F. VASOPRESSIN

Vasopressin (Anti-diuretic hormone, ADH) plays an important role in the long term control of blood pressure through its action on the kidney to increase water resorption. It has short term vasoconstrictor actions.

Several selective analogues of vasopressin have been synthesized. Of these one clinically used preparation is 1-diamino {D-Arg^6] arginine vasopressin (dDAVP) or desmopressin. This agent was initially developed for the treatment of patients with diabetes insipidus. Desmopressin increase the factor VIII activity of patients with mild hemophilia and von Willebrand disease. It is effective in the control of bleeding in mild surgical process. It can also be administered intranasally. In blood banking procedures this agent is also used to increase the factor VIII and von Willebrand factor in plasma of donor blood.

G. NATRIURETIC PEPTIDES AND RELATED PEPTIDES

The atria and other tissues of mammals contain a family of peptides with nitriuretic diuretic, vasorelaxant and other properties. The family includes the atrial natriuretic peptide (ANP). The brain natriuretic peptide (BNP) and the C-type natriuretic peptide.

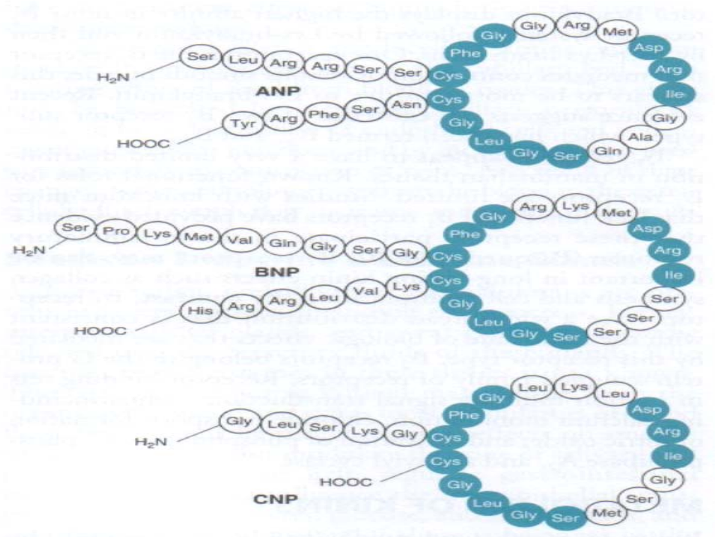


Figure 17–5. Structures of the atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Sequences common to the peptides are indicated in blue.

All of these peptides have a short half-life in the circulation. BNP is shown to improve the hemodynamics and renal excretion of sodium in patients with congestive heart failure. Several analogues of ANP have also been derived. Vasopeptide inhibitors are a new class of drugs that inhibit metaloproteases. Thus, these drugs increase the levels of natriuretic peptides and decrease the formation of angiotensin II. Recently developed drugs include omapatrilat, sampartilat and fasidotrilat. These drugs enhance vasodilation, reduce vasoconstriction and increase sodium excretion.

H. ENDOTHELINS

The endothelins represent a series of peptides with potent vasoconstricting properties that were first isolated from aortic endothelial cells.

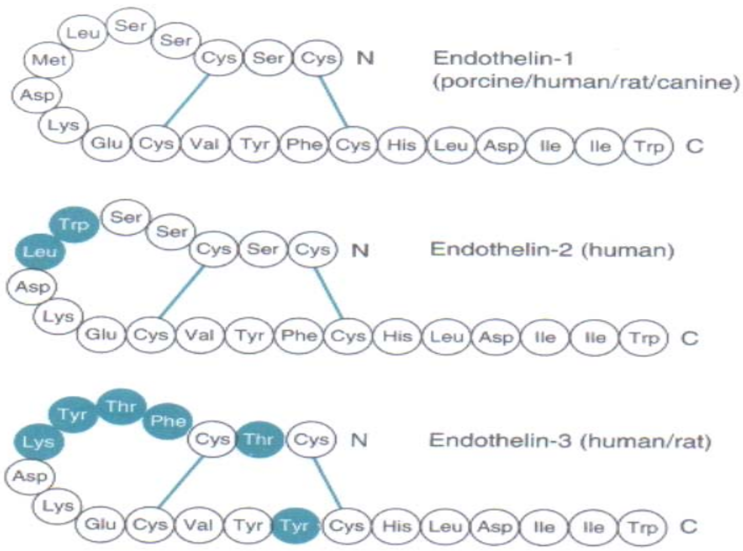


Figure 17–6. Structures of the endothelin peptides endothelin-1, endothelin-2, and endothelin-3. Sequences different in the three peptides are shown in blue.

Three isoforms of endothelin are identified, namely ET_1, ET_2 and ET_3 . Each endothelin is a 21 amino acid peptide. It is predominantly present in vascular endothelium. The endothelin are rapidly cleared from the circulation.

Endothelins produce a dose dependent vascular constriction in most vascular beds. Two receptor subtypes are found for endothelins. ET_A and ET_B. The signal transduction mediated actions of endothelins are illustrated on Figure 17-7. As can be seen, endothelins have multiple actions which are mediated through the ET_A and ET_B

receptors

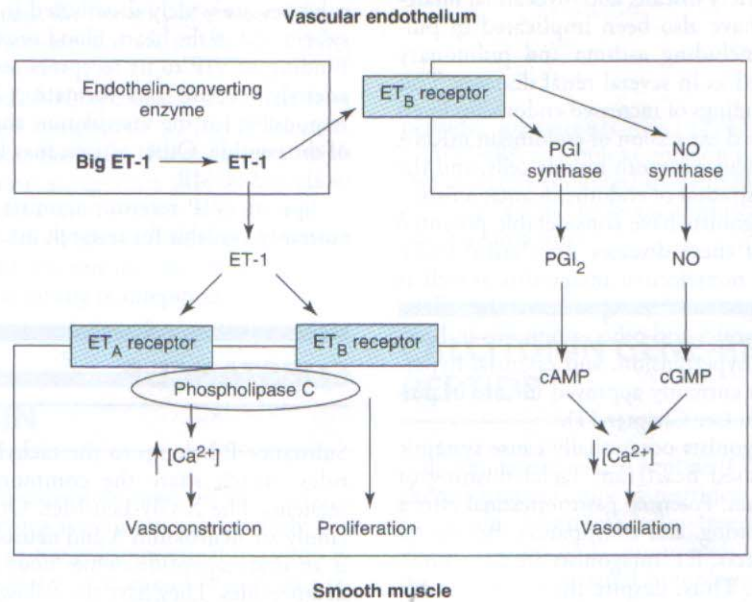
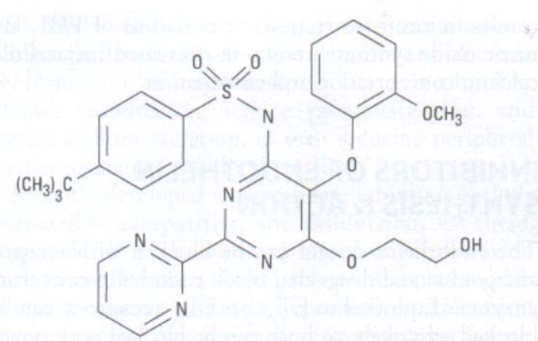


Figure 17–7. Signal transduction mechanisms mediating the effects of ET-1 on vascular smooth muscle.

Inhibition of Endothelin

Both the selective (ET_A and ET_B) and non-selective antagonists for the actions of endothelins have been developed. An example of non-selective antagonists is Bosentan. It is active both orally and intravenously. Bosentan is approved for the management of pulmonary hypertension.



Bosentan

I. VASOACTIVE INTESTINAL PEPTIDE

Vasoactive intestinal peptide (VIP) is a 28 amino acid peptide related to secretin and glucagons. VIP is present in the central and peripheral nerves where it functions as a neuromodulator. VIP produces marked vasodilation. Specific VIP receptor inhibitors are developed for research purposes only.

J. SUBSTANCE P

Substance P belongs to the tachykinin family which shares the carboxy terminal sequence Phe-X-gly-leu-meth. Other mediators of this family are neurokinin A and neurokinin B which are decapeptides. Substance P induced vasodilation by stimulating the release of nitric oxide. Several inhibitors of substance P have been developed.

K. NEUROTENSIN

Neurotensin is a tridecapeptide and is synthesized in association with neuromodulin N (hexapeptide) in a big protein. In peripheral circulation it causes vasodilation, hypotension, vascular permeability, hyperglycemia and inhibition of gastric motility. Several analogues of neurotensin have also been synthesized.

L. CALCITONIN GENE RELATED PEPTIDE

CGRP is a 37 amino acid containing peptide which is related to the calcitonin family of peptidases. CGRP is present in large amounts in the thyroid gland. CGRP is also found in the CNS and GI tract with substance P. Intravenous administration of CGRP can cause hypotension and tachycardia. CGRP is the most potent vasodilator yet discovered.

M. ADRENOMODULIN

Adrenomodulin is a 52 amino acid and peptide which was first isolated from the adrorenal medullary pheochromocytoma tissues. It is widely distributed and circulates in blood and mediates hypothyroid responses. Circulating adrenomodulin levels are increased during intensive exercise, patients with hypertension, renal failure and septic shock.

N. NEUROPEPTIDE Y

Neuropeptide Y is one of the most abundant neuropeptides in both the central and peripheral nervous system. It consists of 36 amino acids. Besides a CNS effect it produces vasoconstriction and mediates hypertensive responses. Selective neuropeptide Y antagonists are now available and are useful the role of this peptide in hemodynamic disorders

O. UROTENSIN

Urotensin is an undecapeptide with a conserved cyclic heptapeptide sequence. It is a potent vasoconstrictor primarily acting on arterial beds. It is one of the most potent vasoconstrictors, Urotensin levels are increased in patients with end stage heart failure. Specific antagonists of urotensin are also available for research purposes only. These may be useful in patients with end stage heart failure.

DIURETICS

Recommended Reading: Goodman & Gilman's Manual of Pharmacology and Therapeutics Chapter 28; Basic & Clinical Pharmacology (Katzung, 12th edition) Chapter 15

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand the importance of the organic anion transport system and protein binding to the renal action of diuretics.
2. To know the sites of action and the mechanism of action of the diuretics.
3. To know the effects of the different diuretics on electrolyte excretion patterns.
4. To understand the therapeutic applications of diuretics.
5. To know conditions and/or drug interactions that interfere with or contraindicate diuretic use.

DRUGS:

A. Carbonic Anhydrase Inhibitors (acetazolamide, dichlorphenamide, methazolamide, dorzolamide)

B. Osmotic Diuretics (mannitol)

C. Loop Diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)

D. Thiazides (chlorthalidone, chlorothiazide, hydrochlorothiazide, metolazone, indapamide)

E. Potassium-sparing Diuretics (spironolactone, eplerenone, triamterene, amiloride)

F. ADH Antagonists (demeclocycline, lithium, tolvaptan, conivaptan, mozavaptan)

1. INTRODUCTION

A. History of Diuretics

- Diuretics effective for the treatment of edema have been available since the 16^{th} century. Edema is defined as an excessive accumulation of fluid in tissues or cavities.
- Mercurous chloride was known by Paracelsus to be diuretic.
- In 1930, Swartz discovered that the antimicrobial sulfanilamide could be used to treat edema in patients with congestive heart failure—effect attributed to an increase in renal excretion of Na^+.
- Most modern diuretics were developed when side effects of antibacterial drugs were noted, which included changes in urine composition and output.
- Except for spironolactone, diuretics were developed empirically, without knowledge of specific transport pathways in the nephron.
- Diuretics are currently among the most commonly prescribed drugs in the U.S. They are useful for treatment of diverse clinical conditions ranging from kidney stones to heart failure, but they can also have an extremely wide range of adverse effects.

B. Function of the Kidney

- Kidneys control the extracellular fluid (ECF) volume by adjusting NaCl and H_2O excretion.
- Each day the kidney filters more than 22 moles of Na. To maintain NaCl balance approximately 3 lbs. of NaCl must be reabsorbed by the renal tubules on a daily basis.
- Edema can develop when NaCl intake exceeds NaCl excretion, as may occur in congestive heart failure or renal failure.
- Na^+ reabsorption is driven primarily by Na^+/K^+ adenosine triphosphatase (ATPase) located at the basolateral (blood side) membrane of epithelial cells throughout the **nephrons**, the units of the kidney where reabsorption takes place.
- The Na^+/K^+ ATPase is an energy-requiring pump which exchanges 3 Na^+ for 2 K^+, thereby keeping a low Na^+ concentration and a high K^+ concentration within the cell.
- On the luminal side of the tubule epithelium, cell-specific pathways exist for passive movement of Na^+ down its electrochemical gradient from lumen to cell. These pathways form the physiological basis of diuretic action.

C. Review of Renal Anatomy

The substance of the kidney may be divided into an outer *cortex* and an inner *medulla*. The medulla is arranged into pyramid-shaped units called *medullary pyramids*, which are separated by extensions of cortical tissue. The medullary pyramids convey ducts which converge to discharge urine at their apices; the apices of the pyramids are known as *renal papillae*. *Calyces* are funnel-shaped spaces into which one or more renal papillae project. The calyces converge to form the larger funnel-shaped *renal pelvis* from which the urine is conducted to the bladder by the ureter.

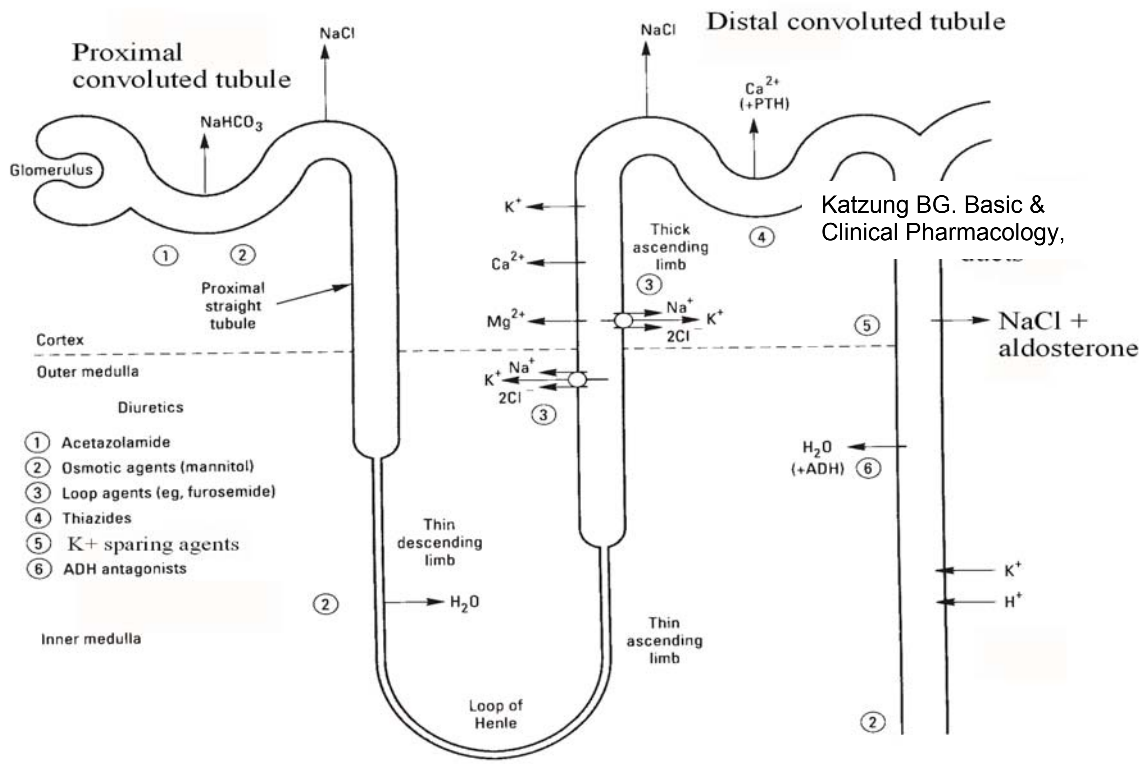
See Figure 16.2 From: B. Young, J.S. Lowe, A. Stevens, and J.H. Heath, <u>Wheater's Functional Histology</u> , 2006, p. 303

Blood enters the kidney via the renal artery which branches to the interlobar, arcuate, and interlobular arteries, and finally to an afferent arteriole, which supplies a *glomerulus*. A glomerulus is a tightly coiled network of capillaries within a capsule of flattened epithelial cells called *Bowman's capsule*. Blood exits the glomerulus via an efferent arteriole.

Elements of plasma are filtered from the glomerular capillaries into *Bowman's space* and the glomerular filtrate then passes into the renal tubule. The renal tubule is up to 55 mm long in humans and is lined by a single layer of epithelial cells. The primary function of the renal tubule is the selective reabsorption of water, inorganic ions, and other molecules from the glomerular filtrate.

See Figure 16.4 From: B. Young, J.S. Lowe, A. Stevens, and J.H. Heath, <u>Wheater's Functional Histology</u> , 2006, p. 304

sterone)



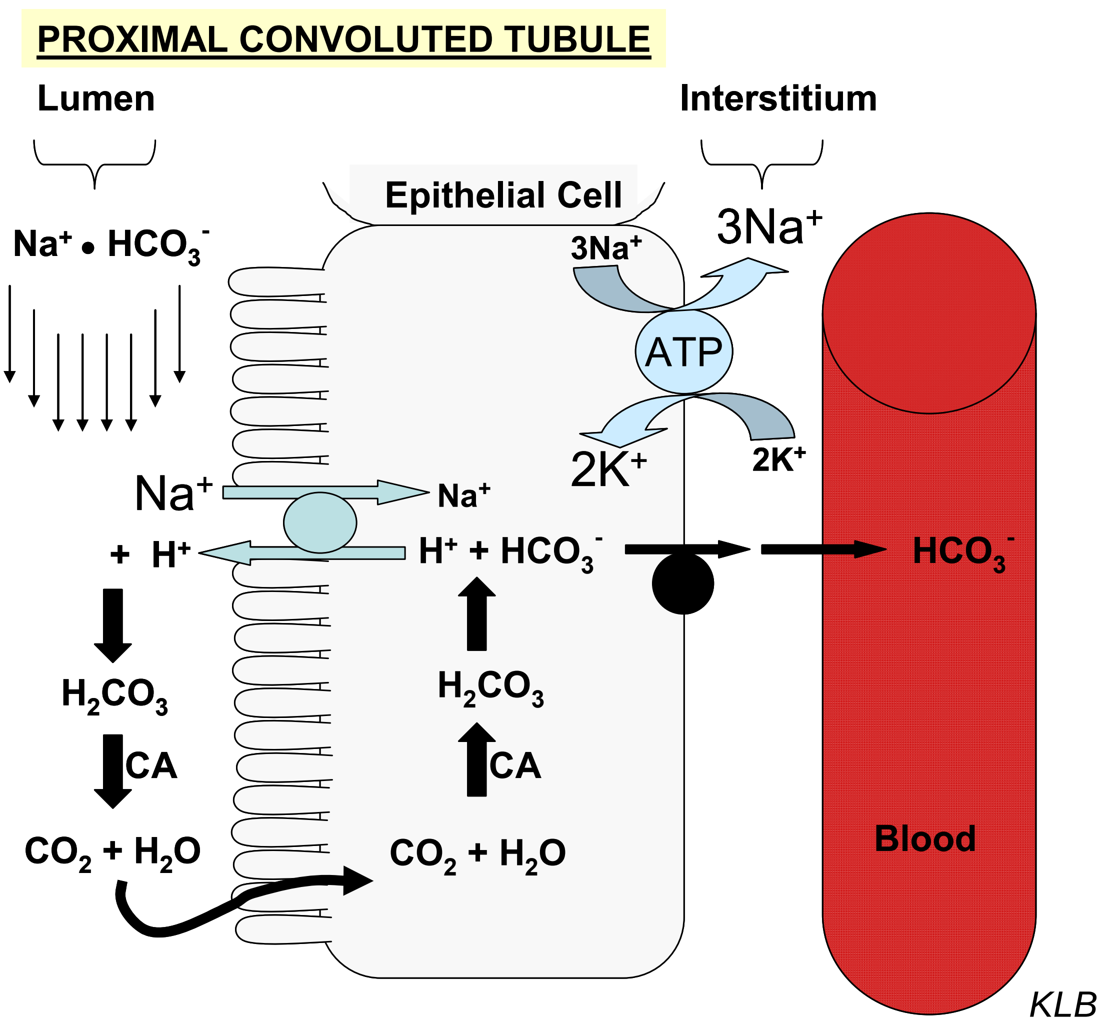
2. DIURETIC PHARMACOLOGY

A. GENERAL CONSIDERATIONS

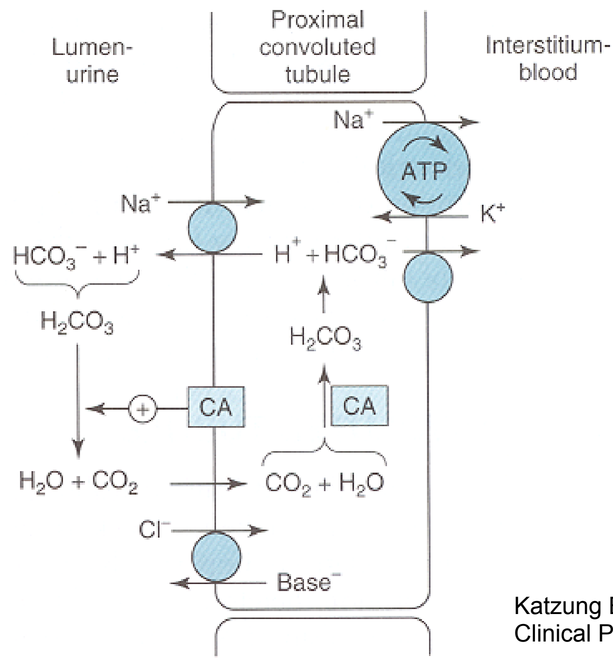
- The primary therapeutic goal of diuretic use is to reduce edema by reducing the extracellular fluid (ECF) volume.
- For this to occur, NaCl output MUST exceed NaCl intake.
- Diuretics primarily prevent Na^+ entry into the tubule cell.
- Once a diuretic enters the tubule fluid, the nephron site at which it acts determines its effect. In addition, the site of action also determines which electrolytes, other than Na^+, will be affected.
- **Except for spironolactone, eplerenone, and some ADH antagonists, diuretics generally exert their effects from the luminal side of the nephron**.
    - It is necessary for diuretics to get into the tubule fluid in order to be effective.
    - Mannitol does this by filtration at the glomerulus.
    - Most other diuretics are tightly protein bound and undergo little filtration. They reach the urine via secretion across the proximal tubule (organic acid or base secretory pathway).

  - Decreased renal blood flow or renal failure reduces diuretic effectiveness as do drugs which compete for the secretory pump (for example, probenecid and NSAIDs compete with acidic drugs and cimetidine competes with basic drugs).

- Tubule epithelial cells: a single cell layer between tubule lumen and interstitial space.
  - Na^+ reabsorption is driven primarily by Na^+/K^+ ATPase at the basolateral (blood side) membrane of epithelial cells throughout the nephron.
  - The Na^+/K^+ ATPase is an energy-requiring pump which exchanges 3 Na^+ for 2 K^+, thereby keeping a low Na^+ concentration and a high K^+ concentration within the cell.
  - On the luminal side, cell-specific pathways exist for passive movement of Na^+ down its electrochemical gradient from lumen to cell.
  - Reabsorption occurs from the tubule lumen, across the epithelium to the interstitial space, and finally into the adjacent blood vessels.



B. PROXIMAL CONVOLUTED TUBULE DIURETICS



Katzung BG. Basic & Clinical Pharmacology,

- The proximal convoluted tubule (PCT) determines the rate of Na^+ and H_2O delivery to the more distal portions of the nephron.
- A wide variety of transporters couple Na^+ movement into the cell to the movement of amino acids, glucose, phosphate, and other solutes.

Carbonic anhydrase (CA) inhibitors (acetazolamide, dichlorphenamide, methazolamide, dorzolamide)

- o Mechanism of Action: Bicarbonate is primarily reabsorbed in the proximal tubule. H^+ secreted into the lumen can combine with filtered bicarbonate (HCO_3^-) to form H_2CO_3 that is then converted to CO_2 and H_2O (catalyzed by carbonic anhydrase). CO_2 diffuses into the proximal tubule where it recombines with H_2O to form H_2CO_3 (catalyzed by cytosolic carbonic anhydrase). H_2CO_3 dissociates into H^+ and HCO_3^-. HCO_3^- exits the proximal tubule on the blood side, while H^+ is again secreted into the tubule lumen. This results in HCO_3^- reabsorption. If CA activity is inhibited, HCO_3^- reabsorption is reduced and therefore much larger amounts of HCO_3^- are delivered to the distal nephron. Because Na^+ is the most abundant cation present in proximal tubule fluid, it is the major cation which accompanies HCO_3^- out of the proximal tubule. In the distal nephron, Na^+ is largely reabsorbed (unlike HCO_3^-) and is exchanged for K^+.

  Therefore **CA inhibitors primarily cause an increase in urinary HCO_3^-, K^+, and water excretion.** Effectiveness is reduced with continued therapy because plasma [HCO_3^-] falls, reducing the amount of HCO_3^- that appears in the urine.

- Pharmacodynamics: Inhibits reabsorption of HCO_3^- in the proximal convoluted tubule.

- Pharmacokinetics: CA inhibitors are relatively weak diuretics. Well absorbed orally; effect begins within 30 minutes and is maximal within 2 hours; duration of effect is 12 hours. Renal secretion is via the organic acid transporter.

- Adverse effects: **Metabolic acidosis** (with prolonged use, due to urinary loss of bicarbonate) and **hypokalemia** (with acute treatment, due to increased delivery of Na^+ and HCO_3^- to the collecting tubule and resulting K^+ excretion). Calcium phosphate stones (due to alkalinization of tubular fluid). Drowsiness, paresthesias & hypersensitivity rxns.

- Contraindications: Cirrhosis (increased urine pH reduces NH_3 secretion and thereby increases serum NH_3; this exacerbates hyperammonemia that can lead to encephalopathies).

- Indications: Generally given for reasons other than diuresis. Because ocular fluid and CSF production are dependent on CA, inhibitors can be used to treat glaucoma or increased CNS pressure. CA inhibitors can be given in conditions where urine alkalinization is beneficial (certain drug overdoses). CA inhibitors can also be used to prevent altitude sickness -- the decrease in serum pH lowers hemoglobin's affinity for oxygen, thereby increasing oxygen delivery to the tissues.

Osmotic Diuretics (mannitol)

- Mechanism of Action: Mannitol is a non-metabolizable osmotic diuretic and is filtered into the tubular space where it markedly increases tubular fluid osmolality. This results in impaired reabsorption of fluid with a resultant increased excretion of water (some Na^+ accompanies). Acts primarily in segments of the nephron that are permeable to water (PCT, descending limb of Henle's loop, and CT (in the presence of ADH)).

- Pharmacodynamics: IV administration causes expansion of intravascular volume; powerful diuretic effect once it reaches the kidney.

- Pharmacokinetics: **NOT** orally absorbed-must be injected IV to reach the kidneys. In pts with normal renal function $t_{1/2}$ is approx. 1.2 hr.

- Adverse effects: The major toxicity is due to increased plasma osmolality. Particularly with reduced glomerular filtration rate (in diseases such as congestive heart failure (CHF) or renal failure), mannitol is distributed in the extracellular fluid (ECF). This moves water out of cells into ECF potentially worsening heart failure. Na^+ follows water movement out of cells leading to hyponatremia.

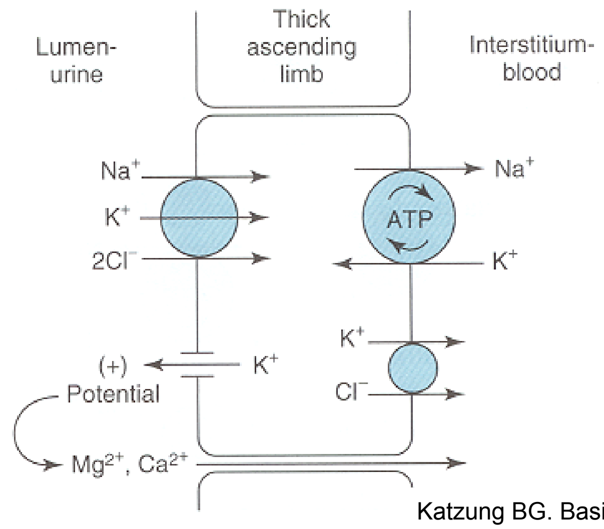
- Contraindications: CHF, chronic renal failure, acute pulmonary edema.

- Indications: Maintain or increase urine volume; reduce intracranial pressure or intraocular pressure (opthamological procedures or glaucoma—requires intact blood-brain or blood-occular barrier); promote renal excretion of toxic substances.

C. LOOP DIURETICS

Thick Ascending Limb:

- Impermeable to H_2O.
- $Na^+/K^+/2Cl^-$ cotransporter on luminal membrane driven by the Na^+ gradient (maintained by the basolateral Na^+/K^+ ATPase).
- Influx of K^+ from both sides raises intracellular $[K^+]$.
- K^+ diffuses back into the lumen creating (+) charge in lumen.
- The (+) charge improves paracellular diffusion of other positively charged ions like Ca^{2+} and Mg^{2+}.



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Loop Diuretics:

- Mechanism of Action: All loop diuretics act primarily by blocking the $Na^+/K^+/2Cl^-$ co-transporter in the apical membrane of the thick ascending limb of Henle's loop.
- Pharmacodynamics: Because this is the same site responsible for concentrating extracellular fluid (ECF) and diluting urine, loop diuretics decrease these processes. The thick ascending limb is a major site of Ca^{2+} and Mg^{2+} reabsorption, processes that are dependent on normal Na^+ and Cl^- reabsorption. Therefore, loop diuretics increase urinary water, Na^+, K^+, Ca^{2+}, and Mg^{2+} excretion. The loop diuretics also cause dilation of the venous system and renal vasodilation, effects that may be mediated by prostaglandins.
- Pharmacokinetics: loop diuretics generally act within 20 min and $t_{1/2}$ is approx. 1-1.5 hr. They are rapidly absorbed from the gut (renal secretion mechanism--organic acid transporter) and can be given i.v. **This class of diuretics are the most efficacious available and can cause excretion of up to 20% of the filtered Na^+.** Rate of absorption is decreased in CHF.
- Adverse effects: All loop diuretics can cause predictable electrolyte imbalances, including hyponatremia, hypokalemia, Ca^{2+} and Mg^{2+} depletion, metabolic alkalosis and volume contraction. Ototoxicity (impaired hearing) and hypersensitivity reactions may also occur. Loop diuretics can also induce mild hyperglycemia (perhaps due to hypokalemic-induced inhibition of insulin release).

- Contraindications: Caution in patients susceptible to hypokalemia. Adverse effects of digoxin are also more common in patients with low potassium levels (hypokalemia), since digoxin normally competes with K^+ ions for the same binding site on the Na^+/K^+ ATPase pump.

- Indications: Loop diuretics may be used for conditions refractory to less potent diuretics, or where a short acting diuretic is indicated. Specific indications include lowering blood pressure, reduction of acute pulmonary edema or edema associated with congestive heart failure, reduction of acute hypercalcemia or acute hyperkalemia.

- **Additional Loop Diuretics**

  - **BUMETANIDE**

    About 40X more potent than furosemide

    Shorter half-life than furosemide: ~ 1 hr

    50% metabolized by the liver

  - **TORSEMIDE**

    Longer half-life than furosemide: ~ 3 hrs

    Longer duration of action, too: ~ 5-8 hrs

    Better oral absorption than furosemide

    80% metabolized by the liver

  - **ETHACRYNIC ACID**

    Last resort; used only when others exhibit hypersensitivity

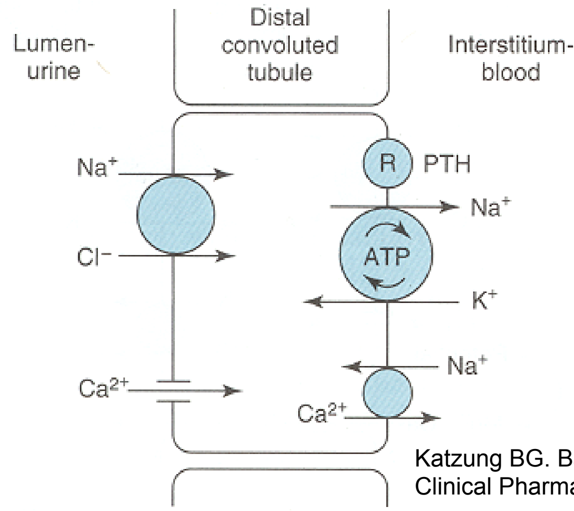
    No CA inhibition

    Nephrotoxic and ototoxic

D. DISTAL CONVOLUTED TUBULE DIURETICS

Distal Convoluted Tubule:

- Impermeable to H_2O.
- The Na^+ gradient drives the Na^+/Cl^- cotransporter.
- Ca^{2+} reabsorption is controlled by parathyroid hormone (PTH), which regulates production of Ca^{2+} channels inserted in the luminal membrane.
- Intracellular Ca^{2+} is pumped out the basolateral border by:
  - Na^+/Ca^{2+} countertransport; high capacity exchanger.
  - The Ca^{2+} ATPase pump; low capacity pump.



Katzung BG. Basic & Clinical Pharmacology,

Thiazides (e.g. chlorothiazide) and thiazide-like drugs (metolazone, indapamide):

- Mechanism of Action: This is the most commonly prescribed class of diuretics. They inhibit Na^+ and Cl^- co-transport in the cortical thick ascending limb and early distal tubule.
- Pharmacodynamics: They have a **milder diuretic action** than do the loop diuretics because this nephron site reabsorbs less Na^+ than the thick ascending limb. In addition, if glomerular filtration rate falls, less fluid reaches the distal tubule and thiazides may only have a small impact on Na^+ and water excretion. These compounds then are **relatively ineffective in renal insufficiency**. Thiazide diuretics tend to increase Ca^{2+} reabsorption.
- Pharmacokinetics: All are well absorbed from the gut. Onset of action is within approx. 1 hr; effects can be long lasting but vary with the drug used (6-48 hr). Bioavailability is decreased in patients with renal disease, hepatic disease, and CHF.
- Adverse effects: Hyponatremia & hypokalemia, dehydration, metabolic alkalosis, hyperuricemia, hyperglycemia*, hyperlipidemia*, weakness, fatigue, paresthesias & hypersensitivity reactions.

*Hyperglycemia has been linked to diuretic-induced hypokalemia. K^+ deficiency inhibits insulin secretion by pancreatic ß cells, although diuretic-induced changes in glucose metabolism are not conclusively related to altered K^+ homeostasis—impaired glucose tolerance has been observed even when low dose thiazide diuretic therapy is combined with a K^+ -sparing diuretic. Hyperglycemia with diuretic therapy may be exacerbated by an increase in sympathetic nervous system activity, which also decreases peripheral glucose utilization.

Hyperglycemia tends to increase with increasing doses of thiazide diuretics, is less common with loop diuretics, and is generally reversible on termination of the diuretic therapy. Short-term thiazide diuretic therapy can dose-dependently elevate serum total cholesterol levels, modestly increase low-density lipoprotein cholesterol levels and raise triglyceride levels, while minimally changing high-density lipoprotein cholesterol concentrations. The mechanisms of diuretic-induced dyslipidemia remain uncertain, but have been related to worsened insulin sensitivity and/or reflex activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system in response to volume depletion. Supporting this latter notion is the fact that doses of diuretics which are low enough so as not to activate the sympathetic nervous system, do not increase lipid values; in contrast, higher diuretic doses are more apt to be associated with reflex sympathetic nervous system activation and dyslipidemia.

- Contraindications: Caution in patients that are susceptible to hypokalemia.
- Indications: Hypertension treatment. They can be used in CHF, nephrotic syndrome and other Na^+-retaining states. Thiazides can also be used to reduce tubular Ca^{2+} concentration to prevent kidney stones.

Additional thiazide or thiazide-like diuretics:

- CHLOROTHIAZIDE
  - 1/10th the potency of Hydrochlorothiazide
  - Half-life of 1.5 hrs
- METOLAZONE
  - 10X more potent than Hydrochlorothiazide
  - Half-life of 4-5 hrs
- INDAPAMIDE
  - 20X more potent than Hydrochlorothiazide
  - Half-life of 10-22 hrs; metabolized extensively by the liver
- CHLORTHALIDONE
  - Same potency as Hydrochlorothiazide

- Metolazone is a quinazoline diuretic that has the same sites of action and side effects as the thiazides. **Metolazone is the strongest inhibitor of Na^+ and water reabsorption of the thiazide and thiazide-like diuretics. It is one of the few distal nephron diuretics that can be efficacious in patients with severe renal insufficiency and may be given in combination with a loop diuretic in these patients if diuresis with either agent alone is inadequate.**

E. COLLECTING TUBULE DIURETICS

Principal Cells:

- The Na^+ gradient drives influx of Na^+ through its channel.
- The efflux of K^+ follows its concentration gradient.
- Na^+ absorption exceeds K^+ secretion causing net (–) charge in the tubular lumen.
- Net (–) charge repels Cl^- and attracts K^+ into lumen.
- Aldosterone increases expression of Na^+/K^+ ATPase & channels
- ADH regulates water channels and water reabsorption.

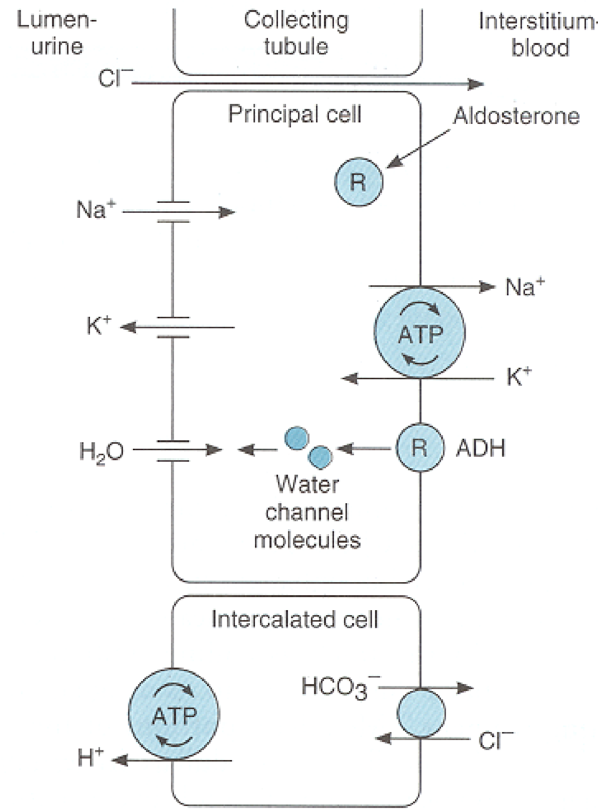
Intercalated Cells:

- Luminal membrane

  Proton pumps actively transport H^+ into the lumen (expression is increased by aldosterone).

- Basolateral membrane

  HCO_3^-/Cl^- passive countertransporter



Katzung BG. Basic & Clinical Pharmacology,

THE TRANSPORT PROPERTIES OF THE COLLECTING TUBULE ACCOUNT FOR SOME ADVERSE EFFECTS OF DIURETIC DRUGS THAT EXERT DIRECT EFFECTS AT MORE PROXIMAL SEGMENTS OF THE NEPHRON:

Hypokalemic effects of CA inhibitors:

1. Increased HCO_3^- in tubule leads to increased lumen negative potential.
2. The lumen-negative potential enhances K^+ efflux from the principal cells.

Hypokalemic effects of Loop & Thiazide diuretics:

1. Increased Na^+ and Cl^- in tubule leads to increased lumen negative potential.
2. The lumen-negative potential enhances K^+ efflux from the principal cells.

Metabolic alkalosis with Loop & Thiazide diuretics:

1. Increased Na^+ and Cl^- in tubule leads to increased lumen negative potential.
2. The lumen-negative potential enhances H^+ efflux from the intercalated cells.

Potassium sparing diuretics

These agents are often given to avoid the hypokalemia that accompanies the agents previously described. They should **never be given in the setting of hyperkalemia or in patients on drugs or with disease states likely to cause hyperkalemia.** The latter include *diabetes mellitus*, *multiple myeloma*, *tubulointerstitial renal disease*, and *renal insufficiency*. Potassium supplements and ACE inhibitors/ARBs can cause hyperkalemia and should not be combined with K^+ sparing diuretics.

Commonly Used Medications That Can Cause Hyperkalemia	
Medication	**Mechanism**
ACE inhibitors/ARBs	Prevent angiotensin-II (AngII) -induced aldosterone release
Renin inhibitors	Prevent AngII production & its stimulation of aldosterone release
NSAIDs	Block prostaglandin-induced renin secretion/aldosterone release
Digitalis overdose	Inhibits the Na^+/IK^+-ATPases of the renal tubule epithelial cells
Trimethoprim	A cationic antibiotic agent, trimethoprim blocks Na^+ channels in the apical membrane of the principal cells of the collecting tubules
Pentamidine	Same mechanism as trimethoprim—blocks distal potassium secretion into the collecting ducts
Heparin	Decreases aldosterone release by reducing both the number and affinity of the AngII receptors in the zona glomerulosa
Salt substitutes	Contain potassium—absorbed into circulation to directly elevate serum potassium levels
Succinylcholine	Activates AChR in neuromuscular junction moves potassium from intracellular to extracellular fluid
Cyclosporine	Multifactorial, including hyporenin-hypoaldosteronism and interference with aldosterone action in the principal cells of the collecting tubules
β blockers	Prevent sympathetic activation of renin release

Spironolactone and eplerenone

- Mechanism of Action: Spironolactone & eplerenone are competitive antagonists of aldosterone binding to the cytosolic mineralocorticoid receptor in the principal cells of the collecting tubule — they block the actions of aldosterone (increased Na^+ and H_2O retention).

- Pharmacodynamics: Block aldosterone-stimulated Na^+ reabsorption and K^+ and H^+ secretion in the late distal convoluted tubule and collecting tubule. This results in mild diuresis due to decreased Na^+ reabsorption. Also reduce aldosterone-stimulated ammoniagenesis throughout the nephron.

- Pharmacokinetics: Given orally, spironolactone takes up to 2 days to be effective with a $t_{1/2}$ approx. 20 hr. Undergoes substantial hepatic metabolism and acts through the blood side of the tubule. A weak diuretic because its site of action reabsorbs only modest amounts of Na^+.

- Adverse effects: Major side effects are hyperkalemia and metabolic acidosis. Spironolactone can cause gynecomastia or amenorrhea (mildly enhances estrogen levels/activity) due to cross-reactivity with androgen receptors. Eplerenone is considerably more expensive than spironolactone, but it does not inhibit testosterone binding and therefore it does not induce gynecomastia or other related anti-androgenic side effects.

- Contraindications: **Do not use in setting of hyperkalemia**.

- Indications: Greatest efficacy in patients with high plasma levels of aldosterone (e.g. hyperaldosteronism due to adrenal tumor or hyperplasia). Also useful in patients with secondarily elevated aldosterone, e.g. cirrhosis, CHF. May be effective in treating hypertension, often in combination with loop or thiazide diuretics.

Amiloride and triamterene

- Mechanism of Action: Both agents block Na^+ channels in the apical membranes of the late distal tubule and collecting tubule epithelial cells.
- Pharmacodynamics: Because K^+ and H^+ secretion in this nephron segment are driven by the electrochemical gradient generated by Na^+ reabsorption, K^+ and H^+ transport into the urine is reduced.
- Pharmacokinetics: Both agents are effective orally. Secreted into PCT by organic base transporter. $T_{1/2}$ of amiloride and triamterene are 21 and 4 hr, respectively. These compounds are primarily eliminated by the kidney. Relatively weak diuretics.
- Toxicity: The most severe side effect is **hyperkalemia**, but metabolic acidosis can also occur. Nausea and vomiting are the most frequent side effects while hyponatremia may be problematic in the elderly.
- Indications: Usually given together with another diuretic, often a thiazide or loop diuretic. This combination can result in normal K^+ excretion (hypokalemic effect of thiazide or loop balances hyperkalemic effect of amiloride or triamterene).
- Contraindications: similar to Spironolactone -- **Do not use in setting of hyperkalemia**.

ADH Antagonists: Demeclocycline, Lithium, Tolvaptan, Conivaptan, Mozavaptan

- Demeclocycline: tetracyline antibiotic – nephrotoxic
- Lithium: Psych drug used for treatment of mania – nephrotoxic
    - Both demeclocycline and lithium inhibit ADH-stimulated water reabsorption in the collecting tubule—poorly characterized mechanisms may include reduction of either cyclic AMP formation or insertion of aquaporin 2 water channels in the luminal membrane.
- V_2 vasopressin receptor antagonists: tolvaptan, conivaptan, mozavaptan, (lixivaptan, satavaptan, and OPC-31260)
    - Induce increased, dose-dependent production of dilute urine.
    - Tolvaptan is effective orally and has a half-life of 6 to 8 hours.
    - Conivaptan: combined V_{1a} and V_2 receptor antagonist: intravenous formulation of conivaptan is available for the treatment of euvolemic hyponatremia.
    - Potential adverse effects: hypernatremia, thirst, dry mouth, hypotension, dizziness.
    - Indications: SIADH; euvolemic or hypervolemic hyponatremia; congestive heart failure.

CHANGES IN URINARY ELECTROLYTE PATTERNS IN RESPONSE TO DIURETIC DRUGS

	Urinary Electrolyte Patterns		
Agent	NaCl	$NaHCO_3$	K^+
Carbonic anhydrase inhibitors	+	+ + +	+
Loop agents	+ + + +	-	+
Thiazides	+ +	±	+
Loop agents plus thiazides	+ + + + +	+	+ +
K^+-sparing agents	+	-	-

Some diuretic formulations with trade names:

Acetazolamide (Daimox)
Amiloride and Hydrochlorothiazide (Moduretic)
Bumetanide (Bumex)
Conivaptan (Vaprisol)
Chlorthalidone (Hygroton, Thalitone)
Chlorothiazide (Diuril)
Dichlorphenamide (Daranide)
Eplerenone (Inspra)
Ethacrynic acid (Edecrin)
Furosemide (Lasix)
Hydrochlorothiazide (Esidrix, Ezide, Hydrodiuril, Microzide, Oretic)
Indapamide (Lozol)
Mannitol (Osmitrol)
Metolazone (Mykrox, Zaroxolyn)
Methazolamide (GlaucTabs)
Spironolactone (Aldactone)
Torsemide Oral (Demadex Oral)
Triamterene (Dyrenium, Midamor)
Triamterene and Hydrochlorothiazide (Dyazide, Maxzide)

3. DIURETIC THERAPY

A. Edema (excessive accumulation of fluid in the interstitial space)

Capillary Filtration: movement of water across the capillary wall is determined by:

i. Hydrostatic pressure gradient between capillary & interstitial space (P_{cap}-P_{is})

ii. Oncotic pressure (π_{is}-π_{cap})

$$\pi=\sigma RT(C_{cap}-C_{is})$$

Where

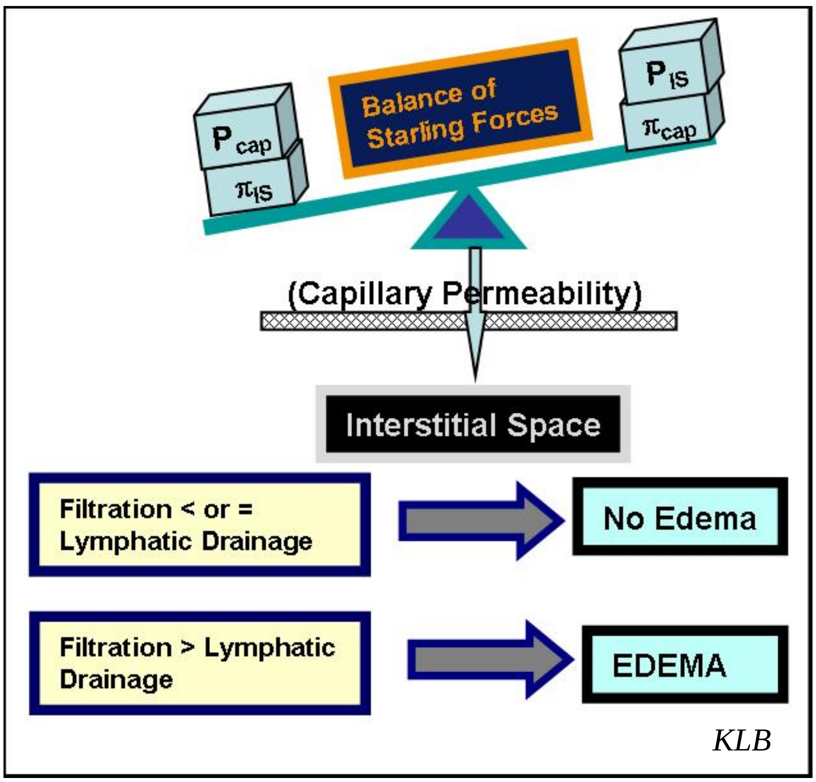
σ = Reflection coefficient

R = Gas constant

T = Absolute temperature

C_i & C_o = Solute concentrations (i.e. [albumin]) in capillary & interstitial space

iii. Capillary permeability



Diuretics will tend to decrease capillary hydrostatic pressure and increase plasma oncotic pressure to favor absorption over filtration.

B. **Kidney Diseases**

- Most cause retention of salt & H_2O.
- Renal insufficiency reduces efficacy of most diuretics because of reduced glomerular filtration (cannot sustain naturiesis).
- Diabetic nephropathy—often associated with hyperkalemia—may be treated with thiazides or loop diuretics.

C. Hepatic Cirrhosis

- Portal hypertension, hypoalbuminemia
- Leads to a reduction in plasma volume.
- Activates renin-angiotensin-aldosterone axis.
- 2° hyperaldosteronism results in Na^+ retention in kidney.
- Associated with ascites and peripheral edema.
- Spironolactone is effective.
- Resistant to loop diuretics.

D. Congestive Heart Failure

- The failure of the heart to effectively pump blood leads to poor renal perfusion, which causes the kidneys to release renin. Plasma renin-angiotensin rises. Angiotensin stimulates aldosterone release, which causes Na^+ retention (and edema).
- If aldosterone is high and if distal tubular sodium supply is also high, as may occur with thiazide or loop diuretic therapy, kaliuresis will be sustained.
- K^+ depletion (hypokalemia) can lead to ventricular arrhythmias and impaired cardiac performance (significantly increased risk of coronary events, stroke, and sudden death).
- Spironolactone may be an effective adjunct or alternative diuretic to prevent hypokalemia-induced cardiac dysfunction.
- ACE inhibitors may be combined with thiazide or loop diuretics, but should not be combined with spironolactone.

Heart Failure

- Left heart failure (acute):
  - ↑hydrostatic pressure in lung capillaries.
  - Pulmonary edema.
  - Life-threatening—requires rapid, aggressive therapy such as i.v. loop diuretic.
- Right heart failure (chronic):
  - Redistribution of extracellular fluid volume from arterial to venous circulation.
  - Venous, hepatic, splenic congestion, & peripheral tissue edema.
  - Oral loop diuretics often are effective if carefully managed.

E. Hyponatremia

Hyponatremia, defined as a serum sodium concentration ($[Na^+]$) less than 136 mEq/l, is the most common electrolyte disorder in hospitalized patients (Kennedy *et al.* Br Med J 2:1251-1253, 1978).

Hyponatremia may be associated with:

a) Hypovolemia: causes include diarrhea, vomiting, excessive sweating; infusion of 0.9% saline is usually an effective treatment.

b) Euvolemia: causes include Syndrome of Inappropriate ADH secretion (SIADH), hypothyroidism, adrenal insufficiency; saline infusion may be ineffective or worsen hyponatremia.

c) Hypervolemia: causes include congestive heart failure, cirrhotic liver disease, nephrotic syndrome; saline infusion may not improve hyponatremia, and will likely worsen edema.

In May 2009, <u>tolvaptan</u> (Samsca; Otsuka), a selective vasopressin V_2 receptor antagonist, was approved by the US FDA for the treatment of clinically significant hypervolemic and euvolemic hyponatraemia (serum sodium concentration <125 mmol per litre or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis and SIADH. Conivaptan (Vaprisol; Astellas), a vasopressin V_{1a}/V_2 receptor antagonist is also approved in the United States for euvolemic and hypervolemic hyponatraemia. (Ghali *et al.*, *Nature Reviews Drug Discovery* **8**, 611-612 (August 2009)). Mozavaptan, another selective vasopressin V_2 receptor antagonist, was approved in October 2006 for hyponatremia caused by SIADH due to ADH producing tumors.

F. Hypertension

SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE.

Chobanian *et al.* (2003) *Hypertension* 42: 1206 –1252.

- For uncomplicated hypertension, a thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes.
- Two or more antihypertensive medications will be required to achieve goal BP (140/90 mm Hg, or 130/80 mm Hg) for patients with diabetes and chronic kidney disease.
- For patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered.

G. Nephrogenic Diabetes Insipidus

- Characterized by a loss of effect of ADH on the kidney.
- Thiazide diuretics first reported to be an effective therapy in 1959 by Crawford & Kennedy (Nature 183 : 891–892, 1959).

H. Nephrolithiasis

- ⅔ of renal stones contain calcium phosphate or calcium oxalate.
- Hypercalciuria may be treated with thiazide diuretics and ↓NaCl intake.

I. Hypercalcemia

- Potentially life-threatening.
- Can be treated with i.v. loop diuretics and saline infusion.

4. DIURETIC RESISTANCE

Edema refractory to a given diuretic drug. Causes include:

- NSAID co-administration (block prostaglandin-induced increase in RBF, increase expression of $Na^+/K^+/2Cl^-$ co-transport in TAL, compete for organic acid transporter in PCT).
- Congestive heart failure (CHF) or chronic renal failure (reduced RBF decreases delivery of diuretics to tubule; build-up of organic acids competes for secretory transport into tubule).
- Nephrotic syndrome (protein in tubule binds to diuretic drugs and limits their actions).
- Hepatic cirrhosis, CHF, renal failure (decreased GFR results in increased PCT absorption of Na^+; decreased delivery of Na^+ to the distal nephron decreases effect of drugs that target Na^+ transporters or channels in these segments).

Therapeutic strategies may include increasing dose, decreasing dosing interval, or adding another drug with a different site of action (i.e. combination therapy).

5. COMBINATION THERAPY

Loop + Thiazide Diuretics:

- only in patients refractory to one or the other.
- may be too robust and lead to K^+ wasting.

K^+-sparing + Loop or Thiazide:

- prevents hypokalemia.
- avoid in renal insufficiency.

6. LIST OF DRUGS COVERED IN LECTURE:

A. Carbonic Anhydrase Inhibitors (acetazolamide, dichlorphenamide, methazolamide, dorzolamide)

B. Osmotic Diuretics (mannitol)

C. Loop Diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)

D. Thiazides (chlorthalidone, chlorothiazide, hydrochlorothiazide, metolazone, indapamide)

E. Potassium-sparing Diuretics (spironolactone, eplerenone, triamterene, amiloride)

F. ADH Antagonists (demeclocycline, lithium, tolvaptan, conivaptan, mozavaptan)

Diuretic Class (site and mechanism of action)	Main Indications	Other Uses
Carbonic Anhydrase Inhibitors Acetazolamide, dorzolamide, methazolamide, and dichlorphenamide inhibit CA in luminal membrane of **proximal tubule**, reducing proximal HCO_3^- reabsorption.	To reduce intraocular pressure in glaucoma. To lower $[HCO_3^-]_p$ in "mountain sickness". To raise urine pH in cystinuria.	Hypokalemic periodic paralysis.* Adjunctive therapy in epilepsy. Solid hypoxic tumors?
Osmotic Diuretics Freely filterable, non-reabsorbable osmotic agents like mannitol, glycerol, and urea act primarily on the proximal tubule to reduce the reabsorption of H_2O and solutes including NaCl.	To treat or prevent Acute Renal Failure (ARF).	To reduce intra-cranial or intra-ocular pressure. To enhance urinary excretion of chemical toxins.
Loop Diuretics Furosemide, bumetanide, torsemide, and ethacrynic acid inhibit the Na^+/ K^+/ $2Cl^-$ cotransport system in the thick ascending limb of Henle's loop (ALH).	Acute Pulmonary Edema. Hypertension. Congestive heart failure (CHF)—in the presence of renal insufficiency or for immediate effect). ARF, CRF, ascites, and nephrotic syndrome	Hypercal**cemia.**
Thiazide Chlorothiazide, hydrochlorothiazide, chlorthalidone, metolazone, indapamide inhibit NaCl cotransport in early distal convoluted tubule (DCT).	Hypertension. Edema due to CHF, hepatic cirrhosis, renal disease. Idiopathic Hypercalci**uria** (renal calculi).	Nephrogenic Diabetes Insipidus (prevent further urine dilution from taking place in the DCT).
K^+-Sparing Diuretics Spironolactone & eplerenone competitively block the actions of aldosterone on the collecting tubules. Amiloride and triamterene reduce Na^+ entry across the luminal membrane of the principal cells of the collecting tubules.	Chronic liver disease: to treat secondary hyper-aldosteronism due to hepatic cirrhosis complicated by ascites (spironolactone, eplerenone). To prevent the hypokalemic effects of other diuretics.	Primary hyperaldosteronism (Conn's syndrome)—spironolactone, eplerenone.
ADH Antagonists Doxycycline, lithium, tolvaptan, conivaptan, mozavaptan, etc. prevent ADH-induced water reabsorption in the principal cells of the collecting tubule.	SIADH Euvolemic or hypervolemic hyponatremia.	Congestive Heart Failure (CHF).

*may require dietary potassium supplements to prevent potassium wasting.

Main Side Effects of Diuretics
Carbonic Anhydrase Inhibitors Metabolic acidosis (due to HCO_3^- depletion with prolonged treatment), hypokalemia (acute effect) Drowsiness, fatigue, CNS depression, and paresthesia.
Osmotic Diuretics Acute expansion of ECF volume and increased risk of pulmonary edema, hyponatremia (with impaired renal function); hypernatremia (prolonged use with normal GFR). Nausea and vomiting; headache.
Loop Diuretics Hypokalemia; hypomagnesemia; hyponatremia; **hypovolemia**; Hyperuricemia* Metabolic alkalosis Ototoxicity and diarrhea (mainly with ethacrynic acid)
Thiazide Hypokalemia; hyponatremia; hypovolemia; Hyperuricemia due to enhanced urate reabsorption* and hypercalcemia due to enhanced Ca^{2+} reabsorption Metabolic alkalosis Hyperglycemia (insulin resistance); hyperlipidemia. Hypersensitivity (fever, rash, purpura, anaphylaxis); interstitial nephritis.
K^+ - Sparing Diuretics Spironolactone: **hyperkalemia**, gynecomastia, hirsutism; menstrual irregularities; testicular atrophy (with prolonged use). Amiloride: **hyperkalemia,** glucose intolerance in diabetic pts. Triamterene: **hyperkalemia**; megaloblastic anemia in pts with liver cirrhosis.
ADH Antagonists Lithium, doxycycline: nephrotoxic Tolvaptan, conivaptan, mozavaptan: hypernatremia, thirst, dry mouth, hypotension, dizziness

* The proximal tubule is the major site of uric acid handling; both reabsorption and secretion occur in this segment, with the net effect being the reabsorption of most of the filtered uric acid. Thiazide and loop diuretics decrease uric acid excretion by increasing <u>net</u> uric acid reabsorption; this can occur either by <u>enhanced uric acid reabsorption</u> or by <u>reduced uric acid secretion</u>—or a combination of both effects**. Hyperuricemia can cause gout.**

Interactions	
Interacting Drugs	**Potential Interactions**
ACE inhibitors / K^+ - sparing diuretics	⇒ increased hyperkalemia ⇒ cardiac arrhythmias (monitor serum K^+ closely)
Aminoglycosides / Loop diuretics	⇒ ototoxicity and nephrotoxicity. (monitor hearing and serum creatinine closely)
Anticoagulants / Thiazide & Loop diuretics	⇒ increased anti-coagulant activity with loop diuretics; decreased anti-coagulant activity with thiazide diuretics.
ß- Blockers / Thiazide & Loop diuretics	⇒ hyperglycemia, hyperlipidemia, hyperuricemia. ⇒ increased plasma levels of propranolol
Carbamazepine or chlorpropamide / Thiazide diuretics	⇒ increased risk of hyponatremia (monitor Na^+)
Digoxin / Thiazide & Loop diuretics	⇒ hypokalemia ⇒ increased digoxin binding & toxicity (monitor K^+ and cardiac function)
NSAIDs / Thiazide & Loop diuretics K^+ sparing diuretics	⇒ reduced diuretic effect, increased risk of salicylate toxicity with high doses of salicylates (thiazide & loop d.). ⇒ increased risk of hyperkalemia with K^+ sparing diuretics
Quinidine / Loop & thiazide diuretics	⇒ polymorphic ventricular tachycardia (*torsade de pointes*)
Sulfonylureas / Loop diuretics	⇒ hyperglycemia
Steroids / Thiazide & Loop diuretics	⇒ increased risk of hypokalemia (monitor serum K^+ closely)

REVIEW QUESTIONS:

1. How do diuretic drugs reach their sites of action?
2. Why does acetazolamide produce an alkaline urine (pH = 8.2)?
3. Why do thiazide and loop diuretics cause potassium loss?
4. How do thiazide and loop diuretics affect calcium excretion?
5. How do carbonic anhydrase inhibitors cause a diuresis?
6. Which class of diuretics would cause increased excretion of magnesium?
7. What is the mechanism of action of amiloride?
8. What class of diuretics interferes with sodium reabsorption in the proximal tubule?
9. How would the combination of a loop diuretic and thiazide diuretic influence sodium excretion?
10. What are the effects of spironolactone on urinary potassium excretion?
11. What is the most common reason for diuretic use?
12. What are the most common adverse effects associated with diuretic therapy?
13. Which diuretic drugs would be indicated to reduce edema/ascites in patients with hepatic cirrhosis?
14. Which thiazide-like diuretic is most likely to be efficacious in patients with severe renal insufficiency?

ANTI-HYPERTENSIVE DRUGS

Date: November 15, 8:30 AM and 9:30 AM

Reading Assignment: Chapter 11, 12th Edition of Katzung, pp: 169-191.

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Hypertension is one of the most pervasive diseases in the US today and is one of the most important predictive risk factors for the development of cardiovascular disease. Even mild to moderate reductions in blood pressure can have a significant impact on morbidity and mortality due to cardiovascular disease.

    a. *Be familiar with the definition of hypertension and the currently accepted criteria for staging of hypertension.*
    b. *Recognize how the stage of hypertension at diagnosis influences management of the disease.*

2. Several different drug classes are effective as anti-hypertensive agents. These include diuretics (three major classes include thiazide-, loop- and potassium-sparing diuretics), calcium channel blockers (two major classes include dihydropyridines and non-dihydropyridines), sympatholytic agents, non-specific adrenergic blocking agents, alpha-adrenergic antagonists (including non-selective and selective alpha1-blocking agents), beta-blockers (including non-selective as well as selective blockers and those with intrinsic sympathomimetic activity), vasodilators (for treatment of resistant and emergent hypertension), angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists.

    a. *Recognize the mechanism of action of each class of anti-hypertensive agent.*
    b. *Know the prototypical drugs for each class and additional drugs mentioned in the lecture that have particular advantages compared to the prototypes.*
    c. *Recognize the major side effects of each class of anti-hypertensive drug*
    d. *Recognize dangerous drug interactions associated with each class of anti-hypertensive agent as well as conditions in which the class of drug is contraindicated.*

3. Several drugs produce compensatory responses that may attenuate the drugs initial anti-hypertensive effects. Therefore, combinations of anti-hypertensive drugs from different classes are commonly used to counter the compensatory response of another drug resulting in a more robust anti-hypertensive effect.

    a. *Recognize the most commonly used drug combinations and why these drug combinations are more effective than either of the compounds alone.*
    b. *Recognize potentially dangerous or ineffective combinations and why they should be avoided.*

4. Current anti-*hypertensive* therapy involves a stepped-care approach in which therapeutic response to certain drugs or drug combinations are assessed first before adding additional drugs. Using this method the clinician attempts to gain the desired anti-hypertensive effect with the least toxicity. Numerous clinical trials over the years have provided compelling evidence that certain anti-hypertensive drug classes may be particularly beneficial, not effective or even detrimental in certain populations of hypertensive patients. Therefore, the stepped approach includes caveats that allow physicians to provide the best clinically proven effective care for hypertension in certain patient subgroups at the onset of treatment, or for hypertension in the presence of additional pathology at the onset of treatment.

   a. diagram the stepped-care approach and understand the underlying logic behind the algorithm.
   b. Recognize the exceptions to the approach and what drug regimen should be substituted in cases of other pathologies e.g., heart failure, diabetes, myocardial infarct etc.,

ANTI-HYPERTENSIVE DRUGS I & II

Approximately 76 million Americans (1 of every 3) aged 20 and older have elevated blood pressure (hypertension). Approximately 5-10% of these patients have an identifiable cause (i.e., Cushing's disease, renal artery constriction, aortic coarctation, pheochromocytoma or primary aldosteronism). The remainder are said to have "primary" or "essential" hypertension.

American Heart Association Statistics as of Dec 2011

- Among individuals with hypertension, ~20% do not know they have it.
- Of all hypertensive patients, 30% are not on therapy (special diet or drugs).
- Only 48% receive adequate therapy.
- African Americans are more likely to suffer from hypertension than Anglo-Americans (~44% vs. 32%).
- Educational and income levels correlate inversely with blood pressure
- Patient compliance is a major obstacle to therapy
- Estimated 10% increase in prevalence by 2030
- Women have lower rates then men when young, but higher rates >65 yoa
- 30% of Americans have "pre-hypertension" (120-139/80-90 mmHg)

Sustained hypertension leads to:

1) Damage of blood vessels in the brain, heart and kidney
2) Atrial fibrillation

The risk of end organ damage increases proportionately with the magnitude of blood pressure elevation.

Primary Risk Factors

Family history
African American ethnicity
Male gender
Post-menopausal female
>20 lbs excess body weight

Associated Risk Factors

Excess Alcohol consumption
Diabetes
Use of oral contraceptives

Inactivity

Diagnosis

- Based on repeated, reproducible measurements of elevated blood pressure
- Not on patient symptoms.

Classification

For Adults Aged 18 Years and Older*

Category	**Systolic**	**Diastolic**
Normal	< 120	< 80
Pre-Hypertensive	120 - 139	80 - 89
Hypertension - Stage 1	140 - 159	90 - 99
Stage 2	≥160	or ≥100

*(*Adapted from JNC-VII; see report for additional details)*

Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure (JNC) provides intermittent reports with updated guidelines, the latest being the JNC VII report, published in Dec. 2003. JNC VIII is expected out at the end of 2012. The JNC VII guidelines suggest much more stringent control of blood pressure for "normotensive" individuals, i.e., lifestyle modifications for those in the normal range 120/80. Target BP is now 115/75 mm Hg. The JNC's recommendation for lifestyle modifications can be found in their report (see link below) and is summarized in the following table.

http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm

Table 5. Lifestyle modifications to manage hypertension*†

Modification	Recommendation	Approximate SBP Reduction (Range)
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2).	5–20 mmHg/10 kg weight loss[23,24]
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg[25,26]
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg[25-27]
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg[28,29]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons.	2–4 mmHg[30]

DASH, Dietary Approaches to Stop Hypertension.
* For overall cardiovascular risk reduction, stop smoking.
† The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

Pharmacological Interventions:

Main Categories

***First line drugs of choice**

- ***Diuretics**
- ***Calcium Channel Blockers** (CCBs)
- Centrally-acting Agents
- Alpha Adrenergic Blockers
- ***Beta Adrenergic Blockers** (BBs)
- Vasodilators
- ***Angiotensin Converting Enzyme inhibitors** (ACEIs)
- ***Angiotensin Receptor Blockers** (ARBs)

Pharmacological intervention targets resistance arterioles, capacitance venules, the heart, kidneys and the central nervous system to alter cardiac output (CO) and total peripheral resistance (TPR).

$$MAP = CO \times TPR$$

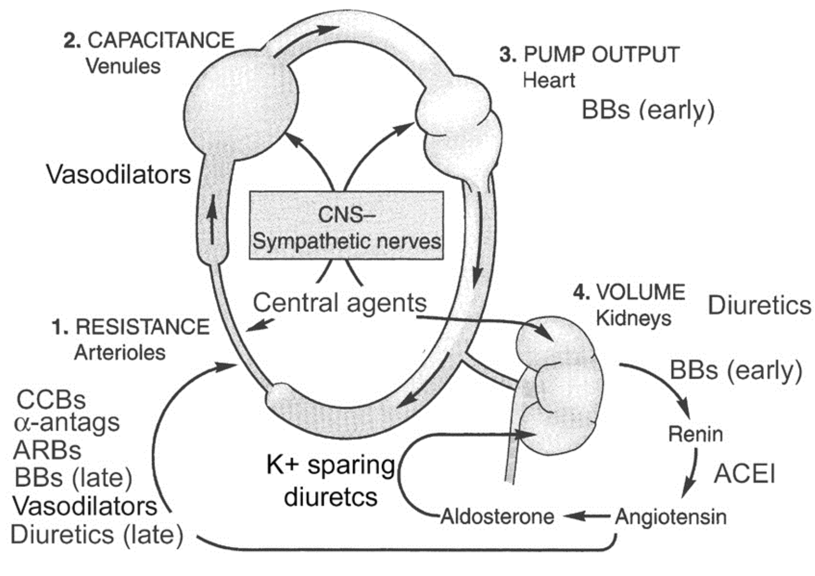


Figure 11–1. Anatomic sites of blood pressure control.

From Katzung, Basic and Clinical Pharmacology, 10th Ed., p.160

4 main physiological mechanisms of hypertension

1. LV ejection too high – rare, but observed in young African American men with hyperdynamic circulation (Rx – lower contractility)

2. Intravascular volume too high – not typical as most newly diagnosed hypertensive patients have lower intravascular volume. (Rx – lower plasma volume)

3. Venous tone too high - can occur even with low intravascular volume, not known if this is common in hypertension. (Rx – lower venous tone by lowering sympathetic drive)

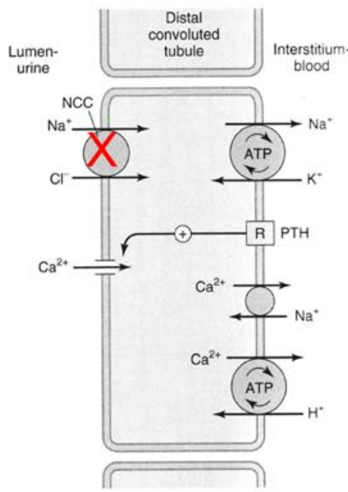
4. Arterial vascular resistance is too high - commonly observed, particularly in elderly patients with stiff arteries, causes high systolic pressure (Rx – lower arterial tone by using arterial dilators)

Diuretics -

Primary Mechanisms of Action: depletion of sodium by inhibition of Na+ transport across the apical membrane of loop of henle and distal convoluted tubule following filtration into renal lumen; also some have carbonic anhydrase inhibitor activity;

- reduction of blood volume (early)
- prostaglandin-dependent decrease in total peripheral resistance (later)
- efficacy of up to 10-15 mm Hg when administered alone
- more when used in combination with other agents

Thiazide diuretics - hydrochlorothiazide (Hydrodiuril)**, chlorthalidone** (Hygroton) inhibit NaCl transporter in distal convoluted tubule

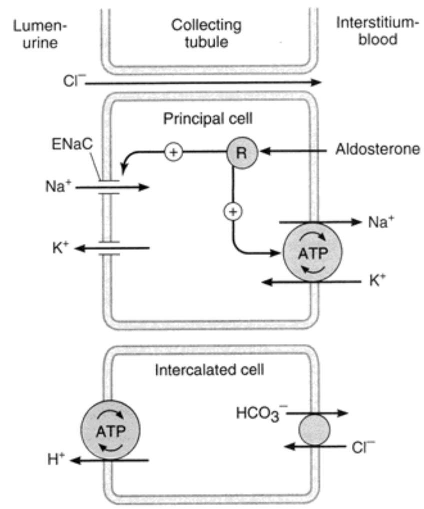


From Katzung, Basic and Clinical Pharmacology, 10th Ed., p.239

- used as monotherapy in mild to moderate hypertension with normal cardiac/renal function
- most frequently used antihypertensive agents in the U.S.
- very effective, particularly when used in combination with other classes
- inexpensive
- first line therapy for treatment of uncomplicated hypertension.
- not as effective in pts with renal insufficiency – may need higher dose or combine with other drugs to achieve goal

Side Effects:

Hyponatremia
Hyperglycemia - impairs insulin release, diminishes glucose uptake (high dose)
Hyperuricemia – dehydration stimulates uric acid reabsorption in proximal tubule
Increased LDL/HDL-can return to normal after prolonged use
Impotence
Hypokalemia and metabolic alkalosis – increased delivery of Na^+ to collecting duct increases Na+ diffusion across ENaC channel, resulting in negative lumen charge and increased K^+ and H^+ secretion into the lumen. Hypokalemia is likely responsible for hyperglycemic and hyperlipidemic effects of diuretics. However, these effects can be avoided by using lower, but still effective doses.



From Katzung, Basic and Clinical Pharmacology, 10th Ed., p. 240

The following maneuvers should help prevent diuretic-induced hypokalemia:

- Use the smallest dose of diuretic needed.
- Restrict sodium intake to less than 100 mmol/day.
- Increase dietary potassium intake.
- Use a concomitant beta blocker, ACEI, or ARB, which diminishes potassium loss by blunting the diuretic-induced rise in renin and aldosterone levels.

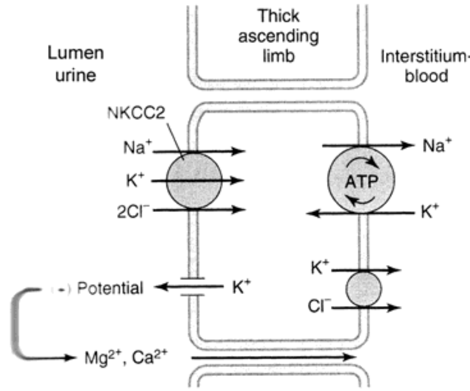
Selected Drug Interactions:

NSAIDs – inhibits prostaglandin production, reduces efficacy
β-blockers – enhances hyperlipidemia and hyperglycemia

Contraindications:

Existing hypokalemia - arrhythmia

Relative Contraindication - Pregnancy



Loop Diuretics – **furosemide** (Lasix) - inhibits $Na^+/K^+/Cl^-$ transporter on apical membrane of cells in the thick ascending loop of henle

shorter duration of action than thiazide-type diuretics; less effective than thiazides in patients with normal renal function due to rebound sodium retention. Reserved for pts refractory to thiazides, and pts with moderate to severe renal insufficiency or congestive heart failure,

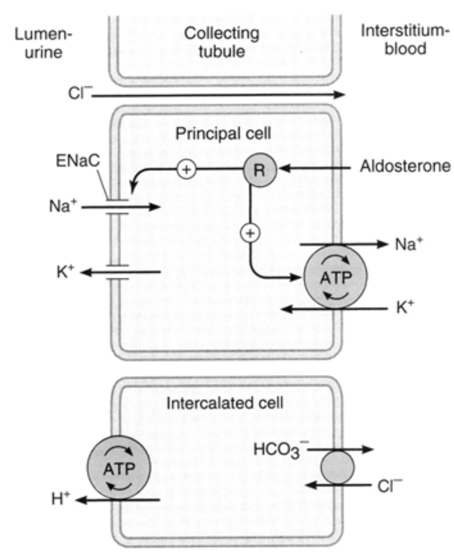
Side Effects:

Metabolic Alkalosis
Hyponatremia
Hypokalemia
Hyperuricemia
Impaired diabetes control
Increased LDL/HDL
Hypomagnesemia – K^+ diffusion into lumen through ascending limb cells normally drives Mg^{2+} reabsorption, blockade if transporter reduces K^+ diffusion.
Reversible ototoxicity

Selected Drug Interactions:
NSAIDS - inhibit prostaglandins which are required for efficacy
Aminoglycosides – enhance ototoxicity and nephrotoxicity

Potassium-Sparing Diuretics - two types: aldosterone receptor antagonists: **spironolactone** (Aldactone) and **eplerenone** (Inspra) and ENaC blockers: **triamterene**, **amiloride**

Only used in combination with other diuretics (i.e., thiazides) to correct hypokalemia; not normally used alone for treatment of hypertension. Aldosterone stimulates incorporation of ENaC in apical membrane of collecting tubule. Na+ flux into cells through ENaC drives K+ efflux due to negative charge in lumen. Blockade of sodium entry reduces electrical driving force for K+ loss.



From Katzung, Basic and Clinical Pharmacology, 10th

Eplerenone less likely to cause gynecomastia due to more selective binding of aldosterone receptor (vs. androgen receptors)

Side Effects:
Hyperkalemia
Gynecomastia, impotence menstrual irregularities - spironolactone has agonist effect on androgen steroid receptors

Selected Drug Interactions:

NSAIDs – both types of drugs depend on prostaglandin synthesis
ACE inhibitors or ARBs–any antagonist of angiotensin II production (β-blockers, ARBs) further reduces aldosterone secretion and contributes to hyperkalemia

Contraindications:
should not be used in combination with drugs that inhibit renin-angiotensin system

Therapeutic Notes on duiretics:

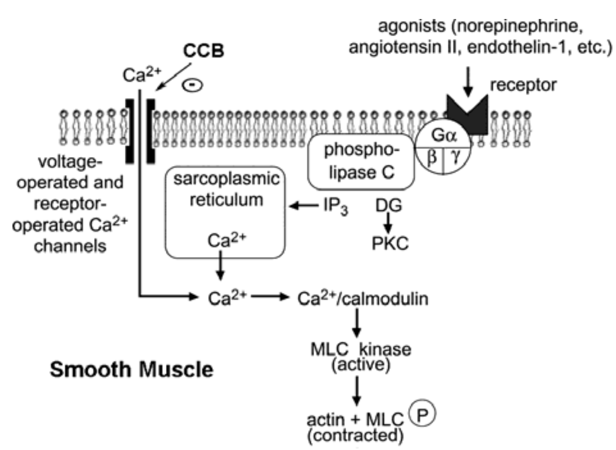
- Thiazide diuretics available as fixed-dose combinations with potassium-sparing or other antihypertensive drugs
- Often used in combination with antihypertensive agents that impair vascular responsiveness (i.e., vasodilators) since blood pressure becomes very sensitive to blood volume contraction in the presence of vasodilators.
- Thiazides are not as useful in patients with renal insufficiency (glomerular filtration rate < 30 ml/min).
- Side Effects are minimal at lower doses.

Calcium Channel Blockers

Primary Mechanisms of Action: All types will:

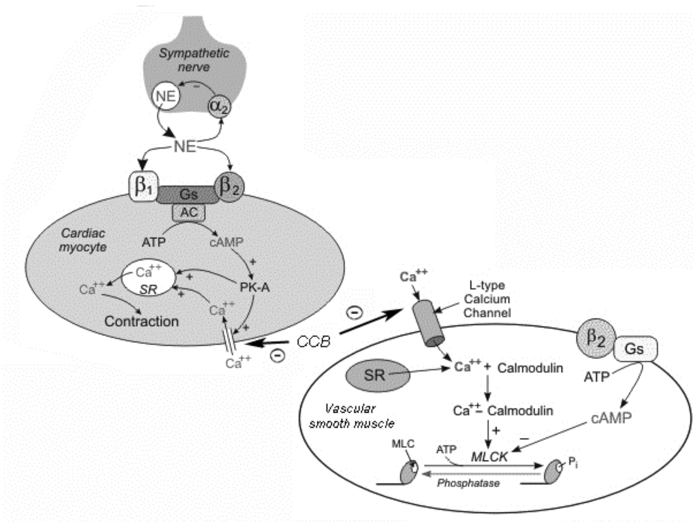
1) inhibit Ca^{2+} influx into vascular smooth muscle through L-type calcium channel

2) relax peripheral vascular smooth muscle and decrease total peripheral resistance via inhibition of myosin light chain



kinase activity which requires activation by calcium-calmodulin; thereby disrupts angiotensin II and alpha$_1$- adrenergic mediated vasocontriction.

Two main types: dihydropyridines and non-dihydropyridinnes. Non-dihydropyridines reduce calcium current in cardiac pacemaker cells and reduce conduction velocity in AV node (probably T-type calcium channels); lower heart rate and contractility (latter due to decreased calcium-induced calcium release from myocyte sarcoplasmic reticulum) and can reduce cardiac output. These agents are referred to as heart rate lowering agents.



Nifedipine (Procardia) - Dihydropyridine relatively selective vasodilator, less cardiac effects, short acting form can induce ischemia, extended release form used for chronic hypertension, long half-life requires only once a day dosing, metabolized by P450 system, therefore avoid in pts with liver disease and consider drug interactions due to induction or inhibition of enzymes.

Side Effects: **acute tachycardia** (reflex sympathoexcitation), headache, flushing, peripheral edema (arteriole dilation > venous dilation). Slow release formulas are used for hypertension.

Diltiazem (Cardizem) – Non-dihydropyridine. Inhibits sinus node as well as L-type calcium channels of myocytes and vascular smooth muscle. Therefore reduces both cardiac output and peripheral resistance

Side Effects: **bradycardia** (slowed rate and conduction) dizziness, headache, edema

Verapamil (Calan) – Non-dihydropyridine, greatest effect on heart

Side Effects: constipation (probably due to anti-cholinergic effects), **bradycardia**, can still cause dizziness, headache, edema at higher concentrations

Relative Contraindications for CCBs: caution should used in prescribing to pts with liver failure since the drugs are metabolized by the liver. Can increase concentrations of statins when given in combination due to competition for liver enzymes. **Patients with SA or AV node conduction disturbances whould not be given verapamil or diltiazem.**

Therapeutic Notes:

- CCB's rarely associated with abnormalities in electrolyte, carbohydrate, or lipid metabolism. The drugs do not alter plasma concentrations of uric acid.
- Verapamil and diltiazem should be used with caution in patients receiving beta-blockers due to inhibition of cardiac conduction.

Patients taking **short-acting** nifedipine, diltiazem or verapamil were 1.6 times more likely to have myocardial infarction than patients taking other antihypertensive drugs though additional studies have found no increase in mortality or morbidity with extended release calcium-channel blockers.

Sympatholytic Drugs

Primary Mechanisms of Action:

reduce sympathetic drive to heart and/or blood vessels thereby decreasing venous return, cardiac output, total peripheral resistance and renin release

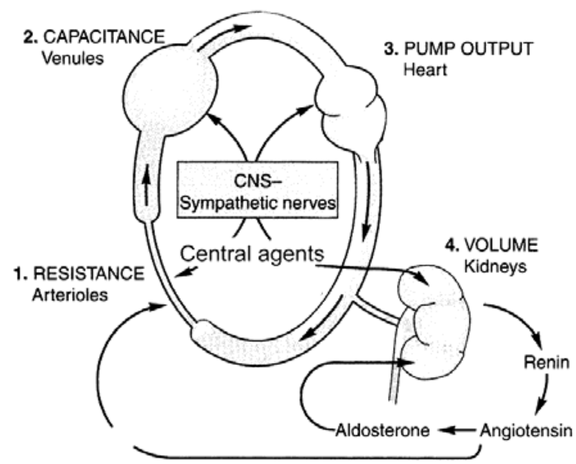
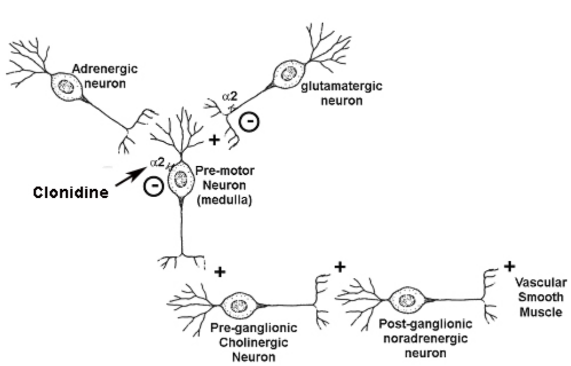


Figure from Katzung, Basic and Clinical Pharmacology, 10th Ed., p. 160.

Centrally Acting Agents - reduce sympathetic output from vasopressor centers in brainstem

Clonidine (Catapres) - alpha$_2$ agonist at medullary cardiovascular regulatory centers; decreases sympathetic outflow from CNS

Side Effects: sedation (12-35% patients) and dry mouth (25-40% patients), marked bradycardia is rare, but can be significant; side effects may be reduced by transdermal preparation (although discontinued in 20% patients because of contact dermatitis).



Selected Drug Interactions: may potentiate actions of other CNS depressants

Therapeutic Notes: relatively short half-life, must withdrawal slowly to prevent rebound hypertension, nervousness, insomnia, etc.; must warn patients about missing doses; available in tablet form or as a transdermal system; patients must be instructed to dispose of transdermal systems properly, has little effect on plasma lipids. **Guanfacine** has similar effects and longer half-life therefore, better than clonidine but not as popular.

Methyldopa (Aldomet) - dual mechanisms of action: crosses BBB, transported into adrenergic neurons where it is eventually converted to methylnorepinephrine and released by synaptic transmission in CNS, agonist at alpha$_2$ adrenergic receptors, decreases blood pressure chiefly by decreasing sympathetic tone; also competes for DOPA decarboxylase thereby prevents production of dopamine and subsequent NE or EPI in peripheral nerves.

Side Effects: sedation, nightmares, movement disorders, hyperprolactinemia (inhibition of dopamine production); rarely anemia (1-5%)

Selected Drug Interactions:

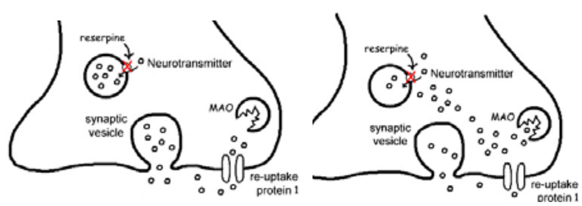
Levodopa – methyldopa inhibits DOPA decarboxylase which converts Levodopa (L-DOPA) to dopamine, therefore reduces L-DOPA's therapeutic effects.

Contraindications:
Liver disease

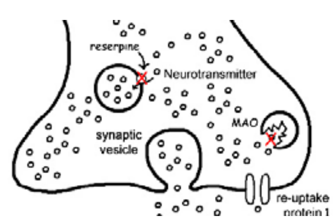
Therapeutic Notes: probably the most extensively used hypotensive agent in management of hypertension in pregnant women

Indirect Adrenergic blocking agents - reduce norepinephrine release in heart and blood vessels; some decrease in cardiac output, primary effect is decrease of total peripheral resistance

Reserpine (Serpasil) - disrupts norepinephrine vesicular storage; both central and peripheral action though peripheral actions predominate; side effects significant at doses used for monotherapy; therefore, typically given in combination with diuretics, low dose combo highly efficacious with minimal side effects, once a day dosing and inexpensive generics make it useful.



Side Effects (usually only seen at higher doses that are no longer used clinically): sedation,



diarrhea, depression, bradycardia, nasal congestion

Selected Drug Interactions:
Potentiates effects of CNS depressants
MAOIs – counteracts effects of reserpine since reserpine's effects depend upon metabolism of catecholamines in cytosol, combination can also cause hypertensives crisis due to increase in cytosolic catecholamines and reversal of uptake transporter

Alpha Adrenergic Antagonists - act at post-synaptic receptors to block arterial and venous constriction

Phenoxybenzamine (dibenzyline) –non-selective, limited use due to tachycardic effects (use beta blockers only after initiation of alpha blocker), used in patients with hypertension due to pheochromocytoma

Prazosin (Minipress) – is prototype, but has shorter half-life. More commonly prescribed are **terazosin** and **doxazosin** which can be dosed 1 per day; alpha 1 selective antagonists have less tachycardia than direct vasodilators or non-selective α-adrenergic receptor antagonists, decreases resistance in both arterioles and veins, therefore can promote postural hypotension, though newer drugs have slower onset and longer duration and show less postural hypotension; less effect on cardiac output than beta blockers, therefore preferred by active patients, beneficial decrease in LDL/HDL ratio

Side Effects: first dose produces precipitous fall in blood pressure, fluid retention, dizziness (10% of patients), headaches (8% of patients), weakness (7% patients);

Therapeutic Notes: alpha1 adrenergic-antagonists do not impair exercise tolerance, ALLHAT study indicates best result is obtained when combined with diuretic to reduce fluid retention.

Beta-Adrenergic Antagonists - Mechanisms of action include:

- decreased myocardial contractility and CO
- decreased renin secretion and hence decreased levels of angiotensin II
- lipophilic compounds may reduce sympathetic activation through CNS effects

Three generations of drugs:

- non-selective
- cardiac selective

- vasodilatory - act both by traditional means and by increasing nitric oxide release or blocking α-adrenergic receptors.

Beta blockers are also categorized according to their lipid solubility which influences their side effect profile and clearance route.

Propranolol (Inderal) - first generation- nonselective; useful in mild to moderate hypertension; in severe hypertension, used as adjunct to prevent reflex tachycardia that accompanies treatment with direct vasodilators, and compensatory sodium retention with diuretics, 4 hr half life requires multiple daily doses, lipophilic therefore demonstrates some CNS-dependent side effects.

Nadolol (Corgard) - non-selective; longer half-life allows single daily dosing, better patient compliance, hydrophilic, excreted by kidney.

Pindolol (Visken) - non-selective; partial agonist (some intrinsic sympathomimetic activity, ISA); less bradycardia than other beta-blockers, used in patients with symptomatic bradycardia or postural hypotension.

Metoprolol (Lopressor) **-** (2nd generation) $beta_1$ selective, fewer respiratory side-effects, lipophilic with CNS side effects, but may have central sympatholytic effect.

Atenolol (Tenormin)- (2nd generation) $beta_1$ selective, hydrophilic, no CNS effects, excreted by kidney

Labetolol (Trandate, Normodyne) – (3rd generation) mixed beta/alpha receptor antagonist; lipophilic, some ISA.

Carvedilol (Coreg) **-** (3rd generation), non-selective blocker with additional alpha receptor antagonist properties, vasodilatory, has antioxidant properties.

Side Effects

All: bradycardia, impotence, increased serum triglycerides, decreased HDL levels, hyperglycemia (less so with cardioselective), low exercise tolerance (less so with 3rd generation drugs)

Non-selective: increased airway resistance, cold extremities

Lipophilic: insomnia, nightmares, mild chronic fatigue, depression

Drug Interactions: CCB's increased risk of conduction disturbances

Contraindications: **cardiogenic shock**, sinus bradycardia (greater than 1st degree block) **bronchial asthma**, severe congestive heart failure (though protective in compensated heart failure).

Therapeutic Notes: must be withdrawn gradually to avoid rebound hypertension, all classes roughly equivalent in efficacy as antihypertensive agents, can mask insulin-induced hypoglycemia, may be associated with higher incidence of diabetes, are generally less effective than a diuretic alone for treatment of the elderly. Latest data suggest BBs should only be used as first line drug in hypertensive patients with coronary artery disease, congestive heart failure (compensated) or tachyarrhythmias.

Vasodilators

Primary Mechanism of Action: dilate small arteries thereby decreasing peripheral resistance

Hydralazine (Apresoline) - dilates arterioles preferentially therefore less postural hypotension, orally effective, used both for treatment of resistant hypertension and hypertensive emergencies in pregnancy, not very efficacious long term.

Side Effects: tachycardia, aggravation of angina, fluid retention, nausea, vomiting, sweating, flushing, lupus-like syndrome (avoided with lower doses)

Drug interactions: NSAIDS can reduce effectiveness

Contraindications: coronary artery disease, reflex sympathoactivation increases cardiac work, vasodilation in unobstructed coronary vessels "steal" blood from obstructed regions that are less responsive to vasodilator.

Minoxidil (Loniten) – short term use for resistant hypertension, K+ channel opener, little effect on venous vasculature therefore no postoral hypotension, not as effective long term.

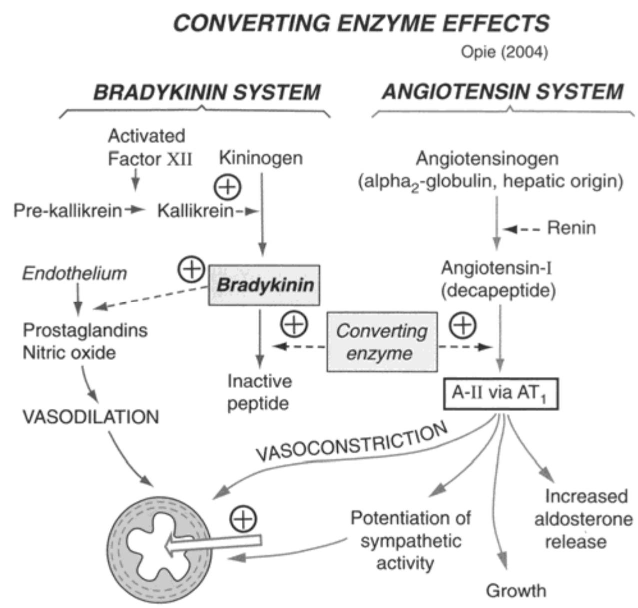
Side Effects: tachycardia, aggravation of angina, fluid retention, nausea, vomiting, sweating, flushing, hypertrichosis

Nitroprusside (Nitropress) - used to treat hypertensive emergencies; immediate onset, but brief duration, of action; very efficacious, must monitor blood pressure, also dilates veins, does not stimulate increased cardiac work like other vasodilators.

Side Effects: nausea, vomiting, muscle twitching, prolonged infusion can lead to build up of metabolites that can cause cyanide poisoning

Angiotensin Converting Enzyme (ACE) Inhibitors

Primary Mechanisms of Action: inhibit production of angiotensin II (inhibits vasoconstriction and sodium-retaining activity); decrease total peripheral resistance, probably also mediated by increased bradykinin which can protect endothelial lining of vasculature and stimulate vasodilatory prostaglandins. Reduces aldosterone secretion



Modified by KES from Opie and Gersh, Drugs for the Heart, 6th Ed. p. 106

Captopril (Capoten) - biological half-life requires multiple daily dosing (2-3x), generics available

Enalapril (Vasotec) - converted to active metabolite enalaprilat in liver, longer onset of action, longer half-life, generic, dose 1 or 2x per day.

Lisinopril (Zestril, Prinivol) - not prodrug, water soluble excreted unchanged by kidney, long half-life allows 1x daily dosing, more predictable onset and duration of action than prodrugs.

Side Effects: hyperkalemia, rash, dry cough, angioedema (0.3% overall, 0.6% in African Americans)

Drug Interactions: can exacerbate hyperkalemia when given with potassium sparing diuretics.

Contraindications: Ang II is important in fetal renal development, therefore, **drugs that interfere with angiotensin II production should not be given to pregnant women** particularly **in their second and third trimester**; renal perfusion pressure in pts with bilateral renal stenosis is largely dependent upon Angiotensin II and therefore treatment with ACEI can produce renal failure.

Therapeutic Note: prolongs survival in patients with heart failure or LV dysfunction after MI, or at risk of LV dysfunction, preserves renal function in patients with diabetes, 11% decrease in CV events or all cause mortality compared to patients on thiazide diuretics showing similar fall in pressure.

Angiotensin II receptor Blockers (ARBs)

Primary Mechanism of Action: Angiotensin II bind to AT1 and AT2 receptors. AT1 receptors mediate the vasoconstrictor and sodium retaining effects of Ang II. ARBs do not inhibit bradykinin metabolism and therefore do not induce the dry cough associated with ACEIs. The risk of angioedema is also reduced. However, ARBs are relatively new and require significantly more testing to determine their advantage over ACEIs. They are typically used in pts who do not tolerate ACEIs.

Losartan (Cozaar) - selective AT1 receptor antagonist. Short half-life, many newer "sartans" are available with longer half-lives, e.g., candasartan.

Side Effects: hyperkalemia, no evidence of dry cough as with ACEIs

Drug interactions: same as ACE inhibitors

Contraindications: same as ACE inhibitors

Therapeutic Notes: monotherapy with renin angiotensin system blocking agents is less efficacious in patients of African decent (Hypertension 26:124-130, 1995) due to more common incidence of low renin levels characteristic of salt-sensitivity, though effectiveness is greatly improved when combined with diuretics (AADVANCE trial), half-life 6-9 hrs therefore can be given 1-2x per day, very well tolerated with very few side effects that influence patient compliance.

Hypertension Treatment Considerations

- Combinations of drugs with different sites of action are more effective
- Most patients require 2 or more drugs to achieve goal

Drugs with the same mechanisms of action should rarely be combined. Appropriate combinations include:

thiazide diuretics + K^+ sparing diuretiecs, ACEI, or ARBs (counteract hypokalemic effects of thiazides) thiazide diuretics + BB (counteracts volume contraction-induced sympathetic activation)

CCBs + ACEIs (reduce fluid retention by CCBs)

Bad combinations include ACEI + K^+ sparing diuretics (both promote hyperkalemia)

Most antihypertensive agents are used for indications other than hypertension as well. Certain classes of antihypertensives are preferred when patients have additional conditions

Compelling Indications

Diabetes mellitus - ACE inhibitors
Heart failure - ACE inhibitors, Diuretics
Myocardial infarction - beta-blockers (non-ISA), ACE inhibitors

Some Considerations for Choosing Treatments (unless otherwise contraindicated).

Pregnancy

If antihypertensive are taken prior to pregnancy, most can be continued except ACE inhibitors and angiotensin II receptor blockers.

Methyldopa is most widely used when hypertension is detected during pregnancy.

African Americans

Larger doses of BBs, ACEIs or ARBs may be required for response when used as monotherapy, but these drug classes produce good results when given in combination with diuretics.

Diuretics have been demonstrated to decrease morbidity and mortality, and hence should be first choice (ALLHAT study).

Ca^{2+} blockers and combination alpha/beta blocker are also effective as monotherapy.

Elderly

Smaller doses, slower incremental increases in dosing, and simple regimens should be used.

Close monitoring for side effects (i.e., deficits in cognition after methyldopa; postural hypotension after prazosin) is appropriate.

Diabetes mellitis

ACEI, alpha-antagonists, and CCBs can be effective, and have few adverse effects on carbohydrate metabolism. ACE inhibitors often given to diagnosed diabetics prior to development of hypertension

Hyperlipidemic

Low dose diuretics have little effect on cholesterol and triglycerides.

Alpha-blockers decrease LDL/HDL ratio. Calcium-channel blockers, ACE inhibitors, angiotensin II receptor blockers have little effect on lipid profile.

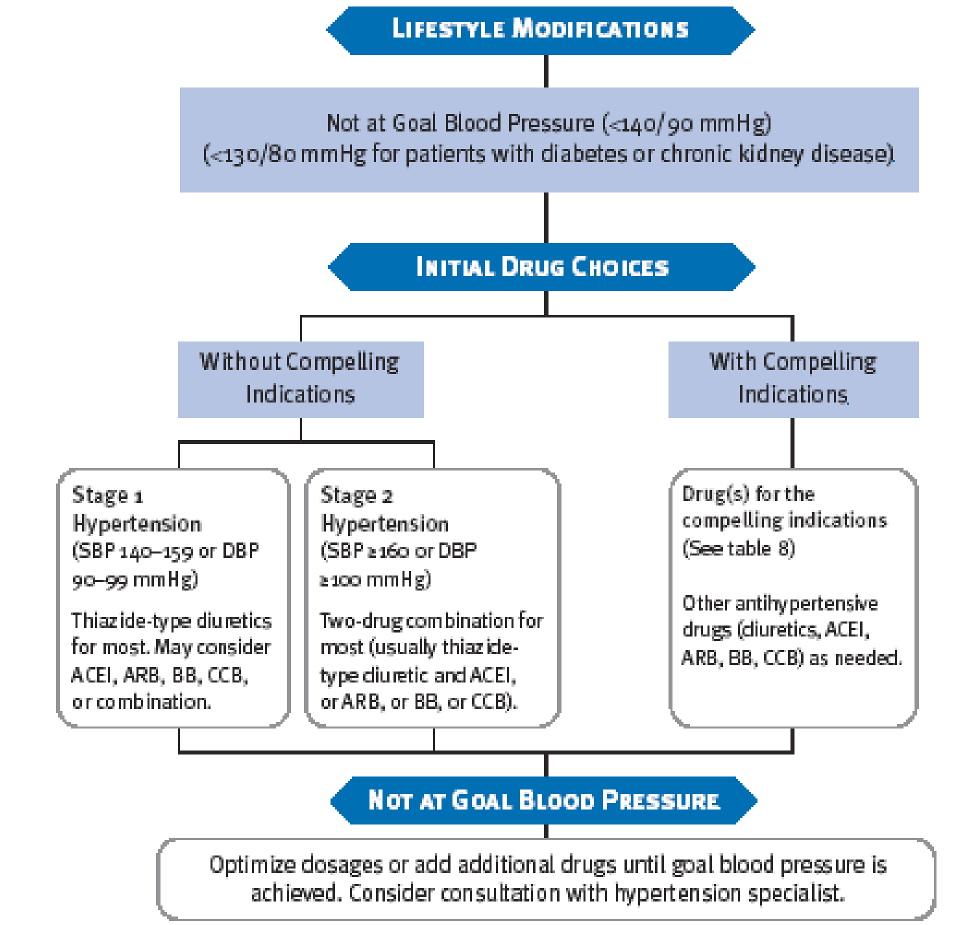
Obstructive airway disease

Avoid beta-blockers.

Overview of Treatment Strategies

FROM JNC VII

Figure 1. Algorithm for treatment of hypertension



DBP, diastolic blood pressure; SBP, systolic blood pressure.
Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

Drug Name	Generic Name	Mechanism of Action	Indication
Hydralazine	Apresoline	**Vasodilator**	**Resistant hypertension, pregnancy induced hypertension**
chlorthalidone	Hygroton	**Thiazide diuretic**	**1st line drug in uncomplicated hypertension**
Furosemide	Lasix	**Loop diuretic**	**Hypertension in severe renal insufficiency**
Spironolactone	Aldactone	**Aldosterone receptor antagonist**	**Used in combination with other anithypertensive that deplete K+**
Eplerenone	Inspra	**Aldosterone receptor blocker**	**Combination treatment of hypertenion with drugs that deplete K+**
Triamterene	Dyrenium	**ENaC inhibitor**	**In combination with diuretics to spare K+ loss**
Amiloride	Amiloride	**ENaC blocker**	**Combined with diuretics to minimize K+ loss**
Nifedipine	Procardia	**Ca+ channel antagonist**	**1st line drug in hypertension,** used in diabetes and hyperlipidemia
Diltiazem	Cardizem	**Ca+ channel antagonist**	**1st line drug in Chronic hypertension**
Verapamil	Calan	**Ca+ channel antagonist**	**1st line drug in hypertension**
Clonidine	Catapres	**α2-agonist**	**Chronic Hypertension**
Guanfacine	Tenex	**Alpha 2 agonist**	**Hypertension**

Methyldopa	Aldomet	**Alpha 2 agonist**	**Hypertension in pregnancy**
Reserpine	Serpasil	**Depletes monoamine from storage vesicles**	**Resistant hypertension**
Phenoxybenzamine	Dibenzyline	**α-blocker**	**rx for pheo. before surg.,**
Prazosin	Minipress	**α-blocker**	**Chronic Hypertension, benign prostatic hyperplasia**
Terazosin	Hytrin	**α1-blocker**	**Chronic hypertension**
Doxazosin	Cardura	**α1-antagonist**	**Chronic hypertension**
Propranolol	Inderal	**β-blocker**	**Hypertension with angina, MI, or arrhythmia**
Nadolol	Corgard	**β-blocker**	**Long-term angina, hypertension**
Pindolol	Visken	**β-antagonist (with partial agonist activity)**	**Chronic Hypertension**

Metoprolol	Lopressor, Toprol	**β1-antagonist**	**Hypertension, long-term angina rx**
Atenolol	Tenormin	**β1-blocker**	**Chronic Hypertension,** angina, MI, arrhythmia, HF
Labetolol	Normodyne	**Mixed alpha/beta Receptor antagonist**	**Chronic Hypertension**
Carvedilol	Coreg	**Mixed alpha/beta receptor blocker and NO generator**	**Chronic hypertension and CHF**
Hydralazine	Apresoline	**Vasodilator**	**Resistant hypertension, pregnancy induced hypertension**
Minoxidil	Loniten	**vasodilator**	**Resistant hypertension**
Nitroprusside	Nitropress	**Vasodilator**	**Acute Hypertensive crisis**
Captopril	Capoten	**ACE inhibitor**	**1st line drug in chronic hypertension,** used in HF, MI and Diabetes
Enalapril	Vasotec	**ACE inhibitor**	**1st line drug in chronic hypertension, used in HF,**
Lisinopril	Zestril	**ACE Inhibitor**	**1st line drug in chronic hypertension**
Losartan	Cozaar	**ARB**	**1st line drug in chronic hypertension**

ANTI-ANGINAL DRUGS

Date: Friday, November 16, 2012 – 8:30 am
Reading Assignment: Katzung, *Basic & Clinical Pharmacology*, 10th Ed., pp. 147-158; 183-197

KEY CONCEPTS AND LEARNING OBJECTIVES

A. To briefly review the pathophysiological basis for the development of angina pectoris and other ischemic coronary syndromes.
B. To examine the mechanisms by which nitrates, beta-blockers, calcium-channel blockers and ranolazine relieve angina.
C. To briefly discuss nonpharmacological approaches to the relief of angina and other ischemic coronary syndromes.

LIST OF IMPORTANT DRUGS

Organic Nitrates:	Nitroglycerin Isosorbide dinitrate
Calcium Channel Blockers:	Nifedipine Nicardipine Amlodipine Verapamil Diltiazem
Beta Receptor Antagonists:	Propranolol Nadolol Atenolol Metoprolol Carvedilol
pFOX Inhibitor	Ranolazine

ANTI-ANGINAL DRUGS

I. MYOCARDIAL ENERGY BALANCE

A. Oxygen Supply and Oxygen Demand are tightly coupled

B. Oxygen Supply to Myocardium = Myocardial O_2 delivery +Myocardial O_2 extraction

1. Myocardial O_2 extraction nearly maximal at rest (75% of available O_2)
2. Any increase in O_2 supply must occur by increase in O_2 delivery (increased flow)

C. Determinants of Myocardial Blood Flow

1. Diastolic Perfusion Pressure (Aortic Diastolic Pressure - End-diastolic Pressure)
2. Coronary Vascular Resistance (extrinsic compression and intrinsic regulation)

D. Regulation of Coronary Vascular Resistance

1. Mechanical Compression: Majority of blood flow occurs during diastole- compression of intramyocardial blood vessels during systole
2. Metabolic Regulation - increased myocardial work $\Rightarrow$ increased myocardial blood flow
   a) Adenosine
   b) O_2
   c) CO_2
   d) K^+
   e) Lactate
   f) NO_2
3. Neural Regulation
   a) Sympathetic stimulation causes vasoconstriction, but
   b) Sympathetic stimulation also causes increased myocardial work, with increased production of metabolites, and therefore,
   c) *net* effect is VASODILATATION.

II. DETERMINANTS OF MYOCARDIAL OXYGEN CONSUMPTION (DEMAND)

A. Heart Rate

B. Myocardial Wall Stress - LaPlace's Law: σ = Pressure x RADIUS / 2 x thickness

1. Pressure is the Intraventricular Pressure (pressure inside the chamber)
2. Ventricular Volume (Preload) – affects diastolic wall stress
3. Impedence to ejection (Afterload) – affects systolic wall stress

C. Contractility (Force of Contraction)

III. PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA

A. Myocardial Ischemia occurs when O_2 Demand EXCEEDS O_2 Supply

1. Increased Myocardial O_2 Demand in Setting of Fixed Coronary Artery Obstruction
   a) Exercise
   b) Sympathetic Stimulation (emotional stress, fear, drugs)
   c) Arrhythmias (especially tachycardias)

2. Acute Reduction in Coronary Blood Flow

a) Decreased Perfusion Pressure (hypotension)
b) Vasospasm
c) Thrombus/Embolus

B. Hypoxia vs. Ischemia (reduced O_2 vs. reduced flow/increased demand)

C. Cardiac Functional Impairment Caused by Ischemia
1. Decreased LV Compliance (increased myocardial stiffness – Increased LVEDP)
2. Decreased force of contraction - Regional wall motion abnormalities
3. Decreased C.O. in severe or global ischemia
4. Electrical instability (ventricular arrhythmias)
5. Cell Death

D. Ischemia leads to infarction (cell death) if there is an absolute reduction of flow for a sufficient period of time
1. No flow ⇒ Irreversible injury in 30-45 min
2. Marginal flow ⇒ Infarction may not occur for several hours
3. Coronary Collateral Vessels - some degree of protection from ischemia

E. Common Causes of Myocardial Ischemia
1. Atherosclerotic Coronary Artery Disease
2. Severe Aortic Stenosis
3. Severe Hypertension
4. Severe Anemia
5. Congenital Heart Disease

IV. ANGINA PECTORIS – Clinical Manifestation of Myocardial Ischemia

A. Anginal Syndromes – Clinical Presentations
1. Exertional Angina
2. Unstable (Crescendo Angina)
3. "Silent Ischemia"
4. Variant Angina

B. Acute Myocardial Infarction

V. THERAPY OF MYOCARDIAL ISCHEMIA

A. Drug Therapy
1. Organic Nitrates
2. Calcium Channel Blockers
3. Beta Adrenergic Receptor Blockers
4. Ranolazine

B. Coronary Revascularization
1. Percutaneous Coronary Interventions (PCI) – Balloon angioplasty, stenting, atherectomy, etc.
2. Coronary Artery Bypass Grafting (CABG)

from Katzung, 10th Ed. Pg. 185

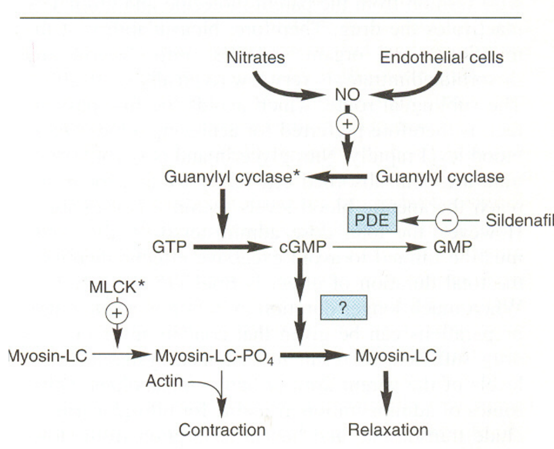


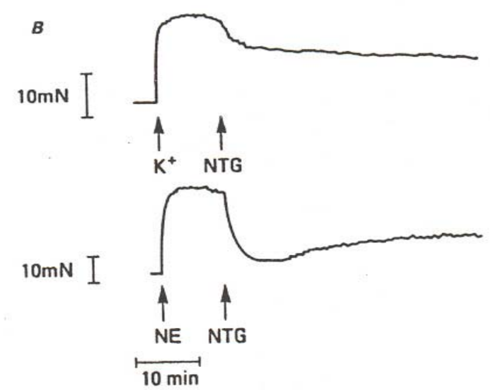
Figure 12–2. Mechanism of action of nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in smooth muscle cells. (MLCK*, activated myosin light chain kinase [see Figure 12–1]; guanylyl cyclase*, activated guanylyl cyclase; ?, unknown intermediate steps. Steps leading to relaxation are shown with heavy arrows.)

VI. ORGANIC NITRATE THERAPY (Rx) for EXERTIONAL and VASOSPASTIC ANGINA

A. Mechanism of Action in Smooth Muscle

1. Organic Nitrates ($R\text{-}O\text{-}NO_2$) combine with cysteine residues (R-SH) in vessel wall to form Nitrosothiols that release Nitric Oxide (NO)
2. NO directly stimulates Guanylyl Cyclase in vascular smooth muscle to produce cGMP
3. cGMP -? activates a cGMP-dependent phosphatase
4. Phosphatase de-phosphorylates myosin light chain leading to smooth muscle relaxation
5. Organic nitrate-induced vasodilatation is ENDOTHELIUM-INDEPENDENT

From Katzung, 10th Ed. Figure 12-3, pg. 187 Effects of nitroglycerin (NTG) on contractions of human vein segments in vitro.



Vein segments denuded of endothelium were first "contracted" with either potassium chloride (K^+) to cause membrane depolarization and calcium influx (upper panel); or with norepinephrine (NE) to cause release of calcium from intracellular stores (lower panel). The veins were then treated with nitroglycerin (NTG), which caused vasodilation.

B. Systemic Effects of Organic Nitrates

1. Dilate venous capacitance vessels and decrease venous return
2. Reduced wall tension and myocardial oxygen consumption
3. Reduced afterload (systemic arteriolar vasodilator)
4. Direct coronary artery vasodilator

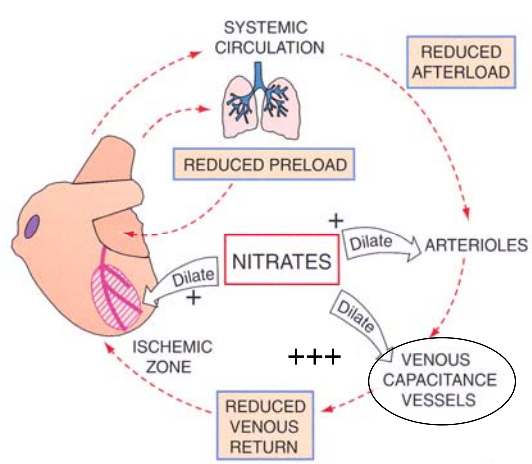
C. Clinical Use of Organic Nitrates

1. Angina Pectoris (Exertional, Unstable, Variant)
2. Hypertensive Emergencies
3. Congestive Heart Failure

D. Most Commonly Used Organic Nitrate Preparations

1. Nitroglycerin
   a) Sublingual

Major Effect of Nitrates is to Dilate Venous Capacitance Vessels



Modified by AMS from Opie and Gersh, *Drugs for the Heart*, 6th edition.

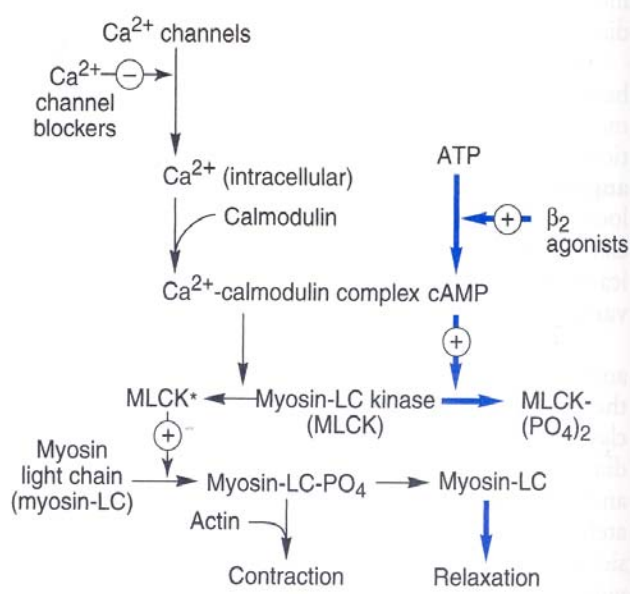
b) Transdermal (ointment, patches)
c) Intravenous
2. Isosorbide dinitrate
a) Sublingual
b) Chewable
c) Oral

E. Nitrate Use in Exertional Angina
1. Terminate exercise-induced myocardial ischemia (Sublingual Nitroglycerin)
2. Prevent exercise-induced myocardial ischemia
a. Sublingual Nitroglycerin
b. Oral isosorbide Dinitrate
c. Nitroglycerin patch or ointment
3. Terminate coronary artery spasm

F. Nitrate Side-Effects
1. Exaggeration of Therapeutic Effects
a) Orthostatic Hypotension
b) Reflex Tachycardia
c) Headache
2. Nitrate Tolerance
a) Repeated exposure to high doses of long-acting nitrates - depletion of cysteine stores?
b) Nitrate-free intervals - reduces tolerance

VII. Ca^{2+} CHANNEL BLOCKERS Rx for ANGINA

A. Mechanism of Action in Smooth Muscle
1. Vascular smooth muscle contraction is highly dependent on $[Ca^{2+}]_i$
2. $[Ca^{2+}]_i$ - Ca influx vs. release of Ca^{2+} from intracellular stores.
3. Vascular smooth muscle cells express L-type Ca^{2+} channels
4. Little or no Ca^{2+} induced Ca^{2+} release in VSM
5. Other ways to increase $[Ca^{2+}]_i$: Release of Ca^{2+} from IP_3-sensitive stores (α_1-adrenergic agonists, endothelin, vasopressin, angiotensin II)
6. $[Ca^{2+}]_i$ rise required for activation of Ca^{2+}-calmodulin dependent Myosin Light Chain Kinase (MLCK)



Katzung, 10th Ed., Fig 12-1, pg. 184.
Cellular actions of calcium channel blockers on smooth muscle

7. Unlike cardiac muscle, myosin phosphorylation is required for activation of smooth muscle myosin ATPase activity
8. Therefore, Ca^{2+} channel blockers reduce $[Ca^{2+}]_i$ entry, and thus decrease $[Ca^{2+}]_i$ preventing smooth muscle contraction.
9. Ca^{2+} channel blockers are potent arteriolar vasodilators, but have little or no effect on venous capacitance vessels.

B. Ca^{2+} channel blockers also affect Ca^{2+} entry in CARDIAC muscle
1. Negative inotropic agents
2. Decrease rate of SA nodal Phase IV depolarization (decrease heart rate)
3. Slow AV nodal conduction velocity

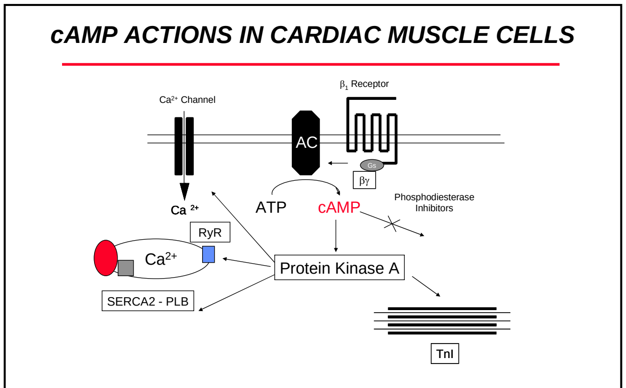
C. Clinical Use of Calcium Channel Blockers
1. Angina Pectoris
2. Hypertension
3. Arrhythmias
4. Hypertrophic Cardiomyopathy
5. Migraine
6. Raynaud's Phenomenon

D. Calcum Channel Blockers for Exertional Angina
1. Dihydropyridines
   a) **Nifedipine** (short acting)
   b) **Nicardipine** (intermediate acting)
   c) **Amlodipine** (long-acting)
2. Phenylalkylamines - **verapamil**
3. Benzothiazepine - **diltiazem**
4. Diarylaminopropylamine ether – **bepridil**

E. Calcium Channel Blocker Characteristics – Systemic Effects
1. Negative Inotropic Effects (decreases myocardial O_2 consumption)
   - Verapamil>diltiazem>nifedipine
2. Negative Chronotropic Effects (decreases myocardial O_2 consumption)
   - Verapamil>diltiazem>nifedipine
3. Vasodilatory Effects (decrease afterload ⇒ decrease myocardial O_2 consumption)
   - Nifedipine>diltiazem>verapamil
4. Dilate coronary vasculature and prevent coronary artery spasm

F. Calcium Channel Blocker Side-Effects
1. Verapamil and Diltiazem
   a) Bradycardia
   b) Heart Block
   c) Congestive Heart Failure
   d) Hypotension
2. Dihydropyridines
   a) Reflex Tachycardia
   b) Peripheral Edema
   c) Hypotension

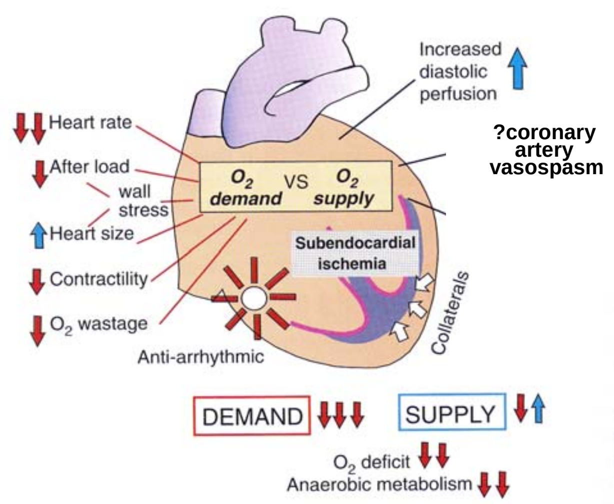
VIII. BETA BLOCKER Rx for ANGINA



AMS Slide. Beta adrenergic receptor activation increases cAMP levels in cardiomyocytes.

A. Beta Receptor Subtypes
   1. β_1 Receptors -Cardiac Muscle
   2. β_2 Receptors
      a) Cardiac muscle
      b) Bronchial Smooth Muscle
      c) Vascular Smooth Muscle

B. Mechanism of Action - Related to Cardiac Effects (not vasodilators)
   1. β_1 adrenergic receptor - present in variety of myocardial cells (conduction system + muscle cells)
   2. Regulates Ca^{2+} influx (L-type Ca^{2+} channels) and Ca^{2+} storage/release by sarcoplasmic reticulum (Ryanodine receptors (RyR) and SR Ca^{2+}ATPase (SERCA2-Phospholamban))
   3. β_1 adrenergic <u>stimulation</u> causes -
      a) Increased heart rate
      b) Increased AV nodal conduction velocity
      c) Increased force of contraction (positive inotropy)
   4. β_1 receptor antagonists therefore **counteract** the effects of sympathetic stimulation on the heart
      a) Decrease HR
      b) Decrease myocardial contractility (i.e., they are negative inotropes)
      c) Decrease mean arterial blood pressure (decrease afterload)
      d) All three interventions markedly decrease myocardial O_2 consumption
   5. Decrease in heart rate increases myocardial O_2 delivery - increased diastolic perfusion time, decreased vascular compression.



Effects of beta blockers O2 supply and demand in the ischemic heart.

Modified by AMS from Opie and Gersh, *Drugs for the Heart*, 6th Edition

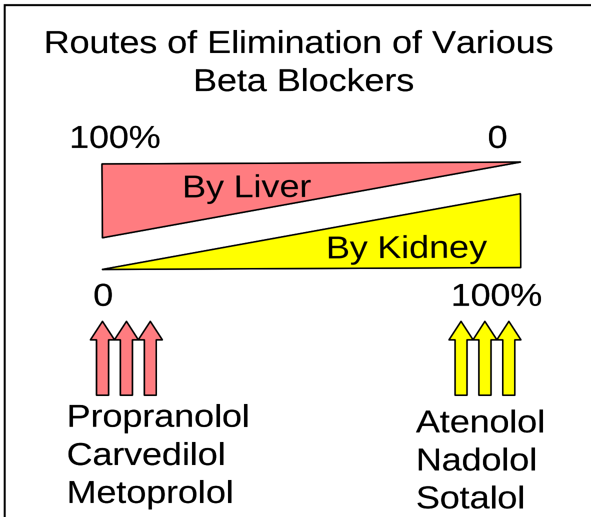
C. Clinical Use of Beta Blocking Agents
   1. Exertional Angina Pectoris
   2. Hypertension
   3. Arrhythmias
   4. Dissecting Aortic Aneurysm
   5. Mitral Valve Prolapse
   6. Post-MI prophylaxis
   7. Hyperthyroidism
   8. Migraine

D. Beta Blocker Characteristics
   1. Cardioselectivity (nonselective vs. β_1 selective)

2. Duration
3. Lipid Solubility
4. Routes of Elimination
5. Intrinsic Sympathomimetic Activity

E. Beta Blockers in Common Use for Exertional Angina
1. Nonselective
    a) Propranolol
    b) Nadolol
2. Cardioselective
    1. Metoprolol
    2. Atenolol
3. Nonselective with Intrinsic Sympathomimetic Activity
    a) Labetalol
    b) Pindolol
4. Cardioselective with Intrinsic Sympathomimetic Activity (Acebutolol)

F. Routes of Elimination: Liver vs. Kidney (see adjacent figure).



Modified by AMS from Opie and Gersh, *Drugs for the Heart,* 6th Edition

G. Beta Blocker Side-Effects
1. Bronchospasm
2. Peripheral vasospasm
3. Exaggeration of cardiac therapeutic effects (bradycardia, heart block, acute CHF)
4. Central nervous system effects (insomnia, depression, fatigue)

H. Relative Contraindications to Beta Blocker Therapy
1. **Acute** congestive heart failure
2. Marked bradycardia (<55 bpm)
3. Advanced heart block (1st, 2nd, 3rd degree)
4. Severe peripheral vascular disease
5. Insulin-dependent diabetes mellitus
6. Sexual impotence
7. Bronchospasm (COPD, Asthma)

IX. RANOLAZINE – A NEW CLASS OF ANTI-ANGINAL DRUGS

A. pFOX inhibitors inhibit mitochondrial enzymes of beta oxidation.
1. Under normal conditions the heart can use either glucose or fatty acids to generate ATP.
2. Metabolism of glucose uses oxygen more efficiently than the metabolism of fatty acids.
3. During acute myocardial ischemia, fatty acids rise precipitously, inhibiting pyruvate dehydrogenase. As a consequence, glucose oxidation is depressed. This is particularly undesirable when oxygen supply is limited as in myocardial ischemia.

4. Ranolazine partially inhibits fatty acid oxidation, allowing the heart to use more glucose as a fuel by relieving the inhibition on pyruvate dehydrogenase.
5. The net result is reduced lactic acid accumulation, less intracellular acidosis, and a reduction in the severity of the myocardial ischemic response.

B. Ranolazine is a relatively new drug - approved by FDA in January, 2006

C. Use originally limited to patients who continue to have angina despite nitrates, beta blockers and calcium channel blockers

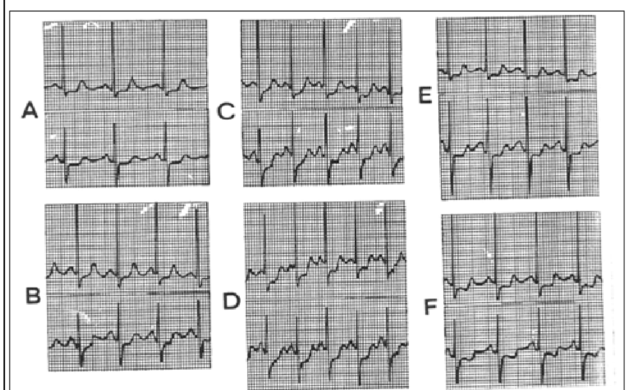
D. Now approved for "first-line" use in exertional angina

E. Electrophysiological Effects – blocks late Na^+ current, prolongs action potential duration (Risk of EADs and Torsades de Pointe)

X. USE OF PHARMACOLOGICAL AGENTS IN PATIENTS WITH ANGINA PECTORIS

A. Double Product
1. Myocardial Oxygen Consumption ~ Heart Rate x Systolic Blood Pressure
2. Improved exercise tolerance as an indicator of drug efficacy

Exercise-Induced ST Segment Depression during Treadmill Test. (from AMS)



A. REST
B. 1 min
C. 2 min (ST depression noted)
D. 3 min
E. 4 min
F. 5 min (Patient complains of chest pain and SOB –test terminated)

B. Symptom-limited Exercise Stress Testing (see adjacent figure)

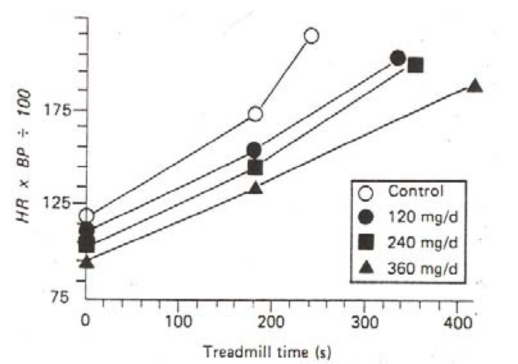
C. How long can a patient exercise before developing signs and symptoms of myocardial ischemia?

D. Development of Angina

E. Development of ST-T wave changes on exercise ECG

F. Effects of Anti-Anginal Drugs on Treadmill Exercise Performance
1. Increased exercise duration
2. Angina and ST segment changes occur at same double product

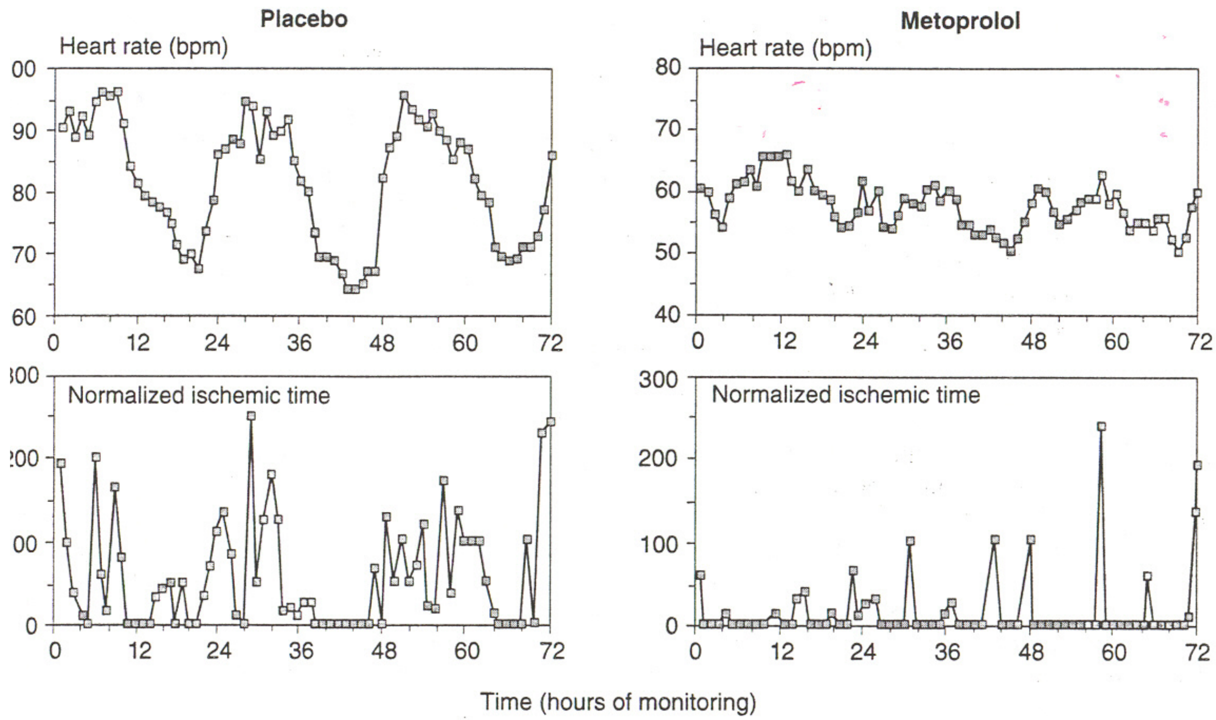
From Katzung,10th Ed., Fig. 12-5, pg. 195. Diltiazam Effects on Exercise Tolerance



G. Benefits of Anti-Anginal Drugs Translate to Activities of Daily Living
1. Less frequent anginal episodes
2. Shorter duration of anginal episodes
3. Increased exercise tolerance

H. Pharmacological Treatment of Exertional Angina
1. Nitrates, Ca^{2+} channel blockers and beta blockers all increase time to onset of angina and ST segment depression in patients with exertional angina

2. Increased exercise tolerance without significant change in angina threshhold (angina occurs at same double product)
3. Nitroglycerin - effective in aborting anginal episode as well as in prophylaxis
4. Long-acting nitrates - prophylaxis of exertional angina
5. Monotherapy vs. Combination therapy
    a) nitrate + beta blocker



From Katzung, 8th Ed., Fig. 12-6, pg. 195. Metoprolol Effects on Heart Rate and Normalized Ischemic Time

    b) nitrate + Ca^{2+} channel blocker
    c) nitrate + Ca^{2+} channel blocker + Beta blocker: reserved for patients with normal LV function, refractory to single or double combination
    d) Beta blocker or verapamil block reflex tachycardia and increased contractile activity associated with nitrates
    e) Beta blocker or Ca^{2+} channel blocker useful in patients with angina and hypertension
    f) Beta blockers contraindicated in patients with ASTHMA, COPD, and **acute** CHF.

I. Pharmacological Treatment of Vasospastic Angina (Prinzmetal's variant angina)
    1. Nitrates and Ca^{2+} channel blockers are much more effective than beta blockers
    2. Revascularization if fixed obstructive lesions also present

J. Pharmacological Treatment of Silent Ischemia
    1. Silent ischemia usually associated with increase in heart rate and BP (increased double product)
    2. Beta blockers particularly effective in reducing total ischemic time

K. Pharmacological Treatment of Unstable Angina

1. Triple drug therapy if tolerated (nitrates, beta blockers, Ca channel blockers)
2. IV nitroglycerin
3. Aspirin and heparin

XI. NONPHARMACOLOGICAL TREATMENT OF ANGINA PECTORIS

A. Exercise Training (“Training Effect”)
B. Percutaneous Transluminal Coronary Angioplasty (PTCA)
C. Coronary Artery Stents
    1. Bare Metal Stents
    2. Drug Eluting Stents
D. Intra-Aortic Balloon Pump (IABP)
E. Coronary Artery Bypass Grafts (CABG)

XII. REVIEW QUESTIONS

1. What are the mechanisms by which organic nitrates decrease the severity of myocardial ischemia?

2. What are the mechanisms by which the calcium channel antagonists decrease the severity of myocardial ischemia?

3. How can a beta-blocker increase blood flow to an area of ventricular muscle supplied by a stenotic coronary artery?

4. Why should nadolol be expected to cause less mental depression and fatigue than propranolol?

5. What would be the hemodynamic effects of the administration of a nitrate in combination with a beta-blocker?

6. Why are "pure" arteriolar vasodilators such as dipyramidole not effective in treating myocardial ischemia?

7. What can be done to minimize nitrate tolerance?

8. What drugs are useful in treating variant angina?

9. What are the major side-effects of nifedipine?

SUMMARY

Drug Class	Indications	Mechanism of Action	Clinical Effect	Adverse Effects	Contraindications
NITRATES *Nitroglycerin* *Isosorbide dinitrate* *Erythrityl tetranitrate*	Exertional angina; Variant Angina; Unstable angina	Reacts with cysteinyl residues in vessel wall to increase the concentration of Nitric Oxide in vascular smooth muscle cells, causing vasodilation, especially of venous capacitance vessels	Terminates episodes of exercise-induced angina; prevents exercise-induced and vasospastic angina	Orthostatic Hypotension; Reflex Tachycardia; Headache; Nitrate Tolerance	Systemic hypotension
CALCIUM CHANNEL BLOCKERS *Nifedipine* *Nicardipine* *Amlodipine* *Verapamil* *Diltiazem*	Exertional angina; variant angina; Unstable angina	Blocks calcium influx via L-type Ca channels in vascular smooth muscle cells and cardiac myocytes, thereby causing vasodilation and decreased contractility	Prevents episodes of exercise-induced and vasospastic angina	Bradycardia; Heart Block; Congestive Heart Failure; Hypotension; peripheral edema; reflex tachycardia (nifedipine)	Advanced heart block; Congestive heart failure; Systemic hypotension
BETA BLOCKERS *Propranolol* *Nadolol* *Atenolol* *Metoprolol* *Carvedilol*	Exertional angina; Unstable angina Post-MI prophylaxis	Blocks β-receptors in cardiac myocytes to reduce contractility	Prevents exercise-induced myocardial ischemia	Bronchospasm; Peripheral vasospasm; Bradycardia; Congestive heart failure; Heart block; Depression, fatigue; blocks sympathetic response to insulin-induced hypoglycemia impotence	Advanced heart block; Acute CHF; insulin-dependent diabetes mellitus; asthma, COPD
RANOLAZINE	Originally indicated for use in patients with chronic stable angina unresponsive to other agents; now approved for initial use in exercise-induced angina	Inhibits fatty acid beta oxidation in cardiac myocyte mitochondria	Chronic exertional angina	Prolongs QT interval	Long QT syndrome; contraindicated for use with other drugs that prolong QT interval.

DRUGS TO TREAT CONGESTIVE HEART FAILURE

Date: Friday, November 16, 2012 – 9:30 am
Reading Assignment: Katzung 12th edition, Chapter 13

KEY CONCEPTS & LEARNING OBJECTIVES:

A. To briefly review the pathophysiological basis for the development of ACUTE congestive heart failure.
B. To examine the rationale for the use of diuretics, inotropic drugs, and vasodilators in the treatment of acute congestive heart failure.
C. To briefly discuss nonpharmacological approaches for the treatment of acute congestive heart failure.
D. To briefly review the pathophysiological basis for the development of ventricular remodeling and CHRONIC congestive heart failure.
E. To examine the rationale for the use of digitalis, diuretics, ACE inhibitors, ARB's, beta blockers and aldosterone antagonists in the treatment of chronic congestive heart failure.
F. To briefly discuss nonpharmacological approaches for the treatment of chronic heart failure

LIST OF IMPORTANT DRUGS

Loop diuretics:	Furosemide
Other Diuretics:	Thiazides Spironolactone Eplerenone
Organic nitrate vasodilators:	Nitroglycerin Isosorbide Dinitrate Nitroprusside
Other vasodilators:	Niseritide Hydralazine
Inotropic agents:	Isoproterenol Dopamine Dobutamine Norepinephrine Digoxin

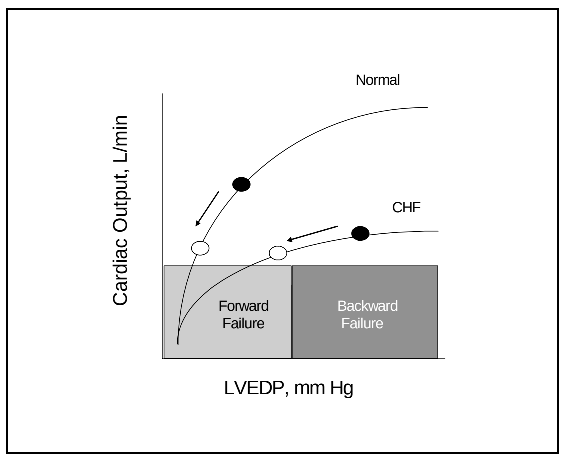
Phosphodiesterase inhibitors:	Inamrinone (aka amrinone) Milrinone
Angiotensin Converting Enzyme (ACE) Inhibitors:	captopril, enalapril, lisinopril
Angiotensin Receptor Blockers (ARB):	losartan, valsartan, irbesartan, candesartan
Other vasodilators:	hydralazine
*Beta-blockers:	carvedilol, metoprolol, bucindolol

TREATMENT OF CONGESTIVE HEART FAILURE

I. CONGESTIVE HEART FAILURE SYNDROMES
- A. Acute Congestive Heart Failure
- B. Acutely Decompensated Chronic Congestive Heart Failure (ADHF)
- C. Chronic Congestive Heart Failure
  - 1. Systolic Heart Failure (Heart Failure with Reduced Ejection Fraction)
  - 2. Diastolic Heart Failure (Heart Failure with Normal or Near-Normal Ejection Fraction)

II. TREATMENT OBJECTIVES IN ***ACUTE*** CONGESTIVE HEART FAILURE
- A. Early recognition and treatment
- B. Decrease symptoms
  - 1. Rapidly reduce pulmonary congestion (reduce preload)
    - a) Diuretics
    - b) Venodilators
    - c) Niseritide
  - 2. Increase forward cardiac output
    - a) Inotropic agents (beta adrenergic agonists; phosphodiesterase inhibitors; digitalis glycosides)
    - b) Arteriolar vasodilators (nitroprusside)

III. DIURETICS
- A. Mechanism of Action in Acute CHF
  - 1. Reduce intravascular volume to reduce filling pressure (preload)
  - 2. Reduce extracellular fluid, thereby reducing edema formation
  - 3. Preload reduction can have little effect on cardiac output in patients with CHF (flat portion of Frank-Starling Curve)



AMS Slide: Frank-Starling Curve in CHF.

- B. Clinical Use in Acute CHF
  - 1. Loop Diuretics (inhibit $Na^+K^+/2Cl^-$ Transporter in the Loop of Henle)
    - a) Furosemide (Lasix®)
    - b) Bumetanide
    - c) Torsemide
  - 2. Thiazide diuretics (inhibit Na^+ and Cl^+ reabsorption in distal tubule) can be added in combination with Loop Diuretics in patients ‘resistant’ to furosemide
    - a) chlorothiazide
    - b) chlorthaladone

- C. Adverse Effects of Diuretics
  - 1. Overdiuresis - can precipitate low output state.
  - 2. Hypokalemia - may precipitate arrhythmias (increased automaticity)

3. Hypokalemia - increases binding of digoxin to Na pump. Potentiates digitalis toxicity
4. Hypomagnesemia
5. Hyperuricemia
6. Ototoxicity (Loop Diuretics)
7. Allergy (Loop and Thiazides are sulfa drugs!)
8. Diuretic resistance-overcome by using combination of diuretics acting at different sites in the nephron

IV. VENODILATORS

A. Organic Nitrates

1. Aim of therapy is to increase venous capacitance and reduce central venous filling pressure (DECREASE PRELOAD).
2. Reduced preload will ultimately reduce pulmonary capillary hydrostatic pressure and filtration of fluid across capillary membrane, thus reducing interstitial edema formation - (i.e., reduce Backward Failure)
3. **Nitroglycerin** (IV, sublingual, topical)
4. **Isosorbide dinitrate** (oral)

B. Niseritide

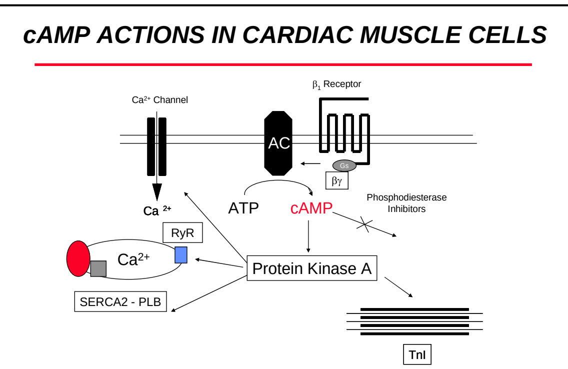
1. Human Recombinant Brain Natriuretic Peptide (hBNP)
2. "Normally" produced by ventricular myocardium in response to "chronic" stretch
3. Activates vascular smooth muscle and renal BNP receptors
4. Raises cGMP levels in VSMC and renal epithelial cells, leading to both vasodilatation (especially of the glomerular afferent arteriole) to increase GFR
5. Induces vasodilatation and natriuresis

V. INOTROPIC AGENTS USED TO TREAT ACUTE CHF

A. Beta-Adrenergic Agonists

1. Mechanism of action

a) Activation of Adenylyl Cyclase, causing increased production of cAMP.
b) cAMP activates Protein Kinase A (PK-A), which phosphorylates key intracellular regulatory proteins.
c) Phospholamban - major target for beta adrenergic effects in cardiac muscle. Phosphorylation de-represses inhibition of SERCA2 (SR Ca Pump).
d) PLB phosphorylation therefore increases SR Ca loading- more Ca for EC coupling.



AMS Slide. Beta adrenergic agonists and phosphodiesterase inhibitors increase cAMP levels in cardiomyocytes, and increase contractility.

e) PK-A also phosphorylates L-type Ca channels, increasing Ca current - more Ca trigger.
f) PK-A also phosphorylates the RyR receptor, altering its gating properties.
g) PK-A also phosphorylates TnI, reducing myofilament Ca sensitivity.

2. Mechanical effects of beta adrenergic agonists
   a) Increased velocity of fiber shortening and force of contraction
   b) Increased ventricular emptying (Stroke Volume increases)
   c) Decreased end systolic and end-diastolic volume
   d) Increased Heart Rate; AV nodal conduction velocity
   e) Increased Myocardial O_2 consumption
3. Systemic effects of beta adrenergic agonists
   a) Increased CARDIAC OUTPUT
   b) Increased renal perfusion
4. Clinical Use of Beta Adrenergic Agonists
   a) Acute Heart Failure following CV surgery
   b) Used in conjunction with arteriolar vasodilators in Acute Mitral Regurgitation and other conditions.
   c) Cardiogenic Shock and other forms of Shock
   d) less useful in Acutely Decompensated Chronic CHF because of down-regulation of cardiac β receptors and toxicity of chronic beta adrenergic stimulation
5. **Isoproterenol** (IV, short half life)
   a) activates cardiac β1 and β2-receptors
   b) Increases heart rate more than contractility (useful in heart block, idioventricular rhythm); not useful in CHF due to ischemic heart disease
   c) Reduces vascular resistance in kidney, skeletal muscle
   d) can produce systemic hypotension
6. **Dopamine**
   a) catecholamine-like IV drug with short half-life
   b) Low doses (0.5-5 μg/kg/min) of dopamine activate cardiac β_1-receptors, releases norepinephrine from sympathetic nerve terminals, and causes renal vasodilatation
   c) High doses (5-10 μg/kg/min) activates α_1-adrenergic receptors and causes vasoconstriction
7. **Dobutamine**
   a) Synthetic analog of dopamine; given IV with short half-life
   b) Directly stimulates β_1-receptors. Increases contractility more than heart rate (opposite of isoproterenol)

B. Phosphodiesterase Inhibitors (**Inamrinone, Milrinone**)
1. Mechanism of Action
   a) Inhibit the degradation of cAMP, thereby increasing cAMP levels in cardiac muscle.
   b) Vasodilators, perhaps by inhibiting degradation of cGMP

2. Systemic Effects of Phosphodiesterase Inhibitors
    a) Increased C.O.
    b) Reduce pulmonary capillary wedge pressure
    c) Reduce peripheral vascular resistance (direct)
    d) No change in heart rate, systolic BP.
3. Clinical Use of Phosphodiesterase Inhibitors
    a) Especially useful in patients with acute decompensation of chronic CHF (ADHF), as drugs bypass β receptor down-regulation.
    b) Can be used in patients who are receiving β-blockers
    c) Oral agent (Milrinone) increased mortality in chronic CHF, probably by increasing frequency of arrhythmias.

C. Digitalis Glycosides

1. Mechanism of Action
    a) Partial inhibition of Na/K ATPase (Sarcolemmal Na Pump)
    b) Increased $[Na^+]_i$ leads to enhanced Na/Ca Exchange
    c) Increased $[Ca^{2+}]_i$ stored in Sarcoplasmic Reticulum
    d) More Ca released from SR stores during each contraction.
2. Mechanical Effects of Digitalis Glycosides on Cardiac Performance
    a) Increased velocity of fiber shortening and force of contraction
    b) Increased ventricular emptying (SV increases)
    c) Decreased end-systolic and end-diastolic volume
3. Systemic Effects of Digitalis Glycosides in CHF
    a) Increased C.O.
    b) Increased renal perfusion
    c) Decreased sympathetic tone (reduced heart rate, vasoconstriction)
4. Parasympathomimetic Effects of Digitalis Glycosides
    a) Sensitizes baroreceptors
    b) Increases central vagal stimulation
    c) Prolongs AV nodal conduction velocity and Effective Refractory Period
5. Direct Electrophysiological Effects of Digitalis Glycosides
    a) Increased Ca causes activation of K conductance
    b) Shortening of AP Duration
    c) Membrane depolarization (Na pump inhibition)
    d) Delayed afterdepolarizations (DAD's) and abnormal automaticity
    e) Digitalis Intoxication - VPBs, V tach, junctional tachycardia, etc.
6. Clinical Use of Digitalis Glycosides
    a) Because of potential for side-effects, digoxin is now primarily used in patients with CHF and Atrial Fibrillation with rapid ventricular response (slows ventricular rate)
    b) DIGOXIN - know your pharmacokinetics!
    c) Incidence of toxicity reduced by frequent measurement of serum levels (Therapeutic range of Digoxin = 1-2 ng/ml; Toxic range >2.5 ng/ml)
    d) Digibind antibodies used to treat digitalis toxicity

VI. OTHER INTRAVENOUS VASODILATORS

A. Nitroprusside

1. effective in acute hypertensive emergencies and severe CHF
2. Rapidly lowers systemic vascular resistance, must be titrated to avoid hypotension
3. Often used in conjunction with dobutamine in acute CHF (cardiogenic shock, acute valve rupture, etc.)
4. Limited by accumulation of cyanide, and thiocyanate (short-term use only)

VII. NONPHARMACOLOGICAL THERAPY FOR ACUTE CHF

A. PCI/Surgical Therapy
   1. Acute Revascularization
   2. Urgent Valve Repair/Replacement

B. Ultrafiltration

C. Intra-aortic balloon pump (IAPB)

D. Ventricular assist devices (VADs)
   1. Impella Percutaneous LVAD
   2. Heartmate (I and II)

VII. TREATMENT OBJECTIVES IN CHRONIC CONGESTIVE HEART FAILURE

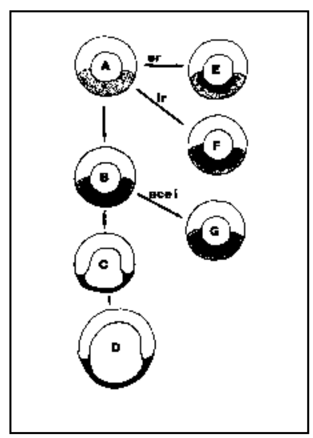
A. Early recognition of ventricular dysfunction even in the ABSENCE of symptoms

B. Prevent Ventricular Remodeling

C. Decrease symptoms once they develop:
   1. Reduce pulmonary congestion
   2. Increase cardiac output
   3. Improve exercise capacity
   4. Increase quality of life

D. Improve survival

VIII. VENTRICULAR REMODELING



A. Post-MI ventricular remodeling

Mitchell and Pfeffer: "LV enlargement and distortion of regional and global ventricular geometry occurring after myocardial infarction."

Whittaker and Kloner: "Any architectural or structural change that occurs after myocardial infarction in either the infarcted or noninfarcted regions of the heart."

Samarel: Hypertrophy and dilatation of noninfarcted segments occurring weeks to years after acute MI.

B. Early Recognition and Treatment of Ventricular Dysfunction

1. Structural changes in the ventricular myocardium *represent* a disease process.
2. Remodeling often *PRECEDES* the development of symptoms of CHF (dyspnea, PND, edema, etc.) by months to years.
3. Remodeling is predominantly a *growth-mediated* response, and results from an interplay between mechanical factors, and systemic and locally derived neurohormonal factors.
4. ***Efforts directed at preventing or slowing the progression of ventricular remodeling will prevent or delay the development of CHF.***

C. Drugs That Prevent or Slow the Progression of Ventricular Remodeling and Improve Survival (Anti-Remodeling Rx)
1. ACE inhibitors (captopril, enalopril, lusinopril)
2. Angiotensin II receptor antagonists (losartan, valsartan, irbesartan, candesartan)
3. Beta blockers (carvedilol, metoprolol, bucindolol)
4. Other vasodilators (hydralazine + isordil)
5. Aldosterone antagonists (spironolactone, eplerinone)

IX. Angiotensin Converting Enzyme (ACE) Inhibitors (**Captopril, Enalapril, Lisinopril)**

A. <u>Mechanism of Action</u> - Block conversion of Ang I to Ang II in lung and other tissues; Also prevents degradation of Bradykinin (kininase inhibitor)
B. Reduce circulating levels of AngII - potent vasoconstrictor
C. Reduce aldosterone secretion by adrenal gland
D. Inhibit local ACE in myocardium, kidneys and blood vessels.
E. Hemodynamic Effects - Decrease Preload + Decrease Afterload
F. Studies in chronic CHF indicate that early use of ACE inhibitors improve symptoms, prevent ventricular remodeling, and prolong LIFE.
G. Now considered **first line** drugs in patients with **chronic CHF**
H. Side effects are due to bradykinin (cough, angioedema).
I. Other side effects include hypotension, impaired renal function, and hyperkalemia.

X. ANGIOTENSIN II RECEPTOR ANTAGONISTS (ARBs) (**Losartan, Valsartan, Irbestartan, Candesartan**)

A. Newer agents, selective AT_1 receptor blockers
B. Unlike ACE inhibitors, they do not prevent bradykinin degradation
C. Used in patients intolerant to ACE inhibitors

XI. BETA BLOCKERS in CHRONIC CHF

A. Recent clinical trials have shown that beta blockers (given in addition to digoxin, diuretics and ACE inhibitors) increase survival and prevent deterioration of LV performance over time in patients with mild-moderate chronic CHF.
B. <u>Mechanism of Action</u> - Thought to involve reduction in heart rate and prevention of deleterious effects of chronic sympathetic stimulation
1. Prevents activation of the "fetal gene program" (ie., prevents downregulation of αMHC, SERCA2a)
2. Prevents SR Ca Leak
3. Prevents beta receptor down-regulation

4. Prevents myocardial apoptosis
5. Decreases structural LV remodeling

C. Must be used with caution – Beta blockers can precipitate worsening of CHF symptoms

D. Specific Agents
1. **Carvedilol** (combined α_1 and nonselective beta blocker)
2. **Metoprolol** (selective β_1 receptor antagonist)
3. **Bucindolol** (combined α_1 and nonselective beta blocker)

XII. ALDOSTERONE ANTAGONISTS in CHRONIC CHF (**spironolactone, eplerinone**)

A. Aldosterone antagonists are Diuretics – inhibit aldosterone effects on distal tubule (prevent Na+ and H_2O reabsorption).

B. Aldosterone has other important roles in the pathophysiology of heart failure.
1. Promotes sympathetic activation
2. Promotes parasympathetic inhibition
3. Stimulates myocardial and vascular fibrosis
4. Causes baroreceptor dysfunction
5. Impairs arterial compliance

C. RALES Trial – tested effect of adding spironolactone to ACE inhibitor, loop diuretic, and digoxin on long-term outcome in patients with chronic CHF.

XIII. RATIONALE FOR DRUG THERAPY IN SYMPTOMATIC, CHRONIC CHF

A. Similar to Acute CHF, but limited to oral agents

B. Reduce pulmonary congestion and edema formation
1. Loop Diuretics
2. Thiazides
3. Aldosterone antagonists
4. Venodilators (ACE inhibitors, ARBs, nitrates)

C. Increase Cardiac Output
1. Increase Contractility - (Digoxin)
2. Reduce Afterload (ACE inhibitors, ARBs, hydralazine)

XIV. INOTROPIC AGENTS IN CHRONIC CONGESTIVE HEART FAILURE

A. Currently limited to oral Digoxin (partial Na^+K^+ ATPase inhibitor)
1. Digoxin has no effect on survival in patients with chronic CHF
2. Very narrow therapeutic window

B. Other inotropic agents not currently approved by FDA:
1. Ca^{2+} sensitizers: levosimendan
2. Myosin activators
3. Oral phosphodiesterase inhibitors: milrinone–increased mortality in Phase III

XV. OTHER ORAL VASODILATORS

A. Selective Arteriolar Vasodilators (e.g., **Hydralazine**)
1. Reduced systemic vascular resistance
2. Increase forward C.O. (reduced afterload)

3. The magnitude of reduction in vascular resistance is GREATER than the decrease in mean arterial blood pressure - increased output maintains the arterial pressure.
4. Particularly useful in patients with hypertension and CHF.
5. Used in combination with organic nitrates
6. Ca Channel blockers - although they are potent arteriolar vasodilators, they are CONTRAINDICATED IN CHRONIC CHF BECAUSE OF NEGATIVE INOTROPIC EFFECTS

B. Venodilators

5. Aim of therapy is to increase venous capacitance and reduce venous filling pressure (DECREASE PRELOAD). This will reduce capillary hydrostatic pressure and filtration of fluid across capillary membrane, thus reducing interstitial edema formation - (Backward Failure)
6. **Isosorbide dinitrate** (oral)
7. **Nitroglycerin** (patch, topical ointment)

XVI. NONPHARMACOLOGICAL THERAPY FOR CHF

A. Revascularization for Chronic Ischemic Heart Disease
B. Valve Repair/Replacement for Chronic Valvular Heart Disease
C. Aneurysmectomy
D. Left ventricular assist devices (LVADs)
    1. Bridge to Transplant
    2. “Destination Therapy”
E. Biventricular pacing (“Cardiac Resynchronization Therapy” or “CRT”) and implantable cardioverter defibrillators (ICDs)
F. Cardiac Transplantation

XVII. REVIEW QUESTIONS

1. What is the rationale for using arteriolar vasodilators to treat acute CHF?

2. How does intravenous nitroglycerin decrease pulmonary edema in acute CHF?

3. What is the goal of diuretic therapy in acute CHF?

4. Why do inotropic drugs like dobutamine cause an increase in urine output in acute CHF?

5. What are the hemodynamic effects of dopamine and how do they differ from the effects of dobutamine?

6. How is niseritide beneficial in acute decompensation of chronic congestive heart failure?

7. Why is inamrinone given to patients who are refractory to dobutamine?

8. What is the mechanism by which digoxin increases cardiac contractility?

9. What are the beneficial effects of digoxin on the autonomic nervous system in CHF?

10. What is the rationale for using arteriolar vasodilators to treat chronic CHF?

11. How does captopril decrease pulmonary edema formation in chronic CHF?

12. What agents have been proven to improve **survival** in chronic CHF?

13. How would nitroglycerin be beneficial in chronic CHF?

14. Why are beta-blockers given to patients with chronic CHF?

15. What is meant by the term "Destination Therapy"?

SUMMARY – Drugs to treat Acute CHF and ADHF

Drug Class	Indications	Mechanism of Action	Clinical Effect	Adverse Effects	Contraindications
DIURETICS *Furosemide*	Reduce intravascular volume thereby reducing filling pressures; reduce extracellular fluid thereby reducing pulmonary and peripheral edema formation	Inhibits Na reabsorption by the Na/K/Cl transporter in the Loop of Henle	Diuresis	Overdiuresis; Hypomagnesemia; Hypokalemia, Hyperuricemia; Ototoxicity; Allergy Diuretic resistance	Electrolyte imbalances, volume depletion
NITRATES *Nitroglycerin* *Nitroprusside*	Reduce preload by causing vasodilation of venous capacitance vessels; Reduce afterload	Reacts with cysteinyl residues in vessel wall to increase the concentration of Nitric Oxide in vascular smooth muscle cells, causing vasodilation	Decrease filling pressures, decrease arterial blood pressure	Hypotension; Reflex tachycardia; Methemoglobinemia; Nitrate tolerance	Systemic hypotension
NISERITIDE	Acutely decompensated chronic congestive heart failure in hospitalized patients	Activates vascular smooth muscle and renal BNP receptors; raising cGMP levels in VSMC and renal epithelial cells	vasodilatation (especially of the glomerular afferent arteriole) to increase GFR; Induces vasodilatation and natriuresis	Hypotension, ventricular arrhythmias	Reduced LV filling pressures; systemic hypotension
BETA ADRENERGIC AGENTS *Isoproterenol* *Dopamine* *Dobutamine* *Norepinephrine*	Low cardiac output due to acute CHF; cardiogenic shock	Stimulates cardiac beta adrenergic receptors to increase myocardial cAMP	Increased heart rate, increased contractility, increased cardiac output	Arrhythmias; increased myocardial O_2 consumption, angina, vasoconstriction (norepinephrine)	Ventricular arrhythmias; severe peripheral vascular disease
DIGOXIN	Acute CHF; Atrial fibrillation with rapid ventricular response	Partially inhibits NaK ATPase, thereby increasing reverse-mode NaCa exchange and increasing SR Ca stores	Increased contractility; decreased AV node conduction velocity	Arrhythmias; heart block; anorexia; nausea, vomiting	Hx of VT/VF, hypokalemia
PHOSPHO-DIESTERASE INHIBITORS *Inamrinone* *Milrinone*	Acutely decompensated chronic congestive heart failure in hospitalized patients, esp. those on beta blockers	Inhibit the degradation of cAMP in cardiomyocytes, thereby increasing cAMP levels in cardiac muscle; Inhibit the degradation of cGMP in vascular smooth muscle, thereby inducing vasodilation	Increased contractility; vasodilation; increased cardiac output	Arrhthmias; hypotension	

SUMMARY – Drugs to Treat Chronic CHF

Drug Class	Indications	Mechanism of Action	Clinical Effect	Adverse Effects	Contraindications
DIGOXIN	chronic CHF; Atrial fibrillation with rapid ventricular response	Partially inhibits NaK ATPase, thereby increasing reverse-mode NaCa exchange and increasing SR Ca stores	Increased contractility; decreased AV node conduction velocity	Arrhythmias; heart block; anorexia; nausea, vomiting	Hx of VT/VF, hypokalemia
DIURETICS *Furosemide* *Thiazides* *Spironolactone* *Eplerinone*	Chronic CHF	Furosemide: Inhibits Na reabsorption by the Na/K/Cl transporter in the Loop of Henle Thiazides: Inhibit Na reabsorption in distal tubule Spironolactone/ Eplerinone: Antagonizes effects of aldosterone in distal collecting duct	Diuresis; Reduce intravascular volume thereby reducing filling pressures; reduce extracellular fluid thereby reducing pulmonary and peripheral edema formation; Prevent LV remodeling and fibrosis (spironolactone, eplerinone)	Furosemide: Overdiuresis; Hypomagnesemia; Hypokalemia, Hyperuricemia; Ototoxicity; Allergy Diuretic resistance Thiazides: Hyperuricemia, hypercalcemia; Allergy Spironolactone: Hyperkalemia; gynocomastia	Electrolyte imbalances, volume depletion
ACE INHIBITORS *Captopril* *Enalopril* *Lisinopril*	Chronic CHF	Blocks conversion of Angiotensin I to angiotensin II in lungs and other tissues	Reduces preload by causing vasodilation of venous capacitance vessels; Reduces afterload; prevents LV remodeling	Hypotension Cough	Systemic hypotension
ANGIOTENSIN II RECEPTOR BLOCKERS *Losartan* *Valsartan* *Irbesartan* *Candesartan*	Chronic CHF, especially in patients intolerant to ACE inhibitors	Blocks AT1a receptors in vacular smooth muscle and cardiac myocytes	Reduces preload by causing vasodilation of venous capacitance vessels; Reduces afterload; Prevents LV remodeling	Hypotension	Systemic hypotension
BETA ADRENERGIC BLOCKING AGENTS *Carvedilol* *Metoprolol* *Bucindolol*	Chronic CHF	Blocks beta adrenergic receptors on cardiac myocytes	Decreased heart rate, Decreased myocardial damage due to chronic sympathetic stimulation; prevents LV remodeling	Worsening CHF; Bradycardia; Heart block; Depression; bronchospasm; peripheral vasospasm	Acute exacerbation of chronic CHF, asthma, COPD, insulin-dependent diabetes mellitus