

PCOL425 Exam Review: December 5, 2008

DRUG-RECEPTOR INTERACTIONS

Know general characteristics of signal-transducing receptors

- Bind to a ligand (drug or endogenous molecule)
- Participate in a signaling cascade
- Distinguish from non-receptor-mediated drug action
- Graded or Dose-Response effects (vs. all-or-none)

Understand “occupational theory” of drug action

- Molecular basis (ligand-receptor interaction)
- Mathematical description
 - Occupational theory: $\text{Response} = \text{Max Response} * [D]/(Kd + [D])$
 - Shapes of dose-response curves
- Significance of Kd
 - ligand dissociation constant
 - half-max binding when $[D] = Kd$

Understand the difference between Potency and Efficacy

Know the general mechanism of drug-receptor interaction, and recognize dose-response curves for:

- Agonists
- Antagonists
 - Competitive
 - Non-competitive
- Partial Agonists
- Inverse Agonists

Biochemical Classification of Receptors: Know the general characteristics and mechanism of action for:

- Membrane-bound receptors
 - G protein-coupled
 - Ligand-regulated ion channels
 - Tyrosine Kinase-linked
 - Guanyl cyclase-linked

(Know some specific examples of each type)

- Cytosolic/nuclear “soluble” receptors

Understand basic mechanisms of receptor regulation

- Desensitization, homologous or heterologous
- Spare receptors

Overview of Autonomic Pharmacology

Pharmacological (not anatomical) Division of PNS: Cholinergic vs. Adrenergic

Cholinergic: All preganglionic and parasympathetic postganglionic Acetylcholine is the neurotransmitter at ganglia, nmj, and muscarinic tissue synapses

Adrenergic: Postganglionic sympathetic neurons (most). Norepinephrine is the transmitter

Exceptions:

Cholinergic transmission in sympathetic system - all ganglia, adrenal medulla, sweat glands (muscarinic)

Dopaminergic innervation in sympathetic system - renal blood vessels

Important steps of Neurotransmission: Synthesis, storage, release, recognition, and metabolism.

Know where drugs can intervene, and what are the differences between cholinergic and adrenergic systems in terms of these 5 steps.

Cholinergic Neurons: Rate limiting step is choline transport into neurons. Most important mechanism of degradation is AchE

Adrenergic Neurons: Know the enzymes involved in synthesis and degradation. Use of VMA in 24-hr urine for diagnosis of pheochromocytoma (how does it work). Uptake is one of the many mechanisms for removal of released NE. Negative feedback by an autoreceptor (what is this).

Receptor Functions

Agonistic vs antagonistic

Direct-acting vs. indirect-acting (e.g. inhibition of AchE has same effect as Ach overdose)

Know for major organ systems which type of innervation predominates and what its effect is. If both types are present, know their opposite effects. 1) Eye 2) Heart 3) Vascular smooth muscle 4) Bronchial smooth muscle 5) GI tract 6) Genitourinary tract 7) Glands (sweat, salivary) [remember: "Flight or Fight" vs. "Rest and Digest"]

If you know the predominant innervation of the systems above, you will be able to predict the physiological consequences resulting from pharmacological activation or blockade of adrenergic or cholinergic receptors.

"Functional types" of cholinergic synapse/receptors: Muscarinic receptors at end organ (G-

protein linked receptors) Nicotinic receptors at nmj, ganglia (ion-channel linked receptors)

Activation of Muscarinic receptors causes DUMBELS syndrome: Defecation, Urination, Miosis, Bronchoconstriction, Emesis, Lacrimation, Salivation

Activation of adrenergic receptors causes different effects: Relative potency of Epi, NE, and Isoproterenol. Know the major difference between $\alpha 1$ and $\alpha 2$ receptors. Know how different tissue distribution results in different effects: $\beta 1$ (heart), $\beta 2$ (blood vessels), and $\beta 3$ (adipose tissue).

CHOLINERGIC NEURONS

Acetylcholine is the transmitter; know its synthesis and breakdown

Activity terminated by hydrolysis of transmitter by AchE

Know the 2 “functional types” of cholinergic synapse/receptors

Muscarinic receptors at end organ (G-protein linked receptors)

Nicotinic receptors at nmj, ganglia (ion-channel linked receptors)

Both types activated by acetylcholine and its stable ester analogs

(bethanachol, carbachol)

(Why is Ach not an effective drug?)

Know the physiological consequences of activation of Muscarinic receptors

Drop in blood pressure due to activation of non-innervated muscarinic receptors causing NOS release and relaxation in vascular smooth muscle

often accompanied by reflex tachycardia

Useful muscarinic agonists - pilocarpine (glaucoma), bethanechol (bladder or gi atony)

Inhibition of AchE has the same effect as Ach “overdose” (prolongs its action at the synapse)

types of Ach inhibitors - reversible (eg Neostigmine, Physostigmine)

irreversible (organophosphate pesticides and nerve gasses)

Effects - primarily muscarinic (dumbels syndrome); nicotinic effects (ganglionic and nmj) only at high doses

Death can be caused by respiratory insufficiency (bronchoconstriction, secretion, central depression, depolarizing ganglionic blockade)

Antidotes - Atropine -blocks muscarinic end-organ effects

Pralidoxime - reactivates AchE

Clinical uses of AchE inhibitors (reversible): glaucoma, myasthenia gravis, atropine poisoning, Alzheimers disease (semi-experimental)

Muscarinic Antagonists: Atropine, scopolamine

autonomic effects: tachycardia, pupil dilation, cycloplegia, loss of secretion, bronchodilation (once used as antiasthmatic) vasodilation, decreased gut motility

central effects: hallucination, delirium, treat motion sickness (scopolamine)

Antidote to atropine poisoning: Physostigmine (penetrates CNS)

Atropine useful in treating poisoning due to AchE inhibition

Ganglionic Blockers (Antinicotinic)

Competitive inhibitors - Mecamylamine and Trimethaphan

These do not affect muscarinic or NMJ nicotinic receptors

Originally used vs hypertension (vasodilation due to interruption of sympathetic vascular tone), Trimethaphan used in extreme emergency (dissecting Aortic aneurism), but not otherwise useful due to multiple, often unpredictable side effects (global ganglionic blockade)

Nicotine will initially stimulate postsynaptic ganglionic nicotinic receptors (agonism), producing sympathetic effects in the cardiovascular system and parasympathetic effects in the gut; however, it is not hydrolyzed by AchE and a depolarizing ganglionic blockade (antagonism) results with complex effects

Neuromuscular Blockers (Antinicotinic) act at NMJ

Competitive (non-depolarizing) blockers: Tubocurarine, pancuronium, vecuronium

Useful for producing skeletal muscular paralysis during surgery

Have some antiganglionic and antivagal (muscarinic) side effects

Depolarizing blocker: succinylcholine

activates nicotinic receptor (initial fasciculations), then repolarization is inhibited and blockade results

Also useful in surgery due to rapid onset; beware of genetic defect in serum esterase (greatly prolonged paralysis)

ADRENERGIC NEURONS

Norepinephrine is the main transmitter; epinephrine is a “long distance” transmitter
also dopamine

Know important steps in adrenergic transmitter (catecholamine) metabolism:

Synthesis, vesicular uptake and storage, triggering of release, release, activation of postsynaptic receptors, activation of presynaptic receptors, uptake, catabolism

Know examples of drugs that can affect each of these steps

Subtypes of postsynaptic (and presynaptic) receptors: alpha 1 and 2, beta 1 and 2 (and 3), dopaminergic;

Important sites of alpha 1 receptors - vascular smooth muscle, iris radial muscle, piloerector muscle

alpha 2 - presynaptic terminals (feedback) Platelets

beta 1 - heart

beta 2 - bronchial smooth muscle, uterus, liver (glycogenolysis)

dopaminergic - renal vascular smooth muscle

Know relative selectivity of drugs (adrenergic agonists and antagonists) for alpha and beta receptors

for beta agonists and antagonists, know relative selectivity for beta 1 and beta 2

Know effects of alpha and beta activation and blockade on following systems:

Vascular smooth muscle, peripheral resistance

Heart, cardiac output (also reflex- know this pathway)

Bronchial smooth muscle

Eye (adrenergic, radial muscle, Dilation, myDriasis)

Uterus

Indirect Acting Drugs:

Acting on Metabolism: Metyrosine, Tyramine, Phenelzine, alpha methyl dopa

Acting on release: Amphetamine, guanethidine, bretylium

Acting on vesicular transport and storage: reserpine

Acting on uptake: Cocaine, imipramine

alpha 2 agonists: clonidine

Cardiovascular Pharmacology

DIURETICS

Focus on the following points:

- Definition of diuretics and the purposes of diuretic therapy.
- Please remember the table of different types of diuretics: types, examples, sites and mechanisms of action.
- Several diuretics are sulfonamide derivatives.
- Major clinical indications of each types of diuretics, particularly those explained by their mechanism of action.
- Side effects of each types of diuretics related to their mechanisms of action. Particularly pay attention to the distortion of water and electrolyte balance.
 - Carbonic anhydrase inhibitors inhibit carbonate reabsorption and proton excretion.
 - Osmotic diuretics inhibit reabsorption of water by osmotic force. It also expand volume of extracellular compartment and may increase heart burden.
 - Loop diuretics inhibit the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ symport in thick ascending limb of loop of Henle.
 - There are two types of loop diuretics (example: furosemide and ethacrynic acid).
 - Loop diuretics inhibit reabsorption of most ions in the tubular fluid.
 - The difference between loop diuretics and thiazide diuretics.
 - Thiazide use and mechanism of action.
- Difference between potassium-sparing diuretics and other diuretics.
- Different types of potassium-sparing diuretics and their use.
- Drug interaction between diuretics and between diuretics and other drugs.

CALCIUM ANTAGONISTS.

Intracellular calcium concentration is tightly control by a number of mechanisms, including Ca^{2+} ATPase, Na^+ -driven Ca^{2+} antiport, compartmentalization of calcium into mitochondria, and Ca^{2+} sequestering compartment, and inactivation of free calcium by Ca^{2+} binding proteins.

Ca^{2+} entry into the cell occurs via receptor-dependent entry via voltage-dependent Ca^{2+} channels. There are three major types of voltage-dependent Ca^{2+} channels: L-type, long lasting, T-type, transient, and N-P-type.

Alpha subunit of L-type Calcium channel is a major target of Calcium Antagonists.

Molecular biological studies of alpha subunit of L-type Ca channels determined domains responsible for channel inactivation, excitation/contraction coupling, voltage sensing, and binding sites of three major group of Ca antagonists:

NIFEDIPINE, VERAPAMIL, AND DILTIAZEM.

Ca antagonists reduce probability of Ca^{2+} channel opening.

Ca antagonists selectively interact with L-type channels in vessels and heart.

As a result of vascular selectivity, Ca antagonists increase coronary perfusion that leads to

improved oxygen supply. They also decrease peripheral vessel resistance that leads to decrease in blood pressure. Together, these effects result in improved heart performance.

Because of their properties, Ca antagonists are used in treatment of angina and hypertension. Verapamil and diltiazem that have selectivity to sino-atrial node can be used in treatment of supraventricular dysrhythmia.

New calcium antagonists have selectivity toward T-type calcium channels. They do not have negative inotropism; they do not have sympathetic activation. They can reduce heart rate, they are highly selective towards coronary vessels, they have minimal side effects.

ACE Inhibitors

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The human body synthesizes hundreds of biologically active peptides that can interact with or affect the function of all organ systems in normal and pathological conditions.

Peptide Hormone Synthesis:

- All peptide hormones are synthesized as large precursor molecules
- Proteolytic processing (usually two steps) is required to generate the active peptide

Regulation of Peptide Hormone Activity:

-Peptide activity is regulated primarily by proteolytic cleavage by peptidases, many of which reside on the cell surface.

Cleavage of a peptide bond in a peptide hormone can result in activation, inactivation or modulation (i.e., altering the receptor specificity of a peptide)

Approaches in Designing Therapeutic Agents Targeting Peptide Hormones:

- Use peptides
- Advantages: Potent; A variety of biological activities; Readily synthesized
- Disadvantages: Rapidly degraded; excreted by kidney; short action; poorly absorbed; inconvenient administration; expensive to synthesize
- Block the degradation of an endogenous peptide by peptidase(s) (ACE inhibitors work here)
- Use an antagonist for a peptide receptor
- Block the synthesis/processing of the peptide (ACE inhibitors work here)

Angiotensin I Converting Enzyme:

- Plasma membrane bound facing extracellular space
- Highly expressed in endothelial cells
- Contains two homologous active site domains
- Typically cleaves a dipeptide from the C-terminus of peptide hormones
- Despite its name, can cleave a variety of peptides in addition to angiotensin I

ACE Inhibitors:

- Highly successful drugs – 10 approved in the US
- Effective for treatment of hypertension, congestive heart failure and diabetic nephropathy

- Also preventive agents in heart attacks or in patients at risk for cardiovascular disease or diabetes; effects that go beyond antihypertensive activity.
- Classical mechanism: inhibit conversion of angiotensin I to II and block bradykinin degradation
- Cause a decrease in systemic vascular resistance, increase in sodium excretion (decreased blood volume) and decrease stress or reflex-induced sympathetic stimulation
- No change in heart rate
- Side effects: dry cough, angioneurotic edema, developmental defects in 2nd or 3rd trimester of pregnancy.
- Some therapeutic and side effects may be due to inhibition of degradation of other peptides or novel actions

DRUG TREATMENT OF HEART FAILURE

Understand the two major therapeutic issues in CHF: Volume control and cardiac contractility

volume control

(diuretics, ace inhibitors, natriuretic peptide)

Know the key role of angiotensin

Why is control of volume and afterload one key to controlling symptoms of CHF?

Positive Inotropic agents

- used in conjunction with diuretic agents, ACE inhibitors, vasodilators
- increase cardiac output (at constant preload and heart rate)
- increase intrinsic contractility of heart

Why is enhancement of cardiac contractility one key to controlling symptoms of CHF?

Cardiac glycosides

- increase cardiac contractility by direct action on cardiomyocyte
- (Na,K)-ionic pump is receptor for cardiac glycoside
- *digoxin* and *digitoxin* are commonly used glycosides
- antiarrhythmic action against supraventricular arrhythmia: slowing of A-V conduction (negative dromotropic effect)
- negative chronotropic action: due to reflex bradycardia (vagal effect)
- *indications*: for use in low output heart failure particularly when atrial arrhythmias are present
- digitalis toxicity: ventricular tachyarrhythmias; gastrointestinal upset; CNS symptoms such as dizziness, convulsion

Other inotropic agents

dobutamine

PDE (phosphodiesterase) inhibitors

amrinone

milrinone

Secondary drugs:

vasodilators

beta blockers

What is the rationale for these?

ANTIARRHYTHMIC AGENTS

There are four classes of antiarrhythmic drugs. Note that side effects of overdoses of these drugs is often arrhythmia.

- Group I: Na channel blockers. Useful for treatment of ventricular tachyarrhythmia and occasionally atrial tachyarrhythmia
- Group II: Beta-adrenoceptor blockers. Useful against supraventricular tachyarrhythmias.
- Group III: Action potential prolonging agents. Used against ventricular arrhythmias due to reentry circuits. *Bretyllium* is a 'chemical defibrillator'.
- Group IV: Calcium channel blockers. Highly effective in treatment of supraventricular tachyarrhythmias.

ANTIANGINAL AGENTS

These substances are for symptomatic treatment of angina

Know the three basic mechanisms of anti-anginal drugs:

- *Nitrates and nitrites*. Mechanism of anti-anginal effect: Nitroglycerin and related substances restore oxygen supply-demand balance through redistribution of coronary flow, reductions in preload, afterload, and total peripheral resistance.
- *Beta-adrenoceptor blockers* reduce cardiac contractility and heart rate by antagonizing beta-effects of endogenous catecholamines, thus resulting in diminished myocardial oxygen consumption.
- *Calcium channel blockers* reduce afterload and thereby decrease oxygen demand of the heart.

OVERVIEW OF ANTIHYPERTENSIVE DRUGS

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Know classification of antihypertensive drugs (AHDs) based on their mechanisms.

Think about how blood pressure (BP) is maintained:

BP = cardiac output (CO) x peripheral vascular resistance (PVR). Therefore, the anatomical sites of action for these drugs are heart, kidney, blood vessels, and part of the brain.

Why diuretics have been used as first-line AHDs? How are they further divided into 3 groups based on mechanisms of action? Know why they are useful when combined with several other AHDs.

α -agonists and blockers:

Know the difference between α_1 and α_2 adrenergic receptors. What are the sites of actions? Know how centrally acting AHDs work and what are the common adverse effects.

Know the basic mechanism of peripherally-acting AHDs is to block one or more key steps of sympathetic neurotransmission. Examples:

- β -blockers: To antagonize β_1 and/or β_2 -AR, therefore reduce CO and PVR.
- α_1 -blockers: To antagonize α -AR and reduce PVR.
- Ganglion-blockers: To block both sympathetic and parasympathetic ganglia, and nicotinic cholinergic receptors on postganglionic neurons.
- Blocking adrenergic neurotransmitter synthesis (reserpine) and release (guanethidine): The net effect is depletion of NE and reduced PVR and CO.

For direct vasodilators, know their clinical usage and their action mechanisms. Why these are not commonly used as first-line drugs?

Know how ACE inhibitors and angiotensin-II receptor antagonists work. What is the major difference between these two drugs in their action? What are the major adverse effects?

Know why more than one drug is often given to patients with moderate or high level of hypertension. Give several examples for the benefit of combined use of AHDs.

What kind of medications should be avoided if a patient is to take AHDs (sort out by different categories of AHDs)?

ANTI-ANEMIA DRUGS

Anemia caused by impaired production of red blood cells (rbc) can be categorized into:

Aplastic anemias
Megaloblastic anemias
Hypochromic anemias

Hypochromic anemias - microcytic rbc; **iron** deficiency

Iron absorption: Absorbed from food through the mucosa of duodenum and jejunum
 Transported in blood by as an iron-transferrin complex
 Endocytosed through the transferrin receptor on target cells
 Heme iron >>> non-heme iron
 Ferrous salts >>> ferric salts

Cause of iron deficiency: Dietary insufficiency
 Blood loss
 Interference of iron absorption

Treatments:

Oral therapy: Ferrous sulphate; administered when fasting
Parenteral therapy: iron dextran; intramuscular or intravenous injections

Megaloblastic anemias - macrocytic rbc; **vitamin B12 or folate** deficiency

Interrationships of vitamin B₂ and folate metabolism - methyltetrahydrofolate donates its methyl group to vitamin B₁₂. The active metabolite N^{5,10}-methylenetetrahydrofolate supports the conversion of dTMP to dUMP for DNA synthesis.

Vitamin B₁₂ absorption: Released from food particles and binds to Intrinsic Factor
 Absorbed through the mucosa of ileum
 Transferred in blood in a complex with transcobalamin II
 Uptake by target cells or by the liver

Cause of vitamin B₁₂ deficiency: Dietary insufficiency
 Deficiency of Intrinsic Factor (Addisonian pernicious anemia)
 Damage to the ileal mucosa
 Deficiency of Transcobalamin II (very rare)

Treatments: Oral preparations to supplement deficient diet
 Cyanocobalamin injection for problems with absorption

Folate absorption: Reduced and methylated
Absorbed through the mucosa of duodenum and jejunum
Transported in blood as tetrahydrofolate to target cells or to the liver
Enterohepatic cycle of folate for reabsorption

Cause of folate deficiency: Dietary insufficiency; malnutrition and alcoholism
Damage of the small intestine

Treatments: Oral preparations
Folic acid injections

Aplastic anemias - disturbed stem cell kinetics

Erythropoietin: Growth factor to stimulate red cell production
Produced primarily by the kidney

Recombinant erythropoietin is administered parenterally to treat anemia in anephric patients.

Myeloid Growth Factors:

GM-CSF: granulocyte/macrophage colony-stimulating factor

G-CSF: granulocyte colony-stimulating factor

Treatments of neutropenia

ANTI-THROMBOTIC DRUGS

Hemostasis and thrombosis involve: Blood coagulation
Platelet aggregation

The basis of therapy of thrombosis: Anticoagulants
Anti-platelet drugs
Plasminogen activators

Anticoagulants and anti-platelet drugs - to prevent the formation of thrombi
Plasminogen activators - to lyse existing thrombi

Anticoagulants:

Heparin

Mechanism of action: Negatively charged and binds to lysine residues of anti-thrombin III, thereby activating anti-thrombin III to neutralize thrombin and other clotting factors

Absorption: Highly charged

Crosses membrane poorly, drug of choice for pregnant women Administered parenterally

Complications: Hemorrhage
Thrombocytopenia

Coumarins - Warfarin (Oral anticoagulants)

Mechanism of action: Vitamin KH, is required for the conversion of Glu to Gla residues in several clotting factors. Warfarin blocks the reduction of vitamin KO to vitamin KH,.

Absorption: Given orally
In plasma, 99% is albumin-bound. Only the free form is active.
Crosses the placenta, cannot be used during pregnancy

Complications: Hemorrhage

Anti-platelet drugs:

Aspirin

Mechanism of action: During platelet activation, arachidonic acid is released and is metabolized by cyclooxygenase to prostaglandin H₂ and thromboxane A₂. The latter two compounds are potent platelet agonists. Aspirin acetylates cyclooxygenase, rendering it inactive.

Complications: Gastrointestinal bleeding
Aspirin also acts on cyclooxygenase on endothelial cells to block the formation of prostaglandin², a natural platelet inhibitor - used low doses of aspirin.

Dipyridamole

Mechanism of action: The increase of intracellular calcium in platelets is essential for platelet activation. Cyclic AMP (CAMP) sequesters calcium into its platelet storage sites. Dipyridamole inhibits CAMP phosphodiesterases to prevent the breakdown of intracellular CAMP, thus blocking platelet activation.

Complications: Non-specific and not effective

Recommended uses: Used in combination with warfarin to prevent thromboembolism in patients with artificial heart valves.

Plasminogen Activators:

Fibrinolysis: plasminogen is converted to plasmin which degrades polymerized fibrin in blood clots.

Drugs used for fibrinolysis:

Tissue-type plasminogen activator (t-PA) - serine protease
- synthesized by endothelial cells
- fibrin specific

Urokinase (single chain urokinase-type plasminogen activator) - zymogen
- synthesized by kidney cells
- fibrin specific

Streptokinase - produced by β -hemolytic streptococci
- forms a complex with plasminogen and change its conformation
- NOT fibrin specific, leading to degradation of fibrinogen and fibrin

ANTI-ATHEROSCLEROTIC DRUGS

Atherosclerosis - LDL in blood penetrates into the subendothelium and becomes oxidized. Oxidized LDL causes transendothelial migration of monocytes/macrophages which in turn ingest oxidized LDL to form foam cells in fatty streaks. Further proliferation of smooth muscle cells and deposition of extracellular matrix results in atherosclerotic plaque formation.

- affects large and medium sized arteries
- elevated LDL and TG levels are associated with increased risk
- HDL levels are inversely related to risk

Regulation of cholesterol and triglyceride (TG) metabolism:

1. Exogenous pathway: Chylomicrons (CM) are degraded by lipoprotein lipase
Uptake of TG by adipose tissue and muscle
Transport of CM remnants to liver
2. Endogenous pathway: Liver synthesizes and secretes VLDL
VLDL is degraded by lipoprotein lipase to form IDL and LDL
Uptake of IDL and LDL by LDL receptor-mediated endocytosis
3. Reverse transport of cholesterol: As cells die, cholesterol is released and trapped in HDL
Cholesterol in HDL is esterified by LCAT and transferred to VLDL, which then is metabolized to IDL and LDL
4. De Novo Cholesterol Synthesis: Liver is the major site of cholesterol synthesis
HMG-CoA reductase is the rate limiting enzyme
5. Enterohepatic Circulation: Bile salt is synthesized by the liver, released into the intestine and recycled

Therapeutic strategy

- identify patients at risks
- modify diet and lifestyle
- pharmacologic therapy

Drug Therapy

Bile salt sequestrants

- anion exchange resins binding negatively charged bile acids
- increased cholesterol conversion to bile acid
- increased cholesterol synthesis and LDL receptors in liver
- increased LDL uptake and decreased serum LDL and cholesterol levels
- increased HDL/LDL ratio

Niacin (nicotinic acid)

- inhibits a hormone-sensitive lipase involved in lipolysis in adipose tissue
- decreased free fatty acid available to the liver for TG synthesis
- decreased production and release of VLDL by the liver
- decreased serum levels of VLDL, LDL and TG
- decreased HDL clearance
- increased HDL/LDL ratio

Statins

- HMG-CoA reductase inhibitors
- cells express more LDL receptors
- decreased cholesterol and VLDL production and release by the liver
- decreased HDL clearance - increased HDL/LDL ratio

Fibrates

- stimulate lipoprotein lipase
- increased VLDL clearance
- reduced serum levels of TG and LDL
- decreased HDL clearance
- increased HDL/LDL ratio

Ezetimibe

- Interferes with dietary cholesterol absorption