Antibiotics Summary

Comparison	Antibiotics				
Disruption	DNA Replication	Protein Synthesis	Plasma Membrane Structure	DNA Transcription	Cell Wall Synthesis
Example	Sulfonamides.	Streptomycin. Tetracycline.	Gramicidin A.	Nalidixic Acid	Penicillin.
Mechanism	Competitive inhibitors of DHPS, preventing the catalysis of PABA into folic acid, preventing nucleic acid synthesis.	Inhibit translational activity of ribosomes, inhibiting protein synthesis.	Makes the bacterial cell membrane more permeable towards cations and hydrophilic molecules, upsetting the ionic balance within the cell.	Inhibits gyrase enzyme which supercoils DNA around histone-like proteins, preventing replication and expression of DNA.	Irreversible inhibition of transpeptidases which forms cross links between peptidoglycan molecules of the cell wall, weakening it.
Structure	p-amino group. p-substituted benzene ring and sulfonamide group with secondary N.	-	Hydrophilic channel through the membrane. Masks cations with a hydrophobic coat.	Bicyclic ring system with a pyridine ring and a carboxylic acid at position 3.	Strained β-lactam ring. Free carboxylic acid that forms carboxylate and binds to charged N of a lysine residue in the binding site. Bicyclic system that confers strain on β-lactam ring. Acylamino side chain.
Bacteriostatic/ Bactericidal	Bacteriostatic since they only stop growth and division of bacteria.	Bactericidal since proteins cannot be synthesized, leading to death.	Bactericidal as it leads to cell death.	Bacteriostatic at low concentrations, bactericidal at high concentrations.	Bactericidal since it causes cell death from osmotic pressure.
Remarks	Folic acid is not synthesized in humans since humans can transport folic acid into cells. Bacteria can make more PABA to reverse competitive inhibition.	-	-	-	Need to know mechanism of inhibition of transpeptidases.

Penicillin

Acid Sensitivity	Cause	Ring Strain	High ring strain causing high angle strain and torsional strain. Acid catalyzed ring opening breaks open the highly strained β-lactam ring.
		Reactive C=O	The C=O group of the β-lactam is highly susceptible to nucleophiles due to the lack of resonance stabilization since that would introduce a double bond in the 4 membered β-lactam ring, leading to increased ring strain. Hence, the lone pair on N is localized and the C=O group is more electrophilic than expected.
		Neighboring Group Participation	The neighboring acyl group of the side chain can participate in the opening of the β-lactam ring in a self-destruct mechanism [need to know mechanism].
	Modifications		An electron withdrawing group in the side chain draws electrons away from the C=O group and reduces the tendency of O to act as a nucleophile, reducing neighboring group participation. This can make penicillin resistant to acid hydrolysis and hence allows it to be given orally.
Penicillin Resistance	Cause		Penicillinases are enzymes produced by penicillin resistant bacteria which catalyze the same ring opening caused by acid hydrolysis. Bacteria can confer resistance onto another by the exchange of plasmids containing the gene for production of penicillinases. Completing an entire course of antibiotic treatment eases the burden on the body's natural defenses and allows it to kill off totally even the penicillin resistant bacteria. Otherwise, the remaining bacteria may further mutate and develop greater resistance to the drug*.
	Modifications	Steric Shields	A bulky group on the side chain acts as a steric shield to prevent binding to penicillinases and hence prevent ring opening. However, if the side chain is too bulky, this can prevent penicillin from binding and hence inhibiting transpeptidases too. A five-membered heterocycle can act as a steric shield and an electron withdrawing group, stabilizing the penicillin.
		Penicillinase Inhibitor	Clavulinic acid is a non-competitive inhibitor of penicillinase that fits the active site and forms permanent covalent bonds with the enzyme active site, resulting in irreversible inhibition.
Ampicillin and Pro-Drugs			Ampicillin is acid resistant due to the electron-withdrawing amino group. It is however sensitive to penicillinases since the phenyl group is insufficiently bulky to be a steric shield. Ampicillin is poorly absorbed through the gut wall since both the amino group and carboxylic group are ionized. The polar groups can be masked with a protecting group in a pro-drug. An ester group must be further away from the penicillin skeleton since the bulky skeleton acts as a steric shield and prevents esterase enzymes from metabolizing a methyl ester.
Side Effects			Nausea, vomiting, stomach pain, headaches, diarrhea and fever.

Analgesics

Comparison	Analgesics	
Types	Narcotic	Non-Narcotic
Examples	Morphine.	Paracetamol, aspirin.
Definition	Drugs that relieve pain.	
Structure	Morphine-like. Aromatic ring for van der Waal's interactions, basic N atom for ionic bonds when protonated and phenolic –OH for hydrogen bonding with the receptor binding site.	R-C6H4-O- skeleton.
Mechanism	Depresses the central nervous system and affect the capacity of the brain to appreciate pain. Binds to morphine receptors in the central nervous system. Natural ligands to these morphine receptors are endorphins.	Prevent pain receptors from responding normally to pain stimuli. <u>Aspirin</u> Non-competitive inhibition of cyclo-oxygenase (COX) enzyme by acylating the serine residue in the active site, reducing transmission of pain information to the brain. COX turns arachidonic acid into prostaglandins, hormones that transmit pain information to the brain and cause inflammation. Aspirin also inhibits the production of a clotting agent from arachidonic acid.

Comparison		Analgesics		
Types		Narcotic	Non-Narcotic	
			Paracetamol	Aspirin
Effects	Analgesic	Yep.	Yep.	Yep.
	Antipyretic (reduce fever)	Nop.	Yep.	Yep.
	Anti-inflammatory	Nop.	Nop.	Yep.
	Anticoagulant	Nop.	Nop.	Yep.
Side Effects	Tolerance and addiction	Yep.	Nop.	Nop.
	Increased GI tract blood loss and tendency to bleed	Nop.	Nop.	Yep.
	Nausea and vomiting	Nop.	Less.	More.
	Death from overdose	Yep.	Yep.	Yep.
	Others	Lethargy, apathy, loss of consciousness.	-	-

Stimulants

Comparison	Caffeine	Nicotine	Amphetamine
Definition	Stimulants are drugs that wake up the central nervous system, increasing heart rate, respiration rate and blood pressure. This mimics the physiological effect of the neurotransmitter noradrenaline and the hormone adrenaline.		
Structure	Similar to the adenine part of adenosine molecules.	-	Similar to the structure of adrenaline, with a benzene ring with a two carbon chain and an amine group at the end of the chain. Adrenaline is fat insoluble while amphetamine is fat soluble.
Mechanism	Competitive antagonist to adenosine receptors on cells of the central nervous system, increasing the amount of adrenaline and noradrenaline released from the pituitary gland. Inhibits cAMP phosphodiesterase that breaks down cAMP, increasing cAMP levels and intensifying the normal effects of adrenaline.	Agonist at acetylcholine receptors at cholinergic synapses, stimulating nerve transmission and increasing adrenaline levels in the bloodstream. Production of alkaloids that inhibit monoamine oxidase enzymes that destroy dopamine, increasing dopamine levels.	Open up carrier protein channels in the pre-synaptic nerve plasma membrane, causing noradrenaline and dopamine to leak into the synapse. Release serotonin from pre-synaptic vesicles. Inhibit re-uptake of noradrenaline and dopamine into pre-synaptic nerve. These cause a rapid increase in the synaptic concentration of noradrenaline, dopamine and serotonin and increase the strength of nerve impulses.
Nicotine Addiction	Since the body attempts to keep nerve transmission rate steady, if there is continual stimulation of dopaminergic or cholinergic receptors, the number of these receptors on the post-synaptic membrane will decrease to reduce the stimulation. This happens very quickly with nicotine. This means that the dosage of the drug needs to be increased to achieve the same effect, and if the drug is withdrawn, there will not be enough receptors to produce the same level of neurotransmission that the body requires, resulting in withdrawal symptoms until more receptor proteins are synthesized.		
Adrenaline	Activates adrenergic receptors in cells, causing the release of chemicals that activate enzymes that produce cAMP.		

Definitions

Agonist	A drug that **mimics the natural ligand** for a receptor and will dock sufficiently strongly to a **binding site** for the receptor to **change its shape** adequately for the active site or ion channel to open, hence exerting the **same physiological effect** as the natural ligand.
Antagonist	A drug that **binds to the receptor** but **does not cause the required change in the shape** of the receptor. Thus, it **does not yield the desired physiological effect** and **blocks the binding site** from the natural ligand.
Competitive Reversible Inhibitors	Inhibitors that **compete with the natural substrate** for the **enzyme active site** by binding **reversibly** to the active site through **non-covalent intermolecular interactions** (i.e. hydrogen bonding, ionic bonding and van der Waals interactions). They can be **displaced** by **higher concentrations** of the natural substrate.
Non-Competitive Inhibitors	Inhibitors that **do not bind to the enzyme active site**. They usually bind to a **different region** of the enzyme, producing an induced fit that **changes the shape of the active site** of the enzyme, thereby **preventing the catalysis** of the substrate. **Increasing concentration** of substrate will have **no effect** on level of inhibition.
Irreversible Inhibitors	Inhibitors that bind **irreversibly** through **formation of covalent bonds** to the **active site**, hence **blocking the active site** so that the natural substrate can no longer bind. **Increasing concentration** of substrate will have **no effect** on level of inhibition.
Allosteric Inhibitors	Inhibitors that bind to a **different part of the enzyme** at the **allosteric site** and **does not compete** with the natural substrate for the active site. Upon binding, an **induced fit** occurs which **alters the shape of the enzyme active site** such that the natural substrate can no longer bind with the enzyme. **Increasing concentration** of substrate will have **no effect** on level of inhibition.
Pro-Drug	A compound that must undergo **chemical conversion** by **metabolic processes** before becoming an active pharmacological agent. It is the **precursor** of a drug.