Mechanism of Drug Action and Drug Targets

Receptors
Neurotransmitter receptors in the plasma membrane of postsynaptic cells fall into two broad classes: ligand-gated ion channels and G protein–coupled receptors. Synapses containing either type can be excitatory or inhibitory, but the two types vary greatly in the speed of their response.

Ligand-Gated Ion Channels (Fast synaptic signalling)
Binding of the neurotransmitter to the extracellular binding domain on a ligand gated ion channel causes an immediate conformational change that opens the channel portion of the protein, allowing ions to cross the membrane and causing the membrane potential to change within 0.1 – 2 milliseconds. Binding of ligand to excitatory receptors opens cation channels that allow passage of both Na+ and K+ ions, leading to rapid depolarization of the postsynaptic membrane; in contrast, binding of ligand to inhibitory receptors opens Cl– channels, leading to hyperpolarization of the postsynaptic membrane.

G Protein coupled receptors (GPCRs) (Slow synaptic transmission)
Many functions of the nervous system operate with time course of seconds or minutes; regulation of the heart rate, for instance, requires that action of neurotransmitters extend over several beating cycles measured in seconds. In general, the neurotransmitter receptors utilized in slow synapses are coupled to G proteins. GPCR signalling is also common in non-neuronal cells. Binding of the neurotransmitter leads to a conformational change in the receptor, that results in activation of a specific G protein. The G-protein may directly binds to and activate or inhibit ion-channels. In other cases, the receptor-activated G protein activates (or inhibits) adenylate cyclase or phospholipase C, triggering a rise in cytosolic cAMP or Ca2+, respectively; these second messengers in turn affect the ion conductance of a linked ion channel, or trigger kinase cascades that result in phosphorylation/dephosphorylation of target proteins. The postsynaptic responses induced by neurotransmitter binding to GPCR are intrinsically slower and longer lasting than those induced by ligand-gated channels.

In this lecture, the diversity of receptors for and responses to a single kind of neurotransmitter is illustrated by acetylcholine. Synapses in which acetylcholine is the neurotransmitter are termed cholinergic synapses. Acetylcholine receptors that cause excitatory responses lasting only milliseconds are called nicotinic acetylcholine receptors. They are so named because nicotine, like acetylcholine, causes a rapid depolarization. These receptors are ligand-gated channels for Na+ and K+ ions. Other acetylcholine receptors are called muscarinic acetylcholine receptors because muscarine (a mushroom alkaloid) causes the same response as acetylcholine. There are several subtypes of muscarinic acetylcholine receptors present in different cell types; all are coupled to G proteins, but they induce different responses. The M2 receptor present in heart muscle activates a G protein that causes the opening of a K+ channel and thus a hyperpolarization lasting seconds when post-synaptic. Presynaptic M2 receptors, in addition to inhibiting adenylate cyclase, inhibit the opening of voltage gated calcium channels, leading to decreased ACh release from the nerve terminal. The M1, M3, and M5
subtypes are coupled to Gq and activate phospholipase C; the M4 subtype activates Gi and inhibits adenylate cyclase. Thus, a single neurotransmitter induces very different responses in different nerve and muscle cells, depending on the type of receptor found in the target cells.

**How drugs act at receptors**

**Affinity**: a measure of how tightly a drug binds to the receptor. If the drug does not bind well, then the action of the drug will be shorter and the chance of binding will also be less. This can be measured numerically by using the dissociation constant $K_D$. The $K_D$ is the concentration of drug when 50% of receptors are occupied. Thus, the higher the $K_D$ the lower the affinity of the drug (the more drug it’ll take to bind to the receptors).

**Potency** is a measure of how much a drug is required in order to produce a particular effect. This is defined in a concentration response curve by the EC50 – the concentration of drug required to produce 50% of maximal response. If a drug has high potency drug only a small amount is required to induce a large response.

**Efficacy** is the ability of a drug produce a response. Agonists are described as having affinity and efficacy, partial agonists are drugs which bind with affinity, but do not produce maximal response – *even at 100% receptor occupancy*, thus they are less efficacious than full agonists. Antagonists are drugs which have no intrinsic efficacy – they can bind to the receptor (i.e. they have affinity), but do not induce a conformational change in the receptor. They produce their effects by preventing agonist from binding.

**Enzymes**

Many enzymes form useful drug targets eg acetylcholinesterase (neostigmine); cyclooxygenase (aspirin), angiotensin converting enzyme (captopril). Often the drug mimics the natural substrate acting as a competitive inhibitor of the enzyme (eg captopril); in other cases the binding is non-competitive and irreversible (eg aspirin). Drugs may also act as false substrates, where the drug molecule undergoes transformation to form an abnormal product that subverts the normal metabolic pathway. An example of this is the anticancer drug fluorouracil, which replaces uracil as an intermediate in purine biosynthesis, but cannot be converted into thymidylate, thus blocking DNA synthesis and preventing cell division. Some drugs require enzymic degradation to convert them from a prodrug into an active form. Other drugs may be converted into a toxic or reactive metabolite. We will consider the example of acetylcholine esterase inhibitors in the lecture.

**Carrier/Transporter Molecules**

Transportation of polar molecules across lipid membranes often requires a carrier protein. The carrier proteins embody a recognition site that makes them specific for a particular permeating species, and these sites can also be targets for drugs, whose effect is generally to block the transporter. We will consider the example of the serotonin transporter, which are the drug target for selective serotonin reuptake inhibitors (SSRIs), for depression.
Ion Channels

Ion channels are protein molecules that span the cell membrane, and can switch between open and closes states, allowing the controlled entry or exit of specific ions across the cell membrane in their open state. Ion channels are highly selective for the ions that they control. The channels are all gated i.e they have particular triggers that allow for their opening. You are already familiar with two forms of gating – ligand gated ion channels, which are an integral part of a receptor, and second messenger gated ion channels, which are opened either by G-proteins directly, or downstream effector molecules such as cAMP. The third major class of gated-ion channel are the voltage gated ion channels, which open in response to voltage changes across cell membrane. These channels open when the membrane becomes depolarized, and are critical to the mechanism of membrane excitability (development of action potentials). Channel opening is usually short lasting. Drugs may bind directly within the ion channel and prevent the flow of ions, or may bind elsewhere on the molecule and increase or decrease the probability of the channel opening in response to a change in voltage. Local anaesthetics are a class of drugs which block pain pathways by blocking voltage gated sodium channels and therefore preventing the action potential that carries the pain signal from the site of injury to the brain.