How do drugs act?

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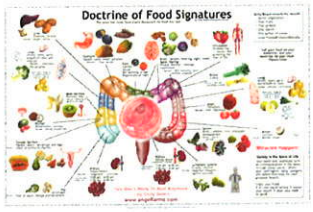
Doctrine of Signatures (not how drugs work)

In the Middle Ages (and currently in some circles on the West Coast), drugs were believed to work according to their appearance.

Rusty iron particles or red wine for anemia; saffron for jaundice; tomatoes for the heart; walnuts for the brain; mandrake roots for all ailments.

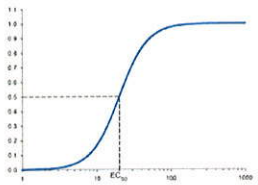


The mandrake root: looks like a human; good for every ailment!

Binding to receptors (how most drugs work)

The body produces a vast array of molecules, for example hormones and neurotransmitters, that control essentially all bodily functions (such as growing, moving, breathing, surviving).

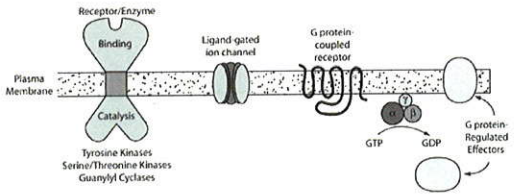
When these molecules (let's call them "ligands") interact with or bind to their specific receptor proteins, they trigger a series of changes in the cell referred to as a "response". Typically, the magnitude of the response is proportional to the number of receptors that are occupied by the ligand.

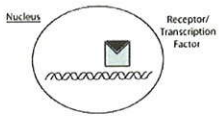


The EC50 is the dose that gives halfof the maximal effect.

Note that the graph is semi-logarithmic, allowing us to visualize effects of a broad range of ligand concentrations

Types of Receptors





Most receptors are located on the cell surface, although some are found inside the cell.

Enzymes as drug targets

Some drugs target enzymes instead of receptors.

Enzymes increase the rates of chemical reactions that occur normally in cells.

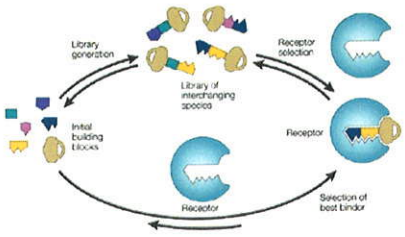
Nearly all drugs that target enzymes inhibit their activities; only a handful increase enzyme activities.

Among the familiar drugs that inhibit enzyme activity are :

1. Aspirin, which reduces pain by inhibiting an enzyme known as "cyclooxygenase".
2. Penicillin, which kills bacteria by inhibiting an enzyme that they need to build their cell walls.

Both of these drugs are "suicide inhibitors" because they irreversibly modify the enzymes they inhibit.

Specificity



Ramstrom and Lehn 2002 Nature Reviews in Drug Discovery 1, 26-36.

Nature Reviews | Drug Discovery

A given hormone or neurotransmitter usually has a strong preference for binding to its own specific receptor. This specificity, ensures that the molecules elicit a unique response.

Drugs are often less specific than natural molecules and can bind to other receptors. This leads to the adverse or side effects that are common to many drugs (as we shall see later).

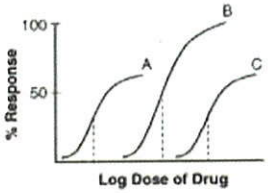
"I stopped taking the medicine because I prefer the original disease to the side effects."

Key terminology: Affinity and Intrinsic Activity; Potency and Efficacy

Affinity refers to the strength of attraction between a drug and its receptor. Intrinsic activity refers to the drug's ability to produce an effect once it is bound. Both of these properties are determined by the chemical structures of the drug and its receptor.

Potency is related to the amount of drug needed to produce an effect.

Efficacy is the magnitude of effect that can be produced by a drug.



Which drug is the most potent?

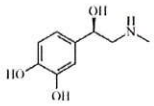
Which drug is the most efficacious?

Key terminology: Agonists

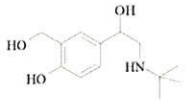
Agonists are molecules that activate their receptors and thereby elicit a response. The response could be to increase or decrease the cell's activity.

The body generates its own, natural agonists that activate specific receptors. Drugs that bind to the same receptors and activate them are also called agonists.

Example:
Natural agonist:
Epinephrine (Adrenaline)
(relaxes airway smooth muscle, among many other effects)



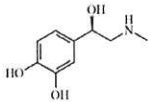
Agonist drug:
Albuterol
(used in asthma)



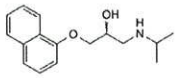
Key terminology: Antagonists

Most antagonists block the cell's response to an agonist by "sitting" on the agonist's binding site on the receptor and preventing the agonist from gaining access to it.

Example:
Natural agonist:
Epinephrine
(increases heart rate)

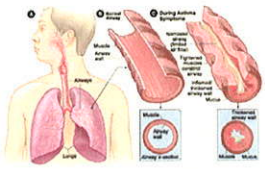


Antagonist:
Propranolol
(slows heart rate)



Combined use of agonists and antagonists

When *albuterol*, an agonist, binds to its specific receptor (an *adrenergic receptor*) on cells in the respiratory tract, the smooth muscle cells relax , the airways widen, and breathing is easier.



When *ipratropium*, an antagonist, binds to a different receptor (a *cholinergic* receptor), it prevents the receptor from binding its biological agonist (*acetylcholine*). Since acetylcholine causes contraction of smooth muscle cells and narrowing of the airways, blocking its effect widens the airways and makes breathing easier.

Take-home message: Agonists and antagonists can be used together to treat the same disorder – as long as they work on different receptors.

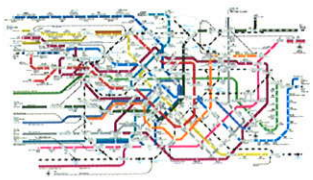
Example: How do drugs alleviate depression ?

Short answer: We don't know

Dallas DART

Lungs (asthma)

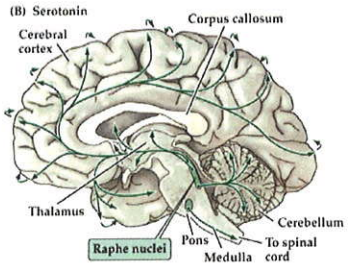
Tokyo Subway



Brain (depression)

Biochemical basis for depression (hypothetical)

Depression may be due to a deficiency of neurotransmitters, particularly norepinephrine and serotonin, in the synapse.

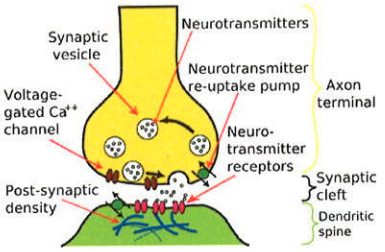


norepinephrine

serotonin

Serotonin and norepinephrine regulate functions in nearly every area of the brain.

Neurotransmission



Step 1. When the nerve cell is excited, neurotransmitters (e.g., norepinephrine and serotonin) are released from *synaptic vesicles.*

Step 2. Neurotransmitters activate receptors on the surface of the next neuron in the pathway.

Step 3. To avoid excessive stimulation, excess neurotransmitters are taken back up through "re-uptake pumps"

Most currently used anti-depressant drugs work by blocking the re-uptake of neurotransmitters

Neurotransmitter re-uptake inhibitors

1. Tricyclic Antidepressants (TCAs)

TCAs block both serotonin re-uptake transporters (SERTs) and norepinephrine reuptake transporters (NETs) – but are also antagonists of many receptors. Result : many adverse effects!

a) Blurred vision, dry mouth, constipation, urinary retention, and more (blocking cholinergic receptors).

b) Low blood pressure and fainting (blocking adrenergic receptors).

c) Drowsiness (blocking histamine receptors)

d) Worst of all, they block *ion channels* in the heart: cardiac arrest and death.

Conclusion: TCAs are effective (for about 60% of patients), but caution must be used and elevated doses must be avoided.

2. Selective Serotonin Reuptake Inhibitors (SSRIs; including Prozac, Paxil, others)

These are far safer than TCAs. SSRIs specifically block SERTs, but that's not why they are safer. They simply don't bind to as many different receptors as TCAs – so fewer side effects.

Monoamine oxidase inhibitors for depression and Parkinson's Disease

Norepinephrine and serotonin are degraded (metabolized) by monoamine oxidase type A (MAO-A).

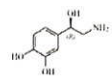
Drugs that inhibit the activity of MAO-A were among the first to show anti-depressant activity (more than 50 years ago).

But dangerous adverse effects soon appeared (next slide), so MAO-A inhibitors are only used in special cases today.

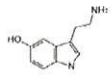
The neurotransmitter dopamine, which looks like norepinephrine, is greatly reduced in the brain of Parkinson's Disease (PD) patients. So here the goal is to elevate dopamine levels.

Dopamine is metabolized by MAO-B, which is inhibited by different, much safer drugs than those that inhibit MAO-A. These are used in PD.

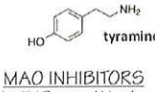
Deadly problem with monoamine oxidase inhibition: The Cheese Effect



norepinephrine

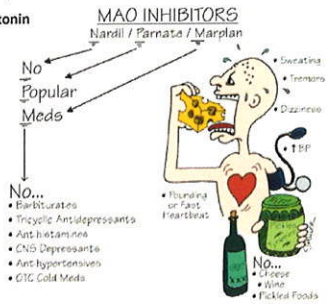


serotonin

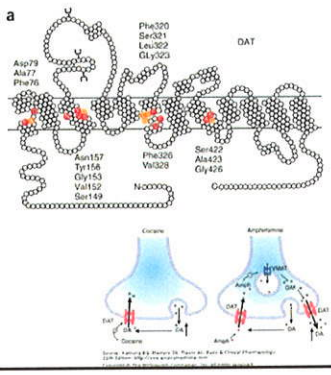


tyramine

MAO-As not only degrade norepinephrine and serotonin, but also tyramine, which is abundant in some foods (particularly cheese). Excess tyramine can cause deadly hypertension. This has been called the "Cheese Effect"



The dopamine transporter (DAT) looks like SERT and NET, and is a key player in drug abuse.



More this afternoon!