

## Lecture 25B • 06/22/12

### Neurotransmitters and psychoneuropharmacology

#### Blood-brain barrier

There is a barrier that prevents most chemicals in the bloodstream from easily crossing into the brain. You might imagine that the control center for us, you might have some extra protection around so if you had some temporary variation in your blood chemistry, that the rest of your body that might not be so sensitive to it might be able to withstand it, but your brain might not. There are experiments that have been done before where if, for example, you inject a dye into some form of mammal, and then if you were to examine the brain tissue [as compared to other tissues] afterwards, you'd find that that dye could accumulate throughout the body, but won't be found in the brain. In regular capillary cells, there are gaps between the [somewhat] loose cells which allow for more easy flow of chemicals across. But, the cells in capillaries in the brain are much more tightly linked or knit. There are transport systems that allow the transport of certain chemicals across, but some of the passages of the those chemicals are very specific. d-Glucose, the biologically active form of glucose, is able to easily cross into the brain, but l-glucose, the form that is not biologically active, is not able to easily cross into the brain. There's the nervous system itself, then there's the central nervous system and then the control center, the brain. Some compounds might act on the rest of the body, but when your doing drug design, one of the things that you have to take into account is – will this substance then cross into the blood-brain barrier, if this is something that is supposed to be psychologically active.

There is also another issue in drug design in general, which is: can it make it all the way to the stomach? [The environment in] the stomach is about pH 2, which means 0.01 M HCl. Lots of compounds don't survive those conditions for very long, and of course there's some biological processes that happen even before whatever medication you might take makes it down to your stomach. [what chemicals do which channels allow across? transport sites?]

#### Neurotransmitters

If you have two nerve cells, the way that messages get communicated from one nerve cell to another is the release of these chemical messengers called neurotransmitters. Nerve messages within the cell are electrical impulses. Benzocaine acids on these ion channels. If you allow ions to flow in or out of the system, you're changing charge. If you build up a difference in charge, you generate an electrical impulse – that would be a nerve impulse. The gets to the end of the nerve cell, causes the release of one of these neurotransmitters that then flow across that gap [synapse] to hit another nerve cell and hit what's called a receptor site. When you have a molecule that's the right shape – there may be lots of molecules that have very related shapes – you get something that can fit onto that receptor site, it's going to activate and cause another nerve impulse. Of course, if you have a family of chemicals that might be able to sit on that reactive site, you might get a variety of responses. Even if you have something like the opiod receptor site – one of the most important receptor sites as far as far as addressing pain medication – there are a whole series of opiods. There might not necessarily be just one specific type of opiod receptor, so there might be families of related receptors that might have a differential response to these different very related chemicals.

Once neurotransmitters get released, that's the message, but if you want to keep sending fresh messages, somehow those neurotransmitters have to be gotten riden of afterwards. There's a couple of different ways that that could occur. If you have simple reabsorption, that's what is what is known as reuptake. [For example,] a serotonin-specific reuptake inhibitor (SSRI) is a compound that prevents serotonin from being re-taken up. If you allow that compound to sit at that gap between nerve cells, then that's like that message is being sent more. Serotonin is one of the major mood-[regulating] chemicals [awareness, consciousness]. It's thought that by using these SSRIs to allow serotonin to stay between certain nerve cells for a longer period of time that that has an antidepressant action; SSRIs are one of the major classes of antidepressants – psychologically active chemicals. Reuptake is one way of clearing out that gap between the nerve cells.

There are also chemical reactions that we could perform. [back of coke bottles; phenylketoneurics; MAOIs – monoamine oxidase inhibitors] A lot of neurotransmitters are amines. One of the ways to get them out of the system is to change the functional group; the body can do that through oxidation. If you want to prevent that oxidation, prevent that compound from being removed, that would be an inhibitor – thus the term monoamine oxidase inhibitor.

#### Sodium and potassium channels

Charge can be built up if you allow ions to flow. If you don't allow ions to flow, that could be a really bad thing. These are a series of example compounds that have exactly this bad effect. Tetrodotoxin [one of the most poisonous toxins there is]; batrachotoxin[?] [poison blow darts] [These two compounds] block sodium channels, so it doesn't let the charge build up, which means you just stop sending nerve signals. If that affects everything in your body, it's just like telling every nerve in your body to stop, stop breathing [is it limited to CNS?]. Sodium channel agents can be very, very dangerous things – or, when used properly, they can be used to [block] pain, because pain is just a nerve impulse.

You dull the impulse, not get rid of what's causing it, but if you dull that impulse, you dull the pain. [three related compounds] Notice that they're all either benzoic acid-style esters or have, most importantly, this tertiary amine functional group ending. Novocaine and xylocaine are relatively similar in structure; then we have more notorious chemical, cocaine, which is [similar to] benzocaine. All of these compounds act by acting on the sodium channels. Some compounds, though, might have action on other [receptors, or receptors in other parts of the body]; that's part of the reason that cocaine is a bit more problematic compared to these other [related] chemicals.

One of the most common kind of neurotransmitters is this molecule acetylcholine. [choline appears in context of phospholipids][Voyager] The acetyl choline system controls things like vasodilation – the size of blood vessels – iris contraction, lens contraction, bronchial constriction, gastrointestinal action, muscle contractions – which means all throughout your body. It turns out that there are different receptors for this acetylcholine, and they fall into two broad categories – one is the nicotinic receptor and the other is the muscarinic. Notice the similarity of muscarine to acetylcholine itself. [what's the connection to nicotine] There can be subclasses of these receptor sites for neurotransmitters.

There are what are known as agonists and antagonists. Agonists are compound that, when they bind, they enhance the action of that receptor site; antagonists are compounds that, when they bind, they reduce the action of whatever system that receptor site is related to.

AChE inhibitor – AChE stands for acetylcholine esterase; acetylcholine is an ester. Once it's released, one of the ways of removing this from the body is to break down this ester back into choline and acetic acid. Acetylcholine esterase is a [n enzyme] that breaks this down, which means removes it from the neurotransmitter sites. [AChE inhibitors] prevent the de-esterification and allows that neurotransmitter to stay around for longer [having an effect]. If you don't allow this reset ever, it's kinda the same effect as blocking the message. If all you're doing is sending the same message forever, that can have as bad an effect as if the message never gets generated. Organophosphates tend to be particularly lethal compounds. [sarin, Tokyo subway; VX] It acts on these acetylcholine neurotransmitter systems.

Dopamine system. Tyrosine, if you first hydroxylate it, put an extra hydroxy group, and then you decarboxylate it, you make the compound dopamine. The dopamine system is highly related to mood and energy. Dopamine is related to a class of compounds called amphetamines. There's a naturally-occurring version of this. Again hydroxylate dopamine and then methylate it and you get adrenaline. Adrenaline causes this huge release of energy – that's related to the dopamine neurotransmitter system. This is one of the classes of compounds that can be affected by monoamine oxidase inhibitors, because we have an amino group here. If you have low energy, for example, you might need these compounds to stick around longer, which is why we would have these monoamine oxidase inhibitors [what's the real story?][MMPP – dimerol synthetic – incorrect synthesis, reverse ester – caused Parkinson's symptoms – cautionary tale][amphetamines – realization that legal and illegal drugs are directly related structures – Ritalin, amphetamine, methamphetamine][ethnopharmacology – what some consider illegal is used by others for religious purposes][tripping]

Serotonin – one of the most important neurotransmitter systems in terms of [awareness, mood]. It is largely the neurotransmitter site that a lot of modern classes of antidepressants act on. [MAOI] Tryptophan, if you decarboxylate, turns into tryptamine, which is you add just a hydroxy group turns into hydroxytryptamine, which is the compound serotonin. That's partly why tryptophan has this sleepy effect that it supposedly has, because it acts on the serotonin neurotransmitter system. [acylized ether – melatonin][structural similarity to psilocybin and LSD][structures of antidepressants]

[Cautionary tale of working in the laboratory] He was a government research working on fungi that created these related compounds called ergots. This was just one of the compounds he was working with that he accidentally had slip through his glove. He went home that afternoon ... imagine that the biochemical system that you have to perceive the world around you, you're messing with directly, so just a little tiny bit of this compound can cause a huge change in your perception – see things differently, hear things differently, dramatic effects on change in consciousness. He was working in the lab, went home one day – the world all around him was all colors and sounds. [thought would be used medicinally, but entered into recreational use][x originally intended for therapy – opening up, the ability to empathize and push past certain emotional barriers] Some of these compounds have been used in therapeutic settings before they reached the street [before they reached 18 - 25 year olds that don't quite understand the effects these compounds will have 30 or 40 years in the future].

Cannabinoid. There are a huge range of endocannabinoids – THC is only one [well-known] cannabinoid – which are compounds that the body produces. The body has these neurotransmitter systems in it. [why? why do humans have receptors for primarily plant-based compounds] Legitimate research in some of these classes of compounds can often be complicated by both political and social policies. [long history why a lot of these compounds are illegal, very little of which has to do with science][The fear is that is something positive is discovered about these substances, it could have a huge political effect][politics, money, religions, they all get mixed together – these are all substances that effect what does it mean to exist] When you start changing peoples' existence, it starts making people uncomfortable.

Opioids. We are wired to respond to these plant-based chemicals. If we look at morphine versus codeine versus heroin, they have exactly the same core structure – a tetracyclic tertiary amine structure. The only difference between morphine, which is a prescribed drug, and heroin, which is an illegal drug, is this acetyl group. What is the difference between the compounds? Both of these are pain-mitigating compounds; that's one of their primary functions, that's what one the primary functions of the opioid neurotransmitter system is. Heroin, which derived from a natural plant product, when it's hydrolyzed, breaking the ester, turns into morphine. Morphine, because it has these -OH groups, is more polar, less lipophilic. Heroin crosses the blood-brain barrier much more easily, but it turns into morphine once it hydrolyzes. The both really are the same compound once they reach the brain, so if you ever have to have morphine during an operation, you effectively, in a way, have had heroin.

Histamines. [allergies][benzodiazepins, caffeine, penicillin, thalidomide, GABA]  
[intentions for textbook]

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No structures available for this lecture.