

Lecture 26A • 06/25/12

Neurotransmitters and psychoneuropharmacology – the effect of different classes of compounds on the nervous system and on the brain

Blood-brain barrier

You might imagine that if your control center were somehow to get damaged, that even if the rest of you is fine, you'd be in some trouble. There's this system that's been developed where the brain is heavily isolated from the rest of the body. There are ways that we can demonstrate that. For example, if you were to take some poor, unfortunate lab critter and inject it with some kind of dye, just into the normal blood stream, then if you were to examine the creature afterwards, you'd find that yes, that dye did end up throughout the body, but won't end up in the brain. Part of it has to do with blood vessels. If you look at capillaries throughout the rest of the body, the junctions between different cells of the capillary are not quite as tightly packed with each other, but if you look in the capillaries of the brain, instead, they're very, very tightly packed together, so there's not as much ability for a physical diffusion, for things to just make it through the gaps. There are transport systems, because obviously the brain can't function without some source of fuel, glucose being one of the primary sugars used as fuel in the brain. d-Glucose, the biologically active form of sugar, is the only one that easily crosses into the brain; l-glucose almost doesn't make it across at all. So, there's stereospecificity to the types of compounds that could be brought across, and there's a transport system that helps allow these necessary chemicals across. If you were trying to design some kind of drug to treat some kind of psychological condition, there's first the issue that you've got to get it into you. Your stomach is pH 2, which means that lots of compounds that have acid-sensitive groups, they might start to decompose as soon as they get in you before they can even be ingested and then get through your blood stream. Even once they get through your blood stream, there's this issue of whether things are going to cross into the blood-brain barrier. Something as simple as polarity can affect that [morphine and heroin].

Neurotransmitters

There's this gap that occurs between different nerve cells. Nerve impulses are generated first by displacement of charge. [benzocaine] Ions move either in or out of a cell, creating an imbalance in terms of charge, which generates that electrical impulse. Once that impulse gets to that between different nerve cells, there are these neurotransmitters that act as messengers carrying the message across that gap. One nerve cell will release the messages, these neurotransmitters; the other one has what are called receptor sites. There's not necessarily just one type of receptor for one type of neurotransmitters, nor can one compound sometimes only affect one neurotransmitter site, you might have one compound that affects multiple sites, causes all kinds of effects. We have the ion channels that generate the charge, generate the electrical impulse signal; we have the gap; we have neurotransmitters being released; and then they hit different receptor sites. What do you do with the neurotransmitters afterwards? The neurotransmitter sitting there keeps binding with that receptor site, it's like it keeps sending a message. What if you had a condition where you've got an excess of these neurotransmitters? For example, if you had dopamine, which is related to energy, if it was sitting there activating too much, you'd be wired. How could you tone that down? By somehow removing that neurotransmitter from that gap. One way is for it simply to be absorbed again, which is known as reuptake. [SSRIs – they act to prevent that compound from being taken up, the idea being that that allows the neurotransmitter to do its job and keep on messaging, and it's thought that in the serotonin system, that helps to affect mood]. What if you wanted to get rid of it? There's a couple of mechanisms that can occur by. Aside from the transmission of the signal, there's chemically what do you do with the messenger afterwards.

Sodium ion channels

If the sodium channel is what is used to generate this charge, and if you somehow close that channel off, you don't allow charge to flow across, you're blocking that signal. In many cases, that's a good thing. For example, pain: pain is nothing more than a nerve signal; if you can block it, it doesn't get rid of what's causing the pain, but at least it helps mitigate your experience of it. That's what benzocaine plus some of these related structures are good at doing. Some of these compounds have more beneficial effects, and some of them have some problematic effects. What a substance does, biologically, is different from socially what we've ended up doing with it. There'll be plenty of examples of compounds that have medical uses or may have started out purely for medical uses, but at some point or another ended up being used "recreationally", they got into uses not originally intended. Cocaine is an interesting example because it shows up in cultures around the world. There are many cultures in South America, for example, that, instead of having coffee, you'll just pick off a few coca leave, you have a bit of lye, which is base. Cocaine and these [related structures] are all amines, so if you have acidic conditions you're going to make salts, which makes things water soluble, but if you mix it with a base, it turns it back into a regular amine [freebasing] that makes it more organic compatible, more [lipophilic]. As a leaf that's just chewed, it acts as a stimulant [is that a good thing or not? depends on social context][abused – reacts with other neurotransmitter sites][procaine, xylocaine] This is for positive effects on the ion channel. If you were to close off the ion channels that regulate breathing, for example, that might not be such a good thing. [example chemicals that are ion-channel blockers that do too good a job or block the wrong ones: blowdarts]

One of the most wide-spread of common neurotransmitters is the acetylcholine system. [choline in phospholipids] There what's known as acetylcholine esterase – you can name almost any function that you want to and add the word 'ase' afterwards and that's how you name the enzyme that does that job. Acetylcholine esterase is a de-esterifying agent; it will break the acetylcholine back down into acetic acid and choline. If you have a nerve that releases this, acetylcholine esterase will come along, break it back apart; that's one way of flushing that messenger out of your system. There are also what are known as AChE inhibitors, acetylcholine esterase inhibitors, that prevent that from happening, that allow that neurotransmitter to stay around longer in the body. The acetylcholine neurotransmitter system has two main classes of receptors: the nicotinic and the muscarinic. The niconintic, that's the same nicotine that's in tobacco, which is partly why tobacco is one of the most addictive substances on the planet. It might not have the same sociological or physical effects as some of the other 'drugs', but it is difficult to kick the habit because it's effectively a neurotransmitter agent. You smoke, you're getting this neurotransmitter in your system, your system gets acclimated to it. You stop smoking, the body says: 'where'd the neurotransmitter go'? [If you've ever been around anybody that's stopped smoking, usually they're not necessarily the most pleasant people. There's the habit and the action of smoking itself, but then there's the fact that you're readjusting your neurotransmitter levels. Any time that you mess with something system-wide, your system responds to it, usually in the case of stoping smoking by being cranky or suddenly put on wait because you've got food cravings you didn't have before.]

Agonists and antagonists: agonists are compounds that, when they bind to the receptor site, they enhance the behavior of whatever that receptor site is. There are antagonists, which is where it binds, but it ends up having a decreasing effect, attenuates the effect of that neurotransmitter system. [organophosphate – sarin and VX, Tokyo subway]

Dopamine

Tyrosine, if we hydroxylate it on the benzene ring, this turns into DOPA. If you decarboxylate it, you get to an amine called dopamine. [Many neurotransmitters have amine functionality], and many of these compounds will have this two-carbon linker to some other structure. How can we get rid of these compounds? [MAOIs] Monoamine oxidase inhibitor. If you have an amine, one of the ways that the body gets rid of it, in terms of its functionality, is to oxidize it – turn it into a different functional group, won't respond any more. A monoamine oxidase is something that can commonly be used to get rid of these compounds, to flush them out the neurotransmitter sites. Monoamine oxidase inhibitors will prevent that reuptake. Dopamine can be turned into norepinephrine, which turns into epinephrine, known otherwise as adrenaline. The amphetamine system is mainly related to energy, in the sense of how aware, how awake, how active are you; it indirectly then has something to do with mood.

Looking at that structure, then look at this structure here. [Ritalin – used to mediate attention span][MMPP – reverse ester – made in attempt to make demerol][X] The dopamine system is related to energy. [Amphetamine, methamphetamine – nasty, practically identical to dopamine, actively interfering with your neurotransmitter system] If your body starts getting used to this chemical that is so much like a neurotransmitter (it's not the exact same structure like the case of nicotine, but it's so active on the receptor site that the receptor site gets used to it. [incredibly addicting drugs – make you stay up for days on end, lose logical function][mescaline][We have politics, which regulates how we're supposed to behave and regulating drugs, and then there's science. The two have very little to do with each other, because if you looked at the science, if we made laws based on science, things that are illegal now would be legal, things that are legal now would be illegal. If you compared the effects of alcohol to some of these substances, one would wonder why in the world are these substances illegal where alcohol is legal? That's because alcohol has been in our culture ever since we've had history. There's some reason that alcohol survived. In other cultures, some of these other substances are given a prominence that they aren't in this culture. Ethnopharmacology – going to different cultures around the world, finding these substances that might have been used in traditional medicines – or often in religious rituals. If one aspect of religion is revelation is mystery, if you can take something that takes you into that space where you're dealing with mystery, then at different points in different places at different times, some people thought that was a good thing. Mescaline – comes from cactus, strong effect. What is the role of these substances in other cultures? It's a reflection on our own culture – why are we driven to take these things, and why do certain ones end up being bad and certain one end up being good. This has a chemical basis, but it's got some awfully human effects. If you're going to be in science, you need to know what you do has an effect on the world itself. You knowledge, you can help guide how you behave in the world and how you devise something] Look at the close structural semblance between that and amphetamine. [what does having that methyl group do] How much does that methyl group have an effect? How many different functional groups do we have to put on here before something's legal and useful? Ritalin, that's a prescribed medication, that's just an extended methyl group, and it's just got an ester on there. Those two changes somehow make this a useful chemical.

Serotonin

Tryptophan – the 'sleepy' chemical that you would have in turkey. Why is that so? You do a decarboxylation, you get to tryptamine; you do a hydroxylation, you get to serotonin. Why is it called 5-HT? Because it's 5-hydroxytryptophan. Serotonin is also related to melatonin, which is related to your sleep cycle. These are your mood and sleep system drugs. These are thought to have some of the most profound effects on your general psychological make-up, which is why it is this neurotransmitter system that, at least at one point, was the most heavy focus of psychiatric research, developing more effective antidepressants. [Serotonin-specific reuptake inhibitor (SSRI) – antidepressants]

Look at the shape of all of these [serotonin derivatives]; notice that it's got this indole moiety. That identical piece is found in both LSD and psilocybin. These are both rather infamous chemicals, in the sense that they cause a whole range of effects. [hallucinations, time perception, hearing, taste, smell] [timothy leary] Some poor researcher who was doing some research on a series of compounds known as ergots that come from these different fungi. He got some on his hand, because there was a hole in his glove, and he tripped. He didn't know what it was, he was just working with the compound, a little bit got on him, he went back home, and it was the most fascinating bike ride he'd ever taken. He later on went back and said: wow, this might have some sort of therapeutic use, which is where it was originally intended. Then, of course, someone else got a hold of it and realized [it had the potential for enabling revelations] Mystery and revelation [religion], some people thought that they found it in here. [DMT – this is not a how-to lecture – a careful balance – PTS][PCR – use Nobel prize money to buy acid and go surfing][psychonaut][What is good? What is bad?]

Cannabinol – very popular class of chemicals

The cannabinoid neurotransmitter system is somewhat related to memory [?]. How can you do legitimate research in these compounds if someone who might be funding you is worried that you might have found out something bad, that you might find out something good. [this substance is illegal because of politics, not science – scare in 20s and 30s targeting specific groups; cotton industry against hemp][Denver – neon sign] How can you do the research because how can you get funding because what if, oh my goodness, you might say that there might be something beneficial from it? [DMT? for PTS] Endocannabinoids – things that get produced in the body. Why is it that we as animals have a plant-based receptor site? [Opioid receptors.] THC – this is one of a hundred cannabinoids that might be in a particular strain.

Opioids. Look at morphine; look at the two -OH groups on either side of morphine. Look at heroin: it's the exact same structure, but it has these two acetyl groups on it. The acetyl groups make it more lipophilic, which means this can pass more easily into the blood-brain barrier, but in the brain, it gets hydrolyzed and it turns into morphine. [Heroin, one of nastiest in terms of effects] It does a really good job of killing pain and killing concern; we have a neurotransmitter site that's programmed to accept it. Why do we have this receptor site? Maybe in certain circumstances, it's ok to kill off the pain? How did we develop as creature to tolerate pain at all, if we had some system to deal with it? [runner's high]

Histamine

[GABA]

The end.