

BRAIN SCIENCE PODCAST

with Ginger Campbell, MD

Episode #8:

How Neurons Communicate

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This is the *Brain Science Podcast*. The podcast for everyone who has a brain. And I'm your host, Dr. Ginger Campbell. On the *Brain Science Podcast*, I explore how recent discoveries in neuroscience are unraveling the mysteries of how our brains make us who we are.

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This is episode 8 of the *Brain Science Podcast: How Neurons Communicate*. I've been having a lot of requests that I talk a little bit about the chemistry of the brain. So today I wanted to talk about neurotransmitters, but I realize that I needed to give you some background information, so the topic is expanded slightly. My main reference for this episode is the textbook *From Brain to Neuron* (should be *From Neuron to Brain*), which was published in 2001. I'll put a link to this book in the show notes.

I'd like to welcome any of you who are new listeners but also to warn you that this episode is a little different from the typical ***Brain Science Podcast*** episode. Usually I discuss a book that is aimed at general audiences. So this episode is a little bit more technical than usual. On the other hand, I have several listeners who are studying neuroscience in college. You might find this information to be only a review. Please send me feedback if you spot any errors. For most of you, you may prefer to listen to this episode- because it's kind of long and heavy- you may want to listen to it in three separate parts, and I've put some musical breaks in to sort of clue you in to where the topics change. Or you could just listen through all the way once and then go back and listen again to get the details.

As usual, I would really appreciate your questions and feedback. You can post your questions

and feedback at the website brainsciencepodcast.com, or send me e-mail at docartemis@gmail.com. If I get some good questions I may also be able to use them in the next podcast. With respect to e-mails and comments, I appreciate those of you who have written to me. If I have a chance I'll put some e-mails at the end of the episodes. As I mentioned, this is a long episode so let's get started.

The first thing that we need to talk about is the principles of neuron signaling. One thing that surprised researchers when it was initially discovered is that neuron signaling is virtually identical in all neurons, which is why we can use other animals to discover how the nervous system works. I'm not going to talk about how the measurement techniques were developed, although this is a fascinating subject if you're really into the meat of neuroscience. I refer you to the text. This is an excellent text in terms of describing the scientific method and technique.

One key discovery that is important to recognize, and this is a pretty old one but is still important to understanding the principles, and that is the resting membrane potential of the neuron is negative. What that means is that the charge of the inside of the neuron is negative relative to outside the neuron. Now this is actually true for every cell in the body, but it is really important in neurons. Now there's two types of signaling that neurons can do. They can do electrical signaling, and they can do chemical signaling. And it is with chemical signaling that neurotransmitters come in.

First I'm going to talk just briefly about electrical signaling. There are two types, and they're both ultimately caused by ions flowing into or out of the neuron. There is something called local graded potentials, which depend on passive conduction, and these can only spread very short distances because basically the signal starts at one size and shrinks as it spreads. So you could sort of think of these as the analog signals. But neurons really don't conduct these signals very well, which is why they are called local. The only place I know of that they're really significant is in the photoreceptor cells of the cornea. In this situation the local graded potentials can work because the photoreceptor cells are very short. So they kind of represent an exception to the general rule that action potentials are needed to signal from one neuron to the next.

The action potential is the second type of electrical signaling and it's the most important because this is the main way that electrical signals go from neuron to neuron and from neuron to end organs like muscles. Since these are all-or-none signals, basically spikes, you can think of them as digital. When a certain voltage threshold is passed, then a voltage spike occurs. And it gets transmitted from one end of the neuron to the other and all action potentials look exactly the same.

Now I'm not going to get into the technical stuff about which ion gates open and so forth, but the basic principle is that the action potential involves opening and closing of ion channels, but in this case, compared to the local graded potential, there's a chain reaction. As the action potential propagates down the neuron- so the channels open so that the action potential goes from one end of the neuron to the other without changing. In other words the size is exactly the same when it gets to the other end, as opposed to the local graded potential which dies out within a short distance. Now since all action potentials look the same, information is actually communicated by frequency or by changes in frequency. In general a strong signal would be having a high frequency, that is lots of action potentials in a short time.

In the nervous system, the synapse is really where the action is. That's the space between the neuron and the next neuron, or between the end of the axon, which is the output end of the neuron, and an end-organ like a muscle. What happens is that when the action potential reaches the end of the axon, the voltage spike causes the release of chemical signals called neurotransmitters. The neurotransmitters go into the synapse. They reach the target cell and then interact with receptors on the membrane of the target cell, whether that be another neuron or a muscle cell or whatever. Whether the signal is excitatory or inhibitory really depends on the receptor. Now remember that the next neuron probably has synapses from many other neurons. So it's actually the sum of the excitatory and inhibitory signals coming in that determine whether an action potential will occur in the next neuron. Or in the case of a muscle whether or not it will contract.

Now what I just described is a chemical synapse. If the receptor is actually an ion channel itself that is being opened or closed, then this is called a direct chemical synapse. Now all receptors are membrane proteins. If the receptor actually is not an ion channel but itself will

then influence an ion channel or send a chemical message that interacts somewhere within the cell, then that's called an indirect chemical synapse. If when the receptor receives the neurotransmitter it causes the release of another chemical signal within the cell, the second chemical signal is called, quite logically, the second messenger. It's important to understand that this whole process occurs on probably every cell of the body, not just neurons. It's just neurons are the only ones that can make action potentials. An electrical synapse would be one that current flows from one neuron to the next. And this is actually very common in invertebrates. And it has been discovered to exist in mammals, although its role doesn't seem to be very important.

So the membrane proteins, or the receptors, are a key player not just in neurons but, as I said, in cells all over the body. Ion channels are membrane proteins through which positive and negative charges enter or leave the cell. Some of these are passive channels, which means that they just allow ions to go down their concentration gradient. There are also active channels. These require energy. They're often described as pumps because they move ions against the concentration gradient. Both active and passive channels are probably involved in action potentials. You don't really need to know anything about ion channels but I will be referring to them so you just need to have a simple concept of what they are.

One key idea I do want to mention kind of as an aside is that although these channels are very small, they are bigger than the ions that pass through them, which means they are not sub-atomic. And there isn't any need to ascribe quantum mechanics to their behavior.

There are two ways that membrane proteins are important to our discussion of neurotransmitters. First of all, as I said, receptors are membrane proteins. Also, other ion channels may be opened and closed as the result of a signal from a neurotransmitter. A lot has been discovered about the structure of these receptor proteins, and obviously they are under genetic control. We begin to have an overlap between neurobiology and genetics.

Another key discovery is the fact that each neurotransmitter has many different kinds of receptors- maybe 20-50 per neurotransmitter- and the effects of each receptor are different. There are also multiple types of ion channels for each ion, and all of these channels and

receptors and genetically determined.

Just to sum up before we take a brief break, the first principle that you need to understand about neuron signaling is that the action potential is the digital signal that the neuron transmits, but between neurons there are chemical synapses. The neurotransmitters interact with the receptors on the so-called postsynaptic cell. It is actually the sum of all the incoming signals at the postsynaptic cell that determine whether or not the next cell passes the signal on.

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Hopefully you're still with me and you're wondering when we're going to get around to talking about neurotransmitters. Let's reflect on [how] what we have learned so far implies about how the brain is different from a digital computer. Well obviously all this chemical signaling is a key difference. It means that there's a lot higher level of complexity in the signaling in the brain. I'm going to come back to this theme often because I think it's really important to keep this in mind when you hear claims about what can be done with artificial intelligence. While the action potentials have a digital quality, everything else about how the brain works is strikingly different from a computer. Obviously there's part of it that can be modeled, but the complexity of the overall whole far exceeds today's most complex computer. It is often noted that the brain's ability to constantly rewire itself at the level of the synapse far exceeds anything that has been modeled. No doubt someone really brilliant is going to eventually figure out how to simulate a smaller brain, but I think it's fair to say that right now our knowledge is too incomplete for that to be accomplished.

OK. What are neurotransmitters? In his book *In Search of Memory*, Dr. Eric Kandel defined neurotransmitters as follows. He says a neurotransmitter is "a chemical substance that is released by one neuron and binds to a receptor of another neuron, altering the flow of electrical current or internal biochemical events within the second cell. The specific action of the neurotransmitter depends on the receptor. " And, as I mentioned earlier, there are many kinds of receptors for a single neurotransmitter. This comes from page 443 of the excellent glossary at the end of this book.

Now it's not the structure of the compound that makes it a neurotransmitter. It's really its function. For example, glutamate, which is a simple amino acid, is the main excitatory neurotransmitter in the brain. Obviously it's not an excitatory neurotransmitter when it's incorporated into other proteins. And the same substance might be a neurotransmitter in the brain and a hormone elsewhere in the body. An example of this is the compound epinephrine, which used to be called adrenaline because it came from adrenal gland also. And this was before they figured out that epinephrine, which is known as a neurotransmitter, was the same thing as adrenaline. And you'll see this a lot of times when you see compounds that seem to have more than one name, and it can be very confusing because a lot of things were named before their structure was determined, and then it turned out that they were actually identical. And I'll give you some examples of this later.

It's because of these principles that it doesn't make sense to talk about neurotransmitters in isolation. That's the reason why I seem to be approaching this subject so indirectly, trying to give you the background you need to really understand them.

Now the first neurotransmitter to be extensively studied was acetylcholine. This is the neurotransmitter that is released at the neuromuscular junction, i.e. where nerves connect to muscles. So it was possible to study it in the days when our techniques of measurement were less advanced than they are now. But it turns out that acetylcholine is important in the nervous system, and I'll come back to that later. At any rate, the neuromuscular junction is an example of a direct chemical synapse. That means the receptors are themselves ion channels. Basically the acetylcholine opens channels that allow positive charges, or cations, to flow down their concentration gradient into the cell. An inhibitory signal would open channels permeable usually to chloride, which is negatively charged, which then would tend to push the membrane potential away from the threshold for firing. So again it's the sum of the signals coming in that determine whether firing actually occurs.

It's also been shown that receptors desensitize if they're exposed to prolonged or repeated exposure. You might think of this, it might be part of what happens with addiction. It takes more and more of the same drug to get the same effect because of this receptor desensitization. In the mammalian central nervous system- that includes us- there are three

major neurotransmitters that act through direct chemical synapses. So they're called ionotropic neurotransmitters and the receptors are called ionotropic receptors. These are GABA, glycine, and glutamate, which I already mentioned is the most prevalent excitatory neurotransmitter. GABA and glycine are inhibitory. But these three, along with many others including dopamine, histamine, and norepinephrine, can also participate in the indirect synaptic transmission. And I'll talk about that some more in a few minutes.

One characteristic of a chemical synapse is the so-called synaptic delay. Experiments have shown that there is a delay between the release of the neurotransmitter into the synapse and the appearance of the action potential in the target cell, and that this delay is about 1 millisecond. Electrical transmission obviously lacks this delay. Another advantage of electrical transmission is that it's more reliable in the sense that it can't be blocked by toxins or anything in the synapse. There is evidence that direct electrical transmission is involved at lower levels like reflexes. but post-synaptic cells can actually have both things going on. They can be receiving synapses of both types. When you consider the delay and the reliability issues, you might ask, "Why do we have chemical synapses?" This is something you might want to think about.

So now let's talk about the indirect chemical synapse, because this is where things get really interesting but much more complicated. The basic idea is that the neurotransmitter interacts with the so-called metabotropic receptors. The metabotropic receptors then release the so-called second messenger. The second messenger then might interact with an ion channel- usually this would be a potassium or calcium channel- or, and it may do both, it may send signals to the nucleus to increase or decrease various proteins in the cell. And this happens even in invertebrates. If you've been listening to the show since the beginning, you probably remember we talked about this briefly when we talked about Dr. Kandel's work with the *Aplysia*. And what was happening- a neurotransmitter was causing a kinase to be released which is a type of enzyme. And it went to the nucleus and basically strengthened the synthesis of proteins that then came back down and helped to strengthen the synapse.

Why is this important? Well first, the signal can be amplified so that a very small amount of neurotransmitter can have a big effect. And secondly, the signals to the nucleus are what

makes plasticity possible. An almost endless variety of receptor properties allows a fairly small number of neurotransmitters to produce extremely diverse effect. Now when it comes to the second messengers, the biochemistry of what they do can be kind of intimidating. And I'm just going to briefly mention a couple of examples.

The first one probably to be studied was cyclic AMP because it's important in a lot of other cells in the body. Basically it causes the activation of a protein kinase, which as I said is an enzyme, which then puts a phosphorus molecule (correction: phosphate molecule) onto a protein in a certain calcium channel. And this causes the shape of the channel to change and opens the channel.

Nitric oxide and carbon monoxide are also second messengers. This would be carbon monoxide actually made inside the cell, not externally. And calcium, which turns out to be an extremely important ion in the body, can itself act as a second messenger. So it's the same principle as before. It's not the messenger but who it talks to that matters. Now it's probably not surprising if I tell you that this indirect chemical transmission has even more delay built into it, but the key is that the effects also last longer. The changes may last for days or longer, perhaps even years. And this is what we were talking about when we talked about Dr. Kandel's work on memory.

So how are the neurotransmitters released? The action potential comes down to the cell and stimulates their release. Well they're actually contained in little vesicles. So because they're in little vesicles they get released in clumps or quanta. And a lot of work went into actually proving this mechanism. Another important principle is that everything gets recycled. Now obviously this indirect chemical synapse is very important for memory and neuroplasticity. And these are subjects that we're going to talk about in more detail in future podcasts.

[music]

OK. Now we're ready to talk a little bit about the neurotransmitters themselves. There are two types of neurotransmitters. There are the so-called neuropeptides, which are relatively larger molecules since they're peptides which means they're made out of amino acids, and then there

are the smaller so-called low-molecular-weight transmitters like acetylcholine. Some other low-molecular-weight transmitters include norepinephrine, epinephrine, 5-hydroxytryptamine (which is more commonly called serotonin), histamine, adenosine triphosphate (i.e. ATP), gamma-aminobutyric acid (which we usually call GABA for short), glycine, and glutamate. Now if you've had any chemistry at all you recognize that these are compounds that have other functions in the body besides being neurotransmitters.

The key difference between a neuropeptide and a low-molecular-weight transmitter is really not about size. It's the fact that the neuropeptides are synthesized in the cell body and put into vesicles and then transmitted down to the axon terminal, while the low-molecular-weight transmitters are made right in the terminal. And these were the ones that were discovered earlier. There is a hypothesis called the SNARE hypothesis that is trying to explain how the neuropeptides get synthesized and transmitted. That is definitely beyond the scope of our discussion.

One key idea is the fact that some neurotransmitters are released in many regions of the brain while others are found only in small groups of cells. And this has therapeutic implications, because if you try to give somebody something that is going to cause an increase of a neurotransmitter, if it a neurotransmitter whose normal action is only in small areas, you tend to get side effects when it appears in the places where it's not normally supposed to appear.

Now the neuropeptides are actually what you might be thinking of when you hear about neurotransmitters if you only listen to mass media presentations. Because, for example, the endorphins- you know the runner's high? The endorphins are neuropeptides. Another one is corticotropin or ACTH. Again something you may not have heard of unless you had chemistry. That one sends important messages to the adrenal gland. There's vasopressin, which not surprisingly is involved in blood pressure control, oxytocin, which is involved in breastfeeding and also seems to be involved in having a calming influence on the mother and also seems to have a role in monogamy in the sense that animals with oxytocin tend to be monogamous. Substance P is a neuropeptide which is involved in the perception of pain. And then there's glucagon and insulin. Now you might have heard of these if you know anything at all about diabetes because glucagon is one that tends to cause release of sugar from cells, and insulin

causes cells to take up sugar. So this is a good reminder that a compound can be both a hormone and a neurotransmitter.

You might have heard of catecholamines. Those include some of the ones I mentioned before—dopamine, norepinephrine, epinephrine, and also one called DOPA. These tend to be important in the sympathetic nervous system. Especially in mammals there's the release of epinephrine and norepinephrine by the sympathetic nervous system to raise blood pressure and to raise heart rate. At the same time, the adrenal medulla, which is part of the adrenal gland, also makes epinephrine and norepinephrine. I think this shows that there's really blurring of the distinction between the nervous system and the endocrine system the more we begin to learn.

Now one neurotransmitter that you've probably heard of because it's gotten a lot of press although they don't necessarily tell anybody that it's a neurotransmitter, and that is serotonin. It's also a low-molecular-weight one, which means it's made right there at the axon terminal. Well the way it's synthesized is important. It starts out from the amino acid tryptophan and is converted into something called 5-HTP. And the enzyme that does this is the same one that is needed to convert DOPA to dopamine. Neurons can't make the amino acid tryptophan.

I'll be coming back a little bit more to the functions of serotonin in a few minutes. First I want to talk about what happens to the neurotransmitter after it gets released. Well, acetylcholine is actually broken down by a specific enzyme called acetylcholinesterase, which is the one that gets blocked when you have certain kinds of organophosphate or pesticide poisoning. Glutamate, which is just an amino acid, is mostly just taken up by the glial cells, which are support cells in the brain. Larger neurotransmitters get removed by various uptake mechanisms. And this is used to invent drugs or to discover mechanisms of drugs. For example cocaine blocks reuptake of norepinephrine, which is why cocaine makes people feel, you know, jazzed up and jittery. Tricyclic antidepressants usually block the reuptake of norepinephrine and how this works isn't very well understood. The newer antidepressants are mostly of the class called serotonin reuptake inhibitors. That's because they block the uptake of serotonin. An example of this would be Prozac.

So obviously the rate of neurotransmitter synthesis has to be subject to both long- and short-term control. For example stress can lead to excess sympathetic tone and excess sympathetic neurotransmitters and result in hypertension. We don't really have drugs yet that target the neurotransmitter synthesis itself. Most of the current drugs are aimed at either blocking the effect or, depending on if you want more or less of the substance a blood pressure (medicine) like Lopressor or Inderal, which is the old one which is a so-called beta-blocker. It basically works by blocking the receptors for the sympathetics so that it will lower the blood pressure.

Right now we know how to aim drugs at the receptors and at the reuptake. But we don't know how to affect the synthesis, although this is probably going to come when we have more understanding of the genetic components.

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Let's talk about how neurotransmitters function in the central nervous system. First of all GABA, as I mentioned before, is the main inhibitory neurotransmitter. So it turns out that there's three types of GABA receptors. And it's the most common one that is affected by anticonvulsants like barbiturates and drugs like benzodiazepines. Glutamate, as I have mentioned, is the major excitatory neurotransmitter and it's known to have two ionotropic receptors.

Just a little aside about glutamate. As I mentioned, glutamate is the major excitatory neurotransmitter in the central nervous system, and the way that it's removed is by uptake by the glial cells. Now you may or may not know this, but the major metabolite of Nutrasweet™, or aspartame, is glutamate. I think this probably explains why people who drink caffeine-free sugar-free diet-type drinks still feel they get a lift from these drinks and in fact they seem to be particularly habit-forming. I personally try to avoid Nutrasweet™ although it is impossible to avoid completely, because I'm concerned about disrupting the balance in my central nervous system. I'm thinking, my body's got to get rid of all this glutamate somehow, and there's no proven relationship between this and any particular neurological disease. There is a lot of anecdotal evidence. But one problem is, I don't think anyone can get funding to determine whether Nutrasweet™ causes neurological diseases.

Getting back on the subject of the neurotransmitters, GABA and glutamate can both act on those metabotropic receptors- the ones that use second messengers. What about acetylcholine? That's the one that's the major neurotransmitter at the neuromuscular junction. Well it turns out that it's also important in the central nervous system, and I'm going to talk about that in a few minutes. Some of these new drugs for Alzheimer's disease are actually targeting this problem and trying to increase the amount of acetylcholine, because it's known that it's the certain system in the forebrain called the forebrain cholinergic system that's degenerating in dementia. One problem is that this is an example of an approach that can't be sufficiently targeted, so you get a lot of side effects and you don't really get very much of the increase in acetylcholine at the place where you need it.

Before I close, I want to talk a little bit more about the specific neurotransmitters, although I've given you little tidbits here and there. I would think that it would be a good idea to be able to remember that GABA and glycine are the key inhibitory neurotransmitters, because it may turn out that inhibition is more important than excitation. Think about it. We are inundated by inputs. Now obviously the sensory input that our body gives our brain is more than we can deal with. So how our body inhibits the signals that don't make it to consciousness is pretty important.

And then, I mentioned acetylcholine a minute ago. It has two types of receptors- so-called muscarinic and nicotinic receptors. And it appears that the nicotinic receptors have a role in addiction. It has been shown that- that's why they're called nicotinic, as in nicotine- and that seems to be what nicotine interacts with. And I don't know if they know exactly why that makes you addicted yet, but it's definitely something going on in the brain. It also seems like acetylcholine is really important in a lot of the older parts of the brain, because the cholinergic nuclei- and that's just little clumps of neurons that make acetylcholine- they send projections to the cortex, the hippocampus, amygdala, thalamus, and brainstem. The cortex is pretty new but all those other structures are old. Even so, studies show that the cholinergic system is important for learning, memory, and cognition. Although this shouldn't really surprise us now that we know that even simple creatures are capable of learning and memory. And as I mentioned before, this is the system that seems to be most damaged in Alzheimer's disease.

Perhaps when you think of the word *neurotransmitter* you're actually thinking of neuropeptides, which have been gathering increasing attention and interest since they were discovered in the late '70s. Some preliminary research that led up to their discovery: first of all, early on they realized there were peptides that were active in the GI tract. They seemed to be released by the sympathetic nervous system, so it was sort of a clue. Substance P, which is released in peripheral nerve endings, was discovered in 1931, but I'm not sure exactly when they figured out that it was a neurotransmitter related to pain. Finally, in the '70s they discovered that there were peptides in the brain that acted like opiates. And this is really what led to the sort of tremendous breakthroughs and real interest in the area of the neuropeptides.

A good personal account of these early discoveries is Candace Pert's autobiography, *Molecules of Emotion*. Now Candace Pert's kind of gone over to the, I won't say to the dark side, but she's kind of gone over to the the New Age movement and I think the latest edition of her book has posted on it on the book cover, "Appeared on *What the Bleep Do We Know?*" And this might tend to make you want to avoid this book, but it's a good book anyway. First of all it was written before she got into all that stuff, but it's a combination of a biography and science book, somewhat like Dr. Kandel's *In Search of Memory*. In fact she actually kind of has an alternating chapters style in which alternating chapters are almost like little mini-lectures about the principles of neurotransmitters. You might decide she explains it better than I did. And then the chapters about her own personal story give you an insight into what the science was like and especially an insight into what it was like to be a woman scientist in the late '70s- it was really a hard road. She did not get the Nobel Prize even though he co-workers on the project did. I still recommend the book.

Now as far as these neuropeptides go, they've only discovered three so-called opiate receptors, but they've got a lot of other molecules that seem to... they call them ligands, which means they think that they're interacting, so there's probably more so-called endogenous [originating within the body] opiate receptors. Another important area of research relates to the discovery that peptides and other substances known to be important elsewhere in the body turn out to be active in the central nervous system, such as the so-called biogenic amines. These include norepinephrine, epinephrine, dopamine, histamine, and serotonin. So it turns out that they,

although they were originally discovered because of their activity in other parts of the body, it turns out that they are also CNS neurotransmitters. CNS means "central nervous system." They're usually made by clusters of neurons called nuclei, but they have widespread effects in the central nervous system and they seem to be neuromodulators.

For example, norepinephrine comes from an area in the pons where there is a nucleus called *locus ceruleus*, but its projections go up into what's known as the reticular activating system. And it seems to regulate attention, arousal, and circadian rhythms. Serotonin comes from the brainstem, the nucleus called the raphe nuclei. It sends projections to the spinal cord and to the ascending reticular activating system. It's known to be involved in sleep-wake cycles, and mood, and a lot of other complex actions that we're just barely beginning to understand.

You might have been surprised to hear me mention histamine in that list since you've probably heard of histamine. It's the one involved in immune reactions like when you break out in hives. And in the body it's usually released by mast cells. Throughout the body they've studied the H1 and the H2 receptors, and these receptors have even been cloned. The H2 receptors are in the GI tract, and drugs that block H2 receptors are things like Pepcid™ and Zantac™, Tagamet™; ones you take to block stomach acid. The neurons that make histamine in the brain seem to be concentrated into a fairly small area that includes part of the hypothalamus, but they send axons out to reach all parts of the brain. These seem to innervate not just neurons but glial cells, small blood vessels, and even capillaries. Histamine seems to be regulating arousal and energy metabolism through indirect mechanisms which have not really been totally understood yet.

Dopamine is the one that is important in Parkinson's disease. It's made in an area called the substantia nigra- called that because it stains dark on microscope slides- which is located in the basal ganglia, and it's also made in other nuclei of the midbrain. So these are brainstem areas. It's important for the control of movement. So a person with Parkinson's disease will have tremors and extreme stiffness and difficulty walking, and then later on in the course they'll have mental problems and sometimes even dementia.

Now treating Parkinson's disease provides an excellent example of the difficulties in trying to

treat a disease by replacing a neurotransmitter. First off, dopamine can't cross the blood-brain barrier. But its precursor, which is called L-DOPA, can. They give people who have Parkinson's disease L-DOPA. And it helps but it can cause side effects because it causes imbalances in other areas of the brain. On the other side of the coin, anti-psychotics, which also affect neurotransmitter levels, can cause patients to have symptoms that look a lot like Parkinson's disease. And these get called Parkinsonian side effects.

So it's easy to see why in the future, researchers hope that they'll be able to target the receptors more specifically. And I guess eventually target the actual synthesis.

So you can see why neurotransmitters present many interesting areas for researchers. They're still trying to figure out where the neurotransmitters are made and where the different types of receptors are located, and how all this is controlled genetically. If you want to know more of the nitty-gritty of this, the textbook *From Neuron to Brain* is a great place to start.

[music]

OK- I guess this gets the award for the extremely long, possibly boring episode. But I do think I need to summarize before I quit. What do you need to know out of all this?

Well the basic things to remember are simply that a neurotransmitter is a chemical substance, usually released by a neuron, that interacts with a receptor on a target cell to produce an effect. It's considered a neurotransmitter if it's acting in the nervous system or being released by a neuron. And, from our recent discoveries, we can see that almost any compound that reaches the nervous system has the potential to interact with membrane proteins and have some effect. Fortunately most man-made chemicals can't cross the blood-brain barrier. Drugs that are intended to have CNS effects have to be designed so that they can cross.

Another important principle is that many chemical compounds in the body have effects both in the periphery (or the body) and in the central nervous system. And I didn't even get a chance to mention how the central nervous system interacts with the immune system. So the main implication of all this is that we can't study the brain or the body in isolation from each other. One of the most surprising discoveries in all this is the realization that the

communication is entirely two-way. There's no such thing as mind over matter.

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OK I wanted to talk about e-mails today but obviously this episode has already run too long so I'm going to have to save those. Please do send me feedback at docartemis@gmail.com or post comments at the website brainsciencepodcast.com. Thanks for listening and I'll talk to you again in a couple of weeks.

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-transcribed by Jenine John

Dr. Campbell would like to thank Ms. Johns for her scrupulous work on transcribing this episode. She hopes that this transcript will help listeners who want to understand this potentially difficult material better. (transcript posted 11/30/08)