

Transcript for Dr. Amanda Freeman's Video: Learning About GABA, Part 1

SLIDE 1

This is a human brain. It weighs roughly 3 pounds and consists of almost 100,000,000,000 (one hundred billion) neurons. Just for perspective, the height of a stack of 100,000,000,000 (one hundred billion) one dollar bills measures 6,786.6 miles. This is sufficient to reach from here to the International Space Station AND BACK, 14 times.

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These neurons are not all identical, as can be seen in this image of a discrete region in the brain. This happens to be a rat brain, but the same holds true in the human brain. This piece of tissue is stained with a chemical that makes the cell body of neurons blue. You'll notice that some of the neurons are packed tightly and some are more widely spaced. Some of the neurons are large, and some are tiny. Similar to these differences in their physical characteristics, neurons have different functions and methods of communicating with other neurons.

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This highly magnified image shows an individual neuron, and the red arrow is pointing to the cell body. Neurons range in size, and the smallest ones have a cell body that is 4 microns in diameter (a micron is one one-thousandth of a millimeter) and the largest is approximately 100 microns in diameter. This is the same as the thickness of a piece of paper that you would put in a printer.

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This cartoon illustrates the flow of information between two neurons.

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If we take a closer look at the junctions between these two neurons, we'll notice that there are discrete locations where these two neurons are close enough to communicate. These



structures are called synapses. Each neuron has an estimated 1,000 – 10,000 synapses, which means that there one hundred trillion to one quadrillion synapses in our brain. We refer to the upstream neuron, the blue one, as the presynaptic neuron and the downstream neuron, the red one, as the postsynaptic neuron. Communication from the presynaptic neuron tells the postsynaptic neuron how it should act. Can you imagine having 1,000 – 10,000 people telling you how to behave?

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Now let's take an even closer look at the synapse. The presynaptic neuron communicates with the postsynaptic neuron by releasing chemicals, referred to as neurotransmitters, which bind to receptors on the surface of the postsynaptic neuron. The types of neurotransmitters released, and the types of receptors present, determine the types of communication that can occur. Again, if we liken this to our communication, our words are like neurotransmitters which relay our message to another person. Each word has a different meaning, much like the different types of neurotransmitters. For example, "yes" communicates a very different message from "no".

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An "excitatory" neurotransmitter drives activity in the postsynaptic neuron. We can think of this as "go" or "yes".

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An "inhibitory" neurotransmitter decreases activity in the postsynaptic neuron. We can think of this as "stop" or "no".

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l-Glutamic acid, better known as Glutamate, is the principle excitatory neurotransmitter in the brain. Glutamate is used to communicate at approximately 50% of the synapses in our brain. That means that half of our synapses are "go" synapses.



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γ-aminobutyric acid, better known as GABA, is the principle inhibitory neurotransmitter in our brain. GABA is used to communicate at approximately 40% of the synapses in our brain.

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The remaining synapses in our brain use other neurotransmitters to communicate, including: acetylcholine, dopamine, norepinephrine, serotonin and others. These neurotransmitters can be excitatory or inhibitory, depending upon the receptor present. If we continue the analogy with our communication, these neurotransmitters are like homonyms – the same one can have different meanings. For example, the word "row" can refer to "moving a boat with oars," as in "row a boat," or it can be a line of things like a "row of chairs." The meaning depends on the context. In neuronal communication, the context is dependent on postsynaptic receptors.

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Now that we know what GABA is, let's talk about what GABA has to do with sleep.

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There are multiple neurotransmitter systems that the brain uses to promote wakefulness. These include histamine, serotonin, norepinephrine, acetylcholine, and hypocretin/orexin. These systems have overlapping projections that are widespread throughout the brain. This redundancy indicates the importance of wakefulness and the need for a backup system to maintain wakefulness, should one of these systems be disrupted. Now, we know in the case of narcolepsy with cataplexy (type I narcolepsy) that the redundancy does not perform perfectly when hypocretin/orexin is lost; otherwise, these patients would not fall asleep at inappropriate times.

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Although there are 5 wake-promoting neurotransmitters, there is only one neurotransmitter system that promotes sleep. This is GABA. Think about that for a moment. There are five wake promoting neurotransmitter systems and only one to promote sleep. In the past, it has been thought that when there is a deficit in wakefulness,



as in hypersomnia, one of the 5 neurotransmitter systems is broken. The fact that a loss of function results from a loss of brain is very common – think about stroke or Parkinson's disease. We know that particular functions are disrupted due to the loss of activity in the brain. Even in the example of narcolepsy with cataplexy, it is clear that a loss of function underlies sleep disorders as well.

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This publication by Dr. David Rye and colleagues at Emory University, which first described GABA-related hypersomnia, brought light to the possibility that a deficit in wakefulness could also be due to excessive activity of the sleep-promoting system. So, what does it mean to have excessive activity of the GABA system? Since GABA is the inhibitory neurotransmitter, this means that there is too much inhibition in the brain and a stronger drive to sleep dominates the wake-promoting effects of other neurotransmitter systems.

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Not only was this publication a paradigm shift, the researchers identified a substance in the cerebrospinal fluid, which is still unnamed, that increased GABA's inhibitory effects. When GABA is applied to cells experimentally, we can record the resulting inhibition that is shown as a downward dip. If the cerebrospinal fluid from a patient with GABA-related hypersomnia is applied to the same cells, there is no response. However, if the substance is applied simultaneously with GABA, this combination potentiates the resulting inhibition. In other words, this inhibition is stronger – in fact, in this figure, the inhibition is twice as strong. That's the difference of someone saying "stop" and someone yelling "stop". This method of examining the substance and its effect on GABA signaling, is time- and labor-intensive. Not knowing what the substance is also limits the different ways in which we can examine where it comes from and what it does.

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Understanding the possibility that too much GABA underlies the excessive sleepiness in hypersomnia is important because it represents a change in the way we think about how sleep and wake are regulated. Since we still have many questions about the substance, and the mechanisms by which it is causing excessive sleepiness, it is important to support ongoing research.