

## How to Enhance Your Gut Microbiome for Brain & Overall Health | Huberman Lab Podcast #61

In this episode, I discuss the profound effect the gut has on the nervous system. I cover the structure and function of the gut-brain axis and the role of the gut microbiome in the brain and overall health. I describe how the gut controls hunger or satiety by affecting neurons in our brain. I also contrast the many pathways by which the gut influences the brain: direct vs. indirect pathways, chemical vs. mechanical, and fast vs. slow signaling. Additionally, I discuss what defines a healthy microbiome and how your lifestyle impacts the gut microbiome, including the effects of stress, fasting, antibiotics, pets, environment, prebiotics and probiotics. I address how different foods shape the gut microbiome, in particular, the emerging data that fermented foods can increase the diversity of healthy gut microbiota. Throughout the episode, I explain peer-reviewed and textbook findings that reveal the critical role of the gut microbiome in supporting mental and physical health and I outline simple tools that anyone can use in order to enhance their gut microbiome health.

#HubermanLab #GutHealth #Microbiome

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- Welcome to the Huberman Lab Podcast where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, we are going to discuss the gut and the brain, and we are going to discuss how your gut influences your brain and your brain influences your gut. As many of you probably know, there is a phenomenon called your gut feeling, which tends to be something that you seem to know without really knowing how you know it. That's one version of the gut feeling. The other is that you sense something in your actual gut, in your body, and that somehow drives you to think or feel or act in a particular way, maybe to move towards something or to move away from something. Now, today, we aren't going to focus so much on the psychology of gut feelings but on the biology of gut feelings and how the gut and brain interact. Because indeed your gut is communicating to your brain both directly by way of neurons, nerve cells, and indirectly by changing the chemistry of your body, which permeates up to your brain and impacts various aspects of brain function. But it works in the other direction,

too. Your brain is influencing your entire gut. And when I say entire gut, I don't just mean your stomach, I mean, your entire digestive tract. Your brain is impacting things like how quickly your food is digesting, the chemistry of your gut, if you happen to be stressed or not stressed. Whether or not you are under a particular social challenge or whether or not you're particularly happy will in fact adjust the chemistry of your gut and the chemistry of your gut in turn will change the way that your brain works. I'll put all that together for you in the context of what we call the gut microbiome. The gut microbiome are the trillions of little bacteria that live all the way along your digestive tract and that strongly impact the way that your entire body works at the level of metabolism, immune system, and brain function. And of course, we will discuss tools, things that you can do in order to maintain or improve your gut health. Because as you'll also soon see, gut health is immensely important for all aspects of our wellbeing at the level of our brain, at the level of our body, And there are simple, actionable things that we can all do in order to optimize our gut health in ways that optimize our overall nervous system functioning. So we will be sure to review those today. This episode also serves as a bit of a primer for our guest episode that's coming up next week with Dr. Justin Sonnenburg from Stanford University. Dr. Sonnenburg is a world expert in the gut microbiome and so we will dive really deep into the gut microbiome in all its complexity. We'll make it all very simple for you. We will also talk about actionable tools in that episode. This episode is a standalone episode, so you'll get a lot of information and tools,

00:03:02 AG1 (Athletic Greens), LMNT, InsideTracker

but if you have the opportunity to see this episode first, I think it will serve as a nice primer for the conversation with Dr. Sonnenburg. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public. In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Athletic Greens. Athletic Greens is an all-in-one vitamin mineral probiotic drink. I've been using Athletic Greens, which is now called AG1, since 2012 so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still take Athletic Greens once or twice a day is that it covers all of my foundational vitamin and mineral needs and also because it contains high quality probiotics and prebiotics, which

is a topic that we're going to talk a lot about today. With Athletic Greens, I can be sure that I'm getting all the vitamins and minerals that I need. So if I'm missing anything in my diet, I can compensate for that with the Athletic Greens. Plus it has the probiotics and prebiotics that can also compensate for any deficiencies that I might have in creating the right environment for my gut microbiome. If you'd like to try Athletic Greens, you can go to [athleticgreens.com/huberman](https://athleticgreens.com/huberman) to claim a special offer. They'll give you five free travel packs, which make it very easy to mix up Athletic Greens while you're in the car or on a plane or otherwise on the move, and they'll give year's supply of vitamin D3 K2. While not everyone needs additional vitamin D3, many people do even if they're getting sufficient sunlight. So you get the year's supply of vitamin D3, and it also has K2 in there. K2 has been shown to be important for various aspects of calcium regulation, cardiovascular health, and so on. Again, go to [athleticgreens.com/huberman](https://athleticgreens.com/huberman) to claim this special offer. Today's episode is also brought to us by LMNT. LMNT is an electrolyte drink that contains no sugar. It does however contain sodium, magnesium, and potassium. I've talked about sodium on the podcast before. I think sodium can indeed be problematic for some people with hypertension or pre-hypertension, but for many people, sodium is a great thing. It can increase blood volume in ways that can be helpful to them. It can improve nerve cell function in ways that can be helpful to them, and for me, anytime I'm exercising and sweating a lot, I want to replace my electrolytes and that means replacing sodium for adequate neuron function, muscle function, and so on. LMNT is formulated to help anyone with their electrolyte needs and is perfectly suited for people who are following a ketogenic, low carbohydrate, or paleo diet. LMNT contains a science-backed electrolyte ratio of 1000 milligrams of sodium, 200 milligrams of potassium, and 60 milligrams of magnesium. If you'd like to try LMNT, you can go to [drinklmnt.com/huberman](https://drinklmnt.com/huberman) to claim a free LMNT sample pack. You only pay the cost of shipping. Again, that's [drinklmnt.com/huberman](https://drinklmnt.com/huberman) to claim a free sample pack. Today's podcast is also brought to us by InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the things that impact your immediate and long-term health can only be assessed with a quality blood test. And nowadays with the advent of modern DNA tests, you can also get insights into, for instance, what your biological age is and how that compares to your chronological age. Now, one of the major problems with a lot of blood tests and DNA tests out there is that

you get numbers back, they'll tell you if those numbers are in range and out of range but they don't tell you anything about what to do with that information. With InsideTracker, they make everything very simple in terms of directing you towards particular protocols. So these could be nutrition protocols, supplementation protocols, or lifestyle behavioral protocols to help you bring those numbers into the ranges that are best for you. If you'd like to try InsideTracker, you can visit [insidetracker.com/huberman](https://insidetracker.com/huberman)

00:06:55 Your Gut-Brain Axis

to get 20% off any of InsideTracker's plans. That's [insidetracker.com/huberman](https://insidetracker.com/huberman) to get 20% off. Okay, let's talk about the gut and the brain and how your gut and your brain communicate in both directions. Because as I mentioned before, your gut is communicating all the time with your brain and your brain is communicating all the time with your gut. And so the two are in this ongoing dance with one another, that ordinarily is below your conscious detection although you're probably familiar with the experience of every once in a while getting a stomach ache or of eating something that doesn't agree with you, or conversely eating something that you find particularly delicious and that sensation or that experience rather being a whole body experience. Your mind is excited about what you're eating or just ate, your gut is excited about what you're eating or just ate, and it seems to be a kind of unified perception of both brain and body. Today, we're going to talk about how that comes about in the negative sense. Like, you know, when you meet someone you really dislike or when you have a stomach ache, and in the positive sense, when you interact with somebody that you really, really like and you'd like to spend more time with them, for instance, or when you eat something that you really, really like and you'd like to spend more time with that food, so to speak. Now, the gut and the brain represent what we call a biological circuit, meaning they include different stations. So station A communicates with station B, which communicates with station C, and so on. And as I mentioned earlier, it is bidirectional. It's a two-way street between gut and brain. I want to make the important point at the outset that when I say the word gut, when I refer to the gut, I am not just referring to the stomach. Most of us think that the gut equates to the stomach because we think of having a gut or not having a gut or having a gut feeling of some sort. But in the context of gut-brain signaling and the related microbiome, the gut includes the entire digestive tract. That's right, from start to finish the entire digestive tract so much so that today we're going to talk about, for instance, the

presence of neurons, nerve cells, that reside in your gut that communicate to specific locations in the brain and cause the release of specific neurochemicals, such as the neurochemical dopamine or serotonin, that can motivate you to seek more of a particular food or type of interaction or behavior, or to avoid particular foods, interactions, and behaviors. And some of those neurons, many of those neurons, in fact, reside in your intestines, not in your stomach. They can be in the small intestine or the large intestine. In fact, you actually have taste receptors and neurons located all along your digestive tract. You have neurons that are located all along your digestive tract and they are communicating to your brain

00:09:44 Gut-Brain Anatomy

to impact what you think, what you feel, and what you do. Okay, so for the gut-brain axis, we need to deal with the brain part and then we need to deal with the gut part. Let's just quickly talk about the brain part because there the word brain is also a bit of a misnomer in that when we say the gut-brain axis, it does include the brain but includes a lot of other things as well. So as many of you probably know by now, if you're listeners of this podcast, and if you don't, that's fine, your nervous system includes your brain and your spinal cord and those together constitute what's called the central nervous system. Your neural retinas, which are lining the back of your eyes and are the light sensing portion of your eyes are also part of your central nervous system. So actually your eyes are part of your brain. They're the only parts of your brain that are outside the cranial vault. So your retinas, your brain proper, and your spinal cord make up the central nervous system. The other parts of your nervous system constitute what's called the peripheral nervous system, which are the components of your nervous system that reside outside the retinas, brain, and spinal cord. Now, this is very important because today we're going to talk a lot about how the gut communicates with the brain. And it does that by way of peripheral nervous system components, meaning nerve cells that reside in the gut and elsewhere in the body that communicate to the brain and cross into the central nervous system to influence what you think and what you feel, okay? So that's the nervous system part of what we call the gut-brain axis, brain, again, just being a shorthand for including all the elements I just described. Gut, as you now know, includes all the elements of the digestive tract. Let's talk about the architecture or the structure of the gut of your digestive system. Now, not surprisingly your digestive system, aka your gut,

begins at your mouth and ends at your anus. And all along its length, there are a series of sphincters that cut off certain chambers of the digestive tract from the other chambers. Now, also along this tube that we call the digestive tract, there's great variation in the degree of acidity, or pH as it's sometimes called. That variation in acidity turns out to give rise to different little microenvironments in which particular microbiota, microbacteria, can thrive or fail to thrive. And so the way I'd like you to think about the digestive tract, this gut component of the gut-brain axis, is that it's not just one component. It's not just your stomach with a particular acidity and a bunch of microorganisms that work particularly well to make you feel good and make your digestive pathways work well. It's a series of chambers, little microenvironments, in which particular microbiota thrive and other microbiota do not. And certain behaviors that you undertake and certain experiences that you have will adjust those microenvironments in ways that make particular microbiota, certain bacteria, more likely to thrive and others less likely to thrive. We'll talk about how that was set up for you early in life. Actually from the moment that you came into the world, that microbiome was being established. It was actually strongly impacted depending on whether or not you were born by C-section or by vaginal birth. And it was strongly impacted by who handled you when you came into the world, literally the hands that were on you. How much skin contact you had, whether or not you were a preemie baby or not, whether or not you had pets at home, whether or not you were allowed to play in the dirt, whether or not you were allowed to eat snails or whether or not you were kept in a very antiseptic environment. All of those experiences shaped these little microenvironments and shaped what constitutes best or worst for those microenvironments, okay? So you have this long tube that we call the digestive tract and it's very, very long. In fact, if we were to splay it out, we were to take all the curves and turns out of the intestine, we would find that it is very long. It's approximately nine meters long. Now, the structure of that digestive tract turns out to be very important in terms of gut-brain signaling. Once again, it's a tube and the hollow of that tube is called the lumen, L-U-M-E-N. But the walls of the tube are not necessarily smooth, at least not for significant portions of the digestive tract. For much of the digestive tract, there are bumps and grooves that look very much like the folds in the brain, but these bumps and grooves are made up of other tissues. They're made up of what's called a mucosal lining, so there's a lot of mucus there. And if we were to look really closely, what we'd find is that there are little hairy-like cellular processes that we call microvilli that are able to push things along the digestive tract. The microbiota reside



everywhere along the lumen of the digestive tract, starting at the mouth and all the way to the other end. And they reside within those microvilli and they reside within the lumen. And if we were to look really closely at the bumps and grooves along the digestive tract, what we would find is that there are little niches, little areas in which particular things can grow and reside best. Now, that might sound kind of gross, but it actually is a good thing, especially what's growing and residing there are microbacterial organisms that are good for your gut and that signal good things to your brain. And we will talk about what that signaling looks like and how that's done and accomplished in just a few moments. But I want you to get a clear mental picture of your gut, something that we don't often see. And often when we think about the gut, again, we just think about the hollow of the stomach,

00:15:32 Microbiota vs. Gut Microbiome

food going in there, and getting digested, but it's far more complex and actually far more interesting than that. Now, I've been referring to the gut microbiome and to the microbiota and these bacteria. Let me define those terms a little bit more specifically just to avoid any confusion. The microbiota are the actual bacteria. The microbiome is used to refer to the bacteria but also all the genes as bacteria make, because it turns out that they make some important genes that actually impact all of us. You have loads and loads of these little microbiota, these bacteria. In fact, right now you are carrying with you about two to three kilograms, so that's more than six pounds, of these microbiota, these bacteria. And if we were to look at them under a microscope, what we would see is these are relatively simple little organisms. Some remain stationary so they might plop down into the mucosal lining or they might hang out on a particular microvilli or they might be in one of those little niches, and others can move about, but they basically fill the entire lumen. They surround and kind of coat the surface of the microvilli and they're tucked up into any of those little niches that are available to them to tuck into. If you were to take the head of a pin and look at it under the microscope, you could fit many, many hundreds, if not thousands or more of these little microbacteria. And the reason I say many, many thousands or more, I'm giving a kind of broad range there, is that they do vary in size and, again, they vary as to whether or not they can move or they don't move. Now, they're constantly turning over in your gut, meaning they're being born so to speak and they're dying off. And some will stay there for very long periods of time within your

gut and others will get excreted. About 60% of your stool, as unpleasant as that might be to think about, is made up of live and dead microbacteria. So you're constantly making and excreting these microbacteria. And which microbacteria you make and how many stay inside your gut and how many leave, meaning how many are excreted, depends a lot on the chemistry of your gut and depends very strongly on the foods that you eat and the foods that you do not eat. Now, just because what we eat strongly influences our microbiome, meaning our microbacteria, does not mean that there are not other influences on what constitutes our microbiome. Our microbiome is also made up by microbacteria that access our digestive tract through our mouth, through breathing, through kissing, and through skin contact. In fact, one of the major determinants of our microbiome is who we interact with and the environment that we happen to be in. And that actually includes whether or not we interact with animals. In a little bit, I'll talk about some data as to whether or not you grew up in a home that had animals, whether or not you grew up in the home, whether or not there was a lot of social contact, meaning skin contact, or whether or not you grew up in a more animal sparse, contact sparse environment and how that shapes your microbiome. But the simple point is that what you eat influences your microbiome, but also what you do, what you think, and what you feel, and many of the low microbacteria that get into your digestive tract do so by way of social interactions. In fact, if you ask a neurobiologist what the role of the microbiome is, they'll tell you almost certainly that it's there to impact brain function. But if you have friends that are microbiologists, such as I do, they'll tell you, well, maybe the brain and nervous system are there to support the microbiome. It's the other way around. You have all these little microorganisms that are taking residence in our body. They don't really know what they're doing as far as we know. We don't know that they have consciousness or they don't. We can't rule that out, but it seems pretty unlikely. Nonetheless, they are taking advantage of the different environments all along your digestive tract. They are taking advantage of the sorts of social interactions, for instance, the people you talk to and that breathe on you, the people that you shake hands with, the people that you kiss or don't kiss, the people that you happen to be romantically involved with or not, your dog, your cat, your lizard, your rat,

00:20:01 Roles of Gut Microbiome

whatever pet you happen to own is impacting your microbiome. There's absolutely no

question about that. So hopefully now you have some sense of the architecture of the digestive pathway and you have some sense of the trillions of little microbacteria that are living all along the different components of that digestive pathway. But what we haven't talked about yet, and what I'd like to talk about now, is what those little microbiota are actually doing in your digestive tract. In addition to just living there for their own intents and purposes, they are contributing, for instance, to your digestion. Many of the genes that those microbiota make are genes that are involved in fermentation and genes that are involved in digestion of particular types of nutrients. And in a little bit, we will talk about how what you eat can actually change the enzymes that those microbiome components make, enzymes largely being things that are responsible for digestion. They catalyze other sorts of cellular events but in the context of the digestive pathway, we're talking about enzymes that help digest your food. So those microbiota are indeed helping you in many ways. And if you lack certain microbiota that can help you digest, it stands to reason that you would have challenges digesting certain types of foods. The other amazing thing that these microbiota do is they change the way that your brain functions by way of metabolizing or facilitating the metabolism of particular neurotransmitters. So one of the ways that having certain microbiota present in your gut can improve your mood or degrade your mood, for instance, is by way of certain microbiota being converted into or facilitating the conversion of chemicals, such as GABA. GABA is what we call an inhibitory neurotransmitter. It's involved in suppressing the action of other neurons. And that might sound like a bad thing, but all types of sedatives, for instance, alcohol, and a lot of neurons that naturally make GABA can help quiet certain circuits in the brain, for instance, circuits responsible for anxiety. In people who have epilepsy, the GABAergic neurons, as they're called, can all often be disrupted in their signaling, meaning they're not cranking out as much GABA and therefore the excitatory neurons, which typically release other molecules like glutamate can engage in what's called runaway excitation and that can give rise to seizures. So the simple message here is that the microbiota by way of making neurochemicals can influence the way that your brain functions. So you want to support those microbiota and we will give you tools to support those microbiota. But the takeaway at this point is that those microbiota are making things locally to help digest food. Other microbiota are helping to make certain neurotransmitters like GABA, and we'll also talk about dopamine and serotonin. And so the very specific microbiota that reside in your gut have a profound influence on many, many biological functions,

## 00:23:03 Neuropod Cells: (Subconscious) Tasting with Your Stomach

especially immune system function, brain function, and digestion. So that should give you a fairly complete picture of your gut microbiome. Now I'd like to talk about how your microbiome and your brain communicate, or more accurately, how your microbiome and the rest of your nervous system communicate. Neurons, which simply means nerve cells, are the cells that do most of the heavy lifting in your nervous system. There are of course other cell types that are important. Glial cell, for instance, very, very important cell types. You have endothelial cells, which are responsible for blood flow, pericytes and other types of cells, but the neurons are really doing most of the heavy lifting for most of the things we think about in terms of nervous system function. You have neurons in your gut and that should not surprise you. Neurons reside in your brain, your spinal cord, your eyes, in fact, all over your body, and you've got them on your heart and in your heart, and you've got them in your lungs, and you've got them in your spleen, and they connect to all the different organs and tissues of your body. So that's not surprising that you have neurons in your gut. What is surprising, however, is the presence of particular types of neurons that reside near or in the mucosal lining just next to that lumen of the gut and that are paying attention, and I'll explain what I mean by paying attention, to the components of the gut, both the nutrients and the microbiota, and thereby can send signals up to the brain by way of a long wire that we call an axon, and can communicate what the chemistry and what the nutritional quality and what the other aspects of the environment are at the gut at a given location up to the brain in ways that can influence the brain to, for instance, seek out more of a particular food. Let me give you a sort of action-based picture of this. Let's say like most people, you enjoy sweet foods. I don't particularly enjoy sweet foods but there are a few that I like. I'm a sucker for a really good dark chocolate or really good ice cream or I got this thing for donuts that seems to just not quit although I don't tend to indulge it very often, I do like them. If I eat that particular food, obviously digestion starts in the mouth. There are enzymes there, it gets chewed up, the food goes down into the gut. These neurons are activated, meaning that causes the neurons to be electrically active when particular components, certain nutrients in those foods are present. And for the cell types, or I should say the neuron types that matter here, the nutrients that really trigger their activation are sugar, fatty acids, and amino acids. Now, these particular neurons have

the name enteroendocrine cells but more recently they've been defined as neuropod cells. Neuropod cells were discovered by Diego Bohorquez's lab at Duke University. This is a phenomenal set of discoveries made mostly in the last 10 years. These neuropod cells, as I mentioned, are activated by sugar, fatty acids, or amino acids, but have a particularly strong activation to sugars. They do seem to be part of the sweet sensing system. And even though I'm focusing on this particular example, they represent a really nice example of how a particular set of neuro cells in our gut is collecting information about what is there at a particular location in the gut, and sending that information up to our brain. Now, they do that by way of a nerve pathway called the vagus nerve. The vagus nerve is part of the peripheral nervous system. And the vagus nerve is a little bit complex to describe if you're just listening to this. If you are watching this, I'll try and use my hands as a diagram but really the best thing to do if you want really want to learn neuroanatomy is to just imagine it in your mind as best you can and if you can track down a picture of it, terrific, but here's how it works. Neurons have a cell body that we call a soma, that's where all the DNA are contained. That's where a lot of the operating machinery of the cells are contained and a lot of the instructions for that cell of what to be and how to operate are contained. The cell bodies of these neurons or the relevant neurons are actually up near the neck. So you can think of them as a clump of grapes, 'cause cell bodies tend to be round or oval-ish. And then they send a process that we call an axon in one direction out to the gut and they'll send another process up into the brain. And that little cluster near the neck that's relevant here is called the nodose ganglion, N-O-D-O-S-E. The nodose ganglion is a little cluster of neurons on either side of the neck. It has a process that goes out to the gut and a process that goes up into the brain. And again, these are just one component of the so-called vagus nerve. The vagus nerve has many, many branches, not just to the gut. There are also branches to the liver, branches to the lungs, branches to the heart, branches to the larynx, and even to the spleen, and other areas of the body that are important. But right now we're just concentrating on the neurons that are in the gut that signal up to the brain. And what the Bohorquez lab has shown is that these neuropod cells are part of network. They're sensing several different nutrients, but in particular, when they sense sugar, they send signals in the form of electrical firing up to the brain in ways that trigger activation of other brain stations that cause you to seek out more of that particular food. Now, this brings us to some classic experiments that at least to me are incredible. And these are highly reproducible findings showing, for instance, that even if you bypass taste by

infusing sweet liquid or putting sweet foods into the gut, and people can never taste them with their mouth, people will seek out more of that particular food. And if you give them the option to have a sweet food infused into their gut or a bitter food infused into their gut or a sweet versus sour, or a more sweet versus less sweet food, people have a selective preference for sweet foods even if they can't taste them. Now, this is important to understand in the context of gut-brain signaling because we always think that we like sweet foods because of the way they taste. And indeed that's still true, but much of what we consider the great taste of a sweet food also has to do with a gut sensation that is below our conscious detection. How do we know that? Well, the Bohorquez lab has performed experiments using modern methods and they're classic experiments showing that animals and humans will actively seek out more of a particular sweet food even if it bypasses this taste system. And the reverse is also true. There have been experiments done in animals and in humans that have allowed animals or humans to select and eat sweet foods, and indeed that's what they do if they're given the option. And yet to somehow eliminate the activation of these neurons within the gut that can sense sweet foods. Now, there are a couple different ways that those experiments have been done. In classic experiments that date back to the '80s, this was done by what's called subdiaphragmatic vagotomy. So this means cutting off the branch of the vagus that innervates the gut below the diaphragm so that the other organs can still function because the vagus is very important, but basically cutting off the sweet sensing in the gut, still giving people the opportunity to taste sweet foods with their mouth, and they don't actively seek out quite as much of the sweet food when they don't have this gut sensing mechanism that we now know to be dependent on these neuropod cells. More recent experiments involve selective silencing of these neuropod cells. And there have been a lot of different derivations of this sort of thing, but the takeaway from it is that our experience of and our desire for particular foods has everything to do with how those foods taste. It also has to do, as you probably know, with their texture and the sensation of those foods in our mouth, and even indeed how they go down our throat sometimes can be very pleasing or very unpleasant. And it also has to do with this subconscious processing of taste that occurs in the gut itself. And again, when I say gut, I don't just mean in the stomach. There are actually neurons, neuropod cells, further down your digestive tract which are signaling to your brain about the presence of sweet foods, as well as foods such as amino acid rich foods or foods that are rich in particular types of fatty acids signaling up to your brain and causing you to seek out more of those foods or

to consume more of those foods. Now, you're probably asking, what is the signal? How does it actually make me want more of those foods without me realizing it? Well, it does that by adjusting the release of particular neuromodulators. For those of you that are not familiar with neuromodulators, these are similar to neurotransmitters, but they tend to act more broadly. They tend to impact many more neurons all at once and they go by names like dopamine, serotonin, acetylcholine, epinephrine, and so forth. Sometimes people refer to those as neurotransmitters. Technically they are neuromodulators. I'll refer to them almost always as neuromodulators. The neuropod cells signal by way of a particular branch of the vagus through that nodose ganglion that we talked about before and through a number of different stations in the brain stem, eventually cause the release of the neuromodulator dopamine. Dopamine is often associated with a sense of pleasure and reward but it is more appropriately thought of as a neuromodulator that impacts motivation, craving, and pursuit. It tends to put us into modes of action, not necessarily running and moving through space, although it can do that too, but in the context of feeding, it tends to make us look around more, chew more, reach for things more, and seek out more of whatever it is that's giving us that sensation of delight or satisfaction. And again, that sense of delight and satisfaction, you might experience only consciously as the way that something tastes on your mouth but it actually is caused again by both the sensations in your mouth but also by the activation of these neuropod cells. So this is an incredible system of gut-brain signaling, and it is but one system of gut-brain signaling. It turns out it's the system that we know the most about at this point in time. There are other components of gut-brain signaling that we'll talk about in a moment, for instance, the serotonin system. But in terms of examples of gut-brain signaling for which we know a lot of the individual elements and how they work, I think this neuropod, neuron sensing of sweet foods, fatty acids, and amino acids in the gut and communicating that up to the brain by way of the vagus and causing us to seek out more of the foods that deliver those nutrients is an incredible pathway

00:34:13 Ghrelin: Slow Modulation of Your Brain in Hunger

that really delineates the beauty and the power of this gut-brain axis. Let me talk about timescales. Here I'm talking about a particular type of neuron that is signaling up to the brain using electrical signals to cause us to want to seek out a particular category of foods. That's happening relatively fast compared to the hormone pathways of the gut

which also involve neurons. So your gut is also communicating to your brain by way of neurons, nerve cells. But some of those nerve cells also release hormones. And those hormones go by names like CCK, glucagon-like peptide 1, PYY, et cetera. A good example of a hormone pathway, or what's sometimes called a hormone peptide pathway, that is similar to the pathway I've talked about before but a little bit slower is the ghrelin pathway. Ghrelin, G-H-R-E-L-I-N, increases with fasting. So the longer it's been since you've eaten, or if you're just eating very little food compared to your caloric needs, ghrelin levels are going to go up in your bloodstream and they go up because of processes that include processes within the gut and include the nervous system. So it's a slow pathway driving you to seek out food generally. As far as we know, the ghrelin system is not partial to seeking out of sweet foods or fatty foods or so on. Ghrelin increases the longer it's been since you've eaten sufficient calories and it stimulates a feeling of you wanting to seek out food. Well, how does it do that? It does that again by impacting neural circuits within the brain, neural circuits that include what we call the brain stem autonomic center. So it tends to make you feel alert and quite, we say, high levels of autonomic arousal. If you haven't eaten in a while, you might think that you just get really exhausted, right? Because we all hear that food is energy and caloric energy is what we need to burn, but you actually have a lot of energy stored in your body that you would be able to use if you really needed energy. But typically if we haven't eaten in a while, we start to get agitated and we get agitated by way way of release of the neuromodulator epinephrine, which causes us to look around more, move around more, and seek out food. That all occurs in brain stem autonomic centers and in the hypothalamus. We did an entire episode on feeding behavior and metabolism as well and you can find those episodes at [hubermanlab.com](http://hubermanlab.com) so I don't want to go into a lot of detail about hypothalamic and brain stem centers. But there's a particular area of the brain called the nucleus of the solitary tract, the NST as it's called, that's very strongly impacted by these circulating hormones and tends to drive us toward feeding behavior. So the important point here is that we have a fast system that is paying attention to the nutrients in our gut or the absence of nutrients in our gut, and stimulating us to seek out food or to stop eating certain foods, and we have a slower hormone-related system that also originates in the gut and impacts the brain. But all of those converge on neural circuits for feeding. The neural circuits for feeding include things like the arcuate nucleus of the hypothalamus, they include a bunch of other neurochemicals, but the point is that you've got a fast route and a slow route to drive you to eat more or eat less, right, to



seek out food and consume it or to stop eating, to essentially kickstart the satiety mechanisms as they're called, and those are operating in parallel. It's not like one happens first then stops then the other. They're always operating in parallel. And I bring this up because there's a bigger theme here which we see over and over again in biology, which is the concept of parallel pathways. You've always got multiple accelerators and multiple brakes on a system. It's very, very rare to have just one accelerator and one brake on the system. And this will become important later when we talk about tools for optimizing your gut microbiome

#### 00:38:02 Glucagon Like Peptide 1; GLP-1

for healthy eating and for health healthy digestion and for healthy brain function. I want to take a moment and talk about glucagon-like peptide 1, which is also called GLP-1. GLP-1 is made by neurons in the gut and by neurons in the brain. This is a fairly recent discovery but it's an important one. GLP-1 tends to inhibit feeding and tends to reduce appetite. There are a number of drugs released on the market now, one for instance goes by the name semaglutide, which is essentially an GLP-1 agonist. It causes the release of more GLP-1. It's being used to treat type II diabetes, which is insulin resistant diabetes. This is different than type I diabetes where people don't actually make insulin. It's also being used as a drug to reduce obesity. And it seems pretty effective at least in certain populations. There are certain foods and substances that increase GLP-1. I've talked about a few of these on the podcast. One that I'm a particular fan of for entirely other reasons is yerba mate tea can stimulate the release of GLP-1. In South America, it's often used as an appetite suppressant, probably in large part because of its effect on GLP-1 release, but probably also because it does contain caffeine, which is a bit of a stimulant, which also can be involved in lipolysis, which is the utilization of fat stores for energy and so forth. A brief mention about yerba mate. There are some reports out there that yerba mate can increase certain types of cancers. The data that I've seen on this is that it tends to relate to whether or not those are smoked versions of the yerba mate tea, the amount of consumption, and the debate is still out. So I invite you to look at those papers. You can search for those online. Nonetheless, yerba mate is one source of GLP-1 stimulation. Semaglutide is another source. It also can be stimulated by various foods, nuts, avocados, eggs, and so forth. Certain high fiber complex grains will also stimulate GLP-1. I raise this as not necessarily a route that you want to take in order to

reduce food intake. I don't even know that that's your goal. But that GLP-1 is another one of these gut-to-brain signaling mechanisms that adjusts appetite that is dependent on diet, depends on what you eat or drink, and that the GLP-1 pathway does seem particularly sensitive to the constituents of diet. There's at least one quality study I was able to find showing that the ketogenic diet for instance, which almost always involves ingestion of very low levels of carbohydrate can increase GLP-1. Although, as I mentioned before, there are other foods that fall outside the range of what we would consider ketogenic that can also stimulate GLP-1, and as I mentioned, there are prescription drugs, like semaglutide, there are other ones as well now, that stimulate GLP-1. So how does GLP-1 reduce appetite? It does that, in part, by changing the activity of neurons in the hypothalamus, this cluster of neurons just above the roof of our mouth, that themselves make GLP-1 and that cause the activation of motor circuits for reaching, chewing, all the things that we associate with feeding behavior. So I use GLP-1 as an example of a pathway that you might choose to tap into by ingestion of yerba mate or by ingestion of the foods I mentioned, or if it's something that interests you, ketogenic diet. But I also mention it simply because it's another beautiful example of how a hormone pathway can impact the activity of brain circuits that are directly involved in a particular behavior. So yet another example of how gut is communicating to brain in order to change what we think we want or to change what our actual behaviors are. So the next time you find yourself reaching for food, or you find yourself wanting a particular sweet thing or fatty thing or something that contains a lot of amino acids, a protein rich food, keep in mind that that's not just about the taste of the food, and it's not even necessarily about the nutrients that you need or don't need. It could be, but it's also about this subconscious signaling that's coming from your body all the time, waves of hormones, waves of nerve cell signals,

00:42:22 Tools: 'Free Will' & Food Cravings

electrical signals that are changing the way that your brain works. And this raises for me a memory of the episode that I did with Dr. Robert Sapolsky, who's a world expert colleague of mine at Stanford, who is expert on things like hormones and behavior. But we got into the topic of free will, which is a bit of a barbed wire topic as many of you know. It gets into the realm of philosophy, et cetera. And we were kind of batting back and forth the idea, I was saying, "Well, I think there's free will, and can't there certainly

be free will or certainly the idea that we can avoid certain choices?" And Robert was saying, "No." In fact, he said, "Nah," he doesn't believe that we have any free will. He thinks that events in our brain are determined by biological events that are below our conscious detection and that occur seconds to milliseconds before we make decisions or assessments and, therefore, we just can't control what we do, what we think, and what we feel. And at the time I sort of didn't buy it. I thought, I don't know. I just, I guess I really wanted to believe in free will. And to some extent I still do but as we talk about how these neurons in our gut and these hormones in our gut are influencing our brain and the decisions that we are making, at the level of circuits, like the hypothalamus and the nucleus of the solitary tract, these are areas of the brain way below our frontal cortex and our conscious perception. Think these are examples that really fall in favor of what Dr. Sapolsky was arguing, which is that events that are happening within our body are actually changing the way our brain works. So we might think that we want the cupcake. We might think that we don't need to eat something or do need to eat something and that is entirely on the basis of prior knowledge and decision-making that we're making with our head, but in fact, it's very clear to me based on the work from the Bohorquez lab, classic work over the years dating back to the '80s, and indeed back to the '50s that we'll talk about in a moment, that our body is shaping the decisions that our brain is making and we're not aware of it at all. Now, the good news is that whether or not you believe in free will or not, the simple knowledge that this whole process is happening can perhaps be a benefit to you. You can perhaps leverage it to get some insight and understanding and perhaps even a wedge into your own behavior. You might think, ah, I think I want that particular food, or I think I want to avoid that particular food, but actually that's not a decision

00:44:46 Mechanical Cues from Gut to Brain

that I'm making on a purely rational basis. Has a lot to do with what my gut is telling my brain. So we've largely been talking about chemical communication between the gut and the brain. Chemical because even though these neuropod cells are communicating with the brain by way of electrical activity, what we call action potentials, and in neural language we call those spikes, spikes of action potentials, spikes of action potentials, meaning those neural signals, cause the release of chemicals in the brain like dopamine. So it's chemical transmission. Similarly, hormones, even though they act more slowly,

hormones like neuropeptide Y like CCK, like ghrelin, they are signaling chemically. They're moving through the body, they're going in there affecting the chemical output of different cells, and they're changing the chemistry of those cells and the chemistry of the cells that those cells talk to. So that gives us one particular category of signaling from gut to brain, which is chemical signaling. But of course there are other forms of signals and those fall under the category of mechanical signaling. You're probably familiar with this. If you've ever eaten a very large meal or consumed a lot of fluid, you experience that as distension of the gut and that doesn't just have to be distension of the stomach, but distension of your intestines as well. That distension is registered by neurons that reside in your gut, the signals go up to your brain, and communicate with areas of the brain that are responsible for suppressing further consumption of food and/or fluid, and, under certain circumstances, can also be associated with the activation of neural circuits that cause vomiting or the desire to vomit. So if ever you've eaten too much or you've eaten something that doesn't agree with you, that information is communicated by way of mechanosensors that sense the mechanics of your gut, possibly also the chemistry of your gut, but mostly the mechanics of your gut, signal up to the brain, and activate brain centers that are involved in stopping the eating behavior, and activation of an area of the brain stem that is affectionately referred to as the vomit center among neuroanatomists. This is a area that more appropriately is called the chemoreceptor trigger zone, the CTZ, or area postrema and neurons in this area actually will trigger the vomiting reflex. So the way that the gut and the brain communicate is both chemical and mechanical, and it can be both for sake of increasing certain types of behavior. Today, we're talking mainly about feeding behavior up until now anyway but also ceasing to eat, closing your mouth, moving away from food, turning away from food, all behaviors that we're familiar with anytime we feel kind of sick on the basis of activation of this mechanosensor for gastric distress. So we've got chemical signaling and mechanical signaling. And I also want to emphasize that we have direct and indirect signaling from the gut to the brain. Direct signaling is the kind of signaling of the sort I've been talking about mainly up until now, which is neurons in the gut communicating with neurons in the brain stem that communicate with neurons in the hypothalamus. And, of course, those are also going to interact with neurons of the prefrontal cortex which is the area of a brain involved in decision making the, you know, I think it was the shrimp that made me sick. I'm going to, I just don't want any more of that. Or I'm never going back to that restaurant again because after I ate there about an hour later, I started feeling really not well. I felt, you

know, kind of feverish, but my gut didn't feel well, my digestion was really off. All of that kind of information is handled in the prefrontal cortex at a conscious level, but the immediate decision to stop eating or to eat more of something to move towards something or away from it, that's made by neural circuits that reside at the, we would say, the subconscious level but what we really mean is below the level of the neocortex. Below the cortex means essentially below our level of conscious awareness. So we talked about two types of information within the gut that are communicated to the brain, chemical information, meaning information about the nutrients that happen to be there, and mechanical information, distention of the gut or lack of distention and so forth. And we talked about how these neuropod cells can signal the release of dopamine and circuits

#### 00:49:05 Dopamines, Vomiting

within the brain to cause you to seek out more of something. Now, in a very logically consistent way, dopamine is also involved in the whole business of vomiting. You might think, well, that doesn't make any sense. I thought dopamine was always a good thing. It's involved in moderation and reward, et cetera. But it turns out the area postrema, this vomit center in the brain stem, is chockablock full of dopamine receptors. And if dopamine levels go too high, it can actually trigger vomiting. And this we see in the context of various drugs that are used to treat things like Parkinson's. Parkinson's is a deficiency in dopamine or a lack of dopamine neurons typically that causes a resting tremor, difficulty in movement, because dopamine's also associated with a lot of the neural circuits for movement. Many drugs that are used to treat Parkinson's like L-DOPA increase levels of dopamine so much, or at least activate dopamine receptors to such a great degree in certain areas of the brain that they can cause activation of things like the trigger to vomit. Now, this should also make sense in the natural context of if you gorge yourself with food, gorge yourself with food, gorge yourself with food, the neurons in your gut that respond to that are simply detecting the presence of nutrients but they don't really make decisions themselves. They don't know to stop eating. Your brain knows to stop eating or to eject that food. And so it's a wonderful thing that those neurons are communicating with areas of the brain not just that stimulate consuming more food but that are communicating with areas of the brain, for instance, area postrema, that when dopamine levels get too high, cause us to either stop eating that food or in the case of

vomiting to eject that food. So I raise this not to give you a kind of a disgusting counterexample to what we call appetitive behaviors, the things that we like to do more of, but simply to give you a sense of just how strongly even these reflexes that we think of as feeling sick and vomiting or the desire to seek out more food are really being controlled by a kind of push-pull system, by parallel pathways that are arriving from our gut and the same neurochemicals, in this case dopamine, are being used to create two opposite type behaviors, one behavior to consume more, one behavior to get rid of everything you've already consumed. So our brain is actually sensitive to the amount of signaling coming from our gut not just the path by which that signal arrives. Our brain is very carefully paying attention to whether or not the levels of dopamine that are being triggered are within a normal range for typical eating behavior or whether or not we've gorged ourselves to the point where enough already. Now, of course, mechanical signals will also play into area postrema and into the vomiting reflex. If we have a very distended gut, we feel lousy. It just, it actually can hurt very badly, and we will have the desire to vomit, or we will just simply vomit. Mechanical and chemical signals are always arriving in parallel.

#### 00:52:06 Indirect Signals from Gut Microbiota

They never work in unison. And so now we have chemical signals, mechanical signals, and now I'd like to talk about direct and indirect signals because almost everything I've talked about up until now are direct signals, a neural pathway that converges in the brain to create a particular feeling, thought, or behavior, but there are also indirect pathways. And that's what takes us back to the gut microbiome and to these little microbiota. And to just give you the takeaway message at the front here and then I'll give you a little more detail as to how it comes about, you have neurotransmitters in your brain and in your spinal cord and in your eyes and in your peripheral nervous system. They cause the activation or the suppression of nerve activity, meaning they either electrically activate other nerve cells or they cause other nerve cells to be less electrically active. And they do that by way of neurotransmitters. But as it turns out, the gut microbiota are capable of influencing metabolic events and in some cases are capable of synthesizing neurotransmitters themselves. So what that means is that these little bugs, these little microbiota that are cargo in your gut, the six pounds of cargo, they actually can make neurochemicals that can pass into the bloodstream and into your brain and actually

impact the other cells of your body and brain indirectly, so without involving these very intricate nerve pathways that we've been talking about. In other words, the foods you eat, the environment of your gut microbiome, can actually create the chemical substrates that allow your brain to feel one way or the other, to feel great or to feel lousy, to seek out more of a particular type of behavior or to avoid that behavior. And that would constitute indirect signaling. So I've been talking a lot about the structure and function of the gut-to-brain pathway, focusing mainly on feeding behaviors and in some cases avoiding feeding or even ejecting food from the digestive tract, I'd like to drill a little bit deeper into this indirect signaling pathway from the gut to the brain because it bridges us nicely from neuronal signals in the gut to the brain, hormonal signals from the gut to the brain, to what also includes the microbiome, which is what we started talking about at the beginning of the episode. As I mentioned a couple of minutes ago, certain gut microbiota can actually synthesize certain neurotransmitters that can go impact the brain. And we actually have some knowledge about which microbiota can synthesize particular neurotransmitters. For instance, the neuromodulator dopamine can be synthesized by or from bacillus and serratia. Now, these are just names of microbiota. I don't expect that any of you would necessarily recognize them. These aren't the sorts of things that you necessarily would run out and buy to get more dopamine. But the point is that particular gut microbiota can create dopamine in our gut that can get into our bloodstream and can generally change our baseline levels of dopamine within the brain and other areas of the body. I mentioned baseline levels of dopamine because as I talked about on an episode all about dopamine but I'll just repeat the basics here now, we have baseline levels of transmitters or neuromodulators that act as sort of the level of the tide, the overall level, and then we can have peaks of dopamine that are created by behaviors or by ingestion of particular foods or drugs, et cetera. So bacillus and serratia tend to increase our baseline levels of dopamine. So if it turns out that we are creating the right gut microbiome environment that these particular gut microbiota can thrive in, well, then our baseline levels of dopamine will be elevated and in general, that leads to enhancement of mood. Similarly, there are other gut microbiota, for instance, candida, streptococcus, various enterococcus, these always have these kind of strange and not so attractive names, at least to me as a neurobiologist. Nonetheless, those particular microbiota support the production of or can even be metabolized into serotonin, which is a neuromodulator associated with mood, with social interactions, with a huge number of different types of events and behaviors. Again, these gut microbiota when present and

allowed to thrive in our gut will increase our overall levels of serotonin and riding on top of that level of serotonin will be the serotonin that's specifically released in response to certain behaviors. And I really want to drive home this point of baselines and peaks. The baseline level of serotonin might set our overall mood, whether or not we wake up feeling pretty good or really lousy if our serotonin levels happen to be very, very low, whether or not we tend to be in a kind of a calm space or whether or not we tend to be somewhat irritable. But then of course individual events as we go about our day, maybe a compliment that we get or maybe somebody says something irritating to us, whatever it may be will also influence levels of serotonin, but those serotonin events are going to be related to events at particular neural circuits in the brain. And this is an important topic because I think that a lot of people hear quite accurately, oh, 90 to 95% of our serotonin is manufactured in the gut. And indeed that's true. It's manufactured from the sorts of microbiota that I just described. And there are many, many experiments now, mostly in animal models, but also some in humans that show that if the gut microbiome is deficient in some way to these particular bacteria, that serotonin levels drop and people's mood suffers, maybe even their immune system functions, maybe even it exacerbates certain psychiatric illnesses. However, a lot of people take that to mean that the serotonin of the brain all comes from the gut or mostly comes from the gut. That's not the case. It's still the case that you have neurons in the brain that are responsible for releasing serotonin directly in response to certain things like social touch or through other types of positive social experiences. So we've got gut microbiota that can literally be turned into dopamine and raise our baseline levels of dopamine. We've got gut microbiota that can literally raise our baseline levels of serotonin. And indeed there are other gut microbiota like lactobacillus or bifidobacterium, excuse me, hard complex names to pronounce, bifidobacterium that can give rise to increases in GABA levels, this inhibitory neurotransmitter that can act as a little bit of a mild sedative, can reduce irritability, et cetera, but that's just the baseline, the kind of tide of those neuromodulators. Again, I want to emphasize that we still have neurocircuits within the brain and body that are specifically releasing in a very potent way dopamine, serotonin, and GABA. So the two things act in concert. Even though the gut and the brain are acting both in parallel and directly influencing one another, it is a powerful synergistic effect. And there are now hundreds of studies, maybe even thousands by this point, mostly performed in animal models, typically mice, but also some studies in humans that show that creating the correct environment for these gut microbiota to thrive really does



enhance mood and wellbeing.

#### 00:59:30 Gut Microbiome “Critical Periods”

And that when our gut microbiome is not healthy, that it really can deplete our mood and sense of wellbeing. Now, there are two major phases to creating a healthy gut microbiome. One you can control and the other one is less under your control. I get into this in a lot of detail in the episode with Dr. Sonnenburg, which is coming out immediately after this one, the following Monday, that is. But for now I want to just capture a few of the main points about the early establishment of the gut microbiome. It turns out that the environment that we are exposed to, the things that come into contact with our skin and digestive tract and any other mucosal lining, even the urethra, the nasal passages, any opening to the outside world that brings in certain, excuse me, certain microbiota in the first three years of life is going to have a profound impact on the overall menu of microbiota that we will be able to carry within our body. And it really does seem that getting exposure to and building a diverse microbiome in those first three years is critical. There's a lot of speculation and some data as to cesarean delivered babies having less diverse microbiomes compared to vaginally delivered babies. There have been attempts, although not conclusive attempts, to link that to the presence of autism spectrum disorders, which at least by some statistics seem to be of higher probability in cesarean deliveries although there are other studies that refute that, and I want to make that clear. However, it's clear that babies do not get much, if any, exposure to microbiota inside of the womb, maybe a little bit, but not much. But that is during the birth process and in the days and weeks immediately after they arrive in the world that their gut microbiome is established, that those gut microbiota take residence within the gut. So it will depend on whether or not they were breastfed or bottle fed. It'll depend on whether or not they were exposed to a household pet or not, whether or not they were held by multiple caregivers or just by one, whether or not they were a preemie baby and were contained in a particularly restrictive environment in order to encourage their further development before they could be brought home or not. I don't want to give the picture that if you were isolated or you were delivered by C-section, that you're somehow doomed to have a poor microbiome. That's simply not the case. However, it is the case that the more diversity of microbiota that one can create early in life is really helpful for long-term outcomes in terms of brain-to-gut signaling, gut-to-brain signaling,

and for sake of the immune system. There are some decent studies showing that if children are exposed to a lot of antibiotic treatment early in life, that can be very detrimental to establishment of a healthy gut microbiome. And fortunately that reestablishing a healthy gut microbiome can help rescue some of those deficits. So doctors nowadays are much more cautious about the prescription of antibiotic drugs to children in their early years, not just up to three years, but extending out to five and seven and 10 years. And even in adults, they're very, very careful about that, or they ought to be. One reason is the existence, or I would say, the proliferation of antibiotic-resistant bacteria that are becoming more common in hospitals and elsewhere and that can cause serious problems. But in addition to that, because of this understanding that the gut microbiome is influencing and actually creating neurotransmitters

01:03:08 How Gut Health Controls Overall Health

that can impact mood and mental health, impact immune health, and so on. As I mentioned earlier, there are hundreds if not thousands of studies emphasizing the key role of the microbiome on brain health, psychiatric health, et cetera. I want to just highlight a few of those studies and in particular, some recent studies that come from labs that have been working on this sort of thing for a very long time. One of the more exciting studies comes from the work of Mauro Costa-Mattioli's lab, which is at Baylor College of Medicine. Mauro's lab has been working on mouse models of autism spectrum disorder for a long time, and looking at social behavior using a mouse model for a long time. And they've been able to identify particular types of microbiota that when they take residence in the gut can help offset some of the symptoms of autism, at least the symptoms of autism that exist in these mouse models, okay? So again, this is not human work. This is work being done on mouse models for the simple reason that you can do these kinds of manipulations, where basically they took mice that were in germ free-environments or non-germ-free environments, or they exposed mice to particular microbiota and not other microbiota and they discovered that a particular microbiota called *L. reuteri*, it's L. R-E-U-T-E-R-I. Treatment with *L. reuteri* corrects the social deficits present in these autism models and it does so by way of activating our old friend the vagus nerve, but not simply because the vagus nerve triggers the release of dopamine, but it turns out that this particular gut microbiota *L. reuteri* can correct the social deficits in this autism spectrum disorder model. It does that by way of a vagal

nerve pathway that stimulates both dopamine release and oxytocin release. And they establish this really mechanistically by showing, for instance, if you get rid of the oxytocin receptor, you don't see this rescue. Now, those are mouse models so we have to take those with the appropriate grain of salt, but they're really exciting. And they come to us in parallel with other studies that are being done, taking the microbiomes of people who have one condition or lack of condition, and putting it into people who have one condition or another condition. Let me explain what I mean by that. The early discovery of the gut microbiome and its potential to impact health was not in the context of the gut-to-brain pathway but rather it was in the context of colitis. This dates back to studies in the '50s, whereby people with very severe intractable colitis for which no other treatment was going to work received fecal transplants. So yes, that's exactly as it sounds. Taking the stool of healthy people who do not have colitis, transplanting those stools into the lower digestive tract of people who do have colitis, and they saw significant improvement, if not rescue of the colitis. That was one of the first indications that something within stool, of all things, could actually rescue another individual from disease, which sounds kind of wild and crazy, and may even sound disgusting to some of you, but as I mentioned at the beginning of the episode, almost 60% of stool is live or dead bacteria, microbiota, and it really opened up this entire field of exploring how different microbiota might have therapeutic effects. And indeed, that has been shown to be the case also in fecal transplants for certain psychiatric illnesses. These are still ongoing studies. They vary in quality. These are hard studies to do for all sorts of reasons, getting the appropriate patient populations, getting agreement, et cetera, making sure that everything's handled properly. But what this involves is fecal transplants from individuals that lack a particular psychiatric condition or metabolic condition into people who have a particular metabolic condition and there has been tremendous success in some cases. One of the more powerful and salient examples is for obesity. There's some people for which even if they ingest very low numbers of calories, even if they go on a liquid protein diet, simply can't lose weight. These are somewhat rare disorders but these are people that would either get gastric bypass surgery. Some people are now getting these fecal transplants from people that have healthy weight and they take the stool from them, they put it into lower digestive tract, and they can see substantial improvement in weight loss in people that were otherwise unable to do that. In some cases, actually they can start eating relatively normal levels of food and still lose weight. So pretty remarkable and that tells us there's something in these microbiota that's really powerful. Now, how those effects are

generated isn't clear. One idea is that it's impacting the metabolome, components of the metabolism, almost certainly that's going to be the case. Another idea is that it's impacting neurotransmitters which change behavior and food choices within the brain. Although, as I mentioned, some of these people are already eating very little food to begin with so that's a little bit harder of an argument to create. There are also some somewhat famous examples now of how fecal transplants can lead to negative outcomes. But those negative outcomes further underscore the power of the microbiome in impacting bodily health. One key example of this, for instance, is transfer of fecal matter into another person in order to treat something like colitis and it effectively does that, but if the donor of the stool, of the fecal matter happened to be obese or have some other metabolic syndrome, it's been observed that the recipient can also develop that metabolic syndrome simply by way of receiving that donor's particular microbiota. So these microbiota can create positive outcomes or they can create negative outcomes. Now, most of us of course, are not interested in or pursuing fecal transplants. Most people are interested in just creating a healthy gut microbiome environment for sake of immune system and brain function. And we will talk about how to do that in just a few minutes. But I just want to further underscore the power of the microbiota in shaping brain chemistry and in shaping things like mood or other aspects of mental health that typically we don't associate with our gut. There are several studies published in recent years, one that I'll just highlight now, first author is Tonya Nguyen, N-G-U-Y-E-N. The title of the paper is "Association of Loneliness and Wisdom with Gut Microbial Diversity and Composition, an Exploratory Study". It's an interesting study. Looked at 184 community dwelling adults, excuse me, ranging from 28 to 97 years old. They explored whether or not having enhanced microbial diversity somehow related to these variables that they refer to as loneliness and wisdom. They used a number of different tests to evaluate those. Those are common tests in the psychology literature, not so much in the biology literature, but nonetheless, there are ways of measuring things like loneliness and wisdom, wisdom in this case, being the opposite of loneliness, at least in the context of this study. And what they found was the more microbial diversity, the more diverse one's microbiome was, the lower incidence of loneliness. And they did this by taking fecal samples, profiling them for RNA. So essentially doing gene sequencing of the stool of these individuals, getting ratings of how lonely or not lonely they felt, and correlating those. And that's just but one study. I point it out because it's particularly recent and it looked like it was particularly well done. There is another study that I'll just refer you to.

This was a study published in 2020 in "Scientific Reports". The title of the study is "Emotional Wellbeing and Gut Microbiome Profiles by Enterotype". What I particularly like about this study is that they were able to correlate the presence of certain microbiota with feelings of subjective wellbeing and lack of or presence of depressive symptoms. They did high-throughput gene sequencing of the microbiomes of individuals. So that meant measuring the microbiota, figuring out which microbiota were present, how diverse their microbiome was in general. Gut microbiome diversity is a good thing. And then to correlate that with what's called the PANAS score. PANAS stands for positive affect negative affect schedule. This is a test that my lab has used extensively, that other labs to use to evaluate mood and wellbeing. And they defined what were called three enterotypes, three different categories of people that ate very different diets that tended to fall into categories of having more or fewer emotional symptoms that were negative or more fewer emotional symptoms that were positive and whether or not they tend to be more depressed, anxious, or have more stress-related behaviors, et cetera. And what they were able to derive from this study was some strong indications about what types of things we should ingest in our diet, maybe even certain things that we should avoid, but certainly the types of things that we should ingest, that can enhance mood and wellbeing and can tend to shift people away from more depressive-like anxiety and stress-related symptoms. Before we get into what the particular food items were

01:12:25 What is a Healthy Gut Microbiome?

that lend themselves to a healthy microbiome, I want to raise a bigger and perhaps more important issue, which is what is a healthy microbiome. I think if you asked any number of world experts, and I certainly ask this of Dr. Sonnenburg, what is a healthy microbiome, they're all going to tell you it's a microbiome that has a lot of diversity, that includes a lot of different types of bacteria. And that makes sense because it logically would include the bacteria that produce GABA and dopamine and serotonin, and that support the immune system, and do a number of different things. But is it simply the case that adding microbiota diversity is always a good thing? Well, that doesn't seem to be the case. Probiotics and prebiotics, both of which can enhance microbial diversity, can improve mood, digestion, immune system, and so on. That's been established but it's mainly been established in the context of post-antibiotic treatment or people that are recovering from illness or people that have been very stressed or have been dealing with

all sorts of challenges, mental or physical, and they are an attempt to replenish the gut microbiome. However, it's also clear that excessive microbiota brought about by excessive intake of probiotics can lead to things like brain fog. There's actually some good studies that point to the fact that certain metabolites of the microbiome, certain chemicals produced in the gut and in the body can actually lead to brain fog states. This is thought to come about through the lactate pathways of the gut that can then impact the brain. If you want to look more into this issue of whether or not probiotics taken in excess perhaps can lead to brain fog, I'd encourage you to look at a particular paper. This is a paper published in "Clinical and Translational Gastroenterology". And the title of the paper is "Brain Fogginess, Gas, and Bloating, a Link Between SIBO Probiotics and Metabolic Acidosis". It was published in 2018. We can provide a link to this study. And there are several other studies in the references that point to the fact that in some cases, excessive intake of probiotics and excessive proliferation of gut microbiota can actually be problematic. I mention this not to confuse you but because it is confusing out there. We all would think that just increasing microbial diversity is always a good thing but there are thresholds beyond which excessive microbial diversity might be problematic.

#### 01:15:00 Tools: Enhance Your Gut Microbiome

I think everyone agrees that having too few microbial species living in us is not a good idea. Now, none of that answers the questions that I think everyone really wants answers to, which are, what should we do, what should we not do to improve our gut microbiome? I mean, clearly we can't time travel back to when we were zero to three years old and get a dog if we didn't have a dog, get breastfed if we weren't breastfed, be delivered vaginally as opposed to by C-section if we didn't have that opportunity. We just can't time travel and do that. All of us, however, should be seeking to improve the conditions of our gut microbiome because of the critical ways in which it impacts the rest of our brain and bodily health. So what should we do, what shouldn't we do? Clearly we know that stress can negatively impact the gut microbiome. However, some forms of stress that can quote unquote negatively impact the microbiome include fasting, long periods of fasts, which makes sense because a lot of microbiota need food in order to thrive. In fact, many if not all of them do at some point. There are other questions such as should we eat particular foods and how often should we eat those foods? We've all been told that fiber is incredibly important because of the presence of prebiotic fiber,

which can essentially feed the microbiome, but is fiber really necessary and how necessary is it to encourage a healthy microbiome? Clearly, there are a number of people following relatively low fiber diets, such as ketogenic diets, and those can have, in some cases, anti-inflammatory effects and can sometimes also improve certain microbiota species. So it can all be rather confusing. And for that matter, I asked our resident expert, Dr. Justin Sonnenburg at Stanford, all of these questions. And he answers them very systematically in the episode that comes out after this one. But I don't want to withhold anything from you so I'll just give a very top contour version of those answers and then you'll get more in-depth answers during that episode. I asked about fasting. And the reason I asked about fasting is that years ago, I was at a meeting as part of the Pew Biomedical Scholars Meeting and one of the other Pew Biomedical Scholars was an expert in gut microbiome and I said, "Hey, are probiotics good for the microbiome? And if so, which ones should I take?" And his answer was very interesting. He said, "You know, in certain cases they can be, especially if you're traveling or you're stressed, but it turns out that the particular bacteria that they put in most probiotics don't actually replenish the microbiota that you need most." And I thought, "Oh, well, why don't they make ones that replenish the microbiota that you need most?" And his answer was, "Well, they don't replenish those but they replenish other ones that then in turn encourage the development of the microbiota that you do want once you start eating the appropriate foods. So they change the environment which makes the environment better, which indirectly supports the proliferation of quote unquote good microbiota." Okay, so that was a somewhat convoluted answer but I did appreciate his answer. Then I asked him about fasting. I said, "Well, a lot of people are getting interested in intermittent fasting now. People are spending a significant portion of each 24-hour cycle avoiding food for sake of time restrictive feeding. What does that do to the gut microbiome? Does it make it healthier or does it make it unhealthier?" Well, my colleague from Yale and Dr. Sonnenburg both confirmed that during periods of fasting, especially prolonged periods of fasting, we actually start to digest away much of our digestive tract. Now, the whole thing doesn't start to disappear but there's thinning of the mucosal lining or the least disruption of the mucosal lining. A lot of the microbiota species can start to die off. And so it was surprising to me, but nonetheless interesting that fasting may actually cause a disruption to certain healthy elements of the gut microbiome. But again, there's a caveat. The caveat is that when people eat after a period of fast, there may be a compensatory proliferation, meaning an increase in

healthy gut microbiota. So you start to get the picture that fasting is neither good nor bad. You start to get the picture that particular diets, meaning certain restriction diets or macronutrient-rich diets may not be good or bad for the microbiome. And yet there are some answers that arrive to us from Dr. Sonnenburg, but from other experts in the field, that there are certain foods and certain things that we can ingest which definitely enhance the microbiome and make it healthier than it would be were we to not ingest those foods. So next I'd like to talk about what I think is a really pioneering and important study in this area. This is a study that was carried out by the Sonnenburg lab in collaboration with Chris Gardner's lab, also at Stanford, where they compared two general types of diets in humans, diets that were fiber rich, which has been proposed time and time again to enhance microbiota diversity and to enhance gut-brain signaling even and to enhance the immune system perhaps, and diets that were enriched in so-called low-sugar fermented foods. Before I dive into that study and what the conclusions were because they are very interesting and very actionable for all of us, I do want to touch on probiotics because I want to avoid confusion. It is not the case that ingestion of probiotics will always lead to brain fog. I want to make that clear. It is the case that ingestion of probiotics, even if those probiotics don't directly contain the microbiota species that one is trying to proliferate, can be useful for improving microbial diversity. In general, it seems that maintaining a healthy gut microbiome involves ingesting certain types of foods, and we'll talk about those in a moment, but perhaps also augmenting the microbiota system through prebiotics or probiotics at a fairly low level on a consistent basis. So these are not high dose probiotics except under conditions of dysbiosis where, for instance, if somebody has done a round of antibiotics and they need to replenish their gut microbiome, there are foods and there are pill form and powder form prebiotics and probiotics that can be very useful. Or in cases where people have been very stressed or are undergoing excessive travel or have shifted their diet radically, maybe that's due to travel, maybe that's due to illness, maybe that's due to stress. But when there are a number of different converging events that are stressing or depleting microbial diversity, that's when at least I believe it can be useful to support the gut microbiome through the ingestion of quality probiotics or prebiotics. So it would be under conditions where people are stressed or their system is generally stressed for environmental or illness-related reasons that it might be useful to lean towards higher doses of prebiotics or probiotics than one might normally use but that under normal conditions, that one would focus on quality nutrients through diet and focus on ingestion



of probiotics at a fairly low to moderate level, and/or prebiotics at a fairly low to moderate level. That just seems like the logical approach based on the experts that I've spoken to. But certainly if your doctor prescribes or suggests that you take high levels of probiotics for any reason, you should definitely pay attention to your physician, and you should obviously pay attention to your physician in any a case. You should never add or remove anything from your nutritional plan or supplementation plan without consulting a physician. So what should we do in order to maximize the health of our gut-brain axis as it's called? How should we support the diversity of the good microbiota that help us create all these neurotransmitters that we want, improve our immune system function, and so on and so forth? Well, some of that is going to be through the basics. When I say the basics, I mean the foundational things that really set us up for overall health. So this is going to be getting deep sleep of sufficient duration 80 plus percent of the time. I mean, if you could get a hundred percent of the time, that'd be great but very few people accomplish that. It's going to be proper hydration. It's going to be proper social interactions. It's going to be proper nutrition. And we'll talk more about nutrition in a moment. It's going to be limiting excessive, prolonged stressors or stress. And indeed we've done episodes about, just about all of those things but certainly about stress we have an episode of the Huberman Lab Podcast that you can find at [hubermanlab.com](http://hubermanlab.com) all about mastering stress, how to avoid long periods of intense stress, what to do to offset those. Given that stress can disrupt the microbiome,

#### 01:23:49 Foods to Enhance Microbiota Diversity; Fermented Foods

whether or not you're fasting or not, those tools ought to be useful. Now, in what I consider to be a landmark study exploring the relationship between the gut microbiome, food intake, and overall health is this paper from Justin Sonnenburg's lab and Chris Gardner's lab, both of which are at Stanford. And the paper entitled "Gut Microbiome-Targeted Diets Modulate Human Immune Status" was published in the journal "Cell", which is among the three top journals perhaps in the world, "Nature", "Science", and "Cell" really being the apex journals for overall science, and especially for biomedical sciences. Now, this is a very interesting study. It was done on humans. There were two major groups. One group of humans was instructed to increase the amount of fiber in their diet and in fact ate a high fiber diet. The other group was instructed to eat a high fermented food diet. Now, both groups started off not having eaten a lot of fiber or a lot

of fermented foods and were told to increase the amount of either fiber or fermented foods that they were ingesting over a four-week ramp up period and that was to avoid any major gastric distress. It turns out that if you're not already accustomed to eating a lot of fiber, increasing your amount of fiber dramatically can cause some gastric distress but if you ease into it over time, as we'll see, there's a mechanism behind this, which was unveiled in this study, but if you ease into it over time, then the system can tolerate it. Likewise high fermented foods can be readily tolerated if there's a ramp up phase of ingesting maybe one serving a day, then maybe two servings, and ramping up in this case as high as six servings per day. However, after this ramp up period, the group assigned to the high fiber condition maintained high fiber intake for six weeks and the high fermented food group maintained high fermented food intake for six weeks after which they went off either the high fiber or the high fermented food diet and there was a four-week follow up period during which they gradually returned to baseline. Throughout the study their gut microbiome was evaluated for the diversity of gut microbiota. And there were also a number of measures of immune system function, in particular measures of the so-called inflammatome. The immune system has a lot of different molecules involved. I did a whole episode about the immune system if you're interested in learning what some of those molecules are, various cytokines and signaling molecules that reflect either high inflammation states or reduced inflammation states in the brain and body. You're welcome to check that episode. It's also at [hubermanlab.com](http://hubermanlab.com). Regardless, in this study, they explored the sorts of immune markers that were expressed in either of the two groups and compared those. The basic takeaway of this paper was that contrary to what they predicted, the high fiber diet did not lead to increased microbiota diversity, at least not in all cases. And that was somewhat surprising. You know, the idea is that prebiotic fiber and a lot of the material in fruits and vegetables and grains and so forth are supposed to support microbial diversity and the proliferation of existing microbiota. And that is not what they observed, although I want to be very clear in pointing out that the results do not indicate that fiber is not useful for health overall, but it does point to the fact that increasing fiber intake did not increase microbiota diversity, which in general, as I mentioned before, is associated with improvements in microbiota function, health, and overall wellbeing. Now, the high fermented food diet condition was very interesting. It resulted in increased microbiome diversity and decrease inflammatory signals and activity. So there was a twofer. Basically by ingesting high fermented foods in fair abundance, right? You know, four to

six servings or more per day is a lot of fermented food intake. We'll talk about what some of those foods were. But the outcome was very positive. There was a clear increase in microbiome diversity and decreased inflammatory signals. So things like interleukin-6, a number of other interleukins and cytokines that are associated with increased inflammation in the brain and body were reduced significantly. Now, let's talk a little bit about this notion of number of servings, et cetera. One somewhat minor point of the study, but I think is useful in terms of taking an actionable stance with this is that the number of servings of fermented foods was not as strong a predictor of improvements in the inflammatome, meaning reduced inflammation and improvements in microbiota diversity, as was the duration of time that the individuals were ingesting fermented foods. In other words, the longer that one is consistently ingesting fermented foods on a daily basis, the better the outcomes in terms of the gut microbiome and for reducing inflammation. So I think that's an important point. And I make that point, especially because for a lot of people, even if you do this ramp up phase, six servings per day of fermented foods can seem like quite a lot. So what are these fermented foods? I think many of us are familiar with certain cheeses and being fermented and beer being fermented and kombucha is fermented. In this study, they focus specifically on low-sugar fermented foods. So this would be plain yogurt, in some cases, kimchi or sauerkraut. An important consideration, however, is that it needs to contain what are called live active cultures, which means there actually have to be microbiota that are alive inside the sauerkraut. One way you know whether or not that's happening is if you purchase sauerkraut or pickles or kimchi from a jar or a container that's on the non-refrigerated shelf or the non-refrigerated section of your grocery store, it is not going to contain live active cultures of microbiota. And likewise, if you consume yogurt that has a lot of sugar or other components added to it, it's not going to have the same positive effect on the microbiome, at least that's the prediction given some of the relationship between the sorts of microbiota that live in sugar versus plain type yogurts. They gave people the option of consuming any number of different low-sugar fermented food. So that again that could be sauerkraut, kimchi, things like kefir, natto. In Japan, they consume natto which is a fermented food. Beer was not one of the fermented foods that was included in the fermented food list. And when we say six servings per day, that is indeed six, six ounce servings, or six, four to six ounce servings. It was not six servings of what's listed on the package. So again, that turns out to be a fair amount of fermented foods. How should you gauge whether or not you're getting enough of this? Well, if you decide to

take on this protocol of ingesting more fermented foods, which at least by my read of this study and some of the follow up work that's being done, sounds like a terrific idea if you want to improve your gut microbiome for all the great reasons that one would want to, brain-body health, reduced inflammation, and on and on, well then you definitely want to focus on fermented foods that you enjoy consuming. So for you if that's kefir, or for you that's plain yogurt, or for you that's sauerkraut, which happens to be my personal favorite, then you want to make sure that it's going to be something that you are going to enjoy ingesting quite a lot of and that you're going to be okay with ingesting probably throughout the day. Now, people follow different meal schedules, of course, but this does require not just eating all the fermented foods just before bedtime or at one meal. I suppose you could do that, but in general, it's going to work best in terms of limiting gastric distress by spreading it out throughout the day. I also want to mention brine. Brine is the liquid that surrounds sauerkraut. It's that very salty fluid. And that contains a lot of active live cultures. And they did include or they allowed people to include brine in this study. And in discussions with Dr. Sonnenburg, which we'll go into in more detail on the episode that comes out next week, we talk a lot about the particular value that brine might hold in terms of bringing about microbiota diversity because of the richness of live cultures that it contains. I do want to focus for a moment on the high fiber condition because there were some interesting observations about the people that were placed into that condition. First of all, increasing the amount of fiber definitely increased the number of enzymes that can be used to digest fiber. This is in keeping with this idea of this ramp up phase where accumulation of more fiber intake can over time lead to less gastric distress but also to more utilization of fiber which overall should be a good thing. So while they didn't observe an increase in immune system function or an increase in microbiota diversity, there was an increase in these fiber digesting enzymes. They also observed what they called personalized immune responses. There were some subgroups within the high fiber group that had interesting changes in terms of their reactions to, or I should say their inflammatome, meaning the inflammatory markers they expressed, as well as their microbiota diversity. So there were essentially three groups. One group actually showed an increase in inflammatory markers. So that was quite surprising and probably not wonderful for the message that fiber is always good for us but that was a small cohort within the fiber intake group. Another group and still another group, both showed reductions in baseline microbiota diversity although to varying degrees. So I don't want to paint the picture that fiber is bad but fiber certainly did not

have the positive effects on microbiota diversity that the high fermented food diet did. So my read of this study, and I think the stance that many others have taken as a consequence of these data, is that we should be increasing our fermented food intake, that that's simply a good thing to do in order to support our gut microbiome and to reduce inflammatory signals in our brain and body. And there are a number of different ways to do that. I mentioned some of the particular foods. However, anytime you're talking about ingesting fermented foods, especially the high quality ones that come from the refrigerated section of the grocery store, and that have low sugar content, et cetera, we do have to be considerate of cost because certain things like kombuchas, for instance, can be quite costly. I should also mention some kombuchas actually contain alcohol, some do not, or contain very little amounts of alcohol. One way to avoid the high cost of fermented foods while still being able to accumulate a lot of fermented food intake is to simply make those fermented foods yourself. And this is something that we've started exploring and experimenting with in our home. One simple way to do this is to just make your own sauerkraut. It involves very few ingredients. It basically involves cabbage, water, and salt, but there's a specific process that you need to follow in order to create these large volumes of sauerkraut at home using that low cost method. The best resource that I know of in order to follow a great recipe to make homemade sauerkraut would be the recipe for homemade sauerkraut that's contained in Tim Ferriss's book, "The 4-Hour Chef". There's an excellent protocol there. It involves chopping up the cabbage, putting into a bowl, mashing it up with your hands, which can be fun, putting water in there, some salt, covering it, and then keeping it in a particular environment, and then routinely scraping off some of the material from the surface. You have to do that in order to make sure that you're not getting microbes and things growing in it that are bad for you. So you definitely want to pay careful attention to the protocol, but that's a very, very low cost way of generating lots and lots of fermented foods so you don't go broke trying to improve your microbiome. The other thing that you can do if you're really obsessed with kombucha or something like that, to avoid the high cost of kombucha is there are ways that you can get the scoby, which basically allows you to make your own kombucha at home. I've never tried this, but when I was a post doc, there was an undergraduate in the lab, I think, well, I won't out him, but he's now gone on to medical school and I think he's passed his residency and is a practicing doctor, but nonetheless, he was always making kombucha at home. He told me it was exceedingly easy, but then again, he had a number of other skills and attributes that made me think

that he could do pretty much anything with ease, whereas I tend to struggle with even basic cooking. So maybe if you're feeling a little more adventurous, you could explore making your own kombucha. But there are a number of different protocols and recipes out there for making your own low-sugar fermented foods. So you needn't run out and buy fresh sauerkraut all the time. I should also mention for those of you that are interested in getting your fermented intake from pickles, jarred pickles rarely if ever contain ferment. Mostly they're just soaked in vinegar, water, and with some spices, but there are some that contain ferment. You actually have to look for that on the container. And I don't know, maybe someone out there knows how to make natto and knows how to make kimchi well and things of that sort. It certainly is the case based on the data from the study that ingesting more servings of fermented food per day

#### 01:37:07 High-Fiber Diets & Inflammation

ought to be beneficial for our gut microbiome. And since this is an episode not just about gut microbiome but gut-brain health, I should mention that one form of signaling between the gut microbiome and the brain which we did not discuss and I'll just touch on briefly is that when the inflammatome or the genes and markers of inflammation are kept in a healthy range, there's an active signaling of that immune system status to the brain. There's an intermediate cell type that communicates immune status to the brain. And that cell type is the microglial cell. It's a type of glia as the name suggests. When there's a lot of inflammation in the body, these microglia actually get activated and can start eating away at various components of the brain and nervous system. And I don't mean massive eating away. They're not going to digest the whole brain but these microglia are sort of the resident macrophages of the brain. Macrophages are in the periphery and they gobble up debris and things of that sort. The microglia on a regular basis are eating up debris that accumulates across waking cycles and in response to micro-damage to the brain that occurs on a daily basis. So they have a lot of important basic everyday what we call housekeeping functions. But when there's a lot of inflammation in the body, when there's a massive immune response, the microglia can be hyperactivated and that's thought to lead to any number of different cognitive defects or challenges thinking, or maybe even some forms of neurodegeneration over time, although that last point is more of a hypothesis than a well tamped down fact at this point. There's still a lot of investigation to be done in humans. The animal data, however, are very, very strong that

when the immune system is activated or chronically activated or hyperactivated that neural tissue, meaning brain tissue and other central nervous system tissue can suffer. So there are a lot of reasons to want to not just improve microbiome diversity, but to also improve immune system function and to limit the number of inflammatory markers that are present in the body because of the way those inflammatory markers can signal deleterious events in the brain. And while eating fermented foods and making your own fermented foods and buying high quality fermented foods might seem like an inconvenience, I would say that from the perspective of cost-benefit or effort-benefit, it's actually quite a good situation where if you can just ramp up the number of fermented foods or servings of fermented foods that you're eating per day over a period of a few weeks so that you're tolerating that well, that ought to have a very positive effect on your microbiome diversity and indeed on gut-brain function. And I'll be the last to suggest that people completely forego on fiber. I think there's some debate out there as to how much fiber we need and whether or not certain forms of fiber are better than others. I'm not going to get into that debate. It's barbed wire enough without me injecting my own views into that debate. But I think there's ample evidence to support the fact that for most people ingesting a fair amount of fiber is going to be a good idea. I would just say that make sure that you're also ingesting a fair amount of fermented foods. And along the lines of fiber, in an accompanying article published in "Cell", which was sort of a what we call a news and views piece about the Sonnenburg and Gardner paper, they make a quite good point, which is that the increase in fiber intake that led to the increase in carbohydrate active enzymes, these CAZymes as they're called, these are enzymes that help digest fiber, quote, "indicating an enhanced capacity for the microbiome to degrade complex carbohydrates present in fibrous foods". So in other words, eating more fiber and fibrous foods allowed for an increase in these enzymes that allow you to eat still more fibrous foods or to better digest fibrous foods that are coming in through other sources. So there is at least one utility for increasing fiber

#### 01:40:58 Artificial & Non-Caloric Sweeteners

even though it's separate from the gut microbial diversity and reducing inflammation. And I'd be remiss if I didn't touch on some of the data and controversy about artificial sweeteners and the gut microbiome. I want to be very clear that what I'm about to tell you has only been established in animal models, in a mouse model, at least to my

knowledge. What the studies have shown, and there were several, but one published in the journal "Nature" a few years back is the one that got the most amount of attention is that animals that consume large amounts of artificial sweeteners. In particular things like saccharin or sucralose show disruptions in their gut microbiome. I'm not aware of any studies in humans that show the equivalent effect. And I'm not aware of any studies in humans that show the equivalent effect for things like plant-based, low-calorie sweeteners, things like Stevia, monk fruit, and things of that sort. And at least by my exploration, I couldn't find any data specifically related to the sweetener aspartame. So right now it's somewhat controversial and actually this is kind of a third rail topic out there. When one group will come out saying that artificial sweeteners are bad because they disrupt the gut microbiome, the response generally from a number of people as well, that's only been shown in animal models. And indeed that's true. So right now I don't think that there's a strong case one way or the other. I think that people should basically ask themselves whether or not they like artificial sweeteners or not, whether or not they're willing to risk it or not, and obviously that's an individual choice. I also want to point out a recent study from Diego Bohorquez's lab, which actually shows, however, that neurons in the gut, those neuropod cells, are actually capable of distinguishing between real sugars and artificial sweeteners. This is a really interesting body of work. It was published just now, just recently, I should say, February 2022. The title of the paper is "The Preference for Sugar over Sweetener Depends on a Gut Sensor Cell". And to make a long story short, what they showed was there's a category of neuropod cells that recognize sugar in the gut and signal that information about the presence of sugar in the gut to the brain via the pathways we talked about before, the nodose ganglia, the vagus, dopamine, et cetera, et cetera. Interestingly, the very same category of neurons can respond to artificial sweeteners and signal that information to the brain, but the pattern of signaling and indeed the signature pattern that is conveyed to the brain and received by the brain is actually quite a bit different when these same neurons are responding to artificial sweeteners versus actual sugar. And this is very interesting because what it means is first of all that neurons have incredible specificity in terms of what they are signaling from the gut to the brain. And it also means that there may be a particular signal that the brain receives that says I'm receiving some intake of food or drink that tastes sweet but doesn't actually offer much nutrients in the direction of sweetness, meaning that it doesn't have calories despite being sweet. Now, again, this is all subconscious processing. And like with the previous studies we were just discussing



about artificial sweeteners generally and the gut microbiome generally, it's unclear how this relates to humans at this point in time. But given the similarity of cellular processes and molecular processes at the level of gut-brain in mice, I think it stands to reason that these neuropod cells very likely are capable of signaling sweet presence of real sweetener versus artificial sweetener

#### 01:44:27 Structure & Function of Gut-Brain Axis

in humans as well, although that still remains to be determined empirically. So I'd like to just briefly recap what I've covered today. I started off by talking about the structure and function of the gut-brain axis. I described the basic structure and function of the digestive pathway, and how that digestive pathway harbors microbial species, meaning many, many little bacteria that can signal all sorts of things to the rest of the brain and body. And indeed, we talked about the various ways they do that. We talked about direct pathways, literally nerve networks that extend from the gut up to the brain and from the brain back to the gut. And we talked about indirect pathways, how some of the gut microbiota can actually synthesize neurotransmitters that get out into the bloodstream, can impact the body, can impact the immune system, and can get into the brain and act as neurotransmitters in the brain just as would neurotransmitters that originate from within the brain. We also talked about what constitutes a healthy versus unhealthy microbiome. And it's very clear that having a diverse microbiome is healthier than having a non-diverse microbiome. But as I pointed out, there's still a lot of questions as to exactly what microbiota species you want to enhance and which ones you want to suppress in the gut in order to achieve the best gut-brain axis function. We talked about how things like fasting might impact the microbiome and how some of that might be a little bit counterintuitive based on some of the other positive effects of fasting, or if we're not just discussing fasting, some other types of somewhat restrictive diets either restrictive in time or restrictive in terms of macronutrient intake, how those may or may not improve the health of gut microbiome. And the basic takeaway was that because we don't know exactly how specific diets impact the gut microbiome, and we don't know how fasting either promotes or degrades the microbiome, we really can't say whether or not they are improving or degrading the microbiome at this time. However, it is clear that stress, in particular chronic stress, can disrupt the gut microbiome. It's also clear, of course, that antibiotics can disrupt the gut microbiome. And that brings us to the topic of

prebiotics and probiotics. And I emphasized the fact that for most people, ingesting high quality non-processed foods that includes some prebiotic fiber but also that includes some probiotics will probably be healthy but not excessive levels of probiotics. High levels of supplemented probiotics of the sort that would come in a probiotic pill or even prescription probiotics would probably lend themselves best to when people were under severe chronic stress or had just come off a serious round or an ongoing or repeated rounds of antibiotics. That does not mean that ingesting probiotics in any form or any kind is not good. It just means that the very high dose probiotics, again, typically found in prescription form or capsule pill form probably are best reserved to cases where of course your doctor prescribes them. You should always follow your doctor's advice. But in cases where perhaps you are jetlagged, you're traveling excessively for any reason, or working excessively, you're not getting enough sleep, or your diet is radically changed from normal. And we talked about how increasing the amount of fiber in your diet might be useful for increasing fiber digesting enzymes and the assimilation of fibrous foods but that it's really the ingestion of fermented foods and, in fact, getting anywhere from four or even up to six servings a day of fermented foods can be immensely beneficial for reducing inflammatory markers in the body and for improving microbiota diversity all along the gut and thereby improving signaling and outcomes along the gut-brain axis. So we went all the way from structure to function to the four kinds of signaling, mechanical, chemical, indirect, direct, probiotics, fiber, and fermented foods. And I tossed in a little bit at the end there also about ways that you can make your own fermented foods at home in order to try and offset some of the costs. Also, it's just kind of fun to do. And some of those actually taste quite good. I've actually found that the fermented sauerkraut that we're making at home actually rivals the sauerkraut that you can buy out of the refrigerated section at the grocery store. And I am by no means a skilled cook or chef and basically have no culinary skill whatsoever. So if I can do it, you can do it. I hope you found this information useful and perhaps also actionable. One of my motivations for doing this episode was, again, as a primer for the episode with Dr. Justin Sonnenburg where we go really deep into the gut microbiome, less so into the gut-brain axis, but really deep into the gut microbiome, what it is, what it does, what it doesn't do, and some of the emerging findings from his lab that are yet to be published. And I also was excited to do this episode because I think many of us have heard about the gut microbiome. We hear about these bacteria that live in our gut. We hear about the gut-brain axis or that 90% or more of the serotonin that we make is made in our gut. We hear about the gut as

a second brain and so forth. But I think for many people, they don't really have a clear picture of what the gut microbiome is and the pathways and mechanisms by which it can signal to the brain and to the other parts of the body. So I hope that today's information at least improved the clarity around that topic

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and leaves you with a more vivid picture of this incredible system that is our gut-brain axis. If you're enjoying and/or learning from this podcast, please subscribe to our YouTube channel. That's a terrific, zero-cost way to support us. In addition, please subscribe to the podcast on Spotify and Apple. And on Apple, you can leave us up to a five star review. On YouTube, we have a comment section, please, of course, give us feedback in comments but please also make suggestions about topics and guests that you would like us to include on the Huberman Lab Podcast. We do read those comments. In addition, please check out the sponsors mentioned at the beginning of today's podcast. That's perhaps the best way to support this podcast. And we have a Patreon. It's [patreon.com/andrewhuberman](https://patreon.com/andrewhuberman). And there you can support the podcast at any level that you like. On many previous episodes of the Huberman Lab Podcast, we talk about supplements. While supplements aren't necessary for everybody, many people derive tremendous benefit from them. One of the key issues with supplements, however, is that the quality of supplements can vary tremendously and oftentimes that relates to the precision, or I should say the lack of precision, with which companies put different amounts of supplements in the capsules and tablets that are listed on the bottle. For that reason, we partner with Thorne, T-H-O-R-N-E, because Thorne supplements have the highest degree of stringency in terms of the quality of ingredients and the specificity of the amounts of the ingredients. That is, what is listed on the bottle is actually what is contained in the capsules and tablets and powders. If you'd like to see the Thorne supplements that I take, you can go to Thorne, that's [thorne.com/u/huberman](https://thorne.com/u/huberman) and there you can see the Thorne supplements that I take. You can get 20% off any of those supplements. And if you navigate deeper into the Thorne site, you can get 20% off any of the other supplements that Thorne makes. That's [thorne.com/u/huberman](https://thorne.com/u/huberman). And if you're not already following us on Instagram and Twitter, it's Huberman Lab on Instagram. It's also Huberman Lab on Twitter, and there I cover science and science-

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