



ANXIETY SUMMIT5

Gut↔Brain Axis



FIX THE BRAIN TO FIX THE GUT

Guest: Dr. Datis Kharrazian

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Trudy: Welcome to the Anxiety Summit, Season 5. The focus this season is gut-brain axis. I'm Trudy Scott, food mood expert, certified nutritionist, author of *The Antianxiety Food Solution*, and host of The Anxiety Summits. Today we have Dr. Datis Kharrazian. And our topic is Fix the Brain to Fix the Gut. Welcome, Dr. Kharrazian.

Dr. Kharrazian: Thank you, Trudy. Thanks for having me.

Trudy: It's a real pleasure to have you here. And I'm excited to share some new things that I learned recently from you in your very excellent neuroinflammation training, and excited to bring this information to my anxiety community and everyone tuning in.

Let me just read your bio here and then we will go right into our questions. One of the reasons I'm really interested in sharing this topic is because we hear, "Focus on the gut first," and in actual fact, there are many instances where we need to actually focus on the brain in order to get the gut working. So hence the title, Fix the Brain to Fix the Gut.

Dr. Datis Kharrazian is a clinical research scientist, academic professor, and functional medicine healthcare provider. He's an associate clinical professor at Loma Linda University School of Medicine, and a research fellow at Harvard Medical School and the Department of Neurology at Massachusetts General Hospital.

Dr. Kharrazian earned a PhD in Health Science with concentrations in immunology and toxicology, and a Doctor of Health Science degree from Nova Southeastern University. He completed his postdoctoral research training at Harvard Medical School and Massachusetts General Hospital. Dr. Kharrazian earned a Master of Science degree in human nutrition from the University of Bridgeport, a Doctor of Chiropractic degree from Southern California University of Health Sciences, and a Master of Medical Sciences degree in Clinical Investigation from Harvard Medical School.

He is the author of *Why do I Still Have Thyroid Symptoms?* and *Why isn't my Brain Working?*, the creator of several functional medicine and urology online courses and the founder of the Kharrazian Institute, a postgraduate institute for functional medicine and restorative neurology. Let's get right into Fix the Brain to Fix the Gut.

And as I said in the introduction, we hear this mantra that healing begins in the gut and we need to focus on the gut first. But integrative functional neurology teaches us that the brain has to be fixed in many instances, in order for the gut to be able to work properly. And I'd love you to talk about this in the context of brain injuries, traumatic brain injuries or TBIs, why this is so important that we are aware of this aspect

Dr. Kharrazian: Sure. So one of the things that I think we need to understand is some of the research has been done with traumatic brain injuries. And there's been an explosion of research done here in the United States because of the NFL football players and also the soldiers that are going to Iraq with shock, brain injuries, or blast injuries. And what we've learned is that there is really this condition called posttraumatic encephalopathy, which means once you get a head injury, the inflammatory response in the brain turns on a cascade of events, and symptoms may present 5, 10, 15 years later.

And when the brain gets injured, I think most people are usually thinking, "Well, how were your symptoms right afterwards? And did you recover?" And maybe, sometimes people will feel a little dizzy and feel a bit off for a few days and they think everything's fine. And then 10 or 15 years later, they really start to have all these types of brain and neurological symptoms, which they may not even know are brain and neurological symptoms like depression, like anxiety, like mood disorders, like inability to motivate.

And then these things also have effects on the gut. So many times, sometimes these patients really end up with having chronic GI issues as a consequence of a traumatic brain injury that was 5 or ten years ago. And this is because there's intimate relationships between different regions of the brain, and how it controls gut function.

Trudy: And there's a really good study that you had shared in the training that I did, "The bidirectional gut brain microbiota axis, as a potential nexus between traumatic brain injury, inflammation, and disease." Can you share a little bit about some of this bidirectional mechanism that we see and how we actually have this injury affecting the gut?

Dr. Kharrazian: Sure. Well, let's start with the gut because the gut is what everyone focuses on. Let me get that out of the way and then focus on the brain, which most people don't focus on. So for the most part, the gut has two main pathways to get to the brain. One is through neurological input through the vagus nerve.

So there's a nerve, that's a bidirectional nerve from the gut enteric nervous system or the brain of the nervous system of the gastrointestinal tract, up to the brainstem and into the brain. And different messenger systems in the gastrointestinal tract, like neuropeptides and gut hormones and cytokines, and different immuno kinds of messengers can actually activate this vagus nerve in the gut, and then directly communicate with the brain.

And those are called catalyzed pathways, meaning there's a specific neurological pathway track. Then there's what's called non-catalyzed pathways, which are chemicals. So we also know that in different peptides, different what are called postbiotics, the bacteria in the gut release these different chemicals that can enter our systemic circulation. There's different gut hormones and peptides that are released. Things like CCK, things like ghrelin, and these things can actually cross the blood-brain barrier and impact the brain.

So our gut is constantly communicating with our brain. And that's something which is very exciting for everyone because we're learning how different bacteria in our gut can change our mood or brain functions, or memory and so forth. So that's where a lot of the focus is right now at the brain-gut axis or really what we should call the gut-brain axis. The most overlooked part, however, in the literature is the brain-to-gut-axis. And this is a really critical part of a healthy gut function. So there's several different pathways in which the brain really controls the gut. One of the pathways is through the vagus nerve.

So the vagus nerve not only brings information from the gut to the brain, but information from the brain goes down to the gut. The vagus nerve has different regions. One area of the vagus nerve is called the nucleus accumbens and nucleus ambiguus. And this is an area of the brain where the nucleus ambiguus activates parasympathetic activity that then controls the blood flow to the gut.

So when there is injury to the brain, in the brain or the brain is starting to degenerate, there's less activation to these brainstem centers. And all of a sudden, there's less gastrointestinal motility, which is what's called the parasympathetic autonomic function. There's reduced blood flow to the gut, which means that the gut can't heal as well. So if the gut gets inflamed or injured or has a leaky gut, it's very hard to heal it if there's not proper blood flow, to get nutrients to the injured gut tissue.

And then we also know that within the vagus nerve, there's another nuclei, this is the vagal motor nuclei and that's what controls motility. That's what controls how the smooth muscles in the gut constrict and allow food particles to go through. And when people have the vagal motor nuclei involved, they usually have difficulty swallowing; they typically have constipation. And when they can't move their undigested food across their gut, then that leads to bacterial overgrowths and yeast overgrowths, and abnormal gut environment. And then these patients end up with all the different things you'd see abnormal in a gastrointestinal profile, and they can't produce enzymes.

So we know that these autonomic centers in like the gut, through the vagus can have a dramatic impact on gastrointestinal motility, enzyme production, and also, these things can then impact the environment and cause things like dysbiosis, abnormal bacterial growth, and you can get a whole host of things that take place from there. And this is just one of the areas.

There's also other areas in the brain that are more specific, like the cingulate gyrus and the insular cortex, which cause dysautonomia, where you can get increased sympathetic tone and just completely shut off the parasympathetics of the gut.

And then even the gut itself has what's called a somatotopic map where the brain perceives the gut. And when a certain region of this area of the brain is injured, the brain can't process word to contract the colon and the small intestine to move food across. So you can have a host of different types of brain injuries that cause gut issues. And these patients typically are overlooked in the healthcare system, and they can take digestive support and change their diet to relieve their symptoms, but it never cures them until they get their brain functioning back.

Trudy: So an example of this could be someone with chronic SIBO, small intestinal bacterial overgrowth. And they're doing everything possible to try and improve motility, to address the bacteria that's in the small intestine, everything to try and heal themselves and then just not getting answers. This would be a time then you maybe need to go to take a step back and say, "Has there been some kind of injury to the head? And is this something that may be causing this chronic situation that's going on?"

Dr. Kharrazian: Absolutely. And when you look at phrenic brain injuries, they're not all the same. One of the things that we know is that, first of all, if the person's lost consciousness, if a person has a history of actually losing some degree of consciousness, then there is a significant injury to the brain. That's what we do know.

And we also know that it's not how hard you hit your head; it's what was going on with the brain environment before the impact to the brain. So if your blood sugar was low or if you're a smoker, or if your brain was already inflamed from your diet, if you're diabetic, these things can actually make an impact much more devastating. So we tend to sometimes think these brain injuries are trivial, but they're not.

So if you take a scenario where someone, for example, had reduced oxygen to their brain or they were in an inflammatory state, and then they bumped their head and they lost consciousness for like, let's say, a minute or two, then there are some dramatic changes that take place in the brain. And one of the things that has been shown is that these immune cells in the brain called neuroglia, they actually change their shape and they become what are called primed glial cells, and their anatomy forever changes; and then these cells are active all the time. And it takes very, very little inflammation throughout the body to activate them again. And then the brain starts to have this increased neuro inflammatory response and neuro degenerate, and then you have this devastating vicious cycle.

Trudy: It's very interesting that you talk about what's going on in the body when you have these head injuries because typically, when you think of traumatic brain injury, you think about what you talked about right at the beginning, where someone's a football player or they've had an obvious concussion. We're not thinking about small bangs. Is it cumulative as well, if you've had a number of small bangs to the head; that could be problematic as well?

Dr. Kharrazian: Yes, sure. I mean, cumulative injuries are a part of it. But the key thing is really the stage where you have metabolic factors that exaggerate an inflammatory response with an injury. So we all have little bumps here in there, but those aren't as critical as having the right environmental mix of things that caused the brain to be inflamed, plus some impact.

Trudy: So the examples you gave, some of these metabolic factors that could make the head bang or the concussion worse. You mentioned blood sugar instability, maybe toxin exposure, autoimmune. If you've got something, you've just been diagnosed with an autoimmune disorder. Anything else?

Dr. Kharrazian: People that have poor circulation to the brain, people that have cold hands and cold feet, people that are anemic, the brain has to have oxygen to stay out of an inflammatory cascade. People that have asthma; lung disorders. Any of these preexisting things before traumatic brain injury can really lead to an exaggerated inflammatory response and even lead to what are called glial cell priming. Where the inflammatory response continues for decades and decades after the injury.

Trudy: Okay, great. Very interesting. Earlier on, you said, there is not as much knowledge in the literature but it's not as much as that or it may be that as well. But there's also not as much knowledge of this aspect in the functional medicine world. Would you say that's a fair statement?

Dr. Kharrazian: Well, there's definitely a lot of information in the literature. We have the functional medicine community just focusing on the gut. But in the field of neurology, neuroscience, and traumatic brain injuries, it's very, very clear. There's lots, there's an abundant amount of research. So I think what happens is these patients that have neurological issues, they get overlooked.

And one of the major problems too with functional medicine is... and I'm telling you this as a functional medicine practitioner, but every type of system and every model has weaknesses, right? It has limitations. One of the biggest limitations we see is that functional medicine practitioners don't do an exam. They do lots of tests, and then very little examination.

And there's also a thing in the literature that's happening in the field of medicine, it's called hyposkillia, where the art of doing an examination is almost gone. So it's kind of like, you go in, and someone will check your blood pressure, do your vitals, quickly run through a meaningless exam, listen to the heart and then say everything's fine. And then order lab work and an MRI or just your lab test, it's missed. And that same level of inefficiency transcends into functional medicine.

So when you have people that walk into a healthcare system where there's no emphasis on a detailed examination and there's very little understanding of things like traumatic brain injuries, and it's all about the gut, you have many patients that are going to have chronic gut issues and fail in the functional medicine model. Which is something that's out there. But not to say functional medicine doesn't help a lot of people, it just seems to help a lot of people when it's a gut to brain issue and it's overlooked when it's a brain to gut issue.

Trudy: And that's why I really wanted to have you talk about this aspect because I'm late to the party and I just discovered this whole world of

integrative functional neurology. I've been hearing about it for the last year and recently having done your neuroinflammation training for practitioners, it just opened my eyes to this whole world out there that we may be missing, as nutritionists, functional medicine doctors. I know there's a lot of practitioners who tune into this as well. So I really wanted to bring this. So I really appreciate you bringing this to light and we can just improve things for everyone involved.

Dr. Kharrazian: The other thing I want to add to that is, I think we tend to focus on, when we're sick... well, first of all, if you have brain related symptoms, if you have lack of focus, attention, concentration, poor balance, depression, sensory perception abnormalities, sensitivity to sound, and sensitivity to light, those are brain symptoms that tells you your brain is not functioning well. Your brain is unhealthy. Okay?

Now, if you've cleaned up your diet, and you've gone off every inflammatory food, like you see people start with gluten and then gluten and dairy and then paleo and then autoimmune paleo, and then they keep cutting things out.

And there's no more inflammatory foods in your diet and you're taking handfuls and handfuls of supplements and your gut is still messed up. And you still have brain symptoms, depression, focus, concentration, attention issues or again increased sound and light sensitivity, if you have those things, then you may want to focus on your brain.

When I say focus in your brain, this is where the brain has to have connectivity. So, one of the things that happens is neurons have to fire to connect to each other. And we know this neuron connectivity doesn't take place with supplements or diet. Neuron connectivity takes place with using the brain and activating the brain.

Now, nutrition and diet can create the best environment for neurons to connect to each other and diet nutrition, and lifestyle impact the chemistry of the brain can promote things like brain derived neurotrophic factor, to make this more efficient and slow down neurodegeneration. But the end the day, neurons have to fire to connect to each other, branch into what's called plasticity. And plasticity can't happen without activation. Just like a person who had his arm in a cast after breaking it and then the muscles atrophy, there's no supplement or diet you're going to take to bring your muscle back. You're going to have to actually move it. It's the same thing with the brain.

So one of the things I think people that may be searching for answers that have chronic anxiety or chronic gut issues, whatever the case may be is, if you still have brain related symptoms, maybe you need to really focus on your brain health. And if you do, then you want to activate your brain. Now, very

generally, the things that activate the brain are going to be specific to regions of the brain, but for the most part, it's very simple.

If you have balance issues, you should do things like yoga, you just close your eyes and see if you fall apart. Any physical exercise, especially exercise that involves coordination, is phenomenal for the brain. I mean, if you play tennis, if you play ping pong, and to be quite honest, whatever is hard for you to do is really the best thing to do to rebuild your brain.

So, if you have a hard time remembering phone numbers, or doing math calculations, that's what you need to focus on. So, really simply, just think about what are you bad at, and then that becomes your exercises. So maybe its focus and concentration, maybe it's recall, maybe it's numbers, maybe it's directions; maybe it's your balance. So all those things are very simple things to do.

In the functional neurology world, you can have a lot of fun and do a detailed examination, and break it down to the track, to the nuclei, to which side and do all that if you really want to for fun and then do some exercises to activate them. But at the end of day, for a lot of people, they're on their own and they don't have anyone to count on. They can just go, "What can't I do? The things I can't do or the things I need to do."

Avoid things like, "I've always been done with math," that's not a personality thing. If you're bad with math, that means your left inferior parietal lobule is degenerating or never been healthy. If you're bad with balance, it's not a personality thing; that means your vestibular cerebellum is not healthy or degenerating, or injured, or whatever the case. So look at functions of the brain and see what you're not doing well and then try to activate those things with creative stuff. Maybe if you can't remember numbers or letters, maybe it's good to try to learn a foreign language, even if you don't learn the language, its rehabilitation for your brain.

Trudy: So powerful and so simple and I'm going to have to ask you to repeat the bad math one because that's an area of mine that's a problem. And what is the area of the brain that you mentioned?

Dr. Kharrazian: This is the left inferior parietal lobule.

Trudy: Okay, good.

Dr. Kharrazian: It's left side of 97% of the population. So there's 3% that on the right.

Trudy: Okay. Thank you Thanks for that because that's just so powerful. Get those exercises for the brain. Like you would exercise your muscles, you're doing some exercise the brain and heal the brain.

Dr. Kharrazian: And there's so many apps these days and online programs people can take to try to improve their memory and cognitive skills, whatever it is. But activation is a key part of it. And throughout the world there's phenomenal physical therapists that do brain and stroke rehabilitation, occupational therapists, balance therapists, all these things are phenomenal stimulus for the brain but even just physical exercise. I mean, look at adults, think about when you were younger, you used to play sports, you used to do things. Those things are phenomenal for the brain.

And the other key thing is that when there is a brain injury and the brain needs to reconnect, where supplements and digestion can't do that alone, exercise raises brain derived neurotrophic factor and brain derived neurotrophic factor helps this connected pathway. And the more intense the exercise is, the greater BDNF a person releases. Sometimes you get people in a functional medicine model that have both the brain gut axis issue, meaning their brain is involved and the gut is involved, and now their gut is so bad, their brain is inflamed.

So maybe you do have to work on the diet and nutrition, and inflammatory food removal first and try to heal the gut the best you can. And once that inflammation is down, really engage in activities. So if you used to play soccer when you were a kid, play soccer. If you used to play tennis, you know, do something. Any type of movement activity is phenomenal for just brain rehabilitation in all areas. Any kind of complex sports is hitting major regions of the brain, pretty much parietal lobe, frontal lobe, occipital lobe, pre motor areas. It's fantastic.

Trudy: Can you mention a few apps that are helpful in this area?

Dr. Kharrazian: Well, I think the most popular one, the one that I have a lot of my patients use is Lumosity. That's an online one, that's good. There's an app called Orientate, that's fantastic. Any of the basics, like if you're bad at math, you can just get a math app and just start doing calculations. Like, when my daughter was learning multiplication tables and stuff, we got her an app.

And if you need to do math and division, those can be very useful. So remember, what are you bad at? And search for an app that activates that area. If you're really bad with directions and images and recalling where you put your keys, you can even play things like Tetris. And Tetris helps refocus

shapes in different areas that activates the areas of your brain involved with memory and shape recall. So those are some of the most commonly used ones.

Trudy: Excellent. So let's go back to the traumatic brain injury. And can you talk a little bit about how it actually affects the blood brain barrier and what the implications are of having a leaky blood brain barrier and a leaky gut?

Dr. Kharrazian: So, very, very, very interesting information on this. And it's pretty clear. There's no question about this in the neurology literature at this point that when there's a traumatic brain injury, within minutes, the blood brain barrier breaks. The blood brain barrier becomes permeable.

So what happens is when there's an injury to the brain, neurons have these connections called axons and they start to break apart. When these axons break apart, there is a release of protein signals called heat shock proteins and these heat shock proteins activate what are called astroglial cells. And these astroglial cells open up the blood brain barrier.

And this is done intentionally because when these neurons get injured, this debris creates an ongoing inflammatory cascade and the blood brain barrier is opened to allow T cells and macrophages to come into the brain to get rid of the debris. But unfortunately, if there's any systemic inflammatory proteins, those also come into the brain. And then the person can really never have the blood brain barrier heal again, for many, many, many years. So we know that traumatic brain injury opens the blood brain barrier. Initially enough, research has clearly shown that within minutes not only does the blood brain barrier open up but the gut barrier opens up too.

And we know that when someone gets a traumatic brain injury, they get this kind of double hit in their immune response. Their blood brain barrier becomes permeable. Their gut-brain barrier becomes permeable. They're prone to inflammation in the gut and they're prone to inflammation in the brain. Inflammation in the gut promotes inflammation in the brain. The brain gets more inflamed, it can't control the vagal pathways and the gut pathways, and then you get this whole vicious cascade of all these things. So, not to say the gut is not important. The gut is important because in the very beginning stages you have to really go on an anti-inflammatory protocol.

So we will have patients go, immediately after traumatic brain injury, into an anti-inflammatory food diet. It can be an autoimmune paleo diet where they're getting rid of lectins and nightshades and wheat and dairy. But even more powerful would be actually to have them go on a ketogenic diet. And when they go on a ketogenic diet, most of the inflammatory foods are really restricted anyways. We make sure they're on a ketogenic diet that avoids dairy, when they have a brain injury, we don't want it. Milk proteins are very

inflammatory for the brain. There's some potential cross reactivity with myelin and with milk proteins. We've published some studies on that. And we know that ketosis helps with anti-inflammatory effects with the brain.

So, many times after a traumatic brain injury, we put the person on a ketogenic diet. That also helps with leaky gut patterns. And then we start putting them on lots of different flavonoids that can cross the blood brain barrier. Even though the blood brain barrier may be permeable, we want to use high amounts of flavonoids like resveratrol and turmeric, curcumin, green tea extract; those things all really help reduce brain inflammation. And once you get the inflammation under control, you have this ongoing battle with the gut.

And then at some point, you'll activate the brain and you have to do this in a combination treatment model to really break someone out of this vicious cycle. And this vicious cycle can last with some patients for many, many years. They can have it for like 10 years and it's just gotten worse and worse. And they'll see someone who kind of treats their gut and they'll see someone who kind of treats one thing and maybe they'll do some neurofeedback. But they never really get out of the vicious cycle. So they're always chronic.

Trudy: So, what you described here is for someone who's just had a traumatic brain injury, this is the approach. Now what if someone is hearing that maybe there's something going on, maybe they had some injuries to their head a few years ago, they've got some of the issues that you talked about. The cognitive issues, maybe the depression, and the brain fog. And now they're thinking, "Oh, maybe there's something that I can do." So everything you've talked about here, can be done after the fact, years later, because we've got to start fixing the brain and getting those neurons talking to each other. We've got to provide the nutrients, as you said earlier, so you've got the right environment for this healing to happen. So all of this can be done later. Is that correct?

Dr. Kharrazian: Yes and most of the patients I see are patients with a traumatic brain injury, maybe 5, 10, 15 years ago. They're not acute patients. I don't have a practice that really works for acute patients. It takes some time to get in. But they're all patterns where things happened years ago and there's still tremendous potential for change. I mean, the brain is amazing. You can always reconnect neurons that are injured and completely dead, and you can reconnect. It's such an amazing tissue and there's no other tissue in the body like the brain.

Trudy: Amazing. I'm glad we talked about both, the acute TBI because that's going to happen at some stage for a lot of people. So they know that they can do that. And then for the chronic, there is hope, there is something that we

can do. Can you talk a little bit about what tests you use to determine leaky blood brain barrier?

Dr. Kharrazian: So there's a test for the blood brain barrier. I like the blood brain barrier protein test from Cyrex. It's called Array number 20. And it lets you know if there's any breakdown to the blood brain barrier. And the antibodies circulate around for two to four months, so it's a very stable marker. The test in most reported literature is S100 B protein and that can be done by most conventional labs anywhere in the world. S100 B is released and goes up in circulation after traumatic brain injury. And there's other things that can raise S100 B levels too but it's a very well-known marker for acute brain injury. That one is not a stable marker, so it can fluctuate up and down from one day to the other. But if either one of those are high, then that's a pretty good indication the blood brain barrier has permeability.

Trudy: So I've got the S100 B and what was the other one?

Dr. Kharrazian: Array 20 blood brain permeability from Cyrex Labs.

Trudy: And the Array 20, that's got a number of different markers on there.

Dr. Kharrazian: Yes. It's just a composite blood brain barrier protein antibody.

Trudy: So while we're talking about the leaky blood brain barrier, I want to just talk briefly about GABA and the GABA challenge that you have proposed as a tool for testing leaky blood brain barrier. And as you know, I use GABA extensively with clients with the physical type of anxiety, the low GABA physical type of anxiety. And I've always been a huge fan of you and your work but we do have a professional difference of opinion in this area.

And I've never actually been a proponent of using the GABA challenge, and I've been pretty vocal about it. So I'm really glad that we had a discussion about this in the Facebook group of your neuroinflammation training, and you shared some insights because I was asking some questions about this. And I'd love you to just share some of what we talked about in that discussion. Because if we don't talk about it, my community is going to say, "Hey, why didn't you talk to Dr. Kharrazian about this?"

Dr. Kharrazian: Sure, no problem. I don't think we have this big a disagreement. I think we just have different ways of looking at what's out there and what we are observing as people working with people, patients who have anxiety. So ultimately, we have a bunch of theory right now and a bunch of potential models, but we don't have any clear studies to show what's really happening.

So, one of the things that I proposed in my book before... you understand, I was working with brain patients for over 20 years now. And before we had S100 B readily available for many years, it was only in research; you couldn't get it from conventional labs, even though research was showing it. And the blood brain permeability test was not available either.

These have really become more available the past five years and prior to that, we didn't really have a great test to evaluate if the blood brain barrier was breached. And in an effort to work with what's out there, what we could do, one of the things that I was doing was doing a test what we called the GABA challenge test. It was really based off the lactulose mannitol test. So the lactulose mannitol test is a well-established test in gastroenterology where they measure leaky gut.

So, in that test what the person does is they consume a monosaccharide and a disaccharide, lactulose and mannitol. Lactulose is a disaccharide, it's very large, and mannitol is very small. And if mannitol doesn't get absorbed, then there's a malabsorption issue. And if lactose, which is very large; that should not get through the tight junctions of the gut, gets absorbed in a post urine test, after they drink it, then it shows they have leaky gut. So the whole premise of when you find particle sizes too large to cross, can be a clue to an indication of permeability.

So the GABA challenge that I write about in my book, *Why isn't my Brain Working?* was really a way for us to have patients consume GABA. If you look at the molecular weight of GABA, the Dalton size, it's several hundred Daltons. Several hundred Daltons cannot cross the blood brain barrier. So the concept was, well if someone is taking GABA and they have an effect, then there's a potential for it to cross the blood brain barrier.

And it was kind of following the theory of the lactulose mannitol test. So there's patients out there who take GABA and nothing happens and some patients take it and go, "It was amazing. Best thing ever. It finally helped me sleep," or, "Helped reduce anxiety for me." So, one of the theories was that maybe for some of these people, their blood brain barrier is breached.

Now I know we talked and there is actually the possibility of other pathways that can impact GABA, maybe directly to the gut itself, through the vagus, so I don't discount those possibilities because we still don't know. I mean, ultimately, there'd have to be a study designed where they look at it. And it would have to be an animal study, there's no way you can get an IRB for human studies to check if it's crossing the brain. It's some really advanced isotope tracing techniques and I just don't think the level of dyes they would have to consume to look at the gut and the brain in peripheral and separate... it wouldn't be possible. So the real answer is, we don't know.

For me, I still am always suspicious if someone takes GABA and they have a reaction. I always want to go and check the blood brain barrier. And it's not 100%, I mean, I can tell you without question, there's people who take GABA, you do a blood brain barrier test, they feel benefit from it, but their blood brain barrier doesn't have any markers to show permeability.

So it's not hard for me to consider the possibility that there's some exogenous pathways too. But at the same time, it's also really hard to look at the molecular weight of GABA and look at what can cross a healthy blood brain barrier. This Dalton size, we're talking nanoparticles to a huge, huge particle. So I don't know but I think we'll just have to see what happens. And ultimately, if you feel better with GABA, that's great. If it's not harmful to you, and if you feel like taking it, that's great.

I like to also use things like Valerian root, passion flower, and hops because those compounds cross the blood brain barrier. They cross the blood brain barrier and they bind to GABA receptors. So, the other thing too with actually using GABA is when you [inaudible] neurotransmitter, you always have the potential for your neurotransmitter receptor sites to down regulate. And this is seen all the time too, patients take GABA and they feel great and then they have to increase their dose and they don't get the effect as they first did. And they increase the dose and finally, they just don't get much of an effect from it. And that's potentially due to receptor site down regulation.

Which is not as common if you take agonists like Valerian root or passion flower, or hops or GABA calm, these things bind to GABA receptors. So I did a review in my book, where I went over all the literature of the different GABA compounds, which have been published in the literature. But I'm not going to deny the possibility that there is a potential exogenous source but I also can't let go the possibly that the blood brain barrier is permeable. So I'm still waiting.

Trudy: Yes, I think it's great because the fact that you write about that and you taught about that, and you teach about it. It got me looking into the research further and it got me more curious; and it's good, it's good to have a healthy discussion and a healthy debate, and be open to possibilities. I'm very open to having my mind changed if something comes up. I just see GABA works so well with my clients and we use very, very small amounts I know with your GABA challenge, it's... what is the amount, its 1,500 milligrams, I think or 1,500 to 2,000? So I'll start my clients on 125 milligrams of GABA sublingually and get results. I have not noticed the effect that they need more and more, and more. So that's interesting that you say that. But yeah, it's good, I'm glad that we've had this discussion.

And the other thing that you did say in the online discussion, you said, if someone has a response to taking oral GABA, in other words, taking a GABA supplement does help them, you would want to test for the blood brain barrier permeability, just to see what's going on. And I like that you say we can track. I've actually been in discussions with Cyrex and said, "Hey, why don't we monitor people who are doing the Cyrex test and have a response to GABA, either therapeutically for the anxiety or with your mechanism?" In order to do this GABA challenge and we might start to see some patterns, which I think would be very interesting.

Dr. Kharrazian: Yes, the best we can do with the data in that scenario is just the correlation statistical analysis. But it still wouldn't answer it.

Trudy: No, I know. But maybe that will trigger someone to want to do a study. So, the good news is we're seeing more and more research on GABA in the literature. So, it's exciting. Well, thank you for discussing that with me.

So, when we were talking about the acute TBI, we talked on some of the nutraceutical approaches, and you mentioned resveratrol, curcumin; some of the polyphenols. And then I wanted to just mention something about those polyphenols. Curcumin is actually very high in oxalate. So if someone has an oxalate issue that could be problematic.

I personally have an oxalate issue and if I take higher levels of curcumin or even just an average amount, my oxalate pain issues in my feet go through the roof, and I've had that with a number of clients. But after doing your course, I went and looked at the other polyphenols to see if there was an oxalate issue. And resveratrol actually counters issues with oxalates, which I thought was very interesting. So I think with any of these, we've got to look at other factors. It's going to benefit you in one way but is it problematic? And it goes back to biochemical individuality.

Dr. Kharrazian: Exactly, personalized medicine and there's no substitute for trial and error and seeing what a person responds to and kind of working through it. I know for myself, when I work with patients, it's always a matter of an endurance game. And we just one by one, try one thing and see what happens and look at the response, and then develop that personalized approach. And I think if you're a patient looking to work with a functional medicine provider, or you're trying to figure out your own solutions for your health problems, realize that there's so many variables involved in the clinical model. Just like oxalates, as you brought up; that there is always trial and error.

You're going to have to try various things and see what works and develop a plan. And you've got to be careful to too many things all at once. That can

make you lose your picture of what's actually helping you or what's making it worse. So, for myself, I just work with chronic patients and with chronic patients, if you don't take it one step at a time and one mechanism at a time, you can't figure it out. So, just some words of advice if you're out there trying to figure out what the best strategy is. Just be aware that there's no doubt that you'll have to do some trial and error.

Trudy: Excellent, and one at a time, I think is so wise because if you have a bad effect, you can just backtrack and say, "What was the last thing that I added? What's the last thing that I tried?" and see what it is. Take it out and see if the symptoms resolve.

Dr. Kharrazian: Exactly.

Trudy: So a question I had about polyphenols. You mentioned that microbiomes have different responses to polyphenols. I think that's really interesting. And again, it goes back to this biochemical individuality.

Dr. Kharrazian: Yeah, exactly. It's a great point. So there's very clear research that the actual polyphenols we take or the different flavonoids and food products we eat and carrots and blueberries and pomegranate, and all the different great things about it; different teas, they don't have an effect on our receptors until they get metabolized by gut bacteria, for the most part all them. So they have to be metabolized by gut bacteria. And the less diverse the gut bacteria you have, the less potential you have to actually convert some of these flavonoids. So, different bacterial species can activate and convert certain flavonoids. No one has figured that are exactly in the literature, they just know that diversity is a key factor, which allows polyphenols to have more of an effect.

And it may not just be one strain of bacteria, it may be a combination of bacteria. They're all working together. And they're at the point in the whole microbiome research where they're saying it's not one or two, it's actually a combination of things. And we're going to have to use machine learning to even have a good chance to figure this out because it's beyond our ability as a human being to bear with all these variables are. What we do know though is that different flavonoids have different effects with different microbiomes. So if you take a person who's got a lack of diversity in their gut, maybe because they've been on chronic antibiotics or they just don't eat many vegetables. Diverse vegetable proteins and fibers lead to microbiome diversity.

So, this happens all the time with people that are sick. They just kind of only eat one or two foods. They just kind of find their favorite food to eat every day for breakfast, lunch, and dinner and then they lose their gut diversity. And when they take flavonoids, they don't have the same effect. And not only do

flavonoids become active when you have blood bacteria in the gut, but flavonoids also convert to metabolites that can cross the blood brain barrier, only when gut bacteria metabolizes them. So the active ingredients in pomegranate or green tea or resveratrol, or whatever, have to be metabolized to an end product that then becomes active and can bind to receptors, and even have the ability to cross the blood brain barrier.

Trudy: Fascinating, amazing. And, yes, we have so much to learn. The body is incredible, but we have so much to learn still.

Dr. Kharrazian: And that goes again to your point, like you don't know, like diversity. We don't have all the tests in the world to validate each patient and figure out the solution. It is still an ongoing field in medical research in how all these things work. So you could have one person who does very good with pomegranate extract, and it really has a huge effect on them and someone else who takes green tea extract, and they've had no effect with pomegranate. So it's kind of daunting when you think of all the possibilities, but it is what it is.

Trudy: I'm really glad you raised this point, because a lot of times I'll see in Facebook discussions, someone will say, "What did you take? I want to go and take it and I want to use it because it made you feel so good." And we kind of assume that what works for someone else is going to work for us. So, going back to what you said and trial and error, and figuring out what's going to work for you. And it depends on what's going on in your gut. It depends what stresses you have. It depends on so many different factors.

Dr. Kharrazian: Right. And even worse than that is you have a practitioner that something worked for them, so they think it works for everyone the same way. And then that happens all the time too.

Trudy: Yeah, I'm sure it does. So, going back to the nutritional aspect of this, and you talked about having to do the activation and how important that is to get the neurons communicating. We've talked about the polyphenols. Something else you talk about, which I don't hear a lot of people talk about is butyrate for helping with the synthesis of tight junction proteins in the brain. No, the research is on the gut, isn't it? I think that's what it is, in the gut. And you're proposing that it would probably work for the brain. Is that correct? Did I get that one right?

Dr. Kharrazian: Well, we know that butyrate dampens brain inflammation, taken orally. If you reduce brain inflammation, you're going to heal the blood brain barrier, the same cellular messenger pathways are involved. But this is one of the new breakthroughs in research in the gastrointestinal field and actually, a lot of it in the field of neurological autoimmunity, where they're

finding that orally ingested butyrate... and butyrate is normally produced by gut bacteria from fiber.

So when you eat a high fiber diet, your gut bacteria, assuming you have healthy diverse gut bacteria, they then produce butyrate and then butyrate binds what are called G coupled proteins on regulatory T cells. And this calms down intestinal inflammation, systemic inflammation, and even brain inflammation.

The glial cells in the brain have a pro-inflammatory, anti-inflammatory response called an M1M2 response and it switches them into an M2 anti-inflammatory response. So in various animal studies where they can actually do post mortem studies and cut the brain and look at brain inflammation, they know that if they induced an MS like pattern, and then give them butyrate, it calms down the inflammatory response in the brain. There's several papers now... Well, not several, there's two papers I know of that have shown that it actually increases the synthesis of [inaudible] proteins, and nothing's ever been shown to do that.

So we know when people have leaky gut, everyone's taking glutamine to provide fuel for the small intestine. And that has been shown in several studies to have tremendous benefits for leaky gut and what they call endotoxemia, the bacteria crosses from leaky gut. But butyrate, I think is the next big hit and the most underutilized supplement in gut issues, great inflammation issues, and I use a lot of butyrate in my practice. And butyrate is available everywhere. It's not an expensive supplement, it's just short chain fatty acids. And if you can't find it, you can just take fiber. You can take psyllium seeds and flax seeds, and hemp seeds, put them all together in the morning with a little bit of water and drink it and you'll produce your own butyrate.

Trudy: I love it. And that's one of the reasons I wanted to ask this question because I don't hear many people talking about it, and we hear about glutamine a lot, and if we've got something that's going to be more effective, then we need to use it obviously. I know that you are very active in formulating products through Apex. I just wanted to mention that because there is actually an Apex Energetics product that does contain butyrate and some other short chain fatty acids. Is that correct?

Dr. Kharrazian: Yes.

Trudy: And what is that product's name? I'm sure people are going to want to know what it is.

Dr. Kharrazian: Well, it's called Enterovite™. Unfortunately, it's only available in the US.

Trudy: I will make sure that folks know that. Thanks for sharing that. And then going back to what you said, take some fiber. Again, you said psyllium, flax seeds, and did you say chia seeds? What was the other one?

Dr. Kharrazian: Chia seeds, hemp seeds, yeah. You get a mixture of chia seeds, flax seed, hemp seeds, and psyllium husks. Just get half a teaspoon, mix them in cup with some water and drink it. You get a huge source of butyrate production happening.

Trudy: Excellent.

Dr. Kharrazian: You have to start slow because you may get bloated if it's too much for your colon to handle but you start with a dose you can tolerate and kind of build up. And it's a great way to start the morning.

Trudy: Excellent. And then just going back to what I said earlier about oxalates, if you have an issue with oxalates, then the chia seeds may be problematic or you may need to use less of those. So again, just figuring out what can work for you based on what's going on with you.

This has been fantastic, Dr. Kharrazian. I just wondered if there's anything else we wanted to talk about in terms of activating the vagus nerve. No, we didn't talk about that because we talked about activating the brain. Anything that you want to share about in terms of activating the vagus nerve, seeing it's so important?

Dr. Kharrazian: Sure. So, in my brain book, *Why isn't my Brain Working?...* Autobiography. No, just kidding but in that book, I talk about different exercises for the vagus. So, gargling is one of the key things. We just have patients gargle with water. When you gargle with water, you activate the palatine muscles in the back of the throat and that activates the vagus. That's really the easiest one for people to do. There's just more complex things out there. And if you do a literature search, there's 20 things you can do to activate the vagus, but gargling is by far the most effective.

So we'll have patients take two or three glasses of water per day and just kind of get through them. So, maybe drink a quarter of a glass and gargle for as long as they can with that. Maybe its 10 seconds, maybe 30 seconds and then they spit it out or swallow and then they go through the rest of glass. They'll do that two or three times a day and if the vagus nerve needs to be activated, then that should work pretty quickly. Your biggest clue that your Vagus nerve needs to be activated is you have constipation and motility issues, and you

also have noticed it's hard to swallow supplements or food. Those all suggest lack of vagal activity.

Trudy: Would there be a situation where someone may not have issues with swallowing but have constipation issues and maybe a vagal nerve issue?

Dr. Kharrazian: It actually is possible. There's some patients who don't realize they have a swallowing issue. It's worth a try too. Now, if it's going to work, it's going to work within the first day or two. I mean, you don't have to do it for months and months, hoping it'll work. A lot of people will be constipated, and they'll just gargle for, let's say, three to five minutes. Then they'll notice through the change in their motility right away, so it's an immediate response.

Trudy: Okay, good to know.

Dr. Kharrazian: It's also a trial. You can just do it for a few days and see if it's working or not.

Trudy: That's not something that you would do as a real... just like you would exercise every day, you wouldn't do something like this in order to activate the Vagus nerve. It's not needed if you don't have issues.

Dr. Kharrazian: I personally don't do it if patients don't need it. But there are some people that are vulnerable, people that have had traumatic injuries, for example. People that have Parkinson's disease, we do it preventively all the time with them because they have [inaudible] where they infiltrate and aggregate into their vagal motor nuclei in the enteric nervous system. So we try to get that gut pathway to the enteric nervous system as healthy as possible. But those are the only ones I do it on a routine basis, at least in my practice.

Trudy: Well, Dr. Kharrazian, this has been absolutely fantastic. I have thoroughly enjoyed it and I'm sure my community has enjoyed it as well. I would love to just give you the opportunity to share some resources where people can learn more about you and your work. I know you have some resources for the public and then you also have resources for healthcare professionals.

Dr. Kharrazian: Yes, so I have three things. I have my books. I have a book on the thyroid, *'Why do I Still Have Thyroid Symptoms?'* A book on the brain, *'Why isn't My Brain Working?'* Those are available on Amazon. And then I have a program designed for healthcare professionals, which is at the Kharrazian Institute. Kharrazian is spelt K-H-A-R-R-A-Z-I-A-N Institute. And we have a new program every four months, where we talk about different clinical models

for treatment of various conditions. We just did one on inflammation. We're doing one on the gastrointestinal system and then on autoimmunity, and so on and so on.

And then at Dr. K News [drknews.com], I have several online programs for just patients. One is a program called 'Save your Brain', where we go into a six week program where we teach you how to rehabilitate and recover your brain and how to do your own neurological exam, and how to activate certain areas. And we also go into lifestyle, nutrition and lifestyle things that can help the brain. And then we also have a program on oral tolerance, where we talk about how to improve your immune system's tolerance issues, which is to reduce your reaction of your own body to foods and to chemicals. Which I think is also another overlooked area of functional medicine that people talk about. So we try to teach people those concepts and have them use them in their lifestyle to improve their inflammation, autoimmunity, and their health.

Trudy: Well thank you and I can thoroughly endorse your material. I just went through the Kharrazian Institute Neuroinflammation, two day training, which was absolutely phenomenal. So I can certainly attest to that. And I have your books. So thank you very much for being a wonderful researcher, wonderful resource, and educator. And we really appreciate everything that you do in this space, Dr. Kharrazian. Thanks again for being on the Anxiety Summit.

Dr. Kharrazian: Thank you so much, Trudy. Wonderful.

Trudy: Thank you. And thank you, everyone for joining us on another great interview on the Anxiety Summit 5, gut brain axis. Please join us for other great interviews.