Build Your Resilient Gut
MICROBIOME & BEYOND

By Kiran Krishnan
Microbiologist & Microbiome Expert

Common GI Problems & Solutions:

Why Do We React to Everything - Understanding Oral Tolerance

Video Transcript:

I really want you guys to understand oral tolerance because this is such an important part of how your body responds to the world around you and to the things you consume, the things you're around, the things that touch you or are near you, breathe in all of those things.

So I'll do some painstaking explanations of it because more often than not when people are emailing me or even practitioners are emailing me and reaching out, asking about complicated patient cases, "This is a patient with mast cell activation and histamine intolerance and hypothyroidism, and a skin rash and a metabolic issue."

All those things kind of go hand in hand and, "Oh and the patient can't eat much. There's about seven foods that she or he can eat." All of those things, even though they seem like independent complications are driven by the same issue of loss of oral tolerance. And so understanding this issue of oral tolerance becomes really important and then understanding what are the mechanisms involved in it. And then of course, most importantly, what are some of the things you can do to help support your system in order to improve oral tolerance?

So keep in mind that oral tolerance is a really, really resounding component of how your immune system behaves when it's exposed to all the things that you're exposing it to on a day-to-day basis. Most of which are things that are benign that you don't want your immune system reacting to. So this goes beyond allergies and sensitivities. It starts there, but it goes into much more complicated and serious conditions all driven by the

same thing. So let me start the screen share, and of course, please let me know if the screen share looks weird or anything.

Okay. Module five. Common GI Problems and Solutions. This is the second part. Last week's module was the same topic, but we addressed a lot of issues in the stomach and mostly the upper GI. So we talked about GERD and reflux and gastroparesis and issues like that.

And as I mentioned, and I emphasized this quite a bit last week, is that these conditions kind of cascade into each other. The digestive tract being connected from the mouth all the way to the rectum are parts of the system that are dependent on things that are upstream. We talked about how a dysfunctional stomach with low stomach acid can lead to SIBO and how SIBO can lead to large bowel problems. But we talked about how dysfunctional oral microbiome can lead to stomach issues, and then stomach issues can lead to small bowel issues. So they cascade.

And similarly, those issues can also lead to other small bowel issues, which we'll tackle today, and then large bowel issues as well. So they're all interconnected, and this is likely why most people experience more than one of these issues at a time. Not because they're unlucky and because two or three separate things went wrong, it's because they are experiencing a cascading effect of dysfunction. A lot of it which is rooted in a dysbiotic microbiome that then causes dysfunction in the immune system tolerance and so on.

So let's jump in. Make sure I can click here. How We Lose (and Restore) Oral Tolerance. Again, my disclaimer from last week as well. Please don't take this as medical advice. This is educational material to give you a strong overview on how all these systems work. So don't use this as a diagnostic tool, and if you're going to diagnose yourself or think you have something, please check with a healthcare practitioner about any conditions you may be experiencing.

Of course, any product or other solutions we talk about in here are not really treatments designed to treat a particular disease state. These are really ways of supporting underlying systems so they function better to treat complicated conditions like we're going to be talking about. Please check with a healthcare practitioner. So we want to make sure we're doing that and not having people freaking out and diagnosing themselves as a result of all this.

All right, so what is oral tolerance? So the term tolerance is really critical here, and it's not just oral, but oral tolerance is the word used for it. And the reason for that is because the vast majority of antigens, so if you're not familiar with that term, an

antigen is anything that your immune system can react to. So when people say, "Oh, that is antigenic," or "it has antigenic properties," that means that it's something that may elicit a response from your immune system.

For example, for 99.9999% of people in the world, stainless steel is not antigenic. So you could touch stainless steel, you could put your hands on it, you could lay on it. It might be uncomfortable and cold, but it doesn't elicit an immune response because it's not antigenic. But most biological compounds do have an antigenic component to it, and most biological compounds, the antigenic component is the protein part of it. So proteins tend to be the most antigenic compounds.

Now, often it's the size of the protein that matters. So proteins can be massive molecules and structures. We talked about this when we talked about diet and digestion, where, keep in mind that a chicken breast, for example, when you look at a chicken breast, the protein is thousands if not millions of amino acids like a string of pearls, and then they're all attached together in a particular sequence, and then they're folded into these three-dimensional structures, which then looks like a piece of steak, or a chicken breast, or egg, or wherever the protein is.

In order for that protein to be digested, it has to unfold the folded three-dimensional structure, go back to a string of pearls, and then the string of pearls has to be cut up into smaller sections of pearls or individual pearls, we call amino acids. Now, when you get to an amino acid level, that's not antigenic. Amino acids don't typically elicit an immune response. The big folded protein doesn't usually elicit an immune response.

What typically does in a protein is a peptide. A peptide is a certain number of amino acids. Typically, it's 9, 10, 11, 12 amino acids in a row that make a very short string of protein. Those peptides tend to be the immunogenic component of any protein. If it's much longer than that, it tends not to be, if it's much shorter than that, it tends not to be, if it's an amino acid by itself, it tends not to be.

So when you have foods that tend to have a lot of peptides or during the process of digestion, you digest this big protein into individual peptides, that's the kind of thing that can stimulate the immune response. So that creates antigenic properties.

Now, bacteria, viruses, toxins that are not proteins can also elicit an antigenic response or an immune response, but all of that is technically supposed to be tolerated. We will talk about that but in a second. But I wanted you to really understand the protein part of it because what you may hear or you look at stuff, you look up stuff, is they'll talk about

peptides being the allergenic or antigenic component. This is one of the reasons why gluten can be so intolerant for so many people because the gluten gliadin proteins in wheat tend to have this 10, 11, 12 amino acid sequence peptide formation. So they're very antigenic that way versus other crops that don't necessarily have that type of antigenic peptide. So that's an important thing.

Now, oral tolerance in itself refers to the immune system's ability to recognize harmless antigens, so things that would normally elicit an immune response, so food proteins, gut bacteria, environmental components and so on that it shouldn't be attacking and tolerate it. So remember, I think I talked about this in a couple modules that the immune system in general is produced with all of the capability of functioning without any of the knowledge to function.

The analogy I always give with an immune system is think about the immune system as an army with all of the soldiers and guns and tanks and all of the equipment to fight a battle. But they have no general, they have no plans. They don't know who the enemy is, they don't know who to fight, who not to fight. They're sitting there with the capability to do it, so your thymus, your bone marrow, produces most of your immune cells. Those immune cells are produced in a naive state, meaning they have the capability, but they don't have the knowledge as to what they're supposed to do.

Those immune cells then go to other parts of the body like your lymph nodes, your gut mucosa, your mucosal lining, where they get tutored by the microbiome. So it's the microbiome's job to teach the immune system what to attack and what not to attack.

So oral tolerance, the critically important oral tolerance, and you'll see as we go through today, how important oral tolerance is. This critically important component of your body is very much dependent on your microbiome. We don't have any other systems in our body to train our immune system. It's the microbiome that is the boot camp for your immune system.

And if you don't have the right microbes or you have a dysbiotic microbiome, your immune system is not getting training, which means your immune system will likely either A; under react to things, which means you're going to be getting sick all the time, and you can't defend yourself from basic things like colds and flu's, or which is more likely it becomes over-reactive, where it reacts to everything that it should be tolerant too. So keep that connection in mind.

Immune system has all the capabilities, no direction, no general, no intelligence. It

comes out into the body, the immune cells, and they're supposed to interact with the microbes that line your entire mucosal lining, your skin and everything else and learn from the microbes what is friend and what is foe. The reason why it has to do this, and the reason why it's not born with any sort of intelligence is because the immune system is supposed to be adaptable to changes in your environment.

Throughout the seasons, in Chicago alone, the antigens in the air change. We have a season called cold and flu season. There's a reason why in late fall and winter, cold and flu is elevated in terms of prevalence and you don't really see it in the summer. So my immune system, as I'm going into the cold and flu season, needs to know that my exposure level to these things are heightened. So my immune system has to adapt to that and upregulate the T cells and the B cells that defend me against the cold and the flu virus.

In the summertime, I don't need to worry about that, but maybe in the summertime, I go on a trip to Alaska, somewhere else, where they have other viruses or other antigens that are present there that I'm not experiencing in Chicago's summer. Now my immune system has to adapt to that location, to the antigens in that location so it can defend me.

So the immune system is one of the few systems in the body that is constantly adapting, and the only way it can do that is if it's born naive, it's getting the information from the microbiome, which is the forward-facing component of the immune system, and it's therefore the microbiome adapting the immune system to teach it what to attack and what not to attack. So that is oral tolerance.

If you have a dysfunctional microbiome, a dysbiotic microbiome, meaning too many pathogens, those pathogens are not talking to the immune system the same way. They're not training the immune system. In fact, they would rather the immune system did not function properly so that they can have their heyday and proliferate and make their toxins and take over the system. So if you have elevated levels of pathobionts or potentially pathogenic organisms or pathogenic organisms, those microbes are not going to be helping the immune system, the immune system starts to get confused and go haywire. So that's a very important component to understand.

And a well-functioning gut immune system that allows us to eat a variety of things, be in a variety of environments, be around lots of people and pets, and all of that stuff without overreacting to antigens that we're being exposed to because a well-balanced gut immune access means that our immune system has all the intelligence it needs to

understand what is friend and what is foe. So it can protect you against the things that could make you sick, but it's also tolerant of all the things you're exposed to on a regular basis that are not harmful to you.

I put this here just to show you some of the complex interactions that are going on between your immune system and your microbiome and so on. This is a depiction of the small bowel. If you remember, the small bowel is made up of villi and microvilli that's not depicted here, which is typically like the finger-like projections, but of course you've got the intestinal epithelial cells. So that's the shoulder-to-shoulder soldier cells that make up the one cell-thick barrier between things being inside the body. And then on top of those cells is that mucous layer. So that's what you see depicted here in blue. And then the intestinal epithelial cells as those cell structures. Within the intestinal epithelium, as mentioned before, there are lots and lots of immune cells. So you see here things... Let me see if I can do an annotation.

So if you see here things like the paneth cells. Paneth cells or these enteroendocrine cells, I don't know if there's L cells that are being depicted here, but you've got all these cells that have these unique functionality and paneth cells are one of those border cells that are immunological cells as well. So it's a part of the immune system. So one of the things that the paneth cells is doing is taking in signals from the microbiome, that's going here through the mucosa, and then the intestinal epithelial cells is eliciting an immunological response, which then secretes chemical signatures to the paneth cells to release antimicrobials to protect the microbiome.

Then you also have dendritic cells, which are roaming around this area here, which is the blood circulation area. And then these dendritic cells are really the basolateral layer that is now officially inside the body. Dendritic cells can reach across the intestinal epithelium and engage with microbial antigens, microbial peptides and so on. And as a result of reaching across and trying to understand who's there and what they're doing, these dendritic cells can then activate T cells or T helper cells, activate other T cells, B cells, which are plasma cells, and cause the release of antibodies like secretory IgA.

And then you've got things like short-chain fatty acids, which are really important. So short chain fatty acids are a key part of building oral tolerance because short-chain fatty acids are anti-inflammatory. And one of the things that it does is that it binds these receptors on the lining of the gut and when it binds these receptors, it provides tolerance and inhibits the activation of things like macrophages and dendritic cells. And then it activates something called Treg cells.

I'll be talking about Treg cells quite a bit. Because they are a very, very important component of this entire oral tolerance system. So Treg cells stands for T regulatory cells. These are the cells that monitor many of the immune responses going on in the body and then suppress the unfavorable immune responses. So the importance of Treg cells cannot be overstated because without them, your immune system will be going haywire, attacking everything.

You'd be sensitive to absolutely everything. Everything you eat, everything you encounter, most people, most microbes and so on. The Treg cells function specifically to learn about immune responses that are not beneficial and then suppress them. So that's why they have this suppressive like function on dendritic cells and macrophages and mast cells, which we'll talk about mast cells as well. So Tregs, critically important. One of the key upregulators of Tregs are microbial byproducts like short-chain fatty acid, like butyrate for example, and other microbial peptides. So really, really important thing to note and keep in mind. And again, I'll reinforce that as we go along as well.