THE ROLE OF HUMAN MILK OLIGOSACCHARIDES IN INFANT DEVELOPMENT AND THE POSSIBLE ROLE IN FOOD ALLERGY

Lisa Renzi-Hammond, PhD

Laura Plante: Hello listeners. I'm Laura Plante, podcasting for Abbott Nutrition Health Institute. And we're lucky to have with us today Dr. Renzi-Hammond from the University of Georgia, where she's a director and associate professor in the College of Public Health. Dr. Renzi-Hammond's research focuses on using nutrition to prevent neurodegenerative disease and improve brain health across the lifespan through an initiative fittingly called CARE, which stands for Cognitive Aging, Research, and Education. Part of improving brain health means focusing on brain itself, and part of improving brain health means focusing on all the other body systems that affect the brain, such as the digestive and immune systems. To tie all this work together, we've invited Dr. Renzi-Hammond to share her knowledge on the role human milk oligosaccharides play in infant development and their possible role in the dietary management of infants with food allergies. Dr. Renzi-Hammond, thank you for sharing your time with us today.

Dr. Renzi-Hammond: It is such a pleasure to be here, Laura. Thanks for having me.

Laura Plante: Before we begin, Dr. Renzi-Hammond, you're a neuroscientist. Why the interest in human milk, oligosaccharides, or HMOs? My educated guess is that there's a gut-brain axis story here.

Dr. Renzi-Hammond: And, in fact, your educated guess is very, very, very good. So, from a personal perspective, I mean, you're absolutely right. As a neuroscientist, we all live a very siloed existence when it comes to science, when it comes to health. We sort of study our thing. We know our thing. We are encouraged to become experts in our thing, right? And then the need to sort of venture outside of our silos is… it doesn't appear very often. So as a neuroscientist, I am aware that every single person listening to this podcast theoretically has a body. I don't see you, but I'm pretty sure that you have one. And historically, I would have said that I kind of didn't care about it very much, that really it was just your brains that I was sort of after and… and found exciting and interesting and wanted to study. And I think that's true of all of our specializations in health, too. So, if you're in neonatology, your youngest patient is profoundly young. And when they leave you and they go off and they do what they do, you might hear back from them, but it's, you know, from a sort of medical perspective, they're sort of less interesting when they leave, right? They're no longer our charges anymore. So, we all kind of get into these little silos and we forget that we are treating, in medicine, whole humans that grow up to become adult humans that make really good or really bad decisions. And as neuroscientists, we are not brains in vats, right? We are connected human beings. So, it's funny. You know, I teach my students all the time the next most dense concentration of central nervous system… we've sort of got brain and spinal cord for the CNS, but the next most dense concentration of nervous system tissue is right there in the gut. You've got a little tiny brain down there controlling so much of your behavior, you would be absolutely shocked. I mean, think of the very words that we use to describe the way that we feel. They're taste words. Like, we might say, "oh, that is disgusting. I'm completely disgusted by what you did." Disgust means bad taste, right? Or I might say, "that is so sweet," if there's something that you did that I really loved. So, so much of our decision making actually comes from the gut. I mean, we even talk about having gut feelings and making a gut decision. So, it would be really sort of irresponsible, I think, as a neuroscientist, to live only in the brain and not figure out how the rest of the nervous system is informing that brain, shaping it, and helping it develop.

Laura Plante: Thank you for sharing that background. How interesting. And now that we understand a little bit better how you got interested in HMOs, what are HMOs?

Dr. Renzi-Hammond: So, I love that you asked me that question because when we talk about this sort of beautifully connected nervous system that we just, that you know, that we just described, I think the important thing to realize is that all of this… all of this physiology that we're talking about, building and connecting, it all requires fuel, right? So, if you were to ask me how to feed a brain, I would tell you that you should… that although we say really trite things like you are what you eat, it must absolutely be true, right? The raw material that is making you, it's not coming from space, right? It's coming from whatever is available in your blood supply. So, it's coming directly from your diet. The vast majority of things that exist in the brain come straight out of the foods that we eat. So how then do we grow this connected nervous system, right? The brain seems pretty straightforward. If you eat it, it'll sort of end up in there. But for the rest of our bodies, and especially as we're growing this nervous system from scratch, we have to think about nutrition in a slightly more complex way. So human milk oligosaccharides, HMOs… I would call these one of the big driving components of human milk that actually feeds and helps develop that other nervous system down there, right? The one that's in the gut. So human milk oligosaccharides, if you were to ask me and ask most of the rest of us, what is the ideal food for an infant and why, we would say that it is human milk. If you look in human milk and you siphon off the water and you just look at those solid pieces… if I were to ask you, what do you think human milk is made of, you'd probably be able to tell me: it's fat, it's sugar, it's protein. It's all the stuff that grows a person. And you would be right. But the most abundant, solid component of human milk outside of lactose and lipids is actually these human milk oligosaccharides. They are different from those macronutrients, and yet they are more abundant than some of those major categories of macronutrients like protein. They're different, they're non-digestible, and if you were to say, alright, I got 30 seconds, what's so special about these? I would tell you that they are selective prebiotics and then you might yawn, and I would say, but don't, but don't. It's so much more important than that. If you sort of think about what we're built of, right. We are, in fact, we're made of us, and we're made of all kinds of little microbes that are inhabiting us. In fact, those microbes outnumber us 10 to 1. I mean, we are… if you think about the raw material that is you, you are made of about 10%, you in about 90% other stuff that's living on you and in you. And those human milk oligosaccharides, they're there in baby's gut actually helping develop that gut. And I'm so eager to talk more about that topic in just a minute because I think that it's those HMOs that are helping to also help develop a brain.

Laura Plante: So, HMOs are components then of human milk, although they sound very different from other nutrients we find in that milk. So specifically, how do HMOs support infant development?

Dr. Renzi-Hammond: Now, that is sort of the incredible question, right, because we know this molecule is present in human milk. So, we know that the moms of the world are making about 150 different human milk oligosaccharides that are making up that most abundant, solid component of human milk outside of lactose and lipids. So, they've got to be doing something, right? Mom is putting a ton of work in to build something that is supposed to go out there and ideally affect baby's physiology. So how does that happen? So, the first thing to say is that we absolutely know that human milk oligosaccharides, they mediate a lot of development. They have an immune modulating effect. They influence gut health. We're getting more and more evidence on how they are changing brain development. I mean, it's really, really exciting. So, in sort of the digestive side, what human milk oligosaccharides do is they are selective prebiotics. They are there, you know, to sort of feed those gut bacteria that are growing in babies. But once you have those bacteria in place… I mean, remember, one full kilogram, 1000 grams of the wet weight of the intestinal tissue is bacteria. They are that important. If you think about sort of our old school medical model, right, of think about germ theory, right, that illness is caused by a pathogen. And if you just destroy the pathogen, you're all good. Most of the things that we're concerned about for development are not… they're not pathogen issues. We need these bacteria to do all the things that they do. So human milk oligosaccharides are prebiotics. They're helping to sort of grow that healthy colony of bacteria. And once you have that colony of bacteria, those bacteria will help you digest your food. They'll synthesize your vitamins. They make neurotransmitters. They do all the things that we want those bacteria to do. Now, there's also, I mentioned, an immune modulating effect, and that's really important because it's sort of hard… again, think siloed medicine, right? It's sort of hard to talk about the immune system and not talk about the gut because so much of our immune system resides in the gut. So human milk oligosaccharides, first of all, they are receptor decoys. So, if you think about what happens when you ingest a pathogen, right? Let's use your mouth as an example, because that is a big, massive entry point for all kinds of things that you may not want to get into your body. So, when baby ingests some sort of a pathogen and that pathogen actually makes it down, it's going to be looking for some sort of a surface sugar to actually bond to, right? It's got to dock somehow if it's going to do any sort of damage. So, it's looking at… sort of fishing around in the lumen of the gut, looking for one of those surface sugars to bond to. If you have human milk oligosaccharides that have just been delivered from a recent feed from mom… those human milk oligosaccharides are homologous structures for those surface sugars. That pathogen finds an HMO instead of that surface sugar, it's going to be out in the next bowel movement and have no chance to infect baby. So, they're receptor decoys. They also are immune modulating. There's a small percentage of HMOs that are actually absorbed into the blood supply from the gut. So, although they do a lot of their work down there in the gut itself, some of them are absorbed and they can circulate around and do all sorts of things for us. So, they're able to modulate the immune system in that way. They can control things like inflammatory cytokine production. And we have some evidence that they can actually improve cognitive function, one, by communicating with those… helping to sort of grow those bacteria that synthesize neurotransmitters for the enteric nervous system and partly again through circulation. So, they're doing these incredible things. They're facilitating growth and affecting body composition. There's even some evidence in animal models that they can protect from necrotizing enterocolitis, which is the ultimate disease of dysbiosis, right? Growing the colony of bacteria that doesn't belong in and support the gut. So, I could probably speak for an hour on all of the things that HMOs are actually doing to support physiology. But it's really special. This one subset of molecules does so much work in infant physiology. It's staggering.

Laura Plante: I'm curious, you've talked about a lot about selective prebiotics. So how are HMOs any different? How do they differ from other prebiotics that we're consuming throughout our life?

Dr. Renzi-Hammond: Yeah, you know, we say sort of we have an, you know… I want to say an adage, it might be more like a law in biology, right? That structure dictates function. If you know how something is built, you know what it's going to do when you put it into some sort of a human system. So, if you look at really commonly, I'll speak now for just a second about infant formula is… simply because infant formulas, unlike human milk, have this sort of task of having to add fibers, right? We want to support bacterial growth. And so, very often you need a fiber substance to do that. So, if you look at the fibers that are commonly used like galacto-oligosaccharides or fructo-oligosaccharides or polydextrose, things like that, these are sort of big, hunk, and bulky fibers. And what they tend to do is float all boats. Lots and lots and lots of different types of bacteria like to chomp on these fibers and use them to support growth. So that being said, of course, when it comes to something like baby's gut, it's not that those fibers aren't good. They are. But when it comes to baby's gut, we don't necessarily want to float all boats. We don't want to promote dysbiosis. We want to make sure that we're growing just the right colony of bacteria in there to support baby's needs. So, what we really want to do is grow those sorts of bacteria like lactobacillus strains, like bifido bacillus strains that we know are associated with really robust digestive and immune system health. So those bifidobacteria will do just an incredible amount of things for you. If you have them in there, those bifidobacteria will do things like synthesize short chain fatty acids, which growing colonocytes are going to use those to basically support that rapid development that they have to do. So certain types of bacteria in the gut are really sort of extra beneficial to a growing GI tract, and bifidobacteria are among those species. If you look at what human milk oligosaccharides do, they don't feed the sorts of bacteria that you really want to limit in babies' guts. So, they don't feed the sort of enteropathogenic E. coli or salmonella or any of that stuff that you don't want in there. They really only feed those bifido strains and a couple of others that really facilitate good digestive health in an infant. So that selectivity is so deeply important. Those bacteria, when you grow them, will help support your immune system. They'll help synthesize those short chain fatty acids to beef up that mucosal layer. And the other sort of interesting thing about beefing up that gut mucosal layer using those short chain fatty acids is that, over time, those short chain fatty acids will start to lower the pH of the gut. And when that happens, you're less likely to colonize those sorts of bacteria that we know are culprits in things like sepsis, necrotizing enterocolitis, the sorts of things we really want to avoid in infants.

Laura Plante: Let's go back to talking a little bit more about infants and the immune system. So, is there any research on HMOs like 2FL and food allergy prevention?

Dr. Renzi-Hammond: So, if you had to ask me, “Lisa, if we're thinking about future uses of HMOs, where should we be going? Where should we be looking?” I have lots to say about that one. But one of the first things I would say about that is one is if we look around at the things that are affecting infants and young children today, right, if you think… sort of put on a pediatrician's hat and say, “what am I seeing a lot of?” If you're listening to this podcast and you are a pediatrician, food allergy might actually be on your list. And if you think you're the only one seeing it and you're wondering, “why am I seeing so much of this?” It is… It's there. And we're seeing an increase actually all over the place. It's not just in the US, it's not just in Canada. It's not a North American problem. We're seeing it everywhere. So, if you look at food allergy and you ask the question, “what is it? What is happening in the case of food allergy?” What we're looking at is sort of a runaway immune response here. You know, there are things that our immune systems are supposed to react to, like pathogens. That is a big thing. Our immune system has to be able to determine what is a pathogen and what is not. If you start looking at what causes food allergy, essentially, we're having an immune response. Our bodies are essentially telling us that food that we're putting into our bodies… that food is a pathogen, right? We're going to mount this big immune response and try to get rid of it. And that is… think about that for a minute. That is probably the most… you know, if you think about us from sort of an evolutionary perspective with selective pressures… attacking, having these immune responses to food could not be more counter to the way that our bodies are supposed to handle these things. So why are we seeing so much of it now? And you may notice, depending on your practice, listeners, that you are seeing a couple of different types. So, all over the world, all food allergy is on the rise. We are seeing allergic responses to all the things that we usually do. Cow’s milk protein, shellfish, tree nuts, soy, wheat, all the, all the usual suspects tend to be popping up. But each culture is now experiencing an increase in allergens and allergic responses to allergens that are specific to their communities. So, for example, we're seeing in places like Mexico, Central America, and the northern part of South America, citrus allergy, or beef allergy. We're starting to see in places like India chickpea allergy, right? Or if we're looking in Far East Asia, things like a bird's nest allergy. I mean, there are really cultural-specific set of allergens that we're sort of seeing starting to produce responses in kids that we haven't seen in high frequencies before. So, it's everywhere. This is a really, really big problem. So, what is allergy? Right. We said it was this runaway immune response. So, in order to not have allergic responses to things that we shouldn't be having them to, it's all about immune system regulation. When we are born, if you think about how the immune system develops, our immune systems, our big task early in life is to get our immune systems synchronized, right? We have our adaptive immune response and our innate immune response. In a newborn, that innate immune response is crazy high. I can say this as a mother with absolutely no irony to every mother out there who's listening to this, you know that birth is a very oxidatively stressful and inflammatory time period, right? So innate immune systems are working overtime. Infants have really high concentrations of innate immune cells after birth. And then over that first year of life, they tamp down and look more like a standard adult immune system response. When it comes to adaptive immunity, that one takes time, right? It requires microbial challenges. It requires exposure to pathogens to really get that immune system working really well. At a year of life, we're still not necessarily up to adult levels of antibody production, right? It's just… it has to take time and exposure to get there. So, our job is to synchronize these two systems, and it requires environmental input. Just as you need microbial challenge and exposure to pathogens to get that adaptive immune system working appropriately, for our innate immune system, we have to have environmental exposure to tamp down on that runaway inflammatory response. We tend to see in infants who are raised in really sterile environments, as only children, you know, in sort of very urban, very clean settings, we tend to see more food allergy, for example, than we do for kids who are raised in more rural settings with lots of exposures and big family sizes. So, there's a real environmental exposure piece here. One of the environmental exposures that our kids need to be exposed to, and human milk does this beautifully, right, is human milk oligosaccharides. Those HMOs can actually bind to white blood cells, for example, and tamp down that runaway pro-inflammatory response that infants are so good at generating. So in order to get that to reduce our risk of allergy, it's not just the spaces we live. It's not just the sort of microbes that we develop and foster. It's actually having access to molecules that mom provides to be able to control that sort of runaway inflammatory response. It's a big sort of concerted strategy with HMOs… really is a significant part of it.

Laura Plante: Given most of our listeners are health care providers, how is this area of research and discovery on HMOs relevant to the health care community?

Dr. Renzi-Hammond: So, we know this. We know that breast milk is best. As I have been describing, what human milk oligosaccharides are, in your heads, you should be thinking, “oh, mom, does this. Mom already does this, mom already does this, right?” Biology is such a beautiful system. Mom is already spending a ton of caloric energy to turn lactose into human milk oligosaccharides to be able to give her infants. She does this not to necessarily grow her infant's own tissues, but to grow and support all of those other systems that her infant needs to survive in the world, right? We don't live in a sterile vat. We live in a world with microbes. And we have to sort of choose carefully which ones enter us. Mom helps us do that. Here is the problem. And I… for those of you who know who I am, I'm a scientist in the United States where we do not have a federally sort of a federally supported, federally mandated maternity leave. Here in the US, we really struggle with this. We try very hard to support human milk feeding whenever we possibly can, and yet we still hear the same stories. We'll hear a mom who's a gig worker or a contractor saying, “I don't have maternity leave and there's no place for me to pump. Every time I pump, I lose money. I don't have any place to store it. Is it really worth me going through all of this trouble when I know that in just a few weeks I'm going to be back at work, unable to keep it going?” We want every infant to receive human milk, but even under the best circumstances, with the best public policies, with well supported maternity leave, access to lactation consultants, it is still not the case that every single mom is able to produce human milk. Very often I have friends who have adopted children say, “what do I feed? I don't know what to do. Should I be buying milk on the internet? How do I do this?” So, I think it's really imperative that as we work hard to try to increase the amount of human milk feeding in the world, we don't leave formula behind. It's going to have a use. And it's… we need to make sure that we never have a health disparity that's the result of how someone feeds. You know, I never want to, as a public health person, lay two infants down next to each other and say, I can tell that you were the formula feeder, and you were the breast feeder because one of you is doing great and one of you is not. We can never leave formula behind. So, I think if you're listening to this and thinking, “what should I be doing here?” One: every moment that you spend promoting human milk feeding is worth it. Two, though, is that as you're looking around at formula and you're starting to sort of think about what should I be looking for? Human milk oligosaccharides can actually be added into infant formulas. 2-fucosyllactose is available I think in the entirety of North America. So, it's one of those sorts of situations where, you know, I hear this all the time, especially coming from Georgia, where Coca-Cola products are sort of everything, is that it's all just sort of Coke and Pepsi, right? None of it is water, which is what we should be drinking. It's all Coke and Pepsi. And it doesn't really matter what you do, but of course it does. If you have a product that's made of ingredients, ingredients must matter. And 2-fucosyllactose is actually available in infant formula. It's this important and you can actually find it.

Laura Plante: Your passion for this area of research is undeniable. And I was going to finish off by asking you if you were excited about any new avenues of research. But I think it's safe to say it's not a question of if, but rather a question of what are you most excited about when it comes to new research on HMOs, Dr. Renzi-Hammond?

Dr. Renzi-Hammond: Oh, you know me. I love that question because yes, there is so much to be excited about. When you think about all of this, right, you're probably thinking about it through a professional lens. I have people. People need advice. They need recommendations. I can do this. I can give that advice.

But what about us? How many of you listening to this have an allergy that you're not in love with? How many of you, when you get anxious or sort of distraught, feel it in your gut? What are those sorts of things that are keeping you up? That are making you worry about your own health and physiology? And I would say that for so many of us, the answer is… "it's" it lies somewhere in the world of dysbiosis. So much of what we go through now… we are… it is related to our lifestyles. So, there are actually trials right now looking at human milk oligosaccharides for adult issues. For example, there was recently a trial on irritable bowel disease. I think we are seeing… we've sort of discovered, or I should say rediscovered, a molecule that could potentially really change human health and physiology, not just in how we develop these systems, but in how these systems go on and affect us throughout our entire lifespan. And that is so exciting.

Laura Plante: Dr. Renzi-Hammond, this was very informative. Thank you so much for sharing your expertise and for explaining the science behind HMO research in such a compelling way.

Dr. Renzi-Hammond: Thank you so much, Laura. It was a blast to be here.

Laura Plante: Listeners, we encourage you to follow the link on our podcast page to view a complete recording of Dr. Renzi-Hammond's session at the Canadian Nutrition Society's annual conference: Role of Human Milk Oligosaccharides in Development of the Gut Microbiome and Relevance to Human Health. We hope you enjoyed this podcast. To receive updates on more educational content and nutrition resources, you can register and become an ANHI.org member through the link at the top left of our home page. Thank you, everyone.

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