

David Roberts:

Hi everyone, it's David here, and I have with me Dr. John Gildea, and today we're going to be talking about autophagy. Autophagy is the ... It's a natural process where older cells that maybe have some damage are shown the door. They're degraded to allow new cells to come in. We are excited about autophagy because that's the benefit that you get when you fast. I think back in early September, 30 of you did a fast with us and ended up doing the ProLon fast, the fasting mimicking diet. Again, the goal there was to stimulate autophagy and stem cell proliferation. Well, the cool thing is that sulforaphane also stimulates autophagy. John is going to talk about that, and just some of the things he appreciates about autophagy that maybe we haven't heard before. John, why don't you take it away?

John Gildea:

I like this topic mostly because it's not talked that often about in the context of health and wellness, but it is a hot topic because so many people are afraid of the diseases that a defect in this process causes, so Parkinson's and Alzheimer's disease, some diseases that people fear more than death itself is losing your faculties, losing your ability. And then also how hard it is on the family around you having to take care of you.

Basically, in both of those diseases, you have proteins, and different in the two, Parkinson's and the different proteins that misfold. Basically autophagy is a cleanup process where misfolded proteins are bound to a system where they're conjugated and taken to a special lysosome. Most people know that proteins are degraded inside the cell in a lysosome, but in autophagy, a new organelle is made called a autophagosome, where it'll digest these misfolded proteins. In both Parkinson's disease and in Alzheimer's disease, this getting rid of misfolded proteins is therapeutic and prevents that. There are a lot of things that prevent that and stimulate autophagy, but sulforaphane is actually a really good inducer of autophagy. In the case of Alzheimer's disease, most people have heard, Dr. Bredesen has a therapeutic program that has been shown to be effective against Alzheimer's disease.

David Roberts:

Bredesen protocol. Dale Bredesen.

John Gildea:

Bredesen.

David Roberts:

Down at Duke, is he? [Bredesen is at UCLA].

John Gildea:

I'm not sure where he is now. Maybe he is. But in the case of his protocol, one big part of his therapy is consumption of cruciferous vegetables and lots of different sources of it. Sulforaphane itself, in broccoli, would be a really high concentration of the therapeutic component of cruciferous vegetables. It's a known therapy for Alzheimer's disease. I haven't seen as many, at least as complete as the Bredesen protocol for Parkinson's disease, but likely that they would have similar etiology, and you have misfolded proteins. Those tau-isms are those groups of proteins where you have misfolded proteins causing dysfunction in the brain. Depending where in the brain that those misfolded proteins accumulate is where you get the dysfunction. A lot of them are very similar.

David Roberts:

John, we've talked about autophagy having a component where older cells leave and make room for newer cells. And then there's the protein component. Where do those proteins reside? Are they in our blood, or in the cells themselves? And can you talk more about that, where they're located?

John Gildea:

Yeah. In neurons, in Alzheimer's, is where the misfolded proteins happen. It's where the dysfunction is. It's why it's particularly damaging in the brain, because there's not as much repopulation in the brain. Pretty neat papers relatively recently in the Parkinson's world where some of the dysfunction, at least they have models for this, is that you get autophagy starting in the nerves that are in your gut. And then those misfolded proteins propagate, kind of like a prion, in that the misfolded protein tends to bind into another protein and make it misfold. So it acts like a virus, like a prion, and travels backwards up the nerves back into the brain. At least the kind of cutting edge stuff that happens in Parkinson's is that it starts in your gut and moves backwards, up through the neurons, and is propagated back into your brain.

David Roberts:

Is that similar with Alzheimer's? Because an inordinate number of folks with Alzheimer's have gut issues.

John Gildea:

I haven't seen as much on the Alzheimer's front, except it is known that it has this prion activity, the misfolded proteins tend to misfold other proteins. And it was pretty hard to understand some early studies in mice where they made antibodies against the alpha/beta subunits that cause disruption in Alzheimer's. And they were able to somewhat block the disease in mice. I think, in hindsight now, it's because those proteins act like prions, and when they leave one cell and go into another cell, the antibodies would have a possible way to block propagation of the disease.

I think there's a lot of stuff that's known in that area. And you're right. The AMP kinase, the nutrient sensing is a big component of stimulating autophagy, so doing both simultaneously probably is even also synergistic in trying to get your misfolded proteins refolded. Most people know that curcumin as well affects the misfolded proteins. These same proteins that tend to misfold have pockets of hydrophobic exposed areas on it. And those hydrophobic areas tend to be where curcumin binds, and that's how curcumin blocks the buildup of the misfolded proteins also. Two different mechanisms, both curcumin and sulforaphane would be anti tau-ism, but specifically Parkinson's and Alzheimer's.

David Roberts:

When you were talking about doing ... Was the synergy, were you talking about fasting? Were you talking about the synergy between the sulforaphane and curcumin, or doing both as in fasting and sulforaphane?

John Gildea:

Yeah. So fasting and sulforaphane, fasting and curcumin. And then also sulforaphane and curcumin show synergy in a lot of different ways.

David Roberts:

Yeah. Have you ever taken sulforaphane on an empty stomach, John?

John Gildea:

Yes. A brick of it one time. That's how we found out it was safe, right?

David Roberts:

That's right. Yeah. Oh, the brick. That's right, yeah. Think Rice Krispie Treat sized block of ... And were you fasting at that time, when you had it?

John Gildea:

I can't remember. I definitely felt the shape of the inside of my stomach for the first time. But I definitely ... I take sulforaphane with a meal. I'm one of those sensitive people.

David Roberts:

Yeah. I've felt that same. I feel a thing, it's like this pre-nausea, where you take too much, and then it doesn't hurt you, it doesn't hurt your kidneys, but it just makes you nauseous. I think I took eight capsules, can't remember why. It seemed like good idea at the time. But that pre ... Like, "Oh, I'm starting to sweat," type of thing. And then it's just like, "Oh, I haven't eaten. That was not wise." So if you do fast and take sulforaphane, realize that maybe just one capsule, and that it's definitely potent. Going back to autophagy, we talked a lot about the neurons and proteins in the brain. Can we talk about other places that maybe autophagy is important, outside of the brain?

John Gildea:

Yeah. It definitely happens everywhere. It's just much more obvious in the brain because it's directly connected to the way you think and feel. But buildup of misfolded proteins happens everywhere, and I think some of the stuff you were leaning towards might be cells that become senescent, where you have the same misfolded protein. The cell gets into a state of senescence, where it's no longer dividing. But it's, anyway, cranking up its ATP production and using it to make cytokines, so it causes inflammation. Sulforaphane is known to cause senolysis, so senolytic cells, lysis. And the clearing of those cells is a big component of why you might feel better after you start sulforaphane, is if you're older and you're clearing those senescent cells out, similar to what fasting does, it can really make you feel better and lower your threshold of cytokines that you're producing, and lower your inflammatory level. So yeah, senolytic is linked with autophagy also, if the cells are too far gone in the cells outside of your brain, it'll cause them to lyse.

David Roberts:

Yeah, that's a good point. And going back to how with Parkinson's and the research ... By the way, the paper about the Parkinson's, the proteins going up the nerve to the brain, is that one we could include in this?

John Gildea:

Sure.

David Roberts:

Yeah. So if you could send me the link to that, we'll try to include that into the notes here. But that leads to the question of gut health and doing things to really have a healthy gut, like lowering carbohydrate

intake. Are there any links to having good microbiome, good gut health, and those proteins not moving up the nerves?

John Gildea:

Yeah. A lot of inflammation that people feel is initiated in your intestines. And of course there's a lot of nerves in your intestines as well, so when you have inflammation in your intestines, that's why it feels so terrible. The gas that sometimes you can get when you're sick can produce such sharp pains, really bring you to your knees. It's because there's so many nerves down there. And one way to really rile up your immune system and cause inflammation is to have a leaky gut, so those cell-cell junctions that are along the interior sites of your intestine, keeping them intact is a great first barrier. And NRF2 induction is a known player, major player in keeping your cell-cell junctions intact.

In most states where you have disruption of cell-cell junctions, both when a cell, say, is leaving a tumor, in the case of loss of cell-cell adhesion, NRF2 induction tends to cause cell-cell junction stability. That's one of the reasons it prevents metastasis, is it keeps cells from leaving the primary tumor. It's also involved in all the steps in that area. But the general idea of keeping cell-cell junctions intact is important for general organ health, your intestines, keeping those cells communicating with each other through tight junctions and also gap junctions, we've shown. The same thing happens in the kidney. You want those cell-cell junctions intact, so it can behave like an organ, like a single unit. That's a big part of anti-inflammatory components of NRF2 induction.

David Roberts:

What are some of the things you do for ... Two questions. One, we talked about curcumin, sulforaphane, and fasting for autophagy. Any other things to stimulate autophagy? And then also, what you do for your own gut health?

John Gildea:

The other big component of autophagy is exercise. I often link another form of autophagy called mitophagy. This is where your organelles inside your cell, that are producing the energy, are mitochondria. The dysfunctional mitochondria that accumulate over time are gotten rid of by autophagy also, but it's a specific form of it called mitophagy. The best way to induce that is through this pathway called PGC-1alpha. Very hard exercise, strong exercise, going into oxygen debt tends to stimulate mitophagy. And another couple of my favorite supplements that I like to take are PQQ, is a PGC-1alpha inducer. And so is CoQ10. Exercise plus those two things seem to get the mitochondria functioning really well.

I have those sort of lumped together with a lot of things that help migraines, all kinds of ... Your energy metabolism is involved in everything. For gut health, the second part of that question was, what do I think are really important for gut health? I think sulforaphane would be a really good one, and then only slightly after that, I would say quercetin. Zinc should be on everybody's everybody's list. And then, besides that, avoiding a couple of things like vegetable oils.

David Roberts:

Canola, soy, cottonseed. What else?

John Gildea:

And then all of the things that disrupt gut health, which can be, depending who you are or where you are in your health journey, could be lowering things that tend to cause disruption. Gluten would be one. From dairy, fructose can be one in sensitized people. Some of the prebiotics people can be very sensitive to, so fructooligosaccharides (FOS). That's how the FODMAP diet got into favor, is eliminating a lot of things that cause gas and bloating in the people that are susceptible. That's another nice thing about sulforaphane. Sulforaphane blocks the ill effects of fructose in intestine, or advanced glycation end products.

David Roberts:

Okay. Yeah. Yeah. And the oils you were mentioning there too, that's the GMO? It's basically GMO oils is where you were going with that? Genetically modified, so the biggies are soy, canola. Soybean oil, canola oil, and then the fructose could be just regular fructose, but it could be also high fructose corn syrup, which is also genetically modified, to get a one-two punch there. So great-

John Gildea:

Yeah, those oils are so highly processed. Most people probably know that you need omega-6 fatty acids, but those oils, by the time they end up in your mayonnaise or salad dressing, most of the times, they're superheated more than five times, so they're completely oxidized. So they would have the opposite effect of the actual good source of omega-6 fatty acids. Most people need to reduce their omega-6 fatty acids dramatically, especially from those sources where they're oxidized. And then the opposite of that is get a good source of omega-3, eating fish and all that good stuff.

David Roberts:

Yeah. Canned fish, like sardines, that can be a good source. What's your main source of omega-3s, John?

John Gildea:

Cod liver oil and I do krill oil.

David Roberts:

Oh, yeah. Do just pour the cod liver oil on a spoon and take it that way, or in a smoothie, or what?

John Gildea:

I do it in a shot glass, actually. I put a tiny bit of orange juice in the bottom of a shot glass. And then I do 15 ml of cod liver oil, and I do a little shot.

David Roberts:

And they're nasty.

John Gildea:

I have gotten used to it. It doesn't bother me in the slightest, but ...

David Roberts:

Gotcha. Well, this is great. John, thank you so much. So autophagy, basically sulforaphane is great for autophagy. Fasting. Fasting mimicking diet like ProLon, and curcumin. Exercise, going into oxygen debt.

Those are all some great ways to stimulate autophagy. So we'll leave it there. John, this was super helpful, so thanks for your time.

John Gildea:

You're welcome.

David Roberts:

All right. Some of the links that we mentioned will be in the notes, and thanks for joining us. Have a good day.