Dr. Rhonda Patrick: Micronutrients for Health & Longevity | Huberman Lab Podcast #70

My guest is Rhonda Patrick, Ph.D. She earned her doctoral degree in biomedical science from St. Jude Children's Research Hospital at the University of Tennessee Health Science Center and has become one of the leading public health educators on the brain and general health, aging, cancer, and nutrition. We discuss the four major categories of micronutrients that regulate cellular and organ stress and antioxidants, inflammation, hormone regulation, immune system, and longevity. Dr. Patrick provides actionable protocols for obtaining key micronutrients from food and/or supplement-based sources. Additionally, Dr. Patrick outlines protocols for deliberate cold and deliberate heat exposure to benefit metabolism, cardiorespiratory fitness, mental health, and lifespan.

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- Welcome to the Huberman Lab Podcast, where we discuss science and science-based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today, my guest is Dr. Rhonda Patrick. Dr. Patrick is known to some of you as a podcaster and one of the premier educators in the landscape of mitochondria, metabolism, stress, and other aspects of brain and body health. Her podcast, FoundMyFitness, is one of the premier podcasts in the world for disseminating knowledge about how the brain and body work and how we can use behavioral tools, micronutrients, supplements and other protocols in order to maximize our immediate and long-term health. Dr. Patrick did her formal training in cell biology, exploring the links between mitochondrial metabolism, apoptosis, which is naturally occurring cell death, which is a healthy form of cell death that occurs in our brain and body throughout the lifespan, and cancer biology. She then went on to do postdoctoral training with Dr. Bruce Ames, investigating the effects of micronutrients, meaning vitamins and minerals, and how they affect metabolism, inflammation, DNA damage, and the aging process. She has published landmark review articles and primary research, meaning original research articles, in some of the premier journals in the world, including Science, Nature Cell Biology, Trends in Cell Biology, and FASEB. Indeed, Dr. Patrick is an expert in an extraordinarily broad range of topics that impact our health. For today's episode, we focus primarily on the major categories of micronutrients that are essential for brain and body health. I have to confess that before the discussion with Dr. Patrick, I was aware of only one of the categories of micronutrients that we discuss, and so you'll notice that I'm wrapped with attention throughout the discussion. And I think that you'll want to have a pen and paper handy because she offers not only a very clear understanding of the biological mechanisms by which other micronutrients operate, but some very clear and actionable tools and items that we can all embark on if we are to optimize our brain and body health. We also discuss behavioral protocols. Dr. Patrick is well known for her understanding of the

scientific literature on sauna and the use of heat and cold for optimizing things like metabolism, longevity, cardiovascular health, and I'm delighted to say that we discus that as well, and how behavioral protocols can interface with supplement-based and nutritional protocols. I'm confident that you'll learn a tremendous amount of information from Dr. Patrick, much of which is immediately actionable. And if you're not already following and listening to her excellent podcast, you'll absolutely want to do that. It's foundmyfitness.com is the website where you can get access to that podcast. It's also on Apple and Spotify and YouTube as FoundMyFitness. Dr. Patrick also has a terrific newsletter that I recommend signing up for. It's foundmyfitness.com/newsletter is where you'll find it, and it includes research on fasting, micronutrients,

00:03:12 Momentous Supplements

sleep, depression, fitness, longevity, and far more, along, of course, with actionable protocols. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous supplements. Our motivation for partnering with Momentous is to provide people one location where they can go to access the highest quality supplements in the specific dosages that are best supported by the scientific research and that are discussed during various episodes of the Huberman Lab Podcast. If you go to livemomentus.com/huberman, you will see those formulations. I should mention that we are going to add more formulations in the months to come. And you'll see specific suggestions about how best to take those supplements, meaning what dosages and times of day, and, in fact, how to combine those supplements with specific behavioral protocols that have been discussed on the podcast and are science supported in order to drive the maximum benefit from those supplements. And many of you will probably also be pleased to learn that Momentous ships not just within the United States but also internationally. So, once again, if you go to livemomentus.com/huberman, you'll find what we firmly believe to be the best quality supplements in the precise dosages and the best protocols for taking those supplements

00:04:27 The Brain-Body Contract

along with the ideal behavioral protocols to combine with those supplement formulations. I'm pleased to announce that I'm hosting two live events this May. The first live event will

be hosted in Seattle, Washington, on May 17th. The second live event will be hosted in Portland, Oregon, on May 18th. Both are part of a lecture series entitled "The Brain Body Contract," during which I will discuss science and science-based tools for mental health, physical health, and performance. I should point out that, while some of the material I'll cover will overlap with information covered here on the Huberman Lab Podcast and on various social media posts, most of the information I will cover is going to be distinct from information covered on the podcast or elsewhere. So, once again, it's Seattle on May 17th, Portland on May 18th. You can access tickets by going to hubermanlab.com/tour, and I hope to see you there. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is, however, part of my desire and effort to bring zero cost to consumer information about science and science-related tools to the general public.

00:05:30 AG1 (Athletic Greens), Thesis, InsideTracker

In keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is Athletic Greens. Athletic Greens is an all-in-one, vitamin mineral probiotic drink. I've been taking Athletic Greens since 2012, so I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens, and the reason I still take Athletic Greens once or twice a day, is that it helps me cover all of my basic nutritional needs. It makes up for any deficiencies that I might have. In addition, it has probiotics which are vital for microbiome health. I've done a couple of episodes now on the so-called gut microbiome and the ways in which the microbiome interacts with your immune system, with your brain to regulate mood and essentially with every biological system relevant to health throughout your brain and body. With Athletic Greens, I get the vitamins I need, the minerals I need, and the probiotics to support my microbiome. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman and claim a special offer. They'll give you five free travel packs, which make it easy to mix up Athletic Greens while you're on the road, plus a year's supply of vitamin D3 K2. There are a ton of data now showing that vitamin D is essential for various aspects of our brain and body health. Even if we're getting a lot of sunshine, many of us are still deficient in vitamin D3. And K2 is also important because it regulates things like cardiovascular function, calcium in the body, and so on. Again, go to athleticgreens.com/huberman to claim the special offer of the five free travel packs and the year's supply of vitamin D3 K2. Today's

episode is also brought to us by Thesis. Thesis makes what are called nootropics, which means smart drugs. Now, to be honest, I am not a fan of the term nootropics. I don't believe in smart drugs in the sense that I don't believe that there's any one substance or collection of substances that can make us smarter. I do believe, based on science, however, that there are particular neural circuits and brain functions that allow us to be more focused, more alert, access creativity, be more motivated, et cetera. That's just the way that the brain works. Different neural circuits for different brain states. And so the idea of a nootropic that's just going to make us smarter all around fails to acknowledge that smarter is many things, right? If you're an artist, you're a musician, you're doing math, you're doing accounting, a different part of the day, you need to be creative, these are all different brain processes. Thesis understands this, and, as far as I know, they're the first nootropics company to create targeted nootropics for specific outcomes. They only use the highest quality ingredients, which, of course, is essential. Some of those I've talked about on the podcast, things like DHA, ginkgo biloba, phosphatidylserine. They give you the ability to try several different blends over the course of a month, discover which nootropics work best for your unique brain chemistry and genetics and goals, and, with that personalization, design a kit of nootropics that's ideal for the different brain and body states you want to access. I've been using Thesis for more than six months now, and I can confidently say that their nootropics have been a total game-changer. My go-to formula is the Clarity formula, or sometimes I'll use their energy formula before training. To get your own personalized nootropic starter kit, go online to takethesis.com/huberman, take a three-minute quiz, and Thesis will send you four different formulas to try in your first month. That's takethesis.com/huberman and use the code Huberman at checkout for 10% off your first order. Today's episode is also brought to us by InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better understand your body and help you reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term health can only be assessed with a quality blood test. What's unique about InsideTracker is that, while there are a lot of different tests out there for hormones and metabolic factors, et cetera, with InsideTracker, you get the numbers back in terms of your levels, but they also give you very clear directives in terms of lifestyle, nutrition, and supplementation that can help you bring those values into the ranges that are best for you and your health goals. And that's very different than a lot of the other programs,

where you get a lot of information, but you don't really know what to do with that information. InsideTracker makes that all very easy to understand and very actionable based on the very easy-to-use dashboard at InsideTracker. If you'd like to try InsideTracker, you can visit insidetracker.com/huberman to get 20% off any of InsideTracker's plans.

00:09:42 Stress Response Pathways, Hormesis

Just use the code Huberman at checkout. And now for my discussion with Dr. Rhonda Patrick. Rhonda, welcome. This has been a long time coming. Even longer than you know because, even before we discussed you coming on this podcast as a guest, I've been watching your content for a very long time. So I want to start off by saying thank you. You were the spearhead to break through from academic science to public education. So I consider you first in, and the rest of us are just in your wake. So, thank you for that. It's been- - Oh, that is so kind. Thank you. Thank you so much. Well, it's absolutely true. - I am so excited to be here having a conversation with you. - Thank you. It's absolutely true. If anyone does their research, they'll realize that the statement I just made is absolutely true and there isn't even a close second. Any other public facing educators that have formal science training and do regular posting of content came in several years after you initiated it, so we're all grateful. I have so many questions, but I want to start off with kind of a new but old theme that you're very familiar with. So temperature is a powerful stimulus, as we know, for biology, and you've covered a lot of material related to the utility of cold but also the utility of heat, and, as I learn more and more from your content and from the various papers, it seems that there's a bit of a conundrum in that cold can stimulate a number of things, like increases in metabolism, brown fat, et cetera, et cetera. Hopefully, you'll tell us more about those. But heat seems to be able to do a lot of the same things. And I wonder whether or not the discomfort of cold, deliberate cold exposure, and the discomfort of heat might be anchoring to the same pathway. So, would you mind sharing with us a little bit about what happens when we get into a cold environment on purpose, and what happens when we get into a hot environment on purpose? And I'm hoping that this might eventually lead us to some point of convergent understanding, so if you would. - I would love to. Let's take a step back. I think you brought up a really important point here. And I think that point has to do with the intermittent challenging of yourself and whether that is through temperature

changes, like cold or heat, or through other types of stressors, like physical activity, or perhaps even dietary compounds that are found in plants. These are things like polyphenols or flavanols. Humans, we evolved to intermittently challenge ourselves. And before we had Instacart, where you could basically just get your food delivered to you, before the Industrial Revolution occurred, we were out hunting. And I say, we, not us but humans. We were out gathering. We were moving, and we had to be physically fit. You couldn't catch your prey if you were a sedentary slob, right? You were moving, and you had to pick your berries. You had to move. And so physical activity was a part of everyday life, and caloric restriction or intermittent fasting was also a part of it. This is another type of challenge. We didn't always have a prey that we caught, or maybe temperatures were such that there was nothing for us to gather, right? So food scarcity was something common as well as eating plants, so getting these compounds that I mentioned. These are all types of stress, intermittent challenges, that activate genetic pathways in our bodies. These are often referred to in science as stress response pathways because they respond to a little bit of stress. Physical activity is strenuous. Fasting's a little bit stressful. Heat, cold. These things are all types of little intermittent challenges. And there is a lot of crosstalk between these stressors and the genetic pathways that they activate. And these genetic pathways that are activated help you deal with stress. And they do it in a way that is not only beneficial to help you deal with that little stressor, exercise or heat, it stays active, and it helps you deal with the stress of normal metabolism, normal immune function happening, just life, aging, right? So this concept is referred to as hormesis. This is a little bit of stressful challenge that activates these stress response pathways in a beneficial way, that is a net positive, that actually has a very profound antioxidant, anti-inflammatory response, or whatever the response is. It could be the production of more stem cells. These are cells that help regenerate different cells within tissues, or something like autophagy, which is a process that can clear away all the gunk inside of our cells, pieces of DNA, protein aggregates. So you'll find that the stress response pathways are activated by a variety of stressors. So, for example, one pathway is called heat shock proteins, and, as their name would imply, one would go, "Oh, they're activated by heat." Well, correct. They are activated very robustly by heat. And we can talk about that. You can eat a plant like broccoli sprouts, which is high in something called sulforaphane. This is a compound that is sort of like a hormetic compound, or, as David Sinclair likes to say, it's a xenohormetic compound. I love that. I love that term. And it activates heat shock proteins among other things. It

also activates a very powerful detoxification pathway called Nrf2, which helps you detoxify things like carcinogens that you're exposed to. Well, guess what? Heat activates that. So what I'm getting at is there is overlap. Cold also activates heat shock proteins. You're like, "Really? Cold?" Yes, it activates. These are stress response pathways, and they are activated by various types of stressors. Now, you're going to more robustly activate heat shock proteins from heat versus cold, but there is some overlap. So I think that sort of forms the foundation there. - Yeah, that's very helpful. And it brings to mind, in the context of the nervous system, I always tell people you only have a small kit of neurochemicals to work with. There isn't dopamine for Netflix, and then dopamine for relationship, and dopamine for work, et cetera. Dopamine is a generic pathway by which motivation, craving, and pursuit emerge, et cetera, just like adrenaline is a generic theme of many different behaviors. It seems that it is the job of biological systems to be able to take a diverse range of inputs, even unknown inputs. Like, we don't know what technology will look like in three years, but you can bet that some of those novel technologies will tap into the very systems that I'm talking about now. And there certainly will be other stressors to come about that will tap into these pathways. I have two questions related to what you just said

00:16:38 Plants, Polyphenols, Sulforaphane

before we talk a little bit more about cold and heat. You mentioned plants as a route to creating intermittent challenge. There's a lot of debate, mostly online, about whether or not plants are our friends or plants are trying to kill us. The extreme version from the carnivore types, pure carnivore diet types, is that plants are trying to kill us. From the plant-based diet folks, it seems like it's more about what's healthy for the planet, animals, and maybe for us. But, if we set aside that argument, and we just raise the hypothesis that plants have compounds that are bad for us, but maybe by consuming them in small amounts, they're creating this hormesis type scenario, so then I think we conceivably solve the problem. We could say, yes, plants are bad for us, but, in small amounts, they provide this hormetic response and they're good for us, right? So, in the same way that too much heat is bad for us, too much cold is bad for us, can kill us, can kill neurons, but, appropriately dosed, in an intermittent challenge type of scenario, it can be good for us. Is that how I should think about plants and these compounds? Do you think of them as good for us or as bad for us? They're a very sharp blade, and we want

to use them potently. - I actually think that it's almost impossible. I mean, you'd have to eat nothing but the same plant all day, every day in large. The bioavailability of these compounds in the plants, they're attached to a food matrix. It's not like taking it in a supplement form as well. It's such that it's very difficult to make it toxic. Now, there are some cases, for example, if you eat cabbage, and I think there's some group in Africa or somewhere that that's all they eat is cabbage, and there is a goitrogen in cabbage. It's not sulforaphane. It's another compound. But that's all they eat, every day. Nothing but that. - They get goiter. The thick neck. - Yeah, and they're iodine deficient on top of that. So I do think, you can, of course, make. I mean, there are types of plants that are toxic in small quantities, right? - Hemlock. - [Rhonda] Hemlock, exactly. - Will kill you. Folks, don't play this game with hemlock. - But you're not going to get poisoned from eating your serving of broccoli at dinner, right? So, I mean, it depends on the plant. These generalizations are kind of, they're just not useful, and I think that a lot of people online in the blogosphere, they gravitate towards them because it's just easier, and it's a lot more sensational. - I eat plants, meat, and starches. I'm one of those rare omnivores out there now. - I do, too. - I feel like it's rare to be an omnivore. But I think, once you step out of the social media, as you said, the blogosphere, most people, I would say, 99% of people on the planet are probably omnivores. - Right. - And someone will probably correct me, but I doubt the number falls below 98. - I think, if you look at data, and when we have carnivore data, I can't wait to see it, but, right now, it's a lot of, okay, well, this is a lot of anecdotal evidence, and there's a lot of good starts with anecdotes, but people change a thousand things at once, and they don't realize that, but they do. And so anecdotal data is only so good, right? It's a starting point. And so we don't really know long-term what carnivore diets are going to do. They may be beneficial short-term. They may be beneficial for reasons of elimination of other things. Who knows, right? Lots of possibilities. But I do think, with respect to plants, that there's so much evidence, like, for example, sulforaphane is one that I really like because there's just evidence that sulforaphane is a very powerful activator of the Nrf2 pathway. And this is a pathway that regulates a lot of genes, a lot of genes that are related to glutathione production, genes that are involved in detoxifying compounds that we're exposed to from our food, like heterocyclic amines. In fact, there have been GWAS studies. These are studies that are genome-wide associated studies, for people listening that aren't familiar. People have a variety of versions of genes, and we have a gene that's able to make heterocyclic amines to basically detoxify it so it's not as harmful. And people that don't have a certain

version of that

00:21:12 Tools 1: Sulforaphane - Broccoli Sprouts, Broccoli, Mustard Seed

that's doing it well are very prone to colon cancer and increased cancer risk, but if they eat a lot of broccoli and cruciferous vegetables, that negates that risk because they're getting sulforaphane, which activates a lot of the glutathione transferase and synthase genes. So glutathione's a major antioxidant in our brain, in our vascular system, in our body, basically. So there's evidence that eating things like compounds that are like sulforaphane or broccoli or broccoli spouts, which have up to 100 times more sulforaphane than broccoli, are activating glutathione in the brain. There's human evidence of that. I mean, that's amazing. - [Andrew] That is amazing. - In Plasma. Yeah. - Sorry to interrupt. I just want to make sure. So broccoli sprouts are different than broccoli, and you just told us that they're much richer in these compounds. So, note to self, I should have broccoli sprouts, not just broccoli. Can we cook the broccoli and still get these nutrients, or do we have to eat it raw? I confess, eating raw broccoli is really aversive to me. - So the sulforaphane is formed from a compound called glucoraphanin, which is in the broccoli, and the enzyme that converted into sulforaphane is myrosinase, and it's heat sensitive. So you do somewhat lower the sulforaphane levels when you cook the broccoli. However, there was a study a few years back that showed adding one gram of mustard seed powder, ground mustard seed powder, which also contains the myrosinase enzyme, to your cooked broccoli increases the sulforaphane by fourfold, so... - This is great 'cause, I confess, I like broccoli if it's cooked to the appropriate density, not too mushy but definitely not raw. The idea of eating raw broccoli to me just sounds horrible, but I like the way mustard seed sounds. So just a little bit of mustard seed powder added to the cooked broccoli can recover some of these compounds. - Yes, so what I do is I will lightly steam my broccoli, and then I add a little bit of my Kerrygold butter, and then I add some mustard seed powder on the top of that. And it's got a little kick. It's just a little spice. And if you don't taste that, it's expired. It should have a little kick. - And because I know people will want to know how often and how much, are you eating this every day or most days of the week? - Well, I had shifted to supplementation with sulforaphane. I'm admitting right now that I've been terrible about it the past, I don't know, six months or so.

00:23:50 Tool 2: Moringa & Nrf2 Antioxidant Response

- The supplementation or the broccoli? - Yes, the supplementation. And so there's another way to get. There's another compound, and it's actually called moringa. And Dr. Jed Fahey, who's really the expert on sulforaphane. He's a good friend of mine. He's been on the podcast a couple of times. He basically thinks, and has done a lot of research on marina as well, that it's like the cousin, and it activates the Nrf2 pathways similarly to sulforaphane. And so I've been buying this Kuli Kuli moringa powder. I don't have any affiliation with him. - Kuli Kuli is a brand? - Kuli Kuli's the brand. - That you have no affiliation to. - I have no affiliation, but Jed Fahey has researched it, like that specific brand, and so it's legit. It's science backed in terms of actually containing moringa and activating Nrf2. And I add it to my smoothies. So that's what I've been doing. - What are some dose ranges? And, of course, we give the usual recommendations that people should talk to their physician, et cetera, et cetera. But, if people are going to, what do you take? That's always the... - A big, heaping tablespoon. - Let's take the David Sinclairian approach, where he'll talk about what he does, as a way to deal with this. Of course, everybody's different and should, in all seriousness, anytime you add or delete something from your consumption should consult some trusted healthcare professional, trusted by you. Do you recall the dosages? - I do a big, heaping tablespoon. - So Kuli Kuli moringa. It sounds like a song.

00:25:25 Sulforaphane: Antioxidants (Glutathione) & Air Pollution (Benzene Elimination)

- It's with a K. I know, it does. But, for people also listening, it's like, "Well, why would I do that?" I mentioned the glutathione in the brain. I mentioned it in plasma. It's been shown to lower DNA damage in people, in white blood cells. There's been several different studies in China. In China, there's a lot of air pollution. And I mentioned that it's a very powerful activator of Nrf2. And I know you're familiar with Nrf2. Nrf2 is a transcription factor that is, it is binding to a little specific sequence in a variety of different genes, and it's turning them on, or, in some cases, turning them off. It's regulating what's being activated or what's not being activated, being turned off. And some of the genes are basically these detoxifying pathways. We talked a little bit about the glutathione, but there's also ones that are involved in airborne carcinogens, like benzene. So benzene's found in air pollution. I mean, cigarette smoke. If you're smoking cigarettes still, please

try to quit. - Yeah, you're mutating your DNA. - [Rhonda] Yeah, it's the worst. - To say nothing of the lung cancer, you're mutating your DNA. - And heart disease risk. Heart disease risk. But, anyways. People, and this has been repeated in more than one study, that literally after 24 hours of taking, I can't remember off the top of my head what the dose of sulforaphane from broccoli extract, broccoli seed extract was, or broccoli sprouts extract, not the seed. It was the sprouts. Anyways, they started excreting 60% benzene and acrolein. That's something that we get in cooked food. - It's coming out in their urine? - Coming out in their urine. Yeah. - Well, I'm not a smoker, and I have to be honest. It's rare that I hear of a supplement for the first time 'cause I've been deep-diving on supplements since I was in my teens.

00:27:10 Plants & Stress Response Pathways, Intermittent Challenges

This is fascinating, and it brings back to this question that we had before, and I appreciate that you've answered it very clearly. Plants have compounds that are good for us. They're not just stressing us. They're activating pathways that are reparative. That's what I'm taking away from everything you're telling me. - Right, and that our bodies, we're supposed to be getting that stress to have those pathways activated. You know, right? I mean, this is conserved among different animals. This is something that is, it's supposed to happen. And, in our modern day world, we don't have to eat plants. We don't have to move anywhere or exercise. We don't have to go through periods of not eating food because we can have it at our fingertips at any second, right? So, I mean, we've got this conundrum of, we're never activating these stress response pathways that we're supposed to activate. We're supposed to. - I find that fascinating, and again, drawing a parallel to the nervous system, so what I'm hearing you say is that, historically, we would have to go through some stress, some confront cold or confront heat, or confront effort or hunger, have to exercise, essentially, in order to obtain these compounds, and then those compounds are reparative. Yeah, I feel that resembles the dopamine pathway. I always say there's nothing wrong with dopamine. People think about dopamine hits as bad or dopamine is bad. There's absolutely nothing wrong with dopamine. The problem is dopamine, especially high levels of dopamine, released without the need for effort to access that dopamine is problematic. So a line of cocaine gives you a ton of dopamine with no effort except to ingest the drug, whereas working for four years or more to get your degree will release a lot of dopamine and a lot of cortisol

along the way, as we know, and it's considered a healthy accomplishment in most cases, a tremendous amount. We're approaching the spring, and there'll be a lot of graduations. Weddings are coming up now that the pandemic is hopefully slowing. And there'll be a lot of dopamine. High levels of dopamine are great, but only after the effort of having done something in order to access it. And so that's what I'm taking away from what you're saying is that we need to go through this intermittent, different types of intermittent challenge, and we are rewarded with particular compounds that are reparative, both for the challenge, but then make us stronger.

00:29:35 Traumatic Brain Injury, Sulforaphane, Nrf2

Hormesis really is, it seems, a case of what doesn't kill us, makes us stronger. So you mentioned- - Can I add to that one thing you just said? - [Andrew] Please, please. - Because this has been shown with, for example, sulforaphane in animal studies, you precondition, give the animal sulforaphane, and then you expose them to hypoxia or some kind of ischemic stroke condition, whatever they do to induce that, and the sulforaphane, it basically protects them. Their precondition and their stress response pathways are primed, and so, when they're then exposed to the ischemic stroke, their outcomes are so much better, so much better than the animals that didn't get the sulforaphane 48 hours before or whatever it was. And this has been shown in multiple animal studies with sulforaphane specifically in the brain. I know Mark Mattson. Dr Mark Mattson. He's often thought of as the intermittent fasting king, but he's a neuroscientist, and he did publish some work and talks about sulforaphane as well. - I'm really glad you brought that up, that example up, because many of the questions I get on social media and elsewhere are about traumatic brain injury. And TBI is just one example. And people always think, "Oh, sports. It's football." Whenever you say TBI, people always think football. And I just want to just take a moment to editorialize. 90% or more of traumatic brain injury is construction work, at-home accidents. Football players, hockey players, martial artists are a tiny fraction of the people who have TBI and concussion of various kinds. It just so happens that, within those communities, many of them, 75% or more, experience those. So it's salient within those communities, but concussion is prominent. People are always asking, "What can I do "in order to offset brain injury? "I had a concussion two years ago. What can I do?" And it's been a tough question because we really don't have anything for them. I mean, you tell them sleep well, eat well, exercise,

but it sounds like some of these reparative pathways either should be explored in the context of brain injury or, I'm guessing, are being explored in the context of brain injury. - Yeah, so a couple of things there. One is that, I mean, traumatic brain injury, it's terrible, but it's so interesting because it's also like literal, real-time brain aging. You're able to accelerate it and understand. So I often think of, when I think of traumatic brain injury, I think of so much overlap between Alzheimer's disease and dementia and these neurodegenerative diseases because there are a lot of similarities there. And so, sulforaphane, I personally think, and I do think there's been some animal research with TBI and sulforaphane, mostly preconditioning rather than treatment. So, again, it's like, well, if you want a healthy lifestyle thing and you're a construction worker, or you're fill in the blank, that's going to. I mean, anyone that drives a car, you're at risk to some degree, right? - [Andrew] Or bicycle. - Bicycle, yeah. - Around Stanford, I would say people demonize motorcycles, people demonize a lot of things, but moving fast through space on a small object next to a 3,000 pound vehicle, I mean, we have a number of friends that have died. We have a number of people with traumatic brain injury. I'm not against cycling or cyclists, but it's a risky sport by any stretch. So, in taking things like moringa or eating my broccoli sprouts, maybe cooking them a little less than I'm currently cooking them, putting on the mustard seed. Is there evidence that? Well, first of all, Nrf2 is expressed in neurons, so those cells should be protected. Are there other cells of the body that could possibly gain protection from these pathways? - Well, lungs for one, but just even in plasma cells. I think Nrf2 is pretty ubiquitously expressed. Liver. There's so many animal studies that have looked at all those things. I try to kind of gravitate towards human ones 'cause it's a lot more relevant. But I think, overall, like I mentioned, DNA damage lower. It was like 24 or 34% lower in human blood cells after broccoli sprout powder supplementation. - [Andrew] Wow. - And I made a video on this years ago, 2016 maybe, and I think I have the references on there to exact amounts. I can't remember. - We can link to the video. - But it's kind of an old video. It's 2016. But I also had Jed on the podcast, and he did talk about this. But it's also been shown in randomized controlled trials to help treat autism and autistic symptoms. Yet again, it's doing interesting things in the brain, and I think it does have something to do with the oxidative stress, the glutathione, which would be relevant for TBI treatment. It hasn't been shown empirically that that helps with treatment, but I do think someone could do that study. I think that it should be done, honestly, because it's a low-hanging fruit, I mean, if there's any impact. And there is at least one preliminary study that glutathione is

increased in the brain after humans are basically taking sulforaphane. - Which is, really, for people listening, that's so important because a number of compounds that people take in supplement form don't cross the blood-brain barrier, or they get metabolized in ways that what's listed on the bottle almost becomes irrelevant for what your cells actually experience. So that's very reassuring. We will get back to heat and cold and this theme that I tried to surface,

00:35:08 Tools 3: Omega-3 Fatty Acids (ALA, EPA & DHA), Fish Oil, Oxidation

but I just find this too interesting to diverge at this point from these themes. So, what other compounds or micronutrients do you place in the top tier of useful, interesting? There are animal studies. Maybe there are hopefully also some human studies. We've talked about a few. I know you've talked a lot about omega-3 fatty acids. So, if you had to do your top three, your superstars of nutrients for the brain and body, sounds like we've got one set, what would you put alongside them? - Omega-3, the marine omega-3 fatty acids. So these are found in marine types of animals, fish, cold water fish, fatty fish. So there's three fatty acids. There's one from a plant, and that's often referred to as ALA, people call it short, alpha-linolenic acid, and then there's eicosapentaenoic acid, or EPA, and docosahexaenoic acid, which is DHA. Yeah, but EPA- - I'm amazed you can pronounce two of the most difficult words to pronounce and spell right next to ophthalmology, which, if you can spell it. I know people who have appointments in ophthalmology departments that don't know how to spell ophthalmology. Little secret. There's an extra P in there. So the ALA. I'm not going to attempt to pronounce it because your pronunciation was perfect of both of these two compounds. And you said are marine sources, so fish, so sardines, cod, this sort of thing, but what about krill? I've seen krill oil. A few years back, people were saying krill is a better source for omega-3s than is fish oil. I took some krill oil capsules, made me itch all over, so I stopped. - Do you have a shellfish allergy? - No, I don't think so. - No, okay. - I don't think so. I'm not a big fan of shellfish, but I'll have oysters every now and again, or shrimp or something, and feel fine. - Yeah, we can talk about sources. So krill is a source mostly of a type of DHA and EPA that's in phospholipid form. So it's a phosphatidylcholine omega-3 fatty acid, and that's different than most of the, well, if we're talking about fish oil supplements, that's a different story, but if you're talking about comparing fish to eating krill, like we're talking about the food. - Oh, I would never eat krill. - Okay. Are we talking

about the supplements? - Yes, I apologize. - Fish oil supplements. - Yeah, krill supplement versus fish oil supplement, and, if it fits in the conversation, talking about great sources of omega-3s in their whole form. I have a bad feeling you're going to tell me sardines. - Sardines are, yeah, they're awesome. Anyways. - Except for the taste. - And for the potential contaminants. Mercury, I think, was one. No. Yeah, it was mercury. And Joe was telling me about, he used to eat sardines everyday. Joe Rogan was telling me that he used to eat sardines every day, and then he had really high mercury levels. And I was really shocked because sardines are low in the fish groups. The higher up you get, like swordfish and sharks, like, really high mercury 'cause they're eating all the other fish, right? But I think some brands, and if you look at ConsumerLab. ConsumerLab, it's like a third-party site that I'm not affiliated with, but I'll use them because they do a lot of analysis of different foods and supplements. And so you can look at some of their sardines, and they have a list of ones that are pretty decent. But, anyways, back to your question about fish oil supplements versus krill oil supplements. So one of the major differences is that fish oil supplements, if you get a high quality one, it's in a triglyceride form. So you've got a glycerol backbone with three fatty acids that's attached, and those are either DHA or the EPA. Or, if you have a lower quality fish oil supplement, then you have what's called ethyl ester form. And, typically, the reason for that, when fish oil is purified, it's run through this column with alcohol or something. They cleave it off, the glycerol backbone, and then it's just kind of easier to leave it like that than re-esterifying it, which costs more money. So you can get it in ethyl ester form, which isn't as bioavailable. And, in fact, if you don't take it with food, you're going to be in trouble. You're not going to absorb much of it at all. - Would you see this on the packaging? Is it going to say it's in this ethyl form? - Some official brands will put it on their website, perhaps on their packaging, but, most of the time, you'll have to dig for it on the website and/or call them. But I think, for the most part, ones that are higher end will market it, like triglyceride form. And it's not that ethyl ester's bad. It just means take it with food. So one of the major prescription omega-3s out there is, both of them actually, Lovaza, which is a mixture of DHA and EPA, as well as Vascepa, which is a highly purified EPA. These are both prescribed by physicians to patients with hypertriglyceridemia, so high triglycerides among other things, I think maybe dysregulation of lipids as well. - This is amazing. For people, so these are prescription drugs that are essentially very high-potency, purified omega-3s, but they're given to people for lipid issues. So this is the treatment of issues with fat metabolism by giving people fat. - Yes. - I just want to push home, again, I'm not

carnivore keto or anything, I'm an omnivore, but to just push home that one thing that's so wonderful that you've done over the years and you continue to do is to move away from these very broad, sweeping statements about fat is bad. Here's a case where we're saying fat is not only good, it can be used to combat issues with fat metabolism. And fats are not just one thing. They're many things. So anyway, I just want to put a little highlighter and a point of appreciation there and make sure that people are sensitized to the fact that, if you hear that fat is bad, you have to ask, what kind of fat? And here we're talking about these omega-3s. Okay, so the triglyceride form can be taken with or without food, and there's prescription forms. I don't know if I can get ahold of the prescription form unless- - You have high triglycerides. - Or I have a friend with high triglycerides. No. It's illegal, folks. Don't share prescription drugs. - Or you talk to your doctor and you say, "I'm already taking this from..." I mean, I don't know how it works. Anyways. - What's the dosage that you recommend people get? One way or another. - All right, okay, so the dosage that physicians prescribe for high triglycerides, for example, is four grams a day. - Four grams of EPA. - Yes, of the Vascepa. I think Lovaza's also prescribed at four grams a day. And you can get either of those from your physician. My father-in-law just got one of 'em prescribed. We were buying our own omega-3 for years and years. It's like, hey, you can actually get this and health insurance can cover it. And it's a really purified form, but you have to take it with food. That was the bottom line. I've totally gone on tangents, but you're asking more interesting questions anyway. - Well, normally I ask about mechanism and then I talk about protocols, but in the- - Or the why. - [Andrew] Or the why. - I mean, we haven't gotten there yet. - And we definitely will get there, but I think a number of people nowadays are just really excited about what they can do for their health, and so, here, we're just raising the importance of omega-3s, and then we'll definitely get to the why and the underlying mechanism. - Yeah, I think four grams is, I mean, in fact, Bill Harris, Dr. Bill Harris, he's just one of the pioneers on omega-3 fatty acid research. He was on our podcast last August. And he was saying the reason FDA chose that was literally just because how much they could get people to take. It wasn't like an upper end, like anything above that is unsafe. That wasn't the case. I mean, it was just purely cost and compliance, so what they can get into a pill, the amount they can get, and how many pills they can get people to take. - I'm smiling because our good friend Satchin Panda at the Salk Institute, who's done a lot of important work on intermittent fasting and other incredible work on circadian rhythms, et cetera. When I was talking to him in preparation

for an episode on intermittent fasting, I said, "Why the eight-hour feeding window?" And he said, "Well, the graduate student "who ran those studies had a partner." I think it was a girlfriend, as I recall. Hope I didn't get that backward. And the partner said, "Listen, you can be in lab "10 hours a day, but you can't be in lab 14 hours a day "if you want this relationship to work." And so it was eight hours of feeding window, plus some measurements and time to walk into the lab, park the car, et cetera. And so the eight-hour feeding window that everyone holds so holy was actually just born out of this relationship between these two graduate students. Had they been single, I was single all through graduate school, or most of it anyway, and I lived in the lab. So, if it'd been me, intermittent fasting would mean eating 14 hours a day. That was a joke. Not a good one, but just want to make clear. I'm joking. But the point that you're making is a really good one, that the four gram amount is not a threshold based on anything except the threshold of people's willingness to actually take this stuff. And I think that's important for people to hear. Because so often we hear the eight-hour feeding window, four grams of EPA, 150 minutes of cardio, and it's really a question of what you can reasonably do in a study. - So I take four grams a day. I take two in the morning, two grams in the morning, and I take two grams in the evening. I take my EPA in the morning, and I take my DHA in the evening. - You split them. - I do. I don't know. I don't think it's necessary, necessarily. I just happen to get a certain fish oil supplement that separates them. And so, like Lovaza, Lovaza's a great one, and it's all in one, and it's easier. - What if someone doesn't have a prescription? So I take over-the-counter fish oil. I know I feel better 'cause I've done the experiment of going on and off. I take them mainly for, I don't have depression, but my mood is better. My joints feel better. I just feel better. And I like to think that my platelets are slipperier, and they're cruising through any little obstructions in my veins or arteries. That's the image I have in my head, but I don't have any data to support that part. - Yeah, I mean, so, if you're asking for, like, where do people get these fish oil supplements? - Let's say I look at the bottle, and it says two grams per serving, but then I look, and it's 750 milligrams of EPA or 1,000 milligrams of EPA. Let's say half of it is EPA. Then, do I want to hit a threshold of EPA or a threshold of what's listed on the bottle, on the front of the bottle? Because my understanding is that we need to hit a threshold level of EPA in order to derive these important benefits. - I think two grams is a good threshold. Now, the International Fish Oil Standards, IFSO, they have a website where they do third-party testing of a ton of different fish oil supplements from around the world, and they measure the concentration of the omega-3

fatty acids in the actual supplement, because nothing is ever what it says on the bottle, and then they also measure contaminants, so mercury, PCBs, dioxins, things that you'd find potentially in fish that are harmful to humans, and they also measure mercury and then oxidized fatty acids. So these omega-3 fatty acids are polyunsaturated fatty acids, which are extremely prone to oxidation. So please keep your fish oil in the refrigerator because it's colder. Yeah, they're extremely prone. - Mine's in the cupboard, so now I know. - The shelf life's increased. Lower oxidation. - No, it makes perfect sense. Yeah. - So, anyways, they measure that. And I typically like to look for, they give you a total oxidation number. It's called T-O-T-O-X. TOTOX is what we call it for short. And I like it to be at the least under 10, ideally under six. It's really hard to find all the right mixtures of things, but people can go to this website, and they can browse through the products. I've put together an Excel sheet, which I have a YouTube little screencast that I'm yet to publish, press the publish button on, but it, basically, you have to go back and check and update 'cause these are from different lot numbers of the products. They do have up to like 20, 27 or something. And so I've gone through and found my top picks of high EPA brands and high DHA brands. If I were to buy some, the ones that I would choose because of the low total oxidation and the high concentration of either EPA or DHA. Now, people can go and do this themselves. It just takes some work. - No, I'm glad that you did the work. I'm going to put up a tweet every week. - Oh no! - With you tagged until this list is published online. Sorry, Rhonda, but I'm going to do it. I know it's very sadistic of me, but in service to the community and myself. - Yes, and I chose five brands from each, and I tried to find one in Europe and one in Canada. - Great. - So there's a great selection of US and other. - Thank you for doing that work. I don't want to do that work, and I trust you. So, yeah, I try and get two grams per day of EPA from supplementation.

00:48:40 EPA Omega-3s & Depression

I'll now put it in the refrigerator. Mood is better. I made that decision mainly based on the data that I'm aware of, looking at comparison of people doing that anywhere from two to four grams of EPA per day compared to SSRIs, selective serotonin reuptake inhibitors, in treatment of depression, and I don't want to take an SSRI if I don't have to, and fortunately, I don't have to, but the data, by my read, are remarkable. People that take these things in sufficient doses, meaning the EPAs, are able to get by with much lower dosages of SSRIs for depression relief or, in some cases, to come off their SSRIs

completely or avoid going on antidepressant medication. Now, of course, this is not something people should cowboy. Mental health issues are serious. But what other reasons, I'd love your thoughts on that, on the mental health part, so maybe you could tell us what are some things that getting to two to four grams of EPA per day is going to help with in our brain and the rest of our body. - So, do you know? So I actually published a paper back in 2015 about the role of omega-3 and vitamin D in depression, bipolar disorder, schizophrenia, and impulsive behavior. But, so, within that paper, doing background research, and this was a review article, by the way, I was just connecting dots 'cause I love doing that. - I'm going to grab that paper. I confess, I don't know the paper, but I love quality reviews because the references they're in are so useful. - Well, there's a huge role for inflammation, the cause of inflammation in depression. And I think we did a short animated video on this as well, years ago, back when I was publishing that work, where people are injected with lipopolysaccharide. This is something that we're generating from our gut, mostly from our gut permeability, which happens a lot. Endotoxin, it's also called. It's endotoxin lipopolysaccharide. It's basically the outer membrane of bacterial cells when bacteria die, so like when the immune cells in our gut come into contact with the bacteria because we drank alcohol five days in a row or whatever, we release endotoxin, or something stressed us out. We release endotoxin into our body, and that causes inflammation. And so you can inject people with lipopolysaccharide and cause depressive symptoms. However, if you take those same cohort of people, give them EPA, and I think it was somewhere around two grams, and then inject them with lipopolysaccharide. We're establishing causation here, right? It totally, the depressive symptoms, versus a placebo. So the placebo was saline control. So this was a placebo controlled because obviously it's hugely important for depression. It ameliorated the depressive symptoms that was caused by lipopolysaccharide. - Amazing, and LPS, lipopolysaccharide, is no joke. Years ago, when I was working on thermal regulation, we would inject animals with LPS to induce fever. The vagus nerve registers the presence of LPS signals to these particular hyperglycemic areas and cranks up body temperature because, basically, it's a signal that the body is infected. Amazing. So I will continue with my two grams per day. Maybe I'll ramp it up to four. I'm not doing the DHA separately. There's DHA in the same supplement. - Yes. - [Andrew] Is that okay?

00:52:02 Krill Oil vs. Fish Oil Supplements?

- Yes. Yeah, yeah. And to kind of... Boy, we've got a lot of things to hit back on because one of your original questions was krill oil versus fish oil. - Yes, still in the cue. - DHA, specifically, in phospholipid form, it's more bioavailable. So, if you're comparing exact quantity or concentration in triglyceride form versus phospholipid form, you will get more in your plasma cells, in your plasma, plasma cell, in your plasma with krill oil. However, krill oil supplements are so low dose. I mean, good luck getting two grams of omega-3 from krill oil. And also, krill oil supplements are notoriously rancid. I don't know for whatever reason. - Maybe that's what made me itchy all over. - I think they're just... I haven't found a good krill oil supplement. I pretty much stay away from it. I mean, if you smell it too, I mean, it just smells rancid. So, but the thing is, and I also published a paper on this back in 2019, yeah, something like that, about DHA in phospholipid form getting into the brain through a different mechanism than DHA in triglyceride form. And so it's going through a transporter called the MFSD2A transporter. And I think it's very relevant for people with an APOE4 allele, so- - People with an Alzheimer's susceptibility. - Right, so like 25% of the population has an allele and a gene called APOE4, and, basically, it's APOE, but the four is referred to as the bad kind of version of it. This is something in our bodies. It's also in our brain. And if people have one of these versions, if they got one from their mom or their dad, they have a twofold increased risk for Alzheimer's disease. If they get two, which is much more, it's less common. I think it's like 2% of the population or something has two alleles, but they have like a 10 or 11-fold increased risk of Alzheimer's disease. So there is a role for phospholipid form DHA in the brain, but you also make phospholipid DHA inside your body.

00:54:23 Benefits of Omega-3 Fatty Acids, Omega-3 Index & Life Expectancy

And you can do that by taking in more triglyceride forms. So two grams or more is the magic number, I think. So kind of back to the why for fish oil. I personally think it is one of the most powerful, anti-inflammatory things, dietary lifestyle, things that we can get easily, relatively easily, that is going to powerfully modulate the way you think, the way you feel, and the way you age. And a variety of different types of studies kind of led me to that conclusion, a variety of observational studies. So there's been lots of work by Dr. Bill Harris and his collaborators looking at, it's called the Omega-3 Index. So this is actually the omega-3 level in red blood cells. So red blood cells turn over about every

120 days. So it's a long-term marker of omega-3 status. This is very different from 99.9% of any study you see or any lab that you go to to get your omega-3 levels tested. You're getting your plasma phospholipid levels tested, which is kind of like you can think of it as, what did I eat a couple days before? Oh, I had fish. My omega-3 levels are great. But did you eat fish like that every week, or was it like you went out to dinner? So it's not a great biomarker for long-term omega-3 status. It's kind of like the fasting blood glucose levels versus the HbA1c, which is like a long-term marker of your blood glucose levels. So the Omega-3 Index. He's done a variety of studies, observational studies. So, for people listening, these are studies that are obviously flawed because they're not establishing causality. You're looking at people's lifestyles. But, in the case of Bill Harris's work, he's measuring something. So he's measuring the Omega-3 Index. And he's measuring the Omega-3 Index in people, and then looking at their mortality risk, for example, or their cardiovascular disease risk. And what he has found is that, first of all, standard American diet has an Omega-3 Index of 5%. Japan, by contrast, has an Omega-3 Index of around 10 to 11%. Big difference there. And they also have about a five-year increased life expectancy compared to people in the US. - Do you think that's mainly due to their fish intake, seafood intake? - So what he showed was, I think it's a big part of it. I mean, you can't says it's the only thing, but what he showed in his data was that, and I think it was Framingham Study, where he looked at the Omega-3 Index, and people that had a Omega-3 Index of 4% or lower, so close to what the standard American is but a little bit lower, they had a five-year decreased life expectancy compared to people that had an 8% Omega-3 Index. And so big difference there, right? Five years life expectancy. But here's the really interesting thing, Andrew. He also looked at smokers, smokers and their omega-3 levels, and so he stratified it, and he found smokers that had no omega-3 were like the worst of all. I mean, it was just like worse, right? We all know smoking is bad for us and will take years off our life expectancy. - [Andrew] Absolutely. - But smokers that had the high level, like smokers that were taking their fish oil or eating fish or whatever it was they were doing to get them up to 8%, they had the same life expectancy as non-smokers with the low Omega-3 Index. - [Andrew] Wow. - Right? - Wow. That's amazing. And it's also amazing to me that people still smoke cigarettes. But I see a lot of people vaping, and I know a lot of people consume cannabis. Have there been any studies specifically of vaping or people smoking marijuana? - Life expectancy? - All-cause mortality. - I haven't seen those. I haven't seen those. - They're not motivated enough to come in as research subjects. That was, again, a poor joke. It is hard to study people,

marijuana use, unless, I'm told by my colleagues that study this stuff, unless you offer people marijuana, in which case they'll do it. But, again, they're actually not very good research subjects in all seriousness 'cause they are not very motivated or consistent, and they forget their appointments. So that's incredible. And you mentioned that the data on pollution related to the plant compounds earlier. So it's almost like these things are, again, are acting in a reparative way. - The omega-3s are, I mean, they are resolving inflammation. They're blunting inflammation. They're doing so many different. They affect so many different parts of the inflammatory pathway, which is, I think, plays a huge role in the way we age, the way our brain ages, the way we feel, our mood, our joints, all that. And so it's amazing that it's not, you know.

00:59:24 Tool 4: Food Sources of EPA Omega-3s

- I love fish oil. I feel better when I take it. I try to eat some fatty fish a couple times a week. I do want to just touch on food sources for a moment. First of all, are there plants that are rich in omega-3s? And second, I have some friends who are really into meat. I like meat a lot, my dad's Argentine, but I don't eat very much of it. I try and eat high quality meats in relatively limited amounts, but I do eat pretty often. But I've been told by these sources of a questionable authority that, if an animal grazes on really good grasses, for instance, that the meat can contain a lot of omega-3s, which, in principle, makes sense based on this Omega-3 Index. 'Cause you're telling me that a lot of this omega-3 is sequestered into the red blood cells. So, if I'm eating high quality, grass-fed meat and the grasses had omega-3s, do my steaks have omega-3s or no? - So there was a study published that compared conventional meat, so meat that animals are fed corn or soy or whatever it is. - Which is terrible. - [Rhonda] Yeah. - For animals and people, as far as I can tell. I'm sure I'll get some attacks, but that's okay. I won't read those comments. Again, a joke. I read all the comments. But it seems to me that these animals have to either be taking fish oil or eat plants that are very rich in omega-3s in order for the meat to actually contain sufficient omega-3s. - So the meat, comparing the conventional meat to the grass-fed or pasture-raised cows or cattle, there were higher levels of alpha-linolenic acid. And ALA, it can be converted into EPA and DHA, but the conversion is very inefficient and very dependent on a variety of factors, including genetics. Genetics, a huge regulator. Some people can do it much better. Others, you're getting like 5% of conversion to EPA. Estrogen is a major regulator of making that more

efficient. It makes sense because pregnancy, when your estrogen just goes through the roof. These omega-3 fatty acids play a very important role in brain development. Women are supposed to be converting any ALA they can into the longer-chain omega-3 fatty acids. So estrogen does affect that, but I would say plant sources. So, if you're looking for the ALA, plant sources would be walnuts, flaxseeds. Those are probably the highest. But, if a person is a vegan or a vegetarian, their best bet is to actually get microalgae oil. And you can supplement with microalgae oil because microalgae, they do make the DHA. And so that would be a better source for people that are vegetarian and vegan rather than doing the flaxseed oil because that conversion inefficiency, the enzymes that convert ALA into EPA and DHA, again, it's inefficient. - And then, for people that eat fish, sardines, you said. - [Rhonda] Salmon. - Salmon, and you have to eat the skin, as I understand. - You don't have to, but it's good. - [Andrew] It's rich with omegas. - The oil, yeah. And the reason I say, I think the best would be wild Alaskan salmon versus the farm-raised because the farm-raised, again, they're feeding 'em corn. They're feeding 'em grain and stuff. - [Andrew] Really? - And then, they give 'em astaxanthin. So astaxanthin is a carotenoid. It's the carotenoid that's in things like krill, crustaceans that make their red pigment. - Yeah, it's also being used now as a supplement, and there's a prescription form to try and rescue some age-related vision loss because of the role of the vitamin A pathway and photoreceptors. - Yeah, well, actually the carotinoids themselves, so like lutein, zeaxathin, they're really good at sequestering singlet oxygen, which is damaging, right? - Yeah, as we age, because the retinal cells, the cells of the eye are so metabolically active, they accumulate a lot of reactive oxygen species, and mitochondrial repair and limiting reactive oxygen species is a major theme of trying to rescue vision. That's a whole other podcast and story. There's some really interesting data now on the use of red light to try and trigger these pathways. - I've seen some. That's my good friend of many years and amazing scientist Glen Jeffery's lab at University College London. We should talk about that at some point, if not today. - I saw that study, like 2020, was it? - Now, they have a second study. - Oh, do they? They've done, okay. - It's looking real. - [Rhonda] That's exciting. - I mean, they're cautious. They're appropriately British and cautious about it. I always joke if those studies had been done over here, everyone would already know about it. Glen is a very conservative guy, but they've done this stuff now in pigs, in rodent models, and now also two studies in humans. It's looking pretty interesting. So sardines but also anchovies. By the way, I hate all the food items that I'm describing. I can barely tolerate salmon. I don't like fish at

all. Actually, I like live fish. - So fish oil's good for you. - I had fish tanks when I was a kid. No, I find fish, unless it's in sushi form, I find it absolutely repulsive, and I don't know why. I probably have some mutation. - So raw fish is actually higher in mercury than cooked. - Okay, well, that's good. I don't really like sushi that much anyway. You're giving me great reasons to not eat fish, except I should eat these other fish sources or supplement more heavily. That's the message I'm getting. - I eat sardines. Every day, my first meal almost is a can of sardines and an avocado. - Avocado is good. - I love it, yeah, with a little bit of lemon and then some little hot sauce. - Does avocado have omega-3s? - Avocado is very good in monounsaturated fat. It's not really high in polyunsaturated fat. Omega-3, really, it's either the DHA and EPA that's in the marine sources fish, or it's the plant ALA source, which is the flaxseed or the walnuts. - It's rough. I mean, all these companies now are making these plant-based products that taste like meat. My wish is that they would just make a fish that tastes like a steak, but that's- - The fish come out albino, the ones that they farm raise, because they don't eat any of the- - I'm joking. I don't want a genetically modified fish that tastes like a steak. Although, I love the taste of steak. The point here is that, if one doesn't see themselves regularly consuming these fish sources of omega-3s,

01:06:07 Omega-3 Supplementation, Omega-3 Index Testing

it seems to me that the only way to really get them is from supplementation. - And supplementation is a good way to get a high dose. And to get back to your dose point, there was a couple of studies that, basically, I think there was some way they showed that people that are in the 4% Omega-3 Index range, in order to get to the 8%, the five-year increased life expectancy if we're comparing the two groups, was to supplement with at least two grams. It was about two grams a day. And I think it was a little bit less if it was triglyceride form, but I think two grams is a good, safe number. So most Americans that are not eating a lot of fish and they're not supplementing are probably around a 4 to 5% Omega-3 Index. And to get to the 8%. And I think that's a good empirical way of thinking about it, right? Okay, well, I want to get to that 8%. By the way, I'm almost 16% Omega-3 Index. - Yeah, I was going to ask about testing. So, where and how can somebody measure their Omega-3 Index? Which, again, just to remind people, is essentially the percentage of omega-3s that you have in your blood with the caveat that the Omega-3 Index will be heavily biased by what you ate in the previous days. -

Not the Omega-3 Index. Okay, so, the Omega-3- - Sorry, I misunderstood. I thought you said, in red blood cells, if I ate salmon two days ago, my Omega-3 Index is going to go up. - No, that was plasma. - [Andrew] I misunderstood. - So most people are measuring, if you look at a lot of studies, and honestly, Andrew, I think a lot of the reason for conflicting data is because people are measuring plasma omega-3 levels. - [Andrew] Okay. - The phospholipids. It's in a phospholipid, right? Your phospholipids are carrying things. These are lipoproteins. They're carrying things like omega-3 and triglycerides and stuff and shuttling 'em around. The Omega-3 Index is actually in the red blood cells, and red blood cells take 120 days to turn over. So, if you're going to do a baseline test, if you want to know before supplementing what your level is, you have to wait 120 days before doing the second test after supplementing to know how much you went up because that's how long it takes for your red blood cell to turn over. So the Omega-3 Index. Bill Harris has a company that he co-founded. It's called OmegaQuant, and they measure the Omega-3 Index. They have a variety of different index tests. You can do a basic one or a little more advanced. - This is from a blood draw. - It's a little blood spot thing, yeah. And he uses money to funnel back into doing lipid research. He's out there doing all sorts of interesting studies on omega-3s, so it's great. But the Omega-3 Index is great. I think that, honestly, more people and more researchers should be using it because the conflicting data, it always comes down to what we're measuring, the sensitivity of it. Are we even measuring anything? So you're giving someone 500 milligrams of DHA, and you don't see any effect. Well, did you measure what their levels were? And did you measure the Omega-3 Index? There's all sorts of problems with randomized controlled trials, and I think that we need to, as scientists, we need to come together and make some progress. I mean, you know? Let's all talk to each other. Let's figure things out. This test is out there. It should be used. It should be used not just by Bill's group, but everyone. - Yeah, well, and I'm learning so much from you. And I agree we need more collaboration. I've always enjoyed really fruitful collaborations in my lab at Stanford. Collaborating is just so much more fun. Online, there seems to be a bias more towards creating silos as opposed to bridges, but I appreciate that you bring up the need for more collaboration. And knowing which measures are best, and, in this case, now, thank you for the clarification, I understand this Omega-3 Index is going to be best. So, basically, now, when I look at you, I think, you are 16% omega-3. - And dolphins are 19%. I'm almost- - Is that your goal? You're trying to get there. - It is. [laughs] - Interesting. Actually, they should probably do something where you're trying to achieve

the omega-3 ratio of your favorite species. Now that we've covered a bit of how to get these things

01:10:22 Benefits of Omega-3s

into one system, depending on what one eats, et cetera, and some of the better measurements, how is omega-3 and some of these other related lipids, how are they having these positive effects? In my mind, and this is incredibly elementary, but my understanding is that, at some level, they're making platelets more slippery. Is that true or not? I'm happy to be wrong. How is it possibly impacting my mood? Is it through the synthesis of membrane on neurons that allows neurons to release more transmitter, like serotonin and dopamine? What are some of the purported, reported, and known mechanisms? - I think some of the most well-known mechanisms do have to do with the omega-3 fatty acids being very powerful regulators of the inflammatory process in some way, shape, or form, whether that has to do with resolvins that are produced from the metabolites of DHA, for example. Resolvins play a role in resolving inflammation. You want your inflammatory response to be activated when it's supposed to be, but you want to resolve that inflammation and the inflammatory response in a timely manner, right? And resolvins help do that. And so resolvins are one, and then there's these specialized pro-mediating molecules, the SPMs, that also help resolve the inflammation. There's, like you mentioned, the leukotrienes and prostaglandins, and these things are being affected by EPA, and they do affect platelets and platelet aggregation, and they do affect that whole pathway as well. I think there's just so many different ways and inputs. And so, when we talk about inflammation, honestly, that's a big general term, but when you're talking about serotonin release at the level of neurons, we know that these inflammatory molecules cross the blood-brain barrier. I just mentioned ago about injecting people with lipopolysaccharide and causing and depressive symptoms. It's known that omega-3, actually specifically EPA, is able to help serotonin. Inflammation inhibits the release of serotonin, and so EPA is actually able to blunt inflammatory responses along with DHA as well. DHA does that through resolvins and stuff. And this then helps more serotonin be released because you're not having so much inflammation getting into the brain and affecting serotonin release, right? That's one mechanism. And then, another would be, well, DHA itself has been shown, it's a very important fatty acid that makes up cell membranes, many cell membranes, including in our neurons. And, as you very well

know, Andrew, the structure and function of receptors of transporters, these membrane-bound proteins on the surface of our cells, including neurons, are affected by the membrane fluidity, like how rigid and how fluid the cell membrane is, and DHA plays a role in that. And so, for example, in animal studies, if you make an animal deficient in DHA, their serotonin receptors, dopamine receptors, they're affected because the structure of them is affected through the fluidity of the membrane. And so I think that's another mechanism. And I'm talking sort of general 'cause I'm not a neuroscientist. - No, but it makes perfect sense. We know, for instance, neuroplasticity almost always involves the recruitment of more receptors or an improvement in some feature of receptors to neurotransmitters. And they literally move laterally in the membrane. They kind of float around like little rafts. Sometimes they are, in fact, in lipid rafts. So it makes perfect sense that these molecules like DHA, which are part of the structural fat of the neuron, because, of course, the outsides of neurons are basically fat, not just the myelin that people have heard of, but the actual membranes, that getting that right, you wouldn't want it as rigid as concrete, but you wouldn't want it as soft as... Need to come up with something here. What's that gooey stuff that kids play with? It's like that goo. Anyway. - Oh, yeah. - Yeah, it's disgusting, and it's too soft to be a membrane for a neuron. - You get it in those machines, like the claw machines. - Someone put it in the comments and tell me what that disgusting gooey stuff is. You don't want your neurons to be that gooey, and yet you don't want them to be like concrete either. - It's a balance. Yeah. - It's a balance.

01:14:40 Tool 5: Food Sources of DHA Omega-3s

And, in mentioning DHA, I realize I'm backtracking, but I want to make sure that we close all the hatches for people. We talked a lot about EPA, but are food sources of DHA that you find particularly attractive, either by taste or by potency for DHA, what are just a few that we could throw out? Because I am aware that there are supplements where you can get a nice ratio of EPA to DHA, or you take them separately, as you do. But if I want to make sure that I'm getting enough DHA, what do I need to be sure I'm eating on a regular basis? - Well, the fish is packaging the DHA and EPA in the ratio, but I also do eat salmon roe, which is very salty, and it's a really high source of the phosphatidylcholine DHA that we talked about. - So this is fish eggs. - It is, and actually- - [Andrew] That I like for some reason. - Oh, do you? - Yeah, so I'm discovering

something about myself. This was not meant to be nutritional psychotherapy, but you're doing that for me anyway. I'm discovering that, yeah, I like eating embryonic fish. I just don't like eating the actual fish. - Okay, well. - Okay, so fish eggs are okay. So caviar, basically. - Caviar, yes. And that's a good source of the phospholipid form. And I was consuming that a lot because I wanted to get the phospholipid form. - [Andrew] Yum! - And it's actually really good. There's been some animal studies in piglets and rodents as well showing that consuming phospholipid DHA during fetal brain development gets like 10 times more DHA in the brain. Again, it's- - Makes sense based on fetal development. So, do I need to buy beluga caviar? Stuff can get pretty expensive at $200 a tin. - I don't think you need to. I think it's a matter of preference. And if you're supplementing with your two to four grams of fish oil, I mean, you're going to get phospholipid form anyway 'cause your body's going to make it. - Okay, I've seen some containers of what I assume to be quality fish eggs that are not at the caviar level that you can find in the better grocery stores that aren't super expensive. - [Rhonda] Right. - I wouldn't dip as low as to go eat, for instance, like fishing bait. Like, when we were kids, we used to go fishing, and you'd put the fish egg on the thing. That's probably not good. - No. - Although it's good enough for the fish apparently. Okay. Only half joking here, folks. I'm just trying to protect you from yourselves. Don't get any crazy ideas about eating fishing bait. Okay, so that's great to know. So we have these plant-based compounds,

01:17:07 Vitamin D & Sun Skin Exposure

we have the omega-3s, so EPA, DHA, and then you mentioned there's a third category. What would you place in your third category of foods or supplement-based nutrients that our health, brain and/or body health, can really benefit from? - I mean, I think the most obvious would be vitamin D, which is actually, as you know, a steroid hormone that we produce when we're in the sun. Depending on the time of year, we can make it in our skin. And depending on how much melanin we have on our skin, or whether or not we're wearing sunscreen or how old we are, there's a sliding scale on how efficient that process is. - As I understand, there's an inverse relationship, where the darker your skin is naturally, the more vitamin D you need to consume. Is that right? - Well, the darker your skin is, the harder it is. So there was a study out of the University of Chicago, this was several years ago, where they looked at African Americans and compared African Americans to Caucasians with light skin, fair skin, and how well they could make vitamin

D from sun exposure, and how long they had to be in the sun to make X amount. And it turns out that African Americans with darker pigmentation, which protects them from the burning rays of the sun, it's a natural sunscreen, had to stay in the sun six times as long as someone with none of that natural sunscreen. So I think the take-home there is a lot of people with darker skin living in Sub-Saharan Africa, or people living in India with darker skin, or in the Philippines, you know, these equatorial regions where you tend to see darker skin because it's protection from the burning rays of the sun. - An adaptation. - They are in the sun more, and they're getting more vitamin D, but people that maybe moved to United States, to like Minnesota, or in a place where UVB radiation isn't getting to the atmosphere 12 months out of the year. It's only getting there four months, for example. Or even living in our modern day society, where people just don't go outside anymore. I mean, we're inside. We're at our laptops in school. We're at work. We're in our cubicle, whatever. So supplementation does play a major role, not only for people with darker skin that aren't outside all the time, but for everyone. 70% of the US population has inadequate vitamin D levels. 70 of the whole US. - [Andrew] Amazing. - So this is everyone. And so I think that insufficient levels defined as less than 30 nanograms per milliliter, and that's defined by the Endocrine Society, looking at a lot of different aggregate studies, all-cause mortality, for example. There's been a lot of different meta analyses of all-cause mortality studies, where vitamin D levels really seem to be ideal between 40 to 60 nanograms per milliliter. And so, in order to get to that level, if you are not outside all the time, live in Southern California, where you're always outside without sunscreen on. I always wear sunscreen because I'm trying to protect my skin from so many wrinkles and stuff, but also skin cancer is somewhat of an issue as well. So, basically, the point is that vitamin D is a steroid hormone, meaning it actually binds to a receptor and another receptor dimerizes with it, the retinoid receptor, and that complex goes into the nucleus of a cell, where your DNA is, and it recognizes little sequences of DNA called vitamin D response elements. They're called VDREs. They're specific sequences of DNA that this complex, vitamin D bound with the vitamin D receptor, goes inside and recognizes and turns on a whole host of genes, turns off a whole host of genes. I mean, this is important stuff. Imagine 70% of the population having insufficient testosterone, right? It's a steroid hormone. - We might be headed there, but probably not. No, I think that names are very important, and I think that one of the issues is that vitamin D is called vitamin D. It's not called DHEA or variant blah, blah, blah. It doesn't sound like a hormone. I'm glad that you're mentioning skin as the major

interface between the environment and vitamin D synthesis because a lot of people think of skin as just a protective sheath around us or something to adorn ourselves with earrings or tattoos or whatever, but skin obviously serves those roles, but the skin is an endocrine organ. It has the capacity to make things that impact hormones and to make hormones. There's this beautiful study out this last year. This took place over in Israel, where they had people get outside for 20 or 30 minutes a day, three times a week, exposing a culturally acceptable yet substantial amount of their skin during that time, and saw big increases in testosterone and estrogen. And this is through a keratinocyte-linked pathway involving p53. This was done in humans, but they did some knockout studies in parallel. And what this study told me or reminded me is that skin is an endocrine organ. So the idea that sun could trigger the activation

01:22:18 Role of Vitamin D, Gene Regulation

of production of a hormone is really interesting and makes total sense. So, when vitamin D gets into cells, and it's binding to these VDR - [Rhonda] Es. - Es, what sorts of things are they triggering? So, for testosterone, we know it's going to trigger protein synthesis, muscle growth, tendon strength, et cetera, With estrogen, it's going to keep your neurons going, your joints feeling good. I always remind people that, by the way, 'cause guys always seem to want to increase their testosterone and reduce their estrogen. Just remind people, if you reduce your estrogen, guys, your libido will plummet to near zero. Don't crush your estrogen. It'll also make you stupid. If you're not already stupid, it will make you stupid. So estrogen's vitally important for males and females. When vitamin D gets into cells, what sorts of things is it stimulating? - Okay, so, first of all, it's regulating more than 5% of the protein-encoded human genome. I say more than because, when I was looking at this data really in depth starting in 2012 to 2014, it was that, and then it's now grown. But one of the important things that you'll find interesting that I published on back in 2014 was that I'd gone through this big, published database, where someone had published all these genes they found VDREs in, and basically I found that tryptophan hydroxylase-1 and tryptophan hydroxylase-2 was on there. And so then I started looking at the sequence, and I was doing some in silico work, and it turns out that the VDREs in tryptophan hydroxylase-2. So, for people listening, tryptophan hydroxylase is an enzyme that converts tryptophan into serotonin. So tryptophan is an amino acid that we get from our food. You convert tryptophan into serotonin in the gut, but you also

do it in the brain. However, serotonin does not cross the blood-brain barrier. So tryptophan has to get into your brain, and then you have to convert it to serotonin in your brain. Well, the enzyme that does that in your brain is called tryptophan hydroxylase-2, and it's activated by vitamin D. The one in the gut is actually tryptophan hydroxylase-1. Some of my published work hypothesized that it might actually be repressed by vitamin D because it has a sequence. The sequence itself, this 12 nucleotide sequence, can determine, to some degree, whether it's going to be activated or turned off. And I was able to kind of look at that and think, oh, maybe this and that. Since then, there have been some groups that have confirmed more with in vivo and/or in vitro studies. Mine was all in silico and all that stuff, but anyways. So serotonin, a really important one. This is regulating our immune cell, immune system. It's regulating our blood pressure. That's water retention. Bone, of course, homeostasis. 5%. More than 5%. I can't tell you. Like, so much. - And with 70% of the US population deficient,

01:25:30 Tool 6: Vitamin D Testing & Vitamin D3 Supplementation

I'm beginning to think that this could be the linchpin on a number of really important issues. So supplementing vitamin D3 is what I normally hear. I do. I think I end up taking 5,000 IUs, sometimes 10 IUs of vitamin D3 per day. Just done that for a long time, and I've had my levels tested and they're in range. But I have a family member, I'll just mention this. I have a family member who was not feeling well, just kind of feeling off, a little low, had some digestive issues, this went on a long period of time, was taking, on my recommendation, 15,000 IUs of D3 and was still deficient in D3. Now takes, and I'm not suggesting anyone do this. This is a special case, perhaps, but no chronic illness that we're aware of. Needs to take 30,000 IUs per day in order to bring their D3 range just into normal, which, to me, is striking because they eat quite well, they're a healthy weight, et cetera, and it's made a tremendous difference in terms of their mood. Now, of course, this is correlative. Now they feel better. They're doing it. Who knows? They're probably also getting outside more. But I think people need to get tested. They need to get their D3 levels tested. But where and what is a good starting range for people to think about D3 supplementation, and, again, foods that can increase D3? - So vitamin D3 is a good way to supplement with it. Vitamin D2 would be a plant source. You often find it fortified in foods like milk, usually D2. - Does anyone still drink milk besides kids? - Out here, it's like you can't find cows milk. - [Rhonda] I mean, all the lattes that you're

getting. - Oat milk, soy milk. What's the other one? - [Rhonda] They're fortified in those as well. - Oh, they are. Okay. - [Rhonda] They are, yeah. They're fortified in- - I have a hard time finding cows milk. - Almond milk and oat milk and all that stuff, yeah. They're in all that stuff. Vitamin D is naturally to some degree in fatty fish. You think about cod liver oil, right? It has vitamin D, but you're not going to correct a deficiency with eating fish for your vitamin D. You're either going to correct it with sun exposure, being in the right area, having the right amount of sun, and being the right age, because, as you get old, you become very inefficient at converting vitamin D, making vitamin D3 in your skin. - Well, that's probably what was going on here 'cause this person is getting up in their age. - There's a lot of single nucleotide polymorphisms. We talked about APOE4 before previously, but there's a variety of genes that people have, very common, actually. In fact, I've had many people that have done that exact same thing. So measuring your vitamin D levels before and after supplementation is the only way you're going to figure that out, right? Very important. If you don't measure it, you don't know. You can't know what you don't measure. So there's a variety of SNPs that basically make that conversion inefficient. And, in fact, there've been a lot of these Mendelian randomization studies. So these are studies where scientists will look at commons SNPs, people that have these common variations of a gene. That's more than 1% of the population. So it's not a random mutation. It's actually found in a sizeable percent of the population. And then, they've looked at various outcomes. And a lot of times, they'll look at genes that are also involved in some kind of lifestyle factor, so vitamin D, and SNPs that basically make the conversion of either vitamin D precursor into D3, or D3 into 25-hydroxy vitamin D, or into the active steroid hormone, which is 1,25-dihydroxyvitamin D3. And there's a variety of different SNPs that show. So you're not looking at vitamin D levels at all. You're looking at just the SNPs. And you know, if they have it, they have low vitamin D. So it's really a way of doing a beautifully randomized controlled trial with an observational study because you're not biased. Vitamin D levels are also associated with health. People that have higher vitamin D are either outside more, they're more physically active, or they're aware of their health and their supplementing, right? So you always have to worry about that when you're doing an observational study. Dealing in randomization is beautiful for that reason, where you're now just random. People randomly have these genes, and there's no health status. If you have the SNP, like your friend, like your family member was healthy and all. They were healthy, and yet they couldn't get their D levels up, right? So these Mendelian randomization studies have

found that people that can't convert into the precursor, the 25-hydroxy vitamin D, which is usually what's measured. It's the most stable form of vitamin D in the body. They have a higher all-cause mortality, if they can't do it. So people that don't have it have a lower all-cause mortality. They have a higher respiratory-related mortality. They have a higher cancer-related mortality. So, to me... Now, why did I get on this rant? Oh, because your family member. So, basically, they also are more likely to get multiple sclerosis. This has all been done with Mendelian randomization. And so it really does hammer home the importance of measuring your vitamin D levels and being very proactive about that. I mean, you can get it done anywhere. Your doctor will do it. You ask 'em to do it, you know. So supplementation wise, typically, if you don't have one of those SNPs, for the most part, taking 1,000 IUs of vitamin D will raise blood levels by around five nanograms per milliliter. So let's say you're deficient, you're 20 nanograms per milliliter, and you want to get to 40. You're going to need at least 4,000 IUs, if you are normal and don't have any of these SNPs that change your metabolism of vitamin D, right? - Does it matter when you take it relative to sun exposure, time of day, with or without food? - I've seen some not so great preliminary evidence suggesting maybe time of day is important. I don't think it. Like, I can't seem to find anything that really suggests. Because for it to actually be converted into the hormone, I mean, it's stored. - It's slow-acting. These steroid hormones are slow-acting. - Yeah, it's not like immediate thing. So maybe we'll get some new data that's like otherwise, but I just don't, yeah. - It simplifies the problem anyway. So, for people who are going to be stubborn and not get their D3 levels tested or their D levels tested, and simply say, "Oh, I'll just take some D3." That was me, by the way, until I got tested. I threw 5,000 IUs into the mix and figured, well, it's not going to kill me. It'll bring my vitamin D levels up. I realize that's a bit of a coarse way to approach it, but I feel fine, and I'm still breathing and ambulatory. So, is that reasonable? 1,000 to 5,000 IUs for most people will be reasonably safe. Again, just assuming that people are going to just jump to it without the blood test. - Of course, I think that, if we look at the literature, the scientific literature, it is extremely hard to get hypercalcemia, which would be the major concern with really high levels of vitamin D3 supplementation. I mean, we're talking like hundreds of thousands of IU a day for a long time. - Hundreds of thousands. - Yes, yes. Now, the upper tolerable intake was set by the Medicine Institute to be 4,000. It was kind of like one of those things where it's safe. I personally take 5,000 IUs a day as well, and my levels really hover around 50 nanograms per mill. I don't put sunscreen on all the time. I do put it on my face and I wear a hat, but some of my skin is

being exposed, so I do make it from the sun as well.

01:33:15 Tool 7: Skin Surface Area & Sun Exposure, Vitamin D

- I'm glad you brought up the fact that you keep arms exposed. Because, in these studies that I mentioned before, looking at sun exposure on skin and increases in other hormones, testosterone, estrogen, mainly, it became clear from looking at those data that the amount of skin that you expose is important, which makes perfect sense once you hear that, but I think most people are thinking, oh, I'm out in the sun, but are you wearing shorts and a t-shirt, or are you wearing a sweatshirt and it's a hoodie? Are you all covered up out in the sun? Well, that might be great for setting your circadian rhythm by way of light through the eyes 'cause that's the primary mechanism for that. But seems to me that the more of your body surface that you can safely and appropriately, please, folks, appropriately expose to the sun, the more vitamin D you're going to create. So laying out on your back deck in shorts and a t-shirt with arms exposed and legs exposed is a very different stimulus than walking around in jeans and a sweatshirt. - Absolutely. - Right? Okay, okay. Especially if you have sunscreen on your face. I know it almost seems like trivially simple,

01:34:23 Vitamin D & Longevity

but I'm not sure that people are used to thinking about their skin as a interface to create these hormones. - Yeah. - So surface area matters. - And by the way, there have been studies looking at people that are deficient in vitamin D. In this case, it was African Americans that were given a 4,000 IU a day vitamin D supplement to bring them back to sufficient levels. This was a smaller study than I would like, but it reversed their epigenetic aging by three years. Because, again, it's a hormone. It's regulating more than 5% of your protein-encoding human genome. There's been studies looking at vitamin D receptor knockout mice. And I use this a lot in my presentations when I'm talking about vitamin D and longevity. If you look at these animals, the vitamin D receptor, as I mentioned earlier, vitamin D binds to the receptor, and then it complexes with the retinoid receptor, and they go into the nucleus as a complex and turn on and turn off genes. Well, if you get rid of that receptor, which is what you can do in animal studies, you can determine what effects there will be with no vitamin D. Like, how do you

study no vitamin D? And so what was found was that these animals, and, in fact, I don't think it was a complete knockout 'cause I think it might be embryonic lethal, but- - [Andrew] Some hypomorph. - Yes. - Which is basically geek speak for a gene is vastly reduced in its function, number and function, number, people know what I mean, but isn't eliminated completely. - Right, well, these animals, if you look at them after the age of four months, I mean, the mice look like. I mean, they're accelerated aging. They're wrinkled. They have no hair. Their lifespan's shorter. I mean, you can look at this animal and not know anything about mice or work with them and be like, "That animal looks like it's..." Of course, mice lifespans are only like two, two and a half years, but, like, 500 years old. - Looks like it went to graduate school twice. - [Rhonda] Yeah. - Actually, graduate school's a lot of fun. I like to think I aged backwards in graduate school, which is not true. I look at the photos. I definitely aged forward. You, on the other hand, look exactly the same way you did 10 years ago. I'm not saying that to flatter you, but it's absolutely true. I mean, the data or the data. It's remarkable. So I'm definitely going to try and get my omega-3 percentage up there. I'm not going to hinge it all on that,

01:36:46 Sun Exposure & Sunscreen

but clearly you're doing a lot of things right. So, if I'm taking vitamin D3, I still need to get out into the sun. Correct? - Absolutely. - Okay, I think a lot of people don't know that, or, at least, I have family members that have been a little bit resistant. Like, "I take my vitamin D "so I don't need to get outside as much." I think people are really afraid of getting out into the sun because they're worried about melanomas. And, to be honest, I'm as scared of sunscreen as I am of melanoma. Some of the things in sunscreen are really spooky, mainly the compound. And here, I'm not one of these conspiracy. I drink tap water. Listen, folks. People cringe, but I drink tap water. I have the occasional croissant or donut. 90%, 80% of the time, I'm doing the right things, the right way, I think. Although, I'm now going to improve on them with this new knowledge. But I don't like what I see in most sunscreens. Because, if you look at these compounds, they cross the blood-brain barrier. I don't want compounds crossing the blood-brain barrier. - Titanium dioxide? - Dioxide, some of the triclosans that are also in these cleansers. I mean, once you know a little bit about neurons, folks, you realize the neurons you got are basically the ones you've got for your entire life. There's a reason why there's a blood-brain barrier, a blood-ovary, and a blood-testes barrier. It's because the genetic material

resides in the testes, the ovaries, and the brain. Those neurons don't turn over. There are a few new neurons but not that many unless you're a mouse, frankly. And so protecting those is very key, and a lot of the things in sunscreen are downright dangerous. So I think there are sunscreens that are safe, but it's very hard to figure out which sunscreens are free of these compounds. I'm amazed that they're still on the market, frankly. - I've always geared towards the ones with the minerals that are reflecting it. It is somewhat difficult to penetrate things all the way through the skin and get into the bloodstream, but I don't know. Maybe some of these compounds get in there easily. I have seen the evidence with some of those things. - Yeah, there is some evidence they go transdermal. - And they get in. Okay, well, I know that some of them react with the sun and, while they do protect from the UVA and/or B, they form massive reactive oxygen species and carcinogen. I mean, it's like the very thing you're trying to protect yourself from might actually cause- - [Andrew] Right. - We don't know. It's completely speculation. There is, I think, some more and more evidence coming out with some of those compounds. I can't remember all of 'em off the top of my head, but a lot of high-end ones also have. It's the chemical sunscreen ones. - Right, right. - [Rhonda] The chemical ones. - I'm proposing that we do a journal club. A journal club, folks, is where academics get together. Well, they read papers, then they get together, and they pick apart the papers. There's a strong correlation between being an early graduate student and being the most critical. 'Cause once you've actually published some papers, you realize that, most studies, people are doing their best within the context of what they can do. But it'd be great to do a journal club at some point about sunscreens 'cause I'd love to really figure out what's in these compounds. People are using them like crazy. And I'm not one of these people who's like, oh, I won't use commercial toothpaste or anything like that. Like I said, I drink tap water. I use commercial toothpaste, whatever. But when it comes to sunscreen, it freaks me out because some of these compounds do go transdermal and some of them cross the blood-brain barrier, and I'd like to keep my neurons free of that stuff. Anyway, we're speculating now. - Wear a hat. - Wear a hat, but get out in the sun and get your D3 levels up. Okay, so, we talked about these plant-based compounds, the omega-3s, and D3. Unless there's something else that you just absolutely must throw into the mix, I probably will return us to the conversation that I opened up with, which was about cold and heat, which, admittedly, I pulled us off that path,

01:40:30 Role of Magnesium, Magnesium Sources, Dark Leafy Green Vegetables

so I take full responsibility for that. But before I do that, I just want to offer you the opportunity. Is there anything to supplement-based or food-based compounds that you think are especially useful for brain and/or body health? - I do think magnesium is important in there as well. I mean, I think, again, about 40% of the US population doesn't get enough magnesium. It's an essential mineral we're supposed to be getting from our diet. - Involved in everything. - It is. It's also involved in vitamin D metabolism. And, in fact, being deficient in magnesium may make it more difficult for you to actually make vitamin D hormone, so that 1,25-dihyroxyvitamin D. So one of those other factors, again, we talked about genetics, but there's also magnesium status as well. Considering 40%, that's a big number. Now, magnesium's also involved in making ATP, the energetic currency of our cells. Basically, all of our cells need ATP to do anything. It's also involved in utilizing ATP as well as DNA repair enzymes. These are enzymes that are involved in repairing damage to our DNA. I personally think that magnesium insufficiency causes an insidious type of damage daily that you can't look in the mirror and see. When you're deficient in vitamin C, you're like, "My gums are falling apart. "I have scurvy, right?" But you can't see DNA damage. You can't see it, but it's happening. It's happening right now in my body, and it's happening in your body. It's happening. Normal metabolism is happening every day. But we repair that damage. We have repair enzymes in our body called DNA repair enzymes. They require magnesium. Magnesium is a co-factor for them. What that means, a co-factor means, enzymes need it to function properly, and so, without that co-factor, they're not doing it properly. The way I like to think about magnesium. It's easy. 'Cause people go, "What food should I eat?" Naturally, that's the next question. Well, magnesium is at the center of a chlorophyll molecule. Chlorophyll is what gives plants their green color. So dark, leafy greens are high in magnesium. Basically, what does the 40% insufficiency in the US tell us? People aren't eating their greens. They're not eating their greens. They're eating their packaged food. They're eating their processed food. The standard American diet isn't really high in dark, leafy greens. So dark, leafy greens are how I like to get my magnesium. I think it comes along with all these other important. I mean, you get calcium in them. You get vitamin K1. You're getting a lot of other micronutrients, and you're getting other compounds that we don't know about, and ones that we know about, like sulforaphane, right? - As with broccoli, do I need to eat the dark, leafy greens raw? And, in this case, I'm a little more

open to it because I actually like the taste of, dare I say, kale. And kale's a dark, leafy green, right? - Yes, and it's high in lutein and zeaxanthin as well. - I'm a trichromat, meaning I'm not color blind, but I just want to make sure it falls under the strict category. 'Cause every once in a while, I'm like, "Oh, I eat my vegetables." I like avocados, and people remind me avocados are not a vegetable. I love vegetables also. So kale, what are some other examples? - Kale, spinach, chard, like Swiss chard, rainbow chard, romaine lettuce. - Is the bitterness an important component to this? - For magnesium, no, but for sulforaphane, for cruciferous vegetables. That would be the brassica family. But your question about cooking them. So magnesium, it is bound to the food matrix, and it can be somewhat less bioavailable. So cooking it can somewhat release the magnesium, but it goes into the water too. So you have to either steam it or kind of like get your water in. - You can drink the water. - Yeah, I personally don't worry about it. - Okay, great. - [Rhonda] I just don't worry. - Well, if you don't worry, I'm not going to worry. - But I also do supplement with magnesium. So supplementation with magnesium, I mean, we could go on and on. Let's keep this short and sweet because we're going to get back to the other stuff.

01:44:50 Tool 8: Magnesium Supplements: Citrate, Threonate, Malate, Bisglycinate

But it can cause GI distress at high doses. I personally like to take around 130 or 135 milligrams. That way, it's not like a huge bolus to my gut. - But I think it depends on the form of magnesium too. - Yes, yeah. I mean, you can take magnesium threonate, for example, and it doesn't affect the gut as much. - Magnesium citrate. - Citrate is what I take. - [Rhonda] I take Thorne. - It's a pretty potent gut stimulus. I feel like it's a little bit harder to digest. - 135 milligrams should be pretty good. And citrate, actually, oh boy, do we want to go here? - I mean, it's up to you. We don't have to. Personally, I've been supplementing with magnesium for a long time. I use threonate and bisglycinate and malate for different reasons. So, yes, I would love to go there if you're willing. - I would say malate would be the best, and that has to do with the short-chain fatty acids being good for the gut and a lot of work done by a former colleague of mine and good friend, Mark Shigenaga, showing that the short-chain fatty acid, citrate, malate, lactate, but specifically malate, really, and lactate are the major ones that get into the gut epithelial cells and are an energy source for the mitochondria and the goblet cells, so anyways, whole other topic. - That's okay. I take malate because I was told that it would be helpful.

First of all, it doesn't make me sleepy like some of the other forms of magnesium, which act as a mild sedative for me. They do tap into the GABAergic pathway, a neurotransmitter, folks, that, in general, broad sweeping generalization here, can have somewhat of a sedative quality, which is why I take magnesium threonate and/or bisglycinate before sleep, 30 to 60 minutes before sleep. Definitely enhances my transition time to sleep and the depth of sleep. No question, in my experience. There's some data that threonate can be neuroprotective, although those studies are still ongoing. I'm getting the sense that maybe you're a little more skeptical of that than I am. - Yeah, no, I've seen the studies with the threonate. I think, looking at the actual data from the one clinical study, there wasn't statistical significance until all three of the pieces of data were pulled together, but that really could just be because their sample size was too small, right? - Yeah, I'm thinking that paired with the, there's some work- - [Rhonda] The animal stuff. - Yeah, Guosong Liu's work on. This is getting kind of inside ball of neuroscience. The quality of the labs matters, folks, and that's something that's not accessible to people outside of fields. Guosong Liu and some of the other folks at that time at MIT, I think very highly of their work. And so the animal studies are indeed just animal studies, but I was pretty impressed by what they did in those studies. Very pioneering when you think about this being done 10, 12, 15 years ago. And then, yes, we need more human clinical data. But, for me, I figured that, given the safety profile of mag threonate, given that it helps me sleep better, and sleeping better is just better for everything, frankly. That's why I take it. And bisglycinate and threonate seem to be somewhat interchangeable, but I don't know of any reports that bisglycinate can be neuroprotective. But malate I take during the daytime. For me, and, again, this is subjective, it has a tangible effect in improving the recovery time from exercise. I don't know that I've been sore from a workout since I started taking malate, and I used to get very sore from even kind of trivial workouts. So I don't know what's going on there, but I keep taking it. - Malate, again, the short-chain fatty acid, and when you do intense exercise, you release endotoxin from your gut. I'm just going back to the interesting work 'cause the malate being the short-chain fatty acid and Mark Shigenaga showing, this is all an animal research by the way, but it was feeding these animals malate. It really protected the gut, endotoxin release, and it affected metabolic syndrome and all sorts of things. But I think malates awesome, and I always try to eat green apples. They're really high in malic acid. - [Andrew] Oh, good to know. - And tart cherries. Tart cherries are really high in it as well. - They also taste really good. - But I was really interested in the

magnesium threonate stuff. I take a supplement called Magnesi-Om by Moon Juice. And it's like a little powder. It's got a little bit of monk fruit, but it tastes good. So I do it a little bit before bedtime as well. Probably several more hours though because I don't like to drink tons and tons of fluids before I go to bed. And it has magnesium threonate, and a variety of other versions of magnesium in it as well, and I really like it. But I thought the magnesium threonate stuff was super interesting. I would love to see more clinical data as well, but I think, once we get it, it'll probably be like, oh yeah, it's getting into the brain, and it's awesome, so, you know, why wait? - And along those lines, I once put out a post that said, I feel like there are a number of different categories of health information consumers online and understanding which one you're in for which topic can alleviate a lot of the strain and stress of finding the information. There's some people that are perfectly comfortable with data from a mouse study. It's like, "If it's done in mice, great. I'll try it." Other people say, "No, it has to be done in humans." Double-blind, placebo-controlled studies. Randomized clinical trials, et cetera. Then, other people just say, "You know what? "I don't even care about any of that. "Just tell me what you do." And then, other people say, "You know what? "I don't even care what you do. Just tell me what to do." And then, there's this other category which are, if it's in pill form or powder form, they'll take it. And so I think a lot of the battles of people picking apart people's posts and things have to do with the fact that people don't realize that people are showing up to the table in one or some combination of those stances. We know people that will try anything, and we know people that won't take anything. So the idea here is to create an array of possibilities for people, and I think the animal data are very impressive. We should have you back on to talk- - I take it with the hope of, because I feel like the animal data is very promising. - Right, there you go. - And so I'm like, it probably is, so why not?

01:50:57 Tool 9: Deliberate Cold Exposure Protocol & Mood/Anxiety

- Well, and obviously you're doing things right. So cold and heat converge on some common pathways related to what you called intermittent challenge, which I love. I think, intermittent fasting, cold, heat, exercise, I mean, maybe even intermittent sleep deprivation. I keep waiting for the intermittent sleep deprivation movement. I will say, I pull a few all-nighters per year just for work demands and procrastination and deadlines. I'm the worst combination of academic 'cause I'm both a procrastinator and a

perfectionist, so you end up pulling some all-nighters. The sleep I get the next night is pretty amazing. I must say, it's the sleep of gods, but I don't recommend anyone use sleep deprivation for that. But I could imagine that we also evolved having some sleepless nights. So this idea of intermittent challenge is a really attractive one, and I want to make sure that we credit you with the phrase intermittent challenge. - No, credit Dr. Mark Mattson. - Okay. Dr. Mark Mattson gets credit. - Who's published, and he has used that- - He used those words. - Oh, that phrase. - Yes. - Okay, great. We'll make sure. - Just like Dr. David Sinclair, I love the xenohormesis. It was in one of his publications so many years ago, and I just love it. Brilliant. A brilliant term. So Mark Mattson gets credit. - Those Harvard guys are pretty smart. I mean, it's a good school, I guess. Of course it's a good school. We will credit the appropriate people. Thank you for that clarification. So you've talked a lot about the use of what I call deliberate cold exposure, only to distinguish it from cold that you might just be accidentally exposed to, but it's sort of obvious when we say cold exposure. There are some amazing data on cold. The other day I saw a post from you, and you've included this in talks before. I did not know this until I learned it from you, so credit to you, that even 20 seconds of immersion in, I think, it was four degree. - 49 degree Fahrenheit. - 49 degree Fahrenheit. Okay, I was translating to Celsius, but 49 degree Fahrenheit water, so cold water, can lead to long-lasting increases in epinephrine, adrenaline, and I have to presume other neuromodulators and neurochemicals as well. What are some cold protocols that you find particularly interesting or attractive from the standpoint of, I dunno, pick your favorite, metabolism, neuro/mood effects, brown fat stimulation, which, of course, weaves back to metabolism. We could do an entire episode all about cold, but what I'd love to know is, what sort of activity or stimulus do you think is a reasonable and particularly potent one to use in terms of cold? - So, today, I did three minutes at 49 degrees Fahrenheit. I have a cold tub. - So you get in up to your neck? - Well, I try. I keep floating up. It's like really hard. I would say maybe most of my shoulder. I mean, really I'm floating up. I was telling my husband. I was like, "There's too much water in here for me." - Or too much salt in there? Is it like the Dead Sea where you float on top? - Is there salt in there? I don't know. He takes care of all the stuff that, you know. It's the Plunge. - By the way, the podcast nor I am sponsored by Plunge. They did give me one. That thing is fantastic. Also, 'cause it circulates the water. - It does. - Which makes sure that you break up the thermal layer, and it's even colder. - It is even colder. It sucks! Anyways, so look, I'll be honest here. I wish I did more cold than I do. I do cold when I'm

going to go on a podcast. I definitely do cold when I'm going to do a podcast, when I'm going to give a talk or when I'm anxious. I need to make it more of a ritual. I love doing the sauna. I hate the cold. I hate it, unless it's summertime. It's a lot easier for me to get in the cold in the summertime. But what I do love about the cold is how I feel after. And I feel less anxious. I feel good. I feel more focused, which is why I'll usually do it before any type of public speaking, or when I'm just anxious, I'll just get in there. And so the 20 seconds at 49 degrees, I think it was 49 degrees Fahrenheit was really a good number because time and temperature, time, or duration, I guess, would be a better word, and temperature do matter, but you can do 20 seconds at a colder temperature, which is I prefer, or you can do a minute or longer at a warmer temperature. I think there was another study showing 59 degrees Fahrenheit at one hour was like two to three, but who wants to do one hour at 59? - Yeah, I'm familiar with that study. So this really reveals just how absolutely nerdy I am and maybe why some times and relationships in my life were challenged. I love reading the method sections of papers. So people can come at me with a number of things about papers, and I might miss something. Surely I miss certain things, like anybody does, but the methods I relish in reading the methods, and that paper is really interesting 'cause they had people sit in lawn chairs basically in swimming pools for an hour. It was chilly. It wasn't super cold. I mean 60 is not. It's not warm, but it's not ice-cold obviously. But an hour is ridiculous at some level. But the increases in dopamine were massive and lasted hours. So the mood enhancing effects that you report, you're not imagining that. Those are almost certainly a consequence of having slowly elevating but significantly elevated dopamine that goes on for hours. That's almost a dreamlike profile for dopamine. Because most everything else, like an Adderall or Ritalin, a cup of coffee and a pre-workout drink or something, is going to give you a big spike in adrenaline and dopamine and a big crash. And somehow, it creates this really nice, contoured profile. So whatever you're experiencing there is very nicely supported by the data. - Well, I need to get doing it more. I've had a couple of scary experiences going from hot to cold. - Can you explain? - Blood pressure changes, I think, where I basically went straight from a really hot jacuzzi. I was in there for like 30 minutes. I was doing heat stress. - Jacuzzi, okay. - Yeah, 104 degrees Fahrenheit. - [Andrew] That's toasty. - For 30 minutes, and then I went straight into, at the time, it was our pool, it was in February, it was wintertime, and it was 50. It was in the 50s. It was cold. And I was in there, and I was listening to Simon and Garfunkel, I was trying to stay in a long time, get on my cold, and I was trying to impress Dan 'cause he'll stay in there

for like 15 minutes. - [Andrew] Wow. - But I started to feel really blinkey, like low blood pressure or something, and I got scared, so I got out, and then I couldn't stand, like I had vertigo or something, and I was so scared. I was so scared. And I've had a couple of times too where just going straight from the sauna to it, to the Cold Plunge, where I'm starting to feel, I'm like, ooh, I feel a little blood pressure change or something. It makes sense. The sauna is causing vasodilation and the Cold Plunge or cold exposure is causing vasoconstriction, so it's like a very just shock to my system. And so, now, I wait. I wait like a few minutes before going in. But I do need to kind of like make the cold more routine. Because I talk all about the science. I'm familiar with all the science, and the norepinephrine or noradrenaline, it's affecting brain and mood. You know way more about that than I do. I know how I feel, and I know it's a neurotransmitter, and it is released, at least, in rats, they've shown. Or was it mice? I think it might've been rats. But multiple studies showing that it's released from the cold in the brain. - And now, in humans as well. - Oh, in the brain, they've shown. - So, in that study, we could put a link to this, it's published in 2000 in European Journal of Physiology, that big dopamine increase. They also looked at epinephrine and cortisol and saw some really. Yeah, so this has been done. - They did brain. Oh- - [Andrew] Oh, no, no- - The plasma, yeah. Yes, plasma. - Very hard to measure dopamine directly from the brain unless you're doing microdialysis. No, unfortunately, unfortunately, their skulls were intact. Fortunately, for them, unfortunately, for the research community, their skulls were intact, so they couldn't measure directly in the brain.

01:59:22 Tool 10: Cold Exposure, Mitochondria UCP1 & Heat Generation

But obviously, there's a correlate there. It's a very real effect. But the advantage of not doing it too often is that you're not cold adapted. Now, it's very hard for anyone to get truly cold adapted. Some people start to look forward to the cold. And what I think they're looking forward to is the feeling afterward, that dopamine rush. But, if you get cold adapted, then it certainly blunts some of the effect. - But I want to be cold adapted because that means I have more mitochondria in my adipose tissue and perhaps even muscle. That's been shown. - So maybe there's a good opportunity to, so cold and UCP1, if you could educate us on UCP1. I find this really interesting, and I learned about it from you. - Yeah, well, so norepinephrine actually released in the plasma. It does act as a hormone. Vasoconstriction is one thing it does, but it also regulates a variety of

molecular functions that have to do with adaption to cold, one happening to be, shivering is a very inefficient way to produce heat, which is what your body's trying to do when it's exposed to cold, and your muscles are basically contracting and producing heat from that, but that's just not very efficient. So the more eloquent way to do it, or elegant, I guess, way to do it is to basically have your mitochondria produce tons and tons of heat. So the way it does this is by activating a gene called UCP1, uncoupling protein 1. Norepinephrine is upstream of that, activating it. What that does is, essentially, so mitochondria are these little organelles inside of your cells that are responsible for producing energy. Usually, that's in the form of adenosine triphosphate, ATP, and that's what lets everything function inside of your body, from your neurotransmitter production to your heart beating, et cetera. However, you can uncouple your mitochondria. Basically, your mitochondria, they're like a little battery, so they have, well, they have a double membrane, first of all, their structure, but they have a negative charge on the inside, and they have a positive charge on the inner membrane, so in between the outer membrane and the inside part. - Like a neuron. - Like a neuron, yeah. - [Andrew] Yeah, cool. - So I guess, it's like a neuron. It's like a battery, negative and positive. Well, basically, you can uncouple that charge, and so that positive charge proton start leaking out of the mitochondria, and your mitochondria freak out. So this is called uncoupling it. It's maximum respiration, as we call it. They try to make as much energy. They're like, "I got to get that proton back, "that gradient, electrochemical gradient." And so they just go insane. In this case, it's uncoupled energy, so the energy they're making is actually heat, not ATP, but you're essentially burning substrate, so who cares? You're burning glucose. You're burning lipids. You're basically burning things and making heat. And so that's what uncoupling does, and that is a much more efficient way of producing heat than shivering. So, as you become more adapted, maybe the longer duration that you've stayed in the cold or the more times you've done it, you'll no longer shiver anymore.

02:02:30 Tool 11: Cold & Fat ‘Browning’, PGC-1alpha, Metabolism

You will start to then just do this uncoupling type of thermogenesis, as it's called. And another type of adaptation that occurs is you actually produce more mitochondria in your adipose tissue. And that actually happens, also regulated by norepinephrine or noradrenaline, through a protein called PGC-1alpha. And what that protein does is it makes more mitochondria in your adipose cell. So, per adipose cell, you're getting more

mitochondria. It's a beautiful way to basically make more heat. It's one of those things where it's like, your body's going, "Okay, I'm going to be exposed "to this cold next time. "How can I make sure I don't die? "Oh, I can have more mitochondria, "and I'm going to make more heat." And so you're making more mitochondria in your adipose tissue. And this is often referred to as the browning of fat. And the reason for that is because, if you look under a microscope at a lipid droplet, basically, a fat cell, not a lipid droplet, adipocyte, you'll find that it looks darker because there's more mitochondria in there. So it's referred to as browning fat. I don't want to get into the whole beige fat, brown. You know, there's this whole, I'm sure you've had experts on that talk all about that. - No, not yet. I always think of white fat, beige fat, brown fat. And beige is kind of, white can be converted into beige. - Right, and beige can take on thermogenic characteristics essentially, and so you can activate beige fat so that it's thermogenic in the sense that it's burning glucose and/or fatty acids and producing heat. So the more you expose yourself to cold, the more you can brown your fat, so to speak, and therefore you can tolerate the cold for longer periods, which people do notice, and you can then have the thermogenic qualities of having more brown adipose tissue or beige, activated beige, adipose tissue. You'll get a lot of naysayers out there saying, "Oh, brown fat doesn't regulate metabolism at all." And the reality is there's thousands of researchers trying to pill up brown fat and thermogenic. They're trying to make it a pill because it does affect metabolism. It's not the only thing. It's certainly, if you're obese and trying to lose weight, you're not going to do that just by doing cold exposure. You need to do dietary and exercise changes predominantly, but it does affect metabolism. And this has been shown in human studies, so it is an interesting, it's another possible mechanism for affecting metabolism,

02:05:08 Cold Exposure & High-Intensity Interval Training (HIIT), PGC-1alpha, Muscle

and that's an adipose tissue, but you also make more mitochondria and muscle tissue. And this is regulated, not via norepinephrine, but it is still PGC-1alpha, interestingly, not that anyone else really cares but me, and maybe you do, Andrew. - I'm eating this up. - So PGC-1alpha responds to norepinephrine in adipose tissue to make more mitochondria, but, in muscle tissue, it's unclear what the regulator is. Cold exposure does it. So this was shown at least in a couple of studies I've seen, where people that were exercising, I believe, or maybe it may have been men only that were exercising, did

some training, and then did cold water immersion, something like 50 degrees Fahrenheit, 15 minutes, and PGC-1alpha, which is a biomarker for mitochondrial biogenesis, which is the generation of new mitochondria. By the way, that's awesome. You want more mitochondria in your muscle. It's associated with improved muscle mass, improved endurance. Mitochondria are essentially, they're making energy in your cell. We don't make more mitochondria normally. You have certain inputs, high-intensity interval training, exercise can do it. - Can actually make more mitochondria. - Yes, yeah, and that's been shown in people. - Weight training or just high-intensity interval training? - I haven't seen weight training. I've seen it in high-intensity interval training, endurance training, but that doesn't mean that it hasn't been shown, I just haven't seen it, or that it hasn't been looked at. - That's good to know. I'm always looking for reasons to finally do more HIT type, high-intensity interval training work. I do weight training, and I do low-intensity cardio. - There was a brilliant study by, at the time, he was a postdoc, Matthew Robinson, and he's now gone on to start his own lab at the University of Oregon Health Science Center. - [Andrew] Great place, yeah. - And he did a study where both young and older people, they had this whole high-intensity protocol, which I can't remember what it was, but their protocol for X amount of time. I'm sure it was at least a month. They then measured biomarkers of mitochondrial biogenesis in their muscle tissue, and the amount of mitochondrial biogenesis in old people specifically, it happened in both young and old from HIT, from the high-intensity interval training, was, I mean, it was enormous, at least 50%, I think. - [Andrew] Fantastic. - So it was just like, whoa! And so, why would you want that? Well, mitochondria, your cells are turning over. You make new cells. You replace old ones. With your mitochondria, you don't really do that for the most part. You can. Mitochondrial biogenesis does happen, but you have to stimulate it to happen. And what happens with your mitochondria is they essentially are bobbing around inside of your cells, and then they fuse with other mitochondria, exchange all their content, mitochondrial DNA, and then fizz back apart. And that's how they kind of stay young-ish. But, as you age, you keep doing that

02:08:04 Tools 12: Exercise, HIIT, Tabata & Sauna

with the same pool of mitochondria, then you're going to get a bunch of old mitochondria mixing old stuff together, right? So, why wouldn't you want to bring up new, healthy, young mitochondria into that pool, right? So, in my mind, when I hear mitochondrial

biogenesis, I'm like, aging. That's the first thing I think of. So, anyways, cold exposure does that. Other things as well, so. - Amazing. And please, thank you for offering to somehow filter the level of detail, but I assure you that listeners of this podcast are familiar with drinking from the fire hose of mechanism, and that was really helpful. And, again, this is just one example of maybe four or five other things that you've said, at least, that are going to inspire me to change my behaviors. I'm going to start doing some high-intensity interval training. Dr. Andy Galpin was on this podcast recently, and he told me that the subtle zone 2 cardio and the weight training's great, but that I really should be doing some max heart rate work per week, going into max heart rate for 90 seconds, then resting and repeating that, maybe even mild repeats. I'm just curious, as a brief aside, before we talk about heat, what sort of cardiovascular or other types of training do you do? Do you do HIT? I imagine you are doing high-intensity interval training. If you could just give us a sense of the contour of your week as it relates to exercise. Because you've been very gracious in sharing some of what you do for supplements and food, what about exercise? - So it all depends on my week, of course, and what I've got going on with my son and my work schedule. But I do a lot of high-intensity interval Tabatas on a stationary cycle. I use Peloton because I just like that instructor there telling me what to do, and then me competing with everyone else. I'm like, ah, you know? So it works for me. - You're revealing something about your psychology. This is good. We just learned about. So this podcast is actually just a decoy for psychological assessment of the guest. No, I'm kidding. So, now, we know you're competitive. Good. - [Rhonda] Yeah. - That explains a lot of how you got through graduate school and then do what you do. So you're getting on the Peloton, and what does it look like for someone who's not familiar with Peloton? I know what they are, but I've never been on one. You're pedaling against the instructor for how many seconds? - So there's a bunch of people that are online, either doing the class with you at the same time or all time doing it, so you can kind of toggle on what you want, and you can try to compete against the all time number. - So it's really competitive. - [Rhonda] Oh, yeah. - Okay. - And the instructor is just there to, like, whip you. You know, make you. The brilliance with Peloton is... I used to do what's called rush cycle. It's basically you go in and group cycle and have an instructor there, and you do all this high-intensity interval training stuff. And I loved it because there was a competitive aspect to it that had me working harder than I would work if it was just me in the room, like without an instructor or anyone there, and it was just like, I'm at a gym, any gym, and I'm just on a stationary cycle listening to a podcast, doing something,

which is fine if that's your groove, right? But there is something about that group setting that kind of holds you accountable too, right? And the Peloton made it somehow virtual. It was amazing. And I remember being back at rush cycle, this is before pandemic, and people talking about Peloton in my class, and I'm like, "Oh, that's ridiculous. Why would I do that? "That's never going to work. I need to be here." And then, the pandemic hit and I was all over the Peloton, and it works for me really well. So I tend to do that at least three times a week. Sometimes I do it more, like I'll do four. And I do a 10 minute, just 10, because it's efficient, and I push my ass. I push myself really hard. - That's the Tabata. - It's 20 seconds on, 10 seconds off, and it's 10 minutes. - And on means you're pedaling like your life depended on it. - [Rhonda] You're maxing it. - And there's a lot of resistance in the pedals? - I always do resistance. I like the power. I do the power. There's a part where you're sitting cycling, and you're trying to go really fast, but I always crank the resistance up. I always go above what they give me. And then, there's a part where you're standing, and then you really crank the resistance up, which I really do, and you feel it in your glutes. - It's like going up a hill. - Yeah, exactly. And so they break it up, and most of the time you'll have those two parts. And I love the efficiency of it. You get it done. And people sometimes hear me, go, "10 minutes? "Oh, really? You think you work?" I'm like, look, you do max Tabata for 10 minutes, and it's intense. - Yeah, most people can't sprint for the gate of an airplane they're about to miss, carrying a backpack. So, if I think about that, and I've just described myself, sprinting through the airport and going, "All right, Andy Galpin, "I got my 90 seconds max heart rate in for you, "carrying this thing." But 20 seconds on, 10 seconds off, repeating that over and over for 10 minutes, so, by the time you're done, you're cooked. - And then, because I'm competitive during the recovery that they give you at the end, I'm pushing it max, so I get the numbers higher. - Great. So three times a week. - [Rhonda] It's a trick. - Yeah, three times a week, and then I always have my sauna on preheating up, takes about an hour and a half, and I get it to about 189 degrees Fahrenheit. I hop right in the sauna after my Peloton. - So the elevated heart rate continues. Is that the rationale? - Yeah, I literally down a bunch of water, and then I get in, and then I either read a science paper,

02:13:30 Tool 13: Sauna, Endorphins/Dynorphins, Mood

prepare for a presentation or a podcast, or I hash over things in my mind. And it's interesting because something about getting in the sauna, I think the stress, the heat

stress of it. So I started doing the sauna in 2009 in graduate school. - You're an early adopter. - I started doing it every day. I lived across the street. I lived in a studio apartment with Dan. We lived in this small studio apartment, smallest apartment you could ever imagine, and it was across the street from a YMCA, 'cause I was poor in graduate school, very poor, very poor. - I recall. I lived in my lab. - Wow, really? - But, then again, I lived in my lab as a postdoc. I admit, I lived in my lab with my bulldog as a faculty member for other reasons. But I get it. When you're a graduate student, you're poor, basically. - Yes, and so I used to go to the sauna before going into the lab, and I started noticing that I was, all of a sudden, able to handle stress better, like the stress of my six-month setback because of a failed experiment, which is crushing, on top of the pressure from my advisor and my own pressure 'cause I'm very competitive with myself, and I put a lot of pressure on myself. So I was having a hard time. I was very stressed out in graduate school. And this sauna started to really noticeably affect my anxiety and my ability to handle stress. And I was like, what is going on here? So I started looking into the literature and started getting interested in the effects on the brain. And, in fact, at the time, I had a friend who was not actually experimentally but theoretically looking into the opioid system. So, when you get in the sauna, you release a lot of endorphins. Endorphins are the feel-good opioids that make you feel good, but you also release something called dynorphin. And dynorphin is an endogenous opioid that binds to a receptor called the kappa opioid receptor. Dynorphin is responsible for that dysphoric feeling when you're in the sauna and you're hot, and when you're running, doing exercise, and you feel uncomfortable. Well, I think that's dynorphin. I'm speaking absolute, but I think it is. - No, I think it is. I mean, there's evidence in alcoholics that some of the symptoms of withdrawal that they experience are related to dynorphin. And dynorphin is known to negatively impact the dopamine receptor system. So, basically, it's the feel-like-garbage pathway. - Right, you feel like garbage, and so you think that that would not be good, but this is where my friend comes in. He was looking at the effects of treating morphine or heroin addiction. And people that are using those drugs, they, basically, the endorphins or the morphine or heroin, they bind to a receptor in the brain called the mu opioid receptor. And, as they take these drugs, that mu opioid receptor becomes downregulated, and so you need more and more of the drug to feel as good as you did. Well, endorphins also bind to that receptor. And he was looking into some of the other drugs that are like salvinoria, salvinorin, or something. Salvia it's called. It binds to the kappa opioid receptor. It also makes you kind of feel

uncomfortable. Anyways, he had put some studies in front of me that showed basically binding of either dynorphin or whatever ligand to the kappa opioid receptor basically sensitizes the mu opioid receptor to the feel-good endorphins and also changes, I think it also upregulates it or something, so, basically, there's a lasting effect of feeling good. So the endorphins that you release later from hugging someone, or a joke you're laughing at, or whatever, you feel it for longer, right? And so, anyways, with respect to the sauna, it's a big sort of hypothesis of mine. I did kind of publish that part of my hypothesis in a review article, but I do wish more people would kind of look into that. That'd be amazing.

02:17:45 Tool 14: Mild Stress, Adrenaline & Memory

But what I was getting at, I think, was, I would use the sauna to memorize things. This is way back in the day, and I still do it. And I wanted to talk to you about this because you're a neuroscientist, that there's something about being in the sauna. And I don't know if it has to do with the stress response. Like, when you have an emotional trigger, you remember things better, right? - Absolutely. There is a clear and known explanation mechanism for this. - So, in the sauna, you also release norepinephrine, just like you do in the cold. There's a lot of overlap. It is a stressor, but I use it to remember things. Like, I'm going through something. I want to go through a presentation, or a talk, or a podcast, or whatever. And I go in that sauna. And you should try it, if you haven't already. I don't know if you have. - I have a sauna and Cold Plunge now, and I haven't tried preparing. I read books in the sauna in the evening. It's a time I insist on having my phone out of there, initially because I thought I'd cook the phone, but also just to get some separation from the phone and screens in the evening, so I read books. The only challenge, sometimes you're dripping sweat onto the books, but I'm willing to forego a few pages of a book. The idea that being in this semi-stressful environment would aid in the learning and retention of information is really well substantiated. There's this beautiful work by a guy named James McGaw. I don't know if his lab's still active, but he was at UC Irvine for a while, and then I think at University of Arizona as well. They have a great memory group at both places, very strong in learning and memory, both places. And he was the one that really defined this kind of inverted, u-shaped function for the relationship between adrenaline and memory. Basically, if you're too relaxed and not stressed enough, you're not going to remember any information. At peak levels of stress, you actually are a memory machine, at least within the context of whatever it is you're trying

to learn. So what you're describing very well matches with that. Then, of course, it tapers off as you really increase adrenaline to the point where people are starting to lose autonomic function, where they're panicking basically,

02:19:53 Sauna, Vasodilation & Alzheimer's and Dementia Risk

but obviously, you're keeping it in range. The other thing that I would like to ask you about is, in the sauna, of course, there's vasodilation, and perfusion of blood to the brain is a wonderful way to enhance cognition. There's even some really nice data showing that, during inhales as opposed to exhales, people are better at learning information. Believe it or not, during the inhale, you're taking in and absorbing and remembering more than during exhales. And these are beautiful studies done in humans, of course. So I can imagine that vasodilation, getting more perfusion of blood to the brain, plus a little bit of stress, or maybe a lot of stress from the epinephrine, and then, of course, there's going to be the, I don't want to call it placebo, but there's going to be the context, the condition, place context of it. Like, if we had a good experience remembering something in the sauna once, the positive association effect of that location is real. Just like, if people go to a new city and they get robbed, like, if you go to Cincinnati, I've never been to Cincinnati, but you get robbed in Cincinnati, your purse gets taken or your wallet gets taken, you kind of hate Cincinnati as a tourist. But that could happen in any number of different cities, right? The opposite is also true, so if something good happens someplace. So I'm imagining that it's a combination of those effects, but it would be very hard to do this in the cold. I feel like the cold is a very potent. I think it takes you too far down that curve, the McGaw curve. - I have to sing songs or something when I'm in there. - [Andrew] Distract yourself. - Oh yeah, I sing songs. - But afterward, you're very efficient at learning. - After I am. With respect to the sauna, the vasodilation does occur, so there's a lot of overlap between moderate-intensity aerobic exercise and heat stress. As you can imagine, when you're exercising, you're elevating your core body temperature. You're sweating. When you're actually in the sauna, blood does get redistributed to the skin to facilitate sweating, but, much like exercise, blood flow in general is improved to the brain, to the muscles, everywhere. So, I think, generally speaking, and there's studies showing that sauna use is associated with a much lower risk of dementia and Alzheimer's disease. People that use it four to seven times a week have greater than 60% reduction in dementia and Alzheimer's disease risk compared to

once- - Amazing, how many? Oh, sorry, I didn't mean to cut you off. You said people who use it, I apologize, but maybe you could tell us again, people use it four to seven times per week have... - They have a greater than 60% reduction in dementia risk and Alzheimer's disease risk compared to people that use it only one time a week. People that use it two to three times a week have something like a 20, a little greater than 20% reduction in risk. There's a dose-dependent effect on dementia risk and Alzheimer's disease risk. It also has a profound. There's a big link between the cardiovascular system and the brain. Obviously, blood flow, a big one, right? You need to get blood to your brain. But cardiovascular mortality, so mortality from cardiovascular disease. If people use, or actually this was men. If men use the sauna four to seven times a week, it's a 50% reduction in cardiovascular related mortality compared to one time a week. Again, dose-dependent manner, two to three times a week is something like 24% lower death from cardiovascular disease. There's also lower sudden cardiac deaths, like a heart attack. That's like 60 something, greater than 60% lower, if men use it four to seven times a week versus once. Again, a dose-dependent thing. The thing that's so profound there also to me when, again, looking at the methods, when I look at the data, and this is all work from Dr. Jari Laukkanen. He's in the University of Eastern Finland and just one of the world experts on sauna use, especially with respect to cardiovascular health. What some of his data has also shown is that, if you look at the duration, the time spent in the sauna, so I mentioned the temperature I do is about, I do 189 degrees Fahrenheit. Typically, I go in there. I'm pretty heat adapted. So the more you do the sauna or any sort of heat stress, whether it's a hot tub or jacuzzi, you become adapted. You basically start to sweat at a lower core body temperature to cool yourself down. All these sort of physiological changes start to happen earlier. And so, I stayed in for like 30 minutes, so I stayed in a long time. That's a lot. You have to listen to your body. Most of the studies that I just talked about, the duration, the time spent in the sauna, when I said 50% reduction in cardiovascular disease related death, what was shown was that men that were in the sauna for only 11 minutes, even if they used it four to seven times a week, that reduction was only like 8% instead of 50. It had to be greater than 19 minutes, so like 20 minutes is the sweet spot, at about 174 degrees Fahrenheit. And most of the saunas in Finland, by the way, they're humid, so they put hot water, they put water on hot rocks to create steam, so it's usually between 10 to 20% humidity in the Finnish sauna. So those studies were, I would say, most of the time, you're going to find that their humidity is also elevated. But, to me, the dose-dependent nature of it and the

duration, to me, that's very strong data that this is more causal than some corollary thing. Because that's always the problem with observational studies, including these, which they corrected for a whole host of factors, like cholesterol, exercise, just everything, everything under the sun, they corrected for those. And, on top of that, you have the dose-dependent nature of the duration, the time spent in the sauna, and the frequency. So, to me, it's like, something's going on here. - Yeah. - Plus there's been studies,

02:25:30 Sauna Benefits, Cardiorespiratory Fitness, Heat Shock Proteins (HSPs)

intervention studies, where it's comparing directly, head-to-head moderate-intensity aerobic exercise on a stationary cycle to 20 minutes in a sauna. Physiologically the same things happen, so heart rate elevates while you're doing the activity, blood pressure increases while you're doing the activity, but then, after, heart rate decreases, resting heart rate decreases below baseline, blood pressure is improved, so it decreases below baseline. This is happening the same in moderate-intensity cycling versus sauna. So, again, the sauna, this heat stress, there's something about it that really mimics this moderate-intensity aerobic exercise, which is really great for people that can't go for a run, that can't even get on a bike, so disabled people. Granted, there are some safety concerns. They're pretty mild, but they do exist. So people that had a recent heart attack or have some rare kind of heart disease or problem. Drinking alcohol, never do that. Elderly people prone to low blood pressure. Always talk to a physician before doing the sauna. It is stressful. - Pregnant. - Pregnant women, yeah. I definitely avoided saunas when I was pregnant. I think it's very relevant for disabled people and also people that are sedentary or been sedentary most of their life. Like, my mother, I've been able to get her in the sauna because she's not. I did get her on the Peloton once, but it's really much easier. She feels like it's a spa treatment, and she can listen to her music in there. Like, I care about her health, but she's mostly been a sedentary person. And so I find it much easier to convince her to get in the sauna than to get on Peloton. Ideally, you do both. The question would be, well, I exercise, I run, I do my high-intensity interval training. Why do I need to get in the sauna? And the reality is, and so I published all this in a review in the Experimental Dermatology last year, I guess, late last year. Basically, cardiorespiratory fitness, which is a marker of, it's a marker of health. Cardiorespiratory fitness is improved in people that do exercise and sauna compared to exercise alone or sauna alone. So, for those healthy, fit people out there already exercising, there's a

synergistic effect by also adding a sauna into that routine. And, to me, that's great. And there's so many beneficial things happening with the heat stress. In addition to mimicking aerobic exercise, there's the heat shock proteins that we talked about earlier. And those, it kind of brings me back to my early days of science when I at the Salk Institute for Biological Studies doing research on little nematode worms that we or someone else injected amyloid beta 42, the peptide, the 42-amino acid peptide that is involved in amyloid plaques found in the brain correlating with Alzheimer's disease and other brain disorders. We injected those into the muscle tissue of worms. And, basically, these worms become paralyzed with age because the aggregated proteins, these proteins aggregate. Well, heat shock proteins, one of the main things they do is they basically make sure the proteins inside of your cells maintain their proper three-dimensional structure and are folded right, and so they don't, they're not prone to aggregating and forming these plaques in your arteries and also in the brain. Back to my worm studies I was doing, I would elevate heat shock proteins in these worms, and it would totally correct the problem, where they would no longer become paralyzed. They'd move around like they were young. So, many animal studies have been done looking at Alzheimer's disease, a human-like Alzheimer's disease in a rodent, and heat shock proteins protecting from it. Heat shock proteins are robustly activated in humans. This has been shown to, even 50% higher over baseline levels after just 30 minutes at 163 degrees Fahrenheit in the sauna. And they stay activated, at least, in rodents, for 48 hours, at least. So having these heat shock proteins around, making sure they're properly taking care of our proteins so they're not aggregating in our brains and in our plaques, could be another potential way that sauna's protecting from Alzheimer's disease and other cardiovascular health as well as longevity. There's people that have SNPs in heat shock protein factor 70 that, if they have one of them, so they got one from their parents where they have more active heat shock protein 70, they live on average one year longer than people that don't have that SNP. And if they have two versions, if they got one from their mom and one from their dad, they live on average two years longer than people that don't have that SNP. - [Andrew] Wow. - So it's also been associated with human longevity as well as in lower organisms. So you can heat shock a worm or a fly and they live 15% longer. This is work done by Gordon Lithgow at the Buck Institute years and years ago. So, anyways, I guess what I was getting at was the heat shock proteins are part of that stress response pathway that we talked about earlier. They're also activated by cold as well. Cold shock does activate heat shock proteins. Not

as robust. Sulforaphane activates them. Again, it's one of the reasons I think we should get all of these things because they are more robust inputs. The input activating mechanisms are more robust for different ones. So there is crosstalk. I guess it'd be more accurate to say there's overlap. But it's also like, you want to get the most robust from all of them, right? I do, so that's why I want to do the sauna and exercise and eat my broccoli sprouts and all that stuff.

02:31:29 Insulin signaling, FOXO3 & Longevity

- It's super interesting. A couple of questions came up for me. One is, you mentioned these SNPs, these nucleotide repeats, basically genes that some people have more of or less of than others that can predict longevity in some sense. Is that the FOXO3 pathway? - That's one that can. Yeah, I mean, FOXO3 is, in fact, if you go back to the worm studies I was talking about, that was one of the first things when you see it with your own eyes. You can take these worms that, you basically decrease their insulin signaling pathway and their IGF-1. Worms have what are called homologous genes, so they have a lot of similarities to humans. They have an insulin-like receptor, they have an IGF-1-like receptor, and they make something like FOXO3, which we have. And, basically, if you decrease that insulin signaling pathway, then FOXO3 is always active in those worms, and they live like 100% longer. And not only do they live longer, they are like a very young worm. I mean, you look at this thing and you're like, "This looks like the worm that was just born like hours ago. "What's going on? This thing's at the end of its life." Now, as a side note, the thing that always got me on this was, by the way, this was discovered by Cynthia Kenyon. This was back in the '90s. Honestly, I'm not sure that anything has been as exciting in the worm world since then, but I thought it was a really big finding. The only caveat there is that the worms go through this dauer. It's called a dauer stage when this happens, when you decrease their insulin signaling and stuff, and they go into this like metabolic stasis. They're not eating as much or moving. And so it's like, okay, well they live 100% longer, but they go into this weird state, you know? - I know people like this, some in the longevity community. They know who they are. But they'll get the last laugh 'cause I'll be dead,

02:33:22 Tools 16: Sauna Protocols, Hot Baths & Fertility

well fed but dead, and they'll still be going. So, in terms of the many data on sauna, and I also just want to acknowledge these Finnish groups that did this work. It's really pioneering, right? When you think 20 years ago, long before social media or any of this, and they're out there, up there, I should say, measuring cortisol and growth hormone and all this stuff in people getting in and out of sauna. Very, very interesting. So 20 minutes seems like the threshold at 170 degrees Fahrenheit. More times per week seems to be better than fewer in terms of all-cause mortality, cardiovascular risk according to what I just learned from you. - Four would be a good, I think, minimum effective dose. - Four times a week, and you combine it with the cold. I've also seen a protocol, where, it's a very extreme protocol, I don't recommend this to people right off the bat, where they had human subjects get into the sauna for 30 minutes, get out for five, 30 minutes, get out for five, 30 minutes, for a total of two hours of exposure, but that was what led to these massive 16-fold increases in growth hormone. And they had to do it very seldom. So it sounds like these protocols you're describing, 20 minutes done four times per week, are far more reasonable for most people to access. But I know people are probably desperate to know, what if they don't have a sauna? A sauna is kind of a unique item, so I have a couple questions. Can people use hot baths? With the appropriate warning, of course. Without getting into description of the mechanics and the underlying biology, it's pretty obvious that the testes, if they get too warm, you'll kill sperm. That's the reason why the testes are housed in a structure called the scrotum that can move around, so just to be, you know, we are biologists, just talking about realities here. So, if you're trying to conceive children or keep your sperm healthy, guys should probably stay out of warm, hot baths. - For at least six months. That's been shown. - [Andrew] Six months. - So sperm motility goes down and sperm production goes down, but that is completely corrected if they stay out of the sauna for six months. So through six months later, it's back to normal. - Great, that's a very useful information, I'm sure, to a number of people out there. So, if people don't have access to a sauna, and we get this about cold too. People always say, "What about cold showers?" And I always say, well, the studies have mainly been done on immersion 'cause it's hard to keep things controlled in cold showers. It just doesn't make for a very good experiment 'cause you get a bigger person, less of them is under the shower, and so it doesn't make for a good experiment. So it's not as good as immersion, but, with heat, I could imagine that a hot bath would work almost as well. - Yeah, so there's been some studies looking at, for example, activation of heat shock proteins, also brain-derived neurotrophic factor

increases with heat stress. And so the hot bath at around 104 degrees Fahrenheit, which is typically what studies will use for temperature, which is actually cooler than what I. I crank my bath hot. It's so hot. - But you're very heat adapted. - I'm very heat adapted, yeah. And it's 20 minutes from the shoulders down, and that is a very robust activation in heat shock proteins and in brain-derived neurotrophic factor. And then, heat shock proteins are also protecting against muscle atrophy, so that's also having to do with the protein structure and the muscle tissue as well. And this has been studies in animal data as well as some recent human data as well. It was local hyperthermia or local heat treatment, but essentially it showed that it protected. There was a study where they were looking at muscle disuse, and it was something like the local heat treatment prevented almost 40% of the muscle atrophy from disuse. And it's funny 'cause I used to use the sauna when I was injured and stuff. I would go in the sauna. Because I didn't know at the time 'cause I was a graduate student, but I knew just from experiments that I'm not losing as much muscle. I feel better. At the time, I was reading all about the growth hormone and stuff back then. And I knew about heat shock proteins, so I kind of knew, but that data wasn't around yet, and so now we have the data. And I've always felt like I wasn't losing my muscle, like I should've been, when I was doing the sauna. And I was doing it literally seven days a week. It was hardcore. - This is also during graduate school?

02:37:41 Tool 17: Exercise & Longevity, Osteocalcin

- Yeah, now, I'm doing the sauna, like a bare minimum, I do three, but I try to do four. It all depends on my schedule. I also like to do long runs. Long being like three miles, not like campaigns, which are long. But I really, for me, and we were talking about this earlier off camera that the runs, for me, are for my brain. And I'd get this mind-wandering effect, where I daydream and I think about things. I work through problems. I get creative. I come up with ideas. And this is all happening on the runs. And so I miss my runs if I don't do 'em, and I miss it because of the brain effects I get from it. And when I exercise, it's funny, because I'm a female, and you'd think that I'd be exercising to stay fit and in shape and care about my figure, but, when I exercise, literally what I'm thinking about is my brain. And I'm like, "This is the best longevity drug there is. "This is it right here, Rhonda. "You're always wondering. You're always wanting to know. "You're wanting to do the best." If you don't exercise, you're missing that essential dose. And so

that, for me, is the motivation, the dopamine seeking thing I'm looking for. Admittedly, I do not do enough strength training. And I have to do it. Have to, have to, have to. I'm so after the endurance and the HIT, and I really need to add that in. Because muscle mass is also extremely important for aging as well, you know? So that's my fault. - Well, the brain effects are really interesting. I also run. I try and get one longer run per week and a few other runs, and I do it without a phone. I don't listen to podcasts. I occasionally will listen to music, but I really try not to. I also find that my mind solves problems. I feel like it washes out the cobwebs, so to speak. Some of the most brilliant and prolific neuroscientists that I know who've had very long careers. Eric Kandel, Nobel Prize winner at Columbia, comes to mind for all his work on memory, used to swim a mile a day, and now I think swims half a mile a day, but he's in his late 90s and he's still sharp, which is incredible. And his lab has done some work showing that any load-bearing exercise repeated, so endurance work, unlike the Peloton or cycling, that's really load-bearing, although you're cycling really hard with the resistance, but causes the release of osteocalcin from the bones, which acts in an endocrine way, sort of like a hormone, can actually travel to the hippocampus and, at least in these animal studies, induce the proliferation of neurons, growth of synapses, BDNF, a number of downstream things, which kind of makes sense, if we were to put a just so evolutionary story on this. A body that's active can signal to the brain that the body still needs cognition. An inactive body, in some ways, is depriving the brain of any signal about what the body is doing, right? Obviously, I'm making this up as conjecture, but we know in various ocean animals that they'll swim around for some period of their life, and then they'll have a completely stationary portion of their life, and basically, the brain degenerates. You don't need much of a nervous system if you're not moving. So I think there's really something there, and also just letting the ideas and mind drift. I love that you, and I appreciate that you shared your protocols, because I think, right now, we're in an interesting time in public health information history, where people are just kind of getting bombarded with cold is good, heat is gold. Cold is good. Heat is good. Excuse me, I misspoke. There are all these micronutrients, and, of course, macronutrients are important too. Today, you've really enriched us with the description of the underlying mechanisms and the logic behind them, but also sharing what you do is really informative because I think people need a jumping-off place, and obviously they need to start someplace, and getting heat adapted, et cetera, takes time. But I really appreciate that you're willing to share your protocols

02:41:37 Tools 18: Red Light Sauna? Infrared Sauna? Sauna & Sweating of Heavy Metals

and that you do the things that you teach and educate people about. As a final question, because I have to ask, red light sauna or no red light sauna? I've been a little bit vocal about my feelings that none of the red light saunas I've ever been in got hot enough, and it was frustrating, so I feel like it's neither here nor there. However, I do acknowledge that red light and low-level light therapies are now known to do a number of interesting things. There was a Nobel Prize in 1908 for phototherapy for lupus, so it's not like a new thing the idea that light could do things positive for our biology. But, do you have a red light in your sauna? Do you think it's useful? And I mention this because this is the number one question I get about sauna, red light or no red light, or some intermediate answer. - So I don't have an infrared sauna, but I have a sauna that has lights. It makes red light, but I don't think it's the red light that you're talking about. - Okay. - It's not activating it at a specific wavelength, which is... - It's usually, so the range that seems to be helpful, and, I confess, I use a red light panel for other things, is 670 nanometer out to about 720 nanometer, so it looks like red and very dim lights, dim red and bright red. And the idea is that red light can travel, the photon and energy is such that it can travel down through the deep layers of the dermis of the skin. - I don't have a red light in my sauna. I don't know if it's essential or not. I don't think so. Based on all the studies I've talked about, I think, the potential effect on mitochondria is interesting. I do think there's a lack of really good, solid evidence in humans, but that might only be because it's just not studied enough. And that's usually the case, so perhaps. There's the Joovv, right? The Joovv. They have those red light panels and stuff. - Joovv and KOZE are the two ones I know, K-O-Z-E and Joovv. As far as I know, I'm probably going to insult both companies at the same time, but I'd rather insult them both at the same time than just compliment one or insult one. Both of them seem excellent for getting the appropriate wavelengths of red light. And I do not have a relationship to either of those. - Yeah. Well, I personally think that the sauna in and of itself, it's about the heat stress. And typically the question I get is, infrared sauna or regular sauna? And there are some differences as well. Infrared saunas. Maybe the infrared saunas are the ones that have the red light that you're talking about. Infrared saunas only get up to around 140 degrees Fahrenheit. So, as I mentioned, the studies were about 174 degrees Fahrenheit. And so you really

have to stay in a longer period of time. However, there have been some studies coming out of Japan. They use infrared sauna. They have this whole protocol. It's called Waon therapy. They get people in infrared saunas, and then they wrap 'em in a towel, and they stay warm for X amount. So the whole protocol ends up being like an hour long, but, again, it's 140 degrees Fahrenheit, so it's an infrared sauna, and it's been shown to improve a variety of, like, coronary heart disease and conditions, heart-related conditions. There have been some improvements. So, obviously, there's evidence that infrared saunas can be beneficial for cardiovascular health. I've used infrared saunas many times at my in-laws. They have an infrared sauna. And I have to crank that thing up for a while until it's maxed, and then I have to sit in there for an hour at least. I do sweat a lot, and that's another thing we didn't talk about. You do sweat some heavy metals. And some heavy metals are excreted predominantly through sweat and others through urine. So, for example, cadmium, there's like a 125-fold increase in cadmium excretion from sweat when you get in the sauna. Also, lead is something like 17-fold excretions higher. Another one is aluminum. It's about fourfold higher. So infrared, you do sweat a lot too, and that's because the main difference is that you're heating your body up through thermal radiation versus the ambient air. A standard sauna is a heater, and the heater's heating up the air, and that's how you're heating yourself up. So it is a little bit of a different mechanism. I prefer regular saunas. Most of the data out there is from the heat stress itself. Like, your heart rate's elevating when you're in there. You're feeling hot. You're getting that cardiovascular. That's what you're feeling when you're in a hot sauna. And that, for me, takes a really long time in the infrared sauna, like at the very end. But I do think there are some benefits from infrared. And they are more affordable. They're less of a fire hazard. But, again, hot baths are, I think, a good alternative modality for heat stress compared to like a regular sauna. - Great, that's a really helpful answer. Like I said, I use the red light, but not in the sauna. And thank you for reminding us of that 174 degree Fahrenheit threshold that is mainly used in all these studies. We covered a lot of territory, but I just want to thank you again. It was extremely thorough and extremely informative. My notes always look a little bit like they were drawn out by a macaque monkey who has no knowledge of the English language, but I can decipher this to tell you that there are at least 10 additions to my current protocols that I'm going to add. And I'll have lots of questions, so I apologize in advance for that. But, on behalf of the listeners and just directly from me, thank you so much for your time. I learned a ton. - My pleasure. Thanks for having me on. It was a really awesome

conversation, so I enjoyed it a lot.

02:47:20 FoundMyFitness Podcast, Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Patreon, Momentous Supplements, Huberman Lab on Instagram & Twitter

- Let's do it again. - Totally. - [Andrew] Great. Thank you for joining me for my discussion with Dr. Rhonda Patrick. I hope you found it as interesting and as actionable as I did. Once again, if you'd like to learn more about Dr. Patrick's work, sign up for her newsletter, and, to listen to her excellent podcast, go to foundmyfitness.com. You'll find links to the newsletter as well as the podcast there, or you can go direct to the podcast by going to FoundMyFitness on YouTube, FoundMyFitness on Apple, or FoundMyFitness on Spotify. And, once again, the newsletter is foundmyfitness.com/newsletter. If you're enjoying and/or learning from the Huberman Lab Podcast, please subscribe to our YouTube channel. That's a terrific, zero-cost way to support us. In addition, please subscribe to the podcast on both Spotify and Apple. And, on Apple, you have the opportunity to leave us up to a five-star review. If you have suggestions of topics or guests or feedback of any kind, please put that in the comments section on our YouTube page. In addition, please check out the sponsors mentioned at the beginning of today's podcast. That's the best way to support this podcast. We also have a Patreon. It's patreon.com/andrewhuberman. And there, you can support the podcast at any level that you like. As also mentioned at the beginning of the episode, we are now partnered with Momentous supplements. So, if you go to livemomentus.com/huberman, you'll find what we firmly believe to be the highest quality supplements available in the specific dosages that match the peer-reviewed science and recommendations made on various episodes of the Huberman Lab Podcast. You'll also find specific protocols of how much to take and when, what time of day, what time of night, et cetera. And you'll also find behavioral tools that can synergize with those supplements. Many of you will also be pleased to learn that Momentous supplements, of course, ships within the United States but also internationally. If you're not already following us on Instagram and Twitter, please do so. It's hubermanlab on both Instagram and Twitter. There, I teach science and science-based tools, some of which overlap with the content of the Huberman Lab Podcast, but much of which is distinct from the content

of the Huberman Lab Podcast. Thank you, once again, for joining me for my discussion with Dr. Rhonda Patrick, and, as always, thank you for your interest in science.