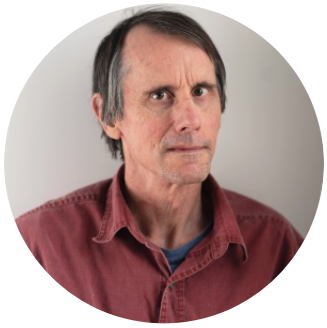
Intermittent Fasting And Optimizing Mitochondria

Ari Whitten, MS
with Mark P. Mattson, PhD



Ari Whitten, MS
So welcome. Dr. Martin. Thank you so much for coming on to this summit. It is an absolute pleasure to have you. Your you're one of the most prolific researchers in the field of were medic stress one of my primary areas of interest and a topic that I think is of great importance and is greatly underappreciated. So I feel this topic your topic is an enormous contribution, enormously important contribution to to this summit that I want to encourage everybody to listen to and maybe listen to twice. Even so, welcome to the summit. I appreciate you coming on.

Mark P. Mattson, PhD
I'm glad to meet you and talk with you. And I look forward to the conversation on good stress.

Ari Whitten, MS
Yes, absolutely. So maybe we can start there. So there is still a lot of people who are not quite familiar with this idea of good stress and wear stress. The word stress is really immediately associated with all bad things. And a lot of people are under the impression that sort of we need to go through life in a way where we minimize stress as much as possible and avoid stress and eliminate stress from our lives. And the elimination of stress equals good health. So can you explain why what's missing from that paradigm?

Mark P. Mattson, PhD
I think one way I look at this, I'm kind of a cell biologist. So I you know, I pretend I'm a cell and nervous cell in the brain, a muscle cell in your biceps, a liver cell, you know, whatever cell in your intestine and the easiest way to think of this is from the standpoint of exercise, because that's what most people can relate to during exercise. Your muscle cells are under a lot of stress. There's a big burst of free radical production in your muscle cells. Their energy demand obviously goes way up, so they're requiring more ATP. So they're under a bio energetic type of stress. And it turns out that that's good as long as it doesn't last too long and as long as it's not too intense. In fact, in the long term, if you have these intermittent bouts of mild stress exercise, your muscle cells get bigger, stronger, better endurance and more resilient to age and disease. And some of the things happened with cells throughout your body in response to various physiologic stresses. In the case of nerve cells in your brain, when you exercise them, when you use them, they become stronger, more resilient, and better able to cope with life's bad stresses. And actually, it

turns out pretty much the same things are occurring in muscle cells and brain cells when they're active. Again, there's these ion sodium influx. So there's a big what we call ionic stress, big increase in activity. The ATP demand increased free radical production, but it turns out that the actual ions that flux into the neurons, for example, calcium, the free radicals that are produced superoxide free radical in the mitochondria and some of the downstream things. Hydrogen peroxide, which is not a free radical, but it can generate free radicals. Those are actually signals that signal genes in our DNA, and particularly genes that encode proteins whose function is to help the cells be more resistant to future stress.

And then when you get you know, we'll go into more detail on this. I'm kind of summarizing it when you have these repetitive bouts of metabolic challenge, whether it's exercise, fasting, using your brain cells and then recovery, resting, eating, sleeping, it kind of optimizes the health and what we call plasticity of the cells. In the case of nerve cells in the brain, we find with running will exercise in mice or rats and intermittent fasting every other day, fasting over a period of several weeks. These genes and proteins increase that, help them resist stress, but also actually with an increased number of synaptic connections between nerve cells and and so on.

So anyway, that's kind of the idea and that's in addition to pretending your cell when you know and thinking about this and what you're experiencing as a cell under these things that we know are good for overall health and maybe have anti-aging effects, think about it from an evolutionary perspective. Animals in the wild, they have to get food to survive and they have to reproduce. And to do that, to get food, for example, up here, a predator, which is perhaps the easiest way to think about this. Pretend you're a wolf and you're in a pack and it's winter. And I'm from Minnesota originally, so in the winter in Minnesota, unlike Costa Rica, if you even have a winter, I don't know now a.

Ari Whitten, MS
It's a wet and dry season.

Mark P. Mattson, PhD
Right.

Ari Whitten, MS
So rains part of the year, but it's still very hot.

Mark P. Mattson, PhD
You look out the windows, you look out in the woods and Minnesota in the winter and you see white and you don't see any vegetation. And so, you know, animal, the both the prey and the predators out there survive the winter. Actually, the the prey like deer, for example, they actually dig through the snow and get stuck underneath. But like wolves, they have to be able to they often go weeks. It's not unusual for them to go a week or more without killing a prey animal. And so they're hungry, gone away, no food, and they have to be able to work together with their pack

mates to corner first, you know, track down corner and then work together to kill the deer in this example. And so their brains and bodies have to be functioning really well in that food deprived state. So they're under stress. That's how stress actually turns out during exercise. Like, you know, if you go on a run, go on a bike, ride, your cortisol levels, your stress hormone levels, go up during the exercise, adrenaline or it's also called epinephrine. And another adrenal hormone, cortisol, which people have probably heard about. And with regards to bad stress. But then they tend to come back down, you know, after the stress and. Yeah. So anyway, these cycles of stress recovery, stress recovery, you know, as long as you have a recovery period, in the long run, things turn out better than if you wouldn't have subjected yourself to the stress.

Ari Whitten, MS
Okay. So basically the sort of modern, the common modern societal paradigm that we have of stress avoidance as the path to good health is missing this big key that actually a life with some transient stressors of specific types, as you've described, paired with good recovery periods, is likely to, would you say, lead to better health than the complete absence of stress in one's life?

Mark P. Mattson, PhD
Yeah. Then and it's very obvious you compare couch potato lifestyle to someone who exercises regularly, doesn't know very, you know, moderation in calorie intake keeps their brain intellectually engaged. They are the couch potato person, if I can use that term, which, you know, it's kind of slang, but it's kind of describes someone who's sedentary, overindulgent, and it's not subjecting their brain to challenges. And in the case of good stress, I kind of I kind of like to use the word challenge instead of stress. It kind of makes it clear that you're challenging yourselves in your organ systems, and they're responding to that challenge in good ways. And yeah, so cells and organs, systems and individuals who are sedentary overeat don't keep their mind active. They become complacent. And these genes and encoded proteins that evolved to help us resist stress in the long run. They're downregulated, they're not activated. And since they're not activated. So, for example, oxidative stress free radicals, exercise, fasting, increase genes that encode antioxidant enzymes. These are proteins that remove the free radicals right after they're produced in our cell. And actually, there's been an, you know, this here exercise physiologist. There have been studies, I think initially in Germany where they loaded up people with vitamin E.

Ari Whitten, MS
Yeah, Michael Risk does research where they use antioxidant supplements paired with exercise.

Mark P. Mattson, PhD
Yeah. And it negated some of the beneficial effects of that exercise because what's happening is that those free radicals, they're produced during the exercise are an important signaling function and yeah, a few swamp. We can do this in a culture dish for a lot of our. We kind of go back and forth in our studies of the brain between nerve cells in culture, which will form kind of neuronal circuits in culture, and they'll communicate with each other. We can study them. We have other preparations where we take slices of brain and we can record electrical activity. And then we

have mice and rats where we can, you know, highly control the conditions. We can take our brain tissue, measure these genes. I'm talking about the protein and stress proteins. We can measure all those things and then move on to humans and we can get to human studies. I think pretty soon because you know, intermittent fasting, which is now, as you know, kind of a hot thing in kind of lay public health conscious people. And I can talk a little bit about and the evolution of the the first the animal research and then the human studies and intermittent fasting. But anyway, the point is that if you take cultured neurons, say, for example, and you swamp them with vitamin E, and then you expose them to some stress, that could be the amyloid protein that accumulates in Alzheimer's disease or others. Then they actually they can be more vulnerable if you downregulate their intrinsic defenses against free radicals.

Ari Whitten, MS
Okay. So we so let me let me.

Mark P. Mattson, PhD
Ask the kind of the take home message is don't waste your money buying antioxidants unless they're things like sulforaphane or curcumin that actually impose a stress on the cells. And then the cells respond by up regulating their intrinsic antioxidant defense.

Ari Whitten, MS
Right. And so that is actually not a direct antioxidant, as it's often claimed to be. It's an indirect antioxidant in the same way that essentially exercise is and is an antioxidant. It works by being a pro oxidant that stimulates the mechanisms at the cellular level and at the mitochondria level that upregulate the internal antioxidant defense system.

Mark P. Mattson, PhD
Yeah. Yeah.

Ari Whitten, MS
And you're saying the so I think what, what a lot of people do when they hear this talk of oxidants and antioxidants, the whole conversation and I think even within the functional medicine community has largely been reduced down to this kind of simplistic model of oxidative stress is bad, is harmful, oxidants are harmful, and therefore, what we need to do is support our we need to use antioxidants to quench these damaging free radicals. So we need to use our glutathione. Supplements are vitamin C, supplements are vitamin E, supplements are vitamin A, are what are glutathione, iron and Aniceto cysteine. And we're getting rid of all these bad guys of oxidants by using these antioxidant supplements. And what you're saying is actually the paradigm is not set, not that simple. We have these oxidants are actually serving a positive role in our body and they're needed. They're not all bad guys. We don't want to just suppress them constantly. What we want to do is support our bodies, endogenous, internal regulation of the proper amount of oxidants relative to antioxidants. By using these external stressors or medic stressors to build that internal antioxidant system into a more robust system is exactly.

Mark P. Mattson, PhD
I was invited in 2015. Yeah. I wrote an article for Scientific American and the take home message of the article was that the chemicals in plants that are good for, you know, in the skin of fruits, which is actually a really good example when you think about it from Andalusian standpoint, you know, and now there's, you know, sulforaphane in broccoli, etc., etc., and sprouts. They why are they in the plants and why why does it seem like every chemical that seems to be good for health plan derived chemical has a very bitter taste. They do they have a bitter taste, even caffeine. If you take caffeine powder and put it on your tongue, it is very, very bitter. So a lot of these chemicals, Phillip, everything, are human caffeine, even. And this lab is that if you if you put something with sugar in it on your counter, it'll attract the ants. If you put coffee beans or tea leaves on your counter, the ants, they'll stay away.

Why? Because it's caffeine, maybe. And other chemicals in these that plant their function is to keep insects and herbivores and humans from eating any or much of the plant. We did a collaboration with a group when I was at NIH. There's a chemical in old tomato dying. It's president really high levels in the the skin of green tomatoes and it's called to Madeleine and and then as as the tomato ripens in terms of red, the levels of tomato dying in the skin go way down. And this this chemical has very bitter taste. I don't know if you've ever eaten raw a green tomato. Yeah, yeah. So it's actually probably better for you.

But anyway, from an evolutionary standpoint, it would be bad if birds or perhaps other, you know, herb and herbivores ate the tomato when it was still in a green state because the seeds inside the tomato and they are not, they have not yet matured. Right. But then when the, as the tomato ripens turns red, the seeds mature and then when it's ripe a bird eats a native seeds, they fly away, the seeds know go through their GI tract, some of them make it out the other end. And that's how, you know, an evolutionary way that plants that move, they distribute themselves over generations by having their animals carry the seeds. But again, you know, so that's just one example of undoubtedly hundreds, maybe thousands of examples of these chemicals that induce stress on ourselves. Those are the chemicals that are good for our health.

Ari Whitten, MS
Okay. There is a somewhat popular movement that has emerged, the latest sort of dietary trend, which is the anti plant trend, and like the carnivore diets and this sort of thing. And one of the things that they do that the diet gurus within that paradigm are have are doing a lot of is they take all of the same chemicals that you just referred to in in the context of saying, hey, these chemicals are very beneficial for human health. And they say the same thing that you said, which is that these chemicals are designed as toxins to ward off people from eating it. And they say, therefore, they are harmful for human health because they are plant toxins that evolved to essentially prevent people from eating them. Therefore, these are these these are toxic compounds that should be avoided because they're damaging us. What do you think is wrong with that?

Mark P. Mattson, PhD
Well, it can look at it in a number of ways. So there's at least four, four different ways in which we evolved to prevent ourselves from overdosing on toxic plants. One has better taste, two is vomiting, three is the liver has enzymes called cytochrome p450. Those that detox the biochemicals and and there's you know, it's very clear when you look at the evolution of these enzymes they evolved to get rid of potentially toxic chemicals in plants. So what that means is every time you eat a ingest, these chemicals, whether it's from the plant itself or if you take sulforaphane, it's only in your system a short amount of time and then it's metabolized and essentially you pick out the metabolites. Okay, so, so these are kind of one way to look at it. Natural insecticides in the way.

But since plant materials have food value, calories, you know, other things, fiber proteins, you know, did perhaps even plants have that? It was a value for us to be able to in other animals to be able to consume these to get those nutrients we need in environments where there's not meat available all the time, which my understanding of evolution is that human evolution is that it's often the case. There's a lot of environments and also our non-human primate ancestors, for example, apes that lived there, essentially, they're mostly herbivores living in the arboreal canopy right in the forest. And they feed on different fruits throughout the year and stuff. Then and. Right. So then the, the fourth way besides bitter taste vomiting, making sure these potentially toxic chemicals don't accumulate in our system.

The fourth way is direct activation of adaptive stress response signaling pathways in cells, the kind we already talked about. Transcription factors like interrupt, to which you've probably heard of. So for thing activates that transcription factor that induces a number of antioxidant enzymes heme oxygen aces one called nq o one. But there's also protein chaperons commonly referred to as heat shock proteins. It turns out that they kind of protect proteins in cells under stressful conditions and they're not all upregulated only by going in the sauna at 140 degrees for a half hour. But exercise, even fasting, interestingly, we found. So the other thing that evolved during evolution is that it's kind of activation of pathways that help cells tolerate not just one kind of stress, stress, you know, stress the initiating factor, but multiple different ones.

And let me say one other thing about evolution. So iron we need iron to live. We need small amounts of copper to live. Iron and copper, toxic in the ionic form. And if you can and I've thought about this a lot, I can't remember if my intermittent fasting book I wrote about the iron. So the reason iron we can ingest quite a bit of iron and it wasn't damaged as we evolved iron binding proteins that bind up the iron right away when it gets in our system because it's the free iron so called fe2 plus ferric form and solution that's toxic. It causes production of free radicals in cells. And then another one, oh, another one selenium. Copper is toxic to by itself, but there's copper binding protein selenium. You measured and you mentioned that you mentioned Salerno proteins. I can't know why, but it turns out a number of antibiotics and enzymes, selenium is an essential part of the antioxidant enzymes. They're called Salerno proteins. So

these are critical for our survival, but only because we evolved the ways. We have not only available ways to prevent them from being toxic to us, but we evolved ways to use them to our advantage that it does.

Ari Whitten, MS
So I think if I can play devil's advocate, what someone might say, let's say a carnivore diet guru might say in response to that would be, well, you agree that these are toxic compounds, so why not just avoid them altogether? What what? So what is your argument in favor of still consuming these things which you are saying based on what you what you explain so far, it sounds like does it mean that they may have some slight amount of toxicity?

Mark P. Mattson, PhD
It well, I guess it matters how you use the term toxicity. They impose a mild amount of stress if you don't consume them. You do not activate these adaptive stress response pathways and you're doing essentially the same as being sedentary and overeating. Okay. So yeah, I'm not too keen on the carnivore diets. I don't know about you, but I.

Ari Whitten, MS
Agree with you. I agree with you. I just want to do you.

Mark P. Mattson, PhD
Thing as well. You know, there's still a lot of debate on, you know, human evolution, certainly from we do eat meat and there are probably certain hunter gatherer populations who eat meat. But my understanding of, you know, even the existing modern day hunter gatherers, which are mainly a few groups in Africa, to my understanding, most of their calories don't come from meat. You know, it comes from eating probably root fruits and nuts and that kind of stuff. And also, you know, so I used to I grew up on a farm, my dad and my grandpa and then me and my brother trained and race harness, horses, trotters and pacers. And we also had cattle, so we were around the number of herbivores every day. We also had dogs, carnivores.

And I noticed something when I look in the mouths of a horse or a cow and compare what I see in the mouth of a dog. The herbivores teeth are made for grinding. Mm hmm. And the dog's teeth with the big canines and, you know, mouth. All the teeth are shorebirds for tearing and these carnivores, when they when they eat, they don't they don't chew 20 times before they swallow those. Swallow the meat whole. Okay. Then I opened my own mouth and I look in the mirror and I look in the mirror. And I see a lot of a lot of teeth that to me, they look a lot like horse and cows. Teeth more than dogs teeth. Yeah. And I think to myself, you know, I'm not too smart, but I know to me that maybe, you know, we evolved a lot for eating things that we had to grind with our teeth to get at the nutrients. So, you know, yeah, let's, let's throw that one back at our our meat eating friends.

Ari Whitten, MS
And indeed indeed. And you wouldn't argue that humans are vegan. You're arguing in favor that humans are omnivorous.

Mark P. Mattson, PhD
Absolutely. And of course, I'm still, you know, the that issue I eat fish. I don't eat red meat. Okay, I. Yeah, I. I think the data is pretty clear on that. Mm hmm. And, you know, I don't know if you remember this, but Atkins himself, right? Right. I think he had got heart disease. Yeah. Yeah. And, I mean, that's not science. That's an animal one. But on the other hand, there are definitely pro anthropogenic fats and. And better fats. Mm hmm. You know, so, you know, personally, I. I probably get I get most of my calories and fat and complex carbohydrates, but my fats are nuts and fish, mainly. And then how about olive oil? Maybe olive oil? Yeah, that's. That's right. I do olive oil.

Ari Whitten, MS
And avocados.

Mark P. Mattson, PhD
Occasionally. When my daughter makes guacamole.

Ari Whitten, MS
Nice. Okay. I don't want this to get lost because we've delved into some details of specifics and some biochemical pathways and internal antioxidants and all this sort of stuff. I want to zoom out for a second talk. Can you can you express some words about how you see the importance of or medic stress more broadly, as in terms of like ranking the magnitude of its importance in human health relative to, let's say, common things that people think are extremely vital for good health, like, let's say, eating a good, nutritious diet. Let's say, you know, doing meditation and mindfulness, yoga, de-stressing stuff, avoiding psychological stress and let's say sleeping well and enough hours. So where would you put your medical stress in terms of the importance of like how much of modern disease epidemics can be attributed to lack of hermetic stress in the modern human lifestyle?

Mark P. Mattson, PhD
Cause since it's not really possible with existing knowledge to put exact percentages on that. Mm hmm. I think our lack of hermetic stress is a big factor, and calorie restriction data and intermittent fasting data are perhaps the strongest in that regard. As you know, and I'm sure our listeners know, that if you take rats and mice or even monkeys and put them on a diet that has fewer calories than start that when they're young, they live longer, and as they age, they develop fewer spontaneous cancers and other, you know, age related diseases in humans, people with obesity have shorter life spans dramatically than someone who goes through their life. A normal BMI. And the incidence of chronic diseases associated with overeating, sedentary lifestyle, insulin

resistance and obesity has increased a lot really since since technologies for making it so that many of us don't have to exercise at all to to live get food support our families. You know. So exercise has become less critical for survival and getting by and passing our genes on and, you know, overabundance of high calorie density, addictive foods, foods in which there are chemists who get paid to make them addictive. So, yeah. So anyway, I think energy intake is really a big factor in health. Maybe number one, it together with regular exercise, are the two most important things. And both of those are hermetic stresses.

Ari Whitten, MS
So you're so the way that most people would think of nutrition would be solely in the context of eating nutritious foods, eating a wholesome diet with nutritious foods. And what you're saying is maybe the biggest piece of good nutrition is not eating too much.

Mark P. Mattson, PhD
Yeah, absolutely.

Ari Whitten, MS
And it sounds like maybe periods of restricted food intake.

Mark P. Mattson, PhD
Yeah. I think so. And keeping it cause I'm a neuroscientist. So if you think about the brain to keeping intellectually engaged like we're doing now. Mm hmm. You know, socially engaged. Very important to, you know, a lot of work showing in the brain, keeping intellectually engaged, socially engaged. Physical exercise is good for your brain, to everybody. Anybody who exercises regularly knows that if for some reason, injury or whatever, they're not able to exercise, they become their mood goes way down that, you know, become maybe someday depressed, irritable, can't concentrate. So, yeah, as far as mood exercise is really potent. And antidepressant and mood elevator. Mm hmm. Sleep is critical to, you know, in regards to brain health. But body health is, too. And by the way, the the brain controls the body.

The brain controls every organ in our body. It doesn't matter, you know, heart blood vessels, muscles, whatever. And so yeah. So I think those three are the most important meditations are good, you know, relaxation techniques. Although, you know, I mentioned cortisol a while back, right? So people subjected to chronic psychosocial stress, the kinds of stress you can't control, uncontrollable stress, you know, chronic worrying, you know, that can kind of precipitate insomnia. And then the insomnia causes tiredness and then that feeds back again, you know, depressing mood. And it's kind of you get into this vicious cycle and. Yeah, so that that's that's, you know, brain health and by extension body. But anyway so cortisol levels are chronically elevated in someone, you know, in that situation, chronic stress having trouble sleeping. You know, being tired all the time. Mm hmm. But interestingly, there is this there is this paradox within the calorie restriction studies that if you take animals and monkeys, too, and you put them on like 30% daily calorie restriction, or if you do, we do intervene every other day. Fasting,

for example, in animals, daily time restricted eating has a anti-aging effect right in it counteracts a lot of disease processes in animal models, but the cortisol levels are elevated. And so this was like a paradox, you know, what's going on here, that the caloric restriction, the fasting, like it seems to be like a kind of a chronic low level stress or a selling goes up, but the animals are more healthy. So we did studies back in. I had a graduate student in the late nineties. The way that cells respond to cortisol, there are two proteins that are transcription factors. One is called the MINERALOCORTICOID receptor or M.R. The other is called the glucocorticoid greatest glucocorticoid receptor J.R in chronic uncontrollable stress.

Bad stress levels of m are going down and levels of g r go up. We found with in animals adapted to intermittent fasting. It's the opposite. Levels of them are go up. Levels of g are go down. So even though the circulating hormone levels are high, although they're not as high with intermittent fasting as they are with chronic psychosocial stress, they're still elevated. Even though the cortisol levels are elevated, the way the cells are responding is different. And in fact, we have ways of selectively activating m.r, the good cortisol receptor pharmacologically, we can add a drug that will activate m.r and we find that had beneficial effects, neuroprotective effects on the brain.

Ari Whitten, MS
So that's when you upregulate m.r. But downregulate gfr.

Mark P. Mattson, PhD
Yeah.

Ari Whitten, MS
Okay. So you're saying did you say chronic psychosocial stress elevates GFR?

Mark P. Mattson, PhD
Right.

Ari Whitten, MS
Okay. And caloric restriction also elevates cortisol, but it down regulates glucocorticoid receptors.

Mark P. Mattson, PhD
That's right. And so.

Ari Whitten, MS
Okay, so what is the adaptive function of higher cortisol levels in that context? So the body is adaptively saying we want to raise cortisol because that's serving some beneficial purpose in that context, but we're simultaneously going to downregulate. GFR Is it is it that cortisol is higher to help facilitate higher blood glucose in the absence of calories or that the lower intake of

calories? But the body's still trying to minimize the harmful effects of the glucocorticoids on the brain or other tissues. What's going on there?

Mark P. Mattson, PhD
The answer is we don't know for sure. Okay, because a lot of experiments would be required. So there's a number of possibilities. One is what you said that, you know, mobilization. Gluconeogenesis Right. And and and another would be the anti-inflammatory function. We do know that fasting has an anti-inflammatory effect, that we've shown this not only in animals, but humans. One of our first our first human study we published in 2007, which was one of the earliest, if not the earliest intermittent fasting study in humans, was in a dozen asthma patients, and they were overall overweight. They had moderate to severe asthma. And we put all of them we changed their eating pattern to one in which every other day they consumed only 400 calories. Okay. So that's, you know, extremely low calorie intake and so on. The 400 calorie days, we measured ketones and glucose and all sorts of stuff I could mention.

But ketones were up on that 400 calorie day, which you might expect because 400 calories isn't enough to keep your liver replete with glucose. Okay. So at two weeks, four weeks and two months, we evaluated their asthma symptoms. We measured airflow in their young in their lungs. And we took blood samples on consecutive, I'll call it, feeding and fasting days. And what we saw is that not right away, but between two weeks and a month of the initiation of the intermittent fasting. Now asthma symptoms, their airflow in the lungs, improved blood markers, pro-inflammatory cytokines like tumor necrosis factor decreased, and markers of oxidative damage to proteins and lipids in the blood went down.

And I should mention this two week to a month time window, it turns out to be kind of consistent in terms of the minimum amount of time it takes to adapt to intermittent fasting so that there's very clear improvements in health indicators. So in other words, if you passed one day, you're not going to see any rapid change in, you know, whatever heat shock proteins, antioxidants and these things. It's interesting. It seems to be like a cumulative effect of the repeated bouts of the metabolic challenge. Again, similar exercise, right. If you've been sedentary and you go, if you run one day, you're not going to be in shape the next day.

It takes maybe a a month and that's something that kind of has stood out to me. And pretty much everything we've measured with intermittent fasting in animals or humans, it takes several weeks to a month. Insulin sensitivity in the brain, changes in neural network activity, resistance of neurons to stress, and miles of Alzheimer's, Parkinson's, etc.. So again, I see this making the analogy that exercise is pretty interesting. These cycles of stress recovery, stress recovery over a period of many days and weeks lead to kind of an amplification of the stress resistance and and optimal moving towards optimal function. Well, kind of a scenario.

Ari Whitten, MS
And how do mitochondria specifically play into that? What's going on at the level of the mitochondria as a result of exposures, systematic exposures to who are emetic stress.

Mark P. Mattson, PhD
Yeah. So they're, they're not okay. Yeah. So they're a number of things at the molecular level upregulation of superoxide dismutase to increase levels of this. That's in my opinion, the most important antioxidant enzyme in cells. There's a number of different antioxidant enzymes, catalase, glutathione, peroxidase, which are the Salerno protein and axon enzymes. But the superoxide removes the initial free radicals produced in the mitochondria. When the mitochondria burn, you know, burn glucose with oxygen, you know, you have to have oxygen to have a fire. So you have to have oxygen to generate ATP and as a byproduct and not just a byproduct, but also a useful factor. So this, again, the superoxide is produced transiently and has a signaling function. But then, you know, some of it will be stopped up by the antioxidant enzyme to make sure it doesn't stay around very long.

Another molecular change in the mitochondria that that others and we studied from the perspective of nerve cells in the brain is called Sirt three SRT three are two and three. And I think, you know, your listeners will be like buried in their science background. So, you know, I'm trying to go back and forth between getting into some of the science and then moving back to, okay, what's that mean? But there's a family of enzymes called Sirtuins SRT, U.S.A. that have been shown to be involved in energy metabolism, stress responses, you know, being able to allow cells to weather this stress and find kind of anti-aging roles. And they are initially discovered in yeast actually by Len Quarante up in Boston and you know, as much as you can study lifespan and a single celled organism yeast he had evidence that one of the served to insert one enhance longevity in the yeast and then in other animals.

These seem to be important roles but anyway this surgery in the mitochondria, it will increase the activity of superoxide dismutase two it will increase the expression and activity of the certain proteins in what's called the electron transport chain, which generates ATP, the energy currency of cells. So Sirt three enhances ATP production while at the same time preventing too much accumulation of free radicals in the mitochondria. We also discovered that it will gets complicated but there's mitochondria are an important organelle or compartment of cells that determine whether or not cells live or die under stressful conditions.

There's a process called apoptosis programed, cell death that it's evolutionarily this mechanism evolved as a way we could remove cells from a tissue that are damaged, dysfunctional and potentially dangerous, particularly from the standpoint of becoming cancerous. So as you probably know, some cancers form in tissues where there are cells that that proliferate like in our gut, you know, colon, colorectal cancer or breast cells or prostate cells and so any way all the time there are some cells that are having gene mutations caused by free radicals that may put

that cell into a trajectory for cancer. And there's these kind of sophisticated mechanisms that that will kill the cell, will essentially kill itself by this process of apoptosis and the mitochondria control that. And we found out in nerve cells anyway the circuitry and protect neurons from dying in experimental models that are relevant to Alzheimer's for example. And so in these models, intermittent fasting increases Sirt three in the mitochondria that protects against free radical damage. It also keeps the cell alive and functioning. And in fact, you know, so yeah, I don't know. That's kind of a couple of things in mitochondria and.

Ari Whitten, MS
What do you think about the role of loss of mitochondria or mitochondrial capacity with aging and lack of paramedic stress as a driver of disease and the potential of automatic stress to induce mitochondrial growth and biogenesis to combat that?

Mark P. Mattson, PhD
Yeah, that's a good, good follow up to that. Yeah. So I kind of mentioned the response to the stress aspect, but there's also an aspect to the cycling between our medic challenge and recovery. And that is, is the growth and plasticity component. So the actual the metabolic challenge itself, whether it's exercise or fasting or these plant quote unquote toxic chemicals during the challenge cells going to a a conserved and resist stress mode. So this process called autophagy is initiated to remove damaged things, including dysfunctional mitochondria. And then during the recovery period, eating, sleeping, resting cells go into a growth and plasticity mode. So during the challenge, overall protein synthesis in cells goes down.

There's a pathway called M tau that goes down. And then during the recovery period, amino acids are taken up and they're incorporated into proteins. Your muscle cells will grow, you know, when you exercise repeatedly over a period of days and weeks. And we found new synapses will form over periods of days and week, many days and weeks and in fact, we had evidence, we had but one paper in cell metabolism, one in nature communications. We had evidence that exercise and intermittent fasting over time induces mitochondrial biogenesis, increase the number of healthy, functional mitochondria and using genetic tools. If we block mitochondrial biogenesis, when we subject the cells to exercise or fasting like stressors, then new synapses cannot form. So that was pretty interesting because that showed that actually if the cell does not produce more mitochondria, it cannot form new synapses.

Presumably because you need more mitochondria to provide that energy for that synapse to function. Mm. And yeah, so that there's, there's actually a protein called brain and brain derived neurotrophic factor that's upregulated in response to stress and it will trigger mitochondrial biogenesis and synapse formation. It was known for a long time that media now is important for learning and memory and synapse formation. But it wasn't known that mitochondria were critical or for those actions of brain.

Ari Whitten, MS
Dr. Mattson, I want to ask you briefly, do you have a hard cutoff in 3 minutes from now or can you go a bit longer?

Mark P. Mattson, PhD
I can go a little longer. Okay.

Ari Whitten, MS
So let's do a little deeper dove on intermittent fasting. So there's been a number of studies that have come out over the last ten years or so that have compared intermittent fasting approaches to just calorie restriction, daily calorie restriction. And many of those studies, some of the measured different things, some of them measure overall improvement in metabolic health markers or or just weight loss. But many of these studies have found that when equivalent levels of calorie restriction take place and roughly the same amount of weight is ultimately lost, there are roughly equivalent levels of improvement in markers of metabolic health or in terms of weight loss. And many people in the evidence based fitness community have argued, based on these studies, that kind of, you know, kind of pooh poohing intermittent fasting as as kind of silly. It doesn't there's no magic to intermittent fasting. It's just one form of calorie restriction has as one of the most prolific researchers in intermittent fasting. What would you say in response to that? And do you believe that there are unique benefits of intermittent fasting that go beyond just calorie restriction?

Mark P. Mattson, PhD
They are both quantitative in some measures and actually many studies quantitative differ as in when you adjust for weight loss or match weight loss over time between daily calories stretching that has no fasting mode, that is breakfast, essentially breakfast, lunch, dinner versus some intermittent fasting regimen. The first study to show that actually was the one that really led to the popularization of intermittent fasting and kind of the virality of it on the Internet. And that was with collaboration with Michelle Harvey in England, who works with overweight women and the way the study was designed, where there are 50 women in each arm of the study, 50 of the women ate breakfast, lunch and dinner. And each meal they had approximately 20% fewer calories than their estimated daily calorie intake.

And then the intermittent fasting group was two days a week. Women made only 600 calories. And those two consecutive days, the other five days, they were instructed to eat as they normally would, breakfast, lunch and dinner over six months period. Both groups. And the reason we had that we we calculated that their weekly calorie intake in both groups would be the same and apparently was because both groups of women lost the same amount of weight over six months, 8 to 10% of their initial body weight. Both groups of women had improvements in, you know, all sorts of indicators belly fat, insulin sensitivity, lipid profiles, other things. However, the women on time to hundred men fasting had statistically significantly greater improvement in

insulin sensitivity. And we think this makes sense because if you don't it and most of these women, they're not doing a lot of exercise. And so it kind of makes sense on the two days that they're eating only 600 calories. They're in a ketogenic state and indeed we measured ketone. And so during that time they're using fats. Ketones are going up. And another thing happens when you have an extended time window with taking in no or few calories whether it's a daily time restricted eating, you know, with a six hour, eight hour time window or five two intermittent fasting. So when the cells are under that condition where glucose blood glucose levels remain low, normal ketones are up, essentially the cells go again and our pathway goes down. And but what happens is then the cells respond by increasing their ability to take up glucose, take up amino acids when, the individual eats.

So that's actually what increased insulin sensitivity is as increased glucose transporters in the membrane to remove the glucose same with amino acid transporters are upregulated and I think, you know, in studies in overweight or people with obesity or animal models which in most cases the control group animals are they're overeat and are sedentary. So what's happening is you're taking, you know, metabolically unhealthy individuals. And over some time period, a lot of these studies are just a few months at the most. And, you know, they're losing about the same weight in whatever daily time, restricted eating or calorie restriction. And you're seeing improvements in lot indicators in both groups.

But my prediction is in people with a normal BMI who, you know, are already exercising and, you know, eating a diet with a healthy composition that the intermittent fasting is going to have additive beneficial effects on some health indicators and some performance indicators. And we've actually shown this in animals where whether a certain strain of an of mice we use that when you when you do every other day fasting they're actually not calorie restricted over time because on the day they have food, they eat twice as much food as they normally would.

And we found beneficial effects on brain and we found improvements in treadmill training, endurance over time. My own feeling based on kind of educated guess and some I guess, circumstantial evidence is that maybe for endurance athletes and maybe even for resistance training, it's better to do the exercise in a fasted state when you're kind of combining the two evolutionarily. In my view, most important stressors are challenges, food deprivation, having to spend a lot of physical and mental energy. And we found, for example, we measured median health levels in the brains of animals. If you know, both are running, we'll exercise and intermittent fasting, whether it's a daily time restricted eating or every other day fasting. Over time we get an increase in beat in app level, increased number of synapses. When we combined the running wheel exercise with the intermittent fasting we get, I'd say they're additive.

Not necessarily effects. I my own South, I did a lot of distance running, trail running and I used to so I'd go into the lab, I don't eat breakfast, so I go into the lab work in the morning. I find I'm most productive. My brain's working the best in the morning when I haven't eaten anything, I drink some green tea, I think. Little caffeine, a little in that toxin. It is a toxin. So for all those people who

worry about toxins, stop drinking coffee or tea or otherwise, I don't want to hear it from you. Yeah, so. And then. But anyway, and then I take my lunch with me so that I'd save time and didn't have to go out and eat or anything since they keep working through lunch. Sometimes I'd forget my lunch and then I'd usually go on a trail run. There's some nice trails on the way home where I can go, like our trail run. And I just kind of notice on the days that I didn't, he hadn't seen anything that day. I was running better. And actually this is another one, you know, anecdotal thing, but I was timing myself and kind of and yeah. So I think again, if you're that human, our human ancestors and you haven't got food for a long time, you know, you can live for weeks, even month without food.

You've got, you know, should have plenty of that stores and maybe we evolved to function really well in that state and I want to see what happens with endurance athletes. I know now a lot of them are taking ketone aster and so on and it seems to work. We actually were involved in some of that. The basic science work on developing the ketone aster. And I don't know, I don't think in the long term that's going to give you the overall health benefits of intermittent fasting, just like it's not going to replace exercise. So in fact, you know, you take the ketone ester, I don't know. Here's my hypothesis. We'll see what happens. If you take it right before the event, it might help you in that event. But then I'm not sure how. You know, we mentioned that if you sop up the free radicals with antioxidants, you don't get some of the benefits of the exercise. I'm not sure. I'm just kind of skeptical that there's any one thing we're going to be able to drink and tag. And so the only supplements I take, I do take vitamin D and multivitamin. That's pretty much it.

Ari Whitten, MS
Okay. Within the realm of intermittent fasting, I think definitions are important. And the way I see it, you could sort of maybe break it down into three broad categories that kind of intersect with this idea, this concept of intermittent fasting. One is time restricted eating. And so what you're daily feeding and eating and fasting windows are another one is something like occasional 24, 36, 48 hour fasts, let's say the five two diet that you mentioned earlier, where someone might normally five days a week fast, two days a week, or do something like a partial fast or like a fasting mimicking diet where it's a very low calorie diet for several days.

And then the other one would be something like a true hardcore fast of a three or five or ten day fast or something to that effect. So how would, as one of the most prolific researchers in this area, I have two questions. Number one is more theoretical or more abstract, which is, do you think that there are any unique special benefits to prolonged fasting that one would not get from, let's say, having a daily six hour fasting window? And then the second part of this is speaking about this whole sort of the three dimensions I just mentioned. How what what do you think is optimal? How should somebody be structuring their approach to daily their daily eating and fasting windows and the use of maybe more extended duration fasts?

Mark P. Mattson, PhD
What I'm going to say is, as far as human data, you know, as you point out, you know, every every eating pattern you mentioned daily time restricted eating five to intermittent fasting, what Walter Longo calls fasting, mimicking diet. Although my take on it is other beneficial effects he sees is due to the fasting aspect and it has nothing to do with any specifically, is it? It's fasting or very low calorie diet for five consecutive days a month or and then the long term fasting been best studied by by these fasting clinics in Europe like the butcher and I know Francois Wilhelm Toledo Wilhelmi, the director of that institute. So that's where people it's like a resort and it's getting mad and it's rich people. So they come in usually once a year and fast for ten days straight or 14 days. And she has a lot of data on measuring various health health indicators right when they arrive, but before they start fasting.

And then, you know, at the end of the fasting period, the ten days, what they don't have is year by year progression, you know, health long term. There have been no human studies that directly compare in the same study daily time restricted eating, tied to intermittent fasting or the five days of fasting diet. My own impression is that daily time restricted eating may be the easiest for most people to incorporate into their lifestyle, their daily lifestyle, like exercise or many people, you know, find that exercise. You know, they exercise every day for a certain amount of time or, you know, maybe mix it up between aerobics and it's just it's easier to. And as far as when that eating window, you know, there's it's still unknown. There's some thinking about, well, you know, how does circadian rhythms play into this? And so on. My take in that on that is for diurnal species, you know, like us and other animals, they sleep at night, wake up in the morning in the wild. Food is not waiting for them.

Their breakfast isn't waiting for them. When they wake up, you know they've slept. So obviously they haven't been eating. When they're sleeping, they wake up and then they have to get out looking for food. So I think skipping breakfast is the easiest because just get up, go about your business, get to work, you can still eat lunch, you know, at work with friends, you know, and dinner with family and then don't eat anything within, say, 3 hours before you go to sleep. I do a six hour time, one to usually noon to six and yeah, I think it's definitely not good to eat a lot right before you go to bed for a lot of reasons, you know, reflux, gastric reflux.

But I think people in general although you know, so that's kind of my take on it and a lot of the clinical trials so I mentioned that this work with women at risk for breast cancer led to the popularization of intermittent fasting. What happened was a producer at the BBC, Michael Mosley, picked up on that study when we published that study from England. And he's an M.D. actually. And so he did a documentary, I think it was called Eat Fast, Live Longer that aired on the BBC in 2013. A couple of years after we published the paper, he came to my lab, Walter Longo's and Christa Berrios. And then it was Sue. It was so before then, if you would have Googled intermittent fasting terms, intermittent fasting, the top things that wouldn't show up would be scientific publications from Know My Lab, a few other labs. And then now if you Google

intermittent fasting, it's hard to find the science. You get a lot of random people in many cases they're I think it's okay because I see it like the exercise thing that the more people can be exposed to something that's going to be good for their lifestyle, the better. But again, as far as the science says, you have to go through a lot of pages. So the way to find out about science Club Med Hub Med Pub Med is that that's it. Start with the review articles, intermittent fasting review or or Mrs. Brain review, you know, you know, whatever. Don't, don't just Google something. And then because this is leading to a lot of problems with misinformation, I'm not too worried about it from intermittent fasting and exercise because, you know, it's pretty much all good.

These are it's pretty hard to hurt yourself by running a mile or not eating breakfast. But there are other things that are out there that people aren't going on pub med, they're not looking at the science. Then there's these random people who get a lot of I don't know, they're very flamboyant people, you know, and they're they made it, you know, they're not scientists. They're not MDs in, you know, and then they're get like following on YouTube or whatever and then people I think it so anyway anything hear check it with actually was published in the scientific literature which you can most of the papers are freely accessible by the general public.

Ari Whitten, MS
My last question to you. In your book, The Intermittent Fasting Revolution, you describe certain dark forces that are contributing to poor health and disease. What are those forces and how should people avoid them?

Mark P. Mattson, PhD
Yeah, I think people know of at least two of those. One is the pharmaceutical industry and the other is the fast, fast, fast food industry.

Ari Whitten, MS
By the way, just just as I can't resist linking that your answer to that with the previous comment, because it's also the case that pharma is funds enormous amount of scientific literature that I would say falls very squarely into the category of misinformation or is misrepresented or is not reflective of the full body of evidence for things like the file drawer for effect and suppression of studies that don't fit with their preferred findings that never see the light of day, or just using statistical manipulations to and and relative data to make a statistical case for something that is misrepresented.

Mark P. Mattson, PhD
Yes, that's the whole point. Then they're profit driven. And so here's the thing. You know, we have essentially one of the worst health care systems in the world now, at least, you know, I mean, from industrialized countries. Right. Western Europe, way of us. And we have little or no emphasis on preventative medicine, fasting, exercise, you know, healthy diet. It's the same Erdogan's letting someone get sick and then treating their symptoms with a drug. So obviously, you know, there's the only way drug companies are interested in fasting or exercise is if they can

come up with a pill that perfectly mimics mimics and actually actually working on that. But I think it's not we messed around with this in animal studies and there are certain things that can have a short health benefit by mimicking fasting, you know, these pathways. But in the long run it's very touchy system. But anyway, so yes, drug companies fund clinical trials the way the clinical trials system is supposed to work and most cases it does work is that drug companies, you know, they develop a drug and, then they put in money to pay for clinical trials and then, you know, this is the reason a lot a lot of an initial trials that look promising ultimately fail. But you'll see this a lot the early studies may be just done in one place.

And maybe there was an investigator involved in those trials of that particular health care system or medical center that had some connection with this drug company. And, you know, and then so the initial results will come out with, you know, drug X, potential treatment for Alzheimer's disease, and then that's actually called phase two trial. That's after doing safety studies to make sure that the drug isn't causing any obvious really bad effects. So the phase two trials is like initial efficacy. Then phase three trials are are multicenter whether, you know, there should be and usually many different medical centers over the country that enroll patients in the study and then they're done in a double blind manner so that neither the patient nor the doctors treating the patient know whether the person is actually getting the the drug or a placebo.

And then there is a monitoring board for the clinical trial of the well investigator scientists, a clinical clinicians in that area of the field of research who they monitor the trial so that you know the data the handling of the data. If there's going to be some change in the trial, they have to be alerted that if there's an adverse reaction of a patient to the drug, they have to report that. And then and then all the data from all the centers are gathered and analyzed together. So that's the big phase three trials. And, you know, so that system generally, you know, I'm pretty confident works pretty well as far as, you know, ending up in the final analysis with the drug that is having an effect. But it doesn't always work. And sometimes drugs get like the coded right a get early approval it's called like you know, whatever it's not full approval by. The FDA, it's kind of called under emergency authorization, emergency use.

And they and by definition, the FDA is approving them without as much data as they normally would because there seems to be some urgency to do that. But yeah, that's one thing I've noticed. For example, well, I don't want to get into my own home, my own health issues, but it turns out I have a genetic mutation in a gene that's involved in regulating, signaling neurons that convey pain. Mm. I'm hypersensitive to pain. It's actually a voltage dependent sodium channel that's in the nociceptive neurons or the pain neurons, and it's a gain of function so that the neurons are firing, you know. So for example, over the years I have a problem, like right now I'm sitting on a pillow in a donut cushion because I've had this for like decades, just like pressure from sitting will cause a lot of pain. But anyway, so I take a couple drugs for that. One is the laxative and another is I'm gabapentin now, but so what happens is some drug, a drug company will market some drug that has some effect, you know, metformin celecoxib for diabetes, which does improve glucose regulation. And then after a while it goes off patent. So that means any

generic, any company that makes generic drugs can make it and sell it for a lot less. And then what happens is the drug company that made the original drug, they have their chemists modify the additional molecule a little bit in a way that may not even change its activity. It may have pretty much the same activity. And then they do a clinical trial and they see it's having an effect, beneficial effect, and it's because it's doing the exact same thing. Yeah. And then now they have the patent on that and so they can be the sole source for that drug and in charge, you know, just outrageous price for it. So I see this happen lot. It's happened with antidepressant drugs a lot. You know, you start out with Prozac and then paroxetine and then duloxetine, which actually does that. But anyway, so this is another thing that the drug companies do.

But the question is how we get around that. The clinical trials are do we want the government to take over everything, you know, from the base? Right now, we we mainly and I was at the NIH for 20 years, as I mentioned, you know, so scientists at the NIH you know, we can't take any money from any company. We can have stock in any company that has anything to do with anything working on, you know. So I couldn't have stock in any biotechnology firm, so I just didn't have any stock and anything related to health care. And, you know, so there's and we had a we had a salary, you know, a set salary.

Our salary didn't depend on, you know, how many patients we treated or, you know, whatever. And, you know, so do we want the government to take over everything where all the basic research is done in government labs? You know, and how are you going to do it? You'd have to have a huge number of clinics, government run clinics all over the country by doctors and salaries. You know, there's the people that are developing the drugs in the government don't get any make any extra money if the drug becomes, you know, isn't that what we want or, you know, or do we want to figure out how to have more rigorous oversight and accountability to the existing system?

Ari Whitten, MS
MM So on an individual level, are there any things that you'd recommend for people avoid those dark forces?

Mark P. Mattson, PhD
Yeah, preventative medicine, you know, diet and lifestyle and you know, try to avoid going to doctors. And I father would always say, don't go to doctors, you're going to end up being sick, you know, but there are certain situations where you need drugs. But the thing is, what's happened is there have been some remarkable advances right in medicine. Right. Four in heart, for example, where 50 years ago someone would have, you know, atherosclerosis, then the heart attack, they're probably going to die. They don't die from that one. They're going to die from a heart attack with in another few years. And now there's, you know, bypass surgery and heart trans people who would like Dick Cheney, who would have died 40 years ago, who are still alive and but what's happening is then you have these people, the risk factors for heart disease are bad diet and lifestyle. Right. So now you have people with bad die in the lifestyle. They get heart

disease, they keep them alive. That's good for them. But then, you know, they may not change diet and lifestyle. And so all this kind of adds up to a big drain on the health care system ultimately. Mm hmm.

Ari Whitten, MS
Dr. Mattson, to wrap up, linking things back up with her medical stress and mitochondrial function, mitochondrial health, what would be the final thoughts or practical tips that you want to leave people with on that topic?

Mark P. Mattson, PhD
Yeah, in our challenges, exercise, intermittent fasting and calorie restriction. Keeping your mind active. Sana has evidence that cold called stress actually does amazing things to mitochondria. There's these proteins called uncoupling proteins that they're increased in the mitochondria and that's a whole nother story. Maybe we can talk about that. Just we actually did I.

Ari Whitten, MS
Just got in I just got out of an ice bath right before starting this interview with you.

Mark P. Mattson, PhD
And it it does bitter tasting art. Some of the plants.

Ari Whitten, MS
Yes. That's been go have I've been fasting and I'm going to go have some food with some bitter tasting compounds after this is over.

Mark P. Mattson, PhD
Now, better is better.

Ari Whitten, MS
You can wonderful any anything else as far as fasting that you want to mention to people as far as a practical way to incorporate that?

Mark P. Mattson, PhD
Well, this two week to a month adaptation period is critical. I can't count how many times I've had someone come to me and say, I tried skipping breakfast. I can't do it. I get hungry and irritable. And I'd say, Well, how many days did you do that? And they'll say, I Just did it one day. Yeah, that's what's going to happen. It's same with exercise. If you've been sedentary and try to go run five miles, you're not going to feel good. You're not adapted. So it takes time to adapt. You can, you know, if you're doing daily time restricted eating, you can kind of gradually narrow the eating window or you can just go cold turkey and, you know, start skipping breakfast for a couple of weeks and and I think there's a very high probability, you know, by then and certainly by a

month, you will no longer be hungry during that time period that you had previously been eating. So that's kind of the key thing, this adaptation period.

Ari Whitten, MS
Okay. And as far as like the practical specifics of daily feeding and fasting windows or incorporation of extended fast, do you have any thoughts on that?

Mark P. Mattson, PhD
The daily you know skipping breakfast the is the for me me and I think most people's daily routine the easiest so that don't have to sacrifice you know social interactions that you know, usually occur around meals, right? I mean, meals with the family and with friends is a social thing. So you don't want to, you know, go to lunch and then you be not the only one that's eating. I mean, you can do that if you want, but it's just easier. You can enjoy the food and if you eat a healthy diet. The other thing I found is I actually enjoy food a lot more when that. But you can't restrict the eating window too much. At least I can't, because if you're eating the things that are bulky and have a lot of fiber, vegetables, fruits, then your stomach's only so big. So for me, six window, 6 hours is a good time window where I can eat lunch, maybe a healthy snack, and then dinner and get enough calories to maintain my body weight and with my current exercise routine. Yeah.

Ari Whitten, MS
Beautiful. Dr. Mattson, thank you so much for coming on the summit. I am appreciative of you taking the time to do this and all the extra time for our allotted hour. We've gone another half an hour over. So thank you so much for doing that. And this was excellent and thank you so much for all of your work in this topic of romantic stress. It's been amazingly enlightening for me and I think for many people. And I think helping to to really change the lives and change the health trajectory for many, many thousands of people. So thank you so much. And I look forward to our next conversation.

Mark P. Mattson, PhD
Thanks, Ira. And thanks for everything you do and trying to help educate people. It's very important. People can take charge of their own health and. One thing I didn't mention is you can make it a family thing. Hmm. Intermittent fasting. Mm hmm. You know, and I know of pediatricians who work with families who there's children with obesity, which is turns out, unfortunately, there are children, you know, ten year old children, middle school children with obesity and insulin resistance. And a pediatrician up in New York that I know has had success in getting the parents to switch their eating pattern to essentially breakfast, skipping one with the child and then the child's eating school lunch and then and, you know, so that's the other thing, you know, what's the home environment like and what are other people doing? You know, exercise is often better to do with one friend, whether it's a team, sport or individual thing that you can still do running or whatever. So, you know, making a lifestyle, a social thing and, you know, family life. And then you're outside of that family life and then, you know, it turns out that,

you know, you mentioned, you know, so you're in Costa Rica and you know, you mentioned this is a whole other topic. But psychedelics, right. Which is now they're being decriminalized in Oregon and District alarming and I think that's moving forward and they're non-addictive and you know, like all of us are going to say about them, about psychedelics. Yeah. Yeah. So this is you're not sure. But I think it would be interesting to look at whether they're having like some of the effects are having on like our medical effects that are for some reason long lasting.

Ari Whitten, MS
But certainly the subjective experience is oftentimes very traumatic in nature. I mean, you're subjected to lot of trials and tribulations, having to face fears and deal with a lot of difficulty.

Mark P. Mattson, PhD
Yeah, interesting thing there. Depression standpoint is, you know, electroconvulsive shock is still used in some patients who are refractory to drugs and you know, cognitively therapy or other types of behavioral therapy. And, you know, obviously it's inducing like mild epileptic seizures, like some very severe rigorous activity in the neural circuits. And that has a potent, long lasting effect in increasing beat NF levels. There's antidepressant learning and memory promoting protein and psychedelics also seem to have a long term effect and increasing. So that's pretty, pretty interesting. So, you know, maybe that also fits into the Nemesis type perspective on general health and mental health.

Ari Whitten, MS
Yeah, actually, if you have a second, there's one last thing I would love for you to comment on since you brought that up. I know obviously as a neuroscientist, you're very well versed in this intersection between or misuse in the brain. There was interesting paper I read several months ago, maybe a year ago, that was the researchers were arguing that one of the primary driving forces, the evolution of human intelligence at the level of the brain is was actually horn medic stress and that there is also this sort of irony embedded in there because humans ended up using this higher cognitive function and intelligence to create an environment where we minimize or eliminate many of the emetic stresses that drove all of these these benefits. And from perspective, that drove the development of intelligence.

And we created environments with climate controlled indoor rooms. So we don't have to be exposed to the and to the cold. We instead of having to deal with food scarcity and going out to hunt and gather our food, we brought the food to us via farming and technology to store food and things like that. We eliminated all the discomforts, all the physical activity. All these were medic stressors from our life and all the food scarcity. And now, ironically, we're suffering a major health consequence is that are in large part driven by an environment with too little water medic stress. And now we're tasked with having to use our high intelligence in order to reintroduce romantic stressors into our life.

Mark P. Mattson, PhD
Doesn't seem like a very efficient way to do it. Now, you know what? What? What is said? I exactly agree with that. And the first chapter in my book, Intermittent Fasting Revolution, was covered. A lot of what you just said and I, you know, I have a podcast myself. I don't know if you knew that.

Ari Whitten, MS
I saw it.

Mark P. Mattson, PhD
Yeah.

Ari Whitten, MS
It's called but didn't know that until I read your bio. But now I will. I will listen to it.

Mark P. Mattson, PhD
It's called brain ponderings. And you know, I have several podcasts relevant to what you just said. One was on evolution of that actually more than one evolution of prefrontal cortex, which is a brain region and very important for decision making. And there's there's really good literature on evolution of primates and foraging that the prefrontal cortex played an important role in in enhancing decision making in terms of when to leave a particular area where food is getting scarce and then make the effort to move maybe a long distance away to another region where, you know, there may or may not be food and those kind of critical decisions for survival. But yeah, there's and I had I've had podcasts from with Steve Koonin on Ketogenic Diet and all that kind of stuff then yeah. But if anyone's interested in anything about the brain, it's me. One neuroscientist in conversation with another neuroscientist who is much more of an expert on the particular topic of the podcast. But I have enough knowledge to kind of ask some reasonable questions.

Ari Whitten, MS
Hey, Dr. Mattson, thank you so much again for your time. I greatly look forward to our next conversation. And, and where so is the best place to find you the The Brain Ponderings Podcast. If somebody is interested in learning more from you or following your work, you also have the book, The Intermittent Fasting Revolution. I people can get that on Amazon. Is there anywhere else you want to direct people to PubMed?

Mark P. Mattson, PhD
That's an MP and then.

Ari Whitten, MS
To browse through your 900 publications?

Mark P. Mattson, PhD
Yeah. If they put medicine MP review and then whatever they are studying, whatever. But then the last thing is I have another book is coming out this summer. The title is Sculptor and Destroyer. Huh. Tales of Glutamate. The brain's most important.

Ari Whitten, MS
Very interesting. I'm excited to read that.

Mark P. Mattson, PhD
Yeah.

Ari Whitten, MS
And does it tie in to the Horde medic stress story as well?

Mark P. Mattson, PhD
Very much so. Okay. Yeah, glutamate. It's more than 90% of our neurons deploy. Glutamate is their neurotransmitter. It is the neurotransmitter that excites other neurons. Mm hmm. The other neurotransmitters, dopamine, serotonin, cell choline. The only way they affect our behavior at all is by modifying the ongoing activity in the glutamate neurons.

Ari Whitten, MS
Interesting.

Mark P. Mattson, PhD
And neurons can be excited to death by glutamate. Yep. So it's a stress excited cytotoxicity. Yeah. But you need some excitatory stress, otherwise you're going to become complacent. And weather.

Ari Whitten, MS
Very interesting. I look forward to reading that. Thank you so much, Dr. Mattson, again, I really look forward to more conversations in the future.