Introduction and guest background

That's why your program is important because I'm emphasizing and I think you're emphasizing that We can do a lot for ourselves and our loved ones, and don't rely necessarily on the healthcare system.

In this country, everything is for profit. And you've got the food industry who, in all these, well, many cases, billion, multi-billion dollar industries are lobbying congressmen, senators, and so we get all this ultra-processed food that's no good.

We have the monoculture, so we've got all these farms, either corn, soybeans, or wheat, I guess. And then they take the corn and put it in, make it into high fructose corn syrup and get you addicted to that.

Then the healthcare system, and I hate to say this, but it really, in this country, it is geared to let people get sick and then treat them. Rather, there's very little emphasis on preventative medicine.

Welcome back to the Think Well, Age Well podcast. I'm your host, Dr. Heather Sandison, and I am absolutely honored to welcome Dr Mark Mattson today. He is one of the most highly cited neuroscientists in the world.

Dr Matzon is the former chief of The Laboratory of Neurosciences at the National Institute on Aging, And he is currently an adjunct professor of neuroscience at Johns Hopkins University School of Medicine.

Over the course of his remarkable career, he has advanced our understanding of the molecular and cellular mechanisms that control the formation and plasticity of neuronal networks in the brain.

and also contributed to our understanding of how those processes are affected as we age and in the context of neurodegeneration. His pioneering work has revealed how the brain responds adaptively to challenges such as fasting and exercise, and how these insights can be translated into interventions that promote optimal brain function throughout life.

You can see why I'm delighted to have him here. He is also a fellow of the American Association for the Advancement of Science and the recipient of prestigious honors, including the Metropolitan Life Foundation Medical Research Award and The Alzheimer's Association Zenith Award.

He's the author of The Intermittent Fasting Revolution, as well as Sculptor and Destroyer. It's a true privilege to have him here today to share his wisdom on aging well and protecting our brains.

Thank you, Dr. Matson, for joining us. Well, it's nice to join you Heather, and you can just call me Mark. So you've had this exceptionally distinguished career both at the NIH and at Johns Hopkins.

Looking back, what drew you into studying brain aging and neurodegenerative disease? Well, it didn't start out that way. I was going to be a veterinarian.

And I grew up on a farm. Me and my dad and grandpa trained and raced harness horses, trotters, and pacers. This is in Minnesota. So I went to Iowa State University pre-med.

Back then, in the early 70s, you could apply for veterinary medicine school during your second year of undergraduate. So I applied, didn't get in, and during the next year I decided not to reapply because I got interested in neuroendocrinology.

I had a course that covered that. And then so I went on to graduate school in Texas and studied the adrenal gland and how the production of cortisol, the stress hormone, is controlled by a protein released into the blood from cells

up in brain region called the hypothalamus.

And then my PhD work was at University of Iowa, and I studied a neuroendocrine system that controls molting in crabs. And it may sound very far removed from humans, but things tend to be conserved during evolution.

And turns out the molting hormone is a steroid that's produced from cholesterol, similar to cortisol. The production of the molting hormone is controlled by a protein produced by certain neurons in the brain of a crab.

So I studied that. But then I got interested in aging during my postdoc research in Colorado. I was studying cultured neurons taken from the brains of embryonic rats.

And there's a reason we take them out of the embryonic brain, because you can't really get neurons to live if you take out an adult brain. Because the neurons have all these elaborate connections, and if try to separate them, it just kind of tears them apart and they die.

But anyway, so we can put these nerve cells from the hippocampus of rats in culture, in their initially spheres. And then over a period of a few days, they'll grow several short extensions from the round cell body.

One of them starts to grow really fast, that becomes the axon. The other ones grow a little slower and they branch a lot, and those are the dendrites.

How brain aging research began

And the individual neurons will form synapses with each other. Actually, you can image the activity electrical activity of these neural networks, and there's like this spontaneous activity, so they're communicating with each other in culture.

I discovered that glutamate, which is an amino acid, it's also a neurotransmitter. In fact, that's the most prominent neurotranmiter in the brain. About 90% of the neurons, nerve cells, in their brain use glutimates as their neurotransmitters.

It's excitatory. It stimulates them. So the main neural networks throughout our brain is neurons that use glutamate as a neurotransmitter. And then the other neurons they use the neurotansmitters such as serotonin, dopamine, for example.

The only way they affect our behaviors is by modifying the ongoing activity in the glutamine neurons. Interesting. This is my second book called Sculptor and Destroyer.

So in postdoc, I discovered that glutamate plays a role in the formation of synaptic connections between nerve cells during brain development. And then I also discovered, that if you expose nerve cell to a very high level of glutimate for too long a time, or if expose them to almost normal levels of under conditions where the neurons aren't getting enough energy, then the neuron dies.

So neurons can be excited to death by glutamate. It's called excitotoxicity. That got me interested in neurons degenerating, which happens in Alzheimer's, Parkinson's.

Stroke, traumatic brain injury. Severe epileptic seizures, which is really a dramatic example of excessive activation of glutamate receptors by glutammate.

Okay, so then, long story short, then my career took off from there. I got a faculty position at University of Kentucky, I was there 11 years in the Sanders Brown Center on Aging.

and Colonel Sanders and John Y. Brown, who was a former governor. Anyway, they gave some money to build the building and stuff. Right, so that work continued.

My graduate students and post-docs showed that, provided evidence anyway, we think pretty strong that during aging, the ability of nerve cell networks to control their activity within normal limits becomes compromised.

There tends to be a hyper-excitability. It turns out that Alzheimer's patients, they have a much higher incidence of seizures, epileptic seizures than do age-matched neurologically normal people without Alzheimer's disease.

And then we found in, we have some nice mouse models that are relevant to Alzheimer where the mice get the amyloid accumulation and the so-called neurofibrillary tangles in the neurons.

We found just by recording from neurons, or even you can do it with an electroencephalogram, record EEG from these Alzheimer's mice and as they age they will develop hyper excitability and even seizures.

And then we found that and then I was interested in and this is a time when all this The amyloid story was really hard and, you know, there's going to be a cure for Alzheimer's disease and we're going just to able to remove the amlyloids and all of a sudden the person is back to normal and unfortunately that was kind of pipe dream.

And for a couple of reasons. One is by the time someone's diagnosed, there's already a lot of damage. A lot neurons have died already. So removing the amyloid, the best one could hope for is to halt the progression.

However, it's not that simple as removing amlyloids and all of a sudden things are better because There's a lot going on in the brain during aging and in Alzheimer's in addition to the amyloid.

It's playing a role, but it's not the only factor. Okay, so then here's where we get to diet and lifestyle. So since, I hope it's okay if I keep talking without you asking.

Please, yes. This is exactly where I want to go. You've got a book called, well, you've your books behind you, which is fantastic, but also hormesis, right?

This whole idea that we've talked about quite a bit on this show, what is the role of stress and how do we figure out the difference between good stress and bad stress.

You talk a lot about fasting and exercise, and these are two really great examples of hormesis, of putting this concept of the hormetic effect to work.

So yes, please dive into it. Go for it! Yeah, use it or lose it is the idea. And it's definitely true with exercise. If you don't exercise your muscles, they get weaker.

And so that's very important to do throughout your life, assuming you can. And then one way to look at this, my training was in biology, so my undergraduate degree, even my PhD was biology.

Biologists often think of things in terms of evolution, you know, how is it that such and such gives an advantage to this individual. And so physical exercise, spending a lot of physical exertion, and food scarcity, being able to withstand and overcome food, scarcity are two very important things evolutionarily.

In fact, there's quite a bit of evidence that food is a major driver of evolution in general. So the idea is that in most environments and animals in the wild, there's a limited amount of food available, or there may be sometimes a year when there is quite a bit of available and others not.

And so the animals have to be able to get through that period with little or no food. An easy way to look at this is from the viewpoint of a predator.

where many predators will go two weeks without killing prey. For example, imagine some wolves in the winter in Wisconsin. And they have to find a deer, for example.

Track it down, chase it, and kill it. They haven't eaten for two week. So their brain and their body has to function

really well in a food-deprived state in order for them to be successful.

And presumably then individuals whose brains and bodies did function really well under those conditions had a survival advantage and passed on whatever genes enable them function well in response to fasting or food deprivation.

And so based on your book, your research, what does this mean for humans now? How much do we need to fast to get the benefits? And then how much fasting is bad?

Do we worry about frailty, especially as we're aging? Yeah, those are good questions. For people who are overweight, intermittent fasting has been shown in many randomized controlled trials to be effective.

and people losing weight.

Hormesis, fasting, and the metabolic switch

So intermittent fasting is eating patterns where the individual goes with an extended period with no calorie intake, so at least 10 to 12 hours with not food intake.

And the reason for that time frame is when you eat a meal, particularly if it has carbs, That energy goes and replenishes stores in the liver, which is glucose essentially.

And the livers holds about 700 calories worth of energy. It takes about 10 to 12 hours if you're just kind of normal daily activities to deplete the lever energy and then switch to using fats and the ketones that are produced from those fats.

Okay, so this we call the metabolic switch seems to be very important. A lot of people, if they eat breakfast, lunch and dinner, evening snack, they may never have the metabolic switch occur.

And do you not produce glucagon for a bit? Or is that the reserve that you… Because I was thinking it usually takes about 72 hours to achieve ketosis.

No, yeah. There's kind of two phases of ketosis. So when your liver glucose stores are replete, ketone levels are very low, pretty much undetectable with the normal ways of measuring.

And then after about 10 to 12 hours, you get an initial rise up into like, 200-300 micromolar range, which is like 0.2-0.3 millimolar. And then, it's interesting, kind of stays there, and then by two days, there's a definite increase up into the millimer range or higher.

So we think this initial switch and elevation of ketones is important. A lot of scientists are finding the study ketones that it's not only an energy source for cells, including nerve cells in our brain, but it acts as a hormone.

It will affect the expression of genes in cells and in good ways. And yeah, so this is kind of an emerging picture of this, we call it biphasic, elevation in ketones in response to fasting.

Initial rise where you may still have some glucose available ketone, but the ketons are serving as a hormone. Maybe it's like an early alert. And I can talk about what the ketones do in the brain, but one…

Yes, would you please? What are the benefits or what are their risks? Is it worth it to do the fasting and to maybe even restrict carbohydrates at some level?

If our metabolism isn't getting into ketosis, is it is worth to to this? And why? what Are the Benefits for the Brain? Many people ask me, well, what about the mind diet?

Why didn't I just go on the Mind Diet or the Mediterranean Diet? Why is getting into ketosis potentially different?

Yeah, it's a good question. The Mediterranean diet is excellent in the diet composition.

Intermittent fasting is not a diet. That's one thing that I should make clear. It's an eating pattern. A diet it is what you eat, how much. intermittent fasting kind of takes the dietary composition out of the equation.

Okay, so if you're overweight, you are going to have to reduce calorie intake and or exercise, increase your exercise to lose weight. This metabolic switch that I mentioned, that's when you start using the fats, okay?

Otherwise the fat stays in your fat cells, and then the are used for energy. Ketones is kind of the main energy source that comes from fats. For normal weight people, if you're within the healthy body mass index and you exercise regularly, and you're eating a high quality diet like Mediterranean diet, then we don't know.

There's no data to say whether intermittent fasting, at least in humans, will give additional benefits. there are some data suggesting that some of the benefits of intermittent fast can be dissociated from any reduction in calorie intake.

And we think that may have to do with the signaling function of the ketone. Another important thing is that, okay, with exercise, as you know, it's important to exercise.

Your muscles aren't going to maintain their strength and endurance or even get stronger and better endurance unless you exercise however you need a recovery period.

You're muscles don't grow while you're exercising. They grow during the recovery period, eating, resting, sleeping. And so it's pretty clear with exercise you need regular switching back and forth between the metabolic challenge, the exercise, and a recovery.

With intermittent fasting, kind of a similar idea is happening. Certain events happen in our cells and organ systems during the fasting period that puts them in a stress-resistance conserve resources mode, and then during a recovery period, eating, sleeping, cells adopt a growth and what we call plasticity mode.

So as far as the brain goes, we've seen some things that are actually similar to the effects of exercise in muscle cells. So with regular exercise over periods of days and weeks, in each muscle cell in your muscle, the number of mitochondria, of the energy factory of this cell, will increase.

Okay? We have evidence for a similar thing in nerve cells in the brain that with, not right away, but after two weeks to a month or so of intermittent fasting, We have evidence that the number of mitochondria in each nerve cell increases, and at least in mice, the numbers of synapses between neurons increases.

So there's this evidence for promotion of growth and adaptive plasticity. The whole idea of the hormesis idea, that recovery period is often kind of ignored.

But any challenge you do, whether it's sauna or ice water bath or exercise or fasting or even what you and I are doing now, intellectual challenges, which is actually a stress on your nerve cells, You and me, me trying to remember what I'm saying or think ahead and you trying understand what i'm seeing.

There's increased activity in the neural networks and our neurons in our brain and that's a stress. So they're experiencing increased free radical production.

Increased what we call ionic stress, It gets a little complicated into the neurophysiology, but neurons are, the membrane of a neuron is kind of like a battery.

You have a positive charge on one side, negative charge and the other. And when the neuron as quiet, not active, that's just kind maintained. Then when a neurons gets the stimulation by glutamate, for example, then positively charged are Pores in the membrane called ion channels for sodium, which has a positive charge, and calcium, that has positive charges, rush in and then you get depolarization of the membranes.

That's what firing of neurons are. And that's a lot of stress. They have a big increase in, the mitochondria activity increases in neurons when they're active, just like in muscle cells so more ATP can be produced.

Free radicals are produced as a consequence because of mitochondria, a major source of free radical. But it's okay because that activity and that stress actually stimulates the cells to increase their intrinsic antioxidant defenses.

It bolsters their mitochondrial resilience. We've found enhancement of DNA repair, the ability to repair DNA damage by free radicals, and other things.

Oh, a big one is neurotrophic factors. There's a protein called brain-derived neurotrophy factor, BDNF, that it's been known for a long time that its production increases in neurons when they're active.

It was also shown quite a while ago that exercise, running wheel exercise for example, in mice or rats, has a big increase in BDNF levels in the brain.

Ketones, BDNF, and brain resilience

We found that intermittent fasting will increase BdNf. And B-D-N-F plays critical roles in learning and memory. It plays a critical role in growth and formation of new synapses between neurons and in protecting neurons against stress.

So there's a lot of things going on during these challenge recovery cycles. And I think you're sort of alluding to this, but the factors like sleep and social engagement, things outside of just fasting and exercise, even diet composition, how do these play a role in neuroplasticity as we age?

Yeah, social interactions, there's good epidemiological evidence that people who keep socially engaged have lower risk of cognitive impairment and dementia.

And I think the same is true with regular engagement in intellectual activities. It doesn't necessarily have to be direct one-on-one social interaction.

writing or even reading where you have to think a lot. But yeah, and then the diet composition, I'm of the opinion that Mediterranean-type diet seems to be really good, plant-based, these blue zones, which you've probably heard of.

My understanding is in all of those areas of the world where there's exceptional longevity, the diet is mainly plant-based. fruits and vegetables and nuts and beans or that kind of thing.

Some meat, some milk, but not loading up on red meat and lard or junk food. They don't eat ultra-processed food, they don' have a lot of simple sugar or certainly don"t have high fructose corn syrup.

The things to avoid are the simple sugar and high fructose corn syrup and too much saturated fat. What do you personally do? Have there been things that you've discovered throughout your research that have had an outside impact on your personal decision-making as you're aging?

Yeah, a little bit. So I've skipped breakfast for like 35 years and although I didn't do it because of science, I did it, because a situation that actually it's more than that.

It's closer to 45 years. When I was a graduate student at University of Iowa, we lived about seven miles from the laboratory and I I'd get up, eat breakfast, then get on my bike and ride to the lab, and then I would ride back at the end of the day.

And I started having a lot of problems with gastric reflux and chest pain from it. It kind of makes sense. You don't want to exercise when your stomach's full, particularly if there's like orange juice in it, And so, I found if I just don't eat breakfast and get up and ride the bike in, then that improved the reflux symptoms a lot.

And then, yeah, so I never switched back. But the one thing, all right. I'm a little peculiar in a lot of ways, but one of them is, so I've had a lotta pain issues throughout my life, and I didn't, that's one, right?

The reflux pain, I had that off and on for actually several decades, partly because of what I was eating, maybe I eating my evening meal too spicy a food or something, Then I started to have problems where just sitting down, fork, standard time, you know, or so I'd start to get pretty bad pain in my rear end.

And so, I've had to sit on the doughnut cushion with other cushions for decades. Then, as I did a lot of distance running and trail running, mountain bike riding, and I start have some, this is about, 15 years ago or a little more, no, more than that, closer to 20. Started to have some pain in my feet, kind of tingling, burning pain.

And I went to the neurologist at Hopkins and he diagnosed me with some sort of neuropathy, peripheral neuopathy. But it didn't bother me enough that I was still running and stuff.

In fact, in 2016, I ran my last half marathon trail race. And then I had was having some knee problems, so I started mountain biking a lot. Then I have a mountain bike accident in 2019. Oh dear.

Yeah, and it was not good. Bottom line is I tore some muscles off my pubic bones. Ouch. From the inner leg muscle and even my rectus abdominis on one side.

And I had surgeries on those and I really had a difficult time recovering the physical therapy. I was getting like extreme pain from it. And so then I went back to my neurologist, who's actually a friend of mine, and we did genome-wide exome sequencing.

Essentially we sequenced all the genes in my genome. And it turns out I have a mutation in, it gets a little technical, but a voltage-dependent sodium channel.

that's expressed almost exclusively in neurons that convey pain, nociceptive neurons. And the mutation, essentially my neuron, my sensory neurons, that sense pain fire much more easily than yours are, these are very rare mutations actually, one in a hundred thousand are even more rare than that.

But it means that you feel more pain, literally. You feel pain than other people. Yeah. Oh, how awful. Now, one thing I didn't do all this time, so I started running in the early 1970s, distance running.

And back then, even the elite runners, their training was they ran. They didn' do any cross training or resistance training. And I never, and then so I just kept doing that mainly, do some stretching and stuff.

I coached high school cross country for seven or eight years here in Maryland.

Lifestyle factors for healthy aging

But I didn't do any resistance training. And so since I had the mountain bike accident and all these pain things and the neuropathy is getting worse, my ability to exercise is declining.

And my muscle mass is starting to go down. So I'm trying to maintain my mass now. But in hindsight, I wish I would have done the resistance training in addition to just the aerobic endurance training.

Get the combination. What else are you learning as you get older? So this is one takeaway, right? I the strength training, in addition to the aerobic exercise, getting both of those in.

What other things, if you were giving advice to someone in their 30s or 40s about what it's like to age well, whether it is personally, professionally, what have you learned being someone who's in it?

Well, we know what things to do throughout your adult life. to increase your chances of, you know, aging well and being functional and then dying when you're 100. And that, exercise, don't overeat, healthy diet composition, keep

socially engaged, intellectually challenged, Keep busy kind of bottom line.

However, There's genetics and there's a lot of luck. So what people can do during their adult life it greatly increases the probability they will age well.

It doesn't guarantee it. But it also, if they have kids, it's important to set, you know, be kind of a role model for your kids. Health habits are often adopted early in life based on what the parents do.

So, not always, but often, more often than not, if someone grows up in a family where neither parent exercises and both parents eat a lot of junk food and, you know, whatever, watch TV a taxing their brain, either stressing or challenging their brains.

Those kids are more likely than not to adopt the same lifestyle. So I think people in their 30s and 40s, if you have kids, you should be thinking about your kids' health habits.

You can tell them what's healthy, but leading by example is much better. Kids pick up on what you're doing. Not necessarily what you're saying. Yeah. So I think this is a huge problem in this country, this transgenerational propagation, if you will, of poor health habits.

Well, it's easy, right? In society these days, we're told you can sleep when you die. And the least expensive, most convenient food is not what's good for us.

We need to work extra because it is expensive. I'm a parent. And I'm also an atropathic doctor whose focus is on brain health, and I find it challenging.

I have resources close by to great healthy food. We are very active as a family. we go backpacking and surfing and spend time at the beach and outside.

But it's hard to prioritize those things. It's so much easier to turn on the TV or to spend the afternoon scrolling and to work more and buy the convenience food, so it really is You're going against the grain of what you're told to do in society, really, when you go to adopt a healthier dietary pattern or exercise habits, or even getting to bed early, right?

It's so easy to stay up and binge on Netflix and to watch more TV and not get to the bed. So I think it's challenging. I you are absolutely right. It is what we need to, but it is hard.

Oh yeah, it's hard. I was, you know, kind of fortunate, I guess, was in situations where I could. So for example, when I as at University of Kentucky, we live just three miles from the lab and I'd run in and back to the Lab every day and that was my exercise and Actually, I could run in to the lab about as fast as I can drive, park, and then walk.

Right. You know, so I'd have my six miles a day and it's not really taking any time out of the day. I never had a membership to any fitness club, but it depends where you live.

A lot of people can't do that. And it sounds like this was part of your identity. It kind of always has been. You're a runner. That's something you've always done.

And something that you prioritize. I think there's a lot of people who would say, oh, it's too hot outside, or it too cold outside. Or I'm going to be sweaty.

We come up with all of these excuses, but it has really been a big part who you are. Yeah, I guess I didn't worry about being sweaty, probably the people in my lab didn' like it.

But usually it's cooler in the hot days, it is cooler the morning. I get up early and get into the lab by 6.30 or so. Three miles you don't sweat a lot unless it really hot.

Yeah. Professionally, what directions in neuroscience and aging research are you most excited to see next? Yeah, that's a good question. There's huge amount of research going on.

A lot of discoveries on mechanisms, the GLP-1 stories. Pretty interesting. We'll see how that plays out. Essentially, they work by suppressing appetite.

That's the main way they works, so the individuals who take them are hungry less often. You know, there's a lot of scientists are trying to determine whether some way we can mimic the effects of exercise or intermittent fasting or even intellectual challenges, I guess.

I don't know. And I think it's unlikely that any one thing, the suppressing appetite, you know if it is safe, i'm not sure what's going on from the standpoint of Are any of these people developing anorexia or not?

If you think about it from an evolutionary perspective, there's so many different signaling mechanisms, literally thousands and thousands of genes and proteins involved in our responses to exercise or fasting or using our brain.

And there doesn't seem to be any one like key switch that you can turn on by popping a pill in your mouth. So I don't see any time soon that that's going to be happening.

I know a lot of people are, you hear about these people who are doing these extreme hacking things where they're trying to, whatever, take a hundred different vitamins or whatever and chemicals and I don't know.

Personal habits, exercise, and aging advice

So we go back to these blue zones, right? The people that live the longest and functioning well the long and they're not doing any of that stuff. They're just, yeah.

There's no evidence that beyond regular exercise, moderation and calorie intake and keeping your brain engaged, there's not drug or simple trick to to live a long time.

And that's why your program is important because I'm emphasizing and I think you're emphasizing that we can do a lot for ourselves and our loved ones and don't rely necessarily on the healthcare system.

In this country, everything's for profit. And you've got the food industry who, and all these, well, in many cases, billion, multi-billion dollar industries are lobbying congressmen, senators.

And so we get all this ultra-processed food that's no good. Monoculture, we've got all these farms, either corn, soybeans, or wheat, I guess. And then they take the corn and put it in, make it into high fructose corn syrup and get you addicted to that.

The healthcare system, and I hate to say this, but in this country, it really is geared to let people get sick and then treat them. Rather, there's very little emphasis on preventative medicine.

I mean, you can go in for annual physical and your doctor can tell you, well, if you've gained some weight, your blood glucose is up. It's getting now towards insulin resistance.

You should cut back on your calorie intake and get some more exercise. Then they turn them loose for a year. And they come back the next year, they're heavier and now they do have insulin resistance.

And there has to be some way to follow up and have some regimen way, to communicate with the person, get them into a specific routine. I think they should have for like obese people who had trouble losing weight, like a one month rehab.

A referral to a health coach and having that covered by insurance potentially to talk to someone about optimizing some of these lifestyle choices and implementing, but yeah, kind of a rehab, a place where you can go and or an

intensive sort of outpatient program for getting your lifestyle choices on track.

That would be amazing, right? If it were about health, that's what we would do and be doing. But unfortunately, it's about profits for pharmaceutical companies and reducing the cost to insurance companies.

It's challenging. That's really challenging and frustrating. But that's why it is on us, right? We have to take responsibility. We had to learn and understand our own bodies and experiment with these different things like intermittent fasting and exercise and find what works for us.

I'm curious, is there anything… Intermittent fasting, you know, that it safe and one key thing is that It takes a couple weeks to a month to adapt to the new eating pattern so that you're no longer hungry during the time period you'd previously been eating.

So if you start skipping breakfast tomorrow, tomorrow you are going to be very hungry and irritable in the morning. But if can stick with it for a few weeks you'll find that, and we know why, The neuroendocrine systems that control your hunger and appetite, they don't just change like it takes time to change.

Feedback loops. Yeah. Makes a lot of sense. So if you could leave our listeners with one key specific piece of advice for keeping their brains sharp and resilient, what would it be?

Keep engaged in intellectual activities. Always be learning new things. I love it. Potentially listening to brain ponderings and learning more from Dr.

Matson. This has been a really incredible conversation. Your decades of research have given us a roadmap for how fasting and exercise and other lifestyle choices to protect our brain and keep us thriving.

Future therapies and closing thoughts

If you, our listeners, would like to dive deeper, I encourage you to check out Mark's books, The Intermittent Fasting Revolution and Sculptor and Destroyer, or tune into his podcast, Brain Ponderings, for more fascinating insights.

Here at Think Well, Age Well my mission is to make dementia rare and optional so that aging can be joyful and full of possibility. If today's episode has inspired you, please share it with a friend, subscribe wherever you listen, and join us again next week for more conversations with incredible people like Dr.

Matson on living long and living well. Thank you. Is there anything else you wanted to add? No, it's not really. Yeah, I mean, if people are having memory problems, there are some things that can be done.

So the ketones, actually there's some early kind of preliminary studies published, clinical trials showing that Have you heard of medium-chain triglycerides, MCTs?

Yes, of course. They're like the short-chained fatty acids that are immediate precursors to the ketones. To beta-hydroxybutyrate, yeah. Yeah. And Steve Kunane up in Canada has done some trials, and there's multiple trials going on now in patients with, in the early stages of Alzheimer's disease, with the Ketone Ester.

which was developed at NIH where I was. And I think it's really promising. Demetrios Kapagiannis, who was a neurologist under me, did a trial of intermittent fasting in, which I didn't mention, in older people with obesity and insulin resistance.

They're between 55 and 70, obese and insulin resistant and randomly assigned to 5-2 intermittent fasting or the USDA healthy living diet. And anyway, we published this in, where did we publish it?

Cell metabolism. Yeah, cell metabolism, which is actually a good journal. And the bottom line was that after two months, the intermittent fasting did improve memory in multiple domains and executive function.

Then Dr. Kapagiannis is now doing a trial of ketone ester in patients with early Alzheimer's disease. That's exciting. I can't wait to see the results of that and see that published.

That was fantastic. Yeah, we certainly see it helps. It makes a big difference when we can get people into ketosis. Ah, good. Yep. Yes, it's really fun.

Thank you so, so much for being here and for taking the time. And I know that you're busy. You've got lots going on. Yup. All right. So it is really a privilege to have you.

My wife and our granddaughter just came back from the library. Oh, well, go enjoy them. Thank you so much for listening to the Think Well, Age Well podcast.

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