Introduction and Guest Background

Welcome back to this episode of the Reverse Alzheimer's Summit. I'm so delighted to introduce you to my guests today. Dr. Mark Mattson. He has a Ph. D.

in neuroscience and just four years ago, retired as the chief of neuroscience at the National Institutes of Aging. He's now on faculty at Johns Hopkins, where he's teaching and cheerleading research on intermittent fasting in particular.

He's the author of the book Sculptor and Destroyer Tales of Glutamate The Brain's Most Important Neurotransmitter, which we're going to dove into the content of today here on this show.

And that book will be available in August of 2023. So get that preordered right now. The intermittent fasting revolution is his other book, which can be found today on Amazon.

And he's also the host of the podcast Brain Ponderings. And I found him through one of his interviews on YouTube where he was discussing ketosis with absolute phenomenal clarity and articulation.

And I learned so much of it. So I'm so thrilled to have the opportunity to talk to you today. Dr. Mattson, welcome. Well, I'm glad to talk with you. Dr.

Sanderson's okay. So the camp. I call you Heather. Oh, absolutely. Thank you. Please do. So I want to dove into this glutamate conversation before we hit record.

You were already. You didn't know it, but you were singing to the choir. So I agree that glutamate is the brain's most important neurotransmitter. And I also offer that I thought GABA was up there as well.

And you find you're surprised that a lot of neuroscientists, a lot of psychiatrists don't realize this. So will you explain what made you draw that conclusion, that glutamate is so important to our brain function?

Well, I think most neuroscientists would agree with that. But so more than 90% of the neurons in our brain deploy glutamate as their neurotransmitter, and then maybe 8% or so is the inhibitory neurotransmitter gaba.

So the core circuitry throughout our brain, hippocampus, cerebral cortex, all throughout, it's just glutamatergic excitatory neurons being modulated by local animal artery activity of gaba allergic neuron.

The other neurotransmitters serotonin, acetylcholine, dopamine, norepinephrine, they're the neurons that produce those are few a number and located in discrete regions.

So for example, dopamine, those neurons are in the substantia nigra or another region called the VTA and then the serotonin norepinephrine neurons are in the brains.

Then they have axons so that cause up into the cortex and synapse on glutamatergic neurons. So the only way any of the other now transmitters affect our behavior are learning and memory storage of memories is by modulating the activity of the excitatory mm.

Neurons. So it's almost like a default mode. And that's the most evolutionarily, evolutionarily and ancient system where the early nervous systems essentially had some excitatory neuron that would respond to some stimulus touch, for example, or a chemical in the environment of a simple organism.

And then inhibitory neurons involved evolved and they'd have like this reflex behaviors. And then so that kind of car

circuitry just kind of amplified increased numbers of neurons going up the phylogenetic tree up to humans.

Why Glutamate Matters in the Brain

And yeah, so it's the learning and memory neurotransmitter in Alzheimer's disease and the neurons that die, but they generate have neurofibrillary tangles.

They're predominantly glutamatergic neurons. And so the deja dysfunction and degeneration of those neurons is responsible for Alzheimer's disease. And I've done a lot of work.

My lab, many people going through my lab over the years, trying to understand what's going wrong with aging and what happens during normal aging, that kind of puts neurons at risk.

And then also what environmental factors a diet, lifestyle and genetics, how they influence this to determine whether person you know continues to function really well or declines.

Okay. Tell us everything you learned. Okay. So I'll go back actually to when I was a postdoc and I was in a lab, the head of the lab, his name is Ben Carter at Colorado State University.

And his lab had been studying snail brain neurons. And the reason is they're are ten times as big as neurons in our brains. So there you can actually see them with just a simple magnification.

And but anyway, they discovered that actually serotonin affected the outgrowth of the nerve cells as they grow and form synapses. And so then I started looking at Penn with similar idea that neurotransmitters have a function even before synaptic connections are made, and may play a role in the establishment, the wiring of the brain during development.

So I was I learned a method for culturing hippocampal neurons. So we take embryonic rats and actually we even were able to get some human neurons and we put them in culture and we can under the microscope, watch them grow over days and days grow, dendrites and axons form connections and exhibit kind of spontaneous activity.

And by manipulating glutamate, I discovered that glutamate plays a critical role in the development of synapses during brain development. And then I got interested in the death of neurons, because it turns out so glutamate and excitatory neurons, it depolarize is the membrane which can cause the neuron to fire. And if a neuron is exposed to too high levels of glutamate for too long a time period, they can be excited to death.

And that can be easily observed in cultured neurons where you can just look at the same neurons before and in different time points after exposing to different concentrations of glutamate.

And you'll find that low concentrations don't have too much effect on the neurons, maybe inhibit the outgrowth of dendrites a little bit, a little higher concentrations cause formation of synapses, but if you get too high, neurons will die.

And we kind of worked out what the mechanism is, why they're dying. It has to do with when a neuron is exposed to glutamate, there's calcium influx into the nerve cell and too much calcium for too long in time inside was fell.

So this doesn't have anything to do with dietary calcium or anything like that. It has to do with the way the nerve cell handles calcium glutamate cause elevation in calcium that can damage and kill neurons.

And then I found that this excited, toxic process, particularly when it's kind of slow or over a period of many days, causes changes in the neurons that are similar to what seen in the neurofibrillary tangles in Alzheimer's disease.

With this protein called tau, you probably are listeners I've heard of before. Yeah. Okay. So the other thing many of our listeners have heard of before is Namenda or a moment in and this is the one of the drugs that's often prescribed for people who are diagnosed with Alzheimer's or even moderate, mild cognitive impairment.

And this has a role to play in terms of this neurotransmitter glutamate that you're talking about. And my understanding is that it's an antagonist, so it actually blocks glutamate.

So is it is it essentially working on this mechanism that you're describing of glutamate toxicity in that excess calcium? Can you describe the connections there?

Yeah, absolutely. The the Melman team, well, there's the the receptor for glutamate through, which is actually an iron channel through which calcium can flow when glutamate binds to that glutamate receptor.

It's called the NMDA receptor. And so Memantine will block the opening of that channel. So we're going to make cell binds to the receptor, but the calcium doesn't flow in. And this momentum was developed by Stuart Lipton.

It was known for a long time and that was when he was at Harvard and this was back like at the same time. And then we were this was in the 1980s. I was doing the work on this medicine.

It was the late eighties, early nineties, I think, when Stuart Lipton started working on this in relation to Alzheimer's. So we kind of did cell culture work.

It suggested this. We'd also shown actually my most highly cited paper where I actually did the experiments myself was where I found that amyloid beta peptide at levels that are accumulating on the surface in neuron but are too low to actually damage the neuron.

Even those low levels of amyloid can make neurons vulnerable to being excited to death by glutamate. MM So the amyloid renders the neurons vulnerable to being damaged by glutamate.

And so the Memon team well first I would say it doesn't have a dramatic effect in Alzheimer's patients, but in the clinical trials it did slow the progression somewhat.

The thing is it's kind of tricky because glutamate is critical for learning and memory. Right? Right. So and this is actually why in contrast to, say, antidepressant drugs that affect serotonin or anti-spike, drugs that affect dopamine, you know, they they can have some side effects, but they're not like major.

But with mantiene and other drugs that inhibit glutamate receptors, it's kind of a tricky business because if you give them too much, then that that's going to by itself impair learning and memory.

I think there's a very fine balance here. Yeah. And you know, it's interesting. It was back and then I was in the nineties I, I really got a little discouraged that there's going to be any drug that's going to have a dramatic effect that's going to, you know, reverse, completely reverse the short term memory impairment of someone who already has Alzheimer's disease.

So I got really interested in risk reduction. And what can people do during their adult life to make it less likely they'll develop Alzheimer's? And that's actually how I got into the intermittent fasting, because so aging is the major risk factor for Alzheimer's disease.

And there's a lot of bad things, if you will, going on.

Glutamate Toxicity, Alzheimeru2019s, and Memantine

As we get older and older, there's increased accumulation of oxidative damage molecules in our cells, that is, proteins, DNA lipids that are damaged by free radicals attacking them there, as we talked about glutamate and GABA and this kind of excited to worry inhibitory balance and the importance of that and keeping brain functioning within normal limits and with aging and also quite dramatically actually in Alzheimer's disease, there's hyper excitability of neurons.

In fact, people with Alzheimer's, they have greatly increased incidence of seizures compared to people who don't

have Alzheimer's. And there's been a number of studies where the neurologists record EEG electroencephalogram.

So electrical activity in the brain and in people with mild cognitive impairment, early Alzheimer's disease. And in those people, you know, even if they don't have any seizures, there is evidence of some hyper excitability going on.

Yeah. So it turns out we can get this will lead to the ketones. It's kind of interesting how this all happened, but so and when was this in the mid 1990s.

Until then, there were really no really good animal models of Alzheimer's disease. That is, models where there'd be the amyloid beta peptide plaque accumulation and the tail tangles and cognitive impairment.

And so and probably your listeners have heard of a couple of the genes that mutations in which can cause early onset inherited Alzheimer's disease. Yeah.

Like the AP and the piece in one and piece into a really common. Well they're not common at all in the population but they're associated with that early onset.

And I think there's some semantics that get confused here. So early onset, when we say early onset, what we mean is onset in your forties and fifties.

So in those early decades of life where you wouldn't expected not the early stages of the disease. So that's a different thing. And typically the typical Alzheimer's, the much more common Alzheimer's is that late onset.

But the early stages and you're having it happening in your sixties and seventies is that I understanding that. Right. And that's associated with the EPO e status.

Yeah, that's exactly right. What you said and so. Right. So the problem has mice don't develop, you know, no matter how old they get, they never develop the amyloid accumulation or Talbert allergy.

And it's probably because of that actually the gene, a gene for the amyloid precursor protein is different sequence and tau too. But anyway, so then what now is when families that harbor those mutations Presnell and one piece that go into our AP were identified, then animal models started to be made where investigators introduced the mutant human gene into the mice.

And so we, we actually made in collaboration with George Martin, University of Washington, made a place in Illinois, 1 million mice. And it didn't develop any amyloid pathology at all.

And the reason is because the the endogenous mouse the mouse amyloid doesn't aggregate. And we did find some abnormalities. And but but then anyway, then we sent those mice to Franklin, Florida at UC Irvine, and he made a mouse called a3x tagged mouse that has mutations in amyloid precursor protein presnell and one and how the mutation a mutation can cause frontotemporal dementia, which is what now I'm trying to think what's the movie?

The movie who's forgotten? The actor that recently diagnosed with. Was it Bruce Willis or. Ramos-Horta? Yeah, but that's essentially Tao pathology, but not amyloid anyway.

So bottom line is we had mice then get as they age, amyloid accumulation plaques and neurofibrillary tangles like pathology learning and memory deficits.

So since aging is a major risk factor, we asked whether an intervention known to slow down aging and extend lifespan would would affect the development of the disease and the cognitive impairment.

So we took the three x TGA device, the Alzheimer's mice at a young age before there's any amyloid or tau pathology and we put them on either every other day fasting or daily time restricted eating on calorie restriction, actually to 30% daily calorie restriction or just their normal and libitum feeding where they have food available all

the time and eat multiple times every day.

And then we let them go for a year and then at the end of the year we tested their learning and memory and we looked at the and quantified the amyloid and pathology in their brain.

And the bottom line is that normally every other day fasting and the the daily calorie restriction, 30% ameliorated the cognitive deficits and and less and not completely but a lot the amyloid and tail pathology.

And so it did this surprise you? Did you immediately start eating less? Actually, I had already. So this another interesting story from the intermittent fasting thing when I was a graduate student at the University of Iowa in early 1980s, I lived like seven miles from the campus and I was riding my bike in and back every day and so on.

Up till then I'd eat and breakfast all the time, but I started to get like bad reflux, esophageal reflux, you know, because I'd eat like whatever cereal and orange juice.

Then I'd get on the bike, you know, right in. And plus I'm in graduate school, graduate school, probably under a lot of stress. So I found if I didn't eat breakfast like it had a big effect in helping with the gastric reflux.

So I haven't eaten breakfast since 1983. Oh, wow. Except, I mean, I could probably count on one hand the number of times I had eaten breakfast got. And did you notice that not only did your gut feel better, do you feel like your health outcomes are different because of it?

Yeah. That also I'm I found I'm really productive in the morning hours before I eat anything. And so I essentially eat all my food within a six hour time window every day between noon and six usually.

And then I well, it depends since we moved when we moved to Maryland, when I got a position at National Institute on Aging, we lived 25 miles away, so I can't ride my bike or run or anything.

So I did then is I I've got to run before I eat anything as much and yeah. Anyway, so that's kind of my routine now. I don't eat breakfast and I exercise between 11 and 12 and then I eat lunch and dinner and but anyway, so this gets to the ketosis and so if, if you were to stop, if you were to, okay, go to sleep at night and then get up in the morning, don't eat anything.

Then about mid-morning it's that to be a rise in ketone levels in your blood because you will have then depleted all your liver glucose stores which are always used first by cells in our body, brain, heart, muscle.

And then what happens when that glucose in the liver is depleted? Fats are released from fat cells into the blood fatty acids. They go into the liver and they're converted into ketones which can be used for an energy source.

And this is why animals, including humans, a lot of predators, particularly, they can go a week or more without eating anything out, eating anything. And during that time, they're essentially running out their fat stores and the ketones. And then in relation to Alzheimer's, this go even more interesting because I knew this has been known, I think since the late 1980s that there's a method called pet imaging positron emission tomography.

And it was shown back then that and this is they inject into your blood essentially radial labeled glucose or a modified form of glucose called two deoxy glucose or fluoro deoxy glucose till they injected into your blood.

It goes to your brain and it's taken up by cells and then over time will accumulate depending on how well the cells in case the brain neurons can take it up.

So it was known by imaging how much glucose is accumulated in the neurons that Alzheimer's patients, there's a big a dramatic deficit in the ability of the neurons to take up glucose from the blood and and use it for energy.

Right. And we had found again and this was back in the 1990s again that the amyloid beta peptide impairs the ability of neurons to take up glucose, but it doesn't impair the ability of the neurons to take up ketones.

This kind of feels like a chicken or the egg situation because we we know that glucose is also highly toxic to the neurons right in excess and then even insulin itself in excess can be toxic.

So there it's like, ah, the it almost sounds like this self-perpetuating cycle because the glycol toxicity can lead to inflammation, which can express itself as amyloid plaques, and then the amyloid plaques themselves sound like they inhibit successful utilization of glucose.

Yeah, that's really good interpretation of what I said and the.

Intermittent Fasting, Ketosis, and Brain Energy

Yeah, and there's an investigator up in Montreal, Steve Kinane, who's he's done pet imaging with radial label glucose and radial label ketone in the same people.

Had one nice study where he just had normal, healthy people and he had them go on ketogenic diet for a I think it was a couple of weeks and then he did well, he did the imaging before and after they were on the ketogenic diet.

During the time they were on the ketogenic diet, it was very clear during the in the ketogenic state whether it's fasting or not, eating any carbs and eating that, the neuron switched from using glucose to ketones.

And you're right, there is it is something called carbo toxicity or glucose toxicity. And as you know, and I'm sure your listeners have heard from you several times, type longstanding Type two diabetes is a risk factor for age related cognitive impairment.

Alzheimer's and also vascular dementia. Yeah, so are, you know, as you know, there's a big increase in the number of people with Alzheimer's. And a lot of that has to do with the baby boomers, right.

Getting to be the end of the day, danger zone, age range. But part of it's also, I think because of the epidemics of obesity and type two diabetes, which exacerbating that and I still think a lot of the general public isn't really aware of this, that this is like a big deal.

And yeah, and I'm just I'm a little bit concerned with, you know, someone with type two diabetes, ideally, you know, they would be able to somehow get them on an eating pattern, say intermittent fasting, eating pattern, exercise program, you know, healthy diet.

No, don't take any simple sugars and avoid bad fats. You know, we kind of know what kind of a good a good diet. And I'm a little concerned that people have heard this in the news right lately.

This GLP one receptor agonist that what is it? I never know that the trade names company names of these drugs because I know that and actually this they were developed at NAIA when I was there by Josephine Egan was a diabetes expert and Nigel Gregg, who is actually in my lab.

Oh, they're really good for controlling blood glucose. And they do. They increase insulin sensitivity. They also suppress appetite. And that's why they're being marketed now for obesity.

But I'm concerned this then that, you know, this is something I put I have a chapter in my book, Intermittent Fasting Revolution book called Beware of the Dark Forces.

And that's for profit. You know, pharmaceutical companies, fast food industry. Great. Big agriculture, monoculture lobbyists, even, you know, so everybody knows who's listening to this.

We're going to overall the wealthiest country in the world, although we have a high level of poverty and we have put more money into health care and have worse health outcomes.

And it's because the systems all geared, completely geared to letting people get sick and then giving them a drug.

Right. Or that geared it all towards risk reduction prevention, you know, education beginning at early level.

And now all these bad habits fostered by advertisement and so on, it's transgenerational. So kids that grow up in a family whose parents, you know, are sedentary, eat fast food all the time, maybe even smoke, although, you know, the kind of the rigorous campaign by the government against smoking where they, you know, show up someone with a black lung or someone with whatever throat, cancer, talking through a red tube.

I mean, I think there should be ads that may be getting controversial. But, you know, how do we get people to recognize that they're being. I'm a Bob Dylan fan, so they're they're only pawns in their game.

Right. And this is exactly why I invited you on is because I I heard you speaking to some of these more controversial subjects. I mean, ketosis is controversial. Right.

And I could, as you're describing this whole process and I mean, I feel exactly the same way you do. And I'm so grateful that I'm not the only one saying it is that society is set up to keep us sick.

Right? Not only is it cheaper to eat food that isn't good for us than it is to eat vegetables and the stuff that is good for us. It takes so much time.

It requires times to make food. And if we're working two and three jobs just to pay rent, it doesn't work. There's no way to get healthy and get ahead of it.

And then we're also, we're told, like it the message is that there's going to be a drug that's going to save us. We're piling loads and loads of money.

I mean, the NIA, right. This there's a whole I don't know if you're familiar with Carl Herb's book around how not to study a disease, but as the name was was formed, right, there was this lobbying to get funding for it.

And so they made Alzheimer's. This kind of there's this inflation of what Alzheimer's meant and what it ended up doing was supporting pharmaceutical companies in terms of finding a drug and not a drug that cures it, but a drug that sort of maintains things so that people are on it long term so they can make more money.

And I don't mean to be super conspiracy theorist here, but I do think kind of going back to the wegovy and the micro or the peptides that you're talking about, these weight loss peptides, everyone's talking about them a ton right now because it sounds like the silver bullet and it's it's the promise of better living through chemistry, right?

That there's going to be this magic bullet so that we can get away with sitting on the sitting on the couch and eating ice cream. Right. And not have to pay for it.

And yet these these drugs, I hope that there's a place for them that they they can help and support us, but not without the foundations that you're speaking to so clearly of a good diet, exercise, good sleep, good social connections, purpose and meaning in life and all of the things that really help support health at a at a cellular level and at a social level.

Yeah, yeah, yeah. We're, we're on the exact same wavelength. Yeah. It's so, it's so nice to hear from some of here. John Hopkins, right. Like just to give it credibility.

There's there was a lot of tunnel vision back and I understood, you know, I was involved in research on Alzheimer's. And early on I met I said this already early on I thought this focusing on the amyloid beta peptide and putting all these moneys up.

And that was and I was on study sections. I was at University of Kentucky for 11 years at their Alzheimer's Research Center. And and I was on grant reviews for NIH and NIH and yeah, the study sections were kind of dominated by amyloid people who thought any other ideas were, you know, off.

And we just need to focus completely on this. Right? The refrain was, if you're not studying amyloid, you're not studying Alzheimer's. Yeah. And yeah, I don't know.

And that's again, that's why I got interested in general mechanisms of aging. And we've done a lot of work on mitochondria and you know how mitochondrial function declines during normal aging and how they're adversely impacted in Alzheimer's disease and we did a lot of preclinical studies with certain things, for example, that we're involved in.

Well, the GLP one receptor agonist, it turns out neurons throughout the brain have receptors for GLP one and and therefore respond to these drugs that are given for diabetes and now for obesity.

And we found that they can have good, good effects on the neurons. So when people report that they stop craving alcohol, even. Though that that's. I didn't know that. And that's interesting.

Yeah. Cravings for for food as well as alcohol and drugs. From what I understand, they have a handful of patients who have been prescribed them from other people.

And one of the side effects is a reduction in cravings generally, which I mean for. But that's just like an action on the dopamine system and prevention of food intake.

Yeah. Was generally thought to be on the hypothalamus where the Senate where you know, hypothalamus responds to leptin and ghrelin and GLP one this satiety and hunger centers, you know, but if, if it's inhibiting, craving, craving for alcohol so it'd be interesting to see what other drugs do, right?

Yeah. Yeah. I'm definitely curious what's going to happen with those meds, but I think you you bring up this really great point of like aging is the primary risk factor for developing Alzheimer's.

We have no control over our biological age over winter excuse me, our chronological age. We have no control over when we were born and how long we've been on this planet.

But we do have control over our cell health and our biological age, if you will, around how well our mitochondria are functioning, how well our neurons are functioning, if we're creating new ones, if we're creating new connections.

And there are some really foundational pieces, including diet, which you're an expert on that impact, that. So can you just break down for us like how does the ketogenic diet help with cell health and reducing that aging process or slowing the aging process?

Okay. So ketones are taking taken up in the neurons and they go into the mitochondria and they can be used to produce ATP and there are less free radicals produced when ketones are used to produce ATP compared to when glucose is used.

So that's one way, probably some reduction in free radical production. Another thing is there's a lot of evidence now that ketones have signaling functions.

My lab in a lab up at NYU, the same time we published papers showing essentially the same thing that one of the ketones beta hydroxybutyrate or a it will induce the production of a protein called BD and brain derived neurotrophic factor, which is well known for its important roles in learning and memory.

It also protects neurons against stress. Did some of the early work in cell culture showing that? And yeah, so we think that's you know there's multiple mechanism whereby the ketones may benefit neurons and probably some yet to be discovered out.

One other one is they seem to enhance gabaergic tone, enhance the inhibitory control of the glutamatergic neurons by GABA. So essentially they increase the amount of GABA released in synapses and that kind of keeps the neurons from being overexcited.

And we found intermittent fasting does that. And what's interesting, the intermittent fasting is that it takes at least two weeks and then by a month we definitely see these effects for these effects that occur with intermittent fasting, enhanced GABA tone, upregulation of BD and F so it doesn't happen like overnight.

It takes these cycles of fasting, recovery kind of like exercise, right? You know, you exercise intermittently. You can optimize and help optimize health and fasting.

Eating is kind of the same thing where during the challenge period, whether it's exercise or fasting, signaling pathways are activated in neurons that help them become more resistant to stress in the future and function better.

But then it's during the recovery phase know eating, sleeping, resting that the cells actually grow, increase the number of mitochondria form new synaptic connections.

So it's but if they're never challenged if the neurons are never subjected to the mild stress of fasting or the mild challenge of exercise, an analogy with muscles and they never they never get stronger and they're more prone to stress.

They become complacent, etc.. You know, I'm noticing Ray behind you, there's a book with the title for Mrs., so maybe we can put it in in that context because I think a lot of a lot of our listeners are familiar with that concept of like, we need to stress the system in order to get more resilience and advocate. For now, this is my intermittent fasting revolution.

Oh yeah. So is that the intermittent fasting revolution? Levitt Did you write the head medic books you were Mrs. Book. Well, me, myself, then. A guy named Ed Calabrese.

Oh, yeah, of course. Yeah. Him and I did this book. It's it's an edited volume, so it's not just him and me. It's it is chapters. Like, I think me and people in my lab wrote three chapters and wrote one.

Then we invited other people. And they were okay. This is fantastic. So can do you put ketosis in that. I certainly put exercise in that kind of went under that for a medical ketosis and an intermittent fasting for sure.

And then I also oxygen therapy like the Wim Hof breathing. I don't know how familiar you are with that, but like oxygen deprivation can be another way.

Are there other solitary heat and cold.

Diet, Stress Resilience, and Neuroprotection

Cold and toxic chemicals in plants. And are the secondary metabolites? Yeah. So I wrote an article. I got invited to write an article for Scientific American in 2015 and called What Doesn't Kill You.

And then the artists there did like they have this picture of this alien beat coming down. But, but anyway, so it turns out that the chemicals in the skins of fruit are, you know, kind of the vegetables and things are good for our health.

The reason they're in the plants is to keep insects and herbivores and omnivores from eating much or too much of them. And so they're not antioxidants in the sense that they scavenge free radicals.

What they do is they're actually toxins. And so when our cells are exposed to them ourselves, respond with that with adaptive stress responses. And that increased the expression of genes encoding and and enzymes.

So there's kind of classic pathway that called nerve to pathway where there's chemicals such like sulforaphane and broccoli and some others, they'll activate this transcription factor and increase the expression of several enzymes that remove free radicals.

So we evolved at least four ways to deal with these potentially toxic things in the plants. So the plants are good for

us in that sense. And when we could get energy from all right, but we didn't want to die from eating them.

So bitter taste. So all the chemicals that are good for your health have a bitter taste. So if you just take the pure chemical and put it on your tongue, caffeine even, and if you take any of these chemicals and put them on your kitchen counter, or if they're in coffee beans or tea leaves, your ants aren't going to they'll stay away from them.

So that's a kitchen experiment demonstrating that these are at least insect antecedents. The insects don't like whatever it is and they these things and similar if you take green tomato green tomatoes they're very bitter.

And there's a chemical called Famotidine that's in the skin of the green tomato. We actually published a paper on this and then it had some good effects on cultured neurons.

But anyway, and then as the tomato ripens and turns red, levels of the tomato didn't go way down in the skin again. It has a very bitter taste. And so from an evolutionary perspective, what's happening there is that if an animal eats, you know, animal bird, it's the green tomato.

The seeds aren't yet developed in the tomato. And and therefore, there's no chance that that tomato plant is going to propagate itself through the seeds.

Right. But then when it becomes ripe and the seeds are mature, then that chemical goes away. The birds can eat the tomato and the seeds and then fly over there and poop out the seeds and maybe few of them.

Although the more I learn, the more reverence I have for nature. So I think in, in your list of things to be worried about, right? It mono cropping. Did I hear you say that monoculture.

Well corn you know. Ray so I'm a natural. Corn soybeans wheat that's it. I mean, that's not good. So I'm a natural Catholic doctor. And I remember learning from one of my instructors who taught me about botanical medicine and even traditional Chinese botanicals that wild crafted or the wild herbs actually are more potent and more beneficial than the monarch dropped. Herbs.

And it's because of the stress that they're under in nature and humans. You know, it's so interesting because humans are no different when we're under the right types of stress and not too much of it, we do better.

And this is that whole idea of the hermetic effect. We reproduce more protection and we actually become more resilient. But toxins, you know, we a lot about toxins on this on this summit.

And I certainly support many of my my dementia patients for on reducing toxic burden. And these are things like glyphosate roundup that's going to be found in those monarch crops and then other other toxins in the environment that we're exposed to from plastics and phthalates and PCBs and petrochemical.

Here's here's the thing. So these the natural pesticides that are the things that are involved to keep the insects and stuff, we evolved. Our liver is loaded with enzymes that rapidly remove these potentially toxic chemicals.

So they're all in our system a very short time. These natural things, the manmade chemicals, DDT is like the classic example. They keep accumulating in our system.

The concentrations just keep building and building because we haven't we didn't evolve with these. We have no way of getting rid of them quickly and yeah, and then, you know, the third way is that is the cells just have learned or not learned evolved to respond in good ways to these stressors because again, it's an advantage for us to be able to eat fruits and we evolved.

So our non primate ancestors before, you know, came down to the ground and started walking upright. They spend all their time in the canopies of the trees and they'd forage for fruits and nuts and, you know, they'd they'd have to there's a lot of evidence that that pressure to be able to know where different fruits will be at different times of year, you know, where to go sometimes maybe long distances had an important impact in and evolution of the prefrontal

cortex which is the most expanded brain region and in humans now and that's involved in in decision making and kind of top down control of our behavior, keeping our emotions in check.

Make the interpretation of pattern recognition like seasons and cyclic patterns. Well, yeah, but the hippocampus, spatial pattern recognition, cognitive maps, absolutely.

The strong connection between the hippocampus and the prefrontal cortex. But yeah, the hippocampus is really critical for spatial navigation and learning and remembering where you've gone, what you saw, you know, and then you can.

And then we evolved language so we can even come back and tell someone where we went. That's another thing I in my podcast I have on Brain Ponderings, I've had there's a scientist at Johns Hopkins, Jen Carneiro, who does a lot of work on this spatial navigation system in the brain. And, you know, we talked about how people having G. P. S.

is that going to adversely affect that function of their hippocampus down the road? And I'm a little concerned that, you know, we're not people. We're just sitting here like we're doing now, which is good.

I'm enjoying it, but I think it's important to move through our environment a lot and learn things. And probably everybody has had the experiment experience.

You like. If you need to do some critical thinking about anything in your life or your work, you take a walk or you go on a run right? And I think it's not just that you're by yourself, it's that you're actually moving physically and, you know, your brain pretty much all of its working when you're doing that because your sensory motor systems are working, you're learning and memory is working and so on.

So yeah, so here you're kind of describing the evolution towards Homo sapiens, us and sometimes people will refer to the kitchen as sort of like an ancestral diet, something more similar to what our hunter gatherer ancestors, maybe not our non primate or primate ancestors, but it's a little more recent than that.

Do you see it that way or do you? I think it still is controversial among anthropologists, even. Yeah, there's a lot of this clone of we're omnivores, that's for sure.

If you look at our teeth, they look a little bit more like a horse than they do like a dog's herbivore versus carnivore. Carnivore. And, you know, people can make the case that, well, maybe, you know, we don't have canine and stuff for tearing because we invented fire.

But I'm not sure that's the anthropological evidence. The other thing is you probably heard of the blue zones, right? And if you look at their diet composition, these are these kind of islands of longevity in different places in the world, Okinawa, Sardinia, Loma Linda, the Seventh Day.

Adventist, Yreka. And Costa Rica. And their diets are mostly complex carbohydrates, beans, root crops. They do eat some meat, but and also that I wish someone to look this and actually seen this.

It would be interesting to look at their eating patterns. I did the talk, talked to someone who said, at least in Okinawa group, they don't eat breakfast, lunch and dinner.

They know their food with a more compressed time window each day. So they may even be, you know, fasting long enough to cause this metabolic switch to ketosis.

Mm hmm. You know. So can you guess? What I've noticed is that it takes most people about 72 hours or about three days to get into ketosis. But are you seeing that a lot of people can get into ketosis quicker than that just through intermittent fasting?

Yeah. So there's kind of two phases of keto, an elevation. There's an early phase that occurs like 12 to 14 hours

after the onset of fasting and that goes from barely detectable levels or non detectable levels up to like a couple of hundred, 200 to 300 micro molar.

And then they kind of stay like that for maybe another 12 hours or more. And then between one day and two days, there's a big increase up in in a millennial or range.

Right.

Research, Prevention, and Hope for Families

And the most common way people measure the ketones, it's not sensitive enough to pick up the kind of some Miller molar and you know. Yeah those lower levels.

Them more so yeah and then then with intermittent fasting in humans a lot of the work now and there are many clinical trials it's really interesting before they're virtually no clinical trials until the last six or seven years.

And there's an interesting story on how that happened. After we did all our animal studies in the 1990 and early 2000 that collaborated with a couple of groups doing human studies, one in asthma patients, and with them, we published a paper in 2007 where we purported that if we have as overweight asthma patients every other day eat only 400 calories for two months, that had dramatic beneficial effects on their asthma symptoms and reduced inflammation, increased airflow.

And then we collaborated with a group in England, Michelle Hardy, in a study of 100 women overweight, wind up women randomly assigned to eat what's now called five to intermittent fasting.

Two days a week, only about 600 calories. Two consecutive days. Yeah, another five days. Eat normally. And then the control group was 25% calorie restriction at breakfast, lunch and dinner.

Mm hmm. And anyway, so over six months, both groups of women lost about the same amount of weight. But we found a bigger improvement in insulin sensitivity in the five two intermittent fasting, then a BBC producer picked up on that study and did a documentary that aired in 2013, and it's after that aired that all of a sudden on the Internet, there'd be a lot of chatter about intermittent fasting before that.

If you Googled intermittent fasting, you'd get some scientific articles, the top hits. Now, it's hard to find the actual science unless you go to PubMed.

So the intermittent fasting kind of crazy. This is something that you think will probably stick around with limited calories having and you skip breakfast because some people skip dinner and say that, oh, it's better breakfast and lunch and skip dinner and have a more of a window between dinner and or your last meal and sleeping.

Do you notice some benefits with one or the other, or do you think it's just really about having that compressed feeding window? For me, it's all I think it depends on your work schedule.

Right. What what were the easiest? Was the skim breakfast and get to work and then, you know, again, eat lunch, come home, eat dinner. And if you if you eat breakfast and lunch and you're not eating dinner, see my mother.

Your mind works best when you're in the fasted state. Yeah. So I mean if you, if you eat a meal, particularly if it has any carbs, you often feel sleepy afterwards.

That's like the opposite of being cognitively sharp, you know, functioning well. So for me it does fit my daily schedule. I get up early in the morning work and exercise, so I do all my like critical thinking and writing in the morning and then after noon, work stuff is like stuff I could do with the brain without having to focus a lot.

Use a lot of brainpower. Dr. Mattson This is just the most fascinating conversation. And I am I can't wait to get your books and read them and learn more from you.

It is an it's such a pleasure to have you here. And I just couldn't be more grateful for your time. I have an I submitted for the four or five deadline a grant application to the NIH and I it and so wish us luck we our program officer over there was really helpful and was also suggesting that this was.

A program office. Oh gosh, I got to I would have to look his name up, but he was so helpful. Um, never mind that. Probably. No. Probably. But he was just very in it, not overly, but just saying that our, our approach, this kind of multifactorial approach is the direction that the NIH does want to go.

And I was so heartened by that, because I feel like my mentor, Dr. Dale Bredeson, you know, he's been saying this for a while. And and, of course, we always need more research.

You know, I would collaborate a little bit with Dale a long time ago. I used to say, I told you I was a University of Kentucky. Dale from Kentucky. Yeah, right, right. And then he.

And so yeah, we cleared whatever name on like one paper to paper that said. Oh that's great, he'll be here. So he's a co-host of the summit and so he'll, he'll be excited when he's writing.

I absolutely will. And you so you probably know he's been sort of like yelling into the wind about this for a while. And the IRBs and sort of the research was really focused on these these single interventions.

And it's so much easier to test that right. It fits into our model, that scientific model that we've created. But the model doesn't meet the complexity of the disease.

And so we've needed this switch towards a more multimodal intervention. And I feel so grateful that I sort of I'm arriving at all of this at a time when the NYA and JH they're encouraging this and funding it.

And so I'm very hopeful that we'll get their support. You know, it's interesting. I'd like to think I had a little bit to do with that because, you know, because, you know, doing all this work on intermittent fasting and then yeah, so then I got involved in some human studies and other people and then and I and I finally put out a request for applications for clinical trials of intermittent fasting in various diseases.

So they're funding quite a bit of human work. If you go on clinical trials that God, there's over 150 ongoing trials of intermittent fasting now. Oh, that's phenomenal. Dinesh is his name.

Dinesh Jun is the name of my program officer now. Okay. And yeah, I just couldn't be more grateful for you pioneering and spearheading that shift. I have personally seen many, many, many patients, countless patients reverse their cognitive decline.

And even not often. But but sometimes we people see people even with severe dementia, reversing their decline and getting better. And the amount of suffering that can be reduced is, I think, is massive, especially as you mentioned, as the demographics shift and as more of the baby boomers are getting older and more of our population is aging, we need some sort of solution.

And I've watched it work. And so, yes, we absolutely need more research. There's no question about that. But from my perspective, just morally, I can't wait for more research to tell everyone that it's possible, because I've just watched it happen too many times.

And the risks of things like intermittent fasting and getting more exercise and getting better sleep and having more connections and doing everything you can about those modifiable risk factors.

There isn't risk associated. It's not going to cause brain swelling and hemorrhaging rate. These are things that actually reduce blood sugar and and help with all reduce mortality and morbidity overall.

And so it's just like common sense, but it's been uncommon practice to do the research and to and to really dig into this and get the word out about how hopeful it is.

I think this is ultimately the ideal thing scenario that this could focus on families, too, not just in the vigils, because, you know, we want we want our kids to grow up healthy. And, you know, if there's some way I've had pediatricians contact me about intermittent fasting, you know, with childhood obesity, they see, you know, kids in the kids with obesity in their early like in their early teens.

And there's one pediatrician up in New York who's had success where he gets the parents and the kid to switch their eating pattern to intermittent fasting.

You know, and we've got this built into our trans generationally. That breakfast is the most important meal. You need to have three square meals a day, but that's actually abnormal from a evolutionary standpoint.

And it doesn't hurt kids to eat only two meals a day, especially if they have obesity. Right. Right. So my my NIA Grant proposal is for caregivers and to get caregivers the support that they need to be doing this and encouraging them to do it as well, because they're at higher risk for developing dementia later on as well.

And so this is kind of similar. It's getting families so much smaller through the spouse involved. Yeah, because there's multiple people, particularly with dementia or with with children. Right.

You have a dependent they're not going to be the decision maker. So you need multiple people involved. If the kid is a boy for. Right. Yeah. And they should, you know, as soon as they're I guess ideally, you know, the parents can tell them about this when they're high school or something or you.

Know, they can learn to prevent early on. Yeah. Yeah. Well, that's so exciting. And I couldn't be more grateful to you for this conversation, for the time and for the work that you're doing in the world.

Thank you. Okay. Heather, enjoyed talking with you again. Say hi to Dale. I absolutely will. By.