Bonus: Intermittent Fasting Boosts Brain Power: Mark Mattson, Ph.D., with Dave Asprey

Announcer:

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Dave Asprey:

You're listening to Bulletproof Radio with Dave Asprey. Today's guest is the foremost scientific researcher on the topic of intermittent fasting, a guy that I'm really, really excited to talk with because there's so much academic research that goes back quite a while now about what intermittent fasting does. But it's one of these precious pieces of knowledge that hasn't entered our consciousness, where it has been fringe knowledge. And it's just now becoming something that not just bio-hackers do, but your mom might do. In fact, my mom does do it and it makes a really big difference. He's also an expert on what it does for your brain. And he's one of the foremost researchers looking at cellular and molecular mechanisms of neuro-degeneration like Alzheimer's and Parkinson's. If you read my book, 'Headstrong', I actually referenced some of his work in that book. I'm talking about Dr. Mark Mattson, who's a professor of neuroscience at Johns Hopkins. Welcome to the show, Mark.

Mark Mattson, Ph.D.:

Thanks, Dave. I'm looking forward to talking to you. I've followed your Bulletproof website for a long time, and when I can listen to your podcasts, which are always both informative and entertaining. So I'm looking forward to our discussion.

Dave:

Well, let's get in on fasting and just go in for people who and we've heard about fasting. You have pictures of people in robes fasting for days on end and things like that. Talk to me about the difference between calorie restriction and actual fasting and what you've learned about that over the course of your career.

Mark:

The differences have to do with the frequency of food intake. A typical human liver can store about 700 calories worth of glucose in the form of glycogen. And if you're just moderate activity or like we are now, it takes 10 to 12 hours to use up those 700 calories. And then when those calories go, then you start using fats. The fatty acids are released, then those are the precursors of the ketones. And so it's possible to reduce your daily calorie intake, but as you mentioned in your introduction, eat meals frequently. Every time you eat a meal, you replenish the glucose stores in your liver. And so your fats are never mobilized. Your ketones never go up. So fasting by definition, if you're in a fasted ketogenic state, that's a sufficient time period with not eating to be designated as fasting. If your ketones never go up, you haven't hit a fasting state.

Dave:

What do you do? You've been studying this stuff for a long time. What do you when you wake up in the morning? What's a typical day for you? What's a typical week?

Mark:

I never eat breakfast and I usually try to work out midday or early afternoon. I used to run a lot, do a lot of trail running, had some knee osteoarthritis because I had a meniscus tear probably. But so now I'm mountain biking. Maybe two or three days a week I'm on the trails on mountain bike. The other days, I usually just do some walking or stationary bike. But I pretty much always do that before I eat around midday, early afternoon. And then I eat all my food within usually a six hour time window, sometimes five hours. So the rationale for exercising at the end of the fasting period, it's pretty simple, you get an extra boost in the ketogenic state. But there's also a number of we call pathways or signaling mechanisms that are activated by exercise, both exercise and fasting to get amplification of those pathways.

Dave:

Is this mTOR you're talking about?

Mark:

Well, yeah, that's one and autophagy.

Dave:

Some of my favorite words. Can you define them for people who don't know what they are, mTOR and autophagy?

Mark:

Okay and this again relates to the notion of the metabolic switch from glucose to ketones and what happens then. So when your glucose levels are high, normal, particularly after eating a meal, there's a pathway called the mTOR pathway in cells that are activated. And that pathway stimulates the uptake of the glucose. It also stimulates the uptake of amino acids from proteins in your diet. And then the cells increase their protein synthesis. And they're in a growth state. However, while they're in the growth state, they're also accumulating molecular garbage. So when cells are in a growth state and your glucose protein levels are up in your blood, it can help the cells grow. But if that stays chronically on there's accumulation of molecules damaged by free radicals and dysfunctional mitochondria. Those damaged molecules are normally removed from the cells by a process called autophagy. It's the cells garbage disposal.

Dave:

In fact, we just had a recent interview on metabolic autophagy that was very well received. And it's a very important thing, getting rid of the garbage. And you're saying that if you do an intermittent fast and then exercise at the end of it, you're going to turn up autophagy and you're going to turn up mTOR which allows you to take amino acids and put it into the cells or no? Because those don't go at the same time.

Mark:

No, then they go on up. So during the fasting and exercise, mTOR pathway is inhibited. The cells go into a stress resistance mode and they're trying to conserve energy molecules, recycle proteins. So autophagy, it's a garbage disposal, but it's also a recycling bin.

Dave:

So you can incinerate garbage to make energy?

Mark:

To make energy, but also to break down damaged proteins, but then take the amino acids from those proteins that are not damaged and use them to make new proteins.

Dave:

And you get this from fasting.

Mark:

And exercise, both. And when you combine them, you get a further enhancement of the autophagy. Then when you eat and rest, then what happens is the cells have cleaned out the garbage. And then when you eat and rest, the mTOR pathway is active. The cells synthesize a lot of new proteins and they can grow. For example, your muscle cells. When you exercise regularly, your muscle cells don't get bigger during the exercise, they get physically bigger during the rest period.

Dave:

So it's about recovery?

Mark:

Right. But if you don't exercise, the cells never get the signals that enhance their ability to grow when you do rest. So the cycles of metabolic challenge, recovery, challenge, recovery. And the challenges of fasting and exercise and then eating and resting, sleeping is very important. Those intermittent challenges we think can optimize health.

I published an article in Scientific American in 2015. And the whole take home message of the article was that many of the chemicals that are in fruits, vegetables, tea, coffee, plants, that are good for our health. The actual reason they're in the plants, the evolutionary reason, is that they are noxious agents. They're toxins and caffeine is a good example. If you pure caffeine and put it on your tongue, you wouldn't want to eat it. It's very bitter tasting. And caffeine is a natural pesticide produced by coffee, beans and tea leaves. And if you take coffee, beans or tea leaves and put them on your counter and put most any food next to it, and there's ants in your house. The ants will avoid the coffee beans and the tea and they'll go for the other things that don't have the bitter tasting chemicals.

Dave:

It's fascinating. Nicotine's that way too. And caffeine, nicotine are two of the smartest drugs from nature that increase human cognitive performance. And they both kill bugs, which doesn't mean they're bad for us, although nicotine in high doses from any mechanism is bad.

Mark:

No, but what's interesting here, Dave, is that some of those chemicals activate the exact same responses in cells that are activated by fasting and exercise. And one of those pathways, which I'm sure you've heard of is the Nrf2–ARE pathway. For example, there's a chemical sulforaphane that's present in high levels in broccoli.

Dave:

Broccoli sprouts.

Mark:

And green leafy vegetables. But the key thing of this pathway is it's an antioxidant defense pathway. So when this Nrf2–ARE pathway is activated by exercise, fasting, some chemicals in plants, then cells boosts their intrinsic antioxidant defenses and are more resistant to being damaged by free radicals. And this is really why the trials of vitamin E, vitamin A, vitamin C and a lot of different diseases, cancers, et cetera, pretty much uniformly failed. You don't want to swamp your cells continuously with these chemicals that scavenge the free radicals, because then the pathway such as the Nrf2 pathway are never activated because they're activated by the stress of the fasting, the exercise, or the chem.

Dave:

There are lots of studies on mice done with water only fasting. And so there are people out there say, "Oh, well, if they just had water, so you should only have water." But all this stuff I know, even traditional Chinese medicine, they at least had tea or coffee or pine bark tea or whatever the heck, depending on where you're from. So I always say, look, when you've been fasting, have your coffee, have your tea, enjoy your life. But the purists are like, "Oh, we don't know what it does to your gut bacteria." Where are you on the spectrum of "You should only do what the mice did" versus "have a little fun."

Mark:

I think it's actually a good idea, at least from the standpoint of the brain to drink tea or coffee.

Dave:

During a fast?

Mark:

Yeah.

Dave:

And you'd be fine with an herbal tea as well then?

Mark:

Yeah.

Dave:

Got it. And there's all sorts of different herbal teas you can do. What about mushrooms? Medicinal mushroom kind of teas and people love. I don't like chaga very much at all, but I've really gotten some benefits from lion's mane. I just had the lifecycle guys on about that. And I just had Paul Stamets on who's a famous mushroom guy. I love Paul. He was so cool. Is there anything that you've come across on using mushroom extracts? Not actually eating them because there'd be calories, during fasting?

Mark:

No studies. I am interested in mushrooms. Last few years I started foraging. I've got Paul's big thick-

Dave:

'Mycelium Running '? I think I've got it right back there.

Mark:

Yeah. And I actually bought some nice, what'd I get? Oyster and shiitake mycelia from his company in the spring and they're out in the wood chips right now.

Dave:

Beautiful. I'm just starting commercially growing cordyceps on my farm here in BC which is really cool.

Mark:

Oh nice. And Paul, he's from your neck of the woods.

Dave:

He's one island over. He came out for the interview. It was fantastic. It sounds like you guys know each other.

Mark:

I don't know him. But fascinating chemicals in mushrooms. A lot more work needs to be done. There are some reasonable studies with things like turkey tail tea and some of the things Paul talked about. But on the other hand, it's an area where there's a big need for a lot of better science. As you know, finally, they're starting to do studies now with hallucinogenic mushrooms. One of the scientists at Hopkins in fact has shown in a couple of published studies now that the psilocybin mushrooms are beneficial in people with depression. And they're not addicted. In contrast to the opioids, which is a huge problem. These chemicals in mushrooms that seem to have some interesting effects on the nervous system are not addictive, which would seem to be a big advantage.

Dave:

It seems nonsensical that alcohol and nicotine and the opiates are legal and cause a lot of harm. But I don't know how anyone could be really addicted to the strong hallucinogens. There are people who disassociate because they're so traumatized. But it's not an addiction. That's a just deep seated trauma response, which is a different animal. At least my wife says so and she's a Karolinska trained drug and alcohol addiction emergency doctor. So I'm going to believe her there. She says there are people who abuse them, but they're not addicted versus the actual addiction.

I'm really interested in compounds that I know that you're interested in. Nerve growth factor, NGF and BDNF, brain derived neurotropic factor. And I wrote about those in 'Headstrong' and there's old studies on mushrooms. There's a compound, I use one in my supplements from the fruit of coffee and polyphenol that raises BDNF. Coffee itself probably does, according to some other research. Fasting, I believe raises BDNF. Can you walk through your perspective on increasing nerve growth factor and brain derived neurotrophic factor? What do you believe works and how important is it for living a long time with a good brain?

Mark:

Well, both BDNF and NGF are important for the development of the nervous system, for the survival growth synapse formation, and then the fine tuning of the structure of the brain during development. If

you eliminate the genes of either NGF or BDNF from mice, they die during development. So they're critical. In the adult brain, BDNF is particularly important throughout the brain, all over the brain, in promoting the growth survival of neurons. It's critical for learning and memory. And we showed in my lab when I was back at the University of Kentucky in the early 1990s, that BDNF protects nerve cells against various types of stress, oxidative stress, metabolic stress, something we call excitotoxic stress, which is unconstrained neural network activity that occurs dramatically in epilepsy. But we think to a less dramatic extent in brain aging and Alzheimer's disease.

So NGF, on the other hand, there are only a small but important group of brain cells that are responsive to BDNF in the adult brain. Exercise is a potent stimulator of BDNF production in the brain. Intermittent fasting stimulates BDNF production, and the combination of exercise and fasting give an additive effect in boosting BDNF. And I had a graduate student, Alexis Stranahan, who showed that many years ago in the studies where she combined running wheel exercise and daily time-restricted feeding, daily short fast, and found she got additive effect in increasing BDNF and then actually protecting synapses against diabetes, which is another angle on this. It turns out that obesity and diabetes are not only bad for your heart, they're bad for your brain, particularly as you get older. And we think that intermittent fasting, well, we actually know it, intermittent fasting and exercise can reverse diabetes and obesity in humans. If a person can switch their eating pattern and get on an exercise program. And BDNF plays a role in that. So in individuals who are obese and or diabetic, BDNF levels are lower in their brains compared to normal weight, metabolically, healthy people.

Dave:

One of the things that really changed my life when I weighed 300 pounds and I was having all kinds of cognitive dysfunction in my twenties and early thirties, I started using a thing they called the Russian sleep machine. A cerebral electrical stimulation with alternating current between the ears, very different than the tDCS we use now. And it turns out there are studies that show both tDCS and CES or alternating current raise BDNF very meaningfully.

Mark:

That's interesting.

Dave:

And I'd go to sleep with this thing and I swear my brain helped to turn back on. And now at 40 Years of Zen, the brain upgrade place that I started, we use a clinical grade neuroscience level system that lets you have specific frequencies that are tuneable and controllable by a computer. And we do that to prime the brain for better learning of altered states that you learn through neurofeedback. And you go all the way down to companies like Halo who's been on the show who makes the tDCS headset.

When I do exercise, especially lately, I can't keep up very well with my nine year old at ping pong. Ping pong is a high reaction time thing. It keeps your brain young. Dr. Ayman told me to buy the ping pong table. I did. So I started saying, all right, I need some more BDNF here. My son's kicking my butt and we've got the pro-grade carbon fiber paddles. And we're going at it, he's good either that or I'm bad. But I'm just not a good competitor for him. So I started running the electrical current over my brain again, using the Halo. And all of a sudden my learning went up. 20 minutes after doing it, it's like the ball slows down and I can hit it. And so I believe that's a BDNF thing. But have you seen electrical stimulation, magnets, lights, go into the bottom of swimming pools, I don't know, any other crazy tech like that, that's going to make our brains more plastic?

Mark:

The answer is yes. And first I want to go back to when you were young and obese. And you did this alternating current stimulation of your brain. Did that reduce your appetite? The reason I ask is it turns out that BDNF suppresses appetite.

Dave:

Interesting. I don't think it did. I'm going back to all the different times I'd use it. I would oftentimes use it when I was sleeping or when I wanted to write, even when I was writing actually all my books, there were times where I'd changed the frequency on my device to go up into the gamma ranges.

Mark:

Did it help you lose weight?

Dave:

It could have. I feel like the thing that really helped me lose weight was getting rid of the inflammatory foods and things that were inhibiting mitochondrial function was the number one thing. But it could have had an impact. But for me it was well, I just wanted ketosis. And then I came out of ketosis and I went in and out and that got half my weight down. And then the other half was, oh, hey, guess what? Certain foods are going to make you inflamed, no matter what. So you got to change the type of fat that makes you go into ketosis. You got to get rid of the night shades if you're sensitive, like I am. And that was the genesis of the whole bulletproof diet approach which was these foods may or may not be good for you, but don't assume they're all good because if you're still fat after you tried hard. So for me, it was finding the guilty suspects.

Mark:

So let's get back to stimulation and BDNF. BDNF was discovered in an animal model of epileptic seizures. There was a lab out in California that was just looking for genes that are responsive to epileptic seizures and BDNF is highly responsive. So as you know, one of the treatments for depression, which is still used in people who don't respond well to anti-depressant drugs is electroconvulsive shock therapy. And it's as highly antidepressant and it's highly potent in inducing BDNF expression.

Dave:

Wow. I didn't know that.

Mark:

Also the antidepressant drugs themselves, the serotonin and norepinephrine re-uptake inhibitors, Prozac, Paxil, et cetera. They increase the BDNF levels in the brain. And in animal studies, we have ways we can genetically manipulate the mice so that they can't respond to BDNF. Those mice do not show an antidepressant response to those drugs. So all together, the available evidence says BDNF, it's an antidepressant, endogenous antidepressant. I mentioned it's potently upregulated by exercise. Exercise is a really good antidepressant. And in fact, people who exercise regularly and then have some injury and they stop exercising, that can often precipitate an episode of depression. Because they've been going along exercising and all of a sudden, probably their BDNF levels are going down. So anyway, there is some evidence that even low direct current stimulation or transcranial magnetic stimulation can increase BDNF levels. Caffeine. Caffeine will increase BDNF levels. There you go.

Dave:

I'm intrigued about what you do to manage your BDNF levels. And I want to just warn everyone, look, you're an expert on aging, but you're also the age you are, and you're a male. And you have your genetic and lifestyle factors that we all have. So this isn't do what you do, but I want to know what you do specifically for BDNF and NGF to keep yourself strong in those things. And then I want to know why you do it. So what's your personal practice for managing those? Do you even measure them?

Mark:

Well, that's a problem because we'd have to measure them in the brain, or at least the cerebrospinal fluid. So it turns out that there is BDNF and NGF in the blood. But the levels of those trophic factors in the blood in animal studies are not well correlated with levels in the brain. It turns out that nerve cells are not the only cells that produce BDNF. Your heart cells, interestingly, produce BDNF, and there's other cells. But anyway, the bottom line is unfortunately unlike ketones, which we can easily measure from a finger stick and blood, we can't measure BDNF or NGF. There's no way noninvasively to do that. So I'm just going by what the animal studies say.

So again, my normal routine is don't eat breakfast, drink a lot of green tea in the morning. Don't drink green tea a couple hours before I exercise, which I said is around midday, say one o'clock okay. Because I found I can get some gastric reflux actually if I drink tea right before I exercise. But then anyway, so then I exercise in the fasted state. My diet during the six hour time window I eat is what most people would consider a variety of healthy foods, vegetables, fruits, a lot of nuts, yogurt. If I eat meat, it's usually fish, occasionally chicken, but not so much. Whole grains, there's a lot of literature out there on whole grains, one way and the other. And there are people who are sensitive to the gluten and so on. But my take on the scientific literature is that whole grains are generally good for health.

Dave:

So you eat whole grains?

Mark:

I eat whole grains.

Dave:

How do you stay in ketosis if you eat whole grains and fruit?

Mark:

Well, I go into ketosis in the morning.

Dave:

There you go. I was hoping you were going to say that. We'll probably agree to disagree on whole grains for the average person. But some people tolerate them really well. I know they completely shred other people over time. So those are in the [crosstalk 00:27:45]

Mark:

But Dave, well, I don't know. So refined grains are not good. But the whole grains have a lot of fiber, which is good for your gut microbiota.

Dave:

Unquestionably.

Mark:

And if you look at the actual scientific studies, there's epidemiological evidence that whole grains are good, even in the blue zones, which most of your listeners will be familiar with, regions in the world where an unusually large number of people live to be a hundred.

Dave:

The ways to raise ketones externally. There's MCT oils and different ones do different things. There's ketone salts and different ones do different things. And Dr. Veech raised the bio identical issue there. I actually had the ketone salt product ready to ship, and I canceled it because I'm not selling something that might feel good, but cause harm later. But there are people who are advocates of them, especially short-term use and things like that. And then there's the Esters, which Dr. Veech and I talked about, you talked about and I actually synthesized some six years ago, but they're $40,000 a kilo. I couldn't commercialize them. And there's still a hundred dollars for three doses things for people that do it.

Is there a risk? Let me put it another way. There is a risk with blood sugar. If your blood sugar levels are high, it doesn't mean that you have more energy and you've done a good thing. It means you're not metabolizing blood sugar. If your ketone levels are exceptionally high, is there any similar situation where, hey, they're high because you can't metabolize them. You're going to drain them as fast as you can. Or should we not worry about, my ketone levels are higher than your ketone levels things?

Mark:

This is a good question. We know that with long-term fasts of weeks or even months, or do we know? We assume that it's important that the ketones would be high because the cells are using the ketones for energy. But as far as exogenously elevating ketones with MCTs or Ketone Ester, long-term chronically, we don't know. My current thinking is intermittent elevations may be better than continuous. And the cycling between activating mTOR and inhibiting it, upregulating autophagy then going into a growth mode that's switching back and forth is important. And as much as the ketones play roles in that, and in fact, we showed ketones can stimulate BDNF production. But however, this is a very interesting, it turns out that BDNF is normally produced by neurons in an activity dependent manner. That is it's produced when a neuron is electrically active. And so it's produced when and where it's needed. And we found if we swamp neurons with BDNF continuously, it's actually bad for them.

And we did this in a published study where we were looking at the autonomic nervous system. Remember I said that intermittent fasting increases parasympathetic activity and reduces heart rate. So we had evidence there was a role for BDNF in that. But it gets a little complicated. But the parasympathetic neurons that send their axons to the heart, the neurons themselves are located in the brainstem. They use acetylcholine is a neurotransmitter. And so BDNF, if we [inaudible 00:31:50] apply BDNF to those neurons, they produce more acetylcholine, heart rate goes down. However, if we continuously swamp those neurons with BDNF, then they deplete the acetylcholine and the heart rate actually goes up. So my point is, your systems are very intricate and are producing things where and when they're needed. And it may not be good to continuously swamp the system. So we don't know for sure with ketones, but my intuition says maybe it's not such a good idea to just have ketones up 24/7 chronically.

Dave:

I'd say the jury's out on it. I've gone from using Brain Octane just in my morning coffee to I pretty much put it on every meal. But my ketone levels are generally not above 0.3 except in the morning. So I think they're higher than physiological, but they're not high. And what I feel like that does is that affects my ghrelin levels. So I'm just not hungry. And so I can go long times without food. My brain, it just feels effortless. And we know that your neurons will use ketones even in presence of glucose because of the studies you talked about earlier. But the glial cells, the repair cells in the brain, and I know I'm simplifying what glial cells do there, but they like glucose more than ketones. So that's why I'm really concerned about the keto bro diets out there. If you eat another carb again, you're a bad human being thing. Because it feels like there's a role for carbs.

Mark:

I think there is too, Dave. And there was a recently published study. It suggests the paleo diet's not good long-term. I don't think it's a good idea just to eat only fats and protein. In fact too much protein is definitely bad from the standpoint of aging.

Dave:

The paleo diet is [inaudible 00:34:08] protein and way too much protein. In fact, my new anti-aging book that's coming out soon, I've wrote a lot about protein restriction. In fact, there's one day a week of protein fasting was part of the original bulletproof diet because it increases autophagy to have less than 15 grams. But for you, what kind of protein is worse than what kind is best?

Mark:

Well, usually in animal meats, you've got a mixture of fats and protein. And so the fish story is strong. You can't go wrong eating fish. Ideally some of the smaller fish with regards to the mercury issue. But red meat, you don't need it at all. You get plenty of protein. Everything's all goofed up. Our parents told us you don't get any dessert, which is sugar, unless you've finished your meal. So eat all, eat a lot, over eat, and then you can have your sugar.

Dave:

Yeah, overeat.

Mark:

And you got to eat your meat, drink your milk to get protein. So kids are getting too much protein. The mTOR pathway is over-activated. Their cells aren't removing the garbage. And in fact, the huge problem that's hard to tackle is how to change the family environment. Kid's habits, their eating habits, whether or not they exercise throughout their life. For many people, it's determined by what their parents are doing. And the animal studies, the biggest impact of the intermittent fasting is on average lifespan.

Dave:

But not total lifespan.

Mark:

Not maximum, although there are some effects. So now the other thing is health span.

Dave:

That matters more.

Mark:

I'm starting to, I mentioned, get some orthopedic issues now, which is really my only health issues right now.

Dave:

People who are interested in your work, probably the easiest way to find you is Googling Mark Mattson. And you're the first couple of pages of results. And your TED Talk is totally worth watching and just thanks. Thanks for the decades of work on anti-aging and fasting and neurology. I find it fascinating. You've done a good thing.

Mark:

Well, thanks, Dave. I've enjoyed a lot and you keep up the good work too. As I said, at the beginning of our conversation, there's a big need for translating this basic research into practical things that people can apply to their own lives.

Dave:

Well, I will keep doing my best. I'll ask the hard questions and just to reiterate for people listening. I think we're both serious. If someone out there wants to do a PhD or some other kind of research project on antioxidants and intermittent fasting, it's a wide open area that totally needs attention. And I never thought about that until today. So you stimulated a new idea. Thank you.

Mark:

Okay, Dave.

Dave:

If you liked today's episode, you know what to do. Head on out there and skip breakfast. You'll like your life better if you do that, most likely. And if you hate your life and just skip breakfast, you got to figure out, all right, what's going on with my metabolism because I'm probably not as resilient as I'd like to be. And then you can work on that. And if you want to know how to do that, there's a whole variety of episodes of Bulletproof Radio. We've talked about a few of them today. Listen to this one again, get the show notes. You could read 'The Bulletproof Diet'. You could read 'Headstrong'. I talk about intermittent fasting in both of those books. And there's just so much knowledge available right now on the blog and in other places. And really, if you don't know what else to do, wake up, skip breakfast, don't put sugar in your coffee. Don't put artificial sweeteners in it and see what happens and you just might be okay.