The Effects of Creatine Supplements on Brain Function Concu...

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SPEAKERS

Dr. Eric Rawson, Dr. Mike T Nelson

D **Dr. Mike T Nelson** 00:00

Hey, welcome back to the flex diet podcast. I'm your host, Dr. Mike T Nelson. And today, I've got Dr. Eric Rossen. On the podcast. We're talking all about creatine, and a little bit about muscle physiology, how it can help performance. But our main topic is use of creatine as a supplement and brain health, potentially for risks of concussion and other matters. So I'm actually recording this little intro here from Costa Rica. So maybe you'll hear some few other noises in the background. No, no howler monkeys yet that we've seen. But I'll be down here for a little while. So super excited to have Dr. Rawson on the podcast. As always, this is brought to you by the Flexa diet certification. We were just opened last week and will open again, looks like around June of this year 2022. So you can get on to the waitlist by going to flex diet.com flxdt.com. That'll also put you on the daily newsletter, where I send all sorts of stuff related to body composition and performance and increasing and improving those without destroying your health. So go to flex diet.com lexdt.com. So very excited to have Dr. Ralston on the podcast here. As I mentioned, I was able to see him and this past November. Thanks to Dr. Sarah Campbell, who's been on the podcast a couple times. She invited me to be a guest speaker out at the mid atlantic ACSM the conference, and it's so happened I ran into Dr. Roston there, which was great. He gave a great talk at ISSN a few years ago, I got to speak with him after they're also talking about creatine and brain health. So Dr. Rossen received his PhD from the University of Massachusetts Amherst, where he studied under the direction of Dr. Priscilla Clarkson was a big name in this area. So over the past two decades Dr. Rosen's research has focused on the interaction between nutrition and skeletal muscle. In particularly he has studied the effects of a dietary supplement creatine on muscle and brain function. He is currently the Associate Editor for Applied Physiology, Nutrition and Metabolism, amino acids, and the Journal of Strength and Conditioning research has delivered more than 100 professional presentations. He is a co editor of the texts for nutrition for elite athletes, and a co author on the 11th edition of nutrition for health, fitness and sport, in addition to many other publications, so we're super honored to have him here. He is a professor at Messiah University. So sit back and listen to this podcast from Dr. Eric Roslin all about the dietary supplement creatine and its effects on muscle and especially on neurology and brain health.

D Dr. Eric Rawson 03:21

Okay, well, I guess we should start at the very beginning, which would be my interest in Yeah. In Korea teen? Well, my prior to creatine supplementation, my interest was in creatine metabolism. And that comes from my interest in all types of high intensity exercise. Yes. So I loved your talk on that at the ISSN in Vegas a couple years ago, I thought that was a really good synopsis of kind of the history of creating even just throwing in just the exercise history and everything involved. And that was also entertaining. Yeah, good little characters and stuff in it. So it was a good one. The animated little Dr. Lawson's? Yes. Yeah. Well, yeah, so So I mean, creating certainly predates me, you know, for those people who, who, you know, keep clamoring for more research. We're talking about a nutrient that was discovered in 18 132. Yeah. And you know, that there was Justus von Liebig, you know, was selling an extractive meat supplement, basically a high creatine supplement in the 1800s. Oh, wow. And we have, you know, human creatine supplementation studies dating back to 1926. So we've been at this for a quite a long time, and for me as an exerciser, and as an athlete, I was always interested in the strength and power sports and in high intensity exercise and the more science I learned, the more time I spent thinking about creating And phospho creatine and and the energy production pathways for high intensity exercise. Then in the early 90s, you know, Roger Harris and Aaron silverland and Eric coltman, published their seminal work that showed, you know, and this is not common that when you orally ingest a supplement, it actually easily increases your muscle concentration. So their 92 paper, which was a very straightforward, very simple biopsy and blood study, they fed people, creatine, their blood levels increased and their muscle levels increased about 20%. And they also were able to show in that paper, that exercise increases further muscle creatine uptake. So I was, you know, headed to graduate school at the time, and I was interested in the interactions of nutrition and exercise and anything and everything that could make you bigger, and stronger, and faster, if we're talking about 30 seconds or less. As much as I appreciate the endurance athletes and how superhuman they are. That's, that's not my thing. I watched that from a distance. You know, I'm all about strength and power and sprinting. So creatine was just a natural area for me to be drawn to. And my original line of research was, along with everyone else, studying the effects of creatine supplementation on muscle function, you know, how we can improve strength and power and enhanced resistance to fatigue. And we, at the time, we're really thinking that, you know, all of these compounds that we study, and all of these training techniques that we study, things that increase muscle mass things that increase muscle, you know, improve muscle function. Can we be studying all of these compounds and techniques in older adults, which wasn't really the philosophy at the time, if you had, you know, you're studying protein, you're studying protein and in young, healthy, strength trained individuals. So we started a line of research on creatine supplementation in older adults, which we thought was, you know, a very, very valuable pursuit. And along the way, of improving the muscle function of older adults, there was this strange paper that was a wonderful paper a strange to us, at the time, from descent and colleagues published in 1998, where they fed people 20 Grams of Creatine per day for about a month, which was definitely more than you need to improve muscle function. Typically, they use the kind of just the loading phase for about a week, you know, five to seven days at 20 grams is pretty common. That's plenty. Loading. Yeah, plenty to saturate the muscle. So this was excessive, but they showed about a 10% increase in brain creative. And we were scratching our heads thinking, why would we want to improve? brain creates and we were confused, because we were muscle physiologists. And we were basically neck down muscle physiologist, we, you know, try to ignore the brain and all of our thinking and research and we're kind of successful at that. And this paper got us all thinking, and the next step was to

really think about the brain and nutrition and nutritional interventions. And, you know, I think a lot of people shy away from this research. One is because we're, we're muscle people, you know, biopsies that sells everything. Yeah, more testing more biopsies. You're good. You know, handgrip and biopsies and tests. But it's hard to study the brain, right? It's really hard to get at what's happening in the brain and the brain is certainly very protective. So you're not just going to, you know, give someone you know, some random nutrient and the brains going to happily absorb it. You know, the, the reason creatine supplements are so successful in improving muscle function is because creatine is synthesized outside of the muscle, right? So you and I may eat about one gram of creatine per day and then our bodies might produce about one gram of creatine per day but it's 95% of it is stored in our skeletal muscle, but none of it is manufactured there. So creatine a synthesized in the liver and pancreas and kidneys and transported to a skeletal muscle where it's taken up stored and used for energy production. So skeletal muscle is designed to take up external creatine. It's designed to take up exogenous creates and that's why the system Let's work. The brain is different. So you know that the brain has this incredibly high metabolic demand. Right? Like, like 20% of the body's energy. Yeah. Yeah, I wait and it, but it's synthesizes its own Korea done. So it appears to be at least a bit resistant to outside sources of brilliant, and the brains for the resistance, you know, that's what the blood brain barrier is for. Brain is pretty resistant to a lot of things we could throw out it and I think people shied away from this research. But I think it as of now we have a very promising body of research. It's, you know, a small body of literature compared to the muscle literature. Yeah, but very, very promising. And I think people forget how uncommon it is to take an oral supplement that actually like if we just look at muscle first that actually makes it to muscle, your I mean, you can think of like how many, like I remember when I was in my master's, was an ATP, as a supplement was being tried and touted. And you're like, oh, from marketing standpoint, this makes great sense, right? It's the, you know, energy that your body is using for muscle contraction. So let's just take it as a supplement. And you could get it as a supplement, but didn't pan out, you know, go down the list between all the other intermediates pyruvate, citrate maybe, you know, like most of them other than maybe beta alanine, which was Roger Harris's work again, most other intermediates just haven't really panned out. Right. And this has been, you know, the, the entirety of my career. So I, you know, as a young man, I, as an athlete, I started seeing these advertisements and these products appear. And over and over again, it just turned out that nothing survived digestion, right? On the rare case that it survived digestion, it didn't get where it was supposed to go, it didn't get to the tissue. If it you know, if we were trying to improve, you know, mitochondrial levels of a compound, it didn't get into the mitochondria. If we were trying to improve muscle levels, it didn't get into the muscle, and this was over and over again, which I think is why creatine research exploded the way it did. People were so excited. Thanks to Rogers original work that showed Yes, you know, if you eat this stuff, your muscle levels will increase, and significantly enough to improve performance, uncertain tasks. Yeah. And in the the earliest study, like how did they measure brain creating, because we've talked about this in the past two, and I think that's kind of a major limiter of the research like muscle, we can do biopsies, it's kind of a pain, you got to get different approval, but most labs can do it. It's something that I want to say is relatively easy to do. Now, you're not going in and doing a biopsy of your brain to try to look at creatine levels. So what are your what are your options there, that the options are very few. And you're right. biopsies are, you know, quite standard in the exercise science and in the Nutrition and Metabolism worlds muscle biopsies. And the great thing about that is that if I read biopsy papers from two different labs, right, I can look at a paper from Mark Tarnopolsky lab, or from Paul Green Hoffs lab, you know, we're talking about the different countries. And I can compare those data. Yes. And I can compare the creatine values and the phospho creatine values and I can have some faith in you know, how these values relate to one another. When it comes to brain create, then all bets are off. Right. So the first issue is we're not going to do biopsies. Right. So we're going to do this

with an MRI with, you know, nuclear magnetic resonance spectroscopy. Some people just call it magnetic resonance spectroscopy. We're going to use spectroscopy, which means you need an MRI. Right? So you say okay, well, well, my hospital has an MRI. You're competing against diagnostic radiology. So you for lat for magnet time. So you walk in and you say, Well, I've got this creatine supplementation study and I want to improve, you know, reaction time in football players. And they say, this is diagnostic radiology. We're saving people's lives here. This magnet runs 24 hours a day and right, you have we could give you 30 minutes, you know, a month from now in the middle of the night. Yeah, sorry. It's not. It's not just you have to have a magnet. You have to have access to a facility that has a research dedicated magnet. So now that that's even smaller, And then you have to have people there who are experts in measuring brain creatine and are interested in that research. So it's a very small group. And right now, I think we have I think there's a dozen studies that have measured, create the brain creates and in response to create the supplementation, right, and nine of those studies have shown a significant increase. I think that's, that's important. Certainly, that doesn't rival the muscle biopsy body of literature. But nine of 12 studies is quite significant. To me, they were different countries, different populations. It is, you know, it's very difficult to compare these data, some labs only have the ability to measure total creatine. So a proton NMR. And some only have the ability to measure phospho creatine, so phosphorus. So again, with the biopsies you always get total creatine phosphate, creatine and free creates and but with the magnet, not only are there very few labs who can and will do this, but some of them only measure phospho creatine, which gives us half the story. And some of them only measure total creatine, which gives us the other half of the story. So it's, you can compare percent change in the level of brain creatine. But when it comes to, you know, like what we do with biopsies, millimoles per kilogram of dry muscle, we measure, we have percent change, and we have a concentration, we have an absolute value. We don't really do that with the brain measurements, or we do it, but the values can be wildly different. So even though I can compare the percent change from lab to lab, what I can't do is say, your research volunteers have lower creatine to start with in mind.

D Dr. Mike T Nelson 17:03

So you can compare baselines from one to the other, it's exact percentage change from

D Dr. Eric Rawson 17:08

and that lab. That's important, because what we're trying to do is figure out if if some of the differences in the increase, or the fact that there is a lot of variability, and some people even appear to show a small decrease with supplementation? Is this because they're of their starting levels of this because of their brain baseline levels of creatine? Or is it some other factor, which wasn't measured, you know, typically with the, you know, the brain research, they measure chronological age, maybe body weight, but not much more. You know, in the exercise science community, we were big phenotype people, you know, so we measure cardiorespiratory fitness must, you know, muscular fitness, we, you know, have really elaborate body composition test. And we try to describe people as well as possible in terms of a biological age, a chronological age, but that's missing from this brain, creatine supplementation body of literature. And it makes it even harder to compare the groups. So I don't know if your people were different from mine. And that doesn't explain why three of the studies didn't show an effect. I don't know if you know, your volunteers are different from mine. And that's why you found a 3% increase, and I found a 10% increase. Hmm. So I think I think overall, we can say that it's possible to

increase brain, creatine with oral supplementation. But we really don't have a good understanding of the the optimal supplement dose. And that's because we simply don't have dose response studies yet.

D Dr. Mike T Nelson 18:55

Is it possible you can have sort of non responders like we see with muscle? So if we back up a little bit for people listening? How would you classify someone as a creatine, non responder from a muscle standpoint? And do you think kind of what you're alluding to there with brain levels that that may be going on in the brain also? Yeah, so that's a great, great question. And and I don't, I don't so much care for the the expression non responder because I think I don't like it matter. It's the common term. Yeah. Isn't it more a matter of low, moderate or high responders? I think in skeletal muscle, it's difficult to find someone who has a 0% increase in muscle creatine in response to supplementation.

D Dr. Eric Rawson 19:40

So you have people with a small gain of 5% and other people with a 10 to 15%. An increase and then still other people with 2025 30 or more percent increase in muscle creatine, these incredibly high responders, but with skeletal muscle because it's designed to take up exogenous create them everybody who takes careers and supplements has some sort of an increase. Now with the brain, it appears that there are increases in some individuals decreases in other individuals and no change and other individuals. Now, this is very much complicated by the the range of values, right. So, on average, you might get a 20% increase in muscle. So, muscle biopsies are plus or minus 3% in their accuracy, if on average, we're getting a 20% increase, we're going to be able, statistically to find that increase. But in the brain, if it's more like a 5% increase, and the the accuracy or the, you know, the repeatability of magnetic resonance spectroscopy is plus or minus three or 4%. Finding 5% is really cutting it close. And in some cases, if you just have one very high responder, or a very low responder could really pull the data in a different direction. So it's, it's a nice body of literature, but it's small. And there are some limitations right now, for us to really comment confidently on low responders, medium responders and high responders, especially with our inability to, you know, combine datasets from different labs and compare baseline data. You know, again, we've, we've measured in the same individuals, simultaneous changes in muscle and brain, total creatine, with supplementation, and we found the standard increase in muscle levels. And statistically, we found no change in brain levels. Because the variability was so high, some people increased, some people decreased, some people had no change. The only other data set I'm aware of that is done that is from our colleagues in Brazil, and with Hamilton, Rochelle, and Ruth Otto, and that fantastic lab, but they measure phospho creative. Hmm. So I can, I would have no ability to compare our data directly to their data. And those are really the only two datasets that I know of that have done simultaneous changes in muscle and brain, I think we can safely say the brain increases are much less than skeletal muscle increases. And that makes sense to me physiologically,

D Dr. Mike T Nelson 22:39

yeah. Is there any animal data we can kind of look at because you could obviously do more will say invasive things to animals, and you can generally do to humans, but then you're left with

the problem of, well, it's a mouse, rat, whatever, and not a human.

D Dr. Eric Rawson 22:56

I've been very vocal about how animal data can confuse the literature. And I think creatine supplementation is one of the best examples of the confusion that can come from relying on on animal models. So if we look at skeletal muscle, humans, on average might have a 20% increase in muscle creatine in response to a standard supplementation protocol. racehorses have no increase, really. And that's where some of the original research came from.

D Dr. Mike T Nelson 23:38

And that puts a little bit of a kink in my I looked at a lot of racehorse literature, because they're drug tested. They don't care how much they spend, and they're all tested for time. Right. So you if there is an effect, they're probably going to find it now. Okay, and you're left with the effect of well, does that matter in humans? Yeah. But you see him try all sorts of crazy stuff.

D Dr. Eric Rawson 24:00

I think that that the comparative physiology work is fantastic. And certainly, racehorses are amazing athletes, as are the as are the jockeys. But you can't compare those two species. Well, what if we look at a more traditional rat model? You know, we have data going back to the early 1900s, that shows strongly that when you try to create them load a rat, it doesn't ever get into the muscle, it might accumulate in the liver, but not in the muscle very successfully. And those data were reproduced in the early 1900s in mice too. So there's a lot of people using animal models for creatine work, and the skeletal muscle work, I don't think can be directly compared to human work. Thankfully, we have a lot of people who can do muscle biopsies to replicate the animal data or augment the animal data And then that takes us to the brain. Right? Not only it's, it's not just humans have a very tiny increase in brain creative and supplementation. And animals have a large increase. It's their species differences as well. So if you compare, you know, rats and mice and hamsters and humans, you get completely different increases in brain creating, so that you have to be very, very careful interpreting the animal data, whereas the human data seemed to land in the five to 10% increase range for brain creates in some of the animal studies. Well, most of the animal studies, you're you're looking at a 30 to 50% increase in brain creates.

D Dr. Mike T Nelson 25:49

Yeah. Remember, in the early mouse studies I'm creating years ago, and I think it was a was it a TBI study where they, I think they supplemented one of the groups and the other group, they did not. And they flagged them all in the head and like that incidence of TBI and stuff, and I was like, Oh, crap, this is amazing. And then you kind of poke and look around the research a little earlier and later, and there's like, just a dearth of like, human data, you know, so you're left with Well, this is interesting, but where's it going? And does it transfer? You know?

D Dr. Eric Rawson 26:25

Yeah, I think that's a very important discussion to have. With your listeners, I try to have these discussions with with my students and with athletes. When you look at the animal models of mice and rats, you have about a 30 to 50% increase in brain creative. And then if you use a traumatic brain injury model, or hypoxic Brain Injury Model, you get somewhere between a 36 and a 50%. Reduction in damage. Yeah, from brain injury. Yeah, that's so impressive. So how do we translate that to humans, who, on average, might have a 5% increase, but some people don't appear to have an increase at all? Right? Are we you know, are we prepared to speak beyond the data? My perspective here is probably different from some people. I think we have a number of good studies to say, to suggest that creatine supplements improve cognitive processing. We have a number of good studies showing that creatine supplements increase brain create them to improving brain energetics. And brain energetics are very disrupted with traumatic brain injury,

D Dr. Mike T Nelson 27:49

your glucose metabolism just gets thrown offline. So anything that can kind of pinch it and help that process appears to help and at least has backing a mechanistic data to Sure.

D Dr. Eric Rawson 28:00

And it's not just glucose metabolism, it's brain creatine decreases with traumatic brain injury, and there's problems with membrane depolarization. There's a real energy crisis going on. Yeah. And if we have a dietary supplement that's been well studied, for efficacy and muscle, there's promising data on improving brain energetics and brain function. And we have decades of safety data, both clinical trials and post marketing. Because we're talking about millions of exposures.

D Dr. Mike T Nelson 28:33

It's got to be hundreds of millions by now.

D Dr. Eric Rawson 28:36

So is it really, you know, the right thing to say we have to wait for more data? Or is the prudent response that if you're a high risk individual, if you're a high risk athlete and you you might receive muscular benefits from creatine supplements, then you should be considering about the potential benefits on traumatic brain injury. And that would be either a reduction in the severity of the injury or an enhancement in the recovery from the injury. So I think that's actually the prudent reply right now. And the conservative reply is to not avoid creatine and say we all you know, the animal models don't translate well to human models. It's really hard to study concussion in humans, right. We don't know who's going to get a concussion, certainly, and that the pathology, at least the symptoms appear to vary wildly from from individual to individual.

D Dr. Mike T Nelson 29:38

Yeah. What is the mechanism of injury? How did you get hit? Like what part of the brain could be affected? You could, I mean, there's, you know, kind of broadly three different types but you talk to like I work for the karega Institute. So yes, a lot of clinical neurologist so they're dealing with my buddy, Dr. Jeremy Shimo. Here in the Twin Cities deals with TBI like Day in and day out. And they've kind of come upon just doing customized testing for everyone because it's hard to quantify what type of injury that particular person had, which then makes a broad research of that even harder, because how do you, you scan a whole bunch of people? Do you run them through tests? And then you try to sub divide them into groups? Or, you know, what do you do? You can't do the standardized. Let's take a bunch of people and humans and let's whack half of them on the head and give them a TBI

D Dr. Eric Rawson 30:33

is you can propose those studies, but they never see it. Good

D Dr. Mike T Nelson 30:36

luck with IRB. Yeah.

D Dr. Eric Rawson 30:38

Well, I think you've struck upon something there. And that's you and I, if we compared our skeletal muscles, they would not be identical. But there would be enough similarity that we you and I would have confidence if we both did resistance training. And then we wanted to study the effects are close to creatine supplements and want to use biopsies to study the effects. Or if we wanted to induce muscle damage, and we wanted to study the effects and follow recovery and regeneration, we kind of have this perspective that skeletal muscle is similar enough across individuals, similar individuals, not necessarily old versus young, or transverse train, but similar individuals. But with the brain where we're in a different place, right. So where the brain injury was, matters, in terms of the the the etiology here, but also, and this is something that a lot of us have struggled with, with this particular body of literature, is how do we measure brain function. So again, using skeletal muscle as a model, if I if I measure strength, with you know, a knee extension and you measure strength with elbow flexion we still understand each other's data. And they're, they're still quite comparable, you know, arm versus leg or grip strength versus, you know, elbow flexion. But if you look at those creatine supplementation, cognition studies, the way people assess brain function is remarkably different. And they're clearly taxing, if you will, different systems or different areas. Right, so it's hard enough to take a healthy resting individual, give them creatine supplements, measure some sort of cognitive processing outcomes and compare it to another study. If you put concussion on top of that. It becomes, you know, mind numbing with, you know how large the study would have to be, and how many different variables we'd have to control for you obviously need like a nationwide or sport wide intervention or a particular network of colleges. And I think some of these projects are underway, but they are certainly very, very difficult. And I have to say that there's a political aspect to concussions, because there's return to play issues. And there's money involved and things like that, where, at least at some levels of sport, well, at all levels of sport,

I'll be more honest, at all levels of sport. There isn't always accurate reporting. Right. So if we enter people into a research study, the accuracy of the data is paramount. And the data have to be pristine. But if you are a youth athlete, and you've just had your third head injury, are you going to report that if it means you're you're you've lost the season? And the same in college, and certainly the same in certain professional

D Dr. Mike T Nelson 33:54

sports? Yeah, as you mentioned, standardized testing for it too. Right? Because that was the argument I made a while ago that the data is going to be, as you mentioned, far from clean and a massive undertaking. But because you're talking about concussions, and you're talking about humans, you could in theory, set something up where it's a self report of these athletes used x amount of creatine, these did not. We followed them for three to five years rate of concussion. But again, like you said, they're all sorts of messy issues with reporting under reporting, who did the what test did they do? How did they say they had a concussion? Who you know, what, they got messy real fast.

D Dr. Eric Rawson 34:35

I agree. And but I have to say that what I've learned from you know, the, my transition from doing you know, nutrition and muscle work to nutrition and brain work, is that there's a time and place for open label trials. And there's a time and place for self report and survey type data. You know, if you can get better reporting within an anonymous online survey. And you can increase your sample size from a dozen to hundreds. There's value in that. And I think there's two very interesting studies that are worth reading. And I think you're familiar with them. They're on children with traumatic brain injury in a hospital setting. And these were very, very severely injured children. And no, it wasn't a double blind, placebo controlled investigation with all of these wonderful controls that we use in our research. This was an open label trial, these were patients who needed help. And they showed rather remarkable improvements in the recovery from brain injury, from memory to headaches to to, you know, a lot of the outcomes of interest when we're talking about concussion. And I think those two studies are well worth a read. And they really, they really speak volumes about how important some of these open label trials can be in informing our decisions. So it again, I come back to what's the prudent decision to tell an athlete to stay away from a nutrient with an excellent safety profile? Real muscular benefits that have been studied and published hundreds of times and possible protective effects on the brain, what's the prudent recommendation there to stay away or if you're a high risk person to, to consider, you know, creatine supplements. But I think the open label trials have have kind of opened my eyes to the possibilities of that type of research, as well as what you mentioned, kind of an anonymous type of self report, survey research, which we're all taught is weak. Yeah, that's weak research. You can't control anything? Well. There might be some real value there, combined with the human studies and the brain imaging studies and everything else. I'll tell you, I think one of the most fascinating studies that I've come across is on retired NFL, professional football players, and many years into retirement, that the athletes who are reporting symptoms that they have the reporting basically concussion related symptoms, many years into retirement, that's related to brain creatine levels. So it speaks to almost a permanent disruption in energy metabolism. Certainly, I think that group

group that would be worthy of an investigation of the effects of supplementation on on brain energetics and cognitive processing. So there could be a you know, not just an acute suppression of brain Korea and levels here could be very long lasting.

D Dr. Mike T Nelson 38:06

Yeah, I mean, I've gotten lots of mostly interesting emails from people because I've been relatively vocal of like, if you're an athlete, and you may take your knowingly and you volunteered to play, you know, and say, in the UFC, or American football or whatever, where you know, the chance of getting hit in the head, that's just part of what you signed up to do that. I'm like, Yeah, you should probably look at creatine as a supplement. And people are like, Oh, but there's very little data on it. And I'm like, but you have to make an educated decision for each athlete and each coach and whoever, like what is the the risk profile? And what is the what is the risk? And what is the reward? Right. And in this case, we've got a like you said, we have a really good idea what is the potential downside, we've got hundreds upon hundreds of studies, we've got long term data on creatine, we've got more data on creatine was atomic on on thing, like there's more data on creatine, and there is like the, you know, tomato soup in my cupboard. And there's more data on that, that almost any other nutrient. And we haven't really seen many downsides per se, other than maybe a little bit of weight gain. I mean, no one increases performance. So I think it's up to each athlete to make their own decision. But in this case, I think you can make a pretty good argument that the might be more benefit than there is downside, especially since you know, we don't have finished trials to show if there is a benefit. And if there is, you know, what is the benefit? So you're, you're also running full speed into another human being. Right, so out of all the things that those athletes I'm worried about, right? I get, you know, parents of kids that are like, Oh, I just found out my son went to college. He's 19 and he's taking creatine and I'm like, what was he in a sport? Well, he's playing football. They're like, okay, and so, how long has he been playing football? He's been playing since fifth grade. Like, okay, so you've, you've let him run full speed into another human being. And now you're worried about the thing that we actually have a lot of data on which I understand it, you know, I get it, but at the same point, it just seems a little weird.

D Dr. Eric Rawson 40:18

Right? Our role as educators does not end at any point. No. And, and I'm okay with that. One thing that that is, I found helpful, but it really, it makes some people feel like they were themselves walked into another person or a brick wall, is when I remind them that were we're not talking about a drug. Right? We're talking about a nutrient, not as dinner, right? In many cases, the dose we're talking about, you know, a maintenance dose three to five grams per day, in a large athlete, they might be consuming that with their high protein high creates and foods. So if we're talking about, you know, creatine supplementation maintenance phase, we might really be talking about an extra hamburger a day. Yeah. You know, if we're, if we're talking about large athletes, which a lot of the times we are, so are you really afraid of the creating content of an extra burger a day, then? Where does the anxiety come from with, you know, this dietary supplement, that's just, you know, the ways it feels to some people that they need to be more cautious with a dietary supplement, because it may, you know, have some sort of effects. But, you know, I'm, you know, I asked people, are you that worried about vitamin C? Yeah. Are you that worried about a calcium supplement? Okay, so why are you so worried about this? If it comes down to, you know, an extra hamburger a day, would you be

worried about that, and then I can, that usually gives me a little bit of a breakthrough. And then I can start showing them the, you know, all of the studies on you know, the lack of a negative effect on muscle function, you know, no effect on muscle injury, muscle damage, muscle inflammation, you know, no effect on on, you know, renal function, and on and on and on. And once I share with people the amount of safety data that are available there, they're usually quite surprised. When once again, I think, you know, the internet is doing a great job at misinforming people, and giving them confidence in their their misinformation.

D Dr. Mike T Nelson 42:36

And there's also just something weird, which is a whole nother topic about supplements that enhance performance. They're just and I think it's because of a lot of the misinformation on the internet itself. Like, like, you mentioned, talking about vitamin C knowing gets too worried about calcium, but you start talking about something that is touted like creatine as performance enhancing, then people start getting all weird.

D Dr. Eric Rawson 43:05

I agree. It's been my experience that there's different reactions for different types of substances. Yeah, I I know many people who they would take a weight loss supplement without hesitation, but a muscle building supplement, it gives them pause. Yeah, as if that somehow automatically comes with, you know, a higher risk when I think most of us would agree that the history of dietary supplements it's the weight loss supplements that pose a greater risk, particularly with stimulants. And then if you're introducing a stimulant to an overweight person with you know, hypertension and other comorbidities, that's, that's problematic, but it's the muscle building supplements that are often the ones that give people a bit of a bit of a fright. And I do also meet people who, without hesitation, they'll they'll develop an interest and a good feeling about a medication but be quite quite fearful of a dietary supplements. So weight loss, medications, weight loss drugs are a good example. Many of those drugs have failed to be approved because of adverse effects. Many of them have been removed from the market, thank goodness for post marketing surveillance because of adverse effects. But that that's not a history that we often talk about. I talk about it in my courses. And then the students are often in shock that they've not heard any of this information. But you know, if they went home and told their parents, I'm going to start taking protein powder, there would be some real concern there.

D Dr. Mike T Nelson 45:00

there's some there's some some biases in there that are very, very deep and very old, I think. Yeah. If you were to speculate if someone is a, an athlete or like myself, like I do kiteboarding. And some of the things I think about is if I'm 20 plus feet up in the air, and I get dropped on my head, you know, I wear a helmet have some protective gear, but you know, there's a potential for stuff to just go wrong. You know, so before a trip, I'll usually use like 20 Grams of Creatine per day, figuring maybe if I bought my creatine levels up in my brain a little bit, I'm hedging my bets in that direction. Like if you were to guess any idea on loading dose, you had mentioned the four week study, I think, at 20 grams per day, if we're trying to get better levels of creatine in the brain.

D Dr. Eric Rawson 45:50

Yeah, it's a this is a crapshoot,

D Dr. Mike T Nelson 45:53

I know, the million dollar question.

D Dr. Eric Rawson 45:55

It really is because we have so few labs who can do this work and we just don't have the dose response studies. So that paper from 98 and with from Duchenne and colleagues that showed 20 grams per day for about a month increase brain creatine levels, and they have different regions of the brain measured, it was a very well done study. Whereas we also have some Huntington's data with a very high dose of creatine. When you look at, you know, a normal, physically active, healthy individual. We really don't, we were really not close to optimizing that the dose. I wish we were closer. I think the starting point should be what we know to improve muscle function and muscular health, so 20 grams per day for five days. And that's because we have excellent safety data on that dose. So I think that's a good place to start. I think the issue is here, that we're still looking at the brain, like it is very similar to skeletal muscle. And I think the differences in creatine transporters on the blood brain barrier, compared to in skeletal muscle is and the fact that creatine is synthesized in the brain is going to make the answer to this question very, very difficult to find. And what I mean by that is, if you look at the biopsy work with muscles, you just feed people create them. And every time you take a biopsy, their muscle growth is increasing, right day 12345. With the brain, it's possible that you ate 20 Grams of Creatine per day. And at some point in the day, there was a temporary increase in brain creatine. But your brain reacted to that by perhaps decreasing endogenous production, or reducing brain create than uptake. So it's possible if you're a young, healthy, physically fit individual, and you have the appropriate or normal levels of brain create them that no matter how much of the supplement you take, it will only budge a little, and the brain will shut it down. Now, if you're stressed, sleep deprivation, intense exercise, acutely stress temporarily stressed, it could be that that little bit of extra creatine you got into the brain is really going to attenuate any loss and function that you could have from that stressful situation. So maybe, perhaps the brain is smarter than us. And the brain doesn't want you to have this 20% increase. But the three, four or 5% increase is more than adequate. When you stress the system to make sure you don't go below some critical threshold. That's a different population than someone who's chronically stressed. I old frail elders, people with certain types of diseases, schizophrenia, certain types of depression, and certain individuals can have kind of chronically suppressed brain created levels, that's a different situation they the exogenous creates in is serving a different purpose, and it's to get them back up to a sufficient level. Whereas you and I maybe are getting a little bit of an extra reserve, you know, above the sufficient level the function normal. It's difficult to know that that's kind of all theoretical at this point. But I think 20 grams per day for five days and then the five gram loading dose, because that's where all the safety data are now that's where all the muscular improvement data are, I think that's where we start with, but what we really need is, we need you to lie in an MRI. And I feed you create them, and measure, you know, what happens to your brain creates and levels over time. And I need you to keep coming back to the clinic. So that one day, I give you a five gram dose and one day, I

give you a 20 gram dose, and we look at these small changes over time, instead of just muscle biopsy, Day Zero and muscle biopsy day five. Yeah, cuz I think we're missing a lot with with the, the brain and were ignoring the fact that brain and skeletal muscle are, are not as similar as we would like,

D Dr. Mike T Nelson 50:50

Yeah, I'm down for MRIs anytime. But, and like you said, it may be a completely just different kinetics to write I mean, you may give someone a bolus dose of let's say, five or 10 grams of creatine and you see a little spike and then it tails off, and then maybe it goes up a little bit and then goes down. And maybe chronically that line is going up. But you might be missing those peaks, depending upon when you put them in the MRI scanner, and, you know, all sorts of stuff. We just have no idea. Yeah, it's

D Dr. Eric Rawson 51:19

it's much more difficult research to do. And I hate to see us immediately jump to the animal models, because I think in this case, you know, humans with a 5% improvement, you know, 10% of the high end animals with a 30 to 50% improvement. I don't know that we want to make those comparisons, rather than, you know, come up with more novel ways to to examine humans. And, you know, oddly enough, I think the way we're going to get this done is with some really, really well done case studies. Yeah. You know, I know most of us are taught that case studies are, are, are a weaker form of science, especially retrospective case studies, but but they do have value. And I think what might enlighten us a little bit is to have one person in the magnet using different doses. And even you know, we need to even challenge the assumption that brain creates and is stable.

D Dr. Mike T Nelson 52:22

Yeah. I, I've often wondered that it's not, and that, that just throws a monkey wrench in everything. Yes, it does, like unstable, nonlinear.

D Dr. Eric Rawson 52:35

You know, so with with muscle creatine, we have this safe assumption that if I'm at rest on Monday, my muscle creatine is the same as it is, if I'm at rest on Wednesday or Friday, I'm not sure that's the case here with brain create the levels.

D Dr. Mike T Nelson 52:49

Yeah, and just think of how intermittent muscle is to from blood flow to force output to use to temperature it goes from like zero to like, just ridiculously high levels, but it doesn't stay there long, right? It goes back down like exercise did not exercise where your brain you can do things to concentrate more or not. But, you know, the old studies where they put them in the fMRI, and they found the default mode network, because people are lying there. And you're like,

Okay, now don't do anything. This is a control part of the experiment. Like, wait a minute, what's going on here, you know, and they give them like psilocybin, and they see, like, massive changes in default mode network. And they're like, whoa, what? What's going on? Right? So a lot of times stuff that we think is just neutral, not doing anything, we tend to find that there's more going on than what we sort of imagined initially to. Absolutely, yeah, it makes me think of animal data, like the CLA data, like from, you know, I remember reading that early on, and looking at all the RAD studies. And I'm like, holy crap, this stuff's amazing. Like, the rats get leaner, they get stronger, and the safety data and human was was was was okay. And then time after time, you look at all the human studies, and it just doesn't really pan out at all. And the handful of studies it did, in my opinion, were pretty shoddy and not really the best best studies. But if you are a mouse or a rat, it was amazing.

D Dr. Eric Rawson 54:19

That's the truth. And, you know, I would also say that I've been encouraging people in recent years to evaluate the safety of a supplement or nutrient first. And I think CLA is an interesting example, because some of those animals became insulin resistant, right? They basically drifted towards diabetes. And this is ultimately going to be marketed as a weight loss supplement in a population that's probably at least pre diabetic if, if not. And if you had evaluated the safety before the efficacy You would have said, I don't want to make people more diabetic, you wouldn't you would not have, you wouldn't have gotten to the part about, you know, nutrient partitioning or you know, reducing body fat. And I think one of the great things about creatine is we have so much safety data, right. So if we start with the safety data, and we look at muscle and kidney and thermal regulation, and liver and heart, and we have confidence going forward, that this has a very, very good safety profile. Then we have all of the muscular data, which are showing a effect in terms of improving muscle function, enhancing fatigue resistance, increasing strength, resistance training adaptations, and then I think we can go into the brain the interpretation of the brain data with more confidence, because we already know about the safety profile. And we already know about the other benefits. And unfortunately, I think a lot of supplements are evaluated in reverse. Yes, we want that we want the answer to the question. Does it work?

D Dr. Mike T Nelson 56:06

Yeah, I remember talking to Roger Harris a couple years ago about creatine ethyl Ester, right. So for listeners, like they tried to make all these new forms of creatine that were better than creatine monohydrate. And pretty much all of them have failed. But he was saying that his understanding was that they did almost no toxicology or testing on it at all. They just put it in water and saw that it dissolved. And so that was their whole marketing scheme of like, oh, like, you put it in water and it dissolves. So it's got to be more bioavailable, and just, you know, ran out to the marketplace. And I guess it turned out later that it didn't appear to have much toxicology effect. But he was saying that initially, they had no idea and they just released it and go, there you go. Like, oh, man.

D Dr. Eric Rawson 56:50

Yeah, it's, it's interesting. It's, you know, it's a very interesting industry. You know, I think what I try to relate to my students and athletes and parents and and anyone I'm working with, is if

someone is offering you a supplement that has better absorption, right, then I think you should slow yourself down and say, Well, what's wrong with the absorption? Right?

D Dr. Mike T Nelson 57:18

That's the problem. Original. So

D Dr. Eric Rawson 57:20

creatine monohydrate, is absorbed about 99%. Yeah. Okay, improve on that. Yeah. So once you get to that point, well, it's it's already, you know, absorbed about 99%, then why do you need any of these other products? And then that's always been my contention is that this is well absorbed. And the, that's where the safety data are. So 99% of the safety and efficacy data are on creatine monohydrate. Exactly, what is your rationale for trying, you know, one of these alternative types of products?

D Dr. Mike T Nelson 57:58

Yeah. Which brings me to my last question, which I'm sure you get a lot of. If you were to predict for both either brain or muscle, what do you think is the next creatine monohydrate that the the supplement industry has been desperately trying to come up with for decades?

D Dr. Eric Rawson 58:22

I don't think we're going to see something that's as well absorbed, well tolerated, as creates, and I don't think we're going to see something that improves muscular performance across such a broad range of populations as creatine, even beta alanine, the muscle buffer is effective, it's safe. There's a lot of research to support its effectiveness. But it's only going to be effective for people doing a particular type of exercise for a particular length of time. Whereas creatine has more broad effects on muscular dystrophy patients, sarcopenia older adults, you know, different types of athletes. I don't think there's anything there that could match creatine in terms of its broad effects, and excellent safety profile. I think there are some, there's some tweaking to do with some compounds. There are some, you know, there's a very old research on creatine precursors.

D Dr. Mike T Nelson 59:32

Yeah, it keeps popping up every now and then there's simply no

D Dr. Eric Rawson 59:36

reason to take them because you can just take create all the safety and efficacy data are, but there there are, you know, there's at least one compound that that's there's only a few studies but it it's very interesting in terms of just the brain and an increasing brain create the levels

essentially trying to Get into the brain without the brain, you know, resisting the exogenous creates them. And I think that's interesting, but I just don't see a product, you know, that's going to match all of the things that we've learned about creating these past few decades, I have the I had the great opportunity to be part of a writing group. Somewhat surprisingly, the International Olympic Committee put together a writing group to come up with a consensus statement on dietary supplements and athletic performance. And, you know, we all had to write these massive review articles. And then we get into a room and I'm in this room with these amazing scientists, everybody's 10 times smarter than me. And I have to defend what I wrote. And then we argued for like a week straight and rolled that into a consensus document, which is would have been published a few years now. But the number of dietary supplements that we can actually confidently say, improves athletic performance is incredibly small. And creatine is certainly one of those compounds. But, you know, over the past several decades, you know, of research, we're still down to, you know, a number of compounds we can count, essentially on one hand, and I don't see another, I don't I'm not aware of anything coming that that's, that's going to blow me away, like creatine

D Dr. Mike T Nelson 1:01:34

did? Yeah. Do you think lactate may be useful as a supplement?

D Dr. Eric Rawson 1:01:40

It could be, you know, a

D Dr. Mike T Nelson 1:01:42

lot of unknowns, a lot of metabolic

D Dr. Eric Rawson 1:01:44

intermediates are interesting, but I think context is going to be extremely important. And that's what I mean about the broad appeal of creatine across patients on age groups. I don't see that coming. It's possible, you know, as I said, with some of the buffers, like beta alanine and sodium bicarbonate, I'm not going to take sodium bicarbonate.

D Dr. Mike T Nelson 1:02:07

I've tried like the, the dose where you see a performance effect compared to the dose or you want to like crap, your pants is really close.

D Dr. Eric Rawson 1:02:17

The adverse effects are well known. And also, I think the data on beta alanine and and sodium bicarbonate indicate that, for me to have a beneficial effect, I would have to be exercising

longer.

D Dr. Mike T Nelson 1:02:32

It's longer than 32nd guy, right longer than

D Dr. Eric Rawson 1:02:35

a set of squats longer than a set of deadlifts. So I think with lactate, and some of these other intermediates and compounds were going to see, maybe they work in very unique circumstances. I think nitrate is very interesting. And I think that has more broad appeal closer to something like like creatine, that it can be used clinically, obviously, there's positive effects on blood pressure, resting blood pressure, beneficial effects on different types of exercise performance. But, you know, Britain, still very, very unique compound to study. And I think, hopefully the next few years brings us a lot more of the answers we seek on brainwork.

D Dr. Mike T Nelson 1:03:22

Awesome, well, thank you so much for all your time and sharing all your knowledge today. We really appreciate it. If people want to find out more about you, where would they go? I don't know if your lab is taking any graduate students or if people are interested, or what do you got going on?

D Dr. Eric Rawson 1:03:37

You can find me on on Twitter, where a lot of nutrition and exercise scientists gather. You can find me on Twitter, you can email me at Messiah University. I'm a professor at Messiah University in Pennsylvania, my emails online, you can find me at different types of conferences. Feel free to come up to me and let's have a chat. This is the stuff we all love, love talking about nutrition and muscle and dietary supplements. So happy to be of service and I appreciate the opportunity to be a guest on your show.

D Dr. Mike T Nelson 1:04:18

Oh, thank you so much. And are you going to the neural sports conference in Florida and then ISSN again, or

D Dr. Eric Rawson 1:04:24

I'm hoping to make it to ISSN in the summer?

D Dr. Mike T Nelson 1:04:28

I think it's June I think

D Dr. Eric Rawson 1:04:31

June okay. There's probably two summer meetings on my calendar. And I'm hoping we're all back at meetings. Yes, yeah. This year. I know weird. We saw each other in the fall. I'm not gonna be able to do too much travel and and the first part of the winter I have too much going on in the lab and with the department but hopefully we're all back conferencing this summer.

D Dr. Mike T Nelson 1:04:59

Cool. Awesome. Well, thank you so much for your time. We really appreciate it. Thank you. Huge thanks to everybody for listening to the podcast. Big thanks to Dr. Eric Rawson for taking time out of his very busy schedule to share all his research here. We've got some of the publications listed below that you can check out and really appreciate all his time and his dedication to research and science in this area. If you're listening to this and you enjoyed it, feel free to pass it on to some of your friends or if you're interested in doing more research on the effects of creatine and other supplements for brain health and even TBI and concussion. Spread the word was I would love to see more human research on this very important topic. As I mentioned the podcast we've got great information showing that creatine monohydrate, in general has shown to be very, very safe as a supplement. However, it'd be great to have more data to see what are the effects on brain health. Thanks to Dr. Eric Rossen. If you enjoyed this, make sure to sign up to the Flex diet.com site where you can get on the waitlist for the next version of the flex diet certification. It'll open most likely around June of this year is kind of what I'm thinking, go to flex diet.com flxdt.com. And when you get on the waitlist, you will automatically be on the newsletter which has lots of great free information for you to improve body composition, improve your performance at the gym, add some more muscle and do all that without destroying your health in the process. So thank you so much. Again, if you've enjoyed this, feel free to subscribe and share it around to other people. That really, really helps us out to spread the word in these areas. Thank you so much. We'll talk to you all very soon.