Episode 599: Mara Labs on How to Hack Sleep, Glucose and Aging with Berberine
This episode is sponsored by Just Thrive Health. Thanks to our modern world, it’s impossible to cut out all stress. Ever feel tightness in your tummy sitting in rush hour traffic, or can’t sleep because of your never ending “to-do” list? That’s because your gut - not your brain - is responsible for your stress response. The solution, then, isn’t just to stop or avoid stress, but instead find effective ways to manage it. Just Calm, the brand-new product from Just Thrive, represents a revolutionary new approach to uplifting your body, mind, and soul, naturally. Just Calm has been clinically proven in multiple studies to help: Reduce perceived stress, Balance cortisol, improve sleep quality and even encourage focus and flow.

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importantly, has more than 25 years of public health experience on three continents. And he's one of the co-founders of the gut supplement, RESTORE, which is now called ION. I'm also here with John Gildea, who is a Johns Hopkins-trained Ph.D. with 65 scientific publications from over 20 NIH-funded studies. He is an expert in cell culture and exosomes performing all the science behind the supplement called RESTORE, which is now called ION.

And John was instrumental in the stabilization of sulforaphane in broccoli, which I've talked about on here before because this was a compound that was previously not able to be stabilized into supplemental form. But in this episode, we talk all about berberine and its implications when it comes to sleep, glucose, insulin, and aging. They explain what berberine is and the berberine glucose connection, as well as how it affects ketosis and how to use it therapeutically. They talk about the melatonin connection and how melatonin also affects the glucose cycle. We talk about the timing of berberine for better sleep and appropriate cortisol response, including a study that showed that berberine was more effective than Valium at sleep. And it also may increase deep sleep, which is that restorative cycle of sleep, so beneficial for the brain, and also flushing of things like the liver. We talk about the many types of berberine and why some don't pass through the gut barrier effectively and how to know if one is.

We talk about the c-Myc gene connection to berberine, and how berberine blocks glucogenesis, and how it increases butyrate, which is beneficial for the brain as well as other things, and how berberine can be fasting mimicking for this reason. We also talk about myostatin and how it inhibits muscle growth, and how to use things like berberine to help muscle growth while staying lean. And then we talk about berberine's relationship to dopamine and serotonin as well as timing, berberine, and other supplements with workout, food, and sleep for best results. Very, very fact-packed episode. These guys know a lot, and it has inspired me to experiment even more extensively with some of these compounds, which I'll be reporting back in a couple of months, what my personal results are. But if you want to join us, we're gonna dive deep into the science today. I know you will learn a lot. So, let's join David and John. David and John, welcome. Thanks for being here.

David: Katie, it's great to be here. Thanks for having us.

Katie: I'm excited to learn from you guys today, especially about something that I've only loosely researched but experienced the results of. And we're gonna get to go deep on that topic in a minute. But before we do, I have notes in my show notes, of some pretty fascinating facts about you guys. If I'm reading this right, David, you have swum from Alcatraz. And John, you have the fastest lacrosse shot, I believe. So I would love to just hear a little bit of those stories, because I'm sure those are not part of your normal scientific background.

David: Yeah. Why don't you go first?

John: Yeah. So in high school, before I enjoyed academics, I was more of in the jock genre, and played lacrosse. And during one of the half times at a Penn game, they had a fastest shot in Pennsylvania contest. And my teammates suggested I try and go in that, and won the contest. And interestingly, the shot was recorded at 110 miles per hour, and was actually unofficially the fastest shot recorded until relatively recently.

David: Wow, that's awesome. Yeah, and so I grew up swimming. I swam in college. And just love swimming, and got a love for open water swimming. And so my sister-in-law lived in Oakland. And so our family was out there. And I'm, like, you know, let's just... Looked online, and there is this swim, and I was like, "Let's just do it." And, you know, they kind of take you on a boat, and you go out, then you jump in near Alcatraz, not right at it, because I think it's just a park, so it's not legal to go that close. But then you swim in. And so, funny story,
I was swimming behind this 14-year-old who had done it, like, 11 times. And so she's really fast. And you kind of basically have to eye the presidio, which is yellow. You're swimming, like, almost at an angle, you're not swimming towards the park, and then the current takes you. And so, you have to cut to get this really small opening. And this 14-year-old didn't cut where I thought we should. And so it ends up she was right. And so I just caught the lip and was, like, had to go full sprint to get into this little opening. So swim against the current. But it was the most fun open water swim I've ever done. So, I hope to go back with my boys this year or maybe next.

Katie: I love it. That is no small feat. And I love that it sounds like neither of you trained specifically for those endeavors. They were just things that seemed fun because of training you already had. I love that.

Well, you guys are also very well accomplished in the research world. And this is what I'm most excited to talk to you about today. Specifically, I know you guys actually have many projects that you've worked on and many supplements. But the one I'm most excited to learn about is Berberine, which I'm guessing most people have at least heard of at this point, because I've seen a lot of studies coming out about this. And it's being talked about quite a bit. But I think for anybody who isn't maybe familiar with what it is and what it does, maybe start off broad and just kind of give us an overview of what Berberine is.

David: Yeah. I mean, I'll dive in and then John has a different take on it. But so, we got into the ketogenic diet with my late wife, Mara's breast cancer. And so, basically, you know, keto being 80% fat, 15% protein, 5% carbs. So basically, if you aim for no carbs, you're getting 5% carbs. And really, you're trying to get keto adapted, so your mitochondria can use ketones for energy to make ATP as opposed to glucose. And so you feel really good when you're doing it. After she died, I, you know, largely did a ketogenic diet. And at some point, just about five years ago, we heard about Berberine, and that it was good for blood glucose. And I'm like, "Oh my gosh, like, any hack we can do..." Because I'm not always on the ketogenic diet. And then you cycle on and off, and any hack to kind of get back on it I thought was amazing. And so, we started playing around with it, and mainly because of the benefits in lowering blood glucose. And that's how, you know, I was introduced to it. But yeah, John, what are your thoughts on that?

John: Yeah, so I think some of the best data on Berberine is that it lowers A1C, and some models, you know, reverses insulin resistance. So, that's sort of a central feature for me of what Berberine is able to do. And the interesting part about that is that, you know, A1C is average sugar over a couple of months. So, it really takes six weeks or so before you see that change in blood and blood glucose, with just plain Berberine. I believe it does work in that area. It's helpful. But when you make it bioavailable, it's not bioavailable, it's very, very low, like, 0.68% bioavailable. So if you get a little bit more in, it actually has a more direct effect on blood glucose levels. And so we were mostly interested in seeing if you could use it as a jumpstart into ketosis, because we were working with a lot of patients that had a tough time getting into ketosis. And so anything that can get you in quicker, with less fasting, we thought that would be beneficial, especially for more vulnerable patients that had a hard time getting into ketosis.

As you probably know that age dependence is really big too, because, you know, babies get into ketosis in, like, an hour. And it's graded into age. So, as you're up in age with the people that we were working with, for cancer, they sometimes couldn't get into ketosis. So, we wanted to drop blood glucose so we could get the butyrate up. And that was basically the first set of data we generated after we figured out how to make it more bioavailable was near instantaneous drop in blood sugar, and induction in butyrate without prolonged fasting.
David: It's interesting, Katie, a lot of the papers that you read, or we read, they put these molecules, like, curcumin, like, Berberine, directly on cells, and things happen really quickly. And so a lot of our research, especially while my wife was alive, is you see these really amazing things that impact things like cancer, inflammation. But how do you know if you intake it orally, it actually is doing that same thing? And then how much do you need to take to get that same effect in the paper? And so, you know, that's been a lot of how we think about things is, we see a paper, that's really amazing, but then how do you make it applicable to us as kind of in our daily lives?

Katie: Yeah, I think that's such an important point anytime we're talking about the scientific literature is, often we see these headlines and buzzwords in the news about the effects that something is having. I think people often don't realize what's happening in a petri dish in a lab is not necessarily at all what's going to happen in the human body when you have so many other variables introduced. And so I love that you guys are looking at that part of the equation. I also think this is really relevant right now, because I've seen so much in the last two years about, as we know, metabolic syndrome being drastically on the rise. There are people talking about kind of the metabolic implications of cancer, and a lot of theories about cancer being glucose feeding, specifically, or, like, at least, there's implications of glucose with cancer. And so I think this is a really valid and important topic to be talking about right now. And because also we know that excess glucose in the body, from what I understand, also leads to inflammation within the body. But you guys can probably explain what's happening physiologically a little bit better when we have chronically elevated glucose.

David: Yeah. I mean, I'll just say one thing really quickly, is that, you know, a lot of us, me included, eat meals late, especially if you go out to dinner. And one of the things that happens is, when your melatonin kicks in with the evening and nighttime, it arrests your insulin's ability to metabolize the glucose, so you're having glucose all night, in your blood. And so, one of the great things about Berberine is that, it can really impact that, if you take a couple one or two at night, and they actually get through your gut barrier. It can really cause a dent in the lowering of that blood glucose, which can really change a lot of different things, like you're saying, with these inflammation and different issues, diseases that are inflammation based. And so I don't know, John has more of the physiological....

John: Yeah, absolutely. So, sometimes it's good to just put a little bit of a framework into what we're talking about, just because I think it's not super well understood, sort of, you know, what insulin resistance is, and glucose, and glucose storage, and things like that. So, I think a good way to remember about these pathways are that, any maneuver that you do that lowers insulin would be life prolonging. And that's validated through many model organisms, and experiments, even in clinical studies. So, the opposite would be, is, if you raise your insulin. So a lot of people don't understand is that, insulin, its job is two different things. Its job is to hit the receptor on every cell in your body, and allow glucose to be taken into the cell, so it can be used in an energy production. And what's going wrong in type 2 diabetes is that, that insulin receptor is becoming less sensitive to insulin. So you're literally starving your cells, and your glucose is going up.

And that combination is bad because excess glucose around produces what I usually describe as sugar rust. So you get glucose attached to all different kinds of molecules, and the accumulation of that are called advanced glycation end products. And then you can have lipids and proteins conjugated that way. So it's similar to reactive oxygen species as well, that they're just doing damage. And so having high circulating blood glucose levels does a lot of bad things. And they're sort of associated with many... It's the bad direction of all things. You rapidly age, you get inflammation, and you get inappropriate storage of energy too. So that's another one.

I'm not sure how far we want to go with this. But, you know, in type 2 diabetes, your blood sugar is high, and your insulin is high, and that says store your energy. And so you store your energy in your muscles, your liver,
and eventually your pancreas. And it's when those organs get filled up with glycogen, and then there's no more room to store energy, and then you start storing it as fat. And so you get your fat accumulation in those organs, and they start losing function. And so that's why exercise works. This is very simple, is that, you burn up all your glycogen that are in your muscles, and then you have more room to store glucose. And so your glucose levels go down. And because your blood glucose levels are down, that's the signal to make less insulin also. So, that's sort of a big picture of how insulin works and how excess sugar causes problems.

Katie: And I think the sleep implication alone is huge, because I've had a lot of people on here that talk about the rise in sleep problems, especially in the U.S. And of course, the reason for that is, of course, very multifaceted. But it's the reason I often recommend them personally, try not to eat for at least three or four hours before bed, for that reason, so there's not glucose in the body all night. And also the reason I always recommend getting morning sunlight, which we know has an effect on that circadian cycle and resetting the melatonin clock. But it sounds like for many people, especially if there's insulin resistance in this equation, or there's already existing glucose issues, just avoiding food or especially carbs before bed may not solve that problem. So this is kind of like an extra boost to that.

I also love that you mentioned exercise because this is one of those areas like quality sleep that I feel like every expert agrees, that is very beneficial, and especially when we're talking about the metabolic syndrome and glucose equation. But it seems like this is also a very both/and situation. That it's probably great to avoid food before bed, it's of course important to exercise. And since we're seeing such a drastic rise in these problems, something like Berberine can really help sort of get those things into range. And if they do, is the body able to then maintain normal glucose and insulin regulation more easily once those numbers have started eating out?

John: Yeah, as you regain your insulin sensitivity, your insulin levels are able to drop. And if someone is interested in trying to improve their health, that would be a great metric to measure as opposed to the glucose itself. They kind of follow each other. But, you know, the better metric is insulin. And I think the other half of that equation that would be probably really good to talk about is, you mentioned in the morning, your circadian rhythm. So one of the things that happens first thing in the morning is you get a cortisol spike. And cortisol is a glucocorticoid. And that means that it causes a release of sugar. So that's how it wakes you up. So, don't think of sugar as always being bad. So that part of the circadian rhythm is a good part of that. But stress, prolonged stress, chronic stress, raises your cortisol levels. And basically, that's another big reason for why your blood sugars are high, is you're constantly stimulating the sympathetic part of your nervous system. And you're getting your blood sugars high, because you're stressed out, basically. So when you talk about the big effects that help almost everybody, that would be another one that probably you've talked about, is reducing stress. And so that will directly translate to blood sugars.

Katie: Yeah. And one thing I've mentioned before when it comes to the stress equation, because probably everybody listening has heard of how stress can have negative effects on the body, and has maybe gotten the recommendation of reduce your stress levels, which is often easier said than done. But I feel like often, the stress conversation is focused more on the mental health side. And it seems like there's very much a cycle here where when our physiological and biological health is not optimal, it actually causes more perception of mental stress. And mental stress also then has physiological effects, as people have talked about on here before. And so they kind of compound each other. But that also means that you can use that to your advantage when you're working on managing stress. You can use things that are making a biological difference, along with stress management techniques to improve that cycle more quickly, as well.
And I also think of a lot of things you just mentioned lining up with the... A lot of people have now had PCOS. This has been pretty drastically on the rise. And insulin resistance is a very common thing in women who have PCOS. So I would guess just anecdotally, that someone who has PCOS and is struggling with insulin levels, this might be something they could add to their toolkit to help get those numbers and range, which might then also help their body recover from the other parts of that as well.

John: I have to look into that. It sounds very plausible. I know quite a bit about estrogen and things like that. But I haven't directly tried to connect it to Berberine.

David: Yeah, it's interesting, you know, in terms of the sleep side and the glucose side. I mean, one of the main testimonials we get from Berberine is, it's impacting sleep, and people sleep. In fact, you know, in creating some marketing material, I found out to people who actually use our product. And was just like, "What are you guys noticing?" And it was thinking, you know, they'll share with me how their blood glucose numbers are dropping, how their ketone numbers are rising. And 75% of the people that came back were like, "Oh, I sleep great." And at that point, I'd actually didn't know that the connection with sleep outside of, you know, just lowering blood glucose. You know, when I travel, which I don't do very often, but occasionally, I'll get stuck on a red eye. And so one of the things, you know, combining kind of exercise and what we're talking about, is... It doesn't have to be just with traveling, if I have a bad night's sleep, or several in a row. A reset I try to do is really, 30 minutes high intensity exercise. And then in the evening, taking our BerbElite product as well as our BrocElite product, and that inevitably helps with a reset, get a really good night's sleep.

Katie: Yeah, and it makes sense. I've talked to quite a bit on this podcast about how sleep is one of those keys to help, like I said, that every expert seems to agree on. I've never had a single person in almost 600 episodes, come on here and say sleep is not important. We're well aware that sleep is very important, and yet many people still struggle to get not just enough sleep, but quality sleep. And especially, there's been a lot of talk about the deep sleep range of sleep and how important that is for body recovery. And that's definitely what I noticed, because I've experimented with the BerbElite product. And I often wear a glucose monitor just because I love the data. I don't have diabetes, I just really enjoy seeing my response to different things. And the two things that stood out to me were, an increase in deep sleep. Because my total sleep is pretty dialed in already, and I prioritize sleep. But I saw my deep sleep number increase with use. And then also my glucose response, I definitely noticed a difference, I think, relatively quickly after taking it. And so I'd love for you guys to delve into that. You mentioned earlier, you know, it's hard to often correlate between what's happening in a lab and what's actually happening in the body. And I know you guys have looked into this with yours specifically. So, can you walk us through what sets yours apart? And was I imagining that or was I actually seeing a pretty rapid response to my glucose after taking it?

David: Yeah, I might dive in. And so, with a lot of the studies that you read on the impact of Berberine on blood glucose, it's over weeks, so six to eight weeks. So it takes a decent amount of time to see an impact on blood glucose numbers. And again, that's because the typical Berberine supplements on the market actually don't pass through your gut barrier at a large amount. Like John said earlier, they're like, 0.68% bioavailable. So that's, you know, you take a gram, you get 6.8 milligrams through. So that's not enough to really impact things. And so, one of the neat studies, you know, we did was looking at how quickly does it work. And so, when you eat your dinner, and then wake up in the morning, take two of our capsules, what we found in sort of a preclinical study was an 11% drop in blood glucose numbers within three hours. And then what's also neat about that is that we saw an increase from zero ketones to, like, 0.5 millimoles per liter. So that's the measure. So you actually are in sort of a light ketosis.
John: It's interesting, going back to sort of the analogy we're talking about. So what happens at nighttime is your little mini hibernation when you're sleeping. And so there are a lot of things that happen during that time. But the melatonin blocking insulin function is basically inside that cell, it's experiencing low glucose. So if you lower your glucose in your whole body, say you take Berberine right before bed, your blood glucose will lower and then you'll get an even bigger dip in the drop in functional glucose going inside the cell. Probably important to introduce a new concept here, in order to talk about sleep a little bit better, is, one of the differentiators between Berberine and some of the other things that lower blood glucose is that, it's a direct binder of a very well-studied gene called C-Myc. C-M-y-C. And MyC is a component of the cell that has a long history. But it's called a carbohydrate binding transcription factor. So it binds to things that are involved in up-regulating glucose utilization.

And so because Berberine binds C-Myc, and inhibits its activity, it is functionally lowering how your cell feels glucose. And so it's reducing that. So it would work together with melatonin and other things that would drive your circadian rhythms, such that your heart rate reduction during the night will be better, just kind of a classic hibernation phenomenon. You're really slowing down your metabolism and then you're also lowering your blood pressure. And when you lower your blood pressure, you repair capillaries everywhere in your body and kind of in your head, is a very vulnerable capillary bed. And so you're able to repair capillaries throughout your body.

So that's part of the connection to nighttime dipping in pressure and heart rate, turning off your sympathetic nervous system, is through this C-Myc mechanism. And so, when you turn off that that system, your brain's response to that is to lower the electrical activity down into the delta wave frequency. And during that delta wave frequency is what deep sleep basically is. You get rhythmic synchronization of your brainwave activity. And that's the only time that your brain is able to move the lymphatic system, so the lymph in your brain. And that's the only time you can detox your brain, basically. You can move toxins around to get rid of them. So, there's kind of more avenues we could talk about in that area, but there's a very clear connection to deep sleep and brain detox.

Katie: Which I feel like that's an increasingly important conversation as well, that flushing of that cerebrospinal fluid, which, at least what I've seen, is helping break down those amyloid plaques that can build up in the brain. And of course, that could be a connection to a lot of these mental or, like, Alzheimer's and deteriorating brain conditions. So I think I expect to see a lot more research on that as well.

I'm curious, I mean, that's a pretty substantial ability to affect glucose, like you guys just mentioned in that study. Do you see this separate of even dietary changes? Like, I would guess the best answer is both/and when it comes to dietary changes, or Berberine. But I know the last stat I saw was that most Americans are consuming 16 to 20 teaspoons of added sugar per day. So on average, Americans are not doing great with this. But I'm curious if it still has a benefit, even if people aren't necessarily changing their diet?

John: I think it still would reduce it. So it would lessen that hammer of having a giant spike in glucose. Obviously, would work better if you didn't eat the sugar in the first place. That's what I think.

David: I guess, we can just be straightforward. There are a number of folks who have gotten back to us who take our product specifically so they can cheat. You know, they're on the diet, and they're like, "Oh, I want to go eat some pizza." And then they're like, "This is great." And so, I mean, one of the things it does, though, is, there's sort of a satiation caused from an increase in your butyrate levels. We were just talking about this. It seems like people are sharing in testimonials that they want to eat less. What's up that? Sounds like it's butyrate. And then I think the other thing we haven't talked about, which is important and it's related, is how
Berberine blocks what's called gluconeogenesis. And so that's where when you have a low blood glucose, your body, your liver, wants to transform things like lipids or proteins into glucose. And that if your body's gluconeogenesis is turned on, then you really have a difficulty in having a low blood glucose. And that can be seen with cancer patients. I know that was one thing we saw is cancer, a tumor can do that as well, which is awful.

Katie: Yeah, and the liver effects, you guys mentioned. I know I've seen papers about also the pretty drastic rise in nonalcoholic fatty liver disease in the U.S., even among children now, which is a pretty concerning statistic, because we typically didn't see that until people were older. And now we're seeing it at younger and younger ages. And so if, like, any tools that can help with that is also gonna have a whole-body beneficial effect. And you've mentioned butyrate a couple times. For anyone who's not maybe as familiar with that, can you explain why that is beneficial, and why we would want to encourage that?

David: Why don't you dive in?

John: So butyrate is basically...I understand it as a protective mechanism for when you're not able to eat frequently. It's an alternative energy source. And so it's insulin independent. It doesn't need insulin to bring glucose into the cell. So it basically bypasses that whole system and it also is able to fuel your cells' energy metabolism with less inflammation. So if you run off glucose versus if you run off of butyrate, butyrate is actually more efficient at converting oxygen into ATP, and producing less of the damaging effects of when you run off of glucose. So it decreases inflammation. And usually anybody who has done a prolonged fast, it might be the first time they'll actually feel what it feels like to be without inflammation. I know that was the case for me the first time I did a prolonged fast. I was like, "Oh, this is what it feels like without having sort of generalized pain all over the place." And I think the other thing that people really feel is, when the brain runs off of butyrate, it feels really good. So it's a protective feeling of when your brain is really running well.

Katie: Absolutely, that was my experience as well. I typically start the year with a long 7 to 10 day fast, which I realized biologically, you could argue that long is not necessarily beneficial. But I do it for the sort of mental spiritual benefits at that point. But I find myself often getting a lot of writing done, because my brain is so clear, and I'm so focused with likely the excess butyrate. But the fact that this is able to increase butyrate in the body seems like it would also be very beneficial for athletes who want to be able to rapidly use glycogen and/or butyrate, especially if they're doing longer events. Do you know if it's been studied in athletes at all, or if it's beneficial in that way?

John: I know the most studies that I know about it is... I'm sure it'll butcher his name, but it's Navy Seals that are doing re-breathing. Dominic D'Agostino. Very prolific researcher on butyrate. So when you have these rebreathers in Navy Seals, where they can't release the bubbles, you can only be in that scenario for a short period of time before you induce seizures and a lot of bad effects. And what they found was that you can take external butyrate or you can go on a ketogenic diet, and it prevents the harm that happens from using these rebreathers. So that's kind of a good framework to sort of understand how butyrate works. And there's a lot of research now on, if you just take butyrate, you can actually just take beta hydroxy butyrate. It's not very tasty, but if you just take, like, 10 grams of it, that amount of butyrate will help athletic performance. And I always feel like I have to talk about the other half of your butyrate being very high, is that, you tend to spill sodium and minerals. So you have to be careful about making sure you eat more salt.

David: Dominic D'Agostino.

John: D'Agostino, that's right.
David: He's in Florida, I believe. But yeah, and then I just had with butyrate as well. I mean, there is a shift in your microbiome. And actually, my son did a science fair project looking at that. And so basically, it shifts to a much more diverse microbiome when you have more butyrate in your gut. And so, obviously, the microbiome composition, we're still learning quite a bit. But that's super important to have it more diverse.

Katie: And I'm also curious, it seems like a lot of people have turned to Metformin for similar kind of effect in the body. And certainly, Metformin has been talked about even sort of off label use for its anti-aging benefits. I've always been pretty cautious and not tried Metformin, just because of some data I've seen. But I'm curious if you guys could compare and contrast to Metformin since a lot of people seem to be experimenting with it for even the anti-aging side, separate actually needing it for glucose regulator.

John: At least for me, the pathways are pretty clear, in that, Metformin is an AMP kinase activator. So that pathway is a classic fasting pathway. When you fast, you activate AMP kinase. So taking Metformin is mimicking fasting. And so that relates also to mTOR. And so those are very clear studies in terms of longevity. And, of course, it's a pharmaceutical compound. And most pharmaceutical compounds at some point have, you know, side effects or accidentally hitting some other pathways. And so in the case of Berberine, it's a natural product, it's been around forever. Your body knows how to metabolize it. And so also activates AMP kinase. But that combination of inhibiting C-MIC at the same time is the big differentiator for me. So you're both activating the pathways that mimic, you know, the metabolic response to fasting. But you're also decreasing the functional activity of carbohydrate response elements. So it's like, it's two different pathways both in glucose regulation.

David: I think the other thing too, Katie, is, you read a lot about, especially bodybuilders or athletes, are really hesitant to use Metformin because of the muscle issues. You can't bulk up your muscle as easily. Another differentiator is, Berberine inhibits the enzyme called myostatin, that degrades muscle. And so there's not the same issue with Metformin as with Berberine.

Katie: That's exciting to know, even on a personal level. I've been consuming more protein than I used to, because I'm trying to get a lot stronger right now. But I'm aware of the potential implications with mTOR. And so I've been strategically using short fast and intermittent fasting along with Berberine. Just to kind of make sure everything stays in really good ranges while I'm doing that. And you've mentioned taking Berberine at night and how that can be valuable for sleep. And we talked about the cortisol spike in the morning being beneficial. So I'd love to talk a little bit more about timing and dosing for people who are wanting to use Berberine most strategically. What would that look like in an average day, with timing in relation to food and exercise potentially? Are there any tricks to using it the most efficiently?

David: Why don't you dive in and then I'll share my perspective.

John: Yeah. Because it is functionally blocking the activity of glucose and things like that, I think the first thing in the morning would, depending if you're diabetic or not, and what you're trying to accomplish, whether you would want to take it first thing in the morning. But I think for sure, I would take it a little bit later if I were trying to do any kind of body building, things like that. People may not know about myostatin, but it has kind of been a holy grail for a lot of pharmaceutical searches. Most people know about it, in that, myostatin inhibits muscle growth. And so when it's mutated, I'm not sure if you've ever seen those, either dogs or cows that look like Arnold Schwarzenegger. That's what it is. It's actually a myostatin knockout animal. And so they become super muscular. And so, when you take both sulforaphane and Berberine, are capable of inhibiting myostatin, you're able to add muscle more easily. So for most people, that's a big one.
David: You know, one of my favorite papers on Berberine... And this happened, like I said, after I gathered these testimonials from our BerbElite customers, and saw that sleep was sort of the main reason people were taking it. I'm like, "Well, what's going on here?" And so that there's a paper that basically compares Berberine with valium as a sleep aid, and how Berberine was superior to valium as a sleep aid. And this is just even the Berberine that doesn't get through, is superior, which was really interesting. It was over a longer period of time than how ours would work. But it showed a 25% increase in dopamine, which is really huge. And 30% increase in serotonin levels, just from the use of the Berberine. So, I think from a sleep standpoint, both of those are important.

Katie: Okay, so afternoon and evening, probably for timing on this for the most part?

David: Yeah. So, I mean, what I say, and it's on the label, if people... Everybody's on a budget. And so my thought as far as biggest bang for the buck would be take both capsules. If it's two capsules a day, take both in the evening. And like John wisely said, it really depends on what you're after. If you're after sleep, two in the evening. If you're doing other things, maybe not. But yeah, if it's sleep, then two before bed.

John: Yeah. Say for instance, you're trying to drain your liver of fat, fatty liver, getting your blood glucose levels low and keeping it low, and basically running your metabolism off of that fat all day long will drain it more quickly. So say for a person who's fighting insulin resistance, getting to that drained fatty liver, or the same thing happens with muscles, is fatty muscle, will get used up. And that's why exercise along with, you know, some of these things that lower your blood glucose levels are going to work together to meet that goal. But, like, in your case where you're trying to put a little bit more muscle on, I would do it outside of that cortisol window.

Katie: Awesome. I'm excited to experiment more with that.

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Also, for just clarity, can you explain the difference between Berberine and curcumin? I know you also have a curcumin product. So, how are those used differently? Can they be used together? Or just kind of walk us through similarities and differences.

John: So I started playing around with all the favorite molecules that I used to show from screens that I did. We were trying to start a company for doing personalized medicine and we were trying to figure out combinations that would really help people that had advanced cancers. And so what jumped out of that very early on was sulforaphane, and curcumin, and Berberine and a few other ones that we might introduce in the coming months and years, is that, those first three, actually four, quercetin also, they’re synergistic. And so, a lot of people talk about things being synergistic. But we used what was considered the most strict test of synergy, is where you take the compound, and you dilute it until you can’t see an effect. If you’re looking at say a kinase or Nrf2 activation, any of these things that are known targets of sulforaphane, Berberine, you dilute it until you don’t see anything. And then you dilute say, sulforaphane, until you don't see anything. And then when you add those two together, plus nothing, and you see an effect. And so, for all our first four products, we know that they pass that test for synergy. And so sulforaphane, an additional ingredient in our BrocElite, curcumin and Berberine, and then also quercetin.

They fulfill that very strict criteria for synergy. And so, when you just take say, one supplement by itself, the concentration that ends up being in blood or being in contact with your cells may not reach the level that they see in a cell culture. For instance, curcumin, often in cell culture to see inhibition of its primary target is NF kappa B, so inflammation, is in the range of 20 to 30 micromole. But you can see an effect in the low micromole levels, if you combine two those together. So, what I usually say about curcumin, is curcumin, its main target is inflammation. So it's best to activate at inhibiting NF kappa B. And then Berberine, its primary target would be AMP kinase and C-MyC, so they're covering that territory. And if you start looking at a bunch of those papers, you realize that the same molecules are involved in the same targets. And so when you work towards a pathway, and two different signaling pathways, is the most likely avenue for synergy. So, sulforaphane, Berberine, curcumin, are in those categories. Sulforaphane is Nrf2, Berberine, AMP kinase, curcumin is NF kappa B.
David: Yeah. And I'd say also, Katie, our curcumin formula, we actually bind to a protein. It's formulated slightly differently. We actually want to bind the BerbElite to a protein as well and increase its bioavailability even more. But we are a very small, kind of mom and pop company, and so you can think of us as a sort of a microbrewery that makes supplements. We do everything here. So we're making the powders we put into the capsules. And so right now, we determined that if we do a combo with Berberine and sulforaphane, it actually makes it pretty bioavailable, but it's about half bioavailability as if we'd bound it to the protein. And how that compares to regular on the market is, you don't see it above background. If you take a Berberine product, you really don't see anything. And so with our BerbElite product, currently, it moves the needle. And you see it too in, like, you experienced with your glucose monitor, like we experienced in our clinical trial, it actually moves the needle with blood glucose and ketones quickly, within hours versus weeks.

Katie: Yeah, I was extremely excited when I first found your sulforaphane products, because I knew previous to that, my understanding was that it had not been yet put into a capsule in an effective way. And so there were a lot of years of growing broccoli sprouts in my kitchen, and doing the whole thing with temperature, and mustard seed, and trying to make sure I was preserving everything in them. And, you know, broccoli sprout smoothies on their own don't taste super great. So I'm extremely glad to have capsules now. So I guess you guys have given so much great information. And for my own personal use trying to integrate in an optimal scenario, what would be, like, my dosing on a lot of these different things in a given day and timing? Because I'm excited to actually experiment with these over the next few months while I'm in this muscle building phase, and wanting to keep an eye on my glucose and just see how it affects me.

John: And if you're designing a strategy for your goals, I would probably tell you that one of the things that's pretty well known is, if you are fasting, your growth hormone levels increase. So that's very important. But what a lot of people miss out there is, in order to get an anabolism, you know, the muscle building, you have to increase your TGF alpha. Or IGF, sorry, IGF1, in order to create that. So, fast before your workout. Within 20 minutes at the end of your workout, eat no sugar, but take branched chain amino acids. And so, in that case, you will get your IGF1 induction, and your growth hormone induction increased. And it sustains until you eat your next meal. And so if you eat any sugar in between there, it turns that system off. And so, try to extend that out to your next meal. And then you'll have growth hormone and IGF1 high for those few hours afterwards to maximally induce myogenesis.

David: So, like, if you have a whey protein, that would be an ideal branched chain amino acid source.

Katie: Okay, got it. I'm excited to experiment that. And I think another relevant topic that I know could be an entire episode all on its own, but I want to at least touch on. I think when asked, John, what your TED Talk would be in a week, if you were to give one. You said why most people need much more salt in their diets, not less. And I think this is another really relevant conversation. I've actually seen a lot of data about sodium consumption in nursing moms, for instance, and how it affects milk supply. But I think for a lot of years, we've gotten the message that salt is bad, and a lot of people are afraid of sodium. And you mentioned the keto diet, which I know changes your relationship with minerals and electrolytes. But can you just kind of briefly give us an overview on what could be, I'm sure, not many episodes of why we maybe don't need to fear sodium and why we perhaps need more of it?

John: It's another hat that I wear, is, I run an analytical lab that does testing for salt sensitivity. And so, the big broad picture there is that, only around 20% population is actually salt sensitive. So that means that if you eat excess salt, your blood pressure will go up. And so the whole rest of the population can eat salt without harm. And so, that's sort of the background for it. And then in your area of interest right now, is your ability to work out. So, if you take extra salt before your meal, what has been shown to happen is that you're able to maintain
cooling during your exercise much better. And so you can sustain vigorous exercise for a longer period of time. If you're low in salt, then you'll overheat. And so that's kind of a symptom of, if that's the reason you stop, is because you're overheating, it maybe that you're low in salt. So that whole area, I think, is an area that's, you know, very much in the medical world. And, you know, we're doing the studies to prove right now. We have a lot of the pathways figured out there. But one probably to talk about here, just to pique interest is that, we discovered that about 15% of the population, if you go on a low salt or a high salt diet, the blood pressure goes up on the low salt arm of the diet.

So, actually going on a low salt diet is harmful for 15% of the population. And so, probably the only other connection to what we've been talking about so far, is that a lot of people don't know that insulin resistance is very closely related to salt sensitivity. So, if you are insulin resistant, there's a much higher chance of you being sensitive to excess salt. So even in the people who should reduce their salt or salt sensitives, those people can actually reverse that effect if you take care of your insulin problems. So we always talk about, you know, what is the bad white crystal, and what's the good one. And so it's certainly a mixed bag and depends on your personal status. But even in the few people, 20% of the population that should curtail excess salt, if they were able to get their insulin resistance under control, they would most likely be less salt sensitive. And then in the other arm, you should eat excess salt. I found out that from my own study because I'm what's called inverse salt sensitive. So I have the reverse paradoxical increase in blood pressure on low salt.

Katie: That's fascinating. I'm an inverse modulator on a lot of the GABA pathways, and so I have to be careful of not taking that at night, or I'm up all night, which is the opposite of most people. But that's fascinating. I did not know that about the temperature side. I had Dr. Craig Heller on here to talk about the glabrous regions of skin in the cool hand study and how temperature regulation seems to really make a difference in both your intensity and your duration of exercise. I've been experimenting with my kids who are athletes in cooling hands between pole vault jumps, for instance. But that's really fascinating to know about that side of the equation as well, which will further encourage them on their mineral consumption and salt consumption. Are there any cautions to be aware of for people with taking Berberine to be aware of anytime it should or should not be taken, and/or contraindications for taking it?

John: I'm not sure. I'll let David talk about that.

David: So it does lower your blood glucose. And so you need to be careful. Of all our supplements, the Berberine, especially our forum, can move your blood glucose numbers. And so you just want to not take too much. I'd say that's important. And then, on a side note, too, I know you're friends with Robb Wolf, who's a fan of salt. It'd be great to get he and John together to have a chat. I listen to him on your podcast, I'm like, "Oh my gosh, they would be best buds."

Katie: Yeah, maybe we can do a follow up round two after I do a couple months of experimentation with this and have glucose results to share. And I would love to get Robb on. He's always such a fun conversation and know so much. That'd be exciting.

David: And then I'd say also, if you're doing keto and you're using Berberine, I mean, and John alluded to this, but like, I remember I was doing a really strict keto kind of militant keto, and wasn't aware of the salt implications. And, like, I had tachycardia and arrhythmia one night and I text John, I'm like, "Could this be the Keto?" He's like, "Yes." And so thankfully, I had some potassium citrate, magnesium citrate, and sodium chloride, you know, in the house. And so I just mixed together a little, you know, mixture of these salts and chugged it. And, like, within 30 minutes, everything was fine. Like, you can really mess yourself up because you're dropping so much salt on a ketogenic, if you're in strict keto.
John: And I learned a new pathway for me that I was not aware of, is if you're pretty consistently being low sugar consumption, and you are walking around with a glycogen lowered liver and muscles, if you suddenly go out to dinner and have a very sugary meal, you actually use potassium in order to store glycogen. And so you can become potassium deficient and have heart palpitations from that. So it’s another salt related issue that people can be aware of. You know, if you are consistently ketogenic or eating low sugar, and you've drained your glycogen levels, obviously, drained your fat levels in your liver and muscles, and then you’re also glycogen lowered, you have to be careful about that binge eating more so than most people, because it can really make you feel pretty rotten.

Katie: Good to know. I've taken so many notes, and I'm excited to keep experimenting with Berberine and track my results. I'm such a data nerd. So I have spreadsheets that I put all these things into. And I'm excited to play with it. A couple of last quick questions before we wrap up, since our time has flown by. The first being, if there are books or number of books for either of you that have had a profound impact on your life? And if so, what they are and why.

John: May I go first? Yeah, so my favorite book was by Weston Price, "Nutrition and Physical Degeneration." And so I always like going back and reading very old books that had it right. And I think that's the most amazing version of that, that I've ever seen, where they haven't changed their stance on the consumption of any of the sort of foods that were really vilified throughout the years. And sort of almost 90 years before its time, predicted many of the nutrition research that's pretty solid right now. Where, you know, they said very early on that these large number of native societies that ate a certain way, produced healthy people without dental cavities. And then it turns out that he discovered what they called at the time was Price Factor. But later on was discovered to be vitamin K2, the necessity of high fat-soluble vitamins in the proper ratios. The wrong vilification of saturated fats and on, and on, and on, and on. So they literally were 80 to 90 years ahead of their time. And so, that book was very eye opening to me.

David: Yeah. For me, how I think of life, we are heavy on the physical on this podcast, Katie. But we really have to keep in mind the mental and spiritual aspects of our life too. So, I mean, one of the things I do daily, or try to at least, is, I love the Proverbs in the Bible. And so the wisdom there, the nuggets that you can... And me and my boys will do that around the breakfast table. And then also, just the different messages. I love the Gospel of John in the Bible as well. And I tend to find myself gravitating back towards reading that. So, that just feeds me spiritually, for sure. And again, I really strongly believe we’re integrated.

Katie: Well, I will link to both of those as well in the show notes at wellnessmama.fm for anyone listening. And lastly, I'm sure a lot of people are wondering right now where they can try Berberine. And I know we have a link that has a special discount of up to 27% that will be in the show notes at wellnessmama.fm. But if you guys can just talk about where people can find it and how they should start.

David: Yeah. So the link is...it's a bit long, so get your pencils out. But it's https://mara-labs.com/pages/wellness-mama-berbelite. I'm so sorry that that's so long. However, that is the website.

Katie: And like I said, we'll have a clickable link in the show notes at wellnessmama.fm for all of you guys listening. As well you can find that as well as all the show notes that I've been taking. I took many, many notes on this one. And like I said, I'm very excited to continue to integrate this one and see what the results are. But thank you both so much for your time and being here. I definitely learned a lot and I look forward to continuing the conversation.

David: Katie, it was wonderful being with you. It was so enjoyable.
John: Yeah, nice to meet you. Hope to talk to you often.

Katie: And as always, thanks to all of you for listening and sharing your most valuable resources, your time, your energy, and your attention with us all today. We're so grateful that you did. And I hope that you will join me again on the next episode of the "Wellness Mama" podcast.

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