DANNY LENNON: Welcome back to the podcast, Greg Potter. How are you today, sir?

GREG POTTER: I'm very well. Yeah, good to be here, it feels like quite a lot has changed since I last spoke to you on this podcast, four years has gone by, and we've had a global pandemic, and we've got the possibility of World War 3. But all is well.

DANNY LENNON: Yeah, certainly a lot has changed, both on a world level, but also, I think in relation to some of the things that you've been doing, and we'll probably certainly circle back to that towards the end of the podcast, and get into some details. But there's a lot that we want to discuss on, I suppose, this bidirectional relationship between sleep and diet, and there's a number of subcomponents that we can talk about. But given that we'll be looking at both sleep timing, eating timing, how sleep itself impacts various aspects of diet and vice versa, I think it might be best if we start with a refresher of some key terms for people listening, some of these they've probably heard on previous podcast episodes, but just to make sure that we're completely clear on things that will come up later on, can you maybe, first of all, explain to people just at an overview level, some of the basics around what sleep architecture is or

what a normal sleep architecture in terms of sleep stages looks like, and then, some of the useful terms there that we might touch on a bit later?

GREG POTTER: Absolutely. I think a helpful starting point is the two-process model of sleep regulation, and it's a simplistic way of describing the way that sleep proceeds. So one component of the two-process model is known as sleep homeostasis, and this simply describes the fact that the longer you've been awake, the sleepier you feel, in general. It's not like that relationship is monotonic, but, in general, that's true, in the same way that the longer you've been without food, the hungrier that you feel. The other process is driven by your body's clock, and this is the circadian process; and to counter the accumulating sleep pressure during the daytime, the longer that you've been awake, there is an increasing drive to be awake. There's a temporary dip around lunchtime, which explains the so called post-lunch slump, and why typically feel slightly sleepy at around 2:00 p.m. or so. And then around the end of the day, when you'd typically fall asleep, there's a sudden drop in this wakefulness drive, that no longer opposes the sleep pressure, and so hopefully, you can quickly fall asleep and stay asleep. Now, if we move now to sleep architecture, then what I just described does influence the architecture, and the more sleep homeostasis that you have, or sleep pressure that you have, the more slow wave activity you'll tend to see during sleep. And these are large, high amplitude brainwaves that start around the bridge of the nose and sweep back through the brain, and they have all sorts of different restorative processes in your body and your brain, and your body likes to get a certain amount of this type of sleep. And you see particularly large amounts of slow wave activity during the deepest stage of sleep, which is slow wave sleep, and then, as sleep proceeds, you see less and less of this deep sleep, and more and more rapid eye movement sleep or REM sleep.

But if I just pan back a second, I'll describe the different sleep stages, so when you're first nod off at the start the night, you typically enter stage one non-rapid eye movement sleep; and it has a few different characteristics such as slow eye movements, but you can think of it as a bridge from wakefulness to sleep. You'll then descend into a slightly deeper stage of sleep named stage two non-REM sleep very creatively named I know, and that's characterized by a few different features, but you see quite a few sleep spindles during the stage of sleep, which are particularly important to the formation of certain types of memories, and this stage two sleep makes up the largest proportion of sleep. It's roughly 50% or so of sleep on average. And then, from there, you'd typically go into slow wave sleep or deep sleep, and this probably makes up roughly 20% or so of your entire night of sleep. And I mentioned slow waves earlier, but there are other things that take place during the stage of sleep, which are particularly important to some of its consequences, so one of these is that your body synthesizes a lot of its growth hormone. This has restorative actions in various different bodily tissues such as connective tissues. It's during the stage of sleep when you consolidate various different types of memories, in particular declarative memories or fact based memories, and interestingly, the stage of sleep also seems to be particularly critical for the formation of memory in your immune system. So there's been some work showing that if you look, for instance, at vaccination responses, then it might be that slow wave sleep is somewhat predictive of how many antibodies somebody will produce in response to a vaccination.

And then there's rapid eye movement sleep, so after ascending back into maybe stage two sleep temporarily, you might then enter rapid eye movement sleep; although in the first sleep cycle of the night, you might not see any rapid eye movement sleep whatsoever. And sleep

cycles recur roughly every 90 minutes or so, although you do wake up during sleep, and so, it's not like you just have five 90-minute cycles strung perfectly back to back in a seven and a half hour sleep episode. But when you do enter rapid eye movement sleep, this has characteristic eye movements, your eyes dart from side to side, your skeletal muscles, and most muscles that don't fulfill essential processes such as your heart beating or your diaphragm, and some of your spiritual muscles are temporarily paralyzed, and the reason presumably is so that you don't act out your dreams. And this rapid eye movement stage of sleep has some important cardiovascular health benefits; it seems to be particularly helpful for emotion regulation, you can think of it as a kind of emotional first aid, and it also might underlie some of our human ingenuity, it seems to be critical for creativity. And there's a nice model of REM sleep named NEXTUP that was put forward by Robert Stickgold and Antonio Zadra recently, and that stands for network exploration to understand possibilities, it's during the stage of sleep that your mind takes a lot of your recent experiences, and it also considers some of your long term autobiographical memories, and it looks for weak associations between these different things so that it can better understand the world, make predictions about things that might come up in the future, and REM sleep also has a bunch of other roles too. So for instance, it seems to be very helpful to understanding the gist of things, if you were doing a multiple choice questionnaire test, and you weren't sure what the right answer was, if you'd had lots of rapid eye movement sleep the night before, you'd probably be more likely to pick the right answer out. So I'll pause there, Danny, but hopefully that introduces some of the key concepts.

DANNY LENNON: Yeah, fantastic. I think that really sets the stage nicely for us. Now, as I mentioned, there's kind of two different ways we can look at this kind of bidirectional relationship. So to start, maybe, if

we consider the influence of sleep on diet, there's a few components of this to dig through, and I think maybe if we start with, well, what do we know about shortened sleep or sleep curtailment and how that impacts aspects of diet, now even within that, there's probably a few different places to touch on, we could look at eating behavior, we could look at the actual physiology underpinning that as even two separate things. So let's maybe first turn to that first aspect of eating behavior, and that might relate to things like hunger, appetite, food reward, and how all these things impact energy intake and food intake overall, what do we know about how sleep, and then, in particular, curtailed sleep may have an influence on a number of these eating behaviors, either hormonally or psychologically?

GREG POTTER: A good starting point is a systematic review that was published three years ago by some scientists at the University of Chicago, and they looked at different randomized control trials of sleep restriction, which is letting somebody have some time in bed to sleep, but less than normal, or sleep deprivation, which is depriving somebody of sleep entirely. And they found that, unsurprisingly, sleep loss increased people's hunger, as a result of that, they did consume more food, something to the tune of 250 or so calories each day. And that brings up a related point, which is that there's also research showing that when people don't get as much sleep as they would like, they might have lower compliance with different diet interventions. And because sleep restriction didn't seem to affect total daily energy expenditure much, it did result in energy imbalance, and small amounts of weight gain, most of these interventions were quite brief. So, on average, it was less than half a kilo, but obviously, if you add up that weight gain over time, then you might see something more substantial. And then, perhaps related to some of what I just described, there was a reduction in insulin sensitivity too. But there are interesting nuances to these findings, and one

of these is that it might be that sleep loss affects men and women differently.

Marie-Pierre St-Onge has done some really nice work on this recently, and in one of her review papers, she looked at different RCTs and compared men to women; and, in general, the data seemed to show that men respond worse to sleep loss than women; and it might only be men that increase their food intake, and a lot of that seems to be driven by snacking. And when you think about some of the mechanisms that are at play here, one of them, of course, is just that the shorter your sleep, the more time each day you have in which to eat. And so, it might just be that you spread out your food and take more. And if some of that food intake occurs very late in the day, shortly before sleep, then you might also be consuming more of your daily energy intake at a suboptimal circadian phase, we might want to circle back to that later. But just digging into some of what St-Onge discussed, a couple of studies have found that women didn't increase their food intake in response to sleep restriction. So one of these was done by some researchers at Temple University, and this was a nicely controlled study, and they just found that after a couple of nights of five hours in bed, the women didn't eat differently, they didn't have any change in their appetite or appetite regulating hormones either. Another study wasn't quite so tightly controlled, but they had similar findings, the difference in this case was just that the study was free living. And then, more recently that review, St-Onge just published some work showing that in a cross sectional study, only among men was less efficient sleep, meaning that the men who spent a smaller proportion of their time in bed actually asleep, so they were awake more in bed, was sleep associated with how much people were eating. So it was only in men that low sleep efficiency predicted increased food intake. And I can go into some additional mechanisms, but I'll pause there, Danny.

DANNY LENNON: Yeah, no, that definitely throws up a lot of interesting questions, and maybe throws up more questions than we currently have answers to. But even if we take people in general, before we look at some of these specific differences between sexes, we can look at maybe a finding where we see this increased food intake with some degree of sleep restriction; and in cases where that happens, then, I suppose, the natural follow-on question people have is, well, do we know exactly what is causing that, because presumably, there's a lot of different things we could point to, right? We could look at, maybe, is there a hormonal change in certain appetite hormones, is there something going on at the level of the brain that changes the drive to consume food, is it more on a behavioral side like you may be alert to where people's preferences for different types of food is going to change, or they're just less likely to adhere to making certain dietary choices. And then, more globally, we know that things like decision making can become impaired when we have poor sleep, so how do we even go about parsing what exactly is going on, and with the totality of the evidence, what is your sense of what we know most about why we may see in some people, at least, an increased food intake with restricted sleep?

GREG POTTER: My sense is that, whereas, it was once thought that some circulating factors like leptin and ghrelin, in particular, might underlie a lot of the changes in food intake that we see, the brain is far more important. And so, just to briefly dig into that, leptin is obviously a hormone that's synthesized primarily by fat tissue and it signals to the brain your energy status. So, in general, the more fat mass that you have, the higher your leptin levels; and leptin has all sorts of functions in reproduction and appetite regulation and so on. But, in general, you would expect that lower leptin levels would predict higher food intake, however, you don't necessarily see that sleep loss reduces leptin levels. And then, ghrelin is the other hormone that I mentioned that's

synthesized primarily by some cells in the stomach, and that is a hormone that promotes food intake. So you see pulses of ghrelin around habitual meal times, but, in general, the longer that somebody's been without food, the higher their ghrelin levels. And so, again, you might expect higher ghrelin levels after insufficient sleep, but you don't necessarily see that, and so, with that in mind, a lot of people turn to the brain and use different types of imaging to try and understand whether it might be that different patterns of electrical activity and blood flow in the brain are predicting food intake, and that indeed seems to be the case. And interestingly, if we look at different aspects of food intake, bearing in mind that all of our senses will affect our food intake, what we see in the environment, the smells that we're exposed to, how we perceive the taste of food and so on, then what we see is that there are different patterns of electrical activity in the brain in response to food images. We seem to respond differently to the smells of food too, looking at those different brain activity changes. And then, it might be that we don't necessarily perceive food as tasting differently, but very sweet foods are perceived as being more palatable after insufficient sleep; and so, whereas normally, a lot of our food intake is probably driven by homeostatic regulation, that's different in the modern context from how it probably used to be, you certainly likely see an increase in hedonic food intake after insufficient sleep. And as you touched on Danny, we're more impulsive in general, and we tend to favor smaller sooner rewards, so delicious foods over large later ones; and we could skip those foods, and we could have better health and a more attractive physique, for example. And then, it could also be that there are changes in mood at play, so maybe sleep loss promotes food intake related to anxiety or feelings of distress, emotional eating; but, in general, it's just that we're less able to override our impulses related to food, we're not able to exert the same cognitive control, and a lot of that seems to be driven by

the fact that parts of the brain are involved in rational decision making, so that the prefrontal cortex, in particular, communicate differently or maybe less effectively with some other areas that are involved in eating decisions and the rewarding properties of food.

DANNY LENNON: So with some of that in mind, and then also tying that back into the idea that you mentioned previously, that we have this data that is suggestive of men responding worse to sleep loss than women, at least, in the context of impact on later energy intake, given what we know about some of these mechanisms, what has been put forward as maybe the most plausible reason why, if a reason indeed has been put forward as to why there could be sex differences in this situation – and I'm sure some sort of evolutionary biology argument could be also factored in there, but do we actually have a good sense right now as to why we're seeing these differences, or is it just this is an observation that has been noted, but we don't really know as to what's going on?

GREG POTTER: I certainly don't know that, so then maybe somebody has a hypothesis, but going back to the fact that there have been a couple of RCTs of food intake in women alone, and not many of food intake in men alone, and how that food intake responds to changes in sleep, I think it's too early to draw conclusions, and obviously, these types of studies are quite difficult to do if you control them rigorously. And so, for that reason, they're often relatively underpowered to detect some of the bases of those between sex differences, so I think we need to watch the space to be honest.

DANNY LENNON: So far, much of that discussion relates to what is happening maybe on a more acute basis or a shorter term basis at least of when we have a certain degree of sleep curtailment for one night or multiple nights maybe in a row, what is the impact on, say, energy intake over those days, what is the impact of dietary behavior. We have then a different question then of,

okay, over a long period of time, people who are chronically sleep restricted or, let's say, sleeping less than would be best for health, what impact that may have on risk of say excessive weight gain or of developing various chronic diseases. So if we focus first on the weight gain issue, because it factors into more of what we're just discussing, does any of that data play out or is it coherent with the idea that if we're chronically sleep restricted, that ends up that we may over consume either calories, or either nutrients that are maybe not so good in terms of an overall dietary pattern, is that coherent with what we see from maybe the larger observational data of people who are most sleep restricted?

GREG POTTER: Yeah, I think it is, and obviously, we need a different type of study to look at some of those questions. But, in general, the prospective research that has been done is pointed to people who report not getting much sleep, and there are different cutoffs that are used for that; some studies will make the cutoff at the five-hour mark, some will make it at the six-hour mark for what constitutes short sleep. Those people are more likely to go on to develop obesity in years to come. And looking at one meta-analysis, they're at something like 45% higher odds, and then, obviously, related to that increase in obesity risk, you're also going to see an increase in risk of various different other cardiometabolic health problems. So you see similar relationships for type 2 diabetes development, for the development of the metabolic syndrome and so on too. And at the other end of the spectrum, you do sometimes see that longer sleep predicts worse metabolic health outcomes, but at the level of the individual, I don't think that it's the case that getting more sleep is maybe ever a bad thing, perhaps there are some very rare exceptions to that. But rather, what's going on in that case is either that somebody has some sort of systemic inflammatory condition, which is causing them to sleep more, because different immune factors have key roles in

sleep regulation, I mentioned sleep homeostasis earlier; and some inflammatory cytokines, for example, are involved in some of those processes. So if you have some sort of disease, then that might increase your sleep need, and then, the other issue is that a lot of these types of studies use quite crude questions, asking people how much sleep they get, and many will conflate sleep with time in bed. Say that you have depression, and you struggle to get out of bed each day and you spend 11 hours in bed, you're only actually asleep for seven of those hours, but you get asked how much sleep you get, and you put 11 hours. If that's the case, then it's no great surprise that you see that relationship between long sleep and poor health outcomes.

DANNY LENNON: One final thing that relates to this is when sometimes a distinction is made between the risk of, let's say, excessive weight gain or the impact then of the converse of if people are increasing their sleep time, and presumably sleep quality, does it have an impact on reducing, let's say, body mass. Then there's the issue of focusing on, well, what we're really concerned with here is probably body composition, and there's probably much less data in this area, I'm presuming. But I did want to ask your kind of thoughts generally in this area, and, in particular, one of the studies that I think is most commonly cited here and pointed to because there are such stark results, and it was a Nedeltcheva paper, I think 2010, where they compare these two groups, one restricted to five and a half hours in bed, the other to eight and a half; and you see the same amount of weight loss in both groups, but the group that was restricted to five and a half hours has much less fat mass lost and lost much more lean mass relative to the other group. So I'm just wondering, do we see this type of finding replicated in other places, is this something that you broadly think is something that we can be pretty sure is going on, or what is the situation with impacts on body composition changes specifically?

GREG POTTER: Yeah, there's a lot there to unpack, so forgive me if this is quite a long answer, but the Nedeltcheva paper is widely cited, because, in my opinion, it is a really good study; and just to briefly describe it, what they did was they took overweight adults, and these people, they're good sleepers; so it's always important to bear that in mind when it comes to manipulations and time in bed as we might come back to later; but they crossed them over between two conditions, and in one, they had enough time in bed with similar amounts of what they would normally have; and in another, they only had five and a half hours in bed each night; and each of those conditions last two weeks, and there was quite a long wash out between the conditions. At the same time, they gave them a controlled energy deficit, which was based on a presumably accurate assessment of their metabolic rate, and the diet was quite similar to a diet that a lot of people would use for weight loss. So I think the external validity is okay, and what they found, as we touched on is that while weight loss in the two conditions was very similar, there was no significant difference between the two conditions. For sleep group, the group that had insufficient time in bed lost 55% less fat mass than the other group, and that seemed to be driven by a change in substrate use towards less oxidation of fat. And they also found that the insufficiency group had increased ghrelin and hunger, and that's a really important point, because in this study, they're controlling food intake. And so, if these people are losing more fat free mass, less fat mass, and they're more hungry, then if you take this outside the laboratory, there's a good chance that they're going to have worse body composition and a given body weight, but also, they're going to eat more in total, so their weight loss is going to be compromised.

So the question is, has that been replicated? Obviously, it's a difficult study to replicate, when you look at the different methods that they used. They used doubly labeled water and

DXA scans and so on; and these are really expensive methods, but [inaudible 00:26:37] did a really nice study a few years later, and their study was probably more ecologically valid, and what they did was they took overweight and obese people, and they divided them into two groups. One group was just calorie restriction, and the other one was calorie restriction plus sleep restriction on five nights each week, so they were trying to mimic the conditions that a lot of us might experience working nine to five jobs, and sleeping in the weekends. And they found that, sure enough, the sleep restriction group did reduce their sleep duration, which is important; and over the course of the whole week, they had just under three hours less total sleep. And again, in keeping with Nedeltcheva's findings, they found the sleep restriction group lost less fat mass, and a bit more fat free mass, and they found similar changes in their substrate oxidation too. So that suggests that those early findings of the Chicago folks are probably consistent with what's going on, and the question is, well, what are some of the changes that underlie those differences. I think, in general, insufficient sleep probably promotes skeletal muscle catabolism, and that might be in part driven by reduced testosterone in men, for instance, increased cortisol. You see a flattening of the diurnal cortisol rhythm each day, and you see an overall probable increase in cortisol too, and obviously, that has some catabolic effects in some tissues. And you see a reduction in skeletal muscle protein synthesis, that baseline too, and there's been some nice work in the last couple of years by Nicholas Saner, which had people go through a period of sleep restriction, looked at basal muscle protein synthesis, found that it's lower than what they would normally see; and then, giving people different exercise intervention, so just high intensity intermittent training, and found that, in many ways, exercise is able to offset some of the negative cardiometabolic effects of insufficient sleep that you see. So there's a take home point, it's really important that if you are

sleepy, don't skip exercise because you're tired; you can offset many of the detrimental consequences of the exercise by doing some exercise.

But there are a few other things that you mentioned, which I'll just touch on, Danny. So one was sleep extension, and I feel guilty in a way because when I've spoken about sleep on various podcasts, I've often emphasized the bad stuff that happens when you don't sleep well; and the corollary of that is that if you take somebody and you improve their sleep, then you tend to see all sorts of improvements. And this is true of sleep extension studies, a lot of people habitually just don't get enough sleep, and if you give them more time in bed, they prolong their sleep, and they experience all sorts of beneficial associated consequences too. So Tasali, for example, who's published a few studies on this now, one of the early studies that those researchers did found that sleeping more resulted in less sleepiness, a lower appetite, a reduced desire for sweets and salty foods. And then, they very recently published a fascinating paper on sleep extension in which they took overweight young adults who were habitually getting less than six and a half hours of sleep each night, and they divided them into two groups; so one was just carrying on the way they were previously, and the other aimed to get at least eight and a half hours in bed each night. And they only looked at a period of two weeks, but what they found was that the sleep extension group slept about 17 minutes longer, and importantly, their sleep efficiency didn't change. We might come back to this later, but obviously, it's not just sleep duration that matters, different metrics of sleep quality matter too, and the regularity of your sleep does as well. And they found that, whereas the control group actually slightly increased their energy intake in their body weight, the sleep extension group produced both, and the difference, on average, between the groups is about 270 calories each day, and I think over time that might be clinically significant.

So I know you've spoken to Kevin Hall recently, he's a superstar in the field of bodyweight regulation and nutrition, but if you look at his dynamic prediction model, then if that was sustained over time, then a difference of 270 calories each day would predict about a 12 kilo difference between the groups over three years. So I think that is meaningful. And the final thing that I'll just mentioned here is going back to the idea that sleep quality matters, there are rare instances in which if you ask somebody to spend less time in bed, they will actually sleep more. So if you take somebody who has insomnia, and they spend lots and lots of time in bed, wide awake, hoping they will sleep, and you restrict their time in bed, it's called bedtime restriction therapy or sleep restriction therapy, then, if you match their time in bed to their actual sleep capacity, the first few days absolutely suck, because they're really sleepy during the day and their sleep quality hasn't yet improved. But shortly thereafter, their sleep quality improved so much that they actually end up sleeping more than they did at baseline. And so, as another take home point, it's really important that you match your time in bed to your actual sleep capacity; and so, for somebody who has insomnia, that might mean reducing your time in bed; whereas for a lot of people, I'd say, the majority of people, it's more likely the case that if you extend your time in bed, then you're going to benefit.

DANNY LENNON: Yeah, that itself is fascinating to think about because, and, I suppose, after the fact, it seems like, oh, that makes sense, but in some ways, it's maybe counterintuitive. But the idea that it would be appealing to many people who are having sleep issues to say, well, I'll give myself the best chance possible, and so, I'll go into bed early, and maybe try and relax, and I'll just stay in, and I'll give myself 10 hours, and hopefully, I'll find seven or eight good hours within that, whereas for some people that might be counterproductive if they're just spending more time staying awake, that's really, really

fascinating. One of the things I did want to follow up with, because you mentioned, Greg, that often the focus, at least, in a lot of discourse, but also then within research is a focus on sleep duration, and one of the other aspects that maybe has started to get a bit more attention, and I know that you've talked about, is the impact of chronotype. So there seems to at least be good reason to believe that differences in chronotype can be associated with a variety of outcomes that are even independent of sleep duration. So before we talk about some of those, could you maybe, again, briefly describe to people what's the best way to conceptualize what a chronotype is, and then with that, what do we know about different chronotypes being associated with different health outcomes that may be distinct from just the number of hours someone is sleeping?

GREG POTTER: Yeah, absolutely, and I'll start with a definition of what chronotype is. It's the differences between people in different outputs that are regulated by their circadian system, and that might just sound like a word salad, but you can think of that as whether you are more of a morning lark or a night owl, relative to other people at the same age and biological sex as yourself. And, as you mentioned, chronotype has been associated with all sorts of different health outcomes, and, to be honest, I think a lot of those associations are difficult to chalk up to differences in chronotype itself. I do think that chronotype does exist, and some people don't seem to, but one of the issues with chronotype is that nowadays, in our modern context, we have very weak time cues, and these time cues are involved in training or synchronizing our circadian clocks each day with the world around us – the most important of these is the light dark cycle. But a few other factors might be important, one of which is the timing of our food intake, one of which is the timing of our patterns of physical activity. And if you give people very strong time cues, they spend lots of time outdoors during the day and then nights

are dark, and they have consistent eating-fasting patterns, then chronotypic differences between people will rapidly decline, but they are still there. And if you look at the far ends of the chronotype continuing their circadian rhythm sleep-wake disorders, there's advanced sleep phase syndrome, delayed sleep phase syndrome; and we know something about some of the different genetics that might underlie those differences between people. And so, the way that I've come to think about this is that, whereas a lot of people think of chronotype as being trait like, something which is largely genetically determined, I think in our modern environments, it's more state like, and it's only really by doing something like going camping, as we spoke about previously, Danny, that you can see what your true chronotype is.

Now, bearing in mind what I just said, if you look at cross sectional data, then, in general, late chronotypes have less healthy behaviors, they're more likely to smoke, there might be some associations with some aspects of diet, such as alcohol intake, although, to be honest, the quality of a lot of that research isn't fantastic. And they're more likely to have different types of health problems, mood disorders, poor cardiometabolic health and so on. But going back to what I was just saying, I think a lot of that is driven by less healthy lifestyle behaviors that result in late chronotype, and so, it's not chronotype per se that's at play there.

DANNY LENNON: Yeah, and I think a lot of people listening could think of examples of where if someone is more likely to be, that has a lifestyle where they're staying up longer, that comes with certain other behaviors that tend to get wrapped within that, however, given that there may be are preferences, and there is at least at the extremes, different chronotypes that we could talk about, and there's disability, I suppose, in some way to maybe, as you mentioned, rather than being an inherent thing, that it's just a function of how we typically set up our lifestyle

to some degree, one of the interesting things then to consider is the habitual sleep and wait times that we tend to have. And this is something where, again, you tend to see most recommendations about a kind of a state, or, I suppose, a consistent sleep-wake time, no matter what that is, for an individual. One of the problems then that comes up is in relation to when we have a sudden and maybe dramatic change in these sleep and wake times, and I know just a bit earlier you mentioned this concept of a circadian phase shift, people may have heard of more colloquial terms like social jetlag, which has been mentioned in literature as well, can you maybe just talk about this issue of not only just changes in sleep duration, but if we see a change in sleep timing, how this might fit into this whole picture, whether that's related to chronotype or not, or just these circadian phase shifts, and then potential implications of that?

GREG POTTER: Yeah, of course, and on the subject of social jetlag, I think it's no coincidence that the negative associations between chronotype or late chronotype and different health behaviors and health outcomes map very closely to the associations between social jetlag and the same outcomes, because late chronotypes are more likely to experience more social jetlag than early birds are. And just to come now to your question, a key concept to understand is that these different dimensions of sleep-health interact, and when I say dimensions of sleep-health, I'm referring to sleep duration, I'm referring to sleep timing, I'm referring to the quality of sleep; and there are a few different components of that, one is how long it takes you to fall asleep, your sleep latency, one is your sleep efficiency that I mentioned earlier; you could look more closely at what's going on in the brain and body, and then think about sleep architecture, which I discussed briefly at the start; and you can also consider things such as how well you breathe during sleep; and then there's the variability of all those different things that I just mentioned. And so, just to

touch on some of those, if you look at sleep regularity, then that's going to influence the regularity of your diet timing too, which is probably, by itself, important. There's some work showing that people who have more regular sleep tend to have more successful weight loss attempts. There was a study a couple of years ago of PREDIMED participants that showed that quite nicely. If you look at sleep quality, then again, there are data showing that sleep efficiency predicts weight loss success, and thinking of a study by some Japanese researchers that found that people who wake up five or more times each night lost less weight than people with fewer wake episodes.

And there have also been some interventions to try and improve some of these different aspects of sleep quality; and, Danny, you'd probably find this study particularly interesting if you haven't seen it before, but there was some work by Dr. Pål Jåbekk at Oslo Metropolitan University a couple of years ago, which was a sleep hygiene intervention alongside resistance training. And the intervention didn't have a dramatic effect on people's sleep, but people in the sleep hygiene group lost more fat mass, and the other – well, they lost fat mass and the other group actually gained a non-significant amount of fat. And so, it seems that if you take people with relatively good sleep, and you do what you can to improve their sleep quality, then that could improve how they adapt to resistance training, thereby improve their body composition. And then, if we look at people with different types of sleep disorders, and take the example of obstructive sleep apnea, which is basically intermittent collapse of the upper airway, which leads to hypoxemia, fragmented sleep, increased activity of the sympathetic nervous system and so on, and all sorts of negative downstream consequences on brain functioning, cardiometabolic health, and there was a really nice paper a few years ago by Marie-Pierre St-Onge, I mentioned earlier, that was basically a very small study that looked at

people with obstructive sleep apnea, and they either gave them sham continuous positive airway pressure, which is basically a way of treating these people by providing a continuous stream of airflow during the night, and that keeps the upper airway open, and thereby helps minimize apneas and hypopneas during the night. And they gave people either CPAP or sham CPAP, and they found that while total energy intake wasn't different between the groups, during the actual CPAP, if you looked at fixed eating occasions, specifically, so breakfast, lunch, and dinner, then daily energy intake was lower in the active CPAP condition, as opposed to the sham one. And so, that's a very small scale study, but it's an interesting suggestion that there might be something at play there. And I'll pause there, Danny, I realize that was quite a long tirade.

DANNY LENNON: No, not at all. I think that highlighted one really kind of crucial factor that so often we see these different dimensions of sleep talked about separately. And so, as you mentioned, when we really have to think of them collectively, because each one will have some degree of influence on the other with duration, timing, latency, architecture, sleep regularity, all those different dimensions that you discussed, that because of the implements of each other, considering them alone is probably not going to be appropriate way to appraise this issue. Based on what we've just discussed, and getting into some of these concepts around circadian rhythms, we've talked about social jetlag, circadian phase shifts and so on, if we start looking at kind of, I suppose, the second half of that bidirectional relationship we mentioned at the start of the episode, and we now start looking at how food intake affects sleep, there's a number of different sub components we could look at here of how the total amount of food we're consuming, the macronutrients, different nutrients, etc., but I do want to start actually with timing based on what we've just discussed. And there's a number of, at least, a number of cross sectional

studies that have shown that calorie intake that occurs kind of close to melatonin onset, and we can maybe describe that for people in a bit more detail is associated with this increased body fat, and also adverse effects on glucose tolerance. And it seems that this relationship may not be evident when we're looking at calorie intake relative to clock time, but more so when we're looking at it relative to that dim light melatonin onset. So can you maybe start with explaining what that concept is, and what your thoughts are on this area around timing of food intake relative to sleep, and what that may mean, or what it doesn't mean, or where the kind of current consensus you think is on that particular question?

GREG POTTER: Yeah, again, there's a lot in there to unpack. So I'll do my best, but one of the things that you touched on there was when people eat, relative to their biological clocks versus the social clock, and related to this, I think it's always worth thinking about your diet timing relative to your sleep-wake cycle, the reason being that while this is less true of some people, shift workers, for example, in general, your sleep timing somewhat approximates the timing of your biological clock, and so, it's likely that beginning about an hour or 45 minutes or so before, when you would habitually fall asleep, and when you would habitually wake up in the morning, that's your biological night. And at this time, your body is well suited to certain processes, and it's also not well suited to others, one of which is food intake, and digesting and metabolizing that food. And so, you mentioned blood sugar regulation there, Danny, and there's been quite a lot of work on this now. There's a meta-analysis three years ago by some Australian scientists, but they basically found that if you look at blood sugar and insulin responses to the very same meal consumed in either the first part of the day, so between, say, 7:00 a.m. and 4:00 p.m., to later in the day, the biological nighttime, then you see substantially lower responses when something is consumed in the morning. And

we know quite a lot about some of the different bases of that, so if you look, for example, at the clock in the gap, and that influences glucose absorption, if you look at the pancreas, then that influences melatonin, that influences insulin secretion, and melatonin, which is synthesized by the pineal gland in the brain, inhibits insulin secretion. So during the biological night, you're going to see more amplified insulin responses to a given glucose bolus. And then there are clocks in skeletal muscle, and adipose tissue and so on too, that all affects local insulin sensitivity, and so, all of these changes, in particular, in some of these peripheral clocks, contribute to your postprandial responses.

Now, with that said, if we look at the subject of when we eat, and our general health and our sleep in particular, then starting with sleep, I think a relevant concept here is time restricted eating, and I won't go into what that is, because I'm sure that most people will be familiar with that, given your previous episodes. But some of the initial work on time restricted eating by Satchin Panda suggested that among overweight people, time restricted eating might slightly improve some measures of sleep quality, so they just use the simple assessment of sleep satisfaction, but more recently, the work on time restricted eating and sleep hasn't been particularly clear. There have been relevant studies by Pam Taub, did some work with Satchin Panda, and they found, again, a small increase in some subjective metrics of sleep quality. But Krista Varady, who has done a lot of work on different forms of intermittent fasting, took obese people and put them on an eight-hour time restricted eating condition for 12 weeks, and they found that their PSQI scores, and the PSQI is an instrument that's used to assess the quality, didn't budge. And the reason is likely just that their baseline PSQI scores are quite good, and it's always important to bear in mind how well somebody sleeps at baseline, because if their baseline sleep is good, then there's going to be an effect that means

that you're not going to be able to move the dial in the right direction that much.

And then, very recently, Varady's published a review on the effects of time restricted eating, alternate day fasting on sleep, and basically concluded that while both can be effective for weight loss, they don't clearly seem to affect sleep quality necessarily. But that is just time restricted eating, and there are lots of different things to consider beyond that, and I'll add that if you look at all the different studies of time restricted eating done to date, then I think it generally is a good thing. You're going to see large positive effects in people with worse cardiometabolic health at baseline, but you can look in all the studies done tends to slightly reduce food intake, slightly reduced body weight, perhaps slightly improve some aspects of blood sugar regulation, blood lipids, blood pressure too. And there has been some work very recently too showing that even among healthy young adults, early time restricted eating can yield some quite impressive health benefits, and thinking specifically of some work by Eileen Mao who's in Beijing, that divided people into either an earlier eight hour time restricted eating condition or a later one; and they found that the early one led to improved body composition, improved blood sugar control, lower markers of inflammation, improved gut microbiota diversity. And these people are quite healthy at baseline, so I want to be clear that I think that time restricted eating for most people is a really helpful thing to do. And I also think there's an interesting interaction between when we eat and what we just given that most people consume their alcohol relatively late in the day; if you implement time restricted eating, and all of a sudden, you're finishing your final calorie intake at 7:00 p.m., you're probably going to inadvertently reduce how much beer and wine you consume, which is going to be good for you, and it's going to be good for your sleep. So I think in many instances, these studies that haven't found clear effects of time restricted

eating on sleep are underpowered; and I think if you could look at everybody who has gone from not using time restricted eating to using it, you probably find some effects on sleep, on average. Sorry, Danny, I'm almost done...

DANNY LENNON: No, it just raises a number of interesting questions, and I think you rightly point out that there could be the potential for something like time restricted eating or some other change in meal timing overall, that has then other indirect effects on aspects that will impact sleep. For example, you mentioned the change in alcohol consumption, and so, indirectly then, this change in meal timing is impacting sleep via this other mechanism. One thing I did want to ask about, and we can maybe cover this if we talk about macronutrients as well, but I think it's one of the most common things I see anecdotally recommended from people or they've heard it somewhere on the internet is the value of a high carbohydrate meal at the end of the day being something that enhances sleep. And it's something that I commonly see echoed, but is this something that is actually rooted in strong evidence that we can reliably see that such an intervention impacts sleep in some positive way, or, what is your take on such recommendations?

GREG POTTER: Yeah, it's a really good question, I think it's another instance in which I don't think we know much about what some of the underlying mechanisms might be. But we always make hypotheses and then test those hypotheses, and it's often the case that whatever we look at, if there's some signal, then we chalk it up to that being the main factor that's at play. I don't know what's truly going on here, but if we just focus on carbohydrate intake and sleep, in general, then it seems that higher carbohydrate diets tend to lead to more rapid eye movement sleep and less slow wave sleep. And there's been a meta-analysis published on that last year, and the mechanisms that they put forward are, if we look at fat intake and sleep, then fat seems to stimulate a lot of CCK

production, much of that's made in the small intestine, relative to carbohydrate. And if you look at preclinical research, then if you inject animals with CCK, then you see a dose dependent increase in slow wave sleep, and then the effects of the high carbohydrate intake on REM sleep are thought to relate to brain tryptophan. If you consume a bolus of carbohydrate, in particular, high glycemic index or glycemic load carbohydrate late in the day, then in response to that, you're going to see a sharp spike in insulin synthesis, and therefore, it released in the bloodstream too, and that's going to drive various different amino acids, so branched chain amino acids, for instance, in skeletal muscle, it's going to probably slightly reduce skeletal muscle protein breakdown too. And what that's going to mean is that tryptophan is going to have less competition for entry into the brain via the large neutral amino acid transporter. And because tryptophan is a precursor for melatonin via serotonin, you might see increase melatonin production, and some downstream effects on sleep structure, sleep architecture, because, again, if you just look at how much tryptophan is in the blood, then it tends to correlate positively with the amount of rapid eye movement sleep that people get, although interestingly, if you give people exogenous melatonin, then you don't really see big changes to sleep architecture.

Now with that said, you asked about the final meal specifically, and so, what do we see if we give somebody a bolus of carbohydrate at that time, the first study that I'm aware of that looked at this was by Ahmad Afaghi, I think that's how you pronounce his name. And like later studies, they used a high glycemic index rice in the final meal, and they found that it shortened sleep latency compared to a low glycemic index rice. More recently, there's been some research that's particularly relevant to the athletes or exercising people among us by Christoforos Giannaki, who is a researcher based out in Cyprus, and they did a really well

controlled study of post workout evening, high glycemic index rice intake, and its effects on sleep. So they took healthy recreationally active people, and they had people do some sprint interval training at about 6:00 p.m., and then, afterwards, they had a meal, either containing lots of high or low glycemic index rice, and they looked at their sleep using PSG, which is largely considered the gold standard way of assessing sleep. And then, they also looked at their performance in a couple of different exercise tasks, and cognitive tasks the next day to see if any changes to their sleep structure had some knock over effects to their performance, and what they found was that total sleep time and sleep efficiency were greater after the high glycemic index final meal, and sleep latency was much shorter. So these people fell asleep a lot faster after the high glycemic index meal, and then, related to those changes in sleep perhaps, they also found that performance in the cognitive tasks slightly improved, although there weren't any changes to exercise performance between the groups. And so, based on that, it might be that for somebody who is in good cardiometabolic health, they have good glucoregulation, particularly if they exercise late in the day, which is going to improve things such as blood sugar control, because you're going to see an increase in non-insulin mediated glucose uptake in skeletal muscles, then having that kind of bolus of carbohydrate at the final meal might be good for their sleep. But one thing I always emphasize to people is that you always have to think about what you're optimizing for, and so, it could be that if you took someone with less good blood sugar control, say, somebody has pre-diabetes, and you gave them a similar bolus of white rice at that time of day, maybe you'd see some small positive effects on their sleep, I don't know. But if you looked at their mean blood sugar levels over time, then maybe you'd see that those are worse, recognizing also that your budget response to your final meal are also going to influence your blood sugar responses to the first meal the

following day, for example. And so, for those people, perhaps over time, that could contribute to increased risk of various different glucoregulation related disorders, whether that's diabetes or different types of dementia, so just have to bear in mind those nuances.

DANNY LENNON: Yeah, thanks for that. And that in itself brings up another couple of questions that we can get into. Now that we've discussed this issue around timing, both overall dietary timing and just this specific issue of, say, carbohydrate timing in a particular meal, and then, beyond that, when we're looking at more broader issues related to macronutrient manipulations, I'm not sure if we really see much of note beyond some of the things you said of it actually impacting sleep reliably in a certain way, in a sense that we could broadly recommend some type of macronutrient breakdown, at least, I'm unaware of that, but it seems interesting then to focus in on perhaps some specific nutrients and individual foods or even at a supplemental level. One thing that I did want to touch on because you'd raised, and you mentioned the example of tryptophan is, I suppose, one of the difficult things to try and parse through in some of this literature is do the nutrients that we may have some reason to believe for either a mechanistic reason or even from a high dose supplementation trial, does that have the same impact when we are getting foods that tend to be associated with those certain nutrients? So, for example, if we're looking at things like supplemental melatonin or high dose supplemental tryptophan, and we may potentially see an impact of some of these and some different ways on either sleep or maybe on circadian biology, it's hard to find then research maybe that's supporting the idea that, oh, if we eat more foods that are associated with being high in tryptophan, that we have this reliable effect on sleep. So can you maybe just talk about how you see that picture of those distinct differences between what we might see from a supplemental dose of something versus foods that get associated with

a nutrient, and how we should think about issues like that?

GREG POTTER: Yeah, that's a really good question, and I don't feel like I have a particularly good answer to it, but there are a few things that I'll mention. So one is total tryptophan intake over the day, and obviously, there are lots of factors at play too, so there are the other amino acids that you consume and how that influences uptake of tryptophan. There's the timing of the tryptophan intake too, so yeah, maybe tryptophan is providing additional substrate for the synthesis of melatonin. But if you're taking that at a time of day at which your pineal gland is not synthesizing much, if any, melatonin, then it's probably not going to have much effect on your nighttime sleep structure, so when you consume certain foods is going to matter. And then, there's the interaction between different foods that contain the same nutrient or the same substance, and the example that comes to mind here is tart cherries or some other phytomelatonin rich food. And phytomelatonin, so plant based melatonin is actually relatively ubiquitous. There are some plants that are incredibly high melatonin, but haven't been studied for their effects on sleep to my knowledge, and the example that stands out is pistachios. Pistachios have something like 233 micrograms per gram of dry weight. And to give people an idea of what that means, but those 300 micrograms of melatonin is often used in jetlag. So that would suggest that you need to consume slightly more than one gram of pistachio to get that dose of melatonin. So with that said, what would happen if you took that alongside, or if you consumed a handful of pistachios alongside supplemental melatonin, would that influence the response to melatonin? I don't know, and to my knowledge, it hasn't been studied. Melatonin’s interactions with some foods has been studied a bit in particular, Marta Garaulet and some others have looked at how exogenous melatonin administration influences glucose responses to

oral glucose tolerance tests, and look to when there are differences between people who can't carry a risk variant of one of the genes that encodes one of melatonin receptors. That might sound a little bit difficult to understand, but basically, about a third of people worldwide carry a risk variant of a particular gene, MTNR1B that increase their risk of diabetes, and that seems to be because melatonin in those people affects their insulin responses differently to people who don't carry that, and as a result, the blood sugar excursions following meals are greater. So if you gave somebody a bolus of glucose, and someone carried that particular gene, and around the time you gave them the glucose, he gave them some melatonin too, then you'd see more exaggerated blood sugar responses to the intake of glucose as a result of melatonin. Now, sorry, Danny...

DANNY LENNON: No, no, go ahead, please.

GREG POTTER: So just on the subject of plant based melatonin, that brings up whether the effects of something like tart cherries on sleep is due to or are due to the melatonin per se, or whether there are other things in the cherries that are at play. And yeah, maybe you give people tart cherry juice concentrate, and you look at their excretion of 6-alpha toxin melatonin, which is the primary urine metabolite of melatonin, you find that, sure enough, after intake of the cherries, you see an increase in the urinary excretion of that, and you see an improvement in some sleep metrics, and you therefore assume that the improvement is due to the melatonin, you don't really know if that's the case, because obviously, tart cherries are rich in many different polyphenols and so on. But, just on the subject of tart cherries, they do seem to consistently improve different aspects of sleep; and one of the great things about cherries too is that they're good for general health, and they seem to be very helpful for exercise performance. Philip Chilibeck's published a meta-analysis looking at endurance exercise,

finding that there might be some improvements, and Glyn Howatson has done a lot of work on both exercise and sleep. And if you look at one of his papers that collated all the findings on recovery from exercise, then there were quite large effects of tart cherry juice intake on muscle soreness, on the recovery of muscle strength and power. And so, I think, regardless of whether those effects are mediated by how the cherries affect sleep, it's a good thing to consume. So I've realized I've just thrown a lot on the table and pushed over to your side, Danny, but there was quite a lot in there to get into.

DANNY LENNON: No, I appreciate it. So as things currently stand, because you see differing opinions on something like melatonin, even if we were to either take supplemental melatonin, or then something like, let's say, a concentrated tart cherry juice with the idea of doing the same thing, being a source of melatonin, you see kind of differing opinions of where it's best used. So in some cases, people tend to associate with sleep; other people then will say, well, actually, it's not really as reliably going to impact sleep on an ongoing basis, but it's probably more likely to be beneficial for, as you say, jetlag or social jetlag, or when there's changes in sleep coming up. Where do you think it's best for people to currently conceptualize the use of melatonin where most of the evidence would suggest it is beneficial or isn't beneficial, or where people may be using it appropriately or inappropriately?

GREG POTTER: So I'd probably draw a line between tart cherry juice and melatonin, the reason being that you can use melatonin judiciously to shift the phase or the timing of your body's clock; and there's a well demonstrated so called phase response curve for melatonin, and I won't go into too much detail about the phase response curve, but the principle is that if you take an appropriate dose of melatonin – and the dose that's used for shifting the clock is often between about 300 micrograms and one

milligram, sweet spot's probably in there – if you take that dose of melatonin about four hours or so before you habitually fall asleep, then you will tend to pull your sleep a bit earlier. And so, if you are flying to the east, then that would be helpful. If, however, you take the melatonin around the time that you wake up each day, then you would extend your biological nighttime, and that would tend to push your clock later if you repeated that behavior over time. And so, theoretically, that could be helpful if you were going west, and you could take an appropriate circadian phase, although practically, that doesn't really pan out, but we won't get into that.

With respect to tart cherry juice, obviously, it contains phytomelatonin, but the variation from one cherry to the next is likely to be substantial. And we don't have a phase response curve for the use of tart cherry juice, I'm just saying that if you're using melatonin to alter the time of your body's clock, then I'll probably use the supplemental form. One of the big issues of melatonin is just that, at least, going by analysis a few years ago, there can be huge variation between what's reported on the label, and what supplements actually contain. And that particular study found that some products contained about 80% less than the label claimed, and some contained about 480% more melatonin than the label claimed, and some of them were contaminated with serotonin. And even within a particular product, if you opened one bottle of melatonin capsules, and tested five of them, you'd see quite large variation from one capsule to the next. So just bear that in mind, but melatonin can definitely be helpful in many instances, if you can source an appropriate melatonin; and when I say appropriate, I mean, the dose corresponds to what you need, and the form too. So melatonin is typically metabolized quite quickly, its half-life is something like, it's around 45 minutes. However, there is a time release form of melatonin, the stuff that's used clinically is named Circadin, and that has a

half-life of more like two to three hours; and for that reason, if you take it, then you better mimic your body's overnight melatonin profile. And based on that, that type of melatonin is typically helpful for sleep maintenance issues, it's used sometimes among elderly people who have insomnia and struggle to stay asleep through the night, and it's been shown to reduce the frequency and duration of nighttime awakenings in those people. But if you're just using melatonin to move your clock around, then as I touched on earlier, I think the fast release stuff of 300 micrograms to one milligram, it's probably about right. And then, there are many other applications of melatonin too, so people are interested in using it for cardiometabolic health problems, there's some interesting work looking at the use of melatonin over time and blood sugar control, and that's intense evidence that can be helpful, and for that reason, could prove beneficial in conditions such as type 2 diabetes, polycystic ovary syndrome; and then people are keen to try it for COVID-19 too, and I think one of the interesting things to consider is the interaction between the supplements and the foods that you consume in your environment. So if you take the case of somebody with severe COVID-19, who's in the hospital, and in the hospital, there's a horrible light-dark cycle in which, during the daytime, there's very weak light, and during the night time, there's also very weak light, and you're therefore having your body clock disrupted at exactly the time when you want to support your health as much as possible, then maybe taking melatonin in that context, could both help with the timing of your body's clock, but also because of melatonin's non-receptor dependent effects could help with various different inflammatory issues that contribute to the pathogenesis and the advancement of COVID-19. So sorry again, there was quite a lot in there, but there's a lot to discuss related to melatonin.

DANNY LENNON: Yeah, and I think probably even focusing on any of these particular compounds or

nutrients, we could probably do individual episodes on each, so with time constraints in mind, and again, we probably don't have time to go through everything that is often suggested as a nutrient or an individual supplement or an ingredient that has some degree of benefit for promoting better sleep. But maybe just to touch on just a couple of quick ones that I tend to hear most often talked about, and maybe you can just give us a quick overview as to whether there is good evidence that they can have a benefit or not, we see probably a few different classes of things, on one side, you may see individual micronutrients like magnesium is commonly suggested, then you can see various amino acids that get suggested for sleep, we've already mentioned tryptophan, glycine is another one that sometimes comes up in these conversations. And then, you can have other compounds or herbal compounds such as valerian root, which does seem to have at least some suggestive evidence behind it as well. So of those or any others that you think are particularly the most commonly discussed, which ones do you think people should be aware of as having some degree of potential benefits, some that maybe lack evidence, and you wouldn't suggest they go for, or at a very broad, broad level, knowing that we can't get into too much detail on every single one, how would you conceptualize individual nutrients like this, and which ones have that benefit for promoting better quality sleep?

GREG POTTER: Sure. So what I'd say is that you need to think about somebody's sleep endotype, so the biological bases of why they're struggling with their sleep. Some people struggle because of pain, some people struggle because of anxiety, and so on, and therefore the sleep phenotype too. So as a result of nighttime anxiety, maybe somebody struggles to fall asleep; as a result of their pain, they struggle to stay asleep. And those factors are going to determine which supplements are most likely to help; and I'll just add that you need to also think about the totality of the effects of the supplement. If

you're an athlete, and you're struggling to sleep through the night, then you might want something that's both shown to help with sleep, but also in some way support your exercise performance. And there are also a bunch of other factors too related to things like the interactions' team and so on, I won't get into those. So you mentioned magnesium, and magnesium is an interesting one because it's very widely used for sleep, however, in my opinion, the evidence that it supports sleep health is quite weak. The thing about magnesium is interesting though, it's the second most common nutrient deficiency in so called developed countries after vitamin D. And so, a lot of people stand to benefit from supplementing it even if it's not benefiting their sleep. And if you look at cardiometabolic health, for example, then people with poor cardiometabolic health and magnesium consistently improved their fasting blood sugar levels, their blood lipids, I mean, this probably relates to that, but probably the benefits to their blood pressure and those effects are going to be most prominent in people with low blood levels of magnesium. So you also need to think about your status too, but in terms of its effects on sleep, there haven't been many good studies, there have been a couple of systematic reviews recently suggesting that maybe magnesium slightly speeds sleep onset at the start of the night, possibly modestly improves total sleep duration, but you need to also consider that there are different things that you can do for your sleep that are going to have much more dramatic effects on your sleep than taking a lot of these different supplements.

With respect to other supplements that you could take, we touched briefly on L-tryptophan earlier, I'm not terribly impressed by the use of L-tryptophan as a sleep aid to be frank, and its effects don't really map perfectly to taking melatonin. The other thing with melatonin is that if you can get some good stuff, then the safety profile is excellent for most people. Some people would push back against that, but I

think that's a defendable statement. You also mentioned some plant based compounds such as valerian, and again, the quality of the evidence supporting the use of valerian is very, very weak. I don't really think that it supports that at all. So just to touch on a couple of supplements that I think are interesting and helpful, given the totality of their effects, I think one of them is ashwagandha, and that's a so called adaptogen, meaning that it helps people better cope with stress. And there have been a few studies looking at ashwagandha for different types of sleep issues, showing some modest benefits, but the cool thing about ashwagandha is that it seems to be good for many aspects of health. And if you think about why people struggle with sleep nowadays, then stress related sleep issues are especially pervasive; and there was a review recently suggesting that of all the different supplements that were included, only ashwagandha consistently reduced morning cortisol, and it also seems to consistently raise testosterone in men; and again, if you're struggling with stress, then that's probably going to compromise your production of testosterone.

And then, perhaps related to those effects on testosterone, it also seems to speed adaptations through resistance training, so people get stronger and grow muscle slightly faster when they take ashwagandha, it might also lead to some modest amount of fat loss in those people too; and then, with respect to endurance exercise, give people ashwagandha over a few weeks, if anything, it might slightly boost their VO2 Max, which is one of the determinants of endurance exercise performance. Safety profile looks pretty good, there are a few case reports of some liver issues. Is that ashwagandha, or is that contamination? I don't know. With those types of case series, it's always really hard to tell. And then another one I think is particularly interesting is L-theanine, and there's quite a lot of overlap in terms of their actions and how they help with sleep because L-theanine is also something that's probably

most useful for people who are struggling with stress related sleep issues. But L-theanine is just an amino acid that is widely consumed in tea, it's the most abundant amino acid in tea. And it consistently helps with different stress and anxiety issues, both physiological stress responses, so if you look at salivary cortisol responses, for example, to different types of stresses, and subjective stress, so just how stressed you feel, and a bit like ashwagandha, there are some other positive effects of L-theanine intake, in particular, on cognition; it's often paired with caffeine as a so called nootropic, because it seems to help put people in a relaxed state of focus, and it seems to be particularly helpful for the ability to maintain attention and to switch seamlessly between different tasks. Safety profile is really good, and there are also standardized versions of both of those supplements out there on the market. So for ashwagandha, the most widely studied is KSM 66, a dose of 600 milligrams. For L-theanine, it's often some theanine which is a synthetic form, and it's often used at 200 to 400 milligrams a day. So I think those are two of the better ones out there.

DANNY LENNON: Nice, yeah. Thank you for that. And, as you mentioned, nootropics and caffeine, that kind of brings me on to maybe one of the final things I want to ask in this area is that so far we've looked at some of these different nutrients and different supplements that have been proposed to have a benefit for improving sleep; on the other side then we can think about, well, what potential foods or supplements or otherwise can help rescue someone from the acute consequences of poor sleep. So if they, in general, have relatively good sleep, they're taking care of all the big blocks related to getting overall good quality sleep hygiene, but then, on certain occasions, they're going to have a poor night or two of sleep for some reason, and they want to try and rescue some of those consequences. Typically, this is either in a physical way through training, or maybe more so in a cognitive way, in terms

of just cognition that gets impaired through very poor sleep. When it comes to any particular nutrients or supplements to focus in on, you, of course, mentioned caffeine and nootropics, and maybe there are others, but what do you think has, again, some good quality evidence to suggest that on an acute basis, if someone does suffer some poor sleep, that they can maybe get back some of that loss in cognition and/or physical performance through use of certain compounds?

GREG POTTER: Yeah, it's a really interesting question, and, again, I do think it depends a little bit on the way that the sleep is compromised. Just as an example of this, there's some interesting work looking at people who have obstructive sleep apnea showing that if you give them supplemental nitrates, then you can offset some of the negative effects of poor sleep on the cardiovascular system, you can improve the blood pressure, for example. But with that said, there are some common ways by which different forms of this sleep disruption affect our bodies, and you can think about different bodily systems with respect to those effects. You can think about the brain, the immune system, the musculoskeletal system, and so on, but just to touch on a few of them, obviously, caffeine is the most widely used, but I actually think that creatine monohydrate comes into its own in this particular situation. And when people think of creatine, they obviously think of a muscle building or strength enhancing supplement for the most part, or at least they have done historically, because now there's quite a lot of interest and research on other uses of creatine; and the thing about creatine is that some of those effects on the musculoskeletal system are mediated by changes in muscle phosphocreatine stores.

Creatine supplementation also increases creatine stores in the brain though, not to the same extent that it does in the muscles, probably by about 3 to 10% in the brain. And the relevance of this to sleep is that I

mentioned sleep homeostasis earlier, and the main proxy of that sleep homeostasis or sleep pressure that accumulates with extended wakefulness is the concentration of adenosine, but between the cells in the brain; it's the concentration of the adenosine and the ATP actually. But whereas caffeine blocks the interaction of adenosine with its receptors, and thereby promotes alertness, creatine actually reduces the accumulation of the adenosine and the ATP in the brain during wakefulness. And because of that, creatine seems to probably reduce the depth of sleep, because that adenosine signaling promotes slow wave activity, in particular, and it might slightly shorten sleep duration and reduce rebound sleep after sleep deprivation. So if you deprive somebody of sleep entirely, then the night after that when they're allowed to sleep, you can see that their sleep extends quite substantially. And those changes to sleep architecture might sound bad, but the fascinating thing about creatine is that creatine supplementation seems to be good for pretty much everything that's been steady state. And it also has been shown to help preserve both cognitive and physical performance after insufficient sleep.

That's why people like Christian Cook are looking at passing accuracy in rugby players. There's some earlier work by researchers looking at different cognitive tasks and how creatine can preserve performance in those after sleep loss. And bearing in mind that creatine is very safe, and the most common side effects is a small increase in skeletal muscle, which is the best side effect ever, I think it's a really good candidate. And then another one that is more widely used now than it used to be is L-tyrosine. And L-tyrosine is just an amino acid that your body can make from phenylalanine too, and importantly, it's a precursor to the catecholamine neuromodulators, so dopamine, and thereafter, noradrenaline. And obviously, those are important to things like alertness, attention, motivation, reward, and when your brain is

working overtime, which is true if you're sleep deprived or sleep restricted, then it cranks through these catecholamines faster than normal. And if you supplement with L-tyrosine, then you can provide more substrate to maintain optimal levels of those catecholamines during these times when your brain is working very hard, and you don't have to be sleep deprived to experience some of those benefits. Anytime you're doing something that's very cognitively taxing, you're likely to experience some benefits, and anytime you're doing anything that demands increased levels of those neuromodulators, one of them would be called exposure, you might experience some benefits if your signaling of those catecholamines is suboptimal. So basically, taking a couple of grams of L-tyrosine an hour before some sort of cognitively taxing task can be helpful to maintain the performance. There are probably some nuances to consider, but we don't need to get into those now.

So I think those are two of the more interesting ones, but there is an array of different compounds that we can take to offset some of these negative effects of poor sleep, and shameless plug, I actually recently formulated a product for a nutrition company Resilient Nutrition, the product's name is Switch On, and it's, to my knowledge, the only product that's been designed to offset some of the effects of poor sleep on different body systems. And obviously, I'm not claiming that you can use it to replace sleep, there's no way that you could ever do that with some sort of supplement or drug, or maybe you could with sufficient knowledge, but we're a long way from that, but people seem to find it very helpful, and I myself take it when I haven't slept well. And the nice thing is that or rather frustrating thing is that we often sleep poorly before things that are really important to us, whether it's some sort of important presentation at work or a wedding. And so, if there was something that you take in the morning to help you return

towards your best, then that would be helpful, and that's what that product is really for.

DANNY LENNON: Yeah, fantastic, and like you mentioned, I think we could spend a lot more time focusing on each one of these small areas that we've dived into, and we could talk about them for an extensive period each. But with regret, we're going to have to leave it there, I think. Before I do wrap up though, Greg, is there anything that we have left an open loop on that you wanted to close off? Is there any particular topic that we didn't get to that you want to mention something on? Is there anything left unsaid before we start closing this thing out that you'd like to mention to people?

GREG POTTER: Yeah, maybe a couple of things, one was just on the subject of diet composition. The total amount of energy you have available matters. And I mention that because if you take somebody who's overweight or obese, and you put them in an energy deficit in which they are consuming less energy than they expend, and they therefore lose weight, their sleep tends to improve. And at the extreme, if you look at bariatric surgery patients, you often see that if they had obstructive sleep apnea, then that goes into remission after they lose substantial amounts of weight, but the interesting thing, of course, is that if you take somebody who's already lean, and you put them in an energy deficit, then their sleep often goes out the window. And at the extreme, you can look at any anorexia patients, they tend to have substantially shorter sleep than the rest of us. And if you then have them eat substantially more, and then get their weight back to a healthier level, then you also see that their sleep duration extends and their sleep improves. So there's just that interaction between energy availability and sleep that is important. And the only other thing that came to mind, Danny, is just I realized that we've gone into detail on a few subjects and haven't really touched on some simple things that people can do to start sleeping better if they are

struggling with their sleep. So I don't know if you want to touch on that, I'm happy to skip it if you like.

DANNY LENNON: Yeah-no, let's definitely get into that, and I want to echo what you said in relation to some of the impacts of extended calorie restriction, particularly, depending on if someone is already lean, so we see this quite a lot, of course, in athletes, I think anyone who's listening who is maybe at the extreme, someone who's competed in bodybuilding, and during those periods of times is where you see extensive calorie restriction in very lean situations, the impact that it has on sleep. But there's also been some nice work from Ian Duncan and his colleagues on sleep during the weight cutting process for athletes making weight, and so, again, you see some disturbances there, which echoes what you said of usually these negative impacts on sleep often happen in time, the exact time we don't want them. So the night before someone has a fight, for example. But yeah, I think that's a great way to round this out. So with all these kind of interesting details that we've discussed so far, if we are to pare it back to some pragmatic things that people can do that you think actually have some real value that they can start implementing, what are some of those things that you would like to leave people with?

GREG POTTER: So, one of them is count a few times, and that is just matching your time in bed to your actual sleep capacity. And one way that a lot of people can think about this is just how much sleep they would get, and when they would want to go to sleep and wake up respectively, if they're on holiday, or if they're on a desert island, and didn't have a care in the world. And I realized that often we have to wake up to alarm clocks for work and so on, but if you're consistently not getting enough sleep, then there are simple things that you can do to get more sleep, and this is particularly relevant now as we enter Daylight Savings Time too, which is a travesty, but that's a conversation for another day. And

with that in mind, if you can set your alarm clock as late as possible, ideally, spend as much time outdoors in daylight within two hours of waking up as possible, the reason being that that will tend to speed up your body's clock and thereby help you fall asleep early the following night; then you're likely to experience some benefits.

And the other side of the day matters too. If we think about the COVID pandemic, then a lot of us are using our smartphones more than ever, and this is probably also exaggerated by what's going on in Ukraine, and your patterns of screen time are really important. If you use your phone or other devices too much too close to sleep, and you kind of tend to push your body's clock back because of the light exposure, but those devices affect your sleep in other ways too, of course. So maybe the content is very stimulating, maybe you're scrolling through social media and you lose track of time passing. Based on that, I think if you can turn off any devices that have screens at least 30 minutes before you go to bed, then you're going to experience some benefits, and there's been some work looking at young people with problematic smartphone use showing that when they do this, they fall asleep faster, they sleep longer, the sleep quality gets better, and as a result of those changes, they feel better, and their working memory improves the next day too.

Another key factor to consider when working from home, I sort of touched on earlier, but it's the idea of stimulus control of behavior, which is probably talked in previous podcasts, Danny; but the idea is quite simple is that our brains are very good at creating associations between things, and that is generally very adaptive, but sometimes it's maladaptive. As an example of this, if you're driving and you're approaching a red light, then you've learned to realize that you need to brake as you approach the red light, so you brake reflexively. The problem with sleep is that if you spend lots of time in bed awake,

because you have insomnia, then you learn to associate your bed with being awake, and you need to retrain yourself to associate your bed with somewhere that you sleep, and the way that you do that is quite simple, you save your bed for sex and sleep only, so no fights with your bed partner or anything like that, no smartphone use, you don't nap during the day, because even a short nap will reduce some of that sleep pressure that's accumulated with prior weight from this, you only go to bed when you're actually sleepy. So yeah, you might plan to go to bed at 10 tonight, but if you're wide awake at 10:00 p.m., you shouldn't go to bed, and then if you've been lying in bed for 15 minutes or so, intending to sleep, and you haven't yet fallen asleep, then you should get out of bed, go to a different room and do something relaxing and ideally kind of boring in dim lighting. So that might be reading a book, it might be watching a rerun of something on TV, and then again, only return bed when you're actually sleepy.

And then, with respect to stress, some of our stresses is driven by what's going on in the world, a lot of it comes from work related issues, nothing, just tying up loose ends at the end of the working day by spending 15 minutes or so, noting anything that you didn't get to today, making a to-do list for the next day is going to help offload some of those concerns from your mind. And then if you can, you shouldn't be doing any work outside of certain hours. The issue that a lot of people face I think is that they respond to emails at 9:00 p.m., and they end up getting more emails at that time, because of that, and they don't have a clear division between their work life and the rest of their life, and as a result that impinges on their sleep and how they feel and how they function. And then the other one is obstructive sleep apnea is really, really common now. There was an analysis a few years ago by Atul Malhotra, who's possibly the world's leading expert on the subject that suggested that obstructive sleep apnea might now affect about a billion middle

aged adults worldwide. And the reason, of course, is that people are getting heavier and heavier over time. If you look at the risk factors for obstructive sleep apnea, then a key one is just how heavy you are, because that's going to influence the likelihood of your upper airway collapsing during sleep; and obstructive sleep apnea is also particularly relevant at the moment because people who have it are much more likely to experience severe COVID-19. Obviously, COVID-19 is in part a respiratory disorder, so anything that compromises your breathing during sleep and leads to associated inflammatory consequences and so on is going to be problematic. So based on that, just seeking some help if, say, your bed partner has witnessed you stop breathing during the night, or if you snore heavily, could be transformative for you. And there's a website which is stopbang.ca, where you can find a questionnaire that's widely used to approximate somebody's likelihood of having obstructive sleep apnea. And if you complete the questionnaire that's there, and it flags you as potentially having it, then go and see your doctor, because if it turns out you have it, and you then use something like CPAP or some sort of alternative therapy, then you will feel so much better as a result of that. And as we discussed today, you might also find that improves your eating habits, your body composition and so on too.

DANNY LENNON: Fantastic. An excellent way to round this thing out, Greg, and I want to say, thank you for taking all this time to go through these issues that I find completely fascinating and interesting. Before I do maybe get to the final question that I'm sure you faced before, if people want to find you on the internet or on social media, any of that type of thing, where is the best place for them to get hold of you and your work?

GREG POTTER: My social media handle is @gregpotterphd. My website is gregpotterphd.com, it desperately needs updating. And I have also contributed

quite a lot to the blog at resilientnutrition.com, so if you find subjects like creatine and sleep or caffeine, coffee, or time restricted eating interesting, then you'll find lots of content there; and I also wrote a freely available eBook named the Principles of Resilient Nutrition that you can download on that site too. So if you do so, then I hope that helps.

DANNY LENNON: Awesome. And that will of course be linked in the show notes for everyone listening. With that, Greg, I'll leave you with the final question that I always in the podcast on, and it is, of course: if you could advise people to do one thing each day that would have a positive impact on any area of their life, what might that one thing be?

GREG POTTER: I feel like a total letdown here, because I think I'm giving the same response that I did last time, but I'd say, check out the website 80,000 Hours, I think it's 80000hours.org, and the reason is that most of us spend a lot of time at work over the course of our lives. But we don't spend that much time thinking about what we do at work, and so, if you could spend a bit of time identifying whether you feel that your career is on the right track, and you feel that you're contributing to the greater good while meeting the different things that you want in your life in terms of your lifestyle and so on, then, you might be able to dramatically affect the total amount of good that you do over the course of your career, and what 80,000 Hours does is provide people with a way of systematically thinking through those steps, and obviously, this is more relevant to people who are early in their careers. But, on average, most of us change jobs many times now over the course of our careers, the role is changing quickly, and we need to develop certain skills that are going to future proof what we do. And so, I think just sometimes pausing and thinking through what our skills are, what we most value, and how we can best contribute is worth doing, and they put out a lot of free content, it's really high quality, and they're part of the

larger Effective Altruism community, which is also worth checking out too. So if that nudges just a couple of people to go and have a look, then I'll feel like that that's been worth me mentioning.

DANNY LENNON: Fantastic. That again, for everyone intrigued, will be linked in the show notes as well, if you want to click through on that easily. And so, with that, Greg, let me say thank you so much again for taking the time to do this. I've really, really enjoyed this, and I'm sure people will get a lot out of this, and will certainly lead them down some various different avenues to go and explore more on a number of the topics we brought today. So yeah, thanks for coming and doing this.

GREG POTTER: Anytime, thanks Danny.