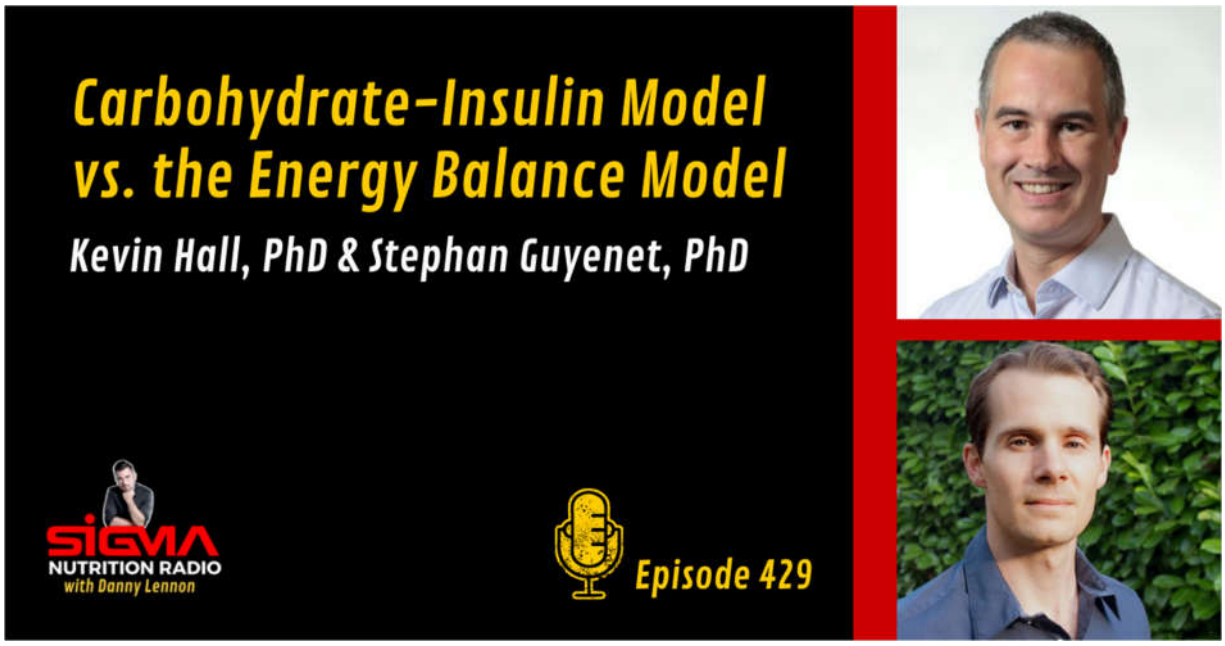

Danny Lennon (00:00:00):

So here we are. You're very welcome to this special discussion that we're having on the podcast today. I am delighted to be joined by two guests, and we've got a lot to get through. I'm here with Dr. Kevin Hall and Dr. Stephan Guyenet. Welcome to you both.

Kevin Hall (00:00:16):

Thanks for having me.

Stephan Guyenet (00:00:17):

Good to be here.

Danny Lennon (00:00:19):

I'm sure we won't belabor getting into much of what we've got to discuss by going through introductions and so on. I think most people at this point will be fairly familiar with that, but I thought to kind of set the stage, we might need to work through a bit about why are we discussing models of obesity in the first place? What a model of obesity should entail, and some of the, I suppose, overview points that maybe someone who hasn't been deeply embedded within this debate that we're going to talk about today should be aware of.

Danny Lennon (00:00:53):

Clearly, the pathogenesis of obesity is complex, and so we need to have some degree of a model to be able to explain that we, which is what we're going to be getting to today. One of these models is, as we're going to refer throughout this conversation, the Energy Balance Mode, which has largely been, I'd say the consensus position of obesity scientists to this point. It's something that a recent publication that Dr. Hall has put out, that we're referring back to several times probably throughout this episode, covering this model and its representation. But there are then also some who propose that this is not

the correct model to look at obesity through, but rather that there is a model called the Carbohydrate-Insulin Model of obesity that is better able to explain obesity pathogenesis.

Danny Lennon (00:01:44):

Specifically, what we'll probably spend most of our time discussing in relation to this Carbohydrate-Insulin Model is one that has been most recently published, or a vision or an updated version of this model, put forward by Dr. David Ludwig and colleagues in a prospective published in the American Journal of Clinical Nutrition in December of 2021. With that, I thought maybe a useful place to start would be before getting into specifics of either model or any of the specific papers that I wanted to discuss, but to clarify for people what a valid model of obesity even is. So in other words, maybe I'll start with, Kevin, could you maybe outline what any model of obesity would need to have in order for us to consider it valid?

Kevin Hall (00:02:34):

Sure. I think one, maybe even a step back in terms of why do we even consider models as important in science at all? I think that most of us, because there's a lot of people who are basically like, "You should just do experiments and generate data and outcomes, and that's all you need to progress science forward." What they don't realize is that most of those experiments and most of that data was generated by some hypothesis, which was in turn generated by some model of how you think the system works, whether that model has been explicitly described or not. And the purpose of a model is to integrate your knowledge about a particular biological system or any system, a physical system, any sort of system at all, try to explain the observations that have already been made in an integrated and consistent way, and then be able to design experiments to test the validity of that model, to basically push your understanding forward.

Kevin Hall (00:03:38):

Everybody has a model. If you're thinking about a system, whether or not you explicitly acknowledge that or not is immaterial. You have a model about how you think the system works. That's why you generate the hypothesis that you are generating to design a certain experiment. And so the model that you develop is basically your best guess about how the system works. It is the best way to think about how previous studies have generated data that are consistent with each other and explain the system at hand. That's the way I think about models, and so for obesity in particular, a model of obesity has to explain a couple of things. One is why has obesity prevalence across, not just the US and Canada, but also the UK and around the world, why has it increased so rapidly over the past 30 or 40 years? And secondly, why is it that some people seemed to be more susceptible to gaining excess body fat than others? Those are two key things that a successful model of obesity would have to include.

Danny Lennon (00:04:52):

I think perhaps we'll certainly come back to the individual variability aspect that you just mentioned later on, particularly when we discuss some of the genetic components around this, but for this population level average obesity prevalence that you bring up, that's probably useful to get us started in terms of thinking about the primary driver of this. And I think this is much about where this debate centers, and depending on who you're talking to, you'll see this framed in different ways, of we have one prevailing model, and now another model put forward. Some people may see it as some sort of head to head between these two models, but how accurate that kind of view is we can debate, but

certainly we're going to be focusing on this Energy Balance Mode and the Carbohydrate-Insulin Model most predominantly in this discussion.

Danny Lennon (00:05:42):

So to start off, before we work through the complexities and the nuances of both of these, much of which there's several points. As a departure point for people listening, I'm wondering can we get a quick overview of what we're going to mean by each of these models? Now, of course, we're going to lose something due to the simplicity of this, and maybe I'll start with you, Stephan, from your perspective, how do you tend to maybe summarize or characterize the two models that we're discussing? Before we dig into any of the actual deep details behind it.

Stephan Guyenet (00:06:20):

Yeah, sure. I'll do the Carbohydrate-Insulin Model and then I'm going to let Kevin do the Energy Balance Mode, since he wrote the paper on that in this context. Carbohydrate-Insulin Model originally was very, very simple. It's the idea that eating carbohydrate increases your insulin levels, insulin causes fat to go into fat tissue, and you basically have this sucking out of circulating metabolic fuels from the bloodstream and starving of other tissues that causes this downstream increase in food intake, and maybe a decrease in energy expenditure. So essentially, you have the increased energy intake is downstream of this fattening process that's occurring via insulin. That was the original model. The new model is a lot more complicated than that, and I think I wouldn't be able to give all the details in a concise manner, but it still has insulin at the center of the model.

Stephan Guyenet (00:07:40):

Insulin is kind of hypothesized to be the primary biological node that these fattening effects are acting through, although there are other influence as well in the new model. But it still is focused primarily on high glycemic carbohydrate impacting this insulin node, and then impacting various tissues that are causing the fattening process, and then the energy imbalance is downstream of that. So it maintains this focus on the reversed causal direction, let's say. Instead of higher calorie intake causing the fattening process, the fattening process is causing the higher calorie intake. I do want to say that in this paper, there is in the figure, there is a small arrow from energy intake to adiposity. So I think they're not saying that this is not at all a factor. I think they're just saying, they're de-emphasizing its importance, let's put it that way. And the other thing that's really notable about the model in the current paper is that it really de-emphasizes the brain. I mean, the brain plays almost no role, and in fact, in the text, if you read it, they really kind of try to downplay the role of the brain. So yeah, that's an overview of the Carbohydrate-Insulin Model as presented in that paper.

Danny Lennon (00:09:16):

Perfect. Thanks for that, Stephan. It brings up a number of points that we'll circle back to. I've made a note of a number of those key issues, that I think there's lots to dig into. So with that, maybe, Kevin, I'll hand it over to you. What is the first way you'd introduce the Energy Balance Mode to those listening?

Kevin Hall (00:09:33):

I think one of the four or most differences with the Energy Balance Mode, which again is not our model, it's basically a synthesis of what obesity science has been progressing towards over many decades now, is that it seems like the brain plays a predominant role in regulating body weight. And we're increasingly understanding how both individual variability in the genetics of body weight regulation is responsible for

differences in brain gene expression in different regions of the brain, primarily regions that operate below our conscious awareness, that affect the control of food intake primarily, although there are certainly some discussion to be had about how that impacts physical activity behaviors as well.

Kevin Hall (00:10:31):

But the really exciting thing I think is that we are beginning, and primarily in mouse models at this point, but just now beginning to understand how this is not just a static system that is regulating body weight and controlling food intake to maintain one sort of fixed body weight set point or something like that. But there are interactions with the food environment in particular to that are impacting circuits in the brain that have been traditionally thought of as separable hedonic versus homeostatic circuits, but now we recognize that for a long time it was known that the hedonic circuits in hunger can impact liking and wanting of food or drugs of abuse, for example. But now we're realizing that, and this is the really exciting research, that we're realizing that areas of the brain that are typically thought of as hedonic also feedback to these homeostatic regions, to modulate basically the control of food intake. Devaluing foods that don't drive obesity, for example, when exposed to foods that do drive obesity.

Kevin Hall (00:11:47):

This is really exciting emerging science where this is like the tip of the iceberg of what's known about control of food intake that's been building over decades now by neuroscientists and obesity scientists. It's just really exciting to see this come to fruition, and so the Energy Balance Mode is saying, "Look, if we want to explain the rise in obesity prevalence, as well as between person variability in susceptibility to obesity, we have to understand these gene environment interactions." Where that seems to take place is in the brain, which we've known for decades controls food intake, regulates body weight, and now we're beginning to better understand that that's happening in response to both changes in the food environment, which are well documented, of which refined carbohydrates and high glycemic load diets play a potential role, but probably not the only role.

Kevin Hall (00:12:50):

We also know that there are signals from the body that depend on both the energy status of various organs. I mean, the body has to know when it's growing and what the energy needs of growth are in various tissues, and we don't understand those processes very well, but there is some indication that there is signaling going on in various peripheral organs to the brain to control food intake and regulate growth and development. And so the Energy Balance Mode is really a synthesis of these different ideas to try to understand, again, those two fundamental considerations. What explains why prevalence of obesity has gone up, and what explains between person variability and susceptibility to those, what we believe are environmental changes, primarily in the food environment, but also physical activity environment can play a role within that framework also.

Danny Lennon (00:13:45):

So given the complexities of some of those relationships you've just outlined, and particularly talking about the role of the brain, this interaction with the food environment, one useful thing I think to preemptively head off would be when people sometimes hear the Energy Balance Mode, that's going to get equated with colloquial usage of calories in, calories out. I think one of the points that you have strained to make is that when we're talking about the Energy Balance Mode as an explanatory model of the obesity pathogenesis, that is distinctly different from talking about just the principle of energy

balance as we would see in physics. Can you maybe just elaborate on that point? Because I think it's particularly important for people to be clear on that.

Kevin Hall (00:14:32):

I think that this was the main reason why we got this team of scientists together, because we all knew that there was confusion among lay folks about this idea that, oh, the principle of energy balance, which is basically a law of thermodynamics, essentially, which has nothing to say about obesity pathogenesis, right? The Carbohydrate- Insulin Model obeys the principle of energy balance, right? So all of these models have to do that. They all have to obey the laws of physics. What I think that you're right in pointing out was that there's widespread confusion that maybe obesity is just because people aren't counting their calories well enough, that they should just have more willpower to actually do that, count their calories and balance the calorie outputs with their calorie intake.

Kevin Hall (00:15:28):

I think everybody for decades now has realized that it's not that simple and that researchers have a very hard time measuring accurately and precisely how much somebody is eating in terms of their calorie intake. Why would we expect individuals to do this? This is not just a simple accounting problem, this is a biological problem. And so I think that part of the reason for us to get together and write this paper in response to the prospective that was put forward by Ludwig and colleagues was because this was perpetuating these misconceptions about what the Energy Balance Mode was, and they seem to confuse use these sorts of ideas, that saying that the Energy Balance Mode is really just saying that calories are the only thing that are important. It doesn't consider any biological mechanisms. It's a tautology. If you're gaining weight, you are therefore necessarily in positive energy balance. It doesn't say anything about causality.

Kevin Hall (00:16:33):

It seemed like there was a conflation of the principle of energy balance with the Energy Balance Mode of obesity, which has been being developed, like we said, for decades. And so our main goal of this paper, we had two main goals, was to really put forward what we think the current best representation of the Energy Balance Mode is. Distinguish it as clearly as we possibly can from these myths that have been perpetuated about what the Energy Balance Mode implies about why some people have obesity and others don't, and then also contrast it with the Carbohydrate-Insulin Model. That was the purpose of that paper.

Danny Lennon (00:17:15):

Perfect. I think there's two potential ways we could go here. We could look at some of those criticisms of the Energy Balance Mode that appeared in that Ludwig paper and work through some of those, or we could look at the Carbohydrate-Insulin Model that they put forward in that paper. So if you guys are okay with it, I was thinking of starting with some of the criticisms of the Energy Balance Mode that appear within that paper, and to get some discussion on some of those points. I have a couple of segments here from that. The full paper, for everyone listening, will of course be linked in the show notes, but on this idea of making sure we're understanding the Energy Balance Mode accurately, what the representation was in that paper, from that paper directly, Ludwig and colleagues state, "The Energy Balance Model considers all calories metabolically alike for practical purposes." And the reference they gave there was a 2017 review from Schwartz, Leibel and others, which was an Endocrine Society statement paper.

Danny Lennon (00:18:21):

And indeed, when you go to that paper, you see it stated, "The impact of diet on obesity risk is largely by its effect on calorie intake, rather than by changes of either energy expenditure or the internal metabolic environment." Stated differently, "A calorie is a calorie." "Thus, habitual consumption of highly palatable and energy dense diets predisposed excess weight gain, irrespective of macronutrient content." So that's what they are referring to when they say that this model sees all calories as alike for practical purposes. In the last couple of days, I know that particular statement has been responded to by the authors of that referenced 2017 statement, which we can certainly get into. But at this point, maybe I'll first start with you, Stephan. In relation to this idea about all calories being metabolically alike, and again, quoting that paper, can you maybe give your thoughts on this particular idea and what type of representation you felt that was of the model?

Stephan Guyenet (00:19:34):

This paper, the Endo Society scientific statement, I'll just say was co-authored by my former scientific mentor, Mike Schwartz, as was the comment in response to David Ludwig's paper in AJCN. So I'll just say, first of all, I don't completely agree with that statement. I think that I wouldn't confidently say that there's no effect at all of macronutrients. And in fact, Kevin Hall and I published a reanalysis of one of David Ludwig's meta-analyses suggesting that there is a small impact of macronutrients on energy expenditure. So there could be some independent effect, but I think the way that I've always conceptualized it is that there's not large differences, right? The difference between carbohydrate and fat predominant diets does not have anywhere near the same impact on energy balance and adiposity as the energy value of the diet.

Stephan Guyenet (00:20:51):

So if we're talking about which lever is larger, the energy content of the diet is a much larger lever than the macronutrient composition of the diet. And so I think if you want to say to a close approximation, macronutrients don't make a large difference, at least throughout the range of typical consumption, I think that is a statement that I would stand behind. I don't think I would agree with the idea that they're perfectly identical, and any deviation from perfectly identical constitutes falsification of the model. That's not really a concept that I would agree with. But the other point I want to make is everybody understands that different macronutrients have different physiological effects. That is not something that's at play here, and I think that's another point of confusion.

Stephan Guyenet (00:21:50):

Often, people will say, "Well, obviously they're metabolized differently, so this statement is incorrect." But what they're talking about is specifically their impacts on energy balance and adiposity, not how the macronutrients are metabolized. That is a place where, given the fact that these macronutrients are metabolized in very different ways, it is kind of remarkable that they have very similar impacts on adiposity for the same number of calories. So those are my thoughts on that.

Danny Lennon (00:22:23):

Excellent, yeah.

Kevin Hall (00:22:24):

Maybe I could...

Danny Lennon (00:22:25):

Please.

Kevin Hall (00:22:25):

... make a couple points there too. I mean, that issue about how the heck the body is able to achieve this, even in a close approximation, that was the subject of my research when I first joined the NIH. I mean, I was fascinated by that idea, right? And this is a very old idea, and it's also a very old idea that it's only approximate. Max Rubner back in the late 19th century is the one who came up with this isodynamic law, which basically said, if you swap out equal number of calories, as determined outside the body in a bomb calorimeter, with the dietary approach inside a dog, you basically get the same effects in terms of body composition. But then he quickly realized, as did others, that didn't hold true during overfeeding, and that protein caused greater energy expenditure than carbohydrate and fat, and you got different effects. And others in humans, very shortly thereafter at the beginning of the 20th century, found that carbs and fat didn't preserve nitrogen balance isocalorically in humans.

Kevin Hall (00:23:32):

So the idea that the null hypothesis, that there is absolutely no difference between macronutrients and their effects on all practical purposes for metabolism, it's just been known to be wrong for a very long time. The question is whether or not these are meaningful and large differences that confer some sort of substantial advantage to one diet over another for a particular outcome. And I think in this particular case, the come of interest is adiposity, fat accumulation or fat loss. I think that's, like what Stephan said, that was the focus of that Endocrine Society statement. But this idea that the true null hypothesis is that there's absolutely no significant difference between any macronutrient on a calorie for calorie basis in terms of metabolizable energy intake, is something that I don't even think on the basis of energy expenditure, or energy intake is even more variable, something that anybody has put forward for, any serious person anyway, has put forward for decades.

Danny Lennon (00:24:48):

Yeah, and I guess that's one of the points that I think you also made in that paper, that these differences we may see in relation to say macronutrients or food quality are accounted for within the Energy Balance Mode of obesity. Whereas, the caricature is almost that this is a model that only cares about energy and calories, as opposed to any of these other variables, per se, as long as we can control calorie intake or energy expenditure to a certain amount.

Kevin Hall (00:25:21):

Right. I mean, it's even worse than that, right? Because you probably also have on your list of characterizations of the Energy Balance Mode that it doesn't consider any biological mechanisms, which I found just like, what? I mean, again, that's that refers to the law of physics, so I don't know if it's an intentional confusion or a real confusion, but they seem to flip-flop back and forth between discussing a physics, which absolutely has nothing to say about obesity, with an actual biologically motivated conceptual model or theoretical model of what drives excess fat accumulation in modern societies.

Danny Lennon (00:26:07):

Another point, and this may be a slight deviation, but I think is worth bringing up at this point, that I wanted to get to nonetheless and is related to very much this control or this regulation at the level of

the brain, is maybe a brief discussion around body fat set point, or at least different models of regulating body weight. Because the same group that we've just mentioned, who authored their Endocrine Society 2017 statement, as I mentioned, have just in the last couple of days published a letter to the editor in response to the Ludwig paper. I'm just going to read a very brief quote from it, because it sets up something I want to ask you both about. That letter to the editor states, "In mischaracterizing the Endocrine Society's scientific statement, Ludwig et al. ignore its main thrust, which views obesity as a complex disorder of energy homeostasis that is characterized by the biological defense..."

PART 1 OF 4 ENDS [00:27:04]

Danny Lennon (00:27:03):

... energy homeostasis that is characterized by the biological defense of elevated body fat mass in our obesogenic environment. A large literature now exists not only in support this concept, but in the identification of underlying mechanisms. None of this work is acknowledged. By sidestepping this crucial and well-developed aspect of obesity pathogenesis, Ludwig at all provide a selective and one sided view of the issue."

Danny Lennon (00:27:26):

So with that, and knowing your background, Stephan, and much of the work that you've done research on, that you've written about, your work with Dr. Schwartz that you've just mentioned as well, who has been involved in this area for such a long period of time, I thought it's worth getting into this discussion around not only brain regulation, but defending of higher body weights and fat mass, given the fact that this seems to be almost completely left out of the carbohydrate insulin model put forward. First of all, can you maybe just introduce again this idea and how does this fit into this type of conversation?

Stephan Guyenet (00:28:06):

So the first evidence was published in 1840 that the brain has something to do with body fatness. It was this guy, Bernard Moore, who was a physician in Austria, I believe who described a patient who had suddenly developed extreme obesity. Her name was Eliza Mozer.

Stephan Guyenet (00:28:28):

They did an autopsy on her and they found that she had a tumor in a part of the brain called the hypothalamus. And over the ensuing 180 years, research has shown that this is the only known part of the body that actively regulates body fatness, the hypothalamus.

Stephan Guyenet (00:28:48):

The brain in general, but particularly the hypothalamus has a neuro biological system in it that regulates body fatness. And it responds to various signals from internal milieu, as well as the environment, but probably the single most important signal it receives is a hormone called leptin that circulates in proportion to body fat mass.

Stephan Guyenet (00:29:16):

And this forms a negative feedback loop where similarly to how your home thermostat works, if temperature drops, your thermostat kicks on the heat to bring temperature back up. Similarly, if leptin

levels drop because you're losing fat, your hypothalamus kicks in a coordinated, physiological and behavioral program to bring back the loss fat.

Stephan Guyenet (00:29:43):

And this is really important because, like I said, there's 180 years of research behind this demonstrating that this is the system in the body that regulates body fatness. And it obviously has very tight links to systems regulating food intake. It also impacts energy expenditure.

Stephan Guyenet (00:30:06):

It basically it has its tendrils in everything that could possibly impact adiposity. And so, relating back to your previous question of the previous topic of whether the energy balance model considers the biological mechanisms of obesity, these are the biological mechanisms of obesity, as far as we can tell. And to have that not represented at all, all of this biological information that we have about body fat regulation, about the only known system in the body that regulates body fatness, to have that not appear in the carbohydrate insulin model at all, that to me is really something.

Kevin Hall (00:30:57):

I guess, maybe I'll take a little bit of a different take because I don't think it's quite as bad as Stephan is saying. I think that if I try to put a charitable hat on in terms of interpreting what the folks promoting the carbohydrate insulin models say is, they presume all of that.

Kevin Hall (00:31:14):

But what they're trying to say is that there's a signal from the periphery that's driven by fat accumulating in the adipose tissue under the influence of insulin, which can dominate those other signals like leptin. And so I'll put the charitable hat on and say that they're going to presume that part of the model is this feedback control system, regulating body weight that includes leptin and includes a variety of GI peptides and pancreatic hormones and all sorts of things.

Kevin Hall (00:31:49):

And what they're going to say is that, no, we know that the brain plays a role, but what they're saying is that we have to explain why these high glycemic load diets in particular in other things that can the adipose tissue and insulin directly, how those things can then take over that system and reset the set point at a higher level.

Kevin Hall (00:32:10):

And so I agree with Stephan that it's not explicitly mentioned, it's not stated, but I'm going to put the most charitable hat on as I can and say that what they're saying is that those systems that we've been studying for decades can be overridden in a relatively straightforward way by partitioning excess energy into fat storage, which then tells other tissues like the liver and the muscle by hypothetical mechanisms, that they are starving of energy and then that can then thereby alter the setting on the set point, if it's a set point, if it's a dual intervention point model as my colleague John Speakman prefers to think about it.

Kevin Hall (00:32:53):

Those parameters in the brain are thereby altered by these peripheral signals driven by excess fat accumulation, driven by insulin and whatnot. So I don't think that they necessarily negate the brain, but I think that what they're downplaying is what we have as obesity scientists thought of as the most important drivers of what regulates body weight, what controls food intake and how insulin and body fatness play a role in signaling to the brain to control food intake.

Kevin Hall (00:33:27):

I don't think that it's reasonable to say that they don't think that the brain controls food intake. I just think that they think that there's a signal that dominates what the rest of us in the obesity field have been focusing on for decades.

Stephan Guyenet (00:33:42):

I mean, I think what they're saying is that this adiposity and energy intake regulatory system is not itself a major causal factor. It's basically a puppet of these hormonal influences being pulled in one direction or another, that was my take based on it. And I mean, the fact that they don't view it as important, I think is highlighted by the fact that it doesn't appear in their figure or really hardly at all in the text except to argue against it.

Kevin Hall (00:34:15):

That's fair.

Danny Lennon (00:34:16):

So one of the things that seems to be in agreement with the models, from what I can tell is that there is a large impact of the food environment, but it just seems to be, there's a disagreement of what aspect of the food environment is most deleterious to some degree.

Danny Lennon (00:34:33):

One that I think certainly was downplayed or maybe even largely questioned within the carbohydrate insulin model paper was that the discussion around ... they stated that the energy balance model puts the driving force of over consumption down to hyper palatable energy dense and processed foods.

Danny Lennon (00:34:55):

Now, each of these, we could talk about separately, but they often come together, and there was at least a questioning of to what degree even at all, much of these are playing. So as an example, in reference to these types of hyper palatable processed foods being a key driver of over consumption in the Ludwig paper, they stated, "Surprisingly little evidence relates palatability directly to chronic over consumption, i.e., relative to energy requirements in laboratory animals or humans under normal conditions."

Danny Lennon (00:35:27):

They also state, "In the absence of clear correlates to intrinsic food properties, hyper palatable foods have been defined as those that drive food intake, another topology of the energy balance model, which simultaneously attributes increased food intake to hyper palatable foods." So with that, and I'll start again with you Stephan, how do you think we should consider the role of palatability first, specifically in this and what is your typical response on hearing how it was put forth in the Ludwig paper of maybe this

isn't something that we can really define that well, we don't really seem to have much evidence that it's correlating to over consumption? What is the first initial responses you had to that?

Stephan Guyenet (00:36:18):

So first of all, I want to address this idea that hyper palatable foods are defined as those that drive food intake and that this is a tautology of the energy balance model. I don't know who is defining palatability by the impact of a food on intake. If that were true, that would certainly be a circular argument.

Stephan Guyenet (00:36:47):

Obviously, if you're defining palatability by how much of a food people eat, and then you say palatability causes increased intake, obviously that's a circular argument, but that's not how palatability is defined. The way palatability is defined and measured is you ask people on a semi quantitative scale and Kevin could talk more about this because this is something that he's done in his research, but palatability can be directly measured, which makes it not a circular argument.

Stephan Guyenet (00:37:23):

And then at that point, you can say, how does the palatability of food, for example, correlate with energy intake at a meal. And John de Castro's work has shown in free living people that palatability is actually pretty strongly correlated with food intake at a meal.

Stephan Guyenet (00:37:43):

I think there's still some debate. I think there's valid debate about the role of palatability per se, in kind of long term calorie intake and body fatness. And they actually cite some rodent studies that I think are informative in that regard and I think our legitimate counter arguments where they manipulated the food using non-nutritive substances, showed that the animals preferred one diet over the other yet they were not gaining more weight on the preferred diet.

Stephan Guyenet (00:38:16):

So I think that's a valid counter argument. However, I think the discussion doesn't address the main point of food reward in my view, which is not liking, but motivation and learning. So food reward basically has three components. There's the liking, there's the motivational drive, and then there is the learning or reinforcement.

Stephan Guyenet (00:38:43):

And the idea here is that some foods are more motivating than others. And that's not a surprise because some foods are predicted to cause more dopamine release in the brain than others. So if you think about plain lentils versus pizza, whole grain bread versus a brownie, why are we more motivated to eat pizza than plain lentils?

Stephan Guyenet (00:39:04):

Why can we feel full after a meal, not wanting any more chicken and pasta, let's say yet, we're prepared to eat hundreds of additional calories of ice cream. That's not because we're lacking circulating fuels. Why do many people lose control around foods like ice cream, eating them more frequently and in larger quantity than they really want to? A big part of the answer to that is food reward.

Stephan Guyenet (00:39:28):

And that's presumably mediated by the fact that some foods cause more dopamine release than others. And as Kevin said, we know that there's crosstalk in the brain between regions that govern food reward and those that regulate appetite and body fatness. I suspect those are going to turn out to be important in obesity, but that remains to be determined.

Stephan Guyenet (00:39:47):

What is clear though, is that food reward causes us to select refined calorie, dense, low satiety foods and eat more of them than we otherwise would. And this is a thing that I've never really understood about the food reward critics. Let's say you think refined carbs are the real cause of obesity. Why do we eat refined carbs rather than whole grains? Why do we eat sugar? Does that really have nothing to do with the fact that we like them and we're drawn to them motivationally?

Stephan Guyenet (00:40:18):

If food reward isn't the explanation, then why do we eat cookies, ice cream, pizza, fried foods, even though we know those foods are unhealthy? I don't think there's any other plausible explanation for why we eat those foods other than food reward.

Danny Lennon (00:40:34):

So a couple of points that are really important to emphasize I wanted to recap on, you made that distinction between thinking just about palatability versus this more all encompassing idea of food reward, which there are three parts, the liking, the motivational drive and the learning.

Danny Lennon (00:40:52):

And within that, you gave a couple of really useful practical examples that I think help people in that way out. On the other side, one practical example, related to foods that I've seen used as a counterpoint and I tried to make sure I wasn't categorizing anything that was in any of these papers is I actually came across a recently published lecture that was given by Dr. David Ludwig at the Harvard School of Public Health, just published on February 1st, 2022.

Danny Lennon (00:41:20):

And about 10 minutes into that, if people watch along, they see he starts raising some of these criticisms of the energy balance model and he attempts to do that with a practical example that I think can sound quite compelling. So I'd be interested in hearing your thoughts based on what you've just said.

Danny Lennon (00:41:36):

And if I have it correct, he compares three different foods. So first he compares olive oil to sugary drinks. With them he states that both of these are considered palatable. So they're very tasty. They both are extensively processed and they both are single macro nutrient extractions from plants and olive oil has 25 times energy density of the sugary beverage.

Danny Lennon (00:42:01):

But yet we know that sugary beverages are, of course are associated with much more deleterious outcomes. And olive oil generally is associated with positive health outcomes. He finally then goes on to compare them to baked potato chips, giving the example that this is a food with much less processing.

So basically just slice and bake them has lower energy density again than the olive oil, but has adverse health outcomes associated with it relative to olive oil.

Danny Lennon (00:42:27):

So I'm hearing that for people that they're of course then saying, well, does that actually undermine this palatability issue, the energy density issue and so on, because on the basis of that example, that kind of makes sense? I'm just wondering, and either of you can jump in to start, your kind of thoughts on that type of equivalence or example that's used in the palatability and processing discussion.

Kevin Hall (00:42:54):

Sure. Maybe I'll start. And I think one of the things that I think again, which is brought up in terms of palatability and food reward, which is the sole focus on the idea that these things are entirely under your conscious control and awareness, right? So, that's explicitly mentioned in the Ludwig et al. perspective that these things are under your conscious control.

Kevin Hall (00:43:24):

And yet what we know about it is that the brain regions that are involved in these multifaceted notion of food reward, which also includes, habitual behaviors, so not just learning, but also then forming habits and social norms and how those inform your opinions about things, it's not just as Stephan mentioned conscious liking, which is identified mostly with palatability. That's what people report when you say, what do you think, was that tasty or not?

Kevin Hall (00:43:57):

It's so much more multifaceted and important to think about these other aspects that motivate how much we're willing to work, or how much we're willing to go out and obtain foods, how habitual it is for us to kind of sit down at the television and eat those potato chips, which might have kind of made that connection in the past and it's very difficult to kind of break those habits, those habits are forming, you're partially aware of them, but it's only when you make the concerted effort to kind of make yourself aware of them that they are almost automatic.

Kevin Hall (00:44:33):

That's kind of one of the definitions of a habit. But to kind of take you with those points. I mean, they are potentially interesting examples of why some foods and not other foods might relate to food choice, but I don't know anyone who guzzles olive oil, right? Just saying that olive oil tastes good, well, it doesn't taste good on its own necessarily.

Stephan Guyenet (00:44:58):

I mean, it's a weird juxtaposition putting soda next to straight up olive oil.

Kevin Hall (00:45:03):

It's just not normal for people to walk around with a bottle of olive oil, and use that as your example. But I think again, the point here is that there isn't, whether intentional or not, an oversimplification that's put forward by Ludwig and colleagues about, what drives our food choices as well as how much we eat.

Kevin Hall (00:45:29):

We've done studies where we agree, palatability has very little to do with differences in energy intake. We've done a couple of ad libitum feeding studies over weeks and weeks in people where people rate the meals equally palatable. And yet they are consuming many more calories on one type of diet versus another type of diet. And those diets are not individual foods, but they're put into patterns that are representative of certain kinds of ways that people actually eat these kinds of meals, as opposed to an artificial example, like here's a single serving of olive oil versus a single serving of a soda versus a single serving of potato chips.

Kevin Hall (00:46:12):

So I agree that it is far too simple to think of palatability and how tasty a food is or how tasty a cuisine is, because I know there's a subsequent slide about how the French and the Italians should be the most obese countries in the world because they have the tastiest food. Well, I'm not going to argue, I think that their food is incredibly tasty, but I think the point is, is that when isolate down and oversimplify the things that drive people to consume excess energy solely on palatability, absolutely right, that does not explain everything.

Kevin Hall (00:46:50):

There's no doubt about it. And I don't think any serious person is actually proposing that, that's the reason why, in and of itself, why we have an obesity epidemic and why some people and not others, although there very well may be associations between palatability ratings and genes that help predict BMI and also predict liking of different kinds of foods, and opioid receptor availability in the brain is correlated with liking and correlated with BMI.

Kevin Hall (00:47:23):

So it doesn't say that these are unimportant factors, but they play a role within a very complex multifaceted system of food intake control and how the food environment kind of plays a role. And so I think that the sympathetic way to think about this is that we don't have that all figured out by any means. I think that's a very valid point is, this is still a huge work in progress, especially in humans.

Kevin Hall (00:47:54):

And we don't know all of the factors in the food environment and how they have downstream effects on these different circuits in the brain, especially in humans, much better understanding of that in rodent models, especially mice. And so I am sympathetic to the idea that we don't have that fully worked out.

Kevin Hall (00:48:13):

And it's a perfectly valid criticism to say that we don't have it fully worked out. We don't fully understand why some people and not others are more susceptible. We don't fully understand what aspects of the food environment are most driving excess calorie intake as according to the energy balance model, but nobody serious is putting forth the idea that, oh, it's all about liking. It's just about how tasty the cuisine is. Or it's just about how energy dense the olive oil is compared to the soda. I mean, it's a very odd example.

Stephan Guyenet (00:48:48):

And I would add a couple of things to that. One is that, Danny, when you were describing that slide, you were talking about it in terms of health. And that's a much broader thing than talking about body fatness, which is what we're talking about. And I think if you're talking about olive oil, that's an ingredient, whereas soda is a freestanding thing that you can consume, I think a better comparison would be to compare granulated sugar, a refined carbohydrate that you would use in cooking versus soybean oil, a refined fat that you would use in cooking.

Stephan Guyenet (00:49:29):

I think that is a better comparison. And if we're comparing the fating properties of those two substances, I don't think it's clear at all that the sugar is more fattening. And in fact, I would argue probably the soybean oil is more fating, it certainly is an animal models.

Danny Lennon (00:49:44):

So with that perfectly actually tees us up to maybe talk specifically about the carbohydrate insulin model seen as something you just said there is clearly against some of the predictions we would make from such a model. So maybe to introduce this for people again, I'll read out just one line that's directly from that paper, and then we can start working through the kind of chain of events that is proposed by this model.

Danny Lennon (00:50:12):

So it states, "The carbohydrate insulin model proposes a reversal of causal direction. Over the long term, a positive energy balance does not cause increasing adiposity, rather a shift in substrate partitioning favoring fat storage drives a positive energy balance. Among modifiable factors, dietary glycemic load has central importance." So there's a number of things I want to open the tab on here that are important. One that we've already mentioned already is this kind of reversal of causal direction.

Danny Lennon (00:50:43):

And then within that there's two components that are also worth a discussion themselves. One relates to this substrate partitioning and then also around glycemic load. So for people listening, glycemic load is this product of glycemic index by the total carbohydrate amount. So simplistically, we are thinking about foods that will tend to cause greater post pineal glycemia or greater rise in blood sugar after meals as a maybe overly simplistic way to think about it for now. So one of the things that you outlined at the start Stefan, was that this updated carbohydrate insulin model moves us further away from the idea that it's necessarily all tied adipose tissue or fat cells only, and moves a bit further away from it solely being carbohydrate and its impact on insulin and carbohydrate being this ultimate cause of obesity, which maybe was a view some expressed in the past.

Danny Lennon (00:51:41):

So this shift towards multiple pathways with it seeming having a central role for the pathway driven by glycemic load seems to be a really important update with a number of implications from that, for what it means for this model. So maybe we can start with what that then does mean for this model and if that's a relatively accurate categorization of the model to this point or any other points you would like to add to make sure we're working with a good understanding for people. Either of you can start with that if you wish.

Stephan Guyenet (00:52:17):

Kevin, do you want to get this one? Oh, you're on mute.

Danny Lennon (00:52:23):

You're on mute. Sorry, Kevin.

Kevin Hall (00:52:25):

Sorry about that. No, I think that it's really fascinating to have seen the evolution of the carbohydrate insulin model. And one of the things that we point out in our paper, which is that there is a continued insistence that it necessarily reverses the causal direction.

Kevin Hall (00:52:48):

And yet one of the things that we point out is that as a result of the evolution and the addition of parallel pathways that don't flow through adipose tissue, fat accumulation. So maybe to give the readers a little bit of a background here, around 2007 was when I see Gary Taubes put together a long history of observations about different ideas that regulate body fatness and really put together what I at least, I've done a pretty exhaustive search trying to figure out who put together this idea that it's centered at the adipose tissue.

Kevin Hall (00:53:32):

That basically it's the hormonal regulation of adipose tissue that is the primary driver of obesity and everything else about energy intake and energy expenditure is downstream of that. And specifically that carbohydrates via insulin is the primary culprit. Gary, as far as I can tell is the originator of those sets of ideas together. Now some of those ideas have been around before. David Ludwig had ideas ...

PART 2 OF 4 ENDS [00:54:04]

Kevin Hall (00:54:03):

Some of those ideas have been around before David Ludwig had ideas about high glycemic load diets causing dips and glucose and being sensed by the brain as an energy deficit. Lustig had these interesting ideas about hyperinsulinemia playing a role on dopamine and lectin sensitivity in the brain, but they did not go through the adipose tissue as the primary driver. And it's really, that's the only way you get this reversal of causation, right? That the idea that what happens first and most importantly, is that the adipose is somehow signal to be accumulating fat and starving other tissues of calories. And that's the primary driver of why the brain then senses it needs to eat more calories to make up for that deficit in these other tissues, and folks like Mark Freedman have for decades been hypothesizing that ATP in the liver is one of those signals that the brain senses and maybe, he postulated back in the nineties that maybe high carb, high fat diet somehow divert energy away from the liver.

Kevin Hall (00:55:19):

And therefore that's one of the signals that could drive obesity. But it was really Gary who put together this idea that it's really all through the fats, essentially sucking in calories away from other tissues that are then sensed by the brain to drive excess intake and decrease expenditure. And so that's the reversal of causal direction that they're talking about as opposed to the way the energy balance model thinks about it, which is changes in our food environment, and are integrated with signals from our body in response to both those foods, as well as energy needs of various tissues. And those changes in the food

environment have somehow altered where our body weight is being regulated by changing at a subconscious level reward properties, as well as homeostatic factors in this bidirectional circuit.

Kevin Hall (00:56:17):

So the interesting point was that after Gary had put these hypotheses together in what I call the adipo-centric carbohydrate insulin model, because all pathways go through the adipose tissue. David Ludwig came along and said, well, maybe we don't have to be so specific about carbs and refined carbs. Maybe all factors somehow affect insulin or somehow affect adipose tissue biology directly, but they still all point either via insulin or via adipose tissue as being the primary drivers and then all roads to increased intake and decreased expenditure follow through that same path.

Kevin Hall (00:57:01):

The really fascinating part about this new most comprehensive formulation of the carbohydrate insulin model is that they abandon that comprehensive paradigm, that idea that all roads flow through adipose tissue. They have these new parallel factors like, oh, the glycemic load of the diet presumably being sensed by the brain, maybe even having some rewarding properties, as Stephan mentioned, somehow influences energy intake. Maybe it's because of the dynamics of glucose and insulin in part, but it's something else as well, which is why there's this dashed new line directly from the glycemic load of the diet to energy intake, as opposed to first passing through adipose tissue. So if according to the new model, the strength of that pathway, whatever it is, and it's not really specified what it is, but if it exists and it really does bypass the usual necessary flow through adipose tissue, then there is no necessary reversal of causal direction anymore.

Kevin Hall (00:58:08):

It's really in my view, if that is the case, if that pathway is dominant, I'm not saying they're postulating that it is dominant, but if it does become dominant and we don't have any data to suggest that it's not, then the carbohydrate insulin model in its most comprehensive formulation is really just a version of the energy balance model. It's a simplified version whereby it's the glycemic load of the diet that's driving excess calorie intake, but nonetheless it's the usual direction of causation. And I find that really fascinating that that's the evolution that seems to have taken place here. So in some sense, there is some convergence between the models. Although I would argue that the energy balance model is more comprehensive and has a greater evidentiary support that not all of obesity, the increase in prevalence is due to high glycemic load diets, which is still what the new carbohydrate insulin model is focused on.

Danny Lennon (00:59:11):

Stephan, anything you'd like to add at that point?

Stephan Guyenet (00:59:19):

No, that's it.

Danny Lennon (00:59:22):

With regards to glycemic load, and again, this relatively, or at least from my reading of that paper, it seems to be given this quite central part. And trying to work through that chain of events, I think you outlined some of them already, Kevin, and again from what I can tell, I've made a couple of notes that we can maybe go through, but it seems to me on this consumption of a high glycemic load meal, you get

this increase in insulin secretion, suppression of glucagon. And this state basically promotes the uptake of glucose into cells, stimulates lipogenesis, and after a few hours that once all nutrients have been absorbed, we start to see that levels of glucose in the bloodstream seem to go from that high level that they are in the early postprandial state to a much lower level in the late postprandial state. That happens relatively quickly.

Danny Lennon (01:00:20):

And that swift drop is proposed to then be perceived as a big problem by the brain that sees this as critical tissues and organs like the liver being deprived of energy. And so the proposal is that a response is mounted to that perceived shortfall, cause increases in hunger and craving for high glycemic load foods again, creating what they term a “vicious cycle”. And additionally, there are suggestions that this may impact energy expenditure and all of that is what drives positive energy balance. So the changes in obesity prevalence at the population level that we talked about at the outset of this episode can be then explained by this increase in total carbohydrate intake, but particularly the intake of high glycemic load diets or glycemic load meals.

Danny Lennon (01:01:14):

And then maybe take that one step further when they're looking at interventions to reduce fat mass and body weight, it is suggested that “weight reduction produced by carbohydrate restriction would decrease the insulin to glucagon ratio, enhance lipolysis and [inaudible 01:01:29] and result in lower spontaneous food intake”. So it seems like, and maybe that's an oversimplified chain of events, and I again, encourage people to read the whole paper, but from what I can tell on the glycemic load side, would that be, is there anything that you would say is incorrect about that interpretation of what they're putting forward? Or is my understanding of what they're proposing relatively okay on that front, before we move on?

Kevin Hall (01:02:00):

It sounds right to me.

Danny Lennon (01:02:03):

Okay, cool.

Kevin Hall (01:02:05):

I should be clear, your interpretation of what they wrote sounds right to me. I don't necessarily say, but I agree with that.

Danny Lennon (01:02:12):

Yeah, no, I was just making sure I'm not representing anyone. So I was looking for that. So with that then, and they outline a number of what they call testable hypotheses that arise in this model, much of those center around glycemic load. So at this point, I'm wondering based, if we keep the focus on glycemic load for now, and not only their proposed mechanism by which that is going to have this effect on positive energy balance, but also some of the testable hypotheses they put forward, what were on reflection, your conclusions to that part of their paper, and specifically the thoughts around glycemic load? And I can start with either of you, I'd like to hear both of your thoughts. So, maybe Kevin, if you want to start and Stephan, come to you.

Kevin Hall (01:03:00):

Sure. Yeah. I think that the one nice thing about the carbohydrate insulin model, especially when you go through those hypothetical mechanisms, is first of all, many of them sound plausible, right? But the second thing is that they offer very readily testable hypotheses, right? Because if what you said was true, then I should just be able to take a bunch of people, give them access to only foods that have very high glycemic load, that we can measure and see, and make sure that insulin goes up substantially after those meals.

Kevin Hall (01:03:41):

And that insulin has all of those effects that we are suspecting it does, and let them eat however much they want. And if this model is correct, these high glycemic load diet at should give rise to excess calorie intake, especially if you then compare them to a diet that is designed to actually minimize glycemic load as much as is reasonable and still have palatable meals that people are still familiar with the foods and don't have some sort of neophobia, but minimize these glycemic excursions, which is the definition of glycemic index, and also minimize the amount of carbs that people are eating and minimize the amount of insulin.

Kevin Hall (01:04:27):

You could do that experiment. Right. And, we actually did that experiment, right? We brought people in to the NIH for a month, had them stay with us 24 hours a day, seven days a week. And in random order, we gave them either this very high glycemic load diet that did in fact result in large glucose excursions, large insulin excursions, or a ketogenic diet, which resulted in very minimal glucose excursions and minimal insulin excursions. And the prediction seems obvious to me, at least what the carbohydrate insulin model should result in. Right. If we have these huge excursions in large amounts of insulin that's trapping and sucking fat into fat tissue and causing this internal starvation, then gosh darn it people should be hungrier and should eat more calories.

Kevin Hall (01:05:21):

When they're on that diet, then the alternative ketogenic diet, not to mention the fact that the ketones that they're experiencing are supposed to also have an independent appetite suppressing effect. And in fact, what we saw was exactly the opposite and in not a small effect size, either we're talking about 700 calories per day, more energy intake on the ketogenic diet than this high glycemic load diet that had all of the expected changes in glucose and insulin. And it just seems to me that that is a beautiful test of that hypothesis. And it's entirely dismissed in this paper by Ludwig because it was only one month long and they compared it to the effects of, oh, plate color and utensil size also have transient effects on people's food intake choices. And yet we don't consider seriously studies that change the color of plates and utensil sizes having a meaningful impact on obesity or mechanisms of obesity.

Kevin Hall (01:06:36):

Again, I think it's a little bit of misdirection. This was a very clear test of something that should have happened in their model. And no one's suggesting that these effects on the brain, in fact, I think Dr. Ludwig has a single meal study, looking at using arterial spin labeling in the brain of people who've consumed a single meal. This was several years ago, basically showing that these effects of these higher glycemic load meals in single meals can be detected right away. And I think he misinterprets the meaning of those FMRIs results, but they clearly have immediate effect. And so if we've had lots of discussions about fat adaptation, but I don't think we have a lot of discussions about, why no one talks

about how it should take a really long period of time for people to feel the internal starvation of fat being sucked into their fat cells by this huge insulin excursion.

Kevin Hall (01:07:39):

No one says that that should take a long period of time to happen. Certainly the physiology suggests that insulin acts very rapidly at the level of the fat tissue. So why didn't those people eat more calories and gain weight on this very high glycemic load diet? Is it possibly because other factors are playing a more dominant role, like the fiber content of the diet, the fact that they had very low ultra processed foods, the fact that the energy density of the diet was much lower. What determines how many calories people eat, ad libitum, when they're not trying to change their weight, and they're not participating in a weight loss study or a weight gain study is complicated. We don't fully understand it, but what we can do is we can design diets that test very specific things like does energy density per se play all the role?

Kevin Hall (01:08:30):

No, I don't think so because the ketogenic diet had a very high energy density and people did not gain weight. They didn't gain body fat. It's a much higher energy density than people typically consume. So I don't think that alone plays a role. It's obviously multifaceted. And to suggest that one factor dominates, especially when there's clear experimental data in humans demonstrating exactly the opposite, and then to dismiss it as, oh, well, that's basically just like saying plate color or utensil size is the most important factor. It just boggles my mind.

Danny Lennon (01:09:06):

Yeah. And, this wasn't set up to directly test this particular question, but it came to mind when thinking about some of these controlled feeding studies that we have. And another one of your studies that you ran, Dr. Hall, was this comparison of ultra processed foods making up the diet versus more unprocessed food diet. And from memory, I think if we looked at the glycemic load specifically of each of those were relatively similar, but of course the results of that study show significant differences in caloric intake based on that. I'm wondering, does that fit into this particular point at all?

Kevin Hall (01:09:43):

I think it does. I think it does play into that. And I found it fascinating that the Ludwig paper didn't cite that study at all. They just ignored it and suggested that there was a conflation between palatability, the conscious liking of foods and processing and food reward. And what we showed in that study was that, again, in both of these studies, people liked the meals equally, in both the ultra processed food study and this study that varied the glycemic load by a huge amount. And yes, that did not predict which diet people ate more of. And as you mentioned, the ultra processed food study, the glycemic load was identical between the two diets. And not only that, we had objective measurements of glucose excursions, and they were also identical between the two diets. And so the idea that factors other than glycemic load can play a major role in determining ad libitum food intake seems pretty strong at this point.

Kevin Hall (01:10:51):

Now there's legitimate criticisms about whether or not the effect sizes that we're measuring persist over long periods of time or whether or not these results you can extrapolate them to the free living environment where people are living their day to day life. Absolutely true, and those are concerns that people should have. But when it comes to testing the physiology of these different predictors, and I

would argue our ultra processed food study was designed to test one of the aspects of the energy balance model, which is that there's something about ultra processed foods that drive excess consumption and the fact that we know that the prevalence of these foods has increased dramatically over the past 30 years, we were trying to falsify that part of the model, right?

Kevin Hall (01:11:40):

We were trying to say, can you design an experiment that the energy balance model predicts that some factor of ultra processed foods and the food environment and the increasing availability is driving excess energy intake. Well, let's design a study that tests that idea, and that's what we did. And we couldn't falsify that aspect. That provided more support towards the energy balance model and this impact of the food environment, albeit in a very artificially, but highly controlled sense.

Danny Lennon (01:12:10):

Stephan, if I ask you about the proposed pathway of glycemic load having this seemingly central role, what do you see as the most valid and then on the other side, disputable points that were put forward in that paper specifically?

Stephan Guyenet (01:12:31):

Well generally, it's not at all implausible that glycemic load could impact appetite and body fatness. That's a very reasonable hypothesis to have, although I don't think it's very strongly supported by current evidence. And part of the reason is that glycemic load is actually very hard to isolate in human diets. Or I should say a better way to put that is, it is rarely isolated in diet trials. So, if you're comparing a diet of beans and nuts to a diet of white bread and soda, of course you're going to see differences, but can you attribute that specifically to differences in glycemic load? Or could you attribute it to the various other differences between those two diets? I'm using that as an extreme example, but this type of issue applies to nearly all studies on glycemic load. I shouldn't say nearly all, it applies to the majority of studies on glycemic load that they are confounded by other food properties. And so, you can call something a high glycemic or low glycemic load diet, but that doesn't mean that that's the causal factor that is causing observed differences. So I think there's actually quite a ways to go to demonstrate that this is actually a really important causal factor in terms of research. But the second thing I want to say, as I said before, I don't think it's at all an unreasonable hypothesis, totally plausible. However, the thing that I think is much harder to support, which is what the paper is suggesting, is that this is the primary dietary determinant of body fatness. If you want to say, this is a factor in a more complex landscape of factors, I think that's very reasonable. If you want to say, this is the primary factor, you run into some big empirical problems with the scientific literature. And one of them is that we have lots of randomized controlled trials that compare diets that differ greatly in glycemic load. And for example, we have dozens of studies that compare low carb diets versus low fat diets. And there's either no difference or very little difference at six months and one year, if you follow people up on those diets. So one of the best studies, probably the best study in this regard is the diet fits trial, which was a very rigorous trial in which people were randomized to receive a healthy, low carbohydrate or healthy low fat diet. Neither group was instructed to consciously modify their calorie intake in any way. So they were just eating to appetite, and they were followed up over a year.

Stephan Guyenet (01:15:38):

And over the course of that year, there were very large and sustained differences in glycemic load. But the weight loss at the end was the same. So, and David Ludwig's own studies show this too, it's not this

dominant factor that steamrolls everything else. If you want to say it's part of the picture. I think that's very reasonable. I don't think that's been proven beyond reasonable doubt yet, but I think that's a reasonable hypothesis. And then animal studies are the same. We have this incredible study from John Speakman, who's one of the co-authors of Kevin Hall's new paper where they put mice on, I can't remember how many diets, like 36 different diets.

Kevin Hall (01:16:25):

Yeah, I think it's like 29 or something.

Stephan Guyenet (01:16:28):

Yeah. And they varied the amount of carbohydrate versus fat in those diets systematically to see how it impacted body fatness. And basically what you see is if you take out carbohydrate and put in fat, animals get progressively fatter and fatter and fatter, the more you do that up until about 60% fat. And then if you go beyond that, to where it's a very low carbohydrate diet, then they don't get as fat anymore. And so to suggest that the glycemic load is this dominant factor, it's not consistent with human data, it's not consistent with animal data. But could it be involved? Yeah, sure. It could be involved.

Kevin Hall (01:17:16):

Yeah, I should clarify that our paper that I just mentioned about the high glycemic load versus ketogenic diet study does not exclude glycemic load as playing a role, is just that other factors, which are, there's so many other factors varying between those diets, and I think that's what Stephan is trying to point out that it's almost impossible to specifically isolate glycemic load. Certainly in a two arm study you'd have to have so many different other multiple comparisons between different substitutions in the diet in order to try to isolate the effects of glycemic load. And that's very rarely done. And so I completely agree with what Stephan said that these... No one is saying that the high glycemic load diets are healthy, that you should try to maximize them, that they play absolutely no role in the development of obesity.

Kevin Hall (01:18:16):

It's just that they are proposed in the carbohydrate insulin model to be the dominant factor. And therefore there's a very high bar to cross to say that while we know that there are all these other changes in the food environment that may have contributed substantially to excess calorie intake and obesity, that this is the primary thing that has changed. And therefore there's a very high standard to suggest that this one thing is dominant over all others and specifically via the mechanisms that are proposed, which are also quite under suspicion in terms of their robustness to experimental interrogation. And then the other thing that's interesting is that the responses to... these are not new data sets.

Kevin Hall (01:19:10):

So Ludwig and folks did respond to the Speakman study and they have responded to the diet fit study and other randomized control trials. And their argument is well, in the animal study, yeah, that's true. But they really used a lot of saturated fat in the high fat diets, but now you're shooting yourself in the foot because you're saying that it's really the saturated fat is more fattening than the glycemic load, but wait a second, I thought you told me that that was dominant in your animal models and there's something specific about saturated fat in rodents that is so fattening, that can't be recapitulated in humans, even though there's no good evidence to suggest that saturated fat isn't actually obesogenic in

some sense. So, there's this double standard of evidence, which I thought was really frustrating to deal with in the Ludwig paper.

Kevin Hall (01:20:08):

And the other point that I just wanted to make was, if glycemic load really did play this huge causal driver, especially via the mechanisms of the carbohydrate insulin model, which again seemed perfectly reasonable and plausible hypotheses, the argument why these randomized controlled trials don't lead to substantial effect sizes is because it's hard for people to stick to these diets. Well, that alone should tell you that you're not treating the root cause of obesity in these folks, because if you are removing the root cause of obesity, which is this increased hunger by starving liver and muscle cells, telling the brain, then if you've removed that it should be a lot easier for you to stick to these diets. And less other factors in the food and environment are making it more difficult for you to stick to those diets and our...

PART 3 OF 4 ENDS [01:21:04]

Kevin Hall (01:21:03):

And are making it more difficult for you to stick to those diets and are influencing your food choices in a way that dominates the Carbohydrate-Insulin Models prediction. So it doesn't hold together. If you treat the root cause of something and that's the dominant factor, then you should see a substantial effect size. And what you see is nil, nothing. In a free living environment and in a control feeding environment where you limit access to diets that veer away from these things, the effect sizes are large and in the opposite direction. So it's frustrating to see these kinds of things summarily dismissed as unimportant for the implications, for the model.

Stephan Guyenet (01:21:49):

Yeah. And there's another point that I want to add here while we're talking about things that are proposed to be dominant versus one part of a more complex landscape is the objection that I have to the Carb-Insulin Model is that it's like throw away everything you thought you knew, this is the new model of obesity. If the idea was okay, there's this complex landscape, maybe this mechanism is playing a role. I think that's totally possible. I think that's still in play scientifically that maybe this type of a mechanism could be playing a role. I think that is in play scientifically and I don't have any objection to that, but saying this...

Stephan Guyenet (01:22:37):

When you say that this is the explanation for obesity, or this is the primary explanation for obesity, which is what they're saying, you're setting a very high bar as Kevin said for yourself in terms of the evidence requirement for that. And I don't think it meets the evidence requirement. If you say this is one part of a more complex landscape, that's very difficult to disprove and it's also much easier to conversely it's much easier to support a model like that. And I think that is something that I think is not at all unreasonable. And actually along these lines, I want to acknowledge a comment that David Ludwig recently published with, I don't remember who the guy's name is. Do you remember Kevin?

Kevin Hall (01:23:25):

Thorkild Sorensen. Yeah. Thorkild Sorensen, Copenhagen.

Stephan Guyenet (01:23:29):

In this formulation, they basically said, well, they put Energy Balance Model and Carbohydrate-Insulin Model on equal footing in this model where, Hey, maybe these are co contributors. And I think that's a step in the right direction because I think again, saying this is the cause of obesity, this is the dominant mechanism. I think that's very hard to support with the evidence we currently have. But saying, there's this more complex landscape, this might be a player I think that is a much more plausible way of framing it. So I was personally glad to see that.

Kevin Hall (01:24:14):

Yeah. I agree with that. And I think that it's definitely a step in the right directional though I will note that they call the push model. They say that explicitly excludes any other aspect of the diet, other than calories as playing a role, which is again, nobody is suggesting that. So it can't possibly be aligned with the Energy Balance Model. The one thing I will say, which I am sympathetic to in terms of a criticism of the Energy Balance Model. And Gary Taubes pointed this out on social media. Is that it is a much more difficult model to falsify. And I think you mentioned this too Stephan because it is so multifaceted in terms of the potential drivers of excess calorie intake. We tried with the ultra-processed food to eliminate certain things that we thought would potentially be dominant at a time and say, okay, well, that's probably not as important as we thought, but it doesn't exclude all the other things.

Kevin Hall (01:25:14):

And like we mentioned, the difficulty of designing diet trials that isolate one thing over the other is incredibly difficult. And so I am sympathetic to the argument that it's very difficult to falsify design a specific experiment that falsifies the Energy Balance Model. I think that is a valid criticism. It doesn't mean it's impossible. It doesn't mean that we can't falsify individual pieces as being the most important drivers. And that's the way that science is going to progress forward. But in ways that we think we have done a reasonable job at falsifying certain aspects of the Carbohydrate-Insulin Model, not with one individual experiment, but with a series of experiments poking at different predictions that the model makes. You can subvert those predictions by saying, oh, we didn't meet it on short time scales. It's only on long time scales or if you really have to get down to ketogenic diets to see the effects take place.

Kevin Hall (01:26:16):

You can always modify in an ad hoc basis that way. And it seems like that's been some of the evolution of the Carbohydrate-Insulin Model as we've poked and prodded at it from various different directions. So in some sense, they gave us a very nice plausible model to design clear what I think are clear experimental tests, which is not the case with the Energy Balance Model. Because it seems like the biology is more complicated and, unfortunately, because we're focusing on the brain as the primary organ controlling food intake in response to this very complex set of signals, both from the environment and from our internal hormones and nervous system. Signals, it's very difficult to poke at that in the same way. And so the skeptic, and I think that Gary Taubes will probably be the first to point that out is...

Kevin Hall (01:27:15):

One criticism is that this is like string theory. In physics string theory might explain the data, but it's almost impossible to design a particle accelerator powerful enough to test a prediction of string theory and therefore, is it just philosophy or is it science? Well, I don't know. I think we could have that discussion, but I think that it still serves as a useful model. And you can poke at various individual pieces like the ultra-processed food piece.

Stephan Guyenet (01:27:45):

Yeah, or the central role of the brain. I would say that I have a little bit of a perhaps a different view of this, but I don't view falsification as really the goal of experimentation. I view changing the probability of different hypotheses as the goal. And maybe that's a subtle distinction, but this idea that we should be trying to falsify things, and that's the goal of experimentation. I think experimentation can change probability in either direction. And I think that there are certain predictions that have been made that I think have been pretty strongly supported about the Energy Balance Model. And one of them is the genetics, which I'm sure will talk about. If genome-wide association study are all pointed toward adipocytes and insulin as the primary mechanism of differences in body fatness in the population, I would probably maybe I would've been a co-author on David Ludwig's paper.

Stephan Guyenet (01:28:58):

I think there really are ways that this has been tested and supported. I don't know if there's one test you can do to definitively support or refute the whole model, but I don't this is biology we're talking about. It's complicated. You have to test various facets of it individually.

Kevin Hall (01:29:26):

Yeah. I completely agree, Stephen. I'm using the falsification as the surrogate for the maximum change in posterior probability, which is how you should design experiments to change your posterior probability as much as you possibly can. That's going to have the maximum impact on moving things forward, as opposed to, we thought it was this effect and maybe it's a little bit bigger or a little bit smaller so, yeah.

Danny Lennon (01:29:51):

Yeah. And even a step beyond that, if we think of this pragmatically for people trying to make dietary decisions or people that working in healthcare, et cetera, in lieu of having 100% clear answer, which is almost entirely impossible anyway. But it is very much about, well, right now, given that we need to make decisions in this present day, what is the highest probability of being accurate? And this is where we come back to things that we've mentioned on this podcast, nauseum around what do we see across many different lines of evidence. Is there something that converges that seems to be true, which of all this different data that we have from the mechanistic road of models to human intervention trials, to the nutritional epidemiology do those seem to fit best with one of these models? Yes or no and, therefore, we can make based on probability. We can go with one of them in the moment.

Danny Lennon (01:30:48):

And I think what seems to be at least obviously over a position that's probably in line with what we've been discussing here. And what I suspect both of you would say is that the weight of evidence and therefore the probability for one of these models is not like the other. The reason I bring that up is it kind of triggers off a one of the frustrations I sometimes have that I need to control in myself when I see the picture painted online in some quarters of this almost being an equal head to head of two models that have always been battling out. And these are the only two explanations, and it's almost like a coin flip for which is right. And we just need more evidence and we need the studies to be done. Whereas I think that's an unfair categorization of what we're actually dealing with, and as I think both of you have noted throughout this discussion when we're talking about the Energy Balance Model here, this is not just simply a new hypothesis put forward, but rather just a way of conceptualizing what we know about obesity science to date.

Danny Lennon (01:31:51):

And I think there's sometimes in my mind at least my bias opinion, a false equivalence put forward as to what we're dealing with. This is somehow a 50/50 coin flip out of which one will be right and we have to do more studies to find out, whereas I think we can probably make a lot of assumptions that have a high probability of being accurate from what we already know. Is that something that resonates or is there something that you would want to add to that at all?

Kevin Hall (01:32:23):

Yeah, sure. I think that the misrepresentation of the Energy Balance Model, I think is we can discard that. I don't think any reasonable person believes that this is all about willpower and calorie counting. And if you just counted your calories more accurately that this would solve the problem and you wouldn't have hunger if you're losing weight. And so the caricature of the Energy Balance Model, which we as authors of this paper, struggled with the terminology, because again, it seemed like there was some confusion and conflation between the principle of energy balance as a law of physics versus what modern obesity science thinks of versus this debacle of the energy balance network that happened with Coca-Cola several years ago. The term energy balance has problems, but at the end of the day, we felt somewhat pigeonholed into it because John Speakman and I in a previous article in science had referred to it as the Energy Balance Model. Ludwig preferred to like a conflation of the principle of energy balance with a hyper palatable food, being the driver as being the Energy Balance Model.

Kevin Hall (01:33:42):

So we felt like we had to stick with that terminology. Although everybody recognized, it's probably not ideal and has its own baggage that we just couldn't bring ourselves to calling it something new. So the point is that there is a set of mischaracterizations and ideas out there that when you put head to head against the Carbohydrate-Insulin Model, hell I prefer the Carbohydrate-Insulin Model to those ideas. Those ideas are basically blame people that have obesity for their poor willpower and the fact that they're not counting calories and that's ridiculous. And the advice to just eat less and move more completely ineffective, completely agree with all of those things that it might be a good idea for many people to reduce the glycemic load of their diet independent of its effects on body weight as a major driver.

Kevin Hall (01:34:37):

Yeah, sure. I think I'd agree with that too. Sugar? Yeah, probably minimize sugar consumption. There's lots of things that we can agree with when it comes to practicalities. One of the things that we were trying to be very careful about is that the Energy Balance Model does not say that people can't thrive on very low carbohydrate and low glycemic low diets. Those diets can be very effective for weight loss for some people. But does it actually explain the main driver of common obesity and is it the root cause of all people's common obesity by the specific mechanisms that are specified in this model? No, I don't think so. And I don't think it is. Like you said a toss up between the two models. This has been the culmination of modern obesity science over decades and decades versus this idea of a specific means by which carbs, maybe high glycemic load and refined carbs drive insulin, which traps fat and fat tissue with downstream effects or, and now maybe an independent arrow going from glycemic load to energy intake. Yeah. I don't think it's a toss up, but again, I'm highly biased.

Stephan Guyenet (01:35:57):

Yeah. I think in this regard, the way I like to think about it, because you can make complex mechanistic arguments and find data for almost everything. So to me, what I like to do is go back to the basics and say, if this were true, what are just some of the really basic things that we would expect to observe right off the bat? And some of those are, for example, carbohydrate should be the most fating macronutrient in animal models of obesity, it's not dietary fat is. High glycemic carbohydrate should be the most powerful way to increase body fatness in humans. It's way down the list, energy balance is the most powerful way. We should see evidence that people with obesity have "internal starvation" such as reduced metabolic rate, reduce lean mass, reduced blood glucose and fatty acid levels.

Stephan Guyenet (01:36:57):

What we see is the opposite of that. Obesity appears to be a state of internal excess. We should see that high carbohydrate, low fat diets are fating, but, in fact, what we see is that there's slimming. And if there's a difference between the weight loss effectiveness of low carb and low fat diets in RCT is its pretty modest. And we should see that elevated insulin levels predict fat gain over time. So if you take 100 people with high insulin today, compare them with 100 people with low insulin, you should see that the people with high insulin are gaining a lot more fat over time then the flow insulin, and that's not observed. We should see that the genetics of obesity revolve around insulin and fat cells not observed. So there's just all these really, really basic things that right off the bat you would predict really basic straightforward things that right off the bat you would predict if this was true and those predictions are not satisfied by the evidence. So I agree that it's really not... These hypotheses are really not an equal footing in my opinion.

Danny Lennon (01:38:13):

Yeah. Those are certainly a lack of compelling evidence for a number of those predictions as you've outlined. And you've given examples brilliantly there from various different types of literature, each of which we could probably spend multiple hours talking about probably even like the genetic stuff alone. But for the sake of time, and maybe to start wrapping this up before I get both of you, maybe to give some concluding remark, is there any topic that we haven't got into that you think is crucially important to get into? Are there any open loops that we need to close off before I get you to maybe each give some concluding remarks?

Stephan Guyenet (01:38:51):

We're all good.

Kevin Hall (01:38:52):

I can't think of anything off the top of my head. No.

Danny Lennon (01:38:54):

Fantastic. Okay. So with that, maybe let's move to some closing statements and simply hear based on any of what we've discussed today, or even the broader discussion on this particular topic. What are some of the most crucial things that you would like to get out to people. What is something that is an important concept here to grasp? It doesn't have to be an overview of everything, but one particular point that sometimes maybe gets lost or is a good final concluding remark you like to leave people with. And so maybe I'll turn to you Stephan first for yours and then I'll come to you, Kevin. So any closing statement at all that you would like to give for people? We'll jump into that now.

Stephan Guyenet (01:39:38):

Yeah. I would say that we have this, what we observe in obesity, key facet of obesity is that people are defending a higher body weight. And that seems related to this circuit between leptin in the brain certainly seems heavily related to brain activity. And we don't really understand why that is. So I would say that highlighting that as a key research objective is an important objective for understanding how obesity occurs and is maintained.

Danny Lennon (01:40:19):

And Kevin I'll turn over to you for your concluding remarks.

Kevin Hall (01:40:24):

Yeah. So I think just to piggyback on what Stephan just said, this is a really exciting time for the neuro science of obesity. And I think that some of the really exciting work is going on in mouse models using really sophisticated experimental techniques. And we are learning more and more about these interactions between circuits that are regulating body weight and controlling food intake. And I think that we're going to learn a lot more in the near future about how that works. And so we have a lot more to learn, but it's a really exciting time because I think the pace of discovery is accelerating. What I think most people maybe confused is number one, this Energy Balance Model of obesity does not say that carbohydrate content and refined carbohydrates are not problematic even outside of the context of adiposity and why some people might be extraordinarily successful, minimizing glycemic load and going on low carbohydrate diets is perfectly consistent with the Energy Balance Model.

Kevin Hall (01:41:37):

You don't have to believe that the Carbohydrate-Insulin Model is the mechanism by which your diet is succeeding for you or could succeed for you to adopt such a diet and thrive. I think that it's perfectly reasonable that there's a lot of people who do extremely well in physicians, in increasing number of physicians are prescribing these kinds of diets for management of metabolic syndrome and Type 2 diabetes. And I think that research underlying that should progress forward and it's very exciting. But in no way, does the excitement surrounding the clinical utility of those kinds of diets depend on the Carbohydrate-Insulin Model, it's completely independent. You can denounce the Carbohydrate-Insulin Model as the mechanism and still have all of the benefits of those kinds of diets. But in addition, if the Carbohydrate-Insulin Model is incorrect and there is not one single factor like glycemic load driving all of obesity, it opens the door for personalized nutrition as well. That there are some people who respond extremely well to low carbohydrate diets and others who might respond extremely well to lower fat diets or alternative kinds of formulations of the diet.

Kevin Hall (01:42:56):

And there's another exciting area of research, which basically the logical extension of the Carbohydrate-Insulin Model is this one factor of glycemic load being the dominant driver, driving the root cause of common obesity. Well, then there really is only one diet that should work for you, which is a low glycemic load diet. Whereas if there are multiple pathways to obesity that involve different combinations of gene expression in the brain that alter these neural circuits and make you more susceptible to certain factors in the food environment, rather than others, then it should be possible, at least in theory, to design a diet that should work for you. That might look very different from the diet of another person who has a different combination of factors in their brain. And so I think that this is the

exciting science moving forward both on the mechanistic understanding as well as these practical implications.

Kevin Hall (01:43:49):

And I'm actually somewhat encouraged by some of the convergence as this Carbohydrate-Insulin Model has moved forward, both in terms of the AJCN paper although I don't like the way they mischaracterize the Energy Balance Model. They are adding parallel pathways that make it look more like the real end Energy Balance Model. And as Stephan pointed out this newer paper by Sorensen and Ludwig, trying to integrate these models even more, although I have lot more to say about that maybe another time. But I think that there is areas where we can agree. No, one's I don't think suggests that high sugar diets are good for you. Everybody could benefit from reducing the sugar content of their diet.

Danny Lennon (01:44:36):

Excellent. Yeah. Plenty more to discuss, as you said, and perhaps that is for another time, but I want to say thank you to both Dr. Kevin Hall and Dr. Stephan Guyenet for coming on and discussing this topic. Very much appreciate the time that you've both given up for this as well as the insight and thoughts. It's very much appreciated for me and I'm sure for listeners. For everyone listening, anything we've discussed about this episode will be linked up in the show notes. I, of course, encourage you to go and read the papers that we've mentioned if you haven't done so already, but I'm sure many of you have. And so hopefully this has enhanced your understanding and been thought provoking in that particular regard. And with that, thank you to my two guests. And thank you for everyone listening. And I'll be back another episode soon. Here we go.