Society for Endocrinology

Hormones: The Inside Story

Episode 1 – Are my hormones making me fat?

Hello and welcome to Hormones: The Inside Story, the brand new podcast brought to you from the Society for Endocrinology - we are gonna be getting to grips with the little things inside us that are pulling the strings.

I'm Georgia Mills, and I've been speaking to some of the best and brightest endocrinologists - long fancy word for hormone experts - to bring you six episodes about everything from doping to jet lag and how our hormones are secretly running the show, and maybe how knowing what's going on backstage can help US live better.

Now before we get to the juicy stuff, we should probably start with a quick hormones 101.

A hormone is our body's internal postage system, a way of sending messages or instructions around the body. They're small chemicals, made by our endocrine glands, which sail around the body through our blood stream before hitting a receptor - where they start making their changes. There are loads of hormones - about fifty - and they all affect us in different ways and can interact with each other, helping to keep us alive and thriving (and sometimes making us act a little bit strangely). There isn't really any aspect of life and health which isn't impacted by our hormones - which is why understanding THEM can help us to understand ourselves.

So let's jump into our very first topic. Are my hormones making me fat?

It's no secret that our nation's waistlines are expanding. Up to two thirds of adults in the UK are currently classed as overweight or obese, and with those extra pounds comes an increased risk of diseases ranging from heart disease and diabetes to cancer, as well as increasing the chances of ending up in hospital with COVID-19.

We all come in different shapes and sizes, that's a given, but why are some of us bigger than others, and why can it be so difficult to reach and stick to the weight you want? In this episode we'll look at the link between your hormones and your eating habits - with the help of some food-obsessed Labradors - plus can hormones explain why some types of diets just don't work, and will we ever put weight-loss in a pill?

Now body weight is extremely complicated - there are social and environmental factors like poverty, discrimination and stigma which all have their part to play - but hormones make a big difference too.

Giles - Do your hormones play a role? I think undoubtedly.

This is Giles Yeo, he's a geneticist at Cambridge University who came into his area of research through slightly unconventional beginnings.

*Giles - My PhD, o*ddly enough was on the genetics of the Japanese pufferfish - "*fugu rubripes*". Now don't start!

Giles has stepped away from pufferfish work, for better or for worse, and now is a leading expert on genetics and bodyweight.

Giles - So what does this have to do with hormones? Well, what your brain needs to do in order to influence your feeding behaviour is to know what is happening in your body.

As with all our systems there are a whole bunch of hormones doing different things, but we do have a star performer.

Giles - One of those critical hormones is going to be called leptin. So your brain needs to know, broadly speaking, two pieces of information in order to influence food intake. The first is how much fat you have. OK. And that's important because how much fat you have is how long you would last in the wild without any food. OK, not a problem today, but a problem in a past 40 foot, for instance.

So to keep our brains informed about our weight, our fat stores release leptin.

So, the more fat you have, the more leptin you have and informs your brain how much fat you have.

But as well as knowing how big you are, there's something else we need to know, to plan our next meal.

Giles - The second piece of information that your brain needs to know is what you have just eaten and what you are currently eating. So these are your short term signals.

These signals can't be released from fat stores- they need an immediate alert from the food's point of entry. So...

Giles - These signals are going to come from your gastrointestinal tract, your food to poop chute. And they're going to come from your gut, and these are gonna be hormonal signals from your gut. So your brain then senses these long term and short term signals and influences your food intake.

So your hormones tell your brains two things. How much fat you have stored and how much you have just eaten. But given that we have the same hormones in play, the same systems - why is it that some people are bigger than others? Why do some people just seem to find it so easy to keep their weight where they want it, and others have an uphill struggle.

Well, to find out we're going to step away from humans for a bit. We're a messy species to study when it comes to studying us - we change our behaviour when we're being watched, we're terrible at remembering what we ate and drank, and are unsurprisingly reluctant to be fed scientifically standardised meals for months on end. But luckily there's another species that struggles with their weight, who are slightly less concerned with other people's opinions.

Eleanor - What I tell people at parties is that I study the genetics of obesity via the medium of Labradors.

This is Eleanor Raffan. She's a vet and a geneticist at Cambridge University, who's really bringing the lab into the laboratory.

Eleanor - You can't ever predict what will happen when you have a canine research subject.

Labradors are of interest because - as lab owners will know - they are famously difficult pets to keep trim, compared to other types of dog, sometimes going enormous lengths to get a snack.

Eleanor - And I've got stories of a Labrador whose owner says that from early in the summer, the dog will sit under the apple tree in the garden for hours on end because sometimes an unripe apple will fall and any *food* is better than no food.

It's not just labs. Pugs and retrievers are also very predisposed to be overweight.

Eleanor - That breed related risk is too clear to be just down to fad and fashion and what people think those dogs should look like. It's more to do with something inherent to their biology.

So Eleanor and her team made it their mission to find out what was going on, with the help of some willing pet owners.

Eleanor - We've got hundreds of Labrador owners who have taken the time and the effort to recruit their dogs to our study. So they've told us about their dogs. They've taken their dogs to their vets to have them weighed. And then they've sent us slobber samples from which we can extract DNA.

One of Eleanor's experiments involves finding out how hungry a dog gets between meals with a test I like to call 'The Impossible Sausage'.

Eleanor - We put a sausage in a box and let the dog see the sausage and put it in this kind of sealed plastic container with holes in the lid so they can smell it, but they can't get to it.

A canine nightmare! And all Eleanor has to do is watch how long the dog tries to reach this impossible sausage

Eleanor - And the lengths to which some of these really highly food-motivated dogs will go to try and get to that sausage is hilarious. You know, they'll paw at it and they'll push it around, pick it up and yap at it! And, yeah, make a huge amount of effort.

Some dogs give up fairly quickly, others go into full-on, frenzied 'mission from dog' my-life-depends-on-this-sausage mode.

Eleanor - We've had to get pretty handy with the gaffer tape to try and kind of tape up those boxes. There's always a bit of hooliganism when you've got dogs and food around the place.

And so Eleanor took this behaviour, she also looked at the dog's body weight and the levels of fat. Then, she started looking for clues in the dogs DNA - their genetic material - and she found something.

Eleanor - Quite a lot of Labradors and even more flat coated retrievers carry a mutation in a gene called POMC.

POMC is a gene that carries the instructions to make another hormone called - stay with me - Proopiomelanocortin, which - you'll be pleased to hear - I'm not going to be saying again. A genetic change, or mutation, in this gene is linked with some changes in the dog's behaviour around food.

Eleanor - So what we found in both Labradors and flat-coated retrievers was that dogs that carried this mutation tended to be what we call highly food motivated.

So this genetic mutation seems to make dogs hungrier which makes them more likely to gain weight. But how does a gene make a hungrier dog? This is where the hormones come in. Remember leptin - the hormone produced by fat.

Eleanor - So when you've got more fat laid down for a period of fasting to come, you produce more leptin. And that leptin, as is the nature of hormones, goes off in the bloodstream and acts elsewhere in the body, primarily in the case of the system we're talking about in the brain, in an area of the brain called the hypothalamus, where it acts on its receptor.

Leptin goes to the brain, where it triggers a chain reaction involving more hormones which eventually hit receptors in the brain telling you to eat less food. So more fat in your body - releases more leptin - which tells your brain you don't need to eat as much, ergo you feel less hungry.

Eleanor - And that's obviously quite a sensible kind of mechanism to act as a brake on hunger when the body's energy reserves are full.

But for our dogs with a broken POMC gene... it doesn't work like it should.

Eleanor - When the POMC mutation is there in the dogs, it means that that mechanism doesn't work properly.

So the system that tells you when the tank is full, doesn't kick in and this means it doesn't matter how much fat you've got - your brain thinks you need food!

Eleanor - The upshot of all of that is that the mechanism that should say, right, we've got good energy reserves now, it's okay not to eat all the time is broken. And so these dogs, even when they've got big energy reserves, when they're overweight, when they're fat, don't have that brake on hunger and continue to pursue food.

This means it's not a case of being greedy, it's a case of never ever reaching that contented 'full' feeling after a big meal.

Eleanor - And so these are dogs who you kind of scavenge more vigorously in the home environment and who kind of beg their owners for food more often and who are more prone to stealing food and things like that.

Georgia - Mastered the puppy dog eyes.

Eleanor- Exactly. Exactly. And anyone who's got a dog will note it's very hard to resist that kind of big brown eye treatment for too long if you've got a snack and you know, the dog will be pathetically grateful if they get some extra fees.

So some dogs like labs and retrievers, can have a really strong genetic component of weight, driven by their hormones which affects how hungry they are. But is this true for humans? Well, while we haven't done impossible sausage experiments on people, we do know that genetics are really important. Back to Giles!

Giles - The heritability of body weight is around 50 to 70 percent. So we now know probably about 300 or so more genes that are involved. And those genes happen to influence your feeding behaviour. *So the genetics of body weight is about how the brain controls feeding behaviour.*

Like dogs, it seems to be that our genetics are affecting how much we want to eat and how full we are after we have eaten. And like dogs, it seems that it's not the hormonal changes that are important, but the sensing of the signals, from our receptors - they are key.

Giles - There is no evidence that shows that the actual genetics of the hormonal levels influences - at the moment at any rate - interestingly, influences your body weight. There are genes that encode for those signals, of course. But the genetics of

body weight appears to indicate that it's in the sensing rather than in these signals that influences your body weight.

And even tiny differences in our receptor sensitivity can have a big impact on our bodyweight.

Giles- *S*o imagine you've had a big meal. I don't know; a thousand calories? Fifteen hundred calories, whatever, say a thousand calories. But, imagine if your brain is slightly insensitive to the signals and only senses 800 calories. Well, then your brain is going to think, well, I'm going to need to eat more to make my 1000 calories, driving you to eat more, even though you've already had the 1000 calories. And in that way, you and I could be sat eating exactly the same meal. We ordered exactly the same thing off the menu. But yet, I might feel hungrier than you even when we finished everything, because my brain is slightly less sensitive to the signals that actually emerge after the meal.

And as no two brains are alike, we all have receptors of different sensitivities, so this is a big part of why our weights are so different.

Giles - *B*ody weight in many, many ways is not a choice. You might say, well, that's silly. I've chosen to eat this pizza today. And you're right. Each meal could be considered a binary choice and probably is. But we do not gain weight or lose weight overnight, sadly! Our body weight, such as it is now, is the function of thousands of different food decisions that have been made over the past few years. Correct. Now, imagine that because of your genes, you are five percent less likely to say no. Okay. In any given binary situation. So over thousands of different decisions, five percent less likely to say no is thousands, tens of thousands of different calories, which is why different people are different, different sizes. Someone who is skinny simply finds it easier to say no.

So big question: are my hormones making me fat, can we blame them?

Giles- I don't like blame because, two different reasons, because when you say blame, then you can almost use it as an excuse. I guess you could, technically speaking, but it's not deterministic I guess that's my point. People think that genetics, particularly in these complex characteristics such as body weight, people think that your genes gives you a point in space and time, meaning that your genes indicate you're going to be 78.2 kilograms when this is not the case. What happens is your genes give you a bracket of possibilities. OK. So that was because of someone's genes. You're never, ever going to be a stick insect. You’re never, ever gonna be really, really skinny. But that doesn't mean that within the range of possibilities that you have, you can't be heavier and lighter than you might actually be. So your hormones do influence your bracket of possibilities, but you can do something about it. I guess the analogy that I use is the hand of poker analogy where you can have good hands and you can have bad hands but you can actually win with a bad hand of poker, even though it's more difficult.

So... our genetics via our hormones are a huge part of what makes us the size we are. But as Giles says, it's the hand you're dealt - that doesn't mean we can't win - it's just going to be harder.

But does knowing about how our hormones work, just like knowing the rules of poker can help, mean we can work with our bodies rather than against them?

Jose - I'm Jose Areta, I'm a lecturer in sports, nutrition and metabolism at Liverpool John Moores University, and I do research at the Research Institute for Sport and Exercise Sciences.

Jose's work looks at what happens when the amount of food we eat isn't enough to sustain our activities, aka - the crash diet.

Jose - People don't eat enough calories to maintain their feet. Normal physiological function and this can be done, you know, by either complete fasting or, you know, reducing energy intake drastically by eating like very little.

This type of diet certainly makes sense on paper. Reduce your food intake so much that you need to use fat stores to maintain your energy levels, and bye bye fat stores. There's just one problem.

*Jose - The body. Doesn't really like to lose weight. Basically, there's a quite deep hormonal change that makes our bodies and our behaviour sort of hold on to the weight that we have. V*ery low calorie diets basically can reduce body weight, you know, quite quick early on, the first, let's say, a few weeks or months. But, you know, long term, they don't seem to be as effective as other, you know, more normal ways of losing weight,

And this is thanks to our hormones, who helpfully alert the brain when we reduce the amount we eat.

Jose - One hormone released by the gut that is called ghrelin increases our hunger when we are not eating. This is something that goes from basically our guts to our brains and increasing the level of hunger.

And of course there's our old friend leptin - the hormone released by fat. Our brains get used to the levels of leptin, even desensitised, and so when that level drops- our brains are NOT happy.

Jose - When there's not enough dietary energy available, even without changes in these like fat mass cells, there is a decrease in leptin. And this also drives an increase in hunger and a whole lot of other cascade of responses that regulate energy balance.

So you're more hungry - which will surprise precisely no one who's ever been on a diet, but that's not all.

Jose - So when you're not eating enough calories, you know, there's a decrease in this hormone that, you know, drives a decrease in, for example, resting metabolic

rate. So at rest your body uses less energy and is partly driven by the effect of this hormone.

In other words, you start burning fewer calories. A dramatic decrease in food like this effectively sounds the alarm that there's not enough food, and your body does everything it can to get you back up to where you were before.

Jose - It's kind of like your phone going in power saving mode. What this system does is save energy for the essential processes for survival, i.e. the phone staying on and you being able to make a phone call and then sort of taking energy from the systems that are not immediately necessary for survival.

Which makes sense - back in the day before the supermarket if we were running low on food, we had to preserve what energy we have to maximise our chance of making it to the next meal.

Jose - So we don't have a physiology and adapted for the modern style of life, for there's so much food available and we exercise so little. So basically we are tooled with a set of responses that allows us to survive in a very different environment from the environment that we live in. And this is likely one of the reasons why we see the degree of overweight for example we see today in the UK, 60% of the population is overweight or obese.

And these quite dramatic hormonal changes can be dangerous.

Jose - This cascade of events then can also be related to reducing bone metabolism, can lead to weaker bones or reduce skeletal muscle mass, you know, skeletal muscle protein synthesis decreases.

So your bones get weaker, and you basically become hard-wired to try and keep as much of your fat as possible. So if you ARE trying to lose weight, crash dieting is something to stay away from, Jose recommends slower, long-term food plans which involve getting enough protein and exercising regularly which are not going to send your body into this panic, and have your hormones working against you.

Jose - And I think this is an important message for people who are trying to lose weight to try to do it in a healthier way.

So hormones make it harder to lose weight. And this might be why the weight loss industry is worth billions with new fads and weight loss promises around every corner. Sometimes things work, sometimes they don't, sometimes they're downright dangerous.

But will we ever see a science backed weight loss intervention which can trick our brains into feeling full? A diet pill if you will.

A quick look on google and you'll know that slim pills are not the stuff of the future - they're for sale right now. But it's buyer beware - some of this stuff simply won't work - and some you can find online will contain chemicals that have been banned for safety reasons. It's not easy to make a pill to make you feel full, but our gut hormones can get around this.

Giles - Most of the gut hormones or in fact, all of your gut hormone bar one, make you feel fuller. Ghrelin is the only one that actually makes you feel hungrier. But everything else that comes up from the gut all make you feel fuller.

So you just add in a hormone that makes you feel fuller, it slips into the brain, targets exactly the right neurons and WHAM! No battling the hunger pangs all day.

Giles - And so that is probably being the best chance of a therapeutic treatment for obesity.

But this isn't something that's widely available yet, for a couple of reasons.

Giles - First, there you have to inject because you can't just eat it. We haven't figured out a way of getting it past the stomach effectively yet. The cauldron of the stomach.

The acidic churning cauldron, which takes apart most molecules - not an ideal place for a delicate little structure. So most of them are injections - not as palatable.

Giles - But secondly, there is only a small therapeutic window. The other role that gut hormones play is to make you puke. Why is that? Because if you have food poisoning for, say, for example, you eat anything and suddenly you realise: toxin! What you've got to do is before it gets absorbed into the body and kills you. OK, not good. You eject, eject, eject. *So your gut hormones really go up and you go "urgh", so that is another biological role of gut hormones.*

An injection which can make you vomit - doesn't sound fun! But there are some treatments out there that are solving these issues - they're gut hormone mimetics - they look - to our body - like gut hormones, and pharmacologists have managed to get doses that don't lead to spewing, and one drug has developed an oral form only last year, which can slip past the stomach effectively - and was tested as a treatment for obesity this year.

But there's still a problem … no hormone is an island.

Giles - The hormonal mildew in our blood is not just one hormone. That's just not the way we work. It is the mix of hormones. But there's so many that I think to get the full effectiveness, we're gonna need to understand the full mix, not just of one, but 10, 20, 30 hormones mixed together*. That's very complex!*

So, while we are getting pretty good at learning what hormones do - getting the precise recipe of the hormonal stew that would be most effective is a

whole different story. But there's another type of treatment for obesity that might help us crack it. Bariatric surgery.

Giles- Bariatric surgery is the replumbing of your guts. The most popular one is something called Roux-en-Y in which you reduce your stomach volume to just about a tablespoon. And you remove about a meter of gut, to a meter and a half of small gut.

Georgia - That seems very, very small. *Most of my meals are many tablespoons!*

Giles- So here's the interesting thing. Right. They were assuming that, well, if we do this, then you can eat, you absorb less, you lose weight.

It turns out that that's not the way it works.

First, reducing your stomach to a tablespoon sounds very drastic, but actually your numerous studies have now shown that actually your stomach copes. And you can actually eat quite a lot, even with a tablespoon size stomach and your stomach begins to change in size again.

So your stomach can stretch and shift things around - team up with that second stomach for dessert, and still technically consume just as much. But this surgery still *works*! So why?

Giles -it turns out that bariatric surgery such as Roux-en-Y does not work through absorption. It does probably a little bit of it, but the vast majority is the change in hormones. You've got hormones because what effectively happens is food that is slightly less diet because your food goes down your guts and gets digested as it goes down. So if you remove a portion of gut food that is less digest*ed.*

And because food that is less digested ends up further down the gut, it changes gut hormone levels, which, as I already said, makes you feel fuller. You eat less. You lose weight.

Georgia - Right. So it works, but not for the reasons people thought it would.

Giles - Yeah. Yeah. As with most things in life. But it does work, yeah.

So if we mimic this process - find out what the hormonal levels changes are and copy them with a drug - this could be the real key to an effective 'diet pill'. Because while bariatric surgery is effective, it's not ideal.

Giles - *Bariatric surgery is a major operation. and it is permanent. And so many people don't want to do that. And so taking something like a therapeutic mimic of bariatric surgery, I think is far more palatable to many people.*

There have been experiments - in which people were given a mixture of these gut hormone mimics, and they were effective - people started losing weight, without surgery! So while there are challenges ahead - it's definitely coming - which should be a game changer for people who need it.

So hormones clearly have a massive influence on our body weight - and while they're not the only factor that affects weight - societal and economic factors also play their part - they do bear a significant portion of the load. We're living in bodies that have adapted for years to try and survive in uncertain food conditions- they're just not set up for the supermarket shelves of today - and their tendency to hold on to weight can make dieting a frustrating process. But the more we understand about the hormones at play - the more we can try and make sure we attain a healthy body weight safely and importantly without being shamed. As Giles says - while body weight is something we can control - we shouldn't judge someone else for theirs, unless we've walked a mile in their hormones.

Giles - *I just think it's important for people to know that your body weight is not a choice. So people who are who are heavier, who are obese are not bad, they are fighting their biology. And while we need to eat less to lose weight, I think we as a society need to know that for some people, it will always be more difficult than others and we have to understand that to put together a long term cogent strategy for us to be able to solve the problem. .*

Thanks to Giles Yeo, Eleanor Raffan and Jose Areta, for helping out with the first episode of Hormones - The Inside Story.

Next time we'll be heading to the land of nod to find out about the hormones that help you sleep - and more importantly what happens when your sleep pattern changes. Remember jetlag, you know - from when travel was a thing? Is it possible to hack our hormones to help us shift time zones? And most importantly - what happens to a horse without an alarm clock? Join me next time to find out.

You and Your Hormones is a podcast from the Society for Endocrinology. Explore more about the world of hormones at yourhormones.info, follow them on twitter @soc_endo and find them online at endocrinology.org

This show was produced by me, Georgia Mills. Kat Arney is the executive producer and it was made by FIRST CREATE THE MEDIA. Thanks for listening, and goodbye.