Episode 3: Glucagon: The Overlooked Hormone

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SPEAKERS

Gretchen Repasky

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TRANSCRIPT

Gretchen Repasky 00:05

Insulin is a word that's more or less familiar to everyone. And as diabetes is such a common disease, many people also know the term insulin resistance. But, do you know what glucagon is? And have you heard the term glucagon resistance? Well, today, we're going to look at some ambitious research on the hormone glucagon and its impact on type 2 diabetes. And we have two experts here in the studio who are going to help us out. First we have Alex Hamilton. Alex is a postdoctoral fellow at Lund University in Sweden, and a guest researcher at the University of Copenhagen in Denmark, and Nicolai Wewer Albrechtsen is a clinical researcher and Associate Professor at the Novo Nordisk Foundation Center for Protein Research at the University of Copenhagen and Rigshospitalet, also in Denmark, Nicolai examines how our GI tract regulates metabolism and how type 2 diabetes can arise when communication between organs goes awry. I'm your host, Gretchen Repasky. And this is Postdocs Talking, where we're shining the spotlight on diabetes and metabolism research, and how that science connects to society.

Gretchen Repasky 01:21

Well, welcome to you both Alex and Nicolai, it's really great to have you here in the studio today.

Nicolai Wewer Albrechtsen 01:26

Likewise

Alex Hamilton 01:27

Pleased to be here.

Gretchen Repasky 01:28

Our listeners might know that last year, 2021, was the 100th anniversary of the discovery of insulin. But they might not know that 2022 is also a significant year. It marks 100 years since the first evidence of glucagon-mediated metabolism. Alex, can we asked you to please set the stage for us? Why is glucagon significant? And how does that relate to your work and what real life problem your work deals with?

Alex Hamilton 01:59

Well, I think when we look at the past, there's been a real focus on insulin as a hormone. That's the hormone that's most synonymous with diabetes. But there has been kind of multiple evidence that's built up over the years that shows glucagon is also very important. And that diabetes is a bi-hormonal disorder. It's not just insufficient insulin secretion. It's also excessive glucagon. And it's the combination of these two hormones - insulin, which lowers blood glucose and isn't working properly in diabetes, and glucagon, which increases blood glucose, which is heightened in diabetes, that are driving the hyperglycemia that you see. So this makes it really important to research this hormone. And that's partly what I'm doing. We're trying to understand how the α-cell, which is the cell that secretes glucagon, works, trying to delve deeper into what causes it to hyper-secrete and become dysregulated in diabetes. Because by doing this, we can really understand diabetes better, and also target an area which has perhaps been overlooked. Glucagon's role is very significant. And it has been, there's been this real - if you look at β-cell research and insulin research, there's so much research. We know so much about them. We know what the basic mechanism of how they secrete insulin. If we look at the α-cell, there's very little consensus. There's a lot of theories, which kind of contradict one another. So there's a real need to research this field. And that's what I'm hoping to do, basically.

Gretchen Repasky 03:28

That's really, really interesting, because what is it that has led to this kind of discrepancy in a way between the two hormones? Was it sort of a lag of getting started with glucagon research, or is there something more complex?

Alex Hamilton 03:40

Yeah, I think, initially, like insulin was discovered first in 1921, I think, and I think glucagon was...Nicolai can correct me if I'm wrong...but it was kind of just viewed as a contaminant that just caused kind of a hyperglycemia contaminant. So it was viewed like this for numerous years. And then it was kind of, not until really 1975, when people began to see it more as a bi-hormonal disease, when they saw that glucagon was elevated in diabetes, you had hyperglucagonemia, which is the clinical term for high glucagon levels. And that these were present in all forms of diabetes. And they were also needed. You couldn't just have insufficient insulin secretion. So I think it was partly just that initial...they found insulin and there was this excitement about it, and

then just got kind of carried away. And then like 50 years later they're like hang on, this is still here, but that's kind of carried on. I think people still really focus on the β-cell. Like we've got remember, how do we treat diabetes? We treat type 1s with insulin, and eventually type 2s also take insulin so it's insulin is just known. We know it can be, it can help diabetes massively. It does. It's a huge discovery that has helped people with diabetes, the lives of people with diabetes. So glucagon has perhaps been overlooked for that reason, but I'd say if we found out more about glucagon, we can even improve the treatment of those people with diabetes. A lot of the problems we have with insulin such as hypoglycemia is caused by problems in glucagon secretion, as well. So if we can discover more about it, that would really be helpful.

Gretchen Repasky 05:10

Let's walk down that road a little bit. Can you tell us a little more specifically, now kind of inside the big picture, what are your main research questions? You were hinting a bit there about what you what you're looking at with α-cells. But tell us a little bit more specifically about what you're trying to find out.

Alex Hamilton 05:27

So I'm basically looking at the regulation of the pancreatic α-cells. So I'm not looking at glucagon's action, as Nicolai does. I'm looking more at kind of the cell itself, and how it's regulated. And specifically how its regulated by metabolites. So looking at how things, like our group looks at, or how things like fatty acids, and amino acids, which are the constituents of protein, interact with the α-cell, and how they affect glucagon secretion. And this is kind of very important, because previous research is more focused on glucose. Again, it's coming from that position where a lot of the previous work on β-cells, and β-cells use glucose, or sugar basically, as a fuel. So I think researchers, when they look to the α-cells, they they've looked at it very much in a glucose-centric manner, where they're thinking it's similar to the β-cell. It's in the same area of the body. Maybe it's regulated in the same way. But what you're actually looking at is two completely different cell types. The β-cell is active in the fed state. It's secreting when your energy levels are quite high, when you've just had a meal. The α-cell is a very strange cell type, and then it's most active when you're fasted. So it's more likely that it's not going to be regulated by a fuel which is low when you're fasted, which sugar is. Your glucose levels are low when you're in a fasted state. So it's more likely to be regulated by things like fatty acids, which elevate in the fasted state, and also potentially amino acids as well. So that's where my research comes in. And like there's been this real shift recently, to look more at these other metabolites, not just focusing on glucose. And that's why this is a really exciting area now, because there's a lot of research coming out, saying we kind of got it wrong thinking of glucagon just in terms of glucose metabolism. There's other things going on.

Gretchen Repasky 07:05

So if I'm remembering back all the way to my university biochemistry, and learning metabolic pathways days, I'm thinking about how different organs in our bodies have preferred fuel sources...so does the α-cell then have a preferred fuel source? Would it be these fatty acids and amino acids? Is that kind of what you mean by being regulated by?

Alex Hamilton 07:27

That's what we think. Yeah, so we think it's using fatty acids and amino acids. And, but other researchers in the past have more sort of seen it as more it's using glucose. But our research looks more at using fatty acids and amino acids as a fuel source. And that just from like, just intuition that makes more sense

Gretchen Repasky 07:48

Yeah it does.

Alex Hamilton 07:50

It makes more sense that it would use those and rely on those as its energy substrate, especially.

Nicolai Wewer Albrechtsen 07:55

Perhaps just from a historical perspective, I think these are exciting times, because we are just on the edge of a paradigm shift towards the understanding of what is the biology of glucagon, because that's the textbooks is glucose, right? But that might likely not be the case. As an example, take patients with glucagon-producing tumors. They have really, really high levels of glucagon. Glucose can be normal. Amino acid, you cannot measure it in the blood samples. And what does this patient get? They get a very phenotypical skin rash, which is called necrolytic erythema. And when you give amino acids to those patient, the rash goes away. So I think that's sort of one of many arguments towards that in fact, glucose is just one part of glucagon biology. And that's actually what you're addressing here. So that's why I think it's so exciting to be here.

Alex Hamilton 08:58

Yeah. And it's not just - as Nicolai said it's not just about the α-cell running on fats and amino acids. It's also it being a regulator, which Nicolai, which shows all the amino acids. It also regulates their levels in the blood. It's not just controlling glucose. So we're looking at hormone, we're not just looking at the α-cell being different we're looking at the actions of glucagon being different. So it's a really exciting time to research this hormone, and hopefully after 100 years we'll actually make some progress.

Gretchen Repasky 09:25

Say a little bit more for me so I understand. So when you're talking about regulating amino acids is that regulating endogenous amino acid breakdown, exogenous amino acid breakdown, is it regulating?

Nicolai Wewer Albrechtsen 09:36

Perhaps I could chip in there. One of the things I dream about every night, almost every night. So after glucagon is secreted from your pancreas, it sort of, you know, flows through your blood to the liver. And there you have the glucagon receptor. And besides having its effect on a glycogenolysis it also drives a process this is called ureagenesis. So ureagenesis is a detoxification of ammonia to urea, which can then be excreted through the kidney, right, because it's water soluble. So a central part here is actually the catabolism of amino acids, from whole amino acids to urea. And there, glucagon has some extremely powerful effect. And what is perhaps even more interesting is if you put it into the aspect of diabetes, some of these processes are actually inhibited or impaired in diabetes. So I think that's there might be a link there that has been completely overlooked. So it's not only the regulation on the pancreatic level, it's actually also on the other side, the actions of glucagon.

Alex Hamilton 10:47

A question with regards to that, because you're talking about with ureagenesis, but obviously, the amino acids can also be targeted for gluconeogenesis. Do you think glucagon is also having that action? Even in - so in the fasted state, you would imagine that would even say, after a protein-rich meal, would it be telling the liver: synthesize glucose? Or is it more: produce urea? Like do you know?

Nicolai Wewer Albrechtsen 11:10

Yeah, I don't know. That's why I guess we are here. But you know, a common mistake that is actually to read in the textbooks you are referring to, because there is also a term that gluconeogenesis - so that's the production endogenous production of glucose from fatty acids and amino acids - that's something that takes hours. That's a lie. It can actually go within minutes. So I think there are some fundamental biology, we've been sort of missing here. And what we can see is that glucagon is sort of, it's almost like you're driving a car, and glucagon can put your liver into a different gear. So going from reverse to forward. And when you are eating a protein-rich meal, what glucagon does is it puts it from parking to forward. And that sort of accelerates the turnover of amino acids. Because what is the problem when you're eating, let's say, a steak, what happens is that insulin, the β-cell is highly activated, so you have an overshoot of insulin. So that's a problem because your glucose levels are going down. What glucagon does is two things, it increases endogenous glucose production from amino acids and glycogen in the liver. But it also removes the driver for the hyperinsulinemia - the amino acids. So you can see this is a beautiful sort of homeostasis, that which glucagon has a central role in.

Gretchen Repasky 12:35

And this example that we're talking about here. This is all kind of in the normal state or non-diabetic state. So what about then can you run through that in the diabetic state?

Alex Hamilton 12:47

So the, in a diabetic, what they, so they would be taking insulin, say and that would, it would lower their blood glucose, but then the glucagon response would be absent. And the mechanisms underlying that - they're not as - some think it's because say with type 1 diabetes, they don't have β-cells. So you don't have that inhibitory, you don't have that release of the inhibitory effect of the cells.

Gretchen Repasky 13:15

You don't have that possibility

Alex Hamilton 13:16

So, that the signal the β-cells produce disappears. So the α-cells just don't respond. They just don't respond to a drop in blood glucose. There's also evidence for intrinsic defects, that the, kind of, the effects of high sugar levels that a diabetic would have, basically interfere with the intrinsic regulation of the α-cell, and it becomes kind of sick, let's say. And this means that basically, they don't respond. And this is kind of very, you when you hear about people with diabetes having hypoglycemia, which is pretty much the worst thing, well, one of the worst things that makes their life the most difficult, that's a lot of that's to do with glucagon. So, that would be another reason for kind of trying to work out how this one works and restore our α-cell function.

Nicolai Wewer Albrechtsen 14:02

And perhaps I could just chip in there because we talked about diabetes being one disease, right? And that's, again, a textbook issue. That's not the case. Of course, beside of type 1 diabetes, where you have insulin deficiency, and type 2 diabetes, where you initially have impaired insulin action and at some point also insulin deficiency. There's actually also subgroups of type 2 diabetes, okay? That's one aspect. But also other diseases like fatty liver disease, NAFL, non-alcoholic fatty liver disease. That is actually a common, dysmetabolic feature, up to I think it's 60% of all patients with type 2 diabetes. So you can see there is a huge co-morbidity that can have some impact on the biology we're just discussing from a more physiological point of view. Because what we also know is that if you have fatty liver disease, that is sort of diminishing some of those enzymes, we just been addressing some of the ureagenesis enzymes, some of the gluconeogenic enzymes, and more. Most importantly, what we can see is that if you give glucagon to some of those patients with NAFLD, the effect of some of the enzymatic effect is diminished. So, and that is a

terminology that we talked about glucagon resistant, right? What is it? So just let's remind our listener too, that diabetes is a heterogeneous disease.

Alex Hamilton 15:45

Yeah, so like the absent glucagon response I talked about, you're not going to see that in every person with diabetes, it's more people who take insulin. So mainly people with type 1 diabetes, or late stage type 2, so that the dynamics are different in each and yeah, Nicolai's right. There's been subtypes found that where you have like differences in kind of insulin resistance or β-cells failure. And it's I think you're what you're kind of looking at as a spectrum of, like, different than the like different, different disease manifestations.

Gretchen Repasky 16:13

So how does the obese state fit into that spectrum? Does it fit into that spectrum? Or is it its own?

Nicolai Wewer Albrechtsen 16:21

So you can you can say how many people in the world are obese? Almost 50%, right? Or overweight, at least right? But it's not 50% of the world population that has diabetes, how can that come? There is genetic predisposing the β-cells not to be able to sort of honor the demanding insulin resistance, right. That's one aspect. And there might be other things. One of them that might be a player here is the again to fatty liver disease. You can actually be slim, and have non-alcoholic fatty liver disease. Of course, that's not what you imagine. But that can occur, and we can see it on our study participants in our clinical trials. And you can also have severely obese people that do not have fatty liver disease, okay. How can that come? We do not know. But the point here being that obesity is a central driver in general for diabetes and fatty liver disease, but it's a more complex thing. So obesity, again, is probably not only one thing.

Gretchen Repasky 17:34

After the isolation of insulin in 1921, the cause of all diabetic abnormalities was assigned to a lack of insulin. Steadily however, the role of glucagon in diabetes has gained traction. In 1975, based on clinical observations and studies in dogs, diabetes was proposed as a bi-hormonal disease caused by both insufficient insulin secretion and glucagon excess. This early work was expanded upon by using glucagon receptor knockout mice. Neither β-cell destruction nor a high fat diet resulted in these mice developing diabetes. These findings then led to clinical trials of glucagon receptor antagonists in humans. And while these trials showed some promising effects on blood sugar levels, there were also adverse events that still need to be resolved. The emerging importance of glucagon in diabetes has driven the need to study the regulation of pancreatic α-cells, the cells that secrete glucagon. This is a challenging task. Various models of how glucose controls glucagon secretion have been proposed, but no consensus has been reached. Recently,

the field has shifted to alternative energy sources in a bid to resolve the enigmatic regulation of glucagon secretion. For example, it's been proposed that glucagon is a key regulator of amino acid homeostasis. High amino acid levels in the blood stimulate glucagon secretion, which in turn promotes amino acid breakdown in the liver, a process termed the liver-α-cell axis.

Gretchen Repasky 19:23

Let's go from there and go a bit deeper Alex into your studies. Can you give us an example of some specific questions, some experimental setup you had? Maybe touch a bit on what technology you're using or what's essential for you?

Alex Hamilton 19:39

So I kind of follow on a lot of what the liver-α-cell axis looked at actually amino acids. I'm looking at how they regulate glucagon secretion. And looking at it specifically on the α-cell. What effect do they have on the α-cell? So to do that, we're using various different experimental approaches. So we're measuring secretion, which is the obvious readout. So you add an amino acid. Does it increase glucagon secretion? But then a lot of like my background is more imaging. So microscopy. So looking at, we have molecular probes and dyes that can track how certain things in the cell change. So for example, ATP, which is the energy currency, basically of the cell. If we add amino acids, do we see an increase in ATP? What happens? Because if we see an increase that tells us that metabolizing it as a fuel. And we do this in different kind of fuel environments, so with fats, without fats, just to see what the interaction is, because a lot of the previous research, as I said, it came from β-cells. And what they did is they just use glucose, just glucose all the time. Whereas we're kind of overlaying it with other fuel substrates, and just seeing how these interact, and what role they have.

Gretchen Repasky 20:49

I could actually imagine an endless number of combinations that can be tested, the variety of amino acids.

Alex Hamilton 20:57

We have to stop eventually.

Gretchen Repasky 20:59

Does it affect how you set up your assays? Are you doing some kind of medium or high throughput analysis with your imaging?

Alex Hamilton 21:04

I'd say it's generally medium-high throughput, just because one of the pitfalls with this technology is we're trying to look at α-cells. And α-cells, why it's quite a difficult thing to study, which we haven't mentioned is that they're not very numerous, like in a rodent islet, they're making up about 20% of the islet, β-cells around 70%. Slightly different in humans where about 40% are α-cells. But, this means they're more difficult to image because like, or detect, so the throughput you get from them is less. So, you need to get out. And that also added to that they behave - whereas β-cells behave like as you'd expect, they're very synchronous because they're what's known as, electrically coupled. So, they have connections called gap junctions, which means when one turns on they all turn on at once. And if you look at, say, calcium oscillations in a β-cells, it's very like synchronous. α-cells aren't like that. They just, they're very heterogeneous. Some are active. Some are not.

Gretchen Repasky 21:58

So they don't have any kind of like autocrine sort of signal?

Alex Hamilton 22:03

As far as I'm aware, they don't have gap junctions between them, and they're not electrically coupled. So that means when we look at them, you've got to collect a lot of data to actually get the full picture because they're behaving differently. Like my PhD was also on α-cells. And I was looking at calcium oscillations. And you saw lots of different dynamics going on in different α-cells. So that makes them more difficult to study. We have to do more experiments to actually understand how the cell type works. So it's a challenge, but it's a good challenge to have.

Gretchen Repasky 22:32

So your main readouts then for looking at the effects of the combinations of what you're adding is, is an imaging readout. So tell us a little bit more about what kind of imaging you're doing.

Alex Hamilton 22:42

So the main type of imaging I'm doing at the moment is ATP imaging. We use a genetic probe called PercevalHR. And what we basically do is - this is in a vector. It's an adenoviral vector. So we'll isolate our islets from a mouse, and then we infect with this Perceval virus. And then after a day, they express. I should mention, this virus is under the control of a glucagon promoter. So the Perceval gene basically is under the control of the glucagon promoter. So we'll only express in the α-cells. So then I will image them using confocal microscope. And then basically, we excite with a laser and the probe emits, it has as an emission wavelength which we collect. And when we see increases in ATP, you should see an elevation in the signal of this dye. So then you can basically analyze that. But that's one of them numerous dyes we use. So you can also do calcium

imaging, where you measure the calcium in the cells. You can do measurements of membrane potential using dyes like fluoroval and things like that. So there's lots of other things we can look at to try and decipher what's what.

Gretchen Repasky 23:53

Your main goal with this is to really see the metabolic activity/state change in the cell.

Alex Hamilton 23:59

And, how that then affects so you'll get a change in metabolism, which will then affect things like the membrane potential and the calcium dynamics because what you've got to remember β-cells and α-cells, islet cells are like neurons. They're excitable cells. So they are electrically active. Basically, they produce action potentials. And this is how they secrete. The metabolism is coupled to the electrical activity. And this leads...this means when the cell is more active, basically you get an increase in calcium which stimulates secretion. So it's trying to put all of that together into a mechanism. And that's what's difficult because mechanisms are very difficult to get in science.

Gretchen Repasky 24:41

Nicolai, I'd love to hear what you're thinking about the pros and cons of Alex's approach.

Nicolai Wewer Albrechtsen 24:47

Clearly, this is super exciting. I'm, you know, just thinking about how can I get my hands on the confocal microscopy? I think there's a lot of excellent opportunities here to really go into depth about how the different nutrients, sense and activate the α-cells. So I think from that perspective, there is, it's a strong model. I think if we go from it, not from your science only, but from a larger perspective, I think one of the issues with glucagon research has, as a colleague wrote in the journal *Diabetes*, 'every year, there's a new gimmick about glucagon'. And the background for that is that the translations from cell lines to mice to humans are not so good here. If we talk about cell lines, remembering that the islet consists of multiple cell types, and now you actually pick out one of them, which you want to study, but we do know that the other cell types are actually also - they are living in sort of a homeostasis. And that I think, is one of the issues. It's not like that you shouldn't do it, but you should think about it. And thirdly, there are species differences, mice to humans, mice to rats. So it's super, super complex. So that's sort of, I think, some of the pros. That is what you mentioned, and some of the not so pro, that is sort of the problems of actually translating your findings into humans. And in the final point – patients; what can we do for the patient?

Gretchen Repasky 26:35

So yeah, Alex, could you maybe talk a little bit about your work in this context, too? Do you have? So you said most of your islet are coming from mice? And are you also moving your studies into humans and what are your challenges that you face there?

Alex Hamilton 26:48

So I'm based in two countries. I work at the University of Copenhagen as a guest researcher, but I'm also part of Lund University. So my supervisor in Denmark is Jakob Knudsen, and then in Sweden is Lena Eliasson. But the good thing about working in Sweden is we have a human islet resource. So we get human islets from donors basically. And we get them, we can get them quite regularly. So like once a week, but then other times, they're not as available. So a lot of our research we try and replicate in human islets. And I'll just add to Nicolai's point, that's really important because actually, rodent and human islets - there are similarities. But there's, as I said, there's differences in the number of cells, you've got more α-cells in human islet, also just the morphology. So a rodent islet, it has a β-cell core. So it's also β-cells secrete insulin. And then a mantle, which is α- and δ-cells. Whereas a human islet isn't like that. It's just a kind of a mix of all the cell types, more or less. So that has obviously implications for how the signaling works, so the paracrine signaling the signaling between the cell types. So we really need to try and move on to humans so we can answer these questions. But the limitation with that, as that always has limitations, is that the quality of the human islets. These are coming from donors. You're going to have things like ischemia or lack of oxygen, changes in metabolism. Especially for someone like me who's looking at metabolism that's going to be affected by these processes. So you really need to, yeah, but I think it's really needed. Like, I think, obviously, mouse work is valuable. But I think that as there's no point that we can't replicate in humans, and then from there, go to towards clinical studies. But we are we're trying to. Most projects I've worked on, because I'm based at Lund, as well, we try and get human islets as well, just to really confirm what we're seeing. And I think a lot of journals if you want to publish high, they require human islet data, usually as well. So there is a drive towards this.

Nicolai Wewer Albrechtsen 28:46

Just to add in here, I think it's also very important to mention that, of course, if you - if sometimes we're sort of blinded towards that we can do all the things in humans, why are we doing animal studies? And that's completely wrong. Because obviously, we cannot do a bit about the sort of very basic foundation about 'what is an α-cell,' and 'what's the fuel.' So that would never be done in humans. So of course, the model has some limitations that the clinical models of studies also have. So I think just it's important to recognize that that the area you are working with here is of course essential. It cannot go. It's not saying yes or no to one sort of approach, but we should see it as a whole that sort of supports each other right, and it's an example the one of the amino acid transporters. So we just talked about amino acids being a potential central fuel in mice α-cells, that was not the same in human islets, then it was actually another transporter. So you can just

see this as a very basics example. Small thing really matters, but if we need to do them because otherwise we will never figure it out.

Gretchen Repasky 29:59

Mmhm. And it's that synthesis of all of the different approaches coming together, that will reveal the best next questions to ask.

Alex Hamilton 30:09

Yeah, and I think that collaboration between different groups, I think in Copenhagen, actually, you've got a lot of researchers working on this area. So I think it's an exciting place to be for this type of research.

Gretchen Repasky 30:21

Studying metabolism and cell signaling in these ways is extremely challenging, because it's really hard to replicate the physiological state or to really know how the physiological state changes in a micro environment, isn't it?

Alex Hamilton 30:35

Yup. And, just deciphering where the effects coming from, and what contribution each thing is having. So what are the metabolic pathways or the electrogenic uptake, or there could even be receptor mechanisms as amino acid receptors that have been shown on α-cells as fatty acid receptors, which are G protein coupled receptors, which could also stimulate glucagon secretion? So it's kind of like there seems to be a lot of redundancy and like working out exactly what's going on is difficult. So we'll try.

Gretchen Repasky 31:05

Well, you're off to a really impressive start and trying to figure it all out. So I'm wondering, yeah, thinking about the discoveries you're making, and then those that may come down the road? How do you see that as beneficial someday for society?

Alex Hamilton 31:21

So first of all, to be honest, like we're very far from the clinic with the research I'm doing. I'm working with rodent islets. So I don't think we could, but there's the potential, obviously, to find drug targets this way. But I think just generally just where we're trying to understand an area, which has been neglected somewhat, but equally has huge potential. And, as Nicolai said, like the α-cell, there's very little consensus. There's a lot of gimmicks. So if we can actually come up

with a consensus and understand how the cell type works, it could have huge implications. It could produce - t could be something we can target. Like, we know, glucagon is needed to treat, for diabetes to develop. So it could be really important. And there already are drugs as glucagon receptor antagonists that are being trialed, which act more on the liver. These come with problems. So they have like, so although they improve the blood glucose homeostasis, they also affect things like...

Nicolai Wewer Albrechtsen 32:22

Amino acids.

Alex Hamilton 32:23

Amino acids there which kind of proves their model and then also, LDL so like bad cholesterol, basically. Can you think of anything?

Nicolai Wewer Albrechtsen 32:31

Yeah, hepatic steatosis. So they actually cause NAFLD. At least one of the glucagon receptors does. But there are others on trials that may or may not. Just to, because you say that you're far from clinical research, but I actually disagree with you. Because actually, some of these insights in amino acid metabolism and glucagon has actually generated a very concrete example from basic research to clinical application. And that is using amino acids or certain amino acids as a readout, so as a biomarkers for the many clinical trials that are now examining dual, glucagon, dual agonist, with GLP1 and the triple agonist, actually there was - there are at least two published papers where they actually refer to some of the studies of these recent events, that amino acid may actually be the biological primary role of glucagon. So they actually used it to say, here in this study, we use this triple agonist and we see effect on this and this and this, and given alone we can actually see that here we have a glucagon activity. So my point being here, of course, this is not a new drug, but it's actually a marker of the drug efficacy on a number of metabolic features.

Gretchen Repasky 33:49

And so can that be used then to aid in diagnosis or to aid in treatment monitoring?

Nicolai Wewer Albrechtsen 33:54

So for those patients, it was that that is a marker for the efficacy, the effect of the triple agonist, so one was on glucose, of course, one on lipid and another one was an on amino acid levels.

Gretchen Repasky 34:10

So then more the disease treatment progression.

Nicolai Wewer Albrechtsen 34:13

Yeah, exactly. Of course, one of the PhD students just defended her PhD here the other day, and one of her argument was actually that some of these markers can also be used as a biomarker for the integrity, or the metabolic health of the α-cell. So if we go like 30 years back there was developed a range of models for insulin sensitivity and insulin resistance. And all those are used in whatever clinical markers of DPP4 inhibitors, GLP1 agonist and so forth. So my point being these are very valuable tools for when you are developing different sort of compounds but also when you're developing new compounds. For example, when Company X wants to develop an agonist or whatever, how can you monitor the effects on whatever, animal or human? You need to have some good markers of it? Right? On glucagon sensitivity, like you have on insulin sensitivity. So now we just came up with one.

Gretchen Repasky 35:22

Yeah, we just linked Alex's work exactly to that role. So there must be a pharmaceutical interest in the work you're doing.

Alex Hamilton 35:29

Yeah. And also, like, when we, when I talk about glucagon receptor antagonists, they're targeting the liver. But equally, we could talk about α-cells themselves like and that's, as I said, my research focuses mainly on α-cells themselves. So if we can find out how they work, we can actually find other ways to not necessarily reduce glucagon's action, but change the secretion profile, as I said, like, in a normal individual, your glucose will be high in the fasted state and low in the fed state. But in diabetes, we're seeing that it's dysregulated, with very high fed levels, and sometimes low levels in response to low blood sugar levels. So if we can find a way to reverse that, then that will be really very important. And it could, it could really help people with diabetes who, you know, have hypoglycemia, or just reduce the, the hyperglycemia, basically. So it basically improve and it wouldn't just be used separately, it'd be used, obviously, in conjunction with the drugs that sensitize for insulin, increase insulin secretion, things like Metformin which decrease glucose production in the liver. So it's better basically another. Yes, another piece of the jigsaw, basically, solving diabetes.

Gretchen Repasky 36:37

Yeah, this is what I really wanted to ask you is what, what kind of effect then does it really have on a person with type 2 diabetes? How will their life be different?

Alex Hamilton 36:48

Good question. So it's further, far down the road. But I think also in terms of personalized medicine, when Nicolai, you talked about NAFLD, and like just looking at patients looking at their profile, I said, it's not just that it's what type 2 diabetes, there's subtypes. And if we can see NAFLD, we can have a readout of glucagon sensitivity, as you said, for amino acids and things like that, we can produce more kind of personalized care. And that will, that means we're not kind of going with this one size fits all approach. And can really make life easier for people with type 2, because often they have very poor glucose control. And that's partly, I think, partly because they develop it so late, whereas the type 1, they live with it throughout their life, so they become very attuned to controlling their glucose. But hopefully, with drugs that actually target a hormone that is also causing the effects of diabetes, it's not just insulin, then we can really help them just have normal and more normal long term glucose levels. And this helps in the long term, because a lot of the secondary complications that come with diabetes, talking about amputation what's the liver one...nephrology?

Nicolai Wewer Albrechtsen 38:11

The kidney failure

Alex Hamilton 38:13

Kidney failure, and various other different complications. If we can have better glucose control, these will appear less and later in life so that we can extend the lifespan of people with diabetes. And it means they're not, you know, in the later years of life, they're not going blind or losing limbs and things like that, and not having the kind of cardiovascular problems of the micro vasculature and micro vascular problems.

Nicolai Wewer Albrechtsen 38:35

Yeah, perhaps from a pharmacological a patient care of you? I don't know if you thought about if you were to put your money into glucagon agonist, or meaning activating glucagon, or glucagon antagonists, so meaning, you know, inhibiting the effect, what would you put your money on?

Alex Hamilton 38:52

Antagonists. Yeah, I think just because if we're looking at diabetes, like type 2, which generally is high blood sugar, which is the problem there. So finding a way to reduce that without causing hepatic steatosis and all those other adverse effects, I think that's what I would go for. But equally, I think just trying to lower the α-cells output as well, perhaps, and see how that's regulated. And also, like, I think diet research, like, it doesn't necessarily have to be a pharmacological approach. There's a lot of research with the effects of things like calorie restriction where you can reverse

type 2, obviously, that's something that's very difficult to stick to, but these are things are now being rolled out by the NHS in England. And like there's also some research in kind of looking at restricting specific amino acids and things like that. Methionine is one and this improves metabolic health. That's in mice. So if we don't have

Gretchen Repasky 39:49

Does that in any way link to any of your findings? Have you tested methionine?

Alex Hamilton 39:54

It may in the future, so we might do studies where we put mice on kind of protein-fed diets and see that, but that we will do in vivo studies where it's not just me looking at islets. But yeah, I think there's definitely, yep, with that approach where we actually just understand diet better, and like tailoring that to people with diabetes. Obviously, like, that's still very difficult for you to stick to. That's one of the I think one of the limitations of these very low calorie restrictive diets. But if we can find way of just changing the nutrient profile. Things like fasting, as well as evidence that they could have an effect as well, switching from animal to plant protein has been linked to helping with diabetes management as well. So there is - it's not just a pharmacological approach.

Gretchen Repasky 40:37

Do either of you have an opportunity - perhaps Nicolai more so you, to interact with people with diabetes and hear what they experience and be able to integrate any of that or have that inform the work that you do the research that you do?

Nicolai Wewer Albrechtsen 40:56

What can you say? I think there are many areas there. Of course, if you talk about hyperglycemia, which is a major issue in type 1 diabetes, the dual, so glucagon is being used as a rescue sort of thing. And there was a lot of trials, examining that, for example, at Steno and so forth. So that is a directly form sort of approach. But I think from my personal sort of research, I think it's more the complexity, that you have diabetes, but you actually have other things as well. And then when we do a liver scan of them, you know, see how much fat they have in the liver, they are surprised either to have liver fat or not to have liver fat, because they whatever, eat too much or are obese and so forth. So it, I think those small, small puzzles, actually, you know, make me think about how can that be? How can you, you know, have a BMI of 40 and have a normal liver? How can that be? So I think that's my personal take on that, how it can inform me and made me a bit curious about what is happening in our body.

Gretchen Repasky 42:04

Very interesting. Yeah. Everybody's a puzzle.

Alex Hamilton 42:07

Yeah, my experience of it is, it's more through public engagement events, which I more did in the UK, or speak some English speaker. But that was - I basically showed them some of the data I'd been doing like calcium imaging, and just tried to explain it to them. But it was a bit like what Nicolai said, like, it was more that I realized, like, what more of what a struggle is, it's not just often type 2 diabetes, these people have like, there's multiple health problems. And just that, we can easily say, like, oh, take this drug, like, use this diet, but actually producing care that actually gets to the root of the problem and that people can stick to and it's quite difficult. It's a real challenge. And yeah, and I think, yeah, just explained my research, like, it kind of helped. See, like, where we've got where we got to go with it.

Gretchen Repasky 43:00

Exposure to seeing those challenges can change also how you approach your work. Yeah. Well, I'd like to wrap us up now. And so Alex and Nicolai, let's go back to the beginning when I asked our listeners if they know what glucagon is. Hopefully, now they're a little bit more informed. And if they've heard the term glucagon resistance, so what take home message do you want to leave our listeners with?

Alex Hamilton 43:30

I think it's I think the main thing is that that diabetes is bi-hormonal, that glucagon's important and that it's been overlooked, and that there's that the research into it could have large effects on society, both in terms of kind of drug development, but also informing us on how diet affects hormone secretion and things like that. And that we're not just looking – whereas previously, we've looked at it in terms of glucose and things like that. There's growing research that shows regulation of metabolism by these islet hormones is different. There's fats and amino acids involved. So basically, to shorten that, basically that glucagon is vitally important, and by researching that, we could have it could have huge implications for the treatment of diabetes.

Nicolai Wewer Albrechtsen 44:22

Yeah, glucagon is a wonderful hormone. That's what the listeners should remember. And it's wonderful because we know so little about it actually. The physiological actions of glucagon, I personally believe lies in protein metabolism. So that means amino acid metabolism, lipid metabolism, and final glucose metabolism. So I sort of you know, reverted it rather being glucose on the top to being on the bottom. And also there are other areas popping up appetite, cognitive function of glucagon, renal a function of glucagon. So you can see we can sit here for the next 100 years and discuss this. We just, you know, poked on the tip of the iceberg, I think.

Gretchen Repasky 45:10

Well, it's been a really, really fun discussion with you both and I'm very happy that you were here. I'm very happy that you could spare the time to sit and talk with us and to share your work with our listeners. Thank you very much.

Nicolai Wewer Albrechtsen 45:21

Thank you.

Alex Hamilton 45:23

Thank you.

Gretchen Repasky 45:25

And I wish you all the best as you continue to push our understanding of the role of glucagon and of the alternative fuel sources and that ranking order of importance of how we should think about them. Thank you both.

Thousands of researchers around the world are dedicating their careers to better understanding and improving diabetes prevention, care and treatment. You can learn more about our guests today, Alex and Nicolai, and their work at our website, Danish Diabetes Academy.dk/podcasts, where we have short bios, additional information and photos of them at work. Our show today was produced by the podcast agency Kontekst & Lyd. Thank you to the Danish Diabetes Academy for keeping Postdocs Talking. Thanks for listening!