S1 00:03 [music] Welcome to the Sports Medicine podcast, brought to you by the Sydney and JL Huffines Institute for Sports Medicine and Human Performance, in the Department of Health and Kinesiology at Texas A&M University. At the Huffines Institute, we're always working to facilitate, apply, and bring you the most up-to-date coverage of the wide world that is sports medicine and human performance, all in a language you can understand and share with your friends. And now, here's our host. The director of the Huffines Institute, Dr. Tim Lightfoot.

S2 00:32 Hello and welcome to the weekly edition of the Huffines Institute for Sports Medicine and Human Performance podcast. I'm your host, Tim Lightfoot. And I want to thank you so much for taking the time to download us and listen. If you've been listening the last four weeks or so, you have found that we are trying a new format. We're trying what we call the stories behind the studies. It's our contention that every published scientific paper actually has a story behind it that's often untold and unknown because science papers are usually technically written, sometimes dry, sometimes boring, but there's nevertheless always an entertaining story behind each of them. And so we've been asking exercise scientists to come back and tell us those stories behind the studies. Today, we welcome back to the podcast Dr. Jim Fluckey. Welcome back to the podcast, Jim.

S3 01:16 Thank you. Appreciate being here.

S2 01:17 I'm glad to have you. And longtime listeners of the podcast will know - this is a trivia question for you - that Dr. Fluckey was actually our first podcast from the Huffines Institute, that number one, that came out on October the 7th, 2010. He then came back. He reprised his role in episode number 94. That was November the 2nd, 2012. And so we waited five more years for him to gather more material and come back to us. Dr. Fluckey--

S3 01:44 Yeah. Unfortunately, Dr. Lightfoot, it takes me about five years to gather the material [laughter].

S2 01:49 Hey, many of us, yes. Dr. Fluckey is currently a full professor here in our division of kinesiology. He's the chair of the graduate faculty here. His general research area is protein turnover and regulation in muscle. He talks a lot about making muscles grow, and making them shrink, and what does that the best way. He has 57 scientific publications at this point. Several different grant agencies have funded him and he continues to be an active scientist. And so today, we're going to start off with a question, Dr. Fluckey. Of all your studies you've done, which one's been the most memorable?

S3 02:24 From a matter of context, I'm not sure where you're going with this, but there have been some papers that have been more or less difficult to-- and actually, more difficult to publish than we'd anticipated.

S2 02:39 Okay. So you get to pick one of them.

S3 02:41 All right. So let me go back to a paper that we got published in 1999.

S2 02:47 Now, tell the audience. This will be on our website. So it'll be linked to this podcast. So if you want to see what the paper reads like, you can download it there. And this is the story behind that study. So what makes that paper-- well, give us a context. What was the paper about?

S3 03:02 Well, before I studied protein turnover, I kind of grew up in a glucoregulatory world. And in fact, my master's thesis and a lot of the studies that I was doing as a master

student and early on as a PhD student were involved with exercise and diabetes.

S2 03:19 Okay. The gluco is the glucose, part of-- when you said glucoregulatory--

S3 03:23 Yeah. So that's the glucoregulatory part. And the diabetes I'm talking about is non-insulin dependent diabetes, which is a type 2 diabetes. So in other words, the individual can secrete insulin. Even though the insulin is being secreted, the glucose uptake by the muscle, and which is what I study, isn't as effective as it is in a normal tolerant individual.

S2 03:43 So it's the form that so many people have nowadays?

S3 03:45 I think it's an overwhelming problem in our population. So the bottom line is, early in the '80s, we found out that exercise per se is a really good countermeasure therapeutic agent for somebody with type 2 diabetes because after they exercise, glucose disposal is much better. And when I did my first postdoc, I had the opportunity to go to the Copenhagen Muscle Research Center over at the University of Copenhagen, where I had the opportunity to work with just some amazing scientists in the glucoregulatory world.

S2 04:22 And for our listeners, Copenhagen is amazing place, really well known.

S3 04:26 Yeah. And probably, at that time, it was one of the premier labs in the world, particularly for exercise physiology. So I had the opportunity to go over there. And that particular group, in fact, was under with Henrik Galbo and a man named Thorkil Ploug, was the very first to show that you didn't require insulin at all for glucose uptake with exercise. And so people got really interested in, first of all, why does exercise work, and then to understand on the mechanistic basis, how is that different than insulin-dependent glucose uptake? So when insulin attacks the cell or attaches to the receptor, it facilitates glucose uptake. And exercise can do the very same thing without the insulin.

S2 05:14 And that's why type 1 diabetics sometimes need to cut back on their insulin if they're exercising because exercise--

S3 05:19 Is a synthesizer. It's so to speak. And so ultimately, use of exercise-- the good news is, exercise can help somebody who's moderately impaired glucose tolerant look very normal for up to about 48 hours. That's the good news. The bad news is, it goes away after about 48 hours, which compels you to exercise at least every other day during the disease state. So there was a lot of interest in how the muscle was able to communicate glucose uptake independent of insulin.

S2 05:55 How did it all work [then?]?

S3 05:55 And how did it all work? And so there were a number of groups that were looking at glucose uptake in response to muscle contractions and how did that compare to insulin. And the old adage is that, when you have insulin stimulating glucose uptake and then you add exercise to it, it's more than the insulin alone. And we used to call this--

S2 06:18 So it's a synergistic [crosstalk]--

S3 06:20 Yeah. We used to call this an additive effect. But you should know that doing studies on muscle contractions, whether it's in humans, and rodents, whatever, they're very difficult to control from one animal to the other or one human to the next. And so at the end of the day, if you didn't see this additive effect, was it because it didn't work in some people, or was the exercise not effective? And so there were a few studies that came out early on by an outstanding group of insulin-glucose uptake, people at Washington University. Early on, we knew that if you contracted the muscle, it would

stimulate glucose uptake, or if you deprived the muscle of oxygen, you could have glucose uptake. And it looked very similar.

S3 07:10 As an aside, one of the groups I worked with in my second postdoc, they capitalized on that effect because people with type 2 diabetes, they couldn't stimulate them to have glucose uptake with insulin. But if you introduced hypoxia or muscle contraction, they were just fine. And so it forced that lab to focus on insulin signal transduction as being a problem. And that's, I think, where the field is today, looking at the signal transduction. But back to the hypoxia versus muscle contraction, there was this group out of Washington University, was basically comparing the hypoxia-mediated glucose uptake with the contraction-mediated glucose uptake. And their final conclusions were that it was the same mechanism that facilitated that. And in fact--

S2 08:00 We should tell the audience so that-- at that time, it was thought that with moderate exercise, the muscle became hypoxic.

S3 08:05 Yeah, that's exactly right.

S2 08:07 It's not like you had to go up an altitude or anything else. That was thought at the time that hypoxia played a role in this.

S3 08:12 Yeah, which is kind of the whole mindset. And often, the hypoxia was attributing or being considered the component behind the contraction-mediated glucose uptake. And so when this study came out-- and it was a very good study. But after the study came out, there were a number of papers starting to emerge in the literature that was actually using hypoxia as a surrogate measure for contractions and then comparing the hypoxia versus insulin-stimulated glucose uptake, with the assumption that contraction and hypoxia were the same mechanism. So--

S2 08:48 Right. Okay. So they really get in trouble when they start to say they're the same thing?

S3 08:52 And they look like the same thing--

S2 08:54 At that time.

S3 08:54 --according to that paper. Yeah. But I had the opportunity to work with Henrik Galbo over at the Copenhagen Muscle Research Center. And I got--

S2 09:02 And if you're listening, and you don't know that is, look him up on the Internet.

S3 09:04 Yeah. And I think you'll be amazed. At that time and maybe since even, he might have been considered the world's foremost exercise endocrinologist. And the work that his group did with our understanding of insulin stimulation for glucose uptake and contraction-mediated glucose uptake has been phenomenal. But something didn't sit well with him in that study. And so as a postdoc from America over in Copenhagen, I was tasked with figuring out whether or not we could reproduce that work. And ultimately, the biggest concern I had with some of those prior papers is that they would render the tissue hypoxic, in other words, remove the oxygen, and then try to stimulate that muscle to contract.

S3 09:52 And so muscle contractions at best were minimized. And so my concern was maybe, maybe we were seeing more of the effect of hypoxia than we were of the muscle contraction. So in the paper, we spent a lot of effort trying to describe how we did that so we could have really potent muscle contractions that ultimately ended up in the presence of hypoxia. And when we did that, we found that the effect of hypoxia, stimulated glucose uptake, the effect of muscle contraction-stimulated glucose uptake, but the effect combined together was greater than one or the other alone, suggesting that there was another mechanism at play between hypoxia and muscle

glucose uptake. And the issue here is that--

S2 10:41 It goes back to that synergistic ideal.

S3 10:43 You bet. And ultimately, the issue there is that if you're using hypoxia to understand the mechanism of muscle contraction, but it may not be the same mechanism, you might be led down the wrong path when it comes to trying to figure out how we can stimulate glucose uptake either by administering some kind of pharmacology to mimic exercise or whatever. And so I tell you, where this paper became really memorable is when we went to submit it for publication and--

S2 11:12 So before we get to that, was this in humans? Did you use humans? [crosstalk]--

S3 11:15 No, we used rats.

S2 11:17 This is rats. Okay.

S3 11:17 And this was a rat study that--

S2 11:19 And that was what the WashU people were using, right?

S3 11:24 Yeah. Yeah. Everything was almost the same. We changed a few things.

S2 11:27 Almost impossible to do in humans. At that time, at that time.

S3 11:30 Well, yeah. And to be honest, there's not too many humans that are going to allow you to take all their oxygen out of their muscles--

S2 11:37 Their muscles, right.

S3 11:37 --and study how that all works, but--

S2 11:40 If you want to volunteer, you can let Dr. Fluckey know, but most of the time, that won't happen.

S3 11:44 Yeah. After the subjects start turning blue, people get concerned.

S2 11:48 Yeah. So I'm sorry, I interrupted. You said it became memorable. When?

S3 11:51 Well, it became memorable when we went to go to publish this. We recognized that the group out of Washington University is a very potent group, and they have done brilliant work. And they didn't do anything. Their work was well done from the standpoint of experimentally. It's just that we were concerned they weren't getting the type of muscle contractions as they wanted, so we developed this other approach. And sure enough, we get this additive effect. But when we go to publish that, it was summarily dismissed all the time. It would come back rejected because everybody knows that the hypoxia muscle mechanics or muscle contractions is the same mechanism. What are we doing?

S2 12:28 Supposedly. So you guys were going up against dogma at that point.

S3 12:32 We really were going up against some dogma here. So ultimately, we submitted it, the last ditch effort here, and this is by no means a ditch effort because the Acta Physiologica Scandinavica--

S2 12:45 That's a good journal, yeah.

S3 12:46 --is an outstanding journal. But Dr. Galbo really wanted to see if we could get this published in an American journal instead of the Scandinavian journal, where they do a lot of work, and I've published there since. It's an amazing journal. We wanted to get it in-- we went to Acta and, still, it took eight months. They wanted some follow-up experiments. We had to prove some things beyond a shadow of a doubt before it

finally got accepted. And then it's one of my lesser-sided papers [laughter]. But I got to tell you, about 12, 14 years later - and I don't remember exactly; it was at least a decade later - there have been a number of studies come out from very prominent physiologists in the glucoregulatory world who now completely acknowledge that the mechanism of hypoxia is indeed a much different mechanism than muscle contraction for the stimulation of glucose uptake. And in fact, it's kind of becoming a more fiercely investigated thing all over again, in that we are beginning to understand there are a lot of molecules at that time.

S3 13:50 Back in the '90s, we didn't even know some of these molecules existed. And now we're finding out that these molecules play a role in this whole contraction-mediated glucose uptake, and we're separating these mechanisms much more easily. So we're starting to get a handle on muscle contraction-mediated glucose uptake, which is through a very specialized enzyme that has been considered a nutrient sensor in the cell, but it does far more than that, called AMP kinase, and it's a very interesting reading, very hot topic. And then we thought, for a long time, that calcium was the mode of operation for mechanical contraction. But that's going to have to be revisited soon because there's a number of studies suggesting that that may not be the player. It may not be AMP kinase, but it may not be calcium too. And so we have to kind of figure out how we're going to address the hypoxia issue all over again.

S2 14:41 What's interesting about this conversation is you're now, I think, the second person that we've interviewed in this format and I think second out of five that have said that publication issues were what made the study memorable for them, because of the difficulty of getting studies published. And I'm not sure that the public understands what an ordeal that can be, especially if you're running up against established dogma out there.

S3 15:05 Yeah. And I think, nowadays, with the need to be the first to be out there, the problem with the need to being first is, if you're first, you become the dogma. And so some of these early studies that come out-- and again, they may be very well-crafted studies. But they become the dogma. And if you have data that differ from that, sometimes it's very difficult to get those data published because you're going against maybe only one or two other papers out there at that time showing that it doesn't work that way, or that you're showing that it works differently than what was first perceived. And the next thing you know, nobody wants to publish it.

S2 15:46 Yeah. You almost have to have an exorbitant level of proof to get it published because it's like they go, "No, that's not what everybody else thinks." And so you really have to work hard to prove that what you've shown is the correct thing.

S3 15:58 Yeah. So there again, even when Acta looked at it, it was another eight months before we finally got it into press because they wanted us to demonstrate that the cells were really hypoxic. They wanted to demonstrate that the muscle contractions were maximal. A number of things that we had the burden of proof to prove because the other paper came out before us.

S2 16:19 And I guess, in a way, that's good. That means that science doesn't change very quickly.

S3 16:24 Right. And what it means, it's working. The peer review system is working to some extent, as long as you're given an opportunity as being the one going up against dogma. A message to all these associate editors out there is that authors, I think, should have an opportunity to at least counter your arguments as a reviewer, at least have an opportunity to say, "Hey, this is why we approached it in the way that we did. These are why our data look like they do," because that can't happen if it's

automatically rejected. And so you have no venue for communication, basically, a dialogue between the journal, the reviewers, and the scientific editors to have an opportunity to say, "Hey, this needs to be out there."

S2 17:11 And the listeners may not understand, that's the way science publishing works mostly, is you put in the article, you put in the manuscript to the journal for consideration, and at any time, then the editor can say, "Reject," and send it back to you. And there is no further discussion. The only time you can continue that discussion is if they say something like, "Revise," or, "Major revision," or something like that. But as soon as they say, "Reject," you're done. The conversation with that journal is over.

S3 17:36 Definitely.

S2 17:36 And so then you have to go to a different journal. So how many journals did you wind up going to? I know you said Acta was the last one.

S3 17:41 Yeah. I'm trying to remember, but it was at least two journals. And unfortunately, those two journals were heavily inundated by Washington University at that time. And again, a credit to that lab, I admire every one of those professors that came out of that program because they are pioneers in our field, and they are at the top of the heap. But the reach was long. And so there was a very little chance we were going to have a reviewer that didn't have some interaction with that lab at one time or another.

S2 18:12 Now, the head of that lab, you had shared with me that, a little bit later on, you had another interaction with that person. And you were actually able to share some more information with that person, more rationale. And that person came back and said, "Well, maybe you have a point after all [laughter]." Is that correct?

S3 18:26 Yeah. No, that's absolutely correct. We tried to publish a paper a number of years later while I was at the University of Arkansas. Again, I was trying to do somewhat of a novel methodology to approach an idea. And there was dogma in the literature at that time about a very specific weight of the muscle that you were trying to incubate. And ultimately, the reviewers rejected the paper because they said, "No, no, no, no." And ironically enough, they rejected it because they thought my tissues weren't going to be hypoxic [laughter]. And so I had an opportunity to just contact the editor.

S2 19:10 Who was the same person from Washington, yeah.

S3 19:11 Who was the same person from that lab, and he allowed me, at least, the privilege of reading the letter. And ultimately, what happened is I explained to him the types of studies that we did in order for us to ensure that our tissues weren't hypoxic, that we were looking at normal tissues in this particular instance. And he came back and said, "You may be onto something here. We may have been a little quick to react." And so one of the other memorable papers, in fact, was that he says, "We've already rejected it, but I'm going to give you an opportunity to resubmit that paper." And so we resubmitted the paper. And I think three days later, it was accepted for publication.

S2 19:51 Which is amazingly quick in the science world.

S3 19:53 So it really looks good on paper that it was submitted on one date, three days later or so, it was accepted. But again, it was a hardship getting the paper into press. But that was one of those things where that dialogue allowed for an effective communication between the people doing the study and the people reviewing the study. And we basically came to a conclusion that, in our case, the investigators had a point. And it was up to the scientific community, after it was in press, to ultimately figure out whether these data were something that we could stand on.

S2 20:29 Right. And I think for the listening public also, hopefully it's reassuring to them that not everything gets into press. I mean, not everything gets published. There is a process that everything has to go through, as onerous as that process is, sometimes, for all of us.

S3 20:43 Yeah. But worth it. And I'll tell you, the review system, the peer review system, does keep you on your toes. And I tell my grad students that all the time. You are going to come up with data and it's not about what the data are telling you. It's about, can you trust what the data are telling you? And can you defend what you did to elaborate to people why those data may look like the way they do?

S2 21:10 Right. Right. Science works.

S3 21:12 Science works.

S2 21:13 That's why people can trust science, most of the time.

S3 21:15 I hope so.

S2 21:16 Yeah. That's why we're doing what we do. Well, thank you so much for being with us today, Jim.

S3 21:22 It was real fun. Thank you for inviting me back.

S2 21:24 Well, you're welcome. And I want to thank all of you for taking the time to download and listen to us. Let us know if you like this format, or if you want us to go back to the old one. Again, our email address is huffines@tamu.edu. We hope that you join us next week when we have another one of these interesting stories from the world of science. And until then, we hope that you stay active and healthy. [music]

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