Episode 187: PACAP and Migraine

Lindsay Weitzel
Hello everyone, and welcome to Head Wise, the weekly webcast and podcast of the National Headache Foundation. I'm Doctor Lindsey Weitzel, the founder of Migraine Nation, and I have a history of chronic and daily migraine that began at the age of four. I'm excited to tell you that I am here today with a brand-new guest that has never been on headlines.

This is Doctor Andy Russo. Hello, Doctor Russo, how are you?

Andrew Russo
Great. Thank you.

Lindsay Weitzel
Doctor Russo is a professor of molecular physiology, biophysics and neurology at the University of Iowa. He has published extensively in the migraine field, and most recently has published on both CGRP and PACAP and their role in migraine. Today, we're going to focus on something called PACAP or pituitary, a cyclic activating polypeptide. This is one of the molecules that is being looked at as another drug target for migraine.

And I think we all want to hear about our next drug target. So, I can't wait to hear what he has to say. So, thank you for being here, Doctor Russo.

Since you've not been a guest on head before, can you please tell our audience who you are and why you are so motivated to work in this field?

Andrew Russo
Yeah. First off, thanks so much, Lindsay, for giving me a chance to talk about one of my passions. Just CGRP and, now the evolution of the field to include PACAP as well. How did I get into this? Well, there's really two directions. The one that I really should say first is that I have two daughters who have really bad migraines.

And so, I live firsthand. I've lived for many years with people with migraine, and I know how debilitating is. And awful. So, that's first foremost. One of the, I guess, things that drives me to want to find a cure. But to be totally honest, I didn't start out working on migraine. I was working on the neuropeptide C chirp, and quite honestly, migraine was not the reason why I was working on a.

I started on CGRP before we had any indication is involved in migraine, but I got into the migraine field because of a ski trip. I was riding on a ski lift, a ski meeting, and I thought I'd been working on a cure at that point for well over a decade and knew about its role in migraine being speculated upon.

I thought maybe there's something I can do as a basic scientist with mice or rats in the working with mice, only with mice to try to figure out just what is CGRP doing that could be causing a migraine. So, combination of personal interest from my daughters and scientific interests because of,
that's one of the beauties of being a scientist.

You can ask weird questions, in this case, a question inspired by being in high altitude of Breckenridge and on a ski lift. I figured, let's give it a go. So that was back in the early 2000, and it's been an exciting journey. I gotta say, upfront and very exciting.

Lindsay Weitzel
That is an amazing story. I did not know that story. Thank you for telling us. It also brings in my home state. I am in Colorado.

So, I love that you got to loop in your personal life and your family life and what you do for a living, and what a great story. So, it's kind of special that we got to hear that.

So, you've done a lot of work on the CGRP pathway. A lot of people in our audience found relief with these medications and are very grateful for them. And there are also many who did not. So, before we get to pack up,

my first question is actually going to be related to CGRP. Do you feel we've exhausted the CGRP pathway when it comes to drug targets for migraine, or is there more we can learn in order to make a more effective migraine medication related to this pathway?

Andrew Russo
That's a great question.

The answer is very short. No, we have not exhausted the, the pathways procedure appears to be working. I'd be targeted for therapeutics. I will give a big plug for my favorite pathway that hasn't been looked at. And that's within the brain. Drug companies are hesitant to have a drug go into the CNS, and understandably so.

Our brain is precious, and we don't want to muck it up. And there is a risk of side effects whenever you start marking up the brain. I think it's going to be totally reasonable. And this is just prediction. I don't know for sure, of course, but based on work we've done with mice, I think that it's very reasonable that we can dampen CGRP activity in the brain and reduce migraine symptoms.

The reason for that is that right now, we know that the CGRP drugs are mainly acting in the periphery outside the blood brain barrier. And I want to put a caveat on that, that we are not 100% sure that's part of science. There's always caveats. There could be a very small amount of the drugs getting across the blood brain barrier that are having their effects.

Certainly, that's a possibility.

We know from our mice that there are different sites of CGRP action outside the brain and inside the brain that both can lead to similar symptoms that are migraine like, behaviors. Lighter version for photophobia.

Cutaneous eyelid danger for touch sensitivity, and grimace for spontaneous just thinking feeling. So long answer your professor talking. They don't stop talking. Short answer is, yes. I think there's, more, future for CGRP drugs that. No, we have not exhausted the, the potential for their actions.

And the major area we need to look at is inside the brain. So that's what we're looking at now with our mouse models. And we've shown that the CGRP blocking drugs, when injected into the brain, appear to be not having side effects on the mice.

Of course, we need the next go to people and make sure they're interesting.

Lindsay Weitzel
So just out of curiosity, because I think a lot of people are going to wonder when you said that you're injecting them into the mouse brain with the idea in a human body model, be more like making a really small molecule that would cross the blood brain barrier. You wouldn't necessarily be injecting it into a human brain, correct?

Andrew Russo
Right. Correct. Correct. Okay. And part of the excitement on this, I'm going to get ahead of myself here,

towards the future. Directions beyond and beyond. PACAP Which I do want to talk a lot about PACAP mainly, but if we can find out where in the brain CGRP is active, then we can start having more targeted transcutaneous stimulation.

So, using Neuromodulators that did not enter the skull, but still send signals to the brain to then potentially help migrate. And so, we're I'm very excited about the small molecule potential there more lipophilic to cross the blood brain barrier.

And most excited about that. But also, the potential eventually the neuromodulators to be able to know where to target activity.

Lindsay Weitzel
And it's also helping you find the location where these molecules are actively helping migraine. Correct.

Andrew Russo
Yeah.

Lindsay Weitzel
Yeah. Right.

Andrew Russo
Because that's something we can do in mice. We can't so easily give people to start circuitry figured out.

Lindsay Weitzel
All right. This is awesome. We don't often get to talk to someone who works in science. So, I think that our audience is going to find this very exciting.

Andrew Russo
And so, I get a headache when the other.

Lindsay Weitzel
A lot of I might already have one. So, we're probably in a safe zone. So, moving into the topic of the day, why don't you talk to us and just,

tell us what PACAP is? This is the other molecule that we mentioned that is looking like it could maybe be another promising drug target.

Andrew Russo
Yeah. So, PACAP, like CGRP, has a just awful acronym. It's pituitary delay cyclase activating polypeptide. Seriously? I mean, who thought that up? Yeah.

It's like the name, though, gives you kind of a clue what it does. It activates a signaling pathway involving at least cycles. So, making cyclic AMP that is similar to what CGRP does.

And so, getting into the comparison of CGRP and PACAP, the initial thought was, well, maybe it's just a CGRP wannabe and they'll be acting similarly.

I think that, to some extent has held true that pack up can induce migraine in migraine patients, just like CGRP in but what we've done is we've now and other labs have dived a little bit deeper beyond that superficial but very important similarity.

They're both causing migraine. They're asking are they acting in the same way? Are they dependent on each other or are they independent? And the so the comparison of what this peptide with the awful acronym PACAP is doing with what CGRP is doing at the molecular level. When you start looking at that level, drilling down deep, there's similarities, but differences.

So, I can't say for sure if the differences are important for PACAP actions versus CGRP actions. But we know that we have a, a cast of different pathways that they can take, and they're not identical pathways.

So, moving forward in the field we and others want to do is try to figure out which pathways are important, for each of their activities.

Is it the one shared cyclic AMP pathway that they're using? I don't think so. What we've done with mice in other labs, I've done with mice.

From what we've seen with the symptoms reported by patients, I don't think they'll be the same. And the final reason why I think they'll be different is they're expressed in different parts of the, the nervous system.

Lindsay Weitzel
Okay.

Andrew Russo
CGRP is mainly in the trigeminal nerve pack, is mainly in the spinal palatine ganglia. And those, those parasympathetic nerves from that

ganglia. So different ganglia to different parts of the nervous system. But they will.

Lindsay Weitzel
Quickly tell our audience where the spinal palatine ganglia are.

Andrew Russo
Somewhere in here.

Lindsay Weitzel
It's more central. It's then the trigeminal nerve, which is where you said CGRP was.

Andrew Russo
They're both in the periphery. They're both nervous. Yeah. They're not that far apart. And I don't really know how to point up my body without taking my head off.

Lindsay Weitzel
So, it's up here and here.

Andrew Russo
They're both up here. They're both. Yeah. Yeah. So,

Andrew Russo
Yeah. Actually, I teach med students, and right now they're learning neuroanatomy. With cadavers, it's a lot easier to pointed out in a cadaver than a person.

Lindsay Weitzel
Yeah. Okay. Go ahead, tell me.

Andrew Russo
So, they do have. They do overlap. There's some pack up in the trigeminal nerve. The traditional nerve and the and the sphenoid palatine nerve are to each other.

So just because you're in different real estate doesn't mean they're necessarily not working together or not doing the same thing. But I think it's another clue, along with our preclinical mouse data, that they work independently.

Lindsay Weitzel
So, the two-molecule seed, CGRP and PACAP, they mostly, work in different areas, but they're both areas related to migraine.

So, I think that's probably the most important point that we were just making. To summarize that.

Andrew Russo
Correct, I thank you.

Lindsay Weitzel
Yeah. So, some companies are already investigating pack up as a drug target for migraine. Do you think it looks promising for us that this could be another drug target? Kind of like CGRP?

Andrew Russo
Absolutely. So, we are all waiting with bated breath for Lundbeck, a Danish company, to announce the results from their phase two clinical trial with a monoclonal antibody that binds PACAP, similar to the monoclonal antibodies that bind CGRP, they have been so effective as preventative drugs for many people. Not all, but many people. So, the trial results are very similar in terms of the efficacy of the antibody in reducing the number of migraine days suffered by, people with migraine per month.

So that's very exciting. Very encouraging. The details that were just released, about two weeks ago in Seoul, Korea, at the initial headache Congress. And there's a lot of excitement there about this. So, moving forward, that is now setting up phase three clinical trials to really nail down the efficacy and,

I think this it looks very promising.

It's the hottest it's the newest kid in the block, and it's the hottest kid in the block right now in terms a schedule for helping migraine patients be I think the biggest question that, again, will be, will the people who are not helped by the CGRP targeted therapies be helped by this pack of targeted therapy? We don't know the answer to that.

It's clearly purely speculative, based on what I said earlier about their similarities and differences between them, I really think that they will be acting in on different mechanisms. And migraine. So, I think that they will potentially help patients who don't. So, help get help and how to CGRP drugs. Okay. But conversely, I think so I think there will be overlap.

Some people respond to CGRP drugs will respond to a PACAP drugs. It's all been either or the two circles overlapping. But I'm really hopeful that the pack of drugs will work with people that respond well to the CGRP drugs.

Lindsay Weitzel
I think, a question that's been on my mind ever since I first read, about pack up and its possibility as a molecule, in, that is affecting migraine. Is it possible that a, a really good therapeutic, or drug could come out that targets both pathways?

And I'm wondering if that is something that, people could work on in the future.

Andrew Russo
Absolutely. I think that combinatorial therapy is, a no brainer, actually, for, for migraine treatment.

Migraine is not due to any one single molecule. It's, I think, remarkable that the CGRP targeted drugs have worked as well as they have. So, it makes a lot of sense to me that you combine drugs targeting CGRP, PACAP, that you'll have more efficacious treatment.

So better response among people who respond to one or the other.

And so, the analogy I use for is a football analogy.

So, we're in football season here in Iowa. We're a Big Ten school. And this Iowa city lives and breathes on the Hawkeye football games. The town. It was crazy every week with a game. So, the analogy I have, I think is appropriate for not just Hawkeye fans.

But if you're not a fan, you should be fan. It's like having someone covering a wide receiver with the seed. You're probably going for the long shot ball being thrown to the receiver, but also having somebody come in for the run. So, while waiting for the running back to do an end run around the line, I think that that is the way I kind of viewed the drugs that are targeting the peptides, as opposed to drugs that would target a neurotransmitter, a neurotransmitter blockage is maybe effective for migraine.

But I'm worried more worried about that because that's more like the football analogy. The defensive line there. It's a solid line blocking. And quarterback may try to sneak through but he's not going to get very far running through the through the line okay. You can get to the line definitely. But by blocking that line you're

really cutting down all information flow across that.

Blocking out information flow. The drugs blocking peptide action. And in the wide receiver or hitting the running back going around the line. Those are getting the extra flow of information. And then the analogy kind of breaks out a little bit there. I'm sorry I'll keep working on it. But the but blocking the running back you're

going to hopefully cover up something that blocking the wide receiver did not do it. So having the drugs on board, you're more likely to get these two mechanisms right. Possible migraine transmission.

Lindsay Weitzel
Right.

Andrew Russo
Yeah, I need to go to that.

Lindsay Weitzel
The drugs that block the peptides are more specific. Is that part of what you're saying with this analogy then the ones that block the neuropeptide,

the neurotransmitter neurotransmitters. Excuse me. And so,

this part of why we have less side effects, perhaps with the ones that block the peptides, and we would possibly have the chance to block more than one peptide at a time and do a better job, which is where the question first started.

I actually do like that analogy. That was that was great. So,

Andrew Russo
My colleagues who work, there are transmitters would, would,

get their hackles up that saying their drugs not as good, but they're. Yeah. So

there's risk with every drugs. I don't want to sugarcoat the risk with a pack of drugs. We're very, very, aware. But so far, they've been remarked the CGRP of drugs. And from the phase two trials, the adverse effects with the antibody have been remarkably, minor.

There are some definitely some side effects, but, the target, I mean, I you listen to the target side effects on anything advertised, and they list off all these horrible things and deaths. Well, that hasn't been the case with the CGRP. Targeted therapies, at least so far. So, I'm happy that they've been, that they've been relatively safe.

And I think a lot of it is because of the mechanism of neuropeptide action that they're modulating activity. Not they're not the key transmitter, but they're the ones that give the added boost to a signal. So.

Lindsay Weitzel
Interesting, interesting way of looking at it, I think I think that that's an awesome analogy and a great point that I actually had not thought of. So, we have covered that. You don't believe that we've exhausted all possibilities for medications in the CGRP pathway, and migraine that PACAP is a very promising,

molecule in migraine as a drug target, and that the pathway is promising and that even putting the two together could be promising.

Is there anything else that you would like to cover having to do with these two pathways? As someone who's written quite a bit and I've read I have read your papers and I'm very impressed and I love them.

Is there anything else that you would like to add before we go today?

Andrew Russo
I think that a lot of it is figuring out what your trigger is and avoiding the. The answer is not all with drugs. And, but sometimes you just can't avoid those triggers. My, one of my daughter's triggers is stress, and I just don't get stressed.

Imagine how well that would over. Yeah. So it isn't that easy to avoid the triggers, but if you can minimize the triggers, that's the place to start with. Lifestyle.

Modifications. So, I think that that's what I encourage people with is to try to do a combination of the pharmaceuticals and the behavioral modifications, if possible.

That sounds a little bit like a preacher, and I don't want to sound like a preacher. Sure. Because as I said, with my daughter, it's easy to say, don't get stressed. But, you know, you can't avoid those triggers. In which case, what,

I'm excited about is the second aspect of migraine is that it's been socially a stigma for, for, for so long to admit that you have migraine is seen as a weakness.

It's, I think unfortunate, but that stigma is still out there. I'm real excited by the fact that by identifying neuropeptide CRP as being so crucial to the process, there were hopefully taking migraine beyond the fuzzy. Well, it's just a headache business. Oh, yeah. This is actually a neurological disorder. And it is a neurological disorder that involves the imbalance of signaling, most likely in different parts of the brain, as well as signaling in the periphery, as well.

So, I'm hoping that we can get beyond the labeling of it as being just another headache or just a headache to understanding what's going on. And my last thought of it is just more of a scientific curiosity. Bring it back around full circle, that I think that migraine is given us a clue to how the brain deals with sensory processing and CGRP is increasing.

I believe that transmission of information from light, sound, touch, smell, even interception, you know where of your body. And that's pretty cool. It's pretty cool. So how is how a CGRP doing that? And maybe migraine is a consequence when you get a little bit too much of that sensitization to sensory input, which is also, I think, intriguing that the body kicks in this pain mechanism, perhaps as a protective step.

So, you don't have too much sensory input. So, I was wondering if that full circle as a scientist, and as a father of daughters with it, I see the excitement for me is both helping people with drugs and also with lifestyle. And secondly, to understand how our brain works and processing information and migraines, giving us an opportunity to try to figure out how that's working.

Lindsay Weitzel
That was that was a very great way to end this episode. Thank you for that. We don't very often get to hear the viewpoint of a scientist working in the field of migraine. So, I want to thank you so much for being with us today. That was an awesome new perspective that we have not really had before.

So, thank you to you. And thank you to everyone who joined us today. And please join us again next week for the weekly videocast and podcast of the National Headache Foundation.

Andrew Russo
All right. Thank you. Bye.