MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD LEADING EXPERTS

TRANSCRIPT

UNLOCKING THE MYSTERY OF MIGRAINE PATHOGENESIS

PETER GOADSBY, M.D.

Introduction (00:05)**:** Mapping the pathways — like the pain pathway, light sensitivity, sound sensitivity — putting that together to try and understand what's better for the individual who's sitting in front of you, what's more likely to work is, I think, a really desirable goal. For a start, it's cheap. I mean, it doesn't cost anything to ask someone, "Are you sensitive to light?" You don't have to have a fancy computer to do that; you can have a wonderful time on an app doing it, but you know what I mean? It's the sort of information that you could use everywhere in the world and make therapy better. We haven't gotten there yet, but this pathway analysis and linking that into individual symptoms — that's certainly one of my goals in the next period of time and the research we do.

Carl Cincinnato (00:55)**:** Even today, experts don't know exactly how and why a migraine attack occurs. Researchers often debate the evidence behind different theories, which has led to the development of new treatments like triptans, CGRP monoclonal antibodies, and gepants. In this interview, we're going to explore different frameworks that may help explain how a migraine attack occurs. We're also going to consider how these theories may explain why some treatments are more effective than others. Before we jump in, it's important to remember that frameworks are a simple way to describe incredibly complex mechanisms in the body. After all, if this was simple, we'd already know exactly what happens and how. Dr. Peter Goadsby joins us today to help us simplify some of these complex mechanisms, so you don't have to be a scientist to understand. Dr. Goadsby, welcome back to the Migraine World Summit.

Dr. Goadsby (01:44)**:** Thank you. Thanks for the invitation.

Carl Cincinnato (01:46)**:** To start off with, can you describe what pathology or the pathophysiology means for migraine?

Dr. Goadsby (01:52)**:** There are two words that are bandied around in this conversation quite a lot: One is "pathogenesis," and the other one is "pathophysiology." Now, pathogenesis talks about where the disorder and where the attacks come from, what starts them, if you like — the causality. And pathophysiology, strictly, is about what happens during the attack once you've got it. So, pathogenesis: Why do you have migraine and someone else doesn't? Pathophysiology: What hurts? Why do you have nausea? Why are you sensitive to light?

Carl Cincinnato (02:34)**:** What is a migraine pathway?

Dr. Goadsby (02:37)**:** Migraine pathways are concepts, almost, of how connections in the brain, and with nerves in the head, are engaged or turned on during migraine. They're explanations that we use to try and build a frame to understand what's going on, and a frame that we can test, and a frame that we can then [use to] begin to develop new therapies and new approaches to management.

Carl Cincinnato (03:09)**:** Could the different pathways that are activated in migraine also have implications for treatment?

Dr. Goadsby (03:18)**:** Yes. If we understood all of the pathways, and if we understood all of the connections, and all of the chemicals involved, and we understood how they produced

individual symptoms, that will be fantastic. You could have, for example, a person who's got a lot of nausea — and if you understood exactly what was going on, you could target therapy at that. In comparison to someone who has, for example, dreadful light sensitivity and has to wear sunglasses all the time — you could be targeting at that. Now, there's probably overlap, but I think we know enough to say that those pathways have differences. So, the better we get at this, the better we'll get at therapy.

Carl Cincinnato (04:01)**:** So, let's talk about some of the theory behind some potential pathways, maybe some symptoms that may be associated, and if there are potential treatments. And I appreciate that a lot of these pathways don't necessarily explain the full picture, but it'd be interesting to understand some of the theory behind it, as much as possible, in plain English. So, the trigeminal pathway is often mentioned in migraine. Can you talk about what this is?

Dr. Goadsby (04:28)**:** The trigeminal pathway that's so often referred to in migraine is the quintessential pain pathway, if I could say it that way. And it refers to the nerves that supply sensation to the head — the front of the head, the trigeminal nerve; and the back of the head, the occipital nerve — that also, branches of which or parts of it, supply the structures inside the skull. And they all go to the same group of nerve cells, both the front and the back, go to the same group of nerve cells within the brain. And that system of lining them up — that pathway — is what, generally speaking, people are referring to when they're talking about the trigeminal pathway.

Carl Cincinnato (05:17)**:** What kind of symptoms can that express in patients?

Dr. Goadsby (05:20)**:** We think that's why most people say ... When they say the word "headache," they generally hold their head up at the top here [gestures to top of head]. They don't hold this bit of their head, or this bit — they call that the "face" [gestures to cheek and chin]. They'll hold it up here [again gestures to top of head]. You go anywhere, to an old church and see a gargoyle: It's holding it up here [gestures to top of head] because this is the first division. And when you've got migraine, for example, or cluster headache, then the activation of the pathway is saying to you, "Oh, there's something going on out here," [gestures to top of head over eye]. Whereas actually, in the mind for the pain, it doesn't have to be much going on out there because the perception is coming from inside [points to top of head] — there's this interesting overlap. So as you start to understand something like the first division and its pathway, you can understand why pain can feel a bit diffused — it can move around. Because this pathway is meant to tell you something bad is happening and you need to do something about it. It's not meant to tell you to take your skull off and dig around because that's just not a thing.

Carl Cincinnato (06:29)**:** So, if you have pain expressed in the second and third division — so, around that upper jaw area, maybe the sinuses, and then in the lower area of the jaw around the teeth — with a migraine attack, that might inform the trigeminal activation of that pathway?

Dr. Goadsby (06:46)**:** Yes. And that's precisely why many patients with migraine will get pain here in the second division [gestures to below the eyes] and they'll think sinus, and they'll end up seeing sinus doctors and such. And it'll take a while for the penny to drop that, actually, it's migraine. It's important that the localization can be a bit of a red herring. So you need to know that these pathways overlap, and that's something that doctors learn about,

and particularly neurologists; we're pretty obsessed with nerve pathways, so it's an area of comfort and interest.

Carl Cincinnato (07:28)**:** And what implications does that have for treatment, if you identify with this trigeminal pathway?

Dr. Goadsby (07:34)**:** Well, at the moment I'd say it has none at some level, because all that the activation of the trigeminal system tells you is that there's a problem in the head. Well, you already knew that when you came to the doctor; that wasn't a terribly revealing exercise. I think that your introduction sets out the goal. What we've done so far is a reasonable job of coming up with a description of migraine that works pretty much everywhere in the world. And that if you apply it in clinical studies or in clinical trials, you'll get pretty much the same result, pretty much everywhere in the world. So, you can study something and then it's useful to pretty much everyone who's got migraine — to a proportion of them.

Dr. Goadsby (08:20)**:** What we haven't done is the next level. Again, what physicians and researchers would call — another fancy word — endophenotyping: meaning getting a history; like, you've got throbbing, you've got nausea, you've got light sensitivity, you've got sound sensitivity, you've got smell sensitivity. But not everyone has all of those. And the detail of that is the "endo" — within the phenotype — is what *you* have. Using these pathways and mapping the pathways — like the pain pathway, light sensitivity, sound sensitivity — putting that together to try and understand what's better for the individual who's sitting in front of you, what's more likely to work is, I think, a really desirable goal. For a start, it's cheap. I mean, it doesn't cost anything to ask someone, "Are you sensitive to light?" You don't have to have a fancy computer to do that; you can have a wonderful time on an app doing it, but you know what I mean? It's the sort of information that you could use everywhere in the world and make therapy better. We haven't gotten there yet, but this pathway analysis and linking that into individual symptoms — that's certainly one of my goals in the next period of time and in the research we do.

Carl Cincinnato (09:44)**:** I think it's still helpful. Like even just knowing that information about the trigeminal pathway makes you realize that if you're going to take [something for] a sinus headache, or sinus treatments, or something for your eyes, or something for your jaw — but it's actually just a reflection of that trigeminal pathway — that those treatments aren't going to work. You need something specific to migraine.

Dr. Goadsby (10:04)**:** Imagine for a moment that you've got pain in the head here [gestures to below the eyes] or over here [gestures to forehead], and when that activates, you also get some eye watering and some nasal stuffiness, and it feels a bit uncomfortable. People will think, "Oh, sinus, OK." If you didn't ask any other questions about light sensitivity, sound sensitivity, what's the pain like, what happens with mood, all the other questions, you might think, "Oh, [gestures to forehead] pain, sniffliness — that's sinus." It's clear that a large proportion of migraine patients will get misdiagnosed because that rest of the depth of history doesn't get given. And what they're simply telling the doctor is about a pathway that we know about, and we know exactly why. And as we've been able to explain it to physicians, I think ... that just [that] knowledge is having a useful effect in them asking [the questions]. You just have to ask the next couple of questions, and you'll realize whether you're going down the "sinus road" or going down the "migraine road." So, it's an example of a pathway. If you know about it, and you ask a few questions about it, or if you're a

patient and you're getting these symptoms, ask yourself, "Do you get other symptoms? Do you get the light sensitivity? Do you get other symptoms?" And if you do, maybe you don't have a sinus problem — maybe you've actually got a migraine problem and you've got a cranial autonomic activation.

Carl Cincinnato (11:23)**:** Serotonin is something that we hear a lot about in the pathophysiology of migraine. Can you tell us about the potential serotonin pathway, the symptoms that might be expressed, and maybe the implication for treatments, if there are treatments that specifically target serotonin?

Dr. Goadsby (11:39)**:** Yeah. The serotonin pathway is such ... That means a couple of things. Once you start talking about a chemical, "pathway" can have two meanings, two big meanings, anyway — several meanings — but let's take two big meanings. One meaning is: Where's the serotonin coming from — the biochemical pathway? How is it synthesized? How is it made? That's a pathway. And the other place is where is it used: What are the anatomical pathways? What nerves use serotonin? So you can manipulate the serotonin biochemistry — how it's made, how it's cooked, so to speak. Or you can try and manipulate it in a way that manipulates the nerve pathways that are involved.

Dr. Goadsby (12:21)**:** In migraine, probably when we think about serotonin pathway, we're talking about the pathways that use serotonin. Whereas, to give you an example, in mood [disorders], in depression — when you talk about serotonin, the medicines at work change the way the serotonin is taken back up into nerves. So it's a little bit more about the cooking than it is about the pathway. I mean, it's a rough distinction. But it's useful because you can throw a phrase around and it'll mean something totally different, and people think you're in the same place; and before you know it, you're often in a very different place. So, the serotonin pathway — the implication in migraine is the way serotonin interacts with certain nerve pathways. So serotonin interacts with the trigeminal pathway. The serotonin can turn trigeminal neurons off. And serotonin can interact with pathways that process light and sound within the brain. And the way that all works — the other part of the triangle, if you want — is what are called the serotonin receptors. It's another thing that people talk about a lot in the migraine world. And the receptor is the place where the serotonin acts.

Carl Cincinnato (13:42)**:** If we respond to triptans, does that also mean we might respond to maybe an antidepressant because it's activating in a similar way?

Dr. Goadsby (13:49)**:** Yes, well, the simple answer to that unfortunately is "no" — for a few reasons that we understand, and I guess, a lot of reasons that we don't. It's another thing that says serotonin is involved in throwing up, in vomiting ... The serotonin-3 receptor has been studied in considerable detail to develop antiemetics — antinausea — drugs for cancer chemotherapy. And we use these drugs sometimes in migraine. So there are other things that serotonin does — because of the 14 receptors, it's a messy story. So, the receptor profile that seems important just in mood is serotonin. If you look at the drugs that are used that overlap with depression — what are called tricyclic antidepressants because of their structure — they actually fix serotonin, noradrenaline, and dopamine. They're what pharmacologists call "dirty" because they do a number of things, which of course they're “clean” when you take them but “messy” from a professional perspective.

Dr. Goadsby (14:56)**:** And the literature is reasonably clear that the purer serotonin drugs are actually not useful in migraine ... There's more going on in migraine in terms of migraine

prevention — prevention pathophysiology — than acute attacks. And certainly if you change serotonin levels, the serotonin can affect any one of the receptors that are in the brain, so that gets even messier. So there's no correlation of that. And I think that's because serotonin is such a, you might say, “promiscuous transmitter;” it's happy to talk to 14 receptors, interact with them indeed.

Carl Cincinnato (15:36)**:** So, you mentioned serotonin's role on dopamine. Can you tell us about the role that dopamine plays, its pathway in the context of migraine, what symptoms that it might affect, and if there are any potential treatments as a result of its involvement?

Dr. Goadsby (15:51)**:** So, you can see that if a person yawns — [tracked by] using a diary system, electronic, couldn't go back and change it — more than 90% of the time, if they have that [yawn], they'll go and have a migraine attack. OK. So what do we know about yawning? You can activate dopamine receptors in migraine patients and get them to yawn, whereas if you activate a dopamine receptor in a nonmigraine patient, they don't yawn. Interestingly enough, you can even do that in experimental animals. So yawning seems to have a dopamine component to it. Now, what's emerged from the imaging — some wonderful imaging work, we've been interested in this; Arne May has done some incredible work [with] imaging. You have to really let me give a shout-out to the patients who get involved in this: The patients that he's been studying, who will have their brain imaging done every day for a month — 30 days — suffer an attack, not treat it, just really provide something to the community.

Dr. Goadsby (16:50)**:** And the areas ... One of the areas we've shown in the work we've done, and that Arne has shown, is activation in a region that would overlap with an area called the hypothalamus. [It] won't surprise you to learn that, among other things, this area has dopamine. What I think is exciting at this level is that you can just get into one thing — just yawning. Just yawning. And then you can narrow down what chemical might be involved. You start to think about what brain area is involved. There are five dopamine receptors and some variants; which ones are going to be important? That kind of opens up a whole new way of thinking about that symptom. Now a Holy Grail, from my perspective, is treatments that you could take before the pain even comes. Why wait for the pain? That doesn't sound like a good idea at all. If we could understand this earliest phase — this premonitory phase — when the attack is sort of building up and we could stop it in its tracks, you wouldn't have to have the pain. So, our research is really quite focused, at the moment, on the early premonitory phase for this specific reason.

Carl Cincinnato (18:11)**:** GABA is something that comes up as well in the description of migraine. Can you tell us what this is; potential symptoms that we might experience as a result of GABA, and if there's any implication for treatment?

Dr. Goadsby (18:23)**:** Yeah. So, as you say, GABA — gamma-aminobutyric acid, to its friends — is mentioned. GABA is the most important inhibitory transmitter in the nervous system; what that means is [it’s] the transmitter that turns things off — GABA. There are receptors that ... Unsurprisingly, it's a chemical, so there are GABA pathways, there are GABA nerves, there are GABA receptors; just the same thing as I said for serotonin. What interacts with that? Those of you who've used benzodiazepines, like diazepam — it acts on the GABA receptor at what's called, unsurprisingly, a benzodiazepine site; they're sedatives, as you well know. At the moment, the GABA ... While it's clear that migraine has a turning-on and turning-off — some things are turned off and some things are turned on — it's not rocket

science to say that. And so, it's not rocket science to think that the turning-on things have the certain chemical involved — glutamate would be one of them. And the turning-off things have got some chemicals involved — GABA must be one of them. I don't think we've gotten to a point where we understand enough about how to narrowly target that. Because if you broadly target GABA transmission, you're going to turn a lot of things off that you don't want to turn off. And those people who take benzodiazepines and have sedation effects will know exactly where I'm going with that. I think that's much further away than understanding dopamine because it's so ubiquitous; there's so much GABA in the brain that if you start playing with it, you could be pretty sure that the first couple of passes of that are going to be associated with all the side effects. You know ... migraine patients have got it bad enough, that producing new drugs with new side effects, that's not a thing — that's not very helpful.

Carl Cincinnato (20:27)**:** If people have done some of the history and looked at some of the theories behind migraine, you'll hear about this vascular theory of migraine or the vascular pathway. Can you tell us about this theory?

Dr. Goadsby (20:38)**:** The vascular theory of migraine is, conceptually, that the migraine pain is generated by an enlargement of blood vessels, which as they enlarge, stretch [or] change the nerves that are innervating. So as you stretch something out, it gets uncomfortable, so to speak. And that's broadly speaking. So the term vasodilation, as a manifestation: The concept is, if you constrict the vessel, you stop that dilation, [then] the pain will go away. Now a subhypothesis of that is around migraine aura — the idea that the jagged lines that move across the visual field are because there's a turning-on, and then there's a turning-off of the brain — a constriction. And after that constriction associated with loss of vision, you get a dilation — an increase — and that's what causes the pain. I'm not trying to do a disservice to the vascular people; I think that's broadly the idea. I mentioned earlier on the ditans — the fact that you can take a drug that has no vascular effect — full-stop, new paragraph — and you can stop a migraine attack, tells you that the vascular theory is ... It's a difficult thing to keep a hold on.

Carl Cincinnato (22:14)**:** One of the things I've noticed with this vascular theory is that when I exercise, particularly when I do vigorous exercise — which I really enjoy and I find is a prophylaxis for migraine, a preventive — I have these veins in the side of my head [gestures to forehead] that are definitely dilated, like enlarged and throbbing, yet no pain. But when I feel myself having a migraine attack, those veins feel exactly the same. And so, for me, that's kind of how I'm thinking about this vascular theory — yes, you can have dilation, but unless there's a sensitivity involved, for me, it's not painful.

Dr. Goadsby (22:47)**:** Exactly. Just as everyone [who's] sitting watching this, who's not having migraine, is throbbing: heart, all the vessels in my head — I'm very happy that they're open and they're throbbing. And everyone without a migraine is throbbing. And when migraine people are sitting without migraine, they're throbbing, guaranteed. Because that's the way it works — boom, boom. Now ... all you need to do is change how you perceive the throbbing; to have a problem you don't actually need to change the throbbing. I think the soundest way of thinking about this ... When I think about it, my favorite way of thinking about it is when I think about light sensitivity. It's crystal clear that the amount of light you actually get from the sun — the photons that hit your retina — on a migraine day and a nonmigraine day, they're the same. So, the only game in town for light sensitivity, and sound, and smells, is that the brain misinterprets the signal that it gets. And I think of Occam's razor: the idea that you take the simplest explanation. So, it's my view that the substantial part of what's going

on is misperception of normality: dysfunction in the way the brain is supposed to ignore light and sound and ignore the fact that you throb. Because it would send us crazy if we could feel throbbing all the time, and the system was not designed for that.

Carl Cincinnato (24:15)**:** Inflammation is mentioned in migraine, and people may have heard migraine described as a neuroinflammatory disorder. Can you tell us about how that plays a role or its pathway in migraine and potential symptoms?

Dr. Goadsby (24:28)**:** Very often here, migraine is described as a neuroinflammatory disorder. Again, like as with the vascular side, that's an idea, not a proven thing, in my view, at all. The idea is that there's a reaction in the covering of the brain — the meninges — that is sterile rather than infective. So if you have bacteria — bacterial meningitis — you'll get an inflammation; that is, cells that come in to try and scoop up the bacteria, you might say, and break it down. The concept of inflammation in migraine is that those reactions are occurring without any inflammation, so that's called a sterile — no infection — inflammation. I don't see that there's ever been any definitively convincing evidence that [that] occurs. I don't think of migraine as a neuroinflammatory problem; I think it's simply a neural issue.

Carl Cincinnato (25:31)**:** Well, you'd simply take anti-inflammatories, wouldn't you, if you thought that migraine was primarily an inflammatory disorder?

Dr. Goadsby (25:36)**:** You might start that way, by taking anti-inflammatories. But I'm guessing that there are people watching this who've taken anti-inflammatories, and it didn't make a blind bit of a difference to their migraine. Because if anti-inflammatories sorted everything out, I'm not sure that there'd be a lot of shows like this on. So I'm very lukewarm on that concept. You know, drugs like naproxen, for example, are useful for some people. There's no doubt about that. But just as they're useful for some people ... you know, if you say naproxen and ibuprofen and say to the people listening, "You all should respond to that," they'd think we were *crazy* because I'd wager that there are many people who listen to this who don't respond to those *one little bit*. There are other things going on, just as nothing works for everybody. But as you know, things that don't ... If something was the answer — if it was like diabetes and you just had to understand what blood glucose was — if you knew what that was, that would be a thing. It would be the single thing — but it's not like that in migraine.

Carl Cincinnato (26:44)**:** And I think that's why it's so challenging because triptans are an effective treatment, and they're helpful for probably the majority of people with migraine. But I've never responded to a triptan, unfortunately. But I do respond to naproxen and anti-inflammatories. It's not a perfect response, but it's a better response than I get from triptans. But that's not ... Like, I'm an exception to probably the majority there and trying to figure out why — like, is it because my migraines are more inflammatory or activating on that pathway? So I think this discussion is helpful to understand the potential mechanism of action and the implications for treatment.

Dr. Goadsby (27:21)**:** And we're going to see that evolve further with the gepants, the CGRP-receptor antagonists, and the ditans — the serotonin-1F receptor agonists. There'll be people who will say exactly what you just said, but they'll say it with different things. And as we develop more of these medicines and we try to nail down what it is about X responder, or the gepant responder versus the ditan responder, we'll get some insights into the disorder. That's a kind of iterative process. If you understand the disorder better, you get

better understanding how to use it. The other thing to say is: Migraine is not static. So, I see patients who have responded perfectly well to a medicine, and then it doesn't work. It doesn't work — a very frustrating situation. I mean, what is that about? Because the pathways are not static — they're changing and they're evolving. And we need to understand that longitudinal dimension of this, as well.

Carl Cincinnato (28:23)**:** Are there any final thoughts you'd like to leave with the audience?

Dr. Goadsby (28:26)**:** I would say, if you're talking about pathways, and pathophysiology, and pathogenesis, and all the things that we've been talking about ... The first thing I'd say is that we don't understand everything about migraine. Anyone who tells you that they understand everything are really lost — completely lost the plot. That's not the case. Anyone that tells you that research in migraine is not useful has also lost the plot, because the research is delivering therapies — and it's not delivering to everybody, but *understanding* is delivering therapies. And the third thing is that understanding the basis of something delivers something that people can hold their hands on. It's fantastic, I think, that I can explain to you why your eye might water. That is just knowledge that's important. So, I think that there'll be people with migraine watching this who've gone nowhere over years. And I've liked to often say that: Even if everything's hopeless, things are actually changing on a pretty regular basis; so don't give up. There are people like, you know, research people babbling with our own terminology, trying to do something useful. And things will improve. Every day you lose to migraine is a day you shouldn't lose. Let's try and join hands and really demand more resources so that your migraine gets understood the way it should be. So you can have all the life that you want.

Carl Cincinnato (30:04)**:** Dr. Peter Goadsby, thank you so much for your time on the Migraine World Summit. And thank you for all the research, work, and passion you've invested into this condition on behalf of patients worldwide. It's been a pleasure interviewing you.