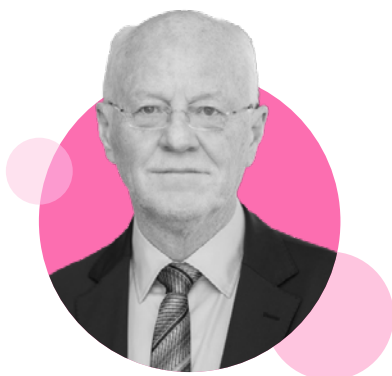




Interviews

EMJ had the pleasure of speaking with Peter J. Goadsby, Joanna Wardlaw, and Angelo Antonini about the latest advances in neurology, spanning migraine therapeutics, small vessel disease and lacunar stroke, and the evolving landscape of Parkinson's disease. They discussed how emerging models of disease pathophysiology, including the 'gut-first versus brain-first' theory of Parkinson's, alongside advances in diagnosis and treatment, are reshaping clinical understanding and improving outcomes for patients.

Featuring: Peter J. Goadsby, Joanna Wardlaw, and Angelo Antonini



Peter J. Goadsby

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**I think migraine is
fundamentally a disorder
of sensory modulation**
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Q1 When you began your work, the vascular theory of migraine was still dominant. What specific observations most clearly convinced you that vascular change was epiphenomenal rather than causal?

When I first heard people talk about migraine, there were two things that struck me as odd about the vascular theory. The first was that, at the time, there was a concept that migraine was caused by some sort of circulating serotonin-releasing factor producing vasodilation. That struck me as an odd thing to suggest because anything that circulated would go to both sides of the head, whereas migraine is predominantly one-sided, so that didn't make any sense to me.

The other thing was that, at the time, James W. Lance's group at the University of New South Wales, Australia, was interested in the symptoms that occur before pain, the so-called premonitory symptoms, such as concentration impairment and fatigue.

It was simply impossible for me to think about blood vessels causing people to be fatigued. Maybe that was just because I didn't know enough at the time, but it didn't seem to make any sense to me.

So, because the existing explanations didn't make sense, it made me think that there was likely to be a neural explanation, a central nervous system explanation, instead.

Q2 Your work led to the discovery that migraine involves the release of the neuropeptide calcitonin gene-related peptide (CGRP) from trigeminal sensory nerves, and ultimately the development of gepants, CGRP receptor antagonists. The success of gepants is extraordinary, but many patients either partially respond or do not respond at all. What does non-response teach us about migraine heterogeneity?

CGRP pathway blockers come in two forms. There are gepants, and there are also the CGRP

monoclonal antibodies that bind either to CGRP itself or to the receptor. The work that I did identifying CGRP was conducted with Lars Edvinsson at Lund University, Sweden. Only about half of migraine sufferers who are treated will have a useful response, and about 40% will have a spectacular response. So, what that tells you is that there are other aspects of the pathway, other transmitters, that must be involved. That's frustrating for the people who don't respond, of course, but I see it as an opportunity. To me, it says there's more to do, and, invariably, the researchers' clarion call is that more research is needed.

Q3 One of the most fascinating aspects of gepants is their dual acute and preventive role. What does that duality reveal about migraine pathophysiology?

First, it establishes that the notion that there's a strict demarcation between preventive treatments and acute treatments must be wrong.

If you look at the literature, it's not the first example of this, but it's certainly the clearest example. It suggests that the limitation on an acute drug not becoming preventive, or a preventive drug not being used acutely, is largely due to either pharmacokinetics or pharmacodynamics.

Preventive drugs, generally speaking, are not absorbed very quickly. If you take drugs like topiramate or propranolol, they're absorbed relatively slowly, so they're impractical simply from a pharmacokinetic point of view. You can't get them on board fast enough. And then, there are unexpected consequences. Triptans are great acute treatments, and they would probably be good as preventives, except for the blood vessel constriction aspect. In a proportion of people, they increase blood pressure, and their ability to induce headaches, so-called medication overuse headache, which isn't universal but happens in a substantial proportion of patients, means that taking them every day carries so

many downside risks that you wouldn't think about using them as preventive treatments.

The overarching point for me is that if you attack the right mechanism, or block the right mechanism, then it really becomes a question of pharmacokinetics, absorption, and side effects as to whether you'll be able to use the medicine in both an acute and a preventive fashion. I suspect that's going to be the general rule as we get more specific drugs, that you'll be able to develop drugs that can do either.

A really good example is eptinezumab, a monoclonal antibody given intravenously that works quite well acutely. Its intravenous administration is as effective as a gepant given orally. So that's a clear-cut example of a preventive treatment working acutely. Then, of course, you have all the gepant data for a class that started as acute treatments and also works preventively.



I think the other important thing is that it makes early medicine development a lot easier, because you no longer have to think about models and systems in terms of whether they're preventive or acute; it's simply not a relevant concept. What you're trying to do preclinically in the laboratory is understand the drivers in the biology and then target them. If you come up with a medicine that has a long half-life, and there are more people who need it as a preventive medicine, then you may go down that road. If you come up with a medicine that's incredibly quickly absorbed and has a short half-life, then you may go down the acute treatment road. At that point, development starts to be driven by those considerations and not by the mechanism itself.

Europeans will be familiar with flunarizine, which they tend to think of purely as a preventive medicine, but there's actually a randomised, placebo-controlled trial showing that it can be an effective acute treatment when given intravenously. Now, no one really does that; it was never developed that way, and it's not especially practical intravenously, but it does show you that the principle is there, and that the underlying principle is probably correct.

Q4 CGRP-targeted therapies represent one of the clearest examples of translational neuroscience succeeding in medicine. Do you worry that increasingly restrictive treatment pathways risk delaying biologically appropriate therapy until migraine has already become entrenched?

In an ideal world, you'd give every person in front of you the treatment that's ideal for them. But we don't actually know what's ideal for everyone sitting in front of us. Are there people who would

be better off getting onto these newer medicines earlier? Sure. Is that practical from a cost point of view? No.

Do I look at the long game? Yes. If I look at the gepant tablets, they'll eventually come off patent, and someone will make a cheap generic version. Triptans were like that 25 years ago. Back then, doctors would tell patients that triptans were expensive, whereas now no one says that anymore because they've all gone generic.

So, in the short term, yes, cost restrictions are a downside, but in the medium term, I accept the consequences of medicines being expensive initially, because I think it facilitates the development process. Ultimately, with tablets, you leave something behind. Look at propranolol; there was a time when propranolol was expensive. Now, it's generic, cheap as pennies and widely useful.

The fact that the WHO now lists sumatriptan as an essential medicine for every country because it's become cheap enough is remarkable. If you'd said something like that 30 years ago, people would not have believed, "These medicines are too expensive," and so on. Thirty years later, the money that was sloshing around, so to speak, has left a legacy: a cheap, effective medicine such as sumatriptan that WHO believes the developing world should be able to use. That really is a legacy, one generation leaving something behind for the next.

I think the same thing will happen with gepants and the tablet medicines that follow. So yes, currently it's a downside, but in the longer term, if we keep developing new medicines, you only have to come up with something really spectacular for a

quarter of people every 20 years. In 100 years, you've more or less got the problem figured out. That's actually not too bad.

In the history of humanity, migraine is a very old problem; descriptions go back to around 4,000 BC. So, to think that we might get most of it sorted within 100 years is pretty good going.

Just out of interest, how do we know migraine was being described in 2,000 BC?

There are hieroglyphic depictions of people holding or applying things to their heads, which some people interpret as representations of headache disorders. More interestingly, there are translations of medical writings from Mesopotamia dating back 3000 years.

When you read those texts, you can clearly see themes that resemble migraine. If someone is described as having pain or discomfort in the head, avoiding light, and vomiting, particularly if the patient is a woman, there's a good chance they're describing migraine.

Scholars who study those ancient languages have pulled together these descriptions and published them in collections and books, and when you go through them, you can recognise clinical patterns that are remarkably familiar today.

Q5 Aura remains one of the most neurologically intriguing phenomena in medicine. What aspect of aura physiology do you think is still most poorly understood?

I think how it starts is still poorly understood. I can trigger an aura in the laboratory by poking a needle into the brain during recordings, but clearly that's not

what's happening in people in real-world situations. So how does it happen *de novo*?

To understand the beginning of something is to understand how to stop it. We understand quite a lot about the process itself, but I don't think we yet understand what triggers it at the very outset, and that seems to me crucial if we're going to understand how to prevent it.

Do you have any theories?

I think the predisposition is there all the time, but it's normally being suppressed, and the suppression systems are cycling up and down. I suspect it's more than one suppression system.

Let's say you have the inherited tendency. The reason I say that is because we've seen, with functional imaging, that you can trigger an attack of migraine experimentally. If you look at people with the inherited tendency who are triggered into a migraine without aura, and then specifically look at those who have a history of aura, they don't necessarily develop aura during the experiment. But if you look at the blood flow in that group after giving them, say, a nitroglycerin trigger, you can detect reduced occipital cortex blood flow. It's not at a level that's producing symptoms, but you can measure it.

I think there's a biological signature there all the time. They always have the biology, or at least the predisposition, and then something pushes the system past a threshold that kicks the process off. I suspect that threshold is controlled by multiple systems in the brain, because most things in the brain have redundancy built into them.

My guess is that there are several cycling regulatory signals, perhaps five different systems, and they all have to reach their nadir at roughly the same time. That alignment may take time, and it's probably influenced by other circumstances as well. So, I think it's a combination of having the predisposition and then developing synchronous dysfunction in the systems that normally keep the biology in check.

Now, whether that synchronisation is random or whether something actively causes it, I don't know. At the moment, it's essentially an untestable hypothesis.

Q6 Do you think migraine with aura and migraine without aura are fundamentally the same disorder expressed differently, or biologically distinct entities that we continue to group together for clinical convenience?

I think it depends on how high up you want to look at it from. You know, everyone on Earth looks the same if you're far enough away. When I look at migraine with and without aura, it still strikes me as migraine. I think aura is a particular physiology that can be involved in migraine, but I'm not sure that aura is quintessentially what migraine is about. I probably have a slightly disruptive view about that.

I think migraine is fundamentally a disorder of sensory modulation, a problem with controlling incoming information, a heightened sensitivity to sensory input: photophobia, allodynia, vertigo, and so forth. Aura seems a little separate from that process because, as we currently understand it, the best model for aura is cortical spreading depression, or cortical spreading depolarisation, and that is

not fundamentally a sensory dysmodulatory process, although the disinhibitory aspects would also explain aura.

So, are they fundamentally the same? I think people with migraines probably do share the same underlying problem. I don't think the biology of aura itself is fundamentally the same, although its facilitation may be. Both seem to involve a failure to properly contain abnormal activity, if I can put it that way.

The nervous system really likes to keep things in check. The body is like that generally, all physiology is. If your heart rate goes up because of sympathetic activation, the vagus nerve tries to bring it back down again. That's homeostasis. The drive toward homeostasis is very strong and very well developed in humans.

I suspect that, at its core, migraine involves dysfunction of systems that would otherwise maintain homeostatic control. That's the fundamental thing that migraine with aura and migraine without aura share. So, in the bigger picture, I would definitely be more of a lumpier than a splitter when it comes to migraine with aura versus migraine without aura.

Certainly, from a preventive standpoint, both forms seem to respond to the same preventive treatments. I don't think we've really answered whether that's equally true for acute treatments. We certainly haven't addressed it fully with the gepants because we don't yet have an injectable formulation to study that question properly. The jury is still a little bit out there, but, overall, my answer would be yes.

Q7 Research has shown that frequent use of codeine-containing medicines for migraine can contribute to medication-overuse headache and dependence risk. Why do opioid-containing agents such as codeine remain so entrenched in migraine care despite the evidence against them?

The dependence risk is fundamentally an opioid issue. Whether you have migraine or not, if you repeatedly expose someone to opioids, there's a risk of dependence. Medication-overuse headache is a different and more interesting phenomenon, because it can be produced by triptans, which don't have abuse or dependence potential, and it can also be produced by opioids like codeine, which do have dependence potential. So, I don't think dependence itself is the key issue in medication-overuse headache because they're actually quite distinct phenomena.

One of the things the medicines associated with medication-overuse headache have in common is that their receptors are found in brainstem sensory-modulating regions. For example, in the periaqueductal gray you'll find both triptan receptors and opioid receptors.

Another common feature is that these medicines are all agonists; they activate the receptor. So, you can imagine repeated activation continually driving those systems. By contrast, antagonists such as the CGRP blockers prevent activation but don't themselves turn the receptor on. If you repeatedly activate a system, you're going to induce downstream changes in second messenger pathways and broader network function. I think that, at some level, is probably the biological basis of what's going on.

So why do opioids remain entrenched in migraine care? Partly because they're old, familiar drugs that people are used to using for pain. If you think migraine is fundamentally just a head pain problem, then the logic becomes: first use paracetamol, then a non-steroidal anti-inflammatory, and, if that doesn't work, scale up to codeine. There's a familiarity factor, but also a tendency to lump migraine together with other pain conditions, which I think is a mistake because migraine is certainly much more than just pain. Then, there's the safety. People really don't die taking 30 or 60 mgs of codeine, and you don't necessarily need a sophisticated diagnosis to prescribe it; you can simply say "head pain."

Q8 Finally, what are the most important translational gaps that remain in migraine medicine today, and which of your current research directions are aimed at closing them?

One of the things we're quite interested in at the moment is understanding vertigo in migraine, and particularly this condition called vestibular migraine, where vertigo is a prominent component. We want to understand why about half the people we see have some degree of vertigo associated with their attacks.

Very often, vertigo is not the main feature, but for people with vestibular migraine, it's a really big deal. In the same way, for some people with migraine, light sensitivity is a big deal, and they come to the clinic wearing sunglasses. But for others, light is not such a major issue. We don't really understand why.

At the moment, we're particularly interested in understanding how vertigo and migraine fit together, how they affect each other, and how best to treat that aspect of the disorder. Very little systematic work has been done to look at that physiology, and that's one of the translational gaps we're trying to address.

