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Endogenous Pathways in Migraine Care: Harnessing the Body's Natural Systems

Announcer:
You're listening to *On the Frontlines of Migraine* on ReachMD. Here's your host, Ashley Baker.

Ashley Baker:
Welcome to *On the Frontlines of Migraine* on ReachMD. I'm Ashley Baker, and joining me to discuss endogenous treatments for migraine pain is Dr. Adriana Della Pietra. She's a Postdoctoral Research Scholar in the Department of Molecular Physiology and Biophysics at the University of Iowa Carver College of Medicine.

Dr. Della Pietra, we're so glad to have you here today.

Dr. Della Pietra:
Thank you, Ashley. Thanks for inviting me. It's a pleasure to be here.

Ashley Baker:
Let's start with a broader perspective, Dr. Della Pietra. What do we mean when we talk about endogenous treatments in the context of migraine care?

Dr. Della Pietra:
When we talk about endogenous treatments, we mean therapies that mean to amplify the built-in systems of our own body in order to achieve treatment of migraine, or headache more in general. For instance, increasing natural levels of neuromodulators or strengthening inhibitory brain circuits, rather than introducing a compound which is external—so an exogenous compound—that might trigger a specific target very well, but might not work for everyone. So don't get me wrong. Exogenous compounds can be great. We have, recently introduced in the market, the CGRP monoclonal antibodies. It's been a few years now. And they work great for a lot of migraine patients, although there is still roughly 50 percent of the patients that remain untreated, so we do have to find a solution for those patients as well. And for those patients, it might work to exploit some natural mechanism that counteracts their pain and enhances it. And, in this case, it might be more successful than introducing a specific exogenous compound. So, in general, we could harness inhibitory pathways that are already ongoing to counteract pain or modulate the endocannabinoid system or hypothalamic circadian rhythm to improve migraine in these patients. So, overall, there are several endogenous-based strategies that aim just to amplify whatever is already built in the patient's body in order to counteract the migraine pain they're having.

Ashley Baker:
With that in mind, what role does the endocannabinoid system play in regulating migraine pain? And how can we enhance this system therapeutically?

Dr. Della Pietra:
So the endocannabinoid system I like call our personal, natural, safe cannabis that is there for our body to exploit. So it's produced in all of our body, in our brain, and in our peripheral nervous system, so it's everywhere, and it's naturally a descending controlling system that counteracts pain in our body among other things. So if we could harness the potential of the endocannabinoid system, we could have basically a natural painkiller that works very similarly to cannabis but without the side effects, because it already acts naturally in our body.

Therapeutically, there are certainly different ways to raise endocannabinoid levels or to maintain the levels of endocannabinoids pretty high, because what happens usually in our body is that we do produce endocannabinoids to counteract pain—but this is usually not

enough, because the pain associated with migraine is huge, and endocannabinoid's tone is not enough to fight it. So what we can do is to use the compounds that help and enhance the action of the endocannabinoid system. One strategy that has been tested recently is to inhibit the degrading enzymes of the endocannabinoids. In this way, the endocannabinoids do not get destroyed, and their tone can be maintained higher for a longer time. So in this way, the migraine pain should be reduced or disappear.

Now, the thing is that most of these compounds were shown promising in preclinical studies—so we are talking about mice and rat studies—and administering these compounds did reduce some migraine symptoms, like allodynia, and it did reduce also trigeminal hyperalgia. But none of these compounds still made it to clinical trials. We're also now currently testing in our laboratory a compound, AKU-005, which is a multiple inhibitor of these degrading enzymes. And we are also testing it preclinically on a CGRP migraine model, and we hope that being this is the second step—because it was very successful on cell and tissues, and now we are at the animal stage—we hope that if this works will progress to clinical trials. But research needs time always.

Ashley Baker:
And outside of the endocannabinoid system, what are some other promising endogenous mechanisms or targets currently under study for migraine relief?

Dr. Della Pietra:
A great source for that, I think, is the collection we put together with Professor Andrew Russo in *The Journal of Headache and Pain*. We tried and collected all the ongoing research on the endogenous systems that we can exploit in order to get treatment for migraine and for other headache-related diseases. And there are actually many ongoing researches that are based on targeting delta opioid receptors or enhancing GABAergic inhibitory pathways. Another study looked at the potential of pregnenolone sulfate, another compound, in order to reduce neuronal excitability that causes pain, CSD, and many events during migraine.

And another proposed mechanism is the circadian rhythm regulation, because migraine is a disease that is linked to sleep quality and a correct sleep cycle, and also, dividing very well your day in day and night. And the circadian rhythm is impaired in many of these patients, and there is the thought that this might be related to certain genes that peak or are below expression in a certain specific time of the day. So, this is also regulating the circadian rhythm with future pharmaceutical interventions that could produce a benefit for these patients.

And finally, also, some patients do have a genetic component that determines the migraine, so another proposal is to look for biomarkers and eventually develop some gene-targeted therapies.

Ashley Baker:
For those just tuning in, you're listening to *On the Frontlines of Migraine* on ReachMD. I'm Ashley Baker, and I'm speaking with Dr. Adriana Della Pietra about the role of endogenous pain regulation in migraine care.

So, Dr. Della Pietra, we often hear about lifestyle factors like sleep, stress and exercise in migraine management. What's the biological rationale behind their impact on endogenous pain control?

Dr. Della Pietra:
The lifestyle is known to be an important factor in determining migraine pathophysiology, severity, and migraine attack frequency, and it kind of connects with many of the endogenous systems that I just talked about. For example, sleep and circadian rhythm are connected to each other, and they can control the hypothalamic circuits and serotoninergic tones. And also, one hot topic that is coming out recently is the glymphatic clearance, so the system that is believed to clear out your brain from the accumulation of noxious molecules, among others in the brain, and that glymphatic clearance works very well when you sleep. So of course, if you sleep better, and with high quality, then it's believed that your glymphatic clearance is enhanced, and so you don't have accumulation of noxious molecules, pro-inflammatory molecules, and you will be made, maybe, less likely to develop headache attacks than later on.

Also, stress and exercise can alter the endocannabinoid system, so there is also a molecular component in that. And they can worsen migraine symptoms and migraine attack frequency. So when we talk about lifestyle components, it's important to know that they are not just behavioral advice, but they do have a real, therapeutic power. In most of patients, alone, they do not solve the problem. They're not magic, but if you have a good lifestyle combined with a therapy, the power of the therapy might increase a lot, and that's why it's important to, in migraine patients, have sleep quality, stress management, and to exercise in the right way. So you don't want to exercise too much. Then you are too stressed about it. So there is a right balance of your body that you have to maintain, and this helps the pharmaceutical treatment. It's not the cure, but it helps.

Ashley Baker:
Now, from your perspective, which patients might benefit most from an endogenous first or integrative approach to migraine treatment?

Dr. Della Pietra:
This is a new avenue of research, so it's difficult to say, even if patients will for sure benefit from these treatments. But I would say the patients that nowadays remain untreated. So we have this 50 percent, roughly, of patients that have no treatment working for them right now. So as soon as something new is out, including this endogenous treatment, why not try that on these patients? And I'm afraid, though, that for this treatment based on endogenous mechanisms, we still have to wait many years of research before they reach commercialization or even clinical trials. There are some endogenous mechanisms that can be exploited, like the lifestyle-related ones and the so-called chronotherapy, which is linked to the circadian rhythm research. So it's believed that even the drugs already available in some patients, given at a certain time of the day rather than another, might be more effective, because maybe their target is more present in that specific time of the day. So giving a CGRP monoclonal antibody in the morning rather than in the evening or vice versa in some patients could help. Not necessarily, but it could because maybe they have a peak of CGRP at a certain time of the day. So shifting the time is something that can be done even immediately by practitioners. For the other mechanisms, we might have to wait a few years still.

Ashley Baker:
Before we wrap up our program, Dr. Della Pietra, do you have any final thoughts you'd like to leave with our audience?

Dr. Della Pietra:
Yes. I would just like to specify that these endogenous approaches will not replace the drugs that already exist, but will be a new addition to expand our toolbox for treating the patients. And we need, for sure, to continue research, and that continuing to work and fund and advocate for research that goes from cell culture to clinical trial is key in the end to reach a treatment for the patient. And, of course, I would advise, while the untreated patients wait for these new treatments to come out, to use whatever they have available and to look at the lifestyle and talk to their practitioners about that. But we are working on it, and we will do what we can to speed up research and get to good treatments for the missing patients.

Ashley Baker:
With those key takeaways in mind, I want to thank my guest, Dr. Adriana Della Pietra, for joining me to discuss how we can improve migraine management through endogenous treatments.

Dr. Della Pietra, it was great having you on the program.

Dr. Della Pietra:
Thank you so much for having me here.

Announcer:
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