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The Role of CGRP in Migraine Pathophysiology

Announcer:
Welcome to ReachMD. This medical industry feature, titled “The Role of CGRP in Migraine Pathophysiology” is sponsored by Amgen.

Here’s your host, Dr. Jerome Lisk.

Dr. Lisk:
With migraine as a major global health problem that affects over 10% of the population, approximately 1 billion globally, and about 12% in the US, now more than ever it’s vital that healthcare professionals have a deep understanding of its pathophysiology.[1,2] Data has highlighted the role of calcitonin gene-related peptide, or CGRP for short, and its receptor as a component of migraine pathophysiology.[3] So today we’re going to review the role of CGRP in migraine pathophysiology and how approaches to targeting CGRP signaling impact our ability to treat migraine.

Dr. Lisk:
This is ReachMD, and I’m Dr. Jerome Lisk. Here with me today is Dr. Merle Lea Diamond, an emergency and internal medicine physician at Diamond Headache Clinic in Chicago, Illinois.

Dr. Diamond, welcome to the program.

Dr. Diamond:
Thank you so much. I’m so happy to be here!

Dr. Lisk:
Okay, to start off Dr. Diamond, would you please describe migraine as you currently understand it?

Dr. Diamond:
Yes, absolutely, and that’s a great place to start. Recent insights into migraine pathophysiology have contributed to our evolving understanding of this disease. Migraine used to be thought of as an idiopathic vascular disease.[4] However, we now know that migraine is a complex neurological disease that is impacted by a wide range of factors, including genetics, the environment, anatomical, metabolism, hormones, and even medications.[5] Neurologically speaking, activation of a number of different pathways brings about the underlying symptoms of migraine, including both the pain and non-pain symptoms associated with migraine disease.[5] Overall, we now understand that migraine manifests with altered brain connectivity and is also associated with structural and functional changes in the brain.[5]

So to sum it up, a wide range of factors and mechanisms are involved in migraine, and altered brain signaling and functioning in migraine patients lead to the activation of various pathways in response to a trigger, which can then lead to the release of neuropeptides, and ultimately, migraine symptoms.[5]

Dr. Lisk
So now let’s talk about calcitonin gene-related peptide, or CGRP. How is it associated with migraine?

Dr. Diamond:
Well, before we talk about the role of CGRP in migraine, we need to discuss the distinct brain regions and neuropeptide pathways that have been implicated in the underlying pathophysiology of both the pain and non-pain symptoms of migraine. Migraine attacks are associated with pain and non-pain symptoms, such as light and sound sensitivity, cognitive dysfunction, nausea, food cravings,

irritability, fatigue, neck discomfort, as well as intense head pain.[6] One region implicated with leading to these symptoms is the trigeminovascular system, which relays pain signals to the brain. CGRP was found to be the most abundant neuropeptide in the trigeminal nerve; in fact, it's expressed in 35 to 50 percent of neurons in the trigeminal ganglia.[4] In addition, there are three lines of clinical evidence that led to the realization that CGRP may play a causal role in migraine. First, the infusion of CGRP can induce migraine-like attacks in patients with a history of migraine.[3] Second, clinicians uncovered that plasma CGRP levels significantly increase during natural migraine attacks[7], and third, that CGRP levels return to normal when a patient's migraine attack was treated with a triptan, which is a migraine-specific medication.[8]

Dr. Lisk:
So let's dig deeper into that, Dr. Diamond. What exactly is CGRP, and what does it normally do in the body?

Dr. Diamond:
So CGRP is a 37-amino acid neuropeptide that's produced in central and peripheral neurons.[9] It's a member of the calcitonin family of peptides, which includes CGRP, amylin, adrenomedullin, and calcitonin.[10] The calcitonin family of peptides bind to certain transmembrane receptors referred to as the calcitonin family of receptors.[11] Of these receptors, only the CGRP receptor has been implicated in migraine pathophysiology.[11] The role of the other calcitonin receptors in migraine is currently unclear.[11] While CGRP binds with CGRP receptor with the highest affinity, in vitro data suggest that CGRP also has a high affinity for the AMY-1 receptor, a different receptor in the calcitonin family.[10,11] However, the physiological function of the AMY-1 receptor in migraine is not well understood.[11] CGRP signaling in the trigeminovascular region regulates neuron sensitization and neuropeptide release, which are key events that underlie migraine pathophysiology and are targeted by anti-migraine therapies.[9,12,13]

Looking specifically at what happens when CGRP binds the CGRP receptor, a signal is sent into the cell to release other molecules that mediate downstream effects, such as vasodilation, and depending on where that occurs, neurogenic inflammation[14], nociceptive activation, central sensory activation, central sensitization[15], cortical spreading depression[4], hypothalamic dysfunction[16], and descending control of brainstem functions may then occur[16], all of which are associated with migraine.

Dr. Lisk:
So, for those just tuning in, you're listening to ReachMD. I'm Dr. Jerome Lisk, and here with me is Dr. Merle Lea Diamond to talk about the role of calcitonin gene-related peptide, or CGRP for short, and the CGRP receptor in the pathophysiology of migraine.

So Dr. Diamond, it seems that CGRP can have many effects in the trigeminalvascular system, depending on where exactly its receptor is expressed. How does CGRP receptor expression--and CGRP expression and distribution itself--affect migraine and its treatment?

Dr. Diamond:
That's exactly right. Both CGRP and its receptor are expressed in the central and peripheral nervous systems. Antibody therapies are large proteins that do not readily cross the blood-brain barrier.[9,16] The fact that antibody therapies have been able to target CGRP signaling suggests a peripheral site of CGRP activation in migraine, and/or the possibility that the role of CGRP in migraine is mediated through parts of the brain that lie outside the blood-brain barrier. Trigeminal CGRP and its roles in vasodilation, neurogenic inflammation, and peripheral sensitization are likely the most relevant peripheral actions of CGRP in migraine.[4] Within the trigeminalvascular system, the CGRP receptor is localized in many discrete regions and is expressed on vascular smooth muscle cells, neurons, glial cells, and mast cells.[14,17] With all that being said, the wide distribution pattern of CGRP and its receptor complex could be acting as a neuromodulator of migraine symptoms.[4]

Dr. Lisk:
So Dr. Diamond, now that we have a better understanding of both how CGRP and its receptor play a role in migraine, how do CGRP-targeting therapies work? And what is the ultimate goal here?

Dr. Diamond:
So before I explain how these therapies work, let me answer your second question first. The ultimate goal is to reduce CGRP and the CGRP receptor complex from initiating the intracellular signaling cascade that will result in a migraine and its associated symptoms. Now with that end goal in mind, let's talk about how we get there. CGRP signaling-targeted therapies can help reduce the interaction between CGRP and its receptor, thus reducing the downstream signaling.[9] To date, two modalities of treatments targeting the CGRP pathway have been developed: monoclonal antibodies and small molecules.[9]

Dr. Lisk:

And as we're coming to the end of our program, Dr. Diamond, final thoughts and key takeaways you would like to share with our listeners?

Dr. Diamond:
Ultimately, there are two main takeaways here. The first is that CGRP plays a role in many key events that underlie migraine pathophysiology, making the CGRP pathway a clinically relevant therapeutic target in migraine prevention.[4] The second takeaway is that the goal of CGRP signaling-targeted therapies is to prevent CGRP and its receptor complex from initiating intracellular signaling that leads to migraine symptoms.[9]

Dr. Lisk:
Why I couldn't think of a better thought to leave our audience with, so I'd like to thank my guest, Dr. Diamond for giving us a better understanding of the role CGRP and its receptor play in migraine pathophysiology.

Dr. Diamond, it was great speaking with you today.

Dr. Diamond:
Thank you so much for having me on!

Announcer:
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USA-334-84582