The Role of Serotonergic and CGRP Pathways in Migraine with and without Aura

Isabella Foster*

Department of Neuroscience, University of Waikato, Hamilton, New Zealand

Opinion

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***For Correspondence:** Isabella Foster, Department of Neuroscience, University of Waikato, Hamilton, New Zealand **Email:** **isabella.foster@waikato.ac.nz**

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ABOUT THE STUDY

Migraine, a complex neurological disorder, affects millions globally and is characterized by recurring episodes of headache and associated symptoms such as nausea, photophobia and phonophobia. A subset of migraines includes an aura, defined as transient neurological symptoms preceding or accompanying the headache. Two critical pathways implicated in the pathophysiology of migraine serotonergic pathways and Calcitonin Gene-Related Peptide (CGRP) signaling play significant roles in both Migraine with Aura (MwA) and Migraine Without Aura (MwoA).

Serotonergic pathways in migraine

The serotonergic system has long been associated with migraine pathogenesis. Serotonin (5-hydroxytryptamine or 5-HT) modulates vascular tone and nociceptive signaling, both integral to migraine development. Migraine attacks are linked to fluctuations in serotonin levels; during an attack, serotonin concentrations decrease, which promotes vasodilation of cranial blood vessels and sensitization of trigeminal nociceptors.

In MwA, serotonergic dysregulation is particularly tied to Cortical Spreading Depression (CSD), a phenomenon marked by a wave of neuronal depolarization followed by inhibition. CSD is believed to trigger the visual and sensory disturbances characteristic of aura. Serotonin receptors, specifically 5-HT1B/1D, play a role in mitigating CSD by regulating neuronal activity and reducing cortical excitability. Triptans, 5-HT1B/1D receptor agonists, remain the cornerstone of acute migraine treatment, underscoring the importance of serotonergic pathways. These agents inhibit the release of vasoactive neuropeptides, induce vasoconstriction and reduce central pain transmission. However, their efficacy is similar in both MwA and MwoA, suggesting that serotonergic modulation is equally relevant across subtypes.

CGRP pathways in migraine

The Calcitonin Gene-Related Peptide (CGRP) is a neuropeptide extensively studied in migraine pathophysiology. CGRP is released from trigeminal nerve terminals during a migraine attack and contributes to vasodilation, neurogenic inflammation and central sensitization. Elevated CGRP levels are observed in migraine patients during attacks, with normalization following symptom resolution.

In MwA, CGRP release may be secondary to CSD, as CSD activates the trigeminovascular system and promotes the release of vasoactive neuropeptides, including CGRP. The interaction between CSD and CGRP release highlights the layered complexity of MwA.

In MwoA, CGRP's role is predominantly in the activation and sensitization of the trigeminovascular system, independent of cortical phenomena. This distinction underscores the more direct contribution of CGRP to headache generation in MwoA.

The advent of CGRP-targeted therapies, such as monoclonal antibodies and CGRP receptor antagonists (gepants), has revolutionized migraine treatment. These agents are effective in both MwA and MwoA, supporting CGRP's central role in the migraine spectrum. Interestingly, CGRP-targeted therapies are particularly useful in chronic migraine and in patients unresponsive to triptans, expanding treatment options for refractory cases.

Commonalities and interactions

While serotonergic and CGRP pathways are distinct, they interact within the broader migraine pathophysiology. For instance, serotonin regulates CGRP release via 5-HT receptors, linking the two pathways. Additionally, both systems contribute to the activation and sensitization of the trigeminovascular complex, a fundamental process in all migraine subtypes.

Genetic studies also reveal overlap, with variations in genes affecting both serotonin receptors and CGRP signaling implicated in migraine susceptibility. These findings suggest that despite clinical differences between MwA and MwoA, the underlying mechanisms are interconnected, offering insights into unified therapeutic strategies.

CONCLUSION

The serotonergic and CGRP pathways play pivotal roles in the pathophysiology of migraine with and without aura. Serotonin dysregulation influences both cortical excitability in MwA and trigeminovascular sensitivity in MwoA, while CGRP signaling drives vasodilation and neurogenic inflammation across subtypes. Despite differences in their mechanisms, the two pathways converge in activating the trigeminovascular system, highlighting their interconnectedness. Advances in understanding these pathways have led to targeted therapies like triptans and CGRP antagonists, offering effective treatment options for both subtypes. Continued research into these mechanisms will further refine migraine management, ensuring personalized care for patients regardless of aura status.