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Unanswered questions in headache: How does a migraine attack stop?

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Abstract

Much research in migraine focuses on understanding its initiation. But as migraine is typically self-limited, its offset may be as important as its onset. We pose the question “how does migraine stop?” to three investigators with different backgrounds. The consensus is that the termination of a migraine attack, rather than being the passive loss of a trigger, must itself be an active biological process.

The study of headache is still at an early stage, and many important questions remain unanswered. In this occasional feature, we pose unanswered questions to distinguished clinicians and scientists. Our goal is to focus on what we know from both the clinical and laboratory realms and initiate a dialogue that will lead to further insights. Our first question is ‘How does migraine stop?’ Our focus is on the neurobiology of the “natural” conclusion of a migraine attack, setting aside the clinical resolution that can be brought about by abortive drugs.

Our question is deceptively simple. One might think of the cessation of migraine as a passive decay process, in which a stimulus, or the response to it, fades with time. This may well be the case for certain elements of the migraine attack, like the ‘bruised’ feeling, responsive to anti-inflammatory drugs, which can persist for days after an attack. But for most patients the attack itself has a characteristic duration, and offset of pain is relatively abrupt, faster than expected from a simple decay. It is also not uncommon that certain events, such as emesis or sleep, appear to completely abort migraine. All of these features imply active regulation, rather than a passive process.

Given our knowledge of sensory and autonomic function, active rather than passive termination of migraine should not be surprising: feed forward and feed back loops are obligatory components of any sensor-effector system. And migraine, as a disorder of sensation and pain, must function on an underlying circuit anatomy. Dr. Luis Villanueva makes this clear in his contribution. He emphasizes that the structures involved in migraine are part of conserved feedback loops that are designed to modulate sensory inputs. Indeed his group has identified neurons in somatosensory and insular cortex that directly feed back onto afferents in the trigeminal nucleus caudalis and thalamus. They have also shown that spreading depression in the cortex can modulate the activity of these afferent nuclei¹. This circuitry, along with nested autonomic loops in the brainstem, should be capable of both generating and terminating headaches, and Dr. Villanueva leaves us with this lesson.

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Disclosures

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We are very pleased to receive an original contribution from Dr. Timothy Houle and colleagues. Dr. Houle studies and models migraine triggers in an attempt to predict attacks. His group designed their study to test how stress behaves as a migraine trigger. Here they have turned their data around on itself asked whether high stress predicted cessation of attacks. They found that while high stress was strongly associated with the likelihood of attack initiation, its association with attack termination, though positive, did not reach statistical significance. At first glance it is surprising that there was any positive association of stress with migraine termination. But the finding may not be as counterintuitive as it seems: patients vary in their response to stress, some responding to increases and some to decreases. Those who have migraine during release from stress might be expected to have an association between attack termination and increased stress. It might be informative to classify patients based on their stress response to prove or disprove this hypothesis. It would also be very interesting to apply Dr. Houle's methodology to other physiologic events thought to be attack triggers and terminators.

While many triggers are reported for migraine initiation, we are aware of only a very few 'triggers of termination.' Dr. Robert Shapiro highlights the termination triggers for us, and poses hypotheses as to their possible anatomy and physiology. The most common terminator is sleep. The most striking (because the effects can be almost instantaneous) is emesis. Both sleep and emesis are highly conserved, highly regulated, brainstem-dominated autonomic responses. Dr. Shapiro outlines the structures that might be involved in both sleep and emesis-mediated migraine cessation: periaqueductal gray, dorsal raphe, locus ceruleus, and area postrema, among others. He echoes the point of Dr. Villanueva that the termination process is likely active not passive, especially considering how regulated sleep and emesis are as biological processes². A practical hurdle is that it is difficult to dissect brainstem autonomic function. There is considerable redundancy in these mission-critical networks, making it hard to isolate cause from effect. However there are many new tools in the neuroscientific toolbox, including genetic and optogenetic techniques, which offer hope that these circuits may reveal their secrets.

In summary, migraine termination is likely an active process; it is likely mediated by conserved sensory-autonomic pathways that are experimentally testable; and it does not appear to be related to the events that trigger the attack. We thank our contributors for their insights, and welcome further discussion online and in the journal.

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