Published in final edited form as:

Headache. 2012 May ; 52(Suppl 1): 12–14. doi:10.1111/j.1526-4610.2012.02136.x.

The neurobiology of throbbing pain in migraine

Andrew H. Ahn, MD PhD

Abstract

Virtually everyone can recall an experience, migraine or not, in which pain had a throbbing, pulsatile quality, particularly in association with intense pain. Its pulsatile character strongly reinforces the common presumption that it coincides with the heart beat. For migraine, a cerebral vascular origin of the throbbing quality is a central tenet of the prevailing scientific view of migraine pain. However recent data challenge this perspective, with implications for our understanding of throbbing pain not only for migraine but also for the pathophysiology of throbbing pain in other conditions as well.

A throbbing pain quality is very relevant to migraine. Throbbing headache is prevalent in the general population¹, and associates with migraine in clinical practice², making this the single pain quality explicitly suggestive of the diagnosis of migraine³. More than just a diagnostic consideration, however, throbbing pain is clinically relevant in its association with the highest levels of severity, frequency, and disability⁴. Although allodynia is a well-recognized feature of the progression of the migraine attack as well as a predictor of the lack of response to currently available therapies⁵, the same data also shows that the throbbing quality also serves to predict treatment resistance. It also predicts progression of other comorbid conditions such as depression⁶.

Over the years, the throbbing quality of pain has come to be known as “vascular,” with the presumption that throbbing percepts arise from the mechanical activation of localized pain-sensory neurons by the dilation of closely apposed blood vessels. In addition, the prevalence of throbbing pain in other conditions that implicate a vascular connection, such as cerebral sinus thrombosis⁷, sickle cell crisis^{8,9}, giant cell arteritis¹⁰, and spontaneous cervical artery dissection¹¹ also abundantly support this point of view.

Accordingly, early studies of migraine emphasize the role of vasodilation as a mechanism of pain, being the focus of the so-called vascular theory, which hypothesized that a primary vasodilation of the cranial blood vessels was the cause of migraine pain¹². This observation has since been repeated with ever-greater technical precision, most recently with high field MRI imaging technology¹³. However, perhaps even beyond the uncertain fate of the vascular theory itself¹⁴ arterial pulsations underlying the percepts of throbbing pain still remains the axiomatic starting point for the present view that a trigeminovascular afferent unit, and a brain, are required for a migraine attack¹⁵.

However, few studies have directly examined the relationship between vascular pulsations and the subjects' perception of throbbing. For example, Blau and Dexter observed that digital compression of the superior temporal artery can substantially relieve migraine pain¹⁶, but it is difficult to interpret in physiological terms the significance of this maneuver in

Contact: The University of Florida College of Medicine, Department of Neurobiology, 100 South Newell Dr., Gainesville FL 32610, ahn@neurology.ufl.edu.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest related to this manuscript.

terms of vascular dilation or sensory nerve activation, as compression of the carotid artery can also aggravate pain¹⁷. Another indirect, anatomical argument for vascular percepts is that dural arteries, which are constrained within inelastic structures such as the skull and dura, transmit increased vascular pressures to the associated perivascular afferents¹⁸. Although increases in intracranial pressure would make it more likely to trigger or accentuate throbbing pain¹⁹, even low intracranial pressure can in some circumstances accentuate throbbing pain²⁰.

In physiological terms, the traditional view predicts that normal arterial pulsations dilate the vessel lumen and mechanically activate closely associated pain-sensory neurons. However, experiments specifically designed to obtain electrophysiological evidence for this relationship have either been negative^{21, 22}, or show that the properties of stretch-activated afferents would be better suited to mediate autonomic reflexes related to blood pressure homeostasis^{23, 24}.

Another approach that we thought could be used to address this question, though with certain limitations, is to correlate the arterial pulsation events directly with the perceptual events, in real time. In a series of patients reporting throbbing migraine pain, it was of no difficulty to obtain a description of the throbbing rhythm of that pain²⁵. In the course of a usual clinical evaluation, the patient indicated the throbbing rhythm in real time by a series of hand taps on their lap or on a desktop. The result was that there was little correspondence between these events. Overall, the throbbing rate (62 bpm) was substantially slower than the heart rate (80 bpm), and there was no temporal correspondence between the two rhythms.

However, because the origin of migraine pain is still controversial²⁶, the ability to generalize to other painful conditions is uncertain. Our follow up study thus focused on throbbing percepts in dental pain, where the peripheral origin of the pain is indisputable²⁷. In this group, the overall throbbing rate was 44 bpm and the average heart rate was 73 bpm. In addition, by simultaneously recording the throbbing pain rhythm and the arterial pulse we were able to compare the spectral properties of their variability, which showed that the mechanisms underlying these two complex biological rhythms were distinct.

Within the broader context of pain in general, it is also important to note that throbbing pain is common in conditions involving isolated lesions of the central nervous system. In these conditions, such as post-stroke central pain²⁸ and multiple sclerosis²⁹ the pain is referred to an unrelated, usually contralateral body region, which is fully inconsistent with a vascular model, or of any other peripheral source for the throbbing percept. In addition, Isnard and colleagues recently reported a patient with sensory seizures manifested by throbbing pain, and whose clinical and electrographic abnormalities resolved with the ablation of a focal area of cortical dysplasia within the right posterior insula³⁰ in the absence of any appreciable vascular abnormality.

Especially through the use of modern imaging techniques³¹, many lines of evidence support the idea that our awareness of pain is widely distributed within the brain³², including areas such as the insula³³. Our studies lay a novel mechanistic framework for future studies aimed at determining the central representation of the throbbing percept, such as by using functional brain imaging techniques. These studies thus represent new opportunities to identify a novel “pacemaker” for the throbbing percept, and possibly in circuits that are important for our perception of the most salient and disabling aspects of pain, such as throbbing pain. The range of possible future interventions could include the search for a traditional approach, such as with medications, but also could include stereotactic transcranial magnetic stimulation (TMS), deep brain stimulation of targeted circuits, and gene therapy to modulate targeted brain circuits.

Acknowledgments

This work was supported in part by a grant from the NIH (NS066091).

REFERENCES

1. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache*. 1998; 38(7):497–506. [PubMed: 15613165]
2. Kelman L. Pain characteristics of the acute migraine attack. *Headache*. 2006; 46(6):942–953. [PubMed: 16732840]
3. IHS CS. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004; 24(Suppl 1):9–160. [PubMed: 14979299]
4. Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia*. 2011; 31(3):301–315. [PubMed: 20813784]
5. Burstein R, Cutrer MF, Yarnitsky D. The development of cutaneous allodynia during a migraine attack clinical evidence for the sequential recruitment of spinal and supraspinal nociceptive neurons in migraine. *Brain*. 2000; 123(Pt 8):1703–1709. [PubMed: 10908199]
6. Kolotlylo CJ, Broome ME. Predicting disability and quality of life in a community-based sample of women with migraine headache. *Pain Management Nursing*. 2000; 1(4):139–151. [PubMed: 11709867]
7. Wasay M, Kojan S, Dai AI, Bobustuc G, Sheikh Z. Headache in Cerebral Venous Thrombosis: incidence, pattern and location in 200 consecutive patients. *J Headache Pain*. 2010; 11(2):137–139. [PubMed: 20112042]
8. Ballas SK, Delengowski A. Pain measurement in hospitalized adults with sickle cell painful episodes. *Ann Clin Lab Sci*. 1993; 23(5):358–361. [PubMed: 7694538]
9. Witkop M, Lambing A, Kachalsky E, Divine G, Rushlow D, Dinnen J. Assessment of acute and persistent pain management in patients with haemophilia. *Haemophilia*. 2011; 17(4):612–619. [PubMed: 21323802]
10. Rozen TD. Brief sharp stabs of head pain and giant cell arteritis. *Headache*. 2010; 50(9):1516–1519. [PubMed: 20561065]
11. Arnold M, Cumurciuc R, Stapf C, Favrole P, Berthet K, Bousser MG. Pain as the only symptom of cervical artery dissection. *J Neurol Neurosurg Psychiatry*. 2006; 77(9):1021–1024. [PubMed: 16820416]
12. Graham JR, Wolff HG. Mechanism of migraine headache and action of ergotamine tartrate. *Arch Neurol Psychiatry*. 1938; 39:737–763.
13. Asghar MS, Hansen AE, Amin FM, van der Geest RJ, Koning P, Larsson HB, et al. Evidence for a vascular factor in migraine. *Ann Neurol*. 2011; 69(4):635–645. [PubMed: 21416486]
14. Goadsby PJ. The vascular theory of migraine--a great story wrecked by the facts. *Brain*. 2009; 132(Pt 1):6–7. [PubMed: 19098031]
15. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. *Lancet Neurol*. 2009; 8(7):679–690. [PubMed: 19539239]
16. Blau JN, Dexter SL. The site of pain origin during migraine attacks. *Cephalalgia*. 1981; 1(3):143–147. [PubMed: 7346182]
17. Raskin NH, Prusiner S. Carotidynia. *Neurology*. 1977; 27(1):43–46. [PubMed: 556819]
18. Shevel E, Spierings EH. Role of the extracranial arteries in migraine headache: a review. *Cranio*. 2004; 22(2):132–136. [PubMed: 15134413]
19. Chou CH, Fuh JL, Hu HH, Wu JC, Wang SJ. Throbbing pain is related to Queckenstedt's test effect in migraine patients. *Cephalalgia*. 2009; 29(3):373–378. [PubMed: 19055510]
20. Suh SI, Koh SB, Choi EJ, Kim BJ, Park MK, Park KW, et al. Intracranial hypotension induced by cervical spine chiropractic manipulation. *Spine*. 2005; 30(12):E340–E342. [PubMed: 15959358]
21. Strassman AM, Raymond SA, Burstein R. Sensitization of meningeal sensory neurons and the origin of headaches. *Nature*. 1996; 384(6609):560–564. [PubMed: 8955268]. This is a seminal

paper, but also contains an experiment in which increased vascular pressure did not produce an afferent signal.

22. Levy D, Burstein R, Strassman AM. Calcitonin gene-related peptide does not excite or sensitize meningeal nociceptors: implications for the pathophysiology of migraine. *Ann Neurol*. 2005; 58(5):698–705. [PubMed: 16240341] . This study directly addressed the question of whether vasodilation could activate nociceptors, and was negative.
23. Malliani A, Pagani M. Afferent sympathetic nerve fibres with aortic endings. *J Physiol*. 1976; 263(2):157–169. [PubMed: 1018230]
24. Goder R, Habler HJ, Janig W, Michaelis M. Receptive properties of afferent nerve fibres associated with the rat saphenous vein. *Neurosci Lett*. 1993; 164(1–2):175–178. [PubMed: 8152597]
25. Ahn AH. On the temporal relationship between throbbing migraine pain and arterial pulse. *Headache*. 2010; 50(9):1507–1510. [PubMed: 20976872] . The conclusion was that there was that the two rhythms are independent.
26. Strassman AM, Levy D. Response properties of dural nociceptors in relation to headache. *J Neurophysiol*. 2006; 95(3):1298–1306. [PubMed: 16492942] . This excellent review clearly spells out the need to determine the nature of the pain of migraine more precisely, and that vasodilation is still a controversial stimulus for a nociceptive signal
27. Mirza AF, Mo J, Holt JL, Kairalla JA, Heft MW, Ding M, Ahn AH. Is there a relationship between throbbing pain and arterial pulsations? *J. Neurosci*. 2012 in press.
28. Leijon G, Boivie J, Johansson I. Central post-stroke pain--neurological symptoms and pain characteristics. *Pain*. 1989; 36(1):13–25. [PubMed: 2919091]
29. Houtchens MK, Richert JR, Sami A, Rose JW. Open label gabapentin treatment for pain in multiple sclerosis. *Mult Scler*. 1997; 3(4):250–253. [PubMed: 9372509]
30. Isnard J, Magnin M, Jung J, Mauguiere F, Garcia-Larrea L. Does the insula tell our brain that we are in pain? *Pain*. 2011; 152(4):946–951. [PubMed: 21277680]
31. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain*. 2005; 9(4):463–484. [PubMed: 15979027]
32. Lee MC, Mouraux A, Iannetti GD. Characterizing the cortical activity through which pain emerges from nociception. *J Neurosci*. 2009; 29(24):7909–7916. [PubMed: 19535602]
33. Craig AD. How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci*. 2009; 10(1):59–70. [PubMed: 19096369]