Editorial

Cephalalgia
An International Journal of Headache

International Headache Society

Migraine and serotonin: The quest for the Holy Grail goes on

Cephalalgia
2014, Vol. 34(3) 163–164

DOI: 10.1177/0333102413506129
cep.sagepub.com

SAGE

Jean Schoenen

Serotonin has been thought to be pivotal in migraine pathogenesis since the early days of headache research. Sicuteri (1) and Lance (2) were pioneers in unraveling that serotonin metabolism was disturbed in migraine, and their findings were confirmed with refined methods by Ferrari and Bruyn (3). Those data pointed toward a cycling profile of 5-HT metabolism: a decreased disposition and enhanced metabolism leading to serotonergic receptor supersensitivity between attacks, contrasting with serotonin release and transiently decreased turnover during attacks. The major shortcomings of these early studies are that they chiefly explored systemic 5-HT metabolism in blood and urine and assumed that the same changes would occur in brain 5-HT metabolism. The development by Diksic and collaborators (4) of a method that measures trapping by the brain of the radio-labeled precursor of 5-HT synthesis, α-[^{11}C] methyl-L tryptophan (^{11}C-AMT), to evaluate central 5-HT synthesis was a major advance for pathogenic studies in migraine and other brain disorders. Surprisingly, since the development of this method 35 years ago, only three studies have been performed in migraine: one by Chugani et al. (5), and two by Sakai et al., including the one published in this issue of *Cephalalgia* on the effect of eletriptan on ^{11}C-AMT brain uptake (6). The results are only partly concordant, even in the studies coming from the same group.

In the article published in this issue, Sakai et al. (6) report that the PET-detected brain trapping of ^{11}C-AMT, expressed as the K complex (K*) and thought to reflect 5-HT synthesis capacity in the brain, is significantly decreased (−20%) 1 hour after 40 mg eletriptan p.o. in six female migraineurs studied interictally, whereas there is a mild non-significant increase in six healthy control participants. The eletriptan-induced decrease predominates in the upper dorsal brainstem, superior parietal, parahippocampal and occipital cortices. Sakai et al. (6) explain their findings by an increased sensitivity of 5-HT1A and 5-HT1B autoreceptors caused by a chronic interictal hyposerotonergic state. It is known that activation of these autoreceptors decreases 5-HT release and synthesis, and there is indirect evidence for interictal low, but ictally heightened, 5-HT neurotransmission in migraine (review in 7). The effects of eletriptan are in line with those published by the same authors (8) showing that sumatriptan injected during an attack produces a 33% reduction of ^{11}C-AMT uptake. The increase of the latter found after preventive treatment with beta-blockers in migraine patients (5) could be the counterpart, as beta-blockers are able to antagonize 5-HT1A receptors (see 5). That 5-HT receptors/transporter can be upregulated interictally in migraine was evidenced by two PET studies showing increased 5-HT1A receptor (9) and 5-HT transporter (10) availabilities in brain and brainstem, respectively. Nonetheless, to confirm that the eletriptan effect is caused by hypersensitivity of 5-HT1A/B autoreceptors, studies using specific receptor agonists/antagonists would be necessary.

Sakai et al. (6) found no significant difference in ^{11}C-AMT uptake between migraine patients interictally (K*: 5.7 µl/g/min) and healthy control participants (K*: 5.0). This is somewhat surprising as the same authors reported K*values previously of 4.71 in migraineurs between attacks (8) and 7.7 and 6.6 in healthy females and males (11), which would suggest reduced 5-HT synthesis in migraine and fit the authors' hypothesis of a low serotonergic state with receptor upregulation. The finding by Chugani et al. (5) that K* values were clearly greater in 11 migraine patients interictally (7.75) than in healthy control participants (5.46), is in line with the trend for a regionally more marked increase of 5-HT synthesis in migraine reported in this issue (6). Sakai et al. (6) explain the apparent paradox by similar proximal rate limiting mechanisms in migraine and in control subject participants but different distal feedback mechanisms including autoreceptor sensitization.

Headache Research Unit, University of Liège, Citadelle Hospital, Liege, Belgium

Corresponding author:
Jean Schoenen, Headache Research Unit, University of Liège, Department of Neurology, Citadelle Hospital, B-4000 Liege, Belgium.
Email: jschoenen@ulg.ac.be

One cannot exclude, however, other confounding factors related to methodological issues. A shortcoming of all three studies performed in migraine up to now is that none of them controlled for occurrence of an attack after the PET recording. It is known that both clinical premonitory symptoms and central nervous system changes may occur 24 hours or more before the migraine attack and that changes in serotonin metabolism and transmission are likely to follow the same temporal pattern (7). K* values could vary depending on whether they are (6,8) or are not (5) corrected for unlabeled free plasma tryptophan levels. Although ^{11}C-AMT uptake in brain areas is proportional to their 5-HT content, the major part of ^{11}C-AMT is not metabolized into α-methyl 5-HT. A large AMT pool remains unmetabolized or is diverted towards the kynurenin pathway (12). Under normal circumstances, the metabolites of this pathway are in a 1/100 to 1/1000 ratio over brain tryptophan, while the sum of 5-HT and its metabolite 5-HIAA are one-fifth of the brain's concentrations of tryptophan. However, after inflammation or ischemia, metabolites of the kynurenin pathway may markedly increase because of induction of their synthesizing enzymes (12). Whether this may also occur in migraine is not known.

Whatever the limitations of the ^{11}C-AMT PET method may be, it still remains the only way, although indirect, to evaluate in vivo serotonin metabolism in the human brain. Until better radio-labeled tracers and/or techniques become available, it seems worthwhile to explore further the role of 5-HT in migraine along the same path, paying greater attention to the migraine cycle, the effect of antimigraine drugs and the correlation with neurophysiological data and genetics.

Our masters did not wait for more extensive data on brain serotonin in their patients to jump ahead and develop novel drugs that interfered with serotonergic transmission and were effective in migraine prevention (13,14). Interestingly, methysergide, one of these drugs, remains one of the most effective prophylactic treatments in 2013. Unfortunately, 2013 may also be the last year of its commercial use, as the European Medicines Agency is planning to take methysergide off the market, although the complication of fibrosis does not occur if the guidelines for use are followed, that is 6 months of treatment alternating with 1 month of drug holiday, and the majority of my fellow migrainologists strongly support the drug.

References

1. Sicuteri F. Headache as possible expression of deficiency of brain 5-hydroxytryptamine (central denervation supersensitivity). *Headache* 1972; 12: 69–72.
2. Curran DA, Hinterberger H and Lance JW. Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxymandelic acid excretion in normal and migrainous subjects. *Brain* 1965; 88: 997–1010.
3. Ferrari MD, Odink J, Tapparelli C, et al. Serotonin metabolism in migraine. *Neurology* 1989; 39: 1239–1242.
4. Nishizawa S, Leyton M, Okasawa H, et al. Validation of a less invasive method for measurement of serotonin with alpha-[11C] methyl-tryptophan. *J Cereb Blood Flow Metab* 1998; 18: 1121–1129.
5. Chugani DC, Niimura K, Chaturvedi S, et al. Increased brain serotonin synthesis in migraine. *Neurology* 1999; 53: 1473–1479.
6. Sakai Y, Nishikawa M, Diksic M and Aubé M. α-[^{11}C] methyl-L tryptophan-PET as a surrogate for interictal cerebral serotonin synthesis in migraine without aura. *Cephalalgia* 2013 (this issue).
7. Coppola G and Schoenen J. Cortical excitability in chronic migraine. *Curr Pain Headache Rep* 2011; 16: 93–100.
8. Sakai Y, Dobson C, Diksic M, et al. Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis. *Neurology* 2008; 70: 431–439.
9. Lothe A, Merlet I, Demarquay G, et al. Interictal brain 5-HT1A receptors binding in migraine without aura: a 18F-MPPF-PET study. *Cephalalgia* 2008; 28: 1282–1291.
10. Schuh-Hofer S, Richter M, Geworski L, et al. Increased serotonin transporter availability in the brain stem of migraineurs. *J Neurol* 2007; 254: 789–796.
11. Sakai Y, Nishikawa M, Leyton M, et al. Cortical trapping of α-[11C]methyl-l-tryptophan, an index of serotonin synthesis, is lower in females than males. *Neuroimage* 2006; 33: 815–824.
12. Chugani DC and Musik O. Alpha[C-11]methyl-L-tryptophan PET maps brain serotonin synthesis and kynurenine pathway metabolism. *J Cereb Blood Flow Metab* 2000; 20: 2–9.
13. Sicuteri F. Prophylactic and therapeutic properties of 1-methyl-lysergic acid butanolamide in migraine. *Int Arch Allergy Appl Immunol* 1959; 15: 300–307.
14. Lance JW, Anthony M and Somerville B. Comparative trial of serotonin antagonists in the management of migraine. *Br Med J* 1970; 2(5705): 327–330.