REVIEW ARTICLE

The Mystique of Migraine Part IV: Is it the blood? — RJ Henbest

Prof RJ Henbest

MD, CCFP, MClSc (Fam Med)
The Dept of Family Medicine: Medunsa, PO Box 222, Medunsa, 0204

Curriculum vitae

Ronald J Henbest was born in Edmonton, Alberta (Canada) where he qualified in 1974 with a BSc in Maths and Psychology and in 1978 with an MD from the University of Alberta. He then completed two years postgraduate study (residency) in Family Medicine with the Department of Family Medicine at the University of Western Ontario (Canada) and obtained his CCFP from the College of Family Physicians of Canada. Ron joined the Department of Family Medicine at Medunsa in 1980. He has a particular interest in the doctor-patient interaction and its importance for healing. He returned to the University of Western Ontario in 1984 to take their Master of Clinical Science Degree in Family Medicine (MClSc), which emphasises patient care, teaching and learning, and research. His thesis on Patient-Centred Care involved the development of a method for measuring patient-centredness and testing it against patient outcomes. In 1989, Ron returned to his home city, Edmonton, for a period of 21 months where he was engaged as an associate professor in the Department of Family Medicine at the University of Alberta. During this time, he also completed further training in systemic family therapy. In October 1990, Ron returned, with his wife Judy and son Benji, this time as associate professor and deputy head of the Department of Family Medicine at Medunsa.

Summary:

This paper is the fourth in a series on migraine. The first concerned the nature and diagnosis of migraine. Subsequent papers addressed questions about its aetiology, beginning with, "Is it vascular?", followed by "Is it neurogenic?". This paper presents a humoral theory, describes the platelet abnormalities and disturbances in 5-hydroxytryptamine (5-HT, serotonin) levels that occur with migraine, reviews the anti-migraine drugs that interact with 5-HT receptors and considers the possibility of migraine being an endotheliopathy.

S Afr Fam Pract 1994;15:17-22

KEYWORDS:
Migraine; Etiology; Blood Platelets; Physicians, Family.

Introduction

The longstanding debate about the pathophysiology of migraine has primarily concerned itself with two main contenders: the vascular theory[1,2] and the neurogenic theory.[3] This paper concerns a third, less known contender that may link the two – namely the blood.

In the late 1950s and the 1960s, the vascular hypothesis had led to the study of the vasoactive agents known at that time – noradrenaline, 5-hydroxytryptamine (5-HT, serotonin), histamine, acetylcholine and bradykinin.[4] Methysergide was found to antagonise certain peripheral actions of 5-HT and consequently was introduced as the first drug capable of preventing or reducing the intensity and frequency of migraine attacks.[5] Shortly thereafter, 5-hydroxyindole acetic acid (5-HIAA), a major metabolite of 5-HT, was observed to be excreted in increased amounts in the urine.[6,7,8] These findings led to the hypothesis that serotonin played an important role in the pathogenesis of migraine.

Subsequent studies revealed that platelet levels of 5-HT fall consistently at the onset of headache, that migrainous episodes may be triggered by drugs releasing 5-HT, and that abnormal platelet behaviour occurs. This led some to conclude that migraine is a platelet disorder that should be included among the common disorders of the blood.[9,10]

However, the changes in circulating 5-HT levels were later thought to be pharmacologically unimportant [11] and interest in the humoral role of 5-HT in migraine declined.

Today, there is renewed interest, in large part due to the introduction of a new serotonin agonist, sumatriptan, for the treatment of migraine.[12]

Humoral Theory

The humoral theory of migraine was that 5-HT was released from platelets at the onset of a migraine attack and acted directly to constrict small intracranial arterioles and large extracranial arteries. Adsorption of 5-HT was thought to sensitise vessel walls to painful distention thought to occur as a result of a lessening of the

... The Mystique of Migraine: Part 4

constrictor effect once the plasma 5-HT levels subsided.

Platelet Abnormalities

Fascinating changes take place in the blood during migraine attacks. The platelets change shape and degranulate. Platelets contain alpha and dense granules. The alpha granules contain Beta Thromboglobulin (BTG) and platelet factor 4 (PF4). The dense granules contain 5-HT, nucleotides, and calcium.

In 1981, Hanington et al[10] published the results of two studies conducted to test the hypothesis that migraine is caused by a primary abnormality of platelet behaviour. The first study demonstrated that platelets taken from patients with classical migraine during a headache-free period showed significantly greater spontaneous aggregation and adhesion than platelets from controls. Increased circulating platelet aggregates were hypothesised to be

Platelets from migraine differ significantly in their behaviour from normal platelets – could this explain the onset of migraine?

responsible for the prodromal symptoms of migraine. The second study demonstrated that 5-HT release within three days of a migraine attack was significantly less than that measured during a migraine-free interval, corresponding to the commonly observed clinical refractory period between attacks of migraine. They concluded that platelets from migraine patients differ significantly in their behaviour from normal platelets and that these differences could explain the onset and recurrence of attacks.

The hypothesis that the aura might be due to mechanical obstruction rather than vasoconstriction is supported by earlier observations of increased platelet aggregation in response to epinephrine, thrombin, arachidonic acid, stress, starvation, the ingestion of various tyramine triggers, and or estrogens.[13]

Soon thereafter, D'Andrea et al[14] showed significant differences in B-TG and PF4 plasma levels between migraine patients and controls during headache-free periods. B-TG and PF4 levels were significantly elevated in 50% of the migraine patients, suggesting that there may be two groups of migraine patients: one with normal B-TG and PF4 plasma levels and the other with elevated levels. During migraine attacks, B-TG and PF4 plasma levels increased significantly compared to basal values, indicating that a platelet release reaction occurred during the headache phase.[15] The highest values recorded were in those patients whom had elevated levels during headache-free intervals. Thus, migraine was thought to be a condition that was not only associated with increased platelet activity during an attack, but also, at least in some, also during headache-free periods.

5-HT and 5-HT Receptors

5-HT was named serotonin by its discoverer, Irvine Page, because of its first known action – that of a powerful vasoconstrictor.[16] It is carried in the blood almost entirely within platelets[4] and its actions may be divided into peripheral and central effects.

Peripherally, free 5-HT acts as a humoral agent in the circulation,

Migraine is a condition associated with increased platelet activity – during, and outside an attack

constricting large arteries but dilating arterioles and capillaries.[4] It is a potent constrictor of extra-cranial arteries,[17] but has less effect on the internal carotid circulation. It also has an antidiuretic effect which may be relevant to the oliguria of the early phase of the migraine attack and the polyuria that is common as the headache subsides. In addition, the adsorption of free 5-HT to cranial vessels is thought to sensitise them to give rise to pain when distended.[18]

Centrally, serotonin-containing neurones from the midbrain raphe project rostrally in the medial forebrain bundle and are distributed to the hypothalamus, dorsal thalamus and diffusely to the cerebral cortex where it exerts a vasoconstrictor action on large arteries and veins but dilates arterioles.[19]

A number of molecular, biochemical,

... The Mystique of Migraine: Part 4

and physiological observations suggest that multiple 5-HT receptors exist in the central nervous system. 5-HT receptors have been classified into three main types (HT1, HT2 and HT3), each having a number of subtypes.[20] Theoretically, each receptor subtype provides a target site in the central nervous system that can be pharmacologically manipulated.[21]

Disturbances of 5-HT Levels

Disturbances of platelet and plasma 5-HT levels and 5-HT breakdown products have been demonstrated and a 5-HT releasing factor identified.

Platelet 5-HT has been repeatedly found to fall rapidly at the onset of the headache phase of a migraine attack with falls ranging from 15 to 52%.[7,8] The drop in 5-HT level

Platelet 5-HT falls rapidly at the onset of the headache phase

seems to be specific for migraine rather than a more generalised response to pain or stress.[22] As noted earlier, the release of 5-HT from the platelets of migraine patients is significantly reduced for at least three days after an attack.[10]

Plasma 5-HT concentrations have been found to be significantly increased in patients with migraine headaches versus controls[23] and to increase during the headache phase.[4] As well, the main breakdown of 5-HT, 5-HIAA, has been shown to be excreted in the urine in increased amounts after migraine headache.[6,7] However, it would seem that the plasma 5-HT changes probably do not have an important role in the regulation of arterial tone as internal carotid arterial infusions of serotonin have failed to show any effect on regional cerebral blood flow (rCBF) in humans.[11]

There is evidence from a number of studies for the presence of a 5-HT releasing factor of low molecular weight in the plasma during migraine headache but not at other times.[24,25,26]

It is important to note that the diurnal and individual variations in blood levels of 5-HT make it unhelpful to take random plasma or platelet 5-HT levels. Other conditions have been found to be associated with disturbances of 5-HT, including decreased levels of 5-HT in the brain, cerebral spinal fluid, and platelets in patients with chronic alcoholism, epileptic seizures, depression, and parkinsonism.[27]

Experiments Suggesting a Link Between 5-HT and Migraine

Intramuscular reserpine has been shown to cause marked release of 5-HT from platelets and to induce a typical headache in migrainous patients whereas normal subjects experience only a dull feeling of discomfort.[22,28,29,30] Slow intravenous injection of serotonin has been shown to alleviate both reserpine-induced and spontaneous migraine.[28,29]

The intriguing controversy about the involvement of endogenous 5-HT in the genesis of migraine has further been fuelled by the observation that the 5-HT receptor agonist, m-chlorophenypiperazine (m-CPP), a metabolite of the antidepressant

The drop in 5-HT level seems to be specific for migraine

trazadone, causes severe headaches.[31] These occurred 8 to 12 hours after administration of a single dose of m-CPP in about 54% of patients; subsequent analysis showed that 90% of these had a history of migraine. An argument has been that this effect of m-CPP is mediated via activation of 5-HTIC receptors in the brain.[32]

Anti-Migraine Drugs That Interact With 5-HT Receptors

The data suggest that drug interactions with specific 5-HT receptor subtypes may be the basis for their efficacy in both the acute and prophylactic treatment of migraine. The interactions that have been analysed most extensively have involved the 1A, 1D, 2, 1C and 3 receptor subtypes. The 1D and 1A receptors seem to be important for acute migraine relief, the 1C and 2 receptors for prophylactic activity.[21]

The anti-migraine drugs that interact with 5-HT receptors include: ergotamine (1928), dihydroergotamine (1945), methysergide (1959), cyproheptadine (1964), pizotifen (1968), and amitriptyline (1973).[33]

... The Mystique of Migraine: Part 4

Sumatriptan, the most recent addition to this list, is a designer drug, synthesised to selectively activate a particular subpopulation of 5-HT receptors; namely, the 5-HT 1A and especially 1D subtype receptors.[34,35] Sumatriptan's effectiveness and the fact that it acts predominantly on pathologically distended arteries raises the question of whether migraine is a "low 5-HT syndrome", due to either a low serotoninergic drive from the perivascular nerves or a reduced number of 5-HT receptors on the smooth muscles of the artery.[19]

Although all of the above drugs have the ability to block or stimulate 5-HT receptors, none of them is selective enough for 5-HT receptors nor effective enough clinically to convincingly argue that this is their mechanism of action. Their benefit may result from their pharmacological effects, be they mediated through 5-HT receptors or otherwise, independently of any pathophysiological involvement of endogenous 5-HT.[36,37] The vasoconstrictor action of sumatriptan alone could account for its clinical efficacy, regardless of the receptor mechanism involved.

An Endotheliopathy

In a recent review article on the pathogenesis of migraine, Appenzeller[38] makes a case for migraine being an endotheliopathy. The essence of his argument is that the endothelium mediates vascular homeostasis. The endothelial cells synthesise a large number of vasoactive molecules, some of which also have transmitter roles in the autonomic nervous system. The large molecules include fibronectin, heparin sulfate, interleukin-1, and tissue plasminogen activator. The smaller molecules include prostacyclin, endothelium-derived relaxing factor (EDRF), platelet-activating factor, endothelin-1 and angiotensin II. Two of the smaller molecules, prostacyclin and EDRF, may be of particular importance for migraine.

Prostacyclin is a powerful vasodilator that is released by endothelial cells in response to disturbances of its membrane. The disturbances may be either mechanical or chemical and include those caused by increased pulsatile pressure, endogenous mediators (including 5-HT) and some drugs. The very short half-life of prostacyclin in the circulation, less than one circulation time, makes it is a local (paracrine) hormone rather than a circulating one. It acts locally to relax the subendothelial smooth muscle cells and to prevent platelet aggregation.

Drug-interactions with specific 5-HT receptor subtypes may be the basis for their success in treating migraine

Endothelium-relaxing factor (EDRF), which has now been shown to be identical to nitric oxide, is indispensible for vasodilation induced by ACH. It is an example of another local hormone, being rapidly inactivated by haemoglobin in the circulation. A focal abnormality in its release may be important in the pathogenesis of migraine auras.

Thus, the endothelial cell is not just a semipermeable membrane between blood and vascular smooth muscle. Rather, it is a highly active metabolic endocrine organ that produces a number of substances important for vascular and neural homeostasis.

Discussion

1. Are the platelet abnormalities primary or secondary?

One of the most consistent and relatively specific biologic alterations that attends migraine attacks is decreased platelet 5-HT levels.[20] Further, the detection of changes in platelet activation in migraine sufferers between attacks, led to the hypothesis that platelet activation was the primary rather than a secondary feature of migraine.[10] However, a primary platelet abnormality implies a peripheral source for the abnormality in 5-HT levels which leads us to a contentious second question.

2. Is the abnormality in 5-HT peripheral or central?

A primary peripheral abnormality of 5-HT (the humoral theory) has seemed unlikely for a number of reasons. Firstly, there has been doubt about whether the amount of 5-HT released from platelets is sufficient to cause significant vasoconstriction. Although the fall in platelet 5-HT in migraine attacks is sufficient theoretically to result in a pharmacologically significant transient increase in plasma 5-HT, it

... The Mystique of Migraine: Part 4

has been assumed that the plasma 5-HT changes do not have an important role in the regulation of arterial tone because of studies that show no difference in arterial tone with infusion of 5-HT. Secondly, headache is not a feature of the carcinoid syndrome where plasma 5-HT levels are excessive.[39] Thirdly, the consistent localisation of neurological phenomena and the alternating pattern of hemicrania would be difficult to explain by a global action of circulating 5-HT. Fourthly, there is no evidence that 5-HT receptors in human temporal arteries differ between migraine sufferers and nonsufferers.[40] Finally, absolute levels of 5-HT do not correlate with headache.

Understandably, this led to the consideration of a central mechanism with 5-HT acting as a neurotransmitter rather than as a peripheral vascular agent. Brainstem raphe nuclei containing 5-HT have important upstream and downstream connections[4] and it has been hypothesised that the headache is mediated via 5-HT by the trigemino-vascular system.[3] Of interest, the increased amounts of 5-HIAA measured in the urine during attacks are considerably more than can be explained by the release of 5-HT from platelets.[21] Thus, it may be that changes in the plasma levels of 5-HT and its metabolite, 5-HIAA, reflect more important disturbances in 5-HT levels in the brain at the onset or during a migraine attack.

However, the postulation of local hormone effects rendered through prostacyclin and EDRF, for example, circumvents most of the arguments above and allows for a platelet abnormality to be reconsidered as the primary event in migraine, rather than as a secondary manifestation of a systemic disturbance of 5-HT.

3. Prophylaxis for patients at risk?
Patients with continuous platelet activation; that is, those with increased B-TG, PF4, and 5-HT plasma levels during headache-free intervals as well as during headaches, would seem to be at risk for cerebrovascular accidents. The argument for prophylaxis with anti-platelet drugs[14] would be even more compelling if the platelet abnormalities (with increased aggregation and adhesion) are primary.

> The endothelial cell may be the most likely site of the primary abnormality in migraine

4. A common mechanism?
Patients with migraine are not the only ones to have continuous platelet activation; patients suffering from tension type headaches also have been found to have elevated B-TG, PF4, and 5-HT plasma levels both during and between headaches. Certainly, one potential explanation for this could be that the elevation of these substances is a nonspecific consequence of the pain. However, the platelet decrease in the same substances (which presumably leads to the plasma increase of the same) seems not to be a generalised response to pain or stress[22] and thus provides one possibility for a common underlying mechanism for migraine and tension-type headaches.

5. Is migraine an endotheliopathy?
I think this hypothesis deserves further consideration. The endothelial system would seem to have the capability of mediating all of the manifestations of migraine and the concept of local hormones provides a mechanism for the localisation of both aura and headache.

Conclusion

The location of the primary abnormality of migraine remains a mystery. Previous papers presented the evidence for it being vascular,[2] and neurogenic.[3] This paper presented evidence of platelet abnormalities, disturbances in 5-HT levels, and recent cellular research concerning the endothelial cell that informs us of its potential to mediate all of the manifestations of migraine. But perhaps none of these theories hold the answer. The next paper in this series considers the possibility that the primary event in migraine is psychological.

References

1. Henbest RJ. The mystique of migraine. Part 1: Its nature and diagnosis. S Afr Fam Pract 1991;12:512-9.
2. Henbest RJ. The mystique of migraine. Part II: Is it vascular? S Afr Fam Pract 1992;13:165-71.
3. Henbest RJ. The mystique of migraine. Part III: Is it neurogenic – is the brain responsible? S Afr Fam Pract 1993;14:107-15.
4. Lance JW, Lambert GA, Goadsby PJ, Zagami AS. 5-Hydroxytryptamine and its

... The Mystique of Migraine: Part 4

putative aetiological involvement in migraine. Cephalgia 1989;9(suppl 9):7-13.

5. Sicuteri F. Prophylactic and therapeutic properties of 1-methyl-lysergic acid butanolamide in migraine: preliminary report. Int Arch Allergy Appl Immunol 1959;15:300-7.
6. Sicuteri F, Testi A, Anselmi B. Biochemical investigations in headache: increase in the hydroxyindoleacetic acid excretion during migraine attacks. Int Arch Allergy 1961;19:55-8.
7. Curran DA, Hinterberger H, Lance JW. Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxymandelic acid excretion in normal and migrainous subjects. Brain 1965;88:997-1007.
8. Fozard JR. Serotonin, migraine and platelets. Prog Pharmacol 1982;4:136-46.
9. Hannington E. Migraine: a blood disorder? Lancet 1978;ii:501-3.
10. Hanington E, Jones RJ, Amess JAL, Wachowicz B. Migraine: a platelet disorder. Lancet 1981;ii:720-3.
11. Olesen J. Effect of serotonin on regional cerebral blood flow (rCBF) in man. Cephalgia 1981;1:7-10.
12. The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. N Engl J Med 1991;325:316-21.
13. Deshmukh SV, Meyer JS. Cyclic changes in platelet dynamics and the pathogenesis and prophylaxis of migraine. Headache 1977;17:101-8.
14. D'Andrea G, Toldo M, Cortelazzo S, Milone FF. Platelet activity in migraine. headache 1982;22:207-12.
15. Gawel M, Burkitt M, Rose FC. The platelet release reaction during migraine attacks. Headache 1979;19:323-7.
16. Page IH. Serotonin (5-hydroxytryptamine). Physiol Rev 1954;34:563-88.
17. Lance JW, Anthony M, Gonski AG. Serotonin, the carotid body and cranial vessels in migraine. Arch Neurol 1967;16:553-8.
18. Sicuteri F. Vasoneuroactive substances and their implication in vascular pain. Res Clin Stud Headache 1967;1:6-45.
19. Friberg L, Olesen J, Iversen HK, Sperling B. Migraine pain associated with middle cerebral artery dilation: reversal by sumatriptan. Lancet 1991;338:13-17.
20. Raskin NH. Serotonin receptors and headache. N Engl J Med 1991;5:353-4.
21. Peroutka SJ. Developments in 5-hydroxytriptamine receptor pharmacology in migraine. Headache 1990;8:829-39.
22. Anthony M, Hinterberger H, Lance JW. Plasma serotonin in migraine and stress. Arch Neurol. 1967;16:544-52.
23. Takeshima T, Shimomura T, Takahashi K. Platelet activation in muscle contraction headache and migraine. Cephalgia 1987;7:239-43.
24. Anthony M, Hinterberger H, Lance JW. The possible relationship of serotonin to the migraine syndrome. Res Clin Stud Headache 1969;2:29-59.
25. Dvilansky A, Rishpon S, Nathan I, Zolotov Z, Korujn AD. Release of platelet 5-hydroxytriptamine by plasma taken from patients during and between migraine attacks. Pain 1976;2:315-8.
26. Muck-Seler D, Deanovic Z, Dupelj M. Platelet serotonin (5-HT) and 5-HT releasing factor in plasma of migrainous patients. Headache 1979;19:14-17.
27. Rolf LH, Wiele G, Brune GG. 5-hydroxytryptamine in platelets of patients with muscle contraction headache. Headache 1981;21:10-11.
28. Kimball RW, Friedman AP, Vallejo E. Effect of serotonin in migraine patients. Neurology 1960;10:107-11.
29. Lance JW, Anthony M, Hinterberger H. The control of cranial arteries by hormonal mechanisms and its relation to the migraine syndrome. Headache 1967;7:93-102.
30. Carroll JD, Hilton BP. The effects of reserpine injection on methysergide treated control and migrainous subjects. Headache 1974;14:149-56.
31. Brewerton TD, Murphy DL, Meuller EA, Jimerson DC. Induction of migraine-like headache by the serotonin agonist chlorophenylpiperazine. Clin Pharmacol Ther 1988;43:605-9.
32. Fozard JR, Gray JA. 5-HT1c receptor activation: a key step in the initiation of migraine? Trends in Pharmacol Sci 1989; 10:307-9.
33. Humphrey PPA. 5-Hydroxytryptamine and the pathophysiology of migraine. J Neurol 1991;283:S38-44.
34. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous Sumatriptan. JAMA 1991;265:2831-5.
35. McCarthy BG, Peroutka SJ. Comparative neuropharmacology of dihydroergotamine and sumatriptan (GR 43175). Headache 1989;29:420-2.
36. Feniuk W, Humphrey PPA, Perren MJ, Connor HE, Whalley ET. Rationale for the use of 5-HT1-like agonists in the treatment of migraine. J Neurol 1991;238:S57-61.
37. Humphrey PPA, Feniuk W, Perren MJ. Anti-migraine drugs in development; advances in serotonin receptor pharmacology. Headache 1990;30:12-16.
38. Appenzeller O. Pathogenesis of migraine. Med Clin N Amer 1991;75:763-89.
39. Salmon S, Bonciani M. Fanciullacci M, Marianelli L, Michelacci S, Sicuteri F. A putative 5-HT central feedback in migraine and cluster headache attacks. In: Critchley M, Friedman AP, Gurini S, Sicuteri F, editors. Advances in Neurology, Vol 33, Headache: physiopathological and clinical concepts. New York: Raven Press, 1982:265-74.
40. Skarby T, Tfelt-Hansen P, Gjerris F, Edvinsson L, Olesen J. Characterization of 5-Hydroxytryptamine receptors in human temporal arteries: comparison between sufferers and non-sufferers. Ann Neurol 1982;12:272-7.