Published in final edited form as:
Curr Opin Support Palliat Care. 2014 June ; 8(2): 137–142. doi:10.1097/SPC.0000000000000044.

Serotonin, $5HT_1$ agonists, and migraine: new data, but old questions still not answered

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Abstract

Purpose of review—The serotonergic system has long been linked to migraine but recent studies highlight how much is still unclear about this link. And recent data add to the uncertainty of where/how triptans act and why they are headache specific.

Recent findings—Markers of 5HT levels in the brains of migraine patients show no changes between attacks. Several recent meta-analyses show the most convincing data on genetic differences in the serotonergic system for 5HT transporters. Findings of additional triptan actions on peripheral trigeminovascular neurons and in the hypothalamus add more fuel to the debate on where these drugs act. A growing list of studies show efficacy of multiple triptans and other $5HT_{1b/1d}$ agonists in pre-clinical models of non-headache pain arguing for reevaluation of whether these drugs have efficacy in other pain states. Despite these issues, serotonergic drugs continue to be the gold standard for abortive agents with new members on the horizon ($5HT_{1f}$ agonists).

Summary—Given the clear efficacy of serotonergic drugs for migraine, continued study on the role of the endogenous 5HT system may lead to more novel therapies. And with the list of studies demonstrating efficacy triptans in models of non-headache, clinical studies should address whether these drugs work for other types of pain.

Keywords

migraine; serotonin; 5HT; triptan

Introduction

Migraine is a complex neurological disorder most notably characterized by intense unilateral throbbing headache but also consists of associated symptoms such as nausea, vomiting, photo- and phonoallodynia (pain caused by light/sound), cutaneous hypersensitivity, aura, and changes in mood or energy levels. The 2012 Global Burden of Disease study by the The Lancet placed migraine as the 8th most burdensome disease on the planet and the 4th most in women [1], as migraine is approximately 3 times more prevalent in females. Studies on the pathophysiology of migraine have examined potential mechanisms in the trigeminovascular

The author declares no conflicts of interest relevant to this manuscript.

system as well as a variety of brain and brainstem regions [2–5] but the pathophysiology remains poorly understood.

Some of the only pain therapeutics with truly novel mechanisms of action (i.e. not simply reformulations of opiates) that have been developed over the last several decades are used for migraine. The triptans, a group of $5HT_{1b/1d}$ agonists [6], revolutionized the treatment of migraine upon their release in the early 1990s (and calcitonin gene-related peptide (CGRP) receptor antagonists are a more recent example [7]). The efficacy of serotonergic drugs added to many years of research connecting 5HT to migraine. The focus of this review will be on recent developments in the role of the endogenous 5HT system in migraine, some unresolved issues surrounding the use of triptans for migraine, and the future of serotonergic drugs as migraine therapeutics.

Contribution of endogenous 5HT signaling to migraine attacks: where do we stand?

Since the discovery by Sicuteri and colleagues of increased urinary excretion of the 5HT metabolite 5-HIAA (5-hydroxyindoleacetic acid) during migraine attacks [8], the debate has continued on whether 5HT levels are increased, decreased, or unchanged between or during migraine attacks [9, 10], primarily because measurements of 5HT and its metabolites have been made in the blood (e.g. in platelets) or urine and not in the brain. Using PET imaging with uptake of the radiolabeled 5HT precursor α-[^{11}C] methyl-L tryptophan (^{11}C-AMT) to examine 5HT synthesis, which at this time is one of the only methods of examining 5HT levels in the brain, a recent study by Sakai et al found no difference in ^{11}C-AMT uptake between female migraine without aura patients (interictally) and normal controls [11*]. The authors did find that eletriptan decreased ^{11}C-AMT uptake in migraine patients but not in healthy controls, suggesting a increase in agonist-receptor efficacy in migraine. In any case, the observation of no change in interictal ^{11}C-AMT uptake is in contrast to the decrease in ^{11}C-AMT uptake in migraine patients previously shown by this group between attacks [12] and the increase in uptake shown by Chugani et al [13] also in the interictal phase, both studies using the same PET method as the recent work. Thus, 53 years after the initial suggestion that changes in 5HT levels (in the brain) contribute to migraine, there is still no clear answer to whether this occurs in the brain, at least during the interictal phase.

The development of genetic analysis techniques such as genome-wide association studies (GWAS) has made it more possible to determine whether there are underlying genetic differences between common migraine patients and controls [14, 15], but so far no 5HT-related genes have been identified with these types of analyses. More targeted genetic studies (e.g. linkage analyses) have asked whether differences in the 5HT system occurs in migraine patients. No differences have been found in genes for tryptophan hydroxylase, monoamine oxidase (A or B) and aromatic amino acid decarboxylase, and in most studies of the receptors [9, 16–18]. In contrast, a genetic association in a small number of families was found in the gene for the $5HT_{1d}$ receptor in migraine with aura patients, and the association (an undertransmission of alleles) may lead to decreased expression of the $5HT1_d$ receptor [19*]. There is growing evidence that pharmacological activation of $5HT1_d$ is efficacious for migraine (see below). Thus, this may be one of the only 5HT-receptor genetic differences in

migraine patients identified thus far that suggests any pathological role for changes in the 5HT system.

There have also been positive findings with genetic analyses of 5HT transporters (5HTT). Single nucleotide polymorphisms in the 5HTT have been identified and are found to be associated with migraine [20, 21]. Several other polymorphisms of the 5HTT exist including a long and short form of the 5HTT gene-lined polymorphic region (5HTTLPR) and the intron 2 variable number tandem repeat (VNTR) region [22]. Two recent review/meta analyses were performed on studies that examined an association between these polymorphisms and migraine. The analysis on the 5HTTLPR polymorphism concluded that there was no association with migraine [23]. In contrast, two independent groups performed an analysis of VNTR, both with positive associations. The first found that patients with certain polymorphisms in this region had an increased susceptibility to migraine [24*]. The second found that specific alleles of this polymorphism are protective against migraine [25*]. Combining these studies, one might propose that the genetics at this site play a key role in determining migraine susceptibility. However, these studies should be replicated in a larger numbers of patients to confirm the associations. Further, the relevance of these findings are not yet clear as no changes were found in 5HT uptake in platelets with VNTR polymorphisms [26] so it is unknown whether changes in neuronal 5HT uptake would occur with VNTR polymorphisms in migraine patients.

Thus, despite decades of debate and examination of 5HT and its signaling components in migraine, and the general consensus in the field that 5HT plays an important role in this disorder, the above studies highlight the fact that a clear role for this transmitter has yet to be conclusively demonstrated.

Triptans: where do they act and why are they specific for headache?

It is clear that triptans act at the cellular level by activating $5HT_{1b/1d}$ and in some cases $5HT_{1f}$ receptors, but many questions remain about their mechanism of action. One major unresolved question in the field, despite over 20 years of use, is where and how they act [27]. The best recognized mechanism of action of triptans is vasoconstriction [28], a mechanism targeted since vasodilation has long been thought to contribute to migraine. Using magnetic-resonance angiography of intra-and extra-cranial vessels in migraine patients, studies have both shown [29] and not shown vasodilation during migraine [30]. However, both of these studies used provocative vasodilatory agents to elicit migraines. A more recent study with patients experiencing spontaneous attacks found no extracranial vasodilation and only a small degree of intracranial vasodilation [31**], leading the authors to conclude that vasodilation is not the cause of migraine. If there is no vasodilation during natural migraines, the efficacy of triptans is likely due to action on neurons.

Recent studies have further documented the actions of triptans on primary afferent trigeminal neurons. Sumatriptan was found to modulate ionic currents in dural-projecting trigeminal neurons *in vitro* including voltage-gated calcium currents (confirming an earlier report [32]) and now demonstrating modulation of potassium currents [33*]. This drug also inhibited calcium influx in individual neuronal fibers in the dura via calcium channel

modulation [34]. Sumatriptan was found to inhibit the capsaicin/noxious heat/proton-sensitive transient receptor potential channel vanilloid 1 (TRPV1) in trigeminal neurons [35*], consistent with other reports where sumatriptan inhibited both cytokine production in response to capsaicin [36] and capsaicin-induced CGRP release from trigeminal neurons [37]. Thus, one potential non-vascular mechanism of action is via triptan modulation of various ionic currents on trigeminal afferents that carry pain information from the meninges.

Whether triptans require access to sites in the brain to produce their actions is not clear [38]. Asghar and colleagues found no change in blood-oxygen-level-dependent (BOLD) signal (an imaging technique that measures blood flow and oxygenated hemoglobin movement as a surrogate for neuronal activity) in the visual cortex of humans after sumatriptan dosing in healthy volunteers [39]. In contrast, a pharmaco-fMRI study showed activation of several pain-related brain regions after dosing sumatriptan in healthy volunteers [40] and thus triptan activity in the brain may be region specific. However, the critical site of action of triptans in the brain is still not known. Prior reports of possible CNS triptan action in the periaqueductal grey (PAG; [41]) have been extended with a recent finding showing that endocannabinoids in the PAG modulate meningeal afferent traffic in the brainstem and these actions are mediated by PAG $5HT_{1b/1d}$ receptors [42*]. Triptans have also been proposed to work in other brain regions [43–45], but recent studies have further implicated serotonergic activity in the hypothalamus as capable of modulating nociceptive input in the trigeminal nucleus caudalis. After lesioning the A11 nucleus of the hypothalamus, Charbit and colleagues found increased activity in nucleus caudalis neurons receiving meningeal input and this increase was attenuated by intravenous naratriptan [46]. A subsequent study found that microinjection of naratriptan directly into the paraventricular nucleus of the hypothalamus decreased the activity of caudalis neurons both basally and in response to meningeal stimulation [47**]. These studies implicate a serotonergic descending component from the hypothalamus to the brainstem that may modulate noxious input and may also contribute to the efficacy of triptans. Given the suggested role of the hypothalamus in migraine pathophysiology [48–50], potential triptan actions in this brain region add to the possible mechanisms of action of these drugs. Better understanding of which brain regions are necessary for triptan efficacy, or even whether CNS activity is required, will greatly aid in the development of new migraine therapeutics.

The other major question with the triptans is why they have no efficacy for non-headache pain [27, 51]. 5HT has long been implicated in non-headache pain (for a recent review see [52]) so the answer to this question has traditionally been based on vascular actions of triptans or differences in the trigeminovascular system versus spinal systems. With recent doubts on the vascular hypothesis of migraine (see above), this leaves the latter as the more likely explanation. Expression of $5HT_{1d}$ is higher on meningeal afferents than those innervating temporalis muscle [53], nasal mucosa, and lacrimal glands [54]. And $5HT_{1b/1d}$ receptors inhibit synaptic inputs in the nucleus caudalis [55*] while $5HT_{1a}$ receptors perform this function in the spinal system [56*], suggesting an anatomical difference in central modulation of afferent input [57]. However, other studies found no qualitative differences in expression levels of $5HT_{1b/1d/1f}$ between trigeminal ganglia and 4 different levels of dorsal root ganglia [58]. And numerous studies of late have shown efficacy of triptans in animal models of trigeminal nerve injury [59, 60], pancreatic pain [61],

nociceptive responses in hindpaws following formalin [62, 63], carrageenan [62], or capsaicin injection [64], plasma protein extravasation of hindpaws due to capsaicin or electrical stimulation [65], and selective $5HT_{1b}$ and $5HT_{1d}$ agonists given locally in the paw reduce formalin-induced nociception [66*] (Table 1). This continually growing list of studies demonstrating efficacy of triptans (or $5HT_{1b/1d}$ agonists) outside of headache argues for reevaluation of whether triptans do actually have efficacy for some forms of non-headache pain. If not, a mechanistic basis for this should be conclusively determined as it could provide important clues for the development of new migraine therapeutics.

The future of serotonergic drugs for migraine

The efficacy of triptans for migraine indicates a role for the serotonergic system in the treatment of this disorder. Outside of new formulations of drugs classically used for migraine, such as inhaled dihydroergotamine or triptans [67, 68], the future of serotonergic migraine drugs lies most clearly with selective $5HT_{1f}$ agonists (e.g. lasmitidan [69]). Some triptans have efficacy at this receptor but several studies have shown that selective agonists of $5HT_{1f}$ have efficacy in preclinical migraine models and more importantly, several clinical trials have demonstrated efficacy of these drugs as abortive agents for migraine (reviewed recently by [70–72]). And although these drugs have been proposed to act centrally, the selective $5HT_{1f}$ agonist LY-344864 inhibited evoked CGRP release from isolated dural tissue with efficacy similar to sumatriptan [73] so a peripheral mechanism cannot be ruled out. Future studies will determine whether these agents have efficacy and tolerability equal to or greater than triptans but they may ultimately find a place in the treatment toolbox due to their lack of vascular issues and cardiovascular risk.

Additional future 5HT-based avenues are combinations of triptans and other drugs [74], a strategy that has already been used successfully with the sumatriptan/naproxen combination. One novel combination takes advantage of the potential efficacy of nitric oxide synthase (NOS) inhibitors for migraine [75] and combines these compounds with triptans or other $5HT_1$ agonists. The dual neuronal NOS (nNOS) inhibitor/$5HT_{1b/1d}$ agonist NXN-188 was recently found to inhibit evoked CGRP release from dura mater, trigeminal ganglia, and nucleus caudalis as well as capsaicin- and electrically-evoked vasodilation in the dura, although this effect was not blocked by a $5HT_{1b/1d}$ antagonist indicating the actions were due to nNOS inhibition [76]. A phase I clinical trial has been published for this compound [77] but the phase II trial results have only been published in abstract form ([78] significant pain relief at 4–24 hours but not at 2 hours). Ultimately, efficacy and tolerability of this combination, as well as any advantages over triptans, await future study.

Conclusion

The role of endogenous 5HT in migraine continues to be elusive despite the connection proposed by Sicuteri 53 years ago. Although analysis of brain 5HT levels during migraine and genetic studies of migraine patients have yet to provide a conclusive answer, the clear efficacy of triptans continues to implicate 5HT in migraine. While the mechanism of action of triptans has yet to be resolved, the most perplexing issue with these drugs is their purported lack of efficacy in non-headache pain. There is no clear mechanistic reason for

why this is the case. One might speculate that this is due to the way in which triptans are administered i.e. at the onset of pain. Analgesics are in most cases of non-headache given after pain has been established, and in the case of neuropathic patients, pain may have been present for months or years. Triptans may indeed have efficacy for other forms of pain if given early e.g. before a surgical incision and this issue warrants further study. Better understanding of the role of 5HT in migraine and the mechanism of action of triptans may enable development of novel serotonergic agents beyond the $5HT1_f$ agonists on the horizon.

Acknowledgments

Funding for this work is provided by the National Institutes of Health Grants NS072204 and GM102575 as well as Amgen and Sova Pharmaceuticals

The author wishes to acknowledge funding from the National Institutes of Health, grant numbers NS072204 and GM102575. Research support is also provided by Amgen and Sova Pharmaceuticals.

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Key points

- Changes in 5HT levels in the brains of migraine patients have yet to be conclusively demonstrated.
- Genetic studies of migraine patients have only shown a few differences from healthy controls, most notably in 5HT transporters.
- Recent studies show new actions of triptans both on peripheral trigeminovascular neurons and in the hypothalamus, adding to the uncertainty of where these drugs act.
- A continually growing list of preclinical models show pain-relieving actions of triptans outside of headache arguing that these drugs may have efficacy for other pain states.
- Development of selective $5HT_{1f}$ agonists and combinations of triptans with other agents show that there is still a future in targeting the serotonergic system for migraine.

Table 1

Efficacy of triptans in non-headache preclinical pain models

Model	Effect	Drug	Reference
Infraorbital nerve ligation	Reduction in facial mechanical hypersensitivity	Naratriptan	59
Infraorbital nerve ligation	Reduction in facial mechanical hypersensitivity	Zolmitriptan	60
Pancreatic inflammation	Reduction in referred abdominal hypersensitivity	Sumatriptan	61
Hindpaw formalin injection	Reduced formalin-induced flinching	Sumatriptan	62
Hindpaw carrageenan inflammation	Reduced hindpaw tactile hypersensitivity	Sumatriptan	62
Abdominal acetic acid injection	Reduced acetic acid-induced writing	Sumatriptan	62
Hindpaw formalin injection	Reduced formalin-induced flinching and secondary tactile hypersensitivity	Sumatriptan	63
Hindpaw capsaicin injection	Reduced hindpaw thermal hyperalgesia	Sumatriptan	64
Hindpaw capsaicin injection	Reduced vasodilation and plasma extravasation	Sumatriptan	65
Saphenous nerve stimulation	Reduced vasodilation and plasma extravasation	Sumatriptan	65
Hindpaw formalin injection	Reduced formalin-induced flinching	CGS-12066A[#] GR-46611[##]	66

[#] $5HT_{1b}$ agonist

[##] $5HT_{1b/1d}$ agonist.