Mechanisms of Action of the 5-HT$_{1B/1D}$ Receptor Agonists

Stewart J. Tepper, MD; Alan M. Rapoport, MD; Fred D. Sheftell, MD

Recent studies of the pathophysiology of migraine provide evidence that the headache phase is associated with multiple physiologic actions. These actions include the release of vasoactive neuropeptides by the trigeminovascular system, vasodilation of intracranial extracerebral vessels, and increased nociceptive neurotransmission within the central trigeminocephalic complex. The 5-HT$_{1B/1D}$ receptor agonists, collectively known as triptans, are a major advance in the treatment of migraine. The beneficial effects of the triptans in patients with migraine are related to their multiple mechanisms of action at sites implicated in the pathophysiology of migraine. These mechanisms are mediated by 5-HT$_{1B/1D}$ receptors and include vasoconstriction of painfully dilated cerebral blood vessels, inhibition of the release of vasoactive neuropeptides by trigeminal nerves, and inhibition of nociceptive neurotransmission. The high affinity of the triptans for 5-HT$_{1B/1D}$ receptors and their favorable pharmacologic properties contribute to the beneficial effects of these drugs, including rapid onset of action, effective relief of headache and associated symptoms, and low incidence of adverse effects.

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The pathophysiology of migraine is fairly well understood, and evidence supports contributory roles of both neural and vascular mechanisms. The manifestation of headache in migraineurs is probably associated with activation of the trigeminocephalic system, followed by the release of vasodilatory neuropeptides. Changes in circulating levels of the neurotransmitter serotonin (5-HT) are characteristic of migraine and may contribute to the pathogenesis of the disorder. Recent progress in understanding the pathophysiology of migraine includes the identification of the physiologic roles of vasoactive neuropeptides associated with migraine and the characterization of 5-HT receptor subtypes.

Increased understanding of the pathophysiology of migraine has led to the development of improved migraine treatments such as the 5-HT$_{1B/1D}$ receptor agonists, collectively known as triptans. The emergence of the triptans has revolutionized the management of migraine by providing options for the highly selective stimulation of 5-HT$_{1B/1D}$ receptors, while reducing or eliminating unwanted activity at other receptor subtypes, thus improving therapeutic tolerability. This article focuses on the mechanisms of action of the triptans in relation to current concepts of the pathophysiology of migraine and the clinical role of these drugs in the management of patients with migraine.

PATHOPHYSIOLOGY OF MIGRAINE

The manifestation of headache in migraineurs has been attributed to activation of the sensory trigeminocephalic system and the subsequent release of vasoactive neuropeptides. In the genetically susceptible patient, activation of the
The trigeminovascular system can be initiated by a variety of triggers, including stress, certain foods or drugs, odors, trauma, and changes in sleep habits. The release of vasoactive substances from trigeminal nerve terminals in patients with migraine induces inflammatory reactions in meningeal blood vessels, characterized by vasodilation, plasma protein extravasation, and activation of trigeminovascular afferents. Studies in animals support the observation that pain-producing intracranial extracerebral vessels in the dura mater (peripherally), not the brain, are responsible for the generation of headache in patients with migraine.

Vasoactive neuropeptides found within the trigeminal neurons that innervate intracranial blood vessels and contribute to the manifestation of head pain in migraineurs include calcitonin gene-related peptide (CGRP), substance P, and neurokinin A. Calcitonin gene-related peptide is the most potent vasodilator neurotransmitter mapped to the trigeminal system, and its action is endothelium independent. Substance P, a nondecapeptide involved in nociceptive transmission, has endothelium-dependent vasodilatory effects on the cerebrovascular bed. Neurokinin A is a decapeptide with a profile of action and localization in the trigeminal system that is similar to that of substance P but with less potent vasodilatory effects and longer-lasting effects on blood vessel permeability. The critical neuropeptide in the generation of migraine seems to be CGRP rather than substance P or neurokinin A.

Neurogenic inflammation within the meninges has been suggested as a potential model to explain the source of head pain in patients with migraine, but it has been unclear whether neurogenic inflammation occurs during an acute migraine attack. Studies in animals demonstrate increased endothelial permeability and leakage of albumin into the dura and the retina after high-intensity electrical stimulation of the trigeminal ganglion, but no increased endothelial permeability or protein extravasation has been documented in human retinal or choroidal vessels during migraine attacks or the headache-free interval in migraineurs. These findings suggest that other fundamental processes, probably in the central nervous system, are key to the pathophysiology of a migraine attack.

The autonomic nervous system may contribute to the pathophysiology of migraine. Hyperfunctioning of both the sympathetic and parasympathetic nervous systems has been suspected in patients with migraine, based on vasoconstrictor reactions to temperature changes, cardiovascular responses, and other investigations. The normal responses of cranial arteries during increased sympathetic activity cast doubt on a major role of sympathetic dysfunction in the pathophysiology of migraine, but mild parasympathetic hypofunction with denervation hypersensitivity could be a contributing factor.

The role of nitric oxide in the pathophysiology of migraine and other vascular headaches is supported by the observations that both glyceryl trinitrate (a nitric oxide donor) and histamine (an activator of endothelial nitric oxide formation) cause dose-dependent headaches with several migraineous characteristics. Patients with migraine respond to nitric oxide delivered by nitroglycerin by developing an early nonmigraine headache and then a delayed, migraine-like headache several hours after dosing—a headache not seen when healthy control patients are given nitroglycerin, which suggests an increased vulnerability in migraineurs to one or more of the toxic effects of nitric oxide, including enzyme inhibition and the formation of peroxynitrite with lipid peroxidation.

5-HT RECEPTORS

The role of 5-HT in migraine is supported by the observations that urinary and platelet 5-HT levels decrease, and that circulating levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, increase during migraine. The ability of 5-HT–depleting and 5-HT–releasing agents such as reserpine and fenfluramine to induce migraine-like symptoms provides further evidence of the role of serotonin in the pathophysiology of migraine. Intravenous infusion of 5-HT aborts both reserpine-induced and spontaneous headache, but the clinical use of 5-HT in migraine is precluded by significant untoward effects.

The 5-HT receptors are highly heterogeneous, broadly distributed, and classified into 7 different families on the basis of their amino acid sequences and other properties. The 5-HT1 receptors are the largest subfamily of 5-HT receptors and typically demonstrate a high affinity for 5-HT. The 5-HT1 receptors are further subdivided according to their physiologic functions, binding affinity, and other features.

The cloning of 5-HT1 receptors and the development of 5-HT1 receptor agonists with specific affinity for 5-HT1 receptor subtypes provided evidence for substantial populations of 5-HT1 receptors on vascular endothelium and human meningeal blood vessels. The messenger RNA for the 5-HT1 receptor is abundantly expressed on neuronal tissues and vascular smooth muscle cells, and evidence suggests that this receptor mediates contraction of vascular smooth muscle. Both the 5-HT1A and 5-HT1D receptors have been localized in human trigeminal ganglia and trigeminal nerves, but only 5-HT1D receptors have been detected in trigeminal nerves projecting peripherally to the dural vasculature and centrally to the brainstem trigeminal nuclei. The 5-HT1D receptors are thus localized peripherally to inhibit activated trigeminal nerves and prevent vasoactive neuropeptide release, and centrally to interrupt pain signal transmission from the blood vessels to sensory neurons located in the brainstem.

Local application of 5-HT1D receptor agonists inhibits firing activity by second-order trigeminal neurons, and this activity is shared by ergonovine, a non–specific 5-HT1 receptor agonist. These observations support the presence of inhibitory receptors on these neurons that are capable of decreasing trigeminal neuronal traffic and thus pain transmission in migraine and other primary headaches.

MECHANISMS OF ACTION OF THE 5-HT1D RECEPTOR AGONISTS

Studies of the mechanisms of action of 5-HT1D receptor agonists, or triptans, provide important insights into
the pathophysiology of migraine. The triptans have at least 3 distinct modes of action, all of which may be additive in their antimigraine effects (Table 1).6,15 These effects include vasoconstriction of painfully distended intracranial extracerebral vessels by a direct effect on vascular smooth muscle, inhibition of the release of vasoactive neuropeptides by trigeminal terminals innervating the intracranial vessels and dura mater, and inhibition of nociceptive neurotransmission within the trigemino-cervical complex in the brainstem and upper spinal cord.13 Other possible antimigraine effects of the triptans include modulation of nitric oxide-dependent signal transduction pathways, nitric oxide scavenging in the brain, and sodium-dependent cell metabolic activity.16-18

Sumatriptan and rizatriptan have been shown to act selectively to cause vasoconstriction in isolated human middle meningeal arteries and are 10 times more potent in these arteries than in human coronary arteries.10 The maximal response evoked by both agents is less than that of 5-HT.20 These observations and those of Maassen VanDenBrink et al19 suggest that therapeutic plasma concentrations of the triptans do not reach levels likely to cause myocardial ischemia in patients with normal coronary circulation. However, given that there are some 5-HT1B receptors in coronary arteries, triptans are contraindicated in patients with cerebrovascular or cardiovascular disease.

The normalization of vessel diameter in cerebral arteries in migraineurs can be achieved without frank vasoconstriction through inhibition of CGRP release, and this mechanism may contribute to the relief of headache in patients treated with triptans. Studies in anesthetized rats demonstrate that rizatriptan has no direct vasoconstrictor effects, and blocks electrically stimulated dural vasodilation and plasma protein extravasation by inhibiting the release of CGRP via activation of prejunctional receptors located on trigeminal sensory nerve terminals.22 Sumatriptan inhibits potassium-stimulated CGRP secretion from cultured trigeminal neurons in a dose-dependent manner and may also inhibit the release of substance P.23 These observations support the concept that sumatriptan and other triptans may block a deleterious feedback loop in migraine whereby neurogenic inflammatory agents sensitize the trigeminal ganglia neurons to sustain elevated levels of CGRP.

The dilation of meningeal blood vessels may evoke a sensitization of central trigeminal neurons that may underlie the symptoms of headache and allodynia in migraineurs.24 The inhibition of evoked trigeminal nucleus firing by 5-HT, and the blockade of this activity by a 5-HT1B/1D agonist with central nervous system penetration suggest that triptans inhibit trigeminal activity centrally.25 Rizatriptan has been shown to have central trigeminal antinociceptive activity in addition to peripheral vasoconstriction and inhibitory effects on the trigemino-novasculature,26 and these effects may be mediated by the 5-HT1D receptor.

### Table 1. Antimigraine Mechanisms of the 5-HT1B/1D Receptor Agonists

<table>
<thead>
<tr>
<th>Location</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Selective constriction of pain-producing intracranial extracerebral blood vessels</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Reduction of trigeminal sensory nerve activation and inhibition of vasoactive neuropeptide release</td>
</tr>
<tr>
<td>Central</td>
<td>Inhibition of neurotransmitter release from activated trigeminal nerves in the brainstem and upper cervical spinal column</td>
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</tbody>
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*Data from Hargreaves and Shepheard and Goadsby.15

### Table 2. Comparison of Efficacy of Approved and Investigational Oral Triptans at Most Commonly Used Doses

<table>
<thead>
<tr>
<th>Sumatriptan 50 mg</th>
<th>Zolmitriptan 2.5 mg</th>
<th>Naratriptan 2.5 mg</th>
<th>Rizatriptan 10 mg</th>
<th>Almotriptan 12.5 mg</th>
<th>Frovatriptan 2.5 mg†</th>
<th>Eletriptan 80 mg†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache response at 2 hours‡</td>
<td>50-61 (Medical Economics Inc)</td>
<td>62-65 (Medical Economics Inc)</td>
<td>NA§</td>
<td>67-77 (Medical Economics Inc)</td>
<td>57-65 (Pharmacia Corp)</td>
<td>38-40 (Deleu and Hanssens)</td>
</tr>
<tr>
<td>Complete relief of pain at 2 h</td>
<td>30-32 (Paffenrath et al)</td>
<td>22-39 (Spencer et al)</td>
<td>NA</td>
<td>40-44 (Dooley and Faulds)</td>
<td>18 (Spierings et al)</td>
<td>NA</td>
</tr>
<tr>
<td>Headache recurrence at 24 h</td>
<td>29-34 (Perry and Markham; Paffenrath et al)</td>
<td>13-39 (Spencer et al)</td>
<td>27-45 (Dulli; Klassen et al; Mathew et al)</td>
<td>28-47 (Bornhof et al; Kramer et al)</td>
<td>19-27 (Deleu and Hanssens; Spierings et al)</td>
<td>9-14 (Deleu and Hanssens)</td>
</tr>
</tbody>
</table>

*All data are presented as percentage of patients (reference). NA indicates unavailable data.
†Not yet approved for use in the United States.
‡Response is defined as a decrease in pain from moderate or severe to mild or none.
§Headache response to naratriptan was reported at 4 hours, not 2 hours. Sixty percent to 66% of patients taking 2.5 mg of naratriptan reported headache response at 4 hours.27
¶Complete as a decrease in pain from moderate or severe to none (ie, pain free).
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 Significant differences in safety among the triptans have not been demonstrated, although the clinically used doses of naratriptan and almotriptan yield few adverse effects, producing a tolerability similar to that seen with placebo. Typical adverse effects of the triptans are fatigue, dizziness, paresthesias, warm sensations, and neck, chest, and throat tightness. The tolerability of individual triptans is relative and cannot be predicted on the basis of lipophilicity, bioavailability, absolute dose size, or any combination of these variables. Because all triptans are 5-HT_{1B/D} agonists in the low nanomolar range, differences in their adverse effects profiles are unlikely to be mediated through 5-HT_{1B/D} receptors.

The first triptan to be developed and approved for clinical use in patients with migraine was sumatriptan, which is available in injectable, intranasal, and oral formulations. The limitations of sumatriptan include low bioavailability, short plasma half-life, and low liposolubility. These and other drawbacks prompted the development of triptans with improved pharmacokinetic properties.

Zolmitriptan has a significantly higher oral bioavailability than sumatriptan (40% vs 14%). Zolmitriptan has efficacy similar to that of sumatriptan for the relief of a single migraine attack, and a high consistency of response in open-label extension studies longer than 1 year, with 95% of attacks aborted by 4 hours with 1 to 2 doses of 2.5 mg or 5 mg. Zolmitriptan is generally well tolerated, with mild, brief adverse effects typical of all triptans.

Naratriptan, compared with sumatriptan, has greater bioavailability (about 60%); a longer elimination half-life (5.0-5.5 hours); better lipophilicity, and thus, better central nervous system penetration; and less reversibility in 5-HT receptor binding. Comparative trials have shown that 2.5 mg of naratriptan is less effective than 100 mg of sumatriptan in terms of the likelihood of achieving headache relief, but has almost no adverse effects. Naratriptan has a lower headache recurrence rate than sumatriptan and rizatriptan when directly compared, but the time to recurrence is not longer with naratriptan.

Rizatriptan has a rapid onset of action, high bioavailability, and a favorable adverse effects profile. In direct comparisons of oral sumatriptan and rizatriptan in patients with migraine, 10 mg of rizatriptan had a slightly quicker time to headache relief in hazards ratio analysis against both the 50-mg and 100-mg doses of sumatriptan and better effects on several other secondary measures of efficacy, including reduction of functional disability and the proportion of patients who were pain free at 2 hours. As with sumatriptan, rizatriptan is not affected by concurrent use of oral contraceptives or medications metabolized by the hepatic cytochrome P 450 3A4 system. Doses of rizatriptan must be halved when administered concomitantly with propranolol, but not with other β-blockers.

Almotriptan is structurally related to sumatriptan, but its potency at the 5-HT_{1D} receptor is lower than that of sumatriptan, though its potency at the 5-HT_{1B} receptor is similar to that of sumatriptan and rizatriptan. Results from a randomized, double-blind, placebo-controlled trial indicate that almotriptan is effective across multiple attacks, with 2 of 3 attacks relieved in 75% of patients treated with 12.5 mg of almotriptan.

Frovatriptan has one of the highest affinities for the 5-HT_{1B} receptor and a long elimination half-life (as long as 25 hours). Frovatriptan seems to have a slower onset of action than most other triptans. About one third of patients in open-label extension studies longer than 1 year reported pain relief in less than 2 hours after dosing, with headache recurrence rates of less than 10%.

Eletriptan has affinity for 5-HT_{1B/D} receptors that is 4 to 8 times higher than that of sumatriptan. Eletriptan is a substrate for P-glycoprotein, an important efflux transporter at the blood-brain barrier. This finding suggests that eletriptan has the potential for increased central nervous system concentrations and drug-drug interactions when coadministered with medications that are substrates or inhibitors of P-glycoprotein. In addition, eletriptan is metabolized by the cytochrome P 450 3A4 system, and dose reduction may be mandated in the prescribing information when eletriptan is administered with medications that also are degraded by cytochrome P 450 3A4, such as macrolide antibiotics and antifungal medications.

CONCLUSIONS

Triptans are a major clinical advance in the treatment of migraine. The clinical efficacy of these drugs in migraine is related in part to their multiple mechanisms of action at vascular, neural, and central physiologic sites implicated in the pathophysiology of migraine. In combination with their highly selective affinity for 5-HT_{1B/D} receptors, the triptans have favorable pharmacologic properties, characterized by high oral bioavailability, rapid onset of action, and low incidence of adverse effects. These features underlie the beneficial effects of the triptans in patients with migraine, including rapid relief of headache and associated symptoms and improvements in productivity and health-related quality of life. Future studies may identify additional mechanisms of action of the triptans and the optimal role of these agents in the management of patients with migraine.

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REFERENCES


