5-HT_{1F} Receptor Agonists: A New Treatment Option for Migraine Attacks?

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Summary: Migraine is a debilitating disorder of the CNS. Although therapeutic options for migraine attacks have tremendously advanced with the development of triptans more than a decade ago, several conditions (such as vascular disease) restrict their use. Moreover, some patients do not respond to triptans and other currently available medications. Therefore, treatment alternatives are needed. Study data show that 5-HT_{1F} receptor agonists successfully abort

migraine attacks. These data also suggest a favorable vascular side-effect profile of these substances, which could be beneficial for migraine treatment in subjects with cardiac or vascular disease. We discuss the current knowledge of 5-HT_{1F} receptor-mediated effects, in part by comparing them to triptans, and we also summarize data from basic research and clinical trials. **Key Words:** 5-HT_{1F}, serotonin receptor, migraine, treatment, triptans.

CURRENT TREATMENT OPTIONS

Migraine attacks can be treated effectively with non-steroidal anti-inflammatory drugs, pain killers, the first generation triptan (sumatriptan), and newer triptans such as rizatriptan or almotriptan. To date, these 5-HT_{1B/1D} agonists represent the gold standard for the treatment of migraine attacks. A meta-analysis showed that 59% of all patients achieve a headache response with 100 mg sumatriptan orally. Approximately 29% of subjects are pain-free after 2 h, and 20% of subjects show sustained pain freedom (pain-free by 2 h after dosing and no headache recurrence or use of rescue medication through 24 h). With some of the newer triptans, higher success rates of as much as 40% for the 2 h pain-free endpoint can be seen.¹ Despite the good efficacy of triptans, it has been estimated that approximately 25% of all migraine patients do not respond to triptan treatment, even when the drug is used correctly (i.e., according to prescribed dose, time, and route of administration).² The reasons for treatment failure remain obscure.

Triptans are supposed to have three important mechanisms of action: 1) vasoconstriction, 2) inhibition of

neuropeptide release, and 3) inhibition of signal transmission to second order neurons within the trigeminal nucleus complex.³ The inhibition of calcitonin gene-related peptide and substance P release attenuates peripheral consequences of trigeminal stimulation (e.g., neurogenic inflammation) and also central pain transmission. However, it is still an unsolved question as to whether neuronal or vascular or both mechanisms are responsible for the anti-migraine effect of these compounds.

5-HT₁ RECEPTORS AND MIGRAINE

Triptans exert their function mainly through binding at the 5-HT_{1B} and 5-HT_{1D} receptor. The 5-HT_{1B} receptor can be found on smooth muscle cells in cerebral and coronary vessels, and this receptor mediates triptan induced vasoconstriction.^{4–8} Experimentally, various isolated blood vessels from several species contract in response to triptans. The vascular effects of 5-HT_{1B/1D} agonists are more pronounced in cranial vessels than in peripheral arteries, probably due to the predominance of the 5-HT_{1B} receptor in the cranial vasculature.⁹ In contrast to cerebral arteries, vasoconstriction in coronary arteries is mainly mediated through 5-HT₂ receptors. However, 5-HT₁ receptors also participate to a smaller extent in cardiac vessel constriction,¹⁰ mostly through activation of the 5-HT_{1B} receptor subtype.⁷ Because the vasoconstrictive potency of the triptans is low in cardiac

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vessels, it is unlikely that therapeutic plasma concentration can lead to myocardial ischemia in patients without coronary heart disease and normal coronary circulation.¹¹ However, rare cases of stroke,^{12,13} myocardial infarction,^{14–16} and arrhythmia¹⁷ have been reported in relation to triptan use. Therefore, the use of triptans is not recommended in patients with manifestation of or at certain risk for cerebrovascular or coronary artery disease. For patients with the aforementioned risk and for people older than 65 years of age, new drugs without vascular side effects, but with the same or even better potency than triptans are needed to abort migraine attacks.

Unlike the 5-HT_{1B} receptors, the 5-HT_{1D} receptors can be mainly found on neuronal tissues. Expression of both the 5-HT_{1B} and the 5-HT_{1D} receptor have been detected in the trigeminal ganglion^{4,18,19} and expression of the 1D receptor subtype has additionally been detected on sensory trigeminal fibers.^{5,20} The suggestion has been made that triptans exert their effects by reducing neurogenic inflammation and inhibiting neurotransmitter release mainly through the stimulation of the 5-HT_{1D} receptor. Although neurogenic inflammation (first described in experimental animals) has never been convincingly demonstrated in man, neuropeptide release (i.e., calcitonin gene-related peptide) could be shown in migraine and cluster headaches.^{21–23}

The notion that selective 5-HT_{1D} receptor agonists do not mediate vascular effects was previously believed to offer a safe strategy for migraine treatment. However, a randomized, double blind, placebo-controlled study with a selective 5-HT_{1D} receptor agonist (PNU-142633) failed to show any statistically significant treatment effects. Surprisingly PNU-142633 was also associated with cardiac adverse events, such as chest pain, mild atrioventricular block and QTc prolongation.²⁴ The findings of this study suggest that the anti-migraine effects of triptans are mediated through a 5-HT receptor other than the 1D subtype.

In addition to serotonin 1B and 1D subtypes, several other HT₁ receptors have been cloned. Among these, the so-called 5-HT_{1F} receptor appears to be promising for the treatment of migraine. This hypothesis is supported by the fact that triptans also have a high affinity for the 5-HT_{1F} receptor in addition to the affinity at the 1B and 1D receptors.^{25,26} The 5-HT_{1F} receptor is a member of the 5-HT₁ receptor family of G protein coupled receptors that inhibit adenylyl cyclase, which is prominently expressed in the brain, uterus, and mesentery.^{27,28} In detail, the 5-HT_{1F} receptor can be found in parts of the trigeminal system, such as the trigeminal ganglion (only messenger RNA [mRNA])⁴ and the trigeminal nucleus caudalis (mRNA and protein).^{29–31} This receptor is also expressed in the neocortex and the hippocampus³⁰ and mRNA can be detected in human brain vessels.⁴ Isolated

microvessels and capillaries consistently show the expression of 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptor mRNA. In contrast to the 1D receptor subtype, expression of 5-HT_{1F} mRNA can not be found in microvascular cell cultures of endothelial or smooth muscle cells of cerebral vessels.⁸ However, the mRNA of the 5-HT_{1F} receptor (and various other 5-HT receptors) can be detected in astrocytes, which are intimately associated to intraparenchymal blood vessels.^{8,32} Pharmacological activation of 5-HT_{1F} receptors through selective agonists does not lead to vasoconstriction of cerebral arteries.^{26,33} Moreover, no vasoconstrictive activity of 5-HT_{1F} receptor agonists could be observed in peripheral arteries.^{25,34,35} In conclusion, the 5-HT_{1F} receptor is very unlikely to be involved in the regulation of the vascular tone in the human brain. Therefore, novel selective serotonin 1F receptor subtype agonists without or with only minimal affinity to 5-HT_{1B} or 5-HT_{1D} receptors could be promising for anti-migraine therapy.

5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors share some interesting properties, as they have been found to be co-localized with glutamate in trigeminal ganglia neurons in the rat.³⁶ Glutamate is a major excitatory neurotransmitter in the CNS, and is supposed to be involved in the mechanisms of cortical spreading depression, the hypothesized pathophysiological correlate of the migraine aura.³⁷ Furthermore, glutamate is believed to contribute to the activation of the trigeminovascular system and central sensitization.³⁸ Most recently, it has been described that effective prophylactic treatment of migraine reduces elevated plasma glutamate levels in these patients.³⁹ The co-localization of the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors and glutamate could indicate a possible inhibition of glutamate release by 5-HT_{1F} receptor agonists and/or triptans, which could provide an additional explanation for their anti-nociceptive effects.

A general analgesic action of 5-HT_{1F} receptor agonists is unclear. In one study, the 5-HT_{1F} receptor agonist LY334370 did not abort hyperalgesia in rats and also failed to modify spinal nociceptive reflexes in the rabbit.⁴⁰ However, newer, contradicting data show an antinociceptive effect of the 5-HT_{1F} receptor agonist LY344864 in the rat formalin test (quantification of nociceptive behavior after injection of formalin into the hind paw).⁴¹ More data are needed to answer this question.

Several selective 5-HT_{1F} receptor agonists have been developed in the past. Among these are LY334370,⁴² LY344864,⁴³ and LY349950.⁴⁴ The latest synthesized 5-HT_{1F} receptor agonist that has been proposed to be effective in migraine is COL-144.⁴⁵ Some of these substances have been tested in experimental migraine models.

5-HT_{1F} RECEPTOR AGONISTS INHIBIT NEUROGENIC INFLAMMATION

An experimental animal model that has been widely used to study efficacies of acute anti-migraine therapies is the so called “neurogenic inflammation” model. In this model neurotransmitter release from trigeminal fibers is measured indirectly by quantifying plasma protein extravasation in the dura mater after electrical stimulation of the trigeminal ganglion.⁴⁶ Intravenous administration of several 5-HT receptor agonists led to an attenuation of dural plasma protein extravasation. The strongest effects were expressed by the 5-HT_{1F} receptor agonist LY334370, followed in a rank order by naratriptan > LY302148 > LY306528 = zolmitriptan > dihydroergotamine > sumatriptan > rizatriptan > L-694,247. Interestingly, the potency of the 5-HT₁ agonists in this model was correlated to their affinity to the 5-HT_{1F} receptor, whereas no correlation could be found between potency and affinity to the 5-HT_{1B} and 5-HT_{1D} receptors. The authors concluded that inhibition of plasma protein extravasation is primarily mediated through the 5-HT_{1F} receptor, explaining a possible anti-migraine effect of the 5-HT_{1F} receptor agonists.²⁵ In a similar study design, the administration of the 5-HT_{1F} receptor agonist LY344864 intravenously 10 minutes or orally 75 minutes before trigeminal stimulation also led to a dose-dependent reduction of plasma protein extravasation in the dura mater.⁴³ It is noteworthy to mention that antagonists of the neurokinin-1 receptor and agonists of the 5-HT_{1D} receptor block neurogenic inflammation, but they do not abort migraine attacks.^{24,47} Lately, Peroutka postulated that the ability of drugs to selectively inhibit neuronal plasma extravasation in rodents has no predictive value for the efficacy in the acute treatment of migraine.⁴⁸

Activity of the 5-HT_{1F} receptor can also be measured by assessing the binding of the stable analogue [35S]GTPγS. This assay can be used to analyze neuronal 5-HT_{1F} receptor coupling in substantia nigra, and LY334370 was the most potent compound compared to the other tested compounds, such as sumatriptan, naratriptan, zolmitriptan, methysergide, and dihydroergotamine. Furthermore, there was a statistically significant correlation between the 5-HT_{1F} receptor agonist potency in [35S]GTPγS binding and the degree of inhibition of trigeminal nerve-stimulated dural plasma protein extravasation.⁴⁹

5-HT_{1F} RECEPTOR AGONISTS DECREASE STIMULUS INDUCED C-FOS IN THE TRIGEMINAL NUCLEUS CAUDALIS

One experimental model uses chemical, mechanical, or electrical activation of C- and Aδ fibers of the trigeminal nerve to induce the expression of the immediate early gene c-fos within cells of the trigeminal nucleus

caudalis.⁵⁰ Sumatriptan has been shown to decrease c-fos-like immunoreactivity in the trigeminal nucleus caudalis after noxious meningeal stimulation, indicating inhibition of the activity of neurons.⁵¹ Both sumatriptan and the 5-HT_{1F} receptor agonist LY344864 (intraperitoneally) also decrease intracisternally administered capsaicin induced c-fos-like immunoreactivity within laminae I and laminae II of the trigeminal nucleus caudalis in mice. Sumatriptan was approximately 15-fold more potent than LY344864. Blocking experiments revealed that sumatriptan attenuates c-fos-like immunoreactivity via 5-HT_{1B} receptors, whereas LY344864 acts via 5-HT_{1F} receptors.⁵² As LY344864 is able to cross the blood-brain barrier,⁴³ this substance is likely to inhibit the response via central 5-HT_{1F} receptors on trigeminal nucleus caudalis neurons. Sumatriptan has no strong ability to cross the intact blood brain barrier,⁵³ and there is also no clear evidence that the blood brain barrier disrupts during a migraine attack.⁵⁴ Therefore, it was proposed that sumatriptan predominantly acts on peripheral 5-HT_{1B} receptors (e.g., terminals of the trigeminovascular neurons). However, several animal studies demonstrated a CNS effect of sumatriptan. These findings imply that sumatriptan exerts antinociceptive activity also within the CNS,⁵⁵ in addition to its peripheral trigeminovascular effects.

In another study, the oral pretreatment of rats with the 5-HT_{1F} receptor agonists LY334370 and LY397584 significantly decreased the number of second order neurons in the trigeminal nucleus caudalis, which stained positive for induced c-fos protein. The blocking potency of both compounds (minimal effective dose of LY334370 1 μg/kg and of LY397584 1 mg/kg) was clearly different, which was attributed to differences of their ability to penetrate the blood brain barrier.⁵⁶ The latter could influence the properties of 5-HT_{1F} receptor agonists to inhibit c-fos expression in the trigeminal nucleus caudalis.⁵⁷ In summary, the finding that stimulation of the 5-HT_{1F} receptor was able to modulate the activity of the trigeminal system identifies this receptor as a possible target for anti-migraine drugs. Based on these findings, the efficacy of 5-HT_{1F} receptor agonists to abort migraine could be dependent on their ability to cross the blood brain barrier.

5-HT_{1F} RECEPTOR AGONISTS AND VASCULAR PROPERTIES

The development of triptans was based on the vascular theory of migraine (i.e., the vasodilatation of brain vessels activates trigeminovascular nerve endings and leads to the generation of pain). Accordingly, triptan-mediated vasoconstriction would then lead to migraine pain relief.

Different animal models exist to investigate vascular properties of drugs. The vasoconstrictive effects of sumatriptan were first demonstrated in the isolated saphenous

vein of the dog, which is a tissue that shows contractile responses to anti-migraine agents similar to the human middle cerebral artery.⁵⁸ Other studies also identified the saphenous vein of the rabbit as a tissue with contractile response to serotonin receptor agonists similar to both the human cerebral arteries and also to the coronary arteries.⁵⁹ 5-HT_{1B}, 5-HT_{1F}, and, to a smaller extent, 5-HT_{1D} receptor mRNAs have been identified in human cerebral arteries.⁴ The 5-HT_{1B} receptor mRNA has also been found in human coronary arteries⁷ and in peripheral blood vessels.^{60,61} The 5-HT_{1F} mRNA receptor could only be detected in a very low amount in human coronary arteries.³³ The mRNA of all three receptors has been detected in the saphenous vein of the rabbit.^{61,62} Although sumatriptan, zolmitriptan, rizatriptan, and naratriptan contracted the saphenous vein of the rabbit, no contraction could be achieved with high doses of the 5-HT_{1F} receptor agonist LY344864. A significant correlation between the contractile potency and the affinities at the 5-HT_{1B} and 5-HT_{1D} receptors, but not the 5-HT_{1F} receptor could be demonstrated for these ligands.³⁵ Another 5-HT_{1F} receptor agonist (i.e., LY334370) failed to produce a contractile response in the rabbit's saphenous vein in doses as great as 10^{-4} M in a similar study. Modest precontraction with PGE_{2 α} augmented the contractile response to sumatriptan and ergotamine. Some vasoconstriction could be archived with LY344864 after precontraction with PGE_{2 α} but only when doses exceeded 10^{-5} M (i.e., concentrations that probably also activated 5-HT_{1B} receptors).⁶³ Application of LY334370 in concentrations up to 10^{-5} M to human cerebral vessels had no significant vasoconstrictor effect.⁴⁰ These findings are supported by another study in the human middle meningeal artery using agonists with different affinities to the 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptor, and several 5-HT_{1B} and 5-HT_{1D} receptor antagonists. A significant correlation between vasoconstrictor potency in human middle meningeal artery and binding affinity to the 5-HT_{1B} receptors was observed. In contrast, a weak, but not statistically significant relationship between vasoconstrictor potency and binding affinity at 5-HT_{1D} receptors, and no relationship between vasoconstrictor potency and 5-HT_{1F} receptor affinity, could be found in these vessels. Most importantly, these results led to the conclusion that vasoconstriction in the middle meningeal artery is 5-HT_{1B} receptor-mediated without any contribution from 5-HT_{1F} receptors.²⁶

In summary, several studies demonstrate the existence of 5-HT_{1F} receptors on cerebral and also peripheral blood vessels. However, activation of the 5-HT_{1F} receptor does not lead to vasoconstriction. Therefore, vasoconstriction can not be a mechanism that accounts for the antimigraine effect of these compounds.

5-HT_{1F} RECEPTOR AGONISTS IN THE TREATMENT OF MIGRAINE ATTACKS—CLINICAL TRIALS

A number of 5-HT_{1F} receptor agonists have been developed, but the first published substance to enter a clinical trial was LY334370, a substance with a 100-fold higher selectivity for the 5-HT_{1F} receptor than the 5-HT_{1B} and 5-HT_{1D} receptors.²⁵ Phase I studies were presented in 1998 and showed good tolerability in a dose $\leq$ 400 mg with central side effects similar to these of triptans (weakness, somnolence, and dizziness). Cardiovascular side effects were not reported. Adverse events were mostly mild to moderate in severity and did not last longer than 24 hours.⁶⁴ A phase II study was later conducted with 99 migraine patients who had moderate or severe migraine headaches in a randomized, placebo controlled, double blind, parallel design of three single oral doses (20, 60, or 200 mg) of LY334370 and placebo. In the 200 and 60 mg treatment groups, the following outcomes after 2 h were significantly better than in the placebo group: headache response, pain freedom, sustained response, and sustained pain-free rates. The primary endpoint was the sustained response after 2 h, which is defined as a reduction in migraine headache from moderate to severe to mild or none. The primary endpoint was achieved in 31% for 60 mg LY334370, 52% for 200 mg, and 8% in the placebo group. The pain-free rate at 2 h was 23% in the 60 mg group and 34% in the 200 mg group (placebo, 4%). These rates are slightly higher than in most of the triptan studies. However, an active triptan comparator was not included in the study. Headache recurrence rate was low, which was attributed to the long half-life of LY334370 (14–16 h). The most frequent adverse events (i.e., asthenia, dizziness, somnolence, and paresthesia) were observed much more often after treatment with LY334370 than commonly seen with triptans (Table 1). The relatively high effective doses in this trial were still lower than the drug concentrations that are needed to constrict the human cerebral or coronary arteries. Based on the experimental and clinical data, the authors of the study concluded that LY334370 mediates its anti-migraine action not through peripheral vascular effects, but through central mechanisms (i.e., blockade of transmission of nociceptive impulse within trigeminal nucleus caudalis).⁶⁵ Unfortunately, clinical trials of LY334370 were halted in 1999 for toxicity in animals and no further development for the compound is in sight.

Because of these promising clinical data, a series of new 5-HT_{1F} receptor agonists were developed that finally led to the synthesis of COL-144 (CoLucid Pharmaceuticals Inc. [Research Triangle Park, NC]; formerly LY573144). This substance, which has recently been given the name Lasmiditan, is an agonist with greater selectivity and improved bioavailability compared with

TABLE 1. Commonly Reported Adverse Events of the 5-HT_{1F} Receptor Agonist LY334370

Event	Placebo	LY334370			<i>p</i>
	(n = 30)	20 mg (n = 27)	60 mg (n = 33)	200 mg (n = 26)	
Asthenia	0 (0%)	2 (7%)	17 (52%)	7 (27%)	<0.001
Dizziness	0 (0%)	1 (4%)	10 (30%)	9 (35%)	<0.001
Somnolence	1 (3%)	1 (4%)	7 (21%)	6 (23%)	0.031
Paresthesia	1 (3%)	1 (4%)	4 (12%)	5 (19%)	0.138

The most commonly reported adverse events of the 5-HT_{1F} receptor agonist LY334370 in clinical trials were CNS side effects. Please note that typical triptan side effects, such as tightness of chest and muscle aches are not reported herein.

LY334370. COL-144 has a high affinity to the 5-HT_{1F} receptor (binding $K_i = 2.21 \pm 0.22$) with a very low affinity to other 5-HT₁ receptors (5-HT_{1B}: $K_i = 1043 \pm 124$; 5-HT_{1D}: $K_i = 1357 \pm 156$). Unlike triptans, COL-144, which is not considered to be a triptan, has functional selectivity for 5-HT_{1F} receptors which is >450-fold higher than for 5-HT_{1B} and 5-HT_{1D} receptors (Table 2). The substance does not cause constriction of the saphenous vein of the rabbit in concentrations up to 10^{-4} M. COL-144 also inhibits stimulus-induced c-fos expression in the trigeminal nucleus caudalis of the rat and reduces dural plasma protein extravasation in a standard experimental setup in experimental animals 1 h after oral dosing.⁴⁵

The efficacy and an improved tolerability of COL-144 in migraine headaches was demonstrated in a first placebo-controlled study. The study involved 130 patients who were not on prophylaxis and who had moderate to severe migraine headaches. These patients received doses from 2.5 to 45 mg of COL-144 or a placebo as an intravenous infusion for 20 minutes. The headache response of the patients was superior in the 10, 20, 30, and 45 mg dose groups compared to the placebo (54.2 to 75%

vs 45.2%) with a statistically significant linear dose-response rate. COL-144 was generally well tolerated with a similar adverse event profile as LY334370 (i.e., paresthesia, dizziness, and heaviness). Cardiac side effects were not observed.⁶⁶

The oral compound of COL-144 was studied afterward in a phase I trial in healthy males, in dosing ranges from 2.5 to 400 mg. All doses were well tolerated with no clinically significant effects on vital signs, orthostatic responses, safety laboratories, or electrocardiograms. The most common adverse events at doses of 100 mg and greater were drowsiness, dizziness, and paresthesia. Doses of 50 mg and greater achieved plasma levels previously associated with efficacy of the intravenous administration route with a slight delay in T_{max}.⁶⁷ Data from both studies have only been presented in abstract form so far. Just recently, a double blind, placebo-controlled phase II study with the oral formulation of COL-144 in doses ranging from 50 to 400 mg in the acute treatment of migraine attacks was performed, but the results have not yet been evaluated. So far, this is the most promising 5-HT_{1F} receptor agonist in clinical trials.

CONCLUSION

Experimental and clinical data show that activation of the 5-HT_{1F} receptor is efficacious in animal models of migraine, and more importantly in the acute treatment of migraine attacks. Cerebral vasodilatation might be one element in the generation of migraine pain. The lack of 5-HT_{1F} agonists to constrict cerebral vessels, but to alleviate migraine attacks, supports the hypothesis that vasoconstriction is not fundamentally necessary to terminate migraine attacks. Moreover, the efficacy of 5-HT_{1F} agonists also supports the hypothesis that central mechanisms (such as the transmission of nociceptive signals within the trigeminal system, which can be attenuated by the activation of the 5-HT_{1F} receptor) are key elements in the pathophysiology of migraine.

Oral 5-HT_{1F} receptor agonists are a promising class of drugs for the acute treatment of migraine attacks. They appear to have a safety advantage in comparison with the

TABLE 2. Activation of 5-HT Receptors in Substantia Nigra through Various Triptans and the 5-HT_{1F} Receptor Agonists

Drug	Receptor; EC ₅₀ (GTPγS) nM			
	5-HT _{1A}	5-HT _{1B}	5-HT _{1D}	5-HT _{1F}
Sumatriptan	>10.000	70	3	247
Zolmitriptan	~10.000	20	1	417
Rizatriptan	>10.000	119	5	2540
Naratriptan	~10.000	7	2	19
Frovatriptan	1150	20	2	367
LY334370	1590	1340	226	1
LY344864	ND	ND	ND	25
COL-144	>10.000	~10.000	>1.000	43

Stimulation of GTPγS binding, EC₅₀ nM (concentration at which 50% of the effect is observed). COL-144 has a high selectivity for the 5-HT_{1F} receptor, but only very low activation of the 5-HT_{1B} and 5-HT_{1D} receptors. ND = not done. (Table according to Nelson et al.⁴⁵ and Ramadan et al.⁶⁸)

5-HT_{1B} and 5-HT_{1D} receptor agonists, especially in patients with contraindication to triptans because of known cardiovascular and/or cerebrovascular disease or because of an elevated vascular risk profile. A significant number of migraine patients do not respond to triptans or non-steroidal anti-inflammatory drugs. It is not yet known whether new 5-HT_{1F} receptor agonists effectively abort attacks in these subjects, but this is of great interest. Further phase III clinical studies are needed to confirm the efficacy and an improved adverse event profile in large patient groups. Moreover, head-to-head trials comparing triptans and 5-HT_{1F} receptor agonists could finally demonstrate the theoretical advantage of this new drug class with respect to adverse events, assuming at least an equal efficacy of both substance classes.

REFERENCES

- Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT_{1B/1D} agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002;22:633–658.
- Diener HC, Limmroth V. Advances in pharmacological treatment of migraine. *Expert Opin Investig Drugs* 2001;10:1831–1845.
- Goadsby PJ. The pharmacology of headache. *Prog Neurobiol* 2000;62:509–525.
- Bouchelet I, Cohen Z, Case B, Seguela P, Hamel E. Differential expression of sumatriptan-sensitive 5-hydroxytryptamine receptors in human trigeminal ganglia and cerebral blood vessels. *Mol Pharmacol* 1996;50:219–223.
- Longmore J, Hargreaves RJ, Boulanger CM, et al. Comparison of the vasoconstrictor properties of the 5-HT_{1D}-receptor agonists rizatriptan (MK-462) and sumatriptan in human isolated coronary artery: outcome of two independent studies using different experimental protocols. *Funct Neurol* 1997;12:3–9.
- Hamel E, Fan E, Linville D, Ting V, Villemure JG, Chia LS. Expression of mRNA for the serotonin 5-hydroxytryptamine_{1D} beta receptor subtype in human and bovine cerebral arteries. *Mol Pharmacol* 1993;44:242–246.
- Nilsson T, Longmore J, Shaw D, Olesen JJ, Edvinsson L. Contractile 5-HT_{1B} receptors in human cerebral arteries: pharmacological characterization and localization with immunocytochemistry. *Br J Pharmacol* 1999;128:1133–1140.
- Cohen Z, Bouchelet I, Olivier A, et al. Multiple microvascular and astroglial 5-hydroxytryptamine receptor subtypes in human brain: molecular and pharmacologic characterization. *J Cereb Blood Flow Metab* 1999;19:908–917.
- Longmore J, Razzaque Z, Shaw D, et al. Comparison of the vasoconstrictor effects of rizatriptan and sumatriptan in human isolated cranial arteries: immunohistological demonstration of the involvement of 5-HT_{1B}-receptors. *Br J Clin Pharmacol* 1998;46:577–582.
- Connor HE, Feniuk W, Humphrey PP. 5-Hydroxytryptamine contracts human coronary arteries predominantly via 5-HT₂ receptor activation. *Eur J Pharmacol* 1989;161:91–94.
- MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. *Circulation* 1998;98:25–30.
- Cavazos JE, Caress JB, Chilukuri VR, Devlin T, Gray L, Hurwitz BJ. Sumatriptan-induced stroke in sagittal sinus thrombosis. *Lancet* 1994;343:1105–1106.
- Jayamaha JE, Street MK. Fatal cerebellar infarction in a migraine sufferer whilst receiving sumatriptan. *Intensive Care Med* 1995;21:82–83.
- O'Connor P, Gladstone P. Oral sumatriptan-associated transmural myocardial infarction. *Neurology* 1995;45:2274–2276.
- Mueller L, Gallagher RM, Ciervo CA. Vasospasm-induced myocardial infarction with sumatriptan. *Headache* 1996;36:329–331.
- Abbrescia VD, Pearlstein L, Kotler M. Sumatriptan-associated myocardial infarction: report of case with attention to potential risk factors. *J Am Osteopath Assoc* 1997;97:162–164.
- Laine K, Raasakka T, Mantynen J, Saukko P. Fatal cardiac arrhythmia after oral sumatriptan. *Headache* 1999;39:511–512.
- Bonaventure P, Voorn P, Luyten WH, Leysen JE. 5HT_{1B} and 5HT_{1D} receptor mRNA differential co-localization with peptide mRNA in the guinea pig trigeminal ganglion. *Neuroreport* 1998;9:641–645.
- Rebeck GW, Maynard KI, Hyman BT, Moskowitz MA. Selective 5-HT_{1D} alpha serotonin receptor gene expression in trigeminal ganglia: implications for antimigraine drug development. *Proc Natl Acad Sci U S A* 1994;91:3666–3669.
- Smith D, Hill RG, Edvinsson L, Longmore J. An immunocytochemical investigation of human trigeminal nucleus caudalis: CGRP, substance P and 5-HT_{1D}-receptor immunoreactivities are expressed by trigeminal sensory fibres. *Cephalalgia* 2002;22:424–431.
- Fanciullacci M, Alessandri M, Figini M, Geppetti P, Michelacci S. Increase in plasma calcitonin gene-related peptide from the extracerebral circulation during nitroglycerin-induced cluster headache attack. *Pain* 1995;60:119–123.
- Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 1990;28:183–187.
- Juhasz G, Zsombok T, Modos EA, et al. NO-induced migraine attack: strong increase in plasma calcitonin gene-related peptide (CGRP) concentration and negative correlation with platelet serotonin release. *Pain* 2003;106:461–470.
- Gomez-Mancilla B, Cutler NR, Leibowitz MT, et al. Safety and efficacy of PNU-142633, a selective 5-HT_{1D} agonist, in patients with acute migraine. *Cephalalgia* 2001;21:727–732.
- Johnson KW, Schaus JM, Durkin MM, et al. 5-HT_{1F} receptor agonists inhibit neurogenic dural inflammation in guinea pigs. *Neuroreport* 1997;8:2237–2240.
- Razzaque Z, Heald MA, Pickard JD, et al. Vasoconstriction in human isolated middle meningeal arteries: determining the contribution of 5-HT_{1B}- and 5-HT_{1F}-receptor activation. *Br J Clin Pharmacol* 1999;47:75–82.
- Adham N, Kao HT, Schecter LE, et al. Cloning of another human serotonin receptor (5-HT_{1F}): a fifth 5-HT₁ receptor subtype coupled to the inhibition of adenylate cyclase. *Proc Natl Acad Sci U S A* 1993;90:408–412.
- Adham N, Borden LA, Schechter LE, et al. Cell-specific coupling of the cloned human 5-HT_{1F} receptor to multiple signal transduction pathways. *Naunyn Schmiedeberg Arch Pharmacol* 1993;348:566–575.
- Waeber C, Moskowitz MA. [3H]sumatriptan labels both 5-HT_{1D} and 5-HT_{1F} receptor binding sites in the guinea pig brain: an autoradiographic study. *Naunyn Schmiedeberg Arch Pharmacol* 1995;352:263–275.
- Pascual J, del Arco C, Romón T, del Olmo E, Castro E, Pazos A. Autoradiographic distribution of [3H]sumatriptan-binding sites in post-mortem human brain. *Cephalalgia* 1996;16:317–322.
- Bruinvels AT, Landwehrmeyer B, Gustafson EL, et al. Localization of 5-HT_{1B}, 5-HT_{1D} alpha, 5-HT_{1E} and 5-HT_{1F} receptor messenger RNA in rodent and primate brain. *Neuropharmacology* 1994;33:367–386.
- Hirst WD, Cheung NY, Rattray M, Price GW, Wilkin GP. Cultured astrocytes express messenger RNA for multiple serotonin receptor subtypes, without functional coupling of 5-HT₁ receptor subtypes to adenylyl cyclase. *Brain Res Mol Brain Res* 1998;61:90–99.
- Bouchelet I, Case B, Olivier A, Hamel E. No contractile effect for 5-HT_{1D} and 5-HT_{1F} receptor agonists in human and bovine cerebral arteries: similarity with human coronary artery. *Br J Pharmacol* 2000;129:501–508.
- Centurion D, Ortiz MI, Sanchez-Lopez A, De Vries P, Saxena PR, Villalon CM. Evidence for 5-HT_{1B/1D} and 5-HT_{2A} receptors mediating constriction of the canine internal carotid circulation. *Br J Pharmacol* 2001;132:983–990.
- Cohen ML, Schenck K. 5-Hydroxytryptamine(1F) receptors do not participate in vasoconstriction: lack of vasoconstriction to LY344864,

- a selective serotonin(1F) receptor agonist in rabbit saphenous vein. *J Pharmacol Exp Ther* 1999;290:935–939.
36. Ma QP. Co-localization of 5-HT(1B/1D/1F) receptors and glutamate in trigeminal ganglia in rats. *Neuroreport* 2001;12:1589–1591.
37. Moskowitz MA, Macfarlane R. Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev* 1993;5:159–177.
38. Ramadan NM. The link between glutamate and migraine. *CNS Spectr* 2003;8:446–449.
39. Ferrari A, Spaccapelo L, Pinetti D, Tacchi R, Bertolini A. Effective prophylactic treatments of migraine lower plasma glutamate levels. *Cephalalgia* 2009;29:423–429.
40. Shephard S, Edvinsson L, Cumberbatch M, et al. Possible anti-migraine mechanisms of action of the 5HT1F receptor agonist LY334370. *Cephalalgia* 1999;19:851–858.
41. Granados-Soto V, Arguelles CF, Rocha-Gonzalez HI, Godinez-Chaparro B, Flores-Murrieta FJ, Villalon CM. The role of peripheral 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1F serotonergic receptors in the reduction of nociception in rats. *Neuroscience* 2010;165:561–568.
42. Overshiner CC, Adham N, Zgombick JM, Branchek TA, Calligaro DO, Phebus LA. LY334370 is selective for the cloned 5-HT1f receptor. Paper presented at: 26th Annual Meeting of the Society for Neuroscience; 1996.
43. Phebus LA, Johnson KW, Zgombick JM, et al. Characterization of LY344864 as a pharmacological tool to study 5-HT1F receptors: binding affinities, brain penetration and activity in the neurogenic dural inflammation model of migraine. *Life Sci* 1997;61:2117–2126.
44. Xu YC, Johnson KW, Phebus LA, et al. N-[3-(2-Dimethylaminoethyl)-2-methyl-1H-indol-5-yl]-4-fluorobenzamide: a potent, selective, and orally active 5-HT(1F) receptor agonist potentially useful for migraine therapy. *J Med Chem* 2001;44:4031–4034.
45. Nelson DL, Phebus LA, Johnson KW, Wainscott DB, Cohen ML, Xu YC. COL-144: Preclinical profile of a selective 5-HT1F receptor agonist for migraine. *Cephalalgia* 2009;29:122–123.
46. Markowitz S, Saito K, Moskowitz MA. Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. *J Neurosci* 1987;7:4129–4136.
47. Goldstein DJ, Offen WW, Klein EG, et al. Lanepitant, an NK-1 antagonist, in migraine prevention. *Cephalalgia* 2001;21:102–106.
48. Peroutka SJ. Neurogenic inflammation and migraine: implications for the therapeutics. *Mol Interv* 2005;5:304–311.
49. Wainscott DB, Johnson KW, Phebus LA, Schaus JM, Nelson DL. Human 5-HT1F receptor-stimulated [35S]GTPgammaS binding: correlation with inhibition of guinea pig dural plasma protein extravasation. *Eur J Pharmacol* 1998;352:117–124.
50. Mitsikostas DD, Sanchez del Rio M. Receptor systems mediating c-fos expression within trigeminal nucleus caudalis in animal models of migraine. *Brain Res Brain Res Rev* 2001;35:20–35.
51. Nozaki K, Moskowitz MA, Boccalini P. CP-93,129, sumatriptan, dihydroergotamine block c-fos expression within rat trigeminal nucleus caudalis caused by chemical stimulation of the meninges. *Br J Pharmacol* 1992;106:409–415.
52. Mitsikostas DD, Sanchez del Rio M, Moskowitz MA, Waeber C. Both 5-HT1B and 5-HT1F receptors modulate c-fos expression within rat trigeminal nucleus caudalis. *Eur J Pharmacol* 1999;369:271–277.
53. Dixon CM, Saynor DA, Andrew PD, Oxford J, Bradbury A, Tarbit MH. Disposition of sumatriptan in laboratory animals and humans. *Drug Metab Dispos* 1993;21:761–769.
54. Edvinsson L, Tfelt-Hansen P. The blood-brain barrier in migraine treatment. *Cephalalgia* 2008;28:1245–1258.
55. Tfelt-Hansen PC. Does sumatriptan cross the blood-brain barrier in animals and man? *J Headache Pain* 2010;11:5–12.
56. Katofiasc M, Johnson KW, Phebus LA. The selective 5-HT1F agonists, LY334370 and LY397584, inhibit both central and peripheral branches of trigeminal sensory afferents in rats. *Cephalalgia* 2000;20:419–420.
57. Shephard SL, Williamson DJ, Williams J, Hill RG, Hargreaves RJ. Comparison of the effects of sumatriptan and the NK1 antagonist CP-99,994 on plasma extravasation in Dura mater and c-fos mRNA expression in trigeminal nucleus caudalis of rats. *Neuropharmacology* 1995;34:255–261.
58. Humphrey PP, Feniuk W, Perren MJ, et al. GR43175, a selective agonist for the 5-HT1-like receptor in dog isolated saphenous vein. *Br J Pharmacol* 1988;94:1123–1132.
59. Cohen ML, Johnson KW, Schenck KW, Phebus LA. Migraine therapy: relationship between serotonergic contractile receptors in canine and rabbit saphenous veins to human cerebral and coronary arteries. *Cephalalgia* 1997;17:631–638.
60. Ullmer C, Schmuck K, Kalkman HO, Lubbert H. Expression of serotonin receptor mRNAs in blood vessels. *FEBS Lett* 1995;370:215–221.
61. Wurch T, Palmier C, Colpaert FC, Pauwels PJ. Recombinant saphenous vein 5-HT1B receptors of the rabbit: comparative pharmacology with human 5-HT1B receptors. *Br J Pharmacol* 1997;120:153–159.
62. Bard JA, Kucharewicz SA, Zgombick JM, Weinshank RL, Branchek TA. Cloning and characterization of rabbit and dog 5-HT1F receptor subtypes: a comparison of the pharmacological profile to the human species homologue. *Soc Neurosci Abstr* 1996;22:528.8(abstr.).
63. Cohen ML, Schenck K. Contractile responses to sumatriptan and ergotamine in the rabbit saphenous vein: effect of selective 5-HT(1F) receptor agonists and PGF(2alpha). *Br J Pharmacol* 2000;131:562–568.
64. Gossen D, de Surray JM, Onkelinx C. First human dose study with LY334370, a selective 5HT1f agonist. 12th Migraine Trust International Symposium, 1998.
65. Goldstein DJ, Roon KI, Offen WW, et al. Selective serotonin 1F (5-HT(1F)) receptor agonist LY334370 for acute migraine: a randomised controlled trial. *Lancet* 2001;358:1230–1234.
66. Reuter U, Pilgrim AJ, Diener HC, Färkkilä M, Ferrari M. COL-144: a selective 5-HT1F agonist for the treatment of migraine attacks. *Cephalalgia* 2009;29:122.
67. Pilgrim AJ, Dussault B, Rupniak NMJ, White J, Mazur D, DiSanto AR. COL-144, an orally bioavailable selective 5-HT1F receptor agonist for acute migraine therapy. *Cephalalgia* 2009;29(Suppl 1):24–25.
68. Ramadan NM, Skljarevski V, Phebus LA, Johnson KW. 5-HT1F receptor agonists in acute migraine treatment: a hypothesis. *Cephalalgia* 2003;23:776–785.