

5HT_{1F}- and 5HT₇-Receptor Agonists for the Treatment of Migraines

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Abstract: Serotonin was the first neurotransmitter believed to be involved in cephalic pain transfer forward to the cortex, but the precise mechanism was confirmed only after sumatriptan, a 5-HT_{1B/1D} high affinity agonist, was introduced in the acute treatment of migraine. Although very efficient for migraine relief, activation of 5-HT_{1B} receptor may also cause vasoconstriction outside brain, within the heart arteries for example. Unlike 5-HT_{1B}, the 5-HT_{1D} receptor is not located in vascular tissues but exclusively within neuronal, but high affinity agonists for 5-HT_{1D} failed to prove clinical significance in randomized trials. The recent clone of 5-HT_{1F} receptor together with data showing that sumatriptan exerts high affinity for this receptor subtype generated high expectations. Potent agonists for 5-HT_{1F} receptors were effective in animal models for migraine and later clinical trials showed efficacy even in humans, introducing the first line future anti-migraine drugs. Apart from 5-HT_{1F}, another new cloned 5-HT subtype receptor, the 5-HT₇ also attracts attention. Recently developed and clinically tested selective 5HT₇ antagonists SB-269970-A and SB-656104-A suggest that the receptor may play a role in other CNS disorders including anxiety and cognitive disturbances, suggesting a potential role for the migraine prophylaxis. These data and speculations are discussed in details in this paper with special references.

INTRODUCTION

Migraine relief has been hypothesized for decades to be associated with activation or blockage of serotonin (5-hydroxytryptamine, 5-HT) receptors [1]. Although not all studies agreed [2], 5-HT infusion aborted spontaneous or reserpine-induced attacks in reports by Kimball [3] and Anthony [4]. The subsequent discovery of sumatriptan almost 20 year ago [5] fuelled the research in migraines but also in the field of serotonin and its receptors. Although 5-HT exerts its effects *via* 14 receptor subtypes at least [6], there is evidence for a role in pain transmission within the peripheral parts of the trigeminovascular system only for 5-HT₁ subtypes, the 5-HT_{1B} and 5-HT_{1D} in particular. The main action of sumatriptan, the first among several compounds classified into this triptan class of medications, was found to be on activation of these receptor subtypes (5-HT_{1B}, 5-HT_{1D}). Unfortunately these medications have some degree of vasoconstriction [7-9] that is related to chest symptoms, mainly tightness and pressure observed in some patients [10]. There is pharmacological and anatomical evidence that the vascular effects of sumatriptan are mediated by 5-HT_{1B} receptors [11-12]. Therefore, agents that modulate trigeminal pain through non-5-HT_{1B} receptors might retain their antimigraine efficacy while losing their cardiovascular side-effects. Based on their predominant neuronal location in the trigeminal system [12, 13], 5-HT_{1D} receptors have been proposed as better targets for anti-migraine drugs [14-16]. However selective 5-HT_{1D} agonists effective in animal models for migraine failed to prove clinical efficacy [17]. In 1993 Adham and colleagues encoded an additional human 5-HT receptor subtype [18]. The mRNA for this gene was detected in the human brain but was not detected in kidney, liver, spleen, heart, pancreas, and testes. High-affinity (K_d = 9.2 nM) ³H-labeled 5-HT binding was detected in native tissues. Competition studies revealed the following rank

order of potencies for serotonergic ligands at this new receptor: 5-HT > sumatriptan >> 5-carboxyamidotryptamine > 8-hydroxy-2-(di-1-propylamino)tetralin > spiperone. 5-HT produced a dose-dependent inhibition of forskolin-stimulated cAMP accumulation (EC₅₀ = 7.9 nM) in transfected cells. These properties distinguished this receptor from any previously characterized and established a fifth 5-HT₁receptor subtype (5-HT_{1F}) coupled to the inhibition of adenylate cyclase [18]. This 5-HT₁ subtype has become a new attractive target for future antimigraine drugs because it lacks vasoactive properties [19] and is expressed by neurons in the trigeminal ganglion (TG) and nucleus (TNC) [12, 20].

LOCALIZATION OF 5-HT_{1F} RECEPTOR

Molecular and autoradiographic studies revealed that the RNA for the 5-HT_{1F} receptor is localized on glutamate-containing neurons on various relays in the trigeminovascular system, including the human TG [12], the TNC [21, 22], the periaqueductal grey and the substantia gelatinosa [23], cerebral vessels [12], and on non-trigeminovascular sites such as the neocortex and the hippocampus [24]. No data for the distribution of 5-HT_{1F} receptors neither below the brainstem level of the spinal cord nor within the peripheral nerves are available. Low levels of mRNA for the 5-HT_{1F} and 5-HT_{1D} receptors have been found on human cerebral and coronary vessels [12, 25]. Further characterization of the mRNA distribution of the 5-HT₁ receptors in humans indicated the presence of 5-HT_{1B} and 5-HT_{1D}, but not 5-HT_{1F}, receptors on cerebral microvascular smooth muscles, and expression of all three subtypes on astrocytes [26].

PHARMACOLOGY OF 5-HT_{1F} RECEPTOR

The 5-HT_{1F} receptor functions *via* multiple transduction pathways including cAMP, Ca²⁺ and of G_i/G_o protein(s) dependent mechanisms [27]. The immunohistochemical colocalization of 5-HT_{1F} with glutamate in rat TG [28] raised the hypothesis that this receptors may modulate the glutaminergic system [29]. No data for interactions with other major brain neurotransmission systems exists so far. The

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assessment of the potency of various 5-HT₁ receptor agonists in constricting the rabbit saphenous vein (RSV) has demonstrated a strong positive correlation between contractile potency and affinity at the 5-HT_{1B} ($r = 0.93$, $P < 0.003$), but not at the 5-HT_{1F} receptor [30]. Similar conclusions were reached in RSV experiments using ergotamine, various triptans and two selective 5-HT_{1F} agonists [30, 31]. Therefore, preclinical vascular contractility experiments indicate that activation of the 5-HT_{1F} receptor has no vasoactive effects. This has been shown in human isolated coronary and cerebral arteries [25]. Thus, as mentioned before, this receptor exerts attractive pharmacology and localization properties to serve as a potential target for antimigraine treatments. To date, several (?) specific agonists have been developed and tested in animal models for migraine.

5-HT_{1F} RECEPTOR IN ANIMAL MODELS FOR MIGRAINE

A wide range of animal models are employed to approach migraine, varying from gene modulation to electrophysiological studies [32], including dural protein extravasation, neurogenic dural inflammation and expression of c-fos protein within TNC [33]. LY 344864 {(R)-(+)-N-[3-(N,N-dimethylamino)-1,2,3,4-tetrahydrocarbazole-6-yl]-4-fluorobenzamide}, is a selective 5-HT_{1F} receptor agonist, with an affinity of 6 nM (K_i) at the 5-HT_{1F} receptor. It possesses little affinity for the 56 other serotonergic and non-serotonergic neuronal binding sites examined. When examined for its ability to inhibit forskolin-induced cyclic AMP accumulation in cells stably transfected with human 5-HT_{1F} receptors, LY344864 was shown to be a full agonist producing an effect similar in magnitude to serotonin itself. After an intravenous dose of 1 mg/kg, rat plasma LY344864 levels declined with time whereas brain cortex levels remained relatively constant for the first 6 hours after injection. Oral and intravenous LY344864 administration potently inhibited dural protein extravasation caused by electrical stimulation of the trigeminal ganglion in rats [34]. In later studies LY 344864 decreased the number of capsaicin-induced c-fos-like immunoreactive cells within both rat (ID₅₀=0.04 and 0.6 mg kg⁻¹) and mice TNC [35,36]. The effect of sumatriptan, but not of LY 344864, was prevented by pretreatment with the antagonist SDZ 21-009, which displays high affinity for rat 5-HT_{1B} receptors, indicating that activation of 5-HT_{1F} receptors is sufficient to modulate the activity of the rat trigeminal system [35]. Additionally, other selective 5-HT_{1F} agonists, LY334370 and LY397584, inhibited both central and peripheral branches of trigeminal sensory afferents in rats [37]. It is important to note that activation of 5-HT_{1F} receptors has no general analgesic properties, as it has been shown in animal models of somatic pain [38]. Interestingly, activation of 5-HT_{1F} was effective even in electrophysiological migraine models, inhibiting the activation of second-order neurons in the TNC produced by electrical stimulation of the dura mater in anesthetised rats indicating for a central mechanism of action in blocking the transmission of nociceptive impulses within the TNC [38]. Other highly selective agonists for 5-HT_{1F} receptors have shown positive results in animal models for migraine [39-41], further establishing the role of 5-HT_{1F} receptor in modulating pain neurotransmission within the trigeminal system. Several 5-HT_{1F} agonists have subsequently been tested in the clinic.

5-HT_{1F} AGONISTS IN CLINICAL TRIALS OF MIGRAINE TREATMENT

Clinically, phase I studies have shown that LY334370 was well tolerated up to a dose of 400 mg. Its side effects included weakness, somnolence, and dizziness, but there were no cardiovascular effects (assessed by blood pressure, pulse, or ECG). The compound had good oral bioavailability with a t_{max} , between 1 and 2 h and an elimination half-life of 15 h [42]. Subsequently, data from phase II studies have been published showing that oral doses of 60 and 200 mg of LY334370 given to patients with migraine headache of moderate to severe pain produced significant pain relief at 2 h compared to placebo and a significant proportion of patients were pain-free at 2 h compared to placebo [43]. Based on these data, the number needed to treat (NNT) with 60 or 200 mg LY334370 to achieve 2 pain-free hours post dose was 4.5 and 3.1 respectively. By comparison, two pain-free hours post dose NNTs for oral sumatriptan 100 mg and rizatriptan 10 mg were calculated to be 4.7 and 3.1 [44, 45]. NNTs for 2-hour sustained response (defined as improvement from moderate or severe pain to mild or no pain after two hours, with neither worsening from two to 24 hours nor use of rescue medication) were 3.4 and 2.3 for 60 and 200 mg LY334370 [43]. For oral sumatriptan 200 mg and 10 mg rizatriptan the sustained response NNTs were calculated to be 5.6 and 6.7 respectively [44, 45]. LY334370 was advanced in clinical development through phase II clinical trials. However, prior to initiation of phase III trials, preclinical toxicity studies indicated that the liver was a potential target for injury when LY334370 was administered to beagle dogs for longer than 1 month [46]. Further development was then stopped. It is important to note that liver toxicity was not observed in rats who were exposed to LY334370, and liver enzyme elevation was not observed in humans who received LY334370. However, animal liver toxicity was not observed with other selective 5-HT_{1F} receptor agonists, and to our knowledge liver injury has not been reported with triptans that have high 5-HT_{1F} receptor binding affinity such as naratriptan. Taken collectively, these observations suggested that the liver injury which was observed in dogs following LY334370 administration was likely a species-specific, drug-related, non-mechanism-related toxicity [29]. However, activation of 5HT-1F receptors remains an important pathophysiological consideration in the understanding of migraine mechanisms and may still be an active target for future antimigraine compounds lacking vasoactive properties.

THE 5-HT₇ RECEPTOR

The 5-HT₇ receptor was cloned in 1993 and physiological investigations showed that activation of the 5HT₇ receptor mediated relaxation of smooth muscles both in the GI-tract and the cardiovascular system. Further, 5HT₇ receptors may play a role in circadian pacemaker function and sleep [47]. Recent observations showed that 5-HT was actually able to produce vasodilatation of intra- and extra-cranial blood vessels through a mechanism pharmacologically resembling the 5-HT₇ receptor type. Messenger RNA encoding this subtype is highly expressed in cranial vessels and human trigeminal ganglia [48,49]. Recently developed and clinically tested selective 5HT₇ antagonists SB-269970-A and SB-656104-A suggest that the receptor may play a role in other CNS disorders including anxiety and cognitive dis-

turbances [50]. In migraine probably both peripheral mechanisms at level of blood vessels and meningeal tissue and central mechanisms in hippocampus and thalamus are activated. 5-HT7 antagonists may play a role where hyperalgesia is involved in migraine attacks [47]. Although 5-HT7 antagonists have not yet been tested in animal models for migraine, there is indirect evidence suggesting that these agents may be useful in migraine prophylactic treatment: they mediate smooth muscle relaxation in canine cerebral arteries [49]; most of the migraine preventive 5-HT receptor antagonists display relatively high affinity for 5-HT7 receptor, which significantly correlates with their pharmaceutically active oral doses [51]. However, further studies are required to confirm the potential role of the receptor in headache disorders. Limited current experience suggest that there are interesting opportunities for the development of novel therapeutic agents to treat migraines and possibly other headaches acting at the 5-HT7 receptor.

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