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Is selective 5-HT$_{1F}$ receptor agonism an entity apart from that of the triptans in antimigraine therapy?

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Abstract

Migraine is a neurovascular disorder that involves activation of the trigeminovascular system and cranial vasodilation mediated by release of calcitonin gene-related peptide (CGRP).

The gold standard for acute migraine treatment are the triptans, $5\text{-HT}_{1B/1D/(1F)}$ receptor agonists. Their actions are thought to be mediated through activation of: (i) 5-HT_{1B} receptors in cranial blood vessels with subsequent cranial vasoconstriction; (ii) prejunctional 5-HT_{1D} receptors on trigeminal fibres that inhibit trigeminal CGRP release; and (iii) $5\text{-HT}_{1B/1D/1F}$ receptors in central nervous system involved in (anti)nociceptive modulation. Unfortunately, coronary arteries also express 5-HT_{1B} receptors whose activation would produce coronary vasoconstriction; hence, triptans are contraindicated in patients with cardiovascular disease. In addition, since migraineurs have an increased cardiovascular risk, it is important to develop antimigraine drugs devoid of vascular (side) effects.

Ditans, here defined as selective 5-HT_{1F} receptor agonists, were developed on the basis that most of the triptans activate trigeminal 5-HT_{1F} receptors, which may explain part of the triptans' antimigraine action. Amongst the ditans, lasmiditan: (i) fails to constrict human coronary arteries; and (ii) is effective for the acute treatment of migraine in preliminary Phase III clinical trials. Admittedly, the exact site of action is still unknown, but lasmiditan possess a high lipophilicity, which suggests a direct action on the central descending antinociceptive pathways. Furthermore, since 5-HT_{1F} receptors are located on trigeminal fibres, they could modulate CGRP release.

This review will be particularly focussed on the similarities and differences between the triptans and the ditans, their proposed sites of action, side effects and their cardiovascular risk profile.

Keywords: triptans; ditans; serotonin; migraine; cardiovascular safety

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Abbreviations:

5-HT	5-hydroxytryptamine
BBB	blood brain barrier
CGRP	calcitonin gene-related peptide
DHSC	dorsal horn of the spinal cord
$logD_{pH7.4}$	distribution coefficient at physiological pH
MMA	middle meningeal artery
ND	not defined
NTS	nucleus tractus solitarius
PAG	periaqueductal grey area
pEC_{50}	negative logarithm of the half maximal effective concentration
PVN	hypothalamic pararaventricular nucleus
TG	trigeminal ganglion
TNC	trigeminal nucleus caudalis

1. Introduction

Migraine is a debilitating neurovascular disorder characterized by recurring unilateral pulsating headaches of moderate to severe intensity, associated with nausea, photophobia and/or phonophobia, lasting from 4 to 72 hours (Headache Classification Committee of the International Headache Society, 2013). In the Global Burden of Disease Study, migraine was ranked as the third disabler in women, sixth disabler when taking both genders into account, and the most disabling of all neurological disorders, affecting approximately 15% of the world population (Steiner, Stovner, & Birbeck, 2013), with a profound negative effect on the patient's quality of life (Ruiz de Velasco, González, Etxeberria, & Garcia-Monco, 2003). Furthermore, this neurovascular disorder represents an economic loss of €20 billion in Europe every year (Gustavsson et al., 2011). Thus, migraine is a public health problem that affects both the individual and society

1.1 Pathophysiology of migraine

Throughout the years, several theories regarding the pathophysiology of migraine have emerged (Goadsby et al., 2017). In the late 1930's and early 1940's, Wolff's group described migraine as a disorder of vascular origin, with an intense extracranial vasodilation as the cause of migraine pain (Graham & Wolff, 1938; Ray & Wolff, 1940). Decades later, Moskowitz introduced the neurogenic theory, where trigeminovascular axons from blood vessels of the dura mater released vasoactive peptides producing an sterile inflammatory response followed by pain (Moskowitz, Romero, Reinhard, Melamed, & Pettibone, 1979). Nowadays, migraine is considered as a neurovascular disorder that involves activation of the trigeminovascular system (Edvinsson, 2017; Edvinsson & Uddman, 2005), presumably followed by vasodilation mainly mediated by the release of calcitonin gene-related peptide (CGRP), a neuropeptide present in perivascular sensory fibres (Goadsby, Lipton, & Ferrari, 2002; Villalón & Olesen, 2009).

1.2 Treatment of migraine

Despite the long history of migraine treatment, effective antimigraine drugs have been, until very recently, limited in number (for references see Villalón, Centurión, Valdivia, de Vries, & Saxena, 2003). Basically, pharmacological treatment of migraine can be divided into prophylactic drugs, designed to reduce the frequency and severity of migraine attacks, and acutely acting drugs, aimed to

reverse the attack once it has begun, including the associated symptoms. The majority of migraine patients only need acute treatment, nevertheless, migraineurs that suffer from frequent attacks or have contraindications for the use of acutely acting drugs, are also prescribed prophylactic drugs (Dib, 2008). The prophylactic treatment will not be discussed here as it is falls beyond the scope of the present review.

The acute treatment can be further subdivided in specific (ergot derivatives, triptans, gepants, "ditans"), and non-specific (nonsteroidal anti-inflammatory drugs, analgesics) antimigraine drugs (Dib, 2008; Marmura, Silberstein, & Schwedt, 2015). While non-specific drugs aim to treat migraine as a general headache or other pain, specific treatment is developed based on the neurovascular basis of migraine. Thus, these drugs target the modulation of the trigeminovascular system, the CGRP-mediated vasodilation (i.e. extracranial vasoconstriction, inhibition of CGRP release, CGRP receptor antagonism) and/or the pain perception pathway, amongst others. On this basis, CGRP receptor antagonists (gepants) are a likely candidate for the acute treatment of migraine, and indeed, they were effective in clinical trials (Doods et al., 2000; Edvinsson & Linde, 2010; Villalón & Olesen, 2009); however, due to pharmacokinetic and/or hepatotoxic limitations none of the gepants have yet reached the market (Negro, Lionetto, Simmaco, & Martelletti, 2012). Currently, a potential concern with gepants includes the cardiovascular side effects when used chronically, considering the physiological protective role of CGRP in maintaining cardiovascular homeostasis in ischemic events (for further references see MaassenVanDenBrink, Meijer, Villalón, & Ferrari, 2016). Several drugs targeting the CGRP receptor are presently under development for the acute and prophylactic treatment of migraine (Schuster & Rapoport, 2017; Tso & Goadsby, 2017).

During the last 40 years, the target for selective antimigraine drugs has been the serotoninergic signalling. Long before the discovery of CGRP and its fundamental role in migraine, increased urinary and plasma levels of serotonin (5-hydroxytryptamine, 5-HT) and its metabolites were described (Sicuteri, Testi, & Anselmi, 1961; Somerville, 1976). Further studies showed that an intravenous infusion of 5-HT was capable of aborting migraine attacks (Kimball, Friedman, & Vallejo, 1960) and that efficacious antimigraine drugs like methysergide and ergotamine were acting on, amongst other receptors, 5-HT$_1$ receptors (Apperley, Feniuk, Humphrey, & Levy, 1980; Humphrey et al., 1988). In

this review, the main focus will be on the triptans, 5-HT$_{1B/1D/(1F)}$ receptor agonists, that are currently considered the gold standard for acute migraine treatment, and on the novel "ditans" (in this review defined as selective 5-HT$_{1F}$ receptor agonists), not only developed based on the neurovascular origin of migraine, but also in view of the cardiovascular risk profile of migraine patients (Chang, Donaghy, & Poulter, 1999; Etminan, Takkouche, Isorna, & Samii, 2005; Linstra, Ibrahimi, Terwindt, Wermer, & MaassenVanDenBrink, 2017; Sacco, Ornello, Ripa, Pistoia, & Carolei, 2013; Scher et al., 2005; Schurks et al., 2009; Spector et al., 2010; Tzourio et al., 1995; Vanmolkot, Van Bortel, & de Hoon, 2007) .

2.   Triptans

As mentioned in the above section, the role of serotoninergic neurotransmission in migraine led to the design of antimigraine drugs that targeted the 5-HT receptors (Kimball et al., 1960; Sicuteri et al., 1961; Somerville, 1976); however, the exact 5-HT receptors involved in the relief of migraine attacks were unknown. Indeed, intravenous infusion of 5-HT was able to abort migraine attacks, but considering that there are fourteen 5-HT receptors (Villalón & MaassenVanDenBrink, 2017), and they were all activated, numerous side effects were observed (Kimball et al., 1960). After several studies using selective agonists and antagonists, it was demonstrated that the therapeutic action of 5-HT was mediated by "5-HT$_1$-like receptors" that constricted cranial blood vessels (Apperley et al., 1980; Feniuk & Humphrey, 1992; Humphrey et al., 1988), and the first triptan was developed: sumatriptan (Humphrey, 2007). In the early 1990s, sumatriptan was officially introduced to the market (The Subcutaneous Sumatriptan International Study Group 1991). In view of the low oral bioavailability and lipophilicity of sumatriptan (Fowler et al., 1991), as well as the vast market potential, "second generation" triptans (zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, donitriptan and avitriptan) were developed, with a chemical structure similar to sumatriptan (see Fig. 1), but in general with higher oral availability and lipophilicity (see Table 1), as well as a longer plasma half-life (de Vries, Villalón, & Saxena, 1999; Tfelt-Hansen, De Vries, & Saxena, 2000; Villalón & MaassenVanDenBrink, 2017).

2.1 Mechanism of action

Initially, it was described that the therapeutic action of 5-HT on migraine was mediated by activation of "5-HT$_1$-like" receptors (Feniuk & Humphrey, 1992). Years later, based on structural, transductional and operational criteria, these receptors were classified into 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors (for further references see Hoyer et al., 1994; Saxena, de Vries, & Villalón, 1998).

Triptans are 5-HT$_{1B/1D}$ receptor agonists, and a grand majority of them are also 5-HT$_{1F}$ receptor agonists (see Table 2, Fig. 2). Sumatriptan, as previously mentioned, has low lipophilicity (see Table 1) and cannot cross the blood brain barrier (BBB). For a drug to be considered able to cross the BBB, it should have a distribution coefficient at physiological pH (logD$_{pH7.4}$) higher than -1 (Brodie, Kurz, & Schanker, 1960; Levin, 1980). Notably, second generation triptans were developed with higher lipophilicity (Fowler et al., 1991) but their ability to cross the BBB is in controversy, since their reported logD$_{pH7.4}$ values are not consistent amongst studies (see Table 1). Furthermore, it is important to consider the possible interactions between triptans and BBB efflux transporters (e.g. P-glycoprotein) that limit the central actions of triptans, as it has been reported for eletriptan (Evans et al., 2003).

2.2 Cardiovascular (side) effects

The initially proposed therapeutic action of triptans is through the selective vasoconstriction of cranial blood vessels due to the high expression of 5-HT$_{1B}$ receptors in this vasculature (Feniuk & Humphrey, 1992; Longmore et al., 1997) in comparison with peripheral blood vessels (MaassenVanDenBrink et al., 2000). In agreement with this, *in vitro* studies have shown that at therapeutic concentrations triptans contract the middle meningeal artery (MMA) (MaassenVanDenBrink et al., 2000). Furthermore, magnetic resonance angiography studies demonstrated that migraine attacks are associated with dilation of the extra- and intracerebral arteries, ipsilateral to the headache side; and that contraction of dural (but not intracranial) arteries by triptans, is associated with headache relief (Asghar et al., 2011), although it is worth mentioning that further results of the same group have been inconsistent (Amin et al., 2013; Benemei et al., 2017; MaassenVanDenBrink, Ibrahimi, & Edvinsson, 2013) and it is still a matter of debate to what extent the vascular action of the triptans contributes to their therapeutic efficacy.

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Unfortunately, studies have consistently shown that triptans induce an increase in blood pressure (Hoon, Willigers, Troost, Struijker-Boudier, & Bortel, 2000) and contraction of coronary arteries (MaassenVanDenBrink, Reekers, Bax, Ferrari, & Saxena, 1998a; MaassenVanDenBrink et al., 2000; MacIntyre, Bhargava, Hogg, Gemmill, & Hillis, 1993; Nilsson et al., 1999), which is more pronounced in the distal than in the proximal portion of the human coronary artery (Chan et al., 2009).
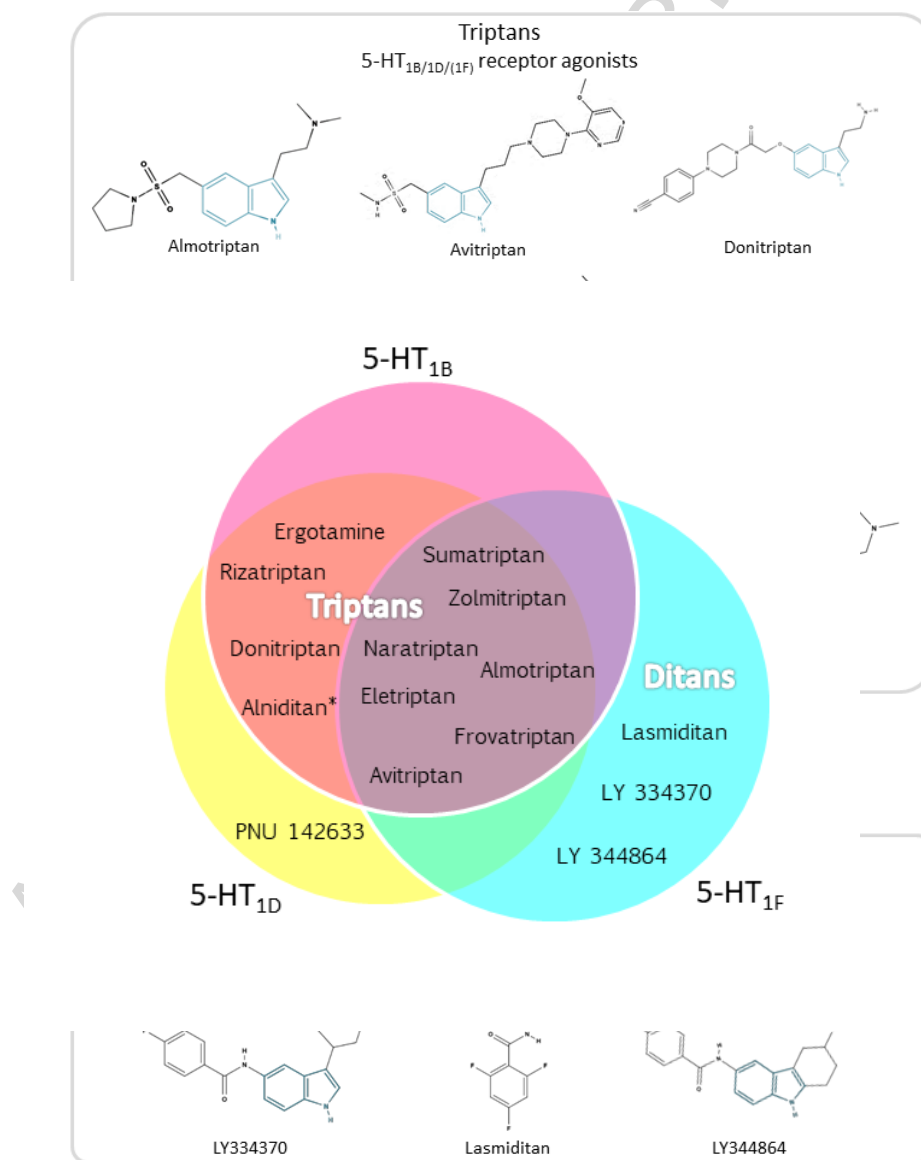

Fig. 1. Chemical structures of the triptans, alniditan and the selective 5-HT$_{1F}$ receptor agonists. It is worth remarking the presence of the indole group (in blue) in all the structures, with exception of lasmiditan and alniditan (Villalón & MaassenVanDenBrink, 2017).

Table 1. Reported $LogD_{pH7.4}$ values for triptans. Compounds with values higher than -1 are considered to be able to cross the BBB.

	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Almotriptan	Eletriptan	Frovatriptan
Fox (2000)	-1.5	-1	-0.2	-0.7	ND	ND	-1
Ferrari, Goadsby, Roon, and Lipton (2002)	-1.3	-0.7	-0.2	-0.7	+0.35	+0.5	ND
Glennon and Dukat (2002)	-1.7	-0.8	-1.2	-1.4	-0.5	+0.2	-2.1
Milton et al. (2002)	ND	ND	ND	ND	ND	+1.1	ND
Pascual and Muñoz (2005)	-1.3	-0.7	-0.2	-0.7	-2.1	+0.5	ND
Cheng et al. (2012)	-1.4	-1.5	ND	-0.8	+0.4	+0.2	-1.9

ND. Not defined

Table 2. Summary of pEC_{50} values of cAMP (5-HT_1 and 5-HT_7) and IP (5-HT_2) assays of individual antimigraine drugs at 5-HT receptors (Rubio-Beltrán et al., 2017). These values represent the negative logarithm of the molar concentration of these compounds at which 50% of their maximal response is exerted.

	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}*	5-ht_{1E}	5-HT_{1F}	5-HT_{2A}	5-HT_{2B}	5-HT_7
Ergotamine tartrate	9.78	9.94	9.43	5.95	5.97	9.25	8.72	7.09
Sumatriptan succinate	<5	7.32	8.30	5.99	8.03	<5	<5	5.22
Zolmitriptan	<5	7.87	9.51	8.18	8.00	<5	<5	6.28
Naratriptan hydrochloride	<5	8.05	8.80	7.75	8.38	<5	<5	<5
Rizatriptan benzoate	<5	7.08	8.11	7.34	6.54	<5	5.49	<5
Almotriptan malate	4.00	7.08	7.75	5.00	7.79	<5	5.20	5.00
Eletriptan hydrobromide	<5	8.00	9.04	7.53	8.13	6.07	6.81	6.45
Frovatriptan racemate	<5	7.98	8.36	5.04	7.10	<5	<5	7.42
Donitriptan hydrochloride	5.94	9.96	9.51	4.77	<5	8.10	7.61	5.23
Avitriptan fumarate	<5	8.57	9.27	5.52	7.09	6.91	6.41	5.38
Alniditan dihydrochloride	7.00	8.87	8.20	5.68	5.92	<5	7.15	6.32
Lasmiditan hemisuccinate	<5	<5	6.64	6.17	8.43	<5	<5	<5
LY334370 hydrochloride	5.84	6.52	6.92	7.53	9.08	<5	<5	<5
LY344864 hydrochloride	<5	<5	6.93	6.22	8.72	<5	<5	<5

* pEC_{50} values correspond to $[^{35}S]GTP\gamma S$ assay

Fig. 2. Summary of agonist profiles of triptans, ditans (here considered as selective 5-HT$_{1F}$ receptor agonists) and other 5-HT receptor ligands, for 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors (pEC$_{50}$>7). *In view of the high affinity of alniditan for the 5-HT$_{1B/1D}$ receptors (pEC$_{50}$ cAMP 8.87 and 8.20, respectively), we classified it as a triptan, despite its generic name (Rubio-Beltrán et al., 2017).

Currently, although there is still a debate on whether the therapeutic action of triptans relays on their vasoconstrictive properties, it is clear that coronary vasoconstriction is a drug class effect of the triptans as 5-HT$_{1B}$ receptor agonists (MaassenVanDenBrink & Saxena, 2004). Therefore, triptans are contraindicated in migraine patients with cardiovascular disease (Dodick et al., 2004). Additionally, it is important to consider that migraineurs are known to have an increased risk of haemorrhagic (Sacco et al., 2013) and ischemic (Chang et al., 1999; Etminan et al., 2005; Schurks et al., 2009; Spector et al., 2010; Tzourio et al., 1995) stroke, with women presenting a higher risk (Linstra et al., 2017). Also, an altered arterial function (Vanmolkot et al., 2007), and a higher risk of myocardial infarction and coronary heart disease (Scher et al., 2005) have been described. Nonetheless, the use of triptans does not seem to increase the risk of stroke, myocardial infarction, cardiovascular death, ischemic heart disease or mortality (Chan, Vermeersch, de Hoon, Villalón, & MaassenVanDenBrink, 2011; Hall, Brown, Mo, & MacRae, 2004; Wammes-van der Heijden,

Rahimtoola, Leufkens, Tijssen, & Egberts, 2006). However, taken together, their coronary vasoconstrictor potential justifies the contraindication of the triptans in patients with cardiovascular risk factors.

2.3 Neuronal effects

Although sumatriptan does not cross the BBB (Ferrari et al., 2002), it has long been speculated that during a migraine attack there would be a disruption of the BBB, which would enable the triptans, even those with a low lipophilicity, to exert a central effect. However, it has recently been demonstrated that there is no disruption of the BBB during a migraine attack (Amin et al., 2017; Hougaard et al., 2017), thus excluding a central action for the triptans, except for those with a high lipophilicity. Besides the potential role for blood vessels in the pathophysiology of migraines, this suggests that actions of the triptans can well be mediated through neuronal structures that are not protected by the BBB, as it is the case for the pituitary gland, choroid plexus and, most importantly, the trigeminal ganglion (TG) (Eftekhari et al., 2015), a key structure in migraine pathophysiology. Indeed, treatment with sumatriptan reduces CGRP plasma levels as migraine lessens (Goadsby & Edvinsson, 1993). More recently, sumatriptan was also shown to inhibit capsaicin-induced trigeminal CGRP release in healthy volunteers (Ibrahimi, Danser, Terwindt, van den Meiracker, & MaassenVanDenBrink, 2016). Furthermore, expression of prejunctional 5-HT_{1D} receptors has been described in trigeminovascular nociceptive neurons (Classey, Bartsch, & Goadsby, 2010; Hou et al., 2001; Longmore et al., 1997) which could suggest a role in the modulation of CGRP release, as well as plasma protein extravasation (Buzzi & Moskowitz, 1990). Remarkably, based on the prejunctional location of 5-HT_{1D} receptors in the TG, PNU-142633, a selective 5-HT_{1D} receptor agonist, was developed for the acute treatment of migraine, and showed a superior potency over sumatriptan for blocking plasma protein extravasation. Unfortunately, it was not effective in the acute treatment of migraine (Gómez-Mancilla et al., 2001). It is worth mentioning that PNU-142633 was developed based on the gorilla 5-HT_{1D} receptor, which could explain its lack of efficacy, and thus a role for the 5-HT_{1D} receptor in the treatment of migraine cannot categorically be ruled out. Besides, it has been shown that activation of 5-HT_{1B}, but not 5-HT_{1D} receptors inhibits CGRP release in the pithed rat model (González-Hernández et al., 2010), indicating that, while 5-HT_{1D} receptor activation may

contribute to the therapeutic actions of triptans, it may not be their main site of action. Further studies are needed to completely elucidate the role of 5-HT$_{1D}$ receptor activation in migraine treatment.

As discussed earlier, second generation triptans were developed with higher lipophilicity than sumatriptan (de Vries et al., 1999; Tfelt-Hansen et al., 2000). Therefore, some of them may be able to cross the BBB (Ferrari et al., 2002; Muñoz-Islas et al., 2006). Although the lipophilicity of triptans correlates with central side effects, it does not seem to be related to their efficacy (Pascual & Muñoz, 2005), and there is no consistency in the lipophilicity reported in literature (see Table 2). Nevertheless, we cannot categorically exclude additional therapeutic actions mediated via activation of 5-HT$_{1B/1D/(1F)}$ receptors in the central nervous system by highly lipophilic triptans (Deleu & Hanssens, 2000). In accordance with this, it has been shown that vasodilation of the canine external carotid artery induced by intracarotid administration of capsaicin, is inhibited by spinal (but not intravenous) administration of sumatriptan via activation of 5-HT$_{1B}$ receptors; in contrast, intravenous administration of the highly lipophilic donitriptan inhibits the capsaicin-induced vasodilation, also mediated by activation of 5-HT$_{1B}$ receptors (Muñoz-Islas et al., 2006; Muñoz-Islas et al., 2009).

Several studies have described 5-HT$_{1B}$ and (presynaptic) 5-HT$_{1D}$ receptors in the dorsal horn of the spinal cord (DHSC) (Castro et al., 1997), substantia nigra, globus pallidus (Castro et al., 1997; Lindhe et al., 2011), nucleus tractus solitarius (NTS), trigeminal nucleus caudalis (TNC) (Castro et al., 1997; Longmore et al., 1997), periaqueductal grey area (PAG) (Bartsch, Knight, & Goadsby, 2004; Castro et al., 1997), the ventroposteromedial nucleus of the thalamus (Shields & Goadsby, 2006), hypothalamic paraventricular nucleus (PVN) (Robert et al., 2013) and the rostral ventromedial medulla (Vera-Portocarrero, Ossipov, King, & Porreca, 2008), structures previously associated with nociceptive and anti-nociceptive pathways (Baumeister et al., 1988; Condés-Lara et al., 2006; Fields, Basbaum, Clanton, & Anderson, 1977; Foreman, Beall, Coulter, & Willis, 1976; Gerhart, Yezierski, Fang, & Willis, 1983; Lewis, Baldrighi, & Akil, 1987; Loher, Burgunder, Weber, Sommerhalder, & Krauss, 2002; Olszewski, 1950; Reynolds, 1969). Furthermore, it has been shown that spinal 5-HT$_{1B/1D/1F}$ receptors are involved in the serotonergic descending inhibitory pain system (Ávila-Rojas et al., 2015; Granados-Soto et al., 2010; Kayser, Aubel, Hamon, & Bourgoin, 2002; Kayser, Latremoliere, Hamon, & Bourgoin, 2011; Vidal-Cantú et al., 2016). Of special interest, intravenous

administration of naratriptan (Cumberbatch, Hill, & Hargreaves, 1998; Goadsby & Knight, 1997) results in inhibition of the spinal TNC. Also, the PAG, more specifically the ventrolateral division, is activated by afferents from the TG (Hoskin, Bulmer, Lasalandra, Jonkman, & Goadsby, 2001; Keay & Bandler, 1998; Knight & Goadsby, 2001), and microinjection of naratriptan in this structure inhibits nociceptive dural responses (Bartsch et al., 2004). Moreover, the PVN, that has been previously shown to participate in the endogenous modulation of pain (Condés-Lara et al., 2006; DeLaTorre et al., 2009) sends projections to the PAG (Condés-Lara et al., 2015) and the spinal trigeminal nucleus (Robert et al., 2013), and microinjection of naratriptan in this structure, attenuates dural-evoked trigeminovascular responses (Robert et al., 2013). Thus, indeed highly lipophilic triptans could not only act through the vasoconstriction of extracranial vasculature and inhibition of the release of CGRP, but also through the activation of the descending inhibitory pain system and/or the inhibition of nociceptive transmission (see Fig. 3). Interestingly, most of these studies were performed using naratriptan, a highly lipophilic triptan that has a high affinity for the 5-HT_{1F} receptor (see Table 2). Furthermore, although antagonists were used to confirm the role of $5\text{-HT}_{1B/1D}$ receptors, there is no selective antagonist commercially available for the 5-HT_{1F} receptor yet. Therefore, the involvement of this receptor in the neuronal actions of triptans can neither be confirmed nor excluded and requires further studies.

3. Ditans and the 5-HT_{1F} receptor

Triptan monotherapy is ineffective for approximately 25% of migraineurs and in 40% of acute migraine attacks (Diener & Limmroth, 2001). Several studies have tried to elucidate the lack of efficacy in some migraineurs, but were unable to explain why some patients are responders to the triptans while others are nonresponders. Whereas a difference in efficacy could be due to pharmacokinetic factors for some of the oral triptans, pharmacokinetics did not seem to be responsible for differences in efficacy in response to subcutaneous sumatriptan (Visser et al., 1996), nor polymorphisms in the 5-HT_{1B} and 5-HT_{1F} receptor genes were able to explain differences in clinical responses to sumatriptan (MaassenVanDenBrink et al., 1998b; MaassenVanDenBrink et al., 1998c; Mehrotra et al., 2007). Moreover, as previously discussed, migraine patients are known to have an

increased cardiovascular risk; therefore, it is important to develop novel effective antimigraine drugs that are devoid of cardiovascular side effects.

Several triptans bind to the $5\text{-}HT_{1F}$ receptor (see Table 2). Also, as will be discussed later, $5\text{-}HT_{1F}$ receptors are expressed in several structures associated with migraine pathophysiology and with the (neuronal) therapeutic actions of triptans. This led to the development of selective $5\text{-}HT_{1F}$ receptor agonists as possible option for migraine treatment. Several selective $5\text{-}HT_{1F}$ receptor agonists have been developed (see Fig. 1), including LY344864, an aminocarbazole, LY334370, a 4-(3-indolyl)piperidine (Glennon & Dukat, 2002) and lasmiditan (COL-144, LY573144), a piridinoyl-piperidine (Nelson et al., 2010). While the selective $5\text{-}HT_{1F}$ receptor agonists were referred to as SSOFRAs (Selective Serotonin One F Receptor Agonists) for some time, in the last years the term "ditan" has been accepted as a synonymous of selective $5\text{-}HT_{1F}$ receptor agonist (Hoffmann & Goadsby, 2014). In this context, it is important to consider alniditan, a $5\text{-}HT_{1A/1B/1D}$ receptor agonist with only low $5\text{-}HT_{1F}$ receptor affinity (see Table 2), suggesting that the suffix "ditan" is merely to distinguish novel acutely acting ($5\text{-}HT_1$ receptor agonists) antimigraine drugs from triptans, without any structural (see Fig. 2) and/or pharmacological criteria (see Table 2). As the following paragraph is only focused on $5\text{-}HT_{1F}$ receptor agonists, alniditan will not be further discussed when ditans are mentioned.

3.1 Location

The human $5\text{-}HT_{1F}$ receptor was first identified and cloned in 1993 (Adham et al., 1993). It has been described in the TG (Bouchelet, Cohen, Case, Séguéla, & Hamel, 1996; Classey et al., 2010; Kovalchin, Ghiglieri, Zanelli, Ings, & Mathers, 2016), globus pallidus, NTS, substantia nigra, PAG, DHSC (Castro et al., 1997), caudate nucleus (Waeber & Moskowitz, 1995), caudate putamen, nucleus accumbens (Lucaites, Krushinski, Schaus, Audia, & Nelson, 2005), and the TNC (Amrutkar et al., 2012; Bruinvels et al., 1994; Castro et al., 1997; Waeber & Moskowitz, 1995). Interestingly, it has also been shown to be expressed on cerebrovascular tissues (Bouchelet et al., 1996) as well as peripheral arteries (Nilsson et al., 1999).

3.2 Preclinical studies

Selective 5-HT$_{1F}$ receptor agonists were developed as a novel therapeutic option for migraineurs, including those with increased cardiovascular risk. Therefore, the main concern was to study the (lack of) vascular effects, as well as their efficacy on predictive models of migraine treatment.

3.2.1 Cardiovascular (side) effects

An established *in vitro* model used to analyse potential contraction of human arteries is the contraction of the rabbit saphenous vein (Cohen, Johnson, Schenck, & Phebus, 1997). LY334370 (Cohen & Schenck, 2000; Johnson et al., 1997), LY344864 (Cohen & Schenck, 1999; Cohen & Schenck, 2000) and lasmiditan (Nelson et al., 2010) lacked vasoconstrictor effects in this model. Furthermore, in two *in vivo* studies in dogs, intracarotid administration of LY344864 did not affect carotid blood flow (Centurión, Sánchez-López, De Vries, Saxena, & Villalón, 2001), and responses to continuous intravenous infusions of lasmiditan, in escalating cumulative doses, failed to constrict the coronary and carotid arteries; sumatriptan, on the other hand, constricted both arteries at clinically relevant doses (Rubio-Beltrán et al., 2016). Furthermore, in *in vitro* studies in human mammary and coronary arteries, lasmiditan was also devoid of vasoconstrictor properties, while sumatriptan was shown to contract already at subtherapeutic concentrations (Rubio-Beltrán et al., 2016; Rubio-Beltrán et al., 2017). It is worth mentioning that in this study, also a threshold stimulation with the thromboxane A$_2$ analogue U46619 was performed to potentially "unmask" vasoconstrictor responses in the internal mammary artery; notably, sumatriptan contracted at even lower concentrations, while lasmiditan failed to produce vasoconstriction. Similarly, pharmacological activation of 5-HT$_{1F}$ receptors failed to produce vasoconstriction in human cerebral and MMA (Bouchelet, Case, Olivier, & Hamel, 2000; Razzaque et al., 1999).

3.2.2 Neuronal effects

A number of studies have shown that intravenous administration of the selective 5-HT$_{1F}$ receptor agonists LY334370 (Johnson et al., 1997), LY344864 (Phebus et al., 1997) and lasmiditan (Nelson et al., 2010) inhibits protein plasma extravasation in the dura mater. However, it is important to consider that the selective 5-HT$_{1D}$ receptor agonist PNU-142633 also showed a high potency for inhibiting protein plasma extravasation, but was not effective in the acute treatment of migraine (Gómez-

Mancilla et al., 2001). Similar failures in the acute treatment of migraine were observed with endothelin receptor antagonists (May et al., 1996) and the highly potent inhibitor of protein plasma extravasation CP 122,288 (Roon et al., 2000). Therefore, it seems likely that 5-HT$_{1F}$ receptor agonists act through additional pathways, for instance, modulation of the trigeminovascular system, inhibition of the CGRP-mediated vasodilation and/or modulation of the pain perception pathway (see Fig. 3). In accordance with these potential mechanisms, activation of 5-HT$_{1F}$ receptors has been shown to inhibit the activation of second order neurons in the TNC in mice (Mitsikostas, Sánchez Del Río, & Waeber, 2002), rats (Mitsikostas, Sánchez del Río, Moskowitz, & Waeber, 1999; Nelson et al., 2010; Shepheard et al., 1999; Vila-Pueyo et al., 2016) and cats (Goadsby & Classey, 2003), suggesting a modulation of the trigeminovascular system. Moreover, an *in vitro* study with LY344864 showed an inhibition of CGRP release in rat dura mater, but not in TNC or TG (Amrutkar et al., 2012). In contrast, a recent study showed that lasmiditan inhibits CGRP release in mouse dura mater, TG and TNC (Labastida-Ramírez et al., 2017), although only supratherapeutic concentrations were studied. Therefore, more *in vitro* and *in vivo* studies (e.g. closed cranial window model) are required to confirm 5-HT$_{1F}$ receptor involvement in the inhibition of CGRP release. Nonetheless, in the pithed rat model it has been shown that activation of 5-HT$_{1F}$ receptors inhibits the release of CGRP from perivascular nerve fibres (González-Hernández et al., 2011).

Furthermore, the expression of 5-HT$_{1F}$ receptors in the globus pallidus, NTS, the DHSC (Castro et al., 1997), caudate nucleus (Waeber & Moskowitz, 1995), putamen and the nucleus accumbens (Lucaites et al., 2005), structures associated with (anti)nociceptive pathways (Fields et al., 1977; Foreman et al., 1976; Ikeda, Takasu, & Murase, 2014; Lewis et al., 1987; Lineberry & Vierck, 1975; Loher et al., 2002), suggests a possible role for 5-HT$_{1F}$ receptor activation in the modulation of nociceptive impulses.

3.3 Clinical studies

Twenty years have passed since the development of LY334370 (Shepheard et al., 1999); nowadays, two more 5-HT$_{1F}$ receptor agonists have been synthesized, namely, LY344864 (Phebus et al., 1997) and lasmiditan (Nelson et al., 2010). Only LY334370 and lasmiditan have reached clinical trials.
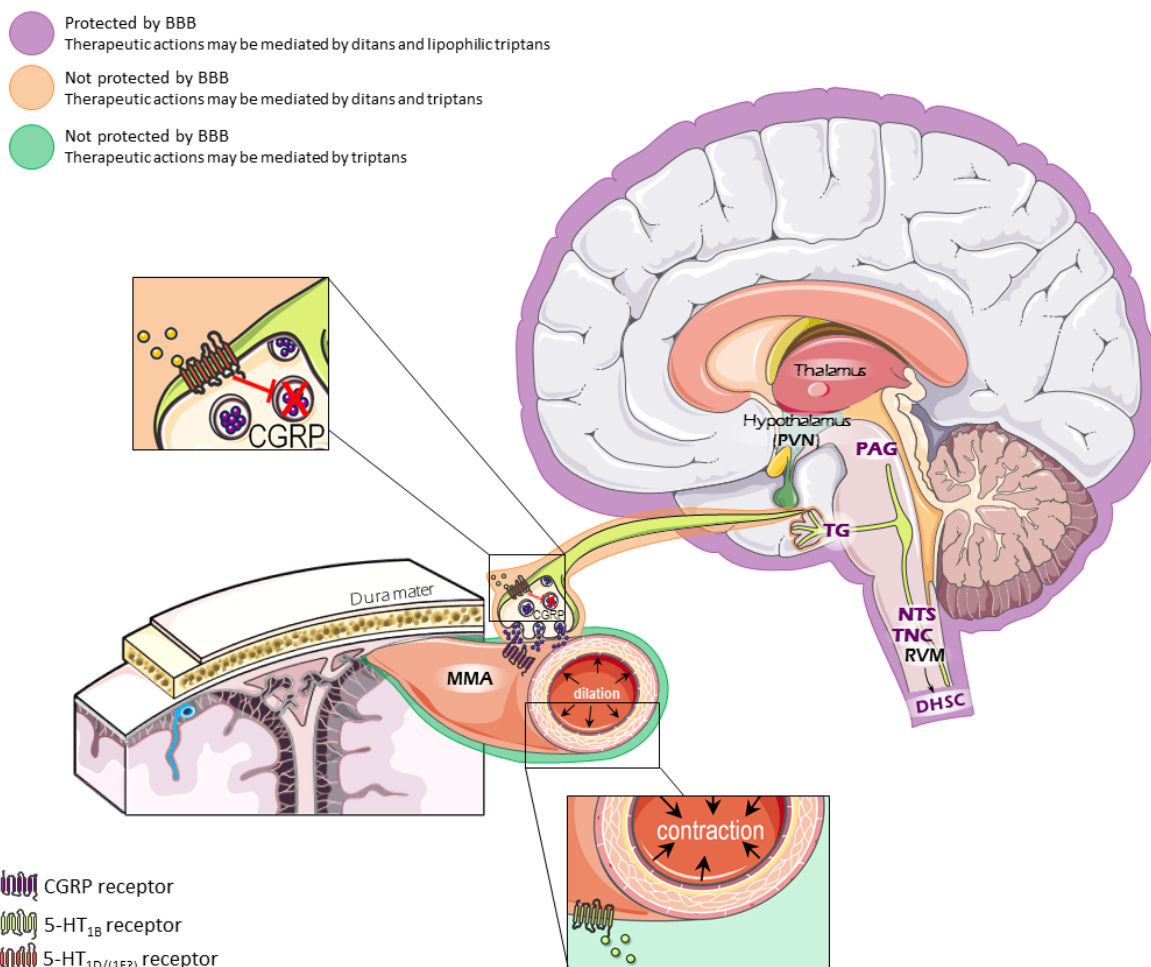
therapeutic action of triptans is through the selective vasoconstriction of the MMA (green), as well as the inhibition of CGRP release from the sensory fibres and the modulation of the TG, since they are not protected by the BBB, where also 5-HT_{1F} receptors have been described (orange). Highly lipophilic triptans could also act on the ventroposteromedial nucleus of the thalamus, PVN, PAG, LC, NTS, TNC, RVM and the (DH) SC, where 5-HT_{1B} and 5-HT_{1D} receptors have been described and whose activation could also modulate the activity of the TG and/or the (anti)nociception pathways (purple). Furthermore, 5-HT_{1F} receptors have also been reported in PAG, TG, TNC and the (DH)SC, which suggests a role in the modulation of the trigeminal responses as well as possible action on the (anti)nociceptive pathways (**BOLD** letters). BBB: blood brain barrier; CGRP: calcitonin-like related peptide; DHSC: dorsal horn of the spinal cord; MMA: middle meningeal artery; NTS: nucleus tractus solitarius; PAG: periaqueductal grey area; PVN: paraventricular nucleus of the hypothalamus; RVM: rostral ventromedial medulla; TG: trigeminal ganglion; TNC: trigeminal nucleus caudalis.

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3.3.1 LY334370

The prototype for the 5-HT$_{1F}$ receptor agonists reached phase II of clinical trials (Goldstein et al., 2001), and the results were favourable for the acute treatment of migraine, as sustained headache response rates were higher on 60 mg (37%) and 200 mg (52%) compared to placebo (8%; p<0.001). However, further trials were halted due to observed liver damage in beagle dogs after treatment for longer than one month (Ramadan, Skljarevski, Phebus, & Johnson, 2003). It is worth mentioning that liver damage was not reported in other species, discarding hepatotoxicity as a drug class effect.

3.3.2 Lasmiditan

Considered as the most promising of the 5-HT$_{1F}$ receptor agonists, lasmiditan differs from LY334370 and LY344864, as it does not possess the indole group (see Fig. 1).

Five phase I trials have been completed (Liefaard et al., 2009; Pilgrim et al., 2009; Raffaelli, Israel, Neeb, & Reuter, 2017) for intravenous and oral formulations for safety, bioavailability, tolerability and pharmacokinetic studies. In 2007, a phase II study for the intravenous formulation was conducted (Ferrari et al., 2010), and later on, in 2009 for the oral formulation (Farkkila et al., 2012). In both cases, lasmiditan was shown to be safe and effective in the acute treatment of migraine.

Phase III trials are ongoing, with preliminary statements showing positive results as the percentage of patients pain free at two hours was higher for 100 mg (28%) and 200 mg (32%), compared to placebo (15%; p<0.001; "CoLucid Pharmaceuticals Announces Achievement of Both Primary and Key Secondary Endpoints in the SAMURAI Phase 3 Pivotal Trial of Lasmiditan in Migraine," 2016). It is worth mentioning, that the first phase III trial ("SAMURAI", NCT02439320) included a majority of migraineurs (80%) that had cardiovascular conditions or cardiovascular risk factors (i.e. obesity, hypertension, hyperlipidemia), the main group of patients that would benefit from the lack of vasoconstrictive properties. Two more phase III trials ("SPARTAN", NCT02605174: "GLADIATOR", NCT02565186) are under way and are aimed to compare different doses of lasmiditan, and to evaluate the safety and efficacy of long term use, respectively. Recently, preliminary results from SPARTAN have been released and showed that at two hours following the first dose of lasmiditan, the percentage of pain-free patients was statistically significantly higher for 50 mg (28%, p=0.003); 100 mg (31%, p<0.001) and 200 mg (38%, p<0.001) compared to placebo

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(21%) (Wietecha, Kuca, Case, Selzler, & Aurora, 2017). Only patients that received lasmiditan in previous trials are allowed to be included in the GLADIATOR trial. It is worth mentioning that no direct comparison has been performed between triptans and lasmiditan in clinical studies. Future phase III trials with a triptan as an active comparator would allow a better evaluation of their efficacy.

4. Conclusions

Triptans are 5-$HT_{1B/1D/(1F)}$ receptors agonists and are considered as the gold standard for acute migraine treatment that have been proven effective. Unfortunately, they are contraindicated in patients with cardiovascular diseases due to their vasoconstrictor (side) effects (MaassenVanDenBrink et al., 1998a; MaassenVanDenBrink & Saxena, 2004). Furthermore, triptans are not effective in 25% of migraine patients (Diener & Limmroth, 2001); thus, it is important to develop new antimigraine drugs that are cardiovascularly completely safe and at least equally effective. The vasoconstrictor properties of triptans are thought to be mediated via activation of 5-HT_{1B} receptors in blood vessels; this has led, in view of the contraindications in patients with cardiovascular pathologies, to the development of antimigraine drugs targeting the 5-HT_{1D} and 5-HT_{1F} receptors. While 5-HT_{1D} receptor activation was not effective in the acute treatment of migraine (Gómez-Mancilla et al., 2001), the 5-HT_{1F} receptor agonists have shown to be effective (Farkkila et al., 2012; Ferrari et al., 2010). Furthermore, predictive preclinical models of migraine have shown that lasmiditan does not cause vasoconstriction and that its antimigraine effects are likely mediated via neural modulation (Labastida-Ramírez et al., 2017; Nelson et al., 2010; Rubio-Beltrán et al., 2016; Vila-Pueyo et al., 2016). Thus, 5-HT_{1F} receptor agonists may provide migraine patients with another type of specific acutely acting antimigraine drug, with a cardiovascular safety advantage over the triptans, and with a mechanism of action that is likely to be, at least partly, different from that of the triptans.

Based on the lack of vasoconstrictive properties and its presumably neuronal mode of action, 5-HT_{1F} receptor agonists can be considered as an entity apart from that of the triptans in antimigraine therapy.

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