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Potential mechanisms of prospective antimigraine drugs: A focus on vascular (side) effects

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ABSTRACT

Currently available drugs for the acute treatment of migraine, i.e. ergot alkaloids and triptans, are cranial vasoconstrictors. Although cranial vasoconstriction is likely to mediate—at least a part of—their therapeutic effects, this property also causes vascular side-effects. Indeed, the ergot alkaloids and the triptans have been reported to induce myocardial ischemia and stroke, albeit in extremely rare cases, and are contraindicated in patients with known cardiovascular risk factors. In view of these limitations, novel antimigraine drugs devoid of vascular (side) effects are being explored. Currently, calcitonin gene-related peptide (CGRP) receptor antagonists, which do not have direct vasoconstrictor effects, are under clinical development. Other classes of drugs, such as 5-HT_{1F} receptor agonists, glutamate receptor antagonists, nitric oxide synthase inhibitors, VPAC/PAC receptor antagonists and gap junction modulators, have also been proposed as potential targets for acute antimigraine drugs. Although these prospective drugs do not directly induce vasoconstriction, they may well induce indirect vascular effects by inhibiting or otherwise modulating the responses to endogenous vasoactive substances. These indirect vascular effects might contribute to the therapeutic efficacy of the previously mentioned compounds, but may alternatively also lead to vascular side-effects. As described in the current review, some of the prospective antimigraine drugs with a proposed non-vascular mechanism of action may still have direct or indirect vascular effects.

Contents

1. Introduction

Migraine is defined as a neurovascular disorder characterized by attacks of a severe, debilitating and throbbing unilateral headache associated with autonomic nervous dysfunction including nausea and vomiting, photophobia and phonophobia as well as neurological symptoms (Goadsby et al., 2002; Olesen et al., 2009). Based on clinical features, three distinct phases of migraine can be discerned: a trigger, an aura and a headache phase (Goadsby et al., 2002). In Western countries this disorder affects approximately 18% of women and 6% of men (Bigal & Lipton, 2009). Migraine represents an enormous socio-economic burden to the individual as well as to society (Andlin-Sobocki et al., 2005), and profoundly affects the patient's quality of life (Ruiz de Velasco et al., 2003).

Abbreviations: AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CGRP, Calcitonin gene-related peptide; CNS, Central nervous system; CSD, Cortical spreading depression; DHE, Dihydroergotamine; EDHF, Endothelium-derived hyperpolarizing factor; eNOS, Endothelial nitric oxide synthase; GTN, Glyceryl trinitrate (also called nitroglycerin); 5-HT, 5-Hydroxytryptamine; I.v., Intravenous route of administration; MCA, Middle cerebral artery; iNOS, Inducible nitric oxide synthase; L-NAME, Nω-nitro-L-arginine methyl ester (L-NAME); NMDA, *N*-methyl D-aspartate; nNOS, Neuronal nitric oxide synthase; NO, Nitric oxide; NOS, Nitric oxide synthase; PAC receptor, PACAP receptor; PACAP, Pituitary adenylate cyclase activating polypeptide; RAMP1, Receptor activity modifying protein 1; SSS, Superior sagittal sinus; VIP, Vasoactive intestinal peptide; VPM, Ventroposteromedial thalamic nucleus; VPAC receptor, VIP and PACAP receptor.

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1.1. Pathophysiology of migraine

Although elusive for a long time, our understanding of the pathophysiology of migraine progressed significantly, evolving slowly from a malady of supernatural causes (Villalón et al., 2003) to a disorder of vascular (Graham & Wolff, 1938; Wolff, 1938), neurogenic (Moskowitz et al., 1979; Moskowitz, 1993) or neurovascular (Durham, 2008; Villalón & Olesen, 2009) origin. Currently, migraine is considered a neurovascular disorder involving activation of the trigeminovascular system (Olesen et al., 2009), with the primary dysfunction located in brainstem centers regulating vascular tone and pain sensation (Link et al., 2008). This activation results in cranial vasodilatation mediated by the release of vasoactive neuropeptides including calcitonin gene-related peptide (CGRP), which seems to play a pivotal role in migraine pathophysiology (Villalón & Olesen, 2009).

1.2. Currently available antimigraine drugs

The history of the treatment of headache in general, and migraine in particular, spans millennia, from the Neanderthal era to the Space Age (Edmeads, 1999). With this long history, it is surprising that effective antimigraine drugs had been, until very recently, limited in number. In the last decades, there have been big steps in the development of antimigraine drugs (Olesen et al., 2006). Besides analgesics, specific antimigraine drugs can be divided into: (i) agents that abolish an individual migraine attack (acute antimigraine drugs; i.e. ergots and triptans); and (ii) agents aimed at its prevention (prophylactic drugs; such as β-adrenoceptor blockers, antiepileptics, etc.). Many patients need treatment to abolish attacks (acute treatment), but only patients with frequent attacks additionally need prophylactic treatment by drugs taken daily to reduce the number and/or severity of attacks (Olesen & Goadsby, 2006).

In acute antimigraine treatment triptans represent a considerable advance (Goadsby et al., 2002), but their vasoconstrictor side-effects warrant caution in patients with cardiovascular pathologies (Dodick et al., 2004). Other side-effects such as dizziness, nausea, fatigue, chest symptoms and paresthesia prevent some patients from using triptans. Furthermore a number of patients do not respond well to the triptans; indeed, triptan monotherapy is ineffective or poorly tolerated in 1 out of 3 migraineurs and in 2 out of 5 migraine attacks (Mathew et al., 2009). The advent of CGRP receptor antagonists such as olcegepant (previously referred to as BIBN4096BS; (Olesen et al., 2004)) and telcagepant (MK-0974 (Ho et al., 2008a,b; Ho, Dahlöf, et al., 2010)) bodes well for migraineurs who are poor or non-responders to triptan treatment. As subsequently discussed in this review, these "gepants", which have an efficacy comparable to triptans, seem to have a better safety and tolerability profile (Villalón & Olesen, 2009; Durham & Vause, 2010).

1.2.1. Ergot alkaloids

The ergot alkaloids ergotamine and dihydroergotamine (DHE) (also called "ergots"), were the first specific acute antimigraine drugs for several decades until the advent of the triptans (Silberstein & McCrory, 2003). The ergots were originally developed as sympatholytics, but it was later suggested that their antimigraine therapeutic efficacy was probably mediated by vasoconstriction of cranial blood vessels (for review, see Müller-Schweinitzer, 1992). As both ergotamine and DHE display affinity for a wide variety of receptors including 5-HT (5-hydroxytryptamine, serotonin), dopamine and noradrenaline receptors (Müller-Schweinitzer, 1992), they are considered "dirty drugs". As expected from this pharmacological profile, their most important pharmacological effect is arterial constriction (Müller-Schweinitzer & Weidmann, 1978; Müller-Schweinitzer, 1992). Indeed, at therapeutic concentrations, ergotamine and DHE induce a potent vasoconstriction in the external carotid (extracranial) vascular bed of anaesthetized dogs mainly by activation of α-adrenoceptors and 5-HT (mainly 5-HT_{1B}) receptors (Villalón et al., 1999; Valdivia et al., 2004). Whereas both ergotamine and DHE constrict the cranial vascular bed, there is a difference in their capacity to constrict peripheral blood vessels. Ergotamine induces contraction of peripheral arteries, including the pulmonary (Cortijo et al., 1997), cerebral (Müller-Schweinitzer, 1992), temporal (Ostergaard et al., 1981) and coronary (MaassenVanDenBrink et al., 1998) arteries. In contrast, DHE is a more potent constrictor of venous capacitance vessels than of arteries (Silberstein, 1997). In humans, blood pressure is transiently increased for about 3 h after parenteral therapeutic doses of ergotamine and DHE (Tfelt-Hansen, 1986; Andersen et al., 1987), which is likely caused by an increased peripheral resistance (Tfelt-Hansen et al., 1983). Moreover, a much longer lasting constrictor effect on peripheral arteries (ergotamine) or veins (DHE) is induced. This is most likely caused by a slow diffusion from the receptor biophase (Martin et al., 1995); the effects last much longer than expected from the plasma concentrations (Tfelt-Hansen & Paalzow, 1985; MaassenVanDenBrink et al., 1998; De Hoon et al., 2001). Thus, overall, based on in vitro, in vivo animal data and human clinical research, both ergotamine and DHE have the propensity to induce potent and longer lasting clinical effects in some patients, although the side-effect profile of DHE is more favorable as compared to that of ergotamine (Silberstein & Young, 1995; Saper & Silberstein, 2006).

Besides a vascular mode of action, which was originally believed to be the exclusive mechanism of the antimigraine efficacy of ergot alkaloids, the neuronal properties of these compounds most probably also contribute to their clinical effects. The neuronal activity is probably mediated via their agonist activity at 5-HT_{1B}, 5-HT_{1D} and $5HT_{1F}$ receptors on trigeminal nerve terminals resulting in inhibition of the neuronal release of vasoactive peptides and preventing vasodilatation in migraine (Hoskin et al., 1996).

1.2.2. Triptans

Triptans are 5-HT receptor agonists, displaying affinity mainly at the 5-HT_{1B} and 5-HT_{1D} receptor subtypes (for references, see Villalón et al., 2003). The development of the triptans was prompted by the hypothesis that 5-HT was involved in the pathophysiology of migraine (for further details, see Section 2.2). The factor restricting the clinical use of 5-HT as an antimigraine agent was the prevalence of side-effects on the gastrointestinal and cardiovascular systems (Kimball et al., 1960; Anthony et al., 1967) as well as the need for an intravenous (i.v.) infusion of 5-HT. The antimigraine efficacy of 5-HT clearly suggested the existence of a specific 5-HT receptor involved in the relief of migraine headache. The identification of the 5-HT receptor type (nowadays called the 5-HT_{1B} receptor) responsible for the beneficial effects of 5-HT provided the possibility to develop antimigraine drugs devoid of the side-effects observed with the ergot alkaloids (Humphrey, 2008). The first triptan developed, sumatriptan, was introduced in the early 1990s (Humphrey & Feniuk, 1991), and it did indeed change the lives of numerous migraineurs (Goadsby et al., 2002). Compared to the ergot alkaloids, sumatriptan induces fewer side-effects due to its increased selectivity on the 5-HT_{1B} and 5-HT_{1D} receptors (Brown et al., 1991), thereby avoiding peripheral vasoconstriction as mediated, e.g., by the 5-HT_{2A} receptor for which ergotamine displays affinity. Further, the vasoconstrictor effects of sumatriptan are not sustained during a long period as is the case for the ergot alkaloids (MaassenVanDenBrink et al., 1998). Limitations of sumatriptan are its low (14%) oral bioavailability (Fowler et al., 1991), and headache recurrence within 24 h in about one third of patients; nevertheless, recurrence can be treated effectively with a subsequent dose of sumatriptan (Ferrari & Saxena, 1993; Visser et al., 1996). In order to overcome these limitations, over time, additional triptans have been developed with chemical structures similar to sumatriptan, but with a higher lipophilicity (for references, see Villalón et al., 2003). Whereas the pharmacodynamic profile of these so-called 'second-generation' triptans resembles that of sumatriptan, there are

differences in their pharmacokinetic properties, which may lead to advantages including earlier onset of action (Ferrari et al., 2001). The antimigraine action of triptans is most likely mainly based on their potent vasoconstrictor effect on cranial blood vessels mediated via the 5-HT_{1B} receptor (Humphrey & Feniuk, 1991; Saxena & Pfelt-Hansen, 2006). The high intracranial 5-HT_{1B} receptor density compared to extracranial blood vessels probably renders the triptans relatively selective for producing intracranial vasoconstriction (Longmore et al., 1998). Nevertheless, in keeping with their agonist activity at the 5-HT_{1B} receptor, the triptans also have the potential to induce extracranial vasoconstriction. In vivo, in humans it was shown that sumatriptan as well as second-generation triptans induce vasoconstriction, increase blood pressure and decrease buffering capacity of conduit arteries after the intake of equipotent therapeutic dosages (De Hoon et al., 2000; Vanmolkot et al., 2002; Vanmolkot & de Hoon, 2006). In vitro, constriction of coronary arteries was confirmed (MaassenVanDenBrink et al., 1998; Nilsson et al., 1999), which is larger in distal than in proximal sections of the coronary artery (Chan et al., 2009). Consequently, the triptans are contraindicated in individuals with active cardiovascular disease and uncontrolled hypertension (Dodick et al., 2004). However, a retrospective case-control study has recently demonstrated that the use of triptans in patients with cardiovascular risk factors (for whom these drugs are contraindicated) did not increase the incidence of ischemic cardiovascular complications (Wammes-van der Heijden et al., 2006). Moreover, 5-HT_{1B} receptor expression does not differ between normal and atherosclerotic coronary arteries (Edvinsson et al., 2005).

It is generally accepted that, besides inducing vasoconstriction in cranial blood vessels, two additional mechanisms of action probably contribute to the therapeutic action of the triptans, namely: (i) inhibition of the release of neuropeptides in perivascular nerve terminals of the trigeminovascular system (Goadsby & Edvinsson, 1993); and (ii) direct inhibition of neuronal activation, reducing central pain transmission via activation of 5-HT_{1D} and 5-HT_{1F} receptors (Goadsby et al., 2002; Waeber & Moskowitz, 2005).

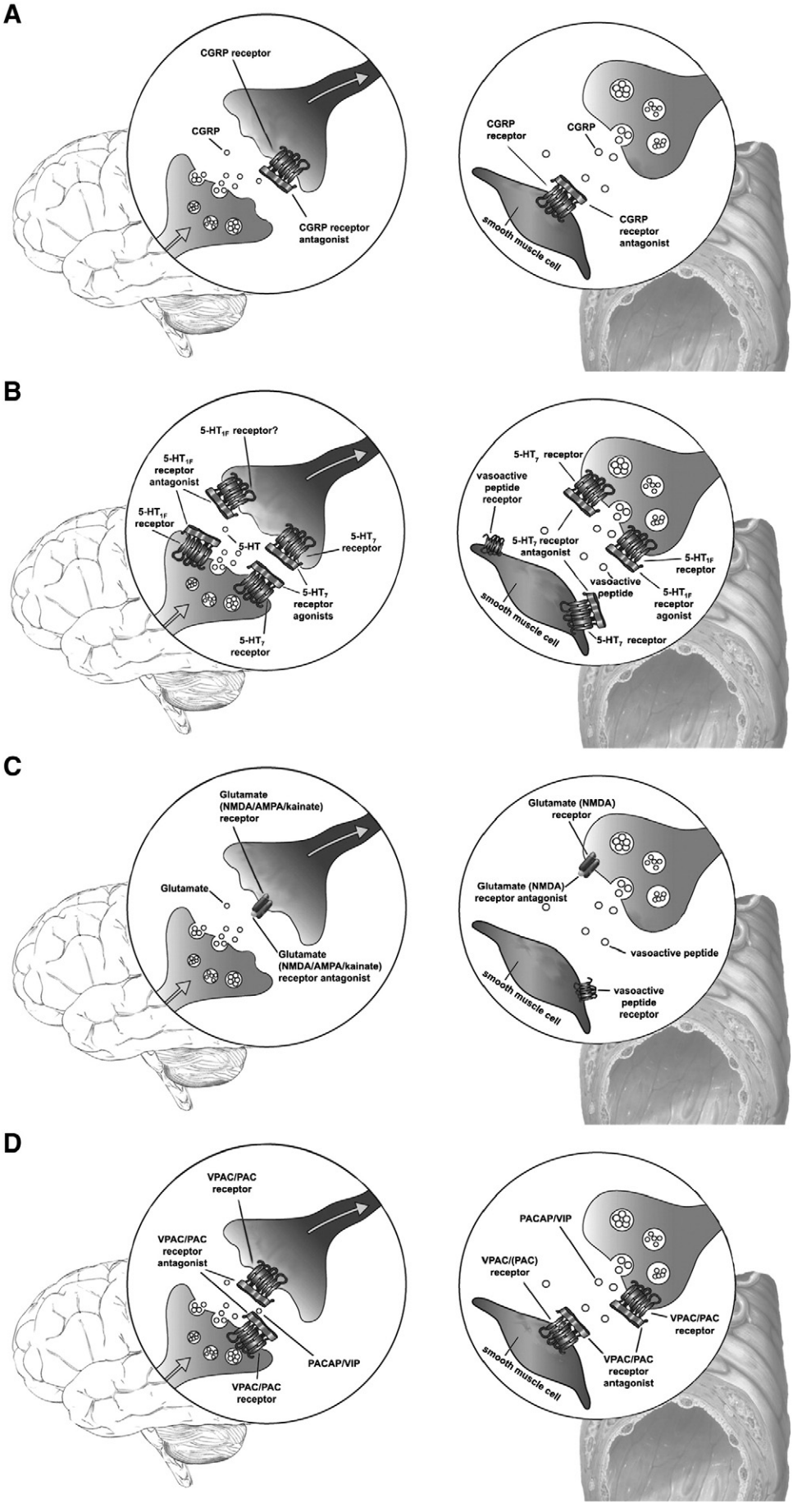
2. Vascular effects of prospective antimigraine drugs

Since the currently available antimigraine drugs have shortcomings and may cause cardiovascular side-effects due to their vasoconstrictor properties, research now has focused on the development of antimigraine drugs devoid of vasoconstrictor effects. Several ligands that act centrally and affect neuronal transmission have been described to be potential targets for the prophylactic or acute treatment of migraine (Ramadan & Buchanan, 2006). Some of these compounds may, however, also affect the release or action of vasoactive mediators. Examples of potential neuronal targets for future antimigraine drugs are: the CGRP receptor, glutamate receptor, VPAC/PAC receptor, NOS synthase, 5-HT_{1F} receptor and gap junctions. However, if such antimigraine compounds would indeed inhibit the release of vasoactive agents or block the receptors involved in vasodilatation, these compounds will directly or indirectly induce vascular (side) effects. On this basis, the present review analyzes the preclinical as well as clinical experimental data on the vascular effects of several prospective antimigraine drugs. In the following sections, the (neurogenic) mechanism of action of a number of prospective antimigraine drugs, their (potential) vascular (side) effects (see also Fig. 1) and, when possible, their main clinical benefits and limitations are discussed.

2.1. CGRP receptor antagonists

CGRP is a potent vasodilator in several species (Edvinsson et al., 1987; Bell & McDermott, 1996; Gupta et al., 2006b) and is expressed throughout the central and peripheral nervous system (Poyner, 1992). Several lines of evidence support that CGRP plays an important role in the pathogenesis of migraine (Edvinsson & Goadsby, 1990). Elevated levels of CGRP have been observed in the jugular vein during a migraine attack and these levels were normalized after pain relief with sumatriptan (Goadsby et al., 1990). Moreover, i.v. administration of CGRP can induce a migraine-like headache in migraine patients (Lassen et al., 2002) and, thus, disruption of CGRP signaling represents a valid strategy for the treatment of migraine (Doods et al., 2000; Ho et al., 2008b). CGRP is found in the central nervous system (CNS) (particularly in striatum, amygdalae, colliculi and cerebellum), as well as in the vessel wall of intracranial arteries (Arulmani et al., 2004a; Durham, 2008; Link et al., 2008). CGRP is located in primary spinal afferent C and Aδ fibers projecting to the trigeminal nuclear complex in the brainstem (Liu et al., 2008). Moreover, in the trigeminal nucleus caudalis and at C1/C2 levels, CGRP acts at second order neurons to transmit pain signals centrally through the brainstem and midbrain to the thalamus and higher cortical pain regions (Goadsby, 2007a). In addition, components of the functional CGRP receptor complex, such as calcitonin-like receptor and receptor activity modifying protein 1 (RAMP1) have recently been localized on trigeminal neurons (Eftekhari et al., 2010), and it is suggested that they modulate the prejunctional CGRP production (Lennerz et al., 2008). In the cranial circulation, CGRP is released by perivascular nerve fibers after trigeminal nerve activation where it induces vasodilatation of cranial arteries by binding to the CGRP receptor (Edvinsson, 1985; Uddman et al., 1985; Goadsby et al., 1988). CGRP initiates vasodilatation through interaction with these G-protein coupled receptors of the B-type that are primarily coupled to the activation of adenylyl cyclase. In vitro, this vasodilatation is independent of endothelium in human cerebral, meningeal (Edvinsson, 1985; Jansen-Olesen et al., 1996; Gupta et al., 2006a) and coronary (Gupta et al., 2006b) blood vessels, although in animals an NO-dependent component seems to be present (Akerman et al., 2002), while other studies provided evidence against an endothelial mechanism, but suggested that the dilatation is associated with activation of adenylyl cyclase (Edvinsson, 1985). Likewise, in vivo in the human peripheral circulation, CGRP-induced vasodilatation is, at least in part, dependent on the release of nitric oxide (NO) (De Hoon et al., 2003). Blockade of the functional CGRP receptor complex, which consists of the calcitonin-like receptor component and RAMP1 (Conner et al., 2002), prevents vasodilatation induced by CGRP. CGRP receptor characterization has in the past relied on the use of the peptide antagonist $CGRP_{8-37}$. Recently, the more potent CGRP receptor antagonists olcegepant and telcagepant, which are effective in the acute treatment of migraine, became available (Olesen et al.,

Fig. 1. Schematic representation of a synapse in the CNS (left panels) and a neurovascular junction (right panels). **A:** stimulation of post-synaptic CGRP receptors in the CNS by CGRP released from CGRPergic neurons may produce neuronal activation (left panel), whereas stimulation of vascular CGRP receptors by CGRP released from sensory perivascular nerve terminals may induce vasodilatation (right panel). Thus, CGRP receptor antagonists may affect neurotransmission as well as vasodilatation. **B:** stimulation of pre- and post-synaptic 5-HT_7 and 5-HT_{1F} receptors in the CNS by 5-HT released from serotonergic neurons may affect neurotransmission. On the other hand, on the neurovascular junction, stimulation of prejunctional 5-HT_7 receptors may increase the release of neuromediators (heteroreceptors; e.g. CGRP) resulting in vasodilatation, whereas stimulation of prejunctional 5-HT_{1F} receptors may inhibit the release of neuromediators (heteroreceptors; e.g. CGRP). Stimulation of vascular 5-HT_7 receptors results in vasodilatation, whereas 5-HT_{1F} receptors are not functional in blood vessels. Thus, both 5-HT_7 receptor antagonists and 5-HT_{1F} receptor agonists may block neurotransmission in the trigeminovascular system. **C:** stimulation of post-synaptic ionotropic glutamate receptors in the CNS by glutamate released from glutamatergic neurons may produce neuronal activation (left panel), whereas stimulation of neurovascular glutamate NMDA receptors by glutamate released from nerve terminals increases the release of vasoactive peptides from sensory perivascular nerves (right panel). Therefore, glutamate receptor antagonists may affect neurotransmission, while NMDA receptor antagonists additionally will affect vasodilatation. **D:** stimulation of pre- and post-synaptic VPAC/PAC receptors in the CNS by PACAP or VIP released from peptidergic neurons may produce neuronal activation (left panel), whereas stimulation of neurovascular VPAC/PAC receptors by PACAP or VIP released from peptidergic neurovascular terminals may produce release of vasoactive peptides and vasodilatation. Taken together, VPAC/PAC receptor antagonists might affect neurotransmission as well as vasodilatation.


A
CGRP receptor
CGRP
CGRP receptor antagonist
CGRP receptor
CGRP
CGRP receptor antagonist
smooth muscle cell
B
5-HT1F receptor?
5-HT1F receptor antagonist
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5-HT
5-HT7 receptor
5-HT7 receptor agonists
5-HT7 receptor
vasoactive peptide receptor
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vasoactive peptide
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Glutamate (NMDA/AMPA/kainate) receptor
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PACAP/VIP
VPAC/(PAC) receptor
VPAC/PAC receptor
VPAC/PAC receptor antagonist
smooth muscle cell

2004; Ho et al., 2008b). Although the previously mentioned compounds were originally designed to prevent the neurogenic vasodilatation occurring in the pathogenesis of migraine, these antagonists also seem to display central effects that may be clinically important in the treatment of this disorder (Villalón & Olesen, 2009).

2.1.1. Central effects

It remains unclear whether the antimigraine action of CGRP receptor antagonists is mediated via a central or a peripheral mechanism. Several arguments suggest a central mechanism of action, namely: (i) the lack of presynaptic CGRP receptors in the meninges, which implies that exogenous CGRP is unlikely to directly modify the innervating sensory nerve fibers (Lennerz et al., 2008); (ii) the fact that exogenous CGRP in the meninges, including meningeal vasodilatation, are not sufficient to activate or sensitize meningeal nociceptors in the rat (Levy et al., 2005). This suggests that an action of CGRP on the dura mater cannot account for the activation of peripheral afferents during migraine (Levy et al., 2005); (iii) olcegepant inhibits the post-synaptic nociceptive transmission in the trigeminal system by i.v. administration, but not by topical administration on the dura (Fischer et al., 2005); and (iv) given the very high clinical doses reported to achieve antimigraine efficacy compared to the in vitro receptor binding characteristics of telcagepant, the need for penetration through the blood–brain barrier has been suggested (Olesen et al., 2004; Edvinsson, 2008; Ho et al., 2008b). However, the discrepancy between the high clinical doses and the binding affinity in vitro is probably not only explained by penetration of the blood–brain barrier, but also by other factors, which will be explained in the later part.

2.1.2. Vascular effects

Olcegepant has a high affinity for the primate CGRP receptor (K_i: 0.014 nM), and potently antagonizes in vitro the vasodilator response to CGRP in human cranial arteries (Edvinsson et al., 2002; Verheggen et al., 2002; Gupta et al., 2006a). Besides its direct antagonist effect in cranial arteries, olcegepant is capable of blocking the vasodilatation induced by stimulation of the trigeminal nerve. Moreover, olcegepant: (i) dose-dependently antagonized CGRP-mediated neurogenic vasodilatation caused by trigeminal ganglion stimulation in monkeys and rats (Doods et al., 2000); (ii) blocked the changes in facial blood flow induced by brainstem trigeminal nucleus caudalis activation in rats (Escott et al., 1995); and (iii) attenuated capsaicin-induced carotid arteriovenous anastomotic vasodilatation (Kapoor et al., 2003). However, due to its physicochemical properties and for reasons of bioavailability, olcegepant needs to be administered i.v., which reduces its therapeutic value. In contrast with olcegepant, telcagepant (MK-0974) is orally bioavailable (Paone et al., 2007), and has also been shown to be effective as an antimigraine drug (Ho et al., 2008a,b; Connor et al., 2009). Pharmacological characterization of telcagepant showed that this drug displays equal affinity for native and cloned CGRP receptors as determined by radioligand binding experiments (K_i: 0.77 nM) (Salvatore et al., 2008). Moreover, telcagepant antagonized in a concentration-dependent manner: (i) CGRP-induced cAMP accumulation in cells expressing the recombinant human CGRP receptor (Salvatore et al., 2008); (ii) the vasodilator effect of α-CGRP in human isolated cranial arteries (Edvinsson et al., 2010); and (iii) capsaicin-induced dermal vasodilatation, which is caused by endogenous CGRP release via activation of the transient receptor potential cation channel, subfamily V, member 1 (also called TRPV1 receptor) in the rhesus forearm (Salvatore et al., 2008).

In addition to its role in the cranial circulation, CGRP is also important in the peripheral cardiovascular system. CGRP is a potent peripheral vasodilator which affects the myocardium. The human coronary circulation is innervated by a dense supply of CGRP-positive fibers (Gulbenkian et al., 1993) and the CGRP receptor components are found in human coronary arteries (Gupta et al., 2006b; Chan, Edvinsson, et al., 2010). Indeed, both olcegepant (Gupta et al., 2006b) and telcagepant (Chan, Edvinsson, et al., 2010) antagonize the vasodilator effect of α-CGRP in human isolated coronary arteries. Moreover, increased cAMP levels induced by α-CGRP are reduced when coronary arteries are pre-treated with olcegepant (Gupta et al., 2006b) or telcagepant (Chan, Edvinsson, et al., 2010), suggesting that the blocking effect is mediated via the CGRP receptor. CGRP increases heart rate (Franco-Cereceda & Lundberg, 1988) and has positive inotropic effects on isolated human trabeculae (Saetrum Opgaard et al., 2000). Hence, blockade of the CGRP receptors might affect cardiovascular responses induced by CGRP. However, in vivo haemodynamic studies in dogs have reported no effect of $CGRP_{8-37}$ on coronary or myocardial regional blood flow (Shen et al., 2001). Olcegepant has also been reported to have no effect on myocardial vascular conductance in rat and pig (Kapoor et al., 2003; Arulmani et al., 2004b), nor does olcegepant alter baseline haemodynamics in animals (Arulmani et al., 2004b). These data suggest that endogenous CGRP is not important in cardiovascular regulation under resting conditions in cardiovascularly healthy subjects. On the other hand, CGRP receptor antagonists might display adverse effects in pathophysiological conditions. CGRP is proposed as a pivotal player in ischemia-reperfusion (Kwan et al., 1990; Huang et al., 2008) and ischemic preconditioning (Wolfrum et al., 2005). Indeed, CGRP has a protective effect during coronary (Li & Peng, 2002; Li et al., 2008) and cranial (Rehni et al., 2008; Cai et al., 2010) ischemia, which was demonstrated both in pre- and post-conditioning ischemic reperfusion models. Moreover, $CGRP_{8-37}$ (Lu et al., 1999) and olcegepant (Chai et al., 2006) blocked the protective effect of CGRP in an isolated rat heart model. Based on these observations, it may be suggested that a CGRP receptor antagonist, especially after chronic use as would be the case when used as a prophylactic drug, might attenuate the cardioprotective effect of CGRP. Nevertheless, the effect of CGRP receptor antagonism on ischemic preconditioning has until now been demonstrated only in isolated rodent hearts, and the pathophysiological significance of this observation is uncertain. In addition, in the setting of pathology, in vivo studies of $CGRP_{8-37}$ and olcegepant in rat and pig report no effect on coronary ischemia/reperfusion infarct size (Kallner et al., 1998; Wu et al., 2001). Further, $CGRP_{8-37}$ had no effect on myocardial blood flow in dogs with heart failure produced by previous myocardial infarction and rapid ventricular pacing (Shen et al., 2003). Moreover, another study in dogs reported no effect of topically administered $CGRP_{8-37}$ onto the left ventricular surface on coronary artery microvessel diameter prior to and at 10 min following coronary artery occlusion (Sekiguchi et al., 1994).

Taken together, although CGRP receptor antagonists under some pathophysiological conditions might negatively affect the body's protective mechanisms, it should be kept in mind that CGRP receptor antagonists do not have vasoconstrictor properties per se in human cranial and coronary arteries (Gupta et al., 2006a,b; Chan, Edvinsson, et al., 2010), as the triptans do. This, as discussed in the later part, may be an advantage in view of cardiovascular safety, particularly in migraine patients suffering from cardiovascular pathologies (Villalón & Olesen, 2009).

2.1.3. Clinical effects

Boehringer-Ingelheim's BIBN4096BS (olcegepant) was the first CGRP receptor antagonist entering the clinical development phase and provided proof-of-concept for the involvement of CGRP in migraine pathophysiology (Olesen et al., 2004). Being the first of a generation of CGRP receptor antagonists, olcegepant showed promising cerebral and systemic haemodynamics in humans, and thus made this potential new class of antimigraine drugs in favor of the triptans (Petersen et al., 2005). The study by Petersen et al. (2005) with olcegepant was inconsistent with the assumption that CGRP receptor antagonists could alter the tone of cerebral and extracerebral arteries. Under resting conditions, no effect of olcegepant was seen on regional and global cerebral perfusion, middle cerebral artery (MCA)

blood flow velocity, temporal and radial artery diameter, blood pressure or heart rate. The same group further showed that olcegepant effectively prevents CGRP-induced headache and extracerebral vasodilatation without significant effects on cerebral hemodynamics (Petersen et al., 2005). After h-α-CGRP infusion, olcegepant had no effect on blood flow velocity and regional perfusion of the MCA compared to placebo, however, it prevented dilatation of the superficial temporal and radial arteries as well as reflex tachycardia resulting from systemic vasodilatation.

Although an additional neuronal action cannot be ruled out, in line with its limited ability to penetrate through the blood–brain barrier (Edvinsson & Tfelt-Hansen, 2008), it is suggested that olcegepant treats migraine headache predominantly by acting at the level of the large dural blood vessels which are not protected by the blood–brain barrier. Resolving the question whether CGRP receptor antagonists exhibit their antimigraine effect in the CNS or through a vascular mechanism of action outside the CNS, is a very relevant issue in the future development of new and safe CGRP receptor antagonists. To that end, additional research is needed in order to answer this question.

Unfortunately, due to its low oral bioavailability, the further development of olcegepant was early terminated. Recently, with BI44370 (Durham & Vause, 2010), the company has a new CGRP receptor antagonist ready for phase III clinical development. Given the fact that the efficacy of olcegepant was comparable to that of the triptans in acute migraine, while it had the major advantage of not inducing a direct vasoconstrictor response, validated the CGRP receptor as a valuable target and inspired many companies to develop CGRP receptor antagonists as an effective and safe alternative for the triptans.

The first orally available CGRP receptor antagonist developed after olcegepant was the Merck compound MK-0974 (telcagepant). It is structurally derived from olcegepant (Williams et al., 2006; Paone et al., 2007) and has a promising antimigraine profile (Ho et al., 2008b). Indeed, telcagepant showed an efficacy comparable to that of zolmitriptan, but with fewer side-effects. The most commonly frequent adverse effects with telcagepant were dry mouth, somnolence, dizziness, nausea and fatigue (Edvinsson & Linde, 2010). Adverse effects that occur after the use of triptans like asthenia, paresthesia, chest discomfort, fatigue, myalgia, dizziness and throat tightness, are less frequent after the use of telcagepant (Edvinsson & Ho, 2010). Remarkably, an efficacy and tolerability study in patients with stable coronary artery disease (Ho et al., 2008a) did not demonstrate a significant difference in 2-hour headache freedom between telcagepant (13/52, 25.0%) and placebo (10/53, 18.9%). However, the study design and lower than expected number of patients enrolled may have been the reason for this negative result. The side-effect profile of telcagepant with intermittent dosing, as required for the acute treatment of migraine, looks excellent. Unfortunately, a small number of patients taking telcagepant twice daily for three months as prophylactic treatment showed marked elevations in liver transaminases (Tepper & Cleves, 2009). It has been suggested that this is a result of drug accumulation with daily dosing, since this is not seen in acute intermittent dosing. As a consequence of this potential for hepatotoxicity, Merck Research Laboratories announced a delay in filing the U.S. application for telcagepant for the acute treatment of migraine.

During the exploratory phase of the clinical development, studies focused on a biomarker model involving capsaicin-induced changes in dermal blood flow which are the result of local CGRP release. Therefore, inhibition of the increase in dermal vascular blood flow by telcagepant served as a surrogate for the dose at which clinical efficacy could be expected (Sinclair et al., 2010). After topical application of capsaicin on the human forearm, orally administered telcagepant effectively inhibited the CGRP-mediated increase in dermal blood flow (Van der Schueren et al., 2007, 2008b). Comparable results were obtained with a follow-up highly potent CGRP receptor antagonist, MK-3207 (Kennedy et al., 2009). As neither MK-0974 nor MK-3207 affected dermal blood flow under resting conditions, this argues against direct vasoconstrictor effects of CGRP receptor antagonists while they are very effective at preventing CGRP-mediated vasodilatation. The blockade by MK-3207 in the capsaicin biomarker model, guided the dose selection for further clinical trials with the compound. Unfortunately, the clinical development program for MK-3207 was discontinued (http://www.merck.com/newsroom/news-release-archive/research-and-development/2009_0910.html) after delayed, asymptomatic liver test abnormalities in extended Phase I studies were reported (Hewitt et al., 2009).

Limited data about specific vascular effects of telcagepant in a clinical setting are available. No effects on vital signs including blood pressure and ECG were reported in the first published safety data (Ho et al., 2008b). High doses of telcagepant, i.e. 560 and 600 mg, daily for up to 8 days had no clinically significant effects on 24 h mean ambulatory blood pressure or heart rate (Blanchard et al., 2010).

In a pharmacodynamic drug-interaction study with sumatriptan (100 mg) (De Hoon et al., 2009), a supratherapeutic dose of telcagepant (600 mg) did not significantly increase mean arterial blood pressure when administered as monotherapy to migraineurs during the interictal period. Co-administration, however, with sumatriptan resulted in an increased mean arterial blood pressure, comparable to the increase reported after administration of sumatriptan alone (De Hoon et al., 2000).

When looking specifically at cardiac safety, one study investigated the effect of telcagepant on spontaneous ischemia in patients with stable coronary artery disease (Behm et al., 2008). No episodes of chest pain were reported on the days of dosing of telcagepant or placebo. No obvious treatment-related changes in vital signs or ECG safety parameters appeared. Apparently, two 300 mg doses of telcagepant, administered 2 h apart, did not exacerbate spontaneous ischemia. However, important questions including the long term safety of CGRP antagonists, e.g. in a prophylactic setting, or in patients having an ischemic event, remain unanswered.

With the medical need for patients with coronary artery disease in mind, the effect of telcagepant on the haemodynamic response to therapeutic doses of glyceryl trinitrate (GTN; also called nitroglycerin) was investigated in healthy volunteers in order to exclude a potential pharmacodynamic interaction (Van der Schueren et al., 2008a). First, telcagepant did not influence brachial artery diameter under resting conditions. Secondly, telcagepant did not affect GTN-induced decrease in arterial stiffness nor did it affect GTN-induced increase in brachial artery diameter. The study concluded that CGRP receptor antagonists have no influence on the vasodilator response to an exogenous NO donor.

Although available data show no interference of CGRP receptor antagonists on resting haemodynamics, CGRP blockade under clinical ischemic conditions could have clinical consequences. However, in an acute setting, a single oral dose of telcagepant did not reduce exercise tolerance in patients with exercise-induced myocardial ischemia at T_{max} post telcagepant (Ho, Behm, et al., 2010). Exercise duration, maximum heart rate, chest pain or maximum ST segment depression did not differ between placebo and telcagepant in patients with chronic angina and limiting exercise-induced cardiac ischemia (Ho, Behm, et al., 2010). Although these data show no interference of acute CGRP receptor antagonism with myocardial ischemia, the effects of chronic CGRP blockade under clinical ischemic conditions remain unknown.

In the wake of telcagepant, many companies have targeted the development of CGRP receptor antagonists, now that its clinical efficacy in migraine has been demonstrated. Therefore, more studies will be performed in the future to test the vascular effects of this new class of drugs, which will provide more information about central and/or peripheral mode of action and additional reassurance about their cardiovascular safety profile.

2.1.4. Discussion

Summarizing data from both clinical and preclinical studies, it seems clear that: i) CGRP receptor antagonists are clinically effective in the treatment of migraine, probably to a similar extent as the triptans. It is not known yet whether responders and non-responders to triptans will respond to CGRP receptor antagonists in a similar way; and ii) the site of action of CGRP receptor antagonists is not yet clear, and may be both vascular and neuronal. The discrepancy between the high clinical doses of gepants and the in vitro binding affinity (the plasma concentrations used to achieve antimigraine efficacy are considerably higher than their in vitro pA_2) is not only explained by the penetration of the blood–brain barrier, but also by other factors, namely: (i) high protein binding of these compounds (about 95–96%) (Edvinsson & Linde, 2010); (ii) a concentration of drug equal to the pA_2 value may not be sufficient to decrease a functional responses since it only shifts the concentration response curves two-fold to the right; most likely a concentration of a least 10 times pA_2 would be needed to functionally inhibit the relaxations to CGRP; (iii) as nerve terminals releasing CGRP are located in the adventitia close to the media layer of the blood vessels, the concentration of telcagepant at the receptors may be substantially lower than that at the lumen of the blood vessel, i.e. the plasma concentration. The latter phenomenon is unlikely to occur in vitro, where the antagonist can reach the CGRP receptors from both the luminal and abluminal sides. Thus, although both a vascular and neuronal action of CGRP receptor antagonists may currently not be excluded, it seems that the fact that these drugs do not induce direct vasoconstriction is an advantage over the currently available antimigraine drugs. Moreover, in dogs, during acute regional myocardial ischemia induced by atrial pacing in the presence of coronary stenosis, neither CGRP nor $CGRP_{8–37}$ affected coronary flow and severity of ischemia, whereas sumatriptan exacerbated ischemia severity with concomitant reduction in coronary blood flow (Lynch et al., 2009b; Regan et al., 2009). Likewise, in the dog, $CGRP_{8–37}$ had no effect on myocardial reactive hyperemic response following brief mechanical coronary artery occlusion, whereas sumatriptan reduced peak reactive hyperemic coronary artery blood flow, reactive hyperemic flow and the repayment of coronary blood flow debt (Lynch et al., 2009a). These findings are consistent with the contractile response, unrelated to relaxation to CGRP, observed with triptans in human healthy (MaassenVanDenBrink et al., 1998; Chan, Edvinsson, et al., 2010) and diseased (Edvinsson & Uddman, 2005) coronary arteries. Notwithstanding the previously mentioned studies on the safety of CGRP receptor antagonists, the consequences of CGRP receptor blockade under ischemic conditions remain unknown. As it has not been excluded in human studies that CGRP is involved in ischemia-reperfusion and ischemic preconditioning, CGRP receptor antagonists should be used cautiously in patients with ischemic heart disease. Therefore, specific prudence is called for CGRP receptor antagonists in a prophylactic setting.

2.2. 5-HT receptor ligands

Serotonin (5-hydroxytryptamine; 5-HT) was one the first monoamines proposed to be involved in the pathophysiology of migraine on the basis of several lines of evidence, including: (i) some drugs that deplete monoamines (reserpine) can provoke a migraine attack (Kimball et al., 1960); (ii) high quantities of 5-hydroxyindole acetic acid, a metabolite of 5-HT, are excreted during a migraine attack (Sicuteri et al., 1961); and (iii) a slow i.v infusion of 5-HT can abort an attack of migraine (Kimball et al., 1960; Anthony et al., 1967). Side-effects and the need for an i.v. infusion precluded the clinical use of 5-HT as an antimigraine agent. Side-effects included: gastrointestinal effects, changes in heart rate, vasodilatation in some vascular beds (e.g. cutaneous blood vessels) and vasoconstriction in others (e.g. the external carotid bed) (Kimball et al., 1960; Anthony et al., 1967). The antimigraine efficacy of 5-HT clearly suggested the existence of a specific 5-HT receptor involved in the relief of migraine headache but, admittedly, the association between 5-HT and the mechanisms underlying the pathogenesis of migraine is circumstantial. It is undeniable that the cranial vasoconstrictor activity of sumatriptan and the second-generation triptans, mediated by the $5\text{-}HT_{1B}$ receptor, is associated with their efficacy in the acute treatment of migraine (De Vries et al., 1999; Villalón et al., 2003). Unfortunately, the $5\text{-}HT_{1B}$ receptor, being not exclusively confined to cranial blood vessels, is most likely also responsible for the moderate hypertension and coronary constriction noticed with these drugs. The development of antimigraine agents without cardiovascular side-effects, but capable of inhibiting trigeminal CGRP release, would avoid the vasoconstrictor action of the triptans and would represent a major improvement over current treatments (Ramadan & Buchanan, 2006). Therefore, in an attempt to avoid coronary vasoconstriction, other avenues have been explored: (i) $5\text{-}HT_{1D}$ and $5\text{-}HT_{1F}$ receptor agonists; and (ii) $5\text{-}HT_7$ receptor antagonists.

As described previously, the triptans have a high affinity for $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors. However, most triptans show also high pK_i values for the $5\text{-}HT_{1F}$ receptor (De Vries et al., 1999; Goadsby & Classey, 2003). The $5\text{-}HT_{1B}$ receptor has now clearly been linked to vasoconstriction (Villalón et al., 2003), whereas stimulation of $5\text{-}HT_{1D}$ or $5\text{-}HT_{1F}$ receptors induces inhibition of the trigeminovascular system without vasoconstriction (De Vries et al., 1999; Goadsby & Classey, 2003). This led to the synthesis of a series of isochroman-6-carboxamide derivatives, including PNU-109291 and PNU-142633, which have been described as highly selective $5\text{-}HT_{1D}$ receptor agonists (Ennis et al., 1998; McCall et al., 2002) (see Table 1). In

Table 1
General characteristics of the main 5-HT receptors involved in (potential) antimigraine treatment.
Modified from Villalón and Centurión (2007).

Receptor	Agonists	Antagonists	Transduction	Distribution	Function
$5\text{-}HT_{1B}$	Triptans CP-93,129 (rat)	SB224289	$G_{i/o}$	Cranial blood vessels	Vasoconstriction
$5\text{-}HT_{1D}$	PNU-109291 PNU-142633	BRL15572	$G_{i/o}$	Presynaptic neurons	Autoreceptor
$5\text{-}HT_{1F}$	LY344864 LY334370 Lasmiditan	(non-selective) Methysergide[a] (non-selective)	$G_{i/o}$	CNS	(−) Trigeminal system
$5\text{-}HT_7$	5-CT>>5-HT AS19	SB269970 SB258719 Lisuride[b] Methysergide[b]	G_s	CNS, smooth muscle, cat atrium	Circadian rhythm, relaxation, tachycardia (+) Trigeminal system

5-CT, 5-carboxamidotryptamine; (−), inhibits; (+), stimulates.
[a] It is also a partial agonist at $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors.
[b] Non-selective prophylactic agents with a high affinity for $5\text{-}HT_7$ receptors.

addition, three potent and selective 5-HT_{1F} receptor agonists have been reported (with their corresponding pK_i values at 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors, respectively), namely: (i) LY344864 (pK_i values: 6.3, 6.2 and 8.2); (ii) LY334370 (pK_i values: 6.9, 6.9 and 8.8); and lasmiditan (also known as COL-144 and LY573144, pK_i values: 5.9, 5.8 and 8.6) (Johnson et al., 1997; Phebus et al., 1997; Ramadan et al., 2003; Nelson et al., 2010).

Despite acknowledging that most of the evidence supporting the role of 5-HT in the pathophysiology of migraine is circumstantial, this monoamine has been shown to produce, via activation of 5-HT_7 receptors: (i) direct vasodilatation of cranial blood vessels (Villalón et al., 1997; Villalón & Centurión, 2007); (ii) excitation in neuronal systems (Cardenas et al., 1999); (iii) hyperalgesic pain and neurogenic inflammation (Taiwo et al., 1992; Pierce et al., 1996); (iv) neuroinflammatory processes (Mahé et al., 2005); and (v) central sensitization and activation of pain pathways (Brenchat et al., 2009). All of these processes have been demonstrated to participate in migraine pathophysiology.

2.2.1. Central effects

The 5-HT_{1F} receptor agonist LY334370 exerts a central mechanism of action by inhibiting the transmission of nociceptive impulses within the trigeminal nucleus caudalis (Shepheard et al., 1999). Likewise, selective agonists at 5-HT_{1D} (PNU 142633; McCall et al., 2002) and 5-HT_{1F} (LY334370; Phebus et al., 1997) receptors inhibit the trigeminovascular system (Ramadan et al., 2003). This led to the exploration of the effects of selective 5-HT_{1D} and 5-HT_{1F} receptor agonists as antimigraine drugs that would partly act like the triptans, but without vascular effects. There is a high correlation between the potency of various 5-HT_1 receptor agonists in the guinea pig dural plasma protein extravasation assay and their 5-HT_{1F} receptor binding affinity (Ramadan et al., 2003). However, the relevance of plasma protein extravasation in migraine is no longer tenable (Peroutka, 2005). More recently, Nelson et al. (2010) have shown that lasmiditan: (i) is a more selective agonist for 5-HT_{1F} receptors (selectivity ratio of about 500-fold relative to other 5-HT_1 receptor subtypes) than the first generation 5-HT_{1F} receptor agonist LY334370 (selectivity ratio of about 100-fold relative to other 5-HT_1 receptor subtypes); (ii) potently inhibited, when given orally to rats, markers associated with trigeminal ganglion stimulation, including induction of immediate early gene *c*-Fos in the trigeminal nucleus caudalis; and (iii) displays chemical properties and a pharmacological profile that differ from that of the triptans. Furthermore, 5-HT_{1F} receptors are located on glutamate-containing neurons and their activation might inhibit glutamate release (Ma, 2001), which may be relevant to its antimigraine action (Martínez et al., 1993). Indeed, most triptans show high pK_i values for 5-HT_{1F} receptors (Dahl et al., 1990; De Vries et al., 1999; Goadsby & Classey, 2003).

On the other hand, Agosti (2007) has hypothesized that activation of 5-HT_7 receptors may mediate the release of neuropeptides (substance P and CGRP), neurogenic inflammation and hyperalgesia in the trigeminovascular system during a migraine attack. In agreement with this hypothesis, it has recently been shown in anesthetized rats that the selective 5-HT_7 receptor antagonist SB269970 (see Table 1) caused a significant decrease in serum CGRP concentrations following electrical stimulation of the trigeminal ganglion, an effect which was reversed by the putative 5-HT_7 receptor agonist AS19 (Wang et al., 2010).

2.2.2. Vascular effects

Unlike the triptans (5-$HT_{1B/1D/1F}$ receptor agonists), 5-HT_{1D} and 5-HT_{1F} receptor agonists are devoid of contractile effects on coronary and cerebral blood vessels (Bouchelet et al., 2000; McCall et al., 2002). PNU-109291 and PNU-142633 do not produce vasoconstriction in in vivo (canine external and internal carotid bed) (Centurión et al., 2001) or in vitro (cerebral arteries) (Bouchelet et al., 2000) preparations. Likewise, LY344864, LY334370 and lasmiditan were devoid of vasoconstrictor activity (Bouchelet et al., 2000; Nelson et al., 2010). Together with the fact that the 5-HT_{1B} receptor antagonist SB224289 (see Table 1), which displays little affinity at the 5-HT_{1F} receptor (Hagan et al., 1997), completely blocked sumatriptan-induced external carotid vasoconstriction (De Vries et al., 1998), it is clear that the 5-HT_{1F} receptor is not involved in the vascular effects of sumatriptan and the second-generation triptans. It therefore implies that if LY334370 and lasmiditan turn out to be effective in migraine at clinical doses devoid of 5-$HT_{1B/1D}$ receptor interaction, the mechanism of action will not be via cranial vasoconstriction.

Interestingly, prophylactic antimigraine drugs such as methysergide (Sicuteri, 1959) and lisuride (Del Bene et al., 1983) display high affinity for 5-HT_7 receptors (Hoyer et al., 1994) and are capable of blocking 5-HT_7 receptor-mediated vasodilatation in the canine extracranial external carotid circulation (Villalón et al., 1997), which shows a direct (relaxant) effect of the 5-HT_7 receptor on cranial blood vessels. More recently, it has been shown in anesthetized rats that the selective 5-HT_7 receptor antagonist SB269970 (see Table 1) caused a significant decrease in serum CGRP concentrations following electrical stimulation of the trigeminal ganglion and that this effect was reversed by the putative 5-HT_7 receptor agonist AS19 (Wang et al., 2010). These findings, taken together, suggest that 5-HT_7 receptors may play a role in the pathophysiology of migraine.

2.2.3. Clinical effects

Despite the previously mentioned trigeminal inhibition, PNU-142633 proved to be ineffective in the acute treatment of migraine (Gómez-Mancilla et al., 2001), whilst LY334370 did show some efficacy when used in doses which may have interacted with 5-HT_{1B} receptors (Goldstein et al., 2001; Ramadan et al., 2003). Though clinical studies demonstrated that LY334370 is effective in treating migraine headaches without coronary side-effects (Ramadan et al., 2003), it was recognized that more studies on the role of the 5-HT_{1F} receptor in migraine were warranted (Goadsby & Classey, 2003). In this respect, the potency, selectivity and pharmacological profile of lasmiditan at 5-HT_{1F} receptors (as previously mentioned) made it an ideal drug to definitely test the involvement of 5-HT_{1F} receptors in the therapy of migraine headache (Nelson et al., 2010). Indeed, Ferrari et al. (2010) have recently reported the results of a randomized, multicenter, placebo-controlled, double-blind, group-sequential, adaptive treatment-assignment, proof-of-concept and dose-finding study using lasmiditan in 130 subjects during a migraine attack. Lasmiditan (at 20 mg i.v. and higher doses) proved effective in the acute treatment of migraine without inducing: (i) serious adverse events or withdrawals due to non-serious adverse events; (ii) triptan-like chest symptoms or chest discomfort; and (iii) significant changes in vital signs or ECG parameters or in hematological or clinical chemistry parameters. Adverse effects were generally mild and included dizziness, paresthesia and sensations of heaviness (Ferrari et al., 2010). Further studies to assess the optimal oral dose and full efficacy and tolerability profile are expected with great interest. Clearly, lasmiditan's non-vascular neuronal mechanism of action may offer an alternative antimigraine treatment, particularly in patients with cardiovascular pathologies and for whom antimigraine vasoconstrictor agents are contraindicated.

2.2.4. Discussion

The clinical efficacy of 5-HT_{1F} receptor agonists has been demonstrated; some preclinical experiments and clinical observations argue in favor of the potential effectiveness of selective 5-HT_{1F} receptor agonists in migraine. While it remains to be confirmed that the 5-HT_{1F} receptor agonists are devoid of 5-HT_{1B} receptor activity at clinical doses, these antimigraine drugs have potential advantages as compared to the triptans.

Furthermore, the preclinical data on 5-HT_7 receptors suggests that this receptor may play a role in the pathophysiology of migraine. The

antimigraine efficacy of selective 5-HT_7 receptor antagonists in clinical trials is awaited with great interest. However, the involvement of the 5-HT_7 receptor in vasodilatation and CGRP release suggests potential direct and indirect vascular effects. Therefore, the safety of 5-HT_7 receptor antagonists should be considered with caution.

2.3. Glutamate receptor antagonists

Glutamate is an excitatory neurotransmitter in the mammalian CNS and plays an important role in the mediation of excitatory synaptic transmission. Glutamate exerts its effects by activating ionotropic (ligand-gated ion channels) and metabotropic (G-protein coupled) receptors. Glutamate has been suggested to be involved in the pathophysiology of migraine (Pollack & French, 1975) as it is found in neurons of structures related to migraine pathophysiology, including the trigeminal ganglion, trigeminocervical complex and the thalamus (Kai-Kai & Howe, 1991). Indeed, glutamate and CGRP are co-released from trigeminal ganglion neurons by calcium channel-dependent mechanisms (Xiao et al., 2008), and increased levels of glutamate have been found in the trigeminocervical complex after stimulation of dural structures (Oshinsky & Luo, 2006). Moreover, glutamate levels were found to be elevated in the cerebrospinal fluid of migraine patients compared with controls, suggesting an excess of neuroexcitatory amino acids in the CNS (Rothrock et al., 1995). In addition, cutaneous allodynia, which is a sign for the development of central sensitization, has been observed in migraine patients during an attack (Burstein et al., 2000), and glutamate release (and to some extent glutamate receptor activation) is involved in central sensitization induced by peripheral sensory stimulation (Burstein, 2001).

Since activation of glutamate receptors by glutamate triggers post-synaptic excitatory potentials (Salt, 2002), and experimentally-produced pain increased the extracellular levels of glutamate in rat ventroposteromedial thalamic nucleus (VMP) (Salt, 2002), it has been suggested that glutamate also plays a role in the transmission of nociceptive information in the sensory thalamus. Moreover, the *N*-methyl-D-aspartate (NMDA) glutamate receptors are activated during cortical spreading depression (CSD), which is considered to be involved in migraine aura (Gorji et al., 2001; Salt, 2002). In view of the fact that glutamate seems to play a significant role in migraine processes, pharmacological management of glutamate receptors may provide further insight into potential therapy for the treatment of migraine. Indeed, several studies have suggested that ionotropic glutamate receptor antagonists affect processes involved in the pathophysiology of migraine.

The ionotropic glutamate receptors are ligand-gated ion channels and are divided into NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors (Monaghan et al., 1989). They primarily mediate fast synaptic transmission and have been identified in the superficial laminae of the trigeminal nucleus caudalis (Tallaksen-Greene et al., 1992) and the sensory thalamus among other pain-related areas of the rat brain (Halpain et al., 1984). Moreover, messenger RNA of NMDA and kainate receptors has been found in the trigeminal ganglion (Sahara et al., 1997).

2.3.1. Central effects

Different NMDA and non-NMDA glutamate receptor antagonists have demonstrated to attenuate mechanisms that are putatively involved in the pathophysiology of migraine, including inhibition of trigeminovascular nociception in the trigeminocervical nucleus (Storer & Goadsby, 1999; Goadsby & Classey, 2000; Classey et al., 2001). Further, the NMDA receptor has been implied to mediate antinociceptive effects in the descending brainstem nuclei (Jensen & Yaksh, 1992). The NMDA receptor antagonist MK-801 reduces c-fos protein expression in the trigeminal nucleus caudalis after intracisternal capsaicin injection or other painful stimuli (Mitsikostas et al., 1998; Mitsikostas et al., 1999; Hattori et al., 2004), while it increases c-fos-like immunoreactivity in the periaqueductal grey, dorsal raphe nucleus and nucleus raphe magnus (Hattori et al., 2004). Moreover, MK-801 blocks cell firing in the trigeminal cervical complex induced by electrical stimulation of the superior sagittal sinus (Storer & Goadsby, 1999; Goadsby & Classey, 2000). Interestingly, the NMDA receptor antagonists MK-801 and memantine prevent CSD, while the AMPA/kainate receptor antagonist, NBQX (2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(F)quinoxaline) has no effect (Lauritzen & Hansen, 1992; Nellgard & Wieloch, 1992). Since systemic administration of the glycine site selective NMDA receptor antagonist, L701324, prevents the induction of CSD (Obrenovitch & Zilkha, 1996), a role for the NMDA receptor subunit 1 that carries the glycine binding site of the NMDA receptor has been suggested (Andreou & Goadsby, 2009b). Taken together, the NMDA receptor mediates diverse mechanisms that may be of clinical relevance in the treatment of migraine.

The AMPA/kainate receptor antagonists CNQX and NBQX are also capable of reducing c-fos protein expression in the trigeminal nucleus caudalis after intracisternal capsaicin injection (Mitsikostas et al., 1998; Mitsikostas et al., 1999). Moreover: (i) trigeminal ganglion stimulation-induced c-fos expression in the trigeminal cervical complex, and this response was attenuated after i.v. administration of the AMPA/kainate receptor antagonist, tezampanel (LY293558 or NGX424) (Weiss et al., 2006); (ii) cell firing in response to electrical stimulation of dural structures in the trigeminocervical complex is blocked by CNQX; and (iii) trigeminovascular-evoked responses in the cat trigeminal cervical complex is dose-dependently inhibited by the AMPA receptor antagonist, GYKI52466 (Storer & Goadsby, 1999). Since the AMPA/kainate receptor antagonist, tezampanel, blocked the dural plasma protein extravasation after electrical stimulation of the trigeminal ganglion, while the specific AMPA receptor antagonist, LY300168, had no effect (Johnson et al., 2001), it has been suggested that the effect of tezampanel might be mediated via the kainate receptor rather than the AMPA receptor (Johnson et al., 2001).

The clinically active kainate receptor antagonist, LY466195, inhibits c-fos expression in the trigeminal cervical complex induced by trigeminal ganglion stimulation (Weiss et al., 2006). Moreover, the kainate receptor antagonist UBP302 blocked the cell firing induced by electrical stimulation of dural structures in the ventroposteromedial (VPM) nucleus and post-synaptic firing in response to kainate receptor activation (Andreou et al., 2009). It is noteworthy that the VPM nucleus may be involved in the transmission of painful sensory information to the cortex when the trigeminovascular system is active (Andreou & Goadsby, 2009a); hence, the pharmacological effect of LY466195 in the treatment of migraine might be partly explained by blocking the glutamatergic neurotransmission through kainate receptors in the VPM nucleus (Andreou & Goadsby, 2009a).

2.3.2. Vascular effects

Although glutamate plays an important role in the mediation of excitatory synaptic transmission, it may also induce vascular effects since activation of ionotropic glutamate receptors on neurons may lead to the release of vasoactive substances and production of NO, which is mediated by calcium influx, and therefore activation of intracellular signaling pathways (Bhardwaj et al., 1997). A direct effect on vascular tone may be less likely, since it has been demonstrated that increased glutamate levels did not affect vascular tone in pial arteries of rats, cats and humans (Hardebo et al., 1989).

As described in the previous section, it is suggested that treatment with ionotropic glutamate receptor antagonists would be active at central sites involved in the pathophysiology of migraine, without affecting vascular mechanisms. However, the finding that the NMDA receptor antagonist, MK-801, reduced capsaicin-evoked CGRP release (Garry et al., 2000) points to potential indirect vascular effects of glutamate receptor antagonists. This is supported by the finding that the NMDA receptor antagonists ketamine and MK-801 are capable of

inhibiting neurovascular CGRP release (Chan, Gupta, et al., 2010). Moreover, activation of neuronal NMDA receptors results in the release of NO, which causes vasodilatation (Busija et al., 2007). However, the AMPA receptor antagonist, GYKI52466, did not affect CGRP release nor the vasodilatation induced by endogenous CGRP (Chan, Gupta, et al., 2010); these findings are in accordance with the finding that AMPA receptors are absent in the peripheral trigeminovascular system (Sahara et al., 1997).

The kainate receptor antagonist, LY466195, does not induce vasoconstriction per se, nor does it affect the vasoconstriction to sumatriptan in the rabbit saphenous vein (Weiss et al., 2006). Moreover, LY446195 and the kainate receptor agonist UBP302 did not affect the vasodilatation of dural blood vessels induced by electrical stimulation or exogenous CGRP in a neurogenic dural vasodilatation model (Andreou et al., 2009; Chan, Gupta, et al., 2010). In contrast with LY446195 and UBP302, the antiepileptic drug topiramate, which is effective in migraine prophylaxis, probably at least partly through blockade of kainate receptors, attenuated the vasodilatation induced by electrical stimulation and infusion of an NO donor, but not the CGRP-induced vasodilatation in the same model (Silberstein et al., 2004). The fact that activation of kainate receptors effectively blocked neurogenic dural vasodilatation suggests that kainate receptor antagonists may be capable of indirectly preventing the vasodilatation induced by activation of the kainate receptor during a migraine attack. Although the vascular effects of kainate receptor antagonists are not known based on their agonist effects, it is suggested that kainate receptor antagonists might indirectly affect vascular tone.

2.3.3. Clinical effects

In patients taking the NO donor GTN for reducing the risk of cardiac ischemia, infusion of ketamine, an NMDA receptor antagonist, was proposed to be effective against NO-induced headache (Roffey et al., 2001). Moreover, in a small open-label study, intranasal ketamine reduced the severity and duration of the neurological deficits due to the aura in 5 out of 11 patients with familial hemiplegic migraine (Kaube et al., 2000).

Several kainate receptor antagonists are effective in the acute treatment of migraine, including the mixed AMPA/kainate receptor antagonist tezampanel (Sang et al., 2004) and the kainate receptor antagonist LY466195 (Johnson et al., 2008). Tezampanel is well tolerated and showed no vasoconstrictor liability in clinical trials (Murphy et al., 2008). However, due to the mixed AMPA and kainate receptor action of tezampanel, it is not clear which receptor is responsible for its antimigraine effect (Murphy et al., 2008). Tezampanel has been FDA approved to enter phase 3 for acute migraine treatment, its oral prodrug NGX426 is awaiting outlicencing for the migraine and pain program (http://www.raptorpharma.com). Although LY466195 is effective in the treatment of migraine, its therapeutic potential may be limited because of mild reversible visual distortions (Johnson et al., 2008).

In the wake of successful proof of concept of glutamate receptor antagonists for migraine treatment, other compounds are in clinical development. The AMPA receptor antagonist, BGG492 from Novartis, is currently under investigation, but no results have been reported so far.

2.3.4. Discussion

The finding that the NMDA receptor antagonist MK-801 reduced capsaicin-evoked CGRP release (Garry et al., 2000) points to potential indirect vascular effects of glutamate receptor antagonists. This is supported by the fact that ketamine and MK-801 are capable of inhibiting neurovascular CGRP release (Chan, Gupta, et al., 2010). Moreover, activation of neuronal NMDA receptors results in NO release, which causes vasodilatation (Busija et al., 2007). This property may represent a therapeutic mechanism of action of glutamate receptor antagonists in the treatment of migraine, but might also result in cardiovascular side-effects (Chan, Gupta, et al., 2010). However, before conclusions may be drawn about the relevance of such effects, more clinical data on the use of NMDA receptor antagonists should be available. Moreover, obviously, it has to be kept in mind that ionotropic glutamate receptors are involved in several mechanisms in the brain and spinal cord; thus, blockade of these receptors may induce neurological side-effects. Based on the study of glutamate receptor antagonists in stroke, it is known that antagonism of the NMDA receptor causes adverse psychotomimetic effects, including hallucinations, agitation, peripheral sensory disturbance, catatonia, nausea and vomiting. Moreover, except for neurological symptoms, NMDA receptor antagonists also induce effects associated with stimulation of the sympathetic nervous system, like hypertension (Muir, 2006). In addition, glutamate has recently been described to uncouple blood flow and glucose metabolism; however, this is not mediated via the ionotropic glutamate receptor (Hirose et al., 2009).

In contrast to NMDA receptor antagonists, as described previously, AMPA receptor antagonists do not affect CGRP release and vascular tone (Sahara et al., 1997; Chan, Gupta, et al., 2010), although they block responses in the trigeminocervical complex (Storer & Goadsby, 1999). This suggests that AMPA receptor antagonists might display antimigraine efficacy, which would most likely be unrelated to a vascular mode of action. However, blockade of the AMPA receptor might have toxic effects on glial cells, at least in patients with brain ischemia (Elting et al., 2002). These observations warrant further research on the potential central side-effects of these ligands.

Finally, the kainate receptor antagonist LY466195, which is effective in the treatment of migraine (Johnson et al., 2008), seems to be devoid of vascular effects (Weiss et al., 2006; Chan, Gupta, et al., 2010). Given its effects on the trigeminocervical complex and the VPM nucleus, it seems that the antimigraine efficacy of LY466195 could involve a purely central effect, unrelated to vascular CGRPergic pathways and/or its receptors. However, kainate receptor antagonists have been described to induce anxiolytic-like effects in an animal model, and thus further human studies are needed to predict their safety in humans.

2.4. VPAC/PAC receptor antagonists

The parasympathetic nervous system has long been implicated in the pathophysiology of migraine and, indeed, the parasympathetic outflow to the cephalic vasculature may trigger the activation and sensitization of perivascular sensory afferents and thereby migraine pain (Yarnitsky et al., 2003). Pituitary adenylate cyclase activating polypeptides (PACAPs) and vasoactive intestinal peptide (VIP), which are released by the parasympathetic efferent nerves to regulate cerebrovascular tone and haemodynamics of the brain (Gulbenkian et al., 2001), have been suggested to play a role in the pathophysiology of migraine. In fact, these peptides also activate or sensitize intracranial sensory nerve fibers leading to the perception of pain (Uddman et al., 1993; Edvinsson & Goadsby, 1998; Schytz et al., 2009). PACAPs and VIP are structurally closely related peptides and belong to the secretin/glucagons/VIP peptide family. They are widely distributed in the central and peripheral nervous systems and are associated with various physiological functions (Dickson & Finlayson, 2009). The action of PACAP is mediated via the $VPAC_1$, $VPAC_2$ and PAC_1 receptors, while VIP induces its effects only via the $VPAC_1$ and $VPAC_2$ receptors. These three receptors are G_s-protein coupled receptors and activate adenylate cyclase to induce their effects (Dickson & Finlayson, 2009; Vaudry et al., 2009). Elevated VIP levels have been reported in the plasma of the cranial circulation in a subgroup of migraine patients with pronounced autonomic symptoms (Goadsby et al., 1990).

2.4.1. Central effects

VIP and PACAP are widely distributed throughout the brain and periphery (Dickson & Finlayson, 2009). In relation with migraine,

immunostainings reported the presence of PACAP and VIP in different regions of the brainstem nuclei (Tajti et al., 2001) as well as in perivascular nerves (Uddman et al., 1993). However, only PACAP was detected in the trigeminal cervical complex and in the C1 and C2 levels (Uddman et al., 2002). Moreover, mRNA expression of VPAC and PAC receptors is found in the trigeminal, otic and superior cervical ganglia (Knutsson & Edvinsson, 2002).

Migraine-like headache induced by PACAP38 has been suggested to be caused by activation of peripheral sensory trigeminal fibers mediated via direct sensitization (Schytz et al., 2009). Moreover, mast cell degranulation caused neuronal activation of C-fibers innervating the dura (Levy et al., 2007); significantly, mast cells surrounding cerebral and dural blood vessels are in close proximity to parasympathetic and sensory nerve fibers (Edvinsson et al., 1976; Ottosson & Edvinsson, 1997; Rozniecki et al., 1999). Hence, it has been suggested that PACAP38 may activate peripheral sensory trigeminal fibers via mast cell degranulation. In addition, a facilitatory effect of PACAP38 on second order trigeminal neurons has been suggested as a possible mechanism for the migraine-like headache induced by PACAP38 (Schytz et al., 2009). In agreement with these findings: (i) the PAC receptor antagonist, PACAP6-38, attenuates nociception in animal models of chronic inflammatory as well as persistent pain (Ohsawa et al., 2002; Davis-Taber et al., 2008); and (ii) inflammatory pain disappears in PACAP gene knockout mice (Mabuchi et al., 2004).

2.4.2. Vascular effects

In vitro and in vivo studies have demonstrated that VIP and PACAP act as potent vasodilators on cranial blood vessels in various species, including humans (Dickson & Finlayson, 2009; Vaudry et al., 2009). VPAC/PAC receptor agonists induced vasorelaxation with different efficacy and potency in the human cranial and coronary arteries (Saetrum Opgaard et al., 2000; Jansen-Olesen et al., 2004; Chan et al., in press). Different vasodilator responses to PACAP and VIP between several blood vessels were described in: (i) the rabbit posterior cerebral artery and coronary artery (Dalsgaard et al., 2003); (ii) the rat basilar artery and middle cerebral artery (Baun et al., 2009); (iii) the guinea pig aorta and pulmonary artery (Cardell et al., 1991); and (iv) the human proximal and distal coronary arteries (Saetrum Opgaard et al., 2000; Chan et al., in press).

It can be suggested that vasodilatation induced by PACAP and VIP vary not only in different species, but also in the region of the arteries from the same species. Possible explanations for these differences in the vascular responses are selective activation of the three types of the VPAC/PAC receptors on different tissues, tissue-dependent factors such as the levels of receptor protein expression and coupling efficiency of the receptors (Dickson & Finlayson, 2009). Moreover, several splice variants of the receptors, which are to a certain extent tissue specific, have been described to affect cellular function by altering receptor pharmacology and signaling (Dickson & Finlayson, 2009).

VIP is more potent to induce vasodilatation than PACAP38 in human cranial and coronary arteries (Jansen-Olesen et al., 2004, 1996; Chan et al., in press). In accordance with these findings in human arteries, a lower vasodilator potency of PACAP was also found in the rabbit posterior cerebral artery (Dalsgaard et al., 2003) and the rat basilar artery (Baun et al., 2009), but this difference was not seen in the rat middle meningeal artery (Baun et al., 2009). Taken together, since several lines of evidence indicate a lower vasodilator potency of PACAP38 compared to that of VIP, it seems that PAC_1 receptors, which are activated by PACAP38, but not by VIP, are of minor importance in mediating vasodilatation.

It is suggested that the PACAP- and VIP-induced vasodilatation of the temporal artery seen in healthy volunteers and migraine patients (Hansen et al., 2006; Rahmann et al., 2008; Schytz et al., 2009) is probably mediated by perivascular nerve activation (Chan et al., in press), since: (i) these peptides are present in perivascular nerves (Uddman et al., 1993; 2002); and (ii) direct stimulation with these peptides in human isolated meningeal arteries induced only minor relaxations (Chan et al., in press). The PAC_1 receptor is most likely involved in this mechanism since only the PAC_1 receptor antagonist PACAP6-38, but not $VPAC_1$ receptor antagonists, blocked the vasodilatation induced by neurogenic dural stimulation (Akerman & Goadsby, 2009) as well as the neuronal firing in the trigeminal cervical complex after salivatory nucleus stimulation (Akerman & Goadsby, 2009).

2.4.3. Clinical effects

PACAP38 and VIP have been shown to (i) decrease mean blood flow velocity in the middle cerebral artery; and (ii) induce vasodilatation in the superficial temporal artery (Hansen et al., 2006; Rahmann et al., 2008; Schytz et al., 2009). Although VIP induces mild headache in healthy volunteers and migraine patients, it does not induce a migraine-like headache (Hansen et al., 2006; Birk et al., 2007; Rahmann et al., 2008). In contrast, PACAP38 induces migraine-like headaches in healthy volunteers and migraine patients (Schytz et al., 2009). Since PACAP38 displays a higher affinity for the PAC_1 receptor, activation of this receptor may result in migraine-like headaches. Accordingly, antagonism of the PAC_1 receptor may be a putative target for migraine treatment. However, to date, no selective PAC_1 receptor antagonists have been investigated in migraine.

2.4.4. Discussion

Since PACAP38, but not VIP, induces migraine-like headaches in migraine patients (Rahmann et al., 2008; Schytz et al., 2009), and only PACAPs interact with the PAC_1 receptor, it could be suggested that the PAC_1 receptor is involved in migraine pathophysiology. This mechanism is unlikely to be related to cranial vasodilatation, since PACAP induces only a limited cranial vasodilatation. In contrast, VIP, which does not induce migraine-like headaches, induced a more pronounced vasodilatation than PACAP in cranial arteries (Chan et al., in press). Therefore, the PAC_1 receptor may play a role in activating the central mechanisms involved in migraine, and antagonists for the PAC_1 receptor may be considered as potential antimigraine drugs with a limited vascular side-effect. However, since PACAP and VIP display a high degree of homology, antagonists for the PAC_1 receptor may also have affinity for the VPAC receptor, which could lead to an increased vascular tone via inhibition of vasodilator responses. Further, we cannot categorically exclude the possibility that PAC_1 receptor inhibition will affect cerebrovascular tone and haemodynamics of the brain. Obviously, clinical data are needed to confirm or exclude the therapeutic potential of this target.

2.5. NO synthase inhibitors

NO is a signaling molecule that is present in most tissues throughout the body. The formation of NO from L-arginine is catalyzed by three different enzyme isoforms of NO synthase (NOS) and involves several cofactors. Endothelial NOS (eNOS; which is expressed in vascular endothelium) and the neuronal NOS (nNOS; which is found in both central and peripheral neurons) are activated by an increase in intracellular calcium, whereas inducible NOS (iNOS; which is normally not detectable), can be activated in many cells by a variety of stimuli unrelated to intracellular calcium (Bredt, 1999). Moreover, iNOS can produce 1000 times more NO than eNOS and nNOS (Olesen, 2008). One of the mechanisms in which NO is involved is the decrease in intracellular calcium by phosphorylation of ion channels mediated via activation of a cascade of second messengers and kinase (Olesen, 2008). This mechanism causes vasodilatation in smooth muscle cells, whereas in neurons it has a variety of functions such as involvement of nociceptive processes (Olesen, 2008). Since the NO donor GTN triggered headache, and migraine patients are more sensitive to this trigger, the role of NO in migraine has extensively been investigated

(Olesen, 2008). Although dilatation of cranial blood vessels induced by NO was considered as the cause of migraine headache, primarily neuronal effects have also been forwarded as a potential mechanism (Goadsby, 2006).

2.5.1. Central effects

NO is suggested to be a key molecule in the cascade of nociceptive processes in the CNS that lead to migraine pain and other vascular headaches. Sensitization of the spinal cord may be associated with the generation of NO (Wu et al., 2000), which is primarily caused by nNOS activation since nNOS inhibition reduces central sensitization (Coderre & Yashpal, 1994). However, eNOS may also play a role as suggested in nNOS deficient mice (Wu et al., 2001; Tao et al., 2004). Certainly, pain responses are increased by NO donors in neuropathic and inflammatory pain models (Coderre & Yashpal, 1994; Mao et al., 1997). In addition, responses to facial and dural stimulation in rats (Jones et al., 2001), as well as to noxious stimulation of the first synapse in the trigeminal spinal nucleus (Lambert et al., 2004), are potentiated by NO. GTN infusion leads to fos protein expression in the trigeminocervical complex, which indicates that NO donors can activate the trigeminal system (Tassorelli & Joseph, 1995a). Moreover, neurons within the trigeminocervical complex that express NOS are activated by GTN (Tassorelli & Joseph, 1995b). The systemic administration of GTN increases the levels of NOS-immunoreactive neurons in the rat dura mater with a delay of hours (Reuter et al., 2001). This is in line with the biphasic response in trigeminal neurons induced by NO (Olesen, 2008), which is parallel to the biphasic headache response reported in migraine patients after exposure to GTN, as will be discussed below (Koulchitsky et al., 2004).

Inhibition of NOS decreased the activity of neurons with meningeal input in the rat spinal trigeminal nucleus (De Col et al., 2003). The non-selective NOS inhibitor, Nω-nitro-l-arginine methyl ester (L-NAME) inhibits c-fos expression in the trigeminocervical complex after stimulation of the superior sagittal sinus in the cat (Hoskin et al., 1999), while the iNOS inhibitor GW274150 has an analgesic effect in rat models (De Alba et al., 2006).

2.5.2. Vascular effects

Since NO is a potent endogenous vasodilator, NO may induce migraine by inducing cranial vasodilatation (Olesen, 2008). In animal models, i.v. administration of NO donors causes meningeal vasodilatation (Akerman et al., 2002). Further, the NOS inhibitor L-NAME reduces resting dural arterial blood flow as well as electrically-evoked dural increases in flow (Messlinger et al., 2000). Interestingly, L-NAME inhibited dural vasodilatation induced by endogenous and exogenous CGRP, while nNOS inhibitors, but not inhibitors of eNOS, blocked only the dural vasodilatation induced by endogenous CGRP (Akerman et al., 2002). This suggests an indirect action of NO produced by nNOS (Akerman et al., 2002), which seems to be in line with the fact that NO has been described to activate sensory nerve fibers to release CGRP (Wei et al., 1992). Alternatively, both NO and CGRP may display direct vascular effects and can be released with trigeminal activation. Indeed, the presence of nNOS in neurons in the trigeminal ganglion as well as those colocalized with CGRP has been demonstrated (Edvinsson et al., 1998). Moreover, eNOS might be responsible for vasodilatation induced by *exogenous* CGRP since this was partially blocked by L-NAME and eNOS inhibitors in rat dural arteries (Akerman et al., 2002). In contrast, in human blood vessels, the dilation to CGRP seems to be mediated mainly via an increase in cAMP levels in smooth muscle cells, without involvement of the endothelium (Jansen-Olesen et al., 2003; Gupta et al., 2006b; Chan, Edvinsson, et al., 2010). Nevertheless, CGRP-induced vasodilatation in the human forearm, was shown at least in part, to be mediated by NO (De Hoon et al., 2003). Since NO synthesized by eNOS is known to have a variety of antiatherosclerotic actions, it was suggested that inhibition of eNOS activity might result in an increased risk for myocardial infarction (Tsutsui, 2004). However, the absence of eNOS in transgenic mice did not cause spontaneous myocardial infarction, which was possibly the results of compensatory mechanism by other NOS isoforms, since nNOS was upregulated in eNOS deficient mice (Lamping et al., 2000; Huang et al., 2002; Tsutsui, 2004). Since disruption of all the three NOS isoforms causes myocardial infarction (Nakata et al., 2008), the design of NOS inhibitors as a treatment target for migraine has to be selective.

2.5.3. Clinical effects

NO causes an immediate headache in migraine sufferers and less often in control subjects (Olesen, 2008). GTN dilates cerebral and extracerebral arteries in humans (Dahl et al., 1990; Schoonman et al., 2008); these pronounced vascular effects might suggest that this vasodilatation is the trigger to mediate NO-induced migraine. However, several arguments have been forwarded against such a vascular mechanism, namely: (i) in a 3 T magnetic resonance angiography study, migraine induced by GTN was not associated with cerebral and meningeal vasodilatation (Schoonman et al., 2008), and (ii) the phophosdiesterase inhibitor sildenafil, which inhibits the breakdown of cGMP (the second messenger of NO), did induce a migraine-like headache in migraine patients, while in that study cerebral arteries were not dilated, and cerebral blood flow was not increased (Kruuse et al., 2003). Although these observations are important and interesting, it should be kept in mind that: (i) Schoonman et al. (2008) could only study the large, extracranial parts of the middle meningeal artery due to methodological limitations (for details, see MaassenVanDenBrink et al., 2009); and (ii) although Kruuse et al. (2003) did not observe dilatation of cerebral arteries, sildenafil has been demonstrated by others to affect the cerebrovascular reactivity (see, for example, Diomedi et al., 2005).

It is interesting that migraineurs experience a delayed headache several hours after a NO donor infusion, which might be partly mediated by the increase nNOS activity in the trigeminal system that induces CGRP release and dural vasodilatation, since nNOS inhibitors inhibit the vasodilatation induced by perivascular electrical stimulation. Moreover, it has been shown that the premonitory symptoms reported in spontaneous migraine (Giffin et al., 2003) are also seen in GTN-induced migraine (Afridi et al., 2004) and these symptoms occur well after any vascular change would have occurred (De Hoon et al., 2003). Although, NO does not contribute to a basal tone in human cerebral arteries, it has a mild dilator tone in cerebral arterioles (Lassen et al., 2005). Moreover, inhibition of NOS with L-NAME produced an increase in systemic blood flow without changes in the velocity of blood in middle cerebral artery or on the diameter of the radial artery (Hjorth Lassen et al., 2003). However, L-NAME has been shown to increase blood pressure and decrease heart rate (Hjorth Lassen et al., 2003; Lassen et al., 2005).

Since Lassen et al. (1997) first described the efficacy of the non-selective NOS inhibitor L-NMMA in the treatment of migraine, clinical research on the role of NO in migraine was accelerated, as reviewed by Olesen (2008). Although L-NMMA showed encouraging results, its clinical potential is rather limited in view of its pharmacokinetic profile and its vasoconstrictor properties (Lassen et al., 2005). As L-NMMA inhibits nNOS, iNOS and, most importantly, also eNOS, NOS inhibitors should be selective when used as antimigraine drugs. Since the role of eNOS in migraine is debatable (Borroni et al., 2006; Toriello et al., 2008) and, most significantly, blocking eNOS could disturb systemic blood pressure and heart rate (Moncada & Higgs, 1995), selective eNOS inhibitors do not seem a logical pharmacological target for prospective antimigraine drugs. Two selective iNOS inhibitors, GW274150 and GW273629, were developed for inflammatory conditions (Cuzzocrea et al., 2002; Chatterjee et al., 2003; Dugo et al., 2004; Alderton et al., 2005). In preclinical studies, GW274150 seemed to reduce organ injury in hemorrhagic shock (McDonald et al., 2002) and reduced experimental renal ischemia/reperfusion injury (Chatterjee et al., 2003), which increased the hope for a beneficial vascular profile of iNOS inhibitors. Although GW274150 seemed to display analgesic effects in rat models

of inflammatory and neuropathic pain (De Alba et al., 2006), clinical studies could not establish its efficacy in acute migraine treatment (Van der Schueren et al., 2009). This lack of efficacy might be assigned to the unfavorable pharmacokinetic profile of GW273629 (Van der Schueren et al., 2009). However, other randomized controlled trials with GW274150, another potent and selective iNOS inhibitor with a more favorable pharmacokinetic profile than GW273629, also failed in the prevention (Hoye et al., 2009) and acute treatment (Palmer et al., 2009) of migraine. This suggests that iNOS is not a promising target for migraine treatment (Goadsby, 2010). Only one selective nNOS inhibitor is currently in clinical development, namely NXN-188 (Vaughan et al., 2010). However, this molecule also shows affinity for 5-$HT_{1B/1D}$ receptors and, therefore, its clinical effects cannot exclusively be attributed to nNOS inhibition. At the moment, NXN-188 appears to be well tolerated in healthy volunteers and exhibits linear pharmacokinetics over the dose range studied in five phase I, randomized, double-blind parallel studies with single and multiple doses (Vaughan et al., 2010). Further clinical investigation will be performed to overview the pharmacodynamic profile of NXN-188, to assess its efficacy in acute migraine treatment and to obtain more data about its vascular mechanism of action.

2.5.4. Discussion

In view of the pharmacological lines of evidence described previously, it seems clear that NO is involved in the pathophysiology of migraine, probably via both vascular and neuronal mechanisms. Although NOS inhibitors may represent an interesting therapeutic option in migraine, the use of non-selective NOS inhibitors or selective eNOS inhibitors seems impeded by their cardiovascular side-effects such as increased blood pressure and decreased heart rate. While the results of clinical trials with iNOS inhibitors in migraine were disappointing, the results of trials investigating the effects of nNOS inhibition are awaited with great interest. In addition to the NOS inhibitors, other pharmacological targets that inhibit the formation of NO should be explored, as for example tetrahydrobiopterin, which is the most important cofactor in the conversion of L-arginine to NO and L-citrulline (Olesen, 2010). The role of NOS inhibition in the regulation of gap junction coupling is also under investigation (Kameritsch et al., 2003; Lee & Cheng, 2008), based on the facts that NO: (i) enhances the de novo formation of endothelial gap junctions by increasing the incorporation of Cx40 into the plasma membrane due to protein kinase A activation (Hoffmann et al., 2003); (ii) regulates coupling in cells expressing Cx35, a connexin expressed in neurons throughout the CNS (Patel et al., 2006); (iii) is involved in the control of gap junction intercellular communication and Cx43 expression (Yao et al., 2005); and (iv) inhibits the intercellular transfer of small molecules by a specific influence on Cx37 (Kameritsch et al., 2005). Taken together, these studies suggest interesting parallels between the NOS system and gap junction modulation (to be discussed in the later part) in antimigraine drug development.

2.6. Gap junction modulators

As discussed previously, the pathophysiology of migraine is not yet fully understood. However, CSD is thought to provide the basis for migraine aura, and may serve as a trigger for migraine pain (Hadjikhani et al., 2001; Goadsby, 2007c). Prophylactic drugs, such as topiramate and valproate, suppress CSD in a dose dependent manner (Ayata et al., 2006). Further, the neuronal changes in CSD have been demonstrated to be preceded by vasomotor changes in the cortex (Brennan et al., 2007), raising the question whether CSD should be considered as a primary neuronal or primary vascular event (Goadsby, 2007b). Both CGRP and NO are likely to be involved in the vasodilatation induced after CSD (Wahl et al., 1994).

2.6.1. Central effects

Tonabersat (SB-220453) is a benzopyran compound, which has been demonstrated to inhibit CSD in animal models (Smith et al., 2000), CSD-induced release of NO (Read et al., 2000), as well as trigeminal nerve ganglion stimulation-induced carotid vasodilatation (Parsons et al., 2001) and plasma protein extravasation (Chan et al., 1999). While it was not originally known which mechanism mediated these effects of tonabersat, it was later demonstrated that this drug may act, at least partly, via inhibition of increased neuron satellite glia signaling via gap junctions (Damodaram et al., 2009). In general, gap junctions: (i) are formed between the cell membranes of two adjacent cells and serve as intercellular conduits that allow for direct transfer of small molecular weight molecules, such as ions, that regulate cellular excitability, metabolic precursors, and second messengers; (ii) consist of two hemichannels (each from one cell), each consisting of a hexamer of connexins, arranged around a central pore; (iii) are found in most neurons and glial cells and function to facilitate neuron–neuron, glia–glia, and neuron–glia communication; and (iv) are abundant in the CNS and allow for extensive intercellular coupling between cells that form a communication network.

2.6.2. Vascular effects

Besides the neuronal functions mentioned previously, gap junctions have also been postulated to be responsible for the endothelium-derived hyperpolarizing factor (EDHF) phenomenon (Félétou & Vanhoutte, 2009; De Wit & Griffith, 2010). The gap junctions may allow passive spread of agonist-induced endothelial hyperpolarization through the blood vessel wall via direct intercellular communication. Although we have previously demonstrated that tonabersat does not display direct vascular effects (MaassenVanDenBrink et al., 2000) and that the compound produced no cardiovascular effects in experimental animals (see Silberstein, 2009), it is not clear whether tonabersat affects endothelium-dependent relaxations. As mentioned in the later part, only few cardiovascular adverse events have been reported in clinical trials with tonabersat, while a causal relationship with administration of the drug was not always evident. In view of the knowledge now available about the supposed mechanism of action of tonabersat, it would, however, be prudent to perform experimental studies specifically devoted to the potential effects of tonabersat on endothelium-dependent relaxation. In this context, it is interesting to mention that the role of EDHF is dependent on estrogen plasma levels (Chataigneau & Schini-Kerth, 2005; Nawate et al., 2005), while this dependency seems to differ between cranial and peripheral blood vessels (Golding & Kepler, 2001; Xu et al., 2001; Nawate et al., 2005). These facts, together with the higher prevalence of migraine in women, also seem to be related to changes in estrogen levels. Thus, it seems feasible that tonabersat would display a hormone-dependent effect in migraine. Obviously, it would first have to be determined whether such indirect vascular effects of tonabersat, mediated via EDHF, have any clinical relevance.

2.6.3. Clinical effects

Currently, only one compound specifically targeting CSD, tonabersat (SB-220453), was clinically tested. In a phase II proof-of-concept study, tonabersat failed to meet the primary endpoints (Goadsby et al., 2009), i.e. reduction in migraine days between tonabersat and placebo. The reduction in mean monthly headache days after 3 months, 4.4 days in the tonabersat group and 3.7 days in the placebo group was not significantly different. However, secondary endpoints were more positive: responder rate, defined as a 50% reduction in migraine attacks, was 62% for tonabersat and 45% for placebo, and rescue medication was reduced by 1.8 days in the tonabersat group compared with placebo. As tonabersat was also well tolerated, further clinical research was initiated. Indeed, a randomized double-blind, placebo-controlled crossover study showed promising effects of tonabersat in aura prophylaxis (Hauge et al., 2009). In this clinical trial, patients with at least one attack of migraine aura per

month were included. The number of attacks of aura significantly decreased from 3.2 during placebo treatment to 1.0 during tonabersat treatment. The number of migraine headache days, however, did not significantly differ between placebo and tonabersat treatment. Thus, tonabersat was effective in preventing the attacks of migraine aura, but had no effect on non-aura attacks. These results are in line with the hypothesis that auras are caused by CSD and that this phenomenon is not involved in the attacks without aura.

Besides the use of tonabersat in a prophylactic setting, several trials were also conducted to test its efficacy in the acute treatment of migraine (Dahlöf et al., 2009; Silberstein, 2009). Unfortunately, tonabersat was not superior to placebo. However, these trials were conducted in a heterogeneous group of migraine patients (with and without aura), limiting the power of the study. Overall, tonabersat seems to be well tolerated with no indications of serious cardiovascular side-effects. The most common adverse events after treatment with tonabersat were dizziness and nausea (Silberstein et al., 2009).

The fact that tonabersat seems to act specifically on CSD and aura could explain why this drug was not effective in the GTN-induced migraine headache model (Tvedskov et al., 2004). As this model only induces migraine-like headache without aura (Christiansen et al., 1999), and tonabersat is only effective in migraine with aura (Hauge et al., 2009), negative results could have been expected a priori with the current knowledge. The apparent synergism between GTN and tonabersat resulted in a serious hypotension in two subjects.

We conclude that suppression of CSD seems to be most useful in a prophylactic setting to increase the aura threshold. In view of the safety results obtained so far, it is tempting to speculate that this new class of antimigraine drugs will show a beneficial cardiovascular profile. However, the potential for cerebral hypotension (Tvedskov et al., 2004) should be kept in mind. Moreover, gap junctions not only have functions in the brain (Nagy et al., 2004), but also play an important role in the electrical coupling of cardiomyocytes and, as such, are determinants of the speed and direction of cardiac conduction (Kleber & Rudy, 2004; Hesketh et al., 2009; Jansen et al., 2010; Boulaksil et al., 2010). The consequences of tonabersat's effects on glial cell communication via gap junction inhibition (e.g. connexin26; Damodaram et al., 2009) could also negatively affect connexins in the myocardium. Indeed, connexin alterations may cause arrhythmias in heart disease (Kleber & Rudy, 2004; Severs et al., 2004; Hesketh et al., 2009; Jansen et al., 2010; Boulaksil et al., 2010). Furthermore, gap junction communication is a key player in the mechanisms leading to ischemic preconditioning-induced tolerance against infarction and arrhythmias during ischemia-reperfusion of the heart (Miura et al., 2010). However, not all connexins are distributed in all tissues (Severs et al., 2008; Hesketh et al., 2009); hence, connexin-specific drugs may solve this issue in the future.

In short, there is at least a rationale for the hypothesis that connexins form the link between migraine with aura and the increased cardiovascular risk, since: (i) the gap junction modulator tonabersat inhibits aura; (ii) gap junctions and connexin alterations play an important role in cardiac disease; and (iii) migraine with aura is associated with an increased risk for cardiovascular disease (Bigal et al., 2009; Schurks et al., 2009). This is translated into the hypothesis that inhibition of the neuronal gap junction system for migraine aura treatment could possibly be undesirable with respect to cardiovascular safety, although no excessive cardiovascular side-effects have been reported so far.

2.6.4. Discussion

It remains to be established whether migraine with and without aura are driven by different pathophysiological mechanisms. As inhibition of CSD, which is only observed in migraine with aura (Lauritzen et al., 1983; Olesen et al., 1990; Hadjikhani et al., 2001), does not prevent the non-aura headache, it seems that aura is a symptom in parallel with the non-aura headache. In conclusion, the therapeutic potential of tonabersat may be limited as it only prevents the aura, but not the non-aura headache (Dodick, 2009). These findings seem to confirm some hypotheses about aura, but, as with all interesting science, more knowledge also means more questions.

3. Implications, future directions and conclusions

Many prospective antimigraine drugs with a putatively selective neuronal mechanism of action may display indirect vascular effects. In contrast to the currently available antimigraine drugs (ergots and triptans), the prospective antimigraine drugs do not directly induce vasoconstriction, but they may inhibit either vasodilatation induced by neuropeptides (e.g., CGRP receptor antagonists) or the release of such peptides (e.g., some glutamate receptor antagonists).

While the vasoconstrictor potential of the ergots does seem to involve a realistic risk (Tfelt-Hansen et al., 2000), similar concerns existed about the use of the triptans in view of case reports on coronary ischemia in relation to triptan use (e.g., Ottervanger et al., 1993). The triptans are in clinical use for about two decades, and it is now clear that the incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low, and thus the cardiovascular risk–benefit profile of triptans favors their use in the absence of contraindications (Dodick et al., 2004). Moreover, even in patients with cardiovascular risk factors (for whom these drugs are contraindicated) the use of triptans did not seem to increase the risk for ischemic cardiovascular complications (Wammes-van der Heijden et al., 2006). However, the fact that triptans have the propensity to constrict the coronary artery (MaassenVanDenBrink et al., 1998) warrants these drugs to remain contraindicated in patients with cardiovascular disease.

It remains to be elucidated whether the indirect vascular effects of the prospective antimigraine drugs discussed in this review contribute to the therapeutic efficacy of these compounds. Alternatively, the vascular effects could be relevant in view of the cardiovascular side-effect potential of the drugs. For some of the prospective antimigraine drugs, such as telcagepant, data obtained from clinical trials (Edvinsson & Linde, 2010) are already available; these data suggest that telcagepant is cardiovascularly safe, even in patients with increased cardiovascular risk, since this drug did not exacerbate spontaneous ischemia in a small cohort of patients with stable coronary artery disease (Behm et al., 2008). This confirms telcagepant's favorable cardiovascular side-effect profile when used as an acute antimigraine treatment. For some of the other prospective drugs no, or only few, clinical data are available; on theoretical grounds, we expect the cardiovascular side-effect profile to be mild as well. Thus, the probably improved cardiovascular safety profile of the new generation antimigraine drugs may be of clinical relevance for patients in which the triptans are contraindicated. However, it should be kept in mind that when the prospective drugs are used chronically as prophylactic (instead of acute) antimigraine drugs, the cardiovascular side-effect profile may be less favorable than expected for acute use. Obviously, further research is warranted before any definite statements can be made on this topic.

Finally, some drugs that are discussed in this review, such as kainate receptor antagonists, and possibly 5-HT_{1F} receptor antagonists, seem to be completely devoid of vascular effects. The demonstrated efficacy of these compounds confirms that a vascular action is not an essential feature for antimigraine efficacy. Whether a completely non-vascular mode of action will clinically be an advantage over compounds with mild (in)direct vascular effects is awaited with great interest.

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