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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