Migraine: Pathophysiology, Pharmacology, Treatment and Future Trends

Carlos M. Villalón*, David Centurión, Luis Felipe Valdivia, Peter de Vries and Pramod R. Saxena

Departamento de Farmacobiología, CINVESTAV-IPN, Czda. de los Tenorios 235, Col. Granjas Coapa, Deleg. Tlalpan, C.P. 14330, México D.F., México and *Department of Pharmacology, Erasmus University Medical Centre Rotterdam “EMCR”, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

Abstract: Migraine treatment has evolved into the scientific arena, but it seems still controversial whether migraine is primarily a vascular or a neurological dysfunction. Irrespective of this controversy, the levels of serotonin (5-hydroxytryptamine; 5-HT), a vasoconstrictor and a central neurotransmitter, seem to decrease during migraine (with associated carotid vasodilatation) whereas an i.v. infusion of 5-HT can abort migraine. In fact, 5-HT as well as ergotamine, dihydroergotamine and other antimigraine agents invariably produce vasoconstriction in the external carotid circulation. The last decade has witnessed the advent of sumatriptan and second generation triptans (e.g. zolmitriptan, rizatRIPTAN, naratriptan), which belong to a new class of drugs, the 5-HT(_1B/1D/1F_ receptors) and presynaptic inhibition of the trigeminovascular inflammatory responses implicated in migraine (via 5-HT(_1B_) receptors). Moreover, selective agonists at 5-HT(_1D_) (PNU-142633) and 5-HT(_1F_) (LY344864) receptors inhibit the trigeminovascular system without producing vasoconstriction. Nevertheless, PNU-142633 proved to be ineffective in the acute treatment of migraine, whilst LY344864 did show some efficacy when used in doses which interact with 5-HT(_1B_) receptors. Finally, although the triptans are effective antimigraine agents producing selective cranial vasoconstriction, efforts are being made to develop other effective antimigraine alternatives acting via the direct blockade of vasodilator mechanisms (e.g. antagonists at CGRP receptors, antagonists at 5-HT(_1F_) receptors, inhibitors of nitric oxide biosynthesis, etc). These alternatives will hopefully lead to fewer side effects.

INTRODUCTION

Migraine is a syndrome that affects a significant fraction of the world population, with a higher prevalence in women (15%) than in men (6%) [1]. Migraine is characterised by an intense and throbbing unilateral headache associated with anorexia, nausea, vomiting, photophobia, phonophobia and/or diarrhoea (common migraine). Sometimes the headache may be preceded by a focal neurological phenomenon (“aura”) followed by headache (classical migraine); this aura consists of certain motor (weakness or paralysis) and/or focal neurological (scintillating scotoma) symptoms.

HISTORY OF HEADACHE TREATMENT

A variety of methods have been used throughout the ages in an attempt to abort this pain; these may have been the most appropriate at that time, and were probably seen as “cutting edge”. Today they seem at best amusing, and at worst cruel and barbaric.

The earliest concepts in migraine were those of the supernatural, with migraine believed to be due to malevolent beings within the head; treatment based on this idea included incantations and application to the head of substances intended to drive out the demons and spirits [2]. The people living in the Neolithic period (8500-7000 BC) used the method of trepanation, which involved removing circular chunks of skull so that the spirits causing the headache could escape. Although the scientific rationale behind trepanation is not understood, it is surprising that this procedure was performed as a treatment for migraine as late as the mid 17th century [2,3].

The oldest known medical manuscript, the Ebers Papyrus (dating back to about 1200 BC and discovered in the necropolis of Thebes), contains an ancient Egyptian prescription for migraine based on earlier medical documents including an Egyptian papyrus of 2500 BC, as shown in Fig. (1). Believing the gods could cure their ailments, a clay effigy of a sacred crocodile with herbs stuffed into its mouth (dating back to about 1200 BC) was firmly bound to the head of the patient by a linen strip [3]. Admittedly, this process may have relieved the headache by collapsing distended vessels which were causing the pain.

Around 400 BC Hippocrates released migraine from the realms of the supernatural by attributing it to vapours rising from the stomach to the head and he described, for the first time, the visual symptoms (“aura”) of migraine [2,3]. Many years later, in the 2nd century (AD) Galen wrote of “a painful disorder affecting approximately one-half of the head” [4]. His term for this, “hemihinha”, was gradually transmuted into “migraine”. Galen, like Hippocrates, believed that this headache was caused by vapours rising from the stomach to
the head [4]. The hippocratic/galenic concept of migraine survived into the 17th century, when Thomas Willis published in 1664 his hypothesis that “megrim” was due to dilatation of blood vessels within the head (the first enunciation of a vascular theory) [2,3]. This theory was strengthened by the fact that migraine intensity was decreased by a compression of the superficial temporal artery. In the 19th century, however, the vascular origin of migraine was undermined by a conflicting theory that the prime event was a neurological dysfunction. Thus, in 1873, Edward Liveing proposed that migraine was due to “nerve storms evolved out of the optic thalamus” [2]. However, like the vascular theory, there was nothing but conjecture to support this neurogenic theory [2,3]. Towards the end of the 19th century attempts were made to reconcile both theories. Thus, Moebius stated in 1898 that “parenchyma is the master, circulation the servant”, and that both brain and blood vessels dysfunctions were necessary to produce an attack of migraine [2]. Almost simultaneously, ergot (the product of the fungus Claviceps purpurea that grows upon rye) was introduced in 1884 by W.H. Thomson as an effective remedy for migraine [5]; physicians, however, were aware of the intoxication risk when taken frequently (ergotism or St. Antony’s Fire), with descriptions dating back to the Middle Ages [6]. Ergotism is characterized by gangrene of the feet, legs, hands and arms due to a potent and long-lasting vasoconstriction. Thus, the introduction of ergot and the subsequent isolation of the first pure ergot alkaloid, ergotamine, by Stoll in 1920 [7] represent a remarkable accomplishment as the beginning of an effective therapy for the treatment of migraine.

THEORIES OF MIGRAINE IN THE EARLY 20\textsuperscript{TH} CENTURY

The antimigraine efficacy of ergotamine was established in the 20\textsuperscript{th} century, with the advantage over ergot that the occurrence of ergotism was less frequent [8]. However, due to the lack of any scientific studies there was still a controversy between the opposing vascular and neurogenic theories of migraine. Fortunately, Harold Wolff was the first researcher to place migraine on a scientific basis [9-11]. During a significant number of migraine attacks, pulsations in the temporal branches of the external carotid artery were demonstrated using an external tambour and pain could be relieved either by physical compression or by ergotamine [9]. These and other findings [10,11] seemed to establish the vascular theory of migraine beyond any doubt. Nevertheless, in 1983, the vascular theory apparently weakened when [12] demonstrated that blood flow changes similar to those known to occur in migraine could be produced by electrical stimulation of brainstem structures. This finding revived the neurogenic theory, stimulating studies which investigated the relationship between the trigeminal nerve and the cranial vasculature. Thus, in 1984, Moskowitz [13] showed that trigeminovascular axons from blood vessels of the pia mater and dura mater release vasoactive peptides producing a sterile inflammatory reaction with pain. During this neurogenic inflammation, the trigeminal ganglion is stimulated and this induces neurogenic protein extravasation; then some vasodilator peptides are released, including calcitonin gene-related peptide (CGRP), substance P and neurokinin A. In fact, some studies have demonstrated that antimigraine drugs like ergotamine can block neurogenic plasma extravasation in rat dura mater [14,15]. However, very recent lines of evidence (discussed below) have shown that drugs which exclusively block neurogenic plasma extravasation in rats (without producing vasoconstriction) do NOT have antimigraine action in humans [16,17].

VASCULAR OR NEUROGENIC THEORY?

Admittedly, there is no definitive evidence thus far to categorically exclude the vascular or the neurogenic theories of migraine in view that all acute antimigraine drugs invariably produce both cranial (carotid) vasoconstriction (shown in animals and humans) and inhibition of the trigemino-vascular system (centrally and/or peripherally; shown only in rats and guinea-pigs) [18,19]. It is likely that new tools for the investigation of migraine will resolve this conceptual stalemate and allow a unified theory of migraine to evolve. For convenience, the present review will consider the pathophysiology and therapeutics of migraine on the basis of a neurovascular hypothesis.

MIGRAINE PATHOPHYSIOLOGY

Based on the clinical features of migraine, three distinct phases can be discerned: an initiating trigger, an aura and, finally, the headache. Although limited information is available about the trigger phase, there is indeed now a better understanding of the pathophysiology of migraine [20,21]. Some results indicate that the initiating trigger, involving the brainstem as ‘migraine generator’ [22], may be linked to a ‘familial’ channelopathy [23,21]. The subsequent events leading to the symptoms observed during the aura and headache phases can be explained on the basis of a neurovascular hypothesis [24,25,21]. Thus, as illustrated in Fig. (2), once the “migraine generator” has been switched on,
Fig. (2). Diagram showing putative changes in migraine and the therapeutic targets of acutely acting antimigraine drugs. These drugs are believed to owe their antimigraine efficacy to direct vasoconstriction of dilated cranial blood vessels (1), inhibition of trigeminally-induced cranial vasodilatation (2), plasma protein extravasation (3) and/or central neuronal activity (4). Only lipophilic, brain penetrant triptans (not sumatriptan) exert central trigeminal inhibitory effects. For details see text. Modified from [18] 1999a Eur.J.Pharmacol. 375: 61-74. TNC, trigeminal nucleus caudalis.

Regional cerebral blood flow decreases, possibly following a wave of cortical spreading depression [26]. In patients where cerebral blood flow falls below a critical value, the corresponding aura symptoms may appear. The reduced cerebral blood flow is then followed by a vasodilatation during headache, probably due to changes in the activity of the neurones innervating cranial arteries (e.g. in the dura mater, base of the skull and scalp). Besides noradrenaline and acetylcholine, immunohistochemical studies have demonstrated the presence of several vasodilator transmitters in perivascular nerves supplying intracranial blood vessels, including 5-HT, vasoactive intestinal peptide (VIP), nitric oxide (NO), substance P, neurokinin A and CGRP [27]. As discussed elsewhere [28], NO may also be involved in migraine pathophysiology and inhibition of its synthesis seems to be of therapeutic relevance [29]. In any case, cranial vasodilatation leads to enhanced blood volume following each cardiac stroke, with a consequent augmentation in pulsations within the affected blood vessels, as shown in Fig. (2). The augmented pulsations can then be sensed by "stretch" receptors in the vessel wall and the resultant increase in perivascular (trigeminal) sensory nerve activity provokes headache and other symptoms. This trigeminal stimulation may also release neuropeptides, thus reinforcing vasodilatation and perivascular nerve activity [for details and references, see 25]. As illustrated in Fig. (2), within the framework of the neurovascular hypothesis of migraine, acutely acting antimigraine drugs (e.g. ergotamine) would constrict dilated cranial extracerebral blood vessels [30,31,24], reduce neuropeptide release and plasma protein extravasation across dural vessels [15,32] and inhibit impulse transmission centrally within the trigeminovascular system [33,20].
TREATMENT OF MIGRAINE

The drugs used in the treatment of migraine can be divided into two groups: agents that abolish the acute migraine headache (acute antimigraine drugs; e.g. ergotamine; sumatriptan) and agents aimed at its prevention (prophylactic drugs; e.g. methysergide) [8,34,35]. Both groups include specific drugs and non-specific drugs, but the present review will be exclusively focussed on the development of acute antimigraine drugs.

Acute Antimigraine Drugs

Non-specific Drugs

These drugs are used to treat the symptoms accompanying the headache, such as antiemetics (metoclopramide), non-steroidal anti-inflammatory drugs (NSAID’s; e.g. aspirin) and anxyolitics/sedatives (chlorpromazine) [34,35]. NSAID’s are the most popular agents because, in addition to being cheap, effective and easy to administer, they allow the patient to control his/her own therapy. Unfortunately, they produce headache after long-term use [8,34,35].

Specific Drugs

These drugs can abolish the headache by producing selective vasoconstriction of extracranial blood vessels, including the external carotid bed. Examples include the ergot alkaloids, ergotamine and dihydroergotamine [34,35]. Although highly effective, the use of ergotamine should be restricted to patients having infrequent severe migraine attacks [8] in view that it may produce: (i) prolonged peripheral vasoconstriction symptoms which are reminders of ergotism (numbness and tingling of the fingers and toes); (ii) cardiac pain suggestive of angina pectoris and palpitations as a result of coronary vasospasm; and (iii) nausea and vomiting by a direct effect on the CNS emetic centres (problematic side effects since these are part of the symptomatology of a migraine headache). Evidently, ergotamine is contraindicated in patients with peripheral vascular disease, coronary heart disease and hypertension. These side effects are partly explained by the capability of ergotamine and other ergots to interact with a wide variety of different receptors types including serotoninergic (5-HT1A, 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2B, 5-HT2C, 5-ht3A/B, 5-HT3c) dopaminergic (D2-like) and adrenergic (α1 and α2) [for references see 36].

IN SEARCH OF THE IDEAL ANTIMIGRAINE DRUG

As previously pointed out, the introduction of ergotamine opened a new era of rational pharmacotherapy in the acute treatment of migraine; however, its side effects, contraindications and interactions with an array of different receptors led to the speculation that a more selective cranial vasoconstrictor agent would be an effective antimigraine drug devoid of the inconveniences associated with ergotamine. Thus, in 1972, Humphrey and colleagues initiated a long-term project aimed at identifying novel therapeutic agents in the treatment of migraine [37]. The goal of this project was to develop selective vasoconstrictors of the extracranial circulation based on the vascular theory of migraine (see above) and the lines of evidence supporting the role of 5-HT in its pathogenesis [8,38], namely that: (i) during an attack of migraine, high quantities of 5-hydroxyindole acetic acid (5-HIAA) are excreted [39]; (ii) some drugs that deplete monoamines (reserpine) can provoke a migraine attack [40]; and (iii) a slow i.v infusion of 5-HT can abort an attack of migraine [40,41]. The factor restricting the clinical use of 5-HT as an antimigraine agent was the prevalence of side effects [40,41], including changes in heart rate, vasodilatation in some vascular beds (e.g. cutaneous blood vessels) and vasoconstriction in others (e.g. the external carotid bed), gastrointestinal effects, etc [42,43]. The antimigraine efficacy of 5-HT, nevertheless, suggested the existence of a specific 5-HT receptor involved in the relief of headache; hence, it was proposed [44] that a drug which could mimic the beneficial effects of 5-HT without its side-effect profile would provide an effective therapy for migraine. The aim, therefore, was to identify such a drug which would selectively constrict the cranial blood vessels (abnormally dilated during migraine). This aim was strengthened by the knowledge that 5-HT appeared to be intrinsically more active as a vasoconstrictor of cephalic blood vessels (i.e. the external carotid bed), and that the 5-HT receptors on such vessels are different to those on peripheral vessels [45,46].

CLASSIFICATION OF 5-HT RECEPTORS

With the conjunction of operational (selective agonists and antagonists and ligand binding affinities), transductional (intracellular transduction mechanisms) and structural (molecular structure) criteria, 5-HT receptors have been divided into seven main families, namely: 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-htr5a, 5-htr5b and 5-htr7 receptors (see Table 1). With the exception of 5-htr5a and 5-htr5b receptors, the other receptors have been functionally identified [42,47-50,18]. To distinguish recombinant receptors from native, functional receptors in whole tissues, lower case letters are used to identify recombinant receptors [47]. This review restricts itself to the 5-HT1 receptor family since this is the receptor type involved in the therapeutic efficacy of acute antimigraine drugs [18,19]. The 5-HT1 receptor is a highly heterogeneous family, which includes at least 5 subtypes, namely, 5-HT1A, 5-HT1B, 5-HT1D, 5-htr5a and 5-htr5b receptors (see Table 1). As discussed below, the selective antimigraine drugs (sumatriptan and second generation triptans) are agonists at 5-HT1B/D receptors and produce selective vasoconstriction of the carotid vascular bed [18,19].

SUMATRIPTAN: A SEMINAL DISCOVERY

After analysing several tryptamine derivatives, one in particular drew attention, namely 3-[2-(di-methyl-amino)ethyl]-1H-indole-5-methane sulphonamide (sumatriptan, previously known as GR43175), which was synthesised in 1984. This compound was more selective than 5-carboxamidotryptamine for the 5-HT receptors producing vasoconstriction in the dog saphenous vein and extracranial blood vessels, and displayed much less activity in other...
vessel systems [51,44]. Moreover, many studies showed that sumatriptan is an agonist at 5-HT\textsubscript{1B/1D} receptors [47]. This drug mediates constriction of cranial large arteries (i.e., the external carotid bed) [52-54], is effective in aborting migraine attacks [24], but it has coronary side-effect potential [55].

**EXPERIMENTAL MODELS PREDICTIVE OF ACUTE ANTIMIGRAINE ACTION**

The experimental models currently known for the discovery and development of antimigraine drugs are based on the vascular or neurogenic theories of migraine [18]. These basically include:

Models Based on the Involvement of Cranial Vasodilatation in Migraine

These models consider cranial vasodilatation as an integral part of the pathophysiology of migraine and that the ergot alkaloids and sumatriptan owe their therapeutic efficacy primarily to the constriction of dilated vessels [24]. There are several ways to investigate the effects of antimigraine drugs on cranial blood vessels, both in vitro and in vivo. Two of these models are discussed here.

(i) Contraction of isolated cranial blood vessels. Several isolated blood vessels, including human cranial arteries, contract in response to acute antimigraine drugs [18,19]. This effect is more marked on cranial blood vessels where, contrary to most peripheral arteries, the 5-HT\textsubscript{1B} rather than 5-HT\textsubscript{1D} receptor is predominant [56].

(ii) Constriction of the canine external carotid bed. Over the years [54], this vascular model (as discussed below), has proven its worth and has been highly predictive of antimigraine activity in the clinical setting [18,19]. Another advantage it offers is that one can simultaneously study a number of major vascular beds in order to evaluate the craniovascular selectivity of the drugs [45,57], as was the case in the preclinical development of sumatriptan [58]. It must, however, be realised that this model will pick up only

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**Table 1. Classification of 5-HT Receptors**\(^{ab}\)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Agonists</th>
<th>Antagonists</th>
<th>Transduction</th>
<th>Localization</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT\textsubscript{1A}</td>
<td>8-OH-DPAT</td>
<td>WAY 100635</td>
<td>(+) Adenylyl cyclase</td>
<td>Raphe nucleus</td>
<td>Central hypotension</td>
</tr>
<tr>
<td>5-HT\textsubscript{1B,c,d}</td>
<td>Sumatriptan</td>
<td>SB224289</td>
<td>(+) Adenylyl cyclase</td>
<td>Cranial blood vessels</td>
<td>Vasocostriction</td>
</tr>
<tr>
<td>5-HT\textsubscript{1D}</td>
<td>PNU109291</td>
<td>BRL15572</td>
<td>(+) Adenylyl cyclase</td>
<td>Presynaptic neurons</td>
<td>Autoreceptor</td>
</tr>
<tr>
<td>5-HT\textsubscript{2A}</td>
<td>5-HT</td>
<td>Methiothepin</td>
<td>(+) Adenylyl cyclase</td>
<td>Cortex</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-HT\textsubscript{2C}</td>
<td>LY344864</td>
<td>Methysergide</td>
<td>(+) Adenylyl cyclase</td>
<td>CNS</td>
<td>(-) Trigeminal system</td>
</tr>
<tr>
<td>5-HT\textsubscript{2B}</td>
<td>DOI</td>
<td>Ketanserin</td>
<td>(+) Phospholipase C</td>
<td>Smooth muscle, platelets</td>
<td>Contraction, aggregation</td>
</tr>
<tr>
<td>5-HT\textsubscript{2B}</td>
<td>BW723C86</td>
<td>SB204741</td>
<td>(+) Phospholipase C</td>
<td>Rat fundus, endothelium</td>
<td>Contraction, release of NO</td>
</tr>
<tr>
<td>5-HT\textsubscript{3}</td>
<td>Ro 60-0175</td>
<td>SB242084</td>
<td>(+) Phospholipase C</td>
<td>Choroid plexus</td>
<td>CSF production?</td>
</tr>
<tr>
<td>5-HT\textsubscript{4}</td>
<td>2-Methyl-5-HT</td>
<td>MDL72222</td>
<td>Na(^+)/K(^+) channel</td>
<td>Peripheral nerves</td>
<td>(+) Neuronal activity</td>
</tr>
<tr>
<td>5-HT\textsubscript{5}</td>
<td>Renzapride, BIMU8</td>
<td>GR 113808</td>
<td>(+) Adenylyl cyclase</td>
<td>Gastrointestinal tract, pig and human atrium</td>
<td>(+) Neuronal activity, tachycardia</td>
</tr>
<tr>
<td>5-h\textsubscript{2A,2B}</td>
<td>5-HT, ergotamine</td>
<td>LSD</td>
<td>?</td>
<td>CNS</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-h\textsubscript{2C}</td>
<td>5-MeO-Tx5-HT</td>
<td>Ro 04-6790</td>
<td>(+) Adenylyl cyclase</td>
<td>CNS, smooth muscle, cat atrium</td>
<td>Circadian rhythm, relaxation, tachycardia</td>
</tr>
</tbody>
</table>

\(^{ab}\)Modified from Saxena and Villalón; [42,47-50,18]. In order to distinguish recombinant receptors from functional receptors in whole tissues, lower case letters (5-ht) are used to identify recombinant receptors.

\(^{a}\)CNS, central nervous system; CSF, cerebrospinal fluid; LSD, lysergic acid diethylamide; 5-MeOT, 5-methoxytryptamine; 5-CT, 5-carboxamidotryptamine; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; NO, nitric oxide; (+), inhibits; (+), stimulates.

\(^{b}\)The antimigraine drug sumatriptan as well as second generation triptans are agonists at 5-HT\textsubscript{1B/1D} receptors. There is no selective agonist at 5-HT\textsubscript{1B} receptors thus far.

\(^{c}\)GR127935 equi-potentatively antagonizes 5-HT\textsubscript{1A,1D} receptors and displays moderate affinity for 5-h\textsubscript{2A} receptors.

\(^{d}\)There are no selective agonists or antagonists thus far. Very high doses of methiothepin are required to produce effective blockade.

\(^{e}\)DOI is an equipotent agonist at 5-HT\textsubscript{2A,2B} and 5-HT\textsubscript{2C} receptors.

\(^{f}\)Although there are no selective agonists yet, sumatriptan must be inactive at 5-HT\textsubscript{4} and 5-HT\textsubscript{5} receptors. Mesulergine is an antagonist showing an almost 300-fold selectivity for the cloned 5-h\textsubscript{2C} receptor (pK\textsubscript{D}G=8.2) over the cloned 5-h\textsubscript{2A} receptor (pK\textsubscript{D}G=5.8).
those putative antimigraine drugs that would be effective by constricting dilated cranial blood vessels, whatever the mechanism.

Models Based on the Involvement of the Trigeminovascular System in Migraine

These models consider that the above described vasoconstrictor action may be unnecessary for antimigraine action and that the efficacy is due to a presynaptic action on sensory nerve endings, inhibiting neuropeptide release and the process and/or consequence of “neurogenic inflammation” [15,32]. One of these models is:

Inhibition of plasma protein extravasation after stimulation of the trigeminal nerve in the rat and guinea pig. In this model, sumatriptan inhibits neurogenic plasma protein extravasation [15,32]; this effect is antagonised by the 5-HT1B/1D receptor antagonist GR127935 (see Table 1) in both the rat and guinea pig, implying the involvement of 5-HT1B/1D receptors [59]. Moreover, in the guinea-pig the selective 5-HT1D receptor agonist PNU109291 (see Table 1) potently inhibits dural plasma extravasation [60,61]. Indeed, the selective 5-HT1F receptor agonists, LY334370 and LY344864 (see Table 1), inhibit plasma protein extravasation in the guinea pig and rat [62,63]. Importantly, the activity of PNU142633 in this model does not translate into antimigraine activity in clinical trials [17]; in contrast, LY334370 displayed antimigraine activity at doses that may interact with extracranial vasoconstrictor 5-HT1B receptors [16]. Moreover, [64] has questioned the involvement of plasma extravasation in migraine, based on the lack of retinal permeability changes during migraine attacks.

Irrespective of the validity of each model, there is little doubt that the models with more tradition for the development of potential antimigraine drugs are those based on the vascular theory of migraine (see above) [45,57]. In fact, sumatriptan was developed on experimental models based on this theory [44], particularly the canine external carotid bed [58]. For this reason, the present review will be particularly focussed on our pharmacological research on 5-HT and the canine external carotid bed.

THE CANINE EXTERNAL CAROTID BED: A RELIABLE EXPERIMENTAL MODEL TO DEVELOP ANTIMIGRAINE DRUGS

As previously described, all effective acute antimigraine drugs available thus far produce selective vasoconstriction of cephalic blood vessels (i.e. the external carotid bed including its temporal branches and arteriovenous anastomoses) [18,19]. Experiments are carried out in anaesthetised mongrel dogs and catheters are placed in the inferior vena cava via a femoral vein for the administration of antagonists and in the aortic arch via a femoral artery, connected to a pressure transducer for the measurement of blood pressure. The right common carotid artery is dissected free and the corresponding internal carotid and occipital arteries are ligated. Thereafter, an ultrasonic flow probe (4 mm R-Series) connected to an ultrasonic flowmeter is placed around the right common carotid artery, and the flow through this artery is considered as the external carotid blood flow [52-54]. Bilateral cervical vagosympathectomy is systematically performed in order to produce one of the main features of migraine, i.e. external carotid vasodilatation [57]. Under these conditions, 5-HT and ergotamine can produce selective external carotid vasoconstriction [57]. These findings confirmed the previously observed antimigraine action of ergotamine [9-11] and 5-HT [41,40] (see above). Interestingly, Vidrio and Hong reported that 5-HT produced vasodilatation in animals with intact vagosympathetic trunks [65]. These discrepancies were explained in terms of the vascular sympathetic tone [66], establishing that in animals with interrupted vagosympathetic trunks (and the resulting external carotid vasodilatation) 5-HT produces vasoconstriction, producing the opposite effect in dogs with intact vagosympathetic trunks [67].

PHARMACOLOGICAL PROFILE OF THE RECEPTORS MEDIATING EXTERNAL CAROTID VASOCONSTRICTION IN VAGOSYPATHECTOMIZED DOGS

It had been previously shown that methysergide (non-selective 5-HT receptor antagonist), but not mianserin or cyproheptadine (5-HT2 receptor antagonists), blocked the vasoconstrictor responses to 5-HT in the external carotid bed [68,57]. Since methysergide is a non-selective antagonist, these data suggested that a novel (methysergide-sensitive) 5-HT receptor was involved. With the advent of more selective antagonists, it was shown that the vasoconstrictor response to 5-HT was significantly blocked by high doses of methiothepin (a 5-HT1-like receptor antagonist) but not by ritanserin or tropisetron, antagonists at 5-HT2 and 5-HT3 receptors, respectively [52]. Interestingly, sumatriptan, a selective “5-HT1-like” receptor agonist, mimicked the vasoconstriction to 5-HT, and this response was also blocked by methiothepin. These data suggested the involvement of “5-HT1-like” receptors, but not 5-HT2 or 5-HT3 or 5-HT4 receptors [52].

In 1994, the classification schemes proposed by the NC-IUPHAR subcommittee on 5-HT receptors [47] considered the “5-HT1-like” receptors to be different from 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1F receptors. Considering this, we suggested that 5-HT1A, 5-HT1B or 5-HT1D are not involved in the external carotid vasoconstrictor responses to 5-HT since these were not blocked by: (i) (±)pindolol, a 5-HT1A/1B Receptor antagonist; (ii) propranolol, a β-blocker with affinity for 5-HT1B receptors; and (iii) metergoline, a ligand with the highest affinity for “5-HT1B” receptors. However, we recognised that metergoline was a non-competitive and non-specific antagonist and that its affinity did not correlate with its blocking properties at functional responses. Thus, we had to wait for more selective 5-HT1D receptor antagonists.

With the advent of GR127935 in 1996, a selective “5-HT1B/1D” receptor antagonist [69], we observed that the vasoconstrictor responses to 5-HT and sumatriptan, which were unaffected by saline, were potently and selectively antagonised by this antagonist [53]. However, the profile of antagonism was different. Indeed, not only was the
vasoconstrictor response to 5-HT completely abolished, but also a dose-dependent vasodilator response was unmasked. In the case of sumatriptan, the vasoconstrictor response was dose-dependently antagonised without unmasking the vasodilator effect observed with 5-HT [53]. These findings suggested that the “5-HT1-like” receptors mediating the vasoconstrictor responses to 5-HT and sumatriptan belong to the 5-HT1D receptor subtype [53]. In addition, a further analysis of the vasodilator response to 5-HT in animals systemically pretreated with GR127935 revealed that this effect is mediated by 5-HT1 receptors [70].

However, it had been reported that in humans the 5-HT1D receptors had two variants, called 5-HT1Dα and 5-HT1Dβ receptors. Sumatriptan, GR127935, metergoline and methiothepin were not able to discriminate between 5-HT1Dα and 5-HT1Dβ receptors. Subsequently, these receptors were redefined respectively, as 5-HT1D and 5-HT1B since the 5-HT1Dβ receptor was considered a human homologue of the rodent 5-HT1B receptor [71]. Thus, although the rodent 5-HT1B receptor exhibits a pharmacological profile (sensitive to β-blockers) which differs from that of the non-rodent species (see Table 1), they are encoded by the same gene (but different species). With this new nomenclature (vasoconstrictor 5-HT1B/1D receptors), the need for more selective compounds was evident. The advent of selective and silent antagonists (agonists devoid of intrinsic activity) for 5-HT1B and 5-HT1D receptors shed further light on this matter [72]. Thus, as shown in Fig. (3a), the external carotid vasoconstrictor responses to 5-HT and sumatriptan were dose-dependently and specifically antagonised by the selective 5-HT1B receptor antagonist, SB224289, but not by the selective 5-HT1D receptor antagonist, BRL15572 see Fig. (3b); [73]. These data clearly indicate that 5-HT1B, but not 5-HT1D receptors mediate the external carotid vasoconstrictor responses to 5-HT and sumatriptan. In addition, the 5-htr1F receptor agonist, LY344864 was inactive as an agonist or antagonist in this model [36], a finding that excludes the potential role of these receptors. The implication of these findings within the context of the vascular theory of migraine would be that the vascular 5-HT1D receptor is one of the main targets of antimigraine drugs. Obviously, the introduction of a selective 5-HT1B receptor agonist for the treatment of migraine (devoid of the ability to inhibit the trigeminovascular system) is awaited with interest.

MECHANISM OF ACTION OF ERGOTAMINE AND DIHYDROERGOTAMINE

Although the antimigraine properties of ergotamine and dihydroergotamine are clearly established [7,9,6], the mechanisms involved in their vasoconstrictor action are not well understood. These drugs can produce external carotid vasoconstriction and can interact with 5-HT1, 5-HT2, 5-htr, 5-HT6, 5-HT7, α-adrenoceptors and dopamine receptors [36]. Thus, we investigated the mechanisms involved in these vasoconstrictor effects. Interestingly, both drugs produced dose-dependent vasoconstrictor responses in the canine external carotid bed. As shown in Fig. (4), these responses were partially blocked by the 5-HT1B/1D receptor antagonist, GR127935, or by the α2-adrenoceptor antagonist, yohimbine, but not by the α1-adrenoceptor antagonist, prazosin. Interestingly, the vasoconstrictor responses to these drugs were abolished by the combination of GR127935 and yohimbine, confirming that 5-HT1B/1D receptors and α2 adrenoceptors are involved [36]. It should be emphasised that the blockade of the above antagonists was specific, since the doses of prazosin, yohimbine and GR127935 were high enough to block the carotid vasoconstrictor responses to phenylephrine, clonidine and sumatriptan, respectively [36].

Although, the above findings show the involvement of 5-HT1B/1D receptors and α2-adrenoceptors on the vasoconstrictor responses to ergotamine and dihydroergotamine, it remains to be established whether 5-HT1B or 5-HT1D receptors as well as α2A, α2B or α2C-adrenoceptors are involved. In addition, these ergot alkaloids may have other properties such as inhibition of protein plasma extravasation [74].

PHARMACOLOGY OF SUMATRIPTAN AND SECOND-GENERATION TRIPNTANS

Despite its efficacy in migraine treatment, sumatriptan has certain limitations, including low oral bioavailability, high headache recurrence (possibly due to a short t½) and contra-indications in patients with coronary artery disease [19,18]. Therefore, a number of pharmaceutical companies decided to develop newer triptans having agonist activity at 5-HT1B/1D receptors. Several such compounds (zolmitriptan, rizatriptan and naratriptan) are already on the market, while others (eletriptan, almotriptan and frovatriptan) are in different stages of clinical development [19,18]. These compounds will be referred to as the second-generation triptans, since they are tryptamine derivatives and pharmacologically comparable to sumatriptan. Zolmitriptan, rizatriptan, naratriptan and eletriptan seem to be at least as effective as sumatriptan in migraine therapy [21,75] and the outcome of elaborate clinical trials with the other triptans is awaited with interest.

RECEPTOR BINDING PROFILE OF TRIPNTANS

Sumatriptan as well as the second-generation triptans display high affinities at 5-HT1D receptors, mainly the 5-HT1B and 5-HT1D receptors (see Fig. [5]) [76-80]. With the exception of rizatriptan and almotriptan and, to some extent sumatriptan, all other compounds, particularly zolmitriptan, have a high affinity at the 5-HT1A receptor. These compounds also interact with the 5-htr1F receptor. Sumatriptan, zolmitriptan, eletriptan and frovatriptan display a μM affinity at the 5-HT1 receptor, which mediates smooth muscle relaxation [50].

PHARMACOKINETICS OF TRIPNTANS

The pharmacokinetic properties of second-generation triptans have been studied in human volunteers and migraine patients, as shown in Fig. (6) [81-94]. Subcutaneous sumatriptan (6 mg) is quickly absorbed with a tmax of approximately 10 min and an average bioavailability of 96% [95]. After oral administration of therapeutic doses (100 mg) of sumatriptan, however, the tmax is substantially longer (1.5 h) and, more importantly, the bioavailability is rather
low (~14%). Intranasal or rectal administration of sumatriptan does not seem to improve these parameters much [96]. The oral bioavailability of second-generation triptans, especially naratriptan and almotriptan, is much improved [see Fig. (6)]. The latter can be partly attributed to the more lipophilic nature of these drugs. Interestingly, the $t_{max}$ after oral administrations of zolmitriptan, naratriptan, almotriptan and frovatriptan is not much better than that of sumatriptan, whereas rizatriptan and eletriptan seem to reach their peak plasma levels quicker compared to sumatriptan.

With the exception of rizatriptan, triptans are degraded slower than sumatriptan. Especially frovatriptan has a plasma half-life of 26-30 h [see Fig. (6)] and, in view of the putative relation of this parameter with headache recurrence, the results of clinical trials with frovatriptan are awaited with
interest. In contrast to sumatriptan and naratriptan, active metabolites have been reported for zolmitriptan, rizatriptan and eletriptan. It is not known, whether and if so, to what extent, the metabolites contribute towards the amount and duration of therapeutic activity and recurrence rates. We are not aware whether the metabolism of almotriptan and frovatriptan results in the formation of active metabolites.

CORONARY VASCULAR EFFECTS OF TRiptANS

In the human coronary artery, 5-HT$_2$ receptors are more important, but about 20-30% response is mediated by 5-HT$_1$ receptors [95]. Accordingly, sumatriptan moderately constricts the human coronary artery, both in vivo [96] and in vitro [98]. That is why this drug is not recommended in patients with coronary artery disease. The other second-generation triptans are slightly more potent (except eletriptan), but show similar efficacy [79]. Recently, it has been shown that eletriptan shows craniovascular selectivity for the human middle meningeal artery over the human coronary artery or human saphenous vein to produce constriction [99]. Indeed, eletriptan was less potent to produce coronary vasoconstriction than sumatriptan, but both sumatriptan and eletriptan were equipotent to produce meningeal vasoconstriction. Although both drugs are contraindicated in patients with coronary artery disease, they have a limited propensity to produce coronary effects in healthy subjects [98].

FUTURE TRENDS IN THE EFFICACY OF ANTIMIGRAINE DRUGS

It is undeniable that the cranial vasoconstrictor activity of sumatriptan and the second-generation triptans, mediated by the 5-HT$_{1B}$ receptor, is associated with their efficacy in the acute treatment of migraine [18,19]. Unfortunately, the 5-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. Therefore, in an attempt to avoid coronary...
vasoconstriction at least four new avenues are being explored: (i) 5-HT$_{1D}$ receptor agonists; (ii) 5-HT$_{1F}$ receptor agonists; (iii) 5-HT$_7$ receptor antagonists; and (iv) blockade of receptors for CGRP and substance P.

5-HT$_{1D}$ Receptor Agonists

A series of isochroman-6-carboxamide derivatives, including PNU-109291, have been described as highly selective 5-HT$_{1D}$ receptor agonists (pK$_i$ values: 5.2 and 9.0 at 5-HT$_{1B}$ and 5-HT$_{1D}$ receptor, respectively) [61] (see Table 1). PNU-109291 is devoid of carotid vasoconstrictor effect in the anaesthetised cat, but potently inhibits dural plasma extravasation in the guinea-pig [61]. Moreover, these 5-HT$_{1D}$ receptor agonists do not produce vasoconstriction in \textit{in vivo} (canine external and internal carotid bed [100]) or \textit{in vitro} (cerebral arteries; [101]) preparations. More recently, it has been shown that PNU-142633 is ineffective in patients with migraine [17]. Clearly, inhibition of dural plasma extravasation by itself is not predictive of antimigraine activity.

5-HT$_{1F}$ Receptor Agonists

Two potent 5-HT$_{1F}$ receptor agonists, LY344864 (pK$_i$ values: 6.3, 6.2 and 8.2 at 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptor, respectively [62]) and LY334370 (pK$_i$ values: 6.9, 6.9 and 8.8 at 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptor, respectively [62]) have been described. Both compounds potently inhibit dural plasma protein extravasation [62,63], but are devoid of vasoconstrictor activity [101]. Together with the fact that SB224289, which displays little affinity at the 5-HT$_{1F}$ receptor [72], completely antagonises sumatriptan-induced external carotid vasoconstrictor effects [73], it is evident that the 5-HT$_{1F}$ receptor is not involved in the vasoconstrictor effects of sumatriptan and the second-generation triptans. It therefore implies that if LY334370 turns out to be effective in migraine at doses devoid of 5-HT$_{1B/1D}$ receptor interaction, the mechanism of action will not be via cranial vasoconstriction. In fact, it has recently been reported that LY334370 is clinically effective to abort migraine attacks [16]. However, it has to be emphasised that LY334370 displayed antimigraine activity at doses that may interact with extracranial vasoconstrictor 5-HT$_{1B}$ receptors [16]. In the absence of the importance of dural plasma protein extravasation (see above), further experiments will be needed to explain the efficacy of LY334370.

5-HT$_7$ Receptor Antagonists

Methysergide and lisuride, prophylactic antimigraine drugs, have high affinity for 5-HT$_7$ receptors [47]. In
addition, it has been shown that 5-HT7 receptors mediate vasodilator responses in several vascular tissues [102] including the canine external carotid bed [70]. Thus, it would be expected that selective antagonists at 5-HT7 receptors might have antimigraine properties, although this remains to be determined.

**Blockade of Receptors for CGRP and Substance P**

Electrical stimulation of the trigeminal ganglion produces release of potent vasodilator peptides such as substance P and CGRP [103]. Further evidence suggests that during an attack of migraine an increase in plasma levels of CGRP is observed [104]. The release of CGRP is blocked by dihydroergotamine and sumatriptan [103], indicating that the blockade of this mechanism could be another strategy to develop antimigraine drugs. Recently, it has been shown that the CGRP antagonist, BIBN4096BS, potently and dose-dependently inhibited the increases in facial blood flow induced by electrical stimulation of the trigeminal ganglion [105]. These findings, in conjunction with the ability of BIBN4096BS to antagonise CGRP-induced vasorelaxation of the human temporal artery [106] and porcine carotid arteriovenous anastomosis [107] strongly suggest that blockade of vascular CGRP receptors may have potential therapeutic usefulness in the treatment of migraine. In addition, a new nonpeptide CGRP antagonist, SB-273779, which blocked the CGRP-induced hypotension in anaesthetised rats [108], represents an opportunity to analyse its potential antimigraine activity.

Lastly, it has been shown that lanepitant, a very potent antagonist of the receptor for substance P (an NK1 receptor antagonist), was not clinically effective in preventing migraine [109], although it inhibited the neurogenic dural inflammation. Thus, these results suggest that blockade of NK1 receptors is not a good strategy to abort an attack of migraine.

**CONCLUDING REMARKS**

Migraine treatment has been described over the centuries (even millennia!). Their writings, from ancient times to the present, mirror the evolution of scientific thought, with migraine metamorphosing from a disease attributed to supernatural causes to a molecular disorder. With this long history, notwithstanding, it is extremely surprising that effective antimigraine drugs had been, until very recently,
limited in number. Indeed, in comparison to other areas of pharmacology, the therapeutic approaches to headache have advanced minimally over the past 100 years. Fortunately, in the last decades, there have been big steps in understanding the pathophysiology of migraine and in the development of antimigraine drugs. Evidently, new approaches need to be explored (e.g. drugs that inhibit the trigemino-vascular system) in order to obtain selective drugs with less cardiovascular adverse effects.

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