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Review

Pharmacological aspects of experimental headache models in relation to acute antimigraine therapy

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Abstract

The last decade has witnessed a tremendous progress in the acute therapy of migraine, with sumatriptan, belonging to a new class of drugs, now known as 5-$HT_{1B/1D/1F}$ receptor agonists, leading the way. The undoubted success of sumatriptan stimulated the development of new triptans as well as other suitable pharmacological tools and experimental models to probe into complex migraine mechanisms. In this review, we discuss the main experimental models for migraine, against the background of the disease pathophysiology and 5-HT receptors considered most important for migraine therapy. We believe that the use of these migraine models will provide even better treatment for migraine patients in the next millennium.

Keywords: 5-Hydroxytryptamine; 5-HT receptor; Migraine; Migraine model; Serotonin; Sumatriptan; Triptan

1. Introduction

Migraine is a syndrome that affects a substantial fraction of world's population, with a higher prevalence in females (15–18%) than in males (6%; Lipton and Stewart, 1997). Migraine is characterised by attacks of intense, pulsatile and throbbing headache, which is typically unilateral and is accompanied by anorexia, nausea, vomiting and photo- and/or phonophobia. In about one third of patients, the headache is preceded by aura symptoms, consisting of certain sensory (pins and needle feeling or numbness), motor (weakness or paralysis) and/or focal neurological (characteristically a homonymous, spreading, scintillating scotoma) symptoms (migraine with aura). The majority of patients, however, do not present with such symptoms (migraine without aura) (for review, see Ferrari, 1998).

In the last decade there has been a tremendous progress in the acute therapy of migraine, with sumatriptan belonging to a new class of drugs, now known as 5-$HT_{1B/1D/1F}$ receptor agonists, providing the lead (Humphrey et al., 1988, 1990; The Subcutaneous Sumatriptan International Study Group, 1991). This seminal discovery by Humphrey and colleagues was based on the findings that a novel 5-HT (now 5-HT_{1B}; see below) receptor mediates selective carotid vasoconstriction, which is also observed following small doses of the well-known antimigraine drug ergotamine (Saxena, 1972; Saxena and De Vlaam-Schluter, 1974). The success of sumatriptan in migraine therapy undoubtedly resulted in heightened research interest in the field of migraine. This, in turn, led to a better understanding of the pathophysiological processes involved in migraine as well as the development of new triptans (for reviews, see Ferrari, 1998; Goadsby, 1998; De Vries et al., 1999a) and other prospective drugs (Fig. 1). This review is devoted to the pharmacological aspects of experimental migraine models recently employed in the development of acutely acting antimigraine drugs. To provide relevant background, the pathophysiology of migraine and 5-HT_1 receptor subtypes that are important in relation to antimigraine potential will also be discussed briefly.

2. 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

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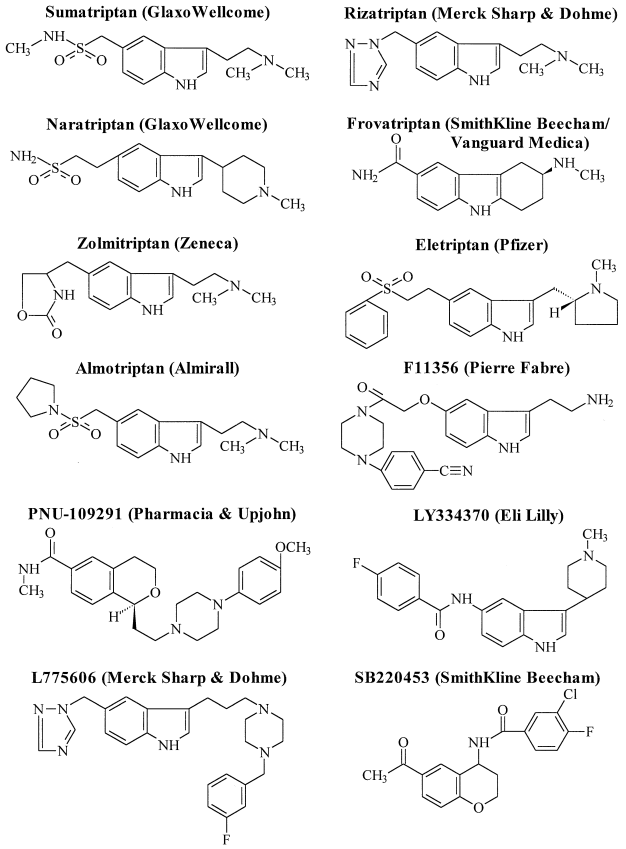

Fig. 1. Chemical structures of current and prospective drugs for the acute treatment of migraine. Besides sumatriptan, zolmitriptan, naratriptan and rizatriptan, which have already been marketed, the other 5-$HT_{1B/1D}$ receptor agonist triptans also include eletriptan, frovatriptan, almotriptan and F11356. PNU109291 and L775606 are selective agonists at the 5-HT_{1D} receptor, while LY334370 is a selective 5-HT_{1F} receptor agonist. SB220453 is a ligand for a novel uncharacterised receptor.

(e.g., Goadsby, 1997; Ferrari, 1998). Some results indicate that the initiating trigger, involving the brainstem as 'migraine generator' (Weiller et al., 1995), may be linked to a 'familial' channelopathy (Ophoff et al., 1996; Ferrari, 1998). The subsequent events leading to symptoms observed during the aura and headache phases can be explained on the basis of a neurovascular hypothesis (see Ferrari, 1998; Ferrari and Saxena, 1993; Saxena, 1994). As illustrated in Fig. 2, once the 'migraine generator' has been switched on, regional cerebral blood flow decreases, possibly following a wave of cortical spreading depression (see Read and Parsons, 1999). In patients where cerebral blood flow falls below a critical value, corresponding aura symptoms may appear. The reduced cerebral blood flow is then followed by a vasodilatation during the headache phase, probably due to changes in the activity of the neurones innervating cranial extracerebral large arteries and arteriovenous anastomoses (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 nerve fibres supplying intracranial blood vessels, including 5-HT, vasoactive intestinal peptide (VIP), nitric oxide, substance P, neurokinin A and calcitonin gene-related peptide (CGRP) (for review, see Gulbenkian et al., 1999). As discussed elsewhere (Olesen et al., 1994), nitric oxide may play an important role in migraine pathophysiology and inhibition of its synthesis seems to be of therapeutic relevance (Lassen et al., 1998). In any case, cranial vasodilatation leads to enhanced blood volume following each cardiac stroke and rapid diastolic runoff, with a consequent augmentation in pulsations within the affected blood vessels. 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 associated symptoms. This stimulation of the trigeminal nerve may also release neuropeptides, thus reinforcing vasodilatation and perivascular sensory nerve activity (for details and references, see Saxena, 1994).

Acutely acting antimigraine drugs constrict dilated cranial extracerebral blood vessels (Saxena and Ferrari, 1989;

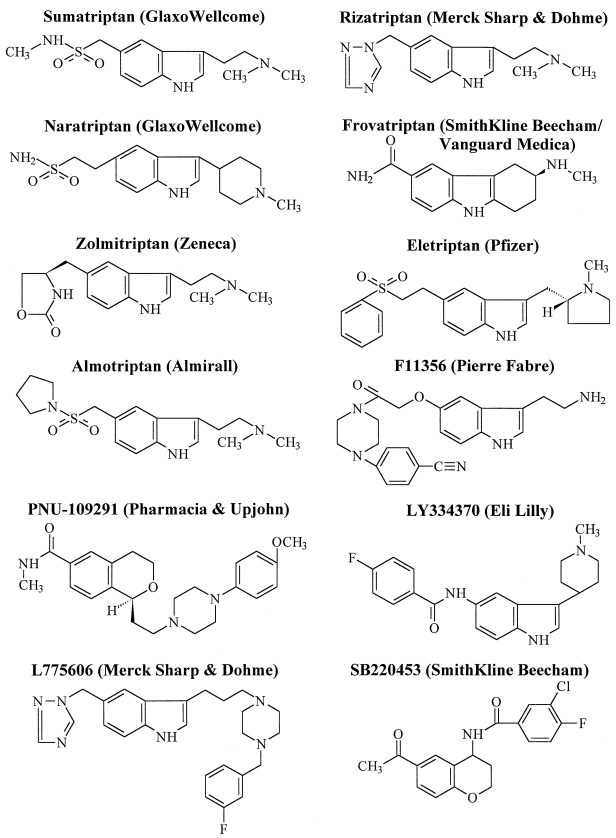

Fig. 2. Diagram showing putative changes in migraine and the therapeutic targets of acutely acting antimigraine drugs. These drugs are believed to owe their antimigraine efficacy to direct vasoconstriction of dilated cranial blood vessels (1), inhibition of trigeminally-induced cranial vasodilatation (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. Based on Saxena (1994). TNC, trigeminal nucleus caudalis.

Humphrey and Feniuk, 1991; Ferrari and Saxena, 1993), reduce neuropeptide release and plasma protein extravasation across dural vessels (Moskowitz, 1992, 1993) and inhibit impulse transmission centrally within the trigeminovascular system (Goadsby, 1997; Goadsby et al., 1991, see Fig. 2).

3. 5-HT$_1$ receptor subtypes relevant to migraine

At the time of its introduction, sumatriptan was regarded as a selective 5-HT$_1$-like receptor agonist (Humphrey et al., 1988, 1990). Indeed, sumatriptan-induced vasoconstrictor as well as the prejunctional neuronal inhibitory actions clearly exhibited the pharmacological profile of 5-HT$_1$-like receptors, which from the very outset were considered heterogeneous (Bradley et al., 1986; Hoyer et al., 1994). As recently argued (Saxena et al., 1998), the term '5-HT$_1$-like receptor' is redundant as the composition of this heterogeneous group is now known. This group comprises of the sumatriptan-insensitive 5-HT$_7$ receptor, which mediates tachycardia in cats and vasorelaxation (De Vries et al., 1997; Eglen et al., 1997; Villalón et al., 1997a,b) as well as sumatriptan-sensitive 5-HT$_{1B}$, 5-HT$_{1D}$ and, in some tissues, even 5-HT$_{1F}$ receptors. Sumatriptan also has a moderate affinity for 5-HT$_{1A}$ and 5-ht$_{1E}$ receptors, but they will not be discussed here because the clinically effective plasma C_{max} of sumatriptan (0.1–0.2 μM; Lacey et al., 1995) is insufficient for an agonist action at these receptors. The agonists and antagonists that discern 5-HT$_{1B}$, 5-HT$_{1D}$ and 5-HT$_{1F}$ receptors, which are relevant to antimigraine action, are listed in Table 1.

3.1. 5-HT$_{1B}$ receptor

The mRNA for the 5-HT$_{1B}$ receptor, previously named 5-HT$_{1D\beta}$ (Hartig et al., 1996), is abundantly expressed on vascular smooth muscle cells as well as neuronal tissues (Bouchelet et al., 1996). Interestingly, the receptor protein seems to be confined to vascular smooth muscle (Longmore et al., 1997). Indeed, there is now overwhelming evidence that the 5-HT$_{1B}$ receptor mediates contraction of vascular smooth muscle (De Vries et al., 1998a, 1999b; Verheggen et al., 1998). As shown in Table 1, the 5-HT$_{1B}$ receptor is potently blocked by the mixed 5-HT$_{1B/1D}$ receptor antagonist, GR127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl) phenyl]-2′-methyl-4′ (5-methyl-1, 2,4-oxadiazol-3-yl) [1,1,-biphenyl]-4-carboxamide hydrochloride monohydrate) (Clitherow et al., 1994; Pauwels, 1996; Skingle et al., 1996), and the recently developed selective 5-HT$_{1B}$ receptor antagonist, SB224289 (2,3,6,7-tetrahydro-1′-methyl-5-[2′-methyl-4′(5-methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carbonyl] furo [2,3-*f*] indole-3-spiro-4′-piperidine hydrochloride) (Hagan et al., 1997; Gaster et al., 1998). Although sumatriptan and the second-generation triptans act as agonist at this 5-HT$_{1B}$ receptor, no selective agonist has been described. It is important to note that the rodent 5-HT$_{1B}$ receptor displays a distinct pharmacology compared to the 5-HT$_{1B}$ receptor in other species (Hartig et al., 1996), despite the 96% amino acid sequence homology in the transmembrane regions (Adham et al., 1992). Thus, CP93129 (3-(1,2,5,6-tetrahydropyrid-4-yl) pyrrolo [3,2-*b*] pyrid-5-one) is a selective agonist, whereas some β-adrenoceptor antagonists, such as cyanopindolol, (−)-pindolol and (−)-propanolol, are selective antagonists at

Table 1
Pharmacological tools to discriminate the different 5-HT$_1$ receptor subtypes

	5-HT$_{1A}$	5-HT$_{1B}$	Rat 5-HT$_{1B}$	5-HT$_{1D}$	5-ht$_{1E}$	5-HT$_{1F}$
Agonists						
Sumatriptan	6.4[a]	8.3[b]	7.3[b]	8.5[a]	5.6[c]	7.6[c]
L775606	7.3[d]	7.1[d]	6.1[b]	9.2[d]	< 5.0[d]	5.4[d]
PNU109291	6.0[e]	5.2[e]	–	9.0[e]	–	–
LY344864	6.3[f]	6.3[f]	–	6.2[f]	5.8[f]	8.2[f]
LY334370	–	6.9[g]	–	6.9[g]	–	8.8[g]
CP93129	5.5 (rat)[h]	6.4[b]	8.1[b]	5.7 (rat)[h]	–	–
CP122288	6.5[i]	8.3[b]	6.8[b]	8.2[i]	6.4[i]	8.5[l]
Antagonists						
GR127935	7.2[j]	9.0[j]	8.8[b]	8.6[j]	5.4[j]	6.4[j]
SB224289	5.5[k]	8.0[k]	–	6.2[k]	< 5.0[k]	< 5.0[k]
BRL15572	7.7[j]	6.1[j]	–	7.9[j]	5.2[j]	6.0[j]
Ketanserin	5.5[l]	5.3[m]	5.7[n]	7.2[m]	< 5.0[l]	< 5.0[l]
Cyanopindolol	8.3 (pig)[n]	7.0[b]	9.0[b]	–	–	–
(−)-Propanolol	6.8 (pig)[n]	5.6[b]	7.7[b]	–	–	–
(−)-Pindolol	7.7 (pig)[n]	< 5.1[b]	7.6[b]	–	< 5.0[c]	< 5.0[c]

All data are given as pK_i at human receptors, except when stated otherwise.
Data from: [a]Leysen et al. (1996); [b]Beer et al. (1998); [c]Adham et al. (1993); [d]MacLeod et al. (1997) (values given as pIC$_{50}$); [e]Ennis et al. (1998); [f]Phebus et al. (1997); [g]Johnson et al. (1997); [h]Macor et al. (1990); [i]Gupta, P. (personal communication); [j]Price et al. (1997); [k]Hagan et al. (1997); [l]Pauwels, P.J. (personal communication); [m]Zgombick et al. (1995); [n]Hoyer (1989).

the rodent 5-HT_{1B} receptor, but not in other species (see Table 1; Macor et al., 1990; Adham et al., 1992; Craig and Martin, 1993; Bruinvels et al., 1993; Beer et al., 1998).

3.2. 5-HT_{1D} receptor

The 5-HT_{1D} receptor, previously called 5-$HT_{1D\alpha}$ (Hartig et al., 1996), is potently antagonised by GR127935 and by the selective 5-HT_{1D} receptor antagonist, BRL15572 (1-(3-chlorophenyl)-4-[3,3-diphenyl (2-(*S*,*R*) hydroxypropanyl) piperazine] hydrochloride) (Price et al., 1997). Additionally, some 5-HT_2 receptor antagonists (ketanserin and ritanserin) can discriminate this receptor from 5-HT_{1B} and 5-HT_{1F} receptors (Hoyer et al., 1994), although this is highly species dependent. Whereas ketanserin shows a selectivity for the 5-HT_{1D} over the 5-HT_{1B} receptor in the rabbit (20-fold; Bard et al., 1996) and human (70-fold; Zgombick et al., 1995), this selectivity is absent in the dog (Branchek et al., 1995) and guinea pig (Zgombick et al., 1997). In contrast to the rat 5-HT_{1B} receptor, the rat 5-HT_{1D} receptor displays similar pharmacology compared to the 5-HT_{1D} receptor found in other species (Hartig et al., 1996; Saxena et al., 1998). All triptans are potent agonists at this receptor, but recently some compounds, including PNU109291 (*S*(−)-1-(1-ethyl-4-methoxyphenylpiperazin)-6-methyl-carboxamido-isochromane) (Ennis et al., 1998) and L775606 (1-(3-[5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl] propyl)-4-(2-(3-fluorophenyl) ethyl) piperazine) (MacLeod et al., 1997), have been reported to be selective 5-HT_{1D} receptor agonists with antimigraine potential (see Table 1). Using receptor specific antibodies, it has been demonstrated that the 5-HT_{1D} receptor is located preferentially on human trigeminal neurones, but not on human dural blood vessels (Longmore et al., 1997). Additionally, the stimulation of 5-HT_{1D} receptor seems to mediate inhibition of transmitter release (Roberts et al., 1997; Schlicker et al., 1997; Saxena et al., 1998).

3.3. 5-HT_{1F} receptor

The 5-HT_{1F} receptor can be distinguished from the 5-HT_{1B} and 5-HT_{1D} receptors using the potent 5-HT_{1F} receptor agonists, LY344864 (*N*-[3-(dimethylamino)-2,3,4,9-tetrahydro-1*H*-carbazol-6-yl]-4-fluorobenzamide) (Phebus et al., 1997) and LY334370 (4-fluoro-*N*-[3-(1-methyl-4-piperidinyl)-1*H*-indol-5-yl]-benzamide) (Johnson et al., 1997). Additionally, most triptans stimulate the 5-HT_{1F} receptor, although rizatriptan (Wainscott et al., 1998) and the non-indole compound alniditan (Leysen et al., 1996) display low affinity, despite being clinically active in migraine (Goldstein et al., 1996; Kramer et al., 1998). Presently, no selective 5-HT_{1F} receptor antagonists are available. The 5-HT_{1F} receptor mRNA and the corresponding protein is preferentially expressed in the neuronal tissue rather than the vascular smooth muscle (Ullmer et al., 1995; Bouchelet et al., 1996). The 5-HT_{1F} receptor seems to mediate inhibition of dural plasma protein extravasation following trigeminal ganglion stimulation (Johnson et al., 1997; Phebus et al., 1997).

4. Experimental models for acutely acting antimigraine drugs

4.1. Models based on the involvement of cranial vasodilatation in migraine

These models are based on the view that cranial extracerebral vasodilatation is an integral part of the pathophysiology of migraine and that the ergot alkaloids and sumatriptan, which do not readily cross the blood–brain-barrier, owe their therapeutic efficacy primarily to constriction of dilated vessels (Saxena and Ferrari, 1989; Humphrey and Feniuk, 1991; Ferrari and Saxena, 1993). 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 will be discussed here.

4.1.1. Constriction of carotid arteriovenous anastomoses in anaesthetised animals

The ergot alkaloids, sumatriptan as well as the newer antimigraine agents decrease carotid blood flow in anaesthetised animals. Consistent with this, sumatriptan evokes a vasoconstrictor action on cephalic arteries during the migraine attack in human volunteers (Friberg et al., 1991; Caekebeke et al., 1992). The apparent rank order of agonist potency in decreasing canine carotid blood flow (with ED_{50} in $\mu g\ kg^{-1}$, i.v.) is: frovatriptan (0.4) (Parsons et al., 1997) > zolmitriptan (2.3) (MacLennan et al., 1998) > eletriptan (12) (Gupta et al., 1996) = naratriptan (19) (Connor et al., 1997) ≥ rizatriptan (30) (Shepheard et al., 1995a) = sumatriptan (39) (Connor et al., 1997). Almotriptan (Bou et al., 1997) and F11356 (4-[4-(2-[3-(2-aminoethyl)-1*H*-indol-5-yloxy]-acetyl]-piperazin-1-yl)-benzonitrile hydrochloride) (John et al., 1999) potently reduce carotid blood flow in the cat and pig, respectively. Using radiolabelled microspheres, it has been shown that the carotid vasoconstriction by sumatriptan (De Vries et al., 1996), zolmitriptan (MacLennan et al., 1998) and eletriptan (Willems et al., 1998) is confined to arteriovenous anastomoses (see Fig. 3), which may dilate during migraine headaches (Heyck, 1969; Saxena, 1995). The involvement of arteriovenous anastomoses in migraine is mainly based on the findings that (i) antimigraine agents decrease carotid blood flow by a vasoconstrictor action exclusively on arteriovenous anastomoses; (ii) during migraine, the oxygen saturation difference between arterial and jugular venous blood decreases and this is normalised after treatment-induced or spontaneous alleviation of the attack (Heyck, 1969; Saxena, 1995). Similarly, sumatriptan (infused into the brachial artery) is able to decrease human

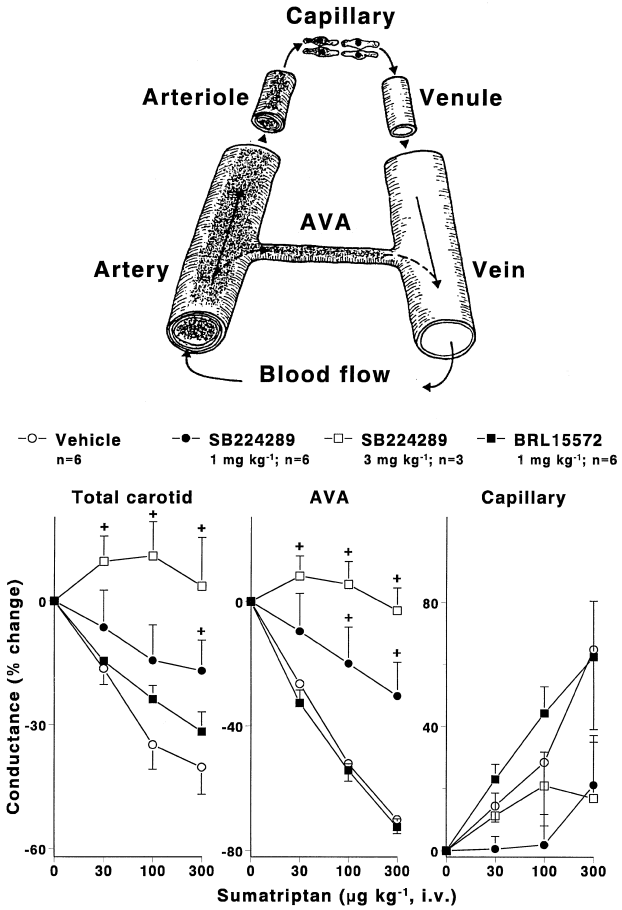

Fig. 3. *Upper panel*. A diagrammatic representation of an arteriovenous anastomosis (AVA). Arteriovenous anastomotic blood flow can be determined using the radioactive microsphere technique (see De Vries et al., 1998b, 1999b). *Lower panel*. Effect (% change from baseline values) of sumatriptan on total carotid, arteriovenous anastomotic and nutrient conductances in vagosympathectomised, anaesthetised pigs, treated with vehicle, SB224289 or BRL15572. All values are presented as the mean ± S.E.M. + $P < 0.05$ vs. response by corresponding dose in vehicle-treated animals. Data from De Vries et al. (1999b).

forearm blood flow by a selective vasoconstrictor action on arteriovenous anastomoses (Van Es et al., 1995).

Using SB224289 and BRL15572, selective 5-HT_{1B} and 5-HT_{1D} receptor antagonists, respectively, it has recently been shown that the constriction of porcine carotid arteriovenous anastomoses as well as the canine external carotid vasculature by sumatriptan is mediated by 5-HT_{1B} receptors and not via 5-HT_{1D} or 5-HT_{1F} receptors (see Fig. 3; De Vries et al., 1998a, 1999b). This conclusion is strengthened by a number of observations. Firstly, the selective 5-HT_{1D} receptor agonist PNU109291 is devoid of carotid vasoconstrictor effect in the anaesthetised cat (Ennis et al., 1998). Secondly, 5-HT_{1D} receptor mRNA or the corresponding protein is poorly expressed in blood vessels (Bouchelet et al., 1996; Longmore et al., 1997). Thirdly, 5-HT_{1F} receptor agonists are devoid of vasoconstrictor activity in the rabbit saphenous vein (Cohen et al., 1998) and the canine carotid vasculature in vivo (Villalón et al., 1999). Lastly, SB224289, which displays little affinity at the 5-HT_{1F} receptor (Hagan et al., 1997), completely antagonises sumatriptan-induced carotid vasoconstrictor effects (see Fig. 3; De Vries et al., 1998a, 1999b). Notwithstanding, some lines of evidence suggest that a novel 5-HT receptor, possibly identical to that reported by Castro et al. (1997) in human brain, mediates 5-HT-induced constriction of porcine carotid arteriovenous anastomoses (De Vries et al., 1998b). Moreover, the ergot alkaloids ergotamine and dihydroergotamine constrict carotid vessels via 5-HT_{1B} as well as non-5-HT_{1B} receptors (De Vries et al., 1998b; Villalón et al., 1999). Significantly, it was recently shown that the ergot-induced carotid vasoconstriction in the anaesthetised dog is abolished by a combination of 5-$HT_{1B/1D}$ receptor and α_2-adrenoceptor antagonists (Villalón et al., 1999). Possibly, the novel 5-HT receptors and α_2-adrenoceptors can be targeted for future antimigraine drugs.

Over the years, this vascular model, particularly with the measurement of arteriovenous anastomotic blood flow, has proven its worth and has been highly predictive of antimigraine activity in the clinic (Saxena, 1995). Another advantage it offers is that one can simultaneously study a number of major vascular beds in order to evaluate craniovascular selectivity of the drugs. It must, however, be realised that this model will pick up only those putative antimigraine drugs that would be effective by constricting dilated cranial vessels, whatever the mechanism. For example, apart from the ergot alkaloids and triptans (see above), nitric oxide synthase inhibitors, which may have antimigraine activity (Olesen et al., 1994; Lassen et al., 1998), constrict cranial arteriovenous anastomoses (Van Gelderen and Saxena, 1994) and nitric oxide donors, which cause headache, can dilate them (Van Gelderen et al., 1995).

4.1.2. Contraction of isolated cranial blood vessels

A number of isolated blood vessels from several species, including the human cranial arteries, contract in response to acutely acting antimigraine drugs (Saxena et al., 1997; De Vries et al., 1999a; Jansen-Olesen, 1999). This effect is undoubtedly more marked on cranial vessels where, contrary to most peripheral arteries, the 5-HT_{1B} rather than 5-HT_2 receptor is predominant (Longmore et al., 1997). Consistent with their binding profile, the newer triptans resemble sumatriptan in their action and potency. Interestingly, eletriptan and zolmitriptan seem to behave as partial agonists in the dog (Gupta et al., 1999) and rabbit (Martin et al., 1997) saphenous vein compared to sumatriptan. The fact that eletriptan and zolmitriptan are as efficacious as sumatriptan in contracting the carotid vasculature (MacLennan et al., 1998; Willems et al., 1998) could be explained in terms of a larger receptor reserve (Kenakin, 1984) in the carotid circulation compared to that in the isolated saphenous vein.

In a number of isolated blood vessels, such as the canine basilar (Skingle et al., 1996) and coronary (Terrón, 1996) arteries, canine (Skingle et al., 1996) and rabbit (Razzaque et al., 1995) saphenous vein and human middle meningeal artery (Razzaque et al., 1999), the contractile effect of the triptans is antagonised by selective 5-$HT_{1B/1D}$ receptor antagonists. It was recently shown that sumatriptan constricts the isolated human temporal artery via 5-HT_{1B}, but not 5-HT_{1D} receptors (Verheggen et al., 1998). Moreover, 5-HT_{1F} receptor agonists seem to be devoid of vasoconstrictor activity in the rabbit saphenous vein (Cohen et al., 1998). Further studies using selective 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor agonists and antagonists are needed to establish if the 5-HT_{1D} and/or 5-HT_{1F} receptor stimulation are indeed completely devoid of vasoconstrictor action.

Studies in isolated cranial vessels can also be used to investigate if the antimigraine drugs can inhibit neurovascular junction by a presynaptic action. It has still not been unequivocally demonstrated that the triptans inhibit the release of neuropeptides (Saxena et al., 1997, 1998).

4.2. Models based on the involvement of trigeminovascular system in migraine

The proponents of the neuronal mechanism believe that the above described vasoconstrictor action may be unnecessary for antimigraine action and the therapeutic efficacy is due to a presynaptic action on sensory nerve endings, inhibiting neuropeptide release and the process and/or consequence of 'neurogenic' inflammation (Moskowitz, 1992, 1993). In addition, it is contemplated that the antimigraine action also involves inhibition of impulse transmission within the trigeminovascular system centrally (Goadsby, 1997; Goadsby and Knight, 1997).

4.2.1. Inhibition of plasma protein extravasation after stimulation of the trigeminal nerve

In the rat and guinea pig, electrical or chemical stimulation of the trigeminal ganglion induces plasma extravasation in the dura mater, as measured by the increased leakage of iodinated ([^{125}I]) albumin (Markowitz et al., 1987). This plasma extravasation is suggested to be due to the antidromic release of neuropeptides, such as substance P, neurokinin A and CGRP, from sensory trigeminal nerve fibres (see Fig. 4; Moskowitz, 1992). Indeed, tachykinin NK_1 receptor antagonists, such as GR82334 ([D-Pro^9 [Spiro-γ-Lactam] Leu^{10}, Trp^{11}] physalaemin(1–11)) or CP99994 ((2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine), and the CGRP receptor antagonist αCGRP-(8–37) block this effect (O'Shaughnessy and Connor, 1994; Shepheard et al., 1995b), although the latter was devoid of effect in rats (O'Shaughnessy and Connor, 1994).

Sumatriptan inhibits neurogenic plasma protein extravasation (see Moskowitz, 1992, 1993) and this effect is antagonised by the 5-$HT_{1B/1D}$ receptor antagonist GR127935 in both the rat and guinea pig, implying the involvement of 5-HT_{1B} and/or 5-HT_{1D} receptors (Yu et al., 1997). In mice, the receptor mediating the sumatriptan-induced effects resembles the 5-HT_{1B} receptor, since sumatriptan loses its activity in mice lacking this receptor (Yu et al., 1996). On the other hand, in the guinea pig the selective 5-HT_{1D} receptor agonist PNU109291 potently inhibits dural plasma extravasation (Waeber et al., 1997; Ennis et al., 1998). In the rat, mainly based on the lower potency of CP93129 compared to that of sumatriptan, Shepheard et al. (1997) suggested that 5-HT_{1D} rather than 5-HT_{1B} receptors mediate inhibition of plasma protein extravasation.

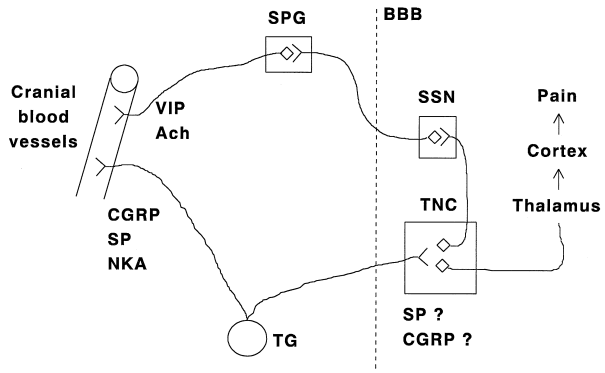

Fig. 4. Schematic representation of the trigeminal innervation of cranial extracerebral vasculature. Cranial blood vessels are innervated by (1) afferent sensory fibres from the first division (ophthalmic) of the trigeminal nerve; and (2) by efferent parasympathetic fibres from the facial nerve. The trigeminal nerve is connected with the facial nerve via a brain stem reflex involving synapses in the trigeminal nucleus caudalis (TNC), superior salivatory nucleus (SSN) and sphenopalatine ganglion (SPG). Redrawn with permission from Goadsby (1997). CGRP, calcitonin gene related peptide; SP, substance P; NKA, neurokinin A; VIP, vasoactive intestinal peptide; Ach, acetylcholine; BBB, blood brain barrier; TG, trigeminal ganglion.

Besides 5-HT_{1B} and 5-HT_{1D} receptors, inhibition of neurogenic plasma protein extravasation can also be effected via other receptor mechanisms. Such inhibitions by 5-carboxamidotryptamine (5-CT) and CP122288 (5-methylaminosulphonylmethyl-3-(*N*-methoxy-pyrrolidin-2*R*-yl-methyl)-1*H*-indole) are observed in 5-HT_{1B} receptor knockout mice (Yu et al., 1996) and are not prevented by GR127935 in guinea pigs (Yu et al., 1997). Moreover, CP122288 is more than a thousand times more potent than sumatriptan in rats, which does not correlate with its affinity at the 5-HT_{1B} or 5-HT_{1D} receptor (Shepheard et al., 1997). A part of the action of CP122288 may be via the 5-HT_{1F} receptor where it displays high affinity (see Table 1). Indeed, the selective 5-HT_{1F} receptor agonists, LY334370 and LY344864, inhibit plasma protein extravasation in the guinea pig and rat (Johnson et al., 1997; Phebus et al., 1997). On the other hand, the response to 5-CT, which displays a very low affinity at this receptor (Hoyer et al., 1994), may be mediated by a novel receptor, possibly identical to the novel receptor found in human

brain (Castro et al., 1997) or that mediating porcine carotid vasoconstriction (see above; De Vries et al., 1998b). The neurogenic plasma extravasation can also be inhibited by the $ET_{A/B}$ receptor antagonist bosentan (Brändli et al., 1996) as well as a 5-HT_4 receptor antagonist (Connor and Beattie, 1999).

Importantly, it should be noted that activity in this model does not necessarily translate into effectiveness in migraine. For example, antimigraine efficacy was not observed with CP122288 (in doses devoid of vasoconstrictor action) (Roon et al., 1997), the $ET_{A/B}$ receptor antagonist bosentan (May et al., 1996) as well as the tachykinin NK_1 receptor antagonists, lanipetant (Goldstein et al., 1997) and RPR100893 ((3a*S*,4*S*,7a*S*)-7,7-diphenyl-4-(2-methoxyphenyl)-2-[(*S*)-2-(2-methoxyphenyl) proprionyl] perhydro-isoindol-4-ol) (Diener, 1995). Moreover, May et al. (1998) recently questioned the involvement of plasma extravasation in migraine, based on the lack of retinal permeability changes during migraine attacks. Finally, it may be questioned whether the effectiveness of triptans in this model is due to presynaptic inhibition of neuropeptide release or via a physiological antagonism of vasodilatation (Humphrey and Goadsby, 1994).

4.2.2. Inhibition of cranial vasodilatation (carotid, dural, cortical) induced by trigeminal stimulation

It has been shown in the cat (Lambert et al., 1984), monkey (Goadsby et al., 1986) and guinea-pig (Beattie and Connor, 1994) that electrical stimulation of the trigeminal ganglion decreases carotid vascular resistance. In contrast to plasma protein extravasation, the carotid vasodilatation is not amenable to blockade by CGRP or tachykinin receptor antagonists (Beattie and Connor, 1994; Raval et al., 1999). This vasodilatation seems to be mediated by VIP, since it is blocked by the VIP antagonist [*p*-Cl-D-Phe^6, Leu^{17}]-VIP (Beattie and Connor, 1994) and VIP antiserum (Goadsby and MacDonald, 1985). As depicted in Fig. 4, VIP can be released upon trigeminal stimulation from facial nerve parasympathetic fibres, which are connected with the trigeminal nerve via a brain stem reflex (Lambert et al., 1984; Goadsby, 1997). Interestingly, the ganglion blocking agent hexamethonium abolishes carotid vasodilatation in the cat (Lambert et al., 1984), but not in the guinea pig (Beattie and Connor, 1994). The latter implies that the nerve pathways differ in these two species. In any case, as discussed by Beattie and Connor (1994), it is unlikely that the effects in the guinea pig involve sensory afferent trigeminal fibres, in view of the lack of immunohistochemical evidence for the presence of VIP in these neurones. The vasodilatation within the feline carotid vascular bed following trigeminal ganglion stimulation is inhibited by endothelin ET_B receptor antagonists, such as BQ788 (*N-cis*-2,6-dimethylpiperidinocarbonyl-L-γ-methyl-leucyl-D-1-methoxy-carbonyltryptophanyl-D-norleucin) (Raval et al., 1999). Whether the latter is a result of inhibition of the vascular effects of endogenously released endothelins or modulation of the release of vasorelaxant neuropeptides from parasympathetic or trigeminal sensory nerves remains to be clarified.

It is important to note that sumatriptan fails to inhibit carotid vasodilatation evoked by trigeminal stimulation, as shown in several species (Spokes and Middlefell, 1995; Lambert and Michalicek, 1996; Raval et al., 1999). Additionally, the endothelin $ET_{A/B}$ antagonist bosentan (May et al., 1996), the tachykinin NK_1 antagonists lanipetant (Goldstein et al., 1997) and RPR100893 (Diener, 1995) are ineffective in the acute treatment of migraine.

The dural vasculature also dilates in response to trigeminal stimulation, as demonstrated using Doppler flowmetry in the cat (Lambert and Michalicek, 1993) and rat (Kurosawa et al., 1995). Recently, Shepheard et al. (1997) have developed a technique in the anaesthetised rat enabling them to determine dural blood vessel diameter through a closed cranial window. Electrical stimulation of trigeminal afferents through the cranial window elicits a dilatation of meningeal blood vessels (see Fig. 5; Shepheard et al., 1997; Williamson et al., 1997a,b). In contrast to the neurogenically-induced increase in carotid blood flow mainly via VIP release (see above), this dural vasodilatation is mediated by CGRP; αCGRP-(8-37) potently inhibits the effect, whereas the tachykinin NK_1 receptor antagonist RP67580 (2-[1-amino-2-(2-methoxy phenyl) ethyl]-7,7 diphenyl-4 perhydro-isoindolone-(3a*R*,7a*R*)) is ineffective (Williamson et al., 1997a,b). It should be noted that the increases in vessel diameter were evoked by short, low intensity electrical stimulation, which primarily stimulate trigeminal sensory Aδ-fibres containing only CGRP. In contrast, the dural plasma protein extravasation evoked by longer, higher intensity stimulation, amenable to blockade by tachykinin NK_1 receptor antagonists (see above), seems to involve primarily C-fibres containing substance P (see Shepheard et al., 1997). In this context, it should be noted that stimulation of the trigeminal nerve in humans results in increased levels of CGRP and substance P in jugular venous blood (Goadsby et al., 1988), but during migraine only elevated levels of CGRP are found (Goadsby et al., 1990). Interestingly, species differences seem to exist, since in the cat the trigeminally-induced dural vasodilatation predominantly involves entirely different mechanisms (Lambert et al., 1997).

The neurogenic dural vasodilatation in the rat is dose-dependently reduced by sumatriptan and rizatriptan, probably by inhibiting the release of CGRP (Williamson et al., 1997a,b). Sumatriptan and rizatriptan affect neither vessel diameter per se nor the dilatation produced by exogenous CGRP or substance P (Williamson et al., 1997a). The 5-HT_1 receptor subtype mediating this effect is likely to be the 5-HT_{1B} receptor, in view of the higher potency of CP93129 compared to sumatriptan (Shepheard et al., 1997). Stimulation of the trigeminal ganglion also increases blood flow to facial skin (Escott et al., 1995a) and brain (Goadsby et al., 1997) via the release of CGRP (Goadsby, 1993;

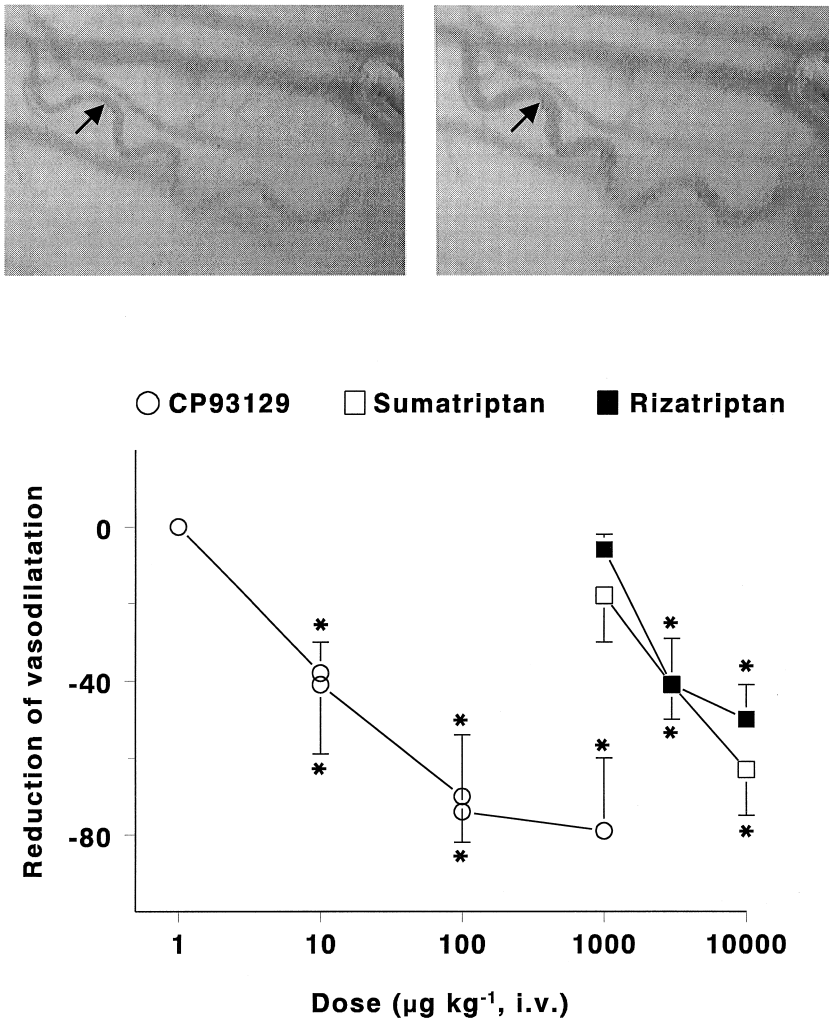

Fig. 5. *Upper panel*. Videomicroscopic image of a branch (30 μm diameter) of the middle meningeal artery (arrow) before (*left panel*) and 30 s after electrical stimulation of perivascular fibres (*right panel*). *Lower panel*. Inhibition of the dural vasodilator response to electrical stimulation of perivascular fibres by CP93129, sumatriptan or rizatriptan. Values are mean ± S.E.M. $^{*}P < 0.05$ vs. control. Taken with permission from Williamson et al. (1997a) and Shepheard et al. (1999).

Escott et al., 1995b). Recently, it was demonstrated that trigeminal stimulation in the cat leads to an increase in nucleus trigeminal caudalis blood flow, being inhibited by intravenously administered sumatriptan (McCall, 1997).

Taken together, it seems that vasodilatation mediated via CGRP release and involving trigeminal sensory Aδ-fibres appears to be a good model for investigating prospective antimigraine drugs. However, it must be realised that the triptans have a low affinity at the rodent 5-HT_{1B} receptor. It is, therefore, of great interest to assess whether this neurogenic dural vasodilatation occurs in other species and, if so, which receptor mechanism is involved.

4.2.3. Central trigeminal neuronal inhibition

Goadsby and colleagues have shown that i.v. administration of zolmitriptan (Goadsby and Hoskin, 1996) as well as naratriptan (Goadsby and Knight, 1997) inhibits action potentials generated in the trigeminal nucleus caudalis after superior sagittal sinus stimulation in the cat. Similarly, in the rts rizatriptan (i.v.) inhibits such potentials evoked by dural stimulation (Cumberbatch et al., 1997). Thus, these drugs exhibit a central inhibitory effect within the trigeminal system and this may partly contribute to their therapeutic effect in migraine (see Fig. 4). However, due to its poor central penetration, i.v. sumatriptan did not affect c-*fos* mRNA expression in the trigeminal nucleus caudalis following trigeminal ganglion stimulation in rats (Shepheard et al., 1995b). This raises the question whether central trigeminal inhibition is predictive of antimigraine potential. On the other hand, it has been argued, though there is little evidence, that the blood brain barrier gets disrupted during migraine. Indeed, after disruption of blood brain barrier by infusion of hyperosmolar mannitol, sumatriptan can inhibit c-*fos* mRNA expression (Shepheard et al., 1995b).

The central trigeminal inhibitory effects of naratriptan in the cat, being susceptible to blockade by GR127935, are

mediated by 5-$HT_{1B/1D}$ receptors (Goadsby and Knight, 1997). Since ketanserin displaced zolmitriptan from its binding sites in the cat brain stem, the involvement of 5-HT_{1D} receptors is likely (Mills et al., 1995). Also, in rats the central trigeminal antinociceptive action of zolmitriptan is mediated by 5-HT_{1D}, but not 5-HT_{1B} receptors (Cumberbatch et al., 1998). Interestingly, CP99994 blocks c-*fos* mRNA expression in the nucleus caudalis in the rat (Shepheard et al., 1995b), but GR205171 ([(2*S*, 3*S*)-2-imethoxy-5-tetrazol-1-yl-benzyl]-(2-phenyl-piperidin-3-yl)-amine dihydrochloride) does not affect the central trigeminal activity as measured electrophysiologically or by c-*fos* expression in the cat (Goadsby et al., 1998). Since both compounds are lipophilic tachykinin NK_1 antagonists, the latter results seem to indicate a species dependent involvement of substance P in the central effects. In any case, the non-lipophilic tachykinin NK_1 receptor antagonists lanipetant (Goldstein et al., 1997) and RPR100893 (Diener, 1995) are ineffective in the acute treatment of migraine, but the clinical efficacy of brain penetrant tachykinin NK_1 receptor antagonists will hopefully provide further insights. It has yet to be established whether CGRP is involved in the central trigeminal inhibition and whether CGRP antagonists are effective in acute migraine therapy.

4.3. Model based on the involvement of cortical spreading depression leading to cranial vasodilatation

The role of cortical spreading depression in migraine (Lauritzen, 1994) is controversial because of difficulty of demonstrating it clinically. However, a promising technique using magnetic resonance imaging, developed by SmithKline Beecham scientists (Smith et al., 1998), offers new opportunities of investigating cortical spreading depression in humans. Meanwhile, animal studies show that cortical spreading depression leads to cranial vasodilatation (Parsons, 1998). Inhibition of this vasodilator response appears to be a novel avenue for developing antimigraine drugs without vasoconstrictor action per se. Indeed, Chan et al. (1999) have recently reported a series of such compounds, in particular SB220453 ((−)-*cis*-6i-acetyl-4*S*-(3-chloro-4-fluoro-benzoylamino)-3,4-dihydro-2,2-dimethyl-2*H*-benzo [*b*] pyran-3*S*-ol; see Fig. 1), which antagonises cortical spreading depression and blocks plasma protein extravasation in rats, but does not interact with 5-HT_{1B} and 5-HT_{1D} receptors. It will be interesting to know whether a drug that prevents cortical spreading depression and/or the consequent cranial vasodilatation would be effective in migraine as a prophylactic and/or acute abortive agent.

4.4. Model for coronary vascular side-effects

In the human isolated coronary artery, 5-HT_2 receptors are more important, but about 20–30% response is mediated by 5-HT_1 receptors (Connor et al., 1989; Bax et al., 1993). Accordingly, sumatriptan moderately constricts the human coronary artery, both in vivo (MacIntyre et al., 1993) and in vitro (MaassenVanDenBrink et al., 1998). Other triptans, for which data are available, are slightly more potent, but show similar efficacy (MaassenVanDenBrink et al., 1998). A correlation analysis of EC_{50} values in the human isolated coronary artery and plasma C_{max} after administration of clinically effective doses suggests that the triptans elicit only a limited coronary constriction in migraine patients without any coronary artery affliction (MaassenVanDenBrink et al., 1998). However, in patients with coronary artery disease (stenosis or hyperreactivity), the second-generation triptans may still cause myocardial ischaemia.

Another interesting point that is brought out by MaassenVanDenBrink et al. (1998) is that the coronary vasoconstrictor effect of ergot alkaloids, but not of the triptans, is resistant to repeated wash and lasts longer. If this finding in human isolated coronary artery holds true for migraine patients, this property of the ergots may be disadvantageous.

5. Conclusions

The seminal discovery of sumatriptan led to the development of new triptans and selective ligands for 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors as well as a better understanding of the disease pathophysiology and a growing number of experimental models for migraine. These experimental models aim at achieving drugs that (i) counteract continued cranial extracerebral vasodilatation either by vasoconstriction or by decreasing neuropeptide release at neurovascular synapse; (ii) inhibit impulse transmission within the trigeminovascular system; and/or (iii) prevent the occurrence of cranial vasodilatation secondary to spreading cortical depression. With regards to the first model the experience has so far been mainly with the ergots and triptans, which primarily act by constricting dilated cranial vessels via 5-HT_{1B} receptors.

The models to study direct vasoconstriction, particularly involving arteriovenous anastomoses, have been highly predictive of therapeutic efficacy in migraine. This cannot be said for the inhibition of neurogenic plasma protein extravasation (mainly involving antidromic release of neurokinins), since several such compounds later proved ineffective in migraine. At least in the rat, triptans do inhibit neurogenic vasodilatation, involving the release of CGRP from Aδ fibres. However, it is yet to be confirmed that CGRP antagonists are effective in acute migraine therapy. Similarly, the antimigraine efficacy of VIP receptor antagonists, which block trigeminally-induced carotid vasodilatation, has not been assessed. Both ergot alkaloids and triptans can interfere with impulse transmission centrally within the trigeminovascular system, but we do not yet know if this property is linked with antimigraine efficacy.

For these reasons, the results of the ongoing clinical trials with selective 5-HT_{1D} and 5-HT_{1F} receptor antagonists, which are claimed to be devoid of vasoconstrictor activity, are awaited with considerable interest. Furthermore, there is now a revival of interest in cortical spreading depression and in compounds that would inhibit either the cortical spreading depression or its consequences, for example cranial extracerebral vasodilatation. One such compound, which binds at novel sites in the brain, has been reported. It is yet to be determined whether such compounds would be effective in migraine and, if so, whether as an abortive or a prophylactic agent.

In view of the research efforts being devoted in developing selective and novel ligands and the use of experimental models incorporating the knowledge of the disease pathophysiology, it is undeniable that acute migraine therapy will continue to evolve in the next millennium. Notwithstanding, we must however also make efforts to advance prophylactic drug therapy in migraine.

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