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REVIEW

Current and prospective pharmacological targets in relation to antimigraine action

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Abstract Migraine is a recurrent incapacitating neurovascular disorder characterized by unilateral and throbbing headaches associated with photophobia, phonophobia, nausea, and vomiting. Current specific drugs used in the acute treatment of migraine interact with vascular receptors, a fact that has raised concerns about their cardiovascular safety. In the past, α-adrenoceptor agonists (ergotamine, dihydroergotamine, isometheptene) were used. The last two decades have witnessed the advent of 5-$HT_{1B/1D}$ receptor agonists (sumatriptan and second-generation triptans), which have a well-established efficacy in the acute treatment of migraine. Moreover, current prophylactic treatments of migraine include 5-HT_2 receptor antagonists, Ca^{2+} channel blockers, and β-adrenoceptor antagonists. Despite the progress in migraine research and in view of its complex etiology, this disease still remains underdiagnosed, and available therapies are underused. In this review, we have discussed pharmacological targets in migraine, with special emphasis on compounds acting on 5-HT (5-HT_{1-7}), adrenergic (α_1, α_2, and β), calcitonin gene-related peptide ($CGRP_1$ and $CGRP_2$), adenosine (A_1, A_2, and A_3), glutamate (NMDA, AMPA, kainate, and metabotropic), dopamine, endothelin, and female hormone (estrogen and progesterone) receptors. In addition, we have considered some other targets, including gamma-aminobutyric acid, angiotensin, bradykinin, histamine, and ionotropic receptors, in relation to antimigraine therapy. Finally, the cardiovascular safety of current and prospective antimigraine therapies is touched upon.

Keywords 5-HT · Antimigraine drugs · CGRP · Noradrenaline · Migraine · Receptors

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Introduction

Migraine is a complex paroxysmal disorder affecting a substantial proportion of the population (Rasmussen et al. 1991), with a 2–3-fold higher prevalence in females than in males (15–18% vs. 6%; Stewart et al. 1992). Migraine is characterized by episodes of usually throbbing, unilateral, and severe headaches, which are in about 15% of patients preceded by reversible focal neurological (mostly visual) 'aura' symptoms that tend to develop gradually over 5 to 20 min and last for less than 60 min (Olesen and Lipton 1994). Migraine attacks may be associated with nausea, vomiting, sensitivity to light and sounds, or movement and, without treatment, typically last 4 to 72 h (Ferrari and Saxena 1993; Olesen and Lipton 1994).

The pathogenesis of migraine headache is not completely understood, but it is thought to involve three key factors, namely, (a) the cranial blood vessels, (b) the trigeminal innervation of these vessels, and (c) the reflex connection

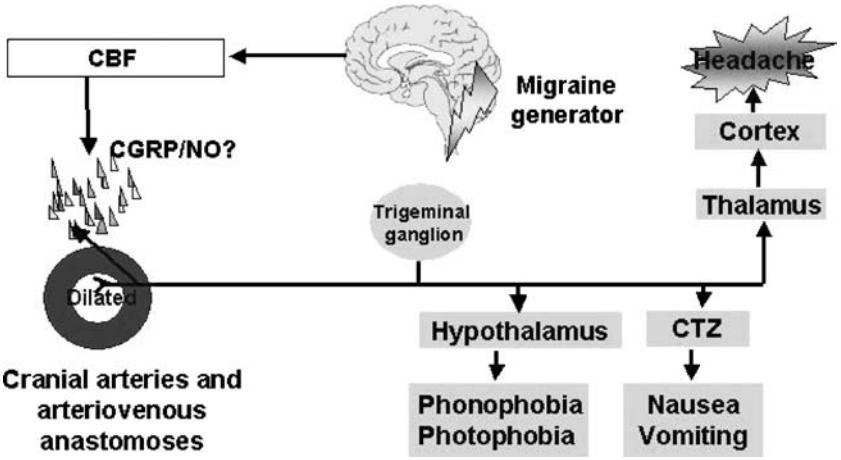

Fig. 1 Schematic representation of the pathophysiology of migraine. The pathophysiologic changes in migraine putatively stem from ion leakage through channels in the brain stem, leading to a decreased cerebral blood flow (*CBF*), possibly owing to cortical spreading depression and, subsequently, neuropeptide release and dilatation of cranial extracerebral blood vessels. The increased pulsation in these blood vessels stimulates the trigeminovascular system, setting in peripheral and central sensitization and leading to headache and associated symptoms (nausea, vomiting, phonophonophobia, and/or photophobia). *CTZ*: Chemoreceptor trigger zone. Redrawn from Saxena and Tfelt-Hansen (2006)

of the trigeminovascular system (Fig. 1) in the cranial parasympathetic outflow (Goadsby et al. 2002a). Although the brain is insensitive to pain, nociceptive stimuli can be generated by large cranial and proximal intracranial blood vessels, as well as by the dura mater. Evidence for peripheral trigeminal activation in migraine is provided by the release of calcitonin gene-related peptide (CGRP; Arulmani et al. 2004; Goadsby and Lance 1990) even though the mechanism of generation of pain is not clear. Studies in animals have suggested that the pain may be caused by a sterile neurogenic inflammatory process in the dura mater (Moskowitz and Cutrer 1993), but this mechanism has not been clearly established to correlate in humans (May et al. 1998). The pain may be an amalgamation of an altered perception—as a result of peripheral and/or central sensitization of craniovascular input that is not usually painful (Burstein et al. 2000) and the activation of a feed-forward neurovascular dilator mechanism that is functionally explicit for the first (ophthalmic) division of the trigeminal nerve (May et al. 2001). Nitric oxide (NO) also seems to be involved in migraine pathophysiology, and inhibition of its synthesis may have therapeutic relevance (Lassen et al. 1998). Cranial vasodilatation during a migraine attack would lead to an enhanced blood volume following each cardiac stroke, with a resultant augmentation in pulsations within the affected blood vessels. The increased pulsations can then be sensed by "stretch" receptors in the vascular wall, and the resultant boost in perivascular (trigeminal) sensory nerve activity provokes headache and other symptoms (Fig. 1; Saxena and Tfelt-Hansen 2006). This trigeminal stimulation may also release neuropeptides, thus reinforcing vasodilatation and perivascular nerve activity (Moskowitz et al. 1989; Villalón et al. 2002).

Receptor subtypes involved in pharmacological treatments of migraine

Both basic research and clinical studies provide evidence for several receptor targets in antimigraine therapy. Several migraine models, based on vascular and neuronal involvement, show that different receptors could be targeted for the development of antimigraine compounds (Arulmani et al. 2006; De Vries et al. 1999b). In this context, it should be emphasized that the currently available migraine models do not entail all facets of this clinically heterogeneous disorder but are rather based on some of the symptoms observed in migraine (e.g., focus on only neuronal or vascular aspects). Thus, no model that mimics all aspects of a migraine attack is available yet. An important vascular in vivo model determines blood flow in porcine carotid arteriovenous anastomoses (Fig. 2). This model is based on the observation from Heyck (1969) that the oxygen saturation difference between the arterial and external jugular venous blood ($OSD_{A\text{-}V}$) was abnormally small during the headache phase of migraine, being consistent with (a) dilatation of carotid arteriovenous anastomoses, (b) the facial paleness and the increase in temporal artery pulsations and swelling of the frontal vein on the side of the headache (Drummond and Lance 1983; Drummond and Lance 1984), and (c) normalization of the decreased $OSD_{A\text{-}V}$ after spontaneous or ergotamine-induced headache relief (Heyck 1969). Other models utilize electrical stimulation of the trigeminal ganglion/nerve to study neurogenic dural inflammation, while the superior sagittal sinus stimulation model takes into account the transmission of trigeminal nociceptive input in the brainstem. More recently, the introduction of integrated models, namely electrical stimulation of the

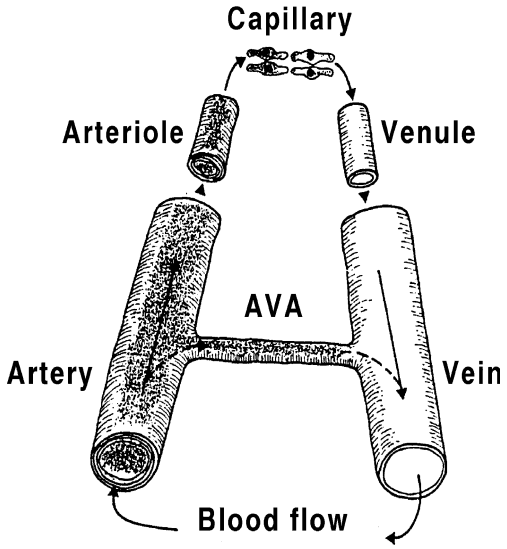

Fig. 2 A schematic representation of a vascular bed containing an arteriovenous anastomosis (*AVA*), which is a precapillary communication between artery and veins. When AVAs are dilated, as proposed to be the case during migraine (Heyck 1969), arterial blood flow will be shunted to the venous side

trigeminal ganglion or systemic administration of capsaicin, has allowed studies on the activation of the trigeminal system and its effects on the cranial vasculature (for review, see Arulmani et al. 2006). This review also contains data on the ability of several drugs to inhibit plasma protein extravasation (e.g., Weiss et al. 2006), although it should be kept in mind that extravasation inhibitors, such as CP-122,288 (Roon et al. 2000), the neurokinin-1 receptor antagonist lanepitant (Goldstein et al. 2001a; Goldstein et al. 1997), and the mixed ET_A/ET_B receptor antagonist bosentan (May et al. 1996) proved ineffective in the treatment of migraine. Thus, the relevance of plasma protein extravasation in migraine is no longer tenable (Peroutka 2005).

On this basis, the present review focuses on recent pharmacological advances in the treatment of migraine, while new therapeutic principles are also presented. The pharmacological targets that will be discussed seem to be promising because of their involvement in either reducing total carotid conductance in porcine or canine migraine models or because of their effects on trigeminovascular nociceptive pathways.

5-HT receptors

Serotonin [5-hydroxytryptamine (5-HT)], being present in high concentrations in enterochromaffin cells of gastrointestinal mucosa and blood platelets, was identified and isolated from the gastrointestinal tract (as enteramine) by Erspamer and colleagues in Italy (Erspamer 1954) and from the blood (as serotonin) by Page and colleagues in the United States (Page 1954). In 1948, the American group deduced that the vasoconstrictor substance serotonin was chemically 5-HT (Rapport et al. 1948) and, shortly afterward, the Italians established that enteramine and 5-HT were identical (Erspamer and Asero 1952). Since then, a number of 5-HT receptors (5-HT_{1-7} and their subtypes) have been identified (Hoyer et al. 1994; Saxena et al. 1998; Saxena and Villalón 1990) as being responsible for a wide host of effects (Villalón and Centurión 2007).

Migraine has been described as a "low 5-HT syndrome", suggesting that 5-HT may play an important role in its pathophysiology and treatment (Anthony and Lance 1989). In this respect, (a) there is an elevation of urinary excretion of 5-hydroxyindole acetic acid, the major metabolite of 5-HT, during migraine attacks (Curran et al. 1965); (b) platelet 5-HT levels were found to drop rapidly during the onset of a migraine attack (Anthony et al. 1967); (c) reserpine, which depletes 5-HT (and noradrenaline), precipitates migraine attacks (Carroll and Hilton 1974); and (d) intravenous injection of 5-HT reduces headache intensity in migraineurs (Anthony et al. 1967; Kimball et al. 1960).

5-HT_1 receptor subtypes

The 5-HT_1 receptor class comprises five different receptor subtypes, which share 41–63% overall sequence identity and couple preferentially to G_i/G_o to inhibit cAMP formation (Lesch and Lerer 1991). One of these, the 5-ht_{1E} receptor, is given a lower-case appellation to denote that, although gene products encoding putative receptors have been identified, no functional role has yet been found.

A number of well-defined selective agonists and antagonists are available to delineate 5-HT_{1A} receptors. The 5-HT_{1A} agonist buspirone was reported to have a prophylactic effect in migraine with anxiety disorder, which was not secondary to its anxiolytic effect (Lee et al. 2005). Further lines of evidence support the hypothesis that migraine without aura is associated with a relative hypersensitivity of central 5-HT_{1A} receptors. This is of relevance given the role of the 5-HT_{1A} receptor in controlling raphe 5-HT neuronal tone and the possible association between migraine, anxiety, and depression (Cassidy et al. 2003). Furthermore, most antimigraine drugs display high affinity for 5-HT_{1A} and/or 5-HT_2 receptor subtypes in human brain (Peroutka 1988). For example, tertatolol, which is a β-adrenoceptor antagonist with 5-HT_{1A} receptor agonist property, decreased porcine carotid blood flow and conductance, indicating active arteriovenous anastomotic constriction. It has therefore been suggested that tertatolol may prove effective in the treatment of migraine (Saxena et al. 1992). However, antimigraine efficacy cannot be explained by drug inter-

actions with a single 5-HT receptor subtype (Peroutka 1988) and, most importantly, several lines of evidence argue against 5-HT_{1A} receptor involvement in the constriction of porcine arteriovenous anastomoses, namely, (a) ipsapirone, a selective 5-HT_{1A} receptor partial agonist, did not induce carotid vasoconstriction (Bom et al. 1988); (b) indorenate, another 5-HT_{1A} receptor agonist, induced porcine carotid vasoconstriction, but metergoline, a drug with higher affinity for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors, failed to significantly antagonize the responses to indorenate, thus concluding that the effect of indorenate was not due to its agonist action on 5-HT_{1A} receptors (Villalón et al. 1990). Therefore, it appears that 5-HT_{1A} receptors do not mediate vasoconstriction in the porcine carotid model and the vascular effects mediated by 5-HT_{1A} receptors seem to be rather limited (if any), while the role of central activation of 5-HT_{1A} receptors in migraine remains speculative.

The unambiguous differentiation of 5-HT_{1B} and 5-HT_{1D} receptor-mediated effects was hampered by the close pharmacological identity of these receptors. However, two antagonists can pharmacologically discriminate between these receptor subtypes, namely, BRL15572 with a 60-fold selectivity for 5-HT_{1D} over 5-HT_{1B} receptors and SB224289 with a 75-fold selectivity for 5-HT_{1B} over 5-HT_{1D} receptors (Price et al. 1997). 5-$HT_{1B/1D}$ receptor agonists induce selective carotid vasoconstriction (Saxena et al. 1998). The 5-HT_{1B} receptor is primarily involved in sumatriptan-induced contractions of human cranial, as well as certain peripheral blood vessels, as illustrated by the observation that vasoconstriction induced by 5-carboxamidotryptamine and sumatriptan is antagonized by SB224289, but not by BRL15572 (van den Broek et al. 2002; Villalón and Centurión 2007; Wackenfors et al. 2005). Moreover, 5-HT_{1D} and 5-HT_{1F} receptors induce presynaptic inhibition of the trigeminovascular inflammatory responses implicated in migraine (Cutrer et al. 1997b; Villalón et al. 2002).

Selective agonists at 5-HT_{1D} (PNU 142633, McCall et al. 2002) and 5-HT_{1F} (LY334370, Phebus et al. 1997) receptors inhibit the trigeminovascular system without inducing vasoconstriction. In addition, a central mechanism of action in blocking the transmission of nociceptive impulses within the trigeminal nucleus caudalis may contribute to the antimigraine effect of LY334370 (Shepheard et al. 1999). Nevertheless, PNU-142633 proved to be ineffective in the acute treatment of migraine (Gómez-Mancilla et al. 2001), while LY334370 did show some efficacy in high doses that may have interacted with 5-HT_{1B} receptors (Goldstein et al. 2001b; Villalón et al. 2002).

There is a high correlation between the potency of various 5-HT_1 receptor agonists in the guinea-pig dural plasma protein extravasation assay and their 5-HT_{1F} receptor binding affinity (Ramadan et al. 2003). However, as previously pointed out, the relevance of plasma protein extravasation in migraine is no longer tenable (Peroutka 2005). Also, 5-HT_{1F} receptors are located on glutamate-containing neurons, and their activation might inhibit glutamate release (Ma 2001), which may be relevant to its antimigraine action (Martínez et al. 1993). Indeed, most triptans show high pK_i values for 5-HT_{1F} receptors (De Vries et al. 1999a; Goadsby and Classey 2003). Thus, although the clinical efficacy of 5-HT_{1F} receptor agonists has not yet unequivocally been demonstrated, some preclinical experiments and clinical observations argue in favor of the potential effectiveness of selective 5-HT_{1F} agonists in migraine.

Since second-generation triptans may be more brain penetrant than sumatriptan (Millson et al. 2000), the relevance of central effects of the triptans should be considered. Although the second-generation triptans have not proven more efficacious than sumatriptan (Saxena and Tfelt-Hansen 2006), they do inhibit trigeminovascular input to the nucleus tractus solitarius via activation of 5-$HT_{1B/1D}$ receptors (Hoskin et al. 2004). In addition, inhibitory actions of 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} receptors in the trigeminocervical complex of the cat have been documented, and 5-HT_{1B} receptor-mediated inhibition is the most potent of the three in terms of inhibition of trigeminovascular nociceptive traffic (Goadsby and Classey 2003). Thus, the 5-HT_{1B} receptor subtype is highly explored in the drug development for migraine, and the present drugs for the acute treatment of migraine (namely triptans) potently stimulate 5-HT_{1B} receptors.

A major disadvantage of triptans is the threat of coronary vasoconstriction (MaassenVanDenBrink et al. 1998), implying that these drugs should not be administered to patients with coronary or cerebrovascular disease (Dodick et al. 2004; Tepper 2001).

5-HT_2 receptor subtypes

The 5-HT_2 receptor class comprises three receptor subtypes (i.e., 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), which exhibit 46–50% overall sequence identity and couple preferentially to G_q/G_{11} to increase the hydrolysis of inositol phosphates elevating cytosolic [Ca^{2+}] (Shih et al. 1991). The anatomical distribution and physiological function of these three receptors appear to be discrete. The 5-HT_{2B} and 5-HT_{2C} receptors display a higher affinity for 5-HT than the 5-HT_{2A} subtype. Although antagonists for each of these receptors are now available, only BW723C86 is known as a selective 5-HT_{2B} receptor agonist. This agonist elicits hypertensive (rather than hypotensive) responses in vagosympathectomized rats (Centurión et al. 2004).

Decreased 5-HT concentrations, as well as an upregulation of 5-HT_2 receptors in platelets, have been observed in

patients with chronic headache, which may be caused by abuse of analgesic substances (Sarchielli et al. 1999). Involvement of the 5-HT_2 receptor in migraine is suggested by the 5-HT_2 receptor antagonist methysergide, which is also a partial agonist at 5-HT_1 receptors, and is used for migraine prophylaxis in severe cases where other preventive drugs are not effective (Silberstein 1998). The 5-$HT_{2A/2C}$ receptor genes have been studied as candidate genes for migraine (Buchwalder et al. 1996), but no mutations in the deduced amino acid sequence of either receptor in the sample of migraineurs was observed. Thus, the authors concluded that DNA-based mutations in the 5-HT_{2A} and 5-HT_{2C} receptors are not generally involved in the pathogenesis of migraine. In contrast, Erdal et al. (2001) reported that the T102C polymorphism of the 5-HT_{2A} receptor gene is related to migraine with aura. Since the sample size used in this study was small, the role of the 5-HT_{2A} receptor in the pathophysiology of migraine or the aura should be considered with caution.

Concerning the 5-HT_{2C} receptor, alternative splicing events yield non-functional isoforms of the 5-HT_{2C} receptor, and as many as seven functional isoforms of the 5-HT_{2C} receptor are produced by adenine deaminase editing of the receptor messenger RNA (mRNA). Although these receptor isoforms show no gross differences in their operational characteristics, they are differentially distributed throughout central and peripheral tissues. The purpose of these isoforms remains speculative, but they may be important in determining cell differences in receptor desensitization, cell-surface distribution, and/or the trafficking of agonist responses through different effector pathways. Thus, there is a need to explore the functions of these isoforms, which might serve as new targets for future antimigraine drugs.

Activation of the 5-HT_{2A} receptor leads to an enhancement of NO production in the trigeminovascular pathway. This NO production may trigger migraine attacks by inducing cerebral vasodilation and sensitization of the perivascular nociceptors and central nociceptive neurons in the trigeminovascular system. Thus, the upregulation of this pronociceptive receptor can increase headache attacks and may contribute to the development of chronic daily headache (Srikiatkhachorn et al. 2002). Also, 5-HT_{2B} receptors, located on endothelial cells of meningeal blood vessels, may trigger migraine headache via the formation of NO. Indeed, 5-HT_{2B} receptor stimulation relaxes the porcine cerebral artery via the release of NO (Schmuck et al. 1996). However, if 5-HT_{2B} receptor antagonists are used in migraine patients, this might lead to coronary side effects as inhibition of NO production may also induce coronary vasoconstriction. Indeed, 5-HT_{2B} receptor mRNA has been demonstrated in human coronary artery (Ishida et al. 1999), and activation of 5-HT_{2B} receptors in human coronary artery induces NO release (Ishida et al. 1998). Selective 5-HT_{2B} receptor antagonists have been described (Forbes et al. 1995; Johnson et al. 2003) and proven efficacious in blocking plasma protein extravasation (Johnson et al. 2003). In addition, 8′-hydroxy-dihydroergotamine, the major metabolite of the antimigraine drug dihydroergotamine, may induce a persistent desensitization of 5-HT_{2B} receptors, which may contribute to its therapeutic efficacy (Schaerlinger et al. 2003). The study of 5-HT_{2B} receptor blockade in migraine prophylaxis is awaited to substantiate the presumed hypersensitivity of these receptors in migraine and, hence, their suspected role in the initiation of the neurogenic inflammatory response (Cohen et al. 1996; Fozard and Kalkman 1994; Kalkman 1994; Schmuck et al. 1996).

5-HT_3, 5-HT_4, 5-$ht_{5A/5B}$, 5-HT_6, and 5-HT_7 receptors

The 5-HT_3 receptor is unique among existing 5-HT receptors in being the only member to belong to the ligand-gated cation channel super-family of receptors (Hoyer 1990; Hoyer et al. 1994). It appears to be located exclusively in neuronal tissue, where it mediates fast depolarization. The receptors are expressed in the central nervous system, as well as in the periphery, where 5-HT_3 receptors are found on autonomic neurons and on neurons of the sensory and enteric nervous system (Barnes and Sharp 1999). Although the 5-HT_4, 5-HT_6, and 5-HT_7 receptors all couple preferentially to G_s and promote cAMP formation, they are classified as distinct receptor classes because they exhibit <40% overall sequence identity with other 5-HT receptors (Hoyer et al. 1994). The 5-ht_5 receptors include two subtypes, namely, (a) the 5-ht_{5A} subtype, which is preferentially coupled to the G_i/G_0 family causing adenylyl cyclase inhibition (Francken et al. 1998; Hurley et al. 1998); (it could also be coupled to inwardly rectifying potassium channels); and (b) the 5-ht_{5B} subtype, the transductional system of which is unknown (see Thomas 2006).

5-HT receptor diversity is increased by the existence of isoforms produced by post-translational modifications. Alternative splicing events yield four functional variants of the 5-HT_4 receptor, i.e., 5-$HT_{4(a)}$–5-$HT_{4(d)}$ (Medhurst et al. 2001; Pindon et al. 2002), and four functional variants of the 5-HT_7 receptor, i.e., 5-$HT_{7(a)}$–5-$HT_{7(d)}$ (Krobert and Levy 2002). The purpose of these isoforms remains speculative, but they may be important in determining cell differences in receptor desensitization, cell-surface distribution, or the trafficking of agonist responses through different effector pathways.

The receptor types mentioned above are not much explored for the development of antimigraine compounds. However, some studies have assessed their role in the

carotid circulation. In one such study, intravenously administered 5-HT was found to be a vasodilator in vivo in the cat dural circulation, and the authors showed that the dilation is not mediated by 5-HT_1, 5-HT_2, 5-HT_4, or 5-HT_7 receptors but primarily mediated by a vagal reflex, initiated via 5-HT_3 receptor activation, and brought about by an increase in parasympathetic tone to the middle meningeal artery as part of the Von Bezold–Jarisch reflex (Lambert et al. 2004). Based on the hypothesis that 5-HT_3 receptor antagonists might well inhibit neurogenic dural inflammation, 5-HT_3 receptor antagonists have been assessed for the treatment of migraine but were unfortunately found to be ineffective (Ferrari 1991). This lack of effectiveness could possibly be explained by their complex, bell-shaped, dose–response relationship, but further trials with adjusted doses were prevented by their alleged toxicity upon chronic administration (Ferrari 1991). A clinical indication of 5-HT_3 receptor antagonists is the prevention of emesis (Hasler 1999). Indeed, control of migraine-associated nausea and vomiting is often achieved with the benzamide dopamine D_2 receptor antagonist metoclopramide (Dahlöf and Hargreaves 1998), which also has 5-HT_3 receptor antagonist activity and reproducibly stimulates gastric motility to increase the availability of orally administered drugs and is thus used in the treatment of migraine (Dahlöf and Hargreaves 1998).

There is evidence to suggest that 5-HT_7 receptors may play a role in central nervous system disorders, including anxiety and cognitive disturbances and also migraine, probably via both peripheral and central mechanisms (Thomas and Hagan 2004). Indeed, mRNA of 5-HT_7 receptors is present in trigeminal ganglia (Terrón et al. 2001). Since dilatation of cranial blood vessels has been proposed to play an important role in the pathogenesis of a migraine attack (Villalón et al. 2002), 5-HT_7 receptor antagonists could well be effective as prophylactic anti-migraine agents (Terrón et al. 2001). A number of 5-HT_7 receptor-selective antagonists, including SB-269970A, SB-258741, and SB-656104A, have been developed (Pouzet 2002; Thomas and Hagan 2004) but, obviously, clinical trials are needed to accept or reject their proposed mechanism of action.

Adrenoceptors

The endogenous catecholamines noradrenaline and adrenaline, which are released upon activation of the sympathetic nervous system, play an essential role in the regulation of a host of physiological responses. Several decades ago, adrenoceptors were introduced to explain the difference in actions of noradrenaline and adrenaline (see Hein and Kobilka 1995). Adrenoceptors are found in nearly all peripheral tissues and on many neuronal populations within the central nervous system. Both noradrenaline and adrenaline play important roles in the control of blood pressure, myocardial contractile rate and force, airway reactivity, and a variety of metabolic and central nervous system functions (Hoffman 2001). Agonists and antagonists interacting with adrenoceptors have proven useful in the treatment of a variety of diseases, including hypertension, angina pectoris, congestive heart failure, asthma, depression, benign prostatic hypertrophy, and glaucoma (Hoffman 2001).

Adrenoceptors can be divided into two major types, the α- and β-adrenoceptors (Bylund et al. 1994), which can be further subdivided into several subtypes based on molecular and pharmacological characteristics, although species orthologs of some adrenoceptor subtypes have been identified (Bylund et al. 1995). α_1-Adrenoceptors mediate their actions through stimulation of inositol phosphate release (Michelotti et al. 2000), while β-adrenoceptors stimulate (Stiles et al. 1984) and α_2-adrenoceptors inhibit (Limbird 1988) adenylyl cyclase.

α_{1A}- α_{1B}-, and α_{1D}-adrenoceptor subtypes

Cloning has identified three α_1-adrenoceptor subtypes. The α_{1B}-adrenoceptor from the DDT cell line (hamster smooth muscle) was cloned first (Cotecchia et al. 1988), followed by the α_{1A} subtype (Ford et al. 1994; Hieble et al. 1995). A third α_1-adrenoceptor was cloned from rat cortex and designated as the α_{1A}-adrenoceptor (Lomasney et al. 1991). However, an identical recombinant rat α_1-adrenoceptor subtype was independently identified by Perez et al. (1991) and denoted the α_{1D}-adrenoceptor. A fourth α_1-adrenoceptor subtype has been postulated and is designated as α_{1L} based on its low affinity for prazosin (Oshita et al. 1991).

α_1-Adrenoceptors are G-protein-coupled receptors and mediate their responses via a $G_{q/11}$ mechanism (Michelotti et al. 2000). This involves activation of phospholipase C-dependent hydrolysis of phosphatidyl 4,5-biphosphate generating inositol 1,4,5 -trisphosphate (IP_3), which acts on the IP_3 receptor in the endoplasmic reticulum to release stored Ca^{2+} and diacylglycerol that (together with Ca^{2+}) can activate protein kinase C. Production of these second messengers activates both voltage-dependent and voltage-independent Ca^{2+} -channels, leading to smooth muscle contraction in both vascular and non-vascular tissues (e.g., prostate, vas deferens, and heart).

In line with the findings suggesting that carotid arteriovenous anastomoses dilate and could play an important role in the pathogenesis of migraine (Heyck 1969), it is reasonable to assume that compounds that induce a cranioselective vasoconstriction may have potential therapeutic use in the treatment of migraine (Willems et al. 2003). The α_{1A}-adrenoceptor is the main subtype of α_1-

adrenoceptors regulating systemic vascular resistance and blood pressure (Docherty 1998; Vargas and Gorman 1995). In view of its widespread distribution, it is rather unlikely that a selective α_{1A}-adrenoceptor agonist would be useful in the treatment of migraine. Considering this standpoint, the α_{1B}-adrenoceptor is a motivating target for future antimigraine drugs, especially when considering that this receptor does not seem to be much involved in the constriction of the systemic vasculature (Piascik et al. 1997; Vargas and Gorman 1995), and, predominantly, α_{1A}-, but not α_{1B}- (or α_{1D}-), adrenoceptors mediate the hypertensive effect induced by intravenous administration of phenylephrine in anesthetized pigs. Figure 3 (left panel) depicts the involvement of α_1-adrenoceptor subtypes in the carotid vasculature (Willems et al. 2001b). In addition, studies in mice have provided several clues to help elucidate subtype-specific physiological functions, for instance, α_{1A}- and α_{1D}-adrenoceptor subtypes play an important role in the regulation of blood pressure (Tanoue et al. 2003). Thus, these subtypes should not be explored for the development of novel antimigraine drugs, although such subtype-selective antagonists might be desirable antihypertensive agents. Therefore, a selective α_{1B}-adrenoceptor agonist could have advantages over the currently available acute antimigraine drugs, which all constrict the human isolated coronary artery (MaassenVanDenBrink et al. 1998; MaassenVanDenBrink et al. 2000).

Using a closed cranial window model, the rat dural vasodilatation in response to electrical stimulation is not affected by pretreatment with an α_1-adrenoceptor agonist (phenylephrine) or its antagonist (corynanthine; Akerman et al. 2001). Although these results suggest that the adrenergic system does not play a significant role in neurogenic dural vasodilatation, the porcine studies mentioned above do suggest that α-adrenoceptor agonists should still be considered for the development of potential antimigraine drugs. Moreover, studies on human subjects suggest that migraineurs have sympathetic hypofunction (Boccuni et al. 1989; Peroutka 2004). Accordingly, drugs targeting on subtypes of α_1-adrenoceptors, which lack systemic vasoconstriction, could hold a promising future in antimigraine therapy.

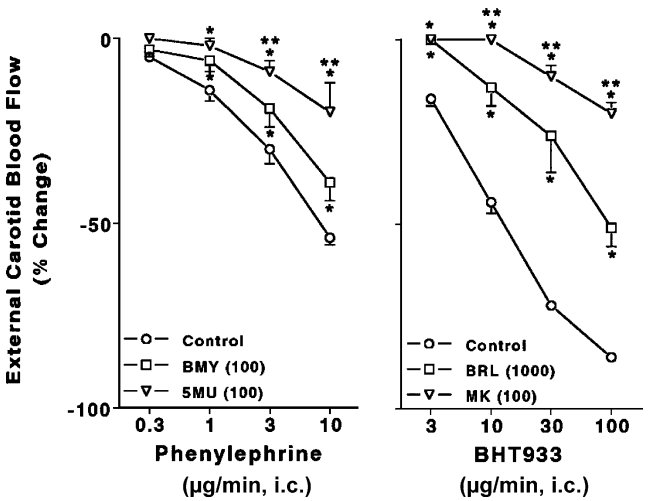

Fig. 3 The effect of α_1 (phenylephrine)- and α_2 (BHT933)-adrenoceptor agonists inducing vasoconstriction in the canine external carotid circulation. Animals were pretreated with the α_1-adrenoceptor antagonists 5-methylurapidil (*5MU*) and BMY 7378 (*BMY*) or the α_2-adrenoceptor antagonists BRL44408 (*BRL*) and MK-912 (*MK*; Willems et al. 2001a). *, P<0.05 vs. corresponding dose of agonist in control curve. **, P<0.05 vs. corresponding dose of agonist after administration of the first antagonist (i.e. BMY 7378 in the left panel and BRL44408 in the right panel)

α_{2A}, α_{2B}, and α_{2C}-adrenoceptor subtypes

Evidence for the existence of α_2-adrenoceptor subtypes has come from binding and functional studies in various tissues and cell lines and, more recently, from cells transfected with the cDNA for the receptors (Bylund 1992). On the basis of these studies, three genetic and four pharmacologically distinct α_2-adrenoceptor subtypes have been defined. The α_{2A}-adrenoceptor subtype, for which prazosin has a relatively low affinity and oxymetazoline a relatively high affinity (Bylund 1988), has been cloned from humans (Kobilka et al. 1987). The second subtype, the α_{2B}-adrenoceptor, has been identified in neonatal rat lung and in NG108 cells (Bylund et al. 1988). This subtype has a relatively high affinity for prazosin and a low affinity for oxymetazoline (Weinshank et al. 1990). A third subtype, the α_{2C}-adrenoceptor, has been identified in an opossum kidney cell line and cloned from human kidney (Murphy and Bylund 1988; Regan et al. 1988). Although this subtype has a relatively high affinity for prazosin and a low affinity for oxymetazoline, it is pharmacologically distinct from the α_{2B} subtype (Blaxall et al. 1991). A fourth pharmacological subtype, the α_{2D}, has been identified in the rat salivary gland (Michel et al. 1989) and in the bovine pineal gland (Simonneaux et al. 1991) and has been cloned from the rat (Lanier et al. 1991). On the basis of the predicted amino acid sequence, the α_{2D} is a species orthologue of the human α_{2A} subtype, and thus, it is not considered to be a separate subtype.

The role of these subtypes as potential targets in the treatment of migraine has been elucidated in porcine and canine migraine models. Studies on these models showed that the canine carotid vascular responses to the α_2-adrenoceptor agonist BHT933 were markedly attenuated by the α_{2A}-adrenoceptor antagonist BRL44408 or the α_{2C}-adrenoceptor antagonist MK912 (given either alone or in combination) but remained unaffected after administration of the α_{2B}-adrenoceptor antagonist imiloxan. Figure 3 (right panel) illustrates the effect of α_2-adrenoceptor

subtypes in the canine carotid vascular bed (Willems et al. 2001a). Similarly, the carotid vasoconstrictor responses produced by BHT933 in anesthetized pigs were markedly attenuated by MK912, while the other antagonists were ineffective (Willems et al. 2003). These results suggest that mainly α_{2C}-adrenoceptors mediate vasoconstriction in the carotid circulation of both species (Willems et al. 2002). We also demonstrated the functional role, as well as the mRNA of α_{2C}-adrenoceptors, in the porcine isolated meningeal artery (Mehrotra et al. 2006). Thus, α_{2C}-adrenoceptor agonists could be useful targets for the development of potential antimigraine drugs.

Additionally, other studies have shown the lack of response to clonidine in menstrual migraine, where the authors speculated about a postsynaptic α_2-adrenoceptor hyposensitivity during the premenstrual period (Facchinetti et al. 1989). Indeed, we have demonstrated an increased function of α_2-adrenoceptors in ovariectomized rats suggesting that, if this phenomenon also occurs in humans, it may contribute to the decreased frequency of migraine after menopause (Mehrotra et al. 2007). Furthermore, it has recently been reported that α_2-adrenoceptors produce a specific NMDA-induced nociception in the trigeminal region in male and ovariectomized female rats, while this response was absent in female rats with circulating estrogen (Nag and Mokha 2006). Thus, a transient vulnerability of the neuroendocrine/neurovegetative systems in female migraine patients could be a factor that facilitates the precipitation of migraine attacks. Clearly, more studies are required in this direction and could possibly open new avenues for the pharmaceutical companies to develop subtype-selective agonists.

β-Adrenoceptors

In 1967, two subtypes of the β-adrenoceptor were identified by comparing the rank orders of agonist potency (Ahlquist 1967; Lands et al. 1967). The β_1-adrenoceptor, the dominant receptor in heart and adipose tissue, was equally sensitive to noradrenaline and adrenaline, whereas the β_2-adrenoceptor, responsible for relaxation of vascular, uterine, and airway smooth muscle, was much less sensitive to noradrenaline in comparison with adrenaline (Lands et al. 1967). Highly selective antagonists for both β_1- and β_2-adrenoceptors have been developed, as well as many potent and selective β_2-adrenoceptor agonists. Subsequently, it has become apparent that not all β-adrenoceptor-mediated responses can be classified as either β_1 or β_2, suggesting the existence of at least the β_3-adrenoceptor subtype (Arch et al. 1984; Bond and Clarke 1988). The β_3-adrenoceptor is insensitive to the commonly used β-antagonists and has often been referred to as the 'atypical' β-adrenoceptor. It is unlikely that all of the atypical β-adrenoceptor responses observed have characteristics consistent with those of the β_3-adrenoceptor and, hence, the possibility of additional subtypes cannot be excluded. Pharmacological evidence has been accumulated for a fourth β-adrenoceptor localized in cardiac tissues of various species (Kaumann 1997). This β_4-adrenoceptor is activated with a low potency by noradrenaline and adrenaline and is blocked by β-adrenoceptor antagonists, such as bupranolol and CGP20712A (Galitzky et al. 1997; Sarsero et al. 1998).

Among all β-adrenoceptor blockers, propranolol and, to a lesser extent, metoprolol, underwent the most extensive clinical testing for cardiac disease and served in many clinical trials as reference drugs when β-adrenoceptor blockers were compared with non-adrenergic drugs (Limmroth and Michel 2001). The efficacy of β-adrenoceptor blockers for the prophylaxis of migraine was discovered by chance when patients with migraine, who received β-adrenoceptor blockers for cardiac disorders, observed a significant reduction of migraine frequency (Rabkin et al. 1966). On the other hand, it still remains controversial whether all β-adrenoceptor blockers have a prophylactic efficacy in migraine or it is limited to individual members of this drug class with specific characteristics. β-blockade results in (a) inhibition of noradrenaline release by blocking prejunctiononal β-adrenoceptors (Lakhlani et al. 1994) and (b) a delayed reduction in tyrosine hydroxylase activity, the rate-limiting step in noradrenaline synthesis, in the superior cervical ganglia (Hieble 2000). It is also suggested that lipophilicity (penetration into the central nervous system), membrane-stabilizing effects and intrinsic sympathomimetic activity are relevant for antimigraine efficacy. Moreover, some β-adrenoceptor blockers have high affinity for certain 5-HT receptor subtypes (Cruickshank and Prichard 1994). The β_1-adrenoceptor affinity appears to play a major role in determining prophylactic efficacy since nonselective agents such as propranolol, moderately β_1-selective agents such as metoprolol, and highly β_1-selective drugs such as bisoprolol (van de Ven et al. 1997; Würz et al. 1991) all are effective prophylactics. Thus, concomitant blockade of β_2-adrenoceptors does not appear to be required for effective migraine prophylaxis. While propranolol, metoprolol, oxprenolol, and alprenolol are very lipophilic and, hence, penetrate well into the central nervous system, atenolol, nadolol, and practolol are only slightly or not at all lipophilic (Cruickshank and Prichard 1994). As several members of the latter group, including atenolol (Forssman et al. 1983; Johannsson et al. 1987) and nadolol (Freitag and Diamond 1984; Sudilovsky et al. 1987), have been reported to be effective in the prophylactic treatment of migraine attacks, high lipophilicity and, hence, penetration into the central nervous system does not appear to be required for prophylactic efficacy. The reports on prophylactic efficacy of atenolol (Forssman et al. 1983; Johannsson et al. 1987),

nadolol (Freitag and Diamond 1984; Sudilovsky et al. 1987), and timolol (Stellar et al. 1984; Tfelt-Hansen et al. 1984) suggest that membrane-stabilizing effects are not required to reduce the frequency of migraine attacks. Finally, it should be noted that only β-adrenoceptor antagonists without partial agonist activity are effective in the prophylactic treatment of migraine (Tfelt-Hansen and Rolan 2006).

CGRP receptors

CGRP is one of the most potent endogenous vasodilators. On the basis of pharmacological criteria, it is known that CGRP may act mainly on $CGRP_1$ and $CGRP_2$ receptors (Arulmani et al. 2004), with h-α$CGRP_{8–37}$ being a 10-fold more potent antagonist at $CGRP_1$ receptors than at $CGRP_2$ receptors (Quirion et al. 1992). While $CGRP_1$ receptors are widely distributed, $CGRP_2$ receptors have only been described in rat vas deferens and are more sensitive to the linear agonists [ethylamide-$Cys^{2,7}$]h-αCGRP and [acetimidomethyl-$Cys^{2,7}$] h-αCGRP than $CGRP_1$ receptors (Dumont et al. 1997). $CGRP_1$ receptors consist of at least three main different entities, namely, the calcitonin receptor-like receptor (CLR), receptor-activity-modifying protein-1 (RAMP-1; McLatchie et al. 1998), and receptor component protein (RCP; Luebke et al. 1996; Poyner et al. 2002), whereas $CGRP_2$ receptors have not yet been molecularly characterized. The molecular components of $CGRP_1$ receptors that have been demonstrated in the human meningeal artery include CLR, RCP, and RAMPs 1, 2, and 3 (Durham 2004; Gupta et al. 2006a; Jansen-Olesen et al. 2003; Oliver et al. 2002). The results from our laboratory also advocate the presence of $CGRP_1$ receptors in human meningeal (Gupta et al. 2006a) and coronary (Gupta et al. 2006b) arteries, while in human distal coronary artery, there seems to be an additional population of CGRP receptors not complying with the current classification of $CGRP_1$ or $CGRP_2$ receptors (Gupta et al. 2006b). Furthermore, RAMP-1 seems to be functionally rate limiting for CGRP receptor activity in the trigeminal ganglion, suggesting that the increase in function of RAMP-1 might sensitize some individuals to the actions of CGRP in migraine (Zhang et al. 2007).

In the recent past, there has been an upsurge in CGRP research and its notable role in migraine pathophysiology. CGRP immunoreactive fibers originating in the trigeminal ganglion innervate cranial blood vessels (Uddman et al. 1985). In animals, stimulation of these sensory nerve fibers has been shown to cause antidromic release of CGRP and subsequent vasodilatation in the cranial vasculature (Brain and Grant 2004; Goadsby et al. 1988). Indeed, CGRP induces a concentration-dependent relaxation in the middle cerebral artery in a pressurized arteriography model in rats only when CGRP was administered abluminally. This suggests that CGRP-mediated vasodilatation is not mediated by luminally situated receptors but by receptors on the smooth muscle cells (Petersen et al. 2005a). Moreover, CGRP receptor antagonists could also act at a central level, as exemplified by the fact that it modulates nociceptive trigeminovascular transmission in the cat (Storer et al. 2004a). Hence, inhibition of CGRP release or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine (Edvinsson 2004).

Further evidence for a role of CGRP in migraine is provided by the observations that plasma concentrations of CGRP, but not of other neuropeptides, in the jugular venous blood are elevated during the headache phase of migraine (Edvinsson and Goadsby 1994). Furthermore, in migraine patients, (a) a strong correlation was found between plasma CGRP concentrations and migraine headache as the changes in plasma CGRP levels during migraine attacks significantly correlated with the headache intensity (Durham 2004; Iovino et al. 2004; Petersen et al. 2005b); (b) infusion of CGRP produced a migraine-like headache (Olesen et al. 2004); and (c) baseline CGRP levels were increased in migraineurs (Fusayasu et al. 2007).

An important breakthrough in the field of CGRP was the development of the potent and selective CGRP receptor antagonist olcegepant (BIBN4096BS; Doods et al. 2000). In in vivo animal models of migraine, olcegepant attenuated the vasodilation induced by trigeminal stimulation and capsaicin-induced carotid arteriovenous anastomotic dilatation (Doods et al. 2000; Edvinsson 2004; Kapoor et al. 2003; Petersen et al. 2005b). In addition, olcegepant has been shown to prevent CGRP-induced headache and extracerebral vasodilatation (Petersen et al. 2005b) but does not significantly affect the induced cerebral hemodynamic changes (Fig. 4). Data from a clinical proof-of-concept study demonstrate the effectiveness of olcegepant in the acute treatment of migraine, with the response rate being similar to oral triptans (Olesen et al. 2004). These lines of evidence are in accordance with recent findings in a larger, ramdomized controlled trial of the orally available CGRP receptor antagonist MK-0974 (Ho et al. 2008), which, similar to olcegepant, is a potent antagonist of the human CGRP receptors (Salvatore et al. 2008). Since olcegepant does not induce vasoconstriction per se, this CGRP receptor antagonist has been argued to be safer than triptans, particularly in migraineurs suffering from cardiovascular pathologies. However, it must be highlighted that CGRP has a protective function during coronary ischemia, which was blocked by olcegepant in a Langendorff rat heart model (Chai et al. 2006). Thus, if these findings hold for humans as well, CGRP receptor antagonists, like the triptans, may also be contraindicated in patients with coronary artery disease.

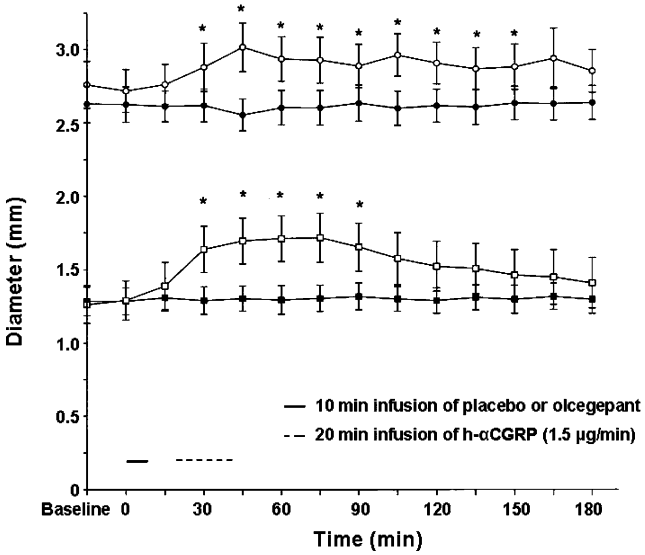

Fig. 4 Diameter of superficial temporal (*squares*) and radial (*circles*) arteries after treatment with placebo (*open symbols*) or olcegepant (2.5 mg, *closed symbols*) measured by high-frequency ultrasound in ten healthy volunteers in double-blind, placebo-controlled crossover study. *Asterisks* denote significant difference ($P<0.05$) between pretreatment with placebo and olcegepant on human α-calcitonin gene-related peptide (*h-αCGRP*)-induced vasodilatation (Petersen et al. 2005b)

Adenosine receptors

Adenosine is present in all body fluids and it differs from ATP in that it is not stored by and released from secretory vesicles. Rather, it exists freely in the cytosol of all cells and is transported in and out of cells mainly via membrane transporters. Adenosine in tissues comes partly from membrane transporters and partly from released ATP or ADP. Adenosine produces many pharmacological effects, both in the periphery and in the central nervous system (Brundege and Dunwiddie 1997). One of its functions appears to be as a protective agent when tissues are threatened (e.g., cardiac or cerebral ischemia), based on its ability to inhibit cell functions and thus minimize the metabolic requirements of the cells. Under less extreme conditions, variations in the adenosine release may play a role in controlling blood flow, matching it to the metabolic needs of the tissue. Adenosine acts on four well-defined G-protein-coupled receptors. These receptors are denoted as adenosine receptors but may also be called P_1-receptors to distinguish them from the receptors for nucleotides, which belong either to the family of transmitter-gated ion channels (P_{2X} receptors) or the family of G-protein-coupled receptors (P_{2Y} receptors). The P_1 receptors are classified as four adenosine receptors, called A_1, A_{2A}, A_{2B}, and A_3, which have been cloned from several mammalian species, including humans (Fredholm et al. 2001). Several studies on knockout and transgenic mice have shown various roles of each of these subtypes (IUPHAR 2006).

Whereas adenosine A_2 receptor gene variation may contribute to the pathogenesis of migraine with aura (Hohoff et al. 2007), adenosine A_1 receptor agonists such as GR79236 seem to have a role in inhibiting trigeminal nociception in humans (Giffin et al. 2003) and could therefore be useful in the treatment of migraine. In the cat, GR79236 induced neuronal inhibition without concomitant vasoconstriction (Goadsby et al. 2002b). In the rat, the adenosine A_1 receptor antagonist DPCPX prevented the inhibitory effect of GR79236 on neurogenic vasodilatation, which was primarily mediated by prejunctional A_1-receptors (Honey et al. 2002). GR79236 has no effect on resting meningeal artery diameter in rats (Honey et al. 2002) and inhibits forskolin-stimulated CGRP release in rats (Carruthers et al. 2001). Likewise, in cats, GR79236 has been shown to significantly reduce the CGRP levels in the external jugular vein (Fig. 5; Goadsby et al. 2002b). However, in pigs, GR79236 has no effect on capsaicin-induced CGRP release (Arulmani et al. 2005), and, consequently, the authors concluded that the antimigraine potential of GR79236 could be due to its postjunctional effects (carotid vasoconstriction) rather than to prejunctional inhibition of trigeminal CGRP release. Thus, although the underlying mechanisms have not yet completely been elucidated, there is evidence that adenosine receptor agonists may be beneficial in the treatment of migraine via neuronal or vascular effects. In view of the latter effects, adenosine receptor stimulation may lead to delayed Ca^{2+} uptake and could, hence, contribute to a delayed cardioprotective effect of adenosine (Ghelardoni et al. 2005), which may have implications for the cardiovascular safety of these compounds.

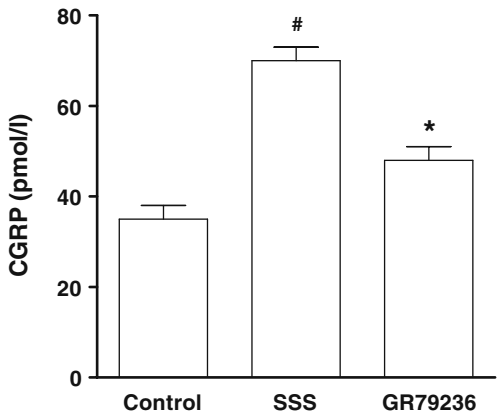

Fig. 5 Cranial CGRP release in anesthetized cats under basal conditions (*control*), after stimulation of the superior sagittal sinus (*SSS*), and after SSS in animals pretreated with the adenosine A_1 receptor agonist GR79236 (30 µg/kg, i.v.). #$P<0.05$ compared to control; *$P<0.05$ compared to SSS (Goadsby et al. 2002b)

ATP and its breakdown products adenosine monophosphate and adenosine are potent dilatators of cerebral blood vessels. During ischemia, ATP binding to metabotropic P_{2Y}-receptors on endothelial cells results in release of NO, which diffuses to the vascular smooth muscles causing vasodilatation and hyperemia (Burnstock 2000). Additionally, ATP contributes to pain in migraine by activating nociceptive terminals of primary afferents located near the basal cerebral and dural vasculature where P_{2X}-receptor subtypes, which are sensitive to the lowered extracellular pH, are suggested to be responsible for excitatory effects on trigeminal sensory neurons (Cook and McCleskey 1997; Cook et al. 1997; Hamilton and McMahon 2000). Furthermore, Zimmermann et al. (2002) showed that ATP (a) has a poor, if any, direct CGRP releasing effect on trigeminal nerve endings in the dura; (b) may contribute to pain in migraine by facilitating nociceptor responses to tissue acidosis via the P_{2Y}-receptor; and (c) may involve release of endogenous prostaglandins. Recently, P_{2X3}-receptors have been shown to be upregulated in trigeminal neurons by CGRP; thus, this mechanism might contribute to pain sensitization and could represent a model of neuronal plasticity in response to a migraine mediator (Fabbretti et al. 2006). Therefore, further research in migraine should focus on the role of P_2-receptors, their subtypes, and how they are implicated in migraine pathophysiology.

Glutamate receptors

Glutamate and its receptors play a major excitatory role in the brain (for references, see Cyr et al. 2001). The effects of glutamate on brain excitability are mediated via the ionotropic NMDA, AMPA, and kainate receptors, as well as the metabotropic glutamate receptor (Sang et al. 2004). Glutamate-like immunoreactivity has been seen in the dental pulp neurons that project to the trigeminal nucleus caudalis (TNC) in the rat (Clements et al. 1991). Indeed, all the major receptor classes of glutamate have been identified in the superficial lamina of the rat trigeminal nucleus caudalis (Tallaksen-Greene et al. 1992). Stimulation of the trigeminal nerve increases extracellular glutamate, which in turn excites TNC neurons (Quartu et al. 2002; Sahara et al. 1997). As glutamate receptors are co-localized in neurons in the trigeminal ganglion with 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, 5-HT_1 autoreceptors may presynaptically inhibit the release of glutamate (Ma 2001). Since glutamate may be involved in the cortical hyperexcitability typical of migraine (Goadsby 2005), the above ionotropic glutamate receptors are being studied as potential antimigraine targets (Sang et al. 2004).

The NMDA receptor antagonist MK-801 and the AMPA receptor antagonist GYKI-52466 are effective in blocking trigeminovascular nociception in the trigeminocervical nucleus (Classey et al. 2001; Goadsby and Classey 2000; Storer and Goadsby 1999). In addition, the NMDA receptor antagonists MK-801 and AP-5 reduce capsaicin-evoked CGRP release (Garry et al. 2000), pointing to potential vascular effects of glutamate receptor antagonists (Jackson and Hargreaves 1999).

Blockade of both NMDA and non-NMDA ionotropic receptors reduces the *c-fos* protein expression in the trigeminal nucleus caudalis after intracisternal capsaicin injection (Mitsikostas et al. 1999; Mitsikostas et al. 1998). Indeed, the mixed AMPA/kainate receptor antagonist LY293558 has been shown to be effective in the acute treatment of migraine (Sang et al. 2004). Also lamotrigine, a sodium channel blocker with antiglutamatergic actions, seemed highly effective in reducing migraine aura and migraine attacks in a controlled open study (Lampl et al. 2005). Similarly, the anticonvulsant topiramate is effective in migraine prophylaxis (Brandes et al. 2004; Diener et al. 2004; Silberstein et al. 2004). This effect may be mediated by blockade on voltage-activated Na^+ and Ca^{2+} channels and/or blockade of AMPA and kainate receptors.

Interestingly, patients taking nitroglycerin for reducing the risk of developing cardiac ischemia or infarction often complain of headache. In these patients, infusion of ketamine, a NMDA receptor antagonist, in concurrence with fentanyl for postoperative pain relief, was proposed to be effective against this NO-induced headache (Roffey et al. 2001). Moreover, in a small open-label study, intranasal ketamine was reported to reproducibly reduce the severity and duration of the neurologic deficits due to the aura in five out of 11 patients with familial hemiplegic migraine (FHM; Kaube et al. 2000). Remarkably, in a subpopulation of patients with FHM, a mutation in the gene encoding for the glutamate transporter, which decreases the expression of the transporter, has been reported (Jen et al. 2005). This mutation may increase the levels of glutamate, leading to cortical hyperexcitability. On the other hand, there is ample evidence, both from basic and clinical studies, that decreased concentrations of ionized magnesium (Mg^{2+}) are associated with a decreased threshold for triggering a migraine attack (Mody et al. 1987; Ramadan et al. 1989; Sarchielli et al. 1992). Decreased Mg^{2+} concentrations also can activate NMDA receptors and, thus, can increase neuronal excitability. In agreement with this hypothesis, the infusion of Mg^{2+} provided sustained headache relief (Bigal et al. 2002), and oral Mg^{2+} has been demonstrated to be an effective prophylactic in menstrual migraine (Facchinetti et al. 1991). Thus, glutamate receptor modulators seem to be of benefit in migraine treatment; indeed, the NMDA receptor antagonist memantine and the NR2B subunit containing antagonist, CP-101,606, decreased spreading depression (Peeters et al. 2007), a potentially important factor in

migraine pathophysiology. However, stronger basic and clinical evidence for the delineation of their exact role in the pathogenesis of migraine, as well as their cardiovascular safety, is awaited with great interest.

Dopamine receptors

Dopamine is a catecholamine that serves as a neurotransmitter in the brain (Carlsson et al. 1957; Carlsson et al. 1958). Dopamine is synthesized from tyrosine, which is sequentially converted to L-dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase. L-DOPA is then converted to dopamine in cytoplasm by the enzyme DOPA decarboxylase (Hoffman 2001). The distribution of dopamine in the brain is highly non-uniform and more restricted than the distribution of noradrenaline. A large proportion of the dopamine content in the brain is found in the corpus striatum and the limbic system. Dopaminergic neurons lack dopamine β-hydroxylase and thus do not produce noradrenaline. Pharmacological evidence suggests that dopaminergic neurons have a role in the production of nausea and vomiting. Dopamine exerts its action by five receptor subtypes that have been cloned. The D_1-like receptors (D_1 and D_5) are closely related G-protein-coupled receptors ($G_{s\alpha}$-protein subunit) that stimulate adenylyl cyclase activity. In contrast, D_2-like receptors (D_2, D_3, and D_4) are coupled to $G_{i\alpha}$-protein subunits with a similar pharmacology and inhibit the formation of cAMP. Their isoforms are encoded by homologous genes displaying several introns (Alexander et al. 2007).

The vascular and nervous systems, both likely to be involved in migraine pathophysiology, both respond to dopamine (Akerman and Goadsby 2007). Dopamine and related receptor agonists have vasoactive effects on blood vessels in vitro and in vivo, inducing vasoconstriction or vasodilatation, depending on the species, vascular bed, and dose (Hughes et al. 1986; Smith et al. 1990; Takenaka et al. 1993; Villalón et al. 2003; Yu et al. 2002).

The dopamine agonist lisuride is useful in the prophylaxis of migraine (Del Bene et al. 1983; Herrmann et al. 1978; Somerville and Herrmann 1978), although its exact mechanism of action is still to be unraveled. As lisuride is an extremely potent 5-HT_{2B} receptor antagonist (Hofmann et al. 2006), it is reasonable to assume that the antimigraine action of this drug could be mediated, at least partly, via blockade of 5-HT_{2B} receptors. More recently, haloperidol, which blocks D_1, D_2, 5-HT_2, H_1, and α_2-adrenergic receptors in the brain, was reported to be effective in the acute treatment of migraine in a randomized, double-blind, placebo-controlled study, although the majority of patients suffered from side effects (Honkaniemi et al. 2006). Dopamine causes vasoconstriction in rat dural arteries, but this effect is most likely mediated by α_2-adrenoceptors and not dopamine receptors (Akerman and Goadsby 2005). In addition, dopamine-containing neurons may play a role in modulating trigeminovascular nociception; when dopamine was administered microiontophoretically (and not intravenously), it inhibited the activation of trigeminocervical neurons in response to middle meningeal artery stimulation (Bergerot et al. 2007). Furthermore, pharmacological studies with dopaminergic agonists like apomorphine suggest that migraineurs may present a dopaminergic hypersensitivity, even interictally (Blin et al. 1991; Cerbo et al. 1997; Peroutka 1997). The increased density of D_5, D_3, and D_4 receptors in blood lymphocytes in migraine patients may reflect the dopaminergic hypersensitivity and may thus represent a relatively simple and reliable peripheral marker of altered dopaminergic function (Barbanti et al. 1996; Barbanti et al. 2000). In addition, high platelet levels of dopamine have been observed in migraineurs (D'Andrea et al. 2006). Several association studies on D_2-like receptors and migraine with or without aura have been reported, but with contradictory results (Maude et al. 2001; Mochi et al. 2003; Peroutka et al. 1998; Peroutka et al. 1997). Thus, it appears that if dopamine and its receptors are at all involved in the pathophysiology of migraine, the exact mechanism of action still remains unclear.

Endothelin receptors

Endothelin was identified by Yanagisawa et al. (1988), who isolated, analyzed, and cloned the gene of this potent vasoconstrictor in a very short space of time. There are three isoforms of endothelin, namely, ET-1, ET-2, and ET-3, which are variably distributed and derived from separate genes. ET-1 is the main isoform and is produced in the cardiovascular system, ET-2 is mainly produced in the kidney and intestines, whereas ET-3 is predominant in the central nervous system. ET-1 mediates its action through binding to specific G-protein-coupled receptors, ET_A and ET_B. ET_A receptors are mainly present in vascular smooth muscle and mediate vasoconstriction and cell proliferation, whereas activation of ET_B receptors present in endothelial cells causes NO-induced vasodilatation and prostacyclin release (Attina et al. 2005).

Increased peripheral plasma levels of ET-1 (Hasselblatt et al. 1999; Kallela et al. 1998), even several hours after a migraine attack (Farkkila et al. 1992), led to suggest the involvement of ET-1 in migraine pathogenesis. Evidence of association of migraine and the ET_A receptor gene polymorphism (ETA-231 A/G) in a French population-based study (Tzourio et al. 2001) has added a new candidate gene for migraine. In rats, ET-1 is one of the most potent inducers of Leão's spreading depression

(Dreier et al. 2002), but Goadsby et al. (1996) reported no effect of endothelin receptor antagonists in preventing spreading depression in cats. The major setback for the hypothesis of involvement of ET-1 in migraine pathogenesis comes from a study showing the lack of efficacy of the mixed ET_A/ET_B receptor antagonist bosentan in migraine (May et al. 1996). However, the ET_A and ET_B receptors are likely to mediate opposite effects, and it is feasible that more selective endothelin receptor antagonists may be effective in the acute treatment of migraine. In addition, the efficacy of endothelin receptor antagonists in migraine prophylaxis is still to be evaluated.

Female sex hormone (estrogen and progesterone) receptors

The female sex steroid hormones estrogen and progesterone regulate numerous biological functions via two main mechanisms, which are mediated by genomic (transcription-dependent) and/or non-genomic (transcription independent) pathways (Kelly and Levin 2001; Lau 2002; Orshal and Khalil 2004). Ovarian steroids are lipophilic in nature, and their low molecular weight allows them to cross the blood–brain barrier by passive diffusion (Aloisi 2003). In the central nervous system, these hormones induce a wide array of physiological effects.

The genomic actions of sex steroids encompass two different receptors (ERα and ERβ) for estrogens (Enmark and Gustafsson 1999), as well as two receptors (PR-A and PR-B) for progesterone (Kastner et al. 1990). While female sex steroids do not seem to be involved in the pathogenesis of migraine per se, they may modulate several mediators and/or receptor systems via both genomic and non-genomic mechanisms. These actions may be perpetuated at the central nervous system, as well as at the peripheral (neuro) vascular level (Gupta et al. 2007). The receptors of both estrogen and progesterone alter receptor expression and release, as well as synthesis of various neurotransmitters and hormones. For example, CGRP, a facilitator of pain transmission and a potent vasodilator (Bennett et al. 2000; Powell et al. 2000), neuropeptide Y, a regulator of inflammation and central nociception (Silva et al. 2002), as well as the neurotransmitters glutamate (Zhang and Bhavnani 2005), and 5-HT (Smith et al. 2004) have been reported to be genomically modulated by sex steroids. Remarkably, progesterone can act in a synergistic, antagonistic, or neutral manner compared to the effects of estrogens (Attali et al. 1997; Becker and Rudick 1999; Dluzen and Ramírez 1989; Fernández-Ruíz et al. 1990; Hernández et al. 1991). The receptors and mechanisms involved in their non-genomic action are not yet completely deciphered (Gupta et al. 2007; Martin and Behbehani 2006).

Primary evidence for the involvement of female sex hormones in migraine pathogenesis comes from the facts that the prevalence of migraine is 2–3-fold higher in women than in men (Lipton et al. 2001; Stewart et al. 1992) and that reproductive milestones such as menarche, pregnancy, and menopause are associated with changes in migraine frequency and/or severity (Silberstein 2000). Interestingly, individuals with a polymorphism at G594 (exon 8) of the estrogen receptor-1 (ESR1) gene are twice more likely to suffer from migraine than those with the wild-type gene (Colson et al. 2004). Similarly, individuals carrying the PROGINS inserts of the progesterone receptor gene polymorphism are twice as likely to suffer from migraine than control subjects (Colson et al. 2005). It is worth mentioning that the estrogen receptor polymorphism increases its expression (Colson et al. 2004), whereas the progesterone receptor polymorphism negatively impacts its expression. Furthermore, it is interesting that the PROGINS allele of the progesterone receptor acts synergistically with the 594A allele of ESR1 to increase the risk of migraine by 3.2 times (Colson et al. 2005).

Hormonal interventions have been explored as a prophylactic treatment of menses-related migraine or migraine experienced during the pill-free period. Oral estrogens (Calhoun 2004; Somerville 1975) and percutaneous estradiol showed benefit during perimenstrual treatment, which was balanced when delayed by estrogen withdrawal, triggering post-dosing migraine immediately after the gel was stopped (MacGregor et al. 2006a). Furthermore, rising levels of estrogen appear to offer some protection against migraine (MacGregor et al. 2006b). Thus, estrogen patches have been utilized to prevent the rapid decline of estrogen levels during the menstrual cycle (MacGregor 2006; MacGregor et al. 2006a; MacGregor et al. 2006b; MacGregor and Hackshaw 2002; Magos et al. 1983), which is thought to be the main trigger of migraine in these patients (MacGregor 2006). These studies have reported mixed results ranging from no improvement to 80% improvement and are also based on a relatively limited number of patients (n=11–38). Taken collectively, there is a strong evidence for the involvement of female sex steroids, especially that of estrogens, but the therapeutic role of estrogen supplements for conditions like menstrual migraine remains to be established.

Miscellaneous receptors and ion channels

GABA receptors

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system. GABA induces inhibitory hyperpolarization effects in neurons, although excitatory responses can be found at certain loci in

embryonic and postnatal life, as well as in adult hippocampal pyramidal neurons. GABA exerts its effects through $GABA_A$ and $GABA_B$ receptors. $GABA_A$ receptors are ligand-gated ion channels sensitive to bicuculline (Barnard et al. 1998), whereas $GABA_B$ receptors are G-protein-coupled receptors insensitive to bicuculline and stimulated by baclofen (Bowery et al. 2002). Also, $GABA_C$ receptors, which are insensitive to bicuculline, benzodiazepines, or barbiturates, have been described, but these receptors are not yet completely characterized (Barnard et al. 1998; Spedding et al. 2002).

GABA may be involved in the pathophysiology of migraine since (a) increased GABA concentrations in cerebrospinal fluid have been reported during a migraine attack (Welch et al. 1975); (b) increased platelet levels of GABA have been observed in patients with tension-type headache (Kowa et al. 1992), although it should be kept in mind that the pathophysiology of migraine and tension-type headache are obviously different; and (c) sodium valproate and muscimol dose dependently inhibit plasma protein extravasation induced by electrical stimulation of the trigeminal ganglion, and these effects are blocked by the $GABA_A$ receptor antagonist bicuculline (Lee et al. 1995). It thus appears that selective agonists of $GABA_A$ receptors could be clinically effective in the treatment of migraine. Consistent with this view, several agonists at GABA receptors have been used as prophylactic antimigraine drugs. In this context, valproate (Cutrer et al. 1997a; Shaygannejad et al. 2006), baclofen in a small open study (Hering-Hanit 1999), and gabapentin (Di Trapani et al. 2000) may prevent migraine attacks, while valproate has also been suggested to be effective in the acute treatment of migraine in another small open trial (Mathew et al. 2000). Despite the above clinical evidence, it should be kept in mind that not all of the aforementioned compounds are selective in their action at GABA receptors, and the mechanisms involved in their antimigraine effect remain unclear. Several studies have shown that valproate inhibits GABA transaminase and activates glutamic acid decarboxylase to increase brain GABA levels. Moreover, GABA may suppress the hyperexcitability observed in aura (Palmer et al. 2000), probably by blocking Na^+ and/or Ca^{2+} channels (Cutrer 2001). Recently, it has been suggested that $GABA_A$ receptors can inhibit trigeminovascular nociceptive transmission in the cat (Storer et al. 2004b). These findings suggest that the development of more selective $GABA_A$ receptor agonists may be fruitful in the treatment of migraine.

Angiotensin receptors

Angiotensin II is an octapeptide derived from angiotensinogen. Angiotensinogen, released from the liver, is converted to angiotensin I by renin released by the kidney. Then, angiotensin I is converted by angiotensin converting enzyme (ACE), mainly located in the lungs, to angiotensin II. Angiotensin II activates two receptor types, AT_1 and AT_2. The AT_1 receptor is involved in the regulation of arterial blood pressure (vasoconstriction), electrolyte balance (antinatriuresis), thirst, hormone secretion (aldosterone), and renal function (De Gasparo et al. 2000). In contrast, AT_2 receptors can produce opposite effects to those by the AT_1 receptor, i.e., natriuresis and vasodilatation (Widdop et al. 2003).

Although the role of angiotensin II in the pathogenesis of migraine is not established, clinical evidence suggests that several ACE inhibitors such as lisinopril and enalapril can be effective in migraine (Bender 1995; Schrader et al. 2001). Moreover, the angiotensin AT_1 receptor antagonist candesartan (Tronvik et al. 2003) also seems to be effective as prophylactic antimigraine drug, which may be generalized to other drugs from the same class as suggested by an open-label study in 24 patients using olmesartan (Charles et al. 2006). In addition, genetic studies suggest an association between ACE gene polymorphisms and migraine (Paterna et al. 2000). Further, ACE activity in migraine with aura is reported to be significantly higher than in migraine without aura and control subjects (Fusayasu et al. 2007). Despite the above evidence, the role of angiotensin II in the pathophysiology of migraine should be clarified in animal models to understand the mechanism(s) of action involved. This could be useful to rationally develop more selective antimigraine drugs interacting with the renin–angiotensin system.

Bradykinin receptors

The nonapeptide bradykinin belongs to the kinin family and is synthesized by cleavage of high and low molecular weight kininogens through serine proteases (kininogenases; Moreau et al. 2005). Plasma and tissue kallikrein are the two main kininogenases. Once released, bradykinin can activate two main receptors (B_1 and B_2), which are G-protein-coupled and linked to activation of phospholipase C (Marceau and Regoli 2004). The B_1 receptor is generally induced during inflammation by lipopolysaccharide and cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factorα, while the B_2 receptor is constitutive and widely distributed in blood vessels. B_1-receptor-mediated effects include vasodilatation, plasma protein extravasation, inflammatory pain, activation of leukocyte-endothelial cell interactions, and leukocyte accumulation.

Bradykinin is involved in inflammatory responses and locally induces release of NO and PGI_2 (prostacyclin) from the endothelium, as well as substance P and CGRP from neurones. Although this peptide could be involved in neurogenic inflammation during a migraine attack (Geppetti et al. 1990), its precise role in migraine pathophysiology is not well established. Since B_1 receptors are expressed

following noxious stimuli and mediate vasodilatation and neurogenic plasma extravasation, B_1-receptor antagonists may be useful as antimigraine drugs. Moreover, several B_2-receptor antagonists have analgesic properties (Moreau et al. 2005), which could be explained by the capability of bradykinin to stimulate primary afferent nerves during inflammation. Thus, both B_1- and B_2-receptor antagonists might potentially be useful in the treatment of migraine.

Histamine receptors

Histamine is a monoamine mainly stored in mast cells in most tissues. Histamine plays an important role on allergic responses and in the central nervous system as a neurotransmitter. The effects of histamine are mediated by four receptors (H_1, H_2, H_3, and H_4). The H_1 receptor is positively coupled to phospholipase C and mediates, among other effects, smooth muscle contraction, release of NO, and increased vascular permeability. The H_2 receptor stimulates adenylyl cyclase and produces smooth muscle relaxation, positive inotropic and chronotropic effects in the heart, and stimulation of gastric secretion. The H_3 and H_4 receptors are both G-protein-coupled receptors mediating inhibition of adenylyl cyclase, but much of their functional role remains to be determined (IUPHAR 2006).

Clinical evidence has suggested that histamine is involved in the pathogenesis of migraine. Intravenous infusion of histamine induces headache, which is blocked by the H_1 receptor antagonist, mepyramine (Lassen et al. 1995). This effect of histamine could be due to activation of endothelial H_1 receptors that release NO (Lassen et al. 1996). Consistent with these views, histamine produces rat dural vasodilatation, which is sensitive to mepyramine (H_1 antagonist), famotidine (H_2 antagonist), and L-NAME, an NO synthase inhibitor (Akerman et al. 2002). In addition, clinical studies indicate that the histamine metabolite and $H_{1/2/3}$ receptor agonist, *N*-α-methyl-histamine (Hill et al. 1997), can be used as a prophylactic antimigraine drug (Millán-Guerrero et al. 2006; Millán-Guerrero et al. 2003). *N*-α-methyl-histamine can block the plasma protein extravasation induced by electrical trigeminal ganglion stimulation (Matsubara et al. 1992) or by capsaicin in rats and guinea pigs. Moreover, the selective H_3 receptor agonist (*R*)-α-methyl-histamine inhibits capsaicin-induced dural plasma extravasation in the rat (Rouleau et al. 1997). Taken together, it appears that antagonists at $H_{1/2}$ receptors or agonists at H_3 receptors could be useful as acute and/or prophylactic antimigraine drugs.

Ion channels

Recently, knowledge on the role of mutant ion channels in the pathogenesis of episodic neurological disorders has emerged (Hanna 2006). Molecular characteristics of genetic channelopathies have contributed to a better understanding of episodic diseases such as migraine, where new mutations in the P/Q-type voltage-gated Ca^{2+} channel gene CACNA1A, the Na^+ /K^+-ATPase gene ATP1A2, as well as the Na^+ channel gene SCN1A have been demonstrated in FHM (for review, see van den Maagdenberg et al. 2007). Ion concentrations may modulate vascular constriction and relaxation, as well as cortical excitability. For example, decreased Mg^{2+} concentrations are associated with cortical spreading depression in animals (Mody et al. 1987). Indeed, there is evidence for low Mg^{2+} levels in brain during (Ramadan et al. 1989) and between (Lodi et al. 1997) migraine attacks. As mentioned above, Ca^{2+} seems to be involved in the pathogenesis of migraine as mutations in P/Q-type Ca^{2+} channels are related to FHM (Ophoff et al. 1996) and, possibly, also to migraine with and without aura (Terwindt et al. 2001). Further, L-type Ca^{2+} channels modulate the release of CGRP in trigeminal neurons innervating the cranial vasculature (Akerman et al. 2003). Ca^{2+} channel blockers such as verapamil (Ramadan et al. 1997) and flunarizine (Buchanan et al. 2004) are used for the prophylactic treatment of migraine. However, the mechanism of action of these Ca^{2+} channel blockers is yet poorly understood.

Implications, future directions, and conclusions

Disregarding the limitations of basic research, a multidisciplinary approach encompassing both basic and clinical observations will inevitably be needed to understand the role of different receptor systems in migraine. As the pathophysiology of migraine has not yet been completely deciphered, experimental models employed in migraine research are based on only a few symptoms observed in the clinical situation. Thus, there is a need to integrate several neuronal and vascular experimental models, as well as clinical observations in migraine research. To investigate the involvement of certain receptors in migraine, multiple agonists and antagonists should be used.

In view of the concern about coronary vasoconstriction induced by vasoactive antimigraine drugs and stimulated by the discovery of genetic ion channel abnormalities in migraine, research has recently focused on the development of neuronally acting antimigraine drugs. More knowledge on the mechanism of action of these (prospective) neuronally active antimigraine drugs may substantially contribute to the (prophylactic) treatment of migraine. On the other hand, many of these drugs are likely to exert (indirect) vascular effects as well, which may contribute to the therapeutic efficacy but also may lead to cardiovascular side effects.

In conclusion, the results obtained with various (pre) clinical models studying the targets mentioned in the present review, such as CGRP receptor antagonists, adenosine receptor agonists, and glutamate receptor antagonists, are eagerly awaited and will undoubtedly shed further light on the pathophysiology of migraine.

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