Acta Neurol. Belg., 2009, **109**, 252-261

CGRP antagonists: hope for a new era in acute migraine treatment

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Abstract

Calcitonin gene-related peptide (CGRP) has a widespread distribution throughout the trigeminovascular system and other brain areas involved in migraine pathogenesis. Serum levels of CGRP are elevated during the migraine attack and return to normal with alleviation of pain. Intravenous injection of CGRP in migraineurs results in delayed headache similar to migraine. Since CGRP receptor antagonists lack direct vasoconstrictor activity, this therapeutic approach may offer advantages over the current mainstay of specific acute migraine treatment with 5-HT1B/1D receptor agonists (triptans), contra-indicated in patients with underlying cardiovascular disease. Intravenous BIBN4096BS (olcegepant) and oral MK-0974 (telcagepant), two CGRP-receptor antagonists, were safe and effective in the treatment of migraine attacks in Phase I and II trials. In a Phase III clinical trial, the efficacy of telcagepant 300 mg was comparable to that of zolmitriptan 5 mg. We intend to review the rationale for the use of CGRP-receptor antagonists, and to outline current developments and future perspectives.

Key words: Neuropeptides; calcitonin-gene related peptide; migraine; CGRP-antagonists; trigeminovascular system.

Introduction

As at least 10% of the population is affected by migraine, characterized by recurrent attacks of debilitating headache, much research has been done to unravel the pathophysiology of this primary headache in the last few decades (Goadsby *et al.*, 2002). Pain during a migraine attack is neurovascular in origin and generated by the activation of the trigeminovascular system (May and Goadsby, 1999). New insights have led to the development of the triptans, which are selective 5-hydroxytryptamine receptor 1B/1D agonists, for the acute treatment of migraine (Buzzi and Moskowitz, 1991). However, triptans can be associated with side effects and potential vasoconstrictor effects make them contra-indicated in patients with cardiovascular disease, uncontrolled hypertension, hemiplegic or basilar-type migraine, and migraine with prolonged aura. Furthermore, the 2-hour pain-free response is at best 30-40% with the available oral triptans and 60% with subcutaneous sumatriptan (Oldman *et al.*, 2002). Attempts to improve treatment of migraine attacks resulted in the design of small calcitonin gene-related peptide (CGRP) receptor antagonists that provided relief for acute attacks, similar to triptans, and have been proven safe and well tolerated in phase I, II and III studies.

CGRP and its receptors

CGRP is a 37 amino acid neuropeptide that was first described in 1982 by Amara and colleagues (Amara *et al.*, 1982). They found that alternative processing of RNA transcripts from the calcitonin gene, located on chromosome 11, resulted in distinct mRNAs for calcitonin in thyroid C cells and CGRP in nervous tissue (Fig. 1). CGRP was later renamed α-CGRP as an isoform, β-CGRP, was described as the product of a second gene in close proximity to α-CGRP, probably arisen through gene duplication (Brain *et al.*, 1986). α-CGRP and β-GCRP differ in 1 amino acid and have different tissue distributions, but are otherwise similar. CGRP is one of the most abundant proteins in both peripheral and central neurons. CGRP acts on the CGRP receptor complex (Fig. 2). Functional CGRP receptors are heterodimers, composed of a seven-transmembrane domain G protein-coupled receptor called calcitonin receptor-like receptor (CALCRL) and the receptor activity-modifying protein 1 or RAMP-1 (Zhang *et al.*, 2007). A third protein, called receptor component protein (RCP) is required for the G-protein-coupled signal transduction. Binding of CGRP to

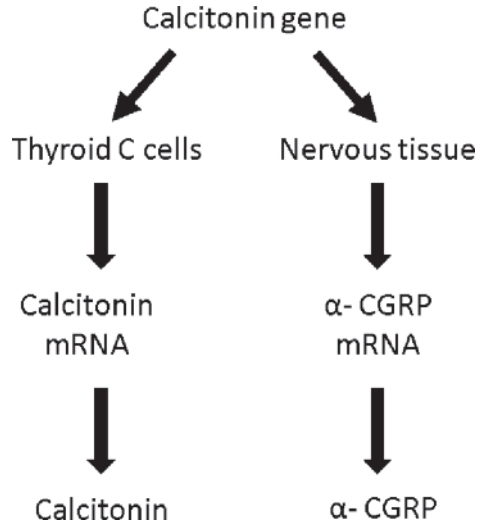

FIG. 1. — Tissue-specific calcitonin gene RNA processing leads to calcitonin or α-CGRP production.

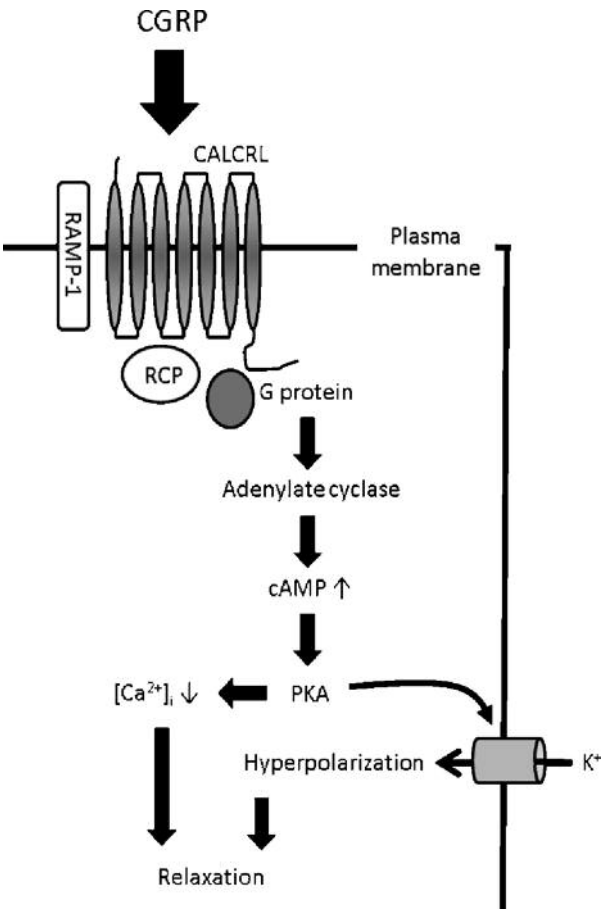

FIG. 2. — CGRP acts on the heteromeric CGRP receptor complex, composed of a seven-transmembrane domain G protein-coupled receptor called calcitonin receptor-like receptor (CALCRL) and a receptor activity-modifying protein (RAMP-1). An additional receptor component protein (RCP) is required for the G-protein-coupled signal transduction. In vascular smooth muscle cells activation of this complex mainly leads to activation of adenylate cyclase, thereby increasing intracellular cAMP level, which causes smooth muscle cell relaxation through hyperpolarization by activation of ATP-sensitive potassium (K_{ATP}) channels through a cAMP-mediated enhancement of protein kinase A (PKA) activity. PKA also activates Ca^{2+} sequestration mechanisms which contribute to smooth muscle relaxation (Brain and Grant 2004).

this complex mainly leads to activation of adenylate cyclase, thereby increasing intracellular cAMP level, which exerts downstream effects. Other heterodimeric and multimeric complexes formed by interaction of CALCRL with different RAMPs, including amylin receptors and adrenomedullin receptors, have been described but a detailed description is beyond the scope of this paper (Hay and Poyner). Some of these receptors also interact with CGRP with high affinity. CGRP receptors are found throughout the body, suggesting the protein modulates a variety of physiological functions in all major systems, and data are available for bone, skin, brain, motoneurons, lymphocytes, uterus, respiratory tract, endocrine system, gastrointestinal tract and cardiovascular system (Ghatta and Nimmagadda, 2004). A role for CGRP and its receptors in some pathophysiological states, including preeclampsia, arterial hypertension, sepsis and cardiac failure, is likely, but not fully explained. A detailed description is beyond the scope of this paper, but we will elaborate further on the role of CGRP in cardiovascular homeostasis. The role of CGRP in nociception will be discussed in the next paragraph. CGRP is the most potent endogenous vasodilator protein thus far discovered. Vasodilation, both arterial and venous, is the result of binding of CGRP on vascular smooth muscle receptors, which leads to hyperpolarization by activation of ATP-sensitive potassium (K_{ATP}) channels through a cAMP-mediated enhancement of protein kinase A activity (Fig. 2). CGRP also has both positive chronotropic and inotropic actions on the heart. The precise function of CGRP in coronary vasomotor tone remains unclear, but CGRP in general has a role in regulation of blood supply to different organs. Following intravenous infusion of femtomolar concentrations CGRP, the peptide induces profound and long lasting vasodilation responses in various species, including human, which may result in profound hypotension (Brain *et al.*, 1985; Girgis *et al.*, 1985; Brain *et al.*, 1986; van Rossum *et al.*, 1997).

CGRP and the brain

CGRP and its receptors are widely distributed in the peripheral and central nervous systems, as

indicated by CGRP mRNA and immunoreactivity studies. One third of the spinal dorsal root ganglia are CGRP-positive. In the brain, CGRP mRNA containing neurons, CGRP-immunoreactive cell bodies and fibers are widely but unevenly distributed, and the reader is referred to the literature for a detailed map (van Rossum *et al.*, 1997). CGRP has been implicated in a variety of brain functions, including olfactory, sensory, motor and integrative functions. All cranial nerve nuclei, except the motor nucleus of the vagus nerve, contain CGRP mRNA (van Rossum *et al.*, 1997).

The trigeminovascular complex consists of neurons innervating pain-producing structures such as the intracranial vessels and dura mater, and it provides the substrate for pain of intracranial origin. Branches of the ophthalmic division of the trigeminal nerve, which pass through the trigeminal ganglion, synapse on second-order neurons in the trigeminocervical complex. From this region a signal is relayed to several thalamic nuclei, and further transmitted to cortical areas. In the posterior fossa, the dural innervation has important contributions from the dorsal root ganglia of the upper cervical segments (Feindel *et al.*, 1960; Arbab *et al.*, 1986). Histochemical studies revealed that about 50% of cell bodies in human trigeminal ganglia contain CGRP, which colocalizes with substance P and neurokinin A (Uddman *et al.*, 1985). CGRP can be released by these trigeminal neurons, at the cell body, and at the central as well as peripheral terminal of these pseudounipolar neurons (Fig. 3). The distribution of CGRP-containing nerves has most extensively been reviewed with respect to its function in the cerebral circulation. The CGRP-containing axons are largely unmyelinated C-fibers or small-diameter myelinated Ad fibers, that act as polymodal nociceptors and are most usually found in nerves innervating blood vessels, both cerebral and dural (van Rossum *et al.*, 1997; Brain and Grant, 2004). In the cranial dura mater CGRP-immunopositive fiber bundles are mainly found as a loose network around arterial vessels. CGRP disappeared completely from the ipsilateral blood vessels after unilateral section of the trigeminal nerve (Uddman *et al.*, 1985). Centrally-released CGRP may act as an effective neurotransmitter in the trigeminocervical complex (Storer *et al.*, 2004), but the exact role of CGRP in nociceptive neurotransmission remains unclear. The significance of the trigeminovascular system for the nociceptive meningeal processes and migraine pain will be discussed in the next paragraph.

CGRP is a powerful vasodilator of cerebral and dural vessels, and 100-1000 times more potent than substance P or 5-hydroxytryptamine (serotonin). It acts mainly directly on smooth muscle cells, thus in an endothelium-independent fashion. In denervation experiments, with unilateral transsection of the trigeminal nerve in cats, basic aspects of cerebrovascular physiology, including control of resting cerebral blood flow, autoregulation, blood gas response and flow-metabolism coupling, were unaltered (Edvinsson, 2008). Further experiments indicated that the CGRP-containing sensory nerve fibres rather counteract vasoconstrictor influences (Edvinsson, 2008). Stimulation of the trigeminal ganglion leads to both antidromic and orthodromic changes in cerebral blood flow. Vasoconstriction of cerebral blood vessels triggers an orthodromic release of mainly trigeminal CGRP, which increases blood flow via a trigemino-cerebrovascular reflex that transverses the brainstem, with its efferent path being through the seventh cranial nerve and autonomic sphenopalatine and otic ganglia (Edvinsson *et al.*, 1995). The trigeminal system can also increase blood flow via antidromic activation and release of vasoactive substances such as CGRP. Finally, antidromic released CGRP acts on meningeal mast cells, which leads to mast cell degranulation (Fig. 3).

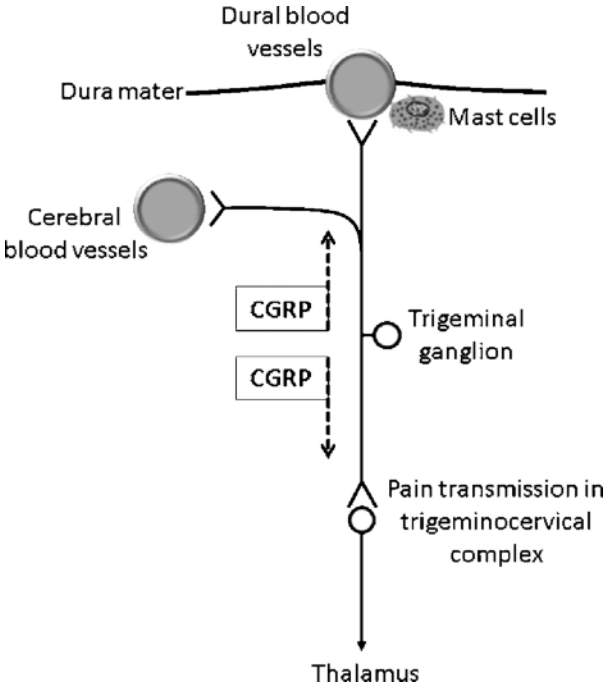

FIG. 3. — CGRP can be released orthodromic and antidromic upon activation of the trigeminovascular system. Antidromic CGRP release is associated with dilation of cerebral and meningeal blood vessel, as well as mast cell degranulation. Orthodromic released CGRP acts on post-synaptic receptors in the trigeminocervical complex, to activate thalamic afferents.

CGRP and migraine

Activation of the trigeminovascular system plays a key role in the pathogenesis of pain in migraine (Goadsby *et al.*, 2002). However, two main issues remain incompletely understood: the primary cause of migraine, leading to repetitive activation of the trigeminovascular system, and the mechanisms of pain generation after its activation. There is currently no universally accepted theory to explain the spontaneous activation of meningeal afferents during a migraine attack. Functional brain imaging with PET suggests that modulation of the trigeminovascular nociceptive input comes from the dorsal midbrain, including the periaqueductal grey and dorsal raphe area (Weiller *et al.*, 1995; May, 2004). The proposal that neurogenic inflammation contributes to the mechanism of migraine headache has been advanced some 20 years ago, based on trigeminal ganglion stimulation studies (Markowitz *et al.*, 1987). Neurogenic inflammation is defined by vasodilation, mast cell degranulation and plasma extravasation, as a consequence of release of inflammatory mediators, such as CGRP, substance P and neurokinin A, from peripheral nerve terminals. More recently an important role of neurogenic inflammation during the onset of migraine headache has been questioned, as there is little evidence for plasma protein extravasation, the most recognized physiological hallmark of neurogenic inflammation, in migraine (Peroutka, 2005; Messlinger, 2009).

There is evidence that CGRP can be released into the circulation during activation of the trigeminal system. Activation of the trigeminal ganglion, by either thermocoagulation of the ganglion as part of the treatment of trigeminal neuralgia or by electrical stimulation in the cat, leads to increases in CGRP levels in the extracerebral circulation (Goadsby *et al.*, 1988). During a migraine attack, an increased level of CGRP-like immunoreactivity has been measured in saliva of patients and in venous jugular blood the CGRP level was substantially elevated (Goadsby *et al.*, 1990; Nicolodi and Del Bianco, 1990). Jugular CGRP elevation is not specific for migraine, as increases in jugular blood CGRP levels have been observed during attacks of cluster headache and chronic paroxysmal hemicrania, two other primary headache disorders (Goadsby and Edvinsson, 1996). Jugular CGRP levels remained normal during tension-type headache and they are not elevated in cervicogenic headache (Ashina *et al.*, 2000; Frese *et al.*, 2005). Elevated CGRP levels have been measured in the cubital vein during spontaneous migraine attacks in children and during nitroglycerine-induced migraine attacks (Gallai *et al.*, 1995; Juhasz *et al.*, 2003; Fan *et al.*, 2009). It is very unlikely that the observed cubital CGRP levels exclusively originate from the cranial circulation, and a contribution from the gastrointestinal tract has been suggested (Tfelt-Hansen and Ashina, 2009). In contrast in a Danish study with an intra-patient comparison design, no change in plasma CGRP level was measured during and outside migraine attacks (Tvedskov *et al.*, 2005). Several reasons for this different finding have been considered, including the severity of the pain at the time of sampling, but the discrepancy remains unresolved (Goadsby *et al.*, 2009; Tfelt-Hansen and Le, 2009). There is however little doubt that CGRP plays an important role in migraine pathogenesis, as confirmed in later pharmacological studies (discussed below). Moreover, CGRP release into the cranial circulation was markedly antagonized by current acute migraine treatment with triptans and dihydroergotamine (Goadsby and Edvinsson, 1993; Knight *et al.*, 1999). A further consideration is that if CGRP were liberated at a very early stage of a migraine attack, it would suggest a causative role for this neuropeptide, whereas increase at a later stage would merely reflect pain activation. Lassen *et al.* therefore studied the effect of human α-CGRP infused intravenous in nine patients suffering from migraine without aura (Lassen *et al.*, 2002). In this double-blind placebo-controlled crossover study, CGRP caused headache in virtually all migraine sufferers, whereas placebo did not. The headache occurred during the infusion and disappeared or diminished after the infusion. After a median of 5 hours, a more severe headache developed in all nine study subjects. This headache had most of the characteristics of migraine and in three of these subjects fulfilled diagnostic criteria of the International Headache Society for migraine without aura (1988). A causative role of CGRP in migraine was therefore suggested, rather than CGRP release being an epiphenomenon of a migraine attack. The time course of CGRP-induced headache as well as additional hemodynamic studies suggest that a pure vascular mechanism is very unlikely (Lassen *et al.*, 2008).

CGRP receptor antagonists

As CGRP receptors are localized throughout trigeminal pathways involved in migraine and as CGRP is released during a migraine attack, CGRP antagonism has become an important target for new migraine treatments (Durham, 2008; Tepper and Stillman, 2008). The first CGRP antagonist was a peptide fragment called $CGRP_{8\text{-}37}$ (Chiba *et al.*, 1989). However this compound was not very potent

and its peptidic nature limited its use. Doods *et al.* used high throughput screening to find a small molecule CGRP receptor antagonist, and BIBN4096BS, later named olcegepant, was selected for clinical trials (Doods *et al.*, 2000). This large hydrophilic molecule completely inhibited the effect of CGRP, released after antidromic stimulation of the trigeminal ganglion, on facial blood flow in marmoset monkeys (Doods *et al.*, 2000). The new non-peptide CGRP receptor antagonist olcegepant proved to be about tenfold more potent than $CGRP_{8-37}$ in blocking the CGRP-induced dilation in bovine vessels (Moreno *et al.*, 2002). Olcegepant was tested in a phase I study published in 2004 (Iovino *et al.*, 2004), Olcegepant was administrated at rising intravenous (IV) doses in 41 healthy volunteers and compared with 14 participants treated with placebo. No clinically relevant drug-induced changes in pulse rate, blood pressure, ECG, respiratory rate, laboratory tests or forearm blood flow were seen. The most common adverse events were transient and mild paresthesias and were seen in 8 of the 41 subjects treated with olcegepant, compared with 4 of the 14 treated with placebo. Furthermore, after administration of human α-CGRP, none of 10 patients treated with 2,5 mg olcegepant IV experienced an α-CGRP-induced headache, whereas 6 out of 10 placebo subjects did. These encouraging results have led to a large international multicenter double-blind, randomized clinical trial in which 126 migraine patients received placebo or 0.25, 0.5, 1, 2.5, 5 or 10 mg of BIBN4096BS IV over a period of 10 minutes (Olesen *et al.*, 2004). Using a group-sequential adaptive treatment-assignment design, the minimal effective dose to treat migraine effects was identified as evidenced by a rate of response of at least 60%. BIBN4096BS, administered IV at 2.5 mg, offered a significantly higher response rate of 66%, than the infusion of placebo (27%). Similarly positive results were found for the secondary endpoints. Nausea, photophobia, phonophobia and functional capacity all improved in parallel with pain response. Pain-free response rate from 2.5 mg olcegepant was 44% at 2 hours and 56% at 4 hours as compared with placebo pain-free responses of respectively 2% and 10%. The rate of recurrence was 19% among patients who received the 2.5 mg dose, and was 46% in placebo-treated subjects. The authors concluded that because of the relatively small sample and special design of their study, the degree to which the data can be compared with traditional designs is highly uncertain. Nevertheless the results were promising. One major downside to BIBN4096BS is the need for intravenous administration, which would limit its possible application. Therefore an oral non-peptide CGRP antagonist was actively searched for. In 2006, Williams *et al.* indentified a novel benzodiazepinone CGRP receptor antagonist and subsequent optimization led to the identification of the potent and orally bioavailable non-peptide CGRP receptor antagonist MK-0974 (Williams *et al.*, 2006; Salvatore *et al.*, 2008). MK-9074, later named telcagepant, proved save and generally well tolerated in a few phase I studies (Sinclair *et al.*, 2007a; Sinclair *et al.*, 2007b). To determine an effective and tolerable dose of telcagepant, Ho *et al.* set up a randomized double-blind phase II trial with a two-stage, adaptive, dose-ranging design (Ho *et al.*, 2008). They enrolled 420 patients that were allocated to treat a moderate to severe migraine attack with MK-0974 (25, 50, 100, 200, 300, 400 or 600 mg), rizatriptan 10 mg or placebo taken orally. Following an interim analysis, the lowest dose telcagepant groups (25, 50, 100 and 200 mg) were discontinued due to insufficient efficacy. In parallel with the olcegepant data, MK-9074 was effective in treating moderate or severe migraine attacks on the primary endpoint of pain relief at 2 hours. The 2 hour pain relief rate was 68.1% with 300 mg telcagepant versus 69.5% with 10 mg rizatriptan and 46.3% with placebo. Similar efficacy was seen for secondary endpoints of pain-free response, 24-hour sustained pain freedom, improvement of associated symptoms and functional disability. The most common adverse experiences for MK-9074 300 mg to 600 mg were nausea, dizziness, and somnolence. A comparable incidence of adverse events was demonstrated among patients treated with telcagepant 300 mg to 600 mg and those treated with rizatriptan. No clinically meaningful differences were observed on physical examination, vital signs, or ECG. Recently, the first phase III clinical trial of an oral CGRP antagonist was published in the Lancet (Ho *et al.*, 2008). In this trial 1380 patients were randomly assigned to receive telcagepant 150 mg or 300 mg, zolmitriptan 5 mg or placebo at 81 sites in Europe and the USA. All active treatments were more effective than placebo on the primary endpoints, including 2 hour pain-free, and the key secondary endpoint of 2-24 hours sustained pain freedom. Telcagepant 300 mg and zolmitriptan 5 mg had comparable efficacy and were both slightly more effective than telcagepant 150 mg on most measures. The 2 hour pain-free rate was 26.9% for 300 mg telcagepant, versus 31.3% for zolmitriptan and 9.6% for placebo. Both doses of telcagepant 150 mg and 300 mg were associated with fewer clinical adverse events than zolmitriptan, suggesting that telcagepant might offer tolerability advantages over current triptan treatments. In an exploratory analysis of 2-48 hours

sustained pain freedom, telcagepant 300 mg was more effective than zolmitriptan but this finding should be treated with caution because the analysis was done without adjustment for multiplicity.

The site of action of CGRP antagonists is a matter of active research. Theoretically the action of CGRP antagonists may be related to blocking neurogenic dilation of blood vessels or through a central effect on transmission of pain. A central effect is supported by the relative large doses of CGRP antagonists needed for clinical efficacy, as well as by experimental data. Indeed, olcegepant microiontophoresis in the trigeminocervical complex neurons inhibited nociceptive trigeminovascular transmission in the cat, and further data supported a post-synaptic effect of olcegepant (Storer *et al.*, 2004). In a rat model of meningeal nociception, intravenous olcegepant reduced spontaneous and heat- evoked activity in the spinal trigeminal nucleus (STN), thought to reflect the activity of central trigeminal nociceptive pathways. In contrast, topical application of olcegepant onto the dura mater was ineffective at lowering the activity of STN, so a central site of action of the CGRP receptor antagonist was suspected (Fischer *et al.*, 2005). Recently evidence from rat experiments has been produced to show that the decrease in STN activity after systemic infusion of olcegepant is associated with reduced activation of second order but not first order trigeminal neurons, indicating that CGRP receptor inhibition is likely to occur in the central nervous system rather than in the periphery including the trigeminal ganglion (Sixt *et al.*, 2009). Finally, brain loci outside the trigeminocervical complex may also play a role in the clinical effect of CGRP receptor antagonists, as they can modulate neurons in the periaqueductal grey (Pzo-Rosich *et al.*, 2009).

Future perspectives

Given the positive results of 2 CGRP receptor antagonist trials with excellent tolerability, the advent of a new class of acute anti-migraine medication becomes a reality. The search for additional antagonists is actively pursued and at the time of this writing, new orally available CGRP antagonists are being tested. Another approach to block the effects of CGRP is either the use of a CGRP antibody, or the use of a specific CGRP-binding RNA-Spiegelmer (a single-stranded mirror-image oligonucleotide). These CGRP scavengers bind the excess of CGRP and thus inhibit its effects. Chronic treatment with anti-CGRP antibodies exerted a long-lasting inhibition of neurogenic vasodilatation in a rat model, which opens up the possibility for their use in the prophylaxis of migraine (Edvinsson, 2008; Zeller *et al.*, 2008).

Since CGRP increase in the extracerebral circulation has been observed during other primary headaches, one might expect an effect of CGRP antagonists on these neurovascular pain syndromes as well. An approximately twofold increase in jugular CGRP concentration during cluster headache attacks and a normalization of CGRP levels after spontaneous resolution or treatment with either sumatriptan or oxygen, have been described in three studies (Edvinsson and Goadsby, 1994; Fanciullacci *et al.*, 1995; Fanciullacci *et al.*, 1997). CGRP may play a role in the pathogenesis of other trigeminal autonomic cephalalgias, such as paroxysmal hemicrania (Goadsby and Edvinsson, 1996). Besides therapeutic implications, these neuropeptide studies illustrate a basic shared pathophysiological phenomenon in different primary headache syndromes. CGRP furthermore has the potential of being used as a biomarker. One example could be the differential diagnosis of migraine and cervicogenic headache, as current diagnostic criteria lack specificity to separate both conditions (Fishbain *et al.*, 2003). Another example could be the diagnosis of migraine in young children, who cannot clearly describe their symptoms (Fan *et al.*, 2009).

Furthermore, CGRP and CGRP receptor antagonists may be used as pharmacological probes to explore the biology of migraine. Petersen *et al.* studied the inhibitory effect of olcegepant on middle meningeal artery and cortical pial artery dilatation induced by CGRP in the rat (Petersen *et al.*, 2004). It seems that olcegepant does not cross the blood-brain barrier (BBB) in the rat, but is very effective in preventing CGRP-induced vasodilatation in vessels without a BBB. With the caution of species differences in BBB function or the possible occurrence of transient BBB changes during the migraine attack, the authors conclude this indicates that dural arteries may play an important role in migraine pathogenesis (Petersen *et al.*, 2004). This is in agreement with results of a later study that showed that olcegepant, CGRP antibodies or CGRP-binding RNA-Spiegelmer only showed an inhibitory effect when applied abluminally but none after luminal application in the middle cerebral artery (Edvinsson *et al.*, 2007).

CGRP administration does not cause the phenotype familial hemiplegic migraine (FHM), a rare inherited condition characterized by severe aura (Hansen *et al.*, 2008). Hence, it is questioned that CGRP blockers would be effective in the treatment of FHM patients. Despite phenotypical similarities between FHM and common types of migraine, the

neurobiological pathways responsible for migraine headache in both entities may thus be distinct. Unfortunately, this group of patients neither can benefit from pain control with triptans, because of potential vasoconstriction effect.

One potential benefit of the new CGRP receptor antagonist class is the absence of vasoconstriction, which allows for the safe administration in migraine patients with cardiovascular disease. However, so far individuals with cardiovascular disease have been excluded from most studies. Olcegepant administration did not produce any change in systemic or cerebral rat or human circulation (Petersen *et al.*, 2004; Petersen *et al.*, 2005). These data suggest that in the resting state, circulating CGRP does not exert a vasodilatory activity. However, activation of sensory neurons by low extracellular pH or inflammatory mediators, produced during ischemia and tissue injury, results in the release of CGRP (Geppetti *et al.*, 1991; Benemei *et al.*, 2009). Thus, the use of CGRP antagonists may raise some concern under conditions of ischemia or infarction. CGRP antagonism does not affect the severity of myocardial ischemia in dogs with coronary artery stenosis, whereas sumatriptan did (Lynch *et al.*, 2009; Regan *et al.*, 2009). Two doses of telcagepant, 300 mg, administrated 2 h apart, did not appear to exacerbate spontaneous ischemia and were otherwise well tolerated in a small cohort of 28 patients with stable coronary artery disease (Behm *et al.*, 2008). Furthermore, telcagepant has no significant influence on the vasodilatory response of healthy male volunteers to therapeutic doses of sublingual nitroglycerin (Van der Schueren *et al.*, 2008). Despite these favorable preliminary results further studies are necessary to determine safety in patients with cardiovascular disease (http://clinicaltrials.gov: NCT00662818). Additional investigation to assess the long-term efficacy and safety profile of CGRP antagonists in patients treating more than one migraine attack are also needed. Recently a Phase IIa clinical trial with telcagepant for migraine prophylaxis was stopped after significant elevations in serum transaminases had been identified in two patients (http://clinicaltrials.gov: NCT00797667). Other potential side effects due to blocking the CGRP activity include exacerbation of Raynaud's syndrome, pulmonary hypertension, congestive heart failure and ischemia-reperfusion injury.

Conclusion

CGRP is the most potent vasodilator peptide in the trigeminovascular system. The discovery of elevated levels of CGRP during migraine headache attacks, supports the hypothesis that activation of the trigeminovascular system, whatever the cause, leads to the generation of head pain and vasodilation of cranial blood vessels. Antagonism of CGRP receptors has thus become an important target for new migraine treatment. The first non-peptide CGRP receptor antagonist BIBN4096BS (olcegepant) is effective and safe in treating migraine attacks, but could only be administrated intravenously. More recently, MK-0974 (telcegepant) at a dose of 300 mg proved to be as effective as zolmitriptan 5 mg in treating migraine headache, but had fewer adverse effects. The potential for a migraine-specific medication without vasoconstrictive effects is indeed enormous. However, only limited data about CGRP receptor antagonist administration in patients with stable coronary artery disease exists and further studies are necessary.

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