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Review article

Targeting of calcitonin gene-related peptide action as a new strategy for migraine treatment

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ABSTRACT

Migraine is a chronic, recurrent disorder, characterized by attacks of severe pain, affecting around 1% of adult population. Many studies suggest, that trigeminovascular system plays a key role in pathogenesis of migraine and other primary headaches. Calcitonin gene-related peptide (CGRP) is an endogenous substance, which is regarded a key mediator released from trigeminovascular system after stimulation of sensory nerve endings, responsible for dilatation of peripheral vessels and sensory transmission. CGRP is and extensively studied peptide as one of the most promising targets in migraine drug research. In the article we focus on the role of CGRP in the pathophysiology of migraine and present current data on CGRP antagonists and CGRP monoclonal antibodies.

1. Introduction

Migraine is a frequent and disabling disorder with notable socioeconomic impact. Its 1-year prevalence is estimated 11% in USA and Western Europe. Chronic migraine (defined as at least 15 attacks per month for a minimum of three consecutive months) affects about 4% of general population. According to the WHO, the total annual cost of all headaches was recently estimated at 155 billion Euros. Moreover, in the European Union alone 190 million work-days are lost every year because of migraine. It is estimated that migraines affect around one in six women and one in twelve men, and are the most expensive brain disorder with respect to associated costs to the society in the EU and United States [13].

Although pathophysiology of migraine is still under evaluation, many data indicate crucial role of CGRP.

CGRP is a 37 amino acid neuropeptide, which was identified in the early 1980s as a member of the calcitonin family of peptides [31,33]. It exists in two forms – CGRPα and CGRPβ. CGRPα is predominantly expressed in the peripheral nervous system (PNS), CGRPβ – in the enteric sensory system, in the gut and in the pituitary gland [32]. Both forms are encoded by separate genes. Primary neurons express more CGRPα than CGRPβ. In the PNS, CGRPα is present in trigeminal ganglia neurons and dorsal horn cells, where it is stored with

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substance P (in primary sensory ganglia) and acetylocholine (in motor neurons). It is expressed in both unmyelinated C-fibers and thinly myelinated Aδ fibers, which innervate inter alia epidermidis, skeletal muscles and enteric system. In the central nervous system (CNS), CGRP was found in structures critical for migraine pathology, such as hypothalamus, superior and inferior colliculi, brainstem, trigeminal complex and cerebellum [38]. Many studies suggest that CGRP may serve as a link between the CNS and the PNS in the pathophysiology of migraine [17].

CGRP receptor, cloned in 1991, belongs to the G protein-coupled receptor superfamily. It is a heterotrimer that contains seven transmembrane domains. It is composed of a calcitonin receptor-like receptor (CLR), a receptor component protein (RCP) and the receptor activity-modifying protein 1 (RAMP1) [22]. Binding of CGRP results in activation of cyclic adenosine monophosphate (cAMP)-signaling pathway, causing raise in cAMP levels [12]. Second type – CGRP2, which was postulated to be CGRP receptor, is not officially recognized by IUPHAR and is suggested to function as amylin and adrenomedullin receptor [15].

CGRP exerts a variety of biological effects, such as chronotropic and inotropic actions in the heart, relaxation of urinary smooth muscle and the dilatation of arterial vessels, which may lead to profound hypotension. CGRP causes vascular relaxation by an endothelium and nitric oxide – independent pathways. Activity of CGRP on venous vessels is poorly documented. Intracranial vessels (dural and cerebral) are supplied by thin CGRP-containing nerve fibers, which originate in the trigeminal ganglion [36].

Data show, that CGRP levels are elevated during migraine attacks and cluster headaches in saliva and jugular venous blood [14]. Moreover, also between attacks venous levels of CGRP have been shown higher in migraineurs, comparing to healthy control. Intravenous infusion of CGRP evokes migraine-like headache (in addition to moderate cardiovascular effects) in patients suffering from migraine [21]. Stimulation of trigeminal ganglion and sensory nerves located around intracranial vessels in humans resulted in release of CGRP, unilateral blood flow increase and ipsilateral facial flushing [9]. During migraine attacks with or without aura there were no changes in the concentration of neuropeptide Y, vasoactive intestinal peptide, substance P. In cranial venous outflow, however, marked increase in CGRP concentration was observed [14]. It is postulated, that pulsating pain during headache phase of migraine attack depends on the vasodilatation of intra and extra cranial arteries, which may be mediated by CGRP [3]. Recent data demonstrated that blockade of CGRP action can prevent or abort migraine.

2. Role of trigeminovascular system and CGRP in pathophysiology of migraine

Trigeminovascular system (TVS) is composed of trigeminal afferents (which cell bodies lie in the trigeminal ganglion), their central projections and blood vessels. Fibers, which conduct pain signals to the brain belong mainly to A delta and C-types nociceptive fibers [27]. Afferent sensory branches of trigeminocervical nerves innervate pain-sensitive intracranial structures, such as meningeal arteries, venous sinuses and dura mater [26]. On the second nociceptive neurons, which are located within the trigeminocervical complex, central projections of the trigeminocervical neurons terminate [2]. Third order neurons are located in thalamic nuclei (mainly within ventralposteromedial nucleus), nociceptive neurons from trigeminocervial complex terminate on them. Thalamic neurons project to primary somatosensory cortex, insular cortex, limbic structures and hypothalamus. This projections are responsible e.g. for conscious perception of the pain [30]. Activation of the brainstem was demonstrated in positron emission tomography (PET) studies during a spontaneous migraine attack [1]. Prior to pain onset brainstem, dorsolateral pons, periaqueductal gray matter and hypothalamus are active [24].

The key role in migraine headache plays sensitization of TVS. The exact nature of triggering stimuli responsible for its activation is still unclear. One of the leading theories proposes that TVS activation is secondary to cortical spreading depolarization, the other describes, that migraine is a primary disorder during which TCC is activated episodically. TVS sensitization and overactivation is accompanied by release of vasoactive mediators (mainly CGRP) from activated perivascular nociceptive afferents, which leads to mast cell degranulation and neurogenic inflammation in dura matter. Moreover, activation of parasymphathetic nerve endings located around dural blood vessels followed by release of acetylocholine, NO and vasoactive intestinal peptide cause vasodilatation. Characteristic features of migraine, such as pulsatile, throbbing headache and cutaneous alodynia, muscle tenderness, photophobia also result from sensitization of perivascular stimuli and higher order neurons, respectively [11].

The trigeminovascular system is involved both in cranial sensory functions and, with antidromic release of CGRP, in a vasodilatation [10]. This supports hypothesis that pathophysiology of migraine involves both altered sensory perception of non-noxious stimuli and altered trigeminovascular activation. In both these processes CGRP plays crucial role – peripherally by mediating vasodilatation via smooth muscle cell receptors and centrally by mediating the transmission of pain in the brainstem and second or third-order neurons [37].

CGRP is present in nerve cell bodies of more than 40% of the neurons in the trigeminal ganglion [9]. It is also present at trigeminal nerve endings, in ascending second order neurons and glia. In animal models of migraine CGRP concentration is increased in trigeminal ganglion [20]. CGRP is released at trigeminal nerve endings in the meninges following the activation of the trigeminal system. This causes vasodilatation and activation of sensory trigeminal pain neurons, innervating dura mater and intracranial blood vessels. Studies show that symptoms of migraine, such as aura, allodynia and photophobia are mediated by CGRP and can be alleviated by blocking its function [40].

CGRP plays crucial role in both initiation and progression of migraine and primary headaches. Thus, blockade of CGRP action should result in symptoms decrease. Various strategies have been employed to affect CGRP function. This includes small molecules or monoclonal antibodies, which compete for

a binding pocket or cleft on parts of CGRP receptors – RAMP1 and CLR. Monoclonal antibodies, neutralizing free CGRP are also under clinical evaluation.

3. CGRP receptor antagonists

3.1. *Olcegepant (BIBN4096)*

Olcegepant was the first CGRP receptor antagonist developed. It binds specifically to RAMP1 extracellular region and thus competes for the binding site of the endogenous CGRP [23]. It was shown clinically effective when administered intravenously during acute migraine attack. The effect was observed 30 min after administration with improvement over a few hours. Doses ranged from 0.25 to 10 mg, pooled response rate achieved 60%. About one third of patients treated suffered from side effects, mainly paresthesias. No intrinsic cardiovascular effects were reported [28]. Although the results with olcegepant were encouraging, drug was effective only after intravenous administration due to its poor oral bioavailability. Moreover, it had poor penetration across the blood-brain barrier (BBB) and although effectively blocked the CGRP-induced temporal artery dilatation, it did not modify the tone of cerebral vessels [29]. As migraine is treated primarily on an outpatient basis, olcegepant studies were discontinued because of difficulties in developing an oral formulation.

3.2. *Telcagepant (MK-0974)*

Telcagepant was the first orally available CGRP receptor antagonist. In pharmacokinetic studies it was rapidly absorbed, with Tmax of 1.5 h and terminal half-life 6 h. Steady state was achieved in 3–4 days after twice daily dosing, separated by 2 h [6]. In Phase 3 clinical trial, with zolmitriptan 5 mg as an active comparator and 1380 patients being randomized, telcagepant 300 mg had similar 2-h efficacy to zolmitriptan and superior to telcagepant, 150 mg. Both doses of telcagepant had superior efficacy but similar tolerability to placebo [18]. Moreover, it was effective in treating migraine associated symptoms, such as photophobia, phonophobia and nausea. However, some patients treated in Phase 2 twice daily showed elevated transaminases after more than 2 weeks of treatment. Such hepatic signs were not observed in acute intermittent therapy, which suggest, that the risk of hepatotoxicity may be dose- and time-dependent. Thus, concerns regarding liver toxicity caused discontinuation of telcagepant development.

3.3. *MK-3207*

In clinical trials it was significantly more effective in pain relief than placebo. However, liver toxicity concerns caused discontinuation of the drug [16].

3.4. *BI 44370*

It was shown more effective than both placebo and eletriptan in Phase 2 study. Tolerability was good, adverse events were noted in 1.4–9.4% of treated patients (depending on dose). However, no further trials have been published [7].

3.5. *BMS-846372/927711*

Discovered in 2012, showed efficacy similar to sumatriptan in Phase 2b study. It was superior to placebo, no significant adverse effects were described. However, only one single attack was treated in each patient involved, so further studies are needed to confirm its tolerability and safety profile [25].

3.6. *MK-1602*

The compound is currently under evaluation [19]. No data on its efficacy or safety has been published yet.

Liver toxicity observed during chronic continuous administration of CGRP antagonists raised concerns about its safe use in the clinics. As migraine is a chronic disease, which should be treated without hospitalization, drugs must be effective in oral for and safe when used chronically. Out of six available CGRP antagonists, three could not fulfill both of this requirements, remaining three are under evaluation. An alternative approach to the treatment of migraine by affecting CGRP function is use of monoclonal antibodies against the CGRP ligand and CGRP receptor.

3.7. *CGRP Monoclonal antibodies (mAbs)*

CGRP mABs are being developed particularly for migraine prophylaxis. They have the slower onset of action and much longer half-life comparing with CGRP receptor antagonists. Moreover, they might be administered once a month or even less frequently, while currently available migraine preventive medications are recommended orally one to three times daily [35]. Although mAbs are macromolecules, which potentially are incapable of crossing the BBB, it is possible, that during migraine attack, BBB is more permeable to allow its central action. mABs are characterized by high selectivity, which allows avoiding toxicities, reported previously for CGRP antagonists. However, as CGRP has many physiological actions in the organism, some concerns, mainly cardiovascular of CGRP inhibitions use, raised. As CGRP is a potent vasodilatator, risk of medication-induced hypertension, counterbalancing the vasodilatatory effect of anti-hypertensive drugs, inhibition of stress induced vasodilatation and inhibition of cardio-protective mechanisms during ischemia might be potential risks for patients treated with CGRP mAbs [5]. Moreover, infusion and administration immunological reactions are other potential undesirable effects.

Several studies have been carried of – three mAbs directly bind to and neutralize excessive CGRP, that is released at perivascular trigeminal sensory nerve fibers and thus prevent the binding of CGRP to its receptor. This includes LY2951742 (fully humanized mAB), ALD-403 (a genetically engineered humanized anti-CGRP antibody) and LBR-101 (also known as TEV-48125). AMG 334 is a humanized mAb against CGRP receptor, which blocks CGRP signaling [4]. All the four antibodies are indicated in the treatment of episodic and chronic migraine.

3.8. LY2951742

This is a humanized antibody, which has been shown to prevent the binding of CGRP to its receptor. Administered subcutaneously has been shown to prevent dermal blood flow increase induced by capsaicin in healthy human subjects, rats and non-human primates [34]. Efficacy of LY2951742 was studied in a phase 2a double-blinded placebo controlled trial in episodic migraine. The compound, administered subcutaneously every alternate week for 12 weeks showed significant decrease in headache days (62.5% vs. 42.3 in placebo group) at week 12. Adverse events (including pain at injection site, erythema, upper respiratory tract infections and abdominal pain) were more frequent in the treatment than in the placebo group. However, no serious adverse events, attributed to treatment, occurred [8].

According to https://www.clinicaltrials.gov two studies are currently recruiting patients with chronic and episodic cluster headaches.

3.9. ALD 403

ALD 403 is a humanized antibody, produced using yeast, not mammalian cells. Half life of the compound is approximately 32 days for the dose 1000 mg. Two different formulations, administered subcutaneously and intravenously were tested in Phase 1 placebo controlled study. In phase 2a study, 163 participants with episodic migraine received a single 1000 mg i.v. dose and were followed for 6 months. Decrease in the number of migraine days (5.6 vs. 4.6 in placebo group, $p = 0.03$) in the second month after treatment relative to number before treatment was shown. Adverse effects were experienced by 57% of patients from ALD403 group and 52% of patients from placebo group. Most frequently upper respiratory tract infections, urinary tract infections, fatigue, back pain, arthralgia, nausea and vomiting were reported [5]. According to https://www.clinicaltrials.gov one study: ''A Multicenter Assessment of ALD 403 in Chronic Migraine'' is currently recruiting patients. The primary outcome measure of the study is change in migraine days from baseline to week 12, estimated enrollment is 600 patients.

3.10. AMG 334

It is the anti-CGRP antibody that targets the CGRP receptor complex, not the free ligand. Its safety and effectiveness is studied in episodic and chronic migraine. It is administered subcutaneously, once a month. In phase I study a statistically significant reduction in monthly headache days were observed at week 12 in patients treated with dose of 70 mg [40]. According to https://www.clinicaltrials.gov two studies are recruiting patients with chronic migraine, further two will start July and August 2015, respectively. All of the studies will assess the compound in migraine prevention, three of the studies will be placebo-controlled.

3.11. LBR-101 (TEV-48125)

It was developed for episodic and chronic migraine from the start. Two studies conducted in monkeys showed, that the agent do not affect cardiovascular and hemodynamic parameters [39]. Similarly, no cardiological side effects were observed up to 3 months post dose in 31 subjects. Pharmacokinetic studies showed, that the half-life is 44–48 days. There are no on-going studies on LBR-101, registered on https://www.clinicaltrials.gov.

4. Conclusion

CGRP is the important neuropeptide in migraine pathophysiology. It seems to mediate not only pain, but also photophobia, aura and allodynia observed in patients. Thus, therapeutical strategies targeting CGRP function seem to be promising. Route of administration and hepatotoxicity limited use of CGRP antagonists, however, effectiveness and safety profile of CGRP monoclonal antibodies seem favorable especially for chronic administration in preventive migraine treatment.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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