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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

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