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REVIEW ARTICLE

Calcitonin gene-related peptide antagonism and cluster headache: an emerging new treatment

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Abstract Calcitonin gene-related peptide (CGRP) is a key signaling molecule involved in migraine pathophysiology. Efficacy of CGRP monoclonal antibodies and antagonists in migraine treatment has fueled an increasing interest in the prospect of treating cluster headache (CH) with CGRP antagonism. The exact role of CGRP and its mechanism of action in CH have not been fully clarified. A search for original studies and randomized controlled trials (RCTs) published in English was performed in PubMed and in ClinicalTrials.gov. The search term used was "cluster headache and calcitonin gene related peptide" and "primary headaches and calcitonin gene related peptide." Reference lists of identified articles were also searched for additional relevant papers. Human experimental studies have reported elevated plasma CGRP levels during both spontaneous and glyceryl trinitrate-induced cluster attacks. CGRP may play an important role in cluster headache pathophysiology. More refined human studies are warranted with regard to assay validation and using larger sample sizes. The results from RCTs may reveal the therapeutic potential of CGRP monoclonal antibodies and antagonists for cluster headache treatment.

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Introduction

Cluster headache (CH) is a disabling neurological disorder encountered in clinical practices. The prevalence of CH is less than 1% of the global population [1, 2]. CH is believed to be one of the most painful conditions in humans [3]. An online interview study reported that 55% of CH sufferers in the US population reported suicidal thoughts and 2% had attempted suicide [4]. The pathophysiology of CH is complex and not fully clarified [3], and current pharmacological treatments are suboptimal [5]. To date, there are no preventive agents approved for CH, only some off-label treatments. Therefore, new acute and preventive mechanism-based treatment strategies are warranted.

Calcitonin gene-related peptide (CGRP) was first identified in the early 1980s [6, 7] and was later shown to be one of the most potent vasodilators of cranial arteries [8]. CGRP plays a key role in the trigeminal-autonomic reflex [9], and in clinical studies, CGRP has emerged as a key signaling molecule in headache pathogenesis [10]. Randomized clinical trials (RCTs) have now demonstrated that monoclonal antibodies and antagonists targeting the CGRP molecule or its receptor are effective in acute [11–13] and preventive [14–17] treatment of migraine. Currently, four RCTs are underway with monoclonal antibodies against CGRP in CH patients [18–21].

The aims of this review are to describe the relevance of CGRP in relation to CH and to outline future treatment perspectives on the use of monoclonal antibodies and antagonists targeting CGRP to better fulfill the therapeutic needs of CH patients.

Pathophysiology of cluster headache

The current consensus on the pathophysiology of CH revolves around the following three features: ipsilateral cranial autonomic manifestations, trigeminal distribution of pain, and circadian and circannual periodicity of attacks [22]. For a more detailed description on CH pathophysiology, interested readers are referred to recent reviews [3, 23].

The cluster attacks are accompanied by lacrimation, nasal congestion, and conjunctival injection [24]. These cranial autonomic symptoms might result from activation of the trigeminal-autonomic reflex through activation of trigeminal sensory afferents [22]. Indeed, vasoactive intestinal polypeptide (VIP), a marker for this activation, is elevated in ipsilateral jugular venous blood during cluster attacks [25]. Recently, studies have reported efficacy of sphenopalatine ganglion (SPG) stimulation as a mechanism for blocking efferent parasympathetic outflow [26]. One study demonstrated that low-frequency induced cluster-like attacks with autonomic manifestations could be reversed with high-frequency SPG stimulation [27]. Interestingly, long-term preventative effects of SPG stimulation on CH attacks have also been reported recently [28].

Although severe head pain is prominent and debilitating for CH sufferers, this aspect has received limited attention. The major focus of clinical research has been on the role of the hypothalamus due to the circadian and circannual periodicity of cluster attacks. It has been suggested that the hypothalamus could function as a modulator of the trigeminal-autonomic reflex [22, 29]. This hypothesis was supported by the pioneering work of May and colleagues [30]. In a structural imaging study, the authors found increased posterior hypothalamic gray matter in CH patients compared with healthy controls. However, this finding could not be confirmed in a larger patient population sample [31]. Functional imaging studies added more evidence to hypothalamic involvement in CH by demonstrating activation of gray matter in the hypothalamus during both spontaneous [32] and nitroglycerine-induced [33] cluster attacks. Furthermore, previous studies have also reported some effect of hypothalamic deep brain stimulation for CH treatment [34–36]. In the context of hypothalamic involvement in CH, it is intriguing that CGRP seems to play a role in neurobehavioral processing and modulation [37], probably via an interaction with dopaminergic neurotransmission [38]. Two studies have also reported elevated dopamine plasma levels in CH patients compared with healthy controls [39, 40]. Thus, CGRP-mediated increases in plasma levels of dopamine might be implicated within the broader frame of hypothalamic involvement in CH pathophysiology.

CGRP and cluster headache

CGRP is widely distributed in the peripheral and central nervous systems in animals and humans [41–44]. In animals, CGRP has been found to be contained in trigeminal afferents [9], which comprise the sole sensory innervation of cerebral vessels [45], and has been shown to be released upon in vitro stimulation of the trigeminal ganglion [46]. In an important study, Goadsby et al. investigated the CGRP response to thermocoagulation of the trigeminal ganglion in humans [47]. CGRP plasma levels were found to be elevated in the extracerebral circulation during electrical stimulation of the trigeminal ganglion. The authors suggested that CGRP is released in response to activation of the nociceptive afferent trigeminal system. In support, CGRP was reported to alter the blood oxygen level-dependent signal in the brain in response to noxious heat stimuli in healthy volunteers [48]. In addition, the effects were reversed by the administration of sumatriptan [48]. This study suggested a modulatory role of CGRP in trigeminal pain pathways. In animal models, CGRP did not activate and sensitize meningeal nociceptors [49]. At present, the exact role of CGRP in trigeminal nociception is not fully clarified. However, Feistel et al. demonstrated that the CGRP antagonist MK-8825 decreased spinal trigeminal activity during nitroglycerine infusion in rats [50].

In 1994, the first study in humans was conducted showing elevated CGRP plasma levels during spontaneous cluster attacks [25]. CGRP changes were examined in blood samples collected from the external jugular vein in 13 patients (10 male vs. 3 female) with spontaneous cluster attacks. Elevated CGRP plasma levels were found during attacks (110 ± 7 pmol/l) compared with controls (41 ± 6 pmol/l). Furthermore, oxygen inhalation or subcutaneous injection of sumatriptan normalized the elevation in CGRP (38 ± 6 pmol/l).

Two studies investigated CGRP indirectly by measuring CGRP plasma levels after triggering cluster attacks using sublingually administered glyceryl trinitrate (GTN) [51, 52]. Both studies assessed baseline CGRP levels before GTN administration and reported elevated CGRP levels in CH patients who were in an active cluster bout. Moreover, CGRP levels returned to normal after spontaneous resolution of attacks or after sumatriptan administration [52]. No increase was found in patients who were in a complete remission state compared to those in active cluster bouts [51]. Another study also reported elevated CGRP levels in the external jugular vein interictally during active period and normal levels in patients in a complete remission state [53]. Interestingly, administration of corticosteroids decreased CGRP levels in the same patients [53].

Methodological limitations in CGRP and cluster headache studies

In the face of developing more refined experiments, lessons can be learned by looking at previous studies investigating CGRP levels during spontaneous or GTN-induced cluster attacks. In these studies, there are several methodological limitations worth noting. First, none of studies investigating CGRP levels during spontaneous or GTN-induced cluster

attacks were placebo-controlled [25, 51, 52]. Therefore, spontaneous decrease in CGRP plasma levels over the course of cluster attacks cannot be excluded. In fact, Fanciullacci et al. reported complete reversal of elevated CGRP levels after spontaneous remission of GTN-induced cluster attacks [52]. The studies also reported conflicting plasma levels of CGRP [25, 51, 52]. Goadsby et al. reported a CGRP concentration of 110 ± 7 pmol/l during cluster attacks [25], while Fanciullacci et al. found a concentration of approximately 50 pmol/l at the peak of attacks [52]. The latter reported baseline CGRP levels of approximately 20 pmol/l [52]. In addition, Goadsby et al. did not measure baseline values and most of the patients were not drug-free at the time of the study [25]. Preventive medication used by patients could also influence measurements of CGRP concentrations in plasma. The discrepancies in plasma results might also be due to assay variation, which raises questions of measurement validity. In view of this, an issue of compartment for measuring CGRP should also be raised. It is uncertain to what extent CGRP concentrations in plasma reflect trigeminal CGRP release. Furthermore, administration of sumatriptan was reported to normalize CGRP levels in both the spontaneous and GTN-induced studies [25, 51, 52]. A possible triptan mechanism of action could be mediated by direct inhibition via presynaptic 5-HT_1 receptors on trigeminal nerve endings [54]. Interestingly, one study found that sumatriptan does not alter plasma CGRP levels in healthy volunteers [55]. The authors speculated that triptans do not have a direct CGRP-reducing effect during trigemino-vascular inactivity.

Future perspectives

Future studies should investigate whether CGRP infusion induces cluster attacks in CH patients. In addition, studies should continue to explore the promise of using CGRP as a biomarker for trigeminal nociceptive activation. Validated assays and large sample sizes should be prioritized. For this purpose, replication of results in different labs and blind study designs would be important. Furthermore, deep phenotyping and data gathering on concomitant acute and preventive medication would play an important role in stratifying the patients. If CGRP monoclonal antibodies and antagonists prove to be effective, it would be interesting to examine whether we can predict the efficacy of these drugs on phenotyped CH sufferers. Also, it would indicate that migraine and CH share a common neurobiological pathway, because a majority of migraine patients get delayed migraine-like headache attacks after CGRP infusion [56–58]. For now, four RCT studies are underway targeting CGRP with monoclonal antibodies [18–21]. In the future, results from these RCTs will be needed in order to conclude on the promise of better acute and preventive CH treatment using monoclonal antibodies and antagonists against CGRP.

CGRP, calcitonin gene-related peptide; CH, cluster headache; RCTs, randomized clinical trials; VIP, vasoactive intestinal polypeptide; SPG, sphenopalatine ganglion; GTN, glyceryl trinitrate

Authors' contributions HA conducted the literature search. All the authors contributed with data interpretation, drafting, and revision of the manuscript. All the authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest Håkan Ashina has no disclosures. Lawrence Newman has received honoraria for his work as a consultant for Allergan, Amgen, Alder, Avanir, Depomed, E Neura, and Supernus. Sait Ashina received honoraria for lecturing from Allergan and Avanir Pharmaceuticals. Sait Ashina is also a principal investigator for Alder Pharmaceuticals trial NCT02974153.

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