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Calcitonin gene-related peptide: an update on the biology

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Abstract

Purpose of review—This review includes the most relevant and recent studies on the biology of calcitonin gene-related peptide (CGRP) as it pertains to primary headaches and particularly to migraine. Especial attention was given to those published within the last year.

Recent findings—The development of CGRP receptor antagonists is discussed in detail, as well as recent advances in our understanding of CGRP actions in migraine. Finally, other important functions of CGRP outside of the nervous system are briefly discussed.

Summary—The advent of CGRP receptor antagonists as a novel therapy for migraine attacks may represent a new era in the acute management of migraine. More than a simple addition to the currently available treatments, this group of drugs may become an outstanding option for patients with cardiovascular disease, given the lack of associated vasoconstriction. Furthermore, nonpeptide CGRP receptor antagonists, CGRP antibodies and CGRP-binding RNA-Spiegelmer are valuable research tools that will further advance our understanding of migraine pathophysiology.

Keywords

calcitonin gene-related peptide (CGRP); CGRP receptor; migraine; therapy

Introduction

CGRP is a multifunctional neuropeptide that plays a key role in migraine pathophysiology [1]. Despite the significant advances that the field has experienced in the last decade, the mechanisms of action of CGRP during a migraine attack remain elusive. Most recently, CGRP has become an attractive and promising therapeutic target for migraine [2]. Here, we will review the latest studies expanding our understanding of this neuromodulator as it relates to primary headaches and more specifically migraine. We will focus on the development of a new generation of acute migraine drugs, the CGRP receptor antagonists, and its implications for clinical practice and research.

Role of calcitonin gene-related peptide in migraine

The complexity and heterogeneity of migraine, a neurovascular disorder, has hindered a systematic study of the underlying mechanisms. Despite these hurdles, major advances have taken place in the past decade leading to a better understanding and treatment of migraine [3]. Multiple studies have progressively directed attention at the neuropeptide calcitonin gene-related peptide (CGRP) [1,4–6].

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Several seminal studies support the pivotal role of CGRP in migraine:

1. Initially, CGRP levels were found to be elevated during spontaneous and nitroglycerin-induced migraine [7,8] and reduced by sumatriptan, coincident with pain relief [9]. However, a recent well controlled study has questioned whether CGRP levels are increased during migraine attacks [10]. This unresolved question may be explained by the reports of higher plasma CGRP levels outside of a migraine attack in migraineurs when compared with nonheadache control individuals [11,12].
2. Subsequently, intravenous administration of CGRP was found to induce a delayed migraine-like headache in migraineurs [13] but not in control individuals [14]. On the contrary, a recent study evaluating the effect of CGRP as a migraine trigger in patients with familial hemiplegic migraine (FHM) found that a small group of genetically well defined patients were not hypersensitive to CGRP [15•]. An important consideration is that FMH patients also failed to demonstrate the hypersensitivity to glyceryl trinitrate (GTN), a known migraine trigger [16,17]. In a thorough review of the role of nitric oxide in primary headaches, Olesen has discussed the potential connection between the nitric oxide and CGRP pathways, which remains controversial [18•]. In addition to these studies, Edvinsson & Edvinsson did not find differences in peripheral microvascular sensitivity to CGRP and nitric oxide in migraineurs and healthy controls [19•]. One possible explanation for the hypersensitivity observed in patients with common forms of migraine is that central actions of CGRP and nitric oxide may be more relevant in migraine than their peripheral actions.
3. Finally, a proof of concept study demonstrated that CGRP receptor antagonists are effective in the treatment of the headache and associated symptoms of a migraine attack [2]. This finding has now been extended with a second antagonist in clinical trials described over the past year [20•,21••].

Altogether, these findings strongly suggest that the direct effect of CGRP on its receptor is crucial in the initiation and perpetuation of a migraine attack. Furthermore, they suggest that modulation of CGRP and/or its receptor will be an effective therapeutic strategy.

Recent studies have added a new dimension to the role of CGRP in sensitization of trigeminal ganglia neurons by adenosine triphosphate (ATP)-gated P2X3 receptors and have been reviewed by Giniatullin *et al.* [22•]. These receptors play a role in chronic pain and their involvement in migraine has been suggested in recent years. In the past year, the signaling pathways used by CGRP to increase P2X3 gene transcription were identified, including a potential amplifying step involving BDNF synthesis [23••]. It is tempting to speculate that transcriptional targets of CGRP (P2X3 receptor, BDNF, and CGRP itself) may not only contribute to long-lasting sensitization of trigeminal afferents, but may also help explain the observed delay in headache onset following CGRP injection.

Blocking the effects of calcitonin gene-related peptide

The actions of neuropeptides may be prevented using different pharmacological and genetic strategies. Here we will discuss two pharmacological approaches currently employed for CGRP. One of them is by blocking the receptor with CGRP receptor antagonists. Another one is by selectively sequestering the released CGRP with CGRP antibodies or CGRP-binding RNA-Spiegelmer, hence preventing CGRP from activating its receptors. Multiple compounds are currently under development aiming to find candidates that are potent and have a satisfactory pharmacological profile [24].

Calcitonin gene-related peptide receptor antagonists

The first CGRP receptor antagonist developed, olcegepant or BIBN-4096BS [25,26], was clinically tested in a proof of concept study that established the effectiveness of this new drug family for the acute treatment of migraine [2]. Due to poor oral bioavailability BIBN-4096BS required intravenous administration.

Subsequently, the oral bioavailable CGRP receptor antagonist telcagepant or MK-0974 has been investigated, initially in phase II [20•,27•] and most recently in phase III clinical trials [21••]. Telcagepant 300 mg was as effective as zolmitriptan 5 mg in the treatment of an acute migraine attack causing less adverse effects [21••,28•]. The pharmacological profile of MK-0974 has been studied in detail [29•]. Similarly to BIBN-4096BS [25,30], MK-0974 exhibits marked species selectivity, with approximately 1500-fold higher affinity for the human receptor than the rat CGRP receptor [29•]. This is regulated by the receptor activity modifying protein 1 (RAMP1), a required subunit of the CGRP receptor. This is an important finding and underscores the need for rodent models expressing human RAMP1 to facilitate the development of future molecules targeting the CGRP receptor [31].

BIBN-4096BS was also shown to effectively block nitric oxide induced activation of rat trigeminal brainstem neurons by Messlinger and colleagues [32••]. An important modification used in this study was prolonged nitroglycerin delivery, which did not lower blood pressure. The finding builds on the authors' previous reports that BIBN-4096BS suppresses both basal and heat-evoked activity of cranial dura mater-responsive spinal trigeminal neurons. Further studies are now called for to address the relationship of nitric oxide and CGRP in migraine.

Most recently BMS-694153, a new potent molecule with a favorable toxicology profile and good intranasal bioavailability in rabbits has been generated [33]. Likewise, in their search for new templates for CGRP receptor antagonists, Nguyen *et al.* [34] have identified a novel pyridinone series. Several recent comprehensive reviews have summarized the available preclinical and clinical evidence that supports the role of CGRP receptor antagonists in the future of migraine therapy [35–38,39••].

Despite having been extensively investigated, the exact sites of action of CGRP receptor antagonists have not been elucidated [40•]. Lennerz *et al.* [41•] have studied the distribution of the CGRP receptor in the rat trigeminovascular system in detail using antibodies recognizing the calcitonin-like receptor (CLR) and RAMP1. They found that CGRP receptors in the cranial dura mater were only seen extraneuronally (in arteries, mast cells and, unexpectedly, Schawann cells) whereas in the trigeminal ganglion and trigeminal nucleus CLR and RAMP1 were found on neurons, although often different neurons. These findings contrast with those of Marvizon *et al.* [42•] who did not find CLR and RAMP1 in central terminals of the afferent sensory neurons in the rat dorsal horn, yet that group had previously observed those proteins in sensory fibers in the periphery [43]. Therefore, this is still a controversial issue that needs to be resolved. However, both groups did see staining of ganglia cell bodies and several groups have reported CLR and RAMP1 RNA in the ganglia and functional CGRP receptors in cultured trigeminal and dorsal root ganglia [23••,31,44]. Therefore, there is a rich opportunity for upregulation and plasticity of CGRP receptors in nociceptive sensory neurons. Both groups found a number of terminals with just one component. For example, the presence of CLR alone suggests that upregulation of RAMP1 by inflammation or other hyperalgesic states could increase CGRP responsiveness.

It has been suggested that CGRP receptor antagonists exert their effect centrally [40•]. This notion is based on the discrepancy between the high in-vitro potency of CGRP receptor antagonists and the large doses necessary for their antimigraine effect *in vivo*. A possible

explanation is that they must cross the blood–brain barrier to reach their target and only a small fraction of the high dose is able to do so, hence the need for high doses *in vivo*.

It is only reasonable to compare the CGRP receptor antagonists with the triptans because triptans act in part by inhibiting trigeminal release of CGRP. In this regard, Harriott and Gold [45•] have addressed the long-standing question of why triptans are selective for migraine over other pain disorders. This selectivity has been puzzling given that elevated CGRP has been implicated in other types of pain. They found that the triptan 5HT1D receptors are more highly expressed in migraine-associated tissues. Although additional tissues need to be examined, their finding suggests that antagonists against the widely distributed CGRP receptors may have therapeutic potential surpassing the triptans for nonmigraine pain disorders.

Importantly, CGRP receptor antagonists do not appear to have the potentially serious cardiovascular side effects of the current mainstream migraine abortive medications, the triptans. Furthermore, they may prove to be effective in patients that do not find relief of their migraine symptoms with triptans or analgesic combinations. About one third of migraineurs treated with triptans do not respond and another third have a partial response with only some improvement and not complete resolution of their symptoms. Future studies should address the effectiveness of CGRP receptor antagonists in the subset of patients that do not respond to the currently available abortive medications. These studies will be of paramount importance to guide clinicians and bring hope to migraine patients.

Selective calcitonin gene-related peptide binding

Specific CGRP antibodies [46•] and CGRP-binding RNA-Spiegelmer (a single-stranded mirror-image oligonucleotide) [47] that inhibit CGRP actions have been recently developed. Similarly to what occurs with the nonpeptide CGRP receptor antagonists, the exact site of action of CGRP antibodies and CGRP-Spiegelmer is unknown, and they are both unable to penetrate the blood–brain barrier [48•].

Of great interest is the fact that CGRP antibodies have a longer half-life than CGRP receptor antagonists, making them an attractive candidate for migraine prophylaxis.

Calcitonin gene-related peptide as a biomarker

The advent of new therapeutic strategies targeting CGRP or its receptor brings us to the question of their potential role as biomarkers in migraine. Will CGRP or RAMP1 be useful in assisting clinicians in their diagnostic and therapeutic decisions? Presently available medications for abortive and preventive treatment of migraine are not free of side effects. Moreover, there are concerns about migraineurs being especially sensitive to the common side effects of these drugs [49]. It is not hard to imagine how helpful it would be know beforehand if an individual patient is likely to benefit from a particular medication.

Additionally, there are specific patient populations such as very young children or patients with cognitive disorders, where biomarkers may facilitate the diagnosis. A recent study evaluated the usefulness of plasma CGRP levels in the diagnosis of migraine and prediction of disability in children. The finding of elevated plasma CGRP level during headache attack and also, although not reaching statistical significance, interictally, proved to be valuable in differentiating migraine from nonmigraine headaches in children [50•].

The calcitonin gene-related peptide receptor

The CGRP receptor is a relatively unique G protein coupled receptor that is a multimer of the CLR, RAMP1 and receptor component protein [51]. RAMP1 is a small single-transmembrane

protein that is required for CGRP binding by CLR [52–54]. In addition to ligand specificity, RAMP1 also influences CLR glycosylation and cell surface trafficking. RAMP1 by itself may represent an attractive drug target in the near future [55•]. The crystal structure of the human RAMP1 extracellular domain has just recently been described by Kusano *et al.* [56], which should facilitate future RAMP1 drug designs. Interaction of CLR with two other RAMP proteins, RAMP2 or RAMP3, yields adrenomedullin receptors. The CGRP receptor can activate multiple signal transduction pathways, although it is most commonly coupled to Gsα to increase cAMP levels [51,57]. In vascular smooth muscle, these paths lead to activation of potassium channels and relaxation. The relevant downstream targets in migraine are not known, but will likely be an area of increasing interest.

In the past year, Hay's group performed a reciprocal mutation analysis of the three RAMP proteins that built on previous mutation and chimeric studies [58•]. The findings extended our appreciation for the importance of residue 74 in RAMP1 and its corresponding residues in RAMP2 and RAMP3 for ligand specificity and binding of the antagonist BIBN-4096BS. However, more importantly, the lack of clear roles for other residues that differ between the RAMPs hint at the complexity of interactions between CLR and RAMP1 to generate the CGRP receptor.

A potentially relevant development in the migraine field is a new mouse model with overexpression of human RAMP1 in the nervous system. These mice are sensitized to CGRP-induced plasma extravasation, a measure of neurogenic inflammation, and may represent a valuable model for the study of migraine pathophysiology and a tool for future drug development [31,59•].

Other important biological functions of calcitonin gene-related peptide

CGRP has other important functions beyond the nervous system.

Using CGRP-knockout mice, Toda *et al.* [60] have found a role of endogenous CGRP promoting tumor-associated angiogenesis and tumor growth. Another recent study supports the cardioprotective role of CGRP against ischemia/reperfusion injury [61]. These and other functions are important considerations when developing therapeutic strategies targeting CGRP or its receptor. Drug-induced upregulation or downregulation of the receptors leading to changes in their response to endogenous CGRP may have deleterious effects in other organs or systems.

Conclusion

Recent clinical and basic research advances have helped clarify the role of CGRP in migraine, although there are still many unanswered questions in the field. CGRP receptor antagonists are emerging as the new generation of migraine drugs. With increased availability of genetic diagnostic tools, it is foreseeable that future research will attempt to examine genetic susceptibility to migraine by studying the CGRP and CGRP receptor genes. From the therapeutic perspective, a novel approach to repress CGRP expression may be through posttranscriptional gene silencing. The therapeutic use of RNAi in neurological diseases is currently being explored and may not be far from the bedside [62].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 323–325).

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