Title
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Journal
Medical Hypotheses, 195

ISSN
0306-9877

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Publication Date
2025-02-01

DOI
10.1016/j.mehy.2025.111570

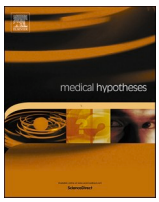
Peer reviewed

Medical Hypotheses 195 (2025) 111570

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/ymehy



Calcitonin gene-related peptide-induced central sensitization: A hypothesis for long COVID symptoms

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ARTICLE INFO

Keywords:
SARS-CoV-2
Long COVID
Central Sensitization
Migraine
CGRP

ABSTRACT

Central sensitization (CS) denotes aberrant processing of sensory stimuli within the central nervous system, wherein innocuous inputs activate pain pathways, leading to pain hypersensitivity. Features observed in CS conditions are often present in patients with long COVID, suggesting a potentially shared pathophysiological mechanism. We hypothesize that elevated levels of calcitonin gene-related peptide (CGRP), a neuropeptide known to play an integral role in the development of CS, may contribute to the persistent symptoms observed in long COVID. This article explores the role of CGRP within the context of CS and proposes its potential relationship to long COVID.

Introduction

Central sensitization (CS) is a process characterized by an alteration in the processing of sensory stimuli within the central nervous system [1]. Typically, sensory stimuli are processed differently based on their intensity and quality. Low-intensity stimuli, such as light touch, activate central pathways specialized for conveying innocuous sensations, while high-intensity stimuli that activate nociceptors exclusively engage central pathways associated with pain perception [2]. In the context of CS, however, this systematic processing of stimuli is disrupted. Increased excitability of dorsal horn neurons enables low-threshold, innocuous inputs to activate pathways that typically transmit pain signals through the spinothalamic tract [2]. These nociplastic changes often involve amplification of the magnitude and duration of the pain, manifesting as pain hypersensitivity.

Pain is signaled by the release of neurotransmitters including glutamate, calcitonin gene-related peptide (CGRP), and substance P from the presynaptic terminals of nociceptors. These excitatory neurotransmitters play a pivotal role in the pathophysiology of CS. Glutamate binds α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and N-methyl-D-aspartate (NMDA) receptors on the postsynaptic neurons of the dorsal horn of the spinal cord [3]. Weak stimulation results in only partial depolarization of the postsynaptic neuron, and the signal is primarily mediated by the AMPA receptor. This is because, under normal circumstances, the NMDA receptor is blocked by a Mg^{2+} ion that prevents the entry of other ions such as Na^{+} and Ca^{2+} through the channel [4]. However, stronger stimulation, such as injury, prompts an increased or sustained release of the neurotransmitters, which adequately depolarizes the postsynaptic neurons. This leads to the expulsion of Mg^{2+} ions from the NMDA receptor, permitting a greater influx of Ca^{2+} [4]. The elevated levels of intracellular Ca^{2+} subsequently activate several signaling cascades, intensifying neuronal responses to noxious stimuli. When this process is accompanied by persistent inflammation, it can lead to sustained activation of these pathways, amplifying pain sensitivity and contributing to the process of CS [1].

The outcome of CS is the emergence of pain from non-nociceptive stimuli, known as allodynia, or increased sensitivity to noxious stimuli, referred to as hyperalgesia. Allodynia occurs when normally

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CGRP, Calcitonin Gene-Related Peptide; CFS, Chronic Fatigue Syndrome; CRLR, Calcitonin Receptor-Like Receptor; FM, Fibromyalgia; IBS, Irritable Bowel Syndrome; NMDA, N-methyl-D-aspartate; RAMP1, Receptor Activity-Modifying Protein 1; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; CSI, Central Sensitization Inventory; CS, Central Sensitization; mAb, Monoclonal Antibody.

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https://doi.org/10.1016/j.mehy.2025.111570
Received 1 August 2024; Received in revised form 2 January 2025; Accepted 4 January 2025
Available online 6 January 2025

innocuous stimuli, such as light touch, provoke pain, whereas hyperalgesia is characterized by an exaggerated response to stimuli that are typically painful [2]. These responses constitute some criteria for diagnosing CS, alongside others such as pain disproportionate to the nature and extent of injury or pathology, and hypersensitivity of sense unrelated to the musculoskeletal system [5]. CS is known to underlie the pathophysiology of various chronic non-specific pain disorders, such as rheumatoid arthritis, fibromyalgia (FM), chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS), and migraine headaches [6,7]. The shared mechanism results in a convergence of symptoms, collectively referred to as CS-related symptoms. While pain is a significant aspect of CS, these manifestations can also present in various non-painful forms, including fatigue, sleep disturbances, paresthesia, and cognitive impairment [8,9]. In recent years, CS has gained renewed attention due to its relevance to post-COVID conditions, which share many symptoms commonly concomitant with these chronic pain disorders [10].

Post-COVID-19 condition is defined by the World Health Organization as the presence of symptoms lasting at least two months, beginning three months after the onset of COVID-19, without an alternative diagnosis [11]. This ailment has been referred to by several terms, including post-COVID-19 syndrome, post-acute sequelae of SARS-Cov-2 infection, chronic COVID-19, or, more commonly, "long COVID." Individuals affected by long COVID may experience a wide spectrum of clinical features, particularly fatigue, myalgia, brain fog, dyspnea, and sleep disorders [12–15]. Importantly, these manifestations closely resemble those seen in conditions related to CS. This observation is corroborated in several recent studies that found elevated levels of CGRP—a molecule involved in the development of CS—in COVID-19 patients [16,17]. Taken together, the persistence of symptoms in long COVID and observed CGRP levels are suspected to be associated with CS.

The hypothesis

We hypothesize that the considerable overlap in symptomatology between long COVID and chronic sensitization disorders (e.g., migraine, FM, CFS, and IBS) points to a shared pathophysiological process rooted in CS. Elevated CGRP levels are posited as a crucial mediator in this phenomenon, potentially driving the development and persistence of non-pulmonary manifestations in long COVID.

Evolution of the hypothesis

Understanding the mechanisms underlying long COVID remains an ongoing challenge. However, emerging evidence supports CS as a unifying factor in the wide range of symptoms observed. Herein, we delineate the connections between long COVID and various conditions known to involve CS. Migraine serves as a well-documented example, commonly accompanied by sensory hypersensitivity symptoms, including photophobia, phonophobia, osmophobia, and allodynia [18]. It is characterized by moderate-to-severe unilateral headache with a pulsating quality, and attacks typically last 4–72 h [19]. Reports indicate that headaches associated with COVID-19 frequently exhibit these migraine-like features [20–22]. Migraine can also present with features that diverge from the standard diagnostic criteria, hence referred to as atypical migraine. These variations include vestibular migraine, cochlear migraine, otologic migraine, and ocular migraine, among others [23]. Atypical migraine is related to a range of vestibular and cochlear manifestations, including tinnitus, otalgia, aural fullness, vertigo, sudden sensorineural hearing loss, hyperacusis, and more [24–28]. There has been a growing recognition of similar vestibulocochlear disruptions in certain COVID-19 cases. For example, a *meta*-analysis of twelve studies demonstrated statistically significant occurrence rates for hearing loss (3.1 %), tinnitus (4.5 %), and dizziness (12.2 %) among confirmed COVID-19 patients [29]. Notably, many studies agree that sensorineural hearing loss is the most common form of hearing impairment observed in these patients [30,31]. Several mechanisms for these complications have been proposed, including direct infection of the inner ear cells by the virus, leading to an inflammatory response and oxidative damage affecting the cochlea, cochlear nerve, or stria vascularis [32]. Interestingly, these effects appear to extend into long COVID, with some patients reporting persisting symptoms post-infection. A large-scale cohort study assessing long-term neurological sequelae of COVID-19 identified an increased risk of migraine and other headache disorders, hearing abnormalities or tinnitus, and dizziness [33]. Other cross-sectional studies have also indicated a higher prevalence of vertigo, tinnitus, and hearing loss in the long COVID cohort compared to similar populations without long COVID [34,35]. We believe that the vestibulocochlear manifestations that develop after the infection may represent a form of CS, suggesting shared underlying processes among migraine, atypical migraine, and long COVID (**Fig. 1**). Furthermore, other neurologic outcomes affecting the peripheral nervous system, such as muscle weakness and paresthesia—predominant symptoms of hemiplegic migraine—are among the most common complaints in long COVID patients [13,36,37]. Deficits in attention and memory are also frequently present in both populations [14,38,39].

Studies have indicated that a previous history of migraine and other primary headache disorders may be a potential risk factor for developing long COVID. It has been observed that patients with a previously confirmed diagnosis of migraine developed a greater number of symptoms or experienced more severe symptoms compared to the healthy controls [40,41]. The interrelationship and perhaps reciprocal effect between migraine and other CS disorders, like FM, CFS, and IBS, seems to underscore the broader consequences of long COVID (**Fig. 2**). For example, an increased frequency of migraine headaches has been observed in individuals with FM, and migraineurs have been reported to face a 1.5-fold higher risk of developing CFS compared to the general population [42,43]. Supporting this, Haider *et al.* assessed 707 patients with a single or comorbid diagnosis of long COVID, FM, and CFS and found that individuals with long COVID exhibited multiple symptoms common to FM and CFS, including pain, fatigue, anxiety, catastrophizing, and kinesiophobia [44]. Additionally, migraine has been cited as a common comorbidity in the IBS population, with an estimated odds ratio of 2.66 [45]. This link extends to long COVID patients, with approximately 12 % at significantly higher risk of developing IBS [46].

Direct assessments of CS symptoms in long COVID populations further substantiate our hypothesis. In a cross-sectional study of 567 persons post-COVID infection, Goudman *et al.* found that 70 % had presentations indicative of CS, as determined by the central sensitization inventory (CSI) [47]. CSI is a self-rated questionnaire frequently used to assess indicators of CS, comprising 25 statements related to health symptoms like myalgia, headache, and poor memory, measured on a 5-point Likert scale [48]. Their subsequent study reported similar findings, with 64 % of 42 patients presenting with these features [49]. Another study employing the same measures (i.e., CSI score $\geq$ 40 points) reported a prevalence of sensitization-associated symptoms in 34 % of 77 patients [50]. Additionally, a case-control study comparing healthy control, a recovered group, and a post-COVID syndrome group found statistically significant elevations in pain intensity and interference, as well as increased levels of CS and insomnia severity within the post-COVID syndrome group [51].

Calcitonin gene-related peptide

CGRP is one of the neurotransmitters that play an important role in neuronal signaling along with glutamate. It belongs to the calcitonin peptide family, comprising calcitonin, amylin, adrenomedullin, and adrenomedullin 2/intermedin, all of which are small peptides made up of 32 to 53 amino acids and consist of N-terminal disulfide bonds and C-terminal amides [52]. In humans, CGRP exists in two isoforms: CGRPα and CGRPβ, also known as CGRP I and II, respectively. Both are 37-amino acid neuropeptides differing by only three amino acids. It is

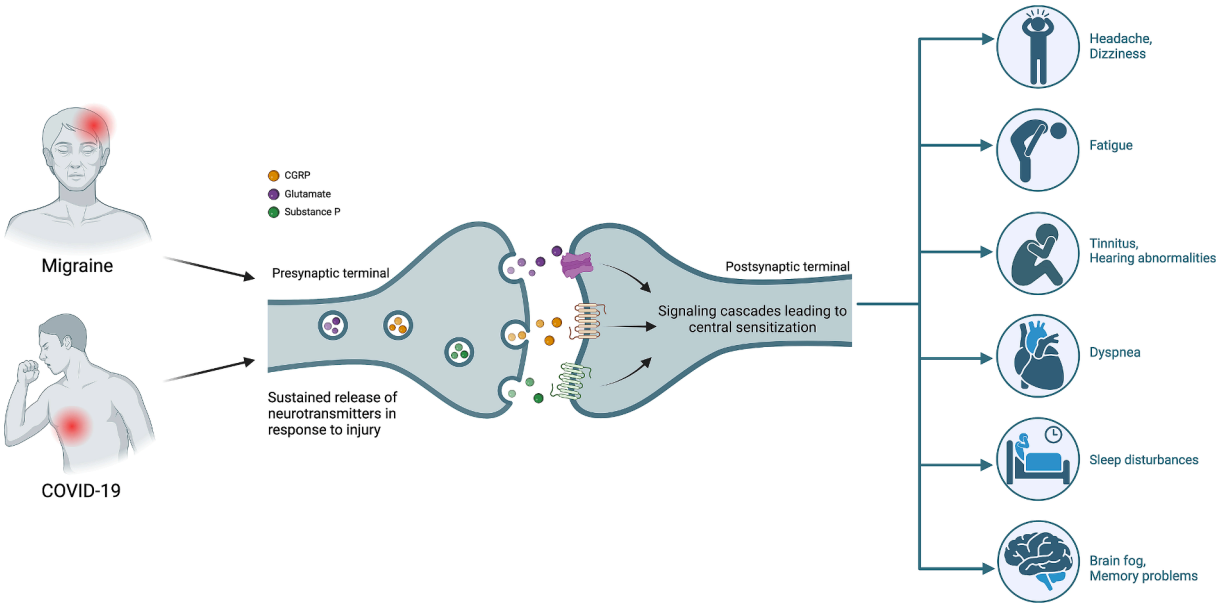

Fig. 1. Central sensitization in migraine and long COVID leading to convergence of symptoms.

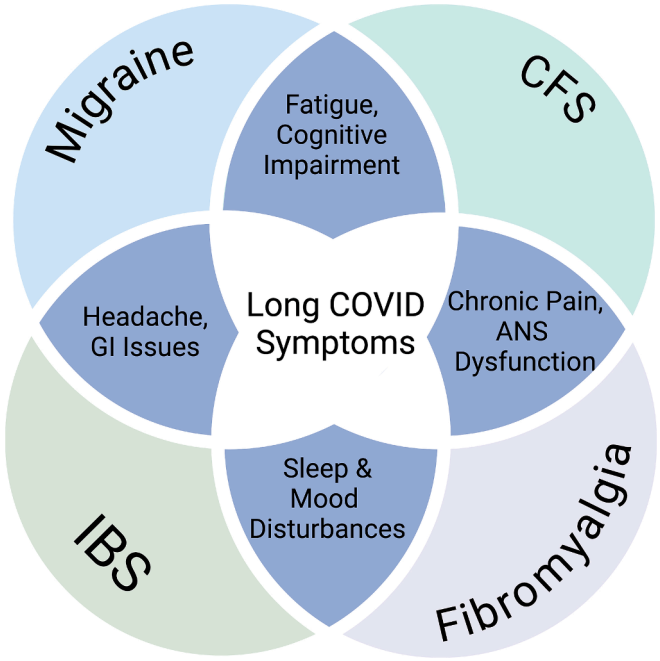

Fig. 2. Intersection of symptoms in long COVID and central sensitization-related disorders.

widely considered that CGRPα is the major isoform in the central and peripheral neuron systems, notably in the bodies of small or medium-sized neurons of trigeminal ganglion and in the dorsal root ganglion. Conversely, CGRPβ is predominantly found in the enteric nervous system [53]. In the dorsal root ganglion, CGRP is expressed in the unmyelinated C fibers and thinly myelinated Aδ fibers, both of which are involved in signaling pain in response to noxious stimuli [54]. It is noteworthy that activation of C-fibers is required for CS [55], which causes poorly localized, dull pain characteristic of the condition.

CGRP receptors are composed of three different proteins. The first is the seven-transmembrane G protein-coupled receptor known as calcitonin receptor-like receptors (CRLRs), which serves as a primary binding site for CGRP. The second component is the receptor activity-modifying protein-1 (RAMP1). RAMP1 is a single-transmembrane domain protein responsible for glycosylation and trafficking of CRLR to the cell surface, where it forms functional receptors [56]. Lastly, the receptor component protein is an intracellular protein that regulates CGRP signaling by binding directly to CRLR [57]. The binding of CGRP at its receptor leads to the activation of multiple intracellular pathways, allowing it to play a diverse role in the human body: serving as a neuromodulator, potent vasodilator, mediator of both pro- and anti-inflammatory activities, as well as regulator of metabolism [53,54].

Role of CGRP in central sensitization

CGRP contributes to the process of CS through several mechanisms. Although it is not clear whether it directly induces nociception, CGRP is thought to facilitate the transmission and enhancement of pain signals. Studies have shown a positive correlation between CGRP levels and the intensity of somatic pain, seen in disorders such as degenerative disc disease, osteoarthritis, and temporomandibular pain [58]. Similarly, blocking the effect of CGRP has been reported to reduce signs of enhanced pain in animal inflammatory pain models [6]. Furthermore, a noticeable incidental decrease in back and neck pain has been found among patients receiving CGRP inhibitor therapy for migraine with comorbid degenerative spinal conditions [59]. These findings allude to CGRP's involvement in nociceptive processing and the exacerbation of pain.

Another pathway through which CGRP participates in CS is by initiating and maintaining inflammatory responses. Once released following tissue injury, CGRP interacts with other inflammatory mediators to sensitize nociceptive neurons in the central nervous system, promoting CS (Fig. 3). Neurogenic inflammation arises from the activation of nociceptors, especially C-fibers, which release a range of inflammatory mediators, including bradykinin, prostaglandin, and neurotrophins. These mediators subsequently release neurotransmitters, notably CGRP and substance P [60,61]. In a study of an inflammatory model in rabbit skin, it was observed that CGRP interacts with interleukin-1, enhancing edema formation and neutrophil recruitment during inflammation [62]. This potentiating effect of CGRP on edema is observed with multiple other mediators, including histamine, bradykinin, platelet-activating factor, N-formylmethionyl-leucyl-phenylalanine, and leukotriene B_4, whereas substance P fails to induce it [63]. Additionally, CGRP can interact with Langerhans cells, a type of

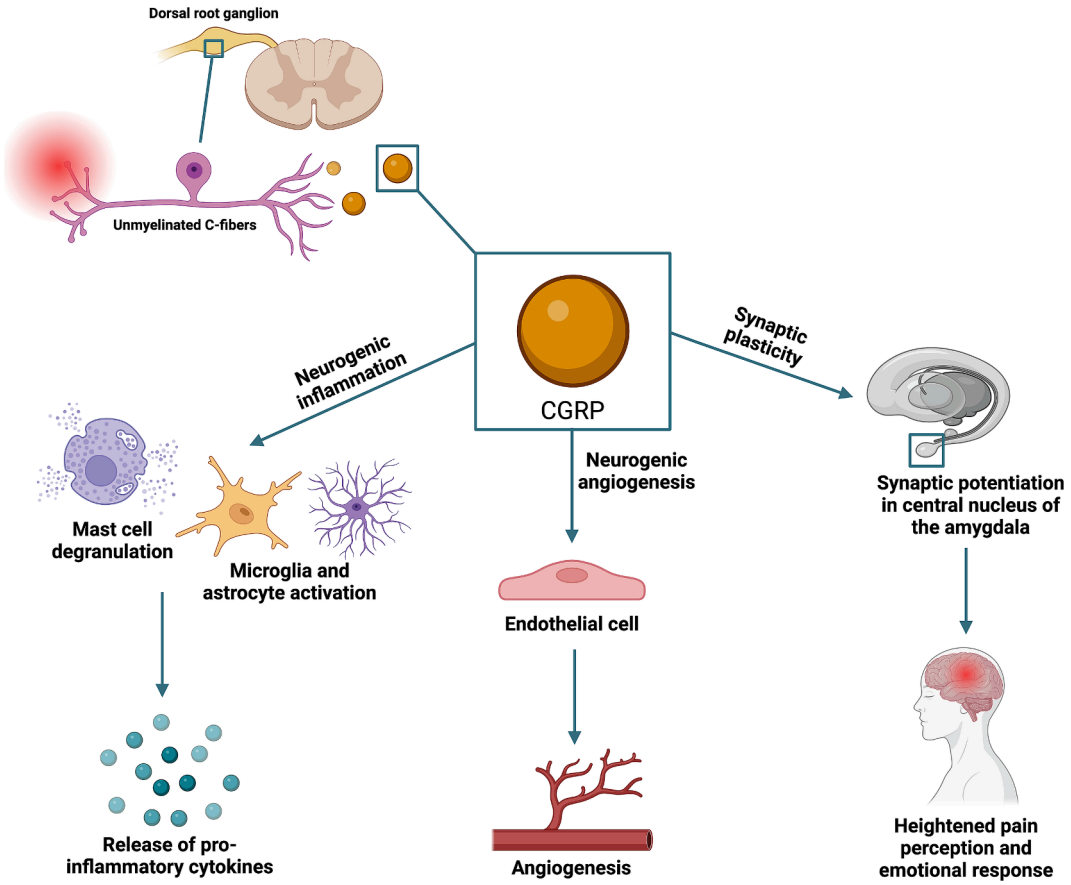

Fig. 3. Proposed mechanisms by which calcitonin gene-related peptide (CGRP) contributes to central sensitization (CS) following tissue injury. Upon release from C-fibers in the dorsal root ganglia, CGRP activates several pathways that promote CS, including neurogenic inflammation, neurogenic angiogenesis, and synaptic potentiation in the amygdala, which intensifies both the perception and emotional impact of pain.

epidermal dendritic cells, by enhancing their Th2 response [64]. CGRP is known to stimulate neurogenic angiogenesis, a process that augments the transition from acute to persistent inflammation. Studies on CGRP knockout mice demonstrated reduced tumor-associated angiogenesis compared to the wild-type mice. Moreover, administration of CGRP antagonists has been shown to inhibit tumor-associated angiogenesis and growth in mice [65].

CGRP's role in the development of chronic pain conditions extends to the modulation of synaptic plasticity in response to inflammation. In a formalin-induced inflammatory pain model, the CGRP knockout mouse displayed diminished synaptic potentiation in the right amygdala following inflammation, in contrast to the wild-type mouse that showed enhanced synaptic transmission [66]. This plasticity is thought to be responsible for the intensified pain perception as well as emotional responses during the progression of chronic pain. Furthermore, CGRP is implicated in the maintenance of ongoing sensitization, thereby perpetuating persistent nociception. Injection of CGRP into the temporomandibular joint capsule promotes cellular events involved in the maintenance of CS, including increased expression of c-Fos and activation of microglia and astrocytes [67]. In an animal model of spinal nerve-injured neuropathic pain, administration of a CGRP receptor antagonist to a rat led to a delayed onset of neuropathic pain and relieved mechanical hyperalgesia [68].

Implications

Since the outbreak, efforts have been made to identify biomarkers and therapeutic targets for COVID-19. Among these, we hypothesize that CGRP represents a promising candidate for further investigations, particularly due to its known involvement in CS conditions.

As observed in multiple CS-related conditions, elevated levels of CGRP have been observed in individuals with long COVID. In an observational cohort study of 135 patients hospitalized from SARS-CoV-2 infection, Rizzi *et al.* described a meaningful association between baseline plasma CGRP levels and the prognosis of the disease. Low levels of CGRP predicted fast clinical recovery with high sensitivity (85.06 %). Conversely, high levels, particularly when above a threshold of 1.23 ng/mL, were associated with an increased probability of pulmonary intravascular coagulopathy [69]. A case-control study involving 51 matched healthy controls with 52 hospitalized patients with COVID-19 found significantly elevated levels of both CGRPα and CGRPβ in the COVID-19 patient group [70]. Headaches in COVID-19 infection often exhibit characteristics resembling migraine, such as moderate-severe intensity or a pulsating sensation [21]. Indeed, a cross-sectional study found that COVID-19 patients experiencing headaches had elevated levels of CGRPα, nearly 30 % higher than those observed in patients without headaches. Even among patients without headaches, CGRP levels were statistically higher compared to healthy controls [21]. These recent findings raise intriguing questions: firstly, whether the elevated levels of CGRP in COVID-19 patients are linked to the development of CS symptoms and, consequently, long COVID; and secondly, the potential of CGRP as a therapeutic target of this condition. Supporting evidence for our hypothesis could have significant implications for the management of long COVID. CGRP-targeted therapies, already proven effective in treating migraine and some other CS conditions, may be repurposed to alleviate a range of symptoms in long COVID patients, including pain, fatigue, dizziness, as well as other neurotologic manifestations.

CGRP as a potential therapeutic target in long COVID

It is pertinent to consider the established significance of CGRP in migraine pathophysiology and its therapeutic implications, including the prospective benefits of blocking CGRP expression in alleviating CS-related symptoms. It is widely accepted that CGRP serves as a biomarker of migraine due to its strong vasodilatory effect, which is known to cause migraine headaches [71]. In addition, CGRP mediates mast cell degranulation, a process believed to promote CS and sustain the painful phase of migraine [72]. Studies have consistently shown elevated levels of CGRP in plasma, saliva, and tear fluid among migraine patients both during and between attacks [73–76]. Consequently, CGRP-targeted therapies, including anti-CGRP monoclonal antibodies (mAb) and small-molecule CGRP receptor antagonists (i.e., gepants), have proven effective in the management and treatment of migraine [77,78]. Specifically, mAbs against CGRP receptors and ligands, such as erenumab, fremanezumab, and galcanezumab, have shown efficacy in reducing allodynia, a hallmark of CS [79]. These treatments have also demonstrated promise in mitigating migraine comorbidities like IBS and other visceral hypersensitivity conditions in animal models, highlighting their potential to attenuate CS [80]. In our clinical practice, we have seen many patients with dizziness, tinnitus, and hyperacusis exhibit the features of CS. Treatment strategies aimed at managing an underlying atypical migraine have led to a notable improvement in these symptoms [81,82].

A recent study investigating the neurological symptoms of SARS-CoV-2 infection in mouse models found that olcegepant effectively reduces plasma interleukin-6 levels, which are often elevated in COVID-19 infection [83]. Interleukin-6 is an inflammatory mediator thought to be involved in CS as well as neuropathological changes [84]. In a related case report, a patient experiencing severe, chronic post-COVID headache was treated with a CGRP receptor mAb and showed significant improvement, with decreased intensity and frequency within 2 days of treatment [85]. In light of these observations, it is worth hypothesizing that anti-CGRP treatments could offer similar benefits in long COVID, particularly in alleviating CS symptoms.

Atogepant has been shown to effectively reduce the responsiveness of Aδ fibers and C-fibers, potentially preventing the sensitization process, although it has limited ability to prevent the initial activation of C-fibers [86]. Consequently, while atogepant may be less effective in preventing the onset of symptoms, it could be particularly useful in halting the progression or possibly reversing the prolonged sensitization state seen in long COVID.

Anti-CGRP mAbs, on the other hand, may offer longer-lasting benefits due to their sustained blockade of CGRP signaling and much longer half-lives compared to gepants [87,88]. Furthermore, while gepants have been associated with hepatotoxicity, anti-CGRP mAbs have not demonstrated any immediate short-term side effects [87]. This safety profile may make anti-CGRP mAbs a preferable option for those at risk for liver dysfunction. Of note, a new post hoc analysis revealed that gepant drugs are more effective for treating acute migraines in women compared to men [89]. The authors suggest that while this disparity may reflect the higher prevalence of migraine in females, it could also indicate differing mechanisms between the sexes. This finding highlights the need for further research into the generalizability of CGRP-targeted therapies across sexes, including their impact on CS-related presentations long COVID.

Multiple studies concur that managing long COVID requires a multifocal approach, mirroring those used in treating complex chronic pain conditions [10,90,91]. Validating CGRP as a biomarker for the development and severity of the condition would serve as an important step in establishing treatment strategies. Current research on CGRP levels in long COVID patients is limited, with only a few studies directly investigating the connection between the two. Larger-scale studies assessing the levels of CGRP in affected individuals could clarify its role in disease progression and its relationship to certain long COVID features, including fatigue, pain hypersensitivity, and neurotological symptoms. Additionally, these research efforts could help identify patient subgroups that may benefit most from CGRP-targeted therapies.

Conclusion

While the current evidence remains limited, findings so far suggest a possible link between CGRP and the development of CS symptoms observed in long COVID patients. The efficacy of CGRP-based therapies in managing CS-associated symptoms underscores their potential relevance in long COVID treatment strategies. Future investigations are imperative to understand the role of CGRP in long COVID and to devise targeted interventions aimed at alleviating the burden of long COVID symptoms and improving patient outcomes.

Declarations

Consent statement/ Ethical approval: Not required.

Availability of data and materials

Not Applicable.

Ethic statement

The manuscript does not need ethic statement.

CRediT authorship contribution statement

Ella J. Lee: Writing – original draft, Visualization, Investigation, Conceptualization. **Cynthia Tsang:** Writing – review & editing, Investigation. **Martha Lucía Gutiérrez Pérez:** Writing – review & editing, Investigation. **Mehdi Abouzari:** Writing – review & editing, Supervision, Conceptualization. **Hamid R. Djalilian:** Writing – review & editing, Supervision, Conceptualization.

Funding

Mehdi Abouzari, MD, PhD; was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant TL1TR001415. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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