DOI:10.4274/tnd.2022.88027
Turk J Neurol 2022;28:1-5

Review / Derleme

CGRP: New Focus in Migraine

CGRP: Migrende Yeni Odak

Necdet Karli[1], Sebnem Bicakci[2], Manal Mehtar Bozkurt[3]
[1]Bursa Uludag University Faculty of Medicine, Department of Neurology, Bursa, Turkey
[2]Cukurova University Faculty of Medicine, Department of Neurology, Adana, Turkey
[3]Novartis Pharmaceuticals, Clinical Pharmacology Specialist, İstanbul, Turkey

Abstract

Migraine is a neurological disorder characterized by recurrent attacks of headache usually accompanied by symptoms such as nausea, vomiting, photophobia and phonophobia. According to the Global Burden of Disease Study 2019 estimates, it affects more than 1.12 billion people worldwide and is a major cause of disability worldwide. Although migraine has been recognized for centuries, its pathophysiology has not been fully understood yet. Several theories have been proposed so far, the most recent being the neurovascular theory. Supported by the developments in neuroradiology and immunohistochemistry, the theory emphasizes the essential role of the trigeminovascular (TGV) system in migraine pathophysiology. It is obvious that the TGV system, regulating the cranial blood flow and nociceptive transmission, contributes to initiation and progression of serial complex events associated with migraine. The identification of vasoactive neuropeptides which had a role in migraine pathophysiology also created an opportunity for development of new treatment strategies in migraine. Calcitonin gene related peptide (CGRP) is one of the neurotransmitters that has attracted most attention since it is abundantly found in the TGV system and plays a significant role in different processes of migraine including vasodilation, neurogenic inflammation, peripheral and central sensitization. It became the focus of research in the last few decades and extensively investigated. Both small molecules antagonizing CGRP receptor and monoclonal antibodies targeting either CGRP or its receptor have been developed and used in migraine treatment. This article overviews the role of the TGV system in migraine pathophysiology and treatment with a specific focus on CGRP.

Keywords: Calcitonin gene related peptide, CGRP, migraine, trigeminovascular system

Öz

Migren bulantı, kusma, ışığa ve sese duyarlılık gibi semptomların eşlik ettiği tekrarlayan baş ağrısı atakları ile karakterize bir nörolojik bozukluktur. Global Hastalık Yükü 2019 verilerine göre dünya genelinde 1,12 milyardan fazla kişiyi etkilemektedir ve önemli bir engellilik nedenidir. Yüzyıllardır bilinen bir hastalık olmasına rağmen, patofizyolojisi henüz tam olarak aydınlatılamamıştır. Bugüne dek çeşitli teoriler öne sürülmüştür; en günceli nörovasküler teoridir. Nöroradyoloji ve immünohistokimya alanındaki gelişmelerin de desteklediği bu teori trigeminovasküler (TGV) sistemin migren patofizyolojisindeki önemine vurgu yapmaktadır. TGV sistemin kraniyal kanlanmayı düzenleyerek ve nosiseptif iletinin yayılmasına katkı sağlayarak migrenle ilişkilendirilen bir dizi karmaşık olayın başlamasına ve sürdürülmesine katkıda bulunduğu açıktır. Migren patofizyolojisinde rolü olduğu gösterilen vazoaktif nöropeptidlerin saptanması migren tedavisine yönelik yeni stratejilerin geliştirilmesi için fırsat yaratmıştır. KT gen ile ilişkili peptid (CGRP), TGV sistemde fazla miktarda bulunması ve migrenin vazodilatasyon, nörojenik enflamasyon, periferik ve santral sensitizasyon gibi farklı süreçlerinde rol oynaması nedeniyle en fazla dikkat çeken nörotransmitterlerden biri olmuştur. Son birkaç dekadda araştırmaların odağı haline gelmiş ve geniş ölçüde çalışılmıştır. Gerek CGRP reseptörünü antagonize eden küçük moleküllü CGRP antagonistleri gerekse CGRP'nin kendisini veya reseptörünü hedef alan monoklonal antikorlar geliştirilmiş ve migren tedavisinde kullanıma girmiştir. Bu derleme, CGRP'ye odaklı olarak TGV sistemin migren patofizyolojisindeki ve tedavisindeki rolünü gözden geçirmektedir.

Anahtar Kelimeler: Kalsitonin gen ile ilişkili peptid, CGRP, migren, trigeminovasküler sistem

Introduction

Migraine is a complex neurological disorder characterized by moderate to severe headache attacks lasting 4-72 hours, usually unilateral, throbbing, and increasing with physical activity. Headache increases with physical activity and symptoms such as nausea, vomiting, photophobia and phonophobia may occur. Prodrome and postdrome symptoms may be experienced at the beginning and end of a migraine attack (1). Of the patients 20-30% describe an aura period in which various focal neurological symptoms are seen, most often associated with vision, before headache (2).

Address for Correspondence/Yazışma Adresi: Necdet Karli Prof. MD, Bursa Uludag University Faculty of Medicine, Department of Neurology, Bursa, Turkey
Phone: +90 224 442 83 08 E-mail: nkarli@yahoo.com ORCID: orcid.org/0000-0002-7734-6451
Received/Geliş Tarihi: 13.07.2021 **Accepted/Kabul Tarihi:** 08.02.2022

According to the Global Burden of Disease 2019 estimates, migraine affects more than 1.12 billion people worldwide with an age-adjusted prevalence of 14.72% (12.81-16.92) (3). It is seen more frequently in women than in men [18.46% (16.09 -21.16) and 10.92% (9.45-12.66), respectively] and its prevalence peaks in the 30-34 age group (3). In a survey-based study conducted in Turkey, the prevalence of migraine was found to be 16.4% in individuals aged 18-65 years, and it was reported that this disease was 3 times more common in women (4). Although migraine can be seen in all age groups, it especially affects individuals in the productive period of life (3,5). Migraine, which is the second most common cause of disability in the world, ranks first in women aged 15-49 in this regard (3,5). It creates a significant burden on both individuals with migraine and the society with its negative effects on social relations, work life and quality of life, and the use of health resources (admission to health professionals, emergency services, hospitalization, imaging, etc.) (6,7,8).

Migraine is a disease known for hundreds of years (2). Advances in neuroradiology and immunohistochemistry in the last half century have contributed significantly to a better understanding of its pathophysiology (2,9,10). This paved the way for the development of migraine-specific treatment options. This study reviews the role of the trigeminovascular (TGV) system in the pathophysiology of migraine, with a particular focus on the calcitonin gene related peptide (CGRP), which has gained attention for its potential as a therapeutic target in the last 20 years.

As can be understood from the diversity of clinical signs and symptoms, migraine attack is a complex process that includes a series of neurological and vascular events (2,9,10,11,12). At different times, opinions emphasizing the role of vascular or neural factors in the development of migraine were dominant (9). In the 1940s, the vascular theory gained strength with the establishment of a relationship between the dilatation of cranial vascular structures and migraine headache in the studies of Graham and Wolff (9). Over time, the vascular theory has become questionable, with scientific findings supporting that migraine cannot be explained by vasodilation alone and that neuronal events are at the center of the process (9). Moskowitz et al. (13) proposed the neurovascular hypothesis in 1979, which suggested that vasoactive neuropeptides released from trigeminal nerve endings might play a role in the development of migraine. The neurovascular theory centered on the TGV system is still valid today (9,11,12).

Migraine and the Anatomy of the Trigeminal Nerve

The trigeminal nerve, with its three branches [ophthalmic (V1), maxillary (V2), mandibular (V3)] is responsible for the sensorial innervation of the entire face and most of the head, including the pain-sensitive intracranial structures (meningeal blood vessels, great cerebral arteries, venous sinuses, and part of the dura mater) (14). The neck and the occipital part of the head are innervated by the upper cervical nerves (C1-C2). The only ganglion of the trigeminal nerve is the sensory trigeminal (Gasser) ganglion. Some of the neurons in this ganglion contain various neuropeptides, especially CGRP, which has a role in the pathogenesis of primary headaches. In addition, some other neurons in the ganglion and satellite glia cells have CGRP receptors (15). Sensory impulses of all branches of the trigeminal nerve reach the spinal trigeminal nucleus (SpV) with central axonal processes from the trigeminal ganglion. SpV itself consists of three different anatomical parts. The part that plays a role in the transmission of pain sensation is called the trigeminal nucleus caudalis (TNC) and it extends towards the spinal cord (16). The TNC forms the trigeminocervical complex (TCC) together with the dorsal horn of the upper cervical (C1-C2) spinal cord. The TCC, which is the meeting place of the central extensions of the trigeminal ganglion and the C1-C2 spinal afferents innervating the adjacent skin, paraspinal and pericranial muscles, is a transition point for the pain signals coming from the periphery to reach the subcortical and cortical areas (9,10).

The Trigeminovascular System and its Role in Migraine Pathophysiology

The TGV system plays an important role both in the regulation of intracranial blood flow and in the transmission of pain (17). It was a concept that was first introduced in 1983 to describe the functional connection between the trigeminal nerve, meningeal vascular structures and the central nervous system (12). This system consists of the trigeminal ganglion, the cranial vascular structures innervated by the trigeminal nerve, and the SpV (17). The brain is a largely pain-insensitive organ, however, it has a rich nociceptive neural network consisting of unmyelinated C and thin myelinated Aδ (delta) fibers originating from the trigeminal ganglion and innervating cranial structures such as the meningeal vessels and large cerebral arteries (9).

Migraine attack is a process involving many central and peripheral neural anatomical structures (9,10,11,12,17,18). Although functional imaging methods have provided important information about this process, the neuronal mechanism that initiates pain has not yet been fully explained (9,12,19,20,21,22).

For many years, it has been thought that the brain stem is responsible for the onset of migraine headache because stimulation of periaqueductal gray matter (PAG) causes migraine-like headaches and because of the monitoring of activation in the dorsolateral pons (DLP) during spontaneous migraine attack by imaging methods. This view became controversial over time, as it was understood that DLP activation was not specific to migraine, the use of triptans did not abolish DLP activation, and PAG activation was not observed in patients with migraine in imaging studies (23).

It has been suggested that cortical spreading depression (CSD), which neurophysiologically corresponds to migraine aura, may be effective in the onset of headache in migraine by activating trigeminal sensory afferents (24,25). This view is based on the similarity between the immediate and delayed activation of CSD in the trigeminal ganglion and spinal TG nucleus in rodents and the immediate and delayed post-aura headache in humans (25). The absence of aura in two-thirds of migraine patients contradicts this view (22). In addition, the sensitizing effect of CSD on peripheral and central TGV neurons is not consistent in electrophysiological studies (2). It has also been suggested that there may be a link between a harmful internal brain event of migraine pain and the activation of trigeminal pain fibers, including the opening of Pannexin 1 mega-channels in stressed neurons, then activation of inflammatory pathways and the transmission of this signal to the trigeminal nerves around the pial vessels (26).

Another structure that has been suggested to play a role in the onset of migraine attack and headache within the framework of clinical and radiological findings is the hypothalamus (10,12,19,20,21,27). Homeostasis in the body takes place under

the control of the hypothalamus. Homeostasis-related symptoms such as fatigue, change in appetite, and recurrent yawning are common in the prodromal period (9,10). In a positron emission tomography study conducted in patients with episodic migraine without aura, the increase in blood supply in the hypothalamus during the prodromal period supported the view regarding the role of the hypothalamus in the early phase of the attack (19). In serial magnetic resonance (MR) sections obtained for 30 days in a patient with migraine without aura, it was shown that there was functional interaction and increased activity between the hypothalamus and TNC in the preictal period, and between the hypothalamus and dorsal rostral pons in the pain phase (21). In a functional MR imaging study including patients with chronic and episodic migraine and healthy volunteers, it was shown that the anterior part of the hypothalamus played an active role in the development of attacks and the chronicity of migraine, and the posterior part in the acute pain phase (27).

It is known that migraine attack is triggered by various internal and external factors (such as insomnia, hormonal factors, hunger, stress, chocolate, cheese, alcohol, light) in susceptible individuals (9,10,12,18). However, in recent years, a different perspective has emerged regarding the role of triggers in migraine. An experimental provocation study with triggers that patients stated based on their own migraine experiences resulted in migraine attacks in only 11% of patients (28). This result suggests that some factors thought to be triggers may actually be a part of the prodromal symptoms of the attack (9,12).

The process that predisposes to headache in migraine is not fully understood yet. However, it is thought that the headache phase begins with the stimulation of the nociceptive trigeminal nerve terminals that innervate the meningeal vessels, large cerebral arteries, and venous sinuses (18). Amongthe three branches of the trigeminal nerve, it is the ophthalmic branch that contributes most to the pathogenesis of migraine. This may explain why pain is commonly felt around the periorbital dermatome (29). Since the central projections from the trigeminal ganglion meet with the upper cervical nerves (C1-C2) that innervate the posterior part of the head in TCC, pain can also be felt in different parts of the head (frontal, temporal, parietal and occipital) and in the upper part of the neck (9,10). Trigeminothalamic processes from second-order neurons in the TCC extend upward to deliver the pain message to the thalamus. Meanwhile, they send collateral extensions to various nuclei in the brain stem, basal ganglia and hypothalamus. Fibers reaching the thalamus transmit sensory information to various cortical areas for processing after making synapses with thalamocortical neurons in the nuclei here. Thus, the clinical picture consisting of pain and accompanying symptoms specific to the attack emerges (9,10,11,29). In addition, the activation of the trigemino-autonomic pathway from TCC contributes to the emergence of autonomic symptoms accompanying headache. There is a reflex connection between the TCC and the superior salivary nucleus (SuS). SuS activates the trigeminal autonomic reflex retrogradely, causing autonomic symptoms such as lacrimation, rhinorrhea, periorbital edema, ptosis, and nasal congestion (9,10,29). On the other hand, parasympathetic messages from the SuS stimulate meningeal nociceptors via the sphenopalatine ganglion, causing the TGV pathway to continue to be activated and re-stimulation of the TCC via central TGV projections (9,10,29).

Calcitonin Gene Related Peptide and its role in migraine pathophysiology

The CGRP is a member of the CGRP family, which also includes calcitonin (CT), adrenomedullin and amylin (AMY) (30). It is a 37-aminoacid-long neuropeptide and exists in humans in two forms (alpha and beta). Alpha CGRP is mainly found in sensory neurons of the trigeminal ganglion, and beta CGRP is found in enteric motor neurons (22). This peptide was defined in 1982, its presence in the TGV system was demonstrated in 1984, and its role in the pathophysiology of migraine was first suggested in 1985 (31). CGRP is expressed in approximately half of the neurons in the trigeminal ganglion. It is stored in vesicles located at sensory nerve terminals and is released through exocytosis after neuronal activation. CGRP is expressed in the central nervous system by sensory neurons in various areas such as the TCC, PAG, hypothalamus, thalamus, and cerebellum (31).

The CGRP can act through all receptors associated with the CT peptide family; however, it has two receptors to which it binds with high affinity. These are CGRP and AMY 1 receptors (17). The distribution of CGRP receptors in the TGV system is similar to that of CGRP; however, they are not found in the same cell body or fiber as CGRP, except in Purkinje cells. CGRP receptors located in the myelinated A delta fibers of the trigeminal nerve are also found in approximately one third of the neurons in the trigeminal ganglion (31). The fact that these receptors are also common in satellite glia cells surrounding CGRP-expressing neurons suggests that they also play a role in neuron-glia cell interaction (31). AMY1, another receptor to which CGRP binds with high affinity, is also located in the trigeminal ganglion, but the function of these receptors in the pathophysiology and treatment of migraine is not yet known (31).

Sensory fibers of the trigeminal nerve contain various neuropeptides/neurotransmitters such as substance P, CGRP, neurokinin A, pituitary adenylate cyclase activating protein, and nitric oxide synthase, which play a role in the activation of TGV system (9,32). Among them, CGRP is the most abundant neuropeptide in trigeminal afferents and has an important role in the pathogenesis of migraine (9,22,30). CGRP is effective in the emergence of peripheral and central events that develop during a migraine attack, with its role in vasodilation, neurogenic inflammation, and peripheral and central synthesis processes (10,11,18,22,29,30). CGRP released from the axonal terminals of nociceptive afferents by stimulation of the trigeminal nerve causes vasodilation in meningeal vessels, increased vascular permeability and extravasation of plasma proteins. Neurogenic inflammation develops as a result of perivascular changes and the release of proinflammatory substances from mast cells in the dura mater. This local inflammatory response in meningeal structures increases the sensitivity of peripheral afferents to stimuli; that is, it results in peripheral sensitization (10,11,12,18,22,29,30). This results in a response at a lower threshold. The pulsatility of the headache becomes more perceivable when leaning forward or coughing is a result of peripheral sensitization (33). CGRP released from neurons in the trigeminal ganglion interacts with satellite glia cells and causes the release of various cytokines and nitric oxide. These substances increase the release of CGRP retrogradely, which leads to a vicious circle, allowing the continuation of trigeminal activation and peripheral sensitization. This situation is thought to be important in terms of the progression of the migraine attack.

Endogenous inflammatory mediators released during a migraine attack activate second-order neurons in the TNC, causing central sensitization. CGRP increases the release of excitatory substances such as glutamate from astrocytes and second-order neurons. On the other hand, CGRP activates α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid and N-methyl-D-aspartate receptors located in nerve endings of primary afferents, second-order neurons and astrocytes, and makes them more susceptible to excitation. This situation contributes to the central sensitization process by causing more release of excitatory substances (2). The clinical manifestation of central sensitization is allodynia. Allodynia, which is a feeling of pain and discomfort that occurs with simple contacts, can sometimes be felt to affect the whole body. Sensitization of neurons in the TCC and thalamic nuclei leads to cephalic and extracephalic allodynia, respectively (33). Persistent sensitization as a result of repetitive activation of the central TGV pathways plays a role in the development of chronic migraine (34).

Table 1. *In vivo* and *in vitro* findings supporting the role of CGRP in migraine pathophysiology

Release of CGRP into the extracerebral circulation in humans as a result of stimulation of the trigeminal ganglion (35)
High CGRP levels in the external jugular vein in the headache phase of migraine attack (36)
High CGRP levels in saliva during migraine attack and decrease after sumatriptan administration (37)
High cerebrospinal fluid CGRP levels in patients with migraine (38)
Intravenous CGRP infusion causing migraine-like attacks in patients with migraine (39,40)

CGRP: Calcitonin gene related peptide

Treatment Approaches Targeting the Calcitonin Gene Related Peptide Ligand or Receptor

The role of CGRP in the pathophysiology of migraine has been confirmed by findings from various *in vivo* and *in vitro* studies (Table 1). Based on these observations, the focus has been on the development of new treatment options targeting CGRP itself or its receptor since the early 2000s (41). The first of these are small molecule CGRP receptor antagonists called gepants. They have come to the forefront with the potential to be an alternative to triptans, which are accepted as standard acute migraine treatment but have limited effectiveness, limitations in use in some comorbid conditions (cerebrovascular and cardiovascular) and drug overuse associated with problems such as headache (42). The development processes of olcegepant and telcagepant, which were the first developed members of this class, were terminated due to the low oral bioavailability of the first and the liver dysfunction of the second in phase III studies (42). These problems were overcome in the second generation gepants developed later; ubrogepant and rimegepant were approved by the Food and Drug Administration for use in the treatment of acute migraine (43). The efficacy and side-effect profiles of these drugs are generally positive and similar; lack of direct vasoconstrictor effects is an important advantage over triptans (44).

Another treatment group developed to act on CGRP-related processes is monoclonal antibodies targeting the CGRP ligand or its receptor (30,31,45). These treatments are the first group of drugs focused on the pathophysiological mechanism for the prevention of migraine attacks. Since their molecular size is large, their potential to cross the blood-brain barrier is low (31,45). Since some of the CGRP and CGRP receptors are located outside the blood brain barrier, it has been predicted that monoclonal antibodies developed against CGRP or its receptor may be effective in the treatment of migraine (31,45). In clinical studies, they reduced the frequency of attacks, the need for acute treatment and disability; and were shown to improve quality of life (45,46,47,48,49,50,51,52). Considering that current preventive treatments should be taken daily, these monoclonal antibodies that require less frequent (monthly or quarterly) administration (31) will increase compliance with treatment in migraine. Their safety and tolerability were generally found to be good in clinical studies (45,46,47,48,49,50,51,52). Due to their high selectivity and high affinity for their target molecules, their undesirable effects are expected to be low. Since they are metabolized by the reticuloendothelial system, the possibility of hepatic and renal toxicity is thought to be low (34). As of the writing of this review, a total of 4 monoclonal antibodies, one against the CGRP receptor (erenumab) and three against CGRP itself (fremanezumab, galcanezumab, and eptinezumab), have been approved by various health authorities for use in the preventive treatment of migraine (43). Research continues to develop new monoclonal antibodies targeting the CGRP pathway.

Conclusion

Developments in the last few decades have contributed greatly to a better understanding of the role of the TGV system in the pathophysiology of migraine. CGRP has attracted attention with its central role in the cascade of events observed during a migraine attack, such as vasodilation, neurogenic inflammation, peripheral and central sensitization. As a result, migraine has become the main focus of drug research based on pathophysiology.

Drugs targeting the CGRP ligand or its receptor have added a new dimension to migraine treatment with their positive efficacy, safety and tolerability profiles in clinical studies. Real-life data will contribute to revealing the place of these new treatment options in clinical practice.

Acknowledgments

Dr. İdilhan Baloğlu Ar provided support in creating tables based on the authors' instructions, compiling author comments, citing references, and language.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Literature Search: N.K., Ş.B., M.M.B., Writing: N.K., Ş.B., M.M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
2. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. Headache 2019;59:659-681.
3. Institute for Health Metrics and Evaluation website. GBD 2019 results tool. Access date: 15 March 2021. Available from: http://ghdx.healthdata.org/gbd-results-tool
4. Ertas M, Baykan B, Orhan EK, et al. One-year prevalence and the impact of migraine and tension-type headache in Turkey: a nationwide home-based study in adults. J Headache Pain 2012;13:147-157.
5. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 2020;21:137.
6. Buse DC, Fanning KM, Reed ML, et al. Life with migraine: effects on relationships, career, and finances from the chronic migraine epidemiology and outcomes (CaMEO) study. Headache 2019;59:1286-1299.
7. Martelletti P, Schwedt TJ, Lanteri-Minet M, et al. My Migraine voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. J Headache Pain 2018;19:115.
8. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. J Headache Pain 2018;19:82.
9. Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev 2017;97:553-622.
10. Dodick DW. A phase-by-phase review of migraine pathophysiology. Headache 2018;58(Suppl 1):4-16.
11. Ashina M, Hansen JM, Do TP, et al. Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol 2019;18:795-804.
12. Haanes KA, Edvinsson L. Pathophysiological mechanisms in migraine and the identification of new therapeutic targets. CNS Drugs 2019;33:525-537.
13. Moskowitz MA, Reinhard JF Jr, Romero J, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine?. Lancet 1979;2:883-885.
14. Madscape. Facial pain and headache. Access date: 14 March 2021. Available from: https://emedicine.medscape.com/article/1048596-overview
15. Messlinger K, Russo AF. Current understanding of trigeminal ganglion structure and function in headache. Cephalalgia 2019;39:1661-1674.
16. Patel NM, Das JM. Neuroanatomy, spinal trigeminal nucleus. [Updated 2020 May 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539729/
17. Walker CS, Hay DL. CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amylin receptors?. Br J Pharmacol 2013;170:1293-1307.
18. Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. Pain 2013;154(Suppl 1):S44-S53.
19. Maniyar FH, Sprenger T, Monteith T, Schankin C, Goadsby PJ. Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain 2014;137:232-241.
20. Stankewitz A, Aderjan D, Eippert F, May A. Trigeminal nociceptive transmission in migraineurs predicts migraine attacks. J Neurosci 2011;31:1937-1943.
21. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain 2016;139:1987-1993.
22. Krishnaswamy R, Malik BH, Khan S, et al. Anti-CGRP monoclonal antibodies: breakthrough in migraine therapeutics. Progress in Neurology and Psychiatry 2019;23:26-33.
23. Borsook D, Burstein R. The enigma of the dorsolateral pons as a migraine generator. Cephalalgia 2012;32:803-812.
24. Close LN, Eftekhari S, Wang M, Charles AC, Russo AF. Cortical spreading depression as a site of origin for migraine: Role of CGRP. Cephalalgia 2019;39:428-434.
25. Zhang X, Levy D, Noseda R, et al. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. J Neurosci 2010;30:8807-8814.
26. Karatas H, Erdener SE, Gursoy-Ozdemir Y, et al. Spreading depression triggers headache by activating neuronal Panx1 channels. Science 2013;339:1092-1095.
27. Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: evidence from high-resolution fMRI. Neurology 2017;88:2011-2016.
28. Hougaard A, Amin FM, Hauge AW, Ashina M, Olesen J. Provocation of migraine with aura using natural trigger factors. Neurology 2013;80:428-431.
29. Goadsby PJ, Holland PR. An Update: Pathophysiology of Migraine. Neurol Clin 2019;37:651-671.
30. Ceriani CEJ, Wilhour DA, Silberstein SD. Novel medications for the treatment of migraine. Headache 2019;59:1597-1608.
31. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies - successful translation from bench to clinic. Nat Rev Neurol 2018;14:338-350.
32. Karatas H, Yemisci M, Eren-Kocak E, Dalkara T. Brain peptides for the treatment of neuropsychiatric disorders. Curr Pharm Des 2018;24:3905-3917.
33. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci 2015;35:6619-6629.
34. Boyer N, Dallel R, Artola A, Monconduit L. General trigeminospinal central sensitization and impaired descending pain inhibitory controls contribute to migraine progression. Pain 2014;155:1196-1205.
35. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. Ann Neurol 1988;23:193-196.
36. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 1990;28:183-187.
37. Cady RK, Vause CV, Ho TW, Bigal ME, Durham PL. Elevated saliva calcitonin gene-related peptide levels during acute migraine predict therapeutic response to rizatriptan. Headache 2009;49:1258-1266.
38. van Dongen RM, Zielman R, Noga M, et al. Migraine biomarkers in cerebrospinal fluid: a systematic review and meta-analysis. Cephalalgia 2017;37:49-63.
39. Hansen JM, Hauge AW, Olesen J, Ashina M. Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. Cephalalgia 2010;30:1179-1186.
40. Lassen LH, Haderslev PA, Jacobsen VB, et al. CGRP may play a causative role in migraine. Cephalalgia 2002;22:54-61.
41. Charles A, Pozo-Rosich P. Targeting calcitonin gene-related peptide: a new era in migraine therapy. Lancet 2019;394:1765-1774.
42. Negro A, Martelletti P. Gepants for the treatment of migraine. Expert Opin Investig Drugs 2019;28:555-567.
43. New Drug Approvals in the USA, Europe and Japan. Accessed date: 15 March 2021. Available at:https://www.genome.jp/kegg/drug/br08328.html
44. Tepper D. Gepants. Headache: The Journal of Head and Face Pain 2020;60:1037-1039.
45. Raffaelli B, Reuter U. The biology of monoclonal antibodies: focus on calcitonin gene-related peptide for prophylactic migraine therapy. Neurotherapeutics 2018;15:324-335.
46. Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017;377:2123-2132.
47. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:425-434.
48. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e2211-e2221.
49. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 2018;38:1442-1454.
50. Silberstein SD, Cohen JM, Yeung PP. Fremanezumab for the preventive treatment of migraine. Expert Opin Biol Ther 2019;19:763-771.
51. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: a randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia 2020;40:241-254.
52. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology 2020;94:e1365-e1377.