Current concept of the pathophysiology of migraine and new targets for its therapy

Tabeeva G.R.[1], Katsapava Z.[1, 2, 3, 4]

[1]Department of Nervous System Diseases and Neurosurgery, I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia, Moscow; [2]Department of Neurology, University of Duisburg-Essen, University Hospital, Essen; [3]Department of Neurology, Evangelical Hospital, Unna; [4]EVEX Medical Corporation, Tbilisi
[1]11, Rossolimo St., Build. 1, Moscow 119021, Russia; [2]Hufelandstr. 55, 45122 Essen, Germany;
[3]Holbeinstr 10, 59423 Unna, Germany; [4]40 Vazha-Pshavela Avenue, Tbilisi 0177, Georgia

Migraine is a common disabling chronic neurological disease. Many neurogenic, vascular, autonomic, and other mechanisms at different levels of the central and peripheral nervous systems are assumed to be implicated in the pathophysiology of headache and other manifestations of migraine. Advances in understanding the neurobiology of migraine have made it possible to clarify the main patterns of neurogenic-vascular relationships that explain the leading clinical manifestations of migraine, as well as to identify some biological markers that have triggered the creation of new targeted therapies for the disease. This review is dedicated to the latest advances in studying the pathophysiology of migraine and to new pharmacological approaches to its treatment.

Keywords: *migraine; pathophysiology; trigeminovascular system; calcitonin gene-related peptide (CGRP); anti-CGRP monoclonal antibodies.*
Contact: *Guzyal Rafkatovna Tabeeva;* ***grtabeeva@gmail.com***
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Introduction

Migraine is a chronic neurological disease which manifests in attacks of severe headache with significant effect on the functional activity of patients, which is considered the second leading cause of years lived with disability according to special WHO studies of all diseases (1). Migraine is one of the most common diseases, its prevalence in the population is 15–18% (2). Along with intense headache, migraine is characterized by prodrome, postdrome with multiple accompanying symptoms that occur both during the attack and in the interictal period. The most common of them (photophobia, phonophobia, nausea, vomiting, asthenia, irritability, decreased concentration, drowsiness, and appetite disorders) can last up to several days. Besides about a third of patients suffer from aura symptoms during headache attacks manifested as signs of neurological deficit in the form of various visual, somatosensory, speech and other disorders. All these features of migraine cause not only a high level of patient distress, but also complicate diagnostics of this disease and understanding of the mechanisms of various phenomena of this disease.

Evolution of migraine pathogenesis concept

Headache is known to mankind for 6000 years and its very first descriptions most likely relate specifically to migraine (3). For almost two centuries, migraine has been considered a nervous system disease along with the obvious involvement of impaired vascular regulation of cerebral blood flow. To a large extent, the basic ideas about migraine were formed in the 17th century thanks to the work of Thomas Willis (4), who suggested that headache during migraine is due to increased arterial blood flow and distension of the cerebral vessels. Later in the classic work «On Megrim, Sick Headache, and Some Allied Disorders: A Contribution to the Pathology of Nerve-Storms» Edward Liveing considers migraine more as a nervous system disease (5).

It was only in the beginning of the 20th century that the era of modern research of the mechanisms of headache during migraine started. The studies of cranial blood vessels in patients performed by Harold Wolff and his colleagues in the 1940s helped formulate the vascular theory of migraine (6). This concept became the leading one for almost five decades and formed the basis for the development of the first specific drug for relief of migraine attacks – sumatriptan. Meanwhile, subsequent studies of the mechanisms of triptans action revealed their neurogenic effects along with the vascular ones, which allowed to demonstrate other mechanisms, including the effects of sterile neurogenic inflammation within the dural vessels, associated with antidromic activation of trigeminal afferents. Since then, experimental studies focused on identification of the main mediators of inflammation and their effect on migraine headache. However, it started to become clearer that the vascular mechanisms did not fully explain the origin of both pain and non-painful manifestations of migraine. In recent decades, the main debate regarding the mechanisms of disease development has concentrated around two main concepts that postulate the leading role of either vascular or neurogenic mechanisms in the initiation and development of headache attacks during migraine (7).

Thanks to the achievements in fundamental neurosciences over the last two decades, our ideas about the neurobiology of migraine have expanded significantly. The complex relationships of the mechanisms of prodrome, aura, postdrome, pain development, as well as the patterns of migraine

as a chronic disease compels to consider it a complex neurogenic disease. There is a strong belief that the onset of a migraine attack is due to the interaction of endogenous and exogenous triggers (8). Meanwhile, the mechanisms that underlie the susceptibility to triggers and, in general, the processes that determine the onset of migraine attacks are not fully understood. There is no doubt that the key element in the pathogenesis of migraine attacks is the activation and sensitization of the trigeminovascular system (TVS), as well as stem and diencephalic nuclear areas (9.10). Besides, the primary dysregulation of sensory information processing probably leads to the formation of a whole complex of sensory manifestations so characteristic of patients with migraine. Symptoms of approaching migraine attack can occur many days before the onset of headache. Moreover, these are mainly non-painful neurological symptoms, which may indicate a wide involvement of various brain regions in the pathogenesis of a migraine attack. The concept of brain «hyperexcitability» (11,12) based on some neurophysiological and neuroimaging data, is often used to explain these phenomena. Interpretation of some patterns of predisposition to migraine attacks can be based on the data of genetic studies. Genes of a rare form of familial hemiplegic migraine were identified as responsible for the formation of severe motor manifestations of aura, and evidence of genetic predisposition to migraine were observed in family studies, indicating the possibility of genetically determined predisposition to the disease (13). Currently the integrated understanding of the pathophysiology of this disease involves the consideration of the continuous pattern of prodrome, aura, headache, postdrome, and interictal state in migraine.

Migraine prodrome

The prodromal phase of migraine can start several days before the first signs of headache and often manifests in such symptoms as fatigue, mood swings, food cravings, yawning, muscle tension and photophobia. Many of these manifestations are characterized by diurnal fluctuations suggesting the role of homeostatic triggers and involvement of hypothalamus, brain stem, limbic system, and some cortical structures in the early stages of attacks (14) on one hand and emphasizing the importance of chronobiological patterns in the pathogenesis of migraine on the other (14, 15).

Studies of cerebral blood flow using positron emission tomography (PET) during the prodromal phase of attack induced by nitroglycerin in patients with migraine headache revealed activation of the posterolateral segments of hypothalamus, tegmental area of midbrain, periaqueductal gray matter (PGM), posterior region of dorsal horns and various parts of the cerebral cortex (16). Studies of functional magnetic resonance imaging (fMRI) in patients with migraine during interictal period compared with healthy individuals showed closer functional connections between the hypothalamus and brain areas associated with pain transmission and vegetative functions, which may explain the origin of some vegetative symptoms observed during interictal and prodromal phases (17). The participation of hypothalamus in the early stages of a migraine attack raises the question of how hypothalamic formations can facilitate the transmission of pain impulses during a migraine attack. There are at least two hypotheses to explain this pattern (18).

The first hypothesis suggests a leading role of increased parasympathetic tone in the activation of meningeal nociceptors. Migraine is characterized by a variety of vegetative manifestations such as nausea, vomiting, thirst, and sometimes lacrimation, nasal congestion, and rhinorrhea. Meanwhile classic migraine triggers, such as stress, transition from sleep to wakefulness and other changes in physiological homeostatic parameters, activate nociceptive pathways by increasing parasympathetic tone (17). The processes of sympathetic activation can also play a part in the mechanisms of inducing migraine attacks by stress. Thus, experimental studies showed that sympathetic activation of vegetative fibers in the meninges due to noradrenaline release contributes to the activation of pronociceptive transmission in dural trigeminal afferents (19). These physiological mechanisms also include the involvement of preganglionic fibers of the parasympathetic neurons of the superior salivatory nucleus (SSN) accomplished through release of neuropeptide molecules contained in parasympathetic efferents that innervate the meninges and meningeal blood vessels (19). Another explanation of the hypothalamic effects on nociceptive afferentation include modulation of nociceptive thalamo-cortical signals and thresholds of cyclic stem activity.

The second hypothesis suggests the role of the modulating effect on nociceptive thalamo-cortical projections of the release of excitatory and inhibitory neuropeptides/neurotransmitters primarily from hypothalamic neurons (15). The balance of these neurotransmitters regulates the excitability of relay trigeminovascular neurons. If neurotransmitter is excitatory, it can switch the activity of thalamic trigeminovascular neurons from a state of hyper-excitability to tonic contraction; if neurotransmitter is inhibitory, it induces a shift from the tonic regimen to hyper-excitability (15). Thus, converging projections from neurons of hypothalamus and cortex can determine whether transmission of nociceptive signals to the cerebral cortex will take place (15). The possibility of transition from prodromal phase to the headache phase is apparently determined by chronobiological patterns, in particular by the current circadian phase of the cyclic activity of the brain stem systems (7,15,20,21). If the cyclic activity of the brain stem is high, the threshold for nociceptive trigeminovascular transmission is increased and nociceptive signals are inhibited. If the cyclic activity of brain stem is low, the threshold for the transmission of nociceptive signals decreases, inducing a migraine headache (15,21). This may partially explain why identical migraine triggers (both exogenous and endogenous) do not always induce an attack, since this can largely depend on the current stage of the cyclic brain rhythm and the degree of modulation of trigeminovascular nociceptive signals (15).

Migraine aura

About one third of migraine attacks are preceded by aura symptoms. These completely reversible focal neurological manifestations in typical cases develop gradually, last for a few minutes and are followed by subsequent headache. The most common type is the visual aura representing about 90% of all its cases. Less common types also include sensory, speech and motor manifestations. A typical visual aura usually starts before the headache phase, but sometimes it can occur simultaneously or even independently of the pain phase of migraine (26). In typical cases, it starts with a blind or flickering spot in the cen-

ter of the visual field. Clinically, these phenomena were first recorded by K.S. Lashley (27), who observed the development of his own visual aura. He described the appearance of scotoma, which increased in size during 1 hour, drifting in the shape of letter «C» from the temporal visual field with a speed of 3 mm/min.

The phenomenon of cortical spreading depression (CSD) described a few years later lies at the bottom of neurophysiological mechanisms that determine neurological manifestations of the aura during migraine. Aristides Leao (22) in 1944 observed depression of activity by electric cortex spreading centrifugally from the stimulation site at a speed of 3 mm/min in experiments on rabbits with electrical stimulation of the cerebral cortex, and suggested that this phenomenon could explain the mechanism of migraine aura. The possibility of initiating CSD in humans was later demonstrated by J. Olesen et al. in experiments with administration of ^{133}Xe into the carotid artery during a migraine aura, which showed a spreading change in regional cerebral blood flow (28). A subsequent neuroimaging study with signal modification depending on the level of blood oxygen (BOLD) during the phase of the visual aura in patients with spontaneous migraine attacks also showed a gradual spreading of signal modification at a speed of 3.5 mm/min, which corresponded to the clinical dynamics of visual phenomena (29).

CSD is a slowly (2–6 mm/min) spreading wave of depolarization of cortical neurons and glial cells which is accompanied by suppression of cortical activity, with temporal characteristics coinciding with the onset or progression of aura symptoms (23), and also accompanied by hyperemia wave succeeded by a long phase of cortical oligemia (24). CSD is initiated by a local increase of extracellular potassium (K^+) concentrations, which chronically depolarizes neurons for a period of approximately 30–50 seconds (24). It is assumed that the initial accumulation of extracellular K^+ results from the repeated depolarization and repolarization of hyper-excitable neurons in the cerebral cortex, and that this accumulation of K^+ additionally depolarizes the cells from which it was isolated. This large outflow of K^+ is associated with a serious violation of the ionic gradients of the cell membrane, the afflux of sodium (Na^+) and calcium (Ca^{2+}) and release of glutamate (24). Distribution of CSD occurs through gap junctions between glial cells or neurons and can trigger nociceptive processes in the trigeminal nerve system and, thus, initiate headache mechanisms (23,25). CSD induced by chemical, mechanical, or electrical stimulation can cause prolonged activation of approximately 50% of meningeal nociceptors, which can last about 2 hours (25). So in general, CSD activates the trigeminovascular system neurons in about half of cases, and this activation of meningeal nociceptors can contribute to delayed vascular changes in the dura mater, which, apparently, are no longer dependent on CSD.

CSD can trigger the activation of stem and trigeminovascular mechanisms without participation of meningeal nociceptors, which leads to dysfunction of pain modulation structures, including the nucleus raphe magnus (NRM) (30), changes the system of nociceptive signals processing in the trigemino-cervical complex (TCC), which most likely happens during migraine aura without headache (26). Therefore, various mechanisms of CSD effect on the initiation of a migraine attack should be considered: through activation of peripheral trigeminovascular system and through modification of the central processes of pain modulation. Nevertheless, despite the convincing clinical and pathophysiological correlations, the role of CSD in the development of a migraine attack remains unclear (31): does the aura trigger a migraine attack or is the aura a parallel process that determines the clinical subtype of «migraine with aura»? Despite these questions the importance of CSD in the development of migraine headache is undoubtful.

Headache

The headache phase during migraine is characterized by cephalgia with a number of key features, as well as non-painful manifestations including nausea, vomiting, photophobia and phonophobia. A pulsating unilateral pain characteristic of migraine is traditionally regarded as a consequence of TVS activation (10). TVS provides the transmission of nociceptive information from the meninges to the CNS. Nociceptive fibers in the first division of trigeminal nerve, originating from trigeminal ganglion (TG), innervate the dura mater and large cerebral arteries. This nociceptive innervation occurs mainly through the ophthalmic division of trigeminal nerve. Afferent projections from TG converge with afferents innervating the skin, muscles and other organs and originating from C_1–C_2 roots on second-order neurons in the TCC, which includes the caudal nucleus of trigeminal nerve (CNTN) and the structure of the posterior horn of the upper cervical spinal cord (7). The convergence of afferent projections with neurons from extracranial structures explains the actual perception of pain in the periorbital, occipital and occipital-cervical regions during migraine (32).

Ascending pathways from the TCC transmit signals to multiple nuclei of the brain stem, thalamus, hypothalamus and basal ganglia, projections of which reach several areas of the cortex, including somatosensory, motor, auditory, visual and olfactory areas, as well as brain regions that are involved in processing of cognitive, emotional and sensory discriminatory aspects of pain signals, which explains such migraine symptoms as photo-, phonophobia, cognitive dysfunction, osmophobia and allodynia (15,33).

Migraine pain involves stimulation of nociceptive neurons in the periphery that innervate the dura mater results in the release of vasoactive neuropeptides, such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-38 activating polypeptide (PACAP), which provides pain transmission along the trigeminovascular pathway. The role and degree of involvement of cerebral artery vasodilation, mast cell degranulation, and plasma extravasation in these processes remains unclear (34). Perhaps CSD initiates the release of ATP, glutamate, K^+, hydrogen ions, CGRP, and nitric oxide (NO). These molecules diffuse and activate meningeal nociceptors (23). This neuronal activation occurs approximately 14 minutes after the induced CSD, which is consistent with the time interval between the onset of aura and the onset of migraine headache (25). It was also shown that CSD can lead to subsequent activation of central trigeminovascular neurons in the spinal nucleus of trigeminal nerve (25). Peripheral trigeminovascular neurons become sensitized to subsequent dural stimuli after activation by endogenous mediators which is reflected in decreased threshold values of reactions and increased degree of their response. Peripheral sensitization is

believed to be responsible for the characteristic pulsating migraine pain and increased pain during bending or cough (15). Sensitization of central trigeminovascular neurons in the TCC and thalamic nuclei is responsible for cephalic and extracephalic allodynia, which is reported by most patients and which is characterized by multiple phenomena (pain in response to touching the scalp, combing, putting on glasses, etc.). Symptoms of central sensitization appear approximately 30–60 minutes after the onset of the headache and fully unfold within 120 minutes(7).

Photophobia, which is considered a typical manifestation of a migraine attack, is a hypersensitivity, discomfort and increased pain in response to exposure to bright light. Photophobia is reported by almost 90% of patients with migraine (35). Understanding the nature of photophobia has become available after a study in blind patients with migraine. In the complete absence of visual perception due to damage to the optic nerve, exposure to light did not affect the characteristics of the migraine headache and light did not cause pupillary reactions and, on the contrary, headache in response to light exposure maintained in blind patients with migraine with partial perception of light and intact optic nerve due to degeneration of rod and cone photoreceptors (36). Light stimulation increases the activity of thalamic trigeminovascular neurons located in the lateral and posterior segments of thalamus, that receive direct projections from photosensitive retinal ganglion cells. The axons of these neurons are projected into the cortical regions involved in pain processing and visual perception (36). Meanwhile the initial increase in the excitability of visual cortex neurons in patients with migraine is considered the main component of its increased susceptibility to visual stimuli.

The concept of brain «hyper-excitability» during migraine is based on the data from neurophysiological studies that show an increased level of neuronal reactions of cortical and stem structures in response to a wide range of stimuli, including visual, somatosensory, auditory, and nociceptive ones (37). For example, studies of event-related potentials showed suppression of the habituation phenomenon in response to repeated stimulation, which is not characteristic of individuals without migraine (37). These facts are also supported by neuroimaging data that show signs of hyper-excitability of various structures, including the interictal period of migraine (38). It is suggested that this general neuronal hyper-excitability may explain increased sensitivity to sensory stimuli and may contribute to the development of central sensitization, since patients with migraine have a higher level of activation in areas of the brain that facilitate pain transmission and decreased level of activation in the projection of pain-inhibiting systems (38).

One of the fundamental preconditions of initial generalized hyper-excitability of brain structures during migraine is the modern understanding of its genetic mechanisms (39). Genetic predisposition to migraine is based on clinical observations and is supported by population-based family studies (40). These studies show that immediate relatives of patients with migraine have a higher risk of disease compared with relatives of the control group (40). First degree relatives of patients with migraine with aura had a 4-fold increase in the risk of migraine, while relatives of patients with migraine without aura showed a 1.9-fold increased risk. Studies of monozygotic and dizygotic twins also revealed a significant genetic component in the development of migraine: monozygotic twins suffering from migraine have a 1.5–2 times higher concordance value compared to dizygotic twins (41,42).

The first identified genetic association was familial hemiplegic migraine (FHM), a rare monogenic subtype of migraine with autosomal dominant inheritance. It is characterized by migraine attacks, accompanied by transient unilateral weakness. There are 5 types of FHM: 1) type 1 FHM – missense mutation in the *CACNA1A* gene (50–75% of families); 2) type 2 FHM – mainly deletion and shift of reading frame in the *ATP1A2* gene (20% to 30% of cases); 3) type 3 FHM – mutations in the *SCN1A* gene at 2q24; 4) type 4 FHM C mutations in the *CACNA1E* gene at 1q25-q31; 5) FHM caused by mutations in other genes *(SLC1A3, SLC4A4, PRR2)* (39). All these mutations in FHM encode mechanisms that affect ion transporters, proteins that ultimately modulate the availability of glutamate at synaptic terminals, which ultimately leads to increased excitability of neurons (43).

Genome-wide association studies (GWAS) of migraine revealed the associated polymorphic variants of the susceptibility genes that cause glutamatergic neurotransmission, the development of synapses and neuroplasticity, pain sensitivity, activity of metalloproteinases, vascular system and metabolism (43). Although the involvement of most genes in the development of the disease remains unclear, data from several GWASs confirm the role of glutamatergic mechanisms in the development of CSD, neuronal hyper-excitability, and trigeminal nociception processes (39).

New targets for migraine pharmacotherapy

Existing migraine treatment strategies have many limitations in everyday practice. One of the main problems of preventive pharmacotherapy is the fact that none of the currently used drugs (antidepressants, anticonvulsants, beta-blockers, Ca^{2+} blockers) was created specifically for migraine treatment and the vast majority of drugs don't have migraine preventive treatment in the list of indications for use. Meanwhile, these migraine preventive measures have insufficient efficacy and sometimes unsatisfactory tolerability. The issue of preventive therapy is also closely related to low treatment adherence among patients with migraine.

Recent advances in understanding the pathophysiology of migraine have prepared the way for the development of new pharmacotherapeutic approaches specifically aimed at various neuronal mechanisms. Some of these approaches are now available for clinical use in some countries while others are at different stages of clinical development. They are promising in terms of higher efficacy and safety of preventive treatment of episodic and chronic migraine. In addition, their development destroys the existing dichotomous separation between acute (symptomatic) and preventive treatment, since some of these new compounds target the neurobiological base of migraine common for both strategies (44). And the most attractive is the targeted approach aimed at specific neurobiological targets, the role of which in the pathophysiological mechanisms of migraine is undeniable. The most studied is the strategy aimed at CGRP neurobiology (44).

CGRP was first identified in 1982 (45) and since then numerous studies demonstrated its key role in the pathophysiology of migraine (46). CGRP is widely expressed throughout the

central and peripheral nervous system, including TVS (46). CGRP is produced in peripheral sensory neurons and many other sites throughout the central nervous system and packing into vesicles with dense nucleus for transportation to axon terminals and other release sites within the neuron (47). During stimulation of nerves that produce CGRP, its release from the vesicles occurs through calcium-dependent exocytosis, but can be stimulated by capsaicin, which is often used in experimental studies. Presynaptic receptors located in trigeminal neurons regulate CGRP release.

Presynaptic serotonin receptors 5-HT1B and 5-HT1D inhibit CGRP release and therefore serve as targets for triptan action (48). The third subtype of the presynaptic serotonin receptor, 5-HT1F, was identified later and is also considered as a target for potential inhibition (49). Activation of this type of receptor also inhibits CGRP release from the trigeminal nerve, and a clinical study showed that the 5-HT1F agonist lasmiditan is effective in the symptomatic treatment of migraine attacks (50).

The CGRP receptor is a complex of several proteins, the center of which is calcitonin receptor-like receptor (CLR). To create a functional membrane receptor with specific affinity to CGRP, CLR must form a heterodimer with a protein that modifies the activity of receptor 1 (RAMP1) (47). RAMPs are transmembrane proteins that alter the pharmacology, functional activity of specific receptor cells associated with the G-protein. The ligand-binding domain of the CGRP receptor is located on the border between RAMP1 and CLR, and therefore coexpression of CLR and RAMP1 is necessary for cell response to CGRP (47). CLR is associated with G-protein that contains the G?s subunit, which activates adenylate cyclase and cAMP-dependent signaling pathways. A receptor-mediated increase in intracellular cAMP activates protein kinase A (PKA), which leads to phosphorylation of many substances, including K^+ sensitive ATP channels (KATP), extracellular signal-regulated kinases (ERK), and transcription factors such as cAMP response element binding protein (CREB). When CGRP is activated in the smooth muscles of cerebral vessels, cAMP increase leads to vascular relaxation and dilation of blood vessels (47).

The discovery of CGRP in the trigeminovascular system in 1985, suggested that this peptide may play an important role in the pathophysiology of migraine (52), especially in connection with its pronounced vasodilating effects in the cerebral arteries, which corresponded to the association of cerebral vasodilation with migraine. Highest levels of CGRP were observed in young people (aged 20–40 years) and their decrease was noted by the age of 60 years, which is consistent with the age-related dynamics of headache attacks observed in migraines (46).

In 1990, P.L. Goadsby et al. conducted an original study of the level of the main neuropeptides identified in the TVS (53). CGRP levels were significantly increased in blood samples from the external jugular vein of patients with migraine during the headache phase while no significant changes were observed in the levels of other neuropeptides. Subsequently, increased CGRP level was detected in plasma, saliva, and cerebrospinal fluid samples (46). The relationship between CGRP release and headache during migraine suggested the possibility of using CGRP as a diagnostic biomarker, however, the instability and short half-life of the peptide sharply limited the reliability of its measurement: in contrast to the clear results of its increase in the blood of the external jugular vein, no change was observed in simultaneously collected peripheral blood samples (46). Subsequent clinical studies with intravenous administration of exogenous CGRP to patients suffering from migraine attacks, showed a reproducible effect of inducing the migraine headache in 57–75% of migraine patients while not inducing migraine headache in healthy controls, convincingly demonstrating the important causative role of this peptide in migraine symptom formation (54).

CGRP effects can be associated with both peripheral and central action during migraine. Calcitonin gene-related peptide (CGRP)is a 37-amino acid neuropeptide with two isoforms (α and β) that is implicated in the pathophysiology of migraine and other headache disorders. In the periphery, CGRP may contribute to pathophysiological events in migraine, including vasodilation, inflammation and protein extravasation(55). Perivascular CGRP release from the trigeminal nerve causes vasodilation and degranulation of mast cells in the dura mater and both components contribute to the neurogenic inflammation of the dura mater (55). The inflammatory cascade can be caused by CGRP exposure not only of the mast cells of the dura mater and satellite glia cells in TG that contain CGRP receptors. In the context of the central CGRP effects the fact of its involvement in the initial phase of hyperemia during CSD is noteworthy, since CGRP receptor antagonists block the transient dilatation of the pial artery (55). Moreover, under experimental conditions the possibility of inducing aura by peripheral CGRP injection was shown (54), which suggests CGRP involvement in the CSD effect on headache during migraine.

Currently, there are clinical studies proving that suppression of CGRP pathway can effectively prevent or treat migraine (44). In modern clinical studies, there are three separate classes of test compounds that directly target the neurobiology of CGRP. These are small molecules that antagonize CGRP receptor (gepants), anti-CGRP ligand or anti-CGRP-receptor monoclonal antibodies (mAbs) (44).

The first receptor antagonist blocking the CGRP receptor, olcegepant (BIBN4096), showed good efficacy in a phase II study: 66% of patients reported headache relief 2 hours after administration compared with 27% in the placebo group (54). However, intravenous drug administration limited its use in clinical practice. The oral drug telcagepant underwent two phase III trials with positive results, however, the registered toxic hepatic effects led to discontinuation of further studies. Several other low molecular weight CGRP receptor antagonists, known as gepants, underwent clinical trials, but until recently, none of them has been marketed. Ubrogepant (NCT02867709) has completed phase III clinical trials where efficacy and tolerability for the acute treatment of migraine has been performed (56). Rimegepant (NCT03461757) completed phase III clinical trials for symptomatic treatment of migraine, while atogepant (NCT02848326) is currently in phase II/III clinical trials for prevention of episodic migraine (54).

The blockade of CGRP with therapeutic monoclonal provides a qualitatively new direction – by using hybridoma technology. A hybrid cell is a cell formed by the fusion of two or more somatic cells, resulting in the communization of cell membranes, cytoplasm, and, most importantly, chromosomes, carriers of the

genetic program of cell activity. The obtained hybrid cell inherits and combines the properties of both parent cells, including the ability to divide and specific biosynthesis. When immunocompetent cells i.e. lymphocytes were used as one partner for hybridization, and infinitely proliferating tumor cells «perpetuating» the productive activity of lymphocytes as the second partner, this led to creation of hybridomas that secrete monoclonal antibodies (mAbs).

A real breakthrough in the use of mAbs in neurology was made by the registration studies of four substances, the main target of which is calcitonin-gene-related peptide (CGRP) or its receptor(CGRP-R) for preventive treatment of migraine (55). Anti-CGRP pathway mAbs represent a completely different paradigm in the treatment of headaches: for the first time a new class of drugs has come into clinical practice that is specifically designed for prevention of primary headaches. All pharmacological agents that were used in preventive treatment of migraine initially had other indications and were used in preventive treatment of migraine as «off-label». Therefore, with a few exceptions, even official indications of these drugs didnXt include migraine preventive treatment. It is worth mentioning that anti-CGRP pathway mAbs in contrast to mAbs used, in particular, for multiple sclerosis, do not alter the immune system and do not have toxicity and are probably safe and well tolerated (56).

MAb therapy has several important advantages over conventional small molecule treatment. Strict targeted specificity («key lock»), long half-life (usually from several weeks to several months), low risk of drug interactions, and limited toxic potential make mAbs attractive therapeutic agents (57). Due to their large size and hydrophilicity mAbs are administered parenterally, which may also be preferable, given the possibility of developing gastroparesis during or between migraine attacks. Finally, mAb dosage regimen as a monthly or even quarterly injections compared with daily oral drug administration is likely to increase patient adherence to treatment (56).

Currently, four representatives of anti-CGRP pathway mAbs completed clinical trials. Three of them (Fremanezumab, Galcanezumab and Eptinezumab) target the ligand, and one (Erenumab) targets the CGRP receptor. All clinical studies of the four mAbs showed similar efficacy and good tolerability (Fig. 1). The proportion of patients with decrease in the number of days with migraine by> 50% ranged from 47.7% to 62% (58). Erenumab, Fremanezumab, Galcanezumab have already been approved for the preventive treatment of migraine.

Fremanezumab is a fully-humanized monoclonal antibody (IgG2Δa) that. potently and selectively binds to both CGRP isoforms to prevent them from binding to the CGRP receptor. (59). Fremanezumab is approved by the FDA and EMA for preventive treatment. In Russia, Fremanezumab (Ajovy) was approved in February 2020 (63). The drug is administered as subcutaneous injections in a dose of 225 mg monthly or 675 mg quarterly. Tmax is 5–7 days, and the plasma elimination half-life is 31 days. Such pharmacokinetic features provide an early manifestation of the clinical effect (a significant difference vs placebo is achieved during the first week of treatment) and duration of the treatment effect (59). A phase III clinical study in 1130 patients with chronic migraine studied the efficacy of monthly injections of 225 mg and quarterly injections of 675 mg of fremanezumab vs placebo (60). The proportion of patients with >50% reduction in the number of days with a headache was 41% after monthly administration and 38% after quarterly administration (18% in the placebo group, p<0.001) (60). The most common side effect was pain at the injection site. Similar results were obtained in another phase III clinical trial in 875 patients with episodic migraine who received monthly injections of fremanezumab at a dose of 225 mg or quarterly injections at a dose of 675 mg (61). The percentage of patients with> 50% reduction in days with migraine headache was 47.7% and 44.4% (after monthly and quarterly administration, respectively) compared with placebo (27.9%, p<0.001). A subsequent analysis showed that fremanezumab is effective and safe as adjunct treatment of patients with migraine receiving stable doses of other preventive agents (62).

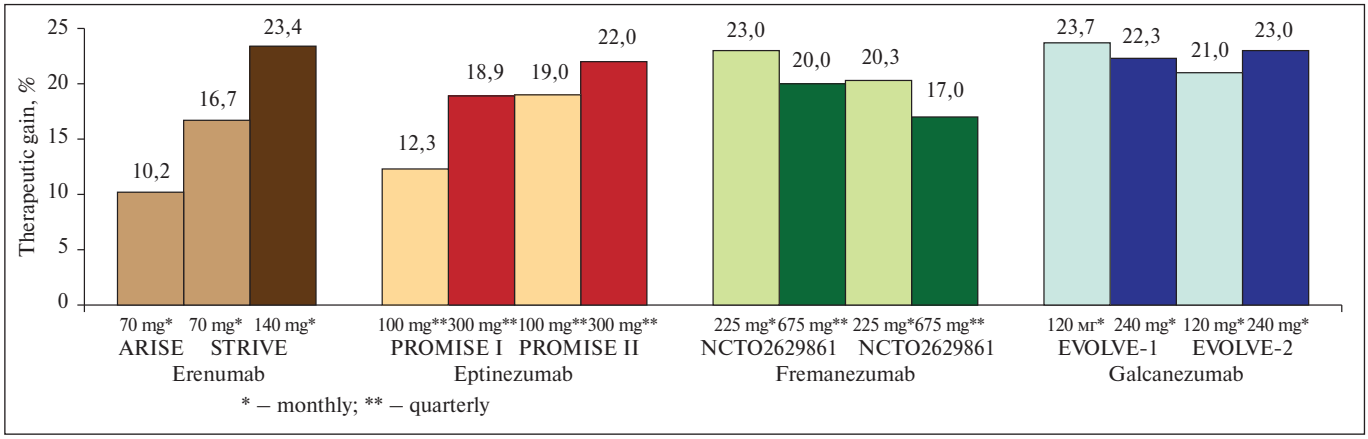

Fig. 1. *MAbs efficacy in migraine preventive treatment (61).*
Overview of the therapeutic gain in percentage of patients with >50% reduction in migraine days with anti-calcitonin gene-related peptide monoclonal antibodies. A darker bar indicates a higher dose. *Therapeutic gain is defined as the difference between percentage of patients in active group compared to percentage of patients in placebo group.*

Conclusion

Migraine is a neurogenic, genetically determined disease, its pathogenesis involves various levels of central and peripheral nervous system. The complex patterns of sequential activation of certain stem, thalamic, hypothalamic and cortical structures determine the characteristic phase changes in the course of migraine. Advances in the study of the pathophysiological mechanisms of migraine onset have expanded our understanding. Identification of the key role of neuropeptides, primarily CGRP, contributed to the development of new classes of drugs for targeted therapy, which are based on new fundamental and clinical studies.

Development of anti-CGRP mAbs is one of the most significant achievements in the field of migraine. The results of phase II and III clinical trials demonstrate their high efficacy in preventive treatment of migraine and at the same time a favorable tolerability profile. A significant advantage of mAbs is convenient treatment regimen in the form of single parenteral administration with 4- or 12-week intervals. Easy use and absence of systemic side effects are important aspects that increase patient adherence to preventive treatment. All currently available oral preventive drugs require long-term (at least 2–3 months) use in the optimal dose to assess their efficacy. During mAb treatment the effect is observed within a week in many patients, as demonstrated by significant difference in key efficacy parameters vs placebo, though some patients were noted to have a later onset of effect (60). All these factors undoubtedly indicate the great therapeutic potential of mAbs, taking into account the possibility of their use in treatment of episodic and chronic migraine, medication-overuse headache, in patients resistant to preventive treatment, that is, in the widest range of patients with migraine.

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Tabeeva G.R. *https://orcid.org/0000-0002-3833-532X*
Katsarava Z. *https://orcid.org/0000-0002-9932-1159*