Research Results in Pharmacology

Research Results in Pharmacology 7(2): 67–82
UDC: 615.225
DOI 10.3897/rrpharmacology.7.67463

Review Article

Migraine pharmacology and brain ischemia

Ruben S. Mirzoyan[1], Tamara S. Gan'shina[1], Ilya N. Kurdyumov[1], Denis V. Maslennikov[1], Anna V. Gnezdilova[1], Alexander A. Gorbunov[1,2], Elena V. Kursa[1], Antonina I. Turilova[1], Leonid M. Kostochka[1], Narine R. Mirzoyan[3]

1 *V.V. Zakusov Research Institute of Pharmacology, 8 Baltiiskaya St., Moscow 125315, Russia*

2 *I.M. Sechenov First Moscow State Medical University (Sechenov University), 8 Trubetskaya St., Bldg. 2, Moscow 119991, Russia*

3 *Yerevan State Medical University after M. Heratsi, 2 Koryun St., Yerevan 0025, Armenia*

Corresponding author: Ruben S. Mirzoyan (cerebropharm@mail.ru)

Academic editor: Mikhail Korokin ♦ **Received** 17 March 2021 ♦ **Accepted** 14 June 2021 ♦ **Published** 29 June 2021

Citation: Mirzoyan RS, Gan'shina TS, Kurdyumov IN, Maslennikov DV, Gnezdilova AV, Gorbunov AA, Kursa EV, Turilova AI, Kostochka LM, Mirzoyan NR (2021) Migraine pharmacology and brain ischemia. Research Results in Pharmacology 7(2): 67–82. https://doi.org/10.3897/rrpharmacology.7.67463

Abstract

Introduction: The aim of this review article was to analyze in details the mechanism of drugs' effects in the treatment and prevention of a migraine attack, as well as to discuss the hypotheses of migraine pathogenesis.

Migraine attack treatment agents: The main agents for migraine attack treatment have an anti-nociceptive activity.

Agents for migraine preventive treatment: β-blocker propranolol also has anti-serotonin and analgesic activities, and most drugs used for the prophylactic treatment of migraine have a vasodilating activity.

Vascular hypothesis of migraine pathogenesis: Despite numerous studies that have expanded our understanding of migraine pathogenesis, the importance of the vascular component in the pathogenesis of this disease has not questioned yet.

Neurogenic hypotheses of cortical spreading depression: It is necessary to take into account the points of this hypothesis in the context of the pathophysiology of migraine.

Neurochemical serotonin hypotheses of migraine pathogenesis: Serotonin plays an important role in the pathogenesis of migraine.

Trigemino-vascular hypotheses of migraine pathogenesis: The trigemino-vascular hypothesis claims to solve the problem of migraine pain.

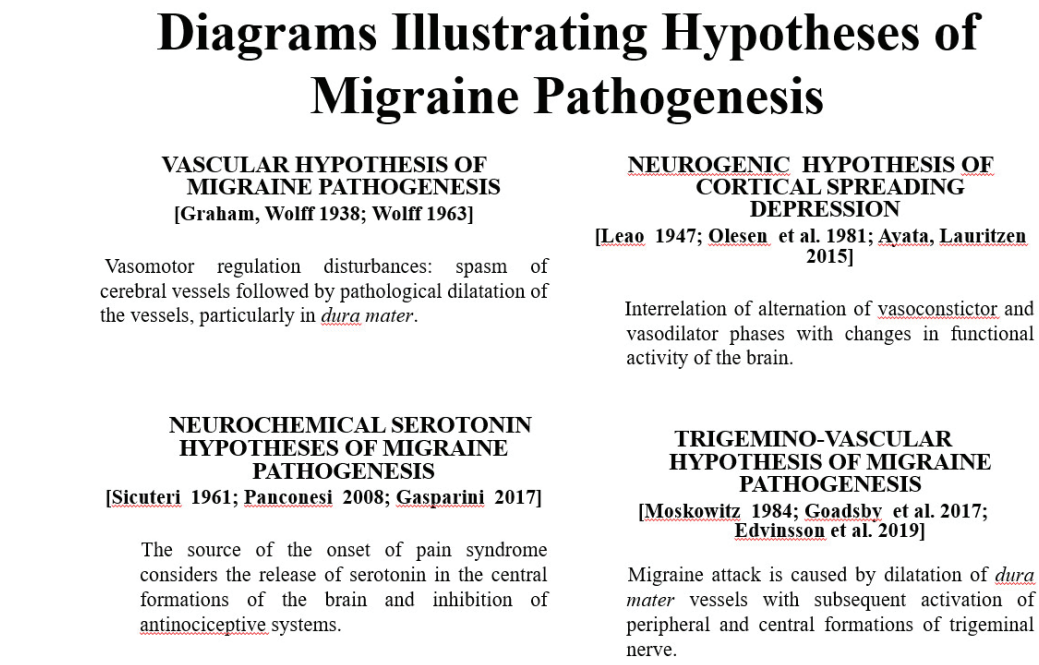
Migraine and ischemic brain damage: Migraine is a risk factor for ischemic stroke and cognitive disorders.

Search for the new anti-ischemic anti-migraine preparations: A methodology for the search for new anti-ischemic anti-serotonin drugs for the treatment of migraine is proposed.

Conclusion: Belonging of a drug to one or another pharmacological group does not always correspond to its therapeutic effect on the pathogenetic processes of migraine. Migraine with its variety of forms cannot fit only one of the proposed hypotheses on the pathogenesis of this disease.

Copyright *Mirzoyan RS et al*. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Graphical abstract:



Keywords

drugs for migraine treatment, migraine pathogenesis hypotheses, migraine and ischemic brain damage, new anti-ischemic anti-serotoninergic drugs for migraine treatment.

Introduction

Migraine is one of the most common neurological diseases in the world and, ranking second among the main causes of disability in the population, significantly impairs the quality of life and productivity of the working population with severe socio-economic consequences (Agosti 2018; Headache Classification Committee of the International Headache Society 2018; Ashina 2020). Despite numerous experimental and clinical studies on the migraine pathogenesis and pharmacological correction, the problem of migraine treatment cannot be considered solved.

In our review of the scientific data on this problem, the mechanisms of action of the drugs used to treat and prevent migraine attacks are analyzed in detail, and migraine pathogenesis hypotheses are considered from this point of view. This approach will allow, on the one hand, understanding the mechanisms underlying the pathogenesis of this complex disease, and, on the other hand, proposing a methodology for finding new means for the treatment of migraine. Therefore the article consists of sections analyzing the pharmacological agents for both the relief and the prevention of a migraine attack. They are followed by a discussion of the hypotheses on the pathogenesis of migraine, which were proposed in the past century. The first vascular hypothesis was proposed by Wolff H.G., one of the authors who identified the key role of cerebral vessels in the regulation of cerebral circulation (Forbes and Wolff 1928).

Taking into account the fact that migraine is a risk factor for ischemic stroke, including cryptogenic stroke, as well as Parkinson's disease and cognitive disorders, the relationship between migraine and ischemic brain injury is highlighted in a separate section. The review ends with the proposal of a methodology for the search of new anti-serotonin and anti-ischemic agents for the migraine treatment.

Migraine attack treatment agents

The main agents with high evidence level of efficacy of migraine attack treatment include: NSAIDs (acetylsalicylic acid, ibuprofen, naproxen, diclofenac, paracetamol, tolfenamic acid), serotonin 5-$HT_{1B/1D}$-receptors agonists (sumatriptan, eletriptan, zolmitriptan, naratriptan) and ergot alkaloids (ergotamine, dihydroergotamine) (Antonaci et al. 2016; Osipova et al. 2017; Urits et al. 2020). The analysis of these drugs' mechanisms of action revealed some of their characteristics. Tolfenamic acid also has an anti-serotonin effect, since it blocks the serotonin-induced spasm of cerebral vessels (Romanycheva et al. 1995; Gan'shina 2003), and the role of 5-HT_{2A} receptors has been revealed in the central antinociceptive activity of paracetamol (Srikiatkhachorn et al. 2000).

It is known that ergot alkaloids act on the 5-HT_{1A}, 5-HT_2, 5-HT_7 types of serotonin receptors, as well as on α-adrenergic receptors and dopamine D_2- receptors. The unequal (vasodilator and vasoconstrictor) effect of ergot

alkaloids on the brain vascular tone, as well as their side effects depend on the mechanisms of the drug actions mentioned above. Interacting with 5-HT_2 receptors, ergotamine and, to a greater extent, dihydrogenated ergot alkaloid dihydroergotamine eliminate cerebral vasospasm caused by serotonin (Gan'shina 2003). Therefore, the efficacy of ergot alkaloids in migraine attacks cannot be associated with their vasoconstrictor effect only (Norris et al. 1975; Antonaci et al. 2016).

Serotonin 5-$HT_{1B/1D}$ receptors agonists – sumatriptan and other triptans – are used for migraine attack relief. This use is based on the neurochemical serotonin (Sicuteri 1972) and trigeminovascular hypotheses of the migraine pathogenesis (Moskowitz 1984). The mechanism of action of these drugs will be presented in a more detailed way in the section on the trigemino-vascular hypothesis of the migraine pathogenesis.

It should be noted that the drugs currently used for the migraine attack relief are not effective enough and have significant adverse effects. In particular, non-narcotic analgesics, triptans and ergot alkaloids form drug-induced or drug-abuse headache, while the presence of ischemic damage of heart and brain, as well as occlusive peripheral vascular diseases in patients limit the use of triptans (Antonaci et al. 2016; Osipova et al. 2017; Urits et al. 2020).

Agents for migraine-preventive treatment

For the preventive treatment of a migraine attack, the following drugs are used: β-blockers (propranolol, metoprolol), ACE-inhibitors (enalapril, captopril), angiotensin II receptor antagonists (candesartan), anti-epileptic drugs (valproic acid, topiramat), calcium channel blockers (nifedipine, nimodipine, verapamil, flunarizin), serotonin antagonists (cyproheptadin, pizotifen), botulinum toxin type A (botox), calcitonin gene-related peptide antagonists (CGRP), and melatonin (Goadsby et al. 2017; Osipova et al. 2017; Silberstein et al. 2017; Jackson et al. 2019; Rau and Dodick 2019; Liampas et al. 2020; Urits et al. 2020). The successful use of clopidogrel for the prevention of migraine attacks in patients with an open foramen ovale has been reported (Guo et al. 2020).

A detailed examination of the above mentioned drugs' mechanism of action reveals the following. Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and slow calcium channel blockers have vasodilating (anti-ischemic) activity. A direct vasodilator effect on cerebral vessels was demonstrated by nimodipine, nifedipine, and captopril (Mirzoian et al. 1994; Semkina et al. 1994; Semkina et al. 1997; Adjienko 1999). Considering the role of calcium channel blockers in the treatment of migraine, two publications about using amlodipine for migraine headache prophylaxis should be mentioned. Dandapani et al. (1998) reported the successful treatment of two patients with migraine by amlodipine. Lucas et al. (2007) demonstrated the effectiveness of amlodipine against the background of unsuccessful treatment of the patient with high doses of β-blockers – atenolol and topiramate (Lucas and William 2007). It is important to emphasize that various amlodipine salts and, to a greater extent, with nicotinic acid (S-Amlodipine nicotinate), have pronounced cerebrovascular anti-ischemic activities, since, along with blockade of calcium channels, they interact with $GABA_A$ receptors in the brain, increasing blood circulation in conditions of global transient ischemia (Kim et al. 2019).

As for the anticonvulsants – valproic acid and topiramate, their GABA-ergic mechanism of action has been confirmed (Calabresi et al. 2007). The GABA-ergic nature of the inhibitory effect of sodium valproate also has been revealed on both the background activity of the spinal nucleus of the trigeminal nerve and its activity caused by electrical stimulation of the superior sagittal sinus (Sokolov et al. 2008). In recent years, there have been reports of the efficacy of another anti-convulsant drug with a GABA-ergic mechanism of action – levetiracetam (Sadeghian and Motiei-Langroudi 2015; Kovalev et al. 2017; Watkins et al. 2018; Tsaousi et al. 2020), which is not inferior to sodium valproate in reducing the frequency of migraine attacks (Sadeghian and Motiei-Langroudi 2015). A decrease in the frequency and intensity of headaches in patients with migraine under the influence of levetiracetam was shown to be accompanied by a decrease in the GABA level in the cerebral cortex, which made it possible to call the amino acid a biomarker of migraine (Li et al. 2018). However, the literature data on the relationship between a migraine attack and the GABA level in brain tissue are not consistent. For example, in the occipital region of the brain in patients with visual aura, a decrease in the content of GABA was revealed compared to the control group (Bigal et al. 2008; Bridge et al. 2015). An increase in GABA levels in migraine sufferers has been reported (Aguila et al. 2016), as well as the absence of changes in the content of GABA in brain tissue in patients with migraine (Stærmose et al. 2019). Therefore, it is impossible to make conclusions about the role of GABA in the pathogenesis and treatment of migraine only by its level in the brain tissue.

It is known that the GABA-ergic innervation of the cerebral vessels, including the "neurovascular unit", performs the neurotransmitter inhibitory function of GABA, which, together with the glutamatergic innervation of the cerebral vessels, ensures the balance of the two opposing factors in the central nervous system: excitatory and inhibitory processes (Hamel 2006; Lecrux and Hamel 2011; Chen et al. 2019; Mederos and Perea 2019). Along with this, GABA lowers the tone of cerebral vessels (Mirzoian and Akopyan 1967), exerting a direct effect on the $GABA_A$ receptors located in the same place (Krause et al. 1980; Napoleon et al. 1987). It has been established that GABA and the necessary components for its synthesis (glutamate decarboxylase) and inactivation (GABA transaminase) are contained in the vessels of the brain (Mirzoian et al. 1969; 1970; Mirzoian et al. 1974), which allowed S.A. Mirzoian to put forward a hypothesis on the GABA system in cerebral vessels (Mirzoian 1983). It is important

to note here that the presence of glutamate decarboxylase in the vessels of the brain was confirmed by Hamel et al. (1982), who revealed its difference from the decarboxylase of the brain tissue, with glutamate decarboxylase being defined as a non-neuronal form of the enzyme. This allows us to believe that the GABA system in the cerebral vessels is non-neuronal, i.e. local. Therefore, GABA plays an important role in the regulation of cerebral vascular tone, not only as an inhibitory neurotransmitter, but also by exerting a local direct effect on the vessels.

Picamilonis, being another GABA-ergic drug which interacts with picrotoxin-sensitive $GABA_A$ receptors of cerebral vessels (Gan'shina 2020), is effective in the prophylactic treatment of migraine (Mirzoyan et al. 2017). In this aspect, the efficacy of the preventive treatment of migraine with the epiphyseal hormone melatonin is of interest (Liampas et al. 2020). Melatonin has an anti-ischemic effect, since it improves the blood supply to the brain in conditions of global transient ischemia, which is realized through the GABA-ergic receptors of the cerebral vessels (eliminated by bicuculline) (Maslennikov et al. 2012). Melatonin is also known to have a pronounced analgesic effect (Chen et al. 2016), which undoubtedly enhances the anti-migraine properties of the drug.

It is known that cyproheptadine and pizotifen, used for the prophylactic treatment of migraine, are antagonists of $5HT_{2B/2C}$ receptors widely represented in the cerebral vessels. The stimulation of these receptors causes vasoconstriction (Lance et al. 1967; Griffith et al. 1982; Chang and Owman 1989). It has been found that other antagonists of serotonin – dihydroergotamine and methysergide also – also prevent cerebral vasoconstriction due to serotonin (Gan'shina 2003).

The literature provides a number of data that propranolol has effects which are difficult to explain by blockade of peripheral β-adrenoreceptors. For instance, propranolol blocks spasms of the human isolated basilar artery caused by cerebrospinal fluid obtained from patients with subarachnoid hemorrhage and cerebral vascular spasms (Boullin and Mohan 1977). The drug exhibits a high affinity for serotonin $5\text{-}HT_{1A,B}$-receptors (Adham et al. 1994) and blocks, like pizotifen, $5HT_{2C}$ receptors in the endothelium of rat jugular vein in *in vitro* experiments (Fozard and Kalkman 1994), and both in *in vitro* and *in vivo* experiments it inhibits cerebral vasospasms caused by serotonin (Romanycheva et al. 1995; Gan'shina 2003). β-adrenoblocker also has analgesic activity characteristic of local anesthetics (Johnstone 1970; Basil et al. 1973) and has a depressing effect on the processes of regulating sympathetic and vasomotor tone, by inhibiting discharges from afferent Aδ- and, to a greater extent, from C-fibers of somatic nerves, which are known to transmit pain impulses (Bendikov et al. 1969). It has been also shown that propranolol dose-dependently inhibits somatosensory responses of the trigemino-cervical complex with Aδ- and C-fibers of the dura mater (Akerman and Romero-Reyes 2019).

Therefore, propranolol, along with blocking adrenergic receptors, also has anti-serotonin and analgesic activities, which is very important when discussing the efficacy of the drug in the treatment of patients with migraine.

In recent years, the efficacy of calcitonin gene-related peptide (CGRP) antagonists, specifically monoclonal antibodies to calcitonin gene-related peptide and CGRP receptor, has been demonstrated in the prophylactic treatment of migraine. The main mechanism of their action is an analgesic effect, which is closely related to the trigemino-vascular hypothesis of migraine pathogenesis; therefore, these drugs will be discussed in more detail in the section of the paper providing a review of this hypothesis.

Summarizing the above two sections on migraine pharmacology, we can conclude that the predominant effects of the drugs to relieve migraine attacks are an analgesic effect and an effect on serotonin receptors, and most drugs used for the prophylactic treatment of migraine have vasodilating activity and also interact with serotonin receptors.

The increased interest in the problem of migraine was the basis for the emergence of hypotheses, the authors of which tried to solve the problem of the pathogenesis and treatment of this hadly explicable disease. We considered it necessary to discuss each of them in details, since this approach will allow considering, as objectively as possible, all the pros and cons of the proposed hypotheses in order to choose a strategy for finding new highly effective drugs to treat migraine.

Vascular hypothesis of migraine pathogenesis

An invaluable contribution to studying the migraine pathogenesis was made by H.G. Wolff and J.R. Graham, who in 1938 for the first time emphasized the role of blood vessels in the genesis of this disease based on the efficacy of ergotamine in the treatment of an attack (Graham and Wolff 1938). They proposed a vascular hypothesis, according to which a migraine attack is caused by an impaired vasomotor regulation and consists of two stages. In the first stage (aura or other prodromal symptoms), there is a spasm of the cerebral vessels, which leads to insufficient blood circulation in certain parts of the brain. During the second stage, there is a pathological dilatation of the vessels, particularly the dura mater, as well as vascular wall atony, which causes the characteristic throbbing pain (Wolff 1963).

Convincing evidence of the vasoconstrictor component of the vascular hypothesis of the migraine pathogenesis with the aura has been obtained in numerous clinical studies with a quantitative assessment of blood flow in various brain structures (O'Brien 1967; Skinhoj 1973; Olesen et al. 1981; Lauritzen and Olesen 1984; Friberg et al. 1987; Olsen et al. 1987). Moreover, significant hypoperfusion during the aura in patients with migraine, revealed by registering the brain blood flow, made it possible to suggest the vascular origin of prodromal neurological deficit (Lauritzen and Olesen 1984; Olsen et al. 1987).

However, there are reports indicating an increase in local cerebral blood flow during an attack in patients with migraine (Olesen et al. 1981; Weiller et al. 1995). These changes remain even after the use of sumatriptan

and complete relief of headache, as well as of phono- and photophobia (Weiller et al. 1995). According to Amin et al. (2013), in patients with migraine without the aura, an attack of pain is not accompanied by dilatation of extracranial arteries, but only a slight dilation of cerebral vessels is observed.

Particular attention should be paid to the above mentioned study by Olesen et al. (1981), who confirm, on the one hand, the vascular hypothesis, and, on the other, the hypothesis of cortical spreading depression. They found that the prodromal phase of the migraine attack in all the studied patients was accompanied by a decrease in blood flow in the occipital lobe, which gradually spreads to the frontal lobes, and an increase in the blood supply to the brain during headaches was observed in three patients. Olesen et al., having discovered two phases of a migraine attack – vasoconstrictor and vasodilator, with the prevalence of the former one – further focused only on the vasodilator and neurogenic components of a migraine attack.

The discrepancy between changes in cerebral blood flow and the phases of a migraine attack found in some studies may be induced by the differences in time and area of blood flow registration and cannot deny that the triggering mechanism of pain syndrome is primary local vasoconstriction.

Thus, despite numerous studies carried out in the later decades using modern methodological techniques that have expanded our understanding of the pathogenesis of migraine, the importance of the vascular component in the genesis of this disease is not questioned (Panconesi et al. 2009; Brennan and Charles 2010; Jacobs and Dussor 2016). The same is true for ergotamine, which is still widely used for the treatment of migraine. Therefore, it is not possible to consider as outdated the vascular hypothesis of the pathogenesis migraine.

Neurogenic hypothesis of cortical spreading depression

In 1947, A. Leao proposed the hypothesis of cortical spreading depression as a pathophysiological mechanism of acute neurological disorders in migraine, stroke and traumatic brain injuries caused by hypoxia, ischemia and hypoglycemia of brain tissue (Leao 1947). Back in 1941, K.S. Lashley (1941) noted rapid movements of scotoma – visual impairments – during the aura in patients with migraine. The spreading decrease in cerebral hemodynamics during a migraine attack has been proved using quantitative methods for recording cerebral blood flow (Olesen et al. 1981; Lauritzen 1994; Cutrer et al. 1998; Hadjikhani et al. 2001).

There is also evidence of an increase in local cerebral blood flow (Olesen et al. 1981), as well as of an increase in blood oxygenation during cortical spreading depression (Hadjikhani et al. 2001) and during visually triggered headache in patients with migraine (Cao et al. 1999).

In connection with the above mentioned, we consider it necessary to discuss in details the relationship of changes in blood supply and functional activity of the brain during cortical spreading depression, which is directly related to the pathogenesis of migraine, as described in (Ayata and Lauritzen 2015), where, thoroughly and convincingly, the phases of changes in the tone of the cerebral vessels in combination with electrophysiological parameters, were considered, with references to numerous scientific data sources. The first phase is constriction of the brain vessels, coinciding with a shift of direct current; the second phase is a maximum vasodilation that occurs during repolarization, followed by the third phase – a moderate vasodilation after the completion of cortical spreading depression and, finally, the fourth phase – prolonged cerebral vascular constriction, lasting at least one hour. The alternation of vasoconstrictor and vasodilatory phases, characteristic of the cortical spreading depression, makes it difficult to assess the state of cerebral circulation in migraine, since it is not always possible to clearly determine during which phase the blood circulation is recorded. Therefore, it is no coincidence that during a migraine attack, along with numerous reports of hypoperfusion, there are also data on cerebral hyperemia.

The phases of hypoperfusion and hyperperfusion revealed during cortical spreading depression, combined with a migraine attack, are consistent with the vascular hypothesis proposed by H.G. Wolff (1963), and, moreover, make it necessary to take into account the points of this hypothesis in the context of the pathophysiology of migraine.

Neurochemical serotonin hypothesis of migraine pathogenesis

In 1961, F. Sicuteri found in patients during a migraine attack an increase in urinary excretion of the main metabolite of serotonin – 5-hydroxyindoleacetic acid (Sicuteri 1978). These data served as the basis for further development and formulation of the neurochemical serotonin hypothesis of the pathogenesis of migraine. The release of serotonin in the central parts of the brain and inhibition of the anti-nociceptive systems are considered as the source of the onset of the pain syndrome (Antony et al. 1967; Sicuteri 1976; Panconesi 2008; Gasparini 2017).

As it is known, the vessels of the brain are richly innervated by serotonergic and noradrenergic nerve fibers emanating from the superior cervical ganglion, locus coeruleus, and raphe nuclei (Steinbusch and Verhofstad 1986; Jackowski et al. 1988; Lincoln 1995). Serotonin plays an important role in the regulation of the tone of cerebral microvessels, which contain various serotonin receptors (Cohen et al. 1996). The ability of serotonin and serotonin receptor agonists to increase the tone of isolated cerebral vessels in various animal species has been demonstrated (Griffith et al. 1982; Chang and Owman 1989). It has been shown that serotonin increases the tone of large vessels, and changes in the arteriole tone depend on a degree of neurogenic vasoconstriction (Lance et al. 1967). The unequal sensitivity of the cerebral arterial systems to serotonin and norepinephrine was revealed in experiments on

cats *in vivo*. (Mirzoian 1976; Mirzoian et al. 1993). Monoamines increase the vascular tone in the carotid system to a much greater extent than in the vertebro-basilar system. In the experiments on rats with simultaneous registration of blood flow in the middle cerebral and common carotid arteries, an unequal response of these vessels to serotonin was revealed. It was showed that serotonin in all the experiments increased blood flow in the common carotid artery, while changes in blood flow in the middle cerebral artery were not uniform. In 50% of the experiments, serotonin significantly and for a long time reduced blood flow in the middle cerebral artery (Mirzoyan et al. 1997).

Studies of cerebral ischemia caused by ligation of the middle cerebral artery are important. The effect of serotonin and norepinephrine on the blood supply to the brain in rats before and after ischemic damage was studied, and it was found that ischemic damage caused by ligation of the middle cerebral artery significantly enhances the constrictor response of cerebral vessels to serotonin, while norepinephrine does not constrict cerebral vessels under these conditions (Mirzoian et al. 1999; 2000). The data on the changes of the cerebrovascular effect of serotonin in conditions of cerebral ischemia were confirmed by Rasmussen et al. (2013), who recorded an increase in the constrictor responses of isolated segments of the middle cerebral artery under the influence of an agonist of serotonin receptors, using a similar model of ischemia. An increase in the activity of serotonin receptors located on the vessels of the brain was also revealed in conditions of global transient cerebral ischemia and in simulated hemorrhagic brain damage (Johansson et al. 2012, 2014). Apparently, an increase in the sensitivity of cerebral vessels to serotonin during ischemia, as well as the absence of tachyphylaxis of cerebral vessels to serotonin after its repeated administrations, explains the important role of serotonin in the pathogenesis of migraine.

In patients with migraine, an increase in the ability of the brain to synthesize serotonin was found (Chugani et al. 1999). Brain 5-HT synthesis was the highest during attacks, the lowest – after administering sumatriptan, and intermediate when patients were migraine free (Sakai et al. 2008). It was found that reserpine, which causes the release of norepinephrine, serotonin and dopamine from the brain tissue, and an agonist of $5HT_{2B/2C}$ receptors – meta-chlorophenylpiperazine (mCPP) – provoke an attack of headaches in patients with migraine (Panconesi 2008).

Thus, these data strongly suggest that serotonin plays an important role in the pathogenesis of migraine. This is due to the fact that the monoamine, on the one hand, is a mediator of the endogenous nociceptive system, and, on the other hand, it has a pronounced cerebrovascular activity, including an increase in the tone of the cerebral vessels.

Trigemino-vascular hypothesis of migraine pathogenesis

The currently widespread trigeminovascular hypothesis of migraine pathogenesis (Moskowitz 1984; Pietrobon and Moskowitz 2013; Goadsby et al. 2017) is based on the fact that a migraine attack is caused by dilatation of dura mater vessels with subsequent activation of the trigemino-vascular system, namely peripheral and central parts of the trigeminal nerve.

It is supposed that migraine causes aseptic neurogenic inflammation of these vessels as a result of the release of vasodilating substances – nitric oxide, substance P and calcitonin gene-related peptide (CGRP) – from peripheral terminals of the trigeminal nerve. This reaction is blocked by sumatriptan and zolmitriptan (Kaube 1993; Hoskin and Goadsby 1998; Amelin et al. 2001). Triptans increase the tone of extracranial vessels (Feniuk et al. 1989; Ullmer et al. 1995; Cohen et al. 1997) and pial arterioles only by direct application and have no effect on cerebral vessels when administered intravenously (Connor et al. 1992). In patients with migraine, sumatriptan, eliminating headache, does not affect the cerebral hemodynamics (Weiller et al. 1995). In experiments on isolated intracerebral arterioles of humans and cattle, the ability of sumatriptan to exert both vasoconstrictor and vasodilator effects was revealed (Elhusseiny and Hamel 2001). It has also been shown that sumatriptan, when administered intravenously to rats, along with stimulating the constrictor reaction of the cerebral vessels, significantly increases the blood supply to the brain, not inferior in strength to nimodipine (Gan'shina et al. 2008). Frequent use of triptans increases vascular tone and the risk of ischemic disorders of various organs (Roberto et al. 2015).

Nowadays the main focus of researchers is on the calcitonin gene-related peptide (CGRP), which has a significant vasodilator activity (Kurosawa et al. 1995; Williamson 1997) and is widely represented in the striatum, amygdala, hypothalamus, thalamus, brainstem and trigemino-vascular system (Yasui et al. 1991; Hokfelt et al. 1992; Van Rossum et al. 1997). It is believed that during a migraine attack or cluster headache, CGRP is released into the cranial venous outflow, resulting in orthodromic stimulation of trigeminal perivascular A-delta and C-fibers, which transmit nociceptive information from the vessels to the spinal nucleus of the trigeminal nerve, and then into the superposed structures of the central nervous system. CGRP, when administered intravenously to migraine patients, can cause symptoms similar to a migraine attack (Bernstein and Burstein 2012). Using immunochemical methods of research, the relationship between CGRP and the transmission of impulses along the C- and Aδ fibers of the trigeminal nerve was revealed (Edvinsson et al. 2019). These results were the basis for the development of agents that affect CGRP – monoclonal antibodies to CGRP or the CGRP receptor.

For the prophylactic treatment of migraine, CGRP antagonists (galcanezumab, erenumab, fremanesum) are used (Goadsby et al. 2017; Silberstein et al. 2017; Agostoni et al. 2019; Yuan et al. 2019; Urits et al. 2020). There was a report on the ability of CGRP antagonists (ubrohepant and remegepant) to relieve a migraine attack, though their analgesic effect is inferior to that of triptans, but superior to placebo (Ha et al. 2021). These

data also confirm the analgesic activity of CGRP antagonists and indicate the conventionality of dividing drugs into two groups – attack treatment and prevention. However, it is important to note that CGRP antagonists (olcegepant and rimegepant), exacerbate the ischemic brain damage in mice caused by occlusion of the middle cerebral artery. This is reflected in the increased neurological deficits, brain infarction size and mortality of animals. The studies emphasize the importance of studying the cerebrovascular safety of anti-migraine drugs (Mulder et al. 2020).

At the same time, a number of researchers believe that the central component of the trigemino-vascular system of the brain is primary in the formation of a migraine attack. Brain stem formations and paraventricular nuclei of the hypothalamus directly control both spontaneous and induced activities of the trigemino-vascular system. It has been shown that a microinjection of a $GABA_A$-receptor agonist muscimol and a $5\text{-}HT_{1B/D}$ receptor agonist naratriptan into these structures of the hypothalamus inhibits both the basal and induced activities of neurons of the trigemino-vascular system of the brainstem, while a GABA antagonist gabazin and a hypophysisadenylate cyclase-activating polypeptide (PACAP) enhance their basal activity (Robert et al. 2013). The primary nature of the neurogenic component in the development of a migraine attack is also reported in (Hoffmann et al. 2019). At the same time, the researchers consider the reaction of the vessels to be a consequence of these processes and confirm their point of view by the fact that drugs affecting vessels have no clinical efficacy. This explanation is difficult to accept, though, since it is a vasodilating activity that most drugs for the treatment of migraine have.

In conclusion, it should be noted that the authors and supporters of the trigemino-vascular hypothesis, using the example of triptans and CGRP antagonists, claim to solve the problem of a migraine pain.

Migraine and ischemic brain damage

In recent decades, numerous clinical observations have appeared indicating the relationship of migraine with ischemic, including cryptogenic, stroke, as well as Parkinson's disease and cognitive disorders. In patients with migraine with and without aura, foci of ischemia occur in the brain tissue, and the risk of developing a stroke increases by 1.5-2 times (Bigal et al. 2010; Cole and Kittner 2010; Eikermann-Haerter et al. 2012; Kato et al. 2016; Zhang et al. 2019; Øie et al. 2020). It was found that in patients with migraine without aura, the concentration of glutamate in the blood plasma was much higher than in the control group. The prophylactic treatment of migraine with topiramate, amitriptyline, flunarizine or propranolol, regardless of the drug, led to a decrease in the frequency of attacks of the disease and a decrease in plasma glutamate levels (Ferrari et al. 2009).

Particularly noteworthy are the data obtained by Li et al. (2015), according to which migraine was most strongly associated with cryptogenic stroke compared to known ischemic stroke, the frequency of which increases with age (Li et al. 2015). As known, cryptogenic stroke (of unknown etiology) is characterized by the absence of visible factors of damage to the cerebral vessels, i.e. there are no atherosclerotic plaques or blood clots. In these cases, the cause of cerebral ischemia can only be a functional factor – a vascular constrictor reaction, which, apparently, unites cryptogenic stroke and migraine.

It was also found that patients with a history of migraine are at increased risk of perioperative ischemic stroke and hospital readmission (Timm et al. 2017).

Migraine, and especially migraine with aura, is a risk factor for the development of Parkinson's disease (Scher et al. 2014; Wang et al. 2016). In patients with migraine, cognitive impairments have also been identified, which are the cause of their disability (Gil-Gouveia et al. 2016; Santangelo et al. 2016). It is known that the main pathophysiological mechanism of cognitive decline and degenerative processes is brain tissue hypoperfusion (de la Torre 2012; Neumann et al. 2013; Duncombe et al. 2017; Smith et al. 2017).

The association of migraine with patent foramen ovale, which is often complicated by ischemic brain damage, has been also found (Takagi and Umemoto 2015; Zhao et al. 2020).

The relationship between migraine, ischemic stroke, Parkinson's disease and cognitive impairment revealed by researchers, on the one hand, confirms the presence of an ischemic component in the formation of a migraine attack, and, on the other hand, poses a challenge for pharmacologists to search for drugs that can protect patients with migraine from brain ischemic damage.

Search for new anti-ischemic anti-migraine preparations

From the data presented in the previous sections, it can be seen that recently the search for new agents for the treatment of migraine has been aimed at creating drugs that alleviate the pain syndrome of an attack by narrowing the vessels of the dura mater. This comprises agonists of serotonin receptors and agents that affect CGRP – monoclonal antibodies to CGRP or the CGRP receptor. However, these drugs do not solve the problem of cerebral ischemia in migraine attacks, which is indicated by numerous literature sources. The relationship of migraine with ischemic brain lesions, as well as the efficacy of vasodilators in the treatment of patients with migraine, indicates the need to address this important aspect of the pharmacology of migraine. Therefore, when developing new anti-migraine drugs in our laboratory for the treatment of migraine, a methodology was proposed for the search for new drugs with anti-ischemic activity. It consists of studying the effect of substances on the constrictor reactions of the cerebral vessels caused by serotonin or an agonist of serotonin receptors (Mirzoyan et al. 1989; Gan'shina 2003). The basis for this drug search methodology was three hypotheses of migraine pathogenesis – vascular, cortical spreading depression and neurochemical serotonin hypotheses.

The proposed approach made it possible to identify cerebrovascular anti-serotonin properties in propranolol and tolfenamic acid, which were mentioned above, as well as in nicergoline (Mirzoyan et al. 1989; Romanycheva et al. 1995). The screening of cerebrovascular anti-serotonin activity in tropane derivatives revealed an original anti-migraine agent – tropoxin (3-(3,4,5-trimethoxybenzoyloxyimino)-8-methyl-8-azabicyclo[3,2,1]octana-hydrochloride), which prevents or significantly weakens constrictor cerebral vascular reactions induced by serotonin (5HT) or $5HT_{2B/2C}$ receptor agonist – meta-chlorophenylpiperazine (m-CPP) – in intact animals and under conditions of ischemic brain damage. The drug exhibits affinity for $5HT_2$ type receptors in the brain, has a central anti-serotonin activity and has an anti-aggregatory effect (Gan'shina 2003; Kozhechkin et al. 2005; Gan'shina et al. 2016). A clinical study of tropoxin indicates its efficacy in an interictal treatment of patients with frequent and severe migraine attacks (Amelin et al. 2001).

However, tropoxin, while significantly weakening the constrictor reactions of the cerebral vessels caused by agonists of serotonin receptors, does not improve blood supply in conditions of global transient ischemia. To enhance the anti-ischemic activity of tropoxin, its combination with drugs that increase the blood supply to the brain in conditions of global ischemia was proposed. In accordance with our earlier data on the cerebrovascular anti-ischemic activity of mexidol and its derivative, 2-ethyl-6-methyl-3-hydroxypyridine hemisuccinate, which have a GABA-ergic mechanism of action, their combination with tropoxin was proposed. It turned out that the combination of tropoxin with mexidol or 2-ethyl-6-methyl-3-hydroxypyridine hemisuccinate preserves the anti-serotonin properties of tropoxin, and an increase in cerebral blood flow is observed under conditions of global transient cerebral ischemia, i.e. there is an increase in its anti-ischemic activity (Gan'shina et al. 2011; Gorbunov et al. 2011).

Further studies identified a new derivative of tropane acylhydrazone – acylhydrazone (2,3,4-trimethoxy-N'-(8-methyl-8-azabicyclo[3.2.1.]octan-3-ylidene) benzo-hydrazide hydrochloride (LK-933), which along with cerebrovascular anti-serotonin activity also has anxiolytic and antiaggregatory activities (Mirzoyan et al. 2017; Mirzoian et al. 2020).

Discussion

An impressive list of drugs belonging to various chemical classes and pharmacological groups is used for the treatment and prevention of migraine attacks, which in itself testifies, on the one hand, to the complex and not fully understood pathogenesis of this disease and, on the other hand, to the insufficient efficacy of these medicines. It must be admitted that little is known yet about the mechanisms of action of these anti-migraine drugs, and a drug belonging to one or another group makes it impossible to get a clear answer about it having a pathogenetic effect on this disease. Medicines often have a wide range of effects on various systems of the body, and only knowing all this, we can make a reliable opinion about the pathogenetic mechanism of its action, which can be illustrated by the following two examples. A β-blocker propranolol, along with its known properties, also has anti-serotonin and analgesic activity. The second example concerns valproic acid and topiramate – anticonvulsants, which when acting on the GABA-ergic system, not only enhance the effect of this inhibitory neurotransmitter in the central nervous system, but also have a vasodilating effect on the cerebral vessels.

Therefore, in order to understand the mechanism of the positive effect of a particular drug, we cannot confine ourselves only to knowledge about its belonging to some group of pharmacological drugs. This requires more complete and reliable data on the targets the drug affects.

When discussing the pharmacology of migraine, hypotheses of the pathogenesis of migraine, none of which are homogeneous, play an important role. It should be recognized that the most significant contribution to the development of the migraine problem was made by H.G. Wolff, who proposed the vascular hypothesis of migraine pathogenesis. The subsequent hypotheses: neurogenic with cortical spreading depression; neurochemical serotonin; and trigemino-vascular hypotheses undoubtedly contributed to the expansion of our understanding of the pathogenesis of migraine, but did not exclude the importance of the vascular factor.

Special attention should be paid to the trigemino-vascular hypothesis of the migraine pathogenesis, which is considered as the main one that determines the pathophysiology of this disease. The authors and supporters of this hypothesis made a significant contribution to the study of the pathogenesis of migraine and to the development of drugs for the disease treatment. However, it should be born in mind that in accordance with the second part of the name of this hypothesis, the source of pain impulses in migraine is the dilation of dura mater vessels. The authors of the hypothesis emphasize that the dilation of these vessels, which corresponds to the second period of the vascular hypothesis and the second phase of the hypothesis of pervasive cortical depression, underlies a migraine attack. In this case, the occurrence of neurological deficit during the prodromal period of a migraine attack is due to the vasodilatation of the dura mater and an improvement in blood circulation. We consider this statement insufficiently substantiated, since the functional disorders characteristic of the prodromal migraine period can only be caused by cerebral circulation insufficiency, and not vice versa. Apparently, vasodilatation is an epiphenomenon, as written by Panconesi et al. (2009), i.e. an contributing secondary factor.

The practical result of the research carried out by the authors and supporters of this hypothesis was the development and clinical implementation of serotonin receptor agonists – triptans, which, however, do not exceed in efficacy the known non-narcotic analgesics and do not solve the problem of pharmacological correction of a migraine

attack. As for the CGRP antagonists, which are used for the prophylactic treatment of migraine, the report of their ability to aggravate ischemic brain damage indicates the need for further research in this direction.

Acknowledging the role of blood supply in providing metabolism and functional activity of the brain, we think it possible to compare the concepts of the pathogenesis of migraine and ischemic stroke. This comparison is made due to the fact that cerebral circulation plays an important role in the pathogenesis of these disorders. Some time ago, when it came to the pathogenesis and therapy of ischemic stroke, the term *reperfusion* had a negative meaning, which was explained by the release of and subsequent damaging effect of free radicals (nitric oxide and oxygen) on the brain tissue, whereas the role of blood circulation was underestimated. However, when the effectiveness of restoring the blood supply to the brain by combining systemic thrombolysis with a recombinant tissue plasminogen activator and mechanical thromboextraction was proven indisputable, there followed a radical revision of the concept of the therapy of this disease. The term *reperfusion* has become an epiphenomenon and has been transformed into reperfusion therapy, i.e. treatment by the restoration of adequate cerebral circulation and not only by a surgical method, but also by drugs with cerebrovascular and anti-platelet activities. A similar situation can happen with our ideas about the pathophysiology of migraine, when the importance of brain hypoperfusion will not be challenged and, as a result, the attitude towards the anti-ischemic orientation of the search for drugs to treat migraine will change.

Therefore, the trigemino-vascular hypothesis of the migraine pathogenesis cannot be considered either the only correct one or the only basis to conduct a targeted search for anti-migraine drugs. We should abandon the idea to monopolize one hypothesis only, but rather recognize all of them on equal terms. Apparently, migraine with its variety of forms due to the individual characteristics of the organism cannot fit only one of the proposed ideas about the pathogenesis of this disease. The proposed hypotheses are convincingly supported by experimental and clinical data. This is most clearly seen when considering the issues of pharmacological correction of migraine. This statement is supported by numerous results indicating the clinical efficacy of drugs with both analgesic and anti-ischemic properties. Therefore, the search for drugs to treat migraine should not be limited to the search for drugs with an analgesic activity. It is important to take into account the ischemic factor of a migraine attack and to provide pharmacological correction of these conditions.

In this regard, there is no doubt about the relevance of the methodology of searching for new drugs aimed at eliminating the vasoconstrictor component in patients with migraine and having cerebrovascular anti-serotonin activity. Studies on the combination of anti-serotonin drugs and drugs with pronounced cerebrovascular anti-ischemic properties are of particular importance. This is a combination of drugs with anti-serotonin and GABA-ergic mechanisms of action, affecting the multidirectional regulation mechanisms of cerebral circulation and contributing to the enhancement of the anti-ischemic action of the anti-migraine anti-serotonin agent. Besides, the essential role of GABA-ergic drugs in restoring the balance between the brain GABA-ergic and glutamatergic systems, which is impaired in ischemic brain damage, should be considered.

It can be assumed that such an integrated approach to developing the anti-migraine agents will contribute to a more successful control of migraine – a complicated disease with a poorly understood pathogenesis.

Conflict of interests

The authors declare no conflict of interest.

References

- Adham N, Tamm JA, Salon JA, Vaysse PJ, Weinshank RL, Branchek TA (1994) A single point mutation increases the affinity of serotonin 5-HT1D alpha, 5-HT1D beta, 5-HT1E and 5-HT1F receptors for beta-adrenergic antagonists. Neuropharmacology 33(3–4): 387–391. https://doi.org/10.1016/0028-3908(94)90068-X [PubMed]
- Adjienko LM (1999) The effect of captopril on cerebral circulation in hypertensive rats before and after cerebral ischemia. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 62(5): 18–21. [PubMed] [in Russian]
- Agosti R (2018) Migraine burden of disease: From the patient's experience to a socio-economic view. Headache 58(l): 17–32. https://doi.org/10.1111/head.13301 [PubMed]
- Agostoni EC, Barbanti P, Calabresi P, Colombo B, Cortelli P, Frediani F, Geppetti P, Grazzi L, Leone M, Martelletti P, Pini LA, Prudenzano MP, Sarchielli P, Tedeschi G, Russo A (2019) Italian chronic migraine group. Current and emerging evidence-based treatment options in chronic migraine: a narrative review. The Journal of Headache and Pain 20(1): 92. https://doi.org/10.1186/s10194-019-1038-4 [PubMed] [PMC]
- Aguila MR, Rebbeck T, Leaver AM, Lagopoulos J, Brennan PC, Hübscher M, Refshauge KM (2016) The association between clinical characteristics of migraine and brain GABA levels: An exploratory study. The Journal of Pain 17(10): 1058–1067. https://doi.org/10.1016/j.jpain.2016.06.008 [PubMed]
- Akerman S, Romero-Reyes M (2019) Targeting the central projection of the dural trigeminovascular system for migraine prophylaxis. Journal of Cerebral Blood Flow & Metabolism 39(4): 704–717. https://doi.org/10.1177/0271678X17729280 [PubMed] [PMC]
- Amelin AV, Ignatov YuD, Skoromets AA (2001) Migraine (Pathogenesis, Clinical Picture, Treatment). SPb Medical Publishing House, St. Petersburg, 200 pp. [in Russian]
- Amin FM, Asghar MS, Hougaard A, Hansen AE, Larsen VA, de Koning PJ, Larsson HB, Olesen J, Ashina M (2013) Magnetic resonance angiography of intracranial and extracranial arteries in patients

with spontaneous migraine without aura: a cross-sectional study. The Lancet. Neurology 12(5): 454–461. https://doi.org/10.1016/S1474-4422(13)70067-X [PubMed]

- Antonaci F,Ghiotto N, Wu S, Pucci E, Costa A (2016) Recent advances in migraine therapy. SpringerPlus 5: 637. https://doi.org/10.1186/s40064-016-2211-8 [PubMed] [PMC]
- Antony M, Hinterberger H, Lance JW (1967) Plasma serotonin in migraine and stress. Archives of Neurology 16(5): 544–552. https://doi.org/10.1001/archneur.1967.00470230096013 [PubMed]
- Ashina M (2020) Migraine. The New England Journal of Medicine 383(19): 1866–1876. https://doi.org/10.1056/NEJMra1915327 [PubMed]
- Ayata C, Lauritzen M (2015) Spreading depression, spreading depolarizations, and the cerebral vasculature. Physiological Reviews 95(3): 953–993. https://doi.org/10.1152/physrev.00027.2014 [PubMed] [PMC]
- Basil B, Jordan R, Loveless AH, Maxwell DR (1973) Beta-adrenoceptor blocking properties and cardioselectivity of M & B 17,803A. British Journal of Pharmacology 48(2): 198–211. https://doi.org/10.1111/j.1476-5381.1973.tb06906.x [PubMed] [PMC]
- Bendikov EA, Butuzov VG, Mirzoian RS (1969) Mechanism of action of propranolol on central processes of regulation of blood circulation [O mekhanizme deĭstviia propranolola na tsentral'nye protsessy reguliatsii krovoobrashcheniia]. Journal of Pharmacology and Toxicology [Farmakologiia i Toksikologiia] 32(6): 678–683. [PubMed] [in Russian]
- Bernstein C, Burstein R (2012) Sensitization of the trigeminovascular pathway: perspective and implications to migraine pathophysiology. Journal of Clinical Neurology 8(2): 89–99. https://doi.org/10.3988/jcn.2012.8.2.89 [PubMed] [PMC]
- Bigal ME, Hetherington H, Pan J, Tsang A, Grosberg B, Avdievich N, Friedman B, Lipton RB (2008) Occipital levels of GABA are related to severe headaches in migraine. Neurology 70(22): 2078–2080. https://doi.org/10.1212/01.wnl.0000313376.07248.28 [PubMed] [PMC]
- Bigal ME, Kurth T, Santanello N, Buse D, Golden W, Robbins M, Lipton RB(2010) Migraine and cardiovascular disease: a population-based study. Neurology 74(8): 628–635. https://doi.org/10.1212/WNL.0b013e3181d0cc8b [PubMed] [PMC]
- Boullin DJ, Mohan J (1977) Effects of (+) and (-)-propranolol on the responses of the human isolated basilar artery to cerebrospinal fluid obtained from patients with subarachnoid haemorrhage and cerebral arterial spasm. British Journal of Clinical Pharmacology 4(1): 27–31. https://doi.org/10.1111/j.1365-2125.1977.tb00662.x [PubMed] [PMC]
- Brennan KC, Charles A (2010) An update on the blood vessel in migraine. Current Opinion in Neurology 23(3): 266–274. https://doi.org/10.1097/WCO.0b013e32833821c1 [PubMed] [PMC]
- Bridge H, Stagg CJ, Near J, Lau CI, Zisner A, Cader MZ (2015) Altered neurochemical coupling in the occipital cortex in migraine with visual aura. Cephalalgia 35(11): 1025–1030. https://doi.org/10.1177/0333102414566860 [PubMed]
- Calabresi P, Galletti F, Rossi C, Sarchielli P, Cupini LM (2007) Antiepileptic drugs in migraine: from clinical aspects to cellular mechanisms. Trends in Pharmacological Sciences 28(4): 88–95. https://doi.org/10.1016/j.tips.2007.02.005 [PubMed]
- Cao Y, Welch K M A, Aurora S, Vikingstad E (1999) Functional MRI-BOLD of visually triggered headache in patients with migraine. Archives of Neurology 56(5): 548–554. https://doi.org/10.1001/archneur.56.5.548 [PubMed]
- Chang J-Y, Owman C (1989) Cerebrovascular serotonergic receptors mediating vasoconstriction: ferther evidence for the existense of 5-HT_2 receptors in the rat and $5HT_1$ –like receptors in gunea-pig basilar arteries. Acta Physiologica Scandinavica 136(1): 59–67. https://doi.org/10.1111/j.1748-1716.1989.tb08629.x [PubMed]
- Chen WW, Zhang X, Huang WJ (2016) Pain control by melatonin: physiological and pharmacological effects. Experimental and Therapeutic Medicine 12(4): 1963–1968. https://doi.org/10.3892/etm.2016.3565 [PubMed] [PMC]
- Chen C, Zhou X, He J, Xie Z, Xia S, Lu G (2019) The roles of GABA in ischemia-reperfusion injury in the central nervous system and peripheral organs. Oxidative Medicine and Cellular Longevity 2019: 4028394. https://doi.org/10.1155/2019/4028394 [PubMed] [PMC]
- Chugani DC, Niimura K, Chaturvedi S, Muzik O,Fakhouri OM, Lee M-L, Chugani HT (1999) Increased brain serotonin synthesis in migraine. Neurology 53(7): 1473–1479. https://doi.org/10.1212/WNL.53.7.1473 [PubMed]
- Cohen ML, Johnson KW, Schenck KW, Phebus LA (1997) Migraine therapy: relationship between serotonergic contractile receptors in canine and rabbit saphenous veins to human cerebral and coronary arteries. Cephalalgia 17(6): 631–638. https://doi.org/10.1046/j.1468-2982.1997.1706631.x [PubMed]
- Cohen Z, Bonvento G, Lacombe P, Hamel E (1996) Serotonin in the regulation of brain microcirculation. Progress in Neurobiology 50(4): 335–362. https://doi.org/10.1016/S0301-0082(96)00033-0 [PubMed]
- Cole JW, Kittner SJ (2010) Meta-analysis of results from case control and cohort studies finds that migraine is associated with approximately twice the risk of ischaemic stroke. Evidence-Based Medicine 15(6): 193–194. https://doi.org/10.1136/ebm1146 [PubMed] [PMC]
- Connor HE, Stubbs CM, Feniuk W, Humphrey PP (1992) Effect of sumatriptan, a selective $5H_{T1}$-like receptor agonist, on pial vessel diameter in anaesthetised cats. Journal of Cerebral Blood Flow and Metabolism 12(3): 514–519. https://doi.org/10.1038/jcbfm.1992.70 [PubMed]
- Cutrer FM, Sorensen AG, Weisskoff RM, Ostergaard L, Sanchez del Rio M, Lee EJ, Rosen BR, Moskowitz MA (1998) Perfusion-weighted imaging defects during spontaneous migrainous aura. Annals of Neurology 43(1): 25–31. https://doi.org/10.1002/ana.410430108 [PubMed]
- Dandapani BK, Hanson MR (1998) Amlodipine for migraine prophylaxis. Headache 38(8): 624–626. https://doi.org/10.1046/j.1526-4610.1998.3808624.x [PubMed]
- de la Torre JC (2012) Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovascular Psychiatry and Neurology 2012: 367516. https://doi.org/10.1155/2012/367516 [PubMed] [PMC]
- Duncombe J, Kitamura A, Hase Y, Ihara M, Kalaria RN, Horsburgh K (2017) Chronic cerebral hypoperfusion: a key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodent models and human vascular cognitive impairment and dementia. Clinical Science 131(19): 2451–2468. https://doi.org/10.1042/CS20160727 [PubMed]
- Edvinsson JCA, Warfvinge K, Krause DN, Blixt FW, Sheykhzade M, Edvinsson L, Haanes KA (2019) C-fibers may modulate adjacent Aδ-fibers through axon-axon CGRP signaling at nodes of Ranvier in the trigeminal system. The Journal of Headache and Pain 20: 105 https://doi.org/10.1186/s10194-019-1055-3 [PubMed] [PMC]

- Eikermann-Haerter K, Lee JH, Yuzawa I, Liu CH, Zhou Z, Shin HK, Zheng Y, Qin T, Kurth T, Waeber Ch, Ferrari MD, van den Maagdenberg AM, Moskowitz MA Ayata C (2012) Migraine mutations increase stroke vulnerability by facilitating ischemic depolarizations. Circulation 125(2): 335–345. https://doi.org/10.1161/CIRCULATIONAHA.111.045096 [PubMed] [PMC]
- Elhusseiny A, Hamel E (2001) Sumatriptan elicits both constriction and dilation in human and bovine brain intracortical arterioles. British Journal of Pharmacology 32(1): 55–62. https://doi.org/10.1038/sj.bjp.0703763 [PubMed] [PMC]
- Feniuk W, Humphrey PPA, PerrenMJ (1989) The selective carotid arterial vasoconstrictor action of GR43175 in anaesthetised dogs. British Journal of Pharmacology 96(1): 83–90. https://doi.org/10.1111/j.1476-5381.1989.tb11787.x [PubMed] [PMC]
- Ferrari A, Spaccapelo L, Pinetti D, Tacchi R, Bertolini A (2009) Effective prophylactic treatments of migraine lower plasma glutamate levels. Cephalalgia 29(4): 423–429. https://doi.org/10.1111/j.1468-2982.2008.01749.x [PubMed]
- Forbes HS, Wolff HG (1928) Cerebral circulation III. The vasomotor control of cerebral vessels. Archives of Neurology and Psychiatry 19(6): 1057–1086. https://doi.org/10.1001/archneurpsyc.1928.02210120090008
- Fozard JR, Kalkman HO (1994) 5-Hydroxytryptamine (5-HT) and the initiation of migraine: new perspectives. Naunyn-Schmiedeberg's Archives of Pharmacology 350(3): 225–229. hhttps://doi.org/10.1007/BF00175026 [PubMed]
- Friberg L, Olsen TS, Roland PE, Lassen NA (1987) Focal ischaemia caused by instability of cerebrovascular tone during attacks of hemiplegic migraine. A regional cerebral blood flow study. Brain 110(4): 917–934. https://doi.org/10.1093/brain/110.4.917 [PubMed]
- Gan'shina TS (2003) Neuromediator mechanism of tropoxin action in comparison to other anti-migraine medications. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 66(3): 17–20. [PubMed] [in Russian]
- Gan'shina TS, Gorbunov AÀ, Gnezdilova ÀV, Kurdyumov IN, Avdyunina NI, Pyatin BM, Mirzoyan RS (2011) Influence of 2-ethil-6-methyl-3-hydroxypyridine hemisuccinate on cerebral blood perfusion in rats under experimental pathology conditions. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 74(8): 17–22. [PubMed] [in Russian]
- Gan'shina TS, Kurdyumov IN, Kurza EV, Avdyunina NI, Pyatin BM, Maslennikov DV, Turilova AI, Mirzoian RS (2020) Cerebrovascular effects of picamilon and succinic acid esters of 5-hydroxyadamantan-2-one in hemorrhagic and ischemic brain disorders. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 83(1): 3–6. https://doi.org/10.30906/0869-2092-2020-83-1-3-6 [in Russian]
- Gans'hina TS, Gorbunov AA, Gnezdilova AV, Turilova AI, Kostochka LM, Pyatin BM, Avdyunina NI, Grushevskaya LN, Mirzoyan RS (2016) Tropoxin – a new drug in migraine therapy. Pharmaceutical Chemistry Journal 50(1): 19–23. https://doi.org/10.1007/s11094-016-1391-4 [in Russian]
- Gan'shina TS, Bezhanian SG, Kostochka LM, VolkovaMIu, Mirsoian RS (2008) Cerebrovascular serotonin antagonists and agonist among tropan derivatives. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 71(1): 6–30. [PubMed] [in Russian]
- Gasparini CF, Smith RA, Griffiths LR(2017) Genetic and biochemical changes of the serotonergic system in migraine pathobiology. The Journal of Headache and Pain 18(1): 20. https://doi.org/10.1186/s10194-016-0711-0 [PubMed] [PMC]
- Gil-Gouveia R, Oliveira AG, Martins IP (2016) The impact of cognitive symptoms on migraine attack-related disability. Cephalalgia 36(5): 422–430. https://doi.org/10.1177/0333102415604471 [PubMed]
- Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S (2017) Pathophysiology of migraine: A disorder of sensory processing. Physiological Reviews 97(2): 553–622. https://doi.org/10.1152/physrev.00034.2015 [PubMed] [PMC]
- Gorbunov AA, Gan'shina TS, Turilova AI, Mirzoian RS (2011) Cerebrovascular and antiserotoninergic activity of the combination of tropoxin and mexidol. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 74(8): 23–27. [PubMed] [in Russian]
- Graham JR, Wolff HG (1938) Mechanism of migraine headache and action of ergotamine tartrate. Archives of Neurology 39(4): 737–763. https://doi.org/10.1001/archneurpsyc.1938.02270040093005
- Griffith SG, Lincoln J, Burnstock G (1982) Serotonin as neurotransmitter in cerebral arteries. Brain Research 247(2): 388–392. https://doi.org/10.1016/0006-8993(82)91266-5 [PubMed]
- Guo Y, Shi Y, Zhu D, Liu R, Qi Y, Luo G (2020) Clopidogrel can be an effective complementary prophylactic for drug-refractory migraine with patent foramen ovale. Journal of Investigative Medicine 68(7):1250–1255. https://doi.org/10.1136/jim-2020-001342 [PubMed] [PMC]
- Ha DK, Kim MJ, Han N, Kwak JH, Baek IH (2021) Comparative efficacy of oral calcitonin-gene-related peptide antagonists for the treatment of acute migraine: Updated meta-analysis. Clinical Drug Investigation 41(2): 119–132. https://doi.org/10.1007/s40261-020-00997-1 [PubMed]
- Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, Kwong KK, Cutrer FM, Rosen BR, Tootell RB, Sorensen AG, Moskowitz MA (2001) Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proceedings of the National Academy of Sciences of the United States of America 98(8): 4687–4692. https://doi.org/10.1073/pnas.071582498 [PubMed] [PMC]
- Hamel E (2006) Perivascular nerves and the regulation of cerebrovascular tone. Journal of Applied Physiology (1985) 100(3): 1059–1064. https://doi.org/10.1152/japplphysiol.00954.2005 [PubMed]
- Hamel E, Krause DN, Roberts E (1982) Characterization of glutamic acid decarboxylase activity in cerebral blood vessels. Journal of Neurochemistry 39(3): 842–849. https://doi.org/10.1111/j.1471-4159.1982.tb07969.x [PubMed]
- Headache Classification Committee of the International Headache Society [(IHS) The international classification of headache disorders] (2018) 3rd edition. Cephalalgia 38(1): 1–211. https://doi.org/10.1177/0333102417738202
- Hoffmann J, Baca SM, Akerman S (2019) Neurovascular mechanisms of migraine and cluster headache. Journal of Cerebral Blood Flow & Metabolism 39(4): 573–594. https://doi.org/10.1177/0271678X17733655 [PubMed] [PMC]
- Hokfelt T, Arvidsson U, Ceccatelli S, Cortes R, Cullheim S, Dagerlind A (1992) Calcitonin gene-related peptide in the brain, spinal cord,

and some peripheral systems. Annals of the New York Academy of Sciences 657: 119–134. https://doi.org/10.1111/j.1749-6632.1992.tb22762.x [PubMed]

- Hoskin KL, Goadsby PJ (1998) Comparison of more and less lipophilic serotonin ($5HT_{1B/1D}$) agonists in a model of trigeminovascular nociception in cat. Experimental Neurology 150(1): 45–51. https://doi.org/10.1006/exnr.1997.6749 [PubMed]
- Jackowski A, Crockard A, Burnstock G (1988) Ultrastructure of serotonin-containing nerve fibres in the middle cerebral artery of the rat and evidence for its localisation within catecholamine-containing nerve fibres by immunoelectron microscopy. Brain Research 443(1–2): 159–165. https://doi.org/10.1016/0006-8993(88)91608-3 [PubMed]
- Jackson JL, Kuriyama A, Kuwatsuka Y, Nickoloff S, Storch D, Jackson W, Zhang ZJ, Hayashino Y (2019) Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis. PLoS ONE 14(3): 0212785. https://doi.org/10.1371/journal.pone.0212785 [PubMed] [PMC]
- Jacobs B, Dussor G (2016) Neurovascular contributions to migraine: Moving beyond vasodilation. Neuroscience 338: 130–144. https://doi.org/10.1016/j.neuroscience.2016.06.012 [PubMed] [PMC]
- Johansson S, Povlsen GK, Edvinsson L (2012) Expressional changes in cerebrovascular receptors after experimental transient forebrain ischemia. PLoS ONE 7(7): e41852. ttps://doi.org/10.1371/journal.pone.0041852 [PubMed] [PMC]
- Johansson SE, Larsen SS, Povlsen GK, Edvinsson L (2014) Early MEK1/2 inhibition after global cerebral ischemia in rats reduces brain damage and improves outcome by preventing delayed vasoconstrictor receptor upregulation. PLoS ONE 9(3): e92417. https://doi.org/10.1371/journal.pone.0092417 [PubMed] [PMC]
- Johnstone M (1970) Reflections on beta-adrenergic blockade in anaesthetics. British Journal of Anaesthesia 42(3): 262–268. https://doi.org/10.1093/bja/42.3.262 [PubMed]
- Kato Y, Dodick DW, Schwedt TJ (2016) Migraine comorbidity with cardiac, cardiovascular and cerebrovascular disease. Neurology and Clinical Neuroscience 4(6): 203–208. https://doi.org/10.1111/ncn3.12077
- Kaube H, Hoskin KL, Goadsby PJ (I993) Inhibition by sumatriptan of central trigeminal neurons only after blood-brain barrier disruption. British Journal of Pharmacology 109(3): 788–792. https://doi.org/10.1111/j.1476-5381.1993.tb13643.x [PubMed] [PMC]
- Kim G A, Gan'shina T S, Kurza E V, Kurdyumov IN, Maslennikov DV, Mirzoian RS (2019) New cerebrovascular agent with hypotensive activity. Research Results in Pharmacology 5(2): 71–77. https://doi.org/10.3897/rrpharmacology.5.35392
- Kovalev IG, Vasil'eva EV, Kondrakhin EA, Voronina TA, Kovalev GI (2017) The role of glutamate and GABA receptors in the anticonvulsive effects of levetiracetam and a 4-phenylpirrolidone derivative (GIZH-290) in rats. Neurochemical Journal 11(4): 332–339. https://doi.org/10.1134/S1819712417040055
- Kozhechkin SN, Kostochka LM, Bezhanian SG, Mirzoian RS, Seredin SB (2005) Interaction of tropoxin and its molecular fragments tropan and 3,4,5-trimethoxybenzoate with serotonin receptors of cortical neurons in the rat brain (a microionophoretic study). Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 68(4): 3–6. [PubMed] [in Russian]
- Krause DM, Wong E, Degener P, Roberts E (1980) GABA receptors in bovine cerebral blood vessels: binding studies with ^{3}Hmuscimol. Brain Research 185(1): 51–57. https://doi.org/10.1016/0006-8993(80)90669-1 [PubMed]
- Kurosawa M, Messlinger K, Pawlak M, Schmidt RF (1995) Increase of meningeal blood flow after electrical stimulation of rat dura mater encephali: mediation by calcitonin generelated peptide. British Journal of Pharmacology 114(7): 1397–1402. https://doi.org/10.1111/j.1476-5381.1995.tb13361.x [PubMed] [PMC]
- Lance JW, Anthony M, Gonski A (1967) Serotonin, the carotid body and cranial vessels in migraine. Archives of Neurology 16(5): 553–558. https://doi.org/10.1001/archneur.1967.00470230105014 [PubMed]
- Lashley KS (1941) Patterns of cerebral integration indicated by the scotomas of migraine. Archives of Neurology and Psychiatry 46(2): 331–339. https://doi.org/10.1001/archneurpsyc.1941.02280200137007
- Lauritzen M, Olesen J (1984) Regional cerebral blood flow during migraine attacks by Xenon-133 inhalation and emission tomography. Brain 107(2): 447–461. https://doi.org/10.1093/brain/107.2.447 [PubMed]
- Lauritzen M (1994) Pathophysiology of the migraine aura. The spreading depression theory. Brain 117(Pt1): 199–210. https://doi.org/10.1093/brain/117.1.199 [PubMed]
- Lecrux C, Hamel E (2011) The neurovascular unit in brain function and disease. Acta Physiologica 203(1): 47–59. https://doi.org/10.1111/j.1748-1716.2011.02256.x [PubMed]
- Li L, Schulz UG, Kuker W, Rothwell PM (2015) Age-specific association of migraine with cryptogenic TIA and stroke: Population-based study. Neurology 85(17): 1444–1451. https://doi.org/10.1212/WNL.0000000000002059 [PubMed] [PMC]
- Li Q, Chen C, Gong T (2018) High-field MRS study of GABA+ in patients with migraine: response to levetiracetam treatment. Neuroreport 29(12): 1007–1010. https://doi.org/10.1097/WNR.0000000000001067 [PubMed] [PMC]
- Liampas I, SiokasV, BrotisA, Vikelis M, Dardiotis E (2020) Endogenous melatonin levels and therapeutic use of exogenous melatonin in migraine: Systematic review and meta-analysis. Headache 60(7): 1273–1299. https://doi.org/10.1111/head.13828 [PubMed]
- Lincoln J (1995) Innervation of cerebral arteries by nerves containing 5-hydroxytryptamine and noradrenaline. Pharmacology and Therapeutics 68(3): 473–501. https://doi.org/10.1016/0163-7258(95)02017-9 [PubMed]
- Lucas L, William JP (2007) Near-complete migraine prophylaxis with amlodipine: A case report. Journal of Pain and Symptom Management 34(6): 571–573. https://doi.org/10.1016/j.jpainsymman.2007.08.004 [PubMed]
- Maslennikov DV, Gan'shina TS, Oleinikova ON, Kurdyumov IN, Mirzoyan RS (2012) GABA-ergic mechanism of the cerebrovascular effect of melatonin. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 75(4): 13–16. [PubMed] [in Russian]
- Mederos S, Perea G (2019) GABAergic-astrocyte signaling: a refinement of inhibitory brain networks. Glia 67(10): 1842–1851. https://doi.org/10.1002/glia.23644 [PubMed] [PMC]
- Mirzoian RS (1976) Different sensitivities of cerebral arterial systems to noradrenaline. Bulletin of Experimental Biology and Medicine [Biulleten' Eksperimental'noĭ Biologii i Meditsiny] 81(1): 47–49. [PubMed] [in Russian]
- Mirzoyan RS, Gan'shina TS, Gorbunov AA, Kurdyumov IN, Maslennikov DV, Turilova AI, Kurza EV (2017) Pharmacology of various neuromediator mechanisms of regulation of cerebral circulation. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 80(9): 35–39. [PubMed] [in Russian]

- Mirzoyan RS, Gan'shina TS, Pukhalskaya TG, Volobueva TI, Vedernikov JP, Dicova M, Nicolova M, Nicolov R (1989) Effects of nicergoline in experimental models related to pathogenesis of migraine. Methods and Findings in Experimental and Clinical Pharmacology 11(11): 671–676. [PubMed]
- Mirzoian RS, Masievskiĭ DD, Semkina GA (1994) The effect of nimodipine on blood circulation in the rat middle cerebral and carotid arteries. Bulletin of Experimental Biology and Medicine [Biulleten' Eksperimental'noĭ Biologii i Meditsiny] 118(10): 410–413. [PubMed] [in Russian]
- Mirzoyan RS, Naplekova PL, Gan'shina TS, Kurdyumov IN, Gorbunov AA, Kostochka LM, Turilova AI, Kudrin VS, Narkevich VB, Voronina TA (2017) New anti-migraine drug with antiserotonin, cerbrovascular, and anxiolytic activity. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 80(4): 8–12. [PubMed] [in Russian]
- Mirzoian RS, Romanycheva NA, Gan'shina TS, Aleksandrin VV, Volobueva TI, Aleksandrov PN (1993) The nonuniform sensitivity of the cerebral vessels to serotonin. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 56(3): 22–25. [PubMed] [in Russian]
- Mirzoyan RS, Semkina GA, Matsievskii DD (1997) Response of the middle cerebral artery to serotonin. Bulletin of Experimental Biology and Medicine 124(10): 988–991. https://doi.org/10.1007/BF02446841 [PubMed] [in Russian]
- Mirzoian RS, Shabalina AA, Gan'shina TS, Kurdyumov IN, Turilova AI, Kostochka LM, Kozlov AV, Annushkin VA, Kornilova AA, Tanashyan MM (2020) Expanding the horizons of antiplatelet therapy. A pilot study of the antiplatelet properties of a new tropane alkaloid. Annals of Clinical and Experimental Neurology 14(3): 53–59. https://doi.org/10.25692/ACEN.2020.3.7 [in Russian]
- Mirzoian RS, Topchian AV, Gan'shina TS, Kostochka LM (2000) Tropoxin and cerebrovascular effects of serotonin. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 63(3): 21–23. [PubMed] [in Russian]
- Mirzoian RS, Topchian AV, Timkina MI, Balasanian MG (1999) The different vascular reactions of intact and ischemic brain to adrenergic exposures. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 62(5): 11–14. [PubMed] [in Russian]
- Mirzoian SA (1983) Neurochemical control of cerebral blood circulation. Journal of Pharmacology and Toxicology [Farmakologiia i Toksikologiia] 46(4): 5–15. [PubMed] [in Russian]
- Mirzoian SA, Akopian VP (1967) Effect of gamma-aminobutyric acid on cerebral circulation and oxygen tension in the brain. Journal of Pharmacology and Toxicology [Farmakologiia i Toksikologiia] 30(5): 572–574. [PubMed] [in Russian]
- Mirzoian SA, Kazarian BA, Akopian VP (1969) Presence of gamma-aminobutyric acid in the cerebral and large vessels of man and animals. Comptes Rendus de l'Académie des Sciences de l'URSS [Doklady. Biochemistry Doklady] 186(1): 231–232. [PubMed] [in Russian]
- Mirzoian SA, Kazarian BA, Akopian VP (1970) Decarboxylase activity of glutamic acid in the vessels of the brain. Comptes Rendus de l'Académie des Sciences de l'URSS [Doklady. Biochemistry Doklady] 190(5): 1241–1242. [PubMed] [in Russian]
- Mirzoyan SA, Kazaryan BA, Akopyan VP (1974) The content and some transformations of amino acids in the tissues of the walls of the arteries of the brain. Comptes Rendus de l'Académie des Sciences de l'URSS [Doklady. Biochemistry Doklady] 214(2): 465–468 [in Russian]
- Moskowitz MA (1984) The neurobiology of vascular head pain. Annals of Teurology 16(2): 157–168. https://doi.org/10.1002/ana.410160202 [PubMed]
- Mulder IA, Li M, de Vries T, Qin T, Yanagisawa T, Sugimoto K, van den Bogaerdt A, Danser AHJ, Wermer MJH, van den Maagdenberg AMJM, Maassen Van Den Brink A, Ferrari MD, Ayata C (2020) Anti-migraine calcitonin gene-related peptide receptor antagonists worsen cerebral ischemic outcome in mice. Annals of neurology 88(4): 771–784. https://doi.org/10.1002/ana.25831 [PubMed] [PMC]
- Napoleone P, Erdo S, Amenta F (1987) Autoradiographic localization of the $GABA_A$-receptor agonist [^{3}H]muscimol in rat cerebral vessels. Brain Research 423(1–2): 109–115. https://doi.org/10.1016/0006-8993(87)90830-4 [PubMed]
- Neumann JT, Cohan CH, Dave KR et al. (2013) Global cerebral ischemia: synaptic and cognitive dysfunction. Current Drug Targets 14(1): 20–35. https://doi.org/10.2174/138945013804806514 [PubMed] [PMC]
- Norris JW, Hachinski VC, Cooper PW (1975) Changes in cerebral blood flow during a migraine attack. British Medical Journal 3(5985): 676–677. https://doi.org/10.1136/bmj.3.5985.676 [PubMed] [PMC]
- O'Brien MD (1967) Cerebral-cortex-perfusion rates in migraine. The Lancet 289(7498): 1036 https://doi.org/10.1016/S0140-6736(67)91545-0 [PubMed]
- Øie LR, Kurth T, Gulati S, Dodick DW (2020) Migraine and risk of stroke. Journal of Neurology, Neurosurgery, and Psychiatry 91(6): 593–604. https://doi.org/10.1136/jnnp-2018-318254 [PubMed] [PMC]
- Olesen J, Larsen B, Lauritzen M (1981) Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Annals of Neurology 9(4): 344–352. https://doi.org/10.1002/ana.410090406 [PubMed]
- Olsen T S, Friberg L, Lassen NA (1987) Ischemia may be the primary cause of the neurologic deficits in classic migraine. Archive of Neurology 44(2): 156–161. https://doi.org/10.1001/archneur.1987.00520140028013 [PubMed]
- Osipova VV, Filatova EG, Artemenko (2017) Diagnosis and treatment of migraine: Recommendations of the Russian experts. SS Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova] 117(1): 28–42. https://doi.org/10.17116/jnevro20171171228-42 [in Russian]
- Panconesi A (2008) Serotonin and migraine: a reconsideration of the central theory. The Journal of Headache and Pain 9(5): 267–276. https://doi.org/10.1007/s10194-008-0058-2 [PubMed] [PMC]
- Panconesi A, Bartolozzi ML, Guidi L (2009) Migraine pain: Reflections against vasodilatation. The Journal of Headache and Pain 10(5): 317–325. https://doi.org/10.1007/s10194-009-0130-6 [PubMed] [PMC]
- Pietrobon D, Moskowitz MA (2013) Pathophysiology of migraine. Annual Review of Physiology 75: 365–391. https://doi.org/10.1146/annurev-physiol-030212-183717
- Rasmussen MNP, Hornbak M, Larsen SS, Sheykhzade M, Edvinsson L (2013) Permanent distal occlusion of middle cerebral artery in rat causes local increased ET_B, $5\text{-}HT_{1B}$ and AT_1 receptor-mediated contractility downstream of occlusion. Journal of Vascular Research 50(5): 396–409. https://doi.org/10.1159/000354242 [PubMed]

- Rau JC, Dodick DW (2019) Other preventive anti-migraine treatments: ACE inhibitors, arbs, calcium channel blockers, serotonin antagonists, and NMDA receptor antagonists. Current Treatment Options in Neurology 70(6): 431–439. https://doi.org/10.1212/01.wnl.0000299095.65331.6f [PubMed]
- Robert C, Bourgeais L, Arreto CD, et al. (2013) Paraventricular hypothalamic regulation of trigeminovascular mechanisms involved in headaches. The Journal of Neuroscience 33(20): 8827–8840. https://doi.org/10.1523/JNEUROSCI.0439-13.2013 [PubMed] [PMC]
- Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R (2015) Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. Cephalalgia 35(2): 118–131. https://doi.org/10.1177/0333102414550416 [PubMed]
- Romanycheva NA, Gan'shina TS, Mirzoyan RS (1995) Individual sensitivity to the cerebrovascular anti-serotonin action of propronolol and tolphenamic acid. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 58(2): 25–26. [PubMed] [in Russian]
- Sadeghian H, Motiei-Langroudi R (2015) Comparison of levetiracetam and sodium valproate in migraine prophylaxis: a randomized placebo-controlled study. Annals of Indian Academy of Neurology 18(1): 45–48. https://doi.org/10.4103/0972-2327.144290 [PubMed] [PMC]
- Sakai Y, Dobson C, Diksic M, Aube M, Hamel E (2008) Sumatriptan normalizes the migraine attack-related increase in brain serotonin synthesis. Neurology 70(6): 431–439. https://doi.org/10.1212/01.wnl.0000299095.65331.6f [PubMed]
- Santangelo G, Russo A, Trojano L, Falco F, Marcuccio L, Siciliano M, Conte F, Garramone F, Tessitore A, Tedeschi G (2016) Cognitive dysfunctions and psychological symptoms in migraine without aura: a cross-sectional study. The Journal of Headache and Pain 17(1): 76. https://doi.org/10.1186/s10194-016-0667-0 [PubMed] [PMC]
- Scher AI, Ross GW, Sigurdsson S, Garcia M, Gudmundsson LS, Sveinbjörnsdóttir S, Wagner AK, Gudnason V, Launer LJ (2014) Midlife migraine and late-life parkinsonism: AGES-Reykjavik study. Neurology 83(14): 1246–1252. https://doi.org/10.1212/WNL.0000000000000840 [PubMed] [PMC]
- Semkina GA, Matsievskiĭ DD, Mirzoian RS (1994) Circulatory changes in the middle cerebral artery and the carotid arteries of rats under the influence of nifedipine. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 57(6): 24–26. [PubMed] [in Russian]
- Semkina GA, Matsievskiĭ DD, Mirzoian RS (1997) Changes in the blood circulation in the middle cerebral and common carotid arteries of rats under the influence of flunarizine. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 60(1): 28–31. [PubMed] [in Russian]
- Sicuteri F (1972) Headache as possible expression of deficiency of brain 5-hydroxytryptamine (central denervation supersensitivity). Headache 12(2): 69–72. https://doi.org/10.1111/j.1526-4610.1972.hed1202069.x [PubMed]
- Sicuteri F (1976) Hypothesis: migraine, a central biochemical dysnociception. Headache 16(4): 145–149. https://doi.org/10.1111/j.1526-4610.1976.hed1604145.x [PubMed]
- Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, Grozinski-Wolff M, Yang R, Ma Y, Aycardi E (2017) Fremanezumab for the preventive treatment of chronic migraine. The New England Journal of Medicine 377(22): 2113–2122. https://doi.org/10.1056/NEJMoa1709038 [PubMed]
- Skinhoj E (1973) Hemodynamic studies within the brain during migraine. Archives of Neurology 29(2): 95–98. https://doi.org/10.1001/archneur.1973.00490260039007 [PubMed]
- Smith EE, Cieslak A, Barber P, Chen J, Chen YW, Donnini I, Edwards JD, Frayne R, Field TS, Hegedus J, Hanganu V, Ismail Z, Kanji J, Nakajima M, Noor R, Peca S, Sahlas D, Sharma M, Sposato LA, Swartz RH, Zerna C, Black SE, Hachinski V (2017) Therapeutic strategies and drug development for vascular cognitive impairment. Journal of the American Heart Association 6(5): e005568. https://doi.org/10.1161/JAHA.117.005568 [PubMed] [PMC]
- Sokolov AYu, Amelin AV, Ignatov YuD, Panteleev SS (2008) Effect of GABA-positive drugs on the background and superior sagittalis sinus-electro-stimulated activity of neurons in the nucleus trigeminaliscaudalis of rats. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 75(5): 3–7. [PubMed] [in Russian]
- Srikiatkhachorn A, Tarasub N, Govitrapong P (2000) Effect of chronic analgesic exposure on the central serotonin system: a possible mechanism of analgesic abuse headache. Headache 40(5): 343–350. https://doi.org/10.1046/j.1526-4610.2000.00052.x [PubMed]
- Stærmose TG, Knudsen MK, Kasch H, Blicher JU (2019) Cortical GABA in migraine with aura – an ultrashort echo magnetic resonance spectroscopy study. The Journal of Headache and Pain 20(1): 110. https://doi.org/10.1186/s10194-019-1059-z [PubMed] [PMC]
- Steinbusch HWM, Verhofstad AAJ (1986) Immunocytochemical demonstration of noradrenalin, serotonin and histamin some observations on the innervation of intracerebral blood vessels, In: Owman C, Haredebo JE Neural Regulation of Brain Circulation. Amsterdam, Els. Sci. Pub. B.V., pp. 181–193.
- Takagi H, Umemoto T, for the ALICE (All-Literature Investigation of Cardiovascular Evidence) Group (2016) A meta-analysis of case-control studies of the association of migraine and patent foramen ovale. Journal of Cardiology 67(6): 493–503. https://doi.org/10.1016/j.jjcc.2015.09.016 [PubMed]
- Timm FP, Houle TT, Grabitz SD et al(2017) Migraine and risk of perioperative ischemic stroke and hospital readmission: hospital based registry study. BMJ 356: i6635. https://doi.org/10.1136/bmj.i6635 [PubMed] [PMC]
- Tsaousi G, Pourzitaki C, Siafis S, Kyrgidis A, Grosomanidis V, Kouvelas D, Papazisis G (2020) Levetiracetam as preventive treatment in adults with migraine: an up-to-date systematic review and quantitative meta-analysis. European Journal of Clinical Pharmacology 76(2): 161–174. https://doi.org/10.1007/s00228-019-02790-2 [PubMed]
- Ullmer C, Schmuck K, Kalkman HO, Lubbert H (1995) Expression of serotonin receptor mRNAs in blood vessels. FEBS Letters 370(3): 215–221. https://doi.org/10.1016/0014-5793(95)00828-W [PubMed]
- Urits I, Clark G, An D, Wesp B, Zhou R, Amgalan A, Berger AA, Kassem H, Ngo AL, Kaye AD, Kaye RJ, Cornett EM, Viswanath O (2020) An evidence-based review of fremanezumab for the treatment of migraine. Pain and Therapy 9(1): 195–215. https://doi.org/10.1007/s40122-020-00159-3 [PubMed] [PMC]
- Van Rossum D, Hanisch UK, Quirion R (1997) Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. Neuroscience and Biobe-

havioral Reviews 21(5): 649–678. https://doi.org/10.1016/S0149-7634(96)00023-1 [PubMed]
- Wang HI, Ho YC, Huang YP, Pan SL (2016) Migraine is related to an increased risk of Parkinson's disease: a population-based, propensity score-matched, longitudinal follow-up study. Cephalalgia 36(14): 1316–1323. https://doi.org/10.1177/0333102416630577 [PubMed]
- Watkins AK, Gee ME, Brown JN (2018) Efficacy and safety of levetiracetam for migraine prophylaxis: A systematic review. Journal of Clinical Pharmacy and Therapeutics 43(4): 467–475. https://doi.org/10.1111/jcpt.12715 [PubMed]
- Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, Coenen HH, Diener HC (1995) Brain stem activation in spontaneous human migraine attacks. Nature Medicine 1(7): 658–660. https://doi.org/10.1038/nm0795-658 [PubMed]
- Williamson DJ, Hargreaves RJ, Hill RG, Shepheard SL (1997) Intravital microscope studies on the effects of neurokinin agonists and calcitonin gene-related peptide on dural blood vessel diameter in the anaesthetized rat. Cephalalgia 17(4): 518–524. https://doi.org/10.1046/j.1468-2982.1997.1704518.x [PubMed]
- Wolff HG (1963) Headache and Other Pain, New York: Oxford University Press, 689 pp.
- Yasui Y, Saper CB, Cechetto DF (1991) Calcitonin gene-related peptide (CGRP) immunoreactive projections from the thalamus to the striatum and amygdala in the rat. The Journal of Comparative Neurology 308(2): 293–310. https://doi.org/10.1002/cne.903080212 [PubMed]
- Yuan H, Spare NM, Silberstein SD (2019) Targeting CGRP for the prevention of migraine and cluster headache: A narrative review. Headache 59(2): 20–32. https://doi.org/10.1111/head.13583 [PubMed]
- Zhang S,Zhang W, Zhou G (2019) Extended risk factors for stroke prevention, journal of the national medical association. Journal of the National Medical Association 111(4): 447–456. https://doi.org/10.1016/j.jnma.2019.02.004 [PubMed]
- Zhao E, Xie H, Zhang Y (2020) A nomogram for the prediction of cessation of migraine among patients with patent foramen ovale after percutaneous closure. Frontiers in Neurology 11: 593074. https://doi.org/10.3389/fneur.2020.593074 [PubMed] [PMC]

Author contributions

- **Ruben S. Mirzoyan,** Doctor Habil. of Medical Sciences, Professor, Head, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: cerebropharm@mail.ru, **ORCID ID** https://orcid.org/0000-0002-7542-8904. The author had a leading role in the planning, analyzing the data and the literature, and writing the review article.

- **Tamara S. Gan'shina,** Doctor Habil. of Biological Sciences, Professor, Lead Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: toma2902@mail.ru, **ORCID ID** https://orcid.org/0000-0003-0442-1761. The author participated in planning the experiments on anti-serotonin activity of the substances, analyzing the literature and writing the review article.

- **Ilya N. Kurdyumov**, PhD in Biological Sciences, Senior Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: raver_not23@yahoo.com, **ORCID ID** https://orcid.org/0000-0003-4251-9217. The author participated in planning the experiments, analyzing the literature and interpreting the data.

- **Denis V. Maslennikov**, PhD in Biological Sciences, Senior Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: vodyanoi.87@mail.ru, **ORCID ID** https://orcid.org/0000-0001-9081-8284. The author participated in planning the experiments on anti-serotonin activity of the substances, analyzing the literature and interpreting the data.

- **Anna V. Gnezdilova,** PhD in Biological Sciences, Senior Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: the_luxory@mail.ru, **ORCID ID** https://orcid.org/0000-0002-8439-2683. The author participated in planning the experiments on anti-serotonin activity of the substances, analyzing the literature and interpreting the data.

- **Alexander A. Gorbunov,** PhD in Biological Sciences, Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology; Associate Professor, Department of Pharmacology, I.M. Sechenov First Moscow State Medical University (Sechenov University); e-mail: gorbunov.mma@yandex.ru, **ORCID ID** https://orcid.org/0000-0002-5773-5177. The author participated in planning the experiments on anti-serotonin activity of the substances, analyzing the literature and interpreting the data.

- **Elena V. Kurza,** PhD in Biological Sciences, Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: duxlink@yandex.ru, **ORCID ID** https://orcid.org/0000-0002-5394-5839. The author participated in planning the experiments, analyzing the literature and interpreting the data.

- **Antonina I. Turilova,** PhD in Biological Sciences, Senior Researcher, Laboratory of Pharmacology of Cerebrovascular Disorders, Zakusov Institute of Pharmacology. e-mail: turilova37@bk.ru, **ORCID ID** https://orcid.org/0000-0002-8622-8430. The author participated in planning the experiments, analyzing the literature and interpreting the data.

- **Leonid M. Kostochka,** PhD in Chemical Sciences, Lead Researcher, Chemistry Department, Zakusov Institute of Pharmacology. e-mail: kostochka.leonid@mail.ru. The author played a leading role in the planning and carrying out the synthesis of the chemical compounds.

- **Narine R. Mirzoyan,** Doctor Habil. of Medical Sciences, Professor, Head, Clinical Pharmacology Department, Yerevan State Medical University, Armenia. e-mail: nanamirzoyan@gmail.com, **ORCID ID** https://orcid.org/0000-0001-5570-488X. The author had a leading role in planning and writing the review article.