Migraine pharmacology and brain ischemia

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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.
Graphical abstract:

Diagrams Illustrating Hypotheses of Migraine Pathogenesis

VASCULAR HYPOTHESIS OF MIGRAINE PATHOGENESIS
[Graham, Wolff 1938; Wolff 1963]

Vasomotor regulation disturbances: spasm of cerebral vessels followed by pathological dilatation of the vessels, particularly in dura mater.

NEUROGENIC HYPOTHESIS OF CORtical SPREADING DEPRESSION

Interrelation of alternation of vasoconstrictor and vasodilator phases with changes in functional activity of the brain.

NEUROCHEMICAL SEROTONIN HYPOTHESES OF MIGRAINE PATHOGENESIS
[Sicuteri 1961; Paconeo 2008; Gasparini 2017]

The source of the onset of pain syndrome considers the release of serotonin in the central formations of the brain and inhibition of antinociceptive systems.

TRIGEMINO-VASCULAR HYPOTHESIS OF MIGRAINE PATHOGENESIS
[Moskowitz 1984; Goodbody et al. 2017; Edvinsson et al. 2019]

Migraine attack is caused by dilatation of dura mater vessels with subsequent activation of peripheral and central formations of trigeminal nerve.

Keywords

drugs for migraine treatment, migraine pathogenesis hypotheses, migraine and ischemic brain damage, new anti-ischemic anti-serotonergic 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$_{1D}$-receptors agonists (sumatriptan, eletriptan, zolmitriptan, naratriptan) and ergot alkaloids (ergotamine, dihydroergotamine) (Antonacci 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$_{1A}$ 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$_{3}$, 5-HT, 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$_1$ receptors, ergot alkaloids dihydroergotamine eliminate cerebral vasospasm caused by serotonin (Gan’shina 2003). Therefore, the efficacy of ergot alkaloids in migraine attacks cannot be associated with their vasiconstrictor effect only (Norris et al. 1975; Antonaci et al. 2016).

Serotonin 5-HT$_1$B/D 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 (Antonacci et al. 1994; Semkina et al. 1997; Adjienko 1999).

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, topiramate), calcium channel blockers (nimodipine, nimodipine, verapamil, flunarizin), serotonin antagonists (cyproheptadine, 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 amlo- dipine. 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 amlo- dipine 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-Langrudi 2015; Kovalev et al. 2017; Watkins et al. 2018; Tsousi et al. 2020), which is not inferior to sodium valproate in reducing the frequency of migraine attacks (Sadeghian and Motiei-Langrudi 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 (Aguiia et al. 2016), as well as the absence of changes in the content of GABA in brain tissue in patients with migraine (Stermose 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 1968, 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.

Picamilon, 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 context, the effect of the preventive treatment of migraine with the epishyseal 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-adrenoceptors. 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-HT_1A,1B 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-adreno-blocker 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 adenergetic 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 badly 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; Breman and Charles 2010; Jacobs and Dusser 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 of 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 vasodilatation 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
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 vasocostringor and vasodilator effects was first shown (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 immunohistochemical 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, fremanezumab) 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).
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-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 hypophysis adenylate 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; Oie 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; Sattanglo 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; Gani‘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 nicerogeline (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-trimethoxybenzoyloxyiminio)-8-methyl-8-azabicyclo[3.2.1]octan-3-one hydrochloride), which prevents or significantly weakens constrictor cerebral vascular reactions induced by serotonin (5HT) or 5HT2A receptor agonist — meta-chlorophenylpiperazine (m-CPP) — in intact animals and under conditions of ischemic brain damage. The drug exhibits affinity for 5HT 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-hydroxypropyridine 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-hydroxypropyridine 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 acylhydrazine — 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


Chen WW, Zhang X, Huang WJ (2016) Pain control by melato


Forbes HS, Wolff HG (1928) Cerebral circulation III. The va-


Friberg L, Olsen TS, Roland PE, Lassen NA (1987) Focal ischaemia caused by instability of cerebrovascular tone during attacks of hemi-


Friberg L, Olsen TS, Roland PE, Lassen NA (1987) Focal ischaemia caused by instability of cerebrovascular tone during attacks of hemi-


Friberg L, Olsen TS, Roland PE, Lassen NA (1987) Focal ischaemia caused by instability of cerebrovascular tone during attacks of hemi-


Hoskyn KL, Goadsby PJ (1998) Comparison of more and less lipo-
philic serotonin (5HT1B/1D) agonists in a model of trigeminovascular

Jackowski A, Crockard A, Burnstock G (1988) Ultrastructure of se-
rotonin-containing nerve fibres in the middle cerebral artery of the
t rat and evidence for its localisation within catecholamine-containing
nerve fibres by immunoelectron microscopy. Brain Research 443(1–2):

Jackson JL, Kurdyumov AA, Kurokawa Y, Nickoloff S, Storch D, Jackson
W, Zhang ZJ, Hayashino Y (2019) Beta-blockers for the pre-
vention of headache in adults, a systematic review and meta-
pone.0212785 [PubMed] [PMC]

Jacobs B, Dusser G (2016) Neurovascular contributions to migraine:
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
pone.0041852 [PubMed] [PMC]

MEK1/2 inhibition after global cerebral ischemia in rats reduces
brain damage and improves outcome by preventing delayed vaso-
doi.org/10.1371/journal.pone.0092417 [PubMed] [PMC]

encephalopathic serotonin (5HT1B/1D) agonists in a model of trigeminovascular

Li Q, Chen C, Gong T (2018) High-field MRS study of GABA+
in patients with migraine: response to levetiracetam treat-
WNF.0000000000001067 [PubMed] [PMC]

Li L, Schulz UG, Muker K, Rothwell PM (2015) Age-specific associ-
ation of migraine with cryptogenic TIA and stroke: Population-based
WNL.0000000000002059 [PubMed] [PMC]

Lucas I, Siokas V, Brotis A, Vikelis M, Dardiotis E (2020) Endoge-
 nous melatonin levels and therapeutic use of exogenous melatonin
in migraine: Systematic review and meta-analysis. Headache 60(7):

Lincoln J (1995) Innervation of cerebral arteries by nerves con-
taining 5-hydroxytryptamine and noradrenaline. Pharmacology
and Therapeutics 68(3): 473–501. https://doi.org/10.1016/0163-
7258(95)02017-9 [PubMed] [PMC]

Lazarus M, Lipton RB, Matharu MS, colleagues (2019) New class of
vascular targets for the treatment of headache and related
head.13828 [PubMed] [PMC]

Lecrux C, Hamel E (2011) The neurovascular unit in brain func-

Kurosawa M, Messlinger K, Pawlak M, Schmidt RF (1995) In-
crease of meningeal blood flow after electrical stimulation of rat
dura mater encephali: mediation by calcitonin generelated peptide.
org/10.1111/j.1476-5381.1995.tb13361.x [PubMed] [PMC]

Lauritzen M, Olesen J (1984) Regional cerebral blood flow during mi-
graine attacks by Xenon-133 inhalation and emission tomography. Brain

Lauritzen M (1994) Pathophysiology of the migraine aura. The

Lauritzen M, Olesen J, Goadsby PJ (2000) Activation of trigemin-
avascular pain pathways by intravenous and intracranial injection of sero-

Kurokawa Y, Odagawa N, Takeo K, Kowalewski A, Bacc P, de la Salle
A, et al. (2018) Comparative effects of platelet activating factor and
serotonin 1B/1D receptor agonists in the rat primary trigeminal
10.1016/j.expneurol.2018.01.010 [PubMed] [PMC]

Krause DM, Wong E, Degener P, Roberts E (1980) GABA recep-
tors in bovine cerebral blood vessels: binding studies with [3H]Gama-
8993(80)90669-1 [PubMed]

Kurokawa Y, Odagawa N, Takeo K, Kowalewski A, Bacc P, de la Salle
A, et al. (2018) Comparative effects of platelet activating factor and
serotonin 1B/1D receptor agonists in the rat primary trigeminal
10.1016/j.expneurol.2018.01.010 [PubMed] [PMC]

Krause DM, Wong E, Degener P, Roberts E (1980) GABA recep-
tors in bovine cerebral blood vessels: binding studies with [3H]Gama-
8993(80)90669-1 [PubMed]


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- Van Rossouw D, Hanisch UK, Quirion R (1997) Neuroanatomical localization, pharmacological characterization and functions of CGRP, related peptides and their receptors. Neuroscience and Biobe-


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