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.

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
[Leao 1947; Olesen et al. 1981; Ayata, Lauritzen 2015]

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

NEUROCHEMICAL SEROTONIN HYPOTHESES OF MIGRAINE PATHOGENESIS
[Sicuteri 1961; Panconesi 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; Goadsby 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-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