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Original Research

Oxidative Stress in the Pathogenesis of Chronic Headache

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This report presents new data on the development of oxidative stress (OS) in chronic headache (HA). The main biochemical characteristics of OS are presented. Changes in MRI spectroscopy and biochemical markers confirming the development of OS in migraine are described. The absence of significant differences in measures of OS in migraine with and without aura is emphasized. Pathophysiological differences between migraine and chronic tension headache, in which OS is not detected, are demonstrated. Possible activation of TRPA1 ion channels and calcitonin gene-related peptide in OS, which provokes migraine attacks, is discussed. Directions for drug correction of OS in chronic headache are considered.

Keywords: headache, migraine, chronic tension headache, oxidative stress, antioxidants.

The WHO estimates that the prevalence of headache (HA; with clinical manifestations at least once in the last year) among adults is about 50%. From half to three quarters of people aged 18–65 years throughout the world had headaches in the past year and more than 30% reported having migraine (MG). Up to 1.7–4% of the adult population of the world suffers from headaches lasting 15 days or more per month. Despite some territorial differences, headaches are a worldwide problem, independently of age, race, level of income, and geographic region [1]. All types of headaches are presented in the International Classification of Headache Disorders, 3rd revision (2018) [2, 3], which considers primary and secondary forms of headache. The most common of the primary forms of headache are tension headache (THA) and MG.

The prevalence of THA in the population is 78%. About 31% of the Russian population had THA in 2009 2011. The most common form is episodic THA (one day with headache per month or every few months), which does not require treatment. In chronic THA, 24–37% of patients experience episodes of HA several times a month; 10% have weekly episodes and 2–3% have 15 or more days with HA per month. The average age of onset of HA is 25–30 years [4].

A population study conducted in 2009–2011 using a door-to-door survey in 35 cities and nine rural areas of Russia found that the prevalence of HA was 20.8%, which is slightly higher than the figures for most countries in the world. Another Russian study showed that the prevalence of HA was 15.9% (HA without aura – 13.5%, HA with aura – 2.4%) [5].

Pathogenesis of HA. Both peripheral and central nociceptive mechanisms are involved in producing HA. Peripheral mechanisms are associated with painful tension in the scalp and neck muscles, hypoxia of these muscles, and the release of pain-inducing proinflammatory mediators into the blood. This leads to increases in the excitability of nociceptive neurons in the posterior horns of the spinal cord [4]. The main central mechanism for the development of THA is a decrease in the activity of the inhibitory antinociceptive system of the brainstem, which facilitates the transmission of pain spikes and leads to the formation of central sensitization, which in turn contributes to chronicization of THA [4].

MG is a chronic neurovascular disease with a hereditary predisposition. The main element in its pathogenesis is the periodic development of perivascular neurogenic inflammation of the cerebral vessels, primarily the vessels of the dura mater (DM). Patients with MG have been shown to have elevated neuron excitability in the cerebral cortex and the trigeminovascular system. When exposed to endogenous and exogenous migraine triggers, the excitability of the trigeminal system, hypothalamus, and cortical and various other brain structures increases, which is accompanied by activation of the trigeminal ganglion, sensory spinal nucleus of the trigeminal nerve, and trigeminal nerve fibers innervating the vessels of the dura mater, i.e., trigeminovascular fibers [5].

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Activation of the trigeminovascular system is accompanied by the release of proinflammatory vasodilating peptides – primarily calcitonin gene-related peptide (CGRP), but also neurokinin A and substance P – from nerve endings. The resulting vasodilation and neurogenic inflammation lead to activation of pain receptors in dura mater vessel walls. Pain spikes enter the sensory cortex of the brain producing a sensation of pulsating headache. Persistent hyperexcitability of the trigeminovascular system and central nociceptive structures, along with depletion of the anti-pain system, gradually lead to the formation of permanent hypersensitivity (sensitization) of pain structures, which contributes to an increase in the frequency of headache attacks and, ultimately, to the chronicization of MG [5].

The advent of drugs associated with CGRP has revolutionized the treatment of MG. However, a significant proportion of patients with MG do not respond to this treatment, so further molecular studies of the pathogenesis of MG are needed. Recent decades have seen a large number of studies addressing oxidative stress (OS), which is a universal pathological syndrome in many somatic and neurological diseases.

The basis of OS is mitochondrial dysfunction, which leads to cellular energy deficiency. Mitochondrial dysfunction has no etiological or nosological specificity in relation to any particular disease, though when it is involved in a disease, it participates as one of the mechanisms [6]. Mitochondrial dysfunction, especially due to disturbances in the electron transport chain, is closely associated with increased production of reactive oxygen species (ROS) and cellular energy deficiency.

OS is characterized by an imbalance between the production and degradation of ROS or reactive nitrogen species (RNS) [7]. The onset of OS is characterized by dysfunction of mitochondria associated with ROS, i.e., molecules with high reactivity which can form as a result of oxygen or nitrogen metabolism. ROS and RNS can be free radicals, such as the superoxide radical and the hydroxyl radical nitric oxide (NO). There are also other radicals, such as hydrogen peroxide and peroxynitrite [8]. ROS induce intramitochondrial enzymatic reactions characterized by the reduction of oxygen via the electron transport chain [9]. In addition, the endoplasmic reticulum and peroxisomes serve as further sources of ROS [10]. Various cellular processes such as protein phosphorylation, activation of transcription factors, immunity, and apoptosis are dependent on cellular ROS concentrations [11].

The main endogenous antioxidant enzymes scavenging ROS are superoxide dismutase, catalase, and glutathione peroxidase [12]. ROS can be mopped up by other non-enzymatic molecules with the ability to scavenge free radicals such as vitamins, melatonin, and glutathione [13]. Failure of antioxidant defenses to scavenge ROS adequately leads to oxidation of sensitive biomolecules. Excessive levels of ROS can damage cellular proteins, membrane lipids, and nucleic acids, causing cellular dysfunction [14]. The NO radical is an endothelium-dependent mediator of vascular vasodilation. NO is normally produced by the enzyme nitric oxide synthase [15]. In conditions of OS, NO reacts with the O_2^- radical to form peroxynitrite, causing damage to the vascular endothelium [16].

The process of lipid peroxidation (LPO) is a mechanism of lipid damage in OS. LPO is characterized by the presence of carbon–carbon double bonds, especially in polyunsaturated fatty acids. The main products of LPO are hydroperoxides such as propanal, hexanal, 4-hydroxynonenal, and malondialdehyde (MDA) [17]. In addition, ROS can damage the structure of DNA via reactions with guanine bases.

OS is involved in the pathogenesis of more than 100 diseases [18], including chronic diseases, which can contribute to their progression. Risk factors for cardiovascular diseases, such as obesity, diabetes, arterial hypertension, and atherosclerosis, are associated with OS [19]. Excessive formation of free radicals and the development of OS underlie cell and tissue damage in any pathological processes leading to apoptosis [20]. From this perspective, there is interest in studying the role of OS in chronic HA. This review discusses data on the two most common types of chronic HA – MG and chronic HDN.

Oxidative Stress in MG. Tuncel et al. [20] proposed a hypothesis regarding the pathological role of impaired mitochondrial oxidative metabolism in MG, which has been confirmed by results from numerous studies. Free oxygen radicals can play a role in the development of MG by regulating cerebral blood flow and energy metabolism and they can change the trigger threshold for MG attacks [21]. Convincing data on the development of OS in patients with MG have been obtained using magnetic resonance spectroscopy (MRS). A review of 56 MRS studies in patients with MG with and without aura was published in 2022 [22]. The metabolites measured by MRS are N-acetyl aspartate (NAA, a marker for neurons), creatine (Cr, a marker for cellular energy production), choline (Cho, a marker for cell membrane turnover), myoinositol (mI, a marker for astrocytes), the glutamate/glutamine complex (Glx, excitatory neurotransmitters), γ-aminobutyric acid (GABA, an inhibitory neurotransmitter), and lactate (Lac, a marker for hypoxia).

NAA is one of the most abundant metabolites in the brain. It contains N-acetylaspartylglutamate (NAAG), glycoproteins, and amino acids. NAA is predominantly of neuronal origin and is regarded as a factor in neuron density and integrity. Decreases in its content are seen on neuron death or dysfunction. Decreases in NAA were recorded in the occipital lobes in patients with MG without aura as compared with healthy controls [23] and in the cerebellum of patients with hemiplegic MG [24], which may indicate decreased neuron viability in these forms of MG.

Decreases in the NAA/Cho ratio were observed in the left thalamus in a cohort with migraine, indicating neuron damage in the left thalamus. Decreased total N-acetylaspartylglutamate (tNAA) levels were found in the anterior cingulate cortex and thalamus in patients with chronic MG as

compared with humans and patients with episodic MG [25]. The anterior cingulate cortex has been implicated in the pathogenesis of MG and pain and is thought to mediate the affective components of pain [26]. It was suggested that thalamus and altered thalamocortical connections play a role in many aspects of migraine, including pain processing, modulation, allodynia, photosensitivity, and multisensory integration [27]. Several studies have demonstrated abnormalities in thalamic structure and function in patients with MG [28].

Lac is the end product of anaerobic glycolysis. Although a marker of glycolysis, it is not present in large enough quantities to be detected in healthy brain tissue. MRS in patients with MG with aura has demonstrated elevated Lac levels in areas of the visual cortex, which has been attributed to hypoperfusion, hypoxia, and mitochondrial dysfunction [29]. Elevated Lac levels have also been demonstrated on MRS in patients with vestibular MG [30]. No changes in glutamate levels were found in 18 MRS studies in MG. Data on GABA levels in MG are conflicting. Two MRS studies reported decreased GABA levels in the occipital region and anterior cingulate cortex [31]. Eight studies in patients with MG found no changes in GABA levels [32]. Like other metabolites measured by MRS, GABA levels may be highly dependent on the time at which measurements were made relative to the time of the last MG attack, the frequency of headache episodes, and the time since the last aura event.

The causes of energy deficiency at various levels detected by MRS in MG patients can be explained in terms of the development of mitochondrial dysfunction and OS due to migraine attacks, which has been confirmed by numerous biochemical studies. A search of the PubMed database with the keywords "oxidative stress, migraine" yielded 283 publications over the past 30 years. A meta-analysis addressing biomarkers of OS included studies involving more than 1100 patients with MG [33]. MG attacks were found to be associated with increases in the level of oxidants and depletion of antioxidant protection, determining a shift in the oxidative-antioxidant balance towards the oxidative pole.

Various publications have analyzed individual biomarkers of OS and antioxidant protection. MDA is the end product of lipid oxidation and may be the main biomarker of OS and an indicator of increased ROS production [34]. MDA levels in patients with MG were significantly higher than those in controls in plasma, platelets, and urine [20, 35]. Thiols are organic compounds containing sulfur in the form of a thiol group (-SH). Thiol groups are capable of destroying ROS and other free radicals by both enzymatic and non-enzymatic mechanisms [36]. A study found significant decreases in thiol levels in 151 patients with MG (74 without aura, 77 with aura) as compared with 70 healthy controls. The decrease in thiol levels could be explained in terms of the effect of high concentrations of ROS [37].

The concentrations of individual antioxidants can be measured in serum (or plasma), though total antioxidant status (TAOS) is often measured. A study of 75 patients with MG without aura showed that TAOS decreased, while the level of total oxidants and the severity of OS increased [38]. Another study also showed a significant decrease in OS in patients with MG with and without aura as compared with the control group [39].

Evidence supporting the view that generalized metabolic dysfunction is a feature of MG was obtained from studies of the activity of mitochondrial enzymes such as monoamine oxidase, succinate dehydrogenase, NADH dehydrogenase, cyclooxygenase, and citrate synthetase, which were decreased in the platelets of patients with MG with and without aura [40]. These biochemical changes are limited to the enzymes of the respiratory chain, which are encoded by mitochondrial DNA – which is more vulnerable to the effects of OS than nuclear DNA [41].

Superoxide dismutases (SOD) are the most important metalloenzymes protecting cells from OS. Of all the antioxidant enzymes studied, SOD is the only one whose activity is most often reduced in patients with MG, including during the interictal period [42]. A meta-analysis of six studies on this biomarker in a number of tissues (erythrocytes, serum, platelets, polymorphonuclear neutrophils) showed that decreases in SOD activity in the interictal period of MG were statistically significant as compared with the control group [33].

In MG with and without aura, measures of OS and the antioxidant defense system did not differ significantly in all the studies. Interesting data were obtained on OS in patients with episodic and chronic MG (EMG and CMG, respectively). One study included 44 patients with EMG, 27 with CMG, and 19 age- and sex-matched controls. Serum levels of MDA, TAOS, and antioxidant enzymes – catalase (CTL), SOD, and glutathione peroxidase-1 (GTP-1) – were analyzed [43]. Serum CTL and SOD levels were significantly lower in the CMG group than in the EMG and control groups. In contrast, GTP-1 levels in patients with CMG were slightly higher than in patients with EMG and the control group. Patients with CMG also had lower mean TAOS values than patients with EMG and the control group. In addition, serum MDA levels were significantly elevated in patients with CMG as compared with EMG patients and controls.

Negative correlations were found between the number of days with HA per month and serum CTL and SOD levels, and also with TAOS. At the same time, a positive correlation was noted between the number of days with HA and the serum GTP-1 level. Thus, patients with CMG had higher levels of OS markers and decreased activity of TAOS and antioxidant enzymes (CTL and SOD). Increases in GTP-1 activity may be associated with a compensatory mechanism whereby this activity can increase after decreases in the levels of other antioxidant enzymes [44]. A number of studies have noted a positive relationship between the number of days with HA in MG and an increase in the level of OS biomarkers with simultaneous decreases in antioxidant enzyme activities, which may point to an inflammatory mechanism in the pathophysiology of the progression of EMG to CMG [38].

Genetic studies have confirmed the assumption that patients with MG have increased vulnerability to OS, suboptimal mitochondrial functioning, and/or altered metabolism [45]. However, it is still unclear whether the accumulation of mitochondrial DNA damage due to OS plays a role in the chronicization of MG.

OS in Chronic THA. A number of studies have addressed OS in patients with THA as compared with migraine patients. One study included 50 patients with MG, 50 with THA, and 50 healthy individuals (the control group) [46]. OS was found to be detectable only in patients with MG. OS biomarkers in THA did not differ from those in the control group, even when blood samples were taken from patients with THA during episodes of MG. These results led to the conclusion that there is no specific evidence that the biochemical changes in THA are similar to those seen in MG, especially the changes affecting OS. This conclusion has also been confirmed in other studies [47, 48].

These data contradict results from a study of 41 patients with THA and 19 healthy individuals of the same age and sex without MG. In the THA group, 20 patients were prescribed treatment and 21 were untreated. Measurements of serum levels MDA and the activity of the antioxidant enzymes CTL and GTL-1 were used to assess oxidant/antioxidant status [49]. A significantly lower level of CTL activity and a higher level of GTL-1 activity were found in the group of patients with THA. In the THA group, serum CTL activity was significantly reduced in both groups of patients, while the serum MDA level was higher in untreated patients with THA. The authors took the view that OS can occur with THA and that drug treatment partially eliminates it. These data require further confirmation, though the indications appear to be that the pathogenetic mechanisms of MG and THA are different [46].

Thus, OS is involved in the pathogenesis of MG, but the question of the mechanisms of actualization of OS in the main manifestation of the disease – HA – remains open. It is now known that CGRP plays a key role in the pathogenesis of MG. Release of CGRP during attacks of MG leads to dilation of cranial vessels and neurogenic inflammation, resulting in activation of the sensory fibers of the trigeminal nerve and modulation of the transmission of pain spikes to the brain [50]. In addition, transient receptor protein (TRP) ion channels are believed to play an important role in the pathogenesis of MG, as they are expressed in trigeminal neurons and brain areas associated with the pathogenesis of MG [51]. These are signal molecules and are able to convert various spikes into pain signals. As TRP are transmembrane proteins, they can link the extracellular environment with processes occurring within neurons [52].

Ion channel subtype 1 of the TRP family (TRPA1) can be activated by products of OS and can stimulate the release of CGRP from nerve terminals. TRPA1 may be a central element of the signaling pathway from OS to CGRP release, which plays a decisive role in the occurrence of MG. TRPA1 is a sensor and modulator of OS and the activity of OS-related enzymes. Lipid peroxides have a longer lifetime than free radicals and may therefore promote more persistent activation of TRPA1. TRPA1 are located in the perivascular sheaths of nociceptive nerve endings and are able to sensitize meningeal nociceptors and second-order trigeminal neurons, which may be important in migraine [53]. The TRPA1-CGRP interaction may therefore be a key factor in OS associated with migraine attacks. TRPA1 may also be regarded as a diagnostic and therapeutic target in diseases associated with OS.

Antioxidants in the Preventive Treatment of MG. Given the role of OS in the pathogenesis of MG, the possibility of using antioxidants in its preventive treatment is discussed. Extensive data have been reported on the use of nutraceuticals in the form of dietary supplements with antioxidant action. A review discussing the potential for using vitamins C, B2 and E, coenzyme Q10, melatonin, and curcumin in MG was presented in 2020 [54]. Nutraceuticals with antioxidant action are often used by MG patients because of their positive effects (reducing the frequency of MG episodes, shortening their duration) and the fact that they have no or only minor side effects.

The TRPA1 ion channel associated with CGRP may be a therapeutic target in diseases whose pathogenesis involves OS. From this point of view, the use of antioxidant pharmacotherapy in the prophylactic treatment of MG is pathogenetically grounded. Mexidol (ethylmethylhydroxypyridine succinate), a drug with a multimodal mechanism of action, is currently in wide use in neurological practice [55]. The main mechanisms are its antioxidant and membranotropic effects and its abilities to modulate the functioning of receptors and membrane-bound enzymes, restore neurotransmitter balance, and increase cellular energy status. Mexidol has the important ability to influence free-radical processes, which are among the basic processes involved in its modifying/damaging effect on the cellular structures of the central nervous system and other organs and tissues [55].

Mexidol occupies a special position among the known antioxidants, as it affects different links in free-radical processes in biomembranes and within cells and does not have the prooxidant effect typical of many other antioxidants in certain conditions [56]. Mexidol has been shown to have a positive effect in the treatment of primary and secondary headaches. Mexidol in combination therapy has been noted to have efficacy in the prevention and correction of disorders associated with migraine. Mexidol has been established as having anxiolytic and tranquilizing properties and the ability to relieve somatoautonomic and asthenoneurotic disorders and activate the activity of the antinociceptive systems. These mechanisms may underlie the pathogenetic direction of the action of Mexidol in migraine [57]. These data provide grounds for the use of Mexidol in complex therapy and for the prevention and treatment of primary chronic hypertension.

The author declares no conflict of interest.

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