

# Migraine and orexin

## Abstract

Migraine is diagnosed in approximately 15% of the population in the developed countries. This disease affects not only patient's well-being, but also economy and social sphere. Despite this significant impact, little is known on the genetic causes of migraine. Several migraine symptoms, including tiredness, yawning, drowsiness, and the desire to eat certain foods, give an idea of migraine connection to orexin system. This system includes orexines – peptides, predominantly synthesized in the lateral hypothalamic area and involved in wake and sleep cycle and many other neurological functions; and their two receptors *HCRTR1* and *HCRTR2*. Here we summarize known data on orexin system polymorphisms and changes in peptide concentration in patients with migraine.

**Keywords:** migraine, orexin A, orexin B, migraine with aura, migraine without aura, SNP, text mining

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Irina Ostroukhova, Olga Rudko, Artemii Tretiakov, Eugene Klimov

Faculty of Biology, Lomonosov Moscow State University, Russia

**Correspondence:** Eugene Klimov, Faculty Biology, Lomonosov Moscow State University, 119234, Moscow, Lenin's Hills, 1-12, Russia, Email [klimov@mail.bio.msu.ru](mailto:klimov@mail.bio.msu.ru)

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**Abbreviations:** MA, migraine with aura; MO, migraine without aura

## Introduction

### Short migraine overview

Migraine is diagnosed in approximately 15% of the population in the developed countries. Remarkably, migraine is approximately 3 times more common in females than in males.<sup>1</sup> Migraine can roughly be divided into migraine with aura (MA) and migraine without aura (MO), as well as into episodic and chronic types. This condition has a strong impact on the patient's well-being and quality of life not only during an acute episode, but throughout life in general, affecting patient's work productivity, family members and other social aspects.<sup>2</sup> WHO views migraine as one of the most invalidating chronic diseases.<sup>3</sup>

Migraine may impact not only on the population's health and life activities, but even the country's economy, as patients suffering from this disorder often have to call in sick, meaning that migraine episodes may disrupt the working process. Despite this impact, migraine genesis and its exact causes are still unknown. However, a hypothesis about the involvement of the orexin system in migraine pathogenesis exists.

### Orexin overview

Orexins (orexin-A and orexin-B) are peptides produced by proteolysis of a prepro-orexin precursor consisting of 130 amino acidic peptides. Orexins are predominantly synthesized in the lateral hypothalamic area. Human gene encoding prepro-orexin is located on the 17q21 chromosome and consists of 2 exons and 1 introne with a total size of 1432 bp. Mature orexin-A is a neuropeptide consisting of 33 amino acids, with 2 disulfide bridges playing a vital role in peptide's functional activity. Mature orexin-B is a 28 amino acid neuropeptide, with 2  $\alpha$ -helix connected with a flexible loop. Orexin-A and orexin-B are homologous by 46%.<sup>4</sup> The orexin-A sequence is fully identical in rat, mouse, pig, bovine and human genomes, which implies peptide's vital functional role.<sup>5</sup> Orexin-B slightly varies among different species, with its isoforms in mouse and rat genomes differing by 2 amino acids from the human orexin-B gene.

Two types of orexin receptors are known – *HCRTR1* (OX1R) and *HCRTR2* (OX2R), both belonging to the  $\beta$ -subtype of G protein-coupled receptors (GPCR). Human *HCRTR1* gene is located on chromosome 1p33, while the *HCRTR2* gene is located on chromosome 6p11. Both genes consist of 7 exons and 6 introns. *HCRTR1* and *HCRTR2* sequences are homologous by 64%. The *HCRTR1* and *HCRTR2* receptor activation leads to the increase of intracellular  $Ca^{2+}$  concentration which results in the Gq-mediated stimulation of phospholipase C.<sup>6</sup> Orexin-A binds to both *HCRTR1* and *HCRTR2* with the similar affinity, while orexin-B has a several times stronger affinity to *HCRTR2* than to *HCRTR1*.<sup>6,7</sup> *HCRTR2* receptor regulates excitement, while *HCRTR1* receptor regulates wakefulness.<sup>8,9</sup>

Orexin neurons project to a number of regions in the brain, i.e. cerebral cortex, cingulate gyrus, paraventricular thalamic nuclei and «migraine generators», such as LC PAG and NRM.<sup>10-13</sup> Orexin neurons' activity is mediated by a number of neurotransmitters: GABA, norepinephrine, and serotonin inhibit orexin neurons; in contrast glutamate, cholecystokinin, neurotensin, oxytocin, and vasopressin stimulate orexin neurons.<sup>14</sup>

The most well-known orexin function is the neuroendocrine regulation of sleep-wake cycles. However, orexins are involved in a large number of processes, predominantly linked to the regulation of food motivation and energy homeostasis. Orexin effect on blood sugar level is known, as well as on metabolic rate in fat tissues, blood pressure, and ovulation. Orexins are involved in the development of motivated behavior and in the formation of psychological dependence, and play a role in the interactions between nervous and immune systems. It is also assumed that orexins regulate negative emotional responses. Wherever orexins are involved in the migraine prodrome is disputed.

### Orexin-migraine linkage

Due to orexin involvement in the regulation of wakefulness and sleep, linkage between migraine and sleep disturbance supposedly may lie in the plane of the orexin system,<sup>15</sup> which may also be true for the pathological genesis of migraine.<sup>16-18</sup> Besides, some symptoms observed in migraine, i.e. tiredness, yawning, drowsiness, and the

desire to eat certain foods, are assumed to be connected with the orexin system as well. In general, *HCRTR1* and *HCRTR2* may play a role in nociceptive modulation in the trigeminovascular system, while orexin-ergic activation of hypothalamus may be linked to the pathological mechanisms of migraine.<sup>19</sup> In this review we summarize known published data on the association of orexins with migraine.

## Methods of literature analysis

Literature search was performed through the TargetInsights service (<https://demo.elsevierextmining.com/>). In the initial search 48 publications were found. All of the publications were precisely analyzed. Reviews and studies on animal models were excluded. Only

4 articles investigating genetic and biochemical markers of orexins in patients with migraine were identified and taken into further analysis.

## Review of the literature data regarding a possible orexin-migraine linkage

Very few studies are aiming to reveal the role of the orexin system in the development of migraine. According to the 2018 study,<sup>20</sup> (Table 1), no alleles were associated with the increased risks of migraine, however the presence of *HCRTR1*\*G1222A allele is likely to be a risk factor for migraine with aura, while the *HCRTR1*\*G29A allele is, in contrast, a possible risk factor for the development of migraine without aura. Genotype GA\*G29A may promote an early onset of migraine.

**Table 1** SNPs in the orexin genes, studied in patients with migraine

Gene	SNP	Sample	Results summary	Reference
<i>HCRTR1</i>	G1222A	Poland, nP (number of patients) = 123, nC (number of controls) = 123	None of the alleles were associated with the increased risk of migraine, however, allele A of <i>HCRTR1</i> *G1222A ( $p = 0,0574$ ) and allele A of <i>HCRTR1</i> *G29A ( $p = 0,0647$ ) were close to the significance threshold.	20
	*G29A		Analysis of the association between migraine episode frequency and headache duration with the <i>HCRTR1</i> *G1222A genotypes, with group A consisting of patients bearing AA and GA genotypes, showed no significant association as well.	
<i>HCRTR1</i>	rs10914456	Italy, nP = 384, nC = 259	Allele A is significantly linked to the increased risk of migraine.	22
	rs4949449			
	rs2271933			
<i>HCRTR2</i>	1246 G/A	Italy, nP = 246 nC = 239	Comparison of clinical parameters of the disease in patients with genotypes <i>HCRTR2</i> * 1246 (G>A) did not show any significant differences. Study suggests that the <i>HCRTR2</i> gene is not a genetic risk factor for migraine.	21

It was demonstrated by the same authors, that an allele A of the G1222A SNP was more common in the subsample of the migraine patients without aura (52%) than in controls (42%), while the GA\*G29A genotype was more common in the migraine patients with aura (16%) than in controls (7%). It is likely that the SNPs G1222A and G29A in *HCRTR1* may be linked to the different subtypes of migraine with *HCRTR1*\*G1222A being a risk factor for MO and *HCRTR1*\*G29A – for MA. It is also possible that the polymorphisms in *HCRTR1* gene may indirectly alter levels of orexin-A. According to the study conducted in 2007 by Pinessi et al.<sup>21</sup> (Table 1), *HCRTR2* gene is not one of the genetic factors predisposing migraine development.

In a study by Rainero et al.<sup>22</sup> in 2011 (Table 1), researchers found that the carriage of an A allele was associated with an increased risk of migraine. According to the results obtained by Kowalska et al. (Table 2), patients with higher orexin-A concentration were characterized by the shorter migraine attacks, however this trend was observed in

the MO subsample only. Increasing trend in orexin-A concentrations was observed in the patients with MA, while patients with MO were lacking this trend.

In general, there were no significant changes in the orexin-A concentrations between the compared groups. The significantly higher orexin-A levels found in the migraine patient sample are likely to act as a compensatory response to chronic headache or, alternatively, as an expression of a hypothalamic response to stress due to chronic pain (Table 2).<sup>23</sup> Studies on the relationship of orexin concentrations and the occurrence of migraines have been carried out in animals, in rats in particular. It was reported that the systemic blockade of orexins did not affect migraine prophylaxis. Rat models showed that intravenous administration of orexin-A significantly suppressed spontaneous excitation of trigeminal neurons. This effect was leveled out by the pretreatment with a selective antagonist of *HCRTR1*.<sup>11</sup>

**Table 2** Relations of orexin concentrations to the migraine symptoms

Protein/peptide	Sample	Results summary	Reference
Orexin A	Poland, nP = 123, nC = 123.	No significant differences in the orexin concentrations.	20
Orexin A	Italy, nP = 57, nC = 20	Significantly higher orexin A levels in the patients with migraine.	23

## Conclusion

Insofar, it is impractical to draw any precise conclusions at the moment, as the studies on the involvement of the orexin system in the pathophysiology of migraine are rather small. However, it is already clear that the *OxIR* gene may be associated with the onset of migraine. It is also likely that the concentration of the orexin-A influences the development of migraine symptoms, such as headache, fatigue, and drowsiness. Further study of the relationship between orexins and migraine will allow a better understanding of the mechanisms of the disease development in general and its individual symptoms.

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## Conflicts of interest

Authors declare no conflict of interest.

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