Arterial Hypertension

Subjects: Biology

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Arterial hypertension (AH) is a common disease worldwide and is a key risk factor for fatal cardiovascular complications [1]. Migraine (M) is the second most common type of primary headache and the most common form of headache with a genetic predisposition [2]. Many studies support the hypothesis that patients with M have an increased risk of developing AH, while patients with AH seem to have an increased risk of M. This allows us to hypothesize about the existence of the M and AH phenotype.

Keywords: migraine ; arterial hypertension ; comorbidity ; nitric oxide ; nitric oxide synthase ; genes ; single nucleotide variants ; single nucleotide polymorphisms

1. Introduction

Arterial hypertension (AH) is a common disease worldwide and is a key risk factor for fatal cardiovascular complications [1]. Migraine (M) is the second most common type of primary headache and the most common form of headache with a genetic predisposition [2]. Many studies support the hypothesis that patients with M have an increased risk of developing AH, while patients with AH seem to have an increased risk of M. This allows us to hypothesize about the existence of the M and AH phenotype. The relationship between M and AH is potentially of great pathophysiological and clinical interest and is being actively studied. The pathophysiological pattern is significantly different in the setting of chronic pain, in which the adaptive relationship between blood pressure and pain sensitivity changes significantly. The association between acute or chronic pain and cardiovascular changes has been confirmed by observations, and some of this circumstantial evidence is supported by experimental models and human studies [3]. AH and M may have common mechanisms such as endothelial dysfunction, lack of autonomic regulation of the cardiovascular system, and involvement of the renin-angiotensin system.

Nitric oxide (NO) is an important autocrine and paracrine signaling molecule that plays a crucial role in the regulation of the physiology and pathology of the cardiovascular system. NO is a very important molecule in the regulation of cerebral and extracerebral cranial blood flow and arterial diameter. Reduced bioavailability of NO in the endothelium is an important precursor to impaired vasodilation and hypertension. NO is also involved in nociceptive processing. NO synthase (NOS) is expressed in three isoforms. NO production requires oxygen as an electron acceptor. NO diffuses freely across the plasma membrane and, therefore, is known to be transported to effector proteins in the same or adjacent cells and exerts its effects (for example, in smooth muscles, endothelial NO targets soluble guanylate cyclase, and sGC to ensure vasodilation) [5].

Single nucleotide variants (SNVs) of genes encoding NOSs can affect the level of their expression and/or activity in organs and tissues.

Increasingly more experimental evidence suggests that eNOS, iNOS, and nNOS have an important impact on cardiovascular function and pain [6,7]. Consequently, their combined effect on the M and AH phenotype in humans is of undoubted scientific and clinical interest. However, this phenotype requires a better treatment. In addition, there are many interesting associative studies of the role of *NOS1*, *NOS2*, and *NOS3* genes in the development of the M and AH phenotype.

Aim: analysis of associative studies of single-nucleotide variants of genes encoding NO-synthases in the migraine and arterial hypertension phenotype.

2. Results

Over the past 15 years, works aimed at finding associations of *NOS1*, *NOS2*, and *NOS3* genes with the development and course of headaches (H) have been carried out using the example of patients with M.

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Alaşehirli et al. (2013) included 120 patients with M and 185 conditionally healthy volunteers from the Turkish population in their study. The results showed that the frequencies of alleles (p = 0.5257) and genotypes (p = 0.2841) of rs2682826 of the *NOS1* gene among patients with M did not statistically significantly differ from those of the control group [2].

Moreover, SNV rs2682826 was studied in the Japanese population. Ishii M. et al. (2014) compared the distribution of SNVs of three genes, including *NOS1* and *NOS3* (see M *NOS3*), in 47 patients with M and 22 patients with drug-induced H. The authors took into account the lack of association of this SNV with M in the Turkish population [2] and emphasized the need to continue work in this direction. They argued their choice of the following study design: during the M attack, the level of NO increases, at the same time it was shown that the synthesis of NO decreases during depression; and depressive disorders represent a comorbid state, which is more common with drug aggravation of H than attacks with M. However, the distribution of genotypes for SNV rs2682826 did not statistically significantly differ between groups (p = 0.254) [8].

García-Martín et al. (2015) continued to study the associations of SNVs of genes encoding NO synthases with the development of M in the Spanish population, with consideration of available biochemical, neuropathological, pharmacological, and experimental data. Taking into account the negative results of the work of Turkish and Japanese colleagues, García-Martín et al. included in their study other SNVs of theNOS1gene: rs693534 and rs7977109. However, the authors did not find significant differences in the distribution of genotypes and the frequency of alleles between the main (197 patients) and control (308 healthy Caucasians) groups [9].

According to the results of studies of theNOS2gene SNVs, allelic associations and associations of genotypes were not found. However, several haplotypes were identified that increase the risk of M.

Specifically, Schurks et al. (2009) conducted a large-scale study of 77 SNVs of 52 candidate genes potentially associated with M, including the genes of the NO synthesis system,OS2andNOS3(see MNOS3), in the American population. A total of 25,713 women were examined, including 4705 patients with M and 21,008 women without a history of M. Among theNOS2gene SNVs, rs1137933 was considered. According to the results of genotyping, this SNV did not show a statistically significant association with a history of M [10].

As a result, De O.S. Mansur et al. did not find associations of alleles or genotypes of the studied SNVs rs2779249 and rs2297518 with an increased risk of developing M, but showed that a haplotype with the simultaneous carriage of allele A was more common among patients suffering from M with aura than among the control group subjects (OR 2.65, 95% CI 1.34–5.22;p= 0.0027). also did not find statistically significant differences in the frequency of the occurrence of alleles and genotypes of theseNOS2SNVs between the control and main groups. At the same time, they further analyzed the gene–gene relationship and found a significant interaction when comparing the group of patients with M and the control group.

The search for associations of theNOS3gene SNVs with M is carried out all over the world. However, the existing results are inconsistent.

(2006) conducted a study in the Italian population, examining 156 patients with M (including 53 patients with aura) and 125 persons without H in general. Asp298 increased the risk of developing M with aura in the studied population. According to the results, the AspAsp genotype of this SNV doubled the risk of developing M (OR 2.21, 95% CI 1.00–5.04;p= 0.05) and increased threefold the probability of having an aura (OR 3.02, 95% CI 1.21–7.51;p= 0.02) compared with the GluGlu + GluAsp genotypes. In addition, analysis of medical history and examination results showed no differences in clinical characteristics between groups.

(2008) continued the associative search in the Spanish population. However, Spanish researchers were unable to confirm the results of their Italian colleagues. None of the formed haplotypes influenced the development of M in the Spanish population. [13] by the fact that the Italian scientists did not carry out the correction for multiple hypothesis testing [14].

(2009) explored three SNVs of theNOS3gene, including rs1799983, rs1800779, and rs3918226. When comparing patients with M with those of the control group, the authors did not find a difference in the frequency of occurrence of alleles and genotypes for all three SNVs. When dividing the patients into subgroups (1309 patients with M with aura and 1997 patients with M without aura) and from the subsequent intergroup comparison of each of the subgroups with the control group, an association of SNV rs3918226 with the development of M without aura was shown (OR 1.13, 95% CI 1.01–1.27;p= 0.04). However, after adjusting for multiple hypothesis testing, it also ceased to be statistically significant [10].

Gonçalves et al. studied five SNVs (rs2070744, rs3918226, variable number of tandem repeats of 27 pairs of nucleotides in intron 4 (VNTR 4 a/b), rs1799983, and rs743506) of theNOS3gene as possible markers of susceptibility to M in the Brazilian population. The sample consisted of 178 women with M (44 of them had aura) and 117 healthy controls. Therefore, we recall that the authors also identified a number of combinations of genotypes with the highest risk of developing M for rs743506 of theNOS3gene and rs2297518 of theNOS2gene (see MNOS2)

The only study found that also examined the VNTR 4 a/b polymorphism was conducted in the Turkish population [16]. It involved 105 patients with M and 97 healthy women. However, the authors did not find statistically significant differences between allele frequencies (p= 0.22) and genotypesp= 0.106) between patients with M and the control group, thus confirming the absence of an association between the development of M and this polymorphism [ibid].

The first two SNVs showed a statistically significant difference between patients with M and the control group (p< 0.0001). When comparing genotypes, the authors proved that, among patients with M, GT heterozygotes and TT homozygotes were much more common than among people without H (OR 3.027, 95% CI 1.830–5.008 and The sample size was almost equal to that used by their colleagues [17] and amounted to 175 patients with M and 125 persons without H as a control group, while more SNVs were studied (rs743506, rs2070744, rs1799983, rs1800779, rs3918226, rs207468799, and rs148554851). However, none of these SNVs showed significant differences in the frequency of carriage of alleles or genotypes in the intergroup comparison (p> 0.05).

In parallel with Turkish studies, a noteworthy study of genesNOS1andNOS3SNVs as risk factors for the development of medication overuse headaches (in patients with M) was carried out in the Japanese population. This work by Ishii et al. SNV rs1799983 of theNOS3gene was studied. The distribution of genotypes was not statistically different between groups (p= 1.00) [8].

(2016) conducted a study in the Iranian population. The authors examined 120 persons, including 60 patients with M and 60 healthy subjects, to study SNV rs2070744. The frequency of carriage of the C allele significantly prevailed among patients with M compared with controls. When comparing genotypes, a statistically significant association was also revealed between this SNV and the development of M in the study population (p< 0.0001)

Two large meta-analyzes were published in 2015 and in 2018.The first one reviewed associative studies of the rs1799983 SNV of theNOS3gene, and the second one explored the rs2070744 SNV of the same gene, as potential risk factors for the development of M. Chen et al. The total number of participants was 1932 persons, including 1055 patients with M and 877 apparently healthy humans. As a result, no statistically significant association was found between the rs1799983 SNV and the risk of M in any of the studied genetic models among all participants. However, analysis of different nationalities' subgroups demonstrated that the CC genotype increased the risk of M compared with the TT + TC genotypes in Caucasian populations (OR 1.62, 95% CI 1.03–2.56,p= 0.04), with this association not observed among non-Caucasians with M (fixed-effects model; OR 0.88, 95% CI 0.51–1.53;p= 0.66) [21].

The results of the latest study in the Spanish population that we found on the subject of this review were published in 2020 by García-Martín et al. (2020), who observed 283 patients with M and 287 healthy volunteers. [21] and studied SNV rs2070744 in representatives of the Caucasian race in Spain. However, the frequencies of alleles and genotypes did not differ significantly between the main and control groups (for the minor allele OR 0.91, CI 0.72–1.12,p= 0.418), although it was shown that homozygotes for the minor C allele were more common among patients with a burdened family history of M [22].

The association of SNVs genes encoding NOS with the risk of AH is being actively studied. Most of the works concern theNOS3gene SNV, while theNOS2gene SNV remains less well understood.

There are very few studies on the association ofNOS1gene SNVs with the risk of AH. A total of 3351 persons took part in the project, including 560 patients with coronary heart disease (CHD), 1158 patients with AH, and 1633 apparently healthy volunteers (control group). (OR 0.81, 95% CI 0.67–0.97,p= 0.02; protective effect of the minor allele T), as well as with SNV rs7314935 Then, four haplotypes were formed.

According to the results of Levinsson et al. [23] (see AHNOS1), of all studied SNVs of theNOS2gene, rs2255929 has a statistically significant effect on the risk of developing AH (OR 1.18, 95% CI 1.03–1.34,p= 0.02) [23].

The study involved 18738 women of the Caucasian race without AH at the time of inclusion. The development of AH was recorded in 5540 of these women after 9.8 years. The presence of gradual progression of AH was assessed within two years and was recorded in 47.4% of women, respectively. However, in carriers of alleles and genotypes of this SNV, no predisposition was shown either to the onset (

In three subsequent associative studies of theNOS2gene with the development of AH, rs2297518 and rs2779249 and their haplotypes were studied. (2013) examined 197 patients with AH and 113 volunteers with normal blood pressure. The SNVs haplotype was found six times more often among patients with AH than among patients with normal blood pressure (OR 6.07, 95% CI 1.57–29.27,p= 0.014) As a result, a statistically significant effect on the risk of developing AH was shown by the haplotype with the simultaneous carriage of alleles A (OR 2.01, 95% CI 1.29–3.12,p= 0.002)

Endothelial NOS controls NO levels and ensures the normal functioning of vascular endothelial cells. As one of the key links in the development of AH is endothelial dysfunction, the main pool of associative molecular genetic studies is aimed at finding associations of the development of AH with SNVs in theNOS3gene.

[24] in the framework of the large American project “Research of the female genome” (see above AHNOS2), threeNOS3SNVs were studied: rs1799983, rs1800779, and rs3918226. According to the results, only rs1799983 increased the risk of developing AH (OR 1.047, 95% CI 1.006–1.089,p= 0.03). The associations of the studied alleles and genotypes of SNV with the progression of an increase in blood pressure were also insignificant [24]. (2008) published these results in another work, where they demonstrated the frequencies of the alleles and genotypes of the three studied SNVs in the study sample, and traced the influence of haplotype carriage on the development and progression of AH.

In 2010, Kingah et al., within the framework of another American project “Atherosclerosis Risk in Community (ARIC)”, studied the association of rs1799983 with AH [29]. The sample was also large enough (15,792 persons), but more diverse, including both women and men, both Caucasians and African Americans. [29] differed from those of the previous studies [24,28]. The authors did not find statistically significant differences in the frequency of genotypes between the main and control groups, as well as depending on race (Caucasians:p= 0.8; African Americans:p= 0.5) [29].

(2011) evaluated the effect of SNVs rs2070744, rs1799983, and rs7830 on the development of AH. The analysis of haplotypes was also carried out, which showed the protective effect of the alleles G rs1799983 and G rs7830. Thus, of the eight haplotypes, TGG (rs2070744, rs1799983, and rs7830) was statistically significantly less common among patients with AH (OR 0.68, 95% CI 0.571–0.810,p= However, unlike colleagues from the southern region of China [30], the authors did not find statistically significant differences in the frequency of occurrence of alleles and genotypes between the main and control groups.

The same three SNVs (rs2070744, rs1799983, and VNTR 4 a/b) were studied in parallel in the Brazilian and Singaporean populations. [31], no statistically significant differences in the frequency of occurrence of alleles and genotypes were found. However, during the formation of haplotypes, a protective effect of the C-Glu-b haplotype (p< 0.00625) against AH was found as well as a provocative effect of the haplotype C-Asp-b (p< 0.00625) in the Brazilian population [32]. OR 1.8, 95% CI 0.9–3.4,p= 0.035), while no association of the rs2070744 and rs1799983 genotypes with AH was found (p= 0.419 andp= 0.227, respectively)

(2014) conducted a study in the Indian population. The study included 700 persons (350 patients with AH and 350 apparently healthy volunteers as a control group). The association of rs2070744, rs1799983, and VNTR 4 a/b with the risk of developing AH was studied. All three polymorphisms showed an association with the risk of AH when exposed to certain external environmental factors [34].

Another association study was conducted in the Sudanese population. The study included 157 patients with AH and 85 healthy volunteers. The frequency of the C allele and the CC genotype was statistically significantly higher among patients with AH than among the control group Therefore, in the studied Sudanese population, SNV rs2070744 significantly increased the risk of developing AH (SS versus TS + TT:

Moreover, we found a number of studies based on a different design and methodology that takes into account other parameters. (2012) identified a locus (rs3918226) A year later, this group of scientists published the results of targeted sequencing, confirming thatNOS3is a susceptibility gene for AH. The development of AH during the study in initially normotensive persons was statistically significantly associated with homozygosis of TT SNV rs3918226

Levinsson et al. (2014, see AHNOS1) highlight the potential involvement of genes encoding NOS in the development of CHD and AH. According to their study, one SNV of theNOS3gene (rs3918226) increases the risk of developing AH (OR 1.32, 95% CI 1.01–1.72,p= 0.04)

3. Conclusions

Therefore, in our review, we synthesized information about SNVs of theNOS1,NOS2, andNOS3genes involved in the development of M and essential AH phenotype. The results of the studies we discussed in this review are inconsistent, which may be owing to different study designs; small sample sizes in some of them; and different racial, ethnic, social, and geographic characteristics. Inhibition of NO production, blockade of steps in the NO-cGMP pathway, or NO scavenging may be targets for new drugs for the treatment of AH and M. Indeed, selective inhibitors of n-NOS and i-NOS are already in early clinical development.
