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AGEs interactions with *RAGE* and their contribution to diabetic retinopathy

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ABSTRACT

Diabetic retinopathy as a complication of diabetes is one of the most common causes of vision loss. It is a dangerous disease, which affects more and more people. It is important to know its different causes, background and to generate new, effective therapeutic threatments. One of the possible causes of diabetic retinopathy is the accumulation of advanced glycation products and over-expression of AGEs receptors (RAGE) leading to tissue damage, oxidative stress formation, and the promotion of other changes and disorders. There are many genetic variants that encode the AGEs receptor (RAGE). Some polymorphisms (*Gly82Ser, 1704G/T, 2184A/G, -429T/C, -374T/A*) may be associated with diabetic retinopathy. This paper aims to systematize knowledge in this field and to show the relationship between these compounds and diabetic retinopathy.

***Keywords*:** RAGE, diabetic retinopathy, signaling pathway, polimorphism, molecular basis

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1. INTRODUCTION

Diabetic retinopathy is a complication of diabetes. It is a degenerative retinal disease in which the blood vessels are damaged. Increased angiogenesis occurs, resulting in vessel fragility, cracking and damage to the retina structure itself (Fig. 1).

Retinopathy is a serious disease with poorly understood molecular background that can ultimately lead to vision loss [1-3].

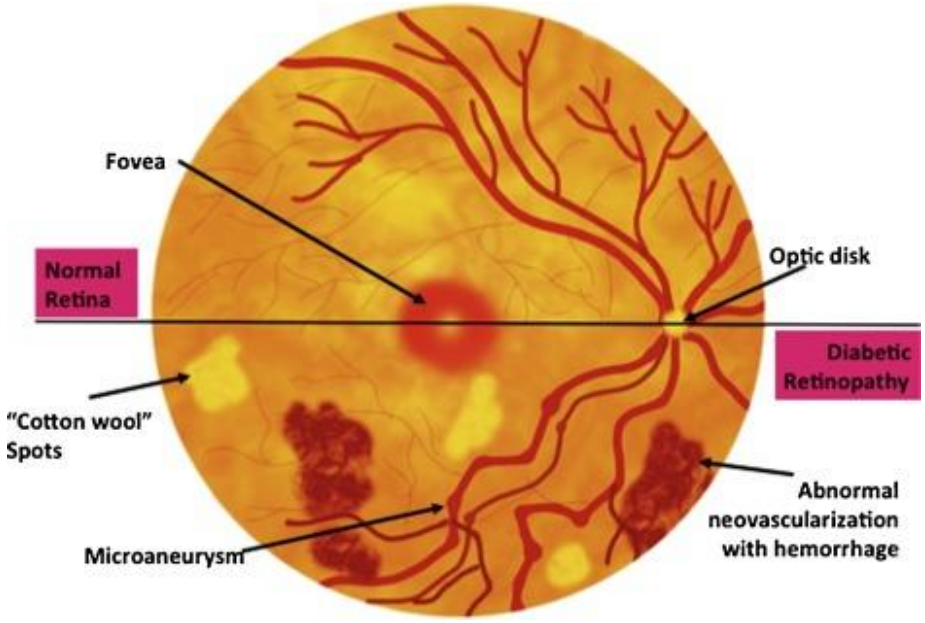

Fig. 1. View of the healthy eye and the changes caused by diabetic retinopathy [32].

It was found that retinopathy is the most common cause of new cases of blindness in adults (20-74 years) [4]. The pathogenesis of diabetic retinopathy is not fully known, but established risk factors include poor glycemic control, hypertension, age and duration of diabetes [5]. The etiology of retinopathy at the molecular level is complex and not fully understood. Many mechanisms are associated with each other causing all kinds of anatomical and patho-physiological changes in microcirculation, and consequently changes in the retina [6]. There are indications that polymorphisms of the *RAGE* gene (*Gly82Ser, 1704G/T, 2184A/G, -429T/C, -374T/A*) may be related to the development of diabetic retinopathy, but there are discrepancies in previous studies [7-9]. It is very important to determine which of the *RAGE* gene variants may be associated with retinopathy. This knowledge can later be the basis for the creation of rapid diagnostic tests and therapeutic treatments for diabetic retinopathy.

2. AIM OF THE STUDY

Until now, it has not been established which of *RAGE* gene polymorphisms are associated with illness on diabetic retinopathy. There are many studies whose authors focus on the answer to the question whether a given genetic variant is related to the disease. Unfortunately, there is

no agreement on this issue depending on the population and other factors. The aim of this work is to present the previous research that have been achieved so far and to show that further research in this matter is indispensable.

3. ADVANCED GLYCATION END PRODUCTS

Advanced glycation end products are products formed in the course of a multistage spontaneous glycation without the involvement of enzymes. Products that undergo glycation can be proteins, lipids, phospholipids, amino acids, and nucleic acids. Originally it was thought that glycation of molecules is a type of protein labeling for subsequent degradation by macrophages [10]. A healthy organism quickly cope with AGEs by eliminating them, however, some of these molecules accumulate in the tissues, which later may result in the formation of chronic diseases [11].

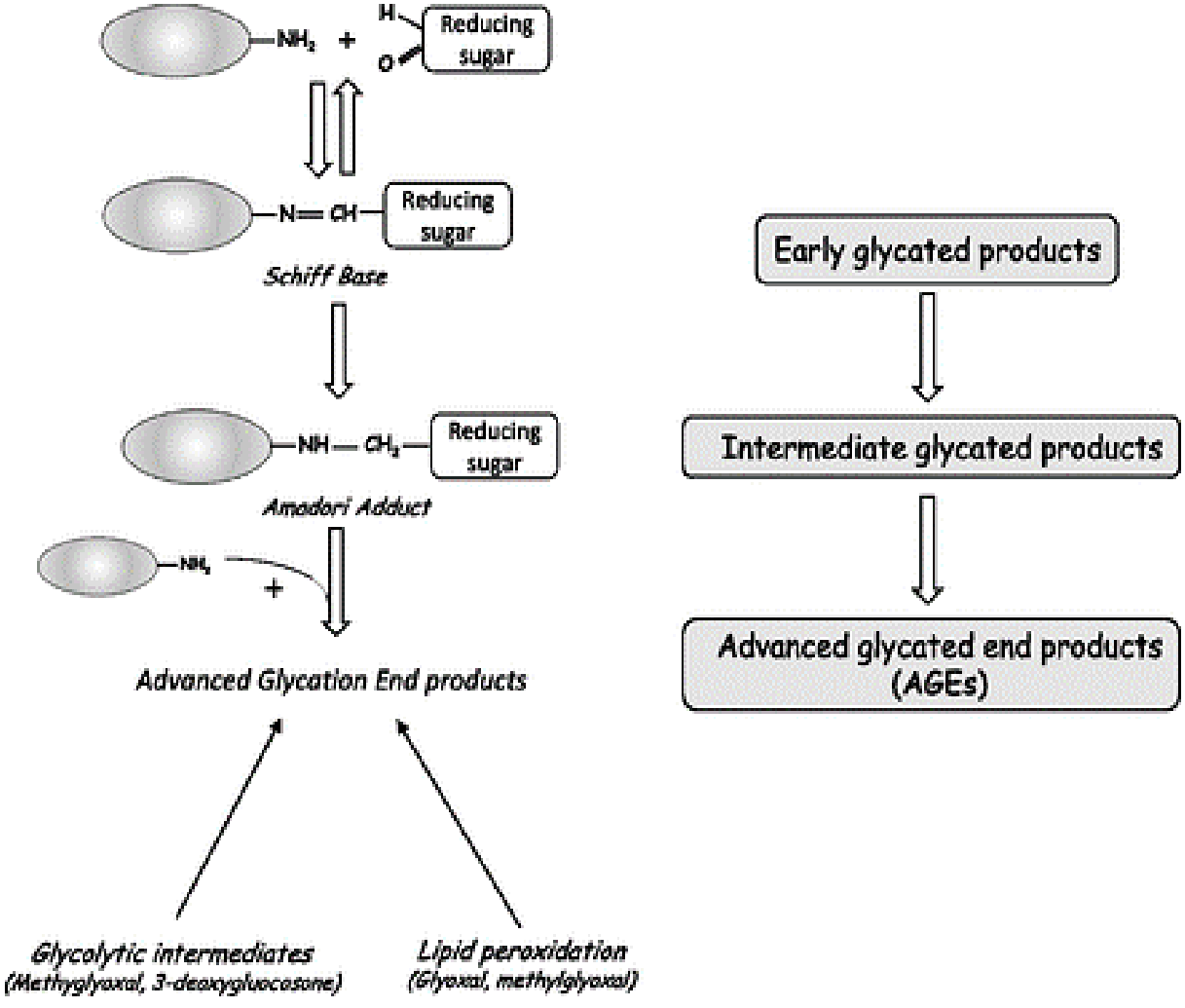

Fig. 2. Schematic formation of Advanced glycation end products [33].

The first stage in the formation of AGEs is the covalent interaction of the amino group of proteins, lipids and the like with the carbonyl group of reducing sugar contained in the reaction medium [12]. The product created in the first stage was called the Shiff bases. In the next stage, lasting up to several weeks, the Shiff's bases is reorganized - the Amadori reaction follows and ARP is created - the reaction product of Amadori (1-amino-1-deoxycetosis) (Fig. 2). Subsequently, in the Mailard reaction, ARP undergoes changes in the presence of oxygen, which results in the releases of free radicals, reactive oxygen species and dicarbonyl compounds [11].

It has been shown that AGEs accumulate with age in the tissues. At increased degree and faster rates, accumulation occurs in diabetics. A correlation was observed between the presence of fluorescent AGEs in the retina of diabetic animals and the degree and duration of hyperglycaemia [13]. It has also been shown that AGEs can damage the walls of the blood vessels and promote atherosclerosis. It has also been proven that AGEs damage many other tissues [14].

AGEs accumulate in various tissues of the eye. In people with diabetes the amount of accumulated AGEs are significantly higher than in healthy individuals. In the retina, AGEs accumulate in vascular cells, neurons and glial cells [15].

AGEs are removed from circulation by binding to various types of receptors. We distinguish 5 types of receptors for AGEs: MSR-1 (macrophage receptor), AGE R1 (receptor corresponding to oligosaccharide transferase 48), AGE R2 (receptor corresponding to 80K-H phosphoprotein), AGE R3 (receptor that recognizes galactosidic moieties), RAGE (receptor binding to advanced glycation end products). The last of the receptors is involved in the production of oxidative stress [11].

4. RECEPTOR FOR ADVANCED GLYCATION END-PRODUCTS

RAGE, or receptor of the advanced glycation end products, is a member of the immuoglobulins superfamily, whose increased expression has been demonstrated in many pathological states for example in Alzheimer's disease [10, 16].

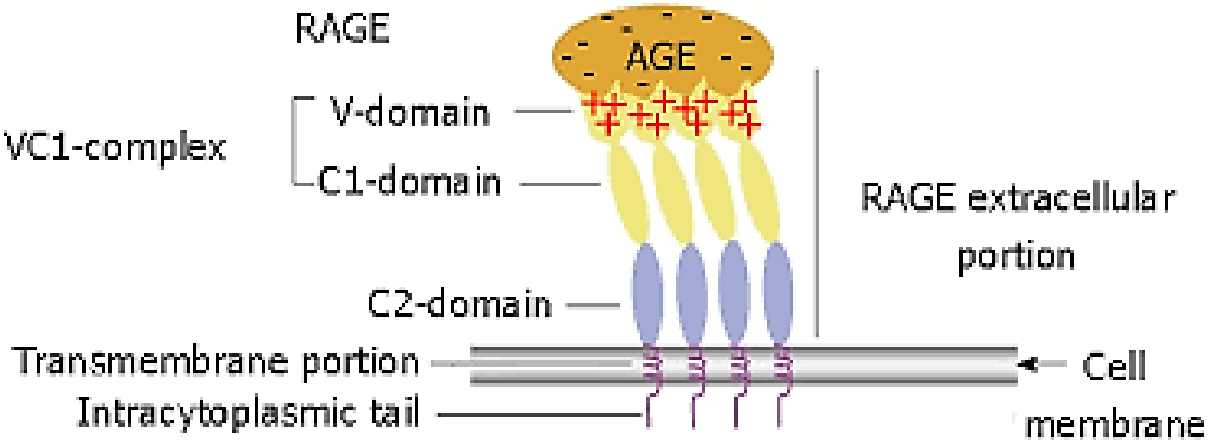

Fig. 3. Receptor of the advanced glycation end products structure [36].

RAGE was discovered during the isolation of endothelial in bovine lungs. It is a protein of approximately 45kD and consists of 403 amino acids in humans. The extracellular RAGE region consists of three domains: one V type domain (variable) and two C type domains (constant), trans membrane region and cytosolic tail (Fig. 3) [14].

Most ligands bind to the V-type domain, while have been show that C-type domains forming an integrated unit that facilitates the binding of ligands [17]. Receptor expression and the consequences of ligand binding are most likely regulated at many levels (Fig. 4) [18].

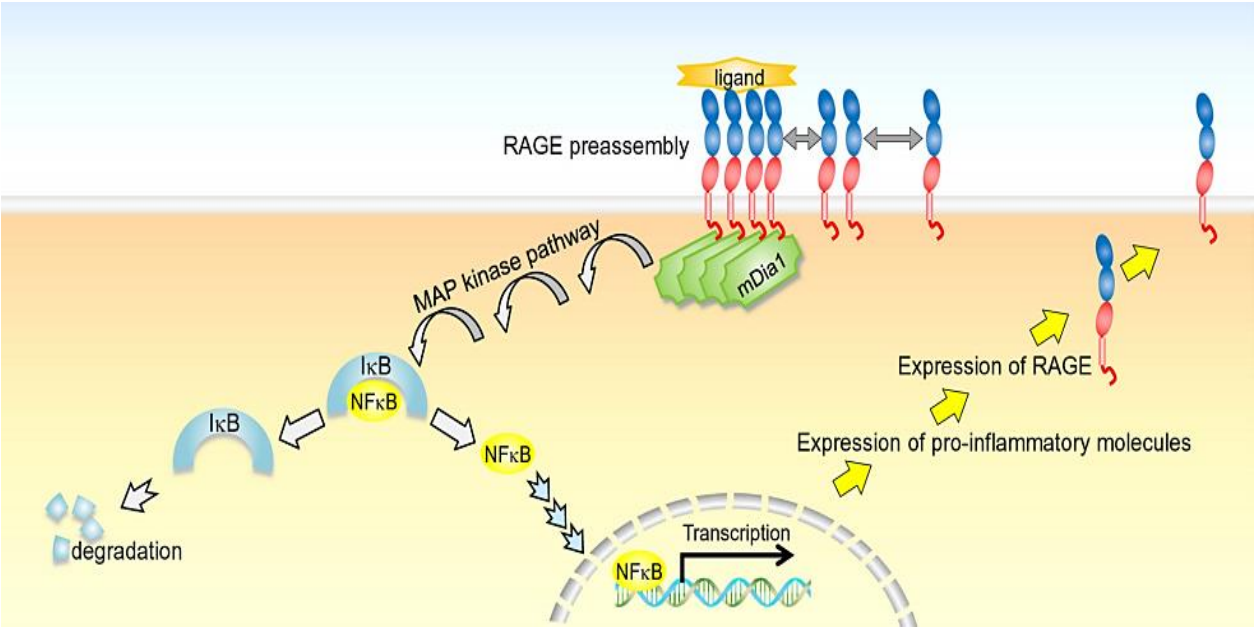

Fig. 4. Ligand binding and signaling cascade leading to *RAGE* expression [37].

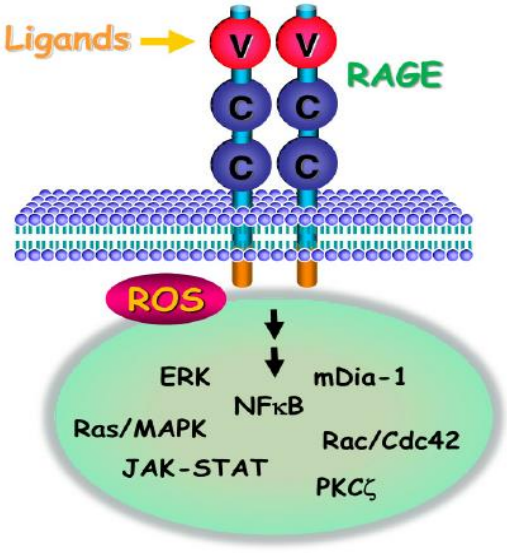

Fig. 5. Intracellular multiple signaling pathways [34].

An important feature of the receptor is that it recognizes whole families of ligands, not a single polypeptide [16]. When RAGE recognizes a ligand, a signaling cascade involving phosphatidylinositol-3 kinases, MAPK (Erk1 and Erk2), Ki-Ras begins, which in turn trigger NF-κB activation and NADH oxidase. The signaling pathway leads further to increase an oxidative stress [19].

It has been shown that the presence of RAGE and its ligands S100 / calgranulin and HMGB1 is elevated in the retina in people with diabetes. HMGB1 interacts with RAGE and activates ERK1, ERK2 and NF-κB which contributes to the generation of an inflammatory response that disturbs the retinal vascular barrier [21]. Many studies suggest that cellular responses mediated by RAGE are composed of multiple signaling pathways (Fig. 5) that are triggered by various ligands [22].

5. *RAGE* GENE AND POLYMORPHISMS

The *RAGE* gene is located on the short arm of chromosome 6, in the locus 6p21.3 (Fig. 6) [20]. It contains 11 exons and 10 introns [22]. Summarizing the work of many scientists, it has been shown that there are about 20 *RAGE* splice variants [20]. Dysregulation of *RAGE* isoforms can have a major impact on many important diseases. Abnormal expression has been demonstrated in Alzheimer's disease, diabetes mellitus, rheumatoid arthritis or atherosclerosis [22]. There are many gene polymorphisms that contribute to the development of a significant number of diseases, but we will focus on presenting polymorphisms that may be important in the development of diabetic retinopathy.

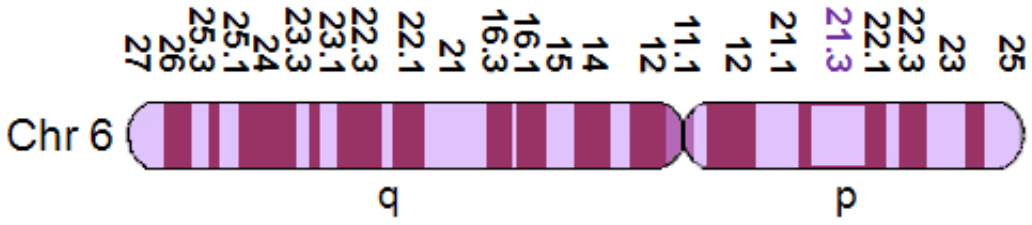

Fig. 6. *RAGE* gene posiction on human chromosome [35].

5. 1. *-429T/C RAGE* gene and polymorphism

Erna et al. investigated the relationship between the occurrence of a mutant T/C allele and the incidence of diabetic retinopathy. They showed that the wild-type allele (T/T) works in a protective way, whereas having a mutant T/C allele increases the chance of developing diabetic retinopathy. The research was carried out on the Indonesian population [8]. Another team Hudson and others was looking for a relationship between polymorphisms of the *RAGE* gene promoter and diabetic retinopathy. They conducted preliminary studies on the prevalence of *-429 T/C* polymorphism in people with type 2 diabetes with retinopathy and without retinopathy and in the control group without diabetes. The results showed a significant increase in the C allele in people with retinopathy compared to those without retinopathy [23]. Yu et al. performed a meta-analysis of many research works in relation to the relationship of

polymorphism *-429 C/T* with diabetic retinopathy. The study showed that there is no statistically significant relationship between polymorphism and disease [24].

5. 2. *-374T/A RAGE* gene and polymorphism

Based on the results of 9 studies, the Tao team performed a meta-analysis of the correlation of having a mutant A/A allele with diabetic retinopathy. It has been shown that the A/A allele is significantly associated with an increased risk of developing retinopathy [25]. In the research conducted by Balasubbu et al. On the Indian population, it was shown that the *-374 T/A* polymorphism is not significantly related to diabetic retinopathy [26]. In Hudson's studies, the *-374 T/A* polymorphic alleles did not differ significantly between groups, but appeared to have a tendency to increase the A allele in the retinopathic group [23].

5. 3. *Gly82Ser RAGE* gene and polymorphism

Cao et al. in their study on the Chinese population, showed that the *Gly82Ser* polymorphism is clearly related to diabetic retinopathy and the A allele may be a risk factor [27]. In the Malaysian population, the relation between *Gly82Ser* polymorphism and retinopathy was studied by Ng et al. They did not show a correlation between the occurrence of polymorphism and an increased risk of developing retinopathy [28]. However, meta-analysis of Yu et al., also showed that the presence of the *Gly82Ser* polymorphism is associated with a higher risk of disease [24].

5. 4. *1704 G/T RAGE* gene and polymorphism

On the basis of 29 publications, a meta-analysis was carried out to show the association of *1704 G/T* polymorphism with diabetic retinopathy. The association between polymorphism and disease has not been confirmed. After exclusion of the article, in which the results differed from the balance according to Hardy-Weinberg's law, the result of the meta analysis did not change [29]. According to Ng et al. polymorphism *1704 G/T* also does not show any relation to retinopathy [28]. The Yashioka team confirms the lack of linking polymorphism with the disease. This study was conducted on the Japanese population [30].

5. 5. *2184 A/G RAGE* gene and polymorphism

Yang et al. conducted a study in which they checked the relationship between the occurrence of *2184 A/G* polymorphism and increased incidence of diabetic retinopathy. According to the model prepared by them, the selected polymorphism is not related to diabetic retinopathy [31].

6. CONCLUSIONS

Despite many tests and analyzes performed, the results do not remain unambiguous. It is obvious that AGEs are involved in damage of the eye tissues, including retina. It has been established that their accumulation in the course of diabetes mellitus is increased. The influence of AGEs on the activation of oxidative stress was demonstrated. Analysis of all the properties of AGEs leads to the conclusion that they are involved in diabetic retinopathy. RAGE or receptors for AGEs show increased expression in many pathological states. Signaling pathways

involving RAGE ligands promote inflammatory response and tissue damage. The presence of different variants of the *RAGE* gene may be responsible for the increased risk of disease. As it has been presented in the article, there are polymorphisms that are candidates for the role attributed to them, but subsequent studies leave no clarity in this matter. Both studies and analyzes are divergent and it can not be determined with certainty which genetic variants promote diabetic retinopathy and which are not. It is important to conduct further research in order to clearly establish the role of individual polymorphisms in the pathophysiology of retinopathy. In addition, the majority of studies carried out so far have been carried out on the Chinese, Japanese, Indian, Indonesian and American populations. Studies in Central European populations are negligible. It is worth carrying out research in these regions of the world to deepen the already available knowledge.

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