Glycative Stress Research

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Review article

Glycative stress and anti-aging
5. Glycative stress and receptors for AGEs as ligands.

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Abstract

The accumulation of advanced glycation end products (AGEs) is caused by glycative stress and induces the deterioration of biological functions and the development of functional disorders *in vivo*. It has been confirmed that some AGE receptors exist in intracellular signaling transduction pathways, where they are signal transducers. The existence of some AGEs has been identified to trap and eliminate AGEs. Of receptors that recognize AGEs, receptor for AGEs (RAGE) and AGE-R2 are involved in inflammation, while AGE-R1, AGE-R3, CD36, SR-A, SR-BI, FEEL-1, 2, ERM and megalin are involved in the degradation and elimination of AGEs. These AGE receptors are found in diversified biological tissues, such as blood vessels, kidneys, nerves and macrophages. Expression of RAGE in biological tissues induces intracellular inflammation and causes organic disorder and tissue injury. Therefore, the control of RAGE expression is a target for the inhibition of glycative stress. Furthermore, the research of the control on the expression of receptors eliminating AGEs and sRAGE would lead to new measures of inhibition of glycative stress.

***KEY WORDS*:** advanced glycation end products (AGEs), receptor for AGEs (RAGE), intracellular signaling

Introduction

The accumulation of advanced glycation end products (AGEs) is caused by glycative stress and induces the deterioration of biological functions and the development of functional disorder *in vivo*. Recent studies have confirmed that some AGE receptors exist in intracellular signaling transduction pathways, where they are signal transducers, and the existence of some AGEs has been identified to trap and eliminate AGEs [1-3]. Receptors are roughly classified into the receptors that are related to inflammation and the receptors that are related to the degradation and elimination of AGEs. The former includes receptor for AGEs (RAGE) and AGE-R2, and the latter includes AGE-R1, AGE-R3, CD36, SR-A, SR-BI, FEEL-1, 2, ERM, and megalin (***Fig. 1***)[2]. These receptors are found in various biological tissues such as blood vessels, kidneys, nerves and macrophages.

1. RAGE

RAGE, belonging to immunoglobulin superfamily, is one kind of single-pass transmembrane protein with a molecular mass of 45 kDa. RAGE is expressed in monocyte, macrophage, nerve, renal tubule cell, and even mesangial cell. RAGE binds, whereas AGEs, amyloid β protein, S100/calgranulins and high mobility group box 1 (HMGB-1) do not, and is involved in the acceleration of inflammation and oxidative stress. RAGE consists of five domains: four extracellular receptors are V domain, two C domains, transmembrane protein domains and one intracellular receptor is intracellular protein domain (***Fig. 2***)[4]. On the other hand, excluding full length RAGE (F-RAGE), which exists on the cell surface, C-terminally truncated RAGE (C-RAGE) and N-terminally truncated RAGE (N-RAGE) exist as splicing variants [5].

Of these receptors, C-terminally truncated RAGE (C-RAGE) is called soluble RAGE (sRAGE). Furthermore, two kinds of sRAGE exist: endogenous secretory RAGE (esRAGE), which is produced intracellularly and secreted extracellularly, and cleaved-type soluble RAGE (CL-RAGE), which derives from proteolytic cleavage; F-RAGE is cleaved by proteolytic enzyme and/or a disintegrin and metalloproteinase 10 (ADAM 10), which is matrix

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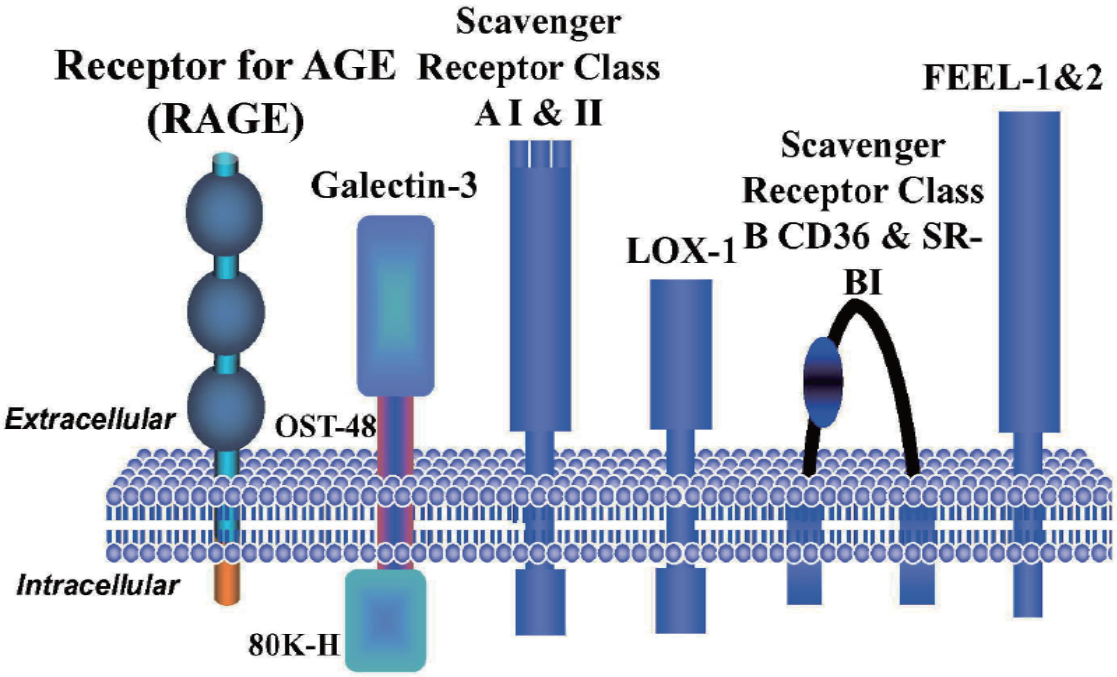

Fig. 1. **Receptors for AGEs.**

The figure is quoted from Reference 2. AGEs, advanced glycation end products; RAGE, receptor for AGE; OST, oligosaccharyltransferase-48; 80K-H, 80 kDa protein kinase C substrate; LOX-1, Lectin-like oxidized low-density lipoprotein (LDL) receptor-1; CD36, cluster of differentiation 36; SR-BI, scavenger receptor-BI; scavenger receptor class B type I; FEEL, fasciclin EFG-like laminin-type EGF-like and link domein-containing scavenger receptor.

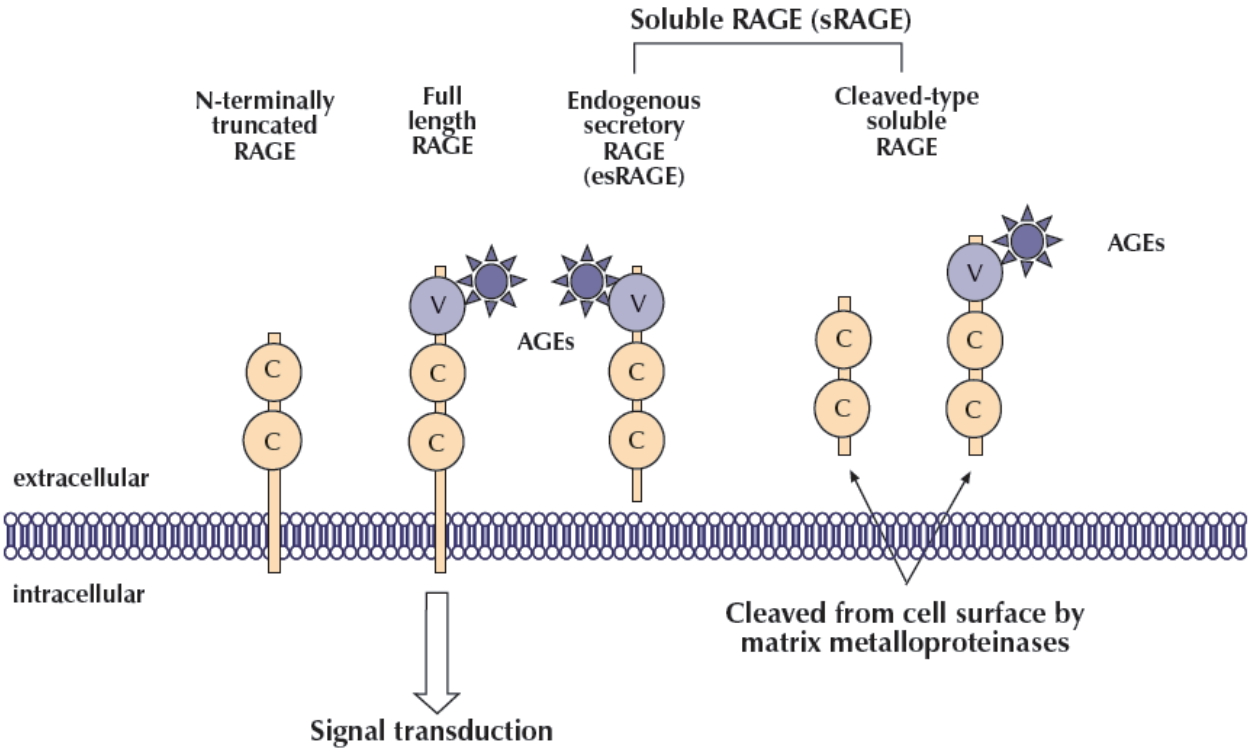

Fig. 2. **Various forms of receptor for AGEs (RAGE).**

The figure is quoted from Reference 4. AGEs, advanced glycation end products; RAGE, receptor for AGE; sRAGE, soluble form of RAGE; esRAGE, endogenous secretory RAGE; C, immunoglobulin-like constant domains; V, immuoglobulin-like variable domains.

metalloproteinases (MMP), and then releases into the blood [6].

F-RAGE binding to AGEs on a cell membrane activates NADPH oxidase and accelerates intracellular oxidative stress. Through the activation of nuclear factor-kappa B (NF-kB), the secretion of cytokine and activity enhancer and also the expression of adhesion factors are induced [7]. In addition, the acceleration of intracellular oxidative stress triggers the inactivation of nitric oxide (NO), as well as the exacerbation of inflammatory response and thrombotic tendency. Thus, it is recognized that AGEs binding to F-RAGE is involved in the development of arteriosclerosis.

Moreover, AGEs promote the formation of autocrine, which is a vascular endothelial growth factor (VEGF) in vascular endothelial cells and then induces angiogenesis [8].

Furthermore, the binding of F-RAGE to AGEs inhibits the formation of prostacyclin (PGI2) in vascular endothelial cells; F-RAGE is involved in the promotion of plasminogen activator inhibitor-1 (PAI-1) synthesis and the inhibition of fibrinolytic system, which is related to the stabilization of the thrombus [9]. AGEs are recognized to increase platelet aggregation and promote the coagulation cascade.

On the other hand, it has been recognized that sRAGE, having the binding site for AGEs, functions as a decoy receptor, which captures extracellular AGEs and hinders the binding of RAGE existing on the cell surface [10]. The blood concentration of esRAGE of type 2 diabetic patients was significantly lower than that of non-diabetic patients, which indicates the possibility of involvement in occurrence of diabetes mellitus [11-12]. In contrast, it has been reported that the case of low blood concentration of esRAGE in type 1 diabetic patients has a high risk of retinopathy (*Fig. 3*) [13]. Furthermore, it has also been indicated that a negative correlation was shown between the blood concentration of esRAGE of type 2 diabetic patients and the severity of carotid atherosclerosis and coronary artery disease [14-15].

2. AGE-R1, -R2, -R3 complex

AGE-R1 is called OST-48 (oligosaccharyltransferase-48), belonging to lectin family, and is one kind of single-pass transmembrane protein with a molecular mass of 48 kDa. AGE-R1 is expressed in endothelial cells, mesangium cells, macrophages and others and has a function of removing AGEs by endocytosis. Furthermore, there was a possibility that AGE-R1 is involved in lifetime extension [16].

AGE-R2 is called 80K-H (80 kDa protein kinase C substrate) and is tyrosine-phosphorylated protein with a molecular mass of 48 kDa, existing in cytoplasm. AGE-R2 is expressed in monocytes, kidney, vascular endothelium, encephalon, nerves and is involved in the activation of intracellular signals.

AGE-R3 is called galectin-3 and is a receptor with a molecular mass of 32 kDa, belonging to lectin family. AGE-R3 has direct AGE-binding through carbohydrate recognition domain on cell and is expressed in macrophages, eosinophils, mast cells, nerves, kidney, and others. Effects of AGE-R3 are the inhibition of adhesion between cells and laminin, which is categorized as matrix, the activation of mast cells, the control of cell proliferation and apoptosis, and the degradation of AGEs by endocytosis. Furthermore, there was a possibility that AGE-R3 would have effects on the inhibition of aging, as the expression of AGE-3 is increased due to aging and diabetes mellitus [17].

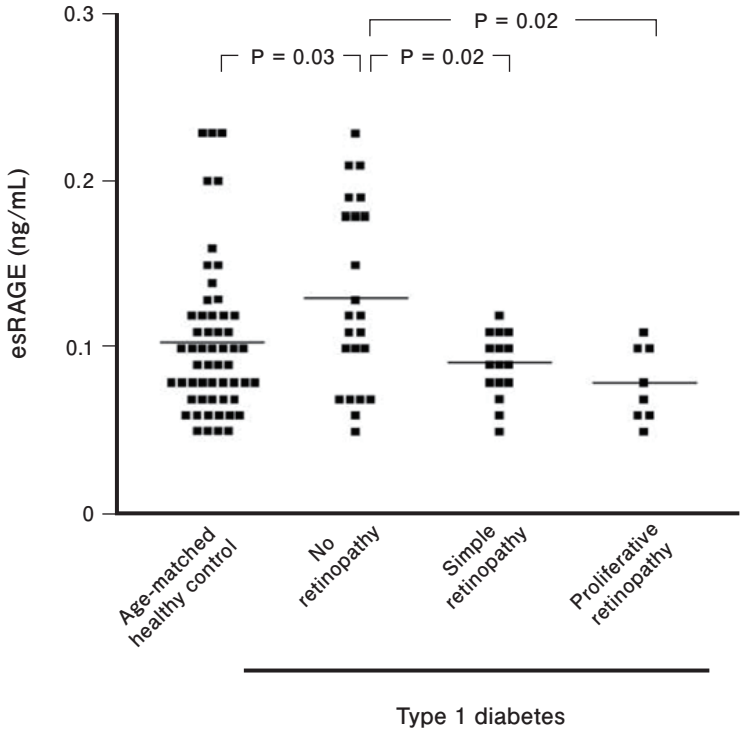

Fig. 3. **Relationship of serum esRAGE to severity of retinopathy in type 1 diabetic patients.**

Horizontal bars indicate mean of each group. Multiple comparison among diabetic subgroups was done by Scheffe's F-test. Data are quoted from Reference 13. AGE, advanced glycation end product; RAGE, receptor for AGE; esRAGE, endogenous secretory RAGE.

3. SR-A, CD36, SR-BI, FEEL-1, FEEL-2

SR-A, CD36, SR-BI, FEEL-1 and FEEL-2 are called scavenger receptors and are involved in the degradation and excretion of AGEs.

SR-A (scavenger receptor class A) recognizes LDL (low density lipoprotein) and oxidized LDL as a ligand. SR-A integrates and foams AGEs on cell surface of macrophage. Thus, it is indicated that SR-A is involved in atherosclerosis [18].

CD36 (cluster of differentiation 36) is expressed in macrophage, vascular endothelial, and adipose cell surfaces. CD36 binds fatty acid, collagen and oxidized LDL and plays the roles of integrating oxidized LDL into macrophage and the transporting fatty acid to adipose cells. It is assumed that CD36 would have protective effects on arteriosclerosis as CD36 integrates AGEs in adipose cell and degrades and removes AGEs [19].

SR-BI(scavenger receptor-BI) is expressed in macrophages, liver, adrenal glands, ovary and has effects to promote the integration of HDL (high-density lipoprotein) in liver [20].

FEEL-1 (fasciclin EFG-like laminin-type EGF-like and link domein-containing scavenger receptor-1) and FEEL-2 are expressed in spleen and lymph nodes and are involved in the intracellular integration of AGEs and the degradation of AGEs [21].

4. Megalin

Megalin is, belonging to receptor gene family, glycoprotein with a molecular mass of 600 kDa and is expressed in renal proximal tubules [22]. Megalin is involved in the reabsorption and the metabolism of mainly low molecular proteins such as vitamin D-bound protein, retinol binding protein, thyroid hormone and insulin. Recent studies have reported that megalin binds AGEs. Recent researches of *in vitro* experiments have reported that megaline binds RAGE and AGEs which pass through glomerule, are trapped by megalin, and then integrated and degraded by lysosomes [23].

5. Other AGEs receptors

ERM (ezrin, radixin, meosin) proteins enhance the linkage of actin filaments to the plasma membrane and play roles in cellular structural change, movement physiology and adhesion. According to current understanding, N-terminal of ERM family proteins binds AGEs [24].

6. Inhibition of glycative stress and AGE receptors

The binding of RAGE to AGEs promotes the acceleration of oxidative stress and induces the expression of cytokine, which induces intracellular inflammation and causes organic disorder and tissue injury. Therefore, the control of RAGE expression is a target for the inhibition of glycative stress. On the other hand, AGE-R1 and AGE-R3 play a role of the protection of organs and biotissues. Furthermore, sRAGE functions as a decoy receptor to the AGEs and inhibits the inflammation due to the expression of RAGE and the development of varied diseases. Therefore, the research of the control on the expression of receptors eliminating AGEs and sRAGE would lead to new measures of inhibition of glycative stress.

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Conflict of interest statement

There are no items deemed to be conflicts of interest in this research.

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