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Therapeutic Implications of Blockers of Advanced Glycation End Products (AGEs)-their Receptor (RAGE) System

Sho-ichi Yamagishi, Kazuo Nakamura, Yuko Jinnouchi, Katsuhiko Takenaka and Tsutomu Imaizumi
Department of Internal Medicine III, Kurume University School of Medicine, Kurume, Japan

Abstract: Non-enzymatic modification of proteins by reducing sugars, a process that is also known as Maillard reaction, leads to the formation of Advanced Glycation End-products (AGEs) *in vivo*. There is a growing body of evidence that formation and accumulation of AGEs progress during normal aging and at an extremely accelerated rate under diabetes, thus being involved in the pathogenesis of various diseases such as diabetic vascular complications and neurodegenerative diseases. Recently, engagement of their receptor, RAGE, is shown to activate its down-stream signaling and subsequently evoke inflammatory responses in various types of cells. Therefore, inhibition of AGE formation or blockade of the RAGE signaling may be a promising target for therapeutic intervention in the AGE-RAGE-related devastating disorders. In this review, we discuss several types of blockers of the AGE-RAGE system and their therapeutic implications in diseases.

Key words: AGEs, RAGE, oxidative stress, PEDF, diabetic vascular complications

INTRODUCTION

The modification, aggregation and deposition of proteins are a prominent part of many pathological processes and can play a direct role in tissue damage. The pathological role of the non-enzymatic modification of proteins by reducing sugars, a process that is known as glycation (also called the Maillard reaction), has become increasingly evident in various types of diseases[1,2]. It is now well established that early glycation products undergo progressive modification over time *in vivo* to the formation of irreversible cross-links, after which these molecules are termed Advanced Glycation End-products (AGEs). AGEs have been implicated in the development of many of the pathological sequelae of diabetes and aging, such as atherosclerosis and diabetic microangiopathy[1,2]. Furthermore, there is a growing body of evidence that RAGE is a signal-transducing receptor for AGEs and that engagement of RAGE by AGEs evokes inflammatory responses in vascular wall cells as well[3]. Recently, it has become clear that the AGE-RAGE system also has a role in neurodegenerative diseases such as Alzheimer's Disease (AD)[4], Parkinson's disease[5], Creutzfeldt-Jakob disease[6] and amyotrophic lateral sclerosis[7]. Thus, inhibition of AGE formation or blockade of the RAGE signaling may be a therapeutic approach. In this review, we discuss several types of blockers of the AGE-RAGE system (Table 1) and their therapeutic implications in diseases.

Table 1: Blockers of the AGE-RAGE system

1. Inhibitors of AGE formation
I. Guanidine structure
(I) Aminoguanidine
(ii) Metformin
II. Vitamin
(I) Pyridoxamine
(ii) Benfotiamine
III. Thiazolidine structure
(I) OPB-9195
IV. Piperazine structure
(I) Tenilsetam
2. AGE breakers
(I) PTB
(ii) ALT-711
3. Inhibitors of the AGE-RAGE signaling
(I) PEDF

Inhibitors of AGE formation

Guanidine structure: Guanidine compounds, such as aminoguanidine (AG) and metformin, can trap α-dicarbonyl compounds, thus preventing their further reactions with amino groups of proteins. This type of drug is one the most studied inhibitors of AGEs both *in vitro* and *in vivo*.

AG (Pimagedine): AG is a prototype therapeutic agent for the prevention of AGE formation. The first report of intervention to prevent AGE formation by AG was the prevention of arterial wall protein cross-linking in diabetic animals[8]. Since then, use of AG to prevent AGE formation *in vitro* and *in vivo* has given evidence of the involvement of AGEs in many disease processes and abnormal physiological states.

Corresponding Author: Sho-ichi Yamagishi, Ph.D., Department of Internal Medicine III, Kurume University, School of Medicine, Kurume, 67 Asahi-machi, Kurume 830-0011, Japan
Tel: +81 942 7580 Fax: +81 942 31 7707 E-mail: shoichi@med.kurume-u.ac.jp

AG was introduced as a hydrazine reagent for trapping reactive carbonyls formed during the Maillard reaction, especially Amadori intermediates, thus impeding their conversion into AGEs. AG reacts not only extensively with Amadori carbonyl groups of glycated proteins but also with dicarbonyl compounds such as methylglyoxal, glyoxal and 3-deoxyglucosone[9].

Diabetic retinopathy is a microvascular complication of diabetes characterized by loss of pericytes, microaneurysm formation and acellular capillaries in the retinal microvessels[10]. Treatment of diabetic rats for 26 weeks with AG prevented a 2.6 fold accumulation of AGE products at branching sites of pre-capillary arterioles and thereby prevented abnormal endothelial cell proliferation and significantly diminished pericyte dropout[11]. In the same study, treatment for 75 weeks with AG decreased the number of acellular capillaries and microaneurysms as well[11]. AG inhibited Vascular Endothelial Growth Factor (VEGF) expression in rats with long-term galactosemia[12]. Furthermore, AGE infusion resulted in significant leukostasis and blood-retinal barrier dysfunction, one of the characteristic features of background retinopathy, by inducing retinal VEGF expression in non-diabetic healthy mice[13,14]. These observations suggest that AG could also exert beneficial effects on early diabetic retinopathy by suppressing AGE-induced retinal VEGF overexpression. A multicenter clinical trial revealed that Pimagedine slowed the progression of diabetic retinopathy, although it was terminated early due to safety concerns[15,16].

AG has also been shown to inhibit the accumulation of renal AGEs and to retard the development of microalbuminuria and mesangial expansion in streptozotocin-induced diabetic rats[17]. AG inhibited the development of diabetic nephropathy in Otsuka Long Evans Tokushima Fatty (OLETF) rats, a model of type 2 diabetes as well[18]. Recently, AG was found to decrease the expression of pro-sclerotic growth factors such as transforming growth factor-β (TGF-β) and platelet-derived growth factor-BB and connective tissue growth factor and thus to prevent the development of glomerulosclerosis and tubulointerstitial fibrosis in experimental diabetic nephropathy[19,20]. AG treatment also prevented albuminuria in diabetic hypertensive rats without affecting blood pressure[21].

Double-blinded, placebo-controlled, randomized clinical trials of Pimagedine (ACTION; A Clinical Trial in Overt Nephropathy) were designed to evaluate the safety and efficacy of AG in retarding the rate of progression of renal disease in patients with overt diabetic nephropathy. Pimagedine therapy reduced the 24 h total urinary proteinuria and prevented the decrease in glomerular filtration rate in patients with diabetes[22]. However, the effects of Pimagedine on serum creatinine doubling were found not to be significant; serum creatinine doubled in 26% of the placebo-treated patients and in 20% of those who received Pimagedine ($p = 0.099$). This study is noteworthy in providing the first clinical proof of the concept that inhibiting AGE formation can result in a clinically important attenuation of the serious complication of diabetes. Reported side effects of AG in clinical therapy were gastrointestinal disturbance, abnormalities in liver function tests, flu-like symptoms and a rare vasculitis[23].

Metformin: Metformin (dimethylbiguanide) was introduced into clinical practice in 1957 as an oral anti-hyperglycemic agent for the management of type 2 diatetes[24]. Metformin is a guanidine compound that is structurally related to AG, thus suggesting that it may also have a potential effect on the inhibition of glycation reactions. Several groups reported inhibitory effects of metformin on protein glycation[25-27].

A number of studies have shown that metformin is beneficial in reducing diabetes-associated vascular risks beyond the benefits expected from its anti-hyperglycemic effect. Chronic metformin treatment prevented functional and structural alterations of the diabetic myocardium associated with glycation[28]. Metformin has also been shown to inhibit AGE formation in peripheral nerves and improved their function in diabetic animals[29]. Blockade of glycation reaction might provide one possible mechanism to explain the beneficial effects of metformin on diabetic vascular complications[30].

Vitamin: Recently, vitamin B complexes such as pyridoxamine and thiamine pyrophosphate have been found to inhibit the formation of AGEs both *in vitro* and *in vivo*.

Pyridoxamine (PM) (Pyridorin): PM, originally described as a post-Amadori inhibitor (so-called Amadorins) of AGE formation, also inhibits the formation of advanced lipoxidation end-products (ALEs) on protein during lipid peroxidation reaction[31-34].

Stitt *et al.*[35] recently reported that PM prevented the development of pericyte loss and formation of acellular capillaries in diabetic rats. PM also inhibited the progression of renal disease and decreased hyperlipidemia and apparent redox imbalances in diabetic rats[36]. Further, PM was found to inhibit AGE/ALE formation and hyperlipidemia and protected against renal and vascular pathology in non-diabetic obese rats as well[37]. Phase II trials are ongoing to evaluate the efficacy

of Pyridorin in inhibiting the progression of albuminuria in patients with early stage diabetic kidney disease. The trials are also monitoring plasma triglyceride and cholesterol levels and several other parameters relevant to diabetes and kidney function.

Benfotiamine: Benfotiamine, a lipid soluble compound of thiamine, was found to be a potent inhibitor of glycation[38]. Hammes and Brownlee *et al.*[39] have recently found that benfotiamine inhibited the three major biochemical pathways (AGE formation, protein kinase C activation and the polyol pathway activation) as well as hyperglycemia-associated NF-κB activation. They showed that benfotiamine prevented experimental diabetic retinopathy by activating the pentose phosphate pathway enzyme transketolase in the retinas, which converts glyceraldehyde-3-phosphate and fructose-6-phosphate into pentose-5-phosphates and other sugars[39].

Thiazolidine structure: Synthetic compounds with thiazolidinedione structure have recently been found to be an effective inhibitor of AGE formation.

OPB-9195: OPB-9195 ((±)-2-isopropylidenehydrazono-4-oxo-thiazolidin-5-ylacetamlide) is known to trap carbonyl intermediates of advanced glycation with an activity about one order of magnitude more potent than that of AG[40].

OPB-9195 prevented the progression of diabetic nephropathy by lowering serum concentrations of AGEs and their deposition of glomeruli in OLETF rats[40]. OPB-9195 was found to retard the progression of diabetic nephropathy in these animals by blocking type IV collagen production and suppressing overproduction of two growth factors, TGF-β and VEGF[40]. OPB-9195 also prevented the progression of diabetic nephropathy in RAGE-overexpressed mice[41].

OPB-9195 has been shown to exert beneficial effects on diabetic neuropathy as well; it improved tibial motor nerve conduction velocity and restored the decrease in sciatic nerve Na^+-K^+-ATPase activity in diabetic rats, which was in parallel with suppression of oxidative stress-induced DNA damage[42]. These observations suggest that reactive oxygen species production induced by AGE-RAGE interactions might be involved in endoneurial vascular dysfunction and nerve injury in diabetic neuropathy. Recently, long-term administration of OPB-91915 has been found to reduce blood pressure and oxidative damage in stroke-prone spontaneously hypertensive rats, suggesting a pathological role for AGEs in hypertension[43].

Piperazine structure: Tenilsetam, (±)-3-(2-thienyl)-2-piperazinone, a cognition-enhancing and possible anti-dementia drug was also shown to have the ability to inhibit AGE formation.

Tenilsetam: Tenilsetam was first introduced as an anti-ischemic and then as a cognition-enhancing drug[44,45]. Now it is used for treatment of patients suffering from AD. Tenilsetam also inhibits reducing sugar-induced polymerization and cross-linking of proteins *in vitro*[46]. Since aggregation of amyloid β (Aβ), the major component of senile plaques in AD, is significantly accelerated by protein cross-linking *via* AGEs, tenilsetam could exert beneficial effects on AD, at least in part, by attenuating the AGE-induced Aβ formation[47].

AGE breakers: AGE s cause proteins that are normally flexible to become rigid. The cells, tissues and blood vessels exposed to AGEs become stiff and increasingly dysfunctional. In diabetic patients, the extent of protein cross-linking is accelerated due to prolonged diabetic exposure. AGE breakers are one the novel types of AGE inhibitors that could eliminate the AGE products both *in vitro* and *in vivo*.

N-phenacylthiazolium bromide (PTB) and ALT-711: Novel AGE-protein cross-link breakers such as PTB and its stable derivative ALT-711, which are able to selectively cleave and break the established glucose-derived AGE-protein cross-links were reported[48,49].

Delayed intervention with ALT-711 attenuated the decrease in large artery compliance in diabetic rats[49]. Further, ALT-711 treatment was found to decrease renal AGE levels and reduce albumin excretion rate in diabetic animals[50,51]. A recent clinical trial has shown that patients who received ALT-711 experienced statistically significant reduction in arterial pulse pressure and an increase in large artery compliance compared to patients who received placebo[52].

Inhibitors of the AGE-RAGE signaling

Pigment Epithelium-Derived Factor (PEDF): Compared to the strategies of preventing AGE formation or breaking preformed AGEs, the manipulation of the AGE-RAGE signaling pathways as a therapeutic option in diabetic vascular complications remains much less developed. However, recently, we have found that PEDF, one of the superfamily of serine protease inhibitors with potent neuronal differentiating activity in human retinoblastoma

cells[53], inhibited the AGE-induced pericyte apoptosis, the ealiest histopathological hallmark of early diabetic retinopathy, through its anti-oxidative properties[54]. Furthermore, PEDF was found to prevent the AGE-elicited chemokine production and angiogenesis, another vascular derangements in diabetic retinopathy[55-57]. Since the levels of vitreal PEDF are decreased in angiogenic eye diseases such as proliferative diabetic retinopathy[58], substitution of PEDF may disrupt inappropriate retinal cell responses to AGEs, thus being a promising strategy for treatment of patients with diabetic retinopathy.

There is a growing body of evidence that the AGE-RAGE system is implicated in the pathogenesis of various diseases such as diabetic vascular complications. Therefore, inhibition of AGE formation or blockade of the RAGE signaling may be a promising therapeutic target for the treatment of AGE-related disorders. Effectiveness of several types of AGE inhibitors or RAGE-signal blockers described here should be confirmed by multicenter, randomized, double-blinded clinical trials.

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