

# Telmisartan, its Potential Therapeutic Implications in Cardiometabolic Disorders

Sho-ichi Yamagishi\* and Kazuo Nakamura

Department of Internal Medicine III, Kurume University School of Medicine, Kurume 830-0011, Japan

Received: April 18, 2005; Accepted: July 12, 2005; Revised: September 06, 2005

**Abstract:** There is a growing body of evidence that the renin-angiotensin system (RAS) plays a pivotal role in the pathogenesis of cardiovascular diseases. Indeed, large clinical trials have demonstrated substantial benefit of the blockade of this system for cardiovascular-organ protection. Although several types of angiotensin II type 1 (AT<sub>1</sub>) receptor blockers (ARBs) are commercially available for the treatment of patients with hypertension, we have recently found that telmisartan (Micardis) could have the strongest binding affinity to AT<sub>1</sub> receptor. Telmisartan will be a promising cardiometabolic sartan due to its unique peroxisome proliferator-activated receptor- (PPAR- )-inducing properties as well. In this review, we focused on telmisartan, and discussed its potential therapeutic implications in cardiometabolic disorders.

**Keywords:** AGEs, diabetes, insulin resistance, oxidative stress, PPAR- , RAGE, RAS.

## INTRODUCTION

Hypertension is a major risk factor for cerebro-cardiovascular diseases, and the renin-angiotensin system (RAS) plays an important role in the development and progression of these devastating disorders in patients with hypertension [1]. Angiotensin II (AT II), a physiologically active major substance of the RAS, acts as a vasopressor by inducing vasoconstriction and elicits water and sodium absorption in the proximal renal tubule by stimulating secretion of aldosterone [2]. Thus, inhibition of pathophysiological effects of AT II is considered beneficial for the treatment of hypertension.

Effects of AT II are mediated by binding of AT II to the AT II receptors. Four subtypes of AT II receptors are known-AT<sub>1</sub>, AT<sub>2</sub>, AT<sub>3</sub> and AT<sub>4</sub>-although details of AT<sub>3</sub> and AT<sub>4</sub> subtypes remain to be elucidated. The AT<sub>1</sub> receptor exists in the blood vessels, liver, kidneys, adrenal cortex, and heart, and cardiovascular effects of AT II are mainly mediated by this receptor [2, 3]. A physiological role of the AT<sub>2</sub> receptor is not well understood; however, it also exists in the blood vessels, kidneys, adrenal glands, heart, and brain, and it is generally thought that the AT<sub>2</sub> receptor may have physiologically opposing effects on AT<sub>1</sub> receptor-mediated actions [3, 4]. Thus, selective blockade of the AT<sub>1</sub> receptor by ARBs (AT II type 1 receptor blockers) may allow free AT II to stimulate unblocked AT<sub>2</sub> receptors, providing possible beneficial effects on cardiovascular systems [5].

ARBs suppress the effects of AT II generated by all pathways, including chymase, whose activity is not inhibited by angiotensin converting enzyme (ACE) inhibitors. Furthermore, ARBs have less adverse reactions; they are

unlikely to cause dry cough and angioedema associated with ACE inhibitors [6]. Therefore, it is plausible that inhibition of the RAS by ARBs may become a promising strategy for the organ protection in patients with hypertension [7-9]. In this review, we focused on telmisartan (Micardis®), a selective AT<sub>1</sub> receptor blocker newly developed by Boehringer Ingelheim GmbH, Germany, and discussed its potential therapeutic implications in cardiometabolic disorders.

## CHARACTERISTICS OF TELMISARTAN

Although several types of ARBs are commercially available for the treatment of patients with hypertension, comparisons of the binding affinity to AT<sub>1</sub> receptor among them remain to be elucidated. Therefore, we first examined the dissociation rate of several ARBs from AT<sub>1</sub> receptor *in vitro*. Angiotensin II time-dependently dissociated telmisartan, olmesartan, candesartan, valsartan, losartan, and an active metabolite of losartan, EXP3174 from membrane components containing human AT<sub>1</sub> receptor; the dissociation rate constant of each ARB was 0.003248, 0.004171, 0.005203, 0.009946, 0.01027, and 0.008561 min<sup>-1</sup>, with corresponding half-lives (*t*<sub>1/2</sub>) of 213, 166, 133, 70, 67, and 81 min, respectively [10]. These results demonstrate that telmisartan could have the strongest binding affinity to AT<sub>1</sub> receptor among various ARBs examined here; the rank order of affinity is telmisartan > olmesartan > candesartan > EXP3174 > valsartan > losartan. Telmisartan may have long-lasting blood pressure lowering effects and superior cardioprotective properties in patients with hypertension due to its strongest AT<sub>1</sub> receptor antagonistic ability.

## BENEFICIAL ASPECTS OF TELMISARTAN ON INSULIN RESISTANCE

The metabolic syndrome is strongly associated with insulin resistance and consists of a constellation of factors such as hypertension and hyperlipidemia that raise the risk for cardiovascular diseases and diabetes mellitus [11].

\*Address correspondence to this author at the Department of Internal Medicine III, Kurume University School of Medicine, Kurume 830-0011, Japan; Tel: +81-942-31-7580; Fax: +81-942-31-7707; E-mail: shoichi@med.kurume-u.ac.jp

Hypertension occurs approximately twice as frequently in patients with diabetes compared with in non-diabetic controls [12-15]. Conversely, recent data suggest that hypertensive patients are more likely to develop diabetes than normotensive persons [12-15]. The association of diabetes with hypertension increases its risk of cardiovascular morbidity and mortality. Indeed, up to 75% of cardiovascular disease (CVD) in diabetic patients can be attributed to hypertension [12-15]. Therefore, the primary goals of treating the metabolic syndrome are prevention of type 2 diabetes and cardiovascular events.

What is the optimal anti-hypertensive approach to target organ protection in these insulin resistant patients? As to these questions, there is widespread agreement that the RAS plays a pivotal role in the pathogenesis of insulin resistance and CVD in diabetes and large clinical trials have demonstrated substantial benefit of the blockade of this system for end-organ protection [16-18]. Indeed, interruption of the RAS with ACE inhibitors or ARBs has been recently shown to prevent the onset of diabetes in hypertensive patients and to reduce cardiovascular and renal disease progression in diabetic patients with hypertension [16-18]. On the basis of these findings, the American Diabetes Association (ADA) currently recommends ARBs as first-line therapy for hypertensive type 2 diabetic patients with micro- or macroalbuminuria. A possible mechanism for the putative diabetogenic effect of the RAS might be its downstream action on the insulin receptor signaling [19]. However, at present, whether we should recommend ARBs for insulin resistant-hypertensive patients or type 2 diabetic patients without nephropathy due to its insulin-sensitizing property remains to be clarified.

Recently, telmisartan was found to act as a partial agonist of peroxisome proliferator-activated receptor- (PPAR-) [20]. Molecular modeling studies suggest that telmisartan might influence PPAR- activity by interacting with regions of the ligand-binding domain that are not typically engaged by full agonists of the receptor. Furthermore, none of the commercially available ARBs were found not to activate PPAR- when tested at the concentrations of therapeutic ranges. Telmisartan also induced PPAR- activity in AT<sub>1</sub> receptor-deficient cell models, thus further supporting the concept that telmisartan could stimulate PPAR- activity independent of its AT<sub>1</sub> receptor blocking actions [21].

PPAR- activity influences the gene expression involved in carbohydrate and lipid metabolism, and pioglitazone and rosiglitazone, ligands for PPAR-, improve insulin resistance in diabetic patients [22]. Moreover, there is a growing body of evidence that activators of PPAR- exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risks for atherosclerosis [22,23]. These observations suggest that due to its unique PPAR- -modulating activity, telmisartan may become a promising 'cardiometabolic sartin', that targets both diabetes and CVD in hypertensive patients [24]. *In vitro*, telmisartan augmented glucose transporter isoform 4 expression and 2-deoxy glucose uptake both in basal and insulin-stimulated state of adipocytes [25]. In animal study, telmisartan administration caused a significant attenuation of weight gain and reduced glucose, insulin, and triglyceride

levels in rats fed a high-fat, high-carbohydrate diet, compared with treatments of losartan, another type of ARB [20]. Furthermore, recently, some clinical papers also reported the insulin-sensitizing effects of telmisartan in hypertensive patients [26,27]. Ongoing clinical trial (ONTARGET) has been designed the efficacy of telmisartan with an ACE inhibitor, ramipril, alone or in combination [28]. This randomized, double-blind, multicenter international studies will provide further information whether telmisartan can improve insulin resistance and subsequently reduce the development of diabetes and CVD in high-risk hypertensive patients.

## **BENEFICIAL ASPECT OF TELMISARTAN ON DIABETIC RETINOPATHY**

Diabetic retinopathy is one of the most important microvascular complications in diabetes and is a leading cause of acquired blindness among the people of occupational age [29]. The prevalence of diabetic retinopathy increases with duration of diabetes. After 30 years of diabetes, nearly all patients in the former group have some degree of retinopathy and the prevalence of proliferative retinopathy is about 60 %.

The lesions of diabetic retinopathy can be grouped into those associated with background, preproliferative and proliferative retinopathy. The earliest histopathological hallmark of diabetic retinopathy is loss of pericytes [30]. Normally, the ratio of endothelial cells (ECs) to pericytes in the retinal capillaries is 1:1, but its levels are reported to decrease to 1:4 after several years of diabetes and eventually to 1:10 with even longer diabetic exposure [30]. In parallel with loss of pericytes, several characteristic changes including thickening of the basement membrane, hyperpermeability, and formation of microaneurysm are observed [31]. These structural and functional abnormalities are followed by microvascular occlusion in the retinas, which ultimately progresses to proliferative changes associated with neovascularization [31]. It has been postulated that many of these changes are the consequent of the loss of pericytes.

Pericytes are elongated cells of the mesodermal origin, wrapping around and along ECs of small vessels [32]. As pericytes contain contractile muscle filaments on their EC side, they have been regarded for a long time just as microvascular counterparts of smooth muscle cells, and implicated in the maintenance of capillary tone [33]. In 1983, D'Amore developed a procedure for isolating pericytes from small vessels, and enabled us to elucidate the functional roles and biological characteristics of pericytes [34]. By using pericyte-EC co-culture systems, we have found that pericytes not only regulate the growth, but also preserve the prostacyclin-producing ability and protect against lipid-peroxide-induced injury of ECs, thus playing an important role in the maintenance of microvascular homeostasis [34-36]. Therefore, the loss of pericytes could predispose the vessels to angiogenesis, thrombogenesis, and EC injury, leading to full-blown clinical expression of diabetic retinopathy. Further, recently, Hammes *et al.* showed that retinal capillary coverage with pericytes was crucial for the survival of ECs, particularly under stress conditions such as

diabetes, and that pericyte deficiency leads to reduced inhibition of EC proliferation, thus promoting angiogenesis in the retinopathy of prematurity model [37]. Taken together, our *in vitro* and their recent *in vivo* observations provide a basis for understanding why diabetic retinopathy develops consequent to pericyte loss, the earliest histopathological hallmarks of diabetic retinopathy.

The local RAS is activated under diabetes [38]. We have recently found that AT II stimulates intracellular reactive oxygen species (ROS) generation in retinal pericytes through an interaction with type 1 receptor. Further, AT II decreased DNA synthesis and simultaneously up-regulated vascular endothelial growth factor (VEGF) mRNA levels in pericytes, both of which were blocked by treatment with telmisartan or an anti-oxidant, *N*-acetylcysteine [39, 40]. These results suggest that AT II-type 1 receptor interaction could induce pericyte loss through intracellular ROS generation, thus being involved in diabetic retinopathy, and that telmisartan could be a promising therapeutic strategy for the treatment of early diabetic retinopathy.

VEGF is a specific mitogen to EC's, also known as vascular permeability factor, and is thought a pivotal factor in the pathogenesis of proliferative diabetic retinopathy. Indeed, some clinical observations have demonstrated that VEGF level in ocular fluid is positively correlated with the activity of neovascularization in diabetic retinopathy [41, 42]. Recently, VEGF level was also found to be associated with the breakdown of the blood-retinal barrier, thus being involved in microvascular hyperpermeability in background retinopathy [43]. These observations suggest that telmisartan might play a protective role against the development and progression of diabetic retinopathy by blocking VEGF overexpression in pericytes as well. Based on these observations, Boehringer Ingelheim Pharma GmbH & Co. KG is now submitting the patent entitled 'Treating diabetic retinopathy with angiotensin II receptor blockers' (DE10319592.0 (2003)).

#### **BENEFICIAL ASPECT OF TELMISARTAN ON ADVANCED GLYCATION END PRODUCTS-THEIR RECEPTOR (AGE-RAGE) SYSTEM**

Reactive derivatives from non-enzymatic glucose-protein condensation reactions, as well as lipids and nucleic acids exposed to reducing sugars, form a heterogeneous group of irreversible adducts called "AGEs". AGEs were originally characterized by a yellow-brown fluorescent color and by an ability to form cross-links with and between amino groups [44], but the term is now used for a broad range of advanced products of the glycation process (also called the "Maillard reaction"), including *N*-carboxymethyllysine and pyrraline, which show neither color nor fluorescence and do not cross-link proteins [45-47].

AGEs are formed by the Maillard process, a non-enzymatic reaction between reducing sugars and the amino groups of proteins that contributes to the aging of proteins and to the pathological complications of diabetes [48-52]. The formation of AGEs *in vitro* and *in vivo* is dependent on the turnover rate of the chemically modified target, the time available, and the sugar concentration. In the hyperglycemia elicited by diabetes, this process begins with the conversion

of reversible Schiff base adducts to more stable, covalently-bound Amadori rearrangement products. Over the course of days to weeks, these Amadori products undergo further rearrangement reactions to form the irreversibly-bound moieties known as AGEs.

A variety of molecular mechanisms underlying the actions of AGEs and their contribution to CVD have been proposed [53-57]. AGEs formed on the extracellular matrix results in decreased elasticity of vasculatures, and quench nitric oxide, which could mediate defective endothelium-dependent vasodilatation in diabetes [58]. AGE modification of low-density lipoprotein (LDL) exhibits impaired plasma clearance and contributes significantly to increased LDL *in vivo*, thus being involved in atherosclerosis [59]. Binding of AGEs to RAGE results in generation of intracellular ROS generation and subsequent activation of the redox-sensitive transcription factor NF- $\kappa$ B in vascular wall cells, which promotes the expression of a variety of atherosclerosis-related genes, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, tissue factor, VEGF, and RAGE [60-69]. AGEs have the ability to induce osteoblastic differentiation of microvascular pericytes, which would contribute to the development of vascular calcification in accelerated atherosclerosis in diabetes as well [70].

The interaction of the RAS and AGE-RAGE system has also been proposed. We have very recently found that AII potentiates the deleterious effects of AGEs on ECs by inducing RAGE protein expression, which was completely blocked by telmisartan [71]. These observations provide the functional interaction between the AGE-RAGE system and the RAS in the pathogenesis of accelerated atherosclerosis in diabetes, thus suggesting a novel beneficial aspect of telmisartan on diabetic vascular complications as well.

#### **CURRENT & FUTURE DEVELOPMENT**

Boehringer Ingelheim GmbH has recently obtained the patents of telmisartan for prophylaxis or treatment of cardiovascular, cardiopulmonary, renal, or insulin resistant disorders [72,73].

Our present findings discussed above suggest the potential therapeutic implications of telmisartan in cardiometabolic disorders. The clinical relevance of this unique sartan should be further studied in patients with cardiometabolic disorders. To develop novel therapeutic strategies that specifically target insulin resistance and CVD may be helpful for most patients with hypertension.

#### **ABBREVIATIONS**

RAS	=	Renin-angiotensin system
AT II	=	Angiotensin II
ARBs	=	AT II type 1 receptor blockers
ACE	=	Angiotensin-converting enzyme
CVD	=	Cardiovascular disease
PPAR-	=	Proliferator-activated receptor-
ECs	=	Endothelial cells

ROS	=	Reactive oxygen species
VEGF	=	Ascular endothelial growth factor
AGEs	=	Advanced glycation end products
RAGE	=	Receptor for AGEs
LDL	=	Low-density lipoprotein

## REFERENCES

- Higaki J, Baba S, Katsuya T, *et al.* Deletion Allele of Angiotensin-Converting Enzyme Gene Increases Risk of Essential Hypertension in Japanese Men. The Suita Study. *Circulation* 2000; 101: 2060-5.
- Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; 355: 637-45.
- de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. International Union of Pharmacology, XXIII. The Angiotensin II Receptors. *Pharmacol Rev* 2000; 52: 415-72.
- Stoll M, Unger T. Angiotensin and its AT<sub>2</sub> receptor: new insights into an old system. *Regul Pept* 2001; 99: 175-82.
- Siragy HM. Angiotensin receptor blockers: How important is selectivity? *Am J Hypertens* 2002; 15: 1006-14.
- Pylypchuk GB. ACE inhibitor- versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother* 1998; 32: 1060-6.
- Brenner BM, Cooper ME, De Zeeuw D. *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345: 861-9.
- Dahlöf B, Devereux RB, Kjeldsen SE, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; 359: 995-1003.
- CHARM Investigators and Committees: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; 362: 772-6.
- Kakuta H, Sudoh K, Sasamatsu M, Yamagishi S. Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor. Comparison with other angiotensin II type 1 receptor blockers. *Int J Clin Pharm Res* (in press).
- Scheen AJ. Management of the metabolic syndrome. *Minerva Endocrinol* 2004; 29: 31-45.
- Khamaisi M, Wexler ID, Skrha J, Strojek K, Raz I, Milicevic Z. Cardiovascular disease in type 2 diabetics: epidemiology, risk factors and therapeutic modalities. *Isr Med Assoc J* 2003; 5: 801-6.
- Sowers JR. Insulin resistance and hypertension. *Am J Physiol Heart Circ Physiol* 2004; 286: H1597-602.
- Sowers JR, Frohlich ED. Insulin and insulin resistance: impact on blood pressure and cardiovascular disease. *Med Clin North A.* 2004; 88: 63-82.
- Watson KE, Peters Harmel AL, Matson G. Atherosclerosis in type 2 diabetes mellitus: the role of insulin resistance. *Cardiovasc Pharmacol Ther* 2003; 8: 253-60.
- Ruilope LM, Segura J. Losartan and other angiotensin II antagonists for nephropathy in type 2 diabetes mellitus: a review of the clinical trial evidence. *Clin Ther* 2003; 25: 3044-64.
- Silverstein RL, Fennes AZ, Ram CV. ARBs and target organ protection. Exploring benefits beyond their antihypertensive effects. *Postgrad Med* 2004; 116: 31-8.
- Ball SG. Benefits of blood pressure reduction in diabetic patients. *J Hypertens* 2003; 21: S31-6.
- Strazzullo P, Galletti F. Impact of the renin-angiotensin system on lipid and carbohydrate metabolism. *Curr Opin Neph Hypert* 2004; 13: 325-32.
- Benson SC, Pershad Singh HA, Ho CI, *et al.* Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR gamma-modulating activity. *Hypertension* 2004; 43: 993-1002.
- Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Angiotensin type I receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation* 2004; 109: 2054-57.
- Takano H, Hasegawa H, Zou Y, Komuro I. Pleiotropic actions of PPAR gamma activators thiazolidinediones in cardiovascular diseases. *Curr Pharm Des* 2004; 10: 2779-86.
- Marx N, Duez H, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors and atherogenesis. Regulators of gene expression in vascular cells. *Cir Res* 2004; 94: 1168-78.
- Yamagishi S, Takeuchi M. Telmisartan is a promising cardiometabolic sartan due to its unique PPAR- $\gamma$ -inducing property. *Med Hypotheses* 2005; 64: 476-8.
- Fujimoto M, Masuzaki H, Tanaka T, *et al.* An angiotensin II AT<sub>1</sub> receptor antagonist, telmisartan augments glucose uptake and GLUT4 protein expression in 3T3L-1 adipocytes. *FEBS Lett* 2004; 576: 492-7.
- Pershad Singh HA, Kurtz TW. Insulin-sensitizing effects of telmisartan. *Diabetes Care* 2004; 27: 1015.
- Miura Y, Yamamoto N, Tsunekawa S, *et al.* Replacement of valsartan and candesartan by telmisartan in hypertensive patients with diabetes. *Diabetes Care* 2005; 28: 757-8.
- Zimmermann M, Unger T. Challenges in improving prognosis and therapy: the Ongoing Telmisartan Alone and in Combination with Ramipril Global End point Trial programme. *Expert Opin Pharmacother* 2004; 5: 1201-8.
- L'Esperance FA, James WA, Judson PH. In: Lifkin H, Porte D Ed, The eye and diabetes mellitus. Ellenberg and Rifkin's Diabetes Mellitus, Theory and Practice. New York, Elsevier, 1990; 661-83.
- Cogan DG, Toussaint D, Kuwabara T. Retinal vascular patterns. IV. Diabetic retinopathy. *Arch Ophthalmol* 1961; 66: 366-78.
- Mandarino LJ. Current hypotheses for the biochemical basis of diabetic retinopathy. *Diabetes Care* 1992; 15: 1892-901.
- Sims DE. Recent advances in pericyte biology-implications for health and disease. *Can J Cardiol* 1991; 7: 431-43.
- Herman IM, D'Amore PA. Microvascular pericytes contain muscle and nonmuscle actins. *J Cell Biol* 1985; 101: 43-52.
- Gitlin JD, D'Amore PA. Culture of retinal capillary cells using selective growth media. *Microvasc Res* 1983; 26: 1455-62.
- Yamagishi S, Kobayashi K, Yamamoto H. Vascular pericytes not only regulate growth, but also preserve prostacyclin-producing ability and protect against lipid peroxide-induced injury of co-cultured endothelial cells. *Biochem Biophys Res Commun* 1993; 190: 418-25.
- Yamagishi S, Hsu CC, Kobayashi K, Yamamoto H. Endothelin 1 mediates endothelial cell-dependent proliferation of vascular pericytes. *Biochem Biophys Res Commun* 1993; 191: 840-6.
- Hammes HP, Lin J, Renner O, *et al.* Pericytes and the pathogenesis of diabetic retinopathy. *Diabetes* 2002; 51: 3107-12.
- Anderson S. Role of local and systemic angiotensin in diabetic renal disease. *Kidney Int Suppl* 1997; 63: S107-10.
- Yamagishi S, Amano S, Inagaki Y, *et al.* Angiotensin II-type 1 receptor interaction upregulates vascular endothelial growth factor messenger RNA levels in retinal pericytes through intracellular reactive oxygen species generation. *Drugs Exp Clin Res* 2003; 29: 75-80.
- Amano S, Yamagishi S, Inagaki Y, Okamoto T. Angiotensin II stimulates platelet-derived growth factor-B gene expression in cultured retinal pericytes through intracellular reactive oxygen species generation. *Int J Tissue React* 2003; 25: 51-5.
- Adamis AP, Miller JW, Bernal MT, *et al.* Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. *Am J Ophthalmol* 1994; 118: 445-50.
- Aiello LP, Avery RL, Arrigg PG, *et al.* Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994; 331: 1480-7.
- Murata T, Ishibashi T, Khalil A, *et al.* Vascular endothelial growth factor plays a role in hyperpermeability of diabetic retinal vessels. *Ophthalmic Res* 1995; 27: 48-52.
- Brownlee M, Cerami A, Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *N Engl J Med* 1988; 318: 1315-21.
- Dyer DG, Blackledge JA, Thorpe SR, Baynes JW. Formation of pentosidine during nonenzymatic browning of proteins by glucose. Identification of glucose and other carbohydrates as possible precursors of pentosidine *in vivo*. *J Biol Chem* 1991; 266: 11654-60.
- Grandhee SK, Monnier VM. Mechanism of formation of the Maillard protein cross-link pentosidine. Glucose, fructose, and ascorbate as pentosidine precursors. *J Biol Chem* 1991; 266: 11649-53.

- [47] Takeuchi M, Kikuchi S, Sasaki N, *et al.* Involvement of advanced glycation end-products (AGEs) in Alzheimer's disease. *Curr Alzheimer Research* 2004; 1:39-46.
- [48] Bucala, Cerami A. Advanced glycosylation: chemistry, biology, and implications for diabetes and aging. *Adv Pharmacol* 1992; 23: 1-34.
- [49] Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. *Lab Invest* 1994; 70: 138-51.
- [50] Brownlee M. Advanced protein glycosylation in diabetes and aging. *Ann Rev Med* 1995; 46: 223-34.
- [51] Yamagishi S, Takeuchi M, Inagaki Y, Nakamura K, Imaizumi T. Role of advanced glycation end products (AGEs) and their receptor (RAGE) in the pathogenesis of diabetic microangiopathy. *Int J Clin Pharmacol Res* 2003; 23: 129-34.
- [52] Matsumura T, Yamagishi S, Brownlee M. In: Leroith D, Taylor SI, Olefsky JM Ed, *Advanced glycation end products and the pathogenesis of diabetic complications. Diabetes Mellitus: A Fundamental and Clinical Text.* New York, Lippincott-Raven Publishers, 2000; 983-91.
- [53] Vlassara H, Palace MR. Diabetes and advanced glycation endproducts. *J Intern Med* 2002; 251: 87-101.
- [54] Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. *Cardiovasc Res* 1998; 37: 586-600.
- [55] Wendt T, Bucciarelli L, Qu W, *et al.* Receptor for advanced glycation endproducts (RAGE) and vascular inflammation: insights into the pathogenesis of macrovascular complications in diabetes. *Curr Atheroscler Rep* 2002; 4: 228-37.
- [56] Schmidt AM, Stern D. Atherosclerosis and diabetes: the RAGE connection. *Curr Atheroscler Rep* 2000; 2: 430-6.
- [57] Stitt AW, Bucala R, Vlassara H. Atherogenesis and advanced glycation: promotion, progression, and prevention. *Ann NY Acad Sci* 1997; 811: 115-27.
- [58] Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest* 1991; 87: 432-8.
- [59] Bucala R, Mitchell R, Arnold K, *et al.* Identification of the major site of apolipoprotein B modification by advanced glycosylation end products blocking uptake by the low density lipoprotein receptor. *J Biol Chem* 1995; 270: 10828-32.
- [60] Inagaki Y, Yamagishi S, Okamoto T, Takeuchi M, Amano S. Pigment epithelium-derived factor prevents advanced glycation end products-induced monocyte chemoattractant protein-1 production in microvascular endothelial cells by suppressing intracellular reactive oxygen species generation. *Diabetologia* 2003; 46: 284-7.
- [61] Yamagishi S, Fujimori H, Yonekura H, Yamamoto Y, Yamamoto H. Advanced glycation endproducts inhibit prostacyclin production and induce plasminogen activator inhibitor-1 in human microvascular endothelial cells. *Diabetologia* 1998; 41: 1435-41.
- [62] Yamagishi S, Yonekura H, Yamamoto Y, *et al.* Advanced glycation end products-driven angiogenesis *in vitro*. Induction of the growth and tube formation of human microvascular endothelial cells through autocrine vascular endothelial growth factor. *J Biol Chem* 1997; 272: 8723-30.
- [63] Lander HM, Tauras JM, Ogiste JS, *et al.* Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. *J Biol Chem* 1997; 272: 17810-4.
- [64] Schmidt AM, Hori O, Chen JX, *et al.* Advanced glycation endproducts interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. A potential mechanism for the accelerated vasculopathy of diabetes. *J Clin Invest* 1995; 96: 1395-403.
- [65] Vlassara H, Fuh H, Donnelly T, Cybulsky M. Advanced glycation endproducts promote adhesion molecule (VCAM-1, ICAM-1) expression and atheroma formation in normal rabbits. *Mol Med* 1995; 1: 447-56.
- [66] Bierhaus A, Illmer T, Kasper M, *et al.* Advanced glycation end product (AGE)-mediated induction of tissue factor in cultured endothelial cells is dependent on RAGE. *Circulation* 1997; 96: 2262-71.
- [67] Tanaka N, Yonekura H, Yamagishi S, *et al.* The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-alpha through nuclear factor-kappa B, and by 17beta-estradiol through Sp-1 in human vascular endothelial cells. *J Biol Chem* 2000; 275: 25781-90.
- [68] Yamagishi S, Nakamura K, Takeuchi M, Imaizumi T. Molecular mechanism for accelerated atherosclerosis in diabetes and its potential therapeutic intervention. *Int J Clin Pharm Res* 2004; 24: 129-134.
- [69] Yamagishi S, Nakamura K, Imaizumi T. Advanced glycation end products (AGEs) and diabetic vascular complications. *Curr Diabetes Rev* 2005; 1: 93-106.
- [70] Yamagishi S, Fujimori H, Yonekura H, Tanaka N, Yamamoto H. Advanced glycation endproducts accelerate calcification in microvascular pericytes. *Biochem Biophys Res Commun* 1999; 258: 353-7.
- [71] Yamagishi S, Takeuchi M, Matsui T, *et al.* Angiotensin II augments advanced glycation end product-induced pericyte apoptosis through RAGE overexpression. *FEBS Lett* (DOI: 10.1016/j.febslet.2005.06.058).
- \*[72] Yamagishi, S.I., Fukuoka, J.P.: DE10319592 (2004).
- [73] Riedel, A., Sendra, J.-M., Leiter, J.M.E., Kauschke, S., Mark, M.: WO04062557A3 (2004).
- [74] Kauschke, S., Mark, M., Kintscher, U., Schupp, M., Unger, T.: WO05011680A1 (2005).