Medical Hypotheses (2007) **69,** 666–668

ELSEVIER

medical hypotheses

http://intl.elsevierhealth.com/journals/mehy

Oral administration of AST-120 (Kremezin) is a promising therapeutic strategy for advanced glycation end product (AGE)-related disorders

S. Yamagishi [a,*], K. Nakamura [a], T. Matsui [a], H. Inoue [b], M. Takeuchi [c]

[a] *Department of Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan*
[b] *Radioisotope Institute for Basic and Clinical Medicine, Kurume University School of Medicine, Kurume, Japan*
[c] *Department of Pathophysiological Science, Faculty of Pharmaceutical Sciences, Hokuriku University, Japan*

Received 5 December 2006; accepted 7 December 2006

Summary The pathological role of the non-enzymatic modification of proteins by reducing sugars has become increasingly evident in various disorders. 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 ''AGEs (advanced glycation end products)''. AGEs have been implicated in the development of many of the pathological sequelae of diabetes and aging, such as diabetic microangiopathy, ischemic heart disease and neurodegenerative diseases. Recently, digested food-derived AGEs are also found to play an important role in the pathogenesis of AGE-related disorders. Diet is a major environmental source of pro-inflammatory AGEs. Indeed, restriction of dietary glycotoxins decreases excessive AGE levels and subsequently reduces the inflammatory responses in patients with diabetes. These observations suggest that inhibition of absorption of dietary AGEs may be a novel target for therapeutic intervention in the above-mentioned AGE-related disorders. AST-120 (Kremezin^{R}) is an oral adsorbent that attenuates the progression of chronic renal failure (CRF) by removing uremic toxins. We have recently found that AST-120 binds to carboxymethyllysine (CML), one of the well-characterized, digested food-derived AGEs in vitro and that administration of AST-120 decreases serum levels of AGEs in non-diabetic CRF patients. These findings suggest that digested food-derived AGEs such as CML may be a novel molecular target for oral adsorbent AST-120 and that AST-120 could exert beneficial effects on CRF patients by adsorbing diet-derived AGEs and subsequently decreasing serum AGE levels. If our speculation is correct, AST-120 may have therapeutic potentials for the treatment of patients with various AGE-related disorders as well. In this paper, we would like to propose the possible ways of testing our hypotheses. Does the long-term treatment of AST-120 decrease serum and tissue levels of AGEs in diabetic patients? Does this treatment also reduce the risk for the development and progression of diabetic vascular complications such as diabetic retinopathy or ischemic heart disease? If the answers are yes, do the serum and/or tissue levels of AGEs after AST-120 treatment predict its beneficial effects on diabetic vascular complications? How

* Corresponding author. Tel.: +81 942 31 7580; fax: +81 942 31 7707.
E-mail address: shoichi@med.kurume-u.ac.jp (S. Yamagishi).

0306-9877/$ - see front matter
doi:10.1016/j.mehy.2006.12.045

about the effects of AST-120 on Alzheimer's disease, another AGE-related neurodegenerative disorder? Does the treatment of AST-120 reduce the risk for Alzheimer's disease and/or improve the cognitive impairment of patients with this disorder? These prospective studies will provide further valuable information whether the inhibition of absorption of dietary AGEs by AST-120 could be clinically relevant.

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 disorders [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 ''AGEs (advanced glycation end products)''. AGEs have been implicated in the development of many of the pathological sequelae of diabetes and aging, such as diabetic microangiopathy, ischemic heart disease, neurodegenerative diseases and melanoma growth and metastasis [3–8]. Indeed, engagement of their cell surface receptor RAGE by AGEs elicits oxidative stress generation, vascular inflammation, angiogenesis, platelet and macrophage activation, thereby being involved in the development and progression of various devastating disorders [3–8].

Recently, digested food-derived AGEs are also found to play an important role in the pathogenesis of AGE-related disorders [9]. In animal models, lowering of dietary AGEs not only slows the progression of diabetic nephropathy, but also reduces neointimal formation after arterial injury in genetically hypercholesterolemic mice [10,11]. Diet is a major environmental source of pro-inflammatory AGEs [9]. About 10% of food-derived AGEs can be absorbed [9]. Restriction of dietary glycotoxins decreases excessive AGE levels and subsequently reduces the inflammatory responses in patients with diabetes [12]. These observations suggest that inhibition of absorption of dietary AGEs may be a novel target for therapeutic intervention in the above-mentioned AGE-related disorders.

AST-120 (Kremezin^{R}) is an oral adsorbent that attenuates the progression of chronic renal failure (CRF) by removing uremic toxins, resulting in the delay of dialysis [13,14]. AST-120 is also reported to reduce carotid intima media thickness (IMT) and arterial stiffness, one of the surrogate markers for atherosclerosis, in CRF patients before dialysis [15]. AGEs represent an important class of uremic toxins as well [16,17]. Further, we have recently found that administration of AST-120 (6 g/day) for 3 months significantly decreases serum levels of AGEs in non-diabetic CRF patients [17]. Patient serum after AST-120 treatment also reduced mRNA levels of RAGE, monocyte chemoattractant protein-1 and vascular adhesion molecule-1 in cultured endothelial cells, compared with serum before the treatment. In vitro, AST-120 was also found to bind to carboxymethyllysine (CML), one of the well-characterized, digested food-derived AGEs [17]. These findings suggest that digested food-derived AGEs such as CML may be a novel molecular target for oral adsorbent AST-120 and that AST-120 could exert beneficial effects on CRF patients by adsorbing diet-derived AGEs and subsequently decreasing serum AGE levels. If our speculation is correct, AST-120 may have therapeutic potentials for the treatment of patients with various AGE-related disorders as well.

In this paper, we would like to propose the possible ways of testing our hypotheses. Does the long-term treatment of AST-120 decrease serum and tissue levels of AGEs in diabetic patients? Does this treatment also reduce the risk for the development and progression of diabetic vascular complications such as diabetic retinopathy or ischemic heart disease? If the answers are yes, do the serum and/or tissue levels of AGEs after AST-120 treatment predict its beneficial effects on diabetic vascular complications? How about the effects of AST-120 on Alzheimer's disease, another AGE-related neurodegenerative disorder? Does the treatment of AST-120 reduce the risk for Alzheimer's disease and/or improve the cognitive impairment of patients with this disorder? These prospective studies will provide further valuable information whether the inhibition of absorption of dietary AGEs by AST-120 could be clinically relevant.

Acknowledgment

This work was supported in part by Grants of Collaboration with Venture Companies Project from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

[1] Brownlee M. Advanced protein glycosylation in diabetes and aging. Ann Rev Med 1995;46:223–34.

[2] 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.

[3] Yamagishi S, Imaizumi T. Diabetic vascular complications: pathophysiology, biochemical basis and potential therapeutic strategy. Curr Pharm Des 2005;11:2279–99.

[4] 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.

[5] 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;7:586–600.

[6] Schmidt AM, Stern D. Atherosclerosis and diabetes: the RAGE connection. Curr Atheroscler Rep 2000;2:430–6.

[7] Abe R, Shimizu T, Sugawara H, et al. Regulation of human melanoma growth and metastasis by AGE-AGE receptor interactions. J Invest Dermatol 2004;122:461–76.

[8] Takeuchi M, Kikuchi S, Sasaki N, et al. Involvement of advanced glycation end-products (AGEs) in Alzheimer's disease. Curr Alzheimer Res 2004;1:39–46.

[9] Vlassara H. Advanced glycation in health and disease: role of the modern environment. Ann NY Acad Sci 2005;1043: 452–60.

[10] Zheng F, He C, Cai W, et al. Prevention of diabetic nephropathy in mice by a diet low in glycoxidation products. Diabetes Metab Res Rev 2002;18:224–37.

[11] Lin RY, Reis ED, Dore AT, et al. Lowering of dietary advanced glycation endproducts (AGE) reduces neointimal formation after arterial injury in genetically hypercholesterolemic mice. Atherosclerosis 2002;1639: 303–11.

[12] Vlassara H, Cai W, Crandall J, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci USA 2002;99:15596–601.

[13] Niwa T, Nomura T, Sygiyama S, et al. The protein metabolite hypothesis, a model for the progression of renal failure: an oral adsorbent lowers indoxyl sulfate levels in undialyzed uremic patients. Kidney Int 1997;62: S23–8.

[14] Owada A, Nakao M, Koike J, et al. Effects of oral adsorbent AST-120 on the progression of chronic renal failure: a randomized controlled study. Kidney Int 1997;63:S188–90.

[15] Nakamura T, Kawagoe Y, Matsuda T, et al. Oral adsorbent AST-120 decreases carotid intima-media thickness and arterial stiffness in patients with chronic renal failure. Kidney Blood Press Res 2004;27:121–6.

[16] Henle T. AGEs in foods: do they play a role in uremia? Kidney Int 2003;84:S145–7.

[17] Ueda S, Yamagishi S, Takeuchi M, et al. Oral adsorbent AST-120 decreases serum levels of AGEs in patients with chronic renal failure. Mol Med 2006;12:180–4.