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Independent determinants of soluble form of receptor for advanced glycation end products in elderly hypertensive patients

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Abstract

Advanced glycation end product receptor (RAGE) interaction plays an important role in atherosclerosis. Although exogenously administered soluble form of RAGE (sRAGE) has been shown to suppress the development and progression of atherosclerosis in animals, the kinetics and role of endogenous sRAGE in humans are not fully understood. In this study, to clarify whether endogenous sRAGE could capture and efficiently eliminate RAGE ligands such as circulating AGEs and high-mobility group box–1 (HMGB-1), we investigated the correlation between sRAGE and RAGE ligands and examined independent determinants of serum levels of sRAGE in hypertensive humans. Two-hundred seventy-one consecutive nondiabetic outpatients with essential hypertension (83 male and 188 female; mean age, 76.5 ± 9.2 yeas) underwent a complete history, physical examination, and determination of blood chemistries, including serum levels of sRAGE, AGEs, and HMGB-1. Univariate regression analysis showed that serum levels of sRAGE were associated with body mass index ($r = -0.313$, $P < .0001$), waist ($r = -0.214$, $P < .0001$), alanine aminotransferase ($r = -0.172$, $P = .005$), γ-glutamyltranspeptidase ($r = -0.213$, $P < .0001$), 24-hour creatinine clearance ($r = -0.348$, $P < .0001$), B-type natriuretic peptide ($r = 0.138$, $P = .027$), tumor necrosis factor–α ($r = 0.138$, $P = .002$), and alcohol intake ($r = -0.155$, $P = .010$). By the use of multiple stepwise regression analyses, 24-hour creatinine clearance ($P < .0001$), γ-glutamyltranspeptidase ($P < .001$), body mass index ($P = .007$), and tumor necrosis factor–α ($P = .024$) remained significant independently. The present study demonstrated for the first time that there was no significant correlation between serum levels of sRAGE and RAGE ligands such as circulating AGEs and HMGB-1 in hypertensive patients. Anthropometric and inflammatory variables and liver and renal function may be the determinants of endogenous sRAGE levels in nondiabetic hypertensive patients.

Reducing sugars can react nonenzymatically with amino groups of protein to form Amadori products [1-4]. These early glycation products undergo further complex reactions such as rearrangement, dehydration, and condensation to become irreversibly cross-linked, heterogeneous fluorescent derivatives, termed *advanced glycation end products* (AGEs) [1-4]. There is a growing body of evidence that AGEs and their receptor (RAGE) are implicated in vascular injury in diabetic and nondiabetic patients [5-8]. Indeed, engagement of RAGE with AGEs is shown to elicit oxidative stress generation and subsequently evoke inflammatory responses in endothelial cells, thus being involved in atherosclerosis [5-8]. Moreover, administration of a recombinant soluble form of RAGE (sRAGE) consisting of the extracellular ligand-binding domain has been shown not only to suppress the development of atherosclerosis but also to stabilize established atherosclerosis in diabetic apolipoprotein E null mice [9,10]. These findings suggest that exogenously administered sRAGE may capture and eliminate circulating AGEs, thus protecting against the AGE-induced vascular cell damage by acting as a decoy receptor for AGEs.

High-mobility group box–1 (HMGB-1) was first isolated from perinatal rat brain as a heparin-binding protein that could promote neurite outgrowth in central neurons in 1987

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[11]. It was originally described as a DNA-binding nonhistone chromosomal protein that had been implicated in diverse cellular functions such as stabilization of nucleosomal structure and regulation of transcriptional factors [12,13]. Furthermore, recently, HMGB-1 has been implicated as a putative danger signal involved in the pathogenesis of a variety of inflammatory conditions; and RAGE has been involved in the HMGB-1-signaling [14]. Indeed, HMGB-1 is not only released passively from necrotic cells, but also secreted actively by immune cells, thus participating in inflammatory processes in various disorders such as septic shock, acute coronary syndromes, and disseminated intravascular coagulation [14]. However, the regulation of HMGB-1 levels in diabetic or hypertensive patients remains to be elucidated.

Recently, endogenous sRAGE has been identified in humans [15,16]. We, along with others, have found that serum levels of sRAGE are higher in diabetic patients than in nondiabetic controls and are significantly correlated with circulating levels of AGEs [17-19]. In addition, serum levels of sRAGE are positively associated with inflammatory biomarkers, including tumor necrosis factor–α (TNF-α) and monocyte chemoattractant protein–1 (MCP-1), and the presence of coronary artery disease in type 2 diabetes mellitus patients [20-22]. Because AGEs have been reported to up-regulate RAGE expression and endogenous sRAGE could be generated from the cleavage of cell surface RAGE [23,24], the above-mentioned observations suggest that endogenous sRAGE levels may be elevated as a counter-system against tissue damage and could reflect enhanced RAGE expression in diabetes. However, the kinetics and pathophysiologic role of endogenous sRAGE in nondiabetic hypertensive patients are not fully understood. Indeed, as far as we know, there is no report to show the relationship between serum levels of sRAGE and RAGE ligands such as AGEs and HMGB-1. Therefore, whether endogenous sRAGE could be inversely associated with circulating AGEs and HMGB-1 by capturing and efficiently eliminating the RAGE ligands in nondiabetic hypertensive patients remains to be elucidated. Furthermore, it is not known which anthropometric, metabolic, and inflammatory factors could be the determinant of sRAGE in nondiabetic hypertensive patients. Therefore, in this study, we investigated the relationship among sRAGE, AGEs, and HMGB-1 and examined independent determinants of serum levels of sRAGE in nondiabetic patients with essential hypertension.

1. Methods

1.1. Subjects

The study involved 271 consecutive nondiabetic outpatients in Nakamura Clinic (76.5 ± 9.2 years old, 83 men and 188 women, 271 with essential hypertension, 184 with hyperlipidemia [HL]). The number of patients who received β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor blockers was 72, 201, 55, and 60, respectively. All the patients with HL received statins. Twenty-eight patients had a history of cardiovascular disease such as myocardial infarction and stroke, and 17 patients had chronic atrial fibrillation. We excluded any patients with inflammatory neoplastic disorders and those who had a recent (<3 months) acute coronary syndrome, stroke, and any acute infection. Patients who consumed steroids were also excluded. All participants gave their written informed consent to participate in this study.

1.2. Data collection

Medical history and use of tobacco and alcohol were ascertained by a questionnaire. Smoking and alcohol were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) (kilograms per meter squared) was calculated as an index of the presence or absence of obesity. Blood pressure (BP) was measured in the sitting position using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 minutes before BP measurement.

Blood was drawn from the antecubital vein for determination of serum sRAGE, TNF-α, MCP-1, and other blood chemistries. Tumor necrosis factor–α, MCP-1, and sRAGE were measured with commercially available competitive enzyme-linked immunosorbent assay (ELISA) kits as described previously [17,20,21]. High-mobility group box–1 was measured with an ELISA kit (Shino-Test, Tokyo, Japan) according to the supplier's recommendation. Measurement of AGEs was performed with a competitive ELISA as described previously [25]. Briefly, 96-well microtiter plates were coated with 0.1 μg/mL AGE–bovine serum albumin (BSA). Afterward, test samples (50 μL) were added to each well as a competitor for 50 μL of polyclonal antibodies directed against AGE-BSA (1:1000), followed by incubation for 2 hours at room temperature with gentle shaking on a horizontal rotary shaker. After incubating each well with alkaline phosphatase–conjugated anti-rabbit immunoglobulin G, *p*-nitrophenyl phosphate was added as a colorimetric substrate. The plate was then read using a microplate reader. In this study, 1 U corresponds to 1 μg of glyceraldehyde-derived AGE-BSA standard. Other blood chemistries were determined enzymatically at a commercially available laboratory (Wakamatsu Medical Research Laboratory, Kitakyushu, Japan). These samples were processed blindly. The ELISA assay was run in duplicate.

1.3. Statistical methods

Because of skewed distributions, the natural logarithmic (ln) transformations were performed for γ-glutamyltranspeptidase (γ-GTP), triglycerides, glucose, TNF-α, MCP-1, and B-type natriuretic peptide (BNP). Mean values with upper and lower 95% confidence intervals

were exponentiated and presented as geometric mean ± standard deviation. The medications for hypertension and HL were coded as dummy variables. Univariate analysis was performed for determinants of sRAGE levels. To determine independent determinants of sRAGE levels, multiple stepwise regression analysis was performed. *Statistical significance* was defined as P less than .05. All statistical analyses were performed with the use of the SPSS (Chicago, IL) system.

2. Results

Demographical data of the subjects are presented in Table 1. Mean serum sRAGE level was 845.9 ± 454.9 pg/mL in this population. Table 2 showed the results of univariate and multivariate analyses for determinants of serum sRAGE levels. Parameters significantly related to serum sRAGE levels were BMI ($r = -0.313$, $P < .0001$), waist ($r = -0.214$, $P < .0001$), alcohol intake ($r = -0.155$, $P = .010$), 24-hour creatinine clearance (24h-Ccr) ($r = -0.348$, $P < .0001$), alanine aminotransferase (ALT) ($r = -0.172$, $P = .005$), γ-GTP ($r = -0.213$, $P < .0001$), BNP ($r = 0.138$, $P = .027$), and TNF-α ($r = 0.201$, $P = .002$). Because these significant parameters could be closely correlated with each other, multiple stepwise regression analysis was performed. Finally, 24h-Ccr ($P < .0001$, inversely), γ-GTP ($P < .001$, inversely), BMI ($P = .007$, inversely), and TNF-α ($P = .024$) remained significant (Table 2) and were independently related to serum sRAGE levels (R^2=0.215).

Table 1
Demographical data of the subjects (N =271)

Age (y)	76.5 ± 9.2
BMI (kg/m^2)	23.2 ± 3.4
Waist circumference (cm)	88.1 ± 8.6
sRAGE (pg/mL)	845.9 ± 454.9
AGEs (U/mL)	8.1 ± 3.8
HMGB-1 (ng/mL)	2.3 ± 0.14
AST (IU/L)	23.3 ± 7.5
ALT (IU/L)	17.5 ± 8.4
γ-GTP (IU/L)	30.5 ± 40.8
Total cholesterol (mg/dL)	201.2 ± 32.1
Triglyceride (mg/dL)	124.8 ± 57.0
HDL cholesterol (mg/dL)	53.1 ± 13.1
LDL cholesterol (mg/dL)	126.1 ± 31.0
Creatinine (mg/dL)	0.9 ± 0.3
24h-Ccr (mL/min)	48.8 ± 16.9
Glucose (mg/dL)	107.0 ± 18.3
HbA_{1c} (%)	5.2 ± 0.4
Uric acid (mg/dL)	5.5 ± 1.3
Systolic BP (mm Hg)	129.0 ± 11.4
Diastolic BP (mm Hg)	72.5 ± 7.0
BNP (pg/mL)	59.3 ± 83.3
MCP-1 (pg/mL)	272.0 ± 225.8
TNF-α (pg/mL)	1.52 ± 1.11
Current smoking (n)	17
Alcohol intake (n)	47

AST indicates aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2
Determinants of sRAGE by step-forward logistic regression analyses

Factors	Univariate[a]		Multivariate[b]		
	β	P	β	F	P
Age (y)	0.083	NS			
Sex (male)	0.109	NS			
BMI (kg/m^2)	−0.313	$P < .0001$	−0.181	−2.726	.007
Waist circumference (cm)	−0.214	$P < .0001$			
AGEs (U/mL)	0.049	NS			
HMGB-1 (ng/mL)	−0.084	NS			
AST (IU/L)	0.002	NS			
ALT (IU/L)	−0.172	$P = .005$			
γ-GTP (IU/L)[c]	−0.213	$P < .0001$	−0.207	−3.347	<.001
Total cholesterol (mg/dL)	0.090	NS			
Triglycerides (mg/dL)[c]	0.029	NS			
HDL cholesterol (mg/dL)	−0.048	NS			
LDL cholesterol (mg/dL)	0.070	NS			
24h-Ccr (mL/time)	−0.348	$P < .0001$	−0.380	−6.203	<.0001
Uric acid (mg/dL)	0.031	NS			
Glucose (mg/dL)[c]	−0.084	NS			
HbA_{1c} (%)	−0.074	NS			
Systolic BP (mm Hg)	0.080	NS			
Diastolic BP (mm Hg)	−0.025	NS			
MCP-1 (pg/mL)[c]	0.066	NS			
TNF-α (pg/mL)[c]	0.201	$P = .002$	0.137	2.276	.024
BNP (pg/mL)[c]	0.138	$P = .027$			
Presence of CVD	0.001	NS			
Current smoking	0.060	NS			
Alcohol intake	−0.155	$P = .010$			
Use of ACE inhibitors	0.042	NS			
Use of ARBs	−0.022	NS			
Use of CCBs	−0.076	NS			
Use of β-blockers	0.114	NS			
HL medication	0.035	NS			
R^2			0.215		

β indicates regression coefficients; NS, not significant; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; ARB angiotensin II type 1 receptor blocker.

[a] Univariate coefficients.

[b] A stepwise multivariate regression analysis was performed.

[c] Log-transformed values were used.

3. Discussion

In this study, we demonstrated for the first time that serum levels of sRAGE were *not* correlated with RAGE ligands such as circulating AGEs and HMGB-1 levels in nondiabetic hypertensive patients. Although exogenously administered sRAGE was shown to block the deleterious effects of AGEs in animal models by acting as a decoy receptor for AGEs [9,10], it is questionable that endogenous sRAGE could also have the same biological effects because serum levels of sRAGE in humans are 1000 times lower than needed for the binding to AGEs and because sRAGE was positively, rather than inversely, associated with circulating levels of AGEs in nondiabetic healthy subjects and diabetic patients [16-18,26,27]. Therefore, the lack of the inverse association

of sRAGE with RAGE ligands and the positive association with TNF-α observed here suggest that endogenous sRAGE could not efficiently capture and eliminate circulating RAGE ligands in nondiabetic hypertensive patients by working as a decoy receptor and subsequently combating AGE- and HMGB-1–elicited inflammation. In the present study, the positive association of AGEs with sRAGE was *not* observed in nondiabetic hypertensive patients. We did not know the exact reason for the absence of correlation between AGEs and sRAGE in these populations. However, we have previously shown that serum levels of sRAGE may reflect tissue RAGE expression and be elevated in response to circulating AGEs in nondiabetic healthy subjects and diabetic patients [16,17,20,23,24]. Accordingly, the kinetics and regulation of sRAGE may differ between hypertensive and normotensive subjects; and tissue RAGE expression could be regulated by factors other than RAGE ligands in nondiabetic hypertensive patients.

We have previously found that serum levels of sRAGE are positively associated with inflammatory biomarkers, including TNF-α, and the presence of coronary artery disease in type 2 diabetes mellitus patients [20-22]. In this study, we found that TNF-α was one of the determinants of endogenous sRAGE levels in nondiabetic hypertensive patients as well. Advanced glycation end product receptor mediates the AGE or HMGB-1 signaling to TNF-α expression in various types of cells [28,29]. Therefore, the present observations support the concept that endogenous sRAGE levels may be elevated as a countersystem against AGE- or HMGB-1–elicited proinflammation and subsequent tissue damage in humans.

In the present study, we found that serum sRAGE levels had the strongest inverse correlation with 24h-Ccr in nondiabetic hypertensive patients. The finding has extended to the previous report by Kalousová et al [30], who showed that serum sRAGE levels increased in patients with decreased renal function, mainly patients with end-stage renal disease. Furthermore, because Tan et al [19] also reported that creatinine levels were one of the main independent determinants of sRAGE concentration in type 2 diabetes mellitus and that serum levels of sRAGE were associated with the severity of nephropathy, our present findings suggest that sRAGE is excreted by the kidney and that the elevation of sRAGE levels may work as a countersystem and play some protective role against accelerated atherosclerosis in high-risk patients with hypertension, chronic kidney disease, and diabetes.

We have previously shown that sRAGE levels are inversely correlated with BMI in Japanese general population [17]. In our hypertensive subjects, BMI was one of the independent determinants of sRAGE as well. Unoki et al [31] have shown that RAGE expression level is up-regulated during the differentiation process to mature adipocytes. Because this expression pattern is opposite to that of TNF-α [32], adipocyte-derived sRAGE production would be decreased in central obesity, which could partly explain the inverse and positive association of sRAGE with BMI and TNF-α, respectively, in our subjects. Furthermore, in this study, γ-GTP was inversely associated with sRAGE. Because RAGE is involved in liver injury and regeneration [33,34], liver may be one of the main sources of circulating sRAGE in humans.

4. Limitations

As far as we know, there is no report to show the relationship between serum levels of sRAGE and RAGE ligands and simultaneously to investigate the independent determinants of sRAGE in patients with essential hypertension. However, there is only 1 article that examined sRAGE levels in hypertensive patients [35]. In that report, sRAGE levels were determined by systolic BP and pulse pressure. We did not know the reason why systolic BP and pulse pressure were not correlated with sRAGE in our subjects. The difference of subject population (age and the presence or absence of hypertension) and ethnicity could account for the discrepancies because they included normotensive as well as hypertensive subjects and therefore may have a much larger variation in BP across their entire population. Furthermore, our study was a cross-sectional one and, therefore, does not elucidate the causal relationships between serum sRAGE levels and anthropometric, metabolic, and inflammatory variables. A longitudinal study is needed to clarify the issue.

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