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Original article

Angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and statins as anti-glycation agents

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Abstract

***Background*:** Angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and statins are widely used for the treatment of cardiovascular and diabetic complications. Recently, advanced glycation end products (AGEs) have been shown to play a role in promoting and accelerating these diseases. ARBs and ACE inhibitors decrease the formation of AGEs via radical scavenging and transition metal chelation both *in-vitro* and in animal models. Statins may decrease the formation of AGEs and slow the aging process through several potential mechanisms.
***Objective*:** The purpose of this study was to evaluate the inhibitory activity of ARBs, ACE inhibitors, and statins against human serum albumin (HSA) glycation.
***Methods*:** Test samples were prepared in dimethyl sulfoxide. An HSA glycation model was generated by incubating HSA and test samples with and without glucose at 60 °C for 40 h. The fluorescence (excitation, 370 nm; detection, 440 nm) of each sample was measured using a Spectra Max paradigm multimode detection platform.
***Results*:** Among the tested statins, only fluvastatin, Lochol (fluvastatin), and Lipovas (simvastatin) displayed weak anti-glycation activity, with pure fluvastatin (IC_{50} = 1.84 mg/nL) having the highest inhibitory activity. Among ARBs, only valsartan and olmesartan exhibited weak anti-glycation activity, with valsartan showing stronger activity (IC_{50} = 2.28 mg/mL). These effects were weaker than aminoguanidine (IC_{50} = 0.063 mg/mL). In contrast, none of the examined ACE inhibitors had detectable anti-glycation activity.
***Conclusion*:** A part of ARBs and statins seems to possess anti-glycation activity, however it is weak compared to aminoguanidine.

***KEY WORDS*:** aging, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, glycation, statins

Introduction

Aging is a complex process for which many theories have been proposed. For example, in the glycation theory of aging, toxic byproducts, particularly advanced glycation end products (AGEs), generated during energy production cause cellular damage and lead to reduced longevity. AGEs are proteins and lipids that are formed through the non-enzymatic reaction between proteins and reducing sugars, such as fructose and glucose. Inhibition of AGEs formation and therapeutic intervention to reduce AGEs may slow the aging process and treating age-related diseases.

Aminoguanidine is a widely used AGEs inhibitor that was first discovered in 1986 [1,2)] as a nucleophilic hydrazine derivative that binds irreversibly to reactive intermediates of early glycated products, particularly 3-deoxyglucosone. Although aminoguanidine prevents AGEs formation and AGE-induced protein cross-linking [3)], this compound has toxic effects, thus limiting its therapeutic potential. The adverse toxic effects associated with aminoguanidine include drug-induced systemic lupus erythematosus, abnormal liver function, flu-like syndromes, and vasculitis [4)]. Aminoguanidine can also damage DNA through hydroxyl- and hydrogen peroxide-formation in the presence of Fe^{+3} [5)]. Side effects related to the trapping of pyridoxal leading to a vitamin B6 deficiency have also been reported [6)]. Due to the numerous potential toxic effects of aminoguanidine, other drugs with demonstrated AGEs inhibitory efficacy in the clinical setting are needed.

Here, we evaluated the AGEs inhibitory activity of several well-tolerated anti-hypertensive drugs and statins

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against human serum albumin (HSA) to assess their potential as anti-glycation agents.

Methods

In-vitro models of glycation using glucose and HSA were used to test the inhibitory activity of anti-hypertensive drugs and statins against AGEs formation [7].

The tested compounds included 12 statins: atorvastatin, simvastatin, pitavastatin, pravastatin, fluvastatin, lovastatin (Wako Pure Chemical Industries, Chuo-ku, Osaka, Japan), Lipitor/atorvastatin (Astellas, Itabashi-ku, Tokyo, Japan), Lipovas/simvastatin (MSD, Chiyoda-ku, Tokyo, Japan), Livalo/pitavastatin (Kowa, Chuo-ku, Tokyo, Japan), Mevalotin/pravastatin (Daiichi Sankyo, Chuo-ku, Tokyo, Japan), Lochol/fluvastatin (Novartis, Minato-ku, Tokyo, Japan), and Crestor/rosuvastatin (Astra Zeneca, Kita-ku, Osaka, Japan); 11 angiotensin II receptor blockers (ARBs): valsartan, telmisartan (Tokyo Chemical Industry, Kita-ku, Tokyo, Japan), candesartan (Sigma-Aldrich, St. Louis, MO, USA), losartan (LKT Laboratories, Inc., St. Paul, MN, USA), Nu-lotan/losartan (MSD); Diovan/valsartan (Novartis), Blopress/candesartan (Takeda Pharmaceutical, Chuo-ku, Osaka, Japan), Micardis/telmisartan (Astellas); Olmetec/olmesartan (Daiichi Sankyo), Avapro/irbesartan (Dainippon Sumitomo, Chuo-ku, Osaka, Japan), and Irbetan/irbesartan (Shionogi, Chuo-ku, Osaka, Japan); 10 angiotensin converting enzyme (ACE) inhibitors: Coversyl/perindopril (Kyowa-Hako Kirin Servier, Chiyoda-ku, Tokyo, Japan), Adecut/delapril (Takeda Pharmaceutical), Captoril/captopril (Daiichi Sankyo), Renivace/enalapril (MSD), Longes/lisinopril (Shionogi), Zestril/lisinopril (Astra Zeneca), Cibacen/benazepril (Novartis), Tanatril/imidapril (Mitsubishi Tanabe Pharma Corp., Chuo-ku, Osaka, Japan), Preran/trandolapril (Sanofi Aventis, Shinjuku-ku, Tokyo, Japan), and Odric/trandolapril (Nippon Shinyaku, Minami-ku, Kyoto, Japan). Test compounds were dissolved in dimethyl sulfoxide (DMSO; Wako Pure Chemical Industries) prior to use.

The HSA model was used to assay the AGEs inhibitory activity of the test compounds as previously reported [7]. For the assay, 100 μL of each test sample (anti-hypertensive drugs, statins, or DMSO [control]) was added to 900 μL of glucose (+) or glucose (–) HSA solution, and the resulting reaction mixtures were incubated at 60 °C for 40 h. The glucose (+) reaction solution contained 0.1 M phosphate buffer (pH 7.4), 40 mg/mL HSA (Sigma Chemical Ltd., Perth, WA, USA), 2.0 M glucose, and distilled water at a 5:2:1:1 volume ratio. The glucose (–) reaction solution contained 0.1 M phosphate buffer (pH 7.4), 40 mg/mL HSA, and distilled water at a 5:2:2 volume ratio.

After the 40-h incubation, sample solution (200 μL), distilled water (200 μL), and 5 μg/mL quinine sulfate (200 μL) were dispensed into a well of black microplate, and the fluorescence (excitation, 370 nm; detection, 440 nm) was measured using the Spectra Max paradigm multimode detection platform (Molecular Devices, Sunnyvale, CA, USA) [7, 8].

The AGEs inhibitory activity of each sample was calculated using the following formula:

Inhibitory activity against AGEs fluorescence, (%) =
(1 – Glu (+) sample – Glu (–) sample) / (Glu (+) control – Glu (–) control) × 100
(Glu means glucose in this formula)

The 50% inhibitory concentration (IC_{50}) against AGEs fluorescence, was calculated from a regression curve of the inhibitory activity for three concentrations of each sample (n = 3). The activity of each extract was compared with the activity of aminoguanidine [8].

Results

The results of the HSA assay for each test compound are presented in ***Table 1***. In the statin group, only fluvastatin, Lochol/fluvastatin, and Lipovas/simvastatin showed anti-glycation activity, with pure fluvastatin having the highest inhibition rate. Among ARBs, Diovan/valsartan and Olmetec/olmesartan displayed anti-glycation activity, with Diovan/valsartan showing stronger anti-glycation activity. In contrast, no ACE inhibitor had detectable anti-glycation activity.

Discussion

Our findings show that the ARBs valsartan/Diovan and olmesartan/Olmetec, and the statins fluvastatin and simvastatin/Lipovas have anti-glycation activity. Notably, none of the examined ACE inhibitors had detectable anti-glycation activity. Although the anti-glycation activities of the ARBs and statins are not as high as that of aminoguanidine (IC_{50} = 0.063 mg/mL) [9], these findings suggest that treatment with these drugs may be effective in preventing AGE-related complications with a reduced risk of adverse effects in diabetic and cardiovascular patients. However these result may be different from the *in vivo* reaction considering the glucose absorbent mechanism and the possibility of enhance insulin reaction are different for each compounds.

Anti-hypertensive drugs such as ARBs and ACE inhibitors decrease the formation of AGEs via radical scavenging and transition metal chelation [10] both *in-vitro* and in animal models of diabetes [11,12]. Furthermore, the results of *in-vitro* experiments and preclinical and clinical studies suggest that ACE inhibitors prevent AGEs formation by promoting expression of the receptor of AGE (RAGE) [11]. Sebekova *et al.* [13] reported that treatment with the ACE inhibitor ramipril for 2 months significantly decreased the fluorescent AGE level in 12 subjects with nondiabetic nephropathy. It is conceivable that blockade of the renin-angiotensin system (RAS) with drugs such as ACE inhibitors may affect AGEs accumulation by either improving renal function or reducing oxidative stress. Culture experiments using NRK-49F cells exposed to AGEs demonstrated that the ACE inhibitor captopril blocks AGE-induced collagen production [14]. In addition, increased protein expression of RAGE was also attenuated by ACE inhibition [14].

ARBs have protective effects against kidney damage and can reduce renal AGEs accumulation and proteinuria in diabetic rodents *in vivo* [12,15-17] to a similar degree to that of ACE inhibitors [18]. For example, *in-vivo* studies using a renal ablation model showed that treatment with the ARBs, losartan, decreased serum AGEs concentrations and improved renal function independent of changes in the profibrotic cytokine transforming growth factor-ß [19]. Here, in contrast, we found that losartan, in both its pure and commercially produced forms, did not display anti-glycation activity. These apparently contrasting results may be explained by the fact that the previous study found that AGEs were reduced in

Table 1. Inhibition of formation of fluorescence AGEs by ARBs, ACE inhibitors and statins.

No	Group	Chemical compound	Product name	Concentration (mg/ml)	Inhibition rate (%)	IC_{50}
1	Statin	Atorvastatin		0.1	-9.8 ± 5.6	None
				0.01	-5.2 ± 3.1	
				0.001	0.1 ± 6.0	
2	Statin	Simvastatin		0.1	-2.7 ± 5.6	None
				0.01	-5.3 ± 7.5	
				0.001	1.7 ± 4.8	
3	Statin	Pitavastatin		0.1	-10.5 ± 2.4	None
				0.01	-10.4 ± 2.0	
				0.001	-4.4 ± 8.3	
4	Statin	Pravastatin		0.1	-24.0 ± 15.7	None
				0.01	-12.7 ± 1.7	
				0.001	-3.6 ± 1.8	
5	Statin	Fluvastatin		0.1	31.5 ± 4.3	1.84 ± 0.90
				0.01	-7.3 ± 7.8	
				0.001	-8.5 ± 6.3	
6	Statin	Lovastatin		0.1	-19.5 ± 7.4	None
				0.01	-23.2 ± 7.2	
				0.001	-16.3 ± 6.6	
7	ARBs	Valsartan		0.1	-5.1 ± 4.8	None
				0.01	-22.8 ± 7.7	
				0.001	-18.3 ± 6.7	
8	ARBs	Telmisartan		0.1	-12.3 ± 2.8	None
				0.01	-30.1 ± 3.5	
				0.001	-23.7 ± 3.2	
9	ARBs	Candesartan		0.1	11.9 ± 3.9	None
				0.01	7.6 ± 4.3	
				0.001	4.2 ± 3.8	
10	ARBs	Losartan		0.1	7.8 ± 6.0	None
				0.01	1.7 ± 5.2	
				0.001	-2.8 ± 6.0	
11	Statin	Atorvastatin-calcium hydrate	Lipitor*	0.1	6.3 ± 4.7	None
				0.01	3.7 ± 6.4	
				0.001	2.1 ± 6.9	
12	Statin	Simvastatin	Lipovas*	0.1	19.4 ± 3.9	> 100
				0.01	5.2 ± 4.2	
				0.001	1.8 ± 6.5	
13	Statin	Pitavastatin calcium	Livalo*	0.1	18.2 ± 1.3	None
				0.01	5.8 ± 3.5	
				0.001	4.9 ± 3.2	
14	Statin	Pravastatin sodium	Mevalotin*	0.1	9.5 ± 4.8	None
				0.01	7.5 ± 5.6	
				0.001	4.3 ± 5.2	
15	Statin	Fluvastatin sodium	Lochol*	0.1	32.1 ± 4.1	14.07 ± 15.39
				0.01	14.1 ± 4.3	
				0.001	10.4 ± 5.7	
16	Statin	rosuvastatin calcium	Crestor*	0.1	17.3 ± 3.4	None
				0.01	15.6 ± 5.2	
				0.001	13.0 ± 5.9	
17	ARBs	Losartan potassium	Nu-lotan*	0.1	23.5 ± 5.0	None
				0.01	20.9 ± 7.1	
				0.001	17.3 ± 8.9	

No	Group	Chemical compound	Product name	Concentration (mg/ml)	Inhibition rate (%)	IC_{50}
	ARBs			0.1	40.0 ± 1.0	
18		Valsartan	Diovan*	0.01	24.5 ± 3.4	2.28 ± 2.37
				0.001	19.1 ± 5.0	
	ARBs			0.1	14.7 ± 5.5	
19		Candesartan cilexetil	Blopress*	0.01	3.4 ± 5.4	None
				0.001	3.4 ± 5.0	
	ARBs			0.1	10.9 ± 4.5	
20		Telmisartan	Micardis*	0.01	10.7 ± 3.0	None
				0.001	14.8 ± 5.0	
	ARBs			0.1	11.8 ± 4.7	
21		Olmesartan medoxomil	Olmetec*	0.01	-5.7 ± 8.9	>100
				0.001	-7.0 ± 7.8	
	ARBs			0.1	-9.4 ± 7.3	
22		Irbesartan	Avapro*	0.01	-11.8 ± 8.1	None
				0.001	-6.2 ± 10.0	
	ARBs			0.1	-12.4 ± 1.7	
23		Irbesartan	Irbetan*	0.01	20.5 ± 52.5	None
				0.001	-13.6 ± 16.2	
	ACE inhibitor			0.1	-9.3 ± 5.4	
24		Perindopril erbumine	Coversyl*	0.01	-6.9 ± 8.1	None
				0.001	-5.6 ± 7.0	
	ACE inhibitor			0.1	5.2 ± 0.6	
25		Delapril hydrochloride	Adecut*	0.01	-8.0 ± 4.8	None
				0.001	-6.0 ± 6.3	
	ACE inhibitor			0.1	-3.8 ± 5.9	
26		Trandolapril	Preran*	0.01	-7.4 ± 3.9	None
				0.001	-4.8 ± 5.5	
	ACE inhibitor			0.1	-6.5 ± 4.6	
27		Trandolapril	Odric*	0.01	-6.6 ± 5.4	None
				0.001	-3.4 ± 5.1	
	ACE inhibitor			0.1	-3.3 ± 2.5	
28		Captopril	Captoril*	0.01	-8.9 ± 2.9	None
				0.001	-4.3 ± 4.6	
	ACE inhibitor			0.1	-3.9 ± 5.3	
29		Enalapril maleate	Renivace*	0.01	-5.2 ± 5.5	None
				0.001	-7.0 ± 6.0	
	ACE inhibitor			0.1	-1.3 ± 5.8	
30		Lisinopril hydrate	Longes*	0.01	-5.7 ± 4.7	None
				0.001	-2.3 ± 6.3	
	ACE inhibitor			0.1	3.7 ± 4.8	
31		Lisinopril hydrate	Zestril*	0.01	7.5 ± 4.2	None
				0.001	6.2 ± 8.3	
	ACE inhibitor			0.1	13.9 ± 3.0	
32		Benazepril hydrochloride	Cibacen*	0.01	6.0 ± 6.4	None
				0.001	2.3 ± 4.8	
	ACE inhibitor			0.1	7.1 ± 3.7	
33		Imidapril hydrochloride	Tanatril*	0.01	-5.0 ± 14.4	None
				0.001	-3.9 ± 8.3	

Data are expressed as mean ± standard deviation. None, non-dose dependent; AGEs, advanced glycation end products; ARBs, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; IC_{50}, 50% inhibitory concentration expressed in mg/mL.*Samples were prepared from commercially available tablets that were grounded into powder. Aminoguanidine IC_{50} was 0.063 mg/mL in our previous study 9).

association with improved renal function and reactive oxygen species (ROS) inhibition [20] whereas our study was limited to examining the direct inhibitory effect of losartan on in-vitro AGEs generation.

The ARB valsartan also has renoprotective effects, which are independent of blood pressure in type 2 diabetes mellitus patients [16,21]. Valsartan treatment also decreases serum AGEs in type 2 diabetic subjects with hypertension [16] though an unknown mechanism, although the anti-oxidative activity of valsartan may contribute to this response [22]. Consistent with this finding, valsartan exhibited anti-glycation activity in the present HSA assay. The ARB olmesartan was recently reported to inhibit the formation and accumulation of AGEs *in vitro* [10] and in diabetic rat models [12,15]. Valsartan treatment also decreases serum AGEs in type 2 diabetic subjects with hypertension [16] through an unknown mechanism, although the anti-oxidative activity of valsartan may contribute to this response [22].

Statins, which are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, may decrease the formation of AGEs and slow the aging process through several potential mechanisms. Evidence suggests that statins are involved in a positive feedback regulation mechanism between C-reactive protein and the AGE-RAGE axis, reduce the AGE-induced formation of intracellular reactive oxygen species ROS, and due to their cholesterol-lowering effects, increase the level of soluble RAGE by inducing RAGE shedding [23-25]. These findings indicate that statins reduce serum levels of AGEs, lower RAGE expression, and increase soluble RAGE levels by inducing RAGE shedding in diabetic patients [25]. Statins are also reported to play a key role in the treatment of AGE-induced diabetic vasculopathy by blocking RAGE-AGE interaction and inhibiting ROS generation [24]. Our present findings demonstrate that statins (fluvastatin and simvastatin/Lipovas) directly inhibit glycation *in vitro*, and suggest that these compounds may also reduce AGEs formation *in vivo*.

In the present HSA assay results, several differences in the inhibitory rates between pure chemical compounds and the corresponding commercial product were observed. These differences may be attributable to the presence of inactive compounds in the commercial products, which may lower or accelerate the relative activity of the test compound.

The anti-glycation activity results for the ACE inhibitor compounds tested here differ from those reported by Miyata *et al.* [10], who showed that ACE inhibitors reduce the production of AGEs, such as pentosidine and N^{ε}-(carboxymethyl) lysine, and those reported by Forbes *et al.* [11], who found that ACE inhibitors have AGE-binding ability . These differences may be attributable to the experimental conditions of each study, such as the medium used for the assays and the incubation period.

Conclusion

We have shown that ARBs and statins possess anti-glycation activity *in vitro*, suggesting that these anti-hypertensive drugs may have AGEs inhibitory activity and therefore be effective for preventing AGE-related complications in diabetic and cardiovascular patients. However, because the difference in chemical structures and glucose absorbance mechanism of tested compounds, their *in-vivo* effects may differ from the *in-vitro* activities determined using the HSA. Therefore, although promising, caution is needed when interpreting the present results, and further study is necessary to fully understand the action of these compounds *in vivo*.

Conflicts of interest statement

The authors have no conflicts of interest related to this study to declare.

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