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**SPECIAL EDITORIAL
ANNOUNCEMENT**

Distribution and Transfer of Cyclosporine Among the Various Human Lipoprotein Classes

W. Mraz, R. A. Zink, A. Graf, D. Preis, W. D. Illner, W. Land, W. Siebert, and H. Zöttlein

CYCLOSPORINE-A (CsA) is a fungal cyclic oligopeptide with an immunosuppressive action in different animal species as well as in man.¹ Since this molecule exhibits a strong hydrophobicity,^{2,3} it may be supposed that CsA is mainly associated with proteins in blood serum.

In this article, evidence is presented for the exclusive association of CsA with lipoproteins in serum from renal transplant patients. Furthermore, it could be demonstrated *in vitro* that there is an exchange/transfer of CsA among the different serum lipoprotein classes and a transfer of the compound from nonlipoprotein proteins to lipoproteins. The physiologic implications of these findings are discussed.

MATERIALS AND METHODS

Sources of Blood Serum and Plasma

Blood plasma samples for the preparative isolation of lipoproteins were obtained from normolipidemic volunteers (Blood bank, Klinikum Grosshadern, University of Munich). For the CsA distribution studies, blood was obtained from renal transplant patients receiving an oral dose of 12–17 mg/kg of body weight of the drug.⁴ The time interval between administration of CsA and blood sampling was 10 hr, unless otherwise stated. Patients who had fasted 8–15 hr were sampled.

Chemicals

Agar, bovine, and human serum albumin and antisera to apolipoprotein A and B were obtained from Behringwerke (Marburg, F.R.G.); antisera to apolipoproteins A-I, A-II, and B from Immuno Diagnostica (Heidelberg, F.R.G.). Metrizamide was purchased from Nyegaard

(Oslo, Norway); the scintillation solution Pico-Fluor 30 and tritiated water as internal standard was obtained from Packard Instruments (Frankfurt, F.R.G.). All other chemicals were of reagent grade and were obtained from Merck (Darmstadt, F.R.G.).

CsA and ³H-dihydro-CsA were gifts of Dr. R. Voges, and the CsA radioimmunoassay kit was provided by Dr. E. Abisch, both from Pharmaceutical Division, Sandoz Ltd. (Basel, Switzerland).

Analytical Methods

Total cholesterol, triglycerides, and choline-containing phospholipids in serum and ultracentrifugal fractions were determined enzymatically by standard methods,⁵⁻⁸ using an automatic analyzer (Hitachi, model 705). Total protein was measured according to the method of Lowry et al.,⁹ using bovine serum albumin as a standard.

Quantitative determination of the main lipoprotein fractions was performed by measuring their cholesterol contents after separation by semimicro-ultracentrifugation (Airfuge, Inc., Beckman Instruments, Palo Alto, CA) at densities of 1.006 and 1.063 g/ml for very low density lipoprotein (VLDL) and high density lipoprotein (HDL), respectively. Low density lipoprotein (LDL) was calculated from the values of total, VLDL, and HDL cholesterol. The required densities were adjusted according to Havel et al.¹⁰

Agarose-gel electrophoresis¹¹ was used for the qualitative analysis of serum lipoprotein distribution as well as for the establishment of the purity of isolated lipoprotein fractions.

To evaluate the serum protein and serum apolipoprotein distribution after ultracentrifugation, double diffusion analysis in agarose gel¹² was performed with antisera to albumin, apolipoprotein A-I, A-II, and B, and antiserum to total serum protein.

CsA concentrations in total serum and fractions obtained after ultracentrifugation of serum were determined by radioimmunoassay.¹³ The measurement of radioactivity was performed in a LKB-Wallac liquid scintillation counter (model 1210 Ultrabeta) with Pico-Fluor 30 as scintillation liquid. Internal standardization with ³H-H₂O was used for quench correction.

Preparative Isolation of Lipoprotein Density Classes

Lipoproteins were isolated from normal human plasma by sequential preparative ultracentrifugation according to Havel et al.,¹⁰ using a model L5-65B ultracentrifuge with a rotor 60Ti (Beckman Instruments, Fullerton, CA).

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Isolated lipoproteins were dialyzed exhaustively against 0.05 mol/liter Tris/HCl buffer, pH 7.4.

Preparation of ^3H -Dihydro-C_sA-Loaded Serum Proteins and Serum Lipoproteins

^3H -dihydro-C_sA, dissolved in dimethyl sulfoxide (DMSO), was rapidly injected into a vigorously stirred Tris/HCl buffer (0.05 M/liter, pH 7.4) containing the desired protein (albumin, lipoprotein, and total serum proteins). The mixture was subsequently equilibrated for 1 hr at 20–22°C by gentle shaking. The final concentration of DMSO in the protein solution did not exceed 70 $\mu\text{mol/liter}$. The protein and CsA concentrations used are given under Results.

Incubation Conditions for the CsA Exchange/Transfer Experiments

Equal amounts of protein solutions previously loaded with ^3H -dihydro-C_sA and unloaded protein solutions were mixed and incubated under gentle shaking for 1 hr at 20–22°C. Subsequently, aliquots of the incubation mixtures were subjected to rate zonal ultracentrifugation, followed by analysis of ^3H -dihydro-C_sA distribution. Experimental details concerning protein and CsA concentrations are given under Results.

Analytical Separation of the Major Lipoprotein Classes

For the analysis of both the distribution and the exchange/transfer of CsA or ^3H -dihydro-C_sA among the serum lipoproteins and proteins, two different methods were used.

(1) Fractionated precipitation of the major lipoprotein classes was performed according to the method described by Burstein et al.¹⁴ with the following modifications.¹⁵ To the aliquots of serum, sodium phosphotungstate and magnesium chloride were added to give final concentrations of 0.55 g/liter and 0.065 mol/liter, 3.0 g/liter and 0.065 mol/liter, and 40 g/liter and 0.4 mol/liter, resulting in the precipitation of VLDL, VLDL plus LDL, and VLDL plus LDL plus HDL, respectively. The clear infranatants or supernatants obtained after low-speed centrifugation were used to measure the CsA contents.

(2) Separation of the main lipoprotein classes by rate zonal ultracentrifugation was performed analogous to Chapman et al.¹⁶ using an SW 40 Ti swinging bucket rotor (Beckman Instruments). Aliquots of the serum sample were layered on top of, or, after appropriate adjustment of the serum density, on the bottom of a discontinuous gradient. The gradients were formed from solutions of NaCl/KBr, sucrose or Metrizamide, varying in density from 1.006 g/ml to 1.25 g/ml, buffered with 0.005 mol/liter Tris/HCl, pH 8.0. After centrifugation (150,000 g at 4°C for 60 hr), fractions were collected from the bottom of the tubes, and the CsA content was measured.

A detailed description of both procedures will be published elsewhere.¹⁷

RESULTS

Relationship Between CsA Concentration and the Concentrations of Different Blood Constituents in Serum of Patients After Cadaver Kidney Transplantation

Though the lipoprotein patterns of our renal transplant patients showed individual differences, the lipid and lipoprotein composition of each patient remained constant over a period of at least several weeks, as could be shown by different methods (lipid analysis, lipoprotein electrophoresis, and quantitative lipoprotein determination). After administration of a standardized dose of CsA⁴ and using a standardized sampling procedure, no correlation between the serum concentrations of total cholesterol, triglycerides, lipoproteins, or erythrocytes and the levels in serum of the drug could be observed.

Distribution of CsA Among the Different Lipoprotein Fractions of Human Serum

Separation by rate zonal ultracentrifugation of serum from patients receiving CsA revealed a close association of CsA with the different serum lipoprotein density classes—VLDL, LDL, and HDL. When the serum sample, after appropriate adjustment of the density, is layered on the bottom of the density gradient, approximately 30% of the recovered CsA is found to be associated with the non-lipoprotein proteins, whereas 70% is found floating in association with HDL and LDL. In this case, only minute amounts of the drug were associated with VLDL. On the other hand, when the serum specimen is layered on top of the density gradient, the total recovered CsA is associated with the lipoproteins, including VLDL. Analogous results were obtained with gradients formed by potassium bromide, Metrizamide, or sucrose. An example is presented in Fig. 1, (A and B). Using fractionated precipitation for the separation of the different lipoprotein classes, it could be demonstrated that 90%–95% of the recovered

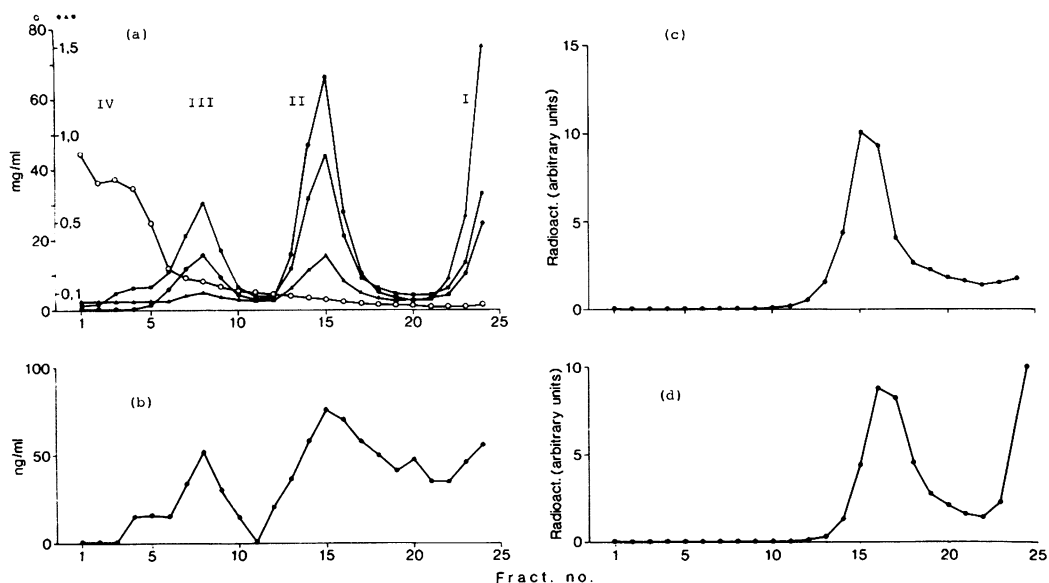


Fig. 1. The in vivo and in vitro distribution of CsA among human serum lipoproteins. Samples (1.0 ml) of total serum or isolated serum lipoproteins were layered on top of preformed gradients, ranging in density from 1.006 to 1.250 g/ml. For adjustment of the densities, NaCl/KBr solutions were used according to Havel et al.,¹⁰ buffered with 0.005 mol/liter Tris/HCL, pH 8.0. After centrifugation (35,000 rpm for 60 hr at 4°C; rotor SW 40 Ti, Beckman Instruments), fractions (0.5 ml) were collected from the bottom of the tubes. (A and B) Distribution pattern of CsA related to the lipoprotein pattern after ultracentrifugation of a patient serum sampled 4 hr after administration of the drug (17 mg/kg body weight). (○) Total protein; (●) total cholesterol; (▲) triglycerides; (■) phospholipids (A) and (●) CsA (B). I = VLDL, II = LDL, III = HDL, and IV = nonlipoprotein protein. (C and D) Distribution pattern of CsA after ultracentrifugation of isolated LDL, previously loaded with ³H-dihydro-CsA, before (C) and after (D) incubation with isolated unloaded VLDL. For further details see Materials and Methods and Table 1.

CsA is associated with the lipoprotein fractions (results not shown).

Transfer/Exchange of ³H-Dihydro-CsA Among Different Lipoprotein Fractions

An exchange/transfer of CsA between different isolated lipoprotein fractions could be demonstrated in vitro after incubation of lipoproteins previously loaded with tritium-labeled CsA and unloaded lipoproteins. Analysis of the distribution of CsA among the lipoprotein classes was performed by measuring the radioactivity after separation of the different density classes by rate zonal ultracentrifugation (see Fig. 1, C and D). All lipoprotein species investigated, that is, VLDL, LDL, and HDL, proved to be donor as well as acceptor lipoproteins. However, using a nonlipoprotein protein (human serum albumin) for the transfer/exchange experiments, only a transfer of ³H-dihydro-CsA to the

lipoproteins could be observed. Some of our results are summarized in Table 1.

DISCUSSION

The results presented in this article clearly show that the hydrophobic oligopeptide CsA is exclusively associated with lipoproteins in human serum, confirming and extending earlier results.¹⁸ Analogous findings were reported recently for different lipophilic drugs^{19,20} and insecticides²¹ and amphiphilic lipids.²²

Using the serum from our renal transplant patients, reflecting the in vivo state, a binding of CsA to lipoproteins could be demonstrated by two different separation methods, rate zonal ultracentrifugation (Fig. 1) and fractionated precipitation. These findings could be confirmed in vitro (A) by selective loading of the lipoproteins with CsA in total serum, and (B) by loading of isolated lipoprotein

Table 1. Transfer/Exchange of ³H-Dihydro-CsA Among the Main Lipoprotein Classes In Vitro

CsA Donor Lipoprotein/Protein Fraction*†	CsA Acceptor Lipoprotein/Protein Fraction*	Distribution of ³ H-Dihydro-CsA After Incubation of Donor and Acceptor Lipoproteins			
		VLDL	LDL	HDL	Albumin (Nonlipoprotein Protein)
VLDL	None	+			
	LDL	+	+		
	HDL	+		+	
	Serum	+	+	+	-
Albumin	None		+‡		-
	VLDL	+			-
	LDL		+		-
	HDL			+	-
	Serum	+	+	+	-

Lipoprotein fractions were isolated, loaded with ³H-dihydro-CsA, and incubated with other lipoprotein fractions as described under Materials and Methods.

*The following concentrations were used: VLDL, 1.0 μmol/liter; LDL, 6.0 μmol/liter; HDL, 3.0 μmol/liter; Albumin 0.55 mmol/liter. The calculation of the lipoprotein concentration was based on the data given in ref. 23.

†Donor fractions contained 500 μg/ml ³H-dihydro-CsA. Specific radioactivity: 1.25 mCi/mg.

‡Radioactivity was recovered in the density range between VLDL and LDL.

fractions with CsA. Moreover, a bidirectional exchange of CsA between isolated lipoprotein fractions (Fig. 1 and Table 1) and a unidirectional transfer of CsA from serum albumin to the different isolated lipoprotein classes could be demonstrated (Table 1). These results suggest a localization of the drug at the surface of the lipoprotein particle.

The question now arises whether there is a similar CsA exchange and/or transfer process between lipoproteins and cell membranes. The elucidation of this physiologically important point may help to understand, at least in part, the immunosuppressive effect on lymphocytes as well as the toxic effect on cells such as hepatocytes.

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