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Influence of prostaglandins on the lipid transfer between human high density and low density lipoproteins

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Prostaglandin (PG) E_1 was demonstrated to stimulate the transfer of phosphatidylcholine and cholesterol esters from human high density lipoproteins (HDL_3) to low density lipoproteins (LDL). The enhancement effect of PGE_1 on the interlipoprotein lipid transfer was seen at low PG concentrations under conditions of spontaneous exchange as well as in the presence of lipoprotein-depleted plasma, or partly purified plasma lipid exchange protein. PGE_2 and $PGF_{2\alpha}$ showed no significant influence on the interlipoprotein lipid transfer. Evidence is presented suggesting that the PGE_1-induced stimulation of interlipoprotein lipid exchange results in enhancement of LCAT-catalyzed cholesterol esterification in plasma. It is proposed that the effect of PGE_1 is due to the previously described PGE_1-induced reorganization of the HDL surface [(1984) FEBS Lett. 173, 291–293] and that PG-lipoprotein interaction may be a factor regulating cholesterol homeostasis.

Prostaglandin; Lipid transfer; Cholesterol esterification; LDL; HDL; (Human)

1. INTRODUCTION

Although PGs appear to play a role in atherosclerosis [1] little is known about their influence on the homeostasis of cholesterol. We have recently discovered that small amounts of PGs can substantially change the surface structure of serum lipoproteins and that these changes appear to be mediated by PG-apoprotein interaction [2]. Lipids, particularly phosphatidylcholine and cholesterol esters, are known to exchange between lipoprotein classes. The exchange which occurs spontaneously and is considerably enhanced in the presence of plasma is thought to play an important role in lipid transfer and metabolism [3].

In human subjects the cholesterol esters of LDL are probably acquired from HDL via transfer involving specific plasma LEPs. A protein which simultaneously facilitates transfer of cholesterol esters and phosphatidylcholine has been detected in human plasma [4]. The purpose of the present work was to investigate whether the alterations of the lipoprotein surface structure brought about by PGs influence the exchange of phosphatidylcholine and cholesterol esters between HDL and LDL. It was found that PGE_1 significantly stimulated spontaneous and protein-mediated lipid transfer from HDL to LDL, whereas PGE_2 was inactive. These differences correlated with the results of our previous study [5], which demonstrated that PGE_1 at low concentration was able to induce a rearrangement of the HDL surface lipids, while PGE_2 was not.

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Abbreviations: PG, prostaglandins; DPPC, dipalmitoylphosphatidylcholine; HDL, high density lipoproteins; LDL, low density lipoproteins; LEP, lipid exchange protein; LDP, lipoprotein-depleted plasma; LCAT, lecithin:cholesterol acyltransferase (EC 2.3.1.43)

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2. MATERIALS AND METHODS

1α,2α-[^{3}H]Cholesterol (43 Ci/mmol) and [*N-methyl*-^{3}H]DPPC (77 Ci/mmol) were purchased from Amersham (England). Protein was determined by the method of Lowry et al. [6] and lipid phosphorus according to Vaskovsky et al. [7].

LDL (1.019 g/ml < d < 1.065 g/ml) and HDL_3 (1.125 g/ml < d < 1.210 g/ml) were isolated from the blood of healthy donors according to [8]. Radioactive cholesterol and DPPC were incorporated into LDL and HDL_3 by coincubation of 5 μl ethanolic solutions of the lipids with 1 ml lipoprotein suspensions for 4 h at 36°C. HDL_3 containing [^{3}H]cholesterol esters were prepared as in [9]. The [^{3}H]cholesterol esters introduced by that procedure into HDL_3 amounted to 97% of the total labeled cholesterol of these lipoproteins.

Partly purified LEP was isolated from the d > 1.21 g/ml infranatant of human plasma by sequential chromatography on phenyl-Sepharose and DEAE-cellulose as described in [10].

Assay of the phosphatidylcholine and cholesterol ester exchange activity was carried out by monitoring the transfer of radioactive lipids from HDL_3 to LDL [10]. After coincubation of the

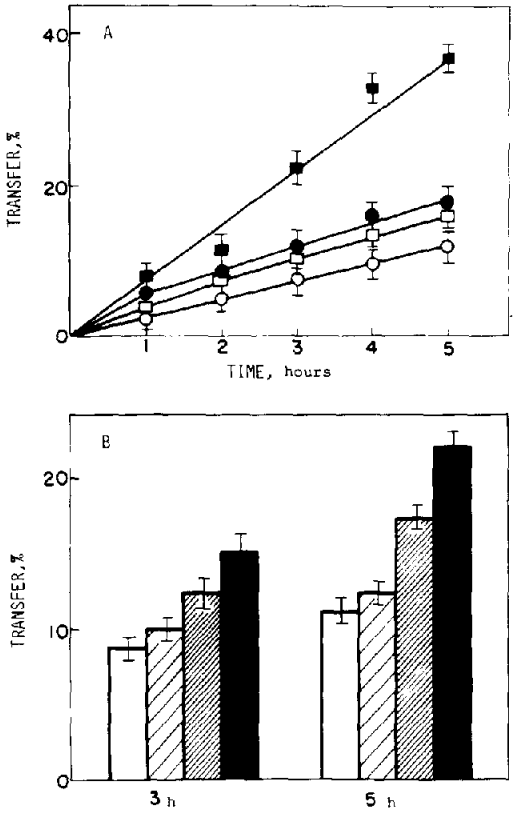

Fig.1. Influence of PGE_1 on the kinetics of lipid transfer from HDL_3 to LDL. (A) Transfer of [^{3}H]DPPC: (○—○) spontaneous transfer; (□—□) transfer in the presence of LEP; (●—●) spontaneous transfer + PGE_1; (■—■) transfer in the presence of LEP and PGE_1. (B) Transfer of cholesterol esters: (▭) spontaneous transfer; (▨) transfer in the presence of LEP; (▨) spontaneous transfer + PGE_1; (■) transfer in the presence of LEP and PGE_1. PG concentration 10^{-8} M. Concentrations of HDL_3 and LDL: 0.3 and 0.6 mg protein/ml, respectively. Samples were incubated at 36°C.

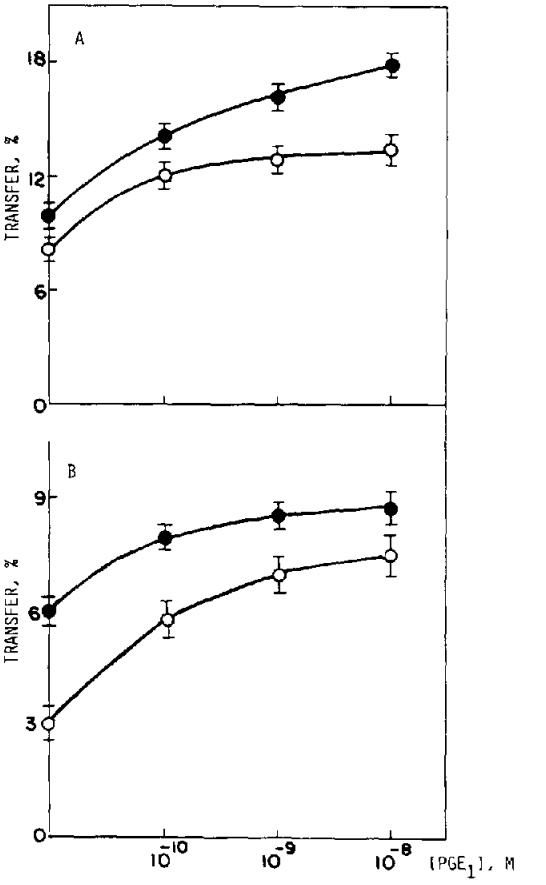

Fig.2. Dependence of rate of HDL_3 to LDL lipid transfer on the PGE_1 concentration in the medium. (A) Transfer of [^{3}H]DPPC. (B) Transfer of the [^{3}H]cholesterol ester. (○—○) Spontaneous transfer; (●—●) transfer in the presence of LEP. Concentrations of HDL_3 and LDL as in fig.1. Samples were incubated for 5 h at 36°C.

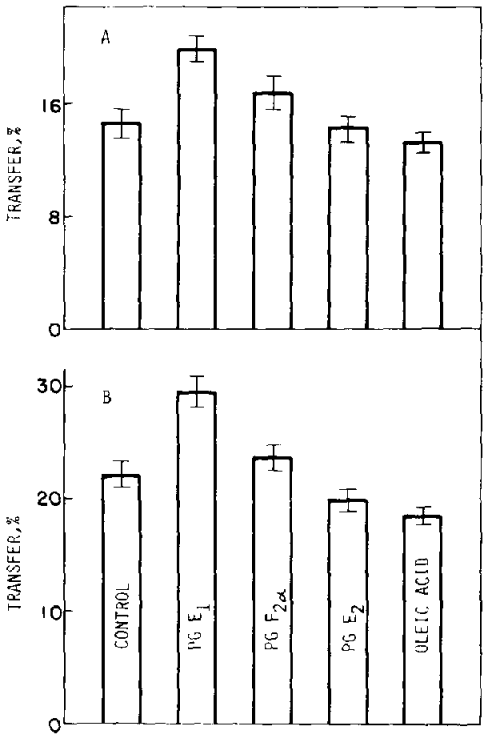

Fig.3. Influence of PGE_1, PGE_2, PGF_2 and oleic acid on the rate of cholesterol ester transfer from HDL_3 to LDL. (A) Spontaneous transfer. (B) Transfer in the presence of LEP. Concentrations of PG and oleic acid: 10^{-8} M. For experimental conditions see figs 1,2.

donor and acceptor lipoprotein the latter was separated from the donor by Mn^{2+} sedimentation in phosphate buffer solution. Under these conditions cosedimentation of HDL_3 did not exceed 6%. This value was taken as 'per cent of transfer at time zero' in fig.1.

Cholesterol esterification assays were carried out by incubation of [^{3}H]cholesterol labeled LDL with LDP and unlabeled HDL_3 as described [11].

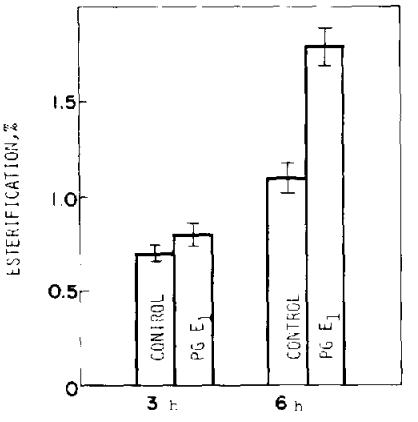

Fig.4. Influence of PGE_1 on the rate of LDL cholesterol esterification in the presence of LDP and unlabeled HDL_3. Concentration of PGE_1 in the medium: 10^{-8} M; 36°C.

3. RESULTS

The time course of [^{3}H]DPPC and [^{3}H]cholesterol ester transfer from HDL_3 to LDL in the absence and presence of PGE_1 is presented in fig.1. At 10^{-8} M PGE_1 the prostaglandin enhanced the spontaneous transfer of [^{3}H]DPPC about 2-fold and considerably facilitated the transfer of cholesterol esters. These effects were markedly augmented in the presence of partly purified LEP.

The lipid-transfer stimulating effect of PGE_1 was concentration-dependent (fig.2). Even at concentrations as low as 10^{-10} M PGE_1 caused more than 50% enhancement of DPPC transfer in both the absence and presence of partly purified plasma LEP.

The influence of PGE_1, PGE_2 and $PGF_{2\alpha}$ on the cholesterol ester transfer from HDL_3 to LDL is shown in fig.3. At 10^{-8} M only PGE_1 was able to enhance the transfer significantly. PGE_2 and oleic

Table 1

Influence of PGE_1 on the cholesterol ester transfer from HDL_3 to LDL in the absence and presence of LDP

	% transfer			
[PGE_1] (M):	0	10^{-10}	10^{-9}	10^{-8}
Spontaneous transfer	2.0 ± 0.1	3.5 ± 0.1	3.7 ± 0.1	5.6 ± 0.2
Transfer in the presence of LDP	2.2 ± 0.1	5.7 ± 0.2	5.9 ± 0.2	6.2 ± 0.2

Concentrations of HDL_3 and LDL were 0.3 and 0.4 mg protein/ml, respectively. Samples were incubated for 3 h at 36°C

acid did not influence the transfer whereas the effect of PGF_2 was not significant.

Table 1 presents data obtained on measuring the influence of PGE_1 on the HDL-LDL cholesterol ester transfer in the presence of LDP. PGE_1 (10^{-8} M) caused an about 200% increase of the transfer and the enhancement effect of the prostaglandin was even higher than in the absence of LDP.

Fig.4 illustrates the influence of PGE_1 on esterification of LDL cholesterol in the presence of LDP and unlabeled HDL_3. Under such conditions, 10^{-8} M PGE_1 caused a 50% increase of cholesterol esterification over 6 h incubation. In the absence of HDL_3 PGE_1 had no effect on the esterification of cholesterol.

4. DISCUSSION

The stimulation of phosphatidylcholine and cholesterol ester transfer from HDL_3 to LDL by PGs depends in a highly specific manner on the structure of the PGs. Among the PGs tested only PGE_1 was able to cause significant enhancement of the lipid transfer. The efficiency of the action of PGE_1 is astonishingly high. Even at 10^{-10} M, PGE_1 increased the transfer of cholesterol ester by about 150% in the absence and about 3-fold in the presence of LDP. Such concentrations correspond to 1 PGE_1 molecule/approx. 10^4 lipoprotein globulae.

The kinetics of spontaneous transfer of phospholipids between lipoproteins are consistent with a mechanism involving a rate-limiting dissociation of monomers from the lipoprotein surface which is then followed by rapid diffusion of the lipid monomer through the aqueous phase [12]. In contrast, kinetic studies of protein-mediated interlipoprotein cholesterol ester transfer suggest that the transfer takes place via formation of a ternary collision complex involving donor and acceptor lipoproteins and the LEP [13]. Since PGE_1 enhances both the spontaneous and protein-mediated transfer in a similar manner, it seems likely that the effect is due to reorganization of the lipoprotein surface by the prostaglandin rather than to interaction of PGE_1 with the LEP. That PGE_1 induces a rearrangement of the HDL surface has been demonstrated previously using fluorescence measurements [5]. The results of that fluorescence study correlate with those of the present work because in both studies PGE_1 was active, whereas the closely related PGE_2 was not. Moreover, the very low PGE_1 concentrations inducing HDL surface rearrangements on the one hand and changing the HDL to LDL lipid transfer rate on the other were approximately equal.

We have previously demonstrated that PGE_1 stimulates cholesterol esterification in whole human plasma [14]. However, esterification experiments carried out with purified LCAT and cholesterol incorporated into lipoproteins, apo-A1 recombinants or HDL_3 did not reveal any effect of the prostaglandin on the cholesterol esterification rate (not shown). This indicated that the PGE_1-induced stimulation of cholesterol esterification in whole plasma [14] might be due to enhancement of the interlipoprotein flux of LCAT substrates and products. To check such a possibility we studied the effect of PGE_1 on the esterification of LDL-cholesterol in LDP in the presence or absence of HDL_3. The results (fig.4) revealed that only in the presence of HDL_3 did PGE_1 cause a considerable increase in cholesterol esterification. Thus, the combined evidence of our studies suggests that the PGE_1-induced rearrangement of the HDL surface may be sufficient to cause an enhancement of interlipoprotein lipid exchange, which in turn facilitates the cholesterol esterification in human plasma by augmenting fluxes of the substrate and product of the LCAT reaction. Since PGE_1 is an anti-atherogenic prostaglandin whereas PGE_2 and PGF_2 are not, the present results suggest further that the influence of PGE_1 on cholesterol homeostasis may be mediated by interaction of the prostaglandin with lipoproteins. This possibility is currently being examined in our laboratory.

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