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Binding of HDL to basolateral membranes of the renal cortex. Evidence for two components in the HDL-membrane association

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Abstract

The binding of porcine ^{125}I-HDL to purified basolateral membrane fractions isolated from pig kidney cortex displays two categories of sites, one with high affinity ($(K_d = (3.0 \pm 0.7) \cdot 10^{-9}$ M) and low capacity ($B_{max} = 52 \pm 32$ ng/mg proteins) another with low affinity ($K_d = (5.3 \pm 0.7) \cdot 10^{-8}$ M) but a higher capacity ($B_{max} = 795 \pm 115$ ng/mg proteins). Binding was competitively inhibited to the same extent by unlabeled HDL from swine, human or rat, demonstrating an absence of species specificity. Porcine LDL partially competed for binding even in the presence of 30 mM EDTA which prevents apo B/E specific binding. Membrane proteins solubilized with CHAPS were analyzed by electrophoresis followed by ligand blotting using porcine ^{125}I-HDL and ^{125}I-apoAI-HDL to show that HDL bound to two proteins of respective molecular masses 120 ± 2 and 95 ± 9 kDa. ^{125}I-apoAI associated mostly with the 95 kDa protein. A 100-fold excess of unlabeled HDL greatly decreased binding to the 95 kDa protein but less to the 120 kDa protein. We conclude that part of HDL binding occurs through the lipid moiety, while another is the result of a specific interaction between apoAI and a membrane protein of 95 kDa.

Key words: HDL; HDL binding; Basolateral membrane; Binding site; Apolipoprotein A-I; (Kidney)

1. Introduction

The renal metabolism of HDL is far from elucidated. During glomerular filtration and uptake by renal tubules, lipoproteins are altered through proteolytic and lipolytic processes. Alterations in the renal function are frequently associated with abnormalities in the composition of plasma lipoproteins and with accelerated atherogenesis. The HDL fraction is particularly affected, featuring a decrease in cholesterol and in the apoAI content of the HDL_2 fraction, together with an increase in HDL_3 [1]. In the nephrotic rat, HDL are 3-fold elevated, depleted with esterified cholesterol and enriched with phospholipids [2]. In contrast with other organs such as liver and steroidogenic tissues where cholesterol ester is taken up preferentially to apoAI, kidney is a site of preferential uptake and degradation of apoAI [3–6]. A specific saturable binding of HDL to rat kidney membrane has been described [7,8] and a human HDL binding protein has been evidenced [9]. There is therefore convergent evidence in favor of the presence of a HDL receptor in the kidney. Moreover, on the basis of in vivo and in vitro evidence obtained in the rat, it has been claimed that receptor sites presented a degree of species specificity [7,8].

In this work we have explored the mechanisms of HDL association with renal cell membranes. The proximal tubule is the major site for reabsorption of filtered protein. While HDL could be first filtered then undergo endocytosis at the brush border pole of tubular cells, a specific binding site is more likely to be located on the basolateral membrane through which HDL could be taken up directely from the circulation. We have evidenced an interaction of HDL with the basolateral membranes of the tubular zone and sought to identify protein binding sites, using a homologous system of porcine HDL and porcine kidney basolateral membranes. We suggest that a 95 kDa membrane protein is

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Abbreviations: HDL, high-density lipoprotein; LDL, low density lipoprotein; PMSF, phenylmethylsulphonyl fluoride; CHAPS, 3-((3-cholamidopropyl)dimethylammonio)-1-propanesulfonic acid; apo, apolipoprotein.

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responsible for the specific binding of HDL through an interaction with apoAI, but that a non specific interaction also occurs between the lipid moiety of the particle and the lipids of the membrane.

2. Materials and methods

Bovine serum albumin (BSA) fatty acid free, CHAPS, PMSF, proteinase inhibitors were from Sigma (St. Louis, MO). Iodine-125 (spec. act. 13.0 mCi/μg iodine) and [^{32}P]ATP (10 Ci/mmol) were purchased from Amersham France. Percoll was from Pharmacia.

Sephadex G 200, nitrocellulose and all electrophoresis chemicals were obtained from Bio-Rad (Rockville Centre, NY).

2.1. Lipoprotein preparations

Porcine HDL and LDL (HDL_p and LDL_p), human HDL and LDL (HDL_h and LDL_h), as well as rat HDL (HDL_r) were isolated by sequential ultracentrifugation from fasting serum added with 1 mg/ml EDTA and 0.1 mg/ml NaN_3.

Rat HDL containing various amounts of apo E, and pig LDL containing various amounts of apoAI, were obtained as selected fractions of total lipoproteins (d < 1.21 g/ml) separated on KBr gradients (d = 1.006 to 1.21 g/ml) at 36000 rpm for 24 h in a SW41 rotor. ApoAI was isolated from delipidated HDL_p by gel filtration on Sephadex G 200.

Apoprotein composition of the various HDL was appreciated by densitometric scanning at 590 nm of 12% polyacrylamide 1% SDS electrophoretic gels stained with Coomassie blue.

Total cholesterol was assayed enzymatically using Boehringer kits (Meylan, France). Protein content was determined by Peterson's method [10] using bovine serum albumin as standard. A summary of the main characteristics of the lipoprotein fractions utilized is given in Table 1.

apoAI and HDL_p were labeled with ^{125}I by the iodine monochloride procedure [11]. Final specific activity was on the order of 250 cpm/ng protein. Less than 3% of the label was extractable with organic solvents and less than 1% was recovered in the TCA-soluble fraction. When specified, HDL was also labeled by exchange with ^{125}I-apoI according to Shepherd [12] in order to avoid labelling of other apoproteins.

2.2. Membrane preparations

Purified basolateral membranes were isolated from pig kidney cortex using the procedure described by Boumendil-Podevin [13]. Briefly, crude membrane fractions were centrifuged in a Percoll gradient, the basolateral fraction was isolated as the uppermost band at d = 1.037 g/ml. The vesicles obtained by this procedure are sealed and mostly (90%) oriented right-side out [13]. Purification was assessed by measure of ouabain sensitive Na^+/K^+-ATPase activity using [^{32}P]ATP in tracer amounts, with or without 1 mM ouabain [13]. As a rule, preparations were enriched 15-fold.

2.3. Binding of labeled lipoproteins to isolated membranes

Binding to membranes

Saturation studies. The binding characteristics of pig ^{125}I-HDL to isolated pig basolateral membranes were determined according to the procedure described by Chacko [14]. Briefly aliquots of membranes (100 μg

Table 1
Composition of the lipoproteins utlized in competitive binding studies

	Cholesterol/ protein ratio	Apoproteins % [a]					
		B	AIV	E	AI	AII	C
Total pig LDL d = 1.025–1.070 g/ml	1.4	94	–	–	5	–	1
Low apoAI pig LDL d = 1.025–1.046 g/ml	1.9	96	–	–	0	–	4
Human LDL d = 1.024–1.060 g/ml	1.33	96.7	–	1.2	0	–	2.1
Pig HDL d = 1.070–1.21 g/ml	0.39	–	8	–	82	3	7
Human HDL d = 1.060–1.21 g/ml	0.36	–	2	3	57	27	11
Total rat HDL d = 1.046–1.21 g/ml	0.47	–	13	9	59	7	12
Low apo E rat HDL d = 1.105–1.150 g/ml	0.30	–	14	0	76	2	8

[a] Evaluated by densitometric scanning of SDS-PAGE gels.

protein) were incubated at 20°C for 1 h with the indicated concentrations of labeled lipoprotein in 0.150 M NaCl, 0.5 mM $CaCl_2$, 10 mM Tris-HCl (pH 7.4) and 1% bovine serum albumin, total volume 0.2 ml. After incubation, 0.175 ml aliquots were centrifuged in a Beckman 42.2 Ti rotor at 38000 rpm for 30 min to recover the membranes. The membrane pellets were washed twice with 0.175 ml cold incubation medium and radioactivity was counted in a gamma spectrophotometer. Non specific binding was determined in the presence of a 100-fold excess of the corresponding unlabeled lipoprotein. Specific binding was calculated as the difference between ^{125}I-HDL bound to the membranes in the absence or presence of excess unlabeled lipoprotein.

Binding parameters were determined using the Ligand-PC program [15]. The two sites model was validated by the extra sum of squares F-test.

Kinetic studies. Association kinetics were characterized at 4°C, 20°C and 37°C using 1.5 μg/ml of ^{125}I-HDL with 0.5 mg/ml of membranes during various times ranging from 5′ to 4 h.

For dissociation kinetics the same proportions of HDL and membranes as for association kinetics were incubated during 4 h at 20°C. The incubation medium was then diluted 100-fold, and after incubation periods ranging from 5 to 120 min the tubes were refrigerated in ice and centrifuged at 100000 × g for 30 min at 4°C to pellet membranes. After washing the pellet and centrifuging, membranes were transfered to counting tubes.

Analysis of $t_{1/2}$ dissociation and $t_{1/2}$ association was achieved using the graph PAD program (H.J. Motulsky, 1987) and K_d calculated.

Competition

Competition studies were performed at 20°C in the presence of 100 μg membrane proteins, 10 μg ^{125}I-HDL protein per ml and the indicated concentrations of the various unlabeled lipoprotein fractions. We verified that competition was the same whether performed at 0°C or 20°C.

2.4. Membrane solubilization and ligand blotting

Crude membranes from kidney cortex or adrenal cortex [9] were solubilized in 30 mM CHAPS, at 4°C, during 16 h, in the presence of proteinase inhibitors: soybean trypsin inhibitor 2 p.100, lima bean trypsin inhibitor 2 p.100, polybrene 2.5 p.100, benzamidine 0.031 p.100. The solubilized proteins were collected in the supernatant after ultracentrifugation at 150000 × g for 1 h.

Ligand blotting

Solubilized protein samples (~ 350 μg) in SDS 1% were heat-denaturated at 100°C for 3 min, prior to electrophoresis in a 7% SDS-polyacrylamide slab gel along with molecular weight markers. Transfer to nitrocellulose was performed under 150 V for 3 h. For ligand detection, nitrocellulose strips were incubated in quenching buffer (20 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1% BSA, 1% low fat dry milk), for 1 h at room temperature. Binding of ^{125}I-HDL, ^{125}I-apoAI-HDL or ^{125}I-apoAI ($2 \cdot 10^6$ cpm/ml) was carried out in the same buffer in the presence or absence of a 100-fold excess of unlabeled HDL, apoAI or LDL. After 1 h at room temperature, the nitrocellulose was rinsed with ice-cold quenching buffer followed by six washes with

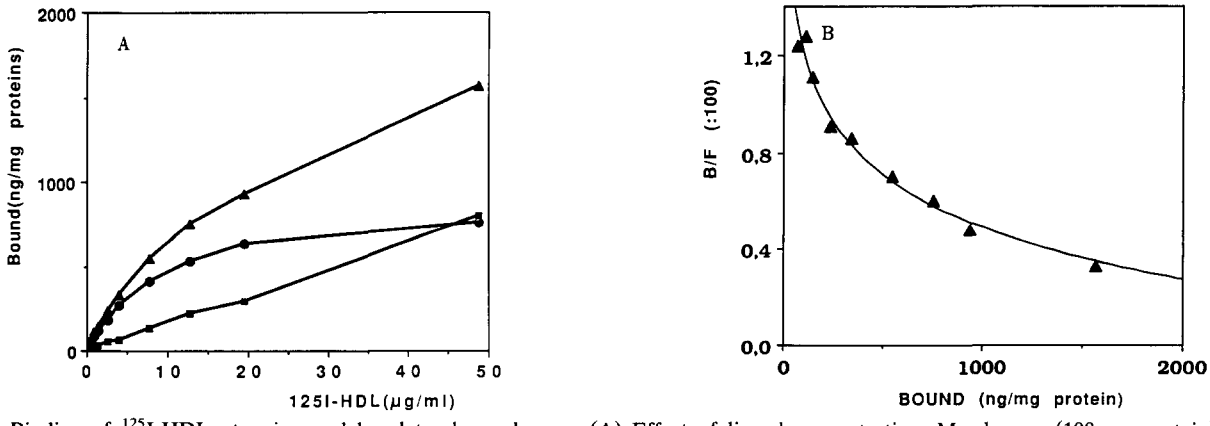

Fig. 1. Binding of ^{125}I-HDL_p to pig renal basolateral membranes. (A) Effect of ligand concentration. Membranes (100 μg protein) were incubated with the indicated concentrations of ^{125}I-HDL_p in 0.2 ml of 0.15 M NaCl/0.5 mM $CaCl_2$, 10 mM Tris-HCl (pH 7.4) for 1 h at 20°C in the absence (▲) or presence (■) of a 100-fold excess of unlabeled HDL_p. Specific binding (●) was obtained by substraction. Data are from one representative experiment out of four. (B) Scatchard transformation of the total binding curve.

Table 2
Binding of ^{125}I-HDL$_p$ to kidney basolateral membranes

	K_d (M)	B_{max} (ng/mg protein)
One category of sites ($n = 3$)	$(4.7 \pm 1.6) \cdot 10^{-8}$	745 ± 200
Two categories of sites		
High affinity ($n = 3$)	$(3.0 \pm 0.7) \cdot 10^{-9}$	52 ± 32
Low affinity ($n = 3$)	$(5.3 \pm 0.7) \cdot 10^{-8}$	795 ± 115

the same buffer for 5 min each. The blots were then dried, autoradiographed and scanned (Shimazu).

3. Results

3.1. Binding to basolateral membranes

Saturation binding

Binding of ^{125}I-HDL$_p$ measured after 60 min incubation at 20°C was saturable: $K_d = (4.7 \pm 1.6) \cdot 10^{-8}$ M $B_{max} = 745 \pm 200$ ng/mg protein. The consistent existence of an inflexion in the total and specific binding curves for 3 to 5 μg HDL protein (Fig. 1A) suggested the existence of two categories of binding sites. Analysis by Ligand program and statistical F-test fit the data to a two-site model significantly better than a single-site model ($P < 0.05$) (Fig. 1B). The calculated binding parameters for three separate experiments are presented in Table 2; the high affinity sites had a very low capacity and the low affinity sites a 15-fold higher capacity.

Association and dissociation kinetics

The kinetics of association of ^{125}I-HDL$_p$ with kidney membranes at 0°C, 20°C and 37°C are illustrated in Fig. 2 showing them to be temperature-dependent. At 20°C, maximum binding was reached after 3 h, but more than 80% of maximum was reached after 1 h. Closer time sequences of association evidenced a fast component ($t_{1/2}$: 7 to 10 min) during which 67% of total radioactivity was bound and a slower component for the remainder (Fig. 3).

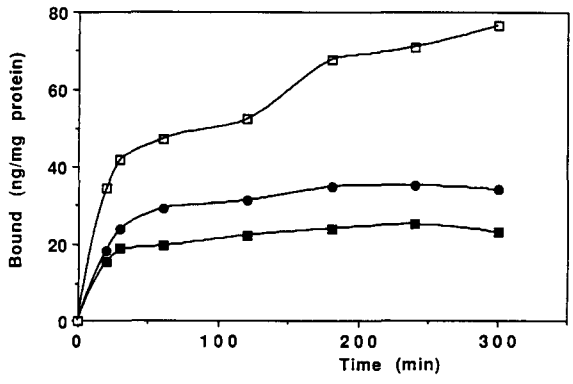

Fig. 2. Association kinetics of ^{125}I-HDL$_p$ binding to pig renal basolateral membranes at 0°C (■), 20°C (●) and 37°C (□) 1.5 μg/ml of ^{125}I-HDL$_p$ incubated with 0.5 mg/ml of membranes.

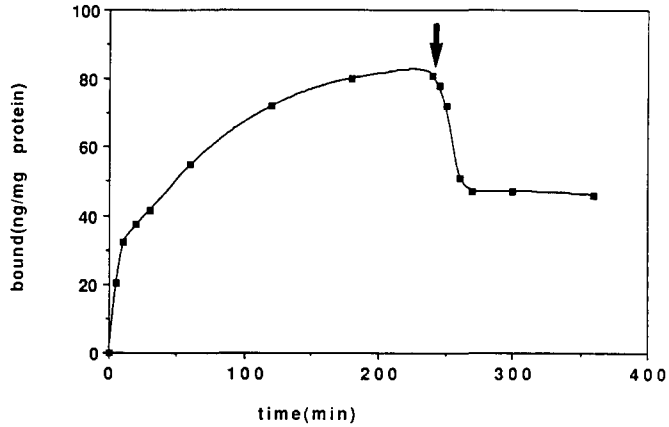

Fig. 3. Association and dissociation kinetics of ^{125}I-HDL$_p$ binding to pig renal basolateral membranes at 20°C. 1.5 μg/ml of ^{125}I-HDL$_p$ was incubated with 0.5 mg/ml membranes for 4 h. Dissociation was initiated by 100-fold dilution of the incubation medium.

Dissociation kinetics were similary characterized by a rapid rate of dissociation and a second mainly irreversible component (Fig. 3). The dissociation constant (K_d) calculated from association and dissociation kinetic data was determined in two separate experiments to be respectively $6.7 \cdot 10^{-9}$ M and $5.3 \cdot 10^{-9}$ M for the fast component (Table 3). These values are on the same order of magnitude as the K_d determined by saturation binding studies for high affinity binding site. We conclude that the high affinity binding follows the laws of mass-action and corresponds to an HDL specific membrane receptor site.

Absence of species specificity of HDL binding

In the homologous competition experiments nonlabeled porcine HDL were used. They competed for the binding of ^{125}I-HDL$_p$ to the extent of 72%. ^{125}I-HDL$_p$ was displaced to about the same extent (Fig. 4) by human HDL$_3$ (< 3% apo E), by rat HDL with (8%) or without apo E (< 2%) obtained by gradient ultracentrifugation. We conclude that there is no species specificity to total HDL membrane binding.

Table 3
Kinetics rate constants for the interaction of ^{125}I-HDL with kidney basolateral membranes of 20°C

		Association k_{obs} (M)	Dissociation k_{-1} (M)	K_d (10^{-9} M)
Exp. 1	fast	$1.9 \cdot 10^{-3}$	$0.77 \cdot 10^{-3}$	5.3
Exp. 2	fast	$1.54 \cdot 10^{-3}$	$0.88 \cdot 10^{-3}$	6.7
	slow	$6.41 \cdot 10^{-5}$		

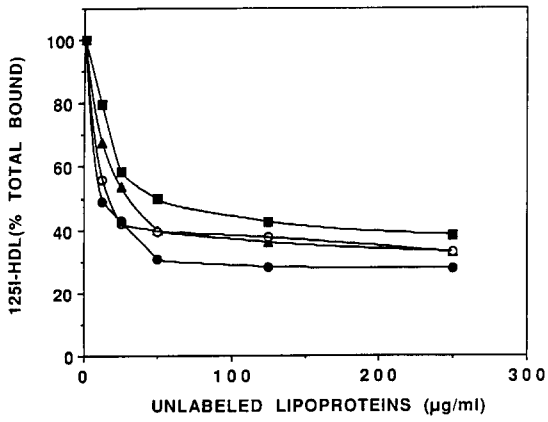

Fig. 4. Competition by different HDL. Each tube contained 100 µg membrane protein, 15 µg/ml ^{125}I-labeled HDL_p and the indicated concentrations of either HDL_p (▲), HDL_h (■), apo E-free HDL_r (●), 8% apo E-HDL_r (○). The data are average from seven experiments (HDL_p) or two experiments (other HDL) each in triplicate.

Competition for binding sites by other lipoproteins

LDL_p partly displaced ^{125}I-HDL from its binding sites (50%) (Fig. 5). Since pig LDL contains a small amount of apoAI ranging from 0% to 6% according to preparations (Table 1), the displacement of bound HDL was tested with LDL_p containing various proportions of apoAI and with LDL_h which is devoid of apoAI. The capacity of LDL for competition was unaffected by its apoAI content (Fig. 5).

It could not be excluded either that the displacement of ^{125}I-HDL by unbound LDL was due to the trapping of HDL by LDL. We therefore followed the distribution of HDL label in the medium after incubation of membranes in the presence of increasing concentrations of LDL. After sedimentation of the membranes together with the bound ^{125}I-HDL, the density of the supernatant, containing the unbound lipoproteins, was adjusted to 1.063 g/ml with KBr and the

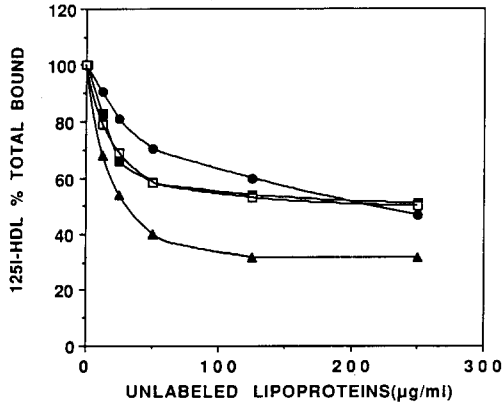

Fig. 5. Competition by different LDL. Each tube contained 100 µg membrane protein, 15 µg/ml ^{125}I-labeled HDL_p and the indicated concentrations of either HDL_p (▲) LDL_p with 5% apoAI (□), LDL_p without apoAI (■), LDL_h (●). The data are average from seven experiments (HDL_p, LDL_p with apoAI) or two experiments (other LDL) all in triplicate.

distribution of both cholesterol and label were examined after 24 h at 45 000 rpm. Cholesterol contents of the $d > 1.063$ g/ml fraction remained constant, corresponding to HDL-cholesterol, while all the added LDL-cholesterol was, as expected, recovered in the $d < 1.063$ g/ml fraction. A small portion of the label (< 5%) was found in the LDL fraction, remaining constant up to LDL concentrations of 75 µg/ml. At higher concentrations, trapping occurred, and up to 20% of the HDL label was in the LDL density range. Thus, the displacement of ^{125}I-HDL by LDL could not be accounted for by trapping at LDL concentrations inferior to 75 µg/ml, while displacement obtained with higher LDL concentrations was probably overestimated.

In order to determine whether the apo B/E receptor was involved in the effect of LDL on ^{125}I-HDL binding, the experiments were repeated in the presence of EDTA 30 mM which inhibits Ca^{2+} dependent LDL binding [16] but has no effect on HDL binding [17]. EDTA did not prevent the displacement of ^{125}I-HDL by LDL. Thus, LDL do not act by masking the HDL receptor sites in their interaction with their own receptor.

LDL affinity, graphically determined as the concentration displacing 50% of bound ^{125}I-HDL in five separate experiments, was $8.0 \cdot 10^{-8}$ M, a value in the same order as K_d for the lower affinity sites.

HDL competitive binding in the presence of LDL

The existence of a strictly HDL-specific binding was explored by following HDL displacement in the presence of LDL_p. After binding of ^{125}I-HDL_p, maximal displacement was first obtained with LDL; unlabeled HDL_p was then added and was found to further displace 15% of initially bound ^{125}I-HDL_p (Fig. 6). The difference between displacement by LDL alone and by HDL + LDL represents specific HDL binding.

3.2. Binding to solubilized membrane proteins

Ligand blot analysis of solubilized membrane proteins from kidney with ^{125}I-HDL_p revealed two protein bands with respective apparent molecular masses of 95 ± 9 kDa and 120 ± 2 kDa (Fig. 7, lane A). In competitive binding studies a 100-fold excess of unlabeled HDL_p inhibited binding to the 95 kDa protein but not at all or only slightly to the 120 kDa protein (Fig. 7, lane B). In direct binding experiments, ^{125}I-apoAI or ^{125}I-apoAI HDL were found to bind mainly to the 95 kDa protein (Fig. 7, lane C). Finally, a 100-fold excess of LDL_p did not compete with binding to either the 95 or 120 kDa proteins. The 95 kDa protein therefore appears to be the specific binding protein of HDL and apoAI. By way of comparison, ^{125}I-HDL_p is shown to bind to solubilized adrenal membrane through a 65 kDa protein (Fig. 7, lane D).

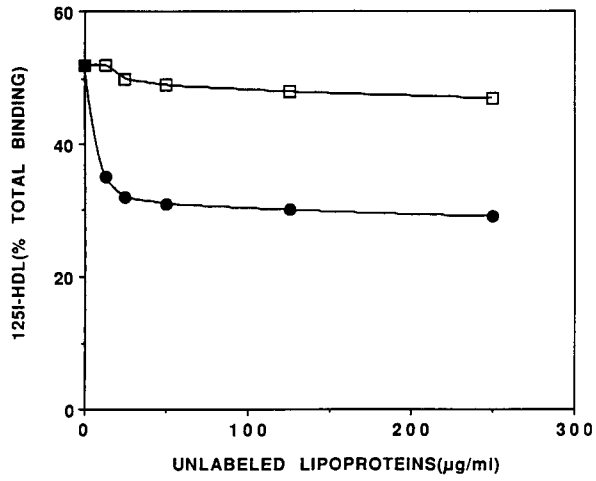

Fig. 6. Competition by HDL_p in the presence of excess LDL. Each tube contained 100 μg membrane protein, 15 μg/ml ^{125}I-HDL_p, 250 μg/ml LDL and the indicated concentrations of either HDL_p (●), or LDL_p (□). The data are the average of two experiments in triplicate.

The ligand blot experiments were performed using crude renal cortical membrane preparations. The use of purified basolateral membranes did not increase the relative amount of binding suggesting that the binding proteins are present within the cell as well on the surface as it seems to be the case in adipose cells [18] and BHK [19].

4. Discussion

The nature of HDL particle interaction with cell membranes had been often questioned [20,21]. HDL may be thought to bind to membranes (1) according to a ligand-receptor model through the interaction of apoproteins AI and/or AII or AIV with a specific membrane protein; (2) through non specific lipid-lipid or lipid protein interactions, apoAI affinity for phospholipids being a well documented fact [22].

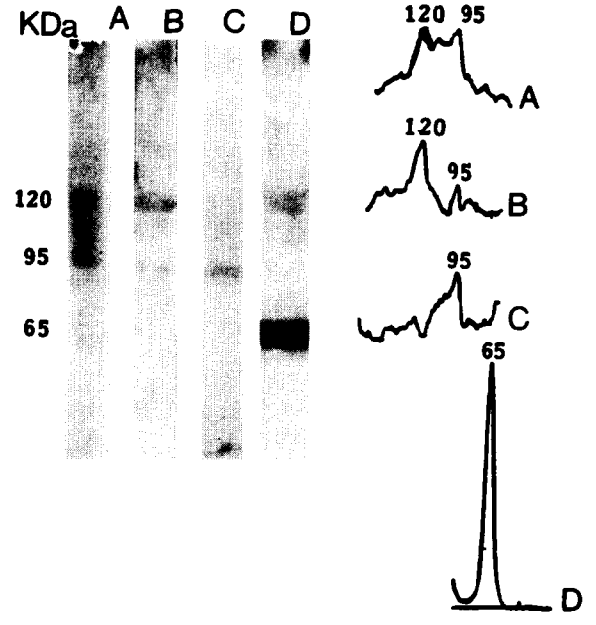

Fig. 7. Ligand blot of solubilized renal cortex membranes with ^{125}I-HDL_p (lane A), ^{125}I-HDL_p in presence of 100-fold unlabeled HDL_p (lane B), ^{125}I-$apoAI_p$ (lane C) and of adrenal cortex membranes with ^{125}I-HDL (lane D).

The use of very small concentrations of labeled HDL (as low as 0.30 μg/ml) has allowed us to evidence in basolateral membranes of pig renal cortex a high affinity binding site ($K_d = 3 \cdot 10^{-9}$ M) corresponding to a limited number of sites endowed with a high degree of specificity towards apoAI; quantitatively, the major part of HDL binds to a category of sites with lower affinity ($K_d = 5.3 \cdot 10^{-8}$ M) with a 15-fold higher B_{max}. Association and dissociation kinetics confirmed the characteristics of these high affinity sites.

The binding characteristics for rat kidney membranes have been established on the basis of a single type of site and correspond to an even lower affinity (K_d $1.4 \cdot 10^{-7}$ M) and an equivalent number of sites (B_{max} 551 ng/mg) as the low affinity site we evidenced in porcine membranes. However, using competition studies we elicited no evidence of the species specificity described in the rat in vivo [4] or in isolated renal membranes towards human HDL [8]. Human HDL_3 (with less than 3% apo E) and rat HDL preparations varying in apo E contents were found to compete to the same extent with HDL_p for binding. It is however possible that the in vivo competition is due to the high affinity receptor which was not specifically considered in the overall competition experiments reported here.

While this work was under progress, the existence of two sites on rat liver plasma membranes, was reported, both of them interacting with human HDL_3, one having a high affinity ($K_d \simeq 5 \cdot 10^{-9}$ M) and low capacity and the other a lower affinity ($K_d = 1.8 \cdot 10^{-7}$ M) but a higher capacity [23]. These binding characteristics are very similar to those we evidenced in kidney. Anterior studies had detected in various cells and tissues a single site with a lower affinity (K_d on the order of 10^{-8} M). It is likely that high affinity binding sites were not detected because the minimal concentrations of HDL used were not low enough. The high affinity sites bind to the carboxy-terminal of apoAI and require an intact molecule [24]. It may be that, in older studies, insufficient attention was paid to the integrity of apoAI.

A partial competition of LDL with HDL for binding was evidenced in membranes. Although not always emphasized, the same phenomenon has been evidenced in isolated rat enterocytes [25], human adipose cells [26] and cultured hepatocytes [27,28]. LDL affinity for HDL binding sites was in the same order as the K_d for the lower affinity HDL sites. In addition, in the presence of maximum concentrations of LDL, unlabeled HDL were still able to displace a further 15% of the ^{125}I-HDL bound to the whole membranes, an

amount compatible with the capacity of the high affinity site. Finally, LDL bound to whole membranes only and not to the protein in the ligand blot experiments. This suggests that their binding was to the low affinity site and corresponded to a lipid interaction. In organs such as the liver and kidney which actively internalize apoAI, it can be speculated that the high affinity, apoAI-requiring component plays an important role. Whether the low affinity, low specificity component is of physiological relevance remains be explored.

Two membranes proteins with apparent molecular masses of 120 kDa and 95 kDa were found to bind HDL in ligand blotting experiments. Apparently, HDL bound to the 95 kDa with more affinity than to the 120 kDa protein, but autoradiographic signals were always lower than those detected using a same amount of adrenal membrane proteins. There is no evidence at present that the two proteins separated by electrophoresis are derived from one another. In adipocytes the binding protein has a molecular mass of 92 or 80 kDa according to whether it is glycosylated or not [18]. In our hands, howewer, treatment by glycopeptidase F was without effect on the molecular mass of the two renal HDL-binding proteins (results non shown). The fact that the 95 kDa protein is the only one to specifically bind apoAI is an indication that it may be responsible for the high affinity, high specificity HDL binding. Other HDL binding proteins have been evidenced with the same method of ligand blotting in several tissues and cells with a molecular mass ranging from 60 to 130 kDa [29–36]. In some types of cells, expression of binding proteins is upregulated when cells become loaded with cholesterol [30–34] but a relation with physiological functions was not evidenced. The precise function of the 95 kDa binding protein in kidney and its involvement in apoAI metabolism, deserve physiological studies on appropriate cells.

In conclusion, saturation binding and ligand blot studies suggest that the binding of HDL to renal basolateral membranes is the result partly of an high affinity but low capacity interaction between apoAI and membrane proteins of 95 kDa and partly of an interaction between the lipids of the particle and components of the membrane having a lower affinity but higher capacity. It remains to be specified whether in the kidney, the two kinds of association are necessary for apoAI catabolism.

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