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Original Article

Enhanced gene expression of scavenger receptor in peripheral blood monocytes from patients on cuprophane haemodialysis

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Abstract

Background. Macrophage scavenger receptor (SR) is implicated in playing a key role in macrophage-derived foam cell formation by taking up a large amount of modified low-density lipoproteins (LDL). It has also been postulated that α_2-macroglobulin receptor/LDL receptor-related protein (α_2MG/LRP) is involved in the development of foam cells by taking up apo E-enriched chylomicrons and VLDL remnants, and lipoprotein lipase-triglyceride-rich lipoprotein complexes. Accumulation of these lipid-loaded monocyte/macrophages in the subendothelial space is considered to be an early event of atherogenesis. Since atherogenesis is considered to be accelerated in dialysis patients, we attempted to investigate whether gene expression of SR and α_2MG/LRP are altered in peripheral blood monocytes from patients on haemodialysis with a cuprophane (Cu) or polymethylmethacrylate (PMMA) membranes.

Methods. Peripheral blood monocytes (PBM) were prepared from patients undergoing haemodialysis with a Cu membrane ($n=9$), patients undergoing haemodialysis with a PMMA membrane ($n=9$), and healthy controls ($n=7$). In a separate experiment we examined SR gene expression in uraemic patients ($n=12$) and healthy controls ($n=9$). SR and α_2MG/LRP mRNA were semiquantitated using reverse-transcription polymerase chain reaction (RT-PCR) assay followed by Southern blotting.

Results. SR mRNA expression in PBM from patients on chronic haemodialysis with a Cu membrane was about twofold higher than that in PBM from patients on chronic haemodialysis with a PMMA membrane or the controls ($P<0.05$). α_2MG/LRP mRNA expression in PBM showed no difference among these three groups. SR gene expression in monocytes from uraemic patients was not increased compared with that in the controls.

Conclusion. PBM from patients under Cu membrane dialysis showed higher gene expression of SR than patients under PMMA membrane dialysis, uraemic patients, or healthy controls. This increased gene expression of SR in monocytes may be associated with the pathogenesis of accelerated atherosclerosis in patients on dialysis with a Cu membrane.

Key words: α_2-macroglobulin receptor/LDL receptor related protein; cuprophane membrane; haemodialysis; polymethylmethacrylate membrane; scavenger receptor.

Introduction

Haemodialysis patients have a high incidence of vascular complications caused by accelerated atherosclerosis, leading to coronary, cerebral, and vascular diseases [1]. The dialysed patient is exposed to a number of classical risk factors of atherogenesis, particularly dyslipidaemia and hypertension [2]. Dyslipidaemia is characterized by hypertriglyceridaemia and low high-density lipoprotein (HDL) cholesterol, with a low HDL : total cholesterol ratio [3]. High levels of chylomicron remnant concentrations [4] and lipoprotein(a) [5] have also been reported in haemodialysis patients.

Recently it has been postulated that lipid peroxidation and particularly the oxidatively modified low-density lipoproteins (OxLDL) are important factors in the development of atherosclerosis [2,6]. Oxidative modifications of LDL generate molecular epitopes that provide chemotactic stimuli for monocyte recruitment and stimulate intimal monocytes to differentiate into resident macrophages. OxLDLs are more avidly taken up by macrophages, thus forming foam cells, which is a process regarded as a key step in the development of the atherosclerotic lesion [6].

There is evidence that oxidative stress may be increased in patients on haemodialysis. Increased serum levels of lipid peroxidation products [7] and the presence of autoantibodies against oxLDL [8] in patients undergoing haemodialysis have been reported. A recent study has shown an increased susceptibility to the oxidation of LDL isolated from patients with

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chronic renal failure treated by haemodialysis or continuous ambulatory peritoneal dialysis [9].

The macrophage scavenger receptor (SR), a trimeric membrane glycoprotein, is implicated in playing a key role in macrophage-derived foam cell formation by taking up a large amount of modified LDL [6,10]. α_2-Macroglobulin receptor/LDL receptor related protein (α_2MG/LRP) is also thought to be involved in the development of foam cells by taking up apo E-enriched chylomicrons and VLDL remnants, lipoprotein lipase (LPL), and LPL-triglyceride-rich lipoprotein complexes [11]. Accumulation of these lipid-loaded foam cells in the subendothelial space is thought to be important in the initiation of atherosclerosis.

Very recently enhanced SR expression in cultured monocyte–macrophages obtained from dialysis patients has been reported [12]. We attempted to investigate whether gene expression of SR and α_2MG/LRP are altered in peripheral blood monocytes (PBM) soon after the blood was collected from patients on haemodialysis. Moreover, we examined whether a different dialysis membrane, such as a cuprophane membrane, has a different effect on SR gene expression in PBM compared with the effect of a polymethylmethacrylate membrane.

Subjects and methods

Patients and controls

Gene expression of SR and α_2MG/LRP in PBM was investigated in nine chronic patients on haemodialysis with a cuprophane (Cu) membrane (AM-SD, Asahi Medical Co., Tokyo, Japan), nine patients using a polymethylmethacrylate (PMMA) membrane (B2, Toray Indust., Tokyo, Japan), and seven healthy controls. Among a portion of these patients, the binding activity of acetyl-LDL was investigated in PBM from five patients using a Cu membrane, four patients using a PMMA membrane, and five healthy controls. In a separate experiment, SR gene expression in PBM was studied in 12 uraemic patients and nine healthy controls. In preliminary experiments we found no differences in the gene expression of SR and α_2MG/LRP in PBM irrespective of whether they were obtained before or after a dialysis session. Therefore heparinized blood samples were obtained from the arterial line before the dialysis session in haemodialysis patients and from the cubital vein in the controls.

Preparation of RNA from peripheral blood monocytes

Ten millilitres of whole blood were collected from the patients and the controls. Peripheral mononuclear cells (PBMC) were isolated by centrifugation on a Ficoll gradient (Lympho Sep, ICN Biomedical Inc., CA. USA) and resuspended in RPMI 1640 (GIBCO BRL, Gaithersburg, MD). To purify the monocyte population, PBMC were incubated in RPMI 1640 supplemented with 10% decomplemented fetal calf serum (Gibco), 100 IU/ml penicillin (Gibco), and 100 µg/ml streptomycin (Gibco) for 1 h at 37°C in 5% CO_2 then adhered to polystyrene dishes. After incubation adherent cells were collected as peripheral blood monocytes (PBM). PBM were immediately lysed in guanidium solution containing 4 M guanidine isothiocyanate, 50 mM potassium acetate (pH 5.1), 0.5% sodium lauryl sarcosinate, and 1%(vol/vol) 2-mercaptoethanol. Total cellular RNA was isolated from the lysate by step gradient ultracentrifugation with cesium trifluoroacetic acid (Pharmacia LKB Biotechnology Inc., Uppsala, Sweden) as previously described [13]. RNA concentration was determined by photoabsorbance at 260 nm. Ratios of OD260 nm to OD280 nm of the samples were ~2.0.

Reverse-transcription polymerase chain reaction (RT-PCR) assay

The amounts of RNA from PBM of haemodialysis patients were too small (1~3 µg) to permit the detection of SR and α_2MG/LRP mRNA by Northern blot analysis. To overcome this problem we employed the semiquantitative RT-PCR method for the detection of SR and α_2MG/LRP mRNA as previously described [13]. Briefly, aliquots (0.5 µg/20 µl) of RNA were reverse-transcribed to single-stranded cDNA by MoMuLV reverse transcriptase (Gibco BRL, Gaithersburg, MA). The cDNA products were heat-denatured and diluted fivefold with distilled water. Next, 5 µl of the diluted cDNA product was mixed with 5 µl of 10 × PCR-buffer (0.1 M Tris-HCl, pH 8.3, 0.5 M KCl, 25 mM $MgCl_2$ and 0.1% gelatin), 4 µl of 1.25 mM each dNTP, 2.5 µl of respective 10 mM sense primer, 2.5 µl of the respective 10 mM antisense primers, and 0.25 µl of Taq DNA polymerase (5 U/µl, Takara Biomedicals, Kyoto, Japan), and the volume was adjusted to 50 µl with distilled water.

The sequence of sense-primer for SR was 5′-AGCATGACAACTGATCAAAG-3′, which was defined by 477–496 bps, and the sequence of antisense primer was 5′-GTCTGAGAATGTT-CCCAATC-3′(817–836 bps) [10]. The sequences correspond to the coding region of SR domain IV, which is common to both type I and type II SR. The sequence of the sense primer for human α_2MG/LRP was 5′-GTGTTTAAGCTGTTGGCGGG-3′(123–142 bps), and that of the antisense primer was 5′-CGAG-GTCATGAGGCTTTTGG-3′(438–457 bps). We used 18S ribosomal RNA(18SrRNA) as an inner control. The sequence of sense and antisense primers for 18SrRNA was 5′-GAACGTCTGCCCTATCAACT-3′ and 5′-CTTGCCC-TCCAATGGATCCT-3′ respectively. A PCR thermal cycle profile for amplification of a target sequence is (1) denaturing for 1 min at 94°C, (2) annealing primers for 1.5 min at 55°C, and (3) extending the primers for 1.5 min at 72°C. The expected size of the PCR products for SR, α_2MG/LRP and 18SrRNA was 360 bp, 335 bp, and 260 bp respectively. Since in the preliminary experiments we found a linear amplification of the PCR products of SR, α_2MG/LRP, and 18SrRNA when PCR was repeated for less than 35 cycles, PCR was repeated for 33 cycles for SR, α_2MR/LRP and 17 cycles for 18SrRNA.

Aliquots (10 µl) of PCR products were electrophoresed in a 1.2% agarose gel, stained with ethidium bromide, transferred to a nylon membrane (Hybond-N plus, Amersham Japan, Tokyo), and fixed by ultraviolet irradiation for 3 min. The blotted membrane was prehybridized in a solution containing 2 × salt sodium phosphate–EDTA (SSPE) (1 × SSPE is 0.15 M Na Cl, 10 mM Na_2HPO_4 and 1 mM EDTA), 5 × Denhardt's solution (0.1% Ficoll 400, 0.1% polyvinylpyrrolidone and 0.1% bovine serum albumin), 0.5% sodium dodecyl sulphate (SDS), and 20 µg/ml of denatured salmon sperm DNA. Hybridization was performed at 52°C for 24 h using the same buffer containing a ^{32}P-labelled oligonucleotide probe specific for each amplified cDNA (5′ - ATTTCTGCTGATACATTGTAAACACGCTCCTCT-

AATTTAC-3′ for SR,5′-CCGAAATCCAAACCCTTCAC-3′ for α_2MG/LRP and 5′-TGCTGCCTTCCTTGGATG-TGGTAGCCGTTTCTCAGGCTCC-3′ for 18SrRNA), which was radiolabelled to a specific activity of 7×10^6 c.p.m./pmol by 5′ end-labelling method with T4 polynucleotide kinase (Takara Biomedicals, Kyoto, Japan). The hybridized membrane was washed for 15 min with a stringency of 2 × SSPE with 1% SDS at the calculated melting temperature. Autoradiography was performed for 15–60 min at room temperature (18SrRNA) or extended for 24–72 h at −80°C (SR and α_2MG/LRP) with intensifying screens. The intensity of the resulting autoradiograms was quantitated by laser-scanning densitometry. Quantitation of the PCR products was normalized with the respective PCR products of 18SrRNA, an inner control for the amount of RNA in each sample. A no-DNA control was used as the negative control.

Binding of ^{125}I-acetyl-LDL

The binding of acetyl-LDL (Sigma Chemical Co., St. Louis, MO, USA) to PBM was performed according to the methods of Goldstein *et al.* [14] in a portion of the patients whose SR gene expression was examined as described above. In brief, ^{125}I-acetyl-LDL (50 000 c.p.m./μg of protein) was added to 1×10^5/ml PBM in the presence or absence of a 50-fold excess of unlabelled acetyl-LDL at 4°C on a rotary shaker. After 2 h the cells were washed three times with ice-cold phosphate-buffered saline (PBS) containing 2 mg/ml of bovine serum albumin, then twice with ice-cold PBS. The cells were solubilized in 0.2 M NaOH. Radioactivity was quantified by gamma spectroscopy, and aliquots were taken for protein determination. Specific binding was determined as total binding minus non-specific binding.

Statistics

Statistical comparisons were performed using an analysis of variance (ANOVA) followed by Scheffe's test or Student's *t* test, as appropriate. All *P* values are two-tailed and significance was set at $P<0.05$. Values were expressed as mean ± SE.

Results

Patients' characteristics

The patients' characteristics are shown in Table 1. There was no difference in age or serum levels of total cholesterol and triglyceride between the patients on haemodialysis with a Cu membrane, patients on haemodialysis with a PMMA membrane, and the controls. No significant differences in body mass index, mean blood pressure, duration of dialysis period, dialysis time, interdialytic weight gain, or serum levels of creatinine were found between patients undergoing haemodialysis with a Cu membrane and patients undergoing haemodialysis with a PMMA membrane. Demographic variables in the uraemic patients and healthy controls are given in Table 2.

Table 1. Patient characteristics

	Chronic haemodialysis patients		
	Control	PMMA	Cuprophane
n	7	9	9
Cause of uraemia		CGN	CGN
Sex (M:F)	5:2	4:5	3:6
Age (years)	54.1 ± 5.5	50.4 ± 4.0	54.1 ± 5.5
Body mass index (kg/m^2)	21.7 ± 1.2	18.6 ± 0.9[a]	18.1 ± 0.6[a]
Mean blood pressure (mmHg)	86.0 ± 3.8	99.8 ± 2.5[a]	96.2 ± 4.1[a]
Duration of dialysis period (months)		39.3 ± 18.6	65.4 ± 18.7
Dialysis time (h/week)		11.1 ± 0.6	11.2 ± 0.7
Interdialytic weight gain (kg)		1.9 ± 0.2	1.9 ± 0.3
Serum creatinine (mg/dl)	0.8 ± 0.1	11.4 ± 0.8[a]	11.3 ± 0.8[a]
Total cholesterol (mg/dl)	197 ± 11	172 ± 9	187 ± 10
Triglyceride (mg/dl)	104 ± 36	112 ± 32	104 ± 13

[a] $P<0.05$ (vs controls). CGN, chronic glomerulonephritis.

Table 2. Demographic variables

	Control	Uraemic patients on conservative therapy
n	9	12
Cause of uraemia		CGN
Sex (M:F)	6:3	6:6
Age (years)	53.2 ± 3.0	51.1 ± 3.7
Body mass index (kg/m^2)	21.9 ± 1.2	22.9 ± 1.2
Serum creatinine (mg/dl)	0.8 ± 0.0	9.1 ± 1.1[a]
Total cholesterol (mg/dl)	210 ± 8	194 ± 17
Triglyceride (mg/dl)	127 ± 24	177 ± 39

[a] $P<0.05$ (vs Control). CGN, chronic glomerulonephritis.

Correlation between the amounts of total RNA and PCR products

Figure 1 shows satisfactory linearity of a typical standard curve between the amounts of total RNA and PCR products of SR,α_2MR/LRP and 18SrRNA.

Gene expression of SR mRNA in PBM

The expression of SR mRNA in PBM in patients on chronic haemodialysis with a Cu membrane was about twofold higher than that in patients on haemodialysis with a PMMA membrane and the controls (2.10 ± 0.36 *vs* 1.21 ± 0.21, 1.00 ± 0.19, $P<0.05$) (Figure 2). Representative Southern blots are shown in Figure 3. No difference in the expression of SR mRNA in PBM was found between uraemic patients and the controls (Figure 4).

Gene expression of α_2MG/LRP mRNA in PBM

The expression of α_2MG/LRP mRNA in PBM was not different between patients on haemodialysis with a Cu membrane, patients on haemodialysis with a PMMA membrane, and the controls (Figure 5).

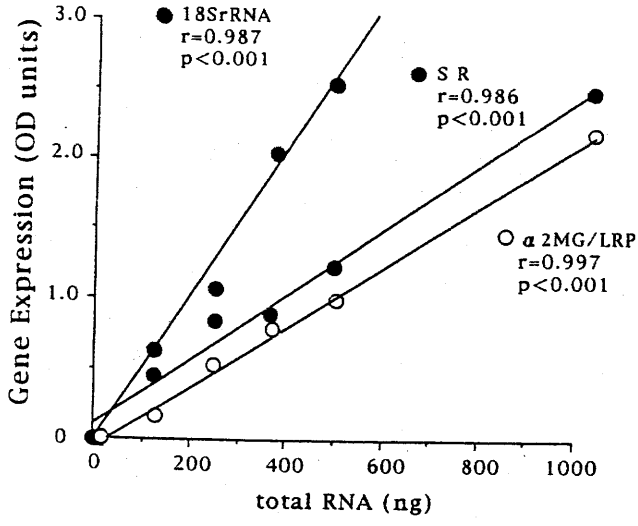

Fig. 1. Correlation between PCR products and initial total RNA from PBM. A linear amplification of the PCR products was found at the respective PCR cycles according to the initial amount of total RNA, which ranged from 100 to 1000 ng. The y axis shows an arbitrary unit representing densitometric values of the respective PCR products.

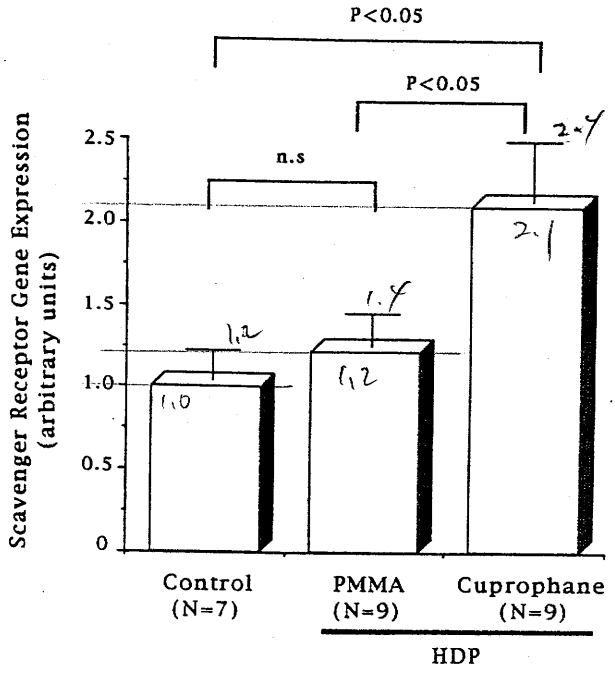

Fig. 2. Gene expression of scavenger receptor in PBM from haemodialysis patients (HDP) and controls. The y axis shows an arbitrary unit representing densitometric values of scavenger receptor PCR products normalized with the densitometric values of 18SrRNA PCR products. The levels of gene expression of scavenger receptor were increased about twofold in HDP with a cuprophane membrane compared to those in HDP with a polymethylmethacrylate (PMMA) membrane or in the controls ($P<0.05$ respectively).

Binding of ^{125}I-acetyl-LDL to PBM

The mean value of specific binding of ^{125}I-acetyl-LDL to PBM from patients on dialysis with a Cu membrane was about 1.5-fold higher than that of the controls.

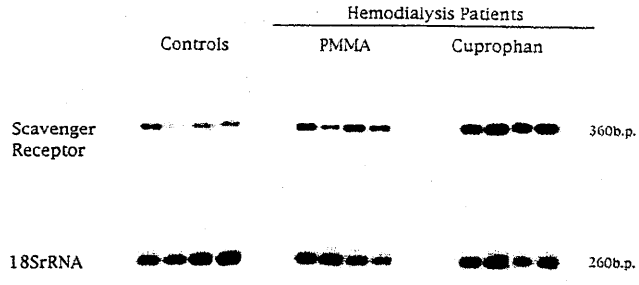

Fig. 3. Representative Southern blots showing scavenger receptor PCR products and 18SrRNA PCR products.

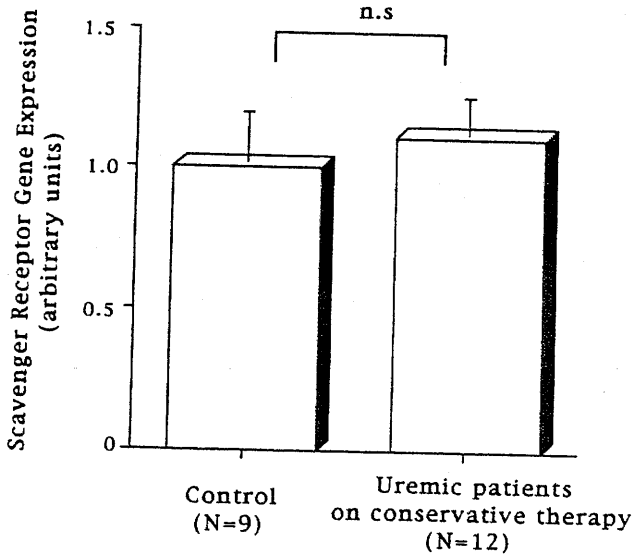

Fig. 4. Gene expression of scavenger receptor in PBM from uraemic patients and controls. The y axis shows an arbitrary unit representing densitometric values of scavenger receptor PCR products normalized with the densitometric values of 18SrRNA PCR products. No difference in the gene expression of SR was found between uraemic patients and controls.

However, the difference was not statistically significant (Figure 6).

Discussion

In atherosclerotic lesions, macrophages accumulate a large amount of cholesteryl ester and are termed 'foam cells'. Accumulation of these lipid-loaded monocyte/macrophages in the subendothelial space is considered to play a key role in the initiation of atherosclerosis [6]. Transformation of the monocyte-derived macrophage into a foam cell is not fully understood, but it involves the uptake of modified forms of LDL by a special type of lipoprotein receptor, the macrophage SR[6,10]. Two different types of SR were identified, both of which were trimeric glycoproteins that appeared to bind their ligands via a collagen-like domain in the extracellular carboxy-terminal portion of the molecule. Both the larger type I and the smaller

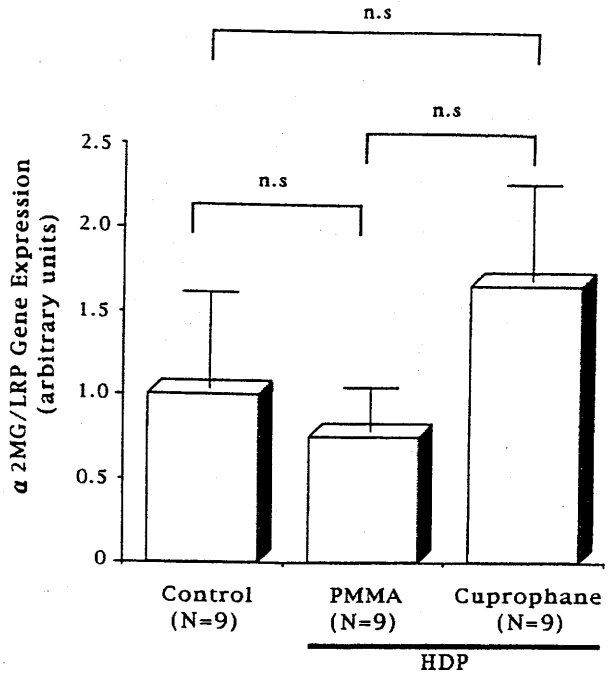

Fig. 5. Gene expression of α_2 macroglobulin receptor/low density lipoprotein receptor-related protein (α_2MG/LRP) in PBM from haemodialysis patients (HDP) and controls. The y axis shows an arbitrary unit representing densitometric values of α_2MG/LRP PCR products normalized with the densitometric values of 18SrRNA PCR products. No difference in the gene expression of α_2MG/LRP was found between HDP and the controls.

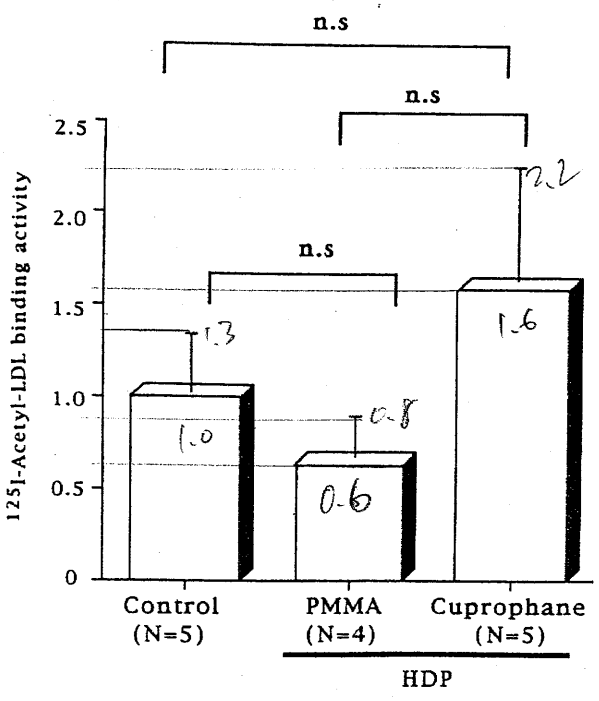

Fig. 6. Binding of ^{125}I-acetyl-LDL to PBM. The mean value of specific ^{125}I-acetyl-LDL binding activity (c.p.m./μg protein) to PBM obtained from the controls is arbitrary expressed as 1.0. The mean value of specific binding of ^{125}I-acetyl-LDL to PBM from patients on dialysis with a Cu membrane was about 1.5-fold higher than that of the controls. However, the difference was not statistically significant.

type II SR mRNA species are generated from a single gene by alternative splicing and are found in macrophage cell lines and macrophage-rich tissues, including atherosclerotic plaques [10]. Both types of receptors show similar affinity and specificity of ligand binding and internalization [10].

In the present study we have demonstrated that the expression of SR mRNA in PBM from patients undergoing haemodialysis with a Cu membrane was about twofold higher than that in PBM from patients undergoing haemodialysis with a PMMA membrane, uraemic patients, or control subjects. Pre- and postdialysis expression of SR mRNA in PBM did not differ. We previously showed that the gene expression of type I SR in human THP-1 monocytic cells increased 12 h after stimulation with phorbol 12-myristate 13-acetate (PMA) and further increased for 72 h [15]. Thus the changes in SR gene expression occur over several hours after stimulation and persist for a longer period. Therefore the increase in SR gene expression in PBM from patients under Cu membrane dialysis may reflect their *in vivo* state, although the stimuli for SR gene expression would have been generated during Cu membrane dialysis.

Since we measured the gene expression of type I and type II SR concomitantly by RT-PCR, it is difficult to determine which type of increased SR gene expression is responsible for the measured increase in SR gene expression. However, Geng *et al.* [16] reported that during the differentiation of human monocytes to macrophages, there was a rapid, selective increase in type I SR mRNA, whereas type II SR mRNA remained at the same level as in the monocytes. Therefore the increased SR mRNA that we measured must be a type I SR mRNA if the changes were related to the differentiation of monocytes to macrophages. Moreover it has been shown that the treatment of THP-1 monocytic cells with PMA promotes the differentiation of macrophage-like cells and induces expression of SR by a protein kinase C-dependent mechanism [17]. It has also been demonstrated that the levels of the second messenger diacylglycerol, which activates protein kinase C, are much more higher in PBMC exposed to a Cu membrane than those exposed to a polysulphone (PS) or polyacrylonitrile (PAN) membrane [18]. Taken together it can be speculated that the increase in SR gene expression in PBM from patients undergoing haemodialysis with a Cu membrane mainly reflects a protein kinase C-dependent increase of type I SR mRNA, which has been induced by diacylglycerol generated by exposure to a Cu membrane.

Ando *et al.* [12] recently reported enhanced SR gene expression and acetyl-LDL binding activity in cultured PBM obtained from four dialysis patients. In contrast to our results they did not find increased gene expression of SR in PBM until the PBM were cultured for 5 days. Since they did not mention the type of dialysis membrane, the reason for the discrepancy in the results remains obscure.

We did not find a significant increase in binding

activity of acetyl-LDL to PBM from patients under Cu membrane dialysis, although the mean value was increased 1.5-fold. Since we performed the acetyl-LDL binding study with fewer patients than in the SR gene expression study, it may not have been possible for the differences to reach a statistical significance.

Cuprophane haemodialysis membranes have been shown to activate several pathways of the inflammatory response, as well as cellular elements, such as monocytes and platelets [2,19]. These inflammatory responses are less evident with non-cellulosic membranes such as the PMMA or PAN membrane [19]. These results are consistent with the present study, which has shown increased gene expression of monocyte/macrophage SR in PBM from patients on haemodialysis with a Cu membrane, but not in PBM from patients on haemodialysis with a PMMA membrane, although the specific stimulus for the activation of the gene expression of SR remains unclear.

We did not find a significant increase in the gene expression of α_2MG/LRP in PBM from patients on dialysis with a Cu dialysis membrane. This result is somewhat unexpected because it has been reported that both SR and α_2MG/LRP are downregulated by lipopolysaccharide and interferon-γ, and upregulated during monocyte differentiation into macrophage [11]. However, Luoma *et al.* [11] have reported that in their study on the expression of SR and α_2MG/LRP in human atherosclerotic lesions, the level of α_2MG/LRP immunostaining seemed to be decreased in some macrophage-rich areas of the lesions, whereas expression in smooth muscle cells appeared to be more consistent. No SR expression was found in smooth-muscle cells [11]. Therefore, it can be speculated that some differences may exist in the regulation of expression of SR and α_2MG/LRP.

It has been shown that dialysis patients have significantly elevated levels of lipid peroxidation products compared to healthy controls and, among patients on haemodialysis, patients on Cu haemodialysis have even further elevated levels of peroxidation products compared to patients on PS haemodialysis [7]. An increased susceptibility to oxidation of LDL isolated from patients with chronic renal failure undergoing haemodialysis or on continuous ambulatory peritoneal dialysis has also been demonstrated [9]. Under these conditions enhanced gene expression of SR in PBM from patients on Cu haemodialysis may contribute to transformation of macrophages into foam cells by taking up oxLDL. It also may lead to an avid adherence to atherosclerotic plaques using SR as an adhesion molecule [20]. These factors would consequently accelerate atherogenesis.

In conclusion, we have demonstrated increased expression of SR mRNA in PBM from patients on haemodialysis with a Cu membrane compared to those in patients on haemodialysis with a PMMA membrane, uraemic patients, or control subjects. The enhanced SR mRNA expression in PBM from patients on Cu haemodialysis may be a possible risk factor for accelerated atherogenesis.

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