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Preferential binding of apolipoprotein E derived peptides with oxidized phospholipid

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ABSTRACT

The physiological function of apolipoprotein E (apoE) includes transport and metabolism of lipids and its C-terminal domain harbors high affinity lipid-binding sites. Although the binding of apoE with non-oxidized phospholipid containing membranes has been characterized earlier, the interaction of apoE or its fragments with oxidized phospholipid containing membrane has never been studied. In this study we have compared the interaction of amphipathic helical peptide sequences derived from the C-terminal domain of apoE with membrane vesicles containing oxidized phospholipid, 1-palmitoyl-2-azelaoyl-*sn*-glycero-3-phosphocholine (PazePC), with membrane vesicles without PazePC. The interaction was studied by monitoring (a) fluorescence emission maxima of the peptides, (b) acrylamide quenching of the peptides tryptophan residues and (c) by measuring the equilibrium binding constants by resonance energy transfer (RET) analysis. Our result shows that peptide sequence 202–223, 245–266 and 268–289 of apoE has higher affinity towards membrane containing PazePC, compared to membrane without PazePC. Presence of 1mM divalent cation or 50 mM NaCl in the buffer decreased the binding of peptides to PazePC containing membrane vesicles suggesting possible involvement of the electrostatic interaction in the binding. These observations suggest that the preferential binding of apoE to oxidized phospholipid containing membrane may play a role in the anti-oxidative properties of apoE.

Apolipoprotein E plays a dominant role in the metabolism of triglycerides and cholesterol and also acts as a modulator of atherogenesis [1]. Two distinct domains have been identified in apoE: 22-kDa N-terminal domain (residue 1–191) and 10-kDa C-terminal domain (residues 201–299), which are linked by a protease sensitive hinge region [2]. The N-terminal domain of apoE contains epitopes for binding to the members of low density lipoprotein-receptor (LDL-R) family and also has a weak lipid-binding property [2]. The C-terminal domain of apoE contains regions for high affinity lipid-binding as well as for self-association [3–5].

The amino acid sequences of exchangeable apolipoproteins are highlighted by the presence of variable number of 22-residue amphipathic α-helical repeats, which confer the ability to bind to the surface of lipoprotein particles [6]. These regions of apolipoproteins also play a major role in the initiation of assembly of nascent high density lipoprotein (HDL) particles by interacting with membrane lipids [7,8]. The C-terminal domain of apoE also contains 22-mer amphipathic α-helical sequences which differentially contribute to the lipoprotein binding capabilities of apoE [3,6]. Binding of apoE to lipoproteins is believed to be initiated by the amphipathic helices of its C-terminal domain [9] and tight association of the apoE C-terminal domain with the lipoprotein surface permits its N-terminal domain to transit between a receptor-inactive helix bundle state and receptor-active states [10]. Thus, interaction of apoE with lipids exerts profound effect on its structure and regulates its functions.

Unsaturated fatty acyl chains of phospholipids, present in the cellular membranes and lipoprotein particles, are spontaneously oxidized by reactive oxygen species (ROS) to produce toxic phospholipid hydroperoxides and a variety of oxidized phospholipids [11]. A growing number of studies suggest that oxidized phospholipids may also act as the key players in triggering the inflammatory response in atherosclerosis [12]. Interaction of apoE with model lipid membrane containing non-oxidized phospholipids has been studied earlier [3–5]. However, the interaction of apoE or its fragments with oxidized phospholipid containing membrane has never been characterized. Towards this, in this study, we have analyzed the interaction of synthetic peptide segments of apo E C-terminal domain with membrane vesicles containing PazePC, which is one of the abundant oxidized phospholipids generated from the ROS mediated oxidation of unsaturated phosphatidylcholines [13]. Our results show that amphipathic peptide sequence 202–223, 245–266 and 268–289 of apoE has higher affinity towards membrane vesicle containing PazePC as compared to membrane vesicles without PazePC.

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Material and methods

Materials. POPC, PazePC and Py-PE were purchased from Avanti Polar Lipids (Alabaster, AL). Hepes buffer, chloroform, acrylamide, sodium chloride, calcium chloride, urea, and EDTA were purchased from Sigma–Aldrich, Bangalore, India. All other reagents were of analytical grade.

Peptides. The following peptides of human apoE C-terminal domain, were synthesized by USV Limited (Mumbai, India): Ac-PLQE RAQAWGERLRARMEEMGS-CONH2; ($apoE_{(202–223)}$), Ac-SRTRDR**W**D EVKEQVAEVRAKLE-CONH2; ($apoE_{(223–244)}$), Ac-EQAQQIRLQAEAFQ ARLKSWFE-CONH2; ($apoE_{(245–266)}$), and Ac-LVEDMQRQWAGLVEK VQAAVGT-CONH2; ($apoE_{(268–289)}$). Except peptide $apoE_{(223–244)}$, rest of the three peptides sequence naturally contains one Trp each. In order to produce an intrinsically fluorescent sequence, Leu229 was replaced by Trp (bold and underlined) within the $apoE_{(223–244)}$ sequence. The purity of the peptides in all cases was found to be >95% by HPLC analysis and the correct mass of peptides was confirmed by electrospray mass spectrometry. All four peptides were acetylated at the amino terminus and amide-capped at the carboxyl terminus. The peptides were dissolved in aqueous buffer at a concentration of 1–1.5 mg/ml.

Preparation of large unilamellar vesicles(LUV). LUV containing either 100% POPC or 50% PazePC and 50% POPC were prepared essentially as described previously [14].

Fluorescence measurements. All fluorescence experiments were performed using Perkin-Elmer LS-50B luminescence spectrometer. Excitation and emission slits were 4 and 10 nm, respectively. Fluorescence emission spectra were recorded between 300 and 400 nm by selectively exciting the peptides Trp at 290 nm. The composition of the buffer used was 10 mM Hepes, 10 mM NaCl, 1 mM EDTA (pH 7.4). In some experiment 1 mM $CaCl_2$ or $MgCl_2$ was used instead of 1 mM EDTA.

(*a*) *Fluorescence emission maxima determination*. Fluorescence emission spectra of individual peptide (final concentration 4 μM) either in absence or in presence of 400 μM of LUV were recorded as describe above. This was followed by spectral correction by subtracting the spectra measured under identical conditions but without the peptide. Fluorescence emission maxima (λ_{max}) were then directly recorded from the corrected spectra.

(*b*) *Fluorescence quenching experiment*. Interaction of the individual peptides with LUV was studied by monitoring the quenching of peptides Trp fluorescence by aqueous phase quencher, acrylamide, as described previously [14]. Briefly, 4 μM of individual peptide either in absence or presence of 400 μM of LUV was serially titrated with increasing concentrations of acrylamide (4 M stock in water) and after each addition of the quencher the emission spectra were recorded as describe above. Maximum fluorescence intensities without and with the quencher (F_0 and F, respectively) were determined and F_0/F values were plotted against the acrylamide concentrations. The experimental data were fitted with the Stern–Volmer equation for the collisional quenching [15]

$$F_0/F = 1 + K_{SV}[Q] \quad (1)$$

where, [Q] is the quencher concentration and K_{SV} is Stern–Volmer constant for the collisional quenching process.

(*c*) *Membrane binding experiments*. Equilibrium binding of the individual peptides to membrane vesicles was measured by RET analysis, as described elsewhere [16]. The Trp of peptide was used as the energy donor while 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-(1-pyrenesulfonyl) (Py-PE, present as 2 mol% in LUV) acted as energy acceptor in RET analysis. Membrane vesicles were titrated into a 4 μM peptide solution, with continuous stirring, to yield a final lipid concentration from 0 to 400 μM. The fluorescence intensities obtained in RET experiments were corrected for change in the fluorescence emission as measured in control experiments. The binding data were analyzed using the following equation:

$$\Delta F = \Delta F_{max}[L]/K_d + [L] \quad (2)$$

where ΔF is the change in the emission intensity at 340 nm at a given lipid concentration, [*L*], relative to the zero lipid level, corrected for the change in intensity when unlabeled lipid was used as control, ΔF_{max} is the saturating level of ΔF calculated by Scatchard plots and K_d is the binding constant of peptide molecules.

Results

The C-terminal domain of apoE contains regions that are involved in high affinity binding to lipid. The four 22-mer synthetic peptides used in this study encompass ~90% of entire apoE C-terminal domain. Binding of these peptides to the membrane vesicles containing PazePC was studied by fluorescence spectroscopy.

Fluorescence emission maxima determination

The propensity of the peptides to interact with membrane vesicles was assessed by analyzing the effect of LUV on the fluorescence emission spectra of the peptides (Fig. 1). In buffer all four peptides exhibited emission spectra with emission maxima at 359 ± 2 nm. Incubation of individual peptides with POPC LUV had no effect on their fluorescence emission spectra and the spectra of peptides in presence of POPC LUV were similar to the spectra of peptides in absence of POPC LUV (Fig. 1). Similarly, incubation of the peptide $apoE_{(223–244)}$ with PazePC/POPC LUV had no effect on the peptides fluorescence emission spectra. However, incubation of the individual peptides $apoE_{(202–223)}$, $apoE_{(245–266)}$, and $apoE_{(268–289)}$ with PazePC/POPC LUV resulted in either one or both of the two effects, i.e., an increase in the fluorescence emission intensity and a blue shift. The extent of blue shift in the emission maxima was different for the peptides. In presence of PazePC/POPC LUV, the emission spectra of $apoE_{(245–266)}$ and $apoE_{(202–223)}$ pep-

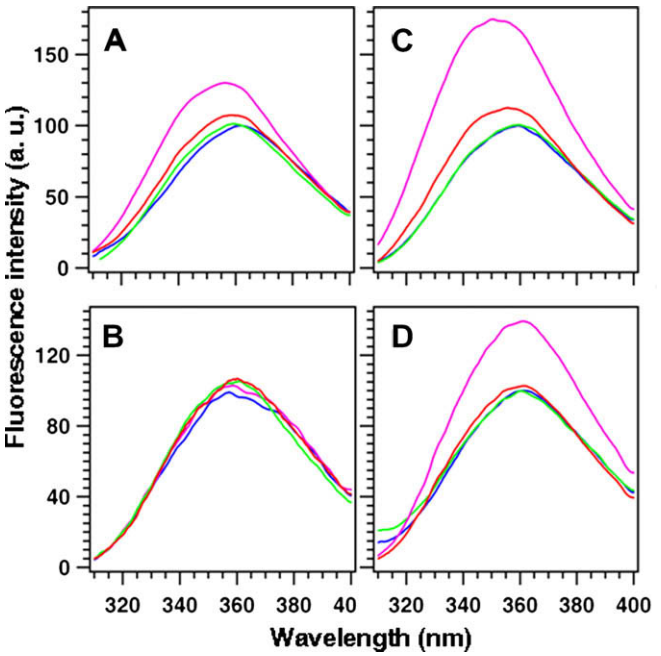

Fig. 1. Fluorescence emission spectra of peptide: A, $apoE_{(202–223)}$; B, $apoE_{(223–244)}$; C, $apoE_{(245–266)}$; D, $apoE_{(268–289)}$ in absence of lipid (blue), in presence of LUV made up of POPC (green) or PazePC/POPC (pink). Inhibitions of binding of peptides to the PazePC/POPC LUV by 1 mM $CaCl_2$ are shown by red colored lines. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

tides exhibited increase in the emission intensities and the blue shift of ~8 and ~4 nm, respectively. Incubation of apoE$_{(268–289)}$ with PazePC/POPC LUV resulted in only increase in the emission intensity without any blue shift in the emission maximum. The emission maximum of Trp is sensitive to its microenvironment and a blue shift in the emission maximum is observed when the Trp is transferred from a medium of high polarity to a medium of low polarity [17,18]. The result indicates that the Trp residues of apoE$_{(245–266)}$ and apoE$_{(202–223)}$ experienced more apolar (hydrophobic) environment in the presence of PazePC/POPC LUV, than in the presence of POPC LUV, suggesting specific binding of these peptides with the membrane vesicles containing PazePC. Presence of 1 mM $CaCl_2$ in the buffer significantly reduced the binding of apoE$_{(202–223)}$, apoE$_{(245–266)}$, and apoE$_{(268–289)}$ peptides to PazePC/POPC LUV (Fig. 1). Similarly, binding of these peptides to PazePC/POPC LUV was also found to be reduced when the interaction of peptides with LUV was monitored in presence of either 1 mM $MgCl_2$ or 50 mM NaCl or in pH 5.0 buffer (10 mM MES, containing 10 mM NaCl, 1 mM EDTA) (data not shown).

Fluorescence quenching experiment

Binding of the Trp containing peptides with lipid generally results in the partition of the Trp residue into the apolar region of the lipid membrane [18]. This decreases the exposure of the Trp residue of the peptides to the aqueous phase quenchers, like acrylamide, thereby decreasing the quenching in the fluorescence emission intensity. To see the interaction of peptides with membrane vesicles, the emission spectra of the individual peptides in absence or presence of LUV were recorded in the presence of increasing concentrations of acrylamide. The Stern–Volmer plots for the quenching of Trp fluorescence of the peptides by acrylamide are shown in Fig. 2. In the presence of PazePC/POPC LUV, compared with POPC LUV or buffer, Trp in apoE$_{(202–223)}$, apoE$_{(245–266)}$, and apoE$_{(268–289)}$ peptides become less accessible to the quencher, suggesting shielding of Trp from acrylamide by the membrane vesicles containing PazePC. The quenching of fluorescence of apoE$_{(223–244)}$ peptide Trp was similar in presence of POPC LUV and PazePC/POPC LUV or buffer. The Stern-Volmer quenching constants (K_{SV}) for a bimolecular collisional quenching process were calculated using Eq. (1) and are given in Table 1. In absence of lipid the K_{SV} values for individual peptides were 13.7–15.0 M^{-1}, suggesting complete exposure of the peptides Trp residue to acrylamide. The K_{SV} values for the peptide apoE$_{(223–244)}$ in presence of POPC LUV and PazePC/POPC LUV were similar to the K_{SV} value for the peptide in buffer suggesting complete exposure of the peptide apoE$_{(223–244)}$ to acrylamide. In presence of POPC LUV the K_{SV} values for the quenching of Trp of peptides apoE$_{(202–223)}$ and apoE$_{(268–289)}$ were lower than in buffer suggesting shielding of Trp by POPC LUV as a result of binding of these peptides to the POPC LUV. In presence of PazePC/POPC LUV the K_{SV} values for the quenching of Trp of peptides apoE$_{(202–223)}$, apoE$_{(245–266)}$, and apoE$_{(268–289)}$ were significantly lower, compared with POPC LUV or buffer, indicating complete shielding of Trp of these peptides upon interaction with membrane vesicles containing PazePC. Compared with POPC LUV, PazePC/POPC LUV was found to be more effective in shielding the Trp residues present in the peptides apoE$_{(202–223)}$, apoE$_{(245–266)}$, and apoE$_{(268–289)}$. However, significantly reduced shielding of Trp of these peptides by PazePC/POPC LUV was observed when the quenching experiments were done in the buffer containing either 1 mM $CaCl_2$ or $MgCl_2$ (data not shown). Taken together, the result of this experiment suggests that peptides apoE$_{(202–223)}$, apoE$_{(245–266)}$ and apoE$_{(268–289)}$ shows preferential interaction with membrane vesicles containing oxidized lipid, PazePC, resulting in the shielding of their Trp form the aqueous phase quencher, as compared to membrane vesicle without PazePC.

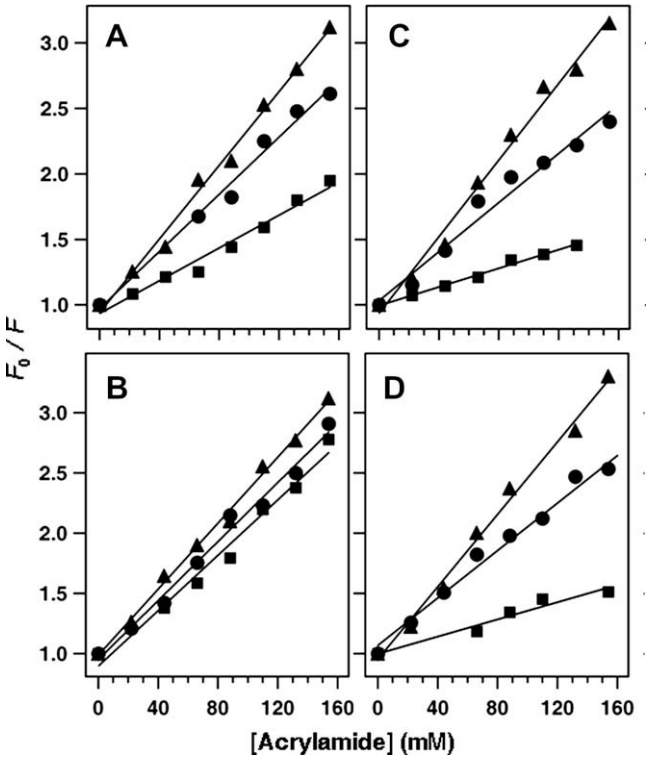

Fig. 2. Stern–Volmer plots showing the fluorescence quenching of peptide Trp by acrylamide: A, apoE$_{(202–223)}$; B, apoE$_{(223–244)}$; C, apoE$_{(245–266)}$; D, apoE$_{(268–289)}$. Peptide in absence of lipid, (▲); in presence of LUVs made up of POPC (●); or PazePC/POPC, (■).

Table 1
Tryptophan emission maxima, fluorescence quenching parameters and equilibrium binding constants of the peptides.

	λ_{max} (nm)[a]	K_{sv} (M^{-1})[b]	K_d (μM)[c]
apoE$_{(202-223)}$			
Buffer	360.3	14.0	–
POPC	359.3	10.9	140.5
PazePC/POPC	356.1	6.2	24.1
apoE$_{(223-244)}$			
Buffer	358.6	13.7	–
POPC	358.1	12.2	N.D.
PazePC/POPC	357.8	11.5	N.D.
apoE$_{(245-266)}$			
buffer	359.8	14.6	–
POPC	358.5	9.4	N.D.
PazePC/POPC	351.3	3.6	3.0
apoE$_{(268-289)}$			
Buffer	361.0	15.0	–
POPC	360.3	9.8	100.2
PazePC/POPC	359.6	3.5	8.1

Reported values are average of 2 experiments. N.D. refers to no detectable binding.
[a] The maximum error of measurements was in the order of ±1.6 nm.
[b] The maximum error of measurements was in the order of ±10%.
[c] The maximum error of measurements was in the order of ±25%.

Membrane binding experiments

Equilibrium binding in solution of the peptides with membrane vesicles was quantitatively determined by RET analysis, as described previously [16]. Since all four peptides contain a single Trp residue each, Trp fluorescence was used as RET donor in analyzing membrane binding of individual peptides. The energy acceptor was 2 mol% Py-PE in membrane vesicles in all cases.

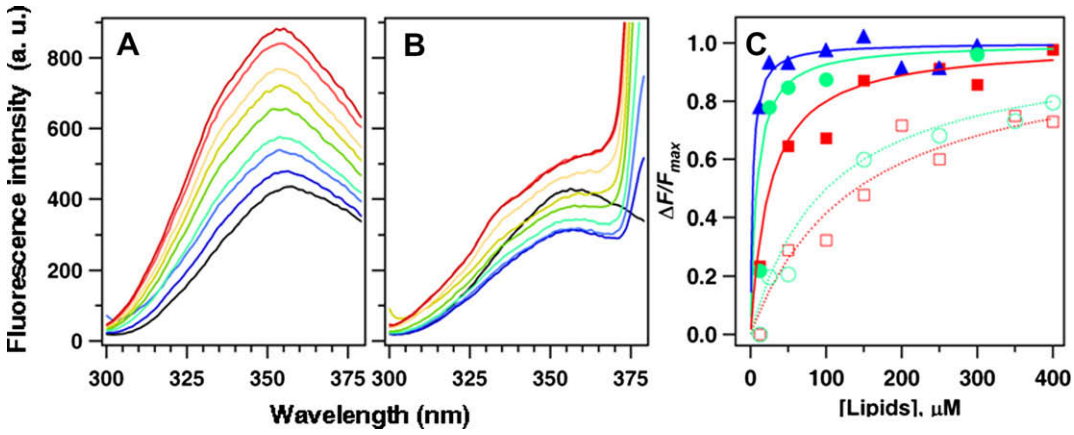

Fig. 3. Representative fluorescence emission spectra of peptide with increasing concentrations of unlabeled PazePC/POPC LUVs (A) and labeled PazePC/POPC LUV which contains 2 mol% Py-PE (B). The change in color from blue to red corresponds to a change in lipid concentration from 0 to 400 μM. Isotherms characterizing binding of individual peptides to POPC and PazePC/POPC LUVs, constructed on the basis of RET experiments. The measured binding data (symbols) were analyzed using a Langmuir-type formalism and the curves (lines) were constructed using Eq. (2): (filled symbols and solid lines) PazePC/POPC LUV and (empty symbols and dotted lines) POPC LUV and (blue ▲), $apoE_{(245–266)}$; (red ■), $apoE_{(202–223)}$ and (green ●), $apoE_{(268–289)}$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

Increasing concentrations (from 0 to 400 μM) of unlabeled vesicle (without Py-PE) were titrated in the peptide solution (4 μM; final concentration) in 10 mM Hepes, 10 mM NaCl, 1 mM EDTA (pH 7.4) which resulted in an increase in the fluorescence emission intensity (Fig. 3A), due to the partition of the Trp residue of peptide in the membrane hydrophobic environment. However, the fluorescence emission intensities of the peptides decreased upon addition of vesicles containing 2 mol% Py-PE, evidently due to energy transfer from Trp residue of the peptides to Py-PE in vesicle membranes (Fig. 3B). We measured RET on the basis of a decrease in the emission intensity of the energy donor (Trp residues of proteins) and not the increase in the emission intensity of pyrene, for the reasons described earlier [16]. Since RET is based on short-range (2.8 nm for the Trp-pyrene pair) dipole–dipole interactions between energy donors and acceptors, the observed effect indicates binding of peptide molecules to membrane vesicles.

RET data was corrected for sample dilution and for increase in emission intensity upon binding to unlabeled membrane vesicles and the binding isotherms were constructed (Fig. 3C). The calculated dissociation constants (K_d) values are given in Table 1. Binding of $apoE_{(202–223)}$, $apoE_{(245–266)}$, and $apoE_{(268–289)}$ peptides to the PazePc/POPC LUV was much stronger as compared to POPC LUV and the affinities of the peptides for PazePc/POPC LUV were in the order: $apoE_{(245–266)} > apoE_{(268–289)} > apoE_{(202–223)}$. Peptides $apoE_{(202–223)}$ and $apoE_{(268–289)}$ showed weak binding to POPC LUV while peptides $apoE_{(223–244)}$ and $apoE_{(245–266)}$ exhibited no detectable binding to POPC LUV. Interestingly, no binding was detected for peptide $apoE_{(223–244)}$ towards PazePC/POPC LUV. This clearly indicates that the peptide sequences $apoE_{(245–266)}$ $apoE_{(268–289)}$ and $apoE_{(202–223)}$ exhibits higher affinity towards membrane vesicles containing PazePC as compared to membrane vesicles without PazePC.

Discussion

The exchangeable serum apolipoproteins are rich in lipid-associating amphipathic helical domains which act as lipid-binding motif [6,9]. Like other exchangeable apolipoproteins, the primary sequence of C-terminal domain of apoE is also characterized by the presence of amphipathic α-helical sequences [6]. In this study we have characterized the interaction of the 22-mer amphipathic helical peptides, derived from the apoE C-terminal domain, with membrane vesicle containing oxidized lipid, PazePC.

Change in the peptide Trp fluorescence was used to monitor the association of peptides with membranes. Incubation of the individual peptides $apoE_{(202–223)}$, $apoE_{(245–266)}$, and $apoE_{(268–289)}$ with PazePC/POPC membrane vesicles resulted in the blue shift in the fluorescence emission maxima and/or increase in emission intensity and significant shielding of their Trp residues from aqueous phase quencher, acrylamide. Equilibrium binding analysis of individual peptides to LUV indicated that these three peptides have significantly higher affinity towards membrane vesicles containing PazePC, as compared to membrane vesicles without PazePC. Peptide $apoE_{(223–244)}$ did not showed any detectable binding to the lipids. Our earlier study has also observed that $apoE_{(223–244)}$ peptide failed to bind to phospholipids.[1] Taken together, these observations clearly indicate that sequence 202–223, 245–266 and 268–289 of apoE binds preferentially with membrane vesicles containing PazePC.

ROS mediated oxidation of unsaturated phospholipids causes a variety of changes in the oxidized acyl chain, including chain shortening and modifications of the acyl chains by polar carbonyl, carboxyl, hydroxide and peroxide functions [19]. One of the abundant oxidized phospholipids generated from the oxidation of unsaturated phosphatidylcholines is PazePC, which possesses a carboxyl function at the truncated acyl chain at *sn*-2 position. This oxidized phospholipid is found to be present in lipoproteins particles [13]. When PazePC is present in the lipid membrane, the truncated oxidized *sn*-2 fatty acyl chain carrying polar carbonyl function protrudes into the aqueous phase thereby exposing the carboxyl function at the membrane surface [20,21]. Due to the ionization of the exposed carboxyl function at physiological pH, presence of PazePC imparts a net negative charge to the membrane surface, which leads to binding of cationic proteins to the membrane containing PazePC [22,23]. The amphipathic α-helical regions of apoE C-terminal domain possesses positively charged amino acids residue cluster at the polar–apolar interface and this arrangement allows the interaction of apolipoproteins with negatively charged lipid more strongly than with zwitterionic lipids. Preferential binding of apolipoproteins and their fragments to anionic lipids compared to zwitterionic lipid has been observed by us[1] and others [24,25]. Binding of the $apoE_{(202–223)}$, $apoE_{(245–266)}$, and $apoE_{(268–289)}$ peptides to PazePC containing membrane vesicles

[1] Abhay H. Pande, Rajan K. Tripathy and Sunil A. Nankar. Membrane surface charge determines lipoprotein complex forming capability of peptides derived from the C-terminal domain of apolipoprotein E. (Unpublished data).

was found to decreased in presence of 1 mM divalent cations (Ca^{2+} or Mg^{2+}) or 50 mM NaCl or upon lowering the bulk pH to 5.0. This indicates the involvement of the electrostatic interactions in the binding of the peptides to PazePC containing vesicles. Lowering pH is known to increase the extent of protonation of the carboxylic acid moiety of PazePC, which prevents its interaction with cationic proteins [23].

The physiological role of human apoE is to distribute the cholesterol and triglycerides by acting as a ligand for the member of LDL-receptor family [1]. It is possible that the peptide sequence 202–223, 245–266 and 268–289 of apo E, by virtue of its preferential binding to PazePC containing membrane, binds to oxidized lipoproteins with higher affinity as compared to non-oxidized counterpart, resulting in the transport and metabolism of these oxidized lipoproteins. It is also possible that these peptide sequences can initiate the assembly of new nascent lipoprotein particles by interacting with PazePC present either in cell membranes or in preformed oxidized lipoprotein particles, resulting in the transport and metabolism of PazePC. Recently, small amphipathic α-helical apoA-I mimetic and apo J peptides have been shown to have anti-inflammatory and anti-atherogenic properties in animals [26]. One common mechanism proposed for the protective action of these peptides involves binding of oxidized lipids present in the circulating lipoprotein particles and cell membranes to form new lipoprotein particles. Sequestration of these oxidized lipids by peptides prevents their inhibitory action on various antioxidant enzymes which are associated with lipoproteins and cell membranes [26].

Acknowledgments

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