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COMMUNICATION

2,2′-Bis(monoacylglycero) PO_4 (BMP), but Not 3,1′-BMP, Increases Membrane Curvature Stress to Enhance α-Tocopherol Transfer Protein Binding to Membranes

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Abstract Previous work revealed that α-tocopherol transfer protein (α-TTP) co-localizes with bis(monoacylglycero) phosphate (BMP) in late endosomes. BMP is a lipid unique to late endosomes and is believed to induce membrane curvature and support the multivesicular nature of this organelle. We examined the effect of BMP on α-TTP binding to membranes using dual polarization interferometry and vesicle-binding assay. α-TTP binding to membranes is increased by the curvature-inducing lipid BMP. α-TTP binds to membranes with greater affinity when they contain the 2,2′-BMP versus 3,1′-BMP isomers.

Keywords α-Tocopherol transfer protein · Vitamin E · Bis(monoacylglycero)phosphate · Membrane curvature

Abbreviations

α-TTP	α-Tocopherol transfer protein
DPI	Dual polarization interferometry
LUV	Large unilamellar vesicle
SUV	Small unilamellar vesicle
DOPC	1, 2-Dioleoyl-*sn*-glycero-3-phosphocholine
DOPS	1, 2-Dioleoyl-*sn*-glycero-3-phospho-L-serine
DOPE	1, 2-Dioleoyl-*sn*-glycero-3-phosphoethanolamine
SM	Sphingomyelin
PI	L-α-Phosphatidylinositol

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Introduction

The human α-tocopherol transfer protein (α-TTP) is responsible for the selective retention of α-tocopherol over other forms of vitamin E in mammalian liver cells, as well as for the eventual secretion of α-tocopherol into plasma via VLDL particles [1]. Its vital role in tocopherol retention in brain is known, but much less well understood [2]. Using cultured hepatocytes, it was shown that expressed α-TTP co-localizes with bis(monoacylglycero)phosphate (BMP) in late endosomes [3]. BMP is a lipid that is only found in late endosomes where it accounts for ~15 mol% of total membrane phospholipids [4] and possesses a distinct sn-1(sn-1′) stereo configuration [5]. The pH-dependent fusogenic property of BMP, including its ability to form multivesicular structures [5, 6], implies that BMP may have the capacity to deform membranes. These membrane deformations strongly suggest that BMP is able to regulate membrane curvature in a pH-dependent manner.

We report here our investigations on the effect of BMP on α-TTP binding to lipid membranes using dual polarization interferometry (DPI) and vesicle-binding assays. While DPI allows the measurement of protein binding affinity to planar lipid surfaces, the vesicle-binding assay allows the assessment of protein binding affinity to lipid vesicles mimicking curved membranes. Our results suggest that α-TTP binding to lipid membranes is influenced by membrane curvature or curvature stress, which is brought about by BMP. This is in agreement with previous work performed by Zhang et al. [7] showing the propensity of α-TTP to bind to highly curved lipid vesicles.

Materials and Methods

Materials

Glutathione–Sepharose beads, DTT, PMSF, Triton X-100 and Bradford reagent were purchased from Sigma (St Louis, MO, USA). DNase I was obtained from Invitrogen (Carlsbad, CA, USA) whilst thrombin was acquired from GE Healthcare (Piscataway, NJ, USA). Protein markers were purchased from Bio-Rad (Hercules, CA, USA). ProtoBlue Safe was from National Diagnostics (Atlanta, GA, USA). All phospholipids were acquired from Avanti Polar Lipids (Alabaster, AL, USA) including 3,1′-(*S*,*R*)-bis(monooleoylglycero)phosphate (3,1′-(*S*,*R*)-BMP) and 3,3′-(*S*,*S*)-bis(monooleoylglycero)phosphate (3,3′-(*S*,*S*)-BMP). 2,2′-(*S*,*S*) Bis(monooleoylglycero)phosphate (2,2′-BMP) was from Echelon Biosciences (Salt Lake City, UT, USA). Numbering for BMP isomers follows that used by the lipid maps database at www.lipidmaps.org. Organic solvents were obtained from Caledon Laboratory Chemicals (Georgetown, ON, CA) and all other reagents and chemicals were from BioShop (Burlington, ON, CA).

Protein Expression and Purification

Human α-TTP was expressed in the *E. coli* strain BL21(DE3) and subjected to glutathione affinity purification as described previously [7]. Pure α-TTP was eluted and stored at 4 °C and remained viable for 1 week.

Lipid Vesicle Preparation

Large unilamellar vesicles (LUVs) were prepared using a LiposoFast extrusion device (Avestin, Inc., Ottawa, ON) and with 100, 200, or 400 nm polycarbonate membranes, while small unilamellar vesicles (SUVs) were prepared by probe sonication. Sizing of the 200 nm vesicles was described previously [7]. For this work, the mean diameter of 400 nm LUVs prepared in high sucrose SET buffer for the vesicle binding assay were measured by dynamic light scattering (DLS) using a BI-200SM Research Goniometer and Laser Light Scattering System from Brookhaven Instruments. Samples were equilibrated for 20 min at 20 °C before data collection. Data were collected at 90° scattering angle and fitted with the method of cumulants [8]. The viscosity of the sucrose-containing buffer was taken to be 1.27 cP. Table 1 lists the diameters for vesicles extruded using membranes containing 400 nm pores.

Dual Polarization Interferometry (DPI) Analysis of α-TTP Binding to Membranes

DPI experiments were performed using an Analight Bio200 (Biolin Scientific). The instrument was first equilibrated with DPI running buffer (10 mM potassium phosphate dibasic, 137 mM NaCl, pH 7.4). 400 μL of 100 nm LUVs prepared in the same DPI buffer (1.0–2.54 mM) were then deposited onto the surface of an unmodified FB80 silicon oxynitride sensor chip at a flow rate of 25 μL min^{-1} for 8 min. Lipid mixtures containing BMP isomers were used at 1.0 mM concentration. Once a stable immobilized lipid layer was formed, 400 μL of α-TTP (50–2,000 nM) was introduced onto the lipid layer using the same flow rate. The sensor chip was regenerated in between each set of lipid and protein injections using 2 % SDS solution followed by 50 % isopropyl alcohol.

The signal produced by the association of α-TTP to lipid membranes on the Analight Bio200 is expressed as a specific adsorbed mass in ng mm^{-2}. Mass adsorption was analyzed using AnaLight Explorer software, version 1.6.0.27583. The mass data over a 480 s time frame for each α-TTP concentration were resolved and fitted to a one-phase exponential association curve (GraphPad Prism). The maximum masses of α-TTP bound to the lipid layer for each injected α-TTP concentration were subsequently used to plot a saturation binding curve to obtain the binding affinity (K_d) of α-TTP to lipid membranes. Data were analyzed using a weighted sum of squares, $1/Y^2$. The equation used for one site binding was $Y = B_{max} \times X/(K_d + X)$, and for one-phase exponential association was $Y = Y_{max} \times (1 - \exp(-K \times t))$. Birefringence measurements were calculated at the maximum mass time points of the lipid and protein layers by fixing the refractive index to 1.47 [9].

Table 1 Measured vesicle diameters for LUVs comprise of endosomal lipids and various BMP isomers in sucrose containing buffer for use in the vesicle-binding assay

	Diameter (nm)	Polydispersity
Endosomal lipids, SUV, by sonication in DPI buffer	112.8	0.202
Endosomal lipids, SUV, by sonication in SET buffer	111.1	0.246
Endosomal lipids, 400 nm LUV in SET buffer	376.4	0.27
85:15, endosomal lipids: 2,2-(*S,S*)-BMP 400 nm LUV in SET buffer	354.1	0.20
85:15, endosomal lipids: 3,3′-(*S,S*)-BMP 400 nm LUV in SET buffer	332.6	0.19
85:15, endosomal lipids: 3,1′-(*S,R*)-BMP 400 nm LUV in SET buffer	365.5	0.27

Rate of α-TTP-Mediated NBD-Tocopherol Transfer to Vesicles

Transfer of NBD-α-tocopherol to unilamellar vesicles was assessed through a FRET assay as previously described [7]. Briefly, SUVs, 100 and 400 nm LUVs were prepared as above, either in TKE buffer (50 mM Tris–HCl, 0.1 mM KCl, 1 mM EDTA pH 7.4) or MKE buffer (50 mM MES, 0.1 mM KCl, 1 mM EDTA pH 5.5) with the exception that the lipid mixtures included 3 mol% tetramethylrhodamine phosphatidylethanolamine (TRITC–PE) as a fluorescence acceptor for NBD-α-tocopherol. Prior to the assay, 4 μM human α-TTP was incubated with 0.45 μM NBD-α-tocopherol for 30 min in the appropriate buffer. FRET assays were initiated upon mixing of this α-TTP-NBD-tocopherol solution with 0.2 mM acceptor vesicles via a stopped flow apparatus while monitoring the fluorescence decay of the NBD-α-tocopherol upon excitation at 466 nm. All fluorescence data were collected at 520 nm for nonlinear regression analysis in Prism GraphPad 5.0 software by fitting the data to a two-phase decay model. The slower rate constant was ignored. Data from four independent experiments were used in the rate analysis.

Vesicle Binding Assay Assessment of α-TTP Binding to Lipid Membranes

With minor modifications, the vesicle binding assay was performed as described in Morley et al. [10]. α-TTP (31.5 μg) was incubated with an increasing concentration of vesicles for 30 min at room temperature followed by filtration using a centrifugal concentrator, YM-100 microcons (Millipore), for 20 min at 10,000*g*. The flow-through contained unbound proteins while vesicle-bound protein was retained above the filter. Vesicle-bound protein was recovered with SET buffer (250 mM sucrose, 100 mM KCl, 50 mM Tris, 1 mM EDTA, pH 7.4) supplemented with 150 μM Triton X-100. All collected fractions were resolved by SDS-PAGE analysis. Protein bands were visualized using colloidal coomassie stain and were quantified by densitometry using Scion Image (Scion Corp.).

Results and Discussion

To determine the effect of BMP on α-TTP binding to membranes, a lipid mixture that mimicked the endosomal membrane was prepared as described by Kobayashi et al. [6]. This lipid mixture consisted of DOPC:DOPS:DOPE:SM:PI:BMP (50:5:20:5:5:15) [6] and was used throughout this work. DPI measurements revealed that the affinity of α-TTP for endosomal lipids without BMP was about twice that of DOPC:DOPS (90:10); $K_d = 810 \pm 168$ versus 1,640 ± 320 nM, respectively. However, in the presence of either 3,3′-(*S*,*S*)-BMP or 3,1′-(*S*,*R*)-BMP the binding affinity of α-TTP increased roughly twofold as reflected by the lower K_d values (500 ± 76 and 337 ± 58 nM, respectively) (Fig. 1; Table 2). DOPC:DOPS was included in all measurements as a means of comparison, since α-TTP is able to bind to this simple lipid mixture. While the BMP molecule brings a negative charge to the surface of membrane vesicles, α-TTP neither binds to nor transfers ligand faster to bilayers containing as much as 25 % phosphatidylserine (PS) a phospholipid that also brings a full negative charge to a membrane surface [7, 11]. The increased affinity of α-TTP for endosomal lipids can be rationalized as follows. BMP is a curvature-inducing lipid [5, 12]. The naturally occurring isomer is understood to be 2,2′-(*S*,*S*)-BMP [5] which can isomerize on isolation to the 3,3′-(*S*,*S*) isomer [13]. Forcing endosomal membranes containing BMP onto a flat surface should lead to an induced curvature stress [14, 15]. The maximum specific mass (B_{max}) of protein bound to the sensor chip, ranged from ~1.5 ng mm^{-2} for endosomal lipids and 3,1′-(*S*,*R*)-BMP to 2.1–2.4 ng mm^{-2} for DOPC:DOPS, 2,2′-(*S*,*S*)-BMP and 3,3′-(*S*,*S*)-BMP. However, in the presence of 2,2′-(*S*,*S*)-BMP the K_d decreased by almost fourfold to 210 ± 38 nM versus endosomal lipids lacking BMP which implies that α-TTP has a much stronger binding affinity to membranes containing 2,2′-(*S*,*S*)-BMP, thus suggesting a plausible role of this natural isomer of BMP in α-TTP binding to lipid membranes.

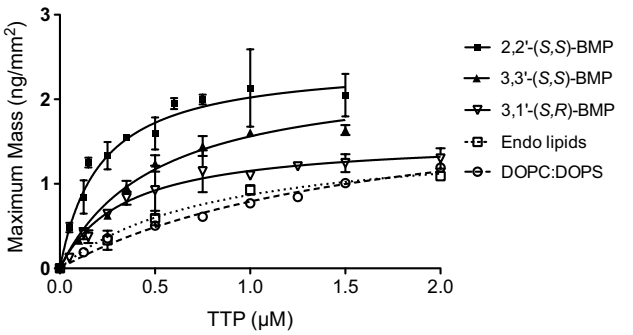

Fig. 1 Plot of maximum specific mass of α-TTP bound to DOPC:DOPS, endosomal lipids without BMP, endosomal lipids with 3,3′-BMP isomers, and endosomal lipids with 2,2′-(*S*,*S*)-BMP at pH 7.5. Data are representative of 4–8 measurements from 2 to 4 independent sample injections

The DPI experiments also speak to the effect of BMP isomers on changes to the apparent order of the bilayer when α-TTP is bound. Table 3 shows the effect of changing lipid composition on the birefringence of the supported bilayers with and without adsorbed TTP. Lipid bilayers are not isotropic when absorbed on the DPI sensor chip and are thus birefringent. The DPI can directly

Table 2 B_{max}, K_d and lipid layer thickness measurements for α-TTP binding to membranes obtained from DPI analysis

Lipid system	B_{max} (ng mm^{-2})	K_d (nM)	Lipid layer thickness (nm)
DOPC:DOPS (90:10)	2.09 ± 0.23	1,640 ± 320	3.30 ± 0.05
Endosomal lipids without BMP	1.58 ± 0.14	810 ± 168	2.71 ± 0.46
Endosomal lipids with 3,1′-(*S*,*R*)-BMP	1.54 ± 0.08	337 ± 57	2.84 ± 0.39
Endosomal lipids with 3,3′-(*S*,*S*)-BMP	2.31 ± 0.15	500 ± 76	2.60 ± 0.23
Endosomal lipids with 2,2′-(*S*,*S*)-BMP	2.45 ± 0.13	210 ± 38	1.60 ± 0.10

Lipids meant to mimic endosomal membranes were DOPC:DOPS:DOPE:SM:PI:BMP (50:5:20:5:5:15). When endosomal lipids lacked BMP the proportion of DOPC was increased from 50 to 65 %

Table 3 Effect of isomeric BMPs on the measured birefringence of supported lipid bilayers

Lipid system	Birefringence	Change in birefringence on injection of 0.5 M TTP (%)
Endosomal lipids only	0.01805 ± 0.000138	−10.0
Endo lipids + 15 % 3,1′-(*S*,*R*)-BMP	0.01672 ± 0.0008	−29.0
Endo lipids + 15 % 3,1′-(*S*,*S*)-BMP	0.016345 ± 0.001	−30.3
Endo lipids + 15 % 2,2′-(*S*,*S*)-BMP	0.016432 ± 0.0011	−52.0

Endosomal lipids meant to mimic the endosome comprised DOPC:DOPS:DOPE:SM:PI (65:5:20:5:5). When the BMP isomers were included the mixture was DOPC:DOPS:DOPE:SM:PI:BMP (50:5:20:5:5:15). The birefringence changes were also assessed at 0.75 M TTP with near identical results (−12.1, −37.4, −35.6, and −53 %, respectively)

measure the birefringence and we can use it to quantify the degree of order or alignment within the layer [9, 16]. The results show that all the bilayers containing BMP isomers and especially 2,2′-BMP had significantly reduced birefringence (29–52 % loss) when exposed to TTP, a result that is consistent with the model of TTP insertion into the bilayer resulting in loss of membrane lipid order.

Using a FRET-based assay and a fluorescent form of vitamin E (NBD-α-tocopherol) we have previously reported the effect of lipid composition and vesicle size on the rate of α-TTP mediated ligand delivery to phospholipid vesicles [7, 11]. Table 4 shows the rate constants for NBD-α-tocopherol delivery to SUVs and LUVs with and without BMP. As expected, transfer rates were higher to SUVs than LUVs, but were also significantly higher when the SUVs contained BMP, especially the 2,2′-(*S*,*S*)-BMP, in which the rate was ~50 % faster than with endosomal lipids alone. The absolute rates of ligand transfer to LUVs by α-TTP are much smaller than for SUVs and increases due to the presence of BMP isomers were not statistically significant, despite suggesting a similar trend.

Table 4 Effect of isomeric BMPs on the rate of α-TTP-mediated transfer of NBD-α-tocopherol to SUVs and LUVs of varying lipid composition

Lipid system	Rate constant for NBD-Toc transfer to SUVs by TTP (s^{-1})	Rate constant for NBD-Toc transfer to LUVs by TTP (s^{-1})
Bovine liver PC	0.174 ± 0.007	0.079 ± 0.004
Endosomal lipids only	0.256 ± 0.006	0.088 ± 0.004
Endo lipids + 15 % 3,1′-(*S*,*R*)-BMP	0.348 ± 0.007	0.100 ± 0.003
Endo lipids + 15 % 3,1′-(*S*,*S*)-BMP	0.353 ± 0.009	0.101 ± 0.003
Endo lipids + 15 % 2,2′-(*S*,*S*)-BMP	0.387 ± 0.010	0.105 ± 0.005

Due to uncertainties generated in the vesicle-binding assay, only the fraction of protein bound was considered and K_d values were not determined from this data. Nonetheless, when performed with 200 and 400 nm (data not shown) LUVs, more protein bound to 3,1′-(*S*,*R*)-BMP-containing vesicles reflecting the enhanced affinity in the presence of this lipid (Fig. 2; Table 5). However, when SUVs replaced LUVs, the effect of BMP was absent, as reflected by the B_{max} values (Fig. 3; Table 6). It was interesting to note that regardless of lipid composition, the amount of α-TTP bound to SUVs were higher in comparison to LUVs implying that α-TTP binding to membranes is influenced by membrane curvature. This observation is consistent with Zhang et al. [7] findings that, compared to LUVs, the ligand transfer rate by α-TTP was greater with SUVs containing only PC compared to LUVs. When α-TTP was replaced with bovine serum albumin (BSA), no specific binding toward these lipid systems were observed (data not shown) which supports the conclusion that α-TTP binding to membranes is not a result of non-specific binding of the protein to the lipids or the centrifugal filter. In addition, it excludes the notion that α-TTP may be trapped between the lipid vesicles. The effect of BMP stereoisomers on α-TTP binding to lipid vesicles was also tested. The outcome of this

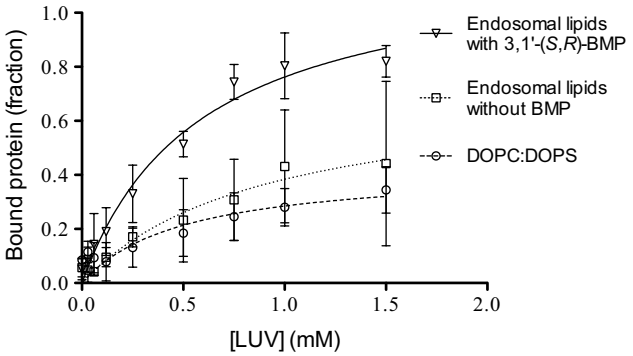

Fig. 2 α-TTP binding to 200 nm LUVs at pH 7.5 (from three separate measurements)

Table 5 B_{max} values obtained from α-TTP-LUV (200 nm) vesicle binding curves at pH 7.5

Lipid system	B_{max}
DOPC:DOPS	0.43 ± 0.095
Endosomal lipids without BMP	0.73 ± 0.294
Endosomal lipids with 3,1′-(*S*,*R*)-BMP	1.21 ± 0.119

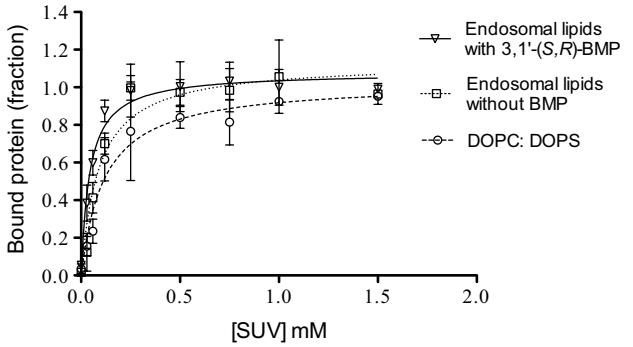

Fig. 3 α-TTP binding to SUVs at pH 7.5 (from three separate measurements)

Table 6 B_{max} values obtained from α-TTP-SUV binding curves at pH 7.5

Lipid system	B_{max} (bound protein fraction)
DOPC:DOPS	1.03 ± 0.053
Endosomal lipids without BMP	1.13 ± 0.051
Endosomal lipids with 3,1′-(*S*,*R*)-BMP	1.08 ± 0.031

investigation showed that 2,2′-BMP enhances binding to a greater extent than 3,3′- or 3,1′-BMP isomers with 400 nm LUVs (Fig. 4; Table 7). We also attempted binding assays at pH 5.5 that would better mimic the environment of BMP containing membranes in the endosome,

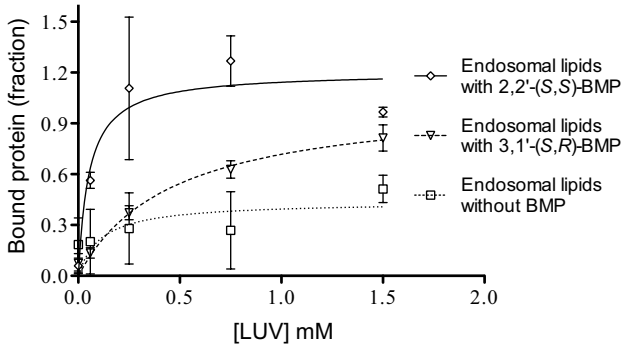

Fig. 4 Comparison between α-TTP binding to 400 nm LUVs containing 2,2′-(*S*,*S*)-BMP, 3,1′-(*S*,*R*)-BMP and without BMP at pH 7.5 (from three separate measurements)

Table 7 B_{max} values obtained from α-TTP-LUV (400 nm) binding curves at pH 7.5

Lipid system	B_{max} (bound protein fraction)
Endosomal lipids without BMP	0.44 ± 0.119
Endosomal lipids with 3,1′-(*S*,*R*)-BMP	1.05 ± 0.086
Endosomal lipids with 2,2′-(*S*,*S*)-BMP	1.20 ± 0.108

but these conditions are close to the pI of α-TTP (5.2) and caused partial protein precipitation. No rate differences were apparent when FRET assays with LUVs were conducted at pH 5.5.

These data suggest that membrane curvature is an important factor influencing α-TTP's binding to membranes, specifically as a result of the local curvature generated by BMP. The recruitment of peripheral proteins to membranes due to by curvature stress in the lipid bilayer is one that cannot be overlooked [14, 17–19]. When a lipid bilayer exhibits curvature stress due to the presence of non-bilayer lipids such as BMP, it promotes exposure of hydrophobic sites between the lipid head-groups, also known as insertion sites, which allow easier access of proteins to bind to the bilayer. In addition, the binding of proteins to a curvature-stressed membrane aids in relieving the curvature stress by allowing lipids that are within close proximity of the protein to splay apart [17–19].

The importance of α-TTP in specifically retaining α-tocopherol in the liver during the absorption of dietary lipids has been well studied [1, 10, 20, 21]. However, the means by which α-tocopherol is packaged into lipoproteins and secreted from the liver remains largely unknown. α-TTP is known to localize to the late endosomal compartment, a membrane system heavily enriched in BMP. Our results add to the existing evidence for a possible role for BMP in enhancing α-TTP's binding to these membranes. The implications of this add to our developing

understanding of the mechanism of tocopherol secretion from hepatocytes.

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