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Letter

Suppression of Amyloid-β Adsorption on Endoplasmic Reticulum Stress-Mimicking Membranes by α-Tocopherol and α-Tocotrienol

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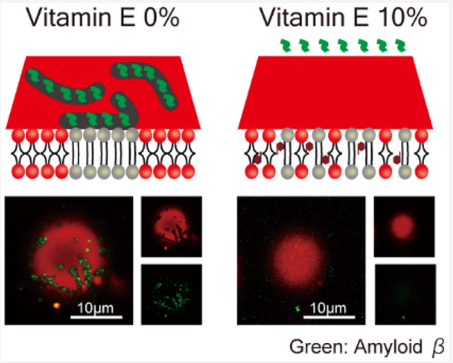
ABSTRACT: Two forms of hydrophobic vitamin E (VE), α-tocopherol (Toc) and α-tocotrienol (Toc3), have been proposed to be effective against Alzheimer's disease (AD), the etiology of which is thought to involve endoplasmic reticulum (ER) stress. However, previous studies reported conflicting effects of Toc and Toc3 on the risk of AD. We prepared liposomes mimicking the phase separation of the ER membrane (solid-ordered/liquid-disordered phase separation) and studied how VE can influence the interaction between amyloid-β (Aβ) and the ER membrane. We found that Toc could inhibit the formation of the solid-ordered phase more significantly than Toc3. Furthermore, Aβ protofibril adsorption on ER stress-mimicking membranes was more strongly suppressed by Toc compared with Toc3. Therefore, we concluded that VE can relieve ER stress by destabilizing the solid-ordered phase of the ER membrane and subsequently reducing the amount of Aβ adsorbed on the membrane. Moreover, Toc exerted a stronger effect than Toc3.



Vitamin E (VE) was discovered as a fat-soluble vitamin that could prevent infertility.[1] α-Tocopherol (Toc), the most abundant form of VE, and α-tocotrienol (Toc3), another form of VE, share chroman rings in the same methylation state. Toc and Toc3 have different hydrocarbon side chains attached to the chroman ring; Toc has a phytyl group, while Toc3 has a farnesyl group. Unlike the phytyl group, the farnesyl group has three *trans* double bonds, making Toc3 more hydrophilic.[2] Negative correlations have been reported between plasma Toc and Toc3 levels and the development of Alzheimer's disease (AD), although several reports have contradicted these findings.[3−5] It is not well understood how Toc and Toc3 inhibit AD.

Endoplasmic reticulum (ER) stress resulting from abnormalities in protein folding is believed to be a major factor involved in the etiology of AD.[6] To reduce ER stress, the unfolded protein response (UPR) is induced to cope with misfolded proteins by increasing protein folding ability, decreasing protein synthesis, and promoting ER-associated degradation.[7,8] If ER stress cannot be alleviated, the UPR triggers cell death. Amyloid-β (Aβ) is prone to misfolding, and the accumulation of Aβ causes AD due to neuronal cell death induced by ER stress.[9,10] The toxicity of Aβ varies depending on its degree of polymerization, with intermediates to the fibrillar structure being highly toxic.[10,11] Previous studies have shown that Aβ oligomers and protofibrils, which are highly toxic Aβ species, have a greater impact on membrane dynamics than monomers and fibrils, which are less toxic species.[12,13] Furthermore, we found that highly toxic Aβ oligomers and protofibrils tend to accumulate on the solid-ordered (S_o) phase of membranes, which is rich in saturated lipids, rather than the liquid-disordered (L_d) phase, which is rich in unsaturated lipids, or the liquid-ordered (L_o) phase, which is rich in saturated lipids and cholesterol (Chol), by using liposomes.[14−16] The ER membrane is known to have low Chol content.[17,18] Saturation of ER membrane lipids is known as ER stress.[19,20] When long-chain fatty acids, such as palmitate, are fed, saturated lipids are synthesized, forming the S_o phase on the ER membrane, leading to cell death.[21] Therefore, we considered that the formation of the S_o phase is related to ER stress. Biomimetic membranes can form a variety of phase states such as the S_o, L_d, and L_o phases.[22] Therefore, we prepared a Chol-free biomimetic membrane that forms the S_o phase as a model for the ER stress membrane.

Recently, Toc, but not Toc3, was reported to reduce the cytotoxicity caused by 24S-hydroxycholesterol (24S-OHC), which is associated with AD.[23] Toc and Toc3 are present in biological membranes and have different effects on membrane properties.[24−26] In this study, we clarify the effects of Toc and Toc3 on the adsorption of Aβ on ER stress-mimicking membranes.

To assess the effects of Toc and Toc3 on ER stress-mimicking membranes, we observed phase separation in liposomes by fluorescence microscopy at room temperature.

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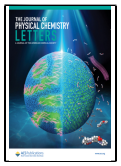

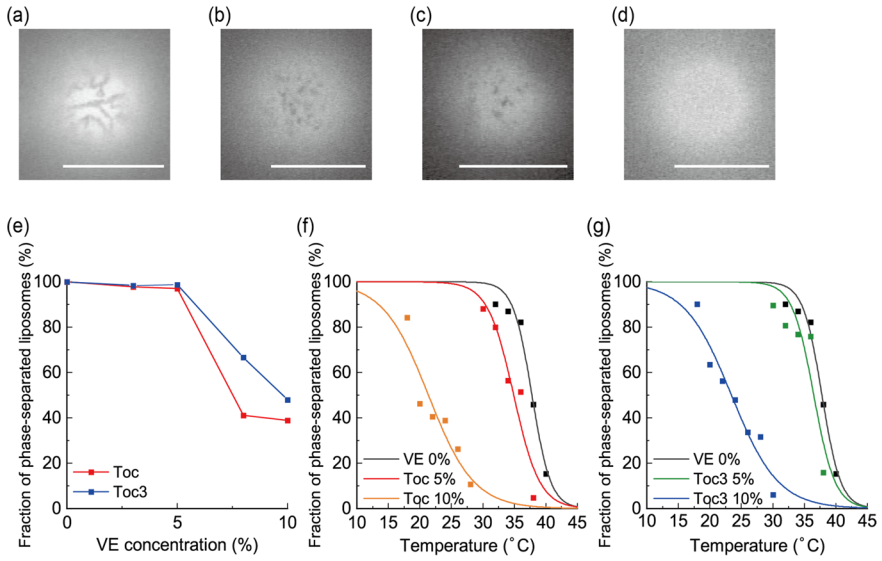

Figure 1. (a) Microscopic images of S_o/L_d phase separation at DOPC/DPPC = 50:50 (0% VE), (b) at DOPC/DPPC/Toc = 47.5:47.5:5 (5% Toc), and (c) at DOPC/DPPC/Toc3 = 47.5:47.5:5 (5% Toc3). (d) Microscopic image of homogeneous liposomes at DOPC/DPPC/Toc = 45:45:10 (10% Toc). Scale bars: 10 μm. (e) Fraction of phase-separated liposomes as a function of VE concentration. (f, g) Fraction of phase-separated liposomes containing Toc and Toc3, respectively, as a function of temperature.

Liposomes were prepared by the natural swelling method. Liposomes were composed of dipalmitoylphosphocholine (DPPC) and dioleoylphosphocholine (DOPC) with and without VE (Toc and Toc3). The chemical structures of DOPC, DPPC, Toc, and Toc3 are shown in Figure S1. Chol is often used to observe the phase behavior of lipid membranes;[22] however, because we focused on the ER membrane with low Chol levels, we did not use Chol. VE was added from 0 to 10% (0, 3, 5, 8, and 10%) with a fixed ratio of DOPC:DPPC = 50:50. As a fluorescent probe, rhodamine B 1,2-dihexadecanoyl-*sn*-glycerol-3-phosphoethanolamine, triethylammonium salt (Rhod-DHPE), which localizes to the DOPC-rich phase, was used. The details of the experimental method can be found in the Supporting Information.

At DOPC:DPPC = 50:50 without VE, phase separation was observed (Figure 1a). The dark and bright regions were the DPPC-rich S_o phase and DOPC-rich L_d phase, respectively. We added VE to this binary lipid mixture. Although S_o/L_d phase separation was also observed at 5% VE, the domain size became smaller (Figure 1b,c). After adding more VEs, phase separation was suppressed and the homogeneous phase appeared (Figure 1d). The fractions of phase-separated liposomes are summarized in Figure 1e. The important difference between Toc and Toc3 was that Toc strongly suppressed phase separation compared with Toc3.

Next, to estimate the effects of Toc and Toc3 on the thermal stability of S_o/L_d phase separation, we measured the miscibility temperature (T_{mix}) of the phase-separated domain, which was defined as the temperature at which the fraction of phase separation was 50%. T_{mix} reflects the thermal stability of phase-separated structures. We measured the fraction of phase-separated liposomes at each temperature, and the obtained experimental results were fitted by Boltzmann's sigmoid function (eq S1) to obtain T_{mix}. The measured T_{mix} values were 37.8 °C (control), 34.9 °C (5% Toc), 21.4 °C (10% Toc), 36.5 °C (5% Toc3), and 23.4 °C (10% Toc3) (Figure 1f,g). The values of T_{mix} decreased as VE concentration increased. In addition, the tendency for a reduction of T_{mix} can be seen more clearly for Toc than for Toc3. These data suggest that Toc and Toc3 disturb S_o/L_d phase separation.

The chain melting transition temperatures (main transition) of DPPC membranes containing Toc and Toc3 were investigated using differential scanning calorimetry (DSC). The details of DSC can be found in the Supporting Information. The thermograph for the DPPC single-component membrane showed two peaks at 37.2 and 42 °C, corresponding to pretransition and main transition, respectively (Figure 2a,b), which was consistent with a previous report.[27] Because pretransition disappeared by adding VE, we focused on the shift of the main transition temperature. As the concentration of VE increased, the peak shifted toward a lower temperature and became broader, indicating that VE inhibited the strong attraction between DPPC molecules and reduced phase transition cooperativity. Moreover, the peak shape became asymmetric. We assumed that this asymmetric peak was composed of two symmetric peaks, and we plotted the changes in the positions of these two peaks (Figure 2c). The details of peak deconvolution and peak changes are shown in Figures S2 and S3. The sharp peak at higher temperatures and the broad peak at lower temperatures corresponded to the DPPC-rich S_o phase and VE-rich phase, respectively. These two peaks shifted toward a lower temperature as the concentration of VE increased. As previously reported, Toc showed a concentration-dependent decrease in the phase transition temperature of DPPC.[28] In this study, we found that Toc3 slightly destabilized these phases compared with Toc. Therefore, VE reduced the thermal stability of both phases.

Because Toc and Toc3 both decreased the thermal stability of DPPC membranes representing the S_o phase in DSC, they may be mainly partitioned into the L_d phase in S_o/L_d phase-separated membranes. However, some amount of VE was incorporated into the DPPC-rich S_o phase because of mixing entropy. We considered that the amount of Toc in the S_o phase was larger than that of Toc3 because Toc3 destabilized DPPC membranes compared with Toc according to DSC. On the

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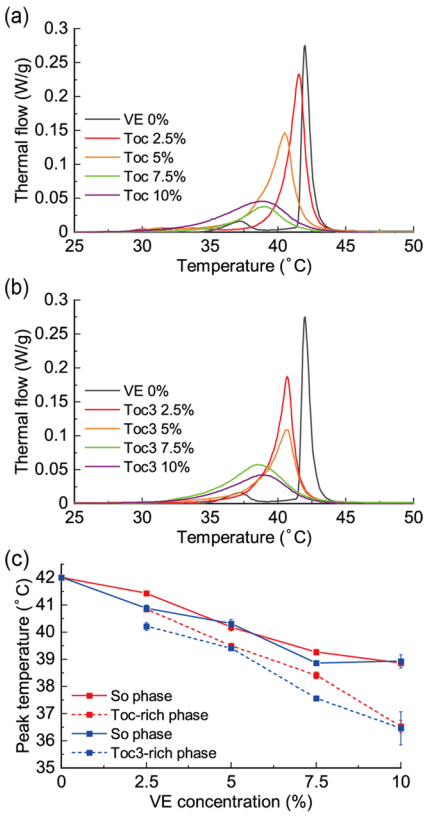

Figure 2. DSC thermograph of membranes composed of (a) DPPC/Toc and (b) DPPC/Toc3. (c) Peak temperature changes of deconvoluted DSC thermographs as a function of VE concentration.

other hand, Toc destabilized the phase-separated structures at room temperature and decreased T_{mix} compared with Toc3. VE incorporated into the S_o phase diluted the favorable interactions between DPPC molecules and decreased T_{mix}.[29] The destabilization effect of Toc was stronger than that of Toc3 because the amount of Toc in the S_o phase was probably larger. In the future, it will be important to measure the exact amount of VE in the S_o phase, for example, by nuclear magnetic resonance.

The differences of partitioning between Toc and Toc3 arose from differences in their chemical structures (Figure S1). From normal-phase high-performance liquid chromatography, it was reported that Toc3, with its unsaturated side chain, is more polar than Toc[2]. In other words, Toc3 is more hydrophilic than Toc. The DOPC-rich L_d phase is more loosely packed than the DPPC-rich S_o phase, making it easier to incorporate water molecules into the L_d phase. Therefore, Toc3 is more likely to be partitioned into the hydrophilic-L_d phase than Toc. In contrast, the amount of Toc in the S_o phase was larger than that of Toc3. Similar behavior has been observed with the addition of fatty acids to lipid membranes, and a saturated fatty acid (palmitic acid) has higher affinity to the S_o phase than a *trans*-fatty acid (elaidic acid).[30]

Next, we added Aβ protofibrils to liposomes containing Toc and Toc3 and observed them at room temperature by confocal laser scanning microscopy. We used Aβ peptide with 42 amino acid residues and fluorescently labeled Aβ (HiLyte Fluor 488, Aβ-488) and mixed them at a ratio of 2:1. The mixed Aβ was incubated for 12 h to aggregate spontaneously into protofibrils.[16] Details of sample preparation can be found in the Supporting Information. At 0% VE, S_o/L_d phase-separated

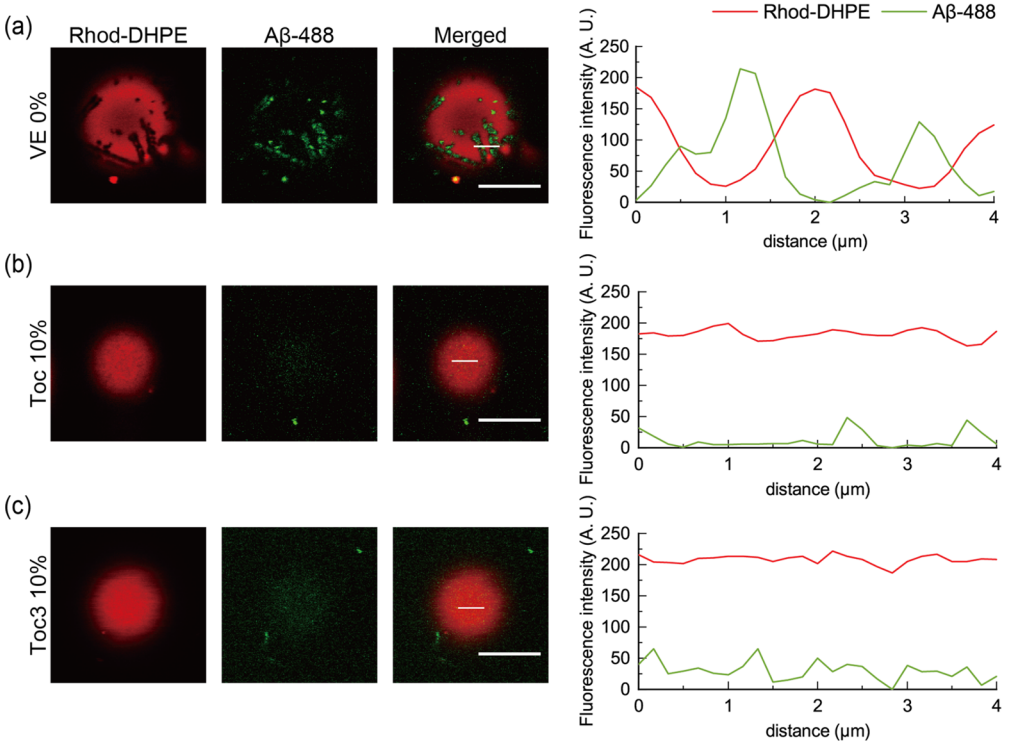

Figure 3. Microscopic images obtained by confocal laser scanning microscopy and fluorescence intensity profiles along the white lines in the merged images. Aβ protofibril adsorption on liposomes containing (a) 0% VE, (b) 10% Toc, and (c) 10% Toc3. Red and green fluorescence represent Rhod-DHPE and Aβ-488, respectively. Red and green lines in the fluorescence intensity profiles indicate the intensities of Rhod-DHPE and Aβ-488, respectively. Scale bars: 10 μm.

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liposomes were observed, and the regions with higher and lower Rhod-DHPE fluorescence intensities corresponded to the L_d and S_o phases, respectively (Figure 3a). The fluorescence intensity of Aβ-488 was higher in the S_o phase, indicating that Aβ protofibrils are selectively adsorbed onto the S_o phase, which is consistent with previous studies.[15,16] At 5% VE, most of the liposomes were phase-separated into the S_o and L_d phases. Similarly, Aβ protofibrils were selectively adsorbed onto the S_o phase (Figure S4). On the other hand, at 10% VE, more than 50% of liposomes exhibited a homogeneous phase, as already shown in Figure 1e. In such liposomes, we could not observe Aβ adsorption onto the surface of liposomes (Figure 3b,c). We concluded that Aβ adsorption correlated to S_o phase formation. Because Toc strongly suppressed the formation of the S_o phase compared with Toc3 from microscopic observations (Figure 1), Toc prevented Aβ adsorption onto the ER stress-mimicking membranes compared with Toc3.

There are various conflicting reports regarding Toc and Toc3.[31,32] The chroman ring structure responsible for their antioxidant effect is the same, and only the hydrocarbon chains are different between them. This may result in their different localization in organelle membranes and membrane subdomains and then cause different effects on diseases. In this study, we found that Toc inhibited S_o phase formation more strongly than Toc3, suggesting that local lipid composition affects the localization of Toc and Toc3. We have shown that 25S-OHC promotes ER stress-induced cell death via changes in membrane properties.[33] 24S-OHC, which has a similar structure to 25S-OHC, also induces neuronal cell death via ER stress.[34] Toc can inhibit this 24S-OHC-induced cell death; however, the mechanism by which Toc inhibits cytotoxicity by 24S-OHC is poorly understood. 24S-OHC is esterified by acyl-coenzyme A:cholesterol acyltransferases residing in ER membrane proteins to form 24S-OHC-ester, which causes the loss of ER membrane integrity.[34] Our findings suggests that Toc has a greater effect on ER membrane properties than Toc3 in the ER stress state and that the Toc-induced changes in ER membrane properties may contribute to the mitigation of the toxicity of 24S-OHC ester.

The ER is one of the most important organelles for lipid metabolism, and the ER membrane changes its lipidome in response to the surrounding environment. Supplementation of cultured cells with saturated fatty acids promotes the synthesis of saturated lipids in the ER, leading to the formation of the S_o phase.[21] We hypothesized that the accumulation of Aβ on the S_o phase causes ER stress. Thus, the higher the saturated lipid content of the ER membrane, the more misfolded proteins may be adsorbed to the ER membrane. Eventually, the UPR fails to adequately alleviate ER stress, and cell death is induced.

VE is expected to be effective in inhibiting the onset of AD,[3,4,35] however, it is not clear whether Toc or Toc3 is more effective in inhibiting AD. One of the reasons for this is that there are multiple mechanisms involved in the pathogenesis of AD. Using ER stress-mimicking membranes, our results have clearly show that by inhibiting the membrane adsorption of Aβ protofibrils, Toc is more effective than Toc3. This is because Toc destabilizes the S_o domain more strongly than Toc3, and a similar mechanism may apply to other molecules such as docosahexaenoic acid and eicosatetraenoic acid, which are thought to prevent AD.[29−31]

The involvement of ER stress has been reported in diseases other than AD, such as diabetes.[39] VE and docosahexaenoic acid are thought to have inhibitory roles in the development of type 2 diabetes.[40,41] Saturated fatty acid intake is a known risk factor for diabetes.[42] Docosahexaenoic acid (DHA) alters the cell lipidome and increases the levels of polyunsaturated lipids.[43] In ternary model membranes (DOPC, DPPC, and Chol), the disappearance of S_o/L_d phase separation occurs when the ratio of DOPC to DPPC increases.[22] However, increasing the unsaturation in the low-T_m lipid in mixtures with desaturated phospholipid in binary model membranes has been shown to increase S_o thermostability.[44] An increased concentration of polyunsaturated free fatty acids in the cell may compete with palmitate for the synthesis of phospholipids in the ER, as shown for the unsaturated oleic acid and DHA.[21,45] Therefore, the effects in ER and model membranes may differ. Thus, preventing the saturation of ER membrane lipids can avoid the induction of the UPR and cell death and alleviate these diseases.

In this study, we investigated the phase behavior and thermal stability of the phase-separated structures in ER stress-mimicking membranes containing Toc and Toc3. From microscopic observations, Toc suppressed S_o phase formation in ER stress-mimicking membranes more strongly than Toc3. On the other hand, DSC showed that the DPPC-rich S_o phase was destabilized more by Toc3 than by Toc. It was also demonstrated that the amount of Toc in the S_o phase was probably larger than that of Toc3, and Toc inhibited the formation of the S_o phase more strongly than Toc3. In addition, Aβ adsorption onto ER stress-mimicking membranes was also reduced by VE, especially Toc, due to the suppression of S_o phase formation. It is considered that the suppression of S_o phase formation by adding Toc has more pronounced effects on the reduction of ER stress-denatured proteins compared with the addition of Toc3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpclett.2c03098.

Experimental details; Figures S1−S4 (PDF)

Transparent Peer Review report available (PDF)

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Notes

The authors declare no competing financial interest.

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