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Structural Dynamics of α_1-Acid Glycoprotein in the Membrane Interaction Revealed by Time-Resolved Vacuum-Ultraviolet Circular Dichroism

Satoshi Hashimoto[a] and Koichi Matsuo[a,b,c]

[a]*Graduate School of Advanced Science and Engineering, Hiroshima University, 1-3-1 Kagamiyama, Higashi-Hiroshima 739-8526, Japan*
[b]*Research Institute for Synchrotron Radiation Science, Hiroshima University, 2-313 Kagamiyama, Higashi-Hiroshima 739-0046, Japan*
[c]*International Institute for Sustainability with Knotted Chiral Meta Matter (WPI-SKCM2), Hiroshima University, 2-313 Kagamiyama, Higashi-Hiroshima 739-0046, Japan*

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α_1-acid glycoprotein (AGP) binds to drugs such as steroid hormones and releases them through membrane interactions, inducing its β-α structural transition[1]. Thus, AGP is used as a model protein for drug transport into the cell membrane. Studies have shown that two α-helices in the N- and C-terminal regions are key interaction sites[2,3] but the detailed membrane interaction mechanism, including electrostatic and hydrophobic forces, remains unclear. Recently, we developed a time-resolved (TR) vacuum-ultraviolet circular dichroism (VUVCD) spectrophotometer using synchrotron radiation to observe hierarchical protein structural transitions[4]. This study employed TR-VUVCD to analyze AGP's structural transitions and membrane interactions. TR-VUVCD spectra of AGP interacting with DMPG liposomes were measured within a 260–180 nm wavelength and 1–700 seconds (FIGURE 1). Analysis of TR data revealed that 90% of AGP's β-α transition occurred within 10 seconds of mixing with liposomes. Additionally, two distinct rate constants indicated that the transition from the native (N-) state to the membrane-bound (M-) state proceeded via an intermediate (I-) state. Secondary structure contents, segments, and sequences of AGP in the N-, I-, and MB-states were calculated from spectra. Physical parameters of each helical segment suggested that in the first step, two helices in the N-state interacted with the membrane, forming three new helices (I-state), and in the second step, an additional helix formed on the membrane (M-state). These insights provide valuable information for understanding AGP's drug delivery mechanism.

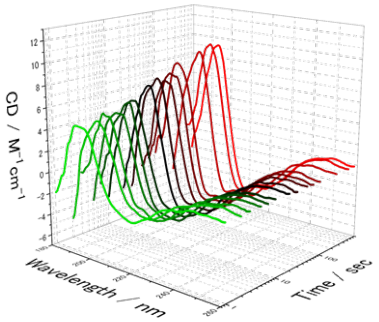

FIGURE. TR-VUVCD data sets in the interaction process between AGP and DMPG liposome.

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