The effect of antiviral drugs on the surface properties and stability of model lipid viral envelopes.

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Lipid viral envelopes protect the viral genetic material and contribute to virion stability, making them attractive auxiliary targets for antiviral agents. Recently, we developed physicochemically relevant model lipid envelopes for two enveloped viruses, influenza A (AH1N1) and SARS-CoV-2, with lipid compositions adjusted to reflect the major phospholipids characteristic of their native membranes [1]. Two-dimensional (2D) models were prepared as Langmuir monolayers and characterized using surface pressure–area isotherms and Brewster angle microscopy, while selected systems were further analyzed by grazing-incidence X-ray diffraction and polarization modulation infrared reflection–absorption spectroscopy. To account for membrane curvature and extend the study to three-dimensional (3D) systems, liposomes and giant unilamellar vesicles of corresponding lipid compositions were also prepared and investigated by dynamic light scattering, zeta potential measurements, and fluorescence microscopy.

These model systems were then used to examine the interactions of two antiviral agents with viral lipid envelopes: oseltamivir phosphate with the influenza A envelope model and amantadine with the SARS-CoV-2 envelope model. In both cases, the drugs altered membrane organization, but the extent and mechanism of these effects depended strongly on membrane composition, lipid charge, and packing. Oseltamivir significantly disorganized the influenza ternary monolayer, shifted the isotherms toward larger molecular areas, reduced the compression modulus, weakened attractive intermolecular interactions, and delayed condensed domain formation, indicating fluidization and reduced membrane order. Its strongest effect was observed for the negatively charged DMPS component, pointing to a dominant role of electrostatic interactions [2].

Amantadine also reorganized the SARS-CoV-2 envelope models, but its behavior depended on the lipid environment. In more fluid DOPC- and PI-containing layers it promoted molecular expansion and incorporation into the membrane, whereas in case of DMPS monolayers stronger electrostatic interactions modified packing in a different way. For the ternary SARS-CoV-2 model, hysteresis analysis and Brewster angle microscopy indicated drug-induced domain formation and phase separation. In 3D bilayer models, amantadine changed liposome hydrodynamic diameter and surface charge, while fluorescence microscopy confirmed its incorporation and bilayer reorganization. Molecular dynamics simulations further supported preferential localization of amantadine near the membrane interface with partial insertion into the lipid layer.

Overall, our results show that standard antiviral agents can directly affect viral lipid envelope organization in a composition-dependent manner. This supports the concept that the lipid envelope, beyond viral proteins alone, may serve as a relevant physicochemical target in the design of new antiviral strategies.

References:

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