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Effects of Cholesterol Peroxidation on the Properties of Lipid Bilayers

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INTRODUCTION

Cholesterol (ChH) is naturally found in all eukaryotic cells and is susceptible to peroxidation. Photodynamically generated singlet oxygen molecules ($^1O_2$) can react directly with ChH via ene addition, producing cholesterol hydroperoxides (ChOOH). The cytotoxic and apoptotic effects of ChOOH can be partly attributed to their effects on the biophysical properties of phospholipid membranes,[1] as well as their ability to disseminate oxidative stress. These abilities relate strongly to the chemical structure of these hydroperoxides, but the underlying molecular mechanisms are not well understood. For this reason, in this work we use molecular dynamics simulations to study the structure-property relations that affect the cytotoxicity of different cholesterol hydroperoxides and peroxyl radicals (ChOO·) at phosphatidylcholine (POPC) bilayers.

METHODS

Atomistic molecular dynamics simulations were used to calculate the properties of the studied systems. Simulation results were analyzed based on the distributions, orientations and degrees of hydration of cholesterol hydroperoxides in membranes.

RESULTS AND DISCUSSION

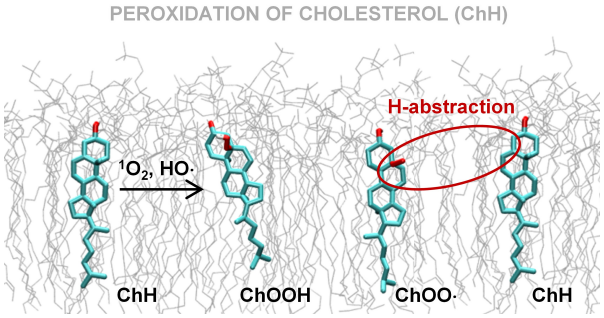

Figure 1. Qualitative scheme of the structure of a POPC bilayer containing cholesterol (ChH) and the peroxidation products: ChOOH and ChOO·.

Simulations showed that after peroxidation, the rigid sterol backbone tilted with respect to the membrane and the generated -OOH groups engaged in H-bond interactions with phospholipids carbonylester groups. The orientation of cholesterol hidroperoxides with respect to the membrane normal depended on the peroxidation site. As a result, some properties of the lipid bilayer were modified such as the thickness, area, deuterium order parameter and the isothermal compressibility module.

CONCLUSIONS

The orientation of cholesterol hydroperoxides with respect to the normal vector of the bilayer showed to be dependent peroxidation site. The effect was analogous to the previously reported "floating" of -OOH groups in phospholipid hydroperoxides.[2] However, the whole sterol was forced to reorient due to its rigid structure. Based on these results, it can be inferred that cholesterol hydroperoxides may decrease the rigidity and destabilize membranes liquid-ordered domains. In the case of cholesterol peroxyl radicals, the -OO · groups did not migrate to the region of polar groups. This may facilitate the hydrogen abstraction reactions and the spread of oxidative stress.

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