IOCT 2025 Conference
The 3rd International Online Conference on Toxins
10–12 September 2025 | Online
MDPI

Cobra Venom Cytotoxin as a Tool for Probing Polymorphic Transitions, Proton Absorption and Permeability of Membranes Made of Phosphatidylethanolamine or Phosphatidylserine

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INTRODUCTION & AIM

Survivin, a protein regulating mitosis, is overexpressed in all cancers. Unlike its expression during G2 and mitosis in healthy cells, survivin in cancer cells is active throughout the interphase, localizing in the nucleus, cytosol, and mitochondria. Mitochondrial survivin has been shown to enhance phosphatidylserine (PS) decarboxylase activity, increasing the concentration of non-bilayer phosphatidylethanolamine (PE), a feature phospholipid in the inner mitochondrial membrane (IMM) that facilitates oxidative phosphorylation by promoting polymorphic transitions and proton absorption to facilitate mitochondrial ATP synthesis. By increasing PE through decarboxylation of PS, survivin may remodel IMM architecture, stimulating cancer development. To investigate the interplay of PE and PS in polymorphic transitions in IMM, this study uses cobra venom cytotoxin II (CTII), which, at low concentrations, promotes lipid polymorphism. By examining lipid polymorphism, membrane permeability and proton absorptivity, we aim to shed light on PE and PS roles in IMM functionality in cancer.

METHOD

Phospholipid liposomes made of either PE or PS were prepared by ultrasonic radiation of phospholipid aqueous dispersions. The effects of CTII interaction with liposomes on membrane polymorphism and permeability were assessed using the ^{1}H-NMR spectroscopy and the $[Cu(H_2O)_2(NH_3)_4]^{2+}$ complex ion spectrophotometry. Proton absorption by membranes in the absence and presence of CTII was quantified by measuring pH differences in an aqueous buffer with and without liposomes.

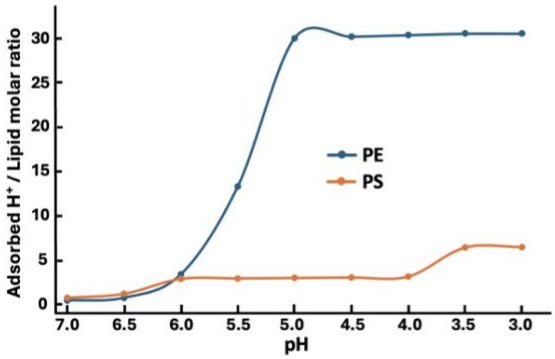

Figure 1. Adsorption of H^+ on the surface of PE and PS liposomes at a lipid concentration of 6×10^{-8} mol/dm³ as a function of the change in pH values. Each data point represents the molar ratio of protons adsorbed per a lipid molecule, calculated from the means of triplicate experimental values, therefore, standard deviations (SDs) for the values of protons adsorbed per a lipid (values on axis Y) were not determined.

RESULTS & DISCUSSION

CTII induced the formation of non-bilayer structures in both PE and PS membranes. In PS membranes, non-bilayer structures increased membrane permeability, whereas the inverted lipid micelles induced by CTII in PE membranes did not affect membrane permeability. Furthermore, CTII-treated PE membranes demonstrated superior proton absorption compared to CTII-treated PS membranes.

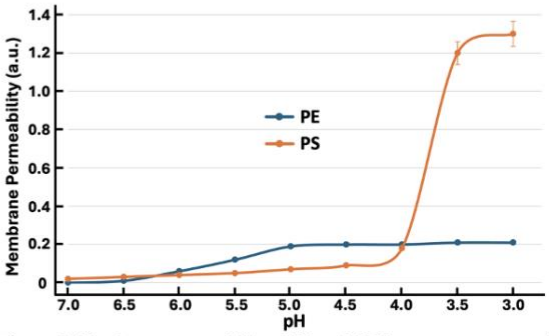

Figure 2. Membrane permeability of PE and PS liposomes, measured in arbitrary units (a.u.) of optical density at a wavelength of 600 nm, as a function of the change in pH values. Lipid concentration was 6×10^{-8} mol/dm³. Each data point represents the mean of triplicate experiments. Error bars indicate the ±standard deviation (±SD) of the triplicates.

This research explains a potential survival mechanism for cancer cells that produce energy through a Warburg effect process, which acidifies their local environment. Mitochondria in these cells have membranes enriched with PE which has a high capacity to absorb protons and act as a buffer that helps maintaining a stable pH gradient across the mitochondrial membrane. This stability protects the function of key energy-producing complexes, like ATP synthase, and allows glycolytic enzymes to function in the acidic conditions that cancer cells create. Therefore, the ability of PE to regulate local pH may allow cancer cells to simultaneously support high glycolytic activity and preserve oxidative phosphorylation. This dual advantage could explain why cancer cells with PE-enriched membranes have a higher survival rate.

CONCLUSION

Superior proton absorption and the inverted micelles formation triggered by CTII in PE membranes—without compromising membrane permeability—may represent key features of the IMM that enhance ATP production, thereby supporting the accelerated proliferation of cancer cells.

REFERENCES

Gasanoff E.S., Dagda R.K. Cobra venom cytotoxins as a tool for probing mechanisms of mitochondrial energetics and understanding mitochondrial membrane structure. *Toxins* 16, 287, 2024.