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Biophysical modulation of lipid model membranes by cobalt and nickel

Cobalt (Co) and Nickel (Ni) are important industrial metals used in the manufacture of a variety of everyday products. Additionally, Co is an essential trace element for humans, involved in the structure and function of vitamin B_{12}. Ni is naturally-present in the human body, but its status as an essential element is not confirmed. Despite their natural occurrence in the human body, increased exposure to Co and Ni, occurring in industrial environments, may result in a variety of toxic effects including: carcinogenesis, lung disease, and neurotoxic effects. The mechanisms of Co and Ni toxicity are not well-understood but may involve a variety of interactions with biomolecules including lipids. Interactions of metals with lipid membranes may affect transport pathways and overall cell integrity.

Lipids are amphipathic molecules that assemble into bilayer structures, thus they comprise the major components of cell and organelle membranes. Our work focused on the interactions of Co and Ni with model lipid membranes in order to identify potential targets by screening key lipid classes varying in headgroup and side chain architecture.

Model membranes of defined composition and liposome size were prepared as large unilamellar vesicles (LUVs) via extrusion under physiologically-relevant conditions of 100 mM NaCl 20 mM Hepes buffer at pH 7.4. The LUVs contained a fluorescent probe called Laurdan which spontaneously incorporates into these membranes and reports on the relative water content in its environment. Thus, the effects of Co and Ni on membrane fluidity could be measured using Laurdan as more fluid membranes exhibit a more polar environment for the fluorophores. The changes in Laurdan fluorescence are quantified by a ratio of fluorescence intensity at 440nm and 490nm. This parameter is known as Generalized Polarization (GP), whereby higher values indicate more rigid, and lower values, more fluid membranes.

$$GP = \frac{I_{440} - I_{490}}{I_{440} + I_{490}}$$

The comprehensive screening of lipid classes revealed electrostatic interactions between positively-charged Co^{2+} and Ni^{2+} ions with negatively-charged lipids. The negatively-charged lipid head group structures included in this study are shown in Figure 1.

It was found that Co and Ni caused rigidification of membranes composed of negatively-charged lipids, as indicated by increased GP values relative to metal-free controls. The inherent fluidity of lipid membranes is temperature-dependent, such that membranes are more fluid at higher temperatures. The effects of Co and Ni were stronger at higher temperatures, suggesting that the metals can induce a greater ordering effect on membranes in the liquid crystalline phase.

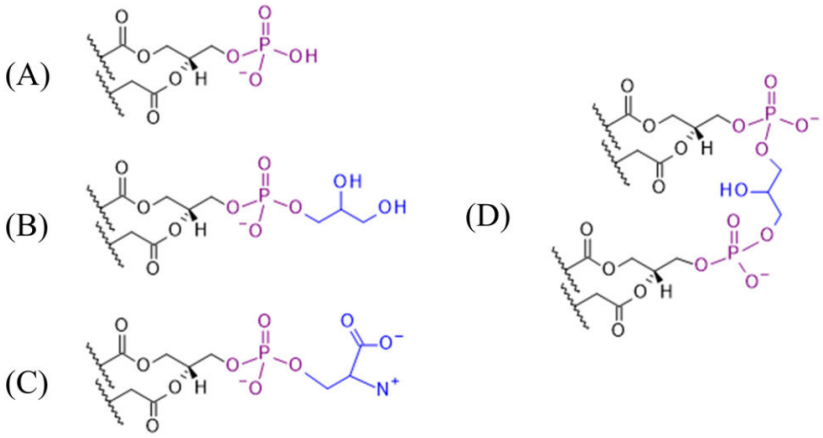

Fig. 1. Structures of negatively-charged lipid head groups used in this study. A) phosphatidic acid (PA), B) phosphatidylglycerol (PG), C) phosphatidylserine (PS), D) cardiolipin (CL). Acyl chains are not shown.

Both Co and Ni can induce rigidification of membranes composed of the major negatively-charged lipid classes: phosphatidic acid (PA), cardiolipin (CL), phosphatidylglycerol (PG), and phosphatidylserine (PS), with effects also dependent on the acyl chain structure. Additionally, LUV size was monitored by dynamic light scattering (DLS). Co and Ni caused swelling and aggregation of LUVs composed of PA and PS.

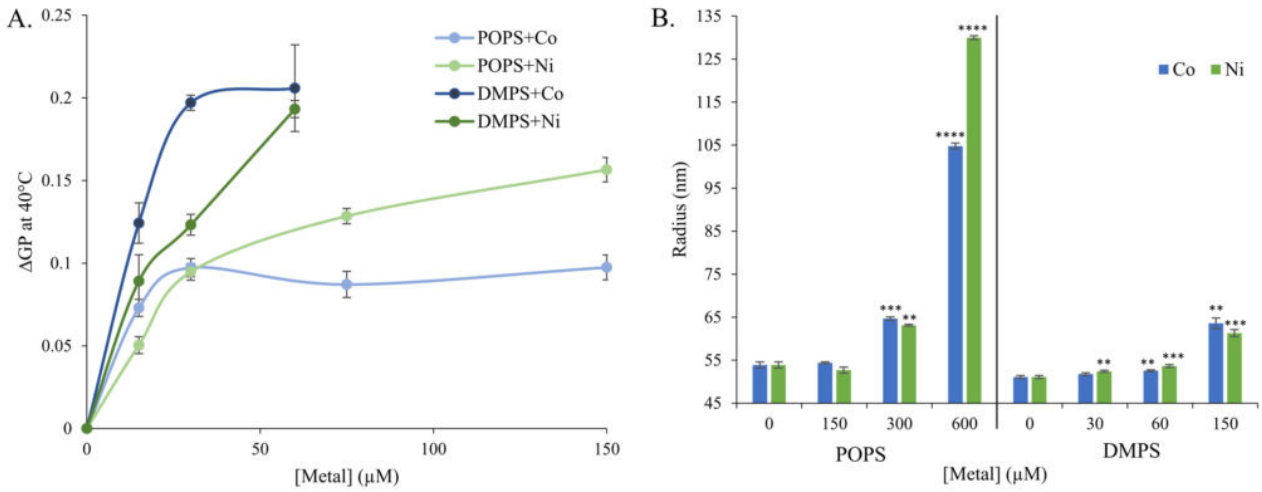

Fig. 2. (A) ΔGP induced by Co and Ni in 0.3 mM POPS and DMPS liposomes at 40°C. (B) Radii of 0.3 mM POPS and DMPS liposomes with various concentrations of Co or Ni.

Negatively-charged lipids are present at minor amounts in membranes and are important in various processes including protein regulation and signalling. Thus, Co and Ni may affect cellular functions through their direct

membrane-rigidifying interactions with negatively-charged lipids. Further study on the potential physiological implications of such interactions are relevant as they may be involved in the toxic effects of Co and Ni.

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