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Thermodynamic stability of complex model membranes: the role of composition, morphology and food fatty acids

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Free Fatty Acids (FFAs) have been shown to be involved in several membrane-mediated cellular processes as lipid-assisted protein transport across the bilayer, fusion of lipid vesicles/cells and signalling for several cell mechanisms (*e.g.* insulin secretion). However, altered plasma FFAs levels typical of obese and/or diabetic subjects have been proposed to contribute to the onset and progression of type 2 diabetes mellitus through both their possible involvement in altered metabolic pathways (1) and their direct action on cell membranes (2). Moreover, the action of FFAs has also been hypothesized to play a role in the interaction of amylin, an amyloidogenic protein, with cell membranes likely leading to the pancreatic β-cells failure by apoptosis (3).

Among several studies highlighting the FFAs-membrane interaction by means of spectroscopic, imaging, molecular dynamics and/or theoretical approaches, few works are devoted to a thermodynamic characterization of the role of FFAs on the overall membrane stability, however without considering the compositional and morphological complexity of real biological vesicles (4).

In such a frame, the present work was aimed at the calorimetric investigation of small, large and giant unilamellar vesicles prepared as pure and mixed systems of phospholipids with different length and unsaturation level. The preparation of a final model membrane was finally achieved mimicking the phospholipid bilayer of Insulin Secretory Granules (ISGs), vesicles located in the pancreatic Langerhans β-cells and which are responsible for insulin and amylin storage and secretion in response to nutrients intake. This study was performed through micro-DSC and allowed to discriminate each single thermodynamic contribution among the main factors that dictate the overall thermodynamic stability of these complex unilamellar systems (phospholipid unsaturations > phospholipid tail length > membrane curvature). The effect of three different FFAs, such as palmitic, stearic and oleic acids, added in different percentages both to a completely saturated ternary model membrane and to an unsaturated one (*i.e.* the final model membrane made by the saturated one including the 5% of 1,2-dioleoyl-sn-glycero-3-phosphocholine, DOPC) was eventually investigated highlighting a strong stabilizing effect as well as more pronounced phase segregations

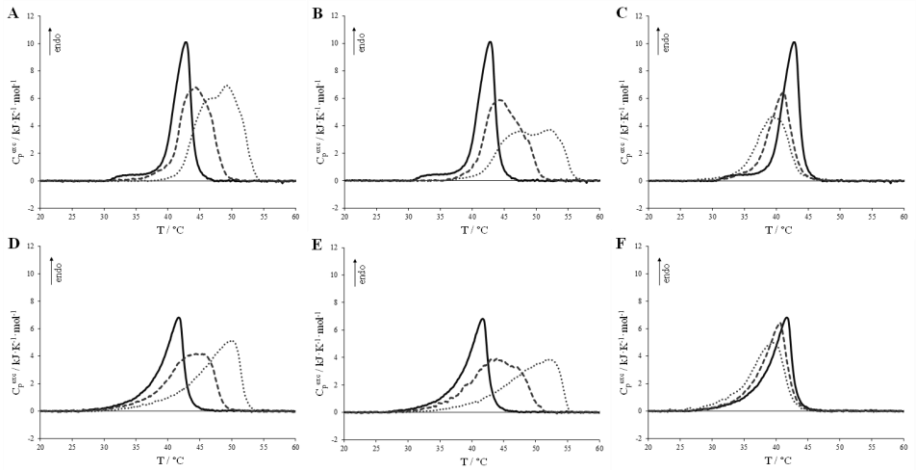

Fig. 1. *Micro-DSC profiles for pure vesicles (solid curves) and vesicles with the addition of the 10% (dashed curves) and the 25% (dotted curves) of FFAs.*
Thermograms are reported for the completely saturated membrane including a) palmitic acid, b) stearic acid and c) oleic acid, and for the unsaturated membrane including d) palmitic acid, e) stearic acid and f) oleic acid.

in the case of saturated acids, whereas the opposite effect was observed in the case of unsaturated FFAs (Fig.1). Moreover, the stabilizing effects deriving from saturated FFAs were more pronounced in less stable membranes, *i.e.* the unsaturated one, whereas the destabilizing effects deriving from the unsaturated FFAs were more pronounced in more stable membranes, *i.e.* the completely saturated one (Fig.2) (5).

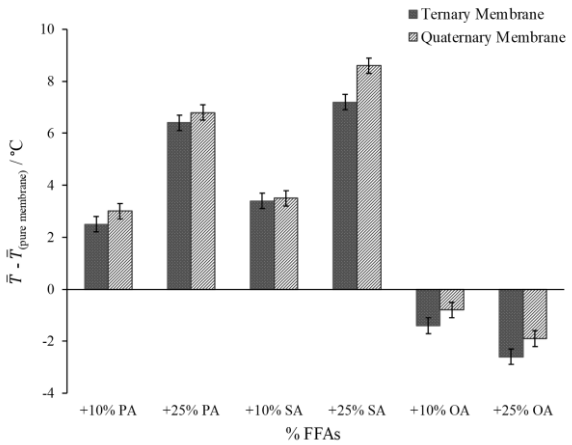

Fig. 2. *Effects of 10% and 25% of palmitic acid (PA), stearic acid (SA) and oleic acid (OA) on saturated (full bar) and unsaturated (lined bar) model membranes in terms of transition average temperature* $\bar{T}$*.*

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