# On a possible membrane structural role of single chain sphingolipids Sphingosine and Sphingosine 1-phosphate in cell fate regulation and Alzheimer's disease.

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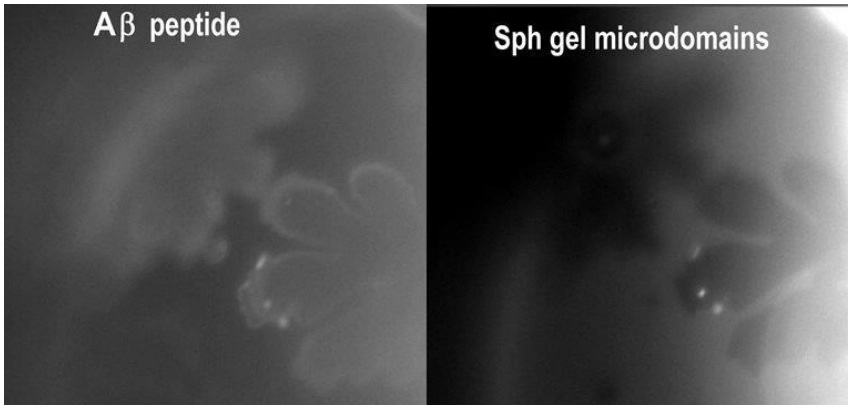
## Abstract

Sphingosine (Sph) and sphingosine-1-phosphate (S1P) are single-chained charged sphingolipids that have antagonistic functions in the "sphingolipid rheostat" determining cell fate and respectively promote apoptosis and cell growth. The antagonistic biological activities of both sphingolipids have been correlated with their direct targeting of enzymes, cofactors or receptors. Besides, an influence of Sph and S1P on Alzheimer disease (AD)-related mechanisms has been recently reported. AD is characterized by impairment of short-term memory, cognitive disorders and ultimately neuronal cell loss. The disease is associated with overproduction of the β-amyloid (Aβ) peptide in the brain. As with other "bioactive" signaling lipids the question remains whether Sph and S1P act also through structural effects at the bilayer level.

We have first investigated the effect of sphingolipids, both incorporated separately or together, in large or giant egg phosphatidylcholine (EPC) unilamellar vesicles on several bilayer properties: membrane zeta-potential, dipole potential, lipid packing, and formation of membrane microdomains. Sph and S1P appear to have distinct, when not inverse, effects on all three properties. Besides, when both sphingolipids are mixed together, their effects on lipid packing are synergistic, whereas their effects on microdomain formation and zeta and dipole potential are mostly antagonistic. These results are interpreted as arising from different electrostatic interactions between lipid headgroups. In particular, Sph and S1P may interact together electrostatically and form a complex. These mostly inverse and opposing effects of both single-chain phospholipids on membrane physical properties might be involved in their antagonistic role in regulating cell fate.




We have also investigated the influence of Sph and S1P on the interaction of Aβ(1-42) with lipid model membranes. A fluorescent Aβ(1-42) binds to EPC giant unilamellar vesicles containing Sph or S1P. With Sph, gel microdomains are present at low temperature and Aβ (1-42) binds preferentially to these domains, especially at their boundaries (see figure). The effect of Aβ (1-42) on the dipole potential and lipid packing of EPC/sphingolipid large unilamellar vesicles was investigated. With most lipid compositions the binding of Aβ(1-42) to LUVs appears superficial. However, with Sph, a deeper membrane penetration is observed. This deeper interaction is reversed by the simultaneous presence of S1P. It is suggested that the influence of single-chain sphingolipids in AD might be related to a selective interaction of Aβ(1-42) with Sph in membranes, that is antagonized by S1P and may be involved in Alzheimer pathology.

**REFERENCES :** Watanabe et al. (2014) Langmuir 30 :13956 ; Watanabe et al. (2015) Colloids & Surfaces A 483:181; Watanabe et al. (2016) Colloids & Surfaces A 510: 317.