TOXICITY OF A SEROTONIN-DERIVED NEUROMELANIN

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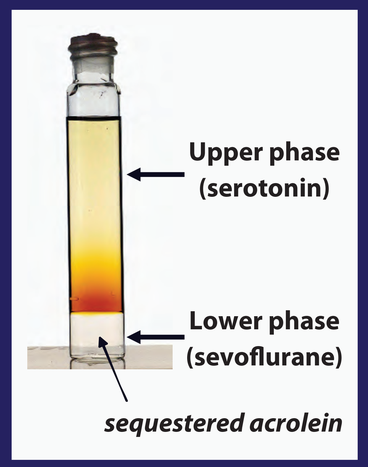
INTRODUCTION

- Postoperative Cognitive Dysfunction (POCD) is associated with increased mortality and disability.
- POCD may develop as a consequence of lipid peroxidative byproducts, such as acrolein, which accumulate with aging.
- Sevoflurane sequesters acrolein, which promotes the formation of a novel species of neuromelanin that may play a role in POCD.
- In this study we examined the properties of a serotonin-derived melanoid-like compound (SDM) and hypothesized that SDM may be neurotoxic.

METHODS

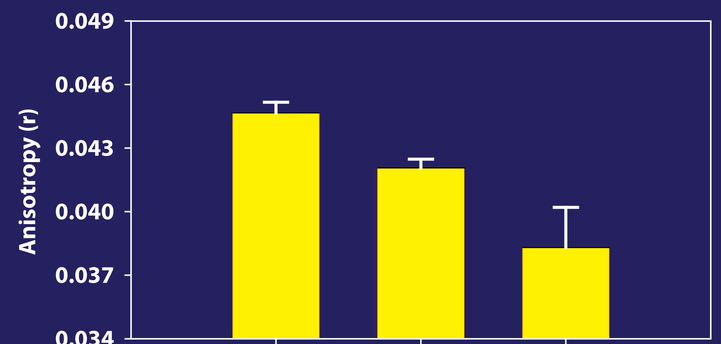
- SDM was produced using a 2-phase system using an upper aqueous phase containing s erotonin and a lower phase containing sevoflurane and acrolein.
- Fraction at the interface was removed and dialyzed.
- Uni-lamellar vesicles (ULVs) of dioleoyl-phosphatidylcholine were made by extrusion.

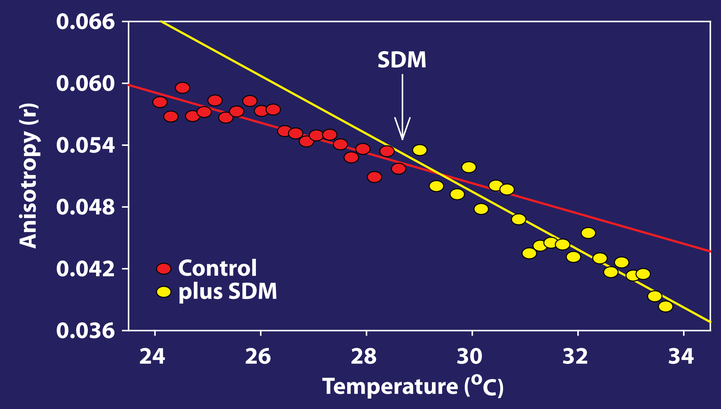


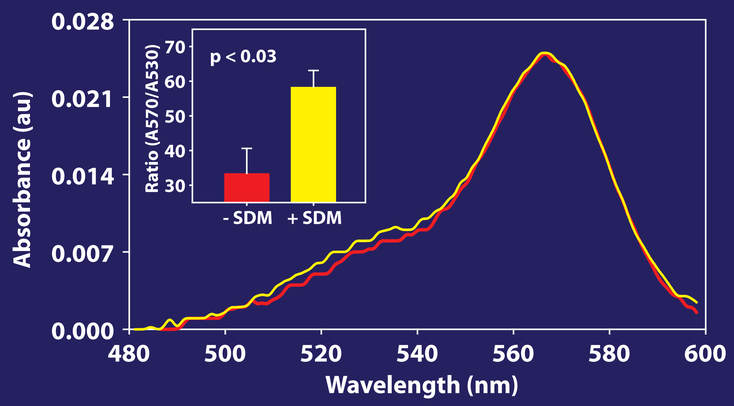
- Interaction of SDM with ULVs was examined using two membrane probes:
  - Diphenyl-hexatriene (DPH)
  - Merocyanine (MC)
- Absorbance spectra of SDM were also examined. Vesicle disruption was investigated by monitoring the leakage of dye from calcein-loaded ULVs.
- Results were analyzed by linear regression and unpaired Student t-tests (p<0.05).

RESULTS

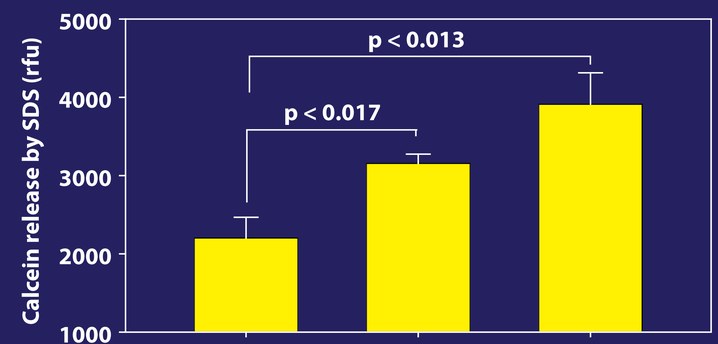
- SDM Promotes Lipid Bilayer Disorganization
  - SDM redistributes phospholipid headgroups
  - SDM enhances membrane fluidity and decreases DPH anisotropy

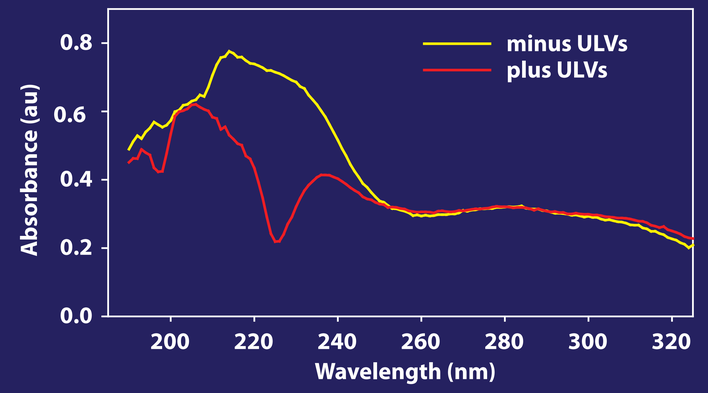






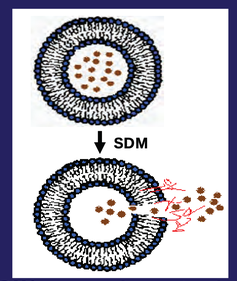
- Consequences of SDM-ULV Interaction
  - SDM increases detergent-mediated dye leakage from calcein-loaded ULVs
  - Effects of ULVs on the SDM absorbance spectrum in the UV range





CONCLUSION/DISCUSSION

- Serotonin-Derived Melanoid (SDM)
  - Disrupts membrane organization
    - Acyl chains
    - Phospholipid headgroups
  - Interacts with ULVs
    - Restructures SDM
    - Vesicle rupture



SDM is an amorphous network of polymers that is shown in red