## Toxicty of a Serotonin-derived Neuromelanin

E.D. Miller, M.D.<sup>1</sup>, E.E. Fibuch, M.D.<sup>1</sup>, N.W. Seidler, Ph.D.<sup>2</sup>

<sup>1</sup> Department of Anesthesiology, University of Missouri - Kansas City School Medicine, <sup>2</sup> Kansas City University of Medicine and Biosciences, Kansas City, Missouri

**Introduction:** POCD (Postoperative Cognitive Dysfunction) is associated with increased mortality and disability [1] and may develop as a consequence of lipid peroxidative byproducts (i.e. acrolein), which accumulate with aging [2]. We previously showed [3] that sevoflurane sequesters acrolein, which promotes the formation of a novel species of neuromelanin (NM) that may play a role in POCD. In this current study, we examined the properties of NM and hypothesized that this novel serotonin-derived melanoid (SDM) product may be neurotoxic.

**Methods:** SDM was produced [3] at the interface of an upper aqueous phase containing serotonin and a lower sevoflurane phase containing acrolein. Uni-lamellar vesicles (ULVs) of dioleoyl-phosphatidylcholine were made using an extrusion technique. The interaction of SDM with ULVs was examined using two lipid membrane probes: diphenyl-hexatriene (DPH) and merocyanine (MC). Vesicle disruption was investigated by monitoring the leakage of dye from calcein-loaded ULVs. Absorbance spectra of SDM were also examined. Statistical analysis involved linear regression and unpaired Student *t*-tests (p<0.05).

**Results:** We observed that SDM decreased DPH fluorescence anisotropy and increased the temperature-dependent change in anisotropy of DPH. SDM increased the ratio of absorbance (570nm/530nm) of MC-bound ULVs. Using calcein-loaded ULVs, SDM increased detergent-mediated calcein leakage. The intense absorbance band below 250nm of SDM was dramatically altered in the presence of ULVs, yielding three well-resolved peaks from a single broad band.

**Conclusion:** From these data we conclude that SDM has the potential of being neurotoxic.

**Discussion**: This study further characterizes SDM as an important species of NM. SDM disorganized the acyl chains and the phospholipid head groups of ULVs. The electronic structure of SDM was dramatically altered upon interaction with ULVs. We also observed that SDM enhanced detergent-mediated leakage of loaded ULVs, suggesting that SDM may be neurotoxic. We propose that inhalational agents that sequester acrolein [3], may promote the production of certain species of NM that deplete local serotonin and enhance neuronal vulnerability.

## **References:**

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