Bilayers at the ILL

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Lipid domain modulation and inhalation anesthesia

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Small membrane lipid domains are important in cell signaling. We investigate modulation of lipid domains by volatile anesthetics. Many volatile compounds produce anesthesia. With no molecular target identified, mechanisms remain puzzling. Large membrane concentrations (~100 mM) are required to produce anesthesia. Hyperbaric pressures (~100 bar) reverse anesthesia.
Using neutron/x-ray scattering, effects of anesthetics on mixing transitions ofternary lipid mixtures exhibiting liquid-liquid phase coexistence were investigated. Multi-layer stacks of DPPC (or brain sphingomyelin)/DOPC/cholesterol (2/2/1) produce two sets of diffraction peaks, giving d-spacings for two lipid phases and their relative amounts which change with temperature and anesthetic concentration. Hydrostatic pressure reverses effects of raising temperature. [1] The contrast variation technique of Pencer gave similar results with small unilamellar vesicles. Clinical concentrations of anesthetics (isoflurane, halothane, xenon, nitrous oxide, chloroform, hexane) shift mixing transitions to lower temperatures. Recently, we demonstrated that hexanol produces similar effects. These neutron/x-ray results for hexanol differ from results with fluorescent dyes that apparently perturb lipid mixing. [2] Volatile anesthetics at clinical concentrations affect lipid mixing, possibly causing changes in membrane lateral pressures or hydrophobic mismatch of membrane-embedded proteins. An elegant example of lipid mixing modulating neural activity is provided by recent work on the potassium channel TREK-1. Hansen and colleagues [3] showed that TREK-1 in planar bilayers is not modulated by anesthetics, while TREK-1 in cells studied with patch clamp is modulated. Fluorescent labels showed that anesthetics produce migration of phospholipase D from lipid domains to TREK-1 where the phospholipase produces phosphatidic acid, a potent modulator of TREK-1. More examples are anticipated.

1. M Weinrich & DL Worcester, *Acta Cryst D* 74 (2018) 1169-1177.
2. CE Cornel et al., *Biophys J.* 113 (2017) 1200-1211.
3. MA Pavel et al., *BioRxiv* (2018) 31973.

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