Title : ANESTHETICS DO NOT FLUIDIZE THE LIPID CORE OF SURFACTANT MICELLE

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A number of reports demonstrated that anesthetics expand, disorder and fluidize the cell membranes. These actions are usually attributed to the change of physical properties of phospholipid bilayers. The phospholipid bilayer membranes undergo the phase transition between the tightly-packed solid gel and the loosely-packed crystalline states. Anesthetics favor the liquid-crystalline state, which is more expanded and more fluid than the gel state. The term, fluidity, in this case is used in a broad sense to denote that the membrane molecules are moving with relative ease. The dilating and fluidizing effects of anesthetics are generally assumed to be a result of the direct action of anesthetics with the lipid tails of the phopholipid molecules which change from the straight all-trans conformation to the kinked conformation containing many gauche-rotations. Therefore, volume expansion and fluidity increase are considered to be a colligative property of the cell membranes responding to anesthetics.

Contrary to the above idea, Eyring et al (1) and Ueda et al (2) proposed that the volume expansion during anesthesia, represented by the pressure reversal, is mainly caused by the release of hydrogen-bonded high-density structures from the membrane surface. This conclusion was based on the observations of the inhibitory action of inhalation anesthetics upon the luminescence of lipid-free light-emitting enzymes solubilized from firefly lanterns and luminous bacteria. In a separate paper, we demonstrate that the release of structured water molecules from the interface of nonionic surfactant micelles does occur by the interaction with anesthetics with the concomitant volume expansion. This report demonstrates that the anesthetics do not necessarily fluidize the lipid core of these micelles. Rather, the inhalation anesthetics immobilized the surfactant molecules indicating stiffening effects.

METHODS: Homogeneous hexa(oxyethylene) dodecyl ether was obtained from Nikko Chemicals (Tokyo, Japan). Its purity was checked by gas chromatography and found to show a single peak. Inhalation anesthetics, halothane, methoxyflurane, and enflurane were the gifts from Ayerst Laboratories, Abbott Laboratories and Ohio Medical Products, respectively. The surfactant was dispersed in 99.8% deuterium water at a concentration of 2% (w/v) (0.0408 molal). The Fourier-transformed high-resolution proton nuclear magnetic resonance spectra were obtained with a Varian SC-300 super-conducting NMR Spectrometer (300 MHz) operating at 20°C with 5 mm tubes. The sample for the NMR measurement was prepared by adding the desired amount of anesthetics to the surfactant micelles. The NMR spectral parameters were used as 3,001.2 Hz for the spectral width, 1.35 sec for the acquisition time, and 8,192 for the data point with 25 transients collected.

RESULTS: The anesthetic-surfactant interaction was characterized by the broadening of proton signals of the surfactant. All anesthetics increased the linewidth of the methylene groups adjacent to the hydrophilic ether moiety of the surfactant molecule, while the signal from the terminal methyl protons of the hydrophobic alkyl chain at the micelle core was unchanged. The linewidth broadening effects of anesthetics were in the order of methoxyflurane > halothane > enflurane.

DISCUSSION: The present results indicate that the movement of protons close to the hydrophilic surface of the surfactant micelles was restricted by the interaction with inhalation anesthetics. The structure became more rigid. The immobilizing effects of the anesthetics were more pronounced at the inferfacial region and the magnitudes followed their clinical potencies. Together with our separate report on the pressure-anesthetic antagonism on the cloud-point temperature of the surfactant micelles, the present results demonstrate that anesthetics expand the volume of the surfactant micelles and decrease the fluidity of the lipid structure.

If the anesthetic molecules, due to their lipophilicity, directly disorder the lipid part of the phospholipid membranes, then the micelle structure should also have been loosened. The present result does not entertain the above idea of the direct lipid-anesthetic interaction, and indicates that the action of the inhalation anesthetics is mainly exerted at the interfacial region.

The phopholipid vesicle and surfactant micelles cannot be formed without water. The anesthetic action appears to be the weakening of the interaction between water and the membrane molecules. The properties of the aggregates of these amphiphilic molecules may strongly be dependent upon the properties of the interfacial region of the structure. Anesthetics may loosen or tighten the structure depending upon the change of the properties of the region that binds water.

REFERENCES:

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