An enthalpic model of anesthesia

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The question of how and where anesthetics act to produce a reversible (hopefully) loss of consciousness is of interest both from a clinical and basic science perspective. General anesthetics range in structure from inert gases to steroids and it is often assumed that they produce anesthesia by interacting through similar mechanisms. At the turn of the 20th century, a good correlation was observed between anesthetic potency and the solubility of anesthetics in fatty isotropic solvents such as olive oil (1). Olive oil possesses long hydrocarbon chains which might be thought to mimic the acyl chains of plasma membranes. For many years, it was thought that anesthetics produce anesthesia by partitioning into lipid bilayers and cause small perturbations in their acyl chain packing as detected by changes in the mobility of fluorescent probes or changes in lipid order parameters measured by NMR or ESR. The correlations of anesthetic potency (in animals) with lipid or membrane solubility are very good and have been used as predictors of anesthetic potency (1). In addition, it was found that general anesthesia can be reversed by hydrostatic pressure as can the anesthetic-induced changes in order parameters measured in lipid bilayers (1). Nevertheless, there are two major problems with the lipid hypothesis of anesthesia. First, the changes in order parameter measured at anesthetic concentrations which produce anesthesia could be obtained by simply changing the temperature less than 1°C. Second, lipids cannot readily distinguish between optical isomers of the common general anesthetic isofluorane, as can some ion channels (2). The paper by Dickinson et al. (3) analyzes the temperature dependence of anesthetic binding to specific sites on a protein in order to test whether such data are consistent with physiological data relating to the temperature dependence of general anesthesia.

A major advance in the understanding of the interactions of general anesthetic molecules with proteins was made when Franks and Lieb (4) showed that anesthetics inhibit the luciferin-luciferase reaction in a lipid-free environment in a manner that was correlated with the anesthetic potency over a 100,000-fold range. In addition, they showed that anesthetics inhibit the luciferase activity by acting as competitive inhibitors of luciferin, thus demonstrating that anesthetics can partition into specific hydrophobic pockets in proteins (an example of the elusive "anesthetic site"). Dickinson et al. (3) analyzed the free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) of transfer of anesthetics into their binding sites in luciferase and compared these parameters to those obtained in lipid bilayers, isotropic fatty solvents and, most importantly, to the temperature dependence of general anesthesia. They found that for all the anesthetics studied, ΔH is much more negative (exothermic) when anesthetics bind to luciferase than when they bind to lipid bilayers and/or olive oil. What was most interesting was the excellent correlation found between the enthalpies of transfer of anesthetics to their binding sites in luciferase and the enthalpies calculated from the temperature dependence of the animal EC_{50} (the anesthetic concentration required to anesthesize half the animals) using $\ln(EC_{50}) = \Delta H/RT + \text{constant}$. This evidence, together with the inability of lipid bilayers to distinguish among optical isomers, effectly dooms the lipid hypothesis of anesthesia. From the temperature data the author's make the suggestion that the anesthetic sites in animals may be similar to those found in luciferase. This argument would be strengthened, however, if similar sites, that are also sensitive to hydrostatic pressure, were identified in a membrane bound transport protein.

As with all thermodynamic measurements, it would be desirable to understand the origins of the enthalpic contributions to binding. That is, how much of the enthalpy change is due to the dehydration of the anesthetics, release of bound water from the protein, conformational changes etc? This, of course, is a very difficult problem that is just beginning to be understood (5). A major advance towards this goal would be made if high resolution x-ray diffraction patterns of a anaesthetic-luciferase complex could be obtained.

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