Title: ANESTHETIC POTENCY OF ALCOHOLS: BIPHASIC EFFECT

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Introduction: Anesthetic potency of alcohols (1-alkanols) increases according to the increase of the carbon-chain length, but suddenly disappears when the chain length exceeds about 10 carbon atoms. The chain length where the anesthetic potency disappears is known as the cutoff point. Lipid membranes exist in at least two phases: ordered solid-gel and disordered liquid-crystalline states. The change between solid-gel and liquid-crystalline states is called phase transition and is similar to water-ice phase transition. At higher temperatures, the membrane is in a liquid state and at lower temperatures it is in a solid state. Shorter-chain alcohols decrease the phase-transition temperature (disordering effect), whereas longer ones increase the phase-transition temperature (ordering effect). The crossover from depression to elevation of the phase transition occurs at about a 10 to 12 carbon-atom length when dipalmitoylphosphatidylcholine is used to form the membrane. The cutoff phenomenon is probably caused by the crossover from depression to elevation of the phase-transition temperature[1]. However, we found that octanol, which is a potent anesthetic, decreased the phase transition temperature at low concentrations but increased it when the octanol concentration was increased. The present study reports details of the effects of alcohols upon the main phase-transition temperature of phospholipid membranes. It will be shown that the action of alcohols is not a simple depression or elevation of the transition temperature; rather, it is depression at low concentrations and elevation at high concentrations, irrespective of the length of the carbon chain.

Methods: Unilamellar dipalmitoylphosphatidylcholine (Sigma) vesicles were prepared by sonication at temperatures several degrees above the phase transition and aged for 7 days at 4 C to obtain uniformity of the vesicle size. Long-chain alcohols (decanol, undecanol, dodecanol, tridecanol and tetradecanol) were mixed with the vesicle suspension by sonication. The transition temperature was monitored by an optical method reported previously. The cuvette temperature was scanned at a rate of 0.5C/min by an electronically controlled device. Both heating and cooling scans were performed to establish melting (gel to liquid-crystalline) and freezing (liquid-crystalline to gel) temperatures, respectively. Nonlinear curve-fittings were performed by the polynomial least square method using a microcomputer interfaced to a PDP 11/23 minicomputer.

Results and Discussion: Contrary to previous reports, all alcohols decreased the transition temperature at low concentrations and increased it at high concentrations. The longer the carbon chain, the lower the alcohol concentration becomes where the crossover in the transition temperature from depression to elevation occurs. With very long alcohols, such as tetradecanol, the crossover occurred at a very low alcohol concentration, hence the effect appeared almost an exclusive elevation. The biphasic effect means that the disordering effect of alcohols on lipid membranes at low concentrations changes into an ordering effect at high concentrations. Thus, the binding of alcohols (and presumably other anesthetics also) to lipid membranes is more complex than previously believed. Anesthetic interaction with membranes may not be a simple binding to membranes, but may have to be treated with mixing of two molecules, forming liquid and solid solutions. Further theoretical and experimental work is needed to clarify the interaction. Nevertheless, the agreement between the cutoff of anesthetic potency and the crossover of the transition temperature at low alcohol concentrations (which is the concentrations used to measure anesthetic potency) strongly supports the concept that specific receptors are not required for anesthetic effects. It has been postulated[2] that biomembranes consist of a mixture of solid-gel and liquid-crystalline domains, and that too much disorder (liquid-crystalline state) or too much order (solid-gel state) equally dysfunctions membrane excitability and causes anesthesia. The disappearance of anesthetic potency in long-chain alcohols that predominantly elevate the transition temperature (ordering effect) does not support the above suggestion that too much order induces anesthesia.

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References

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