A THERMOCHEMICAL ANALYSIS OF INHALATIONAL ANESTHETICS

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Abstract

The mechanism of the anesthetic process is of interest both to the clinician and to the pharmacologist. However, this is still an unsettled issue and a multitude of models have been proposed for the process. Noticing that most models propose either a molecular perturbation by the agents or an effect on some colligative property, we explore in this article the thermodynamical consequences of these postulations. Comparison of these with experimental findings is then made. The comparison shows the inconsistency of many of the models with the facts: (i) it refutes the long accepted conviction, culminated in the 'unitary hypothesis', that general anesthetics act not at a particular receptor site but invariably on all. Some consequences of this finding are demonstrated. (ii) it implies that a simple phospholipid medium is not feasible as an anesthetic site. (iii) it infers that proteins do have the properties required from anesthetic sites.

Keywords: general anesthesia, mechanisms of anesthetic action, membrane bilayers

Introduction

General anesthetics is used for a complete and safe abolition of pain in surgical operations. A common practice involves the use of anesthetic gases and vapors, such as ethers, fluorocarbons and nitrous oxide. These agents act by depressing all excitable tissues in the central nervous system and the action is accomplished by interaction with neuronal membranes. The molecular mechanisms responsible to the loss of feeling in anesthesia is a central issue, still unsettled. However, since nerve membranes involve proteins and lipids, the question is usually presented in the form: does the primary site of action of anesthesia involve a protein, a membrane phospholipid environment or the boundary between both [1, 2]. A multitude of mechanisms concerning the action of anesthetics on these sites have been proposed most of which refer to the lipid bilayer (changes in membrane fluidity, effect on phase transition, changes in membrane thickness, are just some examples of suggested models). An inspection of these
will show, however, that they all attribute anesthesia to either a molecular perturbation, a colligative property, or an adsorption process (the later is applied to proteins but not to the bilayer). We explore here the thermodynamics of the first two effects and show that they do not comply with the proposal that lipids are the primary sites of anesthetic action. The findings also put in doubt the applicability of the colligative mechanisms in general.

Molecular perturbations

Theoretical background

The relation connecting structural perturbations and the thermodynamic work of hole creation in the medium is an interesting one [3]. It is based on two observations:

(i) Structural changes are always expressible in statistical terms using pair correlation functions for the description. Perfect crystals can be described by pair correlation function which are δ functions with peaks at the lattice sites. The pair correlation function $g(r)$ of real liquids is deduced by X-ray diffraction and it reflects and characterizes the structure of these fluids. Peaks in $g(r)$ correspond to first neighbors, second neighbors, etc. These peaks become more and more smeared and their amplitude diminishes with the increase in distance between pairs until they finally fade away, reflecting the fact that liquids have only short range order. The representation of structural information in terms of pair correlation functions applies not only to crystals and liquids but also to those systems which are relevant to the investigation of anesthesia. Perturbations in structure that lead to anesthesia will, therefore, be manifested by changes in the pair correlation function of the medium.

(ii) Considering perturbations from a different point of view, we notice that the thermodynamical work of introducing an agent into the site can be described as resulting from two independent consecutive steps: creation of cavity in the medium and introduction of the solute into this cavity. The first of the two processes is relevant for the description of perturbations since the cavity is a space into which no part of the medium is allowed to enter whereas the space was filled with molecules of the medium prior to the creation of the cavity. Indeed the thermodynamical work $W$ of creating a hole having the size of the solute can thus be expressed in terms of pair correlation functions (or by an equivalent description: the conditional probabilities that the centers of all solvent molecules are being excluded from a spherical shell, once the region enclosed by the shell is known to be free of molecular centers). Noticing the statistical nature of the representation is important for our work because it allows to apply the general and well known Boltzmann theorem of statistical mechanics. This theorem $P(r) = e^{-W(r)/kT}$ connects the reversible work $W(r)$ required to produce the cavity to the probability of forming this cavity by some thermal fluctuation. The force ex-