ELSEVIER

Colloids and Surfaces B: Biointerfaces 22 (2001) 3–22

COLLOIDS AND SURFACES B

www.elsevier.nl/locate/colsurfb

Review

Interactions of some local anesthetics and alcohols with membranes

Petre T. Frangopol [a,*], Dan Mihăilescu [b,1]

[a] *Department of Chemical Physics, Faculty of Chemistry, 'Babes-Bolyai' University, 11, Aranyi Janos Str., R-3400 Cluj-Napoca, Romania*

[b] *Laboratory of Biophysics, Faculty of Biology, Bucharest University, 91-95, Spl. Independentei, R-76201 Bucharest, Romania*

Abstract

A review of the results obtained by our group in the last decade regarding the interactions of procaine, lidocaine, dibucaine and tetracaine with membranes is presented in the context of the literature data. The action upon membranes, in first approximation monomolecular film of stearic acid spread at the air/water interface used as a membrane model, the modification of biomembrane structure and function using diffraction methods, lipid phase transition, fluidity of lipids and proteins, membrane expansion and platelet aggregation were studied. The thermodynamic knowledge of membrane-alcohol interactions improved by using highly sensitive calorimetric techniques are briefly reported. One of the main conclusions is that the physical state of a monolayer model membrane was the result of competitive interactions between film-film and film-substrate interactions. It was taken into account that local anesthetics, such as lidocaine, carbisocaine, mesocaine, showed changes in the bilayer structure, reflected in macroscopic mechanical properties. This restructuring of the lipid bilayer has a significant influence on the operation of functional subunits, e.g. ionic channels formed by gramicidin. The results support the concept of non-specific interactions of local anesthetics with lipid bilayers. The theoretical modeling of the interactions of local anesthetics is closely compared with experimental data. Our new theory of relaxation for these interactions is using a non-archimedean formalism based on a process resulting from superpositions of different component processes which take place at different scales of time.

Keywords: alcohols with membranes; anesthesia mechanism; local anesthetics

* Corresponding author. Tel.: +40-1-413-2375. Fax: +40-1-411-3933..

E-mail addresses: pfrangopol@pcnet.ro (P.T. Frangopol), danm@bio.bio.unibuc.ro (D. Mihăilescu).

[1] Present address: Blvd. Timisoara 17 Bloc H-1/Scara C, Apartment 28, Interfon 228, C 773091 Bucharest 66, Romania.

0927-7765/01/$ - see front matter

PII: S0927-7765(01)00153-9

Contents

1. Introduction

Anesthesia was discovered more than a century ago but the mechanism of action of anesthetics is still unknown and subject of intense experimental and theoretical work. Although it is now well established that anesthesia is brought about by a large number of chemically different molecular species, their exact sites of action and details of their interactions with their molecular components of nerve cells are still subject of considerable controversy. Consequently, especially during the last two decades, a significant amount of interdisciplinary scientific research has been devoted worldwide to the task of obtaining a unified picture of anesthesia mechanism. Attempts to solving this problem can be ascribed to a variety of disciplines, among which chemistry, biophysics, biochemistry, physiology and pharmacology are the most important. These approaches have produced a remarkable amount of scientific data, including both physico-chemical and pharmacological characteristics of various compounds with anesthetic action as well as information on their interactions with different biological and model systems. The investigation itself and the collection and interpretation of information goes beyond the capacity of any individual investigator or labora-

tory. Therefore, naturally, appeared the excellent idea of Kenji Ogli to publish a new international journal "Progress in Anesthetic Mechanism" [1] in 1993 and to organize, periodically the International Workshop on Anesthetic Mechanisms, the second edition, held in 1999. The results achieved thus far have been extensively reviewed [2–11]. Numerous models and theories have been put forward for anesthesia, which are based mostly on biophysical and biochemical data [12–18]. The theories of molecular mechanism of anesthesia: lipid theories, perturbation of physicochemical properties of biomembranes, theories involving the interaction of anesthetics with water, protein theory [19] along with the chemicals that could exert their modulation effect through the lipid domain on transmembrane protein structure and function [20] are particularly well presented.

The terms "local anesthesia" or "regional anesthesia" are used to designate the loss of sensation in a more or less discrete area of the body. Unlike general anesthesia, this loss of sensation is not accompanied by any simultaneous loss of consciousness [21]. All chemical compounds, which are used as local anesthetics, are capable of blocking the initiation or conduction of nerve impulses. However, it should be noted that not all the substances displaying such properties have been accepted for clinical use as local anesthetics [22]. Historically, the first chemical used as local anesthetic was cocaine. Since this discovery of local anesthesia in 1884 by Sigmund Freud in Heidelberg, the search for the replacement by safer and more reliable anesthetic agents became stringent due to the strong addicting liabilities of cocaine. The first man-made local anesthetic agent by chemical synthesis, in 1905, was procaine (P). The following local anesthetic to be synthesized in 1943 was lidocaine. Its versatility and combination of favorable properties soon made it most widely used local anesthetic [21,22]. Many chemicals have been proposed as local anesthetics [23,24] and search for even better local anesthetics has continued up to date. As an example, it is worth mentioning the synthesis of 4-alkylpiperazinoethyl esters of *o*-heptyloxyphenylcarbamic acid, which are two orders of magnitude more active than P or lidocaine [25].

Most of the local anesthetics now in use are amphiphilic molecules, i.e. molecules containing both, hydrophilic group (usually consisting of an amino moiety) and a hydrophobic (or lipophilic) group (generally containing an aromatic ring). The hydrophobic groups are involved in the diffusion and binding of local anesthetic molecules to cell membranes, while the hydrophilic ends confer to these molecules their water solubility characteristics and their ability to spread into the tissues. The presence of an electron donor group in the molecule seems to increase both biological activity and toxicity. The two end groups are usually connected by an alcohol chain with 2–5 carbon atoms in length. The distance of 6–9 Å is critical. Longer molecules are characterized by improved biological activities and liposolubilities [26].

Among the compounds displaying such properties, the tertiary amine type molecules deserve a special mention, e.g. P, lidocaine, dibucaine, tetracaine, butacaine, etidocaine, proparacaine, propoxycaine, etc. The main reason for this special interest from the scientific community could be attributed on one hand to the attempts at elucidating the exact molecular mechanism by means of which they exert their anesthetic action. On the other hand, substantial scientific evidence has been accumulating, which shows that, when interacting with living systems, biomolecules aggregates, or even isolated biomolecules, tertiary amines produce effects which can be regarded either as secondary effects, or as effects having nothing in common with their ability to produce local anesthesia. These new effects range from changes induced in bacterial gene expression to modifications of biomembranes molecular structure and permeability properties, changes of enzyme activities, immune response, ultrastructure of subcellular fraction, etc. Among these effects, an explicit mention should be made of controversy regarding the favorable consequences of the systemic long-term treatment of the aging process and the chronic diseases of the elderly with low doses of P based drugs [27–35].

The mechanism of action of the local anesthetics upon excitable membranes, which appears to be well established so far is (1) diffusion of the uncharged form of the local anesthetic across the