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Molecular dynamics simulations of local anesthetic articaine in a lipid bilayer

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ABSTRACT

In order to investigate structural and dynamical properties of local anesthetic articaine in a model lipid bilayer, a series of molecular dynamics simulations have been performed. Simulations were carried out for neutral and charged (protonated) forms of articaine inserted in fully hydrated dimyristoylphosphatidylcholine (DMPC) lipid bilayer. For comparison purpose, a fully hydrated DMPC bilayer without articaine was also simulated. The length of each simulation was 200 ns. Various properties of the lipid bilayer systems in the presence of both charged and uncharged forms of articaine taken at two different concentrations have been examined: membrane area per lipid, mass density distributions, order parameters, radial distribution functions, head group tilt, diffusion coefficients, electrostatic potential, etc, and compared with results of previous simulations of DMPC bilayer in the presence of lidocaine. It was shown that addition of both charged and neutral forms of articaine causes increase of the dipole electrostatic potential in the membrane interior.

1. Introduction

Local anesthetics (lidocaine, procaine, cocaine, etc) are indispensable part of medical treatment. They have been used for long days in practical medicine to relieve pain in a particular area and thereby facilitate the surgical procedure. Articaine is a relatively new local anesthetic used now in dentistry in many countries [1]. It is an amide type local anesthetic, and instead of benzene ring it contains a thiophene ring which increases its liposolubility. Unlike other local anesthetics, articaine is exceptional in that it contains an additional ester group which is rapidly metabolized by plasma esterase to articainic acid [2]. As a result, its half life, about 20 min, is also very short compared to other local anesthetic [3]. Thus it can rapidly be cleared from the systemic circulation through kidney, minimizing the side effects. Generally, articaine solution contains a mixture of neutral and charged (protonated) forms of articaine with a pKa value of 7.8 [1]. However inside the membrane the equilibrium may be strongly shifted towards the uncharged form as is the case of other ionizable anesthetics [4].

Local anesthetics are believed to remove or smooth pain by blocking of voltage-gated Na^+ or K^+ channels which are responsible for generation of action potential in the nerve endings [5]. The exact molecular mechanism is however not clearly understood yet because there exist many anesthetic molecules having rather different structures but similar actions [6]. Several different mechanisms have been considered in the literature. A prevailing point of view is that local anesthetics interact with the protein of ion channels by direct binding and change their functioning [7–10]. Local anesthetics may also interfere with the phospholipids packing in the membrane which may affect protein structure and function [11–13]. Among other possible pathways changes of membrane fluidity [14], membrane hydration [15], lateral pressure profile [16,17] and changes in the membrane dipole electrostatic potential [16] have been considered in the literature.

Molecular dynamics computer simulation may provide valuable complementary to experiments' information about details of interactions between the molecules. However, despite enormous growth of the number of works on computer simulations of lipid bilayers (for example see recent reviews [18–21]), works on computer modeling of anesthetics in lipid bilayers are rather scant. In papers [22,23] molecular dynamics simulations of general anesthetic halotane in lipid membrane have been described, which demonstrated that anesthetic molecules are associated mostly with polar groups of lipids. The length of these simulations was limited to 4 ns. In a recent paper [24] it was demonstrated that the addition of local anesthetic benzocaine increases disorder in the membrane. In a series of works [25–27], behavior of local anesthetic lidocaine in a model membrane composed of dimyristoylphosphatidylcholine (DMPC, or 14:0/14:0 PC) lipids, as well as changes in the membrane which might be responsible for the anesthetic action were investigated. Among other observations, it was shown [26] that addition of both charged and neutral forms of lidocaine causes noticeable increase of the dipole electrostatic potential in the membrane interior, which may be responsible for blocking of voltage-gated ion channel and thus for the anesthetic action. It seems interesting to compare results obtained for lidocaine–lipid bilayer system with simulations of the same bilayer with other anesthetics, in order to figure out similar features in the behavior of local anesthetics which might be essential for understanding the mechanisms behind the anesthetic action.

To the best of our knowledge so far, there are no published results on molecular dynamics simulations of aritcaine in a lipid bilayer.

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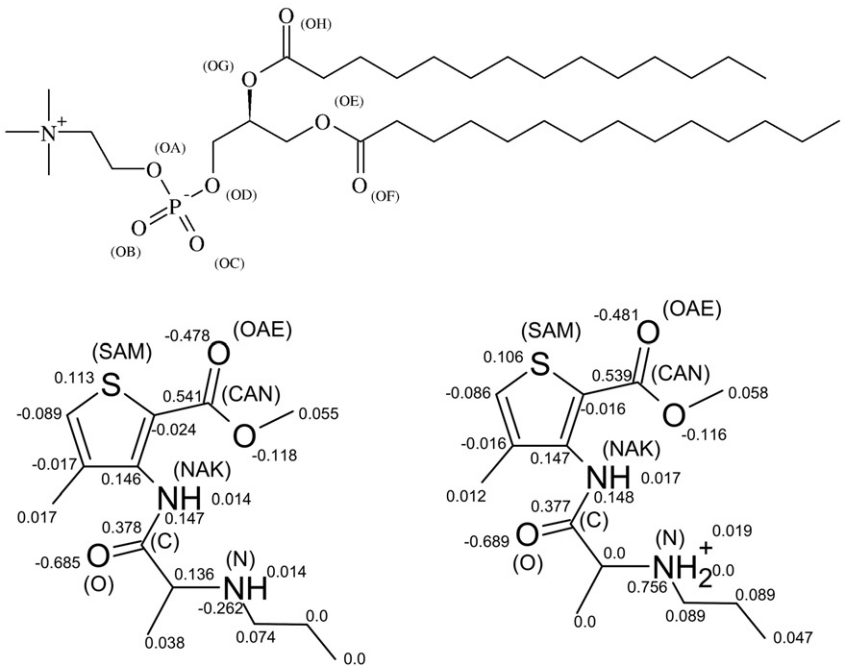

Fig. 1. Molecular structure of DMPC lipid (top), neutral (bottom left) and charged (bottom right) forms of articaine, with partial atom charges and atom names referred in the text.

Experimentally, on the molecular level behavior of articaine in a DSPC lipid bilayer was studied by solid-state NMR [28] and in POPS and SOPS liposomes by differential scanning calorimetry [29]. These studies demonstrated that addition of articaine decreases membrane melting temperature as well as transition entalphy.

The aims of this investigation are the following. First, various characteristics of the behavior of charged and neutral forms of articaine in a model lipid membrane, such as articaine preferential orientation and localization, hydration, hydrogen bond formation, diffusion, etc, will be examined. Second, the effect of articaine on different membrane properties will be investigated. Special attention will be given to the effect of articaine on electrostatic potential across membrane, which was previously hypothesized [26] as a possible mechanism of the anesthetic action. Finally, behavior of articaine in the bilayer will be compared with the behavior of lidocaine which was studied in previous works [25,26].

2. Methodology

2.1. Molecular structures

Five different simulations have been carried out. In each of them 128 DMPC lipids were arranged in a bilayer with 64 lipids in each leaflet, which were hydrated by 3655 water molecules. In addition to this, two of these systems also contained 12 either charged or uncharged articaine molecules, and two other systems contained 36 molecules of either charged or uncharged articaine. For systems with charged articaine, 12 or 36 chloride ions were added to provide electroneutrality. The fifth system contained only lipid molecules and water, the later simulation was carried out for the reference. Given the fact that clinical concentration of articaine solution is 4% [1] and high octanol/water partition coefficient of articaine (257 according to Song et al. [28]), one can expect rather high presence of articaine in lipid membrane at physiological conditions. Also, results of work [28] indicate that a membrane cannot accommodate more than 40 mol% of articaine. By these reasons we can believe that our simulations with 9.3 and 28 mol% of articaine in bilayer represent concentrations which may exist at physiological conditions.

The molecular structures of DMPC lipids, as well as of the charged and uncharged articaine molecules are shown in Fig. 1.

For DMPC lipids, the united atom model based on the GROMOS [30] force field was used with modifications by Berger [31]. The force field was validated previously in works [32–34]. Also, the united atom approach was used to describe articaine drug molecules (except for the polar H atoms bound to the nitrogen atoms). For water molecules, the simple point charge (SPC) model was used [35]. The articaine topology files for the charged and uncharged forms with interaction parameters corresponding to the GROMACS "ffgmx" (known also as GROMOS87) force field were prepared using the PRODRG server [36] (available on-line at http://davapc1.bioch.dundee.ac.uk/prodrg/). The partial atom charges of the neutral and protonated forms of articaine are depicted in Fig. 1.

2.2. Simulation details

During the simulations all the bonds were kept constrained with the LINCS algorithm [37] to remove fast vibrational motion. The time step was set to 2 fs. The temperature was set to 310 K and was maintained using the Noose–Hoover thermostat scheme [38] with a coupling time constant of 0.1 ps. This temperature corresponds to the liquid crystalline structure of the neat DMPC bilayer. It was known from earlier studies that addition of local anesthetics decreases the temperature of the transition to the gel phase in lipid bilayers [39]. That is why the bilayer remains in the liquid crystalline phase upon addition of articaine molecules. The pressure was regulated by Parrinello–Rahman barostat [40] with a coupling time constant of 1.0 ps, which was applied semianisotropically with two degrees of freedom, one in the Z direction and another in the XY direction. The simulation box was allowed to extend in Z direction which is parallel to the bilayer normal and also in the XY plane throughout the simulation. The periodic boundary conditions were applied in all three directions.

The cutoff radius for Lennard–Jones interactions was set to 10 Å. For correct description of the bilayer structure, the long-range electrostatic interactions are essential, and they have been maintained using Particle Mesh Ewald (PME) algorithm [41] with update every 10-th time step. Also, the long-range corrections of the