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Anesthetic and non-anesthetic effects on interfacial lipids around an ion channel

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Abstract. All atom molecular dynamics simulations were used to investigate the anesthetic and non-anesthetic effects on the dynamics of bulk and the interfacial dimyristoylphosphatidylcholine lipids surrounding a gramicidin-A (gA) channel. Two pairs of simulations in the presence and absence of halothane and of hexafluoroethane (HFE) were carried out for 2.2 and 8 ns, respectively. The order parameters, determined from the asymptotes of the autocorrelations of the vector between the nitrogen and the immediate methylene carbon of the choline head group and the C_{i-1}–C_{i+1} vectors for the *i*th carbon (C_i) in the lipid chains, show that the head groups are less ordered in the interfacial lipids than in the bulk lipids, and that neither halothane nor HFE at 5 mol% concentration has significant effects on the ordering of the interfacial or bulk lipid chains. Because halothane and HFE produce distinctly different effects on the global dynamics of gA channel, it is unlikely that anesthetic effects on gA are indirectly mediated through the lipids. © 2005 Published by Elsevier B.V.

Keywords: Molecular dynamics simulations; Mechanisms of general anesthesia; Anesthetics; Non-anesthetics; Order parameters

1. Introduction

General anesthetics interact with membrane proteins crucial for neuronal transmission and brain function. In general, it is difficult to use conventional experimental approaches to disentangle the direct anesthetic action on transmembrane (TM) proteins from the

Abbreviations: DMPC, dimyristoylphosphatidylcholine; gA, gramicidin A; HFE, hexafluoroethane; MD, molecular dynamics; NAMD program, not-another-molecular-dynamic program.

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indirect effects mediated by the membrane lipids. Using gramicidin A (gA) as a convenient model for TM ion channels, we investigated whether the interfacial and bulk lipids play any significant role in mediating anesthetic effects on the ion channel by molecular dynamics (MD) simulations.

2. Methods

Large-scale, all-atom molecular dynamics simulations of a gA channel in a fully hydrated dimyristoylphosphatidylcholine (DMPC) membrane patch were carried out in the presence and absence of halothane and hexafluoroethane (HFE), using the NAMD2 program [1] on the T3E supercomputer at the Pittsburgh Supercomputing Center. The halothane and HFE [2,3] concentrations were about 5 mol% in the lipid bilayers. The simulation procedures are the same as previously reported [4,5]. The motional characteristics of 20–27 interfacial lipids (i.e., those lipids whose phosphorus atoms in the head group form the first and second circles surrounding the gA channel) and 10 bulk lipids (i.e., those that are at least two cutoff distances away from any gA atom) were analyzed. Because $-C_iH_2$ plane at C_i of the lipid aliphatic chains is perpendicular to the vector $C_{i-1}-C_{i+1}$, the order parameters can be calculated from the autocorrelation of vectors $C_{i-1}-C_{i+1}$:

$$S_i^2 = \frac{1}{T^2}\sum_{t=0}^{T}\sum_{s=0}^{T} P_2[\boldsymbol{\mu}_i(t)\cdot\boldsymbol{\mu}_i(s)]$$

where $\boldsymbol{\mu}_i$ (t or s) is the unit vector parallel to vectors $C_{i-1}-C_{i+1}$ ($i=2$–13) at the simulation time point t or s, T is the total simulation time, and P_2[x] is the second Legendre polynomial. The order parameter of the lipid head group is estimated from the autocorrelation of the vector between the nitrogen and the immediate methylene carbon in the choline group. The simulation results can be compared directly with the order parameters measured by the deuterium NMR using the relationship:

$$|S_{CD}| = 0.5S_i^2$$

3. Results and discussion

We found that the head groups were slightly more disordered for the interfacial lipids than for the bulk lipids, with $|S_{CD}|$ being 0.11 ± 0.02 and 0.14 ± 0.02, respectively. Addition of halothane did not significantly change the order parameter of the head groups of the interfacial lipids ($|S_{CD}| = 0.10 \pm 0.01$) but made the head groups of the bulk lipids more ordered ($|S_{CD}| = 0.18 \pm 0.04$). The left and right panels of Fig. 1 depict $|S_{CD}|$ as a function of the carbon number in one of the lipid aliphatic chains averaged separately for the interfacial and bulk lipids. Compared with the parallel 8-ns simulations with and without HFE, the parallel 2.2-ns simulations with and without halothane were not long enough to obtain the true asymptote values from the autocorrelation function, leading to slight overestimation of the $|S_{CD}|$ values in the left panel. However, the general trend is already discernable in 2.2-ns simulations, and major conclusions can still be drawn about the anesthetic effects on the lipids. As shown in the figure, the order parameters varied with the depth in the membrane. The gauche transformation occurs