Computational Biology and Chemistry 46 (2013) 23–31

Contents lists available at SciVerse ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/compbiolchem

Research article

Effect of acetone accumulation on structure and dynamics of lipid membranes studied by molecular dynamics simulations

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ARTICLE INFO

Article history:
Received 22 March 2013
Received in revised form 27 April 2013
Accepted 29 April 2013

Keywords:
Lipid bilayer
Molecular dynamics simulations
Acetone
Toxicomania
Inhalant

ABSTRACT

The modulation of the properties and function of cell membranes by small volatile substances is important for many biomedical applications. Despite available experimental results, molecular mechanisms of action of inhalants and organic solvents, such as acetone, on lipid membranes remain not well understood. To gain a better understanding of how acetone interacts with membranes, we have performed a series of molecular dynamics (MD) simulations of a POPC bilayer in aqueous solution in the presence of acetone, whose concentration was varied from 2.8 to 11.2 mol%. The MD simulations of passive distribution of acetone between a bulk water phase and a lipid bilayer show that acetone favors partitioning into the water-free region of the bilayer, located near the carbonyl groups of the phospholipids and at the beginning of the hydrocarbon core of the lipid membrane. Using MD umbrella sampling, we found that the permeability barrier of ~0.5 kcal/mol exists for acetone partitioning into the membrane. In addition, a Gibbs free energy profile of the acetone penetration across a bilayer demonstrates a favorable potential energy well of −3.6 kcal/mol, located at 15–16 Å from the bilayer center. The analysis of the structural and dynamics properties of the model membrane revealed that the POPC bilayer can tolerate the presence of acetone in the concentration range of 2.8–5.6 mol%. The accumulation of the higher acetone concentration of 11.2 mol% results, however, in drastic disordering of phospholipid packing and the increase in the membrane fluidity. The acetone molecules push the lipid heads apart and, hence, act as spacers in the headgroup region. This effect leads to the increase in the average headgroup area per molecule. In addition, the acyl tail region of the membrane also becomes less dense. We suggest, therefore, that the molecular mechanism of acetone action on the phospholipid bilayer has many common features with the effects of short chain alcohols, DMSO, and chloroform.

1. Introduction

Inhalants such as organic solvents are breathable chemical vapors that can be inhaled to induce psychoactive or mind-altering toxic effects. Habit to take toxic volatile substances, such as glue, acetone, and cleaning agents, is also known as toxicomania disease. Although adequate epidemiological information is lacking, the apparently growing problem of inhalant abuse among young people has raised concerns in both affluent and developing nations. Despite an expanding body of knowledge and promising new avenues of research in fields of intoxication, dependence, and withdrawal, molecular mechanisms of action of volatile organic solvents on cell membranes remains poorly understood.

Over the past few years, several lines of evidence has accumulated indicating that binding and penetration of organic solvents, such as acetone, across biological membranes could lead to alterations in cellular membrane structure (Cantor, 1997; Tsai et al., 2001). The changes in membrane properties induced by acetone action could facilitate entrance of chemicals into and through lipid bilayers due to disruption of its permeability barrier (Tsai et al., 2001; Kezic and Nielsen, 2009). It has been shown by using of ratiometric fluorescent probes that the physico-chemical properties of cell membranes of rat olfactory mucos were modulated under the action of acetone (Posokhov et al., 2001). The observed changes in the cell membranes have been attributed to the accumulation of the acetone within the lipid bilayer (Posokhov et al., 2001; Posokhov, 2011). In addition, it has been found that the main phase transition temperature of DPPC vesicles, representing a model single-component membrane, was decreased with an increase in concentration of acetone (Kinoshita and Yamazaki, 1996). Using the ratio of excimer-to-monomer fluorescence of pyrene-PC, threshold concentrations of acetone for the phase transition at 20 °C

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http://dx.doi.org/10.1016/j.compbiolchem.2013.04.005

have been found to be about 9.4% (v/v). The combination of X-ray diffraction and differential scanning calorimetry experiments has revealed that packing of the head groups at the surface of the DPPC bilayer was changed at higher acetone concentrations, so that the entire DPPC molecules were tend to form the crystallized phase in the plane of the bilayer (Kinoshita et al., 1997).

In many fields of membrane biophysics, in which experimental determination of molecular structures is difficult, molecular dynamics (MD) simulations have now become the powerful supplementary tools (Tieleman, 2006). MD simulations have successfully been applied for studies of binding, distribution, and transport of small organic compounds and ions within lipid membranes (Bemporad et al., 2005; Kyrychenko and Dyubko, 2008; Reigada, 2011). In such simulation studies, accurate MD force field parameters of the solute molecule are very critical. In this respect, the MD parameterizations capable of reproducing the properties and relative partition coefficients for pure acetone and its aqueous mixtures have intensively been studied and reported (Jorgensen et al., 1990; Ferrario et al., 1990). The earlier MD parameterization suggested by Jorgensen et al. has further been validated by combined spectroscopic and MD studies of binary mixtures of water with acetone over their entire range of compositions (Venables and Schmuttenmaer, 2000; Idrissi et al., 2001). In addition, the thermodynamics, aggregation behavior, and transport properties of aqueous mixtures of acetone have attracted considerable computational attention (Thompson, 1996; Weerasinghe and Smith, 2003; Liang et al., 2004). The reliability of the commonly used force fields for acetone has further been proved by computing its free energy of hydration using the multiconfiguration thermodynamic integration method (Helms and Wade, 1997; Reddy and Erion, 1999).

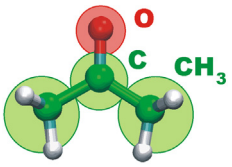
The purpose of the present work is to study interactions, adsorption, and accumulation of acetone in lipid membranes using MD simulations. We studied how multiple molecules of acetone, which were randomly distributed across bulk aqueous solution at the beginning of sampling, could bind and permeate into a POPC bilayer. In addition, we applied a joint refinement of unconstrained MD simulations of passive partitioning and umbrella sampling utilizing the potential of the mean constrained force calculations to study the favorable localization of acetone within a lipid bilayer. One of the goals of the present work was also to examine effects of low concentrations of acetone (2–6 mol%) on the membrane structure. Our MD simulations found that the presence of acetone in the concentration range 2.8–5.6 mol% could lead to small alterations in the structural and dynamics properties of the model membrane. These minor structural changes are often below the sensitivity of most convenient spectral methods; however, they might be detected by ultra-sensitive fluorescence techniques (Posokhov et al., 2001; Posokhov, 2011; Kinoshita and Yamazaki, 1996). In addition, we observed that accumulation of the high acetone concentration (11.2 mol%) in the bilayer could induce some decrease in the membrane thickness resulting in significant disordering of phospholipid packing and the increase in the membrane fluidity.

2. Methods

2.1. Molecular dynamics simulation setup

The force field parameters for acetone were taken from (Jorgensen et al., 1990) (Scheme 1). The model membrane was represented by 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) bilayer. The recently developed GROMOS 53A6L force field (Poger et al., 2010) was used to model the phospholipid bilayer. These parameters, which form the part of the GROMOS 54A7 force field (Schmid et al., 2011), reproduce a broad range of membrane properties (Poger and Mark, 2010, 2012). In the 53A6L force field,

United-Atom Model



acetone

Force Field Parameters

site	q, *e*	σ, Å	ε, kcal/mol
O	-0.424	2.96	0.210
C	0.300	3.75	0.105
CH_3	0.062	3.91	0.160

Scheme 1. An united-atom model and non-bonded force field parameters for acetone: two acetone methyl groups CH_3 with non-polar hydrogen atoms were treated as the united atom site. Electric charges (q) and non-bonded Lennard–Jones parameters (σ, ε) were adopted from Jorgensen et al. (1990).

all carbon atoms of CH_2 and CH_3 groups with non-polar hydrogen atoms were treated as united atoms. The initial configuration of an equilibrated POPC bilayer composed of 128 lipids was used from our previous studies (Kyrychenko et al., 2010, 2011). The Simple Point Charge (SPC) model (Hermans et al., 1984) was used for water.

The MD simulations were carried out at the constant number of particles, constant pressure of $P = 1$ atm, and the constant temperature $T = 303.15$ K (NPT ensemble). Three-dimensional periodic boundary conditions were applied with the z axis lying along a direction normal to the bilayer. The pressure was controlled semi-isotropically, so that the x-y and z dimensions of the simulation box were allowed to fluctuate independently from each other, keeping the total pressure constant. Thus, during MD simulations, the membrane area and thickness were, therefore, free to adjust under the NPT condition. The reference temperature and pressure were kept constant using the Berendsen weak coupling scheme (Berendsen et al., 1984) with a coupling constant of $\tau_T = 0.1$ ps for the temperature coupling and $\tau_{P(x\text{-}y)} = \tau_{P(z)} = 1.0$ ps for the pressure coupling. Electrostatic interactions were simulated with the particle mesh Ewald (PME) (Darden et al., 1993) approach using the long-range cutoff of 1.4 nm. The cutoff distance of Lennard–Jones interactions was also equal to 1.4 nm. All bond lengths were kept constant using the LINCS routine (Hess et al., 1997). The MD integration time step was 2 fs. The MD simulations were carried out using the GROMACS set of programs, version 4.5.5 (Van Der Spoel et al., 2005). Molecular graphics and visualization were performed using VMD 1.8.6 (Humphrey et al., 1996).

3. Results and discussion

3.1. Interactions with a model membrane

Our main goal is to characterize the effect of acetone accumulation on the bilayer properties and to correlate these changes with our experimental observations (Posokhov et al., 2001; Posokhov, 2011). For this reason, the development of a novel MD model and the force field for acetone would be well beyond the scope of our manuscript. For acetone molecules, we used the well-documented force field validated for acetone partitioning between two solvent phases (Jorgensen et al., 1990; Reddy and Erion, 1999). Among a variety of the MD force field available for lipid bilayers, our choice of the GROMOS 53A6L force field for the bilayer (Poger and Mark, 2012) was dictated by our interest in validating of its accuracy for partitioning thermodynamics calculations.

To study the distribution and favorable localization of acetone in a lipid membrane, we first applied unconstrained MD simulations based on passive distribution of acetone molecules between bulk water and a POPC bilayer. Four membrane systems were considered: (*A*) a pure POPC (128 lipids) bilayer in water, the system *A* containing 50 (*B*), 100 (*C*), and 200 (*D*) acetone molecules added, which corresponds to molar percent (mol%) of acetone in