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Molecular dynamics simulations of Oxprenolol and Propranolol in a DPPC lipid bilayer

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ABSTRACT

Extensive microscopic molecular dynamics simulations have been performed to study the effects of tow β-blocker drugs (Propranolol, Oxprenolol) on fully hydrated dipalmitoylphosphatidylcholine (DPPC) in the fluid phase at 323 K. Simulation of 4 systems containing varying concentrations of drugs was carried out. For the purpose of comparison, a fully hydrated DPPC bilayer without drugs was also studied at the same level of simulation technique which has been done on 4 other systems. The length of each simulation was 100 ns. The effects of concentrations of both drugs were analyzed on lipid bilayer properties, such as electrostatic potential, order parameter, diffusion coefficients, and hydrogen bond formation, etc. Penetration of water in the bilayer system was also investigated using radial distribution function analysis. Efficacy of varying concentrations of both drugs has no significant effect on P–N vector. Consistent with experimental results, by increasing the concentration of Propranolol, the thickness of the bilayer was increased.

1. Introduction

The pharmacological action of a drug is a complex phenomenon. Among the factors that have an important impact on this complexity, a special place should be assigned to drug-membrane interaction. This is due to the fact that the interactions between drugs and bio-membranes play a key role for pharmacokinetic parameters such as absorption, distribution, metabolism and elimination [1,2]. Therefore, many efforts have been devoted to understanding the nature of interactions between drugs and bio-membranes [3]. Primary partitioning is the pre-requirements condition for permeability of drug molecules through bio-membranes. Typically, a lipophilicity evaluation is built with bulk phase measurements of drug partition coefficients between an aqueous and organic phase (e.g., *n*-octanol). The basic assumption is that, the lipid bilayer membranes could be effectively represented by bulk phase. This assumption has been brought into question by several investigators [4–6]. The plasma membrane is the most important membrane for drug administration, through which drugs must penetrate to achieve the internal milieu of the target cells [7]. The behavior of the drug in the membrane is controlled by several factors that among these shape, size, hydrophobicity and pK_α are the most influential. In order to improve the efficacy and viability of many drugs, understanding the fundamental interactions between the drug and lipid have a special importance [8]. Since Phosphatidylcholines (PC) bilayers are the most abundant lipids in mammalian membranes, they typically used as simple membrane models, although phosphatidylserines, phophatidylethanolamines, sphingomyelins, and cholesterol are also present [9]. β-Blockers are known as the most efficacious agents for the treatment of heart failure, certain types of arrhythmia, hypertrophic obstructive cardiomyopathy, as well as prior myocardial infarction [10]. Propranolol (Fig. 1a) is a non-cardioselective β-blocker and a prototype β-adrenoreceptor blocking agent, which has earned far-reaching utilization in the treatment of angina pectoris, cardiac dysrhythmias and hypertension [11,12]. It has been specified that (*R*) – (+) – enantiomer has a membrane stabilizing effect [12], therefore the membrane activity of Propranolol may be important in study of its toxicity following overdose [11]. Oxprenolol (Fig. 1b) is a non-selective β-Blocker, which has low membrane stabilizing activity and medium intrinsic sympathomimetic activity. Because of its sympathomimetic activity, Oxprenolol displays less negative ionotropic effect than Propranolol. Consequently, Oxprenolol may help for treatment with a beta adrenoceptor antagonist despite peripheral vascular disease or heart failure. Owing to extensive hepatic metabolism, its bioavailability is low and half-life is short [13,14]. Regarding to the above-mentioned, many

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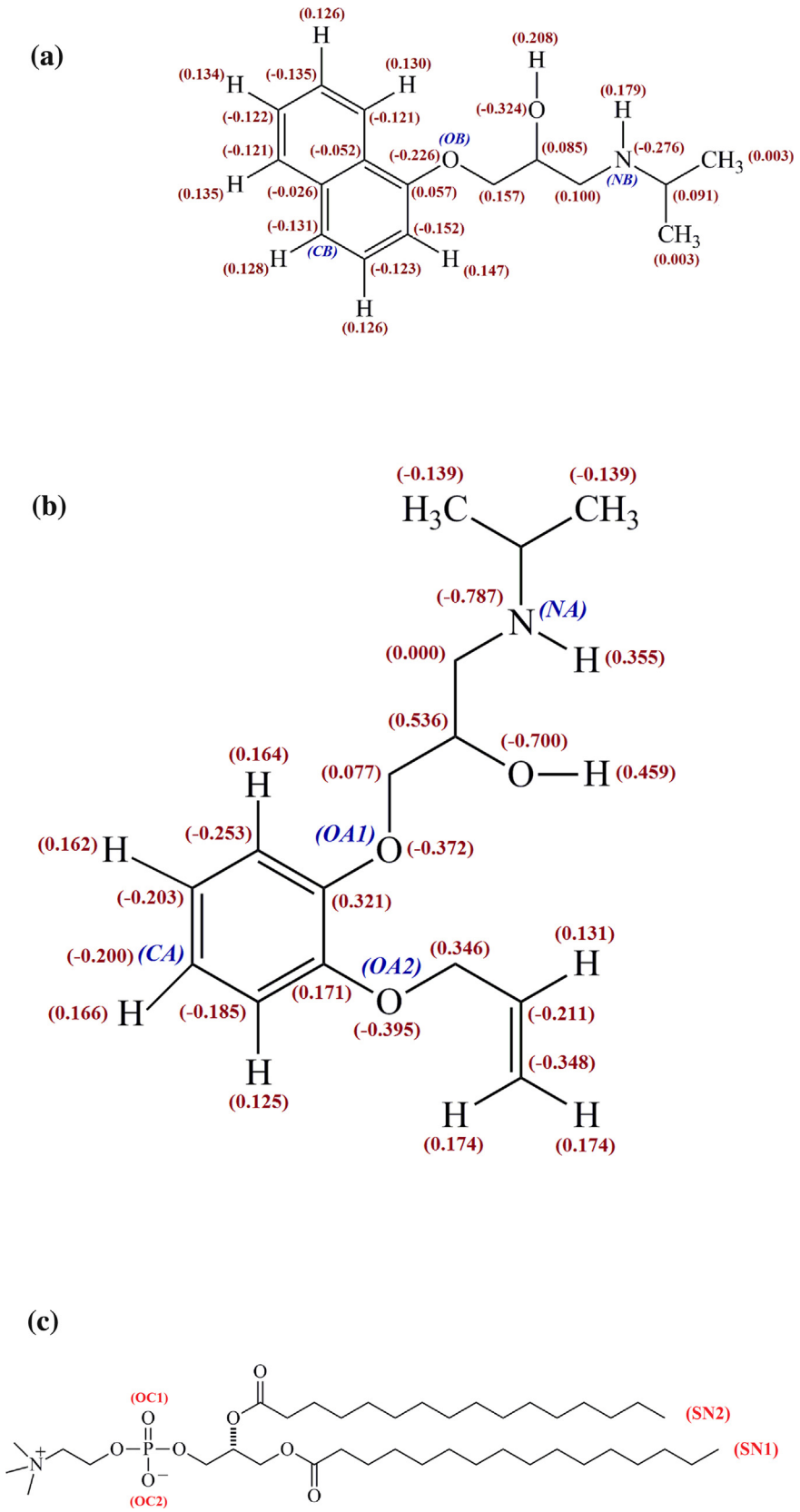

Fig. 1. Molecular structures of Propranolol (a) and Oxprenolol (b) with partial atom charges and atom names referred in the text along with the structure of DPPC lipid (c).

investigations including studies of the effects of Propranolol and Oxprenolol on the lipid membranes have been performed. The results of differential scanning calorimetry (DSC) studies indicated that the dimyristoylphosphatidylcholine (DMPC) thermotropic phase behavior is modulated by these compounds as follows: Propranolol > Metoprolol = Oxprenolol > Nadolol [4]. Some of ther-