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Interaction of neurotransmitters with a phospholipid bilayer: A molecular dynamics study

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ABSTRACT

We have performed a series of molecular dynamics simulations to study the interactions between the neurotransmitters (NTs) γ-aminobutyrate (GABA), glycine (GLY), acetylcholine (ACH) and glutamate (GLU) as well as the amidated/acetylated γ-aminobutyrate ($GABA^{neu}$) and the osmolyte molecule glycerol (GOL) with a dipalmitoylphosphatidylcholine (DPPC) bilayer. In agreement with previously published experimental data, we found the lowest membrane affinity for the charged molecules and a moderate affinity for zwitterionic and polar molecules. The affinity can be ranked as follows: ACH–GLU << GABA < GLY << $GABA^{neu}$ << GOL. The latter three penetrated the bilayer at most with the deepest location being close to the glycerol backbone of the phospholipids. Even at that position, these solutes were noticeably hydrated and carried ~30–80% of the bulk water along. The mobility of hydration water at the solute is also affected by the penetration into the bilayer. Two time scales of exchanging water molecules could be determined. In the bulk phase, the hydration layer contains ~20% slow exchanging water molecules which increases 2–3 times as the solutes entered the bilayer. Our results indicate that there is no intermediate exchange of slow moving water molecules from the solutes to the lipid atoms and *vice versa*. Instead, the exchange relies on the reservoir of unbounded ("free") water molecules in the interfacial bilayer region. Results from the equilibrium simulations are in good agreement with the results from umbrella sampling simulations, which were conducted for the four naturally occurring NTs. Free energy profiles for ACH and GLU show a minimum of ~2–3 kJ/mol close to the bilayer interface, while for GABA and GLY, a minimum of respectively ~2 kJ/mol and ~5 kJ/mol is observed when these NTs are located in the vicinity of the lipid glycerol backbone. The most important interaction of NTs with the bilayer is the charged amino group of NTs with the lipid phosphate group.
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1. Introduction

Many small molecules have intracellular targets, and hence they must pass across one or more phospholipid bilayer membranes to reach the intracellular targets and elicit a response to their pharmacological action. Therefore, small molecule–lipid interactions are inevitable, and a wide range of small molecules have been demonstrated to interact with lipid membranes (Berquand et al., 2005; Barcelo et al., 2004; Hidalgo et al., 2004; Preetha et al., 2007). The nature of these interactions has been studied using different biophysical techniques (Klacsová et al., 2011; Wanderlingh et al., 2010; Peetla et al., 2009) (and reference therein). However, an understanding on a molecular level of how binding to the lipid evokes the biological response remains limited since it is difficult to probe these interactions on a single-molecule level (Peters, 2004; Karplus, 2012; Srinivas and Klein, 2004). Here, computational methods such as atomic-level molecular dynamics simulations have been used to elucidate the structure and dynamics of lipid bilayer membranes and to probe partitioning and permeation of small molecules (Stouch, 1997; Xiang and Anderson, 2002; Boggara and Krishnamoorti, 2010; Tieleman, 2006; Bemporad et al., 2004). A wide range of solutes ranging from small polar molecules such as amino acids, anesthetics to organic solvents and drugs have been studied for their interactions with different types of lipid bilayer membranes (Klacsová et al., 2011; Rodgers et al., 2010; Mojumdar and Lyubartsev, 2010; Marrink and Berendsen, 1994; Shinoda et al., 2004; Tu et al., 1998; Henin et al., 2010; Högberg and Lyubartsev, 2008; Pitman et al., 2004; Pandit et al., 2008; Bennett et al., 2009; Pedersen et al., 2007; Peters et al.,

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2009; Dickey and Faller, 2007; Cerezo et al., 2011; MacCallum et al., 2007; Johansson and Lindahl, 2008; MacCallum et al., 2008; Mukhopadhyay et al., 2004; Norman and Nymeyer, 2006; Bemporad et al., 2005; Li et al., 2008; Ulander and Haymet, 2003; Boggara and Krishnamoorti, 2010). In particular, the mechanism by which anesthetics work has drawn much attention, and two apparently incompatible theories have emerged. One suggests that anesthetic action arises from direct anesthetic–protein interactions (Franks and Lieb, 1984; Franks and Lieb, 1985; Slatter et al., 1993; LaBella et al., 1998; Franks and Lieb, 1982) including ligand-gated ion channels (Weng et al., 2010; Nury et al., 2011), whereas the other one suggests that the lipids of the neuronal membranes are the prime site of anesthetic action. The indirect, lipid-mediated mechanism has been discussed since the anesthetic potency of a chemical species correlates with its octanol–water partition coefficient known as the Meyer–Overton rule (Meyer, 1899; Overton, 1901). This led to the proposition that anesthetics affect the postsynaptic membrane by modulating its physical properties through interaction with its lipid component (Cantor, 1997; Milutinovic et al., 2007). The lipid bilayer perturbation as the primary event is then transmitted to a membrane protein (Richards et al., 1978).

The lipid-mediated mechanism has recently also being linked to the action of neurotransmitters (NTs) (Cantor, 2003; Sonner and Cantor, 2013). Sonner and co-workers provided evidence that ligand-gated ion channels function can be modulated by co-released NTs in a similar fashion as observed for anesthetics (Milutinovic et al., 2007). The authors showed that non-native NTs can affect receptor function by modulating the mechanical properties of the bilayer. These mechanical changes affect consequently the conformational equilibrium of ligand-gated ion channel receptors and thereby their response to the native agonist. Lipid–NT interactions have also been hypothesized to influence neural transmission if the membrane accumulates a reservoir for neurotransmitters and thereby facilitates binding of these molecules to the target protein (Scheidt and Huster, 2008; Hemmings et al., 2005; Vautrin et al., 2000; Vautrin and Barker, 2003; Jodko-Piorecka and Litwinienko, 2013).

The idea of a lipid-mediated mechanism is further supported by a recent work that has suggested that different types of neurotransmitters have affinity for lipid bilayer membranes. Aromatic transmitters such as serotonin and dopamine appears to have high affinity (Peters et al., 2013; Jodko-Piorecka and Litwinienko, 2013; Orlowski et al., 2012), while smaller more hydrophilic NTs such as glycine, glutamate and GABA may show moderate affinity which depends strongly on the composition of the lipid membrane (Wang et al., 2011). These observed affinities appear to be a necessary requirement for an indirect role of bilayer–NT interactions in neural transmission. Analysis of this putative effect clearly requires a deeper insight into *e.g.*, driving forces and structural characteristics of NT–lipid interactions. The affinity of the aromatic NTs was suggested to rely on contact between the (cationic) primary amine of 5-HT and the lipid phosphate group. This provided a strong affinity of 5-HT for the membrane interfaces in spite of the fact that serotonin is hydrophilic with an oil–water partitioning coefficient well below unity. In the current work, we investigate the origin of the weaker membrane affinity found for the non-aromatic NTs with a phosphatidylcholine bilayer using equilibrium molecular dynamics (MD) simulations and umbrella sampling simulations. Specifically, we have calculated the energy cost (potential of mean force (PMF)) for partitioning of NTs into the bilayer, identified the most favorable NT–lipid contacts and analyzed positional distribution and hydration of interfacially located NTs. The NTs studied were the zwitterionic neurotransmitters γ-aminobutyrate and glycine, as well as the charged NTs acetylcholine and glutamate. For comparison and to address the effect of charges on the absorption properties to the bilayer, we also included amidated/acetylated γ-aminobutyrate and the osmolyte molecule glycerol in our study.

2. Methods

2.1. Equilibrium simulations

MD simulations were performed for systems composed of dipalmitoylphosphatidylcholine (DPPC)/water/solutes. The solutes were: glycerol (GOL); the zwitterionic neurotransmitters: γ-aminobutyrate (GABA) and glycine (GLY); the charged neurotransmitters: acetylcholine (ACH) and glutamate (GLU); and the amidated/acetylated γ-aminobutyrate ($GABA^{neu}$). Their structures are displayed in Fig. 1. The abbreviations given in parentheses are introduced for convenience and will be used throughout the text when referring to a certain solute molecule. The bilayer consisted of 72 DPPC molecules (36 per leaflet) and was fully hydrated with

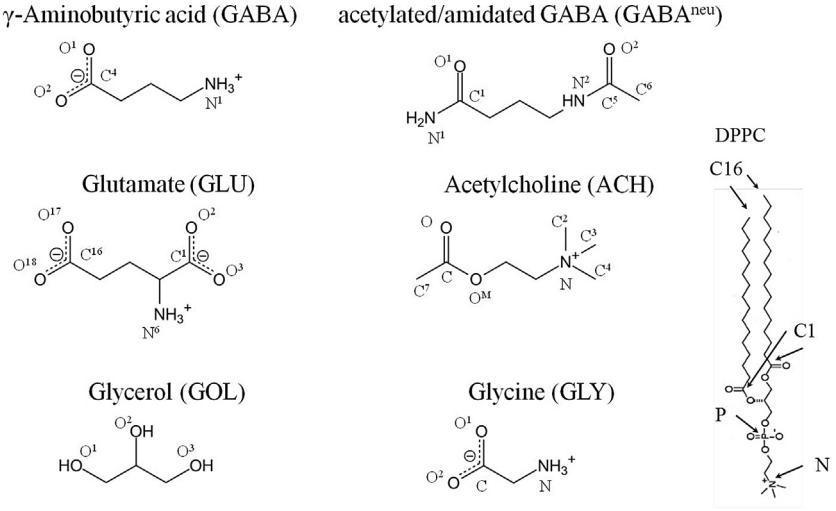

Fig. 1. Structure of the different solutes: γ-aminobutyrate (GABA), glycine (GLY), acetylcholine (ACH), glutamate (GLU) and acetylated/amidated γ-aminobutyrate ($GABA^{neu}$) and glycerol (GOL) as well as 1,2-dihexadecanoyl-sn-glycero-3-phosphocholine (DPPC). For clarity, the hydrogen atoms in the DPPC molecule are not shown. The phospholipid atoms N (choline group, $lipid^{N}$), P (phosphate group, $lipid^{P}$), C1 (carbonyl carbon of glycerol backbone, $lipid^{C1}$) and C16 (carbon in the methyl group (tail), $lipid^{C16}$) are chosen for the calculation of the probability distributions.

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