Computational and Theoretical Chemistry 1127 (2018) 44–51

Contents lists available at ScienceDirect

Computational and Theoretical Chemistry

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

Recognition of trans and gauche phenylethylamine conformers in the active site of human monoamine oxidase B: A MD-simulation and DFT studies

Subrata Dasgupta, Soumita Mukherjee, Bishnu P. Mukhopadhyay *

Department of Chemistry, National Institute of Technology-Durgapur, West Bengal, Durgapur 713209, India

ARTICLE INFO

Article history:
Received 9 January 2018
Received in revised form 31 January 2018
Accepted 31 January 2018
Available online 2 February 2018

Keywords:
Monoamine oxidase B
Neurotransmitter
Phenylethylamine
Molecular dynamics simulation
Density functional theory
Conserved water molecules

ABSTRACT

Phenylethylamine (PEA) is an endogenous amphetamine and as such, it blocks monoamine transporters and to a lesser extent vesicular transport thus elevating the level of corresponding neurotransmitter molecules at the synaptic cleft. In the physiological system, PEA acts as neuromodulator and is primarily metabolized by human monoamine oxidase B (hMAO B) to corresponding aldehyde and ammonia. In this work the stabilization of trans and gauche conformers of protonated phenylethylamine in the active site cavity of hMAO B have been evaluated by MD-simulation and DFT studies. The aromatic phenyl ring of *trans*-PEA is stabilized by Phe343(π)···PEA(π) interaction, where the π-ring of Phe343 is observed to stabilized by π···H—O (Tyr398$_{OH}$) interaction, whereas in gauche conformer hydrogen bonding association of a water molecule with N$^+$-atom of PEA and at the same time its bridging with aromatic π-ring of that substrate through non-covalent (N$^+$···W···π and water···π···water) interaction have provided some extra stability to it. It has also been observed that N$^+$-site of PEA has been stabilized by two to three water molecules along with Leu171$_{OB}$ and Gln206$_{OE1}$/Tyr435$_{OH}$ in the respective trans and gauche conformers. The results provide some interesting chemical insight on the stabilization of both the trans and gauche conformers of PEA in the active site of hMAO B which may be useful for inhibitor design related to neurological diseases.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

The human brain has a network of neuronal cells that play role in control and coordination of the nervous system [1]. The chemical signal messenger (neurotransmitter) molecules are synthesized in the nerve cells, packed into vesicles and released in the synaptic cleft where they can be received by the signal specific receptors present on the surface of post-synaptic neuron [2,3]. Unlike the major neurotransmitters (dopamine (DOP), serotonin (SRO) and norepinephrine (NOR)), Phenylethylamines (PEA) belong to the group of trace amines and function as neuromodulator [4]. Often these messenger molecules from the synaptic cleft revert back through the specific monoamine transporters (MATs) like dopamine transporter (DAT), serotonin transporter (SERT), and epinephrine transporter (NERT)) [5,6] which are also known as neurotransmitter-Na$^+$/cl-dependent symporter [7] and they have been a good drug target for mental disorders [8]. The mazindol [9], nefazodone [10], and venlafaxine [11,12] drugs are well known serotonin-norepinephrine-dopamine reuptake inhibitors (SNDRI), and the most popular antidepressants drugs citalopram [13,14], escitalopram, and fluoxetine [10,15] can act as selective serotonin re-uptake inhibitors (SSRI).

The PEA is an endogenous amphetamine and as such it blocks MATs and to a lesser extent vesicular transport thus elevating the level of corresponding neurotransmitter molecules at the synaptic cleft [16,17]. PEA molecules neither interact with the monoamine receptors nor reabsorbed by pre-synaptic cell rather for most of the time they remain in the cerebrospinal fluid and influencing the distant neuron cells [4]. Again, the most studied central nervous system stimulants (amphetamine and cocaine) which are used as psychoactive drugs can block MATs [18–20]; however, the detail

Abbreviations: PEA, phenylethylamine; DOP, dopamine; SRO, serotonin; NOR, norepinephrine; FAD, flavin adenine dinucleotide; hMAO B, human monoamine oxidase B; MATs, monoamine transporters; DAT, dopamine transporter; SERT, serotonin transporter; NERT, epinephrine transporter; MD, molecular dynamics; R.F., residential frequency; ns, nanosecond; ps, picosecond; fs, femtosecond; K, Kelvin; C-PCM, conductor-like polarizable continuum models; DFT, density functional theory; RMSD, root mean square deviation.

* Corresponding author.
E-mail address: bpmk2@ch.nitdgp.ac.in (B.P. Mukhopadhyay).

https://doi.org/10.1016/j.comptc.2018.01.021
2210-271X/© 2018 Elsevier B.V. All rights reserved.

mechanism remains unclear. Recent binding studies of amphetamine (AMPH), orphenadrine (an anticholinergic drug used in the treatment of Parkinson disease), and cocaine with hDAT provide some structural insight to DAT modulation and are suggesting the uses of orphenadrine as a repurposable DAT drug which unaffect the dopamine binding and transport [21]. Another class of drugs generally used in neuropsychiatric diseases are Monoamine oxidase inhibitors (MAOIs) like selegiline [22], moclobemide [23] and toloxatone [24,25] which are typically used in the treatment of Parkinson's disease and depression [26]. The latter two drugs, selective hMAO A inhibitors are safer alternatives as the MAO inhibitors interact with other drugs leading to hypertensive reactions [27,28]. The flavoenzyme human Monoamine oxidase has two isoforms A and B [29] which differ in substrate and inhibitor specificities [30]. Phenylethylamine is primarily metabolized to corresponding aldehyde and ammonia by human Monoamine oxidase B (hMAO B) [31] through oxidative deamination process, however, the mechanism is still unknown. The enzyme is associated with several neurological diseases so it is considered as an important drug target [32]. The active site of hMAO B is an oval shaped cavity in which the two sides, roof, and floor are lined with different hydrophobic and aromatic residues. The four tyrosine (Tyr188, Tyr326, Tyr398, and Tyr435) residues and Flavin Adenine Dinucleotide (FAD) provide a cage-like structure within which the substrate could bind for catalysis [33]. The X-ray crystallographic studies on hMAO B have indicated the possible role of four water molecules in the stabilization of substrate/inhibitor molecules [34] and subsequent QM studies have shown their possibilities in the involvement of catalytic processes [35,36]. The recent computational studies on trans-PEA and its substituted derivatives complexed with hMAO A and B isoforms have indicated the shifting of a hydride ion from C_α carbon of PEA to the N5 atom of FAD at the rate limiting step of the deamination mechanism [4,37,38] though it remains a challenge for future to check and compare the energetics (difference in reactivity) between trans and gauche conformers of monoamine substrates during the deamination process. In the physiological system PEA is thought to exist in protonated form ($pK_a \sim 9.8$) [37] though its neutral form is suggested to react with hMAO as in some theoretical [35] and experimental studies [39–41], so it remains a challenge for future to perform the detail conformational analysis for neutral PEA.

The recognition dynamics of protonated-PEA in the active site of the enzyme is still unknown, and it may be different from dopamine recognition as the latter molecule is metabolized by both the isoforms [30]. Previous studies on dopamine bound hMAO B complex structure have indicated the presence of few conserved or semi-conserved hydrophilic water sites in the hydrophobic active site pocket of this enzyme which are playing a key role in the recognition of trans conformer of dopamine [42] and also in catalysis [35]. The preference of trans conformation of dopamine in its hMAO B complex [42] may not sustain for PEA in its enzyme bound structure due to more freedom for movement of the phenyl group in the hydrophobic cavity compare to catechol ring of dopamine. Besides, the hydration dynamics of the PEA-hMAO B complex may add a new feature on the role of water molecules in the stabilization of PEA-conformers. In the present work, MD-simulation and DFT calculations have been performed on PEA-hMAO B complex structure for getting a better chemical insight on the stabilization mechanism of trans and gauche conformers in the active site of this enzyme.

2. Materials and methods

The X-ray structure of dimeric Monoamine oxidase B, PDB Id 2XFN, having resolution 1.60 Å and R-value 0.166 was selected from Protein Data Bank. The position and hydrogen bonding interaction of catalytic residues and conserved water molecules to Flavin Adenine Dinucleotide (FAD) in 2XFN structure were examined using UCSF Chimera program [43].

2.1. Preparation of ligand structures

The structures of PEA (protonated form) and FAD were built and geometric optimization (steepest descent method) was carried out with CHARMM force field using Hyperchem 7.52 program until the structure reached the convergence gradient 0.001 kcal/mol. Subsequent geometry optimization of the ligand molecules were separately performed with B3LYP/6-31G level of theory using Gaussian 09 package [44]. Then the FAD molecule was placed in its position as was found in 2XFN crystal structure [45] and the ligand (PEA) was docked into the active site cavity by using Autodock Vina v.1.1.1.

2.2. Identification of conserved water molecules

The 3DSS server [46] and Swiss PDB viewer program [47] were used to find out the conserved water molecules among those X-ray structures. The 2XFN PDB structure [45] was taken as reference and all the other structures were successively superimposed on it. Cut-off distance between the pairs of superposed water molecules was taken to be 1.8 Å and only those were considered which have at least one hydrogen bond with the protein [48]. But in certain instances water molecules were considered to be equivalent where similar type of hydrogen bonding pattern were encountered even if the pair-wise distance criterion was not satisfied due to varying side-chain conformation [49,50]. In the dimeric structure of hMAO B, similar conserved water centers within the catalytic zone of the two monomers were investigated and subscripted by A and B following the identification numbers.

2.3. Molecular dynamics (MD) simulation

MD-simulation of the PEA-2XFN complex structure was performed using NAMD v.2.12 [51,52] with CHARMM36 force field [53–55]. Then each structure was converted to Protein Structure File (PSF) by Automatic PSF Generation Plug-in within VMD program v. 1.9.3 [56]. The crystal water molecules were retained and converted to TIP3P water model [57]. Subsequent energy minimization was performed by the conjugate gradient method. The process was conducted in two successive stages; initial energy minimization was performed for 1000 steps by fixing the backbone atoms, followed by a final minimization for 2000 steps with all atoms of the system to ensure the removal of any residual steric clashes. Then the energy minimized structures were simulated at temperature 310 K and pressure 1 atm controlled by Langevin dynamics [58] using periodic boundary condition. Initially in order to analyze the dynamic stability of conserved water molecules, water dynamics was performed for 2 ns by fixing the ligand and protein residues, allowing the water molecules to move freely. Finally, all-atom molecular dynamics simulation for 50 ns was carried out for protonated PEA docked hMAO B (2XFN) structure. The MD-trajectories were analyzed to investigate the interaction and dynamics of conserved water molecules towards the substrate, FAD and catalytic residues in hMAO B.

2.4. Quantum chemical (QM) calculations

The results of PEA-hMAO B simulated structures were analyzed and few snapshots at 10, 20, 30, 40, and 50 ns were selected for model building and further DFT studies. The trans and gauche conformers of protonated-PEA along with FAD, some active site

Download English Version:

https://daneshyari.com/en/article/7839006

Download Persian Version:

https://daneshyari.com/article/7839006

Daneshyari.com