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Computational study of possible complexes of caffeine and adenosine with adenosine receptor fragments

Valeri Poltev [a,b,*], Efren Rodriguez [a], Alexandra Deriabina [a], Eduardo Gonzalez [a], Nina Polteva [b]

[a] Autonomous University of Puebla, Av. San Claudio y Rio Verde, Puebla 72570, Mexico
[b] Institute of Theoretical and Experimental Biophysics, Pushchino, Moscow Region 142240, Russia

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ABSTRACT

Caffeine (CAF) is a biologically active substance with the broad function spectrum well-known from ancient times and widely used nowadays. The main pharmacological effect of CAF, stimulation of central nervous system, is due to its acting as a concurrent antagonist of Adenosine (Ado) on membrane proteins, namely, adenosine receptors A1 and A2a. In this work we study the atomic level mechanism of this effect. The main question that we try to answer using computer modeling is «How can comparatively small and practically rigid CAF molecule, with its limited possibilities to take part in sufficiently strong intermolecular interactions, compete for binding sites with Ado molecule, which has more hydrogen bonding centers and significant conformational flexibility?» To approach this question we have calculated, using molecular mechanics (MM) method, the minima of interaction energy of CAF and Ado molecules with the fragments of transmembrane receptor domains participating in Ado binding. The MM computations revealed that the most probable conformations of separate Ado molecule correspond to the formation of two intra-molecular H bonds. This conclusion was confirmed at MP2/6-31G(d,p) and MP2/6-311++G(d,p) levels of the ab initio theory. It restricts the possibility of Ado interactions with hydrophilic amino acids of the receptor fragments. Thus, at the deepest minima of the interaction energy, both Ado and CAF form H bonds with no more than three amino-acid residues. The energy values at these minima are rather close to each other. Therefore, two molecules that are substantially different in the number of hydrophilic centers and in conformational possibilities turn out to be similar from the point of view of the energy of complex formation with adenosine receptor fragments.

1. Introduction

Caffeine (CAF) is a natural biologically active substance, known from ancient times and one of the most widely consumed on regular basis nowadays [1,2]. Its name originates from coffee beans, the primary CAF source. Since the Stone Age man consumed CAF from natural sources, such as coffee beans, tea and yerba mate leaves, guarana berries, kola nuts, cocoa beans, and others. Currently CAF is a common ingredient of some soft drinks and drugs. CAF has multiple effects on human beings and mammals in general, it affects functioning of proteins (including enzymes and receptors), nucleic acids, and membranes. Thousands of biological, biochemical, genetics, and medical research works have been performed to clarify different aspects of these actions. The main effect of CAF is stimulation of the central and the peripheral neural systems [3]. There are different points of view on its health effects, each confirmed by clinical studies, starting from declaration that "caffeine produces an astonishing, nearly endless variety of special beneficial effects for the mind, body, and spirit" [4], to CAF "can produce a clinical dependence syndrome similar to those produced by other psychoactive substances and has a potential for abuse" [5]. Nevertheless, the molecular mechanism of action of this molecule is still little-studied.

CAF (Fig. 1) is a rather simple organic molecule, a purine derivative, namely, the 1,3,7-trimethyl-2,6-dioxopurine (1,3,7-trimethylxantine). It has three H-bond acceptor atoms (O2, O6, N9), and no H-bond donor atoms. All the CAF atoms but methyl hydrogens are located in almost the same plane. A combination of hydrophilic and hydrophobic atomic groups enables CAF to be soluble in both polar (water) and non-polar solvents, and to pass through biological membranes.

The main CAF's targets at physiologically significant concentrations are adenosine receptors (ARs). Four types of ARs of mammalian cells have been cloned and characterized, namely,

* Corresponding author at: Autonomous University of Puebla, Av. San Claudio y Rio Verde, Puebla 72570, Mexico.
E-mail addresses: poltev@fcfm.buap.mx, vpoltev@yahoo.com (V. Poltev).

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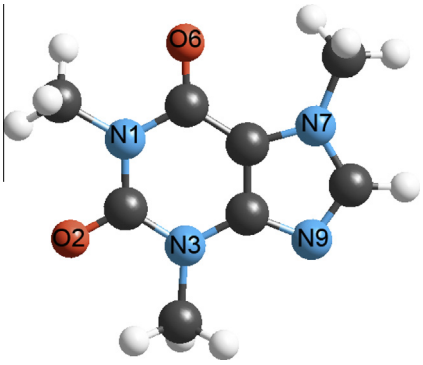

Fig. 1. The ball and stick model and the heteroatom numbering of a CAF molecule.

A1, A2a, A2b, and A3 [6,7]. All ARs are membrane proteins of G-protein-coupled receptor (GPCR) family with a similar primary structure containing more than 300 amino acid residues. Each of the ARs contains extracellular (EC), intracellular (IC) and transmembrane (TM) domains. The peptide backbone of TM domains has an α-helix conformation; each of the seven TM domains consists of about 20 amino acid residues. These domains (and their neighbor residues) play an important role in interactions with adenosine (Ado), its antagonists and its agonists [8]. It is generally accepted that CAF is a competitive antagonist of Ado, interacting with the adenosine receptors A1 and A2a [6,9,10]. The A1 receptors are the ones most diffused throughout the entire body of humans and animals, the interactions with A1 are the most important for physiological effects of CAF [11,12].

Ado itself is a biologically important molecule, a ribonucleoside, a component of nucleic acids and coenzymes. Its base contains three H-bond acceptor groups (N1, N3, and N7) and one H-bond donor group (NH_2); the ribose ring contains O4′ acceptor atom, and its three extracyclic H–O groups can be both donors and acceptors of an H bond. Intercellular Ado plays an important physiological role in receptors activation. To understand this process, a number of Ado antagonists and agonist were synthesized and studied (e.g. [8,13]). All of them, like Ado itself, are much more complex than CAF molecule; they have a greater number of centers of strong interaction with proteins and a considerable conformational mobility. It could be naturally expected that Ado as well as its antagonists and agonists have greater potential for complex formation with ARs than CAF. Therefore, the first question about the molecular mechanism of CAF action, which we are trying to answer below is «How can comparatively small CAF molecule, with practically fixed geometry and a restricted set of centers of sufficiently strong interaction with proteins, compete with much more complex and conformationally mobile Ado molecule, capable to form more H bonds, and, supposedly, more stable complexes with ARs?»

We raised this question in the paper of 2010 [14]. As a first step to the answer to the question we studied a possibility of the formation by the CAF molecule of sufficiently stable complexes with the fragments of TM domains of ARs. Using two different Molecular Mechanics (MM) force fields and two different computer programs, we showed the existence of rather deep energy minima of the CAF interactions with TM domains of the human A1 receptor (most studied of ARs before the first X-ray structure of the A2a receptor complex was published, see below). Such possible complexes are stabilized by two or three H bonds [14,15]. When forming such a complex, the CAF molecule screens several amino-acid residues from interactions with Ado. In previous works we restricted ourselves by rather short fragments of the receptor (of 7 amino-acid residues), taking into account the size and the position of H-bonding centers of the CAF molecule. In the present work we continue to search for an answer to the question about the CAF-Ado competition for the human A1 and A2a receptors binding sites via MM computations for possible complexes of fragments of TM domains with CAF and Ado molecules. As Ado is more voluminous molecule, we selected more extended fragments of the TM domains for the computations (Section 3.2). The computations showed that the values of the interaction energy of CAF with the TM fragments in the deepest minima are similar to those of Ado. This result contributes to understanding the mechanisms of CAF competition with Ado for binding sites of the ARs as the source of the CAF physiological effect.

Recent X-ray and molecular dynamics studies of A2a receptor complexes with the ligands vindicate our choice of the systems for computational studies. Until recently, molecular models of ARs were constructed in homology to the X-ray structure of the bovine rhodopsin. In 2008 the three-dimensional structure of human A2a receptor bound to subtype-selective Ado antagonist ZM241385 has been determined to 2.6 Å resolution [16]. This antagonist has a sufficiently complex structure, containing aromatic rings, H-bond donor groups (OH, NH, and NH_2), and 6 H-bond acceptors. It is built in "the binding pocket" formed by three TM domains and neighbor residues of the third EC domain.

In 2011 this structure was used in the paper [17] to search for the answer, in relation to the A2a receptors, to the question formulated above. The evaluation of the free energy changes on CAF and ZM241385 incorporation into the pocket using molecular dynamic method leads to the conclusion that binding of the specific antagonist, ZM241385, is only 2.4 kcal/mol more favorable than binding of the non-specific antagonist CAF. Due to greater number of possible positions in the pocket of the small CAF molecule compared to more voluminous ZM241385 molecule, the entropy contribution is rather significant (0.9 kcal/mol). The same year new structures of complexes of the A2a receptor with various ligands have been published. These ligands include Ado [18], CAF [19], and the agonist with more complex molecular structure than ZM241385, designated as UK-432097 [20]. The three-dimensional structure of the pocket of the A2a receptor depends on the ligand used in co-crystallization. The CAF molecule forms only one H bond with amino-acid residues in the pocket, while all other ligands form several H bonds; namely, three, six and ten H bonds are formed with ZM241385, Ado, and UK-432097 respectively. Lee and Lyman [21] used these structures for a comparison of Ado and UK-432097 binding to the A2a receptor. Molecular dynamics simulations enable the authors to account for a more potent action of UK-432097 as compared with Ado by stabilizing the active A2a conformation via H-bond network formation, while Ado is able to form several complexes and migrate between a few binding positions [21]. This conclusion, derived from the molecular dynamics trajectories, can be understood from the analysis of the molecular structure of these ligands and their complexes with the A2a receptor. The UK-432097 molecule is more voluminous than Ado, and it is able to form many H bonds in the receptor pocket [20], while Ado forms fewer H bonds, is water-bridged to some amino-acid residues [18], and is able to migrate in the pocket cavity [21]. The CAF-Ado competition cannot be explained by considerations similar to those in papers [17,21], as Ado molecule can form significantly more H bonds than CAF in the receptor binding pocket (and it really seen to forms 6 H bonds in the X-ray structure of the complex [18]), and, like CAF, it has considerable mobility in the pocket [21].

Thus, the molecular structures of recent experimentally determined complexes of A2a receptors with various ligands and molecular dynamics simulation of these complexes do not provide an answer to the question about CAF competition with Ado for receptor binding sites. Taking into account the above considerations and conformational mobility of ARs we surmised that the interactions of the receptor conformations other than those in crystals of