The molecular mechanism for DDT detoxification in Anopheles gambiae: a molecular docking study

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Received 21 December 2010; revised 9 January 2011; accepted 28 January 2011.

ABSTRACT

The epsilon class glutathione-S-transferase of Anopheles gambiae, agGSTe2, is capable of metabolizing DDT. A molecular docking analysis of DDT with agGSTe2 support an E2 elimination mechanism wherein the glutathione sulfur serves as the base to convert DDT to DDE.

Keywords: Malaria; DDT; Anopheles gambiae; Glutathione S-Transferase; Docking

1. INTRODUCTION

Malaria continues to be a devastating disease worldwide with an estimated 1 billion cases and more than 2 million deaths annually [1] with an estimated 800,000 deaths among sub-Saharan African children [2]. House spraying with DDT [1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane] was the primary method of Anopheles gambiae vector control of malaria in the 1950s and 1960s [3], but the advent of DDT-resistant strains of the mosquito resulted in failure of this eradication campaign [4].

Glutathione S-transferases (GSTs) are a major family of detoxification enzymes found in most organisms [5]. The GSTs of A. gambiae are of particular interest because of their involvement in DDT resistance [6,7]. The epsilon class GST of A. gambiae, agGSTe2, is known to be capable of metabolizing DDT, and the X-ray crystal structure has been recently determined [8]. This report presents a molecular docking study of DDT with agGSTe2.

2. METHODOLOGY

Protein-ligand docking studies were carried out using the crystal structure of agGSTe2 with bound glutathione (PDB: 2imi). All water molecules were removed from the structure. Molecular docking calculations for DDT and DDE with agGSTe2 were carried out using Molegro Virtual Docker 3.2.1 [9,10], with a 15-Å sphere centered on the cavity containing the glutathione. The glutathione was treated as a cofactor. Different orientations of the DDT ligand were searched and ranked based on their energy scores. The RMSD threshold for multiple cluster poses was set at <1.00Å. The docking algorithm was set at maximum iterations of 1500 with a simplex evolution population size of 50 and a minimum of 30 runs.

3. RESULTS AND DISCUSSION

The lowest-energy docked poses (Table 1) for DDT with agGSTe2 oriented the DDT molecule adjacent to the glutathione such that the proton on C(2) of DDT was in contact with the sulfur atom of glutathione (Figure 1). In addition to favorable interactions of DDT with the glutathione, important interactions of docked DDT are with Arg 112, Phe 120, Leu 36, and Glu 116, which form a hydrophobic pocket embracing the DDT. Interestingly, the docking energies of DDE are about 4.5-6.4 kJ/mol less than the docking energies of DDT. These docking results support the hypothesis [8] that overexpression of agGSTe2 provides DDT resistance to Anopheles gambiae by readily decomposing DDT to DDE via an E2 elimination mechanism.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Site A</th>
<th>Site B</th>
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<tbody>
<tr>
<td>DDT</td>
<td>−102.1</td>
<td>−104.2</td>
</tr>
<tr>
<td>DDE</td>
<td>−97.6</td>
<td>−97.8</td>
</tr>
</tbody>
</table>

REFERENCES


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Figure 1. Molegro docking poses of DDT into the epsilon class glutathione S-transferase of *Anopheles gambiae*, agGSTe2 (PDB: 2imi). Note that the proton on C(2) of the DDT is in contact with the sulfur atom of glutathione.