Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2

STEVEN LEHRER and PETER H. RHEINSTEIN

Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York City, NY, U.S.A.; Severn Health Solutions, Severna Park, MD, U.S.A.

Abstract. Background/Aim: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). One drug that has attracted interest is the antiparasitic compound ivermectin, a macrocyclic lactone derived from the bacterium Streptomyces avermitilis. We carried out a docking study to determine if ivermectin might be able to attach to the SARS-CoV-2 spike receptor-binding domain bound with ACE2. Materials and Methods: We used the program AutoDock Vina Extended to perform the docking study. Results: Ivermectin docked in the region of leucine 91 of the spike and histidine 378 of the ACE2 receptor. The binding energy of ivermectin to the spike-ACE2 complex was -18 kcal/mol and binding constant was 5.8 e-08. Conclusion: The ivermectin docking we identified may interfere with the attachment of the spike to the human cell membrane. Clinical trials now underway should determine whether ivermectin is an effective treatment for SARS-CoV-2 infection.

Correspondence to: Dr. Steven Lehrer, Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1236, New York City, 10029 NY, USA. E-mail: steven.lehrer@mssm.edu

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*These Authors contributed equally to this study.

Materials and Methods

We used the program AutoDock Vina Extended to perform the docking study (7). The ivermectin molecule is from PubChem CID: 6321424 (Figure 1). Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2 was deposited in the Protein Data Bank 2020-02-21, released: 2020-03-18 (8). We analyzed the human ACE2 receptor because this enzyme apparently differs among species, and the affinity of the virus for the human form may explain its particular infectivity for humans (9).
Results

The root-mean-square deviations of atomic positions (RMSD in Angstroms) are tabulated in Table I. Lower values of RMSD indicate that docking is validated with higher accuracy. RMSD values of 3 or more indicate no docking has occurred. Only one docking position, site 1, with RMSD=0 is highly valid.

Table I. Docking parameters calculated by AutoDock Vina Extended.

<table>
<thead>
<tr>
<th>Site</th>
<th>Affinity (kcal/mol)</th>
<th>Ki (umol)</th>
<th>RMSD (lower bound)</th>
<th>RMSD (upper bound)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>–18.0543</td>
<td>5.84x10^-8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>–16.7427</td>
<td>5.34x10^-7</td>
<td>48.6656</td>
<td>50.524</td>
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<tr>
<td>3</td>
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<td>21.875</td>
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<td>48.55</td>
<td>50.7351</td>
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<tr>
<td>5</td>
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<td>16.1947</td>
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<tr>
<td>6</td>
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<td>47.5979</td>
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<tr>
<td>7</td>
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<td>37.6908</td>
<td>38.7931</td>
</tr>
</tbody>
</table>

Lower values of root-mean-square deviations of atomic positions (RMSD) indicate that docking is validated with higher accuracy. RMSD values of 3 or more indicate no docking has occurred. Only one docking position, site 1, with RMSD=0 is highly valid.

Ivermectin docked in the region of leucine 91 of the spike and histidine 378 of the SARS-Cov2-ACE2 receptor complex, between the SARS-Cov2 protein and the ACE2 protein. The binding energy of ivermectin to the spike-ACE2 complex was –18 kcal/mol and binding constant was 5.8x10^-8.

Computational biochemical methods and docking software have been used to screen potential drugs in the structural protein and non-structural protein sites of SARS-Cov2. Ribavirin (a common antiviral drug), remdesivir, chloroquine and luteolin have been analyzed (10). SARS-CoV-2 main protease inhibitors have been predicted using Autodock (11), among them Hispidin and Lepidine E, two natural compounds, and folic acid (12).

The Vero-hSLAM cell assays performed by Caly et al. might not be entirely relevant to human SARS-CoV2 infection. Vero-hSLAM is an African green monkey kidney epithelial cell line that does not express human ACE2 (13). Therefore, Caly et al. had to use high ivermectin concentrations.

Conclusion

The ivermectin docking site we identified, between the viral spike and the ACE2 receptor, may interfere with the attachment of the spike to the human cell membrane. Our observation is consistent with the findings of Caly et al. and Patel et al.

Clinical trials now underway should determine whether ivermectin is an effective treatment for SARS-CoV2 infection.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors’ Contributions

Drs. Lehrer and Rheinstein contributed equally to this work.

References


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