Binding characteristics of systemic glucocorticoids with the SARS-CoV-2 spike glycoprotein: in-silico evaluation

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a serious threat to people worldwide causing a variety of diseases, manifesting with intestinal, respiratory, hepatic, and neurological symptoms. SARS-CoV-2 predominantly focuses on the lower parts of the respiratory system, infiltrating the epithelial cells of the lungs. It releases the nucleocapsid component which then arrogates the host cell to replicate the viral genome. The therapeutic strategy to counteract SARS-CoV-2 encompasses antiviral drugs, monoclonal antibodies, as well as immunomodulatory drugs, such as systemic glucocorticoids, which may benefit patients with middle and severe COVID-19. In the treatment of COVID-19, systemic glucocorticoids exhibit anti-inflammatory activity by suppressing the cytokine storm mitigating the systemic inflammatory response caused by SARS-CoV-2. In addition, the spike glycoprotein (S protein), which recognizes the host cell receptor and initiates the attachment of SARS-CoV-2 to it, can be considered a potential target for glucocorticoids [1]. However, the mechanism of glucocorticoid inhibitory action against the S protein is currently unclear due to insufficient study of the ligand-binding sites on the S protein.

The aim of the study was to evaluate the binding characteristics of systemic glucocorticoids with the SARS-CoV-2 S protein and to elucidate the topological features of non-covalent ligand-protein complexes.

Molecular docking was performed to study the binding affinity and type of interactions between ligands and the protein targets. AutoDock Vina was used for docking studies against SARS-CoV-2 S protein with ligands [2]. Dexamethasone, methylprednisolone, triamcinolone, and prednisone were selected as ligands to perform molecular docking studies to identify favorable binding sites on S protein. The structures of the ligands were downloaded from PubChem, an open chemistry database at the National Institutes of Health. AutoDock tool was used to prepare ligand structures in the PDB format. Two 3D structures of S protein which have open (RBD-up) and closed (RBD-down) conformations in the receptor-binding domain (PDB ID: 6VYB, and PDB ID: 6VXX), respectively, were used as docking targets (www.rcsb.org). Water molecules were removed and hydrogen atoms were added. Ligand interactions with amino acid residues were identified using the PLIP web tool (https://plip-tool.biotec.tu-dresden.de). Visualization of docking results was implemented in PyMol 2.5.

In silico docking study demonstrated that all glucocorticoids can bind to multiple sites on the SARS-CoV-2 S protein, including the receptor-binding fragment (S1) and the fusion fragment (S2). Methylprednisolone showed the best affinity with S protein in RBD-up conformation than other glucocorticoids, with a binding free energy of -9,7 kcal/mol and an inhibition constant value of $0{,}08 \times 10^{-6}$ M. Triamcinolone demonstrated a high affinity with S protein in RBD-down conformation, at which the binding free energy was -8,8 kcal/mol and an inhibition constant value was $0{,}36 \times 10^{-6}$ M. Our results showed that Tyr369, Lys417, and Ser514 are mainly involved in the stabilization of complexes through the hydrogen bonds. Hydrophobic interactions are primarily mediated by Phe464, Asn1023, and Leu1024. These results are an important basis for the development of potential drugs against SARS-CoV-2.

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