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. 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.

Results and discussion

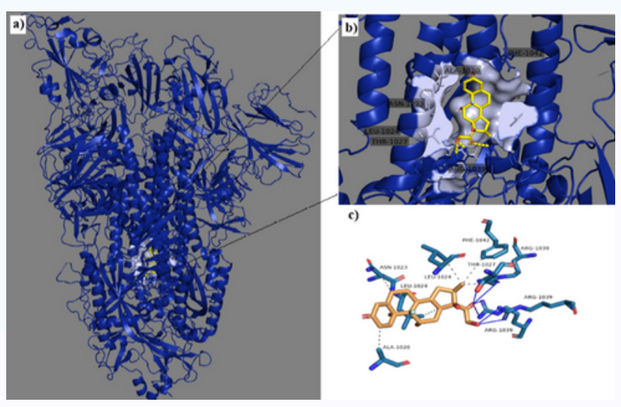

Fig. 1 The ligand binding pocket (a, b); hydrogen bonds (thin blue solid lines) and hydrophobic interactions (gray dotted lines) between dexamethasone and the S protein in "up" conformation (PDB ID: 6VYB) (c)

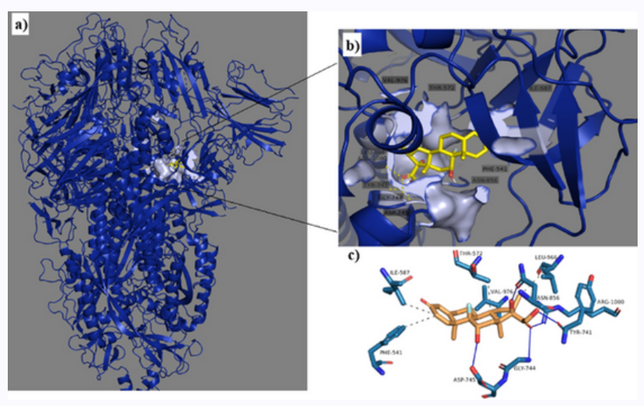

Fig. 2 The ligand binding pocket of dexamethasone (a, b); hydrogen bonds (thin blue solid lines) and hydrophobic interactions (gray dotted lines) between dexamethasone and the S protein in "down" conformation (PDB ID: 6VXX) (c)

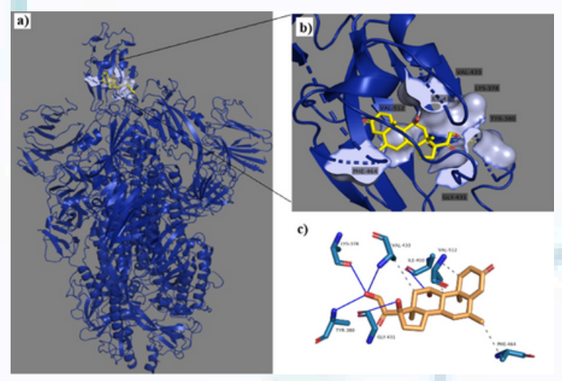

Fig. 3 The ligand binding pocket of methylprednisolone (a, b); hydrogen bonds (thin blue solid lines) and hydrophobic interactions (gray dotted lines) between methylprednisolone and the S protein in "up" conformation (PDB ID: 6VYB) (c)

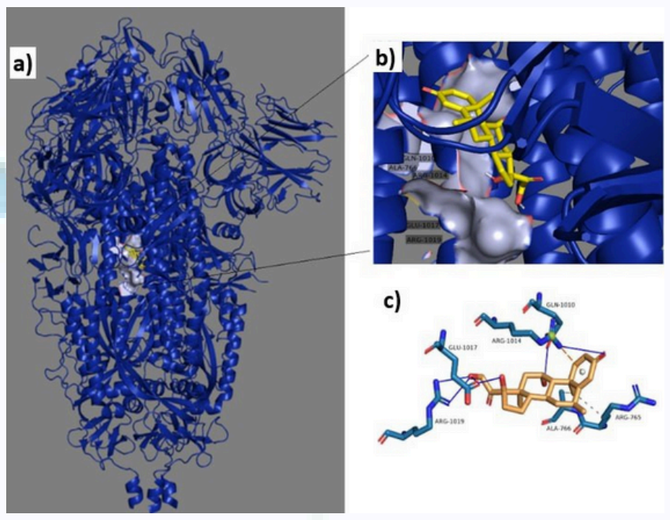

Fig. 4 The ligand binding pocket of methylprednisolone (a, b); hydrogen bonds (thin blue solid lines) and hydrophobic interactions (gray dotted lines) between methylprednisolone and the S protein in "down" conformation (PDB ID: 6VXX) (c)

	DEX		Medrol		TAC		PRED	
	ΔG	k_i	ΔG	k_i	ΔG	k_i	ΔG	k_i
6VYB	-8,4	0,72	-9,7	0,08	-8,4	0,72	-8,7	0,43
6VXX	-8,7	0,43	-8,3	0,85	-8,8	0,36	-8,7	0,43

Table 1. The ligand binding affinity (ΔG, kcal/mol) and inhibition constant (ki ×10^-6 , M) of the ligand-protein complex

Conclusions

Determining the binding characteristics of corticosteroids to the S protein structures of SARS-CoV-2 has several significant implications. If certain corticosteroids show a strong binding affinity to the spike protein, they could be modified for use as potential treatments for COVID-19. Additionally, studying the binding characteristics can elucidate the mechanisms by which corticosteroids may exert their effects against SARS-CoV-2. The high binding affinity of all selected glucocorticoids suggests their potential to destabilize the binding of the SARS-CoV-2 spike protein with the human host ACE2 receptor, thereby hindering viral entry into the cells.

Based on the binding energy score, it was suggested that these glucocorticoids have the potential to be utilized as drugs against SARS-CoV-2 and for the development of effective antiviral drugs.