Peptide WALMART:
A Potential Inhibitor of the Interaction Between SARS-CoV-2 and ACE2

David Wade, Wade Research Foundation, Princeton, NJ, USA

Abstract

The interaction of the SARS-CoV-2 virus spike glycoprotein (S protein) with angiotensin converting enzyme 2 (ACE2), a cell surface protein in lung, artery, heart, kidney, and intestinal cells, is thought to be the first step of infection by the virus. If this interaction could be inhibited, it might be possible to prevent infection by the virus.

Peptide WALMART (Trp-Ala-Leu-Met-Ala-Arg-Thr-amide) was examined for its potential ability to bind to the domain on S protein that interacts with ACE2. Such binding would be expected to inhibit the interaction between S protein and ACE2. The ClusPro 2.0 docking program was used to simulate the binding of α-helical and β-strand models of peptide WALMART with the cryo-electron microscopy structure of the ACE2-binding domain of S protein. The program produced 55 docked models, and in 7 of the models, peptide WALMART was bound to amino acids of S protein that are involved in its interaction with ACE2. Since this interaction is hypothesized as the first step in infection of cells with the SARS-CoV-2 virus, then peptide WALMART may be capable of inhibiting the interaction and preventing infection.

Introduction

There is currently an intense, worldwide effort to find ways to eliminate infection due to the SARS-CoV-2 virus (Figure 1) [1-5]. Infection with the virus is thought to begin with binding of the SARS-CoV-2 surface spike glycoprotein (S protein) to its cellular receptor, angiotensin converting enzyme 2 (ACE2), which is present on the surfaces of lung, artery, heart, kidney, and intestinal cells. Interaction of the receptor-binding domain (RBD) of S-protein with ACE2 occurs via polar interactions between 8 pairs of amino acids (AAs) on both proteins (Table 1). If these interactions could be blocked, it might be possible to prevent infection.

Peptide WALMART is a 7-residue peptide amide with the AA composition [6]:

Tryptophan-Alanine-Leucine-Methionine-Alanine-Arginine-Threonine-NH_2

In the single letter symbolism of the International Union of Pure and Applied Chemistry (IUPAC)-International Union of Biochemistry (IUB) [7] the sequence is:

W-A-L-M-A-R-T-NH_2 or WALMART-NH_2

The sequence of IUPAC-IUB single letter symbols corresponds to the name of a well-known retail company, and, consequently, it has been designated a “name peptide”. Peptide WALMART has been shown to have anticancer, and, potentially, antimicrobial activities.

This study examined the potential ability of peptide WALMART to interact with the S protein RBD by use of the ClusPro 2.0 docking program [8]. The results indicated that peptide WALMART can bind to the critical amino acids on the S protein RBD that are involved in its interaction with ACE2. Consequently, peptide WALMART is a potential inhibitor of this interaction, and may be capable of preventing infection by SARS-CoV-2.

Figure 1. Models of the SARS-CoV-2 virus (left) [2] and the interaction between the viral spike glycoprotein (S protein) receptor binding domain (RBD) with the extracellular peptidase domain (PD) of ACE2 protein (right) [4]. (Left) The turquoise-colored protrusions on the surface of the spherical virus are the S proteins. Each protrusion consists of an aggregate of 3 identical S proteins, which can bind to the ACE2 protein on the surface of lung, artery, heart, kidney, and intestinal cells. (Right) Ribbon diagram of the cryo-electron microscopy structure of a complex of the S protein RBD (red ribbon) with the ACE2 PD (purple ribbon) (PDB model 6LZG). The interactions between the two proteins are mostly polar and involve 8 pairs of AAs (Table 1).

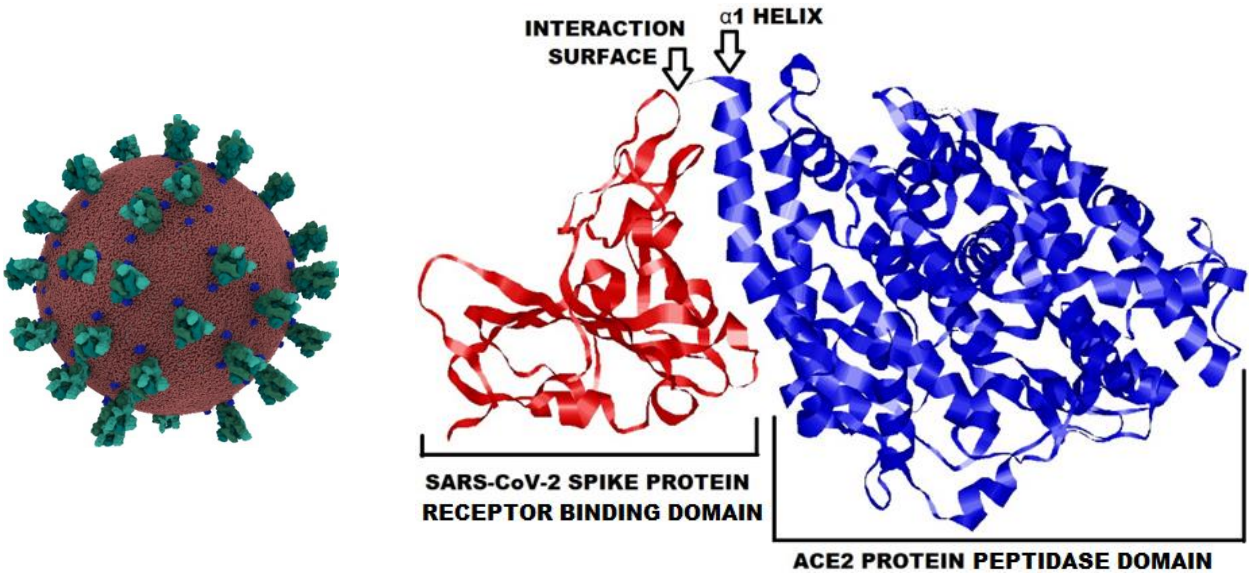


Table 1. The interaction between the SARS-CoV-2 S protein receptor binding domain (RBD) and the ACE2 peptidase domain (PD) is mediated mainly through polar interactions involving the following AA residues [4]. AA names are indicated with their IUPAC-IUB single letter symbols, and their positions in the protein by numbers

Protein:	Pairs of interacting AA residues:							
S-protein RBD	Q498	N501	N501	T500	Y453	K417	Q474	F486
ACE2 PD	Q42	K353	Y41	R357	H34	D30	Q24	M82

Methods and Results

Peptide WALMART was modeled as both a beta (β) strand and as an alpha (α) helix (Figure 2). Each conformational model was then subjected to docking simulations with the S protein RBD, from PDB model 6LZG [4], using the ClusPro 2.0 server [8]. The docking program generated numerous models, and each was examined to determine if peptide WALMART interacted with any of the AAs of the S protein RBD that are involved in its interactions with the ACE2 PD (Table 1). The results are shown in Table 2 and Figure 3. Most docking results (48 models) had peptide WALMART bound to the S protein at positions away from the surface of S protein that interacts with the ACE2 PD, but 7 models had peptide WALMART in direct contact with the critical AAs of the S protein RBD that interact with the ACE2 PD. These interactions included hydrogen (H-) bonds and polar interactions between peptide WALMART and the critical residues of the S protein RBD that bind to the ACE2 PD.

Figure 2. Stick figure models of peptide WALMART in the (top) β-strand and (bottom) α-helical conformations [6]. IUPAC-IUB single letter symbols are located adjacent to their respective AAs, and charges that exist at pH 7 are also shown. The C-terminal end is amidated, and, therefore, lacks a negative charge. The net charge on the peptide at pH 7 is +2. The length of the β-strand conformation is almost twice that of the α-helical conformation. Note: Å = 1 x 10^{-10} meters. The color scheme is gray for carbon, white for hydrogen, blue for nitrogen, red for oxygen, and yellow for sulfur. Models were created as wireframe structures with the Deep View/Swiss -PdbViewer v4.1.0 program [9], transferred to the RasMol program [10] to generate stick figure diagrams, and finally transferred to the Microsoft Paint program for the addition of letters and numbers. Methyl ($-CH_3$), methylene ($-CH_2$) and most methine (-CH=) hydrogens are not shown.

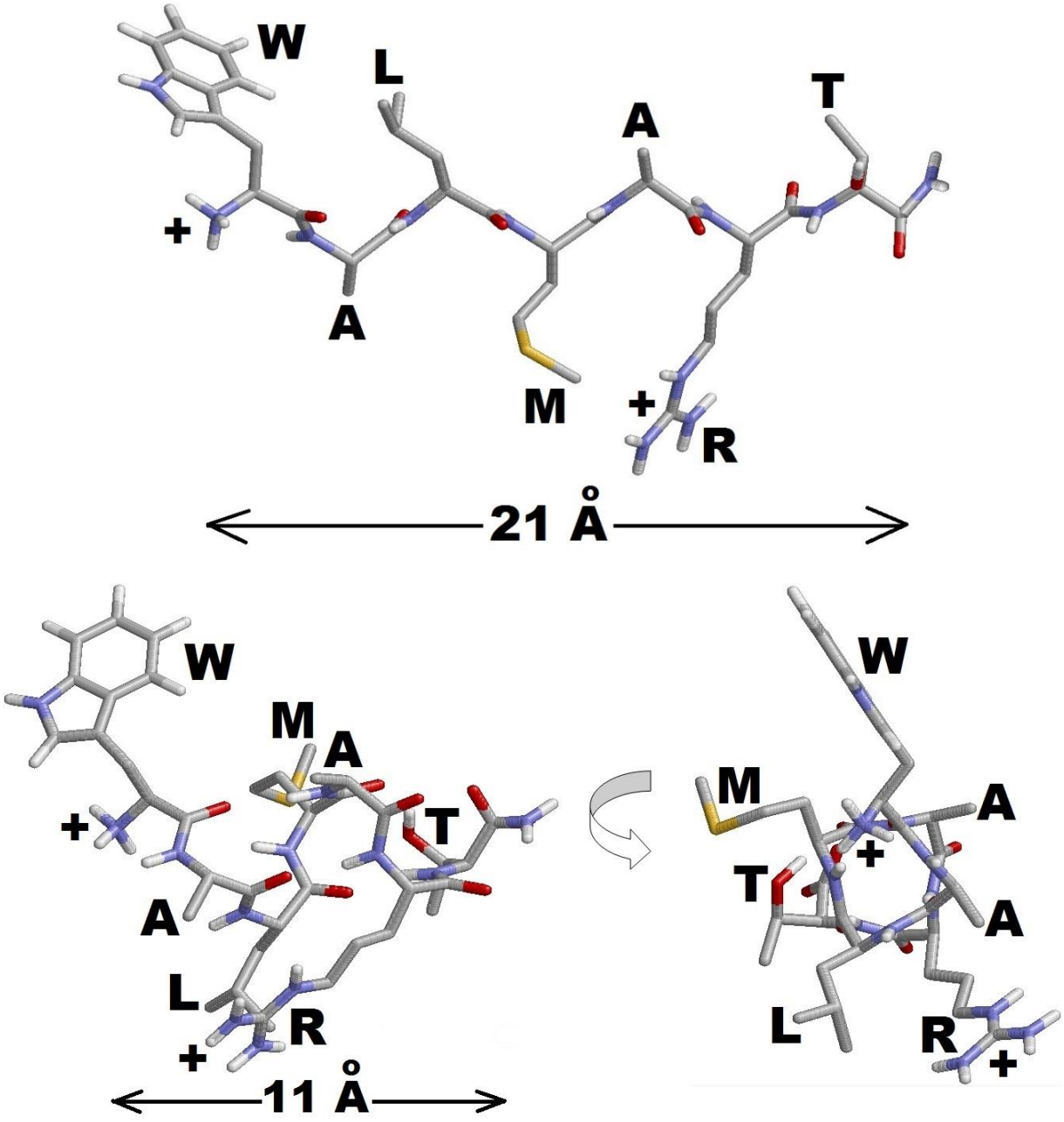


Table 2. Results of ClusPro 2.0 docking of peptide WALMART with the SARS-CoV-2 S protein receptor binding domain (RBD). The docking methods were of 4 types, each of which emphasized different combinations of forces: electrostatic (Elect), hydrophobic, and/or van der Waals (vdW). Seven of 55 models had peptide WALMART in direct contact with the AAs of the S protein RBD that interact with ACE2 (Table 1 and Figure 3). Most of the 7 models with significant contacts occurred when peptide WALMART was in the β-strand conformation. AA names are indicated with their single letter IUPAC-IUB symbols, and their locations in the proteins are indicated with numbers.

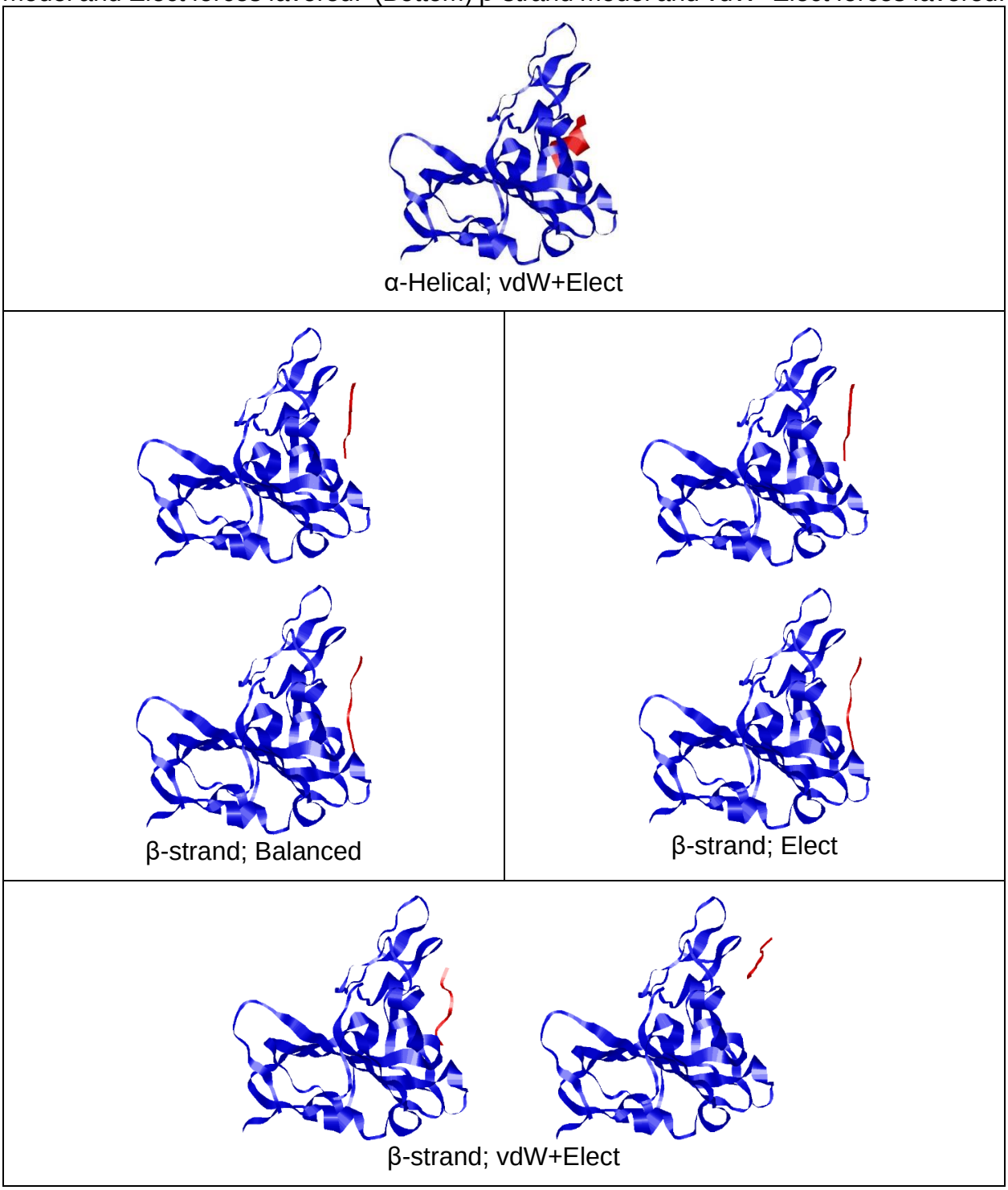
				Contact Residues:		
Conformation of peptide WALMART	Docking method	Number of models generated	Number of models with significant contacts	Peptide WALMART	SARS-CoV-2 S protein RBD	Contact type
β	Balanced	7	1[a]	W1	Y453	H-bond[b]
			1[a]	M4	Y453	H-bond[b]
	Electrostatic favored	9	1[a]	W1	Y453	H-bond[b]
			1[a]	T7; M4	N501; Y453	Polar; H-bond[b]
	Hydrophobic favored	4	0			
	vdW + Elect	23	1[a]	W1	N501; Q498	Polar
			1[a]	T7	K417	H-bond[b]
α	Balanced	2	0			
	Electrostatic favored	2	0			
	Hydrophobic favored	1	0			
	vdW + Elect	7	1[a]	M4	Y453	Polar

Notes: [a]See Figure 3 below. [b]The length of a hydrogen bond is ~1.5-2.5 Å [11].

Discussion

This theoretical study explored the possibility that peptide WALMART could bind to the SARS-CoV-2 S protein RBD in such a manner as to potentially inhibit its interaction with the PD of ACE2, the putative first step of infection of cells by SARS-CoV-2. A molecular docking program, ClusPro 2.0, was used to generate models of peptide WALMART bound to the SARS-CoV-2 S protein RBD, and 13% of the 55 resulting models showed the peptide bound to critical AAs that are involved in the interaction of the S protein RBD with the ACE2 PD. If peptide WALMART were to bind to these critical residues, it could be expected that the peptide would act as an inhibitor of the SARS-CoV-2 S protein and ACE2 interaction. Consequently, peptide WALMART is a potential inhibitor of infection, and it may be worthwhile to subject it to testing for this property.

Figure 3. Ribbon diagram models resulting from ClusPro 2.0 docking of the WALMART peptide (red) with the SARS-CoV-2 S protein RBD (purple). In each model, peptide WALMART interacts with S protein RBD residues that are involved in the interaction with ACE2 (Table 2). (Top) α-Helical model and van der Waals plus electrostatic (vdW+Elect) forces favored. (Middle, left) β-strand model and balanced forces. (Middle, right) β-strand model and Elect forces favored. (Bottom) β-strand model and vdW+Elect forces favored.



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