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Tailored lipopeptide surfactants as potentially effective drugs to treat SARS-CoV-2 infection

Davoud Biria *

Department of Biotechnology, Faculty of Biological Sciences and Technologies, University of Isfahan, Isfahan, Iran

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ABSTRACT

Finding effective drugs to treat SARS-CoV-2 infection as a complementary step to the extensive vaccination is of the great importance to overcome the current pandemic situation. It has been shown that some bio-active unsaturated fatty acids such as Arachidonic Acid (AA) can reduce the infection severity and even destroy the virus by disintegration of the virus lipid envelope. On the other hand, it has been reported that several designed peptides with an activity similar to the angiotensin converting enzyme 2 (ACE-2), which has a high affinity towards the novel corona virus spike protein, can inhibit the viral infection through concealing the spike proteins from the cell surfaces ACE-2. Binding the mentioned peptides to the bio-active lipids like AA will result in a lipopeptide surfactant molecule with the synergistic effect of both the active moieties in its structure to treat the novel corona infection. In addition, the peptide segment increases the aqueous solubility of the lipid segment and enables the targeted delivery of the surfactant molecule to the virus. The resultant lipopeptide would be a potentially effective drug for SARS-CoV-2 infection treatment with the minimum side effects.

Introduction

Since the outbreak of SARS-CoV-2 in the late 2019, many attempts have been made to find effective vaccines and drugs [1]. Despite the fruitful results especially in developing vaccines, several issues such as the low rate of global vaccination, disinclination of some people to vaccination and the appearance of new variants of the virus due to mutations, make it necessary to discover effective drugs to control the corona pandemic conditions. Although a few drugs have been introduced to treat the novel corona virus infections specifically [2], there is still room to find more effective options with optimal characteristics and less side effects [3]. Generally, an ideal drug would be a simple molecule which can destroy the infection effectively with minimum side effects to the adjacent tissues [4]. It seems that a robust remedy can be achieved by targeting the lipid envelope instead of the proteins of the virus because its structure is much simpler and is not prone to change by mutations. It is well known that certain types of surfactants can dissolve and penetrate the lipids of the living cell membranes [5] and there are reports on the positive effect of surfactants on healing the viral infections (e.g., H1N1 flu) [6]. It has been also reported that the pulmonary surfactants acted as a barrier to the viruses and could prevent the infection [7]. On the other hand, there are undeniable evidences on the effectiveness of commercial detergents on destructing the lipid enveloped viruses leading to their deactivation and the observed effect intensified chronically [8]. Therefore, it can be concluded that a well-designed surfactant can be employed as a potential drug against the virus [9]. The surfactant molecule should have strong affinity to the virus, appropriate capability to destruct the virus envelope and minimum side effects on the patients' body.

The hypothesis

The novel corona virus has a lipid envelope containing several proteins including the famous spike protein. Disruption of the lipid envelope by a surfactant will kill the virus by the leakage of its internal content. A lipopeptide surfactant consists of a bioactive lipid hydrophobic tale such as the Arachidonic Acid (AA) and a peptide as the hydrophilic head which designed to have a high affinity to the spike protein of the SARS-CoV-2. The lipopeptide surfactant molecule can target the virus through the peptide head while the lipid tale will interact with and penetrate into the lipid envelope which reduces its integrity and finally leading to the disruption of the membrane and demolishing of the virus (Fig. 1). In addition, the lipopeptide molecule will have a high surface activity which can disrupt the structure of the virus lipid bilayer similar to detergents and destroy the virus. More details on the mechanisms of the action and characteristics of the

* Address: Department of Biotechnology, University of Isfahan, Isfahan P.O. 8174673441, Iran.

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proposed lipopeptide have been explained in the following sections.

Evaluation of the hypothesis

Disruption of the membrane of the enveloped viruses by certain compounds (e.g., a lysine- and arginine-specific supramolecular ligand (CLR01)) known as molecular tweezers has been reported and suggested as a potential treatment mechanism [10]. In the same vein, membrane disintegration can be implemented by simpler compounds like the unsaturated fatty acids (bioactive lipids) to destroy the virus [11,12]. Some of these compounds (e.g., arachidonic acid) have been already approved by FDA and are safe to be used in the lipopeptide surfactant molecule. In fact, interactions of AA with the novel corona virus have shown that it can prohibit the viral infection through the virus membrane disruption as well as the metabolic inference and virus proliferation inhibition [11,13]. However, the administration procedure and virus targeting have not been fully addressed yet [14]. Clearly, AA is hardly soluble in the aqueous phase in the free form and would bind to some proteins (e.g., cytoskeletal proteins and albumin) to enhance its solubility and cell transport [15]. The AA complex with these proteins reduces its desired function as an antiviral drug because it will be unavailable to the virus and the infected cells. The above-mentioned problems can be addressed by binding the AA to a proper peptide to form a lipopeptide surfactant. The peptide part should increase the aqueous solubility of the surfactant through adjusting its hydrophile lipophile balance (HLB) while simultaneously, should have a high affinity for the novel corona virus spike protein to guarantee the targeted delivery of the resultant molecule. In addition to the influence of AA on the viral lipid envelope mentioned earlier, the resultant lipopeptide will be an active surfactant which can intensify the destruction of the virus lipid membrane. The lipopeptide surfactant can be administrated as a solution by injection or an aerosol by a nasal spray. It should be noted that the size of the drug particles is an important factor for the successful administration by a nasal spray because the particle size can affect the drug absorption in the pulmonary level. It is suggested that the aerosol particle size less than 3 μm will have a high chance to reach the lower airways and deposit in the alveoli. In the molecular scale, macromolecules should be under about 40 kDa (5 to 6 nm in diameters) to rapidly absorb from lungs into the blood [16]. Therefore, size of the peptide moiety should be considered as an important parameter in designing stage to assure the possibility of administration by a nasal spray.

On the other hand, the existence of a peptide moiety in the surfactant molecule with high affinity to the virus surface proteins such as the spike protein of the novel corona virus can block the virus entry to the host cells through a competition mechanism. In fact, the peptide part of the surfactant can be designed to have a lower dissociation constant than the host cell surfaces angiotensin converting enzyme 2 (ACE-2) receptors. Therefore, the peptide moiety will bind faster and more tightly to the virus spike proteins and inhibit their binding to the ACE-2 on the cell surfaces. Many researchers have worked on finding peptides with short length and a high affinity towards the spike protein and several peptides have been introduced [17,18] which can be used to design the proper peptide segment for the lipopeptide surfactant. Interestingly, the virus mutations so far have led to changes in the spike protein which resulted in a higher affinity to the ACE-2 receptors and greater infection rates [19]. This means that the mutated virus species will be still vulnerable to the mentioned treatment mechanism because the peptide moiety has been assumed to have a high affinity for the spike protein similar to the cellular ACE-2. The competitive mechanism for treatment of the viral infection has already examined successfully by use of the human recombinant soluble ACE-2 (hrsACE2) as a competitor [20,21].

The synergistic effect of the mentioned mechanisms can be obtained by synthesis of the lipopeptide surfactant molecule which expected to have a significant antiviral activity. After designing the proper peptide with the optimal characteristics, docking and molecular dynamics studies required to confirm the functionality of the surfactant and prove the suggested mechanisms *In-silico*.

The surfactant synthesis can be carried out by binding the carboxylic group of the AA to a terminal amine of the peptide by the formation of an amide group (Fig. 2). This can be a tricky process because it is assumed that the optimal peptide moiety will have an almost similar structure to the binding site of the ACE2 which interacts with the virus spike protein through its *N*-terminal domain [22]. This means that it would be crucial to keep the *N*-terminal domain of the peptide moiety intact to achieve a proper drug activity. As a result, the direct reaction between the AA and the peptide moiety will produce inactive byproducts which are not functional. Therefore, several modifications required to synthesized the surfactant molecule in a multi stage procedure. It seems that there are at least two methods to synthesize the lipopeptide molecule with minimum byproducts. At the first method, an amine group should be added to the C-terminal of the peptide and the *N*-terminal domain in its active site can be protected from the AA carboxylic groups through binding with a

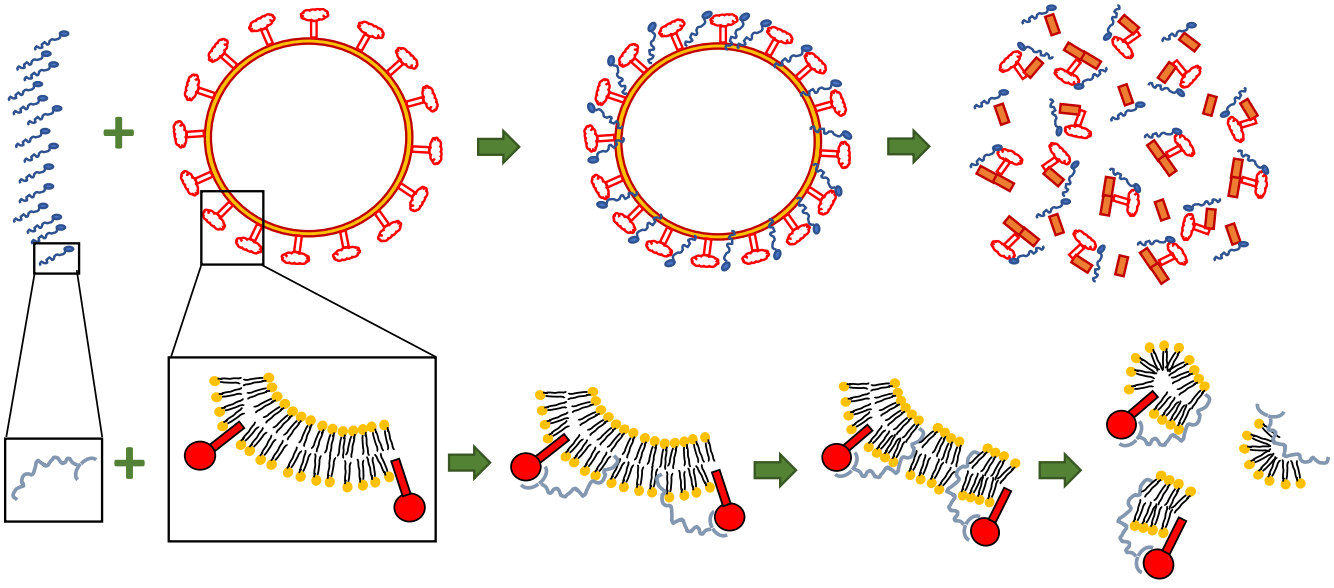

Fig. 1. The interactions of the proposed lipopeptide with the virus: the peptide moieties conceal the spike protein while the lipid tales disintegrate the lipid envelope and demolish the virus.

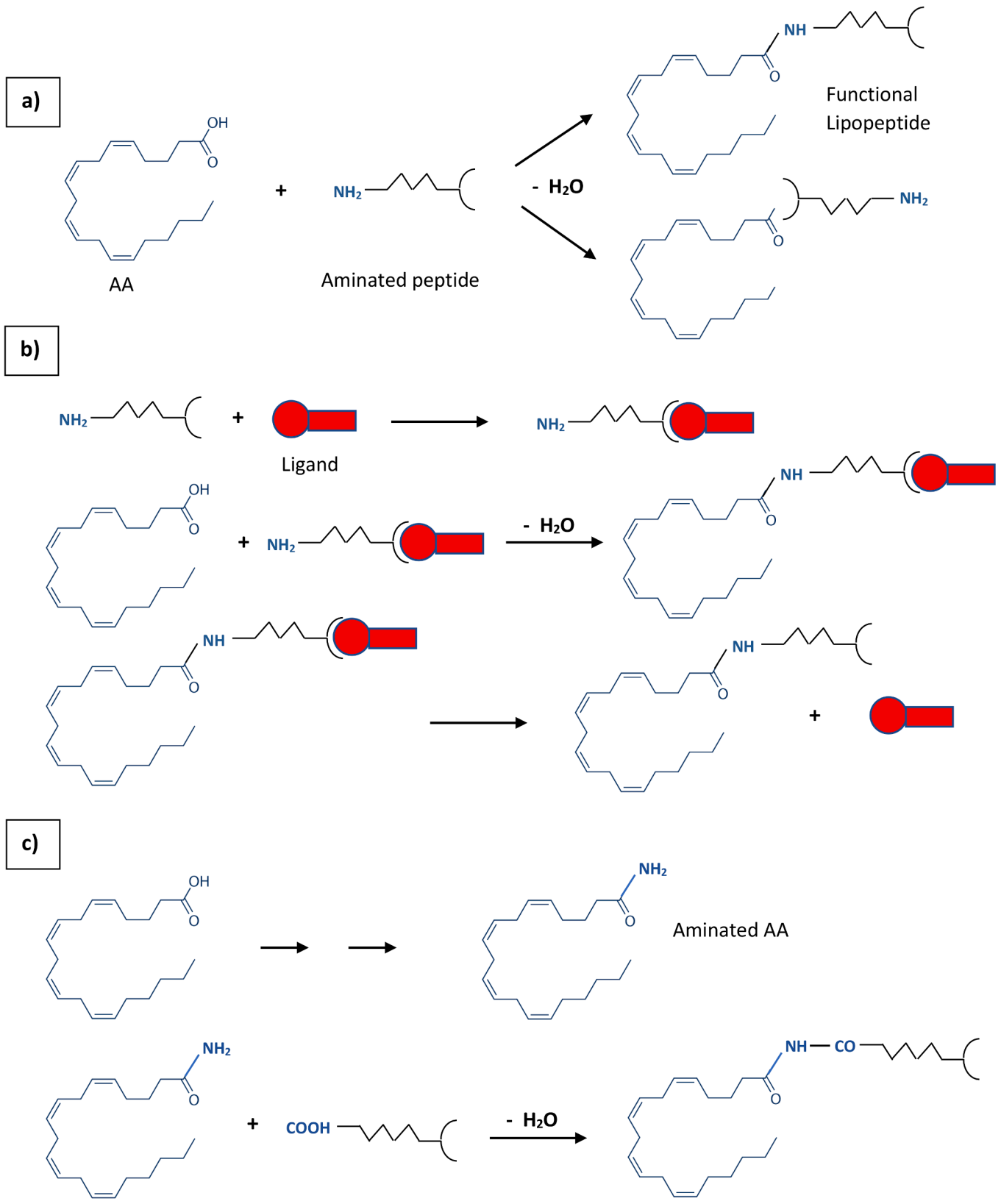

Fig. 2. The lipopeptide molecule production methods from AA and the peptide moiety: a) the AA reacts with unprotected aminated peptide which produces unfunctional byproducts in addition to the desired lipopeptide; b) the AA reacts with ligand protected aminated peptide moiety; c) the peptide moiety reacts with the aminated AA to form the lipopeptide.

specific ligand (e.g., a peptide with an activity similar to the virus spike protein) before the conjugation reaction. However, the utilized ligand binding to the peptide should be reversible and does not affect its activity. At the second method, the amination of the AA molecules before the conjugation reaction will be required. This modification makes it possible to have the amidic bonds between the amine group of the aminated AA and the C-terminal of the peptide. Clearly, experimental analysis needed to select the best procedure for the conjugation reaction.

The antiviral activity of the surfactant should be examined by studying its effect on the SARS-CoV-2 experimentally in comparison with appropriate control experiments. Clearly, appropriate animal and clinical trial phases would be required if the obtained results were satisfactory.

Consequences of the hypothesis and discussion

Development of effective vaccines for the novel corona virus in a short time improved the pandemic conditions significantly. However, the repeated mutations of the virus as well as the low rate of vaccination in some parts of the world make it necessary to obtain suitable drugs to treat the patients and reduce the mortality rate which can help the society back to normal. Recently, a few antiviral drugs (e.g., paxlovid and molnupiravir) have been authorized for emergency use by FDA [2]. Nevertheless, developing more effective drugs to confront the infection through different mechanisms would be beneficial and diversifies our arsenal against the virus. The potentially effective drug concept presented in this paper will have minimum side effects because the lipid and peptide moieties of the proposed surfactant molecule would be safe and not interfere in the metabolic activities of the cells. In addition, it would have a robust function in spite of the frequent mutations of the novel corona virus because the lipid envelope of the virus has been targeted instead of the proteins.

The suggested lipopeptide in this work will have simultaneously both the preventing and treating activities towards the infection. The nasal application of lipopeptide fusion inhibitors have been shown to prevent the infection efficiently in ferrets [23] which has a similar function to the proposed drug in this work by the competition mechanism. The treating of the infection by the bioactive lipids (e.g., AA) [11–13] is another aspect of the functionality of the lipopeptide surfactant which explained in the previous section.

At last, it should be noted that the presented drug concept here is expected to have an affordable cost, long shelf life, and have a variety of administration methods (both the parenteral and nasal) which makes it suitable for treatment of the patients in low-income countries and remote areas.

Consent statement/ethical approval

Not required.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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