International Journal of Biological Macromolecules 88 (2016) 354–360

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Review

An overview on the delivery of antitumor drug doxorubicin by carrier proteins

D. Agudelo, G. Bérubé, H.A. Tajmir-Riahi*

Department of Chemistry-Biochemistry-Physics, University of Québec, Trois-Rivières, C.P. 500, TR (Quebec) G9A 5H7, Canada

ARTICLE INFO

Article history:
Received 31 January 2016
Received in revised form 27 March 2016
Accepted 28 March 2016
Available online 30 March 2016

Keywords:
Doxorubicin
Protein
Drug delivery
Hydrophobicity
Modeling
Spectroscopy

ABSTRACT

Serum proteins play an increasing role as drug carriers in the clinical settings. In this review, we have compared the binding modalities of anticancer drug doxorubicin (DOX) to three model carrier proteins, human serum albumin (HSA), bovine serum albumin (BSA) and milk beta-lactoglobulin (β-LG) in order to determine the potential application of these model proteins in DOX delivery. Molecular modeling studies showed stronger binding of DOX with HSA than BSA and β-LG with the free binding energies of −10.75 (DOX-HSA), −9.31 (DOX-BSA) and −8.12 kcal/mol (DOX-β-LG). Extensive H-boding network stabilizes DOX-protein conjugation and played a major role in drug-protein complex formation. DOX complexation induced major alterations of HSA and BSA conformations, while did not alter β-LG secondary structure. The literature review shows that these proteins can potentially be used for delivery of DOX *in vitro* and *in vivo*.

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1. Introduction

Development of effective polymer-based nanocarriers for the successful application in cancer therapy still remains a great challenge. Nanoparticle therapeutics, based on natural and synthetic polymers with water-soluble polymers, offer promising routes to improve cancer drug delivery. These nanoparticles generally increase drug solubility, improve the therapeutic process by extending the circulation time and enhance uptake into tumors, through the permeability and retention effect [1–4]. Doxorubicin, is an antibiotic with broad spectrum of antitumor activity in a variety of solid tumors including neuroblastoma, has a limited therapeutic index due to toxic side effects such as cardiotoxicity combined with the inability of the drug to penetrate deep into tumor tissue [5–9]. Therefore, the task of delivering doxorubicin directly to the tumor site, while maintaining high efficacy com-

Abbreviation: DOX, doxorubicin; HSA, human serum albumin; BSA, bovine serum albumin; b-LG, beta-lactoglobulin; FTIR, Fourier transform infrared.

* Corresponding author.
E-mail addresses: tajmirri@uqtr.ca, heidar-ali.tajmir-riahi@uqtr.ca (H.A. Tajmir-Riahi).

http://dx.doi.org/10.1016/j.ijbiomac.2016.03.060
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bined with low systemic exposure is a major challenge. Extensive research has been focused on developing effective nanocarriers of diverse materials for delivery of doxorubicin [10–16]. Synthetic polymer conjugated to DOX was used for delivery and enhance drug antitumor activity [17–26]. Protein nanocapsules were found to be effective nanocarriers for DOX delivery *in vitro* [27]. Serum albumins are emerging as versatile protein carriers for drug targeting and for improving the pharmacokinetic profile of peptide or protein-based drugs [28–30]. Interactions of doxorubicin with serum proteins are recently reported [31–33]. Therefore it was of interest to review the binding modalities of doxorubicin to different carrier proteins.

To determine the effect of hydrophobicity on drug-protein interactions in solution, the bindings of DOX to three typical model proteins, human serum albumin, bovine serum albumin and beta-lactoglobulin were reviewed based on our previous studies [31,32] and in the context of recent work in the field [1–27]. HSA and BSA are chosen because they have a similar folding, a well-known primary structure [34], and they are considered as models for studying drug–protein interactions *in vitro*. Beside the marked structural similarities between HSA and BSA some differences are observed in the hydrophobicity of these two proteins [35]. In addition, β-LG was chosen for its higher hydrophobic character as compared to HSA and BSA [36,37]. Such differences in hydrophobicity lead to a different affinity of HSA, BSA and β-LG towards DOX complex formation. In view of the differences in the bindings of these proteins this review can be useful and informative for researcher working on drug delivery systems.

2. Experimental

2.1. Molecular modeling

The structure of free HSA (PDB id:1AO6, chain A) obtained by X-ray crystallography was used as a template [38]. The structure of BSA was predicted by automated homology modeling using SWISS-MODEL Workspace from the amino acid sequence NP-851335 [39,40]. The two proteins share 78.1% of sequence identity, which is sufficient to obtain reliable sequence alignment. The β-LG structure was obtained from the literature report [36]. The docking studies were performed with ArgusLab 4.0.1software (Mark A. Thompson, Planaria Software LLC, Seattle, WA, http://www.arguslab.com). Three dimensional structure of DOX was generated from PM3 semi-empirical calculations, using Chem3D Ultra 6.0. A blind docking approach was taken as the whole protein was selected as a potential binding site. The docking runs were performed on the Argus Dock docking engine using high precision with a maximum of 200 candidate poses. The conformations were ranked using the Ascore scoring function, which estimates the free binding energy. Upon location of the potential binding sites, the docked complex conformations were optimized using a steepest decent algorithm until convergence, within 40 iterations. Amino acid residues within a distance of 3.5°A relative to DOX were considered involved in the complexation as reported in our earlier studies [31,32].

2.2. Fluorescence spectroscopy

Fluorimetric experiments were carried out on a Varian Cary Eclipse. Solutions containing drug 1–100 mM in Tris-HCl (pH = 7.4) were prepared at room temperature and maintained at 24 °C. Solutions of HSA, BSA and β-LG containing 10 μM in 10 mM Tris-HCl (pH = 7.4) were also prepared at 24 °C. The fluorescence spectra were recorded at excitation = 280 nm and emission from 287 to 500 nm. The intensity at 347 nm (tryptophan) was used to calculate the binding constant (K) as reported [31,32,41–48].

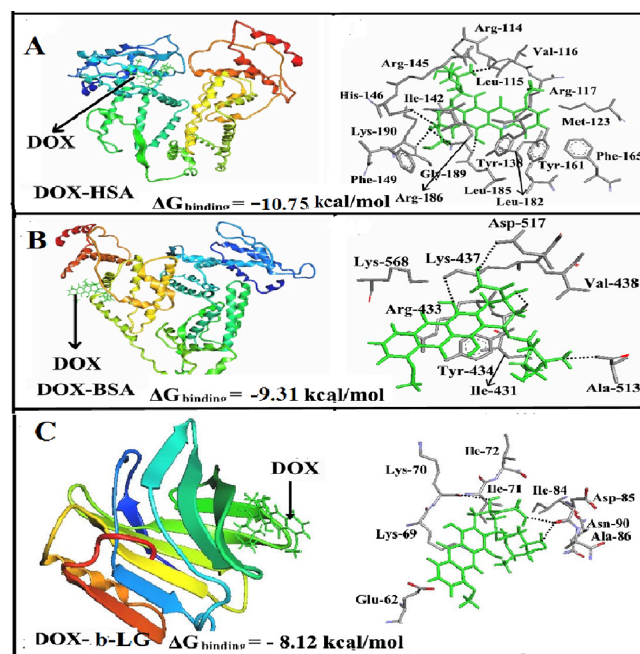

Fig. 1. Best docked conformations of DOX-protein adducts. (A) DOX-HSA, (B) DOX-BSA and (C) DOX-β-LG with the free binding energies.

2.3. FTIR spectroscopy

Infrared spectra were recorded on a FTIR spectrometer (Impact 420 model), equipped with deuterated triglycine sulphate (DTGS) detector and KBr beam splitter, using AgBr windows. Solution of DOX was added dropwise to the protein solution with constant stirring to ensure the formation of homogeneous solution and to reach the target DOX concentrations of 0.125, 0.250 and 0.50 mM with a final protein concentration of 2.5 mM. Spectra were collected after 2 h incubation of HSA, BSA or β-LG with DOX solution at room temperature, using hydrated films. Interferograms were accumulated over the spectral range 4000–600 cm^{-1} with a nominal resolution of 2 cm^{-1} and 100 scans. The difference spectra [(protein solution + DOX solution)−(protein solution)] were generated using water combination mode around 2300 cm^{-1}, as standard [49]. When producing difference spectra, this band was adjusted to the baseline level, in order to normalize difference spectra [31,32].

2.4. Analysis of protein secondary structure

Analysis of the secondary structures of HSA, BSA and β-LG and their DOX complexes were carried out as reported [31,32,50,51]. The curve-fitting analysis was performed using the GRAMS/AI Version 7.01 software of the Galactic Industries Corporation.

3. Results and discussion

3.1. DOX binding sites with HSA, BSA and β-LG by docking

Docking results showed that in the DOX-HSA adduct, DOX is surrounded by Arg-114, Arg-117, Arg-145, *Arg-186 (2.72 Å = H-bond), Gly-189, *His-146 (2.66 Å = H-bond), Ile-142, *Leu-115 (2.11 Å = H-bond), Leu-182, Leu-185, *Lys-190 (2.86 Å = H-bond), met-123, Phe-149, Phe-165, Tyr-138, Tyr-161-and Val-116 with the free binding energy of −10.75 kcal/mol (Fig. 1A and Table 1). In the DOX-BSA complex, drug is surrounded by *Ala-513 (2.99 Å = H-bond), Arg-433, *Asp-517 (2.85 Å = H-bond), Ile-431, *Lys-437 (2.53 Å = H-bond), Lys-568, *Tyr-434 (2.34 Å = H-bond) and Val-438 with

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