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SHORT COMMUNICATION

The Effect of Arsenic Trioxide on All-trans Retinoic Acid Binding to Human Serum Albumin

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Abstract

Tretinoin or All-trans retinoic acid (ATRA) is an efficient medication in leukemia treatment. Arsenic trioxide (ATO) significantly improves the effectiveness of ATRA. In this study, the effect of ATO on ATRA binding to human serum albumin (HSA) was investigated. Fluorescence and UV-Vis spectroscopy and equilibrium dialysis technique were used to determine ATRA binding to HSA in the presence and absence of ATO and of two compounds, warfarin and ibuprofen, specific for binding to HSA sites I and II, respectively ("site markers"). The association constants for ATRA binding and the number of binding sites as well as the thermodynamic parameters of complex formation, were obtained at different temperatures. Fluorescence results showed a static quenching mechanism for ATRA binding to HSA. The calculated thermodynamic parameters revealed that the binding reaction is a spontaneous and exothermic process and also that hydrogen bonds and van der Waals forces have a central role in the binding of ATRA to HSA. Competitive experiments showed that none of markers seriously prevents ATRA binding to HSA. Interestingly, the fluorescence and equilibrium dialysis data showed that ATO increases the binding of ATRA to HSA, and converts the binding mode of ATRA from mainly hydrogen bonding to include hydrophobic interactions as well. These results suggest that ATO can prevent the metabolism of ATRA and keep it in the blood for longer by increasing the binding of ATRA to HSA.

Keywords FRET · Fluorescence spectroscopy · Acute promyelocytic leukemia · RAR-α · Chemotherapy · Cancer

Introduction

Retinoids or vitamin A derivatives are small lipophilic molecules with numerous physiological functions, that new diagnostic strategies are developed using them. All-trans retinoic acid (ATRA) is a medication used for acute promyelocytic leukemia (APL) treatment by FDA license, and it is used as an anticancer drug to treat other diseases as well [1–4]. APL is a type of leukemia, characterized by a chromosomal translocation t(15;17) [5]. This translocation produces a fusion gene blocking the granulocyte differentiation. In most of the cases, the translocation leads to promyelocytic leukemia gene (PML) joining to the retinoic acid receptor gene (RAR-α), and consequently, the respective oncoproteins generation [6]. APL was the most lethal type of acute leukemia, but there was 90–95% complete remission rate of patients using ATRA [7], in addition, ATRA causes differentiation in other cancer cells [8, 9]. However, using ATRA is accompanied by some problems and its efficacy is limited to its side effects [10]. ATRA is poorly soluble in water [11], and its pharmacological levels can lead to retinoic acid syndrome [12].

The evidence shows that APL can be treated using ATRA, through the differentiation of APL cells, as well as catabolism of fusion protein (resulting from chromosomal translocation) [6]. Also, complete remission can be achieved for most patients using ATRA along with chemotherapy, although there has eventually been relapse in about 20% of the improved patients [13]. Arsenic trioxide (ATO) has a significant effect on the treatment of patients resistant to ATRA along with chemotherapy [7, 13]. In fact, ATO has a synergistic effect on ATRA. The ATO low concentrations led to differentiation, and its high concentrations induced apoptosis [14] and, furthermore, ATO plays a role in the catabolism of abnormal protein produced in APL, but with pattern and kinetics different from ATRA [15].

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Drug binding to albumin is the main determining factor of its pharmacodynamics and pharmacokinetics pattern, that could be useful tool in analysis of drug-drug and drug-protein interactions in disease states [16]. However, there has not been any report on the effect of ATO on ATRA binding to HSA. Accordingly, in present study, the effect of ATO on the interaction between ATRA and HSA was investigated using different methods, in order to satisfy this desirable.

Materials and Methods

Materials

Human serum albumin, all-trans retinoic acid, and arsenic trioxide were purchased from Sigma-Aldrich. Other materials were analytical grade from Merck. All solutions were prepared in double distilled water. Sodium phosphate (100 mM-pH 7.4) containing ethanol (10% *v*/v) was used as buffer solution.

Methods

UV–Vis Measurements

Absorbance spectra were recorded at room temperature using a Cary Eclips (Varian) spectrophotometer with a 1 cm quartz cell.

Fluorescence Measurements

Fluorescence intensity spectra of albumin were recorded in the presence and the absence of ATRA, using Perkin Elmer spectrofluorometer through applying a 1 cm pathlength quartz cuvette. The excitation and emission wavelengths were adjusted at 295 and 305–450 nm, respectively. The excitation and emission slit widths were 5 nm. The emission spectra of all samples were recorded at 298 and 310 K. The albumin concentration was 1.2 μM in fluorescence experiments.

Determination of Quenching Mechanism

HSA fluorescence intensity values (at λ_{max}) in the presence and the absence of ATRA were substituted in the Stern-Volmer equation (Eq. 1), in order to determine the quenching mechanism:

$$\frac{F_0}{F} = 1 + K_{sv}[Q] \tag{1}$$

Where F_0 and F are the fluorescence intensities in the absence and presence of ATRA, respectively, K_{sv} is the Stern-Volmer quenching constant, and [Q] is the ATRA concentration in each experiment. The shape and temperature dependence of the plot of F_0/F versus [Q] can be useful in determining the quenching mechanism. If the dynamic or static quenching occurs, a plot of F_0/F versus [Q] yields a straight line and if both are involved, it shows a curvature towards the yaxis. The diffusion-controlled bimolecular rate constant (k_q) is another parameter that can be used in determining the quenching mechanism. Diffusion-controlled quenching typically causes a value about $1 \times 10^{+10}\ M^{-1}S^{-1}$, and values larger than that are the representative of the binding interaction or, in other words, the static quenching. k_q is related to K_{sv} with the Eq. 2:

$$K_{SV} = k_q \tau_0 \tag{2}$$

Where τ_0 is the fluorophore average lifetime in the quencher absence [17].

The Inner Filter Effect

Equation 3 is used to correct fluorescence intensity of the fluorescer, because the fluorescence quantum yield is decreased due to the overlap between the absorbance spectrum of the absorber and the excitation/emission spectrum of the fluorescer.

$$F_{corr} = F_{obs} \times 10^{(A_{ex}+A_{em})/2} \tag{3}$$

Where F_{corr} and F_{obs} are corrected and observed fluorescence intensities of fluorescer, respectively, A_{ex} and A_{em} are the absorbance of the absorber in the excitation and emission wavelengths of fluorescer, respectively [18].

Calculation of the Association Constant and the Number of Binding Sites

The association constant (K) and the number of binding sites (n) can be calculated by the Eq. 4, if there are similar and independent binding sites in the biomolecule [19]:

$$log\left[\frac{F_0 - F}{F}\right] = logK + n\ log[Q] \tag{4}$$

Determination of Thermodynamic Parameters and the Nature of Binding Forces

ΔH^0 and ΔS^0 were obtained from the van't Hoff equation (Eq. 5):

$$lnK = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} \tag{5}$$

Where K is the association constant, R is the universal gas constant, and T is the temperature of the reaction in Kelvin. The Gibbs free energy change (ΔG^0) was obtained from the Gibbs equation (Eq. 6):

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 = -RTlnK \quad (6)$$

The nature of the binding forces in protein-ligand interaction can be determined by the sign and the magnitude of ΔH^0 and ΔS^0. That way, if both are positive, then the hydrophobic forces, if both are negative, the hydrogen bonds and van der Waals forces, and if ΔS^0 is positive and ΔH^0 is negative, the electrostatic forces are dominant in binding, respectively [20].

Energy Transfer between HSA and ATRA

Energy can be transferred from donor to acceptor without producing photon, if the emission spectrum of the donor has overlap with the absorption spectrum of the acceptor [17]. The transfer efficacy can be calculated from the fluorescence intensities of the donor in the absence and presence of the acceptor by the Eq. 7:

$$E = 1 - \frac{F}{F_0} \quad (7)$$

Where F_0 and F are the fluorescence intensities in the absence and presence of ATRA, respectively.

The distance between donor (Trp-214) and acceptor (ATRA) can be obtained by the Eq. 8:

$$E = \frac{R_0^6}{R_0^6 + r^6} \quad (8)$$

Where R_0 is the Förster distance that in which E is equal to 0.5, and r is the distance between donor and acceptor. In addition, R_0 is calculated using the Eq. 9:

$$R_0^6 = \frac{9000(ln10)\kappa^2 Q_D}{128\,\pi^5 N n^4} J(\lambda) \quad (9)$$

Where κ^2 is a parameter related to the spatial orientation of the donor and acceptor transition dipoles, Q_D is the quantum yield of the donor in the absence of acceptor, N is Avogadro's number, n is the medium refractive index, and J(λ) is the overlap integral, describing the degree of spectral overlap between the donor emission and the acceptor absorption spectra. J(λ) is calculated by the Eq. 10:

$$J(\lambda) = \int_0^\infty F(\lambda)\varepsilon_A(\lambda)\lambda^4 d\lambda \quad (10)$$

Where F(λ) is the corrected fluorescence intensity of the donor in the wavelength range of λ - (λ + Δλ) with the total intensity normalized to unity, and, $\varepsilon_A(\lambda)$ is the extinction coefficient of the acceptor at λ in units of M^{-1} cm^{-1} [17].

Competitive Experiments

Intrinsic fluorescence of HSA were obtained in the presence of different ATRA concentrations and constant concentrations of site markers (warfarin for site I and ibuprofen for site II) in order to distinguish the binding site of ATRA on HSA. The association constant and the number of binding sites were calculated in the presence of each site marker by Eq. 4.

ATRA Binding in the Presence of Arsenic Trioxide

Intrinsic fluorescence spectra of HSA were obtained in the presence of different concentrations of ATRA and the constant concentration of ATO. According to the Eq. 4, data were analyzed in order to specify the association constant and the number of binding sites.

Equilibrium Dialysis

Sigma-Aldrich dialysis tubes with 12 kDa MWCO were prepared as follows: first dialysis tubes were boiled for 10 min in a solution containing 2% of NaC_2O_3 and 1 mM EDTA, then those were washed and boiled in double distilled water, and finally those were washed with water and kept in 50% ethanol at refrigerator. HSA (20 μM) was dialyzed overnight at 310 K in the presence of ATRA (20 μM) and in the absence and presence of ATO different concentrations in order to investigate the effect of ATO on ATRA binding to HSA, then the absorbance spectra of samples were recorded to calculate the concentration of the remaining ATRA in the dialysis tubes.

Results

Fluorescence Emission of HSA in the Presence of ATRA at Different Temperatures

Fluorescence spectroscopy is a useful technique in investigating ligand binding to protein. The aromatic residues cause intrinsic fluorescence in proteins and, in the case of human serum albumin, only its tryptophan residue (Trp-214) has a significant contribution in its intrinsic fluorescence [17]. In the present study, HSA intrinsic fluorescence spectra were obtained at different temperatures in the presence of different ATRA concentrations (Fig. 1 a, b). Since the emission spectrum of HSA overlapped with the absorbance spectrum of ATRA (Fig. 2) (ATRA was not fluorescent), the fluorescence

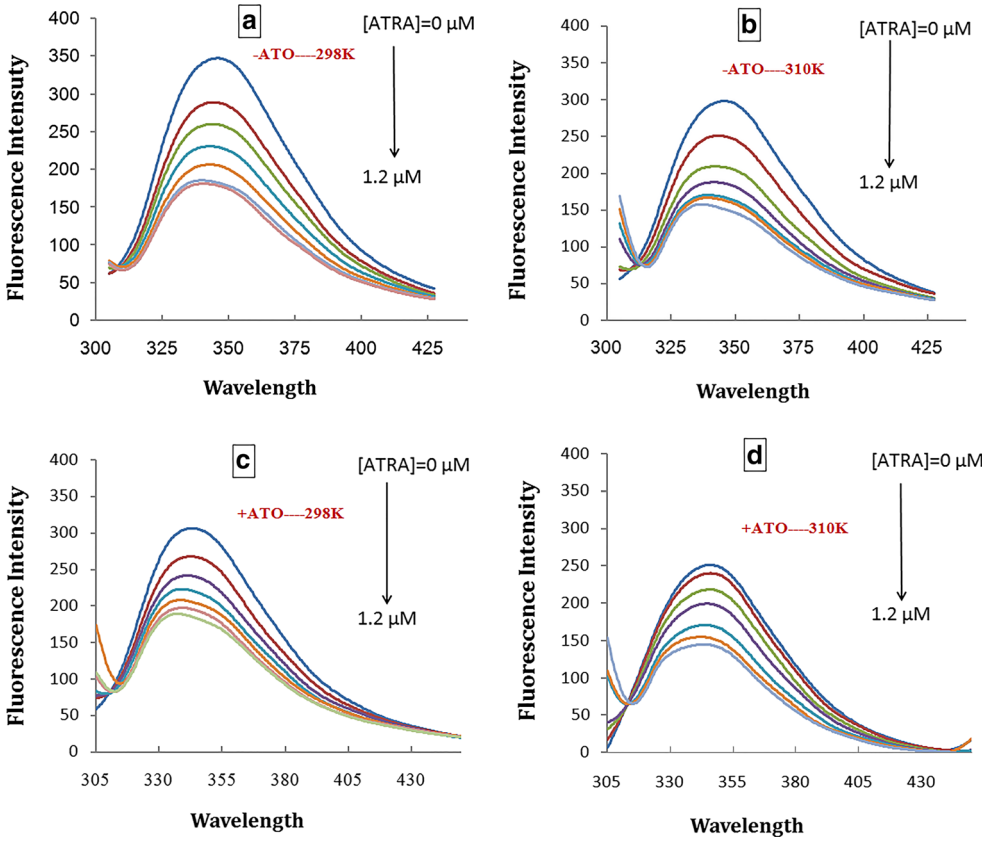

Fig. 1 Intrinsic fluorescence intensities of HSA (1.2 μM) in the presence of different concentrations of ATRA (0–1.2 μM) at 298 K and 310 K in the absence **a** and **b**, and in the presence of ATO ([ATO] = 1.2 μM) **c** and **d**, respectively

intensity was corrected by the inner filter effect equation (Eq. 3). As shown in Fig. 1, ATRA had a quenching effect on HSA, concurrently; binding of ATRA to HSA caused the blue shift in λ_{max}, which indicates the change in Trp-214 residue microenvironment and replacement of Trp-214 in a more hydrophobic region. Based on the described manner in the methods section, the association constants (K) and the number of binding sites (n) were calculated in each case (Table 1). The association constant was decreased by increasing temperature and, the number of binding sites was suggested to be one in both issues.

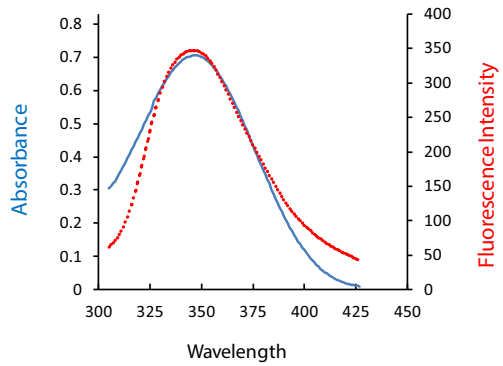

Fig. 2 Spectral overlap between ATRA absorbance and HSA fluorescence spectra

Fluorescence Quenching Mechanism

The quenching mechanism is classified into static and dynamic classes, depending on whether the quenching is caused by the formation of the non-fluorescent complex between the donor and acceptor or the collision between them in the excited state of the donor [17]. The quenching mechanism can be characterized by several methods, such as temperature dependence of K_{sv} or the magnitude of k_q. An increase in K_{sv} with temperature enhancement or a magnitude near $1 \times 10^{+10}$ M^{-1} S^{-1}(diffusion-controlled quenching) for k_q are indicative of dynamic quenching, while a decrease in K_{sv} with temperature enhancement or a magnitude more than $1 \times 10^{+10}$ for k_q are characteristics of static quenching mechanism [17]. In the case of HSA quenching by ATRA, k_q was about $6.5 * 10^{+13}$ indicating the dominance of the role of non-fluorescent complex formation in the quenching mechanism.

Table 1 Binding parameters of ATRA-HSA complex in the absence and presence of ATO at different temperatures

Temperature	K M^{-1}(-ATO)	n (-ATO)	K M^{-1} (+ATO)	n (+ATO)
298	$2.4 * 10^5$	0.93	$5.3 * 10^4$	0.82
310	$4.4 * 10^4$	0.8	$9.8 * 10^5$	1.0

Thermodynamic Parameters and Binding Modes

Thermodynamic parameters of ATRA binding to HSA were obtained (Table 2) using equations described in materials and methods section. ΔG^0 for ATRA binding to HSA is negative, which indicates a spontaneous process; both ΔH^0 and ΔS^0 are negative characterizing the dominance of hydrogen bonds and van der Waals interactions in binding.

Fluorescence Energy Transfer from HSA to ATRA

Based on the FRET method (described in methods section) the distance between the donor (Trp-214) and acceptor (ATRA) is suggested to be about 34.8 Å. Considering that the calculated R is almost equal to R_0 (34.5 Å) it can be concluded that energy transfer from HSA to ATRA is highly possible through FRET mechanism.

Site Marker Competitive Binding Experiments

Table 3 calculated and summarized the association constant and the number of binding sites in the presence of each site marker. As shown it is in Table 3, the site marker I (ibuprofen) causes an increase in binding constant (22%), while site marker II (warfarin) induces a reduction (14%) in binding constant of ATRA to HSA.

ATRA Binding to HSA in the Presence of ATO at Different Temperatures

Moreover, intrinsic fluorescence spectra of HSA were obtained in the presence of ATRA different concentrations and a constant concentration of ATO in order to determine the effect of ATO on ATRA binding to HSA (Fig. 1 C and D), then the relevant parameters were calculated and summarized in Table 1. Although the binding constant of ATRA to HSA was decreased at 298 K(nearly one fifth) in the presence of ATO, it was increased at 310 K (nearly twenty-two times). In addition, unlike K reduction in the absence of ATO, K was increased as the temperature increased in the presence of ATO (Table 1).

Table 2 Thermodynamic parameters of ATRA-HSA complex in the presence and absence of ATO at 310 K

Thermodynamic parameters	In the absence of ATO	In the presence of ATO
ΔS^0 (kJ/mol K)	−0.263	0.717
ΔH^0 (kJ/mol)	−109	187
ΔG^0 (kJ/mol)	−27.5	−35.6

Table 3 The association constant and the number of binding sites in the presence of each site marker at 310 K

Complex	K (M^{-1})	n
HSA + ATRA	$4.4 * 10^4$	0.8
HSA + ATRA + Ibuprofen	$5.4 * 10^4$	0.8
HSA + ATRA + Warfarin	$3.8 * 10^4$	0.8

Fluorescence Quenching Mechanism in the Presence of ATO

Quenching mechanism was obtained in the presence of ATO using previous method. The calculated k_q for this case illustrated that quenching constant (~$5.5 * 10^{+13}$) is more than that for controlled-diffusion ($1 \times 10^{+10}$ $M^{-1}S^{-1}$), which this indicates the significant effect of complex formation on quenching.

Thermodynamic Parameters in the Presence of ATO

Thermodynamic parameters of ATRA binding to HSA were obtained in the presence of ATO (Table 2). The resulting data showed that ΔG^0 is negative, indicating the spontaneous process. Both ΔH^0 and ΔS^0 were positive representing the dominance of hydrophobic interactions in the binding process.

Equilibrium Dialysis Experiments

Binding of ATRA to HSA was also measured using equilibrium dialysis technique in the presence and absence of ATO, in order to confirm the effect of ATO on ATRA binding to HSA (Table 4). The resulting data indicated that HSA could preserve more bonding ATRA, even all available ATRA in the presence of ATO (at ATO/ATRA>0.5).

Discussion

In general, recent study shows that ATRA strongly binds to HSA and has one binding site on it, which is in agreement with previous report [21]; also, its binding is strengthened in

Table 4 [ATRA] remaining in dialysis tubes in the presence of different ATO/ATRA amounts (0, 0.25, 0.5 and 1) after equilibrium dialysis in [HSA] = [ATRA] = 20 μM overnight at 310 K

[ATO]/[HSA]	[ATRA] remaining in tube (μM)
0	15.8
0.25	17.7
0.5	19.9
1	19.9

the presence of ATO. In addition, the binding mode changes from dominance of hydrogen bonds to hydrophobic interactions, and the distance between ATRA and Trp increases 2 Å in the presence of ATO (changes from 34.8 to 36.8 Å). Considering that docking and FT-IR studies have shown that the binding of ATRA to HSA occurs through the formation of hydrogen bonds between the carboxyl group of ATRA and the C=O and C-N groups of HSA [21, 22], an increase in 2 Å at the distance between ATRA and Trp in the presence of ATO is large enough to disrupt these bonds. Recent data suggests that with the loss of hydrogen bonding, ATRA binds to HSA with hydrophobic interactions through its hydrophobic tail. Furthermore, a blue shift in λ_{max} is induced by HSA titration with ATRA (Fig. 1) which it indicates that the placement of Trp residue in a hydrophobic microenvironment, which can be due to the ATRA's proximity to Trp residue. ATRA binding constant is decreased by temperature (Table 1) due to the involvement of hydrogen forces in binding. Interestingly, K has been increased by ATO with temperature, which is due to the involvement of hydrophobic interactions in the binding of ATRA to HSA in the presence of ATO [23]. In addition, the thermodynamic parameters confirm this issue. Given the sufficient distance from Trp, which is characterized by FRET analysis, energy transfer from Trp to ATRA occurs with high probability through the FRET mechanism. It appears that none of the markers is a strong competitor for ATRA binding, due to changes in the binding constant by site markers (Table 3), and these data are in agreement with previous data, which indicates that the ATRA carboxyl group binds to residues from both binding sites simultaneously [21]. The increase in binding constant in the presence of ibuprofen and arsenic trioxide is another point that worth mentioning (Tables 1 and 3); it appears that the binding of ligand to the site II enhances the binding of ATRA to HSA.

Conclusion

Albumin plays an important role in the pharmacokinetics, especially in the case of hydrophobic drugs, that causes better distribution of them by their better dissolving and homogenizing, and this is also true for ATRA. Although binding to HSA helps to dissolve and distribute the drug, but because "free drug" can penetrate into the tissues and cells, and has a therapeutic effect; binding to albumin has a negative effect on the concentration of free drug, so reducing of binding can improve drug efficacy. However, the effect of ATO on ATRA binding to HSA seems different; ATO, which improves the effect of ATRA, increases its binding to HSA. According to the available data, several important reasons have created this paradox that will be discussed further. Firstly, APL disease is associated with a decrease in albumin [24] and, in fact, albumin is absorbed by some cancer cells as a source of energy and amino acids [25]. In these cases, the greater the binding of the drug to albumin, the greater the transfer of the drug to the cancer cells. Unlike cases where binding to albumin prevents the drug from reaching the target cells, in this disease more binding of drug leads to more transmission to cancer cells. Secondly, ATRA reaches the maximum concentration in the patient's plasma within one to two hours, and has a half-life of about half an hour, which it decreases in subsequent intake doses [26]. In fact, the patients who are resistant to ATRA, or patients who have relapsed or are not completely recovered, have a rapid catabolism of the drug [26, 27]. Consequently, in this disease, more drug binding to albumin, which has a long half-life [28] and prevents drug catabolism, can guarantee the survival of the drug in patient's plasma. Thirdly, in the treatment of this type of cancer, the transfer of medication from blood to a specific tissue is not considered, and maintaining the drug in the blood and not transferring it to the tissues is an ideal, which can be achieved by further binding of the drug to the protein. Therefore, ATO, which increases the binding of ATRA to albumin and in fact reduces the amount of free drug, unexpectedly, increases the drug's effect on treating patients who are resistant to ATRA [29].

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Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

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