Biochemical and Biophysical Research Communications 387 (2009) 83–86

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Ibuprofen modulates allosterically NO dissociation from ferrous nitrosylated human serum heme-albumin by binding to three sites

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ARTICLE INFO

Article history:
Received 17 June 2009
Available online 25 June 2009

Keywords:
Ferrous nitrosylated human serum heme-albumin
Ibuprofen-dependent denitrosylation
Ibuprofen-dependent absorbance spectroscopic properties
Kinetics
Thermodynamics
Allostery

ABSTRACT

Human serum albumin (HSA) is a monomeric allosteric protein. Here, the effect of ibuprofen on denitrosylation kinetics (k_{off}) and spectroscopic properties of HSA-heme-Fe(II)-NO is reported. The k_{off} value increases from $(1.4 \pm 0.2) \times 10^{-4}$ s^{-1}, in the absence of the drug, to $(9.5 \pm 1.2) \times 10^{-3}$ s^{-1}, in the presence of 1.0×10^{-2} M ibuprofen, at pH 7.0 and 10.0 °C. From the dependence of k_{off} on the drug concentration, values of the dissociation equilibrium constants for ibuprofen binding to HSA-heme-Fe(II)-NO ($K_1 = (3.1 \pm 0.4) \times 10^{-7}$ M, $K_2 = (1.7 \pm 0.2) \times 10^{-4}$ M, and $K_3 = (2.2 \pm 0.2) \times 10^{-3}$ M) were determined. The K_3 value corresponds to the value of the dissociation equilibrium constant for ibuprofen binding to HSA-heme-Fe(II)-NO determined by monitoring drug-dependent absorbance spectroscopic changes ($H = (2.6 \pm 0.3) \times 10^{-3}$ M). Present data indicate that ibuprofen binds to the FA3–FA4 cleft (Sudlow's site II), to the FA6 site, and possibly to the FA2 pocket, inducing the hexa-coordination of HSA-heme-Fe(II)-NO and triggering the heme-ligand dissociation kinetics.

Human serum albumin (HSA), the most abundant protein in plasma, is characterized by an extraordinary ligand binding capacity, providing a depot and carrier for many compounds. Moreover, HSA affects pharmacokinetics of many drugs, holds some ligands in a strained orientation, providing their metabolic modification, renders potential toxins harmless transporting them to disposal sites, accounts for most of the antioxidant capacity of human serum, and displays (pseudo-)enzymatic properties [1–16].

HSA displays a modular structure containing three homologous domains (named I, II, and III). Each domain consists of two separate helical sub-domains (named A and B) connected by random coils. Terminal regions of sequential domains contribute to the formation of interdomain helices linking domain IB to IIA, and IIB to IIIA (Fig. 1) [2,3,6,8,12,14,15,17–25].

The structural organization of HSA provides a variety of ligand binding sites (Fig. 1). In particular, heme binds to the D-shaped fatty acid site 1 (FA1) located within the IB subdomain, contacting the IB–IIA polypeptide linker and the long IB–IIA transdomain helix. The heme binding cavity is limited by Tyr138 and Tyr161 that provide π–π stacking interaction with the porphyrin and supply a donor oxygen (from Tyr161) coordinating the heme iron [23,25]. Moreover, His146 was suggested as the putative ligand able to coordinate to the heme iron in the sixth position upon drug binding to Sudlow's sites I and II [26–30].

Bulky heterocyclic molecules (*e.g.*, warfarin) bind preferentially to Sudlow's site I, whereas Sudlow's site II is preferred by aromatic carboxylates with an extended conformation (*e.g.*, ibuprofen) [1–3,5–14,26,31–36].

The heme pocket and Sudlow's site I are allosterically-coupled. Indeed, Sudlow's site I ligands affect thermodynamics and/or kinetics of heme binding to HSA and vice versa, thus affecting the heme-Fe-atom spectroscopic properties and reactivity [10–14,26–28,30,37–42]. Similarly, the secondary ibuprofen binding site (FA6) has been suggested to be allosterically-coupled with the heme site [30,40,42]. Eventually, the FA2 site has been described to account for the positive modulation of affinity of the

Abbreviations: Hb, hemoglobin; HSA, human serum albumin; HSA-heme, heme-albumin; HSA-heme-Fe(II)-CO, ferrous carbonylated HSA-heme; HSA-heme-Fe(II)-NO, ferrous nitrosylated HSA-heme; IHP, inositol hexakisphosphate; 1-MeIm, 1-methylimidazole.

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doi:10.1016/j.bbrc.2009.06.117

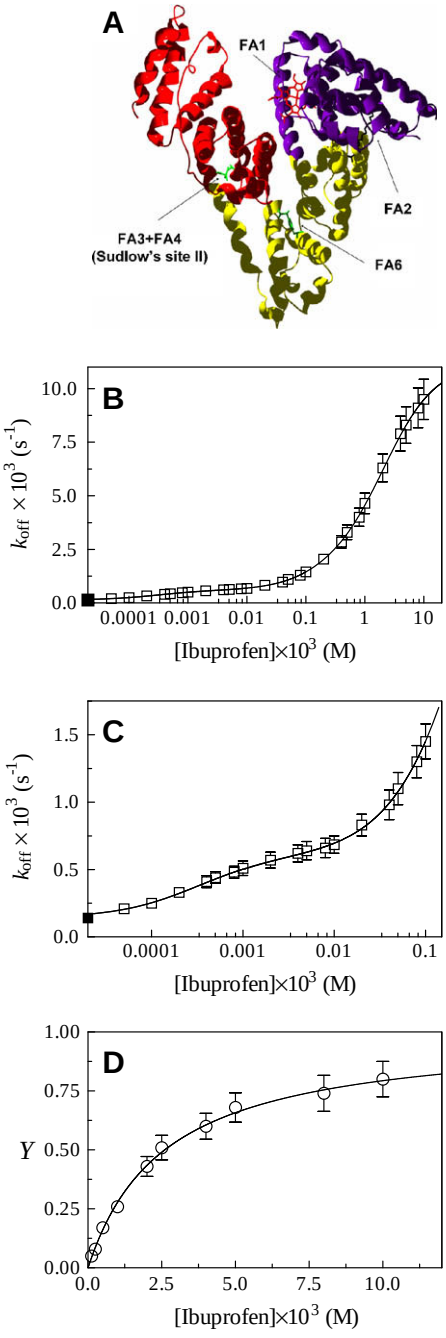

Fig. 1. Ibuprofen-dependent denitrosylation of HSA-heme-Fe(II)-NO. (A) HSA structure highlighting heme (red) and ibuprofen (green) binding; the primary ibuprofen binding site is located in Sudlow's site II within domain III (red ribbon) whereas the secondary ibuprofen binding site is located in FA6 within domain II (yellow ribbon). Heme occupies the FA1 site. The putative modulatory and tertiary ibuprofen binding site is labeled as FA2 at the interface between domain I (purple ribbon) and II (yellow ribbon) and is occupied by a myristate ion (black). HSA and ibuprofen coordinates are from PDB entry 2BXG; heme and myristate positions are obtained by superimposition of domain I coordinates from PDB entry 1N5U. (B) Effect of the free ibuprofen concentration (*i.e.*, [ibuprofen]) on k_{off} for HSA-heme-Fe(II)-NO denitrosylation, at pH = 7.0 and 10.0 °C. The filled square indicates the value of k_{off} in the absence of ibuprofen. The analysis of data according Eq. (2) allowed to determine the following parameters: $k_{off}^1 = (4.6 \pm 0.5) \times 10^{-4}$ s^{-1}, $k_{off}^2 = (1.2 \pm 0.1) \times 10^{-3}$ s^{-1}, $k_{off}^3 = (9.4 \pm 1.1) \times 10^{-3}$ s^{-1}, $K_1 = (3.1 \pm 0.4) \times 10^{-7}$ M, $K_2 = (1.7 \pm 0.2) \times 10^{-4}$ M, $K_3 = (2.2 \pm 0.2) \times 10^{-3}$ M, and $k_{off}^+ = (1.4 \pm 0.2) \times 10^{-4}$ s^{-1}. (C) Enlargement of panel B. The CO concentration ranged between 1.0×10^{-4} M and 5.0×10^{-4} M. The dithionite concentration was 1.0×10^{-2} M. (D) Effect of the free ibuprofen concentration (*i.e.*, [ibuprofen]) on the absorbance spectroscopic properties of HSA-heme-Fe(II)-NO, at pH = 7.0 and 10.0 °C. The analysis of data according to Eq. (3) allowed to determine the value of $H = (2.6 \pm 0.3) \times 10^{-3}$ M. The HSA-heme-Fe(II)-NO concentration was 2.6×10^{-6} M. For details, see text. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

heme for the FA1 binding site, FA2 being the modulator site that controls fatty acid-induced conformational switch [38,40].

Here, the effect of ibuprofen on denitrosylation kinetics and absorbance spectroscopic properties of HSA-heme-Fe(II)-NO is reported. It is important to outline that HSA-heme-Fe(II)-NO displays a severe weakening of the proximal heme-Fe-atom bond, which is restored upon binding of heterotropic ligands, such as bezafibrate, clofibrate, ibuprofen and warfarin [26,27,30]. Ibuprofen modulates NO dissociation kinetics and affects the absorbance spectroscopic properties of HSA-heme-Fe(II)-NO by binding to three distinct sites (*i.e.*, Sudlow's site II, formed by the FA3 and FA4 sites, the FA6 region, and the FA2 pocket). This highlights the allosteric modulation of HSA-heme-Fe(II) reactivity by heterotropic effectors which appears to be linked to the coordination state of the HSA-heme-Fe(II)-atom.

Materials and methods

HSA (⩾96%, essentially fatty acid free), hemin (protoporphyrin IX-Fe(III)) chloride, and ibuprofen were obtained from Sigma–Aldrich (St. Louis, MO, USA). NO (from Aldrich Chemical Co., Milwaukee, WI, USA) was purified by flowing it through an NaOH column in order to remove acidic nitrogen oxides. CO was purchased from Linde AG (Höllriegelskreuth, Germany).

HSA-heme-Fe(II) (=5.2×10^{-6} M) was prepared by adding a 1.4-molar excess of HSA to the heme-Fe(II) solution (1.0×10^{-1} M sodium phosphate buffer, pH 7.0), at 10.0 °C. HSA-heme-Fe(II)-NO (=5.2×10^{-6} M) was obtained, under anaerobic conditions, by blowing purified NO over the ferrous heme-protein solution (1.0×10^{-1} M sodium phosphate buffer, pH 7.0) at 10.0 °C. Then, the excess of NO was pumped off gently before recording kinetics [26–28,39,41,43].

The ibuprofen stock solution (=2.0×10^{-2} M) was prepared by dissolving the drug in 1.0×10^{-1} M phosphate buffer, at pH 7.0 and 20.0 °C [26].

The CO solution was prepared by keeping in a closed vessel the 1.0×10^{-1} M phosphate buffer solution (pH = 7.0) under CO at P = 760.0 mm Hg anaerobically (T = 20.0 °C).

Values of the first-order rate constant for NO dissociation from HSA-heme-Fe(II)-NO (*i.e.*, for NO replacement by CO; k_{off}) were obtained by mixing the HSA-heme-Fe(II)-NO (final concentration 2.6×10^{-6} M) solution with the CO (final concentration, 1.0×10^{-4} M to 5.0×10^{-4} M) dithionite (final concentration, 1.0×10^{-2} M) solution under anaerobic conditions, at pH = 7.0 (1.0×10^{-1} M sodium phosphate buffer) and 10.0 °C [41,44], in the absence and presence of ibuprofen (final concentration, 1.0×10^{-7} M to 1.0×10^{-2} M). Kinetics was monitored between 360 and 460 nm (wavelength interval = 5 nm). Spectra were collected every 30 s.

The time course for HSA-heme-Fe(II)-NO denitrosylation was fitted to a single-exponential process according to the minimum reaction mechanism represented by Scheme 1 [41,44].

Values of k_{off} have been determined from data analysis according to Eq. (1) [45]:

$$[\text{HSA-heme-Fe(II)-NO}]_t = [\text{HSA-heme-Fe(II)-NO}]_i \times e^{-k_{off} \times t} \quad (1)$$

Values of the dissociation equilibrium constants for ibuprofen binding to HSA-heme-Fe(II)-NO (*i.e.*, K_1, K_2, and K_3) were obtained from the dependence of k_{off} on the free ibuprofen concentration (*i.e.*, [ibuprofen]). Values of K_1, K_2, and K_3 were determined from data analysis, according to Eq. (2) [45]:

$$\text{HSA-heme-Fe(II)-NO} + \text{CO} \xrightarrow{k_{off}} \text{HSA-heme-Fe(II)-CO} + \text{NO}$$

Scheme 1.

$$k_{off} = (k_{off}^{1} \times ([ibuprofen]/(K_1 + [ibuprofen]) + k_{off}^{2} \times [ibuprofen]/(K_2 + [ibuprofen]) + k_{off}^{3} \times [ibuprofen]/(K_3 + [ibuprofen])) + k_{off}^{+} \quad (2)$$

where k_{off}^{1}, k_{off}^{2}, and k_{off}^{3} indicate values of k_{off} occurring at $K_1 < [ibuprofen] < K_2 < K_3$, $K_1 < K_2 < [ibuprofen] < K_3$, and $K_1 < K_2 < K_3 < [ibuprofen]$, respectively, and k_{off}^{+} is the k_{off} value obtained in the absence of ibuprofen.

HSA-heme-Fe(II)-NO absorbance spectra were determined between 360 and 450 nm in the absence and presence of ibuprofen (final concentration, 1.0×10^{-7} M $\geqslant$ [ibuprofen] $\geqslant 1.0 \times 10^{-2}$ M) and 10.0 °C. The HSA-heme-Fe(II)-NO concentration was 2.6×10^{-6} M [29].

The value of the dissociation equilibrium constant for ibuprofen binding to HSA-heme-Fe(II)-NO (*i.e.*, H) was obtained from the dependence of molar fraction of the drug-bound HSA-heme-Fe(II)-NO (*i.e.*, Y) on the free ibuprofen concentration (*i.e.*, [ibuprofen]), according to Eq. (3) [45]:

$$Y = [ibuprofen]/(H + [ibuprofen]) \quad (3)$$

Results and discussion

Under all the experimental conditions, the time course for NO dissociation from HSA-heme-Fe(II)-NO conforms to a single-exponential decay for more than 90% of its course, in the absence and presence of ibuprofen (Fig. 1). Values of the first-order rate constant for NO dissociation from HSA-heme-Fe(II)-NO (*i.e.*, k_{off}) are wavelength- and [CO]-independent in the presence of dithionite excess (data not shown).

Values of k_{off} for HSA-heme-Fe(II)-NO denitrosylation increase from $(1.4 \pm 0.2) \times 10^{-4}$ s^{-1}, in the absence of ibuprofen (*i.e.*, k_{off}^{+} in Eq. (2)), to $(9.5 \pm 1.2) \times 10^{-3}$ s^{-1}, in the presence of 1.0×10^{-2} M ibuprofen (Fig. 1 and Table 1). The k_{off}^{+} value here reported (=$(1.4 \pm 0.2) \times 10^{-4}$ s^{-1}, at pH 7.0 and 10.0 °C) is closely similar to that previously obtained (=$(1.3 \pm 0.2) \times 10^{-4}$ s^{-1}, at pH 7.0 and 20.0 °C) [41]. The analysis of the dependence of k_{off} on the ibuprofen concentration (Fig. 1), according to Eq. (2), allowed to determine the values of the dissociation equilibrium constants for drug binding to HSA-heme-Fe(II)-NO (*i.e.*, $K_1 = (3.1 \pm 0.4) \times 10^{-7}$ M, $K_2 = (1.7 \pm 0.2) \times 10^{-4}$ M, and $K_3 = (2.2 \pm 0.2) \times 10^{-3}$ M) (Fig. 1).

Mixing of the HSA-heme-Fe(II)-NO and ibuprofen solutions causes a shift of the optical absorption maximum of the Soret band (*i.e.*, λ_{max}) from 389 nm (*i.e.*, HSA-heme-Fe(II)-NO) to 418 nm (*i.e.*, ibuprofen-HSA-heme-Fe(II)-NO) and a change of the extinction coefficient from $\varepsilon_{389\ nm} = 6.4 \times 10^{4}$ M^{-1} cm^{-1} (*i.e.*, HSA-heme-Fe(II)-NO) to $\varepsilon_{418\ nm} = 1.34 \times 10^{5}$ M^{-1} cm^{-1} (*i.e.*, ibuprofen-HSA-heme-Fe(II)-NO). Values of λ_{max} and ε for HSA-heme-Fe(II)-NO in the absence of ibuprofen here obtained correspond to those reported in the literature [29] and they indeed correspond to those obtained for ferrous nitrosylated penta-coordinated heme-proteins [46]. Absorbance changes of HSA-heme-Fe(II)-NO on the ibuprofen concentration follow a single equilibrium; the analysis of data according to Eq. (3) (Fig. 1) allowed to determine the value of the dissociation equilibrium constant for drug binding to HSA-heme-Fe(II)-NO (*i.e.*, $H = (2.6 \pm 0.3) \times 10^{-3}$ M). The value of the dissociation equilibrium constant for ibuprofen binding to HSA-heme-Fe(II)-NO obtained by absorbance spectroscopy (*i.e.*, H) is in excellent agreement with that of K_3 determined from drug-dependent kinetics of HSA-heme-Fe(II)-NO denitrosylation (see Fig. 1).

Data reported in Fig. 1 indicate that ibuprofen binds to three independent sites of HSA-heme-Fe(II)-NO modulating allosterically NO dissociation kinetics. However, only one binding site is spectroscopically-linked to the chromofore (*i.e.*, the heme-Fe(II)-NO atom).

Values of K_1 (=3.1×10^{-7} M) and K_2 (=1.7×10^{-4} M) for ibuprofen binding to HSA-heme-Fe(II)-NO (present study) are higher than those reported for drug binding to HSA-heme-Fe(III) ($K_1 = 8.0 \times 10^{-8}$ M and $K_2 = 5.0 \times 10^{-5}$ M) [26,30,42], and are comparable to those reported for drug binding to heme-free HSA ($K_1 = 3.7 \times 10^{-7}$ M and $K_2 = 4.0 \times 10^{-5}$ M) [3,26,42,47]. These findings indicate that the redox and the (un)ligated state of the heme-Fe-atom affects allosterically ibuprofen binding to HSA-heme-Fe. Moreover, only one ibuprofen binding site (characterized by K_2) appears to be allosterically-linked to the heme cleft (*i.e.*, FA1).

The analysis of data shown in Fig. 1, according to Eqs. (2) and (3), indicates that ibuprofen binds to three independent sites of HSA-heme-Fe(II)-NO, the value of the third site constant K_3 (=H) is 2.2×10^{-3} M). Ibuprofen primary binding to Sudlow's site II, formed by the FA3 and FA4 sites, and secondary binding to the FA6 region have been substantiated by X-ray crystallography [13]. In order to account for a third, low affinity ibuprofen binding site the modulatory FA2 site may be envisaged. Indeed, the FA2 site acts as the modulatory site that controls fatty acid-induced conformational switch and therefore may account for heme stabilization within the FA1 binding site [38,40]. Actually, preliminary results indicate a positive modulation of heme binding by high (>1.0 mM) ibuprofen concentration that in turn could explain the observed hexa-coordination of HSA-heme-Fe(III) at similar ibuprofen concentration [30].

Ibuprofen binding to FA2 reflects indeed the stabilization of the six-coordinate derivative of the HSA-heme-Fe(II)-NO species, which is instead predominantly five-coordinated in the absence of allosteric effectors that increase heme affinity. Actually, ligand binding to FA2 should affect the Phe149-Tyr150 dyad with a more favorable orientation of Phe149 with respect to the Fe(III)heme moiety (see [26–28,30,40,48]).

The increase of k_{off} for NO dissociation from HSA-heme-Fe(II)-NO upon stabilization of the six-coordinated heme-Fe(II)-NO-atom is reminiscent with what reported for warfarin-induced six-coordination of HSA-heme-Fe(II)-NO [41], and for 1-methyl-imidazole-(1-MeIm-) mediated six-coordination of the heme-Fe(II)-NO model compound [43] (Table 1), clearly indicating that (unlike for the heme-Fe-atom ligand CO [49]) penta-coordinated heme-Fe(II)-NO is characterized by a slower NO dissociation rate than the hexa-coordinated species.

Furthermore, values of k_{off} for NO dissociation from ferrous nitrosylated heme-proteins may also reflect structurally-different stabilization mode(s) of the heme-Fe(II)-bound NO by heme distal residue(s). In fact, the stabilization of the heme-bound ligand is achieved by hydrogen bonding to the heme distal His residue in human Hb [50]. In contrast, Arg145 may stabilize the HSA-heme-Fe(II)NO complex by hydrogen bonding [41].

Table 1
Values of k_{off} for denitrosylation of some heme-Fe(II)-NO systems and heme-Fe(II)-NO coordination state.

Heme-Fe(II)-NO system	Effector	k_{off} (s^{-1})[a]	Heme-Fe(II)-atom coordination
Heme-Fe[b]	—	2.1×10^{-5}	5c
	1-MeIm	2.9×10^{-2}	6c
HSA-heme-Fe	—	1.4×10^{-4}[c]	5c[c]
	Ibuprofen[c]	9.5×10^{-3}[c]	6c[c]
	Abacavir[d]	8.6×10^{-4}[d]	6c[d]
	Warfarin[d]	8.6×10^{-4}[d]	6c[d]

[a] For details, see Scheme 1.
[b] pH = 7.4 and T = 20.0 °C. From [42].
[c] pH = 7.0 and T = 10.0 °C. Present study.
[d] pH = 7.0 and T = 20.0 °C. From [40].

As a whole, present data reinforce the idea that HSA could be taken as the prototype of monomeric allosteric proteins. Furthermore, HSA-heme represents a unique case within heme-proteins since allosteric effectors modulate both heme binding to HSA and the heme-Fe-atom reactivity.

Acknowledgments

This work was partially supported by grants from the Ministry for University and Research of Italy (Department of Biology, University 'Roma Tre', Roma, Italy, 'CLAR 2008') and from the Ministry of Health of Italy (National Institute for Infectious Diseases I.R.C.C.S. 'Lazzaro Spallanzani', Roma, Italy, 'Ricerca corrente 2008') to P.A.

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