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Review

Binding of transition metal ions to albumin: Sites, affinities and rates ☆

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ABSTRACT

Background: Serum albumin is the most abundant protein in the blood and cerebrospinal fluid and plays a fundamental role in the distribution of essential transition metal ions in the human body. Human serum albumin (HSA) is an important physiological transporter of the essential metal ions Cu^{2+}, and Zn^{2+} in the bloodstream. Its binding of metals like Ni^{2+}, Co^{2+}, or Cd^{2+} can occur *in vivo*, but is only of toxicological relevance. Moreover, HSA is one of the main targets and hence most studied binding protein for metallodrugs based on complexes with Au, Pt and V.

Scope of Review: We discuss i) the four metal-binding sites so far described on HSA, their localization and metal preference, ii) the binding of the metal ions mentioned above, i.e. their stability constants and association/dissociation rates, their coordination chemistry and their selectivity versus the four binding sites iii) the methodology applied to study issues of items i and ii and iv) oligopeptide models of the N-terminal binding site.

Major Conclusions: Albumin has four partially selective metal binding sites with well-defined metal preferences. It is an important regulator of the blood transport of physiological Cu(II) and Zn(II) and toxic Ni(II) and Cd(II). It is also an important target for metal-based drugs containing Pt(II), V(IV)O, and Au(I).

General Significance: The thorough understanding of metal binding properties of serum albumin, including the competition of various metal ions for specific binding sites is important for biomedical issues, such as new disease markers and design of metal-based drugs. This article is part of a Special Issue entitled Serum Albumin.

1. Introduction

Albumin plays a fundamental role in distribution of many metabolites, hormones, drugs, and essential transition metal ions in the human body. This is achieved by the presence of several specific binding sites in its molecule. These sites are also used by toxic metal ions entering the human bloodstream. They are best characterized for human serum albumin (HSA) and for bovine serum albumin (BSA), which is often used as a model protein for HSA. Other mammalian albumins have not been studied so broadly. We will use the data obtained for these proteins when necessary, to illustrate key issues relevant for HSA.

The focus of this review is on transition metals, that is those having the *d* electronic subshell partially filled [1]. We will adopt the broad definition of these elements, which includes the d^{10} elements. Table 1 collects the transition metal ions for which HSA binding has been characterized, subdivided into elements being physiological yet toxic to humans. The non-physiological, but often toxic elements which, however, have found use in medicine, are collected in the third subdivision in Table 1. The binding preferences and kinetic properties of these metal ions, provided in the table, are followed by a brief description of their properties. Because of their fundamentally different mode of interaction, we do not discuss those transition metal ions, which form oxyanions, such as MnO_4^- or CrO_4^{2-}. The absence of essential metal cations, Mn(II), Cr(III) and Fe(III) from the first subdivision of Table 1 is due to the fact that they are preferentially transported by a dedicated carrier protein, transferrin [2–4]. Fe(III) binding to albumin is classified as toxic, because it appears to occur *in vivo* only under pathologic conditions of iron overload [5].

2. Brief description of biochemical properties of metal ions interacting with albumin

In this section we briefly describe essential chemical and biochemical properties of the metal ions discussed in this review, in the context of their interactions with albumin. These metal ions are collected in Table 1.

2.1. Copper

Biological chemistry of copper is limited to Cu(I) and Cu(II) ions, and its main roles are to catalyze metabolic oxidations and transfer electrons (e.g. in cytochrome c oxidase, the key element of respiratory chain) [6]. Diamagnetic (d^{10}) Cu(I) prefers soft ligands, such as thiols, and forms complexes with low coordination numbers and linear, trigonal or tetrahedral structures. It exchanges ligands fast in

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Table 1
Transition elements interacting with HSA. States of oxidation indicated are those stable in the bloodstream, and thus relevant to the interaction with HSA *in vivo*.

Element			Oxidation state	Donor atom preferences	Kinetic properties
	Essential (e)/ toxic (t)/ medicinal (m)				
	For human	With HSA			
Cu	e	e	Cu(II)	N > O	labile
Zn	e	e	Zn(II)	S, N, O	Labile
Co	e	t	Co(II)	S, N, O	Intermediate
Fe	e	t	Fe(III)	O	Labile
Ni	t	t	Ni(II)	S, N > O	Labile/inert[1]
Cd	t	t	Cd(II)	S > N > O	Labile
Hg	t	t	Hg(II)	S	Labile
V	t,m	t,m	VO(IV)	O > N	Labile
Au	t,m	t,m	Au(I)	S, P	Intermediate
Pt	t,m	t,m	Pt(II)	N, S	Very inert

[1] Depending on the complex structure.

terms of intracellular transfers of this metal [7], although slower than the very labile paramagnetic Cu(II) ion, which nevertheless forms strong tetragonal complexes with biological nitrogen ligands. The majority of blood serum copper is present in ceruloplasmin, a redox copper protein responsible for oxidation of Fe(II) to Fe(III) to enable its incorporation into transferrin [8]. HSA, controlling the copper distribution among the internal organs, comprises only about 15% of human blood copper, invariably bound as Cu(II), due to oxidative conditions in the blood.

2.2. Zinc

Zinc is an essential metal ion playing multiple roles in human organism. It provides structure to many protein domains, e.g. zinc fingers, forms catalytic centers in many enzymes, serves as activator or inhibitor to others, and, finally takes part in intracellular and intercellular signal transduction. In enzymatic active sites it usually functions as Lewis acid, by lowering the p*K* of coordinated water and/or by substrate activation [9,10]. All the above-mentioned functions are performed by Zn(II), which is the only stable state of oxidation in zinc compounds. Due to its d^{10} electronic structure, Zn(II) exhibits a variety of coordination geometries, with coordination numbers 4 (tetrahedral), 5 (pyramidal) and 6 (octahedral) dictated by the character of its ligands, S/N in structural sites and predominantly N/O in enzymes. Its ligand exchange rates also vary, by several orders of magnitude, depending on the ligand and the complex geometry. Zn(II) is carried in blood by albumin, and the interplay between Zn(II) and fatty acids binding to HSA has been discussed [11].

2.3. Cobalt

Cobalt is an essential element for humans in the form of cobalamin (Coenzyme B12) in which it is tightly bound to a corrin ring and serves as methyl group carrier, using Co(I) and Co(III) oxidation states. However, human beings are exposed to ionic Co(II), the most stable form under ambient conditions, in course of normal nutrition, e.g. yeast contain ionic cobalt in certain enzymes, or due to environmental cobalt exposure [12]. The readily exchangeable Co(II), which can adopt various geometries and coordination numbers between four and six, can be relatively easily oxidized to inert and always octahedral Co(III). HSA has been suggested to be a main transporter of Co(II) in the blood [13,14] and Co(II) binding to bovine serum albumin has been studied since a while [15–17]. Cobalt was included as toxic in Table 1, because HSA can only bind ionic Co(II) which is not incorporated in normal cobalt metabolism in humans.

2.4. Iron

Iron is present in the human body as a cofactor of many enzymes, electron transfer proteins and, last but not least as dioxygen carrier in hemoglobin [18]. It is present as Fe(II) or Fe(III) in the resting states of these enzymes, depending on their function. Geometries of these iron binding sites are generally octahedral, in both oxidation states, and ligand exchange rates are rather fast. Coordination sites involving sulfur (Fe–S proteins), nitrogen (heme) and oxygen donors are known. In the blood serum iron is readily oxidized to Fe(III), its stable form in the presence of oxygen [19]. The inclusion of iron as a toxic element in Table 1 is justified by the fact that albumin is not a physiological carrier of Fe(III), but is likely to bind this ion *in vivo* in the iron overload pathology [5].

2.5. Nickel

Nickel has not been proven to be essential for humans, though it is often claimed so [20]. On the other hand, it is essential for plants and microorganisms, especially the ones thriving in anaerobic conditions. Redox enzymes use Ni(I), Ni(II) and Ni(III) redox states, while the aerobically stable Ni(II) serves as Lewis acid in urease [21]. To humans, nickel is more important as a toxic element. Dusts containing insoluble Ni(II) and aerosols of soluble Ni(II) compounds are human carcinogens. Ni(II) is also a strong allergen, causing allergic contact dermatitis (ACD). Two major geometries of Ni(II) (d^8) are octahedral (high-spin and labile with harder N/O donors) and square-planar (low spin and relatively inert with S/N donors). Albumin is probably the most important Ni(II) carrier in blood [22,23].

2.6. Cadmium

Cadmium is not an essential element for humans, and its essentiality for other forms of life is episodic and limited to marine algae. Many organisms, however, accumulate cadmium in significant quantities, what results in exposure of humans to this element, e.g. with food or tobacco and its eventual accumulation in the human body, with nephropathy and respiratory tract cancers as major diseases [20]. Cadmium is isoelectronic with zinc, and so, Cd(II) is the only stable redox state of the element. However, being a larger and softer ion it forms stronger sulfur and weaker nitrogen bonds than Zn(II) [24]. Similarly to Zn(II), the ligand exchange reaction rates in Cd(II) complexes vary from case to case. Albumin was indicated as one of cadmium targets in blood [25,26], and Cd(II) is also used as a substituent and probe in studies of Zn(II) binding by NMR and absorption spectroscopies [27,28].

2.7. Mercury

Mercury has two stable oxidation levels, Hg(I), and the dominant Hg(II). This metal ion is characterized with low coordination numbers. Linear dicoordinate complexes are most common, followed by trigonal, and only very rarely tetrahedral complexes [1]. Hg(II) forms extremely stable, nearly covalent bonds with thiols and other soft ligands. In the human body Hg(II) undergoes biotransformations yielding lipophilic mono- and dimethylated species, which are severely neurotoxic [29]. Mercury may enter bloodstream by several routes, including inhalation of vapors and consumption of contaminated food. Albumin is the main target for various Hg(II) species in the bloodstream. For example, thimerosal, the ethylmercury complex of thiosalicylic acid used as preservative in injection drugs and vaccines, was shown to decompose and yield Hg(II) complex with albumin within minutes after injection [30].

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