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Why Heme Needs to Be Degraded to Iron, Biliverdin IXα, and Carbon Monoxide?

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ABSTRACT

A large amount of hemoglobin is degraded daily to heme and globin and is replenished by biosynthesis in the bone marrow erythroblasts. "Free heme" can be dissociated from apohemoglobin *in vitro* and, conversely, native hemoglobin can be renatured from them. Then why does heme need to be degraded to iron, biliverdin IXα, and carbon monoxide *in vivo*? Free heme, *i.e.,* a protein-unbound heme, exists in cells at a very minute concentration and exerts regulatory functions such as the repression of nonspecific δ-aminolevulinate synthase expression and the induction of microsomal heme oxygenase-1 (HO-1). The latter gene expression occurs by way of free heme-mediated derepression of Bach1, a mammalian heme-responsive transcription factor that suppresses the activation of the HO-1 gene. All these events occur at free heme concentrations below 1 μ*M*. In contrast, free heme concentration greater than 1 μ*M* can be toxic because it catalyzes the production of reactive oxygen species. To cope with this problem, the body is equipped with various defense mechanisms against high free heme concentrations. HO is one of the major players in these mechanisms, and it catabolizes free heme to iron, biliverdin IXα, and carbon monoxide. These three metabolites of heme by HO reactions have additional important functions and are involved in various critical cellular events. Thus, the breakdown of heme to smaller elements has its own significance in essential cellular metabolism. *Antioxid. Redox Signal.* 6, 819–824.

RED CELL SENESCENCE AND HEMOGLOBIN BREAKDOWN

HEMOGLOBIN IN RED BLOOD CELLS is the most abundant hemoprotein in the body and is maintained by its constant synthesis and degradation. There is ~700 g of hemoglobin in a 70-kg man, and ~1% of it is degraded daily by catabolism and replenished by biosynthesis. Hemoglobin consists of four globin subunits, typically of two different types, and every subunit contains one heme molecule. Heme is composed of protoporphyrin IX and ferrous iron. After ~120 days in circulation, erythrocytes are engulfed by splenic macrophages. Then their components undergo extensive breakdown, that is, globin is degraded to amino acids, and heme is degraded to one molecule each of iron, biliverdin IXα, and carbon monoxide (CO). The metabolism of heme is catalyzed by a sequence of three enzymatic reactions, involving NADPH-cytochrome P450 reductase (CR), heme oxygenase (HO), and biliverdin reductase (BR). The initial step in this sequence is the formation of a ferric heme–HO complex, which is then oxidized by a reducing equivalent provided by CR in the presence of NADPH. HO is the enzyme that catalyzes the regiospecific cleavage of the α-methene bridge of heme to produce iron, biliverdin IXα, and CO, and is the rate-limiting step in the entire sequence (31). Importantly, HO can form an equimolar complex with CR (41), suggesting that the heme cleavage reaction by HO may proceed in a very efficient manner within the binary complex located in the endoplasmic reticulum.

There are at least two functionally active HO isozymes, HO-1 (32) and HO-2 (19), and the one that plays the major role in the catabolism of hemoglobin heme is the heme-inducible HO-1. Biliverdin IXα is reduced to bilirubin IXα, the major bile pigment, by cytosolic BR. BR can also interact

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with the CR–HO complex *in vitro* (41). Thus, biliverdin IXα, formed by the CR–HO complex, can be converted to bilirubin IXα without leaving the enzyme complex in the endoplasmic reticulum. Daily production of bilirubin IXα in a man amounts to ~400 mg, ~75% of which is accounted for by the degradation of hemoglobin heme (2, 17).

WHY IS HEME FROM HEMOGLOBIN NOT UTILIZED FOR NEW HEMOGLOBIN FORMATION?

In vitro, heme and globin can be dissociated from hemoglobin, and *vice versa* intact hemoglobin can also be renatured from heme and apoglobin, at a rapid rate constant of $5 \times 10^4\ M^{-1}\ s^{-1}$ (9). Then why is heme from hemoglobin *in vivo* not utilized as such for new hemoglobin formation? Why should heme be degraded to iron, biliverdin IXα, and CO? There may be several answers to these questions. First of all, for such an event to occur, free globin and "free heme" must travel in circulation from the spleen to bone marrow where new hemoglobin is formed. Both free hemoglobin and free heme are highly toxic. For example, free heme can catalyze the generation of oxygen radicals by the Fenton reaction, leading to oxidation of low-density lipoprotein (LDL) and covalent cross-linking of the LDL protein, apo B (20). Free heme also stimulates the expression of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin on endothelial cells, leading to inflammatory changes in these cells (39). Secondly, cells must manufacture a novel system if free globin and free heme need to diffuse back into bone marrow erythroblasts. It would be, however, extremely difficult because free globin is highly toxic due to its reaction with oxygen to form a peroxy radical (5). Ferric free heme, aside from its ability to form oxygen radicals, must also be reduced to ferrous heme for cellular hemoglobin synthesis by erythroblasts. Such a mechanism would require an additional amount of energy that may be too costly for cells.

VARIOUS DEFENSE MECHANISMS AGAINST TOXIC EFFECTS OF FREE HEMOGLOBIN AND HEME

There are also various built-in defense mechanisms for coping with excessive levels of free hemoglobin and heme in circulation. For example, serum haptoglobin (Hp), an acute-phase protein produced by the liver, specifically binds with hemoglobin, with an association constant of $>10^{-15}$ mol/L (3). The stable hemoglobin–Hp complex is then removed from the blood stream by phagocytes through a receptor-mediated mechanism (26). As a result, virtually no free hemoglobin is present in circulation. The incorporated hemoglobin is degraded, and the heme iron is recycled as the iron atom (14). Upon binding with Hp, cross-linking of apo B and oxidation of lipids induced by the globin radical are completely inhibited (20). Clearance of the hemoglobin–Hp complex in humans occurs at a rate of ~15 mg of hemoglobin per 100 ml of plasma per hour (6, 7). Due to the rapid clearance, serum Hp levels become undetectable following an acute event of hemolysis, because of its consumption by binding with hemoglobin. Thus, Hp functions as an important antioxidant in circulation and protects the vascular system from oxidative damage (15).

A similar detoxifying system is also found for free heme. Free heme, *i.e.,* a protein-unbound heme, is also very toxic and harmful if it travels in circulation. Free heme can be viewed as heme that is formed by its biosynthetic pathway but has not yet been associated with apohemoproteins, or heme that has just come off from hemoproteins but has not yet been degraded by HO. It is also likely that free heme may be in a dynamic equilibrium between an unbound and a bound state (8).

Exposure of cells to hemin, an oxidized form of free heme available as a chemical, stimulates the expression of adhesion molecules such as ICAM-1, VCAM-1, and E-selectin on endothelial cells *in vitro* (39), through the generation of heme-mediated reactive oxygen species (ROS) production, which underscores various types of inflammatory tissue damage. To circumvent this problem, liver also synthesizes hemopexin (Hx), which forms an inert complex with free heme, and delivers it to the liver for further catabolism (21). Hx has the highest affinity for heme in circulation among all heme binding proteins, but can release heme into cells via two unique, similar four-bladed β-propeller domains (23). However, if the level of free heme exceeds the plasma concentration of Hx, significant tissue damage ensues due to the generation of ROS.

Free iron can be toxic because it can catalyze significant ROS generation; however, the toxic effect of iron derived from the catabolism of heme in the cell is largely attenuated due to its sequestration and inactivation by coinduced ferritin (38). Unlike heme, a large amount of iron can also be transported safely in circulation as transferrin-bound iron and delivered to bone marrow erythroblasts. Virtually no iron is lost into urine and stool by this very efficient mechanism. Free heme is also effectively removed in cells by HO-1 and HO-2. For example, K_m values for heme of HO-1 and HO-2 are 1 μ*M* and 0.4 μ*M* (36), respectively, suggesting that they are indeed efficient enzymes for the removal of free heme. HO-1 is also induced by free heme concentrations at or above 5 μ*M* (Fig. 1) (33).

FREE HEME CONCENTRATIONS IN THE CELL

As discussed above, the body appears to maintain free heme concentrations at an extremely low level. Then what might be the exact concentration of free heme? A serum concentration of ~0.5 m*M* heme found in a baby boy with inherited HO-1 deficiency was clearly abnormal and toxic, because it was associated with a vast array of oxidative tissue damage, and ultimately with an early death of the boy (40). As judged from the K_m of the HO-1 reaction (1 μ*M*), free heme concentration in normal cells must be below 1 μ*M* (Fig. 1). There are two principal methods for determination of heme concentrations. One is a pyridine hemochromogen assay, and the other is a fluorometric assay. The pyridine hemochromogen assay is specific, but its detection sensitivity is

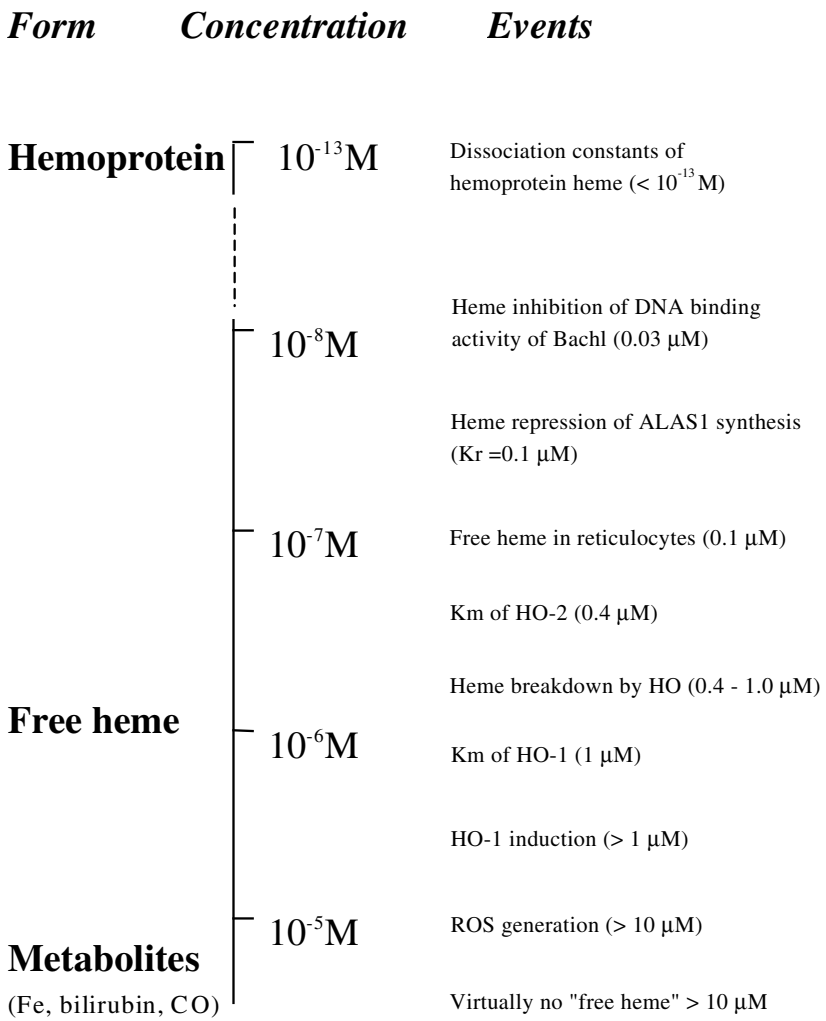

FIG. 1. "Free heme" concentrations in the cell. Free heme exerts distinctive regulatory functions at low and high concentrations. At submicromolar concentrations such as <0.1 μ*M*, it is involved in controlling gene expression for both heme metabolism and biosynthesis. In contrast, at a high concentration such as >1 μ*M*, heme is degraded by HO to yield bilirubin IXα and CO, both of which are then critically involved in the host defense against oxidative tissue injuries. Thus far, free heme > 10 μ*M* was found only in abnormal cells such as in inherited HO-1 deficiency. Thus there is a legitimate reason to keep free heme concentration below 10 μ*M* in the normal cell.

low, because the millimolar extinction coefficient (ΔEmM, $EmM_{557} - EmM_{541}$) is only 20.7 (24). The fluorometric assay is ~1,000 times more sensitive than the pyridine hemochromogen assay, and thus should be able to measure heme concentration in a submicromolar range, but can be interfered with if there are fluorescent porphyrins in the assay sample (29). Thus, it is quite difficult to determine low free heme concentrations in the cell with certainty by conventional methods. The two methods also do not differentiate heme and hemoproteins, and measure all hemoproteins as heme. Dowex AG 1-X8 anion-exchange resin column chromatography was used at high-ionic strength conditions to separate free heme from hemoglobin. By using this method, the amount of free heme in normal human erythrocytes was found to be 0.1–0.15 μ*M*, whereas it was three- to fivefold greater in patients with sickle cell anemia (16). The same method was also used to determine free heme concentrations in reticulocytes in Belgrade rats with hypochromic and microcytic anemia, and the amounts of free heme were estimated to be less than 0.1 μ*M* and 8–10 μ*M* in mature and younger reticulocytes, respectively (8). The former level also was below detection in red cells containing 4–6% reticulocytes (8). In a pulse-chase experiment with ^{59}Fe-transferrin, the free heme pool in reticulocytes in Belgrade rats was shown to behave as an intermediate for hemoglobin biosynthesis, with a rapid half-life of a little over 2 h (8). With the exception in this animal model, no direct demonstration of free heme concentration is known. Indirect evidence suggests, however, that there is a cytosolic free heme pool, as judged by changes in the saturation of tryptophan pyrrolase with heme. For example, rat liver tryptophan pyrrolase heme is rapidly depleted at 30 min after administration of 2-allyl-2-isopropylacetamide, and this depletion is accompanied by an increase of δ-aminolevulinate synthase (ALAS) activity (1). Free heme (0.1–0.3 μ*M*), when added to the medium of chick embryo liver cell culture as hemin, chicken hemoglobin, or human hemoglobin, also specifically inhibited the induction of ALAS by one-half (11) (Fig. 1).

The greatest confounding factor in free heme determination is the fact that free heme is in a rapid dynamic equilibrium between the protein-bound and the unbound state (8, 10). Thus, even when using column chromatography, which

can separate free heme from hemoproteins, results obtained may not necessarily reflect the exact concentration of free heme in cells.

THE REGULATORY ROLE OF FREE HEME

Free heme as such exerts important regulatory functions, but the concentration of such "regulatory heme" must be very low and would likely be below the detection limit. Nonetheless, evidence suggests that free heme at such low concentrations may play an important regulatory role in various cellular events. For example, exogenously added free heme at 10^{-7} *M* represses the synthesis of ALAS1, and at 10^{-6} *M* induces HO-1 in cultured liver cells. As little heme is absorbed by cells, these effects must be occurring at much lower concentrations than the added concentration of heme in the cell. Recently, it was reported that the mammalian transcription factor Bach1, a repressor of HO-1 gene activation (35), binds with an equimolar amount of free heme (22). Heme at 1 μ*M* almost completely inhibits the DNA-binding activity of Bach1 *in vitro*. Interestingly, even as low as 0.03 μ*M* free heme caused a slight but reproducible inhibition of DNA binding by Bach1-MafK heterooligomer. These findings suggest that the physiologically important concentration of free heme in the cell must be below 1 μ*M* and should even be closer to 0.03 μ*M* (22) (Fig. 1).

HEME DEGRADATION PRODUCTS BY HO

The three enzymatic products of HO reaction, *i.e.,* iron, biliverdin IXα, and CO, can obviously be toxic if they are present at enormously high or abnormal concentrations. Under such conditions, iron resulting from heme catabolism may principally be involved in ROS generation, and CO may reach a toxic concentration. Bilirubin IXα, the reduced metabolite from biliverdin IXα, can be toxic at concentrations above saturation with serum albumin, and may influence lipid polarity and fluidity, protein order, and redox status (27, 28). At physiological concentrations in normal cells, however, these three metabolites are not toxic or waste products at all, but have important biological functions. First of all, iron is an essential substrate for new hemoglobin synthesis. For example, mice deficient in HO-1 develop iron deficiency anemia because of low serum iron levels (25). Iron is also necessary for normal development, because a child with congenital HO-1 deficiency was found to have severe growth retardation (40). It is also well known that various organisms use HO for iron acquisition for their cellular growth (30). Secondly, both biliverdin IXα and bilirubin IXα, as well as their glucuronides, are potent antioxidants (34). Conversely, low serum bilirubin levels are also a risk factor for coronary artery disease (12). Thirdly, CO formed from the cleavage of heme by HO, the only CO-forming reaction in the body, has recently been shown to be a neural second messenger, similar to nitric oxide, in the central nervous system (18), and also to suppress apoptosis of endothelial cells via the activation of p38 mitogen-activated protein kinase (4). CO appears to be necessary for appropriate maintenance of enteric smooth muscle resting membrane potential, and exogenous CO restores inhibitory transmission in contracted muscle of HO-$2^{-/-}$ mice. These effects of CO also require soluble guanylate cyclase and the production of nitric oxide (13). HO is also known to colocalize with soluble guanylate cyclase in regions of the human brain (37). As HO-2 expressed throughout the brain is a constitutive enzyme, free heme concentration must be the rate-limiting factor of CO production in the brain.

Thus, in addition to the removal of the prooxidant heme by oxidative metabolism, HO-1 in turn produces a series of metabolites from heme, all of which act as important members of the host defense system and contribute to the suppression of oxidative tissue injuries. High levels of HO-1 may potentially be toxic if an excess amount of free iron is generated; however, it appears such instances are rather rare. The adaptive induction response of HO-1 to various oxidative stimuli, including hemin, suggests an entirely new paradigm for HO-1, and an induction response of HO-1 should now be recognized as a major protective defense of inflammatory processes and oxidative tissue injuries.

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ABBREVIATIONS

ALAS, δ-aminolevulinate synthase; BR, biliverdin reductase; CO, carbon monoxide; CR, NADPH-cytochrome P450 reductase; HO, heme oxygenase; Hp, haptoglobin; Hx, hemopexin; LDL, low-density lipoprotein; ROS, reactive oxygen species.

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