A Potential Strategy for Preventing Complications of Hemolytic Diseases and Toxicity of Hemoglobin-Based Oxygen

Potential benefits of sequestering excessive free hemoglobin in circulation to prevent hypertension and organ damage

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Sequestration of extracellular hemoglobin within a haptoglobin complex decreases its hypertensive and oxidative effects in dogs and guinea pigs

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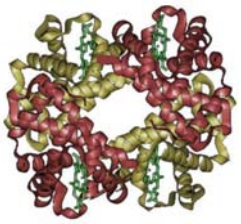


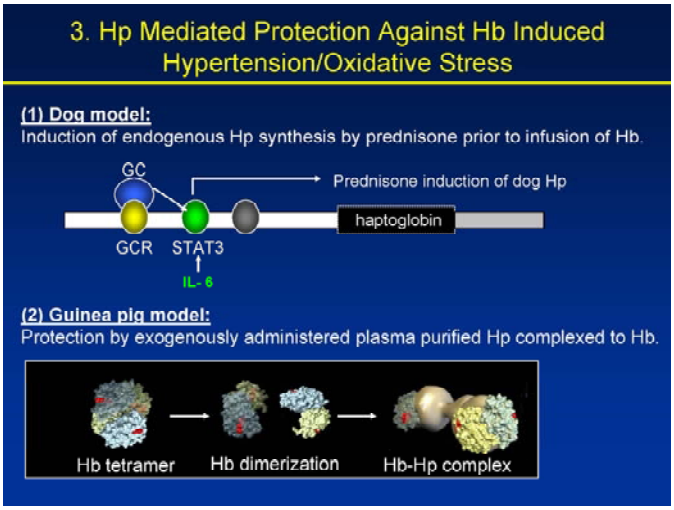
The Trouble with Free Hemoglobin

Hemoglobin (Hb) is normally found in red blood cells where it binds to oxygen and delivers it to the body's tissues and organs. Hemolytic anemia, malaria, and sickle cell disease (SCD) trigger the destruction of red blood cells, freeing Hb into the circulation. Though it plays a vital role as a carrier of oxygen, Hb is highly toxic in its unbound, cell-free state. The effects of cell-free, unbound Hb observed in hemolytic anemia, malaria, and SCD include high blood pressure in the arteries of the lung, peripheral blood circulatory disorders, stroke, kidney damage and, in the cases of SCD and cerebral malaria, acute chest syndrome. For example, free, unbound Hb triggers hypertension by binding to nitric oxide in blood vessels, reducing its ability to dilate blood vessels and lower blood pressure. The deleterious side effects of some of the temporary artificial blood substitutes known as Hb-based oxygen carriers (HBOCs) studied to date are also due to the reactivity of cell-free, unbound Hb. These complications have thus far prevented full clinical development of investigational HBOC products, which to date have relied on modifying hemoglobin in an effort to avoid its toxic potential.

Potential Benefits of Reducing Free Hb in the Bloodstream

Reducing levels of cell-free, unbound Hb in the bloodstream could prevent or lessen the toxicity of this protein when it accumulates during hemolytic diseases. Controlling the toxicity of Hb might also contribute to the successful development of HBOCs, which could be used in emergency treatment of accident victims, wounded soldiers, and patients having a heart attack or undergoing surgery in cases when blood and blood products are unavailable or would be difficult to administer.

Study Using Haptoglobin to Sequester Hb Suggests a Common Approach to Hemolytic Anemia and Development of Safe and Effective HBOCs

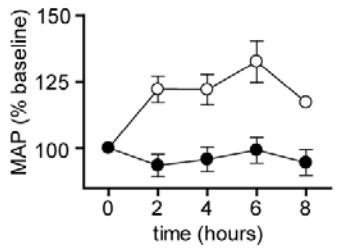


Haptoglobin levels were raised either by drugs (dog) or through exogenous administration (guinea pig).

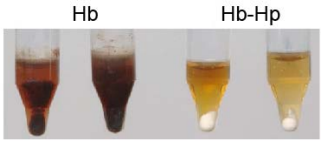
The plasma protein haptoglobin (Hp) is the primary Hb scavenger in the circulation. It irreversibly binds to cell-free, unbound Hb to form a stable complex that is subsequently removed from circulation. Prior research in mice on haptoglobin's ability to decrease Hb-mediated oxidative organ damage has been inadequate, since it is difficult to extrapolate data from the mouse models to humans or other animal species. Therefore, the current study by researchers from CBER (Office of Blood Research and Review) and University of Zurich evaluated the dog model in addition to the guinea pig to study the use of haptoglobin supplementation in countering the toxicities of free Hb.

Researchers activated the Hp gene in dogs by short-term prednisone (corticosteroid) treatment, creating artificially high levels of this Hb scavenger. These animals displayed normal systemic blood pressure and vascular resistance following continuous or escalating doses of free, unbound Hb.

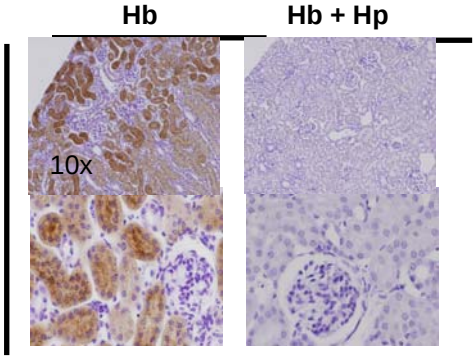
For the other major part of their study, the investigators co-infused purified human Hp and free, unbound Hb into guinea pigs to evaluate the ability of haptoglobin to neutralize it. They observed that Hp prevented Hb-induced systemic hypertension and tissue injury in this animal model.



Haptoglobin decreased hypertension in the dog (closed circles) compared to untreated dogs (open circles)



Urine from guinea pigs treated with free Hb (left pair of vials) is darker than urine from guinea pigs with Hb-haptoglobin complex (right pair of vials)



Kidney tissue damage in guinea pigs due to oxidative stress caused by Hb (left column) is reduced with addition of Hp (right column)

The data show for the first time that increasing haptoglobin levels contributes significantly to the prevention of complications associated with increased levels of free, unbound Hb in the circulation.

The findings also suggest that haptoglobin scavenging of Hb, rather than extensive modification of Hb, might be a simpler alternative strategy for developing safe and effective HBOCs.