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SPONTANEOUSLY ARISING DISEASE: REVIEW ARTICLE

The Pathology of Comparative Animal Models of Human Haemochromatosis

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Summary

Haemochromatosis is one of the most common human hereditary diseases. It is defined as a pathological condition with normal iron-driven erythropoiesis, but toxic accumulation of iron in vital organs, which is caused by mutations in any gene that encodes a protein involved in limiting the entry of iron into the blood. Iron storage diseases have also been described in several mammalian and avian species and these have been proposed as comparative animal models for human haemochromatosis. Genetically engineered mouse strains with mutations in iron metabolism genes model several aspects of human haemochromatosis and study of these animals has facilitated understanding of the disease. Spontaneously arising iron storage diseases in non-murine species also overlap in some clinicopathological aspects with human haemochromatosis. However, the lack of conclusive information on the molecular biology of theses species-specific diseases and the common impact of dietary iron concentration on disease progression in most species limit their usefulness as comparative models.

Keywords: haemochromatosis; hepcidin; iron storage; transferrin receptor

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Introduction

Iron is an essential trace element for the vertebrate organism. It is involved in many biological reactions mainly through its ability to accept or donate electrons and thus catalyze redox reactions. Its ion is part of the active site of several redox enzymes, which are involved in diverse biological functions including cellular respiration and oxygen transport. In physiology, iron ions are mostly incorporated into haeme groups, which consist of heterocyclic porphyrin and

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function as the prosthetic group of metalloproteins. In addition, a major part of the total content of iron in the body is bound to the iron transporter transferrin or stored as haemosiderin. The latter is an inert iron-storage complex, which is built of ferritin and denatured ferritin and is the result of locally increased iron concentration in the spleen and the bone marrow. An increased amount of haemosiderin in the body is referred to as haemosiderosis (Anderson *et al.*, 2007). Storage of free iron as haemosiderin therefore prevents the formation of free radicals and oxidative stress, with resulting cell damage, necrosis and eventually fibrosis.

Due to this ambivalent character and the lack of active mechanisms of iron excretion, there are redundant and highly-regulated central mechanisms of iron uptake, transfer and storage. Imbalances in these regulatory mechanisms of iron uptake and storage therefore lead to increased systemic iron concentrations and consequent pathophysiological changes in different organ systems. In man, hereditary haemochromatosis is the most common iron storage disease. It can be caused by diverse genetic alterations, involving genes, which are associated directly or indirectly with iron metabolism. These mutations trigger a variable clinical and pathological phenotype that may develop within an individual with normal physiological iron content (Table 1). Iron storage diseases with overlaps in the clinical and pathological phenotype have been described in several mammalian and avian species and have been suggested as comparative animal models of human haemochromatosis.

The first part of this review gives a short overview of the current knowledge on regulatory mechanisms of systemic iron homeostasis and the morphological and molecular features of human haemochromatosis. In the second section, naturally occurring and experimentally induced iron storage diseases in mice, Salers cattle, rhinoceroses, deer, birds, non-human primates and miscellaneous animals are described. The review will focus on the question of whether, and in what aspects, these animal diseases are acceptable models of human haemochromatosis.

Iron Metabolism: A Strictly-regulated System

Most of our knowledge of cellular and systemic iron metabolism has come from studies in man and mice and it can be assumed that not all of these molecular features can be transferred directly to other animals. However, as long as there are no studies of the characteristics of iron metabolism in other species it seems reasonable to hypothesize that the main mechanism may be similar (Fig. 1).

The total body iron concentration is mainly regulated by adjusting iron uptake from the gastrointestinal tract, since there are no active mechanisms of iron excretion except for menstruation. Diferric iron (Fe^{+2}) is actively taken up by the divalent metal ion transporter (DMT) 1 in the apical brush border of the enterocytes (Anderson, 2007). Depending on the systemic demand, this intra-enterocytic iron is either sequestered by ferritin lost by enterocyte sloughing into the gut lumen or it will cross the basolateral membrane via the action of the iron export protein ferroportin (FPN) 1 (Anderson *et al.*, 2009). After entry into the circulation the iron is bound immediately to transferrin. Transferrin-bound iron accounts for a minor but very relevant part of the total body iron. It is actively taken up by cells via the transferrin receptor (TfR) 1 as needed and thus connects the different iron compartments of the body: the erythrocytes, the macrophages of the reticuloendothelial system, the liver, the erythropoietic bone marrow and the haemoproteins in other cells. In addition to having a role as a transporter, saturation of transferrin iron binding is also the cardinal systemic signal of elevated total body iron content (Pietrangelo, 2004b).

The iron transport between these compartments is strictly regulated at the level of cellular iron uptake and release. Cellular iron uptake depends on the expression level of TfR1 on the surface of the cell, which in turn depends on the intracellular iron concentration (Huebers and Finch, 1987). In contrast, the influence of TfR2 on iron uptake is most probably restricted to hepatocytes, but it may also be involved in systemic iron metabolism by influencing hepcidin and signalling via the high Fe gene product (HFE) (Kawabata *et al.*, 1999). Of note, loss of TfR2 expression leads to severe hepatocyte iron overload in mice and man (Camaschella *et al.*, 2000; Fleming *et al.*, 2002). In contrast, iron release from the reticuloendothelial system and the liver is regulated systemically (Frazer and Anderson, 2003).

The release of iron from non-enterocytic cells is also mediated by the FPN1 membrane protein (Fig. 1). The amount of iron released is proportional to the amount of the constitutively-active FPN1 expressed on the cell membrane, which is in turn mainly regulated by hepcidin, the central protein in systemic regulation of iron release (Fig. 1) (Nicolas *et al.*, 2001). Hepcidin interacts directly with FPN1 on the cell surface and causes subsequent internalization and degradation of FPN1, thereby inhibiting iron release into the circulation (Nemeth *et al.*, 2004). Hepcidin is the product of the *HAMP* gene in hepatocytes and its expression is decreased in situations of systemic iron deficit and increased in situations of high systemic iron concentration (Pigeon *et al.*, 2001). These