Uptake and degradation of circulating proteins by the liver.
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Publication date: 1976

Citation for published version (APA):
Summary

Circulating proteins, like all proteins in a living animal, are subject to continual replacement or turnover. This process implies both synthesis and degradation. This thesis deals with the degradative part of turnover of circulating proteins.

Chapter 1 starts with a discussion of those factors (nutrition, certain hormones) which affect the rate of degradation of these proteins. From a survey of the literature it is concluded that the effects of these factors on degradation rates are not very specific (Section 1.1). In the second part of this chapter a number of physiological processes are discussed, such as the reactions of antibodies with antigens or those of alpha-macroglobulins with proteases, which have in common the formation of complexes, and result in a greatly enhanced rate of degradation of the specific proteins involved (Section 1.2). A majority of these complexes is selectively endocytosed by the liver where they are catabolized within lysosomes (Section 1.3).

Besides these physiologically important complexes, aggregates of denatured plasma proteins are known to be endocytosed and catabolized by the liver. In the first part of Chapter 2 the role of association and conformation is determining the uptake of these aggregates and other complexes is discussed (Section 2.1). In the second part of this chapter ex-
Experimental studies with modified forms of serum albumin are presented. These proteins are used to study the relation between structure and uptake from the circulation. The results show that neither aggregation nor gross conformational changes are prerequisites for the uptake of proteins. Local differences in surface structure of proteins may result in quite different circulatory survival times (Section 2.2). The chapter concludes with a discussion on the role of protein conformation in the uptake of normal circulating proteins (Section 2.3).

The liver, which plays an important role in the uptake of proteins and protein complexes from the blood, contains two main cell types: parenchymal cells or hepatocytes, and sinusoidal lining cells. Chapter 3 deals with these liver cell populations. Their respective roles in protein uptake are discussed in Section 3. Modified albumins, including a form which has retained the compact conformation of the native protein, are taken up by the sinusoidal cells and catabolized in their lysosomes (Section 3.2). The cell types of liver may differ in relative concentrations of lysosomal enzymes. Sinusoidal cells, which constitute only about five per cent of the liver volume, were found to contribute significantly to the total activity of the important lysosomal endopeptidase cathepsin D in liver (Section 3.3).

Since direct evidence for the involvement of lysosomes in the turnover of circulating proteins is difficult to obtain, an attempt was made to facilitate studies of this problem by blockage of intralysosomal proteolysis. Intravenously injected suramin, a trypanocide known to inhibit a number of enzymes, is shown to be taken up into lysosomes from both hepatocytes and sinusoidal liver cells. Its relatively high concentration in lysosomes of sinusoidal cells results in an ultrastructural appearance of these lysosomes resembling that seen in certain lysosomal storage diseases. After treatment of rats with suramin, accumulation of acid-precipitable radioactivity of injected $^{131}$I-labelled modified albumin was found in lysosomes of liver sinusoidal cells (Section 4.1). This offered the possibility to study involvement of these lysosomes in the turnover of an endogenous substance. Results of preliminary experiments using rat low-density lipoprotein suggest an involvement of hepatocyte lysosomes rather than lysosomes of sinusoidal cells in this process (Section 4.2).

The mechanism of action of suramin has been studied in some detail (Section 4.3). Experiments in vitro show that suramin is a potent inhibi-
In a study of endocytosis of particles (latex spherules) another effect of the drug was found: impairment of fusion between endosomes and lysosomes. Although this mechanism may contribute to the enhancement of accumulation in liver of endocytosed protein and lipoprotein after suamin treatment, inhibition of lysosomal enzymes is probably the main cause of the increased storage.