

subsequent degradation processes are not saturable under physiologic condition. Hence, the renal contribution to the overall elimination of peptides and proteins is reduced if the metabolic activity for these proteins is high in other body regions, and it becomes negligible in the presence of unspecific degradation throughout the body. In contrast to this, the contribution to total clearance approaches 100 % if the metabolic activity is low in other tissues or if distribution is limited (Meibohm, 2006).

A part from general proteolysis and the kidneys, the liver substantially contributes to the metabolism of peptide and protein drugs. Proteolytic degradation usually starts with endopeptidases that attack in the middle part of the protein, and the resulting oligopeptides are then further degraded by exopeptidases. The ultimate metabolites of proteins, amino acids, and dipeptides, are finally utilized in the endogenous amino acids pool (Meibohm, 2006; Crommelin et al., 2008).

The rate of hepatic metabolism is largely dependent on the specific amino acids sequences in the protein. As proteolytic enzymes in the hepatocytes are mainly responsible for the catabolism of proteins in the liver, intracellular uptake of proteins into hepatocytes is a prerequisite for hepatic protein metabolism. While small peptides may cross the hepatocytes membrane via passive diffusion if they have sufficient hydrophobicity, various carrier-mediated energy dependent membrane transporters and receptor-mediated endocytosis are usually responsible for the uptake of larger peptides and proteins (Freeman & Kim, 1978).