Biotransformation of peptide drugs

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Like small molecule drugs, peptide drugs also undergo biotransformation, but in different pathways. While for small molecule drugs, biotransformation is mainly mediated by cytochrome P450 (CYP) and various phase II enzymes like glucuronosyl or sulfo transferases, the most important biotransformation mechanism of peptide drugs is cleavage of the peptide bonds between amino acids by serum and tissue proteases. These biotransformation reactions are complemented by oxidative metabolism of peptide drugs similar to small molecules. While the liver plays a dominant role in small molecule biotransformation, the kidney is the major site for the metabolism of peptides. Typically, peptides suffer from short half-lives due to rapid renal clearance and low oral bioavailability and therefore, they have to be injected parenterally, chemically modified to enhance their stability or delivered using special formulations.
Understanding the biotransformation of peptide drugs is crucial for pharmaceutical development as this may have a significant impact on drug efficacy and safety. The study of peptide biotransformation is rather challenging and requires sophisticated analytical techniques including mass spectrometry based approaches.

Key words: peptide biotransformation, enzymes and proteases, mass spectrometry, software-aided metabolite identification