Development of Prodrug Chemistry Suitable for Application to Therapeutic Peptides

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Bioactive peptides constitute a rich source of new drug candidates. They typically display unique pharmacology, appreciable potency and molecular specificity. The most notable limitations are the parenteral nature of most peptide-based drugs and their relatively short duration of action, as a function of susceptibility to protease degradation and rapid renal clearance. Employment of prodrug chemistry is an attractive approach to minimize the undesirable pharmaceutical properties. While medicinal prodrug chemistry is a well developed field its application has been largely directed at conventional small molecule drugs and approaches to enhancing oral bioavailability. Our work focuses on the development of prodrug chemistry suitable for peptides and proteins with a specific emphasis on pharmacokinetics. A prodrug method divorced from secondary elements such as protease-cleavage is deemed most desirable as a means to maximize reproducible inter- and intra-patient pharmacology. We describe here the use of a prodrug strategy to reversibly inactive peptide hormones at active site amines through site specific formation of reversible amides. The peptide synthesis of such prodrugs is suitable to conventional solid-phase chemical methodology. A set of model peptides were synthesized and their intramolecular degradation to the parent peptide was studied by HPLC and MS methods under physiological conditions. The speed of reaction was observed to be a function of intramolecular chemical cyclization which is controlled by structure of a terminal dipeptide. The observed results with model peptides provide a basis for application to bioactive peptides to study the rate of cleavage in biologically relevant solvents such as plasma in *ex vivo* and *in vivo* settings.