

New technologies to prolong life-time of peptide and protein drugs in vivo

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Most peptide and protein drugs are short-lived species in vivo with a circulatory half-life of several minutes. This is particularly valid for non-glycosylated proteins with a molecular mass of less than 50 kDa. Since peptide/protein drugs are not absorbed orally, prolonged maintenance of therapeutically active drugs in the circulatory system is of primary clinical importance. Another major obstacle of injected polypeptide drugs is the elevated concentration of 100–1000 times above the therapeutical level that may be present in the circulatory system shortly after administration. Such overdosing may lead to undesirable side effects such as over-stimulation or down-regulation of receptor sites.

In this review we describe two new strategies that overcome these two problems of systemically injected peptide/protein drugs. The first strategy includes Fmoc and FMS derivatization of peptides, proteins and low molecular-weight drugs, converting them to inactive prodrugs that undergo reactivation with desirable pharmacokinetic patterns in body fluids. Based on this Fmoc/FMS-technology, we have developed a second strategy, reversible pegylation. Inactive pegylated peptide/protein drugs release the native active parental molecules at slow rates, and in homogeneous fashion under physiological conditions, thus facilitating prolonged therapeutic effects, following a single administration.

Selected publications

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Acknowledgements

Y.S is the incumbent of C.H. Hollenberg Chair in Metabolic and Diabetes Research established by the friends and associates of Dr. C.H. Hollenberg of Toronto, Canada.

International support

These studies are supported by the Kimmelman and Horowitz Foundations; by "Therapy"; Baxter, and J and J research grants.

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