Abstract

Insulin/IGF system is a complex network of three similar hormones (insulin, IGF-1 and IGF-2) and their three similar receptors (IR-A, IR-B and IGF-1R,), which play important roles in maintaining basal energy homeostasis of the organism, in growth, development, life-span but also in development of diseases such as diabetes mellitus, cancer, acromegaly or Laron dwarfism. Despite structural similarities between family members, each member have its unique role in the system. Identification of structural determinants in insulin and IGFs that trigger their specific signalling pathways is important for rational drug design for safer treatment of diabetes or for more efficient combating of cancer or growth-related disorders. In this thesis, we focused on identification of such structural determinants in IGF-1. Comparison of our data with parallel studies with IGF-2 and insulin could give a more complex picture of the problem.

First of all, we developed necessary methodologies for the preparation of IGF-1 analogues. We developed a new methodology for the total chemical synthesis of IGF-1 analogues based on the solid-phase synthesis of fragments and their ligation by a Cu^{I}-catalyzed cycloaddition of azides and alkynes. In parallel, we developed a procedure for a recombinant production of IGF-1 and its analogues in *E. coli*.

Next, to gain an insight into the structural basis of IGF-1 binding specificity for IGF-1R, IR-A and IR-B, especially in comparison with insulin and IGF-2, we generated a series of mutants with specific amino acid substitutions at the positions 49, 45 and 46 of the B domain of IGF-1. In another study, we modified a pair of arginine residues at the positions 36 and 37 of the C domain of IGF-1. For all analogues we tested binding affinities of analogues for the selected receptors and abilities of analogues to activate these receptors.

Our data provided new insights into importance of the studied amino acids in IGF-1 for interaction with receptors for IGF-1 and insulin and may be useful for further rational engineering of new hormone analogues for potential medical applications.