Abstract

Insulin receptor (IR) exists in two isoforms (IR-A and IR-B), which differ in the tissue distribution and probably also in their function, i.e. in their response to insulin binding. It is supposed that IR-A activates mainly mitogenic processes and that IR-B triggers mainly metabolic effects resulting in the uptake of glucose by muscle and fat cells. Insulin can also weakly bind to the receptor for IGF-1 (IGF-1R), a growth factor involved in the regulation of growth and development. Insulin derivatives selectively binding only to one of the receptors would be interesting for the study of the receptors but also potentially for the treatment of diseases such as diabetes or cancer. Here we used our experience in the structure-activity studies of insulin for the design, synthesis and biological characterization of 4 new insulin derivatives in order to modify their selectivity towards the individual receptors. We systematically modified insulin by amidation of the C-terminus of its B-chain or by prolongation of the B-chain by 1-3 carboxyamidated glycine residues. Binding affinities of all new analogues for IR-A and IR-B were determined and for some of the analogues binding affinities for IGF-1R as well. Finally, abilities of analogues to activate autophosphorylation of intracellular subunits of IR-A and IR-B were determined. The study provided new information about the role of prolongation of the B-chain on the receptor binding specificity of resulting analogues. Insulin analogue with Gly-NH_2 at the position B31 of insulin had more than 3-times higher binding specificity for IR-B than for IR-A. Information obtained in this study could be useful for a development of new insulin analogues useful for treatment of diabetes.