Abstract

Insulin receptor is a multi-domain signalling protein acting as a dimer. It comprises an extracellular ectodomain, a transmembrane domain and intracellular tyrosine kinase domain. Upon insulin binding, conformational changes in insulin as well as in insulin receptor occur and trigger the signaling cascade via the kinase domain.

Abnormalities in insulin and insulin receptor function cause *diabetes mellitus*, a widespread disorder which can be consequence of genetic factors as well as lifestyle and is manifested by increased level of blood glucose. A common treatment of *diabetes mellitus* is via insulin analogues with different molecular properties.

Insulin/insulin receptor interactions in the binding pocket are divided into two groups, so-called "site1" and "site2". The molecular details of the interactions in site1 are well known, while site2 residues are still not completely elucidated. It is important to shed light on the binding properties of insulin and insulin receptor, especially site2 interactions, because it could contribute to improved design of new insulin analogues. In this work, we used the very recent breakthroughs in the structural biology of insulin receptor to study the interactions by computational chemistry methods. It was thus possible to assess the noncovalent interactions and conformational changes in this system relevant to *diabetes mellitus* treatment. Especially, we observed that mutations of insulin residues, which are suggested as part of site2, can affect maintaining of the conformation necessary for binding to insulin receptor.

Keywords: insulin, insulin receptor, binding, diabetes, molecular modelling, molecular dynamics, molecular docking