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A theoretical investigation on the geometries of glucagon-like peptide-1 and its interactions with dipeptidyl peptidase DPP-IV

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Glucagon-like peptide-1 (GLP-1) is an interesting candidate for pharmaceutical use in cases of diabetes mellitus type 1 and 2 since it controls the early insulin response to nutrient ingestion of glucose. Unfortunately, GLP-1 imposes a very short half life of only a few minutes in vivo due to degradation by dipeptidyl peptidase DPP-IV. Several studies have been carried out to modify the sequence of GLP-1 in order to prevent degradation while conserving its valuable function. In contrast, CellMed AG investigated in vivo degradation of different GLP-1 analogues that are C-terminally elongated by different amino acid sequences. Some of them showed significantly reduced degradation while conserving the GLP-1 function, but dependence on peptide length and sequence remained unsolved.

In order to unravel the conformational features leading to the experimental observations, GLP-1 and three of its artificially extended analogues have been investigated using molecular dynamics (MD) simulations, molecular modeling, and docking. A realistic structure of the active GLP-1 – DPP-IV complex was modeled using the docking program PLANTS [1] to approach the geometries at the binding interface. To date it is the first modeled structure of this complex. Here, the large side opening was identified as the dynamical path used by GLP-1 to approach the binding site. Subsequently, the atom positions at the interface were refined using the software packages MOLCAD, MolArch, and SYBYL.

The MD simulations revealed that distant charged residues can form temporary salt-bridges leading to a strong bending of the peptide. For the elongated GLP-1 analogues it has been shown that existence of charged residues increased the possibility to form temporary coils that may prevent the GLP-1 analogues from entering the DPP-IV opening. Thereby, the residues mediating the peptide's function remained unburied.

The results of the theoretical studies by MOLCAD could be confirmed in further in vitro studies and may lead to a new class of C-terminally elongated GLP-1 analogues.

References

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