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Research Article

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DPP-IV Structural similarities in rat and human

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ABSTRACT

The dipeptidyl peptidase-4 DPP-IV is the major receptor of the new oral treatments for diabetes type II. This work determined the structural similarities of the protein DDP-IV of the rat and the human through the global alignment in three dimensions and the aminoacidic sequence. The parameters of structural difference of identity between two proteins 0.751 RMSD and high percent identity 83.56% does not localize in the active site of the enzyme, concluded that activity in both species are similar. The important results are useful in the area preclinical, clinical and developments of drugs that focus in the treatment of diabetes type II.

Keywords: in silico; structural similarities; DDP-IV; Diabetes type II; Rat.

INTRODUCTION

The three-dimensional structure of the DPP-IV from the rat, Rattus Novergicus [1] the native human obtained in 2007 [2] shows structurally that both possess a similar domain in its native shape, as is expected to happen when a model organism is used for studies of pharmacological importance. Its similarity is due to an evolutionary conservation in both mammals [3]. There are structural differences in both proteins which, when being away from the potential active site, support the hypothesis that the pharmacophoric domain is similar. The pharmacological effect attributed in a preclinical stage in a rat can be equivalent in a clinical stage in humans.

Currently there are animal models used in the study of type II diabetes, such as the case of Zucker diabetic fatty (ZDF) [4]. Although the ZDF model has two modified genes, there is no evidence that these genes affect the protein conformation of the enzyme DPP-IV [5].

Many drugs have been evaluated in rat on its effect on the enzyme DPP-IV, and sustained human studies [6][7], so that a structural analysis of the similarities in the domain are of relevant importance in the study of the DPP-IV in rat and human.

EXPERIMENTAL SECTION

Through Protein Data Bank obtained the sequences and structures of the 2ONC.PDB for human and the 2GB.PDB of the rat. The sequences alignment performed by the algorithm Needleman-Wunsch [8] as implemented in the Chimera UCSF v1.9. [9]. At a global alignment, the Needleman-Wunsch algorithm used with an assigned BLOSUM-62 value, 30% of the second structure weighting and the remaining weight attributed to the residue similarities.

The gap space assigned by a penalization of 01, 2 Amstrongs as the limit value for the distance among atoms and 5 Amstrongs as a limit for main residue atoms not equally aligned or above the aforementioned value.

The mean root square (RMSD) was used as the deviation criteria at the superposition. The previous value was also obtained by the Chimera UCSF v.1.9 in which, each folding site was analyzed as a deviation; sequence analyses was performed only at the chain B of the corresponding protein. RMSD not analyzed Chain A, as the main goal of the research was to study the prospectus active site, located at chain B.

In both chains of the selected sequences A and B for human and rat performed sequence alignment. Whether the protein structure and function are highly similar, proteins with structure similarities are likely to possess similar functions. The method that pretends to fix two structures according to the RMSD used the 3-dimension alignment at Chimera UCSF Chimera.

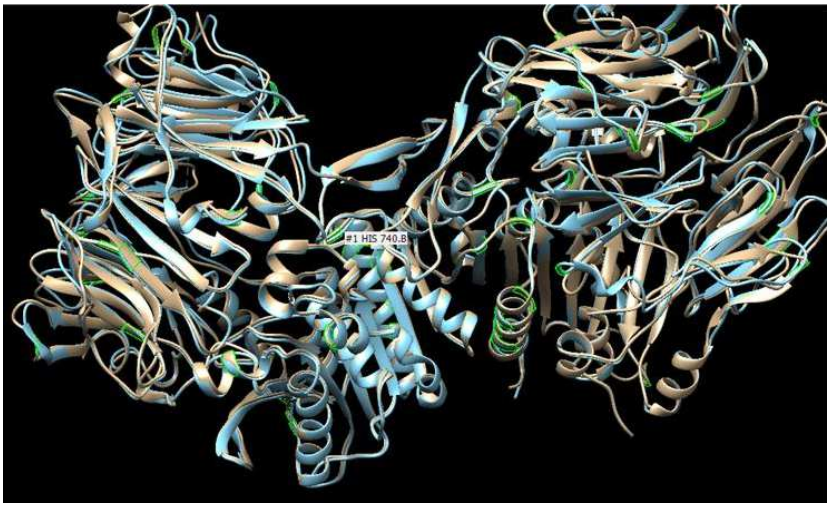
RESULTS AND DISCUSSION

Table 1 Structural comparison between 2ONC.PDB and 2GBC.PDB (chain b)

Calculation	value
RMSD	0,751
Sequence lengths	728730
SDM (cutoff 5,0)	14.972
% identity	83,56

Table 1 shows the results of aligning the sequences of rat and human native, likewise, in Figure 2 show the sequence in their primary structure in alignment. The superimposed structures obtained and aligned in three dimensions; Figure 1 shows one of the potential active site amino acid present in both structures.

Figure-1: Histidine 740/741 amino acid present in both superimposed structures

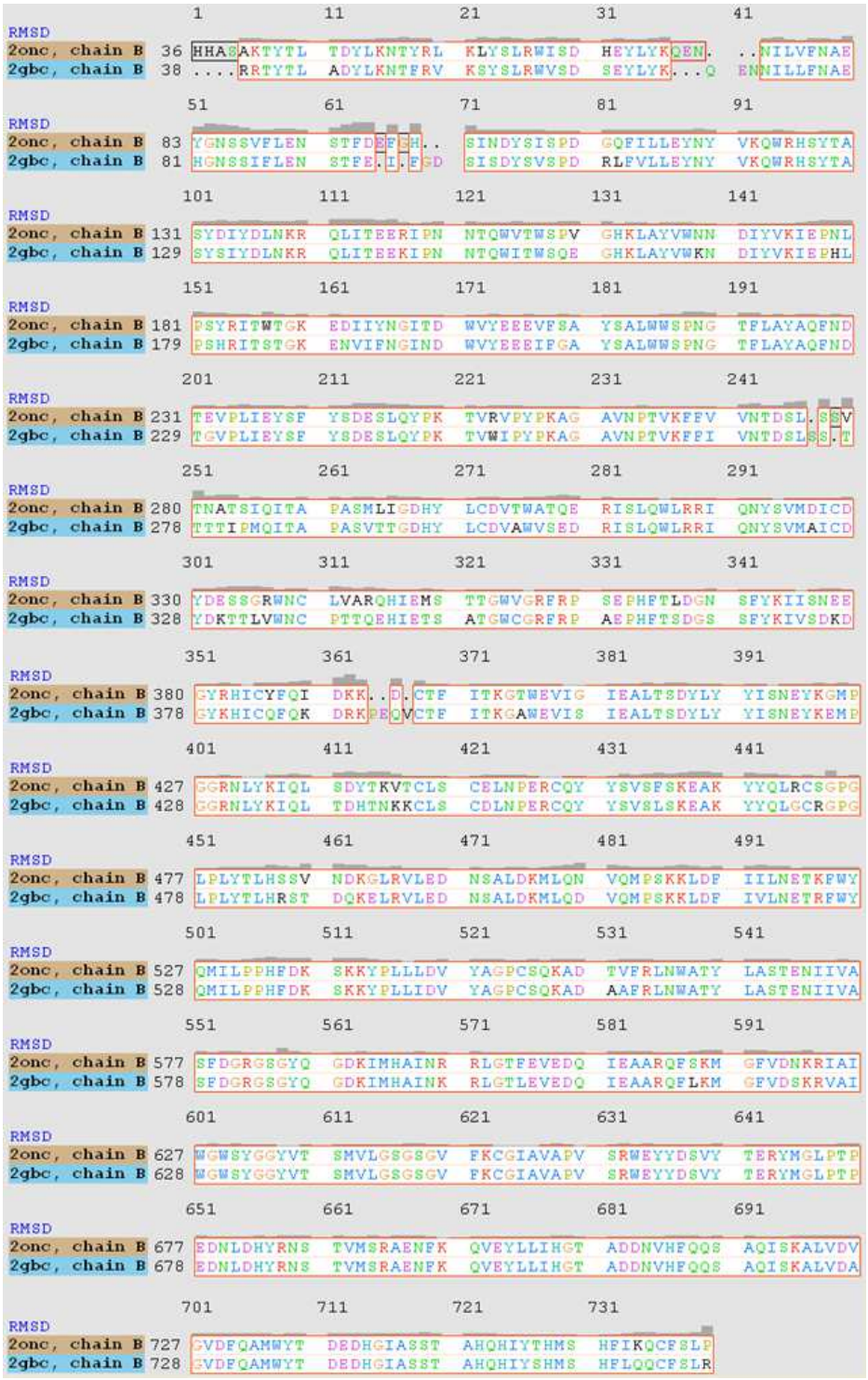


The percentage of identity of chain B of both structures showed considerable disparities at a structure level, close to 17% different among them, however, aminoacids located at the prospectus active site of the DPP-IV S630 and the most important aminoacids located at H740 [10][11] are aligned as showed in Figure 1. Deviation between both structures is negligible (0.886) and aminoacids His740, Ser630 and Tyr547 are placed identically in both proteins.

Aminoacids alignment of both sequences is showed in Figure 2, where the similarity is the highest, however, regardless alignment may be seen in most of them, there´re some aminoacidic differences, which explains the difference in the percentage of identity, as well as the 3-dimension deviation. This is possibly because both proteins has been highly conserved at a point the active site has remained closely intact. The RMSD computed in Table 1 has been coupled to changes of the aminoacids located throughout the structure, however as the aforementioned residues are likely to be similar in the prospective active site, their 3-dimension conformation is identical. Thus a ligand would show an identical pharmacodynamics behavior among both in rat as in human in its native structure. similar results were obtained in previous studies made in animal models (e.g. rats) for the evaluation of inhibitors of DPP-IV where the results in animals were considerably different as the obtained in humans [11][12][13].

Thus, inferring the current changes are not due to the differences at the receptor site but due to other enzymes related with the pharmacological metabolism pathway.

Figure-2: Aminoacidic Sequences of chain B of 2ONC.PDB and 2GBC.PDB



CONCLUSION

The results of the compared 3D structure, Rattus Novergicus 2GBC.PDB and human Native structure 2ONC.PDB, show that both enzymes are identical in the potential active site and the differences are located in the aminoacids on peripheral sites. For this reason the mutations do not modified the response of active site facing a ligand, and the activities of both species must be identical.

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