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Self-organizing Maps - the Heuristic Approach for Understanding Ligand-protein Interactions in Vitamin D Receptor.

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Short Abstract: Since ligand-docking is more dynamic process than crystallography can monitor, we analyzed the action of different agonists using molecular-dynamics simulations, self-organizing maps and in-vitro assays. The combined movement of 40 residues results in the ligand-binding pocket modulation and may serve as an important parameter in smart drug design.

Long Abstract:

INTRODUCTION. Existing crystal structure data has indicated that 1a,25- dihydroxyvitamin D3 (1a,25(OH)2D3) and its analogues bind the ligand-binding pocket (LBP) of the human vitamin D receptor (VDR) in a very similar fashion. Since docking of a ligand into the LBP is a more flexible process than crystallography can monitor, we analyzed 1a,25(OH)2D3, its 20-epi derivative MC1288, the two-side-chain analogues Gemini and Ro43-83582 (a hexafluoro-derivative) by molecular dynamics simulations in a complex with the VDR ligand-binding domain and a co-activator peptide.

METHODS. To group the amino acids forming the LBP of VDR with similar movement patterns we used a data-mining clustering algorithm of self-organizing maps (SOMs). SOMs is an artificial neural network algorithm in the unsupervised learning category which is useful in the visualization and interpretation of large high-dimensional data sets. A map consists of a regular grid of processing units, "neurons". A model of some multidimensional observation is first made, eventually a vector consisting of features, is associated with each unit. The map attempts to represent all the available observations with optimal accuracy using a restricted set of models. At the same time the models become ordered on the grid so that similar models move closer to each other and dissimilar models further from each other. In this study a version of the Visual Data software (Visipoint Oy), whose core is based on a variation of a self-organizing maps, called a tree-structured SOMs, was used. The software implementation consists of several SOMs that are organized hierarchically in an inverted pyramid-like fashion in several layers. The number of neurons at a higher level is four times greater than the number found in the previous level.

RESULTS. The data to which the SOMs was applied to consisted of a set with five variables, where to each single amino acid related 5 values representing a distance for 5 different ligands or conformations (MC1288, Gemini I and II, Ro43-83582 I and II) are assigned. All these values were used as the training pattern. At the beginning, each neuron of the SOM was randomly assigned a weight vector with five variables with a maximal starting resolution of 1024. The weight vectors of the best matching neuron and its neighbors are moved towards the values of the input vectors such that neurons come to represent a group of amino acids with similar dynamics. While the training proceeds, the adjustment of the weight vectors is diminished. Finally, each amino acid is placed into a neuron, which best describes its dynamic pattern and the value of the difference is displayed on each neuron as a bar

graph. The resulting map with a matrix resolution 16x16 was then changed to 4x4 to exclude empty clusters from the matrix. Later a Sammon's mapping algorithm was applied to the matrix to visualize the clustered groups in 2D-space. Next we were investigating the change of the volume of the ligand-binding pocket for different ligands and their conformations. Compared to the LBP of the natural hormone MC1288 reduced the volume by 17 % and Ro43-83582 expanded it by 19 %. The shrinking of the LBP of MC1288 as well as its expansion to accommodate the second side chain of Gemini or Ro43-83582 is the combined result of minor movements of more than 30 residues and major movements of a few critical amino acids. The agonist-selective recognition of anchoring OH-groups by the conformational flexible residues A303, L309 and H397 was confirmed by in vitro assays.

SUMMARY. In summary, variations in the volume of agonists lead to adaptations in the volume of the LBP and alternative contacts of anchoring hydroxyl-groups. The dynamic process of the LBP's selective modulation by different agonists may be of valuable information in judging the potential of the agonists' actions. This founding can be extended also to other nuclear receptors serving as an important parameter in the design of novel drugs.