608/E2

Molecular Simulation Study on the Conformational Changes of Glucocorticoid Receptor DNA - Binding Domain in Complex with DNA

Kalani Kaushalya Jayanetti and Samantha Weerasinghe*

Department of Chemistry, University of Colombo, Colombo 03.

Deoxyribonucleic acid (DNA) and proteins play a significant role in the formation and functioning of biological systems. Some proteins, called transcription factors (TF), bind to DNA and control the rate of transcription of genetic information, by binding to a specific DNA sequence. The glucocorticoid receptor (GR) is one such widely studied TF due to mediating numerous physiological and pharmacological actions on primary stress hormone glucocorticoids. To study the structure of the GR, Rat (*Rattus norvegicus*) GRs are widely used, which consists of two protein chains/DNA binding domains (DBDs) which show conformational changes on binding to DNA. These changes could help in the very important task of understanding the structural and dynamical changes of its structures upon binding. The present study was carried out to investigate the effect of complex forming of DNA and DBDs of the GR on its structure, in comparison to that of their free monomeric states. A series of molecular dynamics simulations were carried out using the GROMACS software, AMBER03 force field for each monomeric structure (two DBDs and DNA) and for the complex (bounded structure of DBDs with DNA); then the structures were compared using different structural and dynamical parameters in terms of root mean squared deviation (RMSD), radius of gyration (RoG), solvent accessible surface area (SASA), and number of hydrogen bonds (NoH). It was observed that there were structural alterations of DBDs and DNA on binding together as a result of gained stability upon binding. However, DNA showed little structural variation between its free monomeric form and complex form, which revealed less effect on the stability of the GR. The reason for this small variation could be the increased number of interactions between DNA and DBDs of the GR. Hence, it could be accepted that the conformational changes of DNA were very little between its two forms, because it attempted to stabilize in both conformations. However, larger structural alterations of the two DBDs of the GR were observed upon binding to DNA. Also, among the two DBDs, one DBD exhibited larger conformational changes on binding to DNA, which led to opening up the structure in complex form, while the other exhibited a folding nature upon binding. However, interestingly, both DBDs showed stabilization of their structures on binding together than in their free monomeric forms.

E-mail: weera@chem.cmb.ac.lk