Ligand Unbinding from the Estrogen Receptor;  
A theoretical study of molecular mechanics and specificity

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The Estrogen Receptor (ER) belongs to the large group of transcription factors called Nuclear Receptors, which regulate several important cellular events. Abundant human diseases like Schizophrenia, Parkinson’s and breast cancer can be related to ER signaling, and make ER an important drug target to which biological activity and biochemical properties have been thoroughly investigated. The ER receptor constitutes of 6 structural domains, where one form the important ligand binding domain (LBD). Upon ligand binding the LBD performs a conformational change, and adapts a biologically active form. The active form of ER can further more recruit coactivators and start transcription of the target gene. Although structural data of the ER in both active and inactive form has been solved, the actual mechanism of ligand unbinding remains elusive. Experimental data show that ligand binding occur with different rates for an agonist and antagonist. Further more, mutational studies of ER reveal that certain mutations affect the agonist association time, while the antagonists remain unaffected. The experimental results indicate that ER ligands have different binding mechanism. To gain insight into this mechanism we have examined the ligand unbinding from the ER subtype α and β, both with different ligands bound and in the context of cofactors with a Molecular Dynamics method. The results obtained show that different ER agonists can unbind the receptor without causing any major conformational changes, while the antagonist can not. Further more, the unbinding showed little effect of the presence of a bound cofactor peptide. Different ER subtypes also show different ligand unbinding pathways for the same agonist, which might explain the observed selectivity between receptor subtypes. Our results verify the experimental data and explain the mechanism of ligand unbinding on a molecular level. The results also gain insight in specificity between the receptor subtypes, an important issue for drug design to ER.