Disruption of a Key H-bond Network Dissociates Glucocorticoid Receptor-Mediated Drug Efficacy from Side Effects for Anti- Inflammation Treatment

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Corticosteroids are commonly used drugs that reduce inflammation by binding to the glucocorticoid receptor (GR) and repressing the proinflammatory genes. However, GR can meanwhile activate many metabolic genes that lead to undesirable side effects. Develop selective corticosteroids that separate drug efficacy from side effects is challenging and requires mechanistic understanding of the drug action on GR. Vamorolone is a recently developed drug that decreases inflammation and reduces side effects observed in other corticosteroid-based treatments. Our structure studies reveal a crucial GR-ligand hydrogen bond is not possible in vamorolone. We identified an unprecedented allosteric intramolecular network derived from this hydrogen bond modulates GR dynamic motions and coregulator binding using atomistic molecular dynamics simulation. Hydrogen deuterium exchange mass spectrometry-derived dynamics data showed that GR has enhanced protein motions after vamorolone binding, leading to the dissociation of coactivator and decreased transcriptional activation. Our integrated structural and biophysical results provide insights into how subtle modifications on a drug exploits structural and dynamic properties in the receptor to dissociate downstream side effects from therapeutic benefits and provide the framework of future development of selective glucocorticoids.