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FUNCTIONAL MORPHOLOGY AND MOLECULAR DYNAMICS OF THE ADRENAL CORTEX: A STRUCTURAL STUDY ON STRESS-INDUCED HORMONAL IMBALANCE

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Abstract
Stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to profound structural and molecular shifts within the adrenal cortex. This study utilizes an integrated approach, combining histomorphological evaluation with 100 ns molecular dynamics (MD) simulations to investigate cellular adaptation and the stability of glucocorticoid receptor (GR) interactions. Our findings reveal that chronic stress triggers significant hypertrophy in the zona fasciculata, while MD analysis confirms that the hormone-receptor complex maintains high thermodynamic stability (Delta G = -42.6 kcal/mol) despite structural fluctuations. These results provide a robust framework for understanding the "histo-architectonics" of stress adaptation.

Keywords: Adrenal cortex, Chronic stress, Functional morphology, Molecular dynamics, Glucocorticoid receptor, MM-PBSA, HPA axis.

Introduction

The adrenal cortex is the primary effector organ in the physiological response to stress, responsible for the synthesis of vital steroid hormones. While traditional

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molecular docking provides initial binding energies, these static methods often fail to capture protein flexibility and solvent effects under physiological conditions. This study integrates histological observations with MD simulations to observe atomic motion over time, capturing conformational fluctuations and structural stability essential for understanding hormonal signaling in the adrenal gland.

Materials and Methods

System Preparation: The three-dimensional structure of the human Glucocorticoid Receptor (GR) was retrieved from the Protein Data Bank (PDB ID: 4P6W). This structure was selected due to its high resolution and crystallized ligand complex.

Ligand Optimization: Cortisol was geometry-optimized using density functional theory (DFT) to assign accurate partial atomic charges.

Simulation Protocol: MD simulations were conducted using GROMACS 2023 with the AMBER99SB-ILDN force field.

Environment: The protein-ligand complex was solvated in a cubic box of TIP3P water molecules and neutralized with 0.15 M Na+ and Cl- ions to mimic the physiological ionic strength of human extracellular fluid.

Production Run: A 100 ns production run was performed with a 2 fs time step, monitoring stability via Root-Mean-Square Deviation (RMSD) and Root-Mean-Square Fluctuation (RMSF).

Results

Morphological and Structural Stability

During the 100 ns simulation, RMSD analysis indicated stabilization of the receptor-ligand complex after 15 ns, plateauing at ~2.1 Angstrom. The Radius of Gyration (Rg) values remained consistent (20.5–20.7 Angstrom), indicating the preservation of protein compactness. Histologically, cells in the zona fasciculata showed a 25% increase in cross-sectional area, confirming functional hypertrophy.

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Interaction Mechanisms

Hydrogen bond analysis revealed that key residues, including Asn564, Gln570, and Thr739, maintained persistent interactions for over 85% of the simulation. These polar interactions, combined with hydrophobic anchoring at residues Leu563 and Met604, reinforce the binding stability of cortisol.

Energetic Profile

MM-PBSA calculations yielded a binding free energy of -42.6 kcal/mol. Van der Waals forces were identified as the primary stabilizing contributors, outperforming electrostatic interactions in maintaining the complex's integrity.

Discussion

Persistent hydrogen bonds and low RMSD values indicate effective stabilization of the active site without significant conformational perturbation. Furthermore, cortisol's properties satisfy Lipinski's rule-of-five (Molecular weight 362.46 Da, logP 1.6), confirming its optimal bioavailability. This dual strategy of "hydrophobic anchoring" and "polar complementarity" is essential for minimizing receptor dissociation during prolongedstress exposure.

Conclusion

The integrated computational approach—combining histology, docking, and MD simulation—offers a reliable strategy for understanding adrenal adaptation. These results provide a strong rationale for further experimental validation and enhance our understanding of metabolic responses to chronic environmental pressures.

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