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Binding Mechanism of Synthesized 5β-Dihydrocortisol and 5β-Dihydrocortisol Acetate with Human Serum Albumin to Understand Their Role in Breast Cancer

Authors : Monika Kallubai, Shreya Dubey, Rajagopal Subramanyam

Abstract : Our study is all about the biological interactions of synthesized 5β-dihydrocortisol (Dhc) and 5β-dihydrocortisol acetate (DhcA) molecules with carrier protein Human Serum Albumin (HSA). The cytotoxic study was performed on breast cancer cell line (MCF-7) normal human embryonic kidney cell line (HEK293), the IC50 values for MCF-7 cells were 28 and 25 µM, respectively, whereas no toxicity in terms of cell viability was observed with HEK293 cell line. The further experiment proved that Dhc and DhcA induced 35.6% and 37.7% early apoptotic cells and 2.5%, 2.9% late apoptotic cells respectively. Morphological observation of cell death through TUNEL assay revealed that Dhc and DhcA induced apoptosis in MCF-7 cells. The complexes of HSA–Dhc and HSA–DhcA were observed as static quenching, and the binding constants (K) was 4.7±0.03×104 M-1 and 3.9±0.05×104 M-1, and their binding free energies were found to be -6.4 and -6.16 kcal/mol, respectively. The displacement studies confirmed that lidocaine 1.4±0.05×104 M-1 replaced Dhc, and phenylbutazone 1.5±0.05×104 M-1 replaced by DhcA, which explains domain I and domain II are the binding sites for Dhc and DhcA. Further, CD results revealed that the secondary structure of HSA was altered in the presence of Dhc and DhcA. Furthermore, the atomic force microscopy and transmission electron microscopy showed that the dimensions like height and molecular sizes of the HSA–Dhc and HSA–DhcA complex were larger compared to HSA alone. Detailed analysis through molecular dynamics simulations also supported the greater stability of HSA–Dhc and HSA–DhcA complexes, and root-mean-square-fluctuation interpreted the binding site of Dhc as domain IB and domain IIA for DhcA. This information is valuable for the further development of steroid derivatives with improved pharmacological significance as novel anti-cancer drugs.

Keywords : apoptosis, dihydrocortisol, fluorescence quenching, protein conformations
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