The Crystal Structure of Murine 11β-hydroxysteroid Dehydrogenase 1: an Important Therapeutic Target for Diabetes

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11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyzes the conversion of 11-dehydrocorticosterone to its active form corticosterone in rodents (or cortisone to cortisol in humans). An excess of active glucocorticoids has been shown to play a key role in metabolic disorders such as diabetes and obesity. Therefore, 11β-HSD1 represents an important therapeutic target for the treatment of these diseases. To facilitate the iterative design of inhibitors, we have crystallized and determined the three-dimensional structures of a binary complex of murine 11β-HSD1 with NADP(H) to a resolution of 2.3 Å, and a ternary complex with corticosterone and NADP(H) to a resolution of 3.0 Å by X-ray crystallography. The enzyme forms a homodimer in the crystal. The structure shows a novel folding feature at the C-terminus of the enzyme. The C-terminal helix insertions provide additional dimer contacts, exert an influence on the conformations of the substrate binding loops, and present hydrophobic regions for potential membrane attachment. The structure also reveals how the 11β-HSD1 achieves its selectivity for its substrate.

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