

Experiment title	Crystal structure of the human mineralocorticoid receptor ligand-binding domain
Experiment number	30-01-586
Date of experiment	20 - 22 April 2003

The mineralocorticoid hormone aldosterone plays an important role in sodium homeostasis and in the regulation of blood pressure. Alterations of this regulation are associated with several pathologies (hypertension, cardiovascular diseases, heart failure). Aldosterone produces its effects through the mineralocorticoid receptor (MR) which is a ligand-activated transcription factor. Aldosterone antagonists bind to MR with the same affinity as aldosterone but maintain the receptor in an inactive conformation (1). Aldosterone and its antagonists bind to the ligand-binding domain (LBD), located at the C-terminal part of the receptor. In the context of this project, we investigated first the structural study of the complex deoxycorticosterone, a potent mineralocorticoid agonist and the complex hMR_{LBD} that carries two point mutations able to enhance the protein solubility.

Crystallization assays for the hMR_{LBD} resulted in reproducible hexagonal crystals of about 300 μ . The protein crystallizes in the P3 space group with cell parameters $a = b = 120.84$ Å, $c = 44.69$, $\alpha = \beta = 90$, $\gamma = 120$ °, with two molecules in the asymmetric unit. During the 30-01-586 experiment, a complete native data set has been collected to 3.0 Å resolution (oscillation range 1°, 60 sec exposition). The statistics of the data collection are summarized in Table I.

Resolution (Å)	2.5
wavelength (Å)	0.979757
No. of observations	129248
No. of unique reflections	24773
R _{sym} (%)	16.6 (59.1)
Multiplicity	5.2 (2.0)
Completeness (%)	98.4 (90.8)
I / σ (I)	3.3 (1.2)

Table I. Statistics of data collection. The values in parenthesis are for the highest resolution shell (2.64 - 2.50 Å)

First assays of molecular replacement searches using the program *BEAST* (*CCP4*) seem to indicate a clear solution for one molecule in the asymmetric unit. Improvements of these results are underway.

Ref 1. Fagart J, Wurtz JM, Souque A, Hellal-Levy C, Moras D, Rafestin-Oblin ME. (1998). Antagonism in the human mineralocorticoid receptor. *EMBO J.*, 17(12), 3317-3325.