Crystal Structure of Free Human Growth Hormone

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INTRODUCTION

Human growth hormone (hGH) is a pituitary hormone exhibiting a wide variety of biological effects, including growth and differentiation of muscle, bone, and cartilage [1]. These functions are mediated through binding of hGH to the human growth hormone receptor (hGHR) and the prolactin receptor (PRLR). The growth hormone system is well characterized by mutagenesis, structural and functional studies. Crystal structures of free hGH [2] and hGH bound to each of its receptors have been determined [3,4]. These studies seem to imply that hGH undergoes surprisingly large structural changes upon receptor binding.

However, the crystal structure of free hGH is only of moderate quality despite the reported resolution of 2.5 Å. The data set used for refinement was merely 67% complete with only 37% of all reflections measured in the highest resolution shell between 2.5 Å and 2.75 Å. No free-R value was used to monitor refinement progress and several criteria, such as the stereo chemistry and Ramachandran plot which are commonly used to assess the quality of a refined structure, indicate that the model is partially inaccurate. The present study was initiated to provide an independent assessment of the structural changes of hGH upon receptor binding.

RESULTS AND DISCUSSION

Crystals of hGH were obtained under the same conditions reported by Chantalat et al. [2]. A single frozen crystal was used to collect a data set with 99.7% completeness at a maximum resolution of 2.7 Å at ALS, beamline 5 in December 1997. The data set is of good quality with an R-sym of 6.1% and 7-fold redundancy. The tetragonal space group $P4_12_12$ of Chantalat et al. was confirmed with cell parameters of a=b=56. 1 Å and c=129.8 Å. Molecular replacement using program AMoRe and the coordinates of the free hGH structure (pdb-entry 1hgu) resulted in an initial R-factor of 46% using all reflections between 10 Å and 3.0 Å. Refinement is in progress.

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