EFFECTS OF GH ON THE IGFs AND IGFBPs IN CHILDREN WITH CHRONIC RENAL FAILURE AND TRANSPLANTATION

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ABSTRACT

The work contained in this thesis involves the retrospective investigation of the insulin-like growth factors and their binding proteins in the serum of children with chronic renal failure (CRF) and transplantation, before and after treatment with recombinant human growth hormone (rhGH). Quantitation of serum IGF-I and IGF-II concentrations, carried out by specific radioimmuno- and radioreceptor-assay respectively, after extraction of the IGFs by means of acid chromatography, revealed that, before rhGH therapy, IGF-I levels were low-normal and IGF-II levels were elevated. Before rhGH treatment, normal IGFBP-3, ALS and elevated IGFBP-1 serum concentrations were found by specific radioimmunoassays. rhGH treatment resulted in a significant increase in serum IGF-I, a moderate increase in IGF-II, IGFBP-3 and ALS concentrations and a substantial fall in IGFBP-1 levels. The technique of Western ligand blotting (WLB) was employed to identify the IGF-binding proteins present in serum by virtue of their ability to bind to the ligands ^{125}I-IGF-I and/or ^{125}I-IGF-II. Five protein bands were found both before and after rhGH treatment, which were identified by Western immunoblotting (WIB) using the immunological properties of the IGFBPs and specific antibodies, to IGFBP-1, -2, -3, -4. A 30 kDa form of IGFBP-3, which apparently has reduced affinity for the radioligand, was only identified by WIB.

IGF-IGFBP complexes in pooled serum from prepubertal and pubertal children of both sexes with CRF and renal transplantation, before and after treatment with rhGH, were analysed by fast protein liquid chromatography under neutral conditions. The distribution of these complexes in the patients was compared and contrasted with age and sex-matched children with normal renal function and the specific effects of rhGH treatment and transplantation were

noted. An increase in ^{125}I-IGF-I binding capacity in the small molecular weight IGF-IGFBP complex was seen in all CRF and transplant sera before treatment. rhGH therapy saw a decrease in the small molecular weight binding complex in all patients.

These findings suggest that an increased small molecular weight binding capacity in CRF, due in particular to increased IGFBP-1, in association with low-normal IGF-I levels results in a reduction in IGF bioavailability and may be responsible for the growth retardation of CRF, which can be reversed by rhGH treatment.