EFFECTS OF TREATMENT WITH IGF-I, GH AND IGF-I PLUS GH IN A RAT MODEL OF CHRONIC RENAL FAILURE

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ABSTRACT

Children who have chronic renal failure (CRF) are frequently growth retarded. Derangements in the GH/ IGF-I axis contribute towards the pathogenesis of this failure to grow, with uraemic resistance to both GH and IGF-I being hypothesised. In the studies described in this thesis, the effects of treatment with recombinant human (rh) IGF-I, rhGH and rhIGF-I+GH in a rat model of CRF were examined.

A rat model of CRF was developed, using a 5/6 nephrectomy two-stage procedure. This resulted in an apparently stable state of chronic renal failure for at least two months from the onset of uraemia, thus avoiding the period of acute renal failure and surgical stress immediately following the surgery. Using this model, the efficacy of 7 days treatment with vehicle, IGF-I (1.7 mg/kg/day), GH (2 mg/kg/day), or IGF-I+GH (1.7 mg/kg/day+2 mg/kg/day) in promoting growth was examined in rats with CRF (n=8 per group). Treatment commenced after chronic renal failure had been present for 7 weeks. Significant increases in body weight gain were found in all groups vs control, with IGF-I+GH causing the greatest response, and increased body weight gains correlating with increased nitrogen retention. GH treatment alone significantly stimulated food intake. IGF-I+GH resulted in close to additive increases in food conversion efficiency (18.8%, 21.5% and 39.6% increases with IGF-I, GH and IGF-I+GH respectively over control level) and longitudinal bone growth (39%, 37% and 67% increases with IGF-I, GH and IGF-I+GH respectively vs control). Serum ALP and phosphate levels were significantly increased, and urinary phosphate excretion significantly decreased, in the IGF-I+GH treated rats. Serum insulin and cholesterol levels significantly decreased with IGF-I and IGF-I+GH treatment. Creatinine clearance did not change, suggesting there were no effects of treatment on kidney function, and remnant kidney weights were unaffected by peptide treatment. Although IGF-I, at the doses used, did not result in a greater anabolic response than GH, IGF-I+GH caused significantly enhanced growth with the potential advantages of reducing serum insulin and cholesterol levels.

The anabolic responses appeared to be relatively greater than in previously published reports using GH treatment in uraemic rats, which may be due to well-established renal failure being present prior to the commencement of treatment. In another study, body weight gain,

FCE and longitudinal bone growth were assessed using lower doses of IGF-I, GH and IGF-I+GH. With respect to the body weight gains resulting from IGF-I or GH treatment at similar doses to previously published reports in normal rats, resistance to at least some of the anabolic effects of the peptides did not appear to be present. However, the renotrophic effects of IGF-I which occur in normal rats were not present, suggesting that some peptide effects were negated by uraemia. Doses of GH up to ten-fold lower than the previous study (0.15 vs 2 mg/kg/day) resulted in similar increases in the rate of longitudinal bone growth, suggesting that the growth plate was particularly sensitive to GH therapy.

The effects of a four week treatment period with IGF-I, GH and IGF-I+GH were then examined, to determine any longer term effects of peptide treatment on the progression of the renal disease. From Day 52 following the onset of uraemia, rats were treated with vehicle, IGF-I (1 mg/kg/day), GH (0.3 mg/kg/day) or IGF-I+GH (0.5 mg/kg/day+0.15 mg/kg/day respectively), with the treatment groups fed either an 8% or 22% protein diet, and a group of sham operated animals included in each dietary group. Changes occurred in the IGF-I+GH treated animals fed the 22% protein diet strongly suggesting that peptide treatment had accelerated the rate of progression of renal failure. These changes included increased remnant kidney weights, greater glomerular hypertrophy, a tendency for increased glomerulosclerosis, increased serum cholesterol and PTH levels, and elevated urinary protein excretion. Although the lower protein diet prevented most of these changes, it slowed, but did not prevent, the increase in urinary protein excretion. Selective increases in spleen weights resulted from IGF-I treatment, and heart weights were increased in the uraemic rats fed the 8% protein diet, with a further increase in heart weight due to IGF-I infusion. Body weight gains were significantly increased by peptide treatment in the first week, but this effect was not sustained throughout the four weeks of treatment. However, longitudinal bone growth was significantly greater in the IGF-I treated rats in the final three days of treatment by 46% and 28% in the 8% and 22% protein groups respectively, and by 35% in the 8% IGF-I+GH group. No significant differences in longitudinal bone growth occurred between the vehicle and GH or 22% IGF-I+GH groups. The loss of significant longitudinal bone growth in the 22% IGF-I+GH treated rats may have been associated with the significant increase in serum PTH levels which occurred in this group.

The results described in this thesis demonstrate that the rat model of CRF which was developed appeared to respond with greater anabolic effects due to GH treatment than have previously been reported, and may provide a valuable tool for investigating the alterations in IGF-I and GH regulation resulting from chronic renal disease. While promising results following seven days of IGF-I+GH treatment were reported, a four week treatment period with IGF-I+GH, in association with a 22% protein diet, appeared to accelerate the progression of renal disease. Further studies will be necessary to elucidate the mechanisms for these changes, to ensure that children do not pay for increases in growth velocity with an earlier requirement for renal replacement therapy.

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