Insulin-like growth factor-1 and growth hormone (GH) have distinct and overlapping anabolic effects in GH-deficient rats

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The anabolic activity of recombinant human growth hormone (rhGH) and insulin-like growth factor 1 (rhlGF-1) given either alone or together were studied in two models of GH deficiency, hypophysectomized and GH-deficient dwarf rats. A range of rhGH doses (0.08 to 50 mg/kg/day, seven daily sc injections) were given either alone or together with one dose of rhlGF-1 (2.4 mg/kg/day, sc infusion). When given alone, or co-administered with rhlGF-1, rhGH produced dose dependent increases in weight gain, bone growth and organ weights. Weight gain in response to rhGH given with rhlGF-1 was comparable to that obtained by a 25-fold higher dose of rhGH given alone. In both animal models absolute weights of the kidneys, liver, spleen and thymus were increased by rhlGF-1 while kidney and liver weight were increased by rhGH. In the hypophysectomized rat, spleen and thymus weights were increased by rhGH but the relative potency of the combination was a 1000-fold that of rhGH alone. The effects of rhlGF-1 and rhGH were additive indicating that the effects of GH or IGF-1 can be greatly increased by their co-administration.

Keywords: IGF-1; GH; additive; anabolic; GH-deficiency

Introduction

The pituitary gland regulates whole body growth, and in particular the growth of the skeleton, by producing growth hormone (GH) in animals and in man. Many of the somatogenic effects of GH are believed to be mediated, at least in part, by the somatomedins (Salmon and Daughaday, 1957), especially by insulin-like growth factor-1 (IGF-1), whose production in many tissues is regulated by GH. Treatment of GH-deficient rats with either recombinant human GH (rhGH) or recombinant human IGF-1 (rhlGF-1) can increase the growth rate toward that of a normal animal, indicating their important somatogenic activity (Moore et al., 1988). However, it is now becoming clear that GH and IGF-1 have not only overlapping but also distinct biological activities.

Other investigators have studied the effects of co-treatment with GH and IGF-1 in the rat and found no additive effects on body weight gain (Skottner et al., 1987) or bone lengthening (Isgaard et al., 1986; Skottner et al., 1987). In mice (Pell & Bates, 1992) an increased activity of the combination of IGF-1 and GH on some measures of metabolism was reported. We have recently shown that the growth responses to low doses of rhGH in hypophysectomized rats are increased if rhlGF-1 is co-administered (Clark et al., 1994).

To test if the additive effects of rhlGF-1 and rhGH on body growth occurred over a broad range of doses of rhGH, or if additivity was restricted to low doses of rhGH, we have now given several doses of rhGH with or without a fixed dose of rhlGF-1 to two animal models of GH deficiency, the hypophysectomized rat and a mutant dwarf rat.

Results

Body weight gain

In both studies, all doses of rhGH produced a maintained weight gain. Likewise, rhlGF-1 produced a significant body weight gain that was first recognized on Day 1 of dosing. Figure 1 shows the mean body weight gains on Day 7 plotted against the logarithm of rhGH dose for the hypophysectomized rats. Over this range of rhGH doses, whether rhGH was given alone or in combination with rhlGF-1, there was a linear relationship between the logarithm of rhGH dose and weight gain. The combination of rhGH plus rhlGF-1 gave greater weight gains than either hormone alone, and this appeared to be additive for all doses of rhGH. Excipient treated hypophysectomized rats gained 4.5 ± 1.7 g, while rhlGF-1 at 2.4 mg/kg/day resulted in a weight gain of 18.2 ± 2.0 g. For rhGH (at 0.08, 0.4, 2, 10 and 50 mg/kg/day) the mean weight gains were for rhGH alone, 14.5, 20.5, 26.0, 32.6 and 36.1 g, and for rhGH plus rhlGF-1 the gains were

Figure 1

Weight gain in hypophysectomized rats induced by treatment with excipient, rhGH, or rhlGF-1 for 7 days. rhGH (0.08, 0.4, 2, 10 and 50 mg/kg/day) was given alone or with rhlGF-1 (2.4 mg/kg/day). The means and standard deviations are presented (n = 6 rats per group)
28.2, 30.7, 34.8, 41.6 and 46.3 g, respectively, for the 7 days. So at each dose of rhGH there was approximately a 10 gram greater weight gain if rhIGF-1 was also administered.

The weight gain responses to rhGH or rhGH plus rhIGF-1 were analysed as a parallel line bioassay against the logarithm of the dose of rhGH. The two dose response lines fulfilled the criteria for a bioassay, as they proved to be statistically linear and parallel. The potency of the rhGH plus rhIGF-1 was 26.6 times that of the rhGH alone (95% confidence limits 14.8 to 51.7), with the difference between the two dose response lines being highly significant (1.49 degrees of freedom [d.f.], \( F = 169.4, P < 0.0001 \)).

Figure 2 and Table 1 show the weight gains of the dwarf rats treated with rhGH and rhGH plus rhIGF-1 for 7 days. The excipient control group of dwarf rats gained the expected small amount of weight (3.9 ± 3.6 g) during the experiment. rhIGF-1 at 2.4 mg/kg/day caused significant weight gain (12.1 ± 3.8 g). The mean body weight gain was increased by rhGH in a dose dependent manner. In dwarf rats, as for hypophysectomized rats, the combination of rhGH plus rhIGF-1 yielded greater body weight gains than either hormone alone, and the effects appeared to be additive over a broad range of doses of rhGH.

The weight gain responses to rhGH or rhGH plus rhIGF-1 were again analysed as a parallel line bioassay against log dose of rhGH. The two dose response lines fulfilled the criteria for a bioassay, as they proved to be statistically linear and parallel. The relative potency of the rhGH plus rhIGF-1 was 28.9 times that of the rhGH alone (95% confidence limits 7.7 to 514.6), with the difference between the two dose response lines being highly significant (1.30 d.f., \( F = 45.75, P < 0.001 \)).

The analysis of the weight gain data in Table 1 confirms that there were clear effects of both rhIGF-1 and rhGH on weight gain, while the lack of a significant interaction between the effects of rhIGF-1 and rhGH again suggests that these effects were additive.

**Bone growth**

Table 1 shows the mean epiphyseal plate width and longitudinal bone growth in the dwarf rats given rhGH and/or rhIGF-1. Both rhIGF-1 and rhGH significantly increased these measures of tibial growth, while the lack of an interaction between the treatments again indicates an additive effect.

**Serum IGF-1 concentration**

Table 1 also shows the serum IGF-1 concentrations in the dwarf rats in blood samples taken at sacrifice (24 h after the last rhGH injection). There were clear effects of both rhIGF-1 and rhGH treatment, and no interaction between the treatments. Treatment with rhIGF-1 increased serum IGF-1 concentrations in the presence and the absence of rhGH treatment. There were decreased IGF-1 concentrations whether the rhGH was given alone or together with rhIGF-1.

**Organ weights**

Table 2 shows the absolute organ weights and the relative organ weights for the dwarf rats. The relative organ weights are expressed as a percentage of body weight multiplied by 10. It is clear that in the dwarf rat the increased body weight caused by rhIGF-1 was associated with increased weights of several internal organs. In contrast, rhGH treatment only increased the absolute weights of the kidney and liver. The relative weights of the kidneys, liver, spleen and thymus were increased by rhIGF-1. The relative weight of the liver was increased by rhIGH-1.