REVERSAL OF DEXAMETHASONE-INDUCED CATABOLISM IN RATS BY INSULIN-LIKE GROWTH FACTOR-I (IGF-I) AND ESPECIALLY DES(1-3)IGF-I

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Administration of IGF-I, and especially IGF analogs that bind weakly to IGF binding proteins have been shown to substantially ameliorate the catabolism associated with glucocorticoid treatment in rats (Tomas et al. 1990). In those experiments, administration of the growth factor was commenced simultaneously with the glucocorticoid treatment and thus its primary action may have been to restrict the development of the catabolic response, rather than reverse it. We have now used a protocol more relevant to the clinical treatment of physical trauma and have examined the ability of the growth factors to reverse an established catabolic state.

Sixty male Hooded-Wistar rats were placed in individual metabolism cages and given an 18% protein diet free of N^{15}-methylhistidine (N^{15}-MH). Ten groups of six rats (130g body weight) were implanted with a mini-osmotic pump to deliver either 18 μg dexamethasone phosphate/d (Dexa, 9 groups) or vehicle. After 2 days, a further pump containing either IGF-I, des(1-3)IGF-I or vehicle to deliver 0, 40, 100, 250 or 625 μg peptide/d was implanted. The group untreated with dexamethasone received growth factor vehicle only. After six days of growth factor treatment muscle protein synthesis rates were determined using a flooding dose of ^{3}H-phenylalanine.

Dexamethasone treatment caused a loss of 8g body weight over the two days prior to growth factor treatment. Subsequent infusion of IGF-I and des(1-3)IGF-I led to a dose related recovery in growth rate whereas control rats lost a further 10g body weight. Average results obtained for the highest rate of IGF infusion are presented in the table.

Treatment	Weight gain (g/6d)	N balance (mg/6d)	Urine N^{15}-MH (μmol/kg/6d)	Protein synthesis (%/d)
No Dexa*	27.2 ± 1.6	1153 ±37	4.51 ± 0.41	10.9 ± 1.0
Dexa+Vehicle	-12.5 ± 2.7	-56 ± 67	6.55 ± 0.20	5.7 ± 0.3
Dexa+IGF-I†	15.9 ± 2.2	595 ± 71	4.98 ± 0.16	6.8 ± 0.3
Dexa+desIGF†	18.4 ± 1.4	670 ± 47	5.02 ± 0.18	8.7 ± 0.5

* Pair-fed to Dexa+vehicle group † Means differ from dexa+vehicle ($P<0.05$)

These data clearly show the ability of IGF-I and the analog des(1-3)IGF-I to reverse an established catabolic state rather than only acting to limit the development of catabolic processes. Both growth factors reduced the rate of muscle protein breakdown and increased the rate of synthesis in accord with the improved nitrogen balances. The des(1-3)IGF-I was more potent than the IGF-I at all dose rates, but especially at the lower rates. These data suggest that growth factor administration may be a useful treatment for human catabolic conditions and that des(1-3)IGF-I is more potent for this purpose than IGF-I.

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