REVERSAL OF GLUCOCORTICOID INDUCED CATABOLISM BY INSULIN-LIKE GROWTH FACTORS

F.M. TOMAS, S.E. KNOWLES, J.L. BURGOYNE, S.L. QUINN and F.J. BALLARD

One of the major factors contributing to the morbidity of trauma such as that resulting from burns, multiple fractures, major surgery or severe infection is the massive loss of nitrogen from the body, which results in wasting of muscle and other tissues. Increased glucocorticoid secretion is a major effector of this response. Nutritional support can reduce the net loss to a only limited extent. IGF-I and some of its analogs have been shown to increase protein accumulation in cells by both increasing protein and DNA synthesis and decreasing protein breakdown (Francis et al. 1988). Other studies have indicated a relatively specific anabolic action on protein growth without the concomitant gluco-regulatory actions of insulin.

Thirty male Hooded-Wistar rats were placed in individual metabolism cages and given an 18% protein diet free of N^{τ}-methylhistidine (N^{τ}-MH). Four groups of 6 rats (150g body weight) were given dexamethasone phosphate (dexa) in the drinking water (1mg/l). A mini-osmotic pump was implanted to deliver one of the following treatments: i) vehicle control, ii) IGF-I, 170µg/d, iii) IGF-I, 425µg/d and iv) des(1-3)IGF-I, 170µg/d. The remaining six rats were untreated controls with vehicle pumps. After 7 days of treatment muscle protein synthesis rates were measured using a flooding dose of ^{3}H-phenylalanine. Dexa treatment caused increased water intake so the dexa concentration was lowered to 0.5mg/l and 0.25mg/l after 3 and 6 days of treatment, respectively.

The body weight and nitrogen loss caused by dexa treatment was partially reversed by treatment with IGF-I and des(1-3)IGF-I (see table).

Group	Weight change (g/d)	N balance (mg/rat/d)	N^{τ}-MH change (µmol/kg BWt/d)	Protein synthesis (%/d)
No dexa	+52 ±1.6*	+211 ±9*	0.00 ±0.01*	8.61 ±0.28*
Vehicle	-34 ±2.1	-79 ±12	+6.53 ±0.83	4.82 ±0.28
IGF-I(170)	-27 ±4.0	-51 ±10	+4.98 ±0.74	5.29 ±0.15
IGF-I(425)	-15 ±2.9*	-27 ±6*	+3.86 ±0.35*	4.95 ±0.19
desIGF(170)	-16 ±3.7*	-27 ±12*	+4.55 ±0.99	5.29 ±0.36

*Differs significantly from vehicle control ($P<0.05$).

Although there was a trend for higher rates of muscle protein synthesis rates the improved nitrogen status of the rats treated with the growth promoting peptides seems more likely due to a reduction in the rate of protein breakdown. N^{τ}-MH excretion, an index of myofibrillar protein breakdown, is substantially reduced at the higher dose of IGF-I.

These and other data indicate that the des(1-3) analog of IGF-I is about 2.5 times more potent in reducing the catabolic effects of glucocorticoid treatment and appears to have potential for the treatment of trauma.

FRANCIS, G., UPTON, F., BALLARD, F., McNEIL, K. and WALLACE, J. (1988). Biochem. J. 251: 95.

CSIRO, Division of Human Nutrition, PO Box 10041 Gouger Street, Adelaide, South Australia 5000