

Tissue and Serum Insulin-like Growth Factor I (IGF I) Concentrations in Rats Subjected to Temporary Protein-energy Malnutrition Early in Life

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ABSTRACT

Rats subjected to temporary protein-energy malnutrition and subsequent nutritional rehabilitation remain smaller than adequately fed animals, have a subnormal insulin secretion and persisting cellular hypoplasia in several tissues. This investigation studies whether impaired production of insulin-like growth factor I (IGF I) is another persisting consequence of malnutrition. Rats were subjected to severe protein-energy malnutrition between 3 and 6 weeks of age and subsequently fed adequate diet up to 12 weeks of age. Serum and tissue samples for analysis of IGF I were obtained at 12 weeks of age. IGF I concentrations were similar in serum, heart, liver and lung of previously malnourished and control rats. In the kidneys of previously-malnourished rats the IGF I concentration was twice that of control rats. Results suggest that during protein-energy malnutrition and subsequent nutritional rehabilitation IGF I tissue concentrations are primarily regulated by the prevailing plane of nutrition. It is speculated that the temporary protein-energy malnutrition blunts the cellular capacity for IGF I production and, except in the kidney, prevents increased IGF I tissue concentrations and associated compensatory growth.

INTRODUCTION

In human and experimental protein-energy malnutrition serum concentrations of insulin-like growth factor I (IGF I) are reduced (3,4,6,15). In experimental animals, but not clearly so in humans, the degree of reduction appears to be correlated with the

protein content of the diet (9,16). Serum IGF concentrations have indeed been suggested as a useful clinical index of undernutrition (17). Serum concentrations of IGF I are unresponsive to growth hormone during protein-energy malnutrition (8,10) and it would appear that IGF I production is primarily regulated by the level of nutrition under these circumstances.

Protein-energy malnutrition also stunts growth by inhibiting both cell replication and growth of individual cells. Glucose tolerance is impaired and the insulin secretory response to glucose severely blunted (11,12). Following nutritional rehabilitation growth is resumed at a normal rate but catch-up is not achieved. Glucose tolerance is normalized but an impaired insulin secretory response to glucose persists (11,12). Several tissues, notably insulin-sensitive organs such as heart, liver, lung and skeletal muscle, retain a lowered protein/DNA ratio as evidence of a persisting cellular hypoplasia (12).

It is as yet unclear whether IGF I production is completely normalized after nutritional rehabilitation of prolonged malnutrition or if a reduced production could explain the absence of catch-up growth and other abnormalities. It is conceivable that low circulating insulin concentrations may diminish IGF I production (10) and the general cellular hypoplasia (11) may provide an insufficient cellular machinery for peptide biosynthesis.

MATERIAL & METHODS

Wistar rats from a local colony (University of Sheffield, Sheffield, UK) were fed standard rat chow (CRM diet, Labsure, Croydon, UK; protein content 18.1%) and tap water throughout breeding, pregnancy and lactation. At three weeks of age young rats were weaned onto either this diet ('normal' diet; the rats subsequently denoted N rats) or onto a semisynthetic low protein diet (kindly provided by R.D.E. Rumsey, Dept of Physiology, University of Sheffield; the rats subsequently denoted LP rats). This diet contains 5% protein and details of its composition have been published elsewhere (14). The low protein diet was maintained for 3 weeks when, at the age of 6 weeks, the LP rats were transferred to normal rat chow up to the end of the experiment at

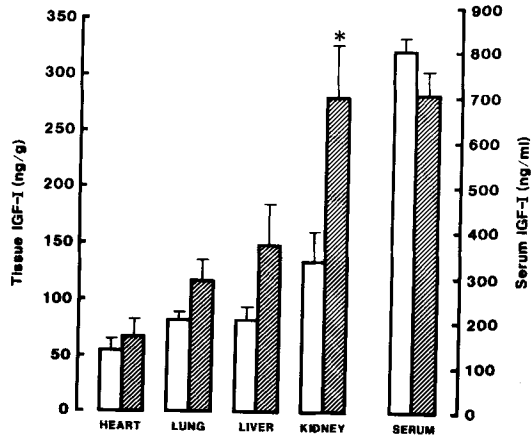


Fig 1. Serum and tissue concentrations of insulin-like growth factor I in 12-week-old rats subjected to protein-energy malnutrition between three and six weeks of age (hatched bars) and control rats fed diet of adequate nutritional value throughout life (open bars). Values are means \pm S.E.M. for 11-17 rats. Significance of difference between the two groups of rats: * $p < 0.02$.

12 weeks of age. Since preliminary experiments suggested there was no difference between male and female rats results from both sexes were pooled.

At 12 weeks of age N and LP rats were killed by cervical dislocation, blood collected from the severed neck vessels, serum separated and stored at -20°C until extracted and assayed for IGF I. Immediately after collecting the blood samples pieces of approximately 0.5 g of heart, lung, liver and kidney were dissected, snap frozen in isopentane cooled in liquid nitrogen and stored at -70°C until extracted and assayed for IGF I.

IGF I in serum was dissociated from its binding proteins by acidification with hydrochloric acid and subsequently separated by reverse phase chromatography on C18 silica gel columns as previously described in detail (13). Frozen tissues were weighed, pulverized under liquid nitrogen and extracted with 1M acetic acid as described elsewhere (1,2).

IGF I in serum and tissue extracts was measured in a specific radioimmunoassay using a polyclonal rabbit anti-human IGF I antibody (kindly provided by J.J. Van Wyk and L.E. Underwood, Dept. of Paediatrics, University of North Carolina, Chapel Hill, NC, USA through the National Pituitary Agency, N.I.H., USA) and

iodinated human recombinant IGF I (Amersham, UK) as standard (5). Insulin, at the concentrations present in serum, does not cross-react in this assay and the cross-reactivity of IGF II is <1%.

RESULTS

The serum IGF I concentration of 12-week-old LP rats fed a low protein diet between 3 and 6 weeks of age was similar to that of N rats (Fig 1). The tissue concentrations of IGF I was similar in LP and N rats in three of the tissues studied - heart, lung and liver. In the kidneys of LP rats the IGF I tissue concentration was twice that of N rats.

DISCUSSION

In the present study tissue concentrations, and not only serum concentrations, of IGF I were measured in view of the suggested auto- or paracrine mode of action of the peptide (1). If IGF I thus acts locally, at the tissue or organ level, the concentrations of IGF I in different organs may best reflect its growth-promoting actions. Indeed, increased tissue concentrations of IGF I during hypertrophy of an individual organ may not be reflected in an increased serum concentration of the growth factor (7).

The present results could therefore be interpreted to suggest that the persisting hypoinsulinemia in the LP rats (11) does not affect the IGF I production in insulin-sensitive organs such as liver, heart and lung. IGF I tissue concentrations may rather be regulated by other hormones and the prevailing plane of nutrition. However, it is notable that these organs exhibit a persisting cellular hypoplasia after the limited period of protein-energy malnutrition (11). By contrast, the kidney, which in the present study showed an increased tissue IGF I concentration, recovered from the cellular hypoplasia induced by protein-energy malnutrition (11). It can therefore be speculated that the temporary protein-energy malnutrition decreases the capacity for IGF I synthesis in several tissues which as a consequence do not have the ability to increase IGF I production to the supranormal levels associated with compensatory or catch-up growth (7).

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