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THE EFFECT ON GROWTH AND METABOLISM OF THE ENDOCRINE CHANGES ASSOCIATED WITH MALNUTRITION

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Most studies of endocrine changes during starvation have been made on children with the severe protein-enery malnutrition disease: Kwashiorkor. Similar hormonal changes undoubtedly occur in farm animals and will determine whether growth can occur on marginally adequate diets. A knowledge of these endocrine changes, and how they regulate metabolism and growth, is clearly essential before diets can be modified to achieve the optimum rate of protein formation relative to food consumption.

In starvation, there is a diminished secretion of insulin by the beta cell of the pancreatic islets. There is also an impaired insulin secretory response to intravenous injections of glucose and glucagon (the pancreatic alpha two cell hormone). When glucose is taken by mouth insulin secretion is still further diminished, probably because starvation atrophy of the gastro-enteric mucosa prevents release of the gastro-enteric hormones, (gastrin, secretin, pancreozymin-cholecystokinin and enteroglucagon) which normally stimulate insulin secretion in anticipation of food absorption. Starvation also decreases the metabolic response to insulin, and in adults, prolonged starvation results in a fall in plasma glucagon concentration.

Although the secretion of growth hormone by the orange acidophils of the pituitary gland is decreased by starvation, there is an even greater decrease in the rate of inactivation of the hormone by the liver and kidney. Consequently, there is an unexpected *increase* in plasma growth hormone concentration. The high concentration is not caused by the low blood glucose and plasma albumin concentrations, but it does seem to be associated with a fall in the plasma concentration of one of the non-essential amino-acids: alanine. Growth hormone normally controls growth by stimulating the liver to release a polypeptid called somatomedin (sulphation factor). In starvation, the liver fails to produce somatomedin and the growth hormone becomes ineffective. Starvation has similar effects on cortisol (from the zona fasciculata of the adrenal cortex): liver inactivation is reduced even more than secretion so that the plasma cortisol concentration rises. Ninety five percent of cortisol is bound to a carrier protein called transcortin which is produced in the liver. Starvation decreases transcortin synthesis so that a larger proportion of plasma cortisol is "free" and unbound and consequently exerts a greater physiologic effect. Cortisol secretion normally shows a marked diurnal rhythm which disappears during starvation.

Starvation leads to thyroid atrophy and a decreased secretion of the thyroid hormones (tri-iodothyronine and thyroxine), despite the increased secretion of the thyroid stimulating hormone from the beta two basophils of the pituitary gland.

A failure of "end-organ response" is characteristic of starvation: normal control systems cease to be effective; glucose and glucagon fail to release insulin, growth hormone can not release somatomedin and the thyroid stimulating hormone no longer stimulates the thyroid gland. Many hormones (including insulin, glucagon, growth hormone, cortisol, thyroid stimulating hormone, corticotrophin, luteinizing hormone, adrenaline and prostaglandin) control their target organs through the release of a deputy hormone or second messenger called cyclic adenosine monophosphate. They activate the enzyme adenyl cyclase on the surface of the target cell, and this enzyme releases the deputy hormone *inside* the cell where it mediates the characteristic actions of the hormone. The failure of "end-organ response" characteristic of starvation, may well represent a change in adenyl cyclase so that it no longer responds to hormones and can not transfer their messages to the cells' interior.

Growth involves protein synthesis, cellular enlargement (hypertrophy), and an increase in cell numbers (hyperplasia). Insulin is essential for the transport of both energy and protein (as amino-acids) into the cells; consequently insulin deficiency associated with starvation prevents individual cells from growing to their usual size. In contrast to insulin, somatomedin regulates cell multiplication; in starvation the deficiency of this peptid decreases total cell numbers. Finally, the excess of cortisol and the lack of thyroid hormones depress protein synthesis and contribute to the growth failure associated with malnutrition.

Although it must be obvious that an adequate supply of both energy and protein is essential for growth, it is possible that a better understanding of the hormonal mechanisms involved will allow small dietary modifications to produce striking improvements in growth rate and protein production.

The metabolic compensations for starvation are also under endocrine control. As glycogen stores in the liver become exhausted, the blood glucose concentration falls, and changes in plasma insulin, cortisol and growth hormone occur to provide an alternative supply of energy. This results in glucose intolerance: a failure to store or metabolise glucose when it is given intravenously or by mouth. The same hormonal changes (insulin deficiency, cortisol and growth hormone excess) promote lipolysis and the release of fatty acids from the fat depôts; fat becomes the major source of energy. Insulin deficiency and cortisol excess also prevent the liver from resynthesising these fatty acids into the very low density pre-beta lipoproteins, which normally carry fat back to the depôts for storage. Consequently, fat accumulates in the liver and contributes to the liver damage characteristic of malnutrition.

Muscle protein synthesis stops, and protein hydrolysis increases during starvation. These changes also result from the disturbance in endocrine balance: from the decrease in thyroid hormone and insulin concentrations, and from the increase in free cortisol concentration. Muscle protein is

hydrolysed to its constituent aminoacids which are transaminated to alanine, and the alanine is carried by the blood to the liver where it is converted to glucose (gluconeogenesis). Alanine also provides oxalo-acetate (through pyruvate) to prime the Krebs' cycle and prevent ketosis that otherwise results from excessive fat metabolism.

The rise in growth hormone concentration during starvation regulates protein breakdown, particularly in the liver. When gluconeogenesis from alanine exceed the muscles' capacity to provide this aminoacid and its plasma concentration begins to fall, there is an increased secretion of growth hormone. Growth hormone inhibits the liver enzymes that convert alanine to pyruvate and glucose, so that gluconeogenesis is slowed to keep pace with muscle protein breakdown. In the early stages of protein deficiency, alanine is released from muscles and in contrast to the essential and branched chain aminoacids, its plasma concentration rises. Prolonged starvation eventually results in a fall in alanine concentration as it becomes transaminated by the liver.

A knowledge of the endocrine regulation of metabolism during starvation suggests that in periods when there is an almost complete lack of food, a small supply of carbohydrate, just sufficient to prevent ketosis, could prevent the breakdown of muscle protein and permit a faster recovery in the rate of muscle growth when food again became available.

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