# Secretion of human growth hormone

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The last 10 years have encompassed the development and intensive application of radioimmunoassay which is the first viable general procedure for the micro-determination of specific protein hormones in physiological fluids (Yalow & Berson, 1960; Margoulies, 1968; Cauwenberge & Franchimont, 1970; Kirkham & Hunter, 1971). Nowhere has this application been more fruitful than in advancing our knowledge of the physiology of pituitary growth hormone (GH) (Glick, Roth, Yalow & Berson, 1965; Hunter, 1968). Though some of the principal findings could have been, and sometimes were, predicted (Young, 1953; Russell, 1957), the intricacy of the changes in the levels of human GH was unexpected. The complexity of the emergent picture is confusing to the non-specialist and an attempt will be made here to outline the main findings which have been compiled from the measurement of plasma GH concentrations in man. A knowledge of this substantial body of results will not inevitably lead to conclusions as to precisely how this hormone affects protein synthesis. However, as we shall see, the results can provide a framework within which this mechanism may perhaps best be viewed.

Confusion may be minimized by first making a few simple statements in summary form.

1. There is about as much human GH in the adult's as in the child's pituitary gland but, although human GH deficiency is in fact quite common in adults, the only clinical manifestation is marked growth stasis which, of course, is seen only in children.

2. The concept 'plasma growth hormone level' in a normal subject has no meaning. Instead of the steady secretion giving rise to slowly changing plasma concentrations which might have been expected for a hormone whose function is regulation of growth – a slowly changing phenomenon – we must think in terms of rapid changes, most of which can now be related to preceding physiological events such as meals, exercise and so on.

4. Despite the obviously different importance of this hormone in adults and children, the plasma concentrations are not so obviously different between the two groups.

5. For much of the time plasma GH human concentrations are undetectable ($< 1$ ng/ml). This does not stem from technical inadequacy, but rather means that the

hormone is secreted in bursts at appropriate times. Plasma concentrations then fall away, often quite rapidly, sometimes at rates which reach the half-life of the hormone (25 min).

The involvement of this hormone in growth is passport enough for giving it a central place in the subject matter of this symposium. Even so, just as we have seen above that it is easy to take a too direct view of the relationship between growth and plasma human GH concentrations, so also it has been necessary to look further than direct action of the hormone on protein (or even) nitrogen metabolism. Indeed, sense and pattern in plasma human GH concentrations first appeared when workers (Roth, Glick, Yalow & Berson, 1963, 1964) looked for changes which could be expected if the hormone were concerned with fat mobilization. This action gives rise to increased plasma free fatty acids (FFA) and is the most sensitive whole-body response to human GH (Raben & Hollenberg, 1959), is a direct action on adipose tissue (Rabinowitz, Klassen & Zierler, 1965) and can be evoked in isolated fat cells provided corticosteroids are present (Fain, Kovacev & Scow, 1965). Increased human GH secretion has been shown to be followed by increased plasma FFA, which in turn cause an increase in the relative contribution of fat to the metabolic fuel mixture as indicated by a fall in respiratory quotient (RQ). These interrelated events have been well shown to occur in an uncomplicated form in the following situations: (1) during exercise in the overnight fasting stage (Roth *et al.* 1963; Hunter, Fonseka & Passmore, 1965); (2) in the early postabsorptive phase after a glucose load at which time a rebound rise in secretion of human GH occurs (Roth *et al.* 1963; Hunter, Willoughby & Strong, 1968). In both situations the rise in human GH and the consequent changes are abolished by small glucose loads given just prior to the anticipated human GH rise.

Prolonged steady exercise in the fasting state gives rise to repeated bursts of human GH secretion (Hunter *et al.* 1965) and the same picture is seen in prolonged fasting without exercise (Hunter, Willoughby *et al.* 1968), but here the bursts are less frequent and their amplitude is smaller. In all of these situations as well as in the marked human GH rise induced by insulin (Roth *et al.* 1963), a fat-mobilizing role for human GH seems clear. The purpose of permitting (if not actually controlling) growth is here subserved at least in part by a protein-sparing action, fat being mobilized and hence amino acids being protected when exogenous carbohydrate is unavailable. The triggering mechanism for human GH release is not fully understood. Clearly hypoglycaemia stimulates and hyperglycaemia abolishes human GH secretion (Roth *et al.* 1963, 1964), but most of the above changes, particularly those associated with exercise and fasting, occur at normal blood glucose concentrations and demonstrably are not related to small changes in blood glucose (Sukkar, Hunter & Passmore, 1968). The hypothalamic receptors which control GH-releasing factor are also responsive to hypoglycaemia and to lack of intracellular glucose induced by fructose or deoxyglucose (Himsworth, Carmel & Frantz, 1972). There is no obvious other substance whose levels in blood could be used to indicate lack of glucose at the hypothalamic level. If the real purpose of GH is to protect the body from wasting amino acids as mere fuel, then perhaps the

beginnings of such wastage might somehow be employed as a triggering mechanism. If this is so, no evidence has yet appeared to suggest what the actual mechanism might be.

The hormonal changes which follow the ingestion of a protein meal are also well described (Rabinowitz, Merimee, Maffezzoli & Burgess, 1966; Sukkar *et al.* 1968). There is first a rise in plasma insulin and at the same time an increase in glucagon secretion (Unger, Ohneda, Aquilar-Parada & Eisentraut, 1969) which is mediated by release of secretin; slightly later comes a rise in plasma human GH. Presumably one purpose served by the increase in plasma insulin is the stimulation of the active transport of amino acids across cell membranes. Even small increases in plasma insulin will block lipolysis, and plasma FFA falls after a protein meal. However, the RQ rises and this cannot be due to increased glyconeogenesis since the urinary N does not increase—in any event it has long been known that ingested protein is not at immediate risk in this way, N balance being struck over a period of days rather than hours. Clearly then the rise in RQ must be due to an increase in combustion of carbohydrate and it is here that the glucagon response is important in stimulating glycogenesis in the liver. The human GH rise would be valuable here in limiting the inhibition of fat mobilization by insulin. If exercise is taken during the absorption of a protein meal, the insulin response is blunted, the human GH rise is markedly increased and the FFA increases are restored to concentrations similar to those seen in exercise in the fasting state (Sukkar *et al.* 1968). Clearly in these situations involving protein meals, an amino acid-sparing role for human GH fits the facts well, though again the mechanism involved in its release is less clear as the changes in plasma insulin are too slight to lower the blood glucose.

The introduction of emulsified fat into the duodenum by nasogastric tube produces no change in plasma insulin or human GH concentrations (Hunter *et al.* 1965).

From the above evidence then, a protein-sparing action mediated by fat mobilization provides a partial, though by no means a completely adequate, explanation for the role of human GH. There remains one further situation in which GH secretion occurs and this is of particular interest because it appears to stand outside any association with increased fuel mobilization. Human GH secretion shows a marked surge during the first 2 h of sleep and is associated with the deeper levels of sleep which are recognized by the electroencephalograph as stages III and IV (Honda, Takahashi, Takahashi, Azumi, Irie, Sakuma, Tsushima & Shizume, 1969). The magnitude of this human GH response is similar to that seen in moderate exercise but, clearly, energy requirements are not increased at this time. Furthermore, the sleep response, unlike any of the other responses, is not altered by hyperglycaemia (Lucke & Glick, 1971). We have either to think in terms of two different triggering mechanisms – one for the sleep response and perhaps one for the rest – or we must find some change which is common to both situations. The proportion of the whole night's sleep which is occupied by stages III and IV is increased by exercise taken during the day, and partly from this finding has come the suggestion that this kind of sleep is associated with rest and, perhaps, restoration of the body. Implication of GH in such a process would be intelligible on general grounds, and the mecha-

nism might involve helping to provide an anabolic milieu or stimulating protein synthesis direct.

The best insight into the relationship between human GH and protein metabolism must surely now come from comparison between its secretion in adults and children. As mentioned above, the differences in plasma concentrations are not outstanding; in fact the response to provocative stimuli – insulin, arginine infusion or the late rise following glucose – are not different. However, plasma human GH concentrations in the resting fasting state are higher in children than in adults (Hunter, Wolfsdorf, Farquhar & Rigal, 1967). Furthermore, children who were at rest and eating normal meals, and whose blood was sampled hourly during the day (Hunter & Rigal, 1966), showed higher plasma human GH levels than those found in a group of adults in a comparative study (Hunter, Friend & Strong, 1966). These differences between adults and children may arise at least in part because children have a higher basal metabolic rate than adults (Cassels & Morse, 1962) and consequently eat larger meals than adults after allowing for differences in body-weight (Hunter, 1968). Although there are no full studies in which human GH is measured during sleep in children, our own results (Hunter & Rigal, 1966; Hunter, Rigal & Sukkar, 1968), accumulated before the sleep response was discovered, strongly suggest that children secrete more human GH during sleep than adults.

In kwashiorkor, but not in marasmus, plasma human GH is continuously high and secretion is not suppressed by glucose. As the protein-deficient child is refed, the normalizing of the human GH response to glucose correlates well with the return of plasma protein concentrations to normal (Pimstone, Barbezat, Hansen & Murray, 1968). The central problem now is how to increase our understanding of the role of GH in the regulation of normal growth. A fuller understanding of the control of secretion in these conditions of protein deficiency and in the response to sleep might bring considerable insight into this problem.

In this paper the role of human GH as a fat-mobilizing agent has been stressed. While an attempt has been made to relate this to growth regulation, this does not necessarily imply that this is the only way this hormone may support growth. A direct action of human GH on protein synthesis is not excluded. However, the pattern of its secretion is not consistent with a simple hypothesis in which growth is proportional to plasma GH concentration.

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