Effects of Growth Hormone on the Rat Adipocyte: A Model for Studying Direct Actions of Growth Hormone

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In addition to stimulating growth in childhood and adolescence, GH is well known to have metabolic actions that probably persist throughout life. There is now abundant evidence that adipose tissue is a target for GH action (1, 2, 3). Furthermore, although its growth promoting effects appear to require the participation of a second secretory product, somatomedin (4), the metabolic effects of GH on adipose tissue appear to be direct, and therefore can serve as a model for studying the initial cellular events that ultimately result in expression of hormonal responses, including, perhaps, production of somatomedin. Although GH interacts directly with fat cells, its effects are certainly not simple and straightforward. Rather, the changes that are seen depend upon both time of exposure to GH and previous history of the tissue.

The findings that I shall describe were obtained in studies of segments of epididymal fat or suspensions of adipocytes isolated from epididymal fat obtained from normal or hypophysectomized rats. Both preparations have advantages and disadvantages, with the adipocytes representing a pure cell population free of diffusion barriers, but partially compromised by the isolation procedure (5, 6). In either adipocytes or tissue segments that have been deprived of GH for at least 3 hours, the initial metabolic responses to GH are much the same as those produced by insulin (7, 8, 9). Figure 1 shows some of the responses that can be demonstrated when segments of adipose tissue obtained from hypophysectomized rats are incubated with GH or insulin.

For these experiments we used a saturating concentration of GH and a concentration of insulin selected to give a response of comparable magnitude. In this and subsequent figures, each data point represents the mean of at least 8 independent observations, and the brackets indicate the standard errors. Very similar effects have been obtained with both isolated adipocytes and tissue segments obtained from normal rats, when tested after 3 hours of incubation.
in the absence of hormones (7). Increased uptake of glucose and conversion of its carbons to CO$_2$ and fatty acids result, at least in part, from stimulation of sugar transport across the cell membrane (6, 10). Stimulation of glycogen synthesis (11) and antagonism of epinephrine induced lipolysis (12) may result from interference with activation of the cyclic AMP dependent protein kinase, and possibly activation of cyclic AMP phosphodiesterase (12). Stimulation of pyruvate decarboxylation requires activation of an intramitochondrial enzyme which may require a second messenger derived from some component of the plasma membrane (13).

The insulin-like responses seldom persist beyond the second hour of incubation with GH, and by the third hour disappear completely despite the continued presence of the hormone (Figure 2). In this respect, the insulin-like effects of GH differ from those of insulin or the somatomedins, which persist for at least as long as the hormone is present (14). The time of onset and disappearance of each response varies some-

![Graph](image-url)

**Fig. 1.** Insulin-like effects of GH. Segments of epididymal fat from hypophysectomized rats were incubated for 1 hour in Krebs Ringer bicarbonate buffer containing 5.5 mM [U$^{14}$C]glucose and insulin or GH to measure glucose uptake, oxidation and conversion to fatty acids and glycogen. Pyruvate oxidation was measured during a 15 min incubation period in medium which contained 0.25 mM [1$^{14}$C]pyruvate and 11 mM fructose, and in this experiment, the concentration of insulin was 1 mU/ml. Antilipolysis was measured in the presence of 10 ng/ml of epinephrine in buffer that also contained 5.5 mM glucose and 4% bovine serum albumin. Each bar is the mean of 8 or 9 independent observations, and the standard errors are indicated by the vertical brackets. The effects of GH and insulin were statistically significant (p<.01) in all cases.
what depending upon the cellular apparatus involved (11, 15). Stimulation of glycogen synthesis and antilipolysis are of particularly brief duration. The insulin-like effects are likely to result from a common event since all have a similar dependence on GH concentration, all are irreversibly set in motion by an exposure of the tissues to hormone lasting less than 5 min (16), and all are subject to the refractory phenomenon (see below).

Even while the insulin-like responses are developing, GH initiates counter-regulatory responses at the level of the genome (Figure 3). Although inhibitors of transcription or translation have no discernible effect on the expression of insulin-like responses, they prevent their termination. In the upper panel of the figure, GH stimulation of glucose oxidation lasted only for 2 hours. Inhibition of RNA synthesis with actinomycin D or protein synthesis with puromycin, shown in the lower 2 panels, prolonged the...

Fig. 2. Time course for the effects of GH on [U\(^{14}\)C]glucose utilization in adipose tissue of hypophysectomized rats. Each point represents the mean and standard error calculated from data obtained from 8 rats. All tissues were incubated for a total of 4 hours. GH (1 \(\mu\)g/ml) was added at time 0 or after 1, 2, or 3 hours of incubation. [U\(^{14}\)C]glucose was added to all tissues only in the fourth hour. Thus, although tissues were exposed to GH for varying periods of time, changes in glucose utilization were measured during the same interval of incubation in vitro. Reproduced by permission from (11).

Fig. 3. The effects of actinomycin D (5 \(\mu\)g/ml) and puromycin (56 \(\mu\)g/ml) on the oxidation of [U\(^{14}\)C]glucose to \(^{14}\)CO\(_2\) by tissues from hypophysectomized rats. The tissues were incubated in the presence or absence of 1 \(\mu\)g/ml GH. The bars represent means of 8 observations, and the vertical lines indicate the standard errors. GH and inhibitors were added at time 0 and the tissues were incubated for 1, 2, or 3 hours before [U\(^{14}\)C]glucose was added to enable measurement of \(^{14}\)CO\(_2\) production in the second, third, and fourth hours. [U\(^{14}\)C]glucose was added directly for measurement of glucose oxidation in the first hour. Reproduced by permission from (17).
insulin-like response at least through the fourth hour. In similar experiments, with actinomycin D, insulin-like effects persisted through the fourth hour even when GH was removed by adsorption to antibodies after only 5 minutes (16). About 15 minutes after exposure to GH, adipocytes begin to synthesize the RNA that carries the information for termination of the insulin-like response (17).

Since the insulin-like effects of GH disappear after 2 or 3 hours even in the continued presence of GH, it should not be surprising that a second exposure to GH fails to induce a second insulin-like response unless many hours have passed (Figure 4). In this experiment, control tissues were preincubated for 3 hours in the absence of any hormone. Oxidation of glucose was more than doubled in response to ovine GH in the next hour, but the tissues on the right of the figure, which were preincubated with human GH for 3 hours, failed to respond to ovine GH in the fourth hour. This refractory phenomenon appears to be quite specific for GH, since the tissues retain normal responsiveness to insulin (17). Refractoriness is not simply a manifestation of the events that terminate insulin-like responses to GH. Removal of GH as late as 60–90 min after initial exposure prevents the appearance of refractoriness in the fourth hour (16) even though synthesis of the RNA that leads to termination of insulin-like responses is completed within this time (17). In fact, when GH was removed within 60 min, metabolism returned as expected to the unstimulated state, but a second exposure to GH in the fourth hour produced a second insulin-like response.

At about the same time that the insulin-like responses are terminating, at least 2 delayed responses become evident: increased lipolysis and decreased glucose utilization (Figure 5). The lipolytic effects shown on the left of the figure are sometimes seen with GH alone, but they are most readily demonstrable in the presence of some other agent such as glucocorticoid or theophylline (18, 19). The effects of GH shown here were seen when adipose tissue from normal rats was incubated in the presence of 100 ng/ml of the synthetic glucocorticoid, dexamethasone. The data on the right of the figure indicate the biphasic nature of GH action on glucose metabolism in adipose
tissue of hypophysectomized rats. The delayed inhibition of glucose metabolism, shown here in the fourth hour, is most readily demonstrable in tissues of hypophysectomized rats that have been pretreated with thyroid hormone, in this case 5 μg of T3 given 3 hours before sacrifice. It is noteworthy that the delayed effects of GH are not subject to the refractory phenomenon, and regardless of which other hormones we may need to make them evident in our in vitro experiments, these are the responses that are generally regarded as the physiologically relevant effects of GH in vivo.

The availability of GH produced by recombinant DNA technology has laid to rest the persistent idea that the various effects described above are due to other pituitary peptides which might contaminate even the purest preparations of GH. We have now had the opportunity to examine responses to a variety of biosynthetic human and bovine GH preparations and have found them to be indistinguishable from those elicited by GH purified from pituitary glands (20). In addition, everything that we have observed with human GH is also produced by rat GH. We therefore wished to know whether the different responses that are intrinsic to GH result from the same or different interactions between GH and adipocytes. At the same time we might ask whether insulin-like responses result from interaction of GH with the insulin receptor and whether refractoriness represents some extreme form of down regulation of receptors.

Meaningful studies of receptor binding required GH labeled to high specific radioactivity without loss of biological potency and isolated fat cells that retain the full range of responses to GH. We have been able to incorporate as many as 5 atoms of

![Fig. 5. Delayed effects of GH in adipose tissue. The data on lipolysis shown on the left were obtained using adipose tissue segments of normal rats incubated with 100 ng/ml of dexamethasone in the presence (●) or absence (○) of 30 ng/ml of hGH. The incubation medium was Krebs Ringer bicarbonate buffer and contained 5.5 mM glucose and 4% bovine serum albumin. Tissues were transferred to fresh incubation medium at the end of each hour, and glycerol released in the preceding hour was measured as an index of lipolysis. Significant lipolytic effects of GH (p<.01) were seen in hours 2, 3, and 4. The data on glucose utilization were obtained using segments of adipose tissue from hypophysectomized rats which had received 5 μg of triiodothyronine 3 hours before sacrifice. Tissues were incubated as described in Figure 3. The concentration of hGH used was 30 ng/ml, and its effects, though opposite in direction, were significant (p<.01) in both the first and fourth hours.](image-url)


125I per molecule of GH with no measurable loss of biological activity (21). Obtaining a responsive cell preparation was more of a problem, since insulin-like responses are most readily demonstrable in tissues of hypophysectomized rats, but adipocytes isolated from these tissues are unresponsive to both insulin and GH (6, 22, 23, 24). This problem was resolved with the discovery that the refractoriness of adipose tissue freshly isolated normal rats gives way to responsiveness within 3 hours of incubation in vitro (7).

Human GH labeled with 125I binds to a limited number of high affinity sites on the surface of adipocytes (8, 9, 25, 26). Specific binding of GH, defined as the difference between the total amount of hormone bound and that which is not displaceable by excess unlabeled GH, was concentration dependent over the range of 0 to about 150 ng/ml (Figure 6A). Binding was competitively inhibited by unlabeled human, bovine, ovine, or rat GH, but not by a 10,000-fold molar excess of prolactin, IGF-I, IGF-II, or insulin. Conversely, unlabeled GH failed to compete with iodinated insulin for binding to adipocytes, indicating that insulin-like responses to GH are independent of the insulin receptor. When the data in Figure 6A are plotted according to Scatchard, they fall on a straight line (Figure 6B), and suggest that there is a single class of about 20,000 binding sites per cell which are 50% occupied at a GH concentration of about 20 ng/ml. Scatchard analysis, however, is not entirely appropriate, since equilibrium conditions do not prevail, and hence these kinetic constants must be taken only as a rough approximations.

We observed no differences in [125I]hGH binding between sensitive and refractory cells, whether binding was assessed under nearly steady-state conditions (8), like those shown in Figure 6, or as a function of time (Figure 7). Thus refractoriness or sensitivity must be determined at some site beyond the binding of the hormone to its receptor. In Figure 8, we compare the concentrations of GH needed to produce half maximal biological responses with the theoretical receptor occupancy curve constructed assuming that there are 20,000 receptors per cell which are 50% occupied at a GH concentration of 20 ng/ml. The Figure in-

![Fig. 6. A. specific binding of [125I]hGH to normal adipocytes as a function of GH concentration. Each ml of cell suspension contained approximately one million cells. Data were obtained by incubating cells with 2 ng/ml of [125I]hGH plus sufficient unlabeled hGH to give the concentrations indicated on the ordinate. Specific binding is defined as the difference between total binding and that seen in the presence of 5 μg/ml of unlabeled hormone. See (8) for experimental details. B. Scatchard plot of data shown in A. R₀=number of binding sites per cells; Kd=ng/ml of GH needed for half saturation of binding sites.](image-url)
Fig. 7. Specific binding of $[^{125}I]hGH$ to adipocytes responsive or refractory to the insulin-like actions of GH. One epididymal fat pad from each of 12 normal rats was cut into small segments and incubated for 15 min in the presence of 1 $\mu$g/ml of ovine GH. The contralateral fat pads were preincubated in the absence of ovine GH. Isolated adipocytes were then prepared from each of the tissue pools, and the cells were incubated for an additional 2 hours in the absence of hormone, collected by centrifugation, and reincubated in the presence of 2 ng/ml of $[^{125}I]hGH$. For determination of nonspecific binding, excess (5 $\mu$g/ml) of unlabeled hGH was added. Each point is the mean of triplicate measurements. Refractoriness and sensitivity were verified by measuring $^{14}$CO$_2$ production by aliquots of cells from each pool incubated in the fourth hour with [U$^{13}$C]glucose in the presence or absence of 1 $\mu$g/ml of ovine GH. Reproduced by permission from (2).

Fig. 8. Theoretical relationship between receptor occupancy and biological responses. The arrows indicate the points on the curve that correspond to a half maximum response for the indicated effects of hGH. The curve was constructed assuming 20,000 receptors/cell, and a half saturating concentration of 1 nM hGH.
dicates good correspondence between receptor occupancy and biological responses, and suggests that there are no "spare" receptors for GH. Half maximal insulin-like responses require about 75% receptor occupancy, while the delayed responses are half maximal at only about 30% occupancy.

We further explored the nature of the GH receptor in the adipocyte membrane by covalently binding labeled hormone to receptor sites using the bifunctional cross-linking reagent disuccinimidyl suberate (27). The cells were incubated with 2 nM [125I]-hGH in the presence or absence of excess unlabeled hormone, washed twice and then incubated with disuccinimidyl suberate. Cell membranes were isolated, extracted, and their proteins then separated by electrophoresis on polyacrylamide gel. Radioactive bands were identified by autoradiography (Figure 9). The principal labeled complex appeared to have a molecular weight of about 130,000 daltons. Since 22,000 was contributed by GH, the binding component has a molecular weight of nearly 110,000 daltons. Two other labeled bands are also prominent on this gel. The band corresponding to 56,000 daltons is seen somewhat inconsistently, and the band which remained near the origin actually consists of two components, one of 240,000 and another of 310,000 daltons. Treatment of the membrane extract with a sulphhydryl reducing agent increased the intensity of the 130,000 dalton complex at the expense of the larger molecular weight complexes, suggesting either that the higher molecular weight complexes were dimers or trimers of the 110,000 dalton unit or contained the 110,000 dalton unit linked to other proteins by disulfide bonds. No bands were evident in gels prepared from cells which had incubated with [125I]-hGH in the presence of excess unlabeled hGH, indicating that the labeled bands represent saturable, high affinity binding sites. Studies with endoglycosidase F, which cleaves carbohydrate from its protein linkages, indicated that about 20% of the mass of the 110,000 dalton binding entity is carbohydrate (28). These observations are consistent with the possibility that GH interacts with a single binding component as suggested by linear Scatchard plots. The binding component

![Autoradiographic analysis of [125I]hGH covalently bound to adipocyte membrane proteins.](image)

Fig. 9. Autoradiographic analysis of [125I]hGH covalently bound to adipocyte membrane proteins. [125I]hGH was covalently linked to adipocytes using disuccinimidyl suberate in the absence (Lanes A and B) or presence of (Lanes C and D) of excess unlabeled hormone. The crude plasma membrane fraction from these cells was solubilized by boiling in sodium dodecyl sulfate (SDS) in the absence (Lanes A and C) or presence (Lanes B and D) of 100 mM dithiothreitol and applied to a 7.5% polyacrylamide gel. Reproduced by permission from (27).
Fig. 10. Release of $^{125}$I from adipocytes previously incubated with $[^{125}\text{I}]\text{hGH}$. Fat cells were preincubated with 2 ng/ml of $[^{125}\text{I}]\text{hGH}$ for 60 min at 37°C. Aliquots of cells were then studied after: (○) addition of excess (5 µg/ml) unlabeled hGH and transfer to a 0°C water bath; (△) addition of excess unlabeled hGH and continued incubation at 37°C; (●) washing twice to remove unlabeled hormone followed by reincubation at 37°C. Each point is the mean of 4 independent observations. The brackets indicate the standard errors.

Binding of GH to the adipocyte surface is virtually irreversible under physiological circumstances (29, 30). When we studied the release of bound $[^{125}\text{I}]\text{hGH}$, we found that virtually all of the $^{125}$I recovered from the cells was soluble in trichloroacetic acid, and was in the form of iodotyrosine. Dependence of release on cellular metabolism is shown in Figure 10. Loss of label was measured at 15 min intervals after addition of a 2500-fold excess of unlabeled hormone or resuspension of washed cells in GH-free medium. The cells that were incubated at 37°C lost their $^{125}$I with a half-time of about 25 min, but essentially no label was lost from cells that incubated at 0°C.

Leupeptin is an inhibitor of lysosomal proteolysis. In its presence, the release of previously bound $^{125}$I labeled hormone was severely reduced (Figure 11B). Furthermore, when hormone destruction was blocked with leupeptin, adipocytes accumulated more and more $[^{125}\text{I}]\text{hGH}$ when the hormone remain-

Fig. 11. The effects of leupeptin on the binding of $[^{125}\text{I}]\text{hGH}$ and subsequent release of $^{125}$I from adipocytes. The time course for specific binding of 1 nM $[^{125}\text{I}]\text{hGH}$ in the absence (●-●), or presence of 0.5 mM (□-□), 1.0 mM (△-△), or 1.5 mM (○-○) leupeptin is shown in panel A. In panel B is shown the release of $^{125}$I from cells washed and transferred to fresh incubation medium after 60 min of incubation with $[^{125}\text{I}]\text{hGH}$. Each point is the mean of triplicate observations. Reproduced with permission from (29).
ed in the medium (Figure 11A). Other inhibitors of lysosomal proteolysis, or of endocytosis, produced similar results (29). These observations suggest that the labeled hormone, and presumably the native hormone as well, is disposed of principally by destruction in the lysosomes.

Uptake and destruction of GH by this pathway, however, appears to be unrelated to hormone action, since hormonal responses are neither enhanced nor blocked in tissues that are incubated in the presence of leupeptin (Figure 12). We could find no difference in the concentration-response relationship for glucose oxidation or stimulation of lipolysis in tissues incubated with leupeptin or other agents that block lysosomal proteolysis, or by colchicine or monensin which are thought to interfere with endocytosis (29).

Ligand receptor complexes typically dissociate when exposed to the acidic conditions that prevail in the endosomes, but at an acidity approaching the endosomal pH, binding of GH to its receptor is at least as great as at neutral pH (26), suggesting that the hormone receptor complex, rather than just the hormone may be destroyed in the lysosomes. The receptor, therefore, must require continuous resynthesis. This idea is supported by the finding that adi-

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**Fig. 12.** Failure of leupeptin to modify the effects of growth hormone on the oxidation of [U-14C]glucose in segments of adipose tissue from hypophysectomized rats. Tissues were incubated with 5.5 mM [U-14C]glucose and the indicated concentrations of hGH for 1 hour. Each point represents the mean of 8 independent observations.

**Fig. 13.** The effects of preincubation with 20 µg/ml cycloheximide, (●—●), 200 µg/ml puromycin (Δ—Δ), or 5 µg/ml actinomycin D (○—○) on binding of [125I]hGH. All cells were incubated for 2.5 hours. Antibiotics were added to different flasks at 30 min intervals to achieve graded times of exposure. After preincubation, the cells were collected, washed, and reincubated for 10 min with 1.5 nM [125I]hGH in the presence or absence of excess unlabeled hGH. Each point represents the mean of triplicate observations. Reproduced by permission from (31).
Adipocytes which preincubated with inhibitors of protein synthesis lost their ability to bind or respond to GH (9, 31). Cells incubated with either cycloheximide, shown by the filled circles, or puromycin, shown by the triangles, lost available surface binding sites with a half-time of about 45 min (Figure 13). To measure turnover of receptors, adipocytes were incubated with inhibitors of protein synthesis for the indicated times. The cells were then transferred to medium which contained 1.5 nM $[^{125}I]$hGH and reincubated for an additional 10 min. Loss of binding occurred at a similar rate when cells were incubated with $[^{125}I]$hGH along with the inhibitor. Since inhibition of RNA synthesis with actinomycin D, shown by the open circles, did not decrease binding, it is likely that the messenger RNA that codes for the GH receptor is stable. A comparably short half-life for surface receptors was demonstrated in other studies using swainsonine to inhibit some glycosidation of newly synthesized receptor protein (32). Within 2 hours virtually all of the 110,000 dalton surface binding sites were replaced with receptors which had an apparent molecular weight of about 100,000 daltons (28).

A further indication that surface binding decrease in specific binding in sham operated animals 8 hours after operation was also significant (p<.01).

Fig. 14. The change in binding of $[^{125}I]$hGH to rat adipocytes with time after hypophysectomy. Specific binding of $[^{125}I]$hGH at 3 ng/ml is shown in panel A and at 30 ng/ml in panel B. Binding was initiated by adding labeled hormone to fat cells at 2 hours prior to the indicated times after hypophysectomy and was allowed to proceed for 2 hours. Binding was determined in cell suspensions prepared from individual animals. For the sham operated and acutely hypophysectomized rats each bar represents the mean for the number of animals given in parentheses. For unoperated and chronically hypophysectomized rats, each bar represents the mean of specific binding in 9-10 experiments each consisting of 5-8 rats. Asterisks indicate a statistically significant effect of hypophysectomy (p<.01).
sites for GH turn over rapidly was obtained when we examined the effects of hypophysectomy on GH binding (Figure 14). GH binding was measured using either a 3 ng/ml trace of hormone, or a concentration of 30 ng/ml which was nearly saturating. By 8 hours after surgery, the ability of adipocytes to bind GH was reduced by about a factor of 2, and this reduction was nearly as great as that seen 15 days after hypophysectomy. Decreased binding resulted from a decrease in number of binding sites rather than decreased affinity, since it was equally evident at saturating and at very low concentrations of GH (33). Curiously, the initial reduction in binding was as profound in adipocytes from rats that were subjected only to sham operation, but binding returned toward normal by 24 hours after surgery in these animals. Right after surgery, the sham operated animals were probably as deficient in GH as the hypophysectomized animals, since stress inhibits GH secretion in the rat (34). GH binding was restored nearly to normal in adipocytes isolated from hypophysectomized rats which received an intraperitoneal injection of GH four hours earlier (Figure 15), but not in rats that received GH 16 hours earlier. These relatively rapid, but short-lived, effects of GH on the availability of its binding sites suggest that the frequent bursts of GH secretion that typically occur in the rat may be needed to maintain the normal binding capacity of adipocytes and perhaps other cells as well.

In summary, GH acts directly on adipose tissue to produce a rich assortment of biological effects. It produces both insulin-like and antiinsulin-like effects, and also controls the cellular changes that determine which of these families of responses will be expressed. In addition, it maintains normal receptor capacity on adipocytes even though biological responsiveness does not correspond to the number of available receptors. Just how the GH signal is processed within the adipocyte and the nature of the immediate post-receptor events continue to provide fertile ground for research, which must ultimately reveal just how GH works.

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