Regulation of Tyrosine α-Ketoglutarate Transaminase in Rat Liver

VI. INDUCTION BY PANCREATIC HORMONES*

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SUMMARY

The role of the pancreatic hormones, insulin and glucagon, in the regulation of hepatic tyrosine transaminase (L-tyrosine: α-oxoglutarate aminotransferase, EC 2.6.1.5) was studied in adrenalectomized rats. Each of these hormones initiated a rapid but limited increase in the enzyme level, which reached a maximum after 2.5 to 3 hours. The optimal doses of insulin and glucagon per 100 g of body weight were 0.75 unit (33 μg) and 150 μg, respectively. Alloxan-induced diabetes in adrenalectomized rats caused a significant increase in the transaminase level after 5 days. Immunochemical-isotopic analyses showed that the pancreatic hormones cause an increase in the rate of transaminase synthesis which is comparable to that caused by hydrocortisone. Effects of the pancreatic hormones on the rate of enzyme synthesis are not additive with one another but are additive with the effect of hydrocortisone. Induction by either insulin or glucagon was inhibited by actinomycin D. A discrete mechanism for induction of this enzyme, which is steroid-independent and which can be initiated in vivo by either insulin or glucagon, is indicated.

Earlier papers of this series (1, 2) described the purification of rat liver tyrosine transaminase (L-tyrosine-α-oxoglutarate aminotransferase, EC 2.6.1.5), the preparation of antitransaminase antiserum, and immunochemical analyses which demonstrated that hydrocortisone elevates the hepatic level of this enzyme by selectively increasing the rate of transaminase synthesis. The preceding paper (3) describes a selective repression1 of the synthesis of this enzyme in the livers of rats treated with the hypophysial growth hormone. In the course of these latter experiments, it was found that under some conditions a capacity for increasing the enzyme level remained in rats deprived of glucocorticoid hormones by adrenalectomy. This prompted a search for extra-adrenal hormonal factors capable of inducing this enzyme, which led to the finding reported here: that the polypeptide hormones insulin and glucagon are both capable of selectively stimulating the synthesis of hepatic tyrosine transaminase. A similar effect of insulin on the glucocorticoid-inducible tryptophan pyrrolase of rat liver was reported several years ago by Schor and Frieden (4).

EXPERIMENTAL PROCEDURE

Treatments—Male rats from the Charles River Breeding Laboratories were fed ad libitum until experiments began; 1% NaCl was given as drinking water after adrenalectomy. Insulin and glucagon were injected intraperitoneally as solutions in 0.15 M NaCl. Alloxan (20 mg/100 g) was given intravenously to adrenalectomized rats that were fasted for 24 hours prior to injection. Actinomycin D was dissolved in a minimal volume of acetone and diluted with 0.15 M NaCl; the amount of acetone given never exceeded 20 μl.

Analytical—Tyrosine transaminase was assayed as described before (5) in supernatant fractions of 20% (weight per volume) homogenates in 0.15 M KCl-0.001 M EDTA (pH 8) that were centrifuged at 81,000 × g for 45 min in some experiments and at 20,000 × g for 15 min in others. The unit of activity is the amount required to form 1 μg of p-hydroxyphenylpyruvate in the 10-min assay employed. Proteins were estimated by the biuret procedure (6). The immunochemical method for measurement of the rate of transaminase synthesis has been described previously (2, 7, 8). Measurements of radioactivity in protein were made on samples pipetted onto filter paper discs that were freed of nonprotein radioactivity by the washing procedure of Mans and Novelli (9). Phosphoenolpyruvate carboxykinase activity was measured by a previously described procedure (10). Mean a selective stimulation and inhibition, respectively, of the rate of enzyme synthesis; no genetic or other mechanism is implied.
Materials—Crystalline insulin was from the Sigma Chemical Company, and "glucagon-free" pork insulin was a generous gift from Dr. Otto Behrens of the Eli Lilly Company. Glucagon (containing lactose) was from Lilly and alloxan from Nutritional Biochemicals. Actinomycin D was a gift from the Merck Sharp and Dohme Research Laboratories. Rabbit antiserum containing antibody to rat liver tyrosine transaminase had the same characteristics as that described before (2). The partially purified transaminase preparations used as carrier in immunochemical experiments were prepared through the DEAE-cellulose step in the purification scheme described previously (2).

RESULTS

Induction by Pancreatic Hormones—The time course of changes in hepatic tyrosine transaminase activity, after administration of insulin (glucagon-free) to adrenalectomized rats, is shown in Fig. 1. The hormone caused a sharp increase in the enzyme level which was readily apparent within 1 hour. Activity reached a peak 3 to 4 times above the untreated (zero time) level 3 hours after the hormone was given, and then declined in the usual first order fashion; it had nearly returned to the base level within 5 hours. The estimated half-life during the declining phase of this transition was 1.6 hours, in agreement with that obtained in measurements of the normal turnover rate of this enzyme (11). The insulin dose required for a maximal increase in enzyme activity was measured 2.6 hours after the hormone was given. A dose (per 100 g) of as little as 0.1 unit (4 μg) was effective, and 0.75 unit (33 μg) of glucagon-free insulin gave a maximal response (Fig. 2). Because of the low tolerance of adrenalectomized rats for insulin, it was necessary in these and subsequent experiments with insulin to inject glucose at periodic intervals to combat hypoglycemic shock. When required, 2 ml of 10% glucose were given intraperitoneally at intervals as frequent as each hour. Glucose administration did not alter the transaminase response to insulin or change the enzyme level in otherwise untreated controls.

Administration of glucagon brought about an increase in the transaminase that was kinetically similar to the insulin effect (Fig. 3). The dose of this hormone required for a maximal increase, measured 2.5 hours after injection, was 150 μg/100 g (Fig. 4).

Peak levels attained after glucagon treatment were generally similar to or slightly higher than the increases caused by insulin, but neither of these protein hormones was as effective as hydrocortisone, which elevates this enzyme 10-fold or more. The steroid-mediated induction also differs kinetically, as there is a lag of 60 to 90 min after hydrocortisone and a more prolonged response which yields maximal enzyme levels after 5 to 7 hours (12, 13).

Inhibition by Actinomycin—Inhibition of RNA synthesis by actinomycin blocks the induction of tyrosine transaminase by hydrocortisone (14) and the repression of this enzyme by growth hormone (3). As seen in Table I, actinomycin similarly prevents the elevation of this enzyme by either of the pancreatic hormones. Since the glucagon preparations employed contained lactose, animals treated with lactose alone were used as controls in this experiment; this sugar was found to have no effect on the transaminase (cp. to controls in Figs. 1 through 4).

**Fig. 1.** Time course of induction of rat liver tyrosine transaminase by insulin. Rats weighing 200 to 320 g and adrenalectomized 1 day before the experiment were given 0.75 insulin unit/100 g ("glucagon-free", Eli Lilly Company) at zero time. They also received 2 ml of 10% glucose at hourly intervals when necessary to combat hypoglycemic shock. Controls (zero time) included two animals given three such glucose injections and three that were untreated. Each of the other points represents the mean (± standard error) of three animals.

**Fig. 2.** Tyrosine transaminase induction in rat liver as a function of insulin dose. Rats weighing 225 to 312 g and adrenalectomized 2 days before the experiment were given insulin ("glucagon-free", Eli Lilly Company) as indicated and killed 2.6 hours after the injection. Glucose was given as described in the legend to Fig. 1. Controls (zero insulin dose) were injected with comparable volumes of 0.15 M NaCl. Each point represents the mean (± standard error) of four rats.

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FIG. 3. Time course of induction of rat liver tyrosine transaminase by glucagon. Rats weighing 210 to 288 g and adrenalectomized 3 days before the experiment were given 100 pg of glucagon (plus 4.2 mg of lactose) per 100 g. Controls received 4.2 mg of lactose/100 g. Each point represents the mean (± standard error) of three rats.

The transaminase level is frequently high in hypophysectomized rats, but can be elevated further by the pancreatic hormones, e.g., as shown for insulin in Table I.

Rate of Synthesis Analyses—Evidence that the changes in enzyme levels brought about by insulin and by glucagon reflect selective stimulation of the rate of transaminase synthesis is presented in Table II. In this procedure the extent of incorporation of 14C-amino acid into the enzyme (isolated by precipitation with antitransaminase serum (2)), in a labeling period which is short relative to the turnover time of the enzyme, is a relative measure of its rate of synthesis, as described in detail in previous publications (7, 8). A control precipitation was carried out to measure the extent of co-precipitation of labeled, nontransaminase proteins, and the radioactivity of control precipitates was subtracted from that of the transaminase-antitransaminase complex to obtain the values reported as transaminase radioactivity in Table II. Labeling of the total soluble proteins was also determined, since the specificity of the hormonal effects on transaminase labeling can best be ascertained when transaminase radioactivity is expressed relative to that of the bulk of the soluble proteins. This expression also provides a correction for hormonal effects on amino acids pools, for pool changes would be reflected in transaminase labeling as well as that of the total proteins. Labeling of the soluble proteins was slightly increased by insulin and appreciably reduced by glucagon (Table II); these changes probably reflect hormonal alteration of the extent of dilution of the isotopic amino acid with unlabeled amino acid.

Insulin effected a nearly 3-fold increase in the rate of transaminase synthesis, measured 2.5 hours after giving the hormone (Table II). This is a time at which the enzyme level is nearing its peak (Fig. 1), and it is clear that the hormonal effect on enzyme synthesis is probably not maximal at this time. In contrast, glucagon caused a 10-fold increase in the rate of synthesis of the enzyme, measured at a time (1.5 hours) when the enzyme level is increasing at the maximal rate (Fig. 3). These analyses demonstrate that transaminase synthesis is increased by the pancreatic hormones, and also show that the time at which the isotopic analysis is made must be carefully considered if quantitative comparisons are desired.

![Graph](http://www.jbc.org/)

Fig. 4. Tyrosine transaminase induction in rat liver as a function of glucagon dose. Rats weighing 210 to 288 g and adrenalectomized 3 days before the experiment were given the indicated dose of glucagon together with a constant amount (4.2 mg/100 g) of lactose, and were killed 2.5 hours after the injection. Controls received lactose (4.2 mg/100 g) alone. Each point represents the mean (± standard error) of three rats.

**TABLE I**

Inhibition by actinomycin D

Hypophysectomy was at least 10 days, and adrenalectomy 3 days, before the experiment. Given by intraperitoneal injection at zero time were: glucagon, 100 μg/100 g (plus 4.2 mg of lactose); lactose, 4.2 mg; insulin, 1 unit/100 g (Sigma); actinomycin D, 75 to 100 μg/100 g. The rats were killed for assay 2.5 hours after treatment in the glucagon experiment and 4 hours after treatment in the insulin experiment. Data are the mean ± standard error.

<table>
<thead>
<tr>
<th>Endocrine status</th>
<th>Treatmenta</th>
<th>Tyrosine transaminase units per mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenalectomized</td>
<td>Lactose (3)</td>
<td>17 ± 3</td>
</tr>
<tr>
<td></td>
<td>Glucagon (3)</td>
<td>87 ± 5</td>
</tr>
<tr>
<td></td>
<td>Glucagon + actinomycin (3)</td>
<td>28 ± 2</td>
</tr>
<tr>
<td>Hypophysectomized</td>
<td>None (2)</td>
<td>51 ± 3</td>
</tr>
<tr>
<td></td>
<td>Insulin (3)</td>
<td>110 ± 16</td>
</tr>
<tr>
<td></td>
<td>Insulin + actinomycin (3)</td>
<td>46 ± 4</td>
</tr>
</tbody>
</table>

* The numbers in parentheses are number of observations.
Alloxan Diabetes—In their study of insulin effects on rat liver tryptophan pyrrolase, Schor and Frieden reported an apparently paradoxical increase in this enzyme in rats made diabetic with alloxan (4). We measured the tyrosine transaminase in the livers of adrenalectomized rats at intervals after intravenous administration of alloxan. After 5 days the rats were frankly diabetic, as indicated by increased blood glucose and by increased levels of phosphoenolpyruvate carboxykinase, an enzyme known to increase in diabetes. Carboxykinase levels increased from a specific activity of 30 in adrenalectomized controls to 87 in the diabetic, adrenalectomized rats. These values are in good agreement with those reported by Shrago et al. (15). Tyrosine transaminase levels began to increase after 48 hours but did not reach significantly higher values until after 5 days, when the level in diabetic animals was 73 ± 10 compared to 28 ± 2 in controls (units per mg of protein, mean ± standard error for seven and six determinations, respectively).

Blockage of Repression—As shown in the accompanying paper (3), the administration of growth hormone to adrenalectomized rats brings about selective repression of the synthesis of tyrosine transaminase. In Table III are reported analyses made 4 hours after administration of a single dose of each of the inducing hormones alone, and of each of these hormones together with growth hormone. The doses used here are optimal for each hormone when tested alone (Figs. 2 and 4, and Reference 1). At these dose levels the induction effect obtains, since the enzyme level increases when the inducing hormones are given either alone or together with growth hormone (Table III). Induction by either insulin or glucagon was somewhat inhibited by the presence of growth hormone, and the steroid induction was markedly reduced when growth hormone was given together with hydrocortisone, as observed earlier by Harding and Rosen (16).

Additivity of Inducing Hormones—The question of whether the three inducing hormones are each capable of inducing transaminase synthesis independently was first analyzed in several experiments in which the effects of the hormones, singly and in combination, were tested in terms of the extent of increase in the enzyme level. A combination of optimal doses of both insulin and glucagon was never more effective than when each was given alone. Combining treatment with either of these protein hormones with hydrocortisone treatment, however, led to quite variable results, with the extent of induction being clearly additive in some experiments but not additive in others.

A consideration of the differences in time course of response to hydrocortisone, on the one hand, and to insulin or glucagon, on the other, points to the difficulty in reaching a conclusion in this type of experiment. The enzyme level rises quickly after insulin or glucagon is given, reaches maximal activity after 2 to 3 hours (Figs. 1 and 3), and then declines, whereas the response to hydrocortisone is initially slower but prolonged for 5 to 7 hours (12, 13). Under these circumstances, if the protein and steroid hormones operated by different mechanisms, their effects on the enzyme level would be expected to be additive at some points in time and not additive at others. However, with this difference in the time course of response, it is conceivable that effects of the different hormones on the same intracellular mechanism, separated in time, could yield additive increases in the enzyme level and lead to the erroneous conclusion that different mechanisms are involved. For this reason we chose to analyze directly the hormones' effects on the rate of enzyme synthesis at time points when each can be expected to be exerting its maximum effect.

In Table IV, data from a representative experiment of this

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**Table II**

**Immunoechemical analysis of induction by pancreatic hormones**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Treatment</th>
<th>Radioactivity in Tyrosine transaminase</th>
<th>Relative radioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Transaminase activity</td>
<td>Radioactive transaminase (A)</td>
</tr>
<tr>
<td>1</td>
<td>None (3)</td>
<td>31 ± 2</td>
<td>100 ± 11</td>
</tr>
<tr>
<td></td>
<td>Insulin (5)</td>
<td>114 ± 10</td>
<td>554 ± 84</td>
</tr>
<tr>
<td>2</td>
<td>NaCl (2)</td>
<td>24 ± 5</td>
<td>63 ± 9</td>
</tr>
<tr>
<td></td>
<td>Glucagon (4)</td>
<td>91 ± 10</td>
<td>642 ± 25</td>
</tr>
</tbody>
</table>

---

**Table III**

**Blockage of growth hormone repression by inducing hormones**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Treatment</th>
<th>Tyrosine transaminase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>units/mg protein</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>28 ± 3 (6)</td>
</tr>
<tr>
<td></td>
<td>Growth hormone</td>
<td>13 ± 1 (8)</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>65 ± 8 (7)</td>
</tr>
<tr>
<td></td>
<td>Growth hormone + insulin</td>
<td>56 ± 2 (3)</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>27 ± 2 (5)</td>
</tr>
<tr>
<td></td>
<td>Growth hormone</td>
<td>15 ± 2 (6)</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td>41 ± 5 (6)</td>
</tr>
<tr>
<td></td>
<td>Growth hormone + glucagon</td>
<td>37 ± 3 (6)</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>200 ± 16 (6)</td>
</tr>
<tr>
<td></td>
<td>Growth hormone + hydrocortisone</td>
<td>161 ± 21 (6)</td>
</tr>
</tbody>
</table>
Additivity of inducing hormones

Rats weighed 200 to 300 g and were adrenalectomized 18 hours before treatment began. Hydrocortisone (2.5 mg/100 g) was given at zero time and insulin (1 unit/100 g) and glucagon (150 μg/100 g) 1.5 hours later. 14C-Isoleucine (23 μC, 160 mC per mmole) was given at 3 hours, and the animals were killed 10 min after isotope administration. Analyses were made as described for Experiment 1, Table III. Radioactivity of the second (control) precipitate averaged 49 cpm and was essentially constant.

Multiple Injections of Insulin and Glucagon—The isotopic analyses presented above (Tables II and IV) show that the initial increase in enzyme synthesis effected by insulin or glucagon is just as large as that which follows hydrocortisone administration. This result calls for an explanation of the relatively limited extent and duration of the increase in the enzyme level which follows treatment with the protein hormones. As a test of the possibility that the response is limited because of rapid metabolism and removal of the protein hormones, we gave repeated injections of either insulin or glucagon at 1.5-hour intervals. The results of these experiments (Fig. 5) show that multiple injections did not appreciably change either the extent or the duration of the increase in the enzyme level which differs in both rate and extent from that initiated by hydrocortisone. The enzyme level rises quickly when insulin or glucagon is given; in contrast, the level remains unchanged for a period of 60 to 90 min after treatment with hydrocortisone. Transaminase synthesis remains elevated for a period of only 2 to 3 hours after treatment with insulin or glucagon, whereas a single injection of hydrocortisone stimulates synthesis for a period of 5 to 7 hours. As a result, the increase in the enzyme level after treatment with insulin or glucagon is limited (3- to 5-fold) in the well known induction of this enzyme by adrenal steroids.

DISCUSSION

These experiments show that synthesis of hepatic tyrosine transaminase is increased in rats treated with either of the protein hormones from the pancreas, insulin and glucagon. This effect is similar for both of these hormones in all properties thus far examined, but different in several important respects from the well known induction of this enzyme by adrenal steroids.

The protein hormones initiate an increase in the enzyme level which differs in both rate and extent from that initiated by hydrocortisone. The enzyme level rises quickly when insulin or glucagon is given; in contrast, the level remains unchanged for a period of 60 to 90 min after treatment with hydrocortisone. Transaminase synthesis remains elevated for a period of only 2 to 3 hours after treatment with insulin or glucagon, whereas a single injection of hydrocortisone stimulates synthesis for a period of 5 to 7 hours. As a result, the increase in the enzyme level after treatment with insulin or glucagon is limited (3- to 5-fold) in

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**Table IV**

Additivity of inducing hormones

<table>
<thead>
<tr>
<th>Hormone treatmenta</th>
<th>Transaminase activity</th>
<th>Radioactivity in transaminase</th>
<th>Soluble proteins</th>
<th>Relative radioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>units/mg proteinb</td>
<td>cpmc</td>
<td>cpm X 10⁸</td>
<td>A X 10⁸/b²</td>
</tr>
<tr>
<td>None (2)...........</td>
<td>31 ± 3</td>
<td>88</td>
<td>1.04</td>
<td>0.91 ± 0.14</td>
</tr>
<tr>
<td>Hydrocortisone (2)</td>
<td>104 ± 10</td>
<td>882</td>
<td>1.29</td>
<td>6.56 ± 2.5</td>
</tr>
<tr>
<td>Insulin (4).......</td>
<td>105 ± 11</td>
<td>600</td>
<td>0.88</td>
<td>6.86 ± 0.78</td>
</tr>
<tr>
<td>Glucagon (3)......</td>
<td>98 ± 2</td>
<td>522</td>
<td>0.82</td>
<td>6.32 ± 0.88</td>
</tr>
<tr>
<td>Hydrocortisone + insulin (3)</td>
<td>269 ± 19</td>
<td>1716</td>
<td>1.15</td>
<td>14.62 ± 0.84</td>
</tr>
<tr>
<td>Hydrocortisone + glucagon (3)</td>
<td>216 ± 24</td>
<td>1880</td>
<td>1.24</td>
<td>13.71 ± 3.4</td>
</tr>
<tr>
<td>Insulin + glucagon (2)</td>
<td>109 ± 6</td>
<td>503</td>
<td>0.89</td>
<td>5.96 ± 1.0</td>
</tr>
<tr>
<td>Hydrocortisone + insulin + glucagon (3)</td>
<td>225 ± 1</td>
<td>1224</td>
<td>0.85</td>
<td>14.32 ± 1.5</td>
</tr>
</tbody>
</table>

a Number of animals in parentheses.
b Mean.
c Mean ± standard error.

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**Fig. 5.** Changes in rat liver tyrosine transaminase after multiple injections of the pancreatic hormones. Rats weighing about 250 g and adrenalectomized 2 days before the experiment were given insulin ('glucagon-free', Eli Lilly Company, 0.5 unit/100 g) or glucagon (150 μg/100 g) at zero time and again at 1.5, 3, and 5 hours for those remaining at these times. Those given insulin (open circles, dashed range lines) were given glucose as described in the legend to Fig. 1; the solid circles, solid range lines indicate those given glucagon. Each point represents the mean (± standard error) of three rats.

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kind are presented. Rates of enzyme synthesis were estimated by pulse labeling followed by immunochemical isolation of the labeled enzyme, as described above. Isotopic amino acid was given 3 hours after hydrocortisone and 1.5 hours after the protein hormone; livers were taken for analysis 10 min after isotope administration. Individual variation in the extent of uptake of isotope into the liver proteins (including the transaminase) is frequently great when such brief labeling periods are employed, and was unusually marked in this experiment. Expression of transaminase radioactivity relative to that of the soluble proteins provides a correction for this variation (as well as for hormonal alteration of amino acid pools, as described above), and hence the variance in this parameter ('relative radioactivity') is given. Averages of the count rates of the enzyme-antibody precipitates and of the soluble proteins are also presented in Table IV as an indication of the magnitude of the changes measured.

These isotopic data clearly demonstrate that (a) the extent of increase in the rate of enzyme synthesis is approximately the same (here, 7- to 8-fold) with each of the inducing hormones; (b) effects of the protein hormones on synthesis are not additive with one another; and (c) induction by either (or both) of the protein hormones is additive with the steroid-mediated induction, yielding a 15- to 16-fold increase in synthesis in animals treated with both hydrocortisone and either insulin or glucagon, or both of these. Changes in the enzyme level are entirely consistent, for hydrocortisone elicited synthesis of about 130 enzyme units compared to about 70 units elicited by insulin or glucagon or both. Combining steroid treatment with the protein hormones resulted in an increase of approximately 200 units of enzyme per mg of soluble protein. Each of the three points made here has been confirmed in other experiments of this type.

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*Mean = ± standard error.
Regulation of protein synthesis in muscle by insulin has been well established (for a review, see Reference 20). In liver, insulin is known to stimulate an increase in the level of glucokinase, which apparently reflects increased glucokinase synthesis (21, 22); this effect of insulin is completely blocked by glucagon (23). Insulin also elevates the glucocorticoid- inducible tryptophan pyrrolase (4), and long term treatment with insulin reduces the level of several hepatic enzymes involved in gluconeogenesis (24). Glucagon has been reported to increase the levels of a variety of hepatic enzymes (15, 95, 96). Although these and other studies demonstrate a wide spectrum of effects of the pancreatic hormones on liver enzyme levels, most of the measurements have been made only of changes in enzyme activity; the extent to which these changes reflect specific alterations in enzyme synthesis is not known.

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REFERENCES

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