Regulation of Tyrosine-α-Ketoglutarate Transaminase in Rat Liver

SUMMARY

The level of tyrosine transaminase (L-tyrosine:2-oxoglutarate transaminase, EC 2.6.1.5) in cultured hepatoma cells was markedly elevated by increasing the concentration of amino acids in the medium. The active component of the amino acid mixture was identified as L-leucine. D-Leucine, D-1-trifluoroleucine, and the deaminated product of leucine, α-ketosaccharic acid, were inactive. At the optimum concentration (5 mM) L-leucine elicited an 8- to 10-fold increase in the transaminase level; the response was maximum at 12 to 14 hours and persisted for at least 24 hours. The half-life of the transaminase, estimated both indirectly from kinetics of change in enzyme activity after addition or withdrawal of amino acids and directly by isotopic-immunochemical methods, was 6 hours in the presence of 5 mM L-leucine and 2 hours after return of the cells to the basal medium (0.2 mM L-leucine). Pulse labeling experiments indicated that L-leucine also increased the rate of tyrosine transaminase synthesis by a factor of 3 to 4. Thus L-leucine increased the level of tyrosine transaminase by a dual effect on both synthesis and degradation of the enzyme. Combinations of L-leucine with the hormonal inducers hydrocortisone and insulin yielded additive effects on the transaminase levels. Hydrocortisone or insulin effectively induced the transaminase in leucine-free medium, and L-leucine further increased, in an additive manner, the enzyme activity of the transaminase. Hydrocortisone synthesis was determined 6 hours later. The concentrations of amino acids used were five times greater than those of the basal medium; the mixture employed contained all 18 amino acids except as indicated.

It is well established that the level of tyrosine transaminase (L-tyrosine:2-oxoglutarate transaminase, EC 2.6.1.5) in rat liver (1) and in cultured hepatoma cells (2-4) can be regulated both by adrenal steroids and by insulin. Elevation of hepatic tyrosine transaminase activity following administration of amino acid mixtures has also been reported, but the active agent in this effect has not been identified. Rosen and Milholland (5) have shown, for example, that the administration of casein hydrolysate (1 g per rat) increases the hepatic tyrosine transaminase in adrenalectomized rats. Tryptophan and tyrosine, when given alone or in combination to adrenalectomized rats, in amounts equal to those present in casein hydrolysate, did not increase the transaminase activity; yet these authors have previously demonstrated (6) a significant increase of tyrosine transaminase in adrenalectomized rats given a large dose of L-tryptophan. Labrie and Korner (7) reported that administration of an amino acid mixture not containing tyrosine and

| Amino acid increased | Concentration | Tyrosine transaminase activity in H35 cells |
|----------------------|--------------|------------------------------------------|
| None                 |              | 100                                      |
| L-Leucine            | 1.00         | 347                                      |
| L-Isoleucine         | 1.00         | 120                                      |
| L-Methionine         | 0.25         | 127                                      |
| L-Tryptophan         | 0.10         | 102                                      |
| L-Tyrosine           | 0.50         | 117                                      |
| L-Valine             | 1.00         | 112                                      |
| L-Lysine             | 0.90         | 106                                      |
| L-Histidine          | 0.25         | 118                                      |
| L-Arginine           | 0.50         | 128                                      |
| L-Threonine          | 1.00         | 109                                      |
| L-Glutamine          | 10.00        | 144                                      |
| L-Cystine            | 0.25         | 120                                      |
| L-Phenylalanine      | 0.50         | 122                                      |
| Mixture              |             | 5 times basal                            |
| Mixture minus L-leucine | 5 times basal | 305                                      |
| Mixture minus L-tryptophan | 5 times basal | 170                                      |
| Mixture minus L-tyrosine | 5 times basal | 341                                      |

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tryptophan was as effective as a complete mixture in increasing tyrosine transaminase levels in hypophysectomized rats. A positive correlation between changes in amino acid transport and tyrosine transaminase activity was noted when these parameters were altered by either hormonal or dietary means (8). Since insulin enhances the uptake of amino acids in the liver (9) as well as in H-35 cells (10), it seemed conceivable that the induction of tyrosine transaminase by insulin could be mediated by enhanced uptake of amino acids. To test this possibility and to analyze further the role of amino acids in transaminase regulation, we investigated the effects of altering amino acid levels on tyrosine transaminase of cultured H-35 cells. The level of tyrosine transaminase in cultured cells was indeed stimulated by increasing the concentration of amino acids in the medium. The active component of the mixture of amino acids was found to be L-leucine. The effect was specific for L-leucine insofar as its analogues, d-leucine and trifluoroleucine, or its deaminated product, α-ketoisocaproic acid, were inactive. Kinetic as well as immunological-isotopic studies revealed that L-leucine increased both the rate of synthesis and decreased the rate of degradation of the transaminase. Addition of L-leucine, in combination with either hydrocortisone or insulin, gave additive increases of the enzyme level, suggesting that induction by hydrocortisone or by insulin is not mediated by this amino acid.

**EXPERIMENTAL PROCEDURE**

Reuber (H-35) hepatoma cells were grown in monolayer at 37° in plastic tissue culture flasks as previously described by Reed and Kenney (11). The growth medium was Eagle’s basal medium enriched 4-fold with amino acids and vitamins and supplemented with 20% fetal calf serum and 5% calf serum. All experiments were performed with early stationary phase (8 to 9 days) cultures maintained for 20 to 24 hours in serum-free, unenriched Eagle’s basal medium (1XBME), unless otherwise indicated.

All tissue culture materials were purchased from Grand Island Biological Company, Grand Island, New York. The labeled compounds were obtained from Schwarz/Mann, Orangeburg, New York. Hydrocortisone (grade A) and insulin (24 units per mg) were from Calbiochem and Sigma, respectively. Columbia Organic Chemical, Inc., Columbia, South Carolina, was the source of α-ketoisocaproic acid.

Cells were lysed in 0.15 M KCl-0.001 M EDTA-0.005 M α-ketoglutarate by alternately freeze-thawing three times in liquid nitrogen and a 37° water bath as previously described (4). The supernatant fractions of cell lysates, centrifuged at 40,000

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**TABLE II**

| Addition                  | Tyrosine transaminase (units/mg protein) |
|---------------------------|------------------------------------------|
| None                      | 52.1 ± 2.7                               |
| L-Leucine                 | 279.1 ± 17.5                             |
| D-Leucine                 | 52.9 ± 4.6                               |
| D,L-Leucine               | 93.8 ± 10.1                              |
| D,L-Trifluoroleucine      | 53.7 ± 4.1                               |

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**FIG. 1 (left).** Effect of varying concentration of L-leucine on tyrosine transaminase levels in H-35 cells. Transaminase activity measurements were made 6 hours after the addition of the amino acid.

**FIG. 2 (center).** Time course of the response of tyrosine transaminase to L-leucine. Leucine (5 mM) was added at zero time to monolayer cultures (△—△), or omitted from controls (○—○).

**FIG. 3 (right).** Kinetics of decay of tyrosine transaminase following removal of L-leucine. Monolayer cultures were pretreated for 12 hours with basal medium (Eagle’s) containing 5 mM L-leucine. At the end of pretreatment this medium was decanted and the cultures were washed three times with fresh basal medium (5 ml per flask). At zero time, basal medium with (○—○) or without (△—△) 5 mM L-leucine was placed on cultures.
rpm for 35 min, were assayed directly for tyrosine transaminase as described by Reel and Kenney (11). The unit of activity is defined as the amount required to form 1 µg of p-hydroxyphenylpyruvate during a 10-min incubation period. Protein was determined by the procedure of Lowry et al. (12) with bovine serum albumin as standard.

In experiments where rates of enzyme synthesis or degradation were measured, monolayer cultures were exposed to labeled amino acids for varying intervals, as described in individual legends. The incorporation of isotope into tyrosine transaminase was measured immunochemically as described by Reel and Kenney (11).

![Fig. 4. Effect of inhibitors on the response of tyrosine transaminase to L-leucine. All additions were made at zero time. a, L-leucine alone, 5 mM (C-C); L-leucine plus cycloheximide, 2 µg per ml (A-A); no addition (O-O). b, L-leucine alone, 5 mM (C-C); L-leucine plus actinomycin D, 0.2 µg per ml (A-A); no addition (O-O).](image)

![Fig. 5. Double diffusion analysis of the reaction of antitransaminase with various transaminase preparations. The central well contained 5 µl of rabbit antitransaminase serum (titer, 100,000 units per ml). To the peripheral Wells 1, 2, 3, and 4 was added transaminase from L-leucine-treated (360 units), insulin-treated (354 units), untreated (366 units), and hydrocortisone-treated (434 units) H-35 cells, respectively. To Well 5 was added 550 units of transaminase from livers of hydrocortisone-treated rats. The enzyme preparation from cells had been partially purified by heat treatment and concentrated by vacuum dialysis. The specific activities of transaminase of hydrocortisone-, insulin-, L-leucine-treated, and untreated H-35 cells were 360, 280, 270, and 66 units per mg of protein, respectively.](image)

![Fig. 6. Immunochemical titration of transaminase preparations. Crude enzyme preparations (105,000 X g supernatant fractions) from hydrocortisone-treated (C), insulin-treated (C), or L-leucine-treated (A) H-35 cells were titrated against anti-transaminase serum sufficient to precipitate 900 units of transaminase from a fresh rat liver soluble fraction. The mixtures were incubated at 4°C overnight and centrifuged to remove the enzyme-antibody complex before assay for transaminase activity that remained soluble. The crude enzyme preparations had specific activities (units per mg of protein) of 550, 334, and 420 for hydrocortisone-, insulin-, and L-leucine-treated cells, respectively.](image)

![Fig. 7. Effect of L-leucine on rate of transaminase synthesis. L-leucine (5 mM) was added at zero time to seven monolayer cultures for each time point (A-A); a comparable number of cultures to which no L-leucine was added served as controls (O-O). [3H]Serine (5 µCi per ml, 1.3 Ci per mm) was added 15 min before collection of cells for analysis. a, transaminase specific activity (units per mg of protein); b, relative radioactivity in transaminase (counts per min in transaminase per counts per mg in total soluble protein X 103). c, radioactivity in total soluble protein (treated/untrated).](image)
cine had no effect on transaminase activity, while n-leucine was only partially effective (Table II).

The amount of n-leucine required to increase the transaminase level significantly in the tissue culture system was 0.4 mM, as indicated by the dose-response curve presented in Fig. 1. A nearly optimum response was obtained at 5 mM, which is 25 times higher than the concentration in 1XBME (Fig. 1). At the 5 mM concentration, n-leucine elicited an 8- to 10-fold increase in the tyrosine transaminase level. The enzyme level reached a new steady state at 12 to 14 hours after leucine addition, one that persisted for at least 24 hours (Fig. 2). The absolute transaminase level increased by leucine varied considerably from one experiment to another, possibly reflecting differences in cell density. According to the theoretical treatment elaborated by Berlin and Schimke (13), the half-life of the enzyme, estimated from the time when the enzyme activity reached 50% of the new steady state, is about 6 to 7 hours. This value is appreciably longer than the reported value of 2 hours for the normal rate of transaminase degradation in these cells. However, estimation of the half-life from the rate of decline in enzyme activity following withdrawal of n-leucine gave the usual half-life of about 2 hours (Fig. 3). These results indicate that n-leucine alters the rate of tyrosine transaminase degradation.

Inhibitor Studies—Inhibition of protein synthesis by cycloheximide completely blocks the induction of tyrosine transaminase by either hydrocortisone or insulin (14). As seen in Fig. 4a cycloheximide similarly prevented the induction by L-leucine. Previously we have shown that the early phases of induction by insulin are insensitive to actinomycin D, whereas the induction by hydrocortisone is always sensitive to this antibiotic (14). As depicted in Fig. 4b the induction by L-leucine was not affected by actinomycin D for the first 3 to 4 hours, which is similar to the effect of this inhibitor on insulin-mediated induction (14).

Immunochemical Analysis—By double diffusion analysis in agar gel, tyrosine transaminase of H-35 cells can be shown to be immunochemically identical with the rat liver enzyme (Fig. 5). A sharp precipitin line showing identity was formed when antisera prepared against purified enzyme from livers of hydrocortisone-treated rats was tested against partially purified enzyme isolated immunochemically. A precipitin line showing identity was formed when antiserum prepared against purified enzyme from livers of hydrocortisone-treated rats was tested against partially purified enzyme from rat liver or enzyme from H-35 cells before and after treatment with hydrocortisone, insulin, or L-leucine. Titration of crude enzyme preparations from cells treated with hydrocortisone, insulin, and L-leucine against the antisera yielded identical equivalent points (Fig. 6). These results demonstrate that L-leucine increases the same tyrosine transaminase present in basal or hormonally induced cells, and that the leucine-mediated increase in transaminase activity reflects an increase in transaminase protein.

On the basis of immunochemical-isotopic analysis, it has been demonstrated that both hydrocortisone and insulin increase tyrosine transaminase synthesis without appreciable effect on its degradation (4, 11, 14). A comparable experiment with L-
The addition of labeled amino acid into the enzyme is a measure of its rate of synthesis (pulse-labeling experiment). The results, reported in Fig. 7, demonstrate that L-leucine increased transaminase synthesis without notable effect on synthesis of the total soluble proteins. The maximum increase in the rate of enzyme synthesis was attained at 4 hours, with 3- to 4-fold induction. This magnitude of increase in the rate of transaminase synthesis cannot entirely account for the extent of increase in enzyme activity. The possibility that L-leucine also alters the rate of tyrosine transaminase degradation was therefore measured directly under chase conditions. The half-life of the enzyme determined in this fashion was 2 hours in the untreated cells, which is in agreement with previous determinations (4). However, the degradation rate in the leucine-treated cells was slower, the enzyme being degraded with a half-life of about 6 hours (Fig. 8). Thus, the increase in the levels of tyrosine transaminase brought about by L-leucine can be attributed to effects on both the rate of transaminase synthesis and the rate of its degradation.

Additivity of L-Leucine and Hormonal Inducers—It has been suggested that the rate of amino acid influx plays an important role in control of amino acid-metabolizing enzymes (15, 16). Since the uptake of amino acid in H-35 cells is enhanced by insulin (10), the possibility that transaminase induction by insulin is mediated by L-leucine was tested. First, we studied the effect of L-leucine together with either hydrocortisone or insulin. The combination of the amino acid with either hydrocortisone (Fig. 9) or insulin (Fig. 10) yielded additive effects on transaminase activity. When L-leucine, hydrocortisone, and insulin were all combined, each exerted its effect independently (Table III). However, since leucine increased the level of tyrosine transaminase by a dual effect on both synthesis and degradation of the enzyme, its effect on degradation alone possibly provided the additive effect. To test this possibility, we studied the effect of L-leucine on transaminase activity in cells maximally induced by either hydrocortisone or insulin. The results, shown in Figs. 8 and 11 demonstrate that L-leucine further increases transaminase activity in cells which have been maximally previously induced with either hormone. The extent of the leucine-mediated increase under these conditions is the same as in nonhormone-treated cells. Secondly, we studied induction of the transaminase by either the steroid or the peptide hormone in leucine-free medium. In these experiments the cultures were placed on leucine-free medium 12 hours before the addition of the hormones, in order to minimize the effect of leucine deprivation on cellular metabolism. Under these conditions, either hydrocortisone or insulin could effectively induce the transaminase (Fig. 12). Thirdly, direct measurements of transaminase synthesis as influenced by the hormonal inducers in combination with leucine showed their effects to be essentially additive (Table IV). The leucine effect on synthesis is small compared to that of the hormones, especially of hydrocortisone, and the limitations of the method are such that these results can only be regarded as supportive of the kinetic evidence already described. Taken together, the data support the thesis that the induction of tyrosine transaminase by hydrocortisone or by insulin is not mediated through leucine and suggest that the mechanism of the leucine effect on enzyme synthesis is different from that utilized by either the steroid hormone or the pancreatic hormone.

Effect of α-Ketoisocaproic Acid on Tyrosine Transaminase—The first of the series of enzymes involved in metabolism of L-leucine is leucine transaminase. The activity of this transaminase can...
Effects of combinations of various inducers on tyrosine transaminase synthesis in H-35 cells

Additions were made to monolayer cultures after 20 hours on 1XBME. The cells were treated with hydrocortisone (5 × 10^{-7} M), insulin (10 milliunits per ml), and L-leucine (5 mM) for 12, 6, and 4 hours, respectively. Cells from seven monolayer cultures of each treatment were combined for analysis. [3H]Isoleucine (10 μCi per ml, 34 Ci per mm) and [3H]Alanine (5 μCi per ml, 16.4 Ci per mm) were added 15 min before collection of cells for analysis.

| Addition          | Tyrosine transaminase | Radioactivity in transaminase |
|-------------------|-----------------------|------------------------------|
|                   | Units per mg of protein | Additive | Relative radioactivity | Additive |
| None              | 39                    | 2.6                              |
| Hydrocortisone    | 573                   | 37.9                             |
| Insulin           | 183                   | 8                                |
| L-Leucine plus L-leucine | 105                   | 5.7                                |
| Hydrocortisone    | 804                   | 30.5                             |
| Insulin plus L-leucine | 262                   | 9.6                              |

a Measured in counts per min in transaminase per counts per mg in total soluble protein × 10^{4}.

be elevated by hydrocortisone in rat liver (17); preliminary analyses indicate that leucine transaminase is present in H-35 cells and its activity can be increased by hydrocortisone.1 To assess the possibility that a metabolite of leucine is responsible for effects on transaminase levels, we tested the effect of the deaminated product of L-leucine, α-ketoisocaproic acid, on transaminase activity in H-35 cells. At a concentration of 10 mM, α-ketoisocaproic acid had no effect on tyrosine transaminase for effects on transaminase levels, we tested the effect of the deaminated product of L-leucine, α-ketoisocaproic acid, on transaminase activity in H-35 cells. At a concentration of 10 mM, α-ketoisocaproic acid had no effect on tyrosine transaminase levels in the cells. These results suggest that it is L-leucine itself, rather than a metabolite, which is the agent active on tyrosine transaminase synthesis and degradation.

DISCUSSION

From these data it can be concluded that the amino acid L-leucine plays a unique role in regulation of the levels of tyrosine transaminase in cultured hepatoma cells. None of the other amino acid constituents of the culture medium have a comparable effect, and neither analogues nor metabolites of leucine are active. Synthesis of the transaminase is elevated 3- to 4-fold by high leucine concentrations, but synthesis of the total soluble proteins of the cells (or of cellular RNA and DNA) is only marginally affected under these conditions. The kinetic patterns of increase in enzyme activity following leucine addition and of decrease following leucine withdrawal are not consistent with a requirement for a stable intermediate formed under the stimulus of leucine treatment and necessary for induced enzyme synthesis. In the preceding papers of this series we argued that such behavior is consistent with an induction mechanism operating on post-transcriptional or translational events in protein synthesis (14). This view is supported by the failure of actinomyein D to block the effect of leucine until 3 to 4 hours after addition of the antibiotic, the time span expected for the transaminase messenger RNA content to decline to negligible levels (14).

1 K.-L. Lee, unpublished observations.

In these respects the effect of leucine on transaminase synthesis is comparable to that of the inducing hormone, insulin; indeed, these studies were initiated to test the thesis that insulin acts via changes in intracellular pools of one or more amino acids. However, the results of experiments designed to assess the potential role of leucine in the induction of transaminase by insulin (or by hydrocortisone) demonstrate quite clearly that the leucine effect is distinct from that of either hormonal inducer. Effects of all three agents are additive, and cells in which transaminase levels have been maximally elevated by insulin (or by hydrocortisone) respond to added leucine in the same fashion as untreated cells. Also insulin (and hydrocortisone) is able to induce transaminase synthesis in the normal fashion when cells are cultured without added leucine in the medium; this result argues convincingly against a membrane- or permeability-associated effect of insulin that would increase intracellular leucine and thereby increase transaminase synthesis.

Unlike either of the hormonal inducers, leucine also slows the rate of degradation of tyrosine transaminase, as determined both by analysis of the kinetics of the leucine-stimulated elevation to a new steady state and by direct isotopic-immunochemical measurement of degradative rate. Leucine slows the usual degradative rate of tyrosine transaminase (4t, about 2 hours) by a factor of 3; this effect, together with the leucine effect on enzyme synthesis, is adequate to account for the 8- to 10-fold elevations in enzyme level we observe upon increasing the leucine content of the medium. L-Leucine does not stabilize tyrosine transaminase against denaturation in vitro; thus the capacity of this amino acid to stabilize the transaminase in vivo would appear to be unlike the well known stabilization of tryptophan pyrrolase by tryptophan both in vivo and in vitro (18).

Walter has suggested (19) than an amino acid derivative, perhaps aminocyl transfer RNA, may be a common intermediate in both protein synthesis and protein degradation. Schimke proposes (20) that the rate-limiting step in degradation of a particular protein may be the first peptide cleavage. If we combine and extend these suggestions we can envision a mechanism of peptide cleavage requiring an unacylated transfer RNA to act as acceptor for the amino acid or peptide product of cleavage. If the transaminase peptide involved in this initial break included a leucyl residue, the effect of high leucine levels on transaminase degradation could then be attributed to lowering the cellular content of unacylated, leucine-specific transfer RNA. In preliminary tests of this hypothesis, wherein the isoeaccepting leucine-specific transfer RNA's of H-35 cells were separated by reversed phase chromatography (21), we have found, in accord with the hypothesis, that one of the three isoeaccepting species is not fully acylated in vivo except at high concentrations of leucine. This species of leucyl transfer RNA may also be capable of limiting the rate of transaminase synthesis unless fully acylated. These speculations require much experimental verification but do have the validity of providing a working hypothesis for future probes into the mechanism of leucine action in this system.

Parenteral administration of L-leucine to adrenalectomized rats on normal or protein-free diets doubles the hepatic tyrosine transaminase levels.1 This effect is not as large as what we observe in hepatoma cultures nor is it as great as that others have found after administering amino acid mixtures or casein hydrolysates (5, 7). Thus the leucine effect on tyrosine transaminase that we describe here is probably a significant com-
ponent of these amino acid effects in animal experiments; however, other factors, perhaps hormonal ones, may also play a role in the animal's response to administered amino acid mixtures.

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