Parallel Control of Hepatic Proteolysis by Phenylalanine and Phenylpyruvate through Independent Inhibitory Sites at the Plasma Membrane

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The intracellular degradation of long-lived proteins in the perfused rat liver is primarily controlled by the multiphasic action of 7 regulatory amino acids: leucine, glutamate, tyrosine, proline, methionine, histidine, and tryptophan (Ref. 2 and reviewed in Ref. 3). The response has been observed in the perfused liver with the regulatory group as a whole and with leucine, glutamate, and tyrosine individually (4, 5). Recently, typical effects of leucine were reported in the isolated rat hepatocyte (6), demonstrating that the multiphasic response is a general feature of amino acid regulation in a single population of cells. Except for differences in degree of inhibition, these features include a primary inhibition at half-normal plasma amino acid concentrations, a zonal loss of inhibition within a narrow range at normal concentrations, and a secondary inhibition at high physiologic levels (2, 4). The zonal loss can be explained by the lack of plasma alanine, which is specifically required for expression of inhibition by the regulatory amino acids at normal concentrations (7, 8).

A basic description of the multiphasic response is reasonably complete except for one point. Since tyrosine exhibits the same multiphasic features as leucine (4) and is closely related to phenylalanine metabolically, tyrosine was initially considered the active regulator and representative of the aromatic group. Although phenylalanine is as inhibitory as tyrosine at 4× normal plasma concentrations (2), nothing is known of its activity at normal levels. Because of the effectiveness of phenylalanine hydroxylase in converting small increases in phenylalanine to tyrosine during a single transhepatic passage (9), it seemed unlikely that the two amino acids would regulate proteolysis in tandem through the same process. Hence, we have considered the possibility that liver might contain more than one regulatory mechanism. To this end, the present study was undertaken to compare the respective roles of phenylalanine and tyrosine and their keto acids in the control of hepatic proteolysis.

EXPERIMENTAL PROCEDURES

Animals—Male rats of the Lewis strain (Harlan Sprague-Dawley, Indianapolis, IN) were used as liver donors for perfusion experiments and hepatocyte preparations. The animals, weighing 120–140 g at the time of perfusion, were routinely maintained on commercial laboratory chow and water ad libitum in a light-controlled room (light off, 1900 to 0700 h). For the determination of protein degradation, liver protein was labeled in vivo with [2]C]valine (Du Pont-New England Nuclear, 250 mCi/mmol; 4 μCi in 0.25 ml of 0.85% NaCl were injected intraperitoneally, 24 and 17 h before perfusion.

Liver Perfusion—Livers were perfused in situ in the single-pass (nonrecirculating) mode as described earlier (10). Unless stated otherwise, all experiments were carried out at approximately 1100 h. When proteolysis was determined, the single-pass phase lasted 40 min. Perilysate flow was then switched to a second stage cyclic perfusion, with 18 μM cycloheximide added, for the measurement of labeled valine release. Finally, the specific radioactivity of released valine was determined in a third stage cyclic perfusion in which exogenous, unlabeled valine was eliminated and the specific activity of released valine allowed to reach equilibrium (11).

The perfusion medium consisted of Krebs-Ringer bicarbonate

1 The number followed by × indicates multiples/fractions of the amino acid concentrations in the standard normal plasma mixture (10).
buffer, 3% bovine plasma albumin (fraction V, Pentex, ICN Biomedicals, Inc., Costa Mesa, CA), 10 mM glucose, and freshly washed bovine erythrocytes (27%, v/v); its preparation has been described in detail elsewhere (10, 11). All additions to the medium were prepared in medium TNaCl with pH adjusted to 7.4 by dilute NaOH.

**Measurement of Protein Degradation**—As detailed in a previous report (11), rates of long-lived protein degradation in livers, previously labeled in vivo with L-[U-14C]valine, were determined from the cumulative release of labeled valine in the second stage perfusion flask described above. In the presence of cycloheximide, rates of label release between 5 and 15 min have been shown to reflect the breakdown of long-lived protein that occurs in the liver during the initial single-pass perfusion (10, 11); uncertainties arising from the degradation of short-lived and endocytosed protein are virtually eliminated by the use previously labeled livers as described (11).

The total accumulation of free [14C]valine in liver and perfusate was computed at each point of sampling between 5 and 15 min (11); proteolytic rates then were calculated by least squares regression after correction for the specific radioactivity of released valine (see above). Values were expressed as nanomoles of valine min⁻¹/liver (100 g body weight). The average valine content of liver protein for a 100-g rat has been shown to be 465 μmol (10).

**Isolated Hepatocytes**—Suspensions of hepatocytes were prepared according to Seglen (12) and purified by Percoll centrifugation (13): 90% or more of the cells excluded trypan blue. The conditions of incubation are given in the legends of Figs. 2 and 3.

**Radiolabeled Phenylpyruvate and Phenyllactate—**[1-14C]Phenylpyruvate was made from L-[1-14C]phenylalanine (ICN Biomedicals, Inc., Costa Mesa, CA, 40 μCi/mmole) according to Rudiger et al. (14); L-[1-14C]phenyllactate was prepared from the same reagent by the method of Moir (15).

**Analytical Procedures**—For the determination of phenylpyruvate, plasma was deproteinized with an equal volume of 15% sulfosalicylic acid (in liver, 1 volume of tissue to 9 volumes of acid) and the keto acid derivatized with o-phenylenediamine (16). Analysis was carried out by reverse phase high performance liquid chromatography according to Livesey and Edwards (16). In measuring rates of phenylpyruvate transamination, label in phenylalanine and tyrosine was determined by the dansylation method of Tapuhi et al. (17). Radioactivity incorporated into liver protein was determined as described by Khairallah and Mortimore (18). Samples with 14C were counted in Liquiscint (National Diagnostics, Inc.) with a Beckman LS 7800 liquid scintillation spectrometer; results were expressed as disintegrations/min.

**RESULTS**

**Proteolytic Dose Responses to Tyrosine, Phenylalanine, and Their Derivatives**—As depicted in Fig. 1A tyrosine exhibited dose-dependent effects typical of the multiphasic responses reported previously for leucine, glutamine, and the regulatory group (4). In addition, responses to the keto acid p-hydroxyphenylpyruvate were closely analogous to those of α-ketoisocaprate in evoking inhibition equal to the corresponding amino acid at levels higher than 1X while failing to inhibit at the lowest concentration (2). The lack of inhibition at 0.5X suggests that tyrosine’s primary inhibition is not mediated through its keto acid despite the fact it is actually transamminated (19). Surprisingly, phenylalanine revealed a dose response curve quite unlike that of tyrosine (Fig. 1B); no effect was seen at 0.5X, but maximal inhibition was achieved at 1X. Effects of phenylpyruvate were identical to those of phenylalanine.

**Hepatic Uptake and Metabolic Fate of Phenylpyruvate**—It is clear from the dissimilar proteolytic responses at 0.5 and 1X (Fig. 1, A and B) that phenylalanine and tyrosine (and their respective keto acids) mediate their effects through different mechanisms. In spite of the established activity of phenylalanine hydroxylase (9, 19), the responses to phenylalanine cannot be explained by its conversion to tyrosine, and the effects of phenylalanine and phenylpyruvate must be conveyed directly through themselves or through metabolites of the keto acid. We initially evaluated the latter by measuring the hepatic uptake and metabolism of [1-14C]phenylpyruvate under steady state conditions. As shown in Table I, ≈55% of the phenylpyruvate taken up was transaminated to phenyl-
alanine (and to tyrosine after hydroxylation), whereas 43% was reduced to phenyllactate; approximately 4% was decarboxylated. To exclude the remote possibility that the keto acid influx was saturated at the concentration tested (300 μM), we determined rates of transamination in isolated hepatocytes and found them to be directly proportional to added phenylpyruvate from 0 to 500 μM (Fig. 2). These data are consistent with a high $K_m$ for phenylpyruvate influx. Similar results have been reported for α-ketoisocaproate transport in isolated hepatocytes (20, 21).

It is clear from results in Table II that the inhibitory activity of phenylpyruvate cannot be explained by its transamination to phenylalanine or tyrosine as both intracellular pools remained unchanged over the effective range of keto acid concentration. We cannot, however, rule out the possibility that phenylpyruvate has other intracellular actions. Although the ineffectiveness of phenyl lactate appears to exclude it as a mediator (Fig. 1B), this could be explained by low rates of conversion of the lactate to the keto acid if the latter is active in the cell. On the other hand, if phenylpyruvate is readily produced from phenyl lactate, the reaction could provide a useful way to assess the intracellular effectiveness of phenylpyruvate.

Intracellular/Extracellular Distribution of Phenylpyruvate—To evaluate the feasibility of this approach, attempts were made to determine the intracellular concentration of phenylpyruvate in the perfused liver. Using a standard correction for extracellular water (10), we obtained strongly negative values, suggesting that its extracellular distribution is smaller than usual. For this reason we employed a pulse-chase technique and compared the wash-out of radiolabeled phenylpyruvate, p-hydroxyphenylpyruvate, and sucrose during perfusion. Livers were perfused for 5 min in the single-pass mode with either 0.3 mM [1-14C]phenylpyruvate, p-hydroxy-[1-14C]phenylpyruvate, or [U-14C]sucrose and then chased with 10 mM unlabeled additions of the same compounds. A typical experiment with phenylpyruvate is depicted in Fig. 3B. After 10–20 s (a period required to clear the perfusion tubing of preexisting medium) label in perfusate plasma abruptly declined, falling off exponentially with half-lives generally less than 10 s. During the chase, 95% or more of the initial label was eluted with uniform kinetics; similar results were obtained for p-hydroxyphenylpyruvate (see Table III). Half-lives for the release of phenylalanine and tyrosine produced from phenylpyruvate during the pulse were significantly greater, ranging from 23 to 50 s (not shown).

In initial experiments we found that the elution of sucrose conformed to a single-compartment model in which the rate of plasma flow and the half-life of elution are inversely related (Fig. 3A). Under steady state conditions of perfusion, the volume of the compartment (eluted space) could be computed as follows,

$$\text{Eluted space (ml/g)} = \frac{\text{plasma flow (ml/s) × half-life (s)}}{\text{0.693 × liver weight (g)}} \quad (\text{Eq. 1})$$

where 0.693 = ln 2. Control experiments revealed that the keto acids do not equilibrate with erythrocyte water for periods up to 60 s. Thus it was not necessary to consider erythrocyte volume in the equation.

The findings in Table III show that the phenylpyruvate and p-hydroxyphenylpyruvate spaces in liver are approxi-

![Fig. 2. Transamination of [1-14C]phenylpyruvate to phenylalanine/tyrosine in isolated rat hepatocytes. Hepatocytes suspensions (cell density, $5.5 \times 10^8$/ml) were incubated at 37 °C for 30 min in Krebs-Ringer bicarbonate buffer containing 0.5% bovine albumin and 6 mM glucose and were gently agitated under 95% O2-5% CO2. 20 μM cycloheximide was added to minimize the incorporation of labeled amino acids into protein. Rates of transamination were computed as described in Table I. The slope represents a least squares regression of three experiments.](image)

![Fig. 3. Elution of [U-14C]sucrose (A) and [1-14C]phenylpyruvate (B) from the extracellular space of the perfused rat liver. Livers were perfused in the single-pass mode for 5 min with one of the above labels, followed by a 10 mM chase (unlabeled) starting at time 0. The 10–20-s lag before the onset of decline represents the time required to wash label from the perfusion tubing. A depicts the inverse relationship between plasma flow and half-life of sucrose elution in a single liver (see text). Open circles, flow = 7.85 ml/min, $t_{1/2} = 5.9$ s; open triangles, flow = 3.33 ml/min, $t_{1/2} = 12.0$ s.](image)

| Phenylpyruvate | Intracellular amino acids |  |  |
| | Phenylalanine | Tyrosine |
| Phenylalanine | 38 μM | 108 ± 9 | 69 ± 9 |
| | 75 μM | 118 ± 3 | 77 ± 5 |

| Phenylpyruvate | Intracellular amino acids |  |  |
| | Phenylalanine | Tyrosine |
| Phenylalanine | None | 111 ± 8 | 78 ± 6 |

TABLE II

Effect of added phenylpyruvate on intracellular (IC) pools of phenylalanine and tyrosine in the perfused rat liver

Livers were perfused under the conditions of Fig. 1 with additions listed below. At the termination of 40 min of single-pass perfusion, samples of affluent and effluent perfusate plasma and of liver were taken, frozen in liquid N2, and stored at -20°C for later analysis. The values are means ± S.E. of four experiments.
p-Hydroxyphenylpyruvate plasma levels. Thus, it seemed possible that only moderate the reversal of the keto acid (23), might be reversed by external phenyl-lactate. Based on in vitro experiments, a ratio of reduced to oxidized substrate of 16:1 or greater appears to be needed for pyruvate (where flow was varied) as with sucrose in Fig. 3A.

In two control experiments in which livers were perfused with phenylpyruvate at an average transhepatic concentration of 198 μM, the total recovery of the keto acid was 29.1 ± 1.8 nmol/g. Taking 0.128 ml/g as the extracellular space of the normal unperfused liver minus erythrocyte volume (22), the conditions in incubation were the same as those in Fig. 2.

The ratio of reduced to oxidized substrate of 16:1 or greater appears to be needed for the reversal (23). The preceding results have shown that intracellular pools of phenylpyruvate are small relative to plasma levels. Thus, it seemed possible that only moderate additions of phenyllactate would be required.

As in the experiments of Fig. 2, the isolated hepatocyte rather than the perfused liver was employed to evaluate phenylpyruvate production, since the process is enzymatic and does not involve proteolytic regulation. α-Keto acid formation was monitored from the accumulation of labeled amino acids in the presence of cycloheximide, a method that provides a close approximation of transamination (compare Table I and Fig. 2). The results in Fig. 4 show that phenylpyruvate is produced at appreciable rates with comparatively small additions of phenyllactate. The overall flux at 300 μM, computed from the double-reciprocal plot (inset), was 28 nmol min⁻¹/10⁸ cells. Values are means of three experiments.

| Liver        | Weight | Plasma flow | Half-life | EC space | EC ratio: keto acid/sucrose |
|--------------|--------|-------------|-----------|----------|----------------------------|
| A            | 7.27   | 7.85        | 6.0       | 156      | 0.859                      |
| B            | 6.59   | 7.85        | 5.9       | 169      | 0.840                      |
| C            | 7.35   | 6.88        | 8.5       | 191      | 0.744                      |
| D            | 7.10   | 6.88        | 7.8       | 182      | 0.786                      |
| Mean ± S.E.  |        |             |           | 0.802 ± 0.019 |                              |

Fig. 4. Conversion of [1-¹⁴C]phenyllactate via phenylpyruvate to phenylalanine/tyrosine in the isolated rat hepatocyte. The conditions of incubation were the same as those in Fig. 2. Inset, double-reciprocal plot of the data depicted in the larger graph: r = 0.999; apparent Kₘ = 0.41; V₀ = 66 nmol min⁻¹/10⁸ cells. Values are means of three experiments.

TABLE III

Calculation of eluted extracellular (EC) spaces for sucrose, phenylpyruvate, and p-hydroxyphenylpyruvate in the perfused rat liver

See text for experimental details.
Acids—As for the location of the site of phenylalanine regulation, the close agreement between the amino and keto acid dose responses in Fig. 1B suggests that they may be recognized at a common site or, alternatively, at independent plasma membrane sites operating in parallel. The possibility that phenylalanine acts through an intracellular locus seems improbable, since we have shown that the intracellular pool does not increase when the external level is raised from zero to 100 g initial body weight.

The fact that 38 μM phenylalanine and 38 μM phenylpyruvate are additive, evoking significantly greater inhibition combined than when given separately (Table IV), suggests that the putative site, or sites, can react with more than one metabolite. Arising from its decarboxylation. More than one action is derived from the inward transport of phenylpyruvate. Although phenylpyruvate levels in the internal vicinity of transporters might be higher at 300 μM than those generated from phenylpyruate at 300 μM, this would not be the case at 75 μM phenylpyruvate where its uptake was lower (Table I and Fig. 2) than the enzymatic production of phenylpyruvate at 300 μM phenylpyruvate (Fig. 4), and inhibition was maximal (Fig. 1B). Thus the total lack of effectiveness of phenylpyruvate up to 300 μM (Fig. 1B) appears to exclude as possible mediators all sites of phenylpyruvate recognition within the cell as well as metabolites arising from its decarboxylation. Moreover, it clearly points to the plasma membrane as the initial site of proteolytic regulation.

### Table IV

| Additions | Proteolysis* | Inhibition |
|-----------|--------------|------------|
| None      | 371 ± 9      | 9          |
| 38 μM Phe | 361 ± 13     | 10         |
| 38 μM PP  | 361 ± 12     | 10         |
| 75 μM Phe | 302 ± 15     | 69*        |
| 75 μM PP  | 300 ± 14     | 71*        |
| 38 μM Phe + 38 μM PP | 327 ± 9 | 44*       |

* 100-g initial body weight.

**DISCUSSION**

The striking dissimilarity in proteolytic dose responses that was observed between two closely related amino acids, phenylalanine and tyrosine, raises new questions concerning the control of long-lived protein degradation in the hepatic parenchymal cell. Although the characteristic multiphasic response to tyrosine has been described previously (4), the finding that phenylalanine, the precursor of tyrosine, evokes a much simpler single-phase inhibition at concentrations below the normal plasma level was unexpected, and its implications are not fully understood. Nevertheless, it is clear from the shape of the curves in Fig. 1, A and B, that the two amino acids act through different mechanisms.

The single-phase responses to phenylalanine and phenylpyruvate are curiously reminiscent of earlier effects of leucine and ω-ketoisocaproate in skeletal and cardiac muscle (25–27) and of leucine in cultured kidney cells (28). It is not unreasonable therefore to suggest that the phenylalanine response in hepatocytes is the manifestation of a basic cellular control mechanism that coexists with the multiphasic action of tyrosine. But regardless of its nature, it is likely to remain unex-

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2 G. E. Mortimore, unpublished data.
pressed in the presence of plasma amino acids as suggested by the following results. When alanine is deleted from a complete amino acid mixture at normal (1x) concentrations, proteolytic rates accelerate to near-maximal values as the multiphasic regulatory amino acids lose their inhibitory effectiveness through the loss of alanine's coregulatory activity (7, 8). If phenylalanine was as effective under these conditions as it is by itself, the above accelerating effect would be significantly diminished. The fact that a decrease is not seen implies that phenylalanine's inhibition is overridden by a dominant stimulatory response to the loss of alanine.

In view of the present findings with phenylpyruvate, it is appropriate to review effects of leucine and α-ketoisocaproate on protein degradation in muscle and to compare the responses in the two tissues. Apart from the aforementioned similarity in dose responses between leucine and phenylalanine and their respective keto acids, studies with rat skeletal muscle have indicated that leucine's action is achieved through products of leucine catabolism, a conclusion based on the fact that its effect is abolished by the transaminase inhibitor cycloserine (25, 26). In the perfused rat heart, however, Chua and co-workers (27) found that with 10 mM pyruvate it is possible to suppress the decarboxylation of α-ketoisocaproate by 95% without affecting its inhibitory effectiveness. Taken together, the results support the possibility that α-ketoisocaproate rather than leucine is the mediator; a-ketoisocaproate rather than leucine is the mediator; a conclusion based on the fact that a-ketoisocaproate can occur only through leucine itself, the above accelerating effect would be seen.

1A). Recent studies have shown that the leucine analogue isovaleryl-L-carnitine can mimic leucine's multiphasic response by medium replacement, inhibition could have been achieved from the outside.

By contrast, responses of the hepatocyte to leucine and its keto acid as well as to tyrosine and p-hydroxyphenylpyruvate (Fig. 1A) are mediated through a multiphasic mechanism. Because leucine is poorly transaminated in liver (2), its inhibitory effects, particularly at low concentrations (0.25–0.5x), can occur only through leucine itself (2). And since the keto acid does not inhibit at the lowest concentration, it must act through an independent mechanism (2); a similar conclusion may be drawn for the action of p-hydroxyphenylpyruvate (Fig. 1A). Recent studies have shown that the leucine analogue isovaleryl-L-carnitine can mimic leucine's multiphasic response curve (5) by reacting at the recognition site, or sites, for leucine (24). Moreover, they appear to be located at the plasma membrane in close proximity to similar sites for glutamine, tyrosine, and other regulatory amino acids (24). Such an association could provide a molecular basis for the complex concerted actions of these amino acids which have been documented previously (2, 8, 11).

Although the exact correspondence between dose responses to phenylalanine and phenylpyruvate suggest, at first glance, that they share a single regulatory mechanism, such a view is not compatible with the differences we observed in the way they interacted with leucine and glutamine (Table V). Since the character of the response is a function of the regulatory site, not the regulator, the responses must have been generated through similar but independent mechanisms. The partial additivity can be explained by a limited ability of phenylalanine to react with the phenylpyruvate sites. However, it is not likely that the cross-reactivity is reversed, i.e. that the keto acid reacts with the amino acid site. If it were, one would not have observed the aforementioned differences in concerted effects.

The final question concerns the location of the regulatory site for phenylalanine. Although evidence in support of the plasma membrane is more indirect than it is for phenylpyruvate, nevertheless it is the most probable choice. Because recognition sites for leucine and glutamine are very likely at the plasma membrane (24), a similar location would provide a simpler model for explaining concerted interactions between the 3 amino acids than one in which the sites are widely separated. The same argument can be used for locating the site for tyrosine. In this instance, though, there is added relevance in the fact that it evokes multiphasic responses. Since the external concentrations at which the sharp inflections occur are the same in multiples (or fractions) of its normal plasma concentration as those of leucine and glutamine (4, 8), an externally facing locus provides a reasonable explanation for the effects.

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