Lack of Inhibition by L-Tryptophan or Quinolinate of Gluconeogenesis in Diabetic Rats*

(Received for publication, September 21, 1973)

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SUMMARY

Administration of L-tryptophan to normal fed rats inhibits hepatic gluconeogenesis at the level of P-enolpyruvate formation but nonetheless causes a paradoxical increase in the assayable specific activity of P-enolpyruvate carboxykinase. Similar results obtain if livers isolated from normal rats are perfused with tryptophan, 3-hydroxyanthranilate or quinolinate.

However, we find that no such inhibition of gluconeogenesis occurs in intact, fed, alloxan- or streptozotocin-diabetic rats following treatment with tryptophan or 3-hydroxyanthranilic acid, nor is there any increase in the already elevated assayable specific activity of P-enolpyruvate carboxykinase. Furthermore, perfusion of livers isolated from alloxan- or streptozotocin-diabetic rats with tryptophan, 3-hydroxyanthranilate or quinolinate does not produce a metabolite crossover between P-enolpyruvate and its precursors nor is there any significant enhancement of assayable specific activity of P-enolpyruvate carboxykinase. Additionally, perfusion of diabetic livers with tryptophan or quinolinate does not inhibit the conversion of radioactive lactate to glucose although such inhibition does occur in livers from normal rats.

The results suggest that tryptophan and certain of its metabolites, including quinolinate, are unable to inhibit gluconeogenesis in diabetic rats under conditions known to cause such inhibition in normal rats.

A convincing body of evidence demonstrates that L-tryptophan is capable of inhibiting hepatic gluconeogenesis in normal rats (2-6), but it has been found to enhance the assayable specific activity of a key gluconeogenic enzyme, P-enolpyruvate carboxy-

* This work was supported by grants from the National Institutes of Health (AM 12705) and the American Diabetes Association and was partially completed during the tenure of P. D. R. as an Established Investigator of the American Heart Association. Data presented in this paper were taken from a dissertation submitted by F. L. A. to the Graduate School of the University of North Dakota. A preliminary report has been presented before the 57th Annual Meeting of the Federation of American Societies for Experimental Biology (1).

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kinase (EC 4.1.1.32) (2-4, 7-9). Tryptophan can also enhance the activities of other hepatic enzymes not involved in its own catabolism (9-12). Nonetheless, crossover plots of the hepatic concentrations of gluconeogenic metabolites have demonstrated that, in vivo, tryptophan actually inhibits the reaction catalyzed by P-enolpyruvate carboxykinase (5). The inhibitory effect of tryptophan on gluconeogenesis is due to quinolinate based on data obtained by perfusing various metabolites of the trypto-

Phan-quinurone-NAD pathway through livers isolated from normal rats (4).

Since a dose of L-tryptophan that causes this inhibition is such that it can be attained by a rat feeding normally over a 24-hour period, it has been postulated that tryptophan could regulate gluconeogenesis in normal rats in response to fasting or feeding (5). Glucose homeostasis could thus be maintained—at least in part—by tryptophan acting through its effector catabolite, quinolinate.

Gluconeogenesis occurs at an accelerated rate in diabetic rats (13-17) and does not appear to be under normal regulatory controls. Also, the kynurenine pathway of tryptophan metabolism is reportedly aberrant in alloxan-diabetic rats (18-21). Foster et al. (2) have reported, moreover, that tryptophan does not elevate the assayable specific activity of P-enolpyruvate carboxykinase from intact, alloxan-diabetic rats. Thus, it appears that the diabetic rat may have lost some control mechanisms which can influence gluconeogenesis in normal rats. Accordingly, we have investigated the ability of tryptophan and its key metabo-

listes to affect gluconeogenesis and P-enolpyruvate carboxykinase activity in intact diabetic rats and in their isolated, perfused livers and the results are presented in this paper.

EXPERIMENTAL PROCEDURE

Animals—Male Sprague-Dawley rats were obtained from ARS-Sprague-Dawley, Madison, Wis. In both intact animal and liver perfusion experiments, liver donors weighed 180 to 200 g. Blood donors were retired male breeders. Unless food was withheld, rats were fed Purina lab chow ad libitum and tap water was available.

Diabetes was induced in 48-hour fasted rats by an intravenous injection of either recrystallized alloxan monohydrate (50 mg per kg body weight) in 0.9% NaCl or streptozotocin (65 mg per kg body weight) in 5 mM citrate buffer, pH 4.5. The rats were immediately refed and offered a 1% solution of glucose in tap water for 24 hours. Rats were considered chronically diabetic if, after 10 days, their blood glucose levels were 22 mM (400 mg/100 ml) or above, and if they exhibited definite symptoms of glucosuria, polyuria, polydiabetes, and weight stabilization or loss.

Intact Animal Experiments—L-Tryptophan (50 mg per ml)
3-hydroxyanthranilic acid (38 mg per ml) were suspended in 0.9% NaCl and administered intraperitoneally at a dose of 3.7 mmole per kg body weight. Controls received an appropriate volume of vehicle. Three or 4 hours after injection, all rats were killed and portions of their livers removed and quick frozen in a tissue press precooled in liquid N2. Perchloric acid extracts of frozen liver samples were prepared and stored as previously described (5). Levels of hepatic metabolites (except citrate) were assayed by enzymatic methods which employ either the oxidation of NADH or the reduction of NAD (22). Citrate was assayed according to Moelerring and Gruber (23). Liver samples for assay of enzyme activity were removed concomitantly with samples taken for metabolite determinations. Supernatant fractions were prepared and assayed for P-enolpyruvate carboxykinase according to Nordlie and Lardy (24) as modified by Foster et al. (7, 25). Protein content of the supernatant fractions were determined by the Biuret method (26).

Technique of Liver Perfusion—Livers were isolated from 12-hour fasted rats (under light ether anesthesia) following cannulation of the bile duct, portal vein, and thoracic inferior vena cava, in that order. Heparin (1500 USP units) was injected into the abdominal inferior vena cava prior to initiation of circulation.

Isolated livers were perfused by recycling 65 ml of perfusate, pH 7.45, consisting of rat erythrocytes1 suspended in Krebs-Ringer bicarbonate buffer (30) containing 5% bovine serum albumin (Cohn Fraction V, Sigma Chemical Company) and oxygenated with 95% O2 and 5% CO2. Preparative for Liver Perfusion Experiments—Livers were "preperfused" for 10 min to permit their equilibration. All lobes flushed out rapidly and resumption of bile flow was almost immediate. Perfusion flow rates were maintained at 3.5 ml per min per g of liver.

Following the "preperfusion" period, an aliquot of perfusate (usually 0.2 ml) was removed for determination of glucose. Perfusate was subsequently sampled at 10-min intervals. At 30 min after the start of the experiment, two samples of tissue were taken from the left lobe. One sample was rapidly homogenized (within 10 s) in 5% perchloric acid, processed, and assayed for metabolites as described above. The other sample was homogenized in ice-cold 0.25 M sucrose and centrifuged at 105,000 X g for 1 hour, and the supernatant fraction was assayed for P-enolpyruvate carboxykinase as described above.

When L-tryptophan, 3-hydroxyanthranilic acid, or quinolinic acid was added to the perfusate, such addition (unless otherwise stated) was made immediately after removal of tissue samples (that is, at 30 min). Tryptophan was dissolved in 0.9% NaCl; 3-hydroxyanthranilic acid or quinolinic acid were added as their sodium salts at neutral pH; all were added to the perfusate at a final concentration of 2.4 mM. Unless indicated otherwise, sodium L-lactate was added 30 min after the start of the experiment to a perfusate concentration of 20 mM. In experiments involving radioactive lactate, a tracer dose of sodium 1-2-[14C]lactate (50 μC total radioactivity with a specific radioactivity of 20, 29 or 29 mCi per mmole) was mixed with the unlabeled sodium L-lactate. All additions were made in 5 ml or smaller volumes.

Two samples of tissue were removed from the median lobe at 120 min of perfusion (that is, 60 min after addition of lactate and 90 min after addition of tryptophan or a metabolite thereof). Soon after, fructose was added to a perfusate concentration of 10 mM, and its conversion to glucose was used as an additional criterion of viability of the liver, particularly in cases where glucose production from lactate had been blocked. Subsequently, the experiment was terminated, and the liver was weighed.

Four criteria of viability of perfused livers were in order of importance: (a) glucose production from lactate and fructose, or both; (b) constant perfusate flow rate; (c) general macroscopic appearance of the liver (compared to its appearance in the living animal); and (d) production of bile. There was no evidence of localized or generalized anoxia or visible edema in livers perfused for 4 hours. Terminal pH measurements on the perfusate ranged from 7.3 to 7.6. Per fusate flow rate was constant; although a slight fall in flow rate was observed after removal of tissue samples, the original rate was rapidly regained. The hematocrit did not decrease by more than 1%. Bile was produced at a rate similar to that reported by others (81); moreover, perhaps, the rate of bile production by any given liver remained constant.

Analysis of Perfusate Glucose—Glucose was determined by the glucose oxidase method (Glucostat, Worthington Biochemical Corp.). Radioactive glucose in the perfusate was separated from its labeled precursor (lactate) and other charged products by chromatography on AG1-X8, chloride form, 200 to 400 mesh (Bio-Rad Laboratories, Richmond, Calif.). This procedure was found to quantitatively remove all the glucose in the sample. Aliquots of the eluate were counted in a liquid scintillation spectrometer. Quenching, determined with the internal standard [7-14C]benzoic acid, was less than 9%. Values for radioactivity appearing in perfusate glucose are adjusted to take into account the wet weight of liver at the time of perfusate sampling. The results are thus expressed as radioactivity in glucose produced per g of perfused liver.

Materials—Bovine serum albumin (Cohn Fraction V) powder, heparin (sodium salt, Grade I, 165 USP units per mg), 3-hydroxyanthranilic acid, and 1,2- (+)lactic acid (30% solution Grade L-III) were obtained from Sigma Chemical Company, St. Louis, Mo. Quinolinic acid (99 to 100% pure obtained from Sigma) was rephrased once from 7-M acetate acid. L-Tryptophan was from Mann Research Laboratories (Division of Beech- Ringer Mannheim Corporation, New York, N.Y., U.S.A. Purified enzymes were from Boehringer Mannheim Corporation, New York, N.Y., and nucleotides were from P-L Biochemicals, Inc., Milwaukee, Wis. 1,2-[14C]-Lactic acid (sodium salt) was purchased from Amersham-Searle, Arlington Heights, III. Streptozotocin (Lot 9548-F322-1, U-9889) was a generous gift from Dr. W. A. Dulin, The Upjohn Company, Kalamazoo, Mich.

All chemicals were of analytical reagent grade and solutions were prepared in deionized, glass-distilled water.

Expression of Results—Values are expressed as means ± S.D. The significance of differences between means was established by the Student's t test. Values for p > 0.05 are not considered significant.

RESULTS

Differential Responses of Intact Normal versus Diabetic Rats to L-Tryptophan or 3-Hydroxyanthranilic Acid

Effects on Hepatic Gluconeogenic Metabolites—Accumulations of intermediary metabolites in fed normal rats treated with tryptophan were initially compared to those found in fed alloxan-diabetic rats similarly treated. Fig. 1 depicts the results obtained with normal fed rats. Accumulations of citrate, aspartate, and malate to levels of 6-, 8-, and 9-fold, respectively, are concomitant with subnormal levels of P-enolpyruvate and 3-phosphoglycerate. These data indicate a crossover-type phenomenon similar to that previously reported by Ray et al. (5). In contrast, no accumulation of hepatic metabolites or a metabolite crossover is seen following administration of either tryptophan or 3-hydroxyanthranilic acid to fed alloxan diabetic rats (Fig. 2). Although data are not presented, there is a similar absence of hepatic metabolism accumulation and of a metabolite crossover in fed streptozotocin-diabetic rats treated with either tryptophan or 3-hydroxyanthranilic acid.

These data indicate that in the fed, intact normal rat, trypto-
The concentrations of gluconeogenic metabolites in the livers of fed normal rats 3 hours after administration of 3.7 X 10^{-3} mole per kg L-tryptophan. Control values for each metabolite are recorded at the bottom of the figure, together with the standard deviations of the means. The experimental data are expressed as multiples of these control values. The number of animals contributing to each point is given in parentheses above the vertical line which indicates a standard deviation from the mean. The number of animals contributing to each control point is shown in parentheses below the value for the particular metabolite. See legend to Fig. 1 for definition of abbreviations.

**TABLE I**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of rats</th>
<th>Vehicle</th>
<th>L-Trp</th>
<th>3-HAA</th>
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<td>56.5</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3</td>
<td>63</td>
<td>176</td>
<td>146</td>
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<td>243 ± 23</td>
<td>254 ± 66</td>
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<tr>
<td>Streptozotocin-diabetic</td>
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<td>243 ± 19</td>
<td>259 ± 61</td>
<td>238 ± 65</td>
</tr>
</tbody>
</table>

* The abbreviations used are: L-Trp, L-tryptophan; 3-HAA, 3-hydroxyanthranilic acid; PEP, P-enolpyruvate; SPG, 3-phosphoglycerate.

* Four hours prior to killing, 3.7 moles of inhibitor per 200 g body wt were given intraperitoneally.

* Data taken from Ref. 2.

* Data taken from Ref. 3.

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Effects on Assayable Specific Activity of Hepatic P-enolpyruvate Carboxykinase: It has previously been shown that the assayable specific activity of this enzyme from livers of alloxan-diabetic rats is approximately 4-fold higher than that of normal rat livers (2, 25). Additionally, the paradoxical increase in the specific activity of P-enolpyruvate carboxykinase which occurs following tryptophan or 3-hydroxyanthranilic acid treatment of normal, fasted rats (2, 3) does not occur upon administration of tryptophan to sialoxan-diabetic rats (2).

In view of the failure of either tryptophan or 3-hydroxyanthranilic acid to elicit the phenomena of hepatic metabolite accumulation and crossover in either alloxan- or streptozotocin-diabetic rats, we investigated further the effects of these two compounds on the assayable specific activity of hepatic P-enolpyruvate carboxykinase of normal and diabetic rats. Data in Table I show that administration of either tryptophan or 3-hydroxyanthranilic acid causes a 2.5- to 3-fold elevation in the specific activity of this enzyme in normal rats but neither compound elicits a significant increase in carboxykinase activity from alloxan- or streptozotocin-diabetic rats. Thus our data confirm and extend those previously reported (2).

**Effect of Tryptophan and Its Metabolites on Gluconeogenesis by Perfused Livers Isolated from Normal or Diabetic Rats**

*General Characteristics of Perfused Livers*: In the absence of exogenous substrate, glucose production averaged 11 pmoles per hour per g of liver wet weight. Following 60 min of perfusion without substrate, the addition of 20 mM L-lactate caused an increase in the mean rate of glucose formation to 32 pmoles per hour per g of liver. Addition of 10 mM fructose, affected an even further increase in the rate of gluconeogenesis to an average of 75 pmoles per hour per g of liver. The rates of gluconeogenesis from 20 mM lactate in livers from diabetic rats are from 1.5 to 2 times higher than those obtained with livers from normal rats.

*Changes in Concentration of Metabolites in Perfused Normal or Diabetic Livers*: Hepatic metabolite levels in normal rat livers perfused with lactate in the presence of previously added tryptophan or quinolinate are shown in Fig. 3. Compared to control values (obtained from livers perfused with lactate only), concentrations of citrate, aspartate and especially malate are elevated concomitant with decreases in the levels of P-enolpyruvate and 2- and 3-phosphoglycerate. Although not shown, a similar pattern of metabolite accumulation and crossover is observed following perfusion with 3-hydroxyanthranilic acid.

Fig. 4 depicts hepatic metabolite levels in livers from alloxan-diabetic rats perfused with either tryptophan or quinolinate. Concentrations of most of the metabolites measured are increased 2- to 3-fold compared to controls, and in sharp contrast to the pattern of metabolite crossover between P-enolpyruvate and its precursors (aspartate, malate, or citrate) observed in normal livers (Fig. 3), no such crossover obtains in the alloxan-diabetic livers (Fig. 4). Similar results (not presented) are obtained with livers isolated from streptozotocin-diabetic rats. The metabolite accumulation seen in livers from diabetic rats following perfusion with 3-hydroxyanthranilic acid (also not shown) is similar to that observed after perfusion with tryptophan or quinolinate.

**Effect on Specific Activity of P-enolpyruvate Carboxykinase**: Although perfusion of livers from normal rats for 60 min with either tryptophan, 3-hydroxyanthranilic acid, or quinolinate as opposed to vehicle causes statistically significant increases in the assayable specific activity of P-enolpyruvate carboxykinase, no such increase is seen following perfusion of livers from alloxan-diabetic rats with the same compounds. Similarly, no significant change is observed in carboxykinase activity following per-
2PG, 2-phosphoglycerate. See legend to Fig. 1 for definition of the other abbreviations.

Fig. 4 (right). Concentrations of glucogenic metabolites in livers isolated from alloxan-diabetic rats following perfusion for 90 min with either 2.4 mM L-tryptophan or quinolinate and for 60 min with 20 mM L-lactate. Control values for each metabolite obtained from livers perfused without inhibitor are recorded at the bottom of the figure with the standard deviations of the means. Experimental data are expressed as multiples of these control values. The number of perfusions contributing to each experimental point is shown in parentheses above the vertical line which indicates one standard deviation. The number of perfusions contributing to each control point is indicated in parentheses below the value for the particular metabolite. 2PG, 2-phosphoglycerate. See legend to Fig. 1 for definition of the other abbreviations.

FIG. 5 (left). The effect of prior addition of L-tryptophan or quinolinate on glucose production from DL-[2-14C]lactate by the isolated perfused normal rat liver. The data are presented as radioactivity appearing in perfusate glucose synthesized from labeled lactate per unit weight of perfused liver; this is plotted as a function of time after addition of radioactive lactate. The livers were perfused for 30 min with or without either 2.4 mM L-tryptophan or 2.4 mM quinolinate before the lactate was added.

FIG. 6 (right). The effect of prior addition of L-tryptophan or quinolinate on glucose production from DL-[2-14C]lactate by the isolated perfused alloxan-diabetic rat liver. The data are presented as radioactivity appearing in perfusate glucose synthesized from labeled lactate per unit weight of perfused liver; this is plotted as a function of time after addition of radioactive lactate. The livers were perfused for 30 min with or without either 2.4 mM L-tryptophan or 2.4 mM quinolinate before the lactate was added.

Fig. 7 (left). Glucose production from DL-[2-14C]lactate by isolated perfused normal livers before and after the addition of 2.4 mM L-tryptophan or quinolinate. The rate of synthesis of labeled glucose per g of liver is depicted as a separate function of time after the addition of radioactive lactate. At the indicated times L-tryptophan (L-Trp) or quinolinate were added in amounts to attain a final concentration of 2.4 mM.

FIG. 8 (right). Glucose production from DL-[2-14C]lactate by isolated perfused alloxan-diabetic livers before and after the addition of 2.4 mM L-tryptophan or quinolinate. The rate of synthesis of labeled glucose per g of liver is depicted as a function of time after the addition of radioactive lactate. At the indicated times L-tryptophan (L-Trp) or quinolinate were added in amounts to attain a final concentration of 2.4 mM.

Pyruvate (4, 5). Venesiale et al. (4) have concluded that quinolinate inhibits the in vivo conversion of oxalacetate to P-enolpyruvate, it also paradoxically enhances the assayable specific activity of P-enolpyruvate carboxykinase well above its normal level (2, 4). Nevertheless, the observation by Foster et al. (2) that tryptophan does not alter the assayable specific activity of carboxykinase from alloxan-diabetic rats suggested that tryptophan might also be unable to inhibit gluconeogenesis in diabetic rats and prompted the experiments reported here.

The absence of a metabolite crossover in data from alloxan-diabetic rats presented in Fig. 2 indicates that neither tryptophan nor 3-hydroxyanthranilic acid can inhibit gluconeogenesis in intact alloxan-diabetic rats. The fact that similar data are obtained with both alloxan- and streptozotocin-diabetic rats suggests that the inability of tryptophan or 3-hydroxyanthranilic acid to inhibit gluconeogenesis in these animals relates to the diabetic condition rather than to the nature of the diabetogenic agent used. Data in Table I indicate that neither tryptophan

**DISCUSSION**

Tryptophan inhibits gluconeogenesis in intact normal rats and in their isolated livers by inhibiting the P-enolpyruvate carboxykinase-mediated conversion of oxalacetate to P-enol-
nor 3-hydroxyanthranilate can significantly alter the assayable specific activity of hepatic P-enolpyruvate carboxykinase from diabetic rat livers and suggest that the two paradoxical effects seen after tryptophan treatment of normal rats may be directly related and thus inseparable. Such a suggestion is consistent with the explanation of these paradoxical effects by Snoke et al. (8).

Data presented in Figs. 4, 6, and 8, as well as additional data not presented, all indicate that neither tryptophan nor 3-hydroxyanthranillic acid inhibit gluconeogenesis nor can they significantly alter the in vitro assayable activity of P-enolpyruvate carboxykinase in livers isolated from either alloxan- or streptozotocin-diabetic rats. Data obtained with intact diabetic rats and their isolated livers are thus in good agreement.

Many of our results would appear to be explainable on the basis of reports that tryptophan metabolism is aberrant in both alloxan-diabetic (18-21) and depancreatized rats (19, 32-34) and, interestingly, also in alloxan-diabetic rabbits (35) and in humans with diabetes mellitus (36). For example, urinary excretion of N'-methylbenzothiazoline is diminished in alloxan-diabetic (18) and depancreatized rats (32) and there is a decreased production of 3-hydroxyanthranilate and quinolinic acid by liver slices from depancreatized rats (34). Furthermore, the activity of picolinic carboxylase which shunts tryptophan metabolism toward glutarate and away from quinolinate is substantially elevated in alloxan-diabetic (19-21) and depancreatized rats (19, 33). Thus, in intact diabetic rats, tryptophan metabolism could be sufficiently aberrant to diminish the amount of quinolinate produced from tryptophan to levels below inhibitory concentrations. If so, presentation of quinolinate to isolated diabetic livers should result in inhibition of gluconeogenesis and enhancement of the in vitro specific activity of carboxykinase.

However, as is apparent from a comparison of metabolite data presented in Fig. 4 versus those in Fig. 3, quinolinate also does not inhibit gluconeogenesis (based on the absence of a metabolite crossover) in alloxan-diabetic rats (or for that matter in streptozotocin-diabetic rats). A similar conclusion is arrived at on the bases of data presented in Figs. 6 and 8, which indicate that addition of quinolinate, either prior to or subsequent to addition of labeled lactate, exerts little if any effect on isotope incorporation into perfusate glucose by diabetic livers as opposed to quinolinate's inhibition of labeled lactate's conversion to glucose in normal livers (Figs. 5 and 7).

These latter data preclude the explanation that the inability of tryptophan to inhibit gluconeogenesis in diabetic rats is simply due to its aberrant metabolism. Nonetheless, the reasons for the inability of quinolinate to inhibit glucose formation in isolated perfused livers are not readily apparent at this time.

Our observations suggest the intriguing possibility that if tryptophan does play a role in the regulation of gluconeogenesis in the normal rat (as has been suggested (5)), then alteration or loss of its role in the diabetic rat could be at least partially responsible for the enhanced rate of glucose formation seen in diabetes.

After examining the effects of quinolinate in isolated perfused rat, guinea pig, and pigeon livers, Söling et al. (37) have concluded that it inhibits only cytosolic P-enolpyruvate carboxykinase activity. Thus, if tryptophan normally participates in regulation of glucose synthesis in other species (such as the human) which possess cytosolic carboxykinase, then loss or modification of its regulatory role could be at least partially responsible for the enhanced glucose formation seen in diabetes mellitus.
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