Influence of Glucagon on the Metabolism of Xylitol and Dihydroxyacetone in the Isolated Perfused Rat Liver

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SUMMARY

Glucagon stimulates glucose synthesis from xylitol and dihydroxyacetone in the isolated perfused rat liver. In addition to increasing the initial rate of glucose production from these substrates, the hormone also increases the efficiency of gluconeogenesis causing at least 90% of the substrate consumed by the liver to be converted to glucose. These effects of glucagon on gluconeogenesis are observed even when quinolinate is added to block entry of compounds through phosphoenolpyruvate carboxykinase. The formation of lactate from xylitol and oxidation of xylitol to CO₂ are inhibited approximately 80% and 70%, respectively, by glucagon. Measurement of the steady-state concentrations of the gluconeogenic intermediates accompanying the stimulation of gluconeogenesis from xylitol and dihydroxyacetone show that the hormone markedly decreases the concentration of fructose 1,6-diphosphate. The mechanism by which glucagon causes the drastic fall in fructose-1,6-P₂ cannot be explained in terms of the known allosteric regulation of fructose 1,6-diphosphatase and phosphofructokinase.

The observations reported in this communication suggest that the effect of glucagon on gluconeogenesis and glycolysis is the result of a complex interaction rather than regulation of one particular enzyme of the gluconeogenic-glycolytic pathway.

Alterations in the concentrations of the gluconeogenic intermediates accompanying treatment of the perfused rat liver with the hyperglycemic hormone glucagon have indicated two possible interactions of the hormone in the gluconeogenic pathway; the first is at a point between pyruvate and phosphopyruvate and the second at the level of the hexose phosphates (1-4). Reports that glucagon does not influence gluconeogenesis from precursors entering the pathway at the level of the triose phosphates (1, 5, 6) have led several investigators to conclude that the hormone is acting primarily at one of the initial steps in gluconeogenesis from pyruvate. Thus several of the studies over the last five years concerning the mechanism of action of glucagon and its second messenger cyclic adenosine 3':5'-monophosphate have centered on the reactions involving the carboxylation of pyruvate, the synthesis of phosphopyruvate from oxalacetate, and the transfer of carbon units from the mitochondria (1-7).

Veneziale, however, has recently demonstrated that glucagon stimulates gluconeogenesis from fructose (8), dihydroxyacetone, and α-glyceroldehyde (9) and that this stimulation does not require the resynthesis of phosphopyruvate from pyruvate.

We have also observed a stimulation of gluconeogenesis from xylitol and dihydroxyacetone by glucagon in the isolated perfused rat liver, which is presented in this report.

METHODS

Perfusion—Male Sprague-Dawley rats weighing 290 to 310 g were fasted 24 hours prior to perfusion experiments. The isolated livers were perfused by the technique previously reported from this laboratory (10). The perfusate consisted of 20% washed bovine erythrocytes (11) in a Krebs-Ringer bicarbonate medium, containing 3% fatty acid-free bovine serum albumin (Research Products Division, Miles Laboratories). Details concerning the perfusions are given in the legend to Table I.

Metabolic Analysis—At the termination of the perfusions, liver samples were quick frozen in tongs cooled in liquid nitrogen, pulverized, and extracted with 6% (w/v) perchloric acid. Metabolites in neutralized tissue extracts were assayed spectrophotometrically by means of established enzymatic techniques (12). The Pi content of neutralized tissue extracts was determined spectrophotometrically by means of established enzymatic techniques (12). The Pi content of neutralized tissue extracts was determined spectrophotometrically by the method of Parvin and Smith (13). Separate portions of the pulverized frozen tissues were taken for glycogen isolation (14) and assayed by the anthrone method (15).

Perfusate samples (2 ml) were deproteinized with 5% (w/v) perchloric acid (4 ml), and glucose was measured in the acid extract by the glucose oxidase method (Boehringer-Mannheim). Other metabolites in the perfusate were measured in neutralized samples of this extract.

Isolation of Radioactive Components—Radioactive glucose in the perfusate was separated from xylitol with the use of a combination of ion exchange resins and hexokinase treatment as follows. Neutralized perfusate extracts (2 ml) were passed through tandem pencil columns, the first containing 2-ml bed volume AG 1-X8 formate form, 50 to 100 mesh overlaid with 1 ml of...
AG 1-X8, 200 to 400 mesh, formate form (Bio-Rad) and the second column containing 2-ml bed volume AG 50W-X8, 50 to 100 mesh, H+ form (Bio-Rad). After application of the sample, the columns were washed with 13 ml of water, and the total effluent (15 ml) was collected. A 2-ml portion of the neutral effluent (containing both xylitol and glucose) was mixed with 0.5 ml of a solution containing 0.4 x Tris-HCl, pH 8.0, 30 mM ATP, 10 mg per ml of hexokinase (type III, Sigma) and 0.05 x MgCl2. This mixture was incubated at 37° for 2 hours, then passed through an anion exchange resin, prepared as described above. Radioactive xylitol was collected by washing the columns with 12 ml of water. The glucose-6-P, representing the perfusate glucose, was eluted from the anion exchange resin with 10 ml of 1 x triethylamine-HCO3 containing 20% (v/v) ethanol.

The anionic products formed from the metabolism of xylitol, referred to here as the "lactate" fraction, were collected by eluting the first anion exchange column used in the isolation of the combined xylitol-glucose fraction with 10 ml of triethylamine-HCO3. Silica gel chromatography (16) of one perfusate extract obtained from a control perfusion with [U-14C]xylitol indicated that greater than 70% of the isotope recovered in this anionic fraction is lactate.

[14C]Glycerogen was isolated by co-precipitating the glycogen contained in the perchloric acid extract of liver samples with carrier shelfish glycogen (Sigma). Carrier glycogen, 0.4 ml of a 2% solution (w/v), was added to 1 ml of the neutralized perchloric extract, and total glycogen was precipitated with 4 ml of absolute ethanol and washed once with 66% (v/v) ethanol. This procedure avoids contamination of the isolated glycogen with other radioactive substances which often occurs when the glycogen is isolated by digestion of the tissue with KOH (17). The values obtained for the radioactivity incorporated into glycogen, however, are comparable with the use of either method.

Radioactive CO2 produced during the perfusion was trapped by aspirating the effluent from the oxygenator through 200 ml of 1 x KOH. A portion of the KOH (2 ml) was acidified in a closed vessel and the CO2 transferred to hyamine hydroxide (Packard).

Scintillation counting was carried out in Bray's solution (18) with the use of a Packard Tri-Carb liquid scintillation spectrophotometer; external standards were used to correct for quenching.

Reagents—Gluconeogenic substrates were obtained from the following suppliers: xylitol and dihydroxyacetone (Sigma), L-lactate (Schwarz-Mann), and pyruvate (Boehringer-Mannheim). [U-14C]Xylitol was obtained from Amersham-Searle and [U-14C]-dihydroxyacetone was purchased from ICN.

Glucagon (a generous gift from Dr. Ron Chance, Eli Lilly and Co., Indianapolis) was prepared fresh daily as 50 µg per ml in 3% bovine serum albumin. Oleic acid (Schwarz-Mann) was neutralized to the sodium salt and complexed with bovine serum albumin (90 mg of protein per rumole of oleate). Quinolinic acid (K and K Laboratories) was recrystallized 3 times from 7% acetic acid. Solutions of sodium quinolinate were prepared immediately before use. The significance of differences between means was established by the Student's t test.

RESULTS

With the recirculating perfusion system used in this investigation, glucose production from either 10 mM xylitol or 10 mM dihydroxyacetone is linear for over 30 min, and with initial concentrations of these substrates of 5 mM, the initial rate of glucose production is linear for approximately 15 min. Following this initial linear phase, the rate of glucose production decreases and essentially stops approximately 60 min after the addition of 10 mM substrates, and 45 min after the addition of 5 mM substrates.

Fig. 1A shows the time course of glucose production from 10 mM xylitol. The initial rate of glucose production from various substrates and differing conditions are given in Table I. Perfusion were carried out both in the presence and absence of quinolinate to estimate the contribution to glucose formation of endogenous precursors that must pass through phosphopyruvate. As shown in Table I, this inhibitor of phosphopyruvate carboxykinase (10) does not decrease the rate of glucose production with xylitol or dihydroxyacetone as the added substrate. Quinolinate does slightly reduce the residual rate of glucose production occurring after the exhaustion of the added substrate; however, the measured total amount of glucose produced from xylitol and dihydroxyacetone is not altered by quinolinate if the measurements are taken shortly after glucose production returns to low rates (60 min after the addition of 10 mM substrates and 45 min after the addition of 5 mM substrates). Data for the total glucose production from various concentrations of dihydroxyacetone and xylitol are given in Table II and represent a combination of experiments carried out both in the presence and absence of 4.8 mM quinolinate.

Glucagon increases both the initial rate of glucose production and the total amount of glucose produced from xylitol and dihydroxyacetone (Fig. 1A and Tables I and II). It should be noted that the enhancement of the rate of glucose synthesis caused by glucagon is similar with both dihydroxyacetone and xylitol as...
Influence of glucagon on rate of glucose production

The first 20 ml of perfusate through the liver was discarded. The livers were then connected to a recirculating reservoir containing 100 ml of perfusate. The livers were perfused for 60 min before the addition of the indicated gluconeogenic substrate, and the perfusion was continued for another 30 to 90 min. Other additions, where indicated, were made to the reservoir at the following times after connecting the liver to the recirculating reservoir: glucagon, 5 μg, at 30 and 60 min; sodium oleate, 0.1 mmole, at 0, 30, and 60 min; and sodium dehydrogenase, 0.18 mmole, at 30 min. The initial rate of glucose production was calculated from the amount of glucose released to the perfusate in the first 30 min after the addition of the substrates. The values shown represent the average ± S.D. Where n = 2, the average is presented.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Additions</th>
<th>Glucagon (μmol)</th>
<th>Initial rate of glucose production (μmol/g·rat·hr)</th>
<th>Added substrate converted to glucose</th>
<th>Total liver glycogen (μmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mM Xylitol</td>
<td>None</td>
<td>(9) 261 ± 29</td>
<td>261 ± 29</td>
<td>(4) 548 ± 25</td>
<td>111 ± 10</td>
</tr>
<tr>
<td>10 mM Xylitol</td>
<td>4.8 mM Quinoline</td>
<td>(9) 295 ± 25</td>
<td>93 ± 12</td>
<td>(4) 548 ± 25</td>
<td>111 ± 10</td>
</tr>
<tr>
<td>10 mM Dihydroxyacetone</td>
<td>None</td>
<td>(11) 185 ± 22</td>
<td>185 ± 22</td>
<td>(5) 173 ± 31</td>
<td>86 ± 3</td>
</tr>
<tr>
<td>10 mM Dihydroxyacetone</td>
<td>4.8 mM Quinoline</td>
<td>(5) 173 ± 31</td>
<td>200 ± 10</td>
<td>(4) 480 ± 18</td>
<td>127 ± 12</td>
</tr>
<tr>
<td>10 mM L-Lactate + 1 mM pyruvate</td>
<td>None</td>
<td>(19) 125 ± 12</td>
<td>125 ± 12</td>
<td>(7) 223 ± 15</td>
<td>127 ± 12</td>
</tr>
<tr>
<td>10 mM L-Lactate + 1 mM pyruvate</td>
<td>4.8 mM Quinoline</td>
<td>(4) 40 ± 15</td>
<td>40 ± 15</td>
<td>(2) 496 ± 90</td>
<td>7 ± 6</td>
</tr>
</tbody>
</table>

* p < 0.03 versus control minus quinoline.
\* p < 0.01 versus control plus quinoline.
\* p < 0.01 versus control minus quinoline.
\* p < 0.05 versus control minus quinoline.
\* p < 0.05 versus control plus quinoline.
\* p > 0.05 versus glucagon minus quinoline.
\* p < 0.01 versus control.
\* p > 0.05 versus control.

Substrates (Table I) and is somewhat greater when lactate is the substrate (Table I).

Measurements of the glycogen content of the livers at the termination of these experiments (Table II) show that the stimulatory influence of glucagon is not a result of its glycogenolytic activity.

In addition to a gluconeogenic activity, it is known that glucagon may also exert a proteolytic and lipolytic effect in the perfused liver (19). Measurements of the additional amount of glucose produced by the livers perfused in the presence of glucagon above that produced in control perfusions, indicate that the effect of glucagon is dependent on the concentration of the original substrate (Table II) and is not a constant value, which would be expected if it were due to a proteolytic activity of the hormone. Similarly, the data presented in Table II show that approximately 70% of the xylitol and dihydroxyacetone added to the perfusate is converted to glucose in control perfusions; whereas, in the presence of glucagon the production of glucose is very nearly equivalent to the amount of substrate added.

Fatty acids do not elicit the same response as does glucagon. Oleate, maintained at a concentration of approximately 1 mM throughout the perfusion (conditions under which gluconeogenesis from lactate is stimulated (20)) does not stimulate the initial rate of glucose production from dihydroxyacetone and only slightly increases the total amount of glucose produced from this substrate (Tables I and II). Also the stimulatory effect of glucagon is observed in the presence of this fatty acid. In one experiment, 1 mM oleate inhibited glucose production from 10 mM xylitol; this inhibition was not unexpected, since the transfer of reducing equivalents from the cytosol to the mitochondria is rate limiting for the metabolism of xylitol (21, 22).

**Table II**

Influence of glucagon on total glucose produced

All conditions are the same as described in Table I. The total amount of glucose produced from each substrate was determined after glucose production returned to low rates after the addition of the substrate. The time required for glucose production to stop after the addition of substrate was dependent on the initial concentration of the substrate and was 45 min with 5 mM xylitol or dihydroxyacetone, 60 min with 10 mM xylitol or dihydroxyacetone, and 90 min with 10 mM L-lactate + 1 mM pyruvate. The values presented represent the average ± S.D. Where n = 2, the average is presented.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Glucagon (μmol)</th>
<th>Total glucose produced</th>
<th>Added substrate converted to glucose</th>
<th>Total liver glycogen (μmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mM Xylitol</td>
<td>(4) 548 ± 25</td>
<td>(4) 548 ± 25</td>
<td>111 ± 10</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>10 mM Xylitol</td>
<td>(4) 548 ± 25</td>
<td>(4) 548 ± 25</td>
<td>111 ± 10</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>5 mM Dihydroxyacetone</td>
<td>(2) 414</td>
<td>(2) 414</td>
<td>108 ± 3</td>
<td>5 ± 3</td>
</tr>
<tr>
<td>10 mM Dihydroxyacetone</td>
<td>(2) 414</td>
<td>(2) 414</td>
<td>108 ± 3</td>
<td>5 ± 3</td>
</tr>
</tbody>
</table>

* Expressed as glucose equivalents.
\* For glycogen determinations.
\* Average of values obtained both in the presence and absence of 4.8 mM quinoline.
\* p < 0.01 for perfusions with glucagon versus control perfusions.
\* Values obtained in the presence of 4.8 mM quinoline.
\* No quinoline present.

Metabolism of [U-14C]Xylitol—The time course of [14C]glucose synthesis from [U-14C]xylitol is shown in Fig. 1B. Calculations based on the amount of [14C]glucose produced in these perfusions indicate that 97 ± 4% (n = 4) of the glucose produced in control perfusions and 93 ± 4% (n = 4) of that produced in the presence of glucagon comes from xylitol. The stimulation of glucose production from xylitol by glucagon is not accompanied by an increased uptake of xylitol from the perfusate from that observed in control perfusions (Fig. 1B). The ratio of xylitol consumed to glucose produced is 1.7 ± 0.1 (n = 4) in control perfusions and 1.27 ± 0.03 (n = 4) with glucagon present (p < 0.01), indicat-
The fate of the isotope from 10 mM \([U-\text{\textsuperscript{14}C}]\text{xylitol}\) after perfusion for 90 min in control and glucagon treatments is given. The data are expressed as the fraction of the isotope added appearing in the various metabolic products. The “lactate” fraction represents the total anionic constituents of the perfusate (see “Methods”). The acid-soluble radioisotope remaining in the liver at the termination of the perfusion represents that amount extracted from quick frozen samples into 6% (w/v) perchloric acid. The perfusions are those represented in Figs. 1 and 2.

<table>
<thead>
<tr>
<th>Added isotope incorporated into</th>
<th>Control</th>
<th>+ Glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>73 ± 3</td>
<td>90 ± 5*</td>
</tr>
<tr>
<td>“Lactate”</td>
<td>6.2 ± 0.4</td>
<td>1.3 ± 0.1*</td>
</tr>
<tr>
<td>CO\textsubscript{2}</td>
<td>5.8 ± 0.7</td>
<td>2.0 ± 0.1*</td>
</tr>
<tr>
<td>Liver</td>
<td>9 ± 1</td>
<td>9 ± 1*</td>
</tr>
<tr>
<td>Acid-soluble</td>
<td>1.5 ± 1.2</td>
<td>0.7 ± 0.1*</td>
</tr>
<tr>
<td>Glycogen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a p < 0.01\) for perfusions with glucagon versus control perfusions.

\(b p > 0.05\) for perfusions with glucagon versus control perfusions.

Fig. 2. Production of “lactate” and CO\textsubscript{2} from xylitol. A, control perfusions; O, perfusions carried out in the presence of glucagon. A, accumulation of lactate (---) and incorporation of isotope from \([U-\text{\textsuperscript{14}C}]\text{xylitol}\) into the “lactate fraction” of the perfusate in experiments with \([U-\text{\textsuperscript{14}C}]\text{xylitol}\) (---) shown in Fig. 1. B, production of \(^{14}\text{CO}_2\) during these experiments. The shaded bars represent control perfusions with 10 mM xylitol and the hatched bars, those carried out with glucagon added. The perfusion conditions and details of the addition of the substrate and glucagon are given in the legend of Fig. 1 and in Table I. The points represent the average ± S.D. of four perfusions. At both time periods shown in B, \(p\) is less than 0.01 for perfusions with glucagon versus control conditions.

Table III
Metabolism of \([U-\text{\textsuperscript{14}C}]\text{xylitol}\)

Glucagon significantly decreases the formation of lactate and \(^{14}\text{CO}_2\) from that observed in the control perfusions with \([U-\text{\textsuperscript{14}C}]\text{xylitol}\) (Fig. 2). The quantitative fate of the isotope from \([U-\text{\textsuperscript{14}C}]\text{xylitol}\) after 90 min of perfusion with this substrate (150 min total perfusion time) is summarized in Table III.

Fate of Dihydroxyacetone—The production of glucose from dihydroxyacetone shown in Tables I and II indicates that the fate of dihydroxyacetone and the influence of glucagon on the metabolism of this substrate is qualitatively similar to that found with xylitol. Quantitative determination of the fate of dihydroxyacetone was hampered by the adsorption of \([U-\text{\textsuperscript{14}C}]\text{dihydroxyacetone}\) to the anion exchange resins used for the separation of the perfusate constituents. The absolute amount of lactate (+pyruvate) appearing in the perfusate from dihydroxyacetone after 30 min of perfusion (without quinolinate) in two experiments was 70 pmol in control perfusions and 30 pmol with glucagon present. One paired experiment with \([U-\text{\textsuperscript{14}C}]\text{dihydroxyacetone}\) indicated that a larger fraction of this substrate is oxidized to \(^{14}\text{CO}_2\) than in the case of xylitol. In the control perfusion 11% of added 5 mm \([U-\text{\textsuperscript{14}C}]\text{dihydroxyacetone}\) was recovered in \(^{14}\text{CO}_2\) after 30 min of perfusion and in the presence of glucagon 6% was recovered in \(^{14}\text{CO}_2\).

Liver Metabolite Concentrations—An investigation of the influence of glucagon on the liver metabolite concentrations with xylitol as the substrate was carried out in the presence of 4.8 mm quinolinate. Tissue intermediates were measured 30 min after the addition of 10 mM xylitol to the perfusate, a time at which glucose production is still linear (Fig. 1). In Figs. 4 to 6, the metabolite concentrations are shown in the sequence occurring in gluconeogenesis. This is done to give a clear presentation of the changes in the concentrations of the metabolites that occur with the various experimental treatments, and no attempt is made to interpret a classical “cross-over” from these figures.

Although quinolinate only slightly influences the rate of glucose synthesis from xylitol (Table I), it appreciably alters the concentrations of several liver intermediates (Figs. 3 and 4). Quinolinate causes the cytosol to become more oxidized than it is in the perfusions with xylitol alone, as is indicated by the ratios of lactate to pyruvate and glycerol-3-P to dihydroxyacetone-P, and causes the mitochondria to become more reduced, as indicated by the ratio of hydroxybutyrate to acetacetate (Fig. 3). The influence of quinolinate on the concentrations of phosphopyruvate and 3-phosphoglycerate (Fig. 4) is presumably a result of the more oxidized state of the cytosol and the equilibrium between glyceraldehyde-3-P and 3-phosphoglycerate (23). The increase in the concentrations of the citric acid cycle intermediates accompanying quinolinate treatment (Fig. 3) has been observed with gluconeogenic substrates other than xylitol and has been interpreted to be a result of the inhibition of phosphopyruvate carboxykinase (10).

The influence of glucagon on the concentrations of the glycolytic-gluconeogenic intermediates in the livers perfused with 10 mM xylitol and 4.8 mM quinolinate is presented in Fig. 5. The concentrations of the citric acid cycle intermediates and the adenine nucleotides in these livers are shown in Fig. 3 and Table IV, respectively.
The decreased flux of xylitol to lactate observed to occur with the addition of glucagon (Fig. 2 and Table III) appears to be the result of an interaction of the hormone with the gluconeogenic-glycolytic pathway at the level of fructose-1,6-P_2 (Fig. 5). In the presence of quinolinate, glucagon has no important influence on the oxidation-reduction state of the liver, the concentrations of the citric acid cycle intermediates (Fig. 3), or the concentrations of the adenine nucleotides (Table IV).

The influence of glucagon on the concentrations of the gluconeogenic-glycolytic intermediates in livers perfused with 10 mM dihydroxyacetone (with no quinolinate) is shown in Fig. 6. With this substrate, too, glucagon lowers the steady-state concentrations of fructose-1,6-P_2 and the triose phosphates. Glucagon had no significant effect on the oxidation-reduction state of the liver or the concentration of the citric acid cycle intermediates in the livers perfused with 10 mM dihydroxyacetone (data not shown).

**DISCUSSION**

Dihydroxyacetone enters the combined gluconeogenic-glycolytic pathway by direct phosphorylation forming dihydroxyacetone phosphate (1, 24). Xylitol is initially oxidized to D-xylulose which is phosphorylated and subsequently converted to fructose-6-P and glyceraldehyde-3-P by nonoxidative reactions of the pentose shunt (6, 21). Whether these substances are converted to glucose or oxidized in the glycolytic chain is dependent on the relative activities of the enzymes that catalyze the physiologically
The adenine nucleotide concentrations were determined in the perchloric acid extracts of the livers indicated in Figs. 3 and 5 for perfusions with 10 mM xylitol and the indicated additions. The values represent the average ± S.D.

<table>
<thead>
<tr>
<th>Additions</th>
<th>(mol)</th>
<th>ATP</th>
<th>ADP</th>
<th>AMP</th>
<th>Pi</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>(5)</td>
<td>1.6 ± 0.4</td>
<td>1.2 ± 0.1</td>
<td>0.31 ± 0.03</td>
<td>4.4 ± 1.7</td>
</tr>
<tr>
<td>4.8 mM Quinolinate</td>
<td>(6)</td>
<td>1.7 ± 0.3*</td>
<td>1.0 ± 0.1*</td>
<td>0.33 ± 0.11*</td>
<td>3.6 ± 0.6*</td>
</tr>
<tr>
<td>4.8 mM Quinolinate + glucagon</td>
<td>(5)</td>
<td>1.9 ± 0.2*</td>
<td>1.2 ± 0.2*</td>
<td>0.32 ± 0.04*</td>
<td>4.7 ± 0.7*</td>
</tr>
</tbody>
</table>

a p > 0.05 for values presented versus appropriate controls.
b p < 0.01 for quinolinate added versus control.
c p < 0.03 for glucagon versus control plus quinolinate.

discussion continued...
genic-glycolytic intermediates upon treatment with glucagon as observed in the present work.

The observations that glucagon not only increases the rate of glucose synthesis, but also causes nearly quantitative synthesis of glucose from all of the substrates tested in this investigation suggest that the gluconeogenic response of the perfused liver to the hormone may not be limited to the regulation of one particular enzyme of the gluconeogenic pathway, but may be the result of a more complex interaction with the basic metabolic control mechanisms of this organ.

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