Adrenergic Control of Glycolysis and Pyruvate Kinase Activity in Hepatocytes from Young and Old Rats*

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The influence of various adrenergic agonists and antagonists on pyruvate kinase activity and lactate production from endogenous glycogen reserves was investigated in hepatocytes isolated from young and old rats. With hepatocytes prepared from juvenile rats (100 to 150 g) 10 μM epinephrine and 10 μM isoproterenol (a β-adrenergic agonist) inhibit pyruvate kinase activity and lactate production; whereas, 10 μM phenylephrine (an α-adrenergic agonist) has no influence on either parameter. With hepatocytes from fully mature adults (300 g and up) epinephrine, isoproterenol, and phenylephrine are all without influence on lactate production from endogenous glycogen reserves. Epinephrine gives a small but reproducible inhibition of pyruvate kinase activity in hepatocytes from adult rats, but isoproterenol and phenylephrine have no significant influence on the enzyme activity. In the presence of 0.5 mM theophylline, epinephrine and phenylephrine give a significant inhibition of pyruvate kinase activity and lactate production, with hepatocytes from both young and adult rats. Theophylline alone has no significant influence on pyruvate kinase activity, but it does give approximately 20% inhibition of lactate production in hepatocytes from both young and old rats. The results of this investigation demonstrate that selective changes in the metabolic response of the hepatocyte to various adrenergic agonists occur as the rat matures; however, similar changes are not observed with glucagon. The selective changes in the metabolic response of the hepatocyte appear to be related to changes in the adrenergic receptor system which occur during development.

Glucagon is known to stimulate glycogenolysis and glycogen synthesis in rat liver. These actions of glucagon most likely are mediated by cAMP and cAMP-dependent protein kinases (1, 2). Epinephrine has similar effects to glucagon on glycogenolysis and glycogen synthesis; however, it has been reported that some of the effects of the catecholamine are the consequence of cAMP-independent, α-adrenergic mechanisms (3-7). Epinephrine and glucagon are also known to modulate the activity of hepatic pyruvate kinase leading to decreased activity of the enzyme at subsaturating concentrations of P-enolpyruvate (8-12). Consistent with these actions, both hormones are capable of inhibiting glycolytic formation of lactate from dihydroxyacetone in rat liver (9). Considerable evidence has been presented suggesting that glucagon modulates pyruvate kinase by a CAMP-induced phosphorylation of the enzyme (13-16). Some controversy exists, however, concerning the regulation of the enzyme by epinephrine. Previous reports from our laboratory (9) and by Chan and Exton (17) indicate that the enzyme may be regulated by α-adrenergic mechanisms, not involving cAMP. Kemp and Clark (18), however, concluded that epinephrine regulates the enzyme by activating cAMP-dependent protein kinase.

It should be noted that epinephrine is a weak modulator of pyruvate kinase compared to the regulation by glucagon (9, 17, 19). A differential sensitivity to the two hormones is also evident in hepatocytes from fed rats, where glucagon but not epinephrine blocks glycolytic formation of lactate from endogenous glycogen reserves (9). To further explore the adrenergic control of hepatic carbohydrate metabolism, we have expanded studies into the differential actions of glucagon and epinephrine in hepatocytes from fed rats. In a separate investigation (20), we found that the nature of the adrenergic receptor systems in rat hepatocytes is dependent on the age of the rat under investigation. This report presents our findings that the differential actions of glucagon and epinephrine on pyruvate kinase activity and glycolytic formation of lactate in hepatocytes from fed rats are also influenced by the age of the rat.

MATERIALS AND METHODS

Unless otherwise noted, details concerning preparation and incubation of the hepatocytes as well as the age grouping of the rats used in the present investigation are identical with that described in an accompanying report (20). Analysis of glucose, lactate, and glycogen content in perchloric acid extracts of hepatocyte suspensions has also been described elsewhere (9, 20). Hepatocyte incubations for enzyme analysis were terminated with (NH4)2SO4 as previously described (9). Pyruvate kinase activity was determined colorimetrically by reacting pyruvate with dinitrophenylhydrazine (21). The enzyme assay was conducted at 95°C and pH 7.5 in a buffer containing 136 mM Tris-HCl, 66 mM KCl, 10 mM MgSO4, 2.5 mM ATP, 1.8 mM P-enolpyruvate, and 1% (v/v) Triton X-100. The reaction was initiated by adding enzyme to the complete assay medium (0.5 ml final volume, containing approximately 25 μl of the hepatocyte extract). After incubating the complete reaction mixture for 6 to 8 min (depending on the enzyme activity), the reaction was terminated by adding 0.5 ml of 0.1% dinitrophenylhydrazine in 2 N HCl. The mixture was kept at room temperature for 10 min, then 1.0 ml of 1.5 N NaOH was added. The samples were kept an additional 30 min at room temperature, centrifuged to clarify the solution (1000 X g for 10 min), and the absorbance at 520 nm was measured. The colorimetric assay was calibrated daily using enzymatically assayed samples of P-enolpyruvate and muscle pyruvate kinase (Sigma). The results obtained using the colorimetric procedures are the same as those obtained using a coupled, continuous recording assay (8, 9). The colorimetric procedure, however, is more suitable for measuring pyruvate kinase activity in a large number of
samples within a reasonable period of time. Glucagon and A23187 were kind gifts of Eli Lilly Co., Indianapolis. Stock solutions of glucagon were prepared and stored in 1 mM HCl at approximately 1 mg/ml. The concentration of glucagon in the stock solutions is determined by absorbance at 278 nm (22), and dilutions were prepared fresh daily in the incubation buffer containing 2.5% bovine serum albumin. Other details are the same as those described in an accompanying report (29).

**RESULTS**

Regulation of Glycogen Metabolism by Glucagon and Epinephrine in Hepatocytes from Young and Old Rats—For the present investigation metabolic activity of the hepatocyte was assessed by measuring the fate of endogenous glycogen reserves. Incubation of hepatocytes from fed rats with no exogenous carbon precursor is accompanied by a linear production of glucose and lactate for over 30 min. These two products account for greater than 80% of the glycogen mobilized during this period with glucose representing 60% of the mobilized carbon. The remainder of the carbon units have not been identified in the present investigation; however, studies by Harris (23) indicate that a considerable portion of mobilized glycogen may be oxidized or converted to lipid. Although lactate represents only 50% of the carbon units from glycogen passing through glycolytic reaction in the absence of hormone treatment, lactate production was used in the present study as an index of glycolytic activity of the cell.

With hepatocytes from adult rats glucagon potently stimulates glycogen mobilization and glucose production. Glucose production and glycogen mobilization are also linear for over 30 min in the presence of 1 μM glucagon. The pancreatic hormone nearly abolishes lactate production by these cells (Fig. 1) resulting in nearly quantitative conversion of mobilized glycogen to glucose. Half-maximal response is observed between 0.1 nM and 0.3 nM glucagon (Fig. 1). Epinephrine also stimulates glycogenolysis in these hepatocytes with optimal concentrations of the catecholamine giving equivalent stimulation to that seen with 1 μM glucagon (Fig. 1A). The maximum stimulation of glucose output by epinephrine, however, is not as extensive as that by glucagon because epinephrine does not inhibit lactate production in hepatocytes from adult rats (Fig. 1C). Thus, in hepatocytes incubated with 10 μM epinephrine, glucose accounts for 70% of the glycogen mobilized with lactate production representing another 15% of the carbon units. The remaining 15% of the carbon units have not been identified, but are assumed to be similar to the unidentified carbon units in hepatocytes receiving no hormone (23).

Experiments similar to that shown in Fig. 1 have also been carried out with hepatocytes from juvenile rats (100 to 150 g). Quantitative aspects of glycogen metabolism and its response to glucagon are quite similar in cells from juvenile and adult rats. Also the sensitivity of glycogenolysis to hormonal stimulation is similar with the two age groups with half-maximal stimulation seen with 0.3 nM and 0.5 μM glucagon and epinephrine, respectively. In contrast to observations with adult rats, however, epinephrine gives a significant inhibition of lactate formation in hepatocytes from juvenile rats. The results of several experiments comparing the regulation of glucose and lactate production by 1 μM glucagon and 10 μM epinephrine in hepatocytes from young and adult rats are summarized in Table I.

Influence of Theophylline on the Adrenergic Control of Glycogen Metabolism—When hepatocytes are incubated with 0.5 mM theophylline, 10 μM epinephrine gives a significant inhibition of lactate production in hepatocytes from both young and adult rats (Table I). The potentiation of epinephrine actions by theophylline, however, appears to be exerted primarily on glycolysis since theophylline has no effect on the stimulation of glycogenolysis by the catecholamine (Fig. 1). Theophylline does give a slight enhancement in the stimulation of glucose output by epinephrine (Fig. 1 and Table I). This enhancement, however, appears to be simply the result of carbon units being diverted from lactate production to glucose output. Theophylline alone has no significant influence on glucose production by hepatocytes from either young or mature rats (Table I). However, the xanthine consistently inhibits lactate production by approximately 20% (Table I).

Response of Pyruvate Kinase to Glucagon and Epinephrine—The response of pyruvate kinase to epinephrine in the hepatocyte is also dependent on the age of rat under investigation. With hepatocytes from juvenile rats we consistently observe that 10 μM epinephrine inhibits pyruvate kinase activity by approximately 40%; whereas, with cells from the older

![Fig. 1](http://www.jbc.org/)
Hepatocytes were prepared from juvenile (100 to 150 g) and mature (300 g and up) rats as indicated. The cells were preincubated for 10 min at 37°C. Individual cell suspensions then received a control determined. The results are presented as micromoles of glucose or ELM glucagon, as indicated. The incubation was continued an additional 20 min, then terminated by addition of perchloric acid. Samples were also taken at the end of the 10-min preincubation period. The amount of glucose and lactate produced over the final 20-min period was then determined. The results are presented as micromoles of glucose or lactate produced per 10^6 cells over the 20-min period. Each value represents the mean ± S.E. of results from the number of cell preparations shown in parentheses.

<table>
<thead>
<tr>
<th>Additions</th>
<th>Glucose production</th>
<th>Lactate production</th>
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<tr>
<td></td>
<td>100–150 g</td>
<td>300 g and up</td>
</tr>
<tr>
<td></td>
<td>umol/10^6 cell</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>14.7 ± 1.8 (7)</td>
<td>23.1 ± 1.7 (16)</td>
</tr>
<tr>
<td>T</td>
<td>15.4 ± 2.3 (5)</td>
<td>19.5 ± 1.3 (9)</td>
</tr>
<tr>
<td>E</td>
<td>24.8 ± 3.3 (6)*</td>
<td>46.8 ± 4.6 (11)*</td>
</tr>
<tr>
<td>E + T</td>
<td>29.4 ± 4.0 (6)*</td>
<td>57.0 ± 5.6 (11)*</td>
</tr>
<tr>
<td>G</td>
<td>32.6 ± 4.1 (8)*</td>
<td>72.2 ± 5.1 (16)*</td>
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*p < 0.01 versus control, paired t analysis.

*p < 0.01 versus E alone, paired t analysis.

*p < 0.01 versus E + T combination.

In hepatocytes from juvenile rats, 10 μM theophylline has no significant influence on pyruvate kinase activity in cells from either young or adult rats (data not shown). The maximal inhibition of pyruvate kinase activity seen with 1 μM glucagon is approximately 60%. No difference in the regulation of the enzyme by glucagon was observed between young and old rats (Fig. 2).

**Influence of α- and β-adrenergic Blockers on the Regulation of Lactate Production and Pyruvate Kinase Activity by 10 μM Epinephrine**—In a separate report, we provided evidence that the maturation of the rat is accompanied by a marked change in the nature of the adrenergic receptor system (20). To explore the relationship of this change with the differences in the regulation of lactate production and pyruvate kinase activity by epinephrine in hepatocytes from young and mature rats, we have examined the influence of α- and β-adrenergic blockers on this response. The results of several experiments examining the influence of 10 μM phenoxybenzamine (an α blocker) and 10 μM propranolol (a β blocker) on the inhibition of lactate production and pyruvate kinase activity by 10 μM epinephrine are summarized in Figs. 3 and 4, respectively.

In hepatocytes from juvenile rats, 10 μM propranolol significantly diminishes the inhibition of lactate production (Fig. 3) and pyruvate kinase activity (Fig. 4) by 10 μM epinephrine. The α blocker phenoxybenzamine has a significant influence on this inhibition. When 0.5 mM theophylline was included in the incubation medium, however, each blocker alone gave only a small reduction in the inhibition by epinephrine (Figs. 3 and 4). In two cell preparations we found that a combination of the two blockers effectively alleviates the inhibition of lactate production by 10 μM epinephrine in the presence of 0.5 mM theophylline (data not shown).

With hepatocytes from mature rats, propranolol has no influence on the inhibition of lactate production (Fig. 3) and pyruvate kinase activity (Fig. 4) by 10 μM epinephrine. The α blocker phenoxybenzamine has a significant influence on this inhibition. When 0.5 mM theophylline was included in the incubation medium, however, each blocker alone gave only a small reduction in the inhibition by epinephrine (Figs. 3 and 4). In two cell preparations we found that a combination of the two blockers effectively alleviates the inhibition of lactate production by 10 μM epinephrine in the presence of 0.5 mM theophylline (data not shown).

**Regulation of Lactate Production and Pyruvate Kinase Activity by Isoproterenol and Phenylephrine**—We also examined the influence of 10 μM isoproterenol (a β-adrenergic agonist) and 10 μM phenylephrine (an α-adrenergic agonist) on the glycolytic processes in hepatocytes from juvenile and adult rats (Figs. 5 and 6). In hepatocytes from the young rats, 10 μM isoproterenol inhibits lactate production and pyruvate kinase activity nearly as well as 10 μM epinephrine (compare Figs. 5 and 6 with Figs. 3 and 4). With hepatocytes from adult rats, however, isoproterenol has no significant influence on either parameter. The α agonist phenylephrine has a significant influence either on lactate production or pyruvate kinase activity in hepatocytes from young or old rats unless theophylline is also included in the cell incubation medium (Figs. 5 and 6). With hepatocytes from juvenile rats these responses
to phenylephrine are partially blocked by propranolol, suggesting that perhaps the α agonist also interacts with the β receptor to a small extent. Phenoxybenzamine partially blocks the inhibition of pyruvate kinase by phenylephrine plus theophylline in cells from adult rats (Fig. 6); the α blocker, however, had no significant influence on lactate production under these conditions (Fig. 5). Interpretation of the latter observation is clouded by the fact that theophylline alone

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**Fig. 3.** Influence of α- and β-adrenergic blockers on the response of lactate production to 10 μM epinephrine. Hepatocytes were prepared from juvenile rats weighing 100 to 150 g or from adults weighing 300 g and up as indicated. The cells were preincubated at 37°C for 10 min with a control vehicle, 10 μM phenoxybenzamine (an α-adrenergic blocker), or 10 μM propranolol (a β blocker). After preincubation, 10 μM epinephrine (A) or 10 μM epinephrine + 0.5 mM theophylline (B) was added, and the incubation was continued for 20 min. Lactate produced over the final 20-min incubation period was determined and is expressed relative to that found with hepatocytes given only control vehicle. The results are the mean of values obtained from the number of cell preparations given in parentheses. The error bar represents 1 S.E. No significant influence of phenoxybenzamine or propranolol was noted in these experiments (not shown for clarity). *p < 0.05 versus control receiving no agonist. +, p < 0.05 versus cells receiving no blocker but otherwise treated the same. Statistical analysis was done by paired t analysis.

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**Fig. 4.** Influence of α- and β-adrenergic blockers on the inhibition of pyruvate kinase by 10 μM epinephrine. Hepatocytes were preincubated with various adrenergic blockers and then received epinephrine in the absence and presence of theophylline as described in the legend of Fig. 3. The reaction was terminated 7 min after addition of epinephrine, and pyruvate kinase activity was determined as described in the legend of Fig. 2. The data are presented as the inhibition of pyruvate kinase and represent the mean of results obtained from the number of cell preparations shown in parentheses. Other details are the same as those given in the legend of Fig. 3.

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**Fig. 5.** Influence of isoproterenol and phenylephrine on lactate production in hepatocytes from fed rats. Hepatocytes from young and old rats were preincubated with α and β blockers as described in the legend of Fig. 3. The cells then received 10 μM isoproterenol (a β agonist, A and B) or 10 μM phenylephrine (an α agonist, C and D) in the absence and presence of 0.5 mM theophylline as noted. The incubation was continued for 20 min with lactate production being measured over this final period as described in Fig. 3. Other details of the experiments are also the same as those given in the legend of Fig. 3.
inhibited lactate production by approximately 20% in these studies (Table I).

**Influence of the Divalent Metal Ionophore, A23187, on Glycogen Metabolism**—Exton and his coworkers (24, 25) demonstrated that 10 μM A23187 stimulates glycogenolysis in rat hepatocytes. This action of the ionophore appears to be dependent on calcium (25) and is not a consequence of its uncoupling actions (26) since Assimacopoulos-Jeannet et al. (24) reported 10 μM A23187 does not influence ATP levels in the rat hepatocyte. We also find that 10 μM A23187 stimulates glycogen mobilization to the same extent as does 1 μM glucagon (Table II). Unlike glucagon, however, the ionophore gives only a small (but statistically significant compared to solvent alone) inhibition of lactate production. Thus stimulation of glucose output by A23187 is not as extensive as that elicited by glucagon. These actions of A23187 on glycogen metabolism resemble those of epinephrine in that lactate production is weakly influenced. Unlike the results with epinephrine, however, theophylline does not potentiate an inhibition of lactate production by the ionophore (data not shown).

**FIG. 6. Influence of isoproterenol and phenylephrine on pyruvate kinase activity in hepatocytes from young and old rats.** Details of the experiments are the same as those given in the legends of Figs. 4 and 5.

**Table II**

<table>
<thead>
<tr>
<th>Additions</th>
<th>Glucose production</th>
<th>Lactate production</th>
<th>Glycogen mobilization (as glucose units)</th>
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<tr>
<td>Control</td>
<td>39.9 ± 3.0</td>
<td>28.7 ± 2.5</td>
<td>64.4 ± 6.6</td>
</tr>
<tr>
<td>DMSO</td>
<td>43.3 ± 2.8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>33.2 ± 3.6&lt;sup&gt;3&lt;/sup&gt;</td>
<td>80.8 ± 11.0&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>A23187</td>
<td>67.3 ± 3.6&lt;sup&gt;3&lt;/sup&gt;</td>
<td>26.4 ± 2.6&lt;sup&gt;3&lt;/sup&gt;</td>
<td>106.9 ± 11.7&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glucagon</td>
<td>94.3 ± 5.8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2.1 ± 0.4&lt;sup&gt;3&lt;/sup&gt;</td>
<td>109.0 ± 9.4&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>3</sup><sup>p < 0.01 versus control.</sup>
<sup>3</sup><sup>p < 0.05 versus control.</sup>
<sup>3</sup><sup>p < 0.01 versus DMSO.</sup>

**DISCUSSION**

The present investigation clearly shows that maturation of the rat is accompanied by selective changes in the adrenergic control of hepatic carbohydrate metabolism. These changes include a specific loss of the capacity for epinephrine to modulate lactate formation from endogenous glycogen reserves (Table I). The ability of epinephrine to stimulate glyco- genolysis, however, does not appear to be greatly altered during this developmental period. Furthermore, the maturational changes do not extend to all hormone systems since glucagon potently inhibits glycolytic formation of lactate in hepatocytes from both young and adult rats (Table I). We believe the changes in the adrenergic control of glycolytic flux seen with maturation are the consequence of alterations in the adrenergic receptor systems which occur during this period (20). The results presented in Figs. 3 and 5 indicate that adrenergic regulation of lactate production in hepatocytes from juvenile rats (in the absence of theophylline) is primarily through β-adrenergic receptors. The inhibition by epinephrine is blocked by propranolol but not phenoxybenzamine. Also, isoproterenol (a β agonist) but not phenylephrine (an α agonist) inhibits lactate formation in these young cells. An α-adrenergic-mediated inhibition of lactate production also is apparent in hepatocytes from juvenile rats; however, it is readily apparent only in the presence of theophylline (Figs. 3 and 5). This latter observation supports previous reports by other workers (1, 17) that methylxanthines may potentiate α receptor-mediated actions of epinephrine and phenylephrine. The present observations coupled with measurements of cAMP levels in hepatocytes from young rats under similar conditions further indicate that β regulation of the enzyme involves cAMP-dependent processes, whereas α regulation is independent of a rise in cAMP levels (20).

The results with hepatocytes from mature rats lead to a different interpretation than that with cells from young rats. The observation that epinephrine, isoproterenol, and phenylephrine all are without influence on lactate production in hepatocytes from adult rats (in the absence of theophylline, Figs. 1, 3, and 5 and Table I) is consistent with an observed loss of β receptor function in hepatocytes from mature rats (20) and a proposed role for β receptor-mediated cAMP-dependent regulation of lactate formation from glycogen reserves. In the presence of theophylline, however, epinephrine and phenylephrine inhibit lactate production exclusively.
through α adrenergic receptors (Figs. 1, 3, and 6). Whether the α regulation of this glycolytic flux is independent of cAMP, as has been demonstrated for α regulation of glycogenolysis and gluconeogenesis (3–7), is not clear since α-mediated events also raise cAMP levels in hepatocytes from adult rats (20). Thus further investigation will be necessary to fully resolve the nature of the adrenergic control of lactate production in hepatocytes from mature rats incubated with theophylline.

Another objective of the present investigation has been to resolve discrepancies in the literature concerning the nature of the adrenergic control of hepatic pyruvate kinase. Whereas Chan and Exton (17) conclude that epinephrine modulates the enzyme predominantly through cAMP-independent, α-adrenergic mechanisms, Kemp and Clark (18) suggest that pyruvate kinase is regulated through a cAMP-dependent protein kinase. Similar to the results concerning adrenergic control of lactate production from glycogen reserves, the present study indicates that both α- and β-adrenergic regulation of the enzyme may occur. Furthermore, the relative contribution of these two pathways depends on the age of the rat under investigation. Thus, β-adrenergic, cAMP-dependent regulation of the enzyme is consistent with several studies showing that pyruvate kinase may be phosphorylated by a cAMP-dependent protein kinase (13–16). The mechanism by which cAMP-independent, α-adrenergic regulation of the enzyme occurs, however, is not known. Exton and his coworkers (24, 25) postulated that cAMP-independent, α-adrenergic regulation of phosphorylase and glycogenolysis in rat liver involves a role for calcium. Thus the calcium-dependent stimulation of glycogenolysis by A23187 may be mediated by a calcium stimulation of phosphorylase kinase (27). Other calcium-modulated protein kinases are known (28), and these may mediate calcium actions on other metabolic processes. The small influence of A23187 noted on lactate production under conditions that the ionophore extensively stimulates glycogenolysis (Table II) does not support a major role for calcium in regulating glycolytic flux. These results support similar conclusions drawn from studies showing minimal influence of the ionophore on pyruvate kinase activity in the hepatocyte (9, 17). Therefore, the biochemical mechanisms for cAMP-independent regulation of glycolytic flux and pyruvate kinase activity remain to be elucidated. Preliminary studies in our laboratory, however, have shown that ultimate modification of pyruvate kinase by epinephrine involves phosphorylation of the enzyme, similar to its regulation by glucagon.† The extent of phosphorylation of hepatic pyruvate kinase in response to epinephrine under a variety of conditions remains to be established, and these studies are currently in progress in our laboratory.

We currently do not know if the differential actions of glucagon and epinephrine seen in hepatocytes from adult rats extend to aspects of carbohydrate metabolism other than lactate formation from the hexose-P level. Isotopic studies by Rognstad and Katz (29) suggest that the differential actions of the two hormones might be limited to glycolytic processes. These investigators found that glucagon potently inhibits recycling of P-enolpyruvate to pyruvate in hepatocytes from fed rats, but that epinephrine either stimulates or has no influence on this recycling. In their studies, however, glucagon and epinephrine equally stimulate gluconeogenesis from lactate (29). Older literature concerning glucagon and epinephrine actions in the perfused rat liver generally indicate that the two hormones (at optimal concentrations) equally stimulate gluconeogenesis (5, 30, 31). Several investigators, however, have recently reported that glucagon stimulates gluconeogenesis to a greater extent than does epinephrine in the isolated rat hepatocyte (4, 17, 32). Interestingly, early studies with the perfused liver involved livers from young rats, whereas many of the recent studies have been conducted with more mature animals. Claus and Pilkis (33) have also pointed out that differential actions of glucagon and epinephrine on gluconeogenesis may be evident only in hepatocytes from fed rats. Thus many factors may influence the metabolic response to epinephrine. The present investigation, however, clearly demonstrates the importance of considering age of the rat when studying the adrenergic control of hepatic carbohydrate metabolism. Future studies into this control certainly must take this age dependence into consideration.

REFERENCES


† M. A. Cimbala and J. B. Blair, unpublished observations.
Adrenergic control of glycolysis and pyruvate kinase activity in hepatocytes from young and old rats.
J B Blair, M E James and J L Foster