Hepatic Glycerol Metabolism in Tumorous Rats: A $^{13}$C Nuclear Magnetic Resonance Study

Katherine Jung-Mei Liu, Yifat Drucker, and Jehad Jarad

Department of Surgery, Cook County Hospital, and Department of Surgery, Hektoen Institute for Medical Research, Chicago, Illinois 60612

ABSTRACT

Cancer cachexia contributes to the demise of a significant number of cancer patients, and severe loss of adipose tissue is a prominent component of this syndrome. One of the products of fat catabolism is glycerol, and its turnover is elevated in the cancerous state. Since glycerol is also one of the most important gluconeogenic substrates, its role in the augmented and abnormal gluconeogenesis of cancer hosts needs to be defined. In the present study, we examined hepatic glycerol metabolism in livers of Fischer 344 rats bearing s.c. nonmetastatic adenocarcinoma R3230AC. Five weeks after tumor inoculation, the liver was removed and perfused with 5 mM $[2-^{13}$C]glycerol while $^{13}$C nuclear magnetic resonance spectroscopy was performed. In the livers of tumorous rats, we found: (a) lipogenesis from glycerol was augmented; (b) the rate of hepatic glycerol uptake was unchanged; (c) glucose production from glycerol was not altered; and (d) conversion of glycerol 3-phosphate to dihydroxyacetone phosphate remains the rate-limiting step. Therefore, it appears that, in cancer hosts, diminished glycerol clearance is not due to reduction in hepatic glycerol uptake or metabolism, and the abnormal gluconeogenesis involves the pathway prior to the entry of glycerol. The exaggerated lipolysis is probably used for the pathological hepatomegaly, and the availability of the cytosolic hydrogen acceptor remains the rate-limiting factor for glycerol metabolism.

INTRODUCTION

Cachexia, commonly observed in cancer patients, is a devastating condition which contributes to their death in many cases. It is associated with alterations in intermediary metabolism which are not correctable with currently available nutritional therapy (1). Among these alterations, abnormal lipid metabolism with severe loss of adipose tissue is a prominent component (2—5) with the subsequent loss of free fatty acids and glycerol (5—8). Unlike free fatty acids which can be used by a variety of tissues, the liver is the primary site of glycerol metabolism because the liver is rich in glycerol kinase, the enzyme required for glycerol metabolism (9—11). After entering the liver, glycerol may enter the gluconeogenic pathway, be used for lipolysis, function as a carrier of reducing equivalents from cytosol to mitochondria, or serve as an oxidative substrate for energy production (11—14). From 38 to 96% of glycerol will be used for glucose formation depending on the length of fasting and the presence of obesity (15). Under physiological concentrations, glycerol is the most important gluconeogenic substrate since the rate of hepatic incorporation of glycerol into glucose far exceeds that for any other substrate (11, 16, 17). Hepatic utilization of glycerol in cancer hosts is of particular interest, since there is elevated plasma glycerol turnover as formation depending on the length of fasting and the presence of obesity (15). Under physiological concentrations, glycerol is the most important gluconeogenic substrate since the rate of hepatic incorporation of glycerol into glucose far exceeds that for any other substrate (11, 16, 17). Hepatic utilization of glycerol in cancer hosts is of particular interest, since there is elevated plasma glycerol turnover as well as augmented and abnormal hepatic glucose production (5, 18, 19). It is not clear whether the alterations in the intermediary metabolism of gluconeogenesis involve glycerol utilization and what role the enhanced glycerol turnover plays in the abnormal glucose metabolism. In the present study, we examined hepatic disposal of glycerol under the indirect influence of a remote tumor using $^{13}$C NMR spectroscopy.

MATERIALS AND METHODS

Animal Preparation. Female Fischer 344 rats weighing between 120 and 130 g were inoculated with adenocarcinoma R3230AC s.c. (tumor; $n = 5$). This nonmetastatic mammary tumor occurs naturally in Fischer 344 rats and has been characterized extensively (20—23). Weight-matched normal rats were either fed ad libitum (the normal group) or pair fed (the pair-fed group; $n = 5$ for each group). Five weeks later, after an overnight fast, the rats underwent ether anesthesia. The livers were removed and perfused with an oxygenated Krebs-Henseleit bicarbonate buffer through the portal vein. The perfusion technique has been described previously (24, 25). In brief, the perfusion medium was recirculated using a peristaltic pump at 5—7 ml/g of liver/min with its pH maintained at 7.35—7.45. After acquiring the $^{13}$C natural abundance liver spectrum, the perfusion medium was changed to one that contained 5 mM $[2-^{13}$C]glycerol (Merck Sharp & Dohme/Isotope, St. Louis, MO). During the perfusion, glycerol levels were monitored using a commercial kit (Boehringer Mannheim Biochemicals, Indianapolis, IN) and UV method (26). The rate of glycerol uptake by the liver was calculated for the initial 30 min of the perfusion. At the end of perfusion, the livers were freeze clamped immediately and then extracted with perchloric acid as well as hexane/isopropl alcohol mixture at a later date (27, 28). $^{13}$C NMR spectroscopy of the perfusate was performed using the same acquisition conditions.

NMR Spectroscopy. The techniques for $^{13}$C NMR spectroscopy of the perfused and extracted liver have been reported previously (29). Briefly, for the perfused liver and perfusion medium, a Nicolet 200-MHz NMR spectrometer with a Helmholtz coil and a 20-mm broadband probe was used in the Fourier transform mode. The temperature of the NMR probe was maintained at 37°C. $^{13}$C NMR spectroscopy was performed with a pulse angle of 45 degrees, a recycling time of 0.78 s, and 2308 acquisitions/spectrum. First, the $^{13}$C natural abundance liver spectrum was acquired while the liver was perfused with the Krebs buffer. Subsequently, the perfusate was changed to one containing 5 mM $[2-^{13}$C]glycerol and three additional spectra of the liver were obtained. The free induction decays were processed using the NMR1 Program (New Methods Research of Syracuse, Syracuse, NY) on a VAX 11/750 minicomputer. The $^{13}$C natural abundance liver spectrum was subtracted from $[2-^{13}$C]glycerol perfused liver spectra prior to $^{13}$C spectral analysis.

All metabolite peak assignments were confirmed by using unlabeled authentic forms of the tentatively identified compounds to the liver extracts. This was accomplished with a Nicolet 360-MHz spectrometer at 20°C after the perchloric acid extracts were dissolved in D$_2$O and the hexane/isopropl alcohol extracts were dissolved in chloroform. The recycling time was 0.91 s, the pulse angle was 45 degrees, and each spectrum contained 2000 acquisitions. When chemical shifts of the authentic compounds coincided with those of the corresponding metabolites, with appropriate peak height increases, the peaks were considered identified. Metabolites were quantified with peak intensity, and statistical comparison among the three groups was performed using the ANOVA test.

RESULTS

The rats ate significantly less following implantation of the tumor (Fig. 1). In addition, when the normal and weight-matched rats were

Received 8/9/94; accepted 12/14/94.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This work was supported by American Institute for Cancer Research Grant 88B58 and National Cancer Institute Grant CA50710.

2 To whom requests for reprints should be addressed, at Room 6428, Main Building, Cook County Hospital, 1835 West Harrison Street, Chicago, IL 60612.

3 The abbreviations used are: NMR, nuclear magnetic resonance; FFA, free fatty acid; $\beta$GCS, $\beta$-[5-13C]glucose; $\beta$GCOZ, $\beta$-[2-13C]glucose; GSPC2, [2-13C]glycerol 3-phosphate; $\beta$GCL3, $\alpha$-[2-13C]glycerol and $\alpha$-[5-13C]glucose; GEC2, [2-13C]glycerol esters.
The pair-fed rats were given the same amount of feeding consumed by the tumorous rats. For normal versus pair-fed rats, \( P = 0.0001 \), for normal versus tumorous rats, \( P = 0.0046 \), and for pair-fed versus tumorous rats, \( P = 0.3099 \). The comparison among groups was made using a two-way ANOVA test at weights for tumorous rats including the carcass and the tumor weight. Due to the irregular shape of the tumors, the tumor weights were not estimated from dimensions measurement to avoid errors. The comparison among groups was made using the two-way ANOVA test.

This finding confirms the need for a pair-fed group to be used as controls. Since the shape of the tumor can be quite irregular, estimating tumor weight by size measurement may be subject to considerable error. Hence, we used directly measured body weights for tumorous rats rather than the projected carcass weights. We also found significant hepatomegaly in tumorous rats (Table 1), as noted by other investigators (2, 30–36). At the time of experiment, the tumor sizes were 16.0 ± 3.0 (SD) g.

Hepatic glycerol uptake rates for the initial 30 min are given in Table 2. Other investigators have reported glycerol uptake rates of 1.3–2.3 \( \mu \)mol/min/g of liver, when normal rat livers were perfused with 5–10 mM glycerol (37–39). Our results are quite comparable to those studies (Table 2). Since a recirculating perfusion system was used, glycerol concentration and the rates of uptake did not remain constant throughout perfusion. Thus, glycerol uptake was not tabulated for the entire perfusion period. When the results were compared between groups, reduced glycerol uptake rates were found when the pair-fed rats were compared to the normal ones. No statistically significant differences were observed between either the normal and tumor group or the pair-fed and tumor group. However, this lack of statistically significant difference between the normal and tumor groups is probably due to the relatively large SD observed for the tumor group (Table 2).

The metabolite peaks, consistently observed in the [2-\( ^{13}C \)] glycerol-perfused livers, were: \( \beta GC5 \) at 76.0 ppm; \( \beta GC2 \) at 74.4 ppm; [2-\( ^{13}C \)] glycerol at 72.3 ppm; \( \alpha GC2,5 \) at 71.5 ppm; and \( \alpha GC2 \) at 69.0 ppm (Fig. 3). Although peaks for \( \beta [1-^{13}C] \) glucose at 96.0 ppm, \( \alpha [1-^{13}C] \) glucose at 92.2 ppm, \( \beta [3-^{13}C] \) glucose at 76.3 ppm, and \( \alpha [\beta [6-^{13}C]] \) glucose at 60.8 ppm were also found in some of the subtraction spectra, they did not appear with sufficient consistency to warrant comparison between groups. Since the peak line width for each metabolite was similar in all spectra, peak intensity was used for quantification. The results are given in Table 3. Liver weight was not used to normalize metabolite quantitation. The coil for the NMR spectrometer used in the present study was sufficiently small that only part of the liver was encompassed by the coil. Despite the larger liver sizes of the tumor group, the volume of liver observed with the coil was identical for all three groups. Therefore, the quantitation of metabolites was not affected by liver sizes.

All metabolites except \( \alpha GC2 \) were present in similar amounts for all three groups in both the livers and the perfusion media. However, \( \alpha GC2 \) was found in significantly greater quantities in the livers of tumorous rats compared to either normal or pair-fed rats \( (P < 0.01) \) in both cases. It was absent in the perfusate spectra; thus, these glycerol esters appeared to remain intracellularly and were not released. In addition, the peak at 71.5 ppm in the perfusate spectra probably only represents \( \alpha GC2,5 \) for the following reasons: (a) glycerol 3-phosphate, being a metabolic intermediate, is probably present only intracellularly; (b) anomers of glucose are present in 36% of \( \alpha \) and 63% of \( \beta \) mixture (40); i.e., the \( \alpha \) form is 57% of the \( \beta \) form. Therefore, we expect to find approximately 57% of \( \beta GC5 \) plus 57% of \( \beta GC2 \) at the 71.5 ppm peak in the perfusate spectra, as was in fact the case (Table 3). It should be noted that markedly elevated levels of \( \alpha GC2 \) were observed in the livers of all rats, and \( \beta GC5 \) appeared in comparable quantities as \( \beta GC2 \) for all three groups. Comparisons have taken into account the contributions from Additional Metabolites, as shown in Table 3.

Table 1 Liver weights (g) for the normal, pair-fed, and tumorous rats at the time of liver perfusion.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pair fed</th>
<th>Tumorous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>7.23 ± 0.95( a )</td>
<td>5.52 ± 0.87( b )</td>
<td>7.63 ± 1.36( c )</td>
</tr>
</tbody>
</table>

\( a \) Mean ± SD.  
\( b \) \( P = 0.02 \) versus normal.  
\( c \) \( P = 0.03 \) versus pair fed.

Table 2 Rate of glycerol uptake (\( \mu \)mol/min/g of liver) for the normal, pair-fed, and tumorous rats.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pair fed</th>
<th>Tumorous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake</td>
<td>2.09 ± 0.31( a )</td>
<td>1.48 ± 0.13( b )</td>
<td>1.47 ± 0.42( c )</td>
</tr>
</tbody>
</table>

\( a \) Mean ± SD.  
\( b \) \( P = 0.01 \) versus normal.  
\( c \) \( P = 0.06 \) versus normal.
Fig. 3. A, $^{13}$C NMR spectrum of a [2-$^{13}$C] glycerol-perfused liver (after background spectrum subtraction) from a tumorous rat. GlyC2, [2-$^{13}$C]glycerol; αGC2,5, α-[2-$^{13}$C]glucose and α-[5-$^{13}$C]glucose. B, $^{13}$C NMR spectrum of a perchloric acid-extracted liver from another tumorous rat. Note that the αGC2 and αGC5 peaks are relatively small compared to the G3PC2 peaks, the splitting of which results from phosphorus coupling. The GEC2 peak was not observed since it was not extractable by perchloric acid. We did observe the GEC2 peak in the hexane/isopropyl alcohol liver extract (not shown).

consideration the peak intensity enhancement due to the nuclear Overhauser effect (41).

DISCUSSION

Much evidence suggests that the lipolytic rate is markedly augmented (5, 6, 8, 42), whereas the capacity for lipogenesis is much less affected, by the cancerous state (43). Hence, there is an overall increase in fat catabolism in cancer hosts. In addition, glycerol clearance appears to be impaired in cancer (8, 44), although glycerol turnover is enhanced (42). Consistent with these observations, the plasma level of glycerol is elevated, ranging from 0.24 to 0.44 mM in the presence of neoplasm (42, 45, 46). This is in contrast to a basal plasma glycerol concentration of 0.10 mM in both human and rats, although the level may increase in fasting, exercise, diabetes, and obesity (11).

In our study we demonstrated decreased glycerol uptake by the liver of pair-fed rats as compared to the normal rats. This is probably
due to the significantly restricted food intake of the pair-fed group. Nonetheless, despite this difference in glycerol uptake, no distinction in the amounts of metabolites generated from glycerol were found between these two groups (Table 3). This may be explained by the fact that glycerol uptake was calculated for the initial 30 min only and that the metabolite appearance was measured for the entire 90 min. On the one hand, the rate of glycerol uptake depends on the glycerol concentration medium; on the other hand, it also affects the glycerol level in the perfusate in our recirculating system. Therefore, the initial difference in uptake did not lead to any difference in the overall production of metabolites. Although glycerol uptake in the livers of tumorous rats also appeared to be diminished as compared to the normal rats (Fig. 1). It should be noted that the production of glycerol esters from glycerol is significantly augmented in the livers of tumorous rats (thus the need for the pair-fed group as control; Fig. 2) and the food composition was the same for all three groups, increased glycerol ester generation in tumorous rats cannot be explained by their nutritional status. Moreover, we did not find any significant differences in the hepatic lipogenic rates between the normal and the pair-fed groups, indicating that the increased glycerol uptake in tumorous rats is due to the increased production of glycerol esters from glycerol, which is very expensive.

Although changes in whole-body glycerol metabolism have been well described in cancer hosts, glucose production from glycerol in the liver does not seem to be affected. This is demonstrated by the similar amounts of C-2 and C-5-labeled glucose generated from C-2-labeled glycerol in all three groups. The predominant 13C labeling at C-2 and C-5 in glucose is consistent with our understanding of the pathway (Fig. 4, 47, 48). In addition, the equal labeling at C-2 and C-5 suggests that, at high concentrations, glycerol is the exclusive substrate for gluconeogenesis and that the equilibration at phosphoglycerate is virtually complete.

It is of great interest that glucose formation from glycerol is not in any way altered by the presence of a remote tumor, although significant dysfunction has been observed in hepatic utilization of other gluconeogenic substrates, such as alanine and lactate (16, 25, 49–57). The primary difference between glycerol and alanine/lactate as the gluconeogenic substrates is that glucose formation from alanine/lactate takes place first in the mitochondria and subsequently in the cytosol, whereas glycerol traverses through only part of the cytosolic pathway (Fig. 5). Therefore, our finding localizes the alterations in the gluconeogenic pathway, brought on by the malignant state, to the part of the pathway prior to the formation of glyceraldehyde 3-phosphate. This is consistent with our previous observation that the fluxes through pyruvate carboxylase are abnormally increased in the livers of tumor hosts (49, 58, 59). Since pyruvate carboxylase is required by alanine and lactate for their entry into the gluconeogenic pathway but not by glycerol (Fig. 5), the altered fluxes through this enzyme do not change glucose production from glycerol.

In contrast, the production of glycerol esters from glycerol is significantly augmented in the livers of tumorous rats. Normally, the most important factor influencing lipogenesis is the nutritional status (60). For example, its activity is augmented after feeding, under well-fed conditions, and when the carbohydrate content of the diet is high. Since the amounts of intake were progressively reduced in tumorous rats (thus the need for the pair-fed group as control; Fig. 2) and the food composition was the same for all three groups, increased glycerol ester generation in tumorous rats cannot be explained by the nutritional factors. In addition, hepatic lipogenic activity is influenced by the serum level of FFA and usually maintains an inverse relation with FFA concentrations (60). However, no FFA was added to the perfusate in our study. Although the liver may release FFA during perfusion, the perfusate in our study. Therefore, the most likely cause for the increased lipogenesis is the cancerous state.

Kannan et al. (43) also observed an augmented lipogenesis from 2-carbon substrates in the livers of 24-h-fasted tumor-bearing mice. In this study, the authors contributed the differences in lipogenic rate between the control and tumor groups to the malnourished state of the tumor animals; however, the control group was not pair fed. Since pair feeding was used in the present study, the elevated lipogenesis that we observed in tumorous rats cannot be accounted for by their nutritional status. Moreover, we did not find any significant differences in the hepatic lipogenic rates between the normal and the pair-fed groups, although the intake of the pair-fed group was significantly reduced compared to the normal rats (Fig. 1). It should be noted that the part of the lipogenesis that we examined was consumed intracellularly, since all of the newly formed glycerol esters were not found in the perfusion medium. Therefore, this exaggerated lipid production from

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Min</th>
<th>Normal</th>
<th>Pair fed</th>
<th>Tumorous</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>βGC5</td>
<td>30</td>
<td>5.97 ± 1.59</td>
<td>4.28 ± 2.56</td>
<td>4.52 ± 1.68</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>14.75 ± 3.44</td>
<td>12.30 ± 3.38</td>
<td>12.57 ± 2.18</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>22.68 ± 5.90</td>
<td>19.55 ± 2.88</td>
<td>20.05 ± 1.89</td>
<td>NS</td>
</tr>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td>26.73 ± 2.78</td>
<td>28.90 ± 3.60</td>
<td>NS</td>
</tr>
<tr>
<td>βGC2</td>
<td>30</td>
<td>5.46 ± 1.25</td>
<td>4.91 ± 1.02</td>
<td>4.78 ± 0.74</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>12.97 ± 3.27</td>
<td>12.21 ± 2.20</td>
<td>12.46 ± 2.38</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>18.74 ± 4.12</td>
<td>19.19 ± 4.62</td>
<td>19.10 ± 2.47</td>
<td>NS</td>
</tr>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td>25.93 ± 8.19</td>
<td>26.92 ± 6.49</td>
<td>NS</td>
</tr>
<tr>
<td>GlyC2a</td>
<td>30</td>
<td>47.97 ± 9.71</td>
<td>46.36 ± 7.31</td>
<td>45.16 ± 5.97</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>27.04 ± 5.43</td>
<td>27.75 ± 3.27</td>
<td>25.15 ± 7.02</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>9.04 ± 3.33</td>
<td>10.86 ± 1.57</td>
<td>8.19 ± 5.21</td>
<td>NS</td>
</tr>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td>0.34 ± 0.74</td>
<td>1.10 ± 1.63</td>
<td>NS</td>
</tr>
<tr>
<td>G3PC2, αGC2,5</td>
<td>30</td>
<td>74.06 ± 26.39</td>
<td>58.08 ± 9.02</td>
<td>72.95 ± 13.78</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>94.51 ± 40.84</td>
<td>78.18 ± 15.02</td>
<td>83.59 ± 24.21</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>47.04 ± 29.92</td>
<td>53.37 ± 12.82</td>
<td>45.74 ± 31.52</td>
<td>NS</td>
</tr>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td>23.69 ± 4.60</td>
<td>23.59 ± 2.73</td>
<td>NS</td>
</tr>
<tr>
<td>GEC2</td>
<td>30</td>
<td>1.90 ± 2.60</td>
<td>2.02 ± 1.98</td>
<td>4.74 ± 3.78</td>
<td>&lt;0.01, NL* vs. TU,</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>4.64 ± 3.29</td>
<td>4.94 ± 1.39</td>
<td>8.85 ± 4.96</td>
<td>PF vs. TU</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>5.36 ± 3.31</td>
<td>6.30 ± 1.18</td>
<td>10.19 ± 3.98</td>
<td>NS</td>
</tr>
<tr>
<td>Perfusion</td>
<td></td>
<td></td>
<td>ND</td>
<td>ND</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Mean ± SD.
* NS, not statistically significant; ND, not detectable; NL, normal; TU, tumorous; PF, pair fed.
glycerol was probably used to support the pathological process of hepatomegaly in tumorous rats (2, 30–36).

Although lipogenesis and gluconeogenesis from glycerol were quite active, most of the $^{13}$C labeling appeared at the [2-$^{13}$C]glycerol and G3PC2 peaks. This sizable collection of intrahepatic glycerol was probably due to the limited glycerol kinase activity (Fig. 4). Glycerol kinase, necessary for the conversion of glycerol to glycerol 3-phosphate, requires ATP for its action. Thus, the availability of ATP determines the flux rate through glycerol kinase. The accumulation of glycerol 3-phosphate in these perfused livers is even more impressive (Table 3). Cytosolic hydrogen disposal is required for the conversion of glycerol 3-phosphate to dihydroxyacetone phosphate by way of glycerol-3-phosphate dehydrogenase (Fig. 4). Hence, glycerol 3-phosphate accumulates when the supply of cytosolic hydrogen acceptor lags behind the conversion of glycerol to glycerol 3-phosphate through glycerol kinase. This is particularly the case when glycerol is present at high concentrations (61, 62). Therefore, our observation with the perfused liver confirms previous findings with isolated hepatocytes; i.e., glycerol metabolism in the liver is regulated by the availability of cytosolic hydrogen acceptors (61, 62). This regulatory process remains intact in cancer hosts.

It is clear that hepatic metabolism of glycerol is relatively normal and does not contribute to the reduced glycerol clearance in hosts with malignancy (5, 8, 44). Therefore, such reduction must be due to abnormal glycerol utilization of other tissues, such as brain, brown fat, heart, and intestinal mucosa, which play relatively minor roles in glycerol disposal under normal conditions (11). Could the lack of differences in glycerol metabolism for the three study groups be attributable to the livers being removed from the hosts in our perfusion setup? Based on our findings of abnormal alanine and lactate metabolism in the perfused livers of tumorous rats, this is unlikely to be the case. We found not only metabolic abnormalities in the perfused livers (25, 49, 50, 57, 58) but also identical abnormalities in the in situ livers of tumorous rats (59). Thus, the changes induced by the cancerous state in hepatic intermediary metabolism, should they be present, appear to be sustained and not directly controlled by minute to minute changes in the humoral factors. Therefore, the relatively normal glycerol metabolism in the livers of tumorous rats represents a lack of cancer effect on this part of the intermediary metabolism.

In conclusion, the hepatic uptake of glycerol is affected by the nutritional state of the host. Although gluconeogenesis is known to be augmented in cancer hosts, the cytosolic portion of the gluconeogenic pathway required for glycerol metabolism is not altered by the tumorous condition. It is still quite possible that glucose production from glycerol is increased in cancer but this is probably due to the elevated plasma glycerol levels rather than to any intrinsic alterations in the metabolism of glycerol. On the other hand, hepatic lipogenesis from glycerol is accelerated in the presence of a remote tumor and is probably an important component of hepatomegaly. Finally, hepatic conversion of glycerol 3-phosphate to dihydroxyacetone phosphate remains the rate-limiting step for gluconeogenesis from glycerol in both normal and cancer hosts.

ACKNOWLEDGMENTS

We wish to thank the Research Resources Center and the Biological Research Laboratory at the University of Illinois at Chicago for their assistance in the completion of this work.

REFERENCES


Hepatic Glycerol Metabolism in Tumorous Rats: A $^{131}$C Nuclear Magnetic Resonance Study

Katherine Jung-Mei Liu, Yifat Drucker and Jehad Jarad


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/55/4/761

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.