Stimulation of Tumor Growth in Adult Rats in Vivo during an Acute Fast

Leonard A. Sauer, Walter O. Nagel, Robert T. Dauchy, Laurie A. Miceli, and Jennifer E. Austin

Laboratory for Cancer Research, The Bassett Institute for Medical Research, The Mary Imogene Bassett Hospital, Cooperstown, New York 13326

ABSTRACT

These experiments investigate an increase in tumor growth that occurs in adult rats in vivo during an acute fast. The effects of feeding, fasting, and underfeeding on the growth of Morris hepatomas 5123C and 7288CTC in Buffalo rats and of Walker carcinoma 256 and Jensen sarcoma in Sprague-Dawley rats were studied. Animals were matched for tumor size and growth during a period of ad libitum feeding preceding the fasting or underfeeding. Tumor growth was documented by increased size and incorporation of [methyl-3H]thymidine into tumor DNA. Fasting increased the rate of growth of the tumors 3 to 4 times over that measured in fed rats. This effect began during the first day of fasting and ended abruptly on refeeding. After refeeding tumor growth slowed to the rate in fed rats. Tumors from fed or fasted rats were not different in cellularity or dry weight/g wet weight.

A positive growth response in the tumor required lipolysis and ketosis in the host. No stimulation was observed during an acute fast in either immature rats or in mature rats whose weights had been reduced by underfeeding. These animals have small fat stores and show no increase in arterial blood free fatty acid or ketone body concentrations during an acute fast. Finally, underfeeding of adult rats raised the blood concentrations of these nutrients to values that were intermediate between those in fasted and fed rats. Tumor growth rates in these rats were intermediate between those in fasted and fed rats. The results support the proposal that an increase in availability of free fatty acids and/or ketone bodies is the stimulus that increases the rate of tumor growth during an acute fast.

INTRODUCTION

During studies on tumor nutrient utilization in vivo in fed and fasted adult rats (1), we observed an increase in the growth rate of transplantable tumors when the host rat was fasted. This was an unexpected finding; earlier studies had shown that the tumor growth rate was about the same during fasting (2-7) or underfeeding (8, 9) when compared to growth in fed animals. Our observation appeared to be the first time that an increase in tumor growth was noted during an acute fast.

The ketone body and free fatty acid concentrations are increased in the arterial blood of adult host rats during an acute fast, and the rate of tumor utilization of these nutrients is increased (1). We suggested that the ketone bodies and free fatty acids were important carbon sources for synthesis of tumor protoplasm and that the increased availability of these nutrients promoted the increase in the rate of tumor growth. An important corollary of this hypothesis is that tumor growth in vivo in the fed state is limited by the availability of these nutrients. In this study we examined this phenomenon further. We have documented the increased rate of tumor growth in adult rats during an acute fast and examined the relationship between the arterial blood concentrations of ketone bodies and free fatty acids and tumor growth. Different dietary manipulations were performed to influence the concentrations of ketone bodies and free fatty acids in host arterial blood. The results support a direct association between the rate of tumor growth in vivo and the abundance of these nutrients in host arterial blood.

MATERIALS AND METHODS

Animals, Tumors, and Tumor Transplantation. Adult and immature male Buffalo and Harlan Sprague-Dawley rats were obtained from colonies established here. The rats were fed a standard laboratory chow (Charles River Rat, Mouse, and Hamster Formula; Agway, Inc., Syracuse, NY), had water ad libitum, and were maintained at a constant temperature of 23°C in a room with lights on at 6 a.m. and off at 6 p.m. Unless otherwise indicated the animals were 3 to 5 months old and weighed about 250 to 350 g at the time of tumor implantation. Morris hepatomas 5123C and 7288CTC, the Walker carcinoma 256, and the Jensen sarcoma were used in these experiments. We have carried these tumors in our laboratory for from 2 to 9 years.

Tumors were grown s.c. either as tissue-isolated or non-tissue-isolated implants. Tissue-isolated tumors were grown in the left inguinal fossa on a vascular stalk composed of the truncated superficial inferior epigastric artery and vein as described previously (10). A carefully measured 3-mm cube of tumor was attached to the end of the stalk with a small suture, and the implant and vascular stalk were enclosed in a paraffin envelope. The skin incision was closed with a few sutures. For the non-tissue-isolated implants a 3-mm cube of tumor tissue was placed under the shaved skin through a small incision in the midline between the scapulae. The wound was closed by a suture. Tissue-isolated tumors were used in most experiments because these tumors do not show large volumes of central necrosis as frequently as do non-tissue-isolated tumors.

Assays and Reagents. Blood samples were obtained by cardiac puncture from tumor-bearing animals lightly anesthetized with ether. Ace- toacetic and 3-OH butyric acids and glucose were measured fluorometrically and spectrophotometrically, respectively, in perchloric acid extracts of whole blood using enzymatic methods (1, 10). Enzymes, nucleotides, and other chemicals used in these assays were purchased from Sigma Chemical Co. Plasma free fatty acids were measured as described by Bergmann et al. (11). Chemicals used in this assay were obtained from Sigma and Eastman Chemical Co.

[methyl-3H]thymidine (6.7Ci/mmol) was obtained from Research Products International, Mt. Prospect, IL. Liquiscint was purchased from National Diagnostics, Somerville, NJ. Kodak N2B2-Nuclear Track Emulsion, D-19 Developer, and Rapid Fixer are products of Eastman Kodak Company, Rochester, NY and were prepared and used as directed.

Method for Measurement of Tumor Weight in Situ. Tumor mass in the living animal was estimated from measurements made through the skin essentially as described by Morrison (12). The rat was lightly anesthetized with ether, and the tumor dimensions were measured with calipers (Manostat brand, dial-type with metric scale and vernier, purchased from Fisher Scientific). Measurements were made through the tumor long axis and then through two other axes at right angles to the long axis and to each other. Two mm were subtracted from each measurement to compensate for the skin thickness. The three dimensions were multiplied. The product, which has units of cm3 but is not a true volume, is directly proportional to tumor wet weight (12). Tumor weight in situ was estimated by substituting the product value in an equation for a standard linear regression line derived from a plot of the product of the three dimensions and weights measured on excised tumors (Fig. 1). Carcass weight was calculated by subtracting the estimated tumor weight from total animal plus tumor weight. Similar procedures have been used by others (3, 5-7) for estimation of host carcass and tumor weights in vivo.

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Experimental Design for Tumor Growth Studies. Tumors were implanted in 10 to 25 male animals of the same age and body weight. Animals were either littermates or from different litters born on the same day. The tumor cubes used as implants were taken from the same tumor. All inoculated animals were housed together in a large cage. After tumor growth was established, six to sixteen rats with the same sized tumors were selected from the large cage and distributed randomly among individual cages. Animals entered the control or experimental groups (3 to 5 rats/group) at this time. Tumor weights in situ in each animal were estimated daily to measure tumor growth rates. All animals had free access to food, and the amount of food consumed by each animal was measured daily. Tumor-bearing rats matched as described above were fed in the ad libitum fed groups at this time. Tumor weights (tumor wet weight and as dpm/Vn tumor DNA) were counted in a Beckman LS100 Liquid Scintillation Counter. Autoradiograms were developed according to the instructions for the emulsion. Developed slides were counterstained with Harris’ hematoxylin for 3 min with Phloxin-eosin for 1 min. Silver grains over the nuclei of labeled cells were counted under oil immersion.

Statistical Analysis. Significance of means was tested by Student's t-test for paired samples (15). Tumor and host carcass weights and analytical data are expressed as means ± SE. Sample sizes required for demonstration of significant differences in tumor weights and incorporation of radioactive thymidine in matched ad libitum fed and fasted rats were estimated as described by Snedecor and Cochran (15).

RESULTS

Effects of Feeding and Fasting on Tumor Growth in Adult Rats. Figs. 2 and 3 show mean estimated tumor and host carcass weights during feeding and during periods of feeding and fasting for tumors growing in adult rats. The effect of feeding, fasting, and refeeding on tumor and host weights in Walker carcinoma 256-bearing Sprague-Dawley rats is also shown in Fig. 2. Tumor growth in the fed rats continued at a fairly constant rate: 1.7 g/day for the fast growing Jensen sarcoma, about 1 g/day prepared in cold saline using a glass-Teflon Potter-Elvehjem homogenizer.

Duplicate one-half ml portions of the homogenate were precipitated with 4 volumes of cold 0.4 N perchloric acid, and the mixture was placed in an ice bath for 20 min. The precipitate was recovered by centrifugation, and the DNA in the pellet was hydrolyzed and assayed as described by Leyva and Kelley (13). Portions of the hydrolysates were counted in a Beckman LS100 Liquid Scintillation Counter. Quenching was corrected by the channels ratio method and by internal standardization. Radioactivity in tumor DNA is reported as dpm/g tumor wet weight and as dpm/μg tumor DNA.

 Autoradiography. The formalin fixed tumor pieces were embedded in paraffin; 2-μm sections were cut and fixed to glass microscope slides. The paraffin was extracted, and the slides were dipped in autoradiographic emulsion, dried, and then stored at 4°C in the dark for 3 to 20 days. The period of exposure depended on the tumor growth rate; faster growing tumors incorporated more radioactivity (14) and were exposed for shorter periods. Autoradiograms were developed according to the instructions for the emulsion. Developed slides were counterstained with Harris’ hematoxylin for 3 min with Phloxin-eosin for 1 min. Silver grains over the nuclei of labeled cells were counted under oil immersion.

Experimental Design for Measurement of Incorporation of [methyl-3H]Thymidine. Two animals, pair-matched for tumor and host carcass weights, were used in these experiments. Food was removed from one animal and the other was fed ad libitum. After 2 days both animals were lightly anesthetized with ether, and [methyl-3H]thymidine (1 μCi/g total body plus tumor weight) was injected i.v. (in the external jugular) as a single injection. The neck incision was closed with wound clips, and the animals were returned to their cages. One h later the animals were sacrificed by ether anesthesia. The skin over the tumors was incised, and the tumors were removed and weighed. A portion of each tumor was placed in phosphate-buffered formalin for autoradiographic analysis, another portion was removed and weighed for estimation of dry weight, and the remainder was weighed and a 20% homogenate
for Walker 256 carcinoma and hepatoma 7288CTC, and about 0.5 g/day for the slower growing hepatoma 5123C. In each experiment the rates of growth during fasting, as estimated from the slopes of the lines connecting tumor weights, were increased about 3 to 4 times over growth rates measured in the same animals before the fast and in the fed rat groups. The increase in growth rate began during the first day of the fast, continued throughout the duration of the fast, and decreased immediately on refeeding. Increments in tumor growth during the period of the fast were, on the average, about 4 g on day 6 at the start of the fast. On day 9, mean measured tumor weight was 16.9 ± 2.4 g (n = 3) in the fasted (C) group and 6.1 ± 0.8 g in the fed (F) group. For the hepatoma 5123C-bearing rats, mean estimated tumor weight was about 4 g on day 5 at the start of the fast. On day 12, mean measured tumor weight was 13.5 ± 1.6 g (n = 5) in the fasted (○) group and 6.1 ± 0.8 g in the fed (•) group. The differences between the mean tumor weights in the fed and fasted groups were significant (P < 0.05) in both experiments. Bars, SE.

Comparison of an Acute Fast on Tumor Growth and Host Lipolysis and Ketosis in Immature and Adult Rats. Fig. 4 shows the effect of an acute fast on growth of hepatoma 7288CTC and Jensen sarcoma in immature and adult Buffalo and Sprague-Dawley rats, respectively. The young and adult rats were implanted on the same day with tumor from a single donor and were matched for tumor size and for tumor growth rates during the initial period of ad libitum feeding. The rate of tumor growth in the immature rats did not change during the period of the acute fast, a finding that is in agreement with the results of previous investigators (2–9). Tumor growth in the pair-matched adult rats showed the typical marked increase in growth rate. Table 2 shows that the metabolic responses of the young and adult host animals shown in Fig. 4 were also different; immature rats showed neither a lipolytic nor a ketotic response to the fast. In adult rats, the concentrations of free fatty acids and ketone bodies in the arterial blood were increased on the first day of the fast and remained high throughout the 3-day fast.

Two other types of experiments were performed to test the relationship of host arterial blood free fatty acid and ketone body concentrations to tumor growth. The first experiments were designed to increase the arterial blood concentrations of the ketone bodies and free fatty acids to submaximal levels. Groups of matched adult tumor-bearing rats were either fed, fasted, or underfed. The quantity of food given the underfed rats were determined by trial and error; the final regimens used were 15, 50, or 60% of the normal ad libitum food intake for that animal. Fig. 5 shows that the tumor growth rates observed in the underfed animals were intermediate between the slower rates observed in fed rats and the faster rates observed in the fasted rats. Table 3 shows that these regimens increased the arterial free fatty acids and ketone body concentrations in the underfed rats to values intermediate between the arterial blood concentrations in fed and fasted hosts. Thus, the rates of tumor growth correlated positively with host arterial blood free fatty acid and ketone body concentrations.

The second experiments (not shown) were designed to examine tumor growth in adult rats after weight reduction. Nine
The results were as follows: (a) the percentage of the tumor and the feeding and 50% underfeeding diets were continued. The fed rats gained about 10 g during these 10 days. Jensen sarcomas were implanted in the 12 rats, compared to 2–3 days for tumors implanted in fed rats; and (c) once established the tumors grew at about the same rate in the caloric restricted rats as in fed rats. [These results were described several years ago by Sweet et al. (17), Rous (8), and Tannenbaum (18) and are now generally accepted as characteristics of tumor implantation and growth in chronically underfed animals (see Ref. 19 for a review)]. One-half of the underfed rats with growing tumors (mean body weight was about 200 g) was fasted for 2 days, and one-half was continued on the 50% underfed diet. Arterial blood samples were collected from these rats during the two days. The fasted animals lost only 10 g carcass weight and showed no lipolytic or ketotic response, indicating an absence of significant fat stores. There was no stimulation of tumor growth in the fasted rats.

### DISCUSSION

In this study we examined the effects of acute fasting and underfeeding on tumor growth in rats. The research was prompted by an observation made earlier (1) that the rate of tumor growth in adult rats is increased during an acute fast. The experiments elucidated the following characteristics of the effect: a new rate of tumor growth is turned on by fasting or underfeeding and turned off by refeeding; the increased rate of tumor growth is observed only in animals that contain significant fat stores; and the extent to which the tumor growth rate increases is directly dependent on the arterial concentrations of the free fatty acids and/or the ketone bodies. The results suggest that the increased rate of tumor growth during an acute fast is dependent on a lipolytic and ketogenic response in the host; and the extent to which the tumor growth rate increases is directly dependent on the arterial concentrations of the free fatty acids and/or the ketone bodies. The results suggest that the increased rate of tumor growth during an acute fast is dependent on the increased availability to the tumor of the ketone bodies and free fatty acids (1). The growth rate of a tumor is a function of the growth fraction and the cell cycle time. Either or both of these parameters may be altered by fasting.

### Table 1: Incorporation of [methyl-3H]thymidine in vivo in Morris hepatomas 5123C and 7288CTC, Walker carcinoma 256, and Jensen sarcoma growing in fed and fasted rats

Tumor implantation, matching of host rats for tumor size and growth, and labeling in vivo were as described under “Materials and Methods.” The numbers in parentheses are the number of tumors examined. Rats were fasted for 2 days.

<table>
<thead>
<tr>
<th>Tumor type or tissue</th>
<th>Time between transplants</th>
<th>Fed</th>
<th>Fasted</th>
<th>Fed</th>
<th>Fasted</th>
<th>Fed</th>
<th>Fasted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoma 5123C (7)</td>
<td>6–8 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatoma 7288CTC (6)</td>
<td>2 weeks</td>
<td>701 ± 151</td>
<td>2741 ± 811</td>
<td>291</td>
<td>130 ± 45</td>
<td>423 ± 100</td>
<td>225</td>
</tr>
<tr>
<td>Walker carcinoma (15)</td>
<td>10 days</td>
<td>790 ± 228</td>
<td>3557 ± 990</td>
<td>350</td>
<td>280 ± 54</td>
<td>730 ± 130</td>
<td>161</td>
</tr>
<tr>
<td>Jensen sarcoma (9)</td>
<td>5–7 days</td>
<td>1623 ± 488</td>
<td>5710 ± 1588</td>
<td>252</td>
<td>500 ± 180</td>
<td>2024 ± 660</td>
<td>305</td>
</tr>
<tr>
<td>Kidney (13)</td>
<td></td>
<td>146 ± 21</td>
<td>128 ± 14</td>
<td>-12</td>
<td>44 ± 7</td>
<td>37 ± 5</td>
<td>-16</td>
</tr>
<tr>
<td>Lymph node (13)</td>
<td></td>
<td>1172 ± 181</td>
<td>1813 ± 170</td>
<td>55</td>
<td>142 ± 15</td>
<td>193 ± 18</td>
<td>36</td>
</tr>
</tbody>
</table>

- Time between transplants.
- Fed — fasted × 100.

* Mean ± SE.
- Means in fed and fasted animals are different (P < 0.05).
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Table 2. Arterial whole blood glucose, ketone body, and plasma free fatty acid concentrations in immature and adult fed and fasted tumor-bearing rats

Blood samples, obtained by heart puncture, were prepared and analyzed as described in "Materials and Methods." There were 3 rats in each of the fed and fasted groups, and the fast lasted 4 days. Blood was collected from a different, single rat on the first 3 days and from all three rats on the fourth day. Mean tumor growth during the four day periods of fast are indicated in Fig. 4. Host animal weights and other data are listed in the text and in the legend of Fig. 4.

![Graph](image)

**Table 2. Arterial whole blood glucose, ketone body, and plasma free fatty acid concentrations in immature and adult fed and fasted tumor-bearing rats**

<table>
<thead>
<tr>
<th></th>
<th>Glucose (nm)</th>
<th>Acetoacetate (nm)</th>
<th>3-OH butyrate (nm)</th>
<th>Free fatty acids (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fed</td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
</tr>
<tr>
<td>Hepatoma 7288CTC-bearing Buffalo rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>6.20</td>
<td>5.47</td>
<td>0.04</td>
<td>0.79</td>
</tr>
<tr>
<td>Day 8</td>
<td>6.64</td>
<td>5.01</td>
<td>0.15</td>
<td>0.86</td>
</tr>
<tr>
<td>Day 9</td>
<td>6.41</td>
<td>4.23</td>
<td>0.07</td>
<td>1.56</td>
</tr>
<tr>
<td>Day 10 (n = 3)</td>
<td>6.25 ± 0.3</td>
<td>5.24 ± 0.8</td>
<td>0.09 ± 0.004</td>
<td>0.93 ± 0.3</td>
</tr>
<tr>
<td>Immature rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>6.70</td>
<td>5.43</td>
<td>0.07</td>
<td>0.06</td>
</tr>
<tr>
<td>Day 8</td>
<td>6.10</td>
<td>5.25</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Day 9</td>
<td>6.56</td>
<td>4.40</td>
<td>0.09</td>
<td>0.10</td>
</tr>
<tr>
<td>Day 10 (n = 3)</td>
<td>5.96 ± 0.2</td>
<td>4.71 ± 0.4</td>
<td>0.10 ± 0.001</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>Jensen sarcoma-bearing Sprague-Dawley rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>6.45</td>
<td>5.15</td>
<td>0.02</td>
<td>0.47</td>
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<tr>
<td>Day 6</td>
<td>6.50</td>
<td>4.42</td>
<td>0.02</td>
<td>0.80</td>
</tr>
<tr>
<td>Day 7</td>
<td>6.43</td>
<td>4.54</td>
<td>0.03</td>
<td>0.91</td>
</tr>
<tr>
<td>Day 8 (n = 3)</td>
<td>6.35 ± 0.1</td>
<td>3.82 ± 0.3</td>
<td>0.07 ± 0.01</td>
<td>0.77 ± 0.05</td>
</tr>
<tr>
<td>Immature rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>4.96</td>
<td>3.47</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Day 6</td>
<td>6.49</td>
<td>4.36</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Day 7</td>
<td>5.75</td>
<td>4.33</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Day 8 (n = 3)</td>
<td>6.96 ± 0.2</td>
<td>4.43 ± 0.2</td>
<td>0.07 ± 0.003</td>
<td>0.06 ± 0.01</td>
</tr>
</tbody>
</table>

* Mean ± SE.
there may be differences in tumors such that slower growing, carcinogen-induced sarcomas do not show an effect due to fasting.

In important experiments, Halperin et al. (22) showed that fasting did not decrease the rate of lipogenesis in Morris hepatoma 7777. The rate of lipogenesis in host liver, however, was decreased approximately 80%. Pyruvate dehydrogenase in hepatoma 7777 was in the active form in either fed or fasted host rats. Under these conditions, an increase in the availability of substrates for tumor lipogenesis, such as occurs during fasting, would be expected to stimulate tumor growth. [The growth rate of hepatoma 7777, as with the other Morris hepatomas studied here, is stimulated by fasting.] Finally, it should be noted that enzymes for activation of the ketone bodies are found in tumor cells. Though absent in normal liver, succinyl CoA-acetoacetyl CoA transferase, a mitochondrial enzyme, is progression linked in the Morris hepatomas (23). Other rapidly growing tumors that have lower activities of the transferase contain the cytoplasmic ATP-dependent acetoacetyl-CoA synthetase. It is not yet known what role the free fatty acids and ketone bodies play in the growth of rat tumors in vivo. Presumably, they serve as carbon sources for lipogenesis and cholesterol synthesis and oxidation.

The factors that regulate tumor growth in vivo in fed animals are not well-defined, and the regulation of tumor growth in starved animals is even less well understood. Although our data point to an effect of free fatty acids and/or ketone bodies in the stimulation of tumor growth during fasting, the exact mechanism has not been established. Other more complex explanations need to be considered. For example, tumor growth may increase in adult rats if their immune functions are suppressed during an acute fast. Immature rats, which might have a less fully developed immune system, may have a smaller immunosuppressive response and decrease in immunosurveillance. Also, hormonal fluctuations during the feeding-fasting transition (24) may be influencing tumor growth. Presumably, these fluctuations do not occur or are different in immature tumor-bearing rats. Experiments are under way to examine these alternate mechanisms.

The finding that the supply of free fatty acids and ketone bodies may be rate limiting for tumor growth in rats will need to be confirmed in human tumors. New chemotherapeutic agents designed to interrupt the metabolism of these important nutrients could aid in the control of tumor growth.

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