Stimulation of Tumor Growth in Adult Rats in Vivo during Acute Streptozotocin-induced Diabetes

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ABSTRACT

The effects of acute diabetes mellitus on the growth of Morris hepatoma 7288CTC and Jensen sarcoma were studied in fed, young (less than 200 g), and adult (greater than 250 g) rats. Animals were matched for tumor size and growth; the rates of tumor growth were the same in fed, young and adult nontumor-bearing rats. Diabetes was induced by the i.v. injection of streptozotocin (65 mg/kg total body weight) into tumor-bearing rats and changes in arterial blood nutrient concentrations were compared to changes in the rates of tumor growth and DNA synthesis. In young rats acute diabetes did not increase the blood concentrations of the fat store-derived nutrients and did not increase the rate of tumor growth. In adult rats, however, acute diabetes raised the arterial blood free fatty acid, glycerol, triglyceride, and ketone body concentrations to high levels and increased the rate of tumor growth about three times over that observed in untreated rats. Progress curves for the mobilization of host fat stores and for incorporation of \([\text{methyl-}^3\text{H}]\text{thymidine}\) into tumor DNA during the onset of diabetes showed that these activities were closely correlated in adult rats. Both processes began to increase 2 to 4 h after streptozotocin treatment, reached an initial peak at 12 to 16 h, decreased to a low point at 18 to 20 h, and then increased again to the new steady state after 23 to 24 h. The results indicate that the rate of tumor growth in rats in vivo is limited by the availability of a substance(s) present in the hyperlipemic blood of adult diabetic rats. The tight relationship between host lipolysis and tumor growth suggests that the substance(s) is derived from host fat stores.

INTRODUCTION

In a previous report (1), we described an inverse relationship between food consumption and the rate of tumor growth in vivo in adult rats. Tumor growth was increased when the host rat was underfed or starved and the increase was inhibited by refeeding. The beginning and continuation of the new rate of tumor growth appeared to depend on catabolism of the host fat store. Adult tumor-bearing rats showed increased levels of blood free fatty acids and ketone bodies 1 day after onset of the underfeeding or starvation. Young tumor-bearing rats, which lack appreciable fat stores, showed no increase in blood fat store-derived nutrients and no stimulation of tumor growth during an acute fast. Subsequent kinetic experiments demonstrated that the catabolism of host fat stores and the increase in incorporation of \([\text{methyl-}^3\text{H}]\text{thymidine}\) into tumor DNA were closely related in time during the onset of an acute fast (2).

In this study we tested the effect of acute streptozotocin-induced diabetes mellitus on tumor growth in young and adult male rats because lipolysis and ketogenesis are prominent features of the diabetic state. We found that acute diabetes stimulated tumor growth in adult rats. Progress curves for increase in blood nutrient levels and increase in tumor growth were closely correlated during the onset of acute diabetes. Young tumor-bearing rats, in contrast to the adult rats, showed no increase in either lipolysis or tumor growth during acute diabetes. The results support the proposal (1) that a nutrient and/or other factor derived from the host fat store limits the rate of tumor growth in vivo.

MATERIALS AND METHODS

Animals, Tumors, and Tumor Transplantation. Young and adult male Harlan Sprague-Dawley and Buffalo rats were obtained from colonies established here. The rats were fed a standard laboratory chow (Prolab mouse, rat, and hamster 1000 formula; Agway, Inc., Syracuse, NY), had water ad libitum, and were maintained at a constant temperature of 23°C in a room with lights from 6 a.m. to 6 p.m. At the time of tumor implantation the young rats were 30 to 45 days old and weighed less than 200 g, and the adult rats were 3 to 5 months old and weighed about 250 to 350 g. Experiments were performed with the Jensen sarcoma and Morris hepatoma 7288CTC, fast-growing tumors that grow at a rate of about 1.4 and 1 g/day, respectively, in fed animals (1). The Jensen sarcoma was originally obtained from Dr. Artemio A. Overjera, DCT Tumor Repository, Frederick Cancer Research Facility, National Cancer Institute, Frederick, MD. Hepatoma 7288CTC was obtained from the Morris Hepatoma Program, Howard University Cancer Center, Washington, DC. Both tumors have been carried in our laboratory for several years.

Tumors were grown s.c. as tissue-isolated implants in the left inguinal fossa (3). A 3-mm cube of tumor was attached with a small suture to the end of a vascular stalk composed of the truncated superficial inferior epigastic artery and vein. The implant and the end of the stalk were enclosed in a paraffin envelope, placed beneath the skin, and the incision was closed. The arterial blood supply to and venous drainage from the implant are established through the epigastic vessels. Tissue-isolated tumors do not show large volumes of central necrosis as frequently as do ordinary s.c. implants, which must obtain their blood supply from the periphery.

Assays and Reagents. Blood samples were obtained by cardiac puncture from tumor-bearing rats lightly anesthetized with ether. Samples were drawn into syringes moistened with a saturated solution of disodium EDTA. Every attempt was made to draw blood from the left side of the heart. Acetoacetic and 3-hydroxybutyric acids and glucose were measured fluorometrically and spectrophotometrically, respectively, in perchloric acid extracts of the whole blood, as previously described (4). Glycerol and triglycerides were measured in plasma before and after enzymatic hydrolysis, respectively, by the method of Wahlfeld (5). Plasma free fatty acids were measured as described by Bergmann et al. (6), using chemicals obtained from Sigma Chemical Co. and Eastman Kodak Co. Streptozotocin was purchased from ICN Nutritional Biochemicals, and regular insulin (lletin I) was from Eli Lilly and Co.

Experimental Design for Measurement of Tumor Growth in Vivo and Incorporation of [methyl-3H]thymidine. Tumors were implanted in male rats of the same age and body weight. The matched animals were either littermates or were from different litters born on the same day, and the tumor cubes used as implants were taken from the same tumor. All inoculated rats were housed in a single large cage. After tumor growth was established, the animals were separated to individual cages. Tumor weights in situ (1) were estimated daily starting when the tumors were judged to weigh 2-3 g. Host carcass weight was calculated by subtracting the estimated tumor weight from total host plus tumor weight. About 5 days after start of the measurements, when the estimated tumor weights were 7 g, the animals were divided at random into groups of 4 animals each.

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To whom requests for reprints should be addressed.
The procedure used for comparison of tumor growth and arterial blood nutrient levels in diabetic and normal, young, and adult tumor-bearing rats was as follows. Each animal was lightly anesthetized with ether. Diabetes was induced in the experimental groups by injection of a ketonemic dose (7) of streptozotocin (65 mg/kg total body weight) in the external jugular vein. (Streptozotocin was prepared in 0.1 m sodium citrate, pH 4.5, on the day of use.) Control rat groups were given injections of an equivalent volume of sodium citrate. The injections were performed at 3 a.m. after a normal period of feeding. The neck wounds were closed with a few sutures and the animals were returned to their cages. Food and water were available ad libitum before and after treatment. Mean daily food consumption was 22.4 ± 1.7 (SD) g for the control adult rats before and after citrate injection, and 21.2 ± 1.2 g and 20.5 ± 0.8 g for the diabetic adult rats before and after treatment, respectively. Mean daily food consumption was 16.0 ± 1.6 g for the control young rats before and after treatment, and 17.8 ± 1.1 g and 17.3 ± 1.3 g for the diabetic young rats before and after treatment, respectively. Host carcass and tumor weights were estimated daily and arterial blood samples were collected at 24 and 72 h after treatment. Immediately after collection of the 72-h blood sample, the anesthetized rats were given injections of [methyl-3H]thymidine (1 μCi/g body weight) in the external jugular vein. The animals were sacrificed 1 h after the injection and the tumors were harvested for measurements of weight, DNA content, and thymidine incorporation (1). A total of 16 young and 16 adult tumor-bearing rats were compared in these experiments.

Determination of the Progress Curves for Mobilization of Host Fat Stores and for [methyl-3H]Thymidine Incorporation into Tumor DNA during the Onset of Acute Diabetes. Groups of young and adult Jensen sarcoma-bearing Sprague-Dawley rats (4 rats/group), matched for host carcass and tumor weight and for rate of tumor growth, were given injections of streptozotocin as described above. To measure mobilized fat stores, arterial blood samples (one sample from each animal in the group) were collected at a specific time after treatment, i.e., at 2-h intervals during the first 16 h, at 1-h intervals from 16 until 24 h, and at 48 and 72 h. Zero time samples were collected from untreated animals. Glycerol, free fatty acids, triglycerides, ketone bodies, and glucose were measured in each sample. Blood samples were collected from 96 young and 112 adult, tumor-bearing, diabetic rats to define these progress curves.

For measurement of thymidine incorporation, the streptozotocin-treated rats were given injections of [3H]thymidine 1 h before sacrifice. Tumors were harvested at the times after streptozotocin treatment listed above; those collected at zero time were harvested from nondiabetic rats. Tumor weight, protein and DNA content, and incorporation of [3H]thymidine into DNA were measured. A total of 24 young and 112 adult, tumor-bearing, diabetic rats were used to define these progress curves.

Important time points were repeated; consequently, the mean of the data from 1 to 3 groups is a single time point. In some experiments the 4 rats in a group were given injections of insulin (30 units, s.c.) 48 h after streptozotocin treatment. Arterial blood samples and tumors were collected from these animals 3 h after insulin injection to determine the effect on blood metabolite levels and on thymidine incorporation.

Statistical Analysis. Significance of means was tested by Student’s t test (8). Tumor and host carcass weights and analytical data are expressed as mean ± SD.

RESULTS

Acute Diabetes and Tumor Growth. Estimates of host carcass and tumor weights in the matched young and adult rats are shown in Fig. 1. Measurements were made daily for 9 days and were started when the tumors were judged to weigh 2–3 g. The growth rate of these tumors is very uniform in fed, matched rats and is the same in both young and adult hosts (1). Daily increments in tumor weight in the ad libitum fed, untreated rats (days 1 through 6) were about 1.4 and 1 g/day for the sarcoma and hepatoma, respectively. Injection of streptozotocin on day 6 (indicated by the arrow) stimulated tumor growth in the adult rats. One day after streptozotocin treatment the growth rates of the Jensen sarcoma and hepatoma 7288CTC were increased to 5 and 3.7 g/day, respectively, about three times faster than before treatment and about three times faster than in the control adult rats. In contrast, the rate of tumor growth in young rats was not changed by streptozotocin.

Concentrations of glucose and ketone bodies in whole blood and of free fatty acids in plasma collected from the host animals shown in Fig. 1 are listed in Table 1. Samples were collected on days 7 and 9, 1 and 3 days after injection of streptozotocin or sodium citrate. Mean glucose concentrations were in the normal range (6 to 7 mM) in the citrate-treated animals, but were 20 to 30 mM in both the young and adult streptozotocin-treated rats. Plasma free fatty acids and ketone bodies were increased 7 to 30 times in the adult diabetic rats. In comparison, the concentration of plasma free fatty acids in the young diabetic rats was doubled 1 day after streptozotocin treatment but returned to normal values after 3 days. Consequently, ketogenesis did not occur in the young, diabetic rats.

Table 2 shows the tumor weights that were recorded at the end of the experiments shown in Fig. 1. Actual measured weights compared favorably with the estimated weights. Tumor weights in control and diabetic young rats were not different from each other, in agreement with the identical growth rates. Tumor protein and DNA content and the rates of [3H]thymidine incorporation into tumor DNA are also listed in Table 2. The DNA content of tumors growing in adult rats was increased about 20% by acute diabetes, even though the tumor protein content remained unchanged, suggesting that the stimulus for tumor growth increases the proportion of the tumor cells in G1 or G2 phase. Tumors growing in young diabetic rats showed a much smaller increase in DNA content. Finally, after 3 days of diabetes the rate of thymidine incorporation into tumor DNA in adult rats was increased two to three times over the rate observed in the nondiabetic adult rats. A smaller increase in thymidine incorporation was observed in tumors growing in young diabetic rats when compared to young control rats.
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Table 1 Arterial whole blood glucose, ketone body, and plasma free fatty acid concentrations in young and adult, streptozotocin-treated, and control tumor-bearing rats

These are the same animal groups that were described in Fig. 1. Arterial blood samples were collected by heart puncture 24 and 72 h after injection of streptozotocin or citrate buffer, on days 7 and 9 of the experiment, respectively (n = 4 animals for each group).

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Glucose (mM)</th>
<th>Ketone bodies (mM)</th>
<th>Free fatty acids (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen sarcoma-bearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprague-Dawley rats</td>
<td>Diabetic</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>31.9 ± 6.0a</td>
<td>7.1 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>24.9 ± 6.0</td>
<td>6.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>72 h</td>
<td>21.1 ± 4.0</td>
<td>7.4 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Immature</td>
<td>23.0 ± 6.2</td>
<td>7.4 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Hepatoma 7288CTC-bearing</td>
<td>Diabetic</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Buffalo rats</td>
<td>23.5 ± 2.0</td>
<td>6.9 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>21.1 ± 2.2</td>
<td>6.6 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>26.2 ± 1.2</td>
<td>6.3 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Immature</td>
<td>25.9 ± 1.2</td>
<td>6.5 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD.

Table 2 Tumor weights, DNA contents, and incorporation of radioactive thymidine into tumor DNA in streptozotocin-induced diabetic and control, young and adult host rats.

The young and adult rat groups are the same as those described in Fig. 1 and Table 1. The animals were given injections of [3H]thymidine (1 µCi/g total body weight) 1 h before the end of the experiment on day 9. Tumor weights, DNA and protein contents, and incorporation of thymidine into DNA and tumor substance were measured after tumor harvest, as described in "Materials and Methods" (n = 4).

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Tumor wt* (g)</th>
<th>Protein content (mg/g tumor)</th>
<th>DNA content* (µg/g tumor)</th>
<th>Thymidine incorporation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen sarcoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12.2 ± 0.4a</td>
<td>183 ± 10</td>
<td>6340 ± 134</td>
<td>523 ± 24</td>
</tr>
<tr>
<td>Acute diabetic</td>
<td>21.7 ± 0.4</td>
<td>176 ± 12</td>
<td>7417 ± 230</td>
<td>1272 ± 8</td>
</tr>
<tr>
<td>Immature</td>
<td>11.8 ± 0.2</td>
<td>173 ± 6</td>
<td>5690 ± 122</td>
<td>498 ± 6</td>
</tr>
<tr>
<td>Acute diabetic</td>
<td>11.7 ± 0.4</td>
<td>176 ± 6</td>
<td>6173 ± 60</td>
<td>548 ± 6</td>
</tr>
<tr>
<td>Hepatoma 7288CTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>10.9 ± 0.6</td>
<td>175 ± 6</td>
<td>4702 ± 182</td>
<td>468 ± 10</td>
</tr>
<tr>
<td>Acute diabetic</td>
<td>19.0 ± 0.6</td>
<td>174 ± 6</td>
<td>6394 ± 30</td>
<td>733 ± 12</td>
</tr>
<tr>
<td>Immature</td>
<td>11.0 ± 0.4</td>
<td>161 ± 16</td>
<td>4718 ± 54</td>
<td>484 ± 6</td>
</tr>
<tr>
<td>Acute diabetic</td>
<td>10.8 ± 0.2</td>
<td>168 ± 6</td>
<td>5020 ± 24</td>
<td>525 ± 12</td>
</tr>
</tbody>
</table>

* Differences in tumor weights between control and diabetic adult rats and in DNA contents and thymidine incorporation between control and diabetic, young and adult rats are significant, P < 0.05.

† Mean ± SD.

Progress Curves for the Increase in Host Arterial Whole Blood Glucose and Ketone Body, and Plasma Glycerol, Free Fatty Acid, and Triglyceride Concentrations during the Onset of Acute Diabetes in Young and Adult Rats. Fig. 2 shows that the glucose concentrations were tripled within 2 h after streptozotocin treatment in both young and adult Jensen sarcoma-bearing rats. The glucose concentrations reached 35 to 40 mM after 10 to 16 h, decreased to about 15 mM at 20 h, and then increased again to steady state values of 30 to 40 mM after 24 h. Similar progress curves characterized by increases to a peak and decreases to a low point followed by increases to a plateau were noted for glycerol, free fatty acid, ketone body, and triglyceride concentrations in the adult, tumor-bearing, diabetic rats. Young tumor-bearing rats showed at most very small increases in blood concentrations of the fat store-derived nutrients after treatment with streptozotocin; the small transient increase in free fatty acid concentration after 24 h noted in Table 2 was not reproduced in this experiment. Injection of insulin decreased the arterial blood concentrations of glucose to the values found at zero time in young and adult diabetic rats and lowered the ketone body, free fatty acid, triglyceride, and glycerol concentrations in adult diabetic rats to nondiabetic levels.

Progress Curves for Increase in [3H]Thymidine Incorporation into the Jensen Sarcoma during the Onset of Diabetes in Young and Adult Rats. An increase in the rate of thymidine incorporation into Jensen sarcomas growing in adult rats was detectable as quickly as 4 h after injection of streptozotocin (Fig. 3). The rate at 4 h was significantly increased (P < 0.05) over that measured at zero time. Progress to the new and faster steady state rate of tumor DNA synthesis was characterized by the same complex phenomena observed during mobilization of glucose and host fat stores. First, the rate of thymidine incorporation increased steadily for 12 h. The peak rate reached at 12 to 16 h was 2 to 3 times faster than that measured before streptozotocin injection. Thymidine incorporation then decreased abruptly to a lower rate (but still faster than the zero time rate) at 18 to 20 h before increasing again to the steady state rate after 23 to 24 h. These cyclic changes in rate of DNA synthesis were highly reproducible, as indicated by the fact that the values at zero time, 12, 18, 19, 20, 24, and 72 h each represent means of data obtained from 8 to 12 tumors. Injection of insulin into the adult diabetic rats caused an abrupt decrease and return of the rate of thymidine incorporation to values observed before onset of the diabetes. As expected from the results shown in Table 2, essentially no increase in thymidine incorporation was noted in tumors growing in young diabetic rats.
The progress curve describing the increase in tumor DNA content in adult animals after streptozotocin treatment (Fig. 3) suggested similarly complicated kinetics. It is interesting that the progress curves for increase in tumor DNA content and for increase in the rate of $[^{3}H]$thymidine incorporation were essentially identical, except that there was not a significant decrease in tumor DNA content after 18 h. Differences in rates of decrease in tumor DNA content and DNA synthesis were also evident after insulin treatment of adult diabetic rats (Fig. 3) and after refeeding of starved adult rats (2). When the rate-limiting substance is removed, the decrease in tumor DNA content, which requires mitosis, is slower than the decrease in the rate of DNA synthesis. Fig. 4 also shows the progress curves for tumor growth rate in adult rats. Tumor growth during the first 24 h after drug treatment may be slower than the steady state rate that is established after 24 h (see also Fig. 1). A lag in tumor growth rate during the first 24 h could be caused by the transient decrease in the rate of tumor DNA synthesis that occurs between 16 and 24 h.

**DISCUSSION**

In this study acute diabetes was induced in tumor-bearing rats to test a hypothesis of tumor growth in vivo. Previously, we observed a stimulation of tumor growth in adult rats during an acute fast (1) that appeared to require the presence and
catabolism of host fat stores. Lipolysis and ketogenesis did not occur during fasting in young tumor-bearing rats and there was no increase in tumor growth rate. We proposed that tumor growth in vivo was limited by the availability of critical nutrients or other factors present in the host fat stores (1). When the blood concentrations of these nutrients are increased, as they are in adult rats during an acute fast, the rate of tumor growth is increased. The results reported here support this hypothesis.

First, acute diabetes stimulated the rate of tumor growth in adult but not in young rats, and the requirement for catabolism of host fat stores for more rapid tumor growth was confirmed. Second, the kinetics of increase in $[^{3}H]$thymidine incorporation into tumor DNA were closely correlated to the kinetics for release of fat store nutrients. Progress curves for mobilization of host fat stores during onset of drug-induced diabetes (Refs. 7 and 9–11; see Fig. 2) are different from those seen during acute starvation (2, 12). The differences result from a more rapid fall in blood insulin and from a transient, secondary insulin release (9) after drug-induced diabetes. In Sprague-Dawley rats this secondary insulin release begins 15 to 16 h after drug injection, reaches a peak at 18 to 20 h, and then declines (9). Concentrations of glucose and the fat store-derived nutrients in the arterial blood show an inverse relationship to the insulin levels (7, 9–11). We observed a decrease in the rate of $[^{3}H]$thymidine incorporation at the exact same time as the decrease in blood levels of the fat store-derived nutrients. Indeed, progress curves for increase of $[^{3}H]$thymidine incorporation into tumor DNA and for increase in plasma free fatty acid concentrations were essentially superimposable (Figs. 2 and 3). This close correlation is additional evidence for a very tight coupling between the rate of tumor DNA synthesis and release of the critical substance from host fat depots (2).

The agent that limits the rate of tumor growth in vivo has not yet been identified. The experimental results described here and previously (1, 2) tend to rule out a direct role for blood glucose, and for insulin or other hormones in the growth stimulation. Glucose concentrations were decreased during starvation and increased during diabetes, but both conditions stimulated tumor growth in adult rats and were without effect in young rats. Also, although changes in insulin and other hormones are probably similar in young and adult rats during acute starvation and diabetes, tumor growth was invariably stimulated in adult and not in young rats. The rate-limiting substance for tumor growth in vivo may be an essential fatty acid. A few years ago, Kidwell et al. (13, 14) showed that the lipid-containing fraction of rat serum stimulated growth of WRK 1 rat mammary tumor cells in vitro. The lipid substance was identified as linoleic acid (13, 14); rat serum contained this fatty acid and pure linoleic acid could replace the requirement for rat serum. Tests of individual unsaturated free fatty acids showed that oleic, linoleic, linolenic, and arachidonic acids all stimulated growth of the WRK 1 tumor cell line (14), but to different extents and at different concentrations. An increased intake of dietary sources rich in unsaturated fatty acids has been reported to increase the incidence of spontaneous (15) and carcinogen-induced mammary tumors (16) and growth of transplantable tumors (17) in rats. Experiments are under way to determine if increased concentrations of linoleic and/or other unsaturated fatty acids are in the blood of diabetic and starved (1) adult rats and are responsible for the stimulation of tumor growth.

The role of insulin and the effects of drug-induced diabetes on tumor growth in rats in vivo have been examined by several investigators. The subject was recently reviewed by Hilf et al. (18). Hilf (19), and Sloan et al. (20). Only studies using streptozotocin-induced diabetes and with recorded host weights will be considered here; diabetes induced by alloxan has been reported to cause increased mortality and severe weight loss; to require insulin supplements in tumor-bearing rats (21); and to cause excessive ketonemia in normal rats (22). Two experimental procedures were followed in experiments of diabetes on tumor growth. In one protocol tumors were implanted into diabetic rats and subsequent rates of tumor growth were compared to growth in nondiabetic rats (20, 23). The results indicated a slower rate of tumor growth in rats that were diabetic for 10 days before tumor implantation. Host body weights at the time of tumor implantation were 150 to 180 g; blood levels of free fatty acids were not reported (20, 23). In other experiments, Hissin and Hilf (24) found that the growth rate of the R3230AC mammary tumor was nearly doubled in 100-g female Fisher rats made diabetic 2 days before implantation. Insulin reversed the growth stimulation. Comparable results were also observed by Cohen and Hilf (25) with this tumor in 115-g female Fischer rats. Blood levels of fat store-derived nutrients were not reported (24, 25). Hissin and Hilf (24) and Hilf et al. (18) suggested that an increased rate of proline transport might be responsible for the faster tumor growth in diabetes.

In a second procedure, Cohen and Hilf (26) induced acute diabetes in rats that were bearing 7,12-dimethylbenz(a)anthracene-induced mammary tumors. About 60% of the tumors regressed (termed insulin dependent). Eighteen % simply stopped growing, and still others, called insulin independent, were unaffected and continued to grow. In the experiments reported by Cohen and Hilf (26), the diabetic rats weighed an average of 256 g and the mean blood glucose concentrations were 21 mm. A few of the insulin-independent tumors in their experiments appear to have grown faster, but not significantly faster, than tumors in the nondiabetic hosts. The dose of streptozotocin (50 mg/kg body weight) used might have been sufficient to increase blood free fatty acid concentrations. However, the emphasis of the study (26) was on differences between the insulin-dependent and insulin-independent tumors, and blood levels of fat store-derived nutrients were not reported.

Historically, young rats were used in studies of diabetes, and tumor growth and host blood free fatty acid, glycerol, triglyceride, and ketone body concentrations were not reported. Consequently, no conclusions can be made about the role that these nutrients might have had in the experiments. It seems clear from our data, however, that tumor growth-promoting substances are present in the hyperlipemic blood of adult, diabetic, tumor-bearing rats that are absent from the blood of young, diabetic, tumor-bearing rats.

REFERENCES

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