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FACTORS ELEVATING LIVER TYROSINE: 2-OXOGLUTARATE AMINOTRANSFERASE ACTIVITY IN TUMOR-BEARING MICE

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ABSTRACT

In the later stage of tumor-bearing mice, the activity of liver tyrosine : 2-oxoglutarate aminotransferase was markedly elevated, whereas no particular change was noted in liver tyrosine : pyruvate aminotransferase activity. Adrenalectomy abolished the elevation of tyrosine : 2-oxoglutarate aminotransferase activity in tumor-bearers. In tumor-bearing mice, liver glycogen level was lowered in contrast to increased tyrosine : 2-oxoglutarate aminotransferase activity. Increased activity of the enzyme was reversed by glucose feeding. Increased activity of the enzyme in tumor-bearing mice was tentatively related to protein catabolism, conversion of protein to carbohydrate in the liver of the host under carbohydrate deficiency, and its possible relation to cancer cachexia was discussed.

INTRODUCTION

There are many studies on metabolic abnormalities of tumor-bearing animal, among which depression of liver catalase activity[1)2)3)] is particularly marked. The mechanism by which liver catalase activity is regulated *in vivo*, however, has not yet been elucidated. Nakahara and Fukuoka[4)] extracted toxohormone, a liver catalase depressing principle, but the significance of reduced liver catalase activity in the metabolism of tumor-bearing host also remains unclear.

Knox *et al.*[5)] and Yamamura *et al.*[6)] reported that liver tryptophan pyrrolase activity in tumor-bearing animal undergoes a biphasic change during tumor growth. The activity of the enzyme can be raised by administration of its substrate tryptophan[7)8)], adrenal cortical hormone and ACTH[9)]. Adrenalectomy[9)] or administration of growth hormone[5)] reduces its activity.

In recent years many studies on liver L-tyrosine : 2-oxoglutarate aminotransferase have revealed the presence of several factors affecting its activity. The enzyme acts on the first step of tyrosine oxidizing system in the presence of 2-oxoglutarate, producing *p*-hydroxyphenylpyruvate and glutamic acid. Activity of the enzyme is raised by administration of adrenal cortical hormone[10)] and

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ACTH[11]. Its substrate tyrosine also raises the enzyme level when the adrenal gland is intact[10][11]. In adrenalectomized animals, tyrosine raises the activity if adrenal cortical hormone is given at the same time[10]. Low protein diet[12] and adrenalectomy[11] lower the enzyme activity of the liver. The fact that induction of tryptophan pyrrolase and tyrosine : 2-oxoglutarate aminotransferase of the liver takes place with concomitant increase in liver glycogen content following administration of cortisol suggests a close correlation to exist between the activity of these enzymes and liver gluconeogenesis[13]. This report is concerned with the investigation of liver tyrosine : 2-oxoglutarate aminotransferase activity in mice during tumor growth and possible factors affecting its activity.

MATERIALS AND METHODS

Tumor: Ehrlich ascites tumor was used throughout this study. Ascites tumor was produced by intraperitoneal inoculation of 5×10^6 cells in each experiment. Solid tumor was produced by subcutaneous transplantation of 10^7 ascites tumor cells into the back. Mean survival time was about 3 weeks in ascites tumor bearers. Ascites did not become bloody till the terminal stage of tumor growth.

Animals: SM male mice, weighing 20 to 30 g, were used. They were fed on mouse food (MF) manufactured by Oriental Yeast Co., Japan, and fresh water *ad libitum*.

Adrenalectomy: Adrenals were extirpated by bilateral subcostal incision under Nembutal anesthesia. After surgical operation, the animals were kept on the same food and physiological saline in place of fresh water.

Enzyme assay: L-Tyrosine : 2-oxoglutarate aminotransferase assay system consisted of 6 μ moles of L-tyrosine, 30 μ moles of 2-oxoglutarate, 30 μg of pyridoxal phosphate and 50 μ moles of potassium phosphate buffer at pH 7.6 in 2.5 ml as described by Kenney[14]. As liver homogenate was used as enzyme, 5 μ moles of diethyldithiocarbamate was added to prevent the decrease of the product by coexisting *p*-hydroxyphenylpyruvate hydroxylase. Reaction was started by the addition of 2-oxoglutarate after 5 minutes' preincubation. After shaking for 10 minutes at 37°C, the reaction was stopped by adding 0.5 ml of 30 per cent trichloroacetic acid. After centrifugation the *p*-hydroxyphenylpyruvate in the supernatant was measured by the modification[15] of Briggs reaction[16].

L-Tyrosine : pyruvate aminotransferase activity was assayed by using the same system, except that pyruvate was used instead of 2-oxoglutarate[17].

Catalase activity was measured by the method of Euler-Josephson[18]. To measure the total activity including catalase activity in intracellular granules[19], the homogenate was treated in 1 per cent deoxycholate before enzyme assay.

Enzyme activity was expressed per 100 g of total body weight in mice bearing subcutaneous tumor and per 100 g of carcass weight (body weight minus ascites)

in those with ascites tumor.

Glycogen content: Glycogen content of the liver was measured by the method of Seifter *et al.*[20].

Tyrosine content: Tyrosine content of the liver was measured by the method of Udenfriend and Cooper[21].

RESULTS

Liver tyrosine : 2-oxoglutarte and tyrosine : pyruvate aminotransferase activity were determined on days 2, 4, 6, 9, 12 and 15 after intraperitoneal inoculation of Ehrlich ascites tumor cells on day 0. As illustrated in Fig. 1, tyrosine : 2-oxoglutarate amino-transferase showed a marked elevation of activity in the later stage preceded by a slight initial depression, while tyrosine : pyruvate aminotransferase, the activity of which was far lower than that of the former in normal mouse liver, was found unchanged in activity during tumor growth. Raised tyrosine : 2-oxoglutarate aminotransferase activity was also noted in the liver of mice bearing subcutaneous tumor. Fig. 2 shows the relationship between tumor size and the enzyme activity. Obviously the enzyme activity rises as the tumor grows larger.

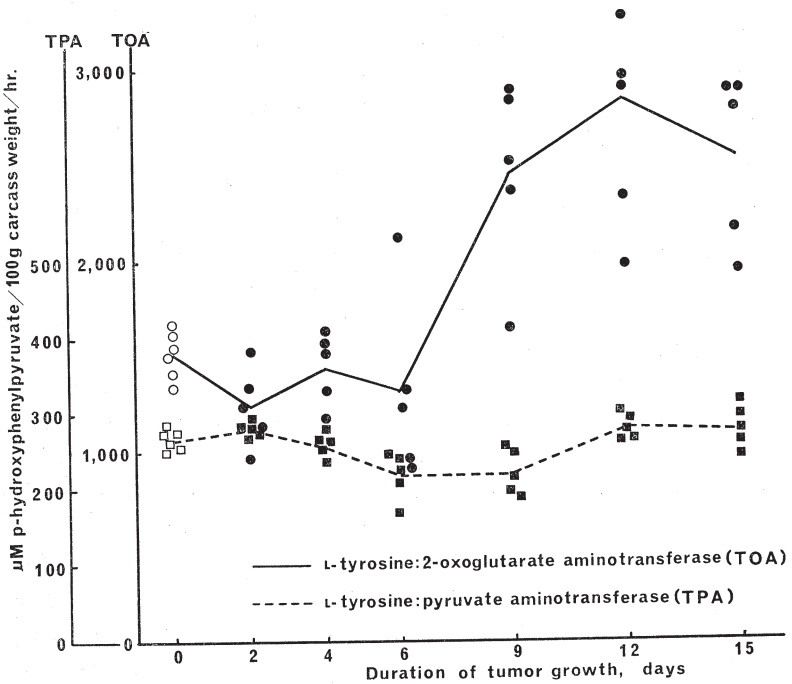

FIG. 1. The levels of liver tyrosine aminotransferases in mice bearing Ehrlich ascites tumor

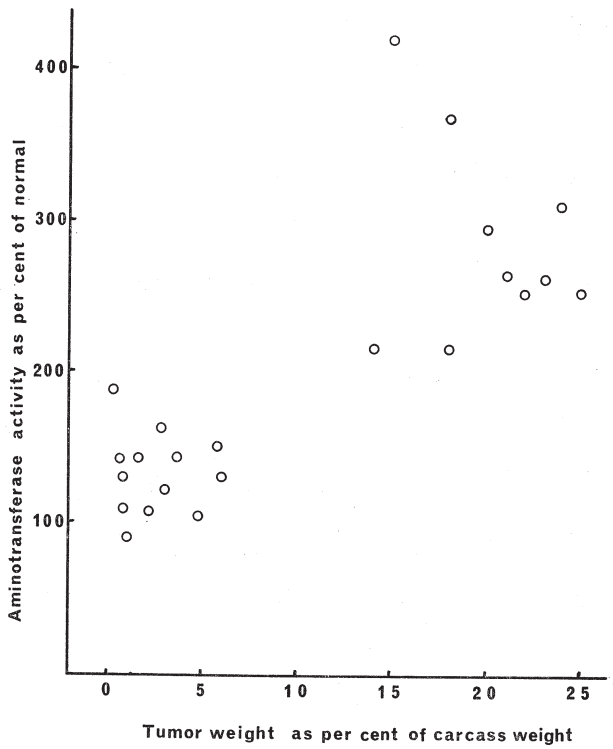

FIG. 2. Effect of tumor weight on liver L-tyrosine : 2-oxoglutarate aminotransferase in tumor-bearing mice

Liver catalase activity, which is well-known to be affected most profoundly in tumor-bearing host, exhibited a progressive depression in mice with ascites tumor as shown in Fig. 3. In Fig. 4, it was found that catalase activity was inversely related to tumor size. Catalase activity appeared to have a reciprocal relation to tyrosine : 2-oxoglutarate aminotransferase in tumor-bearing mice from Figs. 1 and 3 and table 1.

Next, several factors which may affect liver tyrosine : 2-oxoglutarate aminotransferase activity were studied in relation to its activity in tumor-bearing mice.

Adrenal: Ehrlich ascites tumor was inoculated intraperitoneally into mice 3 days after adrenalectomy. These mice survived for 7 days after inoculation, on the average. Eleven days after tumor transplantation liver tyrosine : 2-oxoglutarate aminotransferase activity was elevated to up to 4,250 (expressed as μ moles of *p*-hydroxy-phenylpyruvate produced per hour per 100 g of carcass weight) in non-adrenalectomized mice. In contrast, the activity in adrenalectomized tumor-bearers was 2,390, though it was somewhat higher than that of non-adrenalectomized tumor-free mice, indicating a marked inhibition in the

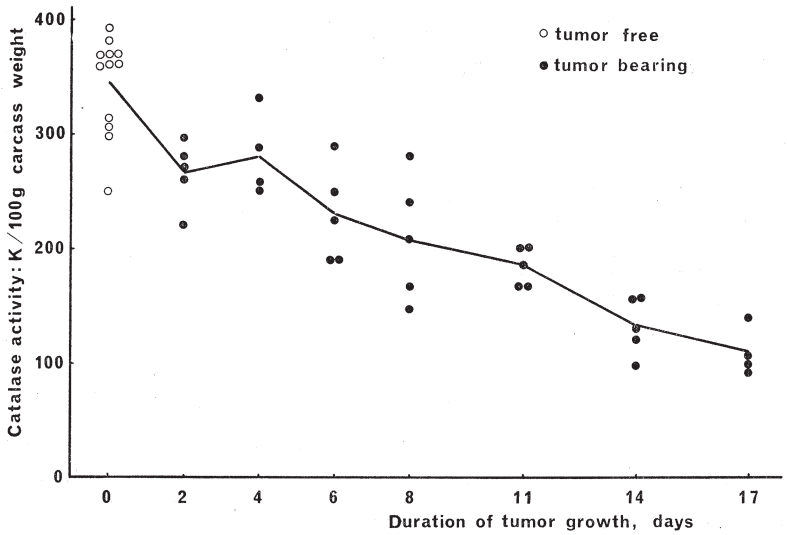

FIG. 3. Liver catalase activity in mice bearing Ehrlich ascites tumor

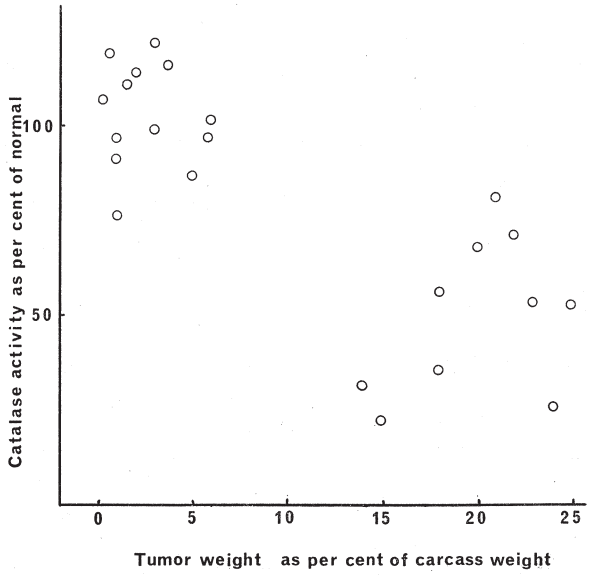

FIG. 4. Effect of tumor weight on liver catalase in tumor-bearing mice

rise of enzyme activity (table 2). In mice bearing subcutaneous tumor, adrenalectomy was performed when the tumor had grown to a size large enough to affect the enzyme level in the liver of the host. The enzyme activity was determined 40 hours after adrenalectomy in mice with subcutaneous tumor which

TABLE 1. Levels of catalase and L-tyrosine : 2-oxoglutarate aminotransferase of the liver in tumor-bearing mice*

group	No. of mice	catalase activity (mean±S.E.M.)	aminotransferase activity (mean±S.E.M.)
tumor free	4	272±18	1,790±150
tumor bearing	5	146±29	3,940±480

S. E. M.: standard error of the mean.
* 5 weeks ater the inoculation of Ehrlich ascites tumor cells subcutaneously into the back.

TABLE 2. Effect of tumor on liver L-tyrosine : 2-oxoglutarate aminotransferase in adrenalectomized mice

group		No. of mice	aminotransferase activity (mean±S.E.M.)
adrenalectomized☆, tumor-bearing*		3	2,390±153
untreated	tumor-bearing*	5	4,250±520
	tumor-free	4	1,403±142

* 11 days after intraperitoneal inoculation of Ehrlich ascites tumor.
☆ Adrenalectomy was performed 3 days prior to tumor transplantation.

TABLE 3. Effect of adrenalectomy on liver L-tyrosine : 2-oxoglutarate aminotransferase in normal and tumor-bearing mice*

group		No. of mice	aminotransferase activity (mean±S.E.M.)
normal	untreated	4	1,790±150
	adrenalectomized	5	1,055±160
tumor-bearing	untreated	5	3,940±480
	adrenalectomized	4	1,890±306

S. E. M.: standard error of the mean.
* 5 weeks after the inoculation of Ehrlich ascites tumor cells subcutaneoualy into the back.

had been transplanted 5 weeks before. In non-tumorous mice the enzyme activity was 1,790 in the non-adrenalectomized and 1,055 in the adrenalectomized. In tumor-bearers, the activity was 3,940 in the non-operated and 1,890 in the operated group (table 3). From these observations, it can be said that the adrenal gland is essential for the rise of the liver tyrosine : 2-oxoglutarate aminotransferase activity in tumor-bearing mice.

Fasting: When mice were deprived of food for the preceding 72 hours, tyrosine : 2-oxoglutarate aminotransferase activity in the liver increased as

TABLE 4. Liver tyrosine level in various conditions inducing liver L-tyrosine : 2-oxoglutarate aminotransferase

group	No. of mice	aminotransferase activity (mean±S.E.M.)	tyrosine μM/g liver (mean±S.E.M.)
control	6	1,917±260	0.306±0.016
tumor-bearing	5	3,928±345	0.340±0.033
control	6	1,678±104	0.311±0.015
fasting, 72 hrs.	6	4,104±602	0.301±0.014
control	5	1,508± 84	0.315±0.028
glucocorticoid	5	8,632± 42	0.250±0.014

S. E. M.: standard error of the mean.

shown in table 4.

Glucocorticoid: Four hours after intraperitoneal injection of 1 mg of prednisolone hemisuccinate into each mouse, a marked elevation of the enzyme activity was noted (table 4).

Tyrosine: Liver tyrosine content was measured to see whether the substrate is related to the increased activity of liver tyrosine : 2-oxoglutarate aminotransferase in fasted, tumor-bearing and glucocorticoid treated mice. Elevated plasma tyrosine level has been reported in tumorous and leukemic rats[22)23)], but reports on the liver tyrosine level were not available. Liver tyrosine content, though it was variable, was in fasted and tumor-bearing mice nearly equal to that of the normals and was slightly decreased in mice injected with gluco corticoid (table 4).

Amount of food intake: As described above, liver tyrosine : 2-oxoglutarate aminotransferase activity was increased in fasted animals. In tumor-bearers,

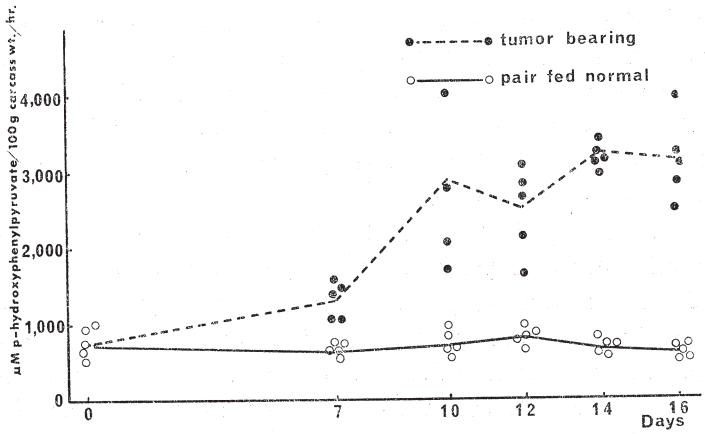

FIG. 5 a. Liver tyrosine : 2-oxoglutarate aminotransferase activity in tumor-bearing and pair-fed normal mice

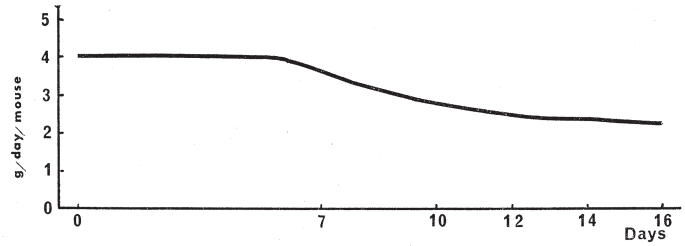

FIG. 5 b. Amount of food ingested

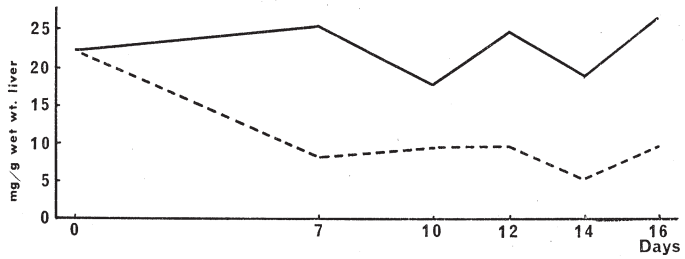

FIG. 5 c. Mean liver glycogen content

anorexia develops inevitably as the tumor grows larger. Daily food intake of mice bearing Ehrlich ascites tumor was measured and the same amount of food was given to control mice (pair-feeding). Figures. 5 a, b, c show tyrosine : 2-oxoglutarate aminotransferase, liver glycogen level in tumor-bearing and pair-fed control mice and intake of food in tumor-bearers, respectively. Food intake began to decrease gradually from the 7th day and fell to about 60 per cent of the initial amount at the terminal stage. Tyrosine : 2-oxoglutarate aminotransferase activity was slightly elevated on the 7th day and markedly elevated level remained the same after the 10 th day on. Glycogen content of the liver appeared low as early as on the 7th day, when food intake was not much decreased, and this lowered level lasted to the end of the observation period. In pair-fed non-cancerous mice, decrease in glycogen content of the liver was not noted even when the food supply was reduced to the amount ingested by tumor-bearers. This result suggests that in tumor-bearing host carbohydrate deficiency appears before anorexia develops and lasts to the end.

Glucose: Liver tyrosine : 2-oxoglutarate aminotransferase activity was determined in mice given 30 per cent aqueous solution of glucose in place of food and water for the preceding 24 hours. As shown in table 5, both in normal and tumor-bearing mice marked decrease in the enzyme level was noted. When 0.5 mg of prednisolone hemisuccinate was given intraperitoneally into mice fed on glucose, marked elevation in the enzyme activity was induced (table 6).

Difference between tyrosine : 2-oxoglutarate and tyrosine : pyruvate aminotransferase: It was already described that no particular change in liver tyrosine :

TABLE 5. L-Tyrosine : 2-oxoglutarate aminotransferase activity of the liver in normal and tumor-bearing mice given glucose

group		No. of mice	aminotransferase activity (mean±S.E.M.)
normal	control	10	1,420± 69
	glucose	5	938± 74
tumor-bearing☆	control	9	3,204±335
	glucose	7	523± 96
normal	control	7	1,235±144
	glucose	4	360± 52
tumor-bearing★	control	4	1,960±229
	glucose	5	565± 88

☆ 5 weeks after subcutaneous inoculation of Ehrlich ascites tumor.
★ 14 days after intraperitoneal inoculation of Ehrlich ascites tumor.
S. E. M.: standard error of the mean.

TABLE 6. Effect of glucocorticoid and glucose on liver L-tyrosine : 2-oxoglutarate aminotransferase activity in normal mice

group	No. of mice	aminotransferase activity (mean±S.E.M.)
fed on MF	5	1,260± 81
MF+glucocorticoid injection	5	2,900±262
fed on glucose	4	352± 28
glucose+glucocorticoid injection	4	4,380±293

S. E. M.: standard error of the mean.

TABLE 7. Effect of glucocorticoid, tyrosine and glucose on activity of two tyrosine aminotransferases of the liver

group	No. of mice	tyrosine : 2-oxoglutarate aminotransferase (mean±S.E.M.)	tyrosine : pyruvate aminotransferase (mean±S.E.M.)
control	7	1,593± 61	265±10
glucocorticoid☆	5	4,428±113	249± 8
tyrosine☆	5	3,706±217	243± 7
glucose★	5	685± 40	150± 5

☆ 4 hours after intraperitoneal injection of 0.5 mg of prednisolone hemisuccinate or 20 mg of tyrosine.
★ Mice were kept on 30 per cent glucose solution for 24 hours before sacrifice.
S. E. M.: standard error of the mean.

pyruvate aminotransferase activity was found in tumor-bearing mice (Fig. 1). Glucocorticoid and tyrosine induced a marked elevation in tyrosine : 2 oxoglutarate aminotransferase activity following intraperitoneal administration, but did not affect tyrosine : pyruvate aminotransferase activity. Glucose feeding

was found to cause a moderate decrease in tyrosine : pyruvate aminotransferase activity (table 7).

DISCUSSION

Transamination is the first step of tyrosine catabolism. According to Ludwig *et al.*[17] tyrosine : 2-oxoglutarate and tyrosine : pyruvate aminotransferase, both participating in this process, are different enzymes. Tyrosine : 2-oxoglutarate aminotransferase has a broad substrate specificity acting on transamination of phenylalanine and tryptophan[24]. Tyrosine : 2-oxoglutarate aminotransferase of the liver can be induced by administration of ACTH and glucocorticoid. In tumor-bearing mice, glucocorticoid dependent tyrosine : 2-oxoglutarate aminotransferase activity was elevated in the later stage, whereas no particular change was noted in glucocorticoid independent tyrosine : pyruvate aminotransferase activity. This finding suggests that adrenal function may be closely related to metabolic abnormalities of tumor-bearing host.

Adrenal change in tumor-bearing animals has long been noted. Adrenal hypertrophy associated with an increase in the cytoplasm and number of cortical cells and increase in lipoid content was reported by Balls and Samuels in rats with Walker 256 tumor[25]. Savard[26] found thymus involution and adrenal hypertrophy associated with lowered ascorbic acid in mice with sarcoma 180, and stated that the tumor behaves as a non-specific stimulus inducing the changes associated with the 'general adaptation syndrome' described by Selye and that these findings coincide with the terminal or exhaustion phase of the adaptation syndrome. Nadel and Burstein[27] reported an increase in corticosteroids excretion in urine of guinea pigs with liposarcoma and leukemia. Hilf *et al.*[28] observed an initial and terminal elevation of adrenal and plasma corticosterone level separated by a decrease in the middle stage in sarcoma 180 bearing mice. Peric-Golia and Jones[29] also reported an icreased plasma corticosterone level in lymphoma-bearing rats. Adrenal hyperfunction is, therefore, a common phenomenon in tumor-bearing host and this may well induce an elevation in glucocorticoid dependent tyrosine : 2-oxoglutarate aminotransferase activity of the liver. The fact that elevated activity of the enzyme was reversed by adrenalectomy in tumor-bearers may support the concept.

Lowered glycogen level of the liver in tumor-bearing mice may be indicative of carbohydrate deficiency developing in tumor-bearing mice. Though anorexia may be a contributing factor, neither decrease in glycogen content nor increase in tyrosine : 2-oxoglutarate aminotransferase activity were induced in the liver of pair-fed normal mice. Carbohydrate deficiency induced in tumor-bearing host may, therefore, be mainly a result of increased consumption of glucose by tumor cells[30] and increased energy expenditure of tumor-bearing host[31].

Besides the presence of tumor, fasting and high protein diet[12] are known to cause an increase in liver tyrosine : 2-oxoglutarate aminotransferase activity. In the latter cases carbohydrate deficiency is due to cessation or decrease of its dietary supply. In the former it is a result of anorexia and increased energy expenditure of the tumor-bearing host, including glucose consumption by the tumor. Elevation of liver tyrosine : 2-oxoglutarate aminotransferase activity, a phenomenon commonly observed under these conditions, should be regarded as a manifestation of accelerated gluconeogenesis, which results from adrenal hyperfuntion under carbohydrate deficiency.

The fact that elevated liver tyrosine : 2-oxoglutarate aminotransferase activity was reversed by glucose feeding may indicate that the major factor in elevating the enzyme activity is an inevitable carbohydrate deficiency in the tumor-bearing host rather than 'a non-specific stress' exerted by a tumor. When glucocorticoid was given, the enzyme activity was markedly elevated in glucose-fed mice. If a tumor acts on the host as a non-specific stress to cause adrenal hyperfunction, elevated tyrosine : 2-oxoglutarate aminotransferase activity should not be lowered by glucose feeding.

Decrease in liver catalase activity has been most remarkable among metabolic abnormalities in tumor-bearing organism and has been frequently used as an indicator of cachexia of the host. In the later stage a marked decrease in liver catalase activity was observed together with concurrent increase in liver tyrosine : 2-oxoglutarate aminotransferase activity. The increased activity of the latter might, to some extent, be related to the development of cachexia, although the existence of a correlation between these enzymes has not yet been made clear. Concerning the cause of cachexia of the tumor-bearing host, nitrogen trap[32] and metabolic disturbances due to toxohormone are now widely accepted. Toxohormone, first extracted by Nakahara and Fukuoka[4] from cancer tissue, is a depressing factor of liver catalase activity. Depression in liver catalase activity, however, is not a specific phenomenon in tumor-bearing animals, but was observed in some conditions other than cancer[33][34]. Fasting[35] and cortisone administration[36] were also reported to depress liver catalase activity. In tumor-bearing host, increased gluconeogenesis and development of anorexia will accelerate protein catabolism in the host. An adaptive mechanism of the host to restore its internal environment which is continuously disturbed by the tumor may be an important factor in the development of cachexia.

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