Tumor Growth in Potassium-deficient Mice*

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SUMMARY

The growth rate of Sarcoma 180 and of a mammary adenocarcinoma in potassium-deficient mice did not significantly differ from that in pair-fed control mice. The potassium concentration of these tumors in potassium-deficient mice was the same as in the control mice, although the potassium concentration of muscle and plasma was only half of that in the controls. The in vivo equilibration of K⁺ in Sarcoma 180 showed that at least 80 per cent of the tissue potassium was exchangeable.

It has been shown by several investigators (1, 4) that protein synthesis and growth rate in potassium-deficient animals are decreased. The possibility exists that the growth rate of tumors in such animals might also be decreased or that the response of a tumor in such animals to an antimetabolite might be greater than the response of a tumor with a normal potassium concentration.

MATERIALS AND METHODS

Two dietary regimens were used in these experiments. The mice to be made potassium-deficient were placed on a potassium-free diet (5) and given daily intraperitoneal injections of 0.1 mg. of deoxycorticosterone acetate in sesame oil 5 days a week. The control mice were placed on precisely the same diet, with the addition of KCl, and received daily injections of sesame oil. The two series of mice in each experiment were pair-fed in an attempt to maintain an equal nutritional status and so decrease the number of variables affecting tumor growth. The tissues excised in each experiment were weighed, digested in LiOH, and analyzed in a Beckman model B flame photometer. In the experiment utilizing K⁴⁺ the tissues, after digestion, were counted with a Packard autogamma scintillation counter.

Experiment 1.—Thirty-two female A strain mice were placed on the low potassium regimen and sixteen on the control regimen. Beginning on the 18th day of the diet, and at 7-day intervals thereafter Sarcoma 180 was transplanted into each axilla of four mice on the control diet and eight mice on the low potassium diet. Five days later the animals were sacrificed, and the plasma, quadriceps muscles, and tumors were analyzed for potassium.

Experiment 2.—Fifteen female A strain mice were placed on the low potassium regimen and fifteen on the control regimen. After 45 days on the diet, Sarcoma 180 was transplanted into each axilla of all mice. Forty-eight hours after the transplantation, six mice on the low potassium diet and six mice on the control diet were started on 5-fluorouracil, 20 mg/kg, given intraperitoneally each day for 5 days. The tumors were measured every other day in the longest axis of the tumor and in the direction perpendicular to this axis.

Experiment 3.—Six female A strain mice were placed on the low potassium regimen and six on the control regimen. Twenty-three days after beginning the diet a spontaneous A strain mammary carcinoma, obtained from Dr. D. J. Ferguson, was transplanted to each axilla of all mice. The size of the tumors was measured in the manner previously described. Forty-nine days after transplanting the tumors the animals were sacrificed, and the potassium concentration of the plasma, tumors, and quadriceps muscle was measured.

Experiment 4.—The in vivo equilibration of tumor potassium was evaluated by injecting 1.2 μc. of K⁴⁺ intraperitoneally into a series of twelve A strain mice 5 days after they had had Sarcoma 180 transplanted into each axilla. After varying time periods up to 180 minutes the animals were sacrificed, and the plasma, tumors, and quadriceps muscle were analyzed for radioactivity and for total potassium.
RESULTS

The first experiment, in which tumors were transplanted into animals that were increasingly potassium-deficient, was done in an attempt to produce a low concentration of potassium in Sarcoma 180. As may be seen from Chart 1, the potassium concentration of both plasma and muscle fell as the time on the diet increased. In the same animals, however, there was no decrease in the potassium concentration of the tumors.

In Experiment 2 the effect of potassium deficiency alone, and of potassium deficiency plus 5-fluorouracil therapy on the growth rate of Sarcoma 180, is compared with the growth rate in pair-fed controls. The mean weight of the mice in each group throughout the experiment is given in Table 1. From Chart 2 it is evident that the lag period of tumor growth was longer in the mice on the low potassium diet. However, once growth had begun, the rate of growth was the same as in the control mice, although this rate was maintained for a shorter period. The same observation is true for the mice on 5-fluorouracil. The potassium deficiency resulted in a longer lag period, but the rate of growth of tumors in potassium-deficient mice given 5-fluorouracil was the same as in control mice given 5-fluorouracil.

The mammary carcinoma used in Experiment 3 is a more slowly growing tumor than is Sarcoma 180 and could be exposed to the experimental conditions for a longer period of time. The mean weight of the two series of mice is given in Table 1. This tumor, similar to Sarcoma 180, showed little difference between the rate of growth in potassium-deficient animals and in control animals. Forty-nine days after inoculation these mice were sacrificed. At that time the potassium concentration of the plasma and muscle of the potassium-deficient group was less than 50 per cent of the control values; however, the concentration in the mammary tumor was 102 per cent of the control.

Because of the difficulty in lowering the potassium concentration of tumors, in Experiment 4 the in vivo equilibration of tumor potassium was compared with that of muscle. The K42 equilibration curves of the two tissues given in Chart 3 are remarkably similar. In each approximately 80 per cent of the tissue potassium equilibrated with plasma within the time period used.

DISCUSSION

It is apparent from these studies that both Sarcoma 180 and the spontaneous mammary carcinomas are able to accumulate potassium in the face of a marked potassium deficiency. That they

<table>
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<td><strong>MEAN WEIGHT OF MICE IN GRAMS</strong></td>
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<td><strong>Days on diet</strong></td>
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<td>0</td>
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do this with great success is evidenced by the fact that there was no change in the growth rate of the tumors and no change in the potassium concentration of the tumors at a time when the muscle potassium was approximately 50 per cent of normal. Liebow et al. (3) found the growth rate of an adenocarcinoma in ABC mice to be decreased in potassium-deficient animals. However, the mice on the low potassium diet were in a poorer nutritional status than were the control mice. When animals with an established tumor were made potassium-deficient, he found no change in the growth rate.

The reason for the delay in the onset of the logarithmic phase of growth of Sarcoma 180 in potassium-deficient animals and the further increase in this lag period when these animals are treated with 5-fluorouracil is not clear. Neither potassium deficiency nor 5-fluorouracil treatment separately or combined decreased the growth rate. It is possible that this phenomenon may be due to a process of selection in which a smaller number of cells remains.

The molecular basis for this increased capacity of a tumor to hold potassium is yet to be explained. The possibility existed that a large amount of tumor potassium might be bound with a high activation energy for exchange. However, the K$^{42}$ studies indicated that at least 80 per cent of the tumor potassium exchanged with the extracellular potassium within 180 minutes. This would make the possibility of an increase in high energy bonding small. The similarity of the two equilibration curves is surprising. The exchange of potassium in most tissues is flow-limited, and, because of the poor blood supply to tumors, it might have been expected that the equilibration curve of Sarcoma 180 would have had a smaller slope.

In previous experiments it was reported that the potassium flux of normal liver per unit of membrane area was greater than that of dimethylaminoazobenzene-produced hepatomas (2). This
behavior was explained by a decrease in the membrane permeability of the hepatoma and by a decrease in the intracellular diffusion coefficient. If this same situation exists in other tumors, it might account for the difficulty encountered in depleting them of potassium.

REFERENCES


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