Control of Food Intake during Growth of a Walker 256 Carcinosarcoma

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SUMMARY

Growth of Walker 256 carcinosarcoma depresses the hyperingestive response of rats to dilution of food with nonnutritive bulk. The depression is much less marked when the dilute diet is presented continuously over a long period than when it is presented for 1 week at a time. It is likely that over the long term another mechanism of food control is invoked to which the tumor-bearing rat has not lost its sensitivity. There is no reduction in feeding response of tumor-bearers to insulin-induced hypoglycemia, so feeding response to hypoglycemia could be the compensatory mechanism invoked. Prolonged exposure to the dilute diet with resultant decrease in nutrient intake by the tumor bearer increased the rate of deterioration of the host but did not significantly affect tumor growth.

INTRODUCTION

Food intake declines below need during tumor growth, contributing to the host depletion that is the central feature of cancer cachexia (4–7). A possible immediate cause for this decline appeared in the finding that the normal hyperingestive response to diluted food is progressively depressed and eventually obliterated by growth of the Walker 256 carcinosarcoma (7). In that study the dilute diet was imposed acutely for periods of 1 week during growth of the tumor. For assessment of the practical importance of the loss of response to nutrient density, it is necessary to determine whether continuous imposition of a diluted diet would have a comparable depressive effect and whether it would lead to more rapid deterioration and earlier death of the host. It was also of interest to determine whether another well-established mechanism of the control of food intake, the response to hypoglycemia, was influenced by growth of the tumor.

The results reported here show that the depressive effect of tumor growth on response to diet dilution does appear on continuous exposure to diluted diet but that the effect is less marked than on short-period exposure. The feeding response to hypoglycemia appears to be unaffected by tumor growth.

MATERIALS AND METHODS

Four groups of 6 adult male Sprague-Dawley rats were used for the dilution experiment; they weighed 235 g at the beginning of the experiment and 295 g at tumor transplant. All groups were maintained initially on a standard casein-based semisynthetic diet (5, 7). After 8 days, 2 groups were transferred to the same diet diluted with 50% of a nonnutritive bulk that kept the diet at the same consistency (7). After a further 7 days, 1 group on the standard diet and 1 group on the dilute diet were inoculated s.c. with 1-mg fragments of Walker 256 carcinosarcoma (6). All groups were then continued on the appropriate diets for a further 27 days. At necropsy, 27 days after tumor transplant, the tumors were excised and weighted. Total adrenal weight and spleen weight were measured in all animals.

A further group of 6 rats was maintained on the standard diet and was treated by s.c. injection daily for the 12th to 8th days before tumor transplant and the 18th to 22nd days after tumor transplant, with zinc protamine insulin (1.5 units/100 g, total body weight).

Food and water were allowed ad libitum at all times, and intakes and body weights were measured daily. The animals were housed individually at 24–26° under a fixed lighting schedule of 11 hr dark and 13 hr light.

From about the 11th day of tumor growth, the linear dimensions of each tumor were measured 5 times a week; from these measurements and the recorded weights of the tumors at necropsy, the tumor weight at each point of tumor growth was calculated (6).

RESULTS

Food Intake and Body Weight on Dilute Diet

Normal Rats. The bulk intake of the dilute diet by normal rats increased within 2 days of exposure to the dilute diet and continued to increase slowly for 3 weeks to about 215% of the intake of undiluted diet, representing an increase of 7.5% in nutrient intake (p < 0.001) compared with rats on the standard diet (Chart 1). Body weight gain fell progressively short of that of rats on the standard diet (Chart 2), reaching a deficit of 43 g after 5 weeks on the dilute diet (25 g deficit during equivalent period of tumor growth only).

Tumor-bearing Rats. After transplant of the Walker 256 carcinosarcoma, bulk intake of the dilute diet fell progressively below intake of the dilute diet by normal rats (Chart 1A) and, up to the 3rd work of tumor growth, represented a declining nutrient intake relative to intake of undiluted food by tumor-bearing rats (p < 0.001) (Chart 1B). Total body weight gain of tumor-bearing rats on the dilute diet fell slightly
Control of Feeding during Tumor Growth

BULK INGESTED

Chart 1. A, average daily food intake of normal rats on standard (●) and dilute (○) diet and of rats with Walker 256 tumor on standard (●) and dilute (○) diet. Means of 6 rats in each group. B, ratios (%) of nutrient intake. », normal dilute/normal standard; ○, tumor-bearing standard/normal standard; «, tumor-bearing dilute/normal dilute. The 50% dilute diet started at Point D, tumor transplant started at Point T.

relative to body weight gain of tumor-bearing rats on the standard diet (Chart 2), reaching a deficit of 12 g during the 4 weeks of tumor growth. The deficit in weight gain of the host only was 16 g.

The summed weight deficits produced by the dilution effect (nontumor, standard diet less nontumor, dilute diet), 25 g, and by the tumor (nontumor, standard diet less tumor, standard diet), 39 g, for the 4 weeks of tumor growth was (25 + 39) = 64 g. The actual weight deficit induced by the simultaneous action of diluted diet and tumor (nontumor, standard diet less tumor, dilute diet) was only 50 g. (The differences shown in the final points in Chart 2 include effects for 2 weeks prior to tumor transplant and are not numerically identical with the values cited here.)

Tumor Size and Survival Time

Up to the end of the 3rd week of tumor growth, tumor size in the standard and dilute diet groups was indistinguishable (50.3 and 53.5 g, respectively) (Chart 2). During the 4th week there was still no significant difference in total tumor size of intact tumors, but the condition of the tumors of the dilute diet group was poorer, with more surface ulceration and exudation and with the hosts eating their own tumors. The condition of the hosts on the dilute diet was also poorer at necropsy with obvious anemia and with ascites and i.p. extravasation of blood. Of the tumor bearers on the standard diet, none died up to the end of experiment (27 days after tumor transplant); of the tumor bearers on the dilute diet, 3 (out of 6) died on or before the 27th day.

Total adrenal weight (172 ± 20 mg) and spleen weight (5.7 ± 0.5 g) were significantly higher than for controls on the standard diet (45.3 ± 1.7 mg and 0.9 ± 0.05 g) in both tumor-bearing groups, with no significant differential effect of diet. In control rats on the dilute diet, adrenal weight was slightly but not significantly higher than normal (52.9 ± 6.1 mg), and spleen weight was normal. (All values as mean ± S.E.)

Feeding Response to Insulin

The hyperingestive response to insulin of tumor bearers was the same as that of normal rats (Chart 3). The compensatory hypoingestion after cessation of insulin treatment was more pronounced in the tumor bearers than in normal animals (p < 0.001).

Chart 2. Total body weight increment during experimental period of normal rats on standard (●) and dilute (○) diet, of rats with Walker 256 tumor on standard (●) and dilute (○) diet, and tumor weights on standard (∗) and dilute (○) diets. The 50% dilute diet started at Point D; tumor transplant started at Point T. Means of 6 rats in each group. Last week of tumor-bearing dilute diet group contain only the 3 rats that survived with intact tumor.
Tumor growth produces a progressive depression of feeding response to reduced nutrient density of food, but the depression is not as marked with chronic exposure to the dilute diet as with acute exposure. Thus, a 50% dilute diet given only in the 3rd week of tumor growth permitted a nutrient intake of only about 55% of requirement (7), while the nutrient intake in the 3rd week of tumor growth after 4 weeks on the dilute diet was 77% of requirement (p < 0.001). This attenuation of depressive effect when the nutrient dilution is chronic is also apparent in normal rats, where the nutrient intake rose by the 4th week of exposure to the dilute diet to 107.5% of the intake of the standard diet instead of declining to about 80%, as occurred with normal rats exposed to the dilute diet for only the 1st and 4th weeks of that period (7).

The final condition of the tumor bearers on the dilute diet, at the end of the 4th week of tumor growth, was certainly poorer than that of tumor bearers on the standard diet. However, the depressions of body weight gain induced by diet dilution and tumor growth imposed separately were not additive when these stresses were imposed together, and the final body weight loss was not nearly as great as would have been expected from the acute response (7).

These results suggest that continued exposure to dilute food and the resultant tissue depletion eventually evoke another feeding control mechanism to which the tumor bearer has not lost its response and that this stimulates food intake in normal rats and partially sustains it in tumor bearers. One of the most thoroughly documented mechanisms of control of food intake in normal animals is the response to hypoglycemia and, particularly, to insulin-induced hypoglycemia (1–3). Tumor bearers show a hyperingestive response to exogenous insulin (8), but there have been no quantitative data that would allow assessment of whether the response is as great as in normal rats. The present results on this point show that tumor growth produces no depression of the feeding response to insulin, so that feeding response to hypoglycemia could be the secondary feeding control mechanism evoked.

The hypoglycemic mechanism of control of food intake is specifically inactivated by chronic damage to the lateral hypothalamus (after recovery from the acute aphagia), while the dilution mechanism is not (1). If only the hypoglycemic and dilution responses were involved, rats with such hypothalamic damage and with growing tumors would show total failure to control or sustain food intake. In fact, lateral hypothalamic damage does not detectably alter food intake during growth of the Walker 256 tumor (6). It seems, therefore, that some other mechanism of feeding control, not thus far identified, must also be potentially available during tumor growth.

ACKNOWLEDGMENTS

Thanks are due to Mrs. B. Moore and Mr. E. McDuffie for valuable technical assistance.

REFERENCES

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