Generation and Compensation of the Cancer Cachectic Process by Spontaneous Modification of Feeding Behavior

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SUMMARY

Daily food intake and corresponding feeding activity (measured as duration) and feeding efficiency (amount of food ingested per unit of feeding activity) were measured both in normal Sprague-Dawley and Buffalo rats and during growth of Walker 256 and 4M mammary carcinomas in Sprague-Dawley rats and of Morris 5123 hepatoma in Buffalo rats. Estimates of meal size and frequency were also obtained. Growth of the carcinomas produced a decline in feeding activity accompanied, early in tumor growth, by a compensatory increase in feeding efficiency with no resultant effect on food intake. This compensated decline in feeding activity was due to reduction in average meal duration. Later, meal frequency was also reduced, with further reduction in feeding activity and reduction in food intake. There was little change in average meal size. The hepatoma produced a different detailed pattern of effect on feeding behavior. These effects are not nonspecific reactions to foreign tissue. The effects imply behavioral compensation for the breakdown of a rapidly responding physiological control of food intake and can be interpreted in terms of successive impairment of feeding control mechanisms that have different response rates and different behavioral modes.

MATERIALS AND METHODS

The work was done with adult male Sprague-Dawley rats growing Walker 256 carcinomas (S-D/W256) or 4M mammary carcinoma (S-D/4M), with adult male Buffalo rats growing Morris hepatoma 5123 (original line) (B/H5123), and with normal adult male rats of these 2 strains. All tumors were grown s.c. in the right flank. The method of tumor transplantation by trochar, of estimation of tumor size from lineal dimensions, and the growth characteristics of the tumors and their systemic effects on the hosts have been described in detail previously (10, 14). The rats were allowed a semisynthetic casein-based diet (8) and water ad libitum. The rats were maintained on a fixed schedule of 13 hr light and 11 hr dark at all times.

Feeding activity was measured as feeding duration, sensed by a modified “eatometer” (3, 16), in which contact by the rat with a sensing grid on the surface of the food drives an accumulating clock and/or an event pen on a graphic recorder. Feeding efficiency is calculated as: food intake (g)/feeding duration (hr), for individual rat days. The sensing and recording system and tests of its validity and reproducibility have been described in detail (16).

Two sets of experiments were done. In the 1st experiment the rats were maintained in the Lucite animal chamber of an indirect calorimeter (9) at 27–29°C. Food and water were available ad libitum within the animal chamber, and total intakes were measured daily. Total daily feeding duration was accumulated on a clock, and timing and duration of individual meals were recorded graphically. The duration of individual meals was measured from the graphic record and adjusted by scaling the summed graphic durations to the clock-accumulated total duration. Each rat was maintained in the calorimeter chamber with complete recording for the week before tumor transplant and for several weeks during tumor growth. In this series, 5 S-D/W256, 6 S-D/4M, and 5 B/H5123 organisms were studied.

In the 2nd set of experiments, groups of rats were maintained individually in Lucite cages at 24–26°C, each with a 24-hr feeding duration accumulation system. One group of 6 Sprague-Dawley rats received s.c. transplants of 1-mg fragments of skeletal muscle; 1 group received 1-mg fragments of W256 carcinoma; and groups of 5 and 6 rats received 1-mg fragments of 4M carcinoma. One group of 6 Buffalo rats received s.c. 1-mg fragments of normal liver and 1 group received 1-mg fragments of Morris 5123 hepatoma. Groups of 5 Sprague-Dawley and 8 Buffalo rats were untreated. Food intake and the corresponding feeding duration were...
recorded 5 days a week. In these experiments, no data were obtained on size or distribution of meals. Each experiment comprised 2 or 3 weeks before transplant of the tumor or normal tissue and 4 weeks after muscle transplant. 7 weeks after liver transplant, and until the rats became moribund after tumor transplant (4 weeks for W256, 6 weeks for 4M, and 7 weeks for H5123).

All rats were started on recorded experiment when aged 55 to 60 days (body weight 200 to 250 g), having received the experimental diet and having been in the experimental cage environment for 1 to 2 weeks prior to this. They were transplanted with tumorous or normal tissue 2 to 3 weeks later (body weight 250 to 350 g). Total final weight at end of tumor growth period (host + tumor) was 340 to 500 g. Equipment failure delayed the effective start (first acceptable records) with the untreated Sprague-Dawley rats (Chart 1a) until body weight was 300 to 350 g, with weight at the end of the no-treatment period for this group of 470 to 520 g.

RESULTS

Daily Food Intake and Feeding Duration and Efficiency

The results reported and illustrated for daily duration and efficiency of feeding are all from the 2nd set of experiments for which most information is available. The corresponding results from the 1st (calorimeter chamber) experiments are substantially identical. Efficiency data are expressed as the means of individual rat days and, therefore, are not identical with the ratio of corresponding intake/duration means.

Control Data: Untreated and Normal Tissue Transplant

Normal, untreated Sprague-Dawley rats, showing no systematic variation in daily food intake, showed no significant systematic variation in daily feeding duration and feeding efficiency. The feeding duration in the last week of study did drop significantly for unknown reasons (Chart 1a). The high food intake of the rats of this group compared with other groups is partly accountable to their body weight (see last paragraph of “Materials and Methods”), and partly to a slightly lower environmental temperature (22–24°) at that time. Sprague-Dawley rats transplanted with normal skeletal muscle showed the same stability in all 3 measures with no detectable effect of the tissue transplant.

Normal, untreated Buffalo rats, showing no systematic variation in food intake, showed a prolonged adaptation to the sensing instrumentation, presumably to the sensing screen on the surface of the food, with an approximately exponential decline in feeding duration and increase in feeding efficiency (Chart 2a; Ref. 16). The Buffalo rats transplanted with normal liver had different general levels of duration and efficiency, and there was an abrupt increase in efficiency immediately after tissue transplant; otherwise they showed a trend similar to that of the untreated animals (Chart 2b). The instrumental adaptation has a time constant (time to reach 63% of full response) of 1 to 2 weeks.

Tumor Bearers

S-D/W256. The Walker 256 tumor induced a significant decline in food intake by the 3rd week of tumor growth, and intake was reduced to about 30% of control by the 4th week. The feeding duration declined significantly by the 2nd week of tumor growth, when the tumor was less than 5 g, and thereafter declined progressively. Feeding efficiency increased markedly during the 2nd week of tumor growth and thereafter showed slight further increase (Chart 1c). The group of larger rats, designated as “no treatment” in Chart 1a, had Walker 256 carcinoma transplanted at the end of the no-treatment period and showed a similar pattern of decline in feeding duration and increase in feeding efficiency (not illustrated).

S-D/4M. The 11 rats with this tumor fell into a group of 5 that showed only a small decline of food intake in the last (6th) week of tumor growth, and a group of 6, with more rapidly growing and finally larger tumors, that showed decline in food intake from the 4th week onward, falling to 46% of control intake by the last week. The group with little decline in food intake showed continuous decrease in feeding duration and increase in feeding efficiency throughout tumor growth (Chart 1d). The group with substantial decline in food intake showed a decrease in duration and an increase in efficiency in the 1st and 4th weeks of tumor growth and a precipitous fall in efficiency in the last week (Chart 1e).

B/H5123. The Morris 5123 hepatoma induced a decline of food intake, starting the 4th week after transplant and reaching a level of about 55% of control by the final (7th) week of tumor growth. Up to the point of beginning of decline in food intake, there was no significant change from the control pattern of duration and efficiency of feeding (Chart 2). On the 4th and 5th weeks after tumor transplant there was an accelerated fall in feeding duration compared with the control pattern. Efficiency passed through a maximum in the 4th week and then declined progressively until the end of tumor growth (Chart 2c).

Duration, Frequency, and Size of Meals

All data on this topic were obtained from the calorimeter studies.

During growth of all 3 tumors, the decline in feeding duration was made up of a decline in average meal duration and a decline in meal frequency (Chart 3). When the tumors were small, reduction in average meal duration was the predominant source of reduction in total feeding duration. Later, when food intake was falling, meal frequency was also reduced. There was little change in average meal size (average amount ingested per meal) even when food intake was falling; only in the final stage of growth of the W256 tumor was there a significant reduction in average meal size (Chart 3a).

This series of experiments was done before the adaptation effect in the Buffalo rats was recognized, and the control period is shorter than would have been desired. Effectively all the change in feeding duration of the B/H5123
organism from the non-tumor-bearing control to the tumor less than 5 g (Chart 3c, Columns 1 and 2) must be attributed to this control adaptation and arises almost entirely from reduction in average meal duration with little change in meal frequency. There was no detectable food scattering by any animal in these experiments.

DISCUSSION

The 3 parameters, food intake, feeding duration, and feeding efficiency, are not independent; any 2 completely determine the 3rd. In these experiments, food intake and feeding duration are what are measured, and efficiency is the derived value. However, the feeding process is most completely described by all 3 parameters, and they are most instructively considered as food intake being the resultant of duration and efficiency of feeding (16). Feeding duration is proportional to, and thus is an appropriate measure of, the energy cost of feeding activity (9).

The predominant immediate cause of the host tissue depletion that characterizes cancer cachexia is a progressive hypophagia (7, 14). This implies a breakdown in the normal control of food intake, and 1 functional site of breakdown has been identified in the progressive failure to compensate for dietary dilution with growth of the Walker 256 tumor (11, 12). It has also been suggested that the hypophagia is partly a result of reduced capacity for all motor activity, with the compartment of motor activity available for feeding activity being progressively constricted (14).

For the S-D/W256 and S-D/4M tumor-bearing organisms, the present results show that the amount of activity used for feeding is indeed progressively depressed during the growth of the tumors. The depression can start very early in...
tumor growth, but for a considerable period it is compensated by a corresponding rise in feeding efficiency with no resultant fall in food intake. This indicates that the cachectic process starts at a very early stage of tumor growth although overt cachexia is not apparent until much later. Impairment of response to food dilution (11) and change in diurnal patterns of total activity and feeding (15) also appear well before overt cachexia. Thus, food intake is being effectively controlled by a behavioral adaptation even when individual physiological components of control have already broken down.

These effects on duration and efficiency are not a nonspecific response to transplanted, nongrafted foreign tissue. They are not likely to be a graft-versus-host response, as the primary feeding abnormality of that syndrome is marked inefficiency of feeding due to massive food scattering (6), which did not occur during growth of tumors.

The reduction in meal duration but with unaltered meal...
size implies greater feeding intensity during a feeding episode but with feeding switch-off occurring at the normal level of gut fill. This suggests that feeding response to preabsorptive signals, particularly gastric distension, is normal and intact, but modulation of the response by metabolic signals reflecting energy and nutrient status is impaired. This is in agreement with the shift, in tumor-bearing animals, toward constant bulk intake and away from the normal constant nutrient intake (11). It is also in agreement with the indication that, in normal rats, maintenance of feeding (primary modulator) producing effects a and c above, has a time constant of 1 to 2 weeks. The different time constants of these 2 modulating processes suggest that they may be identifiable with 2 general models of food intake control: the primary (1-day time constant) process with energy flow from the gut sensed via portal-hepatic receptors (17, 19), and the secondary (1-week time constant) process with depletion of energy reserves sensed via central receptors (4, 5). The feeding response to insulin (a, above) has a time constant of less than 1 day, and it is not clear whether this is yet another modulator or whether it represents a highly specific, fast and intense stimulation of the normally slow (secondary) modulator.

The form of development of hypophagia of the B/H5123 organism is discrepant from that in the other 2 tumor-bearing organisms examined. Here there is no significant early increase in feeding efficiency above that normally occurring in the Buffalo strain, but there are later saturation and decay of efficiency and reduction in meal frequency that are coincident with the overt hypophagia. This adds one more to the already substantial list of differences between the B/H5123 organism and the others and between normal Buffalo and Sprague-Dawley rats (13—16). It also suggests, superficially, that there may be at least 2 quite distinct metabolic routes by which cachexia can develop. However, the argument developed above from the responses to W256 and 4M tumors, when applied to the B/H5123 organism, yields a result that conforms with the pattern that actually occurs in this case. What was described above as the primary (short time constant) modulator does not exist or is greatly attenuated in normal Buffalo rats (13) and is, therefore, not subject to impairment by the tumor. It can be expected, then, that the secondary (long time constant) modulator is already being maximally invoked, independent of the presence of the tumor. This modulation of feeding is abolished at this stage. This is demonstrated as follows. (a) The normal hyperphagic response to exogenous insulin continues during the growth of W256 tumor in Sprague-Dawley rats (12). (b) Continuous imposition of dilute diet during growth of W256 has a less depressive effect on nutrient intake than does imposition of 7-day “pulse” of dilute diet, indicating that a secondary metabolic modulator has been invoked (11, 12). (c) Reduction in meal frequency with a corresponding increase in average intermeal interval is later added to the shortening of meal duration in tumor growth (Chart 3). This last implies a changed threshold for triggering initiation of feeding, indicating that a metabolic control that has continued through most of tumor growth is finally lost or modified.

The primary metabolic modulator, abolition of which is shown by failure to respond to nutrient dilution, has a time constant of 1 to 2 days (time to reach 63% of full response). The secondary modulator, producing Effects b and c above, has a time constant of 1 to 2 weeks. The different time constants of these 2 modulating processes suggest that they may be identifiable with 2 general models of food intake control: the primary (1-day time constant) process with energy flow from the gut sensed via portal-hepatic receptors (17, 19), and the secondary (1-week time constant) process with depletion of energy reserves sensed via central receptors (4, 5). The feeding response to insulin (a, above) has a time constant of less than 1 day, and it is not clear whether this is yet another modulator or whether it represents a highly specific, fast and intense stimulation of the normally slow (secondary) modulator.

The foregoing considerations lead to the tentative suggestion that action of the primary metabolic modulator of feeding is manifested behaviorally by change in duration of feeding, and the action of the secondary, slower modulator by change in efficiency of feeding. Much more information on the normal duration-efficiency characteristics of different stimuli will be necessary before this possibility can be confirmed or elaborated.

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**Chart 3. Food intake, feeding duration, meal frequency, meal size, and meal duration before transplant of tumor with increasing size of:**

- (a) Walker 256 carcinoma; (b) 4M carcinoma (both in Sprague-Dawley rats);
- and (c) Morris 5123 hepatoma in Buffalo rats. Values displayed against tumor size (range and mean ± S.E. at bottom of chart). Numbers in parentheses above food intake blocks (top row), number of rat days in each block. Bars, total S.E. of block mean. Data are from calorimeter series.
expectation is supported by the fact that the spontaneous exponential drift of duration and efficiency in normal Buffalo rats has approximately the same time constant as the secondary modulator. The secondary modulator is finally impaired by the hepatoma as it is by the other tumors, leading to a decline in feeding efficiency and to overt hypophagia and cachexia.

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