Extrahypothalamic Mediation of Changes in Feeding Behavior Induced by Growth of Walker 256 Carcinosarcoma in Rats

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ABSTRACT

Feeding efficiency (amount of food ingested per unit of feeding activity) was chronically depressed in male Sprague-Dawley rats recovered from the acute aphagia or hypophagia of lateral hypothalamic damage. The extent of depression varied with the severity of the acute feeding response to hypothalamic damage. Growth of Walker 256 carcinosarcoma in intact rats increased feeding efficiency. Chronic lateral hypothalamic damage did not significantly attenuate tumor-induced increase in feeding efficiency but lowered the initial and maximum efficiency levels. Growth of the tumor-bearing host was depressed by residual lateral hypothalamic damage, but this depression was not related to the severity of the acute feeding response to damage.

INTRODUCTION

During growth of experimental tumors that eventually induce anorexia and cachexia, there is progressive reduction of feeding activity (measured as feeding duration), starting within the first third of tumor life (time from implant of tumor to death of host) (16). Overt decline of food intake does not occur until the last third of tumor life (16). This reduction of feeding activity before reduction of food intake has been interpreted as an early expression of the anorectic process which is fully compensated for the first two-thirds of tumor life by a simultaneous increase in feeding efficiency (the amount of food ingested per unit of feeding activity).

Several studies have proposed or looked for involvement of the hypothalamic control of feeding in tumor-induced anorexia (1, 9, 10, 14, 22). However, both direct (1, 10, 14) and indirect (17) evidence indicates absence of hypothalamic involvement in the development or course of tumor-induced anorexia.

Lateral hypothalamic damage that produces aphagia has been found repeatedly to be associated with motor abnormality (2–5, 11, 13, 20, 23), and this includes feeding inefficiency (detectable as a great increase in food scattering). Eventual escape from the acute (aphagic) effects with recovery of adequate food intake is characteristic of this type of hypothalamic damage (20, 21), but residual motor deficits persist after escape (4, 11, 20). A preliminary experimental trial indicated that the persisting motor deficits include a severe and maintained elevation of feeding duration and depression of feeding efficiency.

If tumor-associated increase of feeding efficiency were blocked by lateral hypothalamic damage, then this part of the anorexia-cachexia syndrome could be considered to be mediated hypothalaminically, and there would be some basis for continuing efforts to examine cancer anorexia via the hypothalamus. If, however, the tumor-associated increase of feeding efficiency is not blocked or significantly attenuated by hypothalamic damage, then the compensatory responses that delay anorexia and cachexia as well as the anorexia and cachexia themselves would appear to be independent of the lateral hypothalamus. This result would also indicate that there are at least 2 distinct central pathways of mediation of feeding activity and efficiency.

This study examines these questions.

MATERIALS AND METHODS

The work was done on adult male Sprague-Dawley rats of initial body weights of 190 to 200 g. All rats were maintained throughout at an environmental temperature of 23–25°C and in a constant 12-hr light/dark cycle.

The rats were housed individually in "Lucite" cages (living space, 26 x 26 x 25 cm) with 1.25-cm stainless steel floor grids. A standard casein-based semisynthetic diet (12) and water were available ad libitum at all times.

The plan of experiment was to measure simultaneously 24-hr food intake and feeding activity for 2 weeks prior to any treatment, then for 3 weeks following apparent recovery of spontaneous food intake after hypothalamic damage, and finally, during growth of Walker 256 (W256) carcinoma. The period of study during tumor growth (4 or 5 weeks) was continued until the tumor had reduced mean weekly food intake to less than 75% of pretransplant intake.

Body weight, food intake, feeding duration, and water intake were measured 6 times a week. The recorded food intake is the amount apparently consumed corrected for retrieved scattered food. Only the last 4 days of the weekly record were used for analysis to minimize carry-over effects from the 2-day weekend period. All rats were maintained in the basic experimental situation (diet, housing, instrumentation) for 1 week before start of experiment.

Feeding Activity. The food was supplied in a pot clamped to the floor grid and arranged as a modified Fallon contact "eatometer" (7, 18). Animal contact with a grid on the surface of the food is necessary to obtain food. This contact activates a delayed drop-out relay with a 5-sec hold, the output of which operates an electric clock. The clock accumulates the total duration of feeding in a 24-hr period. The physical arrangement of this system, the design of the relay, and the validation of the output as a quantitative estimate of feeding activity have been presented in detail previously (18). Feeding efficiency is derived as food intake/feeding duration (g/hr).

With normal rats, this system gives little difficulty. With acute hypothalamic damage, rats sometimes rest head and paws on the food dish, causing spuriously high accumulated feeding duration. After escape from the acute effects of hypothalamic lesions, this artifact disappears (confirmed by monitoring con-
tact activity from a continuous graphic record). Only postlesion records after escape from the acute effects were used.

**Lateral Hypothalamic Lesions.** Bilateral lesions of the lateral hypothalamus of 34 rats were made with a stereotaxic instrument (Stellar model; Stoelting Co., Chicago, Ill.) under barbiturate anesthesia, using direct anodal current of 1.5 mAmp for 15 sec. The coordinates of the lesions were 1.5 mm caudal to the bregma, 2 mm lateral to the midline (taken as the sagittal suture when that appeared coincident with the superior sagittal sinus and as the midpoint between suture and sinus when these did not coincide), and 8 mm ventral to the dura mater. Thirty-one of these rats survived and eventually recovered spontaneous feeding.

Those rats that remained aphagic or severely hypophagic (less than 25% of preoperative intake) for more than 2 days were tube fed with a vitaminized preparation of evaporated milk (13) and were offered an aqueous chow mash until spontaneous ingestion of the standard diet was reestablished to an extent that permitted body weight gain. The standard diet was offered continuously, and its consumption was measured daily.

At the end of the experiment, the brains of all lesioned rats were dissected out. Serial sections of the diencephalon from optic chiasma to mamillary bodies were inspected microscopically to check that damage was in the classically recognized lateral hypothalamic area. The criterion of success of the procedure was the functional feeding response, and the detailed extent and placement of neural damage were not analyzed.

Acute feeding response to the lesions varied from barely detectable hypophagia to total aphagia for 14 days. After recovery of spontaneous feeding, the rats were divided into 3 groups: those that had shown marginal acute feeding response (slight and transient hypophagia, 11 rats); those that had shown moderate acute feeding response (total aphagia or hypophagia of less than 50% of preoperative intake for 1 or 2 days, 7 rats); and those that had shown severe acute feeding response (total aphagia or hypophagia of less than 50% of preoperative intake for 3 or more days, 13 rats (2 of these were discarded because of malfunction of duration-recording equipment)). Because of the limitations of equipment, only 3 of the marginal group were studied for feeding duration, and these formed a positive control group (operative trauma and central damage without significant effect on food intake); the rest of this group were continued with respect to body weight, food intake, and tumor growth and formed a control group for assessment of effect on food intake of the duration-recording instrumentation. In all cases, the recorded periods for the lateral damage condition started when there had been at least 1 week of spontaneous intake of the standard diet at a level that produced weight gain.

**Tumor Transplantation and Growth.** Fragments of W256 carcinosarcoma (2 to 4 mg) from the viable cortex of a 2-week tumor bearers (Chart 1, b, c, and d). The total increase in feeding efficiency associated with tumor growth was not significantly depressed by hypothalamic damage (Chart 1). However, the tumor-associated increase started from the depressed level produced by the hypothalamic damage, and the maximum efficiency achieved was correspondingly lower than in intact rats. The maximum efficiency achieved by tumor growth in the severely hypothalaminically damaged group was not significantly higher than that of the tumor-free intact rats (Chart 1).

**Host Growth.** Body weight gain of the various groups prior to any treatment varied from 5.5 to 8.0 g/day. The rate of weight gain during the week prior to tumor transplant was 7.0 ± 1.1 (S.E.) g/day for intact rats, 4.1 ± 0.5 g/day for rats with severe or moderate lateral hypothalamic damage, and 2.8 ± 0.3 g/day for rats with marginal hypothalamic damage.

In all groups, host weight (measured total body weight—estimated tumor weight) increased until 3 to 4 weeks posttransplant (tumor weight, 25 to 35 g) and then declined, showing the typical pattern of tumor-induced cachectic depletion (Chart 2a).

Severity of the acute hypothalamic feeding response did not significantly influence weight increment of the host after lateral hypothalamic damage (Chart 2a). The weight increment of the intact host, however, was more than twice that of the hypo-
thalamically damaged groups ($p < 0.001$) (Chart 2a). The intact group attained maximum host weight 6.5 days later than the hypothalamically damaged groups ($p < 0.001$). The presence of the duration-sensing grid over the food did not depress food intake or growth.

**Tumor Growth.** The rate of tumor growth was not significantly altered by hypothalamic damage (Chart 2b).

**Water Intake.** In the intact group, water intake was increased by tumor growth, reaching a maximum of 18% ($p < 0.02$) above the pretransplant intake at the time of maximum host weight. Lateral hypothalamic damage decreased pretransplant water intake by 22% ($p < 0.001$) and eliminated the tumor-induced increase in intake.

**DISCUSSION**

The ventromedial and lateral hypothalamus and associated tracts are involved in the integration of normal feeding behavior (1, 20). From this, it has frequently been considered that tumor-induced anorexia might arise from dysfunction or inappropriate response of this hypothalamic region (1, 9, 10, 14, 22). However, all available evidence indicates that cancer anorexia is independent of the hypothalamus. Damage to ventromedial or lateral hypothalamus that produces hyperphagia or aphagia in tumor-free animals does not alter the development or course of anorexia in tumor-bearing animals (1, 10, 14). Also, the normal feeding response to change in caloric density of diet, which is independent of the hypothalamus, is impaired and eventually abolished by tumor growth; and the normal feeding response to exogenous insulin, which is at least partly mediated by the hypothalamus, is unimpaired by tumor growth (17).

Feeding duration, which is a valid measure of the motor activity devoted to feeding (18), is reduced early in tumor growth, but this is compensated by a simultaneous increase in feeding efficiency so that overt anorexia is delayed until late in tumor growth (16). Motor deficits have been demonstrated repeatedly in association with the aphagia of lateral hypothalamic damage (2–5, 11, 13, 20, 23), and they persist to some extent even after escape from the acute aphagia (4, 11, 20). The present results show that the persistent motor deficits include increase in feeding duration and depression of feeding efficiency. If the hypothalamic damage that produces this depression of feeding efficiency also blocked or significantly attenuated the tumor-associated elevation of efficiency, then it could be inferred that this effect of tumors on feeding is mediated hypothalamically. (The lateral hypothalamus is operationally defined here as the central region damaged by the lesions. It may embrace structures that would not be so defined anatomically.)

However, it is apparent from the results that the increase in feeding efficiency associated with tumor growth is not affected by lateral hypothalamic damage that depressed feeding efficiency. The tumor-associated change in feeding efficiency is, thus, mediated extrahypothalamically. What is affected is the...
Feeding Behavior of W256 Rats

maximum feeding efficiency that is finally achieved. The 2
effects on feeding efficiency are independently produced but
are additive at a later stage in the behavioral pathway.

In spite of the apparent noninvolvement of the hypothalamus
in tumor-induced changes in feeding, the great difference in
weight gain of tumor-bearing hosts between intact and hypo-
thalamically damaged rats (Chart 2a) shows that neural damage
produced by the lesions can influence the vulnerability of the
host to tumor growth. This seems to be a sensitive but nonspe-
cific response to chronic neural damage as it does not vary
with the severity of the acute feeding response to damage. Part
of the effect arises from depression of body weight gain of
tumor-free rats by hypothalamic damage.

In an earlier study (14), lateral hypothalamic damage did not
alter the rate of host weight gain. The rats in the 2 studies were
given the same diet and were maintained in identical conditions,
and there was no grossly observable difference in site and
extent of hypothalamic damage. However, tumors grew much
faster, and anorexia appeared sooner in the earlier study. In
the earlier study, tumors reached 50 g, and food intake had
fallen almost to zero by the end of the third week. In the present
study, tumors did not reach 50 g until the end of the fourth
week, and decline in food intake was not appreciable until the
third or fourth week of tumor growth. Over a period of 12 years,
the growth rate and hypophagic effect of this W256 tumor line
have slowed. The final cachectic effect is the same, but it
occurs later. When the hypophagia due to tumor is rapid, it
dominates the weight change of the host and reduced growth
due to neural damage is not detectable. When the hypophagia
due to tumor is slow or delayed, the reduced growth due to
central damage has adequate time to be expressed and to
become evident.

The depressed growth of the hypothalamically damaged
hosts could be due to: (a) reduced food intake; (b) increased
metabolic drain by the tumor; (c) dehydration; (d) changed
pattern of energy depletion (e.g., shift towards protein from
lipid utilization with reduced energy density of tissue loss); or
(e) increased metabolic rate. There is no evidence of reduced
food intake or increased rate of tumor growth during the
appropriate period in these groups (cf. Charts 1 and 2), so a
and b can be provisionally eliminated. The reduced water
intake caused by lateral hypothalamic damage, in agreement
with earlier studies (6, 14), and the elimination of the tumor-
induced increase in water intake, also found previously (14),
suggest that dehydration may play a part. A detailed carcass
analysis study would be required to examine d. This tumor, by
itself, does not increase total metabolic rate of the host (15).
Lateral hypothalamic damage does increase total metabolic
rate acutely (13, 19), and an attenuated form of this increase
may continue chronically and account for the persistently low-
ered body weight and lipid content that have been found in
recovered lateral animals (8). It is possible that interaction of
tumor and lateral hypothalamic damage might reelevate meta-
bolic rate, but specific calorimetric or carcass analysis studies
would be required to examine this.

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S. D. Morrison
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