Diurnal Distribution of Motor Activity and Feeding during Growth of Tumors

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SUMMARY

The diurnal distributions of motor activity and feeding were examined as indicators of hypothalamic function in three host-tumor organisms: (a) Sprague-Dawley-Walker 256 carcinosarcoma, (b) Sprague-Dawley-4M carcinoma, and (c) Buffalo-5123 hepatoma. The normal, high night/day activity ratio was depressed with growth of tumor in b, but there was no significant change in a and c. The normal, high night/day feeding ratio was depressed with growth of tumor in a, reduced to one in b, and slightly enhanced in c. Changes in diurnal ratios preceded decline in total daily food intake and motor activity. Magnitudes of diurnal ratios of activity and feeding were unrelated in non-tumor-bearing animals. Immediately upon initiation of growth of all tumors, the two ratios became significantly correlated, even when there was no significant change in average magnitude. Hypothalamic dysfunction may be slightly but variably involved in cachectic hypophagia.

INTRODUCTION

Food intake declines during growth of many tumors (3, 10, 17, 20), and total motor activity declines during growth of some tumors (4, 11, 16, 17, 22). Analogous changes occur in advanced clinical cancer (3). It seems likely that the declines in food intake and in activity are linked, but an unequivocal causal relationship has not been established (17).

It has proved difficult to find plausible mechanisms for these effects of neoplastic growth on the host. The most well-known controls of normal food intake arise or are integrated in 2 areas of the hypothalamus, the ventromedial nuclei and the lateral subthalamic areas (12). However, the direct work that has been done on hypothalamic control of food intake in relation to tumor growth has not shown any gross involvement of the hypothalamus in tumor-induced decline of food intake (1, 9, 15). Also, some characteristics associated with reduction of food intake in tumor growth and in lateral hypothalamic damage are not concordant. Lateral hypothalamic hypophagia is associated with an increase in total metabolic rate and total motor activity and with marked food scattering (2, 14). In hypophagia of tumor growth there is little or no increase in metabolic rate, a reduction in total motor activity, and no detectable food scattering (16, 17).

It is, nevertheless, tempting to believe that abnormality of hypothalamic controls is in some way involved in the depression of food intake during tumor growth, although the influence may be more subtle. Abnormalities of non-feeding motor activity are associated with experimental damage to and manipulation of those hypothalamic areas that control feeding (2, 5, 14). Particularly, the normal diurnal distributions of motor activity, feeding, and drinking, all of which in the normal rat occur predominantly during the hours of darkness, are altered toward day-night equality in rats with ventromedial or lateral hypothalamic damage (6, 21). Depression of these diurnal rhythms is, therefore, a possible indicator of abnormal hypothalamic function. Changes in diurnal distribution of feeding and motor activity associated with decline of these behaviors during tumor growth would be indicative of change in hypothalamic function. Three transplantable tumors in rats that differ in growth rate and final tumor size, but that induce a decline in food intake, have been examined in this respect.

MATERIALS AND METHODS

Animals and Tumors. The work was done on 5 Sprague-Dawley rats before transplant and during growth of Walker 256 carcinosarcoma (S-D/W256 organism), on 6 male Sprague-Dawley rats before transplant and during growth of a mammary carcinoma designated 4M (17) (S-D/4M organism), and on 5 male Buffalo rats before transplant and during growth of Morris 5123 hepatoma (B/H5123 organism). (The H5123 used has been carried from the original line of this tumor.) Tumor sizes were estimated from final excised weight at death, and the lineal dimensions of the tumor measured daily during tumor growth (16).

Experimental Methods. Each rat was studied for 4 days a week for a week before tumor transplant and for 4 or 5 weeks of tumor growth (including, in all cases, the last 3 weeks of tumor growth) in a continuous analytical respirometer (13). The oxygen consumption and carbon dioxide production were recorded continuously throughout each 24-hr period (23.5 hr of actual recording). Feeding was also recorded on the graphic record, being sensed by an “eatometer” and transmitted to a signal marker via an ultrasensitive delayed drop-out relay (19).

All rats were allowed food and water ad libitum at all times. A standard semisynthetic diet containing 21% casein was used (13). Body weight, food and water intake, and...
tumor dimensions were measured daily. Environmental temperature of the rats during study was 27 to 29°C. A fixed lighting schedule of 13 hr dark and 11 hr light was maintained at all times.

**Extraction and Computation of Data.** Total daily energy expenditure \( (E) \) was calculated from oxygen consumption and carbon dioxide production measured by planimetry of the graphic record (13). Absorbed metabolizable energy intake \( (I) \) was derived from measured food intake, nitrogen content of food, feces and urine, and bomb calorimetry of food, feces, and urine samples (13). Relative energy (food) intake is expressed as \( I/E\% \) (Chart 1c).

Each 24-hr record of oxygen consumption and carbon dioxide production was partitioned into the part attributable to all spontaneous motor activity and the part attributable to rest (13, 16). The total energy expended on motor activity \( (A_{\text{obs}}) \) was calculated from the gas exchange and was used as a measure of the amount of motor activity (13). The expected motor activity of the host, if there were no effect on it of tumor growth \( (A_{\text{exp}}) \), was calculated from relationships established for normal rats (18), as the motor activity energy of a rat of the same strain and total energy expenditure as the host. Relative motor activity of the tumor-bearing host is expressed as \( A_{\text{obs}}/A_{\text{exp}}\% \) (Chart 1d).

The oxygen consumption attributable to motor activity was measured separately for the hours of light and hours of darkness. The ratio of average hourly oxygen consumption for activity in the dark to that in the light was calculated for each 24-hr period.

\[ \text{Chart 1. Depletion of host tissue and components of energy exchange with growth of 3 tumors. Bars, } \pm 2 \text{ S.E. Relative energy intake calculated as } I/E; \text{ relative motor activity calculated as } A_{\text{obs}}/A_{\text{exp}}(\text{"Materials and Methods")}. \text{ Absolute value of activity energy for control groups is } 25\% \text{ of total energy expenditure N.T., non-tumor-bearing control. Number of 24-hr periods in each group and mean weight at transplant as in Table 1. S.D., Sprague-Dawley; Buff, Buffalo; Hep, hepatoma.} \]

The total durations of feeding in the light and in the dark were accumulated from the graphic record, and dark-light ratios of feeding duration were calculated.

**RESULTS**

Host weight increment (Chart 1a) and relative food (energy) intake (Chart 1c) declined consistently with growth of all 3 tumors. Energy expended on all motor activity declined during growth of W256 and 4M tumors but did not decline with growth of H5123 (Chart 1d). Total daily energy expenditure per animal rose with tumor growth (Chart 1b), but the increase was entirely accountable to the estimated oxidative metabolism of the tumor and the metabolism expected from the body weight and food intake of the host, as previously found for the S-D/W256 organism alone (16). There was no increase in metabolic rate.

The night-day activity ratio was normally (pretransplant) between 2 and 3. For the S-D/4M organism, this ratio declined systematically and significantly \( (p < 0.01) \) with growth of the tumor to 40 g and, thereafter, remained constant (Chart 2a). In the other host-tumor organisms, there was no systematic or significant change (Chart 2a).

The night-day feeding ratios were normally very variable. In both the S-D/W256 and the S-D/4M organisms there was a systematic and significant \( (p < 0.01) \) decline in ratio with growth of the tumor (Chart 2b). This was most pronounced in the S-D/4M organism; the ratio reached the final value of 1.0, demonstrating complete abolition of diurnal rhythm in the later stages of growth of this tumor. The night-day feeding ratio showed a slight but significant increase during growth of H5123 \( (p = 0.05) \) (Chart 2b).

Before transplant of tumor, there was no correlation between diurnal activity ratio and diurnal feeding ratio in...
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Change in coupling between diurnal distribution of motor activity and feeding with tumor growth

<table>
<thead>
<tr>
<th>Stage of tumor growth</th>
<th>Sprague-Dawley-Walker&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sprague-Dawley-4M&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Buffalo-hepatoma 5123&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant control (no tumor)</td>
<td>29</td>
<td>+0.01</td>
<td>N.S.</td>
</tr>
<tr>
<td>Tumor &lt;5 g</td>
<td>32</td>
<td>+0.50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tumor 5-40 g</td>
<td>19</td>
<td>+0.69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tumor &gt;40 g</td>
<td>17</td>
<td>+0.18</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean body weight at transplantation, 236 g.
<sup>b</sup> Mean body weight at transplantation, 228 g.
<sup>c</sup> Mean body weight at transplantation, 232 g.

<sup>d</sup> n, number of 24-hr periods; r, correlation coefficient; p, significance level; N.S., not significant.

either strain of host (Table I). Immediately after transplant, these ratios became significantly correlated in all host-tumor organisms, and this was generally maintained with growth of the tumor, whether or not there was any shift in individual diurnal distributions (Chart 2).

**DISCUSSION**

The effect of tumor growth on diurnal distribution of motor activity and of feeding is not at all uniform in different tumors. Of the 3 tumors studied, only the S-D/4M organism showed systematic decline in diurnal ratio of both activity and feeding, and only in this tumor organism was the feeding ratio reduced to 1. There is no firm association between the shifts in diurnal distribution and the decline of food intake and motor activity; although both food intake and motor activity declined in the S-D/4M organism along with the decline in diurnal ratios, activity declined in the S-D/W256 with no diurnal activity shift, and food intake declined in B/H5123 with an increase in diurnal feeding ratio. The difference in response of diurnal rhythms to growth of the different tumors is not attributable to erratic growth or effect of the tumors in these particular groups; the results corresponded closely with previous findings in respect to growth rate and final weight of tumor, depression of voluntary food intake, depletion of host tissues, and effects on motor activity (Chart 1; Refs. 1, 10, 16, 17; unpublished work). Other diurnal rhythms can be depressed by tumor growth and, again, the degree of depression is variable among tumors (7).

The night-day feeding ratio is reduced to 1 after damage to ventromedial hypothalamic nuclei and after recovery from the acute aphagia following damage to lateral hypothalamic areas (6, 21). However, Kissileff (8) found enhancement of nighttime feeding in “recovered lateral” rats; this discrepancy may be due to strain differences, to siting of lesions, or to the particular food-delivery system used in these experiments. Diurnal ratio of a particular locomotor activity (wheel running) is reduced after damage to either of the hypothalamic areas that affect food intake (21), but this is not directly comparable with the oxygen consumption of total motor activity used as the measure here. Diurnal ratio of total activity measured as oxygen consumption is reduced in rats after lateral hypothalamic damage (14).

The development of coupling between the diurnal ratios in motor activity and in feeding immediately after transplant of tumor, and the maintenance of this coupling with further growth of the tumor, support the hypothesis (17) that changes in motor activity and food intake during tumor growth are causally related; but the large scatter shows, as before, that this is probably only one of the processes depressing food intake. The changes in coupling of diurnal ratios and those changes that occurred in the ratios themselves all appeared before any change in food intake or depletion of body tissue was detectable. (cf. Charts 1 and 2).

These shifts in diurnal ratio are not as well defined as those found after hypothalamic damage. (There are no data on change of coupling of these ratios in hypothalamically damaged animals.) Insofar as suppression of diurnal rhythms is an indicator of hypothalamic abnormality, this supports the previous indications (1, 9, 15) that hypothalamic mechanisms play, at most, a tenuous part in the tumor-induced decline of food intake. It indicates, however, that the hypothalamic contribution may differ in different tumors, or that the hypothalamic contribution to normal feeding may differ for different strains of animal. There are substantial and relevant differences in metabolic characteristics between Sprague-Dawley and Buffalo rats (18).

**REFERENCES**

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Diurnal Rhythms in Tumor Growth


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