The Influence of Thyroid Stimulation on the Incidence of 3-Methylcholanthrene-induced Tumors

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SUMMARY

The incidence of tumors induced by a single s.c. injection of 2 mg of 3-methylcholanthrene was observed in euthyroid and thyroidectomized rats and in rats fed thyroid powder. Thyroid feeding increased the metabolic rate by a factor of 1.6 and reduced the incidence of tumors at the site of injection from 92% in euthyroid rats to 36% in hyperthyroid rats.

INTRODUCTION

Several studies have indicated that rats, hypothyroid from chemically induced thyroid suppression, have an increased incidence of mammary tumors following systemic administration of a chemical carcinogen (1, 4, 8). Jull and Huggins (7), however, reported a decreased incidence of tumors in thyroidectomized rats given 10 mg of MCA by gastric intubation semiweekly for 7 weeks. Others have reported that rats, hyperthyroid from exogenous thyroxin, had a decreased incidence of chemically induced cancers (14).

In a study by D. G. Baker (unpublished experiments), rats were simultaneously given a single 2-mg injection of MCA in the leg and one-half of the animals were immediately placed in an environmental temperature of 2° for the duration of life. As an adaptive response to the low temperature, the rats had an increased metabolic rate and indications of increased thyroid activity. Ninety-six% of the rats in the 2° environment developed tumors at the site of the MCA injection. Only 50% of the rats at the 2° environment developed tumors. These observations suggest that it might be possible to reduce the oncogenic potential of a carcinogen by increased metabolic rate and thyroid activity.

In this study the incidence of chemically induced tumors in euthyroid, thyroidectomized, and hyperthyroid rats was compared.

MATERIALS AND METHODS

The animals were Sprague-Dawley female rats (Simonsen Laboratories, Gilroy, Calif.), 66 to 90 days of age at the start of the experimental period.

For tumor induction, a single 2-mg dose of MCA (Sigma Chemical Co., St. Louis, Mo.) suspended in corn oil was injected s.c. into the right thigh of the rats.

The following treatment groups were compared: (a) euthyroid rats offered a standard diet (Simonsen Maintenance Diet pellets) ad libitum; (b) euthyroid rats receiving the standard diet, but pair-fed with thyroidectomized rats; (c) thyroidectomized (surgical) rats offered a standard diet ad libitum; (d) rats offered the standard diet, to which had been added 0.4% thyroid powder (Sigma), ad libitum; (e) rats offered the thyroid-containing diet, but pair-fed with the euthyroid rats that had the standard diet ad libitum; (f) a group of euthyroid non-MCA-treated rats. The metabolic rates of these rats were measured before and after the implantation of a transplanted rat tumor, GB71, a gliosarcoma maintained in this laboratory for the past 3 years. This group served only to estimate the effects of MCA and the presence of a tumor on the metabolic rate.

In all groups, the dietary regimen was instituted 1 week prior to the injection of MCA. Water was offered to all treatment groups ad libitum.

Food and water intake was measured daily and expressed in g per 100 g of body weight per day. Oxygen consumption was measured for each animal at 2-week intervals using a closed system animal respirometer (Med-Science Electronics, Inc., St. Louis, Mo.). The metabolic rate was expressed as oxygen consumption in ml (at 0°, 760 mm Hg) per 100 g of body weight per min. The average metabolic rate for each rat prior to and after tumor development, where tumors were present, was determined. The mean of these values for each treatment group is presented in Table 2.

All animals were followed for their duration of life. Tumor incidence and survival times were determined. Any rat that failed to survive for more than 150 days following the MCA injections was rejected from the experiment.

RESULTS

Since there was no significant difference in tumor incidence or survival time between the euthyroid rats fed ad libitum or pair-fed with the thyroidectomized rats, the data from both euthyroid groups have been combined. Similarly, the data from the 2 hyperthyroid groups (food ad libitum and pair-fed) have been combined. The only exception to this procedure was in reporting the food and water intake measurements shown in Chart 1. These data have been...
Survival Treatment
groups

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>No. of rats</th>
<th>Survival (days) after MCA injection</th>
<th>Tumor incidence</th>
<th>Induction time (days)</th>
<th>Tumor to death (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid rats</td>
<td>26</td>
<td>352 ± 138*</td>
<td>24/26 (92%)</td>
<td>281 ± 100*</td>
<td>52 ± 38*</td>
</tr>
<tr>
<td>Thyroidectomized rats</td>
<td>14</td>
<td>404 ± 241</td>
<td>10/14 (71%)</td>
<td>206 ± 75</td>
<td>77 ± 42</td>
</tr>
<tr>
<td>Hyperthyroid rats</td>
<td>14</td>
<td>254 ± 160</td>
<td>5/14 (36%)</td>
<td>212 ± 95</td>
<td>45 ± 28</td>
</tr>
</tbody>
</table>

* Mean ± S.D.

The tumor incidence and average survival times are indicated in Table 1. Thyroidectomy produced a small reduction in the tumor induction time compared to that in the euthyroid rats.

Rats made hyperthyroid by thyroid feeding had a reduced tumor incidence. The average induction time was the same as for thyroidectomized rats. Because of the variability, the survival times of the various groups were not considered to be significantly different.

The metabolic rates of the various treatment groups are summarized in Table 2. Thyroid feeding increased the metabolic rate while thyroidectomy resulted in little or no reduction in the metabolic rate compared to the reduction of the euthyroid rats. The injection of MCA alone caused a small reduction in the metabolic rate of euthyroid rats but had no effect on the metabolic rate of thyroidectomized or hyperthyroid rats. The presence of a tumor seemed to increase the metabolic rate of euthyroid rats.

Food intake (Chart 1) was not different in the thyroidectomized and euthyroid groups. The hyperthyroid rats had a significant increase in food and water intake although the food to water ratios were unchanged. In the thyroidectomized rats, water intake was increased and the food to water ratio was depressed. During the 1st week of treatment, and again during the terminal week, food and water intakes were extremely variable in contrast to the uniform intakes throughout most of the life-span of the rats. For this reason, intake measurements for the initial and final 2 weeks of the treatment have not been used to compute the average food and water intakes shown in Chart 1.

In all treatment groups there was a close correlation of the metabolic rate with food intake and body weight.

DISCUSSION

Most studies attempting to elucidate the relationship between thyroid activity and cancer have investigated the influence of a systemically administered carcinogenic agent on mammary cancer. Since the mammary gland is a hormonally responsive tissue, any perturbation in the hormonal balance may influence the pathogenesis of mammary tumors in a complex way, making interpretation of the results difficult. In this study, a minimal carcinogenic dose of MCA was administered s.c. so as to induce tumors only at the site of injection. Thus the tumor incidence, induction time, and growth rate could be determined. Since the s.c. tissue is not known to be a specific target tissue for hormonal action, the carcinogenic response is more directly related to the systemic changes induced by the altered thyroid state. The observation that thyroidectomy produces little or no change in the incidence of MCA-induced tumors is, therefore, not in contradiction to the observations of Eskin et al. (4). They found that the systemic administration of 7,12-dimethylbenz[a]anthracene to rats whose thyroids had been suppressed by propylthiouracil, resulted in an

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Av. metabolic rate (ml O₂/min/100 g body wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid rats</td>
<td>1.3 ± 0.1*</td>
</tr>
<tr>
<td>Thyroidectomized rats</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Hyperthyroid rats</td>
<td>2.1 ± 0.7</td>
</tr>
<tr>
<td>Normal rats (euthyroid rats bearing a transplanted tumor)</td>
<td>1.4 ± 0.2</td>
</tr>
</tbody>
</table>

* Mean ± S.D.
increased number of tumors per rat and a shorter induction time compared to euthyroid rats. Jull and Huggins (7), using systemically administered MCA, noted that in the thyroidectomized rats only 7 of the 12 animals developed tumors, with the mean induction time nearly twice that of the euthyroid rats. Although this study showed no change in the average induction time comparing thyroidectomized with euthyroid rats, there was a slight decrease in the tumor incidence of the thyroidectomized group. Jull and Huggins (7) also found that a small (0.5-mg) daily dose of L-thyroxine did not change the tumor incidence compared to euthyroid rats; larger doses (1 mg/day) significantly reduced the tumor incidence. In this study, a similar reduction in tumor incidence was observed in rats made hyperthyroid by feeding thyroid powder.

Reports of clinical studies indicate that hyperthyroid women have a reduced incidence of breast cancer compared to hypothyroid women (2) and that the treatment of women with thyroid hormone may be an appropriate prophylactic therapy following definitive treatment for breast carcinoma (9).

Griem and Stein (6) and Du Sault (3) report that mice with mammary cancers have an increased proportion of tumor control when the mice receive systemic L-thyroxine, starting prior to the therapy and continued throughout the radiation treatment. A small clinical trial (4 cases) quoted by Griem and Stein (6) supports these conclusions by reporting an increased local control for patients receiving concomitant radiation therapy and thyroid supplement.

The euthyroid rats developed a moderate but consistent increase in metabolic rate after the development of palpable tumors. A similar increase was also found in non-MCA-treated rats after they had received a transplanted tumor. Morrison (11, 12) suggested that the increased energy expended by the tumor-bearing rats was a result of the less efficient end product of tumor metabolism, lactic acid production.

The MCA alone induced a slight depression in the metabolic rate of the euthyroid rats. Newman and Moon (14) found that, during MCA administration, thyroid secretory activity was depressed but returned essentially to normal levels when the MCA-containing diet was discontinued. Since no metabolic rates were measured, it is not clear whether there was any persistent depression of metabolic rate of the treated rats.

When the metabolic rate was expressed per unit of body weight, thyroidectomy resulted in only a small decrease. However, the thyroidectomized rats tended to be obese and somewhat myxedematous, so that if the metabolic rate had been expressed in units of body nitrogen a significant reduction might have been seen.

Thyroid feeding significantly increased the metabolic rate and was consistent with the correlation observed by Jull and Huggins (7) in which hyperthyroid rats developed fewer chemically induced tumors.

Food intake expressed as a function of body weight was closely correlated with the metabolic rate in all experimental groups. Water intake was increased in the thyroidectomized rats. Morrison (10, 11, 13) observed a polydipsia and polyuria in rats bearing a Walker 256 carcinoma. The water intake in this study did not indicate a significant difference in any of the treatment groups before or after the development of palpable tumors, but this could have been due to the units (per g body weight per day) used to express the data.

The present studies support an inverse correlation between metabolic rate and tumor incidence but fail to show a significant effect of food intake, as some investigators (7, 14) have suggested.

REFERENCES

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