Physiological Disposition of Pentobarbital in Tumor-bearing Mice

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SUMMARY

Pentobarbital depressed macromolecular synthesis in Ehrlich ascites cells in vitro, and this depression was proportional to a decrease in oxygen consumption. However, survival time of animals bearing Ehrlich ascites cells was unaffected by pentobarbital. The acute toxicity of the drug was greatly enhanced by the presence of the tumor. Sleeping time was prolonged in mice carrying the following tumors: Ehrlich ascites, Sarcoma 180 ascites, and Yancey plasma cell solid. Seven-day Ehrlich ascites tumor-bearing animals treated with pentobarbital slept about three times longer than normal mice, but both groups awoke at the same plasma levels of the unbound drug. The plasma half-life of unchanged pentobarbital was about four times as long in tumor-bearing mice as it was in controls. No qualitative difference in catabolism other than rate was detected. Renal excretion of unchanged pentobarbital in tumor-bearing animals was 50% of control animals during the first 4 hr. In tumor-bearing mice the sleeping time of the nonmetabolite barbiturate, barbital, was identical with that in normal animals. These data suggest that the tumor affected mainly pentobarbital metabolism. Tumor-bearing mice still responded to the pharmacological challenge of phenobarbital with the apparent induction of drug metabolizing enzymes. The prolonged pentobarbital sleeping time in tumor-bearing mice required the development of some type of tumor-host relationship.

INTRODUCTION

There have been numerous studies suggesting that barbiturates and other anesthetic, narcotic, and tranquilizing drugs are cytotoxic or antimitotic in many diverse organisms and cell types (cf. Ref. 2 for a review). Pentobarbital has been reported specifically to inhibit DNA synthesis in Ehrlich ascites cells (4), and hydrogen bonding between barbiturates and substituted purine bases has been demonstrated in vitro (24, 25). Our interest in the barbiturates as structural analogs of pyrimidines in microorganisms (26–28) led us to reexamine these inhibitory effects of barbiturates in order to determine their potential usefulness as antitumor agents.

During these studies it became apparent that the pharmacological actions of pentobarbital were greatly enhanced in tumor-bearing compared to normal mice, as had been reported for other drugs (14, 22, 29, 34–36, 44, 45). Since this altered response frequently was based on impaired drug metabolism, it also became of interest to characterize the role of tumor growth on the pharmacokinetics of pentobarbital (5).

This paper presents evidence that pentobarbital does inhibit DNA synthesis in Ehrlich ascites cells in vitro, but the effect is not specific and the drug acts as a general metabolic depressant. The drug is more toxic to Ehrlich ascites tumor-bearing mice than to normal mice and this toxicity is primarily related to impaired drug metabolism, a consequence of the development of a tumor-host relationship.

MATERIALS AND METHODS

Animals and Tumors. Male Swiss albino ICR mice weighing 25 to 35 g were used in all metabolism studies and to carry the Ehrlich and Sarcoma 180 ascites tumors. The mice were obtained either from Hazelton-Cariba, Inc., Burtonville, Md., or from Flow Laboratories, Rockville, Md. All animals were kept in plastic cages and fed a standard Purina laboratory chow diet (Ralston-Purina Co., St. Louis, Mo.) and water ad libitum. The Ehrlich ascites carcinoma has been maintained in this laboratory for 8 years and was originally obtained from the Department of Pharmacology, Yale University, New Haven, Conn. The tumor was transplanted to mice routinely every 6 days by i.p. injection of approximately 1 million washed cells. The mean survival time of the tumor-bearing animals was 12.9 days, considering the day of transplantation as Day 0. We carried these cells through 132 serial transplantations during the course of these experiments. The Sarcoma 180 ascites tumor has been maintained in this laboratory for the past 5 years and was also obtained from the Department of Pharmacology, Yale University. This tumor was maintained in the same way as the Ehrlich ascites tumor. BALB/c x A F1 mice carrying the Yancey plasma cell solid tumor were the generous gift of Dr. Richard H.
Chemicals and Supplies. The following nonradioactive chemicals were purchased: PPO and POPPOP from Packard Instrument Co., Downers Grove, Ill.; Omnifluor from New England Nuclear, Boston, Mass.; naphthalene from Eastman Organic Chemicals, Rochester, N. Y.; pentobarbital sodium from either New York Quinine and Chemical Works, New York, N. Y. or Abbott Laboratories North Chicago, Ill.; phenobarbital from either Abbott Laboratories or Merck & Co., Inc., Rahway, N. J.; sodium barbital from Fisher Scientific Co., Pittsburgh, Pa. All other nonradioactive chemicals were of analytical purity and were obtained from Fisher Scientific Co. The following radioactive compounds were purchased from New England Nuclear: \([\text{[2-}^{14}\text{C]}\text{thymidine (43.7 mCi/m mole), [2-}^{14}\text{C]}\text{uridine (55.5 mCi/m mole), L-}\left[{\text{U-}}^{14}\text{C}\right]\text{leucine (254 mCi/m mole), and [2-}^{14}\text{C]}\text{pentobarbital (3.23 mCi/m mole).}

Heparinized capillary tubes (critocaps) and crotoseals were purchased from Arthur H. Thomas Co., Philadelphia, Pa. All other supplies were obtained from Fisher Scientific Co.

Measurement of Radioactivity. The measurement of radioactivity was carried out by placing the radioactive samples in approximately 10 ml of liquid scintillation fluid in glass counting vials. The scintillation fluid used was that described by Bray (8) and consisted of dioxane:ethylene glycol:methanol (41.3:1:5, by volume), containing naphthalene (6%), PPO (0.4%), and POPPOP (0.02%). Radioactivity was measured in a Beckman DPM-100 liquid scintillation spectrometer. Counting efficiency was determined by the external standard method of Wang and Willis (41). The efficiency for \(^{14}\text{C}\) ranged between 60 and 88%.

Incorporation of Radioactivity by Ehrlich Ascites Cells Incubated in Vitro. Ehrlich ascites cells were obtained from the peritoneal cavity of mice, washed, freed of blood by differential hemolysis (11), and suspended in calcium-free buffer (33), pH 7.4, to an approximate concentration of 1 million cells/ml. This buffer also contained pentobarbital at concentrations and the appropriate isotope nucleic acid or protein precursor. The cell suspensions were then incubated at 37°C in separate flasks in a shaking water bath, and aliquots were removed at 30-min intervals throughout a 2-hr period. The cells in these aliquots were precipitated with cold 10% trichloroacetic acid and analyzed for radioactivity on membrane filters according to the method of Brown et al. (9). It was ascertained that \([2-^{14}\text{C]}\text{thymidine incorporation into acid precipitates was an index of DNA synthesis; [2-}^{14}\text{C]}\text{uridine incorporation was a measure of RNA synthesis; and L-}\left[{\text{U-}}^{14}\text{C}\right]\text{leucine was an index of total protein synthesis. Incorporation of these precursors into Ehrlich ascites cells was linear over the period of study in the absence of drug.}

Oxygen consumption of washed Ehrlich ascites cells was measured in a Warburg apparatus according to the standard manometric techniques described by Umbreit et al. (40). Protein was estimated by the biuret reaction as described by Gornall et al. (16).

Estimation of Sleeping Time in Mice. Sleeping time was defined as the time between the loss and return of the righting reflex after an i.p. injection of either pentobarbital (60 mg/kg) or barbital (300 mg/kg). In some experiments, the dose of pentobarbital to tumor-bearing mice was based on the body weights on the day after tumor transplantation. The animal was considered to have lost its righting reflex when it could no longer turn itself over after being placed on its back. Conversely, the mouse was deemed to have regained its righting reflex when it could right itself 4 times within 2 min.

The Fate of \([2-^{14}\text{C]}\text{Pentobarbital in Mice Bearing the Ehrlich Ascites Tumor. Mice bearing the Ehrlich ascites tumor 7 days after transplantation of approximately 1 million cells and their normal controls were given i.p. injections of \([2-^{14}\text{C]}\text{pentobarbital (60 mg/kg; 333 mCi/kg). At intervals, usually 30, 60, 90, 120, 150, or 240 min after dosing, blood was drawn from the periorbital space using heparinized capillary tubes according to the method of Riley (32), and plasma was obtained by centrifugation. Ten-μl samples of plasma were transferred to individual scintillation vials and counted for radioactivity as previously described. The metabolism of \([2-^{14}\text{C]}\text{pentobarbital was determined by chromatographic separation of \([2-^{14}\text{C]}\text{pentobarbital from its radioactively labeled metabolites in both plasma and urine. Normal and 7-day Ehrlich ascites tumor-bearing mice were given injections of \([2-^{14}\text{C]}\text{pentobarbital and plasma was obtained at intervals as described previously. Urine was collected in the following manner. After a dosing with \([2-^{14}\text{C]}\text{pentobarbital, the anesthetized mice were placed on separate grids over 600-ml beakers. After 240 min, the mice were sacrificed, the bladders were removed, and the urine was added to any urine already in the beakers. The total volume of urine plus water used to wash the beakers was recorded. Ten μl of plasma or urine were chromatographed with 150 μg of carrier pentobarbital on Whatman No. 3 paper at 20–25°C using the solvent system of Titus and Weiss (38) [n-butyl alcohol:1% ammonium hydroxide (1:1, v/v)]. The chromatogram was developed by the descending technique for about 12 hr during which time the solvent front moved 30 to 40 cm. In this system unchanged pentobarbital migrated near the front (RF 0.9), whereas the more polar metabolites of pentobarbital remained closer to the origin. After development, the chromatograms were cut accordingly by the RF's for each sample and counted for total radioactivity. The radioactivity for each block was recorded, and the total radioactivity on the chromatogram was then estimated. After correction for background, the \(^{14}\text{C}\) activity associated with unchanged pentobarbital was calculated as a percentage of the total. The absolute amount of unchanged pentobarbital thus identified in plasma was calculated from its specific activity.}

Plasma Protein Binding of Pentobarbital. The determination of plasma protein binding of pentobarbital was carried out by a modification of the method of Toribara et al. (39). One-ml aliquots of plasma from normal and tumor-bearing mice were incubated for 1 hr at 37°C with 1 μCi of \([2-^{14}\text{C]}\text{pentobarbital at the concentration of 2.0} \times 10^{-4} \text{M. After incubation the tubes were chilled on ice and 0.5-ml aliquots of the plasma were inserted into dry, opened
dialysis bags. The bags were bent in a U-shape with the plasma at the bottom and placed in stoppered centrifuge tubes with the ends of the bags held in place by the stoppers. These tubes were then centrifuged for 3.5 hr at 1000 \( \times g \) at 4\(^{\circ}\). Ten-\( \mu \)l aliquots of both the ultrafiltrate and the fluid retained in the bags were placed in separate scintillation vials and counted for radioactivity. The percentage of pentobarbital bound to the plasma protein was determined by the following formula:

\[
\text{% of pentobarbital bound} = \left[1 - \left(\frac{\text{cpm in ultrafiltrate}}{\text{cpm in fluid retained}}\right)\right] \times 100
\]

RESULTS

**The Cytotoxicity of Pentobarbital in Ehrlich Ascites Cells in Vitro.** Baserga and Weiss (4) reported that pentobarbital specifically inhibited DNA synthesis in Ehrlich ascites cells. Our results indicate a progressive inhibition of incorporation of precursor into macromolecules, and of oxygen consumption in Ehrlich ascites cells incubated in vitro with pentobarbital (Chart 1). In addition, a close quantitative relationship was found to exist between the drug-induced decrease in oxygen consumption and the incorporation of [2-\( ^{14} \text{C} \)]thymidine, [2-\( ^{14} \text{C} \)]uridine, or L-[\(-^4 \text{C} \)]leucine into DNA, RNA, or protein, respectively, as the concentration of pentobarbital in the incubation medium was increased (Chart 2). The data suggest that the in vitro depression by pentobarbital of radioactivity incorporated into the DNA, RNA, and protein of the Ehrlich ascites cells was secondary to the well-known depressant effects of the drug on cellular metabolism, thus contrasting with the findings of Baserga and Weiss (4).

**Effect of Pentobarbital on Tumor Growth.** To determine whether these effects of pentobarbital on macromolecular synthesis of ascites cells could be exploited for chemotherapy, the drug was tested for carcinostatic activity. Pentobarbital at 3 different dose levels did not prolong the survival of these Ehrlich ascites tumor-bearing mice (Table 1). In fact, the survival decreased with increasing daily doses of the drug. Furthermore, the weight of the Ehrlich ascites cells recovered from 7-day tumor-bearing mice was not decreased by pentobarbital treatment, being 1.38 ± 0.21 and 1.26 ± 0.13 (in g ± S.E.) for the 0.9% NaCl solution- and drug-treated animals, respectively.

**The Toxicity of Pentobarbital in Mice with the Ehrlich Ascites Tumor.** In normal mice the acute i.p. lethal dose to 50% of the animals of pentobarbital was 125 mg/kg, a value that is similar to those reported in the literature (10, 18, 42). In mice with the 7-day Ehrlich ascites tumor the corresponding dose was 78 mg/kg, a reduction of approximately 40% (Chart 3).

When normal or mice bearing 3-, 5- or 7-day tumors were given injections i.p. of pentobarbital (60 mg/kg), both groups of animals lost the righting reflex within 3 to 4 min. However, following pentobarbital treatment, the sleeping time of mice with this tumor 7 days after transplantation was nearly 2.5 times that of normal mice similarly treated (Table 2). Furthermore, it is also seen in Table 2 that this increase in pentobarbital sleeping time was not unique for
Chart 3. Acute i.p. lethal dose to 50% of the animals of pentobarbital in mice with the Ehrlich ascites tumor. O. normal mice; x. tumor-bearing mice. The probit transformation and values for lethal dose to 50% of the animals were determined as described in the textbook of Goldstein et al. (15). Seven days after an i.p. injection of $10^6$ Ehrlich ascites cells or a corresponding volume of 0.9% NaCl solution to normal mice, animals (5/group) were given injections of pentobarbital at the doses indicated. Other tumor-bearing mice were not given injections and they served as controls. Twelve hr after the mice were dosed, the cages were inspected and the fraction of dead animals per group was recorded.

Table 2
Pentobarbital sleeping times in normal and tumor-bearing mice
On the days indicated, all mice (10/group) received an i.p. injection of pentobarbital (60 mg/kg) and the sleeping times were recorded.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Tumor</th>
<th>Day</th>
<th>Normal mice (min)</th>
<th>Tumor-bearing mice (min)</th>
<th>% control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ehrlich ascites</td>
<td>3</td>
<td>81 ± 9</td>
<td>84 ± 7</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>73 ± 7</td>
<td>93 ± 7</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>66 ± 9</td>
<td>159 ± 26</td>
<td>241</td>
</tr>
<tr>
<td>2</td>
<td>Sarcoma 180 ascites</td>
<td>3</td>
<td>53 ± 6</td>
<td>53 ± 6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>42 ± 6</td>
<td>60 ± 8</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>46 ± 6</td>
<td>74 ± 4</td>
<td>161</td>
</tr>
<tr>
<td>3</td>
<td>Yancey plasma cell solid</td>
<td>3</td>
<td>64 ± 3</td>
<td>61 ± 4</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>52 ± 5</td>
<td>60 ± 8</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>43 ± 6</td>
<td>150 ± 13</td>
<td>349</td>
</tr>
</tbody>
</table>

a Mean ± S.E.

The Fate of Pentobarbital in Ehrlich Ascites Tumor-bearing Mice. After i.p. administration of [2-$^{14}$C]pentobarbital to Ehrlich ascites tumor-bearing mice, the radioactivity in the peritoneal fluid was greater than that in the plasma at 30 min, but at 90, 150, and 240 min after dosing it reached equilibrium values of about 0.9 (Chart 4A). The distribution ratio of radioactivity between ascites fluid and ascites cells was about 1.3 during this time period (Chart 4B).

Normal mice cleared total radioactivity and unchanged pentobarbital from the plasma faster than did the tumor-bearing mice (Table 3). Thus, by 4 hr after dosing, only 12% of the 30-min $^{14}$C levels remained in the plasma of normal mice, whereas for tumor-bearing animals the corresponding level of radioactivity was still 67%. The plasma half-lives for total radioactivity were 61 and 370 min for the normal and tumor-bearing mice, respectively. For unchanged pentobarbital in the plasma after 4 hr, the concentration was only 2% of the 30-min plasma level in normal mice, but for tumor-bearing mice 26% of the 30-min value remained. The half-lives of the unchanged drug were 37 and 127 min in these animals, respectively.

Chart 4. Distribution of radioactivity between ascites fluid and plasma (A) and between ascites fluid and ascites cells (B) in Ehrlich ascites tumor-bearing mice after receiving [2-$^{14}$C]pentobarbital. Seven-day tumor-bearing mice were given injections i.p. of [2-$^{14}$C]pentobarbital. Plasma and ascites fluid and cells were obtained at the times indicated and counted for radioactivity. Points, mean; bars, range of values.
periorbital space into heparinized capillary tubes at the times indicated. Plasma was obtained by centrifugation. Plasma aliquots were counted for total radioactivity and were spotted on Whatman No. 3 paper for chromatography as described in “Materials and Methods.”

The chromatographic profiles of the urines were obtained by spotting 50% of the total radioactivity at the return of the righting reflex in control and tumor-bearing mice. Therefore, the urinary excretion of unchanged pentobarbital was 14.5% of the administered dose in the control mice, whereas for the tumor-bearing mice it was 6.8%.

**Waking Plasma Levels of Pentobarbital in Control and Ehrlich Ascites Tumor-bearing Mice following Administration of [2-14C]Pentobarbital.** Although the time required for the return of the righting reflex in tumor-bearing animals was approximately 3 times greater than that observed in control mice, the plasma levels of pentobarbital or its labeled metabolic products at the return of the righting reflex in control and tumor-bearing mice were similar (Table 4). Approximately 50% of the total radioactivity at this time was unchanged pentobarbital in both groups of mice. The plasma protein concentrations were 6.6 and 5.4 g/100 ml in normal and 7-day tumor-bearing animals, respectively, and the percentages (±S.E.) of [2-14C]pentobarbital bound to the plasma protein were 56.2 ±1.2 and 35.8 ± 5.4 in normal and tumor-bearing mice, respectively. Thus, when the concentration of pentobarbital in plasma was corrected for the fraction of the drug bound, it was found that the waking level of unchanged pentobarbital in the plasma was identical in control and tumor-bearing mice (Table 4).

**Barbital Sleeping Times in Mice with the Ehrlich Ascites Tumor.** In order to distinguish between the roles of metabolism and urinary excretion of drugs in tumor-bearing mice, barbital was used as a comparison since it is excreted almost entirely unchanged by the kidneys (12). Therefore, the sleeping time with this drug depends primarily upon its rate of elimination via the kidney. Control and Ehrlich ascites tumor-bearing mice given injections i.p. of barbital (300 mg/kg) slept for the same length of time whereas, after pentobarbital, 7-day tumor-bearing mice slept approximately 2.5 times longer than did controls (Table 5).

**Effect of Phenobarbital Pretreatment on Sleeping Time in Tumor-bearing Mice.** Ehrlich ascites tumor-bearing ani-

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**Table 3**

**Pentobarbital Disposition in Tumor-bearing Mice**

Animals were given i.p. injections of pentobarbital (60 mg/kg body weight and containing 10 μCi[2-14C]pentobarbital). Blood was drawn from the periorbital space into heparinized capillary tubes at the times indicated. Plasma was obtained by centrifugation. Plasma aliquots were counted for total radioactivity and were spotted on Whatman No. 3 paper for chromatography as described in “Materials and Methods.”

<table>
<thead>
<tr>
<th>Time after dosing (min)</th>
<th>Total plasma ¹⁴C radioactivity (dpm x 10⁻⁵/ml)</th>
<th>% of plasma radioactivity associated with metabolites</th>
<th>Total unchanged pentobarbital (μg/ml)</th>
<th>Tumor-bearing mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>6.36 ± 0.35</td>
<td>27.5 ± 9.0</td>
<td>38.6 ± 5.6</td>
<td>36.2 ± 1.2</td>
</tr>
<tr>
<td>90</td>
<td>4.24 ± 0.63</td>
<td>72.5 ± 1.3</td>
<td>9.7 ± 1.7</td>
<td>27.8 ± 2.2</td>
</tr>
<tr>
<td>150</td>
<td>2.27 ± 0.56</td>
<td>85.9 ± 0.7</td>
<td>2.55 ± 0.34</td>
<td>21.0 ± 4.5</td>
</tr>
<tr>
<td>240</td>
<td>0.78 ± 0.18</td>
<td>89.0 ± 0.5</td>
<td>0.69 ± 0.09</td>
<td>9.37 ± 4.77</td>
</tr>
</tbody>
</table>

Plasma t₅₀ (min) 61 37 370 127

* Mean ± S.E.

---

**Table 4**

**Plasma levels of pentobarbital at the return of the righting reflex in normal and Ehrlich ascites tumor-bearing mice**

Seven-day tumor-bearing mice were given i.p. injections of [2-14C]pentobarbital (60 mg/kg; 333 μCi/kg). The time from the loss to the return of the righting reflex was significantly different (p < 0.05) between normal and tumor-bearing animals. There was no statistical difference between normal and tumor-bearing mice in total plasma radioactivity or the percentage remaining as unchanged pentobarbital. Free pentobarbital was determined from the total minus percentage bound. Determination of the in vitro binding of [2-14C]pentobarbital is described in “Materials and Methods.”

<table>
<thead>
<tr>
<th>Animals</th>
<th>Time for return of the righting reflex (min)</th>
<th>Radioactivity Total dpm x 10⁻⁵/ml</th>
<th>% identified as pentobarbital</th>
<th>Pentobarbital (μg/ml) Total Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mice</td>
<td>41 ± 7</td>
<td>6.15 ± 0.38</td>
<td>58.4 ± 5.4</td>
<td>29.8 ± 2.6</td>
</tr>
<tr>
<td>Tumor-bearing mice</td>
<td>153 ± 35</td>
<td>5.36 ± 0.17</td>
<td>49.7 ± 1.9</td>
<td>21.0 ± 0.7</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
mals, which had been pretreated on days 4, 5, and 6 of tumor growth with phenobarbital (80 mg/kg, i.p.) and then challenged with an anesthetic dose of pentobarbital on Day 7, slept for only 24 ± 4 min as compared to 334 ± 14 min for the nonphenobarbital pretreated tumor-bearing controls. Thus, induction of microsomal drug-metabolizing enzymes with phenobarbital had markedly reduced the sleeping time, indicating that the observed decrease in metabolism was apparently not due to a permanent impairment of the liver cells caused by the tumor.

Effect of Ehrlich Ascites Cells and Ascites Fluid on the Pentobarbital Sleeping Time of Normal Mice. For evaluation of possible factors that may be responsible for the increased sleeping time in tumor-bearing animals, ascites fluid and, separately, ascites cells were injected into normal mice. For these experiments, ascites cells and fluid were collected from groups of 5-day tumor-bearing mice. After centrifugation, the packed cells were suspended in 0.9% NaCl solution such that every 2.5 ml of this suspension contained approximately 1.5 g of tumor cells. Two groups of 8 normal mice each were then given i.p. injection of either 2.5 ml of the cell suspension or an equivalent volume of 0.9% NaCl solution. Two hr thereafter, all mice received pentobarbital (60 mg/kg, i.p.), and the sleeping times were recorded. As can be seen in Table 6, the mice treated with ascites fluid or packed cells did not show the notable increase in sleeping time characteristic of mice in which the tumor has grown for 7 days. This experiment therefore demonstrated that the increased sleeping time could not be related to an immediate effect of the tumor but instead depended on the development of some type of tumor-host relationship.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day of tumor</th>
<th>Normal mice</th>
<th>Tumor-bearing mice</th>
<th>% control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentobarbital</td>
<td>5</td>
<td>73 ± 7*</td>
<td>93 ± 7</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>66 ± 9</td>
<td>159 ± 26*</td>
<td>241</td>
</tr>
<tr>
<td>Barbital</td>
<td>5</td>
<td>447 ± 62</td>
<td>456 ± 39</td>
<td>102</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>467 ± 73</td>
<td>467 ± 51</td>
<td>100</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
* p < 0.01

Table 5
Pentobarbital and barbital sleeping times of normal and Ehrlich ascites tumor-bearing mice

Normal and 5- and 7-day tumor-bearing mice (10 per group) were given i.p. injections of either pentobarbital (60 mg/kg) or barbital (300 mg/kg).

Table 6
Pentobarbital sleeping times of mice 2 hr after i.p. injection of Ehrlich ascites cells

See text for experimental details.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Sleeping time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>95 ± 11*</td>
</tr>
<tr>
<td>2</td>
<td>0.9% NaCl solution (2.5 ml)</td>
<td>84 ± 13</td>
</tr>
<tr>
<td>3</td>
<td>Tumor cell suspension (2.5 ml)</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>4</td>
<td>7-day tumor-bearing mice</td>
<td>178 ± 32</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
have been examined for their contribution to the exaggerated response of tumor-bearing animals to pentobarbital. A significant difference in brain sensitivity to the anesthetic effect of pentobarbital in the 2 groups of animals has been reported previously (13, 36). However, in our experiments, since the waking levels of pentobarbital in tumor-bearing and control animals were almost identical, we are forced to exclude this possibility. The mere presence of the tumor per se, as suggested by Mattes et al. (29), did not prolong sleeping time following pentobarbital administration, since a period of time after tumor implantation was required before the sleeping time was significantly increased. Therefore, some type of tumor-host relationship was involved in developing the inhibition of drug metabolism.

In these experiments, and those of others (22, 36), induction of microsomal enzymes by phenobarbital was still demonstrable in tumor-bearing animals, thus suggesting that the tumor effect on metabolism is not irreversible. Therefore, if a tumor-produced substance is responsible for the depressed metabolism (6, 17, 19, 21, 31, 46), its action can be counteracted. Rosso et al. (36) and Bartosek et al. (3) have recently presented evidence suggesting that there may be some factor in the serum of tumor-bearing rats that can apparently depress hepatic drug metabolism.

REFERENCES


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