Modification of pH of Normal and Malignant Mouse Tissue by Hydralazine and Glucose, with and without Breathing of 5% CO₂ and 95% Air¹

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ABSTRACT

We investigated the effects of hydralazine and glucose on the pH of several normal tissues and on RIF-1 radiation induced fibrosarcomas of mice that were breathing either air or a mixture of 5% CO₂ and 95% air. Our goal was to investigate techniques to maximize the pH differences between normal tissue and tumors. Hydralazine (10 mg/kg) had only minor effects on pH of tumors and muscle; it lowered liver and kidney pH. In animals additionally breathing the air-gas mixture, pH was further lowered in liver and kidney. Glucose (0.6 mg/kg) by itself caused a major reduction in pH of liver, kidney, and adipose tissue. Only minor effects were seen in tumors and muscle. Causing the animals to breathe the gas-air mixture 4 h after glucose injection partially reversed the glucose effect in all normal tissues but caused additional reductions in tumors, particularly in small (<0.7 cm³) lesions. Thus, this last combination led to maximum differential between the pH of normal tissue and of tumor.

INTRODUCTION

The cytotoxic action of many drugs is enhanced at mildly elevated temperatures (1). Most of the experiments that have shown such enhancement, however, were performed at pH 7.4. We have recently demonstrated that for specific anticancer agents, hyperthermic activity can be enhanced manifold at pH values in the range of 6.5 and 7.0 (2). Such pH exists in the interior of some, although not all, solid tumors (3, 4). This suggests a rationale for the combination of whole body hyperthermia with chemotherapy, namely, use of drugs with activity that is enhanced at low pH. Presumably, a degree of specificity of cytotoxic action would then be achieved, particularly in the interior of larger, solid lesions. Since it is these lesions that frequently are resistant to drug treatment, an increase in responses to chemotherapy might be expected. Furthermore, favorable pH differences between tumors and surrounding normal tissue should also be of considerable advantage when systemic chemotherapy is combined with localized hyperthermia or when hyperthermia is used as an adjuvant to radiation therapy.

Unfortunately, the pH differences between normal tissue and tumor are frequently not large (3–5). Furthermore, because of blood flow heterogeneity, portions of many tumors may not be at sufficiently low pH, and well perfused tumors or portions of such tumors may be at a pH not different from that of the surrounding normal tissue. For these reasons, pharmacological methods of manipulating and increasing the difference between intratumor and critical normal tissue pH would be highly desirable. Perhaps the easiest technique of doing so (conceptually at least) is via the use of agents that affect blood flow. The low pH in the interior of tumors presumably reflects two factors: the reduced ability of such tumors to exchange blood with these surroundings, leading to the accumulation of CO₂; and the increased use by tumor cells of anaerobic metabolic pathways (because of the absence of adequate amounts of oxygen). The latter effect leads to increased production and increased accumulation of lactic acid. Any additional reduction in intratumor blood flow, provided it does not completely shut down cellular metabolism, would enhance both of these effects. This, in turn, might lead to lower pH. For the technique to be useful, however, changes in pH of various normal tissues need to be examined. This is particularly true for whole body hyperthermia; all tissues are heated and therefore at risk. Any unforeseen reduction in the pH of one or more critical normal tissues might have fatal consequences.

We have started an investigation to determine methods of attempting to increase the pH differential between tumors and normal tissue. As part of this study, we have examined pH changes in RIF-1 tumors that are induced by a combination of pharmacological manipulation and having the mice breathe 5% CO₂ plus 95% air. The rationale for the use of the gas-air mixture is the possibility that tumor tissue cannot respond to increased CO₂ concentration as readily as a normal tissue. Here, we report on the effects of the vasodilator, hydralazine, and on the use of glucose. In addition to tumor pH, we have measured the pH of several normal tissues: muscle, fat, kidney, and liver. As stated before, our goal was to attempt to develop techniques to maximize the differences between intratumor pH and that of various normal tissues. Hydralazine was chosen as our initial drug because this agent is known to be an effective vasodilator and its pharmacokinetics and toxicity in humans have been well characterized. We chose glucose because several studies by other investigators have suggested its usefulness as a modifier of pH (reviews in Refs. 4 and 6).

MATERIALS AND METHODS

Animals. Adult male C3H mice were used; these mice were housed six to a cage and maintained on a standard laboratory diet and given tap water ad libitum.

Tumors. We used the radiation-induced fibrosarcoma (RIF-1) (7). Approximately 2 x 10⁶ RIF-1 tumor cells were injected i.d. into the flanks of 11–15-week-old C3H mice obtained from the Stanford specific pathogen free colony. The experiments were performed with two different sizes of tumors: the "small" tumors (<0.70 cm³) were ready 2 weeks after cell injection; while the larger tumors (0.70 cm³) were obtained after 3 or 4 weeks of growth.

Hydralazine, Glucose, and Anesthesia. Thirty min prior to initiation of pH measurements, 10 mg/kg of hydralazine HCl (CIBA Pharmaceutical Co.) were injected i.p. This dose was chosen because lower doses did not modify either tumor or normal tissue appreciably. Ten min before the pH measurement commenced, the mice were anesthetized with 67.5 mg/kg of Nembutal sodium solution (Abbott Laboratories). Glucose was administered i.p. 4 h before anesthesia; control experiments indicated that this timing yielded maximum or near maximum pH changes in tumor and liver pH.

5% CO₂-95% Air Inhalation. For the inhalation of 5% CO₂ and 95% air, a plastic chamber was made (approximate dimensions, 26 x 18 x 3

Received 8/3/87; revised 12/4/87; accepted 12/11/87.

The cost of publication of this article was defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ This work supported by Grants CA-04542 and CA-19386 from the National Cancer Institute.

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CM) and supplied with inlet and outlet holes with 1-cm diameters at each side of the chamber. Humidified 5% CO₂ and 95% air was piped into the chamber at a rate of approximately 5 l/min through tubing at 25°C (room temperature). The cover of the chamber and the tube connections were sealed with silicone oil.

pH Measurements. The pH of liver and kidney (right side) of normal male C3H and RIF-1 tumors was measured using miniature capillary glass electrodes (Microelectrode, Inc.; type MI408) with a 1-mm-diameter tip. A reference microelectrode (type MI402) was filled with 3 M KCl/liter saturated with AgCl (Fisher Scientific Co.). The electrodes were connected by a high impedance amplifier to a Corning 125 digital pH meter. Stands were made so that the miniature glass capillary electrodes were secured in a horizontal position that allowed continuous monitoring of pH. The electrodes had a 95% response time of less than 3 min. Therefore, following insertion of the electrode to the tissues, 3 min were allowed for the pH readings to stabilize. Readings were then recorded each minute for 20 min and then each 5 min until 30 min elapsed. All experiments were repeated at least twice, with comparable results. Data shown are from individual experiments.

The pH drift in buffer was less than ±0.02 pH unit/h. Electrodes were calibrated by immersion in buffers at pH 6.0, 6.4, 7.0, 7.4, and 8.0 (Fisher Scientific Co.). Recalibration of electrodes was done following each series of tissue measurements. All calibration and tissue pH measurements were carried out at room temperature (25°C).

The microelectrode and reference capillary were connected by a flexible shaft through a hole in a gas chamber which also accommodated a tube for control of gas flow into the chamber (5% CO₂-95% air). The microelectrode was manually inserted into the tissue and the reference capillary was placed in contact with the mouse tail using electrocardiograph electrode cream (Beck-Lee Corp.). Access to internal organs was gained by abdominal incision. Care was taken to avoid damage to major vessels. The microelectrodes were inserted into the anterior lobe of the liver, or the cortex of the kidney parenchyma, in fat along the epididymis and in the gluteal muscle to a depth of 5 mm. For tumor measurements, the probe was inserted to a depth of about 8 mm. This location was not critical. Previous measurements had shown that pH within the RIF-1 tumors implanted in the flanks was constant and within ±0.1 pH unit over 90% of the tumor. Unless otherwise stated, all normal tissues and tumors were used for only one individual, or a series of continuous, pH measurements.

RESULTS

pH of Normal Tissues and of Tumors in Untreated Animals

The pH values of liver, muscle, fat, and kidney as measured in untreated animals are shown as 0 time values in the appropriate charts. For each tissue, 10 animals were used and the data represent the average pH value; standard deviations of the pH values are typically ± 0.02 unit. These values are well within the range of those reported in the literature (4).

Time Course of pH Changes after Drug Injections

The time course of pH changes in tumors and in liver after injection of 0.6 mg/kg of glucose was consistent with that reported by others (see reviews in Refs. 4 and 6). Data are shown in Tables 1 and 2. The maximum effect, i.e., maximum reduction of pH, occurred approximately 4 h after injection. pH returned to control values about 2–3 h later. For this reason, subsequent experiments on the combinations of glucose and gas breathing were started 4 h after the initial glucose injection. Similar data were also obtained for hydralazine; they showed, consistent with results reported in the literature, that the effect of hydralazine was almost immediate. The effect then decayed with a half-time of approximately 2 h. These control experiments demonstrated typical drug responses and showed that pH measurements were, in general, not artifacts of the measurement technique. Results from two hydralazine and two glucose experiments are shown in Tables 1 and 2. Experiments involving hydralazine and gas were therefore initiated within the first hour after the hydralazine injection.

Effects of Various Treatments on pH of Normal Tissues

Liver. Fig. 1 shows continuous measurements of pH in the liver of animals treated as described in “Methods and Materials.” Even in control animals given injections only of saline, there was a continuous reduction with time in liver pH from control values of 7.2 to about 6.9 after 33 min of probe insertion. This reduction very likely reflects local tissue damage and the concomitant local reduction in blood flow. In animals breathing the CO₂-air mixture, but not given injections of either glucose or hydralazine, pH fell more rapidly than in controls, showing that the gas was effective in lowering pH. Hydralazine, by itself, reduced the liver pH to a value of about 7.0; during continuous measurement this dropped further to 6.7. The combination of hydralazine and breathing the air-gas mixture did not result in a further reduction of pH. Glucose alone reduced pH from 7.2 to 6.5 and this dropped further to a value of 6.2 by 33 min, again very likely reflecting local tissue damage. If the glucose-loaded animals were also breathing the CO₂-air mixture, then there was a measurable reduction in the glucose effect, i.e., the liver pH increased over that seen in animals given glucose only. During the 3-min equilibration time, pH already changed from 6.5 to 6.8; at the end of the continuous measurement, the livers of the glucose loaded animals not subjected to gas were at pH 6.2; those of CO₂-air breathing mice were at pH 6.5.

Kidney. The pH of the kidneys (Fig. 2) proved to be less sensitive to manipulation than that of the liver. Furthermore, as shown by the saline controls, as well as the saline plus gas controls, pH remained more or less constant during the 33-min electrode insertion period; this indicated that there was less endothelial tissue damage done in the kidney than in the liver. Hydralazine by itself was ineffective in lowering kidney pH; glucose lowered it to pH 6.6 (from the pH 6.8 control value). This low pH was also observed in animals that were given hydralazine and were also breathing CO₂ plus air; glucose loaded animals, however, when breathing the CO₂-air mixture showed an increase in pH over that seen with glucose alone, by about 0.2 pH unit.

<table>
<thead>
<tr>
<th>Table 1 pH of liver</th>
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<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Hydralazine (10 mg/kg)</td>
</tr>
<tr>
<td>Hydralazine (20 mg/kg)</td>
</tr>
<tr>
<td>Glucose (0.6 g/kg)</td>
</tr>
<tr>
<td>Glucose (6 g/kg)</td>
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</tbody>
</table>

* Pooled data; n = 12.
" Mean ± SD; n = 6 for all points (except 0 h); one measurement/animal.
" NM, not measured.

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Table 2 pH of “large” RIF-1 tumors

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0 h</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine (10 mg/kg)</td>
<td>6.8 ± 0.05*</td>
<td>6.7 ± 0.1</td>
<td>6.7 ± 0.1</td>
<td>6.8 ± 0.1</td>
<td>6.9 ± 0.1</td>
<td>6.8 ± 0.1</td>
</tr>
<tr>
<td>Hydralazine (20 mg/kg)</td>
<td>6.5 ± 0.1</td>
<td>6.7 ± 0.1</td>
<td>6.7 ± 0.2</td>
<td>6.8 ± 0.1</td>
<td>6.9 ± 0.1</td>
<td>6.8 ± 0.1</td>
</tr>
<tr>
<td>Glucose (0.6 g/kg)</td>
<td>6.9 ± 0.1</td>
<td>6.8 ± 0.05</td>
<td>6.8 ± 0.1</td>
<td>6.6 ± 0.1</td>
<td>6.8 ± 0.1</td>
<td>6.8 ± 0.1</td>
</tr>
<tr>
<td>Glucose (6 g/kg)</td>
<td>6.7 ± 0.2</td>
<td>6.5 ± 0.1</td>
<td>6.5 ± 0.2</td>
<td>6.5 ± 0.2</td>
<td>6.8 ± 0.1</td>
<td>6.8 ± 0.1</td>
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</table>

* Pooled data; n = 12.
** Mean ± SD. n = 6 for all points (except 0 h); one measurement/animal.

Fig. 1. pH of livers of treated animals. Animals were given injections of glucose at —250 min or hydralazine at —30 min. At —10 min, the animals were anesthetized, and at —3 min, the CO2-air mixture (when applicable) was turned on, and the electrodes inserted. Readings were made at 2-min intervals; at 20 min the CO2-air mixture was turned off. Readings continued for an additional 10 min. Each point represents an average of at least 6 mice. Standard errors ranged from 0.05 to 0.15 pH unit, with most values in the 0.08–0.10 range. •, saline only; □, saline and gas mixture; ○, hydralazine (10 mg/kg); ▬, hydralazine and gas mixture; ▲, glucose (0.6 mg/kg); ◊, glucose and gas mixture.

Fig. 2. pH of kidneys of treated animals. For details, see Fig. 1.

Fig. 3. pH of muscle of treated animals. For details, see Fig. 1.

Fig. 4. pH of fat of treated animals. For details, see Fig. 1.

Muscle. Treatments had only mild effects on muscle pH. None of the treatments caused pH to vary more than ±0.2 about control values. Results are shown in Fig. 3.

Fat. pH of adipose tissue followed the pattern shown by liver and kidney. In Fig. 4, we show only the glucose data. Glucose, by itself, reduced pH to a value of 6.9, and this dropped further during the 30 min of electrode insertion (by approximately 0.2 pH unit), again very likely owing to local tissue damage. Causing the animals to breathe the air-gas mixture again somewhat reversed the glucose effects, raising pH to a value of approximately 7.2.

Effects of Various Treatments on pH of RIF-1 Tumors

“Large” RIF-1 Tumors. The various treatments had only a relatively minor effect on the pH of large tumors. Hydralazine reduced pH from control values by about 0.1 pH unit, as did glucose. Within the 30-min interval, pH in the glucose treated animals remained constant. The combination of glucose and gas, except perhaps for the first 10 min, led to tumor pH not significantly different from that seen with glucose alone. The addition of gas to hydralazine treated animals caused only additional, albeit minor, pH reductions. The data are shown in Fig. 5.

“Small” RIF-1 Tumors. The only treatment that appreciably reduced pH in small RIF-1 tumors was the combination of glucose and gas (Fig. 6). This lowered the pH from control values of 6.8 to 6.5. None of the other treatments modified pH appreciably.

DISCUSSION

The data displayed show that hydralazine (10 mg/kg) by itself had only minor effects on the pH of mouse liver and kidney and no measurable effect on the pH of either small or large RIF-1 tumors implanted in the flanks of C3H mice. The lack of effect on the pH of these tumors is rather surprising. Voorhees and Babbs (8) have shown that in dogs a much lower dose...
of hydralazine (0.5 mg/kg) had a major effect on the blood flow of a transplanted venereal tumor. In hepatoma bearing rats, the same group found that after a similar hydralazine injection, blood flow increased in normal tissue but remained constant in the tumor (9). Ward-Hartley and Jain (10) used a dose of 2 mg/kg of hydralazine to study modification of blood flow in rabbits inoculated with the VX2 carcinoma. Normal tissue blood flow remained constant, while tumor blood flow decreased significantly. If such changes were also to occur in mice, we would expect that these would then be reflected in at least moderate pH changes, although the actual changes in pH would also depend on the metabolic rate of the tumors. Whether the differences between our results and those of the studies just cited were tumor size, species, or location specific remains to be answered. The hydralazine-induced reductions in the pH values for liver and kidney are also somewhat surprising because one might expect that the vasodilator would cause increased blood flow and therefore minimize pH variations in normal tissues. However, the changes due to hydralazine alone were, in any case, small.

Several authors have investigated the use of glucose for the reduction of interstitial pH of tumors and of some normal tissues (reviewed in Refs. 4 and 6). In these studies, doses of glucose varying from 0.05 to 20 g/kg were used, and various methods of administration (i.p., i.v., s.c.) reported. pH reductions of almost 1 pH unit at the very high glucose dose have been observed; two mechanisms for the ability of glucose to lower pH have been suggested. In the presence of adequate or high doses of the sugar, stimulation of glycolysis is expected to lead to an accumulation of lactic acid. Particularly in tumors in which blood flow is relatively sluggish, this should lead to increased acidosis, because the excess lactic acid would not be removed as rapidly as in normal tissue. Indeed, several authors following glucose administration have measured higher levels of lactic acid in tumors than in normal tissues. The other reason for reduction of pH is that the administration of glucose has been shown to reduce blood flow (11). Perhaps the most thorough discussion of this subject is by Calderwood and Dickson (12). These workers used the Yoshida sarcoma and showed that injection of glucose led to a rapid accumulation of lactic acid. They also measured changes in blood flow and demonstrated that the maximum pH change occurred after the change in blood flow. This suggests that both mechanisms interact; only when cells metabolize actively does reduction in blood flow lead to appreciably low pH. Conversely, even when cells utilize glucose rather than oxygen, reduction in blood flow is required for sufficient local accumulation of lactic acid and resultant low pH.

Breathing of 5% CO$_2$-95% air (without glucose or hydralazine) caused pH shifts primarily in the kidney, and to a lesser extent in the liver of the mice. In the RIF-1 tumors none of these manipulations introduced pH reductions of more than 0.2 pH unit. Interestingly, turning off CO$_2$ does not cause the pH to return to control values within the 10 min during which we performed our experiments. This seems at first surprising. Apparently, however, CO$_2$ levels in blood decay relatively slowly and therefore act to maintain pH. One hour after the mice had been removed from the CO$_2$ apparatus, pH had returned to control values (data not shown).

The combination of hydralazine and 5% CO$_2$ was also not very effective in shifting tumor pH; the major effect was on the pH of the kidney. This, in some experiments, was reduced by as much as 1 pH unit. The pH of the liver may also have been reduced. It should again be pointed out that insertion of electrodes is associated with some cellular destruction and local tissue damage. This is very likely the cause of the reduction in recorded liver pH during the time the electrodes remains in this tissue, even in the absence of chemical or gas manipulation. Our liver data, therefore, very likely reflect proton concentrations in the extracellular fluid, with some contamination from intracellular components, as well as some artifacts resulting from local damage to vasculature. Extrapolation of the mouse data to the human situation is very difficult, of course. Differences in tumor and tissue dimensions are particularly troublesome. Nevertheless, the results show that care must be taken if hydralazine is to be used during whole body hyperthermia. Severe liver or kidney toxicity might be encountered, with only mildly increased drug effectiveness against solid tumors. Thus, there might be a reduction in therapeutic ratio. This is of particular concern in view of the frequently voiced suggestion that for whole body hyperthermia, liver toxicity may be treatment limiting. If heating of the liver or kidney can be avoided, as during localized hyperthermia, then the combination of gas and hydralazine might be effective in increasing normal tissue-tumor pH differences. The use of hydralazine then becomes even more attractive because Voorhees and Babbs (8) showed that hydralazine should also facilitate the heating of tumors.

However, our most interesting finding, and one that may indeed have direct clinical implications, relates to the combination of low dose (0.6 mg/kg) glucose and breathing of CO$_2$-air. In all the normal tissues examined, breathing of the air-gas mixture partially reversed the pH reduction that we observed after the administration of glucose alone. In the RIF-1 tumors, however, the opposite occurred; breathing of CO$_2$ further reduced intratumor pH. This was particularly noticeable in the small tumors. Thus, the combination of glucose and gas resulted in any case, small.

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in an appreciable enhancement of the pH differences between all normal tissue and tumor. This effect, if also found in humans, could provide a rationale for improved whole body thermochemotherapy if drugs are used with cytotoxicity that, at the elevated temperature, is strongly dependent on pH (2). Means of monitoring pH noninvasively using magnetic resonance imaging techniques now exist (13, 14); thus, clinical studies to examine this are now feasible. Several other drugs have recently been tested that preferentially modify tumor blood flow in rats (15) and glucose has been used in a preliminary study of human tumors (16). An extensive study achieving optimum pH differential between tumor and normal tissue may be desirable. The data presented here do show that even low doses of glucose, coupled with breathing a nontoxic CO₂-air mixture, can achieve an appreciable effect that should result in improved treatment consequences.

REFERENCES

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