Elevated Blood Lactate Is Not a Primary Cause of Anorexia in Tumor-Bearing Rats

William T. Chance, Ramesh Dayal, Lou Ann Friend, and J. Howard James

Abstract: Tumor-bearing (TB) rats exhibit elevated concentrations of lactate in blood contiguous with the development of anorexia. Continuous intravenous infusion of lactate into non-TB rats reduced food intake at plasma concentrations lower than those observed in anorectic TB rats. Levels of neuropeptide Y (NPY) were elevated in the ventromedial (VMH) and dorsomedial hypothalamic regions of lactate-infused rats. The addition of the enhancer of pyruvate dehydrogenase activity, dichloroacetate (DCA), to the drinking water of TB rats (0.1–0.4%) normalized blood lactate concentration but had no significant effect on anorexia. However, the elevated concentration of NPY in the VMH of anorectic TB rats was also normalized by the DCA treatment. No alterations in regional hypothalamic levels of corticotropin-releasing factor were observed within any treatment conditions. These results suggest that, although hyperlactatemia may be involved in maintaining elevated NPY concentrations in anorectic TB rats, it does not appear to be a significant factor in the etiology of experimental cancer anorexia.

Introduction

Malnutrition has long been known to contribute to morbidity and mortality of cancer patients (1), with Warren identifying anorexia/cachexia as a leading cause of cancer deaths in 1932 (2). In addition to limiting aggressive cancer therapy, malnutrition also reduces immunity, quality of life, and prognosis for disease survival (3–5). Therefore, specifying the causes of cancer anorexia may permit the development of effective therapies for its treatment, resulting in improved clinical outcomes.

Studies in tumor-bearing (TB) animals suggest humoral mediation of anorexia because normal rats that share a portion of circulating blood with anorectic TB rats also share the anorexia (6). In addition, food intake returns rapidly toward normal following resection of a subcutaneous tumor (7), and many of the neurochemical alterations are normalized within 24 h of tumor removal (8). These observations suggest that a circulating anorexigenic factor is either secreted by the tumor or is formed due to tumor-induced biochemical alterations in host metabolism.

One factor that may signal anorexia from tumor to brain is lactic acid. As indicated by the pioneering studies of Warburg (9), tumors are avid consumers of glucose through the anaerobic glycolytic pathway, which produces lactate (10,11). We have observed that rats bearing methylcholanthrene (MCA) sarcomas have elevated circulating concentrations of lactate and that treatments that reduce the severity of the anorexia also reduce circulating levels of lactate (12). Studies in our laboratory also showed that the elevated lactate was normalized following tumor resection and the subsequent increase in food intake (7,8). Lactate has been demonstrated to be taken up by the brain (13) by what appears to be a carrier-mediated saturable transport system (14,15). Thus, an elevation in circulating lactate would be expected to result in increased lactate concentration in the brain. Recent reports indicate that lactate has a potent acute anorectic effect when infused intravenously (iv) in non-TB rats (16,17). In the ventromedial hypothalamus (VMH), lactate has been shown to activate gluoresponsive neurons, that is, those neurons that were excited by physiological increases in glucose (18). The implication of this observation is that high lactate may be interpreted by these neurons as high glucose, which may signal satiety to the TB host. In addition, intraventricular infusion of lactate decreased cFOS activity in the paraventricular hypothalamus, which was elicited by glucoprivation (19), suggesting that this metabolite may also reduce neuronal activity when the glucose level is decreased. The observation that lactate spares glucose as an energy source in neurons (20) also suggests a degree of interchangeability between these substrates in the central nervous system. A putative molecular mechanism for lactate-induced anorexia comes from the recent observation that glucose-sensitive neurons in the arcuate nucleus of the hypothalamus contain neuropeptide Y (NPY), the release of which was hypothesized to increase when glucose concentration was reduced (21). Although the effect of

W. T. Chance and R. Dayal are affiliated with Medical Research Service, Veterans Affairs Medical Center, Cincinnati, OH. W. T. Chance is also affiliated with the Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH 45267-0558. L. A. Friend and J. H. James are affiliated with the Department of Surgery, University of Cincinnati Medical Center, Cincinnati, OH 45267-0558.
lactate on these neurons was not assessed, it seems reasonable to hypothesize that elevated lactate may affect NPY release because lactate may substitute for glucose at glucose-sensitive neurons.

In addition to NPY, hypothalamic corticotropin-releasing factor (CRF) has been implicated in experimental cancer anorexia by evidence suggesting elevated CRF in the arcuate (ARC) and paraventricular (PVN) hypothalamus of TB rats (22). More recent studies suggest that the anorexia of infection and the anorectic effects of cytokines may be mediated in part through elevated neuronal activity of CRF (23,24) in hypothalamic neurons known to control appetite. CRF potently reduces food intake when injected into the third ventricle or hypothalamic tissue (25,26). Furthermore, both immunohistological and intracranial injection studies indicate that CRF interacts with NPY within the PVN (27–29). Therefore, assessment of hypothalamic alterations in NPY and CRF within studies of lactate-induced anorexia may prove very meaningful.

Lactic acidosis can be treated employing dichloroacetate (DCA), which increases the activity of pyruvate dehydrogenase by inhibiting its phosphorylation (30). Thus, treatment of children having malaria-induced lactic acidosis with DCA lowered plasma lactate concentration and increased lactate disposal rate (31). In addition, brain lactate and ischemia were reduced in respective experimental models of ischemia-reperfusion injury and malaria by treatment with DCA (32,33). Therefore, DCA may be helpful in lowering increased circulating lactate in TB rats and provide a means of testing the hypothesis of lactate mediation of cancer anorexia.

In the present studies we tested whether chronic iv infusion of lactate into normal rats elicited anorexia. In addition, we assessed whether treating TB rats with DCA would reduce blood concentrations of lactate and prevent the development of anorexia. We also determined the effects of these treatments on the concentrations of NPY and CRF in the hypothalamus of TB and control rats.

Materials and Methods

Subjects and Procedures

Eighty adult, male, Fischer 344 rats were purchased from Charles River Laboratories (Wilmington, MA) and acclimated to the laboratory environment for at least 1 wk prior to initiation of any experimental procedures. These rats were housed individually in plastic shoebox cages or stainless-steel metabolic cages (experiment 2), with all rats except pair-fed (PF) control animals having ad libitum access to rat chow pellets and tap water. Following the acclimatization period, the rats were divided into groups for three separate experiments. The first experiment determined plasma lactate concentrations in TB and control rats prior to and after the development of anorexia in the TB groups. The second experiment assessed whether iv infusion of sodium lactate would induce anorexia in normal rats. The last study determined whether normalization of hyperlactatemia in anorectic TB rats would result in increased food intake.

Experiment 1: Developmental changes in blood lactate in TB rats. Using a 4-mm trocar, approximately 50 mg of fresh MCA sarcoma was inoculated (sc) at the midscapular region of 17 anesthetized (Halothane, Halocarbon, Inc., Rivers Edge, NJ) rats. This tumor was taken from a donor rat in our tumor colony using aseptic techniques. Twelve additional rats received sham inoculations with the empty trocar and were divided into freely feeding (FF) and PF groups. The PF rats were matched individually to the body weight of TB rats and had daily access only to the amount of chow consumed by the TB pair during the previous 24 h. Food intake and body weight were determined for three of the groups for the next 28 days, at which time the FF group and nine TB rats were euthanized by decapitation. The PF rats were sacrificed 1 day later because their feeding lagged behind their paired TB rats by 1 day. The other group of TB rats (n = 8) were euthanized 14 days after tumor inoculation to permit assessment of biochemical changes prior to the onset of anorexia. As we have observed, the MCA sarcoma typically induces anorexia approximately 21 days following inoculation (34). Fischer 344 rats usually tolerate 5 wk of tumor growth, with severe anorexia being observed by 28 days after inoculation. Following sacrifice, blood was collected in beakers using ethylenediaminetetraacetic acid as an anticoagulant. Following centrifugation (3,000 g, 30 min, 4°C) lactate was determined in plasma using a microfluorometric enzymatic assay, according to published procedures (35).

Experiment 2: Lactate infusion in non-TB rats. To determine whether chronic infusion of lactate would decrease feeding in non-TB rats, following anesthetization (ketamine/xylazine: 80/15 mg/kg, im) silastic catheters were implanted into the external jugular vein of 16 adult, male, Fischer 344 rats using aseptic techniques as we have reported (36). An additional eight rats were anesthetized and subjected to sham surgical procedures, which included occluding one jugular vein. The catheters were connected to a feed-through swivel, which allowed free movement of the rats in the metabolism cages. Following 3 days of infusion of normal saline (2 ml/h), none of the catheterized rats were switched to receiving sodium lactate at an initial concentration of 0.1 M (infusion day 4; 22 mg/h). This concentration was increased to 0.2 and 0.3 M on infusion Days 5 and 6, respectively. On infusion Day 7 the lactate concentration was further increased to 0.6 M and to 1.2 M on infusion Day 8, which was the termination day of the experiment. Concentrations of lactate were increased across days to reflect elevated plasma lactate level noted with increased tumor growth in the first experiment. During these treatments all rats had ad libitum access to rat chow and water. Chow intake was monitored daily, whereas body weight was assessed on infusion Days 0, 2, and 5. At the conclusion of the study, each rat was euthanized by decapitation 10 min after the termination of
the infusion, and blood was collected for the analysis of plasma lactate concentrations. Brains were also removed, and a 2-mm-thick coronal section of brain, extending from just posterior to the optic chiasma to just anterior to the mammary body, was taken through the midhypothalamic area using a Zivic-Miller brain matrix. This coronal section was transferred to ice-cold cerebrospinal fluid for dissection into gross dorsomedial hypothalamic (DMH), VMH, and lateral hypothalamic (LH) regions with the aid of a dissecting microscope, as reported previously (37). For these dissections, the medial hypothalamus was localized as tissue between the fornices and extending from the superior aspect of the third ventricle to the base of the brain. This medial section was next separated into VMH and DMH by a single horizontal cut at the midventricular level. Vertical cuts at the suprachiasmatic nuclei and extending dorsally to the superior aspect of the third ventricle defined the LH. Using this dissection scheme, the primary hypothalamic nucleus localized in the DMH region is the PVN, whereas the ARC nucleus is found in the VMH region. Each of these regions was frozen in liquid nitrogen to await biochemical analyses. These samples were processed by radioimmunoassay (RIA) for NPY and CRF concentrations, as we have reported (38). Samples of hypothalamus were extracted in 10 volumes of 0.2 N HCl acid for 10 min. After homogenization over ice and centrifugation, the acetic acid extracts were lyophilized, with the residues being resuspended in 1 ml of assay buffer. The assay mixture consisted of 100 µl sample or standard, 100 µl assay buffer or NPY/CRF-free plasma, and 100 µl NPY/CRF antiserum, which was incubated overnight at 4°C. Next 100 µl of 125 I-NPY or CRF tracer was added, and the mixture was incubated overnight again at 4°C. Then 100 µl of anti-rabbit gamma globulin and 100 µl 10% polyethylene glycol were added, with the mixture being incubated for 2 h prior to the addition of 500 µl 1% BSA assay buffer. Bound and free NPY/CRF were separated by centrifugation (20 min), with the supernatant being discarded and the residue counted for 5 min.

**Experiment 3: Normalization of hyperlactatemia using dichloroacetate.** To permit assessment of whether DCA would reduce blood lactate and improve food intake in TB rats, MCA sarcomas were inoculated, sc, into 15 adult, male, Fischer 344 rats. An additional 12 rats received sham inoculations. Seven days later half of each group of rats was provided with 0.1% solution of DCA in the drinking water. The concentration of DCA was increased to 0.2 and 0.4% 17 and 21 days after tumor inoculation, respectively. This increase in DCA concentration was employed because we did not know what concentration of DCA would normalize circulating lactate level in TB rats. Therefore, we escalated the concentration in a gradual manner and assessed any reduction in feeding or drinking in non-TB rats as evidence of toxicity. The remaining rats were maintained on tap water. All rats in this study had ad libitum access to rat chow. Twenty-five days after tumor inoculation, all rats were sacrificed by decapitation. Blood was taken for the determination of lactate in plasma, and the brain was dissected into DMH, VMH, and LH for the assessment of NPY and CRF by RIA.

All experimental procedures conducted in these experiments were reviewed and approved by the animal care committees of the respective institutions. Determination of statistical significance was accomplished using analysis of variance procedures, with differences of individual means being assessed post hoc by Tukey's conservative t-test. All data presented represent the mean ± SE.

**Results**

**Experiment 1**

In agreement with our previous results (7,8), TB rats exhibited significantly increased concentrations of blood lactate. As may be observed from Fig. 1, plasma lactate was elevated significantly (P < 0.05 vs. FF) prior to the onset of anorexia. Furthermore, as the rats became anorectic, plasma lactate concentrations also increased significantly (P < 0.05) by over threefold compared with either control group.

**Experiment 2**

In the second experiment, continuous iv infusion of increasing concentrations of sodium lactate in normal rats decreased feeding beginning with the 0.2-M (45 mg/h) concentration (Fig. 2). Increasing the dose of lactate did not further decrease feeding until the 1.2-M (269 mg/h) concentration was reached on infusion Day 8. Although the rats still exhibited significant anorexia at the intermediate doses of lactate, they appeared to adapt somewhat with food intake tending to increase on infusion Days 6 and 7 (0.3 and 0.6 M, respectively) compared with the response to the 0.2-M concentration of lactate. Mean body weight of the lactate-infused rats was also decreased (P < 0.05) compared with the noninfused group (227 ± 3 vs. 241 ± 4 g) following the 5 days of lactate infusion. At the conclusion of the experiment, saline-infused rats had intermediate body weights (235 ± 5 g). Plasma lac-

![Figure 1](image_url)
tate concentrations were elevated \((P < 0.05)\) in the lactate-infused rats (5.1 ± 0.4 mmol) compared with noninfused (3.6 ± 0.1 mmol) or saline-infused (4.1 ± 0.4 mmol) groups. Because the rats were euthanized 10 min after the termination of infusion, some of the exogenous lactate may have been metabolized, accounting for the smaller-than-expected plasma lactate concentrations in lactate-infused rats. As illustrated in Fig. 3, hypothalamic concentrations of NPY were increased \((P < 0.05)\) in the VMH and DMH of lactate-infused rats. No change in NPY was observed in the LH of these rats. Levels of CRF were not altered significantly in any of the hypothalamic regions (Fig. 4).

**Figure 2.** Mean ± SE daily food intake by sham-operated, saline-infused, and lactate-infused rats. Normal saline or daily increasing concentrations of sodium lactate (0.1–1.2 M) were continuously infused, iv, at a rate of 2 ml/h. Data were analyzed using repeated-measures analysis of variance.

**Figure 3.** Mean ± SE concentration of NPY, as determined by RIA, in DMH, VMH, and LH taken from sham-operated, saline-infused, and lactate-infused rats. Data were analyzed using one-way analysis of variance for each hypothalamic region.

**Figure 4.** Mean ± SE concentration of CRF, as determined by RIA, in DMH, VMH, and LH taken from sham-operated, saline-infused, and lactate-infused rats. Data were analyzed using one-way analysis of variance for each hypothalamic region.

**Figure 5.** Mean ± SE daily water intake by non-TB (NTB) and TB rats maintained on water or increasing concentrations (0.1–0.4%) of DCA in the drinking water. Data were analyzed using three-way repeated-measures analysis of variance.

**Experiment 3**

The third experiment determined whether treatment of anorectic TB rats with DCA could reduce blood levels of lactate and restore normal feeding. As shown in Fig. 5, all groups of rats tolerated the addition of up to 0.4% DCA in their drinking water. Although the TB rats exhibited reduced water intake by 21 days after tumor inoculation \((P < 0.05)\), there was no difference in intake between the DCA and wa-

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Figure 6. Mean ± SE daily food intake by non-TB (NTB) and TB rats maintained on water or increasing concentrations (0.1–0.4%) of DCA in the drinking water. Data were analyzed using three-way repeated-measures analysis of variance.

Figure 7. Mean ± SE body weights of non-TB (NTB) rats and nontumor body weights of TB rats maintained on water or increasing concentrations (0.1–0.4%) of DCA in the drinking water. Data were analyzed using two-way analysis of variance.

Figure 8. Mean ± SE concentration of lactate in the plasma of non-TB (NTB) and TB rats maintained on water or increasing concentrations (0.1–0.4%) of DCA in the drinking water. Analysis was performed following 4 days of exposure to 0.4% DCA. Data were analyzed using a two-way analysis of variance.

Figure 9. Mean ± SE concentrations of NPY and CRF in VMH taken from non-TB (NTB) and TB rats maintained on water or increasing concentrations (0.1–0.4%) of DCA in the drinking water. Analyses were performed following 4 days of exposure to 0.4% DCA. Data were analyzed using two-way analysis of variance for each peptide.

Figure 10. Mean ± SE concentrations of NPY and CRF in DMH taken from non-TB (NTB) and TB rats maintained on water or increasing concentrations (0.1–0.4%) of DCA in the drinking water. Analyses were performed following 4 days of exposure to 0.4% DCA. Data were analyzed using two-way analysis of variance for each peptide.

In the TB rats drinking the DCA solution, the NPY level was restored to that seen in the water-maintained non-TB rats (Fig. 9). The concentration of NPY also tended to be increased in the non-TB rats treated with DCA, but the difference failed to achieve statistical significance. Levels of CRF were not altered in the VMH (Fig. 9) or in the DMH (Fig. 10) of any treatment groups. In the DMH (Fig. 10), no group exhibited significant alteration of NPY concentration following any treatment.

Discussion

It is clear that the presence of a tumor dramatically alters host metabolism by increasing energy expenditure, secreting toxic products, and consuming metabolic substrates. Tumors are avid consumers of glucose (9) and actually appear to have preference for this substrate over host tissues due to their relative insulin independence (10,11). In spite of the increased rate of glucose metabolism, most, but not all, TB organisms...
Compensate well for this loss of substrate through gluconeogenesis (11), at least prior to the premorbid state. Thus, the MCA sarcoma-bearing rat maintains a near-normal blood glucose level in the face of significant anorexia (12). However, glycolysis is preferred to respiration in many tumor tissues (9,39), with a resulting waste of much of the energy available from glucose. In addition, the resulting lactate has to be converted back to glucose through the energyrequiring process of gluconeogenesis. In animal models of cancer anorexia, it appears that host metabolism can be overwhelmed by tumor-produced lactate, perhaps due to the amount of lactate produced or a deficiency in the TB host in lactate metabolism. Although not all tumors may cause hyperlactatemia (40,41), the MCA sarcoma exhibits a large arteriovenous increase in lactate (42), suggesting the tumor as a primary source of this metabolite. Tumors in humans have also been shown to secrete lactate (43) and produce elevated lactate concentration in blood (44).

The studies presented in this article suggest that experimental cancer anorexia is not mediated by elevated blood lactate. Although lactate infusion reduced food intake in non-TB rats and lactate was elevated early in the course of anorexia and continued to increase as the anorexia became more severe, normalization of circulating lactate concentration by treatment with DCA did not improve food intake in anorectic TB rats. Therefore, it appears that lactatemia may be eliminated as one of the signals from tumor to brain that may elicit experimental cancer anorexia.

As explained by Stacpoole (30), DCA stimulates the metabolism of lactate by increasing activity of the enzyme pyruvate dehydrogenase. A kinase mediates phosphorylation of the enzyme, which maintains the dehydrogenase in a nonactive form. DCA inhibits this kinase and maintains pyruvate in the active unphosphorylated form, which oxidizes pyruvate to acetyl CoA. The increased flow of this reaction also reduces levels of pyruvate precursors, including lactate. That lactate was normalized in TB rats by the DCA treatment suggests that there may not be an impairment in TB rats with lactate metabolism. Rather, the TB host’s capacity for lactate metabolism appears to be overwhelmed by the large amount of lactate produced by the growing tumor mass. As with other conditions in which lactic acidosis is problematic, such as malaria and ischemia (31–33), DCA proved to be an effective treatment for lactatemia in the TB rats.

In addition to providing clear results concerning the relationship of circulating lactate to cancer anorexia, these studies also suggest how NPY may be altered in the hypothalamus as circulating concentrations of lactate are altered. This insight concerning NPY is important because several studies suggest that abnormalities in NPY function may be of primary importance in the mediation of cancer anorexia. Thus, TB rats exhibit a refractory feeding response to NPY, even prior to the onset of overt anorexia (45). NPY release is reduced in the perifornical hypothalamus of anorectic TB rats (46). Although the concentration of NPY in whole hypothalamus was reduced in TB rats (46), other reports suggest that NPY levels and mRNA are elevated in the VMH and arcuate nucleus of anorectic TB rats (38,47). In addition, decreased receptor binding of NPY to hypothalamic membranes taken from anorectic TB rats has been reported (34) as has decreased cyclic AMP synthesis following β-adrenergic stimulation of hypothalamic membranes taken from pre-anorectic and anorectic TB rats (48).

Although it is not possible to determine from the present results how elevated blood lactate resulted in increased NPY in the hypothalamus, one scenario seems consistent with published results. Lactate has been reported to stimulate glucoreponsive neurons in the VMH (18), which suggests that elevated lactate may be interpreted by these neurons as elevated glucose. Muroya et al. (21) reported that glucose-sensitive neurons in the hypothalamic arcuate nucleus contain NPY. They hypothesized that reduced glucose concentration stimulated the release of NPY in this area. If lactate activates these glucose-sensitive neurons, then the release of NPY might be decreased during lactatemia. Thus, elevated concentration of NPY in the VMH of TB and lactate-infused rats may be reflective of decreased release. However, lactate-infused rats also exhibited an elevation of NPY in the DMH section, which was not observed in anorectic TB rats, suggesting a problem in transport, synthesis, or degradation of the peptide in TB rats at this region of the hypothalamus, which contains the NPY terminal-rich PVN. Additional studies assessing changes in NPY mRNA and peptide level are necessary to clarify the significance of these differential changes in NPY within the VMH and DMH regions of TB and lactate-infused rats.

Other studies have demonstrated an effect of lactate or glucose on hypothalamic neurons that may control hunger and/or satiety. Thus, infusion of either lactate (49) or glucose (50) into the VMH blocked the counter-regulatory release of catecholamines and glucagon in hypoglycemic rats. Because the metabolic response to glucoprivation was blocked by these infusions, these studies suggest that these neurons signaled euglycemia or satiety in response to lactate or glucose.

Studies in other animal models suggest that NPY level and/or mRNA are elevated in the hyperglycemic state, including obese Zucker rats (51,52) and diabetic rats and mice (53,54). However, hypothalamic NPY level and mRNA are also increased by food deprivation (53) and are normalized with refeeding (55). In addition, fasting of diabetic mice further increased NPY mRNA in hypothalamus (53), suggesting that factors in addition to altered carbohydrate metabolism are involved in modulation of hypothalamic NPY. One additional factor that appears to be common in these models is reduced blood insulin concentration or dysfunctional insulin receptors. Consistent with this suggestion is the observation that, in anorectic TB rats, plasma concentration of insulin is reduced by over 60% in the presence of near-normal glucose (12). Furthermore, intraventricular injection of insulin blocked elevated NPY level in the PVN and NPY mRNA in the arcuate nucleus of fasted rats (56). Thus, insulin, as well as insulin-induced alterations in blood glucose level may be critical factors in the response of glucose-sensitive neurons.
to release NPY when blood concentrations of these substrates are reduced.

A potential role of CRF has also been suggested for cancer anorexia with elevated CRF being reported in the arcuate and paraventricular hypothalamic nuclei of TB rats compared with PF controls (22). Thus, the interaction of NPY and CRF in these hypothalamic regions of TB rats may be important for the development of anorexia, with an increased CRF/YNP ratio favoring reduced food intake. In the present study, levels of CRF were not elevated significantly in either VMH or DMH regions of anorectic TB rats. This observation is consistent with our previous investigation (38). Although lactate infusion tended to increase CRF concentration in the VMH section, sample variability precluded achieving statistical significance in this group.

These results indicate that increased levels of circulating lactate are not a primary cause of experimental cancer-induced anorexia. However, the lactatemia may be a significant contributor to elevated concentrations of NPY in the VMH of anorectic TB rats because normalization of the lactatemia also normalized level in the VMH.

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