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Altered Glucose Metabolism in Metastatic Carcinoma[1]

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SUMMARY

To evaluate the possible role of altered glucose metabolism in malignant cachexia, metabolic parameters including total glucose turnover, glucose oxidation, and Cori cycle activity were measured in fourteen patients with metastatic carcinoma. Eight patients with progressive weight loss (PWL) were compared to 6 without (controls). Cori cycle activity was significantly increased ($p < 0.02$) in PWL patients, 90 mg/kg/hr (range, 22 to 193) compared to 18 mg/kg/hr (range, 13 to 24) in controls. Total glucose turnover was moderately increased in PWL patients, 196 mg/kg/hr compared to 110 mg/kg/hr in controls. Glucose oxidation was 62 mg/kg/hr *versus* 48 mg/kg/hr, and total caloric expenditure was 36 kcal/sq m/hr compared to 33 Kcal/sq m/hr. PWL patients were metabolically heterogenous and mean values are skewed by four patients with increased glucose turnover, oxidation, and markedly high recycling rates that were equivalent to total endogenous glucose turnover of a normal subject. Total caloric expenditure was greatest in three of the four patients with a marked increase in Cori cycle activity. Energy loss associated with a high rate of gluconeogenesis from lactate has been suggested as an explanation for increased energy expenditure in some cancer patients, thus contributing to mechanisms that promote weight loss.

INTRODUCTION

The association of PWL[3] with cancer is well recognized. Numerous investigations over several decades have failed, however, to clearly delineate the metabolic events leading to cachexia. The contributory role of anorexia and subsequent caloric deprivation is not disputed. On the other hand, a surprising lack of correlation sometimes exists between the degree of weight loss and clinical parameters such as caloric intake, tumor burden, cell type, and anatomic site of involvement. This consideration has prompted investigators to search for alternative metabolic explanations distinct from simple starvation.

High rates of glucose utilization with production of lactic acid are characteristic features of the neoplastic cell (14). Lactic acid so produced may be utilized for energy purposes by other tissues or transported to the liver for resynthesis to glucose. This cyclic metabolic pathway, in which glucose is converted to lactic acid by glycolysis and then reconverted to glucose in the liver, is referred to as the Cori cycle. Utilization of lactic acid by peripheral tissues would normally provide the tumor-bearing patient with maximum energy available from glucose oxidation. Gluconeogenesis from lactate, on the other hand, is an energy-requiring process that, as pointed out by Fenninger and Mider (5), may play an important role in excessive energy expenditure of the host.

Unexplained elevation of the basal metabolic rate has previously been reported in some patients with cancer (5). Similarly, increased Cori cycle activity has also been described in some cancer patients (10, 15). The simultaneous evaluation of energy expenditure, glucose turnover, oxidation, and Cori cycle activity has not been previously described. This study has attempted further to define the possible role of altered glucose metabolism in cancer patients with and without PWL in whom these metabolic parameters have been measured.

MATERIALS AND METHODS

Patients. Ten patients attending an ambulatory chemotherapy unit and 4 recently diagnosed inpatients were selected for study. All had metastatic solid tumors. Relevant details pertaining to clinical status are listed in Table 1. At the time of study, 10 patients were on active treatment programs but none received chemotherapy during the preceding 2 weeks and no patient was receiving steroid hormones. During a 6-week observation period prior to study, 8 patients experienced PWL and 6 patients (controls) either had no change in weight or gained weight as a result of treatment. Two PWL patients (S. M., R. S.) were receiving intensive courses of chemotherapy. In both instances PWL was established prior to the initiation of treatment. No patient was acutely ill at the time of study and none was febrile.

Metabolic Studies and Methods. Plasma glucose turnover and Cori cycle activity were measured by a minor modification of a previously described method (10). Briefly, after an overnight fast patients were rapidly given injections of 90 μCi (5.4 mg) [1-^{14}C]glucose. Plasma samples were deproteinized, and the resultant protein-free filtrate was

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[3] The abbreviation used is: PWL, progressive weight loss.

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Table 1
Summary of diagnoses and clinical status

Patient	Age	Sex	Diagnosis	Remission status	Wt. change[a] (%)
G. S.	49	F	Cancer of breast; bone and visceral metastases	Partial remission	+8
A. M.	58	F	Cancer of breast; lymph node metastases	Complete remission	None
C. C.	40	F	Cancer of breast; lymph node and skin metastases	Complete remission	None
E. L.	66	M	Ileal carcinoid; mesenteric metastases	Progression	+6
H. F.	78	M	Cancer of gallbladder; mesenteric metastases	Progression	None
C. W.	79	M	Cancer of colon; lung metastases	Progression	None
Z. L.	62	F	Cancer of colon; lung and liver metastases	Progression	−16
R. S.	44	M	Cancer of bronchus; retroperitoneal metastases	Progression	−16
J. R.	54	M	Embryonal cancer of testis; metastases to lung and mesenteric nodes	Progression	−13
A. B.	73	F	Cancer of breast; pleural, skin, and mediastinal metastases	Progression	−11
M. B.	46	M	Cancer of colon; liver metastases	Progression	−12
A. G.	78	F	Cancer of stomach; liver and peritoneal metastases	Progression	−10
S. M.	60	M	Cancer of bronchus; bone and liver metastases	Progression	−8
W. R.	76	M	Cancer of stomach; metastases to regional lymph nodes	Progression	−13

[a] Denotes weight change from time of diagnosis.

passed through a column of Amberlite MB-3 (HCO_3^- form). One aliquot of the column eluate was used to determine radioactivity in C-6 of glucose by periodate oxidation and formaldimedone precipitation as previously described (10). Radioactivity in all glucose carbons was determined in a 2nd column aliquot by oxidizing glucose to gluconic acid followed by absorption of gluconate on an Amberlite CG-400 column (7). Calculation of the Cori cycle assumes randomization of carbon through an established sequence of reactions from [3-^{14}C]lactate to [1,2,5, 6-^{14}C]glucose. Net glucose turnover obtained by measuring the rate of decline of blood glucose specific activity plus Cori cycle activity yields estimated total endogenous glucose turnover.

Oxygen consumption, carbon dioxide production, and expired CO_2 specific activity were determined by standard methods and the rate of glucose oxidation was calculated by the equations of Baker *et al.* (1) and Issekutz *et al.* (9). Prior to study, heparinized plasma was obtained for determination of immunoreactive insulin by the method of Hales and Randle (8), β-hydroxybutyrate was obtained by the enzymatic technique of Williamson *et al.* (18), free fatty acids were obtained by the method of Dole and Meinertz (4), and lactate was obtained by Strom's modification (13) of the colorimetric method of Barker and Somerson (2). The patient voided before the study. Urine was collected throughout and at the close of the experimental period. Urinary nitrogen was determined by the automated procedure of Ferrarri (6). Total energy balance was determined by conventional indirect calorimetry.

RESULTS

Metabolic data and ancillary determinations are shown in Tables 2 and 3. Patients are listed in the same order of appearance as in Table 1, in which the corresponding clinical details are given. Fasting plasma glucose concentrations were essentially the same in PWL as in control patients: 85 mg/100 ml (range, 63 to 105) *versus* 91 mg/100 ml (range, 86 to 100). Similarly, immunoreactive insulin levels were 14 microunits/ml (range, 11 to 20) in PWL patients and 15 microunits/ml (range, 12 to 19) in controls (see Table 2). Total glucose turnover was moderately increased in PWL, 196 mg/kg/hr (range, 105 to 286) compared to 110 mg/kg/hr (range, 72 to 151). Glucose oxidation was higher in PWL, 62 mg/kg/hr (range, 40 to 76) *versus* 48 mg/kg/hr (range, 36 to 68), and total caloric expenditure was 36 kcal/sq m/hr (range, 27 to 44) in PWL compared to 33 kcal/sq m/hr (range, 29 to 38). Cori cycle activity was significantly ($p < 0.02$) increased in PWL patients, 90 mg/kg/hr (range, 22 to 193) compared to 18 mg/kg/hr (range, 12 to 26) in controls (see Table 3). Similarly, the fraction of total glucose turnover attributable to glucose recycling was increased in PWL, 43% (range, 19 to 68) compared to 18% (range, 13 to 24). PWL patients were metabolically heterogeneous, and mean values are skewed by 4 patients (R. S., J. R., M. B., and S. M.) with elevated glucose turnover, oxidation, and markedly high recycling rates. In these 4 patients the amount of glucose recycled is equivalent to the total endogenous turnover of a normal subject. The contribution of the Cori cycle largely accounts

Table 2
Metabolic data

Patient	Wt. (kg)	Surface area (sq m)	Plasma glucose (mg/100 ml)	Free fatty acid (mEq/liter	Immuno-reactive insulin (microunits/ml)	Venous blood lactate (mM)	Urinary nitrogen excretion (g/sq m/hr)
G. S.	51.8	1.46	100	1.30	14		0.23
A. M.	68.2	1.76	92	1.31	12	0.84	0.22
C. C.	111.4	1.96	86	1.78	19	1.06	0.36
E. L.	85.2	2.03	88	0.56	15	1.01	0.14
H. F.	51.4	1.55	91	0.95	12	0.84	
C. W.	61.4	1.69	91	0.60	16	1.06	0.11
Z. L.	48.2	1.53	63	1.21	16	1.51	0.21
R. S.	62.9	1.80	86	1.06	10	1.26	0.25
J. R.	60.9	1.76	105	0.91	11	1.62	0.13
A. B.	54.5	1.61	100	0.78	20	1.28	0.13
M. B.	73.2	1.92	66	1.26	11	2.02	0.15
A. G.	46.8	1.36	100	1.55	14	1.21	0.12
S. M.	61.8	1.70	84	1.15	14	2.14	0.31
W. R.	52.3	1.62	76	0.98	18	0.64	0.18

Table 3
Metabolic data

Patient	mmoles/sq m/hr		Nonprotein respiratory quotient	Total caloric expenditure (kcal/sq m/hr)	Total glucose turnover rate (mg/kg/hr)	Cori cycle activity		Glucose oxidation (mg/kg/hr)
	O_2 consumption	CO_2 production				mg/kg/hr	% total glucose turnover	
G. S.	235	210	0.847	31.7	150.6	24.1	16	65.5
A. M.	277	238	0.859	36.0	120.8	19.3	16	68.0
C. C.	260	227	0.873	38.0	71.7	11.5	16	39.7
E. L.	224	219	0.978	29.1	98.0	12.9	13	40.0
H. F.					109.6	22.3	20	37.9
C. W.	269	221	0.821	32.0	107.6	26.2	24	36.4
Z. L.	272	232	0.853	35.3	122.0	58.6	48	57.0
R. S.	304	274	0.901	40.2	221.4	123.9	56	69.7
J. R.	266	253	0.950	33.3	233.9	133.8	57	75.3
A. B.	262	238	0.908	32.4	286.1	60.7	21	58.6
M. B.	364	335	0.920	44.4	283.0	193.0	68	76.0
A. G.	209	200	0.957	26.6	111.0	22.0	19	60.0
S. M.	307	266	0.866	42.0	209.0	101.0	48	60.0
W. R.	275	246	0.895	35.1	105.0	27.0	26	40.0

for the observed differences in total glucose turnover noted in this study between PWL and the control group.

Oxygen consumption was moderately increased in PWL patients, 282 mM/sq m/hr (range 209 to 364) compared to 253 mM/sq m/hr (range, 224 to 277) in the controls. Similarly, CO_2 production was 282 mM/sq m/hr (range, 200 to 335) in PWL patients compared to 223 mM/sq m/hr (range, 210 to 238) in controls. No significant difference was found for nonprotein respiratory quotient between the 2 groups of patients. Total caloric expenditure, O_2 consumption, and CO_2 production were greatest in 3 patients (R. S., M. B., and S. M.) with a marked increase in Cori cycle activity.

Venous lactate concentrations were elevated in PWL patients, 1.76 mM (range, 0.64 to 2.14) *versus* 0.96 mM (range, 0.84 to 1.06) in controls. No patient was considered to have clinically significant lactic acidosis. β-Hydroxybutyrate concentrations did not exceed 0.50 mM, and no difference was noted in plasma free fatty acid concentration or urinary nitrogen excretion.

DISCUSSION

We have studied a heterogeneous group of patients with metastatic carcinoma. In attempting to interpret the data in context with clinical status, it is noteworthy that PWL patients all had progressive disease and complained of anorexia. A degree of altered glucose metabolism was demonstrated in most patients from this group. By contrast, control patients without weight loss did not complain of anorexia and stated that they were eating normally. Essentially normal glucose metabolism was observed in this group, regardless of estimated tumor burden or remission

status, and in these patients the results are in agreement with previous data by Waterhouse and Kemperman (17). These differences may help explain conflicting metabolic data described in previous studies in which such clinical details were not avaliable (10, 11).

Hypoglycemia (12) has been reported as an occasional complication of nonpancreatic malignant disease. The normal fasting blood glucose and immunoreactive insulin concentrations in our patients exclude the possibility of major disturbances in glucose tolerance. The finding of elevated glucose recycling rates expressed either in absolute quantities or as a fraction of the somewhat variable total glucose turnover rate is significant when PWL patients are compared to cancer patients without weight loss. Increased recycling is not found in starvation alone (3), and the absence of significant ketonemia indicates a relative rather than an absolute caloric deprivation in these patients. Elevated Cori cycle activity shows that lactate production rates are increased in PWL patients, and the finding of higher mean venous lactate concentrations in this group lends support to this contention. It cannot, unfortunately, be determined from this study whether increased lactate production results from tumor glycolysis or from possible alternative mechanisms. The lack of clinically significant lactic acidosis testifies to efficient lactate disposal mechanisms, and the Cori cycle, by inference, may represent a major disposal pathway for lactate in PWL patients.

Although an increased rate of gluconeogenesis may be inferred from the high Cori cycle activity observed in PWL patients, this does not of necessity imply accelerated gluconeogenesis from protein-derived amino acids. Several previous investigations have failed to document a nitrogen-losing catabolic state in malignant cachexia (5, 16). In support of this, our data fail to show differences in urinary nitrogen excretion between PWL patients and the controls, the observed values being essentially normal for the conditions of study. Similarly, no differences were observed in nonprotein respiratory quotient or plasma free fatty acid concentration. These last data suggest that our PWL patients retained the ability to mobilize fat as an energy source and that no particular reliance was placed on carbohydrate, as opposed to fat, for purposes of energy supply.

The apparent metabolic heterogeneity of PWL patients is of interest. The moderate increase in mean total glucose turnover and glucose oxidation rates are in accord with previous reports (10, 11). Four patients with higher values (R. S., J. R., M. B., and S. M.) merit separate consideration since their glucose recycling rates were markedly elevated, being roughly equivalent to the total endogenous glucose turnover of a normal subject. Although increased Cori cycle activity has been reported in some cancer patients, this degree of glucose recycling is generally greater than previously described (10, 11) but was similar to 2 patients reported by Waterhouse (15) using different methodology. It may be relevant that all had rapidly progressive bulky tumors and all showed evidence of recent rapid weight loss. That tumor bulk is not the sole prerequisite for increased glucose recycling is evidenced by Patient E. L., who had a very large slowly progressing abdominal mass but normal Cori cycle activity. Three of these 4 patients with markedly increased Cori cycle activity had the greatest values for O_2 consumption and total caloric expenditure. These findings are more apparent when calculated on the basis of body weight rather than surface area and are of interest because inappropriate elevation of basal metabolic rate has been previously described in some patients with cancer (5). As endogenous glucose utilization and caloric expenditure are normally lowered in the face of caloric deprivation, the results in this study are inappropriately high, suggesting an obligatory demand for increased glucose in PWL. Glucose resynthesis from lactate is an energy-requiring metabolic process to which an accurate caloric value cannot be ascribed. The effects of energy loss from glucose recycling, increased caloric expenditure, and reduced caloric intake from anorexia are likely to be additive.

This study emphasizes that many facets of altered glucose metabolism may be associated with malignant cachexia. The possible role of wasteful metabolic pathways through glucose recycling has previously been little recognized and adds to our understanding of this common clinical situation. It should be recognized, however, that our studies may not explain the profound wasting observed in some patients with progressive neoplasia in the absence of significant tumor burden.

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