Involvement of Prostaglandins in Cachexia Induced by T-Cell Leukemia in the Rat

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We have previously demonstrated that experimentally induced T-cell leukemia in the rat results in a rapid and severe cachexia. This weight loss is largely due to a reduction in food intake, but is also accompanied by inappropriately high rates of energy expenditure. Increases in resting oxygen consumption ($\dot{V}O_2$) of 25% to 35% above the levels of pair-fed animals were observed over the period of weight loss. The present study investigated the possible involvement of prostaglandins in the cachexia induced by T-cell leukemia in the rat. Acute systemic injection of the cyclo-oxygenase inhibitors (indomethacin 1 mg/kg or flurbiprofen 1 mg/kg intraperitoneally [IP]) significantly reduced (by 14% and 10%, respectively) the increase in metabolic rate and also reversed the elevated body temperature of leukemic animals. Intracerebroventricular (ICV) injection of indomethacin (0.2 mg/kg) had only modest effects on the increase in temperature or hypermetabolism of leukemic animals. Long-term daily injection of indomethacin or flurbiprofen (1 mg/kg/d IP) had no significant effect on food intake or body weight of leukemic animals, and neither treatment significantly affected disease status. Indomethacin significantly reduced the decline in epididymal fat pad weight of leukemic animals. These data indicate that prostaglandins, produced peripherally, are involved in the acute hypermetabolism associated with T-cell leukemia, but have little or no effect on the hypophagia or body weight loss of leukemic rats.

THE SYNDROME OF cancer cachexia is characterized by anorexia, progressive wasting, and metabolic abnormalities.[1] Sustained weight loss is one of the most common manifestations of a malignant tumor, has been shown to be correlated with disease survival, and frequently has a negative impact on treatment.[2]

Weight loss results from a negative energy balance, which could arise from a decrease in energy intake (food intake) and/or an increase in energy expenditure (metabolic rate). Studies in humans and experimental animals have reported decreases in food intake and increases in energy expenditure[3-6] associated with cancer cachexia. However, the mechanisms underlying these changes remain poorly defined.

Recent evidence in experimental animals has suggested that cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-α), and interferon gamma[7] and prostaglandins (mainly of series 2) have an integral role in cancer cachexia.[8-12] Cytokines (IL-1, IL-6, and TNF-α) are known to induce the synthesis and release of prostaglandins,[13] and prostaglandins influence many host responses to disease by modulating cytokine production.[14]

Prostaglandins may be produced locally by the tumor, or by host tissues via release of cytokines, and some animal and human tumors secrete prostaglandins.[15] Prostaglandins could then enter the circulation to influence energy balance and cachexia, but may also influence these parameters through synthesis and action within the central nervous system.[16,17] Prostaglandins can exert effects by a direct action on the thermoregulatory neurons within the hypothalamus, and have been implicated in changes in food intake, energy expenditure, and body temperature induced by acute and chronic infection, injury, and inflammation.[13]

Arachidonic acid and its metabolites can stimulate thermogenesis directly,[18] inhibit food intake,[19] and have also been implicated in muscle wasting[20] and breakdown of triglycerides,[21] all of which occur in cancer cachexia.

Previous studies investigating the role of prostaglandins in cancer cachexia have focused almost exclusively on solid tumors in rodents. To date, no studies have investigated their possible involvement in the cachexia induced by a nonsolid/hematologic tumor such as leukemia. We have previously demonstrated that injection of leukemic cells in Piebald Variegated (PVG) rats results in a rapid and severe cachexia over days 14 to 17 that is largely due to hypophagia (days 13 to 17) but is also accompanied by inappropriately high rates of energy expenditure (days 12 to 17). This hypermetabolism is mediated by activation of the sympathetic nervous system and increased brown adipose tissue thermogenesis.[22]

Thus, the objective of the present study was to investigate the mechanisms involved in cachexia induced by T-cell leukemia in the rat, and to specifically study the possible involvement of prostaglandins in acute and chronic changes involved in the hypermetabolism and increase in body temperature (oxygen consumption [$\dot{V}O_2$] and colonic temperature [Tc]), hypophagia and cachexia (food intake and body weight), and disease status (white blood cell [WBC] count and spleen weight).

MATERIALS AND METHODS

Animals

All studies were performed on young adult (60 to 80 days old) male Piebald Variegated (PVG) rats (supplied and bred by the Biological Services Unit, University of Manchester, Manchester, UK). Animals weighed 220 to 270 g and were fed a powdered diet (CRM Labsure, Kent, UK) and water. The rats were housed in pairs in wire-bottom cages at 22°C with a 12-hour light/dark cycle (8 AM to 8 PM).

Induction of Leukemia

T-cell leukemia was induced as previously described,[23] and was maintained in rats by serial passage. One hundred microliters of a cell suspension (containing 1×10^5 cells) obtained from enlarged cervical

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lymph nodes of animals approaching the terminal phase of leukemia was injected intramuscularly into the hindlimb of recipient animals.[24] Control animals were injected with 100 μL 0.9% saline.

Intracerebroventricular Injections

Indwelling guided cannulae were implanted in the lateral cerebral ventricle using stereotaxic coordinates (relative to bregma: anterior-posterior [AP] −0.8 mm, midline [ML] 1.5 mm, dorsal-ventral [DV] −3.0) of the brain on day 5 after implantation of leukemia cells, under pentobarbitone sodium anesthesia (60 mg/kg intraperitoneally [IP]). Animals were allowed to recover for at least 7 days before central injection. All central injections were made in conscious hand-held rats. The location of the cannula was subsequently confirmed histologically. Data from animals in which cannulae were incorrectly positioned were excluded from the analysis.

Food Intake and Body Weight

Food intake was measured in pairs of animals, and average food intake was calculated per animal. Food intake and body weight were recorded between 7 and 8 AM. Food intake and any spillage was measured to the nearest 0.1 g; body weight was measured to the nearest gram. Pair-fed animals were given the same amount of food eaten by leukemic animals on the previous day. Food was presented between 5 and 7 PM to ensure that all animals ate during the dark cycle.

$\dot{V}O_2$

Resting $\dot{V}O_2$ was measured in closed-circuit, indirect calorimeters[25] maintained at 24°C for a period of at least 2 hours (between 8 AM and 6 PM) or until steady values were obtained. Animals were placed in individual calorimeters that allowed modest movement (stretching and turning), and were acclimated to the calorimeters before the start of each experiment by prior exposure for at least 2 hours on 2 different days. $\dot{V}O_2$ rates were corrected for standard temperature and pressure–dry and metabolic body size ($mL \cdot min^{-1} \cdot kg^{-0.75}$).

Tc

Tc was determined immediately after measurement of $\dot{V}O_2$ in conscious hand-held rats by means of a plastic-coated thermocouple (Comark, Sussex, UK) inserted into the rectum to a depth of 6 cm.

WBC Count and Organ Weights

Animals were anesthetized with halothane (Zeneca Pharmaceuticals, Cheshire, UK), and blood was collected in heparinized (10 U/mL) syringes by cardiac puncture. Twenty microliters of blood was removed for measurement of circulating WBC count using a Coulter Counter (Coulter Electronics, Bedford, UK). The animals were then killed by cervical dislocation, and the left epididymal fat pad, right gastrocnemius muscle, and spleen were dissected out and weighed immediately.

Flurbiprofen

The acute effect of IP injection of flurbiprofen (1 mg/kg; Boots Pharmaceuticals, Nottingham, UK) on $\dot{V}O_2$ and Tc was assessed on days 13 to 16 postimplantation in control (n = 7), pair-fed (n = 8), and leukemic (n = 9) animals. The chronic effect of flurbiprofen administered daily (1 mg/kg/d IP) on food intake, body weight change, organ weights, and WBC count was assessed in control and leukemic rats (n = 5 for food intake and n = 10 for body weight in each group).

Indomethacin

The acute effect of IP (1 mg/kg) or intracerebroventricular (ICV) (0.2 mg/kg) injection of indomethacin (Sigma Chemicals, Poole, UK) on $\dot{V}O_2$ and Tc was assessed on days 13 to 16 after implantation in control, pair-fed, and leukemic animals (n = 6 to 9 in each group). The chronic effect of daily administration of indomethacin (1 mg/kg/d IP) on food intake, body weight change, organ weights, and WBC count was assessed in control and leukemic rats (n = 3 for food intake and n = 6 for body weight in each group).

Experiments 1, 2, and 3: Acute Effects of Indomethacin and Flurbiprofen on $\dot{V}O_2$ and Tc

In experiments 1 and 2, the effect of peripheral injection (IP) of indomethacin or flurbiprofen on $\dot{V}O_2$ and Tc was investigated. Subsequently, in experiment 3, the effect of central injection (ICV) of indomethacin was investigated. Each experiment was performed in separate groups of rats weighing 250 to 300 g. Measurements were performed on days 13 to 16 after implantation in control, pair-fed, and leukemic rats. At these times, $\dot{V}O_2$ of leukemic rats was significantly greater than that of pair-fed animals. $\dot{V}O_2$ was measured for 2 hours before and 2 to 3 hours after injection of drug or vehicle, and was immediately followed by recording of Tc.

Experiments 4 and 5: Chronic Effects of Indomethacin and Flurbiprofen on Food Intake, Body Weight Change, Disease Status, and Organ Weights

In experiments 4 and 5, rats were divided into four weight-matched groups. Two groups of rats were injected with leukemic cells and the remainder were injected with saline on day 0. Control and leukemic rats were injected daily with the cyclo-oxygenase inhibitor (indomethacin or flurbiprofen) or vehicle.

Body weight and food intake were measured daily (or on the days stated) throughout the experiment. Experiments were terminated when rats appeared moribund and wasted. They were killed, and blood was collected for measurement of WBC count; the spleen, epididymal fat pad, and gastrocnemius muscle were dissected and weighed.

Statistical Analysis

All values are expressed as the mean ± SEM. Data were analyzed using a paired Student's *t* test for comparison of two groups and one-way ANOVA followed by Scheffé's post hoc test for three groups. Results from time course experiments were analyzed using multiple ANOVA (MANOVA) to compare responses over time. Comparisons between groups at individual time points were analyzed using an unpaired Student's *t* test or ANOVA with one- or two-factor analysis as appropriate and followed by Scheffé's post hoc test (for two or three groups, respectively). In all cases, two-tailed probabilities less than .05 were considered statistically significant.

RESULTS

Experiments 1 and 2: Effect of Injection of Indomethacin and Flurbiprofen IP on $\dot{V}O_2$ and Tc

In a preliminary study (data not shown), body weight and food intake were compared in control and leukemic animals. The food intake of leukemic animals declined dramatically from day 12 and the body weight from day 14 onward. On day 17, food intake was significantly reduced by 75% and body weight by 12% compared with levels in control animals. Therefore, in subsequent studies to investigate changes in body weight and metabolic rate, a pair-fed group was included. We have previously demonstrated that weight loss in pair-fed animals is slightly greater (7%, day 17) than in leukemic animals, and that $\dot{V}O_2$ measured by indirect calorimetery is significantly elevated by approximately 25% in leukemic animals over days 12 to 18 compared with pair-fed controls.[22]

The effect of peripheral injection of indomethacin and

flurbiprofen on $\dot{V}O_2$ and Tc in control, leukemic, and pair-fed animals is shown in Fig 1. Indomethacin or flurbiprofen had no effect on $\dot{V}O_2$ of either control or pair-fed animals, but markedly inhibited (14% and 10%, respectively) the increase in $\dot{V}O_2$ of leukemic animals ($P < .01$ and $P < .05$, paired Student's t test). Tcs in control and leukemic rats were slightly greater than in pair-fed animals before indomethacin treatment (36.5° v 36.1°C), but this difference was not statistically significant. Before flurbiprofen treatment, Tcs of control and leukemic rats were significantly increased compared with those of pair-fed animals ($P < .01$ and $P < .05$, respectively, one-way ANOVA and Scheffé's post hoc test). Neither indomethacin nor flurbiprofen affected Tc of control or pair-fed rats. Tc of leukemic animals was slightly reduced (from 36.5° to 36.2°C) by indomethacin treatment, but was significantly reduced after flurbiprofen injection ($P < .05$ v pretreatment values, paired Student's t test).

Experiment 3: Effect of Injection of Indomethacin ICV on $\dot{V}O_2$ and Tc

Injection of indomethacin ICV had no effect on $\dot{V}O_2$ of control or pair-fed animals, but did cause a small (6%; Fig 2) and statistically significant reduction in $\dot{V}O_2$ of leukemic rats ($P < .05$ v pretreatment values, paired Student's t test). However, in leukemic animals $\dot{V}O_2$ remained elevated by 33%

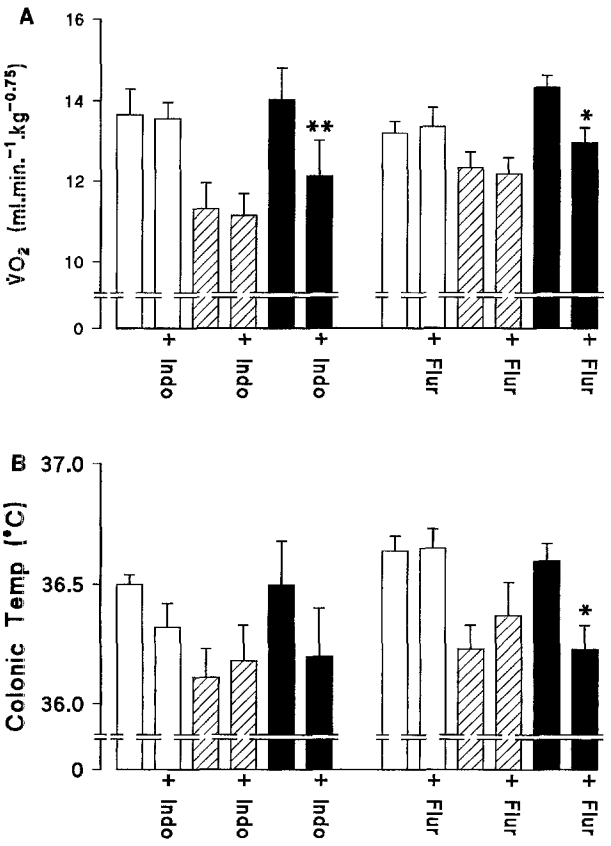

Fig 1. Effect of indomethacin (1 mg/kg IP) and flurbiprofen (1 mg/kg IP) on (A) $\dot{V}O_2$ and (B) Tc in (□) control, (▨) pair-fed, and (■) leukemic rats. Values are the mean ± SEM (n = 6 to 9). *$P < .05$ and **$P < .01$ v pretreatment values, paired Student's t-test.

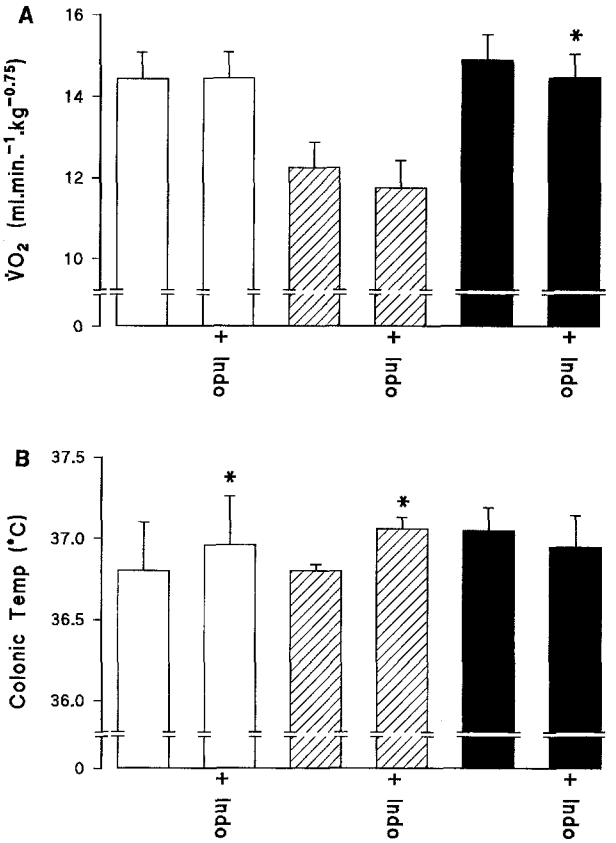

Fig 2. Effect of indomethacin (0.2 mg/kg ICV) on (A) $\dot{V}O_2$ and (B) Tc in (□) control, (▨) pair-fed, and (■) leukemic rats. Values are the mean ± SEM (n = 5 to 6). *$P < .05$ v pretreatment values, paired Student's t test.

compared with the level in pair-fed animals after indomethacin treatment. Indomethacin had no effect on Tc in leukemic animals, but slightly increased (0.3°C) Tc in control and pair-fed animals ($P < .05$ v pretreatment values, paired Student's t test).

Experiment 4: Chronic Effect of Indomethacin on Food Intake, Body Weight Change, Disease Status, and Organ Weights

Figure 3 illustrates food intake and body weight change of control and leukemic rats treated daily with indomethacin or vehicle. Due to the small number of values for food intake (n = 3 cages per group), data were not analyzed statistically. However, indomethacin appeared to have no effect on the food intake of control animals. In both groups of leukemic animals, food intake declined from days 10 to 15 and showed a profile similar to our previous data.[22]

Body weights of control animals treated with vehicle or indomethacin were similar, and increased at a constant rate over the duration of the experiment. The body weight of leukemic rats began to decline form day 10, but body weight in leukemic rats treated with indomethacin was slightly greater (vehicle, 232 ± 5 g; indomethacin, 246 ± 6 g) than in vehicle-treated rats. Over the duration of the experiment, the body weight response to indomethacin was significantly different between control and leukemic animals ($P < .001$, MANOVA, treatment over time). Although the body weight of leukemic rats (treated

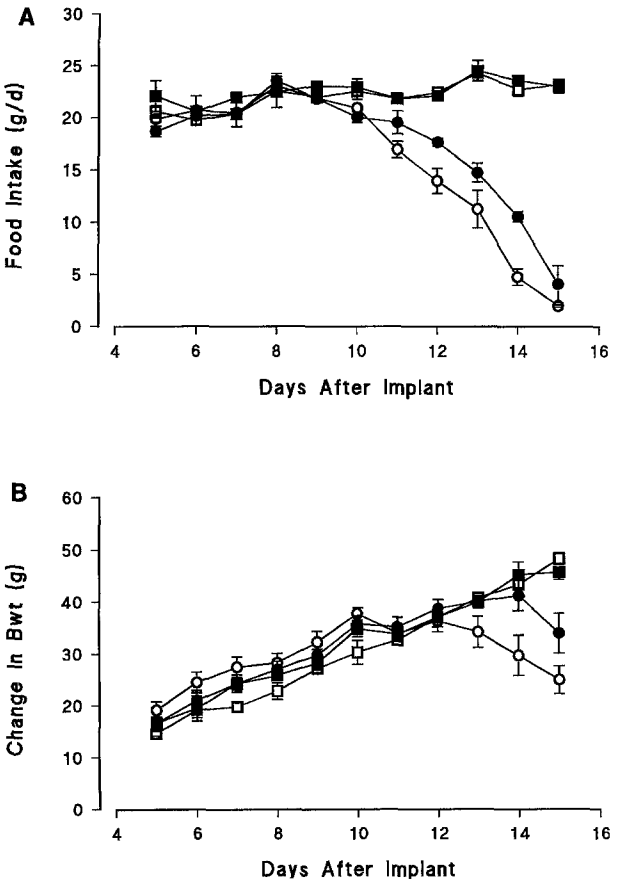

Fig 3. Effect of indomethacin (1 mg/kg/d IP) on (A) food intake and (B) body weight change in control (□, vehicle; ■, indomethacin) and leukemic (○, vehicle; ●, indomethacin) rats. Values are the mean ± SEM; food intake, n = 3; body weight, n = 6. Responses of the groups were significantly different over the experiment ($P < .001$, MANOVA).

with vehicle or indomethacin) was significantly less than that of their appropriate controls ($P < .001$, two-way ANOVA), indomethacin treatment did not specifically affect the response to leukemia, and the final body weight of leukemic animals treated with indomethacin (day 15) did not differ significantly from that of vehicle-treated leukemic rats (Table 1).

The data in Table 1 show the effect of indomethacin on body weight, disease status (WBC count and spleen weight), and epididymal fat pad and gastrocnemius weights on day 15 after implantation in control and leukemic animals. Spleen weight and WBC count were significantly elevated in leukemic animals compared with control animals ($P < .001$, two-way ANOVA; Table 1), but were not significantly affected by indomethacin treatment. Epididymal fat pad and gastrocnemius weights were significantly decreased in both leukemic groups compared with control animals ($P < .01$ and $P < .001$, respectively, two-way ANOVA). Indomethacin treatment had an independent effect on epididymal fat pad weight ($P < .05$, two-way ANOVA).

Experiment 5: Chronic Effects of Flurbiprofen on Food Intake, Body Weight Change, Disease Status, and Organ Weights

The food intake and body weight change of both groups of leukemic animals were significantly different from those of control animals over the duration of the experiment ($P < .001$, MANOVA; Fig 4), but were not influenced by flurbiprofen treatment.

The body weight of leukemic animals treated with vehicle or flurbiprofen on day 17 was similar and less than that of controls. Leukemic animals exhibited a disease profile (increased spleen weight and WBC count) and organ weights (decreased epididymal fat pad and gastrocnemius weights; data not shown) similar to those of the previous experiment. Flurbiprofen treatment did not significantly affect body weight, disease status, or organ weight of control or leukemic animals.

DISCUSSION

The results of this study are consistent with previous data characterizing the responses to T-cell leukemia and showing marked cachexia.[22] In the acute studies, experiments were performed at a time (days 13 to 16) when $\dot{V}O_2$ was elevated in leukemic rats compared with pair-fed, control animals. At this stage of disease, pair-fed and leukemic rats demonstrated a reduction (day 13, 15 and −1 g and day 16, −39 and −13 g, respectively) in body weight compared with control animals. Although pair-fed rats lost more weight, we have shown previously that this is due to greater water loss, and lean and fat mass is lost to a much greater extent in leukemic rats than in pair-fed controls. Previous data have shown that weight loss in leukemic animals is largely due to hypophagia but is accompanied by an inappropriately increased metabolic rate compared with energy intake, which was significantly greater than the $\dot{V}O_2$

Table 1. Body Weight, WBC Count, and Organ Weights of the Rat Groups (n = 6 per group) on Day 15 After Implantation (mean ± SEM)

Group	Final Body Weight (g)	Spleen Weight (g)	WBC Count (×10³/μL)	Epididymal Fat Pad		Gastrocnemius Muscle	
				g	g/100 g BW	g	g/100 g BW
Control							
Vehicle	266 ± 2	0.70 ± 0.01	4.0 ± 1.1	0.95 ± 0.01	0.34 ± 0.01	0.99 ± 0.08	0.37 ± 0.03
Indomethacin	265 ± 2	0.71 ± 0.01	3.8 ± 0.9	0.91 ± 0.02	0.36 ± 0.01	0.98 ± 0.08	0.37 ± 0.03
Leukemic							
Vehicle	232 ± 5	3.89 ± 0.55	227 ± 81	0.59 ± 0.07	0.25 ± 0.03	0.70 ± 0.03	0.30 ± 0.01
Indomethacin	246 ± 6	3.82 ± 0.36	214 ± 79	0.75 ± 0.07	0.30 ± 0.02	0.74 ± 0.04	0.30 ± 0.01
Independent effects (2-way ANOVA)							
Leukemia	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .01$	$P < .001$	$P < .01$
Indomethacin	—	—	—	$P < .05$	—	—	—

Abbreviation: BW, body weight.

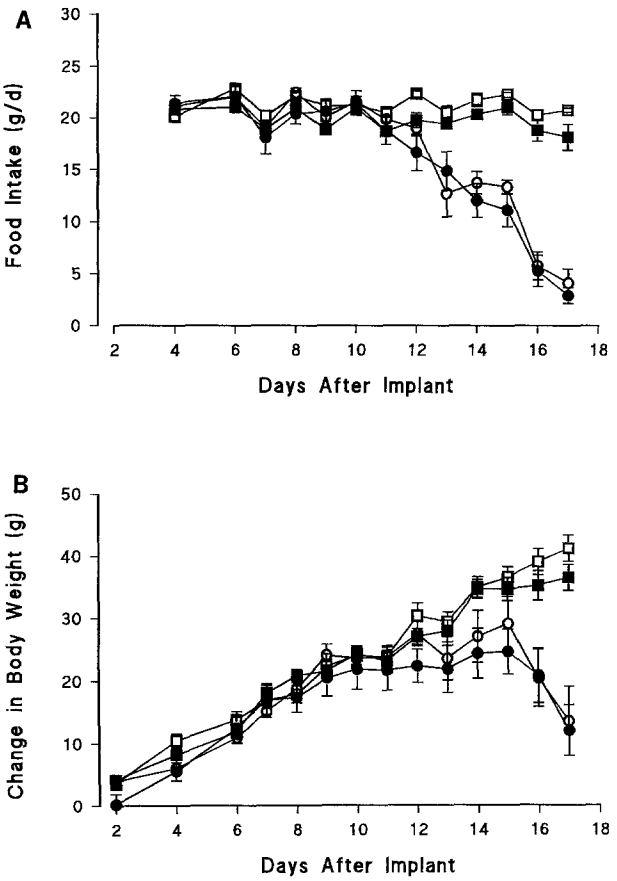

Fig 4. Effect of flurbiprofen (1 mg/kg/d IP) on (A) food intake and (B) body weight change in control (□, vehicle; ■, flurbiprofen) and leukemic (○, vehicle; ●, flurbiprofen) rats. Values are the mean ± SEM; food intake, n = 5; body weight, n = 10. Responses of the groups were significantly different over the experiment ($P < .001$, MANOVA).

of pair-fed nonleukemic animals. Therefore, in the present study, changes in metabolic rate were compared with those in a pair-fed (nonleukemic) group in addition to control animals. In each experiment, $\dot{V}O_2$ was assessed over several days, and the magnitude of the increase in leukemic animals varied from 16% to 25% compared with pair-fed animals and from 3% to 9% compared with controls.

Peripheral injection of indomethacin or flurbiprofen significantly reduced the hypermetabolism apparent in leukemic animals (Fig 1) and also reversed their elevated temperature compared with pair-fed animals. These results indicate that peripherally released prostaglandins are involved in the elevated metabolic rate of leukemic animals, and that prostaglandins may mediate the modest changes in body temperature. Alternatively, it is possible that the attenuation in metabolic rate may be due, at least in part, to a reduction in body temperature, since this may directly decrease the metabolic rate (due to a Q_{10} effect). Doses of cyclo-oxygenase inhibitors similar to those used in the present study have been shown previously to inhibit fever and hypermetabolism in response to systemic inflammation in rats,[26] and other stimuli (Turnbull and Rothwell, unpublished results, 1989). Since neither indomethacin nor flurbiprofen completely abolished the increase in $\dot{V}O_2$, it is possible that the doses used were submaximal, although this seems unlikely, since similar doses have proven effective in other studies.[26]

The study of energy expenditure in cachectic animals with solid tumors is complicated, and the results have been variable.[6,27,28] However, no reports exist in animals with hematological malignancies, and moreover, to our knowledge, no other published studies have investigated the mechanisms underlying the changes in metabolic rate. Similarly, measurements of energy expenditure in cancer patients are inconsistent.[5,29] Only one previous study in cancer patients has investigated the role of prostaglandins in hypermetabolism.[30] Hytlander et al[30] demonstrated that indomethacin administered orally to cancer patients with solid tumors had no effect on metabolic rate, which contrasts with the results presented in this study, but no published data exist on the effect of modifying the production/release of prostaglandins on the hypermetabolism in leukemic patients. This apparent discrepancy could reflect varied responses to different tumor types, ie, solid versus nonsolid/hematological.

ICV injection of indomethacin only slightly attenuated the hypermetabolism of leukemic animals and had no effect on the increase in Tc. Thus, it seems unlikely that leukemic animals exhibit a "true" fever (ie, an increase in the thermoregulatory set-point due to release of prostaglandins in the brain). Inhibition of the hypermetabolism in leukemic rats by central injection of indomethacin was statistically significant but represented only a modest (5%) effect, and indomethacin failed to prevent the increase in $\dot{V}O_2$. This suggests that peripherally rather than centrally released prostaglandins mediate the hypermetabolic responses to leukemia. It seems unlikely that the dose of indomethacin injected ICV was insufficient to block these responses, because in a separate study (data not shown) in leukemic rats a higher dose (150 μg) was also ineffective. The lower dose of indomethacin has been shown previously to suppress febrile and corticotropin responses to central injection of IL-1β,[31] and similar doses of cyclo-oxygenase inhibitors have abolished the increases in Tc and hypermetabolism induced by systemic inflammation.[26] Nevertheless, it is possible that peripherally released eicosanoids cross the blood-brain barrier[25] and influence the metabolic rate in leukemic animals. For example, prostaglandin E_2 (PGE_2), PGE_1, and $PGF_{2\alpha}$, when injected centrally into animals, are potent thermogenic and pyrogenic agents.

Long-term administration of indomethacin caused modest increases in food intake and slightly attenuated the weight loss in rats with T-cell leukemia, but flurbiprofen had no effect on either food intake or body weight. Although administration of either indomethacin or flurbiprofen attenuated the hypermetabolism of leukemic rats, body weight was not significantly affected. This is probably because the metabolic rate of leukemic animals was increased only in comparison to animals with a reduced food intake (pair-fed) and was not significantly elevated compared with control animals. Measurements of organ weight were used to estimate changes in body fat and protein. Indomethacin and flurbiprofen had no effect on gastrocnemius muscle weight in leukemic animals; however, indomethacin significantly inhibited the decline in epididymal fat pad weight in leukemic animals measured on day 15 (Table 1). In

support of the latter finding, others have demonstrated that inhibiting prostaglandin synthesis and action attenuates fat loss in tumor-bearing animals,[8,10] but in contrast to the present study, they also reported an improvement in fat-free mass. The data in the present study indicate that indomethacin preferentially preserved fat, and not lean tissue. However, the fat and muscle masses assessed may not be representative of body fat and lean tissues, so it is possible that lean tissue was also preserved. Direct assessment of total fat and lean masses can be achieved only by body compositional analysis.

These data contrast with several published studies on solid tumors.[8-10] Gelin et al[10] and Tanaka et al[8] demonstrated that in mice bearing a sarcoma or a colon 26 carcinoma, respectively, indomethacin administered either in the drinking water or by daily subcutaneous injection at doses similar to those used in the present study (1 mg/kg) improved appetite and body weight loss and inhibited tumor growth. Sandström et al[9] also reported that in rats bearing a methylcholanthrene-induced sarcoma, indomethacin treatment (at the same dose as used in the present study) in the drinking water significantly improved food intake and tumor growth. In contrast, McCarthy and Daun[32] demonstrated that in rats bearing a Walker 256 carcinoma, long-term systemic administration of indomethacin had no effect on the tumor-induced anorexia or body weight loss. These discrepancies may be explained, at least in part, by differences between leukemia and solid tumors.

Flurbiprofen also had no effect on the parameters of cachexia measured in the present study. It is possible that the dose of flurbiprofen used long-term was insufficient to attenuate the changes in food intake or body weight of leukemic animals, but this seems unlikely, since the same dose given short-term had significant effects on body temperature and thermogenesis. However, differences in pharmacokinetics, solubility, and bioavailability could explain the varied responses to long-term administration. Although flurbiprofen is claimed to be one of the most potent cyclo-oxygenase inhibitors,[33] the potency of indomethacin and flurbiprofen was not compared directly in the present study.

Prostaglandins have been implicated in the growth and proliferation of many solid tumors. However, in the present study, long-term treatment with indomethacin and flurbiprofen did not affect disease status (spleen weight and WBC count; Table 1). The results presented are supported by previous findings that in tumor-bearing animals prostaglandins are not involved in tumor growth.[34,35] These varied effects of indomethacin on cachexia and disease status are difficult to interpret, but may be partly explained by different methods of drug administration, dosages, and, moreover, types and sizes of tumors.

To our knowledge, the present study is the first to investigate the involvement of prostaglandins in the cachexia induced by leukemia and to suggest that prostaglandins may contribute to the acute hypermetabolism (and possibly pyrexia) but are not involved in the chronic effects of hypophagia or cachexia induced by T-cell leukemia.

Overall, the results of this study indicate that prostaglandins produced peripherally are involved in the increased energy metabolism and body temperature of leukemic rats. However, eicosanoids are probably not involved in the long-term changes in food intake and body weight observed in cachexia induced by T-cell leukemia in the rat. This latter finding contrasts with published studies on experimentally induced solid tumors, and indicates that extrapolation from investigations on specific tumor types may not be valid.

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