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Mechanism of Early Tumor Anorexia

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Whether in tumor-bearing rats a temporal relationship exists between an increase in plasma free tryptophan (FTRP), an increase in brain serotonin (5-HT), and onset of anorexia was studied. Rats were assigned to three groups: tumor-bearing (TB), pair fed (PF), and controls. Food intake was recorded daily. In TB rats anorexia developed on Day 18 and thereafter food intake decreased progressively until end of study. After tumor inoculation, tumor became palpable on Day 10 and continued to grow exponentially until end of study. Rats were killed on Days 6, 10, 16, 18, 22, and 26 to determine plasma FTRP, FTRP/LNAA, and brain 5-HT and compared to PF and controls. On Day 6, before tumors became detectable, FTRP and FTRP/LNAA were increased ($P < 0.05$) in TB rats vs controls. Both continued to increase so that by Day 18 when food intake had started to decrease ($P < 0.05$), brain 5-HT increased and correlated with the onset of anorexia ($R^2 = 0.6$, $P < 0.05$). Increases in plasma FTRP the precursor to brain 5-HT occurred in TB rats before physical appearance of tumor and increased until an increase in brain 5-HT occurred, leading to anorexia.

INTRODUCTION

The presence of a tumor profoundly alters the host's metabolic and clinical status. It is associated with changes in general metabolism, but in particular, protein metabolism. Associated symptoms include a reduction in food intake due to cancer-related anorexia [1, 2]. These two cancer-related aspects, (1) impairment of protein metabolism and (2) anorexia, are closely related. Specific alterations of plasma free amino acid profiles have been described in cancer patients [3–8], as well as in tumor-bearing animals [9]. The observed changes in the concentrations of plasma amino acids have been also shown to affect the synthesis of brain neurotransmitters, by altering the bioavailability of their precursor amino acid [10]. Brain serotonin (5-HT) and its precursor, plasma tryptophan, has a role in the pathogenic mechanisms leading to cancer-related anorexia. It has been suggested that increased brain availability of tryptophan results in increased brain 5-HT synthesis and serotonergic activity, thus leading to reduced food intake [11]. Indeed, in cancer patients and in tumor-bearing animals, a strong relationship exists between the presence of anorexia and increased brain tryptophan availability [12, 13]. Temporarily blocking ventromedial hypothalamic (VMH) 5-HT activity with colchicine increased food intake in anorexic tumor-bearing rats for 5 days (Laviano *et al.*, submitted).

However, a limiting factor in the above-cited studies is that plasma free amino acid profiles and brain neurochemistry are assessed at a single time point during the course of tumor growth, usually after the tumor has become physically evident and has been diagnosed. We hypothesize that the changes in the host's protein metabolism occurs very early during tumor growth, before physical appearance of the tumor, as assessed by changes in plasma free amino acids, even before the presence of the tumor becomes clinically evident and contributes to the onset of anorexia.

The syntheses of brain neurotransmitters, known to be influenced by precursor availability, are produced from compounds that must be obtained in whole or in part from the diet and thus, brain neurotransmitters are involved in regulation of feeding. Chance *et al.* [10] studied regional analysis of brain neurotransmitter precursors and metabolite concentrations in rats during food-deprivation, while eating a small amount of food, and while eating to satiation, as compared to fed controls. There were no intragroup changes in dopamine, norepinephrine, and 5-HT concentrations in any regions. Nor were regional differences found between fed controls and the three other treatments. However, there was a significant increase in 5-hydroxyindoleacetic acid (5-HIAA) in all regions measured in all groups vs controls, indicating that changes in the brain 5-HT metabolite were satiety related.

The purposes of our study were to serially measure plasma free tryptophan (FTRP) and the other large

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neutral amino acids (LNAA) and to calculate their ratio (FTRP/LNAA) in order to correlate these with measured brain 5-HT in the tumor-bearing rats during the evolutionary growth of the tumor. These data were compared to those in pair-fed rats and control rats in order to determine if neurotransmitter changes occurred early during tumor growth, which might be related to the development of early tumor anorexia. For the purpose of this study, whole brain rather than regional differences were initially examined. We recognize that if differences in whole brain neurotransmitters were detected, then regional differences and dynamic flux studies would need to be done in subsequent studies. We believe that the changes of whole brain neurotransmitter are capable of linking of the function neurotransmitter with the accompanied changes in feeding behavior as an adequate first approximation.

MATERIALS AND METHODS

General. Adult, male Fischer 344 rats (Charles River, Inc., Wilmington, MA) with an initial body weight of 220–280 g were housed individually in a temperature (26 ± 1°C)-, humidity (45%)-, and light (12-hr light cycle; lights on 0600–1800)-controlled room. Rats had continuous access to water and fresh coarsely ground rat chow (Diet 5008; Ralston Purina Co., St. Louis, MO). Daily food intake of each rat for the preceding day was gravimetrically measured between 0800 and 0900. Then a fresh supply of water and rat chow from the same initial stock were provided.

After a 7- to 10-day acclimatization period, 112 rats were randomly assigned to three treatment groups: control, tumor-bearing, and pair fed. Control and pair-fed rats received a subcutaneous inoculation of 1 ml of 0.9 *N* saline into the right flank, while tumor-bearing rats were given a 1-ml inoculum of methylcholanthrene (MCA) sarcoma cells. The MCA tumor cells were prepared according to the method of Madden and Burke [14]. Based on previous studies in our laboratory [9, 15, 16], an inoculum of 10^6 viable MCA cells led to appearance of a tumor in all rats 10 to 12 days after inoculation.

Experimental design. The study was approved by the Committee for the Humane Use of Animals, SUNY Health Science Center at Syracuse, and was in accordance with the guidelines established by the National Institutes of Health. After inoculation, rats were placed in individual cages with free access to water and chow. Food intake was measured daily. Groups of eight rats were sacrificed 6, 10, 16, 18, 22, and 26 days after inoculation. Because previous studies demonstrated that food intake of tumor-bearing rats decreased approximately 18 days after MCA-tumor inoculation [13], the pair-fed group was studied only for Days 22 and 26.

Twelve-hour fasted rats were anesthetized with 3% chloral hydrate (30 mg/100 g body weight, i.p.) and exsanguinated via cardiac puncture, being killed at 0800. Blood was collected into refrigerated tubes and immediately centrifuged at +4°C. The harvested serum or plasma was stored at −80°C for subsequent analysis. Whole brains were rapidly excised and clamp frozen using aluminum tongs precooled in liquid nitrogen. Frozen tissues were maintained at −80°C until analysis. Each time rats were killed, where applicable, tumors were dissected out and weighed.

Biochemical analysis. Plasma valine, leucine, isoleucine, tyrosine, phenylalanine, and tryptophan concentrations were determined in deproteinated (via sulfosalicylic acid) samples using a Beckman 6300 autoanalyzer (Beckman Instruments, Palo Alto, CA). Plasma free tryptophan was separately measured using HPLC according to the method described by Wolf and Kuhn [17]. Serum was analyzed for albumin and free fatty acids using commercially available kits (Sigma, St. Louis, MO).

Whole brain tissue was homogenized in 2 ml of 0.05 *M* perchloric acid using a Tissumizer (Tekmar) and centrifuged at 14,000 rpm for 45 min at 0°C. The supernatant was collected and stored frozen at −80°C for later analysis. The stored supernatant was thawed and deproteinated with 50% sulfosalicylic acid and centrifuged for 20 min at 5000 rpm at 0°C. The supernatant was filtered through a 0.2-μm Gelman syringe filter and collected for dopamine, 5-HT and the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) analysis, which was performed on a Beckman 344 HPLC, using a Bioanalytical System LC-4B Amperometric Detector, as previously described [18]. Brain dihydroxyphenylacetic acid concentrations were not measured in this study, as they are not an absolute index of dopamine metabolism [19].

Statistical analysis and data management. Data were analyzed using analysis of variance (ANOVA), Scheffe's post hoc *t* tests, and linear regression analysis. A P value of < 0.05 was considered significant. Data are expressed as mean ± SE. The ratio of plasma free tryptophan to large neutral amino acids was analyzed because it is thought to better predict brain tryptophan concentrations [20].

RESULTS

Tumor Appearance and Growth

Tumors became palpable in all tumor-bearing rats 10 to 11 days after inoculation. Tumor weights increased from 3% of host body weight on Day 16 to 8% of host body weight by Day 26.

Plasma Free Amino Acid Concentrations

Temporal changes in the LNAA (valine, leucine, isoleucine, tyrosine, phenylalanine) and plasma free tryptophan are summarized in Tables 1 and 2. Free tryptophan concentrations increased following tumor inoculation, plasma free tryptophan being already elevated by Day 6 after tumor inoculation in the tumor-bearing relative to control rats. This finding persisted throughout the study, the highest concentrations occurring on Days 22 and 26. On Day 26, rats in the pair-fed group also had a significant increase in free tryptophan concentration.

Within 6 days of tumor inoculation, significant decreases in the concentrations of valine, leucine, and isoleucine occurred in tumor-bearing rats relative to controls. Valine, leucine, and isoleucine concentrations in pair-fed group were lower relative to controls on Days 22 and 26. No consistent pattern of change was observed for tyrosine and phenylalanine concentrations throughout the study.

Serum Albumin and Free Fatty Acid

No consistent changes were observed in either albumin or free fatty acid levels (Table 3). The significantly lower mean serum albumin of tumor-bearing rats on Day 22 was due to the low values obtained from three rats; the remaining five rats in this group had normal albumin concentrations.

Changes in Food Intake

Mean daily food intake did not differ between tumor-bearing and control rats for the first 16 days after tumor inoculation. As anticipated, 18 days after tumor inoculation, a progressive reduction in mean daily food intake started to occur in tumor-bearing rats (Fig. 1) so that by Day 25 the mean food intake of tumor-bear-

TABLE 1

Temporal Changes in Mean (Mean ± SE) Concentrations (nmole/50 μl) of Plasma Large Neutral Amino Acids during the Study

Day	Group	Large Neutral Amino Acids				
		Val	Leu	Ile	Tyr	Phe
	Control	8.51 ± 0.37	6.60 ± 0.36	3.89 ± 0.25	3.27 ± 0.07	2.50 ± 0.09
	Tumor-bearing	6.66 ± 0.32	4.77 ± 0.07	3.00 ± 0.07	3.19 ± 0.09	2.31 ± 0.04
	$P <$	0.01	0.01	0.001	0.5	0.036
10	Control	7.89 ± 0.20	5.26 ± 0.22	3.20 ± 0.11	3.65 ± 0.14	2.59 ± 0.08
	Tumor-bearing	6.32 ± 0.21	4.09 ± 0.18	2.62 ± 0.12	3.02 ± 0.14	2.07 ± 0.09
	$P <$	0.002	0.001	0.004	0.009	0.001
16	Control	8.50 ± 0.16	5.98 ± 0.14	3.74 ± 0.09	3.41 ± 0.06	2.48 ± 0.036
	Tumor-bearing	7.25 ± 0.53	5.13 ± 0.26	3.39 ± 0.17	3.44 ± 0.15	2.99 ± 0.15
	$P<$	0.0035	0.003	0.08	0.85	0.0001
18	Control	7.52 ± 0.53	5.07 ± 0.13	3.16 ± 0.05	3.28 ± 0.16	2.54 ± 0.09
	Tumor-bearing	6.34 ± 0.9	4.06 ± 0.13	2.88 ± 0.10	3.22 ± 0.12	2.45 ± 0.06
	$P <$	0.03	0.0003	0.044	0.74	0.42
22	Control	9.13 ± 0.18	6.46 ± 0.13	4.14 ± 0.10	3.38 ± 0.13	2.43 ± 0.07
	Tumor-bearing	6.59 ± 0.47*	4.81 ± 0.34*	3.13 ± 0.15*	3.00 ± 0.16*	2.35 ± 0.11
	Pair-fed	6.28 ± 0.24*	4.37 ± 0.12*	2.89 ± 0.08*	2.80 ± 0.06*	2.10 ± 0.05*,**
	$P <$	0.0001	0.0001	0.0001	0.005	0.01
26	Control	8.70 ± 0.32	6.92 ± 0.24	4.42 ± 0.17	3.39 ± 0.10	2.59 ± 0.09
	Tumor-bearing	6.57 ± 0.41*	4.64 ± 0.31*	3.24 ± 0.15*	2.87 ± 0.16	2.44 ± 0.11
	Pair-fed	8.08 ± 0.58**	5.40 ± 0.32*	3.58 ± 0.20*	3.18 ± 0.22	2.43 ± 0.17
	$P <$	0.01	0.0001	0.0005	0.11	0.62

* Significantly different vs controls.
** Significantly different vs tumor-bearing.

ing rats was approximately 40% of that on Day 18. However, approximately 50% of rats sacrificed on Days 22 and 26 were anorectic, their daily food intake ranging between 0 and 5.25 g/day; the remainder were not anorectic (nonanorectic). No correlation was found between tumor mass and anorexia.

TABLE 2

Mean Plasma Free TRP Concentrations, Mean Values of the Sum of Large Neutral Amino Acids (LNAA) Valine, Leucine, Isoleucine, Tyrosine, and Phenylalanine in Plasma, and Mean Values of the Ratio Free TRP/LNAA (Mean ± SE)

Day	Group	Free TRP (nmol/50 μl)	LNAA (nmol/50 μl)	Free TRP/LNAA
6	Control	0.31 ± 0.01	24.77 ± 0.89	0.014 ± 0.001
	Tumor-bearing	0.41 ± 0.04	20.03 ± 0.40	0.021 ± 0.002
	P	<0.05	<0.001	=0.01
10	Control	0.38 ± 0.04	22.58 ± 0.055	0.017 ± 0.001
	Tumor-bearing	0.44 ± 0.04	18.17 ± 0.39	0.027 ± 0.002
	P	<0.05	=0.0001	<0.01
16	Control	0.26 ± 0.02	24.11 ± 0.78	0.011 ± 0.001
	Tumor-bearing	0.38 ± 0.05	22.20 ± 0.63	0.017 ± 0.001
	P	<0.02	ns	<0.01
18	Control	0.33 ± 0.03	21.58 ± 0.88	0.014 ± 0.0005
	Tumor-bearing	0.38 ± 0.02	18.96 ± 0.48	0.021 ± 0.001
	P	<0.07	=0.01	<0.001
22	Control	0.29 ± 0.01	26.19 ± 0.86	0.010 ± 0.001
	Pair-fed	0.28 ± 0.02	18.43 ± 0.52*	0.015 ± 0.001*
	Tumor-bearing	0.58 ± 0.06*,**	19.88 ± 1.1*	0.027 ± 0.005*,**
	P	<0.001	<0.01	=0.01
26	Control	0.30 ± 0.02	26.01 ± 0.84	0.011 ± 0.001
	Pair-fed	0.65 ± 0.05*	22.67 ± 1.41*	0.033 ± 0.004*
	Tumor-bearing	0.65 ± 0.04*	19.75 ± 0.97*[a]	0.034 ± 0.003*
	P	<0.0001	*=0.05 *[a]=0.004	*<0.001

* Significantly different vs controls.
** Significantly different vs pair-fed group.

TABLE 3

Albumin and Free Fatty Acid (FFA) Concentrations during the Study (Mean ± SE)

Day	Group	Albumin (g/liter)	FFA (mmole/liter)
6	Control	38.7 ± 1.34	0.50 ± 0.07
	Tumor-bearing	42.7 ± 0.37	0.47 ± 0.07
	P	ns	ns
10	Control	42.2 ± 0.91	0.35 ± 0.01
	Tumor-bearing	40.2 ± 0.86	0.38 ± 0.02
	P	ns	ns
16	Control	40.4 ± 0.88	0.55 ± 0.07
	Tumor-bearing	39.4 ± 1.47	0.77 ± 0.07
	P	ns	<0.05
18	Control	39.5 ± 0.96	0.48 ± 0.06
	Tumor-bearing	39.4 ± 0.60	0.56 ± 0.02
	P	ns	ns
22	Control	41.8 ± 0.9	0.40 ± 0.03
	Pair-fed	39.46 ± 1.26	0.49 ± 0.02
	Tumor-bearing	32.9 ± 2.56*,**	0.42 ± 0.06
	P	*<0.005 **<0.05	ns
26	Control	37.44 ± 1.5	0.28 ± 0.03
	Pair-fed	37.88 ± 1.5	0.41 ± 0.05*
	Tumor-bearing	37.9 ± 2.01	0.56 ± 0.04*
	P	ns	<0.05

* Significantly different vs controls.
**Significantly different vs pair-fed group.

Changes in Plasma LNAA and Their Ratios during Tumor Growth

The concentrations of plasma free tryptophan, the sum of the LNAA (valine, leucine, isoleucine, tyrosine, phenylalanine) and the plasma ratio of free tryptophan to LNAA are shown in Table 3. Relative to the control rats, the sum of LNAA was significantly reduced in tumor-bearing rats starting 6 days after tumor inoculation, brought about mainly by a reduction in valine, leucine, and isoleucine.

The ratio of plasma free tryptophan to LNAA was significantly and consistently increased in the tumor-bearing versus control rats starting as early as Day 6 after tumor inoculation. This increase is produced by the early and consistent increase in free tryptophan concentrations and by the decrease in the concentrations of the competing plasma amino acids. On Day 22, when compared to controls, the sum of LNAA was also reduced in pair-fed rats. Consequently, the ratio was also consistently increased despite free tryptophan concentrations being comparable to that of controls. On Day 26, pair-fed rats showed decreased LNAA and increased free tryptophan concentrations; consequently, the ratio of free tryptophan to LNAA was also consistently increased with respect to control rats.

Changes in Brain Serotonin (5-HT) and 5-HIAA

Concentrations of dopamine, 5-HT, and 5-HIAA at the different time points in the study are summarized in Fig. 2. Whole brain dopamine concentrations did not show a consistent pattern during tumor growth. From Day 22 onward, brain 5-HT metabolism (as expressed by the ratio 5-HIAA:5-HT [21]) was significantly increased in tumor-bearing rats relative to control and pair-fed rats (Fig. 3).

Since anorexia appeared only after Day 18, tumor-bearing rats sacrificed on Days 22 and 26 after tumor inoculation were considered together. In these rats, which showed very high plasma concentrations of free tryptophan (Table 3), a significant correlation was found between plasma free tryptophan concentrations and brain 5-HT (Fig. 4). The ratio of free tryptophan to LNAA was also significantly correlated with brain 5-HT concentrations (Fig. 5). In the same rats a significant inverse correlation was also shown between plasma free tryptophan and mean daily food intake (Fig. 6).

DISCUSSION

Our data indicate that protein host–tumor metabolic interactions occur very early during tumor growth, causing changes in plasma amino acids, ultimately leading to altered brain neurochemistry even before the physical appearance of the tumor. Changes in host's protein metabolism are initiated at a very early stage after tumor inoculation, and changes are maintained throughout the course of the disease. Findings underscore that changes in plasma amino acids and brain neurochemistry obtained at single time points from humans with cancer do not adequately provide data on the changes in host–tumor metabolic interactions occurring during tumor growth, from the earliest to latest stages of disease. Such insight is possible only by using an experimental tumor model.

The increase in plasma free tryptophan following tumor inoculation confirms previous data from our group obtained in cancer bearing patients [7, 12, 22, 23]. The reasons for the increase in free tryptophan remain to be established, although in this study it was not related to changes in serum albumin or free fatty acids. Prelim-

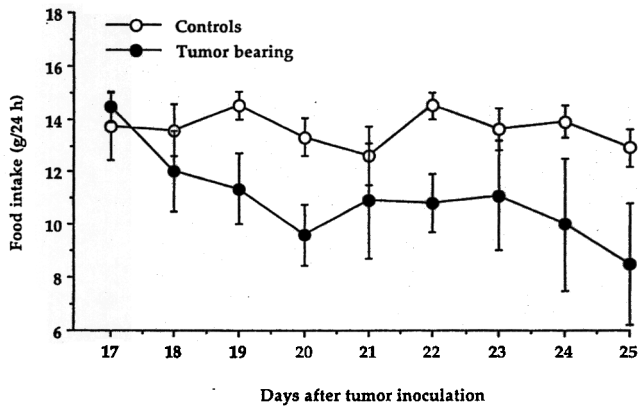

FIG. 1. Mean ± SE daily food intake (g/24 hr) in tumor-bearing and control rats from Day 18 after tumor inoculation onward.

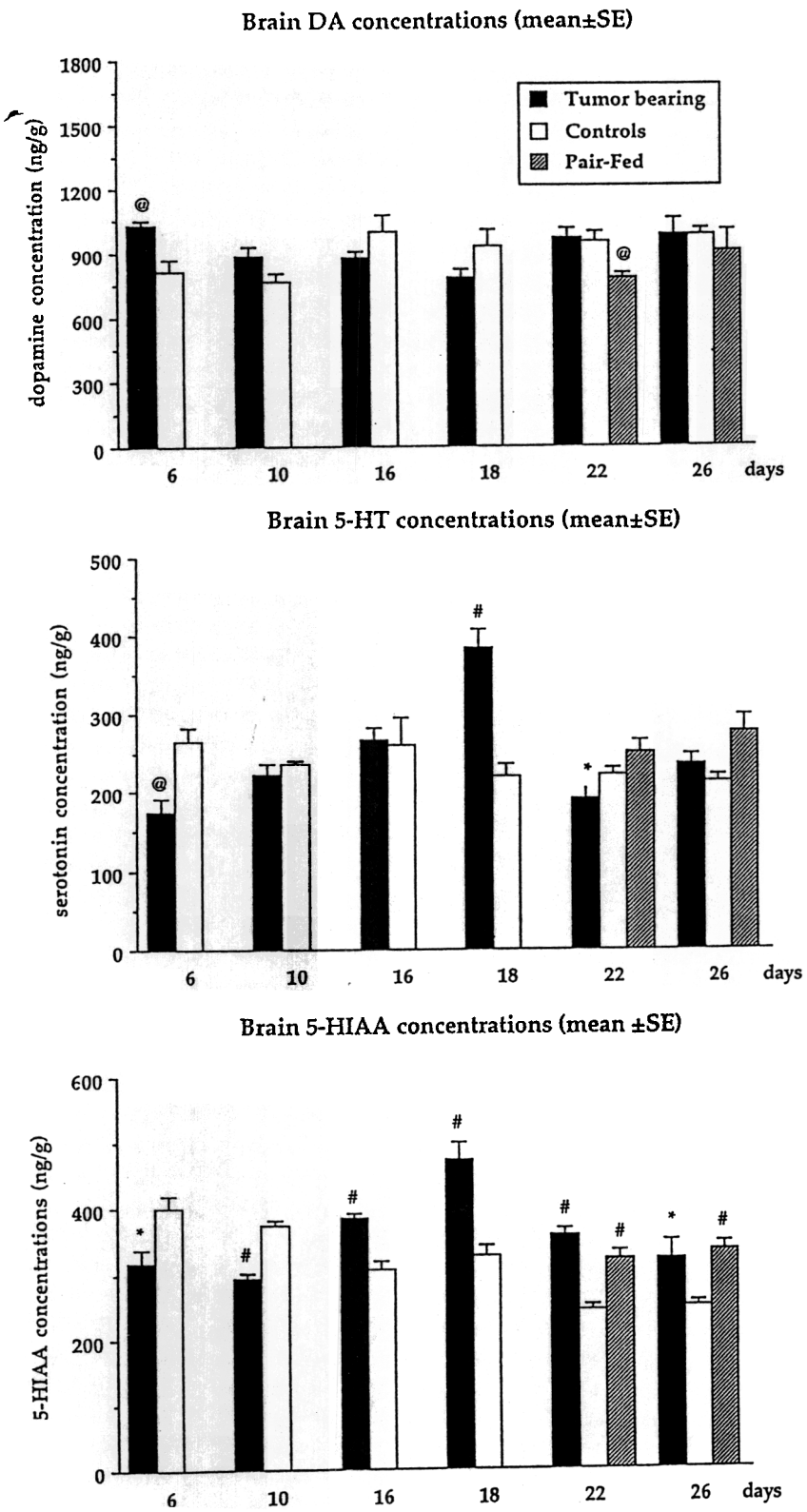

FIG. 2. Brain concentrations (ng/g) of dopamine, 5-HT, and 5-HIAA at the different time points during the study. *$P < 0.05$; @$P < 0.01$; #$P < 0.001$ vs controls, except for 5-HT Day 22 (vs pair-fed).

inary data show that a constant infusion of Interleukin-1α given to normal rats caused an increase in brain tryptophan concentrations. We have, however, shown that free tryptophan concentrations rapidly normalized after tumor removal [22]. The finding of increased concentrations of free tryptophan in pair-fed rats on Day 26 might be related to a deterioration in the rat's nutritional state, because plasma concentrations of this

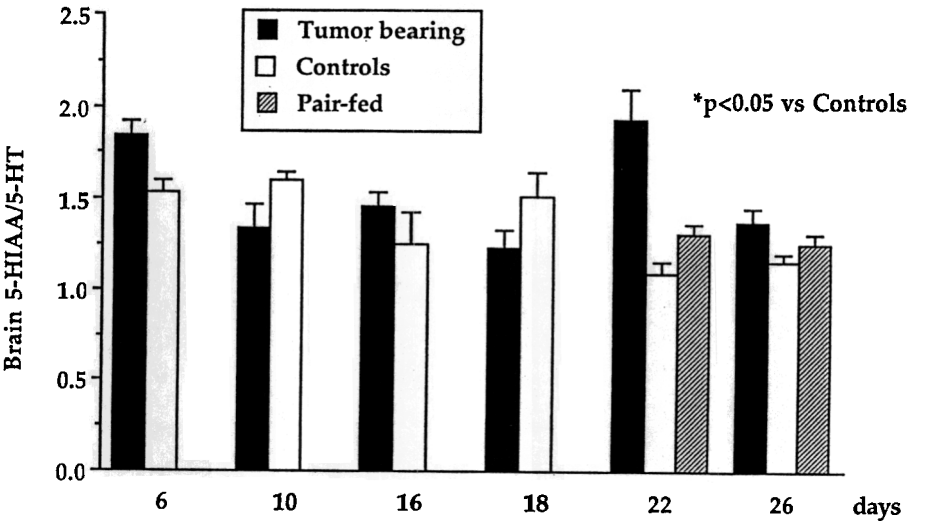

FIG. 3. Brain serotonin metabolism, as expressed by the ratio 5-HIAA:5-HT at different time points during the study. *$P < 0.05$ vs controls.

amino acid may increase with the progression of malnutrition [7].

The early increase of plasma free tryptophan was paralleled by a concomitant early decrease in plasma LNAA concentrations, thus leading to an increase of the ratio free tryptophan to LNAA and, consequently, of brain tryptophan availability [20]. In cancer patients elevated plasma free tryptophan concentrations and increased ratio of free tryptophan to LNAA have been previously shown to correlate with the presence of anorexia [12, 24], at least at a single moment in the natural history of neoplastic patients, namely, tumor diagnosis by screening procedures. However, in our rat model, these changes in plasma free amino acid concentrations occurred long before the appearance of anorexia. A reduction of food intake in tumor-bearing rats was in fact apparent only after 18 days of tumor growth, concomitant with a further marked increase in free tryptophan concentrations and the values of the ratio of free tryptophan to LNAA. These findings suggest the presence of a threshold effect (for tryptophan transport across the blood–brain barrier in the presence of a growing tumor), i.e., a critical concentration in plasma below which there is no decrease in food intake. Once this concentration or a certain value of the ratio is exceeded, anorexia occurs. A similar finding has been reported recently in patients with chronic liver failure [25].

It has been postulated that increased brain tryptophan availability may mediate cancer anorexia, by increasing brain 5-HT synthesis [11]. Indeed, in the present study, we found that plasma free tryptophan con-

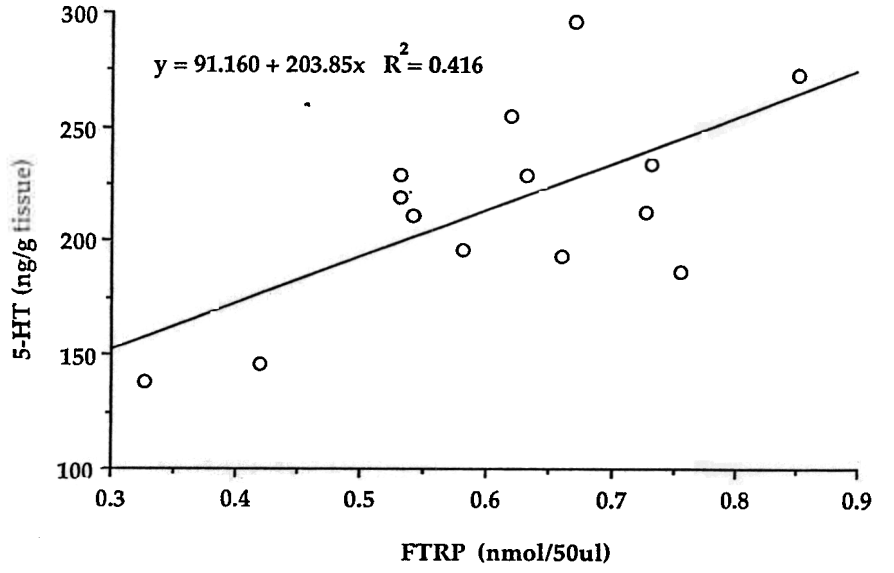

FIG. 4. Correlation between plasma free TRP (nmole/50 μl) and brain 5-HT (ng/g tissue) in tumor-bearing rats sacrificed on Days 22 ($n = 7$) and 26 ($n = 7$). $R^2 = 0.416$; $P < 0.02$.

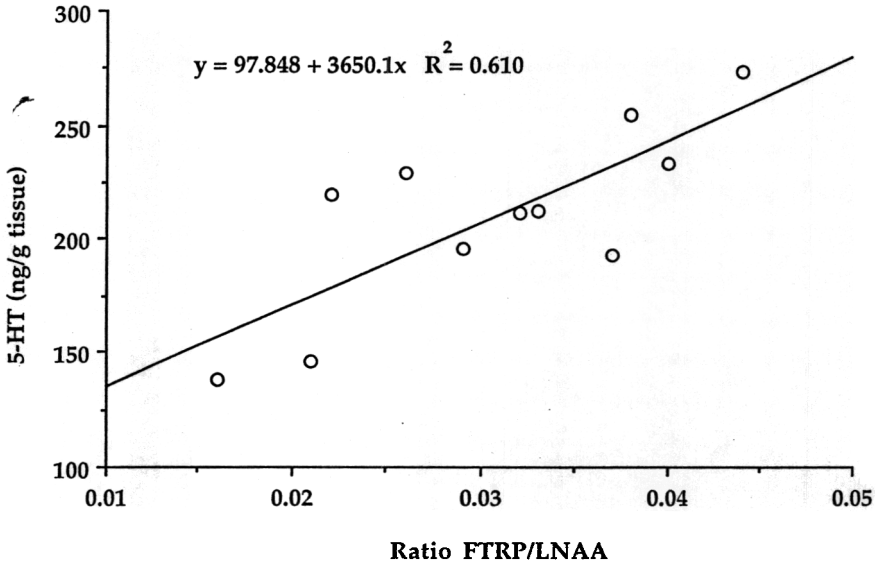

FIG. 5. Correlation between the ratio free TRP:LNAA in plasma and brain 5-HT concentrations (ng/g tissue) in tumor-bearing rats sacrificed on Days 22 (n = 5) and 26 (n = 6). R^2 = 0.610; $P < 0.05$.

centrations and the ratio of free tryptophan to LNAA are directly correlated with brain 5-HT levels and food intake. The analysis of the whole brain concentrations of neurotransmitters further support the role of 5-HT in cancer anorexia. While dopamine concentrations did not show a significant pattern during tumor growth in the three groups studied (as anticipated by the lack of changes in the plasma concentrations of its precursor phenylalanine), brain 5-HT metabolism increased significantly in tumor-bearing rats concomitantly with the consistent development of anorexia.

Surprisingly, despite the significant elevation of brain 5-HT and 5-HIAA concentrations on Day 18, 5-HT metabolism in tumor-bearing rats was not different from that observed in control rats. The lack of consistency in brain 5-HT metabolism data on Day 18 for tumor-bearing rats could be due to our study design, based on previous studies in our laboratory using this model, in which anorexia developed on Day 18 [13]. However, anorexia did not occur uniformly and to the same degree in all rats as of Day 18. Thus, the plasma free amino acid profiles and brain concentrations of neurotransmitters from Day 18 onward in tumor-bearing rats were not as consistent as one would have expected. Supporting evidence comes from the finding that anorectic tumor-bearing rats sacrificed on Days 22 and 26, when considered together, showed increased brain 5-HT metabolism, although not significantly so when compared with nonanorectic rats in the same group (data not shown).

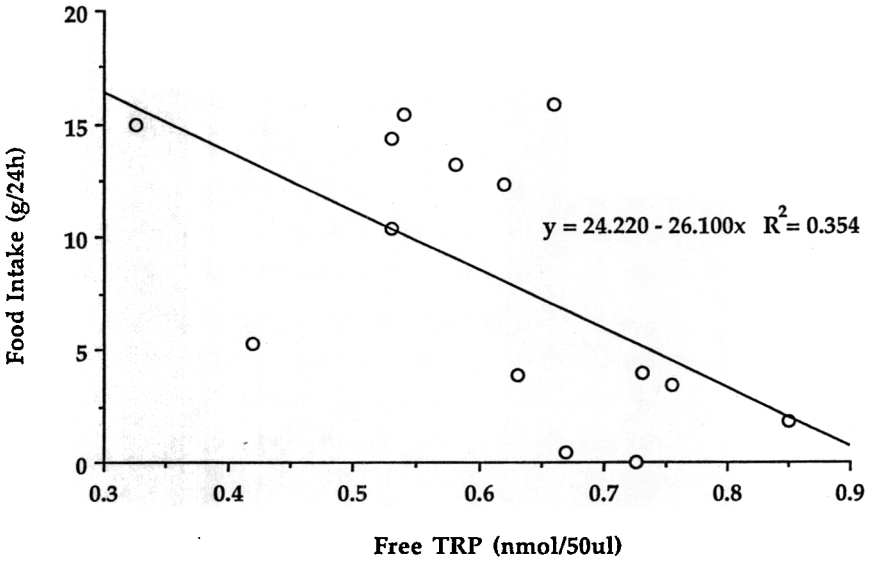

FIG. 6. Correlation between plasma free TRP (nmole/50 μl) and daily food intake (g/24 hr) in tumor-bearing rats sacrificed on Days 22 (n = 7) and 26 (n = 7). R^2 = 0.354; $P < 0.03$.

Despite the high levels of free tryptophan and the ratio, not all the rats on Days 22 and 26 became anorectic, in some of them the food intake being comparable to control rats. This would suggest that in the presence of a tumor there might be other factors influencing the central regulation of food intake in addition to the increased serotonergic activity. The nature of this factor(s), as well as the reasons for the increase of free tryptophan concentrations during tumor growth, are currently under study using a definition of anorexia that is in accordance with that of Chance *et al.* [26]. However, recent evidence suggests a role for endogenous cytokines. Peripheral and intracerebral injections of Interleukin-1 and tumor necrosis factor are known to reduce food intake [27]. In addition, the infusion of Interleukin-1 has been demonstrated to increase cerebrospinal fluid (CSF) and brain tryptophan levels and whole brain concentration of 5-HT [28]. Furthermore, we recently demonstrated that CSF Interleukin-1 levels are increased in CSF of tumor-bearing rats compared to that seen in controls and that it correlates negatively with daily food intake [29]. As the pattern of changes in brain biochemistry observed during Interleukin-1 infusion is similar to that observed in this and other studies involving tumor-bearing rats [10, 30], it is conceivable that peripheral cytokines may have a role in determining the alterations in plasma free amino acid profiles and brain neurochemistry observed during tumor growth. In cancer patients, available data are conflicting. It would appear, however, that cytokine production at local brain, rather than a peripheral site, may have a role in the pathogenesis of anorexia in human cancer [23].

Our data suggest that: (1) changes in plasma amino acids occur early during tumor growth; (2) changes in plasma free amino acid profiles do not consistently alter brain dopamine concentrations; (3) changes in plasma free amino acid profiles do not consistently alter brain 5-HT metabolism, unless a critical value of plasma free tryptophan or free tryptophan to LNAA ratio is exceeded; and (4) changes in brain 5-HT concentrations and metabolism are concomitant with onset of anorexia, indicating a role for brain serotonergic activity in reduction of food intake during tumor growth. Finally, other factors, including cytokines, appear to be operative in the development of cancer anorexia.

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