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The Effect of Raising or Lowering Tryptophan Levels on Aggression in Vervet Monkeys

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CHAMBERLAIN, B., F. R. ERVIN, R. O. PIHL AND S. N. YOUNG. *The effect of raising or lowering tryptophan levels on aggression in vervet monkeys.* PHARMACOL BIOCHEM BEHAV **28**(4) 503–510, 1987.—Social groups of vervet monkeys *(Cercopithecus aethiops)* were given amino acid mixtures that were tryptophan-free (T−), nutritionally balanced (B), or contained excess tryptophan (T+). The T− mixture caused a marked decrease in plasma tryptophan and the T+ mixture a large increase. Behavioral observations were made on the animals after administration of the amino acid mixtures both during spontaneous activity and while the (fasted) animals were competing for food newly placed in the feeder. The only effect of the biochemical manipulations on spontaneous aggression was an increase in aggression of the male animals with the T− mixture. During competition for the food the T− mixture increased and the T+ mixture decreased aggression in the males, while the T+ mixture decreased aggression in females. These data indicate that brain 5-hydroxytryptamine can influence aggression in a primate and suggest that altered tryptophan levels can influence aggression more reliably at higher levels of arousal.

Vervet monkeys Aggression Tryptophan 5-Hydroxytryptamine

THE neuroanatomical pathways of the brain that are served by the neurotransmitter 5-hydroxytryptamine (5HT) have been shown to play an important inhibitory role for a number of behavioral states including arousal, sensitivity to pain, sexual behavior, activity levels, sensitization and habituation to novel stimuli, irritability and aggression [29,45].

The relationship between 5HT function and aggression has been the focus of a particularly large number of studies many of which have employed parachlorophenylalanine (PCPA) as a means of depleting 5HT. PCPA is a relatively specific inhibitor of 5HT synthesis [22]. Thus, PCPA has been shown to increase irritability [22], to facilitate muricide in rats [13, 30, 34, 38] and cats [8], filicide (pup killing) in rats [6], and grillicide (cricket-killing) in mice [23]. These effects may be partially or completely reversed by administration of the 5HT precursor 5-hydroxytryptophan [6, 8, 13, 30, 34, 38] or fluoxetine, a selective inhibitor of 5HT uptake into presynaptic terminals [1]. Also, PCPA has been reported to potentiate brain stimulated (ventromedial hypothalamus) affective attack in cats [21], isolation-induced aggression [28] or territorial aggression [39] in mice, shock elicited aggression in rats [37,41], and spontaneous aggression in monkeys [36]. Although reports of no effect or of a decrease in aggression following PCPA treatment have also been made [5, 24, 25], for the shock-elicited aggression paradigm at least, the inconsistency seems to be due to differences in choice of test parameters between studies [41].

Depletion of brain 5HT by means of electrolytic lesions of midbrain raphe nuclei [17, 46, 49, 50] or administration of the selective 5HT neurotoxins 5,6-dihydroxytryptamine (DHT) and 5,7-DHT [3, 16, 19] also facilitates aggression in various animal models. Again these effects may be reversed by administration of the 5HT precursors tryptophan or 5-hydroxytryptophan [19,50]. Conversely, treatment with drugs that are belived to increase 5HT neurotransmission [15, 27, 32, 40] has been shown to decrease aggressivity.

A non-pharmacological approach to the study of the relationship between 5HT and aggression has been the use of tryptophan-free diets to lower brain 5HT. Because the synthesis of 5HT depends on tryptophan availability [48], limiting dietary tryptophan leads to depletion of brain 5HT levels [2, 11, 14]. Feeding rats a tryptophan-free diet for 4 to 6 days has been reported to induce mouse killing in non-killer rats and to decrease attack latencies of killer rats [14]. The diet reduced brain 5-hydroxyindole levels by about 30% whereas supplementation of this diet with tryptophan reversed the effect on both aggression and brain 5HT. Another study [20] confirmed the finding that a tryptophan-free diet increases

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TABLE 1
BEHAVIORAL VARIABLES

Behavior	Description
Aggress	Threatening (staring at, slapping towards, gaping, head bobbing), hitting, chasing or biting another animal.
*Locomote	Climbing, walking or running for more than 0.5 m.
*Rest	Remaining immobile with relaxed muscle tone for 10 continuous sec.
Approach	Moving to within 0.5 m of another animal and remaining within that distance for 5 sec with no aggression occurring.
*Solitary	Remaining more than 1.0 m from the nearest other animal for 10 continuous sec.
*Groom	Picking through the fur of another animal with the forepaws.
Sex	Genitally inspecting or mounting another animal, masturbating.

*Scored by noting the number of 30-sec intervals in which they occurred.
Other behaviors scored by recording the absolute frequency of occurrence.

muricide and also reported that shock-induced fighting in rats was increased. However, both reports raised the possibility that the increase in muricide is partly the result of reduced food intake, as reflected by a decrease in body weight in rats fed the tryptophan-free diet. When control rats were fed a restricted amount of chow to produce a decrease in body weight equal to that of rats fed the tryptophan-free diet, conflicting results were obtained. In one study the food deprived control rats showed an increased rate of muricide [20], while in the other food deprived control rats did not show increased muricide [14]. Another measure of predatory aggression, cricket-killing by mice, has also been reported to increase in animals fed a tryptophan-free diet [18]. Again this effect may have been due to inadequate food intake rather than to a specific decrease in tryptophan since the food-deprived control animals killed as many crickets and as quickly as experimental animals. These studies suggest that decreasing tryptophan availability might produce changes in aggression in animals similar to those observed with drugs or lesions that decrease 5HT neurotransmission. They also highlight the need to control for effects due to weight loss and inadequate nutrition.

The purpose of the present study was to examine the effects on aggression and other behaviors of a procedure that produces an acute reduction in tryptophan availability to the brain. The study is based on the following rationale: (1) Although means exist for depleting tryptophan in plasma acutely [2,11] we are aware of no published studies that have examined the effects on aggression of acute tryptophan depletion. (2) Acute depletion of tryptophan should avoid the confounding effects due to weight loss and inadequate nutrition that can occur when animals are fed tryptophan-free diets over an extended period. Also, acute tryptophan depletion may have the advantage of producing alterations in 5HT function that are within the normal physiological range. (3) One recently completed study failed to find an effect on a laboratory measure of "aggression" of acute tryptophan depletion in normal human males [42]. This negative finding is difficult to interpret. It may be that altering 5HT function does not affect aggression in normal human males or, on the other hand, it may be that the negative result is simply a reflection of the methodological difficulties inherent in studying aggression in human subjects. Also, the negative finding may be a function of the vast evolutionary differences that exist between humans and the more commonly studied rodent species. Further research with a non-human primate model would help to bridge this gap while at the same time avoiding many of the problems encountered in studying aggression directly in humans.

Thus, we tested the hypothesis that acute dietary tryptophan depletion would produce increases in intraspecies aggression in social groups of non-human primates. We also expected that tryptophan depletion might produce increases in activity levels and sexual behavior and decreases in other positive social interactions.

METHOD

Subjects

Ten adult male and twelve adult female vervet monkeys *(Cercopithecus aethiops)* that had been trapped in the wild on St. Kitts, West Indies (n=19) or were born at the Behavioral Sciences Foundation, St. Kitts (n=3) served as subjects. All were in good health and had been in captivity for at least one year before the beginning of the study. Males weighed 4.3 to 7.2 kg and females weighed 2.3 to 4.3 kg. Subjects were living together in social groups for at least six weeks before the beginning of the experiment. This was sufficient time for the animals to form a stable social group.

Housing

Subjects were housed in three outdoor cages each measuring 3.0×1.5×1.5 m. One cage had two males and five females. The other two cages each had four males and three or four females. Cages were equipped with perches, drinking bottles and feeders. Banana trees and bamboo blinds obstructed the view between cages.

Amino Acid Mixtures

Three amino acid mixtures were tested: nutritionally balanced (B) which served as a control, tryptophan-free (T−) which would lower brain 5HT, and tryptophan supplemented (T+) which would raise brain 5HT. The B mixture contained the amino acids in the same proportion as in milk, except that the non-essential amino acids, glutamic acid and aspartic acid, were left out because of concern about their toxicity at high doses. Dosages were selected on the basis of pilot tests with other animals, and doses that produced significant lowering or elevation of plasma tryptophan were chosen. The 5 hour interval between administration of amino acids and the start of behavioral testing was also chosen on the basis of pilot tests. With the T+ mixture plasma tryptophan rises very quickly and then declines, while the fall in plasma tryptophan occurs slowly after the T− mixture. At the 5 hour time point, plasma tryptophan had fallen to its lowest level with the T− mixture while plasma tryptophan was still ele-

TABLE 2

THE EFFECT OF AMINO ACID MIXTURES ON PLASMA TYRPTOPHAN

	T−		B		T+	
	Total	Free	Total	Free	Total	Free
			Males			
Pretreatment	8.65 ± 0.54	1.82 ± 0.09	9.57 ± 0.34	1.14 ± 0.09	8.53 ± 0.56	1.41 ± 0.12
Post treatment	4.50 ± 0.70	1.11 ± 0.19	11.93 ± 1.40	1.40 ± 0.06	28.42 ± 3.64	8.95 ± 3.59
Percent of pretreatment	52	61	125	122	333	635
			Females			
Pretreatment	9.65 ± 0.85	1.90 ± 0.09	8.43 ± 0.91	1.13 ± 0.03	6.67 ± 0.54	1.50 ± 0.10
Post treatment	3.76 ± 1.05	0.83 ± 0.22	8.94 ± 0.94	1.38 ± 0.01	67.03 ± 14.88	21.26 ± 6.74
Percent of pretreatment	39	62	106	123	1006	1413

Blood was taken from the subjects (males: n=8; females: n=7) just before ingestion of the T−, B and T+ mixtures. Five hours later a second blood sample was taken. Values are given as mean ± SE in μg/ml.

vated after T+ amino acids. The T− mixture (10 g) was composed of 0.55 g L-alanine, 0.49 g L-arginine, 0.27 g L-cysteine, 0.32 g glycine, 0.32 g L-histidine, 0.80 g L-isoleucine, 0.135 g L-leucine, 1.1 g L-lysine monohydrochloride, 0.30 g L-methionine, 0.57 g L-phenylalanine, 1.22 g L-proline, 0.68 g L-serine, 0.65 g L-threonine, 0.69 g L-tyrosine, and 0.89 g L-valine. The B mixture contained the same as the T− mixture plus 0.23 g L-tryptophan, while the T+ mixture contained the same as the T− mixture plus 1.03 g L-tryptophan. All mixtures were stored in pre-measured, single dose vials prior to use. They were suspended in 15 ml of water one half hour before administration.

Behavioral Observations

The behavioral measures (Table 1) that were used as dependent variables were modified from Struhsaker's ethogram for vervets [43]. Interobserver reliability of two observers was 94% (agreements/agreements + disagreements) for all behaviors by the end of a 3 week period of pilot testing these measures. Similar reliability was obtained in previous studies by others [36]. Observations were made from a blind constructed of bamboo that was situated 3 m from the front of the home cage. The subjects could see only the head and shoulders of the observer. A minimum of 20 hours were spent observing the animals before data was collected so that by the beginning of testing animals were habituated to the presence of the observer and generally ignored him. Observations were not made during rainstorms or other disturbances.

Blood Sampling and Plasma Tryptophan Determination

Blood samples (5 ml) were collected from the femoral vein using sterile disposable syringes that had been rinsed with heparin to prevent clotting. Samples were put into sterile test tubes and centrifuged at 3500 rpm for 10 minutes. The plasma was then divided into two parts. One part was placed in a cryotube and frozen for later determination of total plasma tryptophan levels while another part was used to obtain an ultrafiltrate of plasma in an Amicon MPS-1 centrifugal ultrafilter using YMT membranes. The ultrafiltrate was then frozen for later determination of free (non-albumin bound) plasma tryptophan. Tryptophan in the plasma and ultrafiltrate was determined by the fluorometric method of Denckla and Dewey [7].

Design and Procedure

A repeated measures design was used in which each animal was tested on three occasions with each of the three amino acid mixtures (i.e., each animal was tested 9 times). The order of administration of the amino acid mixtures was randomized separately for each of the three social groups and for each of the three cycles of testing. Data from behavioral observations were averaged over the three observation periods.

On days that animals were tested, the group that was to be observed received ripe bananas at 6:30 a.m. All food had been removed from the cage at 7:30 p.m. on the previous day. The animals were given bananas so they would not remain fasting. As bananas contain negligible amounts of protein, they would not be absorbing amino acids that would interfere with the effects of the amino acid mixtures given later. At 10:30 a.m. the animals were run into a tunnel equipped with squeeze cages attached to the rear of the cage where they were lightly anesthetized with a low dose of ketamine hydrochloride (8 mg/kg). They were subsequently administered the appropriate amino acid mixture by nasogastric intubation and then returned to their home cage. Any uneaten bananas were removed from the cage at this time. All animals received the same mixture on the same day. Administration of the amino acid mixtures generally took about 20–25 min to complete. During the period between administration of the mixtures and the start of behavioral testing there were no signs that the amino acids were having any adverse effect on the animals. Five hours after the administration of mixtures an observer, who remained blind as to which mixture had been given, began behavioral observations. Each animal was observed as a focal subject for ten minutes and its behavior recorded on a standard score sheet. The order of observation of animals was randomly determined before each observation session. Following the focal samples, food (Purina high protein monkey chow) was

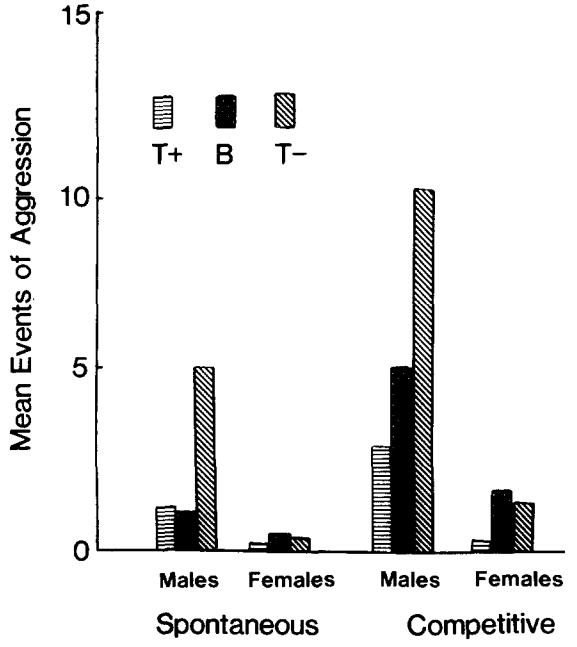

FIG. 1. Spontaneous and competitive aggression in vervets after various amino acids mixtures. The experiment was performed as described in the Method section.

placed in the feeder and all events of aggression were recorded for the next 20 min. This served as a test of provoked/competitive aggression since the baseline level of aggression is raised during the period immediately following food presentation. This is because the animals compete for access to the feeder. On days that animals were not tested, they had ad lib access to chow. At least one day of ad lib chow occurred between test days for any group.

After all the behavioral testing of the amino acid mixtures had been completed, blood samples were collected for determination of plasma tryptophan levels. The same procedure was followed except that a blood sample was collected before administration of the amino acid mixture at 10:00 a.m. and another blood sample was collected 5 hours later. Samples were collected from 8 males and 7 females for each of the three mixtures. As before, one day of rest was allowed between each day on which blood was collected.

Statistical Analyses

Unless otherwise indicated, the data for each behavioral measure were analyzed by a 3 (diet) × 2 (sex) ANOVA with repeated measures on the first factor. Data for approach and groom were subjected to a logarithmic transformation prior to analysis to reduce heterogeneity of variance between cells of the design in order to satisfy the variance assumption of ANOVA. Orthogonal comparisons between means were used to test for location of treatment effects.

RESULTS

Tryptophan Analysis

Analysis of the blood samples that were taken pre- and post-treatment (Table 2) indicates that the T− mixture was effective in decreasing both total and free plasma tryptophan concentrations and that the T+ mixture was effective in producing large increases in both. The balanced mixture produced modest increases in both total and free tryptophan concentrations.

Friedman's two-way ANOVA by ranks of the post-treatment values (expressed as percent of baseline concentrations) indicated significant treatment effects on total plasma concentration of tryptophan for males, $\chi^2_r(2)=14.25$, $p<0.001$, and females, $\chi^2_r(2)=2.3$, $p<0.01$. The dietary treatment also produced significant changes in free plasma tryptophan for both males, $\chi^2_r(2)=14.25$, $p<0.001$, and females, $\chi^2_r(2)=11.1$, $p<0.01$.

Aggression

Figure 1 shows mean levels of spontaneous and competitive aggression for males and females. The highest level of aggression observed was for males during the competitive aggression test. Aggression data were analyzed by non-parametric methods because the data did not satisfy the assumptions (normality, homogeneity of variances) of ANOVA. Pairwise comparisons between dietary treatments were made using Wilcoxon's signed-rank test for correlated groups. A significance level of 0.02 was adopted to compensate for the increased probability of getting a significant result due to chance with multiple pairwise tests on the same data set. This procedure has greater power than Friedman's non-parametric ANOVA and may be applied when only pairwise comparisons are being made [26]. For spontaneous aggression, the only significant comparison between treatment conditions is obtained when T− is compared to B for males ($W=21.0$, $p<0.02$). Thus males show more spontaneous aggression after treatment with the tryptophan deficient amino acid mixture. For food competitive aggression, males were more aggressive when treated with the T− mixture as compared to the T+ mixture ($W=48.0$, $p<0.02$) and females were less aggressive when treated with the T+ mixture as compared to the B mixture ($W=21.0$, $p<0.02$).

Locomotion

Mean scores for locomotion for males and females are shown in Fig. 2. Analysis of variance revealed a significant main effect for dietary treatment, $F(2,40)=4.64$, $p<0.02$, and a significant sex by diet interaction, $F(2,40)=6.91$, $p<0.005$. Subsequent analysis using orthogonal comparisons showed that for males mean scores for T+ vs. B did not differ significantly, but that the mean score for T− was significantly larger than the average of T+ and B, $F(2,9)=9.91$, $p<0.02$. Thus males were more active when depleted of tryptophan. Similar comparisons for females produced no significant result. Thus tryptophan manipulation did not appear to influence activity levels in females. There was no statistically significant correlation between locomotor activity and aggression for either males or females in any of the three treatment conditions.

Resting, Approaching, Being Solitary, Grooming, Sex

Table 3 shows mean scores for resting, approaching, being solitary, and grooming. With scores for resting and approaching, ANOVA showed no significant main effects for sex or treatment, and no sex by treatment interaction. Thus manipulation of tryptophan availability did not affect scores for resting or approaching other animals for either males or females.

For solitary behavior, ANOVA revealed a significant main effect for sex, $F(1,20)=7.92$, $p<0.02$, but no main effect

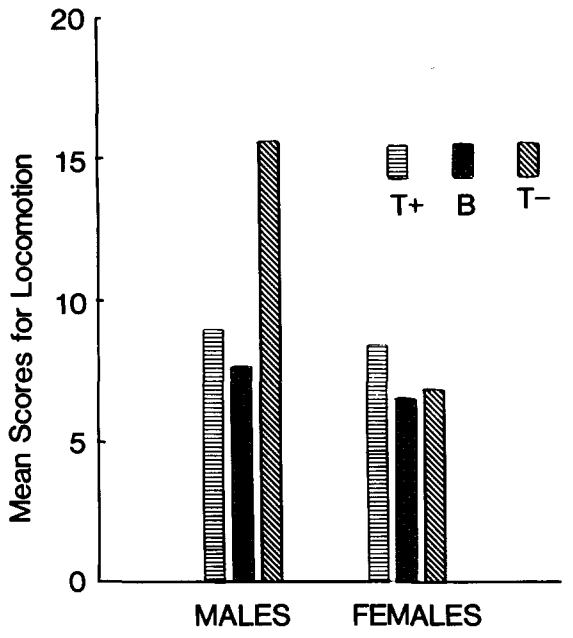

FIG. 2. Scores for locomotion in vervets after various amino acid mixtures. The experiment was performed as described in the Method section.

for dietary treatment and no sex by treatment interaction. Thus females were less likely to be solitary than males on the average, but the dietary manipulation of tryptophan availability did not result in any significant effect for either males or females.

For social grooming, ANOVA of log (x+1) transformed data produced no significant main effects for sex or treatment, and no significant sex by treatment interaction.

It is obvious that the dietary treatments had no differential effect on sexual behavior. Rates of sexual behavior were too low to be analyzed statistically.

DISCUSSION

The dietary manipulation employed in the present study was effective in altering plasma tryptophan. The T− amino acid mixture decreased plasma tryptophan concentrations while the T+ mixture had the opposite effect. The balanced mixture produced a modest elevation. In the rat the decline in plasma tryptophan that follows ingestion of a tryptophan deficient amino acid mixture is accompanied by a substantial decline in brain 5HT [2]. Two mechanisms seem to be responsible for this decline in 5HT although the most important one involves peripheral protein synthesis [11]. Thus, a tryptophan deficient amino acid mixture, like any mixture of essential amino acids, promotes synthesis of new protein. The tryptophan that is incorporated into this protein comes from tryptophan pools in blood and tissues, and therefore its level in plasma and brain falls. Another mechanism might contribute to the decline in brain, but not plasma, tryptophan after ingestion of an amino acid mixture. All large neutral amino acids compete for the same carrier system that transports them across the blood brain barrier [33]. Thus, brain tryptophan will depend not only on plasma tryptophan, but also on the plasma levels of the other large neutral amino acids. In the rat this mechanism seems to play a relatively small role in lowering brain tryptophan after ingestion of a tryptophan deficient meal [11]. In the present study the amount of competing amino acids ingested was the same for the T−, B and T+ groups, so it is likely that competition for the entry of tryptophan into the brain was similar. In humans, as in rats, brain tryptophan levels can be predicted from plasma levels of tryptophan and the other large neutral amino acids [35,52]. There is no reason to believe that plasma tryptophan levels would not be a good predictor of brain levels in the vervet also. CSF studies in humans have also shown that raising or lowering brain tryptophan in humans will raise or lower the rate of 5HT synthesis and that plasma amino acid levels reliably predict changes in the CSF [35,52]. There is good evidence that tryptophan availability in the brain is an important factor controlling 5HT synthesis in the vervet [51]. Therefore, although no measurements of 5HT were made in the present study, there is good circumstantial evidence that the alterations we saw in plasma tryptophan were an index of changes in brain 5HT. Of course the assumption behind studies in which 5HT metabolism or concentrations are changed is that 5HT release is also altered. Measurement of 5HT release in the brain has been problematic but several techniques such as *in vivo* dialysis and *in vivo* amperometry show great promise in this area. In the next few years it should be possible to determine if and under what circumstances the amino acid mixtures do alter 5HT release. Until then, the most reasonable working hypothesis is that they alter aggression by changing functionally active 5HT.

Our results represent an extension of a relatively unexploited technique which is known to decrease plasma and brain tryptophan and brain 5HT in the rat and to lower plasma tryptophan in primates. The major advantages of the technique are the convenience of being able to produce rapid reduction in 5HT synthesis and the avoidance of the confounding factor of weight loss which can occur when animals are maintained on tryptophan-free diets over a relatively long term. None of the monkeys lost weight over the course of the study. The most important application of the technique may ultimately be its use in studying the role of 5HT in mediating human emotion and behavior as discussed below.

The major finding of the present study is that acute tryptophan depletion increased both spontaneous and food-competitive aggression in male animals. In males and females, the T+ mixture inhibited food-competitive aggression although this effect was statistically significant only for the females. Thus our results provide support for the hypothesis that 5HT serves an inhibitory role in aggressive behavior in primates. This is consistent with a large body of research with rodents and also with one study which found increased aggression in similar groups of vervets treated with PCPA [36]. It is unclear why the manipulation used here affected the aggressive behavior in some of the circumstances but not in others. This may be due partly to sex differences in behavioral response to the manipulation. Sex differences in aggressive response following depletion of 5HT by PCPA treatment have been reported for rats [46], while in vervets the mean rate of 5HT metabolism is higher in females than in males [51]. In rats the difference in aggression response is partly a function of strain dependent genetic differences since both sexes of Wistar rats and male Sprague-Dawley rats consistently react to impairment of serotonergic inhibitory control with increased muricide, while Sprague-Dawley females do not [46]. On the other hand, the differences between the sexes observed here may

TABLE 3
THE EFFECT OF AMINO ACID MIXTURES ON BEHAVIOR OF VERVET MONKEYS

Behavior	T−	B	T+
		Males	
Rest	18.0 ± 19.2	12.0 ± 16.8	15.7 ± 19.2
Approach	0.9 ± 1.0	3.3 ± 3.8	2.3 ± 1.7
Solitary	38.5 ± 14.6	35.2 ± 13.8	37.2 ± 11.4
Groom	5.2 ± 6.1	4.8 ± 5.9	2.5 ± 4.9
Sex	0.3 ± 0.7	0.1 ± 0.3	0.1 ± 0.3
		Females	
Rest	30.3 ± 25.0	27.2 ± 22.8	28.8 ± 25.3
Approach	2.3 ± 2.0	2.8 ± 5.8	3.2 ± 2.6
Solitary	22.8 ± 15.1	18.4 ± 16.5	24.9 ± 15.2
Groom	6.5 ± 8.9	10.7 ± 12.9	5.7 ± 7.1
Sex	0.2 ± 0.4	0.1 ± 0.3	0.2 ± 0.4

Values are given as mean ± SD.

be simply an artifact which occurred because the animals were housed in mixed sex social groups. The presence of the males may have inhibited aggression on the part of the females. Further research with differently housed groups (e.g., unisexual groups) would be necessary to determine which possibility is most likely.

Another factor that might help to explain the variability of the results is the level of behavioral arousal of the animals. Thus, the effects of tryptophan manipulation are seen more clearly when the animals are competing for food, and are therefore more highly aroused, than when this added stimulus is not present. In the cat a higher level of arousal is associated with an increased firing rate of 5HT neurons [44]. 5HT is released from neurons and can become functional only in response to neuronal firing. Therefore, it is reasonable to suggest that altered 5HT metabolism may influence 5HT release more at higher rates of firing of 5HT neurons. Although this discussion centers primarily on 5HT neurons, 5HT is only one of many neurotransmitters than can modulate aggression. Obviously the extent to which alterations in 5HT can influence aggressive behavior will depend on the interaction of 5HT neurons with these other systems. Thus, it should not be surprising that alterations in 5HT metabolism will alter aggression in some circumstances but not in others. Differences in arousal may in part explain the results concerning altered tryptophan levels and aggression in humans. Acute alterations of tryptophan availability did not influence aggression in normal male subjects [42]. However, in a clinical trial of the action of tryptophan in pathological aggression there was a significant therapeutic effect, which was particularly marked in patients with poor impulse control [31]. This fits in with the idea that altering tryptophan levels will be more likely to alter aggression at higher levels of arousal. It also suggests that altering tryptophan levels might influence aggression in normal human subjects if they are subjected to a sufficiently arousing stimulus.

Acute tryptophan depletion by a tryptophan deficient amino acid mixture was found to increase the vervets' activity level, as reflected by the locomotion scores, in male subjects. This outcome is consistent with the results of a number of studies of the effect of 5HT on locomotion [10] and provides some additional support for the hypothesis that 5HT has an inhibitory effect on arousal and activity levels. It is possible that the increased aggression seen in the male subjects occurred secondarily to the increased levels of activity produced by acute tryptophan depletion. That is to say, they may have shown a higher frequency of aggressive behavior because, being more active, they encountered each other or invaded each others' space more often, although there was no correlation between aggression and locomotor activity. This is less likely the case for the food-competitive aggression measure however, since the animals concentrated most of their attention on eating and spent little time moving about except to go the the feeder. Most of the aggression in this period resulted from competition for access to food.

Although a number of studies have indicated an inhibitory role for 5HT in controlling sexual behavior in rats, rabbits and cats, no such role has been established in monkeys or humans [12]. In vervets treated with PCPA or the serotonin precursors tryptophan or 5-hydroxytryptophan, no changes in sexual behavior were observed [36]. In our study, the dietary manipulation of 5HT also failed to alter the frequency of sexual behaviors.

Although alterations in the rates of grooming, approaching, resting and being solitary were reported in vervets treated with PCPA, tryptophan, 5-hydroxytryptophan or chlorgyline [36] these behaviors were not differentially affected by our treatments. This discrepancy may be due to one or more factors including the following: (1) differential effectiveness of these treatments in reducing or enhancing 5HT synthesis and function; (b) different routes of administration of tryptophan; (c) potential effects of drugs independent of their effects on 5HT; (d) regional differences in alterations of brain 5HT as a result of different treatments; (e) acute vs. chronic treatment effects.

Although our data show that altering tryptophan availability can change aggressive behavior it gives no insight into the exact behavioral systems involved. It may be that after the T− mixture the neuronal systems mediating aggression are directly activated or disinhibited. Alternatively they may be an alteration in the tonic control of a variety of behaviors of which aggression is one. Lastly there may be behavioral interactions, with altered aggression occurring as a result of a change in a different behavior. For example, the increased locomotion seen with the T− mixture may have caused increased behavioral interactions, including aggression, in the limited space available in the cage. This last possibility is not necessarily any more likely than an increase of locomotion occurring as a result of increased aggression, and thus increased avoidance behavior. Further work would be needed to distinguish between any of these possibilities.

Recent clinical reports have provided evidence of a negative correlation between indicies of 5HT function and measures of aggression in humans. Increased aggressive/impulsive behavior and suicidal behavior have both been significantly associated with decreased CSF 5HIAA in patients with various psychiatric diagnoses [4]. The results of the present study help to establish a causal connection between 5HT functioning and aggressive responding in primates. So far a demonstration of a causal link has not been made for humans. Because of the difficulty in manipulating neurotransmitter systems safely in humans, most of the studies done to date have been correlational in nature. In one prospective study in which amino acid mixtures (similar in composition to those used here) were used to manipulate plasma tryptophan in normal human males, no alterations in aggres-

sive responding were observed [42]. The results of the present study lead to a specific and testable hypothesis about one factor that might help determine whether altered tryptophan will change aggressive responding. As stated above, we feel that altered tryptophan will change aggression more reliably when environmental or other factors elevate the level of arousal in the subjects.

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