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Laboratory-Measured Aggressive Behavior of Women: Acute Tryptophan Depletion and Augmentation

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Plasma L-tryptophan (Trp) reductions have been related to aggression increases in men. Impairment of serotonin synthesis and neurotransmission is one explanation. Using repeated-measures, this Trp manipulation study measured laboratory-induced aggression in 12 women after Trp augmentation (T+), depletion (T−), and food-restricted (fasting control) conditions. Participants were provoked with periodic subtraction of money from their task earnings by a (fictitious) partner. Aggression was defined as the number of point subtractions participants made from their fictitious partner. Participants completed five testing sessions under each condition. T+ decreased aggressive responses and T− increased aggressive responses. Post-hoc analyses showed changes in aggressive behavior were specific to women with higher fasting control plasma Trp, which is consistent with research demonstrating that men with higher levels of baseline Trp are more aggressive. These findings indicate that both T+ and T− can influence aggressive behavior and that certain subgroups of women may be more susceptible to serotonin manipulation.
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KEY WORDS: *Aggression; Women; Tryptophan; Serotonin*

A number of psychobiological syndromes characterized by poor impulse control have been associated with low concentrations of the major serotonin (5-HT) metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF). Serotonin dysfunction has been correlated with impulsive and violent criminal behaviors (Brown et al. 1979, 1982; Lidberg et al. 1985; Limson et al., 1991; Virkkunen and Närvänen 1987; Virkkunen et al. 1994a, 1994b), alcohol abuse and dependence (Badawy et al. 1995; Ballenger et al. 1979; Banki 1981; Borg et al. 1985; Moss 1987; Roy and Linnoila 1989), Gilles de la Tourette's syndrome (Butler et al. 1979; Cohen et al. 1978, 1979), bulimia (Jimerson et al. 1990, 1992), and suicide attempts (Asberg et al. 1976, 1986; Banki and Arato 1983; López-Ibor et al. 1985), as well as with children institutionalized for aggressive behavior (Kruesi 1989; Kruesi et al. 1990, 1992).

Direct experimental manipulation of 5-HT levels and the measurement of resultant behavior have provided stronger evidence for the connection between central nervous system (CNS) 5-HT and impulsive/aggressive behaviors. Serotonin synthesis depends on the availability of the essential amino acid tryptophan (Trp). Thus, manipulation of 5-HT can be accomplished through increases or decreases in dietary Trp, which in turn increases or decreases plasma Trp and ultimately 5-HT in the CNS (Biggio et al. 1974; Gessa et al. 1974;

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Young et al. 1989). This manipulation is postulated to affect brain 5-HT because 5-HT synthesis depends primarily on Trp availability (Fernstrom 1983). Concentrations of 5-HT in the CNS can be decreased by a Trp-deficient amino acid drink that increases plasma concentrations of other large neutral amino acids (LNAA) that reduce plasma Trp due to stimulation of protein synthesis and the consequent use of available Trp and compete with Trp for transport across the blood–brain barrier. Together, these effects reduce available Trp for synthesis of 5-HT in the CNS. Alternatively, concentrations of 5-HT in the CNS can be increased by a Trp-augmented amino acid drink that increases plasma Trp concentrations relative to other LNAAs. Trp manipulation results in significant changes in human CNS 5-HT levels (Carpenter et al. 1998; Young and Gauthier 1981), rate reductions of 5-HT synthesis in the human brain (Nishizawa et al. 1997), and blunted release of 5-HT from serotonergic neurons in vivo (Stancampiano et al. 1997). As a result, by either increasing or decreasing plasma Trp levels, experimenters can manipulate CNS 5-HT function to gauge its acute effect on behavioral measures (e.g., impulsivity and aggression).

As might be expected from the correlation of 5-HT system dysfunction with certain psychobiological syndromes, certain subsets of individuals may be more sensitive to the effects of acute Trp depletion and/or augmentation, which may be manifested as increases or decreases in prospectively measured aggressive responding compared with controls. Studies have shown that men reporting higher hostility and aggression levels (paper-and-pencil measures) also have higher baseline levels of plasma Trp (Eriksson and Lidberg 1997; Møller et al. 1996; Virkkunen and Närvänen 1987; Wingrove et al. 1999). Other studies using normal males have reported conflicting results under Trp depletion (Bjork et al. 1999; Moeller et al. 1996; Pihl et al. 1995; Smith et al. 1986); for example, high-trait aggressive men have shown increases in both subjective paper-and-pencil measures and in laboratory-measured behavioral aggression under Trp depletion, whereas low-trait aggressive men have not (Cleare and Bond 1995). In our most recent laboratory studies (Bjork et al. 1999, 2000), Trp depletion increased aggressive behavior in men with high baseline levels of aggression but did not affect men with low baseline levels.

Most studies of the relationship between CNS 5-HT function and aggressive/impulsive behaviors have relied on men. In our laboratory, we are conducting a series of systematic analyses of aggressive/impulsive behavior of women using a paradigm (PSAP, see below) to prospectively measure changes in aggressive responding as a result of experimental manipulation. Results have shown increased aggressive responding as a function of alcohol consumption (Dougherty et al. 1997c, 1999a) and mood (Dougherty et al. 1999b) as well as increased aggressive responding across the entire menstrual cycle by women reporting moderate to high perimenstrual symptoms (Dougherty et al. 1997a, 1997b, 1998). When aggressive behavior was compared between women and men, these studies have shown no measurable difference in laboratory responses (Allen et al. 1996; Dougherty et al. 1999a). The present study is a continuation of these studies in which we examined the effects of Trp augmentation and depletion on the aggressive responding of women using the Point Subtraction Aggression Paradigm (PSAP; Cherek et al. 1996; 1997). Aggression was defined as the number of point subtractions participants made from their (fictitious) partner after provocation with periodic subtraction of money from their task earnings by the fictitious partner.

The purpose of this study was to determine whether Trp manipulation influences women's aggressive responding in a manner similar to what has been observed in men. We hypothesized that depletion (T−) and augmentation (T+) of plasma Trp concentrations would result in corresponding increases and decreases of aggressive response rates. High-trait aggression and impulsivity paper-and-pencil measures are expected to correlate positively with peak effects of the T− (hour 5) drink and negatively with peak effects of the T+ (hour 3) drink, as seen in previous studies with men.

MATERIALS AND METHODS

Participants

Participants were recruited from the community through newspaper advertisements for paid research volunteers. Applicants completed an initial telephone screening that consisted of general health questions. Potential volunteers were invited to the laboratory for more complete screening, which included a self-report medical survey and a structured clinical interview for DSM-IV Axis I psychiatric disorders (SCID-I/P, v2.0; First et al. 1996). During the laboratory interview, volunteers were told the study investigated motor skill performance after the consumption of two different amino acid beverages, and daily payment was based on their motor performance during experimental sessions. Medical conditions or Axis I psychiatric disorders were exclusionary criterion. The methods of this study were approved by the Committee for the Protection of Human Subjects of the University of Texas-Houston.

An additional screening criterion was the Baseline Day 1 (see below) performance evaluation. The purpose of this day was to familiarize participants with the testing procedure and allow stabilization of aggressive responding rates. Participants whose performance stabilized and remained at zero "B" responses by the end of the baseline day performance evaluation (five sessions)

did not continue into the experimental phase of the study.

Twelve adult females ranging in age from 18 to 36 years ($M = 26.2$, $SD = 6.4$) and with 12 to 18 years of education ($M = 14.4$, $SD = 2.2$) completed this four-day study. Five participants were Hispanic, four were African American, two were Caucasian, and one was Asian. Three of the 12 women were cigarette smokers: two smoked between half and one pack per day and one smoked less than half a pack per day.

To reach our target number of participants ($n = 12$), we enrolled a total of 31 participants. Due to changes in their circumstances during study participation, 12 participants were dropped from the study because they no longer met inclusion criteria (e.g., medication, drug positive). Seven other participants withdrew from the study without explanation. The participants who were not included in the study were 18 to 38 years old (M = 27.7, SD = 5.1) and had 8 to 18 years of education (M = 13.2, SD = 2.8). The ethnic backgrounds included eight African Americans, six Hispanics, four Caucasians, and one Asian.

Procedures

The study was conducted over four days, beginning at 8:00 a.m. and ending at 4:30 p.m. Each day consisted of a different assessment: baseline, T–, T+, and FR (food-restricted fasting control). Participants were asked to refrain from consuming caffeine before arrival at the laboratory each morning, and daily breath and urine samples were submitted upon arrival at the laboratory. Absence of alcohol or other common drugs of abuse was required and was verified with an Alco-Sensor III (Intoximeters, Inc., St. Louis, MO) and the Syva® Rapid Test d.a.u.© (Syva Co., Dade Behring, Inc., Cupertino, CA), respectively. Cigarettes were taken from participants upon arrival in the morning and returned after the last testing session. During their time in the laboratory, one smoking break was permitted at ~1:00 p.m.

Participants completed five testing sessions per day and remained in a waiting lounge between sessions; they were monitored and not permitted to sleep between sessions. Sessions were held each day at 8:30 a.m., 10:30 a.m., 12:30 p.m., 2:30 p.m., and 3:30 p.m. These times were selected to measure behavior in conjunction with changing plasma Trp levels after drink administration. After the last testing session of each day, participants completed a questionnaire that asked them to estimate the number of partners they were paired with during the sessions and to describe the partner(s). This allowed assessment of participants' belief in the fictitious partner. Participants received payment daily, usually between $45.00 and $50.00.

Day 1 consisted of a baseline performance evaluation to familiarize participants with the testing procedure and allow stabilization of aggressive responding rates. On Day 1 only, participants were instructed to eat breakfast as usual and were provided a lunch of a sandwich, chips, and caffeine-free soft drink at noon. Before Days 2, 3, and 4, participants were instructed to follow a low-monoamine diet and to fast from midnight until testing was completed at 4:00 p.m. the following afternoon, when lunch would be provided. On Days 2 and 3, participants were administered a T– or T+ beverage at approximately 9:30 a.m. and were allowed 20 min to consume the drink. Drink administration was double-blind, and the T–/T+ order was counterbalanced. There was a minimum of 48 h between T– and T+ drink administration to ensure that the plasma Trp/LNAA ratios and subsequent neurobiological cascade effects returned to normal before administration of the second drink. Day 4 was the FR fasting control, for which the low monoamine dietary instructions, fasting, and behavioral testing remained the same as on experimental days, but no drink was consumed.

Aggression Measurement. Volunteers completed testing sessions in a 1.8 × 1.8-m sound-attenuated chamber equipped with a 13" computer monitor and a response panel with two buttons labeled "A" and "B" (buttons were connected to an IBM PC–compatible computer in a nearby control room). The volunteers could place the panel in the most comfortable position for responding (i.e., on a countertop or on their lap). The Point Subtraction Aggression Paradigm (PSAP), an externally validated (Cherek et al. 1996, 1997) software program, controlled experimental sessions. During a 25-min testing session, participants could accumulate points (worth money) by repeatedly pressing one button, or subtract points (aggressive response) from their fictitious partner by repeatedly pressing another button. The PSAP measures a participant's aggressive responses to periodic loss of their points (i.e., provocation). Point loss is attributed to the (fictitious) partner paired with the participant.

Before the first testing session, the experimenters read instructions to the participant stating that the goal of each session was to earn as many points as possible because daily payment was based on the total number of points earned. The instructions also stated that 100 presses of button "A" (money-earning response) would earn one point (worth 20 cents), and 10 presses of button "B" (aggressive response) would subtract one point (worth 20 cents) from their (fictitious) partner's point counter. Participants were told they might be paired throughout the day with the same or different partners located in another lab, and that this partner was also responding to earn money and could take points away from their counter. The participant was told that points taken by her partner would be added to the partner's counter, but points she subtracted from the partner were not added to her counter.

All money-earning "A" and aggressive "B" responses were recorded during a session, along with the number of "B" responses per point subtracted and the number of "B" responses per minute. The participant was repeatedly provoked during a session by point subtractions from her counter (the fictitious partner) at random intervals from 6 to 120 s. A retaliatory point subtraction (10 presses of button "B") by the participant after at least one provocation would reduce the frequency of her point loss by initiating a 500-s period free from provocation, called a provocation-free interval (PFI). Once a PFI was initiated, any additional aggressive "B" responses were recorded; however these did not extend the PFI beyond the initial 500 s. The random schedule of 6- to 120-s intervals between provocations was resumed after the PFI time elapsed. Therefore, the participant could not avoid all point subtractions by continually extending the PFI. The first four sessions used a PFI of 500 s, and participants experienced a minimum of three provocations per session. To investigate whether a more frequent rate of provocation would amplify aggressive responding, the PFI was decreased to 125 s for the fifth session, which increased the minimum number of money subtractions to five.

Amino Acid Drinks. The two amino acid drinks consisted of a combined total of 100 g of 13 LNAAs with or without the addition of 2.3 g of L-tryptophan (Trp). A T− drink with the same composition has been used in several aggression studies with male volunteers (see Bjork et al. 1999; Delgado et al. 1990; Moeller et al. 1996; Pihl et al. 1995; Salomon et al. 1994; Young et al. 1989). The LNAAs were mixed with 12 oz of bottled water, 10 ml of chocolate syrup, and 2 drops of peppermint extract. Two additional LNAAs (cysteine and methionine) were consumed in capsules because of their aversive taste and smell. In previous studies (reviewed in Wolfe et al. 1995) the depletion dose has resulted in substantial reductions of the plasma Trp/LNAA ratio, with the lowest ratio achieved between 5 and 6 h after beverage administration (Delgado et al. 1990). Participants were allowed 20 min to consume the beverage and capsules.

Plasma Total Trp Measurement. Blood samples were obtained at 3:00 p.m. on Days 2, 3, and 4 (experimental and fasting control days), ~5.5 h after beverage administration. The plasma was isolated by centrifugation and frozen at −80°C until assay. Plasma total Trp was measured by high-performance liquid chromatography with spectrophotometric detection (260 nm) in a method adapted from Widner et al. (1997). Briefly, 30 μl of 3-nitro-L-tyrosine (Sigma) internal standard solution was added to 500 μl of plasma. Samples were then treated with 20 μl of concentrated perchloric acid (PCA) and centrifuged in a rotor (Sorvall Superspeed RC2-B, SM 24 Rotor, Sorvall Instruments) at 4°C and 10,000 rpm for 15 min, with the supernatant injected directly on the column. The mobile phase was 98% 0.013 M K_2HPO_4, pH 6.5 to 2% acetonitrile, which perfused a Beckmann ultrasphere C18 column.

Psychometric Measurements. As in previous studies with men, in which self-report measures were compared with laboratory-measured aggression and with plasma Trp levels, the psychometric measures used here were to relate the women's self-reports of depression, anxiety, aggression, and impulsivity to state-dependent changes under Trp manipulation and the biochemical measure of the plasma Trp concentration. The Beck Depression and Beck Anxiety Inventories (BDI and BAI, respectively; Beck et al. 1961, 1988) were used as screening tools during the initial interview and as state-dependent (during the past week) measures of depression and anxiety. The Buss-Perry Aggression Questionnaire (BPA; Buss and Perry 1992) and the Life History of Aggression Questionnaire (LHA; Coccaro et al. 1997) were each used as trait-dependent measures of aggression. The Barratt Impulsiveness Questionnaire, v.11 (BIS-11; Patton et al. 1995) and the Eysenck's Impulsiveness, Venturesomeness, and Empathy Questionnaire (I_7; Eysenck et al. 1985) impulsivity subscale were used as trait-dependent measures of impulsivity. The Menstrual Distress Questionnaire (MDQ-C; Moos 1977) was used to assess self-reported menstrual distress related to the most recent cycle. All questionnaires were administered before or after completing the study, not during either the T+ or T− treatment days or the FR fasting control day.

Data Analysis. As in previous studies with men, Pearson's correlations between the psychometric paper-and-pencil measures of aggression and impulsivity (see above) were correlated with laboratory-measured aggressive responses and with plasma Trp concentrations for each condition. The absolute difference of the plasma total Trp concentrations between the fasting control condition (FR day) and the two amino acid conditions was also computed and correlated with the psychometric measures.

Treatment condition × time (3 × 3) repeated measures analyses were used, followed by paired *t*-tests comparing aggressive responses during treatment conditions at 1, 3, and 5 h after drink administration (corresponding to sessions 2, 3, and 4). To more accurately compare changes in responding as a function of experimental treatment, both money-earning "A" responses and aggressive "B" responses for sessions 2, 3, and 4 were computed as a proportion of that day's Baseline Session 1. The variance in aggressive responses (but not money-earning responses) between treatment conditions did not meet assumptions of sphericity. As a result, logarithmic transformations were performed on aggressive response scores before analysis with a multivariate analysis of variance (MANOVA; Pillai's Trace *F*

values reported). Where assumptions of data sphericity in repeated-measures ANOVA are violated despite the transformation, Huynh-Feldt (H-F) corrected p values were presented. Paired t-tests were used for analyses between treatment conditions at each time point. Systat® v8.0 (SPSS, Inc., Chicago, IL) or SPSS© v10.1 (SPSS, Inc., Chicago, IL) was used for all data analyses, and the α level was set at .05.

To assess the magnitude of treatment effects for the aggressive responding during the laboratory measures, estimates of effect sizes were calculated as Cohen's f (Cohen 1988) using $\text{eta}^2/(1 - \text{eta}^2) = \text{Cohen's } f^2$. The statistic eta^2 estimates the magnitude of an effect independent of sample size (American Psychological Association 1994). These estimates are useful when comparing measurement techniques because, unlike p values, the effect size conveys the magnitude of the phenomenon of interest (American Psychological Association 1994; Cohen 1990). For one-way ANOVA, f scores of 0.10, 0.25, and 0.40 are conventional definitions of small, medium, and large effect sizes, respectively (Cohen 1992).

RESULTS

Participants

Because the attrition rate of participants for this study was substantial, we used independent t-test analyses to compare the groups of participants who did ($n = 12$) and did not ($n = 19$) complete the study. These analyses revealed no differences between the two groups of participants when compared by demographics of age, education, and average number of alcoholic beverages consumed per week as well as their scores from the BIS-11, BAI, BDI, and MDQ-C (see Table 1). There was also no difference in the ethnic distribution of the two groups as tested by a Pearson χ^2 comparison [χ^2 (3) = 0.54, $p = .9$].

Additional analyses of data from smokers ($n = 3$) and non-smokers ($n = 9$) showed no differences between the two groups on any dependent variable ($p > .10$).

Biochemical Measures

Plasma total Trp measurements for 10 participants were performed (two participants refused venipuncture). The FR fasting control plasma total Trp concentrations were compared with the T− and T+ treatments. Both treatments produced predictably different plasma total Trp levels. Compared with fasting control FR, the T− treatment reduced plasma total Trp by more than two-thirds (69%), and the T+ treatment more than doubled plasma Trp (209%) [$t(9) = 17.74$, $p < .0001$; $t(9) = 8.20$, $p < .0001$; respectively].

Behavioral Measures

Money Earning Responses. A 3 × 3 (treatment × time) repeated-measures ANOVA showed no difference in money-earning "A" response frequency between the three treatment days or the three times at 1, 3, and 5 h after treatment and no treatment × time interaction (see Figure 1, top). There was no difference in performance between treatments during the fifth session (high provocation session) at 6 h after treatment ($p > .05$).

Aggressive Responses. A 3 × 3 repeated-measures MANOVA was used to analyze the logarithmically transformed aggressive "B" responses. The T+ treatment reduced aggressive responding, whereas the T− treatment increased aggressive responding (see Figure 1, bottom), as indicated by the main effect of treatment [$F(2,10) = 11.02$, $p = .003$, $f = 1.49$]. Consistent with previous literature for peak effects of Trp augmentation (Green et al. 1980; Møller 1981), paired t-tests showed that the T+ treatment reduced aggressive responding compared with FR at each of the three time points, with the greatest reductions found at 1 and 3 h after treatment [$t(11) = 3.16$, $p = .009$; $t(11) = 4.27$, $p = .001$; respectively] and a significant recovery toward baseline session 1 performance by 5 h after treatment [$t(11) = 2.42$, $p = .03$]. As seen in Figure 1 (bottom), the T− treatment showed a trend for a progressive increase in aggressive responding across the day. No treatment differences were observed during the fifth session (high provocation session) at 6 h after treatment ($p > .05$).

Psychometric Measures

Using Pearson's product-moment correlational analyses, scores of the seven psychometric measures (see listing in Materials and Methods) showed no correlation with either aggressive responding at any time point or plasma total Trp levels for any condition ($p > .05$).

Because certain subgroups of men have been shown to be more sensitive to treatment differences than others, we further explored the possibility of individual differences among this group of 10 women. We calculated the absolute difference of plasma Trp levels of the two treatment days (T+ and T−) from the FR fasting control day for each of the 10 women. These scores were correlated with the primary psychometric measures of self-reported impulsivity (BIS-11; Patton et al. 1995) and aggression (BPA; Buss and Perry 1992), and results are shown in Table 2.

BIS-11 and I_7 Impulsivity. There was a positive correlation between BIS scores and the amount of difference in plasma Trp between fasting control and T+ conditions (see Table 2). The participants with the largest differences in plasma total Trp also had the higher scores for the BIS total score, primarily due to the strong rela-

Table 1. Demographic and Psychometric Group Comparisons of Participants Who Did or Did Not Complete the Study

	Participants		
	Complete (n = 12)	Incomplete (n = 19)	t-Test
Measure	Mean (SD)		p
Demographics			
Age	26.17 (6.41)	27.74 (5.07)	.46
Education	14.42 (2.18)	13.21 (2.84)	.22
Alcoholic beverages per week	1.58 (2.02)	2.37 (3.98)	.47
Psychometrics			
Beck Anxiety Inventory	6.75 (4.77)	8.41 (10.19)	.56
Beck Depression Inventory	7.00 (5.89)	8.88 (8.05)	.50
Barratt Impulsiveness Scale			
Subscales			
Attention	13.33 (4.16)	14.73 (4.65)	.42
Motor	23.00 (2.66)	21.93 (3.63)	.40
Non-planning	21.83 (5.32)	21.13 (4.84)	.72
Total score	58.17 (10.00)	57.80 (9.80)	.92
Menstrual Distress Questionnaire			
Subscales			
Behavioral change	1.09 (2.21)	2.17 (3.15)	.33
Negative affect	3.82 (4.73)	8.00 (9.17)	.12
Impaired concentration	1.27 (2.01)	3.28 (5.05)	.15
Arousal	1.36 (2.42)	1.94 (2.94)	.59
Total score	17.18 (17.77)	28.94 (30.93)	.21

tionship with the BIS nonplanning subscale. A trend toward the same effect for the I_7 (Eysenck et al. 1985) impulsiveness subscale ($r = 0.59$, $p = .07$) was also found.

BPA. Alternatively, there was a negative correlation between the BPA and the amount of difference in plasma Trp between fasting control and T− conditions (see Table 2). The participants with the smallest differences in plasma total Trp had the highest total BPA scores as well as the highest anger and physical aggression subscale scores along with a trend for higher scores on the hostility subscale (see Table 2). No relationship with the verbal aggression subscale score was found. Conversely, the participants with the largest plasma Trp differences for the T+ treatment showed a trend toward higher scores on that particular subscale but no relationship to the other BPA scores.

Post Hoc Group Analyses. Because studies have shown that men reporting higher hostility and aggression levels also have higher baseline levels of plasma Trp (Eriksson and Lidberg 1997; Møller et al. 1996; Virkkunen and Närvänen 1987; Wingrove et al. 1999), the 10 women who provided blood samples were divided equally into two groups: low ($M = 6.13$ μg/ml, $SD = 0.63$) and high ($M = 7.54$ μg/ml, $SD = 0.36$) fasting control plasma total Trp using a median split of Trp levels measured on the FR day. These fasting control plasma Trp concentrations fall into the range of values found in other studies in which measurements were taken after 24 h of a low-Trp diet and overnight fasting (Carpenter et al. 1998; Møller 1981). As expected, paired t-tests comparing fasting control FR plasma total Trp concentrations between the high and low groups produced two significantly different groups [$t(6.4) = 4.34$, $p = .004$]; however, there was no difference in plasma Trp levels achieved between these two groups on either the T+ or T− treatment days [$t(4.3) = 0.61$, $p = .6$; $t(4.3) = 0.81$, $p = .5$, respectively]. There were also no differences between groups comparing age, educational level, or reported number of alcoholic beverages consumed per week ($p > .05$).

As shown in Figure 2, a 2 × 3 × 3 (high/low group × treatment × time) repeated measures univariate ANOVA revealed that aggressive responding (point subtraction B responses) was diminished by T+ and increased by T− treatments across the sessions, as indicated by the main effects of both treatment and time [$F(2,16) = 5.99$, H-F $p = .02$, $f = 0.87$; $F(2,16) = 3.66$, $p = .049$, $f = 0.68$, respectively], but the high group was affected by both the T+ and the T− treatments whereas the low group was not [group × treatment interaction, $F(2,16) = 5.14$, $p = .02$, $f = 0.48$]. Paired t-tests showed that the high group difference existed primarily as a result of decreased aggressive responding after the T+ treatment compared with FR fasting control at hours 1 and 3 [$t(4) = 3.19$, $p = .03$; $t(4) = 3.82$, $p = .02$; respectively].

Because peak effects of the T− beverage occur between 5 and 6 h after treatment and peak effects of the T+ beverage occur at ∼2 h after treatment, to examine aggressive responding differences between treatments we compared the T− session 4 (5 h after treatment) with T+ sessions 2 (1 h after) and 3 (3 h after). These

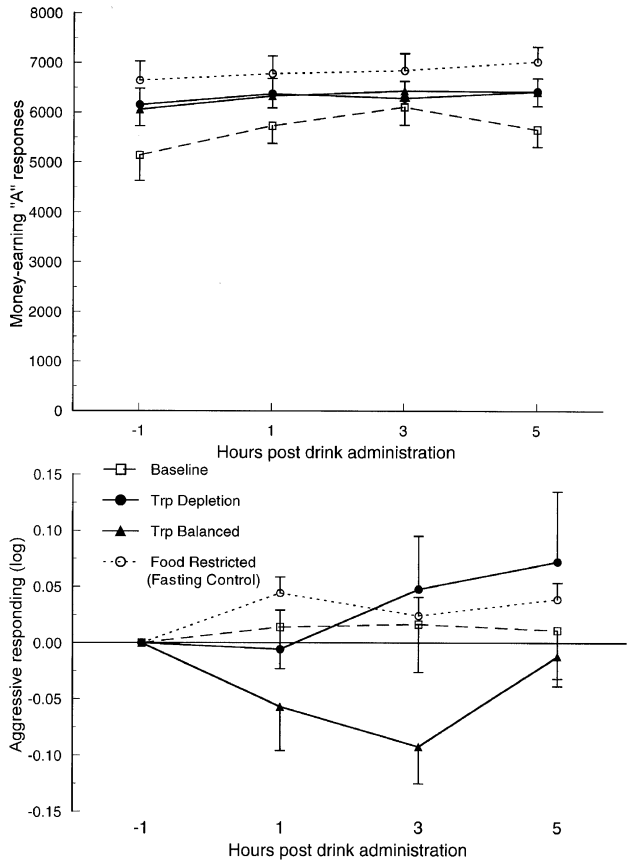

Figure 1. Money-earning (top) and aggressive responses (bottom) of 12 women after Trp augmentation, depletion, fasting control (no drink), and baseline conditions. Money-earning responses are shown as raw scores and aggressive responses are shown as a proportion of each day's baseline session (8:30 A.M., at −1 h to amino acid drink). Error bars represent SEM.

peak effects comparisons showed no treatment differences for the low fasting control plasma Trp group [$t(4) = 1.96$, $p = .1$; $t(4) = 0.68$, $p = .5$; respectively], whereas the high fasting control plasma Trp group showed a trend for a T+ treatment difference at both 1 and 3 h compared with T− at 5 h after treatment [$t(4) = 2.39$, $p = .075$; $t(4) = 2.52$, $p = .065$; respectively].

DISCUSSION

This study is the first to demonstrate that both Trp augmentation (T+) and depletion (T−) can influence prospectively measured aggressive behavior of women. In a manner similar to what has been shown with men, under T− conditions the women showed a trend for increased aggressive responding. However, unlike studies with men, the women demonstrated markedly decreased aggressive responding under the T+ condition, although men have reported feelings of well-being after Trp loading (Cleare and Bond 1995). Also unlike studies with men, changes in aggressive responding (at any time point) due to the effects of Trp manipulation showed no relationship to the women's self-reports of impulsive (BIS-11 and I_7) and aggressive (BPA and LHA) behaviors, although both of these traits were related to the women's sensitivity to the T− and T+ treatments (see Table 2). The greater the participants' sensitivity to the T+ manipulations (greatest plasma Trp *increase* from fasting control levels), the higher their scores on impulsive measures, whereas the greater the sensitivity to the T− manipulations (greatest plasma Trp *decrease* from fasting control levels) the higher their scores on aggressiveness measures, particularly for anger and physical aggression. Taken together, these results support the well-established relationship between aggression and serotonin as well as the idea that certain individuals may differ in their susceptibility to manipulations of the CNS 5-HT serotonin system and that serotonin system changes can be expressed as impulsive or aggressive behavior.

Post hoc analyses produced an interesting preliminary result showing that when the women were divided into two groups—high and low fasting control plasma Trp—there was a distinct difference in aggressive responsivity to CNS 5-HT manipulation. Similar results with men have established a relationship between higher baseline plasma Trp and elevated aggressive behavior (Eriksson and Lidberg 1997; Møller et al. 1996; Virkkunen and Närvänen 1987; Wingrove et al. 1999). The results of this study show that it was the high fasting control plasma Trp women who increased aggressive responding under depletion conditions; however, unlike the men, these women also showed significant decreases in aggression when plasma Trp was augmented. Both the increases and decreases in aggressive responding were found to be specific to the high plasma Trp group only. Higher levels of plasma Trp have usually been assumed to indicate a more functional CNS 5-HT system; however, several studies have now shown this same counterintuitive result. Møller et al. (1996) and Wingrove et al. (1999) both found positive correlations between psychometric measures of aggression in normal men and their plasma Trp and Trp/LNAA concentrations. Higher plasma Trp levels were also found in groups of normal men compared with women (Møller et al. 1996). Virkkunen and Närvänen (1987) found both the total plasma Trp and the Trp/LNAA ratio to be higher in a group of men with intermittent explosive disorder compared with controls. While it has been assumed that low levels of CSF 5-HIAA can be used as an indicator of CNS 5-HT dysfunction, Virkkunen and Närvänen pointed out that low 5-HIAA levels are only a reflection of monoamine oxidase activity and not serotonin release in the brain. Therefore, they speculated

Table 2. Pearson Correlation of Psychometric Measures with Plasma Trp Changes from Fasting Control for T+ and T− Conditions

	Plasma Trp Difference Scores (n = 10)[a]			
	T−		T+	
Psychometric Measures	**Pearson's r**	p	**Pearson's r**	p
Barratt Impulsiveness Scale				
Subscales				
Attention	0.34	.33	0.34	.34
Motor	0.04	.92	0.47	.17
Non-planning	0.27	.45	0.82	.004
Total score	0.29	.41	0.68	.03
Buss-Perry Aggression Questionnaire				
Subscales				
Physical aggression	−0.77	.009	0.25	.49
Verbal aggression	−0.10	.77	0.60	.06
Hostility	−0.61	.06	0.27	.46
Anger	−0.63	.04	0.28	.43
Total score	−0.68	.03	0.39	.26

[a]Absolute difference of plasma total Trp concentrations between experimental and fasting control conditions of the entire group of 10 women.

that in spite of the low CSF 5-HIAA, high plasma Trp may indicate an adequate supply of Trp in the brain but an inadequate serotonin storage resulting in 5-HT system dysfunction. Eriksson and Lidberg (1997) also found higher basal plasma Trp and Trp/LNAA concentrations in men who committed violent crimes compared with nonviolent criminals and controls. They speculated that the underlying mechanism might be an imbalance of peripheral norepinephrine and epinephrine because plasma LNAAs are partly regulated by α- and β-adrenergic activity. One limitation of this study preventing clearer interpretation is the lack of measurements of competing LNAAs. The higher fasting control plasma Trp concentrations reflect probable higher 5-HT synthesis only if there is not a corresponding increase in levels of the other LNAAs. More investigation of the complex interactions of the neurotransmitter systems is needed to clearly determine which mechanisms mediate aggressive behaviors.

Unlike previous findings with men, we found no correlation of the women's fasting control plasma Trp levels with any of the psychometric measures of impulsivity or aggression, although this is consistent with Møller and colleagues' (1996) findings. They suggested that factors such as hormones might contribute to this difference between men and women. Although this study found no relationship between aggressive responding and the level of self-reported menstrual distress, extending studies to females requires the additional consideration of possible interactions with menstrual cycle phase. Because physiological changes across the menstrual cycle are complex, it is possible that the women's menstrual cycle (not controlled for in this study) could have affected our results. Alternatively, perhaps the correlational difference between men and women is a result of a difference in self-reports of aggressive and impulsive behavior.

This gender difference in the relationship between fasting control plasma Trp levels and psychometric measures prompted us to search for other possible explanations, such as treatment sensitivity. Perhaps in women the acute changes in aggressive performance are related to the magnitude of the change in plasma Trp levels induced by Trp depletion or augmentation. After calculating difference scores between fasting control plasma Trp levels and each of the experimental days, we found the Trp− difference scores were correlated negatively with self-reports of aggression—the larger the change between fasting control and acute Trp depletion, the smaller the aggression score; and the Trp+ difference scores were correlated positively with impulsivity scores—the larger the change between fasting control and acute Trp augmentation, the larger the impulsivity scores. This may mean only a subset of women demonstrate responses similar to men. How to define that subset will require additional study with a larger group of women.

The results of this study are interesting and estimates of effect sizes were very large, but the small sample of women who completed testing and the high attrition rate of the participants are limitations that may affect the generalizability of these findings. This study was, however, similar to other repeated-measures Trp depletion studies in which group sample sizes ranged from three to 14 participants (M = 10, SD = 3.5; Bjork et al. 1999, 2000; Carpenter et al. 1998; Hrboticky et al. 1989; LeMarquand et al. 1998; Menkes et al. 1994; Moeller et al. 1996; Møller 1981; Oldman et al. 1994; Salomon et al. 1994). Additionally, the two groups (those who completed the study and those who did not)

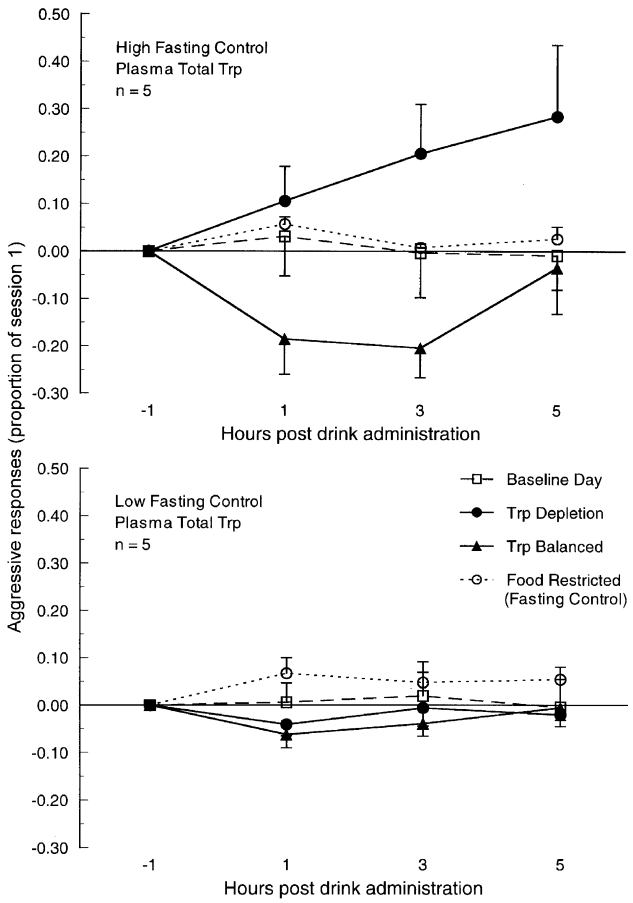

Figure 2. Aggressive responses of women divided into high and low plasma total Ttp groups based on plasma concentrations on the fasting control (no drink) day. Responses are shown as a proportion of each day's baseline session (8:30 A.M., at −1 h to amino acid drink). Error bars represent SEM.

were compared on pertinent demographic and psychometric data, and this comparison did not reveal any differences between the groups (see Table 1). Participant attrition rates are infrequently reported in published Trp depletion studies, but among these researchers it is known that these studies have higher participant losses than other types of pharmacological research given that the amino acid drink and fasting procedures can be unpleasant.

After completing this study with women, we suggest exploration of possible solutions to reduce participant attrition. One potential solution would be to evaluate lower doses of the amino acid drink to improve palatability. A low-dose 25-g T− drink has been shown to produce a 50% suppression of the plasma Trp/LNAA ratio in men and women (Krahn et al. 1996) compared with the 69% decrease of plasma total Trp in this current study. Whether smaller doses of these amino acid drinks would result in behavior changes remains to be determined. A systematic evaluation of the behavioral effects of low and intermediate amino acid drink doses (e.g., 25 and 50 g) would be useful for addressing palatability and the effect on participant attrition. Fasting (in this case a minimum of 16 h) is a nearly universal aspect of this type of research. Two studies (Hrboticky et al. 1989; Menkes et al. 1994) have provided participants with varied amounts of low-Trp food items during participation, but no comparative control was used to evaluate the effect of this addition on either biological or behavioral data. Assessment of the impact on experimental measures of moderate amounts of low-Trp food items ingested at fixed intervals could result in an improved administration method to alleviate discomforts of fasting and increase participant retention.

These modifications in treatment dose and fasting requirements seem feasible given the extremely large effect sizes obtained for the treatment condition × test time interaction ($f = 1.49$) of the principal analysis of aggressive responding. Even the preliminary analysis of the high/low fasting control plasma Trp groups' effect sizes for the treatment condition ($f = 0.87$) and test time ($f = 0.68$) main effects and the group × test time interaction ($f = 0.48$) were sufficiently large to allow modifications of method, particularly if more in-depth studies of this group comparison included somewhat larger sample sizes.

This study demonstrates that Trp augmentation and depletion are an effective means of examining serotonin function and aggressive behavior in women. The post hoc analyses showed that both the increases and decreases of aggressive responding in response to Trp manipulation appear to be specific to women with higher baseline plasma Trp. The low plasma Trp group's aggressive responding under T+ and T− conditions was not different than the FR fasting control condition. Additional work with larger samples is needed to determine whether this is a replicable finding, and, if so, what factors influence the particular sensitivity of some individuals to perturbation of the serotonin system. Further investigation of the complexity of the menstrual cycle interaction with Trp depletion and augmentation may provide insight as to what role cyclic hormone changes play in the expression of aggressive behavior within certain groups of women. Our laboratory will continue to focus on Trp manipulation of aggressive behavior in women with the inclusion of menstrual cycle comparisons of behavioral and biological differences.

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