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The effects of tryptophan depletion and loading on laboratory aggression in men: time course and a food-restricted control

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Abstract Some studies have shown that sharp reduction of L-tryptophan (Trp) concentration in plasma results in increases in laboratory-measured aggression. Conversely, raising plasma Trp has blunted aggression. These effects are presumably due to impaired or enhanced serotonin synthesis and neurotransmission in the brain. In this study, the laboratory-measured aggressive behavior of eight men under both Trp depletion (T-) and Trp loading (T+) conditions was compared to their aggressive behavior under food-restricted control conditions (overnight fast without an amino acid beverage). Subjects were provoked by periodic subtraction of money which was attributed to a fictitious other participant, and aggression was defined as the number of retaliatory responses the subject made ostensibly to reduce the earnings of the (fictitious) other participant. Following ingestion of the T- beverage, aggressive responding was significantly elevated relative to the food-restricted control condition, and this increased aggressive behavior became more pronounced across behavioral testing sessions on a time-course which paralleled previously documented decreases in plasma Trp concentrations. In contrast, no changes were observed in aggressive responding under T+ conditions relative to food-restricted conditions. These within-subject behavioral changes under depleted plasma Trp conditions support earlier indications of a role of serotonin in regulating aggression.

Key words Aggression · Tryptophan · Serotonin · Human · Diet

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Introduction

Decreased serotonin (5-HT) function has correlated with aggressive acts toward self (Asberg et al. 1976, 1987) and others (Brown et al. 1979; Coccaro et al. 1989; Moss et al. 1990), where 5-HT deficits correlate most strongly with impulsive aggression (Linnoila 1983). The relationship between 5-HT and non-impulsive, (purposeful or "instrumental") aggression has also been established in prospective laboratory studies where human aggressive behavior has increased following L-tryptophan (Trp) depletion (Moeller et al. 1996). Trp depletion is induced in humans by the ingestion of a beverage containing 15 amino acids (AAs) without Trp (the T- drink; Perez-Cruet et al. 1974; Young et al. 1988), which both reduces plasma Trp levels and competitively inhibits Trp uptake into the central nervous system (CNS) for 5-HT synthesis (Yuwiler et al. 1977; Wurtman et al. 1981). Trp depletion has been recently shown to reduce cerebrospinal fluid 5-HT metabolite levels in humans (Carpenter et al. 1997), suggesting a CNS impact of this technique. Combinations of these 15 amino acids with the addition of either a proportionally balanced amount of Trp (the B drink) or excess Trp (the T+ drink) have been used as controls for the T- drink (Cleare and Bond 1995; Barr et al. 1997).

A few studies report that human laboratory aggressive responding and/or hostile feelings have increased following tryptophan depletion (e.g. Young et al. 1985; Moeller et al. 1996). In contrast, Trp loading (T+ drink administration) blunted alcohol-induced increases in aggressive responding (Pihl et al. 1995). Other research indicates that increases in aggressive behavior or angry/hostile feelings under Trp-depletion conditions are specific to individuals with high self-reported hostility (Cleare and Bond 1994, 1995), premenstrual syndrome (Menkes et al. 1994), or to those experiencing a high level of provocation-induced arousal (Pihl et al. 1995). Other studies, however, have found little or no effect of T- conditions on mood (Oldman 1994; Salomon 1994)

or behavior (Smith et al. 1986). These mixed findings may have resulted from differences across studies in subject population, how aggression was defined/measured, and whether subjects experienced provoking conditions. Another design shortcoming has been behavioral assessment only during the peak effect of the T- dose, with a comparison of the T- aggression data to those of a different group of subjects who were assigned a B or T+ dose (e.g. Cleare and Bond 1995; Pihl et al. 1995). These designs do not allow examination of either within-subject changes in behavior before and after drink ingestion, or the behavioral effects of both Trp depletion and loading in the same individual.

In several previous studies, subjects were instructed to fast overnight prior to AA beverage ingestion and were not fed during the behavioral testing day over concern that the plasma Trp/LNAA ratio may be influenced by certain types of meals (reviewed in Fernstrom 1991; Young 1991). However, if nutrient deprivation itself exerts cognitive and behavioral effects in humans (Story and Rosen 1987), interpretation and generalizability of these behavioral data may be muddled. In Trp depletion studies in our laboratory, many subjects have commented on their hunger during testing. Taken together with findings that: 1) a bolus dose of free Trp comparable to that contained in the T+ drink has been shown to have (nondiscriminated) sedative qualities in human subjects (Winokur et al. 1986), and 2) the T+ drink itself has blunted aggression in monkeys (Chamberlain et al. 1987) and humans (Pihl et al. 1995), it is possible that increased aggression under "Trp depleted" conditions reported previously may have actually been due in part to a behavioral effect of food deprivation (e.g. irritability) which was counteracted by sedative properties of the disproportionately high quantity of Trp mixed in a T+ drink.

To our knowledge, no study has compared aggressive responding during tryptophan depleting or tryptophan loading conditions in the same subject, and no study has compared aggression under T- or T+ conditions with aggressive responding when food is restricted but plasma Trp is not artificially manipulated. In this study, the aggressive responding of eight adult male controls was assessed in a repeated-measures design: following ingestion of both a T- beverage, a T+ beverage, and under food-restricted conditions, where subjects were fasted but did not experience an AA beverage. The Point Subtraction Aggression Paradigm (PSAP; Cherek et al. 1993) was the laboratory aggression measure used. The PSAP is an externally validated aggression measure which periodically provokes a subject with money losses which are attributed to a fictitious antagonist. The number of retaliatory responses the subject chooses to emit with an intent to reduce the income of the fictitious antagonist is used as an objective measure of aggression.

Our previous study reported that T- drink ingestion in the morning dose-dependently increased PSAP aggression across the day compared to responding across the day when subjects neither consumed an AA beverage nor fasted (Moeller et al. 1996). That study did not include a control drink which contained Trp, however, due to possible contaminants in biotechnologically manufactured Trp (reviewed in Simat et al. 1996). This raises a possibility that those increases in aggression could have been due in part to the aversiveness of hunger interacting with repeated provocation across the day. In contrast, this study included for comparison both a food-restricted condition as well as a Trp loading condition.

Finally, this study was designed to examine the behavioral response to an interaction between T- conditions and high provocation-induced arousal. Young et al. (1988) suggested that since 5-HT neurons fire at higher rates when an organism is aroused (Trulson and Jacobs 1979), Trp depletion may exert a greater effect under arousing conditions. We attempted to test this idea by conditioning subjects to experience minimal provocation during baseline behavioral testing sessions, then subjecting them to a novel, higher frequency of provocation at a time point corresponding to the trough in the plasma Trp/LNAA ratio following T- drink consumption. We postulated that: 1) T- conditions would result in increased aggressive behavior during testing sessions occurring when the Trp/LNAA ratio reaches its lowest level, 2) this increase in aggression under T- conditions would be most apparent under novel, higher frequency provocation conditions, 3) aggressive responding would not appreciably increase under food-restricted conditions, and 4) aggressive responding would decrease slightly under T+ conditions.

Materials and methods

Subjects

Adult males from the community were recruited using newspaper advertisement for paid research volunteers. Applicants completed an on-site interview, and were offered participation if a medical questionnaire and structured clinical interview for DSM-IV (SCID-NP; First et al. 1996) revealed neither a current medical condition nor a current axis I psychiatric disorder. Past psychiatric disorder was not an exclusion criterion. The mean age of the eight subjects who completed the study was 32.6 ± SD 8.6, and mean years of education was 12.3 ± 0.6. Subjects were told that the study was comparing motor performance skills following regular food, no food, and two different AA nutrient beverages. Subjects were briefed that their payment for participating was based entirely on their motor performance. No mention was made of aggressive behavior in the interview or in the consent forms. The consent forms and methods were approved by the University's Institutional Review Board.

Amino acid drinks

The 100 g T- drink used in this study has been a standard dose in studies with male subjects (Young et al. 1988; Delgado et al. 1990;

Salomon et al. 1994; Pihl et al. 1995; Moeller et al. 1996) and consisted of the following quantities of AAs partially dissolved in 350 ml water: 5.5 g L-alanine, 4.9 g L-arginine, 3.2 g glycine, 3.2 g L-histidine, 8.0 g L-isoleucine, 13.5 g L-leucine, 11.0 g L-lysine monohydrochloride, 5.7 g L-phenylalanine, 12.2 g L-proline, 6.9 g L-serine, 6.5 g L-threonine, 6.9 g L-tyrosine, and 8.9 g L-valine. This aqueous suspension was flavored with 10 ml chocolate syrup and 3 drops of peppermint oil. In addition, 2.7 g L-cysteine and 3.0 g L-methionine were administered in nine capsules along with each of the T+ and T− drinks due to their unpalatability in the beverage. This dose has resulted in substantial reductions in the plasma Trp/LNAA ratio in all studies reported (reviewed in Wolfe 1995), with the lowest plasma Trp/LNAA ratio achieved between 5 and 6 h after beverage ingestion (Delgado et al. 1990). The T+ drink consisted of the above with the addition of 10.3 g L-tryptophan mixed into the the drink. This disproportionately high amount of Trp has resulted in highly elevated serum tryptophan levels (Cleare and Bond 1995), and bolus doses of Trp have resulted in increased levels of CSF 5-HT metabolite (Young and Gauthier 1981). Subjects were given 20 min to consume the drink and the capsules, but usually finished within 10 min. Since plasma Trp and LNAA levels before and after T− and T+ drink ingestion have been extensively replicated and documented in previous reports as well as within our own laboratory, the plasma AA levels of these subjects were not measured so that subjects would not have to endure the additional aversiveness of multiple venipunctures.

Aggression measurement

Subjects were seated for 25-min sessions in a 1.8 m × 1.8 m sound-attenuated chamber in which a computer monitor and response panel rested on a countertop. The response panel contained two buttons, labeled "A" and "B", and was connected to a IBM-PC compatible computer in an adjacent control room. Its lead wire was long enough so that the subject could place the response panel on his lap. The PC controlled all experimental events using PSAP software. Briefly, the PSAP measures the subject's aggressive response to the periodic loss of "points" worth money which the subject accumulates during the 25-min testing session by repeatedly pressing a button. Subjects are told beforehand that any such losses result from the responding of another (fictitious) study participant. Prior to testing, each subject was read instructions about the procedure (presented in detail in Cherek et al. 1990). These instructions ensured that each subject understood how the response console operated and that the goal of the session was simply to earn as many points as possible, because he was to be paid entirely based on how many points he earned.

Each subject was told that during each session, his response panel would be connected to a response panel operated by one of several other male participants in a different laboratory area who were also responding to earn money, and that another participant might take points from his counter. The subject was instructed that pressing button "A" approximately 100 times earned him a point worth 20 cents (the money-earning response), and that pressing button "B" 10 times would subtract a point from the counter of the (fictitious) participant at the other response panel (the aggressive response). Finally he was told that any points subtracted from his counter would be added to the other (fictitious) subject's counter, while points he subtracted from the other participant using his "B" button would not be added to his counter. This last distinction provided the subject a rationale for why he might experience point subtractions, but prevented the subject from aggressive responding to earn money.

Once the session began, the fictitious "other participant" (the PSAP software) repeatedly provoked the subject by subtracting a point from his counter every 6–120 s. A subject, however, could reduce the frequency of subsequent point subtractions if he used his B button to ostensibly retaliate in kind by subtracting a point from the "other participant". Completing the first ratio requirement (ten presses) of button B after at least one provocation had occurred would initiate a provocation-free interval (PFI), during which the subject would not experience any point subtractions. The duration of the PFI was programmed to be 500 s in all but three of the 20 PSAP sessions scheduled across the entire study (see below). Aggressive responses emitted after a PFI had been initiated were tabulated but had no effect until another point subtraction occurred. After the PFI had elapsed, the schedule of random (6–120 s) interval point subtractions resumed. Therefore, the subject was unable to avoid all point subtractions, and experienced at least three point subtractions per session. The PFI represents a consequence (negative reinforcement) of aggressive behavior and was designed to simulate the deterrence of further provocation of the subject. PFI induction has proven necessary to prevent the extinction of the PSAP aggressive response over time (Cherek et al. 1990).

To ensure that the subject believed he was paired up with one or more other participants across the day, he completed a questionnaire at the end of the day asking him to describe the other participant or participants. Data from PSAP subjects whose questionnaire responses indicate belief that their points were subtracted by a computer or by an investigator are excluded from analysis and the subject is removed from further study. Point-subtracting behavior as "real" aggression has been externally validated in studies showing that male parolees with self-report histories of violent behavior emit significantly more aggressive responses than non-violent male parolees (Cherek et al. 1996), parolees convicted of violent felonies respond more aggressively than parolees convicted of non-violent crimes (Cherek et al. 1997), and aggressive children with attention deficit hyperactivity disorder (ADHD) responded less aggressively after administration of methylphenidate (Casat et al. 1995).

Study schedule

Subjects participated for 4 days, from 8 a.m. to 4 p.m. Upon arrival at the laboratory each morning, subjects submitted breath and urine samples. Absence of alcohol or other drugs of abuse was verified using an Alcosensor III (Intoximeters, Inc., St Louis, MOG, USA) and the EMIT d.a.u. (Sylva Corp., Palo Alto, Calif., USA) urinalysis, respectively. Subjects were asked not to consume caffeine prior to visiting the laboratory. Subjects underwent five PSAP testing sessions per day and remained in a TV lounge between sessions. Sessions were held at 0830, 1030, 1230, 1430, and 1530 hours. The PSAP session time points were selected to measure behavior in conjunction with the decline in plasma Trp levels across the day following T− drink ingestion. Following testing each day, subjects completed a questionnaire on which they were asked to estimate and describe the number of "other person(s)" they were paired up with in their sessions. The subject was then paid (roughly $50.00 per day).

Day 1 of the study served as a baseline day, when subjects experienced five PSAP sessions to become accustomed to the testing procedure. A relatively long PFI of 500 s (induced by aggressive responding) was selected for all five PSAP sessions to encourage continued use of the aggressive response option (Cherek et al. 1990), and to help condition subjects to infrequent provocation. Subjects typically emit their aggressive responses shortly after a point subtraction. Therefore, with this PFI setting, consistent use of the aggressive response option in retaliation for each point subtraction could reduce the number of point subtractions from as many as 22 points to as few as 3 points. Finally, the baseline testing sessions also allowed for the stabilization of aggressive responding rates. Subjects were instructed to eat breakfast as normal before arriving on the first day of the study. Subjects were served a lunch (sandwich, chips, and caffeine-free soda) at noon. The subject was also given a low protein meal of chips and hot dogs prior to leaving the laboratory, and was given a list of low protein foods to eat in the evening if he became hungry. The subject was also instructed not to eat after midnight or in the morning.

Days 2 and 3 of the study were the two Trp manipulation days, during which subjects consumed AA drinks. Four subjects consumed the T- drink on day 2 and the T+ drink on day 3, while the other four subjects had a reversed dosing order. The drinks were administered by a research assistant blind to drink content at 0915 hours following the first PSAP session, and subjects completed consumption by 0930 hours. Therefore, the five PSAP sessions represented pre-drink baseline, as well as 1, 3, 5, and 6 h post sessions. On days 2 and 3, when subjects were expected to have markedly different plasma Trp/LNAA ratios 6 h after drink ingestion, the PFI of the 1530 (6 h post) PSAP session was reduced from 500 s to 125 s. This was intended to provide a novel experience of high provocation when the subject had been accustomed to minimal provocation. Since the duration of aggression-induced protection from point subtractions was thus reduced by 75%, this PFI adjustment generally had the effect of greatly increasing the number of point subtractions subjects experienced. Lunch was not served until 1600 hours, after behavioral testing was complete for the day. After day 2 of the study, subjects had 1 or 2 days (weekend) off before resuming testing on day 3. This was to allow time for a return to baseline levels of plasma Trp/LNAA ratio before experiencing the second drink. Since subjects were not going to visit the laboratory on the off-day prior to day 3, they were similarly instructed to eat a fast-food meal on the evening prior returning to the laboratory for Day 3 testing.

Day 4 of the study was the food-restricted (hunger condition) follow-up day. As was instructed for the T+ and T- drink days, subjects arrived ostensibly without having eaten anything since midnight. Subjects completed the five PSAP testing sessions as usual, with the PFI of the fifth (1530 hours) PSAP session reduced to 125 s to induce a higher provocation condition as had been the case for the fifth session under T− and T+ conditions. Lunch was similarly not served until 1600 hours. At the conclusion of the study, subjects completed a questionnaire asking them to state what they thought the study was about.

Data analysis

The variance in aggressive responses (but not money-earning responses) differed across sessions and between dose conditions such that the requirement of uniformity of variance for ANOVA was not met. Since the variance increased with the mean, it was stabilized by performing a log transformation of aggressive responses prior to subsequent analyses. Money-earning responses and (log-transformed) aggressive responses emitted in the four PFI=500 sessions were analyzed across sessions (time) and dose conditions (T-, T+, and food-restricted) using a repeated-measures ANOVA with session and dose as within-subject factors. At each time point, aggressive responding rates under T- and T+ conditions were compared separately with rates emitted under food-restricted (control) conditions using paired *t*-tests.

Results

Daily questionnaire responses indicated that all subjects believed in fictitious opponents throughout their participation, and exit questionnaires failed to indicate that a subject thought the study had to do with aggression. No subject submitted a drug-positive urine sample. In addition to the eight men who competed the study, another four were recruited. Two were dismissed at the end of day 1 because they did not emit aggressive responses during baseline testing sessions, and two were released because they could not successfully consume the AA beverage.

Aggressive responding-low provocation

For PSAP testing sessions 1–4 (pre-drink, 1, 3, and 5 h post-drink), the PFI was set at 500 s. As shown in Fig. 1A, the number of aggressive responses per PSAP session increased across the day under Trp depletion (T−) conditions, but remained fairly constant across the day under T+ and food-restricted conditions. This difference was highest 5 h post-drink. The main effects of session ($F3,21 = 0.1206$, $P = 0.947$) and dose ($F2,14 = 0.799$, $P = 0.469$) on aggressive responding were not significant. However, the dose by session ANOVA interaction was significant: ($F6,42 = 2.681$, $P = 0.027$). Aggressive responses under T− conditions were significantly elevated compared to food-restricted control at 3 and 5 h post-drink ($t(7) = 2.717$, $P = 0.030$, and $t(7) = 3.146$, $P = 0.016$, respectively). In contrast, aggressive responses under T+ conditions did not

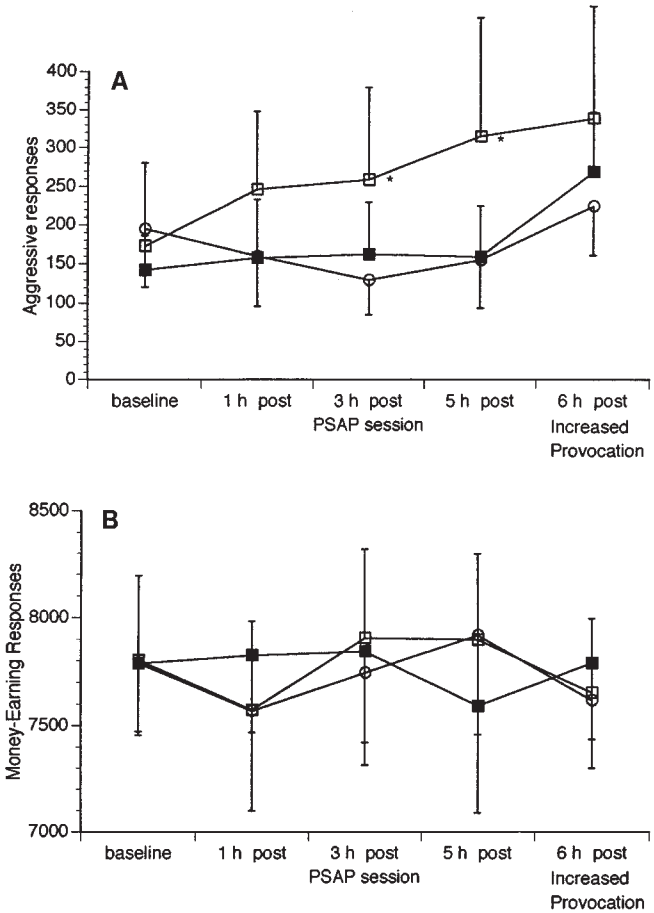

Fig. 1 **A** Aggressive responses (mean ± SEM) and **B** Money-earning responses (mean ± SEM) emitted during PSAP testing sessions under T− (□), T+ (■), and food-restricted (○) conditions. Testing was conducted with a PFI of 500 s at 0830, 1030, 1230 and 1430 hours. For the 1530 hour High Provocation session (*far right*), the PFI had been reduced to 125 s. Amino acid beverages were administered at 0915 hours. *Significantly different from food-restricted control condition (paired *t*-test $P < 0.05$)

differ from aggressive responses under food-restricted control at any point.

Money-earning responding

In contrast to the aggressive responding behavior, money-earning behavior did not differ under the three conditions (T−, T+, and food-restricted). Subjects emitted several thousand money-earning responses in all sessions (Fig. 1B), in all instances emitting far more money-earning responses than aggressive responses. Neither the main effects of dose ($F2,14 = 0.013$, $P = 0.987$) or session ($F3,21 = 0.433$, $P = 0.732$) on money-earning responding was significant, nor was the dose × session interaction ($F6,42 = 0.947$, $P = 0.472$).

Aggressive responding-high provocation

In order to examine the effects of 5-HT perturbation when subjects were aroused (Trulson and Jacobs 1979), subjects experienced a novel, high frequency of provocation at a second time point within the trough in the plasma Trp/LNAA ratio after ingestion of the T− drink. To promote arousal, we reduced the PFI (induced by aggressively responding to a point subtraction) from 500 s to 125 s during the 1530 hours "6 h post" session under all three conditions. This PFI reduction impaired the subjects' ability to prevent point subtractions, causing them to experience on average 10.8 ± SD 2.6 point subtractions, compared to only 5.4 ± 2.1 point subtractions during the previous (5 h post) PSAP session. In response to the doubled provocation, subjects emitted many more aggressive responses under all three conditions than they did under the 500 s PFI condition (Fig. 1, right-most column). Paired *t*-tests indicated that aggressive responses emitted under either T− or T+ conditions did not significantly differ from responses emitted during the food-restricted control.

Discussion

The key finding of this study was that under low-provocation conditions, aggressive responding (but not money-earning responding) was elevated following plasma Trp depletion relative to aggressive responding under conditions of similar food restriction without AA beverage administration. Aggressive responding rates under Trp-loaded conditions were generally indistinguishable from rates emitted under the food-restricted control conditions. In contrast to our hypothesis, however, aggressive responding to novel high-provocation six hours after T- drink ingestion was not significantly elevated compared to responding under food restricted-conditions. Since the plasma Trp concentration is still fully suppressed 6 h after T- drink ingestion (Delgado et al. 1990), and since depression of cerebrospinal fluid levels of 5-HT metabolite following T- drink ingestion lags behind the time-course of the reduction in plasma Trp (Carpenter et al. 1997), it seems unlikely that the lack of a significant difference in aggression at this point occurred due to a remission of the T- drink effects. It is possible that doubling the provocation frequency non-specifically increased aggressive responding to blur dose effects. Earlier findings have demonstrated that point subtraction frequency strongly regulates rates of aggressive responding in the PSAP (Cherek et al. 1991), and changes in provocation frequency also interact with drug effects (Cherek and Dougherty 1995).

Findings of increased anger or aggression following T- drink ingestion have not been universal. Salomon et al. (1994) did not detect increases in self-reported anger/hostility in violent patients, nor did Oldman et al. (1994) detect worsening mood in normal women. These negative findings suggest that subjects need to be provoked somehow in order to detect increases in aggression or hostility. Even with provocation, however, Smith et al. (1986) failed to detect increases in shock intensity delivered to a fictitious opponent in a laboratory aggression measure. It is also important to consider other study design and subject population differences in how Trp depletion may affect aggressive behavior.

In particular, this population differs from a college student sample in socioeconomic status and behavioral history. For example, many of these men had been expelled or suspended from school and/or were high school dropouts, and the aggression history interviews also revealed that most of these subjects had been arrested at least once. It seems likely that several of these subjects would have met DSM-IV criteria for antisocial personality disorder. Money subtraction may have been an especially potent provoking stimuli to these predominantly unemployed individuals. Collectively, we caution that these findings may not generalize to persons of higher socioeconomic status and/or persons with no criminal history.

In conclusion, these data add some clarity to laboratory aggression data obtained under food-restricted conditions in earlier Trp depletion studies. In particular, our results suggest that increases in laboratory-measured aggression under plasma Trp depleted conditions are probably not due to food deprivation alone. It seems unlikely that the absence of a drink administration in the food restriction condition caused any expectancy effects on aggression. All subjects thought the study had to do with button pressing performance (aggression was never mentioned during the study), and rates of the dominant (money-earning) response did not differ across the three conditions. We nevertheless

advocate inclusion of the food-restricted control conditions in behavioral study design in order to account for the effect of hunger on behavior. Finally, these data suggest that experimental conditions which present a modest (but not high) degree of provocation intensity may work best in detecting between-dose differences in aggression. More research should be undertaken to determine the conditions and situations under which reduced plasma Trp can lead to increased aggression as well as to identify persons prone to this effect.

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