BRIEF REPORTS

# Serotonin Function in Aggression: The Effect of Acute Plasma Tryptophan Depletion in Aggressive Patients

Ronald M. Salomon, Carolyn M. Mazure, Pedro L. Delgado, Pedro Mendia, and Dennis S. Charney

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## Introduction

Considerable preclinical and clinical evidence links impulsive, aggressive behaviors to reduced brain serotonin (5-HT) function (Chamberlain et al 1987; Young et al 1989; Higley et al 1992; Åsberg et al 1987, Brown et al 1979, Linnoila et al 1983, Mann et al 1986, Meltzer and Long 1987; Coccaro et al 1989; Virkkunen et al 1989, Linnoila et al 1989). The behavioral effects of decreased 5-HT function can be studied in clinical populations using an amino acid drink to reduce levels of plasma tryptophan (TRP), the precursor of 5-HT (Young et al 1985, Delgado et al 1991). Acute TRP depletion effects on aggression have been studied in healthy subjects. In a placebo-controlled study of the effects of acute TRP depletion, an aggression task with provocation was given to coincide with the lowest plasma TRP levels (40% of baseline). Compared to a balanced diet, aggression (as measured by the severity of shocks given to the nonexistent "partner") was not affected by acute TRP depletion (Smith et al 1986). To further this line of investigation, we studied impulsive, aggressive urges during acute TRP depletion in impulsive, aggressive patients.

## Method

### *Patient Recruitment and Selection*

Thirteen men and 1 woman who were euthymic, medication-free inpatients met criteria for Intermittent Explosive Disorder (DSM-III-R), with or without an Axis II diagnosis. The patients ranged in age from 20 to 53 years (mean 35.8). Impulsive episodes caused by substance abuse, depressive, manic, or psychotic symptoms were not sufficient for inclusion in the study. Patients with substance abuse diagnoses were included if in remission for at least 2 weeks. Six of the 14 had prior major depressive episodes, 2 had been hypomanic, and 8 had abused substances. Buss Durkee Hostility Inventory (BDHI) (Buss and Durkee 1957) "hostility" scores ranged from 24 to 60 (mean 48.6) indicating life-long hostile behaviors. Every patient had been arrested at least once for extreme aggressive behaviors; eight patients reported more than three arrests. Personality Disorder NOS with Antisocial Traits ($n$ = 5), and Antisocial Personality Disorder ($n$ = 3) were the most common Axis II diagnoses (DSM-III-R).

### *Depletion of Plasma Tryptophan Procedure*

Patients gave informed consent and were tested twice, one week apart, in a double-blind crossover design. Low TRP diets on day 1 of active tests are restricted to 160 mg/day TRP and are followed at 8 AM on day 2 with a TRP-free 15 amino acid drink. Control test diets and the control drink include TRP. Details of the procedure and biochemical methods for plasma TRP levels have been published previously (Delgado et al 1991). A modified state-sensitive version of the BDHI (mBDHI, available on request) and Overt Aggression Scale (OAS) (Yudofsky et al 1986) were used to rate hostility. Behavioral ratings and plasma samples were taken four times during each test: while fasting prior to the diet, prior to the amino acid drink, 7 hr later on day 2, and at 12 noon on day 3.

### *Data Analysis*

Changes in behavioral scale scores or in plasma free and total TRP were assessed by analysis of variance (ANOVA) with repeated measures, or analysis of covariance (ANCOVA) when baseline

From the Department of Psychiatry, Yale University School of Medicine (RMS, CMM, PM, DSC); the Department of Veterans Affairs Medical Center Psychiatry Service West Haven, CT (RMS, PM, DSC); the Yale-New Haven Hospital, New Haven, CT (CMM); and the Department of Psychiatry, University of Arizona School of Medicine, Tucson, AZ (PLD).

Address reprint requests to Ronald M. Salomon, MD, Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue, West Haven, CT 06516.

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differences were significant. Main effects of test dose (control versus TRP depletion) and time (change over the time points sampled) were assessed. The interaction of [dose] × [time] indicated the effect of the TRP depletion. Significant interactions revealed by ANOVA were further examined using Dunnet's test for multiple comparisons.

## Results

### *Plasma Tryptophan*

The low-TRP diet and TRP-depleting amino acid decreased plasma free and total TRP levels to 18% and 13% of baseline (day 1), respectively. ANOVA of changes in plasma TRP during TRP depleting and control testing revealed significant effects of dose (free: $F = 38.5$ and total: $F = 47.2$, both: df = 1, 13, $p < 0.0001$) consistent with previous depletion studies (Delgado et al 1991).

### *Behavioral Rating Changes*

Acute TRP depletion did not significantly increase mBDHI scores (Figure 1). Seven hours after the depleting drink (the nadir in plasma TRP concentration), means of the total or eight individual subscale scores were not significantly changed either from baseline (time effect) or compared to control tests (dose effect).

A marginally significant *decrease* in the mean irritability subscale score was observed at the day 3 time point (follow-up) after the active depletion test [ANOVA for (time) × (dose)] (df = 2, 26, $F = 3.292$, $p = 0.05$). Dunnet's test for multiple comparisons showed a statistically significant difference from baseline to day 3 ($t = 3.5$, $p < 0.002$) and from depletion (day 2 at 4 PM) to day 3 ($t = 2.5$, $p < 0.02$). No corresponding changes were shown after control tests. Free or total TRP levels did not correlate with mBDHI subscale scores.

No significant changes during acute TRP depletion were found in OAS scores using ANOVA to test for main effects of (dose) and (time) and their interaction. OAS events (including shouting, cursing viciously, slamming doors, breaking objects, hitting objects with fists) were recorded in 4 of 14 patients during depletion, but only 1 of 14 during control tests (NS, $\chi^2$).

## Discussion

This study did not show changes in hostility during acute TRP depletion in impulsive individuals. This finding suggests that an acute decrease in TRP availability to the brain alone is not sufficient to cause an immediate, marked change in hostility measures. The lack of response may reflect the infrequency of expressions of hostility in a neutral, clinically sterile environment. This negative result also may be caused by the limitations of the dependent measures, the small sample size, or brief time of the depleted state. It is noteworthy that an investigation of acute TRP depletion in healthy subjects studied in a provocative environment also showed no significant effect of the TRP depletion (Smith et al 1986). After reductions in tryptophan levels, impulsive aggressive patients may have clinically significant behavioral changes when studied under provocative conditions.

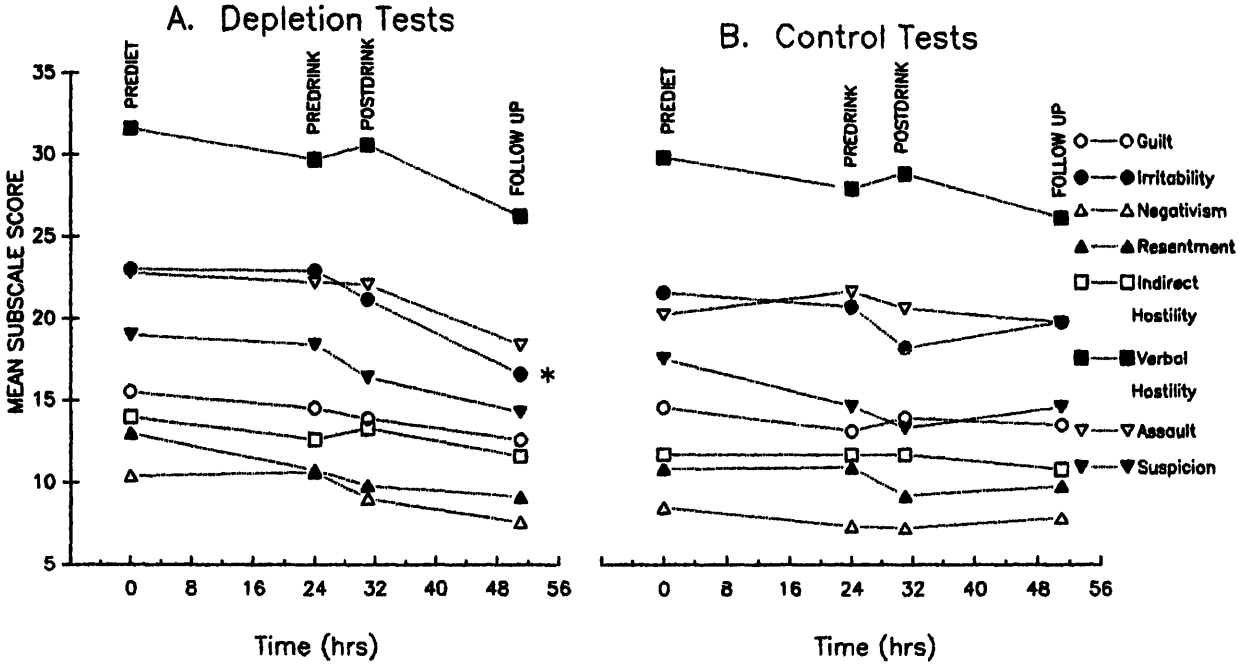


Figure 1. Mean modified Buss-Durkee Hostility Inventory (mBDHI) subscale scores graphed over time for impulsive patients ($n = 14$). A 24-hr TRP-restricted diet began at 0 hr (9 AM day 1), was followed by a mixture of amino acids at 24 hr (9 AM day 2), and the primary outcome measure at 31 hr (4 PM day 2, 7 hr after the drink). Follow-up (12 PM day 3) ratings are shown at 51 hr. (A) mBDHI subscale scores from active depletion tests. See symbol legend at top right. Irritability scores decreased at the day-3 time point (*$p < 0.05$ by ANOVA and Dunnet's test, different from prediet, predrink, and postdrink. (B) mBDHI subscale scores from control tests. See symbol legend at top right. Mean scores are virtually unchanged throughout the study. No significant changes by ANOVA.

"Irritability" subscale scores from the mBDHI improved significantly on the day after TRP depletion but not over the course of control tests. Because this was observed in only one subscale at a marginal (0.05) probability level, this interpretation remains speculative. However, it is similar to a finding from a previous study (Delgado et al 1991) of bimodal changes in depression scores among unmedicated depressed patients after TRP depletion.

In summary, the present data do not demonstrate a change in behavior during acute TRP depletion in impulsive patients. Irritability subscale scores improved in most patients after the TRP repletion following the depletion test. Evidence from this and other studies of aggression with acute TRP depletion in primates and in humans suggests that for future studies, a selected provocation may be required to demonstrate a relationship between reduced serotonin function and impulsive, aggressive behavior.

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