Serotonergic Functioning in Depressed Abused Children: Clinical and Familial Correlates

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Background: *The goal of this study was to examine serotonergic functioning and concomitant clinical and familial correlates in depressed abused children.*

Methods: *L-5-Hydroxytryptophan (L-5-HTP) (0.8 mg/kg) was administered intravenously to 10 depressed abused (MDD-AB), 10 depressed nonabused (MDD-NA), and 10 normal control nonabused (NC-NA) children. The children in the two nonabused cohorts represent a small matched subset of children from a larger interlocking study of the psychobiology of depression. Blood samples for prolactin and cortisol were collected from 30 min before to 2.5 hours after L-5-HTP infusion.*

Results: *The MDD-AB children secreted significantly more prolactin post-L-5-HTP than the children in the other two groups. There were no differences in baseline prolactin or any of the cortisol measures. Total prolactin post-L-5-HTP was significantly correlated with clinical ratings of aggressive behavior (rho = .48). In addition, children with a family history positive for suicide attempt (MDD-AB: n = 7; MDD-NA: n = 5; NC-NA: n = 2) secreted significantly more prolactin post-L-5-HTP than children with no family history of suicide.*

Conclusions: *Dysregulation in the serotonergic system in abused children appears to be related to both familial and experiential factors.* Biol Psychiatry 1998;44:973–981
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Key Words: Child abuse, child depression, serotonin

Introduction

Traumatized and nontraumatized depressed patients have been found to differ on multiple psychobiological parameters (Halbriech et al 1989; Kaufman et al 1997). Depending on the system under investigation, differences between traumatized and nontraumatized patients can be expected in either direction or magnitude. This study examined indices of serotonergic functioning in depressed abused, depressed nonabused, and normal control children. When the serotonin precursor L-5-hydroxytryptophan (L-5-HTP) was administered to nontraumatized depressed and normal control children, the depressed children had a significantly blunted cortisol and augmented prolactin response, with the prolactin findings limited to female subjects (Ryan et al 1992).

There are multiple reasons to predict depressed abused children will have greater serotonergic system dysregulation than depressed nontraumatized children, specifically: 1) abused children have high rates of depression (Pelcovitz et al 1994), suicidality (Van der Kolk et al 1991), and aggression (Lewis 1992)—all behaviors that have been documented to be mediated by serotonergic processes (Petty et al 1996; Risch 1997); 2) the first- and second-degree relatives of depressed abused children likewise have elevated rates of depression, suicidality, and aggressive behavior (Kaufman et al 1998), and serotonergic system dysregulation is greatest in patients with high familial loading for these disorders (Coccaro et al 1994; Halperin et al 1997a; Linnoila et al 1989; Pine et al 1996); 3) measures of maladaptive home environments have been found to correlate significantly with indices of serotonergic functioning in boys at risk for delinquency (Pine et al 1996, 1997); 4) serotonergic mechanisms mediate learned helplessness, the animal model of depression involving exposure to inescapable stress (Sherman and Petty 1982; Petty et al 1994); and 5) long-term alterations in serotonergic functioning have been found in primates in association with suboptimal early rearing conditions (Kraemer and Clarke 1990; Rosenblum et al 1994).

To test the hypothesis that depressed abused children will have greater serotonergic system dysregulation than depressed nonabused children, the L-5-HTP challenge was administered to the children in the study. Given prior reports of greater serotonergic system dysregulation in patients with high familial loading for aggressive behavior (Coccaro et al 1994; Pine et al 1996), the relationship between neuroendocrine parameters post-L-5-HTP and family history of psychiatric illness data was also examined. In addition, as dimensional measures of aggression

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have been found to correlate with indices of serotonergic functioning (Coccaro et al 1989; Mann 1995; Pine et al 1997), clinical rating scale data were also obtained. The data reported in this article were collected as part of a larger study on depressive disorders in maltreated children (Kaufman et al 1997, 1998).

Methods and Materials

Referral

Depressed children were recruited from the inpatient and outpatient clinics at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. Normal control children were recruited through advertisement and personal contacts. The depressed nonabused and normal control children represent a small matched subset of children recruited to participate in a Program Project examining the psychobiology of childhood depression (PO5 MH 41712, Program Director, Neal Ryan, MD), and the depressed abused children were recruited to participate in an interlocking study examining depressive disorders in maltreated children (5K21 MH 01022, Principal Investigator, Joan Kaufman, PhD). A statistician blind to the neuroendocrine data selected the matches individual for individual, matching first by gender, then by race, and next by age within 1 year. The matches utilized in this report are the same matches utilized in prior publications (Kaufman et al 1997). Informed consent to participate in the study was obtained in accordance with the University of Pittsburgh Institutional Review Board guidelines.

Inclusion Criteria

Inclusion criteria common for all subjects were: 1) 7–13 years of age; and 2) Tanner Stage I–II of sexual development (Marshall and Tanner 1969, 1970). Children in both depressed cohorts were required to meet Research Diagnostic Criteria (RDC) for major depressive disorder (MDD), and children in the depressed abused cohort were additionally required to have a lifetime history of maltreatment (e.g., physical abuse, sexual abuse, and/or exposure to extreme marital violence). For the normal control children only, additional inclusion criteria included: 1) no lifetime history of any psychiatric disorder; and 2) low familial risk for affective illness. Inclusion in the normal control cohort was contingent on low family history of affective illness, because nonaffected offspring of depressed adults have been found to have some of the psychobiological findings typical of unipolar patients (Giles et al 1989). In this study, low familial risk for affective disorder was operationally defined as having no first-degree relative with a lifetime episode of any affective disorder or schizophrenia spectrum illness, no second-degree relative with a lifetime history of recurrent, bipolar, or psychotic depression, schizoaffective disorder, or schizophrenia, and no more than 20% of second-degree relatives with a single episode of MDD.

Exclusion Criteria

Exclusion criteria for all groups were: 1) significant medical illnesses; 2) medications (except acetaminophen) within 2 weeks of the study; 3) inordinate fear of needles; 4) obesity (weight greater than 150% of ideal body weight) or severe growth failure (weight or height less than 3% of the National Health Statistic Curve); and 5) mental retardation or the presence of a specific learning disability. All the children in the study were carefully screened for lifetime history of physical abuse, sexual abuse, and exposure to domestic violence. Only children with no lifetime history of maltreatment (e.g., physical abuse, sexual abuse, and/or exposure to domestic violence) were included in the nonabused depressed and normal control cohorts. Additional exclusion criteria for the MDD cohorts only included: 1) concurrent DSM-III-R diagnosis of anorexia nervosa, bulimia nervosa, autism, schizoaffective disorder, or schizophrenia; and 2) MDD chronologically secondary to conduct disorder.

Diagnostic Assignment

Diagnostic assessments of the depressed cohorts were completed by research assistants who administered the Present Episode (Chambers et al 1985) and Epidemiological (Orvaschel et al 1982) versions of the semistructured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS). The diagnosis of MDD was made using RDC (Spitzer et al 1978), with the presence of all positive symptoms confirmed by a child psychiatrist or psychologist. For normal controls, if an initial telephone screen of the family was promising, the child's lifetime history of psychiatric symptomatology was assessed using only the K-SADS-E (Orvashel and Puig-Antich 1987). All symptom ratings were made by interviewing the parent(s) first, then interviewing the child. All children who participated in the study were reinterviewed using a short version of the K-SADS at the time of the psychobiological studies to confirm depressive symptomatology status.

Clinical Ratings

To examine the relationship between the L-5-HTP challenge summary variables and dimensional indices of clinical symptomatology, the Child Behavior Checklist (CBCL; Achenbach and Edelbrock 1983) was completed by the child's mother at time of intake. The CBCL surveys 118 symptoms rated on a 0–2 point scale and generates Internalizing (e.g., depression) and Externalizing (e.g., aggression) Factor Scores. Raw CBCL factor scores are converted to gender- and age-normed t-scores, with t-scores of 70 representative of the 98th percentile in the normed sample. The CBCL has excellent psychometric properties and is one of the most widely utilized questionnaires of child psychopathology.

Abuse Assessment

The majority of the depressed abused children had experienced multiple forms of maltreatment (e.g., physical abuse, sexual abuse, emotional maltreatment), and half were living in conditions of extreme ongoing adversity (e.g., spousal violence, emotional abuse). As stated previously, none of the depressed nonabused or the normal control children had a history of any

Table 1. Demographic Characteristics of the Sample

	MDD-AB (n = 10)	MDD-NA (n = 10)	NC-NA (n = 10)	Statistic	p value
Age (years)	10.3 ± 1.2	10.1 ± 0.8	9.9 ± 1.1	$F(2,27) = 0.33$	ns
Race (black/white)	3/7	3/7	3/7	Fisher Exact	ns
Gender (female/male)	6/4	6/4	6/4	Fisher Exact	ns
Season of neuroendocrine challenge (Winter/Spring/Summer/Fall)	3/4/2/1	5/1/2/2	3/3/2/2	Fisher Exact	ns
Socioeconomic status (SES)	30.0 ± 14.7[a]	39.5 ± 15.7[b]	50.3 ± 9.8[b]	$F(2,27) = 5.28$	.01

MDD, major depressive disdorder; AB, abused; NA, nonabused; NC, normal control.
[a,b]Means with different superscripts are significantly different from one another, $p < .05$.

type of maltreatment. Information about abuse was derived by completing the Psychosocial Schedule for School Aged Children (PSS; Kaufman et al 1993; Lukens et al 1983). The PSS is a semistructured interview that was designed to obtain information about functional impairment, family environment, and abuse history. Both parents and children were used as informants in collecting these data. Supplemental abuse history data were obtained by reviewing the children's medical records. This information was integrated with the information obtained with the PSS, using a method described previously to obtain a "best estimate" of children's lifetime abuse experiences (Kaufman et al 1994). Unfortunately age of onset of abuse and abuse severity indices were not recorded. Child maltreatment history data were reviewed blind to information about the hormonal data.

Family History of Psychiatric Illness

Given the association between indices of serotonin functioning and measures of familial risk for depression (Birmaher et al 1997) and impulsive aggression (Coccaro et al 1994), family history variables were also examined in this report. The family history data were collected as part of the larger study and are described in detail elsewhere (Kaufman et al 1998). Data were collected on 101 first-degree and 290 second-degree relatives, with a comparable number of relatives assessed of the depressed abused (MDD-AB) (15.0 ± 4.1), depressed nonabused (MDD-NA) (12.9 ± 2.8), and normal control nonabused (NC-NA) (14.1 ± 2.7) children [$F(2,27) = 0.95$, ns]. Lifetime psychiatric history of first-degree relatives was determined using the K-SADS-E for relatives ages 6–18 years, and the Schedule for Affective Disorders–Lifetime for relatives over 18 years (SADS-L; Spitzer and Endicott 1978b). Unavailable adult first-degree relatives were assessed using Family History–Research Diagnostic Criteria (FH-RDC; Andreasen et al 1986) method of diagnosis and pedigree acquisition with the children's parent(s) serving as informant(s).

L-5-HTP Challenge

The L-5-HTP challenge was administered in a sleep/neuroendocrine laboratory furnished with many age-appropriate materials, including: books, art supplies, board games, entertainment videos, and computer games. Children were given a lot of one-to-one attention from staff with years of experience conducting biological studies with children. On a rating scale completed immediately after finishing the psychobiological studies, the majority of children who participated in this and other studies conducted in the lab rated the experience "very positive" (Townsend et al 1988; Nelson 1996).

The L-5-HTP challenge was administered on the third day of a larger, multitest psychobiological protocol (Kaufman et al 1997; Ryan et al 1992). An intravenous catheter was inserted at the onset of the protocol, at 5 pm two evenings prior to the L-5-HTP challenge. Other assessments obtained earlier in the protocol included cortisol specimens after IV insertion and sleep electroencephalographic recordings the two preceding nights. The day prior to the L-5-HTP challenge a growth hormone-releasing hormone challenge was conducted at 9:00 am; a reaction time (Matthews et al 1990) and mirror image tracing (Allen and Crowell 1989) task was completed at 1:00 pm, and a corticotropin-releasing hormone challenge was administered at 5:30 pm. Given the array of challenges completed, and blood draw limitations in younger children, no placebo challenges were completed as part of this study.

Children were also given a 3.0-mg/kg dose of oral carbidopa the day prior to the L-5-HTP challenge at 6:30 pm and at bedtime, and a 2.0-mg/kg dose at 7:00 am the day of the L-5-HTP challenge. Carbidopa blocks peripheral metabolism of L-5-HTP, thereby increasing precursor loading of the central nervous system (Magnussen and Engbaek 1979). At the doses utilized in this study, carbidopa has been found to have no effect on prolactin secretion (Mashchak et al 1983). Carbidopa administration permits use of a lower dose of L-5-HTP, increasing probe selectivity, and promoting central instead of peripheral activity.

Baseline blood samples for prolactin and cortisol were obtained through an indwelling catheter (placed 2 days earlier) at 7:30, 7:45, and 8:00 the morning of the L-5-HTP challenge. Blood samples were collected in plastic tubes containing edetic acid (EDTA), then centrifuged immediately in a refrigerated centrifuge. Plasma was separated and stored at −80°C until assayed. At 8:00 AM, 0.8 mg/kg of L-5-HTP in saline solution was infused over 1 hour. A physician was in attendance throughout the procedure. Following L-5-HTP administration, blood samples for prolactin and cortisol were obtained every 15 min for a total of 150 min. The child remained fasting from the previous evening until completion of the challenge. As indicated in Table 1, 36% of the subjects completed the L-5-HTP challenge during the winter, 27% completed it during the spring, 20% completed

it during the summer, and 17% completed it during the fall, with no differences among the groups on season of neuroendocrine testing.

L-5-HTP Challenge Side Effects

The infusion of L-5-HTP was stopped immediately if a child developed nausea as a result of the serotonergic stimulation. This occurred in 3 of the 13 (23%) MDD-AB children, which is roughly comparable to the rate of nausea reported in previous studies (Birmaher et al 1997; Ryan et al 1992). The children with nausea and their matched controls were excluded from all analyses, as the challenge was terminated prematurely. There were no other significant side effects associated with the infusion.

Hormonal Assays

Each patient's samples were analyzed within a complete run so that intraassay coefficients of variation (CVs) are applicable. Prolactin levels were determined on a 50-μL plasma sample, tested in duplicate, using Immunocorp's (Montreal, Canada) solid phase two-site immunoradiometric method. The kit procedure has been slightly modified to increase the sensitivity of the assay to 0.5 ng/mL. Subjects' duplicates with coefficient of variation in excess of 5.0% were reanalyzed. Levels that exceeded 100 ng/mL were diluted and reanalyzed. The intraassay variability of the subject samples had a mean CV of 1.4%. Interassay variation ranged from 7.8 to 11.5% CV. Cortisol values were determined using radioimmunoassays, as described in detail elsewhere (Ryan et al 1992). The intraassay variability of the subject samples had a mean coefficient of variation of 1.2%. Estimates of interassay variability were obtained by measuring hormone levels in commercially prepared sera (Bio-Rad Laboratories, Hercules, CA), and were 15.5 at 2.9 μg/dL (81.1 nmol/L), and 9.3 at 18.7 μg/dL (516.7 nmol/L).

Statistical Analyses

Sample characteristics were compared using analyses of variance, χ^2, and Fisher's Exact Test as appropriate. Problems with missing hormonal data were minimal, with only a few subjects missing one or two data points. Analyzing the data with and without linear interpolation to fill in the occasional missing values yielded similar results, therefore only the interpolated data are reported. Prior to conducting any analyses, summary variables for the hormonal measures and clinical rating scales were examined for normality using the Shapiro and Wilks' W statistic. The data were subject to log or square root transformation where significantly nonnormal distributions were found. In cases where no transformation normalized the data, nonparametric tests were used. The following summary values were used to characterize children's prolactin and cortisol responses to the L-5-HTP challenge: baseline; peak post-L-5-HTP; and total post-L-5-HTP. The baseline values were computed by determining the mean of the three prolactin and cortisol specimens taken at -30, -15, and 0 min pre-L-5-HTP infusion. The peak value represents the highest value post-L-5-HTP, and the total post-L-5-HTP score was computed by determining the area under the curve (AUC) using the 10 prolactin and cortisol specimens obtained from 0 to 150 min post-L-5-HTP infusion. AUCs were derived using the trapezoidal rule. Regression analyses were used to test the effects of age, gender, baseline hormonal levels, body mass index, Tanner stage, and socioeconomic status. Appropriate controls were then made in examining group differences on the raw or transformed summary hormonal measures (e.g., analysis of covariance), with Neuman Keuls tests used to control for multiple comparisons. Spearman correlations were utilized to examine the relationship between the hormone assessments and the clinical rating scale data, and t tests were utilized to compare hormonal values of children with positive versus negative family history of suicide attempts. All values are reported as means ± standard deviations, and p values are based on two-tailed tests with alpha set at .05.

Results

Subjects

After exclusion of children with nausea, the sample consisted of 30 children: 10 depressed abused, 10 depressed nonabused, and 10 NC-NA children with no lifetime history of psychopathology or abuse. There is no overlap in the subjects included in this manuscript and the subjects included in prior reports of serotonergic functioning in depressed children published by this group (Birmaher et al 1997; Ryan et al 1992). Subjects included in the prior reports were recruited during the first phase of funding of the Psychobiology of Childhood Depression Project (PO5 MH 4172, Program Director, Neal Ryan, MD), and subjects included in the present report were recruited during the second phase of funding. The depressed abused and depressed nonabused samples were comparable in terms of the duration (42.7 ± 43.6 weeks) and severity of the current depressive episode (31.0 ± 6.4 12-item K-SADS depression scale score), proportion with a history of inpatient treatment, and comorbid diagnostic profile for all diagnoses except posttraumatic stress disorder (PTSD). As expected, the MDD-AB children were significantly more likely to meet criteria for comorbid PTSD (5 vs. 0, Fisher's Exact Test, $p < .05$). All the children who participated in this study were included in a prior report describing corticotropin-releasing hormone (CRH) challenge data (See Kaufman et al 1997 for an expanded description of the clinical and abuse characteristics of the sample).

The demographic characteristics of the sample included in this manuscript are depicted in Table 1. The mean age of the sample was approximately 10 years of age (range 7–13), 67% of the children in the study were Caucasian, and 40% were male. As the nonabused depressed and normal control children included in this report were selected to match the abused cohort on demographic

Table 2. L-5-HTP Challenge Prolactin Values: MDD abused vs. MDD Nonabused vs. Normal Control Nonabused Children

	MDD-AB (mean ± SD) (n = 10)	MDD-NA (mean ± SD) (n = 10)	NC-NA (mean ± SD) (n = 10)	Statistic	p value
Baseline prolactin[a]	10.7 ± 7.9	9.2 ± 5.4	7.0 ± 2.1	$F(2,27) = 0.93$	ns
Peak prolactin post-L-5-HTP[b]	23.1 ± 8.5[d]	16.3 ± 4.1[e]	15.4 ± 5.4[e]	$F(2,25) = 6.57$[c]	.005
Total prolactin post-L-5-HTP[b]	40.5 ± 13.6[d]	29.5 ± 8.3[e]	26.1 ± 9.2[e]	$F(2,25) = 9.67$[c]	.001

[a]Log transformed values were utilized for the analyses. Raw scores are included in the table.
[b]Square root transformed values were utilized for the anlyses. Raw scores are included in the table.
[c]Analyses were conducted controlling for children's mean baseline prolactin values and body mass index.
[d,e]Values with different supercript letters (d or e) are significantly different from one another, $p < .05$. All significant comparisons remain even after utilizing Bonferonni corrections.

characteristics, there were no differences among the three groups in terms of age, race, or gender. The groups differed in terms of socioeconomic status (SES), however, with the depressed abused children having the lowest SES.

Hormonal Response to L-5-HTP Challenge

PROLACTIN. None of the following demographic factors were related to any of the prolactin summary scores: age, gender, race, or SES. Variability in prolactin values was also not related to the presence of comorbid PTSD or indices of ongoing adversity (e.g., emotional abuse, spousal violence). Peak and total prolactin post-L-5-HTP secretion values were significantly related to children's body mass index (BMI) and mean baseline prolactin values. Subsequent analyses controlled for these variables.

Table 2 portrays the means and standard deviations of the prolactin summary scores, and the results of tests for group differences on these measures. There were no differences in mean prolactin values at baseline. The MDD-AB children, however, secreted significantly more prolactin post-L-5-HTP than the matched subjects in the other two groups ($p < .01$), even after controlling for BMI and mean baseline prolactin values. Effect sizes for the differences between the MDD-AB and MDD-NA and NC-NA children for the peak and total post-L-5-HTP values ranged 0.97–1.23. The MDD-NA children likewise secreted more prolactin than the NA-NC children, but with the small subsample included in this report, this difference failed to reach statistical significance. The results of these analyses are depicted graphically in Figure 1.

CORTISOL. None of the following demographic factors were related to any of the cortisol summary scores: age, gender, race, or SES. Variability in cortisol values was also not related to the presence of comorbid PTSD or indices of ongoing adversity (e.g., emotional abuse, spousal violence). Peak and total cortisol post-L-5-HTP secretion values were significantly related to children's gender and mean baseline cortisol values. Subsequent analyses controlled for these variables. As depicted in Table 3 and Figure 2, however, there were no significant group differences on any of the cortisol summary measures.

Relationship between Prolactin Response to L-5-HTP and Family History of Psychopathology

Dichotomizing the sample on family history of depression or substance abuse was uninformative, as 80–100% of the two depressed cohorts had at least one first- or second-degree relative with a lifetime history of these disorders. Fourteen (47%) of the children in the study had a family history positive for suicide attempt (MDD-AB: $n = 7$; MDD-NA: $n = 5$; NC-NA: $n = 2$), and 7 (23%) of the children in the study had a family history positive for antisocial personality disorder (MDD-AB: $n = 5$; MDD-NA: $n = 2$; NC-NA: $n = 0$). Children with a positive family history of suicide attempts secreted significantly more total prolactin post-L-5-HTP than children with no family history of suicide ($t = -2.87$, df = 28, $p < .01$; suicide positive: 12.1 ± 2.1; suicide negative: 10.1 ± 1.5). In addition, there was a nonsignificant trend for children with a positive family history of antisocial personality disorder (ASP) to secrete more total prolactin post-L-5-HTP when compared to the other children ($t = -1.84$, df = 28, $p < .08$; ASP positive: 12.3 ± 2.5; ASP negative: 10.7 ± 1.8).

Relationship between Prolactin Response to L-5-HTP and Dimensional Clinical Ratings

The MDD-AB and MDD-NA children scored significantly higher than the NC-NA children on both the internalizing [Kruskal–Wallis χ^2 (df = 2) = 15.8, $p < .001$; MDD-AB: 73.7 ± 5.0; MDD-NA: 70.8 ± 12.2; NC-NA: 46.9 ± 9.5] and externalizing [Kruskal–Wallis

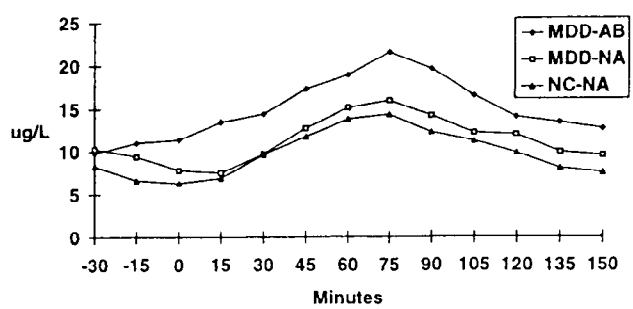

Figure 1. L-5-HTP challenge: prolactin values.

Table 3. L-5-HTP Challenge Cortisol Values: MDD Abused vs. MDD Nonabused vs. Normal Control Nonabused Children

	MDD-AB (mean ± SD) (n = 10)	MDD-NA (mean ± SD) (n = 10)	NC-NA (mean ± SD) (n = 10)	Statistic	p value
Baseline cortisol	408.3 ± 115.9	408.3 ± 113.1	372.5 ± 63.5	$F(2,27) = 0.43$	ns
Peak cortisol post-L-5-HTP	493.9 ± 113.1	413.9 ± 138.0	413.9 ± 157.3	$F(2,25) = 1.13^a$	ns
Total cortisol post-L-5-HTP	849.8 ± 209.7	736.7 ± 240.0	739.4 ± 244.9	$F(2,25) = 1.39^a$	ns

[a]Analyses were conducted controlling for children's gender and mean baseline cortisol values.

χ^2 (df = 2) = 14.2, $p < .001$; MDD-AB: 72.2 ± 6.0; MDD-NA: 64.5 ± 10.9; NC-NA: 48.9 ± 9.4] scales of the CBCL. The scores of the two depressed cohorts on these rating scales were not statistically different from one another, with the means of both groups approximately two standard deviations above the mean of the normed sample.

Children's total prolactin response post-L-5-HTP was significantly correlated with their scores on the CBCL internalizing (rho = 0.42, $p < .05$) and externalizing (rho = 0.48, $p < .01$) scales. Children with greater depression and aggression symptomatology secreted more prolactin after L-5-HTP infusion than children with less psychopathology in these domains.

Discussion

As predicted, when compared to depressed nonabused and normal control subjects, depressed abused children secreted significantly more prolactin after L-5-HTP infusion. The enhanced dysregulation observed in the abused children is consistent with prior human (Pine et al 1996, 1997) and nonhuman (Kraemer 1992; Rosenblum et al 1994) primate studies showing serotonergic system alterations in association with a range of early adverse rearing conditions. In addition, the findings further highlight the importance of experiential (e.g., trauma) factors in explaining heterogeneity in the psychobiological correlates of depression (Halbriech et al 1989; Kaufman et al 1997; Yehuda et al 1995).

Consistent with prior reports (Cocarro et al 1994; Halperin et al 1997a; Pine et al 1996), family history of suicide attempt was associated with subjects' responses to the neuroendocrine challenge. As abused children with a family history of affective disorder are more likely to develop depression than other abused children (Kaufman 1991), there is likely an interaction between experiences of abuse and genetic liability that promotes the onset of depressive disorders in these children (Kendler et al 1995; Risch 1997). The vulnerability to depression may in part be mediated through serotonergic mechanisms (Birmaher et al 1997; Maes and Meltzer, 1995), with the dysregulation in the serotonergic system due to both familial and experiential factors.

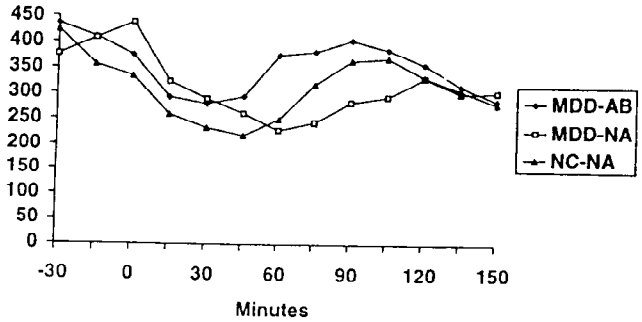

Figure 2. L-5-HTP challenge: cortisol values.

Prolactin secretion values after L-5-HTP infusion were also positively correlated with dimensional measures of aggressive behavior. This association is in the opposite direction reported in studies with adults, in which indices of serotonergic functioning have been found to correlate negatively with ratings of aggressive behavior (Coccaro et al 1989; Mann 1995). Although a negative correlation was reported between cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) levels and ratings of aggressive behavior in one study involving children (Kruesi et al 1990, 1992), and another study examining prolactin response to fenfluramine in aggressive boys with a positive family history of aggression (Halperin et al 1997a), most studies conducted with preadolescents report a positive correlation between measures of serotonergic indices and aggressive behavior. Specifically, a positive association between ratings of aggression has been reported with: CSF 5-HIAA in one other study (Castellanos et al 1994), whole blood serotonin in two studies (Pliszka et al 1988; Unis et al 1997), and prolactin response to fenfluramine challenge in three papers (Halperin et al 1994, 1997b; Pine et al 1997). There appear to be important familial and developmental factors that mediate the relationship between serotonin and clinical symptomatology, with positive associations between serotonergic indices and aggressive behavior most likely to be reported in young preadolescent samples (Halperin et al 1997b). Additional longitudinal investigations of well-characterized samples will be required to resolve the divergent findings in the field on this topic.

Contrary to expectation (Birmaher et al 1997; Ryan et al 1992), differences in the hormonal response to the L-5-HTP challenge were not detected between the depressed

nonabused and normal control children. In addition, no gender effects in children's prolactin response to the L-5-HTP challenge were observed in the present report. Differences between the groups were in the expected direction, however, with girls in both depressed cohorts secreting more prolactin post-L-5-HTP than their male counterparts. Failure to detect the expected results was likely due to the small size of the subsample included in this paper, as the prior L-5-HTP results have since been replicated in a new independent sample of nontraumatized depressed and normal control children (Ryan et al unpublished).

The reduced sample size may also have adversely impacted on our ability to detect cortisol secretion differences among the groups. Different serotonergic mechanisms, however, mediate the secretion of prolactin and cortisol (Meltzer and Maes 1994), with serotonin indirectly stimulating cortisol secretion via inputs on the pituitary that cause adrenocorticotropin (ACTH) release (Meltzer et al 1984). As dissociation between ACTH and cortisol secretion has previously been reported in depressed abused children (Kaufman et al 1997), L-5-HTP effects on the hypothalamic–pituitary–adrenal axis might have been better evaluated through the direct assessment of ACTH secretion.

Additional limitations to the present study include: lack of a placebo control condition; possible confounds resulting from the multiple-measure psychobiological protocol; and the absence of an abuse–no depression comparison group to permit examination of potentially meaningful interaction effects (e.g., abuse by family history of suicide attempt). Further evaluation of the serotonergic system using more central probes, in larger, more representative samples of traumatized children is clearly warranted. These studies will help to clarify the relationship between clinical symptomatology and serotonergic indices in abused children, and facilitate the identification of mechanisms within and outside the central nervous system that promote dysregulation of the serotonergic system in this population.

Numerous child, family, social, and abuse-related factors have been identified that influence the likelihood of abused children developing depressive disorders (Berliner and Elliot 1996; Kaufman, 1996; Toth et al 1992). For example, when compared to nondepressed abused children, abused children who develop a depressive disorder have: more severe abuse histories; increased rates of spousal violence in their families of origin; a greater number of out-of-home placements; fewer available supports; and higher familial loading for affective illness (Kaufman 1991). More research is needed to understand how inherent vulnerability factors interact with experiences of abuse and other psychosocial stressors to produce psychopathology in abused children. Better understanding of the interactions among these factors and psychobiological parameters will promote the development of more effective multimodal interventions for traumatized children (DeBellis and Putnam 1994; Kaufman and Mannarino 1995; Pynoos et al 1996).

Conclusion

Depression, suicidality, and aggressive behavior are frequent sequelae of child abuse. The data presented in this paper provide preliminary support for the hypothesis that the emergence of these symptoms is mediated by serotonergic processes. In addition, the serotonergic system alterations in the depressed abused children in this study appear to be associated with both familial and experiential factors. These findings, together with previous research, highlight the need for controlled studies to evaluate the efficacy of combined psychopharmacologic and psychosocial treatments in traumatized youth.

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