Salivary Cortisol Responses and the Risk for Substance Abuse in Prepubertal Boys

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Investigations of adults with a psychoactive substance use disorder (PSUD) or antisocial behavior have reported diminished secretion of the adrenal "stress" hormone, cortisol. Consequently, we determined whether prepubertal sons of PSUD fathers, at high risk for later PSUD, differed from controls on salivary cortisol concentrations before, and after, an anticipated stressor. The roles of problematic behavioral disposition and state anxiety in the cortisol responses were also examined. A significant risk-group × time interaction for salivary cortisol concentrations was found, with high-risk boys secreting less salivary cortisol than controls when anticipating the task. High-risk boys also had significantly higher scores for aggressive delinquency and impulsivity that wholly accounted for the risk-group × time effect on salivary cortisol. Thus, cortisol hyporesponsivity was associated with the dysregulated behaviors prevalent among high-risk boys. The results suggest that cortisol hyporesponsivity could be a "marker" for later antisociality and PSUD.

Key Words: Psychoactive substance use disorder, salivary cortisol responses

Introduction

To date, numerous investigations have demonstrated that certain biobehavioral characteristics are associated with the liability to psychoactive substance use disorder (PSUD). For example, increased risk for PSUD has been strongly associated with behavioral disorders in childhood and adolescence, such as conduct disorder (Kandel et al 1986; Loeber 1988; Robins and Price 1991; Boyle et al 1992; Moffitt 1993), attention deficit–hyperactivity disorder (Cantwell 1972; Gittleman et al 1985; Barkley et al 1990; Mannuzza et al 1991), and adult antisocial personality disorder (Cadoret et al 1986; Regier et al 1990; Grove et al 1990). These psychiatric syndromes share as common features an impairment in the executive regulation of goal-

directed behavior, such that normal inhibitory mechanisms that typically suppress nonadaptive responses to stimuli appear less effective (Gorenstein and Newman 1980; Moffitt 1993).

Such executive dysregulation is also frequently observed in children who are at increased risk for PSUD based upon the presence of an affected first-degree biological relative. For example, employing indices of impulsivity, aggressivity, and inattention drawn from multiple data sources, investigators have differentiated prepubertal boys whose fathers had PSUD from those with normal fathers (Martin et al 1994). In addition, prepubertal boys with a significant degree of familial aggregation for PSUD have been demonstrated to have elevated externalizing problem behavior scores (Moss et al 1994).

Several psychobiological investigations of antisocial and behaviorally dysregulated adults with and without PSUD have reported diminished secretion of the adrenal "stress" hormone, cortisol (King et al 1990; Virkkunen 1985; Woodman et al 1978). Among normal adults, moderately

higher morning cortisol concentrations have been associated with greater self-efficacy, emotional stability, high life satisfaction, and successful achievement (Brandtstadter et al 1991). In contrast, markedly higher cortisol concentrations are associated with anxiety, depression, introversion, and arousal (Sachar 1970; Rose 1980; Dabbs and Hopper 1990).

In children, findings of reduced basal cortisol concentrations have been associated with aggressivity (Tennes et al 1986), hostility (Tennes and Kreye 1985), and conduct disorder severity (Vanyukov et al 1993) by some, but not all, investigators (Kruesi et al 1989; McBurnett et al 1991). Conversely, shy and behaviorally inhibited children were found to have higher resting salivary cortisol concentrations (Kagan et al 1988). Thus, extreme cortisol responses in children may reflect a biological concomitant of either behavioral dysregulation at lower cortisol concentrations or excessive behavioral inhibition at higher concentrations.

The purpose of this investigation was three-fold. The first aim was to determine if sons of PSUD fathers (as a high-risk group) differed from control boys on salivary cortisol reactivity before and after a defined stressor. Salivary cortisol determinations are a valid, nontraumatic method to assess the dynamics of cortisol responsivity, which is of particular utility in children (Wolston et al 1983). The second aim was to test whether any group differences in cortisol responses were due to variations in perceived anxiety as measured by a state-anxiety questionnaire. Third, we examined whether impulsivity and problematic behavioral disposition accounted for the differences in the salivary cortisol concentrations observed among boys at grater or lesser risk for PSUD.

Method

Subjects

The sample consisted of two groups of boys between 10 and 12 years of age, ascertained through their fathers. Subjects were classified according to whether their fathers qualified for a lifetime diagnosis of PSUD for any illicit drug (family history positive [FHP]; $n = 81$) or had no psychiatric or substance use disorder (family history negative [FHN]; $n = 103$). Fathers in the FHP group were recruited through several outpatient substance abuse treatment facilities, community agencies (e.g., vocational rehabilitation agencies, community action groups, and churches), as well as by word-of-mouth. Fathers in the control group (FHN) were recruited through newspaper and radio advertisements, posters, and a sampling frame purchased from a marketing research firm. Table 1 summarizes the personal and demographic characteristics of the two groups. Between-group differences were evaluated by t tests. It is noteworthy that FHP boys tended to come from families with significantly lower socioeconomic status (SES) (Hollingshead 1990)

Table 1. Characteristics of Prepubertal Boys in Sample

	SA + ($n = 81$) Mean (SEM)	SA − ($n = 103$) Mean (SEM)
Age	10.86 (0.11)	11.1 (0.08)
Family SES[a]	35.62 (1.27)	48.54 (1.32)
Education	4.32 (0.12)	4.74 (0.11)
Psychiatric diagnoses	Frequency (%)	Frequency (%)
Major depression	6 (3.26)	2 (1.09)
Conduct disorder	3 (1.63)	0 (0)
Adjustment disorder	4 (2.17)	4 (2.17)
Attention deficit hyperactivity	13 (7.07)	11 (5.98)
Oppositional defiant disorder	15 (8.15)	7 (3.8)
Anxiety disorders of childhood	18 (9.78)	14 (7.61)

[a] $t = 6.91$, $df = 182$, $p < .001$.
SA = substance abuse; SES = socioeconomic status.

than did FHN boys, consistent with the findings of the NIMH Epidemiologic Catchment Area Study (Anthony and Helzer 1991). This epidemiologic study confirmed earlier studies documenting higher rates of substance abuse disorders among men of lower social status (reviewed in Dohrenwend et al 1992). Consequently, the present analyses controlled for SES.

Assessment Procedure

The procedures and results reported here are components of a 26-hour research protocol implemented at the Center for Education and Drug Abuse Research (CEDAR) to subjects and their family members. The overarching objective is to employ a prospective paradigm to understand the biobehavioral vulnerability and etiologic pathways of substance abuse. Families arrived at the center in late afternoon of the first day. After research assistants obtained written informed consent from the parents and assent from the children, demographic information was recorded. Parents and their sons then were administered psychiatric interviews and self-report questionnaires. The boys slept at the center on the first night to become acclimated to the experimental environment. Beginning at 7:30 AM the next day, after undergoing a fasting venipuncture and eating breakfast, each child was evaluated with a comprehensive battery.

Tests measuring psychological and psychiatric status, peer and family relationships, and neurophysiological and psychophysiological responses to information-processing and arousal-activating tasks were administered according to a fixed schedule. The saliva collection procedures reported herein began at about 9:00 AM. Each member of the family was individually paid for participation; the boy was paid $100, and the parents were paid $200. Effort was made to ensure that the child voluntarily decided to participate in the study and did not do so because of parental coercion. No evidence indicated that coercion was a factor in any of the families studied. This study was approved by the Institu-

tional Review Board of the University of Pittsburgh Medical Center.

Diagnostic Assessments of Index Boys

Both the mother and the index case were administered an expanded version of the Kiddie-SADS-E (Orvaschel et al 1982) to determine the presence of psychiatric disorders in the FHP and FHN boys. A "best-estimate" consensus diagnosis was finalized at a clinical diagnostic conference using the mother's interview about the boy, the boy's self-reports, and any additional relevant clinical information. This diagnostic approach is in accord with the method described by Leckman et al (1982) and recently validated by Kosten and Rounsaville (1992). Rates of the most prevalent diagnoses are displayed in Table 1. The significance of between-group differences in rates of psychiatric diagnoses was determined by Fisher's Exact Test.

Diagnostic Assessment of Parents

The diagnosis of substance abuse in the father was made using an expanded version of the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer and Williams 1983). The interview was administered by a trained research associate. As with the child's psychiatric assessment, a "best-estimate" consensus diagnosis was determined during a clinical conference. Fathers in the FHP group qualified for a lifetime DSM-III-R (APA, 1987) diagnosis of PSUD for any illicit drug. The SCID was given also to the mothers, and the same procedure was used to formulate a diagnosis. The presence of psychiatric illness or substance abuse disorder in the mothers in the FHP group was not an exclusionary criterion; this was necessary for us to obtain a representative sample of the substance abusing population of adult males. Approximately 25% of partners of FHP probands also met SCID lifetime diagnostic criteria for PSUD. The influence of unilineal and bilineal PSUD on the child's behavioral profile is reported elsewhere (Moss, et al. in press). The distribution of lifetime substance abuse diagnoses in the parents is displayed in Table 2.

Saliva Collection Procedures and the Intervening Task

Saliva samples were collected before and after an auditory event-related potential (ERP) task that involved counting high-pitched tones presented at varying probabilities relative to low pitched tones. No subject had prior experience with any form of neurophysiologic testing. Results of the ERP component of this study are reported elsewhere (Brigham et al in press). Furthermore, no attempt was made to induce stress or anxiety. After electrodes were placed on the scalp, subjects were instructed, by the technician, to relax before their "brain wave" test. Subjects were provided

a wax pledged to chew on to stimulate an adequate flow of saliva, and they then expectorated into a polypropylene tube. A minimum of 5 mL of saliva was obtained during this procedure. The auditory ERP procedure lasted approximately 35 minutes. During the procedure, subjects were instructed to listen through headphones to both high- and low-pitched tones, and to count only the high-pitched tones. Upon completion of the ERP task, after electrode removal, a second 5 mL saliva sample was collected using the same sampling procedures. Thus, the initial saliva sample was obtained prior to the ERP task, after electrode placement, when subjects may have experienced anticipatory concerns about this novel procedure. In contrast, the second saliva sample was obtained after they were exposed to the test situation for 35 minutes, and finally completed the ERP study.

Determination of Salivary Cortisol Concentrations

Salivary cortisol concentrations were determined by a radioimmunoassay method (Hiramatsu 1981; Al-Ansari et al 1982). Measurement of salivary concentrations of cortisol is a stress-free approach that avoids potential confounds produced by a stress response to venipuncture. This technique has been shown to correlate highly with serum cortisol concentrations and is thought to reflect the unbound fraction of circulating cortisol (Kahn et al 1988; Galard et al 1991). Specifically, cortisol in blood is predominantly bound to plasma proteins, such as cortisol-binding protein and albumin with the biologically active fraction being the unbound component (Angeli 1978). In that salivary fluid contains no cortisol-binding proteins, salivary cortisol has been shown to directly correlate with plasma-free cortisol, which is the biologically active fraction (Katz and Shannon 1964).

Measures of State Anxiety

Following each of the saliva collection procedures, subjects completed the Spielberger State-Trait Anxiety Scale for Children. This instrument was titled the "How I Feel" scale. It is age-appropriate for prepubertal children and has acceptable psychometric properties (Spielberger 1973). In this investigation, we examined the state anxiety scales (SAnx) associated with each cortisol sample to determine if state anxiety would be reflected in the cortisol responses.

Problematic Behavioral Disposition

The mother and the boy's teacher completed the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock 1983) on the subject's behavior. The CBCL is a well-validated instrument which provides information regarding internalizing and externalizing behavior, social competence, and psychopathology. Since our subjects spanned the age range of 10–12 years, scores were obtained on two versions of the CBCL, which differ slightly in the scales they measure. One

Table 2. Lifetime "Best Estimate" of Frequency (%) of Psychiatric and PSUD Diagnoses Among Fathers and Mothers of Subjects

	SA+ Fathers (n = 81)	SA– Fathers (n = 103)	SA+ Mothers (n = 79)	SA– Mothers (n = 101)
PSUD diagnoses				
Alcohol abuse	36 (19.57)[a]	0 (0)	18 (10)[a]	4 (2.22)
Alcohol dependence	50 (27.17)[a]	0 (0)	18 (10)[a]	3 (1.67)
Opioid abuse	3 (1.63)	0 (0)	3 (1.67)	1 (0.56)
Opioid dependence	22 (11.96)[a]	0 (0)	10 (5.56)[a]	0 (0)
Sedative/hypnotic abuse	4 (2.17)	0 (0)	1 (0.56)	1 (0.56)
Sedative/hypnotic dependence	8 (4.35)[a]	0 (0)	4 (2.22)	0 (0)
Cocaine abuse	7 (3.8)[a]	0 (0)	2 (1.11)	0 (0)
Cocaine dependence	29 (15.76)[a]	0 (0)	5 (2.78)	0 (0)
Cannabis abuse	24 (13.04)[a]	0 (0)	11 (6.11)	2 (1.11)
Cannabis dependence	34 (18.48)[a]	0 (0)	9 (5)	3 (1.67)
Amphetamine abuse	9 (4.89)[a]	0 (0)	2 (1.11)	1 (0.56)
Amphetamine dependence	13 (7.07)[a]	0 (0)	7 (3.89)	2 (1.11)
Hallucinogen/PCP abuse	2 (1.09)	0 (0)	2 (1.11)	0 (0)
Hallucinogen/PCP dependence	3 (1.63)	0 (0)	2 (1.11)	0 (0)
Inhalant dependence	0 (0)	0 (0)	2 (1.11)	0 (0)
Nicotine dependence	9 (4.89)	3 (1.63)	11 (6.11)	4 (2.22)
Other psychiatric diagnoses				
Generalized anxiety	14 (7.61)[a]	2 (1.09)	22 (12.22)	13 (7.22)
Simple phobia	9 (4.89)	1 (0.54)	11 (6.11)	10 (5.56)
Panic disorder	2 (1.09)	1 (0.54)	11 (6.11)	4 (2.22)
Major depression[a]	21 (11.41)	0 (0)	26 (14.44)	21 (11.67)
Dysthymia	1 (0.54)	0 (0)	3 (1.67)	0 (0)
Bipolar disorder	3 (1.63)	0 (0)	2 (1.11)	0 (0)
Obsessive-compulsive disorder	2 (1.09)	0 (0)	2 (1.11)	2 (1.11)
Posttraumatic stress	4 (2.17)	0 (0)	4 (2.22)	0 (0)
Adjustment disorder	6 (3.26)	10 (5.43)	5 (2.78)	8 (4.44)
Antisocial personality	21 (11.41)[a]	0 (0)	1 (0.56)	0 (0)
Borderline personality	3 (1.63)	0 (0)	1 (0.56)	0 (0)

[a] Bonferroni-corrected Fisher's Exact Test $p < .002$; comparison with same-gender parent.

Note: Percentages exceed 100% due to comorbidity and temporal discontinuity. Two FHP mothers and two FHN mothers were not available for the psychiatric assessments. PSUD = psychoactive substance use disorder; SA = substance abuse.

version is appropriate for children aged 6–11 years, while the other version is appropriate for children 12–16 years. Consequently, only those scales that were available for all subjects were used in the analysis. Specifically, mother-rated CBCL scales for aggression, delinquent behavior, hyperactivity, schizoid or anxious behavior, uncommunicativeness, somatic complaints, and obsessive-compulsive behavior were employed. Teacher-rated CBCL scale scores for unpopularity, aggression, inattention, self-destructive behavior, anxiety, and obsessive-compulsive behavior were used.

In order to reduce the number of variables and aggregate the scale scores according to orthogonal underlying problem behavior constructs specific to our sample, the combined mother-teacher CBCL scale scores were subjected to factor analysis with varimax rotation. Factor loadings for the three derived factors account for 65.1% of the variance. The first factor (Factor 1) accounted for 35% of the variance and was comprised of teacher CBCL scale loadings reflecting unpopularity (0.82), obsessive-compulsive behavior (0.80), aggression (0.78), anxiety (0.72), inattention (0.69), and self-destructive behaviors (0.69). The second derived

factor (Factor 2) accounted for 24% of the variance and was comprised of significant mother-rated scales loading for aggression (0.80), delinquency (0.78), and hyperactivity (0.77). The third factor (Factor 3) accounted for 8.5% of the variance and significantly loaded with mother-rated scale scores for anxiety (0.79), uncommunicativeness (0.72), obsessive-compulsive behavior (0.65), and somatic complaints (0.65).

Impulsivity

A computerized task, similar to the well-known continuous performance test, requires that subjects scan changing computer displays of two letters and two dummy characters in a 2 × 2 matrix while searching for the appearance of either of two specific target letters. Subjects were instructed to press a computer key when a target appeared on the screen, and to inhibit a response when a nontarget appeared (Schneider and Detweiler 1987). Commission error "false alarm" scores on this task were utilized as an indicator of impulsive responding.

Statistical Analysis

TESTS OF THE EFFECTS OF RISK GROUP AND TIME ON SALIVARY CORTISOL. After generation of appropriate descriptive statistics to ensure normality, a repeated measures analysis of variance (ANOVA) was performed on the two time-dependent salivary cortisol concentrations according to risk group. Because the groups differed significantly on SES, this measure was used as a covariate. Main effects of time and group were examined, as well as the group × time interaction.

UNIVARIATE TESTS OF GROUP DIFFERENCES ON STATE ANXIETY, PROBLEM BEHAVIOR FACTOR SCORES, AND THE IMPULSIVITY MEASURE. Between-group differences on the state anxiety measure, the problem behavior factors scores, and the impulsivity indicator were evaluated using a one-way ANOVA. Again, SES was used as a covariate.

TESTS OF THE EFFECTS OF PROBLEMATIC BEHAVIORAL DISPOSITION AND IMPULSIVITY ON GROUP DIFFERENCES IN CORTISOL RESPONSES. The repeated measures ANOVA procedures evaluating the effects of group and time on cortisol responses were performed, now using the problematic behavior factor scores and the impulsivity measure as covariates.

Results

Test of the Effects of Risk Group Status and Time on Salivary Cortisol

Pre- and post-ERP salivary cortisol concentrations are displayed in Figure 1 according to risk group status. FHP boys
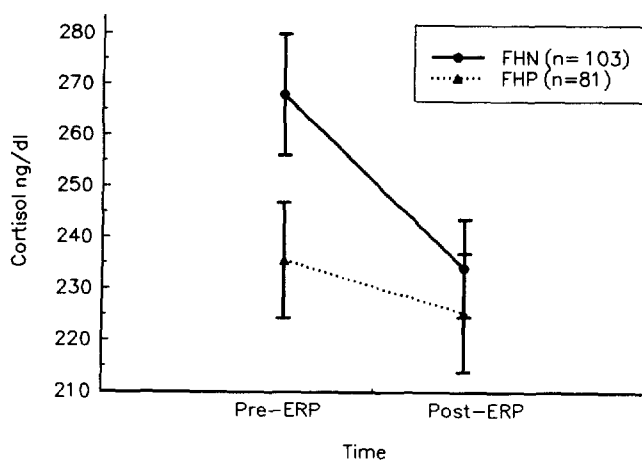

Figure 1. Interaction of psychoactive substance use disorder (PSUD) family history status and time on salivary cortisol concentrations in boys: FHN = family history negative; FHP = family history positive; ERP = event-related potential.

had generally lower pre- and post-ERP salivary cortisol concentrations than did FHN boys. The repeated measures ANOVA procedures revealed a strong main effect of time ($F_{1,187}$ = 15.74, p < .001), and a significant group × time interaction ($F_{1,187}$ = 4.56, p < .05). Graphic display of this interaction suggests that risk-group membership exerted its most robust effects on the initial pre-ERP cortisol concentration (see Figure 1). Univariate t tests revealed a statistically significant difference only for the pre-ERP samples (t = 2.15, p < .05). FHN boys had an elevated pre-ERP cortisol concentration that was diminished by the time of the second salivary sampling procedure. SES was not found to be a significant covariate ($F_{1,187}$ = 0.04, NS).

Univariate Tests of Group Differences on State Anxiety, Problem Behavior Factor Scores, and the Impulsivity Measure

Prior to the ERP procedure, FHP boys had a mean (± SEM) SAnx score of 51.54 ± 0.37, and FHN boys had a mean score of 50.94 ± 0.39. After the ERP procedure, FHP boys had a mean SAnx score 52.01 ± 0.49, while FHN boys were 52.70 ± 0.38. NO significant between-group differences were found for SAnx measures at either time point. Furthermore, SAnx scores did not significantly correlate with salivary cortisol concentrations at their respective time points.

Problem behavior factor scores and impulsive error scores are graphically displayed in Figure 2. The groups differed with respect to the CBCL teacher-rated unpopularity/problem behavior factor score (Factor 1) ($F_{1,189}$ = 5.3, p < .05), such that FHP boys scored significantly higher than FHN boys. For the mother-rated aggressive delinquency problem behavior factor (Factor 2), FHP boys also scored significantly higher than FHN boys ($F_{1,189}$ = 7.17, p < .01); however, for the mother-rated anxious withdrawal factor (Factor 3), no between-group differences were found ($F_{1,189}$ = 2.29, NS).

With respect to the impulsivity/comission errors measure, FHP boys scored significantly higher than FHN boys ($F_{1,189}$ = 6.94, p < .01), suggesting greater response disinhibition.

Test of the Effects of Problematic Behavioral Disposition and Impulsivity on Group Differences in Cortisol Responses

Repeated measures ANOVA analysis using problem behavior factors and the impulsivity measure revealed that the teacher-rated unpopularity factor (Factor 1) did not significantly predict cortisol concentrations; however, when the mother-rated aggressive delinquency factor (Factor 2), and the impulsivity score were used as covariates ($F_{2,188}$ = 4.85, p < .01), the interaction effects of risk-group and time became nonsignificant ($F_{1,189}$ = 2.73, NS). Time, on the
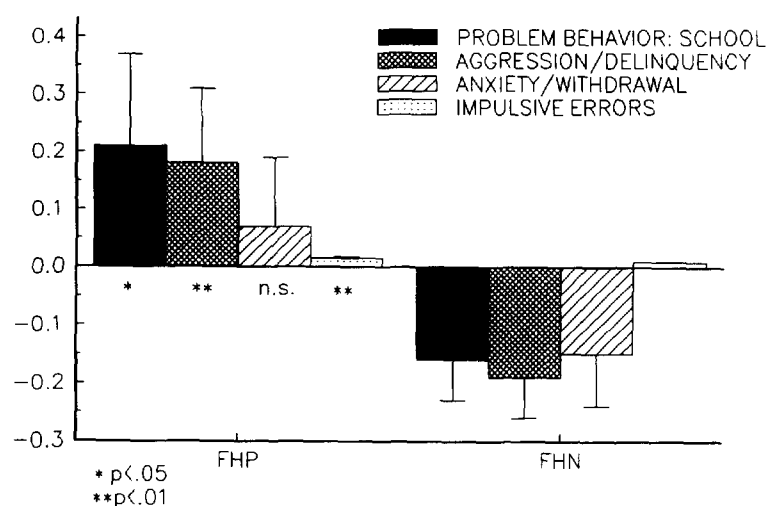
Figure 2. Behavioral disposition measures among boys at high risk (FHP) and low risk (FHN) for psychoactive substance use disorder. FHP = family history positive; FHN = family history negative.

other hand, continued to have a significant effect on cortisol concentrations ($F_{1,189} = 13.66$, $p < .001$). Importantly, the regression coefficients for the significant multivariate effects of impulsivity ($\beta = -0.16$) and the aggressive delinquency factor ($\beta = -0.14$) on cortisol reveal a negative relationship. Thus, the significant association of salivary cortisol concentrations with the interaction of risk-group status and time appear to be wholly accounted for by group differences in aggressive delinquent behavior and impulsivity.

Discussion

This study demonstrates that prepubertal boys at heightened risk for later PSUD show reduced cortisol responsivity to an anticipated stressor in comparison to boys at average PSUD risk. The differences in cortisol responses were apparently not due to variations in perceived state anxiety. This observation is consistent with similar findings among younger children (Tennes and Kreye 1985); rather, this analysis suggests that the cortisol hyporesponsivity observed among FHP boys is associated with the magnitude of their impulsive and aggressive behavior. These results are compatible with observations of reduced cortisol reactivity in adult substance abusers (King et al 1990), and impulsive and antisocial individuals (Virkkunen 1985; Woodman et al 1978). Likewise, these results converge with other investigations of cortisol reactivity in children that have shown an association between diminished cortisol secretion and hostility, aggression, and other dysregulated behaviors (Tennes and Kreye 1985; Tennes et al 1986; Vanyukov et al 1993); however, this report is relatively unique in that cortisol was measured at two defined time points surrounding an anticipated event, while the majority of prior investigations involved single cortisol measurements under varying conditions. The results are also in accordance with numerous early "stress" studies have shown that *anticipation* is a

potent provocative stimulus for cortisol secretion (Rose 1980).

Although the biobehavioral basis of diminished cortisol responsivity is not known, there are several putative explanations for its inverse relationship with behavioral dysregulation and PSUD liability. First, several earlier studies have suggested that chronic exposure to significant stress actually diminishes cortisol reactivity (Mason et al 1968; Caplan et al 1979). In that some sons of substance-abusing fathers (and mothers) may be exposed to chronically stressful home environments (Steinglass 1981), it is not unreasonable to speculate that reduced cortisol secretion may be an adaptation to chronic stress.

An alternative explanation arises from research suggesting that cortisol secretion reflects the arousal state of the organism (Warburton 1979; King et al 1990). Reduced cortisol responsivity would be consistent with the diminished brain arousal state hypothesized by Quay (1965), Hare (1970), and Zuckerman (1972) to be the neural substrate for psychopathy and substance abuse. Such an interpretation is also consistent with our earlier report of a negative association between salivary cortisol concentrations in children, their conduct disorder symptom counts, and with their fathers' antisocial personality disorder symptom. Interestingly, cortisol concentrations were also lower among boys whose fathers had conduct disorder as children and later developed antisocial personality disorder count (Vanyukov et al 1993). Since the current data are cross-sectional, our findings could also be consistent with the idea that variations in cortisol level actually contribute to individual differences in aggressive behavior. Such variation in the cortisol level may therefore underlie individual differences in childhood aggressiveness and delinquency which, in turn, have been demonstrated to be associated with the risk for later substance abuse and associated disorders (Robins and Price 1991; Kellam et al 1983; Kandel et al 1986; Brook et al 1991).

The recent elucidation of the central nervous system effects and functions of adrenal steroids provides another avenue for speculation. Specifically, corticosteroids have been shown to be necessary for normal functioning of the dentate gyrus of the hippocampus Sloviter et al 1989), while sustained high levels also cause degeneration of other specific neural fields in the hippocampus. Furthermore, it appears that the hippocampus has an inhibitory role in the regulation of the hypothalamic-pituitary-adrenal axis (HPA) (Sapolsky et al 1991). Other studies have demonstrated important connections between the hippocampus and the dorsolateral prefrontal cortex. Thus, the cortisol receptors on hippocampus may be involved in cognitive processes such as working memory that permit the guidance of behavior by internal "representations of the outside world" (Goldman-Rakic and Friedman 1991). Neuropsychological investigations of conduct-disordered youth and antisocial adults have revealed a pattern of cognitive impairments on tests that are sensitive to dysfunction of the prefrontal cortex (Gorenstein 1982; Kandel and Freed 1989; Moffitt 1993). This line of reasoning again suggests that the diminished cortisol responses observed could be associated with hippocampal and prefrontal cortical variations whose behavioral ramifications comprise aspects of the liability for antisociality and PSUD.

Clearly, none of the above perspectives are mutually exclusive. In hopes of developing a more focused theoretical model, a prospective developmental study of children where salient environmental variables and salivary cortisol responses are repeatedly measured would be highly informative about the effects of exposure to stressors, biobehavioral mechanisms of adaptation, and their relationship to specific developmental outcomes. Alternatively, future research could be directed toward elucidating the neurocognitive concomitants of specific patterns of cortisol dynamics. Electrophysiological, neuropsychological, and neuroimaging technologies may provide methodologies that are heuristic in exploring the neurobiological concomitants of cortisol responses. The concentration of cortisol in saliva is but one of many possible nonspecific indicators of biological systems involved in the regulation of the behavior phenotype and its development. The complexity of these processes requires concurrent longitudinal studies at different levels of biological organization.

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