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Serotonin Function and Risk for Alcoholism in Boys with Attention-Deficit Hyperactivity Disorder

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Data in animals and adults indicate that central serotonergic (5-HT) function may be involved in the development of alcohol abuse. Despite this, studies exploring this mechanism in individuals at risk for alcoholism are scant. This study used a fenfluramine (FEN) challenge procedure to investigate the relationship between risk for alcoholism and 5-HT function in 7- to 11-year-old boys with attention-deficit hyperactivity disorder (ADHD). The prolactin (PRL) and cortisol (CORT) responses to FEN were examined in 10 sons of alcoholic fathers (FA +) and 30 sons of nonalcoholic fathers (FA −). The FA + group had a significantly greater CORT, but not PRL, response to FEN relative to the FA − group. The discrepancy between the CORT and PRL responses may be due to the different mechanisms that underlie their 5-HT stimulated release. This suggests that, among ADHD boys, those at familial risk for alcohol abuse may differ from those who are not at risk in 5-HT function. ***[Neuropsychopharmacology 18:10–17, 1998]*** *© 1998 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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A substantial animal and human literature exists in support of an association between central serotonergic (5-HT) function and the development and maintenance of alcohol abuse and dependence. Experimental manipulations in animals that deplete central 5-HT increase alcohol consumption (Ho et al. 1974), whereas interventions that increase 5-HT neurotransmission decrease alcohol intake (Lu et al. 1993). Furthermore, several different rat species genetically bred to prefer alcohol, but kept alcohol-naive, have been found to have decreased 5-HT neurotransmission (Murphy et al. 1982; Zhou et al. 1991).

Clinical research in alcohol-dependent individuals has also provided support for the involvement of 5-HT in the development of alcoholism. Alcoholics exhibit abnormalities in a host of parameters of 5-HT function: decreased plasma levels of tryptophan (Branchey et al. 1981); a decreased plasma ratio of tryptophan to other amino acids that compete with it for transport (Branchey et al. 1981); decreased platelet 5-HT content (Bailly et al. 1993); and increased platelet 5-HT uptake (Daoust et al. 1991). Abstinent alcoholics have also been found to exhibit lower cerebrospinal fluid (CSF) levels of the major 5-HT metabolite, 5-hydroxyindole acetic acid (5-HIAA; Ballenger et al. 1979), which normalized after 1 week of drinking (Zarcone et al. 1975). Furthermore, several studies have found blunted prolactin (PRL) and/or cortisol (CORT) responses to challenge with 5-HT agents

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such as fenfluramine (FEN; Balldin et al. 1994), m-clorophenylpiperazine (m-CPP; Krystal et al. 1996), and 6-chloro-2-1-piperazinylpyrazine (MK-212; Lee and Meltzer 1991) in alcoholics, suggesting deficits in central 5-HT function. Finally, clinical trials have found that the 5-HT uptake inhibitors zimeldine and citalprom decreased alcohol intake (Naranjo et al. 1984, 1987).

In aggregate, the evidence indicates that dysfunction in 5-HT neurotransmission may be associated with a propensity toward alcohol abuse and dependence. However, the results from studies using alcoholics as subjects must be interpreted cautiously, because alcohol has been found to affect 5-HT function (for review, see LeMarquand et al. 1994). Given that genetic factors appear to play a role in the development of alcoholism (Bohman et al, 1987), the study of nonalcoholic individuals who are a high genetic risk for alcoholism may prove a fruitful strategy for investigating the neurochemical propensity to alcohol abuse. Interestingly, nonalcoholic relatives of alcoholics have been found to exhibit increased platelet 5-HT uptake (Ernouf et al. 1993, Rausch et al. 1991), which suggests a decreased availability of 5-HT in the synapse.

Longitudinal research indicates that children with attention-deficit hyperactivity disorder (ADHD) are at high risk for developing alcoholism during adolescence (Blouin et al. 1978) and adulthood (Greenfield et al. 1988). Furthermore, family studies show an increased frequency of alcoholism in the parents of ADHD children (Lahey et al. 1988) and higher rate of ADHD among the children of alcoholic parents (Earls et al. 1988).

This study used a neuroendocrine challenge procedure to examine the relationship between risk for alcoholism and central 5-HT function in boys with ADHD. The CORT and PRL responses to a challenge dose of the 5-HT releaser/reuptake inhibitor FEN were compared between boys who have a positive current or past history of alcoholism in their fathers (FA+) and boys with a negative current and past history of alcoholism in their fathers (FA−). The blunted hormonal responses to 5-HT agents in previous neuroendocrine studies of alcoholics (Balldin et al. 1994; Krystal et al, 1996; Lee and Meltzer 1991), along with the findings of abnormalities in platelet 5-HT function in the relatives of alcoholics (Ernouf et al, 1993; Rausch et al. 1991), suggests that the FA+ group should exhibit blunted PRL and CORT responses to FEN relative to the FA− group.

METHOD

Subjects

The subjects were 40 7-to 11-year-old prepubertal boys who met DSM-III-R criteria for ADHD. The children were part of a larger sample in whom the relationship of 5-HT function to aggression was being assessed, and all for whom family history data were ascertained. The sample was ethnically heterogeneous, consisting of 30% (n = 12) Caucasians, 25% (n = 10) African-Americans, and 45% (n = 18) Hispanics. Children with schizophrenia, pervasive developmental disorder, Tourette's disorder, and major affective disorder were excluded from the study. General cognitive ability and academic achievement were assessed using the Wechsler Intelligence Scale for Children–Revised (WISC-R) and the Wide-Range Achievement Test–Revised (WRAT-R), respectively. Children with a full-scale IQ of less than 70 were excluded from the study.

Subjects were divided based on the presence or absence of a lifetime history of alcoholism in their fathers, which was determined before the challenge procedure. Lifetime history of alcoholism in the fathers was defined as a positive diagnosis of alcoholism according to the Family History-Research Diagnostic Criteria (FH-RDC; Endicott et al. 1975). There was no history of abuse of any substance other than alcohol in any of the fathers in the sample. Maternal history of alcoholism was not considered when composing the groups due to the low frequency of a past or current history of drinking in the mothers in our sample (n = 1). The final groups consisted of 10 boys in the FA+ group and 30 boys in the FA− group.

This study was approved by the Queens College and Mount Sinai School of Medicine Institutional Review Boards. After a thorough description of the protocol, signed informed consent and verbal assent were obtained from the parent and child, respectively.

Child Assessment. All but one of the children were initially screened using teacher ratings of behavior on the IOWA Conner's Teacher's Questionnaire (Loney and Milich 1982). Those children with an inattention/overactivity score 1 SD above the mean were scheduled for a comprehensive interview with the parent using the Diagnostic Interview Schedule for Children (DISC-P, version 2.1; Shaffer et al. 1989); the one child missing the teacher ratings was scheduled for the comprehensive interview without them. Diagnoses of ADHD were made based on parent responses to the DISC-P. Psychiatric comorbidity of the ADHD boys in this study was also determined using parent responses to the DISC-P; among the 40 boys, 10 (25%) met DSM-III-R criteria for conduct disorder (CD), 20 (50%) for oppositional defiant disorder (ODD), and 13 (32.5%) for an anxiety disorder. Furthermore, parents rated the frequency and severity of various disruptive behaviors using the Child Behavior Checklist (CBCL; Achenbach and Edelbrock 1983). Finally, a structured demographic interview was used to collect several indirect indicators of family distress, including the number of siblings, parents (biological and step), and other adults in the home, and the professions and educational level of the probands' parents.

Family History Assessment. The family history of each proband was assessed for symptomatology of alcohol abuse using a semi-structured interview of either the child's mother alone ($n = 30$), both parents ($n = 7$), or another relative with whom the child lived ($n = 3$). Initially, each respondent completed a genogram diagraming the child's first- and second-degree relatives. The genogram was then used as a guide while the interviewer systematically asked about the past and present alcohol consumption patterns of each family member. When a positive report of alcohol intake was elicited, additional probes were used to determine whether the drinking was abusive, and if it caused impairment for the individual. Family members were considered to have a lifetime history of alcoholism if they met criteria for a positive diagnosis of alcoholism according to the FH-RDC. Data were obtained for 80 parents, 150 grandparents, and 209 aunts and uncles, for a total of 439 first- and second-degree relatives. Data for siblings were not included in this study because most of them were below the age of risk for alcohol abuse.

Biological Procedure

FEN is a known sympathomimetic agent that releases and blocks the re-uptake of central stores of 5-HT (Rowland and Carlton 1986). The administration of FEN leads to an increase in plasma CORT and PRL (Muhlbauer and Muller-Oerlinghausen 1985; Stoff et al. 1992), and the magnitude of the CORT and PRL responses is considered to reflect overall 5-HT function in the hypothalamic-pituitary axis (Fuller 1992; Coccaro et al. 1989).

Subjects were medication free for a least 4 weeks before the FEN challenge procedure and maintained on a low monoamine (MAO) diet for 3 days before the biological procedure. After an overnight fast, an indwelling intravenous catheter was inserted into a forearm vein at 8:00 A.M. Pre-medication levels of plasma CORT and PRL were determined in two baseline blood samples drawn at 9:45 (-15 min) and 9:55 (-5 min). At 10:00, a 1-mg/kg dose of d,l-FEN was administered orally. Post-FEN plasma CORT, PRL, FEN, and its metabolite, norfenfluramine (NORFEN), were determined via hourly blood samples. Additionally, vital signs were checked every half hour. The children remained awake and fasting during the entire procedure, watching videotaped movies. The protocol ended at 3:00 P.M., at which time the catheter was removed and the child was given a meal.

All blood samples were placed on ice immediately after being drawn. Samples were separated by centrifugation within 2 h after collection. After separation, samples of CORT and PRL remained frozen at −80° C until assayed by radioimmunoassay (Kahn et al. 1994). Post-medication samples of plasma FEN and NORFEN were obtained hourly and were stored at −20°C until assayed by gas chromotography with electrical detection (Krebs et al. 1984).

RESULTS

Subject Characteristics of FA+ and FA− Groups

As shown in Table 1, the FA+ and FA− groups did not differ in age, SES (Hollingshead 1975), IQ, academic achievement, or teacher ratings of behavior. The two groups also did not differ in the number of siblings, biological parents, or other adults living in the household (all p values $> .10$). The FA+ group was rated as being significantly less hyperactive than the FA− group by parental report [t (38) = 2.25, $p = .031$]. Furthermore, the FA+ group was rated by parents as being less aggressive than the FA− group, although this effect did

Table 1. Demographic and Psychometric Characteristics of ADHD Boys with a Positive (FA+) and Negative (FA−) History of Alcoholism in Their Father

	FA+ Group (N = 10)		FA− Group (N = 30)			
Variable	**Mean**	**SD**	**Mean**	**SD**	***t***	***p***
Age (years)	8.9	1.4	9.3	1.3	0.78	NS[a]
S.E.S.[b]	3.8	1.1	3.8	1.0	0.16	NS
WISC-R Full-Scale IQ[c]	99.7	9.9	98.7	13.4	0.22	NS
WRAT-R Reading Score	89.6	11.4	90.6	19.7	0.16	NS
IOWA:[c]						
Inattention/overactivity	11.2	3.2	10.7	2.7	0.45	NS
Aggression	7.2	3.9	7.3	4.5	0.09	NS
CBCL:						
Hyperactivity	68.3	7.2	74.9	8.3	2.25	0.031
Aggression	67.0	12.2	75.7	11.7	2.02	0.051

[a]NS = not significant, $p > .10$.
[b]Incomplete data for six subjects.
[c]No data for one boy in the FA− group.

not quite reach significance [t (38) = 2.02, p = .051]. With regard to psychiatric status, the FA+ and FA− groups did not differ in the frequency of ODD, or CD (all p values > .10), although there was a trend toward a decreased incidence of anxiety disorders in the FA+ group [10% vs. 40%; χ^2 (1) = 3.08, p = .08].

Biological Characteristics of FA+ and FA− Groups

Changes in plasma CORT and PRL were assessed across the two groups over the five post-FEN samples using split plot two-way (group by time) analyses of covariance (ANCOVAs) controlling for baseline hormone level and parental report of hyperactivity, since the latter variable differed across the groups.

As shown in Figure 1, the two-way ANCOVA assessing group differences in the PRL response to FEN across time revealed a significant time effect [F (4, 152) = 39.10, p < .001], but no significant group effect [F (1, 36) = 0.15, p > .10] or group by time interaction [F (4, 152) = 1.05, p > .10]. Furthermore, the FA+ and FA− boys did not differ in peak delta PRL level (peak post-FEN PRL level minus the average of the two baseline samples) [13.6 n/ml vs. 14.5 ng/ml; t (38) = 0.29, p > .10].

As shown in Figure 2, a two-way ANCOVA assessing differences between the FA+ and FA− groups across the five post-FEN CORT samples revealed a significant time effect [F (4, 152) = 7.40, p < .001], a significant group effect [F (1, 36) = 4.71, p = .037], and a significant group by time interaction [F (4, 152) = 6.40, p < .001]. The FA+ and FA− groups did not differ significantly in the CORT response at 60 min or 120 min post-FEN. However, the FA+ group had a significantly higher CORT response than the FA− group at 180 min [t (38) = 2.14, p = .039], 240 min [t (38) = 3.26, p = .002] and 300 min [t (38) = 2.57, p = .014] post-medication. The FA+ group also had a significantly higher peak delta CORT level than the FA− group [17.9 ng/ml vs. 5.4 ng/ml; t (38) = 3.49, p = .001].

The difference in the CORT response between the two groups is not due to differences in drug metabolism as a split plot two-way (group by time) analysis of variance (ANOVA) of total plasma medication level (FEN+NORFEN) revealed a significant main effect for time [F (4, 152) = 27.23, p < .001], but no significant group effect [F (1, 38) = 0.44, p = .512] or group by time interaction [F (4, 152) = 1.03, p = .394].

Family History Characteristics of FA+ and FA− Groups

Independent t-tests revealed that boys in the FA+ group had a significantly greater percentage of alcoholic second-degree relatives than the boys in the FA− group [t (38) = 2.36, p = .024]. As depicted in Figure 3, when the relatives were divided by gender and lineage, the FA+ group had a significantly greater rate of alcoholism in paternal male relatives (i.e., paternal uncles and grandfathers) than the FA− group [t (38) = 2.68, p = .011]. The two groups did not differ in the incidence of alcoholism in their paternal female, maternal male, or maternal female relatives (all p values > .10].

DISCUSSION

The principal finding of this study is that the FA+ group had a significantly larger CORT response to FEN relative to the FA− group, although the PRL response

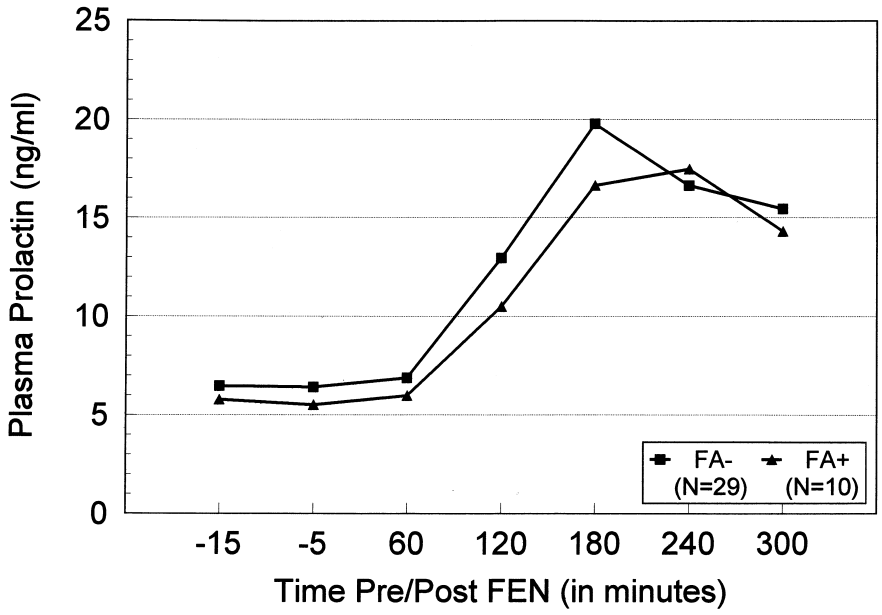

Figure 1. Plasma prolactin (PRL) levels before and after a l-mg/kg challenge dose of fenfluramine (FEN) in sons of alcoholic fathers (FA+) and sons of non-alcoholic fathers (FA−)

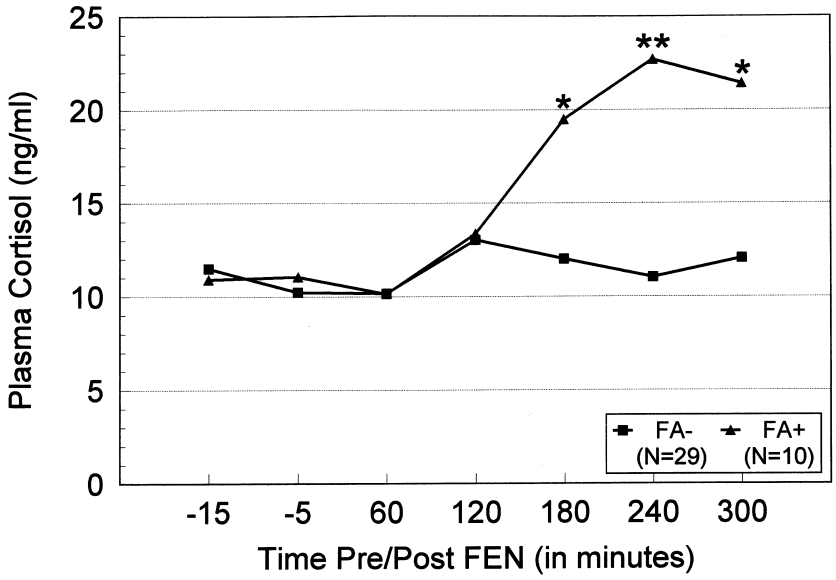

Figure 2. Plasma cortisol (CORT) levels before and after a 1-mg/kg challenge dose of fenfluramine (FEN) in sons of alcoholic fathers (FA+) and sons of non-alcoholic fathers (FA−).

did not differ between groups. This difference in CORT response is not explained by differences in drug metabolism or behavior between the groups. Unfortunately, it is not possible to determine which group had the deviant CORT response as practical considerations precluded the inclusion of normal control subjects in this study. Despite this, our findings suggest differences in 5-HT function between ADHD boys with and without a family history of alcoholism.

Whereas the difference in the CORT response between the FA+ and FA− groups is suggestive of differences in 5-HT function, the lack of a difference in the PRL response between the groups makes such as interpretation tentative. There are two possible explanations for the discrepancy between the two hormonal responses to FEN. First, this discrepancy may reflect the fact that FEN-induced PRL and CORT release are mediated by the stimulation of different postsynaptic 5-HT receptors. The PRL response to FEN requires the selective activation of 5-$HT_{2A/2C}$ receptors, since pretreatment with the 5-HT_2 receptor antagonist ritanserin (Goodall et al. 1993), but not the 5-HT_{1A} receptor antag-

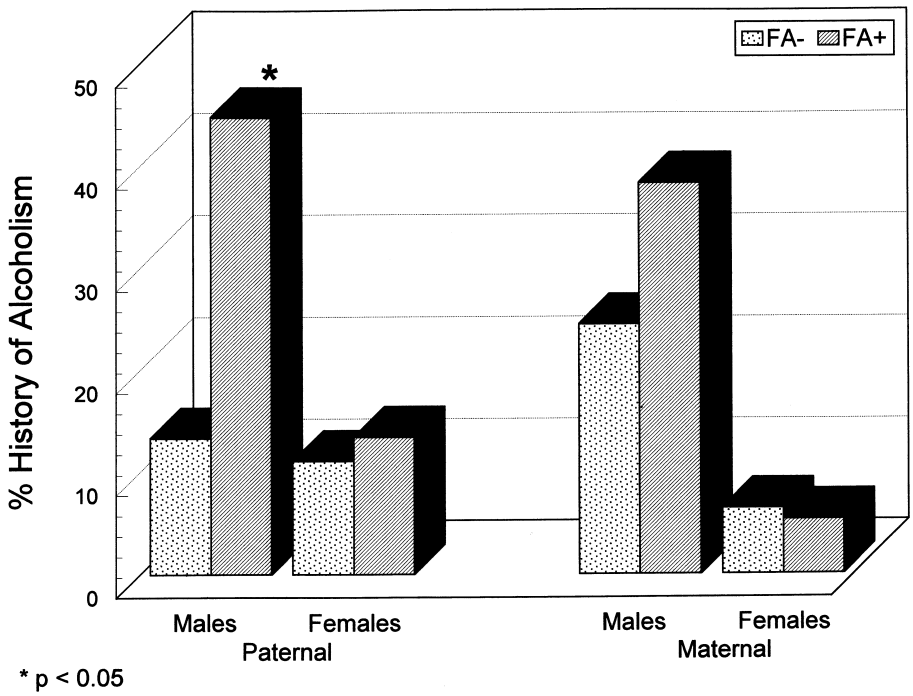

Figure 3. Percentage of paternal and maternal second-degree relatives with a current or past history of alcoholism as a function of a history of alcoholism in the fathers of boys with ADHD.

onist pindolol (Park and Cowen 1995) blocked the response. In contrast, CORT release seems to be induced by stimulation of either the 5-$HT_{2A/2C}$ or 5-HT_{1A} receptors; the CORT response to L-5-HTP was blocked by pretreatment with ritanserin (Lee et al. 1991), but not pindolol (Meltzer and Maes 1994), although the 5-HT_{1A} agonist ipspirone alone stimulated CORT release (Kahn et al. 1994). Thus, an enhanced CORT, but not PRL, response to FEN in the FA+ group may be the result of a postsynaptic phenomenon involving the 5-HT_{1A} receptor.

A second possible explanation for the discrepancy between the hormonal responses to FEN may lie in the fact that the PRL response is considered a measure of central 5-HT function (Coccaro et al. 1989), whereas the CORT response is believed to reflect both central and peripheral 5-HT function (Dinan 1996). Therefore, given that there was no difference in the PRL response, the difference in the CORT response between the FA+ and FA− groups may reflect a peripheral event, possibly at the level of the adrenal cortex (Alper 1990). The determination of the origin of the difference in 5-HT function between ADHD boys with and without a family history of alcoholism awaits future challenge studies using the more clearly central measure of 5-HT function, the adrenocorticotropin hormone (ACTH) response to FEN, in addition to the mixed peripheral/central CORT response.

Our finding of a greater CORT response to FEN in sons of alcoholic fathers is in the opposite direction of the findings of increased platelet 5-HT uptake in the relatives of alcoholics (Ernouf et al. 1993; Rausch et al. 1991). However, Ernouf et al. (1993) interpreted their results to suggest that the 5-HT transporter had been upregulated in some way to compensate for a deficit in 5-HT levels in the relatives of alcoholics. Such a deficit in 5-HT levels would also be expected to result in the upregulation of postsynaptic 5-HT receptors, which could account for our finding of an enhanced CORT response to FEN in ADHD boys with an alcoholic father.

More difficult to interpret is the discrepancy between our finding of an enhanced CORT response to FEN in ADHD boys at risk for alcoholism and the previous findings of blunted hormonal responses to 5-HT challenge in alcoholics (Balldin et al. 1994; Krystal et al. 1996; Lee and Meltzer 1991). Both active and abstinent alcoholics were found to exhibit blunted PRL and CORT responses to challenge with 5-HT agents (i.e., FEN, MK-212, and m-CPP), which the authors suggested were the result of subsensitive postsynaptic 5-HT receptors. The disparity between the current findings and those of the previous challenge studies may be due to either the long-term effects of chronic alcoholism or differences in the samples (adult alcoholics versus prepubertal boys at risk for alcoholism).

Age-related differences in the samples may account for the disparity between the results of our study and those of the previous challenge studies (Balldin et al. 1994; Krystal et al. 1996; Lee and Meltzer 1991). Recent research indicates that central 5-HT function undergoes developmental changes (reviewed in Whitaker-Azmitia et al. 1996), as demonstrated by developmental changes in 5-HT receptor binding in monkeys (Lidow et al. 1991), and children (Biegon and Greuner 1992). Furthermore, Kruesi et al. (1990) found an inverse relationship between age and CSF 5-HIAA in a sample of 6- to 19-year-old patients with disruptive behavior disorders. We previously reported age-related differences in the association between 5-HT function and aggressive behavior in a larger sample of ADHD boys, which included all of the subjects in the present study (Halperin et al. 1996). Thus, developmental changes in 5-HT function may account for the discrepancy between our findings and those reported in alcoholic adults. Importantly, several studies have reported central 5-HT findings in children to be in the opposite direction of that typically seen in adults (Castellanos et al. 1995; Halperin et al. 1994; Pine et al., 1996).

The greater rate of alcoholism in the paternal male relatives of the boys in the FA+ group is suggestive of the familial pattern of alcoholism that characterizes Cloninger's Type II subgroup of alcoholics (Cloninger et al. 1981). Interestingly, studies have found that Type II alcoholism is often preceded by a childhood history of hyperactivity (Tarter et al. 1977) and that 30% to 40% of adult alcoholics exhibit residual symptoms of ADHD (Wood et al. 1983). Unfortunately, data on several parameters used to define type II alcoholics (e.g., age of onset of drinking, frequency of anti-social behavior) were not collected in this study and, therefore, no firm conclusions can be drawn whether the FA+ group comprises a sample of sons of Type II alcoholic fathers.

Two important limitations to the current study are that the FA+ group was composed of only 10 subjects, requiring replication in a larger sample, and that the family history method relied primarily on the report of a single informant. Whereas this method has been found to result in underreporting (Andreasen et al. 1977), reliance on data from a single informant has been found to be more sensitive (i.e., less underreporting) when diagnosing alcoholism relative to other psychiatric disorders (Thompson et al. 1982). This sensitivity is increased only slightly by using multiple informants, as the errors made by the informants tend to be correlated.

Despite these methodological limitations, this study adds to our knowledge regarding the biological factors that may be involved in the development of alcohol abuse and dependence in boys with ADHD. Seven to 11-year-old sons of alcoholics and non-alcoholics were found to differ in their CORT responses to FEN, suggesting that differences in 5-HT function may be associated with the development of alcohol abuse. However, since the CORT response to FEN is a mixed peripheral/central 5-HT signal, the determination of the exact ori-

gin of the difference in 5-HT function between sons of alcoholics and non-alcoholics will require a future study using the more clearly central measure of 5-HT function, the ACTH response to FEN, in addition to the CORT response.

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