CSF Biochemistries, Glucose Metabolism, and Diurnal Activity Rhythms in Alcoholic, Violent Offenders, Fire Setters, and Healthy Volunteers

Matti Virkkunen, MD; Robert Rawlings, MS; Riitta Tokola, MD; Russell E. Poland, PhD; Alessandro Guidotti, MD; Charles Nemeroff, MD, PhD; Garth Bissette, PhD; Konstantine Kalogeras, MD; Sirkka-Liisa Karonen, PhD; Markku Linnoila, MD, PhD

Background: There is an extensive literature describing a central serotonin deficit in alcoholic, impulsive, violent offenders and fire setters. In the present study, we investigated biochemical concomitants of impulsivity and aggressiveness, and the physiological consequences of reduced central serotonin turnover.

Methods: Forty-three impulsive and 15 nonimpulsive alcoholic offenders and 21 healthy volunteers were studied in the forensic psychiatry ward of a university psychiatric department. The subjects underwent lumbar punctures and oral glucose and aspartame challenges, and their diurnal activity rhythm was measured with physical activity monitors. Discriminant function analyses were used to investigate psychophysiological and biochemical concomitants of aggressive and impulsive behaviors.

Results: Alcoholic, impulsive offenders with antisocial personality disorder had low mean cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) and corticotropin levels and high mean CSF testosterone concentrations. Compared with healthy volunteers, they showed increased physical activity during the daytime. Alcoholic, impulsive offenders with intermittent explosive disorder had a low mean CSF 5-HIAA concentration and blood glucose nadir after an oral glucose challenge, and desynchronized diurnal activity rhythm. Healthy volunteers had mean CSF 5-HIAA concentrations that were intermediate between those of alcoholic, impulsive and nonimpulsive offenders. Alcoholic, nonimpulsive offenders had a significantly higher mean CSF 5-HIAA concentration than all the other groups, including healthy volunteers.

Conclusions: In the present sample, a low CSF 5-HIAA concentration was primarily associated with impulsivity and high CSF testosterone concentration, with aggressiveness or interpersonal violence.

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From the Departments of Psychiatry (Drs Virkkunen and Tokola) and Clinical Chemistry (Dr Karonen), University of Helsinki (Finland); Laboratory of Clinical Studies, Division of Intramural Clinical and Biological Research, NIAAA, Bethesda, Md (Mr Rawlings and Dr Linnoila); Division of Biological Psychiatry, Harbor–UCLA Medical Center, Torrance (Dr Poland); Fidia-Georgetown Neuroscience Institute, Washington, DC (Dr Guidotti); Department of Psychiatry, Emory University, Atlanta, Ga (Dr Nemeroff); Department of Psychiatry, Duke University Medical Center, Durham, NC (Dr Bissette); and Clinical Neuroendocrinology Branch, Intramural Research Program, NIMH, Bethesda (Dr Kalogeras).

A LOW concentration of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) has been associated with an increased risk of suicide attempts, unprovoked interpersonal violence, and early-onset alcoholism in men. These findings have been among the most replicated in modern biological psychiatry.[1]

In a series of studies, we observed that compared with Finnish alcoholic, nonimpulsive violent offenders and American healthy volunteers, Finnish alcoholic, impulsive violent offenders and fire setters have relatively low CSF 5-HIAA concentrations.[2,3] They also have low blood glucose nadirs during oral glucose tolerance tests and sleep irregularly in the forensic psychiatry ward.[4] Based on these observations, we have postulated that in alcoholic, impulsive violent offenders, deficient central serotonin turnover is conducive to disturbances of diurnal activity rhythm and glucose metabolism.[5] The neuroanatomical substrate whose dysfunction, secondary to reduced central serotonin turnover, could explain the constellation of our psychobiological findings is the suprachiasmatic nucleus. It receives a serotonergic input from the dorsal and median raphe nuclei[6] and functions as an endogenous circadian pacemaker[7] and also as a regulator of glucose metabolism.[8]

In follow-up and family history studies on offenders, we found a low CSF 5-HIAA concentration and propensity to low blood glucose concentrations to be predictive of recidi-

See Materials and Methods on next page

MATERIALS AND METHODS

SUBJECTS AND PROCEDURES

All subjects gave written informed consent and the study protocol was approved by the Department of Psychiatry and Helsinki University Central Hospital Institutional Review Boards in Finland. An ad hoc prisoner representative of the Helsinki University Central Hospital Review Board evaluated the protocol. In the United States, the protocol was approved by the National Institute of Mental Health Institutional Review Board and the Office for Protection from Research Risks.

Healthy volunteers were recruited through advertisements in the press. They were paid for their participation. Prospective subjects were asked to participate in a psychobiological study elucidating biochemical, behavioral, and genetic correlates of violent behavior under the influence of alcohol. The advertisement further defined that the volunteers had to be free of current or past drinking problems and mental disorders. After recruitment, the volunteers underwent a psychiatric interview and a physical examination and gave a venous blood sample to establish normal blood count, liver enzymes, and serum creatinine concentration. They were asked to follow a low monoamine and caffeine-free diet, not to use any alcohol or medicines for a week prior to admission, and to stay as inpatients in the research ward for 3 days and 3 nights. Only volunteers free of a lifetime and family history of major mental disorders, alcohol dependence, and substance abuse in their first-degree relatives were included in the sample.

On the first full day after a night on the ward, patients underwent a lumbar puncture between 8 and 9 AM. On the next 2 days they underwent double-blinded, random order, oral glucose or aspartame tests starting at 8 AM. Throughout their stay, the volunteers wore physical activity monitors on their left wrist.

Alcoholic, violent offenders and impulsive fire setters were ordered to undergo forensic psychiatric examinations by their trial judges. They spent an average of 1 month being drug-free and on the low monoamine diet in the research ward. The offenders were asked to volunteer and were explained the procedures by a physician not involved in the study. In addition to routine blood tests similar to those administered to the healthy volunteers, γ-glutamyltransferase levels in the 48 hours prior to the start of the study were measured to ascertain alcohol abstinence. The offenders wore the physical activity monitors on their left wrist continuously for 10 days and nights. Following lumbar punctures, they underwent double-blinded, random order, oral glucose and aspartame tests on two consecutive days.

PSYCHIATRIC DIAGNOSES, FAMILY HISTORY, AND CHARACTERISTICS OF THE CRIME

All subjects, including the volunteers, were administered the Schedule of Affective Disorders and Schizophrenia–Lifetime Version test,[14] a structured family history questionnaire,[11] and underwent a clinical interview by one of us (M.V.) to derive lifetime *DSM-III-R*[15] diagnoses and to elicit a family history of psychiatric and substance abuse disorders, alcoholism, and attempted or completed suicide. To maintain reasonable continuity with diagnostic practices in our previous studies, intermittent explosive disorder was diagnosed according to *DSM-III*[16] criteria, which, unlike *DSM-III-R*, permits diagnosis when the behavior is exhibited under the influence of alcohol. The psychiatrist knew the criminal history of the offenders by the time of the interview but was blind to the results of the biochemical and diurnal activity rhythm analyses.

As in our previous studies, the alcoholic offenders were divided in impulsive and nonimpulsive groups by the forensic research psychiatrist (M.V.) based on the characteristics of the index crime described in the police report. (A crime was termed *impulsive* when the victim was previously unknown to the offender, when no provocation or only verbal altercation preceded the attack, no premeditation could be documented, and no economic motivation such as robbery or burglary was evident. Impulsive fire setting excluded setting fires for insurance fraud. Nonimpulsive crimes were all clearly premeditated.)[2,3] The alcoholic, impulsive offender group was further subdivided into groups with antisocial personality or intermittent explosive disorder. This was done to examine whether these two clinically distinct disorders are psychobiologically different as well. Ten subjects in the alcoholic, impulsive offender group were fire setters.

BIOCHEMICAL VARIABLES

All biochemical variables were quantified by investigators who were blind to the clinical characteristics of the subjects.

Monoamine Metabolites

The CSF samples were obtained by a neurologist (R.T.) at 8 AM after bed rest for 1 night with only water permitted after 8 PM. The samples were collected into a large polypropylene tube on wet ice. After the first 12 mL had been drawn, the tube was capped, inverted, and the CSF sample was aliquoted into 1-mL tubes on dry ice. The samples were stored in a freezer at −80°C and shipped via air freight on dry ice from Helsinki to Bethesda, Md, where homovanillic acid (HVA), 5-HIAA, and MHPG concentrations were measured with a liquid chromatographic procedure using electrochemical detection.[17]

Neuropeptides and Hormones

Cerebrospinal fluid concentrations of DBI,[18] CRH,[19] AVP,[20] corticotropin,[21] and free testosterone[22] were measured with separate radioimmunoassays.

Oral Glucose and Aspartame Tolerance Test

At 8 AM, after a 12-hour overnight fast, the subjects consumed 1 g/kg of body weight (4 mL/kg) of glucose solution or an identical volume of an aspartame solution of indistinguishable sweetness (Leiras, Turku, Finland). Fifteen-milliliter blood samples were drawn from an antecubital vein into an

Continued on next page

aprotinin-containing test tube (12.5 mIU/mL, Antagosan Behringwerke, Marburg, Germany) before and 15, 30, 60, 90, 120, 180, 240 and 300 minutes after the administration of the liquid. For the first 2 hours of the test, the subjects rested in bed. Thereafter, they were allowed to move in the ward, but resting was encouraged. Blood glucose concentration was measured with an enzymatic assay.[3] Glucagon was quantified immediately after the samples were thawed with a double antibody separation radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif). Insulin was quantified in antibody-coated test tubes (Coat-A-Count, Diagnostic Products Corporation). Between-assay variation for insulin was 4.6% at 215 pmol/L and for glucagon, 5.1% at 44.8 ng/L. All samples were assayed in duplicate. When results of duplicate determinations showed discrepancies of more than 5%, the samples were reanalyzed.

PHYSICAL ACTIVITY MONITORING

The activity monitors are small watch-size devices with a movement sensor, as well as clock and memory functions that permit continuous recording of activity for a period of 10 days.[23] The data were decoded and stored on an Apple Macintosh computer (Apple Computers, Cupertino, Calif).

DATA ANALYSES

All analyses were computed using the BMDP statistical package.[24] Parametric and nonparametric analyses of variance, correlation coefficients, and post hoc *t* tests were used for comparisons of individual means when appropriate. Bonferroni-correction was used for multiple comparisons within each analysis of variance. Two-tailed probabilities were applied except when clearly dimensional a priori hypotheses were tested as stated in the introduction. Because of the large number of correlational analyses, only results with a probability value of less than .01 were included. Preliminary analyses revealed no differences between the various groups in mean weight, height, or baseline glucose, insulin, and glucagon concentrations. Also age, weight, height, or season of collection did not contribute significantly to the variation of any of the psychobiological variables in the present sample. Therefore, these variables were not statistically adjusted in any of the analyses reported below. All results are expressed as means and SDs.

To directly examine biochemical concomitants of impulsiveness, a stepwise linear discriminant analysis was computed on the CSF biochemical variables for the alcoholic, impulsive-nonimpulsive offender grouping including the fire setters. A similar analysis was conducted on the alcoholic offender–healthy volunteer grouping after excluding the fire setters to investigate biochemical concomitants of aggressiveness or violent behavior. The prior probabilities used were .5 and .5, respectively, and the jackknife was used for estimation of error rates.

Oversampling of alcoholic offenders for the glucose and aspartame tolerance tests and the diurnal activity rhythm monitoring and technical difficulties with lumbar punctures and certain assays led to unequal sample sizes in various comparisons. The sample sizes are, therefore, included in all Figures and Tables.

vist violent criminality after release from prison.[9] Suicide attempts and completed suicides are primarily associated with low 5-HIAA and 3-methoxy-4-hydroxyphenylglycol (MHPG) concentrations in the CSF.[10] Moreover, alcoholic sons of alcoholic fathers, who have been convicted of violent crimes, have the lowest CSF 5-HIAA concentrations.[11] This latter finding suggests that there may exist a familial trait associated with early-onset alcohol abuse, impulsive and violent criminality, and low CSF 5-HIAA concentration. We have also observed that alcoholic, impulsive and nonimpulsive offenders have mean free testosterone concentrations in CSF that are similar,[12] but alcoholic, impulsive offenders have low urinary free cortisol outputs.[13]

In the present study, we attempt to differentiate biochemical concomitants of impulsivity vs aggressiveness or violent behavior. Thus, we investigated age- and sex-matched Finnish healthy volunteers as inpatients in the same psychiatry department as the alcoholic, violent offenders. Furthermore, we examined relationships between symptoms of the putative functional deficits of the suprachiasmatic nucleus and CSF 5-HIAA concentrations. The a priori hypotheses explored are as follows: (1) low CSF 5-HIAA concentration is associated with impulsivity of the index crime, a history of suicide attempts, a disturbance of diurnal activity rhythms, and abnormalities of glucose metabolism; (2) free testosterone concentration in CSF is correlated with aggressiveness or violent behavior rather than impulsiveness; (3) concentrations of the anxiety and adrenocortical stress response-associated neuropeptides, diazepam-binding inhibitor (DBI), corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), and corticotropin in CSF are low in impulsive violent offenders.

RESULTS

DEMOGRAPHIC CHARACTERISTICS AND PSYCHIATRIC DIAGNOSES

Heights, weights, ages, and lifetime *DSM-III-R* diagnoses are indicated in **Table 1**.

BIOCHEMICAL VARIABLES

All γ-glutamyltransferase analyses yielded results that were within the normal range.

CSF Monoamine Metabolite Concentrations

Mean CSF 5-HIAA concentration was significantly lower among the alcoholic, impulsive than among the alcoholic, nonimpulsive offenders. The alcoholic, nonimpul-

Table 1. Demographic Characteristics and Lifetime Psychiatric Diagnoses Among Alcoholic Offenders and Healthy Volunteers

Characteristics	Impulsive Offenders		Nonimpulsive Offenders (n=15)	Control Subjects (n=21)
	Antisocial Personality Disorder (n=23)	Intermittent Explosive Disorder (n=20)		
Mean (±SD) height, cm	179.2±4.5	179.6±5.2	179.3±6.0	179.9±6.5
Mean (±SD) weight, kg	73.5±8.4	79.6±11.4	78.1±12.3	81.8±13.8
Mean (±SD) age, y	26.1±6.2	35.4±10.5	30.2±7.7	27.9±9.1
Conduct disorder	0	0	1	0
Borderline personality disorder	23	17	4	0
Dysthymia	7	8	6	0
Major depressive disorder	0	4	4	0
Passive-aggressive personality disorder	0	1	6	0
Schizoid personality disorder	0	1	1	0
Narcissistic personality disorder	1	1	0	0
Dependent personality disorder	0	1	4	0

Table 2. Mean 24-Hour Physical Activity Monitor Counts*

Area Under the Curve										
ASP	IED	NI	HV	ANOVA	ASP-IED	ASP-NI	ASP-HV	IED-NI	IED-HV	NI-HV
129.6	120.4	103.8	75.3	...	...	...	...	...	...	...
45.6	66.3	54.9	41.7	.0181	...	...	...†	...	...	...
21	16	15	16	...	...	...	...	...	...	...

**ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; HV, healthy volunteers; and ANOVA, analysis of variance.*

†P<.005 with the Bonferroni corrected two-tailed test.

sive offenders had significantly higher mean CSF 5-HIAA concentrations than did the healthy volunteers. Among the alcoholic, impulsive offenders, subjects with antisocial personality and intermittent explosive disorder had similar mean CSF 5-HIAA concentrations (**Figure 1**). Of the alcoholic, violent offenders, 25 had made a suicide attempt. Their mean CSF 5-HIAA concentration was lower than that of the nonattempting offenders (58.8±25.2 vs 68.5±24.7 nmol/L; $P<.05$, one-tailed probability).

In the discriminant analysis on the impulsive-nonimpulsive grouping of the alcoholic offenders, the only variable selected with an overall correct jackknife classification rate of 78% was CSF 5-HIAA concentration. Mean CSF HVA and MHPG concentrations did not differ between any of the groups in the post hoc comparisons, even though analysis of variance showed a significant overall difference at the $P<.05$ level for HVA (**Figure 2**).

CSF Free Testosterone Concentration

Alcoholic, impulsive offenders with antisocial personality disorder had higher mean CSF testosterone concentrations than did healthy volunteers (**Figure 3**). In the discriminant analysis on the alcoholic, violent offenders–healthy volunteers grouping, the first variable entered was free testosterone concentration in CSF followed by 5-HIAA and MHPG concentrations in CSF. The overall correct jackknife classification based on CSF free testosterone concentration was 60%. This was improved to 64% by adding the effects of the CSF 5-HIAA and MHPG concentrations.

CSF Peptide Concentrations

Mean CSF corticotropin concentration was significantly lower among alcoholic, impulsive offenders with antisocial personality disorder than among healthy volunteers (**Figure 4**). Among the alcoholic offenders, suicide attempters had significantly lower mean CSF corticotropin concentrations than did nonattempters (5±1 pmol/L [n=22] vs 6±2 pmol/L [n=38]; $P<.008$). There were no significant differences among any of the groups in mean DBI, CRH, and AVP concentrations in CSF (data on file).

Correlational Analyses

Cerebrospinal fluid concentration of 5-HIAA correlated positively with CSF HVA concentration ($r=.68$; n=67; $P<.01$). Testosterone levels in CSF correlated negatively with AVP concentration in CSF ($r=-.45$; n=37; $P<.01$), and CSF corticotropin concentration correlated positively with that of AVP ($r=.46$; n=38; $P<.01$).

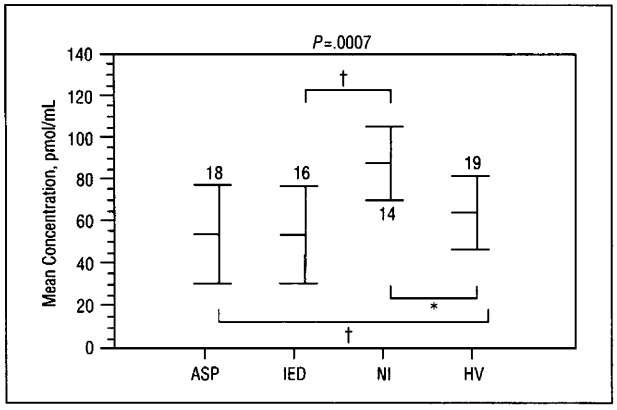

Figure 1. *Mean cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations. ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; HV, healthy volunteers; asterisk, P<.05; and dagger, P<.01.*

Oral Glucose and Aspartame Tolerance Tests

Alcoholic, impulsive offenders with intermittent explosive disorder had significantly lower mean blood glucose nadir during the glucose tolerance test than did healthy volunteers (**Figure 5**). Plasma insulin and glucagon concentrations did not differ significantly between the groups at any point during the oral glucose tolerance test (data on file). There were no significant differences between groups in any of the biochemical variables at any point during the aspartame tolerance test.

PHYSICAL ACTIVITY MONITORING

Alcoholic, impulsive offenders with antisocial personality disorder had significantly higher mean total 10 day-night activity counts than did healthy volunteers. Alcoholic, impulsive offenders with intermittent explosive disorder had indistinguishable day and night activity counts in a striking difference from the other groups (**Figure 6**).

COMMENT

PSYCHIATRIC DIAGNOSES AND CLASSIFICATION OF THE CRIMES

The main apparent difference between our earlier studies and the current one is that all except two of the alcoholic offenders met the criteria for *DSM-III-R* diagnosis of alcohol dependence rather than alcohol abuse. This is because the *DSM-III-R* criteria for alcohol dependence include a number of subjects who were previously defined as abusers according to *DSM-III* classification.[25] To avoid bias, the psychiatrist was blind to the results of all biochemical, physiological, and psychological tests at the time of making the diagnoses. The main weakness of the present design was that the diagnoses were made by the forensic research psychiatrist (M.V.) who was familiar with the crimes and the backgrounds of the alcoholic offenders and aware of who

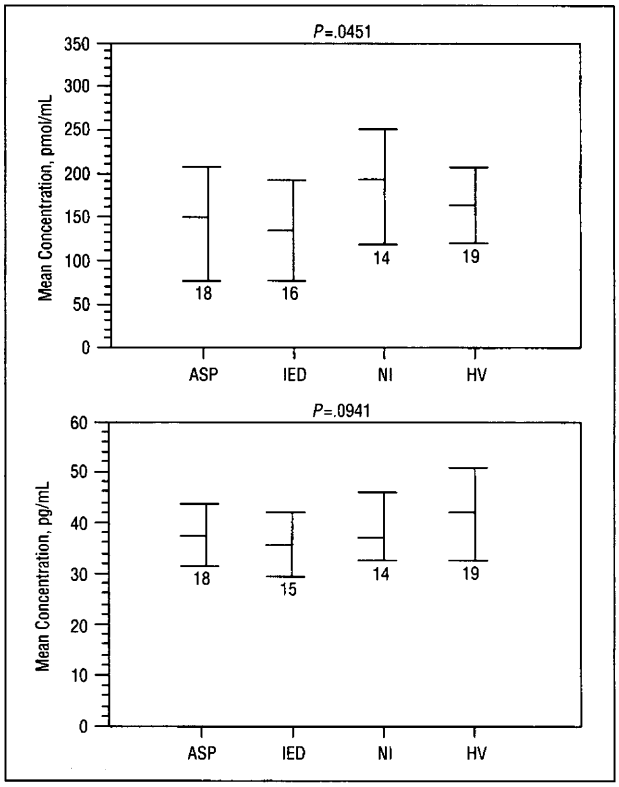

Figure 2. *Mean cerebrospinal fluid homovanillic acid (top) and 3-methoxy-4-hydroxyphenylglycol (bottom) concentrations. ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; and HV, healthy volunteers.*

was an offender and who a healthy volunteer. To partially remedy the situation, the Schedule of Affective Disorder and Schizophrenia interview[14] was used as a source of structured information to bolster the reliability of the diagnostic data.

DIURNAL ACTIVITY RHYTHMS

The present results demonstrate that alcoholic, impulsive violent offenders with intermittent explosive disorder exhibit a profound diurnal activity rhythm disturbance. In rodents, intact serotonergic input to the suprachiasmatic nucleus facilitates entrainment of the circadian activity rhythm by light.[26] If the same principle holds for humans, the disturbed diurnal activity rhythm observed in these offenders may also be secondary to deficient central serotonergic neurotransmission. On the other hand, roughly one half of alcoholic, impulsive offenders with antisocial personality disorder exhibited a clear activity difference between the day and night times despite an equally low mean CSF 5-HIAA concentration. Compared with healthy volunteers, however, they showed increased mean total 24-hour activity counts throughout the monitoring period. This finding is commensurate with the history of attention deficit disorder and hyperactivity in many of the alcoholic offenders with antisocial personality disorder,[4] since this disorder has been reported to be associated with increased diurnal physical activity.[27]

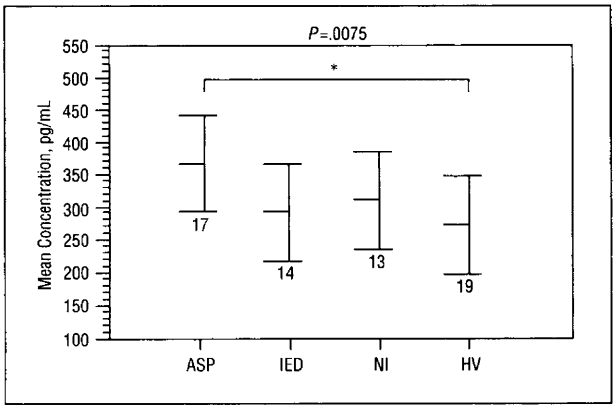

Figure 3. *Mean cerebrospinal fluid testosterone concentrations. ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; HV, healthy volunteers; and asterisk, P<.01.*

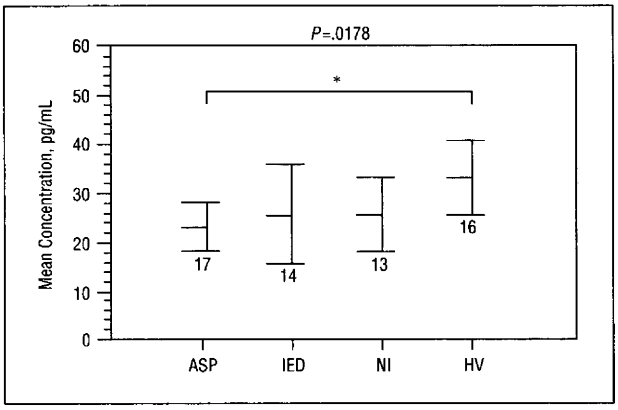

Figure 4. *Mean cerebrospinal fluid corticotropin concentrations. ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; HV, healthy volunteers; and asterisk, P<.05.*

GLUCOSE METABOLISM

In accordance with the previous findings of Virkkunen,[28] mean blood glucose nadir was significantly lower in the alcoholic, impulsive violent offenders with intermittent explosive disorder than in the healthy volunteers. There was, however, no difference between the alcoholic impulsive and nonimpulsive offenders on this variable. Thus, the low blood glucose nadir was not correlated to CSF 5-HIAA concentration across the different groups of offenders. The difference between the intermittent explosive offenders and healthy volunteers could be either secondary to alcohol dependence or due to differences in time during which the two groups were on the low monoamine diet prior to the glucose challenge. No differences between the groups were found in glucagon and insulin concentrations at any point during the oral glucose tolerance test. The appropriate investigation of glucose metabolism in these subjects requires further study using the technique of euglycemic insulin clamp.

CSF 5-HIAA CONCENTRATION

Compared with previous results using American healthy volunteers,[3] the Finnish healthy volunteers with no family history of alcoholism or major depression in their first-degree relatives had relatively low CSF 5-HIAA concentrations. This may be partially owing to the inability to admit Finnish volunteers between early May and early September and the fact that the American healthy volunteers, who were primarily college students, were studied during their summer vacations between June and September when the CSF 5-HIAA concentration reaches its seasonal peak.[29] Thus, the CSF 5-HIAA concentrations among the American healthy volunteers probably represent an overestimate and those among the Finnish healthy volunteers an underestimate of the real mean value. Sampling of additional volunteers during all four seasons is needed to permit a truly adequate comparison between volunteers and violent offenders. In our previous studies, alcoholics, different from healthy volunteers, showed a lack of seasonal variation in CSF 5-HIAA and HVA concentrations.[30] In accordance with this observation, we again did not find any seasonal variation in CSF monoamine metabolite concentrations in the alcoholic offenders despite adequate sampling during all four seasons. The present results replicate our earlier observation[2] of a low mean CSF 5-HIAA concentration in alcoholic offenders with a history of a suicide attempt compared with alcoholic offenders without such a history.

In animal and human studies, indexes of reduced central serotonin turnover have been associated with the inability to tolerate delay and impaired impulse control.[31] A postmortem human study found that 5-HIAA concentration in the prefrontal cortex, but not in other brain regions, correlated positively with 5-HIAA concentration in CSF.[32] This apparent anatomic-neurochemical relationship is intriguing, because of the postulated role of the prefrontal cortex in impulse control.[33] Direct behavioral observation in concert with functional brain imaging and CSF studies will be necessary to support or refute the hypothesized relationships between reduced frontal serotonin turnover, low CSF 5-HIAA concentration, and impaired impulse control in humans.

CSF HVA AND MHPG CONCENTRATIONS

Differences in the mean CSF HVA concentrations between the groups had a similar profile but were relatively smaller than differences in mean CSF 5-HIAA concentrations. As expected, CSF 5-HIAA and HVA concentrations were highly correlated with each other. As we proposed previously,[34] and as supported by the results of the discriminant analysis, the small differences between the groups in mean CSF HVA concentrations are probably secondary to the differences in mean CSF 5-HIAA concentrations. Consequently, frontal dopamine turnover as partially reflected by CSF HVA concentration[34-36] may be less important for impulse control than frontal serotonin turnover.

Of the CSF monoamine metabolites, MHPG showed the lowest correlations with behavioral measures used in the present study. In general, we have been unable to consistently relate static measures of noradrenergic functions to

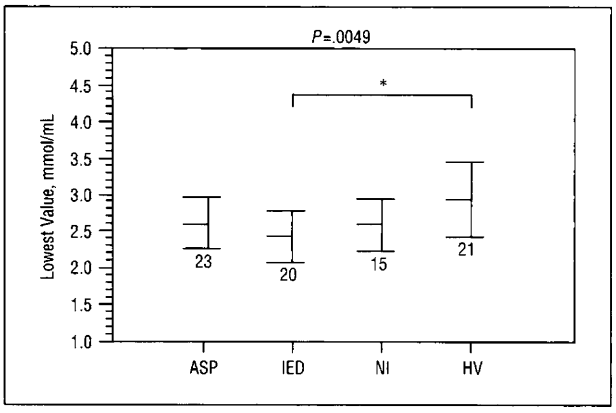

Figure 5. *Blood glucose nadir using the glucose tolerance test during the first 5 hours following an oral (1 g/kg of body weight) glucose challenge. ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; HV, healthy volunteers; and asterisk, P<.01.*

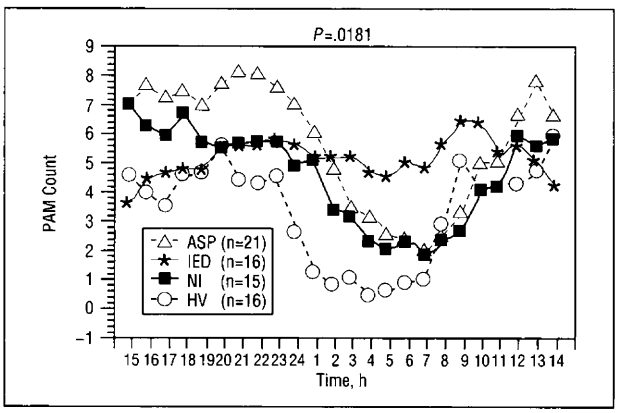

Figure 6. *Mean hourly physical activity monitoring (PAM) counts. ASP indicates antisocial personality disorder; IED, intermittent explosive disorder; NI, nonimpulsive offenders; and HV, healthy volunteers.*

trait measures of impulsivity and aggressiveness,[37] even though we earlier found an association between a history of attempted suicide and low CSF MHPG concentration in Finnish offenders.[10] Recent studies on rhesus monkeys in the wild and neuroendocrine studies in humans have found, however, that increased noradrenergic reactivity may be associated with state measures of aggressiveness and irritability.[38,39]

CSF FREE TESTOSTERONE CONCENTRATION

Mean CSF free testosterone concentration was higher in alcoholic, impulsive offenders with antisocial personality disorder than in healthy volunteers. The high CSF testosterone concentrations could be the result of a lack of inhibition of luteinizing hormone–releasing hormone and luteinizing hormone outputs by circulating cortisol.[40] Thus, the earlier report of low urinary free cortisol outputs in alcoholic, impulsive violent offenders[14] could explain the high CSF testosterone concentrations observed in the current similar group of subjects. In support of this reasoning, Mason et al[41] reported a negative correlation between repeatedly measured plasma testosterone concentrations and urinary free cortisol output in depressed and schizophrenic men.

The literature concerning testosterone levels and human aggressiveness was comprehensively reviewed.[42] According to this review, despite a host of apparently conflicting reports, the following findings are relatively strong: (1) plasma free or saliva testosterone correlates better with aggressiveness than plasma total testosterone concentration; (2) a repetitive pattern of aggressive behaviors that starts early in life is often associated with elevated testosterone concentrations; (3) a pattern of repetitive aggressiveness under the influence of alcohol is associated with elevated testosterone concentrations.

We elected to quantify CSF free testosterone concentrations because this pool of the hormone is directly available to the central nervous system neurons and relatively free of the fluctuations characteristic of plasma testosterone concentration that are due to the pulsatile pattern of excretion of the hormone. Our findings are in general agreement with conclusions based on the above-mentioned review on testosterone and human aggression. Moreover, the results of the discriminant analyses support the notion that the rate of central serotonin turnover is positively correlated with impulse control, and central availability of testosterone with outward directed aggressiveness.[43,44]

CSF DBI, CRH, AVP, AND CORTICOTROPIN CONCENTRATIONS

Alcoholic offenders with antisocial personality disorder had CSF DBI, CRH, and AVP concentrations similar to those in the healthy volunteers but relatively low CSF corticotropin concentrations. At the level of the pituitary, CRH and AVP act synergistically to facilitate the release of corticotropin.[45] Earlier studies showing strong positive correlations in normal volunteers between CSF concentrations of CRH and corticotropin[21,46] and between those of AVP and corticotropin,[46] the latter also replicated in the present sample, support the notion that such a relationship may also exist in the brain.

A large number of animal studies on corticotropin and learning have found that this neuropeptide facilitates consolidation of memory.[47] We speculate that the low mean CSF corticotropin concentration in the alcoholic offenders with antisocial personality disorder may be concordant with the often stated clinical observation that such patients exhibit difficulties with learning from experience. On the other hand, the meaning of the low mean CSF corticotropin concentration among alcoholic offenders who had attempted suicide remains obscure.

In conclusion, among alcoholic, violent offenders and fire setters, low CSF 5-HIAA concentration seems to be associated with impaired impulse control. Alcoholic offenders with intermittent explosive disorder had low blood glucose nadirs after an oral glucose administration and striking diurnal activity rhythm dysregulation. Alcoholic offenders with antisocial personality disorder had high CSF free testosterone and low corticotropin concentrations and showed increased diurnal physical activity. Concentration

of free testosterone in CSF may be associated with outward directed aggressiveness, and that of corticotropin may be associated with learning from experience. Interrelationships between serotonin and glucose metabolism dysregulation need further study to elucidate the basic physiologic mechanisms involved.

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Reprint requests to National Institute on Alcohol Abuse and Alcoholism, Bldg 10, Room 3C103, Bethesda, MD 20892 (Dr Linnoila).

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