Brain Serotonin, Type II Alcoholism and Impulsive Violence

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ABSTRACT. There is ample evidence that low CSF 5-HIAA concentration is associated with a tendency to exhibit impulsive violent behavior under the influence of alcohol. This is especially true for subjects who fulfill criteria for psychiatric diagnoses often associated with early onset alcoholism such as antisocial personality disorder and intermittent explosive disorder. Brain serotonin turnover as indicated by CSF 5-HIAA concentration does not correlate with CSF free testosterone concentration. The latter is more strongly associated with outward-directed aggressiveness and lack of socialization than impulsiveness. CSF ACTH concentration on the other hand correlates positively with socialization. (*J. Stud. Alcohol,* Supplement No. 11: 163-169, 1993)

CRIME STATISTICS show that heavy drinking and violence often co-occur (Pihl and Peterson, 1993). Alcohol-intoxicated individuals are involved in a large proportion of violent crimes, including murder, assaults, sexual assaults and family violence (Collins, 1981; Evans, 1986; Murdoch et al., 1990; Pernanen, 1976; Virkkunen, 1974). Murdoch et al. (1990) examined 9,304 crimes reported in 26 studies from 11 countries. Overall, 62% of violent offenders were drinking at the time of the crime. The incidence of alcohol-related violent crime ranged from 24% to 85%. This high incidence contrasted dramatically with the range reported for alcohol-related nonviolent crimes: 12% to 38%. In Finland the proportion of violent crimes committed under the influence of alcohol is among the highest in the world (Virkkunen, 1974).

Alcohol-induced intoxication may play a direct role in increasing aggression. A recent meta-analysis of 30 experimental studies concluded that "alcohol does indeed cause aggression" (Bushman and Cooper, 1990). The main theories concerning mechanisms by which alcohol increases the likelihood of aggressive behavior posit that it is due to disinhibition, increased stimulation-arousal and/or social expectancies (Bushman and Cooper, 1990; Graham, 1980). Theories of disinhibition postulate that normal physiological and cognitive processes are rendered dysfunctional during alcohol intoxication. Arousal theorists hypothesize that mechanisms involved in triggering aggressive behavior are directly stimulated by the ingestion of alcohol. Recent experiments have produced results that would support each of these theoretical positions (Pihl and Peterson, 1993).

Ethanol acutely increases inhibitory GABAergic neurotransmission (Nestoros, 1980) by increasing ^{36}Cl flux through the GABA-A receptor associated channel (Mehta and Ticku, 1988; Suzdak et al., 1986; Ticku, 1990). Secondly, ethanol decreases NMDA related Ca^{2+} flux and reduces exitatory neurotransmission (Lovinger et al., 1989, 1990). Thirdly, ethanol acutely increases 5HT release and chronically depletes 5HT stores (Badawy, 1986; Badawy and Evans, 1976; Carmichael and Israel, 1975; Hyatt and Tyce, 1985). Initially, ethanol produces a significant increase in serum and brain free tryptophan and in brain serotonin and 5-hydroxyindoleacetic acid (5-HIAA) level in the rat. These changes are, however, followed by significant decreases in all serotonergic measures at 7 hours (Badawy, 1986; Badawy and Evans, 1976). The initial changes appear to be due to a transient ethanol-induced increase in serum free tryptophan concentration produced by catecholamine-mediated lipolysis, which is conducive to displacement of serum protein-bound tryptophan by free fatty acid. Only a few studies have explored effects of ethanol on central serotonin metabolism in humans, but the results roughly parallel those of the animal studies (Ballenger et al., 1979).

Ethanol's effects on the GABA and NMDA systems seem to be associated with anxiolysis during intoxication and withdrawal symptoms such as anxiety and lowered seizure threshold (Lovinger et al., 1990; Ticku, 1990), whereas its effects on 5HT may be associated with symptoms such as impulsivity and aggression especially late during intoxication (Virkkunen and Linnoila, 1990). Anxiolytic effects of alcohol also directly increase the likelihood of aggressive behavior by reducing responses to cues

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of possible punishment and frustrative nonreward (Gray, 1982, 1987).

Individual vulernability variables may render certain subgroups of alcoholics particularly high risk to exhibit violent behavior while intoxicated. One such subgroup may be Type II alcoholics as originally defined by Cloninger et al. (1981, 1988). According to their adoption studies, there are at least two types of alcoholism, Type I and II. They emphasized that Type II alcoholics often exhibit violence while drinking, drive while drinking, have difficulty abstaining from alcohol and have had treatment other than Alcoholics Anonymous.

In contrast, von Knorring et al. (1985), who use the same nomenclature as Cloninger et al., first identify the age at which problems related to alcohol use appeared. Von Knorring's Type II alcoholism diagnosis requires onset prior to 25 years and/or treatment before 30 years of age, as well as at least two social complications where violence while drinking is one of the alternatives. The criteria of von Knorring et al. are much more liberal than Cloninger et al.'s, original criteria. Lamparski et al. (1991) found that a majority of alcoholics with antisocial personality disorder (ASP) are identified as Type II according to the von Knorring et al. criteria. However, alcoholics with ASP account for only one-third of the alcoholics classified as Type II by von Knorring et al. (von Knorring et al., 1985).

What is important is that early onset of alcohol-related problems and violence and other criminality under the influence of alcohol are the central features of Type II alcoholism according to both Cloninger and von Knorring. Other investigators studying alcoholics have also noted that behavioral problems that emerge in the context of excessive consumption of alcohol are important symptoms of alcoholics with ASP (Cadoret et al., 1984; Hesselbrock et al., 1985; Lewis, 1990; Liskow et al., 1991; Schuckit, 1985). According to Irwin et al. (1990), Type II alcoholics usually have an antisocial personality disorder, and they emphasize the importance of the early onset of excessive drinking. Individual biochemical and behavioral vulnerability variables are combined with pharmacological effects of alcohol and environmental cues to produce the outcome of violent behavior during intoxication.

Biological Studies that Relate Brain Serotonin Metabolism to Type II Alcoholism

Abnormal tryptophan/large neutral amino acid (LNAA) ratio in plasma

Tryptophan/LNAA ratio regulates the availability of tryptophan to the brain. This ratio is in turn partially regulated by insulin. Insulin reduces disproportionally plasma concentrations of neutral amino acids other than tryptophan, which is relatively tightly bound to albumin. Thus insulin increases the tryptophan/LNAA ratio and makes more tryptophan available to the brain (Fernström and Wurtman, 1971, 1972).

Buydens-Branchey et al. (1989a,b) have found that alcoholics who have started to abuse alcohol early (before 20 years of age) show an association between low tryptophan/LNAA ratio and depressive and aggressive behaviors. In their study the tryptophan/LNAA ratio was quantified one day after cessation of drinking and it increased progressively for at least 2 to 3 weeks after detoxification. The subjects who had exhibited early onset alcohol-seeking behavior had also often committed crimes of violence, had experienced blackouts (Branchey et al., 1985) and commonly had a history of paternal alcoholism. To experience blackouts when committing impulsive violent crimes is common among impulsive habitually violent offenders (Roy et al., 1986).

Contrary to Buydens-Branchey et al.'s (1989a,b) findings, Virkkunen and Närvänen (1987) found an elevated tryptophan/LNAA ratio among impulsive, violent offenders who had an intermittent explosive disorder and enhanced insulin secretion in the oral glucose tolerance test. Their subjects had maintained supervised abstinence for a few months prior to the study. Thus, the question concerning tryptophan/LNAA ratio among Type II alcoholics compared to healthy volunteers remains open for further investigation.

Platelet MAO activity

Low platelet MAO activity has been associated with Type II alcoholism in large scale studies by von Knorring et al. (1985, 1991). Brain MAOs are the major enzymes that metabolize serotonin. A relatively weak positive correlation between levels of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid and platelet MAO B activity has been observed in volunteers and chronic pain patients (Oreland et al., 1981; von Knorring et al., 1986). Platelet MAO activity has been suggested to be a possible peripheral genetic marker for capacity of the central serotonin system (Oreland, in press; Oreland and Shaskan, 1983).

Platelet MAO activity has been found to be also low among patients with antisocial personality disorder (Lidberg et al., 1985). Personality characteristics such as impulsiveness and sensation seeking correlate inversely with platelet MAO activity (Soloff et al., 1991; von Knorring et al., 1984, 1987).

Low brain serotonin turnover (low CSF 5-HIAA)

We have studied habitually violent criminals who commit crimes under the influence of alcohol and who all have had alcohol dependence or abuse as defined in DSM-III and DSM-III-R. We collected lumbar cerebrospinal

fluid (CSF) for monoamine metabolite measurements during the 1980s and early 1990s from more than 150 alcoholic violent offenders. All of them had undergone forensic psychiatric examinations in the Psychiatric Clinic of Helsinki University Central Hospital (Linnoila et al., 1983, 1989; Virkkunen et al., 1987, 1989). Patients had an early age of onset of alcohol-related problems and repeated tendency to interpersonal violence when drinking. Many patients also had repeated driving problems related to drinking and had alcohol treatments other than AA. Thus, at face value our subjects represent an extreme group of Type II alcoholics.

Those who fulfilled the criteria for ASP and had habitually violent tendencies had had a very early onset of alcohol-related problems, usually in their early teens. Habitually violent offenders with intermittent explosive disorder who commonly fulfilled the criteria for borderline personality disorder had had a somewhat later onset of drinking-related problems, but usually in their late teens. Among nonimpulsive violent offenders alcohol abuse or dependence had started later, and they did not usually fulfill the criteria for Type II alcoholism.

Earlier studies

In a series of such studies on Finnish alcoholic, criminal offenders we have observed that, compared to nonimpulsive violent offenders and American healthy volunteers, Finnish impulsive violent offenders and fire setters who fulfill the criteria of Type II alcoholism have relatively low CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations. They also commonly experience mild hypoglycemic episodes during oral glucose tolerance tests and sleep irregularly while on the forensic psychiatry ward.

Based on these observations we in 1986 proposed a model in which deficient central serotonin turnover in alcoholic, impulsive violent offenders is conducive of disturbances of diurnal activity rhythm and glucose metabolism (Figure 1) (Linnoila et al., 1986). The neuroanatomical substrate postulated to have an important role in the model is the suprachiasmatic nucleus, which receives a serotonergic input from the dorsal and median raphe nuclei and functions as a circadian pacemaker and also as a regulator of glucose metabolism.

In follow-up and family history studies, we have found that low CSF 5-HIAA concentration and the propensity to mild hypoglycemias are predictive of recidivist violent criminality under the influence of alcohol after release from prison (Virkkunen et al., 1989). Moreover, sons of alcoholic fathers, who have been convicted of violent crimes, have the lowest CSF 5-HIAA concentrations (Linnoila et al., 1989). This latter finding suggests that there may exist familial trait associated with early onset alcohol abuse, impulsive and violent criminality under the influence of alcohol and low CSF 5-HIAA concentration.

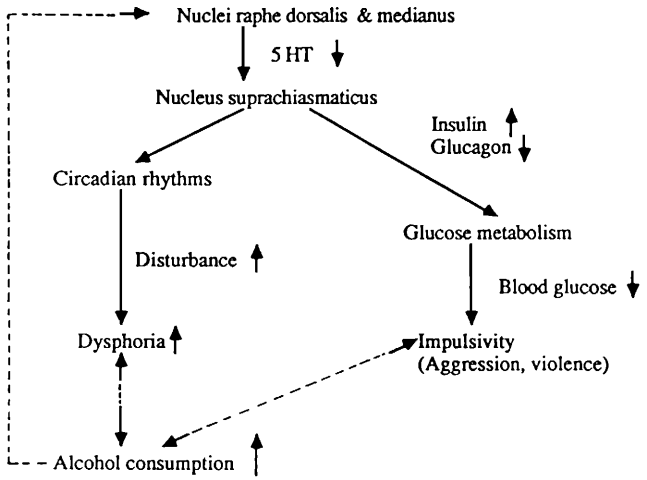

FIGURE 1. Proposed pathogenesis of impulsivity

Low brain serotonin turnover (CSF 5-HIAA) and other psychological and biological variables

In the latest study, we directly tested several aspects of the proposed model (Virkkunen et al., 1993a,b). Furthermore, we for the first time investigated age- and sex-matched Finnish healthy volunteers as inpatients in the same psychiatry department as the violent offenders. The a priori hypotheses explored were:

1. Low CSF 5-HIAA concentration is associated with impulsivity of the index crime under the influence of alcohol; a disturbance of diurnal activity rhythms; abnormalities in glucose metabolism; and personality traits such as impulsiveness, monotony avoidance, irritability, verbal aggressiveness and poor socialization on the Karolinska Scales of Personality; and a high score on the psychopathic deviate scale of the MMPI.
2. CSF-free testosterone concentration is correlated with aggressiveness rather than impulsiveness.
3. Concentrations of corticotropin (ACTH) and corticotropin-releasing hormone (CRH) in CSF are low in impulsive violent offenders who commit their crimes under the influence of alcohol (we have previously reported that similar patients with ASP have low urinary free cortisol outputs; see Virkkunen, 1985).

Method

Subjects

Healthy volunteers ($n=27$) were recruited by advertisement in the Finnish *Red Cross* magazine, which is sent to all blood donors, and in the *Finnish Temperance Organization* magazine. The advertisement stated that the volunteers had to be free of current or past drinking problems

and mental disorders. After recruitment, 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 on the research ward for 3 days and 3 nights. The alcoholic violent offenders ($n = 58$) were on the Forensic Psychiatric Department in the Psychiatric Clinic of Helsinki University Central Hospital.

Procedure

On the first full day after a night on the ward, the habitually violent alcoholic offenders and controls underwent a lumbar puncture between 8 and 9 AM. On the next day they received an oral glucose or aspartame tolerance test starting at 8 AM. On the last day of hospitalization, the volunteers filled out the Karolinska Scales of Personality. Throughout their stay, the volunteers wore physical activity monitors on their left wrist and the offenders wore the physical activity monitors on their left wrist continuously for 10 days and nights. The activity monitors are small watch size devices that have a movement sensor and clock and memory functions that permit continuous recording of activity for a period of 10 days. The data were decoded and stored on an Apple Macintosh computer.

Psychiatric diagnoses and family history

All subjects were administered a SADS-L (Endicott and Spitzer, 1978) and a clinical interview to derive RDC (Spitzer et al., 1978) and DSM-III-R (American Psychiatric Association, 1987) diagnoses. To maintain continuity, intermittent explosive disorder was diagnosed according to DSM-III criteria (American Psychiatric Association, 1980) which unlike DSM-III-R permits the 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.

The offenders were divided into impulsive and nonimpulsive groups based on the characteristics of the index crime as in our previous studies. (A crime was called 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.)

The data on the impulsive offenders are also given as a function of their DSM-III (intermittent explosive disorder) and DSM-III-R Axis II diagnoses. This was done to examine whether ASP and intermittent explosive disorder represent diagnostic entities that are separable behaviorally, biochemically and according to personality characteristics.

Additionally, impulsive offenders who on a minimum of three occasions showed more than 4-hour variation in the timing of the start of their longest inactive (presumed sleep) period during the 10-day activity monitoring we called sleep disordered (ISD) and the rest of the impulsive offenders nonsleep disordered (INSD). None of the volunteers and three of the nonimpulsive offenders showed this degree of variation between any of the nights during the activity monitoring. The rationale for the division of the impulsive offenders into the ISD and INSD groups was to permit a direct test of the hypothesized relationship between CSF 5-HIAA concentration and synchronization of the diurnal activity rhythm.

The data of healthy volunteers with first-degree blood relatives with either alcoholism or major depressive disorder were analyzed separately from those of other healthy volunteers.

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 at 8:00 AM. The samples were stored in a −80°C freezer and shipped air freight on dry ice from Helsinki to Bethesda, where homovanillic acid (HVA), 5-HIAA and MHPG concentrations were quantified with a liquid chromatographic procedure using electrochemical detection.

Neuropeptides and Hormones. CSF CRH, ACTH and free testosterone concentrations were quantified with radioimmunoassays.

Oral glucose and aspartame tolerance test. After a 12-hour overnight fast, at 8:00 AM 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 mL blood samples were drawn from an antecubital vein into an aprotinin-containing test tube (12.5 mIU/mL, Antagosan Behringwerke, Marburg, Germany) prior to 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 on the ward, but resting was encouraged. Glucagon was quantified immediately after the samples were thawed with a double antibody separation radioimmunoassay (Diagnostic Products Corp., Los Angeles). Insulin was quantified in antibody coated test tubes (Coat-A-Count, Diagnostic Products Corp.). Between-assay variation at 30.2 uU/mL for insulin was 4.6% and for glucagon at 44.8% pg/mL 5.1%. All samples were assayed in duplicate. When the results of the duplicate determinations were discrepant by more than 5%, the samples were reanalyzed.

Psychological testing

All tests were scored without knowledge of the subjects' diagnoses or condition, or results of the biochemical analyses. The Wechsler Adult Intelligent Scale (WAIS-R) (Wechsler, 1981) and the Minnesota Multiphasic Personality Inventory (MMPI) (Hathaway and McKinley, 1951) were administered to all offenders as an integral part of the forensic psychiatric examination. Due to time constraints, WAIS-R and MMPI were not administered to the healthy volunteers.

The Karolinska Scales of Personality (KSP), administered to all offenders and healthy volunteers, have 135 questions grouped in 15 scales. The scales have been normalized for the Swedish population, and they are thought to measure relatively stable personality traits. This personality test consists of scales quantifying several personality characteristics such as impulsivity, psychopathy, sensation seeking and socialization which are thought to be associated with Type II alcoholism (von Knorring et al., 1987).

Results

Biochemical variables

CSF monoamine metabolite concentrations. Mean CSF 5-HIAA was again significantly lower among the impulsive than among the nonimpulsive offenders ($p = .0002$). The nonimpulsive offenders had significantly higher mean CSF 5-HIAA than did the healthy volunteers. Among the impulsive offenders, subjects with ASP and intermittent explosive disorder had similar low mean CSF 5-HIAA concentrations. Impulsive offenders with sleep disorder had a significantly lower mean CSF 5-HIAA concentration than did the healthy volunteers ($p<.05$).

Healthy volunteers with a family history positive for first degree relatives with alcoholism or major depression had CSF 5-HIAA and HVA concentrations similar to those of the impulsive offenders. Mean CSF HVA concentrations were significantly lower in the impulsive than in the nonimpulsive offenders ($p = .0180$). This difference was increased in the comparison between the impulsive sleep disordered and the nonimpulsive offenders ($p = .0092$).

CSF hormone and peptide concentrations. Mean CSF testosterone concentrations were higher among offenders than among healthy volunteers ($p = .0294$). The difference was most striking between offenders with antisocial personality disorder and healthy volunteers ($p = .0075$).

Mean CSF ACTH concentration was significantly lower among impulsive offenders than among healthy volunteers ($p = .0069$). The lowest values were observed in the offenders with ASP.

Mean CSF ACTH/CRH ratio, computed as an index of apparent functional CRH receptor sensitivity on ACTH neurons, was significantly lower among impulsive offenders than among healthy volunteers ($p = .0021$). This finding is compatible with the notion of desensitized CRH receptors on ACTH-secreting neurons among impulsive violent offenders.

Oral glucose and aspartame tolerance tests. Impulsive violent offenders had significantly lower mean blood glucose nadir during the glucose tolerance test than did healthy volunteers ($p = .0037$), matching the earlier findings (see Virkkunen, 1986). This difference was exacerbated in the comparisons between offenders with sleep disorder ($p = .0109$) and offenders with intermittent explosive disorder ($p = .0049$) and healthy volunteers.

Plasma insulin and glucagon concentrations did not differ significantly between the groups at any time point during the oral glucose or aspartame tolerance test. This finding is suggestive of increased insulin sensitivity among impulsive violent offenders with low blood glucose nadirs.

When all subjects were included, baseline CSF 5-HIAA concentrations correlated positively with the area under the plasma insulin concentration curve during the oral glucose tolerance test ($r = .29$; $n = 55$).

Physical activity monitoring

Impulsive offenders with antisocial personality disorder ($p = .0181$) and impulsive offenders with sleep disorders ($p = .0206$) had significantly higher mean total 10 day-night activity counts than did healthy volunteers compatible with positive histories for hyperactivity-attention deficit disorder. Impulsive offenders with ASP also showed delayed nighttime sleep-onset-associated reduction in physical activity as compared to healthy volunteers. Impulsive offenders with intermittent explosive disorder had indistinguishable day and night activity counts—a striking difference from the other groups.

Psychological testing

Intelligence quotient. Offenders with antisocial personality disorder had a significantly lower full scale IQ than did offenders with intermittent explosive disorder.

MMPI. Mean psychopathic deviate scale score was higher for all impulsive offenders, and especially offenders with ASP, than for nonimpulsive offenders.

Karolinska Scales of Personality. Mean impulsiveness ($p = .0000$) and monotony avoidance ($p = .0000$) scores were significantly higher and socialization ($p = .0000$) scores significantly lower among offenders with ASP than in any other group of subjects. Offenders with either

ASP or intermittent explosive disorder had significantly higher mean irritability scores than did healthy volunteers ($p = .0006$).

Mean socialization scores were lowest among offenders with ASP followed by offenders with intermittent explosive disorder, nonimpulsive offenders and healthy volunteers. Differences between mean socialization scores were statistically significant for groups other than offenders with intermittent explosive disorder and nonimpulsive offenders.

Correlational analyses

CSF 5-HIAA concentration correlated positively with CSF HVA ($r = .68$; $n = 67$) concentration. CSF 5-HIAA concentration correlated positively with the KSP inhibition of aggression scale score ($r = .28$; $n = 67$) and the area under the insulin concentration curve during the oral glucose tolerance test ($r = .29$; $n = 55$). CSF testosterone concentration correlated negatively ($r = -.41$; $n = 63$) and CSF ACTH correlated positively ($r = .41$; $n = 60$) with the KSP socialization scale score.

Conclusion

Low CSF 5-HIAA in early onset alcoholic, violent criminals is associated with irritability, impulsiveness and diurnal activity rhythm disturbances. High free CSF testosterone is associated with increased aggressiveness and ACTH is associated with socialization. These biochemical factors contribute to a complex interplay with the pharmacology of ethanol and environmental cues which under certain sets of circumstances are conducive to interpersonal violence.

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