Low Brain Serotonin Turnover Rate (Low CSF 5-HIAA) and Impulsive Violence

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The findings of a series of studies by the authors support the idea that most impulsive offenders who have a tendency to behave aggressively while intoxicated have a low brain serotonin turnover rate. The impulsive violent offenders with the lowest CSF 5-HIAA concentrations have diurnal activity rhythm disturbances, and are also prone to hypoglycemia after an oral glucose challenge. Low CSF 5-HIAA combined with hyoglycemic tendency also predicts future violence under the influence of alcohol. Sons of alcoholic fathers, who have committed violent crimes, have very low CSF 5-HIAA concentrations. Vagal tone does not correlate significantly with CSF 5-HIAA but correlates with enhanced insulin secretion, which is most prominent in subjects with intermittent explosive disorder. A polymorphism of tryptophan hydroxylase (TPH) gene is associated with low CSF 5-HIAA and a history of suicide attempts.

Key Words: brain serotonin, impulsive violence, hypoglycemic tendency, activity rhythms, vagal tone, D_2 receptor genotype, tryptophan hydroxylase gene

INTRODUCTION

Early studies

The results of a number of studies (Linnoila et al 1983; van Praag et al 1987) are compatible with the interpretation that low brain serotonin turnover, as indicated by low cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), is associated with increased impulsiveness and impaired control of aggressive behaviors. Similarly, a series of studies (Virkkunen et al 1987, 1988, 1994a) by the authors has found that, compared to nonimpulsive violent offenders and American healthy volunteers, Finnish impulsive violent offenders and fire setters have relatively low CSF 5-HIAA concentrations. They also often experience mild hypoglycemic episodes during oral glucose tolerance tests and sleep irregularly while on the forensic psychiatry ward. Based on these observations, the authors proposed a model in which deficient central serotonin turnover in alcoholic, impulsive, violent offenders is conducive to disturbances of diurnal activity rhythm and glucose metabolism (Linnoila et al 1986). The neuroanatomical substrate, which is 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 both as a circadian pacemaker and as a regulator of glucose metabolism.

In follow-up and family history studies (Virkkunen et al 1989), low CSF 5-HIAA concentration and the propensity to mild hypoglycemia have been found to be predictive of recidivist violent criminal behavior under the influence of

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alcohol after release from prison. 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 a familial trait associated with early onset of alcohol abuse, impulsive and violent criminal behavior under the influence of alcohol, and low CSF 5-HIAA concentrations.

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

In one of the latest studies (Virkkunen et al 1994a, 1994b), several aspects of the proposed model were directly tested. Mean CSF 5-HIAA was again found to be significantly lower among the impulsive than among the nonimpulsive offenders ($p = 0.0002$). The offenders were divided into impulsive and nonimpulsive groups based on the characteristics of the index crime as in previous studies (Virkkunen et al 1989; Linnoila et al 1989). (A crime was called impulsive when the victim was previously unknown to the offender; when no provocation or only verbal provocation preceded the attack; when no premeditation could be documented; and when no economic motivation such as robbery or burglary was evident). All the violent crimes occurred under the influence of alcohol. Offenders with either antisocial personality disorder or intermittent explosive disorder had low mean CSF 5-HIAA concentrations.

Oral glucose tolerance tests

Similar to earlier findings (Virkkunen 1986), impulsive violent offenders had significantly lower mean blood glucose nadir during the glucose tolerance test (GTT) than healthy volunteers ($p = 0.0037$). This finding was strengthened when offenders with intermittent explosive disorder were compared to healthy volunteers ($p = 0.0049$). Plasma insulin and glucagon concentrations did not differ significantly between the groups at any time during the oral glucose tolerance test. This finding was suggestive of increased insulin sensitivity among violent offenders with low blood glucose nadirs.

Physical activity monitoring

The physical activity of subjects was recorded with monitors which are small watch-like devices that have a movement sensor, as well as 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. Because impulsive offenders often complain about poor sleep and sleep very irregularly on the ward, their day and night physical activity rhythms were of particular interest to this study.

Impulsive offenders who, on a minimum of 3 occasions, showed more than a 4-hour variation in the timing of the start of their longest inactive (presumed sleep) period during the 10-day activity monitoring were called sleep-disordered (ISD). The rest of the impulsive offenders were called non-sleep-disordered (INSD). None of the normal volunteers, and only 3 of the nonimpulsive offenders, showed more than a 4-hour variation in the timing of the start of their longest inactive period during the 10-day monitoring of activity. 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. Impulsive offenders with antisocial personality disorder ($p = 0.0181$) and impulsive sleep-disordered offenders ($p = 0.0206$) had significantly higher mean total 10-day and night activity counts than healthy volunteers. This finding is compatible with positive histories for attention deficit/hyperactivity disorder. Impulsive offenders with antisocial personality disorder also showed delayed night-time sleep onset-associated reduction in physical activity as compared to healthy volunteers. Impulsive offenders with intermittent explosive disorder had almost indistinguishable day and night activity counts — a striking difference from the other groups. Impulsive offenders with sleep disorder had a significantly lower mean CSF 5-HIAA concentration than the healthy volunteers ($p < 0.05$).

Psychological testing

Mean Psychopathic Deviate Scale Score on the MMPI was higher for all impulsive offenders, and especially for offenders with antisocial personality disorder, than nonimpulsive offenders. Karolinska Scale of Personality (KSP) mean impulsiveness ($p = 0.0000$) and monotony avoidance ($p = 0.0000$) scores were significantly higher, and socialization ($p = 0.0000$) scores were significantly lower among offenders with antisocial personality disorder than in other groups. Offenders with either antisocial personality disorder or intermittent explosive disorder had significantly higher mean irritability scores than healthy volunteers ($p = 0.0006$).

Vagal tone and low brain serotonin turnover rate (CSF 5-HIAA)

Certain serotonin receptors may participate in the regulation of vagal tone ($5HT_{1A,2A,2C,3}$), although the exact receptor subtypes are still unknown (Percola and Alper 1992; Fozard 1992). Increased vagal tone is a potential cause of the lower resting heart rate among criminals as compared to noncriminals, which has been observed in many studies (Wadsworth 1976; Raine and Venables 1984; Raine et al 1990; Maliphant et al 1990; Kruesi et al 1992). Kruesi et al (1992) found that both CSF 5-HIAA and autonomic nervous system activity were somewhat predictive of subsequent outcomes in adolescents with disruptive behavior disorders. However, only CSF 5-HIAA significantly predicted the severity of physical aggression during follow-up. This finding is in agreement with the original findings of Virkkunen et al (1989).

The relation of resting heart rate and vagal tone to CSF 5-HIAA concentrations among impulsive violent offenders

has been recently investigated (Virkkunen and Linnoila 1993). Vagal tone was measured with a Vagal Tone Monitor (Delta-Biometrics, Bethesda, MD) that computes an index of cardiac vagal tone by accurately quantifying the amplitude of respiratory sinus arrhythmia from the beat by beat heart rate variability according to an equation developed by Porges (1992). Thus far, only a few studies (Porges 1992; Adinoff et al 1992) have been published using this technique.

The vagal tone was investigated during the glucose tolerance test in order to quantify simultaneously insulin, glucagon, C-peptide and glucose concentrations. Prior to the glucose tolerance test, the subjects had undergone lumbar punctures to quantify CSF monoamine metabolites. Vagal tone did not correlate significantly with CSF 5-HIAA, but did correlate with enhanced insulin secretion, especially in patients with intermittent explosive disorder. In most patients with antisocial personality disorder, vagal tone and insulin secretion were similar to those of the age- and sex-matched healthy volunteers.

D_2 receptor genotype (DRD_2) and monoamine metabolites

Brain serotonin and dopamine metabolism(5-HIAA/HVA) mutually regulate each other. Therefore, either a low 5-HIAA or HVA concentration can, under certain circumstances, be indicative of a reduced CNS serotonergic activity (Agren et al 1986; Linnoila et al 1990). A role for the D_2 dopamine receptor in the genetic predisposition to alcoholism has been proposed on the basis of genetic population association studies (Blum et al 1990; Uhl et al 1993). Many studies have, however, failed to replicate the reported association (Conneally 1991). This is especially true of the more recent studies (Goldman et al 1992; Turner et al 1992; Gelernter et al 1993), which have controlled the ethnic background of the research subjects.

An evaluation was made of the D_2/TaqI polymorphism in 29 impulsive violent offenders, 17 nonimpulsive violent alcoholics and 36 Finnish controls free of mental disorders, alcoholism and substance abuse. A measurement was also made of CSF HVA, 5-HIAA and 3-methoxy-4-hydroxyphenylglycol (Goldman et al 1992). There was no significant difference in the A1 allele frequency among the impulsive alcoholics (0.17) as compared with nonimpulsive alcoholics (0.12) or healthy Finnish controls (0.21). There was also no relationship between the D_2/TaqI genotype and the monoamine metabolites of the impulsive violent group who have relatively low CSF HVA and 5-HIAA concentrations as compared to controls.

Human tryptophan hydroxylase gene and low brain serotonin turnover rate (CSF 5-HIAA)

Tryptophan hydroxylase (TPH) catalyzes the biopterin-dependent monooxygenation of tryptophan to 5-hydroxytryptophan (Kaufman 1987), which is subsequently decarboxylated to the neurotransmitter serotonin. Because a low turnover of serotonin in the brain has been found, as indicated by low 5-HIAA in CSF, which is often associated with impulsive violence, polymorphisms of the TPH gene were investigated as potential markers for serotonergic behaviors.

The human TPH gene has been localized to the short arm of chromosome 11 (Ledley et al 1987) and more exactly to the region of 11p15.3 → p14 (Craig et al 1991). Nielsen et al (1992) have recently identified a polymorphism of the TPH gene. By examining introns of the gene, they have discovered two alleles, U and L, that occur with frequencies of 0.40 and 0.60 in unrelated Caucasians.

In a study (Nielsen et al 1994) concerning the TPH genotype and CSF 5-HIAA, the authors studied 70 violent alcoholic offenders and arsonists. Fifty-six of these offenders were impulsive and 14 were nonimpulsive, based on the characteristics of the index crime as described in previous studies (Virkkunen et al 1989) by the authors. The frequency of the rarer TPH allele (U) in this population was 0.41, which is the same frequency for American Caucasians (0.40). The allelic frequencies were similar among impulsive (0.44) and nonimpulsive (0.39) offenders and Finnish healthy volunteers (0.35). However, within the impulsive offenders group there was a highly significant relationship between CSF 5-HIAA concentration and TPH genotype. Impulsive offenders with the UU genotype had the highest CSF 5-HIAA concentration (76 ± 9 nM), while the LL group had the lowest CSF 5-HIAA concentration (45 ± 4 nM). No association of TPH genotype to CSF 5-HIAA concentration was observed in nonimpulsive offenders or controls.

A significant association of TPH genotype with a history of suicide attempts also emerged among the violent offenders. The frequency of the U allele was 0.32 among individuals who had attempted suicide and 0.54 among those who had not. Among the suicide attempters, only 6% (2 of 36) had the UU genotype as compared to 29% (10 of 34) of those who had never attempted suicide. Thus, the presence of the L allele is associated with an increased risk of attempted suicide. Because CSF 5-HIAA concentration correlates with suicidal behavior, this relationship was as expected (Asberg et al 1976; Träskman et al 1981; Virkkunen et al 1989). In the same vein, an association with TPH genotype and a history of multiple suicide attempts was also observed among the violent offenders. These characteristics were most prevalent among subjects with the LL genotype, and to a lesser extent among the UL genotype, which indicates an association between the L allele and self-injurious behavior.

This is the first report to implicate a specific gene in the predisposition to a behavior postulated to be regulated by serotonin. Correlation between CSF 5-HIAA concentration and TPH genotype may be significant only among impulsive offenders, as they are phenotypically more extreme and, therefore, more likely to carry a mutation in the TPH gene.

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