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LOW CEREBROSPINAL FLUID 5-HYDROXYINDOLEACETIC ACID CONCENTRATION DIFFERENTIATES IMPULSIVE FROM NONIMPULSIVE VIOLENT BEHAVIOR

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Summary

Relationships of impulsive and nonimpulsive violent behavior to cerebrospinal fluid (CSF) monoamines and their metabolite concentrations were studied in thirty-six violent offenders. A relatively low 5-hydroxyindoleacetic acid (5HIAA) concentration was found in the CSF of impulsive violent offenders. This was not true for the offenders who had premeditated their acts. Other CSF monoamine or metabolite concentrations were not significantly different between the two groups. Of the groups studied, impulsive violent offenders who had attempted suicide had the lowest 5HIAA levels. A low CSF 5HIAA concentration may be a marker of impulsivity rather than violence.

In 1976, Asberg et al.[1,2] published two articles concerning low concentrations of 5-hydroxyindoleacetic acid (the major metabolite of serotonin) in in the CSF of a subgroup of depressed patients. The authors remarked that their finding provided partial support to the theory postulating defective serotonergic neurotransmission in depression.[2,3] Furthermore, the Swedish investigators pointed out that the depressed patients with low CSF 5-HIAA concentrations were more likely than depressed patients with normal 5-HIAA to have attempted or completed suicide using particularly violent means. Since their initial reports, Asberg et al. have increased the size of their sample, and the original findings have held up.[6,7] Moreover, Brown et al.[8,9] have demonstrated that patients with character disorders, who are prone to impulsive violent behavior towards others, have lower concentrations of 5-HIAA in their CSF than matched controls with character disorder without incidents of impulsive violent behavior. This finding is consistent with pharmacological models of "aggression" in rodents, where alterations of brain serotonin functions have been linked with increased "aggression".[10,11] A genetic basis for increased violent behavior and reduced CSF 5HIAA accumulation after probenecid loading in humans has been suggested by two French pilot studies tying this biochemical marker to violent male criminals with the XYY genotype.[12,13]

Another association between a relatively low 5-HIAA concentration in the CSF and abnormal behavior has been demonstrated in alcoholics and their depressed relatives.[14,15] This observation is of particular interest, be-

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cause at least one form of alcoholism in males is associated with criminal, and at times, violent behavior.[16]

We investigated the relationship of both impulsive violent behavior and premeditated violence to 5-HIAA concentration in the CSF of murderers and attempted murderers undergoing an intensive forensic psychiatric evaluation in the Department of Psychiatry at the University of Helsinki. According to the nature of their acts, subjects were grouped into those who had killed, or attempted to kill, impulsively (= without provocation or premeditation) a person not close to them and those who had killed or attempted to kill after some premeditation (= the victim was known to the offender and a rationale for the act could be construed in the psychiatric examination). Our hypothesis was that of the two equally violent groups, the impulsive offenders would have low CSF 5-HIAA concentrations relative to nonimpulsive offenders who had premeditated their act. Thus, a low 5-HIAA concentration in the CSF of violent offenders would be more of a marker of impulsivity than violence per se.

Methods

Subjects: A total of 36 violent offenders, who signed an informed consent, participated in the study. Participation was voluntary, and the subjects were told that their CSF samples would be used to investigate associations between brain biochemistry and violent behavior. All participants were men. Twenty-one subjects had killed and 15 attempted to kill their victims. All had used cold weapons and a common denominator was the unusual cruelty of the index act. Twenty were diagnosed to have intermittent explosive disorder, 7 antisocial personality disorder (these were all impulsive offenders), and 9 paranoid or passive-aggressive personality disorder (These were all offenders who had somehow premeditated their crime. For the purposes of the present study they were called non-impulsive). Furthermore, all subjects fulfilled the criteria for alcohol abuse, and all subjects with intermittent explosive or antisocial personality disorder the criteria for borderline personality disorder as well. None fulfilled criteria for a schizophrenic or major affective disorder,[17] even though 17 (all in the group of impulsive offenders) had a history of impulsive suicide attempts. Careful history revealed that all impulsive violent offenders had exhibited disturbed behavior at school compatible with either attention deficit or or aggressive conduct disorder[17] and had started to abuse alcohol in their early teens. This was not true of the nonimpulsive violent offenders. According to relatives and court documents all subjects with explosive or antisocial personality disorder had repeatedly demonstrated violent behavior towards others, particularly under the influence of alcohol. Chromosomal analysis conducted on all subjects revealed an XYY genotype in one murderer with intermittent explosive disorder.

The average age of the subjects was 31.5 ± 8.5 (SD) years and height 173.6 ± 5.8 cm, with ranges of 18 to 49 years and 160 to 185 cm, respectively. These demographic variables were similar in the three diagnostic groups. All subjects underwent a one to two month intensive forensic psychiatric evaluation and followup during which their medication was kept to a minimum and they had no access to alcoholic beverages. No drugs, except oxazepam 15 mg for severe insomnia in two subjects, were given during the last two weeks prior to the lumbar puncture. The patients were maintained on a controlled low monoamine diet and they had 8 hours of supervised bed rest prior to the LP, which was done through the 4th lumbar space in lateral decubitus position between 8 and 9 a.m. The fluid was collected into polyproplene tubes on ice. Twelve ccs of CSF were obtained with an atraumatic lumbar puncture,

mixed well and stored in two aliquots at -80°C until analysed for norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-HIAA with liquid chromatography.[18-20] Norepinephrine and DOPAC were not measured in 7 samples because the method was not available when the first samples arrived. All measurements in the laboratory were conducted without knowing the diagnostic grouping of the individuals.

The data were analyzed using an analysis of variance and Student's t-test for independent samples to test the differences between the means of the concentrations of each monoamine or metabolite in the three diagnostic groups of violent offenders. Two tailed probabilities were used.

Results

The difference in the mean (+SD) CSF 5HIAA concentrations between murderers and attempted murderers was not significant (81.9 + 21.4 and 72.7 + 23.9 nM, respectively). Impulsive violent offenders had significantly lower CSF 5-HIAA concentrations than paranoid or passive-aggressive (= nonimpulsive) violent offenders (see Figure I). The 17 offenders (14 impulsive and 3 non-impulsive), who had committed more than one violent crime, had a mean (+ SD) CSF 5-HIAA concentration of 67.9 + 12.2 nM. This was significantly below the CSF 5-HIAA concentration of the offenders, who had committed only one violent crime (87.1 + 23.7; $p<.02$). Moreover, the mean (+ SD) CSF 5-HIAA concentration in the impulsive offenders with suicide attempts was 67.4 + 19.7 nM, which is significantly less than the 91.2 + 22.0 nM ($p<.01$) found in violent offenders without suicide attempts.

Violent offenders with antisocial personality had lower CSF HVA concentrations than violent offenders with paranoid or passive-aggressive personality (Table I). There were no significant differences in the CSF norepinephrine or other monoamine metabolite concentrations between the diagnostic groups. In the whole sample the correlation between age and CSF 5HIAA concentration was not statistically significant ($r = -.02$), whereas height had a negative correlation with CSF 5HIAA concentration ($r = -.52$, $p<.01$). Age and height were both normally distributed within the diagnostic groups.

Discussion

A low CSF 5-HIAA concentration seems to be associated with a tendency towards repeated, impulsive violent behavior which can be directed both towards oneself (suicide attempts) as well as others (attempts of murder) and with early onset alcohol abuse.

Our findings do not contradict the earlier suggestion that some depressed patients without impulsive suicidality could have a relatively low CSF 5-HIAA concentration.[2] The low 5-HIAA subgroup of depressed patients in the Swedish studies may, however, have included patients whose low CSF 5-HIAA concentration could have been produced by withdrawal from previous antidepressant treatment. Thus, the group of impulsively suicidal depressed patients with low CSF 5-HIAA might have been artificially diluted because both previously drug-free and drug-treated patients were included after a relatively short placebo period. If this reasoning is correct, then the association between low CSF 5-HIAA concentration and impulsive suicidality may be stronger than suggested in previous reports. Prospective studies are needed to answer this question.

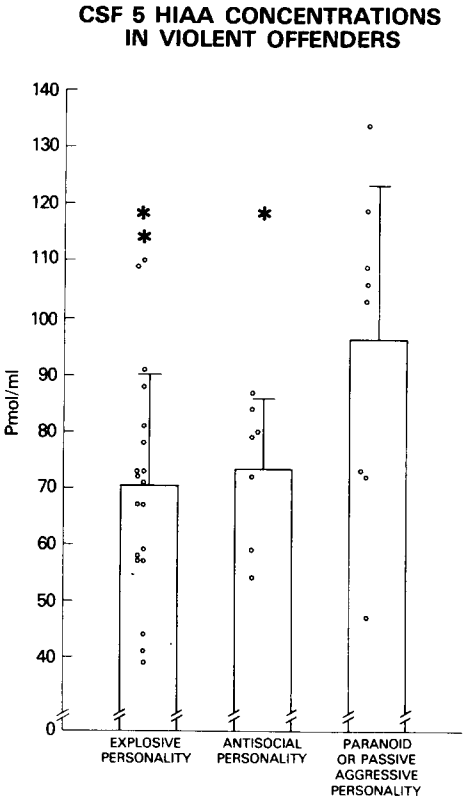

FIGURE I

CSF 5HIAA concentration in three diagnostic subgroups of violent offenders. I = Impulsive and II = Nonimpulsive offenders. Anova p<.01 between the groups. ** = p<.01, * = <.05 Students T = Test, Two-Tailed, between the nonimpulsive and the two subgroups of impulsive offenders.

TABLE I

	Norepinephine	MHPG	DOPAC	HVA
		nM		
I. Explosive Personality	1.1 + 0.6 (n=16)	31.0 + 7.2 (n=20)	2.9 + 1.5 (n=16)	217 + 97 (n=20)
I. Antisocial Personality	1.2 + 0.4 (n=7)	27.1 + 6.7 (n=7)	3.3 + 0.9 (n=7)	184 + 81* (n=9)
II. Paranoid or Passive-Aggressive Personality	1.5 + 0.8 (n=7)	36.4 + 15.4 (n=7)	4.4 + 2.2 (n=7)	253 + 46 (n=9)

CSF monoamine and their metabolite concentrations in the three diagnostic groups of violent offenders. I = impulsive and II = nonimpulsive, * = p<.05 compared to respective concentrations in paranoid and passive-aggressive murderers.

A careful inspection of our data reveals that all acid metabolites of monoamines in the CSF are lower in the impulsive than in the paranoid or passive-aggressive murderers, even though the difference in 5-HIAA is the only one which is clearly statistically significant. This complicates the interpretation of the data, because all acid metabolites of monoamines are transported out of the CSF by the same active mechanism.[22-24] Thus, a low concentration of 5-HIAA could be due to either a low production rate (a defect in serotonin metabolism) or an increased activity of the acid transport mechanism (a membrane phenomenon). This would presume that 5-HIAA concentration is a more sensitive indicator of the activity of the transport mechanism than the other acids. We tend to interpret the data according to the former mechanism, partially because certain animal models of increased "aggression" may be associated with reduced brain serotonin turnover.[10,11]

In another line of investigation, one of the authors has found that the impulsive violent offenders often develop prolonged hypoglycemia due to enhanced insulin secretion after an oral glucose load.[25-27] Futhermore, the hypoglycemia can be aggravated by alcohol. Obviously, interrelationships between low CSF 5-HIAA concentration, drinking history, and the regulation of glucose metabolism need to be further elucidated.

Violent offenders with antisocial personality disorder also had a lower mean CSF HVA concentration than offenders with paranoid or passive-aggressive personality disorder. Any causative significance of the low CSF HVA concentration in patients with antisocial personality disorder awaits further studies.

The implications of our data are limited at the present time. This is because the sample is relatively small and represents an extreme group. However, there may be some persons in whom a defect in central serotonin metabolism is present, who start to abuse alcohol in their early teens and later become violent psychopaths. In such persons experimental treatment with serotonergic drugs should be initiated. This strategy could be used initially in subjects who have a family history of the behavioral disorder.[16]

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