Genetic and Neurochemical Correlates of Violence

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Violence is a complex behavior with multiple causes. Most behavioral phenotypes are not inherited in the same direct sense as, for example, skin color; rather, what is inherited is a multifactorial liability (which, unlike skin color, cannot be directly observed). Liability interacts with a large number of environmental influences; these interactions determine the individual's observed behavior (for example, violence). Thus, there is no genotype that completely determines complex behaviors in humans. Neurochemical traits that are (at least in part) genetically transmitted contribute to the liability for violent behavior. Much of current research into violence explores the role of serotonergic and other neurotransmitter systems. This review is partly based on a book¹ that provides more detailed coverage of genetic and neurochemical correlates of violence.

TWIN STUDIES

Monozygotic (MZ) and dizygotic (DZ) twin pairs were usually compared on concordance rates for criminality or delinquency without separate concordance estimates for violent and non-violent crime. This limits their interpretability for the genetics of violence. In eight early studies of MZ and DZ twins, pairwise concordance for criminality was greater in MZ twins.² A study of a large unselected population of twins showed a large difference in concordance favoring MZ twins and thus supporting genetic influence on criminal behavior.³ However, a study using psychotic subjects⁴ failed to support the findings of greater concordance rates for MZ twins.

Taken together, twin studies tend to support a genetic influence on criminal behavior. However, MZ twins share more environmental influences with each other than DZ twins; environmental effects perhaps raised the monozygotic concordance rates. Thus, twin studies cannot completely separate the genetic from the environmental effects. This separation is accomplished more effectively by adoption studies.

ADOPTION STUDIES

The genetic and environmental effects may be separated when a child is placed in an adoptive home soon after birth: the features (for example, criminality) shared with biological parents may be considered genetic (or at least congenital), whereas those shared with adoptive parents may be environmental in origin. Adoption studies in the United States⁵,⁶ and Scandinavia⁷,⁸ showed concordance between criminal behavior in biological parents and in their adopted-away offspring.

PRE- AND PERINATAL ENVIRONMENTAL INFLUENCES

Recent advances in the understanding of pre- and perinatal events and their effects on the brain have brought into focus the fact that not all congenital abnormalities are genetically transmitted. For example, fetal exposure to alcohol results in aggressive behavior in animals⁹ and in humans.¹⁰ Therefore, if the biological mothers of the adopted-away offspring drank during pregnancy, the elevated criminality among the offspring might be explained by the effects of fetal exposure to alcohol rather than by direct genetic transmission. A genetic effect, however, may be indirect: alcoholism was perhaps genetically transmitted to the mothers. Genetic and environmental (prenatal) effects may thus interact to produce or increase a liability for violent behavior. Genetic and perinatal effects may also interact to affect that liability. Delivery complications may increase the likelihood of violent criminal offending by persons with a family history of mental illness.¹¹

In summary, twin and adoption studies indicate congenital influences on non-violent criminal behavior. The issue of congenital influ-
ences on violent crime is less clear. This evaluation of the data is in agreement with recent reviews. The congenital changes appear, at least in part, genetic in origin, with pregnancy and delivery complications interacting with genetic influences.

Liability for violent behavior is elevated in certain mental disorders that show evidence for genetic transmission (e.g., alcoholism and schizophrenia). These issues are discussed elsewhere.

**NEUROCHEMICAL STUDIES**

**Serotonin**

The neurotransmitter serotonin exhibits inhibitory control over aggression in a large number of animal species. The role of the serotonergic system in human violent behavior has been studied by measuring the cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), by assaying tryptophan content in plasma, and by challenging neuroendocrine functions of central serotonin receptors.

The 5-HIAA level in CSF may reflect central serotonin turnover or presynaptic serotonergic activity in the brain. Low levels of CSF 5-HIAA were discovered in depressive patients who had a history of violent (but not non-violent) suicide attempts. Psychological links between inward and outward aggression have been known for a long time; biological links were substantiated by the discovery that lifetime aggressiveness is negatively related to the CSF levels of 5-HIAA.

This relationship between low CSF 5-HIAA, suicidal behavior, and aggressiveness has been confirmed in a sample of murderers who had a history of alcohol abuse. The murderers whose offense was classified as impulsive had lower CSF 5-HIAA levels than the other offenders. Low levels of CSF 5-HIAA were also reported in arsonists who set fires impulsively. Taken together, these findings led to the proposition that aggressiveness may be the common factor shared by inward and outward aggression. It is not clear whether the serotonergic disturbance reflected by low 5-HIAA levels in CSF underlies violent behavior of patients with schizophrenia. A small negative study did not support this hypothesis.

Tryptophan levels in plasma may contribute to serotonergic mechanisms modulating aggressive behavior. Relatively low plasma levels of tryptophan, the serotonin precursor, were detected in the plasma of alcoholics who reported a history of incarceration for assaultive behavior against people or property. Two small studies reported some beneficial effects of tryptophan treatment in aggressive psychiatric patients.

Neuroendocrine challenges offer an opportunity to indirectly study central serotonergic activity. Fenfluramine releases presynaptic stores of serotonin, blocks serotonin reuptake, and stimulates postsynaptic serotonin receptors. This enhancement of central serotonergic activity is reflected by elevations of prolactin plasma levels. Thus, the size of the prolactin plasma level increase after a single dose of fenfluramine (fenfluramine challenge) is a measure of central serotonin activity.

In patients with personality disorders, the prolactin response was inversely proportional to aggressiveness and impulsiveness. Reduced prolactin response was also related to the history of suicide attempts and alcohol abuse. These results imply a hypofunction of the central serotonergic system in persons prone to impulsive actions, including suicide attempts, alcohol abuse, and aggression.

However, essentially opposite results of a fenfluramine challenge were reported in a sample of drug abusers. A more recent fenfluramine challenge study of detoxified heroin abusers indicated that disturbances of the serotonergic system in these subjects were related to depression but not to aggressive behavior. Taken together, the results of these fenfluramine challenge studies suggest that the hypofunction of the central serotonergic system is linked to impulsive aggression but is limited to a subset of personality disorders yet to be defined. The subset probably includes borderline personality disorder.

Besides fenfluramine, several other agents are used for similar neuroendocrine challenges of the central serotonergic system. One of them is m-chlorophenylpiperazine (m-CPP), a postsynaptic serotonin agonist (and a metabolite of the antidepressant trazodone). Similar to fenfluramine, m-CPP elevates serum prolactin levels; reduced prolactin response (response blunting) reflects a reduction of serotonergic function. Men with the diagnosis of antisocial personality and substance abuse received an m-CPP challenge. The results indicated prolactin response blunting in the antisocial subjects. Psychological assessments suggested that the blunting was associated with assaultiveness and dysphoria but not with impulsivity.

Another challenge method uses prolactin response to buspirone, a serotonin receptor agonist. Prolactin response to buspirone was negatively related to aggressiveness. Thyrotropin-releasing hormone (TRH) stimulates both thyrotropin and prolactin secretion. Blunted prolactin response to TRH was reported in unipolar patients with anger attacks. The attacks were alleviated and the prolactin response was increased after treatment with fluoxetine.

The origin and the nature of the serotonergic dysfunction or functions we discussed remain to be clarified. The dysfunction may be genetically transmitted, perhaps via polymorphism of tryptophan hydroxylase. Experiments in rhesus monkeys demonstrated genetic and rearing environmental contributions to the functions of the central serotonergic system. Brain injury may have contributory effects. It is possible that the dysfunction is linked to alcohol consumption and glucose metabolism.

Cerebrospinal fluid 5-HIAA, plasma trypto-
phan, and neuroendocrine challenges suggest that an unspecified central dysfunction of the serotonergic system is linked to impulsive behavior. Impulsive aggression and violent suicide are subtypes of such behavior. The dysfunction of the serotonergic system is relatively stable (ie, independent of momentary fluctuations in violent or other behavior). This trait nature of the serotonin dysfunction could be an advantage for the potential detection of a propensity for impulsive violent behavior and perhaps for the prediction of dangerousness. Understanding the serotonin function in aggression may lead to specific anti-aggressive treatments.

**Norepinephrine**

Research into the role of norepinephrine in violent or aggressive behavior has generally used similar methods and has been conducted jointly with the serotonin work. Similar to the 5-HIAA relation to the central serotonergic function, the CSF levels of 3-methoxy-4-hydroxy-phenylglycol (MHPG), a metabolite of norepinephrine, are believed to reflect the presynaptic activity of the central noradrenergic system. However, the results with MHPG levels in CSF were less consistent than those obtained studying 5-HIAA.

**Monoamine Oxidase**

Monoamine oxidase (MAO) is involved in the metabolism of serotonin, norepinephrine, and other monoamines. It exists in at least two forms (type A and type B). Both types are present in the brain; type B is in the platelets. Low platelet MAO levels were reported in male student volunteers who had a history of psychiatric contacts or convictions for various offenses. Similar problems occurred among the relatives of the low-MAO subjects. Thus, low MAO levels may be a marker of vulnerability to psychiatric disorders.

Platelet MAO activity was studied in criminal offenders and in control subjects. The subgroup of psychopaths had lower average MAO activity than the other groups, and this difference was significant in comparison with one of the control groups. The authors felt that their results were mediated by sensation-seeking and poor impulse control among their psychopathic subjects. Low MAO activity had been described as a biologic correlate of sensation-seeking. Low-platelet MAO activity was associated with impulsivity and aggressivity (but not with sensation-seeking) in normal men.

Violent behavior was reported in eight male patients located in one large kindred affected by a newly discovered X-linked borderline mental retardation. The locus for this disorder was found in the area on the X chromosome at the locus of MAO type A. Urinalysis showed elevations of MAO substrates and reductions of MAO products. These results imply MAO deficiency.

**Catechol O-Methyltransferase**

Catechol O-methyltransferase (COMT) is important in the initial steps of metabolic transformation of catecholamines. This aspect of its function is thus similar to MAO. By analogy, it would therefore be reasonable to hypothesize that low levels or low activity of the COMT may also elevate the risk for deviant behavior.

The level of COMT enzyme activity is genetically polymorphic in human red blood cells and the liver, with a trimodal distribution of low, intermediate, and high levels of activity. The two alleles responsible for these phenotypic differences were identified. The polymorphism is apparently related to aggressive or threatening behavior in schizophrenic patients. We have replicated this finding in a larger sample; the relationship was present in male but not in female schizophrenics.

**CONCLUSION**

The evidence for a genetically transmitted liability for violence based on traditional twin and adoption studies is somewhat equivocal. Emerging evidence from recent research into genetic and environmental (eg, pre- and perinatal) influences in the same subjects suggests that the liability for violence arises from interactions between these two types of factors.

Physical substrate of the liability for violence is partly neurochemical. The relation between aberrant functioning of the serotonergic system and impulsive violence has been demonstrated in samples of violent criminal offenders, persons with personality disorders, and persons with alcohol use disorders. The evidence in other samples is less clear. Other neurotransmitters, enzymes, and hormones were found to affect violent behavior and are subject to ongoing research. Improved understanding of the underlying neurobiology opens the possibility of rational pharmacologic treatment and prevention of certain types of violent behavior.

**REFERENCES**
