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Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals☆

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Abstract

Considerable evidence indicates that serotonergic mechanisms, particularly the serotonin transporter (5HTT), may mediate central effects of cocaine and may also be involved in impulsive and aggressive behavior. We investigated whether polymorphisms in the 5HTT gene were related to traits of impulsivity, sensation seeking, and aggression among cocaine abusers. Standardized measures of these personality traits were obtained in a sample of 105 severely affected cocaine-dependent African-American subjects and 44 African-American controls. Two polymorphisms of the 5HTT gene were examined involving the 5′ promoter (5HTTLPR) region and a 17 base pair variable-number-tandem-repeat (VNTR) marker among cocaine patients. No significant relationships were observed between polymorphic variants of the 5HTTLPR and VNTR regions and scores on any of the trait measures. Similarly, demographic variables and measures of severity of substance use and depression were unrelated to allele frequencies or genotype distributions of the variants among cocaine patients. As expected, cocaine patients scored significantly higher on total scores of impulsivity, aggression, and sensation seeking compared to controls. The findings do not seem to support an association between these polymorphisms in the 5HTT gene and impulsive-aggressive traits among cocaine-dependent African-American individuals.

Keywords: Serotonin; Genetics; Substance abuse; Personality; Behavior

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1. Introduction

Several studies have found impulsive and aggressive behaviors to be associated with deficits in central serotonin function. For example, reduced concentrations of cerebrospinal 5-hydroxyindolacetic acid (CSF-5HIAA), a serotonin metabolite, have been reported among impulsive and aggressive individuals compared to controls (Linnoila et al., 1983; Stanley et al., 2000). Also, platelet tritiated paroxetine binding, a measure of serotonin uptake sites, has been found to be inversely correlated with impulsivity and aggression among individuals with personality disorders (Coccaro et al., 1996). Although substantial evidence suggests that traits of impulsivity and aggression may be related to cocaine abuse (Brady et al., 1998; Martin et al., 1994), relatively few studies have explored the link between serotonin dysfunction and impulsivity and aggression among cocaine abusers. Most of these studies have utilized hormonal responses to serotonergic agents (e.g. *meta*-cholorophenylpiperazine) and found that alterations in these responses were related to measures of aggression and impulsivity among cocaine abusers (Buydens-Branchey et al., 1997; Handelsman et al., 1998).

Data derived from twin and adoption studies, as well as studies of individuals with personality disorders, suggest that traits of impulsive-aggression may be partially heritable (Coccaro et al., 1993; Plomin et al., 1994). Furthermore, dysfunction of central serotonergic neurotransmission may be one of the genetically and environmentally influenced biological variables that may contribute towards substance abuse (Kendler et al., 1995). Among young rhesus monkeys, heritable influences account for more than 60% of the variance in CSF 5-HIAA metabolite concentrations; moreover, aggressive behavior may be associated with genetically determined concentrations of CSF-5HIAA (Higley et al., 1996). However, among adult human and non-human primates, the influence of heritable factors on the central serotonin turnover is considerably less and environmental factors account for more than 50% of the variance (Higley et al., 1993; Oxenstierna et al., 1986). These findings have led researchers to examine whether variations in genes controlling serotonin metabolism (e.g. the serotonin transporter and the tryptophan hydroxylase genes) may underlie the partially heritable influences on impulsive and aggressive traits among humans. There is some evidence to indicate that a polymorphism in the tryptophan hydroxylase gene may be associated with measures of impulsivity and aggression among normal men and individuals with personality disorders (Manuck et al., 1999; New et al., 1998; Evans et al., 2000).

Recently, the serotonin transporter (5HTT) has generated considerable interest among behavioral genetic researchers due to certain characteristics. The 5HTT regulates the magnitude and duration of serotonergic neurotransmission and serves as an initial target site for antidepressants (Graham and Langer, 1992; Schloss and Williams, 1998). Neuroimaging studies have demonstrated high affinity binding of the cocaine analogue [^{125}I]-RTI-55 to the 5-HTT sites in human brain, suggesting that the HTT may serve as a binding site for cocaine (Staley et al., 1994). Clinical and postmortem studies of cocaine addicts seem to support these findings (Jacobsen et al., 2000; Little et al., 1998). The human 5-HTT protein is found to be encoded by a single and a biallelic repeat polymorphism in the 5′ promotor region of 5-HTT yielding a short and a long variant of the allele (Gelernter et al., 1995; Lesch et al., 1994; Ramammorthy et al., 1993). The short variant has been associated with reduced transcriptional efficiency resulting in reduced serotonin expression and uptake (Lesch et al., 1996). Another polymorphism involves a 17 base pair variable-number-tandem-repeat (VNTR) region located in the second intron of the 5HTT gene with two common alleles and one rare allele (Lesch et al., 1994; Ogilvie et al., 1996). In two large studies from the US, the 5HTTLPR polymorphism was found to be associated with anxiety-related traits (Greenberg et al., 2000; Lesch et al., 1996). Moreover, harm avoidance and the impulsivity and anger-hostility components of neuroticism were strongly associated with the short genotype in Lesch and colleagues' study. Similar results were also obtained from a study of Japanese volunteers (Katsuragi et al., 1999). However, other studies attempting to replicate these findings have