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Polymorphism in the serotonin transporter gene and moderators of prolactin response to *meta*-chlorophenylpiperazine in African-American cocaine abusers and controls ☆

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Abstract

Serotonin (5-HT) function is altered in several psychiatric disorders, including cocaine dependence (CD), and its role in impulsive-aggressive behaviors has been widely studied. However, the relationship between psychopathological and behavioral dimensions and mechanisms of 5-HT alterations remains unclear. We investigated the relationship of a polymorphism in the 5′ promoter region of the serotonin transporter gene (5-HTTLPR) with prolactin (PRL) response to *meta*-chlorophenylpiperazine (*m*-CPP) in a sample of 68 African-American individuals, 35 CD subjects and 33 controls. We also examined whether measures of impulsivity, hostility and sensation seeking influenced the relationship between the 5-HTTLPR polymorphism and PRL response to *m*-CPP in this sample. Individuals with the SS genotype showed significantly heightened PRL response to the challenge compared with the LL and LS genotypes. No influence of gender or substance abuse condition was observed. Hostility was associated with blunted PRL response in the total sample. Cocaine abuse was the most significant moderator of ΔPRL (peak PRL − baseline PRL), and the interaction of genetic, behavioral and psychopathological measures helped predict most of the observed ΔPRL (62.5%). Although these results need replication, variation in the 5-HTTLPR gene appears to influence measures of 5-HT function and interact with disease state and personality dimensions to account for 5-HT disturbances in African-American populations.

Keywords: Serotonin; *m*-CPP; 5-HTTLPR; Substance abuse; Aggression; Behavior

1. Introduction

Altered serotonin (5-HT) function has been suggested in a range of psychiatric illnesses and behavioral phenotypes, including alcohol and cocaine dependence (Johnson, 2004; Muller et al., 2003), with or without heightened impulsivity and hostility (Badaway, 2003; Patkar et al., 2003; Cunningham and Breslin, 2004).

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There is strong evidence linking impulsive and aggressive behaviors with alterations in central 5-HT, not only in clinical populations (Stein et al., 1996), but also in healthy volunteers (Manuck et al., 1998, 2002). Although these findings are well documented, the mechanisms of altered 5-HT function are not known. For example, it is unclear whether 5-HT disturbances predate or are a consequence of substance dependence. One approach to clarify these mechanisms is to examine the relationship between genetic variants and functional expression in a neurotransmitter system.

Genetic studies of the 5-HT system have identified several variations that may have a link with central neurotransmitter function and psychopathology. Among them, the 44-bp insertion/deletion polymorphism in the serotonin transporter gene (5-HTTLPR) has been widely studied. The promoter polymorphism is biallelic, and the short allele is associated with altered activity, reduced transcriptional efficiency (Heils et al., 1996), and lower mRNA production with decreased 5-HT uptake in cultured cells (Lesch et al., 1996). Similar properties of 5-HTTLPR were replicated in some but not all investigations of direct biological indices of 5-HT function, such as platelet 5-HT uptake (Greenberg et al., 1999; Patkar et al., 2004a, b), transporter availability (Little et al., 1998; van Dyck et al., 2004) and CSF 5-hydroxyindolacetic acid (5-HIAA) levels (Jönsson et al., 1998; Williams et al., 2001). Recent studies show that 5-HTTLPR genotypes may in part influence serotonin activity by affecting postsynaptic 5-HT receptor availability (David et al., 2005). This polymorphism has been related to aggression and violence (Arango et al., 2003a,b; Retz et al., 2004), early and severe alcohol dependence (Hallikainen et al., 1999; Feinn et al., 2005) and outcome in cocaine and alcohol abuse treatment (Mannelli et al., 2005). On the other hand, investigations have found no association of 5-HTTLPR with impulsivity, aggression and cocaine abuse (Patkar et al., 2002a,b), heroin dependence (Kotler et al., 1999; Li et al., 2002), or the addictive effects of smoking (Gallinat et al., 2005). Besides possible methodological limitations or influences of concomitant morbidity, the less consistent association of 5-HTTLPR with a risk of substance abuse may be explained by other sources of sample heterogeneity, such as gender and ethnicity (Williams et al., 2003).

Several lines of evidence suggest that neuroendocrine responses to different pharmacologic challenges that result in stimulated 5-HT transmission may be associated with 5-HTTLPR genotypes. For example, a reduced prolactin (PRL) response to clomipramine was found in women with the short allele (Whale et al., 2000). Similar results were obtained following fenfluramine challenge in recovering alcoholics and non-patient male volunteers (Reist et al., 2001), and in healthy subjects of low socioeconomic status (Manuck et al., 2004). Low PRL response to citalopram was also associated with the short/short genotype and specific cerebral metabolic responses in another non-patient group (Smith et al., 2004), while no association was found with depression following dexfenfluramine (Strickland et al., 2003). Among 5-HT challenge agents, *m*-chlorophenylpiperazine (*m*-CPP) shows greater specificity for postsynaptic 5-HT receptors and has considerably lower affinity for the human 5-HT transporter (<4.0) and for dopamine receptors (Hoyer et al., 1994), at the 0.5-mg/kg dose commonly used in oral challenge paradigms (Gijsman et al., 2004). The effects of *m*-CPP on PRL, ACTH/cortisol, temperature and cocaine discriminative stimulus effects have been attributed to partial agonist activity at the 5-HT_{2C} receptor (Murphy et al., 1991; Aulakh et al., 1992; Calogero et al., 1993; Frankel and Cunningham, 2004). *m*-CPP has been widely used to explore central 5-HT receptor function in healthy as well as psychiatrically ill subjects (Kahn and Wetzler, 1991; Murphy et al., 1991; Yatham and Steiner, 1993). *m*-CPP can elicit anxiety, dysphoria and euphoria in normal subjects (Broocks et al., 1998, 2001) and intoxication-like effects in alcohol and cocaine abusers (Buydens-Branchey et al., 1993; Krystal et al., 1994). Cocaine abusers have shown either no difference in PRL response (Handelsman et al., 1998), or a blunted PRL response compared with controls following *m*-CPP stimulation (Buydens-Branchey et al., 1997, 2000; Patkar et al., 2006), similar to alcoholics (Handelsman et al., 1996). Thus, *m*-CPP-induced PRL release seems to be a valid tool to probe the physiological link between 5-HTTLPR genotypes, psychopathological dimensions and behavioral traits.

The objectives of the present study were twofold: First we investigated whether allelic variations in 5-HTTLPR genotypes are associated with the PRL responses to the *m*-CPP challenge in recently abstinent cocaine-dependent individuals and healthy volunteers. Second, we examined the relative contribution of genotype, behavioral measures and cocaine abuse to the *m*-CPP challenge response.

2. Methods

2.1. Subjects

This study was conducted with approval from the Institutional Review Board of Thomas Jefferson University, Philadelphia, PA, in accordance with the