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Low prolactin response to fenfluramine in impulsive aggression

Antonia S. New[a,b,*], Robert F. Trestman[c], Vivian Mitropoulou[d], Marianne Goodman[a,b], Harold H. Koenigsberg[a,b], Jeremy Silverman[b], Larry J. Siever[a,b]

[a]*Psychiatry Service-116A, Bronx VA Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468, USA*
[b]*Department of Psychiatry, Mount Sinai School of Medicine, USA*
[c]*General Clinical Research Center, Mount Sinai School of Medicine, USA*
[d]*Department of Psychiatry, University of Connecticut, USA*

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Abstract

To examine the prolactin (prl) response to d,l-fenfluramine in a large sample of personality disorder patients with impulsive aggression. Patients were screened from clinics at the Bronx VAMC and the Mount Sinai Medical Center and from press releases. One hundred and forty-six personality disorder patients (90M;56F) and 23 normal controls (15M;8F) underwent oral d,l-fenfluramine challenge. The peak change in prolactin(deltapkprl) was calculated by subtracting baseline prolactin from peak response following fenfluramine administration (3 h). Analysis of variance and regression analysis were used to detect group differences in deltapkprl. Deltapkprl in impulsive aggressive men, but not women, with personality disorders was blunted compared with controls. Men with suicide histories also had a blunted deltapkprl compared with those without, which was not accounted for by depression. This study represents a replication of previous studies, in a much larger sample, showing a blunted PRL response to fenfluramine of male patients with personality disorder in relation to impulsive aggression and to suicide attempts.

Keywords: Serotonin; Fenfluramine; Personality disorder; Impulsive aggression

1. Introduction

Impulsive aggression is a common presenting symptom for patients seeking psychiatric treatment. It is seen most commonly in patients with personality disorders, and accounts for a substantial portion of the morbidity and mortality associated with these disorders (particularly borderline and antisocial personality disorders). Impulsive aggression typically manifests in domestic violence, assault, property destruction and suicide attempts. These behaviors result in serious consequences for the interpersonal and occupational functioning of people with this vulnerability as well as for others, and yet little is understood about the neurobiological substrates that predispose to impulsive aggression.

While impulsive aggression is prevalent in patients with personality disorders, only recently have criteria been developed to distinguish those patients with a serious problem of impulsive aggression from those with less severe aggression. This is in part because DSM-IV Intermittent Explosive Disorder excludes patients with a personality disorder, although impulsive aggression most commonly coexists with personality disorders. Revised criteria for Intermittent Explosive Disorder (IED-R) have recently been codified, permitting the diagnosis in the context of a personality disorder (Coccaro et al., 1998). In our sample, 51% of patients with personality disorder meet criteria for IED-R; and of those meeting borderline personality disorder 81% met IED-R, which suggests that disinhibited aggression is closely tied to personality disorders.

Abnormalities in central serotonergic activity have been associated with measures of impulsive aggression in patients with personality disorders (Coccaro et al., 1989a; O'Keane et al., 1992; Siever and Trestman, 1993). Specifically, reductions of serotonergic activity as reflected in diminished cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations have

* Corresponding author. Tel.: +1-718-584-9000x5228; fax: +1-718-364-3576.
E-mail address: antonia.new@med.va.gov (A.S. New).

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been associated with impulsive aggression in patients with personality disorders, as well as in depressed patients, violent alcoholic offenders, mentally disordered violent offenders and normal controls (Lidberg et al., 2000; Linnoila et al., 1989; Linnoila et al., 1994; Roy et al., 1988; Stanley et al., 2000; Traskman-Bendz et al., 1986; Virkkunen et al., 1994). In children with disruptive behavior, low CSF 5-HIAA predicted severity of physical aggression in a 2-year follow-up study (Kruesi et al., 1990).

The association between impulsive aggression and decreased serotonergic activity has also been supported by studies utilizing hormone responses to pharmacologic interventions stimulating the serotonergic system. Prolactin (PRL) response to d,l-fenfluramine, reflecting net serotonergic activity, was blunted in a small number of men with borderline personality disorder compared with other personality disorder patients and normal controls (Coccaro et al., 1989a). This group difference was related to the impulsive aggressive criteria of borderline personality disorder (self-damaging acts, impulsivity, and suicidal gestures and attempts), but not to affective criteria (affective instability and interpersonal difficulties). In addition, PRL responses to fenfluramine were highly correlated with the sub-scales of "assault" and "irritability" from the Buss–Durkee Hostility Inventory (BDHI) but not other sub-scales less specifically related to impulsive aggression. In another study, blunted PRL responses were found in men with antisocial personality disorder (O'Keane et al., 1992). Blunted PRL responses in personality disorder to d-fenfluramine were associated with impulsivity and aggression, although not specifically to borderline personality disorder (Coccaro et al., 1995). Alcoholics show reduced hormone responses to fenfluramine associated with impulsivity (Anthenelli, 1995; Stein et al., 1996), although polysubstance abusers do not (Fishbein et al., 1989; Moss et al., 1990). Children with Attention Deficit Disorder with Hyperactivity (ADDH) and with a family history of aggression also show blunted responses to fenfluramine, while those ADDH without a family history have increased responses (Halperin et al., 1994). The PRL response to other serotonergic agents, such as *meta*-chloropiperazine and ipsapirone, also correlated inversely with impulsive aggression in personality disorders (Coccaro et al., 1995,1997). Studies evaluating PRL responses to serotonergic agonists have been relatively consistent in associating blunted PRL responses with impulsive aggression in personality disorder patients, although not with a specific DSM-IV diagnosis. Finally, support for the role of serotonin in mediating aggression comes from results of our studies using d,l-fenfluramine and *m*-CPP enhanced positron emission tomography, which showed that borderline patients meeting criteria for IED-R have blunted glucose metabolic activation in the cingulate in response to serotonergic activation compared with controls (New et al., 2002; Siever et al., 1999).

Suicide attempts, often viewed as a subtype of aggression, are associated with reduced CSF 5-HIAA in a variety of populations (Asberg, 1997; Asberg et al., 1976, 1987; Banki et al., 1981; Brown et al., 1979, 1982; Lidberg et al., 2000; Ninan et al., 1984; vanPraag, 1983), including personality disorders (Coccaro et al., 1989a). Other studies from our center support correlations between reduced serotonergic activity and self-injurious behavior (New et al., 1997).

The present study represents a new and substantially larger sample of patients with personality disorders who underwent d,l-fenfluramine challenge compared to previous studies. It employs the revised classification of IED-R in the most recent subset of patients studied, allowing a clearer dichotomous relationship between those who do or do not have a primary disorder of disinhibited aggression. Because of the lack of clarity in the phenomenology of the borderline diagnosis, the development of operationalized diagnostic criteria for impulsive aggression allows for a more homogenous study population. This study also differs from previous studies in that it includes both men and women.

2. Materials and methods

Patients were screened from clinics of the Bronx VAMC and the Mount Sinai Medical Center (44%), and from press releases to the public (66%). Patients were excluded if they had evidence of serious medical illness based on history, laboratory or physical examination, a history of substance abuse in the past 6 months, any history of intravenous drug abuse, or a history of alcohol dependence. All patients had a negative urine toxicology screen on the day of the challenge study. All patients were free of medications for at least 2 weeks prior to d,l-fenfluramine challenge (5 weeks for fluoxetine); however, 66% of patients had never had any psychiatric medication and most of those who had taken medication in the past had not done so for many years. All patients were outpatients at the time of the study. Informed consent was obtained from each subject in accordance with institutional guidelines.

Diagnostic evaluation was completed by one or more psychologist. Subjects studied from 1989 to 1994 were assessed using the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer and Endicott, 1978) and the Structured Interview for DSM-III-R Personality Disorders-revised (SIDP-R) (Stangl et al., 1985), including an interview with an informant close to the patient. History of suicide attempts and other self-damaging acts were assigned based on information from unstructured clinical evaluations with a psychiatrist, and from the SADS and the SIDP-R (κ for BPD = 0.81;