Journal of Psychiatric Research 76 (2016) 38–43

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

GH response to intravenous clonidine challenge correlates with history of childhood trauma in personality disorder

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ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form
16 November 2015
Accepted 19 November 2015

Keywords:
Personality disorder
Childhood trauma
Noradrenergic
Clonidine

ABSTRACT

Background: Childhood trauma is a risk factor for personality disorder. We have previously shown that childhood trauma is associated with increased central corticotrophin-releasing hormone concentration in adults with personality disorder. In the brain, the release of corticotrophin-releasing hormone can be stimulated by noradrenergic neuronal activity, raising the possibility that childhood trauma may affect the hypothalamic-pituitary adrenal (HPA) axis by altering brain noradrenergic function. In this study, we sought to test the hypothesis that childhood trauma is associated with blunted growth hormone response to the α-2 adrenergic autoreceptor agonist clonidine.

Methods: All subjects provided written informed consent. Twenty personality disordered and twenty healthy controls (without personality disorder or Axis I psychopathology) underwent challenge with clonidine, while plasma Growth Hormone (GH) concentration was monitored by intravenous catheter. On a different study session, subjects completed the Childhood Trauma Questionnaire and underwent diagnostic interviews.

Results: Contrary to our a priori hypothesis, childhood trauma was associated with enhanced GH response to clonidine. This positive relationship was present in the group of 40 subjects and in the subgroup 20 personality disordered subjects, but was not detected in the healthy control subjects when analyzed separately. The presence of personality disorder was unrelated to the magnitude of GH response.

Discussion: Childhood trauma is positively correlated with GH response to clonidine challenge in adults with personality disorder. Enhanced rather that blunted GH response differentiates childhood trauma from previously identified *negative* predictors of GH response, such as anxiety or mood disorder.

1. Introduction

Childhood trauma, in the form of parental neglect and/or abuse, is a risk factor for later personality disorder symptoms (Luntz and Widom, 1994; Horwitz et al., 2001; Johnson et al., 1999; Johnson et al 2006a,b). While there is an emerging recognition that the development of personality disorder emerges from a complex but not fully understood interaction of genetic and environmental factors (Johnson et al., 2006a,b), childhood trauma may provide a clue regarding which neurobiological factors have a mechanistic role in personality disorder. Research across preclinical and clinical domains has identified the hypothalamic-pituitary axis as one of the primary mediators of the effect of early life trauma on altered adult stress reactivity. Our previous work has examined the relationship between reported early life trauma and adult stress hormone function in adults with personality disorder, finding that childhood trauma is associated with increased central drive of the stress hormone corticotropin-releasing hormone (CRH; Lee et al., 2012). Given that the hypothalamic-pituitary axis can be stimulated by noradrenergic neurons, and that the release of norepinephrine is part of the acute stress response, it is biologically plausible that trauma also has lasting effects on noradrenergic function. The hypothalamic pituitary axis can be activated by the central noradrenergic system, consistent with the role of noradrenergic cell bodies in dynamically modulating arousal and attention to the environment. Other stress-related psychopathologies such as post-traumatic stress disorder have been found to have

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http://dx.doi.org/10.1016/j.jpsychires.2015.11.009
0022-3956/

components of both noradrenergic and HPA-axis dysfunction. There is reason to believe that the noradrenergic system may play a role in trauma-related personality psychopathology. However, empirical data regarding this are not available.

An animal study modelling the effects of maternal maternal care and early life stress on the stress system found evidence that maternal care and stress differentially affect noradrenergic receptor binding in the noradrenergic cell body regions of the brain (Liu et al., 2000). In this study, post-natal handling was found to increase expression of α-2 receptor levels in the locus coeruleus and nucleus tractus solitarius. Extended maternal separation, an animal model of maternal neglect, was not associated with altered α-2 receptor expression, but was found to be associated with greater norepinephrine in dialysate of the paraventricular nucleus of the hypothalamus following restraint stress. Although no clinical research studies have yet examined the relationship between central adrenergic function and childhood trauma, lastingly elevated measures of central catecholamine function have repeatedly been found to be associated with both pediatric and adult post-traumatic stress disorder (reviewed by Pervanidou, 2008).

The growth hormone (GH) response to clonidine challenge has been previously utilized as a pharmacological probe of central α-2 adrenergic receptor function. The α-2 adrenergic receptor is a presynaptic autoreceptor in the locus coeruleus; stimulation of the receptor with clonidine results in decreased firing of noradrenergic neurons. Via stimulation of hypothalamic α-2 receptors, clonidine also facilitates the release of growth hormone via induced release of Growth Hormone Releasing Hormone (GHRH) (Checkley, 1980; Muller et al., 1999). On the basis of this neuroendocrine effect, the GH response to clonidine is considered to be an indirect measure of α-2 receptor sensitivity. The magnitude of GH response has been found to reflect plasma clonidine level (Cubeddu and Hoffman, 1987), as well as the dynamic adrenergic receptor environment (Eriksson et al., 1982).

It remains unknown if history of childhood trauma is associated with abnormal noradrenergic function in non-PTSD adults with personality disorder. To investigate this, a clinical research study was performed using the GH response to clonidine as a probe of central alpha-2 adrenergic receptor function in adults with and without personality disorder. History of childhood trauma was measured using a retrospective instrument, the Childhood Trauma Questionnaire. Based on the existing animal and human data mentioned above, it was hypothesized that the severity of childhood trauma would be related to blunted GH response to clonidine.

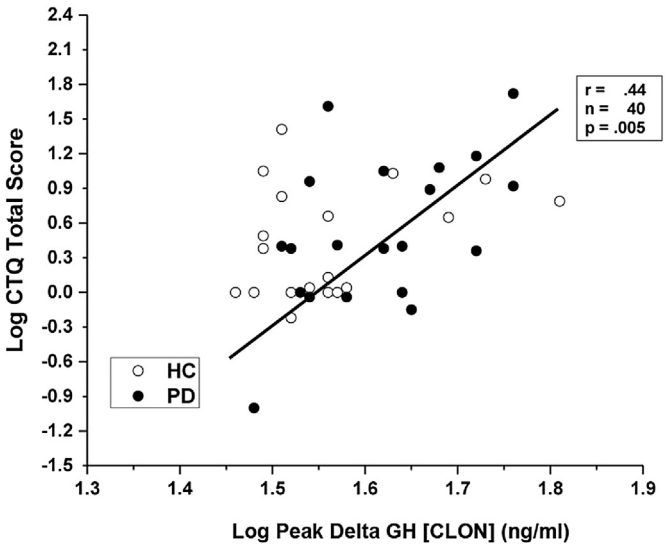

Fig. 1. Correlation between GH Response to Clonidine (Log Peak Delta) and Childhood Trauma (Log CTQ Total Score) in PDs and HCs. In all subjects (n = 40), the log of mean CTQ Total score was positively correlated with the log of peak delta GH response to clonidine (r = .44, n = 40, p = .005).

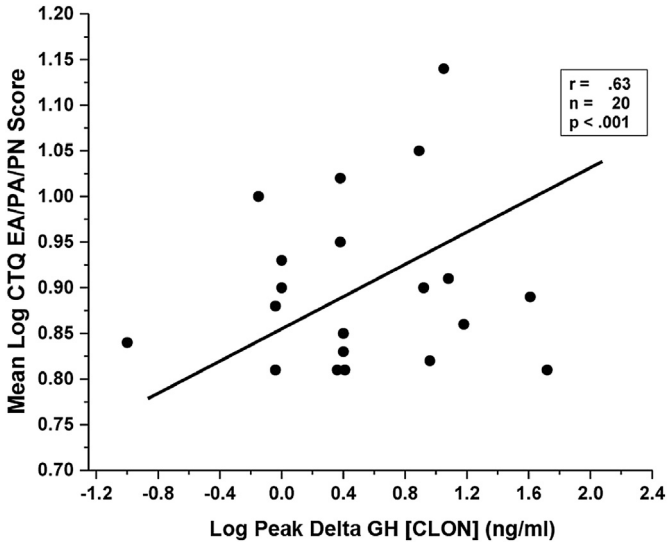

Fig. 2. Correlation Between GH Response to Clonidine (Log Peak Delta) and Childhood Trauma Subscales in PD Subjects. In PD subjects alone (n = 20), Log Peak Delta GH [CLON] was positively correlated with the log of the mean of three CTQ subscale scores (Emotional Abuse, Physical Abuse, Physical Neglect; r = .67, Adjusted R^2 = .34, F [3,16] = 4.27, p = .022).

2. Methods

2.1. Subjects

Twenty subjects with personality disorder and twenty healthy control volunteer subjects participated in this study. All subjects were medically healthy and were systematically evaluated in regard to impulsive, aggressive, suicidal, and other behaviors as part of a larger program designed to study the biological correlates of impulsive aggressive, and other personality-related, behaviors in personality disordered subjects. Personality disordered subjects were recruited by newspaper and public service announcements seeking subjects with, and without, self-reported problems of personality disorder. Healthy control subjects were recruited by newspaper and public service announcements by seeking out subjects interested and willing to participate in biological studies of personality traits. All subjects gave informed consent and signed the informed consent document approved by our Institutional Review Board (IRB) before engaging in any of the studies. Medical health of all subjects was documented by medical history, physical examination, electrocardiogram, and blood hematology, chemistry (including hepatic profile), thyroid function tests, and urinalysis, including a urine screen for drugs of abuse.

2.2. Diagnostic assessment

Personality disorder and syndromal disorder and personality disorder diagnoses were made according to DSM-5 criteria (American Psychiatric Association 2013). Diagnoses were made using information from: (a) the Structured Clinical Interview for DSM Diagnoses [SCID; (First et al., 1997)] for syndromal disorders and the Structured Interview for the Diagnosis of DSM Personality Disorder [SIDP; (Pfohl et al., 1997) for personality disorders; (b)