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Research report

Relationship of temperament and character with cortisol reactivity to the combined dexamethasone/CRH test in depressed outpatients

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ABSTRACT

Background: Evidence shows that depression is associated with hypothalamic–pituitary–adrenal (HPA) axis hyperactivation, although such findings are not entirely unequivocal. In contrast, various psychiatric conditions, including atypical depression, are associated with hypocortisolism. Another line of research has demonstrated that personality is associated with HPA axis alteration. It is thus hypothesized that different personality pathology in depression would be associated with distinct cortisol reactivity.

Methods: Eighty-seven outpatients with DSM-IV major depressive disorder were recruited. Personality was assessed by the temperament and character inventory (TCI). HPA axis reactivity was measured by the combined dexamethasone (DEX)/corticotropin-releasing hormone (CRH) test. According to our previous studies, two subgroups were considered based on their cortisol responses to the DEX/CRH test: incomplete-suppressors whose cortisol response was exaggerated and enhanced-suppressors whose cortisol response was blunted.

Results: The analysis of covariance, controlling for age, gender and symptom severity, revealed that incomplete-suppressors scored significantly higher on cooperativeness than enhanced-suppressors ($p=0.002$). A multivariate stepwise logistic regression analysis predicting the cortisol suppression pattern from the seven TCI dimensions, controlling for age, gender and symptom severity, revealed that lower cooperativeness ($p=0.001$) and higher reward dependence ($p=0.018$) were significant predictors toward enhanced suppression.

Limitations: The neuroendocrine challenge test was administered only once, based on a simple test protocol.

Conclusions: Our findings suggest that (personality-related) subtypes of depression might be differentiated based on the different pattern of cortisol reactivity. Future studies are warranted to further characterize the HPA axis alteration in relation to various subtypes of depression.

1. Introduction

Depression imposes a great burden on afflicted individuals and society, while its pathophysiology remains elusive. One of the repeatedly reported biological abnormalities in depression is the alteration in the hypothalamic–pituitary–adrenal (HPA) axis function (Holsboer, 2000; Kunugi et al., 2010). To quantify the dysregulation of HPA axis, the dexamethasone suppression test (DST) has been enthusiastically studied since Carroll et al. (1981) introduced it as a biological marker for the diagnosis of "melancholia". In serial DST studies, cortisol levels were shown to be increased in depressed patients (e.g., Carroll, 1982). However, it has subsequently become clear that its sensitivity to differentiate depressed patients from healthy controls is not very high (Arana et al., 1985; Braddock, 1986), and elevated cortisol levels were also observed in non-clinical populations under various stressful conditions (Ceulemans et al., 1985; Mellsop et al., 1985). The DST thus failed to fulfill the initial promise as a diagnostic tool for depression.

The dexamethasone (DEX)/corticotropin-releasing hormone (CRH) test, which was developed by Holsboer et al. (1987), Heuser et al. (1994a) in an attempt to enhance the sensitivity of

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the DST, is an integrated challenge test for HPA axis function that combines DEX-pretreatment with CRH administration on the following day; thus, it is essentially a DST followed by CRH challenge. The merit of this combined test is that at the moment of CRH infusion the HPA axis is downregulated due to negative feedback induced by the DEX. A number of independent studies have confirmed that sensitivity of the DEX/CRH test for depression is relatively high (Kunugi et al., 2004; Kunugi et al., 2006; Watson et al., 2006; Ising et al., 2007). However, such findings are not necessarily conclusive because other studies have reported rather low sensitivity of this test for depression, i.e., no more than around 20–30% (e.g., Ising et al., 2005; Nickel et al., 2003; Schüle et al., 2009). Moreover, recent studies using this test have shown that depressed patients exhibit similar (Oshima et al., 2000; Watson et al., 2002; Gervasoni et al., 2004; Van Den Eede et al., 2006), or even attenuated (Rydmark et al., 2006; Veen et al., 2009; Wahlberg et al., 2009) cortisol responses as compared to healthy controls. In these studies, patients had either of the following characteristics: outpatients (Oshima et al., 2000; Gervasoni et al., 2004; Van Den Eede et al., 2006; Carpenter et al., 2009), chronically depressed patients (Watson et al., 2002), depressed patients with psychiatric comorbidity (Veen et al., 2009) or long-term sick-leave patients (Rydmark et al., 2006; Wahlberg et al., 2009). Inconsistent findings across the DEX/CRH studies may therefore result from the heterogeneity of depression, rather than from the limited sensitivity of this neuroendocrine challenge test. A similar interpretation has also been proposed for the original DST (e.g., Fink, 2005).

A promising marker for such phenotypic heterogeneity of depression would be personality traits, given that personality profile of depressed patients is different from that of healthy controls (Enns and Cox, 1997; Bagby et al., 2008) and such profile varies even within depressed patients depending on diagnostic (sub)categories, e.g., melancholic vs. atypical depression (Joyce et al., 2004; Chopra et al., 2005) and bipolar vs. unipolar depression (Bagby et al., 1996; Mendlowicz et al., 2005; Akiskal et al., 2006; Sasayama et al., 2011).

Apart from depression, several lines of research have demonstrated that personality impacts on HPA axis function as measured by the DEX/CRH test. In a non-clinical population, Tyrka and her colleagues have found that low novelty seeking of the Cloninger's temperament dimension (Cloninger et al., 1991), particularly when combined with high harm avoidance, is associated with exaggerated cortisol responses to the DEX/CRH test (Tyrka et al., 2006, 2008). Using another well-established measure of personality, McCleery and Goodwin (2001) observed a relationship between higher neuroticism and blunted cortisol response to this pharmacological challenge test, whereas Zobel et al. (2004) found the opposite relation, i.e., higher neuroticism and greater cortisol response. More specific personality characteristics have also been examined in relation to HPA axis reactivity as measured by the DEX/CRH test. For instance, we reported that non-clinical schizotypal personality to be associated with blunted cortisol response to this test (Hori et al., 2011a). Furthermore, Rinne et al. (2002) observed exaggerated cortisol responses to the DEX/CRH test in female subjects with borderline personality disorder who had a history of sustained childhood abuse. These findings not only suggest that the DEX/CRH test can serve as a useful tool to probe the altered HPA axis function in relation to a wide variety of personality traits but also point to the importance of taking into account blunted cortisol reactivity as well as exaggerated reactivity. Indeed, it is now widely recognized that hypocortisolism, in addition to hypercortisolism, represents impaired HPA axis regulation (Raison and Miller, 2003), which is reflected by the fact that the former has been associated with various stress-related psychopathologies including posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and atypical depression (Heim et al., 2000; Gold and Chrousos, 2002; Fries et al., 2005).

In this context, the present study aimed to explore the relationship between personality traits as assessed by the temperament and character inventory (TCI) (Cloninger et al., 1993) and cortisol reactivity to the DEX/CRH test in depressed outpatients. To this end, we first dimensionally examined this relationship and then compared the personality traits between patients who exhibited exaggerated cortisol reactivity and those who did blunted reactivity. We hypothesized that these two extreme ends of cortisol reactivity would be associated with different temperament/character traits.

2. Methods

2.1. Participants

Eighty-seven depressed outpatients (age range: 21–69; 46 women) were recruited from the outpatient clinic of the National Center of Neurology and Psychiatry (NCNP) Hospital, Tokyo, Japan, or through advertisements in free local magazines and our website announcement. Most of the patients recruited via advertisements or website announcement were regularly attending to a nearby hospital or clinic located in the same geographical area, i.e., the western part of Tokyo. Consensus diagnoses were made based on clinical interviews, observations and case notes by at least two experienced psychiatrists. For those patients under treatment at the NCNP Hospital, the diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Axis I disorders (First et al., 1997). For the remaining patients under treatment at a nearby hospital/clinic, the diagnosis made by his/her attending doctor was confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998; Otsubo et al., 2005) by a trained research psychiatrist. All met the DSM-IV criteria (American Psychiatric Association, 1994) for major depressive disorder (MDD). Patients who were in remission, as defined by the total score on the Hamilton Depression Rating Scale 21-item version (HAMD-21) (Hamilton, 1967) of less than 8, were excluded from the study. Of the total 87 MDD patients, 13 were diagnosed as having comorbid dysthymic disorder. Patients with bipolar disorders were not enrolled as they are shown to have a different personality profile from that of MDD patients (Bagby et al., 1996; Mendlowicz et al., 2005; Akiskal et al., 2006; Sasayama et al., 2011). Patients who were taking carbamazepine were also excluded from the study since it induces dexamethasone metabolism (Privitera et al., 1982). Additional exclusion criteria for study participation were as follows: having a prior medical history of central nervous system disease or severe head injury, having a history of substance abuse/dependence, taking corticosteroids, antihypertensives or oral contraceptives, and being on hormone replacement therapy. The present experiment on our participants was conducted in accordance with the Declaration of Helsinki. After the nature of the study procedures had been fully explained, written informed consent was obtained from all participants. The study was approved by the ethics committee of the NCNP, Tokyo, Japan.

2.2. DEX/CRH test procedure and presentation for neuroendocrine data

The DEX/CRH test was administered to all participants according to a simple test protocol (Kunugi et al., 2006), which was modified from the original protocol of Heuser et al. (1994a). This simple protocol was described in our recent reports (Hori et al., 2010, 2011a, b). Briefly, participants took 1.5 mg of DEX (Banyu Pharmaceutical Corporation, Tokyo, Japan) orally at 2300 h.