



## Relationships between psychological distress, coping styles, and HPA axis reactivity in healthy adults

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### ABSTRACT

Psychological distress and coping styles have been suggested to relate to altered function in the hypothalamic-pituitary-adrenal (HPA) axis, although there remains much to be understood about their relationships. High and low cortisol levels (or reactivity) both represent HPA axis dysfunction, with accumulated evidence suggesting that they are linked to different types of psychopathology. The dexamethasone (DEX)/corticotropin-releasing hormone (CRH) test has been extensively used to identify HPA axis abnormalities in various psychiatric conditions including mood disorders; however, the possible associations of psychological distress and coping styles with HPA axis function have not been well documented using this test. Here, we examined the relationships of HPA axis reactivity as measured by the DEX/CRH test with subjectively perceived psychological distress and coping styles, both of which were assessed with self-report questionnaires, in 121 healthy volunteers. Subjects were divided into three groups by the cortisol suppression pattern, namely the incomplete-suppressors (DST-Cortisol  $\geq 5$   $\mu\text{g}/\text{dL}$  or DEX/CRH-Cortisol  $\geq 5$   $\mu\text{g}/\text{dL}$ ), moderate-suppressors (DST-Cortisol  $< 5$   $\mu\text{g}/\text{dL}$  and  $1$   $\mu\text{g}/\text{dL} \leq$  DEX/CRH-Cortisol  $< 5$   $\mu\text{g}/\text{dL}$ ), and enhanced-suppressors (DST-Cortisol  $< 5$   $\mu\text{g}/\text{dL}$  and DEX/CRH-Cortisol  $< 1$   $\mu\text{g}/\text{dL}$ ). The enhanced-suppressors showed significantly higher scores in obsessive-compulsive, interpersonal sensitivity and anxiety symptoms and significantly more frequent use of avoidant coping strategy, compared to the other two groups. These results point to the important role of enhanced suppression of cortisol, or blunted cortisol reactivity, in non-clinical psychopathology such as avoidant coping strategy and greater psychological distress.

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### 1. Introduction

A wide variety of stress is associated with alteration in the hypothalamic-pituitary-adrenal (HPA) axis function. Studies looking at cortisol as the main output substance of the HPA axis have thus been critical to advancing our understanding of psychobiological underpinnings of various stress-related conditions (de Kloet et al., 2005; Heim et al., 2000). For instance, perceived stress in everyday life (Pruessner et al., 1999), stressful situations such as academic examinations and seafaring (Droogelever Fortuyn et al.,

2004; Liberzon et al., 2008), self-reported symptoms (Van den Bergh et al., 2008), psychological coping styles (Nicolson, 1992; O'Donnell et al., 2008), rejection sensitivity (Tops et al., 2008), sleep status (Backhaus et al., 2004; Lasikiewicz et al., 2008; Wright et al., 2007) and personality profile (Tyrka et al., 2007) have been reported to be associated with alteration in cortisol levels. These studies in healthy subjects have investigated HPA axis function using several different cortisol measures including diurnal cortisol profiles, cortisol awakening response, and cortisol reactivity to psychosocial challenge tests such as Trier Social Stress Test (Kirschbaum et al., 1993).

On the other hand, HPA axis function in clinical populations, particularly in patients with major depression, has been investigated with pharmacological challenge tests including dexamethasone (DEX) suppression test (DST, Carroll et al., 1976) and DEX/corticotropin-releasing hormone (CRH) test (Heuser et al., 1994a;

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Holsboer et al., 1987). The DEX/CRH test 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. In the DEX/CRH test a relatively high dose (i.e., 1.5 mg) of DEX is usually used, whereas DST studies, in particular those which examine the HPA function of post-traumatic stress disorder (PTSD), have used a lower dose (i.e., 0.5 mg or 1 mg) of DEX (e.g., Grossman et al., 2003; Yehuda et al., 2004). Sensitivity of the DEX/CRH test in depressed patients has been shown to be high in prior studies including ours (Heuser et al., 1994a; Kunugi et al., 2004, 2006; Watson et al., 2006b). Moreover, this test has revealed altered HPA axis function in those individuals with specific characteristics: dampened cortisol reactivity in healthy adults reporting childhood emotional abuse (Carpenter et al., 2009), increased cortisol responses in healthy adults reporting childhood parental loss with the exception of attenuated cortisol responses in those with parental desertion and low levels of care (Tyrka et al., 2008b), increased cortisol responses in healthy adults with certain personality traits (Tyrka et al., 2006, 2008a), and attenuated cortisol responses in depressed women on job-stress-related longterm sickleave (Rydmark et al., 2006; Wahlberg et al., 2009). On the other hand, the possible associations of more commonly presented psychopathology such as perceived distress in everyday life and coping styles with HPA axis function have not been well documented using the DEX/CRH test. However, these psychological measures are suggested to relate to altered cortisol level (Heim et al., 2000, 2002; Nicolson, 1992; O'Donnell et al., 2008; Pruessner et al., 1999; Van den Bergh et al., 2008). For instance, severity of daily hassles in the past month was negatively related to cortisol concentrations (Heim et al., 2002). Perceived stress was positively, and burnout was negatively, associated with cortisol levels after DEX administration (Pruessner et al., 1999). Passive coping is suggested to relate to hypocortisolism (Heim et al., 2000). Healthy adults scoring high in either problem engagement or seeking social support showed lower cortisol levels (O'Donnell et al., 2008). Given these findings, it would be of interest to examine HPA axis function in relation to psychopathology at a non-clinical level such as psychological distress and coping styles by using the DEX/CRH test.

Various kinds of psychiatric disorders have been shown to be associated with HPA axis hyperactivity as reflected by the high cortisol levels and impaired negative feedback inhibition due to an impaired corticosteroid receptor function (Holsboer, 2000). On the other hand, a number of psychoneuroendocrinological studies have demonstrated that a variety of conditions are associated with hypocortisolism, including low basal cortisol levels, enhanced sensitivity to the negative feedback, and blunted reactivity of provoked cortisol. Examples of psychiatric conditions characterized by hypocortisolism include PTSD, chronic fatigue syndrome, fibromyalgia and atypical depression (Fries et al., 2005; Heim et al., 2000). Together, while both of these two extremes of cortisol activity can represent HPA axis dysfunction, they are likely to be linked to different types of psychopathology. Concerning hypocortisolism, there remains much to be clarified as to its natural course and meaning. Although hypocortisolism is considered to represent the result of prolonged stress exposure (Fries et al., 2005; Heim et al., 2000; Ising et al., 2005), a condition so-called "allostasis" (McEwen, 2003), there also exists some evidence suggesting that this state could be a preexisting vulnerability to stress-related disorders (Delahanty et al., 2000; Wahlberg et al., 2009; Yehuda et al., 2000).

Arginine vasopressin (AVP), in addition to CRH, is an HPA axis secretagogue. AVP produced in parvocellular neurons of

hypothalamic paraventricular nucleus (PVN) and secreted into pituitary portal vein system plays an important role in stress response (Herman, 1995; Romero and Sapolsky, 1996). It is reported that, in chronic stress paradigms, the expression of AVP in parvocellular neurons increases and pituitary V1b receptor, through which AVP stimulates the ACTH secretion, up-regulates (Aguilera et al., 1994; Aguilera and Rabadan-Diehl, 2000). There also exist clinical studies that support this notion. For example, de Kloet et al. (2008) have recently reported elevated plasma AVP levels in veterans with PTSD. Watson et al. (2006a) measured plasma AVP levels after pre-treatment of DEX in patients with chronic depression and those with bipolar disorder, and found significantly higher post-DEX AVP levels in the patient groups than in healthy controls, suggesting that post-DEX AVP levels could be more sensitive than baseline AVP levels in detecting HPA axis abnormalities. These findings raise the possibility that the post-DEX AVP measure may help understand whether the hypocortisolism, if present, is a result of chronic HPA axis overactivity or a preexisting vulnerability factor for psychopathology.

In this context, the present study sought to examine the relationships between subjectively perceived psychological distress, psychological coping styles and the cortisol suppression pattern to the DEX/CRH test in non-clinical volunteers. We also examined the relationships of these psychological measures with the post-DEX AVP level to see whether the possible low cortisol levels would reflect allostatic shift or preexisting vulnerability. The study hypothesis was that the higher cortisol levels (or less suppression of cortisol) and/or lower cortisol levels (or more suppression of cortisol) would be related to greater distress and a unique pattern of coping strategies. If the low cortisol, together with elevation of AVP, is related to these psychological measures, it would indicate allostatic shift; while if the low cortisol, together with no elevation of AVP, is related to such psychological measures, it may indicate preexisting vulnerability.

## 2. Materials and methods

### 2.1. Participants

From February 2006 to December 2008, 121 healthy volunteers (age range: 20–70; male, 28, female, 93) were recruited from the community, through advertisements in free local information magazines which contained a wide variety of information including healthcare-related information and by our website announcement. Participants were interviewed using the Japanese version of the Mini-International Neuropsychiatric Interview (MINI, Otsubo et al., 2005; Sheehan et al., 1998) by research psychiatrists (H.H., Y.O., T.T. and H.K.), and only those who demonstrated no current Axis I psychiatric disorders, including PTSD, were enrolled in this study. In addition, those who demonstrated one or more of the following conditions during a non-structured interview by an experienced psychiatrist were excluded from this study: past or current contact to psychiatric services, taking psychotropic drugs or had a history of regular use of psychotropics, and the other obvious self-reported signs of past primary psychotic and mood disorders as well as PTSD. Additional exclusion criteria were as follows: having a prior medical history of central nervous system disease or severe head injury, having major systemic medical illnesses, having a history of substance dependence or abuse, or taking corticosteroids or anti-hypertensive medication. No subjects reported that they were on oral contraceptives or estrogen replacement therapies. The present experiments on our subjects were conducted in accordance with the Declaration of Helsinki. After the nature of the study procedures had been fully explained, written informed consent was obtained

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