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Salivary alpha-amylase and cortisol responsiveness following electrical stimulation stress in obsessive–compulsive disorder patients

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ABSTRACT

Salivary α-amylase (sAA) serves as a marker of sympathoadrenal medullary system (SAM) activity. Salivary AA has not been extensively studied in obsessive–compulsive disorder (OCD) patients. In the current study, 45 OCD patients and 75 healthy volunteers were assessed with the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS), the Profile of Mood State (POMS), and the State-Trait Anxiety Inventory (STAI). Measures of heart rate variability (HRV), sAA, and salivary cortisol were also obtained following the application of electrical stimulation stress. The Y–BOCS and POMS Tension–Anxiety, Depression–Dejection, Anger–Hostility, Fatigue, and Confusion scores were significantly increased in patients with OCD compared with healthy controls. In contrast, Vigor scores were significantly decreased in patients with OCD relative to scores in healthy controls. There was no difference in HRV between the patients and the controls. Salivary AA levels in female and male OCD patients were significantly elevated relative to controls both before and after electrical stimulation. In contrast, there were no differences in salivary cortisol levels between OCD patients and controls. The elevated secretion of sAA before and after stimulation may suggest an increased responsiveness to novel and uncontrollable situations in patients with OCD. An increase in sAA might be a characteristic change of OCD.

1. Introduction

Obsessive–compulsive disorder (OCD) is common psychiatric disorder with a 2%–3% lifetime prevalence worldwide (Valleni-Basile et al., 1994; Sasson et al., 1997; Kessler et al., 2005). OCD is characterized by intrusive and inappropriate recurrent thoughts, impulses or images (obsessions) and repetitive behaviors or mental acts (compulsions) (Goodman et al., 1991). Psychiatric interest has concentrated on the specific interactions between stress and OCD (Sasson et al., 1997). Extensive research has associated OCD with abnormal functioning of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis modulates neurohormonal responses to maintain homeostasis in response to stressors (Herman and Cullinan, 1997). Increased activity of the HPA axis in OCD has been reported. Corticotropin releasing hormone (CRH) levels in the cerebrospinal fluid (CSF) have been found to be significantly higher in patients with OCD than in healthy controls (Altemus et al., 1992). Nocturnal adrenocorticotropic hormone (ACTH) and cortisol levels have also been observed to be significantly increased in OCD patients compared with controls (Kluge et al., 2007). Importantly, stress is often a major trigger for the onset of OCD symptoms. Limbic–hypothalamic–pituitary–adrenal (LHPA) axis abnormality has also been reported in patients with OCD. The pituitary gland plays a major role in regulating the body's physical response to stress. Pituitary volumes were significantly smaller in patients with OCD than in healthy controls (MacMaster et al., 2006; Atmaca et al., 2009). OCD patients who have never been treated with medications have smaller pituitary glands relative to the pituitary glands of

Abbreviations: ACTH, Adrenocorticotropic hormone; ANOVA, Analysis of variance; ANS, Autonomic nervous system; CgA, Chromogranin A; Dex/CRH, Combined dexamethasone suppression/ corticotropin releasing hormone stimulation test; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; ELISA, Enzyme-linked immunosorbent assay; Gal-G2-CNP, 2-Chloro-4-nitrophenyl-4-O-β-D-galactopyranosylmaltoside; HAM-D, Hamilton Rating Scale for Depression; HF, High-frequency; HPA, Hypothalamic–pituitary–adrenal; HRV, Heart rate variability; LC, Locus coeruleus; LF, low-frequency; MDD, Major depressive disorder; OCD, Obsessive–compulsive disorder; SAM, Sympathoadrenal medullary; SNRI, Selective norepinephrine reuptake inhibitors; SNS, Sympathetic nervous system; MINI, Mini-International Neuropsychiatric Interview; POMS, Profile of Mood Statec; S.D., Standard deviation; SNP, Single nucleotide polymorphism; SSRI, Selective serotonin reuptake inhibitors; sAA, Salivary α-amylase; STAI, State-Trait Anxiety Inventory, Y–BOCS, Yale–Brown Obsessive–Compulsive Scale

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people who are on medication or individuals without OCD (Jung et al., 2009). Medication may increase the size of the pituitary in people with OCD, and the increase in size may improve regulation of the body's stress response. There are several reports that deserve mention, e.g. lower responses of the HPA axis to stressors described in subjects with high trait anxiety (Jezova et al., 2004) and in patients with panic disorder (Jezova et al., 2010). Some reports indicate that measurement of salivary α-amylase (sAA) measurement may be informative not only as an indicator of autonomic changes but also as a marker for anxiety reports. Higher adrenaline concentrations have been reported in patients with panic disorder (Jezova et al., 2010), which is consistent with current data.

The sympathoadrenal medullary (SAM) system is also associated with anxiety and arousal (Aston-Jones et al., 1994, 1998; Southwick et al., 1999; Berridge and Waterhouse, 2003; Wetherell et al., 2006). It has been suggested that sAA is an index of SAM activity. The basis of this theory is that the sympathetic and parasympathetic branches of the autonomic nervous system innervate the salivary glands. Sympathetic stimulation increases salivary protein secretion, whereas parasympathetic stimulation increases salivary flow rate (Baum, 1993). SAA activity is positively correlated with the acute sympathetic nervous system (SNS) stress response in children and adults (Nater et al., 2006; Gordis et al., 2007). Unlike most salivary analytes, which are actively transported or passively diffused into saliva from plasma (e.g., cortisol and, testosterone), sAA is an enzyme that is locally produced by salivary glands in the oral mucosa. The salivary glands are innervated by sympathetic and parasympathetic nerves, and salivary secretions from various glands (e.g., parotid, submandibular, and sublingual) arise in response to neurotransmitter activation. This suggests that sAA is a prime candidate to measure autonomic activity (Garrett, 1999; Nater et al., 2005). Moreover, studies by Chatterton and colleagues have linked sAA to the SNS component of the stress response (Chatterton et al., 1996, 1997). Only a few studies have failed to observe changes in sAA in response to stressful stimuli including noise (Morrison et al., 2003), the heel prick test in neonates (Schaffer et al., 2008), or a strange situation paradigm (Hill-Soderlund et al., 2008). However, many studies suggest that plasma norepinephrine levels related to the locus coeruleus/autonomic nervous system activity and the stress response in humans can be estimated via the concentrations of sAA. The relationship between OCD and electrical stimuli remains unstudied. Several studies suggest a connection between pain tolerance or sensitivity and emotional distress, such as guilt (Leyro et al., 2010; Bastian et al., 2011). Recently, we reported that sAA and cortisol levels in unremitted patients were significantly elevated compared with levels in controls. Salivary AA levels were significantly correlated with Hamilton Depression Scale (HAM-D) scores in unremitted patients with major depressive disorder (MDD) (Ishitobi et al., 2010). We also reported that sAA levels in female MDD patients were significantly elevated relative to controls both before and after electrical stimulation, while there were no differences in salivary cortisol levels between MDD patients and controls (Tanaka et al., 2012a). We reported that in panic disorder, sAA levels in the alprazolam responder group were significantly elevated compared with the non-responder group and with controls both before and after electrical stimulation (Tanaka et al., 2012b).

In this study, we electrically activated the SAM and HPA systems in patients with OCD and examined the resultant biochemical effects. Our hypotheses predicted between-group differences in sAA and cortisol responsiveness. Changes in autonomic measures were expected to parallel changes in sAA and salivary cortisol levels across the groups.

2. Methods

2.1. Participants

Participants comprised 45 patients with OCD and 75 healthy controls. Patients were interviewed by a psychiatrist using a semi-functional interview based on the DSM-IV (the Mini-International Neuropsychiatric Interview, MINI). A control group composed of healthy volunteers was recruited from the Oita University Hospital staff. Exclusion criteria included a prior history of OCD incidents, a first-degree relative with a history of OCD incidents, a body mass index of 32 or greater, the use of steroid-based medications within the past 3 years, and current tobacco use. Subjects were also asked to refrain from eating 3 h before arrival at the hospital and to refrain from taking medication 5 h before arrival. All subjects provided written informed consent following a description of the procedures and risks, and all subjects had the opportunity to ask questions about the study. The study protocol was approved by the Ethics Committee of the Medical Faculty, Oita University, Japan.

Patients with a current primary diagnosis of OCD were included. Diagnostic exclusion criteria included: any other mental disorders revealed by the MINI (excluding anxiety disorder) and any acute and/or chronic medical illness as assessed by a physical examination and routine laboratory examination. Patients were carefully matched on these variables with healthy control subjects (except for the use of pharmaceutical drug treatments). A total of 62 patients were approached. Fifteen patients did not meet the inclusion criteria, and two patients dropped out during the procedure.

During the interview, the Yale–Brown Obsessive–Compulsive Scale (Y–BOCS) (Goodman et al., 1989) and the Global Assessment of Functioning (GAF) scale were administered. The Y–BOCS is a clinician-administered semi-structured interview and has been regarded as the gold standard for assessing severity of OC symptoms. Its effective use in different ethnic groups has been established (Garnaat and Norton, 2010).

The final study sample consisted of 45 patients with a primary diagnosis of OCD, with 11 of these having a secondary diagnosis of panic disorder. The patients were recruited from patients undergoing their first examinations in the psychiatry outpatient department at Oita University Hospital. Three patients also suffered from generalized anxiety disorder. The mean age of onset of OCD was 28.6 (S.D.=12.4) years of age. All 45 patients were on various drug treatments at the time of testing, including selective serotonin reuptake inhibitors (SSRIs; $n=41$) and tricyclic antidepressants (TCA, $n=4$).

Healthy control subjects ($n=75$) were recruited at Oita University and were matched by age and gender to the patient sample. Of 186 volunteers, six were excluded due to a current or lifetime major mental disorder as revealed by the MINI. From the remaining 182 volunteers, 75 were selected to provide close matches to the 45 patients with respect to age and gender. Table 1 summarizes the characteristics of patients and matching controls.

2.2. Stimulation

Subjects wore stimulator coils, which were connected to a stimulator, on the wrist. This device provided electrical current to the motor and sensory fibers of the median nerve in the right wrist. Subjects were stimulated incrementally until their threshold stimulus, defined as the maximum tolerable stimulus, was reached. We determined the threshold stimulus at the same time that subjects were electrically stimulated for the experiment. To determine the maximum tolerable stimulus, we gave subjects the following instruction: "If you are not able to bear the pain, please inform us". The greatest stimulus lasted 40 s. The whole stimulation period lasted 60–100 s. The mean amplitude of electrical stimulation was between 16 and 22 mA (Table 2). Subjects were told that the level of electrical stimulation would be sufficient to cause pain but would not cause burning or other injury. All participants were tested in the afternoon between 13:00 and 17:00 h. Participants were instructed to refrain from smoking, physical exercise, eating, or drinking caffeinated beverages at least 1 h before testing and after electrical stimulation.

Table 1
Demographic and medical characteristics by group.

	Control	OCD	p or χ^2
N	75	45	
Age (years)	32.7 ± 6.0	34.0 ± 14.0	0.24
Sex (female/male)	28/47	19/26	0.49
Comorbidity (%)	0(0)	14 (31.1)	0.00
Y–BOCS	4.8 ± 1.8	28.1 ± 7.5	0.00

Note. Values are expressed as number, mean (S.D.), or percent Y–BOCS=Yale–Brown Obsessive–Compulsive Scale

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