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Neither cortisol nor brain-derived neurotrophic factor is associated with serotonin transporter in bipolar disorder

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Abstract
Converging evidence indicates the hypothalamus-pituitary-adrenal axis and serotonergic neurons exert reciprocal modulatory actions. Likewise, brain-derived neurotrophic factor (BDNF) has been implicated as a growth and differentiation factor in the development of serotonergic neurons. The aim of this study was to examine the interaction of cortisol and BDNF on serotonin transporter (SERT) in bipolar disorder (BD). Twenty-eight BD and 28 age- and gender-matched healthy controls (HCs) were recruited. ^{123}I-ADAM with single-photon emission computed tomography (SPECT) was applied for measurement of SERT availability in the brain, which included the midbrain, thalamus, putamen and caudate. Ten milliliters of venous blood was withdrawn, when the subject underwent SPECT, for the measurement of the plasma concentration of cortisol and BDNF. SERT availability was significantly decreased in the midbrain and caudate of BD compared with HCs, whereas plasma concentration of cortisol and BDNF did not show a significant difference. The linear mixed-effect model revealed that there was a significant interaction of group and cortisol on SERT availability of the midbrain, but not BDNF. Linear regression analyses by groups revealed that cortisol was associated with SERT availability in the midbrain in the HCs, but not in BD. Considering previous studies, which showed a significant association of cortisol with SERT availability in the HCs and major depressive disorder

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(MDD), our result replicated a similar finding in HCs. However, the negative finding of the association of cortisol and SERT availability in BD, which was different from MDD, suggests a different role for cortisol in the pathophysiology of mood disorder.

1. Introduction

Serotonin is one of the most extensively studied neurotransmitters in the human brain and plays a critical role in influencing human emotion and cognition (Schmitt et al., 2006). Evidence suggests a possible role of the serotonergic system in the etiology of bipolar disorder (BD) (Sobczak et al., 2002). The serotonin transporter (SERT) is a key regulator of central serotonergic activity. Through its role in the reuptake of serotonin, SERT functions to terminate serotonin action at the synapse. Over the past 20 years, molecular imaging, in particular positron emission tomography (PET) and single photon emission computed tomography (SPECT), has allowed for elucidation of the essential contribution of the SERT to the pathophysiology of various psychiatric disorders and psychotropics affecting the serotonergic system (Huang et al., 2010; Spies et al., 2015). Despite limited research data, it has been demonstrated that SERT availability in the midbrain is decreased in the depressive state of BD, however, inconsistent changes in SERT availability has observed in the thalamus, dorsal cingulate cortex, medial prefrontal cortex, and insula (Cannon et al., 2006, 2007; Oquendo et al., 2007). Using single photon emission computed tomography (SPECT) and the novel radiotracer [(^{123})I]-2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine ([(^{123})I]ADAM), we reported that SERT availability in the midbrain was decreased in euthymic BD. In particular, decreased SERT availability closely correlated with illness duration (Chou et al., 2010). However, the mechanism leading to the decreased SERT availability is not clear.

Serotonin is involved in stress adaptation and the regulation of autonomic and endocrine responses to stress. It has been suggested that serotonergic neurotransmission can facilitate and inhibit the hypothalamic–pituitary–adrenal (HPA) axis (Lowry, 2002). Animal studies have shown a profound influence of acute and chronic stress on the release and reuptake of serotonin, on extracellular serotonin levels, and on pre-synaptic and post-synaptic serotonin receptors in raphe nuclei (Lanfumey et al., 2008). Human studies have shown an association between cortisol level and SERT availability in healthy subjects (Frokjaer et al., 2013; Tsai et al., 2012) and in those with major depressive disorder (MDD) (Tsai et al., 2013). An altered HPA axis has been documented in BD (Schmider et al., 1995). However, studies exploring the relationship between cortisol level and SERT availability in BD are lacking.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family. BDNF plays a part in the birth, maturation, differentiation, migration, and survival of neurons, and is necessary for the growth, synaptic plasticity, and long-term potentiation of dendrites (Maisonpierre et al., 1990). It has been demonstrated that BDNF levels decrease during manic and depressive episodes in treated and drug-free BD and that the levels are correlated negatively with symptom severity (Machado-Vieira et al., 2007). Therefore, BDNF has been suggested to be an important mediator in the etiology of BD (Grande et al., 2010; Rakofsky et al., 2012). In animal studies, BDNF has been demonstrated to have a key role in the development and functionality of serotonergic neurons (Daftary et al., 2012; Djalali et al., 2005). Accordingly, interaction of the HPA axis, BDNF and SERT may serve an important role in the etiology of BD.

The aim of the present study was to determine whether the association between cortisol level and SERT availability previously observed in healthy and MDD subjects could be replicated in BD. Additionally, the effect of BDNF level on SERT was measured to explore the interaction between BDNF and SERT.

2. Experimental procedures

The study protocol was approved by the Human Ethics Committee of Taipei Veterans General Hospital (Taipei, Taiwan). All subjects were referred from the Department of Psychiatry and provided written informed consent to participate in the study. SPECT was conducted at the Department of Nuclear Medicine.

2.1 Patient selection

Twenty-eight subjects with euthymic BD and 28 age- and gender-matched healthy controls (HCs) were recruited. Each HC was interviewed by a trained psychiatrist using the Mini-International Neuropsychiatric Interview to exclude the possibility of major psychiatric disorders, or a history of substance abuse. BD patients fulfilled three inclusion criteria: (i) diagnosis of BD type I according to the text revision of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (known as the DSM-IV-TR), (ii) under stable treatment and in a euthymic state, and (iii) stable treatment with valproic acid only for at least two months. The dosage could be flexible initially but need to be fixed thereafter during this two-month period. Previous treatment with antidepressants (if any) should have been discontinued $\geq$1 year prior. The euthymic state was defined as a total score $<$10 on the Montgomery-Åsberg Depression Rating Scale (MADRS), and a total score $<$7 within an 8-week consecutive period on the Young Mania Rating Scale (YMRS). Patients with a history of suicide attempts were excluded. Current substance abusers and individuals with a history of substance abuse, as well as pregnant or breast-feeding women, were also excluded. Only non-smokers were recruited. All participants were of Taiwanese origin.

2.2 Radiochemistry

^{123}I-ADAM was synthesized and prepared by the Institute of Nuclear Energy Research (Taoyuan, Taiwan). Preparation of ^{123}I-ADAM is described elsewhere (Oya et al., 2000). Briefly, 100 mg of a tin precursor of ADAM was reacted with $\approx$5.55 GBq (150 mCi) of Na^{123}I in the presence of hydrogen peroxide in dilute acetic acid. The reaction was quenched 5 min later with $NaHSO_3$. After