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Research report

Association between the serotonin transporter and cytokines: Implications for the pathophysiology of bipolar disorder

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ABSTRACT

Background: Reduced brain serotonin transporter (SERT) has been demonstrated in bipolar disorder (BD). The aim of this study was to explore the potential role of cytokines on reduced SERT in BD.
Methods: Twenty-eight BD type I patients and 28 age- and gender-matched healthy controls (HCs) were recruited. Single photon emission computed tomography with the radiotracer 123I ADAM was used for SERT imaging. Regions of interest included the midbrain, thalamus, putamen and caudate. Seven cytokines, including tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1α (IL-1α), IL-1β, IL-4, IL-6 and IL-10, were measured using an enzyme linked immune-sorbent assay. Results: SERT availability in the midbrain and caudate was significantly lower in BD compared to HCs. IL-1β was significantly lower, whereas IL-10 was significantly higher in BD compared to HCs. Multiple linear regression analyses revealed that there were associations between cytokines, IL-1α, IL-1β, IL-6 and SERT availability in the midbrain but not in the thalamus, putamen and caudate. Furthermore, linear mixed effect analyses demonstrated that these associations were not different between HCs and BD.
Conclusion: While many cytokines have been proposed to be important in the pathophysiology of BD, our results demonstrated that significant associations between cytokines and SERT availability may explain the role of cytokines in mood regulation. However, these associations were not different between HCs and BD, which imply the role of these cytokines is not specific for BD.

1. Introduction

Serotonin is one of most extensively studied neurotransmitters in the brain. Serotonin affects our emotion and cognition (Elliott et al., 2011; Schmitt et al., 2006). Previous evidence has suggested the potential role of the serotonergic system in the etiology of mood disorders, including bipolar disorder (BD) and major depressive disorder (MDD) (Sobczak et al., 2002). The serotonin transporter (SERT) is a key regulator of central serotonergic activity, controlling the reuptake of serotonin and thereby terminating its action at the synapse. Importantly, brain imaging studies have demonstrated reduced SERT availability in the midbrain during depressive (Cannon et al., 2006; Oquendo et al., 2007) or euthymic state of BD (Chou et al., 2010). However, the underlying mechanism is unknown.

Cytokine abnormalities have been proposed to play a pivotal role in the pathophysiology of MDD (Maes, 1995). Until recently, a growing body of evidence, represented mainly by the finding of increased circulating levels of pro-inflammatory cytokines, suggests that immune-mediated mechanisms are related to the neurobiology of BD and its neuro-progression (Barbosa et al., 2014; Goldstein et al., 2009). One of the hypotheses was that pro-inflammatory cytokines stimulate the enzyme indoleamine 2,3-dioxygenase, which converts tryptophan into kynurenine (KYN), resulting in the reduction of the availability of tryptophan, the precursor for serotonin. Pro-inflammatory cytokines also enhance the activity kynurenine-3-monooxygenase, the enzyme that degrades KYN into 3-hydroxykynurenine, shifting the KYN pathway into the production of neurotoxic metabolites (Dantzer et al., 2011). Several meta-analyses have investigated immune function in BD with a particular focus on cytokine alterations (Modabbernia et al., 2013; Munkholm et al., 2013a, 2013b). Although these meta-analyses supported peripheral inflammatory alterations in BD,

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differences in the samples examined make it difficult to generate definite conclusions.

The interaction of cytokines and SERT availability has become the focus of recent studies. A number of pro-inflammatory cytokines, including TNF-α (Mossner et al., 1998a), interleukin-1β (Ramamoorthy et al., 1995), interferon-α, and interferon-γ (Morikawa et al., 1998), have been shown to up-regulate the SERT in cell models. In contrast, interleukin-4, an anti-inflammatory cytokine in the central nervous system, was reported to reduce the uptake of serotonin in a dose-dependent manner (Mossner et al., 2001). These findings suggest that a fine-tuned mechanism exists to communicate the state of the immune response in the central nervous system by differential modulation of the SERT via pro-inflammatory and anti-inflammatory cytokines (Baganz and Blakely, 2013). In the current study, we select the most frequently reported cytokines in literature and examine their interactions with SERT availability.

Previous methods to image SERT in vivo had been hampered by the lack of a suitable radiotracer due to limitations in low signal-to-noise ratio and low selectivity for SERT in different brain regions (Kuikka et al., 1995; Pirker et al., 2000). ^{123}I-ADAM has been demonstrated to be a suitable radiotracer for imaging SERT in the brain regions of midbrain, thalamus, caudate and putamen but not for hippocampus (Chou et al., 2009b). By using ^{123}I-ADAM, we have recently reported there was an association of IL-10 and thalamic SERT availability in euthymic BD (Hsu et al., 2014) but not in other brain regions, including the midbrain, putamen and caudate. This result suggested there might be regional effects of cytokines on SERT availability in different brain regions. Thus, using a within subject study design, this study aimed to examine the interaction between seven cytokines and SERT availability in different brain regions of BD. On the basis of our previous data, we hypothesized the interaction of cytokines and SERT availability is different across individual brain regions between BD and HCs.

2. Materials and methods

This study was approved by the Human Ethical Committee of Taipei Veterans General Hospital. All subjects were referred from the Department of Psychiatry. Single photon emission computed tomography (SPECT) was performed at the Department of Nuclear Medicine.

2.1. Subject selection

Twenty-eight patients with euthymic BD and 28 age- and gender-matched healthy controls (HCs) were recruited. All subjects provided their informed consent prior to entering the study. Each HC was interviewed by a trained psychiatrist using the Mini-International Neuropsychiatric Interview (M.I.N.I.) to exclude the possibility of co-morbidity with major psychiatric illnesses, or history of substance abuse. BD patients fulfilled the following inclusion criteria: (i) diagnosis of BD type I according to the DSM-IV-TR, (ii) under stable treatment in the euthymic state, and (iii) received treatment with valproic acid only. Past use of antidepressants, if any, should have been discontinued for at least one year. Patients who had a past history of suicide attempt were also excluded. Euthymic state was defined as Montgomery–Åsberg Depression Rating Scale (MADRS) scores of less than 10 and Young Mania Rating Scale (YMRS) scores of less than 7 within an eight-week consecutive period. In addition, all participants who had the following conditions were excluded: demonstrated any infectious disease in the previous two weeks, as well as allergies, dermatitis, fibromyalgia, autoimmune disorders, neuro-inflammatory disorders or any medical illness that would require pharmacological treatment with glucocorticoids. Pregnant or breast feeding females were also excluded. Only non-smokers were recruited. All participants were of Taiwanese origin.

2.2. Radiochemistry

^{123}I-ADAM was synthesized and prepared under good manufacturing practice standards by the Institute of Nuclear Energy Research, Taiwan. Preparation of ^{123}I-ADAM has been published elsewhere (Oya et al., 2000). Briefly, 100 mg of a tin precursor of ADAM was reacted with approximately 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 $NaHSO_3$. Following neutralization, the reaction solution was loaded onto an octyl cartridge (Accubond, J&W Scientific, Folsom, CA, USA) and eluted. An injection solution was prepared in 50% (v/v) ethanol. Purified ^{123}I-ADAM was eluted from the cartridge using absolute ethanol and further diluted with a 0.9% saline solution to a specific activity of greater than 12,000 Ci/mmole. The radiochemical purity of ^{123}I-ADAM was normally more than 90%, as determined by high-pressure liquid chromatography on a Hamilton PRP-1 column (4.1×250 mm^2; Hamilton Co., Reno, NV, USA). Elution was performed via an isocratic acetonitrile/5 mM dimethyl glutaric acid (pH 7.0) 90:10 solution at a flow rate of 1 ml/min.

2.3. SPECT measurement

Each subject received one SPECT measurement for SERT imaging and one magnetic resonance image (MRI) to exclude the possibility of an organic lesion in the brain and for co-registration of the brain anatomical location. Thirty minutes after an oral 180 mg $KClO_4$ solution was performed for the protection of thyroid SPECT, a bolus intravenous injection of 5 mCi (185 MBq) ^{123}I-ADAM was performed using a two-head gamma camera system (E-Cam variable angle, Siemens Medical Systems Inc.) equipped with high resolution fan-beam collimators. The system resolution was 7.3 mm. Each subject received a SPECT static measurement 240–270 min after ^{123}I-ADAM injection. All scanning data were collected in step-and-shoot mode at 3° intervals over 360°, while 30-s projection views were obtained from each camera head. The radius of rotation was fixed at 13.5 cm. The image matrix size was 128×128, and the pixel size was 3.9 mm. All images were obtained through a filtered back projection reconstruction algorithm with a Metz filter using a Nyquist frequency cutoff at 0.55 and an order of 30. Photon attenuation correction was performed using Chang's method ($\mu = 0.12$ cm^{-1}) (Chang, 1978), and no scatter correction was employed. To minimize variability in SERT availability introduced by the effect of menstrual cycle (Maswood et al., 1999), all premenopausal female subjects were measured in the follicular phase of their menstrual cycle by oral report.

2.4. MRI acquisition

Each subject was subjected to T1-weighted MRI to confirm the absence of organic lesions in the brain and to co-register with SPECT images for the delineation of anatomical locations. MRI were obtained using a 1.5 T GE scanner Excite-II system (TR/TE = 8.54 ms/1.836; FOV = $260 \times 260 \times 1.5$; Matrix = $256 \times 256 \times 124$; NEX = 1; TI = 400 ms; Flip angle = 15; BW = 15.63).

2.5. Regions of interest (ROIs) defined

ROIs were drawn manually on an individual transaxial MRI image and co-registered with the SPECT image using a pixel-wise modeling tool PMOD version 3.0 software (PMOD Group, Zurich, Switzerland), implemented on a personal computer. The ROIs were selected a priori, which contained SERT-rich regions of the midbrain, thalamus,