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Distribution volume ratio of serotonin and dopamine transporters in euthymic patients with a history of major depression — a dual-isotope SPECT study

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ABSTRACT

Serotonin transporter (SERT) and dopamine transporter (DAT) levels differ in patients with major depression who are in a depressed state in comparison with healthy controls. The aim of this study was to examine the distribution volume ratios (DVRs) of SERT and DAT in drug-free and euthymic patients with a history of major depression. Subjects comprised 13 patients with a history of major depression and 26 sex- and age-matched healthy controls. The euthymic state of depression was defined as a score of 7 or less on the Hamilton Depression Rating Scale. The DVRs of SERT and DAT were approximated using SPECT, with [^{123}I] 2-((2-((dimethylamino)methyl)phenyl)thio)-5-iodophenylamine (ADAM) and [^{99m}Tc] TRODAT-1 as the ligands, respectively. There were no significant differences in the DVRs of SERT or DAT between healthy subjects and euthymic patients with a history of major depression; hence, the SERT and DAT DVRs may not therefore be trait markers for patients with major depression, which helps us to understand more about the pathophysiology of depression.

1. Introduction

The monoamine hypothesis of depression suggests that depletion of monoamine neurotransmitters such as serotonin, norepinephrine and dopamine in the central nervous system may be the pathophysiological basis of depression; however, the precise role of each neurotransmitter in major depression is still under debate.

Previous studies have revealed a decrease in the regional cerebral blood flow in depressed patients (Martinot et al., 1990; Bench et al., 1995; Yao et al., 2008), which returns to levels within the normal range after recovery from depression (Kocmur et al., 1998; Navarro et al., 2002; Ishizaki et al., 2008). Brain activity is also altered before and after treatment for depression (Goodwin et al., 1993). The changes in regional cerebral blood flow and brain activity suggest that the changes in brain function caused by depression may be functionally reversible. Besides regional cerebral blood flow and brain activity, the serotonergic system also plays an important role in the pathophysiology of major depression. A decreased midbrain serotonin transporter (SERT) distribution volume ratio (DVR) in drug-naïve patients with major depression compared with healthy subjects has been reported (Newberg et al., 2005; Parsey et al., 2006; Joensuu et al., 2007), and the diencephalon SERT DVR has also been found to be decreased in depressed patients, this variation being sex-specific and age-dependent (Staley et al., 2006). The magnitude of the decrease in the midbrain SERT DVR was found to be correlated with the severity of depressive symptoms (Newberg et al., 2005; Lehto et al., 2006); however, in other studies, no correlation was observed (Parsey et al., 2006; Joensuu et al., 2007). In addition to these results in patients with major depressive disorder, Lehto et al. also identified a decreased SERT DVR in atypically depressed patients and melancholic patients compared with healthy subjects, and atypical Hamilton Depression Rating Scale (HDRS) scores were found to be associated with midbrain SERT density, which suggests a relationship between serotonergic dysfunction and atypical depression. In other illnesses such as seasonal affective disorder or Wilson's disease, a decreased SERT DVR in drug-free depressed patients has also been documented (Willeit et al., 2000; Hesse et al., 2003).

In addition to the serotonergic system, the dopamine system is also involved in the pathophysiology of depression (Klimke et al., 1999), and a decrease in the dopamine transporter DVR has been found in several studies (Meyer et al., 2001; Neumeister et al., 2001). However, some studies have reported a higher dopamine transporter DVR in patients with major depression in comparison with control

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groups (Laasonen-Balk et al., 1999; Brunswick et al., 2003; Amsterdam and Newberg, 2007; Yang et al., 2008). In patients with Parkinson's disease, a decreased DAT DVR was found to be associated with the development of affective symptoms (Weintraub et al., 2005). With regards to dopamine D_2/D_3 receptors, several studies have reported no difference between depressed patients and healthy controls (Klimke et al., 1999; Yang et al., 2008).

Effective treatments for depression including pharmacotherapy and psychotherapy may result in an increased SERT DVR (Laasonen-Balk et al., 2004; Klein et al., 2006; Lehto et al., 2008a). With regard to the dopaminergic system, dopamine D_2 receptor binding was found to be increased in treatment responders and decreased in non-responders among patients with major depression (Klimke et al., 1999). The DAT DVR has also been observed to be correlated with antidepressant treatment response (Yang et al., 2008). Both dopamine and serotonin levels have been found to be altered after recovery from depression (Laasonen-Balk et al., 2004); however, studies in which that observation was made focused only on change in the DVR of DAT or SERT after recovery from depression (Laasonen-Balk et al., 2004; Lehto et al., 2008a,b), and no study has compared the DVR of DAT or SERT in patients in a euthymic state and those with major depressive disorder. In addition, some of the participants in the study by Laasonen-Balk et al. (2004) were even prescribed antidepressants, and there were no controls. In contrast, only normalization of frontal cerebral perfusion was noted in a single photon emission computed tomography (SPECT) study (Navarro et al., 2002), which suggests that certain neuroanatomic regions of the central nervous system may be functionally and reversibly involved in major depression. Our hypothesis is that the DVRs of SERT and DAT return to normal in euthymic and drug-free patients with a history of depression, and the aim of this study was therefore to investigate the DVRs of SERT and DAT in euthymic and drug-free patients with a history of major depression.

2. Methods

2.1. Subjects

We recruited 13 patients (5 males and 8 females) with a history of major depression who fit the criteria of major depressive disorder according to the DSM-IV; these patients had been experiencing a major depressive episode for 9.12 ± 8.57 years and had been drug-free for more than 3 months, with a mean drug-free duration of 31.92 ± 26.57 months. The average age of the males in the patient group was 37.40 ± 8.32 years (range: 25–47 years) and of the females was 42.63 ± 8.75 years (range: 30–52 years). We also recruited 26 healthy volunteers from the community (10 males and 16 females) who were matched for age and gender. In the healthy group, the average age of the males was 36.81 ± 8.63 years (range: 24–51 years) and of the females was 43.49 ± 9.31 years (range: 28–53 years) (Table 1). All participants, including both the patients and controls, were interviewed by a senior psychiatrist using the Chinese version of the Mini-International Neuropsychiatric Interview to exclude any psychiatric problems (Sheehan et al., 1998). In addition, the exclusion criteria for all participants were a history of significant physical illness, illegal drug usage and cigarette smoking. None of the participants used over-the-counter botanical therapy. All participants in the study underwent a complete physical examination and laboratory evaluation, including blood sugar, HbA1c and MRI, to rule out sub-clinical medical conditions.

Before any procedure was performed, informed consent was obtained from the participants with a history of major depression and the healthy volunteers. The Ethical Committee for Human Research at the National Cheng Kung University Hospital had approved the study protocol. The 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) was used and all patients were in a euthymic state, which was defined by a HDRS score less than 7 (mean = 4.15; S.D. = 1.68). The items in the HDRS related to insight were excluded from this study because these items were not applicable to the controls. The exclusion criteria included 1) a current diagnosis of dysthymia or other mental disorders; 2) serious suicidal risk; 3) any acute or unstable medical condition; and 4) concomitant use of ECT, antipsychotics or antidepressants within the last 3 months. All participants, patients and controls, were assessed using the recent life change questionnaire (RLCQ) (Pai et al., 1985), which was developed and modified from the Schedule of Recent Experience (Rahe, 1975; Miller and Rahe, 1997) and is used to collect information regarding subjects' recent life changes (i.e., in the past 12 months).

2.2. Image studies

2.2.1. SERT DVR in the midbrain

Before SPECT examination with [^{123}I] ADAM, the thyroid gland was protected with 9 ml of Lugol's solution. For brain SPECT imaging, each participant was intravenously administered 185 MBq (5 mCi) of [^{123}I] ADAM in a quiet environment about 10 min after insertion of the intravenous lines. We used a triple-headed rotating gamma camera (Siemens Medical Systems, Hoffman Estates, IL, USA) with fan-beam collimators, which yielded an image resolution of approximately 8.5 mm FWHM. A 20% energy window was symmetrically placed at 159 keV. The SPECT images were acquired over a circular 360° rotation of 120 steps, at 50 s/step, in a $128 \times 128 \times 16$ matrix. The images were reconstructed using Butterworth and Ramp filters (cut-off frequency = 0.3 Nyquist; power factor = 7) with attenuation by Chang's method. The reconstructed transverse images were then realigned parallel to the canthomeatal line, and were of a slice thickness of 2.89 mm.

For semi-quantitative analysis, six consecutive transverse slices on which the midbrain was best visualized were combined to obtain a 17.34-mm-thick slice. The [^{123}I] ADAM SPECT images were acquired in both early (10 min after injection) and late (6 h after injection) phases after IV injection of 185 MBq [^{123}I] ADAM. The early-phase images represent blood–brain barrier transit and mimic cerebral blood flow images, while the late-phase images represent SERT distribution. In this two-step analysis, the late-phase images were co-registered to the early images. The regions of interest (ROIs) of the midbrain (the specific binding sites where SERT is located) and cerebellum (the non-specific site where SERT is lacking) were then manually drawn over the early images, in which the midbrain and cerebellum were better delineated. In addition, magnetic resonance imaging (MRI) (Signa CV-I, 1.5 Tesla, GE Medical Systems, Milwaukee, WI, USA) was used as a rough guide (non-registered) for defining the midbrain and the cerebellum in the SPECT images. SERT binding sites in the midbrain were drawn manually and normalized to the cerebellum (calculated by (midbrain–cerebellum)/cerebellum or the (Mb–Cb)/Cb ratio) by an experienced nuclear medicine specialist who was blind to the participants' clinical data (Yang et al., 2007; Huang et al., 2010).

2.2.2. DAT DVR in the striatum

For brain imaging, each subject was intravenously administered 740 MBq (20 mCi)-TRODAT-1 (a radio-labeled form of tropan derivative for selective labeling of DAT) in a quiet environment about 10 min after insertion of the intravenous line. The SPECT data were obtained using an energy window of 15% centered on 140 keV (Hwang et al., 2004). Imaging of [^{99m}Tc]-TRODAT-1 was initiated approximately 240 min after injection with [^{99m}Tc]-TRODAT-1 and the SPECT images obtained were similar to those produced by SPECT with [^{123}I] ADAM. The data of six consecutive transverse slices (17.34 mm in thickness) with the most intense striatal activity were summed. ROIs were drawn manually over the left and right striatum and the occipital area using individual MRI scans as a reference (non-