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ORIGINAL PAPER

Teijamari Laasonen-Balk · Heimo Viinamäki · Jyrki T. Kuikka · Minna Husso-Saastamoinen · Johannes Lehtonen · Jari Tiihonen

^{123}I-β-CIT binding and recovery from depression

A six-month follow-up study

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Abstract Eighteen depressive outpatients were investigated using single-photon emission computerized tomography (SPECT) with a high-affinity dopamine (DA) and serotonin transporter (SERT) specific radioligand, ^{123}I-labeled β-CIT (2β-carbomethoxy-3β-(4-iodophenyl)-tropane). The patients were tested at the beginning of the study and on follow-up after six months. The severity of depression was evaluated using the 17-item Hamilton Rating Scale of Depression (HRSD). Eight of the eighteen patients had an HRSD score below the median (12 points) on follow-up, and they had a significantly greater increase in ^{123}I-β-CIT binding in the midbrain region compared with those patients who did not recover (ANCOVA: $F = 8.12$; $df = 1, 14$; $p = 0.013$). These results indicate that recovery from depression is associated with an increase in ^{123}I-β-CIT binding in the midbrain.

Key words depression · serotonin transporter · SPECT · recovery · β-CIT

T. Laasonen-Balk, MD (✉)
Mental Health Center
Armilankatu 44
53100 Lappeenranta, Finland
Tel.: +358-5/6164262
Fax: +358-5/6164278
E-Mail: teijamari.laasonen-balk@lappeenranta.fi

T. Laasonen-Balk, MD · H. Viinamäki, MD, PhD · J. Lehtonen, MD, PhD
Department of Psychiatry
Kuopio University Hospital
70210 Kuopio, Finland

J. T. Kuikka, PhD · M. Husso-Saastamoinen, PhL
Department of Clinical Physiology and Nuclear Medicine
Kuopio University Hospital
70210 Kuopio, Finland

J. T. Kuikka, PhD · J. Tiihonen, MD, PhD
Niuvanniemi, Hospital
70240 Kuopio, Finland

J. Tiihonen, MD, PhD
Department of Psychiatry
University of Helsinki
PO Box 320
00029 HUS, Finland

T. Laasonen-Balk, MD
Department of Psychiatry
South Karelia Central Hospital
Valto Käkelänkatu
53130 Lappeenranta, Finland

EAPCN 458

Introduction

^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)tropane (^{123}I-β-CIT) has been used as a SPECT radiotracer to study presynaptic serotonin (SERT) and dopamine (DA) transporter densities in monkeys and in humans (Neumeyer et al. 1991, Laruelle et al. 1993, Kuikka et al. 1995, Tiihonen et al. 1995, 1997). β-CIT binds to both the SERT transporter and the DA transporter (Boja et al. 1992, Little et al. 1993, Bergström et al. 1994, Staley et al. 1994). According to Kuikka et al. (1995), when using β-CIT SPECT in the living human brain, the most prominent SERT activity was found in the medial frontal cortex, hypothalamus, midbrain and occipital cortex, and the greatest DA activity in the basal ganglia. Human studies have shown displacement of midbrain β-CIT uptake by citalopram (Pirker et al. 1995). It may be assumed that some component of β-CIT midbrain uptake is linked with simultaneous binding to the DA transporter in the substantia nigra.

Because depression is a severe disorder but one from which the majority of patients can recover, longitudinal comparison of patients before and after care is possible in order to study neurobiological changes associated with recovery. Some studies have indicated that impaired regional cerebral blood flow (rCBF) (Goodwin et al. 1993, Bonne et al. 1996, Ogura et al. 1998) and lowered SERT levels (a case study) (Viinamäki et al. 1998) in major depression will improve after successful treatment and recovery. Observing the rCBF was not a specific method but it might indicate that reduced rCBF in depression is a state-related property. Ebert et al. (1996)

compared the dopamine D_2 receptor density of depressed patients with that of controls and suggested that lower levels of striatal dopamine are released in depressed patients with psychomotor retardation. They also suggested that an improvement in depression may lead to an increase in striatal dopamine turnover. An increase in dopamine D_2 receptor binding during serotonin reuptake inhibition was found in the striatum and anterior cingulate gyrus in treatment responders, but not in non-responders (Larisch et al. 1997). In one study a depressive group showed a significant linear correlation between treatment response and change in D_2 receptor binding in the basal ganglia during treatment. D_2 receptor binding increased in responders and decreased in non-responders (Klimke et al. 1999).

Malison et al. (1998) have demonstrated in their cross-sectional study a decrease in SERT density in the midbrain regions of subjects with major depression. However, we are not aware of any studies that have compared the specific SERT density of depressed outpatients before and after recovery. In the present study we tested the hypothesis that recovery from depression is associated with an increase in ^{123}I-β-CIT binding in the midbrain.

Materials and methods

The study protocol was approved by the Research Ethics Committee of Kuopio University Hospital. After a complete description of the study to the patients, written informed consent was obtained. The study group consisted of 18 outpatients with depression who were evaluated at the Department of Psychiatry, Kuopio University Hospital. The inclusion criterion was a current diagnosis of depression according to ICD-10 assessed by the attending psychiatrist. Diagnoses were verified by a separate investigator using the Structured Clinical Interview for DSM-III-R (SCID-I) (Spitzer et al. 1992). The severity of depression was assessed at the beginning of the study and on follow-up after six months with the 17-item HRSD (range 0–52) (Hamilton 1960). The mean HRSD score was 13.9 (SD 6.7) at baseline and 9.8 (SD 6.1) on six-month follow-up, and Cronbach's α was 0.76 and 0.78, respectively. Diagnoses were major depression (72%) and other depression (28%) like reactive depression and dysthymia. The same investigator carried out all evaluations and was blind to the study design.

None of the patients were taking psychopharmaceutical medication before the first assessment. During the follow-up period, after the first SPECT scan, six patients used benzodiazepines, one patient the antidepressant moclobemide and temazepam, one the antidepressant amitriptyline and diazepam and one the antidepressant venlafaxin. Before the second SPECT scan, all patients had been drug-free for at least one month. As the depression of the patients was relatively mild, they were treated primarily with supportive therapeutic interactions and counseling.

After six months of follow-up the median HRSD was 12.0. We then divided the patients according to their HRSD score on follow-up into two groups: the responders (HRSD score below 12 points) and the non-responders (HRSD score 12 or more). The mean HRSD score on follow-up was 3.9 (SD 3.1) among responders and 14.6 (SD 2.7) among non-responders. The mean age of responders was 36.4 (SD 11.8) and that of non-responders 47.7 (SD 4.5). The group of responders consisted of 1 man and 7 women while the non-responding group comprised 4 men and 6 women. When recovery was defined according to the criteria defined by Frank et al. (1991), 7 subjects had an HRSD score of 7 points or less (responders), and 11 scored more than 7 points (non-responders).

A dose of 110–185 MBq of ^{123}I-β-CIT (supplied by MAP Medical Technologies Oy, Tikkakoski, Finland) was administered intravenously in a dimly lit and quiet room. Affinity, radiolabeling, radiochemical purity, radiopharmaceutical safety and the dosimetry of ^{123}I-β-CIT have previously been presented (Neumeyer et al. 1991, Kuikka et al. 1993, Bergström et al. 1994, Kuikka et al. 1994). The specific activity was greater than 1.1 x 10^{14} Bq/mmol. The average radiation load received by the subjects was 4 mSv, as given by the effective dose equivalent (Kuikka et al. 1994). The SPECT scans were performed 1h and 21–24h after injection of the tracer using a three-head Siemens MultiSPECT 3 gamma camera equipped with fan beam collimators. The methods have earlier been presented in detail (Laasonen-Balk et al. 1999). The SPECT scans were performed at the baseline and after six months of follow-up. The person analyzing the SPECT data was blind to the clinical outcome of the patients. The specific binding in the midbrain was calculated from 1 hour data as (midbrain – cerebellum)/cerebellum.

Statistical analysis was carried out using SPSS 8.0. Means, standard deviations (SD), frequencies and percentages were used to describe the continuous variables. Groups were compared using the non-parametric Mann-Whitney U-Test with two-tailed p-values. For correlation analyses we used Spearman's correlation for non-parametric and non-normally distributed variables. The correlation between the change in ^{123}I-β-CIT specific binding in the midbrain and the decrease in the HRSD total score was calculated by using a second-degree polynomial fit. Two-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to compare the means of the dependent variable in relation to two grouping variables. Values at the beginning of the study and after six months were compared using the non-parametric Wilcoxon's Two-Related-Samples Test. P-values of less than 0.05 were considered statistically significant.

Results

The specific binding in the midbrain region was 1.29 (SD 0.13) at the beginning of the study and 1.31 (SD 0.12) on six-month follow-up (Table 1). The decrease in the HRSD scores (0–6 months) explained 40% of the change in ^{123}I-β-CIT binding in the midbrain (Fig. 1).

When assessing the increase in ^{123}I-β-CIT binding for the midbrain region, age and gender were used as covariates. The difference between the responders (n = 8) and the non-responders (n = 10) was statistically significant (ANCOVA: F = 8.12; df = 1, 14; p = 0.013) (Table 1). When the recovery criteria of Frank et al. (1991) were

Table 1 The specific binding in the midbrain region at baseline and after six months of follow-up among responders (R) and non-responders (NR)

Recovery criteria by using median HRSD

	R (n = 8)	NR (n = 10)	p-value
Midbrain: baseline	1.25 (SD = 0.14)	1.32 (SD = 0.12)	NS
after 6 months	1.35 (SD = 0.10)	1.28 (SD = 0.13)	0.019
Change	+0.10	–0.04	0.013

Recovery criteria of Frank et al. (1991)

	R (n = 7)	NR (n = 11)	p-value
Midbrain: baseline	1.26 (SD = 0.15)	1.31 (SD = 0.12)	NS
after 6 months	1.35 (SD = 0.10)	1.29 (SD = 0.13)	ns
Change	+0.09	–0.02	0.020

NS not significant

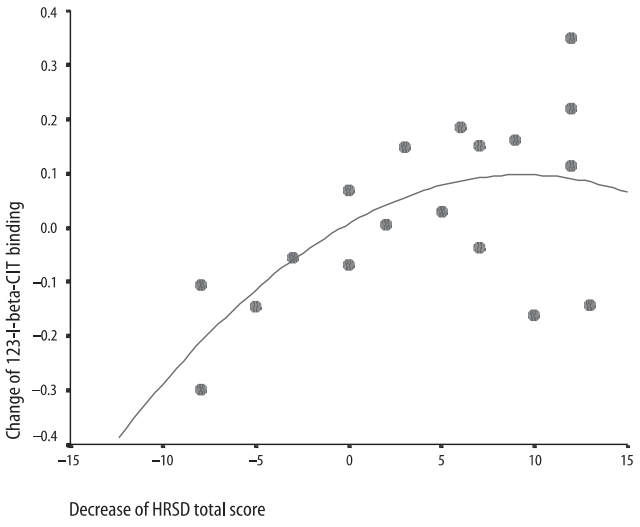

Fig. 1 Change in [^{123}I]-beta-CIT specific binding in the midbrain in relation to decrease in HRSD total score in depression ($R^2 = 0.403$; $p < 0.02$). A second degree polynomial was used in data fit

used (responders = 7 or less points and non-responders = more than 7 points), the difference in the increase in ^{123}I-β-CIT binding (= change) between responders (n = 7; change = + 0.09) and non-responders (n = 11; change = – 0.02) remained significant (ANCOVA: F = 6.91; df = 1, 14; p = 0.020). The difference between the responders and the non-responders in ^{123}I-β-CIT binding of the midbrain region at the six-month follow-up was also statistically significant (ANCOVA: F = 6.98; df = 1, 14; p = 0.019).

Discussion

We made a longitudinal comparison of patients before and after recovery from depression during six months of follow-up and found that the patients who recovered had a significantly greater increase in ^{123}I-β-CIT binding in the midbrain than non-recovered patients. This might imply that SERT density in the midbrain increases during recovery from depression. If our patients had had more severe depression and more patients had been treated with adequate antidepressant medication, it might have caused more notable difference in ^{123}I-β-CIT binding between recovery and non-recovery groups.

We found that in those patients who did not recover from depression during the six months of treatment, ^{123}I-β-CIT binding remained at the same level or even decreased. According to Malison et al. (1998), the decrease in SERT density in depression may be a consequence of transporter downregulation, which may result from 1) a marker for a primary, perhaps etiologic defect in the development or functioning of the 5-HT system, or both, 2) an adaptive, perhaps compensatory attempt by neurons to overcome another etiologic factor, or 3) an unrelated and perhaps secondary sequela of another primary, etiologic lesion. Malison et al. (1998) concluded that the decrease in SERT density may be due to an increased level of extracellular 5-HT.

Our patients did not get any antidepressant medication before the first SPECT scan, and three patients treated with antidepressants during follow-up had at least one month drug free period before the second SPECT scan. We postulate that this arrangement minimized the influence of antidepressant medication on tracer uptake, although the influence of long-term antidepressant medication remains unknown. In this study we did not analyze treatment associations because our study design was observational and therefore there is always a possible two-way process; undertreatment may lead to a worse clinical state, or a worse clinical state may lead to more treatment.

When considering our sample size (n = 18), the use of the median HRSD as a means of differentiating responders and non-responders was appropriate. However, by using two different methods when dividing the groups the findings were similar. This was a strength. One limitation of this study was the small sample size and so we could not totally exclude the possibility of a type 2 statistical error.

We have previously reported a significantly higher ^{123}I-β-CIT uptake in both sides of basal ganglia in patients with major depression compared with controls (Laasonen-Balk et al. 1999). We suggested that up-regulation of the DAT may be the primary alteration, which leads to a lower intrasynaptic dopamine concentration and lower striatal dopaminergic neurotransmission. However, the results of the present study, together with those of Malison et al. (1998), suggest that depression is associated with a decrease in SERT density in the midbrain. Because monoamine pathways are closely related, we assume that recovery from depression may be associated with both dopaminergic and serotonergic neurotransmission. Increase in recovery from depression shows as increase in ^{123}I-β-CIT binding in the midbrain. Our results will require further longitudinal study.

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