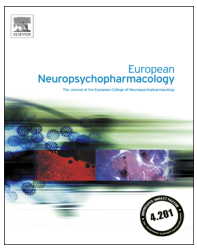
European Neuropsychopharmacology (2015) 25, 873–881

www.elsevier.com/locate/euroneuro



Altered serotonin and dopamine transporter availabilities in brain of depressed patients upon treatment with escitalopram: A [^{123}I]β-CIT SPECT study

A. Rominger[a,*], P. Cumming[b], M. Brendel[a], G. Xiong[a], C. Zach[a], S. Karch[c], K. Tatsch[d], P. Bartenstein[a], C. la Fougère[e], W. Koch[a,1], O. Pogarell[c,1]

[a]Department of Nuclear Medicine, Ludwig-Maximilians-University of Munich, Munich, Germany
[b]Department of Psychiatry, University of Oslo, Oslo, Norway
[c]Department of Psychiatry, Ludwig-Maximilians-University of Munich, Munich, Germany
[d]Department of Nuclear Medicine, Municipal Hospital Karlsruhe Inc., Karlsruhe, Germany
[e]Department of Nuclear Medicine, University of Tubingen, Tubingen, Germany

Received 25 March 2014; received in revised form 25 November 2014; accepted 24 December 2014

KEYWORDS
SPECT;
Major depressive disorder;
[^{123}I]β-CIT;
Escitalopram;
DAT;
SERT

Abstract
Altered SERT and DAT availabilities during treatment with escitalopram were investigated with [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) SPECT in a series of patients fulfilling the criteria for unipolar major depressive disorder (MDD). 27 patients (10 m, 42±16 y) with diagnosis of MDD were recruited for the study. All patients underwent neuropsychiatric testing for assessment of Hamilton Depression (HAM-D) and Beck Depression Inventory (BDI) scores. At baseline, [^{123}I]β-CIT SPECT recordings were acquired 4 h (SERT-weighted) and 20-24 h p.i (DAT-weighted). Follow-up scans and neuropsychiatric testing were performed after six weeks of stable escitalopram medication. Voxel-wise parametric maps of specific/ non-specific ratios-1 ($\sim BP_{ND}$) were calculated. At baseline, DAT-weighted BP_{ND} was 5.06±0.81 in striatum and SERT-weighted BP_{ND} was 0.94±0.18 in thalamus. There were significant negative correlations with age for DAT in striatum ($R=-0.60$; $p<0.01$) and SERT in thalamus ($R=-0.45$; $p<0.05$). Under SSRI treatment there was an apparent 42% occupancy of SERT in thalamus ($p<0.0001$), whereas DAT availability increased significantly by 20% in striatum ($p<0.001$); higher apparent SERT occupancy in thalamus was associated with lesser DAT increase in striatum ($R=-0.62$;

*Corresponding author. Tel.: +49 89 4400 74650; fax: +49 89 4400 77646.
E-mail address: axel.rominger@med.uni-muenchen.de (A. Rominger).
[1]Both authors share senior authorship.

http://dx.doi.org/10.1016/j.euroneuro.2014.12.010

$p<0.005$). The low apparent SERT occupancy may be confounded by alterations in SERT expression during treatment. Thus, [^{123}I]β-CIT SPECT revealed age-dependent declines in DAT and SERT availabilities in un-medicated MDD patients, comparable to that seen previously in healthy controls. At follow-up, the SSRI-evoked increase in DAT was less pronounced in the older patients, even though apparent SERT occupancy and clinical improvement were not age-dependent. Present findings may have implications for escitalopram dosage and side effect profile in younger MDD patients.

1. Introduction

Selective serotonin reuptake inhibitors (SSRI) are now widely used in the pharmacotherapy of depression and other psychiatric disorders in which brain serotonin is implicated (Schatzberg, 2000), and are characterised by a lower incidence of adverse effects as compared to classical tricyclic antidepressants, which interact with several neurotransmitter systems. Given the pharmacological selectivity of SSRIs, their main action is attributed to blockade of plasma membrane serotonin transporters (SERT) in brain (Hyttel, 1994). Studies with SERT ligands have revealed highest binding in mesencephalic, diencephalic, pontine and striatal regions of rat brain *ex vivo* (Cumming and Gjedde, 1993) and human brain *in vivo* (Staley et al., 1994); the distribution of SERT correlates very highly with innervation density and serotonin content in rat brain (Dewar et al., 1993). A meta-analysis of 18 molecular imaging studies shows an approximately 10% reduction in SERT availability in unmedicated patients with depression (Gryglewski et al., 2014), consistent with a hypothesis of attenuated serotonin signalling in major depressive disorder (MDD), which might be rectified by SSRI treatment.

Given the particular association of serotonin innervations with components of the basal ganglia, a primary potentiation of serotonin transmission might be expected to evoke secondary effects on dopamine transmission. Indeed, acute treatment with fluoxetine increased interstitial serotonin levels and dopamine overflow in prefrontal cortex and hypothalamus of rats (Koch et al., 2002), while decreasing dopamine levels in microdialysates from rat striatum (Clark et al., 1996). Acute and chronic treatment with SSRIs reduced the availability of [^{11}C]-raclopride binding at dopamine $D_{2/3}$ receptors in human brain, suggesting a potentiation of dopamine release (Smith et al., 2009), although contrary findings have been reported in a preclinical imaging study (Dewey et al., 1995). Nonetheless, prolonged treatment with SSRIs has consistently been found to evoke a 10–20% increase in the availability of dopamine transporters (DAT) in striatum of healthy young and middle-aged volunteers investigated in a number of molecular imaging studies (Kugaya et al., 2003; Pogarell et al., 2005; Booij et al., 2007; Shang et al., 2007). However, a similar phenomenon has yet to be demonstrated in patients under treatment for depression, nor is it known if such changes are relevant to the antidepressant action of SSRIs.

Insofar as the great preponderance of interstitial dopamine in striatum is cleared via DAT, an SSRI-evoked elevation of DAT release might be expected to alter the tonic/phasic properties of dopamine signalling, which could be relevant to the therapeutic action or side effects of SSRIs in interaction with dopamine antagonists (Ersche et al., 2012). As a matter of convenience in molecular imaging studies of dopamine/serotonin interactions, the abundances of DAT and SERT can be separately determined via single-photon-emission computed tomography (SPECT) with the ambivalent ligand ([^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)tropane) ([^{123}I]β-CIT). The separation of DAT and SERT binding components is possible due to the different distributions of the two sites in brain, and also due to the different kinetics of the association of the [^{123}I]β-CIT to the two binding sites (Brucke et al., 1993; Pirker et al., 2000); In general, mesencephalic and diencephalic [^{123}I]β-CIT binding at early post-injection times reflects SERT, whereas striatal binding at late post-injection times is in the main attributable to DAT (Laruelle et al., 1993; Staley et al., 1994; Pirker et al., 2000).

In the present study we tested the hypothesis that effective treatment of MDD with escitalopram is accompanied by alteration of SERT and DAT availability in proportion to clinical response. Our aim was to investigate with [^{123}I]β-CIT SPECT the SERT and DAT availabilities in a group of MDD patients, first in a baseline untreated condition, and again after six weeks' treatment with escitalopram, a selective SSRI. We tested for correlations between SPECT findings with age, Hamilton Depression (HAM-D) and Beck Depression Inventory (BDI) scores at baseline and post-treatment.

2. Experimental procedures

2.1. Ethics and recruitment

The study was approved by the local ethics committee (University of Munich LMU) and by federal regulatory authorities overseeing the use of radioactive agents. All subjects gave written informed consent for participation in this study, after the neuropsychological and imaging procedures had been fully explained by the research physicians of the Departments of Psychiatry and Nuclear Medicine. The patients were recruited at the Department of Psychiatry, University of Munich and were diagnosed as fulfilling the criteria for major depressive disorder (MDD) by experienced psychiatrists.

Exclusion criteria were age below 20 years, comorbid psychiatric disorders (DSM IV axis I or II), as assessed by structured interviews and checklists adopted from the structured clinical interview for DSM IV (SCID, German version; (Wittchen et al., 1997)), or any other medical or neurological illnesses. Female subjects were required to have a negative urine pregnancy test, performed immediately before the application of the radiotracer. All patients were drug-naïve ($N=26$)