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Research Letter

Psychotherapy increases brain serotonin 5-HT_{1A} receptors in patients with major depressive disorder

Introduction

The serotonin 5-HT_{1A} receptor system is implicated in the pathophysiology of major depressive disorder (MDD) (Stockmeier, 2003) and serotonergic medications are currently widely used in the treatment of MDD. Previous molecular imaging studies in patients with MDD have provided evidence of a widespread decrease in the density of serotonin 5-HT_{1A} receptors in the disease (Drevets *et al*. 1999; Sargent *et al*. 2000; Bhagwagar *et al*. 2004; Meltzer *et al*. 2004; Hirvonen *et al*. 2008, but see Parsey *et al*. 2006 for opposite results). Psychotherapy usually results in clinically identical outcomes with medication in the treatment of patients with mild to moderate MDD (Ebmeier *et al*. 2006). However, nothing is known about the molecular mechanisms mediating the effects of psychotherapy. To test and compare the effects of fluoxetine medication and a brief psychotherapy on 5-HT_{1A} receptor density in patients with MDD we conducted a randomized comparative study. Positron emission tomography (PET) scanning with the 5-HT_{1A} radiotracer [carbonyl-^{11}C]WAY-100635 was performed before and after the intervention to measure alterations in 5-HT_{1A} receptor binding.

Materials and methods

This study was approved by the Joint Ethical Committee of the University of Turku and Turku University Central Hospital, and was conducted according to the Declaration of Helsinki at the Turku PET Centre, psychiatry clinics of the Helsinki and Turku Universities and the Research Department of the Social Insurance Institution in 2000–2004. All subjects gave written informed consent. The study was part of a larger randomized study investigating the clinical, psychological and neurobiological aspects and outcome of MDD, and the study design and patients have been described previously (Salminen *et al*. 2008). In brief, 23 MDD patients participated. They were recruited through five occupational health service (OHS) units providing primary health care, and received short-term psychodynamic psychotherapy (PSY, $n=8$) or fluoxetine (FLU, 20 mg/d, increased up to 40 mg/d if needed, $n=15$) for 16 weeks. Demographic and clinical characteristics of the patient groups are given in Table 1. Of the patients, 22 were completely antidepressant-naive, while one patient in the PSY group had been drug-free for 5 years. At baseline, the patients were evaluated by a psychiatrist, using the Structured Clinical Interview for DSM-IV Axis I disorders (First *et al*. 1997), 17-item Hamilton Depression Rating Scale (HAMD; Hamilton 1967), and the Beck Depression Inventory (BDI; Beck *et al*. 1961). At this time, all patients underwent PET scanning for 5-HT_{1A} receptors. We have previously published 5-HT_{1A} receptor abnormalities in this sample at baseline (Hirvonen *et al*. 2008). After 16 weeks, all patients were re-evaluated by the same psychiatrist. Response to treatment was defined as a reduction of $\geqslant 50\%$ in HAMD total score, and remission was defined as a HAMD total score of $\leqslant 7$.

PET procedures

Preparation of the radioligand [carbonyl-^{11}C]WAY-100635 and PET scanning procedures have been previously described in detail (Hirvonen *et al*. 2007). In brief, subjects were scanned twice with a whole-body 3D PET scanner (GE Advance, USA) and [carbonyl-^{11}C]WAY-100635 before and after treatment. To examine the stability of the PET measurements in the long term, four healthy volunteers underwent two PET scans 383 ± 134 days apart. There were no differences between the groups or between the scans in radiochemical variables (Table 1).

Automated region of interest (ROI) analysis

An automated ROI analysis was performed as previously described (Hirvonen *et al*. 2008). ROIs in the standard space were applied onto each spatially normalized image using Imadeus software (version 1.2, Forima Inc., Finland). The ROI for raphe was drawn directly on the [carbonyl-^{11}C]WAY-100635 template, since this small structure is not readily visible in MR images. Cerebellar white matter was used as the reference region (Parsey *et al*. 2005; Hirvonen *et al*. 2007).

Quantification of [carbonyl-^{11}C]WAY-100635 binding

Binding potential (BP_{ND}) values, representing the ratio of specific and non-displaceable binding (Innis *et al*. 2007) were estimated using the simplified reference

Table 1. *Demographic and clinical characteristics and radiochemical measurements of the study sample*

Characteristic	Fluoxetine	Psychotherapy
n	15	8
Age (years, mean ± S.D.)	39 ± 9	41 ± 10
Females (%)	66.7	37.5
Education level (mean ± S.D.)	1.80 ± 0.8	1.75 ± 0.9
Smokers (%)	22.0	0.0
Body mass index (kg/m^2, mean ± S.D.)	25.5 ± 4.4	28.4 ± 4.2
Baseline HAMD total score (mean ± S.D.)	18.1 ± 3.2	19.9 ± 2.3
Change in HAMD total score (mean ± S.D.)	−10.9 ± 5.7	−14.3 ± 4.4
Baseline BDI total score (mean ± S.D.)	24.4 ± 8.7	22.4 ± 4.2
Change in BDI total score (mean ± S.D.)	−13.5 ± 5.8	−13.6 ± 7.1
Duration of current episode (weeks, mean ± S.D.)	21.7 ± 15.0	41.3 ± 40.0
Recurrent/first-episode MDD (*n*)	2/13	4/4
No. of episodes in recurrent MDD (mean ± S.D.)	0.13 ± 0.4	1.75 ± 3.4
Responders (%)	66.7	87.5
In remission (%)	60.0	50.0
[carbonyl-^{11}C]WAY-100635 radiochemistry		
Injected dose, 1st PET (MBq, mean ± S.D.)	237 ± 16	235 ± 15
Injected dose, 2nd PET (MBq, mean ± S.D.)	231 ± 38	243 ± 39
Injected mass, 1st PET (μg, mean ± S.D.)	0.97 ± 0.43	0.85 ± 0.30
Injected mass, 2nd PET (μg, mean ± S.D.)	1.22 ± 0.42	1.04 ± 0.29
Specific radioactivity, 1st PET (MBq/nmol, mean ± S.D.)	125.1 ± 40.7	100.2 ± 39.0
Specific radioactivity, 2nd PET (MBq/nmol, mean ± S.D.)	135.8 ± 58.8	118.3 ± 58.6
Scan interval, days (mean ± S.D.)	134 ± 23	144 ± 18
Change in cerebellar AUC (%, mean ± S.D.)	0.85 ± 37.6	−0.91 ± 21.2

AUC, Area under the curve; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; MDD, major depressive disorder; PET, positron emission tomography.

$p > 0.05$ in all between-group comparisons unless otherwise apparent.

tissue model (SRTM) with cerebellar white matter as the reference region (Lammertsma & Hume, 1996). The model did not converge in 10 subjects in the dorsal raphe, a small brain structure sensitive to, for example partial volume effects. Thus raphe was omitted from the primary analysis. A more simple area under curve (AUC) ratio method (Hirvonen *et al*. 2007) indicated that there were no statistically significant group × repetition interactions in DRN (data not shown) but further studies with advanced high-resolution PET methodology are clearly needed.

Voxel-based analyses

To facilitate detailed visualization of the results, a confirmatory voxel-based analysis of parametric BP_{ND} maps was performed as previously described (Hirvonen *et al*. 2008) using basis functions (Gunn *et al*. 1998) and SPM2 (Friston *et al*. 1995) running on Matlab 6.5 for Windows (Math Works, USA).

Statistical analyses of ROI-based data

Statistical analyses were carried out using SPSS 13.0 for Windows (release 13.0.1, copyright SPSS Inc., 1989–2004). The data were normally distributed, and were analysed by means of repeated-measures analysis of variance (rmANOVA) with repetition, region (ROI), and hemisphere as within-subject factors, and age as the between-subject predictor of BP_{ND}. Group × repetition interaction was modelled to investigate treatment-group differences in the change in BP_{ND} values between the scans. This was followed by regional models. Sex entered the models as covariate. We also evaluated the reproducibility and reliability of the method of repeated scanning with [carbonyl-^{11}C]WAY-100635 in the four healthy volunteers, by means of absolute variability and intra-class correlation coefficients (ICC). Data are presented as mean ± standard deviation unless otherwise specified. p values < 0.05 were considered criteria for statistical significance.

Results

The clinical outcome in both treatment groups was similar in terms of standard symptom ratings, and 59% of the subjects reached remission and 77% of the

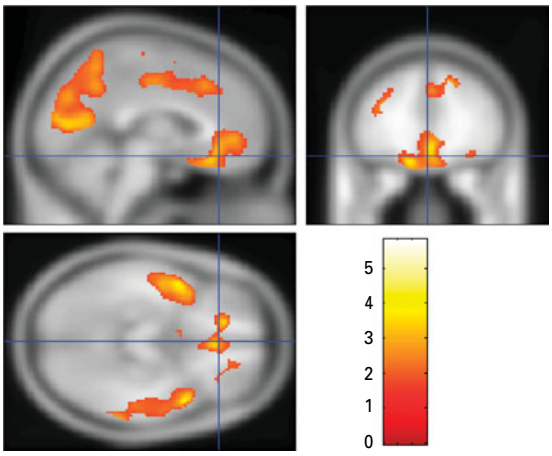

Fig. 1. Visualization of the results from the SPM analysis. The analysis of parametric [carbonyl-^{11}C]WAY-100635 binding potential (BP_{ND}) maps at the voxel level showed two large clusters [$k_E = 9515$, $T_{max} = 5.82$ at (−26, 0, −38) and $k_E = 18\,231$ voxels, $T_{max} = 4.10$ at (−46, −20, 42)] located mainly in frontal, temporal and parietal cortex. These clusters represent significantly increased BP_{ND} in the psychotherapy group as compared with the fluoxetine group. The results are visualized on a T1-weighted MRI template in stereotactic standard space; the colour bar represents the *T* statistic at voxel level.

subjects met the criteria for response at 4 months. Analysis of the change in the 5-HT_{1A} receptor density in the treatment groups revealed a significant increase in the PSY group compared to the FLU group (rmANOVA, group × repetition: $F = 7.24$, $p = 0.014$). The mean effect size across brain regions was 0.85 (range −0.02 to 1.31). When compared with healthy controls, patients in the PSY group demonstrated significantly increased 5-HT_{1A} density after treatment (group × repetition: $F = 16.21$, $p = 0.003$), whereas patients receiving FLU did not differ from healthy control subjects in terms of change (group × repetition: $F = 1.62$, $p = 0.222$). The voxel-based analysis confirmed the results from the main analysis (Fig. 1), showing two large clusters representing significant increase in 5-HT_{1A} density in the PSY group compared to the FLU group in the frontal, temporal, and parietal cortex.

Consistent with the overall analysis, regional analyses showed a significant increase in the PSY group compared to the FLU group (group × repetition interaction) in angular gyrus ($F = 10.80$, $p = 0.004$), dorsolateral prefrontal cortex ($F = 5.44$, $p = 0.030$), insular cortex ($F = 7.61$, $p = 0.012$), inferior temporal gyrus ($F = 9.03$, $p = 0.007$), medial prefrontal cortex ($F = 6.77$, $p = 0.017$), orbitofrontal cortex ($F = 9.26$, $p = 0.006$), supramaginal gyrus ($F = 7.42$, $p = 0.013$), superior temporal gyrus ($F = 6.89$, $p = 0.016$), ventral anterior cingular cortex ($F = 4.44$, $p = 0.048$) and ventrolateral prefrontal cortex ($F = 5.30$, $p = 0.032$). In agreement with these results, patients in the PSY group had a greater increase in BP_{ND} following treatment compared to patients in the FLU group in 7/15 ROIs, as well as in the average of post-synaptic ROIs (Table 2).

The change in the mean post-synaptic 5-HT_{1A} density was not associated with the change in symptom scores in either group (not shown). Neither did baseline 5-HT_{1A} density predict symptom reduction, response to treatment, or remission status (not shown). However, in patients who had reached remission in the PSY group ($n = 4$), increase in the mean post-synaptic 5-HT_{1A} density was tightly correlated with the reduction in HAMD ($R = -0.99$, $p = 0.009$) and BDI total scores ($R = -0.99$, $p = 0.013$).

There were no group differences in the changes in the input function, estimated by AUCs for the reference region time–activity curves (cerebellar white matter) ($p = 0.904$). In the healthy control group, the measurement of neocortical 5-HT_{1A} density was found to be very stable in the long term, with low within-subject variability (6–10%) and good reliability (ICC 0.67–0.87).

Discussion

We found increased serotonin 5-HT_{1A} receptor binding in multiple cortical regions following psychotherapy in patients with MDD. No change was observed in patients receiving fluoxetine medication, although the clinical outcome in terms of symptom ratings was similar in both groups. This is the first direct demonstration of a specific neurotransmitter mechanism involved in the neurobiology of psychotherapy.

The small sample size in the present study sets inherent limitations to the interpretation of the observed results that should be considered preliminary. However, they serve as a starting point for applying other molecular imaging probes in the research for neurobiological underpinnings of psychotherapy in larger study samples. This line of research has thus far received little attention, and the few studies on this topic have documented focal changes in cerebral metabolism or blood flow (Beauregard, 2009). The mechanisms involved in the change in the serotonin system following psychotherapy remain unknown. Given the importance of serotonin in cognitive and emotional processes, and the fact that psychotherapy is a form of emotional learning, the increase in 5-HT_{1A} BP_{ND} following psychotherapy could reflect a top-down modulation of the serotonin system based on increased emotion regulation and decreased stress. Our findings would then be consistent with the hypothesis that psychotherapy could lead to changes in gene expression through learning, by altering the

Table 2. *Regional* [*carbonyl-*^{11}*C*]*WAY-100635* (*binding potential*) BP_{ND} *values before and after treatment for fluoxetine* (*FLU*) *and psychotherapy* (*PSY*) *groups, and for test and retest conditions for the control group*

	Fluoxetine ($n=15$)				Psychotherapy ($n=8$)				Control ($n=4$)				
	BP_{ND}		Change		BP_{ND}		Change		BP_{ND}		Change		$\triangle BP_{ND}$ FLU *v.* PSY
ROI	PET1	PET2	%	*p*	PET1	PET2	%	*p*	PET1	PET2	%	*p*	*p*
AMY	6.24±1.5	6.11±1.6	−1.4	0.650	5.31±1.4	5.78±1.6	+10.5	0.518	6.64±1.2	5.54±0.9	−15.8	0.099	0.123
ANG	3.99±0.7	3.84±0.7	−3.6	0.178	3.32±0.8	3.68±0.9	+11.3	**0.020***	4.50±0.6	4.17±0.6	−7.2	0.169	**0.006***
DAC	5.07±0.8	5.00±1.0	−1.3	0.702	4.29±1.1	4.50±1.1	+5.8	0.269	5.51±0.6	5.62±0.9	+2.1	0.716	0.259
DLP	4.11±0.7	3.95±0.8	−3.7	0.227	3.41±0.9	3.63±0.9	+7.1	0.085	4.71±0.6	4.47±0.7	−5.0	0.280	0.052
HIP	6.39±1.6	6.39±1.7	+1.1	0.990	5.16±1.3	5.95±2.1	+17.2	0.255	7.12±1.6	5.18±0.8	−25.4	0.050	0.158
INS	5.83±1.0	5.73±1.2	−2.2	0.468	4.89±1.1	5.31±1.2	+9.5	0.094	6.54±1.0	5.90±0.9	−9.5	0.086	**0.019***
ITG	3.79±0.7	3.61±0.7	−4.5	0.065	3.24±0.9	3.41±0.8	+6.5	0.111	4.29±0.7	4.00±0.9	−7.1	0.279	**0.021***
MFC	4.91±0.9	4.82±0.9	−1.7	0.466	3.98±0.9	4.31±1.0	+8.3	**0.039***	5.66±0.8	5.29±0.7	−5.9	0.298	**0.030***
MTG	4.76±0.8	4.62±0.9	−2.9	0.257	4.01±1.0	4.21±0.9	+6.2	0.114	5.39±0.7	5.06±0.7	−6.0	0.146	0.054
ORB	5.50±0.9	5.27±0.9	−3.9	0.174	4.59±1.1	5.02±1.2	+9.9	**0.025***	6.13±0.8	5.83±0.9	−5.0	0.256	**0.010***
PC	4.23±1.0	3.89±0.8	−6.7	0.112	3.48±0.8	3.49±0.5	+2.5	0.937	4.46±0.6	4.60±0.8	+2.9	0.497	0.183
SMAR	4.18±0.7	4.04±0.7	−3.2	0.252	3.46±0.8	3.71±0.8	+8.1	0.060	4.75±0.7	4.40±0.6	−7.1	0.156	**0.034***
STG	4.57±0.8	4.36±0.8	−4.2	0.192	3.84±0.9	4.16±0.1	+9.0	0.057	5.03±0.6	4.78±0.7	−4.9	0.326	**0.024***
VAC	5.43±0.9	5.31±1.0	−2.0	0.481	4.70±1.0	4.99±1.3	+6.3	0.142	5.99±0.9	5.77±0.5	−2.7	0.529	0.131
VLP	3.99±0.7	3.84±0.8	−3.7	0.230	3.31±0.8	3.50±0.8	+7.0	0.146	4.62±0.7	4.30±0.7	−6.6	0.166	0.052
Average	4.87±0.8	4.72±0.9	−3.3	0.207	4.07±1.2	4.38±1.3	+8.2	0.055	5.42±0.8	4.99±0.7	−7.6	0.137	**0.014***

AMY, Amygdala; ANG, angular gyrus; DAC, dorsal anterior cingulate cortex; DLP, dorsolateral prefrontal cortex; HIP, hippocampus; INS, insular cortex; ITG, inferior temporal gyrus; MFC, medial prefrontal cortex, MTG, middle temporal gyrus; ORB, orbitofrontal cortex; PC, posterior cingulated cortex; PET, positron emission tomography; ROI, region of interest; SMAR, supramarginal gyrus; STG, superior temporal gyrus; VAC, ventral anterior cingulate cortex; VLP, ventrolateral prefrontal cortex.

p values are from paired *t* tests except for the last column, which gives the *p* value of the group comparison of BP_{ND} changes ($\triangle BP_{ND}$) between fluoxetine and psychotherapy groups. *p* values denoting statistical significance ($p<0.05$) appear in boldface and are indicated by an asterisk.

strength of synaptic connections between nerve cells and inducing morphological changes in neurons (Kandel, 1998).

Previous studies have found reduced 5-HT_{1A} receptor binding in MDD (Drevets *et al*. 1999; Sargent *et al*. 2000; Bhagwagar *et al*. 2004; Meltzer *et al*. 2004, but see Parsey *et al*. 2006), that is not reversed by SSRI treatment (Sargent *et al*. 2000; Bhagwagar *et al*. 2004; Moses-Kolko *et al*. 2007). Our observations are consistent with these findings, since fluoxetine did not alter 5-HT_{1A} receptor binding despite clinical efficacy. Some authors have suggested that reduced 5-HT_{1A} receptor binding could be a trait marker of depression that increases the risk of future depression. Our results would then suggest that psychotherapy may lead to a change in this trait, although BP_{ND} was not decreased specifically in this sample (Hirvonen *et al*. 2008). This is supported by the finding that the relapse rate in MDD patients may be lower in those treated with psychotherapy compared to those treated with antidepressant medication (Hollon *et al*. 2005).

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Declaration of Interest

Dr Karlsson has received lecture fees from AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck and Wyeth, Dr Hirvonen has received lecture fees from AstraZeneca, Bristol–Myers Squibb, Janssen-Cilag, Lundbeck and Novartis, congress travel grants from AstraZeneca and Lundbeck, and research funding from Orion Pharma and Lundbeck. Dr Markkula has received lecture fees from Eli Lilly, GlaxoSmithKline, and Jansse-Cilag. Dr Hietala has received lecture fees from AstraZeneca, Bristol–Myers Squibb, Eli Lilly, Janssen-Cilag, and Lundbeck, congress travel grants from AstraZeneca, Bristol–Myers Squibb, and Eli Lilly, and has acted as consultant for Orion Pharma.

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