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Is treatment-resistance in unipolar melancholic depression characterized by decreased serotonin$_{2A}$ receptors in the dorsal prefrontal – Anterior cingulate cortex?

Chris Baeken [a,b,*], Rudi De Raedt [c], Axel Bossuyt [d]

[a] Department of Psychiatry, UZ Brussel, Vrije Universiteit Brussel (VUB), Brussels, Belgium
[b] Center for Neurosciences, Vrije Universiteit Brussel (VUB), Brussels, Belgium
[c] Department of Psychology, Ghent University, Belgium
[d] Department of Nuclear Medicine, UZ Brussel, Vrije Universiteit Brussel (VUB), Brussels, Belgium

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ABSTRACT

Objectives: Quite a number of patients diagnosed with major depression are resistant to several well carried-out psychopharmacological interventions. It remains unclear as to how the serotonergic system is implicated in the phenomenon of treatment-resistance.
Methods: We examined the involvement of post-synaptic 5-HT$_{2A}$ receptors in the pathophysiology of treatment-resistance in unipolar melancholic major depression with ^{123}I-5-I-R91150 SPECT. 15 antidepressant-naïve (ADN) first-episode depressed patients, 15 antidepressant-free treatment-resistant depressed (TRD) patients and 15 never-depressed individuals, matched for age and gender were studied.
Results: Compared to ADN patients and healthy controls, TRD patients displayed significantly lower 5-HT$_{2A}$ receptor binding index (BI) in the dorsal regions of the prefrontal and the anterior cingulate cortex. No significant 5-HT$_{2A}$ receptor BI differences between ADN patients and controls were observed.
Conclusions: At the cortical level, 5-HT$_{2A}$ receptor BI does not significantly differ in first-episode melancholic depressed patients compared to healthy controls. This observation might imply a limited short-term impact on the serotonergic system in first episode depression. Our results also suggest that when encountered with treatment-resistance, the 5-HT$_{2A}$ receptors in the DPFC-ACC axis are significantly down-regulated. However, whether this assumed underlying pathophysiological mechanism is due solely to abnormalities in the serotonergic system remains to be answered.
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1. Introduction

Major depression is a worldwide mental health problem affecting millions (Nemeroff, 2007a). Unfortunately, not all depressed patients respond to the available pharmacological treatment algorithms and refractory depression is not uncommon (Fava, 2003). It is estimated that treatment-resistance occurs in up to 40% of depressive episodes that are adequately treated with first-line antidepressant therapy (Souery et al., 2006). Ten percent or even more of patients suffering from major depression are resistant to several psychopharmacological interventions, even when adhering to treatment guidelines (Fagiolini and Kupfer, 2003; Berlim and Turecki, 2007). Not surprisingly, it has been proposed that severe treatment-resistance could be a different type of depression (Nemeroff, 2007b). Furthermore, when challenged with clinical non-response, treatment options are limited (Shelton et al., 2010; Ward and Irazoqui, 2010).

The serotonergic system remains one of the main targets of psychotropic drug intervention to treat depression (Neumeister and Charney, 2002). Ascending serotonergic projections arise primarily from the raphe nuclei in the brainstem and 'arborize' widely throughout cortico-subcortical structures, innervating forebrain and limbic areas (Hensler, 2006). Prefrontal cortical serotonergic innervations have been found to be reduced in depressed individuals (Larisch et al., 2001; Arango et al., 2002). Being part of the G-protein coupled 5-HT$_2$ serotonin receptor family, post-synaptic 5-HT$_{2A}$ receptors are implicated in the pathophysiology of many neuropsychiatric disorders including major depression, and they are implicated in several brain functions such as appetite control,

* Corresponding author. Department of Psychiatry, University Hospital (UZ Brussel), Vrije Universiteit Brussel (VUB), Laarbeeklaan 101, 1090 Brussels, Belgium. Tel.: +3224776425; fax: +3224776800.
E-mail address: Chris.baeken@uzbrussel.be (C. Baeken).

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thermoregulation, emotion, personality, cognition, ageing and sleep (Aghajanian and Sander-Bush, 2002; Celada et al., 2004; Frokjaer et al., 2010). These receptors have widespread distributions throughout the cortex, with high densities in the frontal cortex (Barnes and Sharp, 1999). However, it has to be noted that discrepant results in 5-HT_{2A} receptor research in depression have been reported, with some authors demonstrating 5-HT_{2A} receptor increases, others demonstrating decreases, or no differences in receptor ligand binding at all (D'haenen, 2004; Bhagwagar et al., 2006). Confounding variables such as sample size, heterogeneity, age, antidepressant drug status and suicide levels could be an explanation for these observed discrepancies. Nevertheless, there seems to be a growing consensus indicating a decreased cortical 5-HT_{2A} receptor binding in depressed patients compared with normal controls (D'haenen, 2001).

Few studies have examined the differences in 5-HT_{2A} receptor binding between currently depressed antidepressant-naïve (ADN) patients, depressed patients who have been treated with antidepressants, and never-depressed healthy controls (Massou et al., 1997; Messa et al., 2003; Schins et al., 2005). Although negative results are also reported (Schins et al., 2005), Messa et al. (2003) found decreased frontal cortical 5-HT_{2A} binding indices in symptomatic ADN patients as compared to their control group. They suggested that 5-HT_{2A} receptors are reduced in depressive patients during symptomatic periods. However, at this point it is not clear whether these serotonergic abnormalities found in unipolar depressed samples are any different when encountered with treatment-resistance. No studies examined the possible differences at the level of 5-HT_{2A} receptor BI between untreated depressed patients and AD-free depressed patients who were "unsuccessfully" treated with several psychopharmacological interventions.

In the present study, we focused on the 5-HT_{2A} receptors in well-defined gender-controlled homogeneous groups of unipolar depressed patients, using SPECT and the radioligand 4-amino-N-[1-[3-(4-fluorophenoxy)propyl]-4-methyl-4-piperidinyl]-5-iodo-2-methoxybenzamide (^{123}I-5-I-R91150) (Terriere et al., 1995). As age-dependent reductions in 5-HT_{2A} receptor binding indices in the cortex have consistently been reported (Baeken et al., 1998; Meltzer et al., 1998), patients and controls were also matched for age. Because hormonal processes seem to differ between depression subtypes (Porter and Gallagher, 2006), our patient group consisted only of depressed patients with melancholic features. Melancholic depression is characterized by anhedonia, i.e., distinct quality of depressed mood, depression symptoms worse in the mornings, early morning awakenings, psychomotor retardation, weight loss, and excessive feelings of guilt (Gold and Chrousos, 2002). Treatment-resistant depressed (TRD) patients had had a minimum of two unsuccessful treatment trials with serotonin reuptake inhibitors/noradrenaline and serotonin reuptake inhibitors (SSRI/NSRI) and one failed clinical trial with a tricyclic antidepressant (TCA). TRD patients were tapered-off their psychotropic drugs, and all were at least medication-free for at least two weeks before SPECT scanning. Only when necessary TRD patients were kept on a steady dose of benzodiazepines.

Firstly, in line with former research, we hypothesized that compared to never depressed-individuals in both the currently depressed ADN patients and the treatment-resistant depressed (TRD) patients, 5-HT_{2A} receptor BI would be significantly lower in all the cortical areas examined. Secondly, we expected that these reductions in 5-HT_{2A} receptor BI would be even larger in TRD patients compared to ADN patients. Thirdly, because in primary depression clinical symptoms and brain imaging data point to a functional deficit in the frontal cortical regions (Mayberg, 2003), we expected that the differences in 5-HT_{2A} receptor BI would be most apparent in these areas.

2. Materials and methods

2.1. Subjects

The study was approved by the ethics committee of the University Hospital (UZ Brussel) and all subjects gave written informed consent. As the focus of this research is treatment-resistance, fifteen right-handed unipolar melancholic TRD patients (Female:Male (F:M) = 9:6; age = 38.6 ± 9.5*y*) were studied. See also Table 1. They were closely matched with fifteen first episode right-handed medication-free unipolar melancholic ADN depressed patients (F:M = 9:6; age = 36.3 ± 9.8*y*) and fifteen never-depressed medication-free healthy volunteers (F:M = 9:6; age = 37.01 ± 9.8*y*), who were included as control group. In other words, for each female or male TRD patient a suitable female or male ADN patient and healthy control was selected, matched for age as close as possible. Parts of the TRD patient and the control SPECT data were also used for another study, examining the treatment effects of high frequency repetitive transcranial magnetic stimulation in these kinds of patients (Baeken et al., 2011). According to the Diagnostic and Statistical Manual of Mental Disorders criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, text revision. Washington, DC, American Psychiatric association, 2000), all patients were diagnosed with unipolar major depression of the melancholic subtype (ICD-9-CM code 296.23 and 296.33). Current or past psychotic features or a history of bipolarity were considered as exclusion criteria. Patients with substance abuse/dependence were not included in the study. Because in post-mortem studies increased 5-$HT_{2(A)}$ receptor BI are reported in the frontal cortices of suicide victims (van Heeringen et al., 2003), suicidal attempts during the current depressive episode were considered as an exclusion criterion. All participants were in good physical health. Severity of depression was assessed with the 17-item Hamilton Depression

Table 1
Demographic data of the treatment-resistant group of melancholic depressed patients (TRD). HDRS: 17-item Hamilton Depression Rating Scale. F: female. M: male. SD: standard deviation.

TRD Patient	Gender	Age	Thase and Rush stage	Duration current episode (years)	HDRS	Last antidepressant medication before washout	Benzodiazepines (dose/day)
1	F	45	3	3	32	Duloxetine	Clonazepam 1 mg
2	F	49	3	3	32	Amytriptiline	Lormetazepam 2 mg
3	F	32	3	2	29	Venlafaxine	Alprazolam 2 mg
4	F	47	3	12	30	Amytriptiline	Bromazepam 24 mg
5	F	42	3	4	23	Clomipramine	no
6	F	50	3	4	27	Nortryptiline	no
7	F	52	3	5	23	Amytriptiline	no
8	F	45	3	1.5	25	Dosulepine	Flunitrazepam 1 mg
9	F	48	3	5	26	Venlafaxine	no
10	M	25	3	2	22	Clomipramine	no
11	M	40	4	2.5	26	Paroxetine	Alprazolam 1 mg
12	M	34	3	11	23	Clomipramine	no
13	M	39	3	1	27	Clomipramine	no
14	M	34	5	7	21	Fenelzine	no
15	M	54	4	4	27	Fenelzine	no
Mean (SD)		38.55 (9.53)		4.47 (3.25)	26.53 (3.29)		