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Antidepressant short-term and long-term brain effects during self-referential processing in major depression

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ABSTRACT

Acute depression is associated with impaired self-referential processing. Antidepressant effects on the neural bases of self-referential processing in depression are unknown. This study aimed to assess short- and long-term effects of agomelatine on these neural bases in depressed patients and the association between pre-treatment brain activation and remission of depression 6 months later. We conducted a randomized double-blind, placebo-controlled, functional magnetic resonance imaging (fMRI) study during an emotional self-referential task, including three scanning sessions (baseline, after 1 week, and after 7 weeks). Twenty-five depressed outpatients were included, all treated with agomelatine or placebo for 1 week. Then, all patients received agomelatine for 24 weeks. Fourteen matched healthy volunteers (HV) who received placebo for 1 week were also included. After 7 days, only depressed patients receiving agomelatine significantly deactivated the ventrolateral prefrontal cortex during self-referential processing, as observed in HV at baseline. After 7 weeks, depressed patients significantly increased the activation of the ventral anterior cingulate cortex. Finally dorsomedial prefrontal cortex and precuneus activations at baseline significantly separated remitters from non-remitters at 24 weeks. In depressed patients, agomelatine had short- and long-term effects on brain structures involved in anhedonia and emotional regulation during self-referential processing. Activation of the dorsomedial prefrontal cortex and precuneus could be informative in the development of biomarker-based treatment of major depression.

1. Introduction

Major depressive disorder (MDD) is associated with several biases in information processing. Depressed patients prioritize the processing of negative emotional information and show increased attention to the self, namely self-focus (Mor and Winquist, 2002). Increased self-focus in depressed patients involves the cortical midline structures, including the medial prefrontal cortex (MPFC) and the posterior cingulate cortex (PCC) (Lemogne et al., 2009, 2012; Yoshimura et al., 2010; Nejad et al., 2013), as well as the dorsolateral prefrontal cortex (DLPFC; Lemogne et al., 2009).

There is growing interest in the effects of antidepressant drugs on such biases as they play a key role in the initiation and maintenance of depressive symptoms (Harmer et al., 2003, 2004, 2009; Pringle et al., 2011). On one hand, one pilot study showed that long-term administration of antidepressants in depressed patients modulates the activity of the DLPFC during self- processing (Lemogne et al., 2010). On the other hand, although some studies with short-term administration of selective serotonin reuptake

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inhibitors in healthy subjects showed a modulation of midline cortical regions (Matthews et al., 2010; Di Simplicio et al., 2012), short- and long-term neural correlates of antidepressant effects on self-focus in depressed patients are still little known.

The main goal of the present functional magnetic resonance imaging (fMRI) study was to assess both the short- and long-term effects of an antidepressant on the neural correlates of increased self-focus in depressed patients. Here, we used agomelatine, a potent agonist of MT_1–MT_2 melatoninergic receptors and an antagonist of the serotoninergic 5-HT2C receptor (de Bodinat et al., 2010) with established antidepressant efficacy (Taylor et al., 2014).

Since increased self-focus can be defined as a tendency to engage in self-referential processing, we assessed depressed patients making self-referential judgments on emotional pictures during the following three fMRI scanning sessions: before treatment when patients were acutely depressed, after 1 week of treatment with agomelatine or placebo, and after 6–7 weeks of agomelatine.

We predicted that treatment with agomelatine, compared with placebo, would induce in depressed patients early changes in the MPFC and lateral prefrontal cortex (PFC) even in the absence of significant changes in mood ratings and depressive symptoms. Second, we hypothesized that 6–7 weeks of treatment with agomelatine would induce changes in the activity of the medial and lateral PFC, concomitantly with a clinical improvement of depression. Finally, we tested if the activity of brain regions associated with self-referential processing at baseline would be associated with clinical remission 6 months later.

2. Methods

2.1. Subjects

Thirty female outpatients meeting DSM-IV criteria for MDD with the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998) were recruited between October 2008 and June 2011 by psychiatrists (7 centers located in Paris area, France).

Current depressive episode had to be unipolar subtype, longer than 4 weeks, of moderate or severe intensity with total scores ≥ 22 on the 17-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) and Clinical Global Impression (CGI) severity scores ≥ 4 (Guy, 1976). All patients had to be free of psychotropic medication for a minimum of 2 weeks (washout period defined according to the medication) before inclusion. Patients with comorbid conditions were excluded (see Supplementary material 1 for details).

Two subgroups of 15 patients were determined by the blinded allocation of the treatment for the first week: agomelatine (AGO) or placebo (PBO) (see Section 2.2). Two patients of the AGO group and three patients of the PBO group were excluded (one because of excessive head movements in the MRI scanner and four owing to positive drug screening) leading to a final sample of 13 patients in the AGO group and 12 patients in the PBO group. These MDD patients were compared with the 14 HV. All groups were matched for age and gender (see supplementary Fig. 1 for CONSORT flow diagram).

Table 1 summarizes demographic and clinical characteristics of the MDD and HV groups.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the French ethics committee for Biomedical Research of the Pitié-Salpêtrière Hospital (Paris). Each participant gave his/her informed written consent before entering the study, and healthy volunteers were registered on the French National File.

Table 1
Demographic and clinical characteristics of major depressive disorder patients and healthy volunteers (part I) at baseline.

Characteristics	AGO patients group ($n=13$)	PBO patients group ($n=12$)	HV group ($n=14$)
Age (years, mean ± SD)	41.8 (±8.0)	40.1 (±7.6)	41.6 (±7.4)
min–max	27–52	27–50	26–53
Right handed/left handed (n/n)	13/0	11/1	13/1
Education (years, mean ± SD)	14.4 (±1.7)	12.8 (±2.3)	13.0 (±2.3)
DSM-IV classification:			
Recurrent episode (n)	13	11	–
Severity			
Moderate (n)	5	5	–
Severe without psychotic feature (n)	8	7	–
Melancholic features (n)	8	8	–
Duration of the disease (years, mean ± SD)	16.0 (±9.7)[a]	10.0 (±7.2)[a]	–
Current episode duration (months, mean ± SD)	5.4 (±4.2)	3.4 (±2.9)	–
Number of previous depressive episodes (including the current one) (mean ± SD)	2.9 (±1.2)	2.4 (±1.2)	–
HAMD-D-17 score (mean ± SD)	24.4 (±3.3)	25.3 (±2.9)	–
CGI severity of illness score (mean ± SD)	4.8 (±0.6)	4.9 (±0.5)	–

AGO=agomelatine treatment; PBO=placebo treatment; HV=healthy volunteers; SD=standard deviation; n=number of subjects.

[a] p for difference between AGO and PBO patients=0.09.

2.2. Drug treatment and study design

The study was randomized, double-blind, multicenter and placebo-controlled during the first week, with two parallel groups of MDD patients (AGO vs. PBO). Patients took one tablet of AGO 25 mg or placebo, orally per day at around 8 p.m., for 1 week (except for one patient in the AGO group who missed 1 day of treatment) in a double-blind protocol followed by an open-label period with AGO until 24 weeks (W24). At W7, patients had thus received 6 or 7 weeks of treatment with AGO, with two possible sequences of treatment (PBO/AGO, AGO/AGO). All HV took one tablet of placebo per day orally at around 8 p.m., during 1 week in a single-blind protocol (see Supplementary material 2 for randomization).

Each patient was scanned on three occasions, before beginning treatment (W0), after 1 week (W1) and 7 weeks of treatment (W7). Among the 25 MDD patients, all were included for analyses regarding the short-term AGO effects after 1 week (part I), but six patients had missing fMRI data at W7 (see CONSORT flow diagram, supplementary Fig. 1), leading to a final sample of 19 MDD patients for the long-term (W0-W7) AGO effects (part II). The HV were scanned on two occasions, at W0 and after 1 week of PBO (supplementary Fig. 2).

2.3. Clinical assessment

Depression severity was assessed with the 17-item HAM-D scale (Hamilton, 1960) and CGI severity and clinical improvement

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