HIPPOCAMPAL CHOLINE LEVEL PREDICTS SYMPTOMATIC IMPROVEMENT WITH AGOMELATINE IN MAJOR DEPRESSIVE DISORDER: A 3 TESLA SINGLE VOXEL SPECTROSCOPY STUDY

Najib ALLAILI1-2, romain VALABREGUE3, Malgorzata MARJANSKA1,2, Pauline DELAVEAU1, Éric BARDINET1, Marita JABOURIAN4, Judith LAREDO5, Philippe FOSSATI6,7, and Stéphane LEHERICY1,2

1 USR 3246, CNRS, Paris, Île-de-France, France, 2Centre de Neuroimagerie de Recherche - CENIR, Institut du Cerveau et de la Moelle épinière - ICM, Paris, Île-de-France, France, 3Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, United States, 4Department of Radiology, University of Minnesota, Minneapolis, MN, United States, 5Institut de Recherches Internationales Servier - IRIS, Courbevoie, Île-de-France, France, 6Psychiatrie, APHP - GH Pitié Salpêtrière, Paris, Île-de-France, France, 7UMR-S975 ; Inserm ; CNRS, UMR 7225, Paris, France, CRICM, Université Pierre et Marie Curie, Paris, Île-de-France, France

Introduction

There is growing evidence for the implication of the hippocampus in the neurobiology of depression and in the mechanism of action of antidepressants. Several neuroimaging studies evaluating structural changes of the hippocampus in major depressive disorders have reported significant volume reduction in patients compared to healthy subjects (1). In animal studies, chronic stress induced dendritic retraction of hippocampal neurons and decrease in neurogenesis rate that were both reversed by antidepressants (2). In humans, proton magnetic resonance spectroscopy (1H-MRS) provides information on biological processes underpinning hippocampal involvement in major depressive disorder. Yet, because of its small size and its location in the midbrain, it has been studied infrequently. To date, only a few 1H-MRS studies have investigated the hippocampus in depressed patients (3-5). Most studies used low magnetic field strength and/or large volume of interest (VOI) resulting in poor spectral resolution and partial volume effects. In this study, we sought to identify spectroscopic correlates of depressive state and of response to Agomelatine, a new antidepressant with melatonin agonist and 5-HT2C antagonist properties (6,7). All measurements were performed at 3 T in a the volume of 2.4 mL to minimize partial volume effects.

Methods

21 women diagnosed with major depressive disorder (Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition) and 15 matched healthy controls were recruited and signed consent. Patients were free of any medication for two weeks before the spectroscopic examination. After the scanning session, they started a daily oral treatment of Agomelatine (25 mg/day) for at least 6 weeks. Patients’ symptoms were assessed with the 17-item Hamilton Depression Scale (HAMD-D) at baseline (W0) and after 7 weeks (W7). Clinical improvement was estimated by the difference between HAMD-D scores at W0 and W7. All spectroscopic examinations were performed at 3 T (Siemens TIM Trio) using LASER (8) sequence with VAPOR water suppression. All scans were performed using body coil excitation and 12-channel receive phased-array head coil. High-resolution three-dimensional T1-weighted images were acquired for localization of the spectroscopic voxel which was rotated and placed along the long axis of the left hippocampus to cover its body and most of its tail portion (Fig. 1). For each subject, spectroscopic acquisition consisted of 256 water-suppressed averages and 4 water-unsuppressed averages (TE = 65 ms, T2R = 15 s). In vivo spectra were analyzed using LCMModel with a simulated basis set which included 19 metabolites. Quantification of the in vivo metabolite signals was based on the unsuppressed water signal taking into consideration T1 and T2 relaxation of water and partial volume of white matter, gray matter and CSF in the voxel of interest.

For every reliably detected metabolite, group differences were assessed for significance by 2-tailed Student’s t test. Correlation analyses between metabolite concentrations and clinical improvement (∆ HAMD = HAMDw0 − HAMDw7) were performed to identify spectroscopic correlates of response to Agomelatine.

Results

Good quality spectra (SNR = 10.2 ± 1.1; water linewidth = 4.7 ± 0.4 Hz) were obtained from all subjects. Excellent fits for five metabolites with mean Cramer-Rao lower bounds below 5% for N-acetylaspartate and N-acetylaspartylglutamate (NAA), choline containing compounds (tCho), creatine and phosphocreatine (tCr) and myo-inositol (Ins), and below 15% for glutamate and glutamine (Glx), were obtained with LCMModel. Six patients did not undergo follow-up examination (W7) due to various reasons (non-compliance with treatment protocol, need to add anxiolytic medication, etc.).

HAMD score significantly decreased in the patient group between W0 and W7, indicating positive treatment response. Glx was significantly decreased (p < 0.005, Cohen d = 1.07) in the patient group (6.0 ± 1.7) as compared to the control group (8.0 ± 2.0) and tCho showed a trend to decrease (p = 0.12). We observed a highly significant correlation between tCho and ∆ HAMD (N = 15, r = 0.69, p < 0.005).

Discussion

Our results extend to the hippocampus the existing pattern of decreased Glx found in other brain regions during major depression. They also indicate that tCho concentration in the hippocampus before Agomelatine treatment predicts clinical improvement. tCho concentration has been proposed to reflect cell membranes turnover and may therefore be a marker of dendritic remodeling. Further studies are needed to better delineate the biological significance of hippocampal tCho signal in major depressive disorder.

References