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Spectroscopic metabolomic abnormalities in the thalamus related to auditory hallucinations in patients with schizophrenia

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Abstract

Objective: Previous studies have found neurochemical abnormalities in thalamic nuclei in patients with schizophrenia. These abnormalities have been associated with information processing deficiencies and symptom formation. There are no metabolic spectroscopy studies in patients with schizophrenia attending to auditory hallucinations. The aim of the present study is to explore metabolic Magnetic Resonance Spectroscopy (MRS) ratio differences in the thalamus between schizophrenic patients with and without auditory hallucinations and control subjects.
Methods: MRS studies (MRI 1.5 T unit) were performed in 49 patients with schizophrenia (30 with auditory hallucinations and 19 without auditory hallucinations) and 37 controls. ^{1}H MRS imaging was used to acquire 2 transverse slices (TR/TE 2700/272 ms, region of interest 110 × 100 × 23 mm). In the quantitative analysis four elements of volume (9.2 × 9.2 × 23 × 4 mm), added into one spectrum representative of each thalamus, were chosen in the slice passing through the main body of the thalamus. The areas of metabolites were integrated with the jMRUI program.
Results: The patients with schizophrenia had significantly lower bilateral NAA/Cho ratios when compared with healthy subjects. There was also a lower NAA/Cho ratio in the right thalamus in patients with auditory hallucinations compared to patients without auditory hallucinations and control subjects. Significant correlations were found between metabolic ratios and BPRS, PANSS and PSYRATS scores, age of onset of auditory hallucinations, and age of subjects.

Abbreviations: AH, auditory hallucinations; ^{1}H MRS, Proton Magnetic Resonance Spectroscopy; MRI, Magnetic Resonance Imaging; MRSI, Magnetic Resonance Spectroscopy Imaging; NAA, *N*-acetylaspartate; Cho, Choline; Cr, Creatine; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scale; FOV, field of view; 2DTSI, two dimensional turbo-spectrocopic imaging sequence; PRESS, point resolved echo spectroscopy sequences; ANOVA, analysis of variance.

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Conclusions: Choline and NAA ratio abnormalities determined by thalamic spectroscopy may be related to the pathogenesis of auditory hallucinations in patients with schizophrenia.

Keywords: Schizophrenia; Auditory hallucinations; Spectroscopy; Thalamus; Choline; NAA ratios

1. Introduction

Several studies have strongly demonstrated that schizophrenia is a chronic brain disorder structurally and functionally affecting the cortical and subcortical regions of the brain involved in cognitive, emotional and motivational aspects of human behavior (Kasai et al., 2002).

Proton Magnetic Resonance Spectroscopy (^{1}H MRS) allows the investigation of in vivo neurochemical pathology of schizophrenia (Ross and Bluml, 2001). The most frequently described metabolic changes have been shown in the frontal and temporal lobes, basal ganglia, thalamus and cerebellum, suggesting a network disorder involving the corticostriatal and cortico-thalamo-cerebellar circuits (Keshavan et al., 2000). *N*-acetylaspartate (NAA), choline (Cho) and creatine (Cr) are central nervous system compounds most frequently observed in ^{1}H MRS. NAA is mainly located in neurons and is a marker of their viability and function (Abbott and Bustillo, 2006). Likewise, NAA plays a role in mitochondrial oxidative metabolism (Pirko et al., 2005). Cr is a marker for brain cell density in glial and neuronal cells and is also involved in cellular energy metabolism. Cho, as a precursor for neurotransmitter acetylcholine and membrane compounds (phospholipids, phosphatidylcholine and sphingomyelin) is related with the turnover of membranes (Pirko et al., 2005; Ohara et al., 2000; Miller, 2001; Hammen et al., 2003).

Both in vivo neuroimaging and post-mortem studies support a key role of the thalamus in schizophrenia (Sim et al., 2006). The thalamus comprises complex functions such as sensory relay, motor relay, maintenance and regulation of consciousness, attention and memory (Schmahmann, 2003). It has been implicated in deficits in early processing and multimodal integration in schizophrenia, such as filtering stimuli, focusing attention and sensory gating (Sim et al., 2006; Andreasen et al., 1994). Further evidence of the thalamic relevance in schizophrenia comes from morphological and functional neuroimaging studies of high risk individuals with schizophrenia and relatives that proposed thalamic alterations as features of neurobiological risk for schizophrenia (Fusar-Poli et al., 2007; Seidman et al., 2007).

Several ^{1}H MRS studies have shown a decrease in thalamic NAA (Omori et al., 1997, 2000; Deicken et al., 2000; Auer et al., 2001; Ende et al., 2001; O'Neill et al., 2004; Jakary et al., 2005) and Cho levels (Omori et al., 2000; Ende et al., 2001) in patients with schizophrenia as compared to controls, in some cases expressed as ratios to Cr (Omori et al., 2000; Deicken et al., 2000; Auer et al., 2001). These abnormalities were located in post-mortem tissue (Omori et al., 1997) either bilaterally (Deicken et al., 2000; Ende et al., 2001; Jakary et al., 2005) or in just the left thalamus (Omori et al., 2000; Auer et al., 2001). However, other studies did not confirm these results (Hagino et al., 2002; Delamillieure et al., 2002; Jensen et al., 2004). Study reliability is probably a major limitation since most studies seem to be challenged by small sample sizes (Steen et al., 2005), different locations and ^{1}H MRS methodology. Clinical heterogeneity could also explain these controversial findings (Sim et al., 2006). However, Ohara et al. (2000) suggested that in spite of they could not find any differences in metabolic profile in patients with simple schizophrenia, the pathophysiology of this entity may be different from those of other types of schizophrenia which would raise the possibility of studying other clinical subtypes.

It is well-known that the thalamus is a key location for auditory information processing. Moreover, thalamic abnormalities in schizophrenia have been associated with information processing deficiencies and symptom formation (Braff, 1993; Buchsbaum et al., 1996; Crespo-Facorro et al., 1999; Hazlett et al., 1999; Javanbakht, 2006). In particular, psychotic features have been associated with specific thalamic nuclei and disturbance of cortico-subcortical circuits (Sim et al., 2006). However, to the best of our knowledge, there are no ^{1}H MRS studies in patients with schizophrenia attending to auditory hallucinations (AH). The interest of such a study arises from the fact that AH are one of the core symptoms of schizophrenia and could be a good alternative phenotype (Sanjuán et al., 2006a).

The present study had two objectives: a) to explore potential metabolic ^{1}H MRS ratio differences (NAA/Cho, NAA/Cr, Cho/Cr) in the thalamus between patients with schizophrenia and control subjects and b) to examine ^{1}H MRS thalamic differences between schizophrenic patients with and without AH.