学 位 論 文 の 要 旨

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学 位 論 文 名 PROTON MAGNETIC RESONANCE SPECTROSCOPY OF THE ANTERIOR CINGULATE GYRUS, INSULAR CORTEX AND THALAMUS IN SCHIZOPHRENIA ASSOCIATED WITH IDIOPATHIC UNCONJUGATED HYPERBILIRUBINEMIA (GILBERT'S SYNDROME)

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論 文 内 容 の 要 旨

INTRODUCTION

Idiopathic unconjugated hyperbilirubinemia (Gilbert's syndrome, GS) is a relatively common congenital hyperbilirubinemia occurring in 3-7% of the world's population. Recently, it was reported that unconjugated bilirubin might be associated with neurotoxicity in the developing nervous system. The neurodevelopmental hypothesis proposes that schizophrenia is due to subtle neuropathological change occurring in utero or early postnatal life. Therefore, we proposed a relationship between unconjugated bilirubin and the etiology of and vulnerability of schizophrenia. Proton magnetic resonance spectroscopy (^{1}H-MRS), a recent development in MR technology, allows biochemical constituents to be directly assayed in vivo. N-acetyl aspartate (NAA), one of the prominent peaks of ^{1}H-MRS, has been reported to exist mainly intraneuronally. A reduction of NAA is considered to reflect a loss of neurons and axons and/or neural dysfunction. Choline (Cho), a marker of the membrane phospholipids is increased in myelin breakdown. Creatine-phosphocreatinine (Cr) is an energy marker of cells, and myoinositol (mI), a glial marker, is decreased with glial dysfunction. Patients with schizophrenia had lower levels of NAA than healthy subjects. It was reported that unconjugated bilirubin is toxic to astrocytes and neurons, damaging mitochondria and plasma membranes, therefore, we hypothesized that unconjugated bilirubin would affect

some metabolites in the brain. In this study, in order to confirm this metabolic alteration, levels of NAA, Cho, and mI in the anterior cingulate gyrus, insular cortex, and thalamus of schizophrenic patients with GS were studied because many previous brain imaging studies have suggested that the anterior cingulate gyrus, insular cortex, and thalamus are the sites of abnormalities of structure and function in schizophrenia.

MATERIALS AND METHODS

1. Subjects: Schizophrenic patients with GS (n=15) and without GS (n=15) (DSM-IV criteria) were recruited. Diagnoses were determined by consensus of three senior psychiatrists based on extended interviews and medical chart review. Psychiatric symptoms were rated by a senior psychiatrist (T. M.), blind to MRS findings and diagnosis (with or without GS), on the same day as the MRS examination using the Brief Psychiatric Rating Scale (BPRS) and the Positive and Negative Syndrome Scale (PANSS). They were matched with healthy subjects (n=20) for age and sex. Psychiatric symptoms (BPRS, PANSS) were matched with schizophrenia with GS and without GS. All patients were right-handed and treated with neuroleptic agents.

2. ^{1}H-MRS: MRI and spectroscopy were performed on a General Electric (GE) Signa 1.5 Tesla MR Imaging system (GE Medical systems, Milwaukee, WI) using a standard head coil. T_2 weighted fast spin echo images were used to obtain sagittal and axial views of brain. The mean voxel size studied was $8cm^3$ in the left anterior cingulate gyrus, insular cortex, and thalamus. ^{1}H-spectra were acquired with PROBE (Proton Brain Exam), the manufactures' automated MRI protocol. Using the coregistered axial T_2-weighted MR images to identify anatomy, an individual ^{1}H-MRS voxel was selected within each of the following structures (in left hemispheres): anterior cingulate gyrus, insular cortex, and thalamus. The area ratios of each peak were expressed as relative ratio to Cr in each spectrum.

3. Statistics: Analysis of variance (ANOVA) with post-hoc Bonferronis's protected least-significance difference (PLSD) was used to test for group differences in NAA/Cr,

Cho/Cr, and mI/Cr, mean of age, BPRS, PANSS, duration of illness and neuroleptic therapy, and mean dosage of neuroleptics.

RESULTS AND DISCUSSION

The major finding in this study is that the schizophrenia with GS, showed significant decreases of NAA/Cr, Cho/Cr, and mI/Cr in the anterior cingulate gyrus and insular cortex. However, since all metabolite ratios are reduced in patients compared with healthy subjects, we should consider the possibility that our results are consistent with atrophy of brain areas investigated in the patients. In the thalamus, only schizophrenic patients with GS showed significant decreases of NAA/Cr, Cho/Cr, and mI/Cr compared to healthy subjects, and compared to schizophrenic patients without GS, showed significant decreases of only NAA/Cr and mI/Cr. Assuming that NAA is a neuron number and/or viability marker, decreases of NAA/Cr in schizophrenics with GS suggest the effect of unconjugated bilirubin on the structure and/or function of the anterior cingulate gyrus, insular cortex, and thalamus. Cho is a marker of the membrane phospholipid state and decreases of Cho/Cr in schizophrenics with GS suggest the effects of unconjugated bilirubin on the phospholipid state of each region. A decrease of mI/Cr, as a glial marker and/or viability marker, in schizophrenics with GS suggests the effect of unconjugated bilirubin on the glial structure and/or function of each region. However, this study has limitations in that we reached our conclusions from metabolite ratios rather than absolute concentrations. Our findings should stimulate further prospective and laboratory studies on hyperbilirubinemia in schizophrenic patients to evaluate this well-known phenomenon.

CONCLUSION

Our findings suggest that brain metabolism is more severely compromised in the sub-type of schizophrenia with GS.