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GABA concentration in schizophrenia patients and the effects of antipsychotic medication: A proton magnetic resonance spectroscopy study

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ABSTRACT

Gamma-amino butyric acid (GABA) is thought to play a role in the pathophysiology of schizophrenia. High magnetic field proton magnetic resonance spectroscopy (^{1}H-MRS) provides a reliable measurement of GABA in specific regions of the brain. This study measured GABA concentration in the anterior cingulate cortex (ACC) and in the left basal ganglia (ltBG) in 38 patients with chronic schizophrenia and 29 healthy control subjects.
There was no significant difference in GABA concentration between the schizophrenia patients and the healthy controls in either the ACC (1.36 ± 0.45 mmol/l in schizophrenia patients and 1.52 ± 0.54 mmol/l in control subjects) or the ltBG (1.13 ± 0.26 mmol/l in schizophrenia patients and 1.18 ± 0.20 mmol/l in control subjects). Among the right handed schizophrenia patients, the GABA concentration in the ltBG was significantly higher in patients taking typical antipsychotics (1.25 ± 0.24 mmol/l) than in those taking atypical antipsychotics (1.03 ± 0.24 mmol/l, $p = 0.026$). In the ACC, the GABA concentration was negatively correlated with the dose of the antipsychotics ($rs = -0.347$, $p = 0.035$). In the ltBG, the GABA concentration was positively correlated with the dose of the anticholinergics ($rs = 0.403$, $p = 0.015$).
To the best of our knowledge, this is the first study to have directly measured GABA concentrations in schizophrenia patients using ^{1}H-MRS. Our results suggest that there are no differences in GABA concentrations in the ACC or the ltBG of schizophrenia patients compared to healthy controls. Antipsychotic medication may cause changes in GABA concentration, and atypical and typical antipsychotics may have differing effects. It is possible that medication effects conceal inherent differences in GABA concentrations between schizophrenia patients and healthy controls.

1. Introduction

1.1. The Gamma-amino butyric acid (GABA) system in schizophrenia

Gamma-amino butyric acid (GABA) is thought to play a role in the pathophysiology of schizophrenia (Guidotti et al., 2005; Wassef et al., 2003).

1.1.1. Postmortem studies

Postmortem studies of $GABA_A$ receptors in chronic schizophrenia have reported inconsistent findings. Some

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case–control studies have reported increased $GABA_A$ receptor binding in the cingulate cortex (Hanada et al., 1987; Benes et al., 1992), whereas others have found it to be decreased (Squires et al., 1993) or unchanged (Pandey et al., 1997). The $GABA_A$ receptor is composed of various subunits. Ishikawa et al. (2004) found a higher density of alpha 1 and beta 2/3 subunits in the prefrontal cortex (PFC) of schizophrenia patients compared to control subjects.

The 65 and 67 kDa isoforms of glutamic acid decarboxylase (GAD) are key enzymes in GABA synthesis, and a number of studies have investigated their significance in schizophrenia. Bird et al. (1977) found that GAD levels were decreased in the nucleus accumbuns, amygdala, hippocampus, and putamen of schizophrenia patients. Benes et al. (2000) observed no change in GAD density in the anterior cingulate cortex (ACC) of schizophrenia patients. Woo et al. (2004) found a decrease in the number of GAD67 mRNA-containing neurons in the ACC of schizophrenia patients compared to control subjects. Dracheva et al. (2004) reported an increased expression of GAD65 and GAD67 mRNA in the dorsolateral PFC and in the occipital cortex of schizophrenia patients compared to control subjects.

1.1.2. In vivo neuroimaging studies

Neuroimaging studies using radio active ligands have also reported inconsistent findings. Some studies using single photon emission computed tomography (SPECT) have failed to find any evidence of $GABA_A$ receptor binding abnormalities in the brains of schizophrenia patients compared to healthy controls (Busatto et al., 1997; Verhoeff et al., 1999; Abi-Dargham et al., 1999). One study, however, found a significant correlation between task performance and $GABA_A$/benzodiazepine receptor binding in the frontal and occipital cortices of schizophrenia patients (Ball et al., 1998). Using positron emission tomography (PET), Asai et al. (2008) reported no differences in [11C] Rol5-4513 binding (which represents the density of the alpha 5 subunit of the $GABA_A$/benzodiazepine receptor) in the PFC and the hippocampus of schizophrenia patients compared to control subjects; among the schizophrenia patients, the degree of binding was found to be negatively correlated with negative symptom scores.

1.1.3. The effects of antipsychotic medication on the GABA system in the basal ganglia and cingulate cortex

Gunne et al. (1984) reported an inhibition of GAD activity in monkeys following treatment with antipsychotics. Studies in rats have reported that treatment with typical antipsychotic drugs such as haloperidol (Jolkkonen et al., 1994; Delfs et al., 1995a,b; Laprade and Soghomonian, 1995; Sakai et al., 2001), fluphenazine (Chen and Weiss, 1993; Johnson et al., 1994), and sulpiride (Laprade and Soghomonian, 1995) increased the expression of GAD67 and GAD67 mRNA in the basal ganglia, whereas atypical antipsychotic drugs such as clozapine (Delfs et al., 1995a) and olanzapine (Sakai et al., 2001) did not. These changes may be reflected in the dyskinetic and antipsychotic actions of typical antipsychotics (Delfs et al., 1995b; Sakai et al., 2001). Zink et al. (2004) reported that both haloperidol and clozapine increased [^{3}H]-muscimol binding to $GABA_A$ receptors in the ACC, whereas increased $GABA_A$ receptor binding in the basal ganglia was only induced by haloperidol. Although the underlying mechanism is unclear, these results suggest that antipsychotics may affect the GABA system, and that typical and atypical antipsychotics may have differing effects.

1.2. The role of the ACC and the basal ganglia in schizophrenia

Several changes in the ACC of schizophrenia patients have been reported: (1) alterations in GAD levels (Woo et al., 2004), (2) morphological change (Baiano et al., 2007; Fujiwara et al., 2007; Zetzsche et al., 2007), and (3) activation deficits during cognitive tasks (Liddle et al., 2006; Yücel et al., 2007; Brüne et al., 2008; Koch et al., 2008). Menzies et al. (2007) found that GABA-modulating drugs affected working memory performance and induced activation changes in the ACC of schizophrenia patients. The basal ganglia contain the striatum, the globus pallidus, and other structures. The striatum is thought to receive GABAergic interneurons from other regions of the brain, in particular the globus pallidus and the cerebral cortex (Bolam et al., 2000). The PFC is thought to be involved in the pathophysiology of schizophrenia on three levels: morphologically (Meda et al., 2008), functionally (Lee et al., 2006), and histologically (Woo et al., 2008). The PFC tonically inhibits striatal dopamine projections, and it is thought that this is mediated by GABA interneurons (Carlsson, 2001; Akil et al., 2003; Perlman et al., 2004). The globus pallidus is also thought to be involved in the pathophysiology of schizophrenia (Galeno et al., 2004; Spinks et al., 2005). An increase in $GABA_A$ receptor binding in the basal ganglia following the administration of antipsychotics has been reported (Zink et al., 2004).

1.3. Magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) provides an in vivo measurement of brain metabolites such as myo-inositol, N-acetylaspartate, choline-containing compounds, Glx (glutamate plus glutamine), creatine, and phosphocreatine in the human brain. The recent introduction of high magnetic field MRS has enabled the reliable measurement of GABA in specific brain regions. Reduced concentrations of GABA in depressed patients (Hasler et al., 2007) and unchanged concentrations of GABA in panic disorder patients (Hasler et al., 2008) have been reported in areas of the frontal lobe. To the best of our knowledge, no previous ^{1}H-MRS study has examined GABA concentrations in schizophrenia patients. In the present study, ^{1}H-MRS was used to compare GABA concentrations in medicated chronic schizophrenia patients with those of healthy controls using a high magnetic field device. The regions of interest (ROIs) were located in the ACC and in the left basal ganglia (ltBG); the ltBG contain the striatum, globus pallidus, and other structures. The effects of typical and atypical antipsychotic medication on GABA concentrations in the basal ganglia and cingulate cortex were also examined.

2. Method

2.1. Subjects

Thirty-eight patients with chronic schizophrenia and twenty-nine healthy control subjects participated in this