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Review

Phosphorus magnetic resonance spectroscopy studies in schizophrenia

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ABSTRACT

Phosphorus magnetic resonance spectroscopy (^{31}P MRS) allows *in vivo* quantification of phosphorus metabolites that are considered to be related to membrane turnover and energy metabolism. In schizophrenia (SZ), ^{31}P MRS studies found several abnormalities in different brain regions suggesting that alterations in these pathways may be contributing to the pathophysiology. In this paper, we systematically reviewed the ^{31}P MRS studies in SZ published to date by taking patient characteristics, medication status and brain regions into account. Publications written in English were searched on http://www.ncbi.nlm.nih.gov/pubmed/, by using the keywords 'phosphomonoester', 'phosphodiester', 'ATP', 'phosphocreatine', 'phosphocholine', 'phosphoethanolamine','glycerophosphocholine', 'glycerophosphoethanolamine', 'pH', 'schizophrenia', and 'MRS'. Studies that measured ^{31}P metabolites in SZ patients were included. This search identified 52 studies. Reduced PME and elevated PDE reported in earlier studies were not replicated in several subsequent studies. One relatively consistent pattern was a decrease in PDE in chronic patients in the subcortical structures. There were no consistent patterns for the comparison of energy related phosphorus metabolites between patients and controls. Also, no consistent pattern emerged in studies seeking relationship between ^{31}P metabolites and antipsychotic use and other clinical variables. Despite emerging patterns, methodological heterogeneities and shortcomings in this literature likely obscure consistent patterns among studies. We conclude with recommendations to improve study designs and ^{31}P MRS methods in future studies. We also stress the significance of probing into the dynamic changes in energy metabolism, as this approach reveals abnormalities that are not visible to steady-state measurements.

1. Introduction

That there are biochemical abnormalities in schizophrenia is well accepted. Defining the specific abnormalities in living brain has been more problematic. Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) is a specialized neuroimaging technique that allows *in vivo* measurement of multiple functionally important phosphorus-containing metabolites. For brain studies, these fall into one of two broad groups: cell membrane related phospholipids and energy related metabolites.

The phospholipid peaks include phosphomonoesters (PME) largely composed of phosphocholine (PC) and phosphoethanolamine (PEth), and phosphodiesters (PDE) mainly composed of glycerophosphocholine (GroPCho) and glycerophosphoethanolamine (GroPEth). PME components are believed to be freely mobile membrane phospholipid precursors, whereas PDE represent breakdown products of these metabolites. Some of these breakdown products are key intracellular signaling molecules. Because of the reciprocal roles played by PME and PDE in membrane turnover and intracellular signaling, their ratio also has been studied.

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Energy related metabolites include the two main pools of high-energy phosphates (HEP), adenosine triphosphate (ATP) and phosphocreatine (PCr), as well as inorganic phosphate (Pi). The resonances traditionally reported as ATP in fact would be more appropriately labeled NTP, but ATP constitutes about 70–80% of all nucleotide triphosphates (NTP) in the brain and that same proportion of the NTP signal measured by ^{31}P-MRS. We use the term ATP in this report because it is so commonly used in the literature. In addition, ATP (as well as signals from ADP and AMP) can be quantified using three different phosphorus resonances and studies have utilized variable approaches to this quantification. We will not distinguish studies reporting so-called alpha, beta, or gamma ATP measures. ATP synthesized from ADP and Pi in the mitochondria is converted to PCr and is shuttled to cytoplasm. PCr acts as a reservoir for HEP and the transfer of high-energy phosphate groups between ATP and PCr is a reversible reaction catalyzed by the creatine kinases (CK) to generate ATP in response to energy demand. The reaction catalyzed by CKs is critical for maintaining stable ATP levels which are in turn critical for all energy requiring processes including ion pumping and the modification of the activity state of numerous enzymes. Given the importance of the relationship between ATP and PCr, investigators have often reported the ATP/PCr ratio. One additional measure can be obtained from ^{31}P-MRS spectra: parenchymal pH. pH is calculated based on the chemical shift difference between Pi and PCr. Tissue pH falls when lactic acid builds up as a consequence of reduction in oxidative phosphorylation and rise in glycolysis, making pH an index of which metabolic pathways are being used predominantly. For more extensive reviews of the information that ^{31}P-MRS provides, see (Stanley et al., 2000; Fukuzako, 2001; Arias-Mendoza and Brown, 2003).

Because schizophrenia (SZ) is associated with multiple abnormalities in brain biochemistry, ^{31}P-MRS has been used to gain insight into the pathophysiology of this condition ever since the technique became available. Abnormalities with respect to both phospholipid metabolites and energy related metabolites are reported in SZ and these abnormalities could provide significant insights into the pathophysiology of SZ with implications for the development of novel treatments. However, there is significant heterogeneity among studies in subject characteristics, data acquisition methods, and anatomical locations studied, and there is no consensus with regards to the nature of abnormalities. Therefore, we hypothesized that a systematic review of the accumulated literature might provide deeper insights into the role of phosphorus metabolites in SZ pathophysiology.

2. Methods

We searched for ^{31}P MRS studies that included patients with SZ. Articles were identified on pubmed (http://www.ncbi.nlm.nih.gov/pubmed) using various combinations of the keywords “phosphorus”, “31P”, “magnetic resonance spectroscopy”, “MRS”, “schizophrenia”, “psychotic” and “psychosis”. Reference lists of relevant articles were searched for additional studies. Articles were included if they met the following criteria: published in English; measured ^{31}P metabolites *in vivo* in SZ patients; included adult subjects. All studies published by December 2014 were included. We extracted results for the following measures: PDE (or GroPCho and GroPEth), PME (or PCho and PEth), PCr, ATP, PCr/ATP, Pi, and pH.

Studies that included first episode and/or medication-naïve patients were also reviewed separately, as longitudinal studies suggest alterations in phosphorus metabolites with new treatment or over time in the follow up of first episode patients (Miller 2009, 2012; Jayakumar 2010). In addition, we analyzed data collected in frontal and temporal cortices and in subcortical structures separately, as some abnormalities in schizophrenia may be global, while others may vary with location.

3. Results

Online literature search identified 103 potentially relevant articles. 52 of these articles were eliminated due to following reasons: review articles or commentary (n = 30), not including schizophrenia subjects (n = 11), in postmortem samples (n = 3), not using ^{31}P MRS (n = 1), not reporting phosphorus metabolite levels (n = 2) and a combination of factors above (n = 5). Search through the reference lists identified 1 additional study. Overall, we found 42 ^{31}P-MRS studies that compared metabolites with healthy controls, and the rest included only SZ patients. Studies varied in the clinical characteristics of patients, field strengths used to acquire data, regions of interest, data processing methods, and metabolites measured. Eight studies included patients reported as medication-naïve first episode (Pettegrew et al., 1991; Keshavan et al., 1993; Fukuzako et al., 1999; Jayakumar et al., 2003; Gangadhar et al., 2004, 2006; Jayakumar et al., 2006; Jayakumar et al. 2010), 2 studies included separate analyses for medication-naïve and other patients (Stanley et al., 1995; Yacubian et al., 2002) and 4 additional studies included first episode patients (some were taking medication) (Jensen et al., 2004, 2006; Miller et al., 2009; Miller et al. 2012). 7 studies acquired data at 4T and the rest used 1.5 or 2T scanners. For the location of data acquisition 14 studies used chemical shift imaging (CSI) whereas the rest used a-priori defined regions of interest, either single or multiple voxels. There were overlaps in subjects and/or ^{31}P MRS data between several studies: 13/16 of patient and control scans in Miller et al., 2012 were included in Miller et al., 2009 study; subjects in Theberge et al., 2004, Jensen et al., 2006, Volz et al., 1997a and Volz 1998b were subsets of cohorts in Jensen et al., 2002, Jensen et al. 2004, Volz et al., 1997b and Volz et al., 1998a studies, respectively. Also, sample in Volz et al., 1997b study consisted of 10 MF patients in addition to the medicated patients in Volz et al., 1998a, and included separate analysis for MF and medicated patients. We will next review studies comparing two classes of metabolites between patients and controls, and studies investigating the relation of metabolite levels with antipsychotic (AP) use, clinical characteristics and cognition.

4. Phospholipid metabolites

4.1. Frontal lobe

In the frontal lobe (FL), 27 studies reported results on phospholipid metabolites in SZ. One study included a sample of completely medication-naïve (MN) patients (Pettegrew et al., 1991), and two included separate analyses for medication-naïve patients (Stanley et al., 1995; Yacubian et al., 2002). While Pettegrew and Stanley reported reduced PME and elevated PDE in dlPFC, PDE was reduced in the Yacubian study with no change for PME. Another research group published four studies which included only FE patients some using medications. Three of these found increased GroPCho in ACC with no change in any other phospholipids (Jensen et al., 2004; Miller et al., 2009, 2012), and one reported no differences for any phospholipid metabolites in the FL (Jensen et al., 2006). However, GroPCho returned to the control levels in Miller 2009, and 2012 studies at 30 months and 52 months, respectively. In contrast, PDE was reduced in 4 studies that included a mix of medication-naïve patients and chronic patients after a medication wash-out, in the mPFC (Volz et al., 2000), lPFC and mPFC (Smesny et al., 2007), and FL (Volz et al., 1997b; Yacubian et al., 2002). While Smesny and colleagues also found reduced PME in bilateral mPFC, Volz (in both studies) and Yacubian reported no change. The remaining studies included chronic