Abnormal Bioenergetics in the 1st episode Schizophrenia, Preliminary Studied by the Magnetization Transfer 31P-MRS

Fei Du[1], Cagri Yuksel[1], Scott Lukas[1], Bruce Cohen[1], and Dost Ongur[1]
[1]*McLean Hospital, Harvard Medical School, Belmont, MA, United States*

Target Audience: Neuroscientist, Psychiatrist, MR physicist, Pharmacologist, Neuroimaging Scientist

Purpose: Schizophrenia (SZ) is a brain disorder that places a heavy burden on families and communities. There is substantial *postmortem* evidence (1-2) as well as *in vivo* studies of ^{1}H- and ^{31}P-MRS (3, 4) suggesting that patients with SZ exhibit mitochondrial and bioenergetic abnormalities. *In vivo* probes of mitochondrial function and cerebral bioenergetics have the capacity to provide crucial information to characterize the exact bioenergetic abnormalities and delineate their relationships with pathophysiology and symptom presentation. In a prior study, we observed abnormalities of pH, creatine kinase (CK) activity (forward chemical exchange constant, k_f) as well as the phospholipid-phosphodiester (PDE) signal in the prefrontal lobe of chronic SZ patients (5). In the present study we probed for abnormal bioenergetics in 1st episode SZ patients, using the same method—dynamic ^{31}P magnetization transfer spectroscopy (^{31}P-MT-MRS) we used in the chronically ill patients (5).

Methods: Two groups of participants consisting of patients with 1st episode SZ (N=12) and age- and sex-matched healthy controls (HC, N=7) were recruited for these studies. SZ patients were screened with a series of standard psychiatric diagnostic and research scales. Only patients who were taking a non-clozapine second generation antipsychotic were enrolled. For HC, any subject with a history of a medical condition that might affect the central nervous system at the time of scanning was excluded. ^{31}P-MT-MRS related acquisitions were conducted using a 4T whole-body scanner; with experimental details and methods as described before (5).

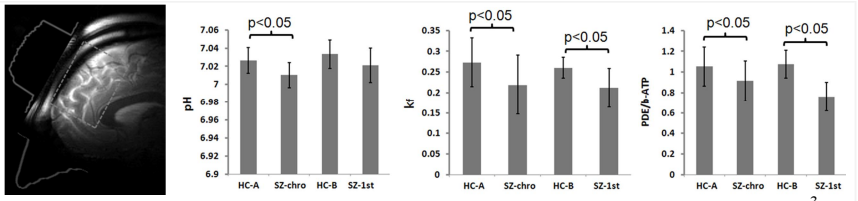

Fig1. **Left:** T_2-weighted brain anatomic imaging and sensitivity profile (6×6×4 cm^3) of ^{31}P-MRS. **Right:** measures of pH, kf and PDE/β-ATP in chronic (SZ-chro) and 1st episode (SZ-1st) SZ patients as well as age- and sex-matched healthy controls (HC-A and HC-B were the matched controls for chronic and 1st episode SZ study, respectively). The data from the chronic SZ patients study were previously reported (Ref. 7).

Results: Although the number of subjects is still small in this pilot study, there were substantial and statistically significant reductions in both CK k_f and metabolic ratio of PDE/β-ATP in 1st episode patients with SZ (see Fig 1). The metabolic ratios of other phosphate-containing compounds related to β-ATP were not significantly altered in these patients. Therefore, the general pattern of bioenergetic abnormalities in 1st episode SZ was similar to that of chronic patients. However, compared to chronic patients, pH abnormalities were not present in the 1st episode SZ patients (see Fig. 1).

Discussion and Conclusion: Using a novel ^{31}P dynamic MRS technique, we provide the first direct *in vivo* evidence for specific bioenergetic abnormalities in SZ patients. Reduced k_f of the CK reaction in patients with SZ is consistent with *postmortem* evidence of abnormalities in CK enzyme activity (1) and oxidative phosphorylation as well as mitochondria-related genes and gene expression (2). The intracellular pH reduction in chronic SZ patients suggests a shift from oxidative phosphorylation towards glycolysis, providing additional evidence that bioenergetic abnormalities exist in these patients. Additionally, reduced CK k_f in the presence of stable concentrations of ATP and PCr at baseline suggests that energy metabolism is dysfunctional in SZ, but that compensatory mechanisms of energy production at baseline are sufficient to approximate those seen in the HC. However, at times of high demand, ATP availability might be compromised, because CK is required to catsalyze the transfer of high energy phosphates from storage in PCr to ATP in order to preserve relatively stable ATP levels needed for maintaining constant neural activity.

What are the most relevant physiological changes in early SZ? A growing literature suggests that accelerated glutamate signaling is present in never- or minimally-treated 1st episode SZ patients (6). This is followed by a decrease in transmitter that parallels disease progression, suggesting an impoverishment of glutamatergic synapses over time (7). Glutamate signaling is an energy-intensive process supported by activation of Na+/K+ dependent ATPases, which is tightly coupled with the CK reaction (8). These relationships reveal that it is not surprising that patients with SZ have significant abnormalities in brain bioenergetics, which were clearly identified using our novel ^{31}P-MT-MRS procedure. Our studies with both 1st episode and chronic SZ patients may help map the interactive mechanisms underlying disease. Combining evidence on bioenergetic and glutamatergic processes, SZ may be characterized by an initial active phase of excessive glutamatergic neurotransmission and bioenergetic activity, which then progressively becomes downregulated in the chronic condition, result in decreased intracellular pH. These findings provide insight into the progression of SZ and highlight the value of using cerebral activity and bioenergetic metabolism as new biomarkers of the pathophysiology of SZ.

References: 1. Burbaeva, World J Biol Psychiatry 2003; 2. Mulcrone, Schizophr Res 1995. 3. Ongur, Psychiatry Res 2009; 4. Pettegrew, Arch Gen Psychiatry 1991; 5. Du, JAMA Psychiatry 2014; 6. Bustillo, Mol Psychiatry 2009; 7. Marsman, Schizophr Bull 2013; 8. Du, PNAS 2008. **Acknowledgements:** R01MH094594 (NIMH) and Foundations from NARSAD and the Shervert Frazier Research Institute at McLean Hospital.