^{1}H MRS Reveals GABA and Glutamatergic Compound Elevations in Subjects at Ultra-High Risk for Schizophrenia

Camilo de la Fuente-Sandoval[1], Pablo L Ortiz[2], Xiangling Mao[3], Patricia Alavarado-Alanis[4], Oscar Rodríguez-Mayoral[5], Francisco Reyes-Madrigal[4], Ariel Graff-Guerrero[6], Rodolfo Solis-Vivanco[7], Rafael Favila[8], and Dikoma C Shungu[3]

[1]Neuropsychiatry & Laboratory of Experimental Psychiatry, Instituto Nacional de Neurología y Neurocirugía (INNN), Mexico City, Distrito Federal, Mexico, [2]Education, INNN, Mexico City, Distrito Federal, Mexico, [3]Radiology, Weill Cornell Medical College, New York, NY, United States, [4]Laboratory of Experimental Psychiatry, INNN, Mexico City, Distrito Federal, Mexico, [5]Early Psychosis Intervention, Hospital Fray Bernardino Alvarez, Mexico City, Distrito Federal, Mexico, [6]Multimodal Neuroimaging Schizophrenia Group, Centre for Addiction and Mental Health, Toronto, ON, Canada, [7]Laboratory of Neuropsychology, INNN, Mexico City, Distrito Federal, Mexico, [8]MR Advanced Applications, GE Healthcare, Mexico City, Distrito Federal, Mexico

INTRODUCTION

Schizophrenia (SZ) is a highly debilitating neuropsychiatric disorder of young adulthood onset that has a population incidence of 1% and is the 9th leading cause of disability worldwide. The diagnosis of SZ, which is currently based primarily on symptoms and behavioral changes, usually requires the onset of the full-blown clinical syndrome. Thus, by the time patients are clinically diagnosed with SZ, multiple brain sites are affected, making the task of sorting out primary from secondary brain lesions challenging. Therefore, there is currently great interest in investigating clinical high risk or prodromal subjects in the field of SZ research, which focus on the few months to years before the onset of psychosis, since such studies offer the opportunity to evaluate dynamic changes that occur with illness progression to identify potential predictors of outcome to psychotic disorders from clinical high risk or prodromal stages. Recently, our group reported the results of a ^{1}H MRS study[1] that found significantly elevated levels of glutamate (Glu) in the striatum of subjects at ultra-high risk (UHR) for psychosis, suggesting early involvement of this excitatory amino acid neurotransmitter in SZ. In the present study, we used ^{1}H MRS to both replicate this dysregulation of the Glu system in subjects at ultra-high risk for SZ, and to investigate whether the inhibitory amino acid neurotransmitter system of GABA is also dysregulated in the early stages of SZ compared to healthy controls. To our knowledge, this is the first study to investigate simultaneously the GABAergic and glutamatergic systems in prodromal SZ.

METHODS

Subjects: Twenty-four subjects at UHR (6 females, mean age= 20.64±3.79) meeting the Structured Interview for Prodromal Syndromes (SIPS) criteria were enrolled into the study. Subjects were excluded from this group if they had (a) any concomitant medical or neurological illness, current substance abuse or history of substance dependence (excluding nicotine), and a comorbid axis I disorder; (b) were considered to be at high risk for suicide; or (c) showed psychomotor agitation. All subjects were antipsychotic-naïve and were able to provide written informed consent. Use of psychotropic medications (such as benzodiazepines) was not permitted for the duration of the study. Twenty-three healthy volunteer (HV) subjects (3 females, mean age= 21.00±3.43) assessed by the SCID-IV-NP, were studied identically as comparison subjects.

In vivo Brain GABA and Glx Measurements by ^{1}H MRS: All *in vivo* brain GABA and Glx (Glu+glutamine) spectra were recorded on a 3.0 T GE MR system from a 4.5x2.5x2.0-cm^3 voxel in the striatum and from a 3.0x2.5x2.5-cm^3 medial prefrontal cortex (MPFC) voxel that comprised the anterior cingulate cortex. Each spectrum was acquired in 13.4 min using the standard J-edited spin echo difference method and an 8-channel phased-array head coil, with TE/TR 68/1500 ms and 512 interleaved excitations. The resulting GABA and Glx peak areas were derived by frequency-domain fitting of the difference edited spectra, and then expressed as ratios relative to the peak area of simultaneously acquired unsuppressed voxel tissue water (W).

RESULTS

Compared to matched HV subjects, the UHR subjects showed significant elevations of both Glx/W (p = .006) and GABA/W (p = 0.04) in the MPFC (**Fig. 1**), as well as elevations of both Glx/W (p = .02) and GABA/W (p = 0.008) in the striatum (**Fig. 1**).

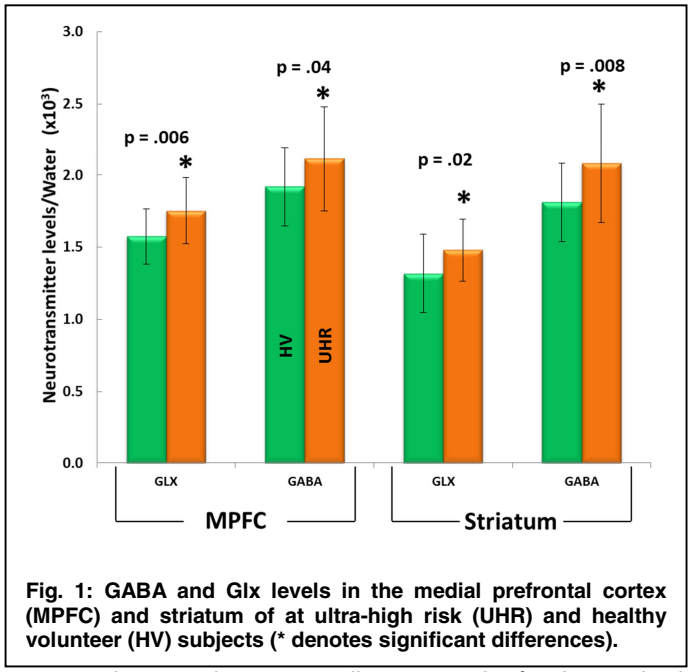

Fig. 1: GABA and Glx levels in the medial prefrontal cortex (MPFC) and striatum of at ultra-high risk (UHR) and healthy volunteer (HV) subjects (* denotes significant differences).

DISCUSSION AND CONCLUSION

This study has found regional elevations of both GABA/W and Glx/W in antipsychotic-naïve UHR subjects. In the context of a recent study[2] that also reported elevations of GABA and Glx in unmedicated patients with SZ, these findings collectively suggest that elevations of the two neurotransmitters may begin or be present at the prodromal stages of the illness and persist through the appearance of the full-blown clinical syndrome, and, potentially, beyond in subjects who remain unmedicated. Our findings of elevations of Glx in prodromal subjects are in general agreement with most prior MRS studies of early stages of SZ. On the other hand, our finding of elevated GABA in subjects at UHR for SZ are novel, and are an apparent contradiction to postmortem data[3], which have reported deficits of the neurotransmitters in SZ. A potential source of this discrepancy between the present *in vivo* MRS data and the *postmortem* data could be that antipsychotic medication use among SZ patients, which may lower or normalize Glx and GABA levels[2], might impede the reliable detection of markers of elevations of these transmitters in *postmortem* brain of SZ subjects exposed to substantial periods of medication treatment. In summary, the present results provide a compelling rationale for longitudinal investigations of brain GABA and Glx as potential noninvasive biomarkers of SZ and of conversion risk to psychosis in subjects at ultra-high risk.

LITERATURE CITED

[1] de la Fuente-Sandoval C et al. *Neuropsychopharm* 2011; **36**:1181. [2] Kegeles LS et al. *Arch Gen Psych* 2012; 69:449. [3] Lewis DA & Moghaddam B. *Arch Neurol* 2006; **63**: 1372.