Progress in Neuropsychopharmacology & Biological Psychiatry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Neurometabolite levels in antipsychotic-naïve/free patients with schizophrenia: A systematic review and meta-analysis of ^{1}H-MRS studies

Yusuke Iwata[a,b,c], Shinichiro Nakajima[a,b,c,d], Eric Plitman[a,e], Yukiko Mihashi[a], Fernando Caravaggio[a], Jun Ku Chung[a,e], Julia Kim[a,e], Philip Gerretsen[a,b,d,f], Masaru Mimura[c], Gary Remington[b,f], Ariel Graff-Guerrero[a,b,d,f,*]

[a] Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, M5T 1R8 Toronto, Ontario, Canada.
[b] Department of Psychiatry, University of Toronto, 250 College Street, M5T 1R8 Toronto, Ontario, Canada
[c] Department of Neuropsychiatry, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, 160-8582 Tokyo, Japan
[d] Geriatric Mental Health Division, Centre for Addiction and Mental Health, 80 Workman Way, M6J 1H4 Toronto, Canada
[e] Institute of Medical Science, University of Toronto, 1 King's College Circle, M5S 1A8 Toronto, Ontario, Canada
[f] Campbell Research Institute, Centre for Addiction and Mental Health, 1001 Queen St. W, M6J 1H4 Toronto, Ontario, Canada

ARTICLE INFO

Keywords:
Schizophrenia
Proton magnetic resonance spectroscopy
Untreated
Antipsychotic-naïve

ABSTRACT

Background: Studies using proton magnetic resonance spectroscopy (^{1}H-MRS) have reported altered neurometabolite levels in patients with schizophrenia. However, results are possibly confounded by the influence of antipsychotic (AP). Thus, this meta-analysis aimed to examine neurometabolite levels in AP-naïve/free patients with schizophrenia.

Methods: A literature search was conducted using Embase, Medline, and PsycINFO to identify studies that compared neurometabolite levels in AP-naïve/free patients with schizophrenia to healthy controls (HCs). Eight neurometabolites (glutamate, glutamine, glutamate + glutamine, *N*-acetylaspartate [NAA], choline, creatine, myo-inositol, and γ-Aminobutyric acid [GABA]) and seven regions of interest (ROI; medial prefrontal cortex, dorsolateral prefrontal cortex, frontal white matter, occipital lobe, basal ganglia, hippocampus/medial temporal lobe, and thalamus) were examined.

Results: Twenty-one studies (N = 1281) were included in the analysis. The results showed lower thalamic NAA levels (3 studies, n = 174, effect size = −0.56, P = 0.0005) in the patient group. No group differences were identified for other neurometabolites.

Conclusions: Our findings suggest that impaired neuronal integrity in the thalamus may be a potential trait maker in the early stages of schizophrenia.

1. Introduction

Proton magnetic resonance spectroscopy (^{1}H-MRS) permits the in vivo quantification of neurometabolites such as glutamate (Glu), glutamine (Gln), *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (mI), and γ-Aminobutyric acid (GABA) (Abbott and Bustillo, 2006). Accumulating evidence suggests these neurometabolites are altered in patients with schizophrenia (Schwerk et al., 2014).

Glutamatergic and GABAergic neurometabolites are of particular interest, given that hypofunctioning *N*-methyl D-aspartate (NMDA) receptors on GABAergic neurons as well as abnormal glutamatergic and GABAergic neurotransmission are implicated in the pathophysiology of schizophrenia (Coyle, 2006). Previous studies have reported increases in Glu, Gln, and Glu + Gln (Glx) levels in the early stages of schizophrenia (prodromal phase and first-episode of psychosis [FEP]) (Bartha et al., 1997; de la Fuente-Sandoval et al., 2011, 2013; Kegeles et al., 2012; Kraguljac et al., 2013; Theberge et al., 2002). A recent meta-analysis observed elevated Glu within the thalamus (Thal), and elevated Glx within the medial temporal lobe (mTem) and basal ganglia (BG), in patients compared to healthy controls (HCs) (Merritt et al., 2016). Conversely, a recent 7T ^{1}H-MRS study found lower Glu levels in the occipital lobe (Occ) of medicated, chronic patients with schizophrenia (Thakkar et al., 2017). Similarly, including both medicated and unmedicated patients, another meta-analysis reported greater age-related reductions in frontal Glu and Gln in patients compared to HCs (Marsman et al., 2013); these results could be confounded by the mixed

* Corresponding author at: Multimodal Imaging Group, Research Imaging Centre, Centre for Addiction and Mental Health, 80 Workman Way, 6th Floor, M6J 1H4 Toronto, Ontario, Canada.
E-mail address: ariel_graff@yahoo.com.mx (A. Graff-Guerrero).

https://doi.org/10.1016/j.pnpbp.2018.03.016
Received 17 January 2018; Received in revised form 2 March 2018; Accepted 20 March 2018

effects of both age and medication as older subjects tend to have a longer history of treatment. Collectively, these results suggest that glutamatergic neurometabolites may be increased in the early stages of schizophrenia and lowered or normalized during later stage of illness. However, no meta-analysis has examined glutamatergic neurometabolite levels exclusively in unmedicated patients with schizophrenia. Moreover, there are a limited number of studies measuring GABA levels (Taylor and Tso, 2015). A recent meta-analysis reported trend-level lower GABA levels with combining all brain regions in patients with schizophrenia (Schur et al., 2016). Notably, this meta-analysis also included both medicated and unmedicated subjects.

Abnormalities in other neurometabolites, including NAA, Cho, Cr, and mI, have also been reported (Brugger et al., 2011; Kraguljac et al., 2012). Lower NAA levels, indicative of reduced neuronal integrity (Brugger et al., 2011; Maddock and Buonocore, 2012), have typically been observed in patients versus HCs (Brugger et al., 2011; Kraguljac et al., 2012; Marsman et al., 2013; Ohrmann et al., 2005). Differences in Cho, which is implicated in cell membrane metabolism (Bertolino and Weinberger, 1999), have not been found in a previous meta-analysis (Kraguljac et al., 2012). However, studies have reported higher Cho levels in patients with FEP (Bustillo et al., 2002; Plitman et al., 2016). Cr, involved in storage and transport of cellular energy, is often used as an internal reference for other metabolites. However, studies have noted both increased and decreased levels of Cr in patients with schizophrenia (Bustillo et al., 2002; Ongur et al., 2009). mI is often interpreted as a marker of glial activity or content (Kim et al., 2005). Both elevated and decreased mI levels have been reported in patients with schizophrenia (Chang et al., 2007; Plitman et al., 2016). Thus, current ^{1}H-MRS findings in schizophrenia is still inconclusive.

Several factors may confound neurometabolite assessment by ^{1}H-MRS in schizophrenia including age/illness-progression or medication status (Brandt et al., 2016; Szulc et al., 2013). One cross-sectional study reported lower Glx, NAA, and Cr levels in medicated patients compared to age-matched unmedicated patients (Ohrmann et al., 2005). However, other studies did not find any differences between age-matched medicated and unmedicated patients (Kegeles et al., 2012; Wood et al., 2008). The effects of medication on neurometabolite levels have also been examined with longitudinal studies. Some studies have reported Glu and Gln reductions, and NAA elevations after AP administration in AP-naïve patients (de la Fuente-Sandoval et al., 2013; Gan et al., 2014; Stanley et al., 1996; Theberge et al., 2007), while other studies did not observe any changes (Choe et al., 1996; Szulc et al., 2011). Due to the limited evidences, it remains unclear whether AP use or age/illness-progression alter neurometabolite levels. Thus, the aim of the present study was to perform a meta-analysis of neurometabolite levels in unmedicated (i.e. AP-naïve/free) patients with schizophrenia.

2. Methods

2.1. Search strategy and selection criteria

Meta-analyses were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) (Moher et al., 2009). Published articles from 1950 to May 2017 were searched without language restrictions, using Embase, Medline, and PsycINFO. The search terms were: (schizophreni* OR psychosis) AND ("never-treated" OR "first-episode" OR untreated OR unmedicated OR naive OR free OR discontinu* OR withdraw*) AND (MRS OR "magnetic resonance spectroscopy"). Three authors (YI, SN, and EP) independently performed the search (last search: May 5th 2017) and assessed eligibility.

Studies were included if (1) they compared ^{1}H-MRS neurometabolite levels between AP-naive/free patients with schizophrenia and HCs, (2) they included at least five subjects in each group, (3) data were sufficient to obtain mean group differences, and (4) neurometabolites were measured in one of the following ROIs: medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (DLPFC), frontal white matter (FWM), Occ, BG, hippocampus (Hipp)/mTem, or Thalamus (Thal). Studies were excluded if they did not present data exclusively from AP-naïve/free patients with schizophrenia.

Given possible data duplication, only one study was chosen to reduce multiple weighting. Possible duplication was detected using items from "the statement of duplicate publications" (Cho et al., 2000). If studies had similar hypotheses, sample sizes, methodologies, results, and at least one author common, we selected the study with the largest sample size.

We measured differences in Glu, Gln, Glx, NAA, Cho, Cr, mI, and GABA levels between groups. When both Gln and Glu levels were reported, they were summed to estimate Glx.

We selected Glu, Gln, Glx, and GABA levels as co-primary outcomes, and NAA, Cho, Cr, mI levels as secondary outcomes. Gln levels were included in the analysis if the data were acquired at field strengths of 4T or above.

2.2. Data extraction

Two authors (YI and YM) independently extracted data. Variables retrieved from each study included: (1) clinical and demographic subject characteristics (i.e. age, gender, diagnosis, duration of untreated psychosis [DUP] [i.e. duration of AP-naïve/free], duration of illness [DUI], and symptom severity, as measured by the Positive and Negative Syndrome Scale [PANSS] (Kay et al., 1987), Brief Psychiatric Rating Scale [BPRS] (Overall and Gorham, 1962), Clinical Global Impression [CGI] (Guy, 1976), Global Assessment of Functioning [GAF] (Endicott et al., 1976), Scale for the Assessment of Positive Symptoms [SAPS] (Andreasen, 1983b), and Scale for the Assessment of Negative Symptoms [SANS] (Andreasen, 1983a); (2) ^{1}H-MRS acquisition methods (magnetic-field strength, echo time [TE]/repetition time [TR], and ^{1}H-MRS sequence [e.g., point-resolved spectroscopy sequence (PRESS), stimulated echo acquisition mode (STEAM), or MEGA-Point Resolved Spectroscopy Sequence (MEGA-PRESS) (Mescher et al., 1998); (3) spectrum quality criteria (e.g. cut off levels for Cramer-Rao lower bounds [CRLB], full width at half maximum [FWHM], signal-to-noise ratio [S/N]); and (4) reporting metabolites ratio [e.g., Cr ratio or water ratio]).

2.3. Data analyses

Meta-analyses were performed using Review Manager Version 5.3 (http://tech.cochrane.org/revman). Analyses were performed when ≥3 studies were available. Effect size (ES = Hedges' g) of neurometabolite levels between the groups were calculated by dividing mean differences by weighted and pooled standard deviations (SDs). In cases where SD values were not reported, they were supplemented using one of the following options: (1) authors were contacted for additional data, (2) if graphic charts were present, we enlarged figures and measured depicted SD values, or (3) SD values were calculated from available data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane-handbook.org). Positive ES values indicate higher neurometabolite levels in the AP-naïve/free schizophrenia patients. The inverse variance statistical method and random effects model were used to adjust for study heterogeneity (DerSimonian and Laird, 1986). Two-sided 95% confidence intervals (CIs) were used to assess significance. Heterogeneity was assessed using the I^2 statistic with $I^2 \geq 50\%$ indicating significant heterogeneity. When heterogeneity was present, we assessed the potential influences of any one study on ESs using leave-one-out sensitivity analyses. The publication bias was assessed using funnel plots, Egger's regression test (Egger et al., 1997), and trim-and-fill procedure (Duval and Tweedie, 2000).

Moderator analyses were conducted to examine the influences of participant demographics on neurometabolite level ESs. Subgroup