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Research paper

Lithium-associated anterior cingulate neurometabolic profile in euthymic Bipolar I disorder: A ^{1}H-MRS study

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ABSTRACT

Objective: In the treatment of Bipolar disorder (BD), achieving euthymia is highly complex and usually requires a combination of mood stabilizers. The mechanism of action in stabilizing mood has not been fully elucidated, but alterations in N-Acetylaspartate (NAA), Myo-Inositol (mI) and Choline (Cho) have been implicated. Proton magnetic resonance spectroscopy (^{1}H-MRS) is the gold standard technique for measuring brain NAA, Cho and mI in vivo. The objective of this study was to investigate the association of lithium use in BD type I and brain levels of NAA, mI and Cho in the (anterior cingulate cortex) ACC.

Methods: 129 BD type I subjects and 79 healthy controls (HC) were submitted to a 3-Tesla brain magnetic resonance imaging scan (^{1}H-MRS) using a PRESS ACC single voxel (8cm^{3}) sequence.

Results: BD patients exhibited higher NAA and Cho levels compared to HC. Lithium prescription was associated with lower mI (combination + monotherapy) and higher NAA levels (monotherapy).

Conclusion: The results observed add to the knowledge about the mechanisms of action of mood stabilizers on brain metabolites during euthymia. Additionally, the observed decrease in mI levels associated with lithium monotherapy is an in vivo finding that supports the inositol-depletion hypothesis of lithium pharmacodynamics.

1. Background

The neurobiology of bipolar disorder (BD) has not been fully elucidated, although some part of the knowledge about its neurobiology has emerged from studies on lithium's mechanism of action as a first-line mood stabilizer (Yatham et al., 2013). Modern neuroimaging techniques, such as proton magnetic resonance spectroscopy (^{1}H-MRS), allow in vivo measurement of three non-glutamatergic brain metabolites implicated in both the neurobiology of BD and lithium´s mechanisms of action: N-acetylaspartate (NAA) (a neuronal marker), Myo-Inositol (mI) (a glia cell marker) and Choline (Cho) (a membrane cell marker) (Berridge, 1989; Silverstone and McGrath, 2009; Stork and Renshaw, 2005). Although ^{1}H-MRS has been widely used in BD research, it remains unclear how these metabolites impact mood and are influenced by mood stabilizer treatment. The latest meta-analysis of ^{1}H-MRS studies (reporting NAA, mI and Cho data) in BD found 43 studies reporting data on 738 BD subjects and 721 HC (Kraguljac et al., 2012), representing a mean sample size of 40 subjects per study. The study concluded that the evidence on brain metabolite levels in BD was based on small studies of multiple brain voxels, with multiple mood states and medications (Kraguljac et al., 2012). The objective of the present study was to gather a large and uniform sample of BD type I subjects during euthymia and investigate the association of lithium use and levels of NAA, mI and Cho in the anterior cingulate cortex (ACC), thereby exploring the mechanisms by which lithium can modulate mood.

N-acetylaspartate (NAA) has the strongest signal on ^{1}H-MRS as this amino acid is present at high concentrations within the brain, predominantly in neurons (Bertholdo et al., 2013). Hence, NAA has been considered a neuronal marker, whose level is decreased in situations associated with a decline in the number of neurons, such as

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neurodegenerative disorders (e.g. dementia, epilepsy and brain trauma) (Moffett et al., 2007). Moreover, NAA levels have been considered an indirect marker of neuronal health and metabolism, since NAA synthesis is dependent on energy metabolism (Moffett and Namboodiri, 2006; Schuff et al., 2006). ^{1}H-MRS studies in BD are difficult to interpret because NAA levels can be sensitive to medications, current mood episode, disease duration and voxel location (Kraguljac et al., 2012; Szulc et al., 2018). A meta-analysis on NAA measured with ^{1}H-MRS reported that current data was insufficient to reach any conclusions about NAA levels in BD patients during mood episodes or on medication effects (Kraguljac et al., 2012). However, some (Brambilla et al., 2005; Hajek et al., 2012; Sharma et al., 1992; Silverstone et al., 2003), but not all (Colla et al., 2009; Scherk et al., 2009; Soeiro de Souza et al., 2015; Wu et al., 2004), cross-sectional studies have shown increased NAA in lithium-treated patients. This information holds, since there is a lack of ^{1}H-MRS studies in BD with samples focusing on a specific mood episode and mood stabilizer treatment (Szulc et al., 2018). Overall, the meta-analysis (Kraguljac et al., 2012) concluded that NAA levels in BD appeared to be decreased in the basal ganglia and increased in the region of the dorsolateral prefrontal cortex. Interestingly, most longitudinal studies have shown no impact of lithium treatment on brain NAA in BD (Davanzo et al., 2001; Friedman et al., 2004; Machado-Vieira et al., 2015; Zanetti et al., 2014). A single prospective study on BD depression type I and II found increased NAA after 4 weeks of Li treatment, (G.J. G. J. Moore et al., 2000), whereas another investigation on BD type I depression showed decreased NAA after 6 weeks of lithium exposure (Patel et al., 2008) .

Myo-Inositol (mI) is essential for cell growth, a possible marker of glia cell proliferation and a precursor in the phosphatidylinositol (PIP) cycle. Berridge (1989) postulated overactivity of the PIP cycle in BD and that correction of this overactivity through lithium explains its clinical benefits for BD (Berridge, 1989; Berridge et al., 1982) by non-competitively inhibiting inositol IMPase and decreasing mI (Allison et al., 1976). Myo-inositol can be measured using ^{1}H-MRS, while inositol monophosphate measurements can be obtained with ^{31}P-MRS as part of the phosphomonoester (PME) peak. The majority of MRS studies investigating mI have employed the ^{31}P-MRS technique and suggest that euthymic BD patients treated with lithium have reduced PME (Kato et al., 1993; 1994b) or non-significantly altered mI levels (Hamakawa et al., 2004; Kato et al., 1995; 1994a; Murashita et al., 2000) relative to healthy controls (HC). On the other hand, the majority of ^{1}H-MRS cross-sectional studies of BD patients have found no alterations in mI levels (Cecil et al., 2002; Chang et al., 2003; Dager et al., 2004; Scherk et al., 2008; Silverstone et al., 2002; Soeiro de Souza et al., 2013), while three have reported increased mI levels (Forester et al., 2008; Sharma et al., 1992; Winsberg et al., 2000). Moreover, according to the latest meta-analysis (Szulc et al., 2018) prospective studies have failed to report lithium-associated changes in mI.

^{1}H-MRS measures Cho spectra peak, representing the sum of Cho-containing compounds [glycerophosphocholine + phosphocholine (GPC + PC) + phosphatydylcholine, acetylcholine and free choline] (Bertholdo et al., 2013), whereas only ^{31}P-MRS can separately measure specific Cho compounds [GPC observed in phosphodiester (PDE) peak and PC observed in PME peak]. ^{31}P-MRS studies in BD have reported both elevated PME and PDE, suggesting abnormal membrane phospholipid metabolism (Kato et al., 1991; 1992; Yildiz et al., 2001). Cho is a cell membrane marker of cellular turnover reflecting cell membrane phospholipid synthesis (e.g. during brain development) (Stanley, 2002) or degradation (e.g. in Alzheimer disease and brain inflammatory processes) (McClure et al., 1994; Tartaglia et al., 2002). Cho has proven important in the neurobiology of BD since *postmortem* brain tissue studies have revealed that lithium inhibits the membrane transport of Cho (Uney et al., 1986) and that lithium-treated patients had increased stores of erythrocyte Cho (Brinkman et al., 1984; Domino et al., 1985; Stoll et al., 1991). Moreover, the use of oral supplementation of Cho for rapid-cycling BD has been investigated, but clinical results were controversial despite showing reduced brain purine levels after 12 weeks (Lyoo et al., 2003). ^{1}H-MRS studies investigating anterior cingulate cortex (ACC) Cho in BD have shown conflicting results, mainly due to differences in voxel selection and sample selection (BD subtype, mood episodes and medications). Some cross-sectional Cho ^{1}H-MRS studies in ACC have reported increased Cho in BD (Cao et al., 2017; Davanzo et al., 2001; Hamakawa et al., 1998; Kato et al., 1996; C.M. C. M. Moore et al., 2000; Sharma et al., 1992; Soeiro de Souza et al., 2013), while other studies failed to confirm this finding (Amaral et al., 2006; Dager et al., 2004; Ehrlich et al., 2015; Ongur et al., 2008; Wu et al., 2004; Zhong et al., 2014).

2. Study aims

The aims of this study were to investigate the association of lithium use in BD type I (specifically during euthymia state) and levels of NAA, mI and Cho in the ACC, thereby exploring the mechanisms that can modulate mood**.** To better investigate the influence of medications and the impact of BD on metabolite levels, 79 healthy subjects (HC) who were medication free and had no family history of psychiatric disorders were also included in this study.

3. Material and methods

One hundred and twenty-nine euthymic BD I subjects were included in the study. The inclusion criteria for patients in this study were: age range between 18–45 years old, diagnosis of BD type I, no medication change and being in euthymia for the past 2 months, Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1967) < 8 points and fulfilling DSM-IV (DSM-IV, 2000) criteria of remission at the time of the scan. Subjects or patients with neurological disorders or comorbid unstable medical conditions, head trauma, current substance abuse, or treated with electroconvulsive therapy in the last six months were excluded. These subjects were examined over the past 8 years by three BD-focused research programs (BIPUSP MRS Study) (Soeiro de Souza et al., 2018) within the Institute of Psychiatry at the Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo. Diagnoses of BD were determined by trained psychiatrists based on the Structured Clinical Interview (SCID-I/P) (First et al., 1996) for DSM-IV TR (DSM-IV, 2000).

Seventy-nine HC were selected from students at the University of Sao Paulo recruited as volunteers through a website based on the following criteria: age range 18–45 years old, no current or past history of psychiatric disorder according to the evaluation conducted by trained psychiatrists using the SCID (First et al., 1996), no family history of first-degree relatives with mood or psychotic disorders, no use of psychotropic medicine for at least three months before enrollment, and no history of substance abuse within the 3 months leading up to enrollment.

The Research Ethics Board of the Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo approved the study (permit 1047/09 and 070,310). Written informed consent was obtained from all study participants.

3.1. Image acquisition

Brain MRI scans were performed on a 3.0T magnetic resonance scanner (Intera Achieva, PHILIPS Healthcare, Best, The Netherlands) with an 8-channel head coil. Each brain scan included anatomical images acquired with a 3D-T1 Fast Field Echo (3D-T1 FFE) sequence; time of echo (TE)/time of repetition (TR)/time of inversion (TI) = 3.2/7/900 ms; flip angle (FA) = 8°; FOV = 240 mm x 240 mm x 180 mm; matrix = 240 × 240) and magnetic resonance spectroscopy (MRS) acquisition. Single-voxel ^{1}H-MRS was performed using the PRESS sequence with number of scans (NS) of 160, TR of 1500 ms and TE of 80 ms. The choice of TE was based on results from a previous study on