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Proton magnetic resonance spectroscopy changes after lithium treatment. Systematic review

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ABSTRACT

1H MRS is widely used in the research of mental disorders. It enables evaluation of concentration or ratios of several metabolites, which play important roles in brain metabolism: N-acetylaspartate (NAA), choline containing compounds, myo-inositol and glutamate, glutamine and GABA (together as Glx complex or separately). Specifically in bipolar disorder brain metabolite abnormalities include mostly NAA reduces and Glx increases in different brain regions. Bipolar disorder is associated with impairment in neurotrophic and cellular plasticity, resilience pathways and in neuroprotective processes. Lithium, which is commonly used in BD treatment, modulates neurotransmitter release, reduces oxidative stress and apoptosis, induces angiogenesis, neurogenesis and neurotrophic response. Thus brain metabolite abnormalities may elucidate the mechanisms of this processes. In the present article we systematically reviewed 26 studies - the majority of them investigated bipolar disorder (7 follow-up and all 11 cross-sectional studies). Moreover we dispute whether the influence of lithium on brain metabolites in bipolar disorder could explain the background of its potential neuroprotective action. The results of our literature review do not equivocally confirm Lithium's influence the metabolite changes in the brain. The majority of the follow-up studies do not support the initially assumed influence of Lithium on the increase of NAA level in various brain structures. The results of studies are inconclusive with regard to levels of Glx or Glu and Lithium intake, rather point a lack of relationship. The above results were reviewed according to the most recent theories in the field accounting for the impact of lithium (1)HMRS measures.

1. Introduction

Proton magnetic resonance spectroscopy (1H MRS) is widely used in the research of psychotic disorders, including schizophrenia and bipolar disorder. 1H MRS evaluates the concentration or ratios of several compounds (metabolites), which play important roles in brain metabolism: N-acetylaspartate (NAA), choline containing compounds (Cho), myoinositol (mI), glutamate/glutamine/GABA compounds (Glx) and creatine (Cr). Numerous studies have indicated that these metabolites are altered in psychosis. NAA has been the most investigated metabolite. It is present in very high concentrations in neurons, and is assumed to be a marker of neuronal vitality and integrity. NAA is involved in myelin lipid synthesis and turnover, control of osmolality, metabolism and neurotransmission. NAA level reduction may reflect loss of neurons or may be a marker of reversible neuronal dysfunction. Particularly, pathological pruning of dendrites or reduction of neuronal perikaryal size may be involved in NAA level decrease in regions of interest (Ross and Sachdev, 2004; Agarwal et al., 2010; Brugger et al., 2011; Maddock and Buonocore, 2012). Creatine is important for CNS homeostasis and is considered to mark cellular energy level. The 1H MRS signal of creatine and phosphocreatine (Cr + PCr) is interpreted as a measure of global health of brain tissue. The concentration of total Cr is similar throughout the brain and is considered relatively stable. For these reasons the signal of Cr is commonly used as an internal standard and other metabolites can be reported as a ratio to Cr (Ross and Sachdev, 2004; Maddock and Buonocore, 2012). Choline containing compounds (Choline – Cho signal) reflect alterations in a neuron's membrane or myelin turnover and can be a measure of overall cell density (Ross and Sachdev, 2004; Agarwal et al., 2010; Maddock and Buonocore, 2012). Although it is not definitely established, the Myo-inositol signal (mI) is usually interpreted as a glial specific marker. The amino acid neurotransmitter glutamate is one of the most abundant metabolites present in the brain. The Glx signal encompasses glutamate (Glu), glutamine (Gln) and GABA signals. Glutamine to glutamate concentration is 1:5 in

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the CNS and GABA concentration is almost ten times lower, so the Glx complex indirectly reflects fluctuations of glutamate levels. The 1H MRS measure of Glx represents a good approximation of the total glutamate-glutamine pool available for the integrated metabolic and neurotransmitter functions of glutamate in the brain (Palmada and Centelles, 1998; Chen and Swanson, 2003; Maddock and Buonocore, 2012). Optimized 1H MRS methods are now widely used and a differentiation of glutamate and glutamine signal is possible - especially at 3 T and more. However, it needs to be emphasized, that it is not possible to distinguish between the intracellular and extracellular content of glutamate (Glodzik-Sobanska et al., 2006). Bipolar disorder (BD) is associated with specific brain changes. Reductions in volume and density of grey matter were found in prefrontal cortex, orbital cortex, dorsal anterolateral prefrontal cortex, amygdala, basal ganglia and raphe nuclei (Soeiro-de-Souza et al., 2012). 1H MRS studies in bipolar disorder also reported brain metabolite abnormalities: mostly NAA reductions and Glx increases in various brain regions. An elevated choline signal in the basal ganglia was also found (Maddock and Buonocore, 2012; Kraguljac et al., 2012; Machado-Vieira et al., 2014) Some studies found a relationship between mood state, stage of illness and MRS findings. NAA levels were lower in the frontal lobe and hippocampus of euthymic patients, whereas Glu/Gln levels were reported higher in adults. Although Myoinositol levels were supposed to be a marker of bipolar disorder, they are increased rather in euthymic and manic bipolar children, but not in adults (Yildiz-Yesiloglu and Ankerst, 2006). Other studies suggested mood dependent variations in mI levels (Machado-Vieira et al., 2014). An increase in Glx levels was found in acute manic, mixed and depressed states in the prefrontal cortex and anterior cingulate cortex (Jun et al., 2014). Data regarding precise glutamate and mI levels remains nevertheless inconclusive. Bipolar disorder is associated with impairment of neurotrophic and cellular plasticity, resilience pathways and in neuroprotective processes (Soeiro-de-Souza et al., 2012). Brain metabolite abnormalities may elucidate the mechanisms of these processes. Lithium modulates neurotransmitter release, reduces oxidative stress and apoptosis, induces angiogenesis, neurogenesis and neurotrophic response (Alural et al., 2015). It has been proposed that lithium exerts its therapeutic effect through inhibition of the enzyme inositol monophosphatase, resulting in reduction of mI levels. However, the data is inconsistent (Maddock and Buonocore, 2012; Soeiro-de-Souza et al., 2012). Lithium could also influence levels of other brain metabolites, especially through its potential neuroprotective effect (Maddock and Buonocore, 2012). In the present article, we argue that the influence of lithium on brain metabolites in bipolar disorder could explain the above conflicting data. We also aim to elucidate the background for its potential neuroprotective action. To address this issue, we systematically reviewed the literature and retrieved all 1H MRS studies addressing the impact of lithium on brain function. Several variables, such as sample size, magnet intensity, illness stage (chronic, treatment-naïve), brain areas investigated, metabolites assessed and main findings were extracted from each study. The before-after and cross-sectional 1H MRS lithium studies are described in specific tables. Although most studies assessed bipolar patients we also discuss 1H MRS studies investigating the effects of lithium in other neuropsychiatric disorders.

2. Methods

2.1. Literature search

We performed a Pub-Med search reaching until November 2017 with the use of keywords “lithium” and “proton magnetic resonance spectroscopy”. Two researchers (A.S. and A.M.) reviewed the database independently and identified relevant abstracts. Then the text of potentially eligible papers was evaluated in full and a second selection was performed. Studies that failed to meet inclusion criteria were ruled out. Points of disagreement were resolved through discussion and consensus. We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Moher et al., 2009) (Fig. 1).

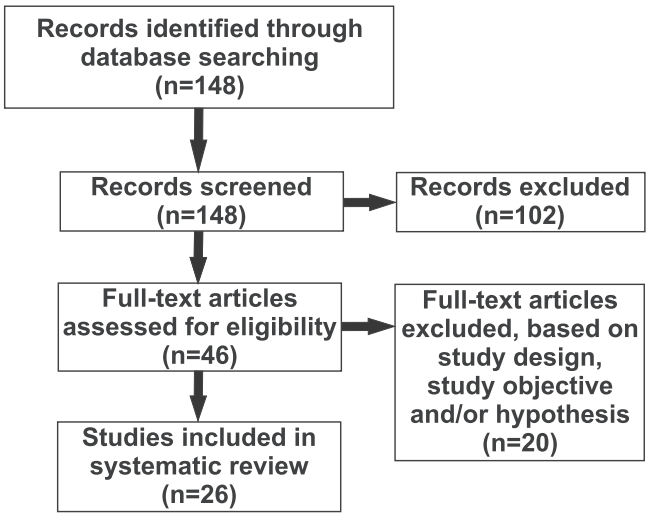

Fig. 1. .Flow chart of selection process for inclusion of studies

2.2. Inclusion criteria

Our inclusion criteria were defined as follows: any original paper appearing in a peer-reviewed journal; study that recruited patients diagnosed with any neuropsychiatric illness, including bipolar disorder according to DSM-V criteria (drug-naïve and/or treated with lithium) and employed 1H MRS technique for the assessment of lithium treatment impact on brain function. Furthermore, since many studies reported various data regarding the lithium treatment used, we decided that the study objective and/or a priori hypothesis should clearly address the issue of 1H MRS changes after lithium treatment.

2.3. Data extraction and variables investigated

The two researchers independently extracted following data: patients’ features - diagnosis, stage of illness and medication status; study design aspects – type of study: cross-sectional or follow-up, sample size, the use of healthy controls group, type of treatment, time of observation, brain region and substances analysed, technique used (i.e. magnet intensity), main findings. Data were processed by two reviewers and summarized in tables. Discrepancies were settled by discussion.

2.4. Data synthesis

Studies which fulfilled the inclusion criteria were reviewed in detail. Separate summary was performed for longitudinal and cross-sectional studies and for NAA, Glx and other metabolites in the specific brain areas (frontal lobes, temporal lobes, occipital lobes, anterior cingulate, basal ganglia, hippocampus).

2.5. Studies retrieved

We identified 26 studies summarized in Tables 1 and 2, most of which investigated bipolar disorder (7 follow-up studies and all 11 cross-sectional studies). Five longitudinal studies addressed the impact of lithium on brain metabolites of healthy volunteers, we also added one study of subjects at risk of psychosis, one of patients infected with human immunodeficiency virus (HIV) and one referring to Canavan Disease (all using a longitudinal design).