European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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SHORT COMMUNICATION

Increased mRNA expression of peripheral glial cell markers in bipolar disorder: The effect of long-term lithium treatment

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Received 31 March 2016; received in revised form 5 July 2016; accepted 13 July 2016

KEYWORDS
Bipolar disorder;
Lithium;
Astrocytes;
Oligodendrocytes;
Glial fibrillary acidic protein (GFAP);
Oligodendrocyte lineage genes (Olig)

Abstract
Neuroinflammation, with microglial activation as an important element, plays a role in the pathogenesis of bipolar disorder (BD). Also, in mood disorders, pathological changes have been demonstrated in macroglial cells, such as astrocyctes and oligodendrocytes. Postmortem brain studies of BD patients to assess glial cells, such as astrocytes and oligodendrocytes and their markers such as glial fibrillary acidic protein (GFAP), Olig1 and Olig2, produced controversial results. On the other hand, investigation of these markers in the peripheral blood of such patients has not been performed so far. In this study, we examined the mRNA levels of GFAP, Olig1 and Olig2, in the peripheral blood of three groups: 15 BD subjects with a duration of illness at least 10 years (mean 20±9 years) but never treated with lithium, 15 subjects with BD treated continuously with lithium for 8-40 years (mean 16±8 years), and 15 control subjects. The groups were age-and sex-matched. Expression of mRNA markers was measured by real-time quantitative reverse transcription PCR (RQ-PCR). We observed increased mRNA levels of the Olig1 and Olig 2 glial markers studied in the BD patients not taking lithium, compared with the control subjects and increased mRNA level of GFAP, compared with lithium-treated patients. In the lithium-treated BD patients GFAP and Olig1 expression was at similar levels to that in the control group.

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http://dx.doi.org/10.1016/j.euroneuro.2016.07.009

Please cite this article as: Ferensztajn-Rochowiak, E., et al., Increased mRNA expression of peripheral glial cell markers in bipolar disorder: The effect of long-term lithium.... European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.07.009

However, Olig 2 expression was even higher than in the BD patients not taking lithium. The possible mechanisms concerning the higher expression of peripheral mRNA markers in BD patients may involve ongoing inflammatory process, compensatory mechanisms and regenerative responses. The beneficial effect of lithium may be related to its anti-inflammatory properties.

1. Introduction

Increasing evidence suggests that neuroinflammation plays an essential role in the pathogenesis of bipolar disorder (BD). An important component of the neuroinflammation in BD is microglial activation (Stertz et al., 2013). In a recent positron emission tomography study, Haarman et al. (2014) demonstrated a significantly increased binding potential of [(11)C]-(R)-PK11195, the marker of microglia activation, in the right hippocampus of bipolar patients, compared to healthy control subjects.

Also, in mood disorders, a pathology of macroglial cells such as astrocyctes and oligodendrocytes has been demonstrated. The most replicated findings from postmortem brain studies in depression include reductions in the packing density and number of glial cells, and alterations in the size and structure of glial nuclei, indicating a loss of glial cells in the fronto-limbic regions. These changes, together with increases in glial cell size in the dorsolateral prefrontal cortex, may suggest the involvement of some compensatory mechanisms. A model of the progression of glial cell pathology in depression has been presented where, initially, genetic and environmental factors (i.e. excess of glucocorticoids, deficiency in neurotrophic substances) lead to a loss of glial cells and the accumulation of extracellular glutamate, resulting in damage to and loss of neurons. This neuronal injury could lead to a proliferation of glial cells and an increase in glia as a result of regulatory activity of the central nervous system (Rajkowska and Miguel-Hidalgo, 2007).

Studies have also been performed assessing glial cells, such as astrocytes and oligodendrocytes, and their markers, in the postmortem brain of BD patients. Astrocytes play a role in maintaining the blood–brain barrier and contribute to neuroinflammatory, degenerative, immune and tissue repair processes, through the production of cytokines. Glial fibrillary acidic protein (GFAP) is a marker of reactive astroglia, being involved in regeneration, synaptic plasticity and reactive gliosis (Middeldorp and Hol, 2011). Oligodendrocytes play a role in promoting the myelination of axons but also exert an anti-inflammatory effect and promote axonal repair by producing cytokines and neurotrophic factors. Olig1 and Olig2 are basic transcriptional factors regulating critical stages of oligodendrocyte lineage development. Olig1 is considered as a marker of oligodendrocyte precursor cells, indicating activity and maturation of oligodendrocytes, while Olig 2 has a role in the development of adult lateral subventricular progenitors, causing expansion of new oligodendrocytes, (Ligon et al., 2006).

In the majority of studies on the GFAP expression, a reduction in GFAP levels was found in BD patients, compared to control subjects. This was observed in such brain structures as the orbitofrontal cortex (Toro et al., 2006) or cingulate cortex (Webster et al., 2005). Hercher et al. (2014) assessed astrocyte and oligodendrocyte populations in postmortem white matter obtained from schizophrenia, BD and non-psychiatric control subjects. In the BD patients, they found an increase in oligodendrocyte density, a reduction in the GFAP area fraction and increased astrocyte clustering in the prefrontal cortex. These findings suggest a glial pathology which could result in a disruption of structural or functional support for axons. On the other hand, in some recent studies, a significantly higher GFAP has been demonstrated in the frontal cortex of bipolar disorder patients (Rao et al., 2010; Feresten et al., 2013). Tkachev et al. (2003) investigated oligodendrocyte-specific gene expression in the post-mortem prefrontal cortices of schizophrenia and BD patients. In the bipolar patients, they found a significant reduction in Olig2 gene expression, with no changes in Olig1 and GFAP genes. This may correspond with the results of a more recent study where Hayashi et al. (2012) observed a reduction in the number of olig2 (+) cells in the prefrontal cortex of bipolar patients.

Lithium remains the first-line drug for the long-term treatment of bipolar disorder. Neuroprotective properties of lithium concerning the central nervous system may play a role in its mood-stabilizing action. This was reflected in studies showing a positive association between lithium treatment and an increase in grey matter volume (Hajek and Weiner, 2016) as well as greater white matter integrity (Gildengers et al., 2015). However, it is not clear how the mechanisms of these phenomena are related to lithium effect on astrocyte and oligodendrocyte functions.

Bergink et al. (2014) suggest that several peripheral immune biomarkers (e.g. high levels of inflammatory cytokines) may reflect microglia activation. On the other hand, peripheral markers of astrocytes and oligodendrocytes in psychiatric illnesses have not been studied so far. Therefore, the aim of the present study was to assess the mRNA expression of the glial cell markers GFAP, Olig1 and Olig2 in the peripheral blood of bipolar patients and control subjects, as well as to evaluate the effect of long-term lithium treatment on such an expression.

2. Experimental procedures

2.1. Subjects studied

The study involved 30 patients with BD during remission, treated at the outpatient clinic of the Department of Adult Psychiatry, Poznan University of Medical Sciences and 15 healthy age-and sex matched control subjects. The BD group was divided into two subgroups: BD Li (+) and BD Li (−).

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