Part 3. Pharmacology of the Bipolar Disorder

Neuroprotective and Neurotrophic Effects of Lithium on Bipolar Disorder

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Abstract

Despite the development of other medications with mood-stabilising properties, such as atypical antipsychotics and antiepileptic drugs, lithium still remains the first-line treatment for bipolar disorder (BPD), and there is increasing evidence for the hypothesis of its neuroprotective and neurotrophic effects as key factors for its clinical effects. Methods: A literature research was conducted using the PubMed database without chronological or language limits to August 2012. The following MESH terms were used: Bipolar Disorder and Lithium combined with: Neuroprotective, Neurotrophic, Neurocognitive effects, GSK-3b, bcl-2, BDNF, hippocampal. Original studies and reviews were selected (in vitro, in vivo and clinical studies). Results: We found evidence in basic studies of neuroprotective and neurotrophic molecular pathways like GSK-3b, Bcl-2, BDNF, glutamate excitotoxicity, AP-1, mitochondrial dysfunction and neurosteroids. Several clinical studies in BPD show increased brain areas, reduced neuronal loss, reduced risk of dementia and one study showed improvement in neurocognitive function (verbal memory) associated with increased hippocampal size in lithium-treated groups versus controls, and other medications. The main areas were hippocampus (HC), anterior cingulate and prefrontal cortex (PFC). Functional Studies with N-Acetyl-aspartate (NAA) also support this hypothesis. Conclusions: Despite basic, structural and functional evidence that shows neurotrophic and neuroprotective effect of lithium, longitudinal studies are needed to clarify the clinical relevance of these findings and their correlation with cognitive performance, which seems to be directly related with functional outcome.

Key words: bipolar disorder, lithium, neuroprotective, neurotrophic, neurocognitive effects, GSK-3b, bcl-2, BDNF, hippocampal.

Introduction

Despite the development of other medications with mood-stabilising properties, such as atypical antipsychotics and antiepileptic drugs, lithium still remains among the first-line treatments for bipolar disorder (BPD) (1;2). Studies continue to discuss mechanisms of action that go beyond the stabilising function; neuroprotective and neurotrophic effects remain targets of investigation (3-5). The results have sometimes been contradictory. The information is becoming more abundant and it is therefore appropriate to undertake an updated and critical review of the current literature, which allows basic studies to be correlated with clinical research.

In order to know whether or not lithium has the following features, the studies must show that its use enhances the growth of a subpopulation of neurons and protects against some kind of injury (oxidative stress, glutamate excitotoxicity, etc.) or the pathological process of disease, in this case the BPD (6;7). According to the available evidence it is difficult to separate the neuroprotective effects from the neurotrophic, or to know the importance of these findings in the BPD (8). Furthermore, the issue of progressive impairment and whether there is correlation between anatomical changes and cognitive deficits remains unclear (6). From this point of view there are also several reasons why a systematic review of the literature, of the effects of lithium on the brain and the clinical implications, is currently needed.

(i) The neuroprotective pathways are common in several treatments for BPD (6;8-10).
(ii) There is a decrease in size of brain areas of bipolar patients (11;12).
(iii) Lithium reverses anatomical changes, reduces apoptosis, favours neurogenesis and synaptogenesis (13-15).
(iv) There is cognitive impairment in BPD, which some authors relate to severity and duration of illness (16;17).
(v) Some studies show that lithium reduces the risk of dementia in BPD patients (18-20).
(vi) Lithium has neuroprotective effects in other neurological diseases (21-23).
(vii) Some results show improvement in memory deficit associated with increased hippocampal volume with lithium (24).

This article will review these areas, based on the main neuroprotective mechanisms and the evidence of in vitro, in vivo and in clinical studies. We shall discuss the role of lithium in neurogenesis and the relationship between cognitive deficits and structural changes as potential therapeutic targets for neuroprotection.

Methods

A literature search was conducted using the PubMed database without language or chronological limits through to August 2012. The following MESH terms were used: bipolar disorder and lithium combined with: neuroprotective, neurotrophic, neurocognitive effects, GSK-3b, bcl-2, BDNF, hippocampal. Nine MESH terms combinations were made, with 585 results. Duplicate papers were excluded and the searches were supplemented by cross-referencing of included studies and review articles. The papers were selected by assessing the abstract according to the following inclusion criteria: original studies and reviews about the hypothesis of the neuroprotective and neurotrophic effects of lithium on BPD. Papers on the effects of lithium in humans or animals were included. Many animal in vitro studies were found. The papers chosen discussed known pharmacological pathways of lithium. One Japanese review was not included by language limitation.

Results

Neuroprotective pathways

Lithium has a mechanism of action that goes beyond neurotransmitters or traditional receptors; it has effects on a series of second messengers (25), signaling pathways and transcription factors (8;25;26). The following is a summary of the most important pathways related to neuroprotection and neurotropism.

Inhibition of GSK3

GSK3 is a serine/ threonine kinase (27), which inhibits a number of antiapoptotic factors such as CREB (cAMP-response element binding protein), Beta Catein and HSF-1 (heat shock factor) (28). Lithium inhibits GSK-3b by phosphorylation of serine residues releases; the control of these factors promotes survival and neuroprotection (29). The effect of GSK3b inhibition has been studied in animal models of depression and mania. It is believed that inhibition of this kinase is associated not only with a stabilising effect but also with the neuroprotective effects (27).

Increased BCL-2

Chronic treatment with lithium can increase the cytoprotective protein BCL-2 in cell cultures of human neurons and in mice brains (30), specifically in the striatum, hippocampus (HC) and prefrontal cortex (PFC), even at subtherapeutic levels (31). The effect is like a "protector" in apoptotic pathways; the mechanisms include regulation of calcium homeostasis and decreasing free radical production, among others (32). In an animal model of ischemia lithium prevented memory impairment associated with low concentrations of P-53 (pro-apoptotic) and BcL-2 increased in CA1 neurons of HC (33).

Protection against glutamate

Lithium also protects against glutamate, which is a powerful excitotoxin (33-35). Chronic exposure of lithium protects neuron cultures of HC, cerebral cortex and cerebellum against glutamate-induced toxicity (7). This effect cannot be identified in short treatments and is not explained by the down-regulation of receptors (36). Possible mechanisms include the decreased phosphorylation of tyrosine residues of the subunit NR2B of the NMDA receptor, thereby inhibiting the calcium influx required to activate the apoptotic pathways (34).

Brain-derived neurotrophic factor and other mechanisms

One of the pathways most involved in this topic is the Brain-derived neurotrophic factor (BDNF) (37). Lithium induces BDNF which, at the same time, activates the receptor tyrosine kinase B (TrkB) and the signaling pathways of phosphatidylinositol 3 kinase/Akt (PI3K/Akt) and the MEK/ERK (extracellular signal-related kinase) (38). In the last pathway, through the RSK kinase (ribosomal S6 kinase) CREB is activated, which is involved in learning and plasticity (38;39) and regulates the transcription of genes such as BDNF and nerve growth factor (38). These pathways have been studied in mouse cortical neurons and are associated with protection against glutamate (33-35). It is also proposed that lithium, through an inhibition of GSK-3b, is responsible for activating the promoter IV of BDNF (40).

A clinical study with patients in mania showed an increase in BDNF at 28 days of treatment with lithium. Others have found an inverse relationship between BDNF and lithium (41). It has been suggested that lithium responders show higher levels of BDNF (42), for example up to 87% after treatment of a maniac episode (43). The responder patients with high BDNF levels showed better neuropsychological performance but more studies are needed to clarify confusing factors.

Lithium also has direct action on the transcription factors (44). There is a protein complex activator known as AP-1, which includes the proteins FOS and JUN, and joins the domain of DNA to regulate the expression of neurotrophins, proteins, membrane receptors, transcription factors, and enzymes involved in the process of neurotransmitters in PFC and HC (31;45). Lithium changes the binding process between AP-1 complex and DNA, thus modulating the transcription of several structural and functional molecules (44).

Lithium has been described as an antioxidant, with increased gene expression of NADH-ubiquinone reductase, which is known as a multi-enzyme complex of the respiratory chain (46;47). Moreover it increases hippocampal neurotrophin-3 (48) and active neurosteroids of PFC in animal models (49).

In vitro – in vivo studies

Based on the research in vitro and in vivo (50-53), neuroprotective mechanisms of lithium have been proposed. Clinical studies with lithium show structural (postmortem and MRI) and functional changes (levels of N-Acetyl-aspartate) (54;55) and many authors have extrapolated these results to molecular findings to defend the neuroprotective hypothesis. However, a direct correlation is unavailable and more studies are needed to clarify this debate (8;56).

Lithium has been studied in human and rodents cell lines as cortical, hippocampal and cerebellar neurons (9), PC12 and neuroblastoma cells (57). It has been shown to prevent cellular death to stressors such as high doses of anticonvulsants (58), quinolinic acid (52;53;58), potassium deprivation (26;53), beta-bungarotoxin (59), glutamate (34-36) and beta-amyloid peptide.

Cross sectional studies

Several studies have attempted to correlate the biochemical effects of lithium with clinical/cognitive findings. There are results in BPD patients using structural and functional methods. Spectroscopy studies show that lithium patients, in comparison with controls, have increased levels of cortical

N-acetyl-aspartate (NAA) (55), a marker of neuronal viability and function which is not found in glial cells (60). This increase has not been reported in patients treated with valproic acid (55). A recent study found in the prefrontal cortex of patients (without lithium) lower NAA levels than in the lithium group ($p<0.001$) or controls ($p<0.05$), with a negative correlation between levels and duration of illness (61). Another study reported a positive correlation between cortical NAA and brain lithium levels (62).

An increasing volume of literature has related structural findings with lithium treatment, with anincrease in cerebral volumes through 4 weeks of 3% (24cm^3) (54) and preventing loss of anterior cingulate volume in the lithium group compared with other medications (63). The increase of gray matter in the right anterior cingulate has been reproduced in other studies (64;65).
Lithium has also been associated with an increase of bilateral hippocampal volume, specifically the hippocampal head, in comparison to valproic acid and lamotrigine (24). The head of HC has the largest amount of CA1 projections to the medial PFC, which shows the role of HC in the fronto-limbic circuit and emotional regulation (66). A higher volume of the hippocampus compared with controls and relatives was recently demonstrated; it was suggested that thickening produced by lithium could be a protective factor against recurrence because this finding was also found in twins (67). An increase of right HC size in adolescents treated with lithium, compared with the controls and valproic acid (68) has also been reported, as has increased hippocampal nerve growth factor in treatment of models of mania (69). Patients without lithium had a lower hippocampal volume than controls ($p<0.005$) but the difference was not significant in the lithium group ($p<0.1$) (70).

Other regions of the hippocampus/amygdala/insula complex, as well as the postcentral gyrus have also shown changes with lithium, related to the treatment duration (71). A meta-analysis with meta-regression techniques correlated lithium with overall increase of gray matter (12) and a meta-analysis showed that the increase was specifically in the HC and amygdala (11). The last meta-analysis found significantly smaller bilateral hippocampal volumes in patients who were not treated with lithium in comparison to healthy controls or patients treated with lithium (72).

Although it is difficult to talk about neurogenesis in BPD because it is a relatively new concept, over the past 15 years several studies have shown there is neurogenesis in the hippocampus (dentate gyrus) of humans and mammals (73;74) and in the neocortex of primates (75); according to some results lithium seems to play a possible role in this area. Bcl-2 protein induced by lithium has been associated with regeneration of axons in mammalian CNS (30;76) and with the increase of thymidine analogs of the cell division in the dentate gyrus within 2 to 3 weeks of therapy (31). Lithium also increased the synaptogenesis of hippocampal neurons, even four hours after administration, and cellular differentiation (14;15).

Longitudinal Clinical Studies

Three longitudinal studies with positive outcomes (24;77;78) showed an increase of hippocampal volume with lithium of 4% to 5% in a follow up from 2 to 4 years and one survey with a small sample size showed improved verbal memory cognitive performance with the California Verbal Learning Test (CVLT), which was not explained by improvement of affective symptoms (24). Four weeks of treatment have also been associated with a significant increase in prefrontal gray matter in responder patients to lithium (78) and according to some reports the effect has a peak at week 10 to 12 and persists after 4 months when it is compared with valproic acid (77). One study showed an increase in prefrontal gray matter volume in healthy volunteers following lithium administration with therapeutic doses during 4 weeks (79), but others had negative results (80).

Neuroprotective effects in several pathologies

A report from the Research Committee of The American Neuropsychiatric Association (21), which evaluated the preclinical and clinical evidence for neuroprotective therapies in neurodegenerative disorders, concluded that the most promising research (low and moderate preclinical evidence) included lithium, in diseases such as tauopathies, frontotemporal degeneration (81), Alzheimer-type

dementia (lithium plus paroxetine, lithium plus valproic acid) (21;82) and amyotrophic lateral sclerosis (83;84).

The effects on dementia have been described from the inhibition of GSK-3b, which decreases the production of beta amyloid from the precursor protein of amyloid (27), and the aggregation and phosphorylation of tau protein (86).

Studies with lithium have shown protection against ethanol toxicity (87), anti-inflammatory effects and an increased proliferation and survival of stem cells in models of ischemia and neonatal hypoxia (45). Some authors using models of cerebral ischemia in mice have linked the neuroprotective effect with the GSK-3b pathway (88). With respect to neurocognition in other disorders, several studies have shown a positive effect in HIV-associated cognitive deficit (89) and in the prevention of neuropsychological sequelae following cranial irradiation (90).

Neurocognition and lithium as a neuroprotective agent

Many studies have shown neurocognitive impairment in BPD including the euthymic phases (85;86). The magnitude of cognitive impairment averages between 0.2 and 1 standard deviation (87;88) and appears to be greater for executive function, attention and processing speed (89;90), although a meta-analysis also demonstrated impairment of verbal memory (91). The cognitive deficits in verbal memory, executive function, ideational fluency, attention and visual/motor processing are major variables related to functional performance (6;92;93). Despite the evidence of cognitive changes in BPD, to conclude that there is progressive impairment may be too preliminary because we need more longitudinal studies with good control of confounding variables (6).

The understanding of the relationship between lithium and neurocognitive effects has changed lately; several years ago the lithium was recognized as an agent causing cognitive impairment (94) but now research has shown a neutral effect (85) and some suggest a positive effect that could be correlated with the described neuroprotective mechanisms (24;66). There is even evidence that lithium significantly reduces the risk of dementia in patients with BPD (18-20).

Discussion

Lithium, within its mechanisms of action, acts on pathways associated with neuroprotection and neurotropism (6;7); there is evidence that lithium favors neuronal survival against multiple exotoxic factors and stimulates in-vitro and in-vivo synaptogenesis (50-53). Few studies can correlate these molecular findings with clinical outcomes but the available literature shows that lithium increases markers of neuronal function such as N-acetyl-aspartate (55;60), prevents the reduction of gray matter when compared with other mood stabilizers and increases the volume in brain areas, including the anterior cingulate, PFC and HC (63;78;95;96). A systemic review attempting to search for the neuroprotective and neurotoxic effect of lithium, found discrepancy between basic and clinical research, with level of evidence C "unclear and conflicting" for this topic. Few clinical studies were identified and some showed indirect evidence of neuroprotective effect (97).

There are structural and neuropsychological alterations in BPD (11;12;16;92;98), although it is unclear whether the cognitive impairment is static or progressive (6;8). Even though lithium is associated with an increase in brain volumes (63;64;67;71), further longitudinal studies are necessary to reproduce these findings and to demonstrate correlation with the neuropsychological and psychopathological features of patients. Such studies could resolve the doubts about the clinical relevance of the neuroprotective and neurotrophic effects. Only one study showed improvement in verbal memory with lithium related to the increased size of HC (24) and several authors demonstrated lower risks of dementia in older adults with BPD treated with lithium when compared with other medications (18;20). Many of the studies appear to show that the hippocampus is a region of strong neurogenesis (99). This brain area has strong connections with the PFC and an important role in verbal memory, which is altered in BPD according to several authors (100;101). Studies that seek to continue the

investigation into this hypothesis should ideally be longitudinal and must have as a primary goal the correlation between neuroanatomical changes, neurocognitive performance and functionality.

The findings of the neuroprotective and neurotrophic effects of lithium on other neurological disorders appear promising (21). Current research not only views lithium as being a mood stabilizer but also as a possible neuroprotective agent (29;36). Studies appear to indicate a strong association between cognitive deficit and functionality (16;92;98). A therapy that protects against the development of the cognitive deficits could be of great value in the treatment of psychiatric patients. On theoretical grounds, lithium has mechanisms that might play such a role but further studies are necessary since the findings are partial and preliminary.

Conclusion

Despite in-vitro and in-vivo studies that show neurotrophic and neuroprotective effects of lithium, structural and functional evidence for bipolar patients is indirect. Beyond the effects related to the prevention of relapses, longitudinal studies are needed to clarify the clinical relevance of these findings and their correlation with cognitive performance, which seems to be directly related with the functionality of the patients.

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