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REVIEW PAPER

Lithium as a Neuroprotective Agent for Bipolar Disorder: An Overview

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Abstract

Lithium (Li^+) is a first option treatment for adult acute episodes of Bipolar Disorder (BD) and for the prophylaxis of new depressed or manic episodes. It is also the preferred choice as maintenance treatment. Numerous studies have shown morphological abnormalities in the brains of BD patients, suggesting that this highly heritable disorder may exhibit progressive and deleterious changes in brain structure. Since treatment with Li^+ ameliorates these abnormalities, it has been postulated that Li^+ is a neuroprotective agent in the same way atypical antipsychotics are neuroprotective in patients diagnosed with schizophrenia spectrum disorders. Li^+'s neuroprotective properties are related to its modulation of nerve growth factors, inflammation, mitochondrial function, oxidative stress, and programmed cell death mechanisms such as autophagy and apoptosis. Notwithstanding, it is not known whether Li^+—induced neuroprotection is related to the inhibition of its putative molecular targets in a BD episode: the enzymes inositol-monophosphatase, (IMPase), glycogen-synthase-kinase 3β (GSK3), and Protein kinase C (PKC). Furthermore, it is uncertain whether these neuroprotective mechanisms are correlated with Li^+'s clinical efficacy in maintaining mood stability. It is expected that in a nearby future, precision medicine approaches will improve diagnosis and expand treatment options. This will certainly contribute to ameliorating the medical and economic burden created by this devastating mood disorder.

Keywords Lithium · Neuroprotection · Bipolar disorder

Abbreviations

AD	Alzheimer's disease
BD	Bipolar disorder
BD I	Bipolar disorder I
BD II	Bipolar disorder II
BDNF	Brain-derived neurotrophic factor
DAG	Diacylglycerol
HD	Huntington's disease
IMPase	Inositol monophosphatase
IP	Inositol monophosphate
IP_3	Inositol-1-4-5 triphosphate
Li^+	Lithium
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PI	Phosphatidylinositol
PIP_2	Phosphatidylinositol-4,5-biphosphate
PKC	Protein kinase C
SCZ	Schizophrenia/SCZ spectrum disorders
GSK3	Glycogen-synthase-kinase 3β

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Introduction

Bipolar Disorder (BD) (American Psychiatric Association. DSM-5 Task Force 2013) is a heritable mental illness (Stahl et al. 2019; Gordovez and McMahon 2020) characterized by cyclical disturbances in mood and behavior (Goodwin and Jamison 1990) and associated with well documented cortical brain abnormalities (Abe et al. 2020).

The efficacy of lithium (Li^+) as a first option treatment for adult manic episodes and for maintenance of Bipolar Disorder (BD) is now well established (Curran and Ravindran 2014; Geddes et al. 2004; Severus et al. 2014; Licht 2012; Cousins et al. 2020). This is also the case for child and adolescent BD (Hafeman et al. 2019).

Li^+ is also the preferred treatment for the prophylaxis of new episodes, either depressive or manic (Geddes and Miklowitz 2013; Licht 2012; Goodwin 2002). Although some clinical guidelines consider antiseizure and neuroleptic agents alongside Li^+ as equally efficacious in BD (Graham

et al. 2018), many psychiatrists adopt Li^+ as the preferred first line treatment (NICE 2014; Goodwin 2002).

Being a Li^+ responder runs in families (Grof et al. 1993) and this appears to have a specific genetic signature: response to Li^+ is associated with genetic variations in glutamate decarboxylase-like protein 1 (GADL1) (Chen et al. 2014). These facts led some authors to postulate a distinct type of BD based on response to Li^+ (Alda 2015).

It is important to point out that Li^+ works best in patients exhibiting typical features of the disorder and that not every BD patient responds to Li^+ (Tighe et al. 2011). In fact, only one third of BD patients are full responders (Kessing et al. 2016) and this response achieves better efficacy if treatment with Li^+ is initiated early in life (Kessing et al. 2014).

Taking into consideration such a variability of responses to Li^+, the Response to Lithium Network (R-LiNK) (Cousins et al. 2020) has been formed to identify which patients will respond to Li^+ and also which ones will benefit from long-term treatment with this medication (see also (Pfennig et al. 2020).

This review focuses on neuroprotection, a term that is closely connected to the neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), or Huntington's disease (HD) (Vajda 2002). These disorders are characterized by exhibiting a series of pathological changes in the brain that progress during the course of illness and ultimately lead to neuronal death, hence the term neuroprogression (Scearce-Levie et al. 2020).

Although research on neurodegenerative disorders has been traditionally reserved for pure neurological syndromes, there is now evidence that the concept of neuroprogression can also be applied to psychiatric entities such as the schizophrenia spectrum disorders (SCZ) or in BD (da Costa et al. 2016; Fries et al. 2012; Kapczinski et al. 2017). SCZ and BD are characterized by progressive structural brain changes, functional and cognitive decline, and a vulnerability to relapse (Dodd et al. 2013). Genome-Wide Association Studies (GWAS) have identified a panoply of genes showing that BD shares common genetic risk factors with schizophrenia and other mental disorders (Gordovez and McMahon 2020).

I will briefly detail possible mechanisms of action of Li^+ in acute episodes of BD. Examples of neuroprogressive changes in BD brains will be given, and putative neuroprotective effects of Li^+ in vitro as well as in vivo on these neuroprogressive processes will be discussed.

It is important to point out that the connection between Li^+-induced neuroprotection in the human brain and the sustained efficacy of this agent in the long- term treatment of BD remains unresolved.

Methods

I undertook a PubMed search updated to March 2021 incorporating search terms such as bipolar, mania, hypomania, Li^+, early intervention, prevention, neuroprogression and neuroprotection and using the Boolean operator AND.

An Example of Pharmacological-Induced Neuroprotection

Pharmacological neuroprotection is defined as the preventive effect of a medication on a neurodegenerative process that otherwise will inexorably progress in the absence of the medication.

Since their introduction in the 50's, neuroleptic or antipsychotic medications have shown efficacy in the treatment of acute psychotic episodes and in the prevention of psychotic relapses (Leucht et al. 2009). However, long-term use of these medications raised concerns on damaging effects on the human brain (Gotzsche et al. 2015).

These effects include brain volume loss in monkeys (Dorph-Petersen et al. 2005) and humans (Haijma et al. 2013; Kubota et al. 2015) and upregulation of dopamine D2 receptors (Muller and Seeman 1977). The latter has been associated with loss of efficacy of neuroleptics over time (Chouinard and Jones 1980).

Nonetheless, there is no substantial evidence that long-term treatment with antipsychotics is deleterious to the brain (Goff et al. 2017). For a review on neuroprotective effects of second generation antipsychotic medications the reader is referred to a systematic review by Chen and Nasrallah (Chen and Nasrallah 2019).

We will apply these concepts of neuroprogression and neuroprotection when we discuss the effects of Li^+ in the BD brain. But I will first discuss possible mechanisms of action of Li^+ during a BD episode. This is because Li^+'s well described molecular targets (see next section) are possibly the first link in a series of putative metabolic cascades regulated by this monovalent cation.

Possible Mechanisms of Action of Li^+ in BD

The exact mechanism of action of Li^+ in BD remains largely unknown. Li^+ acts at molecular, cellular, and system levels, making a description of a single mechanism of action a daunting task (Alda 2015; Malhi et al. 2013; Haggarty et al. 2021).

The enzyme protein kinase C (PKC) is a molecular target for Li^+ (Saxena et al. 2017; Zarate and Manji 2009).

The term PKC designates in fact a family of enzymes expressed in mammalian brain structures involved in regulating mood (Wetsel et al. 1992; Alessenko et al. 1992). PKCs are involved in many metabolic cascades modifying protein function and organizing signal propagation within the cell (Rosse et al. 2010). PKC signaling modulates processes that could be operative in BD (Saxena et al. 2017).

PKC activity is inhibited by Li^+ (Zarate and Manji 2009) both in vitro (Wang and Friedman 1989) and in vivo (Casebolt and Jope 1991) because it affects the translocation of the enzyme from the cytosol to the cell membrane, the region of the cell when it becomes active. Studies performed in patients with BD in the manic phase showed that Li^+ inhibits PKC activity and its aforementioned translocation induced by serotonin (Friedman et al. 1993).

Support for the hypothesis of increased PKC signaling in BD was obtained from the use of the estrogen receptor modulator tamoxifen (TX). This drug crosses the blood–brain barrier (Carpenter et al. 2016) and inhibits PKC (Gunosewoyo et al. 2017). A proof-of-concept study showed the resolution of acute manic symptoms in BD patients treated with TX (Bebchuk et al. 2000). In the last 20 years many papers have been published regarding the antimanic properties of TX (Amrollahi et al. 2011; Zarate et al. 2007). The reader is referred to detailed reviews (Novick et al. 2020; Palacios et al. 2019; Talaei et al. 2016). To date, the FDA has not approved this promising drug for the treatment of manic episodes.

Li^+ increases phosphorylation of glycogen synthase kinase 3ß (GSK3ß), an enzyme which is involved in a signaling pathway that modulates apoptosis and synaptic plasticity (Carter 2007). Increased phosphorylation of this enzyme leads to its inactivation and is associated with decreased excitotoxicity (Carter 2007; Haggarty et al. 2021). Furthermore, gene expression of GSK3ß is correlated with response to Li^+ (Iwahashi et al. 2014).

Overexpression of GSK-3 correlates with neuronal degeneration (Lucas et al. 2001) and increases apoptosis (Bijur et al. 2000; King et al. 2001). The participation of GSK-3 in the therapeutic effects of Li^+ is not well delineated. Instead, Li^+ affects several cellular systems that use G proteins and second messenger systems (prominently the phosphatidylinositol (PI) cycle) that are involved in intracellular signaling cascades involved in cell functioning (Berridge 2016; Berridge et al. 1989).

The most widely accepted hypothesis regarding Li^+ therapeutic efficacy in BD is the myo-inositol (henceforth inositol) depletion hypothesis. This posits that Li^+ exerts its therapeutic effects by depleting inositol in specific areas of the brain. This stems from the pioneering work of Berridge who discovered signal transduction mechanisms involving the PI cycle (Berridge et al. 1989; Berridge 2016).

Of all the postulated targets for the effects of Li^+ in the BD brain, I emphasize the PI cycle because it is a well-researched effect in vitro, and the postulated mechanism of action can be extended to human studies (Jope et al. 1996; Kato et al. 1991; Moore et al. 1999; Pacheco and Jope 1996). See also (Sharpley et al. 2020; Singh et al. 2013).

The Inositol Depletion Hypothesis

I will briefly review here the PI cycle and its special relevance to the mechanism of action of Li^+ in BD. For further details, the reader is referred to comprehensive reviews (Berridge 2016; Berridge et al. 1989; Epand 2017; Harwood 2005). The PI cycle is the major pathway for the synthesis of this phospholipid (and its phosphorylated forms), located at the cytosolic side of eukaryotic cell membranes (Dickson and Hille 2019).

Specific first messengers (postulated neurotransmitters operative in a BD episode, especially GABA (Brady et al. 2013), dopamine (Berk et al. 2007) and glutamate (Beneyto et al. 2007; McCullumsmith et al. 2007) have been suggested as targeted by Li^+. Upon binding to their specific membrane bound receptors, these messengers are linked via the G_q protein to phospholipase C (PLC) a membrane bound enzyme that catalyzes the breakdown of phosphatidylinositol-4,5-biphosphate (PIP_2, a cell membrane phospholipid) into inositol-1-4-5-triphosphate (IP_3) and diacylglycerol (DAG) (Figs. 1 and 2). The cycle proceeds clockwise for thermodynamical reasons and has as a distinctive characteristic: lipids are transferred between

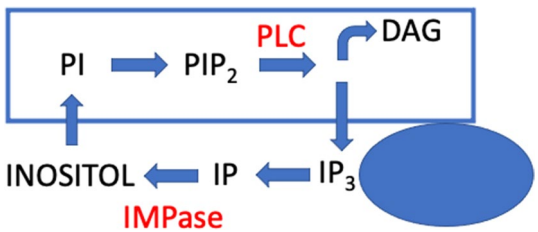

Fig. 1 An extremely simplified diagram showing the phosphatidylinositol (PI) cycle as occurring in two separate membranes: the cell plasma membrane (rectangle) and the endoplasmic reticulum (solid oval). For a more comprehensive description of the cycle see recent reviews (Epand 2017; Harwood 2005). PI, a plasma membrane phospholipid located in the inner leaflet of the lipid bilayer, undergoes a series of phosphorylations to become Phosphatidylinositol-4,5-biphosphate (PIP_2). The enzyme phospholipase C (PLC) becomes active when membrane bound and gives two products from its substrate PIP_2: the lipid second messengers diacylglycerol (DAG) which remains membrane bound, and inositol-1-4-5 triphosphate (IP_3) which is soluble and becomes associated with ER membranes. IP_3 is sequentially dephosphorylated (not shown). The last enzyme in this sequence of dephosphorylations is inositol monophosphatase (IMPase), which has as substrate inositol monophosphate (IP), thus regenerating inositol. PI synthase (an ER enzyme, not shown) forms PI of inositol

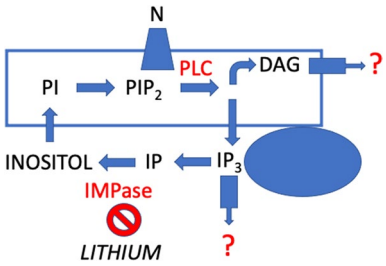

Fig. 2 Two important modulators of the PI cycle: (1) neurotransmitters (N) which bind to G protein coupled receptors (oblong shape) and activate phospholipase C (PLC) and (2) Li^+ which inhibits (crossed circle) IMPase, thus depleting the cell from inositol (see text). The two boxed arrows and the two question marks represent still unknown downstream effects of IP_3 and DAG that may relate to cellular mechanisms operative in a BD episode. Alternatively, these metabolic cascades may also be related to neuroprotective mechanisms. For more details see text

two membranes: the plasma membrane and the endoplasmic reticulum (ER) (Epand 2017) (see Fig. 1).

Both DAG and IP_3 are lipid second messengers: DAG remains membrane bound and activates protein kinase C (PKC) which as described above, is involved in initiating signal transduction cascades. IP_3 penetrates the cytosol and binds to a Ca^{2+} channel in the endoplasmic reticulum, promoting an efflux of Ca^{2+} from this organelle. This efflux of Ca^{2+} is also involved in initiating signal transduction cascades. It is hypothesized that the stimulus (neurotransmitter N in Fig. 2) magnifies the abovementioned metabolic cascades which are implied in the genesis and maintenance of a manic episode and that are in mood regulating areas of the brain.

A series of phosphatases dephosphorylate IP_3. The enzyme inositol monophosphatase (IMPase) has inositol monophosphate (IP) as its substrate, regenerating inositol and ultimately PIP_2 which allows the cycle to be perpetuated (Figs. 1 and 2).

Since the blood–brain barrier limits the availability of plasma inositol, inositol recycling as described above is critical for proper neuronal metabolism.

Among many other actions, Li^+ inhibits IMPase, restricting recycling of inositol and depleting neurons of this molecule (Berridge et al. 1989). After prolonged administration of Li^+, neurons have a reduced ability to re-synthesize PIP_2 after its hydrolysis has been initiated by neurotransmitter receptor activation (Fig. 2). This is the postulated beneficial effect of Li^+ in BD through its effects on IMPase.

In a very interesting paper by Williams et al. (Williams et al. 2002) the hypothesis of inositol depletion as a common mechanism of action for mood stabilizers was tested using cultured explants of sensory neurons from rat dorsal ganglia. The sensory neuron growth cone shows a phenomenon of collapse and expansion, two processes that appear to depend on the presence of inositol.

Drugs clinically used as mood stabilizers such as Li^+, valproic acid, and carbamazepine were able to reduce the frequency of the collapse of neuron growth cones. This effect was reversed by inositol, indicating that inositol depletion is the common mechanism for the three drugs and that inositol phosphate was implicated in the response to the mood stabilizers (Williams et al. 2002).

Further evidence of inhibition of IMPase as an important mechanism of action of Li^+ in BD came with the discovery of ebselen, a selenium-containing small molecule that has anti-inflammatory properties (Singh et al. 2013). Ebselen decreases inositol recycling in mice (Singh et al. 2013) and lowers the concentration of inositol in the anterior cingulate cortex (ACC) of humans as measured by magnetic resonance spectroscopy (Masaki et al. 2016; Singh et al. 2016). This suggests that the drug interacts with IMPase in the human brain.

Recently, a phase 2a randomized double-blind placebo-controlled trial where ebselen was added to anti-manic therapy (antipsychotics but not valproate, since the latter is known to inhibit inositol metabolism (Rosenberg 2007)) showed promising results on manic and hypomanic patients. Young Mania Rating Scale (YMRS) total scores were lower than when placebo was the add-on intervention (Sharpley et al. 2020).

As mentioned before, to date the involvement of the PI cycle in BD is well documented in vivo: this cycle is impaired in the brain of BD patients (Jope et al. 1996). The inositol transporter is overexpressed in BD and is downregulated by Li^+ (Lubrich and van Calker 1999; van Calker and Belmaker 2000). Furthermore, there is an acute reduction of inositol induced by Li^+ in the right frontal lobe of BD patients (Moore et al. 1999) albeit this acute reduction is not associated with a clinical response (Moore et al. 1999). This may explain why Li^+ takes more that 2 or 3 weeks to exhibit efficacy, leaving open the hypothesis of a long-term effect of Li^+ that does not depend on inositol depletion.

Although the emphasis of this review is on the inositol depletion hypothesis, there are also effects of Li^+ in murine tissues that merit consideration since they open new avenues for human research. For example: dysregulation of mesolimbic dopamine neurotransmission has been implicated in BD, suggesting a hyper-dopaminergic state to explain the pathophysiology of the disorder (Ashok et al. 2017). In this respect, Ferrie et al. (Ferrie et al. 2008) showed that rats chronically treated with Li^+ had decreased dopamine release in the *nucleus accumbens*. This effect was not due to increased auto receptor sensitivity or to decreased firing rate of dopaminergic neurons (Ferrie et al. 2008).

Norepinephrine is another catecholamine implied in the mechanism of action of Li^+ (Kovács and Hernádi 2002).

Li^+ was iontophoretically applied to prefrontal cortical rat neurons located in the prelimbic cortical projection region. These neurons are targets for an ascending noradrenergic pathway. Single unit activity recorded from these neurons showed that Li^+ suppressed discharge activity from this pathway, suggesting that it modulates the activity of noradrenergic neurons that target the prefrontal cortex (Kovács and Hernádi 2002).

Finally, an interesting effect of Li^+ on Na^+ and K^+ channels that modulate cortical excitability was shown using brain slices of the mouse olfactory bulb. Treatment in vitro with lithium depolarized mitral cells and blocked action potential hyperpolarization (Butler-Munro et al. 2010). This opens a window into the interesting relationship between BD and epilepsy (Knott et al. 2015).

Neuroprogression in Bipolar Disorder

Accumulated evidence shows that mood episodes in BD have a deleterious effect on the brain, albeit to date no clear-cut neurodegenerative processes have been identified in BD brains (Frey et al. 2008; Sanches et al. 2008).

Compelling evidence from the Bipolar Disorder Working Group (Hibar et al. 2018) shows a cumulative degenerative effect of BD in the cortex of BD patients when compared to unaffected individuals, reinforcing the idea that neuroprogression is operative in the natural course of BD (Kapczinski et al. 2017).

The course of BD varies among patients (Passos et al. 2016). Along the years, especially in cases of treatment non-adherence, there is a worsening in cognitive capacity, refractoriness to pharmacotherapy, and shorter inter-episode intervals (Bauer et al. 2017; da Costa et al. 2016; Kapczinski et al. 2017).

This neuroprogression in the BD brain can be staged as much as staging is used in other branches of medicine (Fries et al. 2012; Grande et al. 2014; Kapczinski et al. 2014; van der Markt et al. 2020; Vieta et al. 2011). These stages are generally labeled as prodromal, early, middle and late and have been associated with specific biomarkers (Teixeira et al. 2019).

Genetic factors, a family history of BD, and sub-threshold mood and anxiety symptoms are characteristic of the prodromal phase. The other stages are associated with conspicuous biochemical changes: (1) activation of inflammatory pathways (Leboyer et al. 2012) (tumor necrosis factor alpha (TNFa) and interleukin 10 (IL10), (2) oxidative stress (glutathione reductase, glutathione N-transferase, (Andreazza et al. 2009); (3) changes in serum neurotrophic factors (prominently decrease of brain derived neurotrophic factor (BDNF) (Scola and Andreazza 2015), and (4) apoptotic mechanisms leading to neuronal death (Uribe and Wix 2012). This is correlated with reduced cortical thickness in the brain, as shown in the study by Hibar et al. (Hibar et al. 2018). The following section deals with this type of evidence at the neuroanatomical level.

Evidence for Neuroanatomical Changes in BD Brains

Imaging studies using magnetic resonance imaging (MRI) and neuropathological examination of BD brains show decreased volumes in hippocampus, amygdala, thalamus, and reduction of cortical thickness (Harrison et al. 2020; Hibar et al. 2018; Hibar et al. 2016; Kempton et al. 2011). Lyoo et al. (2006) reported decreased thickness in the dorsolateral prefrontal cortex (DLPFC) in BD patients. The structural changes in the amygdala may be related to progression of BD (Blumberg et al. 2005).

Diffusion tensor analysis shows changes in white matter tracts connecting the anterior cingulate cortex (ACC) with the amygdala and the hippocampus, and the frontal lobe with the amygdala, the hippocampus, the thalamus, and the cingulate gyrus. This suggests that BD patients have compromised connections between frontal-subcortical and prefrontal lobe-limbic brain regions (Nortje et al. 2013; Wise et al. 2016). A recently published systematic review confirmed that white matter abnormalities seen in BD patients could be prevented by treatment with Li^+ (Espanhol and Vieira-Coelho 2021).

An MRI analysis of cortical volume, thickness, and surface area suggested a difference between patients diagnosed with either type of BD as specified in DSM5 (BD I or BD II) (Abe et al. 2016). This type of study is particularly relevant since both diagnoses present differently in clinical practice: while the manic episodes of BD I can be severe, persons with BD II do not show frank mania. Instead, they are depressed for longer periods of time and do not report their hypomanic episodes as often.

Most of the available studies on BD were performed on BD I and measured cortical volume. Abe et al. used MRI to analyze abnormalities in BD I and BD II patients and healthy controls and simultaneously measured cortical volume, thickness, and surface area to describe the neurobiology underlying these two types of BD (Abe et al. 2016). Decreased cortical volume, thickness, and surface area were decreased in frontal, temporal, and medial occipital brain regions in both BD I and BD II patients as compared to controls. Interestingly, only BD I patients showed low cortical volume and thickness in temporal and medial prefrontal areas as compared to BD II patients (Abe et al. 2016). This study provides evidence that both types of BD have real neurobiological differences and could serve as a template to develop biomarkers for this disorder.

A recent systematic review and meta-analysis on the neuropathology of BD (Harrison et al. 2020) shows that there is not a signature pathological lesion that distinguishes BD from other brain disorders. Instead, there is decreased cortical thickness in the subgenual anterior cingulate cortex (ACC), along with reduced neuronal density in some amygdala nuclei and decreased density of calbindin-positive neurons in the prefrontal cortex (Harrison et al. 2020).

Postmortem human brain studies have yielded interesting results. There is dendritic spine loss in the dorsolateral prefrontal cortex of BD brains (Konopaske et al. 2014) and reduction in the expression profiles of cortical fast-spiking parvalbumin interneurons (Toker et al. 2018) and parvalbumin- and somatostatin-positive interneurons in the parahippocampal region (Wang et al. 2011).

As mentioned before, the course of illness in BD is variable, and progression is not always demonstrable in BD. From a practical point of view, the number of manic episodes is to date the best predictor of neuroprogression in BD (Passos et al. 2016).

Biomarkers can be Used to Track Neuroprotection Effected by Li^+

Neuroprotective effects of Li^+ have been demonstrated in vitro and possibly in vivo (Alda 2015; Manji et al. 2000; Abe et al. 2020; Hibar et al. 2018). These can be evidenced using specific biomarkers such as: (1) imaging techniques that show morphological changes in BD brains, (2) proton magnetic resonance spectroscopy measuring metabolites such as *N*-acetylaspartate (NAA) and glutamine plus glutamate (GLx) that provide evidence for cytotoxic processes; and (3) measuring serum levels of neurotrophins (especially brain-derived neurotrophic factor (BDNF)).

Morphological Changes

Human grey matter is increased in patients treated with Li^+ (Moore et al. 2000). In this respect, the reader is referred to a meta-analysis by Sun et al. (Sun et al. 2018).

BD patients on Li^+ show greater grey matter density in the cingulate and paralimbic cortices as compared to healthy controls (Bearden et al. 2007) and an increase in subgenual ACC, hippocampus, insula, and amygdala (Germana et al. 2010).

A study performed on patients that responded to Li^+ showed an increase in prefrontal and subgenual grey matter volume (Moore et al. 2009). A longitudinal study (Lyoo et al. 2010) showed that this Li^+-induced increase in human brain grey matter can be identified as an anatomical substrate of treatment response in BD (Lyoo et al. 2010).

The hippocampus of BD patients treated with Li^+ for 2 years showed volumes that did not differ from those of normal persons. In contrast, BD patients with limited exposure to Li^+ had lower hippocampal volumes as compared to healthy controls (Hajek et al. 2014, 2012b). Nevertheless, this effect of Li^+ on hippocampal volume is not correlated with the ability of Li^+ to prevent bipolar episodes (Hajek et al. 2014).

Interestingly, patients with BD which were naïve to medication, and were acutely treated with Li^+ (1–8 weeks) showed a volumetric increase of the hippocampus, especially in its head, when compared to healthy controls (Yucel et al. 2008). The same effects of Li^+ on the hippocampus were demonstrated using long-term (2–4 years) treatment with Li^+ (Yucel et al. 2007).

Compelling evidence regarding protective effects of Li^+ in BD brains was obtained by the ENIGMA working group study performed on 6503 BD patients (Hibar et al. 2018). Patients on Li^+ (and not on antiseizure or neuroleptic medications Hafeman et al. 2012; Hibar et al. 2018)) had increased cortical thickness when compared with patients not treated with Li^+.

Measuring Brain Metabolites

Proton magnetic resonance spectroscopy (MRS) allows for the quantitative noninvasive assessment of regional brain biochemistry (Novotny et al. 1998).

N-acetylaspartate (NAA) is a unique metabolite found in the vertebrate brain and second only in concentration to glutamate. It has been used in proton magnetic resonance spectroscopy (Baslow 2003), and it was identified in neurons (Simmons et al. 1991) as a putative marker of neuronal integrity (Baslow 2003).

Hajek et al. (Hajek et al. 2012a) showed that prefrontal NAA levels in Li^+-treated patients are comparable to those of healthy controls. This supports the notion for neuroprotective effects of Li^+ on prefrontal cortex in patients with BD (Hajek et al. 2012a).

Abnormal glutamatergic transmission in the frontal lobe has also been implicated in the BD brain. Proton magnetic resonance spectroscopy ((1)H-MRS) studies have reported increased levels of combined glutamate and glutamine ("Glx"), which have been linked to impairments in N-methyl-D-aspartate (NMDA) receptor function (Chitty et al. 2013, 2015). Finally, there is a probable direct effect of Li^+ on NMDA receptors (Amiri et al. 2020) that merits further inquiry.

Measuring Neurotrophic Factors

There are many in vitro pieces of evidence indicating that Li^+ regulates brain growth factors (Hashimoto et al. 2004)

and programmed cell death such as apoptosis (Dodd et al. 2013) and autophagy (Motoi et al. 2014). Li^+ decreases apoptosis through inhibition of glycogen synthase kinase 3β activity (Klein and Melton 1996).

The BNDF gene (Maisonpierre et al. 1991) is a risk locus for the development of BD (Neves-Pereira et al. 2002; Sklar et al. 2002). Additionally, chronic administration of Li^+ increases BDNF expression in rat brain (Fukumoto et al. 2001).

Neurotrophins have been identified as participating in various stages of BD: BDNF, insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF) are present at different stages of the disorder, suggesting the existence of BD subtypes (Scola and Andreazza 2015). Interestingly, BDNF levels are reduced in the serum of bipolar patients while experiencing a manic episode (Machado-Vieira et al. 2007).

Li^+ differentially accumulates in brain regions known to be neurogenic (for example, the hippocampus). When Li^+ is administered for 28 days to juvenile mice, cell proliferation (but not neurogenesis) increases in their hippocampus. This was determined by the novel imaging procedure Time-of-Flight Secondary Ion Mass Spectrometry (Zanni et al. 2017). Importantly, steady state serum concentrations of Li^+ were analogous to those clinically relevant for treating BD (around 1.2 mM).

A discussion of the mechanisms targeted by Li^+ that could be implicated in neuroprotection are detailed in a review by Niciu et al. (Niciu et al. 2013). What is still unknown is how these effects are correlated with mood stabilization and with the maintenance of Li^+ 's efficacy in the long-term treatment of BD.

Prophylactic Effects of Li^+: When to Treat

Early detection of BD and identifying its proper treatment mirrors the dilemmas emerging in treating SCZ patients. The most accepted model for SCZ is the neurodevelopmental hypothesis. This posits that interactions between multiple genes initiate a series of neuropathological events during gestation which progress into adolescence and adulthood, and that are influenced by environmental factors (Fatemi and Folsom 2009; Murray and Lewis 1987; Rapoport et al. 2012).

The impetus for early detection and early intervention in psychosis (Fusar-Poli et al. 2020; Leopold et al. 2020) offers hope for treating this serious mental condition and serves as a template for other mental disorders such as BD.

Some authors suggest the existence of neurodevelopmental changes in BD. These may be expressed as premorbid neuro-behavioral changes demonstrated by neuroimaging differences comparing the children of BD parents and age matched healthy controls (Sanches et al. 2008). An abnormal maturation of the brain structures involved in the regulation of affect has been postulated to explain the pathophysiology of BD (Sanches et al. 2008). However, the case for neurodevelopmental factors leading to neuroprogression in BD is not as clear as it is the case for SCZ (Valli et al. 2019).

Having discussed the neuroprotective effects of Li^+ in BD patients, the question of a truly preventive or prophylactic use of Li^+ surges spontaneously. It is important to identify in the child and adolescent population and as accurately as possible, who will develop BD and who will respond to pharmacological treatment (Cousins et al. 2020). As mentioned before, starting Li^+ early in life vs. starting late shows that early treatment improves BD outcomes (Kessing et al. 2016).

It remains a crucial clinical question how early psychiatrists should treat BD with Li^+ and the associated ethical concerns need to be examined, as pointed in a paper by Ratheesh et al. (2017).

From a clinical standpoint, there are some indicators that suggest a diagnosis of BD: earlier age of onset (Lish et al. 1994), family history of bipolar disorder (Bowden 2005; Hirschfeld et al. 2003; Manning et al. 1998) or family history of lithium responsiveness in a first-degree relative (Manning et al. 1998). Multiple failed antidepressant trials, rapidly occurring episodes of recurrent depression, and history of prompt antidepressant response followed by sudden decline in response, have also been reported to suggest bipolarity (Perlis 2005).

Despite these clinical indicators, several factors conspire against an accurate diagnosis: (1) a young person may spend most of his/her life in depression (Kupka et al. 2007) and experience late onset of mania (Bolton et al. 2020; Dols and Beekman 2018); (2) differentiating between classical unipolar depression and bipolar depression still remains a dauting task (Cuellar et al. 2005) and because of this, (3) there are delays in diagnosis (Fritz et al. 2017).

Finally, comorbidities such as medical non-psychiatric conditions (Crump et al. 2013), personality disorders (Fan and Hassell 2008) and/or illicit drug use (Levin and Hennessy 2004; Sherwood Brown et al. 2001) influence diagnostic and treatment decisions.

It is expected that in a nearby future, precision medicine approaches will improve diagnosis and expand treatment options (Cousins et al. 2020; Pfennig et al. 2020). This will certainly contribute to ameliorating the medical and economic burden created by this devastating mood disorder.

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Declarations

Competing interests The author declares not to have competing interests.

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