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Lithium Enhances Synaptic Plasticity: Implication for Treatment of Bipolar Disorder

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1. Introduction

Although lithium has remained as the drug of choice in the treatment of bipolar disorder over the past 50 years, the mechanism by which it exerts its therapeutic effects is not well understood. A large body of evidence from molecular, cellular and clinical studies proposes that lithium have positive actions in enhancing neuroplasticity and synaptic plasticity, and these actions are associated with its efficacy in the treatment of bipolar disorder and other psychiatric disorders (Manji et al. 1999; Manji and Duman 2001; Rowe and Chuang 2004; Tsaltas et al. 2009). Lithium modulates intracellular signal transduction pathways involved in the activation of transcription factors (PEBP-2 β , P53, and CREB) and the gene expression of diverse neurotrophic and neuroprotective factors (Chalecka-Franaszek and Chuang 1999; Grimes and Jope 2001; Jope and Roh 2006; Manji et al. 1999; Manji and Duman 2001). Among these factors, brain derived neurotrophic factor (BDNF), B-cell CLL/lymphoma 2 (Bcl-2) and cyclic adenosine monophosphate response element-binding protein (CREB) have been the most extensively studied (Angelucci et al. 2003; Chuang et al. 2002; Fukumoto et al. 2001; Manji and Chen 2002). It is well known that BDNF, Bcl-2 and CREB play important roles in maintaining normal synaptic plasticity in diverse ways (Adams and Cory 1998; McAllister et al. 1999; ; Shaywitz and Greenberg 1999; Silva et al. 1998). Evidence from brain imaging and postmortem studies and studies with animal models suggests that in patients with bipolar disorder, diverse pathological changes in neuroplastic processes lead to impairment in synaptic communications in neuronal circuits involved in the pathophysiology of bipolar disorder. Lithium may enhance synaptic plasticity and thereby restore normal synaptic communications in the circuits by up-regulating neurotrophic and neuroprotective factor such as BDNF, Bcl-2 and activating CREB, the major transcription factor of gene expression of BDNF and Bcl-2, and this action may be associated with the efficacy of the drug. However, this theory has been developed primarily based on molecular biological and clinical studies. This theory has never been fully tested by directly examining the effects of lithium exposure on synaptic plasticity. Only few studies have specifically focused on the effects of lithium exposure on synaptic plasticity.

This study investigated the effects of subchronic and chronic exposure to lithium on synaptic plasticity in the hippocampus. First, the study examined whether 2 weeks and 4 weeks lithium treatment alters functional synaptic plasticity by examining the effects of lithium

treatment on input and output (I/O) responses and long-term potentiation (LTP) of field excitatory postsynaptic potential (fEPSP) of the principal neurons in the dentate gyrus (DG) and area CA1 in hippocampal slices. Second, the study examined the effects of 2 and 4 weeks lithium treatment on structural synaptic plasticity by examining effects of lithium treatment on the density of dendrites of the principal neurons in DG and area CA1, using the Golgi staining and Sholl analysis. The study also examined the effects of the same lithium treatment on the levels of phosphorylated CREB (pCREB), Bcl-2 and BDNF, which play critical roles in developing and maintaining normal synaptic plasticity, in the DG and area CA1.

2. Methods

2.1 Animals and lithium treatment

Adult male Sprague-Dawley rats weighing 200g to 250g at procurement were housed three per cage with food and water available *ad libitum* and housed in a temperature-controlled room with a light/dark cycle of 12/12 hours. For the 4 weeks lithium study, animals were divided as lithium treated group and control groups. Lithium chows (0.24% Li_2CO_3 , Harlan Teklad®, Madison, WI) or control chow was fed for 4 weeks. For the 2 weeks lithium study, animals were treated and fed the same way as the 4 weeks lithium study. At the end of lithium treatment, the blood levels of lithium were confirmed to be within its therapeutic range in human. Animal treatment and experiments were conducted in accordance with the principles and procedures of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2 Effects of lithium treatment on LTP of the principal neurons in the hippocampus

Animals were deeply anesthetized with isoflurane inhalation anesthesia. The brains were removed then hemi-sectioned, the hippocampus was separated from the rest of the hemisphere and placed on the stage of a tissue chopper, and 400 micrometer-thick slices were harvested. Hippocampal slices for electrophysiological recording were incubated in artificial cerebrospinal fluid (aCSF) bubbled with 95% O_2 /5% CO_2 at room temperature until used. Hippocampal slices selected for use were placed in an interface-type chamber and perfused with oxygenated (95% O_2 /5% CO_2) aCSF and allowed to equilibrate for 30 min. The aCSF was exchanged at a flow rate of 1-1.5ml/min and was composed of (in mM) 125 NaCl, 3.35 KCl, 1.25 NaH_2PO_4 , 2.0 CaCl_2 , 2.0 MgSO_4 , 25 NaHCO_3 , and 10 glucose.

For fEPSP recordings in the DG, a bipolar stimulating electrode was placed in the medial perforant pathway fibers, and a glass micropipette recording electrode (2-4 M Ω) filled with aCSF placed in the granule cell dendritic layer using microelectrode manipulators under an illuminated upright microscope. The same protocol was followed for fEPSP recording in hippocampal area CA1. For LTP recording in hippocampal area CA1, the bipolar stimulating electrode was placed in the Schaffer collaterals and the recording electrode in the apical CA1 dendritic layer for fEPSP. To determine the fEPSP I/O function, stimulations (1/20 sec.) at an intensity ranging from just below threshold (~10 μA) until response has reached asymptote (no greater than ~900 μA) were applied, and responses recorded onto a PC utilizing Clampex software. Five stimulations at each intensity level were given during ascending intensities at 10, 30, 50 and 100 μA , then increased by 100 μA until the maximum (900 μA) was reached.

Prior to induction of LTP of the fEPSP, a 15 minute baseline was recorded with stimulations at 1/20 Hz at a stimulation intensity of 500 uA. LTP was elicited with tetanus of 2 trains of 100Hz stimulations for 0.5sec with a 5 sec interval between trains at the same intensity. LTP was recorded at least for 60 minutes following tetanus with 1/20 Hz stimulations, and LTP responses only for the last 10 min. (50-60 min) are used for analyses to avoid the contamination of noises and other neuronal activities. All measures were made utilizing the same Clampex software used in data collection. The magnitude of all the fEPSPs recorded was expressed by measuring the initial slope of the postsynaptic potential waveforms. For each value, mean \pm SEM was determined, and the resulting values between the lithium treated and control groups were compared statistically.

2.3 Effects of lithium treatment on the density of dendrites in the hippocampus

2.3.1 Golgi staining

The Rapid Golgi method was used for this study (Gabbot and Somogyi, 1984). Animals were administered with lithium as described above. At the end of lithium treatment, the chest of animals was opened under deep anesthesia with Nembutal® (75 mg/kg, IP), the left ventricle was punctured, and the right atrium incised to allow the blood exit during saline injection. 0.9% saline was perfused into the vascular system to flush out the blood from the brain. Then, fixative solution (phosphate buffered 10% formalin) was infused. Animals were then decapitated, and the brains were removed. The blocks of hippocampal tissue were separated and fixed in 10% paraformaldehyde and 2.5% glutaraldehyde dissolved in 0.1 M phosphate buffer overnight. The blocks of fixed tissue were kept in staining solutions of potassium dichromate and osmium tetroxide followed by immersion in a solution of silver nitrate. Hippocampal neurons were stained en bloc and the stained blocks were then dehydrated in an graded series of increasing ethanol concentrations with 1% uranyl acetate and embedded in an ascending series of low viscosity nitrocellulose solutions. The nitrocellulose was hardened by exposure to chloroform. This hardened nitrocellulose was affixed to a sectioning block, and sections are cut (at 120 μ M) on an AO sliding microtome. The sections were cleared in alpha-terpineol and mounted on slides under Permount.

2.3.2 Analysis of dendritic materials (Sholl analysis)

The slides of Golgi-impregnated neurons were mounted on a Zeiss microscope, which was equipped with drawing tubes for preparing camera lucida drawings and digital photomicroscopy capabilities. The analysis defined the amount of dendritic material and its spatial distribution. A template of a series of enlarging concentric circles was centered on the soma of each camera lucida drawing of the dendritic trees of neurons. The number of intersections of the dendritic trees with each successive shell was quantified. This generated a profile defining the distribution of the dendritic material at equidistant intervals from the soma (every 10 micron increased from the soma). For each value, mean \pm SEM was determined, and the resulting values between the lithium treated and control groups were analyzed statistically.

2.4 Effects of lithium treatment on levels of BDNF, Bcl-2 and pCREB in the hippocampus

At the end of the lithium treatment, animals were sacrificed, the brains were hemisected, and the hippocampi were separated. Tissues of DA and the areas of CA1 were collected and weight. A volume of protein/peptide extraction buffer equal to 4-9 times the tissue weight was added. Then, tissue blocks were homogenized with an ultrasonic cell dismembrator (Fisher Scientific), boiled for 5 minutes and centrifuged at 15000 for 20 minutes. Thereafter, supernatant was transferred to another set of microtubes for further processing immediately or stored in -80 °C. BDNF, pCREB and Bcl-2 levels were determined by the commercially available ELISA kits with BDNF from Promega ((Madison, WI) and the kits for p-CREB and Bcl-2 from Aldrich-Sigma (St. Louis, MO). Their protocols of ELISA were followed exactly. After completing the entire steps of processing, optical densities of wells microplate were read by an assay reader, FLUOstar (BMG LabTech, Germany). Peptide value of each were converted to and presented as the value of pg/mg wet tissue. The peptide/protein value of each was as the value of pg/mg wet tissue or units of activated enzyme/ml. For each value, mean ± SEM was determined, and the resulting values between the lithium treated and control groups were statistically analyzed.

3. Results

This study has obtained results for the effect of lithium treatment for two and four weeks lithium on functional (LTP) and structural synaptic plasticity (density of dendrites) and on the levels of BDNF, Bcl-2 and pCREB in the DG and hippocampal area CA1 (Table 1).

	2 Week Lithium Treatment		4 Week Lithium Treatment	
	DG	Area CA1	DG	Area CA1
Lithium Effects on Synaptic Plasticity				
LTP	↑	-	↑*	↑
I/O	↑	-	-	➡
Lithium Effects on Density of Dendrites and Dendritic Spines				
Dendrites	↓	↓	↑	↑
Lithium Effects on Levels of BDNF, Bcl-2 and P-CREB				
BDNF	➡	➡	↑	➡
Bcl-2	➡	➡	↑	↑
p-CREB	➡	➡	↑	↑

Table 1. Effects of 2 weeks and 4 weeks lithium treatments on functional and structural synaptic plasticity and the levels of BDNF, Bcl-2 and pCREB in the hippocampus. Shim and Russell 2004; Hammonds *et al.* 2007; Hammonds and Shim 2009; Shim *et al.* 2007; Shim and Hammonds 2009; Shim and Hammonds 2010; *Son *et al.* 2003

3.1 Effects of lithium treatment on LTP of the principal neurons in the hippocampus

Four weeks lithium treatment did not enhance the magnitude of I/O responses (Fig. 2), but significantly enhanced the magnitude of LTP of fEPSP of CA1 pyramidal cells (Figs. 1, 3). Two weeks lithium treatment significantly enhanced the magnitude of I/O responses and LTP of fEPSP of the DG granule cells (Figs. 4, 5). (Shim and Hammonds 2009; Shim et al. 2007).

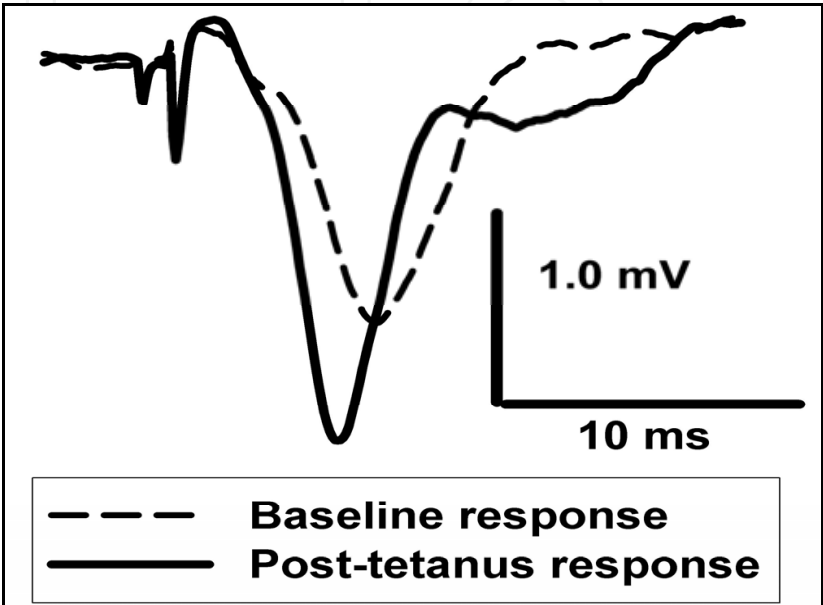


Fig. 1. Typical wave forms of LTP of fEPSP of the granule cells in DG.

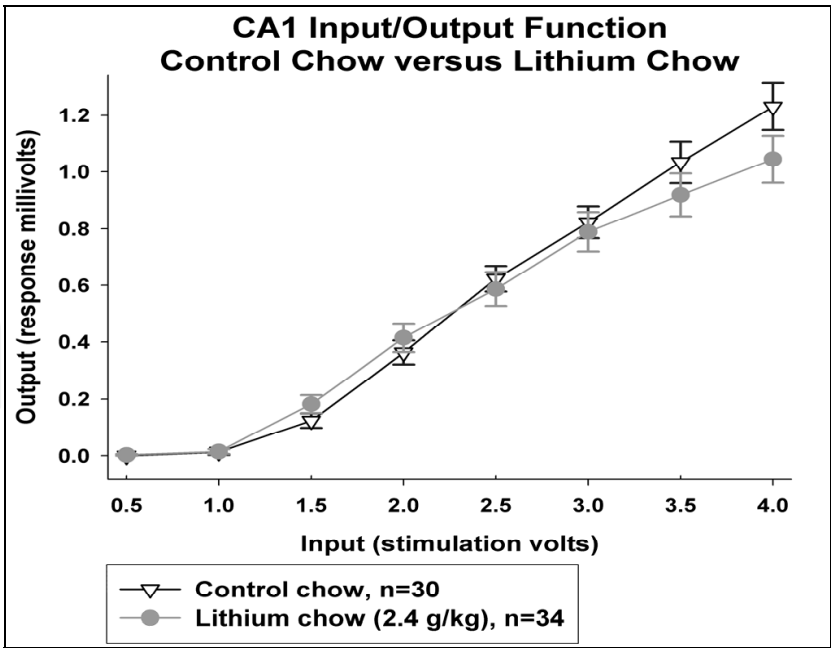


Fig. 2. Effects of 4 weeks lithium treatment on I/O responses of fEPSP in area CA1. There was no significant differences in I/O response between lithium (number of animals (N) =19; number of slices (n) = 34) and control (N =16, n = 30) chow treatment [$p > 0.05$, independent Student's t -tests

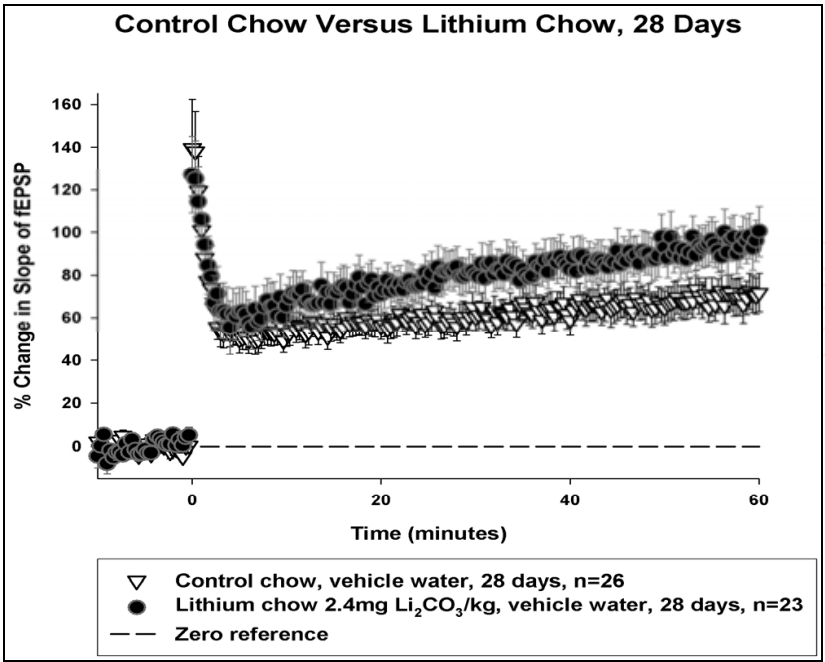


Fig. 3. Effects of 4 weeks lithium treatment on LTP of fEPSP in area CA1. Two trains of 100 Hz tetanus stimuli significantly magnified fEPSP of CA1 pyramidal cells as determined for the last 10 min. of the recordings. There was significant differences in LTP responses between lithium (N = 14, n = 26) and control (N =11, n = 23) treated animals in area CA1 ($p < 0.01$).

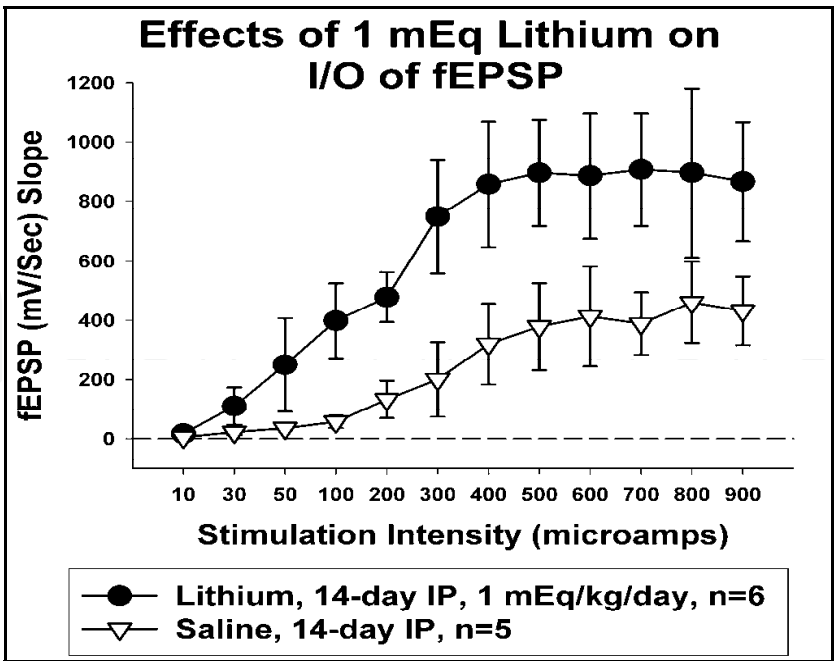


Fig. 4. Effects of 2 weeks lithium treatment on I/O responses of fEPSP in the DG. There was significant differences in I/O response between lithium (N = 5; n = 6) and control (N = 4, n = 5) chow treatment [$p < 0.01$, independent Student's t -test).

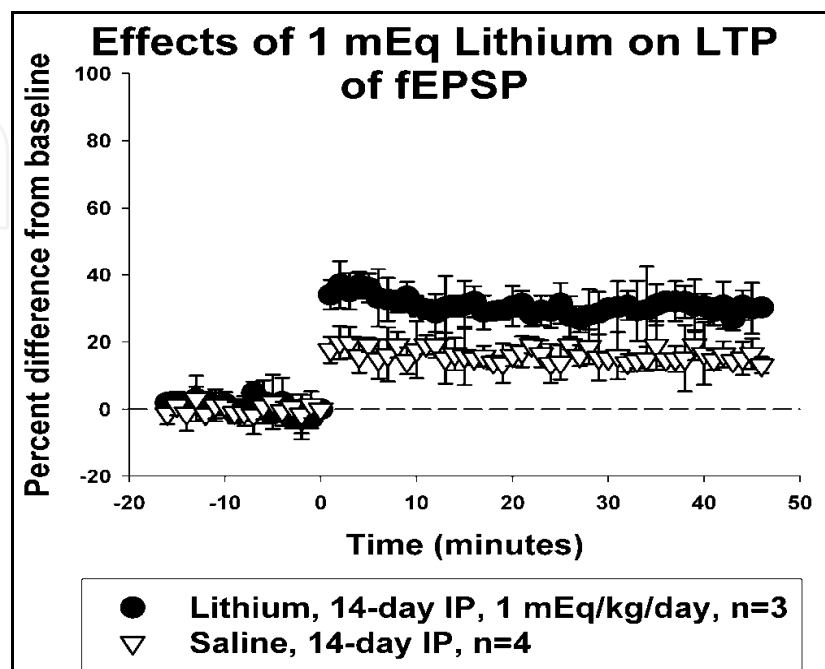


Fig. 5. Effects of 2 weeks lithium treatment on LTP of fEPSP in the DG. Two trains of 100 Hz tetanus stimuli significantly magnified fEPSP of the DG granule cells as determined for the last 10 min. of the recordings. There was significant differences in LTP responses between lithium treated ($N = 4$, $n = 5$) and control ($N = 5$, $n = 6$) animals in the DG [$p < 0.01$, independent Student's t -test].

3.2 Effects of lithium treatment on density of dendrites in the hippocampus

Sholl analysis shows that 4 weeks and 2 weeks lithium treatments redistributed dendritic branches in different manners. In the DG granule cells, 4 weeks lithium treatment increased the number of dendritic branches in nearly the inner 2/3 of dendritic trees, but reduced the number of the branches in outer 1/3 of dendritic trees (Figs. 6, 7). In hippocampal area CA1, the same lithium treatment increased the number of apical dendritic branches in the inner 2/3 of the dendritic trees, whereas, in the distal 1/3 of the apical tree, the treatment reduced dendritic branching (Fig. 8). In contrast, 2 weeks lithium treatment reduced the number of dendritic branches approximately in the outer 2/3 of the dendritic trees of the DG granule cells (Fig. 9). The same treatment reduced the apical dendritic branches of CA1 pyramidal cells throughout dendritic trees except a small proximal region of the dendrites (Fig. 10). Both 4 and 2 weeks lithium treatments redistributed dendritic branches without significant changes in the total number of them in the DG and area CA1 (Shim and Hammonds 2010; Shim and Russell 2004).

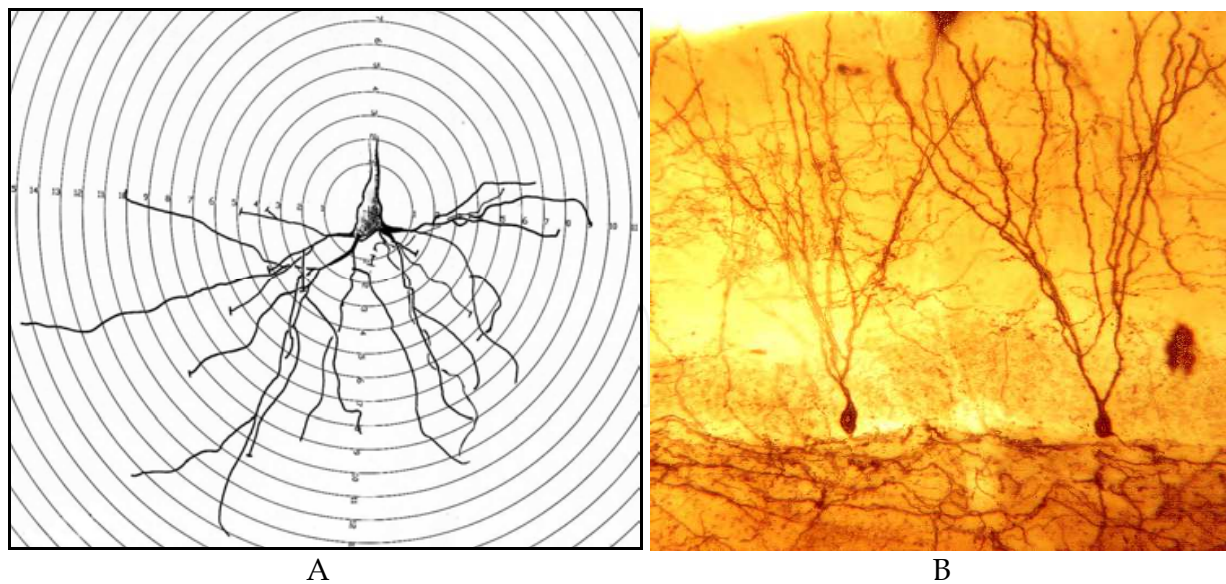


Fig. 6. (A) Golgi impregnated granule cells with well branched and bifurcated dendrites extending into the molecular layers in the DG. (B) Camera lucida drawing of the dendritic trees of hippocampal CA1 pyramidal cells. The dendritic branches of a CA1 pyramidal cell under a concentric shell template for Sholl dendrite density analysis are shown.

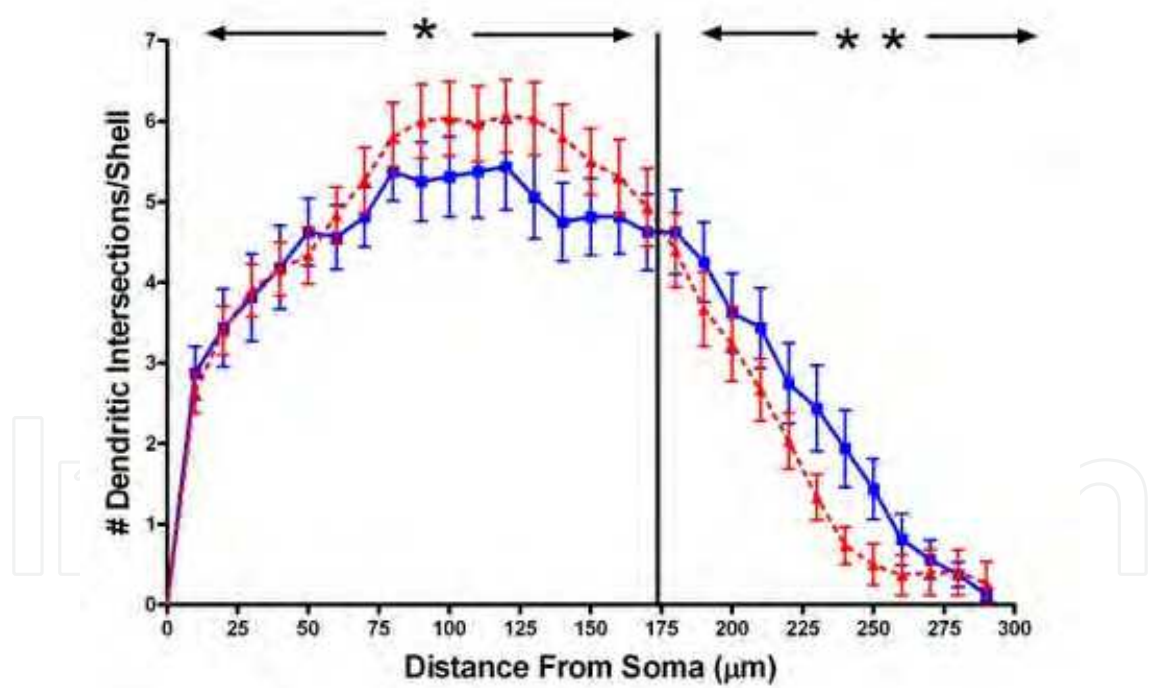


Fig. 7. Effects of 4 weeks lithium treatment on dendrites of the DG granule cells. Lithium-treated animals (lithium-treated animals N = 6, n = 30; controls N = 4, n = 16) have significantly more dendritic branches in the inner 2/3 of dendritic trees (Wilcoxon test, $p = 0.0038$). In the outer 1/3 of dendritic trees, lithium-treated animals have less dendritic branches (Wilcoxon test, $p = 0.0024$) broken line: lithium treated group; full line: control group. The over-all dendritic material of granule cells is not significantly different between the two groups.

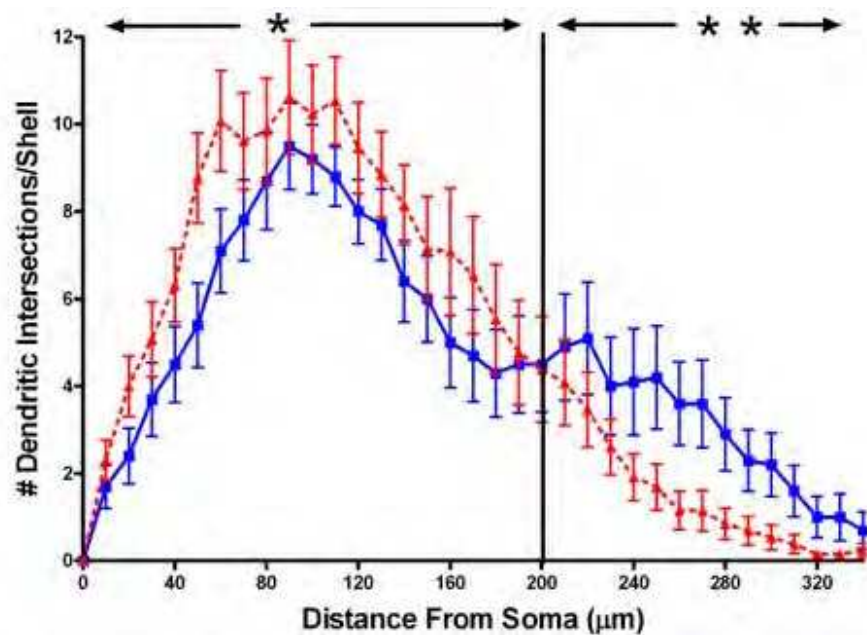


Fig. 8. Effects of 4 weeks lithium treatment on apical dendrites of the CA1 pyramidal cells. Lithium-treated animals (lithium-treated animals N = 3, n = 8; controls N=4, n=10) have significantly more dendritic branches in the inner 2/3 of dendritic branches (Wilcoxon test, $p = 0.0005$). In the outer 1/3 of dendritic trees, lithium-treated animals have less dendritic branches of dendrites (Wilcoxon test, $p < 0.0009$). The total amount of dendritic material of CA1 pyramidal cells is not significantly different between the two groups.

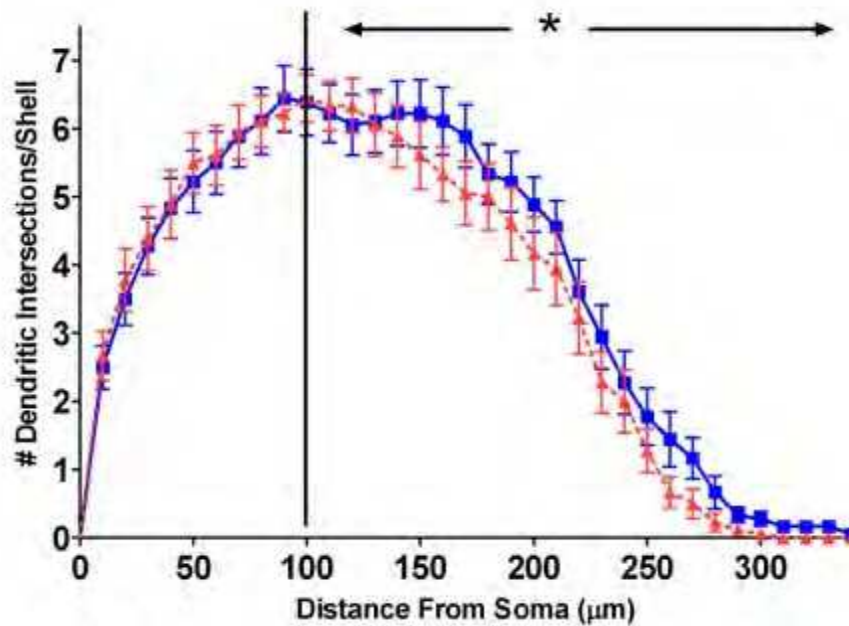


Fig. 9. Effects of 2 weeks lithium treatment on dendritic branches of the DG granule cells. The lithium treated animals (N = 3; n = 18) had significantly less dendritic branches on the outer 2/3 of dendritic tree comparing to those in the control group (N = 3, n = 18) ($p = 0.001$, Wilcoxon test). The over-all dendritic branches of granule cells were not statistically significant between the two groups.

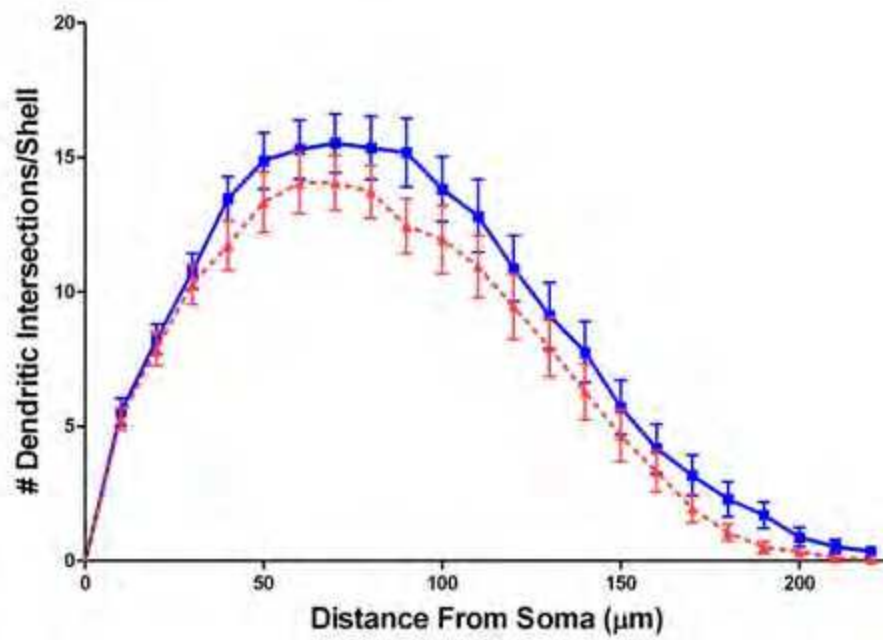


Fig. 10. Effects of 2 weeks lithium treatment on apical dendritic branches of area CA1 pyramidal neurons. The loss of dendritic branches was found in more than the outer 2/3 of the dendritic arbor in the lithium treated group ($p < 0.0001$, Wilcoxon test)(lithium -treated group $N = 3$, $n = 18$; Controls $N = 3$, $n = 17$). The total amount of dendritic branches was not significantly different between the two groups.

3.3 Effects of lithium treatment on levels of BDNF, Bcl-2 and pCREB in the hippocampus

This study have also examined the effects of 4 weeks and 2 weeks lithium treatments on the levels of BDNF, Bcl-2 and p-CREB in the DG and area CA1 using ELISA. Four weeks lithium treatment increased the levels of Bcl-2 and pCREB in the DG and area CA1 (Fig 11B, 11C) (Hammonds and Shim 2009). This treatment increased the level of BDNF in the DG, but did not increase the level of BDNF, in area CA1 (Fig. 11A). However, 2 weeks lithium treatment did not alter the levels of BDNF, Bcl-2 and pCREB in either the DG or area CA1 (Figures are not shown) (Hammonds and Shim 2007).

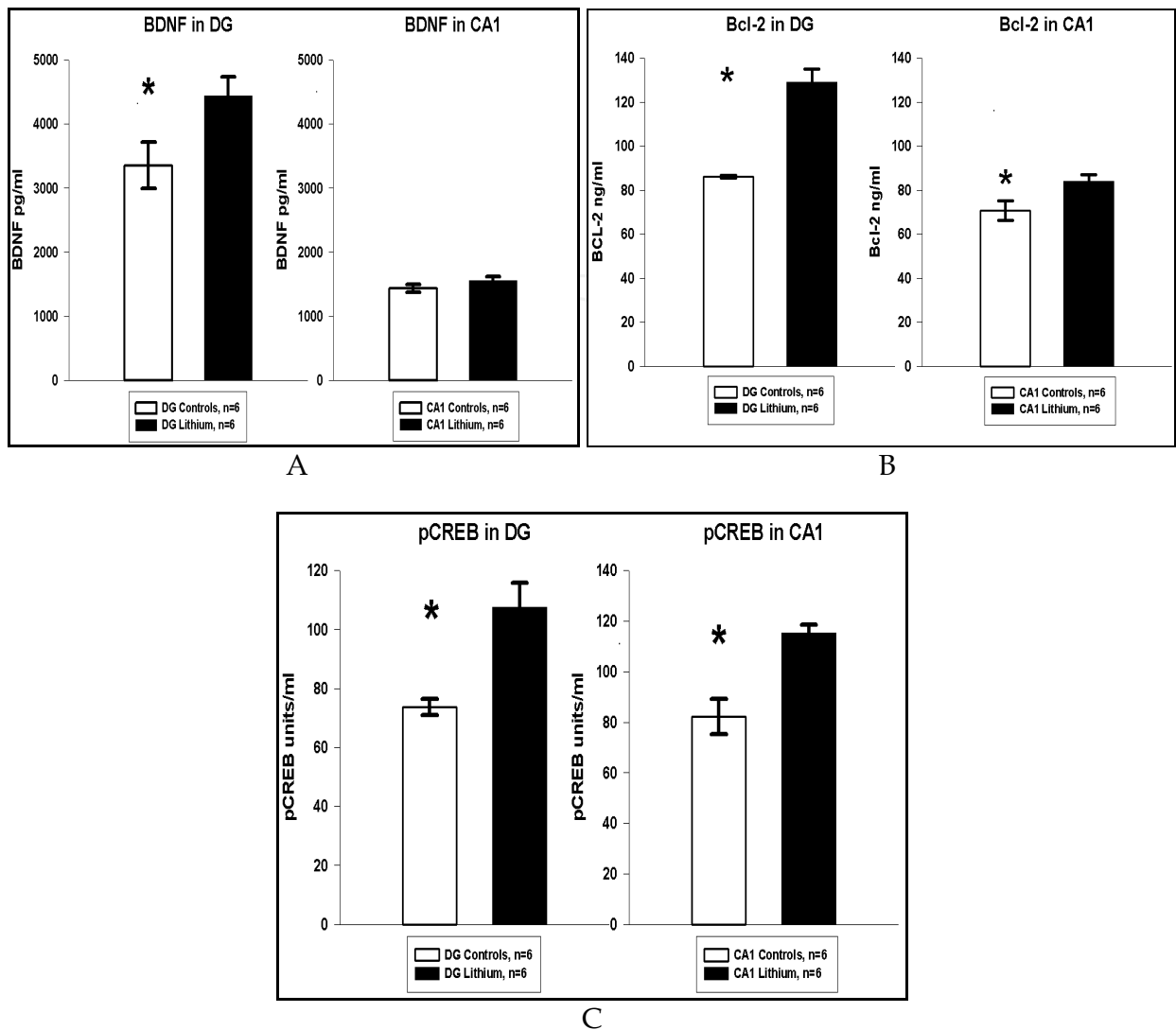


Fig. 11. Effects of 4-weeks lithium treatment on levels of BDNF, Bcl-2 and pCREB in the DG and area CA1. (A) There was significant difference in the levels of BDNF between the two groups (N = 6 of each group) in DG ($p = 0.016$, independent Student t -test), but no significant difference between the two groups in area CA1 ($p = 0.227$). There was significant difference in the level of total free Bcl-2 ($p < 0.001$ in DG; $p < 0.025$ in CA1) (B) and pCREB ($p = 0.001$ in DG; $p < 0.001$ in CA1) (C) between the lithium-treated (N = 6) control groups (N = 6) in both areas Two weeks lithium treatment did not change the levels of BDNF, Bcl-2 and pCREB in the DG and area CA1 (Hammonds et al, 2007..

4. Discussion

Our study found that chronic lithium treatment (CLT) magnified the expression of LTP of hippocampal area CA1 pyramidal cells (Fig. 3) without enhancing baseline synaptic response (Fig. 2), and subchronic lithium treatment (SCLT) magnified LTP and I/O function of the DG granule cells (Figs. 4, 5). Son et al. (2003) also reported that 4 weeks lithium treatment magnified LTP in the DG. Previously, we reported that 2 weeks lithium treatment magnified LTP in the DG (Shim et al. 2007). Our findings combined with others suggest that long-term lithium treatment increases synaptic plasticity in the hippocampus. We recently observed that

acute *in vitro* and *in vivo* (one day) lithium treatment decreased the magnitude of LTP in area CA1 (a manuscript in preparation). These findings together support our hypothesis that prolonged lithium treatment upregulates functional synaptic plasticity in the hippocampus, and this effect may not be associated with the direct chemical effect of lithium, but is likely to be associated with the molecular actions of lithium at genetic levels. Since hippocampal synaptic plasticity is known to underlie memory and learning, we investigated the effects of CLT on learning and memory (Nocjar et al 2007), which showed CLT increases learning and memory. This suggests the possibility that lithium can have therapeutic effects in patients with Alzheimer's disease and other dementia. (Engel et al. 2008).

Our analyses of the effects of lithium treatment on dendrites suggest that prolonged lithium treatment produces a remodeling in the distribution of dendrites of the principal neurons in the hippocampus. Interestingly, CLT and SCLT remodels in distribution of dendrites in different manners. CLT produces an increase in the distribution of dendritic branches with more branches in the segment of highly populated branches of dendritic trees and reduces dendritic branches in the segment of less populated branches (Figs. 7, 8). The consequence of this redistribution is unknown. We hypothesize that CLT produces more branches in the segment of dendritic trees, where synapses with major excitatory input occurs, and the most active synaptic transmission occurs, whereas CLT reduces branches in the segment where less synapses form. This structural remodeling may lead to an enhancement in synaptic transmission in a more efficient manner. SCLT remodels in distribution of dendritic branches in a manner opposite to the manner CLT does. SCLT decreases dendritic branches in dendrite segments, where branches are highly distributed and active synaptic interactions occur (Fig. 9, 10). This unexpected finding is not due to lithium toxicity. In our studies, lithium was administered twice daily (1 mEq/kg a day) for the two weeks lithium study, and no animals died or showed signs of lithium toxicity. It was confirmed that the blood levels of lithium were within the human therapeutic range of 0.51 to 0.78 mEq/L (Baldessarini and Tarazi, 2001). Furthermore, in our 4 weeks lithium treatment studies, animals were fed lithium chow for 4 weeks, and their lithium blood levels were again confirmed to be within the therapeutic range (0.68 to 0.89 mEq/L). Thus, lithium toxicity is not supported as a potential cause for the findings in the current studies. The dendritic segments where SCLT reduces dendritic branching are the region where dendrites receive major excitatory input and form main synapses with the input. Our study shows that SCLT increases baseline synaptic transmission and LTP, which was recorded approximately in the same region of the DG as the region where SCLT reduced dendritic branches (Figs. 4, 5). It is possible that the lithium-induced loss of dendritic branches in these regions could dampen excited synaptic activity as a homeostatic adaptive response to maintain physiologically efficacious synaptic transmission.

Our results show that CLT upregulates Bcl-2 and CREB in the DG and hippocampal area CA1 and upregulates BDNF in the DG (Fig. 11). However, SCLT does not upregulate BDNF, Bcl-2 or CREB in these hippocampal subregions (Hammonds et al. 2007). These findings suggest that CLT, not SCLT, upregulates these neuroplastic proteins, which are actively involved in synaptic plasticity.

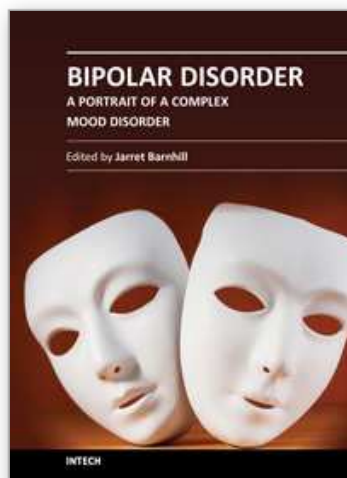
Our results from electrophysiological, morphological and molecular studies suggest that SCLT may increase functional synaptic plasticity. SCLT, however, increases neither the

density of dendrites in the active synaptic regions of dendritic trees of the principal neurons nor the levels of BDNF, Bcl-2 and pCREB in the hippocampus. In contrast, CLT increases functional synaptic strength, which is accompanied with remodels in distribution of dendritic branches in such a way that more dendritic material is available in dendritic regions where the most active synaptic activity occurs. These cellular changes are consistent with the up-regulation of BDNF, Bcl-2 and pCREB in the hippocampus. Thus, CLT may produce more stable and persistent changes in synaptic plasticity in the hippocampus. In contrast, SCLT may increase the functional aspect of synaptic plasticity. These changes may not be accompanied with the increased density of dendrites at active synaptic regions or the up-regulation of neuroplastic proteins. These findings are consistent with the clinical observation that lithium takes 3-4 weeks to show its efficacy in treatment of bipolar disorder and other mental illness (Baldessarinni and Tarazi 2001).

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Bipolar Disorder: Portrait of a Complex Mood Disorder is a step towards integrating many diverse perspectives on BD. As we shall see, such diversity makes it difficult to clearly define the boundaries of BD. It is helpful to view BD from this perspective, as a final common pathway arises from multiple frames of reference. The integration of epigenetics, molecular pharmacology, and neurophysiology is essential. One solution involves using this diverse data to search for endophenotypes to aid researchers, even though most clinicians prefer broader groupings of symptoms and clinical variables. Our challenge is to consolidate this new information with existing clinical practice in a usable fashion. This need for convergent thinkers who can integrate the findings in this book remains a critical need. This book is a small step in that direction and hopefully guides researchers and clinicians towards a new synthesis of basic neurosciences and clinical psychiatry

How to reference

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