Neuropathological and neurochemical abnormalities in bipolar disorder

Benício Noronha Frey, Manoela M Rodrigues da Fonseca, Rodrigo Machado-Vieira, Jair C Soarese and Flávio Kapczinski

Abstract
Objectives: Postmortem, pharmacological, neuroimaging, and animal model studies have demonstrated a possible association of intracellular signaling mechanisms in the pathophysiology of bipolar disorder. The objective of this paper is to review the findings in neuropathology and cellular biochemistry.

Methods: We performed a MEDLINE research, between 1980-2003, using bipolar disorder, signaling, second messengers, and postmortem as keywords, and cross-references.

Results: Neuropathological studies reported a decrease in neuronal and glial cells, mainly in the prefrontal cortex of bipolar patients. Neurochemical studies reported dysfunction in cAMP, phosphoinositide, Wnt/GSK-3b, and intracellular Ca++ pathways in these patients.

Conclusions: The neuropathological and neurochemical abnormalities demonstrated in BD may be related to the pathophysiology of this disorder and the effects of mood stabilizers. However, further studies are needed to clarify the role of the intracellular signaling cascade in the pathogenesis of this disorder.

Keywords: Bipolar disorder; Second messenger systems; Brain chemistry

Introduction
Bipolar disorder (BD) has been known for decades as a chronic mental disorder, with high relapse rates, most of times incapacitating, supposedly having a neurobiological substrate. Although the understanding of neurobiology has expanded in the last years, little is known about the real pathophysiological mechanisms of BD. Recent genetic investigations have reported results which, although conflicting, seem to demonstrate some association, at least in a percentage of ill subjects. Neuroimaging studies showed a series of structural and functional alterations in determined brain regions of bipolar subjects, such as prefrontal and temporal cortices, cerebellum, basal ganglia and limbic system; however, these studies do not allow reaching a more specific cell substrate in these regions. Besides, neuropathological studies (postmortem) showed decrease of glia and neuronal density and plasticity, as well as alterations in intracellular neurochemistry.

One of the models that has been applied to BD is kindling, taken from the model of epilepsy, in which the repetition of crises would cause a process of neuronal sensitization, leading to a progressive threshold decrease, with the increase in the recurrence of epileptic crises (manic). Animal model studies suggest that this process may involve a series of alterations in the genic expression and second messengers. In fact, pharmacological studies have been consistent with these findings, demonstrating the action of antidepressants and mood stabilizers in several intracellular mechanisms which involve the regulation of genic expression and cellular plasticity. This study aims to review the findings in neuropathology and cell biochemistry which seem to be involved in the pathophysiology of BD. A search on MEDLINE, between 1980 and 2003, was performed, using the keywords: bipolar disorder, signaling, second messengers and postmortem. Cross-references of the selected articles were also used.

Neuropathology of BD
Structural neuroimaging studies demonstrated significant alterations in brain volume, suggesting neuronal atrophy and/or loss, in at least a percentage of subjects with BD. Several studies reported a significant decrease in the gray matter in prefrontal and
temporal\textsuperscript{10-11} cortices, besides increase in lateral ventriculi.\textsuperscript{12} Independent studies which studied specific regions of the temporal cortex showed also decrease,\textsuperscript{13-14} and increase\textsuperscript{15-16} in amygdale volume of bipolar subjects. A consistent finding on BD studies is a higher frequency of hyperintensities of subcortical white matter.\textsuperscript{17} These diffuse lesions may signify interruption in the circuits involved in mood regulation. Although less consistently, alterations in basal ganglia\textsuperscript{18} and cerebellum\textsuperscript{18} were also noted among bipolar patients. As a whole, these findings point to a possible dysfunction in the cortical-limbic circuit as an autonomic substrate of BD.

Functional neuroimaging studies provide additional evidence of alterations in the metabolism of glucose and decrease in regional blood flow and cellular energetic phosphates in cortical and subcortical regions in BD.\textsuperscript{19} However, the resolution of the current neuroimaging techniques is limited to millimeters, being, therefore, fundamental postmortem studies which allow a direct study with the cellular and molecular resolution.

In one of the neuropathological studies with a larger sample of bipolar subjects (n=18), Öngür et al\textsuperscript{20} reported a significant decrease (41.2\%) in the density of glial cells in the subgenual prefrontal cortex, Brodmann’s 24th area, among bipolar and unipolar subjects with positive family history for mood disorders. However, this study did not assess if this decrease occurred specifically for astrocytes, oligodendrocytes or microglia. Recently, Rajkowska et al\textsuperscript{21} have not found significant differences in the density and size of glial cells in the dorsolateral prefrontal cortex (DLPFC – Brodmann’s 9th area) of bipolar subjects. However, a more detailed laminar analysis showed a significant decrease (19\%) of the glial density in the sublayer IIIc of DLPFC. This study found also a decrease in the number of average-size cells in glial layers III and V, accompanied by an increase in the number of cells with very large nuclei.\textsuperscript{21} Two independent studies provided additional data consistent with glial alterations in mood disorder. Cotter et al\textsuperscript{22} reported a decrease in the glial density on layer VI of Brodmann’s area 24 among unipolar and schizophrenic subjects but not among bipolar ones (most of them were using mood stabilizers, which seem to have a neurotrophic/neuroprotective effect). Using the same cohort of patients, Uranova et al\textsuperscript{23} investigated the area 10 of the dorsal prefrontal cortex and showed a significant decrease in the glial density on layer VI of bipolar and schizophrenic subjects, and only among unipolar ones with positive family history for ‘severe mental disorder’. As a whole these findings point to the hypothesis that at least one subgroup of bipolar and unipolar subjects, mainly those with positive family history, show some deficit in the glial density in multiple sites of the prefrontal cortex, what may affect their connection with other brain regions.

In the limbic system, Benes et al\textsuperscript{24} reported a significant decrease of non-pyramidal neurons in the hippocampal region CA2 among bipolar and schizophrenic subjects. More recently, the same group has replicated the same finding, although in layer II of the anterior cortex of the cingulate.\textsuperscript{25} These findings suggest a possible association with the decrease in the GABAergic inhibition (non-pyramidal neurons) in the pathophysiology of BD.\textsuperscript{4} In the brainstem it was demonstrated a bilateral increase in the number of pigmented neurons on the locus ceruleus of bipolar subjects compared to unipolar ones.\textsuperscript{26} These neurons are one of the main sources of noradrenaline (NA) in the CNS.\textsuperscript{34} In this sense, a postmortem study by Young et al\textsuperscript{27} reported an increase in NA turnover in the cortex of bipolar subjects. Glial cells regulate the energetic homeostasis of the CNS, by means of glucose reuptake and phosphorylation during neuronal activity. Besides, they participate in the development, maintenance and remodeling of the synaptic connections, through the release of trophic factors and the regulation of synaptic glutamate concentration.\textsuperscript{28} Thus, the findings of reduction in the glial density may result in the decrease in the number of functional synapses in BD. Consistently with this hypothesis of synaptic dysfunction, two postmortem studies which assessed the hippocampal region evidenced decrease in the mRNA expression of synaptic proteins\textsuperscript{29} and in apical dendritic spines of pyramidal cells\textsuperscript{30} in the subicular subregion of BD subjects.

Therefore, the advance of molecular biochemistry applied to postmortem studies point to a dysfunction of the complex intracellular mechanisms, which involve second messengers systems, regulation of the genic expression and synthesis of trophic factors (neuroplasticity), as associated with the pathophysiology of BD.\textsuperscript{1,6-7}

**Intracellular signaling systems**

**G Proteins**

The mechanism which involves the transmission of the information from the synapsis up to the cell nucleus is mediated by an intermediate process called second messengers, such as the cyclic adenosine monophosphate (cAMP) and phosphatidylinositol (PIP\textsubscript{2}) pathways. This process involves three stages: 1) the neurotransmitter binds to the membrane receptor; 2) the activation of proteins which use guanosine triphosphate (GTP) as a cofactor, called G proteins; and 3) the activation of effector systems (through second messengers – see figure 1). G proteins have three subunits (a, b and g), which are closely bound to the internal face of the plasmatic membrane, being activated by the binding of the neurotransmitter to its specific receptor. Multiple CNS receptor systems are modulated by G proteins, including noradrenergic, serotoninergic, dopaminergic, cholinergic and histaminergic receptors, among others. G proteins may have either stimulatory or inhibitory effect on effector proteins, being therefore classified as G\textsubscript{s} (stimulatory protein) and G\textsubscript{i} (inhibitory). In this way, receptor-activated G proteins modulate ion flows, through the regulation of the activity of ionic channels, and control the activity of several effector enzymes. The interest in the study of G proteins in BD has arisen from the findings about the regulatory action of lithium on several G protein subtypes in animal models.\textsuperscript{31-32} Young et al\textsuperscript{33-34} were the first to report an increase in G\textsubscript{i} subtypes in frontal, temporal and occipital cortices of BD subjects. This finding was replicated in one study which demonstrated an increase in agonist-stimulated G\textsubscript{i} activity.\textsuperscript{35} However, these results do not discard the possibility of being effects of pharmacological treatments or of samples with small sizes. In one study, which investigated a larger sample, Dowlatshahi et al\textsuperscript{36} did not find differences in G\textsubscript{i}, levels in bipolar subjects regarding the control group. Nevertheless, they evidenced a significant increase in G\textsubscript{i} among patients who were not using lithium. As a result, the use of the drug might have been responsible for the failure to detect the difference between the total of patients and the control group.
Peripheral blood studies have also confirmed these findings and widened the understanding of the relationship between the functioning of G proteins and mood states. Schreiber et al. were the first to evidence an increase in the activity of G protein in mononuclear leucocytes of manic patients. Other two studies observed increase in mononuclear G levels of non-medicated depressed bipolar patients, whereas other study found increased levels in manic and decreased levels in depressive state. Besides, this increase in G expression was also demonstrated in platelets, but not in lymphoblasts. These studies suggest that mood state and cell type may influence in the finding of increased G in the peripheral blood of bipolar subjects. Taken as a whole, these findings suggest a possible association of the functioning of G proteins in the pathophysiology of DB. However, it has still not been determined if BD is associated with direct dysfunction in the activity of G proteins or these findings represent a secondary manifestation of a dysfunction in other pathways.

Cyclic adenosine monophosphate (cAMP) pathway

One of the effector proteins regulated by G proteins is adenilate cyclase (AC), an enzyme which catalyzes the formation of cAMP, an important second messenger, from adenosine triphosphate (ATP – see Figure 2). One of the main functions of cAMP is the activation of other enzyme, a cAMP-dependent protein kinase (PKA), which integrates the fast neurotransmission alterations in long-term neurobiological alterations. Several studies demonstrated a significant increase in the activity of basal and activated AC among BD subjects, and these alterations may be associated with the dysfunction of G proteins described above. Besides, these studies showed a relationship between AC activity and mood state, with a decrease in the activity of the enzyme among depressed or euthymic patients who relapse after lithium treatment. One postmortem study found a decrease in cAMP binding to PKA in the frontal, temporal, parietal, occipital, thalamic and cerebellum cortices of bipolar subjects, translating an indirect measure of the increase of cAMP activity in these patients. Two more recent postmortem studies which assessed the frontal and temporal cortices, and two platelet studies confirmed an increase in PKA activity in bipolar patients. As a whole, these studies consistently suggest an increase in the activity of the cAMP-PKA pathway in several brain regions of BD subjects.

Studies have also shown that chronic use of lithium decreases AC activation and that this action may be reverted by the increase in GTP concentration, suggesting that the effects of lithium treatment may be attenuated at the level of G proteins. However, basal lithium has increased the formation of cAMP in rat brains. Therefore, it has been suggested that the action of lithium in AC activity is state-dependent: in basal conditions, when the tonic inhibition of the formation of G , mediated cAMP is predominant, lithium increases the formation of cAMP; when AC is activated by the receptor-G complex, the formation of cAMP is attenuated. This 'bimodal' mechanism of action may be one of the explanations of the therapeutic effect of lithium both in depression and mania. Chronic valproate use in clinically-relevant concentration produced a significant increase in b-adrenergic receptors bound to the cAMP pathway on in vitro cells. Carbamazepine, in turn, shows to inhibit basal and activated AC, besides reducing the high levels of cAMP in the liquor of manic patients.

Phosphatidylinositol (PIP) pathway

Several neurotransmission systems use the phosphatidylinositol pathway (Table 1) through the activation of G proteins. In this pathway, G protein activation stimulates the phospholipase C effector protein (PLC), which hydrolyzes a membrane phospholipide, called phosphatidylinositol (PIP), forming two important second messengers: diacilglycerol (DAG) and inositol triphosphate (IP). IP, has a specific receptor situated in the smooth endoplasmatic reticulum which releases Ca^{2+} stocks whenever activated. DAG, in turn,
Table 1 – Regulatory effects of neurotransmitters in the intracellular signaling

<table>
<thead>
<tr>
<th>G-protein bound receptors</th>
<th>cAMP pathway</th>
<th>PIP₂ pathway</th>
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</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Muscarinic</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>GABA</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Glutamate – metabotropic</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Type I</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D₁</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>D₂</td>
<td>-</td>
<td></td>
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<tr>
<td>Noradrenaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α₁</td>
<td>+</td>
<td>-</td>
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<tr>
<td>α₂</td>
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<td>β₁</td>
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<tr>
<td>β₂</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
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</tr>
<tr>
<td>5-HT₁</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5-HT₂</td>
<td>-</td>
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<td>Histamine</td>
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<td>H₁</td>
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<td>H₂</td>
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</table>

cAMP = cyclic adenosine monophosphate
PIP₂ = phosphatidylinositol
GABA = Gamma-aminobutyric acid

has the function of activating protein kinase C (PKC – Figure 3). Several postmortem and peripheral cells studies have demonstrated alterations of this pathway in subjects with BD. One postmortem study evidenced increased G protein and PLC activity in the occipital cortex of bipolar subjects, without alterations in frontal and temporal regions.57 Other study observed a decrease in G-protein activity linked to the PIP₂ pathway, also in the occipital region.58 The authors suggested that these controversial findings may stem from a cellular adaptive process or from the chronic use of lithium. In order to maintain the transmission efficiency of this pathway, the cell needs to keep an adequate supply of inositol for the re-synthesis of PIP₂. As inositol crosses weakly the blood brain barrier, its supply is provided by dephosphorylation of IP₃, through catalization by inositol monophosphatase (IMPase). Shimon et al59 compared brains of bipolar, suicide subjects and controls and showed a significant decrease in free inositol in the frontal cortex of bipolar and suicide subjects when compared to the control group, but did not find alterations in IMPase activity on that region. There were no alterations in occipital cortex or cerebellum. Two platelet studies reported increase in PIP₂ levels among non-medicated bipolar subjects, both in their manic60 and depressive61 phase, whereas other studies found significantly reduced PIP₂ levels in platelets of bipolar subjects after lithium treatment.62-64 These findings support pharmacological studies which demonstrated that lithium in therapeutic concentrations (Ki=0.8mM) is a potent inhibitor of IMPase.65 Therefore, this regulatory action of lithium on the PIP₂ pathway may be one of the mood regulating mechanisms of this drug. More recently, one study using magnetic resonance spectroscopy, an exam capable of measuring in vivo brain neurochemical substances, showed that lithium significantly decreased inositol in depressed bipolar subjects’ right frontal cortex.66 However, although this effect of lithium occurred within 5-7 days, mood improvement has only occurred 3-4 weeks after use of the medication,66 suggesting that this initial effect of lithium modulates a series of posterior cascading events, such as the regulation of genic expression and neuronal plasticity, needed to obtain a significant clinical response.

PKC is an important enzyme in the PIP₂ pathway, acting on the regulation of the neuronal excitability, release of neurotransmitters, genic expression and synaptic plasticity.1 One postmortem study showed significant increase in PKC activity in the frontal cortex of bipolar patients,67 a finding also demonstrated on platelet studies.68-69 Soares et al60 did not find differences in PKC levels on platelets of euthymic subjects treated with lithium. Actually, lithium also showed effects in the inhibition of PKC activity in animal studies.70-71 Therefore, the findings of increase in PKC activity on BD
and its decrease with lithium may be clinically relevant. In this sense, Bebchuk et al. have recently published one study showing possible antimanic effects of tamoxifene, a PKC antiestrogenic-inhibitor.

Wnt (wingless)/Glycogen synthase kinase 3β (GSK3β) pathway
Wnt proteins bind to G-protein binding membrane receptors (frizzled), activating the disheveled protein kinase, which inhibits the glycogen synthase kinase 3β (GSK3β) activity (Figure 4). The interest in the study of the role of GSK3β in BD has arisen from observations that lithium and, more recently, valproate decrease the activity of this protein in therapeutical concentrations. GSK3β is able to phosphorylate an extensive range of metabolic, signaling and structural proteins, besides genic transcription factors. Among these activities, stands out the modulation of proteins associated with cytoskeleton microtubules, such as tau, MAP-1B and MAP-2, and the regulation of programmed cell death (apoptosis). The phosphorylation of tau and MAP-1B by GSK3β is associated with the loss or destabilization of microtubules' conformation and the use of lithium showed to decrease the phosphorylation of tau in human neuron culture. GSK3β is directly associated with the increase in neuronal apoptosis, decreasing the activities of proteins which promote the neuronal survival, such as cAMP response element binding protein (CREB) and the heat shock factor-1 (HSF-1). Besides, lithium, valproate and lamotrigine protected SH-SY5Y cells from apoptosis facilitated by GSK3β. 

GSK3β activity may be modulated by a series of intracellular signaling cascades. More specifically, the phosphorylation of GSK3β by PKA, PKC and Akt decreases, while intracellular Ca++ may increase its activity. Therefore, it has been suggested that the neuroprotecting effects of neurotrophins (NGF, BDNF) and lithium may stem, at least partially, from the inhibition of GSK3β, through the PI3K/Akt pathway. Two postmortem studies did not find alterations in GSK3β levels on prefrontal cortex of bipolar patients. However, even though there is no direct evidence of abnormalities in the Wnt/GSK3β pathway on BD, robust evidence highlights the importance of the regulation of this pathway in the treatment of this disorder.

Intracellular Calcium (Ca++i)
The variation in intracellular calcium levels (Ca++i) modulates the synaptic plasticity, cell survival and death. In fact, Ca++i signaling interacts with several other signaling cascades, including the cAMP and PIP2 pathways. Besides, calcium may interact with other regulatory proteins, such as calmoduline, forming complexes which modulate the activity of other important enzymes including calcium-calmodulin dependent protein kinases (CaMKs). Ca++i-activated PKC decreased PKA activity in fibroblasts, whereas cAMP caused desensitization of IP3 receptors and decreased Ca++ inflow, reducing therefore Ca++i levels. Dubovsky et al. were the first to describe an increase in Ca++i levels in leucocytes and platelets of manic non-medicated bipolar and non-medicated depressed subjects. Besides, using stimuli which increase Ca++i concentrations, it was noted a significantly increased response among non-medicated manic bipolar subjects compared to euthymic patients, who were using mood stabilizers. These studies suggest that the variations in mood state may be related to alterations in Ca++i levels and that these alterations may be reverted with the remission of crises, although other studies have not replicated these findings.

Emagoreishi et al. have recently showed that bipolar individuals with high basal Ca++i levels had a lower production of cAMP after stimulation of b-adrenergic rece-
tors with isoproterenol and higher basal activity of AC bound to G protein, corroborating the findings of increased G-protein activity described before and suggesting that alterations in one pathway may decompensate or induce adaptive alterations in other signaling pathways.

Regulation of gene expression and neuroplasticity

The activity of second messenger’s pathways has as an important final target the modulation of a family of proteins which act as gene transcription factors. These proteins bind to specific DNA sites and regulate the expression of a wide range of genes capable of regulating cellular functions such as proliferation and apoptosis (Figure 5). One transcription factor that has been studied in BD is CREB, a protein situated in the cell nucleus, usually in its inactive form, being activated by several protein kinases, such as PKA, MAPK or CaMK.96 After being activated, CREB promotes the production of mRNA when binding to a specific site in the promoting regions of target genes, with the formation of proteins which may permanently alter specific brain regions’ structure or function. Dowlatshahi et al.96 did not find significant alterations in CREB levels in bipolar subjects in one postmortem study; however, they found decreased protein levels among individuals who committed suicide and those treated with anticonvulsants at their death. Pharmacological studies which examined the effects of lithium in CREB activity found conflicting results,68,78 whereas carbamazepine showed to decrease protein phosphorylation in gliomes.54 Besides, the chronic use of ECT and antidepressants increased the expression of BDNF and its receptor TrkB through the increase in CREB activity,93-94 and GSK3- activity also decreased by GSK3-.

As reported, recent studies have shown that lithium, valproate and carbamazepine may exert therapeutic effects by means of the regulation of the gene expression through transcription factors. Lithium acts on the several second messengers cascading levels, as well as on protein kinases. Besides, there is evidence of the action of lithium in one of the main brain PKC substrates, MARCKS protein (miristoylated alanine-rich C kinase substrate), which is also a protein related to the regulation of neuroplastic events, altering the conformation of the cytoskeleton through actine filaments. Four-week lithium treatment reduced dramatically the expression of MARCKS protein in hyppocampal cells.99 Further studies showed that this action of lithium occurred through the regulation of the protein’s genic transcription100 and that it was dependent on inositol concentration and on activation of the receptor linked to the PIP2 cascade.101 Other study showed that valproate is also capable of reducing MARCKS expression in hyppocampal cells, by means of mechanisms which differed from those of lithium,102 supporting clinical observations on the synergetic therapeutical effect of these two drugs in mood regulation.

Conclusions

Postmortem studies and neuroimaging findings have consistently revealed a significant decrease of volume of determined CNS regions, accompanied by loss or atrophy of neurons, mainly glial cells. Nevertheless, it has not been determined yet if these findings represent early alterations in neuronal migration, cellular losses stemming from the development of the disease proper, biochemical alterations which accompany mood crises or the action of the several medications used. On the other hand, the possible role of cell death/atrophy in the progressive functioning decline found in many patients remains undeciphered. Studies comparing treated patients with those who have never received a medication may help to understand the effects of psychotropics in the cellular morphology and functioning.

Increasing evidence points to the association of intracellular mechanisms, involving the second messengers system as part of the neurobiological alterations of BD. It has been demonstrated an increase in the activity of G proteins and cAMP and PIP2 pathways, which, by means of the regulation of ADN synthesis, modify the proteins involved in synaptic plasticity, neurogenesis and conformation of the cytoskeleton. However, it is still uncertain if these alterations reflect an increase in the subject’s vulnerability (as a result of genetic factors/early life events), effects of established treatments or the disease’s central etiological process. Early prospective studies, assessing the alterations of genic expression during the course and treatment of the disorder are a promising research field. Besides, the enhancement of animal models, such as the use of mutant mice, is needed to test if the alterations in determined intracellular signaling cascades suffice to promote behavioral alterations and if the blocking of these pathways are able to inhibit the action of psychopharmacics.

Lastly, pharmacological studies have revealed the action of the main mood stabilizers in several of these intracellular mechanisms. It is possible, therefore, that the acute effects of these
drugs trigger a cascade of intracellular events, capable of altering the proteinc synthesis, producing reparatory effects in the synaptic plasticity and restoring the nervous transmission. It is still unknown at which point these drugs may interfere in the pathophysiological alterations of BD and stabilize the course and progression of the disease. These breakthroughs in the neurobiology of BD should be cautiously interpreted, without generalizations, as they are initial studies, which should be replicated and conducted with larger and less heterogeneous samples. Besides, abnormalities involving other pathways, such as the purinergic pathways have been also reported.


76. Lucas FR, Goold RG, Gordon-Weeks PR, Salinas PC. Inhibition of GSK-3β leading to the loss of phosphorylated MAP-1B is an early event in axonal remodeling induced by WNT-7a or lithium. J Cell Sci. 1998;111(Pt 10):1531-61.