Published in final edited form as:
Curr Mol Pharmacol. 2009 June ; 2(2): 207–214.

Mood-Stabilizers Target the Brain Arachidonic Acid Cascade

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Abstract

Bipolar disorder (BD) is a severe psychiatric illness characterized by recurrent manic and depressive episodes, without a characteristic neuropathology or clear etiology. Drugs effective in BD target many key signaling pathways in animal and cell studies. However, their mode of action in the BD brain remains elusive. In the rat brain, some of the mood stabilizers effective in treating mania (lithium, carbamazepine, valproate) or depression (lamotrigine) in BD are reported to decrease transcription of cytosolic phospholipase A_2 and cyclooxygenase-2 and to reduce levels of AP-2 and NF-κB, transcription factors of the two enzymes. The anti-manic drugs also decrease arachidonic acid (AA) turnover in brain phospholipids when given chronically to rats. Thus, drugs effective in BD commonly target AA cascade kinetics as well as AA cascade enzymes and their transcription factors in the rat brain. These studies suggest that BD is associated with increased AA signaling in the brain. Developing therapeutic agents that suppress brain AA signaling could lead to additional treatments for BD. In this review, we discuss the mechanisms of action of mood stabilizers and the effects of docosahexaenoic acid on AA cascade enzymes in relation to BD.

Keywords

bipolar disorder; $cPLA_2$; $sPLA_2$; COX-2; AP-2; NF-κB; arachidonic acid; mood stabilizers

INTRODUCTION

Bipolar disorder (BD) is a complex psychiatric disorder, characterized by recurrent depressive and manic episodes. Epidemiological studies show that BD afflicts 1.5 % of the United States population [1] and that BD patients have a 5-to-17 fold increased risk of suicide relative to the general population [2]. However, BD has no characteristic neuropathology and an unknown etiology. Several hypotheses have been proposed to explain BD based on alterations in signal transduction pathways [3]: reduced levels of neurosurvival factors [4], atrophy in brain regions [4–8] and involvement of many genes[9,10]. Recent studies have suggested excitotoxicity [11–14] and neuroinflammation in BD with elevated pro-inflammatory cytokines [15,16]. Some of these pathological processes change arachidonic acid (AA: 20:4n-6) metabolism [17–19] and neuronal plasticity. Excessive AA release could promote apoptosis [20]. A number of medications are employed to treat BD, including lithium, antiepileptics, antidepressants and antipsychotic drugs. However, they differ in structure and modes of action. In this review, we discuss the modes of action of different types of mood stabilizers that share common targets in the rat brain and their use in treating BD.

AA is a nutritionally essential polyunsaturated fatty acid predominantly found in the stereospecifically numbered-2 (*sn*-2) position of membrane phospholipids. AA can be

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hydrolyzed from membrane phospholipids by calcium-dependent AA-selective cytosolic phospholipase A_2 ($cPLA_2$ IVa) or secretory PLA_2 ($sPLA_2$ IIa) [21]. In addition, a Ca^{++}-independent phospholipase A_2 ($iPLA_2$) is thought to be selective for docosahexaenoic acid (DHA, 22:6n-3). The PLA_2 enzymes differ in their calcium requirement, phosphorylation, and substrate specificities [22–26].

A portion of the AA released by $cPLA_2$ is metabolized to bioactive eicosanoids by cyclooxygenase (COX-1 or COX-2), lipoxygenase, or cytochrome P450 epoxygenase enzymes [27]. Of the two COX isoenzymes, COX-1 is usually constitutively expressed, whereas COX-2 is constitutively expressed but also is inducible by various brain insults [28,29]. $cPLA_2$ and COX-2 genes are regulated by many transcription factors including activator protein-1(AP-1), AP-2, nuclear factor kappa B (NF-κB), polyoma enhancer activator 3 (PEA3), cyclic AMP response element binding protein (CREB) and glucocorticoid response element (GRE) [30, 31]. Released AA and its metabolites can modulate signal transduction, transcription, neuronal activity, apoptosis, and many other processes within the brain [32–34] (Figure-1).

Does abnormal AA metabolism play a role in bipolar disorder?

A number of clinical studies have indicated an alteration in AA metabolism in BD patients, with increased hydrolysis of serum phospholipids [35–37] and increased levels of prostaglandins, a product of AA, in saliva [38], cerebrospinal fluid [39] and serum [36]. Genetic studies also indicate a variant in the $sPLA_2$ gene in BD patients [40]. Postmortem studies in BD have demonstrated increased expression of $cPLA_2$, $sPLA_2$, COX-2, and their transcription factors AP-2 and NF-κB in the frontal cortex (Rao et al Unpublished data) [41]. In agreement, a rat model of BD-like behavioral symptoms [42] showed increased AA signaling in the frontal cortex [19]. These findings suggest the upregulation of AA cascade in BD.

MOOD STABILIZERS EFFECTS ON BRAIN ARACHIDONIC ACID CASCADE ENZYMES

Lithium

Lithium has been employed in treating BD for more than five decades, but its mode of action remains unclear. Lithium is a monovalent cation (Figure-2) and is known to inhibit inositol monophosphatase [43], G-proteins [44–46], cyclic adenosine monophosphate (cAMP) [47, 48], glycogen synthetase kinase-3 beta (GSK-3β) [49], protein kinase A (PKA) [50], protein kinase C (PKC) [51–54] and its substrate myristoylated alanine-rich C kinase substrate (MARCKS) [55,56]. Six weeks of chronic lithium administration to rats that produced therapeutically relevant concentrations in brain and blood reduced AA turnover but not DHA turnover in brain phospholipids by reducing transcription of $cPLA_2$ group IVA [57–59]. The decrease in $cPLA_2$ mRNA was ascribed to a selective decrease in AP-2 transcription factor activity and protein levels of the AP-2α and β subunits [60]. AP-2 is recognized on the promoter region of the $cPLA_2$ gene [31]. Chronic lithium had no effect on other $cPLA_2$ - regulating transcription factors (NF-κB, PEA3, GRE) or on expression of $iPLA_2$ group VIA or $sPLA_2$ group IIA [60].

Activation of AP-2 requires phosphorylation by PKA or PKCε [61]. Phosphorylated AP-2 subunits translocate to the nucleus, where they recognize a specific AP-2 binding sequence on chromatin so as to initiate transcription. Chronic lithium treatment decreased PKAα and PKCε protein levels as well as AA-dependent PKC activity in rat brain [60]. The decreased phosphorylation of AP-2 subunits may be responsible for the decreased AP-2 activity [60]. Decreased AP-2 thus likely accounts for the reduced $cPLA_2$ mRNA after chronic lithium administration. The decrease in AA signaling by chronic lithium in turn reduces downstream AA metabolism. Chronic lithium administration decreased activities of COX-1 and COX-2

and the concentration of one of their products prostaglandin E_2 (PGE_2) in rat brain [62] (Figure-3).

Carbamazepine

Carbamazepine (5H-Dibenz[b,f]azepine-5-carboxamide; Tegretol) (Figure-2) is an anticonvulsant also effective in treating bipolar disorder [63]. Chronic carbamazepine treatment protects against NMDA-mediated toxicity [64], inhibits adenylyl cyclase and the synthesis of cAMP [51], reduces expression of G_o and G_s proteins in neostriatum, increases Gβ protein expression in rat frontal cortex [65], and increases brain phosphorylation of MARCKS. Chronic (30 days) carbamazepine administration in rats, which produced therapeutically relevant plasma levels (53.6 μM) [66], decreased the turnover of AA but not DHA in brain phospholipids [67], and decreased brain mRNA, protein, and activity of $cPLA_2$ group IVA but had no effect on $sPLA_2$ group IIA or $iPLA_2$ group VIA expression or activity, similar to lithium [66]. Chronic carbamazepine, like lithium, decreased brain COX-2 activity and PGE_2 concentration [62,66] without altering 5-lipoxygenase or cytochrome p450 protein levels or leukotriene B_4 or thromboxane B_2 concentrations [66]. Carbamazepine decreased the $cPLA_2$ gene transcription factor AP-2 (Figure-3) but not other $cPLA_2$ gene regulating transcription factors (AP-1, NF-κB, GRE or PEA3) [41]. Carbamazepine decreased AP-2 binding activity by decreasing cAMP dependent PKA activity, a known activator of AP-2 [61] (Figure-3), and phosphorylated AP-2 and protein levels of the AP-2α subunit. Unlike lithium, chronic carbamazepine had no effect on PKCα or PKCε protein levels in rat frontal cortex [19].

Valproic acid

Valproic acid (VPA, 2-propylpentanoic acid) is a branched-chain carboxylic acid (Figure-2) used in treating acute mania and mixed episodes in BD [44,68]. VPA shares some biochemical and cellular targets with lithium, including inhibiting the activities of glycogen synthase kinase-3 β [54,69] and PKC [70,71], and increasing AP-1 DNA binding [72,73]. Studies also indicate that VPA directly inhibits histone deacetylase [74]. Chronic (30 days) administration of VPA, to produce therapeutically relevant plasma levels (0.2 mM) [44,75], was shown to decrease the turnover rate of AA but not DHA in brain phospholipids of unanesthetized rats [67,75]. Like lithium and carbamazepine, chronic VPA decreased rat brain COX activity and PGE_2 concentration [76], without altering 5-lipoxygenase or cytochrome p450 protein levels or leukotriene B_4 or thromboxane B_2 concentrations [76]. Two weeks of VPA administration to rats also decreased the *ex vivo* production of COX metabolites from isolated platelets and brain capillaries [77]. VPA decreased rat frontal cortex COX-2 mRNA levels and the binding activity of NF-κB, a transcription factor for COX-2 [19]. It decreased the p50 protein component of NF-κB, without changing the rat frontal cortex protein level of p65. Unlike lithium and carbamazepine, VPA did not change expression or activity of $cPLA_2$ group IVA, nor did it alter $sPLA_2$ group IIA or $iPLA_2$ group VIA expression, or AP-2 binding activity [19]. Because of this difference, we studied the effects of VPA on other enzymes regulating AA turnover within brain phospholipids, namely microsomal acyl-CoA synthetase. VPA was found to act as an ordered noncompetitive inhibitor of microsomal acyl-CoA synthetase *in vitro* (Figure 3), and its K_i for inhibiting arachidonoyl-CoA formation was lower than that for inhibiting formation of docosahexaenoyl- CoA or palmitoyl-CoA [67]. This likely explains why VPA decreased the turnover of AA but not of DHA within brain phospholipids of the unanesthetized rat.

Lamotrigine

Lamotrigine [Lamictal; 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine)] (Figure-2) is a novel anticonvulsant that has been proven effective in the treatment of bipolar depression

[78] and rapid cycling BD [79]. Studies in rodents have revealed that lamotrigine increases brain gamma amino butyric acid (GABA) turnover [80] and hippocampal serotonin (5-HT) and dopamine levels [81], but decreases brain glutamate [82]. Chronic administration of lamotrigine decreased COX-2 protein and mRNA in rat frontal cortex without changing protein levels of COX-1 or of PLA_2 subtypes. Lamotrigine's therapeutic action in bipolar disorder may be related to reductions in AA signaling via COX-2 and the formation of COX-2 derived PGE_2 and other eicosanoids.

Lamotrigine [83] decreased locomotor hyperactivity in amphetamine models of mania, and decreased incorporation of AA into brain phospholipids of unanesthetized rats [41]. Lamotrigine does not delay the onset of mania in patients with bipolar disorder, although it does delay the onset of depressive symptoms [84] and is effective in rapid-cycling bipolar disorder [85]. The mood stabilizers for bipolar also reduce NMDA induced AA incorporation in rat brain [41,86].

Antidepressants—To test the increased AA signaling hypothesis for bipolar mania, we examined the effects of fluoxetine and imipramine which increase switching to mania in bipolar depressed patients. In awake rats, chronic fluoxetine or imipramine increased AA turnover and $cPLA_2$ expression in rat brain without changing expression of $sPLA_2$ or $iPLA_2$ or COX isoforms [41,87]. In contrast, chronic bupropion, an antidepressant that does not switch to manic symptoms in bipolar depressive patients, had no effect on AA turnover or $cPLA_2$ in rat brain [87]. These studies imply that an upregulated AA cascade signaling is related to the manic symptoms in BD.

Topiramate

Phase I clinical trials suggested that topiramate was effective in BD [88] and it was shown to effective in quinpirole model of mania [89]. Despite achieving a therapeutically relevant plasma topiramate level of 18.1 μM after chronic treatment, chronic topiramate did not alter expression of $cPLA_2$ or any of the measured enzymes in the AA cascade, nor did it alter AA or DHA turnover in brain phospholipids of the unanesthetized rat [67,90]. Consistent with these negative findings, four recent double-blind placebo-controlled trials demonstrated that topiramate is not an effective antibipolar drug [91], a finding that was predicted by the AA model [67,90].

Factors contributing to upregulation of AA cascade enzymes—Numerous conditions can influence expression of AA cascade enzymes: neuroinflammation, excitotoxicity, long-term treatment with fluoxetine, dietary deprivation of n-3 polyunsaturated fatty acids, lipopolysaccharide infusion, chronic NMDA administration and genetic factors. Some of these conditions may be implicated in the pathophysiology of BD.

Mood stabilizers effective in the treatment of BD can attenuate inflammation-induced and excitotoxicity-induced AA signaling in rat brain [17,41]. Chronic NMDA administration decreased NMDA receptor (NMDAR) (NR-1 and NR-3A) subunits and increased AA turnover [17] in rat brain, possibly by upregulating $cPLA_2$ group IVA protein and mRNA expression as well as AP-2 DNA binding activity and AP-2α and AP-2β protein levels [41]. Altered NMDA function, an elevated brain glutamate/glutamine ratio, and decreased NR-1 and NR-3A levels have been reported in children and adult BD patients as well as in postmortem brain from BD patients [11,12,92]. Gene variants of the NR1 and NR2 subunits of the NMDAR also have been linked to risk for BD [12,93,94]. In addition, NMDA receptor density and levels of NR1, NR2A and NR3A are decreased in the postmortem bipolar brain, as are densities of the NMDAR-associated post-synaptic proteins PSD-95 and SAP102 [14,95]. The subunit variants can produce increased NMDAR function because NMDAR stimulation by glutamate or

NMDA decreases NR-1 and NR-3A expression [41,96]. In vitro studies indicate that the NR3A subunit co-assembles with other subunits (NR1, NR2A or NR2B) to form NMDARs with reduced activity and Ca^{2+} influx [97,98], and mice lacking the NR3A subunit have increased NMDAR activity [99]. These observations suggest that increased NMDA function leads to increased AA signaling. In contrast, mood stabilizers attenuate NMDA induced AA incorporation in rat brain [17,41]. A recent study showed that rats exposed to chronic NMDA had increased brain protein and mRNA levels of neuroinflammatory markers, such as interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNFα), glial fibrillary acidic protein (GFAP) and inducible nitric oxide synthase (iNOS) [100]. This suggests cross-talk between excitotoxicity and neuroinflammation.

In addition to NMDA excitotoxicity, lipopolysaccharide exposure induced $cPLA_2$ protein expression in an NF-κB and AP-2 dependent manner in rat astrocyte cultures [67,101] and increased AA incorporation and $cPLA_2$ Bactivity in rat brain [41,102]. Excessive release of glutamate may trigger neuroinflammatory reactions, since neuroinflammatory cytokine genes were upregulated with chronic NMDA administration to rats [103]. A combination of excitotoxicity and neuroinflammation could lead to activation of many transcription factors and thereby induce expression of many genes, including those related to the AA cascade. A clinical study reported increased neuroinflammation in BD patients associated with an increase in pro-inflammatory cytokines and attenuated by mood stabilizers [15]. Animal studies have reported that bacterial endotoxin infusion produced pro-inflammatory cytokines (IL-2, TNF α) and a variety of behavioral changes including aggression [104,105]. Clinical reports also suggest a link between increased cytokine levels and aggressive behavior [106,107]. Taken together these studies indicate that inflammation could play a role in BD.

Clinical studies suggest that dietary supplementation of DHA is beneficial in patients with BD [108]. DHA is a polyunsaturated fatty acid (PUFA) that is highly enriched in the brain [109]. It is not synthesized *de novo* in vertebrates but is obtained directly from the diet or synthesized in the liver by the desaturation/elongation of its dietary precursor, α-linolenic (18:3n-3) acid [110]. Dietary deprivation of DHA in rats causes BD-like behavioral symptoms [42] and is associated with increased expression of $cPLA_2$ group IVA, $sPLA_2$ group IIA and COX-2 in frontal cortex [19]. These changes are opposite in direction to the effects of chronic mood stabilizer administration in rat brain, suggesting that dietary supplementation of n-3 PUFAs could attenuate AA signaling in rat brain, in a manner comparable to the action of mood stabilizers. Such supplementation may be beneficial in patients with BD [108], but further testing is required to validate its efficacy.

BD is complex, heterogenous disease that involves multiple genes, and has no appropriate animal model. Consequently, development of a specific drug based on pathology has not occurred. However, available FDA approved drugs are known to target AA cascade markers particularly $cPLA_2$ and COX-2 enzyme expression/or activity. Mood-stabilizers are also reported to attenuate the NMDA and lipopolysaccacharide induced AA signaling in rat brain [41,86]. Increased AA cascade signaling will arise from either excess glutamate or inflammation. Further evaluation of agents such as $cPLA_2$ inhibitors, NMDA antagonists, COX 2 inhibitors is warranted for pre-clinical studies as well as studies in BD patients. Glutamatergic modulating agents are also promising based on pre-clinical and clinical studies. These agents include Riluzole (2-amino-6-trifluoromethoxy benzothiazole), memantine, Ceftriaxone and felbamate [111]. The effects of these drugs have not been studied on AA cascade markers in animal studies.

In conclusion, mood stabilizers share common effects by downregulating the AA cascade in rat brain. Conversely, a pathological upregulation of the AA cascade may play a role in BD symptoms.

Acknowledgments

This work was entirely supported by the Intramural Research Program of the National Institute on Aging, National Institutes of Health. We thank the National Cancer Institute (NCI), Center for Cancer Research (CCR) Fellows Editorial Board, for proofreading the manuscript. The authors have no conflict of interest.

Abbreviations

AA	arachidonic acid
AP-2	activator protein-2
BD	bipolar disorder
$cPLA_2$	cytosolic phospholipase AB_{2B}
COX	cyclooxygenase
DHA	docosahexaenoic acid
$iPLA_2$	calcium-independent phospholipase A_2
NF-κB	nuclear factor kappa B
$sPLA_2$	secretory phospholipase A_2
NMDA	N-methyl-D-aspartate
PGE_2	prostaglandin E_2
PKA	protein kinase A
MARKS	myristoylated alanine-rich C kinase substrate
NMDA R	N-methyl-D aspartate receptor

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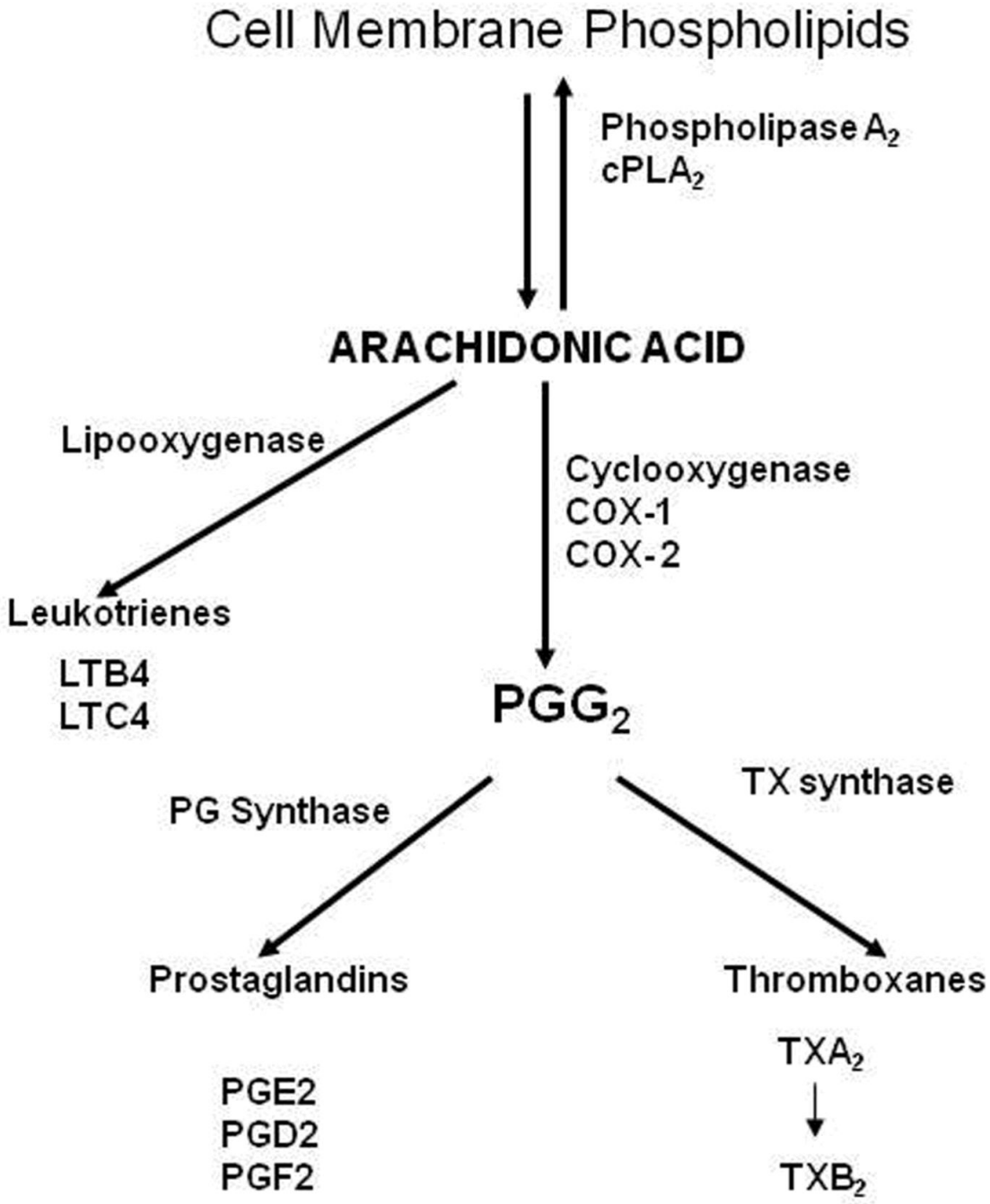

Figure-1.

Arachidonic acid (AA) is released from membrane phospholipids at the *sn*-2 position by the catalytic action of Ca^{++}-dependent cytosolic phospholipase A_2. Released AA directly mediates various cellular actions or is converted into many bioactive metabolites by cyclooxygenases and other enzymes.

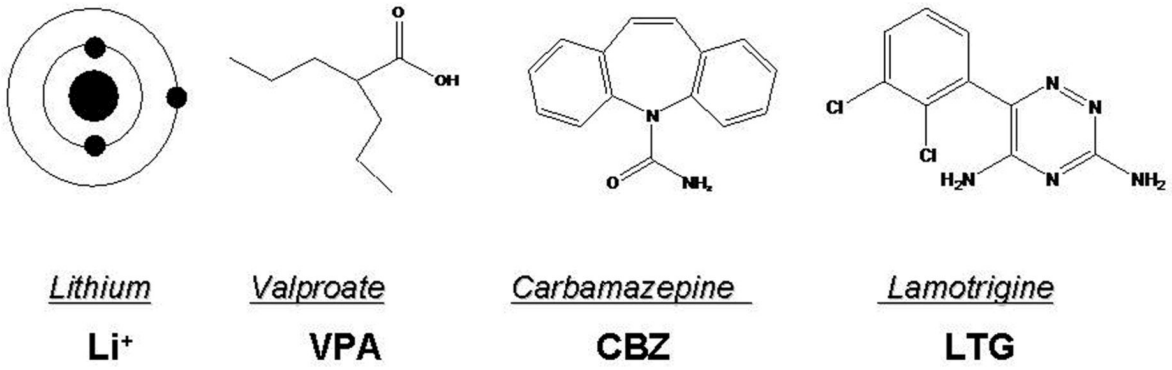

Figure-2.
Chemical structures of mood stabilizers approved for treating bipolar disorder.

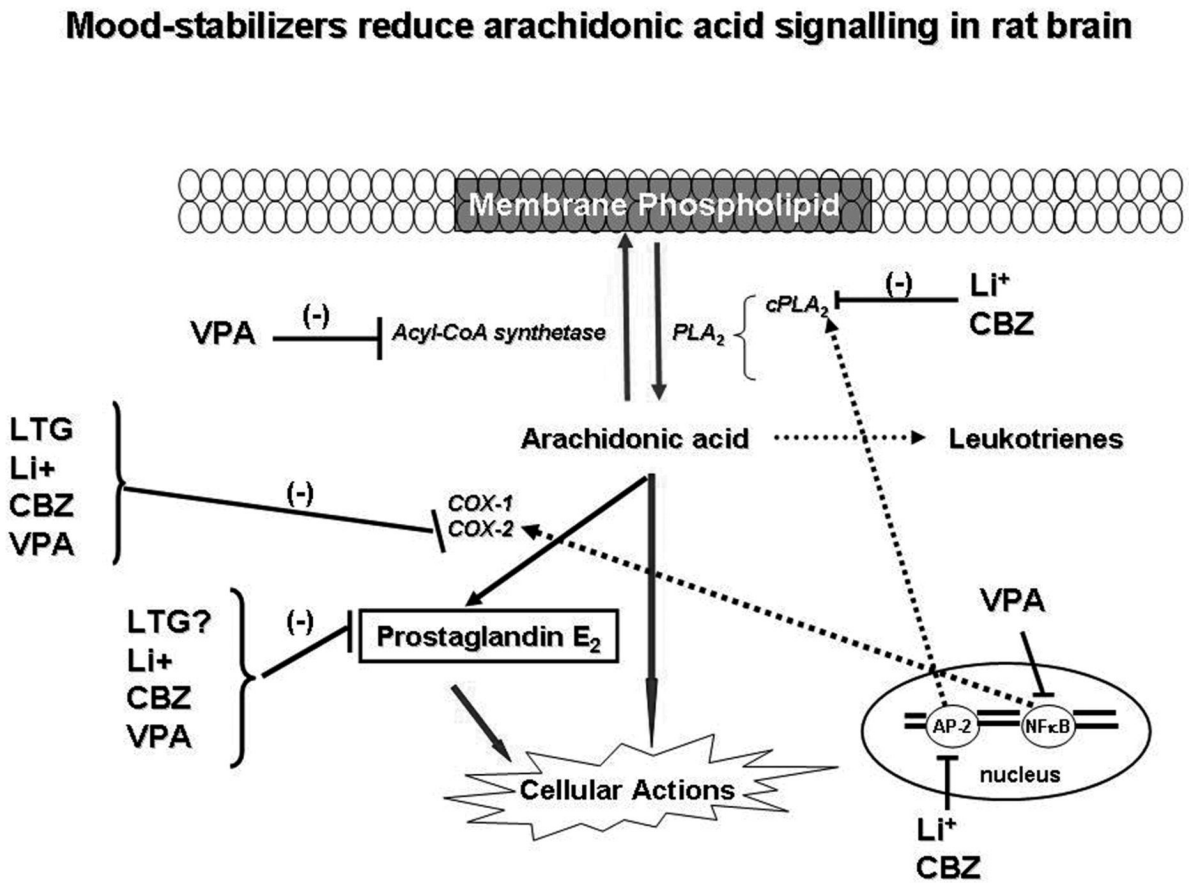

Figure-3.

Chronic mood stabilizer administration to rats reduces AA turnover in membrane phospholipids by either inhibiting acyl-CoA synthethase or transcription of $cPLA_2$. Conversion of AA into eicosanoids is reduced by reduced cyclooxygenase-2 activity.