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BIPOLAR DISORDER AND MECHANISMS OF ACTION OF MOOD STABILIZERS

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Abstract

Bipolar disorder (BD) is a major medical and social burden, whose cause, pathophysiology and treatment are not agreed on. It is characterized by recurrent periods of mania and depression (Bipolar I) or of hypomania and depression (Bipolar II). Its inheritance is polygenic, with evidence of a neurotransmission imbalance and disease progression. Patients often take multiple agents concurrently, with incomplete therapeutic success, particularly with regard to depression. Suicide is common. Of the hypotheses regarding the action of mood stabilizers in BD, the "arachidonic acid (AA) cascade" hypothesis is presented in detail in this review. It is based on evidence that chronic administration of lithium, carbamazepine, sodium valproate, or lamotrigine to rats downregulated AA turnover in brain phospholipids, formation of prostaglandin E_2, and/or expression of AA-cascade enzymes, including cytosolic phospholipase A_2, cyclooxygenase-2 and/or acyl-CoA synthetase. The changes were selective for AA, since brain docosahexaenoic or palmitic acid metabolism, when measured, was unaffected, and topiramate, ineffective in BD, did not modify the rat brain AA cascade. Downregulation of the cascade by the mood stabilizers corresponded to inhibition of AA neurotransmission *via* dopaminergic D_2-like and glutamatergic NMDA receptors. Unlike the mood stabilizers, antidepressants that increase switching of bipolar depression to mania upregulated the rat brain AA cascade. These observations suggest that the brain AA cascade is a common target of mood stabilizers, and that bipolar symptoms, particularly mania, are associated with an upregulated cascade and excess AA signaling *via* D_2-like and NMDA receptors. This review presents ways to test these suggestions.

Keywords

bipolar disorder; brain; lithium; valproic; carbamazepine; lamotrigine; arachidonic acid; phospholipase A_2; mood stabilizer; antidepressant; antipsychotic; mania; depression; rat; kinetics

2. Introduction

2.1. General background

Bipolar disorder (BD) is a major medical, social and economic burden worldwide, and its treatment represents a critical as yet unfulfilled challenge for psychiatry. The estimated lifetime cost of BD in the United States ranges from $11,720 for patients with a single manic episode, to $624,785 for patients with nonresponsive/chronic episodes (Begley et al., 2001). Symptoms

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appear on average at 22 years of age (Goodwin and Jamison, 2007), but the disease often is not diagnosed until 10 years later, with treatment delayed for an additional 10 years (Ghaemi, 2001). Even with intensive treatment in academic centers, BD therapy is inadequate and patients remain symptomatic for half of the year on average (Post et al., 1996).

BD is characterized by recurrent changes in mood. Bipolar I consists of cycles of mania and depression, Bipolar II of cycles of hypomania and depression. With rapid cycling (four or more episodes of depression or mania/hypomania or mixed episodes within a year), the disease has a poorer prognosis (Belmaker, 2004; DSM-IV, 1994). In Bipolar I, which afflicts 1.2 to 1.5% of the adult US population (Narrow et al., 2002), depression is 3-times more common than mania (Judd et al., 2002).

BD patients frequently have multiple medical illnesses in addition to their profound mood disturbances (Evans et al., 2005). Smoking and substance abuse are common (Begley et al., 2001). Obesity and diabetes often are caused by therapy. Sleep apnea and obsessive compulsive disorder can confound the presentation. The suicide rate is 5-17 fold higher than in the general population, attaining a lifetime risk of 10% to 20% (Bostwick and Pankratz, 2000).

There is no agreed upon neuropathology or pathophysiology of BD, and a generally accepted behavioral animal model for the disease does not exist (Cryan and Slattery, 2007; Kato et al., 2007). Some consider BD and unipolar major depressive disorder as part of an overlapping spectrum (Judd and Akiskal, 2003). However, in this review they will be treated as separate entities. BD and unipolar depression differ in their responsiveness to antidepressants (Ghaemi et al., 2004; Sachs et al., 2000), their clinical history including the presence of manic or hypomanic episodes in BD, clinical characteristics of depression (Benazzi, 2007), and family history. BD has a heritability of 86-90%, while major depression has a heritability of 48-75% (McGuffin et al., 2003). Over an 11-year follow-up period, however, 9% of unipolar depressed patients were diagnosed later as Bipolar II and 4% as Bipolar 1 because of the later appearance of hypomanic or manic episodes (Akiskal et al., 1995).

2.2. Heritability and genetics

More than two-thirds of BD probands have at least one close affected relative or a relative with unipolar major depression. Concordance rates in monozygotic and dizygotic twins are 40% and < 10%, respectively (Cardno et al., 1999; Kieseppa et al., 2004). Familial factors can determine responsiveness to lithium, the drug of choice for the disease (Alda, 1999; Grof et al., 2002).

A recent genome-wide association study with replication, involving 550,000 single nucleotide polymorphisms, implicated 88 different risk alleles in BD (Baum et al., 2008) (Figure 1), consistent with a polygenic threshold inheritance (Falconer, 1967). A combination of more than 15 of any of these alleles significantly increased the risk for BD above the risk in the general population, whereas a combination of any 19 increased the risk 3.8-fold. Multiple risk alleles also were identified in other whole genome scans (Schumacher et al., 2005; Sklar et al., 2008; Wellcome Trust, 2007; Wigg et al., 2008; Willour et al., 2003). Comparisons showed, however, that the studies had poor replication of positive findings, typical of measurements having multiple poor sensitivity items and suggesting additional artifacts (Crow, 2007; Sklar et al., 2008). This limitation of this “bottom-up” approach makes it difficult to identify dysfunctional brain metabolic cascades characteristic of BD.

Gene linkage and candidate gene association studies also have identified risk alleles for BD, but such studies compared to whole genome scans are considered underpowered and capable of revealing only part of the genetic disturbance (Baum et al., 2008). Many identified alleles are related to neurotransmission (Kato, 2007). They include the serotonergic (5-

hydroxytryptamine, 5-HT) 5-HT_{2A} receptor (Bonnier et al., 2002), the serotonin reuptake transporter (5-HTT) (Lasky-Su et al., 2005), the dopamine D_2 receptor (Massat et al., 2002), the dopamine reuptake transporter (DAT) (Greenwood et al., 2006; Horschitz et al., 2005), N-methyl-D-aspartate (NMDA) receptor subunits (Martucci et al., 2006), G protein receptor kinase-3 (GRK-3) (Barrett et al., 2003), the L-type voltage-dependent calcium channel alpha 1C subunit (CACNA1C) (Sklar et al., 2008), and the ©-aminobutyric acid receptor (Craddock et al., 2008).

3. Proposed mechanisms of bipolar disorder

3.1. Neurotransmission imbalance

Clinical responses of BD patients to different centrally acting drugs have suggested that BD symptoms arise from an imbalance of neurotransmission, consisting of excessive dopaminergic and glutamatergic transmission and reduced cholinergic muscarinic transmission (Bunney and Garland-Bunney, 1987; Bymaster and Felder, 2002; Janowsky and Overstreet, 1995; Post et al., 1980). Thus, drugs that inhibit dopaminergic transmission, such as olanzapine and haloperidol, have an antimanic action in the disease (Bhana and Perry, 2001; Bymaster and Felder, 2002). In contrast, drugs that stimulate dopamine synthesis (levodopa), bind to dopamine receptors (bromocriptine), or reduce dopamine reuptake (amphetamine), can precipitate mania (Fisher et al., 1991; Peet and Peters, 1995; Sultzer and Cummings, 1989). The cholinesterase inhibitor, physostigmine, and the cholinergic agonist, RS86, have mood-depressing effects in bipolar mania, as well as in schizophrenic and healthy subjects (Berger et al., 1989). Consistent with increased glutamate signaling in BD, memantine (1-amino-3,5-dimethyl-adamantane), an NMDA receptor antagonist approved for treating moderate to severe Alzheimer disease (FDA, 2009), was found beneficial in bipolar depression (Davis et al., 1978; Janowsky and Overstreet, 1995; Teng and Demetrio, 2006), and Riluzole (2-amino-6-trifluoromethoxybenzothiazole), an inhibitor of glutamate release, was reported effective in combination with lithium in an open label trial in BD patients (Zarate et al., 2005).

3.2. Disease progression

Symptom worsening, cognitive decline and progressive brain atrophy have been reported in BD patients, suggesting disease progression. Cycles of mania and depression are reported to increase in frequency with disease duration, and to have shorter inter-episode intervals (Goodwin and Jamison, 2007; Kessing, 1999; Post, 1990). One study found that cognitive deficits were present regardless of mood state, with executive functioning, episodic memory, and sustained concentration most consistently impaired (Osuji and Cullum, 2005). Structural magnetic resonance (MR) imaging demonstrated significant thinning of the cortical mantle, widening of cortical sulci and dilatation of the lateral cerebral ventricles in BD patients, with evidence of atrophy progression depending on symptom recurrence (Coyle et al., 2006; Lyoo et al., 2006; Strakowski et al., 2002). Whether atrophy is a trait marker is not certain, since BD relatives, unlike relatives of schizophrenic patients, did not demonstrate brain atrophy in one study (McDonald et al., 2006). Atrophy, cognitive decline and symptom worsening also have been noted in schizophrenic patients (DeLisi, 2008; Nesvag et al., 2008).

3.2.1. Neuroinflammation and excitotoxicity—Neuroinflammation and excitotoxicity may contribute to progressive atrophy and disease worsening in BD. High levels of C-reactive protein and of pro-inflammatory cytokines have been identified in plasma from BD patients, suggesting a generalized inflammatory process. Postmortem frontal cortex from BD patients demonstrated elevated protein and mRNA levels of a number of inflammatory markers, interleukin (IL)-1β, the IL-1 receptor, inducible nitric oxide synthase, glial fibrillary acidic protein, and myeloid differentiation primary response gene 88 (Rao et al., In press), as well as apoptotic markers (Kim et al., 2008). MR spectroscopy demonstrated an elevated brain

glutamate/glutamine ratio in adults with BD (Michael et al., 2003). Fewer NMDA receptors and reduced mRNA levels of NMDA receptor subunits NR1, NR2A and NR3A were reported on postmortem (Kim et al., 2007b), and densities of NMDA receptor-associated post-synaptic proteins, PSD-95 and SAP102, were reduced (Beneyto et al., 2007). These differences imply excess NMDA receptor function associated with excitotoxicity (Gascon et al., 2005).

4. Treatment of bipolar disorder

There is a clear need for improved treatment of BD. Currently approved agents used as monotherapy do not produce long-term responses in the majority of patients, and patient compliance is difficult to achieve (Post et al., 1996). For example, in a collated analysis of 2300 patients with acute mania who were given a placebo or any of 8 recognized “effective” agents as monotherapy, patients treated with only one agent experienced 45-60% positive symptom responses, compared with a 30% positive response to placebo (Bowden et al., 2005b). Without factoring in inadequate dosage and noncompliance in this study, only half of the already low fraction of drug responders may have had a “veritable” drug response.

BD patients often are treated with more than one agent in various doses and for various times, using combinations of mood stabilizers, antipsychotics, antidepressants and hypnotic benzodiazepines (Bowden, 2003). This approach is called “rational polypharmacy” (Post et al., 1996; Sachs, 1996), but often reduces to adding a drug for a specific symptom as it appears.

4.1. Mood stabilizers and atypical antipsychotics

FDA-approved agents (Figure 2) for treating Bipolar I include the “mood-stabilizers”[1] lithium (as carbonate or citrate salt, approved for mania and maintenance therapy), divalproex (Depakote®, containing sodium valproate and valproic acid (2-propylpentanoic acid) in 1:1 molar ratio; approved for mania), carbamazepine (Tegretol®, 5-carbamoyl-5H-dibenz[b,f] azepine, approved for mania), and lamotrigine (Lamictal®, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, approved as prophylactic treatment of Bipolar I to delay time to occurrence of the different mood episodes) (Bowden et al., 2005b;FDA, 2009;Fountoulakis et al., 2008;Ketter et al., 2005). Topiramate (Topomax®, 2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate), an anticonvulsant suggested from initial observations to be effective in BD, was later found ineffective in four double blind trials (Kushner et al., 2006); it is discussed below in comparative studies with approved mood stabilizers.

Outcome comparisons among FDA-approved mood stabilizers as monotherapy have been reported (Bowden, 2003; Fountoulakis et al., 2008). For example, patients with mania accompanied by two or more depressive symptoms had greater improvement with valproate than with lithium, whereas patients with mania alone had equivalent responses of the order of 30-40% (Bowden, 1995; Swann et al., 1997). Valproate or lithium in acute mania and in maintenance studies was more effective than carbamazepine, with which recurrence occurred 50% more often (Kleindienst and Greil, 2000; Lerer et al., 1987; Vasudev et al., 2000).

Atypical antipsychotic agents that are FDA-approved for acute mania in BD are olanzapine (Zyprexia®), aripiprazole (Abilify®), chlorpromazine (Clozaril®), risperidone (Risperdal®), quetiapine (Seroquel®), and ziprasidone (Geodon®) (Bowden et al., 2005b; FDA, 2009; Ketter

[1]This term was introduced into the psychiatric vocabulary some 20 years ago, based on observations that lithium offered antimanic as well as antidepressant action. It was extended to the anticonvulsants, valproic acid, carbamazepine and lamotrigine, yet the first two have little efficacy against depression and lamotrigine shows little efficacy against mania Sobo, S., 1999. Mood stabilizers and mood swings: In search of a definition. Psychiatric times. 16.. The term “mood stabilizer” has since been modified to identify medication that decreases vulnerability to subsequent episodes of mania or depression and does not exacerbate the current episode or maintenance phase of treatment. Sachs, G.S., 1996. Bipolar mood disorder: practical strategies for acute and maintenance phase treatment. J Clin Psychopharmacol. 16, 32S-47S.

et al., 2005). In addition, quetiapine is approved for bipolar depression and maintenance therapy adjunctive to lithium or divalproex, and aripiprazole and olanzapine are approved for maintenance monotherapy in Bipolar I.

The atypical antipsychotics have a high affinity as antagonists for dopamine D_2 receptors, and many also have high affinities as antagonists for serotonergic 5-HT_2 receptors. Some also have affinities for adrenergic, histamine H_1 and muscarinic M_1 receptors (Kapur and Remington, 2001). No one drug has a clear advantage over the others for treating mania, but as a group they are less likely than conventional antipsychotics to cause troubling extrapyramidal symptoms (Bowden et al., 2005b; Ketter et al., 2005; Simpson, 2005; Yatham, 2005). The atypical antipsychotics are especially useful for rapidly dampening hyperactive motoric symptoms in bipolar mania, before lithium's effects are expressed (Bhana and Perry, 2001; Lieberman and Goodwin, 2004; Post and Calabrese, 2004).

4.2. Antidepressants and switching to mania

The treatment of bipolar mania with mood stabilizers has achieved some success, but treating the three-times more common bipolar depression remains problematic (Fountoulakis et al., 2005). Lamotrigine is of some help, as is fluoxetine (a selective serotonin reuptake inhibitor, SSRI) with olanzapine added, and quetiapine recently was approved as monotherapy (**Section 4.1**). Paroxetine and bupropion were not found useful as adjunctive therapy with mood stabilizers in bipolar depression (Bowden et al., 2005b; Sachs et al., 2007).

Some antidepressants increase the likelihood of “switching” to mania in depressed bipolar patients, when used as monotherapy or with mood stabilizers (Calabrese et al., 1999a; Post et al., 2006). Elevated switch rates are reported with broad spectrum tricyclic antidepressants that inhibit reuptake of norepinephrine and serotonin (Kleindienst and Greil, 2000), SSRIs and monoamine oxidase inhibitors, but not with bupropion, a norepinephrine and dopamine reuptake inhibitor and nicotinic antagonist (Leverich et al., 2006; Post et al., 2006). Switch rates are reduced if an antimanic mood stabilizer is given with the antidepressant (31.6% versus 84.2%) (Ghaemi et al., 2004).

4.3. Treatment side effects

4.3.1. Lithium in healthy volunteers—When administered to healthy volunteers, lithium caused lethargy, dysphoria, a loss of interest in interacting with others, mental confusion (Judd et al., 1977a), slowed performance on cognitive and motor tests (Judd et al., 1977b), and altered circadian rhythm, the most common effect being a delay in the phase of measured rhythms relative to an entraining light-dark cycle (Klemfuss, 1992). Lthium increased auditory and visual evoked responses in healthy volunteers (Hegerl et al., 1990; Ulrich et al., 1990).

4.3.2. Boxed warnings—Lithium, divalproex and carbamazepine have boxed warnings because of safety concerns. Lithium can be nephrotoxic and neurotoxic, whereas divalproex can produce hepatic and teratogenic effects and contribute to pancreatitis. Carbamazepine may produce adverse hematological effects. As a class, atypical antipsychotics have a boxed warning for sudden death in elderly patients. They increase risk for hyperglycemia, diabetes, and cardiovascular dysfunction, and often produce severe weight gain and sedation (Bowden et al., 2005b; Ketter et al., 2005; Simpson, 2005).

4.3.3. Potential neurotoxicity—In animal and cell models, mood stabilizers and antipsychotic agents used in BD were shown to be neuroprotective through a number of processes, including the reduction of apoptosis and stimulation of brain neurotrophic and growth factors (**Section 8.)** (Chang et al., 2009; Chen et al., 1999; Chuang, 2005; Gould et al., 2004b; Lieberman et al., 2008; Lu et al., 2004). Thus, neuroprotection may underlie some of

their action, especially in view of evidence for apoptosis, neuroinflammation and excitotoxicity in the postmortem BD brain (Kim et al., 2008; Rao et al., In press).

On the other hand, as long-term therapy, mood stabilizers as well as antipsychotics may have neurotoxic effects. For example, chronic lithium administration caused neuronal apoptosis in rat brain (Gomez-Sintes and Lucas, 2008), and chronic exposure to atypical antipsychotics produced oxidative brain damage (Martins et al., 2008; Terry et al., 2003). Twelve to 27 months of exposure of macaque monkeys to haloperidol or olanzapine at therapeutically equivalent plasma concentrations caused widespread brain shrinkage and reduced astrocyte numbers in parietal gray matter (Dorph-Petersen et al., 2005; Konopaske et al., 2008).

5. The brain arachidonic acid cascade

> "How can we argue that we are treating [...bipolar disorder...] at a fundamental, etiological level of the illness when we don't know what the chemical problem is, when our best guesses about how various mood stabilizers work are that they work differently from each other, and when we don't know how these proposed mechanisms might or might not be related?"

S. Sobo (Sobo, 1999)

We have yet to convert the disparate data about BD and the agents approved to treat it into a coherent understanding of disease mechanisms and drug targets. The limited efficacy of each of the approved mood stabilizers as monotherapy in bipolar mania (Bowden et al., 2005a; Ketter et al., 2001), the limited treatment of bipolar depression (Sachs et al., 2007), the many untoward side effects of approved agents, and the high morbidity, suicide rate and cost to society of BD, render understanding the disease and designing more appropriate treatments for it of the highest priority.

Many hypotheses have been proposed for the mechanisms of action of agents approved for treating BD, particularly the mood stabilizers. One, the "arachidonic acid (AA, 20:4n-6) cascade hypothesis," asserts that these agents commonly alleviate BD symptoms, particularly bipolar mania, by downregulating brain AA metabolism (Chang et al., 1996; Chang et al., 1999; Rao et al., 2008; Rapoport and Bosetti, 2002). This hypothesis is elaborated in this review. Other hypotheses are considered briefly in **Section 12.** below.

5.1. Roles of arachidonic acid in brain

AA is an n-6 (omega-6) polyunsaturated fatty acid (PUFA) that is esterified predominantly in the stereospecifically numbered (*sn*)-2 position of brain membrane phospholipids, as is the n-3 PUFA, docosahexaenoic acid (DHA, 22:6n-3). Both PUFAs are derived from the diet, directly or by hepatic elongation of their nutritionally essential precursors, linoleic acid (18:2n-6) or α-linolenic acid (18:3n-3), respectively, since vertebrates cannot synthesize them or their precursors *de novo* from 2-carbon fragments, and the brain's elongation capacity is inconsequential (Demar et al., 2005; Holman, 1986; Igarashi et al., 2007).

When released by a phospholipase A_2 (PLA_2) from a phospholipid, AA and its eicosanoid metabolites have multiple biological effects, many of which are modulated by released DHA and its metabolites (Bazan, 2007; Contreras and Rapoport, 2002; Farooqui et al., 2007; Fitzpatrick and Soberman, 2001; Serhan, 2006; Shimizu and Wolfe, 1990). AA and its metabolites can influence multiple processes within brain (Piomelli, 1995), including neurotransmission (Axelrod, 1990; DeGeorge et al., 1991; Rapoport, 2003), membrane excitability (Xiao and Li, 1999), long term potentiation (McGahon et al., 1997), gene transcription (Sellmayer et al., 1997), membrane fluidity (Bazan, 2005), neurite outgrowth (Ikemoto et al., 1997), cerebral blood flow (Stefanovic et al., 2006), sleep, memory and

behavior (Chen and Bazan, 2005; Fitzpatrick and Soberman, 2001; Huang et al., 2007). Many AA metabolites are considered to be pro-inflammatory, whereas DHA and its metabolites are considered anti-inflammatory (Bazan, 2007; Farooqui et al., 2007; Serhan, 2006). AA is released from synaptic membrane phospholipids during normal neurotransmission (Jones et al., 1996), whereas higher quantities are released, together with other fatty acids, during pathological processes such as neuroinflammation, excitotoxicity, ischemia, and convulsions. These high quantities of AA and of concurrently formed lyosphopholipids can cause neuronal damage by multiple mechanisms (Bazan et al., 1981; Chang et al., 2009; Contreras and Rapoport, 2002; Farooqui et al., 2007; Rabin et al., 1998; Rao et al., 2007c; Rao et al., 2007d; Rosenberger et al., 2004).

5.2. Receptors coupled to phospholipase A_2 enzymes

Three major PLA_2 enzyme classes in the mammalian brain mediate receptor-initiated release of AA or DHA as second messengers (Burke and Dennis, 2009): (1) AA-selective cytosolic $cPLA_2$ (85 kDa, Type IVA), which requires < 1 mM Ca^{2+} and phosphatidylinositol-4,5-biphosphate for translocation to the membrane plus phosphorylation for its activation (Clark et al., 1991); (2) secretory $sPLA_2$ (14 kDa, Type IIA), which requires a much higher Ca^{2+} concentration (20 mM) for activation; and (3) DHA-selective "Ca^{2+}-independent" $iPLA_2$ (88 kDa, Type VIA), which is considered "Ca^{2+}-independent" from *in vitro* studies (Strokin et al., 2003), but can be activated by Ca^{2+} derived from intracellular stores such as the endoplasmic reticulum (Nowatzke et al., 1998; Rosa and Rapoport, 2009). $cPLA_2$, which co-localizes with and is coupled to cyclooxygenase (COX)-2 at post-synaptic sites, co-evolved with COX-2. $iPLA_2$ also is found at post-synaptic sites, as well as in astrocytes (Kaufmann et al., 1996; Ong et al., 1999; Ong et al., 2005; Sun et al., 2005; Tay et al., 1995). $sPLA_2$ participates in neurotransmitter release from axonal terminals (Matsuzawa et al., 1996).

Table 1 identifies receptors that are coupled to activation of $cPLA_2$ and/or $sPLA_2$, so as to release AA from membrane phospholipids. Coupling occurs by complex mechanisms as yet incompletely understood, and can involve a G-protein, entry of extracellular Ca^{2+} into the cell (to activate $cPLA_2$), or release of Ca^{2+} from intracellular stores (Balsinde et al., 1998;Clark et al., 1991;Ertley et al., 2007;Nowatzke et al., 1998;Rosa and Rapoport, 2009;Takano et al., 2000). Post-synaptic neuroreceptors mediate AA release during neurotransmission or, with excess glutamate availability, during excitotoxicity, whereas astrocytic cytokine receptors mediate AA release during neuroinflammation (Axelrod, 1990;Basselin et al., 2006a;DeGeorge et al., 1991;Rao et al., 2007e;Rapoport, 2003;Rosenberger et al., 2004).

5.3. Quantifying brain fatty acid turnover

Figure 3 illustrates an outline of the brain AA cascade, when initiated by neuroreceptor-mediated activation of PLA_2 at the post-synaptic membrane (Fitzpatrick and Soberman, 2001;Jones et al., 1996;Rapoport, 2001;Robinson et al., 1992;Shimizu and Wolfe, 1990). Comparable DHA and palmitic acid cascades have been described (Rapoport et al., 2007;Robinson et al., 1992;Sun and MacQuarrie, 1989). In unanesthetized rats, it has been shown that after AA is released from synaptic membrane phospholipid, a small fraction (about 4%) is rapidly metabolized to n-6 eicosanoids by COX, lipoxygenase (LOX) or cytochrome P450 epoxygenase enzymes. The remainder is recycled into membrane phospholipid *via* the brain arachidonoyl-CoA pool, with the help of acyl-CoA synthetase and acyltransferase enzymes and the consumption of 2 ATPs, or is lost by β-oxidation and other pathways. Since AA cannot be synthesized *de novo* in vertebrates, and its circulating precursor, linoleic acid, is almost entirely oxidized after entering the brain, the AA lost by metabolism is replaced by unesterified plasma AA, at a rate J_{in} (Eq. 2, Footnote [2]) (DeMar et al., 2006a;Rapoport et al., 2001).

The kinetics of the brain AA, DHA and palmitic acid cascades have been quantified in unanesthetized rodents by infusing the respective radiolabel intravenously for 5 min, so as to rapidly produce a constant plasma specific activity. At 5 min, the brain is exposed to high energy microwave radiation to stop enzyme activity, and then is subjected to chemical and radiotracer analyses. The resultant data are used to calculate coefficients of incorporation k^*, rates of incorporation J_{in}, half-lives and turnover rates of the *unlabeled* fatty acid in whole brain and in individual brain phospholipids, by operational equations obtained from a kinetic model (Robinson et al., 1992).[2] Regional values of k^* and J_{in} also can be imaged by freezing rather than microwaving the brain, sectioning it in a cryostat, and subjecting the sections to quantitative autoradiography to determine regional radioactivity (Eqs. 1 and 2 in Footnote [2]).

6. Mood stabilizers downregulate global brain arachidonic acid cascade

6.1. Global turnover rates

To compare central drug effects in rodents and humans, appropriate dose regiments should be chosen so as to produce clinically relevant plasma concentrations, since peripheral pharmacokinetics often differ between species. Table 2 summarizes reported clinical plasma therapeutic concentrations of the four FDA-approved mood stabilizers, and experimental plasma concentrations that have been used in rodent studies.

Turnover rates of AA, DHA and palmitic acid in brain phospholipids, as well as values of λ (Footnote [2]) were measured in unanesthetized rats that had been fed a lithium-free diet for 6 weeks, or a LiCl-containing diet that produced a therapeutically relevant plasma lithium concentration (Table 2). As shown in Table 3, each of the three fatty acids had high turnover rates in rats on the control diet, consistent with their participation in active signaling processes that consume ATP (Purdon and Rapoport, 1998). Chronic lithium reduced AA turnover in brain phospholipids by about 80%, without significantly affecting DHA or palmitate turnover (Chang et al., 1996;Chang et al., 1999;Rapoport and Bosetti, 2002). In later studies, chronic sodium valproate and carbamazepine also were shown to reduce AA turnover without altering DHA turnover. In contrast, neither lamotrigine nor topiramate affected turnover of either fatty acid (Table 4), although lamotrigine did reduce AA incorporation coefficients k^* in rat brain (Table 5 below) (Lee et al., 2008a).

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[2]A fatty acid incorporation coefficient k^* is calculated as radioactivity in brain phospholipid at time of death T, $c^*_{brain}(T)$, divided by integrated plasma radioactivity c^*_{plasma} to T, where t is time after beginning labeled fatty acid infusion,

$$k^* = \frac{c^*_{brain}(T)}{\int_0^T c^*_{plasma}\, dt} \quad (1)$$

The rate of incorporation of the *unlabeled* fatty acid from plasma into brain phospholipid equals,

$$J_{in} = k^* c_{plasma} \quad (2)$$

and the turnover rate equals

$$\text{Turnover} = J_{in}/c_{brain}\lambda \quad (3)$$

where λis the steady-state ratio of brain fatty acid-CoA specific activity to plasma fatty acid specific activity. λrepresents the flux of the fatty acid released from phospholipid into brain fatty acid-CoA, compared with the flux of plasma derived-AA (Figure 3).

6.2. Effects on cascade enzymes

6.2.1. Phospholipases A_2 and Acyl-CoA synthetase—Consistent with their reducing AA but not DHA turnover in rat brain phospholipids, chronic lithium and carbamazepine downregulated brain mRNA, protein and activity levels of AA-selective $cPLA_2$, without altering expression of $sPLA_2$ or DHA-selective $iPLA_2$ (Table 4). Reduced expression of $cPLA_2$ was associated with a reduced brain AA-CoA concentration, the sequential product of AA hydrolysis from phospholipid by the enzyme (Figure 3). Lithium's downregulation of $cPLA_2$ was accompanied by reduced binding activity of subunits of a $cPLA_2$ transcription factor, activator protein (AP)-2, which was attributed to decreased brain protein kinase (PK) Cα, PKCε and AA-dependent PKC activities (Rao et al., 2005). Chronic carbamazepine decreased AP-2 DNA-binding and cAMP-dependent PKA activity, as well as AP-2 phosphorylation (Rao et al., 2007b). Chronic sodium valproate did not alter expression of any of the three PLA_2 enzymes or of AP-2 (Bosetti et al., 2003;Chang et al., 2001;Rao et al., 2005), but non-competitively inhibited a microsomal acyl-CoA synthetase that is selective for AA conversion to arachidonoyl-CoA (Figure 3) (Bazinet et al., 2006b). Chronic lamotrigine and topiramate did not change brain expression of $cPLA_2$, $sPLA_2$ or $iPLA_2$ (Ghelardoni et al., 2005;Lee et al., 2008a).

6.2.2. Downstream oxidative enzymes—Once released from brain phospholipid, unesterified AA can be oxidized to bioactive eicosanoids (Figure 3) (Fitzpatrick and Soberman, 2001). Prostaglandin (PG) G_2 is formed in first step in this oxidation, and then is converted to PGH_2 by COX enzymes,. PGD_2, PGE_2, $PGF_{2\alpha}$ and PGI_2 may be produced from PGH_2 *via* PG synthases, thromboxanes (TX) (e.g. TXB_2) *via* TX synthases. In normal brain, PGE_2 is produced preferentially *via* COX-2, TXB_2 *via* COX-1 (Basselin et al., 2007c;Bosetti et al., 2004). Epoxyeicosatrienoic acids and hydroxyeicosatetraenoic acids also are formed *via* cytochrome P450 epoxygenase, whereas hydroxyperoxyeicosatetraenoic acids, leading to leukotrienes, hydroxyeicosatetraenoic acids, lipoxins and hepoxilins are produced *via* lipoxygenases (LOXs) and other enzymes (Bosetti, 2007).

The mood stabilizers approved for BD target many downstream AA metabolic processes. In unanesthetized rats, chronic lithium significantly reduced brain protein and activity of COX-2, as well as PGE_2 concentration (Bosetti et al., 2002a), without changing expression of COX-1, 5-LOX, cytochrome P450 epoxygenase or microsomal PGE synthase-1 (mPGES-1) (Weerasinghe et al., 2004) (Table 4). Chronic lithium also elevated brain 17-OH-DHA, a precursor of anti-inflammatory resolvins and neuroprotectins derived from DHA *via* 12- and 15-LOX, in a rat model of neuroinflammation (Basselin et al., Unpublished observations; Serhan, 2006). Chronic carbamazepine reduced COX activity without changing the COX-1 or COX-2 protein level, and reduced brain concentrations of PGE_2 and TXB_2. Protein levels of 5-LOX and cytochrome P450 epoxygenase, and the concentration of the 5-LOX product, leukotriene B_4 (LTB_4), also were unaltered (Basselin et al., 2007a; Ghelardoni et al., 2004). Chronic sodium valproate reduced brain mRNA, protein and activity levels of both COX-1 and COX-2, and brain concentrations of TXB_2 and PGE_2, their respective preferred metabolites (Basselin et al., 2008a; Bosetti et al., 2003). Protein levels of 5-LOX and of cytochrome P450 epoxygenase and the concentration of LTB_4 were unchanged. DNA binding activity of nuclear factor (NF)-κB, a COX-2 transcription factor, was decreased in relation to a decreased level of its p50 subunit (Rao et al., 2007a). Chronic lamotrigine decreased COX-2 protein and mRNA (Lee et al., 2008a), consistent with a reduction in k* for AA (Table 5 below) (Lee et al., 2007a), whereas chronic topiramate did not significantly change any measured marker (Ghelardoni et al., 2004; Ghelardoni et al., 2005).

7. Mood stabilizers may correct neurotransmission imbalance involving arachidonic acid

7.1. Neuroreceptor specificity

The fundamental assumption of neuropsychopharmacology is that cognition and behavior depend on neurotransmission involving different neurotransmitters, neurotransmitter transporters, neuroreceptors and second messengers (Cooper et al., 2003). Responses of BD patients to drugs other than mood stabilizers that act at specific neuroreceptors have suggested that bipolar symptoms arise from excessive dopaminergic and glutamatergic transmission, reduced cholinergic transmission, and disturbed serotonergic transmission (**Section 3.1.**). If this proposed neurotransmission imbalance involves AA, then mood stabilizers might be effective in BD by correcting the imbalance. This possibility was tested by using quantitative autoradiography to image regional brain AA signaling in unanesthetized rats that had been treated chronically with a clinically relevant dose of mood stabilizer and then acutely administered an agonist to relevant $cPLA_2$-coupled neuroreceptors (Table 1), including cholinergic muscarinic $M_{1,3,5}$, serotonergic 5-$HT_{2A/2C}$, dopaminergic D_2-like (D_2, D_3, D_4) and glutamatergic NMDA receptors.

Results of one such study are illustrated in Figure 5, which presents color-coded autoradiographs of coronal brain sections from rats that had been injected i.p. acutely with NMDA (50 mg/kg) or vehicle, after being fed a LiCl-containing or control diet for 6 weeks (Basselin et al., 2006a). NMDA widely increased AA incorporation coefficients k^* (Footnote [2], Eq. 1) in rats fed the control diet, but not in rats pretreated with the NMDA receptor antagonist, MK-801, or fed LiCl. MK-801 itself reduced k^* for AA by 30% on average.

Results from such imaging studies, summarized in Table 5, indicate that chronic mood stabilizers could correct the proposed neurotransmission imbalance of BD, if the imbalance involved AA as a second messenger. Chronic lithium, carbamazepine and valproate each blocked the k^* increments caused by acute NMDA (Basselin et al., 2006a;Basselin et al., 2007a;Basselin et al., 2008b), and chronic lithium and carbamazepine blocked k^* increments to the D_2-like receptor agonist, quinpirole (Basselin et al., 2005a;Basselin et al., 2008b). These actions on D_2-like and NMDA receptor signaling may be related to colocalization of the receptors in prefrontal cortex, striatum, and nucleus accumbens (Ikeda et al., 2003;Liu et al., 2006;Tarazi and Baldessarini, 1999;Tseng and O'Donnell, 2004). In addition, chronic lithium blocked responses to the 5-$HT_{2A/2C}$ receptor agonist (+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) in auditory and visual rat brain regions (Basselin et al., 2005b). Consistent with the imbalance hypothesis and with evidence that lithium reduces the convulsive threshold to cholinomimetics (Ormandy et al., 1991), chronic lithium augmented k^* responses to the nonspecific muscarinic agonist, arecoline (Basselin et al., 2003). When measured, the direction of the changes in brain PGE_2 and/or TXB_2 concentrations following an agonist in rats treated with mood stabilizers corresponded to the direction of the changes in k^* for AA.

Neither chronic carbamazepine nor valproate produced consistent changes in baseline (resting) k^* for AA. On the other hand, chronic lithium increased baseline k^* in rat auditory and visual cortical cortices, inferior and superior colliculi, and geniculate bodies (Basselin et al., 2003; Basselin et al., 2006b) (Table 5), as it did glucose metabolism in these areas (Basselin et al., 2006c). These effects may be related to lithium's ability to potentiate auditory and visual evoked responses in humans (Hegerl et al., 1990). Lithium's potentiation of $M_{1,3,5}$ receptor signaling and suppression of D_2-like receptor signaling involving AA in rat brain (Table 5) may explain the tremors and occasional extrapyramidal symptoms that it causes in patients (Ghadirian et al., 1996).

When measured by whole brain analysis rather than with quantitative autoradiography, chronic lamotrigine significantly decreased *k** for AA into brain phospholipids by about 15% (Lee et al., 2007a) (Table 5).

7.1.1. Reconciling neurotransmitter-specific effects with global brain effects—

Downregulation of the global brain AA cascade by the mood stabilizers (**Section 6.**) may largely represent downregulation of the $cPLA_2$ activation and AA turnover associated with glutamatergic (e.g. NMDA) receptor signaling, since most brain synapses are excitatory and glutamatergic (Attwell and Laughlin, 2001; Raichle and Gusnard, 2002). Consistent with this interpretation, the NMDA receptor antagonist MK-801 reduced global AA incorporation by 30% in unanesthetized rats (Figure 5), whereas acutely administered antagonists to $M_{1,3,5}$ receptors (atropine), D_2-like receptors (butaclamol, raclopride) or 5-$HT_{2A/2C}$ receptors (mianserin) did not markedly decrease baseline AA incorporation into rat brain (Bhattacharjee et al., 2008; DeGeorge et al., 1991; Hayakawa et al., 2001; Qu et al., 2003).

7.2. Targeting neuroreceptors and their coupling machinery

Suppression of the AA cascade by mood stabilizers may occur at multiple levels: neuroreceptors, their coupling to $cPLA_2$, AA cascade enzyme activities, or gene transcription (Figure 4). Thus, in addition to reducing expression of $cPLA_2$ and activity of COX-2, mood stabilizers can directly modify NMDA receptor mechanisms. Lithium reduced NMDA receptor-mediated Ca^{2+} influx into cells by inhibiting NR2 phosphorylation (Hashimoto et al., 2003). Sodium valproate inhibited PKA and PKC, which phosphorylate the NMDA receptor (Du et al., 2004). It also reduced rat brain expression of NMDA receptor-interacting proteins, postsynaptic density protein PSD-95 and type II Ca^{2+}/calmodulin-dependent protein kinase beta subunit (Bosetti et al., 2005), and inhibited histone deacetylase, which can deacetylate histones on the gene for the NMDA receptor transcription factor, specificity protein-1 (Sp1) (Bai and Kusiak, 1995;Phiel et al., 2001). Sodium valproate blocked induction of Fos and binding activity of AP-1 DNA, which modulates transcription of NMDA receptor subunit, NR2B (Qiang and Ticku, 2005), and it altered NMDA receptor levels in hippocampal neurons (Caldeira et al., 2007).

With regard to G-protein coupled receptors, chronic lithium reduced brain levels of the $G\alpha i_1$ and $G\alpha i_2$ subunits of the inhibitory Gα protein that couples D_2-like receptors to $cPLA_2$ (Sidhu and Niznik, 2000), and guanosine-5'-triphosphate (GTP) binding to these subunits (Wang and Friedman, 1999). Chronic carbamazepine reduced D_2 receptor density, D_2-like receptor coupled $G\alpha_{o/i}$, and D_2-like receptor phosphorylation (Beutler et al., 2005; Montezinho et al., 2006). Chronic lithium and carbamazepine but not valproate increased levels in rat brain of GRK3, which is involved in homologous desensitization of agonist-activated G-protein coupled receptors (Ertley et al., 2007). GRK3 but not GRK4 is reduced in the postmortem BD brain (Rao et al., 2009).

8. Arachidonic acid cascade and neuroprotection

Mood stabilizers have been shown to be neuroprotective in animal and cellular models of neurodegeneration, excitotoxicity, stroke-ischemia-hypoxia, stress-induced neuronal loss, neuroinflammation, and immunological damage (**Section 4.3.3.**) (Chang et al., 2009; Chen et al., 1999; Chuang, 2004; Lee et al., 2000). Part of this neuroprotection might be due to suppression of an upregulated brain AA cascade, which can cause cell damage and behavioral changes (Basselin et al., 2007a; Basselin et al., 2007b; Bazan et al., 1995; Bosetti, 2007), or stimulation of formation of anti-inflammatory DHA metabolites (Basselin et al., Unpublished observations) (**Section 6.2.2.**). Chronic lithium attenuated upregulated AA metabolism in a rat model of neuroinflammation, as did chronic lithium, valproate and carbamazepine in a model of acute NMDA-induced excitotoxicity (Table 5) (Basselin et al., 2006a; Basselin et al.,

2007b). The ability of each of the four approved mood stabilizers to increase rat brain expression of brain derived neurotrophic factor (BDNF) and of the anti-apoptotic factor, B-cell lymphoma-2 (Bcl-2), which are reduced in the BD brain (Dean et al., 2006), also may contribute to their neuroprotective action (Chang et al., 2009; Garrido et al., 2003; Rao et al., 2007d). These effects may be mediated by AA (Chang et al., 2009; Rao et al., 2007d).

9. Antidepressants, switching and the arachidonic acid cascade

Certain antidepressants, when given to BD depressed patients, increase the tendency to "switch" to mania (**Section 4.1.**). This limits therapy for bipolar depression, perhaps unduly in view of the controversy concerning "switching." Increased switch rates are reported for imipramine and fluoxetine, but not for bupropion (Calabrese et al., 1999b; Leverich et al., 2006; Post et al., 2006).

These differences in switch rates correlate with the antidepressant effects on the rat brain AA cascade. Thus, chronic fluoxetine and imipramine, which increase switching, when given to rats to produce a therapeutically relevant plasma concentration (Table 6), increased AA turnover in brain phospholipids; brain $cPLA_2$ expression (activity, protein, mRNA, and phosphorylation), and expression of the $cPLA_2$ transcription factor subunit, AP-2α (Lee et al., 2007b;Lee et al., 2008;Rao et al., 2006). Chronic bupropion, which doesn't increase switching, did not alter any of these markers (Table 7).

10. Animal models with an upregulated AA cascade

There is no generally accepted behavioral animal model for BD (Cryan and Slattery, 2007; Kato et al., 2007). Nevertheless, as FDA-approved mood stabilizers have shown to downregulate parameters of the brain AA cascade in normal rats, animal models having a pathologically upregulated brain AA cascade may help in drug discovery and in considering mechanisms relevant to BD. Table 8 characterizes five such models.

In one rat model, chronic administration of a subconvulsive dose (25 mg/kg i.p. daily for 21 days) of NMDA increased brain markers of excitotoxicity and neuroinflammation (Chang et al., 2008; Rao et al., 2007e), selectively upregulated AA turnover in brain phospholipid, and elevated expression of $cPLA_2$ and AP-2. In a second rat model, 6 days of intracerebroventricular infusion of low dose lipopolysaccharide (0.5-1.0 ng/h) (Basselin et al., 2007b; Lee et al., 2004; Rosenberger et al., 2004) increased AA turnover and $cPLA_2$ and $sPLA_2$ activities in brain, whereas behavior was disturbed when measured after 1 month of infusion (Richardson et al., 2005). The brain AA cascade also was upregulated by feeding rats an n-3 PUFA deficient diet for 15 weeks. This dietary regimen decreased brain DHA by 30% and increased brain docosapentaenoic acid (DPA, 22:5n-6), an AA elongation product, by an equivalent amount. AA turnover was unaffected, whereas DPA turnover was increased (Contreras et al., 2001; Igarashi, 2009; Rao et al., 2007c). BDNF, cAMP response element binding protein (CREB) transcription factor activity, phosphorylated CREB (important in learning and memory) and p38 mitogen-activated protein kinase were reduced in brain (Rao et al., 2007d), and the rats showed aggression, depression and increased locomotion on behavioral tests (DeMar et al., 2006b).

Two genetic mouse models also show upregulated AA incorporation into brain phospholipid. The *COX-2* knockout mouse, which lacks the *COX-2* gene from birth, also has increased $cPLA_2$, $sPLA_2$, and COX-1 expression in brain. The *5-HTT* knockout mouse demonstrates BD-like behavioral disturbances (Murphy and Lesch, 2008) and increased brain $cPLA_2$ activity (Basselin et al., 2009). Regional AA incorporation into brain is elevated by 20-70% in both heterozygous and homozygous knockouts (Figure 7), due to tonic activation of $cPLA_2$-coupled $5\text{-}HT_{2A/2C}$ receptors by elevated synaptic 5-HT concentrations. The $5\text{-}HTT^{+/-}$ mouse is

considered a model for humans having a short (S) compared with long (L) allele of the 5-*HTT* promoter, who are at increased risk for BD and other psychiatric diseases (Murphy and Lesch, 2008).

11. The arachidonic acid cascade in bipolar disorder patients

A small case-control trial reported increased serum PLA_2 activity in BD patients (Noponen et al., 1993). Genetic mapping identified involvement of the $sPLA_2$ gene (Jacobsen et al., 1999), but this was not replicated (Meira-Lima et al., 2003), $cPLA_2$ was not implicated in other analyses (Dikeos et al., 2006; Pae et al., 2004). One study reported decreased cytosolic PGES in postmortem frontal and temporal cortices from BD patients, but not in patients medicated prior to death (Maida et al., 2006).

The postmortem BD compared with control frontal cortex is reported to have increased mRNA and protein levels of $cPLA_2$, $sPLA_2$ and COX-2 (but not of $iPLA_2$), and increased AP-2 and NF-κB levels (Rao et al., 2007b), changes opposite in direction to those produced by mood stabilizers in the rat brain (Table 4). These changes are accompanied by elevated expression of markers of apoptosis, neuroinflammation and excitotoxicity (Kim et al., 2007a; Kim et al., 2008; Rao et al., In press), and may be caused by or related to these pathological processes (Chang et al., 2008; Dinarello, 1988; Rao et al., 2007e; Rosenberger et al., 2004) (**Section 3.2**).

Dietary n-3 PUFA deprivation in rats can upregulate brain AA metabolic markers and disturb AA - DHA interactions (Table 8) (Contreras and Rapoport, 2002;Igarashi, 2009;Rao et al., 2007c). Thus, reports that subjects on a diet low in DHA-containing marine products had an increased prevalence of BD (Noaghiul and Hibbeln, 2003), that dietary n-3 PUFA supplementation ameliorated BD symptoms (Frangou et al., 2006;Ross et al., 2007;Stoll et al., 1999), and that the DHA concentration in the postmortem BD brain was reduced by 30% (McNamara et al., 2008;Schwarz et al., 2008), would be consistent with an association between BD and an upregulated or otherwise dysfunctional brain AA cascade. However, other reports have not confirmed a positive effect of dietary n-3 PUFA supplementation or a decreased brain DHA in the postmortem brain from BD patients (Igarashi et al., Submitted; Keck et al., 2006) or suicide victims (Lalovic et al., 2007). The issue is far from settled.

12. Other proposed mechanisms of action of mood stabilizers

Many brain targets other than the AA cascade have been proposed for mood stabilizers. These include enzymes in which lithium competes for a magnesium binding site (e.g., inositol monophosphatase, inositol polyphosphate 1-phosphatase, glycogen synthase kinase-3 (GSK-3), fructose 1,6-bisphosphatase, bisphosphate nucleotidase, phosphoglucomutase); valproate-inhibitable enzymes (succinate semialdehyde dehydrogenase, succinate semialdehyde reductase, histone deacetylase); specific targets of carbamazepine (sodium channels, adenosine receptors, adenylate cyclase); signaling pathways involving PKC, cyclic AMP, or *myo*-inositol; synaptic mechanisms involving glutamate, GABA, G-proteins and GRKs (Du et al., 2007; Ertley et al., 2007; Li et al., 2002; Manji and Lenox, 2000); processes modulating apoptosis and neuroprotection, including the expression of brain growth and neurotrophic factors (Chen et al., 1999; Chuang, 2005; Gould et al., 2004b); and calcium currents and voltage gated sodium channels (Farber et al., 2002; Stefani et al., 1996). When given chronically to rodents, mood stabilizers altered brain mRNA levels of genes related to ion channel formation and transport, G-protein signaling, lipid, glucose and amino acid metabolism, transcription and translation, the phosphatidylinositide cycle, protein kinases, phosphatases, and apoptosis (Bosetti et al., 2002b; Bosetti et al., 2005; Chetcuti et al., 2006; McQuillin et al., 2007).

Among hypotheses regarding the action of mood stabilizers, the "*myo*-inositol depletion hypothesis" and the "GSK-3 inhibition hypothesis" continue to be explored experimentally and tested in the clinic (Eden Evins et al., 2006; Rowe et al., 2007). Ultimately, of course, which hypothesis if any is valid and could be used for drug discovery in BD will be determined empirically. Compared to the "AA cascade hypothesis," however, neither the *myo*-inositol nor the GSK-3 inhibition hypothesis identifies one common action of each of the four FDA-approved mood stabilizers.

The "*myo*-inositol depletion hypothesis" is that the phosphatidylinositide cycle, which participates in neurotransmission and is initiated by the activation of phospholipase C, is the target of lithium (Berridge et al., 1982; Berridge et al., 1989; Hokin and Dixon, 1993; Lenox and Hahn, 2000). To maintain a normal cycle, the brain must resynthesize *myo*-inositol, which does not readily cross the blood-brain barrier (Barchas et al., 1994). In the cycle, inositol-1,4,5-trisphosphate is serially dephosphorylated to form *myo*-inositol, the last dephosphorylation step being mediated by inositol monophosphatase. Lithium is postulated to reduce *myo*-inositol formation within the cycle by inhibiting inositol monophosphatase, thereby interfering with phospholipase C-mediated neurotransmission events (Berridge et al., 1982; Berridge et al., 1989; Hokin and Dixon, 1993; Lenox and Hahn, 2000). Limitations to the "myoinositol depletion hypothesis" have been thoroughly summarized (Atack, 1996). The hypothesis does not appear to apply to carbamazepine or valproate. While lithium inhibited partially purified inositol monophosphatase activity in the low millimolar range, carbamazepine stimulated the enzyme starting in the low micromolar range, and valproate neither stimulated nor inhibited the enzyme over a wide concentration range (Vadnal and Parthasarathy, 1995) (see Table 2).

GSK-3 also is considered a target of mood stabilizers (Gould and Manji, 2005; Schloesser et al., 2008). GSK-3 modulates the Wnt and insulin signaling pathways, as well as neurotrophic signaling involving phosphoinositide-3 kinase, generally through downregulation (Jope, 2003). While data indicate a lithium action on GSK-3 at a therapeutically relevant concentration, this is not the case for valproate or carbamazepine. Thus, in primary neocortical neurons, GSK-3 was inhibited by 1 mM lithium but *not* by valproate up to a concentration > 100 mM, or by carbamazepine even at 0.5 mM (Di Daniel et al., 2006; Ryves et al., 2005), much higher concentrations than their respective therapeutic concentrations (Table 2). Nevertheless, chronic sodium valproate and lithium, but not carbamazepine, increased rat frontal cortex β-catenin, indirectly suggesting GSK-3 pathway modulating activity (Gould et al., 2004a).

13. Discussion

Following the discovery in 1949 of lithium's efficacy in BD (Cade, 1949), divalproex and carbamazepine were approved by the FDA for bipolar mania, and lamotrigine was approved for delaying the appearance of the different mood states. Lithium and divalproex also are recommended for maintenance therapy. Atypical antipsychotics are especially useful for acute mania. One, quetiapine, is approved for bipolar depression and maintenance therapy adjunctive to lithium or divalproex, and aripiprazole and olanzapine are approved for maintenance monotherapy in Bipolar I. Depression is 3 times more common than mania in BD, but depression is generally inadequately treated. Some antidepressants if administered as monotherapy or with mood stabilizers increase "switching" to mania.

Multiple risk alleles, each with a small individual contribution, are consistent with a polygenic threshold inheritance of BD. To date, however, genetic findings have shown poor replication and have not consistently identified defective brain cascades as likely therapeutic targets. In contrast, a "top down" approach based on identifying a common mechanism of action of agents that have been shown in controlled clinical trials to work or not to work in BD has been more

informative, and is the focus of this review. Two hypotheses that have been generated by this approach are the "*myo*-inositol depletion" and "GSK-3 targeting" hypotheses. While each might explain lithium's mechanism of action, neither convincingly accounts for the actions of the other mood stabilizers or, moreover, why some antidepressants enhance switching from bipolar depression to mania.

The "AA cascade hypothesis," which is closely considered in this review, identifies a common target of the four approved mood stabilizers as the brain AA cascade, and tentatively explains why some antidepressants increase switching of bipolar depression to mania. This hypothesis was derived largely from studies in unanesthetized rats chronically administered FDA-approved mood stabilizers, as well as the clinically-proven ineffective topiramate for comparison. Lithium, carbamazepine and sodium valproate were shown to downregulate AA turnover in brain phospholipids, without changing DHA or palmitic acid turnover. Lamotrigine reduced AA incorporation coefficients k^* in brain phospholipids. The effect on AA turnover of lithium and carbamazepine was ascribed to reduced expression of AA-selective $cPLA_2$ and of its AP-2 transcription factor, whereas valproate's effect was ascribed to its inhibition of an AA-selective microsomal acyl-CoA synthetase. Each of the four agents depressed rat brain COX-2 expression and, when measured, the concentration of the COX-2 - derived AA metabolite, PGE_2. Topiramate, which had been proposed as a mood stabilizer based on initial trials, but later failed Phase III trials, did not alter any brain AA cascade marker. Thus, the AA cascade hypothesis corresponds to proven clinical efficacy of the tested drugs.

The AA cascade hypothesis is consistent with evidence that BD symptoms arise from excessive dopaminergic and glutamatergic but reduced cholinergic signaling, provided that the signaling uses AA as a second messenger. Thus, imaging in unanesthetized rats showed that lithium upregulated muscarinic cholinergic $M_{1,3,5}$ receptor signaling involving AA; lithium and carbamazepine blocked D_2-like receptor-initiated AA signaling; and lithium, valproate and carbamazepine each blocked NMDA receptor-initiated AA signaling (Table 5). The NMDA effects may explain much of the global effects of the mood stabilizers on the AA cascade, since most brain synapses are excitatory and glutamatergic (Attwell and Laughlin, 2001;Raichle and Gusnard, 2002).

More research is needed to examine disease progression and deterioration in BD, which only recently is being addressed. Progression may be a trait feature, but it also may be determined by factors such as diet, substance abuse, obesity, and bipolar disorder drugs. Postmortem studies indicate the presence of neuroinflammation, excitotoxicity and apoptosis in the BD brain, processes that can underlie progression (Kim et al., 2007a; Kim et al., 2008; Rao et al., In press). Chronic administration of atypical antipsychotics has been shown to cause atrophy and astrocyte loss in monkey brain, and chronic lithium produced neuronal death in rat brain (**Section 4.3.**). On the other hand, mood stabilizers and antipsychotics have been reported to be neuroprotective in animal models of neuroinflammation and excitotoxicity, in some cases by downregulating the brain AA cascade.

Observations that mood stabilizers selectivity downregulate the rat brain AA cascade at therapeutically relevant plasma concentrations, and that antidepressants that increase switching of bipolar depression to mania upregulate the cascade, suggest that an upregulated brain AA cascade contributes to BD symptoms, particularly bipolar mania. Cascade-suppressing drugs, as well as dietary n-3 PUFA supplementation (**Section 11.)** might be used to test the relation between disturbed behavior and disturbed AA metabolism in animal models with disturbances of both behavior and AA metabolism (Table 8). Additionally, cascade parameters can be measured in such pathological models, as well as in the normal rat, to screen for new and potentially clinically relevant therapeutic agents for BD. Based on this review and prior suggestions (Chang et al., 1996;Chang et al., 1999;Rapoport and Bosetti, 2002), one would

predict efficacy in BD from NMDA transmission modifiers, inhibitors of $cPLA_2$ or of COX-2 synthetase, such as non-steroidal anti-inflammatory agents including COX inhibitors and aspirin (which can acetylate COX-2 to form specific anti-inflammatory derivatives of AA and DHA) (Breitner, 2003;Farooqui et al., 2006;Ketterer et al., 1996;Rapoport and Bosetti, 2002;Serhan, 2006; Stolk et al., Submitted for publication), other promoters of brain DHA conversion to resolvins and neuroprotectins (Basselin et al., Unpublished observations;Serhan, 2006) including dietary n-3 PUFA supplementation, and inhibitors of AA-selective acyl-CoA synthetase, including valproate-like compounds (Bazinet et al., 2006b;Bialer and Yagen, 2007). These predictions could be tested by direct clinical trials or by analyzing relevant databases (Stolk et al., Submitted for publication).

In addition, the presence of an upregulated brain AA cascade in BD patients could be tested for directly by imaging regional brain AA incorporation parameters (k^* and J_{in}) during manic, euthymic and depressive phases of the disease, with the help of positron emission tomography. Increased AA incorporation associated with neuroinflammation has been measured in this way in patients with Alzheimer disease (Esposito et al., 2007; Esposito et al., 2008; Giovacchini et al., 2004).

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1.1. Abbreviations

AA, arachidonic acid
AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP, activator protein
BD, bipolar disorder
BDNF, brain derived neurotrophic factor
Bcl-2, B-cell lymphoma-2
COX, cyclooxygenase
CREB, cAMP response element binding protein
DAT, dopamine reuptake transporter
DHA, docosahexaenoic acid
DOI, (+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride
FABP, fatty acid binding protein
GRE, glucocorticoid response element
GRK, G-protein receptor kinase
GSK, glycogen synthase kinase
5-HT, 5-hydroxytryptamine (serotonin)
5-HTT, serotonin reuptake transporter
IL, interleukin
5-LOX, 5-lipoxygenase
LTB_4, leukotriene B_4
MR, magnetic resonance
NMDA, N-methyl-D-aspartic acid
NF-κB, nuclear factor kappa B
NR, NMDA receptor
PEA, polyoma enhancer activator
PGE_2, prostaglandin E_2
PK, protein kinase

mPGES, microsomal prostaglandin E synthase
PLA_2, phospholipase A_2
$cPLA_2$, cytosolic PLA_2
$iPLA_2$, calcium-independent PLA_2
$sPLA_2$, secretory PLA_2
PUFA, polyunsaturated fatty acid
sn, stereospecifically numbered
SSRI, selective serotonin reuptake inhibitor
TX, thromboxane

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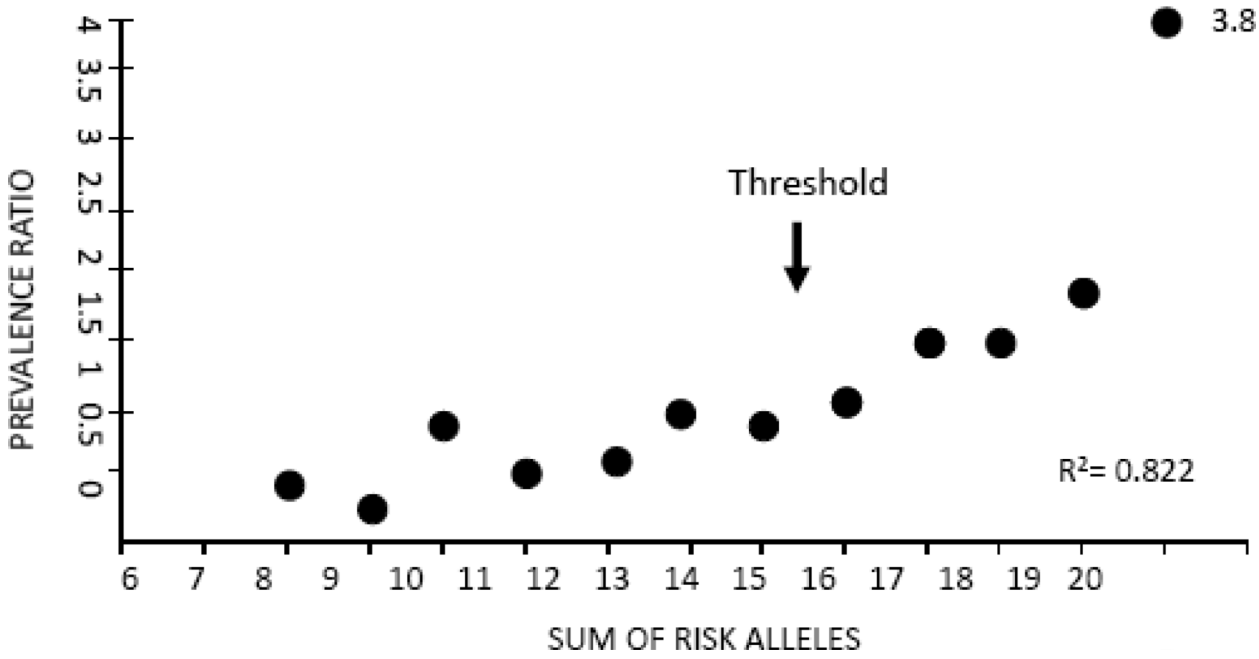

Figure 1. Prevalence ratio of bipolar disorder increases with risk allele burden

A combination of more than any 15 of risk alleles significantly increases the risk for BD above the risk (1.0) in the general population, whereas a combination of any 19 increases the risk 3.8 fold. From (Baum et al., 2008).

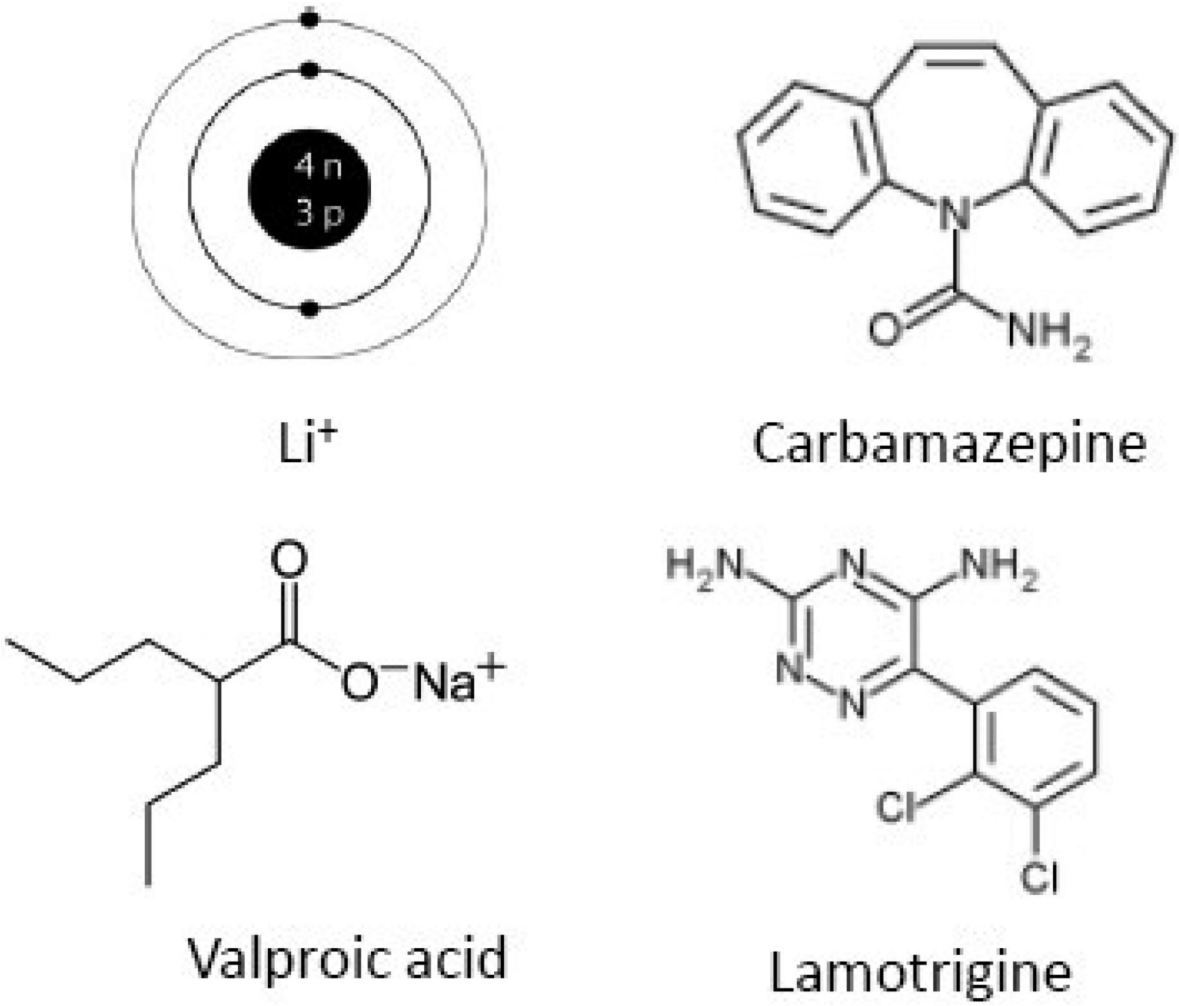

Figure 2.
Chemical structures of FDA-approved mood stabilizers

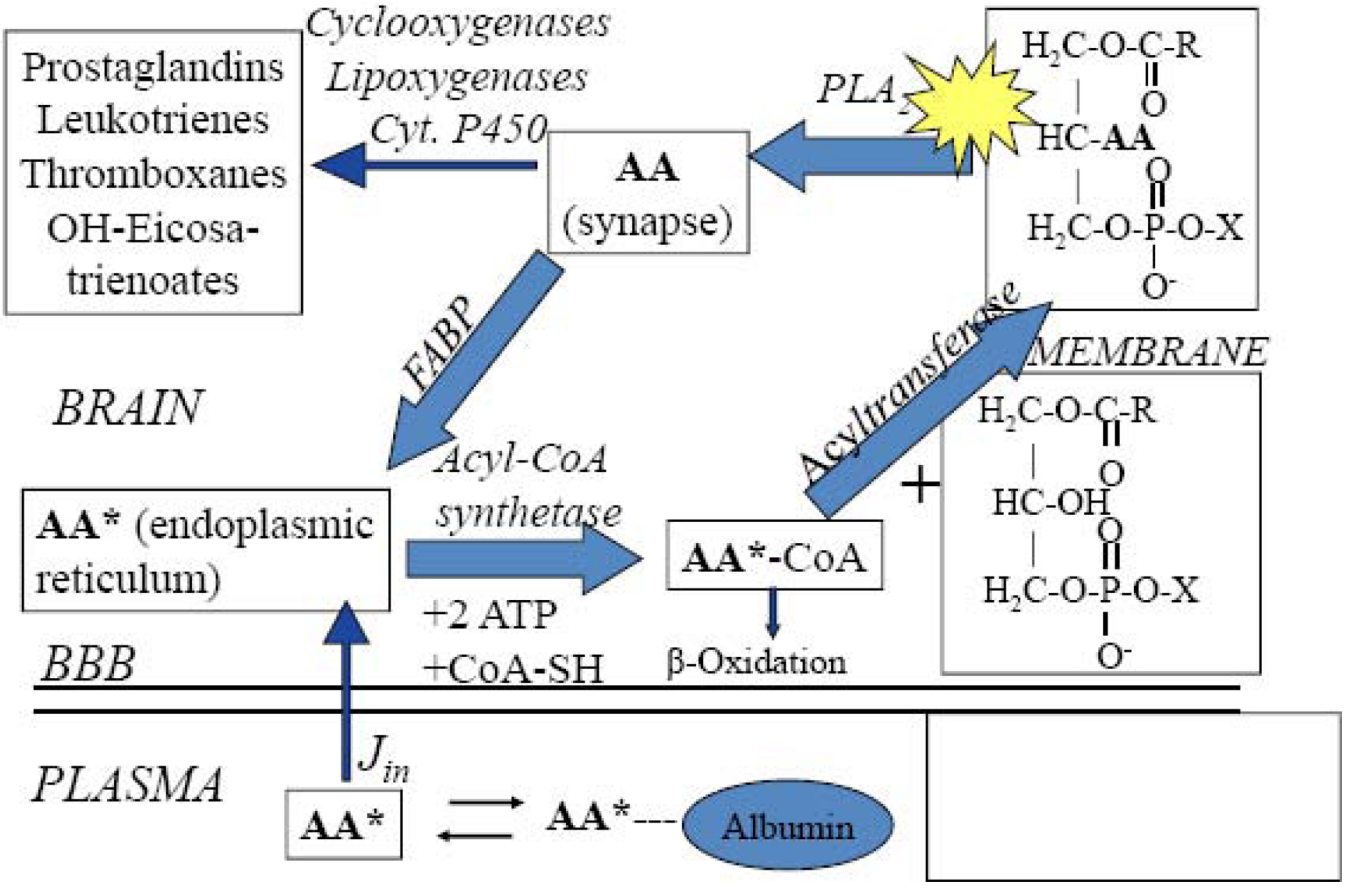

Figure 3. Model of brain arachidonic acid cascade initiated at synapse

AA is liberated from the stereospecifically numbered (*sn*)-2 position of a phospholipid by activation (star) of phospholipase A_2 (PLA_2). A fraction is converted to bioactive eicosanoid, while the remainder diffuses to the endoplasmic reticulum bound to a fatty acid binding protein (FABP). There, it is converted to arachidonoyl-CoA by acyl-CoA synthetase with the consumption of 2 ATPs, then re-esterified into an available lysophospholipid by acyltransferase, or β-oxidized in mitochondria. AA in the endoplasmic reticulum exchanges freely with unesterified unbound AA in plasma, into which labeled AA (AA*) has been infused. Other metabolic pathways are not shown. J_{in}, the rate of incorporation of unesterified unlabeled AA into brain, equals the net rate of loss by metabolism, since AA cannot be synthesized *de novo* in brain. Adapted from (Rapoport and Bosetti, 2002).

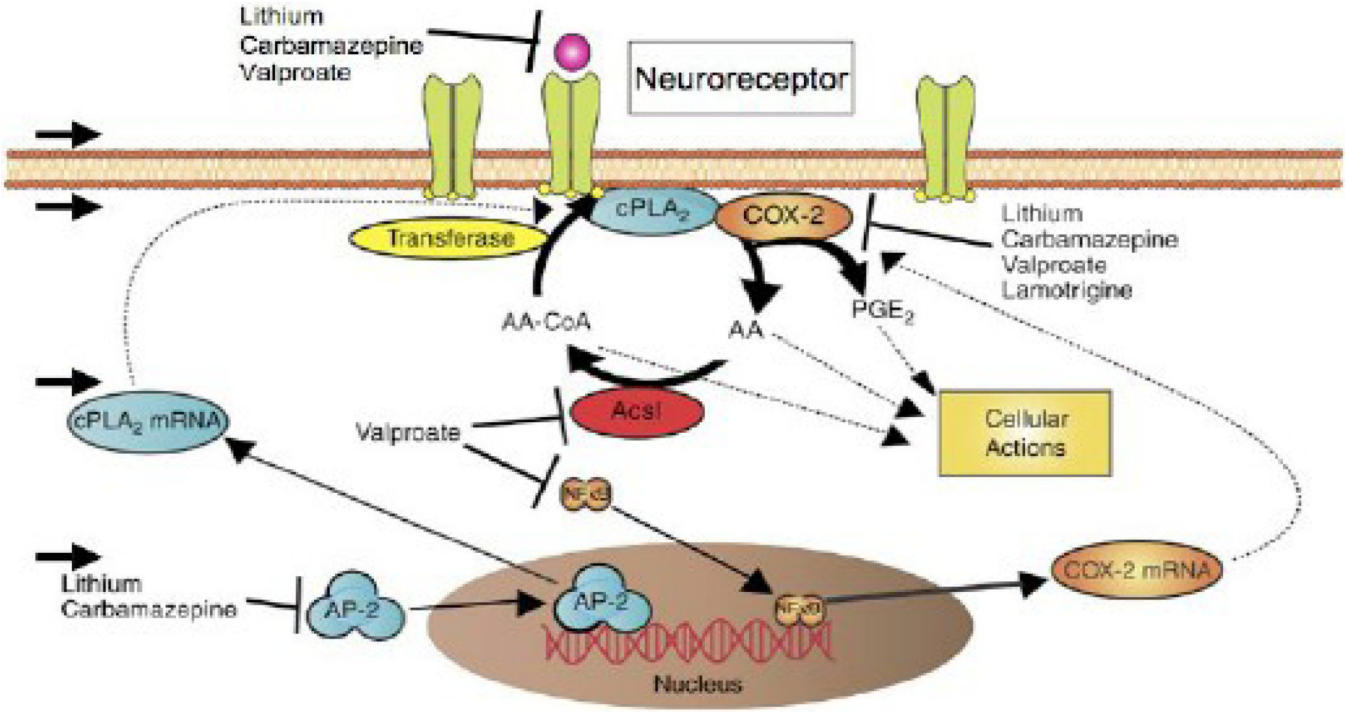

Figure 4. Mood stabilizers downregulate the rat brain arachidonic acid cascade during neurotransmission at different levels

The first level is at the neuroreceptor itself, the second its coupling mechanism with $cPLA_2$. $cPLA_2$ also can be transcriptionally downregulated by drug action on its transcription factor, AP-2 (lithium and carbamazepine), whereas reincorporation of AA can be slowed by drug inhibition of an AA-selective acyl-CoA synthetase (valproate). These effects are correlated with reduced turnover of AA in membrane phospholipids. Drugs also can inhibit formation of PGE_2 and/or TXB_2 by downregulating activity and/or transcription of COX-2 (and expression of NF-κB) and COX-1 respectively. See Text and Table 4 for detailed effects. Adapted from (Rao et al., 2008).

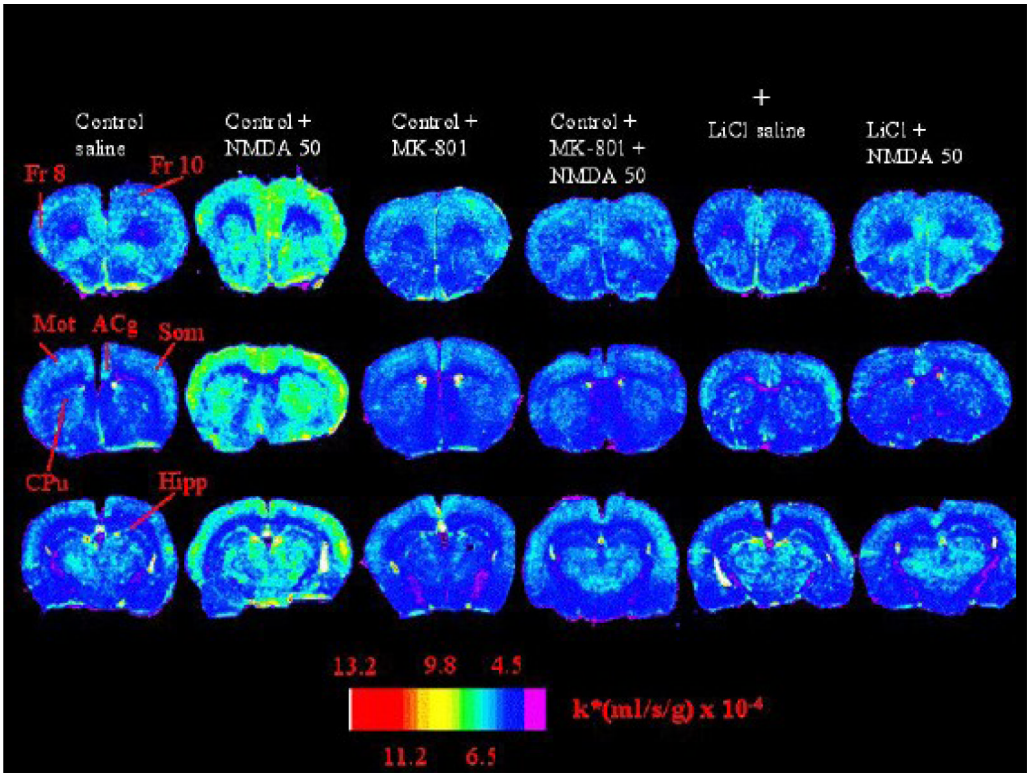

Figure 5. MK-801 and chronic lithium block NMDA stimulation of arachidonic acid signal in rat brain

AA incorporation coefficients *k** in autoradiographs of coronal brain sections. Two left columns: rats on a control diet, that had been injected i.p. with saline or 50 mg/kg NMDA. Two central columns: rats on a control diet injected with MK-801 or NMDA following MK-801; Two right columns: rats on a LiCl diet injected with saline or NMDA. NMDA increased *k** in rats on the control diet, but not in rats pretreated with MK-801 or in rats fed the LiCl diet. Fr 8 and 10, frontal cortex 8 and 10; Mot, Som, motor and somatosensory cortex; Acg, anterior cingulate cortex; CPu, caudate putamen; Hipp, hippocampus. From (Basselin et al., 2006a).

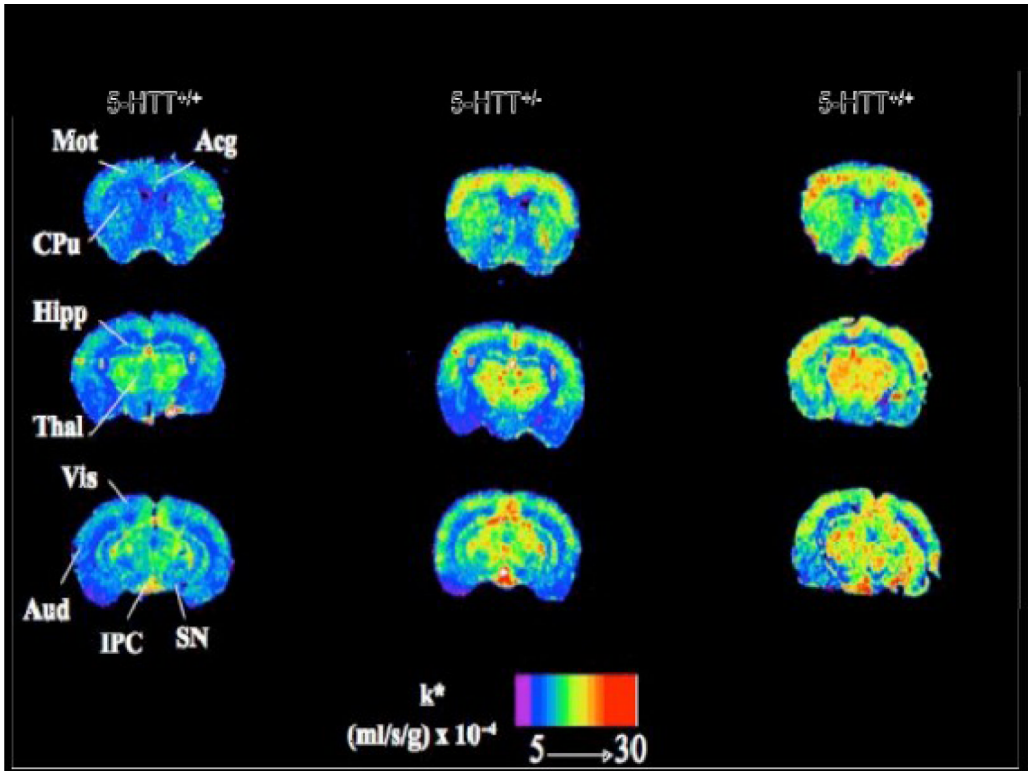

Figure 6. Coronal autoradiographs of brain showing effects of 5-HTT genotype on regional arachidonic acid incorporation coefficients k* in mice

Acg, anterior cingulate cortex; Aud, auditory cortex; CPu, caudate-putamen; Hipp, hippocampus; IPC, interpeduncular nucleus; Mot, motor cortex; SN, substantia nigra; Thal, thalamus; Vis, visual cortex. Adapted from (Basselin et al., 2009).

Table 1

Receptors coupled to PLA_2 activation and arachidonic acid signaling

Neuroreceptors	*Subtype*[1]
–Coupled via G-proteins	
	Cholinergic muscarinic $M_{1,3,5}$(Bayon et al., 1997; DeGeorge et al., 1991)
	Dopaminergic D_2-like(Bhattacharjee et al., 2005; Vial and Piomelli, 1995)
	Serotonergic 5-$HT_{2A/2C}$(Felder et al., 1990; Qu et al., 2003)
	Adrenergic β_2(Pavoine et al., 1999)
	Bradykinin β_2(Prado et al., 2002)
	Metabotropic glutamatergic mGlur1α(Nitsch et al., 1997)
–Ionotropic, coupled via Ca^{2+}	
	NMDA(Basselin et al., 2006a; Weichel et al., 1999)
	AMPA(Gaudreault et al., 2004)
Astrocytic Receptors	*Subtype*[2]
	TNFα(Luschen et al., 2000)
	IL-1β(Dinarello, 1988)
	Purigenic $2Y_2$(Sun et al., 2005)

[1] References mainly for $cPLA_2$

[2] Activation of both $cPLA_2$ and $sPLA_2$

Table 2

Therapeutic concentration ranges of FDA-approved mood stabilizers and topiramate, and concentrations used in experimental rat studies

Drug	Therapeutic plasma concentrations in patients	Plasma concentrations achieved in rat infusion studies
	mM	
Lithium	0.6-1.2(Camus et al., 2003; Eilers, 1995)	0.73(Bosetti et al., 2002b; Chang et al., 1996)
Carbamazepine	0.017 - 0.051(Bialer et al., 1998; Eilers, 1995)	0.053(Ghelardoni et al., 2005)
Valproate	0.20 - 1.5(Bowden et al., 1994; Eilers, 1995; Jacobsen, 1993)	0.21(Chang et al., 2001)
Lamotrigine	0.02 - 0.03(Doose et al., 2003)	0.04(Hassel et al., 2001; Lee et al., 2007a)
Topiramate[1]	0.010 to 0.050(Doose and Streeter, 2002)	0.018(Ghelardoni et al., 2005)

[1] Failed phase III trials(Kushner et al., 2006)

Table 3

Chronic lithium administration selectively reduces arachidonic acid turnover in rat brain phospholipids

Fatty Acid	λ	Turnover Rate (% per hour)		
		PtdIns	PtdCho	PtdEtn
Arachidonic Acid (20:4n-6)				
Control	0.04±0.00	15.3±0.4	18.3±0.6	1.1±0.1
Lithium	0.18±0.02#,**	2.6±0.1**	5.0±0.3**	0.2±0.0**
Docosahexaenoic Acid (22:6n-3)				
Control	0.03±0.00	17.7±1.7	3.1±0.4	1.2±0.1
Lithium	0.03±0.00	31.0±9.0	4.5±1.2	1.6±0.4
Palmitic Acid (16:0)				
Control	0.02±00	29.1±2.6	7.0±0.4	4.1±0.4
Lithium	0.02±00	26.0±1.2	5.1±0.3*	3.5±0.1

[1]After (Chang et al., 1996; Chang et al., 1999; Rapoport and Bosetti, 2002)

Differs from control mean ± SEM (n = 5-6)

LiCl or control diet was fed for 6 weeks, giving brain lithium concentration of 0.73 ± 0.03 mM.

See Footnote [2] for definitions of λ and turnover rate.

PtdIns, phosphatidylinositol; PtdCho, cholineglycerophospholipid; PtdEtn, ethanolamineglycerophospholipid;

* $p < 0.05$

** $p \pm 0.01$

An elevation in λ (Footnote 2) indicates that less AA is being provided by release from phospholipid than entry from plasma.

Table 4

Baseline changes in whole brain arachidonic acid cascade markers after chronic administration of each of four mood stabilizers to rats

Target	Lithium	Carbamazepine	Sodium valproate	Lamotrigine
Fatty acid kinetics				
AA turnover in phospholipids	↓(Chang et al., 1996; Rapoport and Bosetti, 2002)	↓(Bazinet et al., 2006a)	↓(Chang et al., 2001)	Nc(Lee et al., 2007a)
AA-CoA concentration	↓(Chang et al., 1999)	↓(Bazinet et al., 2006a)	Nc(Chang et al., 2001)	Nc(Lee et al., 2007a)
AA incorporation coefficient *k**	Nc(Basselin et al., 2005b)	Nc(Bazinet et al., 2006a)	↑(Chang et al., 2001)	↓(Lee et al., 2007a)
DHA turnover in phospholipids	Nc(Chang et al., 1999)	Nc(Bazinet et al., 2006a)	Nc(Bazinet et al., 2005)	?
17-OH-DHA concentration	↑(Basselin et al., Unpublished observations)	?	?	?
Palmitate turnover in phospholipids	Nc(Chang et al., 1999)	?	?	?
Enzymes				
$cPLA_2$ IVA	↓(Rintala et al., 1999; Weerasinghe et al., 2004)	↓(Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003; Chang et al., 2001)	Nc(Lee et al., 2008a)
$SPLA_2$ IIA	Nc(Weerasinghe et al., 2004)	Nc(Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003)	Nc(Lee et al., 2008a)
$iPLA_2$ VIA	Nc(Bosetti et al., 2002a; Rintala et al., 1999)	Nc(Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003)	Nc(Lee et al., 2008a)
Acyl-CoA synthetase	?	?	↓(Bazinet et al., 2006b)	?
COX-1	Nc(Bosetti et al., 2002a)	Nc(Ghelardoni et al., 2004)	↓(Bosetti et al., 2003)	Nc(Lee et al., 2008a)
COX-2	↓(Bosetti et al., 2002a)	↓(Ghelardoni et al., 2004)	↓(Bosetti et al., 2003; Rao et al., 2007a)	↓(Lee et al., 2008a)
5-LOX	Nc(Weerasinghe et al., 2004)	Nc(Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003)	?
Cytochrome P450 epoxygenase	Nc(Weerasinghe et al., 2004)	Nc(Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003)	?
mPGES-1	Nc(Weerasinghe et al., 2004)	?	?	?
Eicosanoids				
PGE_2	↓(Basselin et al., 2007b; Bosetti et al., 2002a)	↓(Basselin et al., 2007a; Ghelardoni et al., 2004)	↓(Basselin et al., 2008a; Bosetti et al., 2003)	?
TXB_2	(Basselin et al., 2007b)	Nc or ↓(Basselin et al., 2007a; Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003)	?
Leukotriene B_4	?	Nc(Ghelardoni et al., 2004)	Nc(Bosetti et al., 2003)	?
Transcription Factors				
AP-2	↓(Rao et al., 2005)	↓(Rao et al., 2007b)	Nc(Rao et al., 2007a)	?
AP-1	↑(Ozaki and Chuang, 1997; Rao et al., 2005)	Nc(Rao et al., 2007b)	↑(Chen et al., 1997; Rao et al., 2007a)	?
GRE	Nc(Rao et al., 2005)	Nc(Rao et al., 2007b)	Nc(Rao et al., 2007a)	?
PEA3	Nc(Rao et al., 2005)	Nc(Rao et al., 2007b)	Nc(Rao et al., 2007a)	?
NF-κB	Nc(Rao et al., 2005)	Nc(Rao et al., 2007b)	↓(Rao et al., 2007a)	?

Abbreviations: AP, activator protein; GRE, glucocorticoid response element; Nc, no significant change; NF-κB, nuclear factor-kappa B; PEA, polyoma enhancer activator; $cPLA_2$, cytosolic phospholipase A_2; $sPLA_2$, secretory PLA_2; $iPLA_2$, Ca^{2+}-independent PLA_2; COX, cyclooxygenase; LOX, lipoxygenase; mPGES, microsomal prostaglandin E synthase

Table 5

Mood stabilizers modulate neuroreceptor signaling *via* arachidonic acid in unanesthetized rats[a]

		Receptor Subtype			
		NMDA	**D_2-like**	**$M_{1,3,5}$**	**5-$HT_{2A/C}$**
Agonist used		**NMDA**	**Quinpirole**	**Arecoline**	**DOI**
Antagonist used		**MK-801**	**Raclopride or butaclamol**	**Atropine**	**Mianserin**
Mood Stabilizer	**Baseline effect**	***Effect on Response to Acute Agonist, k* for AA[#]***			
Lithium	↑ in auditory and visual areas (Basselin et al., 2005b)	↓ (Basselin et al., 2006a)	↓(Basselin et al., 2005a)	↑(Basselin et al., 2003)	↓ in auditory and visual areas (Basselin et al., 2005b)
Carbamazepine	Nc(Basselin et al., 2008b)	↓(Basselin et al., 2007a)	↓(Basselin et al., 2008b)	?	?
Sodium valproate	Nc(Basselin et al., 2008a)	↓(Basselin et al., 2008a)	?	?	?
Lamotrigine	↓(Lee et al., 2007a)	?	?	?	?

Each mood stabilizer was administered chronically to produce a plasma concentration therapeutically relevant to bipolar disorder (Table 1), and compared with chronic vehicle. Baseline effect on *k** for AA (AA incorporation) was measured compared to chronic vehicle. Effect on responses to agonists shown were also measured and compared to response in saline injected animals. In saline-treated animals, responses to agonists could be blocked by antagonists shown in table. Nc, no significant change; DOI, (+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride.

[a] All but the lamotrigine measurements were obtained using quantitative autoradiographic imaging; [b] *k** for whole brain phospholipid

[#] *k** defined by Eq. 1 in footnote 2

Table 6

Therapeutic plasma concentrations of antidepressants, and concentrations used in experimental rat studies

Antidepressant	Clinical plasma concentrations	Plasma concentrations in rat infusion studies
	mg/L	
Fluoxetine[1]	150-500(Wille et al., 2008)	314(Durand et al., 1999; Lee et al., 2007b)
Imipramine[2]	45-150(Wille et al., 2008)	100 - 600(Daniel et al., 1981; Lee et al., 2007b)
Bupropion[3]	25-100(Wille et al., 2008)	289 (max)(Lee et al., 2008 ; Suckow et al., 1986)

[1] N-Methyl-g-[4-(trifluoromethyl)phenoxy]benzenepropanamine.

[2] (5-[3-(dimethylamino) propyl] -10,11-dihydro-5H-dibenz [b,f]-azepine monohydrochloride).

[3] (±)-2-(tertbutylamino)-1-(3-chlorophenyl)propan-1-one

Table 7

Brain arachidonic acid cascade markers following chronic administration of each of three antidepressants to rats

Target	Fluoxetine	Imipramine	Bupropion
Fatty acid kinetics			
Arachidonic acid turnover in brain phospholipid	↑(Lee et al., 2007b)	↑(Lee et al., 2008)	Nc(Lee et al., 2008)
Enzymes			
$CPLA_2$ IVA	↑(Lee et al., 2007b; Rao et al., 2006)	↑(Lee et al., 2008)	Nc(Lee et al., 2008)
$SPLA_2$ IIA	Nc(Lee et al., 2007b; Rao et al., 2006)	Nc(Lee et al., 2008)	Nc(Lee et al., 2008)
$iPLA_2$ VIA	Nc(Lee et al., 2007b; Rao et al., 2006)	Nc(Lee et al., 2008)	Nc(Lee et al., 2008)
COX-1	Nc(Lee et al., 2007b)	Nc(Lee et al., 2008)	Nc(Lee et al., 2008)
COX-2	Nc(Lee et al., 2007b)	Nc(Lee et al., 2008)	Nc(Lee et al., 2008)
Eicosanoids			
PGE_2	Nc(Lee et al., 2007b)	Nc(Lee et al., 2008)	Nc(Lee et al., 2008)
Transcription Factors			
AP-2	Nc(Rao et al., 2006)	↑ (AP-2α but not AP-2β)(Lee et al., 2008) ↓(Damberg et al., 2000)	Nc(Lee et al., 2008)
AP-1	Nc(Rao et al., 2006)	Nc(Tamura et al., 2002)	?
GRE	Nc(Rao et al., 2006)	?	?
PEA3	Nc(Frechilla et al., 1998; Rao et al., 2006)	?	?
NF-κB	Nc(Rao et al., 2006)	Nc(Lee et al., 2008)	Nc(Rao et al., 2007a)
RNA stabilizing protein	↑(Rao et al., 2006)	?	?

Table 8

Animal models with an upregulated brain arachidonic acid cascade

Parameter	**Model**				
	Chronic i.p. NMDA in rat	**6-day cerebroventricular low-dose lipopolysaccharide[b] *infusion in rat***	**15 weeks dietary n-3 PUFA deprivation in 20 day old rat**	**COX-2$^{-/-}$ knockout mouse**	**5-HTT$^{+/-}$ or 5-HTT$^{-/-}$ knockout mouse**
AA turnover[c]	↑	↑	↑[e]		
AA incorporatio n (k*or J_{in})[d]	↑	↑	↑[e]	↑	↑
CPLA$_2$ IVA	↑	↑	↑	↑	↑
iPLA$_2$ VIA	Nc	Nc	↓	Nc	
SPLA$_2$ IIA	Nc	↑, Nc	↑	↑	
COX-1		Nc	↓	↑	
COX-2		Nc	↑	Absent	
Total COX				↑	↓
5-LOX				Nc	
mPGES-2				↓	
AP-2	↑				
PGE$_2$		↑		↓	↓
TXB$_2$		↑			↓
Altered Behavior		Yes[a]	Yes		Yes
References	(Lee et al., 2008b; Rao et al., 2007e)	(Basselin et al., 2007b; Lee et al., 2004; Richardson et al., 2005; Rosenberger et al., 2004)	(DeMar et al., 2006b; Igarashi, 2009; Rao et al., 2007c)	(Basselin et al., 2006c; Bosetti et al., 2004)	(Basselin et al., 2009; Murphy and Lesch, 2008)

Empty boxes indicate that measurement was not performed

[a] Measured after 1 month of infusion

[b] 0.5-1.0 ng/h

[c] Measured by direct chemical analysis

[d] Measured by direct chemical analysis and/or quantitative autoradiography

[e] Turnover of AA elongation product, 22:5n-6, is increased