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Antimanic therapies target brain arachidonic acid signaling: Lessons learned about the regulation of brain fatty acid metabolism

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Abstract

Bipolar disorder is a major medical, social and economic burden worldwide. However, the biochemical basis of the disorder and the mechanisms of action of effective antibipolar disorder drugs remain elusive. In this paper, we review how combining a kinetic approach to studying the turnover of fatty acids within brain phospholipids of unanesthetized rats along with chronic administration of antimanic drugs (lithium, valproate and carbamazepine) at therapeutically relevant doses, shows that the brain arachidonic acid cascade is a common target of these drugs. The overlapping effects of the three drugs are decreased turnover of arachidonic acid but not of docosahexaenoic acid in rat brain phospholipids, and decreased brain cyclooxygenase-2 and prostaglandin E_2. Whereas lithium and carbamazepine target the transcription of the arachidonic acid-selective calcium-dependent cytosolic phospholipase A_2, valproate is a non-competitive inhibitor of an arachidonic acid-selective acyl-CoA synthetase. Two potential models of bipolar disorder, chronic *N*-methyl-D-aspartate and *n*-3 polyunsaturated fatty acid deprivation, opposite to the antimanic drugs, increase the turnover and markers of the arachidonic acid cascade in rat brain. These observations support the hypothesis proposed by Rapoport and colleagues that the arachidonic acid cascade is a common target of mood stabilizers and that by targeting substrate-specific enzymes the turnover of individual fatty acids can be regulated within the brain.
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1. Background on bipolar disorder

Bipolar disorder is generally characterized by changes in mood, varying from severe depression and mania (bipolar disorder I), to much milder forms of both moods (bipolar disorder II) and rapid cycling [1]. Bipolar disorder I afflicts 1.2–1.5% of the adult US population [2,3] and depending on the severity of the disease these patients have a 5–17-fold higher suicide rate than the general population [4]. Bipolar disorder patients have poor outcomes and a high prevalence of medical illnesses as compared to the general population [5]. Their overall quality of life is profoundly altered, as are social relationships, finances, career and family. Bipolar disorder is a major economic burden [6,7] with the estimated 1998 lifetime cost of individual cases in the United States ranging from $11 720 for persons with a single manic episode to $624 785 for those with nonresponsive/chronic episodes [8].

2. Approaches to studying drug mechanisms of action in bipolar disorder

Despite there being a number of FDA-approved drugs for treating the disease, the mechanisms of action of these agents are not agreed upon. To date, no drug has been developed from a preclinical hypothesis

Abbreviations: Acsl, acyl-CoA synthetase; AP, activator protein; $cPLA_2$, cytosolic phospholipase A_2; COX, cyclooxygenase; DHA, docosahexaenoic acid; GRE, glucocorticoid response element; NMDA, N-methyl-D-aspartic acid; NF-κB, nuclear factor kappa B; PLA_2, phospholipase A_2; $iPLA_2$, calcium-independent phospholipase A_2; $sPLA_2$; secretory phospholipase A_2 PEA, polyoma enhancer activators; PGE_2, prostaglandin E_2; PUFA, polyunsaturated fatty acid *sn*, stereospecifically numbered.

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specifically for bipolar disorder. One approach to study bipolar disorder in the face of a lack of an accepted animal model, is to model therapeutic mood stabilizing drug regimens in rodents to elucidate the mechanisms of action of the drugs and potentially the causes and pathophysiology of bipolar disorder [9]. Although not necessary, it would be helpful to find overlap between activities of mood stabilizers and/or the pathophysiology of the disease itself (i.e. post-mortem brain samples) [10,11]. In this review, we summarize how chronic administration of therapeutically relevant doses of lithium, carbamazepine and valproic acid (Fig. 1) to rats, combined with kinetic, biochemical and molecular biological analyses, supports the hypothesis proposed by Rapoport and colleagues that mood stabilizers generally target the brain arachidonic acid (20:4*n*-6) cascade [12–14], and we describe the mechanisms by which they appear to do so. Many mechanisms of action have been proposed for effective mood stabilizers and readers interested in other proposals on the mechanism of action of mood stabilizers [15], which involve inositol depletion [16,17], glycogen synthase kinase-3 [18], protein kinase C [19], G proteins [20], cyclic adenosine monophosphate or protein kinase A [20], should consider these excellent reviews.

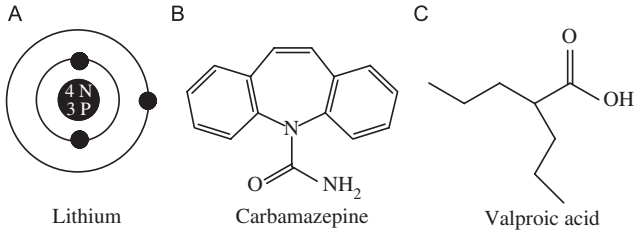

Fig. 1. The structure of 3 commonly used drugs for treating the manic phase of bipolar disorder. (A) Lithium (Li^+, atomic number 3, commonly administered as a lithium chloride or carbonate salt) is an alkali metal with 3 protons and 4 neutrons. (B) Carbamazepine is a 5H-dibenz[*b*,*f*]azepine-5-carboxamide. (C) Valproic acid (valproate, 2-propylpentanoic acid) is a branched chain fatty acid.

3. Précis of a method to measure brain fatty acid kinetics in vivo

3.1. Overview

Unesterified arachidonic acid (as well as other fatty acids) rapidly disassociates with albumin and can cross the blood brain barrier by a passive diffusion mechanism [21,22], while its entry via esterified lipoproteins is unlikely [23,98]. Upon entry into the appropriate brain cell the unesterified fatty acid is then "quenched" by addition of an acyl-CoA group via the action of either an acyl-CoA synthetase (Acsl) [24] or fatty acid transport protein (all of which have Acsl activity) [25–27] (Fig. 2). From here the arachidonic acid can be directed towards an available 2-lyso position of a phospholipid by a yet to be cloned fatty acyl transferase [28,29]. The brain arachidonic acid cascade starts with phospholipase A_2 (PLA_2)-initiated hydrolysis of esterified arachidonic acid from the stereospecifically numbered (*sn*)-2 position of membrane phospholipids to

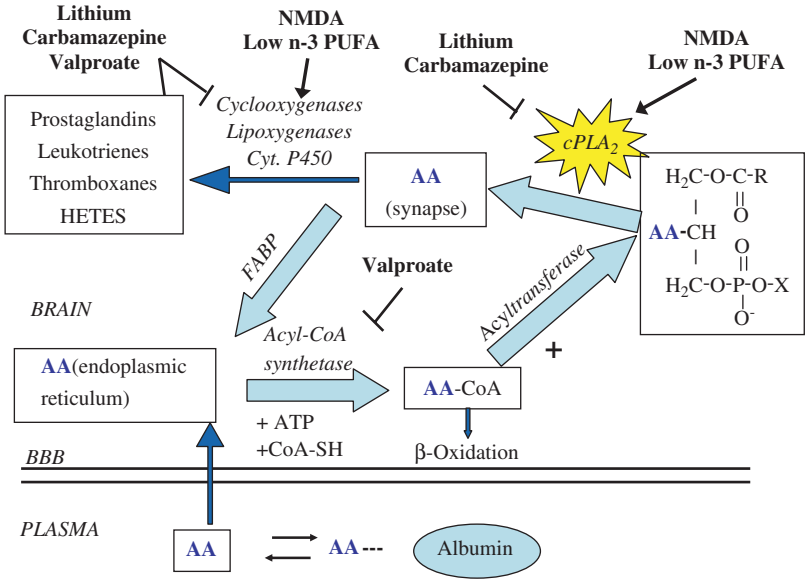

Fig. 2. The regulation of arachidonic acid metabolism within brain phospholipids. Lithium and carbamazepine downregulate $cPLA_2$ and thus decrease the turnover of arachidonic acid, valproate likely does so by targeting an arachidonic acid selective acyl-CoA synthetase. Lithium, carbamazepine and valproate all decrease COX-2 and PGE_2. Two potential models of mania N-methyl-D-aspartate (NMDA) and low *n*-3 polyunsaturated fatty acids (PUFA) increase $cPLA_2$ and COX-2. AA, arachidonic acid; BBB, blood brain barrier; COX, cyclooxygenase; $cPLA_2$, cytosolic phospholipase A_2; Cyt, cytochrome; cytosolic phospholipase A_2; FABP, fatty acid binding protein; HETES, hydroxyeicosatetraenoic acid.

produce the 2-lysophospholipid [30]. In the brain, these enzymes may include arachidonic acid-selective calcium-dependent cytosolic phospholipase A_2 IV ($cPLA_2$), calcium-dependent secretory phospholipase A_2 IIA or V ($sPLA_2$), or calcium-independent phospholipase A_2 VI ($iPLA_2$) [31–34]. However, recent studies have suggested that $iPLA_2$ is selective for the release of docosahexaenoic acid (22:6*n*-3; DHA) [35–37] and new phospholipase isoforms are being discovered and characterized within the brain [38]. Using radiolabeled tracers to follow the metabolism of arachidonic acid (see calculations below), we have shown that the majority (approximately 97%) of the arachidonic acid released by PLA_2 is rapidly reincorporated into brain phospholipids [39,40] via one of several long-chain Acsl and an acyl transferase [41–43], while a quantitatively small but important portion of the released arachidonic acid is β-oxidized or converted to eicosanoids via cyclooxygenase (COX)-1, COX-2, lipoxygenase, cytochrome P450 or epoxygenase. The arachidonic acid loss to metabolic processes is rapidly replaced from the plasma unesterified pool as calculated by Eq. (2), $J_{in,i}$ ($\sim$5 pmol $s^{-1}\,g^{-1}$). Like arachidonic acid, DHA is usually esterified in the *sn*-2 position of brain phospholipids (See the paper in this issue by Rapoport et al., for more details). It is released by a PLA_2 (most likely $iPLA_2$), and the majority ($\sim$90%) is then reesterified into brain phospholipids [39,41,44], while a portion of the non-esterified DHA can be β-oxidized or converted to docosanoids which along with DHA, play important roles in brain signaling [45], anti-inflammation [46,47] and neuroprotection [48]. The actions of DHA and the docosanoids are generally antagonistic to those of arachidonic acid and its eicosanoid derivatives.

3.2. Calculations

The model for determining *in vivo* kinetics of brain fatty acids in rats has been described in detail elsewhere [40,49]. Briefly, unidirectional incorporation coefficients, k_i^*($ml\,s^{-1}\,g^{-1}$) of arachidonic acid, or of other long-chain fatty acids representing incorporation from the plasma unesterfied pool into brain phospholipid compartments *i*, can be calculated as

$$k_i^* = \frac{c_{br,i}^*(T)}{\int_O^T c_{pl}^* dt}, \tag{1}$$

where $c_{br,i}^*(T)$ ($nCi\,g^{-1}$) is radioactivity of brain lipid *i* (due to the fatty acid) at time $T = 5$ min (time of termination of experiment), *t* is time after beginning infusion, and c_{pl}^* ($nCi \cdot ml^{-1}$) is the plasma concentration of labeled arachidonic acid during infusion. The synthesis of arachidonic acid or DHA from its dietary precursors linoleic acid (18:2*n*-6) or α-linolenic acid (18:3*n*-3) within the brain represents less than 0.5% of the arachidonic acid or DHA within the brain, respectively [50,51]. Thus, net rates of incorporation of these two polyunsaturated fatty acids (PUFA) from plasma into brain phospholipid *i*, $J_{in,i}$, and from the brain acyl-CoA into brain phospholipid *i*, $J_{FA,i}$, can be calculated as follows:

$$J_{in,i} = k_i^* c_{pl}, \tag{2}$$

$$J_{FA,i} = \frac{J_{in,i}}{\lambda}, \tag{3}$$

where c_{pl} ($nmol\,ml^{-1}$) is the concentration of unlabeled non-esterified arachidonic or DHA in plasma. A "dilution factor" λ, is defined as the steady-state ratio during [1-^{14}C] PUFA infusion of the specific activity of the brain arachidonoyl-CoA or docosahexaenoyl-CoA pool to the respective plasma specific activity

$$\lambda = \frac{c_{br,CoA}^*/c_{br,CoA}}{c_{pl}^*/c_{pl}}. \tag{4}$$

Because there is no clear evidence of PUFA uptake into the brain other than the passive diffusion of the unesterified fatty acid, the dilution factor λ is believed to reflect only Land's recycling. If other pathways for fatty acid entry into the brain are discovered and quantified it will be possible to adjust the interpretation of the source of dilution, but this will not affect the turnover rate as all fatty acids that enter a phospholipid must pass through their respective acyl-CoA pool and are thus accounted for by the dilution factor [40,52]. A steady state is reached within 1 min after infusion begins [52,53]. The fractional turnover rate of a fatty acid within phospholipid *i*, $F_{FA,i}$ ($\%h^{-1}$), is defined as

$$F_{FA,i} = \frac{J_{FA,i}}{c_{br,i}}. \tag{5}$$

4. Antimanic drugs and the brain arachidonic acid cascade

4.1. Lithium

Lithium (Li^+) was first used to treat bipolar disorder over 50 years ago and is still commonly used to treat its manic phase [54]. We have shown that chronic (6 weeks) intake of chow containing lithium chloride, to produce a therapeutically relevant plasma level ($\sim$0.7 mM) [13,55] of lithium, decreased arachidonic acid turnover within brain phospholipids of unanesthetized rats [13]. This effect was specific for arachidonic acid, as the turnover rate of palmitic acid (16:0) was not altered. Because arachidonic acid is found in the *sn*-2 position of phospholipids, while palmitic acid is esterified to the *sn*-1 position, this suggested an *sn*-2 selective mechanism by which lithium decreased brain arachidonic acid turnover. The decrease in arachidonic acid turnover after chronic lithium was then ascribed to lithium's ability to reduce brain expression (mRNA, protein,

activity) of $cPLA_2$, sparing $sPLA_2$ and $iPLA_2$ [14,56,57]. Chronic lithium also decreased brain COX-2 activity and protein level, and prostaglandin E_2 (PGE_2) concentration [57], without altering the protein level of 5-lipoxygenase or cytochrome P450 [56] (Fig. 2). $cPLA_2$ is selective for arachidonic acid release from brain phospholipids, which was confirmed in an experiment demonstrating that chronic lithium did not decrease the turnover of another *sn*-2 specific fatty acid, DHA [58]. Further investigation showed that chronic lithium decreased the DNA binding activity of the transcription factor, activator protein-2 (AP-2), which regulates $cPLA_2$ and COX-2 gene transcription, but did not affect the binding activity of four other transcription factors that regulate $cPLA_2$ gene expression, AP-1, glucocorticoid response element (GRE), polyoma enhancer activators 3 (PEA3) or nuclear factor κB (NF-κB) in rat frontal cortex [59]. The decreased AP-2 binding activity was ascribed to a combination of decreased AP-2α and AP-2β protein subunits and decreased arachidonic acid dependent PKC activity [59].

4.2. Carbamazepine

Carbamazepine (5H-dibenz[*b*,*f*]azepine-5-carboxamide; tegretol), an anticonvulsant first synthesized in 1960 [60], is now known to be beneficial in bipolar disorder [1]. Like lithium, chronic (30 days) carbamazepine administration to rats, producing therapeutically relevant plasma levels (0.05 mM), decreased brain mRNA, protein and activity of $cPLA_2$ without changing $sPLA_2$ or $iPLA_2$ expression or activity [61]. Consistent with a selective downregulation of $cPLA_2$, chronic carbamazepine decreased the turnover of arachidonic acid but not of DHA in brain phospholipids of unanesthetized rats [39]. Similar to lithium, carbamazepine selectively decreased the $cPLA_2$ and COX-2 gene-regulating transcription factor AP-2, but not other $cPLA_2$ gene regulating transcription factors (AP-1, NF-κB, GRE and PEA3) [62]. Carbamazepine's ability to decrease AP-2 binding activity was ascribed to its ability to decrease cAMP dependent PKA activity and the protein level of its AP-2α subunit [62]. Furthermore, chronic carbamazepine, like lithium, decreased brain COX-2 activity and PGE_2 [61,63], without altering 5-lipoxygenase or cytochrome p450 protein levels and leukotriene B_4 or thromboxane B_2 concentrations [61] (Fig. 2).

4.3. Valproate

Valproate (valproic acid; 2-propylpentanoic acid) is a branched-chain carboxylic acid and like carbamazepine is an anticonvulsant with proven mood-stabilizing properties in the treatment of acute mania [64]. Chronic (30 days) administration of valproate, to produce therapeutically relevant plasma levels (0.2 mM) [65,66], was shown to decrease the turnover rate of arachidonic acid, but not of DHA in rat brain phospholipids [66]. However, unlike lithium and carbamazepine, valproate did not change the expression or activity of $cPLA_2$, nor did it alter $sPLA_2$ or $iPLA_2$ expression, or AP-2 binding activity [14,59,61,62,67,68]. Because of this difference, we examined the effects of valproate on other enzymes regulating arachidonic acid turnover within brain phospholipids, namely Acsl. By isolating microsomes from brain according to the method of Laposata [69], we showed that valproate acts as an ordered noncompetitive inhibitor of Acsl *in vitro* and that its K_i for inhibiting arachidonoyl-CoA formation was lower than that for inhibiting formation of docosahexaenoyl-CoA or palmitoyl-CoA [70]. This difference in K_i was consistent with observations that valproate decreased the turnover rate of arachidonic acid [66], but not of DHA [44] in rat brain phospholipids. Similar to lithium and carbamazepine, chronic valproate decreased rat brain COX activity and PGE_2 concentrations [67], without altering 5-lipoxygenase or cytochrome p450 protein levels and the concentration of leukotriene B_4 [67] (Fig. 2). However, unlike lithium and carbamazepine, valproate did not decrease the activity of the $cPLA_2$ transcription factor AP-2, but valproate decreased COX-2 mRNA and the binding activity of NF-κB, a transcription factor for COX-2 [68]. Valproate also selectively decreased the p50 protein component of NF-κB, without changing the protein or phosphorylation of inhibitor-kappa B alpha or p65 in rat frontal cortex [68].

4.4. Topiramate

Topiramate [2,3:4,5-bis-O-(1-methylethylidenebeta-d-fructopyranose sulfamate] is FDA approved for the management of epilepsy. Based on open-label, investigator-initiated studies [71–73], and its effectiveness in the quinpirole model of mania [74], topiramate was thought to be effective in the management of bipolar symptoms. Because of these early reports, we tested the effect of chronic topiramate on the brain arachidonic acid cascade in rats. Despite achieving therapeutically relevant plasma levels, a decrease in plasma leptin levels and decrease in body weight [75] as reported previously by others [76], chronic topiramate did not decrease brain arachidonic acid turnover, nor did it decrease any measured enzymes of the brain arachidonic acid cascade [41,75]. Subsequently the results of four randomized, placebo-controlled trials indicated that topiramate was not effective in the treatment of bipolar disorder [77].

5. Models of elevated arachidonic acid turnover in relation to bipolar disorder

Lithium, carbamazepine and valproate are reported to decrease N-methyl-D-aspartate (NMDA) mediated

signal transduction [78,79], which is altered in post-mortem samples of patients with bipolar disorder [80–82]. This is of particular interest to the arachidonic acid hypothesis as NMDA mediated receptor stimulation increases the intracellular level of calcium, an activator of $cPLA_2$ [83]. Basselin et al. [84] found that acute administration of subconvulsant doses of NMDA increased the incorporation of arachidonic acid into rat brain and that the increase could be blocked by preadministration of chronic lithium or acute administration of the NMDA antagonist, MK-801 [84]. Another study from our laboratory found that brain $cPLA_2$ protein levels and AP-2 binding activity were elevated in response to chronic NMDA administration to rats [85] and these results coincide with elevated arachidonic acid turnover in brain phospholipids of the unanesthetized rat [99].

Ecological epidemiological observations support a hypothesis that countries with low dietary intakes of fish (a rich source of *n*-3 PUFA) have a higher incidence of bipolar disorder [86], while several [87,88], but not all [89] clinical trials supplementing *n*-3 PUFA reported improved bipolar symptoms. In order to model relatively small declines in *n*-3 PUFA as seen in the general population [90,91], rats were derived of *n*-3 PUFA for 15 weeks post weaning and compared to a group receiving only dietary α-linolenic acid [92]. This deprivation regimen decreased the frontal cortex DHA concentration by 28% [35,93] and increased scores for aggression and depression in the rat, which correspond to symptoms in patients with bipolar disorder [92]. The altered behavioral tests in these rats were accompanied by increased cortical $cPLA_2$ and COX-2 activities, protein expression and mRNA and future testing is needed to confirm if PGE_2 and the turnover of arachidonic acid are increased in this model [35]. Of interest, mice deprived of *n*-3 PUFA for 65 days had augmented amphetamine-induced behavioral sensitization, which could be prevented by chronic lithium [94].

6. Lessons learned and conclusions

The pharmacological approach described herein (chronic lithium, carbamazepine and valproate) in combination with *in vivo* kinetic fatty acid modeling and molecular biology confirms earlier *in vitro* findings that the enzymes which regulate brain fatty acid metabolism are selective. Chronic lithium and carbamazepine decrease the DNA binding activity of the $cPLA_2$ gene regulating transcription factor AP-2, and subsequently $cPLA_2$ mRNA, protein and activity. This downregulated $cPLA_2$ coincides with a selective decrease in the turnover of arachidonic acid in rat brain phospholipids. Valproate is a non-competitive inhibitor of an arachidonic acid-selective Acsl and similar to lithium and carbamazepine, albeit by a different mechanism, also selectively decreases the turnover of arachidonic acid in brain phospholipids. Thus, by targeting $cPLA_2$ or an arachidonic acid-selective Acsl it is possible to selectively inhibit arachidonic acid turnover within brain phospholipids of the unanesthetized rat. More direct testing of the arachidonic acid hypothesis of bipolar disorder could involve the use of drugs that directly inhibit or downregulate Acsl or $cPLA_2$ [95,96]. Candidate compounds or drugs "thought" to be effective in treating bipolar disorder symptoms, such as topiramate, could be screened for their ability to decrease COX-2 and PGE_2, as suggested by the arachidonic acid hypothesis, as well as the turnover of arachidonic acid in rat brain phospholipids in the *in vivo* rat model prior to clinical testing. Because preliminary work in animal models of bipolar disorder suggest there is an upregulation of the brain arachidonic acid cascade, it will be important to test if this extends to humans with bipolar disorder. This could be tested in post-mortem brain samples or *in vivo* using ^{11}C arachidonic acid and position emission tomography [97]. Furthermore, dietary deprivation of *n*-3 PUFA increases rat brain $cPLA_2$ and COX-2 suggesting that chronic low dietary *n*-3 PUFA may increase the brains susceptibility to bipolar disorder or to neuroinflammation [35]. In conclusion, the hypothesis that effective mood stabilizers target key regulatory enzymes of the brain arachidonic acid cascade, thus decreasing the turnover of arachidonic acid but not of DHA in brain phospholipids of the unanesthetized rat, as well as by decreasing COX-2 and PGE_2 concentrations, has shown remarkable consistency in preclinical studies using lithium, carbamazepine, valproate and topiramate (Fig. 2).

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