Review

From Depression-Associated Phospholipid Remodeling to Receptor-Active Lipid Signaling: The LPC-ATX-LPA Axis as a Testable Framework

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From Depression-Associated Phospholipid Remodeling to Receptor-Active Lipid Signaling: The LPC-ATX-LPA Axis as a Testable Framework

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Abstract

Major depressive disorder (MDD) is increasingly understood as a disorder of integrated immune, endocrine, metabolic, neurovascular and synaptic regulation rather than a disease reducible to a single neurotransmitter deficit. Lipidomic studies have repeatedly identified glycerophospholipid abnormalities in MDD, but their mechanistic meaning remains unresolved because changes in bulk lipid abundance do not explain how a metabolic disturbance becomes a receptor-level neural signal. This review argues that the lysophosphatidylcholine (LPC)-autotaxin (ATX)-lysophosphatidic acid (LPA)-LPA receptor (LPAR) axis offers a chemically and biologically coherent route for addressing that gap. LPC is not merely a readout of phospholipid remodeling; it is the direct ATX substrate from which receptor-active LPA can be generated. LPA receptors, in turn, regulate neural excitability, synaptic balance, hippocampal plasticity and stress-related behavior. Human studies report lower serum and cerebrospinal-fluid ATX in MDD, lower CSF LPA 22:6 in MDD and schizophrenia, and negative total-LPA findings that caution against biomarker oversimplification. Experimental studies show that ATX/LPA/LPAR perturbation alters hippocampal function, emotional behavior, stress resilience and synaptic physiology. These findings do not establish a completed depression pathway. They support a more specific hypothesis: depression-relevant ATX-LPA biology may be molecular-species resolved, compartment dependent, regionally organized and shaped by local production-inactivation balance. Reproductive endocrine transitions provide a biologically informative setting for testing this hypothesis because mood vulnerability, systemic lipid remodeling and steroid-sensitive regulation of pathway-adjacent nodes converge in the same clinical context. The decisive unresolved issue is spatial and biochemical: no depression-relevant study has yet demonstrated that defined brain-accessible LPC species, catalytically active ATX, locally generated LPA, local LPA inactivation capacity and receptor-specific circuit output coexist within a single mood-relevant CNS microenvironment. Future work should therefore move from fluid-level association toward pathway closure through targeted and spatial lipidomics, anatomical ATX activity mapping, LPA inactivation assays, BBB/interface analysis, LPAR perturbation and matched circuit or behavioral readouts.

Keywords: depression; glycerophospholipid metabolism; lysophosphatidylcholine; autotaxin; lysophosphatidic acid; LPA receptor; blood-brain barrier; MFSD2A; menopausal transition; postpartum depression; synaptic excitability

1. Introduction

Major depressive disorder (MDD) cannot be adequately explained by monoamine deficiency alone. Monoaminergic mechanisms remain clinically relevant, but they do not account for the delayed onset of many antidepressant responses, treatment resistance, inflammatory comorbidity, metabolic dysregulation, neurovascular abnormalities or impaired synaptic plasticity that are repeatedly described in contemporary depression research [1,2]. The biological problem is therefore

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broader than transmitter depletion. MDD is better approached as a disorder in which several regulatory systems converge on altered brain function.

Lipid metabolism has become one of the most informative entry points into this broader view. Reviews of depression lipid biology have emphasized glycerophospholipids, membrane remodeling and lipid-associated signaling as recurring themes [1,2]. Clinical lipidomic studies have separately reported MDD-associated abnormalities in oxidized fatty acids and acylcarnitines [3], as well as broader serum lipidome changes in real-world patient cohorts [4]. These observations matter because lipids contribute to membrane architecture, inflammatory mediator generation, lipoprotein transport, neurovascular exposure and receptor signaling. Yet a lipidomics signal is not automatically a disease mechanism. A change in lipid abundance may indicate altered synthesis, degradation, carrier distribution or tissue turnover without revealing how a cellular response is produced.

This interpretive gap is particularly important for glycerophospholipid remodeling. Phosphatidylcholine (PC) and related membrane phospholipids can generate lysophospholipid intermediates through phospholipase- and oxidation-dependent reactions [5,6]. Such intermediates are not chemically interchangeable. Some primarily reflect membrane remodeling, whereas others can serve as mobile substrates for extracellular enzymatic conversion. This distinction creates a mechanistic question that current depression lipidomics has not fully resolved: which lipid changes are merely descriptive, and which can plausibly be translated into receptor-level neural output?

Lysophosphatidylcholine (LPC) is central to that question. Psychiatric fluid studies have linked CSF LPA 22:6 to its LPC 22:6 precursor [7], reported serum coupling between total LPA and LPC within MDD [8], and identified an LPA 16:1-containing multilipid serum signature in drug-free female MDD cohorts [9]. These observations do not make LPC a validated disease driver. They show that lysophospholipid biology repeatedly enters the depression literature at a level that is more specific than a generic statement that 'lipids are altered.' LPC also occupies a unique mechanistic position. It can arise from PC turnover during glycerophospholipid remodeling [5,6], and it serves as the immediate substrate from which ATX produces LPA [10]. Its brain-interface relevance depends on molecular species and transport compatibility rather than on total LPC concentration alone [11].

The ATX-LPA-LPAR system then provides a plausible route by which a phospholipid remodeling event could acquire neural relevance. ATX enzymatically converts LPC into LPA [10]. LPA acts through G-protein-coupled LPA receptors and can engage calcium mobilization, PLC/PKC, MAPK, PI3K/Akt and Rho-family signaling [12,13]. These signaling programs are not depression-specific by themselves, but they can influence synaptic organization, neural excitability and stress-related adaptation. The pathway is therefore attractive because it links four levels that are often discussed separately: substrate remodeling, local enzymatic conversion, receptor-active lipid production and functional neural output.

The present review does not claim that LPC-ATX-LPA signaling has already been proven as a unified causal pathway in MDD. That claim would exceed the evidence. Instead, this review asks a more precise question: among the many lipid abnormalities reported in depression, does the LPC-ATX-LPA-LPAR sequence provide a biologically coherent and experimentally testable route from phospholipid remodeling to receptor-level neural dysfunction? This framing extends prior reviews that summarize LPA receptor biology and mood-related phenotypes by beginning one step earlier, at depression-associated lipid remodeling, and by asking how such remodeling could be mechanistically translated into receptor output [14].

Reproductive endocrine transitions sharpen this question without serving as a substitute for direct evidence. The menopausal transition is a clinically defined period of reproductive aging [15], and a subset of women show increased vulnerability to depressive symptoms or depressive disorders during this interval [16]. Estradiol treatment has demonstrated antidepressant efficacy in endocrinologically confirmed perimenopausal depression [17]. The same transition is accompanied by measurable shifts in circulating lipid trajectories and plasma metabolic profiles, including lysophospholipid-related changes [18,19]. Ovariectomized animal models likewise display altered LPC-related metabolic features [20]. The postpartum period highlights a different principle.

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Preclinical work shows that pregnancy-associated GABAA receptor plasticity can shape postpartum behavioral vulnerability [21], while brexanolone and zuranolone trials demonstrate that reproductive-state neurobiology can be therapeutically relevant in postpartum depression [22,23]. These contexts may reveal when a lipid-to-receptor pathway becomes functionally consequential. They do not yet prove that endocrine change drives LPC-ATX-LPA signaling in the brain.

2. Review Scope and Interpretive Boundaries

This article is a critical narrative review. It uses purposive literature sampling rather than a PRISMA-based systematic review or meta-analysis. The objective is not to calculate pooled effect sizes or rank therapeutic interventions. The objective is to construct a mechanistic interpretation of an emerging literature and to define the evidence required before the LPC-ATX-LPA-LPAR sequence can be treated as a pathway-level mechanism in depression.

Literature was identified from PubMed, Web of Science, Scopus and Google Scholar from database inception to 12 May 2026. Search terms included depression, major depressive disorder, anxiety, chronic stress, glycerophospholipid, lysophosphatidylcholine, LPC, autotaxin, ATX, ENPP2, lysophosphatidic acid, LPA, LPA receptor, LPAR1, LPAR2, LPAR3, LPAR5, PRG-1, MFSD2A, blood-brain barrier, phospholipase A2, lipidomics, perimenopause, postpartum depression, estrogen, progesterone, neurosteroid, antidepressant and Chinese herbal formula. Reference lists from key mechanistic studies and recent reviews were also considered.

The review separates evidence into distinct interpretive layers. Biochemical studies establish ATX-dependent conversion of LPC to LPA [10], cell-surface localization of ATX-mediated LPA production [24], and selective ATX-facilitated receptor signaling [25]. Human MDD studies provide data on CSF LPA 22:6 [7], serum and CSF ATX abundance [26], total-LPA analyses in CSF and plasma [27], serum LPA/LPC measurements [8], and LPA 16:1-containing lipidomic signatures [9]. Experimental evidence is considered at several linked levels. Synaptic studies define local lipid-phosphate signaling and receptor-proximal neuronal output [28–30]. Chronic-stress work identifies a hippocampal ATX/LPA deficit that is behaviorally relevant [31]. Receptor-focused studies then address stress-associated hippocampal LPA species [32], ventral hippocampal excitatory-inhibitory transcriptional changes [33], depression-like functional brain activity after LPA1 disruption [34], neurogenesis-sensitive emotional phenotypes [35], GABAergic circuit abnormalities [36], HPA-axis dysregulation [37], sex-dependent affective and transcriptional phenotypes [38], and anxiety-linked LPA 16:0 vulnerability signals [39]. Endocrine-transition studies are used only to define validation contexts. They include perimenopausal depression risk [16], reproductive-stage criteria [15], estradiol treatment response [17], menopause-associated lipid remodeling [18–20], postpartum neurosteroid-sensitive biology [21–23], and estradiol-sensitive brain connectivity in perimenopausal depression [40]. Intervention studies are treated as probes, not as proof. The relevant examples include LPAR1-biased antidepressant pharmacology [41], phospholipid metabolic modulation [42], BBB protection [43], LPA1-linked neuronal signaling [44], a perimenopausal brain-liver model [45], and Yueju Pill-associated antidepressant-like effects [46].

3. From Depression-Related Phospholipid Remodeling to the LPC-ATX-LPA-LPAR Hypothesis

3.1. Why Glycerophospholipid Remodeling Narrows the Field Toward LPC

Depression-associated lipid changes are heterogeneous, and that heterogeneity is biologically meaningful. Reviews of depression lipid biology show that reported lipid findings span multiple classes and mechanistic levels [1,2]. Case-control lipidomics has also identified distinct abnormalities in oxidized fatty acids, acylcarnitines and broader serum lipid profiles [3,4]. Such findings are valuable for phenotype mapping, but they do not automatically identify a mechanistic axis. A review that seeks a pathway-level explanation must therefore privilege lipid changes that satisfy two

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conditions: they should recur in depression-relevant studies, and they should connect to a chemically defined downstream signaling route.

Glycerophospholipid remodeling meets the first condition and creates a rational search space for the second. PC and related phospholipids are major membrane constituents, and their remodeling can generate lysophospholipids with distinct acyl-chain compositions and biological behavior [5,6]. This is important because a bulk decline or increase in a phospholipid class can conceal opposite changes among individual molecular species. The same caution applies to LPC. Total LPC is an analytically convenient measure, but it is a poor substitute for the availability of specific LPC species that can enter transport routes, encounter ATX or participate in receptor-active LPA generation.

LPC therefore deserves attention not simply because it is detected in depression-related lipid studies, but because it converts the lipidomics problem into a tractable biochemical problem. Omori et al. reported lower CSF LPA 22:6 in MDD and schizophrenia, and this signal related to LPC 22:6 rather than to total LPA measures [7]. Riya et al. found no group-level difference in serum total LPA or LPC between MDD patients and controls, but they observed a positive correlation between the two lipid classes within the MDD group [8]. Kim et al. identified LPA 16:1 within multilipid panels that differentiated current MDD, remitted MDD and controls in drug-free female cohorts [9]. These studies do not establish a disease pathway, but they collectively show why the field must move beyond total lipid abundance and toward molecular species with interpretable biochemical relationships.

LPC is also positioned at a transport interface. Nguyen et al. showed that MFSD2A transports DHA in LPC-linked form and also transports selected long-chain plasma LPC species, including LPC-oleate and LPC-palmitate, with lower transport capacity than LPC-DHA [11]. In the same study, LPC species with acyl chains shorter than C14 were not efficiently transported by MFSD2A [11]. Structural work later clarified how substrate binding can drive conformational transitions in this transporter [47]. Independently, Mfsd2a loss disrupts BBB formation and increases endothelial transcytosis, showing that its transport function sits within a broader barrier-regulatory program [48]. These findings do not show that depression-associated LPC abnormalities automatically enter the brain. They show something more important for this review: peripheral ‘LPC’ is not a uniform CNS input. The probability that a circulating LPC species alters brain substrate availability depends in part on molecular species and transport compatibility. This point directly strengthens the case for species-resolved rather than total-LPC interpretation.

3.2. Why ATX Makes LPC Mechanistically Consequential

ATX is the catalytic hinge that transforms LPC from a remodeling product into a candidate receptor-active signal. Umezu-Goto et al. established that ATX has lysophospholipase D activity and generates LPA from LPC [10]. This biochemical step is simple to state, but its implications are often underestimated. Once LPC is recognized as an ATX substrate, the relevant question is no longer only whether LPC is high or low. The question becomes whether a defined LPC species is available in the same biological compartment as catalytically competent ATX.

ATX biology also argues against interpreting circulating enzyme abundance as a direct substitute for local signaling. Fulkerson et al. showed that ATX can bind beta1 and beta3 integrins, thereby localizing LPA production to cell surfaces [24]. Salgado-Polo et al. later demonstrated that ATX facilitates selective LPA receptor signaling, indicating that ATX is not merely a diffusible enzyme that passively raises bulk LPA concentration [25]. ATX can shape ligand delivery geometry, receptor exposure and signaling selectivity. For depression research, this means that serum ATX, CSF ATX, brain-region ATX expression and spatial ATX activity are related readouts, but they are not interchangeable.

This point provides the first major reason why human and experimental findings may appear inconsistent. A patient can have reduced CSF ATX abundance without a parallel measurement of parenchymal ATX activity. A mouse brain homogenate can show lower hippocampal ATX without revealing whether a microdomain near synapses or a vascular interface is locally enriched or

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depleted. Fluid-level measures are clinically informative, but they cannot alone define the anatomical site or functional consequence of LPC-to-LPA conversion.

3.3. Why LPA Receptors Connect Phospholipid Remodeling to Mood-Relevant Neural Output

The hypothesis becomes neurobiologically relevant only when LPA production is connected to receptor output. Six major LPA receptors, LPAR1 through LPAR6, couple to overlapping but non-identical G-protein programs and thereby influence calcium mobilization, PLC/PKC activity, MAPK signaling, PI3K/Akt signaling and cytoskeletal regulation [12,13]. A receptor-based account must therefore specify more than "LPA changes." It must ask which LPA species changes, which receptor subtype is available in the relevant cell population and which functional output follows.

Among receptor subtypes, LPAR1 currently has the broadest mood-related evidence base. A recent systematic review identified LPAR1 as the most recurrent receptor subtype in the literature linking LPA biology to emotional regulation [14]. Primary studies then show that LPA1 deficiency or blockade can modify hippocampal LPA species [32], alter stress-related behavior and ventral hippocampal excitatory-inhibitory gene profiles [33], and induce depression-like behavior with related changes in brain functional activity [34]. Other models connect LPA/LPA1 perturbation to adult hippocampal neurogenesis [35], GABAergic deficits and coping abnormalities [36], altered HPA-axis regulation [37], and sex-dependent emotional phenotypes [38]. Yet the field should not collapse all mood-relevant LPA biology into LPAR1. Trimbuch et al. showed that PRG-1 restrains extracellular lipid-phosphate signaling at glutamatergic synapses and that loss of PRG-1 increases excitatory transmission through a presynaptic LPA2-dependent mechanism [28]. Tüscher et al. extended this logic by linking PRG-1 dysfunction to intermediate psychiatric phenotypes in human carriers and stress-vulnerability phenotypes in mice; selected mouse phenotypes were normalized by ATX inhibition [29]. These findings establish that local lipid-phosphate signaling can alter circuit-relevant physiology even when the key receptor node is not LPAR1.

Direct neuronal physiology reinforces this interpretation. Brandt et al. reported that LPA selectively modulates excitatory transmission and intracellular calcium responses in hippocampal neurons [30]. The importance of this study lies not in claiming that hippocampal LPA signaling is automatically pathogenic in MDD. Its importance lies in demonstrating a functional bridge from a bioactive lysophospholipid to synaptic output. Once this bridge is accepted, depression-related LPC/ATX/LPA findings can be evaluated by whether they converge on a receptor- and circuit-level consequence rather than by whether every fluid compartment changes in the same numerical direction.

4. What the Current Evidence Shows, and Why It Does Not Move in a Single Direction

4.1. Human MDD Evidence Identifies Relevant Nodes, not a Closed Pathway

Human studies provide the most clinically direct but also the most anatomically compressed evidence. Itagaki et al. reported lower serum ATX in 37 patients with MDD undergoing electroconvulsive therapy than in 47 nondepressed controls. In a separate sample, CSF ATX was also lower in 26 MDD patients than in 27 controls [26]. Serum ATX increased after electroconvulsive therapy and was inversely related to depressive symptom burden before treatment [26]. These findings support state-linked ATX abnormality in MDD, but they do not identify the tissue source of the ATX signal or the site at which LPA would act.

Omori et al. moved the field from total analyte measurement toward molecular-species interpretation. They found lower CSF LPA 22:6 in patients with MDD and schizophrenia than in healthy controls, whereas total CSF LPA was less informative [7]. The same study reported that CSF LPA 22:6 was associated with LPC 22:6. However, CSF ATX activity and PLPP1 did not differ significantly across groups, and LPA 22:6 did not correlate with ATX activity in the patient groups [7]. This combination of findings is critical. It indicates that a specific lysophospholipid abnormality

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can exist without supporting a simple model in which lower bulk CSF ATX activity directly explains lower CSF LPA 22:6.

The same findings also expose a second interpretive gap: local LPA signaling is determined by both production and extracellular inactivation. Direct in vivo evidence shows that LPP1/PLPP1 degrades extracellular LPA and contributes to its clearance [49]. Omori et al. measured CSF PLPP1 and found no significant between-group difference among MDD, schizophrenia and control cohorts [7]. This negative result does not support a simple CSF-level PLPP1 explanation for reduced LPA 22:6. It also does not exclude membrane-proximal or region-specific changes in LPA degradation within mood-relevant CNS compartments, because bulk CSF PLPP1 cannot resolve local phosphatase activity at synaptic, glial or barrier-adjacent signaling surfaces. Whether PLPP1 or related PLPP enzymes contribute to compartment-specific LPA signal imbalance in depression therefore remains an open question.

Negative and mixed biomarker studies provide equally important constraints. Gotoh et al. found no association between total LPA in CSF or plasma and MDD diagnosis, symptom severity or psychotropic medication [27]. Riya et al. reported no significant between-group difference in serum total LPA or LPC, even though LPA and LPC correlated positively within the MDD group [8]. These findings should not be dismissed as uninformative. They directly argue against the idea that total circulating LPA or LPC can serve as a general-purpose diagnostic proxy for depression-relevant receptor signaling.

Kim et al. offer a complementary perspective. In female drug-free subjects, LPA 16:1 contributed to multilipid panels that distinguished current MDD, remitted MDD and controls [9]. This result is not evidence of a stand-alone biomarker, and it does not localize the underlying biology to brain ATX-LPA signaling. It nevertheless strengthens the argument that molecular-species-resolved lipid analysis may reveal depression-relevant information that disappears when measurements are collapsed into total LPA or total LPC pools.

4.2. Experimental Models Connect the Pathway to Hippocampal Plasticity, Stress Behavior and Synaptic Physiology

Experimental models provide the functional depth that human fluid studies currently lack. In a chronic unpredictable mild stress model, Wang et al. reported reduced hippocampal ATX and LPA. Hippocampal AAV-ATX supplementation improved depression-like behavior and restored synaptic-plasticity-related molecular readouts [31]. This study matters because it links a regional ATX/LPA deficit to both behavioral and molecular outcomes within a depression-relevant model. At the same time, it leaves a central question unresolved: the study does not establish which LPC species supplied the relevant substrate pool or how that substrate reached the hippocampal ATX compartment.

Receptor-focused studies show that LPA biology is highly context dependent. Tabbai et al. demonstrated that acute stress and LPA1 deficiency reshape hippocampal LPA species, with anxiety-related behavior associated with LPA 16:0 and locomotor measures associated with LPA 18:0 [32]. Moreno-Fernández et al. reported that the LPA-LPA1 pathway modifies stress-related behavior and ventral hippocampal excitatory-inhibitory gene profiles [33]. Moreno-Fernández et al. also showed that either genetic deletion or acute pharmacological blockade of LPA1 induces depression-like behavior with related changes in brain functional activity [34]. These findings show that LPA signaling cannot be interpreted through a single “more is worse” or “less is worse” rule.

Longer-term ligand and receptor manipulations reinforce this conclusion. Chronic central C18:1 LPA administration produced antidepressant-like effects and enhanced adult hippocampal neurogenesis, whereas chronic antagonism of LPA1-3 receptors induced anxiety- and depression-like behaviors and reduced neurogenesis [35]. In a related line of work, LPA1 deficiency was linked to GABAergic deficits, anxiety-like behavior and coping abnormalities, and interneuron precursor transplantation partially improved the phenotype [36]. These data indicate that LPA signaling

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contributes to circuit balance and adaptive behavior, but that its direction of effect depends on receptor context, ligand exposure pattern and neural substrate.

Recent studies add endocrine, sex-stratified and translational dimensions. Moreno-Fernández et al. linked LPA1 deficiency to social avoidance, impaired dexamethasone suppression and abnormal corticosterone rhythmicity [37]. Sánchez-Marín et al. reported sex-dependent emotional phenotypes and region-dependent neurotransmitter-related transcriptional changes in LPA1-deficient mice [38]. Larrieu et al. found higher serum LPA 16:0 in high-risk susceptible humans and high-anxiety mice, and they showed that platelet-derived LPA 16:0 reduces adult hippocampal neurogenesis and stress resilience through LPA1-dependent mechanisms [39]. These findings are especially informative because they show that endogenous LPA species can be behaviorally relevant. They should still be interpreted with care: the strongest cross-species evidence currently centers on anxiety-related vulnerability rather than on clinically defined MDD.

Human and experimental evidence now support a restrained but substantive conclusion. Clinical studies identify ATX changes in MDD fluids [26], species-specific CSF LPA 22:6 abnormalities [7], and negative total-LPA findings that limit biomarker claims [8,27]. Experimental work separately links hippocampal ATX/LPA deficiency to CUMS-related behavioral and synaptic-plasticity phenotypes [31]. PRG-1/LPA2 and neuronal physiology studies connect local lipid-phosphate signaling to excitatory synaptic output [28–30]. LPA1-centered models connect receptor perturbation to stress behavior and excitatory-inhibitory transcriptional balance [32,33], depression-like behavior with altered functional brain activity [34], neurogenesis [35], inhibitory-circuit integrity [36], HPA-axis regulation [37], and sex-dependent emotional phenotypes [38]. Cross-species anxiety-focused evidence further shows that circulating LPA 16:0 can track vulnerability in a specific affective domain [39]. These findings show that the pathway nodes are biologically relevant. They do not yet show that the nodes form one continuous depression mechanism within the same compartment.

Table 1. Evidence architecture for ATX/LPA/LPAR involvement in depression and mood-relevant biology through 12 May 2026.

Study and evidence level	Cohort/model and sample	Compartment or region	Main ATX/LPA/LPAR finding	Interpretive boundary
A. Human clinical, CSF, and serum lipidomic evidence				
Itagaki et al., 2019 [26]; human MDD direct evidence	Serum: 37 MDD patients undergoing ECT and 47 controls; CSF: 26 MDD patients and 27 controls.	Serum and CSF.	Serum ATX and CSF ATX were lower in MDD. Serum ATX increased after ECT and related inversely to depressive symptom burden.	Supports state-linked ATX abnormality, not source attribution or local brain conversion.
Omori et al., 2021 [7]; human psychiatric fluid evidence	CSF from 26 MDD patients, 27 schizophrenia patients and 27 healthy controls.	CSF.	LPA 22:6 was lower in MDD and schizophrenia. Total CSF LPA was less informative. LPA 22:6 rel	Supports species specificity, but it does not establish an ATX-driven conversion site. The signal w

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			ated to LPC 22:6, while ATX activity and PLPP1 were not different across groups; LPA 22:6 did not correlate with ATX activity in the patient groups.	as not MDD-specific and remained uncoupled from measured CSF ATX activity in patients.
Gotoh et al., 2019 [27]; human negative biomarker evidence	CSF: 52 MDD patients and 49 controls; plasma: 47 MDD patients and 44 controls.	CSF and plasma.	Total LPA showed no association with MDD diagnosis, symptom severity or psychotropic medication.	Directly argues against total LPA as a practical diagnostic or severity biomarker of MDD. It does not test molecular species, anatomical ATX pools or local receptor output.
Riya et al., 2020 [8]; human serum evidence	53 MDD patients and 50 matched healthy controls.	Serum.	Serum LPA and LPC did not differ significantly between groups. Serum LPA and LPC correlated positively within the MDD group.	Shows that total serum LPA and LPC are not sufficient for group separation. The within-MDD correlation suggests biochemical coupling, not disease-specific elevation.
Kim et al., 2018 [9]; human serum lipidomics	Female drug-free subjects. Discovery: pooled serum from 10 current MDD, 10 remitted MDD and 10 controls. Verification: 25 individuals per group.	Serum.	LPA 16:1 entered multilipid panels that distinguished current MDD from controls and remitted MDD from controls.	Supports species-resolved lipid signatures, not a stand-alone causal axis.
B. Stress, receptor-loss, ligand-perturbation, and circuit-relevant models				

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Wang et al., 2024 [31]; CUMS direct experimental evidence	CUMS mice; hippocampal AAV-ATX supplementation; HT22-cell assays.	Hippocampus and cultured neurons.	CUMS reduced hippocampal ATX and LPA. Hippocampal ATX supplementation alleviated depression-like behavior, and LPA affected synapse-related proteins and ERK/CREB-linked plasticity readouts.	Supports a region-level ATX/LPA node, not a proven peripheral-to-brain LPC route.
Tabbai et al., 2019 [32]; stress and species-level receptor model	Wild-type and maLPA1-null mice exposed to acute stress.	Hippocampus.	Stress and LPA1 deficiency reshaped hippocampal LPA species. Anxiety-related behavior was associated with LPA 16:0, and locomotor measures were associated with LPA 18:0.	Supports receptor-dependent species redistribution, not MDD diagnosis.
Moreno-Fernández et al., 2020 [33]; chronic stress plus pathway manipulation	Mouse chronic-stress model with LPA-LPA1 pathway analysis.	Ventral hippocampus and behavior.	The LPA-LPA1 receptor pathway modified stress-related behavior and ventral hippocampal excitatory-inhibitory gene profiles.	Shows strong context dependence; LPA exposure is not uniformly beneficial or harmful.
Moreno-Fernández et al., 2018 [34]; genetic versus acute LPA1 inhibition	maLPA1-null mice and wild-type mice after acute LPA1 blockade.	Behavior and functional brain activity.	Both permanent deletion and acute pharmacological LPA1 inhibition induced depression-like behavior with related brain-activity changes.	Supports behavioral necessity of LPA1 signaling.

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Rosell-Valle et al., 2021 [35]; chronic central ligand/receptor modulation	Mice receiving chronic C18:1 LPA or chronic LPA1-3 receptor antagonism.	Mouse brain and hippocampus.	Chronic C18:1 LPA produced antidepressant-like effects and enhanced adult hippocampal neurogenesis. Chronic LPA1-3 antagonism induced anxiety- and depression-like behavior and reduced neurogenesis.	Demonstrates dose, species and receptor-context dependence.
Rosell-Valle et al., 2021 [36]; interneuron-linked receptor phenotype	LPA1-deficient mice with interneuron precursor transplantation.	Dorsal hippocampus.	LPA1 loss was associated with GABAergic deficits, anxiety-like and coping abnormalities. Interneuron precursor transplantation improved the phenotype.	Connects LPA1 signaling to inhibitory-circuit integrity.
Moreno-Fernández et al., 2023 [37]; HPA-axis and social behavior	maLPA1-null mice.	Social behavior and endocrine stress regulation.	Mice showed social avoidance, a blunted dexamethasone response and abnormal corticosterone rhythmicity.	Extends receptor relevance to stress-system regulation.
Sánchez-Marín et al., 2025 [38]; sex-stratified LPA1-deficiency model	Male and female maLPA1-null mice.	Plasma lipid signaling, amygdala and medial prefrontal cortex transcriptional readouts.	LPA1 deficiency produced sex-dependent emotional phenotypes and region-dependent neurotransmitter-related transcriptional changes, together with altered plasma LPA/2-AG signaling.	Supports sex and region as modifiers of receptor interpretation.

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C. Mechanistic bridge and cross-species translational studies				
Brandt et al., 2025 [30]; neuronal physiology	Cultured hippocampal neurons.	Hippocampal neurons.	LPA modulated excitatory transmission and intracellular calcium responses.	Provides cellular output, not disease evidence by itself.
Larrieu et al., 2026 [39]; increased endogenous LPA species in anxiety	Humans: 26 controls, 19 high-risk susceptible individuals and 14 high-risk resilient individuals; anxiety-stratified mice.	Serum, dentate gyrus and adult neural stem/progenitor cells.	Serum LPA 16:0 was higher in high-risk susceptible humans and high-anxiety mice. LPA 16:0 tracked anxiety, reduced adult neural progenitor proliferation and reduced stress resilience through LPA1-dependent mechanisms.	Strong evidence for increased endogenous circulating LPA 16:0 in anxiety-related vulnerability, but not direct MDD-specific evidence.
Tüscher et al., 2024 [29]; translational local lipid-signaling evidence	Human PRG-1 R345T carriers and Prg-1 mutant mice.	Cortical synaptic physiology, fear/memory tasks and mouse behavior.	PRG-1 dysfunction produced intermediate psychiatric phenotypes in humans and increased anxiety, depressive features and low stress resilience in mice. ATX inhibition normalized selected mouse phenotypes.	Supports local ATX-linked lipid-signal excess rather than a bulk-fluid biomarker.

4.3. Why the Findings Diverge: Species, Compartment, Anatomical Pool and Receptor Context

The literature appears contradictory only if one assumes that ATX abundance, LPA concentration, receptor signaling and behavior must move in parallel across serum, CSF and brain tissue. Current datasets do not support that assumption. MDD studies report lower serum and CSF ATX [26], lower CSF LPA 22:6 [7], no diagnostic association for total LPA in CSF or plasma [27], and no serum group difference in total LPA or LPC [8]. A separate serum lipidomic study identified LPA 16:1 within a multilipid signature in drug-free female MDD cohorts [9]. Anxiety-focused translational work, in contrast, linked higher serum LPA 16:0 to vulnerability and reduced stress resilience [39].

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These are not interchangeable measurements. They refer to different molecular species, biological compartments and disease or symptom contexts.

A more defensible interpretation is compartment resolved and molecular-species resolved. Under this interpretation, lower CSF LPA 22:6 can coexist with a locally altered ATX/LPA signaling pool in a specific brain region. A negative total-plasma LPA study can coexist with behaviorally relevant changes in one LPA species or in one receptor-defined neural circuit. These scenarios should not be treated as automatic confirmation of the pathway. They specify the measurement resolution required to test it.

This distinction changes how disagreement is read. Negative total-LPA studies weaken broad biomarker claims, but they do not by themselves refute local receptor-active LPA signaling [8,27]. Conversely, hippocampal ATX/LPA rescue in CUMS mice supports region-level relevance [31]. LPA1-focused studies then demonstrate receptor-dependent effects on stress behavior and excitatory-inhibitory gene programs [32,33], depression-like behavior with altered functional brain activity [34], adult neurogenesis [35], inhibitory-circuit integrity [36], endocrine stress regulation [37], and sex-dependent emotional phenotypes [38]. The anxiety-linked LPA 16:0 findings further show that an endogenous circulating LPA species can track vulnerability in a specific affective domain [39]. None of these animal or translational findings directly explains fluid changes in MDD patients. The task is therefore not to force all datasets into artificial concordance. The task is to determine whether a defined substrate pool, a defined ATX production pool, a defined LPA inactivation state and a defined receptor output converge within the same pathogenic context.

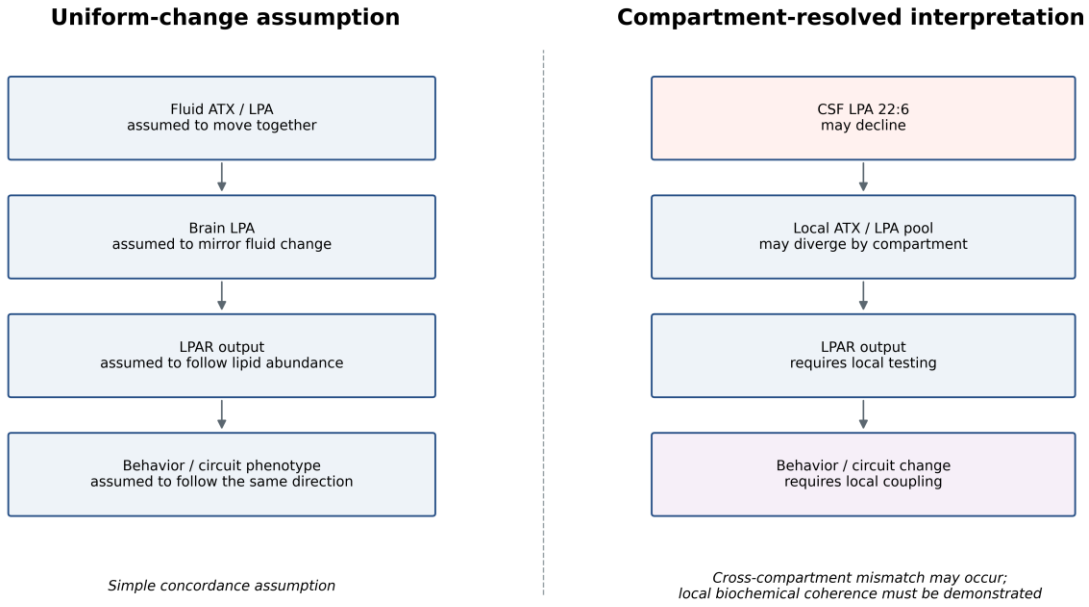

Figure 1. Uniform-change assumption versus compartment-resolved interpretation. A single-direction model expects fluid ATX/LPA changes, brain LPA changes, receptor output and behavioral outcomes to move together. The evidence reviewed here does not support that assumption. A compartment-resolved interpretation allows cross-compartment mismatch but requires local biochemical coherence: a defined LPC/LPA species, catalytically active ATX and receptor-specific output must be demonstrated within the relevant CNS context.

5. The Decisive Missing Link: Spatial Convergence of Brain-Accessible LPC Species and Catalytically Active ATX

The central evidence gap is now sharply defined. The unresolved problem is not whether ATX can generate LPA. That point is established biochemically [10]. The unresolved problem is not whether LPA signaling can alter synaptic physiology. PRG-1/LPA2 work demonstrates lipid-

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phosphate control of excitatory transmission [28,29], and direct neuronal experiments show that LPA modulates hippocampal excitatory transmission and intracellular calcium responses [30]. The unresolved problem is also not whether LPA receptor perturbation can influence emotion-related or stress-related phenotypes. LPA1-focused studies have shown effects on hippocampal LPA species [32], chronic-stress behavioral and transcriptional responses [33], depression-like functional brain activity [34], neurogenesis [35], GABAergic circuitry [36], HPA-axis regulation [37], sex-dependent emotional phenotypes [38], and anxiety-related vulnerability [39]. The deeper question is whether, in a depression-relevant CNS microenvironment, a brain-accessible LPC species, catalytically active ATX, locally generated LPA, local LPA inactivation capacity and receptor-specific circuit output coexist in one experimentally demonstrable sequence.

Human fluid studies reveal why this gap matters. Lower serum and CSF ATX in MDD indicate altered ATX biology in psychiatric illness [26]. Lower CSF LPA 22:6 indicates a species-specific lysophospholipid abnormality [7]. Yet neither finding localizes the ATX source, identifies the LPC source or proves where receptor-active LPA is generated. Omori et al. further showed that CSF LPA 22:6 did not correlate with measured CSF ATX activity in the patient groups [7]. This result prevents a direct leap from fluid abnormality to local catalytic mechanism.

Central ATX anatomy is more complex than a single “brain ATX” variable suggests. Savaskan et al. reported ATX expression in leptomeningeal cells and oligodendrocyte precursor cells, with reactive astrocytic upregulation after neurotrauma [50]. Tachikawa et al. later found high ATX expression in the choroid plexus of developing and adult mouse brain, with predominant localization at the cerebrospinal-fluid-facing apical side of choroid plexus epithelial cells [51]. These data imply that CSF-facing ATX, meningeal ATX, glial ATX and parenchymal ATX should not be treated as interchangeable pools. They may differ in substrate access, local LPA generation and relevance to neural circuits.

The LPC side of the pathway is equally unresolved. MFSD2A-mediated transport establishes that CNS substrate access is selective rather than generic. The strongest evidence concerns LPC-DHA, although selected long-chain LPC species such as LPC-oleate and LPC-palmitate can also be transported with lower capacity [11]. Stress-related BBB dysfunction and higher regional BBB permeability in patients with MDD establish a separate interface abnormality that may alter exposure to circulating molecules [52,53]. Local PC remodeling within neural and glial membranes provides yet another potential LPC source [5,6]. These routes are mechanistically distinct. Regulated transport, barrier leakage and local membrane remodeling should not be compressed into one generic statement that ‘peripheral LPC reaches the brain.’

This anatomical uncertainty explains why future studies must combine source mapping with functional testing. CSF can provide an interface-proximal readout, but it cannot substitute for brain-region-specific receptor output. Brain homogenates can show that an analyte is present, but they can erase perivascular, choroid-plexus, synaptic or glial microenvironments. The key experiment is not simply to measure more ATX or more LPA. The key experiment is to show that the relevant substrate, enzyme, product and receptor output occupy the same biologically meaningful space.

The pathway becomes stronger only when the following sequence is demonstrated within one model or cohort: a defined LPC species is available at a relevant CNS interface or parenchymal compartment; catalytically active ATX is present in the same location; a specific LPA species is generated; local LPA inactivation capacity is characterized; a defined LPAR subtype and downstream signaling program respond; and the resulting output tracks with circuit or behavioral change. Without that sequence, the literature supports an important framework, but not a completed CNS production route.

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Table 2. Direct-evidence requirements for pathway-level validation of the LPC-ATX-LPA-LPAR sequence in depression-relevant biology.

Layer	Minimum measurement	Model-supporting pattern	Model-weakening pattern
Fluid lipid layer	Plasma, serum or CSF PC/LPC/LPA species, not only total LPC or total LPA.	Defined species differ across compartments, such as CSF LPA 22:6 changing while total LPA is unchanged.	Only total lipid values are measured, or species changes do not replicate.
CNS substrate-enzyme encounter layer	Defined LPC species, anatomical ATX localization or activity, and where feasible labeled substrate tracing or spatial lipidomics in interface and parenchymal compartments.	A predicted LPC species and catalytically active ATX converge in the same CNS compartment, with local LPA production linked to the downstream model.	LPC species and active ATX are not spatially linked, or interface pools cannot be connected to parenchymal output.
Local production-inactivation layer	ATX abundance, ATX activity, local LPA species and, where relevant, PLPP1/LPA-dephosphorylating activity in brain region or interface tissue.	Local LPA species relate to a defined production-inactivation state more strongly than to total fluid lipid levels.	Local ATX activity, LPA species and LPA inactivation readouts do not relate to receptor output or behavior.
Receptor output layer	LPAR subtype expression, calcium signaling, PLC/PKC, E/I markers, synaptic readouts.	Specific LPAR subtype output changes in the predicted brain region or cell type.	Receptor signaling changes are absent or nonspecific.
Behavior or circuit layer	Depressive-like behavior, stress adaptation, electrophysiology or imaging readouts.	Pathway perturbation modifies both molecular output and behavior or circuit readout.	Perturbation changes molecular markers but not behavior or circuit function.

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6. Reproductive Endocrine Transitions as Biologically Informative Validation Contexts

6.1. Why the Menopausal Transition and Postpartum Period Matter to This Hypothesis

Reproductive endocrine transitions are relevant to the LPC-ATX-LPA hypothesis because they combine three features that are rarely aligned in a single setting: elevated mood vulnerability, substantial steroid variation and measurable systemic lipid remodeling. The menopausal transition is a defined stage of reproductive aging, and the STRAW+10 framework provides clinically usable staging criteria [15]. Epidemiological and clinical work indicates increased vulnerability to depressive symptoms or depressive disorders during the transition and early postmenopausal years in a subset of women [16]. Estradiol treatment has also shown antidepressant efficacy in endocrinologically confirmed perimenopausal depression [17]. These findings establish that ovarian steroid variation is clinically relevant to mood disturbance, even though they do not identify the molecular pathway that mediates this relationship.

The menopausal transition also carries a metabolic signature. Longitudinal and metabolomic studies report menopause-associated changes in circulating lipids, including shifts in acylcarnitines, fatty acids, lysophosphatidylcholines and lysophosphatidylethanolamines [18,19]. Ovariectomized animal models likewise show LPC-related lipid changes [20]. These studies do not prove ATX-LPA involvement in menopausal-transition depression. They show that a clinically meaningful endocrine transition is accompanied by systemic lipid remodeling of the very class from which the proposed LPC-ATX-LPA route begins.

The postpartum period contributes a complementary principle. Pregnancy and postpartum states are accompanied by major neurosteroid fluctuations, and preclinical work has shown that GABAA receptor plasticity during pregnancy can affect postpartum behavioral vulnerability [21]. The clinical efficacy of brexanolone and zuranolone in postpartum depression further demonstrates that reproductive-state neurobiology can be therapeutically relevant to depressive syndromes [22,23]. Postpartum depression does not provide direct evidence for ATX-LPA signaling. It provides evidence that rapid endocrine transition can alter neural gain and mood vulnerability, thereby making receptor-sensitive lipid signaling a reasonable target for future testing.

6.2. How Endocrine Biology Supports the Hypothesis Without Proving It

The most provocative endocrine evidence sits adjacent to, rather than directly within, the depression pathway. Estradiol and other ovarian steroids modulate PLA2 activity in hormone-responsive cell models [54,55]. Uterine Enpp2/ATX expression varies across the estrous cycle and responds to estradiol exposure [56]. Progesterone and estrogen regulate uterine LPA3 expression in mice [57]. These studies show that steroid state can influence multiple nodes that are upstream of, or embedded within, the LPC-ATX-LPA-LPAR sequence. However, the relevant tissues are mainly uterine or other peripheral hormone-responsive systems, not hippocampus, prefrontal cortex or other depression-relevant brain regions.

This limitation should not lead to dismissal. It should define the next biological question. If endocrine state can reshape pathway-adjacent molecules in steroid-sensitive tissues, and if reproductive transitions can alter mood vulnerability and central network organization, then it becomes reasonable to ask whether analogous regulation exists in brain-interface or brain-region-specific compartments. Hynd et al. reported that transdermal estradiol modulates resting-state connectivity in women with perimenopausal depression, with changes involving reward- and emotion-related networks [40]. This observation does not implicate ATX-LPA directly. It demonstrates that endocrine manipulation can alter central functional organization in the very clinical context proposed for pathway validation.

Reproductive transitions should therefore be interpreted as sensitized test conditions, not as already proven upstream drivers of the LPC-ATX-LPA pathway. Their value lies in experimental

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alignment. They allow investigators to ask whether steroid state, systemic lipid remodeling, BBB/interface biology and receptor-level neural output change together in a way that cannot be seen in unstratified MDD cohorts. A well-designed study would not assume that estrogen fluctuation activates the pathway. It would test whether endocrine state modifies substrate availability, ATX localization or activity, LPA species, receptor output and circuit consequences within the same design.

7. Pharmacological Relevance: Intervention Clues Without Premature Mechanistic Closure

Pharmacological evidence strengthens the biological interest of the pathway, but it should be used with restraint. Kajitani et al. reported that amitriptyline directly binds LPAR1 and acts as a G protein-biased LPAR1 agonist [41]. The same study found that this biased agonism characterized tricyclic antidepressants but not SSRIs, SNRIs, ketamine, vortioxetine or trazodone [41]. This finding matters because it establishes a direct receptor-level connection between an established antidepressant class and LPA signaling. It does not show that ATX activity or circulating LPC/LPA species predict treatment response, and it does not prove that tricyclic efficacy in patients is mediated primarily through LPAR1.

Multi-component interventions provide a different kind of clue. Chaihu-Shu-Gan-San altered phospholipid and bile-acid metabolism in a chronic unpredictable stress rat model [42]. Xiao-Yao-San reduced stress-associated BBB injury through glucocorticoid receptor-mediated upregulation of occludin in experimental systems [43]. Saikosaponin-d was linked to LPA1-associated neuronal apoptotic signaling in vitro [44]. A perimenopausal depression model further used a brain-liver communication framework to examine Chaihu-Shugan-San [45]. These studies do not close the LPC-ATX-LPA-LPAR chain. They indicate that metabolism, barrier integrity and LPA-related receptor biology are experimentally modifiable in settings relevant to stress and affective vulnerability.

Yueju Pill provides a particularly useful example of how a formula-level intervention could be repurposed as a mechanistic tool. Prior work supports rapid antidepressant-like effects and acute enhancement of brain BDNF expression after Yueju Pill administration [46]. Those findings do not establish ATX-LPA involvement. However, if a future study were to pair Yueju Pill or one of its representative constituents with targeted PC/LPC/LPA lipidomics, spatial ATX activity mapping and LPAR perturbation, it could test whether a multi-component intervention acts upstream, within or outside the proposed axis. The intervention becomes informative only when it is embedded in a causal design rather than treated as indirect confirmation by behavioral improvement alone.

8. Criteria for Establishing, Constraining or Refuting the Pathway

The field now needs pathway closure rather than another layer of disconnected association. A persuasive animal experiment would combine a disease-relevant state, such as chronic stress with or without endocrine-transition modeling, with six linked measurements: targeted PC/LPC/LPA species, BBB or interface status, spatial ATX localization or activity, local LPA inactivation capacity where relevant, LPAR subtype and downstream signaling output, and circuit or behavioral readouts. The same model should use perturbation logic. PLA2 manipulation could test whether upstream phospholipid remodeling changes the LPC pool. ATX inhibition, ATX gain-of-function or labeled LPC tracing could test whether LPC-to-LPA conversion occurs in the implicated compartment. PLPP1 or related LPA-dephosphorylating mechanisms should be examined when altered LPA clearance is suspected. LPAR subtype blockade or genetic disruption, together with electrophysiology or calcium imaging, could test whether receptor output is functionally necessary.

Human studies require a parallel but ethically adapted structure. A strong menopausal-transition cohort would include reproductive staging, endocrine measures, antidepressant exposure, metabolic status, targeted lipid species, inflammatory markers and neurovascular or BBB-related imaging where feasible. CSF LPA species can be informative because MDD-associated LPA 22:6

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differences have been detected in this compartment [7]. CSF ATX abundance may also be relevant because reduced CSF ATX has been reported in MDD [26]. Yet recent anatomical work on choroid-plexus ATX indicates that CSF-facing ATX should be interpreted as an interface-proximal signal rather than as a direct surrogate for hippocampal or prefrontal receptor activity [51]. The purpose is not to force all compartments into one direction of change. The purpose is to determine whether a coherent substrate-enzyme-product-inactivation-output relationship emerges within a biologically defined state.

The pathway should also be falsifiable. If a predicted endocrine or stress condition changes mood-relevant behavior without altering targeted LPC/LPA species, interface markers, spatial ATX activity or receptor output in the proposed compartment, the pathway is weak in that model. If a plasma or CSF LPC species relates to brain exposure but not to local LPA generation, ATX activity or receptor signaling, substrate availability alone is insufficient. If ATX inhibition or labeled substrate tracing fails to alter the predicted local LPA species, local ATX-dependent conversion should not be treated as necessary. A framework that cannot fail is not mechanistically useful; this one can fail, and that is precisely why it is worth testing.

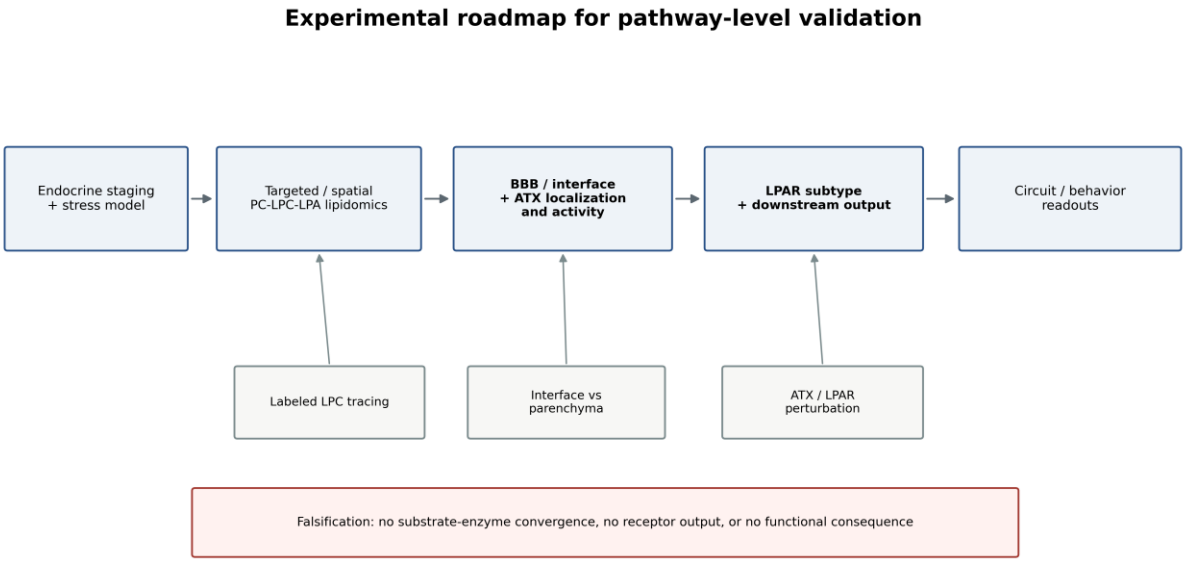

Figure 2. Experimental roadmap for pathway-level validation. The key objective is to show that endocrine or stress context, species-resolved lipid remodeling, BBB/interface biology, spatial ATX localization or activity, LPAR subtype output and circuit or behavioral consequences form one coherent experimental chain. Perturbation and tracing are essential because association alone cannot establish pathway necessity.

Box 1. Falsifiable predictions for future studies.

Prediction	Interpretation
Defined brain-accessible LPC species and catalytically active ATX do not colocalize wit hin the predicted CNS compartment or interf ace pool.	Local LPC-to-LPA conversion remains un substantiated in that model and should not b e treated as an anatomical pathway.
Endocrine transition plus stress changes behavior but not targeted LPC/LPA species, B	The lipid-to-receptor framework is weak in that model.

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BB/interface markers, local ATX activity or LPAR signaling.	
Plasma or CSF LPC species correlate with brain exposure but not with local LPA species, ATX activity or receptor output.	Substrate availability alone is insufficient to explain the phenotype.
ATX inhibition or labeled LPC tracing does not change predicted local LPA species.	Local LPC-to-LPA conversion should not be treated as necessary in that model.
LPAR subtype perturbation changes molecular markers but not behavior, E/I balance or circuit readouts.	Receptor signaling may be associated with the model but not behaviorally necessary.

9. Discussion

The value of the LPC-ATX-LPA-LPAR framework is not that it converts every lipid abnormality in depression into one disease mechanism. Its value is that it identifies a specific explanatory gap and offers a disciplined way to close it. Depression lipidomics has generated an expanding list of altered molecules, but a list of altered molecules cannot explain how a metabolic disturbance becomes a neural signal. LPC is important in this context because it is both a depression-relevant lysophospholipid and a chemically defined precursor of receptor-active LPA. ATX is important because it makes that conversion local and biologically selective. LPARs are important because they translate the lipid product into signaling programs capable of altering synaptic and circuit function.

This perspective differs from a general review of LPA receptors in mood regulation. The current review begins upstream, with depression-associated phospholipid remodeling, and asks which route could plausibly connect that remodeling to receptor output. It then follows the evidence downstream and identifies precisely where the chain remains incomplete. This structure prevents two opposite errors. One error is to overstate fluid abnormalities as proof of a CNS signaling mechanism. The other is to dismiss the pathway because total LPA studies or different compartments do not show uniform directional agreement. Both errors arise from asking measurements to answer questions they were not designed to answer.

The apparent inconsistency of the literature is therefore scientifically productive. MDD studies report lower serum or CSF ATX [26], lower CSF LPA 22:6 [7], and null total-LPA findings [8,27]. Serum lipidomics also identify an LPA 16:1-containing signature in drug-free female MDD cohorts [9]. In parallel, anxiety-focused cross-species work reports higher serum LPA 16:0 in vulnerability states [39]. These observations should not be forced into one simple ‘up’ or ‘down’ narrative. They indicate that the relevant biology is likely to be molecular-species specific, anatomically organized, governed by both LPA production and inactivation, and receptor-context dependent. This is not a rhetorical escape from conflicting data. It is a more demanding hypothesis because it requires precise colocalization, turnover analysis and functional testing.

The endocrine-transition discussion becomes meaningful within this more demanding framework. The menopausal transition and postpartum period are not included as decorative clinical background. They expose a larger mechanistic issue: a lipid-to-receptor signal may become most visible when endocrine state, systemic lipid remodeling and neural responsiveness shift together. Perimenopausal depression risk and estradiol responsiveness establish the clinical relevance of this window [16,17]. STRAW+10 provides a stageable endocrine framework for studying it [15]. Midlife lipid trajectories, plasma metabolomics and ovariectomized rat data show that this transition is accompanied by systemic lipid remodeling, including LPC-related changes [18–20]. The postpartum literature adds a complementary central-neurobiology precedent through GABAA receptor plasticity and neurosteroid-based treatment response [21–23]. Estradiol-sensitive resting-state connectivity in

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perimenopausal depression shows that endocrine manipulation can also alter central network organization [40]. Peripheral studies further show that steroid state can regulate PLA2 activity [54,55], uterine Enpp2/ATX expression [56], and uterine LPA3 expression [57]. The missing study is the one that tests whether these strands converge in a depression-relevant CNS compartment.

The pathway also carries a useful translational discipline. Kajitani et al. demonstrate that LPAR1 is not merely a descriptive receptor but a pharmacologically actionable node for prototypic tricyclic antidepressants [41]. Formula-level and natural-product studies show that stress-relevant phospholipid metabolism [42], BBB integrity [43], LPA1-related neuronal signaling [44], brain-liver communication in a perimenopausal depression model [45], and antidepressant-like responses to Yueju Pill[46] can each be experimentally perturbed. Yet the present review does not treat these observations as clinical validation of the pathway. It treats them as reasons to design better mechanistic studies. Translation becomes credible when intervention, molecular species, anatomical conversion, LPA inactivation and functional output are studied together.

The most important conclusion is therefore methodological and biological at the same time. If the LPC-ATX-LPA-LPAR sequence is validated in depression, it will provide a concrete route by which phospholipid remodeling reaches receptor-level neural output. If the sequence fails under rigorous spatial and causal testing, the field will still gain clarity by learning that depression-related lysophospholipid changes are better interpreted as parallel metabolic states rather than as drivers of receptor signaling. Either outcome is informative. What is no longer sufficient is to treat bulk lipid abnormalities, local receptor phenotypes and endocrine vulnerability as separate observations that never meet in one experimental design.

10. Conclusions

The LPC-ATX-LPA-LPAR axis offers a rigorous candidate framework for studying how depression-associated phospholipid remodeling might become receptor-active lipid signaling. The framework is attractive because it links a measurable substrate, a defined extracellular enzyme, receptor-active lipid products and neural receptor outputs that are already relevant to synaptic physiology, stress adaptation and emotion-related behavior.

Current evidence supports the importance of each node, but it does not yet support a completed depression pathway. Human studies identify species-specific CSF LPA 22:6 abnormalities [7], reduced ATX abundance in MDD serum and CSF [26], and mixed or null total-LPA observations that limit simple biomarker claims [8,27]. Experimental work separately links ATX/LPA deficiency to hippocampal plasticity and depression-like behavior in chronic stress [31]. PRG-1/LPA2 and neuronal physiology studies connect local lipid-phosphate signaling to synaptic output [28–30]. LPA1-centered models connect receptor perturbation to stress-related behavior and transcriptional changes [32,33], depression-like functional brain activity [34], hippocampal neurogenesis [35], inhibitory-circuit abnormalities [36], HPA-axis disruption [37], sex-dependent emotional phenotypes [38], and anxiety-related vulnerability [39]. The decisive missing evidence is spatial and biochemical. Depression-related research has not yet shown that a defined brain-accessible LPC species, active ATX, locally produced LPA, local LPA inactivation capacity and receptor-specific circuit output converge within one mood-relevant CNS microenvironment.

Reproductive endocrine transitions provide a particularly informative validation setting because they align mood vulnerability, lipid remodeling and steroid-sensitive biology without already proving the pathway. Future studies should therefore prioritize species-resolved lipidomics, anatomical ATX mapping, BBB/interface assessment, LPAR subtype analysis, causal perturbation and matched functional readouts. This strategy can establish the pathway, restrict it to specific contexts or reject it. Each outcome would sharpen the biological interpretation of lipid remodeling in depression.

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