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Review

Role of Enzymes Capable of Transporting Phosphatidylserine in Brain Development and Brain Diseases

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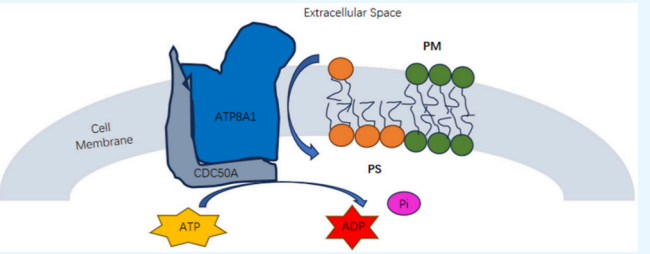
ABSTRACT: Phosphatidylserine (PS) is a common type of phospholipid, typically located in the inner leaflet of the cell membrane, especially abundant in the nervous system. It is an important component of the neuronal membrane and is considered to play a regulatory role in various brain functions, including memory and emotional stability, because its exposure to the outer leaflet of the neuronal membrane can result in abnormalities in various neurobiological processes such as synaptic transmission and neuronal apoptosis. Recently, research on two types of membrane proteins that synergistically mediate the transmembrane transport of phospholipid molecules in eukaryotic cells has become more in-depth and detailed. This review mainly explores the regulation of the expression of phosphatidylserine transporters and their impact on brain development and diseases.



INTRODUCTION

Phosphatidylserine (PS) is abundant in the brain, and numerous studies have shown that PS is involved in various brain functions and pathology,[1] such as activation of membrane signaling pathways,[1] neurotransmission,[2] synaptic modification,[3] and neuroinflammation.[4] PS is a common type of phospholipid, typically located in the inner leaflet of the cell membrane.[5] It is an important component of the neuronal membrane and is considered to play a regulatory role in various brain functions, including memory and emotional stability, because its exposure to the outer leaflet of the neuronal membrane can result in an abnormality in various neurobiological processes such as synaptic transmission and neuronal appotosis.[6,7] Recently, studies verified that two types of membrane proteins, six members of the phospholipid flipping enzymes,[8] and three members of cell division control proteins (CDC)[9] synergistically mediate the transmembrane transport of phospholipid molecules from the outer leaflet to the inner leaflet of the cell membrane and thereby maintain the normal asymmetry of PS distribution.[9]

The members of the phospholipid flipping enzymes, belonging to the P4-ATPase family, that function as PS transporters are ATP8A1, ATP8A2, ATP8B2, ATP11A, ATP11B, and ATP11C. For example, ATP8A2 can actively transport specific phospholipids (mainly PS) through the cell membrane, contributing to maintaining bilayer lipid asymmetry.[20]

Regarding the difference in substrate specificity between ATP8 and non ATP8 families, P4 ATPase can be roughly divided into three categories: enzymes that preferentially flip PS and have a smaller degree of PE (ATP8A1, ATP8A2, ATP11A, ATP11C, DRS2), (ATP8B1, ATP8B2, ATP10A, Dnf1, 2, and 3), and substrate preference unknown enzymes (ATP9A, ATP9B, and Neo1). The main function of the ATP8 family is to transport phosphatidylserine and phosphatidylethanolamine from the outside of the bilayer to the other. The non ATP8 family, such as the ATP9 family, mainly activates protease binding activity and participates in negative regulation of exosome secretion, the regulation of endocytic recycling, and the regulation of retrograde transport, from the endosome to the Golgi apparatus. The ATP11 family is mainly phosphorylated in the intermediate state and drives ion transmembrane uphill transport. During the transportation of PS, the ATP8 family requires the assistance of CDC50, while the ATP11 family does not. There are more members of the P4-ATPase family that are not involved in PS transportation or PS distribution, such as ATP9A.[10] Therefore, they are not discussed in this present review.

In addition, three kinds of CDC proteins, including CDC50A, CDC50B, and CDC50C,[9] are also essential for the normal PS-flipping function of ATP8A1, ATP8A2, and ATP8B2. CDC50s are also called transmembrane proteins 30 (TMEM30) that belong to a very large sort of various transmembrane proteins. CDC50 molecules serve as not only a essential chaperon of phospholipid flipping enzymes but also a regulator of phospholipid flipping enzymes. The auxiliary

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subunit CDC50 may be located at a position closely related to the suggested pathway of extracellular entry and may promote the binding of lipid substrates.[11] Furthermore, the association between P4 ATPase and CDC50 family proteins is necessary for their departure from the endoplasmic reticulum (ER) and proper cellular localization.[12] For instance, the deficiency of CDC50A leads to incorrect localization of the PS flipping enzyme ATP8A2.[3,13,14] Similarly, there are more members of the CDC protein family or transmembrane protein family that are not involved in PS transportation or PS distribution, such as CDC28[15] and TMEM192.[15] Therefore, they are also not discussed in this present review.

In addition to phospholipid flipping enzymes, there are others proteins, such as Xkr8 and TMEM16F, that can influence PS distribution by scrambling of phospholipids in the plasma membrane.[16,17] TMEM16F has 8 transmembrane regions and requires $Ca2^{+}$ to mediate phospholipid scrambling.[16] It takes a role in the PS exposure to the outer leaflet of the membrane in activated platelets for blood clotting. Patients of Scott Syndrome who carry a mutation in the TMEM16F gene suffer bleeding disorders. Xkr8 carries 6 transmembrane regions.[17] The cleaved Xkr8, resulting from caspase 3 and 7, cleaves off the C-terminal tail of it and promotes the PS-exposure to the outer leaflet of the membrane. These proteins play a role in PS distribution. However, they are also not discussed in this present review because they are not phospholipid flipping enzymes.

This paper aims to review the enzymes that can transport phosphatidylserine, the effects of regulating their expression on brain development and diseases,[18] as well as potential pathways and treatments in the future. It mainly introduces the following flipping enzymes: ATP8A1, ATP8A2, ATP8B2, ATP11A, ATP11B, and ATP11C (Figure 1).

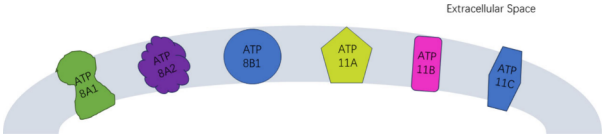

Figure 1. Summary figure showing the types of ATPases that can transport PS from the outer leaflet to the inner leaflet of the cell membrane.

ATP8A1. Both the increase and decrease of ATP8A1 levels are harmful to brain connectivity, but only the increase of ATP8A1 is associated with abnormal social behavior. Therefore, mice with increased levels of ATP8A1 may become potential models for autism research.[19] Autism (ASD) is a complex neurodevelopmental disorder.[20] The ATP8A1 gene is located in the middle of the autism-related 4p 12−15.3 inversion domain, which also includes the chromosome 4p GABAA receptor gene cluster.[21] Therefore, ATP8A1 may also be functionally related to ASD. The research results indicate that the levels of ATP8A1 in the brain of adolescents with autism are higher, and it was found that the expression of ATP8A1 is also related to gender.[22] It is known that the hippocampus plays an important role in learning and memory, and ASD candidate genes related to learning and memory are differentially expressed in the hippocampus of offspring exposed to BPA before delivery.[22] Among these genes, the ATPase phospholipid transporter protein 8A1 encoded by ATP8A1 was significantly upregulated in male offspring in the hippocampus but downregulated in females in the hippocampus. An increase in ATP8A1 expression was found in the hippocampus and temporal cortex of adolescents with ASD,[22] and it is associated with impaired learning/memory and social impairments.[12] PS in healthy neurons is usually distributed in the inner leaflet on the cell membrane. However, PS is also exposed on the outer leaflet of the cell membrane of pruned synapses and neurons that are about to undergo apoptosis.[23] Because ATP8A1 is a physiologically expressed PS single-direction transporter flipping PS to the inner leaflet, both its over- and underexpression will affect the distribution and level of PS, especially on the outer leaflet of the neuronal cell membrane. Too much or too little PS exposure will disturb the normal development and function of the brain due to the abnormal numbers of neuronal apoptosis and synaptic pruning. Based on this association, it may be hypothesized that regulation of ATP8A1 expression may contribute to amelioration of ASD-related microneurobiological pathophysiological processes, such as loss of excitatory synapse. ATP8A1, as a most important enzyme in the brain capable of transporting phosphatidylserine, requires other proteins to assist in transport, and studies have shown that key residues on the transmembrane helix contribute to the free energy of important states.[24] Understanding the energy barrier of phospholipid transporters has important pharmacological applications for developing drugs that regulate their activity. It has therapeutic effects on brain diseases such as Parkinson's disease.

The phospholipid transport mechanism of ATP8A1-CDC50 is that CDC50 has an auxiliary contribution to the action of ATP8A1.[24] In addition, EHD1 localized by recycling endosomes (REs) was observed to have lost membrane localization when binding to PS in vitro and in cells with PS synthesis defects. Ultimately, it was found that PS flipping from ATP8A1 to the cytoplasmic lobules was necessary for EHD1 to recruit RE and regulate its transport through RE.[25] In cells with ATP

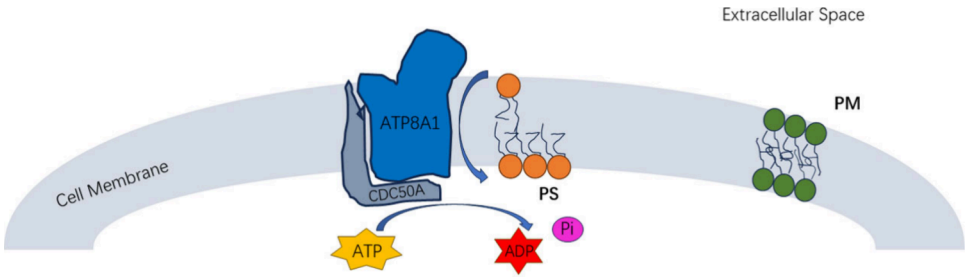

Figure 2. Role and process of the phospholipid flipping enzyme complex formed by ATP8A1 and CDC50A in flipping PS from the outer leaflet to the inner leaflet of the cell membrane.

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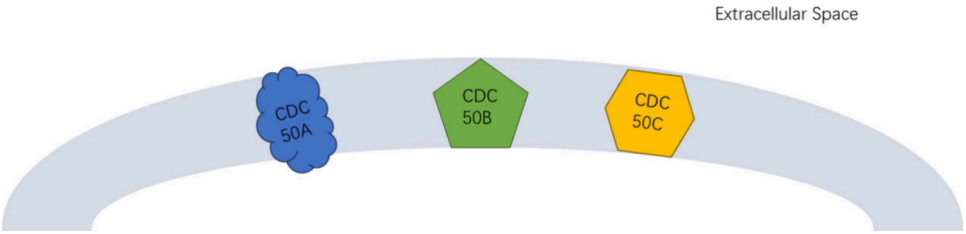

Figure 3. Summary figure showing the types of CDC50 family.

8A1 deficiency, EHD1 is not localized in RE but is dispersed throughout the cytoplasm. The RE localization of EHD1 in ATP8A1 depleted cells is restored through the expression of siRNA-resistant WT ATP8A1 but not through the expression of siRNA-resistant E191Q mutants. These results indicate that the ATPase activity of ATP8A1 is necessary for the RE localization of EHD1. For example, CDC50A is ATP8A1's β, knocking down the expression of subunit CDC50A, which can lead to inhibition of the maturation of PS specific flipping enzymes represented by ATP8A1, resulting in ER inhibition and thereby inhibiting the flipping of PS on the plasma membrane and endosomes (Figure 2).

EHD, as an important factor in protein network regulation, plays a role in promoting endocytosis. The Rab family has proteins that need to bind to EHD1 and colocalize on organelles, indicating that EHD is involved in the recycling pathway based on grid protein independent endocytosis. For its application in the treatment of brain diseases, conditional knockout and insertion of such proteins into mice can be used to generate important data that can be provided.[26] EHD1 colocalizes with transferrin receptors, and in HeLa cells, the recruitment of EHD to ERC is mediated by the Rab 8a effector MICAL-L1. In addition, EHD1 also participates in the recycling of grid protein independent receptors. The mutation showed that the grid protein independent recycling of MHC-I was disrupted through the Arf 6 pathway, while overexpression led to an increase in recycling in HeLa cells.[26] This study is limited to HeLa cells, so we speculate whether they can act on brain cells. The previous text also mentioned that the recycling endosome (RE) localization of EHD1 in ATP8A1-depleted cells is restored through the expression of siRNA[27] resistant WT ATP8A1, and the ATPase activity of ATP8A1 is necessary for the RE localization of EHD1, so the two are interdependent and interact with each other. Moreover, relevant literature has shown that EHD1 has been proven to be an important part of hippocampal neurons, and some brain diseases such as Alzheimer's disease have a connection with memory decline, amnesia, and other symptoms with the hippocampus.[28] Similarly, for the above pathways, can we first screen out apoptotic cell bodies in the hippocampus and then implement this pathway to experimentally confirm whether it can become one of the solutions to such brain diseases.

Connection and Role between ATP8A1 and ATP8A2. There is also a connection between ATP8A1 and ATP8A2, which are both similar but different, and their roles complement each other. ATP8A2 rescued the endosomal defects in ATP8A1-depleted cells,[26] and ATP8A2 is essential for recycling membrane transport in neurons. However, the double knockout of ATP8A1 and ATP8A2 in mice is neonatal lethal, indicating that these two flipping enzymes have redundant effects. Another commonality is that ATP8A2 and ATP8A1 are regulators of intracellular membrane transport, and ATP8A2 can compensate for the loss of ATP8A1 in COS-1 cells that have not been observed to express themeslves.[29] ATP8A2 and ATP8A1 are only related to CDC50A.[30] At present, the neural pathway through which CDC50A and ATP8A2 interact has been studied, as mentioned earlier.

ATP8A2. P4-ATPase ATP8A2 can actively transport specific phospholipids (such as PS) through the cell membrane, participating in maintaining bilayer lipid asymmetry.[31] Related diseases are autosomal recessive diseases that are associated with brain diseases, with or without hypotonia, mental retardation, abnormal movement, chorea, tremor, optic nerve atrophy, and cerebellar atrophy (CARMQ4).[32] Through the study of spontaneous mutants in mice, the main focus was on Wabler lethal (WL) mutant mice, which exhibited peripheral and central nervous system mutations. Pathogenic genes were identified in different WL mutant mice, and the mutation occurred in the encoding phosphatidylserine transferase ATP8A2, which can maintain phosphatidylserine enrichment in the inner lobules of the plasma membrane. Mutations in the gene encoding flippase are rare worldwide and are typically the cause of severe early onset encephalopathy.[33] In the initial report of CAMRQ4,[32] it was predicted that the homozygous mutation of Ile376Met can alter the secondary structure of ATP8A2 protein.[33] Ile376Met patients present with encephalopathy, developmental delay, decreased muscle tone, quadrupedal gait, trunk ataxia, and articulation disorders. The lack of genotype/phenotype correlation in ATP8A2-related diseases suggests that the variability of macrophage activation may also be an important contributor to clinical severity.[32]

ATP8A2-related diseases are classified as other metabolic or complex autosomal recessive inherited diseases, with ataxia being a related characteristic or only occasionally occurring.[32] Current research suggests that autosomal recessive inherited ataxia does not have a specific pathophysiological pathway to explain the occurrence of this symptom, usually due to the extreme sensitivity of the cerebellum, spinocerebellar,[34] and sensory neurons to mild metabolic disorders, as well as partial loss of function.[32]

In addition, the interaction between P4-ATPase catalytic subunits and CDC50 or TMEM30 is essential for the correct folding, transport activity, and exit of P4-ATPase complexes from the endoplasmic reticulum.[29] There are three subtypes of CDC50A, CDC50B, and CDC50C in mammals (Figure 3),[9,35,36] and ATP8A2 can selectively assemble with CDC50A, playing a crucial role in the correct folding and functional activity of ATP8A2. Moreover, relevant literature has stated that almost all CDC50A are associated with ATP8A2. The transmembrane and extracellular regions of CDC50A are essential for the formation of functionally active ATP8A2−CDC50A complexes, and N-linked[30] glycosylated CDC50A plays an important role in the formation of stable

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ATP8A2−CDC50A protein complexes. Certain mutations in ATP8A2 can lead to reduced glycosylation of CDC50A, thereby reducing the formation of glycoproteins.[30] Perhaps it may have some impact on the correct folding of proteins, further leading to brain diseases. ATP8A2−CDC50A has been used for research on brain diseases and will not be further elaborated here.

ATP8B2. At present, there is no treatment that can prevent or slow down the progression of Parkinson's disease (PD),[37] and as cognitive development progresses, there is no single mutation associated with motor progression. However, in gene-based analysis, ATP8B2, a phospholipid transporter protein associated with vesicle formation,[38] is nominally associated with motor progression. Based on genetic testing, ATP8B2 on chromosome 1 is associated with motor progression,[38] although this did not reach a significant correction for the number of mapped genes. This gene has not been reported in PD or other diseases and needs to be tested in other cohorts. There is no detailed explanation.

The phosphorylation of important aspartic acid residues catalyzed by human P4-ATP enzymes ATP8B1 and ATP8B2 heavily relies on their CDC50 subunits, and the enzyme intermediates of ATP8B2 are strictly dependent on the presence of CDC50A.

The effects of ATP8B2 on brain development and diseases, as well as potential pathways and treatments in the future, are not fully understood and require further research.

According to relevant literature, ATP8A2 is the highest gene in MAGMA gene analysis[38] although not significant across the entire genome. We use a new method for PD, following a similar approach to Huntington's disease, where we combine principal component analysis[39] with multiple evaluations.[40] The genome-wide association study (GWAS) of PD has identified 90 independent loci associated with disease risk.[38] This study is the first to use PCA data simplification[41] to evaluate PD progression, based on the successful approach of HD. We have steadily replicated APOE and the association between 4 and cognitive progress and the identification of other potentially important genes.[42] These advances are crucial for understanding the biology of disease progression and specifying therapeutic targets to prevent or slow down PD progression. The mechanism by which ATP8B2 acts on cancer remains to be explored.

ATP11A. ATP11A is highly expressed in human and mouse adult cells and is cleaved by caspase during apoptosis.[43,44] Caspase resistance to ATP11A blocks exposure to apoptotic PtdSer.[32]

High concentrations of calcium ions have a strong inhibitory effect on ATP11A, and in most mammalian cells, the main flipping enzymes on the plasma membrane are ATP11A and ATP11C,[45,46] which can specifically translocate PS and PE from the outer lobe of the plasma membrane to the inner lobe and create newly emerged mutations in the ATP11A gene.[43]

It can lead to severe developmental disorders and progressive neurological decline, and the same heterozygous mutation in mice reproduces the patient's phenotype (growth retardation, reduced brain volume, and ataxia), which can prove that it is a dominant mutation causing symptoms. Many experiments have shown that brain diseases related to ATP11A are caused by mutations in the ATP11A gene. Mutated mice exhibit a significant reduction in brain size, lateral ventricular dilation, and tissue degeneration in different brain regions, accompanied by pyknosis or TUNEL positive neurons, indicating neuronal apoptosis in the brain. Lateral ventricular dilation may be due to hydrocephalus or brain atrophy.[43] According to research, vitamin B1 can be used to treat brain atrophy.[47]

According to amino acid sequencing, it was found that the homology of the transmembrane amino acid sequence between ATP11A and ATP11C was 79%, while the homology with ATP8A1[44] and ATP8A2 was 42% and 39%, respectively, with the highest homology with ATP11C.[48] This indicates that the difference in sequence level between the two is relatively small, making it easy to speculate that ATP11A has more functions that can be similar to ATP11C, and it can be inferred from ATP11C that ATP11A has more functions. The high homology of genes has no research significance; however, most importantly, there is still a 21% gap between them, so the functional difference between the two is caused by this 21%.[49] This can be used for gene function annotation, genetic evolution analysis, protein function, and structure analysis.

ATP11B. Known to regulate synaptic plasticity and support signal transduction between neurons, synaptic dysfunction leads to various neurological and other brain diseases.[21] However, the specific mechanism of this process is still unclear. In this study, abnormal neural and synaptic morphology in vivo and in vitro were observed after hippocampal ATP11B knockout. This finding suggests that to avoid the change of the normal synaptic ultrastructure asymmetric distribution of phosphatidylserine maintained by ATP11B is necessary. Glutamate also plays an important role, increasing glutamate release and receptor expression, which can also increase intracellular Ca^{2+} concentration to achieve the goal.[21] Moreover, changes in ATP11B expression do not impair the integrity of the synaptic structure. More studies have shown that ATP11B does indeed exert ATPase activity in primary hippocampal neurons. In summary, these results indicate that ATP11B regulates the asymmetric distribution of PS in neuronal cell membranes and thus induces the aforementioned morphological changes.

ATP11B can regulate synaptic plasticity through the MAPK14 signaling pathway. This pathway can be used as a research object to explore whether it can become one of the pathways for brain development or brain diseases.[21] The downregulation of ATP11B promotes the externalization of PS, while the upregulation of ATP11B has no significant effect on the localization of PS (Figure 3), indicating that changes in ATP11B expression affect neuronal cell members.

In addition, studies have shown that the microbiota gut brain axis has attracted great attention in studying the mechanisms of brain aging.[50,51] The analysis results indicate that the abundance of certain gut microbiota has changed in ATP11B knockout mice. Specifically, there is an increase in crude salt bacteria that accelerates aging and a decrease in probiotics that delays aging.[52] The deficiency of ATP11B weakens antioxidant capacity and enhances oxidative stress response. Therefore, it can be inferred that the dysbiosis of gut microbiota caused by ATP11B deficiency may accelerate aging. The imbalance of intestinal microbial ecology will lead to the secretion of proinflammatory molecules, which interfere with the permeability of the gastrointestinal tract and blood−brain barrier and then regulate the inflammatory signal transduction pathway that promotes neuroinflammation and neuronal damage and leads to neuronal death. For example, a significant increase in the abundance of proteobacteria belonging to the genus, which was found in the mucosa of PD patients, may

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lead to induced inflammation and incorrect folding of synaptic nucleoproteins.[52] Further research on the potential mechanisms underlying changes in gut microbiota induced by ATP11B deficiency will reveal more details about the microbiota gut brain axis. This study reveals the mechanism of aging from the perspective of microbial communities, providing new ideas for the prevention and treatment of age-related diseases.

Alzheimer's disease is a major social and economic problem in the world's aging population.[53] One of the most common causes of senile dementia is cerebral small vessel disease (SVD). SVD can cause damage to the white matter and deep gray matter of the brain. SVD can lead to various mental illnesses such as depression, impaired gait, or balance. The MRI scan of such patients usually shows white matter abnormalities. Researchers have discovered an ATP11B functional deficiency that leads to EC dysfunction in a rat SVD model. This study provides a therapeutic strategy for treating and reversing SVD in rat models, which may be applied to human SVD in the future.[54]

Interestingly, as we plan to submit to international journals and target readers around the world, scientists have found that ATP11B may not play an important role in SVD in the Chinese population. Therefore, when conducting ATP11B research, it is necessary to conduct different studies based on race and gene and whether it changes with the differences in genes caused by secondary variables other than genes, such as region and climate, or whether there will be changes during individual growth. In addition, SVD is related to age, and if it becomes more severe in later years, it is due to poor white matter integrity and intrinsic quality in youth. White matter abnormalities are also related to ATP11B single nucleotide polymorphism (SNP), which is the most common type of heritable variation in humans. According to relevant literature,[55] SNP masking is a probe that removes the influence of SNP, which can improve hybridization problems. Therefore, further thinking can be triggered to use SNP masking[56] on ATP11B to remove the influence of SNP on ATP11B and achieve the treatment of SVD in rats. After rigorous experiments on rats,[57] we can further speculate whether it can act on human SVD. The extremely low secondary alleles associated with rare variations in ATP11B are potential values for further research on the biological functions of ATP11B.

ATP11C. ATP11C is expressed in the anterior rhombic cells of the posterior brain, pharyngeal arch, and liver.[36] The expression data indicates that functional abnormalities may lead to visual, auditory, neurological, or liver dysfunction, and studies have shown that the transcription levels of ATP11C are associated with ESR2 and mPR in pregnant women β. The expression of mPR is related, and these correlations only exist in postpartum women β.[22] These results indicate that the blood biomarker panel can identify depression in pregnant women, and the expression of these biomarker genes is influenced differently by estrogen and/or progesterone binding during pregnancy and postpartum.

Depression is the fourth largest contributor to the global burden of diseases and belongs to the category of brain disorders.[22] The prevalence of events related to reproductive disorders, such as premenstrual anxiety, perinatal depression, and perimenopausal depression, indicates that fluctuating hormone concentrations pose a particular risk for women. Therefore, genetic factors have an increasing impact on the risk of depression, which may make women particularly susceptible to major biopsychosocial pressures (such as reproductive events). We collected maternal blood samples, and in the pregnancy subgroup, the IDS-SR-30 score is significantly correlated with the transcription levels of ADCY3, ASAH1, ATP11C, CDR2, and ESR2 as well as FAM 46 A, mPR β, NAYA, RAPH 1, TLR 7, and ZNF 291/SCAPER (Supporting Information).[58] Principal component analysis (PCA) is used to decompose the correlation with symptom scores at the transcript level. In postpartum samples, only the transcription levels of CADM 1 and FAM 46 A were simultaneously associated with ESR2 and mPR β significant correlation.[36] ADCY3, ASAH1, ATP11C, CDR2, CMAS, DGKA, MARCKS, NAYA, RAPH 1, and ZNF 291/SCAPER are all associated with mPR alone and β significant correlation. It can be seen from this that research can be conducted on postpartum depression by targeting ATP11C transcription.

More studies have shown that ATP11C is associated with pituitary development. In the family of X-linked pituitary insufficiency, patients were detected to have a 1.1 Mb microduplication at q27 on the X chromosome. This duplication only contains two annotated genes SOX3 and ATP11C[59,60] and has been proven to be a direct tandem copy number gain.[47] SOX3 is mainly used to study thyroid related diseases and will not be discussed here.

RESEARCH STATUS

In some developed countries, extensive and in-depth research has been conducted on the role of enzymes that transport phosphatidylserine in brain development and brain diseases, covering many aspects and fields. Each enzyme that can transport phosphatidylserine has been studied by experts and scholars, and their necessity in treating brain diseases has been determined. However, we still found limitations in their research, such as the fact that ATP8A1 and ATP8A2 do indeed have a synergistic effect; however, there is no in-depth research on this, and synaptic dysfunction leads to various neurological and other brain diseases.[61] The specific mechanism of this process is still unclear, and the mechanism by which ATP11B acts on brain diseases through the hippocampus remains to be studied. Therefore, we can delve deeper into our thinking and put it into practice based on the foundation of our predecessors.

CONCLUSION

Scholars have explored the mechanism of ATP8A1−CDC50 phospholipid transport and conducted in-depth analysis.[26] Overall, they have addressed the challenges and difficulties associated with this issue, contributing to the design of drugs for brain diseases using P-type flipping enzymes.[62] However, research by current scholars on the role of enzymes capable of transporting phosphatidylserine in brain development and brain diseases is still limited and not in-depth enough, and the theoretical and practical improvement of this still needs to be strengthened. Many brain diseases such as Parkinson's and autism are still not well cured or alleviated, but there are still some methods to fix them.[63] What we need to do is to constantly propose ideas, practice ideas, and learn from previous methods and techniques.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05036.

NCBI Gene Summary for NAGA Gene, CBI Gene Summary for AMFR Gene, NCBI Gene Summary for ASAH1 Gene, NCBI Gene Summary for ATP11C Gene, NCBI Gene Summary for CADM1 Gene, NCBI Gene Summary for CAT Gene, Thomas P. Characteristics of membrane progestin receptor alpha (mPRalpha) and progesterone membrane receptor component 1 (PGMRC1), NCBI Gene Summary for CDR2 Gene, NCBI Gene Summary for CMAS Gene, NCBI Gene Summary for DGKA Gene, Membrane progesterone receptor beta (mPRβ/Paqr8) promotes progesterone-dependent neurite outgrowth in PC12 neuronal cells via non-G protein-coupled receptor (GPCR) signaling, NCBI Gene Summary for MAF Gene, NCBI Gene Summary for MARCKS Gene, NCBI Gene Summary for CD59 Gene, NCBI Gene Summary for TENT5 Gene, NCBI Gene Summary for RAPH1 Gene, and NCBI Gene Summary for TLR7 Gene (PDF)

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Author Contributions

All authors contributed to the study conception and design. The idea was put forward by Junhua Yang, discussed with Li Luo. The first draft of the manuscript was written by Yiying Li and Siqi Xu. The manuscript was reviewed and edited by Junhua Yang and Li Luo. All authors read and approved the final manuscript.

Notes

The authors declare no competing financial interest.

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