Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(6): 26812
https://doi.org/10.31083/FBL26812

Review

The Role of Fatty Acid Binding Proteins in Neuropsychiatric Diseases: A Narrative Review

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Academic Editor: Antoni Camins
Submitted: 1 October 2024 Revised: 19 December 2024 Accepted: 14 January 2025 Published: 17 June 2025

Abstract

Fatty acid binding proteins (FABPs) transport lipids in the brain and may be involved in the course of various neuropsychiatric syndromes, e.g., major depressive disorder (MDD), anxiety, schizophrenia, neurodegenerative disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and substance use disorders (SUDs). However, the nature of this link is not sufficiently elucidated. To that end, we performed a comprehensive literature search on the role of FABPs in neuropsychiatric disorders. Literature searches were conducted from Medline/PubMed electronic databases utilizing the search terms ("fatty acid binding protein" OR "FABP") AND ("psychiatry" OR "ADHD" OR "autism" OR "schizophrenia" OR "substance abuse" OR "substance use disorder" OR "addiction" OR "cocaine" OR "ethanol" OR "tetrahydrocannabinol (THC)" OR "nicotine" OR "anxiety" OR "depression" OR "major depressive disorder", OR "neurodegenerative" OR "Alzheimer" OR "Parkinson" OR "dementia"). Of the 1281 publications found, 90 met the inclusion criteria. FABP alterations were found to be involved in pathology and/or associated with the severity of all conditions examined. Elevated levels of FABP2 and FABP7 were found in patients with MDD and ASD, while FABP3 is implicated in dopamine receptor regulation linked to ADHD and SUDs. Moreover, FABPs' involvement in neuroinflammation and lipid metabolism could shed light on new therapeutic strategies. Alterations in FABP expression may contribute to the increased prevalence and severity of certain neuropsychiatric conditions. Our findings, albeit pending further validation via prospective clinical trials, call for further research into the mechanisms by which FABPs affect neurophysiopathology and highlight the therapeutic potential of FABP inhibitors in mitigating such illnesses.

Keywords: anxiety; autism spectrum disorder; attention-deficit (hyperactivity) disorder; fatty acid binding protein; major depressive disorder; neurodegeneration; schizophrenia; substance use disorders

1. Introduction

1.1 What are Fatty Acid Binding Proteins?

Fatty acid binding proteins (FABPs) are a family of proteins that are involved in membrane and intracellular transport of fatty acids and other hydrophobic substances making them critical in cellular lipid metabolism. While there are at least nine subtypes that express unique tissue-specific functions, this review will focus on FABP3, 5 and 7 which are important for transporting lipids in the brain [1,2]. FABP transport of long-chain polyunsaturated fatty acids (PUFAs), is essential for brain development and, proper neurotransmission [3]. Furthermore, changes in brain PUFAs and FABP expression can impact key regulatory proteins and pathways including peroxisome proliferator activating receptors (PPARs) [4], retinoid X receptors (RXRs) [5,6], and the endocannabinoid system (eCBs) [7,8].

FABPs are directly involved in aspects of brain development. Being implicated in neuronal cell differentiation [9] and in neurite growth and with its highest expression in prenatal and early postnatal neurons, FABP5 seems to play a key role in early development [10,11]. On the other hand, FABP7's roles in PUFA metabolism [12], neuronal migration [13], development of neural progenitor cells [14], neural axis patterning [3] as well as in sleep and metabolic function [15] indicate its potential contributions to aberrant development [16,17] and neurodegeneration [18]. The localization of FABPs varies by subtype. FABP3 has been found in cytoplasm and nuclei of neurons [19]. FABP5 is localized in the soma, nuclei, and processes of neurons and glial cells [19]. FABP7 is present in the cytoplasm and nucleus of radial glial cells and immature astrocytes [19–21]. All three FABPs are found to be highly expressed in the hippocampus, olfactory bulb, cerebellum, thalamus, and hy-

pothalamus. FABP3 and 5 are also expressed in the caudate putamen. FABP5 and 7 are both expressed in the amygdala, cerebral cortex and corpus callosum [22,23]. FABP5 is uniquely expressed in the retina and lens [11].

FABP7 shows no strong preference for any specific fatty acid type at physiologic temperature (37 °C) [24]. When bound to Docosahexaenoic acid (DHA), FABP7 localizes to the nucleus affecting gene expression, and is vital to nervous system development. FABP7 deletion has been found to cause aberrant dendritic morphology and decreased spine density in astrocytes and cortical pyramidal neurons. These structural changes are implicated in alterations observed in the medial prefrontal cortex (mPFC) of FABP7 KO mice, including decreased number of excitatory synapse as well as decreased frequency and amplitude of miniature excitatory post-synaptic currents [16]. These mice also have decreased brain glucose metabolism (BGluM) in the striatum, cortex, hypothalamus, and amygdala as well as increased BGluM in the hippocampus, thalamus, periaqueductal gray, superior colliculi, inferior colliculi, cerebellum, and midbrain [25]. In addition, FABP7 appears to be a clock-controlled gene implicated in sleep/wake regulation [15,26]. FABP7 expression fluctuates in concordance with circadian rhythm [27]. FABP7s role in PUFA metabolism and sleep implicate it in disorders involving aberrant development and neurodegeneration.

FABP5 has been shown to play a key role in regulating endocannabinoid (eCB) signaling [28,29], and FABP3 and 5 exhibit a high affinity for epoxyeicosatrienoic acids a class of arachidonic acid-derived eCBs [30]. Such roles suggest that these subtypes are most intimately involved in disorders involving altered neurotransmission. The observation that FABP7 may be associated with long-term structural changes while FABP3 and 5 are rather involved in functional signaling processes is by no means a hard rule, as there is overlap in function between the subtypes. FABP3 and 5 also play a critical role in nuclear receptor activation such as PPAR and RXR signaling [31,32].

In short, FABP3, FABP5, and FABP7 are clinically relevant as they are linked to neurodevelopment and neuropsychiatric disorders. These proteins are crucial for brain lipid transport and function, impacting neurotransmission and receptor pathways. FABP7 tends to influence structural changes in the brain, while FABP3 and FABP5 are more involved in signaling changes, with substantial overlap in functions. However, localization and integration of FABP expression with other biological mechanisms such as sleep, development, and glial cell function, and signaling pathways may be critical to understanding the involvement of FABP subtypes in neuropsychiatric diseases [30].

1.2 Role of Fatty Acid Binding Proteins in Neurotransmission and Development

1.2.1 Retinoic Acid Signaling

Retinoic acid receptors (RARs) are members of the nuclear receptor superfamily, comprising three isoforms, RARα, RARβ, and RARγ [33]. They help regulate gene expression related to cell differentiation, proliferation, and apoptosis [34]. Upon activation by retinoic acid (RA), these receptors form heterodimers with RXR, which along with co-activators interact with retinoic acid response elements (RARE) [35].

RA is transported by both FABP5 and cellular retinoic acid-binding protein (CRABP) to peroxisome proliferator-activated receptor-beta/delta (PPARβ/δ) and RAR respectively [36]. Changing the ratio of FABP5:CRABP can modulate the expression of target genes regulated by these receptors [36]. Inhibition of FABP5 increases the availability of RA for the CRABP/RAR pathway [36]. Thus, studies may aim to assess if FABP5 inhibition results in RAR agonist like effects. In contrast, overexpression of FABP5 should reduce RAR signaling as the transporter would outcompete CRABP for RA. Confirmation and characterization of this FABP5/CRABP counter-regulation mechanism could help explain the role of RAR signaling the observed effects of FABP5 deficit. The role of other FABP subtypes in transporting RA should also be detailed in future studies.

In the brain RARs mediate RA-induced stem cell differentiation into progenitor cells [36], while PPARβ/δ plays a role in the differentiation of progenitor cells into mature neurons. Inhibition of FABP5, leads to an overabundance of neuronal progenitor cells and a corresponding decrease in mature neurons [36] which may be mediated by the proposed FABP5/CRABP-II counter-regulation mechanism. RAR signaling is also involved in adult neurogenesis, particularly in the granular cell layer of the dentate gyrus [37]. Chronic treatment with RA was found to suppress hippocampal neurogenesis while increasing RARα expression in the hippocampi of adult rats [38].

RAR signaling also plays a role in learning and memory. RARβ in particular is likely involved in hippocampal long-term potentiation (LTP) and long-term depression (LTD) [39]. Deletion of the *RARβ* gene leads to deficits in hippocampal synaptic plasticity [39,40]. A deficiency of vitamin A, which is converted to RA causes loss of long-term synaptic plasticity in rats [41]. Age-related decrease in hippocampal LTP reduced by supplementation with RA [42]. The RA isoform is involved in spatial learning and memory, evidenced by deletion causing locomotor deficits and mesolimbic dysfunction in mice [43].

Dopamine signaling is modulated by RARs. Expression and activity of tyrosine hydroxylase (TH) [44,45] and dopamine receptors [46,47] is regulated by RAR signaling. RARα in particular has been found to be essential for striatal dopaminergic neuron differentiation [48]. Combined RARα and RARβ agonist treatment of embryonal carcinoma cells induces a subpopulation of Gamma-Aminobutyric Acid (GABA)-ergic neurons expressing TH and dopamine transporter (DAT). These cells, may correspond to inhibitory dopaminergic neurons in the substantia nigra; their *in vivo* function remains to be investigated [48,49]. Administration of RAR antagonist

LE540, decreases midbrain expression of TH, and striatal expression of dopamine D1-receptors (D1DRs) and homovanillic acid/dopamine ratio [50]. LE540 administration decreases delta power during non-rapid eye movement (NREM) sleep, indicating disturbance to sleep homeostasis which has been associated with a plethora of psychiatric disturbances [51,52]. These findings may have implications for Parkinson's disease, schizophrenia, and depression as mesostriatal dysfunction is thought to play a role in their pathophysiology [52].

Neurological congenital abnormalities observed in schizophrenia cases appear similar to abnormalities caused by vitamin A deficiency. Interestingly, FABP5 overexpression has been observed in post-mortem brains of schizophrenia patients. Future studies may aim to assess if FABP5 overexpression can induce schizophrenia-like behavior in animal models and if these changes are mediated by reduction in RAR signaling.

Severity of autism spectrum disorders are negatively correlated with RA levels. RARs appear to play a role in prefrontal cortex development assisting with PFC-mediodorsal thalamus connectivity and intra-PFC dendritic spinogenesis [53]. These aberrations are commonly associated with autism. RAR signaling also helps normalize prefrontal cortex microglial activation [54]. Upregulation of FABP7 in the prefrontal cortex is generally associated with autism severity [14], however whether its involvement in RAR signaling mirrors that of FABP5 is unclear. Future studies should attempt to interrogate FABP7 involvement in RAR signaling and the role of RAR signaling in the adverse effects of FABP7 upregulation on autism.

Retinoic acid administration has been shown to activate the hypothalamus-pituitary-adrenal axis which is associated with anxiety [55]. Reduction in RAR signaling induced by CRABP-1 knockout reduces anxiety behavior by sensitizing the hypothalamic-pituitary-adrenal (HPA) axis to feedback inhibition [56]. Region specific effects must also be considered. While RA administration is anxiogenic, increased RAR signaling in the nucleus accumbens reduces anxiety-like behavior [57]. Region specific inhibition of FABP5 in the prefrontal cortex and basolateral amygdala produce anxiolytic effects mostly attributed to changes in endocannabinoid signaling [22,58]. Future studies may want to assess the long-term effect of FABP5 inhibition in these regions and if RAR is involved in changes to anxiety-like behavior.

Retinoic acid signaling may be useful in combating neurodegenerative disorders. Stimulation of RAR and RXRs slows down accumulation of amyloids and has antioxidant properties which may have therapeutic uses for Alzheimer's, amyotrophic lateral sclerosis (ALS), and Parkinson's disease [59]. FABP5 is involved in oxidative stress and mitochondrial dysfunction in neurodegenerative diseases [60], thus inhibition may confer both direct and RAR-mediated benefits in treating these diseases. Involvement of RARs in the neuroprotective effects of FABP inhibition should be further examined by future studies.

Both exogenous and endogenous increases in RAR signaling are associated with depression [61,62]. However, FABP5 inhibition is associated with antidepressant-like effects [63]. This contrasts with the proposed FABP5/CRABP5 counter-regulation mechanism. Differences in regional expression and involved RAR subtype may help explain the deviation from the hypothesized counter-regulation mechanism. For example, while RAR signaling in general is associated with depression, RARα signaling has been shown to have antidepressant effects. In FABP deficit models depressive effects of endogenous RAR signaling may also be overshadowed by changes in endocannabinoid signaling. Retinoic acid signaling in the hippocampus seems to play a big role in depressive effects of RAR agonists by inhibiting neurogenesis. By contrast, hippocampal cannabinoid type-1 (CB1) signaling confers antidepressant effects by enhancing neurogenesis and serotonergic activity [64,65]. Deviation from the hypothesized FABP-CRABP counter-regulation mechanism in the case of depression-like behavior could be due to contrasting effects of RAR and CB1 signaling.

Overall future studies should aim to test if the hypothesized FABP-CRABP counter-regulation mechanism is explanatory of behavioral changes induced by FABP modulation. While a relationship between FABP5 and CRABP has be observed, studies explicitly analyzing CRABPs relationship with other FABP subtypes are needed. The role of FABPs in subtype specific RAR signaling also requires more research. RAR signaling could help explain the role of FABPs in schizophrenia, depression, autism, anxiety, and neurodegenerative disorders.

1.2.2 Peroxisome Proliferator Alpha Receptor Signaling

PPARs are members of the nuclear receptor superfamily acting as ligand-activated transcription factors [66]. There are three subtypes PPARγ, PPARα, and PPARβ/δ. Upon activation and heterodimerization with RXRs, the complex binds to PPAR response elements (PPREs) in the promoter region of target genes [66]. Notably, PPARγ can also influence gene expression independently of PPREs by interacting with transcription factors such as Nuclear factor kappa B, Activator protein 1, and Signal transducer/activator of transcription 1 either through direct interaction or by competition for limiting supplies of co-activators [67]. Ligands for PPARs include fatty acids, prostaglandins and oxidized fatty acid derivatives including retinoid acid. Target genes regulated by PPARs in the brain are primarily related to regulation of neuron and glial cell metabolism, synaptic activity, inflammatory processes, and energy balance.

PPARα and PPARβ/δ are expressed at similar levels across all brain regions, except in the PFC and nucleus accumbens where PPARβ/δ is more prevalent [68,69]. PPARγ is the least expressed, however in the PFC it is

more highly expressed than PPARα. While localization of PPARs in neurons have been well documented, PPARγ appears to be the primary subtype expressed in microglia, playing a role in neuroinflammatory responses [70].

Without ligand PPARβ/δ negatively regulates downstream signaling of the other two subtypes [71], meaning that its inhibition impacts the entire PPAR system. FABP5 selectively delivers ligands to PPARβ/δ inducing its transcriptional activity [72,73]. PPARβ/δ mediates the differentiation of progenitor cells into mature neurons, while inhibiting differentiation of neuronal stem cells into neuronal progenitor cells [36]. PPARβ/δ is also involved in hippocampal neurogenesis [74]. FABP5 overexpression in cultured neuroblastoma cells has also been shown to enhance uptake of endocannabinoid anandamide (AEA) [75]. Although earlier studies suggested that AEA may be able to function as a ligand for PPARβ/δ [76,77], more recent research has found that it is the AEA metabolite arachidonic acid (AA) [78] rather than AEA itself that activates PPARβ/δ [31]. However, FABP5 facilitates catabolism of AEA by fatty acid amide hydrolase (FAAH), leading to production of AA [75]. PPARs influence the transcription of not only their own target genes but also other nuclear receptors using coactivators such as PPAR-γ coactivator-1 alpha (PGC1-α) [79]. PPAR-α, in particular, regulates mitochondria metabolism as well as amyloid beta precursor protein (APP) which are both implicated in the pathophysiology of Alzheimer's, Parkinson's, and Huntington's disease [80–83] as well as other neurological conditions [84,85]. FABP5's regulation of cognitive function has been shown to be mediated by PPARβ/δ [31]. The role of other subtypes should be investigated in future studies. The degree to which PPARs rely on FABPs for delivery of ligands would also be a fruitful future direction. Negative regulation of other PPAR subtypes due to ligand-less PPARβ/δ may also play a role. Diverging effects between FABP expression and PPARβ/δ activation such as in neuroinflammation and oxidation should also be explored. While PPARβ/δ activation is anti-inflammatory and antioxidant [86], FABP5 is involved in mitochondrial damage and oxidation [87]. Future studies may want to investigate if FABP5-/- mice experience enhanced neuroprotection from designer PPARβ/δ agonists compared to WT mice. The reliance of designer PPAR agonists on FABP5 transport is unclear, making it difficult to hypothesize the effect of such a paradigm.

Disruption of neuroimmune function is thought to be implicated in the pathophysiology of many psychiatric disorders including schizophrenia and autism [88–91]. PPARγ signaling is decreased in schizophrenia which may relate to its effects on inflammation [89]. PPARγ agonists such as rosiglitazone have been proposed as potential treatments for schizophrenia [92]. However, a pilot study administering rosiglitazone concomitant with clozapine have found no effect on cognitive performance [93]. Pioglitazone, another PPARγ agonist, concomitant with risperidone attenuates symptoms such as distractibility, anhedonia, and asociality as assessed by Positive and Negative Syndrome Scale (PANSS) [94]. Additionally, pioglitazone used to treat glucose and lipid metabolic abnormalities combined with antipsychotic drugs [95] was associated with a decrease in depressive symptoms in schizophrenic patients [96]. FABP3, FABP5, and FABP7 all interact with endogenous PPARγ ligands [30]. Future studies may aim to assess how FABPs interact with these ligands. FABP modulation could enhance the antischizophrenic effects of PPARγ agonists.

PPARα is essential for gene-environment interactions during early postnatal development and plays a critical role in establishing social dominance [97]. PPARα may also be involved in the pathophysiology of schizophrenia [6,98]. Preclinical studies using a maternal immune activation (MIA) model, have shown that fenofibrate, a PPARα agonists reduces dopaminergic dysfunction and subsequent behavior [99,100]. In schizophrenia models using postnatal lesions, fenofibrate was found to reduce prepulse inhibition (PPI) disruption [101] a marker of schizophrenia associated with dysfunction in dopaminergic and glutaminergic neurotransmission [102]. Once again future studies may want to assess how these agonists interact with FABPs.

PPARs are also modulated in models of depression. PPARα activation is associated with anti-depressant-like effects in rodents [103–105], and is involved in the mechanism of action of an antidepressant, fluoxetine [106]. Both PPARα and PPARγ agonists increase hippocampal brain-derived neurotrophic factor levels [92,107] which may mitigate depression by enhancing neurogenesis, neuroplasticity, and restoring reduced hippocampal volume often associated with depression [108]. A review on the PPARγ system and melancholic depression has identified several pathological processes that could be targeted by PPARγ agonists [109]. Melancholic depression is associated with activation of the HPA axis. Notably, PPARγ agonists downregulate cortisol levels suggesting a therapeutic potential in managing HPA axis activation implicated in melancholic depression [110]. The effects of PPARγ on HPA axis activation suggests a role in anxiety, and indeed PPARγ knockout exacerbates anxiety [111]. Restoration of PPARγ function in the amygdala ameliorates anxiogenic effects of PPARγ knockout.

PPARs receptors regulate gene expression pertinent to cell metabolism, neuroinflammation, and neurodegeneration, with implications for schizophrenia, major depression, anxiety, and neurodegenerative disorders. FABPs-PPARs interactions modulate signaling pathways that may contribute to understanding and potentially treating these disorders. Future studies should aim to assess if FABPs can be used to enhance the effectiveness of PPAR agonists. Additionally, PPAR modulation should be examined as contributing mechanisms to behavior observed in FABP deficient mice of all subtypes.

1.2.3 Endocannabinoid Signaling

The eCB system is primarily comprised of the G-protein coupled receptors CB1 and CB2. These GPCRs are activated by cannabinoids, anandamide (N-arachidonoylethanolamine; AEA), 2-arachidonoylglycerol (2-AG), regulatory enzymes, and transport proteins. The eCB system plays a significant role in modulating neuronal synaptic plasticity in the brain, influencing appetite, anxiety, learning, memory, reproduction, metabolism, growth, and development.

Cannabis has been used both medically and recreationally for centuries [112]. *Cannabis Sativa* is a complex plant with varying chemical compositions, though its primary psychoactive component is Δ9-tetrahydrocannabinol (THC) an agonist of the eCB system. Regular users of cannabis also have around a 19% chance of development of cannabis use disorder [113]. Chronic overuse of cannabis is also associated with eCB system dysregulation [114], as well as new onset or worsening of psychotic and mood disorders [115]. On the other hand, controlled pharmacological modulation of eCBs may be effective in several neuropsychological disorders including substance use disorders (SUDs), anxiety- and stress-related conditions, and autism spectrum disorder (ASD) [116].

CB1 activation triggers signaling cascades, ultimately opening voltage-gated calcium [117] and potassium channels [118], reducing neurotransmitter release. CB1 is largely expressed on axonal terminals of cortical glutamate projecting neurons, GABAergic interneurons, medium spiny neurons, and serotonergic neurons [119]. Thus CB1 can modulate, excitatory, and inhibitory neurotransmission at a large scale [116]. While the CB2 receptor is still involved in the central nervous system (CNS), it is widely expressed in the immune system, where CB1 is the main GPCR in the CNS [120].

Positive allosteric modulators (PAM) of CB1 have been shown to relieve withdrawal, attenuate pain, psychosis, and symptoms of neurodegeneration [121–125]. Negative allosteric modulators (NAM), have potential applications in SUD treatment [116,126]. Both PAMs and NAMs are promising candidates for therapeutic interventions in psychiatric disorders.

FABPs play an important role in the intracellular transport of lipids intracellularly. FABP5 and 7 in particular help transport endocannabinoids including AEA and NAEs [127]. These eCBs are too hydrophobic to travel intracellularly to their degrading enzymes without a chaperone, thus FABP inhibition results in accumulation of these ligands. For example, while AEA in wild-type mice is normally catabolized by FAAH, in FABP5/7 knockout (KO) mice, AEA accumulates leading to chronic CB1 activation, affecting memory, learning, stress response, nociception, mood, and addictive behaviors [116]. Compared to wild-type, FABP5 KO mice have significant differences in the expression of eCB synthesizing or degrading enzymes [28]. This isolates the role of FABPs to assisting with the transport across the synaptic cleft. This is also supported by the lack of increase in 2-AG-mediated signaling in FABP KO mice, as the degrading enzyme monoacylglycerol lipase (MAGL) is expressed mainly on presynaptic terminals [120] unlike FAAH.

Exogenous agonists such as THC and Cannabidiol (CBD) have been found to compete with endogenous eCBs for binding to FABP3, 5, and 7, effectively reducing the rate of AEA degradation. While rodent FAAH was found to be inhibited by CBD, no significant effect on human FAAH has been observed, suggesting that the observed increase in serum AEA levels following CBD consumption could be due to modulation of carrier proteins such as FABPs [128]. This shows the role of FABPs in the effects of exogenous agonists.

The modulation of the eCB system, is a common mediator of the effects of FABP inhibition. FABP5 inhibition is known to ameliorate inflammatory, visceral, and neuropathic pain. FABP inhibition modulates levels of AEA, other eCBs, and NAEs affecting CB1 and PPARα signaling. It is suggested that the antinociceptive effects of FABP inhibitors are not directly due to CB1 activation, but rather the elevated AEA and NAEs. ART26.12, an FABP5 inhibitor, is currently being tested for a potential solution to chemotherapy-induced peripheral neuropathy. In mice and dogs, mechanical allodynia, thermal hyperalgesia, and weight loss associated with the chemotherapy treatments were attenuated by the inhibitor and was found to be a potentially safe, well-tolerated, non-opioid analgesic option [129].

eCBs also play a pivotal role in stress and anxiety response. AEA signaling through CB1 receptors co-localized with glutamate terminals, act as a buffering system for limiting the magnitude and duration of excitatory neurotransmission [130]. In response to stress-inducing stimuli, corticotropin-releasing hormone is released, elevating FAAH function, depleting AEA levels within the amygdala, ultimately inducing and potentially intensifying stress and/or anxiety behaviors [130–132]. Conversely, hypothalamic 2-AG levels are found to be increased following stress response and is thought to aid in the recovery from the anxiogenic effects of stress [133]. FABP modulation may be useful in modulating the eCB transmission involved in anxiety and is a direction for future research. While previous studies have modulated FAAH to induce anxiolytic effects via eCB mechanisms [134–136], FAAH is known to induced adverse off target effects [137] which FABP modulation may help avoid.

Previous studies have shown that eCB system modulation influences positive reinforcement, anxiety, stress-induced craving, and relapse [138]. In a study involving Lewis (LEW) and Fischer 344 (F344) rats strains which examined self-administration of drugs, it was found that F344 rats are far less prone to drug abuse due to higher cannabinoid receptor biding in the lateral globus pallidus, a higher N-acyl phosphatidylethanolamine-specific phos-

pholipase D/FAAH ratio in the prefrontal cortex and nucleus accumbens, and lower CB1 gene expression in the prefrontal cortex [139]. These differences in eCB expression suggest eCBs are at least partially responsible for normative reward system and susceptibility to addiction [139]. Once again use of FABP modulators may be able to produce these effects pharmacologically while avoiding side effects of FAAH inhibitors.

Another aspect that can affect an individual's eCB system are adverse childhood experiences (ACEs), a prominent risk factor for anxiety and subsequent cannabis dependence [140,141]. Chronic stress resulting from ACEs can lead to sustained modulation of the eCB system, creating a lasting vulnerability to cannabis abuse [142,143]. Increased MAGL activity reduces the availability of 2-AG, increasing susceptibility to poor stress recovery, as they rely on cannabis to regulate emotions [144]. This suggests applications of eCB modulation as a potential therapeutic target in SUDs. For instance, MAGL inhibition resulting in increased levels of 2-AG, attenuates the effects of withdrawal in opioid-, nicotine-, and THC-dependent rodents [145–148]. Nonetheless, pharmacological manipulation of eCBs warrant caution with failed trials of a CB1 antagonist, rimbonant, causing negative affective states and suicidal thoughts [149,150]. Blocking CB1 receptors in dams during the postpartum period alters maternal behavior and has lasting effects on offspring's social and emotional development [151]. In addition, the effects of cannabis can vary among individuals based on their stress resilience and social dominance, suggesting that these factors should be considered when prescribing THC-containing medications [152]. This case underscores the need for caution in developing eCB-targeted therapies, as they involve intricate neurochemical processes that require careful clinical evaluation [116]. Future research should assess the efficacy of FABP inhibitors in modulating eCB signaling compared to other pharmacological methods such as rimbonant.

In sum, chronic cannabis intake impairs eCB system and triggers/worsens psychiatric symptomatology, whereas controlled eCBs modulation may be beneficial for SUDs, anxiety, and other psychiatric conditions; FABP inhibitors hold some therapeutic potential for pain and stress management. Further research is needed to further elucidate the role of these proteins in psychiatric disorders, however, again, given their role in pain, stress, and reward behavior, it is clear that the modulation of these proteins to subsequently modulate the eCB system is a promising application to where these proteins can help improve lives.

1.2.4 Polyunsaturated Fatty Acid Transport

PUFAs, characterized by the number and position of carbon double bonds in the chain, are crucial for neurodevelopment, mental health, and overall brain function [153, 154]. n-3 PUFAs including alpha-linolenic acid, eicosapentaenoic acid (EPA), and docosahecaenoic acid (DHA), as well as n-6 PUFAs such as linoleic acid (LA) and arachidonic acid (AA) are most salient in the psychiatric domain. Both n-3 and n-6 PUFAs are abundant in brain tissue and essential for many aspects of brain function [153–155]. Altered levels of PUFAs are associated with numerous mental disorders, such as Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), ASD, and schizophrenia [155–160]. PUFA supplementation has led to some improvements in depression, anxiety, ADHD, ASD, dementia, Huntington's disease, schizophrenia, and mild cognitive impairment [161]. Adequate dietary PUFA and intracranial transport is necessary for proper brain physiology and function [162]. These findings underscore the importance of PUFAs in maintaining and potentially improving brain health and function.

FABP3 is primarily expressed in neurons [163,164] transporting both n-3 and n-6 PUFAs in the brain, with a preference to n-6 PUFAs [165]. FABP3-/- mice exhibit a decrease in social motivation and novelty seeking compared to WT mice [166], as well as increased GABA synthesis and abnormal inhibitory/excitatory balance in the Anterior cingulate cortex (ACC) [165,167] with a particular increase in glutamic acid decarboxylase 67 (Gad67). These changes are implicated in the pathophysiology of schizophrenia and autism, and were reversed by methionine administration demonstrating the role of PUFAs in these effects. In a separate study comparing FABP levels in the frontal cortex of post-mortem brains of schizophrenia patients, FABP3, as well as behenic acid and lignoceric acid concentrations, were reduced [168]. Literature indicates that PUFAs play an important role in FABP3s effect on schizophrenia. Future studies should investigate the molecular mechanisms by which methionine combats the effects FABP3 deficiency. Other methods modulating GABA synthesis, Gad67 expression, and ACC excitability should also be used in FABP deficient models.

FABP7 is primarily expressed in astrocytes and precursor cells [163,164]. FABP7 KO mice exhibit increased anxiety behaviors, where FABP7 was previously known to be preferentially bound to n-3 PUFAs [166]. However, in recent literature, it was shown that FABP7 has no particular affinity to any fatty acid (FA)-type at physiological temperatures. The DHA-FABP7 complex, specifically, is found to be preferentially relocated to the nucleus, which can explain the important role this protein plays in DHA- and other n-3 PUFA-related processes [169]. FABP7 down regulation increases anxiety, depression and altered emotional behavior, due to alterations in dopaminergic and serotonergic pathways as consequence to n-3 PUFA deficiency. FABP7 deficiency results in altered astrocyte response and dendritic morphology, as well as decreased spine density and excitatory synaptic transmission in pyramidal neurons [165]. Future studies should test if the effects of FABP7 deficiency can be ameliorated by administration of other compounds, similar to how methionine reduces the effects of FABP3 deficiency [167].

FABP5, expressed in neurons and glia [163,164], has been shown to assist in transport of DHA across the blood brain barrier (BBB) [170]. FABP5-/- mice have been found to have reduced brain DHA. *In vitro* culture of brain endothelial cells and brain capillaries experience a reduction in 14C-DHA uptake. By contrast transfection of COS-7 cells with FABP5 increases DHA uptake. FABP5-/- mice also display deviations on a battery of cognitive assessments. In the T-maze spontaneous alternation task, FABP5 KO mice experienced a reduced percentage of correct spontaneous alterations indicating working memory impairment. This could possibly be mediated by impairment of the PFC and hippocampus [171]. In the water maze assessment, FABP5 KO mice had latency in reaching the target zone indicating impairment of memory retrieval. FABP5 KO mice also required more training to locate the escape platform. No significant differences in platform escape latency were observed once mice were trained indicating that spatial memory retention was unaffected by genotype. In the novel object recognition (NOR) paradigm, FABP5 KO mice had a significantly lower discrimination index indicating episodic memory impairment. This suggests that the deletion of FABP5 adversely affects episodic memory particularly in the perirhinal cortex [172]. In the Y-maze paradigm, a significant difference in time spent in the two arms by female mice indicate a sex-specific effect of FABP deletion on short term spatial memory. This sex difference may be influenced by sex hormones which are known to interfere with the synthesis of long-chain PUFAs, such as DHA [173]. In the contextual fear conditioning paradigm, FABP5 KO mice demonstrated less freezing behavior. This difference was reduced in the 24-hour re-exposure group compared to the 4-hour re-exposure group. This could be mediated by the recruitment of the paraventricular nucleus of the thalamus in memory consolidation after 24 hours [174,175]. While the role of eCB transmission in mediating these effects have been well studied specific examination of PUFAs should be examined in future studies. Results indicate that the reduction of DHA levels due to FABP5 deletion could play a role in impaired working memory, short-term memory, episodic memory, and fear memory formation. The hippocampus prefrontal cortex and perirhinal cortex could be implicated in mediating these changes. Dietary deprivation or oral administration of various PUFAs in FABP knockout models may help clarify the role of specific PUFAs in the effects of FABP deficits. While changes in DHA and AA [176] distribution have been documented in FABP KO models, characterization of other PUFAs may be help inform future research.

1.2.5 Fatty Acid Binding Protein Inhibitors

Due to their critical roles in diverse signaling pathways and their involvement in various pathological conditions, FABPs have emerged as promising therapeutic targets for a wide range of illnesses. 4-(2-(1-(2-chlorophenyl)-5-phenyl-1H-pyrazol-3-yl)phenoxy)butanoic acid, or MF1, is a ligand for FABP3 [177,178]. Initially found to improve the spreading of α-synuclein oligomerization and dopaminergic neuronal loss in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated mouse model for Parkinson's Disease [178], it was also found to be effective in reducing the cognitive and motor deficits in a Lewy body model in mice, suggesting its potential application in treating dementia with Lewy bodies and further application in Parkinson's [179]. MF1 was also found to have an affinity to $GABA_A$ receptor benzodiazepine recognition site, having a mild anti-epileptic effect and is also implicated in the treatment of neurodegenerative disorders with epilepsy [180]. MF1 was also found to be effective in reducing nicotine conditioned place preference via inhibition of FABP3's interaction with D2 receptor, preventing CaMKII activation and increasing cyclic adenosine monophosphate response element binding protein (CREB) and *c-fos* levels [181].

An inhibitor with higher affinity to FABP3, HY11-09 was also developed by the same research team. Where MF1 failed to improve motor deficits in MPTP-treated mouse model for Parkinson's Disease, HY11-09 significantly ameliorated these deficits, via recovery of dopaminergic (DA) neurons from MPTP toxicity at even low dose, by reducing accumulation of pS129-α-synuclein (α-Syn) due to its relatively high binding affinity to FABP3 [182]. HY11-08 is another FABP3 inhibitor, also having affinity to FABP5, showing potential in treating ischemic strokes. HY11-08 administration prevented FABP3/5 accumulation in mitochondria that promotes Bcl-2-associated X protein (BAX) oligomerization, causing mitochondrial pore formation. In addition, FABP5 causes lipid peroxidation, generating toxins, which HY11-08 was found able to prevent [87].

6 [4-(2-(5-(2-chlorophenyl)-1-(4-isopropylphenyl)-1H-pyrazol-3-yl)-4-fluorophenoxy)butanoic acid], or MF6 is another FABP ligand that has applications in neurological disorders, inhibiting FABP5 and 7 [183]. In a multiple sclerosis model, MF6 inhibition attenuated inflammatory cytokines production, improved mitochondrial function, reduced oxidative stress, and prevented oligodendrocyte injury [184]. MF6 was also found to attenuate transient middle cerebral artery occlusion and reperfusion-induced injury in mice, suggesting a potential therapeutic target for ischemic injury, particularly strokes [183]. Similarly to MF1, MF6 was found to attenuate the effects of α-synucleinopathies [185]. In a multiple system atrophy model, MF6 significantly decreased α-syn aggregation and propagation, reduced oxidative stress and inflammation, improved myelin integrity, and Purkinje neuron morphology [185].

Comparisons between the efficacy of HY11-09, MF1, and MF6 on treating neurodegenerative disorders may be helpful in the future. The GABAegic properties of MF1 make it a candidate for combating stress induced addictive and anxiety-like behavior. Characterizing the relative safety of each compound would help assess feasibility of clinical use.

Table 1. Inclusion criteria for articles.

Criteria	Decision
Articles published in English	Inclusion
Published as a scientific peer-reviewed journal article	Inclusion
Keywords defined previously found in titles and/or abstracts	Inclusion
Primary research, meta-analysis and review papers	Inclusion
Papers published before 1985	Exclusion
Case studies and editorials	Exclusion

2. Search Criteria

We searched PubMed utilizing the search terms ("fatty acid binding protein" OR "FABP") AND ("psychiatry" OR "ADHD" OR "autism" OR "schizophrenia" OR "substance abuse" OR "substance use disorder" OR "addiction" OR "cocaine" OR "ethanol" OR "THC" OR "nicotine" OR "anxiety" OR "depression" OR "major depressive disorder", OR "neurodegenerative" OR "Alzheimer" OR "Parkinson" OR "dementia"). Articles were included if they met the following inclusion criteria (Table 1): (1) English language; (2) publication date from January 1985 to August 2024; (3) peer-reviewed articles including pediatric and/or adult population studies, rat and/or mice studies, neuronal culture studies, review papers and meta-analyses; (4) outcomes related to behavior, psychiatric assessment or pathophysiologic mechanism linked to neuropsychiatric disorders directly implicating FABPs; (5) outcomes related to non-FABP proteins or molecules were included only if FABPs were directly implicated in their mechanism of action in article full-text and consensus among authors deemed inclusion appropriate. Case studies and editorials were excluded. Four reviewers independently screened the titles and abstracts of all articles identified from the electronic database searches. Additionally, if it was unclear from the title and/or abstract whether the article should be included, the reviewers independently assessed the full text of the articles for inclusion and exclusion criteria (Table 1). This search and application of inclusion/exclusion criteria yielded a total of 90 articles. All included articles are referenced in tables.

3. Role of Fatty Acid Binding Proteins in Psychiatric Disease

3.1 Depressive Disorders

Major depressive disorder (MDD) is a prevalent mental illness attributable to a confluence of genetic and environmental factors [186,187]. The most common symptoms include depressed mood, psychomotor and vegetative changes, anhedonia, insomnia, and suicidal ideations [186,188,189].

A subset of MDD, known as treatment-resistant depression (TRD), typically occurs in about 40–50% of patents [190] who do not adequately respond to at least two antidepressant trials of sufficient doses and duration [191]. Recent work suggests, however, that such depression subset may more responsive to transcranial magnetic stimulation (TMS) than to another antidepressant [191–197]. Given the gravity and consequences of MDD [198] in terms of disability [199] and suicidality [200] as well the lack of clarity regarding its etiology, elucidating the biological mechanisms behind the formation of MDD and ensuing TRD is obviously critically warranted both from both, clinical and scientific standpoints.

Previous literature has generally strongly linked FABP2 to the development and severity of MDD, though not all literature is consistent. Past clinical studies have found that liver [201] and intestinal FABP2 were significantly elevated in MDD patients, as compared to patients without MDD [202–205]; these FABP2 levels were also used to individually differentiate between depressed and healthy participants [204,206]. Additionally, FABP2 levels were significantly higher in MDD patients who had recently attempted suicide, as compared to MDD patients with no history of attempts and control patients [204,207]. Depressive symptoms, suicidal ideation, and concentration of FABP2 have been found to be positively correlated [207]. In patients with post stroke depression FABP2 concentrations were significantly higher as compared to stroke patients who did not report depression [208]; severity of depression was correlated with FABP2 concentrations [209].

Associations between FABP5 and FABP7 with MDD have also been found [63]. In rodents, FABPs 5 and 7 deletions led to reductions in immobility time during the forced swim test, pointing to a potential antidepressive effect of the FABP deletions. Activation of the CB1 receptor may be the reason for this effect [63]. Thus, future studies should further work to study the antidepressive effects of FABPs, particularly FABP5 and FABP7.

Altered RXR, PUFA, PPAR signaling have effects on depression-like phenotypes. Chronic treatment with retinoic acid was found to suppress hippocampal neurogenesis while increasing RARα expression [38], and was associated with a depressive-like phenotype. N-3 PUFA deficiency is associated with increased depressive symptoms in patients with schizophrenia and bipolar disorder [163,210,211]. PPARα activation is associated with antidepressant-like effects in rodents [103–105]. Given the varied effects of FABP in different regions of the brain, future studies should look to identify if FABP inhibition in the hippocampus or other brain regions alters depressive behavior.

Table 2. Summary of FABP effects on major depressive disorder.

Protein	Association with condition	Previous findings	Sources
FABP7	Positive correlation with depressive symptomology	Associated with depression in schizophrenia, and as a potential biomarker for the disease Knockout alongside FABP5 associated with psychomotor disparities	[63,212]
FABP2	Positive correlation with depressive symptomology	Associated with MDD, observed to serve as a biomarker for MDD, and linked to suicidal behaviors/ideation However, some literature has not identified any association between FABP2 and MDD	[201–207,209,213]
FABP5	Positive correlation with depressive symptomology	Knockout alongside FABP5 associated with psychomotor disparities	[63]

FABP, Fatty acid binding protein; MDD, major depressive disorder.

While previous literature is not fully consistent with regards to the role of FABPs, it does strongly suggest a positive correlation between FABP expression and depression. It follows that the growing body of research implicating FABPs, particularly FABP2, in MDD and suicidal ideation point to a potential therapeutic target for anti-depressive interventions. Discussed involvement of FABPs in depressive behavior is summarized in Table 2 (Ref. [63,201–207,209,212,213]). Further inquiry into the complex interplay of FABPs with RXR, PUFA, and PPAR signaling pathways may offer novel insights into the pathophysiology and treatment of MDD.

3.2 Anxiety Disorders

Anxiety and anxiety-related disorders are some of the most diagnosed mental conditions [214,215]. The primary characteristics of anxiety include excessive worry or fear, apprehension, nervousness restlessness, irritability, dread, feeling on edge, agitation, or inability to relax, distractibility, avoidance behavior, rapid heart rate, shortness of breath, dizziness, and sweating [189,216,217]. Due to the widespread nature of this disorder, as well as the substantial disability [218] associated with the ensuing sequalae, e.g., agoraphobia [219], it's essential to continue inquiry into the mechanisms and therapeutic agents indicated along various stages of anxiety disorders' time course. Preclinical literature by and large supports FABPs role in anxiety and anxiety-related behaviors (Table 3, Ref. [22,23,58,166,204,220–224]). However, observed effects are not entirely consistent.

FABP7-/- animals display an increase in both fear memory and anxiety [23,220] demonstrated by open field test, elevate plus maze, light/dark box, fear conditioning, resident intruder test. A previous review of literature identified FABP7 as a regulator of the startle reflex, but having no effect on anxiety-like behavior assessed by the Novelty Suppressed Feeding Test [221]. Given the large battery of behavioral tests demonstrating that FABP7 deficit is anxiogenic compared to the single contrasting test, literature supports concluding that deficit as causing anxiety-like behavior.

FABP5 inhibition mediates the activity of several memory protein markers related to fear and anxiety including Akt, rpS6, Erk 1 and 2, and JNK 1 and 2 [22]. However, behaviorally, FABP5 inhibition accelerates fear extinction and reduces anxiety levels, without impacting cognition or motor behaviors [22]. Such anxiolytic effects are attributable to increased AEA due to FABP5 inhibition [22] similar to the effect of FAAH inhibition [225]. The anxiolytic effects of FABP5 inhibition are achieved without altering locomotor activity, memory, or learning [58].

Only one study has assessed the effect of FABP3 on anxiety-like behavior [222]. FABP3 deficit was found to impair fear extinction, without altering acquisition.

The clinical data is more scarce. One study observed the effects of a cardiac rehabilitation program on patients who had suffered recent cardiovascular events [223]. While both, an improvement in psychological well-being and a reduction in FABP3 were reported; the two variables were not linearly related [223]. However, other clinical studies have noted a significant link between anxiety and levels of FABP [204,226]. FABP2 was significantly increased in patients with comorbid MDD and anxiety as compared to patients with MDD only [204]. A similar study noted that compared to patients without depression or anxiety, patients with MDD had significantly higher levels of FABP2 in the plasma [226]. Ultimately, existing clinical studies only tangentially inform FABP involvement in anxiety. Studies in patients exclusively selected based on an anxiety diagnosis would help determine whether preclinical models are translatable.

The role of FABP3 and clinical role of FABPs in anxiety are major gaps in the existing literature linking FABPs to anxiety. Overall preclinical literature indicates that FABP7 deficit is anxiogenic while FABP5 deficit is anxiolytic. Existing literature on FABP3 indicates that deficit is anxiogenic, however more research is needed before a conclusion can be made [222]. Investigation into PPAR and PUFA signaling pathways may help further elucidate this link. Respective sections of these signaling pathways contain more detailed information on their potential involvement.

Table 3. Summary of FABP effects on anxiety.

Protein	Association with condition	Previous findings	Sources
FABP5	Inhibition is associated with altered anxiety	Associated with fear/fear memory and anxiety behaviors	[22,58]
FABP7	Inhibition is associated with increased anxiety and fear memory	FABP7 has been linked to the startle reflex and its inhibition increases anxiety and fear memory FABP7 KO mice showed an anxiety related phenotype	[23,166,220,221]
FABP3	Not associated with psycho-emotional status in cardiac rehabilitation patients Associated with PTSD like behavior upon removal in mice	Not found to be linked to psycho-emotional status of patients in coronary artery bypass grafting patients FABP3 KO mice found to display brain activity similar to PTSD subjects	[222,223]
FABP2	Associated with anxiety	Found to be increased in patients suffering from both MDD and anxiety, compared to patients with only MDD	[204]
FABP4	Induction of stress may potentiate secretion of FABP4	Sources of stress were found to be possible factors in inducing release of FABP4	[224]

PTSD, Post-Traumatic Stress Disorder; KO, knockout.

Table 4. Summary of FABP effects on schizophrenia.

Protein	Association with condition	Previous Findings	Sources
FABP3	Associated with physiological function of frontal cortex Hypomethylation of *Gad67* gene in ACC	FABP3 is deficient in the BA8 of schizophrenic patients FABP3 KO mice demonstrate an enhanced inhibitory synaptic transmission	[167,168]
FABP5	Associated with schizophrenia	FABP5 level elevated in postmortem brains, while decrease in blood	[220]
FABP7	Associated with physiological function of PFC Associated with PPI inhibition	FABP7 deficiency in astrocytes alter dendritic morphology, decreased spine density and excitatory synaptic plasticity of pyramidal neurons FABP7 expression is elevated in the PFC and parietal	[14,16,165]

ACC, Anterior cingulate cortex; PFC, prefrontal cortex; PPI, prepulse inhibition; BA8, Brodmann area 8.

3.3 Schizophrenia

Schizophrenia is a chronic neuropsychiatric syndrome characterized by impairments in the perception or expression of reality. Additionally, cognitive impairments such as deficits in attention, memory, and executive function, have been recently recognized as a core feature of schizophrenia [189,227]. Schizophrenic patients may exhibit a variety of symptoms, including hallucination, delusions, or cognitive impairments as well as mood and anxiety symptoms, all of which significantly impair social or work-related functioning [228]. Diagnosed patients tend to also manifest depressive and anxiety disorders [229]. The PFC is crucial for working memory, and reduction in PFC activation linked to social and cognitive impairments observed in schizophrenia [230,231]. There are various linkages between PFC dysfunction and microcircuit malfunction, such as altered the expression of dopamine- [232], N-methyl-D-aspartate (NMDA)- [233], CB1- [234], and 5-hydroxytryptamine- [235] receptors.

FABP7 deficient mice show decreased PPI, a clinically relevant measure of sensoriomotor gaiting [236], which is commonly inhibited in schizophrenia [237]. Notably, post-mortem brains of schizophrenic patients show increased FABP7 expression in the prefrontal cortex [14], which may be attributable to compensatory changes arising in the context of disturbed FABP7 and/or lipid metabolism regulation during developmental stages [14]. However, the role of FABP7 in PPI requires further investigation, as it appears that genomic sequences flanking the FABP7 interval impacts expression of schizophrenia-like phenotype in mice. Depending on the background strain, the effect of FABP7 ablation on PPI can be abolished [238].

NMDA hypofunction is a proposed etiological factor in schizophrenia [239,240], associated with paranoia, perceptual alterations, conceptual disorganization, and fragmented thinking [241–243]. NMDA receptor antagonists, such as phencyclidine and ketamine, produce temporary schizophrenia-like symptoms in healthy individuals [244–246]. Cannabis usage is linked with the risk of developing schizophrenia in adulthood due to earlier exposure during adolescence [247,248]. Cannabinoid, Δ9-THC, administration exhibit similar symptoms observed with antagonist-induced NMDA dysfunction. FABP7 KO mice show increased NMDA binding in the caudal striatum using autoradiography binding while exhibiting no change in locomotion or anxiety-like behavior [249]. Furthermore, Watanabe *et al*. [14] (2007) show a blunted response of DHA on NMDA-induced current in isolated hippocampal neurons of FABP7 KO mice. Suggesting that FABP7 is crucial in maintaining the homeostasis function of NMDA receptors, potentially through alteration in the lipid environment. Additionally, previous studies have shown the cross talk between eCBs and the dopaminergic system is consistently implicated in the pathophysiology of schizophrenia [250,251]. eCB signaling in the ventral tegmental area (VTA) stimulates activation of midbrain dopamine cells and promotes dopamine release in terminal regions such as the nucleus accumbens (NAc) [252–254]. Therefore, alterations in eCB transmission and DHA content induced via FABP7 pathways in the brain may be a reasonable target for further research in schizophrenia. The role of FABP7 in modulating dopamine signaling should also be investigated.

Schizophrenia is also associated with enhanced inflammatory function [255] in part due to diminished PPARγ receptors' activity [89] that normatively promote anti-inflammatory responses via increases in anti-inflammatory genes' expression and down-regulation of pro-inflammatory mediators [256]. Fenofibrate, a PPARα agonists, helps reduce dopaminergic dysfunction and subsequent behavior of schizophrenia under maternal immune activation (MIA) model [99,100], suggesting a new pharmacological target for treating the disorder. As previously described, FABP5 selectively delivers ligands to PPARβ/δ forming heterodimer with RARs; thereby, inducing transcriptional activity [73]. RAR signaling involves regulating the expression and activity of TH [44,45] and dopamine receptors [46,47], which was shown to be an essential marker for schizophrenia. As shown in Table 4 (Ref. [14,16,165,167,168,220]), FABP5 levels are elevated in human schizophrenic postmortem brains while being reduced in peripheral lymphocytes living schizophrenia patients [220], as suggested by the author to be a less invasive biomarker for schizophrenia diagnosis.

FABP7 deficiency in astrocytes caused aberrant dendritic morphology, and decreased spine density and excitatory synaptic plasticity of pyramidal neurons in the PFC [16]. Moreover, FABP7 KO mice show decreased repulse inhibition, increased anxiety behavior, and hyperlocomotion [14,249]. The differences observed could be due to the substrain of mice and method of generation used in the study, where Watanabe *et al*. [14] (2007) and Khan *et al*. [249] (2024) used C57BL/6 and conventional knockout model while Shimamoto-Mitsuyama *et al*. [238] (2020) used C57BL/6NCrl (B6N) and CRISPR-Cas9 model. The mechanism of FABP is still not fully understood, given its potential and complex role in psychiatric disorders, further research is needed. Identifying pharmacological methods of correcting the effects of altered FABP7 expression implicated in schizophrenia is needed from future research.

FABP3 mRNA was found to be significantly lower in the postmortem frontal cortex, specially Brodmann area 8 (BA8), in schizophrenic patients [168]. A significant inverse association were also observed from the same sample, between FABP3 expression and behenic acid and lignoceric acid. However, no correlation was found between FABP3 and major PUFAs, indicating that while FABP3 expression is altered in schizophrenia, it may not be directly linked to PUFA levels in this brain region. As discussed above, FABP3 KO mice show reduced glutamate release in the ACC due to hypomethylation of *Gad67* gene, which IS linked to AN increase in GABA synthesis, enhanced inhibitory synaptic transmission and alteration in

PUFAs [167]. Given its potential and complex role in psychiatric disorders, the precise mechanisms underlying the involvement of FABPs in psychiatric disorders are not fully understood, and further research is needed. This may be a timely endeavor as research points to roles for genetic, inflammatory, and neurochemical factors, including alterations in lipid metabolism and endocannabinoid signaling, that warrant consideration as potential intervention points in schizophrenia.

3.4 Neurodegenerative Disorders

Neurodegenerative disorders can be characterized as conditions that cause progressive damage to neuron structure, function, and/or viability, leading to impairment in movement, cognition and other neurological function over time. FABPs are involved in mitochondrial damage induced by ischemic stroke and consequent neurodegeneration [87] as well as in neuropathology of a group of neurodegenerative disorders namely, synucleinopathies [257].

Synucleinopathies are a group of neurodegenerative diseases characterized by aggregates of alpha-synuclein proteins in neurons, glia or nerve fibers including Lewy body disease (LBD) and multiple system atrophy [219]. The LBD class includes Parkinson's disease (PD), PD with dementia, and dementia with lewy bodies (DLB), while the multiple system atrophy (MSA) class includes MSA with predominant cerebellar ataxia and MSA with predominant parkinsonism. Importantly, FABPs are useful biomarkers in discerning between DLB, PD, AD, and cerebral infarction [68,258–261].

There are no disease modifying therapies for synucleinopathies, and current research is aimed at identifying mechanisms by which α-synuclein (α-Syn) is converted to pathologic oligomers and insoluble fibrils [257]. α-Syn, a 140-amino acid protein, is associated with synaptic vesicles in presynaptic nerve terminals, and β-sheet fibrillar α-Syn aggregates are major components of Lewy bodies [262]. Mutations of α-Syn can cause disaggregation, transcriptional deregulation, and silencing of DNA; dysfunction of golgi and endoplasmic reticulum, and disruption of collagen production [263,264]. α-*Syn* mRNA levels vary significantly across brain structures and change dynamically with age, indicating their importance in brain development and aging [265]. These cellular dysfunctions are associated with DLB and PD particularly in DA neurons. α-Syn aggregation is also associated with loss of DA neurons [266], a major part of PD pathogenesis [267]. Fatty acid metabolism has been shown to be involved in aggregation of α-Syn, and interaction between monomeric α-Syn and fatty acids have been shown to accelerate formation of α-Syn oligomers [268–270], further implicating FABPs in PD pathogenesis. Long chain polyunsaturated FAs in particular have been shown to bind and accelerate oligomerization [268,271,272].

α-Syn-FABP3 aggregates are abundant in damaged DA neurons in a 1-methyl-1,2,3,6-tetrahydropyridine induced PD mouse model [273]. α-Syn oligomerization and its associated toxicity depends on monomer uptake [274–276]. FABP3 has been shown to be critical for α-Syn monomer uptake and oligomerization, as genetic or pharmacological reduction in FABP3 activity attenuates neurodegeneration in PD mouse models [177,178]. *In vitro* analysis demonstrated that in the 1-methyl-4-phenylpyridinium PD model, FABP3 is involved in uptake of α-Syn monomers, axodendritic retraction, and mitochondrial dysfunction in dopaminergic neurons [274].

Although the bulk of literature has examined the role of FABP3 in synucleopathies, FABP5 and 7 may have some involvement. FABPs have been shown to be involved in induced mitochondrial dysfunction and loss of tyrosine hydroxylase, a rate-limiting enzyme in dopamine production [277,278]. FABP3 and 5 has been shown to be involved in mitochondrial dysfunction by triggering pore formation leading to oxidative stress and ultimately cell death [60,87,278,279]. FABP7 has been shown to involved in mitochondrial α-syn accumulation in the oligodendrocytes of multiple system atrophy mouse models [278,280,281]. FABP7 inhibition has been shown to reduce α-syn oligomerization and aggregation, preventing degeneration of glia and oligodendrocytes in multiple system atrophy model cells and mice [185,280,281].

FABPs may also be involved in both susceptibility and severity of strokes and cerebral ischemia/reperfusion injury. Strokes cause activation of a cascade of inflammatory and degenerative mechanisms, which can lead to stroke induced secondary neurodegeneration [282]. Blood FABP4 levels have been shown to positively correlate with poor prognosis in ischemic stroke patients and appears to regulate inflammation using PPARγ related mechanisms [283]. Pharmacological inhibition or genetic deletion of FABP4 has been shown to reduce infarction volume, cerebral oedema, neurological deficits, and neuronal apoptosis. Degradation of tight junction proteins and induction of matrix metalloproteinases-9 (MMP-9) is also reduced following the aforementioned modulations in FABP4 [284]. FABP3 and 5 have been found to be involved in ischemic stroke induced mitochondrial damage as they mediate formation of BAX-containing pores in the mitochondrial membrane [87]. FABP5 also appears to be involved in stroke mediated inflammation by promoting activation of NF-κB through the signaling pathway initiated by interleukin 1 beta and subsequent entry into the nucleus [285]. α-Syn has been implicated in post stroke brain damage has been previously associated with FABPs [286]. FABP7 inhibitor MF6 has been shown to reduce the cerebral infarction volume and neurological deficit in Transient middle cerebral artery occlusion mice by the inhibiting inflammation-related microsomal prostaglandin E synthase-1/prostaglandin E-2 pathway [183]. Further research is warranted to elucidate the specific mechanisms

Table 5. Summary of FABP effects on neurodegeneration.

Subtype	Association with condition	Involved in	Sources
FABP3	↑ in CSF & Serum of PD, PD+D, & DLB patients	α-Syn uptake and oligomerization PD related mitochondrial dysfunction	[68,177,178,259,277,287–293]
FABP4	Serum levels positively correlate w/stroke severity	Regulates inflammation via PPARγ & ERS	[283,284]
FABP5	↓ BBB expression in AD patients ↑ brain expression following hypoxia ↑ brain expression following ischemic injury	PD related mitochondrial dysfunction AD related Omega 3 deficiency	[60,87,278,279,294,299]
FABP7	↑ in CSF & Serum of PD & ischemic stroke ↓ in serum of AD	α-Syn accumulation and oligomerization	[87,185,278,280,281,294]

CSF, cerebrospinal fluid; PD, Parkinson's disease; DLB, dementia with lewy bodies; BBB, blood brain barrier; AD, Alzheimer disease; α-Syn, α-synuclein; PPAR, peroxisome proliferator activating receptor; ERS, endoplasmic reticulum stress; ↑ , increase; ↓ , decrease.

underlying the involvement of FABPs in ischemic injury and explore the clinical potential of FABP inhibitors in for preventing neurodegeneration.

In addition to being directly involved in the pathology of various neurodegenerative disorders, FABPs also serve as biomarkers differentiating between similar disorders. FABP3, in particular, is elevated in cerebrospinal fluid (CSF) and serum in patients with PD, Parkinson's disease with dementia (PDD) and DLB [68,278,287–293]. Higher FABP3 levels are observed in patients with DLB than in PDD and AD, suggesting its potential as a suitable biomarker for this specific diagnosis [294]. However, use of FABP3 as a biomarker should be combined with other diagnostic techniques such as measurement of CSF tau protein [68] and heart to mediastinum ratio [259]. FABP5 and 7 have also been found to be implicated in a range of neurodegenerative diseases serving as distinguishing biomarkers, and signs of neuroinflammation and stroke [294–298]. Reduced FABP5 at the BBB is associated with severity of cognitive decline and DHA depletion in the brain [299]. FABPs appear to be general markers of neuronal and glial damage, as summarized in Table 5 (Ref. [60,68,87,177,178,185,259,277–281,283,284,287–294,299]). Further investigation is required to determine if FABP elevations can be used alone, or in combination with other markers to reliably identify specific neurodegenerative pathologies.

FABPs have also been shown to play a role in RAR and PPAR signaling. Future research into the effect of FABP modulation on these signaling pathways and subsequent behavior and disease states may yield useful results in combating neurodegenerative disorders. RAR signaling is involved in striatal development, a region which is dysfunctional in Parkinson's. PPAR pathways have been shown to be involved in Parkinsons disease, Alzheimer's disease, Huntington's disease, ischemic encephalopathy, and hepatic encephalopathy [78,300]. Mitochondria metabolism and APP are involved in neurodegeneration and regulated by PPAR signaling [84,85]. These signaling pathways are described in more detail in their respective sections of this review.

In conclusion, owing to their role in α-synuclein aggregation and mitochondrial dysfunction, FABPs are implicated in pathophysiology and serve as biomarkers for neurodegenerative disorders like synucleinopathies. In addition, FABPs contribute to ischemic stroke and inflammatory outcomes, calling for further inquiry into therapeutic and diagnostic implications in discerning between related neurological conditions.

3.5 Autism Spectrum Disorder

ASD, is a collection of neurodevelopmental disorders characterized by social impairment, communication difficulties, and restrictive repetitive behaviors. Individuals with ASD are also at increased risk for co-occurring conditions like epilepsy, depression, anxiety, ADHD, insomnia, and self-harm that may necessitate separate diagnosis and treatment [301,302]. FABP and other FA-related processes have been speculated to be a factor in the neuropathology of this complex condition (see Table 6, Ref. [23,166,303–318]).

FABP3, FABP5, and FABP7 polymorphisms are associated with autism [163,166,319]. In post mortem brains of ASD patients, FABP7 expression was found to be upregulated in the prefrontal and parietal cortices [166]. Six missense and two frameshift mutations of FABP3 and FABP7 were also identified in the post mortem brains. The two frameshifts, (FABP3E132fs and FABP7N80fs) were found to be unstable in cultured cells. The two patients with the mutations were found to have hyperlipidemia, meaning their fatty acid uptake into cells may have been decreased, suggesting little to no function in the respective FABPs. Four of the missense mutations showed no changes in intracellular localization where the other two, FABP7 S86G and FABP7 V126L lost their affinity to DHA and linoleic acid. FABP7 V126L was also found to be prone to aggregation, suggesting that mutations in FABPs and subsequent dysfunction can be an underlying cause of ASD. However, more research is needed to show the association of these proteins to ASD to elucidate this causal relationship. The ability for fatty acid administration as well as pharmacological methods of increasing brain uptake of fatty acids, to

ameliorate the effects of reduced FABP7 function should be investigated.

FABP7 plays an important role in n-3 PUFA transport, and is mainly expressed in astrocytes, oligodendrocyte progenitors, and neural stem cells [23,164,169]. DHA was found to be significantly lower in postnatal FABP7 KO mice, exhibiting decreased neurogenesis in the hippocampus, showing the role FABP7 has in neurodevelopment [14,23,166]. With this in mind, it is clear that FABP7 KO are not able to modulate NMDA receptor activation through DHA. Reduced NMDA function is involved in many disorders, including ASD, Bipolar Disorder, Obsessive Compulsive Disorder, and certain types of ADHD, and is suggested that FABP7 could be a common factor in these diseases [23,303–306]. PUFA metabolism during development is also a suggested pathology of ASD and related diseases [23,166]. In short, DHA deficiency via FABP7 dysfunction leading to a lack of NMDA activity, as well as other n-3 PUFA-related processes could be the basis of behavioral and emotional irregularities of FABP7 KO mice [166].

Maternal microbiota and diet have substantial neurodevelopmental implications that can be associated with ASD [320]. Improper PUFA supplementation during pregnancy and poor microbiota due to mother's diet can elicit behavioral, motor, developmental deficits, including an association with ASD itself [307–309]. It's speculated that upregulation of the three FABP subtypes occurs during neurodevelopment continuing through adulthood due to disrupted use or metabolism of omega-3 PUFAs, reflecting the fetal programming and developmental origins of the disease [166,310,311]. This further shows the importance of PUFA supplementation and function in ASD. Since FABPs are largely implicated in the transport of these FAs, this is also a promising future direction in neuropsychiatric research to further elucidate the role of these proteins in the neuropathologies of ASD and related disorders.

ASD is also known to be associated with immune alterations, specifically, an increase in inflammatory cytokines in blood cells and mucosal lymphocytes [321]. Tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-6, IL-8, and IL-12 were all found to be increased in serum and CFS of children with ASD [322–324]. In the case of GI alterations due to chronic systemic inflammation, FABP2, lipopolysaccharides (LPS), and plasma soluble CD14 (sCD14) serve as biomarkers for intestinal permeability. Of these three, serum FABP2 levels were significantly augmented, where sCD14 was reduced [312]. FABP2 is mainly expressed in the intestines and is responsible for leading fatty acids in intestinal lumen to enterocytes [325]. The presence of FABP2 in blood is a marker for inflammation and enterocyte damage [325]. The importance of these results is that these inflammatory factors may be carried into the CNS through the BBB by peripheral immune cells, either activating the production of inflammatory factors or activating the inflammation themselves in the CNS, causing the neuroinflammation associated with ASD [313]. Moreover, higher circulating FABP2 was associated with more severe ASD linked social impairment in young children [312]. Given that these inflammatory factors are associated so closely with this disorder, another promising relation between FABPs and ASD is through inflammation. Whether it be crossing the BBB via FABPs or another mechanism entirely, the role of neuroinflammation in ASD and other disorders such as MDD should be examined for further understanding the relation between these disorders and the role of FABPs in their pathologies.

Another potential aspect of the relationship between ASD and FABPs is short chain fatty acids (SCFAs). SCFA administration to mice elicits behavioral and neuropathological effects consistent with findings in ASD patients [314,326]. Gut related environmental signals can epigenetically modulate cell function, suggesting SCFAs' role es environmental contributors to ASD [315]. This is due to lowered SCFA levels activating inflammatory processes, such as the absorption of LPS, which again, may cause increased permeability in the BBB and elicit the novel neuroinflammation [316]. It was also found that PUFA supplementation on FMR1 KO mice model of ASD improved social interaction and emotional/non-spatial memory [317]. n-3 PUFA is consistently associated with anti-inflammatory action and opposes the aforementioned inflammatory cytokines, such as TNF and IL-6 [318]. This is also important to the relation of FABPs to ASD, since these FA-related factors are so closely associated with this disorder. Not only the role of PUFA, mentioned multiple times, but SCFAs as well are associated with the neuroinflammatory aspects of this disorder. Perhaps the balance between the two types of circulating FA is important to maintain non-pathological conditions, however further research is still needed to uncover the potential link between these two, as well as the potential link to FABPs in these processes. To summarize, FA metabolism dysregulations, including FABPs and their interaction with omega-3 PUFAs, plays a crucial role in the course and development of ASD in conjunction with persistent inflammation, as well as the potential role of FABPs in their interactions with these inflammatory factors, may be the future direction in which we can develop a greater understanding of the adverse impact of this disorder on brain function and behavior.

3.6 Attention Deficit (Hyperactivity) Disorder

ADHD is a neurodevelopmental disorder characterized as a persistent pattern of inattention and/or hyperactivity that interferes with everyday function and overall development [189]. It is one of the most recognized childhood disorders with a global prevalence of approximately as of 2022, 7.1 million, or 11.4% of children aged 3–17 years in the US had been diagnosed with ADHD [327]. Globally, as of 2022, 366.33 million adults were reported to have symptomatic ADHD [328]. With its prevalence, it is necessary to understand the mechanisms involved on the biochemical level to fully understand ADHD function.

Table 6. Summary of FABP effects on ASD.

Compound	Association with condition	Previous findings	Sources
FABP7	Upregulation (upreg) in PFC and parietal cortex KO known to exhibit anxiety and hyperactivity Mutations in postmortem brains of patients with ASD identified	Upreg in development, so compensatory upreg in adulthood may reflect disrupted FA metabolism Patients with FABP7 and 3 mutations were found to have hyperlipidemia, suggesting poor FABP function DHA deficiency affects NMDA function, which is also associated with Bipolar Disorder, Obsessive Compulsive Disorder, and ADHD	[23,166,303–306,310,311]
FABP3	Mutations in postmortem brains of patients with ASD identified KO known to exhibit decreased social memory and novelty-seeking		
FABP5	Associated with ASD and schizophrenia		
FABP2	- Higher levels due to enterocyte damage - Intestinal marker for inflammation	Along with other inflammatory factors, may cross the BBB and may be the cause of ASD neuroinflammation	[312,313]
n3-PUFAs	Insufficient supplementation can lead to ASD-like neurodevelopmental issues	Anti-inflammatory, improves neuro-inflammation and behavior in mice and humans	[307–309,317,318]
SCFAs	Abnormal levels elicit behavioral and neuropathology of ASD in mice	Activated inflammatory action, can increase permeability of BBB and neuroinflammation	[314–316]

ASD, autism spectrum disorder; PUFAs, polyunsaturated fatty acids; SCFAs, short chain fatty acids; DHA, docosahecaenoic acid; NMDA, N-methyl-D-aspartate; ADHD, attention deficit hyperactivity disorder; FA, fatty acid.

Table 7. Summary of FABP effects on ADHD.

Protein	Assoc w/condition	Previous findings	Sources
DHA	Important for DAergic function, specifically D2R expression	DHA deficiency associated with/decreased D2 and upregulated D1 in rats	[336,337]
FABP5	Implicated in uptake of DHA into CNS, via BBB	DA transport also associated with FAs, especially DHA	[336,337]
FABP3	Binds to D2R and regulates D2R	D2R regulates hyperactivity. ADHD implicated with low DA receptor densities	[333,334,338]

CNS, central nervous system; DA, dopaminergic. D2R, dopamine 2 receptors.

Table 8. Summary of FABP effects on THC dependency.

Protein	Abnormality	Important notes	Sources
FABP1/5	Knock out	Alteration in pharmacokinetic of THC	[346,347]
FAAH and MAGL	Pharmacological inhibition	Decrease THC withdrawal symptoms	[148]

FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; THC, tetrahydrocannabinol.

The first pathophysiological models of ADHD from 1997 indicated dysfunction in the frontal cortex and basal ganglia [329]. However, more recent developments point towards a delay in cortical maturation as a key factor ADHD. A review of ADHD literature found reduced volume of gray and white matter in brain regions such as the prefrontal cortex, caudate nucleus, and cerebellum [330].

On a microscopic level, ADHD patients have low dopamine receptor densities with hypofunctionality of the dopaminergic system [330]. For instance, dysregulation of the inhibitory dopamine 2 receptors (D2R) mediate hyperactivity in ADHD [331] mice model [332]. FABP3 binds to and regulates D2R, where FABP3 KO exhibit D2R dysfunction [333]. This is potentially a direct link between FABP3 and ADHD via D2R dysregulation, since this neurotransmitter is so closely associated with this disorder.

Dopamine transport has been hypothesized to be facilitated by FAs, specifically DHA [334]. This fatty acid accumulates in the brain during perinatal cortical expansion and maturation [335]. In order for DHA to continue being produced throughout a mammal's lifetime there needs to be either enough dietary alpha-linolenic acid for DHA synthesis to occur or direct dietary DHA supplementation. For DHA uptake into the brain to happen, it must be carried into the bloodstream and cross the BBB. FABP5 facilitates uptake of DHA across the BBB, suggesting a crucial role in supplementation of DHA for optimal cerebral function [336]. Decreased brain DHA in female rats significantly decreased ventral striatal D2-like receptors and increased D1-like receptors in the caudate nucleus [337]. Potentially, FABP5 dysfunction can decrease DHA uptake into the CNS and affect the DAergic system, and in turn cause ADHD-like symptoms. This is similar to the role of this protein in ASD as previously mentioned. The role of PUFA supplementation and regulation/function via FABP5 in neurons and potentially FABP7 in astrocytes [23,164,169] can be key factors in the relationship between FABPs and this disorder. However, especially for ADHD, there is very little research on this, so future studies examining the role of FABPs in ADHD are needed to uncover these potential relations. In short, through direct activation and regulation of D2R via FABP3, or through diminutions in DHA concentration due to FABP5 are the pathways in which FABP may be implicated in the pathologies of ADHD and present an interesting target for treatment of this disorder (see Table 7, Ref. [333,334,336–338]).

3.7 Addiction Behavior

3.7.1 Delta-9-Tetrahydrocannabinol

Cannabis is one of the most frequently abused substance in the United States, with THC being its primary psychoactive constituent [339]. As indicated above, THC exhibits high affinity for CB1 and acts as a competitive inhibitor of FABP, consequently modulating the activity of eCBs which regulate various physiological responses including positive reinforcement [340,341]. However, evidence regarding the rewarding properties of cannabis is inconsistent, and the underlying mechanisms are poorly understood. Human vaping and use of very high dose THC, repeatedly and daily, have raised alarms and stimulated the use of vapor models to help understand dose and dependence [342]. CB1 agonists have been shown to be involved in modulating DA release in a dose dependent manner in the VTA and striatum, which are two important brain areas involved in drug reward and relapse [343–345].

Despite the central role of FABPs in the mediation of THC's physiological effects, the investigation into FABPs' influence on THC-seeking behavior remains somewhat limited. Previous studies have shown that FABPs modulate the pharmacokinetics of THC as chaperone proteins [346,347]. FABP1 KO mice exhibit reduced rates of THC biotransformation by hepatic function [346] and FABP5-/- mice display a higher level of THC and its metabolites throughout the whole brain [347], resulting in a prolonged pharmacological impact (Table 8, Ref. [148,346,347]). Thereby increasing the risk of adverse effects and potential pharmacodynamic interactions with other compounds. Furthermore, FABP5-/- animals display low clearance in the brain while reducing serum levels immediately following THC administration, further strengthening the role of FABP5 in the distribution of THC in the brain [347]. Deletion of FABP5 in mice resulted in upregulated expression of the D1R receptor in specific subregions of the striatum within the caudal brain [348]. Genetic deletion of FABP5/7, but not pharmacological inhibition, increases sucrose consumption in mice [63]. These findings suggest a potential regulatory association between the *FABP5* gene and the expression of D1-like receptors, implying that the endocannabinoid ligands may play a role in mediating reward-seeking behaviors warranting further investigation to elucidate this relationship.

On the other hand, elevation of AEA in FAAH-/- mice does not alter THC withdrawal response, whereas pharmacological inhibition of FAAH and MAGL decrease withdrawal symptoms using URB597 and JZL184, respectively [148]. Thus, even though FABPs seem to mediate THC's effects in terms of pharmacokinetics and distribution, their

Table 9. Summary of FABP effects on alcohol dependency.

Protein	Abnormality	Important notes	Sources
CB1	Knock out or pharmacological inhibition	Reduces ethanol drinking behavior in mice	[353,354]
FAAH	Knock out or genetic down regulation	Increased preference for and consumed significantly more alcohol	[360,361]
FAAH	Pharmacological inhibition after exposure	Reduce reinstatement of alcohol consumption	[356]
FABP5 and 7	Pharmacological inhibition	Reduced preference for and consumed less alcohol	[362]
TRPV1	Knock out	Increase ethanol consumption	[363]

TRPV1, vanilloid receptor 1.

Table 10. Summary of FABP effects on nicotine.

Protein	Association with condition	Previous findings	Sources
FABP3	Knock out reduces addictive effects of nicotine	Knock out of gene suppressed conditioning and relapse phases, reduced CPP scores, and reduced increase in dopamine receptors	[181,377]
FABP5	Deletion of FABP5 increased addictive properties of nicotine	Global deletion of FABP5 increased reinforcing aspects of nicotine at low doses	[374]
FABP4	Involved in harmful effects of nicotine	Apoptotic and inflammatory impact of nicotine on bronchioles were linked to an increase in FABP4	[376]
FAAH	Associated with rewards from nicotine	Knock out of *FAAH* gene inhibited nicotine rewards	[375]

CPP, conditioned place preference.

precise impact on dopamine signaling and reward-seeking behaviors has not yet been sufficiently elucidated. Future studies could cross-examine biochemical markers, such as D1R receptor expression or TH, to further explore the intricate relationship between the catalytic activities of FAAH and MAGL and the role of FABP in mediating protein expression within the dopaminergic system.

3.7.2 Ethanol

Alcohol is the most commonly used substance in the United States, with 84% of people 18 and older reporting lifetime use, according to data from the 2022 National Survey on Drug Use and Health [349]. Alcohol use disorder is a chronic relapsing disease with devastating biopsychosocial and societal implications. As indicated above, eCBs play a significant role in the control of drug intake and addiction, including alcohol use disorder (AUD). The eCB system regulates Glu and GABAergic synaptic activity within the basolateral amygdala (BLA) and dopamine content in the NAc, which are crucial for the development and expression of withdrawal-induced anxiety [350,351]. It has been reported that the eCB system exhibits a dynamic and neuroanatomically dependent responses to alcohol consumption [350]. Previous research primarily focused on the role of eCBs via genetic or pharmacologic manipulation activity of metabolic enzymes, FAAH and MAGL, and ligand interaction with cannabinoid receptors [352–358]. However, limited studies have examined the role of mediators such as FABP in this context [352,359].

Blockade or deletion of CB1s reduces ethanol drinking behavior in mice with no associated characteristic increases in NAc dopamine release [353,354]. Conversely, stimulation of CB1 increases ethanol preference [355]. Similarly, reduced FAAH levels in the brains via genetic manipulations mice in the brains are associated with increased preference for and consumption of alcohol (see Table 9, Ref. [353,354,356,360–363]) [360,361]. Furthermore, it has been observed that both chronic and acute alcohol consumption can alter the level of AEA in various regions of the brain via calcium-dependent mechanism [352]. However, rats injected with FAAH inhibitor, URB597, in the PFC and BLA consumed significantly less alcohol after the animals had developed a stable baseline of alcohol intake [356], while injection in the peripheral and VTA did not alter alcohol consumption [357]. Additionally, URB597 reduced alcohol consumption in mice in early withdrawal [358]. In short, FAAH is dysregulated in early withdrawal, and FAAH inhibition in early withdrawal may reduce reinstatement of alcohol consumption [355].

Similarly, SBFI26, a nonselective inhibitors of FABP5 and 7, decreased both the preference and consumption of ethanol in mice [362]. Although the inhibition of FABP5 and 7 was expected to increase bound CB1 due to an upsurge in AEA and 2-AG at the synaptic cleft, the opposite was observed, suggesting that FABPs inhibition may interfere with the delivery of endocannabinoids to CB1. FABPs have also been reported to transport AEA, to other targets such as the vanilloid receptor 1 (TRPV1) [364,365]. It was also shown that AEA induces concentration-dependent effects: at higher concentrations, it excites TRPV1 channels, while at low concentrations, it inhibits nociception via CB1 receptors [366]. Furthermore, deletion of TRPV1 channel has been shown to increase ethanol consumption [363]. Therefore, the dual excitatory and inhibitory effects induced by AEA could potentially elucidate the observed contrasting influences on the regulation of alcohol consumption, which warrants more research. All and all, related markers show that FABPs may play a potential function in

Table 11. Summary of FABP effects on cocaine.

Protein	Association with condition	Previous findings	Sources
FABP5	Linked to cocaine self-administration	Interference or removal of *FABP5* gene reduced cocaine seeking behavior and self-administration	[63,391]
FABP7	Linked to cocaine seeking behavior	Knock out of *FABP7* gene resulted in a reduction in cocaine seeking behavior	[63]
FABP2	Positively associated with cocaine usage	Cocaine users had elevated levels of FABP2	[392]

AUD, and more research is necessary to clarify this connection. Future studies should also consider utilizing both pharmacological inhibition and genetic knock model while examining the effect as its potential in yielding bidirectional results. Additionally, examining the behavioral effects of post-alcohol exposure in these models could also offer valuable insights into the potential for therapeutic strategies.

3.7.3 Nicotine

Nicotine is the primary addictive agent of both cigarettes (through tobacco) and e-cigarettes [367,368]. Nicotine addiction can be extremely harmful, resulting in anxiety, depression, altered appetite, along with other symptoms [369,370]. In 2018, around $200 billion in productivity was lost as a result of cigarette smoking [371,372]. A recent study noted that healthcare costs due to smoking in Australia were close to $180 million AUD [373].

FABPs, particularly, FABP3, have been implicated in the addictive properties of nicotine (Table 10, Ref. [181, 374–377]). FABP3 binds to D2R that has been consistently implicated in nicotine addiction pathways [377–379] and may be a target for nicotine addiction treatments [380]. Moreover, FABP3 knockout or inhibition reduced nicotine effects including conditioned place preference (CPP), withdrawal, and relapse to nicotine consumption after some period of abstinence [377] potentially due to D2R dysfunction [338]. The use of FABP4 inhibitor MF1, likewise reduced nicotine-induced CPP [377]. MF1 also inhibits D2Rs upregulation typically seen after chronic nicotine exposure [377].

Other FABPs, specifically FABP4 and FABP5, have been found to be linked to the reward properties of nicotine, as well as its harmful effects. The reinforcing effects of low doses of nicotine were increased in FABP5 KO mice [374] in part owing to CB1 involvement [374,381–383]. Therefore, CB1 antagonists, like rimonabant, decrease nicotine self-administration and conditioning [384]. The FABP4KO genotype exhibited enhanced nicotine reward and withdrawal [375]. FABP4 has also been linked to pro-oxidative, apoptotic, and inflammatory impacts on epithelial cells of the bronchioles [376] that are upregulated by cigarette smoke exposure [376] suggesting it may worsen health effects associated with nicotine use.

FABPs are critical in the transport and regulation of AEA [385] and so FAAH, which degrades AEA, has been implicated in nicotine addiction [375]. One review of literature noted that disruption of FAAH resulted in enhanced reward and withdrawal effects in rats [375] potentially attributable to modulation by components of the PPAR-α receptor [375]. FABPs, specifically, have also been found to be involved in the harmful physiological effects of nicotine.

Ultimately, past literature strongly points to FABPs, namely FABP3, FABP4, and FABP5, being critical in the rewarding properties of nicotine. Future work should focus on more closely identifying the mechanisms through which these FABPs act, as well as the potential roles of other FABPs that have been implicated in other addictive pathways and psychiatric diseases, such as FABP2.

3.7.4 Cocaine

Cocaine use disorder is linked to heightened rates of morbidity and significant behavioral, psychological, and social consequences [386,387]. Cocaine exerts its psychoactive effects by acting in the limbic system in the brain through elevations of dopamine [388]. Cocaine is typically consumed intranasally, but other routes of administration exist, and differing usage patterns have also been found to impact brain structure in different ways [389,390].

Cocaine's addictive properties seem to be derived to a certain extent from FABPs actions (Table 11, Ref. [63,391, 392]).

FABP5 and FABP7 have been linked to the addictive properties of cocaine and cocaine seeking behaviors. One study noted that FABP5 RNA interference in the NAc shell reduced the rates of cocaine self-administration particularly regarding lower unit doses of cocaine [391]. Reduction in cocaine seeking behaviors was replicated in another preclinical study, where FABP5 KO and FABP7 KO mice did not show a stress-induced reinstatement preference for cocaine [393]. Decreased HPA activation is potential mechanism by which deletion of FABP5 and FABP7 reduces cocaine seeking behavior [364,393].

FABP subtypes not commonly found in the brain have also been linked to cocaine use. Among those with cocaine use disorder, there is a positive association between FABP2 concentrations, from blood samples, and cocaine usage [392]. The authors note that further research should be done into studying the link between FABP2 and gut permeability, and the role cocaine plays in this relationship [392].

CB1 signaling has also been linked to cocaine. Notably, CB1 receptor blockade reduced motivation for co-

caine self-administration [394,395] whereas an extensive literature review implicated CB1 receptors in both cocaine reward and self-administration [396].

Nonetheless, the precise nature of cocaine addiction and the endocannabinoid system association remains somewhat inconsistent with reports of similar rates of cocaine self-administration in mice with and without the CB1 receptor [395,397]. However, it should be noted that this study used a dosage of 0.1 mg/kg, which is below typical values.

Overall, past literature strongly points to the involvement of FABPs within the addictive properties of cocaine.

3.7.5 General Addiction Behavior

To summarize, eCB has been previously demonstrated for its involvement in modulating DA release in the VTA and striatum through its effects on glutamatergic and GABAergic neurons [398]. Enhanced eCB signaling drives positive reinforcement and *vice versa* [340,341]. CB1 blockage has been shown to decrease alcohol drinking behavior [353,354], potentially due to dual regulatory effects of AEA. Additionally, eCB dysfunction via alternation in its mediator such as FABP, 2-AG and AEA catabolic enzymes may be a shared substrate underlying various types of substance use disorders (Tables 9,10,11). Pharmacological FAAH inhibition decreases THC withdrawal symptoms [148], reduces reinstatement of alcohol consumption [356], whereas genetic deletion enhanced withdrawal and reward in response to nicotine and alcohol [145,360,361]. Genetic deletion of FABP5 has been linked to increase in D1 expression in the midbrain area [348], along with enhanced motivation for nicotine and sucrose consumption [63,374]. In contrast, FABP5 and FABP7 pharmacological inhibition has been demonstrated to reduce addictive behavior, e.g., reduction in alcohol consumption [362]. However, more research is needed to inform the distinct features of genetic deletion vs. pharmacological inhibition of FABP. Complex FABPs' interactions with the endocannabinoid system, including their impact on dopamine release in reward and motivational pathways, point to their potential role in the pathophysiology of addictive disorders. Further investigation of FABP-related mechanisms may be harnessed toward the development of therapeutic agents for the treatment of addictive and other commorbid disorders.

4. Conclusions

To conclude, the intricate involvement of FABPs in neurotransmission, lipid metabolism and neural signaling pathways highlights their role in a variety of neuropsychiatric disorders, e.g., major depression, anxiety, schizophrenia, autism, ADHD, neurodegenerative conditions and substance use disorders. This realization is driven mostly by rodent data and further clinical investigation is crucial to unravel the translational value of the preclinical findings with the goal of defining novel therapeutic strategies. Specifically, careful inquiry into different FABP subtypes across various brain regions and neurotransmission signaling pathways (e.g., eCBs, PPAR, and RXR) seems to be a relevant and timely endeavor. Additional research is needed in the domain of distinct effects of genetic deletion vs. pharmacological FABPs' inhibition as well as a heuristic value of such inhibitors for clinical indications. The unmet need for effective treatments of the above disorders is urgent and FABPs offer a tangible opportunity for lessening their burden for patients and their families.

Author Contributions

AIP: Conceptualization, Writing, Reviewing, Editing, and Supervision; NY: Writing, Reviewing, Literature acquisition and Editing; HL: Writing, Reviewing, Literature acquisition and Editing; OP: Writing, Reviewing, Literature acquisition and Editing; IE: Reviewing, Literature acquisition and Editing; MSG: Reviewing, Literature acquisition and Editing; ALP: Reviewing, Literature acquisition and Editing; KB; PKT: Conceptualization, Writing, Reviewing, Editing, and Supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was funded by the New York Research Foundation (RIAQ0940).

Conflict of Interest

The authors declare no conflict of interest.

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