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Review

The liver as a metabolic and immune hub in Alzheimer's disease: From mechanisms to therapeutic opportunities

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ABSTRACT

Research on Alzheimer's disease (AD) has traditionally focused on the brain. However, emerging evidence indicates that the liver acts as a silent partner in neurodegeneration. As a core hub for metabolic and immune regulation, the liver communicates bidirectionally with the brain via the liver–brain axis, participating in the regulation of various neurophysiological processes, including neurotransmitter regulation, feeding behavior, and cognition. This review summarizes how liver-derived hepatokines, inflammatory mediators, and metabolic products modulate brain function. We highlight that liver dysfunction disrupts the expression of critical molecules—including fibroblast growth factor 21, insulin-like growth factor 1, lipopolysaccharide, and lipocalin-2—thereby driving AD progression by impairing pathological protein clearance, activating neuroinflammation, exacerbating insulin resistance and oxidative stress, and disrupting lipid metabolism. We also discuss the therapeutic potential of targeting the liver–brain axis through lifestyle interventions (e.g., exercise and diet) and pharmacological approaches, to identify novel strategies to delay AD progression. In summary, we underscore the pivotal role of the liver–brain axis in AD pathogenesis and propose it as a promising target for early diagnosis and innovative therapies.

1. Introduction

Alzheimer's disease (AD), responsible for approximately 60–80% of dementia cases, is a chronic neurodegenerative condition marked by progressive cognitive impairment [1]. Evidence to date indicates that the pathological hallmarks of AD consist of amyloid-β (Aβ) plaque accumulation, neurofibrillary tangles generated by hyperphosphorylated tau, and chronic neuroinflammation [1,2]. Although most current studies focus on the brain, growing evidence indicates that AD is both a neurodegenerative and a metabolic disorder. Peripheral organs may influence the progression of AD via multiple pathways, such as the secretion of bioactive molecules, release of extracellular vesicles (EVs), and participation in Aβ clearance [3].

Beyond the contribution of individual peripheral organs, AD is

Abbreviations: AD, Alzheimer's disease; Aβ, Amyloid-β; CNS, Central nervous system; EVs, Extracellular vesicles; NAFLD, Nonalcoholic fatty liver disease; PBC, Primary biliary cholangitis; BBB, Blood–brain barrier; IGF-1, Insulin-like growth factor 1; FGF21, Fibroblast growth factor 21; ANGPTL8, Angiopoietin-like protein 8; GDF15, Growth differentiation factor 15; LCN2, Lipocalin-2; HMGB1, High mobility group box 1; SELENOP, Selenoprotein P; MANF, Mesencephalic astrocyte-derived neurotrophic factor; NO, Nitric oxide; O_2^-, Superoxide anion; $ONOO^-$, Peroxynitrite; MCP-1/CCL2, Monocyte chemoattractant protein-1; BHB, Beta-hydroxybutyrate; BDNF, Brain-derived neurotrophic factor; HDAC2/3, Histone deacetylases 2 and 3; 14,15-EET, 14,15-epoxyeicosatrienoic acid; sEH, Soluble epoxide hydrolase; LPC, Lysophosphatidylcholine; LPA, Lysophosphatidic acid; TMA, Trimethylamine; TMAO, Indole into trimethylamine N-oxide; IS, Indoxyl sulfate; GLP-1, Glucagon-like peptide-1; LRP1, Low-density lipoprotein receptor-related protein 1; CSF, Cerebrospinal fluid; sLRP1, Soluble LRP1; IDE, Insulin-degrading enzyme; FMO3, Flavin-containing monooxygenase 3; sAβ, Soluble Aβ; TRLs, Triacylglycerol-rich lipoproteins; p-tau, Phosphorylated tau; NASH, Non-alcoholic steatohepatitis; FABP1, Fatty acid–binding protein 1MAFLD; t-tau, Total tau; MAFLD, Metabolic-associated fatty liver disease; NLRP3, Nod-like receptor protein 3; AGEs, Advanced glycation end products; SHBG, Sex hormone-binding globulin; DAG, Diacylglycerol; MDA, Malondialdehyde; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; 24-OHC, 24-hydroxycholesterol; 27-OHC, 27-hydroxycholesterol; ApoA-I, Apolipoprotein A-I; PCSK9, Proprotein convertase subtilisin/kexin type 9; LDL-C, Low-density lipoprotein cholesterol; LDLR, LDL receptors; BAs, Bile acids; TUDCA, Tauroursodeoxycholic acid; DCA, Deoxycholic; n-3 PUFAs, Omega-3 polyunsaturated fatty acids; DHA, Docosahexaenoic acid; AA, Arachidonic acid; MCI, Mild cognitive impairment.

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increasingly understood within a broader framework of multi-tissue communication. Crosstalk among metabolic organs, the immune system, and the gut microbiota modulates neuroinflammation, proteostasis, and cognitive function [4,5]. This multi-organ framework highlights that peripheral dysfunction can transmit pathological signals to the central nervous system (CNS), reshaping the progression of AD. In this context, organ-specific axes have emerged as key determinants of neural homeostasis and potential contributors to AD. Within this broader landscape of peripheral organ interactions, the liver, as the principal metabolic organ, has gained particular attention for its bidirectional communication with the brain.

Substantial clinical evidence supports the liver's involvement in a range of central nervous system (CNS) disorders, including hepatic encephalopathy, depression, Parkinson's disease, and AD [6,7]. Liver diseases, including nonalcoholic fatty liver disease (NAFLD), primary biliary cholangitis (PBC), and viral hepatitis, have been strongly associated with cognitive impairment and AD [8,9]. Moreover, genome-wide association studies reveal that several AD-related genes, including APOE, CLU and ABCA7, are abundantly expressed in hepatocytes [10]. Metabolomic analyses in APP/PS1 mice further revealed that the liver exhibits the earliest metabolic abnormalities among peripheral organs [11]. These results indicate a potential association between liver dysfunction and AD pathogenesis. Recently, substantial breakthroughs have been achieved in deciphering the molecular mechanisms underlying liver–brain interactions, and the liver–brain axis has emerged as a critical focus in AD research. This review provides a detailed summary of the liver–brain axis, its multifaceted role in AD pathogenesis, and emerging therapeutic strategies targeting this axis, offering new insights for both fundamental research and clinical application.

2. Liver–brain axis

The liver-brain axis denotes a bidirectional communication network between the liver and the brain that operates through multiple pathways (Fig. 1). On one side, liver-derived substances—either synthesized de novo or produced via metabolic processes—cross the blood–brain barrier (BBB) and directly modulate cerebral functions. In addition, the liver indirectly modulates brain function, including cognition and emotional regulation, by sensing peripheral metabolic and inflammatory signals [12]. Conversely, the brain regulates hepatic physiological functions such as glucose and lipid metabolism via autonomic innervation [13]. Existing studies have mainly focused on how the brain regulates liver function, while relatively little attention has been given to how the liver influences brain function. Therefore, this review aims to delineate the primary mechanisms through which the liver modulates brain function.

2.1. *Humoral pathway*

The humoral pathway constitutes a central mechanism of liver–brain communication, with the BBB acting as a key interface. In addition to essential substrates such as glucose and amino acids, numerous bioactive substances synthesized or processed by the liver are also capable of

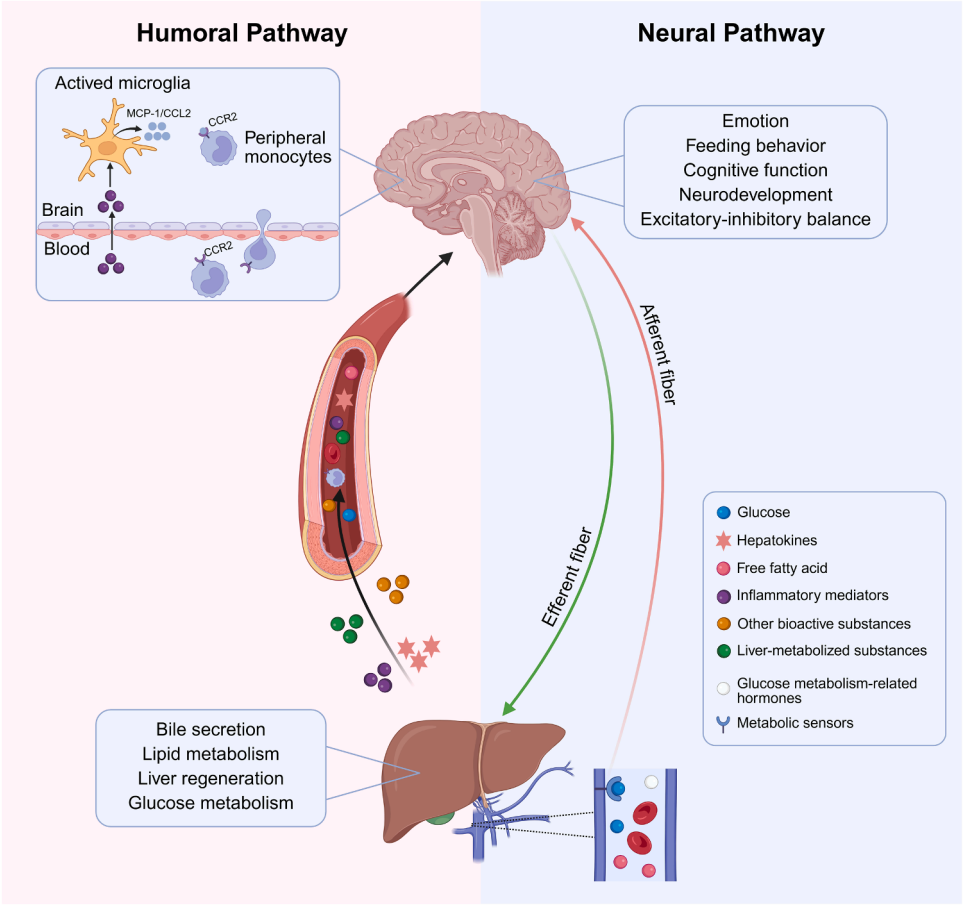

Fig. 1. Key communication pathways of the liver-brain axis. Liver-derived molecules, including hepatokines (e.g., IGF-1, FGF21, ANGPTL8, GDF15, LCN2, SELENOP, MANF, GLP-1), inflammatory cytokines (e.g., TNF-α, IL-6), other bioactive substances (e.g., BHB, LPC) and hepatic metabolites (e.g., lactate) access the brain via humoral pathway. Concurrently, afferent nerves transmit hepatic metabolic signals (e.g., glucose, lipids) to the brain, which integrates these inputs and modulates liver functions (e.g., glucose metabolism, lipid metabolism, bile acid secretion, and liver regeneration) via efferent fibers.

crossing the BBB and modulating brain function.

2.1.1. Liver-derived molecules

2.1.1.1. Hepatokines. The liver synthesizes and secretes a broad range of hepatokines that modulate brain activity, mainly including insulin-like growth factor 1 (IGF-1), fibroblast growth factor 21 (FGF21), angiopoietin-like protein 8 (ANGPTL8), growth differentiation factor 15 (GDF15), lipocalin-2 (LCN2), and hepcidin. IGF-1, a growth-promoting peptide mainly derived from the liver, can cross the BBB and is essential for CNS development and maturation [14]. FGF21, primarily secreted by hepatocytes, crosses the BBB to regulate energy metabolism and suppress sucrose and alcohol intake [15]. ANGPTL8, a hepatokine involved in lipid regulation, is predominantly synthesized in the liver [16]. Peripheral injection of ANGPTL8 decreases the activity of neuropeptide Y neurons in the dorsomedial hypothalamic nucleus, thereby suppressing appetite [17]. GDF15 is another hepatokine that regulates appetite, with the liver serving as its primary source in circulation under conditions of a high-fat diet or obesity [18]. It acts via the glial-derived neurotrophic factor family receptor α-like in the brain to suppress feeding behavior and promote weight loss [16]. Hepcidin, a liver-derived regulator of iron homeostasis, has been shown to cross the BBB. Although it has limited effects on brain iron balance under physiological conditions, hepatic hepcidin expression is significantly elevated during inflammation or iron overload, thereby disturbing cerebral iron homeostasis through modulation of iron transport proteins in the brain [19]. Under chronic stress, the liver becomes a major producer of circulating LCN2, which crosses the BBB and induces anxiety-like behaviors by binding to LCN2 receptor, SLC22A17 (also known as the 24p3R) [20]. LCN2 can also bind to the 24p3R on brain endothelial cells to induce the release of high mobility group box 1 (HMGB1), which subsequently triggers oxidative stress, neuroinflammation, and compromises BBB integrity [21]. Additional liver-derived hepatokines, including selenoprotein P (SELENOP) and mesencephalic astrocyte-derived neurotrophic factor (MANF), may also exert effects on the CNS through the liver–brain axis, although their precise mechanisms remain poorly understood [16,22]. In summary, the liver modulates multiple facets of brain function—including neurodevelopment, emotion, and feeding behavior—through the secretion of diverse hepatokines, which constitute essential components of the liver–brain axis.

2.1.1.2. Inflammatory mediators. The liver functions as a key peripheral immune organ and serves as a major source of circulating inflammatory mediators (e.g., IL-6, TNF-α). These inflammatory mediators compromise the BBB integrity by downregulating tight junction proteins (e.g., claudin-5) and upregulating matrix metalloproteinases, thereby facilitating the entry of peripheral inflammatory molecules into the brain [23]. Once in the brain, these inflammatory signals activate microglia and astrocytes, initiating neuroinflammation and prompting brain endothelial cells to overproduce NO. The interaction between NO and O_2^- generates $ONOO^-$, a potent oxidant that exacerbates oxidative stress and promotes cell death [24]. The liver also modulates CNS function through specific signaling pathways. For example, in a mouse model of liver inflammation, peripheral TNF-α binds to microglial TNF receptor 1, leading to monocyte chemoattractant protein-1 (MCP-1/CCL2) release and subsequent $CCR2^+$ monocyte infiltration into the CNS. This immunological cascade may underlie the behavioral manifestations observed during hepatitis, such as social withdrawal and hypoactivity [25]. In a mouse model of cholestasis, activated brain endothelial cells promote P-selectin–mediated recruitment of TNF-α–secreting monocytes into the CNS, potentially contributing to fatigue and related neurobehavioral disturbances [26]. Collectively, these findings demonstrate that liver-derived inflammatory mediators disrupt BBB integrity and promote peripheral immune cell infiltration, ultimately leading to neuroinflammation and behaviorally relevant neuropathology. These insights underscore the liver's capacity to remotely orchestrate brain function via immunological pathways.

2.1.1.3. Other bioactive substances. Beyond hepatokines and inflammatory mediators, the liver also synthesizes a broad spectrum of bioactive metabolites that modulate brain function via diverse mechanisms. Beta-hydroxybutyrate (BHB), a liver-derived ketone body produced through fatty acid oxidation, crosses the BBB and enhances brain-derived neurotrophic factor (BDNF) expression by suppressing histone deacetylases 2 and 3 (HDAC2/3), thereby contributing to neurodevelopment and cognitive function [27]. 14,15-Epoxyeicosatrienoic acid (14,15-EET), whose circulating levels are regulated by hepatic soluble epoxide hydrolase (sEH), can cross the BBB. Once in the brain, 14,15-EET promotes the formation of A2 astrocytes and enhances the production of neuroprotective molecules, thereby contributing to neuroprotection [28]. Liver-derived lysophosphatidylcholine (LPC) traverses the BBB, where it is subsequently converted into lysophosphatidic acid (LPA), which modulates feeding behavior via activation of the LPA_2 receptor on presynaptic neurons [29]. Endogenous choline synthesized in the liver enters the circulation, crosses the BBB, and serves as a substrate for acetylcholine production, a process essential for maintaining cholinergic neuronal activity [30]. Additionally, the liver also contributes to the synthesis of neurotransmitter precursors, including those for norepinephrine, dopamine and serotonin, all essential for maintaining excitatory-inhibitory balance in the brain [31]. Primary bile acids produced in the liver can also penetrate the BBB and modulate neural activity. Collectively, these liver-derived molecules regulate brain function at multiple levels, encompassing neurodevelopment, glial reactivity, epigenetic remodeling and neurotransmitter homeostasis.

2.1.2. Liver-metabolized substances

As the central metabolic hub, the liver is essential for maintaining CNS homeostasis by metabolizing and eliminating diverse peripheral substances. For instance, the liver transforms circulating trimethylamine (TMA) and indole into trimethylamine N-oxide (TMAO) and indoxyl sulfate (IS), respectively, both of which modulate cognitive function and anxiety- and depression-like behaviors [32]. Circulating propionate is oxidized by the liver, which contributes to the regulation of feeding behavior [33]. Lactate, predominantly cleared by the liver and kidneys, accumulates in both the circulation and brain under hepatic dysfunction, thereby increasing cerebral osmolarity and promoting edema and neuronal injury [34]. Similarly, ammonia—normally detoxified into urea by hepatic metabolism—is elevated in both blood and brain during liver failure. Although astrocytes are capable of converting ammonia into glutamine, excessive glutamine accumulation induces neuronal cell death and cerebral edema [6]. Ammonia may also be converted to ammonium ions, which competitively inhibit potassium channels, thereby disrupting membrane potential homeostasis and resulting in abnormal neuronal excitability [35]. In addition, ammonia directly compromises BBB integrity and induces neuronal senescence, further exacerbating neurotoxicity [6]. Beyond hyperammonemia, hepatic failure induces cerebral edema and intracranial hypertension via multiple mechanisms, including elevated circulating levels of active-matrix metalloproteinase-9 and galactosamine, as well as upregulation of aquaporin-4 in perivascular astrocytic endfeet [36].

Moreover, liver dysfunction—such as adenosine triphosphatase 7B enzyme deficiency or cirrhosis—disrupts systemic metal homeostasis, leading to aberrant cerebral accumulation of copper, iron, and manganese, thereby inducing oxidative stress and neuronal degeneration [37]. In summary, the liver maintains cerebral microenvironmental homeostasis by regulating the systemic clearance of lactate, ammonia and metals. Liver dysfunction facilitates the accumulation of neurotoxic metabolites, compromises BBB integrity, and ultimately contributes to CNS pathology.

2.2. Neural pathway

The autonomic nervous system constitutes a core bidirectional pathway linking the brain and liver. Metabolic sensors located in the hepatic portal vein detect real-time fluctuations in osmolality, glucose, lipids, and other metabolites, transmitting these signals to the CNS via afferent fibers. Following central integration, signals are sent to the liver through efferent fibers to precisely regulate various hepatic functions, including glucose and lipid metabolism, bile secretion, and liver regeneration. In glucose regulation, glucose transporter type 2-dependent glucose sensors in the portal vein detect decreases in blood glucose levels, triggering hepatic vagal afferent activation and ultimately enhancing feeding behavior [38]. Glucose metabolism-related hormones, including glucagon-like peptide-1 (GLP-1), also regulate feeding behavior through a similar neural circuit [39]. For lipid metabolism, elevated lipid levels in the portal vein stimulate hepatic vagal afferents, leading to the suppression of lipid intake and promotion of lipid storage in mesenteric white adipose tissue [38]. Additionally, liver-derived inflammatory mediators may activate vagal afferents, inducing sickness-like responses such as lethargy and fever [40]. Importantly, the liver participates in clearing multiple neurohormones—such as antidiuretic hormone, growth hormone, and prolactin—through receptor-mediated endocytosis and enzymatic degradation, thereby contributing to neuroendocrine homeostasis [16]. Collectively, the liver relays peripheral metabolic and immune states to the CNS in real time via autonomic afferents, playing an essential role in regulating feeding behavior, energy homeostasis, and neuroendocrine stability.

The liver and brain interact via a bidirectional liver–brain axis that consists of both humoral and neural pathways. Through the humoral pathway, liver-derived hepatokines, inflammatory mediators, and metabolites cross the BBB and modulate diverse CNS functions. Through the neural pathway, hepatic sensory receptors transmit peripheral metabolic information to the brain via autonomic afferent fibers, enabling dynamic regulation of CNS metabolic homeostasis. In summary, the liver–brain axis integrates neural and humoral signaling to mediate real-time bidirectional crosstalk between the liver and the brain. This integrated network highlights the liver's essential role in maintaining CNS homeostasis and implicates hepatic dysfunction as a contributing factor to neurological disorders.

3. The regulatory role of the liver-brain axis in AD

Epidemiological studies have demonstrated that individuals with liver dysfunction—such as NAFLD, PBC, and viral hepatitis—have a markedly higher risk of developing AD compared to healthy individuals. This association implicates that impaired hepatic function represents a significant risk factor for AD, in which dysregulation of the liver–brain axis may play a pivotal mechanistic role.

3.1. Pathological protein clearance and production

3.1.1. Aβ

An imbalance between Aβ production and clearance leads to its abnormal accumulation, which constitutes a central pathological hallmark of AD. Approximately 40–60% of Aβ generated in the brain is eliminated into the peripheral circulation, predominantly via low-density lipoprotein receptor-related protein 1 (LRP1) located at the BBB [22]. In AD mouse models, peritoneal dialysis markedly lowers Aβ concentrations in both blood and cerebrospinal fluid (CSF), diminishes cerebral Aβ deposition, and improves cognitive performance, indicating that peripheral Aβ clearance is closely linked to AD progression [41]. The liver serves as the principal organ for peripheral Aβ clearance. Within 120 minutes after intravenous injection of Aβ, approximately 65% of circulating Aβ is taken up by the liver, and partial hepatic blood-flow obstruction elevates Aβ concentrations in circulation and brain interstitial fluid [42]. This process relies largely on hepatic LRP1, which mediates Aβ endocytosis and lysosomal degradation [32] (Fig. 2). Hepatocyte-specific deletion of LRP1 in AD mice exacerbates cerebral Aβ burden and worsens cognitive deficits [43].In models of liver dysfunction, hepatic LRP1 expression is significantly reduced and correlated with elevated Aβ concentrations in both blood and brain, and with cognitive decline [44]. Furthermore, soluble LRP1 (sLRP1), a truncated extracellular N-terminal domain of membrane LRP1, binds approximately 70%-90% of plasma Aβ—thereby blocking its entry into the brain and facilitating peripheral clearance [32]. Consequently, liver disease may elevate plasma-free Aβ by reducing both LRP1 and sLRP1 levels. Liver-derived insulin-degrading enzyme (IDE) can hydrolyze circulating Aβ, whereas its expression is significantly reduced in mice consuming a high-fat diet [45]. Additionally, the liver plays a role in regulating Aβ-associated lipid metabolism (e.g., ApoE), plasma carrier proteins (e.g., albumin, SELENOP), and bile acid excretion—all of which are impaired during liver dysfunction, resulting in Aβ accumulation [22, 32]. Meanwhile, liver dysfunction elevates circulating LCN2, which compromises the BBB integrity and enhances peripheral Aβ influx into the brain [21]. Collectively, liver dysfunction elevates peripheral Aβ concentrations by impairing clearance and facilitating its transport into the brain.

Beyond direct clearance, the liver also modulates cerebral Aβ burden via multiple indirect mechanisms (Fig. 2). For instance, hepatic sEH degrades plasma 14,15-EET, a lipid epoxide that promotes astrocyte-derived ApoE release that activates microglial TREM2 signaling to enhance microglial Aβ phagocytosis [28]. In models of hepatic disease, the expression of sEH is significantly elevated [46]. Hepatic flavin-containing monooxygenase 3 (FMO3) oxidizes gut-derived TMA to TMAO, which crosses the BBB and promotes Aβ aggregation. In APP/PS1 mice, higher plasma TMAO levels correlate with increased hippocampal Aβ deposition [32]. Hepatic FMO3 is significantly upregulated in both acute liver injury and NAFLD, providing a mechanistic link between hepatic dysfunction and cerebral Aβ burden [47]. Additionally, the liver plays a central role in peripheral LPS clearance [48]. Liver dysfunction impairs LPS clearance and promotes intestinal LPS translocation, leading to increased systemic LPS levels [9]. Excessive LPS upregulates Beta-secretase 1 to increase Aβ production, disrupts BBB integrity, and downregulates the LRP1 expression on the BBB, reducing Aβ efflux and facilitating its accumulation in the brain [49]. IGF-1, primarily derived from the liver, facilitates Aβ efflux across the BBB and hepatic uptake [50]. Subcutaneous IGF-1 administration significantly lowers cerebral Aβ burden in AD models [51]. However, IGF-1 levels are significantly reduced in various chronic liver diseases [52]. Moreover, liver-derived ketone bodies such as BHB enhance cerebral Aβ clearance by upregulating BBB Aβ efflux transporters (e.g., LRP1) and Aβ-degrading enzymes (e.g., neprilysin) [53]. In the AD mouse model, long-term administration of BHB-rich ketone bodies significantly reduces cerebral Aβ accumulation, whereas hepatic metabolic disturbances impair this protective mechanism [54].

Growing evidence indicates that liver-derived Aβ can also contribute to AD pathology. For example, hepatoma HepG2 cells are capable of synthesizing and secreting soluble Aβ (sAβ) [55]. In mice, liver-derived Aβ in combination with triacylglycerol-rich lipoproteins (TRLs) crosses the BBB and induces AD-like neurodegeneration and cognitive deficits [56]. Although direct modulation of cerebral Aβ synthesis by the liver has not yet been demonstrated, the liver may indirectly modulate cerebral Aβ production via multiple pathways, including the regulation of systemic inflammation, neurotoxin metabolism, lipid homeostasis, and hepatokine-mediated signaling [57]. In summary, as the central hub for peripheral Aβ clearance, the liver directly clears circulating Aβ via LRP1 and IDE, while indirectly modulating cerebral Aβ homeostasis by regulating systemic levels of 14,15-EET, TMAO, LPS, IGF-1, and BHB. Liver dysfunction impairs these processes and results in increased cerebral Aβ accumulation. Moreover, liver-derived Aβ incorporated into lipoprotein complexes may directly contribute to central Aβ pathology.

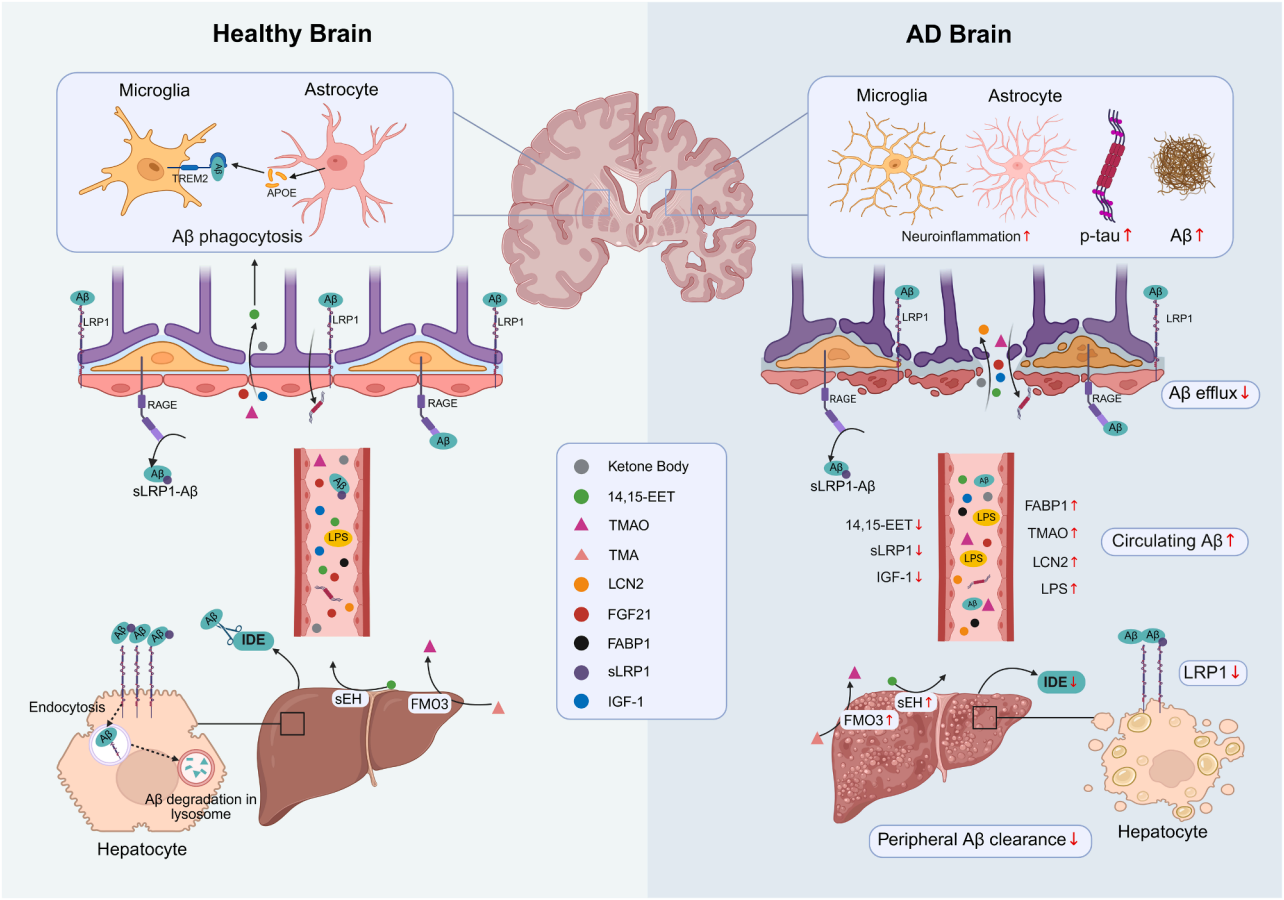

Fig. 2. Liver dysfunction reduces clearance and enhances production of pathological proteins in the brain. Aβ is mainly cleared from the brain to the periphery via LRP1 at the BBB and enters the brain through RAGE. The liver removes circulating Aβ through LRP1-mediated endocytosis, IDE degradation and modulates cerebral Aβ by regulating factors such as 14,15-EET, TMAO, FGF21, IGF-1, LPS, and LCN2. However, the mechanisms by which the liver clears peripheral tau remain unclear. Liver dysfunction reduces LRP1 and IDE, impairing circulating Aβ clearance and promoting its brain accumulation. It also decreases 14,15-EET, sLRP1 and IGF-1, while increasing TMAO, LCN2, LPS, and FABP1, collectively driving Aβ and p-tau deposition in the brain.

3.1.2. *Tau*

Hyperphosphorylation and aggregation of tau protein represent hallmark pathological features of AD. In P301L mice, lowering circulating tau levels leads to decreased accumulation of phosphorylated tau (p-tau) in the brain. Additionally, tau in the CSF undergoes efflux into peripheral circulation, where it is eliminated by organs including the liver and kidneys [58]. However, the mechanisms by which the liver eliminates peripheral tau remain poorly understood. The liver also regulates cerebral tau through several indirect metabolic pathways (Fig. 2). For instance, hepatic sEH degrades plasma 14,15-EET, which elevates p-tau levels and worsens cognitive impairment, whereas intracerebroventricular 14,15-EET administration ameliorates these effects [28]. Liver-derived FGF21 inhibits tau hyperphosphorylation and aggregation via FGF receptor 1 activation in the brain, but circulating FGF21 levels vary across liver disease states [57]. In chronic hepatitis B, liver cirrhosis, and aging models, circulating FGF21 levels are significantly reduced, likely reflecting impaired hepatic synthesis. Conversely, FGF21 levels are elevated in acute hepatitis B, hepatocellular carcinoma, and NAFLD [59]. IGF-1, primarily synthesized in the liver, suppresses tau hyperphosphorylation by inhibiting glycogen synthase kinase-3β, yet systemic IGF-1 levels are generally reduced in chronic liver disease [51]. LPS elevation during liver dysfunction exacerbates tau pathology by inducing neuroinflammation and tau phosphorylation [60]. In non-alcoholic steatohepatitis (NASH) mice, hepatic and systemic LCN2 levels are elevated, correlating with reduced BDNF and elevated p-tau in the brain, however, causality remains unclear [21]. In addition, liver-derived fatty acid–binding protein 1 (FABP1) positively correlates with CSF levels of total tau (t-tau) and p-tau, and its expression is significantly elevated in liver disease models [61]. This suggests a potential role for FABP1 in promoting tau pathology, although the underlying mechanisms remain to be elucidated. Importantly, not all liver diseases are closely associated with cerebral tau pathology. One study found no significant correlation between NAFLD and intracerebral tau deposition, whereas hepatic fibrosis severity positively correlated with tau pathology in the parahippocampal gyrus [62]. However, clinical studies have been inconsistent regarding correlations between liver-function markers and CSF p-tau or t-tau levels. Some report no association [63], whereas others indicate an inverse correlation between plasma total bilirubin and CSF tau levels over a two-year follow-up [64]. This discrepancy underscores the necessity for extensive, multicenter clinical research to clarify relationships between liver diseases and cerebral tau pathology. In summary, the liver is central to the regulation of systemic Aβ and tau metabolism via an intricate metabolic network. Analogous to its role in Aβ clearance, the liver indirectly influences cerebral tau accumulation by modulating circulating levels of 14,15-EET, FGF21, IGF-1, LPS, LCN2, and FABP1. However, unlike Aβ, mechanisms of peripheral tau clearance by the liver remain poorly understood, underscoring the need for mechanistic studies to identify novel therapeutic targets in AD.

3.2. *Neuroinflammation*

Neuroinflammation, marked by activation of glial cells and elevated levels of pro-inflammatory cytokines, accelerates AD progression

through multiple mechanisms, including enhanced cerebral Aβ accumulation [2]. The liver directly regulates neuroinflammation by secreting various molecules, which may be dysregulated in liver dysfunction, exacerbating glial immune responses and promoting AD progression [9] (Fig. 3). FGF21 activates AMPKα/AKT signaling and inhibits NF-κB–mediated cytokine production in the CNS [65]. Similarly, IGF-1 suppresses NF-κB signaling, thus alleviating neuroinflammation [50]. SELENOP, Fetuin-A, and MANF attenuate neuroinflammation by suppressing microglial polarization to the proinflammatory M1 phenotype and decreasing subsequent release of pro-inflammatory cytokines [22]. The above hepatokines are predominantly liver-derived, and their dysregulation in hepatic disorders likely contributes to neuroinflammatory initiation. Liver-derived prochemerin is processed into active chemerin peripherally, which crosses the BBB and engages ChemR23/CAMKK2/AMPK/Nrf2 signaling to suppress neuroinflammatory responses [66]. However, meta-analyses report increased circulating chemerin levels in patients with metabolic-associated fatty liver disease (MAFLD) [67]. This may be due to the bidirectional property of chemerin to regulate inflammatory responses. In liver dysfunction, elevated LPS binds to TLR4/CD14 and activates NF-κB signaling, exacerbating neuroinflammation [9,49]. In NASH, increased LCN2 compromises BBB integrity, triggers HMGB1 release, and activates nod-like receptor protein 3 (NLRP3) inflammasomes, thus amplifying neuroinflammation [21]. Together, the liver suppresses neuroinflammation under physiological conditions through the secretion of anti-inflammatory hepatokines (e.g., FGF21, IGF-1), whereas hepatic dysfunction shifts this balance—diminishing protective factors and elevating pro-inflammatory mediators—thereby promoting AD progression.

In addition to direct neuroinflammatory modulation, the liver drives AD pathology by amplifying peripheral inflammation (Fig. 3). Elevated levels of diverse inflammatory markers are observed in both blood and CSF of AD patients, and proinflammatory factors such as TNF-α, IL-1β, MCP-1, and LPS in the blood are closely linked to a higher risk of AD [40]. The liver serves as a major contributor of peripheral pro-inflammatory cytokines. In diverse liver pathologies, aberrant NF-κB pathway activation leads to the overproduction and secretion of pro-inflammatory factors [68]. Numerous clinical studies report heightened circulating TNF-α, IL-1β, IL-6, and MCP-1 in patients with liver disease [69]. Elevated circulating LPS during liver dysfunction further exacerbates systemic inflammation through innate immune activation [9]. Collectively, hepatokines may directly modulate neuroinflammation via the BBB, while liver-induced peripheral inflammation may further potentiate AD pathology.

3.3. Insulin resistance

Insulin resistance is closely associated with AD pathology and represents a major risk factor for its onset [70]. Chronic hyperinsulinemia from insulin resistance downregulates insulin receptor expression at the BBB, reducing central insulin transport. Meanwhile, chronic hyperglycemia also accelerates AD by causing vascular damage, promoting the buildup of advanced glycation end products (AGEs) and inducing glucose-mediated neurotoxicity [70]. Consequently, diminished central insulin impairs synaptic plasticity and cognitive performance [70]. The liver regulates systemic insulin sensitivity via the secretion of hepatokines and miRNAs, regulation of metabolism, and expression of transcription factors [71]. Liver dysfunction disrupts these regulatory axes, exacerbating systemic insulin resistance and thereby accelerating AD progression (Fig. 3). Specifically, liver-derived molecules, including

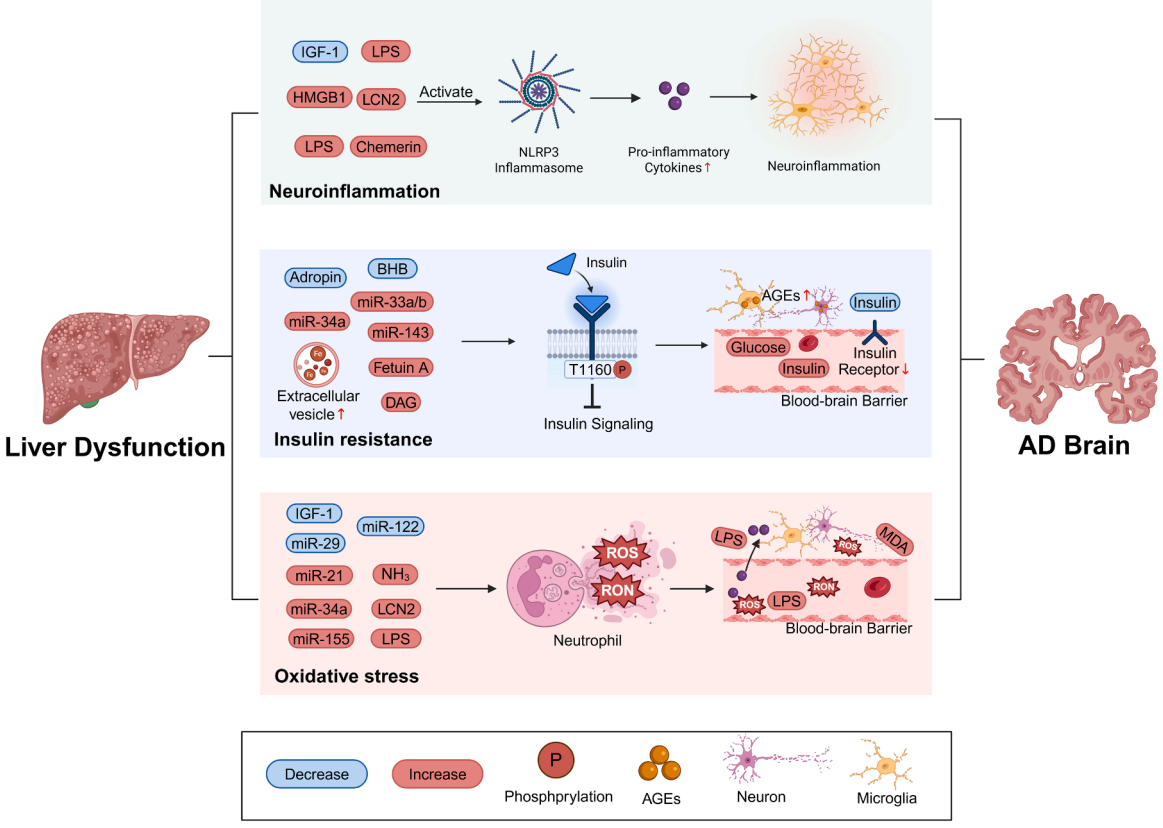

Fig. 3. Liver dysfunction contributes to AD pathology via neuroinflammation, insulin resistance, and oxidative stress. Liver dysfunction increases circulating proinflammatory cytokines and hepatokines while reducing anti-inflammatory ones, thereby promoting neuroinflammation. It also elevates pro-insulin-resistance hepatokines and miRNAs, while depleting protective factors, contributing to insulin resistance. Moreover, increased levels of ammonia, LPS, and pro-oxidative hepatokines/microRNAs, along with reduced antioxidants, exacerbate oxidative stress, impair the BBB and aggravate AD progression.

Activin E, Adropin, FGF21, sex hormone-binding globulin (SHBG), and BHB, enhance insulin sensitivity by increasing adiponectin, suppressing mTORC1-mediated lipogenesis, promoting brown adipose oxidation, and inhibiting lipolysis [72]. Conversely, hepatokines including ectodysplasin A, fetuin A/B, hepatocyte-derived fibrinogen-related protein 1, leukocyte cell-derived chemotaxin 2, pigment epithelium–derived factor, selenoprotein P and ANGPTL3 have been shown to promote systemic insulin resistance [22,71]. In NAFLD, protective hepatokines (e.g., Adropin, BHB) decline, while pro-insulin-resistance hepatokines and miRNAs (miR-33a/b, miR-34a, miR-143) are markedly elevated [71,73]. In addition, hepatocellular iron homeostasis is critical in the maintenance of insulin sensitivity. In NAFLD/NASH, upregulation of hepatocyte RAB27 expression drives excessive secretion of iron-containing extracellular vehicles, which triggers hepatocyte iron deficiency and enhances lipogenesis, exacerbating insulin resistance [74]. Moreover, accumulation of sn-1,2-diacylglycerol (DAG) in hepatocyte membranes activates protein kinase C epsilon, leading to phosphorylation of the insulin receptor kinase at Thr1160 and subsequent impairment of insulin signaling. In patients with NAFLD, sn-1,2-DAG levels in the hepatocyte membranes are significantly elevated, and BACH1 expression is upregulated, which impairs insulin signaling by facilitating the binding of protein-tyrosine phosphatase 1B to insulin receptor β [75]. Additionally, bile acid imbalance, inflammation, and oxidative stress stemming from hepatic pathology contribute further to insulin resistance [72]. In summary, the liver modulates systemic insulin sensitivity through the secretion of hepatokines and miRNAs, as well as the regulation of metabolic homeostasis. Liver dysfunction disturbs the balance between protective and pathogenic hepatokines, impairing iron metabolism, and inducing systemic inflammation, thereby aggravating insulin resistance and fostering AD progression.

3.4. Oxidative stress

Oxidative stress constitutes a central nexus among AD pathologies and acts as a major driver of disease progression [76]. Levels of classic oxidative markers, including malondialdehyde (MDA) and LPS, are markedly elevated in serum and brain tissues of AD patients and animals [76]. The liver is both a primary generator of reactive oxygen species (ROS) and a critical organ for ROS and MDA detoxification. However, chronic liver diseases disrupt redox homeostasis, leading to hepatic and systemic oxidative stress [77] (Fig. 3). The liver mitigates oxidative stress mainly by clearing LPS and secreting FGF21, which boosts serum superoxide dismutase and catalase activities and upregulates antioxidant enzyme mRNAs in the brain [65]. Liver-derived IGF-1 exerts antioxidant effects through activation of the PI3K/AKT-Nrf2 signaling pathway, and intranasal administration of IGF-1 also alleviates oxidative brain injury in rodent ischemia models [50,78]. SELENOP and MANF attenuate oxidative stress by eliminating excess free radicals and modulating antioxidant enzyme activity [22]. Dysregulated hepatokines in hepatic dysfunction may exacerbate oxidative stress. In liver disease, antioxidant miRNAs (miR-122, miR-29) are downregulated, whereas pro-oxidant miRNAs (miR-155, miR-21, miR-34a) are upregulated [79]. Additionally, elevated LPS in hepatic dysfunction triggers ROS overproduction, suppresses antioxidant enzymes, and impairs mitochondrial function [9]. In NASH, increased circulating LCN2 enters the CNS, triggers HMGB1 release, and activates TLR4/RAGE–NOX-2 signaling to induce oxidative stress [21]. Hyperammonemia in cirrhosis impairs neutrophil function and induces ROS and reactive nitrogen species (RNS) production, further aggravating oxidative stress. ROS/RNS also compromise BBB integrity, facilitating CNS infiltration by inflammatory cytokines and neurotoxins [6]. Overall, normal liver function is vital for systemic redox balance. Liver dysfunction induces oxidative stress via reduced antioxidant defenses, dysregulated hepatokines/miRNAs, impaired LPS clearance, hyperammonemia, and BBB disruption. These processes collectively contribute to the progression of AD.

3.5. Dysregulation of lipid metabolic homeostasis

Maintenance of lipid homeostasis is critical for normal brain function, and its dysregulation is a defining feature of AD [80]. As the principal peripheral regulator of lipid metabolism, the liver maintains systemic lipid balance, whereas liver dysfunction disrupts this equilibrium and thereby accelerates AD progression (Fig. 4).

3.5.1. Cholesterol metabolism

Peripheral cholesterol metabolism modulates central cholesterol homeostasis through multiple mechanisms, thereby participating in the regulation of AD pathology [81] (Fig. 4 A). The liver is the peripheral organ maintaining cholesterol homeostasis [32]. Hepatic impairment leads to elevated plasma cholesterol, which compromises BBB integrity, facilitates cholesterol influx into the brain, where it promotes Aβ production within lipid rafts and accelerates Aβ deposition [80,82]. Oxysterols, particularly 24-hydroxycholesterol (24-OHC) and 27-hydroxycholesterol (27-OHC), mediate bidirectional cholesterol exchange between the liver and brain. Specifically, excess cholesterol in neurons is converted to 24-OHC, which crosses the BBB and is cleared in the liver by conversion to bile acids [32]. Conversely, 27-OHC, produced by hepatocytes and other peripheral cells, crosses the BBB to activate liver X receptors in astrocytes, upregulating APOE, ABCA1, and ABCG1. This enhances cholesterol efflux from astrocytes to neurons and facilitates its subsequent conversion to 24-OHC [83]. Several liver diseases disrupt 24-OHC metabolism and elevate plasma 27-OHC, which may increase AD risk by promoting Aβ deposition, tau phosphorylation, and synaptic dysfunction [82,84]. In APP/PS1 transgenic mice, subcutaneous 27-OHC administration exacerbates cerebral Aβ accumulation and cognitive deficits, whereas co-administration of ANS (a 27-OHC inhibitor) reverses these effects, underscoring the pathophysiological role of 27-OHC [85].

ApoE is a crucial cholesterol transporter, with over 90% of peripheral ApoE synthesized by the liver. The ApoE gene encodes three major isoforms—ε2, ε3, and ε4—of which ApoE ε4 carriers exhibit elevated plasma cholesterol levels and are predisposed to sporadic AD. Aβ-ApoE4 complex inhibits LRP1-mediated Aβ clearance, whereas Aβ-ApoE2/3 complexes facilitate Aβ removal [86](Fig. 4 B). Liver-derived ApoE4 impairs synaptic plasticity, exacerbates neuroinflammation, and worsens amyloid pathology, whereas ApoE3 is neuroprotective [87]. Apolipoprotein A-I (ApoA-I), another cholesterol transport protein predominantly produced in the liver, can cross the BBB, where it enhances cognitive performance in APP/PS1 mice by preventing Aβ aggregation and facilitating its clearance from the brain into the peripheral circulation [88]. These findings indicate that liver-derived ApoE and ApoA-I modulate AD progression, while infusion of ApoE3-enriched young plasma may represent a promising therapeutic approach.

Furthermore, the liver may modulate AD pathogenesis by regulating cholesterol-metabolizing enzymes, notably proprotein convertase subtilisin/kexin type 9 (PCSK9) (Fig. 4 C). PCSK9 is synthesized predominantly in hepatocytes and elevates plasma low-density lipoprotein cholesterol (LDL-C) by facilitating the lysosomal breakdown of LDL receptors (LDLR) [89]. In NAFLD, serum PCSK9 is elevated and positively correlates with hepatic steatosis severity. Conversely, in alcoholic liver cirrhosis, serum PCSK9 may be reduced, likely due to impaired hepatic synthetic capacity [90]. Notably, PCSK9 also degrades LRP1, suggesting its role in AD pathology by reducing LRP1-mediated Aβ clearance [91]. Although whether hepatic PCSK9 crosses the BBB remains unclear, its peripheral activity likely influences AD pathophysiology by impairing Aβ clearance and raising LDL-C.

In general, the liver maintains peripheral and central cholesterol homeostasis via regulation of cholesterol synthesis, clearance, oxysterol metabolism, and enzyme activity. Disrupted hepatic cholesterol metabolism exacerbates cerebral Aβ accumulation and promotes neuroinflammation via the liver–brain axis, thus accelerating AD pathology. Emerging therapies targeting the liver–brain axis, including 27-OHC

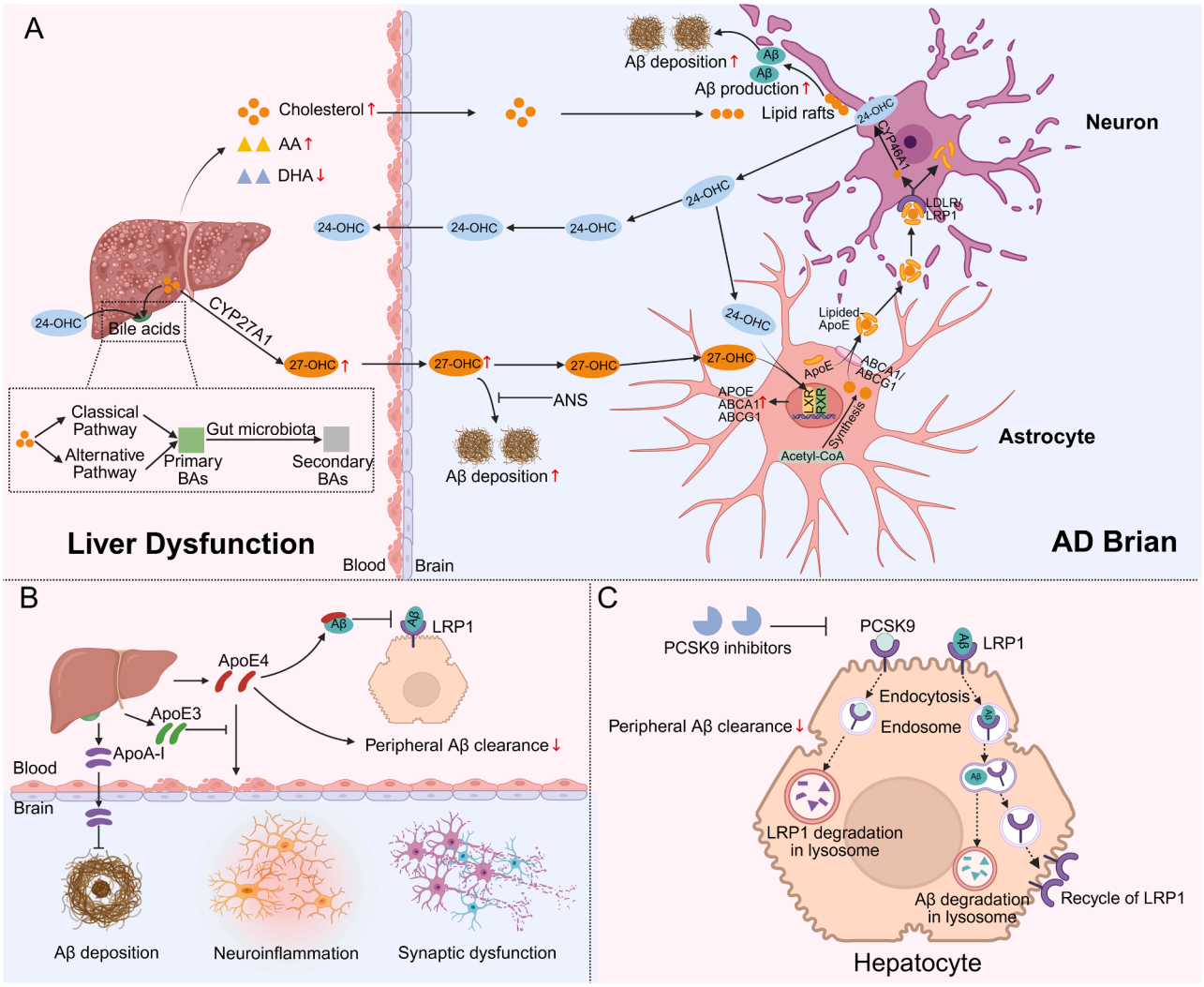

Fig. 4. The influence of hepatic lipid metabolism on AD. A. Neurons convert excess brain cholesterol into 24-OHC for transport to the liver, while 27-OHC produced by peripheral tissues including the liver, crosses the BBB to regulate cerebral cholesterol homeostasis. Liver dysfunction elevates circulating cholesterol and 27-OHC levels while impairing 24-OHC degradation, thereby promoting cerebral Aβ deposition. B. Liver-derived ApoE4 binds circulating Aβ to form complexes, that disrupt LRP1-mediated peripheral Aβ clearance. Additionally, hepatic ApoE4 impairs synaptic plasticity, induces neuroinflammation, and exacerbates Aβ deposition, whereas hepatic APOE3 confers protective effects. C. PCSK9, synthesized in the liver, binds LRP1 and promotes its lysosomal degradation, ultimately diminishing peripheral Aβ clearance.

inhibitors, PCSK9 inhibitors, and ApoE3-enriched plasma, may restore systemic cholesterol balance, enhance Aβ clearance, and mitigate tau pathology, providing promising cross-organ strategies for AD intervention.

3.5.2. *Bile acid metabolism*

Bile acids (BAs), the final metabolites of cholesterol, some of them (e.g., tauroursodeoxycholic acid, TUDCA) cross the BBB to alleviate AD-related pathology and cognitive decline, whereas others(e.g., deoxycholic acid, DCA) are cytotoxic [92]. In patients with AD, primary BA levels decline while secondary BA concentrations increase in both serum and brain, and a higher primary-to-secondary BA ratio correlates with better cognitive performance [32]. As the primary site of BA synthesis, the liver converts cholesterol into primary BAs via classical and alternative pathways, which are further metabolized by the gut microbiota into secondary BAs. Conjugate modification of BAs by the liver is also crucial for preserving their physiological activity [92]. In cholestatic and end-stage liver diseases, circulating DCA increases, potentially compromising BBB integrity and exacerbating AD pathology, whereas PBC may lower DCA levels [6]. Taken together, liver dysfunction-induced alterations in the circulating BA profile may modulate AD progression. Reducing neurotoxic secondary BAs or supplementing TUDCA may hold therapeutic potential.

3.5.3. *Fatty acid metabolism*

Alterations in plasma fatty acid profiles are closely associated with AD. Omega-3 polyunsaturated fatty acids (n-3 PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid, provide anti-inflammatory, antioxidant, and synaptic-protective benefits. In contrast, metabolites of arachidonic acid (AA) promote neuroinflammation and are linked to elevated AD risk [93]. Fatty acid metabolism is centrally regulated by the liver. Plasma 14,15-EET, an ω-6 arachidonic acid metabolite, is degraded by hepatic sEH, impairing microglial Aβ phagocytosis [94]. Notably, hepatic sEH expression increases significantly in various liver diseases [46]. Additionally, hepatic DHA is reduced in AD patients and correlates with cognitive decline [95]. Liver dysfunction impairs DHA synthesis and increases AA levels in liver tissue [95]. Collectively, hepatic alterations in fatty acid metabolism contribute to AD pathogenesis. Modulating hepatic sEH activity or supplementing with 14,15-EET or DHA may offer therapeutic

strategies to ameliorate cognitive impairment in AD.

4. Therapeutic potential of targeting the liver–brain axis

4.1. Exercise

Exercise incorporates complex environmental stimuli and

Table 1
Potential treatments for cognitive dysfunction targeting the liver-brain axis.

Intervention	Model	Duration	Intervention Strategy	Effects on the liver	Effects on the brain
Treadmill exercise [98–100]	AD model rats	4 weeks	5 days per week: Weeks 1-2: 2 × 15min/day, 10/min (5-minute rest) Week 3: 3 × 15min/day, 15/min (5-minute rest) Week 4: 4 × 15min/day, 15/min (5-minute rest)	Upregulate expression of LRP-1; Increase plasma levels of sLRP-1	Increased hippocampal expression of NEP, IDE, and LRP-1; Reduce Aβ burden and $sA\beta_{1-42}$ levels in the hippocampus; Improve spatial learning and memory performance
	APP/PS1 mice	12 weeks	5 days/week, 45 min/session: Weeks 1-8: Gradual speed increase; Weeks 9-12: Maintained at 15 m/min	Reduce the level of AST and ALT; Alleviate hepatic oxidative stress; Enhance the ability of KF cells in the liver to hydrolyze LPS	Decrease LPS accumulation
	TgF344-AD rats	8 months	3 times/week,18 m/min, 45 min/session	Unknown	Reduce Aβ burden and tau hyperphosphorylation in the cortex and hippocampus; Alleviate neuroinflammation and oxidative stress; Improve learning and memory deficits; Mitigate anxiety- and depression-like behaviors
Cycling [97]	AD patients	6 months	3 times/week, 20-50 min/session, moderate intensity	Unknown	Attenuate the progression of cognitive impairment
Structured exercise [96]	MCI patients	6 months	3 times/week, 5-min warm-up + 30-min aerobic + 20-min resistance/session	Elevate the level of CLU in plasma	Promote neurogenesis and attenuate neuroinflammation; Improve both spatial and episodic memory functions
Anthocyanins [121,122]	APdE9 mice	10 months	Fed bilberry extract (1.53 mg/g anthocyanins), blackcurrant extract (1.43 mg/g anthocyanins), or standard Teklad 2016 diet	Alleviate hepatic steatosis and improve hepatic insulin sensitivity	Reduce Aβ generation and aggregation; Improve spatial working memory and learning ability
	MCI patients	12 weeks	6-9 mL/kg Concord grape juice	Alleviate hepatic steatosis and improve hepatic insulin sensitivity	Enhance verbal learning ability
Luteolin [123]	3 × Tg mice	8 weeks	Luteolin (20 mg/kg or 40 mg/kg) i.p.	Improve hepatic insulin resistance	Inhibited Aβ production and accumulation; Suppress cerebral oxidative stress; Reduce neuronal apoptosis; Improve learning and memory performance
Resveratrol-Selenium-Peptide Nanocomposites [124]	AD model mice	16 weeks	50 mg/kg p.o.	Ameliorate hepatic steatosis; Alleviate hepatic inflammation and oxidative stress; Inhibit hepatic fibrosis;	Reduce Aβ deposition in the hippocampus; Ameliorate cerebral oxidative stress; Attenuate neuroinflammation; Improve spatial learning and memory function; Mitigate brain atrophy
Withania somnifera [107]	APP/PS1 mice	7-30 days	1g/kg p.o.	Upregulate hepatic LRP expression; Elevate plasma levels of sLRP	Upregulate cerebral LRP and NEP expression; Promote Aβ efflux from brain to periphery; Reverse Aβ plaque deposition and behavioral deficits in Morris water maze and radial arm maze
Lycopene [108]	Aging CD-1 mice	3 months	0.03% LYC diet	Upregulate hepatic FGF2 expression	Improve spatial memory; Improve neuronal structure; Increase the levels of BDNF and NGF; Increase the expression of synaptic marker PSD-95
Fo Shou San [109]	APP/PS1 mice	8 weeks	High-dose FSS (6.4 g/kg/d), mid-dose FSS (3.2 g/kg/d), low-dose FSS (1.6 g/kg/d) p.o.	Enhance hepatic AP activity; Reduce LPS and MDA levels in both liver and circulation	Reduce neuronal damage in the hippocampal CA1 region; Improve spatial learning and memory abilities; Improve cognition
$Poly_{150}Disc$ [120]	APP/PS1 mice	4 weeks	Intranasal administration every 2 days	Promote Aβ efflux from brain to blood and enhances hepatic Aβ uptake	Promote microglial clearance of Aβ and facilitate Aβ transport to peripheral clearance; Reduce brain Aβ burden; Improve spatial learning and memory abilities

consistently improves cognitive dysfunction in AD. In individuals with mild cognitive impairment (MCI), structured exercise markedly improves cognitive function [96]. Cycling exercise also slows down cognitive decline in AD patients [97]. Among the multiple mechanisms underlying the cognitive benefits of exercise, liver-mediated metabolic regulation is considered one of the most critical pathways. Long-term treadmill exercise upregulates hepatic LRP-1 expression, activates the Nrf2 antioxidant pathway, and enhances Kupffer cell–dependent LPS clearance, thereby reducing brain Aβ burden and improving cognition in AD models [98–100]. A single session of treadmill exercise markedly elevates hepatic FGF21 expression and circulating concentrations in C57 mice, although cognitive effects in AD models remain to be evaluated [101]. Voluntary running wheel exercise promotes hepatic secretion of neuroprotective factors, including BHB and clusterin, which may support cognition in AD by elevating brain BDNF, enhancing neurogenesis, and reducing neuroinflammation [27,36,96]. Moreover, exercise elevates circulating levels of liver-derived glycosylphosphatidylinositol-specific phospholipase D1 and S-adenosylmethionine, both associated with improved cognitive function [102]. Overall, exercise reduces hepatic steatosis and serves as a nonpharmacological intervention for AD via liver–brain-axis mechanisms that enhance the release of liver-derived neuroprotective factors, restore hepatic metabolic homeostasis, and facilitate the clearance of peripheral Aβ (Table 1). However, most evidence derives from animal models, and further clinical studies are needed to define optimal exercise modalities, intensity, and duration for liver–brain–mediated cognitive benefits.

4.2. Diet

Healthy dietary patterns are gaining attention as interventions to enhance cognitive function. High-fat diets impair liver function and exacerbate AD–related pathology and cognitive decline [82]. In contrast, ketogenic diet enhances hepatic ketogenesis to provide alternative energy substrates for the brain, thereby ameliorating AD-related cognitive deficits [103]. The Mediterranean diet reduces hepatic steatosis, improves insulin sensitivity, and enhances cognitive function [104]. Luteolin, recognized for its potent anti-inflammatory and antioxidant effects, inhibits Toll-like receptor signaling in hepatocytes, alleviating hepatic insulin resistance and cognitive dysfunction in AD models [105]. Resveratrol and its nanocomposites reduce hepatic steatosis, inflammation, oxidative stress, and ameliorate AD pathology [106]. Withania somnifera extract ameliorates cerebral Aβ deposition and behavioral deficits in APP/PS1 mice by upregulating hepatic LRP1 and plasma sLRP1 to enhance peripheral Aβ clearance [107]. Lycopene upregulates hepatic FGF21, reducing neuroinflammation, oxidative stress, and enhancing cognitive performance [108]. Additionally, Foshou San increases hepatic alkaline phosphatase activity in APP/PS1 mice, thereby improving the liver's capacity to detoxify LPS, which subsequently ameliorates hippocampal neuronal damage and cognitive deficits [109]. In summary, dietary interventions modulate AD pathology via multiple liver–brain axis mechanisms, including regulation of hepatic metabolism, inflammation, and peripheral Aβ clearance (Table 1). However, their therapeutic efficacy in AD patients remains to be validated in large-scale clinical trials.

4.3. Pharmacological agents

Disorders of lipid metabolism and insulin resistance are hallmark features of AD, targeting these metabolic abnormalities may yield novel therapeutic approaches. Statins reduce hepatic steatosis in NAFLD patients in a dose-dependent manner and decrease Aβ production and deposition in the brain, thereby improving cognitive function [110]. Mechanistically, statins may upregulate hepatocyte LRP1 expression, thereby enhancing peripheral Aβ clearance [111]. However, clinical results remain inconsistent, potentially due to differential BBB permeability of statins and heterogeneous cognitive outcome measures [112]. PCSK9 inhibitors improve hepatic lipid metabolism and attenuate alcohol-induced liver injury [113]. Moreover, the PCSK9 rs11591147 loss-of-function variant is associated with reduced NAFLD/NASH incidence and lower liver fibrosis risk [114]. In AD mice, PCSK9 knockdown reduces cerebral Aβ deposition, attenuates neuroinflammation, and enhances spatial learning and memory [115]. However, Mendelian randomization indicates that long-term PCSK9 inhibition does not significantly affect cognitive function or AD-related biomarkers [116].

GLP-1 receptor agonists, such as liraglutide, not only improve liver function but also reduce brain Aβ burden and neuroinflammation, although clinical evidence remains preliminary [70]. Peroxisome proliferator-activated receptor gamma agonists enhance hepatic lipid metabolism, reduce inflammation, and mitigate AD-related cognitive impairment [117]. Notably, pioglitazone improves cognition in AD patients with type 2 diabetes mellitus, whereas results for rosiglitazone remain inconsistent [70,118]. Portal vein insulin infusion promotes hepatic LRP1 translocation to the plasma membrane, enhancing peripheral Aβ clearance [119]. A novel intranasal nano-delivery system, polyDisc, simultaneously enhances central (microglia-mediated) and peripheral (liver-mediated) Aβ clearance, improving Aβ burden and cognitive performance in AD mice (Table 1) [120]. In addition, both neuroprotective hepatokine analogs/agonists (exemplified by FGF21) and neutralizing antibodies/antagonists targeting pathogenic hepatokines demonstrate therapeutic potential for AD [22].In summary, these pharmacological agents may ameliorate AD pathology via liver–-brain axis mechanisms, such as restoring hepatic metabolic homeostasis and enhancing peripheral Aβ clearance. However, large-scale clinical trials are necessary to verify the efficacy and safety of these treatments.

5. Summary

The liver and brain engage in bidirectional communication via the liver–brain axis, collaborating to maintain metabolic homeostasis and optimal neural function. As a central hub for metabolic and immune regulation, the liver remotely regulates neurotransmitter balance, feeding behavior, and cognition via hepatokines, inflammatory mediators, and metabolites. When hepatic function is compromised, the liver–brain axis is destabilized, marked by decreases in circulating FGF21 and IGF-1 and increases in LPS and LCN2. These alterations impair peripheral clearance of pathological proteins and promote neuroinflammation, insulin resistance, and lipid metabolic disorders, ultimately exacerbating cognitive dysfunction. Although therapeutic strategies targeting the liver-brain axis in AD are nascent, emerging evidence suggests that rational exercise, dietary modification, and pharmacological agents that improve lipid metabolism and insulin sensitivity may restore hepatic function, enhance peripheral Aβ clearance, and slow AD progression. As a critical bridge linking metabolic and neurological functions, the liver-brain axis is becoming a promising target for AD treatment, with the potential to overcome the limitations of conventional CNS-focused therapies and enable integrated, precise interventions.

Despite growing interests in liver–brain interactions in AD, several limitations of the current evidence should be acknowledged. Most mechanistic insights derive from animal models or in vitro systems, which may not fully reflect human hepatic and neural physiology. Clinical evidence remains limited, with small cohort sizes, heterogeneous patient populations, and a lack of longitudinal data to establish causal relationships between hepatic dysfunction and AD progression. These gaps underscore the need for large-scale clinical investigations, integrative multi-organ profiling, and longitudinal tracking of hepatic biomarkers to establish the translational relevance of the liver–brain axis in human AD.

Declaration of generative AI and AI-assisted technologies in the writing process

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CRediT authorship contribution statement

Jiajie Chen: Writing – review & editing, Methodology, Conceptualization. **Luyao Wang:** Writing – original draft, Investigation. **Yingying Zhou:** Software. **Shuoyan Zhao:** Data curation. **Qin Chen:** Project administration. **Kai Zheng:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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