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Review

Organ-Brain Axis in Alzheimer's Disease: A Systemic Perspective on Pathogenesis and Progression

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ABSTRACT: Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder characterized by progressive cognitive impairment and memory decline. Current therapeutic strategies largely provide symptomatic relief and remain limited in their capacity to halt or reverse disease progression. Accordingly, increasing efforts seek to reexamine AD pathophysiology from a systemic perspective and to identify novel therapeutic targets. Although classical AD research has focused primarily on intrinsic brain pathology, accumulating evidence indicates that disease progression reflects complex interactions among multiple cellular and systemic mechanisms. The central nervous system (CNS) is now recognized as functionally interconnected with peripheral organs through immune-mediated and neural communication networks. Within this framework, the concept of the organ–brain axis has emerged, proposing that organ-specific immune microenvironments and inflammation-derived mediators originating from peripheral tissues may modulate immune homeostasis in the brain, neuronal survival, and neurodegenerative processes. In patients with AD, immunological alterations are observed not only within the CNS but also in peripheral organs including the gut, lung, liver, and bladder, and these changes are associated with disease progression. Peripheral immune dysregulation extends beyond localized inflammatory responses, potentially contributing to sustained neuroinflammation, disruption of blood–brain barrier integrity, and pathological activation of microglia and astrocytes. Rather than viewing AD as a disorder confined to the brain, this review adopts a systemic perspective in which peripheral immune environments dynamically interact with central neuroinflammatory pathways. We comprehensively summarize immune cell alterations across major peripheral organs under AD pathology, their interactions with neuronal cells, and the potential signaling mechanisms that mediate organ–brain immune crosstalk.

Keywords: Alzheimer's disease, Gut-brain axis, Lung-brain axis, Liver-brain axis, Bladder-brain axis, immune cell signaling

1. Introduction

Alzheimer's disease (AD) is the most prevalent form of neurodegenerative disorder, primarily affecting the elderly population [1, 2]. It is characterized by progressive memory loss, cognitive decline, and impairments in language and spatial perception [1-3]. Despite ongoing efforts, most current therapeutic strategies are limited to symptomatic relief, and no treatments have yet been developed that fundamentally halt or reverse disease progression [4, 5]. As a result, research continues to focus in elucidating the complex pathophysiology of AD from a multidimensional perspective and identifying novel therapeutic approaches [6-8].

While the hallmark pathological features of AD include β-amyloid (Aβ) plaque deposition and tau protein

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hyperphosphorylation [9, 10], recent studies have revealed that additional factors, such as oxidative stress, mitochondrial dysfunction, metabolic abnormalities, vascular impairments, and neuroinflammation, interact synergistically to accelerate disease progression [11-13]. Among these, the gradual loss of neurons and synapses in the central nervous system (CNS) has long been considered central to both the clinical manifestations and neuropathological features of AD [1, 6, 14]. Accumulating evidence suggests that AD involves pathological alterations beyond the brain, reflecting systemic immune–neural interactions rather than isolated CNS pathology [15-17]. This has led to growing interest in the concept of the *organ-brain axis*, which proposes that various peripheral organs modulate CNS immune homeostasis and influence disease progression rather than serving as primary disease initiators [18, 19]. Immune cells and mediators originating from peripheral organs can influence neuroinflammatory responses, microglial activation, neuronal damage, and increasing evidence points to specific signaling mechanisms by which individual axes contribute to AD pathology [20, 21].

In parallel, accumulating studies have revised the traditional view of the CNS as an immune-isolated site, revealing the integral role of resident and infiltrating immune cells in regulating neuroinflammatory responses and maintaining neural integrity [22, 23]. Key peripheral organs such as the gut, lung, liver, and bladder each maintain distinct immune microenvironments, and disruptions in the function of immune cells within these organs have been shown to influence CNS function through both direct and indirect mechanisms [24, 25]. Among these, the bladder was included due to its strong dependence on autonomic and sensory neural regulation and the high prevalence of functional urinary disturbances in AD, which may reflect CNS dysregulation rather than primary bladder pathology. The gut exemplifies this connection: hyperactivation of T helper 17 (Th17) cells, a reduction in regulatory T cells (Tregs), and pro-inflammatory activation of macrophages and dendritic cells collectively disrupt intestinal immune homeostasis. This dysregulation permits harmful immune stimuli to disseminate systemically, thereby triggering the activation of immune cells within the brain [19, 26, 27]. Similarly, in the lung, inflammation arising from infections or environmental exposures leads to the redistribution of monocytes and hyperactivation of T cells. These immune alterations may impact the CNS via systemic circulation and contribute to neuroinflammatory processes [28, 29]. The liver, as a central regulator of systemic immune responses, may play an important modulatory role. Functional impairments in hepatic macrophages, monocytes, and dendritic cells may amplify systemic inflammation, potentially affecting immune homeostasis in the brain [30, 31]. In the bladder, recurrent infections promote robust inflammatory responses involving T cells and macrophages. Emerging evidence suggests that such peripheral immune activity may affect CNS function through autonomic neural pathways [32, 33].

This review recontextualizes AD pathophysiology by examining how peripheral immune environments modulate CNS pathology through organ–brain communication pathways. Focusing on four peripheral organs including the gut, lung, liver, and bladder, we systematically examine the alterations in immune cell populations within each organ, the interactions between immune and neuronal cells, and the organ-specific mechanisms that mediate these effects. The ultimate goal is to provide an integrated understanding of how peripheral immune disturbances contribute to AD progression and to explore the therapeutic potential of targeting immune-neural interactions within each axis. Importantly, the organ–brain axes discussed in this review are not proposed as primary initiators of AD but rather as modulatory systems shaping disease persistence and progression.

2. Gut-Brain Axis in Alzheimer's Disease

The gut-brain axis represnts a bidirectional communication network linking gut microbiota-driven immune regulation with CNS neuroinflammatory process [26, 34, 35]. In particular, alterations in the composition of the gut microbiota, known as dysbiosis, have a substantial effects on the function of peripheral and central immune cells, which may be associated with disrupted neuronal homeostasis, increased inflammation, and neurodegenerative changes [36-38].

The gut microbiota plays a central role in maintaining the balance of the intestinal mucosal immune system by regulating the differentiation and proportions of regulatory T cells (Tregs) and T helper 17 (Th17) cells [27, 39]. Under healthy gut-brain axis conditions, microbial metabolites such as short-chain fatty acids (SCFAs) promote the differentiation of Tregs, thereby suppressing inflammation [40, 41]. Under dysbiotic conditions, Th17-dominant immune responses promote systemic inflammatory signaling that can influence CNS immune activation [42, 43]. This imbalance in immune cell populations increases the permeability of the blood-brain barrier (BBB), enabling peripheral inflammatory signals to penetrate the CNS and resulting in pathological activation of microglia [44-46]. Abnormally activated microglia secrete pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which contribute to synaptic elimination and neuronal death [47, 48].

Gut-derived immune cells can modulate neuronal function both directly and indirectly. IL-10 produced by Tregs induces an anti-inflammatory (M2) phenotype in microglia, promoting neuronal survival and repair [49, 50]. Conversely, IL-17 released from Th17 cells stimulates astrocytes to increase the expression of neurotoxic markers such as glial fibrillary acidic protein (GFAP) and complement component C3, thereby contributing to neuronal damage [27, 51, 52]. These interactions suggest that immune dynamics within the gut may influence on neuronal viability and function via the gut-brain axis [34].

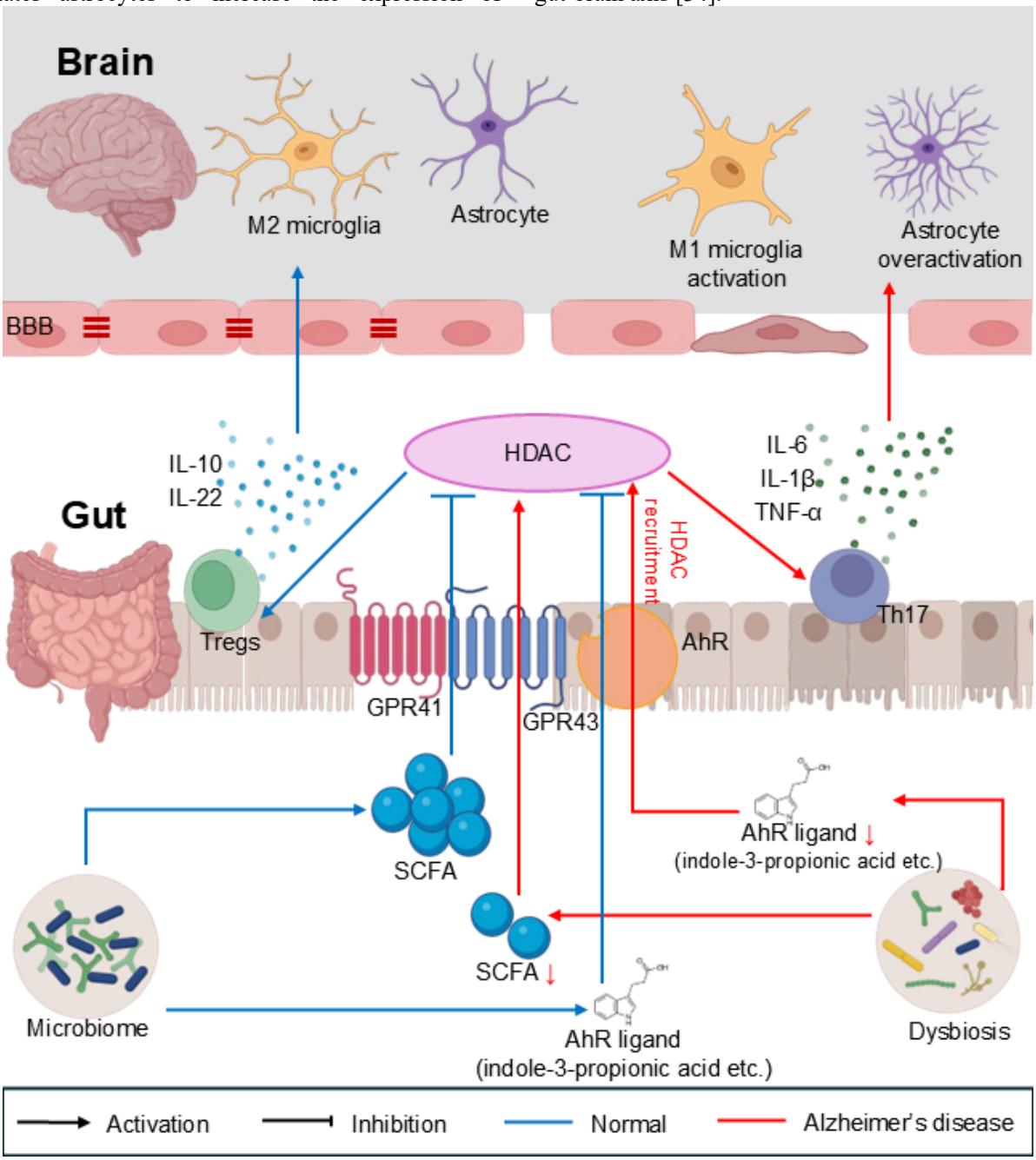

Figure 1. Gut-brain axis signaling mediated by SCFA-GPR41/43 and AhR pathways in normal and Alzheimer's disease conditions. This schematic illustrates the regulatory role of gut microbiota–derived metabolites in modulating neuroinflammation through the gut–brain axis under physiological conditions and their dysregulation in Alzheimer's disease (AD). Under normal conditions (blue arrows), short-chain fatty acids (SCFAs) and tryptophan-derived aryl hydrocarbon receptor (AhR) ligands, such as indole-3-propionic acid, produced by the gut microbiome activate GPR41/43 and AhR signaling, respectively, converging on HDAC-mediated epigenetic regulation that supports regulatory T cell (Treg) function and promotes anti-inflammatory cytokine production, including IL-10 and IL-22. These processes contribute to intestinal immune homeostasis and preservation of blood–brain barrier (BBB) integrity. In AD (red arrows), gut dysbiosis reduces the

availability of SCFAs and AhR ligands, leading to dysfunctional HDAC-centered regulatory signaling. In this context, AhR-dependent HDAC recruitment is altered, favoring pro-inflammatory T cell polarization toward the Th17 phenotype and enhancing the release of pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α. These cytokines contribute to BBB disruption and facilitate a pro-inflammatory neuroglial environment characterized by M1 microglial activation and astrocytic overactivation. Solid arrows indicate activation, blunt-ended lines indicate inhibition, blue arrows represent physiological (normal) conditions, and red arrows represent pathological alterations associated with Alzheimer's disease.

Beyond immune cell-mediated regulation, the gut-brain axis also involves specific cellular signaling mechanisms, particularly the SCFA-GPR41/43 and microbial-AhR mechanisms, which are increasingly recognized for their roles in AD-related neuroimmune modulation. SCFAs are fatty acids produced by gut microbial fermentation of dietary fibers and play key roles in maintaining gut health, modulating energy metabolism, regulating immune responses, and controlling inflammation [41, 53, 54]. SCFAs activate G-protein-coupled receptors GPR41 and GPR43, thereby modulating immune function and inflammatory pathways [55, 56]. Butyrate, in particular, is known to suppress histone deacetylase (HDAC) activity, leading to increased expression of anti-inflammatory genes and enhanced FOXP3 expression in Tregs [57, 58]. In the brain, SCFAs are essential for microglial development and functional maintenance; in germ-free mice, SCFA supplementation has been shown to restore microglial homeostasis [59]. Moreover, SCFAs contribute to strengthening the BBB and suppressing neuroinflammation, suggesting their potential to attenuate AD pathology [60].

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor responsive to tryptophan-derived microbial metabolites such as indole-3-propionic acid [61]. AhR plays a central role in gut–brain immune regulation [62, 63]. In the gut, AhR activation enhances interleukin-22 (IL-22) secretion by type 3 innate lymphoid cells (ILC3s), supporting the maintenance of the intestinal epithelial barrier and suppressing excessive Th17 responses [61, 64, 65]. Within the CNS, AhR suppresses the pro-inflammatory activation of astrocytes and microglia, thereby contributing to immune homeostasis [66]. This dual regulatory mechanism highlights AhR as a gut–brain axis-specific mechanism and a promising therapeutic target for modulating gut-derived neuroinflammatory responses in AD (Fig. 1) [67, 68].

3. Lung-Brain Axis in Alzheimer's Disease

The lung-brain axis is recognized as a bidirectional communication pathway involving the nervous, immune, and humoral systems, in which may act as modulatory factors associated with enhanced neuroinflammatory states during AD progression [69, 70].

In both AD animal models and patients, inflammatory monocytes and macrophages have been found to accumulate within lung tissues [71]. These immune cells often exhibit a shift toward a pro-inflammatory M1-like phenotype, characterized by increased expression of cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) [72]. Activation of lung immune cells may contribute to systemic inflammation that secondarily affects BBB integrity and microglial activation [20, 73, 74]. Furthermore, dendritic cells in the lung undergo changes in antigen-presenting capacity and migratory behavior, which can alter the distribution and functionality of peripheral T cell subsets [75, 76]. Specifically, a reduction in regulatory T cell (Treg) suppressive activity and an increase in T helper 17 (Th17) cells contribute to systemic pro-inflammatory immune responses [77]. These immunological imbalances have also been detected in cerebrospinal fluid and brain tissue, suggesting that immune signaling originating in the lung can amplify CNS immune dysregulation [70, 78].

Sensory neurons activated by pulmonary inflammatory mediators relay signals to the brainstem nuclei via the vagus nerve [79]. In the context of AD, impairments in vagal tone and dysfunction of the cholinergic anti-inflammatory pathway (CAP) have been observed, indicating a diminished capacity of the CNS to modulate peripheral immune signals derived from the lung [80, 81]. In addition, cytokines and extracellular vesicles (EVs) secreted by pulmonary immune cells can cross the BBB and act on resident glial cells, including microglia and astrocytes [82]. These interactions increase the expression of inflammation-related genes, including activation of the NLRP3 inflammasome, thereby promoting a self-sustaining neuroinflammatory loop [83, 84]. Collectively, these mechanisms highlight plays a particularly critical role [71, 84].

Within the lung-brain axis, several physiological and pathological signaling mechanisms have been identified, with the α7 nicotinic acetylcholine receptor (α7nAChR) and substance P-neurokinin-1 receptor (SP-NK1R) pathways being among the most prominent [29]. α7nAChR is a calcium-permeable ion channel widely expressed in both the brain and immune system, playing important roles in neurotransmission and anti-inflammatory regulation [85-87]. Binding of acetylcholine to α7nAChR suppresses the production of inflammatory cytokines by inhibiting the nuclear factor kappa B (NF-κB) pathway [78, 85, 88]. In AD, reduced expression of α7nAChR has been associated with

heightened microglial activation and enhanced inflammatory responses [89]. Another important pathway, the SP–NK1R pathway, involves substance P, a neuropeptide secreted by sensory neurons in the lung [90, 91]. Substance P binds to neurokinin-1 receptors (NK1R), inducing vasodilation, immune cell recruitment, and cytokine production [92-94]. This signaling cascade can propagate through systemic circulation and cross the BBB, contributing to central neuroinflammation. In AD, overactivation of this pathway has been linked to increased BBB permeability and further activation of microglia, thereby accelerating disease progression (Fig. 2) [94-96].

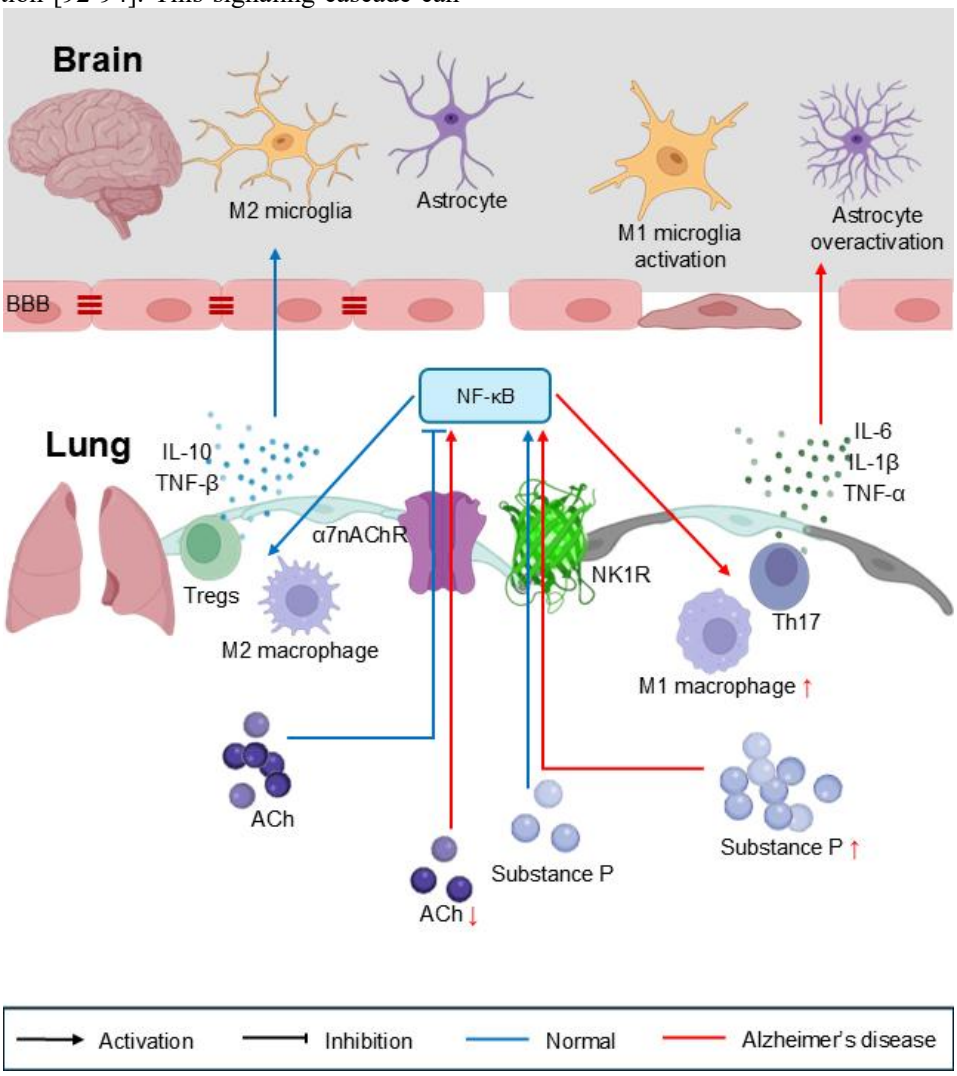

Figure 2. Lung-brain axis signaling mediated by α7nAChR and SP–NK1R pathways in normal and Alzheimer's disease conditions. This figure presents a simplified conceptual schematic of the lung–brain axis, highlighting key neuroimmune signaling pathways under physiological conditions and their dysregulation in Alzheimer's disease (AD). Under normal conditions (blue arrows), cholinergic signaling mediated by acetylcholine (ACh) through the α7 nicotinic acetylcholine receptor (α7nAChR), together with balanced neuropeptide signaling via substance P (SP) and its receptor NK1R, maintains controlled NF-κB activity in lung immune cells. This regulatory environment supports regulatory T cell (Treg) responses, promotes M2 macrophage polarization, and favors anti-inflammatory cytokine production, including IL-10, thereby contributing to blood–brain barrier (BBB) integrity and neuroimmune homeostasis. In AD (red arrows), reduced cholinergic signaling and enhanced SP–NK1R signaling shift NF-κB activity toward a pro-inflammatory state. This alteration favors Th17 responses and M1 macrophage polarization, accompanied by increased production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. These cytokines contribute to BBB disruption and facilitate a pro-inflammatory neuroglial environment characterized by M1 microglial activation and astrocytic overactivation in the brain. NF-κB is depicted as a downstream signaling integrator rather than a dominant hub, emphasizing receptor-mediated neuroimmune regulation. This schematic highlights predominant signaling trends rather than exhaustive molecular complexity. Solid arrows indicate activation, blunt-ended lines indicate inhibition, blue arrows represent physiological (normal) conditions, and red arrows represent pathological alterations associated with Alzheimer's disease

4. Liver-Brain Axis in Alzheimer's Disease

The liver-brain axis refers to a metabolic and immunological communication pathway between the liver and the CNS, and it has emerged as a modulatory linking systemic metabolic and immune disturbances to CNS pathology in AD [97, 98]. The liver plays a central role in maintaining systemic immune and metabolic homeostasis, and chronic hepatic inflammation or metabolic dysfunction can create a pro-inflammatory systemic environment that ultimately exacerbates neuroinflammation [99, 100]. In particular, conditions such as non-alcoholic fatty liver disease (NAFLD) and hepatic fibrosis have been reported to be associated with AD pathology through mechanisms involving altered immune cell function, increased cytokine release, and changes in the blood–brain barrier (BBB) [97, 101-103]. Immune alterations in the liver-brain axis are closely associated with the liver's immunological micro-environment. Kupffer cells, the resident macrophages of the liver, become activated in response to hepatic injury or lipid accumulation and secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [104-106]. These cytokines can enter systemic circulation, promote systemic inflammation, increase BBB permeability, and drive the pathological activation of microglia in the CNS [107, 108]. Additionally, liver damage associated with enhanced activation of T cells, particularly T helper 1 (Th1) and T helper 17 (Th17) subsets, as well as monocytes [109, 110]. These immune cells can infiltrate the brain via the cerebrovascular system and directly convey inflammatory signals to neuronal tissue [111]. Hepatic inflammation-derived signaling has been suggested to be associated with core pathological features of AD, including synaptic loss, amyloid-beta accumulation, and increased tau phosphorylation [112, 113].

The interaction between liver-derived immune cells and CNS-resident cells is also a crucial component of the liver–brain axis [46, 97]. Upon entering the CNS, hepatic T cells can stimulate astrocytes to increase the expression of glial fibrillary acidic protein (GFAP) and complement component 3 (C3), while enhancing the pro-inflammatory M1 phenotype of microglia, thereby promoting neuronal injury [114, 115]. In contrast, regulatory T cells (Tregs) can suppress neuroinflammation through the secretion of interleukin-10 (IL-10) and induce a shift in microglial activation toward the anti-inflammatory M2 phenotype, supporting neuronal survival [116, 117]. Thus, the balance of the hepatic immune environment has a substantial impact on neuroinflammatory responses and neuronal function within the CNS [118].

Among pathways discussed within the liver–brain axis, fibroblast growth factor 21 (FGF21) signaling warrants cautious interpretation with respect to axis specificity. Although FGF21 is predominantly secreted by the liver under metabolic stress [119], it also functions as a systemic metabolic hormone acting on multiple peripheral tissues, making it difficult to distinguish liver-specific FGF21–brain effects from broader systemic metabolic influences [120]. Another important mechanism is the HMGB1-RAGE axis [121]. High-mobility group box 1 (HMGB1) is a damage-associated molecular pattern (DAMP) molecule released by injured cells [122, 123]. It binds to the receptor for advanced glycation end products (RAGE), leading to the induction of inflammatory gene expression and the production of reactive oxygen species [124, 125]. This axis is associated not only with hepatic inflammation but also with amyloid-beta accumulation, tau hyperphosphorylation, and neuronal cell death in the brain [126, 127]. In AD, both HMGB1 and RAGE expression levels are elevated, and inhibition of this signaling cascade has been shown to attenuate inflammation and preserve cognitive function (Fig. 3) [126, 128]. However, current evidence suggests that these axes may not be strictly specific to the liver–brain axis but are rather modulated in secondary response to hepatic dysfunction or systemic metabolic disturbances. At present, no fully liver-specific and independent signaling mechanisms within the liver–brain axis have been clearly defined. Ongoing research is actively exploring the molecular links between liver-derived immune signaling and CNS pathology. These efforts may lay the foundation for the development of novel therapeutic strategies aimed at modulating the liver–CNS immune interface in AD. These signaling pathways are not strictly liver-specific and may reflect secondary systemic effects associated with hepatic dysfunction.

5. Bladder-Brain Axis in Alzheimer's Disease

The bladder-brain axis represents a bidirectional communication pathway between the bladder and the CNS, integrating both immune and neural mechanisms. The bladder-brain axis represents an emerging and hypothesis-driven framework linking peripheral immune activity and neural signaling to CNS dysregulation in AD. Alterations in bladder immune cell activity may contribute to systemic inflammatory signaling associated with CNS immune dysregulation [33, 129].

A variety of immune cells, including macrophages, dendritic cells, and T lymphocytes, are present in the bladder mucosa and surrounding tissues [130, 131]. Under AD-related pathological conditions, these immune

cells become activated and release pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [132, 133]. Concurrently, the suppressive function of regulatory T cells (Tregs) is diminished, leading to an imbalance in immune regulation [134, 135]. This dysregulated immune environment may increase the permeability of the blood–brain barrier (BBB), allowing peripheral immune signals to infiltrate the CNS [136]. The result may be associated with pathological microglial activation, which accelerates neuroinflammation and neuronal damage [74, 137].

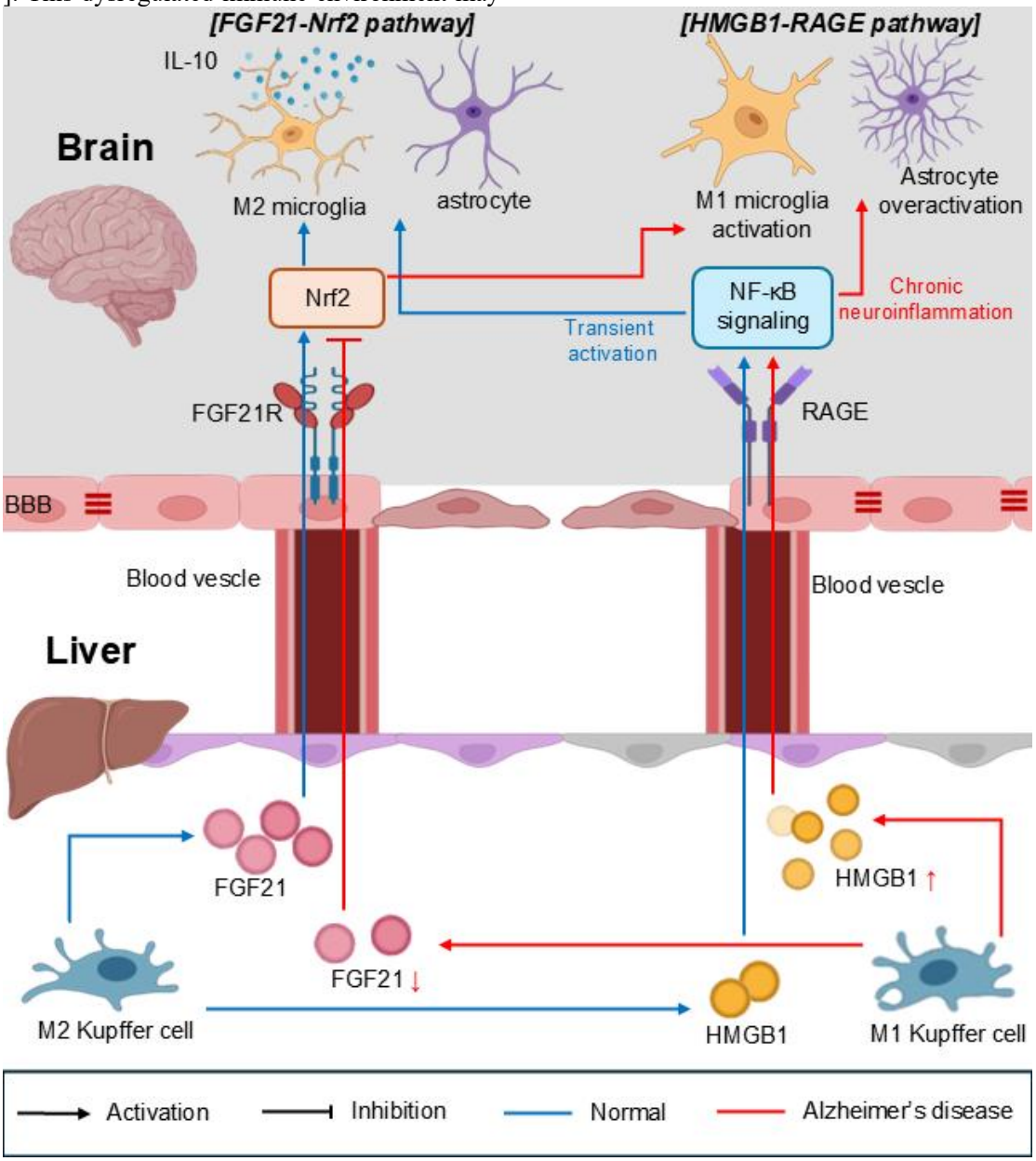

Figure 3. Liver-brain axis signaling mediated by FGF21-Nrf2 and HMGB1-RAGE pathways in normal and Alzheimer's disease conditions. This schematic illustrates distinct liver–brain immune signaling pathways that differentially regulate neuroinflammatory states under normal conditions and Alzheimer's disease (AD. Under physiological conditions, liver-derived fibroblast growth factor 21 (FGF21), primarily produced by M2-polarized Kupffer cells, enters the circulation and crosses the blood–brain barrier (BBB) to activate FGF21 receptor signaling in the brain. This activation induces Nrf2-dependent antioxidant and cytoprotective responses, supporting anti-inflammatory microglial polarization and regulatory mediator production, thereby contributing to immune homeostasis. In AD, reduced hepatic FGF21 availability and impaired Nrf2 signaling weaken this protective axis. In parallel, low-level high-mobility group box 1 (HMGB1) signaling through the receptor for advanced glycation end products (RAGE) under physiological conditions associated with controlled and transient activation of downstream inflammatory signaling required for immune surveillance. In AD, excessive HMGB1 release from M1-polarized

Kupffer cells and increased RAGE expression drive sustained signaling, resulting in chronic NF-κB activation, microglial M1 polarization, astrocytic overactivation, and persistent neuroinflammation. Together, the figure highlights how disruption of the balance between protective and pathological liver–brain immune pathways contributes to neuroinflammatory progression in Alzheimer's disease. Solid arrows indicate activation, blunt-ended lines indicate inhibition, blue arrows represent predominant signaling trends under physiological conditions, and red arrows represent predominant pathological alterations associated with Alzheimer's disease. This figure emphasizes relative shifts in signaling balance between coexisting liver–brain pathways, rather than absolute or exclusive pathway activity.

Immune-neural interactions along bladder-associated sensory pathways have been proposed as potential contributors to CNS immune activation [138]. In particular, sensory signals transmitted from the bladder via afferent neural pathways are thought to contribute to CNS immune activation and the regulation of neuroinflammation [139, 140].

Although research on bladder-specific mechanisms involved in the bladder-brain axis remains limited, certain candidate mechanisms have been proposed [141]. One such example is purinergic signaling through the ATP-P2X3 receptor axis. This axis is initiated when bladder epithelial cells and immune cells release ATP, which in turn activates P2X3 receptors [142-144]. P2X3 receptor has been reported to promote the release of pro-inflammatory cytokines [145, 146] and can influence microglial activation and the regulation of neuroinflammatory responses within the CNS (Fig. 4) [147]. Given the early stage of research, current evidence supporting bladder-specific mechanisms remains limited and largely indirect. Because research on the bladder-brain axis is still in its early stages, there is a lack of comprehensive studies, and no bladder-specific signaling mechanism has yet been definitively identified. However, ongoing investigations continue to explore this axis, and it is likely that novel molecular targets and regulatory pathways relevant to neurodegeneration will be uncovered in the near future. Compared with other organ–brain axes, mechanistic diversity within the bladder–brain axis remains limited, reflecting both the relative novelty of this research field and the complexity of distinguishing bladder-specific immune–neural signaling from systemic inflammatory effects. Consequently, purinergic signaling pathways, such as the ATP–P2X3 axis, currently represent the most experimentally accessible framework rather than a definitive or exclusive mechanism.

6. Conclusion and Future Perspectives

Alzheimer's disease (AD) is not a disorder caused by a single etiology but rather a complex neurodegenerative condition arising from the interplay of diverse pathophysiological factors [2, 3]. This review focuses on the concept of the "organ–brain axis" and provides a multifaceted overview of how immune-mediated interactions between peripheral organs, including the gut, lung, liver, bladder, and the central nervous system (CNS), influence the initiation and progression of AD pathology.

Each organ-brain axis discussed highlights how organ-specific immune environments modulate CNS pathology through complementary mechanisms. Within the gut–brain axis, interactions between the gut microbiota and immune cells modulate the balance between regulatory T cells and Th17 cells, which in turn affect neuroinflammatory responses and neuronal function [27, 39, 49, 50]. The lung–brain axis involves pro-inflammatory macrophages and cytokines originating in the lungs, which disrupt the blood–brain barrier (BBB) and activate microglia, exacerbating neuroinflammation [20, 73, 74, 77]. In the liver–brain axis, hepatic macrophages (Kupffer cells), cytokine networks, and liver-derived acute-phase proteins contribute to systemic inflammation and shape the neuroimmune environment of the brain [104-106]. Hepatic dysfunction can promote pathological activation of microglia and is also linked to tau pathology [112, 113]. Lastly, the bladder–brain axis has been shown to involve the activation of immune cells within bladder tissue, which promotes systemic inflammation [139, 140]. This, in turn, leads to BBB impairment and increased diffusion of inflammatory cytokines into the CNS, thereby aggravating AD pathology [74, 136, 137]. These interactions extend beyond correlative observations and suggest coordinated immune–neural modulation across organ systems. Much of the mechanistic evidence discussed is derived from preclinical models, and direct causal relationships in human AD remain incompletely defined. In particular, most axis-specific mechanisms have been characterized primarily in rodent models, and their translatability to human Alzheimer's disease remains uncertain. Differences in immune system organization, lifespan, and disease progression between experimental models and human patients complicate direct extrapolation of these findings. Moreover, several reported associations reflect correlative relationships rather than direct causal links, underscoring the need for cautious interpretation when integrating peripheral immune alterations into AD pathophysiology.

Recent evidence suggests that biological sex may function as an additional modulatory factor influencing organ–brain immune crosstalk in Alzheimer's disease

(AD) [148, 149]. Sex-dependent differences in immune regulation, hormonal signaling, and peripheral organ physiology have been reported to shape systemic inflammatory tone and neuroimmune communication [149, 150]. In the gut–brain axis, interactions between sex hormones and the intestinal microbiota may influence microbial composition and metabolite profiles, thereby indirectly modulating immune signaling toward the central nervous system [151, 152]. Beyond the gastrointestinal system, sex-biased susceptibility to bladder inflammation and sexually dimorphic hepatic metabolism may further affect peripheral immune activation and the release of organ-derived mediators involved in CNS inflammation [148, 151]. Although direct mechanistic evidence linking sex-specific pathways to organ–brain axes in AD remains limited, these observations highlight sex as an important contextual variable that should be considered in future studies aimed at refining mechanistic understanding and advancing precision-based therapeutic strategies [150].

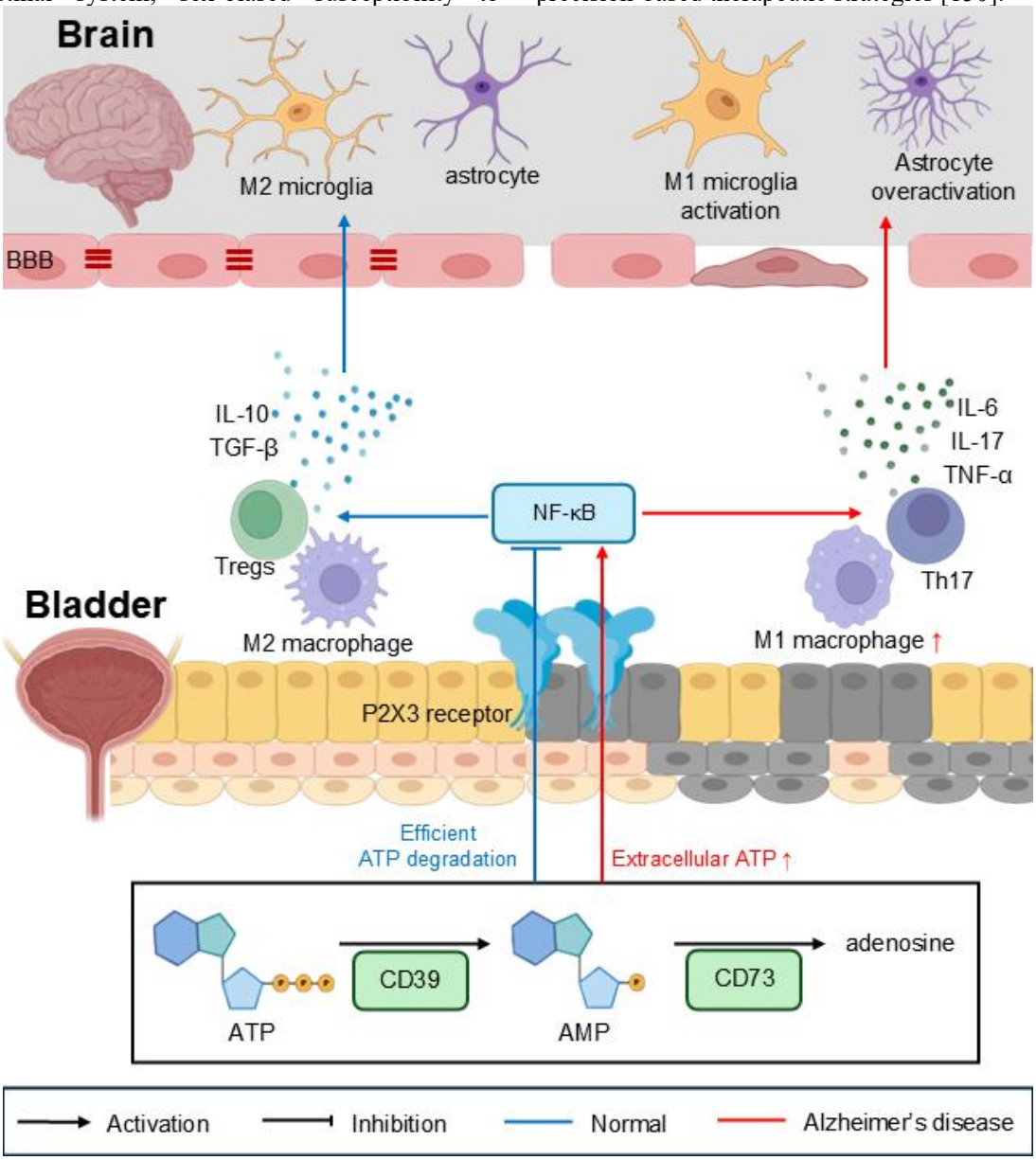

Figure 4. Bladder–brain axis signaling involving ATP–P2X3–dependent pathways under normal and Alzheimer's disease conditions. This schematic illustrates how alterations in purinergic signaling in the bladder modulate immune and neuroinflammatory responses in the brain under physiological conditions and in Alzheimer's disease (AD). Under normal conditions (blue arrows), efficient extracellular ATP degradation by the ectonucleotidases CD39 and CD73 converts ATP to AMP and subsequently to adenosine, thereby limiting ATP-driven inflammatory signaling. This purinergic balance suppresses NF-κB activation, promotes regulatory immune phenotypes including regulatory T cells (Tregs) and M2 macrophages, and favors anti-inflammatory cytokine

production such as IL-10 and TGF-β. These signals contribute to the maintenance of blood–brain barrier (BBB) integrity and support anti-inflammatory microglial states and physiological astrocytic function in the brain. In AD (red arrows), insufficient ATP degradation may results in extracellular ATP accumulation, leading to enhanced P2X3 receptor activation and sustained NF-κB signaling. This shift promotes pro-inflammatory immune polarization characterized by M1 macrophages and Th17 cells, accompanied by increased production of IL-6, IL-17, and TNF-α. Consequently, BBB disruption, M1 microglial activation, and astrocyte overactivation are exacerbated, collectively amplifying neuroinflammatory responses. Solid arrows indicate activation, blunt-ended lines indicate inhibition, blue arrows represent predominant signaling trends under physiological (normal) conditions, and red arrows represent predominant pathological alterations associated with Alzheimer's disease.

This framework of immune-neural communication across the organ–brain axes expands our understanding of AD pathogenesis beyond a CNS-centric view and offers new paradigms for therapeutic development [15, 153]. Modulating the activation of organ-specific immune cells, targeting signaling pathways that are selectively expressed along particular axes, and regulating intercellular communication via microbial metabolites or extracellular vesicles may provide novel opportunities for pharmacological intervention and immunomodulatory therapy [154].

Table 1. Key immune mechanisms and mediators across organ-brain axes in Alzheimer's disease.

Organ-brain axis	Key mechanisms	Shared mediators	Axis-specific mediators	Biomarkers	Therapeutic strategies	Ref.
Gut-brain axis	Microbiota dysbiosis	IL-6	SCFAs	Circulating SCFAs	Microbiota modulation	[55, 56, 61]
	SCFA-GPR41/43 signaling	TNF-α	GPR41/43	Plasma IL-6, TNF-α	SCFA supplementation	
	AhR-IL-22 axis	IL-1β	AhR ligands	Microbial metabolites	AhR targeting	
	HDAC epigenetic regulation	Th17 expansion	IL-22			
	Treg/Th17 imbalance	Microglial activation				
		BBB disruption				
Lung-brain axis	Pulmonary immune activation	IL-6	Acetylcholine	Circulating cytokines	α7nAChR agonists	[69, 85, 94]
	α7nAChR signaling	TNF-α	α7nAChR	Lung-derived EVs	Cholinergic modulation	
	SP-NK1R pathway	IL-1β	Substance P		Vagal neuromodulation	
	Afferent neuroimmune signaling	NF-κB activation	NK1R			
		Th17 responses				
		BBB disruption				
Liver-brain axis	Kupffer cell activation	IL-6	FGF21	Plasma FGF21	Metabolic correction	[97, 119, 121]
	Cytokine amplification	TNF-α	HMGB1	Circulating HMGB1	FGF21 therapy	
	FGF21-Nrf2 signaling	IL-1β	RAGE	Hepatic inflammatory markers	HMGB1-RAGE inhibition	
	HMGB1-RAGE axis	Oxidative stress				
		Microglial M1 polarization				
Bladder-brain axis	Bladder immune activation	IL-6	Extracellular ATP	Urinary cytokines	Purinergic modulation	[33, 132, 142]
	ATP-P2X3 signaling	TNF-α	P2X3	ATP metabolites	Afferent neuromodulation	
	Impaired ATP degradation	Th17 activation	CD39/CD73			
	Sensory afferent pathways	NF-κB signaling				
		BBB disruption				

Table 2. Shared cytokines across representative organ–brain axes under physiological and Alzheimer's disease conditions.

Cytokine	State	Axis-defining organ(s)	Reference
IL-10	Physiological (Normal)	Gut-Brain	[49, 50]
		Lung-Brain	[82]
		Liver-Brain	[116, 117]
		Bladder-Brain	[139, 140]
IL-22	Physiological (Normal)	Gut-Brain	[61, 64, 65]
TGF-β	Physiological (Normal)	Lung-Brain	[82]
		Bladder-Brain	[131]
IL-6	Alzheimer's disease (AD)	Gut-Brain	[47, 48]
		Lung-Brain	[72]
		Bladder-Brain	[132, 133]
IL-1β	Alzheimer's disease (AD)	Gut-Brain	[47, 48]
		Lung-Brain	[72]
		Bladder-Brain	[132, 133]
TNF-α	Alzheimer's disease (AD)	Gut-Brain	[47, 48]
		Lung-Brain	[72]
		Bladder-Brain	[132, 133]

From a therapeutic perspective, each organ–brain axis offers distinct but complementary intervention opportunities, although the level of supporting evidence and translational maturity varies across axes. In the gut–brain axis, strategies targeting microbiota composition, short-chain fatty acid supplementation, and aryl hydrocarbon receptor modulation have shown preclinical efficacy. Lung–brain axis–oriented approaches primarily focus on restoring vagal tone and cholinergic anti-inflammatory signaling, including α7nAChR-targeted interventions. In the liver–brain axis, metabolic correction, FGF21-based therapies, and inhibition of HMGB1–RAGE signaling have been proposed to attenuate neuroinflammation. By contrast, therapeutic strategies targeting the bladder–brain axis remain exploratory and are largely centered on neuromodulation and purinergic signaling regulation (Table 1).

However, several unresolved scientific challenges must be addressed before immune–neural interactions within the organ–brain axes can be therapeutically leveraged. These include elucidating the spatiotemporal specificity of immune cell activation and signaling pathways within each axis, characterizing the higher-order regulatory networks governing organ-to-brain communication, and conducting quantitative and functional analyses of how these peripheral signals are ultimately transmitted to the CNS. It is also essential to investigate how immune microenvironments within each organ operate differently depending on the disease stage of AD or the patient's systemic metabolic status. Furthermore, developing multiorgan biomarkers based on human data, as well as optimizing the delivery routes for drugs or bioactive molecules that target the organ–brain axis, represent key future directions for therapeutic innovation. Ultimately, this review underscores that AD is not solely a brain-centered disease but one in which systemic alterations in immune homeostasis are intimately linked with CNS pathology [15]. Research grounded in the organ–brain axis not only offers new insights into AD pathophysiology but also enhances the feasibility of developing integrated, multiorgan therapeutic strategies [74, 154]. Such an approach may serve as a central component of future precision medicine efforts aimed at delaying onset or halting progression of the disease. Although similar cytokines recur across multiple organ–brain axes, their heterogeneous cellular and regulatory distribution (Table 2) underscores the difficulty of translating shared inflammatory signals into reliable, organ-specific clinical biomarkers. Despite this conceptual promise, reliable organ-specific biomarkers reflecting organ–brain axis activity in clinical Alzheimer's disease cohorts remain limited, representing a major translational challenge. For example, gut-derived metabolites such as circulating short-chain fatty acids exhibit substantial inter-individual variability and lack sufficient specificity to reflect central neuroimmune status. Similarly, liver-associated markers, including aminotransferases or metabolic hormones, often mirror systemic metabolic states rather than liver–brain immune coupling. In the case of the bladder–brain axis, urinary cytokines or inflammatory mediators may primarily reflect local urological inflammation, making it challenging to distinguish CNS-relevant signals in clinical cohorts.

Author Contributions

Y. Kim, J. Jung, A. Clarisse, and S. Yoon contributed to the writing of the original draft and validated the manuscript. Y. Kim prepared all figures and visual

materials. S. Bang and S.H. Yang conceptualized the study and contributed to the reviewed and edited of the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Zheng Q, Wang X (2025). Alzheimer's disease: insights into pathology, molecular mechanisms, and therapy. Protein Cell, 16:83-120.

[2] Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. (2021). Alzheimer's disease. Lancet, 397:1577-1590.

[3] Crews L, Masliah E (2010). Molecular mechanisms of neurodegeneration in Alzheimer's disease. Hum Mol Genet, 19:R12-R20.

[4] Long JM, Holtzman DM (2019). Alzheimer disease: an update on pathobiology and treatment strategies. Cell, 179:312-339.

[5] Xiao D, Zhang C (2024). Current therapeutics for Alzheimer's disease and clinical trials. Exploration of Neuroscience, 3:255-271.

[6] Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L (2024). Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. Signal Transduct Target Ther, 9:211.

[7] Toader C, Tataru CP, Munteanu O, Serban M, Covache-Busuioc R-A, Ciurea AV, et al. (2024). Decoding neurodegeneration: a review of molecular mechanisms and therapeutic advances in Alzheimer's, parkinson's, and ALS. Int J Mol Sci, 25:12613.

[8] Ali N, Sayeed U, Shahid SMA, Akhtar S, Khan MKA (2025). Molecular mechanisms and biomarkers in neurodegenerative disorders: a comprehensive review. Mol Biol Rep, 52:1-19.

[9] Zhang H, Wei W, Zhao M, Ma L, Jiang X, Pei H, et al. (2021). Interaction between Aβ and tau in the pathogenesis of Alzheimer's disease. Int J Biol Sci, 17:2181.

[10] Rajmohan R, Reddy PH (2017). Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons. J Alzheimers Dis, 57:975-999.

[11] Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, et al. (2021). Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res Rev, 72:101503.

[12] Misrani A, Tabassum S, Yang L (2021). Mitochondrial dysfunction and oxidative stress in Alzheimer's disease. Front Aging Neurosci, 13:617588.

[13] Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, et al. (2025). Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. Acta Pharm Sin B, 15:15-34.

[14] Sheppard O, Coleman M (2020). Alzheimer's disease: etiology, neuropathology and pathogenesis. Exon Publications:1-21.

[15] Bettcher BM, Tansey MG, Dorothée G, Heneka MT (2021). Peripheral and central immune system crosstalk in Alzheimer disease—a research prospectus. Nat Rev Neurol, 17:689-701.

[16] Cao Y, Tang K, Ma P, Zhang R, Yang Y, Li T, et al. (2025). The Role of Peripheral Innate Immune Cells in Alzheimer's Disease Progression. Front Immunol, 16:1616939.

[17] Zhang Q, Yang G, Luo Y, Jiang L, Chi H, Tian G (2024). Neuroinflammation in Alzheimer's disease: insights from peripheral immune cells. Immun Ageing, 21:38.

[18] Seo D-o, Holtzman DM (2024). Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. Exp Mol Med, 56:86-94.

[19] Qu L, Li Y, Liu F, Fang Y, He J, Ma J, et al. (2024). Microbiota-gut-brain Axis Dysregulation in Alzheimer's disease: Multi-pathway effects and therapeutic potential. Aging Dis, 15:1108.

[20] Xie J, Van Hoecke L, Vandenbroucke RE (2022). The impact of systemic inflammation on Alzheimer's disease pathology. Front Immunol, 12:796867.

[21] Tan S, Chen W, Kong G, Wei L, Xie Y (2023). Peripheral inflammation and neurocognitive impairment: correlations, underlying mechanisms, and therapeutic implications. Front Aging Neurosci, 15:1305790.

[22] Castellani G, Croese T, Peralta Ramos JM, Schwartz M (2023). Transforming the understanding of brain immunity. Science, 380:eabo7649.

[23] Matejuk A, Vandenbark AA, Offner H (2021). Cross-talk of the CNS with immune cells and functions in health and disease. Front Neurol, 12:672455.

[24] Zhang S, Gao Y, Zhao Y, Huang TY, Zheng Q, Wang X (2025). Peripheral and central neuroimmune mechanisms in Alzheimer's disease pathogenesis. Mol Neurodegener, 20:22.

[25] Xu J, Ma C, Hua M, Li J, Xiang Z, Wu J (2022). CNS and CNS diseases in relation to their immune system. Front Immunol, 13:1063928.

[26] Kearns R (2024). Gut–brain axis and neuroinflammation: the role of gut permeability and the kynurenine pathway in neurological disorders. Cell Mol Neurobiol, 44:64.
[27] Omenetti S, Pizarro TT (2015). The Treg/Th17 axis: a dynamic balance regulated by the gut microbiome. Front Immunol, 6:639.
[28] Kanayama M, Shinohara ML (2016). Lung inflammation regulates autoimmunity in the central nervous system. J Neurol Neuromed, 1.
[29] Park H, Lee CH (2024). The impact of pulmonary disorders on neurological health (lung-brain axis). Immune Netw, 24:e20.
[30] Wu B, Liu Y, Li H, Zhu L, Zeng L, Zhang Z, et al. (2025). Liver as a new target organ in Alzheimer's disease: insight from cholesterol metabolism and its role in amyloid-beta clearance. Neural Regen Res, 20:695-714.
[31] Munawara U, Catanzaro M, Xu W, Tan C, Hirokawa K, Bosco N, et al. (2021). Hyperactivation of monocytes and macrophages in MCI patients contributes to the progression of Alzheimer's disease. Immun Ageing, 18:29.
[32] Rousseau M, Lacerda Mariano L, Canton T, Ingersoll MA (2023). Tissue-resident memory T cells mediate mucosal immunity to recurrent urinary tract infection. Sci Immunol, 8:eabn4332.
[33] Wyndaele M, Charrua A, Hervé F, Aronsson P, Grundy L, Khullar V, et al. (2024). Beyond the urothelium: Interplay between autonomic nervous system and bladder inflammation in urinary tract infection, bladder pain syndrome with interstitial cystitis and neurogenic lower urinary tract dysfunction in spinal cord injury—ICI-RS 2023. Neurourol Urodyn, 43:1283-1292.
[34] Kowalski K, Mulak A (2019). Brain-gut-microbiota axis in Alzheimer's disease. J Neurogastroenterol Motil, 25:48.
[35] Jiang C, Li G, Huang P, Liu Z, Zhao B (2017). The gut microbiota and Alzheimer's disease. J Alzheimers Dis, 58:1-15.
[36] Cerf-Bensussan N, Gaboriau-Routhiau V (2010). The immune system and the gut microbiota: friends or foes? Nat Rev Immunol, 10:735-744.
[37] Maranduba CMdC, De Castro SBR, Souza GTd, Rossato C, da Guia FC, Valente MAS, et al. (2015). Intestinal microbiota as modulators of the immune system and neuroimmune system: impact on the host health and homeostasis. J Immunol Res, 2015:931574.
[38] Goyal D, Ali SA, Singh RK (2021). Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry, 106:110112.
[39] Chen P, Tang X (2021). Gut microbiota as regulators of Th17/Treg balance in patients with myasthenia gravis. Front Immunol, 12:803101.
[40] Kim CH, Park J, Kim M (2014). Gut microbiota-derived short-chain fatty acids, T cells, and inflammation. Immune Netw, 14:277.
[41] Yao Y, Cai X, Fei W, Ye Y, Zhao M, Zheng C (2022). The role of short-chain fatty acids in immunity, inflammation and metabolism. Crit Rev Food Sci Nutr, 62:1-12.
[42] Dopkins N, Nagarkatti PS, Nagarkatti M (2018). The role of gut microbiome and associated metabolome in the regulation of neuroinflammation in multiple sclerosis and its implications in attenuating chronic inflammation in other inflammatory and autoimmune disorders. Immunology, 154:178-185.
[43] Haase S, Haghikia A, Wilck N, Müller DN, Linker RA (2018). Impacts of microbiome metabolites on immune regulation and autoimmunity. Immunology, 154:230-238.
[44] Argaw AT, Asp L, Zhang J, Navrazhina K, Pham T, Mariani JN, et al. (2012). Astrocyte-derived VEGF-A drives blood-brain barrier disruption in CNS inflammatory disease. J Clin Invest, 122:2454-2468.
[45] Cervellati C, Trentini A, Pecorelli A, Valacchi G (2020). Inflammation in neurological disorders: the thin boundary between brain and periphery. Antioxid Redox Signal, 33:191-210.
[46] D'Mello C, Le T, Swain MG (2009). Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factorα signaling during peripheral organ inflammation. J Neurosci, 29:2089-2102.
[47] Wang W-Y, Tan M-S, Yu J-T, Tan L (2015). Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med, 3:136.
[48] Ghoshal A, Das S, Ghosh S, Mishra MK, Sharma V, Koli P, et al. (2007). Proinflammatory mediators released by activated microglia induces neuronal death in Japanese encephalitis. Glia, 55:483-496.
[49] Xie L, Choudhury GR, Winters A, Yang SH, Jin K (2015). Cerebral regulatory T cells restrain microglia/macrophage-mediated inflammatory responses via IL-10. Eur J Immunol, 45:180-191.
[50] Guo S, Wang H, Yin Y (2022). Microglia polarization from M1 to M2 in neurodegenerative diseases. Front Aging Neurosci, 14:815347.
[51] Chandra S, Popovic J, Singhal NK, Watkins EA, Dodiya HB, Weigle IQ, et al. (2025). The gut microbiome controls reactive astrocytosis during Aβ amyloidosis via propionate-mediated regulation of IL-17. J Clin Invest, 135.
[52] O'Callaghan JP, Sriram K (2005). Glial fibrillary acidic protein and related glial proteins as biomarkers of neurotoxicity. Expert Opin Drug Saf, 4:433-442.
[53] Portincasa P, Bonfrate L, Vacca M, De Angelis M, Farella I, Lanza E, et al. (2022). Gut microbiota and short chain fatty acids: implications in glucose homeostasis. Int J Mol Sci, 23:1105.
[54] He J, Zhang P, Shen L, Niu L, Tan Y, Chen L, et al. (2020). Short-chain fatty acids and their association with signalling pathways in inflammation, glucose and lipid metabolism. Int J Mol Sci, 21:6356.
[55] Kim MH, Kang SG, Park JH, Yanagisawa M, Kim CH (2013). Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote

inflammatory responses in mice. Gastroenterology, 145:396-406. e310.
[56] Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, et al. (2024). Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct Target Ther, 9:37.
[57] Choi SW, Gatza E, Hou G, Sun Y, Whitfield J, Song Y, et al. (2015). Histone deacetylase inhibition regulates inflammation and enhances Tregs after allogeneic hematopoietic cell transplantation in humans. Blood, 125:815-819.
[58] Cao T, Zhang X, Chen D, Zhang P, Li Q, Muhammad A (2018). The epigenetic modification during the induction of Foxp3 with sodium butyrate. Immunopharmacol Immunotoxicol, 40:309-318.
[59] Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. (2015). Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci, 18:965-977.
[60] Silva YP, Bernardi A, Frozza RL (2020). The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol (Lausanne), 11:508738.
[61] Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. (2013). Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity, 39:372-385.
[62] Neavin DR, Liu D, Ray B, Weinshilboum RM (2018). The role of the aryl hydrocarbon receptor (AHR) in immune and inflammatory diseases. Int J Mol Sci, 19:3851.
[63] Coretti L, Buommino E, Lembo F (2024). The aryl hydrocarbon receptor pathway: a linking bridge between the gut microbiome and neurodegenerative diseases. Front Cell Neurosci, 18:1433747.
[64] Monteleone I, Rizzo A, Sarra M, Sica G, Sileri P, Biancone L, et al. (2011). Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract. Gastroenterology, 141:237-248. e231.
[65] Aparicio-Domingo P, Romera-Hernandez M, Karrich JJ, Cornelissen F, Papazian N, Lindenbergh-Kortleve DJ, et al. (2015). Type 3 innate lymphoid cells maintain intestinal epithelial stem cells after tissue damage. J Exp Med, 212:1783-1791.
[66] Rothhammer V, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, et al. (2016). Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat Med, 22:586-597.
[67] Sun J, Zhang Y, Kong Y, Ye T, Yu Q, Satyanarayanan SK, et al. (2022). Microbiota-derived metabolite Indoles induced aryl hydrocarbon receptor activation and inhibited neuroinflammation in APP/PS1 mice. Brain Behav Immun, 106:76-88.
[68] Xie L, Wu Q, Li K, Khan MA, Zhang A, Sinha B, et al. (2024). Tryptophan metabolism in Alzheimer's disease with the involvement of microglia and astrocyte crosstalk and gut-brain axis. Aging Dis, 15:2168.
[69] Mumaw CL, Levesque S, McGraw C, Robertson S, Lucas S, Stafflinger JE, et al. (2016). Microglial priming through the lung–brain axis: the role of air pollution–induced circulating factors. FASEB J, 30:1880.
[70] Bajinka O, Simbilyabo L, Tan Y, Jabang J, Saleem SA (2022). Lung-brain axis. Crit Rev Microbiol, 48:257-269.
[71] Greve HJ, Dunbar AL, Lombo CG, Ahmed C, Thang M, Messenger EJ, et al. (2023). The bidirectional lung brain-axis of amyloid-β pathology: ozone dysregulates the peri-plaque microenvironment. Brain, 146:991-1005.
[72] Tang Y, Le W (2016). Differential roles of M1 and M2 microglia in neurodegenerative diseases. Mol Neurobiol, 53:1181-1194.
[73] Galea I (2021). The blood–brain barrier in systemic infection and inflammation. Cell Mol Immunol, 18:2489-2501.
[74] Tejera D, Mercan D, Sanchez-Caro JM, Hanan M, Greenberg D, Soreq H, et al. (2019). Systemic inflammation impairs microglial Aβ clearance through NLRP 3 inflammasome. EMBO J, 38:e101064.
[75] Eisenbarth S (2019). Dendritic cell subsets in T cell programming: location dictates function. Nat Rev Immunol, 19:89-103.
[76] Thornton EE, Looney MR, Bose O, Sen D, Sheppard D, Locksley R, et al. (2012). Spatiotemporally separated antigen uptake by alveolar dendritic cells and airway presentation to T cells in the lung. J Exp Med, 209:1183-1199.
[77] Afzali B, Lombardi G, Lechler R, Lord G (2007). The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. Clin Exp Immunol, 148:32-46.
[78] Li C, Chen W, Lin F, Li W, Wang P, Liao G, et al. (2023). Functional two-way crosstalk between brain and lung: the brain–lung axis. Cell Mol Neurobiol, 43:991-1003.
[79] Steinberg BE, Silverman HA, Robbiati S, Gunasekaran MK, Tsaava T, Battinelli E, et al. (2016). Cytokine-specific neurograms in the sensory vagus nerve. Bioelectron Med, 3:7-17.
[80] Ramos-Martínez IE, Rodríguez MC, Cerbon M, Ramos-Martínez JC, Ramos-Martínez EG (2021). Role of the cholinergic anti-inflammatory reflex in central nervous system diseases. Int J Mol Sci, 22:13427.
[81] Li Y, Ding S, Wang Y (2025). Targeting the cholinergic anti-inflammatory pathway: an innovative strategy for treating diseases. Mol Biol Rep, 52:199.
[82] Kawiková I, Špička V, Lai JC, Askenase PW, Wen L, Kejík Z, et al. (2025). Extracellular vesicles as precision therapeutics for psychiatric conditions: targeting interactions among neuronal, glial, and immune networks. Front Immunol, 16:1454306.
[83] Chiarini A, Gui L, Viviani C, Armato U, Dal Prà I (2023). NLRP3 inflammasome's activation in acute and chronic brain diseases—an update on pathogenetic mechanisms and therapeutic perspectives with respect to other inflammasomes. Biomedicines, 11:999.

[84] Yu X, Xiao H, Liu Y, Dong Z, Meng X, Wang F (2025). The Lung-Brain Axis in Chronic Obstructive Pulmonary Disease-Associated Neurocognitive Dysfunction: Mechanistic Insights and Potential Therapeutic Options. Int J Biol Sci, 21:3461.

[85] De Jonge W, Ulloa L (2007). The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. Br J Pharmacol, 151:915-929.

[86] Wu Y-j, Wang L, Ji C-f, Gu S-f, Yin Q, Zuo J (2021). The role of α7nAChR-mediated cholinergic anti-inflammatory pathway in immune cells. Inflammation, 44:821-834.

[87] Marrero MB, Bencherif M, Lippiello PM, Lucas R (2011). Application of alpha7 nicotinic acetylcholine receptor agonists in inflammatory diseases: an overview. Pharm Res, 28:413-416.

[88] Báez-Pagán CA, Delgado-Vélez M, Lasalde-Dominicci JA (2015). Activation of the macrophage α7 nicotinic acetylcholine receptor and control of inflammation. J Neuroimmune Pharmacol, 10:468-476.

[89] D'Andrea MR, Nagele RG (2006). Targeting the alpha 7 nicotinic acetylcholine receptor to reduce amyloid accumulation in Alzheimer's disease pyramidal neurons. Curr Pharm Des, 12:677-684.

[90] Chuaychoo B, Hunter DD, Myers AC, Kollarik M, Undem BJ (2005). Allergen-induced substance P synthesis in large-diameter sensory neurons innervating the lungs. J Allergy Clin Immunol, 116:325-331.

[91] Joachim R, Cifuentes L, Sagach V, Quarcoo D, Hagen E, Arck P, et al. (2006). Stress induces substance P in vagal sensory neurons innervating the mouse airways. Clin Exp Allergy, 36:1001-1010.

[92] Valentin-Hansen L, Park M, Huber T, Grunbeck A, Naganathan S, Schwartz TW, et al. (2014). Mapping substance P binding sites on the neurokinin-1 receptor using genetic incorporation of a photoreactive amino acid. J Biol Chem, 289:18045-18054.

[93] Mashaghi A, Marmalidou A, Tehrani M, Grace PM, Pothoulakis C, Dana R (2016). Neuropeptide substance P and the immune response. Cell Mol Life Sci, 73:4249-4264.

[94] Johnson MB, Young AD, Marriott I (2017). The therapeutic potential of targeting substance P/NK-1R interactions in inflammatory CNS disorders. Front Cell Neurosci, 10:296.

[95] Eapen PM, Rao CM, Nampoothiri M (2019). Crosstalk between neurokinin receptor signaling and neuroinflammation in neurological disorders. Rev Neurosci, 30:233-243.

[96] Burmeister AR, Johnson MB, Chauhan VS, Moerdyk-Schauwecker MJ, Young AD, Cooley ID, et al. (2017). Human microglia and astrocytes constitutively express the neurokinin-1 receptor and functionally respond to substance P. J Neuroinflammation, 14:245.

[97] D'Mello C, Swain MG (2011). Liver-brain inflammation axis. Am J Physiol Gastrointest Liver Physiol, 301:G749-G761.

[98] Huang Z, Lin HW, Zhang Q, Zong X (2022). Targeting Alzheimer's disease: the critical crosstalk between the liver and brain. Nutrients, 14:4298.

[99] Gehrke N, Schattenberg JM (2020). Metabolic inflammation—a role for hepatic inflammatory pathways as drivers of comorbidities in nonalcoholic fatty liver disease? Gastroenterology, 158:1929-1947. e1926.

[100] Butterworth RF (2013). The liver–brain axis in liver failure: neuroinflammation and encephalopathy. Nat Rev Gastroenterol Hepatol, 10:522-528.

[101] Pinçon A, De Montgolfier O, Akkoyunlu N, Daneault C, Pouliot P, Villeneuve L, et al. (2019). Non-alcoholic fatty liver disease, and the underlying altered fatty acid metabolism, reveals brain hypoperfusion and contributes to the cognitive decline in APP/PS1 mice. Metabolites, 9:104.

[102] Weinstein G, O'Donnell A, Davis-Plourde K, Zelber-Sagi S, Ghosh S, DeCarli CS, et al. (2022). Non-alcoholic fatty liver disease, liver fibrosis, and regional amyloid-β and tau pathology in middle-aged adults: the Framingham study. J Alzheimers Dis, 86:1371-1383.

[103] Mondal A, Bose D, Saha P, Sarkar S, Seth R, Kimono D, et al. (2020). Lipocalin 2 induces neuroinflammation and blood-brain barrier dysfunction through liver-brain axis in murine model of nonalcoholic steatohepatitis. J Neuroinflammation, 17:1-15.

[104] Wan J, Benkdane M, Teixeira-Clerc F, Bonnafous S, Louvet A, Lafdil F, et al. (2014). M2 Kupffer cells promote M1 Kupffer cell apoptosis: a protective mechanism against alcoholic and nonalcoholic fatty liver disease. Hepatology, 59:130-142.

[105] Rao Z, Sun J, Pan X, Chen Z, Sun H, Zhang P, et al. (2017). Hyperglycemia aggravates hepatic ischemia and reperfusion injury by inhibiting liver-resident macrophage M2 polarization via C/EBP homologous protein-mediated endoplasmic reticulum stress. Front Immunol, 8:1299.

[106] Tan Q, Hu J, Yu X, Guan W, Lu H, Yu Y, et al. (2016). The role of IL-1 family members and kupffer cells in liver regeneration. Biomed Res Int, 2016:6495793.

[107] Rochfort KD, Cummins PM (2015). The blood–brain barrier endothelium: a target for pro-inflammatory cytokines. Biochem Soc Trans, 43:702-706.

[108] Block ML, Calderón-Garcidueñas L (2009). Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci, 32:506-516.

[109] Ye Y, Xie X, Yu J, Zhou L, Xie H, Jiang G, et al. (2010). Involvement of Th17 and Th1 effector responses in patients with Hepatitis B. J Clin Immunol, 30:546-555.

[110] Heymann F, Trautwein C, Tacke F (2009). Monocytes and macrophages as cellular targets in liver fibrosis. Inflamm Allergy Drug Targets, 8:307-318.

[111] Chavan SS, Pavlov VA, Tracey KJ (2017). Mechanisms and therapeutic relevance of neuro-immune communication. Immunity, 46:927-942.

[112] Wang Y-R, Wang Q-H, Zhang T, Liu Y-H, Yao X-Q, Zeng F, et al. (2017). Associations between hepatic functions and plasma amyloid-beta levels—implications for the capacity of liver in peripheral amyloid-beta clearance. Mol Neurobiol, 54:2338-2344.

[113] Kim D-G, Krenz A, Toussaint LE, Maurer KJ, Robinson S-A, Yan A, et al. (2016). Non-alcoholic fatty liver

disease induces signs of Alzheimer's disease (AD) in wild-type mice and accelerates pathological signs of AD in an AD model. J Neuroinflammation, 13:1.

[114] Wang G, Jin S, Liu J, Li X, Dai P, Wang Y, et al. (2023). A neuron-immune circuit regulates neurodegeneration in the hindbrain and spinal cord of Arf1-ablated mice. Natl Sci Rev, 10:nwad222.

[115] Wang S, Zhang H, Xu Y (2016). Crosstalk between microglia and T cells contributes to brain damage and recovery after ischemic stroke. Neurol Res, 38:495-503.

[116] Davoli-Ferreira M, de Lima KA, Fonseca MM, Guimaraes RM, Gomes FI, Cavallini MC, et al. (2020). Regulatory T cells counteract neuropathic pain through inhibition of the Th1 response at the site of peripheral nerve injury. Pain, 161:1730-1743.

[117] Zhou K, Zhong Q, Wang Y-C, Xiong X-Y, Meng Z-Y, Zhao T, et al. (2017). RETRACTED: Regulatory T cells ameliorate intracerebral hemorrhage-induced inflammatory injury by modulating microglia/macrophage polarization through the IL-10/GSK3β/PTEN axis. J Cereb Blood Flow Metab, 37:967-979.

[118] Rodrigo R, Cauli O, Gomez–Pinedo U, Agusti A, Hernandez–Rabaza V, Garcia–Verdugo JM, et al. (2010). Hyperammonemia induces neuroinflammation that contributes to cognitive impairment in rats with hepatic encephalopathy. Gastroenterology, 139:675-684.

[119] Xu Y, Zhang A, Zhang G, Qian J (2025). FGF21 attenuates traumatic brain injury-induced ferroptosis via activation of the Nrf2/GPX4 pathway. Neurol Res:1-11.

[120] Chen Z, Yang L, Liu Y, Huang P, Song H, Zheng P (2022). The potential function and clinical application of FGF21 in metabolic diseases. Front Pharmacol, 13:1089214.

[121] Fan H, Tang H-B, Chen Z, Wang H-Q, Zhang L, Jiang Y, et al. (2020). Inhibiting HMGB1-RAGE axis prevents pro-inflammatory macrophages/microglia polarization and affords neuroprotection after spinal cord injury. Journal of neuroinflammation, 17:295.

[122] Scaffidi P, Misteli T, Bianchi ME (2002). Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature, 418:191-195.

[123] Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ (2009). HMGB1 and RAGE in inflammation and cancer. Annu Rev Immunol, 28:367-388.

[124] Kokkola R, Andersson Å, Mullins G, Östberg T, Treutiger CJ, Arnold B, et al. (2005). RAGE is the major receptor for the proinflammatory activity of HMGB1 in rodent macrophages. Scand J Immunol, 61:1-9.

[125] Fan H, Tang H-B, Chen Z, Wang H-Q, Zhang L, Jiang Y, et al. (2020). Inhibiting HMGB1-RAGE axis prevents pro-inflammatory macrophages/microglia polarization and affords neuroprotection after spinal cord injury. J Neuroinflammation, 17:295.

[126] Paudel YN, Angelopoulou E, Piperi C, Othman I, Aamir K, Shaikh MF (2020). Impact of HMGB1, RAGE, and TLR4 in Alzheimer's disease (AD): from risk factors to therapeutic targeting. Cells, 9:383.

[127] Huebener P, Pradere J-P, Hernandez C, Gwak G-Y, Caviglia JM, Mu X, et al. (2019). The HMGB1/RAGE axis triggers neutrophil-mediated injury amplification following necrosis. J Clin Invest, 125:539-550.

[128] Han Y, Chen R, Lin Q, Liu Y, Ge W, Cao H, et al. (2021). Curcumin improves memory deficits by inhibiting HMGB1-RAGE/TLR4-NF-κB signalling pathway in APPswe/PS1dE9 transgenic mice hippocampus. J Cell Mol Med, 25:8947-8956.

[129] Peelaerts W, Mercado G, George S, Villumsen M, Kasen A, Aguileta M, et al. (2023). Urinary tract infections trigger synucleinopathy via the innate immune response. Acta Neuropathol, 145:541-559.

[130] Lacerda Mariano L, Ingersoll MA (2020). The immune response to infection in the bladder. Nat Rev Urol, 17:439-458.

[131] Mora-Bau G, Platt AM, van Rooijen N, Randolph GJ, Albert ML, Ingersoll MA (2015). Macrophages subvert adaptive immunity to urinary tract infection. PLoS Pathog, 11:e1005044.

[132] Güven G, Köseoğlu P, Lohmann E, Samancı B, Şahin E, Bilgiç B, et al. (2024). Peripheral Expression of IL-6, TNF-α and TGF-β1 in Alzheimer's Disease Patients. Turk J Immunol, 12.

[133] Wróbel J, Iwaniak P, Dobrowolski P, Chwil M, Sadok I, Kluz T, et al. (2024). The GPR39 Receptor Plays an Important Role in the Pathogenesis of Overactive Bladder and Corticosterone-Induced Depression. Int J Mol Sci, 25:12630.

[134] Dansokho C, Ait Ahmed D, Aid S, Toly-Ndour C, Chaigneau T, Calle V, et al. (2016). Regulatory T cells delay disease progression in Alzheimer-like pathology. Brain, 139:1237-1251.

[135] Ciccocioppo F, Lanuti P, Pierdomenico L, Simeone P, Bologna G, Ercolino E, et al. (2019). The characterization of regulatory T-cell profiles in Alzheimer's disease and multiple sclerosis. Sci Rep, 9:8788.

[136] Huang X, Hussain B, Chang J (2021). Peripheral inflammation and blood–brain barrier disruption: effects and mechanisms. CNS Neurosci Ther, 27:36-47.

[137] Yang Qq, Zhou Jw (2019). Neuroinflammation in the central nervous system: Symphony of glial cells. Glia, 67:1017-1035.

[138] Cheng C, Li Q, Lin G, Opara EC, Zhang Y (2023). Neurobiological insights into lower urinary tract dysfunction: evaluating the role of brain-derived neurotrophic factor. Am J Clin Exp Urol, 11:559.

[139] Konsman JP, Parnet P, Dantzer R (2002). Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci, 25:154-159.

[140] Griton M, Konsman JP (2018). Neural pathways involved in infection-induced inflammation: recent insights and clinical implications. Clin Auton Res, 28:289-299.

[141] Leue C, Kruimel J, Vrijens D, Masclee A, Van Os J, Van Koeveringe G (2017). Functional urological disorders: a sensitized defence response in the bladder–gut–brain axis. Nat Rev Urol, 14:153-163.

[142] Vlaskovska M, Kasakov L, Rong W, Bodin P, Bardini M, Cockayne DA, et al. (2001). P2X3 knock-out mice

reveal a major sensory role for urothelially released ATP. J Neurosci, 21:5670-5677.

[143] Birder L, Ruan H, Chopra B, Xiang Z, Barrick S, Buffington C, et al. (2004). Alterations in P2X and P2Y purinergic receptor expression in urinary bladder from normal cats and cats with interstitial cystitis. Am J Physiol Renal Physiol, 287:F1084-F1091.

[144] Burnstock G (2014). Purinergic signalling in the urinary tract in health and disease. Purinergic Signal, 10:103-155.

[145] Schiavuzzo J, Teixeira J, Melo B, Dos Santos DdS, Jorge C, Oliveira-Fusaro M, et al. (2015). Muscle hyperalgesia induced by peripheral P2X3 receptors is modulated by inflammatory mediators. Neuroscience, 285:24-33.

[146] Prado F, Araldi D, Vieira A, Oliveira-Fusaro M, Tambeli C, Parada C (2013). Neuronal P2X3 receptor activation is essential to the hyperalgesia induced by prostaglandins and sympathomimetic amines released during inflammation. Neuropharmacology, 67:252-258.

[147] Fabbretti E, Nistri A (2012). Regulation of P2X3 receptor structure and function. CNS Neurol Disord Drug Targets, 11:687-698.

[148] Lopez-Lee C, Torres ERS, Carling G, Gan L (2024). Mechanisms of sex differences in Alzheimer's disease. Neuron, 112:1208-1221.

[149] Price BR, Walker KA, Eissman JM, Suryadevara V, Sime LN, Hohman TJ, et al. (2025). Sex differences and the role of estrogens in the immunological underpinnings of Alzheimer's disease. Alzheimers Dement (N Y), 11:e70139.

[150] Bhargava A, Arnold AP, Bangasser DA, Denton KM, Gupta A, Hilliard Krause LM, et al. (2021). Considering sex as a biological variable in basic and clinical studies: an endocrine society scientific statement. Endocr Rev, 42:219-258.

[151] Caldarelli M, Rio P, Marrone A, Ocarino F, Chiantore M, Candelli M, et al. (2024). Gut–Brain Axis: Focus on Sex Differences in Neuroinflammation. Int J Mol Sci, 25:5377.

[152] Saha P, Sisodia SS (2024). Role of the gut microbiome in mediating sex-specific differences in the pathophysiology of Alzheimer's disease. Neurotherapeutics, 21:e00426.

[153] Zang X, Chen S, Zhu J, Ma J, Zhai Y (2022). The emerging role of central and peripheral immune systems in neurodegenerative diseases. Front Aging Neurosci, 14:872134.

[154] Yin J, Peng W, Lu L, Hong Z, Zhou D, Li J (2025). Mechanistic Insights and Emerging Therapeutic Targets of Alzheimer's Disease: From the Perspective of Inter-Organ Crosstalk. Aging Dis, 16(6):3466–3482.