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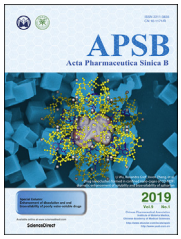

REVIEW

Targeting the blood–brain barrier to delay aging-accompanied neurological diseases by modulating gut microbiota, circadian rhythms, and their interplays

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KEY WORDS

Blood–brain barrier;
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Abstract The blood–brain barrier (BBB) impairment plays a crucial role in the pathological processes of aging-accompanied neurological diseases (AAND). Meanwhile, circadian rhythms disruption and gut microbiota dysbiosis are associated with increased morbidity of neurological diseases in the accelerated aging population. Importantly, circadian rhythms disruption and gut microbiota dysbiosis are also known to induce the generation of toxic metabolites and pro-inflammatory cytokines, resulting in disruption of BBB integrity. Collectively, this provides a new perspective for exploring the relationship among circadian rhythms, gut microbes, and the BBB in aging-accompanied neurological diseases. In this review, we focus on recent advances in the interplay between circadian rhythm disturbances and gut microbiota dysbiosis, and their potential roles in the BBB disruption that occurs in AAND. Based on existing literature, we discuss and propose potential mechanisms underlying BBB damage induced by dysregulated

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circadian rhythms and gut microbiota, which would serve as the basis for developing potential interventions to protect the BBB in the aging population through targeting the BBB by exploiting its links with gut microbiota and circadian rhythms for treating AAND.

1. Introduction

Aging is an uncontrolled biological process that poses challenges to human health and becomes a social problem that can't be ignored[1−3]. Aging is regarded as a common risk factor for various human diseases[4] and by reducing sensory, motor, circadian rhythms, and cognitive functions, aging affects the brain morphologically and functionally, resulting in neurological diseases[5]. Importantly, circadian rhythms disruption, characterized by phase shifts and reduced expression of many genes and proteins involved in circadian rhythms greatly impacts aging and longevity in many ways[6,7]. Disturbances in the circadian rhythms induce disorders of cognitive function, metabolism, mental function, motor control, alertness, blood−brain barrier (BBB) damage, and sleep/wake cycles[8]. A prospective cohort study of 72,242 participants further supported that disturbances of circadian rhythm are a risk factor for the development of common neurodegenerative and psychiatric disorders[9]. Interestingly, the amount and function of different microbial species fluctuate over time during aging, leading to gut microbiota dysbiosis[10]. The gut microbiota continuously exchanges nutrients, genetic material, and metabolites with the host throughout its life cycle which regulates the homeostasis in the host, including brain function and blood−brain barrier (BBB) integrity[11]. In individuals with neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), stroke, and multiple sclerosis (MS), circadian rhythm disturbances and gut microbiota dysbiosis are common symptoms[12−14]. Accumulating data suggest that either circadian rhythms or gut dysbiosis contribute to aging-accompanied neurological diseases (AAND)[15]. Notably, the disruption of the circadian system can alter microbiome communities and perturb host metabolism, energy homeostasis, and inflammatory pathways, and gut microbiota can regulate host circadian rhythms and metabolism as a transducer of dietary cues[16]. Genetic defects of a biological clock, timing or restriction of food availability, and light/dark phase changes can significantly affect microbial oscillations, leading to a reduction in microbial abundance and species[17]. In addition, gut microbiota-derived metabolites, including short-chain fatty acids (SCFAs) and bile acids (BA), can alter circadian rhythms[18], indicating that circadian rhythms and gut microbiota can affect each other, and their interplays can induce subsequent effects.

The BBB provides nutrients to the central nervous system (CNS), maintains homeostasis, and regulates its communication with the periphery, forming a protective barrier for the CNS[19]. The changes and destruction of the structure and functional components of the BBB could occur naturally with the aging process[20]. Aging itself may worsen the disruption of different components of the BBB, thus accelerating the progression of brain damage and an ever-increasing global aging population has stimulated the exploration of the relationship between AAND and BBB, to prevent or delay the prevalence of AAND.

Therefore, there is an urgent need to further investigate the role of the BBB in AAND and the underlying mechanisms of BBB damage induced by aging-accompanied circadian rhythms disruption and dysbiosis of gut microbiota which play important roles in regulating BBB integrity[21,22]. Further elucidation of the interplay of gut microbiota with circadian rhythms could also shed light on the systemic regulatory mechanisms of aging and the BBB. Here, in this review, we first describe how BBB, circadian rhythms, and gut microbiota are altered during the aging process and how these alterations are exacerbated in AAND. We then discuss the effect of the interplay between circadian rhythms disruption and dysbiosis of gut microbiota on BBB integrity. We then discuss and propose potential mechanisms underlying BBB damage induced by dysregulated circadian rhythms and gut microbiota, which could serve as the basis for developing potential interventions to protect the BBB in the aging population through targeting the BBB by exploiting its links with gut microbiota and circadian rhythms for treating AAND.

2. Aging, neurological diseases, and BBB damage

2.1. *Effect of aging on BBB and the underlying mechanisms*

BBB consists of brain microvascular endothelial cells, astrocytes endfeet, pericytes, basement membrane, and the extracellular matrix, and BBB is a highly specialized barrier[19] (Fig. 1A). Aging impairs the structure and function of BBB and aging-related physiological and pathological changes of BBB have been reviewed[20] (Fig. 1B). The decrease of channel ions and surface vector expression in endothelial cells, the increase in vasoactive mediators, and the activation of astrocytes and monocytes/macrophages are the main factors for BBB hyperpermeability[23]. Meanwhile, oxygen and nitrogen free radicals, matrix metalloproteinase (MMP) and cyclooxygenase attack the cell membrane, degrade tight junction proteins (TJPs) between endothelial cells, and destroy the BBB integrity[24−26]. For instance, the effect of reactive oxygen species on BBB function has been documented in superoxide dismutase (SOD)-deficient mice, where ischemia/reperfusion induces increased endothelial permeability to macromolecules[27].

In addition, aging has been reported to be accompanied by the decreased number of vesicles for receptor-mediated endocytosis, as well as the increased number of nests for non-specific protein leakage[28]. Furthermore, a study from aged individuals and rodents showed that the expression or function of the glucose transporter-1 and P-glycoprotein (P-gp), a special protein in cerebral blood vessels, changes with age[29], and the extent of tracer leakage in the BBB depends on the aging process[30].

Aging affected post-stroke BBB recovery by profound alterations in methylation (hypermethylation and repression) in the expression of structural protein (*e.g.*, claudin-5) and genes activat-

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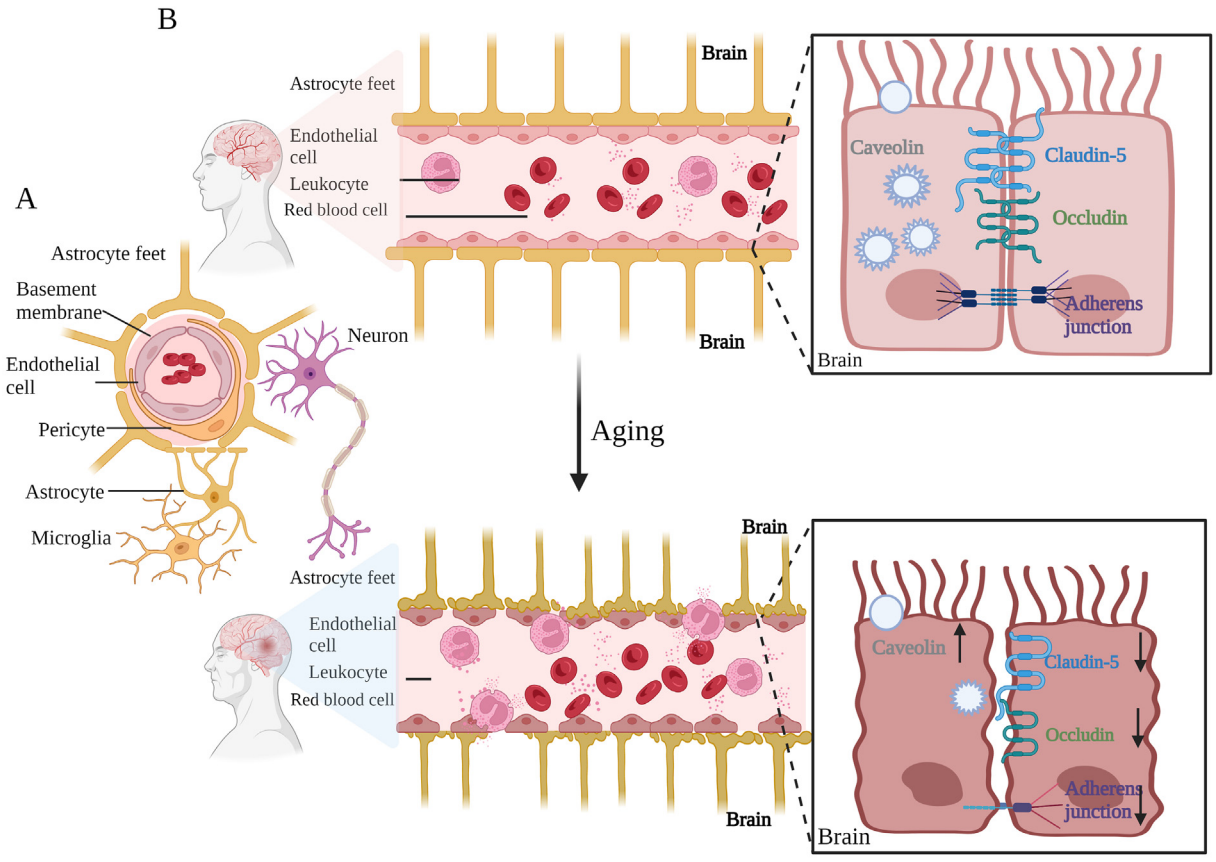

Figure 1 The aging process causes structural and functional impairments of BBB. (A) Components of the blood−brain barrier (BBB). (B) Cross-sectional structure of the healthy BBB with tight junction protein (TJPs) and adherence junction proteins (AJPs) in endothelial cells in adults; disruption of the BBB structure in the elderly, loss of TJPs and AJPs, and overactivation of transcellular pathways.

ion (*e.g.*, *Sox9*, *Snai1*) that is involved in endothelial to mesenchymal transformation, angiogenesis repression and epigenetic regulation, indicating that DNA methylation is critically involved in BBB repair after stroke[31].

2.2. *BBB impairment is a cause of aging-accompanied neurological diseases*

The role of BBB injury in the occurrence and development of aging-related neurological diseases has been a special research focus for a few years[32,33] and we have summarized it in Table 1. Magnetic resonance imaging -based findings indicate that the integrity damage of BBB appears in the hippocampus at the early stage of AD, and this causes synaptic and neuronal alternations and cognitive dysfunction, finally leading to more apparent AD manifestations[34]. ApoE4 catabolizes BBB integrity by activating MMP-9 in pericytes and endothelial cells, resulting in cognitive decline in AD patients[35]. Notably, BBB damage and vascular hyperpermeability are signs of AD, so targeting BBB could be a promising treatment strategy for AD therapy[36].

BBB disruption also is implicated in the pathogenesis of PD[37]. Reduced expression of TJPs, increased vascular permeability, and increased accumulation of oligo-α-syn in activated astrocytes were found in the brain of PD mouse model[38]. In addition, astrocytic vascular endothelial growth factor is an essential mediator in BBB disruption in PD[39]. Of note, BBB dysfunction and decrease of P-gp, have been reported to be detected in PD patients[40]. Therefore, it is assumed that the destruction of BBB occurs ahead of dopaminergic neuron loss in the substantia nigra and contributes to the progress of PD, suggesting that protecting the integrity of BBB is a potential treatment strategy for PD[41].

Age is the most important and nonmodifiable risk factor for all types of strokes. Stroke-induced BBB damage can be caused by inflammation-urged destruction including MMP increase, oxidative stress burst, microglial cell activation, and peripheral immune cell infiltration[42]. Aging-accompanied BBB vulnerability enhances the risk and worsens the outcome of ischemic stroke[43].

MS is a chronic demyelinating neuroinflammatory disease that affects the brain and spinal cord. CNS vasculature in MS patients has shown downregulated expression of TJPs within the lesions compared to the vascular system in normal white matter[44]. In addition, the loss of TJPs and activation of proteolytic enzymes that occur in response to inflammation can promote degradation of the extracellular matrix and destruction of the BBB[45].

Circadian rhythms disturbances and gut microbial dysbiosis are not major pathogenesis in diseases caused by mutations in autosomal dominant genes such as Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS)[46]. HD etiology is entirely due to neurodegeneration caused by autosomal dominant HTT mutations, and BBB dysfunction is in HD[47]. ALS is a genetic variant of spinal cord motor neuron damage that occurs as a result of muscle weakness, atrophy, and spasticity[48,49]. Autopsy studies revealed impaired BBB structure in ALS patients[50], and imaging studies showed early changes in BBB function[51]. These observations raise

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Table 1 Summary of aging-induced BBB damage in AD, PD, stroke and the underlying mechanisms.

Ref.	Neurological diseases	Species	BBB changes	Possible mechanisms
Barisano et al., 2022[34]	Alzheimer's disease	Human	Loss of tight junction (TJ) or adherence junction (AJ) and increased transendothelial translocation	Associated with the loss of pericyte coverage
Zhang et al., 2020[38]	Alzheimer's disease	Human	Increase of BBB permeability	APOE4 can catabolize BBB integrity by activating the MMP9 pathway in pericytes and endothelial cells
Lan et al., 2022[39]	Parkinson's disease	Mouse	Reduce of tight junction proteins	Elevated levels of VEGFA and iNOS
Ruan et al., 2022[38]	Parkinson's disease	Mouse	Loss of endothelial integrity of the brain	Microglia-mediated activation of matrix metalloproteinase-2 and 9
Kortekaas et al., 2005[40]	Parkinson's disease	Human	Decrease of P-gp function	PD patients carry the 1T allele of the MDR3435 gene
Rite et al., 2007[41]	Parkinson's disease	Mouse	Increase of BBB permeability	Inflammatory response and activation of astroglia
Candelario-Jalil et al., 2022[42]	Ischemic stroke	Mouse	Endothelial dysfunction	Increased MMP, oxidative stress burst, microglia activation and peripheral immune cell infiltration
Phillips et al., 2023[31]	Ischemic stroke	Mouse	Persistent BBB dysfunction with increased permeability of the paracellular barrier	DNA methylation
Alvarez et al., 2011[45]	Multiple sclerosis	Human and mouse	Reduced expression of TJ and AJ proteins	Immune cell infiltration and upregulation of pro-inflammatory cytokines

the possibility that the importance of BBB disruption may be overlooked in the diagnosis and treatment of AAND.

Aging and neurodegeneration-associated BBB hyper-permeability has been reviewed by Knox[52] and BBB damage is a cause instead of a result of AAND[44]. Therefore, treatments that could enhance BBB integrity would contribute critically to delaying AAND.

3. Aging, neurological diseases, and circadian rhythms dysfunction

3.1. *Effect of aging on circadian rhythms*

Circadian rhythms are controlled by a set of clock genes, re-pressors including period circadian regulator (*Per1*, *Per2*, and *Per3*) and cryptochromes (*Cry1* and *Cry2*), activators including *Clock* and brain and muscle ARNT-like protein-1 (*Bmal1*)[53]. Circadian rhythm disorders play an important role in many age-related health consequences. An investigation of the prospective association of circadian rhythm disorders and frailty in more than 1000 elderly showed that disturbed circadian rhythms may be an early sign or risk factor for frailty in the elderly[54].

Sleep time, duration, and quality change with the increase of age, the normal circadian rhythms and sleep cycle are disrupted and older adults have less overall sleep and sleep also tends to be more fragmented[55]. Deterioration of circadian input pathways, the suprachiasmatic nucleus (SCN), and output pathways throughout the aging process reduce the robustness of the systemic circadian clockwork system[56]. Decreased neuronal numbers and reduced electrical activity were found in the SCN in the monkey model of normal aging[57]. Aging-related changes in the neuron of SCN lead to a decline in SCN function and disruption in the amplitude and cycle length of circadian behavior, with reduced expression of arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) expression, resulting in a disturbance of the circadian rhythm[58]. Circadian clock gene expression is also one of the changes in aging-related circadian rhythm disruption[59]. Rhythmic expression of the *Bmal1*, *Clock* and *Per2* genes have been shown to decrease or be disrupted with age increasing[60]. Interestingly, the regulation of *Bmal1*, *Clock*, and expression is influenced by the redox status of the orphan nuclear receptor REV-ERB-alpha, which activity is decreased by oxidative stress[61]. In addition to the typical core circadian genes, a large number of clock-controlled genes in the human prefrontal cortex exhibit rhythmic variation[62]. One of the most common damaging effects caused by aging SCN is a significant decrease in pineal melatonin secretion and altered circadian rhythms of melatonin have a negative physiological as well as pathological impact on the elderly[63]. In a word, circadian clock disorder speeds up the aging progress and circadian system damage can lead to harmful health outcomes, especially for the elderly population[64] (Fig. 2).

3.2. *Association between circadian rhythms disruption and aging-accompanied neurological diseases*

Dysfunction of the sleep/wake cycle and alertness are general symptoms of neurodegenerative disease, and disruption of circadian rhythms might deteriorate the disease progress[65]. Disturbed sleep/wake cycle is a common and debilitating symptom of AD[66]. For example, significant loss of AVP and VIP-expressing neurons in the SCN has been demonstrated in AD, and SCN dysfunction and degeneration are at the root of circadian rhythms disturbances

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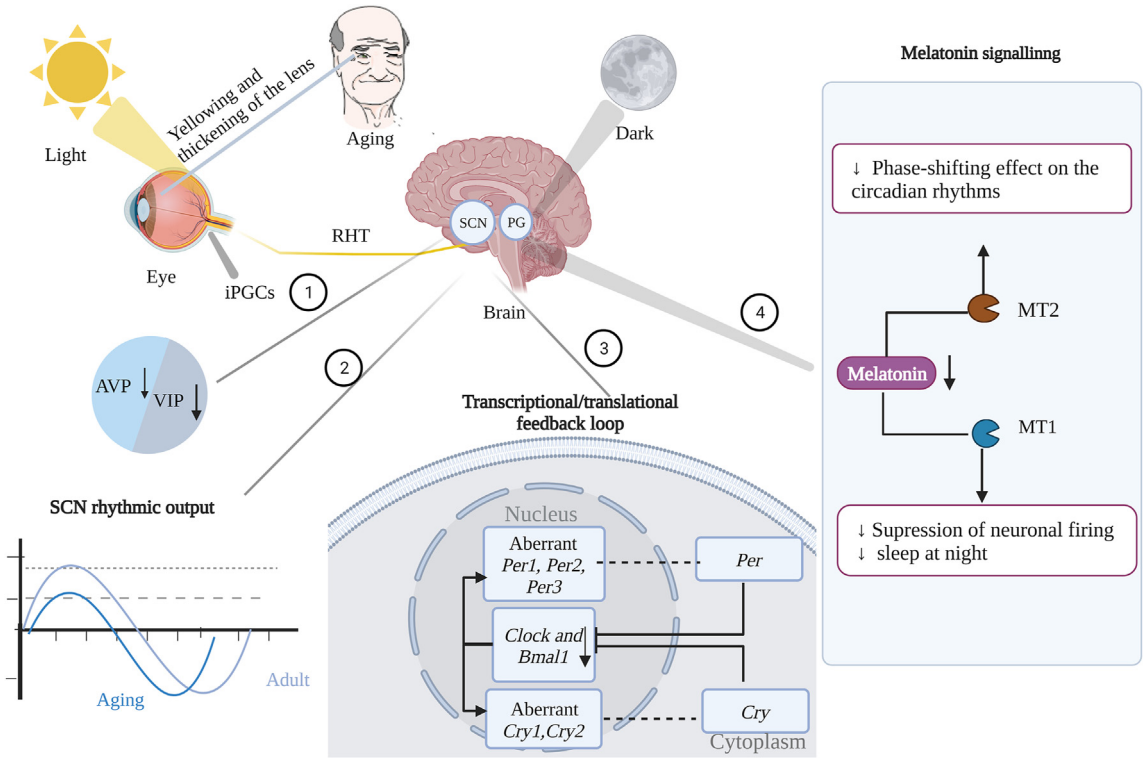

Figure 2 Disruption of circadian rhythms in aging. Light is received by melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) that send signals to the suprachiasmatic nucleus (SCN) *via* the retinal hypothalamic tract (RHT). Gradual yellowing and thickening of lenses due to aging may reduce sensitivity to light, with a concomitant reduction of arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) expression ①, the amplitude of SCN rhythmic output is attenuated in aging (blue line) relative to the young (grey line) ②, aberrant circadian clock genes ③, and a decline secretion of melatonin from the pineal gland (PG) ④.

in AD[67]. Expression of BMAL1 and CLOCK decreased significantly in senescent cells as well as in aged rodent brain tissue[68]. In addition, increased neuronal activity and accumulation of pathogenic proteins in the brain are caused by disturbances in circadian rhythms and sleep. This pathological protein deposition, in turn, leads to neuronal death and promotes neurodegeneration[69]. Inflammation and oxidative stress, which are regulated by sleep and circadian rhythms, further promote neurodegeneration[70]. These results suggest that circadian rhythms disruption may play an important role in AD development.

It is estimated that 80%−90% of PD patients suffer from sleep disturbances[71]. Sleep/wake cycle disruption, circadian rhythms disorder of temperature and heart rate, uncontrolled regulation of clock genes, and diminished neuronal activity in the SCN have been identified in PD patients[69]. Of note, decreased intrinsical photosensitive retinal ganglion cells (ipRGCs) density and complexity of the plexus in PD patients resulted in decreased circadian rhythms and dislocation[72]. In addition, there is also evidence showing that melatonin release patterns are disrupted and that weak light entrainment signals can exacerbate the effect[73]. It has been reported that the circadian rhythm regulation of melatonin secretion in PD patients is decreased[74] and the expression of BMAL1 was significantly lower at night in PD patients, accompanied byrenbha exercise severity and sleep quality[75]. In addition, taking melatonin along with bright light exposure could help improve the quality of sleep in PD patients[73]. Therefore, early detection of sleep disorders and improvement in sleep quality may help delay disease progression and provide long-term clinical benefits[76].

Studies have shown that part of stroke survivors suffer from sleep/wake cycle disorders[77]. Sleep/wake cycle disorders are not only a risk factor for the prevalence of stroke, but also worsen the detrimental effects of stroke, thus hindering the rehabilitation of stroke patients, influencing the outcome of stroke, and increasing the recurrence rate[78].

Circadian rhythms play a key role in innate and adaptive immunity, and circadian rhythms disorders are increasingly recognized as a factor in autoimmune diseases[79]. A study of experimental autoimmune encephalomyelitis (an animal model of MS) suggests that BMAL1 is associated with the accumulation and activation of immune cells and that genetic variability in the Clock gene may be associated with MS risk[79]. Since circadian rhythms play a critical role in health, and chronic disruptions to the clock are accompanied by adverse health consequences[59], active interventions for circadian rhythm deregulation in neurological diseases are required although the importance of circadian rhythms is often overlooked in aging populations.

4. Aging, neurological diseases, and gut microbiota dysbiosis

4.1. Aging-accompanied gut microbiota dysbiosis

The gut microbiota establishes reciprocal relationships with the host and consists of diverse and dynamic microbiota, including bacteria, archaea, viruses, fungi, and protozoa[80]. Highly diverse and stable microbiota play an important role in maintaining overall human health[81]. For example, gut microbiota is crucial for

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regulating aspects of innate and adaptive immune responses, as well as anti-aging, and maintaining the body's dynamic balance[82,83]. In addition, gut microbial metabolites SCFAs, serotonin (5-HT), dopamine and 5-amino valeric acid can regulate neurotransmission and promote the maturation of CNS cells[84]. The microbiota−gut−brain axis mediates bidirectional communication between the gut microbiota and the CNS and is essential for maintaining gastrointestinal and CNS homeostasis as well as microbial homeostasis in humans and animals[85].

Of note, significant changes in the bacterial flora of the fecal microbiome were reported in the elderly compared to infants and young adults[86]. For example, the species diversity of *Bacteroides* increased slightly, while the number of *Bifidobacteria* which are used as probiotics decreased. *Prevotaceae* is commonly found in the stomach of people who maintain a low animal fat and high carbohydrate diet and is lost in centenarians[87]. Notably, the abundance of total bacteria and *Bacillus simulans* in mice feces showed diet-dependent diurnal fluctuations[88] and the number and proportion of *Bifidobacterium* and *Clostridium difficile* in intestinal flora decreased with age[89] (Fig. 3). It has been reported that aging promotes detrimental effects on the gut microbiome, metabolism, neurovascular integrity, cognition, and mental health[90]. In addition, aging-related variations in gut microbiota reveal the disruption of the gut barrier, invasion of microbes into blood, and production of pro-inflammatory cytokines[91]. Changes in the gut microbiota are associated with morbidity and mortality in the elderly population[92] (Fig. 3).

4.2. *Roles of gut microbiota dysbiosis in aging-accompanied neurological diseases*

An imbalance in the gut microbiota is associated with the development and progression of neurological disorders[10,93]. For example, bacterial infection triggered by gut microbial dysbiosis promotes the onset of chronic inflammatory responses in the CNS of vulnerable groups to induce synaptic degeneration and amyloidosis, driving AD development[94]. In a *Drosophila* AD model, *enterobacteria* infection worsens the progress of AD by stimulating immune hemocyte recruitment to the brain, thereby provoking neurodegeneration[95]. In addition, there is a positive association between the increased abundance of *Enterobacteriaceae* and the severity of certain PD symptoms in the majority of PD patients with gastrointestinal problems[96] and PD patients exhibit different gut microbiota-related metabolic profiles relative to healthy individuals, including the level of β-glucuronic acid tryptophan as well as SCFAs concentrations[97]. Gut microbiota is also involved in ischemic stroke[98]. For example, analysis of the cecum flora of mice after ischemic stroke revealed an increase in the relative abundance of *Peptococcus* and a decrease in the proportion of *Prevotella.* When effector T cells are transported from the gut to the brain, they localize to the pia mater and enhance ischemic neuroinflammation by secreting interleukin-17[99]. Additionally, antibiotic-induced gut dysbiosis reduces infarct volume in a mouse model of stroke, an effect that is dependent on gut bacteria[98,99]. Gut microbiota dysbiosis is characterized by less

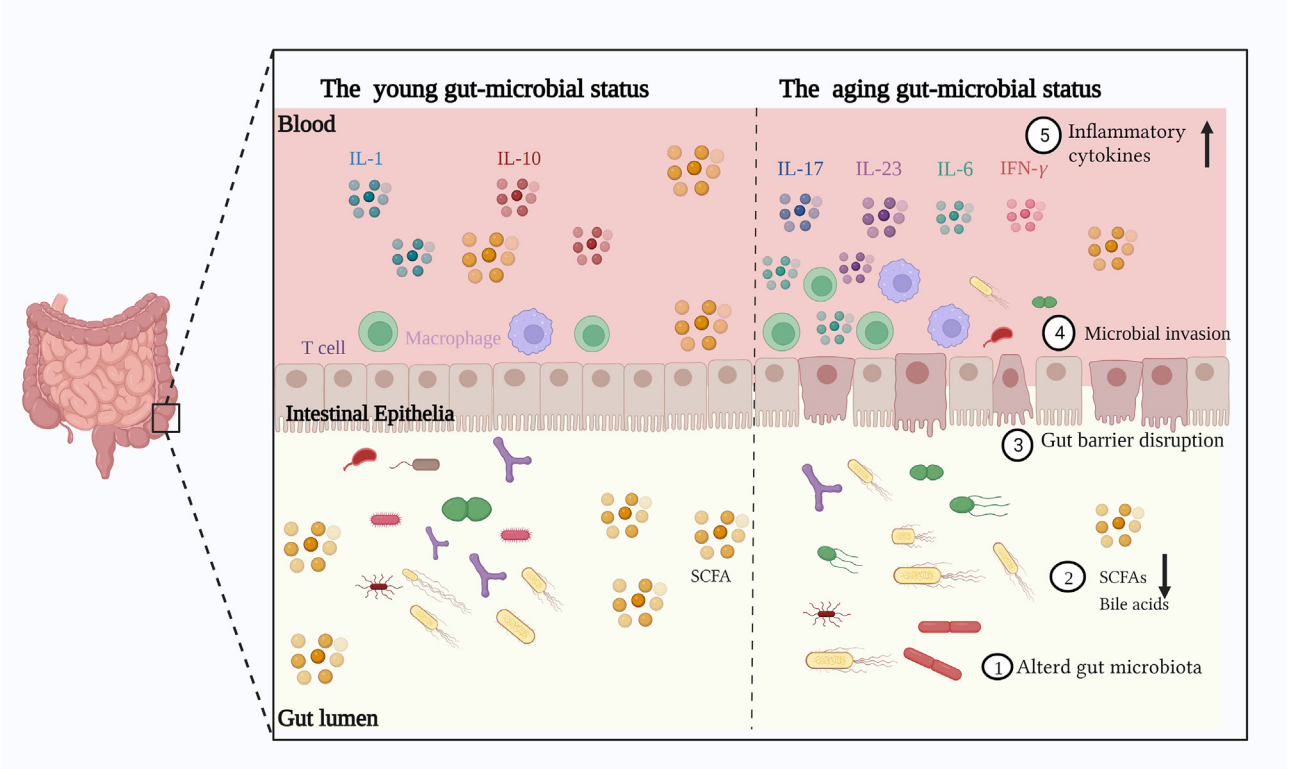

Figure 3 Schematic showing changes in gut microbiota during aging. The increase in harmful microbiota in the gut of older adults results in an imbalance of microbiota homeostasis ①, a decrease in short-chain fatty acids (SCFAs) ②, and disruption of the gut barrier ③ compared to younger adults. In the blood of the elderly, gut microbiota invasive, ④ pro-inflammatory factors interleukin-6 (IL-6), IL-17, IL-23, and interferon-γ (IFN-γ) increased, anti-inflammatory factor IL-10 decreased ⑤.

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microbial diversity (fewer bacterial phyla) and upregulation of pro-inflammatory species *(actinomycetes*, *bifidobacterial*, and *streptococci*) in the gut of MS patients, and disordered microbial diversity resulted in significant downregulation of beneficial SCFA, suggesting that gut microbial population and its metabolites changes are associated with the onset and progression of MS[100].

Direct signal transduction of SCFAs is decreased with age, and the ability to regulate neuroplasticity, epigenetics, and gene expression is lost[101]; however, nutritional intervention with prebiotics, synbiotics, or their metabolites such as SCFAs may help restore aging-related decreased composition and function of gut microbes, enhance gut barrier integrity and reduce chronic inflammation[102]. In addition, sodium butyrate has been shown to alleviate the degeneration of dopaminergic neurons and ameliorate locomotor impairment in PD model[103], prevent 1-methyl-4-phenylpyridinium (MPP^+)-induced neurotoxicity[104], and induce microglial apoptosis accompanied by a robust decrease in LPS-induced pro-inflammatory responses, implicating sodium butyrate in the direct neuroprotection of dopaminergic neurons[105].

5. Circadian rhythms dysfunction, BBB disruption, and aging effect

5.1. Roles of circadian rhythms in BBB integrity

The circadian clock affects the permeability of the BBB and endocytosis across the BBB is upregulated during sleep[106]. Permeability at the BBB is dynamically regulated by circadian rhythms and sleep. An endogenous circadian rhythm in the BBB controls transporter function, regulating permeability across the BBB[107]. Permeability of the drosophila BBB to xenobiotics is higher at night and the permeability rhythm is driven by the circadian regulation of efflux and depends on a molecular clock in the perineurial glia of the BBB[108]. In circadian clock mutants, the

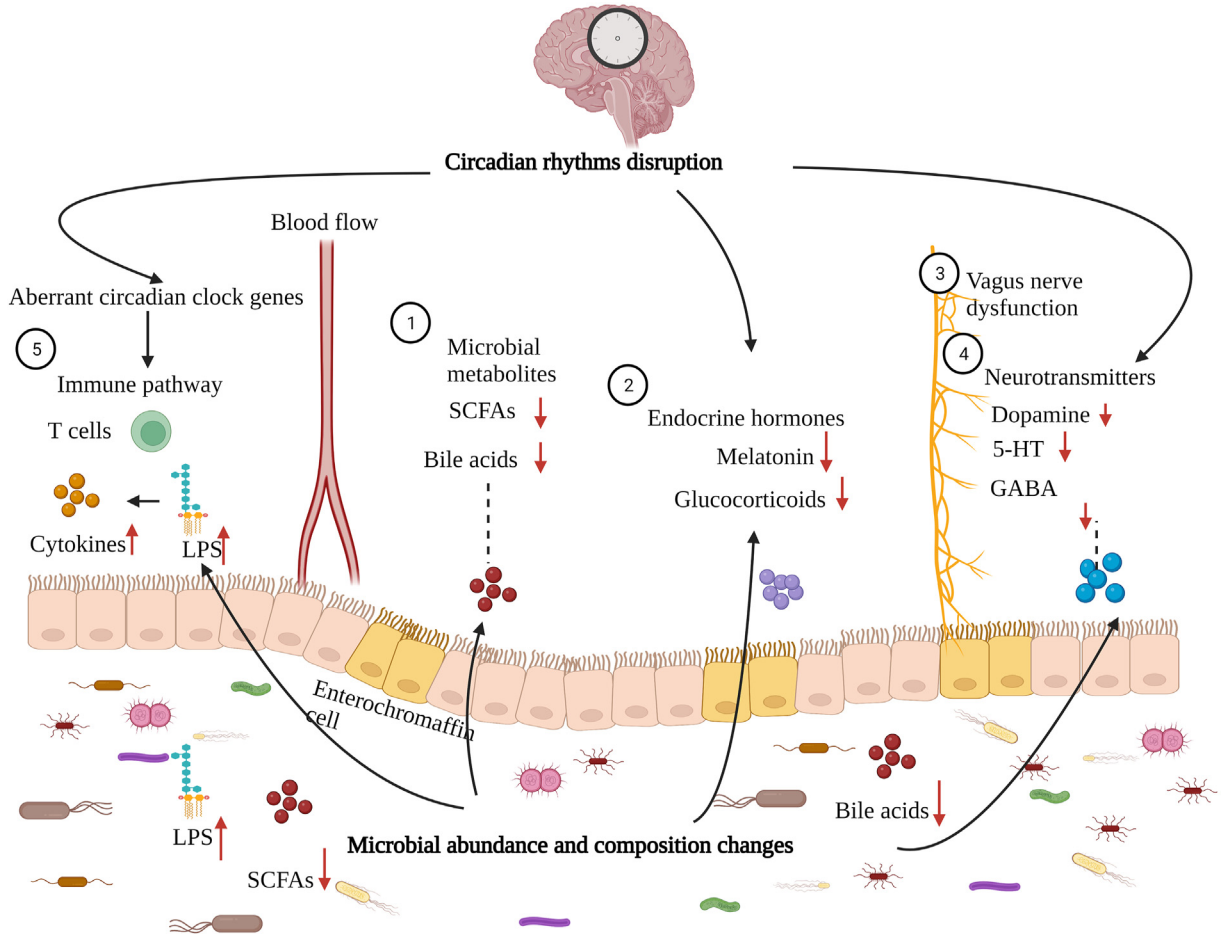

Figure 4 Schematic diagram of the interplay between circadian rhythms and gut microbiota. Circadian rhythms disruption can alter the microbial abundance and composition, and gut microbiota dysbiosis can in turn disrupt the circadian rhythms of the host. ①Gut microbiota dysbiosis reduces the production of metabolites, including short-chain fatty acids (SCFAs) (propionate, butyrate, acetate) and bile acids, affecting circadian rhythms; ②the SCN controls the secretion of endocrine glandular hormones, which play a role in circadian rhythms and affect the gut microbiota, in turn, which can influence the secretion of these hormones through feedback mechanisms; ③ the neural pathway of the vagus nerve is the most direct way for the gut microbiota to communicate with the brain, and gut microbiota dysbiosis is accompanied by a decrease in vagal function; ④gut microbiota dysbiosis and circadian rhythm disorders are associated with decreased synthesis and inactivation of neurotransmitters; ⑤increased release of LPS and defects in clock genes lead to a sustained increase in pro-inflammatory cytokines.

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oscillatory state of heterogeneous material efflux from the BBB is disrupted in mice. In human microvascular endothelial cell lines, the molecular clock was found to drive intracellular magnesium cycling through transcriptional regulation of magnesium transporter TRPM7, which in turn appears to cycle the outflow of xenobiotics, suggesting that the circadian clock is capable of regulating BBB efflux[109].

5.2. Circadian rhythms disruption leads to BBB damage, aging effect

Sleep is important for immune regulation at central and peripheral levels and sleep disorders are a risk factor for developing neurodegenerative diseases[110], and the regulation of sleep by circadian rhythms appear to be vital in maintaining the integrity of BBB[22]. Sleep deprivation (SD) induces a systemic hypo-inflammation characterized by the release of several molecules such as cytokines, chemokines, and acute phase proteins; all of which may promote changes in BBB cellular components, especially in brain endothelial cells[111]. For example, sleep restriction leads to increased activity of several pro-inflammatory mediators, including C-reactive protein, interleukin-1β (IL-1β), IL-6, IL-17, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α)[22,112] (Fig. 4). In addition, SD promotes pericyte detachment from the capillary wall, and the loss of pericyte−endothelial cell interactions occurs concurrently with a decrease in TJPs between epithelia and increased BBB permeability with exogenous tracers[22]. It is well known that sleep and its disorders affect the function of the basic organs and systems of the body. BBB dysfunction caused by sleep disorder plays an important role in neurodegenerative and autoimmune diseases of the CNS[113]. For example, increased sleep fragmentation (SF) in mice with experimental autoimmune encephalomyelitis (EAE) promotes leukocyte infiltration across the blood-spinal cord barrier and impairs immune regulation, thereby worsening EAE[114]. Of note, ablation of *Bmal1* resulted in pericyte dysfunction, BBB hyperpermeability, and marked astrogliosis[115]. A noteworthy study showed that *Bmal1* deficiency leads to transcription downregulation of platelet-derived growth factor receptor beta (*Pdgfr*β), and exhibited age-dependent loss of pericyte coverage followed by BBB hyperpermeability[115]. Interestingly, TJPs were found to be regulated by circadian rhythms at both the mRNA and protein levels. For example, time-dependent oscillations of occludin mRNA and tissue barrier function were lost in circadian-disordered mice (clock$^{-/-}$)[116]. In addition, sleep restriction not only reduced endothelial and induced nitric oxide synthase, endothelin 1, and glucose transporter protein expression in BBB, but also reduced brain uptake of 2-deoxyglucose and the expression of several TJPs[117]. Furthermore, the downregulation of glucose transporter-1 in brain microvasculature, enriched with sleep disturbance and decreased glucose transport across the BBB, also contributes to BBB disruption[117].

There exist age-related differences in the induction of BBB dysfunction by SD or SF. For example, SF disrupted the BBB integrity in aged mice, but not in young mice, suggesting that the aged BBB is more sensitive to SF than adults[118]. Melatonin, which could regulate circadian rhythms and sleep homeostasis[119], showed a declining level in aged rats and humans. We have previously reported that supplement with melatonin alleviated LPS-disrupted BBB integrity by activating AMP-activated protein kinase in old mice[120]. Moreover, melatonin has also been shown to alleviate BBB breakdown in diabetes-induced AD by inhibiting the loss of TJPs[121]. Therefore, restoration of sleep has the potential to enhance BBB integrity[122].

6. Gut microbiota dysbiosis, BBB disruption, and aging effect

6.1. Role of gut microbiota in the BBB integrity

Gut microbiota has been demonstrated to be critically involved in BBB integrity[123]. For example, germ-free (GF) adult mouse brain showed disorganized TJPs and increased BBB permeability with low expression of occludin and claudin-5. However, the conventionalization of GF adult mice through transplant of the fecal microbiota from pathogen-free adult mice or monocolonization of GF mice with either *Clostridium tyrobutyricum* or *Bacteroides thetaiotaomicron* that produced SCFAs restored the function of the BBB and claudin-5 level was elevated[21]. Meanwhile, SCFAs have also been shown to support BBB integrity as beneficial metabolizers[124]. In addition, strains producing sodium butyrate or acetate/propionate modulate BBB permeability in GF animals by fermenting dietary carbohydrates[21]. Of note, low-dose penicillin exposure early in life had lasting changes in the gut microbiota and upregulated occludin and claudin-5 expression in mice[125].

6.2. Association between gut microbiota dysbiosis and BBB disruption in neurological diseases, an aging effect

Gut microbes and metabolites can modulate BBB integrity and brain health[11]. Gut microbiota has been proposed as a potential regulator of the integrity of the BBB, and its regulatory effect begins with the early period of intrauterine life and propagates throughout life[126]. Aging decreases the levels of microbial, accompanied by a reduced ability to protect BBB124. Gut microbial disturbances result in decreased P-gp, increased BBB permeability, and neuronal death due to the accumulation of harmful blood-borne chemicals[127]. For example, dysregulation of the gut microbiota triggers the release of inflammatory cytokines that can activate endothelial cells and actively traverse the brain endothelial cell layer, causing damage to BBB integrity[128]. Microbiome-produced metabolites, such as SCFAs, can cross the BBB and affect brain function[129]. SCFAs increased TJPs spikes, alleviated LPS-induced TJPs mismatches, improved BBB integrity, and modulated mitochondrial network dynamics[130], which is a target for the anti-aging effects of chlorpropamide[131].

Microbiome−BBB interactions have been reported to influence disease progression. For example, the gut microbiome plays an important role in BBB disruption in an animal model of hypertensive cerebral small vessel disease[132,133]. Moreover, stroke leads to dysbiosis of gut bacteria that affects post-stroke outcomes and gut microbiota is causally associated with a poststroke cognitive impairment through LPS and butyrate[134]. For example, cerebral ischemic stroke caused gut microbiota dysbiosis, increased intestinal permeability, disrupted the gut barrier, and triggered gut microbiota translocation[135]. The Puerariae Lobatae Radix and Chuanxiong Rhizoma combination was an effective treatment for cerebral ischemic stroke that relieved the gut microbiota dysbiosis and brain-gut barrier disruption[135]. The decrease in beneficial intestinal microbiota due to aging and the decrease in the production of sodium butyrate may increase BBB permeability and promote postoperative cognitive dysfunction in the elderly[136]. In addition, dysbiosis of the gut microbiota

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promotes the release of toxic metabolites and pro-inflammatory cytokines that disrupt the intestinal epithelial barrier and promote BBB dysfunction, which is believed to be the basis for the development of AD[126]. The gut microbiome also contains a lot of viruses that are critically involved in disease development and recovery by regulating host and host gut bacterial metabolism[137]. In addition, zonulin-dependent alterations in intestinal permeability and gut microbiota dysregulation are accompanied by changes in BBB integrity and behavioral changes that are partially alleviated by microbiota depletion[138]. Excessive intestinal inflammation caused by gut microbiota dysbiosis increases BBB permeability, triggering various common chronic diseases and leading to brain aging[139]. Regulating and supplementing the intestinal microbiota, as well as targeting immune cells and inflammatory mediators, are required to protect BBB integrity[140].

7. Interplays between circadian rhythms and gut microbiota

Circadian rhythms and gut microbiota are inextricably linked. Circadian rhythms disruption and gut microbiota dysbiosis occur during aging (Fig. 4). Moreover, emerging evidence shows that the interplays of circadian rhythm disturbances and gut dysbiosis disrupt BBB integrity and accelerate AAND[141].

7.1. Gut microbiome is one of the key factors that is involved in maintaining host circadian rhythms

Microbial oscillators are generally promoted by plant-based, low-fat diets, and most are abolished by low-fiber, high-sugar, high-fat diets with low fiber content. Genetic, environmental, dietary, and other host factors such as sex and gut immunity determine the composition and behavior of microbial oscillators. Interaction between host and microbe affects the circadian period, with microbes affecting interactions among light- and food-entrainable circadian processes in response to environmental perturbations[142]. A significant difference in composition, localization, and function of the gut microbiome has been reported between day and night, depending on the feeding cycle of the host[143]. Taxonomic analysis of mouse fecal microbiota reveals that hourly-scale fluctuations in microbiota composition and function that follow a 24-h rhythm can lead to strong oscillations[143]. Mice without microorganisms (germ-free, GF) exhibit higher amplitude circadian rhythms in the light/dark cycle and longer circadian periods in constant darkness. Microbial transplantation with fecal contents of conventionally reared mice normalized circadian rhythms in GF mice, suggesting that the simultaneous activity of gut microbes modulates the host's circadian network[142]. Furthermore, microbiota-derived SCFAs can communicate from the microbiome to various parts within the host tissues and regulate the homeostasis of mammals[144]. Of note, microbiota could modulate substance uptake and storage through interleukin 3 regulated-circadian rhythms transcription factors, providing new insights into the regulation of host metabolism by gut microbiota[145].

Disruption of microbiome rhythms affects circadian fluctuations in host physiology and disease susceptibility[146]. Disturbances in microbiome rhythms may at least partially contribute to an increased risk of obesity and metabolic syndrome associated with insufficient sleep and circadian misalignment[147]. Changes in motor activity rhythm cycles and canonical clock gene expression were found in high-fat diet (HFD)-induced gut microbiota dysregulated mice[148]. Circadian rhythm disturbance that is caused by untimely nutrient exposure and overeating increases the risk of disease[149]. Dietary intervention with prebiotics including β-glucan and inulin attenuates the effects of HFD-induced circadian asynchrony while increasing the richness of gut microbial species[150]. In addition, mice fed with heat-killed *Lactobacillus* became active in the dark and showed increased non-rapid eye movement-sleep during light[151]. Probiotic and prebiotic supplementation showed beneficial effects on sleep and fecal metabolite-related alterations[152]. For example, prebiotic-rich diets modulate pre- and post-stress sleep/wake cycles and induce stress protection in circadian physiology and gut microbiota in rats[153], suggesting that probiotics can improve circadian clock and sleep. In a mice model of SD-induced microbiota disorders, probiotic and prebiotic supplementation was found to reverse microbiota disorder by suppressing oxidative stress and inflammation response[154,155]. Furthermore, twelve-week probiotics treatment had a beneficial effect on insulin metabolism markers and triglycerides, and contributed to improving cognitive and metabolic disorders in AD patients[156]. Of note, clinical trials revealed that administration of probiotics (for 12 weeks) or synbiotics (for 4 weeks) could significantly improve motor functions in PD patients[157]. Thus, to better understand the role of intestinal flora in mediating aging-accompanied changes of the circadian rhythm would provide a novel insight into circadian-related insomnia and benefit the treatment of circadian rhythm disturbance and circadian rhythm-related insomnia[158].

7.2. Effect of circadian rhythms on the gut microbiota

Mice and human studies show that gut microbiota exhibits circadian oscillations of the compositional and functional distributions at specific times of the day depending on feeding rhythms[143]. The function of gut microbiota rhythmicity is highly dependent on the host circadian clock[159]. Disruption of the circadian system can alter microbiome communities and perturb host metabolism[160] and lifestyle stressors such as altered sleep and eating patterns that may disturb the host circadian system also influence the gut microbiome[147].

Altered microbiota rhythmicity is associated with other Clock network mutations, including both positive (such as *Bmal1* knockout) and negative (for example, *Per1* and *Per2* double mutant) loop components[160]. Mice deficient in key circadian rhythm genes, including *Bmal1* or *Per1/2*, have disrupted microbial rhythmicity and composition. In addition, Clock gene mutant mice also exhibit changes in microbial richness and diversity in the stool microbiota. The host circadian machinery influences microbial oscillations and composition; however, reciprocally, microbiota modulates host circadian rhythms. Furthermore, a comparison between GF and specific pathogen-free mice confirmed that microbiota induces significant diurnal host circadian rhythms in liver hepatocytes[161]. Interestingly, time-restricted feeding can restore cellular circadian rhythms in *Cry1/2*-deficient and liver-specific *Bmal1* and *Rev-erba/b*-deficient mice[162]. Regular light/dark cycle-regulated *Per2* gene expression is critical for circadian oscillations, and gut microbiota homeostasis. *Per2* knockout altered circadian oscillations in the large intestine, improved gut microbiota diversity, and increased the abundance of *Clostridium*, leading to a decrease in circulating SCFAs[163]. In $Bmal1^{SCNfl/-}$ mice, rhythmic loss of microbial function was shown[164]. Loss of bacterial taxa and their products due to a desynchronization of the intestinal clock may lead to metabolic abnormalities in shift work[164].

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Insufficient sleep and circadian rhythm disorders lead to an altered gut microbial diversity, which may be followed by changes in microbial structure and function[165]. For example, poor sleep quality is linked to a reduced abundance of *Verrucomicrobia* and *Lentisphaerae* and suggests that there may be a connection between SD, gut microbiome, and cognitive accessibility in the healthy elderly[166]. In addition, SD can cause specific changes in the intestinal microbiome, with *Lachnospiraceae* and *Ruminococcaceae* increasing and *Lactobacillaceae* decreasing, which promote intestinal permeability, inflammation in adipose tissue, and insulin sensitivity in mice[167]. Moreover, short-term SD has mild effects on gut microbiome, with *Firmicutes*: *Bacteroidetes* ratio and *Coriobacteriaceae* and *Erysipelotrichaceae* being upregulated, while *Tenericutes* are downregulated[168].

Damage of circadian and feeding rhythms increases intestinal permeability and alters intestinal barrier function and intestinal microbiota composition[169]. For example, under time-restricted HFD conditions, light/dark cycle information transmitted by ipRGCs is critical for the daily oscillations of gut microbes. In addition, paradoxical light exposure, such as dim light at night can alter the composition, relative abundance, and daily oscillations of the gut microbiota[170]. Interestingly, mice exposed to dim light at night had a significant difference in microbial diversity compared to mice exposed to standard light/dark photoperiod[171]. Furthermore, studies have shown that photoperiod disruption results in the down-regulation of genes that promote beneficial host immune responses, while genes related to the synthesis and transport of endotoxin LPS are up-regulated[17]. Of note, dietary prebiotic intervention (β-glucan and inulin) could ameliorate circadian desynchrony induced by shifted light/dark cycle in mice by modulating circadian gene expression[15].

Distinct clustering in terms of beta-diversity was observed when compared with the mice under normal light/dark cycle. For example, diurnal oscillation of intestinal microbiota can be influenced by diet composition and feeding rhythms and play a key role in regulating circadian liver transcriptome and maintaining host circadian rhythms[172]. In addition, apple polyphenol extract modulates bile acid metabolism and gut microbiota by regulating circadian rhythms in daytime-restricted HFD-feeding male mice[173].

7.3. *Possible mechanism underlying BBB damage induced by circadian rhythms and gut microbiota*

7.3.1. *Effects of gut microbial metabolites on BBB*

Gut microbiota is critical for the normal barrier function during pre- and postnatal periods as BBB permeability was increased in GF mice[21]. Gut microbial metabolites could also regulate BBB permeability and modulate microglia homeostasis, neuroinflammation, and cognitive function[174]. One of the key microbial metabolites connecting altered gut microbial composition with brain disorder is SCFA (mainly butyrate, propionate, and acetate) which is produced by anaerobic bacterial fermentation of complex plant-based polysaccharides[15]. Unconjugated BA have also been shown to both increase circadian genes and change the expression of biological clock genes in the mouse ileum, colon, and liver[175].

Butyrate and propionate promote BBB integrity and protect the cerebrovascular system from damage[21,176]. Moreover, colonizing GF mice with butyric acid-producing *C. tyrobutyricum* or acetic and propionic acid-producing *Bacteroides* or oral administration of sodium butyrate restored the BBB permeability[177]. The administration of sodium butyrate increased occludin expression in the frontal cortex and hippocampus and increased brain histone deacetylation, which was also detected in *C. tyrobutyricum* inoculated GF mice[178]. A physiologically relevant dose of propionic acid showed the modulatory effect being independent of TJPs expression in an *in vitro* model of human BBB. Instead, propionate enhanced the integrity of BBB by mitigating oxidative and pro-inflammatory pathways and reducing the expression of low-density lipoprotein receptor-related protein, a specific efflux transporter[178].

The beneficial effect of SCFAs on disrupted BBB is mainly based on the downregulation in paracellular permeability by restoration of junctional complex proteins *via* affecting their transcription, intercellular localization, or proteolytic degradation[179]. In an *in vitro* BBB model, propionate inhibits pathways associated with non-specific microbial infection through a CD14-dependent mechanism, suppresses lipoprotein receptor-related protein-1 expression, and protects BBB from oxidative stress through NRF2 signaling[176]. Protective effects of propionate on the BBB include mitigation against deleterious inflammatory and oxidative stimuli *via* the erythroid 2-like 2 signaling[176].

The gut microbes metabolize tyrosine and phenylalanine to *p*-cresol, which is then metabolized by host enzymes to *p*-cresol glucuronide (pCG). pCG can act as an antagonist of toll-like receptor 4 (TLR4) and can antagonize the effects of LPS and mice that are exposed to pCG show reduced BBB permeability[180]. Metabolism of microbially produced methylamines associated with vascular disease has been shown to correlate with BBB integrity. The methylamine trimethylamine *N*-oxide (TMAO) enhances BBB integrity and protects it from inflammation[178], whereas the TMAO precursor trimethylamine impaired BBB function and disrupted TJPs integrity. Chronic exposure to TMAO can protect mice from inflammation-induced cognitive impairment, inhibiting astrocyte and microglial activity in a brain[181].

SCFAs, particularly butyric acid, may regulate the production of brain-derived neurotrophic factor (BDNF), signal the brain *via* the vagus and induce biosynthesis of neurotransmitters in the CNS. In addition, metabolites may also have negative neuromodulatory activities: *p*-cresol treatment has been shown to modulate oxytocinergic and opioidergic systems, dopamine turnover, and receptor activity in specific brain regions in mice or rats[178].

Aside from the SCFAs, BA metabolism may be a potential link between circadian rhythms and gut microbiota[182]. Secondary BA deoxycholic acid and ursodeoxycholic acid may modulate BBB integrity. For example, injection of deoxycholic acid in rats increased BBB permeability demonstrated by colorimetric assay and albumin immunoreactivity[183]. Increased deoxycholic acid by gut microbiota is sufficient to induce the production of neurotransmitter 5-HT in enterochromaffin cells[184]. Increased circulating bacterially produced BA may increase the BBB permeability by redistributing the localization of occludin, ZO-1, and ZO-2 and inducing the phosphorylation of occludin *via* a Rac1-dependent mechanism[183]. On the contrary, in an *in vitro* model mimicking the effect of severe hyperbilirubinemia on BBB, ursodeoxycholic acid partially restored the barrier integrity by protecting the endothelial cells from apoptosis[185].

BA signaling to the brain encompasses both direct and indirect pathways, that is, circulating BA can cross the BBB to act directly in the brain *via* their receptors or increase the release of fibroblast growth factor 19 to regulate neuronal activity[103]. BA replacement therapies, such as ursodeoxycholic acid, have been used to change internal BA and microbiota composition, and polyphenolic

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compounds, have been shown to significantly alter microbiota composition associated with BA metabolism and immune function[186].

7.3.2. *Effect of neurotransmitters on BBB*

The gut microbiome can produce a variety of mammalian neurotransmitters, such as dopamine *(Bacillus, Escherichia, Lactobacillus, Lactococcus, and Streptococcus*), 5-HT (*Escherichia, Enterococcus, Lactobacillus, and Streptococcus*), acetylcholine (*Lactobacillus and Bacillus*), and gamma-aminobutyric acid (GABA; *Bifidobacterium and Lactobacillus*), all of which affect host health and maintain homeostasis[187,188]. Bacteria have been shown to produce and/or deplete a variety of mammalian neurotransmitters, including DA, 5-HT, or GABA. Accumulating evidence in animals suggests that bacterial manipulation of these neurotransmitters may have an impact on host physiology, and preliminary human studies suggest that microbiota-based interventions can also alter neurotransmitter levels[189]. Furthermore, SCFAs participate in the synthesis of several neurotransmitters and their receptors, including dopamine, 5-HT, and GABA[103].

More than 50% of DA in the human body is synthesized in the gut[190]. DA and its receptors are widely distributed in the gut[190]. It has been shown that *Bacteroides* uniform through fecal bacteria transplantation can increase DAT/dopamine binding efficiency, while *Prevotella copri* is inversely associated with DAT binding[103]. *Lactobacillus plantarum* PS128 has been reported to alleviate striatal DA reduction in MPTP-induced PD models[103] and *L. plantarum* DR7 can reduce DA metabolism-related enzymes, β-hydroxylase and tyrosine hydroxylase[103]. Additionally, *Clostridium coccoides* and *Clostridium septum* have been shown to have β-glucuronidase enzymatic activity, which can convert peripheral DA into its active form[103]. The complete degradation of DA by *Clostridium tetani* and *Bacillus cereus* further verifies that neurotransmitters of the host are modulated by gut microbiota.

DA imbalance is associated with AAND, including PD, which is often accompanied by abnormal dopamine levels-induced circadian rhythm disturbance. The daily rhythmicity of DA can be disrupted by decoupling between the interlocking loops of the clock circuits or by quasi-periodic clock behavior caused by misalignment with the light/dark cycles[191]. The neurotoxin 6-hydroxydopamine has been shown to alter motor activity and clock gene expression in the rat dorsal striatum and rat forebrain[192]. We have recently shown that D1 receptor-mediated endogenous tissue plasminogen activator increase induces BBB damage after ischemic stroke[193]. In addition, it has been reported that LPS-damaged BBB could be repaired by cabergoline, a specific dopamine D2 receptor agonist[194] and phenylethylamine, a full dopamine receptor agonist produced by *Morganella morganii* strains, is capable of crossing the BBB[195].

The gastrointestinal tract contains most of the body's 5-HT. Around 90% of 5-HT is synthesized in the periphery of human body, mainly by enterochromaffin cells[190], which takes up tryptophan from the diet to synthesize 5-HT[190]. Indigenous spore-forming bacteria (predominantly *Clostridia*, can promote the biosynthesis of 5-HT in colonic enterochromophils by increasing the expression of tryptophan hydroxylase 1, the rate-limiting enzyme. The presence of *Clostridium ramosum* promotes 5-HT secretion, furthermore, several gut metabolites have been identified as the signaling molecules to trigger 5-HT synthesis[184]. For example, SCFAs are important determinants of enteric 5-HT production *via* promoting tryptophan hydroxylase 1 transcription[196].

Tryptamine is found in low concentrations in the brain, produced by selected bacterial strains of the *Clostridium sporogenes* and *Ruminococcus gnavus* species, and acts through epithelial serotonin receptor, increasing colonic secretion and gut transit time without affecting the colonic 5-HT excretion[178]. Tyramine, deoxycholic acid, and 4-aminobenzoic acid were found to stimulate 5-HT synthesis both *in vitro* and *in vivo*. Moreover, microbiota-associated metabolites stimulate enterochromaffin cells to release 5-HT[178].

Host-microbiota interactions play critical roles in the regulation of essential 5-HT-related biological processes[184]. For example, primary SP from mouse and human microbiota promotes 5-HT biosynthesis which supplies 5-HT to the mucosa, lumen, and circulating platelets[184]. This increased 5-HT production, which is taken up and distributed by platelets, may work as a hormone-like regulatory signal that could influence membrane permeability in the host organs and tissues in the brain. Transiently increased permeability of the BBB allows for plasma 5-HT to enter the CNS and be distributed by the volume transmission[197]. In addition, tryptophan (Trp) is the only precursor of 5-HT, a key monoamine neurotransmitter involved in the regulation of central neurotransmission and intestinal physiological functions. Growing evidence showed that changes in the composition of the gut microbiota affect the gut-brain axis by regulating Trp metabolism[198]. For example, *Morinda officinalis* oligosaccharides increases tryptophan hydroxylase levels in the gut microbiota to increase 5-HT levels in the brain[199]. In particular, the levels of Trp-derived 3-hydroxytryptamine pathway metabolites were significantly lower in stool samples from AD patients and direct supplementation of Trp by dietary intervention upregulated 5-HT levels in the hippocampus and frontal cortex, preventing memory loss in aged animals[200].

L. plantarum IS-10506 and the probiotic mixture of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* could upregulate the expression of BDNF, accompanied by a 5-HT increase in rat brain. Meanwhile, IS-10506 treatment can increase 5-HT transporter expression in the hippocampus[201]. In addition, treatment of aged senescence-accelerated mice P8 (SAMP8) mice with ProBiotic-4, a probiotic preparation composed of *Bifidobacterium lactis*, *Lactobacillus casei*, *B. bifidum*, and *Lactobacillus acidophilus*, significantly decreased *Firmicutes*/*Bacteroidetes* (F:B) ratio, *Proteobacteria, Pseudomonas* (genus), and *Lachnospiraceae* NK4A136 group increased the levels of claudin-1, occludin, and ZO-1[202].

Plasma 5-HT levels in PD patients are found to be decreased and serotoninergic intervention has been reported to reduce Aβ-42 levels and the risk of cognitive decline in PD[203]. Therefore, the effects of gut microbiota in modulating neurotransmitters both in the periphery and central nervous system can help optimize available methods to prevent or restore dopaminergic deficits in PD[103].

Gut microbiota could also regulate GABA production, an inhibitory neurotransmitter which is involved in various physiological functions and it was found that the levels of GABA in the gut coincide with that in the CNS[204]. Strandwitz et al.[205] isolate a variety of GABA-producing bacteria, of which *Bacteroides* generated a lot of GABA. Transcriptome-based analysis showed that GABA-producing pathways are expressed by *Bacteroides*, *Parabacteroides*, and *Escherichia*. In addition, human intestinally derived *Lactobacillus brevis* and *Bifidobacterium dentium* can also produce GABA efficiently[206]. Interestingly, gut microbiota-derived GABA shows neuroprotective effects in *Clostridium elegans*, highlighting the role of bacterially-produced GABA in keeping brain homeostasis[205].

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7.3.3. Effects of endocrine hormones on the BBB

The microbiota−gut−brain axis and circadian rhythms often interact through the action of hormones, and the SCN directly or indirectly controls many endocrine glands. Hormones secreted from these glands act in circadian rhythms and influence the gut microbiota, which in turn can influence the secretion of these hormones through feedback mechanisms[207]. Glucocorticoids appear to act as feedback messengers to modulate the links among circadian rhythms, the endocrine system, and the gut microbiota[208]. Moreover, previous studies have found that glucocorticoid can regulate circadian rhythms[209], and glucocorticoid therapy can alter the composition of the intestinal microbiota[210].

Notably, long-term gut flora dysbiosis results in overactivation of the hypothalamic−pituitary−adrenal axis (HPA) and the neuroimmune system, as well as altered neurotransmitter levels, followed by dysfunctional signaling, inflammation, and neuronal death[211]. Gut microbial disorders can lead to an increase in LPS, which crosses the intestinal epithelial barrier and activates the HPA, where the adrenocorticotropin-releasing hormone is released, leading to increased BBB permeability[140]. In addition, corticosterone treatment reduces TJPs expression in brain endothelial cells for *in vitro* BBB[212] and RU486, glucocorticoids receptor antagonist, could inhibit the effects of dexamethasone on functional recovery, indicating that barrier recovery was mediated by glucocorticoid receptor signaling[213]. Interestingly, glucocorticoids are also involved in regulating immune responses and demonstrate rhythmic alterations in animal models of MS[79]. Moreover, orexins could initiate and maintain wakefulness, and loss of orexin-producing neurons causes narcolepsy, and modulation of orexin and its effects on sleep appear to modulate Aβ pathology in the brain[214].

7.3.4. Effects of vagus regulation on BBB

The intestine and the brain are connected by millions of nerve cells, and vagus, the 10th cranial nerve that transmits bidirectional regulatory signals between the brain and internal organs, is an essential part of the gut−brain connection[215].

In addition to endocrine and immune signaling pathways, neural pathways involving the vagus is likely to be the most direct route for the gut microbiota to communicate with the brain. Stimulation of the vagus reduces LPS stimulation-induced colocalization of neutrophils and endothelial cell adhesion molecule (ICAM)-1, as well as downregulates gene expression of inflammatory mediators (IL-6, C−X−C motif chemokine ligand 1, CXCL-1) and attenuates inflammatory responses in brain regions[216]. In addition, the neuroprotective effect of a series of noninvasive vagus nerve stimulation (nVNS) stimulation is spatially associated with the protection of BBB integrity from ischemic stroke-induced injury and reduction in infarct size in rats[217].

It is of note that *Paenalcaligenes* hominins travel into the brain *via* the blood and vagus nerve[218]. Vagotomy can prevent the accumulation and infiltration of extracellular vesicles into the hippocampus and inhibit the oral gavage of *Paenalcaligenes hominis*-induced downregulation of BDNF expression in the hippocampus[218].

7.3.5. Effects of immune and inflammation on BBB

Chronic circadian rhythm disturbances have been shown to deteriorate stroke outcomes in a specific direction and schedule by initiating inflammatory responses in the brain[219]. In addition, dual silencing of CRY1 and CRY2 proteins produced a sustained upregulation in pro-inflammatory cytokines IL-6 and TNF-α and upregulated expression of inducible nitric oxide synthase (iNOS) in fibroblasts, demonstrating a direct link between molecular clock disruption and inflammatory response increase[220]. Circadian rhythm disorder regulates the composition of intestinal microbiota[221], which plays a key role in regulating host immunity. For example, dysbiosis of intestinal flora leads to chemokine secretion and subsequently to recruitment of neutrophils, monocytes, dendritic cells, and macrophages[222]. Neutrophils produce ROS, MMP3, lipid carrier protein-2, and neutrophil extracellular traps to degrade TJPs and disrupt BBB structure[223,224]. Moreover, microbiota transfer from intestinal clock-deficient mice into GF mice altered intestinal gene expression and suppressed immune cell recruitment[225] and BaWeiBaiDuSan, a herbal formula, has been shown to alleviate polymicrobial sepsis-induced liver injury in mice by modulating macrophage anti-inflammatory activity and increasing the gut microbiota *Lactobacillus johnsonii*[226]. Notably, age-related changes in the composition or function of the intestinal microbiota lead to a decrease in intestinal epithelial barrier function of the elderly, driving systemic chronic inflammation[227] and contributing to aging-related diseases[228].

The altered gut microbial composition can lead to disruption of the intestinal epithelial barrier, which may permit microbiota-derived factors to enter the circulation[126]. Circulating LPS and high-mobility group box 1 (HMGB1) act as pathogen-associated molecular patterns and danger-associated molecular patterns, respectively, thereby “alarming” the immune system and promoting systemic inflammation. In addition, CNS-produced type I interferons bind to metabolites that are derived from dietary Trp by intestinal microbiota to activate transcription factor aryl hydrocarbon receptor signaling in astrocytes and inhibit CNS inflammation[229]. SCFAs have been shown to have an integral role in promoting microglia maturation and normal function[230].

It has been shown that secoisolariciresinol diglucoside, the main lignan in flaxseed, can prevent systemic inflammatory response-induced BBB permeability by directly inhibiting BBB interactions with inflammatory cells and reducing the inflammatory state of leukocytes[231]. Interestingly, *trans*-10-hydroxy-2-decenoic acid, the exclusive lipid component of royal jelly, can alleviate LPS-induced BBB dysfunction, therefore it may be a potential candidate for the treatment of BBB damage-related diseases[232]. In addition, dietary saturated fatty acid was identified as a key regulator in the gut, altering T helper 1 and Th17/Treg cell homeostasis in autoimmune neuroinflammation[233]. *Dendrobium officinale* polysaccharide (DOP) has received attention as it may alleviate AD-related cognitive impairment *via* regulating microglial activation. DOP treatment appears to reshape the perturbation of gut microbiota caused by circadian rhythm disruption, including the up-regulated abundance of *Akkermansia* and *Alistipes*, and the down-regulated abundance of *Clostridia*. DOP seems to restore histopathological changes, reduce inflammatory cell infiltration, and strengthen mucosal integrity. Furthermore, DOP could reverse the levels of metabolites related to cognitive function improvement[92].

7.4. Molecular mechanisms underlying aging, circadian rhythms, gut microbiota, and the BBB (Fig. 5)

TLR expression and activation occur in response to microbial cues and can be regulated by circadian rhythms, leading to significant functional differences in microbial responses at different times of the day[162,234]. Both LPS and HMGB1 can bind to TLR 4 on multiple types of immune cells in the blood. LPS stimulates TLR4

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receptors by interacting with CD4 and MD-14 proteins, triggering an inflammatory response[235]. The downstream pathways of TLR4 activation include the myeloid differentiation factor 88 (MyD88)-dependent and the MyD88-independent pathways. TLR4 signaling in the MyD88-dependent pathway induces the activation of nuclear factor kappa B (NF-κB), leading to the release of proinflammatory cytokines and several TLR agonists can activate NF-κB[236]. For example, FLZ, a novel squamosamide derivative, reverses PD-related microbiota activation and restores BBB structure *via* TLR4/MyD88/NF-κB pathway to protect PD models[237].

Of note, systemic administration of TMAO prevented LPS-induced impairment of BBB function in mice[181]. The host-gut co-metabolite *p*-cresol glucosinolate improved BBB integrity *in vivo* and prevented LPS-induced BBB permeabilization *in vitro* by acting as a TLR4 antagonist[238]. The TLR4 agonist LTA increases circulating levels of cytokine and cytokine mRNA expression and is also involved in the transcriptional downregulation of TJPs in the brain[239]. NI 0101, an anti-TLR4 antibody, can potentially block TLR4 ligands and inhibit cytokines release[240]. Agonistic anti-TLR4 mAb significantly decreases NF-κB activation and the production of IL-6, IL-1β, and TNF-α[241]. TAK-242, a small-molecule-specific inhibitor of TLR4, disrupts the interaction of TLR4 with its adaptor molecules, thereby inhibiting its downstream signaling events[242]. Therefore, the TLR4 is a potential therapeutic target to block systemic inflammation, thereby preventing BBB dysfunction and alleviating AAND.

SCFAs can pass the cell membrane and inhibit intracellular HDAC. SCFAs-stimulated acetylation of histone and non-histone proteins *via* inhibition of classes I and IIb histone deacetylases, and crosstalk of these signaling pathways with transcriptional factors NF-κB and NRF2 as mainstream mechanisms[179]. NRF2 translocates to the nucleus and binds to the adjacent regions of the *Il-1β* and *Il-6* genes, suppressing the expression of inflammatory factors[243]. For example, microbiota-derived SCFAs program circadian rhythms in the small intestine *via* HDACs[244]. In addition, 3,4-dihydroxyphenylpropionic acid reduces circadian changes in ischemia/reperfusion injury by inhibiting macrophage pro-inflammatory activation through inhibition of HDAC activity[245]. BBB damage induced by increased HDAC expression and histone hypoacetylation play a key role in the recovery after stroke[246]. In stroke, valproic acid treatment could increase histone acetylation and restore BBB integrity[247]. Inhibition of HDACs induces hyperacetylation of NF-κB/p65, leading to regulation of p65 binding to IκB and downregulation of NF-κB transcriptional activity[248]. Considering that small molecular weights of SCFAs can easily enter the brain, SCFAs could be a promising class of HDACIs for PD therapy. Until now, the therapeutic potential of sodium butyrate as HDACIs has been reported in several studies[103].

Gut microbiota has been shown to regulate the amplitude of circadian rhythms of the transcription factor NFIL3. The regulation of NFIL3 was specific for the signals of gram-negative bacteria such as LPS and flagellin[145]. The microbiota-induced

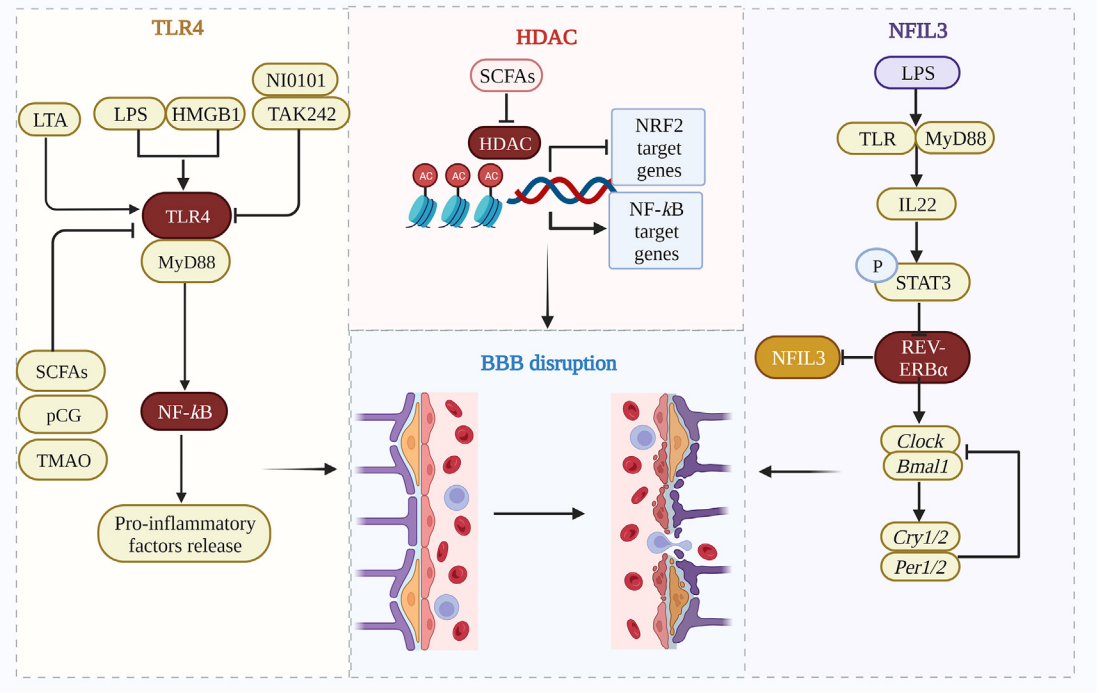

Figure 5 Molecular mechanisms underlying aging, circadian rhythms, gut microbiota, and the BBB. ①Binding of LPS and high-mobility group box 1 (HMGB1) to toll-like receptor 4 (TLR4) signaling in the myeloid differentiation factor 88 (MyD88 -dependent pathway induces activation of NF-κB, leading to the release of pro-inflammatory factors that contribute to BBB destruction; ②increased HDAC expression and histone hypoacetylation lead to BBB damage. SCFAs contribute to the integrity of the BBB by inhibiting HDAC to promote the expression of genes such as NRF2 and increasing nuclear factor kappa B (NF-κB) acetylation and inhibiting its transcriptional activity. ③Activation of the TLR-MyD88 signaling pathway by LPS produces IL-22 to further trigger STAT3 phosphorylation, activated STAT3 inhibits the expression of the biological clock transcriptional repressor REV-ERBα, which leads to an increase in the amplitude of nuclear factor interleukin 3 regulatory factor (NFIL3) expression.

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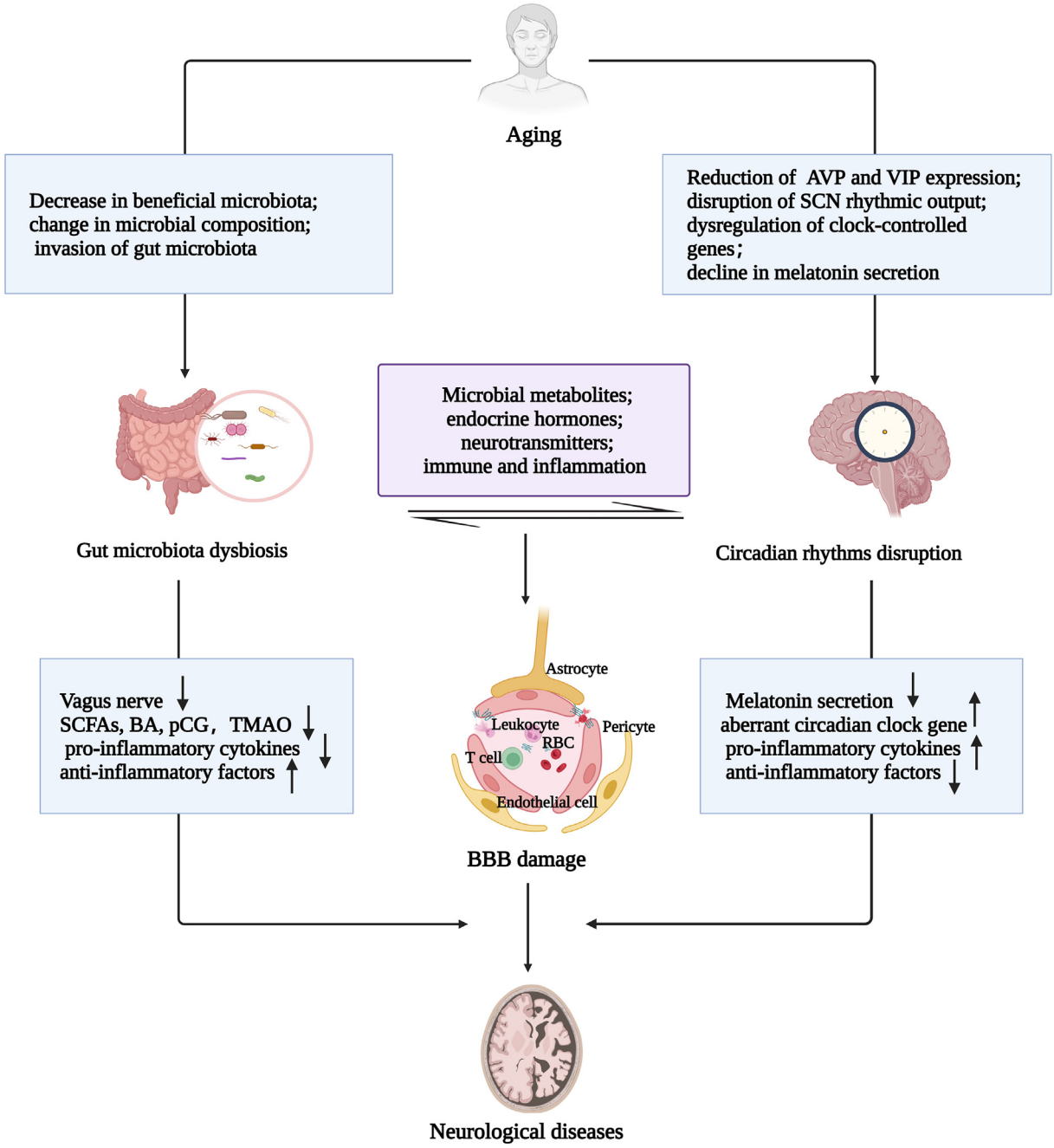

Figure 6 Summary of interplays among circadian rhythms, gut microbiota, and BBB in aging-accompanied neurological diseases.

NFIL3 increase is involved in decreased expression of REV-ERBα protein[145] and the effect is mediated through Myd88 signaling in CD11c^{+} dendritic cells. Briefly, flagellin and LPS are recognized by TLRs on dendritic cells, and IL-23 is recruited to activated group 3 innate lymphoid cells (ILC3s) which could phosphorylate signal transducer and activator of transcription 3 (STAT3) signal *via* IL-22 in 2 intestinal epithelial cells (IECs)[16]. Phosphorylated STAT3 could decrease of REV-ERBα protein expression and REV-ERBα can mediate the circadian rhythms of NFIL3[16].

Altered intestinal microbial composition and an abnormal increase in the ratio of thick-walled bacteria *anaplasma* induced HMGB1 release from the intestine into circulation *via* exosomes[249,250]. NF-κB activation increases glial cell activation and the expression of ICAM-1, IL-6, IL-8, and monocyte chemoattractant protein 1[251], which contribute to BBB disruption[252]; whereas inhibition of NF-κB activity could restore low BBB permeability and upregulate the expression of TJP in rat brain microvascular endothelial cells[253]. Circadian rhythms has been shown to be involved in influencing microglia immune activity, as Clock is a positive regulator of NF-κB-mediated transcription[254]. In another mouse model-based study, DOP was found to improve intestinal barrier dysfunction by upregulating TJPs expression through inhibition of NF-κB activation and neuroinflammation and to modulate the gut microbiota to provide neuroprotection against cognitive impairment[255].

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8. Conclusions

As the pace of human population aging continues to accelerate, aging as a risk factor for neurodegenerative diseases has received increasing attention from society. During aging, alterations in circadian rhythms, gut microbiota dysbiosis, and disruption of BBB integrity can trigger or accelerate age-accompanied neurological diseases. In particular, BBB damage plays a crucial role in the pathological process of age-accompanied neurological diseases. Accumulating evidence supports the potentially important role of dysregulated interplays between gut microbiota and circadian rhythms in promoting BBB disruption and neurological disease pathogenesis. While progress is being made, it is critical to better understand the mechanisms underlying age-related neurological disorders accompanied by BBB disruption and/or interactions between gut microbiota and circadian rhythms. Further research in this direction will bring the translational potential for future clinical applications in promoting healthy aging and treating age-related neurodegeneration. In addition, interventions based on the interplays between circadian rhythms and gut microbiota, such as a healthy and regular diet, adequate sleep duration, and melatonin, may improve some symptoms of aging-related neurological disorders. Regulating circadian rhythms and gut microbiota could restore the structure and function of the BBB and improve neurovascular microenvironment homeostasis, providing potential therapeutic strategies for addressing AAND (Fig. 6).

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Author contributions

Yanping Wang: writing-original draft, writing-review & editing; Weihong Du: writing-review & editing, figure making; Xiaoyan Hu: writing-review & editing; Xin Yu: writing & reference collection; Chun Guo: review & editing; Xinchun Jin: writing-review & editing, conceptualization, supervision; Wei Wang: review & editing, conceptualization, supervision.

Conflicts of interest

The authors declare no conflicts of interest.

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