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*Review*

# Gut Microbiota in Autophagy Regulation: New Therapeutic Perspective in Neurodegeneration

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**Abstract:** Gut microbiota and the brain are related via a complex bidirectional interconnective network. Thus, intestinal homeostasis is a crucial factor for the brain, as it can control the environment of the central nervous system and play a significant role in disease progression. The link between neuropsychological behavior or neurodegeneration and gut dysbiosis is well established, but many involved pathways remain unknown. Accumulating studies showed that metabolites derived from gut microbiota are involved in the autophagy activation of various organs, including the brain, one of the major pathways of the protein clearance system that is essential for protein aggregate clearance. On the other hand, some metabolites are evidenced to disrupt the autophagy process, which can be a modulator of neurodegeneration. However, the detailed mechanism of autophagy regulation by gut microbiota remains elusive, and little research only focused on that. Here we tried to evaluate the crosstalk between gut microbiota metabolites and impaired autophagy of the central nervous system in neurodegeneration and the key to future research regarding gut dysbiosis and compromised autophagy in neurodegenerative diseases.

**Keywords:** gut microbiota; autophagy; neurodegenerative diseases; brain injuries



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## 1. Introduction

Residing inside the intestine, diverse microorganisms, such as bacteria, archaea, fungi, and viruses, collectively defined as gut microbiota (GM), regulate various cellular functions and host homeostasis [1]. The dynamics of GM start from birth onward and are significant for multiple metabolism-related pathways, especially in regulating brain activity [2]. GM can be considered a vital metabolic organ that plays an essential role in neural development, behavior, cognition, and mood and can modulate neuronal diseases [3,4]. This is because of a bidirectional connection between GM and the central nervous system (CNS), which is established through a neural, enzymatic, and immune pathway called the gut–brain axis (GBA) [5,6]. It is emphasized that altering the GM composition by different therapeutic implications remarkably affects CNS [7]. However, this mutualistic crosstalk between the gut and CNS can be disrupted by a harmful change in the GM composition called gut dysbiosis (GD) [8]. Evidence from clinical and pre-clinical studies concluded that

GD is related to neuropsychic and neurodegenerative diseases (NDDs) such as multiple sclerosis (MS) [9], amyotrophic lateral sclerosis diseases (ALS) [10], Parkinson's disease (PD) [11], Alzheimer's disease (AD) [12], and Huntington's disease (HD) [13], to name a few. Mechanistically, GD interrupts the balance of GM-mediated inflammatory and pro-inflammatory processes, inhibits the release of anti-inflammatory cytokines, causes oxidative imbalance, and ultimately disrupts cellular proteostasis function.

In many age-related diseases, including NDDs, the function of proteostasis has been compromised by the over-accumulation of misfolded protein and protein aggregates due to proteasome failure, the central cellular protein degradation system. In such cases, misfolded protein aggregates can be cleared by autophagy, an intracellular lysosomal catabolic process causing the degradation of unnecessary cytoplasmic macromolecules and restoring cellular energy through the biosynthesis of components [14–16]. As the accumulation of toxic misfolded protein is one of the main hallmarks of NDDs [17], disruption of the autophagy may increase misfolded protein aggregates in the brain and promote the occurrences of various types of neurodegenerative disorders [8,18,19]. In addition to the role of GD in promoting inflammation and oxidative imbalance, GD also inhibits the protein degradation capacity by directly regulating autophagy, whereas a healthy gut reversely shows this effect. However, the mechanism by which GM regulates autophagy is still poorly understood. This review summarizes the relationship between GD and NDDs, focusing mainly on autophagy regulation and potential therapeutic interventions to restore intestinal homeostasis and autophagy activation to NDDs.

In addition, followed by GBA, pro-inflammatory cytokines and lipopolysaccharides (LPSs) innervate permeabilization into the intestine and blood–brain barrier (BBB) from the peripheral nervous system to CNS facilitates the accumulation of misfolded protein [8,20]. The consequences of misfolded protein aggregates can cause neuronal death and neurodegeneration [20]. Numerous in vivo studies suggested that gut microbiota-derived metabolites, including neurotransmitters, neuromodulator peptides, short-chain fatty acids (SCFAs), and LPSs, influence attenuating neuroinflammation [21,22]. Studies have reported that gut metabolites are vital in regulating neurodegenerative and neuroinflammatory disorders [5,23,24] by initiating autophagy [25,26].

Besides these, gut metabolites showed a variety of functions in autoimmune, metabolic, and neurodegenerative disorders [27]. Additionally, SCFAs derived from microbiota strongly modulate the pathology of neuronal dysfunction. Gut metabolites upregulate the autophagy flux through GBA and have a direct link with several CNS pathways where autophagy function reduces the spreading of the neuro-inflammatory mediator and contributes to attenuating the progressive neurodegeneration by eliminating the cellular debris [28]. Several studies suggested that various factors, including endoplasmic reticulum stress, oxidative stress, and aging, impair the function of autophagy and play a role in the development of numerous neurodegenerative disorders, including AD, PD, and HD [29]. Moreover, gut metabolites control the permeability of toxic substances into BBB and convey protection from developing oxidative stress [25,30,31]. Moreover, gut metabolites upregulate the multiple pathways associated with autophagy in the epithelial layer and reduce gut barrier injury [32]. Multiple clinical and pre-clinical experiments showed that probiotic supplementation balances GD [27] and thus improves oxidative stress conditions by influencing autophagy [33]. In this review, we summarize the relationship between the dysbiosis of GM and NDDs by regulating autophagy and potential therapeutic intervention to restore intestinal homeostasis.

## 2. Gut Microbiota (GM) and Brain Relationship

The bidirectional relationship between intestinal microbiota and the brain is a well-known phenomenon through which various microorganisms can play a role in cognition, neuro-physiological behavior, and diseases [34]. GM maintains the gut–brain relationship via endocrinal, immune, anatomical, and neural pathways [35–37]. The neuroanatomical pathways between the gut and brain include the autonomic nervous system (ANS) and

vagus nerve (VN) in the spinal cord, and communication between gut and brain through the enteric nervous system (ENS) in the gut and ANS and VN within the spinal cord [38]. The neuroendocrine system is the hypothalamic–pituitary–adrenal (HPA) axis, which functions in response to stress and chemical and mechanical stimuli of GM [34]. GM and brain connection mechanisms also include the production of bacterial metabolites and various immune mediators, such as cytokines, and direct signaling via VN [39,40]. VN can modulate the activity of enteric neurons to communicate with CNS [41]. Gut bacteria influence these central processes through their ability to synthesize neurotransmitters (i.e., γ-amino butyric acid (GABA), noradrenaline, and dopamine) [42], which subsequently influence microglial activation and cerebral function [43]. Moreover, GM modulates the activation of the immune system, along with its ability to produce metabolites, such as SCFAs, that possess neuroactive properties [39]. SCFAs are the main metabolites produced by bacterial fermentation of dietary fibers [44], including propionic acid, butyric acid, and acetic acid, which are responsible for modulating various signaling and exerting neuroactive properties [31]. Many studies suggested that SCFAs may directly interact to regulate brain function, as they are reportedly present in cerebrospinal fluid (CSF) [45].

Bidirectional gut–brain communication is also an essential player in the mechanism of neurodegeneration, as this stimulates the brain for several significant functions, such as neurotransmission of signals, neurogenesis, neuroinflammation, and activation of the stress axes, together with modulating behaviors [46]. Surprisingly, this relationship depends on the microbial community in the individual host, so balancing good and harmful microbe populations is crucial. While the GM composition is critical in CNS regulation and disease progression, different behavioral disruptions also control the GM composition [47]. Thus, the optimum balance between beneficial and harmful microbes is defined as "homeostasis", and the disruption of this balance is called "dysbiosis" [48].

GD has been considered one of the most important causative factors of neurodegeneration [49], which is recognized by the increase of harmful microbes. The hostile bacteria include *Enterobacteriaceae*, consisting of gut commensals *Escherichia*, *Shigella*, *Proteus*, and *Klebsiella*. Increasing these harmful microorganisms release large amounts of harmful metabolites, causing increased permeability of intestinal barriers. Consequently, GD increases systematic inflammation with chronic inflammatory diseases and other metabolic diseases [49]. Again, GD is linked with impaired autophagy and decreased levels of autophagy-related proteins, such as microtubule-associated protein light chain 3 (LC3) [50,51]. Reportedly, intestinal dysbiosis is linked with the disturbance of autophagy; on the other hand, continual autophagy activation is mandatory for the brain to function correctly [52]. Thus, a proper balance of autophagy is required for neuronal development and CNS function. The mutual relationship between intestinal microbiota in controlling autophagy can be targeted as a potential therapeutic approach for NDDs.

## 3. Autophagy and Neurodegeneration

"Autophagy" is derived from a Greek word meaning "self-eating", an evolutionarily conserved process that degrades and recycles cellular components [53]. It can also be defined as a multistep intracellular degradation process by the formation of a double-membrane autophagosome [54,55], which is engulfed by cytoplasm for the bulk degradation of intracellular waste materials, such as damaged organelles [56], misfolded/aggregated proteins [57,58], and intracellular pathogens (e.g., bacteria, fungi, or viruses) [59]. In mammalian cells, three basic types of autophagy have been identified: macroautophagy, chaperon-mediated autophagy (CMA), and microautophagy [57]. Again, macroautophagy is defined as "selective autophagy" that can exclusively sequester and degrade protein aggregates [60]. Macroautophagy is an essential quality control system, which is part of basal constitutive autophagy induced by different stressors, such as protein aggregation and proteasome failure [61]. Major NDDs have been linked to the accumulation of abnormal protein aggregation in neurons, glial cells, and the extracellular space, such as β-amyloid peptide (Aβ) plaques and tau-positive neurofibrillary tangles (NFTs)

in AD [62]; α-synuclein-positive Lewy bodies in PD [63]; tau [64], TDP-43- [65], and FUS-positive aggregates in frontotemporal dementia [66]; and aggregates of a mutant form of huntingtin (HTT) in HD [67]. Thus, autophagy is a neuroprotective mechanism to degrade aggregate-prone cytoplasmic proteins that cause these NDDs [68–73].

Several selective autophagy receptors have been identified that interact with the cargo and components of the autophagic machinery, thus providing a molecular basis for selective degradation [68]. Yeast genetics has been vital for elucidating the molecular machinery involved in autophagy processes [74]. So far, 34 autophagy-related (ATG) genes have been reported in yeast, and 15 of these are "core" ATG genes commonly required for the different autophagy pathways [75]. Autophagy initiates when the mammalian target of rapamycin complex 1 (mTORC1) is inhibited, activating the Ulk1-Atg13-FIP200 complex, which triggers Beclin1, Bcl-2 family proteins, class III phosphatidylinositol 3-kinase (Vps34), and the Atg14l complex to initiate autophagosome formation [76]. Following Beclin1 activation, the Atg5-Atg12 conjugation system and the microtubule-associated protein light-chain 3 (LC3-Atg8) conjugation system regulate the elongation of autophagosome [77]. In the cytoplasm, autophagosomes develop randomly and are carried by microtubules to the microtubule organizing center. Following that, lysosomal acid proteases destroy the contents of the autophagosome, and the degradation products are released for metabolic recycling [78].

As the autophagy pathway is involved in NDDs' causative misfolded protein, a defective autophagy pathway is directly linked to neurodegeneration [69–73,79–83]. In PD, increased alpha-synuclein levels inhibit autophagy by mislocalizing ATG9, a protein with critical functions in autophagosome formation [84]. In HD, the mutant version of huntingtin with expanded polyQ repeats forms toxic protein aggregates that affect the autophagy pathway at various steps. The autophagy protein BECN1 was found to be reduced in the hippocampus of schizophrenia patients [85]. Moreover, some features of autism spectrum disorder, such as social behavior defects or repetitive behavior, are triggered by impaired microglial autophagy [86]. The deletion of the autophagy gene Atg7 in microglia was associated with autistic behavior in mice models [87].

Inducing autophagy by overexpression of autophagy genes or proteins can be essential in reducing neurodegeneration as a therapeutic approach. One study reported that brain-derived neurotrophic factors could provide neuroprotection from hypoxia by inducing autophagy via the PI3K/Akt/mTOR/p70S6K signaling pathway [88]. In a rat model of subarachnoid hemorrhage, autophagy activation by rapamycin or inhibitor 3-methyladenine is connected to neuroprotection against apoptosis through a mitochondrial route [89]. As aggregate-prone proteins are highly dependent on the autophagy pathway for clearance, inducing autophagy can be a potential therapeutic option for treating proteinopathies [90].

## 4. Relation of Gut Microbiota (GM) and Autophagy in Neurodegeneration

There is a smooth balance between GM and autophagy that is regulated bidirectionally. This relationship has recently been in the limelight in many studies because its imbalance is associated with many disease progressions. While the roles of GM and its metabolites in autophagy are excessively studied and highlighted in intestinal homeostasis, few studies focus only on the brain [26,91]. However, our discussion is more directed at explaining the observed and possible mechanisms of GM-mediated regulation of autophagy and vice versa.

Among various NDDs, the relationship between GD and PD is widely studied because GBA is directly involved in transporting misfolding of alpha-synuclein from the gut to the brain at the early stages of pathology [92–96]. The most popular method to study the pathological behavior of PD is using MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which is a neurotoxic-to-dopaminergic neuron once it is metabolized to 1-methyl-4-phenylpyridine (MPP+) [97]. Since MPTP can damage dopaminergic neurons in ENS, it is considered a reliable model for studying GM relations in PD. A recent study shows that MPTP triggered GD and intestinal pathology by changing microbes' composition before motor function

failure, and chronic administration with a low dosage of MPTP is suitable for GM-related studies [98]. Rotenone is another example that has been demonstrated to imitate the clinical and pathological features of PD quite well [99,100], and it is also closely related to GD when PD is induced by chronic administration [101–103]. Using an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-based mice PD model, Liu et al. identified the autophagy interplay between gut and brain concerning GD and PD. They observed that chronic administration of MPTP changes GM composition and alters gut autophagy, and it is also associated with reduced propionate, acetate, and SCFAs [104]. The observation of this study concludes that metabolites that are secreted from the GM are responsible for autophagy regulation. Indeed, the treatment of sodium butyrate in an in vitro PD model (rotenone-treated PC12 cells) induced autophagy by increasing PGC-1α expression [105]. Moreover, sodium butyrate is reported to reduce α-synuclein clearance through activating autophagy-mediated clearance by regulating PI3K/Akt/mTOR-related and Atg5-dependent pathways in enteroendocrine cells [106]. Li et al. discovered that metabolites produced by microbes in the gut are responsible for the induction of mitophagy, reducing microglia-mediated neuroinflammation [107].

Accumulating studies other than NDDs provide strong evidence of autophagy failure caused by GD. For example, Gu et al. reported that GD, induced by bisphenol F, was associated with autophagy reduction and neuroinflammation in zebrafish brains [108]. Unlike MPTP and rotenone, bisphenol F does not directly affect ENS but changes microbial composition by increasing potential pathogenic bacteria [109]. Conversely, the treatment of autophagy inducers was also reported to reshape GM for exerting protective effects against neurotoxicity. For example, in experimental autoimmune encephalomyelitis (EAE)-based MS animal model, the treatment of MCC950 and an autophagy activator, rapamycin, recovered GD in normal mice and slowed down disease progression by inducing autophagy [110]. However, in many cases, GM recovery from GD can also inhibit autophagy for a neuroprotective effect. For example, the remodeling of GM by fecal microbiome transplantation (FMT), which was disturbed by Mn exposure, a neurotoxic condition resembling PD, showed neuroprotection by inhibiting autophagy in the hippocampus through the regulating apelin signaling pathway [111]. Similarly, autophagy inhibition by disrupting beclin1 heterozygous remodels GM from GD, which is induced by arsenite, alleviates neurobehavioral impairments via gut–brain communication [112]. Martin et al. showed that, in the presence of infectious and non-infectious intestinal risks, autophagy proteins inhibit a beneficial microbiota-induced type I interferon (IFN-I) response, suggesting that proteins involved in autophagy regulate immune response to the brain at the gut barrier [113].

Other factors, such as diet and GM-targeted therapies, have also been reported to modulate autophagy in various disease conditions. Wang et al. observed significant changes in the GM of offspring when mother mice were fed high-sugar and high-fat diets for one month and found an increased level of autophagy in the brain with an elevated expression of different LC3 levels [114]. In the aging mice model, supplementation with Urolithin A, derived from the GM through the biotransformation of ellagitannins, induced autophagy through the miR-34a-mediated inhibition of the mTOR signaling pathway and upregulating SIRT1 [115]. Using 3xTgAD mice, Bonfili et al. showed that alterations in the microbiome reduce neuronal proteolysis, but when supplemented with probiotics (SLAB51, composed of nine live bacterial strains), they improved the degradation mechanism of Aβ42 by promoting the ubiquitin–proteasome function [116]. The authors also identified that SLAB51 administration promotes autophagy-mediated clearance by regulating the SIRT1 pathway [117]. Changes in gut flora observed in AD may affect autophagic flux and, thus, the clearance system in the brain, as shown by a few studies that demonstrated that restoring GM via prebiotic treatment triggers autophagy by the PI3K/Akt/mTOR pathway [118]. More detailed studies are required to elucidate the interaction between brain autophagy and GM, especially in neurodegenerative conditions. A good balance between GM composition and autophagy regulation is perhaps essential for proper host

homeostasis. A summary of the autophagy regulation by GM or vice versa is illustrated in Figure 1 and Table 1.

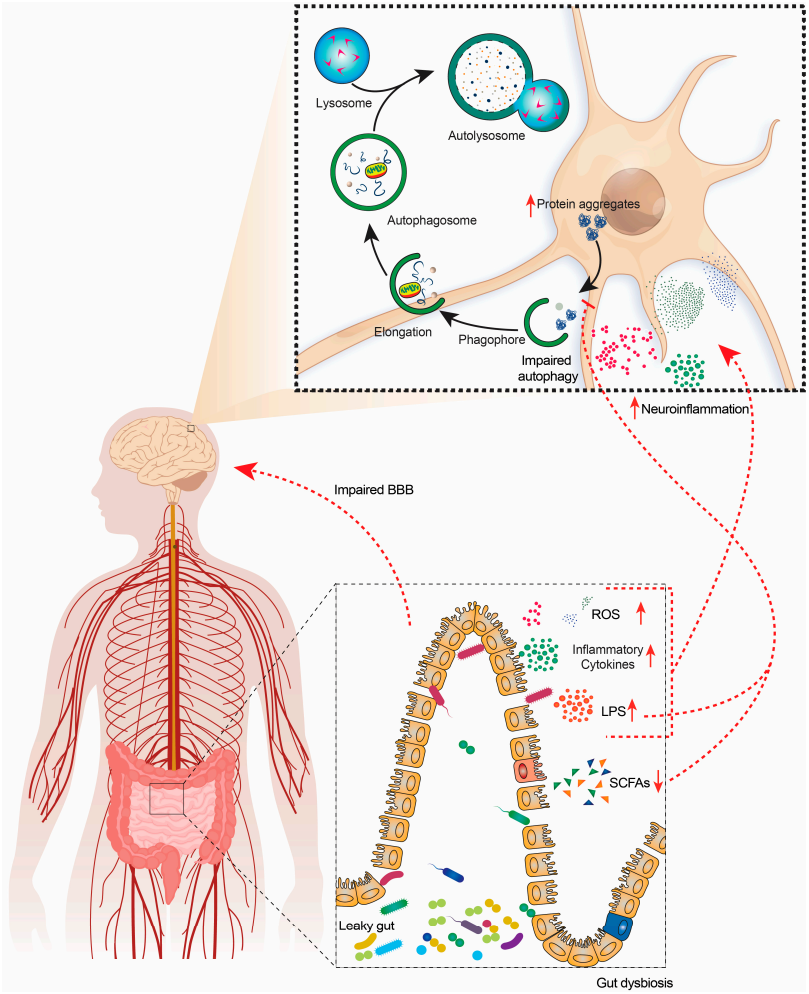


**Figure 1.** Graphical representation of the involvement of GM-derived metabolites in regulating autophagy and brain degeneration. Gut dysbiosis (GD) increases the production of harmful metabolites, such as LPS and inflammatory cytokines, and significantly reduces beneficial metabolites, such as SCFA. GD reduces the integrity of the intestinal epithelial barrier and BBB by releasing harmful metabolites into systematic circulation and the brain. Increased inflammatory mediators cause neuroinflammation, leading to protein aggregation and neurodegeneration. Moreover, due to increased LPS and reduced SCFA, autophagy is disrupted, hindering the clearance of toxic protein aggregates. LPSs, lipopolysaccharides; SCFAs, short chain fatty acids; BBB, blood–brain barrier; ROS, reactive oxygen species.

**Table 1.** Summary of studies that highlighted the reciprocal relationship between gut homeostasis and brain autophagy.

| Study Model | Study Type | Modulators | | Mechanism | Reference |
|---|---|---|---|---|---|
| | | Disease/GD | Autophagy | | |
| Parkinson's disease | In vivo | MPTP (Neurotoxic model for PD) | | • Changes GM composition<br>• Alters gut autophagy<br>• Reduces propionate, acetate, and SCFAs | [104] |
| Parkinson's disease | In vitro (PC12 cell) | Rotenone (Neurotoxic model for PD) | Sodium butyrate | • Sodium butyrate induced autophagy by increasing PGC-1α expression | [105] |
| Multiple sclerosis | In vivo (Experimental autoimmune encephalomyelitis) | | MCC950 and Rapamycin | • Slowed down disease progression<br>• Improved GD and recovered GM composition | [110] |
| Alzheimer's disease | In vivo (3× Tg mice) | | Probiotics (SLAB51) | • SLAB51 induces autophagy and proteolysis<br>• Improve GM composition<br>• Activate SIRT1 pathway | [117] |
| Alzheimer's disease | In vivo (3× Tg mice) | | Probiotics (SLAB51) | • Partial restoration of ubiquitin proteasome system and autophagy<br>• Promote degradation of Aβ42 | [116] |
| Ageing mice model/oxidative damage model on cell | In vivo/in vitro (PC12 cell) | | Urolithin A | • Induces autophagy by inhibiting mTOR pathway<br>• Upregulates SIRT1 | [115] |
| Parkinson's disease | In vivo | Manganese-induced neurotoxicity resembles PD | Fecal microbiota transplant (FMT) | • Provides neuroprotection<br>• Inhibits autophagy by the apelin signaling pathway. | [111] |
| Parkinson's disease | In vitro (Enteroendocrine cells) | | Sodium butyrate | • Reduces α-synuclein clearance by activating autophagy<br>• Activates PI3K/Akt/mTOR-related pathway<br>• Activates Atg5-dependent pathways | [106] |
| Neurological disorder mice model | In vivo | | Microbial metabolite NAMO | • Restores NAD+-dependent mitophagy<br>• Inhibit microglia activation and HSE progression | [107] |
| Alzheimer's disease rodent model | In vivo | $A\beta_{1\text{-}42}$-induced rats | Fructooligosaccharide | • Improves memory by triggering autophagy<br>• Activates PI3K/Akt/mTOR pathway | [118] |

## 5. Role of Gut Microbiota (GM) and Metabolites in NDD Pathogenesis

Numerous studies in humans and experimental animals have pointed to the role of microbiota in the onset and progression of NDDs accomplished by various microbial metabolites via the GBA or CNS [6,95–97]. As stated in earlier sections, different gut microbial metabolites consist of neuromodulators, anti-inflammatory, pro-inflammatory agents, and uremic toxins [90–94] that have been linked to various physiological systems of the host's body together with neural development and the maintenance of brain function, and also maintaining the integrity of BBB [22]. This section discusses the role of microbes and metabolites regulating the pathogenesis of common NDDs, such as AD, PD, HD, MS, and ALS.

### *5.1. Parkinson's Disease (PD)*

The misfolding and aggregation of α-synuclein in damaged brain areas containing cytoplasmic clumps called Lewy bodies (LBs) are the clinical outcomes of PD that are responsible for neuronal loss and degeneration [119–121]. Motor impairment is observed in PD because of the gradual loss of dopaminergic neurons in the midbrain's Substantial Nigra [122]. PD affects around one percent of persons over 65 worldwide; a small percentage suffer from familial PD or parkinsonism [123]. Nevertheless, in addition to these causes, several studies have revealed that PD pathology may develop predominantly through the gut [124–127]. Nearly eighty percent of people diagnosed with PD experience GI symptoms before experiencing motor signs [125]. Faecalibacterium, Lachnospiraceae, and Prevotellaceae were found in the patients' feces at lower levels than in controls [128], suggesting GI problems associated with PD and thus inspiring researchers to investigate the connections between gut microorganisms and the disease.

GM change may affect PD since the mesentery (spleen, pancreas, and GI tract) contributes approximately half of the body's dopamine (DA) production [129]. Altschuler et al. postulated in 1996 that *Helicobacter pylori* (*H. pylori*) infection had a causal role in the pathophysiology of PD [130]. Higher Lactobacillaceae and lower Prevotellaceae may also modify nigrostriatal dopamine activity and slow PD progression by decreasing gut hormones such as ghrelin [131,132]. The connection between GD and alterations in microbial metabolites in PD was also extensively explored. SCFAs are the metabolic by-products of GM activities, including propionate, butyrate, and acetate. SCFAs are being investigated as molecular therapies for reverse NDDs because they tend to regulate the interconnections between the GM and the CNS [31]. PD patients were shown to have lower levels of SCFA-generating microbiota, such as Prevotellaceae and Lachnospiraceae, according to the investigations that were conducted in the past [133,134]. Moreover, the SCFAs acetate, butyrate, and propionate were also found in PD patients' feces in lower concentrations than in age-matched controls [135,136]. Urolithin A (UA) is a metabolite produced when the digestive-tract bacteria act to convert ellagitannins into a different component. Oxidative processes caused by MAO-A can be prevented by using the antioxidant UA, which is suggested as a possible metabolite for treating NDDs [137] since ROS (reactive oxygen species) production has been established as a critical factor in NDDs. UA promotes mitochondrial biogenesis through SIRT1-PGC-1α signaling, resulting in neuroprotection in 6-OHDA-induced PC-12 cells. Both 6-OHDA-induced motor impairments and nigral–striatal dopaminergic neurotoxicity were attenuated when UA was administered to the PD mice [138]. Kujawska et al. showed protection against oxidative damage and α-synuclein aggregation in the PD rat model by administering pomegranate juice where the concentration of UA was 1.68 ± 0.25 ng/g tissue and in plasma 18.75 ± 3.21 ng/mL in the brain [139]. Trimethylamine-N-oxide, also known as TMAO, is a metabolite that is produced by the GM and found in high amounts in seafood, dairy products, red meats, muscle, and egg yolks [140,141]. TMAO has been reported to induce proper protein folding [142] and lessen the production of the aggregation of α-synuclein fibrils [142]. Studies indicate that people with PD had lower levels of TMAO, increasing dementia associated with levodopa-equivalent doses [143]. A disruption in the gut barrier causes the translocation of bacterial components such as

LPS from the intestine into the bloodstream of PD patients. As a result, the Toll-like receptor 4 (TLR4)-mediated pathway is activated, promoting inflammation and exacerbating PD neurodegeneration [144]. In animal models of PD, increased levels of Tryptophan metabolites and KYNA in the brain were found to protect nigrostriatal dopamine neurons against QUIN-induced excitotoxin damage [145]. Additionally, vitamins are necessary minerals that humans can obtain only through diet or microbiota in their digestive tract, where vitamin K is derived from the bacteria Escherichia coli, Klebsiella pneumonia, Eubacterium, and Propionibacterium [146]. It has been demonstrated that vitamin K plays a favorable function as an anti-fibrillogenic on α-synuclein aggregation, which is directly related to PD [147]. In summary, consistent evidence suggests that the microbiota in the gut and the microbial metabolites produced by those microbes have a major influence on the modulation of PD.

### *5.2. Alzheimer's Disease (AD)*

AD is the most common form of dementia, and its proportion is rising as the world's population ages [148]; it is characterized by the accumulation of β-amyloid peptide (Aβ) and a microtubule-associated protein known as tau [149]. Prior to the onset of AD progression, numerous studies in vivo have documented shifts in microbial communities (*Rikenellaceae*, *Erysipelotrichaceae*, *Bacteroidaceae*, *Verrucomicrobiaceae*, *Wolbachia*, *Rikenellaceae*, *Prevotellaceae*, *Proteobacteriaceae*, and *Bifidobacteriaceae*) before any plaque formation in the brain [150], suggesting the involvement of GM in the pathogenesis of AD. Studying the brain function of 8-month-old transgenic (Tg) mice of AD, Gu et al. discovered that Tg mice exhibited lower amounts of SCFA-producing bacteria (such as *Parasutterella* and *Blautia*) and more GD compared to wild-type mice [151]. Notably, there have been a number of recent investigations in which proteins (bacterial, viral, or fungal-derived) and nucleic acid have been found in the brains of AD patients who had already passed away, indicating that microbial metabolites such as SCFAs may be generated locally [152,153]. The SCFAs propionic, butyric, and isobutyric acids were reduced in AD-model mice compared to wild-type mice [154–156]. In contrast, increasing butyrate intake through food supplements has been proven to improve AD pathogenies by boosting memory-related genomic programs and re-establishing DNA acetylation [157]. Butyrate was proven to increase both the survival rate and the motor ability in a dose-dependent manner of R6/2 transgenic mice in a model of HD [158]. Previous studies have identified that SCFAs can prevent Aβ aggregation in vitro [159]. In APP/PS1 transgenic mice, treatment with UA improved cognitive function, reduced neuronal death, and increased neurogenesis [160]. UA can induce autophagy to increase Aβ clearance in neuronal cell lines [161]. Ali et al. provided evidence that anthocyanin, derived from microbial metabolism, modulates p-PI3K/Akt/GSK3β pathways, decreasing amyloid beta oligomer in both in vitro and in vivo models of a model of AD (APP/PS1) [162]. Though limited, new data suggest that anthocyanins may also exert neuroprotective effects by directly preventing protein aggregation and stimulating autophagy, as concluded by Aimee et al. [163]. The expression and activity of Neprilysin are increased by tryptophan metabolites, 5-hydroxy indole-acetic acid (5-HIAA), and kynurenic acid (KYNA), which stimulates the elimination of Aβ in the brain-protecting neurons from Aβ-peptide-induced toxicity [164]. There are several types of metabolites, such as phytosphingosine, dihydrosphingosine, hypoxanthine, and inosine, that have been shown to reduce the symptoms of AD where the administration of xanthoceraside, a molecule with anti-activity of AD, was associated with changes in the levels of these metabolites and a shift in the composition of gut bacterial taxonomy, suggesting novel avenues for treating AD. [165]. It is known that microtubule disassembly and neuronal death are the hallmark pathogenic aspects of AD [166], and TMAO has been reported to rescue the capacity of mutant tau to induce microtubule assembly [167,168]. Like PD, vitamins play an essential role in the modulation of AD [169]. High doses of B vitamins, such as B6, B9, and B12, have been shown to reduce levels of homocysteine, a by-product of vitamin B, and prevent the degeneration of some brain regions linked to cognitive impairment in AD [170].

### *5.3. Huntington's Disease (HD)*

HD is a hereditary autosomal-dominant neurodegenerative illness that is caused by the mutation of the huntingtin (Htt) protein, with an expanded polyglutamine (polyQ) stretch leading to Htt fragments and the formation of aggregates [171,172]. The gut may also play a role in moderating the pathogenesis of HD because its microbiota is disrupted before severe cognitive and motor impairments are set in [173]. Massive changes in the structure of bacterial communities at the phylum and family levels and impacted metabolic systems and enzymes were also discovered in our HD patients [13]. The existence of GD was verified by a 16 s RNA-sequencing genomic profile of the GM from a fecal sample of transgenic HD mice [174], where 16 s rRNA sequencing of R6/1 HD mice showed a sex-specific GM composition. According to a recent clinical study, specific GM components, including *actinobacteria*, are significantly more prevalent in HD patients than in healthy participants by DNA extraction after feces and blood samples had been collected for analysis [175]. In addition, the gut permeability of R6/2 mice with HD was enhanced, and the microbiome was significantly altered. More specifically, Bacteroidetes ($Gram^-$) were more abundant than Firmicutes ($Gram^+$) in these animals [176]. Additionally, KYNA plays a vital role in HD. HD patients exhibit abnormal TRP metabolism and increased oxidative stress. These factors contribute to continued brain dysfunction. Plasma levels of KYNA, 3-HK, and 3-HAA and KAT activity are decreased in HD [177]. GM produces ellagic acid (EA). EA dramatically decreased mHTT levels, neuroinflammation, and oxidative stress, preventing further synapse loss in R6/2 mice [178]. All of these findings point to a link between NDDs and GD, and they emphasize the importance of a balanced microbiota composition in preventing the development of HD.

### *5.4. Amyotrophic Lateral Sclerosis (ALS)*

ALS is a deadly neurological disease that mainly affects adults. It is diagnosed by the selective loss of motor neurons. ALS is also known as familial ALS or fALS since it can be passed down from parent to child in around 10% of all instances [179]. Compared to controls, ALS patients showed lower butyrate-producing bacteria, such as *Eubacterium rectale* and *Roseburia intestinalis* [180], which regulate gut integrity and inflammation [181]. Another study showed that a high production of SCFAs is associated with a high body mass index (BMI) [182] in people; on the other hand, a high BMI is known to be inversely correlated with ALS risks [183,184]. Moreover, the administration of *Akkermansia muciniphila* caused an increase of nicotinamide in the CNS, alleviating various symptoms of ALS, enhancing motor symptoms, and modifying the expression of genes in SOD1-Tg mice [185]. One study showed no statistically significant changes between patient and healthy groups in the levels of KYNA in serum or CSF. Despite this, the concentration of KYNA in the CSF was shown to be significantly greater in patients with severe clinical problems compared to healthy control subjects, and there was no correlation between the KYNA concentrations in the serum and CSF [186]. Consistent with the observations of several experiments, microbiome-targeted metabolite therapies might be potential future routes for preventing ALS due to the multiple connections between ALS and GM.

### *5.5. Multiple Sclerosis (MS)*

Demyelination and axonal degeneration of the CNS are hallmarks of the autoimmune disease known as MS [187]. Patients with MS were shown to have abnormalities in the gut flora associated with feces. *Caulobacteraceae*, *Pseudomonas*, and *Mycoplana* were found in higher abundance in MS patients, but *Enterobacteriales* were found in higher abundance in the healthy controls [188]. Furthermore, in animals hyper-sensitive to a myelin oligodendrocyte glycoprotein, continuous administration of colistin, kanamycin, and vancomycin suppressed experimental autoimmune encephalomyelitis (EAE) progression, but in V14 natural killer T (iNKT)-cell-deficient mice, this activity was lost [189]. The SCFA propionic acid (PA) induces T cells expressions in the gut, which, in turn, has a beneficial effect on the CNS in MS patients [190]. I3S and other aryl hydrocarbon receptor (AHR) agonists can be

generated by symbiotic-bacteria-producing tryptophan metabolites, reducing the harmful activity of astrocytes in MS mice [191]. Reduced numbers of *Parabacteroides*, *Revotella*, and *Adlercreutzia* are associated with a higher risk of multiple sclerosis, even though these bacteria can maintain mucosal surface homeostasis, generate anti-inflammatory effects, and serve as phytoestrogen metabolite producers in MS. [188]. In another study, untreated MS patients were found to have lower levels of *Collinsella* and *Slackia*, both of which belong to the phyla Actinobacteria and Prevotella. In contrast, when comparing treated MS patients to untreated MS patients, the authors found that *Prevotella* and *Sutterella* levels were higher in the treated MS patients [192]. The above findings suggest that the GM population has a major impact on the progression of autoimmune illnesses such as MS and that GM manipulation should be considered a therapeutic option in treating MS in the coming decades.

In addition, gut patients with MS who received tryptophan metabolites improved their cognitive and memory functions [193–195]. The expression of AhR on microglia and astrocytes is boosted by tryptophan metabolites (I3S, tryptamine, indole-3-acetic acid, kynurenine, and kynurenic acid), which also play a role in the regulation of inflammatory processes [196,197]. Since GPBAR1 expresses in glial and immune cells, secondary metabolites, such as bile acid can modulate the reactivity of astrocytes [198]. The SCFAs propionic acid (PA) raises the number of regulatory T cells originating from the gut, and this benefits the CNS in MS patients [190]. As a whole, various metabolites in the digestive tract can prevent the progression of multiple sclerosis.

## 6. Therapeutic Interventions and Future Perspectives

Introducing beneficial GM and re-establishing the balance can be a fruitful method to correct dysbiosis, and, as a result, impaired autophagy can be restored. Many external factors modify the gut community of microbiota. Diet, exercise, lifestyle, environment, stress, etc., are the various factors that affect gut microbial development. The most well-known methods of therapeutic application may include postbiotics and psychobiotics [199], FMT, and diet modification (Figure 2). Psychobiotics are defined as a combination of "prebiotics" and "probiotics" that can especially affect the gut–brain relationship [36]. Probiotics are helpful bacteria, and prebiotics is compounds that promote helpful bacteria growth. Psychobiotics treatments are known to improve neurological and behavioral conditions, as established by many studies [200,201]. Postbiotics include any metabolites or products that the GM produces that can positively or indirectly affect the host [202]. Cell-free supernatant from GM, enzymes, cell fragments, SCFA, and bacterial lysates are especially considered for therapeutic application. Besides restoring intestinal-balance postbiotics, these products help correct immune system disruption [203]. Bacterial peptidoglycan, considered postbiotic treatment, is also responsible for autophagy induction in epithelial cells [204] and the liver [205]. Again, healthy eating and diet play an important role in establishing the balance of GM [206]. Surprisingly, diet modification by caloric restriction can help in autophagy induction [207] and neuropsychiatric conditions [208]. Furthermore, in a recent study, it was proved that the high sugar and high fat (HSHF) diet of a mother amends the GM of the offspring and the expression of neuronal and autophagy markers in the brain during the early life stage [114]. If aspects of the microbiome are easily modifiable, for example, it may be possible to alter autophagic flux through dietary modifications. Foods that promote SCFA formation via microbial fermentation in the colon, such as those prevalent in the Mediterranean diet, reduce the signs of frailty and cognitive impairment in the elderly by altering the richness and character of the intestinal microbiota [209]. FMT has shown great promise to repair the GD that leads to NDDs. To treat dysbiosis, a healthy donor's feces containing gut bacteria can be delivered to the patient by using an enema or nasogastric, nasoenteric, or endoscopic methods [210].

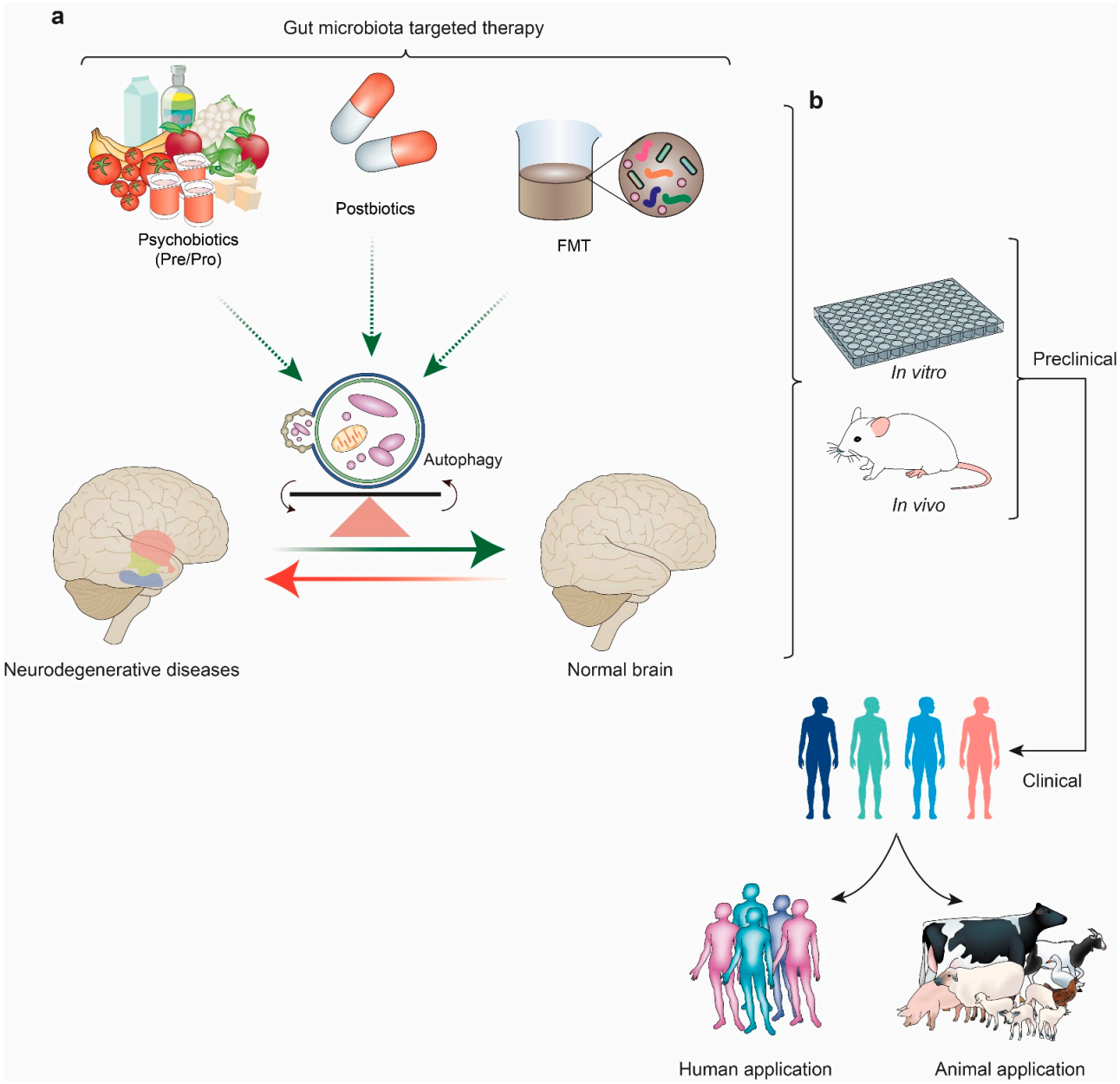


**Figure 2.** Illustration representing the therapeutic application and future research potential of gut microbiota (GM)-derived autophagy regulation in the modulation of neurodegenerations. (**a**) Showing psychobiotics (prebiotics and/or probiotics), postbiotics, and FMT as a therapeutic method to modulate GM. Positive modulation of GM can either initiate or inhibit autophagy and its association with neurodegeneration, a potential aspect that needs extensive mechanistic studies in the future. (**b**) Representing the future research methodologies using GM to establish proper therapeutics. In vitro and in vivo research and clinical trials for proper therapeutic application (in humans and animals) are the main focus of future research regarding GM. FMT, fecal microbiota transplant.

The relationship between GM and the brain is well-studied and evident in numerous in vivo and in vitro studies. In this review, we highlighted the brain and GM relationship and focused on the autophagic mechanism that can be one mechanistic perspective of the relationship. Autophagy is a crucial player in NDDs' progression. Until now, the involvement of GD has been reported in the autophagy of various organs, especially in the intestinal epithelial barrier [211], heart [212], muscles [213], and liver [51]. SCFA is reported to induce hepatic autophagy in a UCP2-dependent pathway, and the loss of the gut

microbiome can impair basal liver autophagy [51]. This review also discussed the possible mechanisms of GM autophagy in CNS and the bidirectional relationship between GM autophagy and nervous system disorder. Thus, GM-mediated autophagy can be a potential mediator in NDD treatment. To understand the mechanism of GM and its metabolites in nervous system autophagy, a further mechanistic study must be performed. Studies in animal models of NDD and human patients must be performed in future research to establish the relationship and possible therapeutic approach. The evidence linking the compromised autophagy of CNS and GM dysbiosis is compelling; however, clinical and pre-clinical studies need more attention for therapeutic application.

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