Review

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Exosomes, Endosomes, and Caveolae as Encouraging Targets with Favorable Gut Microbiota for the Innovative Treatment of Alzheimer's Diseases

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Neurodegenerative diseases are characterized by progressive damage to specific neuronal cells, resulting in cognitive impairments. Alzheimer's disease is one of the most common types of cognitive impairments. Until recently, strategies that prevent its clinical progression have remained elusive. It has been suggested that oxidative stress, mitochondrial injury, and inflammation might lead to brain cell death in many neurological disorders. Therefore, the identification of effective neuroprotective agents is a research priority, and several autophagy-targeted bioactive compounds are promising candidate therapeutics for the prevention of brain cell damage. Some Alzheimer's disease risk genes expressed within the brain are linked to cholesterol metabolism, lipid transport, endocytosis, exocytosis, and/or caveolae formation, suggesting fruitful therapeutic targets for the treatment of cognitive impairments. Among them, a well-known genetic risk factor for late-onset Alzheimer's disease is allelic variation of the Apolipoprotein E (*APOE*) genes. APOE proteins may regulate aspects of cellular homeostasis, which is perturbed in the brain in Alzheimer's disease. Interestingly, the Apolipoprotein E ε4 allele (APOE4) protein is related to autophagy and to the biogenesis of caveolae, endosomes, and exosomes, processes which might consequently be involved in the pathogenesis of neurodegenerative diseases, including Alzheimer's disease. Recent research suggests that modification of the diet and/or gut-microbiota could be effective for treatment of various neurodegenerative diseases. Collectively, this research direction has the potential to improve clinical care through disease-modifying treatment strategies with benefits for patients with neurodegenerative diseases.

Keywords: APOE4; exosome; caveolae; autophagy; neurodegenerative disease; Alzheimer's disease

Introduction

Neurodegenerative diseases are characterized by progressive damage to specific neuronal populations, resulting in motor and/or cognitive impairments [1]. Among these, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease are representative types of neurodegenerative diseases [2]. A well-known genetic risk factor for late-onset Alzheimer's disease is allelic variation in the Apolipoprotein E (*APOE*) gene. However, the biochemical foundation for the risk has been unclear. APOE proteins may regulate some aspects of cellular homeostasis, which is perturbed in the brain in Alzheimer's disease [3]. In addition, gut microbiota and their metabolites play an important role in altering the functions of brain cells, thereby affecting amyloid-β deposition in the brain in Alzheimer's disease [4]. Remarkably, exacerbation of microglial activation, possibly caused by gut microbiota-derived short-chain fatty acids (SCFAs), leads to increased α-synuclein aggregates in the model mice of Parkinson's disease [5]. Furthermore, the activity of the gut microbiota can affect many aspects of gut and brain function including the integrity of the intestinal barrier, the regulation of the endocrine system, and the permeability of the blood-brain barrier (BBB), which might also contribute to the maturation of neuronal cells in the central nervous system (CNS) (Fig. 1). Therefore, gut dysbiosis might contribute to the pathophysiology of various neurological diseases, including neurodegenerative diseases [6]. Several pathways involved in communication within the gut-brain axis, including neural, immune, and endocrine pathways, have been suggested. Key molecules may include neurotransmitters such as dopamine, serotonin, norepinephrine, gamma-aminobutyric acid (GABA), several cytokines, vitamins, and/or nutrients including metabolites such as SCFAs [7]. However, the exact mechanisms through which changes in gut microbiota could impact the CNS remain unclear.

Exosomes emerge from endosomal invagination and contain diverse proteins, lipids, and nucleic acids. Clinically, exosomes may potentially be used for the diagnosis of multiple diseases, including neurodegenerative diseases [8]. In Alzheimer's disease, for example, changes in the endosomal system in neurons are characterized by broad disruption of autophagic compartments [9]. Disruption of the neuronal endosomal pathway in Alzheimer's disease has

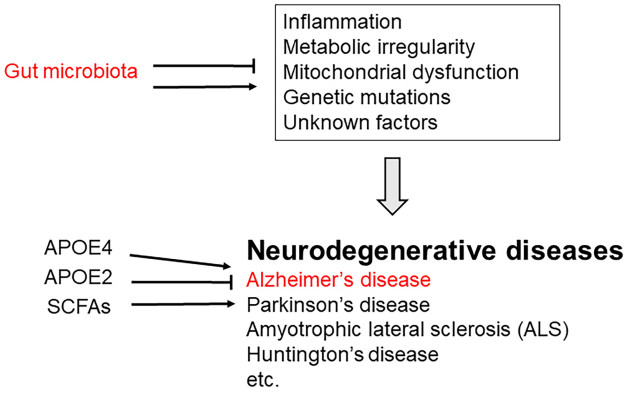

Fig. 1. Representation of the critical factors for the development of neurodegenerative diseases. Neurodegenerative diseases are a group of disorders that trigger progressive loss of neuronal cells. There are various factors that contribute to neurodegenerative diseases, including Alzheimer's disease, as shown here. Several dietary factors and/or modifications of gut microbiota are well-known for interfering with the pathway involved in the development of neurodegenerative diseases. The arrowhead means stimulation and/or augmentation whereas the hammerhead represents inhibition. Some critical events have been omitted for clarity. Abbreviation: APOE4, Apolipoprotein E ε4 allele; SCFAs, short-chain fatty acids. This illustration was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA).

been suggested to result from multiple pathological sources, including intravesicular amyloid-β [10]. Interestingly, the APOE isoform Apolipoprotein E ε4 allele (APOE4) protein has been found to trigger this dysregulation in the endosomal pathway [11]. Correspondingly, it has been shown that expression of the APOE4 leads to the alteration of the neuronal endosomal pathway in human and mouse models of Alzheimer's disease [12]. Therefore, the focus of investigation in these models of Alzheimer's disease-related endosomal disturbance has extended to exosomes, which are created within the endosomal pathway and then secreted into the extracellular zone [13]. Importantly, stable exosomes could allow toxic material to be conveyed between brain regions, which may support the accumulation of this material [14]. Interestingly, it has been shown that endocytic trafficking and autophagy are two key pathways that regulate the integrity and/or composition of the brain neuronal proteome [15]. In addition, endosomes and autophagosomes are both created at the presynaptic terminus in the distal axon [16]. Dysfunction in the autophagic and/or endolysosomal trafficking pathways might be connected to neurodegenerative diseases [17]. Autophagy is a preserved cellular mechanism critical for maintaining cellular balance and can support the recycling of damaged proteins and/or organelles such as mitochondria [18]. However, autophagy can also play a pivotal role in developing various age-related neurodegenerative diseases [19]. Consequently, exosome/endosome trafficking and autophagy might play key roles in maintaining neuronal integrity, and their disruption could contribute to the development of several neurodegenerative diseases. In other words, the autophagy-lysosomal-endosomal system could be a promising target for neuroprotection against various neurodegenerative diseases [20]. Here, the aim of this review article was to summarize possible mechanisms of neurodegenerative diseases, including Alzheimer's disease, and to identify strategies for the development of innovative therapies.

APOE and Caveolin Proteins Involved in the Formation of Caveolae and Exosomes

The *APOE* gene is a recognized risk factor for sporadic Alzheimer's disease, with increased risk for ε4-transporters (*APOE4*) and decreased risk for ε2-transporters (*APOE2*). In particular, expression of the *APOE4* gene has been reported to be the most significant genetic risk factor for late-onset Alzheimer's disease [21]. Therefore, the APOE4 protein might be neuro-damaging, whereas the APOE2 protein could be neuroprotective compared to the neutral APOE3 protein (Fig. 1). The neuronal endosomal system is susceptible during aging, and APOE4 might exacerbate this susceptibility by decreasing exosome release in neuronal cells of the CNS. Increased extracellular levels of endosome-derived exosomes have been detected in APOE2-expressing mice compared with APOE3 mice during aging [22]. In general, Apolipoprotein A—I can upregulate the expression of adenosine triphosphate (ATP)-binding cassette transport A1 (ABCA1) in various cell types, which could cause the redistribution of raft-associated proteins and lipids. In addition, the function of ABCA1 may be associated with caveolin-1 protein [23]. Caveolin-1 can predominantly regulate exosome biogenesis and/or exosomal cargo arranging by controlling cholesterol at the endosomal package [23,24]. Dysfunction of this endosomal-exosomal system might be a critical pathogenic factor in Alzheimer's disease as well as in other neurodegenerative disorders [25]. Interestingly, the APOE4 protein is involved in exosome biogenesis and is also linked to cognitive decline [26]. Exosomes are formed in the endocytic pathway within the multivesicular bodies [27]. Approximately 100-nm vesicles are released from the cell surface when the multivesicular bodies fuse with the cell surface [28] (Fig. 2). As the exosome is a membrane-bound vesicle, integral membrane proteins are also released from the cell within a membrane bilayer in a lipid environment [29]. Caveolin-1 is believed to work as a cell surface protein in the biogenesis of caveolae. In addition, caveolin-1 can be emitted from cells in exosomes, where it has specific effects [30]. Interestingly, greater caveolin-1 expression has been found in both APOE4-target replacement mouse models and human brains with Alzheimer's

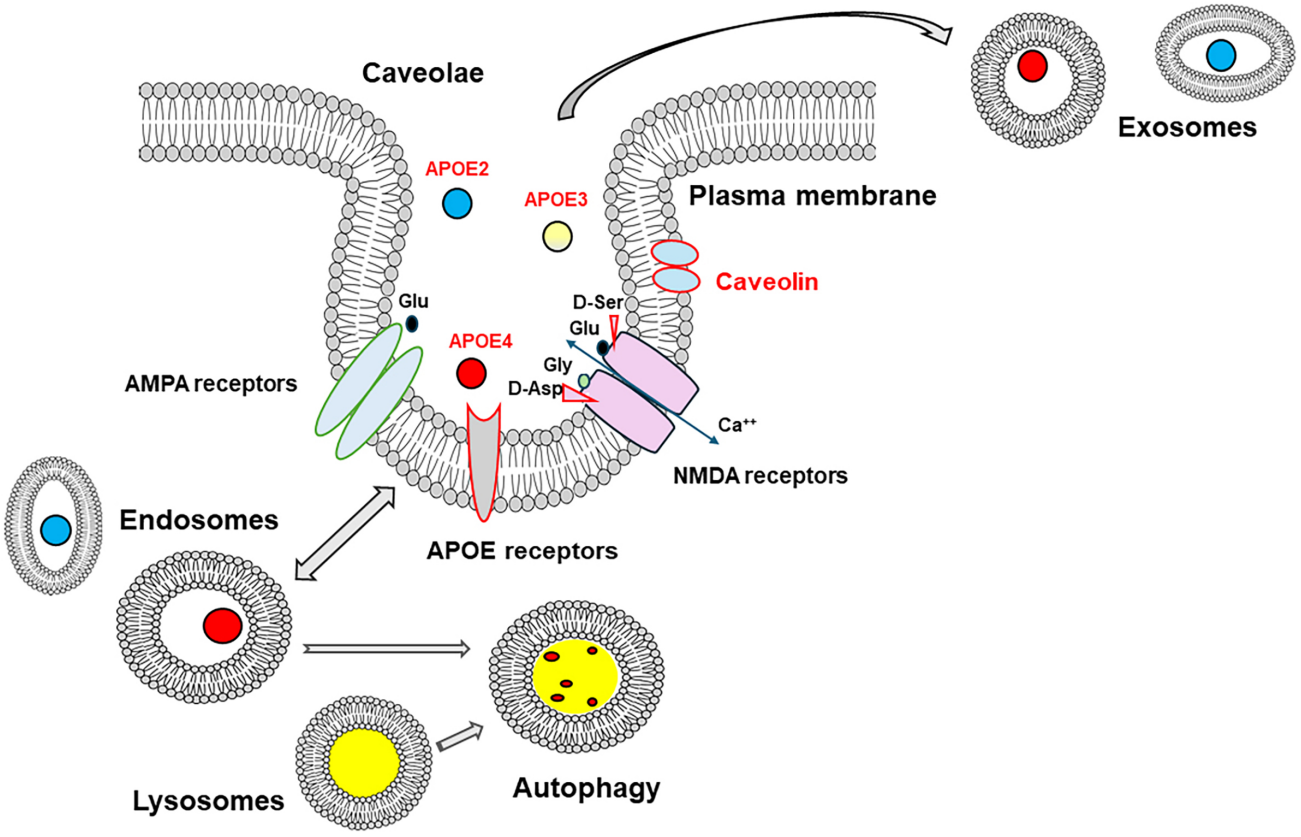

Fig. 2. Schematic representation of caveolae, endosomes, and exosomes. A graphic representation of caveolae associated with APOE receptors and caveolins, with several associated signaling molecules including AMPA and NMDA receptors. Several exosomes and endosomes functionally linked to caveolae are also indicated. For example, APOE could be transferred to endosomes from exosomes or *vice versa*, allowing them to be degraded with lysosomes in some situations. Note that some critical pathways for developing various disease-related signaling have been omitted for clarity. Abbreviation: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA, N-methyl-d-aspartic acid; APOE, apolipoprotein E. This illustration was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA).

disease [31]. Caveolin family proteins, including caveolin-1, caveolin-2, and caveolin-3, are identified as the basic protein components of caveolae in mammalian cells. While caveolin-1 and caveolin-3 are critical for the formation of caveolae in non-muscle cells and muscle cells, respectively, the necessity of caveolin-2 to make caveolae may be controversial [32]. Caveolae are a group of specific membrane microdomains that are characterized by their enrichment with cholesterol and sphingolipids [33]. Both the expression of caveolin-1 and the formation of caveolae are dependent on cellular cholesterol levels [34]. In general, caveolin-1 is a high-affinity cholesterol binding protein [35]. In addition, caveolin-1 has been implicated in cooperating with many lipid transporters [36]. Interestingly, specific pH conditions can expedite cell-to-cell communication via several exosomes, thereby supporting the exchange of specific molecules including caveolin-1 [37]. Caveolin-1 is also considered a scaffolding protein that functions within caveolae, which might exist beyond the plasma membrane in many subcellular compartments. Notably, cholesterol can promote the clustering of amyloid precursor protein in lipid rafts, leading to endocytosis and amyloid-β production [38]. In addition, caveolae and/or caveolins have been suggested to be important for α-secretase cleavage of amyloid precursor protein even in non-neuronal cells [39]. Interestingly, cholesterol accumulation with APOE4 in Alzheimer's disease could induce caveolin-1 expression, which can trap the ABCA1 in lysosomes to activate mammalian/mechanistic target of rapamycin complex1 (mTORC1) pathways leading to cellular senescence [31,40]. However, whether cellular senescence is a cause or consequence of neurodegeneration remains unclear. Removing senescent cells might ameliorate the pathology of neurodegenerative diseases.

APOE and Caveolin Proteins Involved in the Regulation of Autophagy

The APOE family proteins are considered principal cholesterol transporters, and they are mainly expressed in astrocytes in the CNS. In addition, neurons and microglia

can also express these proteins under stress conditions [41]. Several *APOE* genes, especially the *APOE4* gene, are a vital genetic risk factor for several neurodegenerative disorders. Mice expressing the *APOE4* gene display increased proinflammatory cytokines after lipopolysaccharide (LPS) treatment [42]. APOE4 protein has also been associated with vigorous mitochondrial impairment, which may be involved in oxidative stress-response processes [43]. Interestingly, it has been shown that the APOE4 protein can impair the basal autophagy flux [44]. Caveolin-1 deficiency has also been shown to promote basal autophagy by enhancing lysosomal functioning [45]. In addition, caveolin-1 may activate autophagy by binding to the beclin-1/vacuolar protein sorting 34 (VPS34) complex in response to oxidative stress [46]. Current evidence suggests that caveolin-1 can regulate several functions of autophagy in various organs, including the brain, liver, lung, and/or heart [47]. A phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian/mechanistic target of rapamycin (mTOR) signaling pathway has been recognized as an important upstream regulator of autophagy [48]. Moreover, it has been shown that this PI3K/AKT/mTOR signaling pathway could also be involved in the control of neuroprotection [49]. The repression of the PI3K/AKT/mTOR pathway might promote autophagy while activating this pathway could inhibit autophagy [36]. Therefore, the dysregulation of this signaling pathway has repeatedly been reported in various neurodegenerative pathologies [50]. The mTOR is a serine/threonine protein kinase, and there are two types of mTOR complexes, named mTORC1 and mTORC2. mTORC1 is considered a central negative regulator of autophagy, and the PI3K/AKT signaling pathway might be the main upstream modulator of mTORC1 [51]. mTORC2 seems to function as a controller of cytoskeleton organization [52]. Additionally, the mTORC1 can drive downstream activation of a eukaryotic translation initiation factor 4E (eIF4) complex, which subsequently inhibits apoptosis, regulates the cell cycle, and/or supports tumorigenesis [53]. Caveolins are one of the scaffold proteins associated with several signal transduction pathways, which could also regulate cell apoptosis, inflammation, and oxidative stress by regulating the PI3K/AKT signaling pathway [54,55]. It has been shown that caveolin-1 upregulation could inhibit autophagy-induced apoptosis via the PI3K/AKT signaling pathway [56]. Similarly, several APOE signals can also activate the PI3K/AKT pathway that prevents autophagic degradation for preventing lipid peroxidation [57]. In line with this, it has been shown that PI3K/AKT signaling is characteristically regulated by some of the APOE isoforms [58]. Interestingly, docosahexaenoic acid (DHA), a polyunsaturated fatty acid, may directly alter the plasma membrane composition, increasing neuronal survival by modulating the PI3K/AKT signaling pathway [59]. Therefore, upstream factors involved in autophagy regulation, including unc51-like autophagy activating kinase 1 (ULK1), beclin-1, and mTOR might be altered by the DHA treatment of cells [60]. The PI3K/AKT, mTOR, and/or 5′ adenosine monophosphate-activated protein kinase (AMPK) pathways are standard autophagy signaling pathways.

Autophagy and Exosomes/Endosomes Involved in the Pathogenesis of Neurodegenerative Diseases

Autophagy is an essential component of cell-immunity delivering intracellular pathogens, including cytosolic bacteria and/or viruses, to lysosomes for degradation. Some genetic mutations in components of the autophagy pathway might result in inflammatory and/or neurodegenerative disorders [61]. In fact, autophagy is a process that ultimately degrades the cytoplasmic damaged proteins or organelles, which may possibly be impaired in Alzheimer's disease [62]. Autophagy is initiated by a membranous organelle. This autophagosome becomes a two-layer membrane structure, which packages cytoplasmic proteins and/or damaged organelle components. A lysosome combines with the outer membrane, which can create an autolysosome that digests the packaged damaged contents [63]. At present, autophagy is a possible target for the therapy of Alzheimer's disease [64]. For example, greater autophagy might be effective in cleaning up amyloid-β deposition [65]. However, excessive autophagy could damage some normal neurons, which can aggravate the disease progression [66]. Interestingly, exosomes from mesenchymal stem cells can promote autophagy of neurons, which alleviates symptoms of Parkinson's disease [67]. Conversely, dysfunction of the autophagy machinery leads to the accumulation of abnormal proteins and/or damaged organelles, which could be connected to several human diseases such as neurodegenerative diseases, diabetes, autoimmune diseases, cancers, and infections [68]. Restoration of microglial autophagy has been shown to be critical for modifying neurodegeneration [69,70]. In particular, mitophagy is a crucial process for mitochondrial quality control, its failure might lead to the accumulation of damaged mitochondria, causing a risk of damage to neuronal cells [71]. Studies have indicated that mitophagy dysfunction is a crucial factor in the incidence of various neurodegenerative diseases such as Parkinson's disease, ALS, and/or Alzheimer's disease [67,70,71]. This mitophagy is considered as a specialized form of autophagy, selectively reducing damaged mitochondria. Mitophagy could play an indispensable role in various cellular processes, such as apoptosis, mitochondrial turnover, and/or inflammation. In fact, mitochondria dynamics have also been linked to many human diseases including neurodegenerative diseases such as Alzheimer's disease and/or Parkinson's disease [72]. Additionally, a positive

correlation between mitochondrial health and individual longevity has been recognized in various model systems [73].

There is also growing evidence indicating that exosomes have multifaceted functions in Alzheimer's disease. Exosomes have dual roles; they may contribute to neuronal cell death but can also help to alleviate the pathological progression of the disease [74]. Exosomes in the CNS could transmit some messages locally inside cells and broadly across the brain via the cerebrospinal fluid (CSF) [75]. Exosomes, for example, containing specific cargoes with proteins, lipids, and/or nucleic acid molecules might be distantly conveyed from donor cells to recipient cells through mechanisms like endocytosis and/or plasma membrane fusion [76]. Additionally, exosomes are carrier vehicles that can move vigorously between cells, expediting the exchange of important material and/or information. Several key cells within CNS, for instance, neurons, microglia, astrocytes, and oligodendrocytes release exosomes, which may have positive or undesirable effects in both healthy and disease conditions [77]. For example, exosomes have been shown to play a vital role in the formation as well as distribution of senile plaques and intracellular neurofibrillary tangles, which are characterized by the extracellular amyloid-β protein and the hyper-phosphorylation of tau protein in the pathology of Alzheimer's disease [78]. However, exosomes can support the clearance of amyloid-β protein, conveying amyloid-β protein to degrading lysosomes within microglia [79]. Additionally, exosomes might be valuable as accurate biomarkers for Alzheimer's disease. The neuronal endosomal system is fundamentally susceptible during aging, and the APOE4 protein could exacerbate this susceptibility by promoting the enlargement of early endosomes and decreasing exosomal release in the CNS of humans and/or mice [79,80]. In contrast to the early endosome enlargement shown in Alzheimer's disease, the abundance of early endosomes has been detected within cortical neurons of aged *APOE2* targeted-replacement mice [80]. With enhanced technological advancement and scientific understanding, the therapeutic potential of endosomes/exosomes could be further realized.

Strategies Involving Improved Diet and Gut-Microbiota for the Superior Treatment of Various Neurodegenerative Diseases

The bidirectional regulation between the gut microbiota and brain, known as the gut-brain axis, has received significant attention. Recent research has revealed the potential implications of gut-brain axis communication mediated by the gut microbiota and their products in various diseases, including Alzheimer's disease [81]. Compounds associated with the gut microbiota include D-amino acids, neurotransmitters such as dopamine, GABA, norepinephrine, serotonin, and/or lipids such as omega-3 fatty acids [82]. It has been shown that gut dysbiosis could promote aggravation and/or expansion of neuropathies from the peripheral nervous system to the CNS, contributing to the development of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and/or ALS [83]. Gut dysbiosis has been identified as a crucial factor in Alzheimer's disease-development for *APOE4* genetic carriers. Interestingly, inulin has been shown to have the potential to mitigate dysbiosis [84]. Again, the correlation between gut microbiota and the *APOE4* gene in Alzheimer's disease has been reported previously [85].

Pathogenic and/or non-pathogenic species of bacteria could release exosomes, ranging in size from 10 to 300 nm, containing several bacterial proteins, lipoproteins, phospholipids, and LPS, as well as cytoplasmic proteins and DNAs [86]. Of noteworthy interest are exosomes secreted by the gut bacteria, comparable to, yet distinct from, mammalian exosomes, as they develop from the maturing bacterial outer membrane [87,88]. These bacterial exosomes have appeared as novel correspondents within the gut-brain axis, interacting with the host brain via neural pathways [89]. For example, some exosomes from *Helicobacter pylori* can cross the BBB of CNS, causing neuroinflammation through mechanisms involving glial cell activation and possibly causing amyloidogenic pathology [90]. Moreover, neurotoxic exosomes from several pathogens, including *Pseudomonas aeruginosa* contain toxic components such as LPS that can induce a vigorous immune response in the CNS [91]. In contrast, some exosomes from commensal bacteria with probiotic features exhibit therapeutic potential. For example, exosomes from *Lactobacillus plantarum* can decrease amyloid-β-provoked neuropathology in experimental models of Alzheimer's disease [92]. Furthermore, bacterial exosomes generally play significant roles in nutrient acquisition, stress response, biofilm formation, bacterial survival, horizontal gene transfer, and/or antibiotic resistance [93]. In addition, the crosstalk between gut microbiota and the host brain might be important in the development of neurodegenerative diseases, suggesting that changing the gut microbiome could have potential as a therapeutic tactic for neurodegenerative diseases [94]. Furthermore, the occurrence of exosomal transfer may physiologically be regulated by fasting and/or overweight, suggesting that exosomes could partake in the tissue/organ response to alterations in the nutrient condition of the host [95].

Icariin is a flavonoid isolated from *Epimedii Herba*, also termed *Berberidaceae*, which may have beneficial cardioprotective effects. For patients receiving anthracycline chemotherapy against malignancy, icariin may reduce cardiotoxicity by decreasing oxidative stress and through the modulation of caveolin-1 expression levels, thereby promoting the survival of cardiac cells [96]. Interestingly, it has been shown that planned exercise could increase the number of caveolae in the smooth muscles of the intestine, thereby increasing the relative abundance of *Bifidobacte-*

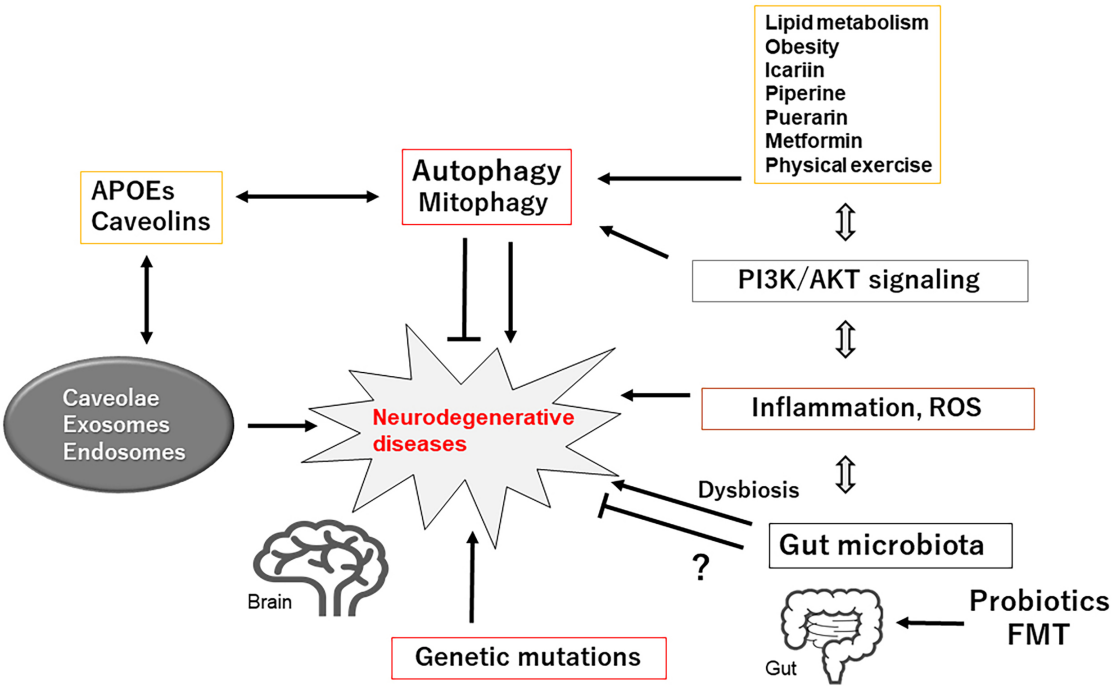

Fig. 3. A hypothetical overview of the neurodegenerative diseases. Caveolae, exosomes, and endosomes with APOE and caveolin proteins might play important roles in regulating the neuron-damaging process for neurodegenerative diseases. Several probiotics and/or FMT could contribute to the modification of gut microbiota, which could also be helpful for the treatment of neurodegenerative diseases. Several activities such as the inflammatory reaction, autophagy regulation, and/or ROS production have been omitted for clarity. Stimulatory effects are indicated with arrows; inhibitory effects with a hammerhead. "?" indicates the author's speculation. Abbreviation: ROS, reactive oxygen species; FMT, fecal microbiota transplantation. This illustration was created using Microsoft PowerPoint 2013 (Microsoft Corporation, Redmond, WA, USA).

ria in the gut microbiome, which correlates with the AKT levels in the gut [97]. In addition, piperine could also protect neurons by activating autophagy, which is related to the control of the PI3K/AKT/mTOR signaling pathway [98]. Furthermore, puerarin, an isoflavone belonging to the flavonoid family, is a bioactive component extracted from *Puerariae radix*, and may possess a protective effect on neurons in the substantia nigra in the brain, suggesting that puerarin could improve Parkinson's disease through neuroprotection and/or antioxidant effects. The neuroprotective effect of puerarin might also be related to the regulation of the PI3K/AKT signal pathway [99]. The regulation of the gut microbiota by puerarin is a possible mechanism for the treatment of Parkinson's disease [100]. These neuroprotective mechanisms of dietary factors seem to be related not only to restoring homeostasis of gut microbiota, but also to the modulation of PI3K/AKT signaling in order to adjust the autophagy condition (Fig. 3).

Future Perspectives

The complicated ecosystem of the gut microbiome is considered a crucial contributor to the homeostasis of the host body, extending its effect beyond the gastrointestinal tract to modulate immune, neurological, and metabolic functions [101]. In line with this, necessary evidence highlights the vital role of the gut microbiota in sustaining general health, especially health in the CNS [102]. In addition, many studies have revealed that gut microbiota dysfunction or imbalance is strongly related to the disease progression of several maladies including neurodegenerative diseases, endocrine diseases, cardiovascular diseases, and/or tumorigenesis [101–103]. With the recognition of the critical role of gut microbiota in both health and disease progression, attempts to modulate its composition have attracted special attention to the development of innovative treatments against those maladies. Furthermore, the gut microbiome regulates of mental health and/or social behavior [104]. Some clinical studies have demonstrated that supplementation with *Lactobacilli*- and/or *Bifidobacteria*-based probiotics can improve cognitive, sensory, and emotional functions in subjects with Alzheimer's disease [103–105]. Certain herbal products can restore dysbiosis, which could also be effective in counteracting the onset of Alzheimer's disease independent of their action of radical scavenging; this indicates that alteration of gut microbiota, with probiotics and prebiotics, could prevent or slow down the progression of neurodegenerative diseases, acting outside the CNS [105]. Notably, herbal medicine can mitigate the progression of neurodegenerative diseases by regulating the gut

microbiota, and has been applied to treat various diseases worldwide for hundreds of years [106]. For example, it is well-known that curcumin and its metabolites seem to promote health benefits by reducing gut dysbiosis. In addition, curcumin undergoes enzymatic modifications by gut microbiota, possibly creating metabolites that are more favorable to humans. The possibility of using herbal medicine in microbiome-targeted therapies may be encouraging for treating disease [107]. In addition, these are frequently inexpensive, safe, and easily accessible, which might also be advantageous. Interestingly, recent findings have shown that gut dysbiosis may be induced by hippocampal myelin damage, which could also be reversed by myelin-targeted drugs [82,108], suggesting that functional impairments of the brain, including neurodegenerative diseases could hamper the regulation of systemic homeostasis by positive gut microbiota. Novel treatments will soon be discovered for targeted therapy on gut-brain axis-related diseases such as neurodegenerative diseases. The important roles of next-generation probiotics for favorable gut microbiota in support of intestinal integrity and homeostasis should be underlined [109]. Therefore, an in-depth understanding of the potential mechanisms by which herbal medicine can regulate the gut microbiota in treating neurodegenerative diseases might help explain the detailed pathogenesis of neurodegenerative diseases [110].

At synapses, glutamate can bind to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-d-aspartic acid (NMDA) receptors. AMPA receptors regulate fast synaptic transmission under resting conditions. In contrast, NMDA receptors regulate the Ca^{2+} flux, which in turn controls long-term potentiation (LTP) and/or long-term depression (LTD) by modulating synaptic mRNA translation [111]. In this regard, APOE proteins regulate neuronal synapse excitability via the AMPA and NMDA receptors [112] (Fig. 2). Interestingly, specific dietary factors can contribute to the synaptic signatures in mouse models of Alzheimer's disease independent of amyloid and/or tau pathology [113]. In addition, advanced glycation end products (AGEs) can accelerate atherosclerosis by activating the caveolin-1/nuclear factor kappa-B (NF-κB) axis of inflammation [114]. Therefore, atherosclerosis could exacerbate Alzheimer's disease [115]. In addition, neurodegeneration and atherosclerosis are well-known within the spectrum of aging-related disorders [116]. A more complete understanding of the molecular mechanisms has great clinical potential for the use of therapeutic dietary modification against various neurodegenerative diseases.

Conclusions

Caveolae, endosomes, and exosomes are structural cholesterol-rich microdomains involved in effective signal transduction, which appear to be involved in a wide range of neurodegenerative diseases including Alzheimer's disease. It has been revealed that significant functions of these structures can be detected in various cell types of the CNS including microglia, astrocytes, oligodendrocytes, and/or neurons. Based on the available evidence and/or reconstitution of caveolae, endosomes, and exosomes with the adjustment of autophagy signaling, these structures could be a promising treatment strategy for a wide range of neurodegenerative diseases.

Abbreviations

ABCA1, ATP-binding cassette transport A1; AKT, protein kinase B; ALS, amyotrophic lateral sclerosis; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AMPK, 5′ adenosine monophosphate-activated protein kinase; APOE, Apolipoprotein E; APOE4, Apolipoprotein E ε4 allele; CNS, central nervous system; CSF, cerebrospinal fluid; DHA, docosahexaenoic acid; FMT, fecal microbiota transplantation; GABA, gamma-aminobutyric acid; LPS, lipopolysaccharide; LTD, long-term depression; LTP, long-term potentiation; mTOR, mammalian/mechanistic target of rapamycin; mTORC1, mammalian/mechanistic target of rapamycin complex1; NMDA, N-methyl-d-aspartic acid; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; ULK1, unc51-like autophagy activating kinase 1; VPS34, vacuolar protein sorting 34.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, MN, AF, SY, NS, and SM; original draft preparation and editing, MN, and SM; visualization, MN and SM; supervision, SM. Each author (MN, NS, AF, SY, and SM) has participated sufficiently in this work of drafting the article and revising the article for the important rational content. Then, all authors gave final approval of the version to be submitted. Finally, all authors have read and agreed to the published version of the manuscript. All authors (MN, NS, AF, SY, and SM) have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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