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Review Article

Autophagy and Signaling Pathways in Cognitive Decline: Emerging Therapeutic Approaches for Aging and Neurodegenerative Diseases

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ABSTRACT

Cognitive decline is a common issue linked to aging and various neurodegenerative diseases, significantly affecting quality of life and overall health. This decline results from several interconnected mechanisms, including imbalances in proteostasis, calcium dysregulation, telomere malfunction, mitochondrial dysfunction, stem cell depletion, and epigenetic changes. These factors contribute to the gradual worsening of cognitive function, underscoring the complexity of the aging brain and the difficulty in developing effective treatments. A critical process involved in cognitive decline is autophagy, a cellular mechanism responsible for degrading and recycling damaged or misfolded proteins and organelles. Autophagy is regulated by multiple signaling pathways, such as phosphoinositide-3-kinase/protein kinase B/mammalian (or mechanistic) target of rapamycin (PI3K-AKT-mTOR) pathway, which inhibits autophagy under nutrient-rich conditions, and the adenosine monophosphate-activated protein kinase, mTOR, and UNC-51-like kinase 1/2 (AMPK-mTOR-ULK1/2) pathway, which promotes autophagy during energy stress. Sirtuins (SIRT), a family of nicotinamide adenine dinucleotide (NAD)+-dependent deacetylases, and transcription factor EB (TFEB), a key regulator of lysosomal biogenesis and autophagy, play essential roles in maintaining cellular balance and protecting against cognitive decline. Given the central role of autophagy in maintaining neuronal health, targeting these regulatory pathways has become a promising strategy for mitigating cognitive decline. Pharmacological modulation of autophagy-related pathways, such as activating AMPK or SIRT1 or inhibiting mTOR, could potentially enhance autophagic activity, thereby reducing the buildup of toxic proteins and improving cognitive function. As research progresses, these approaches may provide new opportunities for treating neurodegenerative diseases and age-related cognitive impairments.

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1. INTRODUCTION

The process of aging is an unavoidable and indisputable phenomenon that affects every facet of our lives. It is linked to a wide array of physiological and psychological alterations, including a decrease in cognitive function that leads to a reduction in self-sufficiency and a diminished standard of living.[1] From a biological standpoint, the process of aging can be attributed to the gradual accumulation of diverse forms of damage protein at the molecular and cellular levels. Over time, this accumulation leads to a progressive decline in physical and mental capabilities, as well as an elevated susceptibility to various diseases.[2] Cognitive functioning typically encompasses a range of mental abilities, such as cognition, learning, language proficiency, reasoning, attention and focus, and visuospatial processing. Numerous theoretical and empirical studies have consistently indicated that cognitive functioning tends to diminish as individuals age, leading to a higher susceptibility among older adults to experience cognition-related challenges, such as cognitive impairment. The aging population is experiencing a significant rise, leading to a notable increase in age-related cognitive decline and dementia, including Alzheimer's disease (AD). This has emerged as a critical health burden. India is expected to encounter significant public health and socioeconomic challenges due to a larger proportion of older individuals experiencing mental health issues and cognitive decline. In addition, cognitive disabilities have a significant impact not only on the individual but also on the family, healthcare providers, and society as a whole. These disabilities can result in substantial physical, emotional, and economic challenges.[3]

Numerous mechanism, including proteostasis, calcium dysregulation, telomere malfunction, mitochondrial dysfunction, stem cell depletion, and epigenetic modifications, have been identified to be associated with cognitive decline.[4] For instance, initial research findings have indicated the elevated intracellular free calcium ions in relation to the aging related cognitive decline.[5] Similarly, mitochondrial dysfunction is another mechanism involved in cognitive decline. Mitochondria play a crucial role in cellular survival, particularly in neurons, by generating the necessary energy for a wide range of cellular functions.[6] The brain and muscles are highly vulnerable to impaired mitochondrial function.[7] Research on the impact of aging on mitochondria has identified several age-related alterations. These include changes such as mitochondrial enlargement or fragmentation, increased occurrence of mitochondria with depolarized membranes, and impaired handling of calcium ions.[8,9] Another crucial mechanism of cognitive decline is telomeric dysfunction. The telomere structure is comprised of repetitive sequences of non-coding nitrogenous bases, specifically 5'-TTAGGG-3'. The primary roles of a telomere include the preservation of chromosomal stability and the prevention of chromosomal degradation. In addition, telomeres serve the crucial function of safeguarding the chromosome ends against DNA end-joining events, preventing intrachromosomal fusion, as well as protecting against DNA damage response and unintended DNA recombination.[10] The phenomenon of age-related telomere shortening has been suggested as a potential factor in the development of neuronal dysfunction, cellular senescence and cognitive decline among elderly individuals.[11,12] The role of telomeres in cognitive decline has been attributed to telomere attrition and telomerase expression, which have emerged as novel mechanisms and potential therapeutic targets.[13]

Similarly, stem cell exhaustion is another mechanism that is known to contribute to cognitive decline. Neural stem cells are present throughout the lifespan of mammals and are located within specific regions of the brain, including the sub-granular zone of the hippocampus, the subventricular zone of the lateral ventricles,[14] and a more recently discovered pool in the hypothalamus[15] where they maintain the capacity for self-renewal and maturation into new neurons and glia. The decline of adult hippocampal neurogenesis is a significant factor in the cognitive deterioration and development of neurodegenerative diseases that occur with age.[16] Furthermore, epigenetic mechanisms play a crucial role in regulating gene transcription within individual cells by modulating chromatin structure, DNA modifications, chromatin accessibility and regulation of transcription during the process of memory formation in the brain. Significantly, alterations in these mechanisms associated with age have been extensively linked to memory decline throughout the entire lifespan.[17] The deterioration of proteostasis is a significant aspect of the aging process, indicating that the age-related decline in the capacity to refold or degrade damaged proteins may play a role in the exponential increase in dementia incidence observed with advancing age.[18] Consequently, this review emphasizes autophagy as a key mechanism of proteostasis and explores its potential as a therapeutic target for mitigating cognitive decline associated with aging or neurodegenerative diseases.

2. LOSS OF PROTEOSTASIS AS A MECHANISM OF COGNITIVE DECLINE

Proteostasis refers to the process of maintaining the proteome's homeostasis through the regulation of protein synthesis, translocation (if necessary), post-translational modifications (if needed to stabilize folded states), folding, and degradation or conversion of toxic oligomers into less harmful amyloid aggregates.[19]

The functionality of proteins is primarily determined by their ability to adopt specific three-dimensional structures through folding within physiological time scales. Cells have evolved sophisticated mechanisms to effectively regulate and preserve the proper folding of proteins. These mechanisms encompass intricate three-dimensional structural patterns as well as specific disordered domains. However, despite the high efficiency of the process, there is always a potential for failure in this precise mechanism. As a result, the occurrence of protein misfolding into a non-native state becomes a plausible outcome. Cells have evolved diverse mechanisms to ensure the preservation of native protein folding. These mechanisms involve intricate chaperone and quality control networks that are capable of addressing protein, organelle, or cellular damage. On a smaller scale, the monitoring of individual protein integrity occurs during their synthesis in ribosomes, in conjunction with co-translational chaperone function. At a broader level, cells employ compartmentalized defense mechanisms and networks of communication that facilitate intercellular signaling. This enables cells to effectively respond to alterations in proteome homeostasis. Collectively, these stratified defenses contribute to the safeguarding of cells against disturbances in protein folding and degradation, thereby preventing the occurrence of misfolded proteins and detrimental consequences.[20] These mechanisms involve chaperones, proteasome and autophagy.

Chaperones are proteins that are present in all cellular compartments and are responsible for maintaining protein homeostasis. An illustrative instance involves a thoroughly researched category of prevalent chaperones referred to as heat-shock proteins. These chaperones are primarily located in the cytoplasm, rely on ATP for their functioning, and frequently operate within a protein network or follow a sequential pathway. Chaperones play a crucial role in the process of binding nascent protein chains, thereby preventing their aggregation. Additionally, they facilitate the formation of secondary and tertiary structures, which are essential for achieving the stable conformations necessary for proper protein function. Chaperones also have a role in regulating the states of active and inactive functional proteins, as well as in subsequent protein processing events such as proteolytic cleavage and post-translational modification. Chaperones play a crucial role in the process of protein unfolding and delivery, working in close collaboration with ubiquitin ligase complexes and proteases to facilitate protein degradation pathways.[21]

The proteasome is an intracellular protease that plays a crucial role in the degradation of the majority of intracellular proteins. The proteasome primarily facilitates the degradation of oxidized, aggregated, and misfolded proteins.[22] The functionality of the proteasome diminishes with age in various tissues, including the nervous system. Furthermore, it is believed that this decline could potentially contribute to cognitive declines associated with aging. However, it has been observed that enhancing the proteasome system may potentially mitigate cognitive impairments associated with aging.[23] The ubiquitin-proteasome system (UPS) is a significant regulatory pathway involved in the identification and elimination of abnormal or damaged proteins. It also plays a crucial role in regulating short-lived proteins in response to both intracellular and extracellular signals. The UPS operates by attaching polyubiquitin chains to target proteins, which subsequently act as a signal for the degradation and proteolysis of the target proteins by proteasomes. Ubiquitin ligases play a crucial role in protein degradation by attaching polyubiquitin chains to target proteins, thereby marking them for subsequent processing by the 26S proteasome. The 26S complex is comprised of a 20S catalytic core and two 19S regulatory particles. These regulatory particles contain subunits that are responsible for recognizing polyubiquitinated targets or regulating the catalytic activity of the 20S core. It is noteworthy that dysfunctions within the UPS have been linked to neurodegenerative diseases, including AD and Parkinson's disease (PD).[24]

3. AUTOPHAGY MEDIATED PROTEOSTASIS

Autophagy is a cellular catabolic pathway that involves the degradation of cellular components from the cytoplasm through lysosomal processes. The process of autophagy is initiated by the development of autophagosomes, which are double-membrane vesicles responsible for engulfing various substances, including misfolded proteins and damaged organelles. Subsequently, the autophagosomes undergo fusion with lysosomes in order to facilitate the process of breakdown and recycling of their contents. The process of basal autophagy is of utmost importance in preserving cellular integrity through the regulation of quality control mechanisms. Additionally, it has the ability to be upregulated in response to various stressors.[25]

There are three pathways through which cytoplasmic contents are transported to lysosomes for the purpose of digestion and recycling. These pathways include microautophagy, chaperone-mediated autophagy, and macroautophagy. The three pathways commonly coexist within mammalian cells and exhibit distinct mechanisms for transporting cytoplasmic cargo to the lysosomal compartment.

Autophagy can further be categorized into two distinct forms: selective and non-selective autophagy. Non-selective autophagy, also known as bulk autophagy, is characterized by a lack of cargo specificity and can be triggered by a range of cellular stimuli, including energy and nutrient deprivation. Selective autophagy enhances the probability of

capturing cargo and facilitates the degradation of various substances, including aggregate-prone proteins (aggrephagy), intracellular pathogens (xenophagy), damaged mitochondria (mitophagy), lysosomes (lysophagy), excessive peroxisomes (pexophagy), and dysfunctional endoplasmic reticulum (ER-phagy).[26] It plays a significant role in maintaining intracellular homeostasis by selectively degrading cellular components that are unnecessary or potentially harmful to the survival of the cell. Autophagy plays a crucial role in the removal of unnecessary, defective, or aggregated proteins and damaged organelles. Additionally, it contributes to processes such as differentiation, cognition, and development. TFEB is widely recognized as the primary regulator of autophagy, as it governs the expression of genes essential for the biogenesis of autophagosomes and lysosomes. Numerous studies conducted on yeast have identified autophagy-related genes (ATG) proteins as the primary factors responsible for coordinating the initiation and progression of autophagy.[27]

The hippocampus plays a crucial role in the regulation of learning and memory within the mammalian brain. The process of memory formation and consolidation is dependent on the hippocampus's ability to integrate new stimuli through neuronal structural reorganization and plasticity. Autophagosomes have been observed to actively form in synapses and neuronal processes within hippocampal neurons by contributing to synaptic assembly, axonal growth, dopamine release, and long-term depression.[28]

Recent preclinical studies have established a correlation between the impairment of general autophagy or specific subtypes of autophagy and the development of pathological conditions, including progeria, accelerated aging diseases, neurodegenerative diseases, and various other disorders. It is worth noting that in certain diseases, while a particular subtype of selective autophagy may be impaired, there may be no alteration or even an increase in general autophagy. An instance of this is when the maintenance of cellular metabolic activity in aged cells helps to sustain hematopoietic stem cell function and prevents the destabilization of the neuronal proteome. In a similar vein, it is worth noting that mitophagy, a process that is diminished in both typical aging and AD, has been found to enhance the period of healthy aging and mitigate the detrimental effects of amyloid β and phosphorylated tau on memory function when activated in older tissues.[29]

3.1. Regulation of Autophagy

3.1.1. PI3K-AKT-mTOR signaling pathway

Autophagy regulation involves a variety of molecules and signalling pathways, with the PI3K-AKT-mTOR pathway being particularly important.[31] The pathway's major components include PI3K, AKT, and mTOR.[30]

PI3K is a growth factor-regulated phosphatidylinositol kinase that regulates autophagy, apoptosis, cell proliferation, differentiation, and vesicle trafficking inside the cell membrane. When activated, PI3K produces phosphatidylinositol 3,4,5-trisphosphate (PIP3) at the plasma membrane.[31,32] PIP3 functions as a secondary messenger, aiding the recruitment and activation of kinases such PI3K-dependent kinase-1 (PDK1) and the serine/threonine kinase AKT, also known as protein kinase B. PDK1 and mTOR2 phosphorylate AKT at various amino acid residues, which is essential for the phosphorylation of several additional target proteins that drive cell proliferation, differentiation, apoptosis, angiogenesis, and metabolism.[30]

The mammalian target of rapamycin complex 1 (mTORC1) complex is a major downstream effector of AKT. It has been demonstrated that activated AKT stimulates mTORC1 by phosphorylating tumour suppressor tuberous sclerosis 2 (TSC2), hence releasing inhibition of the GTPase RHEB (RAS homolog abundant in the brain) and activating mTORC1.[33]

mTORC1 inhibits autophagy by suppressing critical proteins such the ULK1/2 complex and vacuolar protein sorting 34 (VPS34) complex, which are essential for its start and development. Autophagy is effectively prevented in settings of high mTORC1 activation. When mTORC1 activity is lowered, which is commonly due to food deprivation or other stress signals, autophagy is activated.[34] To summarise, mTORC1 suppresses autophagy by phosphorylating and inhibiting the activity of the ULK1/2 and class III PtdIns3K complexes. Thus, the basic technique for experimentally inducing autophagy is to block mTORC1 activity, either through food deprivation or the administration of drugs such as rapamycin.[35]

3.1.2. AMPK-mTOR-ULK1/2

AMPK, a serine/threonine kinase in eukaryotic cells, plays a pivotal role in regulating cellular energy balance. AMPK serves as the primary sensor and regulator of cellular metabolism.[36] It is a heterotrimer composed of one catalytic subunit α (α1, α2), one scaffolding subunit β (β1, β2), and one regulatory subunit γ (γ1, γ2, and γ3), each encoded by distinct genes. When the ADP/ATP or AMP/ATP ratio increases, AMPK is activated, initiating a series of physiological regulatory processes. This activation enhances catabolic (ATP-generating) pathways while simultaneously reducing ATP consumption.[36] Various conditions such as metabolic stress, ischemia, pain, depression, inflammation, exercise, and neurodegenerative changes can trigger AMPK activation.[37]

AMPK, activated by phosphorylation of the Thr172 residue on the α subunit, inhibits anabolic pathways and promotes catabolic processes like autophagy. Over the last decade, research has mostly focused on the hypothesis that glucose restriction induces autophagy by activating AMPK. The conventional hypothesis proposes that AMPK phosphorylates and activates ULK1 to induce autophagy.[38]

When glucose levels are sufficient, AMPK is inactive and mTORC1 is activated. The active mTORC1 phosphorylates ULK1 on Ser757 to prevent it from interacting with and activating AMPK. During glucose shortage, active AMPK suppresses mTORC1[39] by phosphorylation and activation of the neagtive regulator TSC2[40] to relieves Ser757 phosphorylation, resulting in ULK1-AMPK interaction. AMPK then phosphorylates ULK1 at Ser317 and Ser777, activating ULK1 kinase and finally inducing autophagy[39]. Both mTORC1 and AMPK regulate autophagy via ULK1/2, a crucial inducer of the autophagosome-forming complex. AMPK promotes the self-eating mechanism by phosphorylating ULK1, whereas mTORC1 inhibits the self-eating process in nutrient-rich environments by phosphorylating ULK1. However, active ULK1 inhibits both AMPK and mTORC1. Furthermore, upon nutrient depletion, AMPK phosphorylates mTOR complex 1, inhibiting it directly.

In addition to AMPK's inhibition of mTORC1, it has recently been demonstrated experimentally and conceptually that mTORC1 also negatively affects AMPK, creating a double negative feedback loop in the regulatory network. As per a study, mTORC1 directly phosphorylates the AMPK α subunit at Ser345, downregulating AMPK and adversely influencing the cellular phosphorylation of the AMPK catalytic subunit at Thr172. When glucose is scarce, AMPK phosphorylates raptor directly or through the TSC1-TSC2 (hamartin-tuberin) complex to inhibit mTORC1. The dephosphorylation of ULK1 at the Ser757, Ser638, and Ser758 residues is necessary for this inhibition, which also causes the relationship between ULK1 and AMPK to intensify. Next, on various phosphorylation sites (such as Ser555, Ser777, Ser317, and Ser467), AMPK phosphorylates ULK1 therefore promoting autophagy.[41]

However, recent findings have challenged this model. Specifically, the inhibition of mTORC1 has been found to reduce AMPK-mediated phosphorylation of ULK1 at Ser556 (mouse Ser555), a modification believed to promote autophagy.[38] Additionally, nutrient deprivation was observed to decrease, rather than increase, the binding between AMPK and ULK1. Overactivation of AMPK has been linked to impairments in learning, memory, and synaptic plasticity, whereas inhibiting AMPK activity with a selective antagonist enhances hippocampal synaptic plasticity. Notably, pharmacological inhibition of AMPK activity has been shown to reverse AD-associated impairments in long-term potentiation and depression, two critical forms of synaptic plasticity that serve as cellular models for memory and cognition.[42] At present, it remains unclear whether the activation of AMPK during neurodegenerative disorders is beneficial or harmful. AMPK activity seems to have both neuroprotective and pro-apoptotic effects, which may vary depending on the specific neuronal subtype, the type of insult, as well as the intensity and duration of AMPK activation.[43]

3.1.3. SIRT

SIRT is a conserved family of NAD+-dependent class III histone deacetylases, originally recognized for their ability to remove acetyl groups from lysine residues on histone proteins. However, they also act on non-histone proteins and remove various acyl groups from lysine residues. As a result, sirtuins function as energy sensors and transcriptional regulators due to their NAD+-dependent influence on the acetylation state of histones and other transcriptional regulators.[44,45] SIRT1 plays a central role in regulating autophagy and can deacetylate p53 at Lysine residues (Lys373 and/or Lys382), protecting cells from DNA damage-induced apoptosis.[46] Through its deacetylase activity, SIRT1 is involved in regulating various autophagic proteins throughout the autophagic process. The levels and functions of SIRT1 are modulated by several signaling pathways, including AMPK, and some studies suggest that SIRT1 is regulated by ncRNAs. Additionally, SIRT2 influences the functionality of the autophagic system through acetylation, directly binding to TFEB to enhance its mRNA stability.[47] Mitochondrial sirtuins (mtSIRTs), including SIRT3–5, are involved in regulating energy metabolism and metabolic homeostasis through mitophagy. SIRT3 promotes autophagy by activating downstream signaling pathways such as the AMPK/ULK1 pathway, while overexpression of SIRT4 inhibits autophagy by activating the AKT/mTOR pathway. SIRT6 is also crucial for autophagy regulation; its overexpression induces autophagy by attenuating the insulin-like growth factor (IGF)/AKT/mTOR signaling pathway.[47] Sirtuins are particularly activated during calorie restriction and in the presence of the coenzyme NAD. SIRT1 and SIRT3 exhibit neuroprotective effects in neuronal nuclei and mitochondria, whereas SIRT2 is associated with neurodegeneration by affecting the acetylation level of amyloid precursor protein (APP), which is linked to AD. Therefore, therapeutic strategies that selectively activate SIRT1 and/or SIRT3, or inhibit SIRT2, may offer promising approaches for treating neurodegenerative conditions.[48]

3.1.4. TFEB

TFEB is widely acknowledged as the central regulator of autophagy, controlling the expression of genes

necessary for the formation of autophagosomes and lysosomes. TFEB plays a pivotal role in regulating numerous lysosome-related genes and is crucial for the fusion of autophagosomes with lysosomes, suggesting that SIRT2 influences various components of the autophagic process.[47] TFEB, a basic helix–loop–helix-leucine-zipper (bHLH-Zip) protein belonging to the microphthalmia/transcription factor E (MiT/TFE) family, is a key regulator of gene expression within the autophagy–lysosomal pathway. TFEB enhances autophagic flux by driving the formation of lysosomes, the creation of autophagosomes, and their subsequent fusion with lysosomes, thus aiding in the clearance of cellular substrates. Additionally, TFEB plays a role in selective autophagy and lysosomal exocytosis.[49] In response to various stressors, such as starvation, TFEB translocates from the cytosol to the nucleus, where it binds to the CLEAR-box sequence (5'-GTCACGTGAC-3') to enhance the expression of multiple autophagy-lysosome-related genes, thereby inducing autophagy. The activity of TFEB is primarily regulated by its phosphorylation status, which can be influenced by stressors like starvation, ER stress, DNA damage, oxidative stress, mitochondrial damage, pathogen infection, and exercise. During starvation, the inhibition of mTORC1 leads to the rapid dephosphorylation of TFEB, causing it to dissociate from the TFEB/14-3-3 complex. The unbound TFEB then translocates into the nucleus to promote autophagy and lysosome biogenesis. Additionally, TFEB activation can be regulated by the calcium-dependent phosphatase calcineurin. While TFEB's activity and nuclear accumulation are mainly controlled by its phosphorylation status, TFEB activation can also be influenced by reactive oxygen species (ROS)-dependent oxidation.[50] Numerous studies on yeast have identified autophagy-related gene (ATG) proteins as key factors in coordinating the initiation and progression of autophagy.[51]

4. OVERVIEW OF INTERPLAY BETWEEN DIFFERENT SIGNALLING PATHWAYS

Autophagy, a process where cells break down and recycle components, is controlled by the ULK1 complex, which includes proteins like ULK1/2, ATG101, ATG13, and FIP200. Two key pathways, AMPK and mTORC1, regulate autophagy initiation. AMPK activates, while mTORC1 inhibits this process. When autophagy starts, the ULK1 complex activates another complex (VPS34/PIK3C3), leading to the formation of structures called phagophores. These structures eventually become autophagosomes, which engulf cell debris. Two systems, ATG12 and ATG8/LC3, help expand phagophores into autophagosomes. Proteins like MAP1LC3B-II help capture materials for degradation. Finally, autophagosomes fuse with lysosomes, where the contents are broken down. mTORC1 also inhibits the final stages of autophagy and lysosome function by targeting TFEB, a transcription factor crucial for autophagy. Under stress (like starvation), TFEB moves into the nucleus to activate genes involved in autophagy. Other proteins and processes, such as phosphorylation and acetylation, also regulate TFEB and other transcription factors like FOXO3 and ATF4, which control autophagy-related genes 52 One important autophagy regulator is mTORC1. Multiple mechanisms exist for mTORC1 to regulate autophagy in mammalian cells. First off, in nutrient-rich environments, mTORC1 suppresses ULK complex formation, which stops ULK1 and AMPK from interacting and hence suppresses ULK1 activity. The regulation of autophagy is dependent on AMPK, which phosphorylates and activates ULK1 at Ser317/Ser777 when glucose is scarce. Furthermore, by controlling the transcription of genes necessary for autophagy, mTORC1 might indirectly suppress autophagy. One important transcriptional regulator of the genes involved in autophagy and lysosomal biogenesis is the TFEB. In order to prevent autophagy, mTORC1 directly phosphorylates TFEB at its Ser142 and Ser211 locations, keeping it in the cytoplasm. In order to inhibit one another, AMPK and AKT either directly or indirectly control mutual phosphorylation. When Thr172 is phosphorylated, AMPK is triggered. When Ser485/491, or Ser487/491 in humans, is phosphorylated, AMPK activity is inhibited by preventing Thr172 from being phosphorylated. Research has demonstrated that in several cell types, active AKT can directly phosphorylate Ser485/491, which inhibits AMPK. However, AKT activation can also be blunted in reverse by AMPK. AKT's activity is inhibited by AMPK activation, which dephosphorylates Ser473 and Thr308 of AKT.[53] SIRT3 promotes autophagy by activating downstream signaling pathways such as the AMPK/ULK1 pathway, while overexpression of SIRT4 inhibits autophagy by activating the AKT/mTOR pathway. SIRT6 is also crucial for autophagy regulation; its overexpression induces autophagy by attenuating the IGF/AKT/mTOR signaling pathway (Figure 2).[47]

5. DRUGS TARGETING AUTOPHAGY

Autophagy is closely linked to neurodegenerative diseases for two primary reasons. First, defects in the autophagic process can lead to neurodegeneration. Second, neurodegenerative diseases such as AD, PD, and Huntington's disease are characterized by the accumulation of toxic protein aggregates, which autophagy can degrade.[54] Several drugs already approved for human use, such as lithium, mTOR inhibitors (sirolimus/rapamycin, everolimus), and tyrosine kinase inhibitors (nilotinib), are known to enhance proteostasis.[55] Therapeutic strategies to modulate autophagy include dietary control, pharmacological methods, and genetic therapies. Notably, caloric restriction has the potential to induce autophagy by inhibiting mTOR signaling, a

key suppressor of autophagy. In mouse models of AD, stimulating autophagy through a 30% dietary restriction has led to significant improvements in cognitive function and reductions in amyloid-beta plaques and phosphorylated tau. However, long-term dietary restriction may be impractical for AD patients.[56]

5.1. Rapamycin and Analogues

Rapamycin, an antifungal antibiotic, anticancer cytostatic agent, and immunosuppressant approved by the US Food and Drug Administration, is known to inhibit mTOR signaling.[57] mTOR is also implicated in cognitive decline associated with aging. Long-term administration of rapamycin has been shown to improve age-related spatial memory deficits in C57Bl/6 mice. These improvements are linked to reduced mTOR signaling and brain inflammation, along with enhanced hippocampal NMDA signaling.[58] Rapamycin also prevents cognitive impairment and protects hippocampal neurons from Alzheimer's-like pathology and mitochondrial abnormalities. Additionally, rapamycin treatment has been found to normalize streptozotocin (STZ)-induced alterations by reducing hyperactivity of the mTOR/p70S6K pathway in the hippocampus.[59]

Temsirolimus, a rapamycin derivative, has shown a strong ability to stimulate autophagy and prevent neuronal death both in vitro and in animal models of neurodegenerative proteinopathies, such as those caused by polyglutamine expansions in huntingtin or ataxin-3. In transgenic mice overexpressing APP, a model for familial AD, temsirolimus treatment resulted in better cognitive and motor performance compared to untreated age-matched mutants.[60]

Everolimus, another analog of rapamycin, has been shown to inhibit mTORC1 activity, leading to improvements in vascular dementia by restoring the M1/M2 balance in microglia.[61] Everolimus-induced mTOR inhibition has also been reported to reduce levels of human APP/Aβ and tau, as well as to improve cognitive function and reduce depressive-like symptoms in 3×Tg-AD mice.[62] Additionally, another study suggested that everolimus could prevent or improve behavioral, biochemical, and histopathological deteriorations in the intracerebroventricular-STZ rat model of AD.[63]

5.2. Metformin

Metformin, a well-established first-line treatment for type 2 diabetes mellitus (T2DM), has also been shown to protect against cognitive decline in various neurodegenerative diseases. In one study, metformin pretreatment increased AMPK-mediated autophagy in lipopolysaccharide (LPS)-stimulated microglia and in the cortices of rats modeled for post-operative cognitive dysfunction (POCD). This pretreatment also led to improved cognitive function in the POCD model rats.[64] Metformin may additionally influence several other age-related adverse effects, such as neuronal dendritic regression, altered gene expression, and changes impacting hippocampal plasticity and the network activities that underlie cognitive and memory functions. It achieves these effects by acting on central metabolism and several key signaling pathways, including AMPK, mTOR, and PI3K-AKT. Metformin can also modulate the mTOR pathway through AMPK-independent mechanisms, such as inhibiting transcription factors and the PI3K/AKT pathway, as well as directly inhibiting mTORC1.[65,66] These actions contribute to its ability to regulate glucose metabolism, enhance mitochondriogenesis, and promote autophagy.[67] Additionally, metformin has been suggested to improve cognitive impairments in schizophrenia patients, partly due to enhanced functional connectivity in the dorsolateral prefrontal cortex.[68]

5.3. Dapaglitazone

Dapagliflozin, a selective and potent sodium-glucose co-transporter 2 (SGLT2) inhibitor, is commonly used to reduce hyperglycemia in patients with type 2 diabetes. It has also been shown to enhance cognitive function by stimulating hippocampal autophagy, as evidenced by decreased levels of sequestosome (SQSTM)-1/p62 and increased Beclin 1 expression. Additionally, treatment with dapagliflozin resulted in a decreased p-mTOR/total mTOR ratio and an increased p-AMPK/total AMPK ratio, indicating activation of the AMPK/mTOR signaling cascade.[69]

5.4. Nilotinib, Bosutinib and Mastinisib

Nilotinib, a c-Abl kinase inhibitor and AMPK modulator, has been reported to induce autophagy and slow disease progression in PD.[70] Bosutinib, another c-Abl inhibitor, has also demonstrated neuroprotective properties in both animal models and humans through AMPK modulation.[71] Masitinib, a potent inhibitor of several protein tyrosine kinases, including the stem-cell factor receptor (c-kit), is known to induce autophagy by inhibiting signaling pathways upstream of the PI3K/AKT/mTORC1 axis. Preclinical studies have shown some beneficial effects of masitinib in animal models of AD, although further research is needed to clarify how these effects are related to autophagy induction by the compound. Masitinib is currently under clinical investigation for the treatment of AD.[72]

5.5. Natural Compounds

Resveratrol (3,5,4'-trihydroxystilbene), a polyphenolic compound found abundantly in grapes and red wine, has the ability to modulate SIRT1 expression and

activity. Through the induction of SIRT1, resveratrol may promote neurite outgrowth and improve neural plasticity in the hippocampus. Additionally, resveratrol stimulates neurogenesis and mitochondrial biogenesis by enhancing AMPK, which is known to support neuronal differentiation and mitochondrial biogenesis.[73] It has also been suggested that resveratrol activates autophagy by inhibiting the AKT/mTOR pathway.[74]

Ginsenoside-Rg2, a bioactive compound derived from Panax ginseng, induces autophagy through an AMPK/ULK1-dependent mechanism. The protopanaxadiol derivative 1-(3,4-dimethoxyphenethyl)-3-(3-dehydroxyl-20(s)-protopanaxadiol-3β-yl)-urea (DDPU) enhances Aβ clearance by inducing autophagy via the PI3K/AKT/mTOR signaling pathway through PI3K inhibition. Berberine shows therapeutic potential in amyotrophic lateral sclerosis (ALS) by reversing TDP-43 proteinopathy, disrupting mTOR/p70S6K signaling, and stimulating autophagic degradation. Flavonoids like wogonin promote autophagy by inhibiting the AKT/mTOR pathway and increasing Aβ clearance. Curcumin is known to improve cognitive function by stimulating autophagy through downregulation of the PI3K/AKT/mTOR pathway.[75] Cubeben, a sesquiterpene from Piper cubeba, reduces Aβ toxicity in primary neuronal cells, restores autophagy via PI3K/AMPK signaling, and suppresses mTOR activity.[76] Epigallocatechin gallate, also known as (−)-epigallocatechin-3-O-gallate, is a polyphenol compound that induces mTOR-dependent autophagy in HEK293T cells and diminishes the impact of autophagy's negative regulators, such as GADD34, which control apoptosis. Fisetin (7,3',4'-flavon-3-ol), a flavonol in the flavonoid group, has been shown to inhibit mTOR activity and activate the mTOR repressor TSC2 by inhibiting AKT and activating AMPK. Lastly, ouabain, a cardiac glycoside that inhibits the sodium pump,[77] is known to induce autophagy by enhancing TFEB activity through mTOR inhibition[78] (Table 1, Figure 2).

6. CHALLENGES IN TRANSLATING AUTOPHAGY-TARGETING APPROACHES TO CLINICAL APPLICATIONS FOR COGNITIVE DECLINE

Enhancements of autophagy through genetics and pharmacology have demonstrated therapeutic potential in a number of neurodegenerative disease models, including AD. This has led to the discovery of novel anti-AD drugs that are chemical autophagy modulators. Despite the growing number of potential autophagy modulators, several challenges have prevented any from being effectively developed for clinical application.

• **Lack of specificity:** The main barrier to autophagy modulation is the described autophagy modulators' lack of specificity. Many of the chemical compounds that are employed to either stimulate or inhibit autophagy have poor pharmacological selectivity for the autophagy process's targets. For example, rapamycin inhibits mTORC1 with a rather high specificity when administered acutely, but it disassembles mTORC2 when administered chronically.[79]

• **Safety:** Long-term rapamycin or latrepirdine suppression of mTOR also averts AD-like cognitive impairments. However, it is noteworthy that many other essential physiological processes, including gene translation and cell proliferation, are mediated by the mTOR pathway. Long-term mTOR pathway suppression can cause toxic side effects in patients.

• **Autophagy induction not always beneficial:** Although more and more research suggests that the effect of autophagy regulation is context-dependent, autophagy induction is not always helpful. When contemplating autophagy modulation as a therapy, it is important to evaluate the autophagy deficiency, when to intervene, and the duration/strength of the modulation. According to recent research, autophagosomes may be a significant source of Aβ synthesis in the Alzheimer's brain. Inducing additional autophagosomes without increasing autophagic flow can result in increased Aβ synthesis and catabolic contents leaking from vacuoles.[80]

• **Need of understanding selective autophagy:** Currently, several types of selective autophagy have been identified, including mitophagy (mitochondria), ER-phagy (ER), aggrephagy (protein aggregates), and lipophagy, to mention a few. These selective forms of autophagy are frequently seen in specific types of cells/tissues, are triggered by specific stimuli, and are regulated by specific adaptors, making them particularly relevant to certain types of illnesses. Clearly, much more research is required to better understand these types of selective autophagy, from molecular mechanisms to functional consequences in health and illness.

• **Lack of proper tools:** The autophagy research field still faces one technological challenge: a lack of appropriate techniques for quantifying autophagic flux in vivo, particularly in human specimens. Such methods are crucial for converting autophagy information from bench to bedside, as we need to know whether autophagy activators or inhibitors should be used to treat patients with deficient or active autophagy under certain illness settings.[81]

• **Need of appropriate preclinical models:** The large number of unsuccessful clinical trials emphasises how critical it is to advance our knowledge of neural autophagy by selecting better preclinical models and techniques before attempting to predict human therapeutic efficacy.

Preclinical research and drug development are currently conducted primarily in animal models, despite the fact that many age-related disorders only affect humans. While these models are unavoidably significant, there is little use for them in simulating the ageing of the human brain and its neurones, as well as neurodegenerative disorders unique to humans.[82]

• Autophagy activators are being studied for their potential therapeutic use in neurodegenerative illnesses globally. However, researchers are still hunting for chemicals that not only promote the decomposition of stored, hazardous macromolecules, but are also safe and acceptable for long-term usage without causing serious side effects. The strategy of pharmacological stimulation of toxic macromolecule degradation is being tested using both cellular and animal models of neurodegenerative diseases, but due to the relatively recent onset of such studies, there are only a few completed clinical trials, and the majority of them are either ongoing or at the stage of patient recruitment.[83]

7. CURRENT STATUS OF AUTOPHAGY TARGETING DRUG IN COGNITION AMELIORATION RESEARCH

Although the role of autophagy in physiological processes and the pathogenesis of various diseases, including aging, is increasingly understood, there remains a lack of authentic pharmacological autophagy modulators in clinical practice. The only available options are drugs that were originally developed for other purposes but later found to influence autophagy.[84] Despite ongoing research efforts, no autophagy-selective drugs have yet reached clinical development.[85] Current strategies for modulating autophagy pharmacologically largely involve the broad induction of the entire

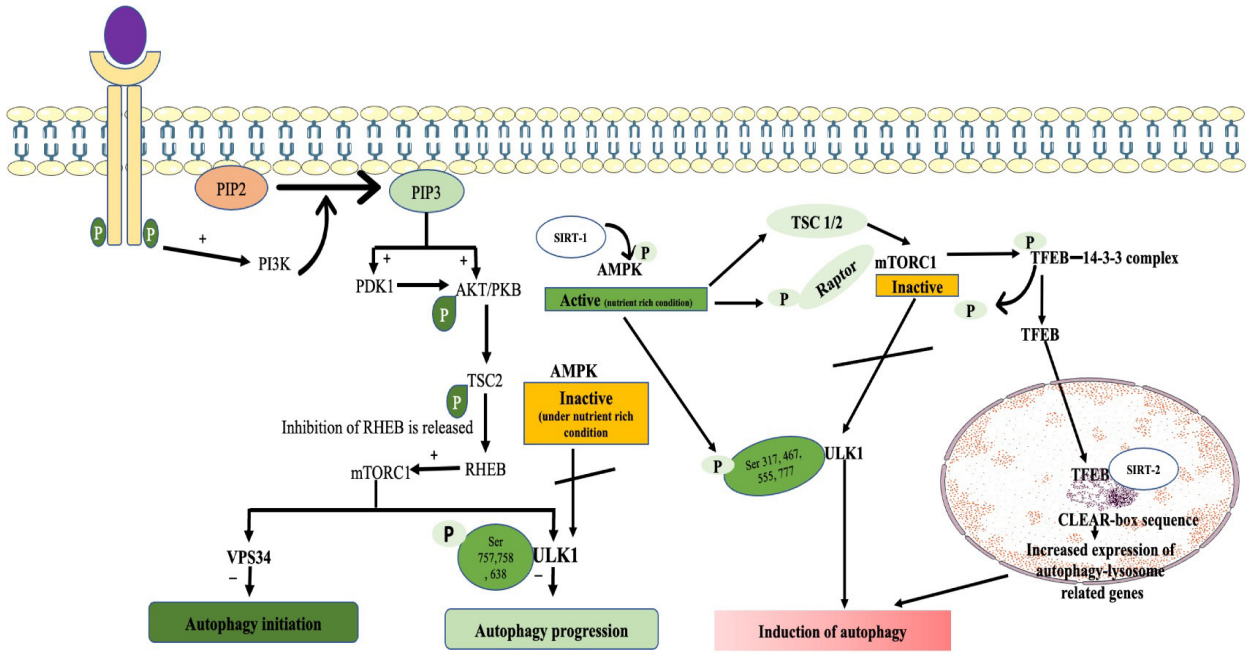
Table 1. Drugs, their mechanism related to autophagy and potential effects on cognitive functions

Drug	Mechanism related to autophagy	Effects
Rapamycin	• Inhibits mTOR1 activity • Reduce hyperactivity of the mTOR/p70S6K pathway in the hippocampus	• Prevents cognitive impairment and protects hippocampal neurons from Alzheimer's-like pathology and mitochondrial abnormalities
Temsirolimus	• Inhibits mTOR1 activity	• Better cognitive and motor performance
Everolimus	• Inhibit mTORC1 activity	• Improvements in vascular dementia by restoring the M1/M2 balance in microglia • Improve cognitive function and reduce depressive-like symptoms • Prevent or improve behavioral, biochemical, and histopathological deteriorations in AD
Metformin	• Increased AMPK-mediated autophagy • Inhibits mTOR1 activity	• Regulation of glucose metabolism, enhance mitochondriogenesis, and promote autophagy • Enhanced functional connectivity in the dorsolateral prefrontal cortex
Dapaglitazone	• Decreased p-mTOR/total mTOR ratio • Increased p-AMPK/total AMPK ratio • Stimulate AMPK/mTOR signaling cascade	• Enhance cognitive function by stimulating hippocampal autophagy
Nilotinib, bosutinib, mastinisib	• Inhibiting signaling pathways upstream of the PI3K/AKT/mTORC1 axis	• Slow disease progression in PD • Beneficial effects in animal models of AD
Resveratrol (3,5,4'-trihydroxystilbene)	• Induction of SIRT1 • Enhance AMPK • Inhibits AKT/mTOR pathway	• Neurite outgrowth and improve neural plasticity in the hippocampus • Stimulation neurogenesis and mitochondrial biogenesis
Ginsenoside-Rg2	• Stimulate AMPK/ULK1-dependent mechanism	• Enhances Aβ clearance in AD
DDPU	• Inhibits PI3K leading to downregulating PI3K/AKT/mTOR signaling pathway	• Enhances Aβ clearance in AD
Berberine	• Disrupts mTOR/p70S6K signaling	• Therapeutic potential in ALS by reversing proteinopathy
Wogonin	• Inhibits the AKT/mTOR pathway	• Increase Aβ clearance in AD
Curcumin	• Downregulate PI3K/AKT/mTOR pathway	• Improves cognitive function
Cubeben	• Upregulate PI3K/AMPK signaling • Inhibits mTOR activity	• Reduces Aβ toxicity in primary neuronal cells
Fisetin (7,3',4'-flavon-3-ol)	• Inhibit mTOR activity and activate the mTOR repressor TSC2 by inhibiting AKT • Activate AMPK	• Neuroprotective
Ouabain	• Enhancing TFEB activity through mTOR inhibition	• Neuroprotective

Abbreviations: AD, Alzheimer's disease; AKT, protein kinase B; ALS, amyotrophic lateral sclerosis; AMPK, adenosine monophosphate-activated protein kinase; DDPU, 1-(3,4-dimethoxyphenethyl)-3-(3-dehydroxyl-20(s)-protopanaxadiol-3β-yl)-urea; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; PI3K, phosphoinositide-3-kinase; PD, Parkinson's disease; SIRT1, sirtuins; TFEB, transcription factor EB; TSC2, tumour suppressor tuberous sclerosis 2; ULK-1, UNC-51-like kinase 1.

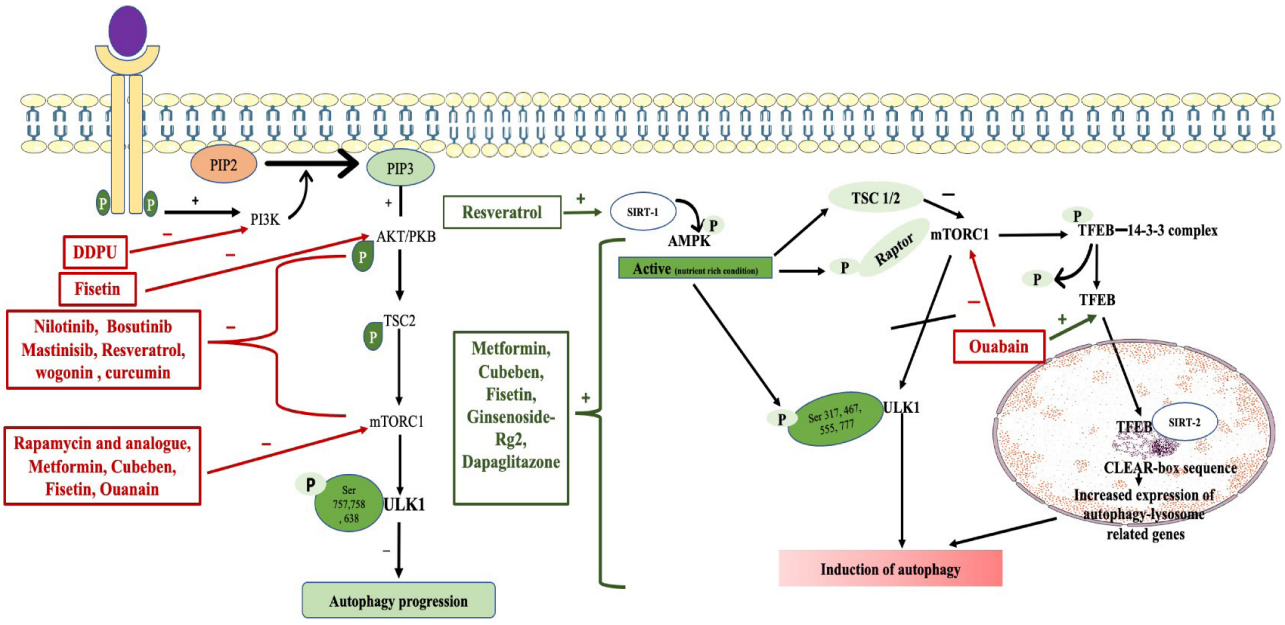
autophagy process. However, this approach carries the risk of toxic effects due to excessive autophagy activation. Therefore, more selective methods targeting specific stages of autophagy are necessary. A comprehensive understanding of autophagy's role in neurodegenerative diseases is also crucial, as interventions using autophagy inducers in these conditions are still in their early stages.[86] Further research is essential to clarify the therapeutic potential of autophagy, given its dual role in promoting

Figure 1. Key signaling pathways involved in autophagy regulation (PI3K-AKT-mTOR, AMPK-mTOR-ULK1/2, SIRT, and TFEB) and their interactions



Abbreviations: AKT, protein kinase B/PKB; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; P, phosphorylation; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphoinositide-3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; RHEB, RAS homolog abundant in the brain; Ser, serine; SIRT, sirtuins; TFEB, transcription factor EB; TSC, tumour suppressor tuberous sclerosis; ULK-1, UNC-51-like kinase 1.

Figure 2. Drugs and compounds targeting autophagy



Abbreviations: AKT, protein kinase B/PKB; AMPK, adenosine monophosphate-activated protein kinase; DDPU, 1-(3,4-dimethoxyphenethyl)-3-(3-dehydroxyl-20(s)-protopanaxadiol-3β-yl)-urea; mTORC1, mammalian target of rapamycin complex 1; P, phosphorylation; PI3K, phosphoinositide-3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; Ser, serine; SIRT, sirtuins; TFEB, transcription factor EB; TSC, tumour suppressor tuberous sclerosis; ULK-1, UNC-51-like kinase 1.

both cell survival and cell death. It is imperative to understand how autophagy-related proteins function in other cellular pathways to predict and minimize harmful off-target effects when targeting these proteins.[87] Additionally, there remains a significant need for detailed in vivo studies to document the various forms of autophagy across different diseases and stages, as well as to elucidate their relationship with different types of cell death, in order to determine when autophagy may be beneficial or harmful.[88]

8. CONCLUSION AND SCOPE OF FURTHER RESEARCH

Over the past few decades, there has been a tremendous exploration of autophagy research to better understand and cure a variety of disorders, including those associated with cognitive decline. The goal of autophagy research going forward is to decipher the many regulatory mechanisms of autophagy in order to identify different checkpoints that can be used to cure different illnesses. Furthermore, it is critical to realise that the lack of specificity in autophagy-related therapies results in a lack of therapeutic effect; for this reason, it is imperative that such therapies be target specific. In order to target particular diseases, it is also crucial to comprehend selective autophagy. In addition, appropriate tool for measuring autophagic inflow must be developed.

Furthermore, a better understanding of repurposed drugs (such as metformin, an anti-diabetic medicine) can save a lot of money and time, thus it should be encouraged. Natural substances, which always have a perception of being safe, must be investigated. Furthermore, an appropriate disease model that reflects the pathogenic alterations associated with autophagy in humans is required in order for the results to be properly translated.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest with any financial and non-financial organization regarding the material discussed in the manuscript.

REFERENCES

1. Mattay VS, Goldberg TE, Sambataro F, Weinberger DR. Neurobiology of cognitive aging: Insights from imaging genetics. *Biol Psychol*. 2008;**79**(1):9–22. doi:10.1016/j.biopsycho.2008.03.015
2. Giaquinto D, De Felice E, Attanasio C, et al. Central and peripheral NPY age-related regulation: A comparative analysis in fish translational models. *Int J Mol Sci*. 2022;**23**(7):3839. doi:10.3390/ijms23073839
3. Kumar M, Srivastava S, Muhammad T. Relationship between physical activity and cognitive functioning among older Indian adults. *Sci Rep*. 2022;**12**:2725. doi:10.1038/s41598-022-06725-3
4. Guo J, Huang X, Dou L, et al. Aging and aging-related diseases: From molecular mechanisms to interventions and treatments. *Signal Transduct Target Ther*. 2022;**7**:391. doi:10.1038/s41392-022-01179-2
5. Barter JD, Foster TC. Cellular and molecular mechanisms for age-related cognitive decline. In: Heilman KM, Nadeau SE, editors.*Cognitive Changes and the Aging Brain*. Cambridge University Press; 2019, p. 16–27. doi:10.1017/9781108554350.003
6. Picard M, McEwen BS. Mitochondria impact brain function and cognition. *Proc Natl Acad Sci U S A*. 2014;**111**(1):7–8. doi:10.1073/pnas.1321881111
7. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. *Nature*. 2010;**464**(7288):529–535. doi:10.1038/nature08983
8. Blinkouskaya Y, Caçoilo A, Gollamudi T, Jalalian S, Weickenmeier J. Brain aging mechanisms with mechanical manifestations. *Mech Ageing Dev*. 2021;**200**:111575. doi:10.1016/j.mad.2021.111575
9. Olesen MA, Torres AK, Jara C, Murphy MP, Tapia-Rojas C. Premature synaptic mitochondrial dysfunction in the hippocampus during aging contributes to memory loss. *Redox Biol*. 2020;**34**:101558. doi:10.1016/j.redox.2020.101558
10. Rossiello F, Jurk D, Passos JF, d'Adda di Fagagna F. Telomere dysfunction in ageing and age-related diseases. *Nat Cell Biol*. 2022;**24**(2):135–147. doi:10.1038/s41556-022-00842-x
11. Gruber HJ, Semeraro MD, Renner W, Herrmann M. Telomeres and age-related diseases. *Biomedicines*. 2021;**9**(10):1335. doi:10.3390/biomedicines9101335
12. Koh SH, Choi SH, Jeong JH, et al. Telomere shortening reflecting physical aging is associated with cognitive decline and dementia conversion in mild cognitive impairment due to Alzheimer's disease. *Aging (Albany NY)*. 2020;**12**(5):4407–4423. doi:10.18632/aging.102893
13. Tsoukalas D, Buga AM, Docea AO, et al. Reversal of brain aging by targeting telomerase: A nutraceutical approach. *Int J Mol Med*. 2021;**48**:199. doi:10.3892/ijmm.2021.5032
14. Nicaise AM, Willis CM, Crocker SJ, Pluchino S. Stem cells of the aging brain. *Front Aging Neurosci*. 2020;**12**:247. doi:10.3389/fnagi.2020.00247
15. Navarro Negredo P, Yeo RW, Brunet A. Aging and rejuvenation of neural stem cells and their niches. *Cell Stem Cell*. 2020;**27**(2):202–223. doi:10.1016/j.stem.2020.07.002
16. Jiménez Peinado P, Urbach A. From youthful vigor to aging decline: Unraveling the intrinsic and extrinsic determinants of hippocampal neural stem cell aging. *Cells*. 2023;**12**(16):2086. doi:10.3390/cells12162086
17. Maity S, Farrell K, Navabpour S, Narayanan SN, Jarome TJ. Epigenetic mechanisms in memory and cognitive decline associated with aging and Alzheimer's disease. *Int J Mol Sci*. 2021;**22**(22):12280. doi:10.3390/ijms222212280
18. Heard DS, Tuttle CSL, Lautenschlager NT, Maier AB. Repurposing proteostasis-modifying drugs to prevent or treat age-related dementia: A systematic review. *Front Physiol*. 2018;**9**:1520. doi:10.3389/fphys.2018.01520
19. Verma K, Verma M, Chaphalkar A, Chakraborty K. Recent advances in understanding the role of proteostasis. *Fac Rev*. 2021;**10**:72. doi:10.12703/r/10-72
20. Díaz-Villanueva JF, Díaz-Molina R, García-González V. Protein folding and mechanisms of proteostasis. *Int J Mol Sci*. 2015;**16**(8):17193–17230. doi:10.3390/ijms160817193
21. Chaplot K, Jarvela TS, Lindberg I. Secreted chaperones in neurodegeneration. *Front Aging Neurosci*. 2020;**12**:268. doi:10.3389/fnagi.2020.00268

22. Jin H, Komita M, Aoe T. Decreased protein quality control promotes the cognitive dysfunction associated with aging and environmental insults. *Front Neurosci*. 2018;**12**:753. doi:10.3389/fnins.2018.00753

23. Davidson K, Pickering AM. The proteasome: A key modulator of nervous system function, brain aging, and neurodegenerative disease. *Front Cell Dev Biol*. 2023;**11**:1124907. doi:10.3389/fcell.2023.1124907

24. Dulka BN, Pullins SE, Cullen PK, Moyer JR, Helmstetter FJ. Age-related memory deficits are associated with changes in protein degradation in brain regions critical for trace fear conditioning. *Neurobiol Aging*. 2020;**91**:160–166. doi:10.1016/j.neurobiolaging.2020.03.001

25. Barmaki H, Nourazarian A, Khaki-Khatibi F. Proteostasis and neurodegeneration: A closer look at autophagy in Alzheimer's disease. *Front Aging Neurosci*. 2023;**15**:1281338. doi:10.3389/fnagi.2023.1281338

26. Karabiyik C, Frake RA, Park SJ, Pavel M, Rubinsztein DC. Autophagy in ageing and ageing-related neurodegenerative diseases. *Ageing Neurodegener Dis*. 2021;**1**:2. doi:10.20517/and.2021.05

27. Metaxakis A, Ploumi C, Tavernarakis N. Autophagy in age-associated neurodegeneration. *Cells*. 2018;**7**(5):37. doi:10.3390/cells7050037

28. Glatigny M, Moriceau S, Rivagorda M, et al. Autophagy is required for memory formation and reverses age-related memory decline. *Curr Biol*. 2019;**29**(3):435–448.e8. doi:10.1016/j.cub.2018.12.021

29. Aman Y, Schmauck-Medina T, Hansen M, et al. Autophagy in healthy aging and disease. *Nat Aging*. 2021;**1**:634–650. doi:10.1038/s43587-021-00098-4

30. Pungsrinont T, Kallenbach J, Baniahmad A. Role of PI3K-AKT-mTOR pathway as a pro-survival signaling and resistance-mediating mechanism to therapy of prostate cancer. *Int J Mol Sci*. 2021;**22**(20):11088. doi:10.3390/ijms222011088

31. Yang CZ, Wang SH, Zhang RH, et al. Neuroprotective effect of astragalin via activating PI3K/Akt-mTOR-mediated autophagy on APP/PS1 mice. *Cell Death Discov*. 2023;**9**(1):15. doi:10.1038/s41420-023-01324-1

32. Xu J, Zheng B, Ma Y, et al. PI3K-AKT-mTOR signaling pathway regulates autophagy of hippocampal neurons in diabetic rats with chronic unpredictable mild stress. *Behav Brain Res*. 2023;**452**:114558. doi:10.1016/j.bbr.2023.114558

33. Dan HC, Ebbs A, Pasparakis M, Van Dyke T, Basseres DS, Baldwin AS. Akt-dependent activation of mTORC1 complex involves phosphorylation of mTOR (mammalian target of rapamycin) by IκB kinase α (IKKα). *J Biol Chem*. 2014;**289**(36):25227–25240. doi: 10.1074/jbc.M114.554881

34. Kim YC, Guan KL. mTOR: A pharmacologic target for autophagy regulation. *J Clin Invest*. 2015;**125**(1):25–32. doi:10.1172/JCI73939

35. Benito-Cuesta I, Ordóñez-Gutiérrez L, Wandosell F. AMPK activation does not enhance autophagy in neurons in contrast to MTORC1 inhibition: Different impact on β-amyloid clearance. *Autophagy*. 2021;**17**(3):656–671. doi:10.1080/15548627.2020.1728095

36. Wang S, Li H, Yuan M, Fan H, Cai Z. Role of AMPK in autophagy. *Front Physiol*. 2022;**13**:1015500. doi:10.3389/fphys.2022.1015500

37. Mei X, Tan G, Qing W. AMPK activation increases postoperative cognitive impairment in intermittent hypoxia rats via direct activating PAK2. *Behav Brain Res*. 2020;**379**:112344. doi:10.1016/j.bbr.2019.112344

38. Park JM, Lee DH, Kim DH. Redefining the role of AMPK in autophagy and the energy stress response. *Nat Commun*. 2023;**14**:2994. doi:10.1038/s41467-023-38401-z

39. Kim J, Kundu M, Viollet B, Guan KL. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol*. 2011;**13**(2):132–141. doi:10.1038/ncb2152

40. Alers S, Löffler AS, Wesselborg S, Stork B. Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: Cross talk, shortcuts, and feedbacks. *Mol Cell Biol*. 2012;**32**(1):2–11. doi:10.1128/MCB.06159-11

41. Holczer M, Hajdú B, Lőrincz T, Szarka A, Bánhegyi G, Kapuy O. Fine-tuning of AMPK-ULK1-mTORC1 regulatory triangle is crucial for autophagy oscillation. *Sci Rep*. 2020;**10**(1):17803. doi:10.1038/s41598-020-75030-8

42. Wang X, Zimmermann HR, Ma T. Therapeutic potential of AMP-activated protein kinase in Alzheimer's disease. *J Alzheimers Dis*. 2019;**68**(1):33–38. doi:10.3233/JAD-181043

43. Muraleedharan R, Dasgupta B. AMPK in the brain: Its roles in glucose and neural metabolism. *FEBS J*. 2022;**289**(8):2247–2262. doi:10.1111/febs.16151

44. Fagerli E, Escobar I, Ferrier FJ, Jackson CW, Perez-Lao EJ, Perez-Pinzon MA. Sirtuins and cognition: Implications for learning and memory in neurological disorders. *Front Physiol*. 2022;**13**:908689. doi:10.3389/fphys.2022.908689

45. Wan W, Hua F, Fang P, et al. Regulation of mitophagy by sirtuin family proteins: A vital role in aging and age-related diseases. *Front Aging Neurosci*. 2022;**14**:845330. doi:10.3389/fnagi.2022.845330

46. Cicero AFG, Ruscica M, Banach M. Resveratrol and cognitive decline: A clinician perspective. *Arch Med Sci*. 2019;**15**(4):936–943. doi:10.5114/aoms.2019.85463

47. Wu QJ, Zhang TN, Chen HH, et al. The sirtuin family in health and disease. *Signal Transduct Target Ther*. 2022;**7**(1):402. doi:10.1038/s41392-022-01257-8

48. Matysek A, Sun L, Kimmantudawage SP, Feng L, Maier AB. Targeting impaired nutrient sensing via the sirtuin pathway with novel compounds to prevent or treat dementia: A systematic review. *Ageing Res Rev*. 2023;**90**:102029. doi:10.1016/j.arr.2023.102029

49. Zhang W, Li X, Wang S, et al. Regulation of TFEB activity and its potential as a therapeutic target against kidney diseases. *Cell Death Discov*. 2020;**6**:32. doi:10.1038/s41420-020-0265-4

50. Yang CB, Liu J, Tong BC, et al. TFEB, a master regulator of autophagy and biogenesis, unexpectedly promotes apoptosis in response to the cyclopentenone prostaglandin 15d-PGJ2. *Acta Pharmacol Sin*. 2022;**43**(5):1251–1263. doi:10.1038/s41401-021-00711-7

51. Metaxakis A, Ploumi C, Tavernarakis N. Autophagy in age-associated neurodegeneration. *Cells*. 2018;**7**(5):37. doi:10.3390/cells7050037

52. Zhang W, Xu C, Sun J, et al. Impairment of the autophagy-lysosomal pathway in Alzheimer's diseases: Pathogenic mechanisms and therapeutic potential. *Acta Pharm Sin B*. 2022;**12**(3):1019–1040. doi:10.1016/j.apsb.2022.01.008

53. Wang H, Liu Y, Wang D, et al. The upstream pathway of mTOR-mediated autophagy in liver diseases. *Cells*. 2019;**8**(12):1597. doi:10.3390/cells8121597

54. Towers CG, Thorburn A. Therapeutic targeting of autophagy. *EBioMedicine*. 2016;**14**:15–23. doi:10.1016/j.ebiom.2016.10.034

55. Heard DS, Tuttle CSL, Lautenschlager NT, Maier AB. Repurposing proteostasis-modifying drugs to prevent or treat age-related dementia: A systematic review. *Front Physiol*. 2018;**9**:1520. doi:10.3389/fphys.2018.01520

56. Barmaki H, Nourazarian A, Khaki-Khatibi F. Proteostasis and neurodegeneration: A closer look at autophagy in Alzheimer's

disease. *Front Aging Neurosci.* 2023;**15**:1281338. doi:10.3389/fnagi.2023.1281338

57. Friedman LG, Qureshi YH, Yu WH. Promoting autophagic clearance: Viable therapeutic targets in Alzheimer's disease. *Neurotherapeutics.* 2015;**12**:94–108. doi:10.1007/s13311-014-0320-z
58. Talboom J, Velazquez R, Oddo S. The mammalian target of rapamycin at the crossroad between cognitive aging and Alzheimer's disease. *NPJ Aging Mech Dis.* 2015;**1**:15008. doi:10.1038/npjamd.2015.8
59. Ding Y, Liu H, Cen M, et al. Rapamycin ameliorates cognitive impairments and Alzheimer's disease-like pathology with restoring mitochondrial abnormality in the hippocampus of streptozotocin-induced diabetic mice. *Neurochem Res.* 2021;**46**(2):265–275. doi:10.1007/s11064-020-03160-6
60. Thellung S, Corsaro A, Nizzari M, Barbieri F, Florio T. Autophagy activator drugs: A new opportunity in neuroprotection from misfolded protein toxicity. *Int J Mol Sci.* 2019;**20**(4):901. doi:10.3390/ijms20040901
61. Chen L, Zhang Y, Li D, et al. Everolimus (RAD001) ameliorates vascular cognitive impairment by regulating microglial function via the mTORC1 signaling pathway. *J Neuroimmunol.* 2016;**299**:164–171. doi:10.1016/j.jneuroim.2016.09.008
62. Cassano T, Magini A, Giovagnoli S, et al. Early intrathecal infusion of everolimus restores cognitive function and mood in a murine model of Alzheimer's disease. *Exp Neurol.* 2019;**311**:88–105. doi:10.1016/j.expneurol.2018.09.011
63. Fanoudi S, Hosseini M, Alavi MS, et al. Everolimus, a mammalian target of rapamycin inhibitor, ameliorated streptozotocin-induced learning and memory deficits via neurochemical alterations in male rats. *EXCLI J.* 2018;**17**:999–1017. doi:10.17179/excli2018-1626
64. Jia P, Che J, Zhang J, Li H, Zhou Q, Guo Y. Metformin ameliorates postoperative cognitive dysfunction through regulation of the AMPK/SIRT1 pathway. *J Integr Neurosci.* 2023;**22**(5):110. doi:10.31083/j.jin2205110
65. Kodali M, Attaluri S, Madhu LN, et al. Metformin treatment in late middle age improves cognitive function with alleviation of microglial activation and enhancement of autophagy in the hippocampus. *Aging Cell.* 2021;**20**(2):e13277. doi: 10.1111/acel.13277
66. Xu X, Sun Y, Cen X, et al. Metformin activates chaperone-mediated autophagy and improves disease pathologies in an Alzheimer disease mouse model. *Protein Cell.* 2021;**12**:769–787. doi:10.1007/s13238-021-00858-3
67. Yu M, Zheng X, Cheng F, Shao B, Zhuge Q, Jin K. Metformin, rapamycin, or nicotinamide mononucleotide pretreatment attenuate cognitive impairment after cerebral hypoperfusion by inhibiting microglial phagocytosis. *Front Neurol.* 2022;**13**:903565. doi:10.3389/fneur.2022.903565
68. Shao T, Huang J, Zhao Y, et al. Metformin improves cognitive impairment in patients with schizophrenia: Associated with enhanced functional connectivity of dorsolateral prefrontal cortex. *Transl Psychiatry.* 2023;**13**:315. doi:10.1038/s41398-023-02616-x
69. Arab HH, Eid AH, Alsufyani SE, et al. Targeting autophagy, apoptosis, and oxidative perturbations with dapagliflozin mitigates cadmium-induced cognitive dysfunction in rats. *Biomedicines.* 2023;**11**(11):3000. doi:10.3390/biomedicines11113000
70. Guo F, Liu X, Cai H, Le W. Autophagy in neurodegenerative diseases: Pathogenesis and therapy. *Brain Pathol.* 2018;**28**(1):3–13. doi:10.1111/bpa.12545
71. Martins WK, Silva MDND, Pandey K, et al. Autophagy-targeted therapy to modulate age-related diseases: Success, pitfalls, and new directions. *Curr Res Pharmacol Drug Discov.* 2021;**2**:100033. doi:10.1016/j.crphar.2021.100033
72. Eshraghi M, Ahmadi M, Afshar S, et al. Enhancing autophagy in Alzheimer's disease through drug repositioning. *Pharmacol Ther.* 2022;**237**:108171. doi:10.1016/j.pharmthera.2022.108171
73. Cicero AFG, Ruscica M, Banach M. Resveratrol and cognitive decline: A clinician perspective. *Arch Med Sci.* 2019;**15**(4):936–943. doi:10.5114/aoms.2019.85463
74. Wang N, He J, Pan C, et al. Resveratrol activates autophagy via the AKT/mTOR signaling pathway to improve cognitive dysfunction in rats with chronic cerebral hypoperfusion. *Front Neurosci.* 2019;**13**:859. doi:10.3389/fnins.2019
75. Shaikh S, Ahmad K, Ahmad SS, et al. Natural products in therapeutic management of multineurodegenerative disorders by targeting autophagy. *Oxid Med Cell Longev.* 2021;**2021**:6347792. doi:10.1155/2021/6347792
76. Gruendler R, Hippe B, Sendula Jengic V, Peterlin B, Haslberger AG. Nutraceutical approaches of autophagy and neuroinflammation in Alzheimer's disease: A systematic review. *Molecules.* 2020;**25**(24):6018. doi:10.3390/molecules25246018
77. Haddy FJ. Role of dietary salt in hypertension. *Life Sci.* 2006;**79**(17):1585–1592. doi:10.1016/j.lfs.2006.05.017
78. Caponio D, Veverová K, Zhang S, et al. Compromised autophagy and mitophagy in brain aging and Alzheimer's diseases. *Aging Brain.* 2022;**2**:100056. doi:10.1016/j.nbas.2022.100056
79. Deng Z, Dong Y, Zhou X, Lu JH, Yue Z. Pharmacological modulation of autophagy for Alzheimer's disease therapy: Opportunities and obstacles. *Acta Pharm Sin B.* 2022;**12**(4):1688–1706. doi:10.1016/j.apsb.2021.12.009
80. Liu J, Li L. Targeting autophagy for the treatment of Alzheimer's Disease: Challenges and opportunities. *Front Mol Neurosci.* 2019;**12**:203. doi:10.3389/fnmol.2019.00203
81. Lu G, Wang Y, Shi Y, et al. Autophagy in health and disease: From molecular mechanisms to therapeutic target. *MedComm.* 2022;**3**(3):e150. doi:10.1002/mco2.150
82. Danics L, Abbas AA, Kis B, Pircs K. Fountain of youth-targeting autophagy in aging. *Front Aging Neurosci.* 2023;**15**:1125739. doi:10.3389/fnagi.2023.1125739
83. Pierzynowska K, Gaffke L, Cyske Z, et al. Autophagy stimulation as a promising approach in treatment of neurodegenerative diseases. *Metab Brain Dis.* 2018;**33**(4):989–1008. doi:10.1007/s11011-018-0214-6
84. Park K, Lee MS. Current status of autophagy enhancers in metabolic disorders and other diseases. *Front Cell Dev Biol.* 2022;**10**:811701. doi:10.3389/fcell.2022.811701
85. Kocak M, Ezazi Erdi S, Jorba G, et al. Targeting autophagy in disease: Established and new strategies. *Autophagy.* 2022;**18**(3):473–495. doi:10.1080/15548627.2021.1936359
86. Park H, Kang JH, Lee S. Autophagy in neurodegenerative diseases: A hunter for aggregates. *Int J Mol Sci.* 2020;**21**:3369. doi:10.3390/ijms21093369
87. Sanchez-Mirasierra I, Ghimire S, Hernandez-Diaz S, Soukup SF. Targeting macroautophagy as a therapeutic opportunity to treat Parkinson's disease. *Front Cell Dev Biol.* 2022;**10**:921314. doi:10.3389/fcell.2022.921314
88. Corti O, Blomgren K, Poletti A, Beart PM. Autophagy in neurodegeneration: New insights underpinning therapy for neurological diseases. *Neurobiol Dis.* 2020;**154**(4):354–371. doi:10.1111/jnc.15002