REVIEW ARTICLE

Regulation of Autophagy in Neurodegenerative Diseases: A Brief Review on Autophagy Therapy for Neurodegenerative Diseases

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ABSTRACT

Autophagy involves the breakdown of complete organelles and macromolecules in the cytoplasm of eukaryotic cells, especially proteins with extended half-lives. During this degrading phase, therapeutic, pharmacological, and fasting approaches are important. All eukaryotic cells engage in autophagy, which is an ancient and evolutionarily conserved phenomenon. It has been discovered in mammals, including humans, as well as the yeast *Saccharomyces cerevisiae* and the fly *Drosophila melanogaster*. Its significance in cell and dysfunction impairing the autophagy process that is connected to a broad array of serious illnesses, including neuronal and metabolic brain diseases. Only a concise summary of the various forms of autophagy and its molecular mechanisms, as well as how they relate to neuronal health, will be provided in this work. Negative regulations are frequently used to define the regulatory networks that govern the autophagy process. This study, however, focuses on alternative strategies to promote autophagy. Metabolic neurodegenerative diseases can be treated by activating this mechanism *via* a variety of drugs or mechanisms. These points are covered and discussed in this article.

Keywords: Autophagy, Autophagy Signalling, Intermittent fasting, Neural health, Neuroprotective, Neurodegenerative disease, Pharmacology, Therapeutic approaches.

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INTRODUCTION

Numerous neurological disorders fall under the umbrella term "neurodegeneration." These diseases can present with a varied range of symptoms, like motor dysfunction, speech problems, and cognitive failure. The loss of neuronal population in the brain is the usual pathophysiological hallmark in neurodegenerative diseases. The exact region of the brain and spinal cord in which neuronal death occurs is used to identify the clinical features of a certain neurodegenerative disease. Parkinson disease (PD) Huntington disease (HD) and Alzheimer disease (AD), are examples of common diseases that fall within the category of neurodegenerative disorders. The estimated societal burden and financial expenses of AD and PD are likely to rise with the expected increase in cases during the coming decades. The anticipated overall health care expenses for AD and related dementias were $214 billion in 2014, with Medicare and Medicaid covering roughly 70% of those costs.[1] These neurodegenerative illnesses are significantly influenced by the cumulation of misfolded proteins. By dissolving proteins or even whole organelles, the mechanism of catabolism helps the recycling of cellular material.[2] Since misfolded protein aggregates are removed during autophagy and neurons have an abundance of autophagosomes, which are essential for the breakdown of proteins. In the quest to treat neurological disorders, research into autophagy is a field that is expanding rapidly.[3] Autophagy has been effectively retained from eukaryotic microorganisms to people over the course of species evolution. Large quantities of the cytoplasm, organisms (pathogen), and soluble proteins are break-down and used in the autophagy process to make new molecules.[4] Ineffective autophagy leaves numerous types of cells in physiological systems, such as neurons, exposed to harm.[5]

MATERIAL AND METHODS

A large database of various online resources was explored and various reviews and research papers are studied using different keywords like probiotic, microflora, neurodegeneration, and psychiatric disorders. This study considers probiotic modulation and its benefits in the therapy of brain illness. Different publications from different websites Google scholar, Springer,

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Taylor and Francis, Elsevier, and Bentham are reviewed for the literature survey.

Autophagy and Neuron Health

Christian de Duve first identified autophagy, which is derived from the Greek word auto-phagocytosis a natural mechanism of the cell that pull-apart dysfunctional constituents by lysosome degradation in 1963.[6] Currently, three different autophagy mechanisms have been identified: chaperone-mediated autophagy, micro, and macro-autophagy as shown in Figure 1.[7] Large protein aggregates or damaged organelles may be degraded using the bulk degradation mechanism known as macro-autophagy. The trans-golgi, endosomes, and other constituents of the plasma membrane are major sources of the phagophore, which are established at the start of the process.[8] To sequester the load in a membrane, these phagophores enlarge to inundate intracellular loads, such as protein clusters and other cell organelles. In the cytoplasm, auto-phagosomes are generated at random and later transferred throughout the length of microtubules in a dynein-dependent fashion to the microtubule-operation centre. Once inside this centre, they develop by joining forces with endosomes and multivesicular bodies prior to combine with lysosomes. Lysosomal acid proteases break down the autophagosomal substrate. The recycling of amino acids and degradation of by-products for the synthesis of the macromolecules and metabolism occurs as a result of lysosomal permeases and transporters. Compared to yeast, mammalian systems have far less[9] knowledge of microautophagy, which is relatively analogous to macroautophagy. Instead of forming an autophagosome and an autophagolysosome, lysosomes simply engulf the cytoplasm. Unmediated pinocytosis of small aggregates of cytosol occurs during micro-autophagy through lysosomes. It is in control of the removal of specific organelles and the ongoing turnover of intracellular components while the body is at rest. Stress or nutrient shortages do not activate it.[10] In expression of the system selectivity or degradation, CMA (chaperone-mediated autophagy) differs significantly from macro and microautophagy. 30% of soluble proteins with the specific pentapeptide are selectively degraded by CMA (KFERQ). A heat-shock cognate 70 which is also called as cytosolic chaperone uniquely identify this amino acid sequence and targets it to lysosomes for further destruction. The CDA receptor recognises the amino-acid sequence as the chaperone-substrate complex moves to the lysosomes. The protein is subsequently unfolded and moved, with the assistance of lysosomal heat-shock cognate 70, across the lysosome membrane for destruction.[11,12] Autophagy involves the reprocessing of macromolecules to dispense new nutrients to the cell. In neurodegenerative pathways, substrates include mutant α-synuclein (Parkinson), tau-protein (Alzheimer), and polyglutamine-expanded protein (Huntington). The major role is performed by autophagy in maintaining the homeostasis of organelles for example dysregulation in mitochondria releases toxic and reactive mediators which are eliminated by the

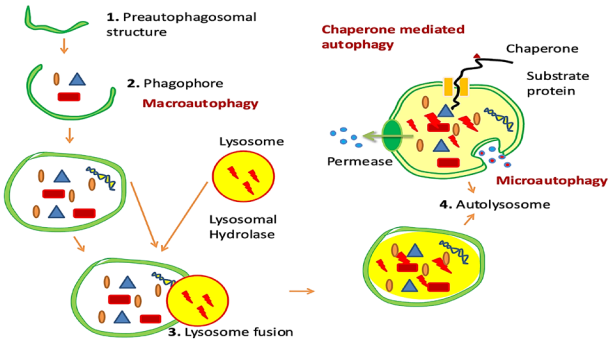

Figure 1: Schematic representation of mechanism involved in autophagy.

autophagy process, in a similar fashion various pathogens are degraded and show protective function in numerous diseases.[13] The phenomenon of autophagy is important for maintaining neuronal health and function, which is firmly related to the availableness of nerve growth factors. Neurons, due to their extreme polarization in nature, may be highly responsive to the accumulation of protein and other aggregated; hence, the autophagy process is important for their viability. The advantageous role of autophagy is to promote the degradation of cellular proteins and maintain normal balance. In a study a mouse model is generated with knockdown tissue-specific ATG7 in the central nervous system, the mouse show the inclusion bodies cumulation and insufficient autophagy in neurons with no effect on proteasome function. The loss of neurons and death in less than 28 weeks of birth occurs. This study suggested the neuroprotective effect and role of autophagy in neurodegenerative diseases.[14]

Regulation of Autophagy

The autophagy phenomenon involves signaling pathways, which are mainly divided into two major groups the mammalian target of rapamycin (mTOR) dependent pathway and the mammalian target of rapamycin (mTOR) independent pathway; these two pathways regulate the autophagy process and various genes involve in microtubule development. The integration of these signaling pathways with other growth factors and kinases helps to maintain a balance between the biosynthesis of proteins and cell growth.[15]

Mammalian Target of Rapamycin (mTOR) Dependent Pathway

In the autophagy process, the mTOR-dependent pathway includes three major sub-pathways: phosphoinositide-3-kinases(P13k), activated-protein kinase (AMPK), and recombination activating genes (Rag).[15] The PI3k pathway work as substrate phosphorylation will not take place when there are insufficient insulin or growth hormones available, the insulin receptor becomes inactive and the P13k-complex becomes inactive.[16] The inactivation of P13k complex is unable to convert phosphatidylinositol-biphosphate to phosphatidylinositol-triphosphate. The lack of phosphatidylinositol-triphosphate causes a lack of activity in phosphoinositide-dependent

kinase-1, which is unable to phosphorylate abstract protein kinase. Similarly, the dephosphorylated tuberous sclerosis protein-1 (TSC-1) complex has a GTPase-activating protein (GAP), which stimulate Ras-homolog enriched in brain (Rheb) GTPase, and Rheb remain in guanosine-diphosphate (GDP) bound form.[17] The raptor protein cannot interact with this particular Rheb variant. Further inactivation of mTOR prevents phosphorylation of unc-51-like-autophagy-kinase (ULk1) and causes dephosphorylation of ULk1 which causes the autophagosome to develop.[18] A sudden shift in the cell's energy balance, a deficiency in growth hormones, or metabolic stress might affect the AMPK pathway and cause autophagy to occur. The cell is alerted to changes in the ATP/ADP ratio by the cellular energy sensor known as AMPK. Changes in this level result in the activation of the liver-kinase-B1(LKB1), that causes activation of the AMPK signaling pathway.[19] This makes it possible for the tuberous sclerosis protein-2(TCP-2) protein to undergo phosphorylation. It's interesting to note that the target protein has another phosphorylated side that the glycogen-synthase kinase-3 (GSK-3) utilizes to add another phosphate group as a result of this AMPK-mediated phosphorylation.[20] It should be noted during extreme hunger conditions, TCP-2 is phosphorylated by AMPK-kinase without the interference of LKB1. Further, this mechanism causes the blockage of interaction with the mTOR, which induces autophagy.[21] Autophagy in the Rag pathway is triggered by the availability or abundance of amino acids. The cell membrane contains two receptors that are in charge of detecting these substances. The solute-carrier 1A5 (SLC-1A5) receptor is the first, which can bind and carry L(Levo)-glutamine to the cell. When L(Levo)-glutamine levels are elevated, certain heterodimeric carriers are stimulated or amplified, which increases the amount of amino acids that are transported into the cell while simultaneously removing L-glutamine from it.[22] The GTPases-complex, which is made up of Ras-related GTP-binding protein and other regulators and is located in the membrane of lysosomes, is unable to trap these compounds in the absence of amino acids or when receptors are dysregulated.[23] Heterodimers of subunits 'a' or 'b' linked to subunits 'c' or 'd' makeup Rag GTPases. When amino acids are present, the heterodimer is activated, resulting in the development of a conformation that involves Rag a/b linked with Rag c/d and GTP that is bound to the GDP.[24] When amino acids are deficient, the complex configuration appears inactive and cannot interact with the Raptor proteins. The complex form in the amino deficient condition is unable to attach to a lysosomal surface as a result it begins the creation of autophagosomes.[25]

Mammalian Target of Rapamycin Independent Pathway

Studies demonstrate that level of inositol and inositol-triphosphate antagonistically regulates the autophagy process. This first support the presence of an mTOR-independent pathway. There are majorly four important pathways involved in it.[26] Any significant alterations in physiological circumstances cause the Ca^{2+}/calpain pathway to becoming active. The concentration of calcium ions in the cell, therefore, activates proteins, and calpain from the cysteine proteinase group is another element that affects this pathway. They can also be activated by ions released from the endoplasmic reticulum, in addition to Calcium ions brought inside the cell by a Ca^{2+} channel.[27] Antagonists of Ca^{2+} channel type L can promote autophagy activation by the Ca^{2+}/calpain pathway. They prevent ions from entering the cell, which prevents calpain from activating.[28] The development of autophagosomes and their fusion with lysosomes are typically adversely regulated by excessive Calcium levels and calpains stimulation. Although calpains are not active and the levels of Calcium ions are too low when the Ca^{2+} channels are closed, the autophagy process can begin. It is important to note that the cAMP-dependent pathway is linked to the Ca^{2+}/calpain pathway. Active calpains promote the G protein's subunit's dissociation and activation when nutrients are there and Calcium channels are not closed.[29] Depending on the inositol concentrations inside cells, a chain of activities is involved in the inositol-activation pathway. Blocking the G protein-coupled receptor, that triggers and activates phospholipase-C, which stimulates this cascade. In these circumstances, 4,5-phosphatidylinositol-bisphosphate does not convert to inositol triphosphate (IP3) or diacylglycerol (DGA) (PIP2).[30] Inositol-5' phosphatase and Inositol-polyphosphatase hydrolyzed two phosphates from Inositol-triphosphate to produce free inositol which is then followed by the hydrolysis of inositol phosphates by inositol mono-phosphatase. There is no free inositol when inositol-biphosphate cannot be converted into inositol-triphosphate, which causes the formation of the autophagosomal membranes and begin the autophagy process.[31] In the cAMP/EPAC/PLC pathway, 3'5'adenosine monophosphate (cAMP) controls autophagy independently of mTORC1 kinase. Adenylate cyclase converts adenosine-5'-triphosphate into cAMP (ATP). Agonists of the imidazoline receptor are the primary activators of these pathways (which act to decrease the cAMP level).[32] These substances reduce the amount of cAMP in the cell by activating this receptor. As a result, the Rap2B protein remains inactive since the exchange protein that is directly induced by cAMP (EPAC) isn't activated. Phospholipase-C is inactive in these circumstances; hence, phosphate-biphosphate is not able to be transformed into inositol-triphosphate. Because cAMP and IP3 both prevent the creation of phagophores, a disruption of the cascade described above causes autophagy to become activated.[33] The phosphor-inositol-kinase-3 complex is of different types of enzymes. The proteins, such as Beclin-1, pVps34, and pVps15, play a critical role in the Beclin-1/PI3K/JNK1 pathway. c-Jun-N-terminal-protein kinase-1(JNK1) phosphorylates the Bcl-2 protein when the body is starved.[34] This prevents the removal of phosphorylated Bcl-2 from the Bcl-complex as well as the interaction of Bcl2 with Beclin-1. In order to generate the Beclin1-hVps34-hVps15 complex, Beclin-1 must be released and then react with hVps34. Later on, the complex activates autophagosome development.[35]

Therapeutic and Pharmacological Approaches to Activate Autophagy in Neurodegeneration

Studies in which critical controlling genes such as ATG5 and ATG7 in the nervous system were genetically inactivated in mice provided a straight verification connection between protein-homeostasis regulation and the autophagy process in CNS.[36] The imbalance of the autophagy process in the brain led to sudden neurodegeneration, widespread neuronal loss, and early animal death. It also promoted the buildup of protein aggregates.[37] Using a pathway-specific strategy, the upregulation of a particular constituent of a pathway has been used to promote selectivity in the activation of autophagy. upregulation of Beclin-1 to stimulate macro-autophagy and decrease neurodegenerative process and α-synuclein clusters in the mice model of PD.[38] The upregulation of lysosome-associated membrane protein type 2A increases chaperone-dependent autophagy which prevents α-synuclein mediated effect in the animal model of PD.[39]

The current focus is on creating smaller compounds that could be employed in clinical settings to imitate the effects of these genetic techniques. For instance, in the context of polyglutamine growth, a polypeptide obtained from Beclin-1 was capable to regain protein homeostasis, resulting in a decrease in polyglutamine repeat aggregates in cultured cells.[40] The understanding that the vitamin A receptors negatively control chaperone-dependent autophagy led to the creation of small compounds that lessen this inhibitory effect without affecting the receptor's other downstream signals. *In-vitro* survival following proteotoxic and oxidative shocks was improved by these new chaperone-mediated autophagy activators.[41] Approaches that only focus on the lysosomal compartment are also gaining popularity since they are preferable in situations where this organelle fails preferentially. The mutation in presenilin-1(gene) causes acidification of lysosomes due to calcium leakage from this compartment, it has been demonstrated that the application of acidic nanoparticles can restore lysosomal acidification.[42] The benefit of specifically targeting the lysosome in these circumstances is supported by the fact that maintaining lysosomal ph increases the autophagy process.[43]

Numerous studies have pinpointed the involvement of oxidative stress and mitochondrial dysfunction in the pathomechanism of neurodegenerative diseases, including PD, HD, and AD. Oxidative end products are produced as a result of the accumulation of ROS, which are byproducts of the energy synthesis of complexes I and III.[44] Because they require more energy, neurons are extremely dependent on mitochondrial energy generation. Reduced membrane potential and ATP production are caused by the respiratory chain complexes' decreased activity, and these changes are linked to neurodegenerative disorders.[45] A characteristic of the majority of neurodegenerative diseases is defective mPTP. The mPTP is opened by calcium ions acting as free radicals, which then release Cyt C and other proapoptotic and apoptosis-initiating proteins.[46] Therefore, the emergence of neurodegenerative diseases is caused by abnormal mitochondria.[47] The use of a gene-therapy approach to specifically modulate autophagy and target protein aggregation in brain diseases has been extensively studied. Although there are just a few known examples with successful outcomes, this field is still little studied.[48] Beclin 1 gene therapy improves synaptic function and reduces α-synuclein buildup in an animal model of PD and another dementia diseases.[49] The mouse model of Machado-Joseph disease was also injected with lentivirus expressing Beclin 1, and this greatly improved motor function and decreased protein aggregation.[50] In the genetically modified mouse model, Beclin 1 gene transfer reduced the pathology of AD. These results are consistent with the acceleration of experimental AD *in-vivo* by Beclin 1 haploinsufficiency.[51] The autophagic pathway's role in the breakdown of APP (amyloid precursor protein) may be involved in these findings. On the other hand, it was recently shown that Beclin-1 haploinsufficiency exhibited significant positive benefits in the amyotrophic lateral sclerosis mice model, increasing longevity.[52]

A pharmacological approach is to selectively degrade abnormal proteins linked to protein misfolding disorders or impaired organelles. High-throughput screening has identified various substances that promote autophagy, and their effectiveness in a number of preclinical illness models has been demonstrated.[53] *In-vivo* and *ex-vivo* models of neurodegenerative illnesses are investigated with rapamycin. Scientists concluded encouraging outcomes that suggest the possibility of speeding the breakdown of proteins including mutant huntingtin (mHTT) and α -synuclein, which are connected to a number of illnesses.[54] In trials utilizing AD animals overproducing the mutant tau protein, the hyperphosphorylated tau protein was shown to be much greater, whereas rapamycin therapy resulted in a considerable reduction in both its level and the number of neurofibrillary tangles.[55] Rapamycin was found to reduce the amount of harmful beta-amyloid in the nervous system and ameliorate cognitive impairment in mice that produce the substance.[56] As a result of the stimulation of lysosomal-autophagy and proteasomal breakdown, the levels of α-synuclein aggregation were decreased in rapamycin-treated cellular models of PD.[57] Another stimulation of the AMPK pathway is resveratrol (Figure 2).

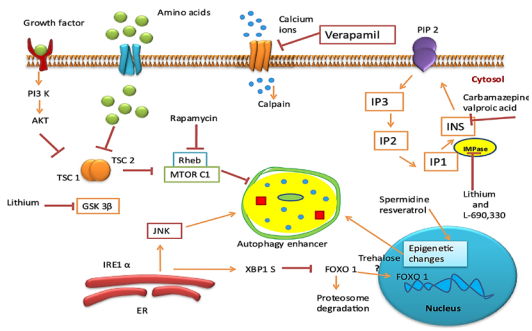

Figure 2: The schematic diagram shows the relation between pharmacological drug targets and autophagy with the pathways involved.

It causes the AMPK kinase to be activated, which stimulates the autophagy process.[58] To determine its effect on PD, resveratrol and cyclodextrin were administered to mouse N2a cells. Cell viability rose and α-synuclein aggregates reduced.[59] Carbamazepine works through a similar mechanism as lithium and valproic acid (Figure 2). Depriving the body of PIP2 and IP3 causes a drop in inositol levels.[60] Studies using the AD mouse model showed that carbamazepine enhanced memory and learning, which was associated with a reduction in amyloid plaques.[61] Carbamazepine decreased the activity of the mTOR kinase in addition to stimulating the mTOR-independent pathway of autophagy activation. It serves as another illustration of how several chemical mechanisms might stimulate autophagy.[62] Minoxidil blocks calpains and promotes autophagy by opening K2+ channels, which limit the entry of Ca2+ ions into the cell.[63] When clonidine binds to and activates the imidazoline receptor, cells produce less cAMP. Clonidine was used as one of the agents inducing autophagy in the research for a treatment option for Huntington's disease and Parkinson's disease. It successfully reduced α-synuclein and mHTT (an amyloidogenic mutant hangin) levels in cells.[64] The autophagy process is started when rilmenidine stimulates the cAMP/EPC/PLC pathway. In a manner similar to that of clonidine, it activates and binds to the imidazoline receptor.[64] Even though there was a decrease in mHTT levels in the mouse HD model, the number of aggregates did not alter. Although rilmenidine was unable to stop the body from losing weight, it corrected muscle parameters and showed a general strategy for treating numerous neurological diseases.[65]

Cellular homeostasis is kept under control by a balance between the production and deterioration of proteins, for example. Long-lived protein aggregates that are misfolded are broken down by autophagy, whereas short-lived protein aggregates are handled by the USP[66]. Autophagy has grown more important in late-onset neurodegenerative disease states because it contributes to the development and pathogenetic mechanisms of neurodegenerative illnesses.[67]

Autophagy in the Treatment of AD

Selective memory loss and dementia caused by aging are the main clinical signs. The accumulation of neuritic plaques and strands in the grey matter, as well as extracellular senile plaques that resemble silk, are all connected to neuronal death. In the early stages of AD, brain cell death is mostly influenced by the levels of tau protein and amyloid beta-peptide (AβP).[68] Scientific investigations have shown that extracellular Aβ-plaques, impaired cholinergic function, intracellular neurofibrillary tangles, including hyperphosphorylated tau proteins, and ultimately defective autophagy make up the major pathogenic route of AD.[69,70] However, neurodegeneration has also been associated with the Aβ-peptide that results from the sequential cleavage of APP by BACE1 and G-secretase. APP is an amyloid precursor protein. This peptide accumulates during the course of AD and has been linked to memory impairments and dysfunctional neurons in the cortex and hippocampus.[71] Particularly, Aβ-peptide appears to be formed in autophagosomes, which also appear to contain presenilin-1 enzymes and APP that help break down APP into Aβ-peptide. Autophagy conditions may also have a substantial impact on the -peptide release into extracellular space, which leads to the development of plaques.[72] Normal brain cells do not have as abundant autophagosomes as do AD brain cells, indicating that autophagy has been induced with a faulty autophagosome-lysosome fusion.[73] Similarly, recent research indicates that decreased Beclin 1 gene expression results in impaired neuronal autophagy, amyloid beta-peptide buildup, and subsequent neurodegeneration.[74] When non-degraded autophagic vesicles were examined under a microscope in the deteriorating brain tissue of Alzheimer's patients, it was clear that autophagic flux had been stopped.[75] Autolysosomal vesicle buildup and impaired autophagic fluxes are common features of Alzheimer's disease cells or animal models.[76,77] For instance, the mutation of presenilin-1 is the most common cause of familial AD, and has been associated with an autophagic arrest.[78] APP mutations have been associated with familial AD and the production of amyloid precursor protein (APP) in autophagic-lysosomal illnesses.[79] Similarly, the production of Aβ-peptides, the cleavage result of APP, led to the formation of enormous autophagic vesicles in the *Drosophila* brain.[80] This data implies that the dysfunctional control of autophagy during the autophagosomal breakdown stage contributes to AD.[81] In AD brains, activated caspases have been seen.[82] Caspases have also been shown to cleave proteins associated with AD, including the APP and tau metabolism, leaving behind beta-amyloid-containing fragments.[83,84] Caspases have been linked to AD in studies to date, although they have not been linked to the onset or course of the disease. All of this information points to autophagy activation as a potential treatment approach for "tauopathies" and beta-amyloid removal.

Autophagy in the Treatment of PD

A characteristic of the condition is the gradual death in the substantia nigra of dopaminergic brain cells. Lewy bodies, which are eosinophilic intracytoplasmic globular deposits in the nuclei of neurons, are the key identifying feature.[85] More research has revealed that the aggregated, insoluble form of α-synuclein that comprises these entities is toxic. This cytosolic protein is widely expressed in presynaptic membranes and is present in large amounts in the brain.[86] It can bind to membrane phospholipids and requires involvement in presynaptic terminal membrane-related processes.[87] The two missense variants in α-synuclein that causes early-onset PD are A53T and A30P.[88] As the disease progresses, dementia becomes more prevalent, and more than one-third of people with PD experience anxiety and depression.[89] The neurodegenerative disease PD has characteristics that are suggestive of impaired autophagy. In a study of familial PD, many PARK genes were discovered to be causative.[90] Many of these genes, including SNCA(PARK4), Parkin (PARK2), UCHL1(PARK5), PINK1(PARK6), DJ-1(PARK7), LRRK2(PARK8), and ATP13A2(PARK9), have been shown to have a role in the autophagic clearance of damaged mitochondria or ubiquitinated proteins.[91,92]

Additionally, Parkinson's patients' affected tissues include protein aggregation and impaired mitochondria. Therefore, autophagy seems to stop the progression of PD diseases.[93,94] Understanding these PARK elements in the control of autophagic processes, as well as other genetic elements linked to neurodegeneration, has benefited greatly from the *Drosophila* model.[95] To recycle α-synuclein, the proteasome system, macro-autophagy, and chaperone-mediated autophagy all collaborate.[96] Only soluble protein types are destroyed by the proteasome. Normally, CMA breaks down a portion of intracellular α-synuclein that has undergone abnormal oxidation or phosphorylation and alters the CMA pathway by losing its sensitivity on the lysosomal membrane for the CMA receptor. They assemble in the cytoplasm rather than entering for disintegration. Furthermore, missense mutations in α-synuclein or dopamine-mediated changes worsen CMA impairment.[97] Patients with PD (PD) have higher amounts of caspases-1, -3, and -8 in their brains.[98,99] In several animal models of PD, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), neurotoxins 6-hydroxydopamine (6-OHDA), and its metabolite 1-methyl-4-phenylpyridinium have been demonstrated to cause increased caspase activation.[100,101] Caspases may or may not have a causative role in the death of dopaminergic neurons, and inhibiting caspases may not be able to stop PD related neuronal cell death.[98]

Autophagy in the Treatment of HD

The main pathogenic alteration in HD brains is the loss of certain neurons in the cortex and striatum. The polyglutamine pattern at the N-terminus of the mutant huntingtin protein grows in HD as a result of an abnormal expansion and repeating of the trinucleotide CAG in exon 1 of the huntingtin gene.[102] The age at which HD first manifests is inversely connected with the size of a polyglutamine area, and the onset of the illness is linked with a growth of the CAG repeat over 35 motives.[103] Misfolded mHTT builds up and causes extra-nuclear inclusion bodies to develop in the brain, which causes striatal GABAergic neurons to selectively die. Uncertainties still exist over how CAG repeats relate to HD. While mHTT expression has been seen in both neurons and other tissues, it is typically found in neural zones, such as cerebellar Purkinje cells, cortex, and substantia nigra.[104] The findings show that the elevated CAG cycle in mHTT encourages the breakdown of aberrant protein molecules. There is presumably a link between deteriorated fragments and their nuclear translocation and subsequent toxicity, particularly those processed by Caspase-6.[105] Additionally, it has been shown that susceptible neurons experience severe impacts from the growing amount of mHTT cleavage products (e.g., mitochondrial malfunction and abnormal neurotransmitter release).[106,107] The toxicities of mHTT are only produced by caspase-6-mediated fragmentation. Thus, if this particular fragmentation is prevented, transgenic mice with a phenotypic of huntington's disease won't develop progressive neurological abnormalities. Inhibiting the HD gene caused complete remission and symptom reversibility in mice with HD symptoms (motor impairment and neuronal inclusions), suggesting that HD may be treatable.[108] HD appears to have major changes in autophagy. As a result, both in laboratory models and human HD samples, a buildup of autophagic vacuoles has been noted.[109,110] Additionally, it has been shown that alternative versions of a number of genes involved in the autophagy and ubiquitination processes are expressed by the oligodendrocytes and neurons of HD patients.[111,112] HTT is also sensitive to ubiquitination, which is necessary for both its degradation via the UPS and autophagy degradation pathways. Two putative KFERQ-like domains that might be targeted by HSPA8 and then destroyed by the CMA process are shown by HTT. The buildup of damaged and misfolded proteins might be significantly impacted by the modification of autophagy gene expression. Thus, the severity of HD was associated with the ATG7 polymorphism.[113] Other alterations have also been reported, for instance in Beclin-1.[114] A substantial impact on how autophagy initiates may also result from the association of mHtt and the Htt protein Rhes with the complex that engulfs Beclin-1.[115] When autophagy was induced in vitro, the quantity of Htt aggregates, and the toxicity of the mHtt protein were all decreased.[116] Two significant findings for Atg7 and Atg16 were found in a recent study on eight polymorphisms affecting the five ATG genes (Bexlin-1, Atg16L1, Atg3, Atg5, Atg7). Early illness start has been linked particularly to the ATg7 polymorphism (V471A), which encodes alanine for valine.[117]

Intermittent-Fasting (IF) and Neuronal Autophagy

The effect of fasting on the liver's autophagy system is being investigated. Approximately, 24 to 48 hours of food restriction were given to male GFP-LC3 mice aged 6 to 7 weeks, which is known to cause fatty acid change and hepatic autophagy.[118,119] Confocal imaging of vibratome slices revealed autophagosomes and elevated autophagy activity in the hepatic cells of mice on a restricted diet. Food restriction also greatly enhanced the size and quantity of neurons autophagosomes inside the cell bodies of neuronal cells. These alterations became apparent after 24 hours of food limitation, and by 48 hours, they were significantly more prominent. Mice who had been fed for 48 hours had cortical neurons with autophagosomes that showed reduced circularity while simultaneously increasing fraction and perimeter, as demonstrated in the hepatic cells.[120] Recent investigations have shown that acute fasting starts autophagy in the central nervous system.[121] According to the study, which examined the levels of LC3 and p62 in cortical tissues from mice fed ad libitum as well as those who had not been fed, a 24 hours fasting period increased the concentrations of the proteins p62, LC3-I, and LC3-II in the cortex of both wt and YAC128 animals.[122] Increased brain-derived neurotrophic factor synthesis is one of the most significant neuronal responses to intermittent fasting, which is confirmed by a plethora of studies.[123] Food deprivation triggers a metabolic switch that increases excitatory synaptic activity in neurons. This calcium influx through membrane channels, along with the activation of several kinases and signalling pathways, leads to the expression of various genes that, in

turn, induce the expression of proteins involved in cellular stress adaptation, including BDNF.[124] In models of PD, IF has enhanced insulin sensitivity,[125] decreased excitotoxicity,[126] decreased neurodegeneration,[126] and offered defence against autonomic dysfunction,[127,128] cognitive and motar decline,[129] as well as protection against these illnesses. By promoting neurogenesis[130] and strengthening the survival of neural progenitors, IF combats further pathogenic aspects of PD.[131] Additionally, the resulting ketosis could facilitate reduced excitotoxicity through the over expression of GABA.[132]

CONCLUSION

As society's elderly citizens become older, neurodegenerative disorders–common, pervasive illnesses of old age–become more prominent. These illnesses are terrible not just because of the financial toll they take on society (medical expenses, lost productivity, etc.), but also they literally strip people of their identity. Knowing this, the results of society's millions of dollars of investments in the search for drugs that can prevent, or at the very least significantly slow down, neurodegeneration, are, at best, unsatisfactory. Thus, in order to halt the course of neurodegenerative diseases, it is crucial to hunt for new targets that may be employed for therapeutic and pharmacological objectives. As mentioned above, experimental medications and treatments that control autophagy have garnered a lot of attention in recent years. While other approaches have been discovered in addition to a number of promising experimental anti-neurodegenerative medications, one must exercise some caution when dealing with medications that modulate autophagy. Clinical results from autophagy modification alone are unlikely to be sufficient. This is owing to the fact that autophagy is very interrelated and that while excessive autophagy may potentially cause the targeted cell to die, extensive autophagy would often favor cell survival. Intermittent fasting in relation to autophagy and neuronal health also shows encouraging outcomes. As a result, when used in clinical settings, medications that modulate autophagy and fight degeneration are most likely to have the intended benefits when the pro-survival benefits of combined therapy are enhanced.

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