

Purposed potential Alzheimer's Disease treatment based on the results from current primary research models

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Abstract. Alzheimer's Disease is one of the most known neurodegenerative diseases that causes over 100,000 deaths till now. The pathology of Alzheimer's Disease is still not fully clear, but the most widely accepted pathology is the chronic endoplasmic reticulum (ER) stress caused by neurotoxicity via amyloid beta (A β) plaques and intracellular tau tangles. In Alzheimer's patients, the abnormal A β plaques and tau tangles cause oxidative stress and induce chronic ER stress, which can hardly be relieved by the normal UPR pathway. One potential treatment for rescuing the excessive ER stress caused by A β accumulation in human neural cells is the Salubral (Sal) treatment. Amentoflavone (AF) treatment is a plausible treatment to alleviate cell death stress due to pyroptosis in Alzheimer's patients. Latrepirdine (LAT) is a treatment that can induce autophagy with the help of ATG5. Mitophagy is a special form of autophagy that degrades dysfunctional mitochondria and does not function well in Alzheimer's patients. Treatment like NMN, UA, and AC can effectively induce mitophagy, decrease memory loss, and relieve common Alzheimer's pathology like A β plaques and tau tangles. In this review, the primary research on four key mechanisms in Alzheimer's etiology - UPR pathway(apoptosis), pyroptosis, autophagy and mitophagy - will be discussed and some potential treatments targeting these four mechanisms will be briefly introduced with the primary research results.

Keywords: Alzheimer's Disease, UPR/apoptosis, pyroptosis, autophagy; mitophagy.

1. Introduction

Alzheimer's Disease is now the most common type of dementia worldwide. Dementia is any type of cognitive decline that can interfere with daily life [1]. The most common symptoms of Alzheimer's Disease include gradual memory loss, abolition of space and time, and neuron cell degeneration. The etiology of Alzheimer's disease remains uncertain and controversial; however, the most widely accepted proposed etiology of Alzheimer's disease is the Endoplasmic Reticulum (ER) stress caused by abnormal accumulation of proteins in the neural cells [2]. ER stress is that ER will be under stress when there are unfolded or misfolded protein accumulations in ER. The major aggregated proteins in the brain cells that are observed in Alzheimer's patients with positron emission tomography (PET) are extracellular amyloid beta (A β) plaques and intracellular tau tangles [3].

Amyloid beta is derived from the metabolism of type I transmembrane amyloid beta precursor protein (APP) cleavage [4]. The product of APP cleavage by the extracellular protease α -secretase near the cell membrane is sAPP α , an N-terminal soluble extracellular peptide that is involved in many pathways like proliferation and metal homeostasis [5]. APP can also be cleaved with β -secretase 1(BACE1), an aspartyl protease that cuts APP into sAPP β and β -secretase-derived APP-CTF fragment(C99) [4]. sAPP β is a soluble peptide which is highly associated with lipid-induced inflammation and insulin tolerance in muscle cells like myotubes [6]. C99 is rapidly cleaved by γ -secretase in endosomes and mitochondria-associated ER membranes (MAM) and A β is generated during the C99 cleavage [7]. A β can aggregate into plaques, which can cause ER stress and activate both the protective unfolded protein response (UPR) mechanism and the apoptotic pathway, and A β accumulation is one of the most common biomarkers observed in Alzheimer's Disease diagnosis [2].

UPR functions in deciding cell fate during ER stress and is crucial for ER homeostasis. When ER stress reaches the threshold, the UPR will be activated to alleviate the stress and maintain ER homeostasis. The core proteins that makeup UPR are protein kinase R(PKR)-like endoplasmic reticulum kinase (PERK, the stress sensor), inositol-requiring protein 1 α (IRE1 α), and activating

transcription factor 6(ATF6). The sensor protein for IRE1 α is chaperone HSPA5, the sensor protein for PERK is chaperone GRP78, and the sensor protein for ATF6 is chaperone Bip. The PERK-ATF4 pathway, IRE1 α -XBP1 pathway, and ATF6-ATF6f pathway will activate the translation of UPR target genes and start ER homeostasis restoration. In the case that the dysfunctional proteins cannot be restored, these cells will enter the apoptosis pathway [8]. Overactive UPR will lead to neuron degeneration, which is one of the pathological processes in Alzheimer's Disease patients.

Tau tangles also known as neurofibrillary tangles (NFTs) are composed of hyperphosphorylated tau proteins. These tau tangles can cause the function loss of physiological mechanisms and toxicity accumulation and is another hallmark of Alzheimer's Disease. The aggregation of misfolded tau proteins also contributes to chronic ER stress and induces overactive UPR like A β accumulation does in the brain [9].

Alzheimer's Disease is an incurable chronic neurodegeneration disease since there are still many unclear mechanisms requiring further investigation and the current medicines barely influence the slowdown of progression in patience. According to the latest statistical resource database, there are around 6.5 million American elderly that are 65 years old and above living with Alzheimer's Disease. By the end of 2060, this number would rise to 13.6 million if there are no effective drugs or treatments invented or developed. Even with the Covid-19 outbreak in 2020, Alzheimer's Disease remains as the 5th death cause in the United States [10].

Even though the cause of Alzheimer's Disease is unclear which makes it impossible to target the disease origin directly now, there are major potential strategies for rescuing Alzheimer's disease like alleviating ER stress and blocking overwhelmed UPR activity. Besides protein accumulations and UPR, pyroptosis-induced inflammation, dysfunction mitophagy and autophagy deficiency are also observed in Alzheimer's Disease Patients. Several compounds or treatments that target different proteins involved in the disease pathology show significant effects in animal models and some even enter clinical trials. In this mini-review, directions for possible disease rescue strategies based on current experimental data and results will be briefly discussed.

2. Salubral Treatment In The A β -Induced Er Stress And Upr Mechanism

Normal temporary ER stress can be rescued by UPR like secretion of protein folding enzymes or apoptosis. However, in Alzheimer's Disease patients, chronic A β accumulation-induced ER stress cannot be easily relieved or regulated by UPR. Under normal conditions, ER chaperones - Grp78/Bip and CHOP - and ER-stress sensors - IRE1, PERK and ATF6 - form a silencing complex together with ER. All the chaperones and sensors can be activated when the inactive complex disassembles. As chronic A β aggregation takes place in the brain, the expression levels of Grp78/Bip and CHOP significantly increase by over 200% of those detected in the control (no A β treatment), which marks the induction of ER stress [2,11]. The ER chaperones will interact with misfolded/aggregated proteins like A β plaques in the cell lumen and activate IRE1 α expression. Both expression levels of IRE1 α and phosphorylated PERK(p-PERK) increase significantly 6 hours after 10 μ M aged A β treatment in the SK-N-SH cells. SK-N-SH cell lines are the model cells of human neuroblastoma cells in vitro that have epithelial morphology [12]. When treated with all-trans-retinoic acid, SK-N-SH cell lines will differentiate into cells that are phenotypically like neurons and can be used to mimic human neuroblastoma cell environments for future experiments related to human neural cells [13].

The phosphorylation of eIF2 α is activated with the increasing p-PERK level in the cell lumen. In the A β -induced ER stress and UPR pathway, PERK plays an important role in the ER stress restoration. The activation of PERK is proved to be related to the increased expression level of both eIF2 α and Grp78/Bip since the knockdown of PERK reduces the phosphorylation of eIF2 α , activation of Grp78/Bip, and increases apoptosis activity. The increasing expression in phosphorylated eIF2 α inhibits the normal cellular mRNAs translation so that the protein production will be temporarily stopped, and the accumulated misfolded/unfolded proteins can be fixed. The PERK-eIF2 α pathway activated by A β -mediated ER stress is a protective UPR pathway that maintains cell viability and

prevents cells from death; thus, the neuron apoptosis caused by A β neurotoxicity in the brain cells is enhanced without the normal PERK activities [2].

Caspase-3 and caspase-4 are members of the cysteine-aspartic acid protease family. Caspase-3 is the predominant proteolytic enzyme that is involved in APP cleavage, the precursor protein of A β in the brain. Many studies show that caspase-3 regulation is related to CHOP and participates in neuroblastoma cell apoptosis induced by ER stress and cell death mediated by A β accumulation [14]. The function of caspase-4 is still unclear; however, according to the current model results, caspase-4 is widely believed to be an inflammatory caspase like caspase-1 that facilitates the inflammatory cell death, known as pyroptosis. The increase in the expression level of caspase-3 and caspase-4 are all detected, indicating an increase in cell death. Combining all the results, hypoxia resulting from long-term A β accumulation can cause excessive ER stress and hyperactive UPR in the cells, which will cause immoderate neuron cell death.

One of the proposed plausible methods based on the primary research models that have the potential to rescue the excessive ER stress caused by A β accumulation in human neural cells is the salubrin treatment. Salubrin (Sal) is a phosphatase inhibitor that conditionally inhibits the dephosphorylation process of eIF2 α . Based on experiments on Alzheimer's mouse models, long-term treatment with Sal can increase the cell resistance to ER stress-induced apoptosis and short-term treatment with Sal can restore cell viability by inhibiting the nuclear factor-kappa B (NF κ B) pathway, instead of directly acting on the ER stress [15,16]. The NF κ B signalling family is involved in the inflammatory cytokine mechanisms and cellular apoptosis and usually remains silent in the cytoplasm. A β aggregation-induced neurotoxicity is related to the NF κ B pathway activation. Active NF κ B proteins translocate into the nucleus of neurons and stimulate A β -induced neuronal death in Alzheimer's patients. With both 50 μ M and 100 μ M Sal treatment in mouse models treated with A β , the expression level of NF κ B p65, one of the key proteins in the NF κ B family, was significantly reduced. Also, according to immunocytochemistry, NF κ B p65 remains in the cytoplasm of the Sal-treated A β cells, which indicates the translocation of NF κ B is inhibited by the Sal treatment [16]. Nevertheless, with the increased expression of Sal in model cells, the activation of cell death markers caspase-3 and caspase-4 and cell inflammatory hallmark caspase-1 are all inhibited, which implies a decrease in cell death. The Grp78 chaperone and p-eIF2 α also significantly increase and the cell viability is significantly higher than the viability detected in the A β cells under the 25 μ M Sal treatment, which indicates the activation of the protective UPR PERK-eIF2 α pathway and increase in cell resistance to A β neurotoxicity by Sal treatment [2]. To sum up, Sal can be considered a potential treatment for relieving cell death stress in Alzheimer's patients.

3. A β In Pyroptosis Induced By Alzheimer's Disease

Besides the apoptosis mechanism triggered by Alzheimer's Disease in the patients' brain cells, pyroptosis is another cell programmed death observed as one of the consequences of Alzheimer's Disease. Pyroptosis is an inflammatory programmed necrosis with the activation of executor gasdermin D (GSDMD) that can cause the production and release of inflammatory cytokines like alarmins or damage-associated molecular patterns (DAMPs). Necrosis is the irreversible body tissue death that happens when the tissue lacks blood supply for a long time. GSDMD is a member of the gasdermin family that can be found in different cell types including the neural cell lines and is involved in the pore structures for the pyroptosis pathway on the plasma membrane [17]. DAMPs are innate immune molecules secreted by damaged or dying cells that signal infection sites in the body [18]. Many current studies have revealed that pyroptosis is a unique inflammatory cell death pathway in neurons with signals like the increased expression levels of caspase-1, IL-18, IL-1 β , and GSDMD, which are highly related to the inflammation mechanisms.

As mentioned in the previous sessions, the pathology of Alzheimer's Disease is highly relevant to ER stress. When A β continuously aggregates, the ER stress increases to its threshold and the UPR pathway is activated to try to maintain the ER homeostasis. The expression levels of UPR proteins like

Bip and IRE1 α significantly increase, indicating the overactivation of IRE1 α based on the comparison with the control condition. The overactivation in the IRE1 α expressions causes a significant increase in TXNIP and NLRP3, which are the markers for excessive ER stress and UPR. High TXNIP expression levels activate the TXNIP-NLRP3-caspase-1 pathway, producing more active NLRP3 inflammasomes. High levels of NLRP3 inflammasome mediate more activations of Caspase-1 as the expression intensity of caspase-1 significantly increases in the immunoblotting results. Caspase-1 is an evolutionarily conserved enzyme that cleaves proteins like the inflammatory cytokine precursors which will lead to cell death processes like pyroptosis. NLRP3 activation also increases the expression intensity of N-terminal-GSDMD(NT-GSDMD). The pore formation by NT-GSDMD on the cell membrane results in cell swelling and the increase in the release of inflammatory cytokine IL-1 β , and IL-18 to extracellular space so that the immune cells can be recruited to prevent further infection [19]. Large amounts of lactate dehydrogenase (LDH) releases are also observed downstream of NLRP3 and determine the cell death; LDH release together with the high levels of NT-GSDMD and inflammatory cytokine IL-1 β , and IL-18, indicates the increasing induction of pyroptosis in the cells [11].

Amentoflavone (AF) treatment is a proposed plausible method that has the potential to relieve cell death stress due to pyroptosis in Alzheimer's patients. AF is a bioflavonoid compound that is found to be effective in many biological mechanisms like anti-inflammatory and anti-oxidative. In the A β transgenic mouse models, 80mg/kg AF treatment can reduce the errors to find food by 45~50%, which implies AF can effectively reduce the A β -induced neurological dysfunction and short-term memory deficit [20,21]. The NLRP3 intensity is high in A β mice and back to almost the same as that in the control group in AF-treated mice. When the relative IL-18, IL-1 β , and caspase-1, levels are set as 100% in healthy mice, these pyroptosis marker proteins are all doubled in the A β mice. In comparison, the expression level of IL-1 β , IL-18, GSDMD, and caspase-1 are all very similar to the healthy control mice group in the AF-treated A β mice, which indicates AF can prevent neural cells from pyroptosis resulting from A β accumulation and increase cell viability [20, 22].

In the human neuroblastoma SH-SY5Y cells, 5 μ M A β treatment can largely reduce cell viability and mimic the brain cells of Alzheimer's patients. However, for SH-SY5Y cells that are treated with 5 μ M or 10 μ M AF 6 hours before the A β treatment, the LDH release decreases by 50% compared to the A β cells without treatment, which marks the decrease in pyroptosis activities. Also, AF increases the AMPK and GS3K β phosphorylation in the SH-SY5Y cells. By investigating the relationship between AMPK and AF, the siRNA AMPK is used to treat mouse models to silence the AMPK expression. The expression levels of caspase-1, IL-18, IL-1 β , and NLRP3 are all restored with AMPK knockdown. This result indicates AMPK acts downstream of AF in regulating pyroptosis and knockdown of AMPK suppresses AF's ability to inhibit pyroptosis in the A β cells [20]. In short, AF can suppress A β -induced neurotoxicity in animal and cellular models by inhibiting pyroptotic cell death via AMPK signalling. Moreover, AF shows significant effects on mitigating short-term memory decay in the Alzheimer's Disease mouse models [20-22]. Thus, with future clinical test trials, AF could be a potentially effective treatment to relieve Alzheimer's symptoms and reduce the severity of Alzheimer's Disease by repressing excessive pyroptotic cell death.

4. Lat Treatment In Autophagy

Autophagy is responsible for regenerating healthy new cells from damaged cells that can compensate for the abnormal cell death caused by ER stress. In the Alzheimer's Disease iPSC-derived neurons, the basal level of autophagy activity is at the minimum level or not even observed with current laboratory techniques. The induction of autophagy is essential in cell survival and ER homeostasis. It also helps regulate A β and assemble tau; thus, dysfunctional autophagy can induce and aggravate Alzheimer's Disease. Autophagy is generally regulated by two types of ER stress, canonical ER stress and non-canonical ER stress.

In the canonical ER stress response, autophagy is mainly involved in the IRE-XBP1 pathway, PERK-eIF2 α -ATF4-CHOP pathway and ATF6 α arm of UPR machinery. In the IRE1-XBP1 signalling,

the accumulation of misfolded proteins which reach the threshold of ER stress will cause the release of the ER sensor chaperone Grp78. Then RNase activity is activated and starts the cleavage of x-box binding protein 1 (XBP1) into XBP1-S. The activated XBP1-S together with IRE1 α will cause LC3-I to convert to LC3-II (microtubule-associated proteins 1A/1B light chain 3B/MAP1LC3B, often referred to as LC3). in endothelial cells and cause autophagy. Also, the IRE1 α -JNK pathway facilitates B-cell lymphoma 2 (Bcl-2) phosphorylation where dissociation of Beclin-1 will also contribute to the induction of autophagy. LC3 facilitates autophagosome maturation via selective cargo recruitment, which is a centre protein in autophagy [23].

In the PERK-eIF2 α -ATF4-CHOP pathway, the ER stress will increase the expression level of PERK and eIF2 α , which will lead to the activation of ATF4. The increasing expression levels of autophagy-related genes like LC3B, p62, ATG5, ATG12, and BECN1 by active ATF4 upregulate autophagy. In the ATF6 α arm of UPR, the hypoxia-induced ER stress will let Grp78 leave the ER sensor and activate PERK, the same as the other two canonical pathways. Activation of PERK can upregulate LC3 and ATG5 with the cooperation of ATF4 and CHOP. Moreover, eIF2 α interacts with ATF4 and CHOP to regulate the expression level of p62, which is crucial in the induction of autophagy [24]. The activation of autophagy is mediated by increasing levels of CHOP and XBP1 [25].

In the non-canonical ER stress response, the canonical UPR elements will interact with other factors to promote autophagy. The inhibition of both BRAF(B-Raf) and MEK can activate cytoprotective autophagy by canonical UPR after the Grp78 release due to ER stress. BRAF is a proto-oncogene involved in cell-cell signalling and cancer induction. Free Grp78 binds to the complex with BRAF and MEK and inhibits the phosphorylation of ERK temporarily [26]. As the activated complex translocates from the cytosol to the ER membrane, the ERK will be re-phosphorylated by PERK. The activated ERK translocates into the nucleus and binds to ATF4, which will cause the ATF4 phosphorylation. The activated AFT4 can increase autophagy genes and autophagy induction.

Another non-canonical pathway that can induce autophagy is the PERK-NRF2 pathway. The ER stress will activate PERK, phosphorylate and stabilize NRF2. Under the stress, NRF2 is free-moving and can be stabilized by p62 binding. NRF2 then translocates from the cytoplasm to the nucleus to increase the expression of autophagy cargo receptors p62 and NDP52. This forms a positive feedback loop of PERK-NRF2-p62 in the PERK-NRF2 signalling. The upregulated p62 binds to LC3-II and LC3 will bind to CCPG1 together with GABARAP, which will lead to autophagy. ER stress can stimulate Ca²⁺ release from ER lumen via the IP3R channel, a Ca²⁺-specific gated channel. As the cytosolic Ca²⁺ gradient increases, the CaMKK β /AMPK pathway is activated, and the mechanistic target of rapamycin(mTOR) phosphorylation will be inhibited. The inhibition of mTOR kinase induces autophagy since rapid mTOR activation suppresses autophagy activity [27, 28].

Latrepirdine (LAT) is a pyridoindole organic compound that belongs to the methylpyridine family. This compound is studied and examined as a potential medical treatment for Alzheimer's Disease. In mouse N2a neuroblastoma cells (cell lines treated with APP and mimicking the environment of Alzheimer's Disease cells), either 5500nM or 50 μ M LAT treatment can significantly increase the LC3-II expression level. The phosphorylated mTOR expression level decreases significantly after the LAT treatment, indicating the ability of LAT on suppressing mTOR activation. The autophagy hallmark, p62, is also examined after LAT treatment and the expression level of p62 slightly decreases after 3- or 6-hour treatment. Since p62 will be degraded during the autophagy process, the accumulation of LC3-II and reduction of p62 together indicate the maturation of autophagosomes and autophagy activation after the LAT treatment. Also, the role of ATG5 is tested with LAT treatment. For ATG5 knockdown, no accumulation of LC3-II is detected and there is a significant increase in both p62 expression level and APP-CTFs intensity without LAT treatment. The accumulation of APP-CTFs indicates the A β aggregation and the high p62 intensity suggests the turnover of autophagy. After treating the ATG5-knockdown cells with 50 μ M LAT treatment, there is no evidence for changes in neither p62 nor APP-CTFs. In comparison, when incubating wildtype cell lines with homozygous ATG5 expressed in 50 μ M LAT treatment, the expression level of APP-CTFs significantly decreases

by 25% than that in ATG5 silenced cells. All the results imply part of A β accumulation results from autophagy failure and LAT regulates autophagy via ATG5 signalling [29].

ER-stress-induced autophagy can increase cell viability and ensure the homeostasis of ER with other normal UPR activities. However, overactive autophagy also induces drug or therapy resistance; thus, finding suitable proteins to target is important. LAT can be a potential treatment for neurodegenerative diseases with more precise and accurate clinical investigations.

5. Nmn, Ua, And Ac Treatment In Mitophagy

More and more recent studies reveal that Alzheimer's Disease is also related to the decrease in mitophagy activities. Mitochondria are important membrane-bound cell organelles that are responsible for cellular respiration, energy production and cell death. Damaged or dysfunctional mitochondria due to oxidative stress or damage are degraded through autophagy to restore cell homeostasis, and this process is called mitophagy. Mitophagy can be induced with mild levels of oxidative stress or ER stress. In Alzheimer's patients, there are decreases in autophagy lysosomal pathways, which is the major intracellular molecules degradation mechanism. As a result, the removal of damaged mitochondria reduces, resulting in the accumulation of dysfunctional mitochondria, also known as mitophagy failure. The impaired mitophagy can lead to an increase in oxidative damage and trigger A β and tau accumulation, as well as synaptic defects and cognition failures [30].

The phosphatase and TENsin (PTEN) homolog-induced putative kinase 1(PINK1) pathway is the dominant mitophagy pathway. The outer layer of dysfunctional mitochondria traps PINK1 and PINK1 recruits mitophagy markers like p62 to the site. In the meantime, the LC3-II conversion takes place and causes LC3 accumulation. The aggregate LC3 recruits marked damaged mitochondria and deliver the dysfunctional mitochondria cluster to the lysosome for mitophagy degradation. For chronic dysfunction mitochondrial accumulation (mitophagy failure), the cells cannot generate enough energy for metabolism, the A β oligomers interrupt Ca²⁺ equilibrium between cells, and the 5' AMP-activated protein kinase (AMPK) is activated. The insufficient cell metabolism, Ca²⁺ imbalance and AMPK activity result in synaptic signal loss, neurotoxicity, and memory loss [31].

In patients with Alzheimer's Disease, the APP-CTFs accumulation induces excessive mitochondrial alteration in the neurons, instead of A β accumulation. The excessive change in mitochondrial causes excessive mitochondria dysfunction. The mitochondrial length becomes shorter and narrower, and the area of mitochondria decreases in Alzheimer's patients. The percentage of damaged mitochondria significantly increases by 50%. A much higher expression level of AMPK-related proteins is observed and implies the memory loss symptom in Alzheimer's patients. The mitophagy events decrease significantly by approximately 33% and the mitophagy protein expression levels decrease in Alzheimer's patients [32]. In the human neuroblastoma SH-SY5Y cells with APP-CTFs accumulation, the knockdown of PINK1 causes fragmentation of mitochondria and increases mitophagy activities; however, the inflammation in brain tissues is increased under this situation [33]. In the Alzheimer's mouse models, the knockdown of PINK1 also increases the expression of NLRP3 and cleaved caspase-1, which increases cell death [32].

The effective drugs for relieving mitophagy failure stress or inducing mitophagy activities are still under investigation. Nicotinamide mononucleotide (NMN), an NAD⁺ precursor, is treated in Alzheimer's mice. The result turns out that 5mM NMN treatment increases the mitophagy receptors and autophagosome marker proteins, indicating the elevation in neuronal mitophagy. NMN also shows a memory increase with the presence of DCT-1[32, 34].

Urolithin A(UA) is a natural compound extracted from pomegranate and can induce mitophagy in muscle cells. The expression level of mitophagy proteins and the intensity of mitophagy events increases significantly, almost doubled, with the 0.1mM UA treatment. The increase in the anti-inflammatory cytokines and improvement in memory are all observed in the Alzheimer's *C. elegans* and Alzheimer's mice with 0.1 mM UA. Since tau overexpression causes pTau accumulation and induces ER stress like A β accumulation, UA treatment can reduce A β aggregation and inhibit the

activation of tau sites with the induction and facilitation of mitophagy, with the help of PINK1. UA also reduces NLRP3 expression levels, proved by the significant decreases in its downstream proteins like IL-1 β and caspase-1, indicating the reduction in neuroinflammation. Actinonin (AC), is a natural antibacterial compound that targets mitochondria-related RNA degradation mechanisms. 1mM AC treatment exhibits similar results as UA treatment does. The mitophagy proteins and events, anti-inflammatory cytokines and memory restoration are all improved with AC treatment [32].

Moreover, UA and AC treatments induce robust neuronal mitophagy and improve associative memory in APP mice (mice treated with APP-CTFs) without influence on memories of wild-type animal models. Damaged mitochondria observed in the hippocampus of Alzheimer's mice are removed by UA and AC. Based on the experiment results, both UA and AC function in normalizing the morphology and size of mitochondria, improving learning and memory retention and relieving common Alzheimer's Disease pathology like A β plaques and tau tangles. UA and AC also have functions in increasing the expressions of proteins involved in microglial phagocytosis, where microglial cells can engulf A β plaques and decrease the chance of A β accumulation. In short, UA and AC treatments remove about 50% of damaged mitochondria via mitophagy induction, and significantly decrease inflammatory cytokines like IL-6, and TNF- α by increasing anti-inflammatory cytokines. The specific combination of 0.1 mM UA, 1 mM AC, and 5 mM NMN treatments are tested and shows evidence of inducing mitophagy, removing or repairing damaged mitochondria, improving the brain memory and thinking function, and relieving common Alzheimer's Disease pathology like A β plaques [32].

6. Conclusion

There are no effective Alzheimer's Disease targeting drugs found on the market. Alzheimer's disease's origin is unclear, so it is hard to design a drug that can directly target the true cause of this life-threatening neurodegenerative disease. The increase in cellular apoptotic deaths and neural pyroptotic inflammations all need effective treatments to decrease the development/severity of Alzheimer's Disease. Treatment like Sal and AF show great effects on regulating the key proteins involved in these mechanisms and rescue cells from death caused by overactive apoptosis and pyroptosis. Autophagy and mitophagy degrade dysfunctional organelles to ensure cellular homeostasis, which are also essential in cell metabolism and are diminished in Alzheimer's patients. They're existing many compounds can induce autophagy; however, overactive autophagy will lead to cell resistance to therapy. LAT is one of the autophagy inducers and functions in Alzheimer's models and has a chance to enter clinical trials. Thus, it is important to examine whether LAT will induce too much autophagy during future investigation. Mitophagy can degrade abnormal mitochondria and is also suppressed in Alzheimer's patients. Natural compounds NMN, UA, and AC show a great increase in mitophagy in Alzheimer's models without changing mitophagy activities in healthy models. The invention of effective drugs and therapies is the priority in the investigation of Alzheimer's Disease. Any treatment that has great relieving effects or can directly function on key proteins involved in Alzheimer's pathology can be detailed and examined to see whether it can become an effective medication or not.

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