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Restoring the acidifying function of lysosomes for Alzheimer's disease therapy

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Abstract. Alzheimer's disease, abbreviated as AD, is a clinical syndrome that often occurs in the elderly, characterized by progressive deterioration of memory and cognitive function. The disease usually manifests gradually, following a slow and irreversible progression. It leads to brain atrophy and eventual cell death. Recent research suggests that Alzheimer's disease may result from nerve cell death followed by the appearance of extracellular amyloid plaques. This study will focus on lysosomal acidification disorders, which lead to lysosomal rupture and subsequent cell death. The abnormal acidic environment in lysosomes is mainly due to the increase in pH value and the loss of activity of V-ATPase. This work will investigate the potential of pharmacological agents and nanoparticles to restore lysosomal acidification by enhancing V-ATPase activity and lowering pH levels. The research demonstrates that nanoparticle-based and pharmacological methods hold promise for addressing the dysfunction in lysosomal acidification, a key issue in Alzheimer's disease.

Keywords: Lysosomal dysfunction, Neurodegenerative disease, Innovative DNA derivative-based nanocarrier, Polymeric or lipid nanoparticles, Nucleolipids (NLs).

1. Introduction

Alzheimer's disease (AD) is a specific form of dementia and is a degenerative condition of the central nervous system that worsens over time. Up tp 2022, it ranks as the fifth most prevalent illness among the elderly [1]. Epidemiological studies show that AD prevalence increases with the aging population [1]. The major hallmark of Alzheimer's disease is an amyloid protein accumulation, also known as age-related plaques, in the extracellular nervous system of the brain. The amyloid cascade hypothesis is one prominent theory explaining the pathogenesis of AD. Current pharmacological interventions aim to decrease the synthesis and deposition of amyloid proteins, but these treatments have shown limited effectiveness. Existing drugs can only delay symptom progression and are ineffective in reversing the disease; furthermore, symptoms often recur after discontinuation. This raises questions about whether current treatments address the root cause of AD. Recent studies have challenged the traditional view,

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suggesting that nerve cell death may actually precede the formation of extracellular amyloid plaques [2]. Some researchers propose that dysfunctions in lysosomal acidification, specifically in autophagy lysosomes of nerve cells, could be an early indicator of AD [2]. Lysosomes and autophagic vesicles combine to generate autophagy lysosomes. Lysosomes can remove useless biomacromolecules and organelles from cells as well as protein deposits that proteasomes are unable to break down. Autophagy is a key process involved in the degradation of proteins and other cellular components within lysosomes [3]. In the context of Alzheimer's disease, autophagic vesicles transport damaged proteins, nucleic acids, and other cellular components to lysosomes for degradation. The proton pump V-ATPase pumps H+ ions from the cytoplasm into the lysosome, creating the acidic environment required for the activity of hydrolytic enzymes. Disruption in lysosomal acidification leads to the accumulation of waste products, including amyloid proteins and their precursors, thereby halting the decomposition process. The hydrolytic enzymes in the lysosome will be released into the cytoplasm when the lysosome can no longer survive rupture, breaking down and digesting cells, rupturing the cell membrane, allowing intracellular waste to flow out, and eventually generating the "extracellular" amyloid plaques we observe. In other words, extracellular amyloid plaques or even the remains of deceased nerve cells combined with amyloid protein form before cell death. Despite its significance, existing research has not thoroughly explored methods to address the barriers related to lysosomal acidification. This study aims to provide a comprehensive overview of strategies to address the challenges associated with lysosomal acidification in Alzheimer's disease.

2. Causes of acidification disorder

According to studies, autophagic lysosome malfunction in nerve cells, or more specifically, the "acidification" issue, which all originate from the function of autophagic lysosomes, is the aetiology of Alzheimer's disease [2].

Lysosomes and autophagy vesicles combine to generate autophagy lysosomes. Autophagy vesicles move the damaged proteins, nucleic acids, and organelles to the lysosomes, which contain enzymes that break them down. This process is analogous to an automatic cellular garbage disposal system. The lysosome's interior is normally acidic (pH 4.5-5.0) and the enzymes found inside can only operate correctly in this acidic environment [4]. The autophagic vesicles will continue to transport cellular waste to the lysosome if lysosomal acidification is hindered then proteins like -amyloid protein and -amyloid precursor protein (APP) metabolite APP-CTF are tough to remove and can only accumulate there. Beta-amyloid is released into the tissue environment when the cellular waste in the lysosome breaks down and further promotes cell disintegration, leading to the "extracellular plaques" that are hallmark of Alzheimer's disease.

This hypothesis was tested in Alzheimer's disease-infected mice by using Specific labeling of autophagic vesicles in neural cells using red green fluorescence tandem probes, where 90% of the autophagic lysosomes in the neocortical area of the brain had already begun to acidify five months after birth, at least five months before they started to build amyloid plaques (10–12 months later). The phenomena of autophagic lysosomes with acidification problem and nerve cell degeneration, however, was seen in the brains of 5xFAD mice with early-onset Alzheimer's disease model at 2 months of age [2]. Proton pump v-ATPase and ion transporters, which shuttle anions and cations across the lysosome membrane, play major roles in controlling lysosome acidification. To keep lysosomes acidic, v-ATPase, an ATP-dependent proton pump, pumps H+ ions from the cytoplasm into them. But because v-ATPase is an electric pump, the electrical gradient it generates needs to be reduced in order to keep the flow of H+ constant. To do this, cations must be released and/or anions must be introduced.

There are mainly two causes of acidification disorder of lysosomes. One of the cause is the higher pH value, which disrupt the acidic environming in lysosomes to function properly [5]. Another cause is V-ATPase losing its viability. As shown in figure 1, V-ATPase regulated by glucose assembly [6]. They work by consuming VATPase to allow hydrogen ions outside the lysozyme to enter the proton pump. Basic methods are used to modulate V-ATPase activity: manipulating the reversible breakdown of V-ATPase.

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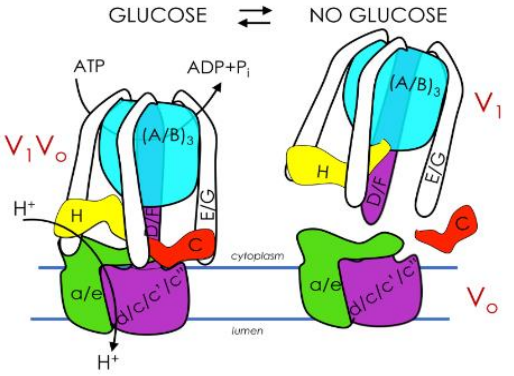

Figure 1. Glucose regulates assembly of V-ATPase [6].

It is crucial to control V-ATPase's activity because it is present in yeast, insect, and mammalian cells frequently. Although glucose does not directly interact with V-ATPase, food depletion accelerates the breakdown of V-ATPase. Huss and other researchers discovered that the amount of ADP bound by the intact V-ATPase was significantly less than that bound by the decomposed V1 component, and they noted that the breakdown of V-ATPase was significantly influenced by the ratio of intracellular ATP to ADP [7]. RAVE (regulator of the H-ATPase of vacuolar and endosomal membranes) is a key player in the control of V-ATPase activity, according to other studies [8]. As seen in Figure 1, when the level of glucose in the environment drops, the amount of aldolase in the glycolytic pathway also drops, causing it to separate from the B subunit, which in turn causes V1 to separate from V0 and the activity of the V-ATPase to decline [6]. When the level of glucose in the environment rises, however, the RAVE complex and aldolase team up to rebind VI and Vo and restore the activity of the V-ATPase [9].

2.1. Using nanoparticles for restoring acidification disorder in lysosomes

Neurodegenerative disease imposes substantial burdens on worldwide health and medical. The three main types of neurodegenerative diseases—Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS)—share certain pathological mechanisms. This research aims to develop therapeutic strategies based on comparable cases in existing literature. Increasing evidence indicates that lysosomal dysfunction, particularly defects in lysosomal acidification, is prevalent in most neurodegenerative diseases. Consequently, regulating the pH levels in lysosomes could be crucial for mitigating the symptoms or progression of these diseases. Furthermore, the ability to cross the blood-brain barrier (BBB) and precisely control drug release, to avoid unintended effects on the central nervous system (CNS), represents another significant challenge. Therefore, this study considers the potential of nanotechnology, leveraging its nanosized and lipophilic properties, to restore defects in lysosomal acidification.

2.1.1. The difficulty in drug delivery in brain – the BBB. Some research had shown many organs can be stained by intravenous injection, besides the brain and spinal cord, therefore suggests the existence of BBB which hinders the blood flow between brain and body [10]. BBB is formed by the junction of endothelia cells, including adherens junctions (AJs) and tight junctions (TJs). The AJs connect cells together to support the tissue support, they play a crucial role in formatting TJs, and the damage in AJs would lead to the damage in BBB. Besides, TJs created by a further complex of proteins crossing the intercellular space (claudins and occluding), and junctional adhesion molecules (JAMs). BBB has autonomy, permeability, and plays an important role in signal transport and normal function of CNS [11].

2.1.2. Precisely control in drug delivery in neuron cells – the CNS. The neurons in CNS communicate with each other through both chemical and electrical signals, even combined, to precisely regulate local

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ionic microenvironment, which is important for neural signal between synapses and axons [12]. Besides, barrier layers especially BBB has a crucial effect in this regulation [13].Even in normal cells under normal physiological conditions, precisely biodistribution and effectively drug delivery are difficult to achieve because of both physical and biological barriers, including shear forces, protein adsorption and rapid clearance, which limit the fraction of administrated drugs reach the target therapeutic site.

However, CNS barriers also has many functions. CNS barrier serves as specific ion channels which make proper ion concentration and composition for normal neural function and signal transportation between synapses [14]. Because CNS and peripheral nervous system (PNS) may use a lot of identical neurotransmitters, the barrier BBB separate central and peripheral nervous system so that avoid mutual interference [15]. Moreover, BBB protect brain avoid macromolecules, especially plasma proteins seeping to brain, which may cause apoptosis [16,17]. BBB plays a c,rucial role in nutrition transport to nervous tissues. So the most important thing in drug delivery in brain is the precision of transportation, or else will affect normal functions. The special barriers existing in brain separates blood circulation, so drug must cross the barrier to exert pharmacological effects. The application of nanotechnology could avoid traditional limitations in drug delivery, from biodistribution to intracellular trafficking, from broad-scale issues to specific-scale issues.

2.1.3. The application of nanoparticles. Methods for regulating lysosomal acidity are few, therefore, it is an important way to improve lysosomal acidity by delivering acidic substances through nanomedical delivery. Nanoparticles which are composed by biodegradable polymers have been reported as a promising method in drug delivery, not only because their non-toxicity to human and cell ability, but also for the ability to go into neuron cells. The size and lipophilicity of nanomaterials make it a nature advantage for delivering drugs across natural protective membranes such as BBB, to the central nervous system [18].

The nanoparticles used to target CNS are mainly PLGA, which can release acids in mildly acidic aqueous environments and has been shown to be effective in reducing lysosomal PH. In particular, the US FDA reported that acidic nanoparticles (aNP) of poly (DL-lactide-co-glycolide) PLGA can traffic to lysosomes and influence on the lysosome PH [18]. However, PLGA NP has a low diffusion capacity in the brain, and to solve this problem, the scientists developed the oil-in-water nanoemulsions(NEs), as reported [19]. Also demonstrated the potential of drug delivery to the brain.

Another problem is that PLGA polymers are less soluble in oil and have limited load rates [18]. To solve this problem, scientists studied the nature of NLs. NLs are small heterozygous bioinspired molecules composed of lipids covalently linked to nucleic acid derivatives, nucleobases, nucleosides, nucleotides or oligonucleotides that have certain structured similarity to cell membranes. At the same time, the scientists also demonstrated the ability of NL to cross the BBB. Besides, scientists also proved low molecular weight acid-based nucleolipid nanocarriers to carry the biocompatible organic acid to lysosome successfully [18].

2.2. Other nanoparticles

(1) Utilizing specially designed photoactivatable, acidifying nanoparticles (paNPs), the researchers have developed another targeted approach to restore the acidic environment within lysosomes. These paNPs are engineered to be localized within lysosomes and, upon exposure to UV light, undergo a photoactivation process that causes them to expand and release their acidic content. This immediate release of acidity effectively lowers the pH of the lysosome, thereby restoring its normal function. Importantly, this restoration occurs within just 1–2 hours after UV irradiation, making it an acute and efficient method for lysosomal rescue. The strategy is also safe, as the paNPs have been tested to be non-toxic up to a concentration of 25 μg/ml [20]. However, this nanoparticles has only been tested to treat the lysosomal acidification dysfuntion under lipotoxicity [20]. Therefore, how to apply it to treat the problematic in brain to deal with Alzheimer's still need to be further researched. Questions such as the method of targeting transportation and where it can be safely used remained to be solved.

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(2) Another strategy employs a novel class of responsive polymeric nanoparticles known as acid-activated acidic nanoparticles (acNPs). These acNPs are engineered from fluorinated polyesters, which allows them to be specifically activated in the slightly acidic environment commonly found in dysfunctional lysosomes. Once localized within these lysosomes, the acNPs undergo a degradation process that releases protons into the lysosomal compartment. This targeted release of protons serves to further acidify the environment, effectively restoring the lysosome's normal acidic pH levels and its associated proteolytic functions. The acNPs have been rigorously tested for safety and have been found to be non-toxic up to a concentration of 100 μg/mL. This ensures that the treatment is not only effective but also safe for cellular application [21].

Similar with paNPs, this nanoparticles is designed for Non-alcoholic fatty liver disease (NAFLD) [21]. So, in order to further applied to brain treatment for Alzheimer's, more tests need to be taken place.

(3) There is another nanoparticle called PLGA-aNP (poly(DL-lactide-co-glycolide) acidic nanoparticles). It is designed to restore impaired lysosomal acidification. Once these nanoparticles are introduced into the cellular environment, they are transported to the lysosome within 24 hours. Upon reaching the lysosome, the PLGA-aNP work to lower the lysosomal pH, effectively re-acidifying the lysosomal environment [22].

This nanoparticle has already been tested as an effective and safe method to solve Parkinson's disease [22]. However, whether it can be used to solve the lysosomal acidification dysfunction for Alzheimer's still need to be proved.

2.3. Pharmacological approaches

Researchs has shown that glycogen synthase kinase-3 (GSK-3), a serine/threonine protein kinase, is strongly related to Alzheimer's [23]. Overexpression of GSK-3 impairs the acidification of lysosomes, by significantly reducing the degree of N-glycosylation of v-ATPase V01A which plays a crutial role in facilitating porton pump self assembly in lysosome [24].

So, another way to restore Lysosomal acidification is by using L803-mts, a substrate competitive inhibitor of GSK-3. Experiments on transgenic mice with AD indicate that the L803-mts treatment can effectively increase the level of mutual v-ATPase by fostering the N-glycosylation process and therefore restore the acidification of the dysfunctioned lysosome [24].

Besides GSK-3 effecting the acidification of lysosome, another possible reason could be the deficient of presenilins as presenilins 1 (PS1) is shown to play an essential role in acidification of lysosomes [24].

Experiments on cells which is lack of PS1 and PS2 indicate that the degree of N-glycosylation of v-ATPase V01A also reduced, and therefore a decrease in mature v-ATPase V01A. After using L803-mts to treat the PS1 and PS2 deficient cells, the level of mature v-ATPase V01A back to normal and the acidification of lysosome is restored. Experiments also shows that other GSK-3 inhibitors, SB-216763 or LiCl can function similarly by increasing the level of N-glycosylation therefore compensate for lysosomal acidification dysfuntion as a result of deficient PS1 or PS2 [24].

The experiment also proved the accessbility of GSK-3 inhibitor treatment though nasal administration, L803-mts for example [24]. However, study still needs to be taken out to uncover the accurate machenism of GSK-3 and determine whether GSK-3 isozymes effects lysosomal acidification differently.

Besides v-ATPase, there is also other Ion channels operating together to maintain the pH value of lysosome [25].

ClC-7 is a Cl-/H+ antiporter which plays an extremely important role in the acidification process of lysosomes. It helps in maintaining the lysosomal membrane voltage, which is beneficial for the V-ATPase to pump in H+ ions [26].

Besides the reduced level of N-glycosylation of v-ATPase V01A, the experiment also shows that ClC-7 levels are markedly reduced in cells lacking of PS1, contributing to lowered Cl- content in lysosomes, affecting their acidification. That is because ClC-7 is abnormally retained in the endoplasmic reticulum (ER), impeding its trafficking to the lysosome [27]. Isoproterenol (ISO), a β2-adrenergic agonist, offers another promising strategy for restoring lysosomal acidification in PS1-deficient cells.

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ISO targets the β2-adrenergic receptor (β2-AR) to upregulate ClC-7 function, thereby normalizing lysosomal Cl- levels and pH. Importantly, the effectiveness of ISO in reacidifying lysosomes is contingent upon the presence and functionality of ClC-7. ISO not only elevates ClC-7 levels in lysosomes but also stimulates its translocation from the endoplasmic reticulum to the lysosome, correcting the impaired intracellular trafficking of ClC-7 in PS1-deficient cells [27]. This multi-faceted approach makes ISO a pharmacologically relevant candidate for treating AD with lysosomal acidification deficits.

3. Conclusion

To date, both nanoparticle-based and pharmacological approaches show promise in addressing lysosomal acidification dysfunction, a key issue implicated in Alzheimer's disease. The benefit of targeted proton release into damaged lysosomes, provided by nanoparticles, allows them to immediately correct the acidic imbalance. Contrarily, pharmaceutical therapies concentrate on making up for defects in particular classes of ion channels that are in charge of preserving the lysosomal environment. Each approach offers advantages and may pave the path for future advancements in Alzheimer's treatments.

In terms of pharmacological treatment, understanding the complex interplay of different types of ion channels that maintain the lysosomal pH is crucial [28]. Unraveling the exact mechanisms of their function and the causes of their dysfunction is vital for the development of targeted therapies. The challenge lies in designing treatments that can specifically address deficiencies in individual types of ion channels. Regarding nanoparticle-based therapies, the majority of current research focuses on lysosomal acidification failure in various organs, such as the liver, with far less research addressing brain illnesses [21]. Consequently, it is extremely difficult to create strategies that specifically target abnormal lysosomes in the brain. The possibility of negative effects as well as the safe and efficient transport of nanoparticles to these lysosomes are still unanswered.

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