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RESEARCH PAPER

Role of Gold Nanoparticles in Inhibiting Amyloid Formation and Reducing Vascular Dementia Risk

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ABSTRACT

Lysozyme amyloid aggregation is associated with vascular dementia and other disorders. However, conventional therapies are limited by the blood-brain barrier. Gold nanoparticles (AuNPs) could modulate amyloid aggregation and provide a novel therapeutic approach. We investigated the effect of AuNPs on lysozyme amyloid formation of Hen Egg White Lysozyme (HEWL). We incubated lysozyme (3 mg/ml) in 60 mM glycine buffer (pH 2.8) at 61°C with gentle shaking to induce amyloid formation. We used various techniques to assess the impact of AuNPs (5-50 µg/ml) on lysozyme amyloid accumulation. We performed independent t-test and SPSS 23.0 software for data analysis. AuNPs inhibited lysozyme amyloid aggregation in a concentration-dependent manner. The lowest concentration (5 µg/ml) was the most effective, as it significantly increased the lag phase and decreased the growth phase of amyloid formation, and also reduced the cytotoxicity of amyloid aggregates on cell viability. Our results suggest that AuNPs act as nano-chaperones and prevent lysozyme amyloid fibril formation, and thus they may have therapeutic potential for vascular dementia treatment.

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INTRODUCTION

Dementia refers to the progressive and detrimental decline of cognitive capacities, notably memory, without concurrent impairment in the level of consciousness, resulting in significant disruption to daily activities [1,2]. Presently, approximately 12 million individuals worldwide are affected by dementia, with projections estimating this number to escalate to 25 million by the year 2040 [3]. Alzheimer's disease is the predominant form of dementia, accounting for approximately 50 to 60% of individuals affected by cognitive decline. Vascular dementia, on the other hand, ranks as the second most prevalent cause of dementia, following Alzheimer's, within the population [4–6]. In individuals aged 65 years and above, the prevalence of vascular dementia ranges from 1.2 to 4.2% [7]. Vascular dementia manifests as a diverse syndrome that can be attributed to various underlying diseases affecting small blood vessels, in addition to risk factors like aging, hypertension, and diabetes [8]. While vascular dementia shares similarities with Alzheimer's disease in terms of cognitive impairments observed in neuropsychological assessments, it is characterized by relatively lesser memory deficits and a greater prominence of executive function impairments [9].

Vascular dementia is a progressive neurodegenerative condition characterized by the deterioration of the nervous system. One of its significant hallmarks is the alteration in the spatial configuration of a protein known as Amyloid β-Protein (Aβ), wherein it transitions from a soluble state to form oligomers, protofibrils, or fibrils. These aggregated Aβ species accumulate as insoluble plaques within the brain. The presence of these misfolded Aβ proteins in the neuronal milieu directly correlates with neuronal inflammation and toxicity, leading to the degeneration of the nervous system and the onset of vascular dementia [1,6]. Consequently, various therapeutic approaches have been proposed to address the accumulation of misfolded Aβ proteins in vascular dementia. These strategies aim to prevent the aggregation of Aβ, inhibit its formation, or promote the restoration of its native folded conformation [5,7]. Moreover, it is crucial to eliminate existing Aβ accumulations from the system, as failure to do so can result in the death of neuronal cells and the subsequent impairment of memory. Therefore, strategies targeting the clearance and elimination of Aβ deposits are also critical in combating the detrimental effects of vascular dementia [10–12]. To date, there is no pharmaceutical product available on the market that can effectively inhibit the formation of amyloid deposits, eliminate existing accumulations, and ultimately ameliorate the abnormal behaviors observed in individuals with vascular dementia. However, nanotechnology has experienced significant advancements in recent years, leading to the production of diverse nanoparticles with broad applications across various disciplines. The exceptional reactivity and distinct physicochemical properties of these nanoparticles contribute to this promising avenue for addressing the aforementioned challenge [13]. An essential criterion for considering any compound as a potential therapeutic candidate for nervous system disorders is its capability to traverse the blood-brain barrier. Consequently, nanoparticles that possess the ability to effectively penetrate this barrier are currently being utilized as carriers for drug delivery [14].

Several research investigations have been undertaken to examine the impact of nanoparticles on protein aggregation phenomena. Schroer et al. [15] demonstrated that magnetic nanoparticles composed of Fe_3O_4 possess the ability to impede amyloid aggregation processes of lysozyme. Notably, these nanoparticles also exhibited the capacity to dismantle pre-existing protein aggregates. Earlier investigations employing different types of nanoparticles have provided evidence of their capacity to hinder the formation of protein aggregates. Javed et al. [16] demonstrated that co-polymer nanoparticles, even at picomolar concentrations, significantly delay the fibrillation process of Islet Amyloid Polypeptide (IAPP). Jo et al. [17] devised a strategy involving nanoparticles encapsulating cadmium and tellurium, which were stabilized by thioglycolic acid. Their research demonstrated that these nanoparticles possess the capability to impede the initial stage of nucleation in Aβ 1-40, resulting in a significant reduction in the extent of aggregation. Research indicates that gold nanoparticles (AuNPs) exhibit diverse functions, encompassing attributes such as antimicrobial and antifungal properties [18–20].

There has been limited research on the involvement of AuNPs in protein aggregation. Recent findings indicate that the toxicity of lysozyme aggregates is substantially reduced

when AuNPs are present compared to when they are absent [21]. Injecting these aggregates, formed in the presence of AuNPs, into the amygdala of rat brains has a diminished impact on memory and behavior, suggesting a decrease in particle toxicity. On the other hand, Asil et al. [22] demonstrated that AuNPs possess the ability to inhibit the buildup of α-lactalbumin (α-LAF), and this effect was associated with the chaperone properties of these particles. Additionally, in a separate investigation, researchers found that AuNPs coated with capsaicin effectively hindered the formation of amyloid deposits in albumin serum proteins [23].

In this research, the impact of AuNPs on the formation of amyloid fibers was examined using Hen Egg White Lysozyme (HEWL) as a standard protein model due to its well-understood structure and mechanism.

MATERIALS AND METHODS

Initially, Bacillus spp. KRA2, was cultivated under favorable conditions in a specialized growth medium known as Luria-Bertani (LB) broth. Following bacterial sedimentation through centrifugation, the extracellular enzyme alpha-amylase produced by the bacteria in the culture medium was isolated and purified using fast performance liquid chromatography (FPLC). The bacterial enzyme α-amylase was incubated with gold (III) chloride ($AuCl_3$) under defined experimental conditions, resulting in the reduction of the positively charged gold ions (Au^{3+}) to uncharged, metallic AuNPs. The formation of AuNPs was evidenced by a color change in the reaction medium and confirmed via UV-vis absorption spectroscopy (Shimadzu, UV Pharma spec 1700 with a resolution of 0.72 nm). The uncharged AuNPs synthesized by the enzymatic reduction of gold ions were isolated from the incubation medium by centrifugation [24]. In summary, the formation of AuNPs was confirmed by the observation of a strong absorption band in the UV-visible spectrum, with maximum absorption at 437 nm compared to the control. The hydrodynamic size of the synthesized AuNPs was evaluated by dynamic light scattering (DLS), which showed a hydrodynamic radius in the range of 80-100 nm. Scanning electron microscopy (SEM) imaging of the AuNPs corroborated the nanoparticle size distribution obtained from the DLS measurements. The SEM analysis visually confirmed the presence of AuNPs with diameters consistent with the size range determined by DLS.

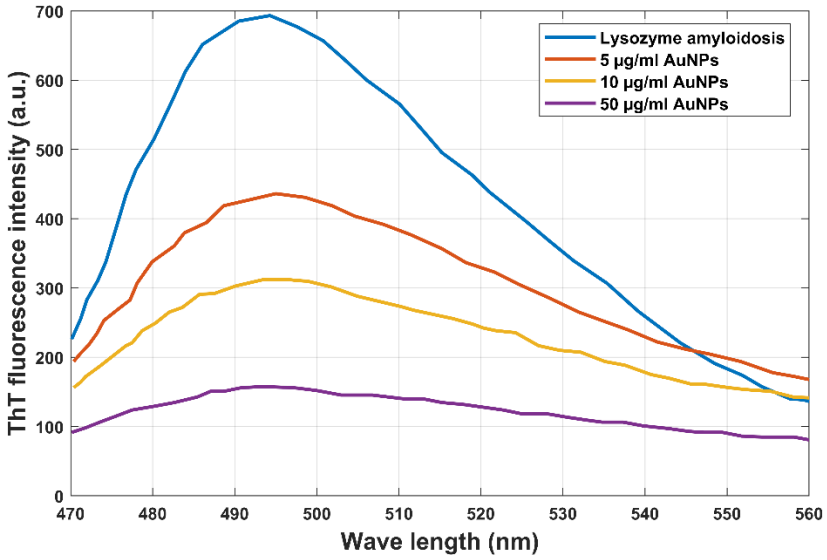
HEWL protein at a concentration of 3 mg/ml was incubated in 60 mM glycine buffer (pH 2.8) at 61°C with continuous stirring at 300 rpm for 24 hours to induce amyloid aggregate formation. To investigate the effect of AuNPs, lysozyme was incubated under identical conditions but with the addition of varying concentrations of AuNPs. After 24 hours, the extent of amyloid aggregate formation was assayed in both the presence and absence of the AuNPs. This enabled determination of the impact of the AuNPs on modulating lysozyme amyloidogenesis under the specified incubation conditions [25]. To assay for the presence of amyloid fibers, a freshly prepared solution of the amyloid-binding dye thioflavin T (ThT), filtered through a 0.3 µm filter, was utilized. The protein samples from the previous incubations were added to the ThT solution and the fluorescence emission intensity was measured using a Varian Cary Eclipse spectrofluorometer (Agilent Technologies). Excitation was at 420 nm and emission was scanned from 480 to 500 nm, with the excitation and emission slit widths both set to 10 nm. An increase in ThT fluorescence emission intensity upon binding to the protein sample indicates the formation of amyloid or amyloid-like aggregates. Thus, changes in ThT fluorescence were used to monitor amyloid formation in the lysozyme samples with and without AuNPs under the incubation conditions tested [26].

1 µl of the sample with formed amyloid fibers was put on small mica pieces. After spreading and drying, an atomic force microscope directly observed the amyloid fibers [27]. Amyloid fibers were prepared with and without nanoparticles (optimal 5 µg/ml). The vials containing these were centrifuged and the supernatant was removed. Cell culture medium (Dulbecco's Modified Eagle's Medium, DMEM) was added to dissolve the sediment. Cells in a 96-well plate were analyzed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [26]. Each experiment was performed in triplicate and repeated at least three times independently. All graphs show the mean ± standard deviation (SD). The data was analyzed using SPSS 23.0 software by independent t-test with a 95% confidence interval.

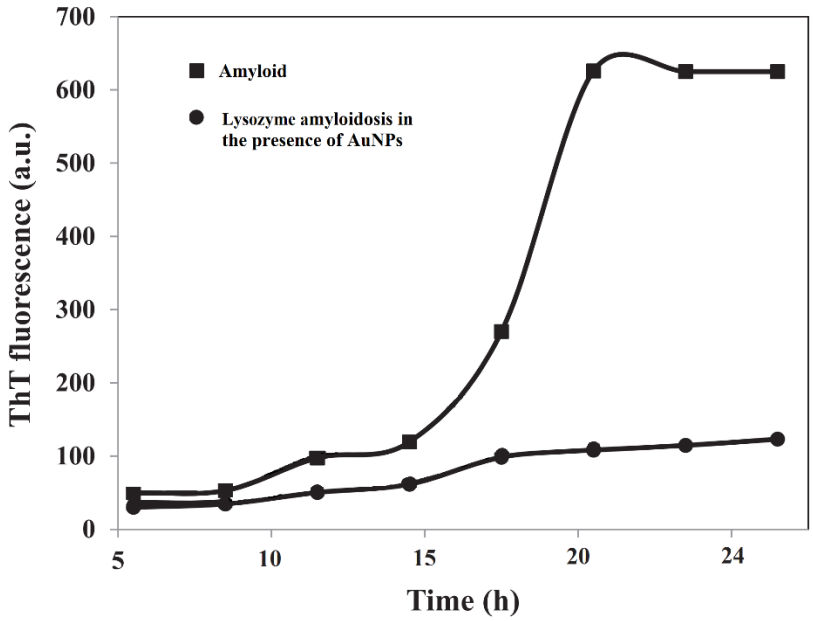
RESULTS AND DISCUSSION

The fluorescence emission spectrum of ThT

solution is an indicator of amyloid aggregate formation. When this dye binds to fibrils, it exhibits a high emission intensity between 480 and 500 nm upon excitation at a wavelength of 420 nm. To determine the optimal concentration of AuNPs that inhibits amyloid fibril formation, the fibrillization process was studied in the presence of varying concentrations of AuNPs in the range of 5-50 µg/ml. By measuring ThT fluorescence, it was possible to assess the effects of different

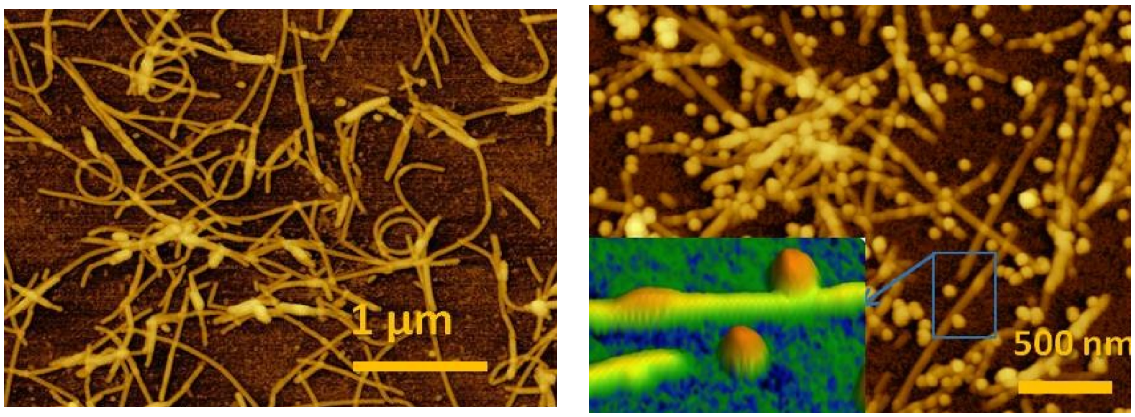


(a)



(b)

Fig. 1. The impact of various concentrations of AuNPs on the inhibition of amyloid fiber formation in HEWL protein after 24 hours: (a) Lysozyme amyloidosis in the absence of AuNPs and in the presence of AuNPs with concentrations of 5, 10, and 50 µg/ml; (b) the kinetics of amyloid formation over a 24-hour period in both the presence and absence of AuNPs.



(a) (b)

Fig. 2. The atomic force microscope image shows 2 mg/ml lysozyme in a glycine buffer with a pH of 2.8 after 24 hours of incubation at 61°C: (a) the sample in the absence of AuNPs; (b) the sample in the presence of AuNPs.

Table 1. The effect of nanoparticles on the cytotoxicity resulting from lysozyme amyloid accumulation.

	Control	Lysozyme amyloidosis	Amyloid + 5 µg/ml AuNPs
MTT cell viability of PC12 (%)	100	38	87

AuNPs concentrations on inhibiting amyloid fibril aggregation. As depicted in Fig. 1(a), the concentration of AuNPs that exhibited the greatest inhibition of lysozyme amyloid fibril formation was 5 µg/ml. An interesting observation was that the inhibitory effect on fibril formation decreased with increasing AuNPs concentrations above 5 µg/ml. After identifying 5 µg/ml as the optimal AuNPs concentration for inhibiting lysozyme fibrillization, the kinetics of inhibition were studied by monitoring ThT fluorescence at different time points over a 6-hour period. This allowed determination of the time-dependence of AuNPs inhibition of lysozyme amyloid aggregation at the optimal concentration. The formation of lysozyme amyloid aggregates without nanoparticles progresses through three kinetic stages over time: an initial lag phase, a rapid growth phase, and finally an equilibrium phase. As illustrated in Fig. 1(b), at this concentration of AuNPs, both the fluorescence intensity and amyloid formation were substantially decreased after 24 hours compared to the control. The nanoparticles appeared to inhibit both the lag and rapid growth kinetic phases of aggregation. Specifically, the nanoparticles extended the lag time and dramatically slowed the fibrillation rate during the rapid growth phase. These effects demonstrate the ability of the nanoparticles to interfere with and suppress the amyloid formation process.

Atomic force microscopy was utilized to visualize the morphology of amyloid fibers formed from lysozyme, with and without AuNPs. In the absence of nanoparticles, mature amyloid fibers lacking branches were observed (Fig. 2). However, in the presence of an optimal concentration of AuNPs, the maturation of amyloid fibers was inhibited, resulting instead in the formation of oligomers and initial nuclei. These results demonstrate that AuNPs can disrupt the assembly of lysozyme into amyloid fibrils.

Lysozyme aggregates were formed with and without nanoparticles present. These aggregates were then transferred to a physiological buffer and added to PC12 cell cultures at a final concentration of 2 µM. As shown in Table 1, the cytotoxicity of these aggregates on cell viability was assessed via MTT assay, as described in the methods section. This allowed evaluation of the ability of the differently formed lysozyme aggregates to impair cell function.

Experiments reveal that lysozyme amyloid fibers exhibit a 62% decrease in MTT recovery versus control cells not exposed to aggregation. In contrast, lysozyme amyloid fibers formed in the presence of AuNPs at an optimal concentration

demonstrate only a 13% reduction in MTT recovery. These results indicate that AuNPs mitigate the cytotoxicity of amyloid fibers, protecting cells from the deleterious effects of amyloid aggregation on cell viability.

The phenomenon of spontaneous protein fibrillation has garnered significant research interest due to its association with a group of prevalent diseases known as amyloid diseases. These diseases are characterized by the accumulation of protein deposits in various parts of the body [28]. In this study, HEWL protein was utilized due to its high structural and sequential homology with the human variant. As a model protein, its fibrillar structure formation, amyloid formation kinetics, and the factors influencing its formation have been well characterized [29,30]. Previous research has investigated the impact of low concentrations of iron nanoparticles (FeNPs) on protein aggregation. Studies by Debnath et al. [31] demonstrated that, at low concentrations, nanoparticles bind to specific sites on protein primary nuclei, preventing their aggregation and inhibiting fibrillation. It has been demonstrated that the addition of nanoparticles can reverse or disrupt the fibrillation process once fiber formation has begun. The introduction of low concentrations of nanoparticles results in an extended lag phase and a reduced elongation phase. The strong interaction between peptides and nanoparticles, facilitated by the adsorption of nanoparticles to specific sites on the nuclei, inhibits the aggregation of nuclei and reduces fibrillation [32].

CONCLUSION

In conclusion, this study demonstrates that AuNPs can effectively inhibit the aggregation and cytotoxicity of lysozyme amyloid fibers at an optimal concentration of 5 µg/ml. AuNPs were shown to extend the lag phase and decrease the growth rate of lysozyme amyloid formation. The inhibitory effect of AuNPs on lysozyme fibrillization was confirmed through multiple techniques, including ThT fluorescence, and atomic force microscopy. Moreover, AuNPs mitigated the toxicity of lysozyme aggregates on cell viability. The ability of AuNPs to modulate protein aggregation makes them promising therapeutic candidates for preventing amyloid deposition in vascular dementia and other misfolding diseases. Further in vivo studies are warranted to assess the efficacy of AuNPs for improving cognitive outcomes in animal models of vascular dementia. Overall, this research elucidates the mechanism by which AuNPs can interfere with amyloidogenesis and points to their potential clinical utility for combating protein misfolding neurodegenerative disorders.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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