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Short communication

Gold nanoparticles as amyloid-like fibrillogenesis inhibitors

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ABSTRACT

Amyloid aggregates are one of the likely key factors leading to the development of Alzheimer's disease (AD) and other amyloidosis associated diseases. Several recent studies have shown that some antidiabetic drugs have a positive therapeutic effect on AD patients by crossing the blood brain barrier (BBB) and preventing or reducing insulin resistance. Nanoparticles (NPs) or nanoscale objects (<600 Da.), are able to cross the BBB at low concentrations, and can specifically target amyloidogenic structures. Thus, NPs are fast becoming indispensable tools for directed drug delivery, particularly when targeting structures or regions in the brain. Here, we have explored the inhibitory effect of gold nanoparticles (AuNPs) on the fibrillogenesis process of insulin fibrils. We found that when AuNPs were co-incubated with insulin, the structural transformation into amyloid-like fibrils was delayed by about a week. Further, the fibrils that formed, exhibited altered structure, shape, and dynamics, which further reduced fibril growth, and the stability of available amyloid-like fibrils with cross-β structure for aggregation. Our results demonstrate that AuNPs disrupt insulin amyloid fibrillation resulting in fibrils that are shorter and more compact, and thus may serve a useful role in new therapeutic and diagnostic strategies for amyloid-related disorders.

1. Introduction

In living organisms, certain proteins associated with disease can undergo misfolding and conformational changes resulting in fibril rich, highly ordered β-sheet structures, or amyloid fibrils [1]. These amyloid fibrils are generally deposited in the brain and/or peripheral tissues, a condition which has been associated with neuropathological diseases such as Alzheimer's, Parkinson's, type II diabetes mellitus (T2DM) and more than 20 other amyloid-related disorders [2,3].

In 1939, Harold Himsworth challenged the conventional wisdom that all forms of diabetes could be attributed to insulin deficiency. He postulated that the state of diabetes might result from "inefficient action of insulin" as well as from its deficiency [4]. The role of insulin resistance in diabetes has been a serious topic of debate ever since [5]. Further, de la Monte et al. proved that brain insulin resistance is similar to regular diabetes, and mediates cognitive impairment, particularly Alzheimer's disease (AD), which has been referred to as "type 3 diabetes" [6,7].

Because researchers hypothesized a common pathological link between T2DM and AD, some currently approved antidiabetic drugs that prevent insulin resistance, and that readily cross the blood brain barrier (BBB), were believed to have therapeutic potential and positive benefits for AD patients [8]. The BBB is a physical and physiological barrier for therapeutic drugs being delivered to the brain. It is easily permeable only to molecules with lipophilicity or weight below 600 Da. [9], thus limiting the carrier system to nanoscale objects [10].

Nanoparticles (NPs) have become the topic of intensive research, due in part, to a diverse variety of therapeutic potential in medical applications. NPs exhibit unique physical, chemical, and electronic properties, and in many cases are biocompatible. With their high surface area and tunable surface chemistry, NPs are becoming an indispensable tool in the biological and biomedical fields [11], for such applications as gene transfection [12], drug delivery [13], cell imaging [14] photo-thermal therapy [15], etc. A typical NP used for drug delivery is a polymeric particle modified with biomolecules (e.g., DNA/RNA probes, antibodies, peptides) [16] in the size range of 10–1000 nm [10].

In the treatment of AD, NPs are capable of modulating intracellular tight junctions [17], overcoming the BBB [18], self-assembling an analogue of Aβ proteins [19], and targeting cerebrovascular amyloids [20]. Yoo et al. established a CdTe NP model offered insight into NP systems that exhibit equal to or even better fibrillation inhibition than the best-known proteins [19]. He further noted that biocompatible NP systems with similar characteristics to toxic CdTe NPs may be sought as alternatives for *in vivo* applications. Moreover, Cabaleiro-Lago et al. proved that NPs can prevent fibrillogenesis as well as temporarily reversing Aβ aggregation [21].

Since various nonpathological proteins and polypeptides have been shown to self-assembly form the amyloid-like fibrils leading to amyloid diseases [3], and NPs have the potential to diagnose

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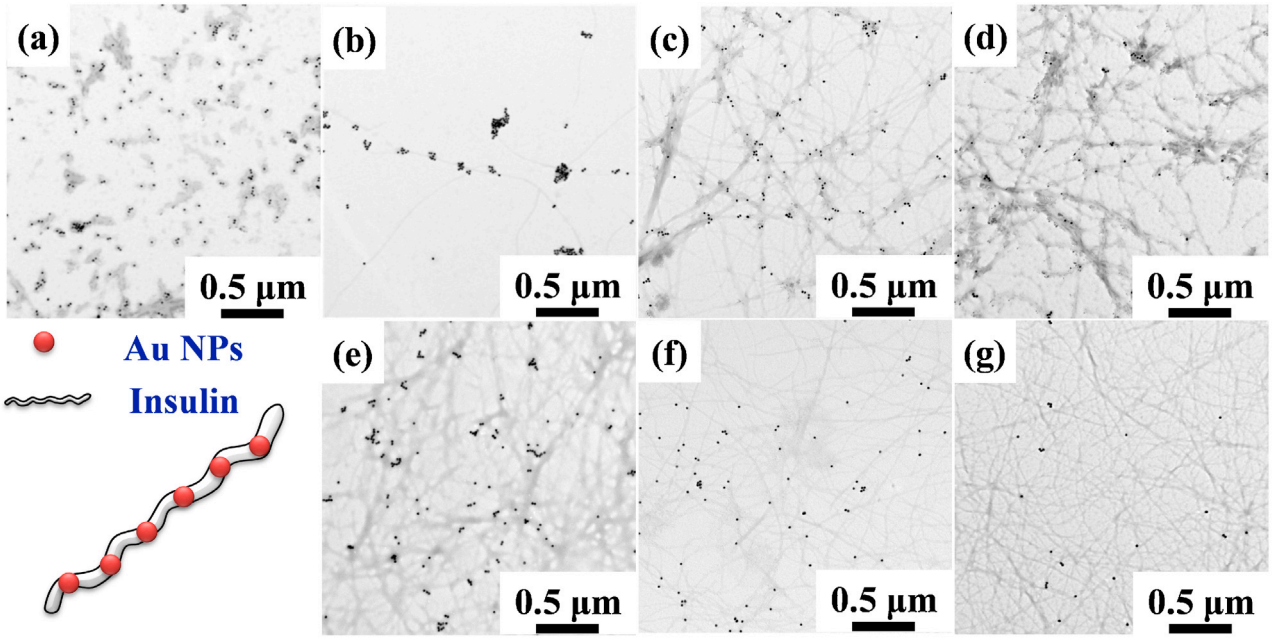

Fig. 1. TEM images of AuNPs bound to insulin fibrils incubated in a solution at pH 1.6 and 80 °C for 2.5 h, and then stored at room temperature for (a) 0, (b) 1, (c) 2, (d) 3, (e) 4, (f) 5, and (g) 6 weeks. The lower left panel shows a diagram of AuNPs absorbed on fibrils. The scale bar in each image is 0.5 μm.

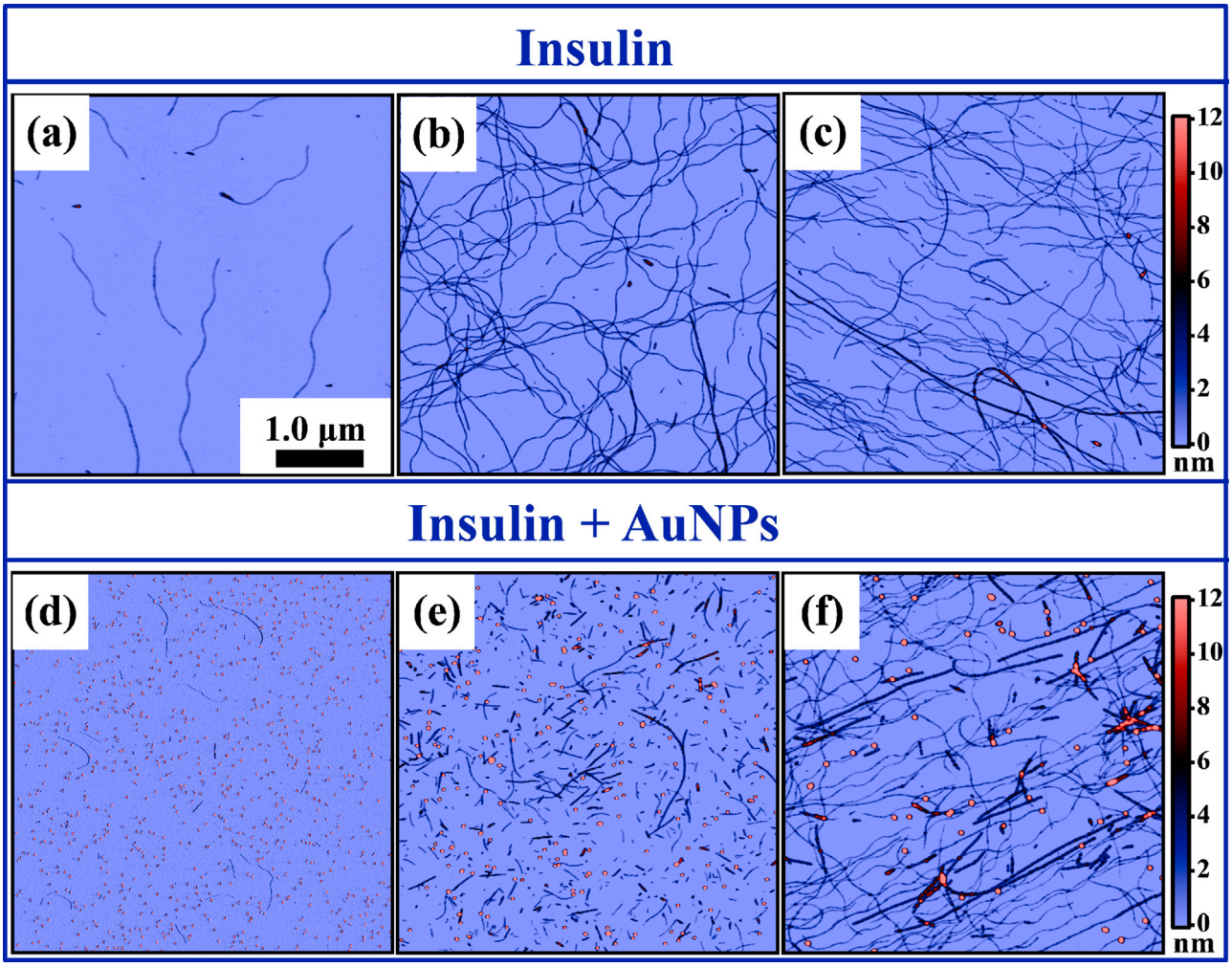

Fig. 2. AFM topographic images of treated insulin following extended incubation at room temperature for 0 (a, d), 3 (b, e), and 4 (c, f) weeks. The top row (a, b, c) are insulin-only samples and the bottom (d, e, f) are insulin with AuNPs. The AuNPs disrupted the natural fibril formation process.