The Antiaggregative and Antiamyloidogenic Properties of Nanoparticles: A Promising Tool for the Treatment and Diagnostics of Neurodegenerative Diseases

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Due to the progressive aging of the society, the prevalence and socioeconomic burden of neurodegenerative diseases are predicted to rise. The most common neurodegenerative disorders nowadays, such as Parkinson’s disease, Alzheimer’s disease, and amyotrophic lateral sclerosis, can be classed as proteinopathies. They can be either synucleinopathies, amyloidopathies, tauopathies, or TDP-43-related proteinopathies; thus, nanoparticles with a potential ability to inhibit pathological protein aggregation and/or degrade already existing aggregates can be a promising approach in the treatment of neurodegenerative diseases. As it turns out, nanoparticles can be a double-edged sword; they can either promote or inhibit protein aggregation, depending on coating, shape, size, surface charge, and concentration. In this review, we aim to emphasize the need of a breakthrough in the treatment of neurodegenerative disorders and draw attention to nanomaterials, as they can also serve as a diagnostic tool for protein aggregates or can be used in a high-throughput screening for novel antiaggregative compounds.

1. Introduction

Undoubtedly, the progress in medical and biological studies has led to increased quality of life and extension of life span. Furthermore, the overall fertility has dropped and these two factors contribute to the aging of the society. Due to this phenomenon, the increase in prevalence of neurodegenerative diseases is predicted to be more visible in the future than it currently is. According to the World Health Organization, it is projected that the number of people aged ≥ 65 will grow from about 524 million in 2010 to around 1.5 billion in 2050 [1]. Neurodegenerative diseases impose burden not only on people affected by this disorder but also on their caregivers. There are three major neurodegenerative diseases whose pervasiveness and incidence significantly rise with age.

First of them and the most common one is Alzheimer’s disease (AD), which affects approximately 30% of people aged 85 or older. After the age of 85, the incidence of AD rises gradually from 6 to 8% per year, in contrast to the 0.5% rise per year when peoples’ age ranges between 65 and 75 [2]. The second most common is Parkinson’s disease (PD), which affects 10-15 per 100 000 people annually [3]. Its prevalence has been more than two times higher in 2016 (6.1 million cases) comparing to 2010 (2.5 million cases) and may reach 2% among people aged ≥ 65. Consequently, it is estimated that in 2050, there will be more than 12 million cases of PD worldwide [4]. Subsequently, amyotrophic lateral sclerosis’s (ALS) annual incidence is approximately 1-2.6 new cases per 100 000 persons. This disease is characterized by rapid progression with average survival 3-4 years from onset, whereas the average age of onset nowadays is 59-60 years [5]. Indeed, there is a variety of symptoms of the aforementioned neurodegenerative diseases, but the exact pathophysiology of these conditions is still elusive. Nevertheless, it should be emphasized that they have some common pathogenic features. Among them, genetic [6] and environmental...
Table 1: Characteristics of the most common neurodegenerative diseases.

| Disease                        | Hallmarks                                                                 | Genetic factors                                                                                       | Ref.     |
|-------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------|
| Alzheimer's disease           | (i) Senile plaques comprising deposits of β-amyloid                        | (i) Presence of specific allelic variants of APOE gene (ε2, ε3, and ε4)                              | [9]      |
|                               | (ii) Intracellular neurofibrillary tangles                                 | (ii) ApoE4 allele specifically in sporadic form of AD                                                |          |
|                               | (iii) Tau protein aggregation                                              | (iii) Mutations of gene coding for amyloid precursor protein (APP), presenilin 1, and presenilin 2   |          |
|                               | (iv) Neuronal loss                                                          | (n or PSEN2) in the familial form of AD                                                              |          |
| Parkinson's disease           | (i) Presence of Lewy bodies—neuronal inclusions of fibrillated aggregates  | (i) Gene mutations: SNCA, Parkin, PINK1, LRRK2, DJ-1, VPS35, PLA2G6, DCTN1, FBX07, and ATP13A2     | [9]      |
|                               | comprising α-synuclein and ubiquitin                                       |                                                                                                      |          |
|                               | (ii) Degeneration and loss of dopaminergic neurons especially in substantia|                                                                                                      |          |
|                               | nigra pars compacta                                                        |                                                                                                      |          |
|                               | (iii) Dopamine deficiency                                                  |                                                                                                      |          |
| Amyotrophic lateral sclerosis  | (i) Presence of ubiquitinated inclusions comprising TDP-43, FUS, OPTN,     | (i) Gene mutations: SOD1, C9orf72, FUS, and TARDBP                                                  | [9–12]  |
|                               | ATXN2, C9orf72, and UBQLN2                                                  |                                                                                                      |          |
|                               | (ii) Slow and progressive degeneration and loss of motor neurons           |                                                                                                      |          |
|                               | (iii) Neuroinflammation                                                    |                                                                                                      |          |

[7] factors can be listed. Yet, the most classical feature of all these diseases is protein misfolding in specific brain regions; thus, these disorders can be classified as proteinopathies (Table 1). The hallmark of proteinopathies is either intracellular or extracellullar accumulation of aggregates in the central nervous system that are abundant in β-sheets. In these diseases, altered forms of proteins, which play a physiological role, accumulate in the brain. They turn out to have pathological functions after modifications of their 3D structure, which in consequence leads to self-aggregation, aggregate growth, and eventually precipitation [8].

Unfortunately, the current and only available treatment of neurodegenerative diseases is strictly symptomatic. Treatment of PD has not significantly changed over decades: L-DOPA treatment is a gold standard for 60 years so far. Apart from levodopa-carbidopa preparations, other dopamine agonists, monoamine oxidase-B inhibitors, cholinesterase inhibitors, and selective serotonin and norepinephrine reuptake inhibitors are also used as a drug regimen [13, 14]. The treatment of AD is not much more sophisticated and is based on cholinesterase inhibitors and NDMA receptor agonist, namely, memantine. It addresses not only the behavioural and cognitive symptoms but also covers for functional ones [15]. A review of treatments for AD in clinical trials can be found in a recent article [16], demonstrating that there is no effective antiaggregative treatment so far. Similarly, the information about PD drugs in clinical trials can be found in another review [17]. When it comes to ALS, there is only one FDA approved drug—riluzole, which has a glutamine agonist activity and extends the survival of patients by only 2–3 months [18, 19].

Due to the abovementioned facts, in this review, we aim to highlight the burden of neurodegenerative diseases and discuss novel approaches to their treatment using nanomaterials (Figure 1). Furthermore, we would like to point out the versatility and impact of the nanoparticles used to combat proteinopathies, on pathological protein aggregation.

2. Protein Aggregation in Neurodegeneration

A body of evidence suggests that the accumulation and transmission of α-synuclein (α-syn) aggregates in the midbrain are highly associated with the pathogenesis of PD [20]. α-Synuclein is a presynaptic protein, which probably plays a regulatory function in modulation of synaptic plasticity, control of presynaptic vesicle pool size, release of neurotransmitters, and vesicle recycling. Its structure can be divided into three regions: an amphiphilic N-terminus, an acidic C-terminus, and a hydrophobic central domain, which is known as the nonamyloid β component (NAC). The NAC region is crucial for α-syn aggregation and formation of β-sheet fibrils, which are the main elements of Lewy bodies [21]. Studies showed that electrostatic forces play a crucial role in α-syn fibrillation; thus, this process can be obstructed by charged nanoparticles [22].

Yet, interestingly, the exact molecular mechanism, time of occurrence, and influence of protein misfolding on the onset and/or progression of these particular diseases are still beyond reach. According to Janezic et al. who introduced a new mouse model for PD studies, neurophysiological changes forerun and are not driven by α-syn aggregate formation [23]. Nevertheless, the search for antiaggregative agents is still highly desirable.

Amyloid β peptide has a leading role in the onset and progression of AD. In this disease, amyloid plaques containing aggregated amyloid-β protein (Aβ) are surrounded by morphologically altered neurons, cause synapse and memory loss, and induce neurotoxicity [24].

As a matter of fact, Aβ is physiologically present and derives from the amyloid precursor protein (APP), which is implicated in regulation of synapse formation. Unfortunately, under particular circumstances, it starts to aggregate and initiates the disease progression [25]. Amyloid-β protein monomers tend to aggregate into several forms, namely, soluble oligomers, protofibrils, and insoluble amyloid fibrils which can further aggregate into amyloid plaques. This
process is accompanied by oxidative stress, leading to the formation of oxidized proteins and lipid peroxidation. Products of lipid peroxidation, especially 4-hydroxynonenal, can in turn disrupt function of glucose and glutamate transporters and of ion-dependent ATPases [26]. Therefore, Aβ advocates synaptic membrane depolarization, uncontrolled Ca\textsuperscript{2+} influx, and mitochondrial damage, which cause undesirable changes in cellular activity [27].

Additionally, tau protein is being hyperphosphorylated because of changes in protein kinase activity, which are a result of Aβ aggregation. The hyperphosphorylated form of tau protein becomes a core of neurofibrillary tangle (NFT) formation, whereas physiologically tau protein fosters the assemblance of tubulin into microtubules and helps to maintain their stability. The link between the existence of NFTs and neuronal dysfunction is straightforward. Notwithstanding, the relation of Aβ and NTFs is intertwined, because the inhibition of tau generation can impact production of Aβ and its derivatives [28].

3. Nanoparticles as Therapeutics of the Future

A nanoparticle (NP) is defined as a particle of matter that is between 1 and 100 nanometres in at least one dimension. Nanoparticles arose as attractive tools for both therapeutic and diagnostic applications, especially in imaging, diagnostics, and drug delivery. They can be synthesized from a broad range of materials, such as polymers, metals, or carbon-based molecules. NPs are also highly functional because of the ease with which their shape, size, and surface properties can be modified. Furthermore, NP properties can be also altered by attachment of other substances to the surface or their entrapment within the NP cavities, if these exist (Figure 2) [29].

3.1. Graphene Quantum Dots. Graphene quantum dots (GQDs) are less than 100 nm in size and are made of single- or few-layer graphene (Figure 3). They have been widely used in nanobiomedicine by virtue of their low cytotoxicity and high biocompatibility [30]. The group of Kim et al. demonstrated that GQDs were able to pass through the BBB. In the brain, they reduced α-syn fibrillization and triggered fibril disaggregation in a time-dependent manner by direct interaction with mature fibrils. The binding between GQDs and α-syn is driven by negatively charged carboxyl groups of GDQs and the positively charged α-syn region. Furthermore, these GQDs did not manifest any long-term toxicity in vivo and in vitro and also were able to prevent neuronal death, diminish Lewy body and Lewy neurite formation, and alleviate mitochondrial damage and dysfunction, and last but not least, they have the ability to prevent neuron to neuron transmission of pathological α-syn. Moreover, experiments performed on a mouse model showed that GQD protected against α-syn preformed fibril-induced loss of dopaminergic neurons and alleviated motor deficits [31].

With regard to AD, GQDs were also used to inhibit Aβ aggregation. The β-amyloid peptide consists of 39–42 amino acids, where several regions can be defined. The His13-Lys16 (HHQK) region plays a significant role in oligomerization and fibril formation. This region is a crucial component of
glycosaminoglycan (GAG) binding site, which facilitates a conformational change of Aβ from soluble and unordered α-helix to stable β-sheet [32]. A construct composed of GQDs and tramiprosate, a mimic of GAGs, which specifically binds to HQQK motif and inhibits Aβ peptide aggregation, showed an inhibition of Aβ aggregation driven by breaking β-sheets. Furthermore, GQDs combined with tramiprosate evidently protected PC12 cells from Aβ-induced cytotoxicity, meanwhile exhibiting a synergistic effect [33].

3.2. Dendrimers. Dendrimers are highly branched, tree-like polymers with unique properties thanks to their terminal functional surface groups (Figure 4). The size, shape, and surface charge change with an increase in generation. Dendrimers are highly functional because of simplicity of modifying their biological and/or physicochemical properties [34, 35]. There is evidence that generations 3, 4, and 5 of PAMAM dendrimers are able to interfere with Aβ aggregation by blocking growth of new fibrils and breaking the existing ones in a concentration- and generation-dependent...
Gold nanoparticles (AuNPs) have been extensively used in biomedicine because of their great biocompatibility, chemical inertness, and effortless size control. AuNPs are also able to abrogate aggregation of pathological proteins. Nevertheless, they may be toxic; toxicity of gold NPs significantly depends on their size, charge, and coating. Large AuNPs (36 nm and 18 nm) increase Aβ fibrillation, whereas smaller ones are able to delay (6 nm) or utterly inhibit (1.9 nm) this process [42]. Particularly, smaller, anionic NPs exhibit better ability to halt protein aggregation. The researchers have studied four different coatings (citrate, poly(acrylic acid) (PAA), poly(allylamine) hydrochloride (PAH), or polyelectrolyte surfaces) and three different sizes of AuNPs (8 nm, 18 nm, and 40 nm). The results altogether demonstrated that PAA-coated, 18 nm AuNPs exhibited superiority in the inhibition of Aβ aggregation and were the least toxic towards human neuroblastoma SH-SY5Y cells [43]. In order to improve the ability of AuNPs to cross the BBB, Prades et al. created an AuNP conjugated with two peptides, where one of the peptide sequences was designed to interact with the transferrin receptor. The authors suggest that this platform can increase the efficiency of drug delivery into the brain [44]. Noteworthy, natural compounds are also able to obstruct amyloid fibrillation and break existing amyloid fibrils, one of which is curcumin [45]. Because of its hydrophobicity and thus insolubility in water, curcumin has to be conjugated with other compounds [46]. Water-soluble curcumin-functionalized gold nanoparticles turned out to efficiently inhibit amyloid fibrillation, but also to break and dissolve Aβ fibrils. Furthermore, these curcumin-AuNPs protect neuro2a cells from Aβ fibril-induced cytotoxicity, giving nearly doubled improvement in viability. It is suspected that the great inhibitory efficiency is a result of nanoparticle binding to the fibrils via curcumin moiety and disrupting the elongation phase of fibrillation [47].

3.4. Antioxidant-Loaded NPs. Apart from the abovementioned example, other phytochemicals have also arisen as useful in prohibiting pathological protein aggregation regarding neurodegenerative diseases (Figure 5). Among them, baicalein [48], chlorogenic acid [49], gallic acid [50], and many other natural compounds [51] are able to inhibit the formation of α-syn aggregates and/or even disaggregate existing ones. Selenium nanoparticles (SeNPs) turned out to be an effective carrier of antioxidants. Their peculiar biomedical applications and wide range of therapeutic properties are ascribed mainly to the ability to modulate redox state. Moreover, SeNPs show low toxicity and great biodegradability in vivo [52]. Yang et al. investigated anti-Aβ-aggregative and antioxidative properties of SeNPs conjugated with chlorogenic acid (CGASeNPs). These authors hypothesized that binding CGA with nanoparticles will improve its bioavailability and stability. They proved that antiaggregative properties of CGASeNPs are contributed by their ability to bind Aβ on their surface. Furthermore, CGASeNPs effectively scavenged ROS and protected PC12 cells against Aβ-induced toxicity [53]. Likewise, the same group designed SeNPs modified with resveratrol and tested their properties against ion metal-
induced Aβ42 aggregation. They obtained similar effects as described above, i.e., that resveratrol and SeNPs exhibit synergistic effect regarding the inhibition of pathological protein aggregation [54]. A nanocomposite engineered from quercetin, SeNPs, and polysorbate 80 can serve as another example of SeNPs combined with antioxidants. In vitro analyses showed that the nanocomposite exhibited greater solubility in water comparing to quercetin per se, which has poor aqueous solubility. On top of that, such nanocomposite had an exceptional antioxidative activity, inhibited Aβ1-42 monomer aggregation, and protected PC12 cells from hydrogen peroxide-induced cell death [55]. Zhang et al. studied both EGCG-SeNPs and NPs conjugated with EGCG and Tet-1 peptide. Tet-1-EGCG-SeNPs showed better efficacy comparing to NPs without the peptide. Both types of NPs not only protected PC-12 cells against amyloid-induced cytotoxicity and inhibited Aβ fibrillation but were also able to dissociate existing fibrils into nontoxic monomeric state. Nevertheless, peptide-containing NPs had overall better performance due to increased neuronal targeting efficiency in vitro [56]. NPs loaded with other antioxidants, namely, ferulic acid (as a powerful anti-inflammatory agent) and tannic acid (acting as an inhibitor of α-syn fibrillation), exhibited potent inhibitory effect on α-syn aggregation, diminished pro-inflammatory responses, and reduced oxidative stress caused by α-syn [57]. Additionally, curcumin-loaded NPs inhibited amyloid-like aggregation of superoxide dismutase (SOD) 1, which occurs in about 20% of familial ALS cases [58].

Nanoparticles loaded with synthetic antioxidants can also serve as antiaggregative agents. Nitroxides exhibited better efficacy in prevention of nitration reactions and were more reactive than natural antioxidant, vitamin E [59]. It has been established that nitroxide-containing redox NPs are able to alleviate typical aspects of neurodegenerative diseases, namely, protect cells against oxidative stress, improve mitochondrial function, and inhibit Aβ aggregation [60, 61].

4. Other Therapeutic Approaches

Unquestionably, transition metals are among the main culprits of pathological protein accumulation. Moreover, they widely contribute to an altered redox state; thus, chelators might bring alleviation of the toxic activity of these metals. Liu et al. created a chelating nanoparticle, in a nutshell—a NP conjugated with 2-methyl-N-(2′-aminoethyl)-3-hydroxyl-4-pyridinone. This construct significantly inhibited Aβ aggregation, protected human cortical neuronal cells from Aβ-induced cytotoxicity, and had no impact on cell proliferation [62].

Given the fact that the nanoparticle efficacy in inhibiting protein aggregation greatly depends on the surface charge, the use of amino acids as coating agents is not surprising; they may enhance biocompatibility of nanoparticles. It is mainly due to the fact that amino acids are zwitterionic. Antosova et al. proved that amino acid-coated superparamagnetic nanoparticles can be quite a powerful tool for treatment of amyloidopathies. The group showed that tryptophan-coated NPs exhibited the best anti-aggregative properties [63]. Furthermore, others demonstrated that histidine-coated nanoparticles can completely suppress amyloid fibril formation [64]. Moreover, lysine-coated Fe3O4 NPs were less toxic than bare iron oxide NPs, strongly bound to monomeric α-syn, and inhibited the early phases of its aggregation [65].

NPs can be also used as safer carriers for gene therapy, instead of viral vectors. Niu et al. created multifunctional magnetic nanoparticles which are a complex platform that combines elements of cell targeting, controlled drug release, and gene therapy. The authors developed a NP that interferes with α-syn synthesis by shRNA, hence
alleviating its toxic effect, so cell death is inhibited both in vitro and in vivo [66].

5. The Dark Side of the Nanoparticles with a Useful Outcome

Despite undoubted success of some nanoparticles as promising antineurodegenerative compounds, it is important to mention that there is also data on their possible contribution to the disease progression. A plethora of evidence suggests that the nanostructures can influence protein fibrillation depending on various conditions, including the coating, size, surface charge, and concentration. Such discrepancy has been seen for example in silica-based nanoparticles, where positively charged silica nanoparticles inhibited α-syn fibrillation and negatively charged one had an opposite effect [67]. Also, it was also established that SiO₂NPs upregulate α-syn expression, inhibit protein levels of the ubiquitin-proteasome system, and induce autophagy by interference in the PI3K-Akt-mTOR signalling pathway [68].

Contrary to that, negatively charged gold nanoparticles act as chaperones and prevent Aβ fibrillation [69]. Yet, regarding α-syn, the opposite effect was seen: gold nanoparticles are also a double-edged sword. Citrate-capped (negatively charged) AuNPs speeded up the formation of α-syn aggregates in nanomolar concentrations, and time of the nucleation phase was dependent on the surface availability. The smaller the NPs (10-14 nm), the more aggregate growth acceleration, whereas particular sizes (22 nm) were able to inhibit the fibrils’ growth; thus, in summary, the AuNP aggregative properties hinge on their size and concentration [70].

Nowadays, numerous NPs have been used in a variety of fields, namely, electronics, pharmaceuticals, cosmetics, and fabrics; hence, their toxicity has started to be more widely observed and studies on the health risks are a bit behind the prompt development of nanotechnology, regardless of a body of evidence of toxic effects of NPs, both in vitro and in vivo [71]. For example, Shah et al. prove that nanoscale-alumina can accumulate in the brains of exposed animals [71]. Also, it was also established that SiO₂NPs upregulate α-syn expression, inhibit protein levels of the ubiquitin-proteasome system, and induce autophagy by interference in the PI3K-Akt-mTOR signalling pathway [68].

6. Conclusions

This review gives an insight into the burden and predictions of the prevalence of the most common neurodegenerative diseases and the lack of effective treatment. Contemporary regimen is solely symptomatic; thus, we wanted to point out the emerging significance of nanoparticles as a promising approach in the treatment and diagnostics of these disorders. Despite the complexity of mechanisms underlying neurodegenerative diseases, some pathological aspects tend to overlap; thus, nanoparticles can act on many levels. Further, both in vitro and in vivo studies are extremely important to the discovery of the most efficient treatment of these diseases.
Abbreviations

Aβ: Amyloid-β protein  
AD: Alzheimer’s disease  
ALS: Amyotrophic lateral sclerosis  
APP: Amyloid precursor protein  
AuNPs: Gold nanoparticles  
BBB: Blood-brain barrier  
CGASeNPs: SeNPs conjugated with chlorogenic acid  
L-DOPA: L-3,4-Dihydroxyphenylalanine  
EGCG: Epigallocatechin gallate  
GAGs: Glycosaminoglycans  
GQDs: Graphene quantum dots  
GSH: Glutathione  
NAC: Nonamyloid β component  
NMDA: N-Methyl-D-aspartate  
NPs: Nanoparticles  
PAMAM: Poly(amidoamine)  
PD: Parkinson’s disease  
ROS: Reactive oxygen species  
SeNPs: Selenium nanoparticles  
SOD: Superoxide dismutase  
α-syn: Alpha-synuclein.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

M. P. wrote the main part of the manuscript. G. B. participated in the revision of the manuscript. I. S.-B. was responsible for the concept of the review and preparation of the manuscript. She was also responsible for providing the funding for the study. All authors have read and approved the final manuscript.

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