Advance in the use of gold nanoparticles in the treatment of neurodegenerative diseases: new perspectives

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Various conditions affecting nerve cells and the nervous system due to the loss of neurons and their connecting networks are described under the superordinate phrase "Neurodegenerative diseases". Such diseases lead to disability due to gradual neuronal death in both the central nervous system and the peripheral nervous system. While many of these diseases have unknown causes, sometimes these are due to medical conditions such as alcoholism, a tumor, or a stroke, or other causes which may include genetic mutations, toxins, chemicals, and viruses. Neurodegenerative diseases can be induced by various neurotoxic events, such as excessive inflammation, reactive oxygen species (ROS) production, and mitochondrial dysfunctions. The main symptoms associated with these disorders are related to movement (ataxia), mental functioning (dementia), or both, causing morbidity and death, thus having social and economic implications. The available treatments for these disorders provide only symptomatic relief, such as extending the lifespan to a few years. Still, a lot of research is in progress to find therapeutic markers for such diseases, as the complexity of the pathophysiology of neurodegenerative diseases and the underlying cell interactions is often imperfectly understood, limiting the development of therapeutic approaches (Khan et al., 2020). These physical constraints and the lack of specificity of current pharmacological approaches explain why most drugs and neurosurgical procedures have not been effective in the treatment of central nervous system disorders. As examples, pharmaceutical drugs used as treatment for Alzheimer's disease have low effects and those for Parkinson's disease loses their activity in a few years.

Combining this unmet clinical need with the global aging population, neurodegenerative disease poses as a significant challenge facing public health resources worldwide (Bordoni and Gabbianelli, 2020). The global cost of dementia is expected to reach over USD 2 trillion by 2030, and in the UK, the total spent on dementia care already exceeds that of cancer and chronic heart disease combined (Bordoni and Gabbianelli, 2020). Thus, there is an urgent need to identify new therapeutic approaches and technologies that can positively affect quality of life, leading to longevity and comfort, as well as reducing the cost of treatment of neurodegenerative diseases (Khan et al., 2020). Because of this, complementary and alternative medicines have always attractive solutions for various diseases, including neurodegenerative diseases. In addition, nanotechnology has provided promising treatments, as nanoscience and technology are emerging fields that can open new horizons for exploring innovative solutions to circumvent and treat neurodegenerative diseases, including Alzheimer's disease (AD), Huntington's disease, and Parkinson's disease (PD) (Khan et al., 2020).

Over the past few decades, inorganic nanoparticles, whose structures exhibit significantly novel and distinct physical, chemical, and biological properties, have elicited much interest given their biological and pharmaceutical potential (Muller et al., 2017a). More specifically, gold nanoparticles (GNPs) have been actively investigated in a wide variety of biomedical applications because of their biocompatibility and easy conjugation to biomolecules (Muller et al., 2017a). However, the effect of the use of GNPs per se in the brain in relation to neurodegenerative diseases is unknown. Interestingly, GNPs have anti-inflammatory and antioxidant properties and could potentially be used to treat neurodegenerative diseases. Furthermore, GNPs are also effective scavengers of ROS, including hydrogen peroxide (H_2O_2) and the superoxide anion (O_2^-), contributing to the activity of antioxidant enzymes (dos Santos Tramontin et al., 2020).

GNP toxicity is an ongoing concern; therefore, it is critical to study the therapeutic and toxic properties of these nanoparticles simultaneously. Daily use of GNPs (10, 20, and 50 nm) for 7 days was shown to cause liver damage and increase the production of ROS in the liver (Abdelhalim and Jarrar, 2012). On the other hand, a study by Muller et al. (2017a, b) administered GNPs (20 nm at 2.5 mg/L) every 24 or 48 hours for 21 days and evaluated any possible liver damage (through liver enzyme and histochemical analysis), serum changes, and the redox state and mitochondrial function of the brain: they observed that administration of GNPs with a 48-hour interval did not show toxicity, thus being a safe and efficient protocol for treatment with GNPs. However, there are different reports on the extent of the toxic nature of GNPs that influence the uptake and distribution of nanoparticles *in vivo*, mainly including particle size, surface charge and functionalization, permeability of blood vessels, and phagocytosis by the mononuclear phagocytic system (MPS). Particle size plays a key role in the biodistribution of nanoparticles. After administration, nanoparticles can be rapidly taken up by the liver, spleen, and bone marrow. Generally, very small particles with a diameter of less than 5–10 nm are rapidly eliminated by renal excretion, those between 150–300 nm are found mainly in the liver and spleen, and those between 30–150 nm are localized in the bone marrow, heart, kidney, and stomach (Klausner et al., 1975; Nakaoka et al., 1997; Banerjee et al., 2002). In addition to the discontinuous capillary endothelium, the enhanced uptake in the liver, spleen, and bone marrow is also attributed to the MPS cells present in the tissues, which are responsible for clearing particulates and macromolecules circulating in the blood (Li and Huang, 2005). Nonetheless, the general correlation of biodistribution and elimination with respect to size may vary greatly depending on the nanoparticle surface characteristics.

The surface charge of nanoparticles can also affect their uptake by the MPS. Positively charged particles are able to form aggregates in the presence of negatively charged serum proteins once administered intravenously that are usually large and may cause transient embolism in lung capillaries (Zhang et al., 2005). Subsequently, the dissociated particles redistribute to the liver. Thus, positively charged nanoparticles often exhibit rapid blood clearance with a significant accumulation in the lungs and liver, whereas neutral or negatively charged nanoparticles have a reduced plasma protein adsorption and a low rate of nonspecific cellular uptake (Wang et al., 2010). In addition, different synthesis methods can neutralize the cationic surface charge, and subsequently decrease nonspecific uptake by the MPS (Wang et al., 2010). Conversely, synthesis of nanoparticles using biological resources such as microorganisms (bacteria, fungi, yeasts, and viruses) and plants is a relatively recent phenomenon (Cabuzu et al., 2015). The processes for the synthesis of inorganic materials at nano- and micro-length scales result in a versatile green nanotechnology allowing the consequent application of GNPs in nanomedicine. Due to their biocompatibility and large surface area-to-volume ratio, GNPs are considered ideal candidates for carrying large amounts of antibiotics without compromising their activity. Furthermore, the size of the gold nanoparticles can be easily tuned using established and robust chemistry (Cabuzu et al., 2015). The combination of low inherent toxicity and tunable stability provides them with unique attributes that should enable new delivery strategies.

Several nano-biotherapeutic approaches have been adopted in the field of nanoparticle-based drug delivery systems to surpass the blood-brain barrier (BBB). The attraction and binding of lipophilic nanoparticles to endothelial cells increases the transport of drug molecules via endocytosis or lipophilic transcellular pathways, and their adsorptive properties towards blood capillaries offers a sustained release of drugs in the bloodstream with a higher probability of penetration across the BBB. Furthermore, functionalized nanocarriers elicit receptor-mediated transcytosis and carrier protein-mediated shuttling of drug molecules across the BBB (Bilal et al., 2020). As the therapeutic potential of drug delivery systems is dependent on the ability of nanocarriers to escape the immune system, penetrate the BBB, and perform task-specific functions in the targeted tissues, any hindrances can vividly reduce their efficacy. In the last 20 years, a large number of nano-delivery systems have been introduced for the treatment and improvement of neurodegenerative disorders. Nanostructured carriers such as magnetic nanoparticles, carbon nanotubes, quantum dots, polymeric nanocapsules, multifunctional nanoliposomes, nanoemulsions, and other cell membrane-based nanocarriers have demonstrated satisfactory encapsulation of cargoes with improved physicochemical stabilities for enhanced brain-targeting ability (Bilal et al., 2020). As drug delivery carriers, nanoparticles

have tremendous potential to improve the therapy of neurodegenerative diseases. The use of nanocarriers for delivering bioactives to treat neurodegenerative diseases has shown many advantages, including the possibility of loading various payloads with synergic effects, controllable delivery (although not possible with individual molecules or micro-delivery platforms), and the amenability for surface modification with target ligands, which can promote the crossing of the BBB for efficient distribution of bioactive molecules into the brain (Khan et al., 2020). By means of specific ligands, such as transferrin, lactoferrin, glucose, and peptides, nanocarriers can penetrate the BBB for effective delivery of drugs, which generally are not capable of crossing the BBB at the targeted site.

Studies have shown the therapeutic potential of GNPs with drug delivery and their potential effects. These beneficial effects of GNPs provide support for new analyses to better understand the process of neurodegenerative diseases. For example, a study from Hou et al. (2020) used GNPs reduced with GSH in a model of AD, where it was observed that GNPs with a size of 3–4 nm exhibited the best inhibition efficiency and protective effect of neurons against amyloid-β (Aβ)42 aggregate-induced cellular toxicity. dos Santos Tramontin et al. (2020), using a cerebral tauopathy model, showed that treatment with GNPs in a model of AD induced by okadaic acid reduced the hyperphosphorylation of Tau and improved cognitive and antioxidant function. Another study showed the potential capacity of GNPs to relieve memory impairment and neural damage in an animal model of AD (Sanati et al. (2019). The observed positive behavioral role of GNPs may be due to the redirection of Aβ peptide fibrillation kinetics, which minimizes the destructive effects of fibrils on p-CREB, BDNF, STIM1, and STIM2. A study from Gao et al. (2017) on the effect of size of GNPs and nanoclusters to inhibit amyloid-β (Aβ) fibrillation showed that nanoparticles with diameters of 36 and 18 nm accelerated Aβ fibrillation, whereas smaller GNPs with a diameter of 1.9 nm could significantly postpone or even completely inhibit this process. This result implied that different nano-entities *in vivo*, such as vesicles, micelles, and proteins, may interact with Aβ and thus influence its aggregation and fibrillation in different ways, suggesting a new direction for studying Aβ fibrillation *in vivo* (Gao et al., 2017). This study also showed that GNPs with small diameters could easily cross the BBB; we believe that due to the increase in the surface area for interaction with GNPs, even if a part is lost, a greater number of GNPs can cross the BBB.

GNPs have also been used in PD models. A study from da Silva Córneo et al. (2020) showed that treatment with GNPs in a PD mouse model induced by reserpine had oxidative stress parameters significantly reduced and motor symptoms improved. GNP treatment also partially improved neurotrophic factors, with the treatment at 20 nm with 2.5 mg/L reversing the symptoms of the induced PD showing no toxicity. Another study from Xue et al. (2019) using GNPs synthesized from the root extract of *Paeonia moutan* (PM-AuNPs) showed *in vitro* results where PM-AuNPs efficiently scavenge the ROS and decrease the levels of inflammatory cytokines in microglial cells. In addition, *in vivo* results confirmed that PM-AuNPs treatment prevented dopaminergic neuroinflammation and increased the levels of dopamine, thereby protecting PD-induced mice from motor disorders. In both studies, the treatment with GNPs reverted the behavioral symptoms induced in the PD models, demonstrating the efficient protective effect of GNPs on dopaminergic neurons without toxicity, preventing side symptoms of the disease.

In order to relate the effects of GNPs with potent drug delivery, new analyses should be applied and tested. As GNPs have high compatibility and interaction with pharmacological drugs, the use of anti-inflammatory or other specific drugs used to treat neurodegenerative diseases such as PD and AD becomes prominent. The use of L-dopa associated with GNPs can decrease the harmful effects of the drug and increase its beneficial effect, in addition to increasing the effect time without loss of its potency. Rivastigmine, a drug used in the treatment of AD and an inhibitor of acetylcholinesterase, is widely used, but has a low half-life: this is a possible gap for use with GNPs, which could improve drug delivery by being a good carrier and facilitate the metabolism by acetylcholinesterase, and thus possibly increasing the effect time of rivastigmine. These possible uses of GNPs are effective and very promising, expanding the range of uses of nanoparticles in the biomedical field as an innovative treatment (**Figure 1**).

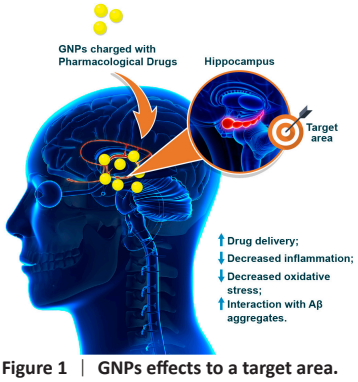

Figure 1 | **GNPs effects to a target area.**
Gold nanoparticles (GNPs) charged with pharmacological drugs reaching to a target area increasing drug delivery, decreasing inflammation and oxidative stress, also increasing interaction with amyloid-β (Aβ).

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