Progress in Materials Science 83 (2016) 152–190

Contents lists available at ScienceDirect

Progress in Materials Science

journal homepage: www.elsevier.com/locate/pmatsci

Size, shape and surface chemistry of nano-gold dictate its cellular interactions, uptake and toxicity

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ARTICLE INFO

Article history:
Received 25 May 2015
Received in revised form 1 April 2016
Accepted 14 April 2016
Available online 16 April 2016

Keywords:
Gold nanoparticles
Uptake
Toxicity
Size
Shape
Corona

ABSTRACT

Colloidal gold is undoubtedly one of the most extensively studied nanomaterials, with 1000s of different protocols currently available to synthesise gold nanoparticles (AuNPs). While developments in the synthesis of AuNPs have progressed rapidly in recent years, our understanding of their biological impact, with particular respect to the effect of shape, size, surface characteristics and aggregation states, has struggled to keep pace. It is generally agreed that when AuNPs are exposed to biological systems, these parameters directly influence their pharmacokinetic and pharmacodynamic properties by influencing AuNPs distribution, circulation time, metabolism and excretion in biological systems. However, the rules governing these properties, and the science behind them, are poorly understood. Therefore, a systematic understanding of the implications of these variables at the nano–bio interface has recently become a topic of major interest. This *Review Article* attempts to ignite a discussion around the influence of different physico-chemical parameters on biological activity of AuNPs, while focussing on critical aspects of cellular interactions, uptake and cytotoxicity. The review also discusses emerging trends in AuNP uptake and toxicity that are leading to technological advances through AuNP-based therapy, diagnostics and imaging.

Contents

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http://dx.doi.org/10.1016/j.pmatsci.2016.04.003
0079-6425/

1. Introduction

The use of gold to promote good health has been extensively documented in literature dating back to the 1st century [1–5], however it was not until 1856 that Faraday's pioneering work set the foundation of modern colloidal chemistry, or rather, nanotechnology [6]. It is now well known that as a particle decreases in size towards the nanoscale (Fig. 1), its inherent properties do not necessarily reflect the properties of the bulk material it is derived from, nor that of its individual atoms – this is indeed the case with gold nanoparticles (AuNPs) [7–12]. Generally speaking, as particle size decreases, the proportion of atoms which are localised on the particle surface grows, compared to those confined to the inside of the particle [13]. This effect gives rise to new thermal, optical, electrical, magnetic, electronic and catalytic properties [13–31].

In the case of metal nanoparticles, particularly, gold, silver and copper, when particle size becomes significantly small relative to the wavelength of light, the large number of surface electrons leads to interesting phenomena such as surface plasmon resonance (SPR) [32–35]. In the case of spherical AuNPs with sizes less than 60 nm, the SPR peak absorbance appears at around 520 nm, accounting for the ruby red colour commonly attributed to AuNPs [36]. Modifications to the size, shape and chemical environment of the particles alter the position of the plasmon band, and hence the apparent colour of the particles in solution [37–40]. It is this phenomenon which explains the use of AuNP suspensions throughout history to create the spectrum of colours possible in stained glass [9,32,36,41,42]. While size and chemical environment influence the position of plasmon bands of AuNPs, the shape of the nanoparticle offers better opportunities to controllably fine-tune the optical properties of these materials [43,44]. For instance, spherical AuNPs possess limited potential for SPR tuning as the intensity and position of the absorption bands are relatively fixed with only a small red shift and broadening seen with increasing particle size [37]. Conversely, altering the distance along which the oscillations are permitted to occur [45], which is achieved through altering the shape of AuNPs, gives rise to interesting optical properties that span the broader visible to near-infrared (NIR) spectrum, making them more suitable for biological sensing, imaging and even therapy [46–54].

Considering the interesting optical properties of AuNPs and their perceived biocompatibility [55,56], there has been significant interest in elucidating the interactions of AuNPs with biological systems, however much of this work pertains to spherical AuNPs. Further, it is commonly thought that changes in particle shape and size could influence the way that particles are recognised, processed and excreted by the body, however this conjecture remains largely untested [48,49,57–62]. Notably, when AuNPs are exposed to biological systems, their surface features such as the presence of capping agents, unreduced metal ions and surface charge, can directly dictate the pharmacokinetic and pharmacodynamic properties of the nanoparticle [63–65], making it difficult to draw valid conclusions by simply comparing the biological activities of AuNPs originating from different laboratories. Therefore, a systematic understanding of the implications of these variables at the nano–bio interface has recently become a topic of major interest [65]. This Review article is an attempt to ignite a critical discussion around the influence of different physico-chemical parameters on the biological activity of AuNPs (Fig. 2).

While concerns exist regarding the practicality of utilising AuNPs *in vivo* due to potential metal accumulation in the body, such concerns have not been thoroughly tested through long-term *in vivo* studies [66]. It is only recently that the importance of such studies has been recognised, and the research community has more seriously started to investigate the influence of *in vivo* factors, such as spontaneous protein corona formation on nanoparticle surfaces in response to exposure to biological

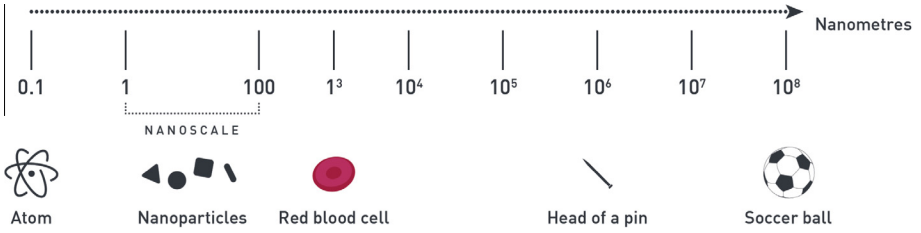

Fig. 1. Depicting the nanoscale relative to other objects.