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Toxicity induced by nanoparticles

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ABSTRACT

Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications. Human beings have been exposed to airborne nanosized particles throughout their evolutionary stages, and such exposures have increased dramatically over the last century. Nanoparticle can modify the physicochemical properties of the material as well as create the opportunity for increased uptake and interaction with biological tissues through inhalation, ingestion, and injection. This combination of effects can generate adverse biological effects in living cells. Nanoparticles have proved toxic to human once in the blood stream, nanoparticles, spleen, bone marrow and nervous system can be transported around the body and be taken up by organs tissue and cell cultures, resulting in increased oxidative stress, inflammatory cytokine production and cell death. Unlike larger particles, nanoparticles may be taken up by cell mitochondria and the cell nucleus studies demonstrate the potential for nanoparticles to cause DNA mutation and induce major structural damage to mitochondria, even resulting in cell death. Size is therefore a key factor in determining the potential toxicity of a particle. How these nanoparticles behave inside the body is still a major question that needs to be resolved. There is a responsibility to test and optimize these new nanomaterials early during the development process to eliminate or ameliorate identified toxic characteristics.

1. Introduction

1.1. Nanoparticles

"A particle having one or more dimensions of the order of 100 nm or less"[1]. In nanotechnology, a particle is defined as a small object that behaves as a whole unit in terms of its transport and properties. Nanoparticles may or may not exhibit size-related properties that differ significantly from those observed in fine particles or bulk materials. Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical and electronic fields[2] due to following advantages:

a) The increase in the ratio of surface area to volume dimensions below the critical wavelength of light renders them transparent, which make them very suitable for packaging, cosmetics and coatings.

b) Have several advantages over more conventional delivery system: Excellent administration performance via oral, injection or dermal routes; enhanced bioavailability and a high level of pharmacological action; applications in controlled and targeted delivery (e.g. for gene therapy), may be stabilized to

give long shelf lives.

c) Used as drug carriers are high stability, high carrier capacity, and feasibility of incorporation of both hydrophilic and hydrophobic substances.

d) Improvement of drug bioavailability and reduction of the dosing frequency.

1.2. Nanotoxicology

Nanoparticle can modify the physicochemical properties of the material as well as create the opportunity for increased uptake and interaction with biological tissues[3]. This combination of effects can generate adverse biological effects in living cells that would not otherwise be possible with the same material in larger form. Nanoparticles are able to cross biological membranes and access cells, tissues and organs inhalation or ingestion. At least some nanoparticles can penetrate the skin even larger microparticles may penetrate skin when it is flexed. Broken skin is an ineffective particle barrier, suggesting that acne, eczema, shaving wounds or severe sunburn may accelerate skin uptake of nanoparticles.

Nanoparticles have proved toxic to human once in the blood stream, nanoparticles, spleen, bone marrow and nervous system can be transported around the body and be taken up by organs tissue and cell cultures, resulting in increased oxidative stress, inflammatory cytokine production and cell death. Unlike larger particles, nanoparticles may be taken up by cell mitochondria and the cell nucleus studies

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demonstrate the potential for nanoparticles to cause DNA mutation and induce major structural damage to mitochondria, even resulting in cell death. Size is therefore a key factor in determining the potential toxicity of a particle. However it is not the only important factor.

Other properties of nanoparticles that influence toxicity include: chemical composition, shape, surface structure, surface charge, aggregation and solubility, and the presence or absence of functional groups of other chemicals. The large number of variables influencing toxicity means that it is difficult to generalise about health risks associated with exposure to nanoparticles each new nanoparticles must be assessed individually and all material properties must be taken into account.

Nanotoxicology is a sub-specialty of particle toxicology. It addresses the toxicology of nanoparticles (particles <100 nm diameter) which appear to have toxicity effects that are unusual and not seen with larger particles. Nanoparticles can be divided into combustion-derived nanoparticles (like diesel soot), manufactured nanoparticles like carbon nanotubes and naturally occurring nanoparticles from volcanic eruptions, atmospheric chemistry *etc.* Typical nanoparticles that have been studied are titanium dioxide, alumina, zinc oxide, carbon black, and carbon nanotubes, and “nano-C₆₀”. Nanoparticles seem to have some different properties from larger particles that are known to have pathogenic effects, like asbestos or quartz. These differences seem to be a result of their size. Nanoparticles have much larger surface area to unit mass ratios which in some cases may lead to greater pro-inflammatory effects (in, for example, lung tissue). In addition, some nanoparticles seem to be able to translocate from their site of deposition to distant sites such as the blood and the brain. This has resulted in a sea-change in how particle toxicology is viewed— instead of being confined to the lungs, nanoparticle toxicologists study the brain, blood, liver, skin and gut. Nanotoxicology has revolutionised particle toxicology and rejuvenated it.

The extremely small size of nanoparticles also means that they much more readily gain entry into the human body than larger sized particles. How these nanoparticles behave inside the body is still a major question that needs to be resolved. The behavior of nanoparticles is a function of their size, shape and surface reactivity with the surrounding tissue. In principle, a large number of particles could overload the body's phagocytes, cells that ingest and destroy foreign matter, thereby triggering stress reactions that lead to inflammation and weaken the body's defense against other pathogens. In addition to questions about what happens if non-degradable or slowly degradable nanoparticles accumulate in bodily organs, another concern is their potential interaction or interference with biological processes inside the body. Because of their large surface area, nanoparticles will, on exposure to tissue and fluids, immediately adsorb onto their surface some of the macromolecules they encounter. This may, for instance, affect the regulatory mechanisms of enzymes and other proteins.

2. Mechanisms of nanoparticle toxicity

The primary mechanism of nanoparticle toxicity involves reactive oxygen species (ROS) and free radical production.

It may result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA. The

smaller a particle is, the greater its surface area to volume ratio and the higher its chemical reactivity and biological activity. The greater chemical reactivity of nanomaterials results in increased production of ROS, including free radicals. ROS production has been found in a diverse range of nanomaterials including carbon fullerenes, carbon nanotubes and nanoparticle metal oxides. The extremely small size of nanomaterials also means that they much more readily gain entry into the human body than larger sized particles^[4–10].

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3. Behavior of nanoparticle with body

Nanoparticles have been found to be distributed to the colon, lungs, bone marrow, liver, spleen, and the lymphatics after intravenous injection^[11]. Distribution is followed by rapid clearance from the systemic circulation, predominantly by action of the liver and splenic macrophages. Clearance and opsonization, the process that prepares foreign materials to be more efficiently engulfed by macrophages, occur under certain conditions for nanoparticles depending on size and surface characteristics.

When inhaled, nanoparticles are found to be distributed to the lungs, liver, heart, spleen, and brain. Nanoparticles are cleared in the alveolar region via phagocytosis by macrophages facilitated by chemotactic attraction of alveolar macrophages to the deposition site. The average half-life ($t_{1/2}$) for nanoparticles in the respiratory tract is about 700 days in humans.

After intraperitoneal injection, nanoparticles have been found to cross the transplacental membrane or cross the peritoneal cavity into uterus. This affected the embryos cranial development and even caused embryo death.

After oral exposure, nanoparticles distribute to the kidneys, liver, spleen, lungs, brain, and the gastrointestinal (GI) tract. Some nanoparticles can pass through the GI tract and are rapidly eliminated in feces and in urine, indicating that they can be absorbed across the GI barrier and into the systemic circulation. However, some nanoparticle systems can accumulate in the liver during the first-pass metabolism.

Contact with nanoparticles through the skin can occur due to occupational exposure during the manufacturing of solvents, pesticides, or pharmaceuticals. Skin exposure to nanoparticles can also occur during nonoccupational situations from the use of cosmetics and in the intentional application of topical creams and other drug treatments.

4. Properties of nanoparticles that induces toxicity

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Typical nanoparticles that have been studied are titanium dioxide, alumina, zinc oxide, carbon black, and carbon nanotubes, and “nano-C₆₀”. Nanoparticles seem to have some different properties from larger particles that are known to have pathogenic effects, like asbestos or quartz. These differences seem to be a result of their size. Nanoparticles have much larger surface area to unit mass ratios which in some cases may lead to greater pro-inflammatory effects (in, for example, lung tissue). In addition, some nanoparticles seem to be able to translocate from their site of deposition to distant sites such as the blood and the brain. This has resulted in a sea-change in how particle toxicology is viewed— instead of being confined to the lungs, nanoparticle toxicologists study the brain, blood, liver, skin and gut. Nanotoxicology has revolutionised particle toxicology and rejuvenated it.

5. The mediators of the toxicity of particles

5.1. Size

Reduction in size to the nanoscale level results in an enormous increase of surface to volume ratio, so relatively more molecules of the chemical are present on the surface, thus enhancing the intrinsic toxicity^[12]. The expression of a dose response relationship on the basis of particle size resulted in a similar dose response relationship between low solubility–low toxicity, particles of different sizes. In studies of low toxicity particles, TiO₂ induced a more severe lung inflammation and particle lymph node burden compared to BaSO₄ when dosed at mass burden in milligrams.

5.2. Chemical composition

The chemical composition and the intrinsic toxicological properties of the chemical are of importance for the toxicity of particles. The effect of carbon black has been shown to be more severe than that of titanium dioxide, while for both compounds the nanoparticles induced lung inflammation and epithelial damage in rats at greater extent than their larger counterparts. Metallic iron was able to potentiate the effect of carbon black nanoparticles, resulting in enhanced reactivity, including oxidative stress.

5.3. Shape

Shape is also likely to be an important factor although there is little definitive evidence. Fibres provide a significant example of the debate about shape, especially in relation to inhalation, where the physical parameters of thinness and length appear to determine respirability and inflammatory potential. The biopersistence of fibres effectively determines their dose.

6. Nanoparticle exposure

The following discussion of nanoparticles exposure highlights the limited exposure studies that have been conducted, as well as studies on the ability of the external surfaces of the body to limit systemic exposure and mechanisms of nanoparticles translocation^[13].

6.1. Inhalation exposure

Inhalation is thought to be an important route of nanoparticle exposure, since nanoparticles can travel great distances in air by Brownian diffusion and are respirable, depositing within the alveolar regions of the lung (Bailey).

6.2. Systemic translocation from lung

Clearance mechanisms in the lungs include the mucociliary escalator and phagocytosis by alveolar macrophages. Several studies in rodents have also demonstrated that nanoparticles deposited in the lungs can translocate to the pulmonary interstitium.

6.3. Neuronal translocation

The ability of inhaled nanoparticles to undergo neuronal translocation from the nasal epithelium to the olfactory bulb is supported by several studies in rats.

6.4. Dermal exposure

The interaction of nanoparticles with skin has received significant attention recently because of the increasing use of nanoscale particles in stain-resistant clothing, cosmetics, and sunscreens. The dermal route of exposure is also important because of the tendency of agglomerated airborne nanoparticles to settle on surfaces and the difficulties in preventing dermal contact with these settled particles. Several studies have been conducted examining the ability of nanoscale TiO₂, used as a ultraviolet (UV)–absorbing component in sunscreens, to penetrate the epidermis in human volunteers, and animal and *in vitro* models

6.5. GI exposure

Recent studies have addressed the issue of GI absorption of nanoparticles following oral exposure. Like occupational and environmental route, resulting from ingestion of contaminated food and water, the swallowing of inhaled particles, or hand-to mouth transfer of particles.

7. Examples of toxicities of nanoparticles

Researchers in the University of Texas in the United States found that carbon nanotubes squirted into the trachea of mice caused serious inflammation of the lungs and granulomas. In a similar experiment carried out at the National Institute of Occupational Safety and Health in Morgantown, West Virginia, in the United States, researchers not only found granulomas in the lungs, but also damage to mitochondrial DNA in the heart and the aortic artery, and substantial oxidative damage, both

foreshadowing atherosclerosis.

Inflammation and oxidative stress can be mediated by several primary pathways:

Hypothetical cellular interaction of NSPs (adapted from Donaldson and Tran 2002) and epidermal growth factor receptor.

The particle surface causes oxidative stress resulting in increased intracellular calcium and gene activation. Transition metals released from particles result in oxidative stress, increased intracellular calcium, and gene activation. Cell surface receptors are activated by transition metals released from particles, resulting in subsequent gene activation. Or Intracellular distribution of NSPs to mitochondria generates oxidative stress.

Studies have shown that they can contribute to adverse health effect in the respiratory tract as well as in extrapulmonary organs^[13]. Result on direct effect of ambient and model nanoparticles have been reported from epidemiologic studies and controlled clinical studies in human, inhalation/instillation studies have in rodent or *in vitro* cell culture system. For example, several epidemiologic studies have found association of ambient nanoparticles with adverse respiratory and cardiovascular effects resulting in morbidity and mortality in susceptible parts of the population, whereas other epidemiologic studies have not seen such association. Controlled clinical studies evaluated deposition and adverse effect of laboratory generated nanoparticles.

8. Regulatory guideline for nanoparticle toxicology

Currently, there is no regulation and guideline in nanomaterial toxicology at all provincial, national level^[3]. In early this year, US–EPA published “Nanotechnology White Paper” in that EPA listed problems or limitation & some requirements in environmental health for development of nanotechnology.

However, it is far way to form a regulations or guidelines are of efficiency toxicological techniques that can efficiently identify real toxicological factors for evaluating nanomaterial toxicity because too many unconcerned factors. To establish such regulations or guidelines in nanomaterial toxicology is depend on the development.

9. Future trends

In the future, nanoparticles could be classified in terms of their biomolecule corona which mediates their interaction with cellular machinery. This would represent a truly new paradigm in the field of nanoscale toxicology and in the design of safe nanocarriers for nanomedicine. With this new opportunity to utilize the unique properties of nanoparticles for research, industry, and medicine, there is a responsibility to test and optimize these new nanomaterials early during the development process to eliminate or ameliorate identified toxic characteristics.

The rapid commercialization of nanoparticles requires focused environmental, health, and safety research, meaningful and open discussion of broader societal impacts and urgent oversight.

10. Conclusion

Nanotechnology is growing at an exponential rate and will undoubtedly have both beneficial and toxicological impact and consequences on health and environment. Possible undesirable results of these capabilities are harmful interactions with biological systems with the potential to generate toxicity. Development of new techniques to show accurate correlations between *in vitro* and *in vivo* studies is imperative to accurately portray nanoparticle effects. Moreover, toxicity studies are critical to establish the full *in vivo* potential of nanomedicine. Understanding the physiochemical, molecular, and physiological processes of nanoparticles is important for nanomedicine to become a reliable and sustainable treatment modality.

Conflict of interest statement

We declare that we have no conflict of interest.

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