PAEDIATRIC RESPIRATORY REVIEWS (2007) **8**, 62–66

Paediatric Respiratory Reviews

REVIEW

Toxicological aspects and applications of nanoparticles in paediatric respiratory disease

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KEYWORDS
nanoparticles;
toxicology;
respiratory diseases;
imaging;
targeting;
gene therapy

Summary Most research in the area of micro- and nano-particles as applied to respiratory disease has been on potential toxic effects. Particulate emissions from industrial processes, coal burning and diesel exhaust have been shown to cause a variety of adverse effects both in vitro and in vivo. However, the vast majority of these studies has focused on larger, micron-sized particles. It is only within the last few years that the emphasis has shifted to nanoparticles as nanotechnology research and its applications have increased. Investigations have also begun into how nanoparticles may be used for therapeutic and imaging purposes in pulmonary diseases such as tuberculosis and cystic fibrosis. Some of these applications, along with recent studies on the toxic effects of nanoparticulate emissions will be reviewed in this article.

INTRODUCTION

Nanotechnology – and in particular the use of nanoparticles – has begun to permeate everyday life. Nanoparticles are used in sunscreens, immunoassays, MRI contrast enhancement, quantum dot lasers, semiconductors, magnetic storage and many other applications.[1] Nanoparticles are particles that fall within the size range of 1 nm to 1000 nm (or 1 μm). Particles at the lower end of this size range typically display different physical properties (electrical, magnetic and optical) in comparison to the properties of the same material in bulk as quantum mechanical effects begin to dominate. For example, magnetic nanoparticles below a few 10s of nanometers generally lose their magnetisation upon removal of an applied field – an effect known as superparamagnetism. This makes it difficult to use many types of magnetic nanoparticles for high-density information storage but it is a property ideally suited to many in vivo applications – such as drug and gene delivery – where the retention of particle magnetisation could lead to agglomeration and clumping of the particles within the body, hindering their ability to deliver the therapeutic agent successfully.[2,3]

In quantum dots, quantum confinement leads to the emission of light in some materials that do not normally emit light when excited, such as silicon. The colour of light in these materials can be varied by varying the size of the particle (the larger the particle, the redder the light) and these quantum dots are now finding applications in biosensing research as well.[4,5]

This article will primarily aim to review the relatively recent application of nanotechnology to paediatric respiratory diseases. Though many therapeutic compounds and viruses delivered to the lung by nebulisers could also be classified as nanoparticles, the general topic of nebuliser formulations for therapeutic applications will not be discussed. Instead, the focus will be the novel use of nanoparticle carriers for drug and gene delivery to the lungs and for imaging, and will touch on aspects of toxicology.

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1526-0542/$ – see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.prrv.2007.02.005

NANOPARTICLE TOXICOLOGY

Unfortunately, one of the main areas of research on the effects of nano- and micro-particles on the lung is in the field of particle toxicity. It has been known for many years that exhaust emissions and air pollution (largely from industrial processes and coal burning) in general contain particulates which can have adverse effects on both paediatric and adult respiratory conditions.[6] This is an area that requires further investigation as more nanoparticlulates are released into the atmosphere and more workers are exposed as nanoparticle manufacture is scaled up for industrial production.

Most studies have concentrated on the effects of PM2.5 (particles with a diameter $<2.5\ \mu m$) and PM10 ($<10\ \mu m$) particulate pollutants but without refining these size groups further. However, it is clear that sub-100 nm particles are released from combustion during industrial processes and, most likely, from diesel engines.[7,8] Murr *et al.* examined carbonaceous nanospherules from diesel exhaust and demonstrated their potential to act as toxic agents deep in the lung.[7] Smaller, silica nanoparticles appear to have a less detrimental effect than larger, micron-sized ones on lung cells in culture,[9] while TiO_2 particles have the opposite size versus toxicity relationship.[10] Obviously, this indicates that the material, as well as its size/shape, are important factors in determining lung toxicity.

Following on from studies on carbon nanoparticles from exhaust emissions, studies have investigated the potential toxic effects of carbon nanotubes and their precursors, spherical C_{60} fullerenes, on the lungs. These studies are likely to expand as the use of carbon nanotubes for a variety of applications is being examined. Some studies have already demonstrated that carbon nanotubes induce inflammatory and fibratory responses in the lungs of laboratory animals. Muller *et al.* showed that multi-walled carbon nanotubes were still present in the lungs of Sprague–Dawley rats 60 days after intra-tracheal administration.[11] In vitro effects ranged from pulmonary lesions to overproduction of tumour necrosis factor alpha (TNF-α). The in vivo effects are similar to those induced by single-walled carbon nanotubes (SWCN) in C57BL/6 mice, in which respiratory deficiencies and decreased bacterial clearance were also observed.[12] In this study, however, the authors reported a down-regulation of TNF-α upon exposure to SWCN. (For a review of these studies see Fiorito *et al.*[13])

Though at present carbon nanotubes do not appear to have a direct bearing on paediatric respiratory problems, as they make their way into industrial applications their potential for toxicity and effects on paediatric respiratory illness clearly will need further investigation.

NANOPARTICLE-BASED IMAGING

Magnetic nanoparticles have been used as magnetic resonance imaging (MRI) contrast enhancement agents for many years.[14] These agents act by introducing local magnetic field perturbations at the site where they are concentrated. This has an effect on the relaxation of water-bound protons in the surrounding tissue, providing improved contrast at the target site. Details of the physical basis underlying MRI contrast enhancement, as well as for magnetic nanoparticle-based targeting for drug and gene delivery, are reviewed in Pankhurst *et al.*[15]

Magnetic nanoparticles (often referred to as superparamagnetic iron oxides [SPIONs] due to their small size and magnetic properties) may be functionalised with antibodies in order to direct them to tumours and other targets within the body. Within the context of lung imaging, this approach has mainly been applied to the imaging of lung tumours.[16] However, Haage *et al.* have demonstrated the viability of using magnetic nanoparticle contrast agents for non-invasive imaging of pulmonary ventilation.[17]

Similarly, quantum dots are being used to track metastatic cancer cells and evaluate the mechanisms behind their extavasation into the lung using fluorescent techniques.[18] Although these techniques are of somewhat limited value to paediatric respiratory conditions, in 2005 Agrawal *et al.* demonstrated that antibody-functionalised quantum dots can be used to detect respiratory syncytial virus (RSV), a respiratory infection of particular significance in infants and young children.[19] Though nanoparticles are not in routine use for lung imaging, these studies demonstrate their potential.

NANOPARTICLE TARGETING OF THERAPEUTIC DRUGS AND GENES

The delivery of therapeutic genes and drugs directly to the lung via nanoparticle carriers is an area of research which holds particular promise for the treatment of paediatric respiratory disorders. Studies in guinea pigs have shown that drugs for the treatment of disorders such as tuberculosis (TB) can be either coupled to or encapsulated within nanoparticles for effective delivery of anti-TB agents.[20,21] These studies resulted in the reduction of bacterial infection and lung pathology and have employed polymer and alginate,[22] time-release particle strategies.

Novel polymer nanoparticles displaying multiple synthetic, low-molecular weight ligands are also being developed which have high affinity for P-selectin and the potential for attenuating P-selectin activity.[23] In a murine model, these particles were shown to be active in vivo and significantly reduced allergen-induced airway hyper-reactivity and peribronchial eosinophilic inflammation. The development of novel magnetic nanoparticles and binding strategies for targeting specific diseases using specific genes and compounds is progressing rapidly. Some of these advances are reviewed in Dobson *et al.*[2,3]

Perhaps the greatest potential for using nanoparticles to treat paediatric respiratory illness lies with nanoparticle-facilitated delivery of therapeutic genes for cystic fibrosis