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Engineered nanoparticles. How brain friendly is this new guest?

Francesca A. Cupaioli [a,1], Fabio A. Zucca [a,1], Diana Boraschi [b], Luigi Zecca [a,*]

[a] Institute of Biomedical Technologies, National Research Council of Italy, Segrate, Milan, Italy
[b] Institute of Biomedical Technologies, National Research Council of Italy, Unit of Pisa, Pisa, Italy

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ABSTRACT

In the last 30 years, the use of engineered nanoparticles (NPs) has progressively increased in many industrial and medical applications. In therapy, NPs may allow more effective cellular and subcellular targeting of drugs. In diagnostic applications, quantum dots are exploited for their optical characteristics, while superparamagnetic iron oxides NPs are used in magnetic resonance imaging. NPs are used in semiconductors, packaging, textiles, solar cells, batteries and plastic materials. Despite the great progress in nanotechnologies, comparatively little is known to date on the effects that exposure to NPs may have on the human body, in general and specifically on the brain. NPs can enter the human body through skin, digestive tract, airways and blood and they may cross the blood-brain barrier to reach the central nervous system. In addition to the paucity of studies describing NP effects on brain function, some of them also suffer of insufficient NPs characterization, inadequate standardization of conditions and lack of contaminant evaluation, so that results from different studies can hardly be compared. It has been shown *in vitro* and *in vivo* in rodents that NPs can impair dopaminergic and serotoninergic systems. Changes of neuronal morphology and neuronal death were reported in mice treated with NPs. NPs can also affect the respiratory chain of mitochondria and Bax protein levels, thereby causing apoptosis. Changes in expression of genes involved in redox pathways in mouse brain regions were described. NPs can induce autophagy, and accumulate in lysosomes impairing their degradation capacity. Cytoskeleton and vesicle trafficking may also be affected. NPs treated animals showed neuroinflammation with microglia activation, which could induce neurodegeneration. Considering the available data, it is important to design adequate models and experimental systems to evaluate in a reliable and controlled fashion the effects of NPs on the brain, and generate data representative of effects on the human brain, thereby useful for developing robust and valid nanosafety standards.

Contents

1. Introduction 21
2. NPs in air pollution 22
3. Nano-strategies in drug delivery to the CNS for diagnostic and therapeutic purposes 22
   3.1. Lipid-based NPs for therapeutic use 22
   3.2. Polymer-based NPs for therapeutic use 24
   3.3. Polymeric NPs in brain imaging and diagnosis (dendritic NPs) 25
   3.4. Inorganic NPs in brain imaging diagnosis and therapy (quantum dots and superparamagnetic NPs) 25
   3.5. Important chemical–physical characteristics of NPs 25

Abbreviations: BBB, blood-brain barrier; CA, cornu ammonis; CNS, central nervous system; IL, interleukin; iPS, induced pluripotent stem; MRI, magnetic resonance imaging; NPs, nanoparticles; LPS, lipopolysaccharide; PEG, polyethylene glycol; PBCA, polybutyl-cyanoacrylate; PM, particulate matter; PS, polysorbate; ROS, reactive oxygen species.

[*] Corresponding author at: Institute of Biomedical Technologies, National Research Council of Italy, Via Cervi, 93, 20090 Segrate, Milano, Italy. Tel.: +39 02 26422616; fax: +39 02 26422660.

E-mail address: luigi.zecca@itb.cnr.it (L. Zecca).

[1] These authors contributed equally.

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4. NPs entry into the CNS 26
    4.1. Uptake mechanism of NPs across the BBB. 26
    4.2. Strategies to enhance the NPs targeting to the CNS 27
    4.3. NPs uptake by nerve endings embedded in the airway epithelia. 28
5. Neurotoxicity of NPs 29
    5.1. Effects on BBB. 29
    5.2. Effects on neurons 30
    5.3. Effects on cellular components 31
    5.4. Effects on glial cells and inflammation in the brain 32
6. Conclusions and perspectives 33
    6.1. The massive environmental invasion of NPs and related safety issues 33
    6.2. Limited reliability of the available data and inadequacy of experimental models used to investigate the biological effects of NPs . . 33
    6.3. Potential of new models using induced pluripotent stem cells to study NPs biology and health risk 34
    6.4. Need to investigate neuroinflammatory, neurodegenerative and carcinogenic effect of NPs 34
Acknowledgements 34
References 35

1. Introduction

During the annual meeting of American Physical Society at the California Institute of Technology in 1959, the physicist Richard Feynman, in his lecture "There's plenty of room at the bottom", mentioned for the first time the possibility of manipulating and controlling things at the small scale (Feynman, 1960). More than fifty years later, today nanoparticles (NPs) are widely used in extensive range of applications in different fields. NPs are nano-objects with all three external dimensions in the nanoscale, where nanoscale is defined as a size range from approximately 1 to 100 nm (ISO/TS 27687:2008) (Fig. 1), and show size-dependent properties that strikingly differ from those of the bulk material.

The NPs can be natural or synthetic. NPs naturally present in the environment derive from natural events such as terrestrial dust storm, volcanic eruptions, erosion and forest fire. Moreover, human activities introduce NPs in the environment, as by-products of simple combustion or generated by combustion engines, power plants and other thermodegradation systems. On the other hand, the advent of the nanotechnological industry is now exposing man to a new category of NPs, the engineered NPs, which encompass multiple chemical compositions, shapes and sizes.

At variance with natural NPs, which are heterogeneous in material, size and properties, engineered NPs are synthesized as homogenous entities with controlled characteristics. These unique features make engineered NPs very versatile, thus they are nowadays used in a wealth of applications, either incorporated into products to enhance or improve their properties, or as new stand-alone products. For example, highly conductive NPs are used in the electronics and telecommunication fields to create sensors and small components in electronic devices, like smartphones (Shipway et al., 2000). Other NPs with special characteristics of hardness and friction are used as abrasives in the nanopolish of ultra-smooth surfaces (Guo et al., 2014); in addition, they can be used as additives in minimum quantity lubrication systems, allowing very low friction and wear, and leading to lower temperature in grinding zone with respect to lubricant devoid of NPs (Li et al., 2013; Guo et al., 2014). NPs may also be applied in materials engineering, since they can form chain aggregates with high plasticity and elasticity, thus improving mechanical properties of rubber and other polymeric materials (Rong et al., 2006). Moreover, NPs can be used as anti-reflection coatings, taking advantage of their specific optical properties (Du et al., 2010).

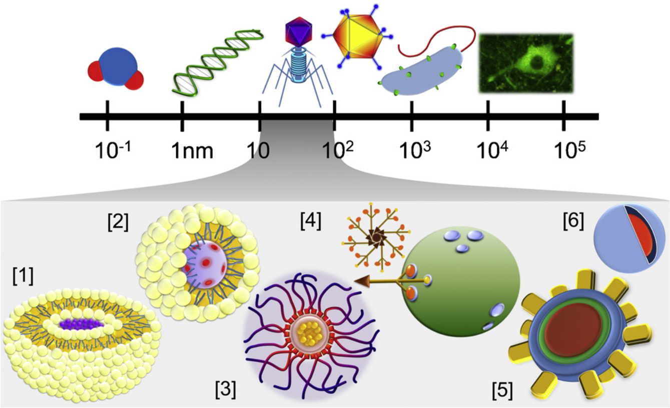

Fig. 1. Scale size of NPs. Length scale showing the size of NPs compared to biologic materials (*i.e.*, water molecule, DNA, bacteriophage, virus, bacterium and neuron) in the nano and micro size. In the bottom panel few types of NPs are represented: [1] liposome, [2] solid–lipid NP, [3] polymeric micelle, [4] dendrimer, [5] quantum dot and [6] iron oxide NP.

Because of their chemical chelation and antimicrobial capacity, some NPs are also used in environmental remediation technologies as removal agent of toxic metals and compounds, or as antimicrobial agents. For example, magnetite and zero-valent iron NPs are used for removal and retention of uranium from contaminated environmental water (Crane et al., 2011), and Ag NPs are effective in eliminating bacterial pathogen population from wastewater (Seo et al., 2012).

NPs, as nanoemulsions, have excellent sensorial and hydrating properties and for this reason they are widely used in the cosmetic industry, for example in lotions, moisture milks, crystal-clear gels, nail polish, hair products, toothpaste, and others (Hougeir and Kircik, 2012). Furthermore, metallic NPs are commonly used in sunscreen lotions (TiO_2 NPs) and as antimicrobial agents (Ag NPs) in detergents and other everyday cosmetic products (Bondarenko et al., 2013).

As in the case of cosmetics and textile products, NPs (*i.e.*, Ag NPs, TiO_2 NPs, etc.) are largely used in the food industry as preservatives that avoid microorganisms proliferation (Hajipour et al., 2012), and they are also employed to encapsulate food additives thereby enhancing flavours and brightening colours (Sekhon, 2010). NPs are also used in food packaging (Fuciños et al., 2012), embedded in the polymer matrix, where they act as gas sensors (UV-activated TiO_2 NPs oxygen sensors), or forming a protecting barrier from UV radiation, or inhibiting gas permeability (Duncan, 2011).

Finally, engineered NPs are largely used in the field of healthcare and life sciences, having numerous medical applications (*i.e.*, drug delivery, magnetic resonance imaging, hyperthermia treatment, etc.) and biotechnological uses (*i.e.*, biosensors, basic research technologies, biomedical engineering, etc.).

The development of nanotechnologies is evolving very rapidly and in parallel NP-containing products are becoming significantly