NANOTECHNOLOGY

Toxicology of Nanoparticles

A. D. Durnev

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The paper considers the basic directions in fundamental and applied studies of the toxic effects of nanoparticles. Of particular importance is the study aimed at evaluation of the dependence of these effects on the shape, size, initial material, surface area, electric charge, and other physicochemical structural peculiarities, as well as on the dosage, mode of application, concentration in the target organ, and duration of action. The differences are stressed in the realization of general toxicity and genotoxicity of nanoparticles and chemical agents. The importance of the development of new methods of preclinical assessment of the safety of therapeutic nanoderivatives is emphasized.

Key Words: *nanoparticles; toxicology*

Further progress in various fields of science and technology is associated with the development of nanotechnologies. This development will be necessarily accompanied by more intensive and close contacts between nanoparticles, on the one side, and humans and ecosystems, on the other. As a powerful tool, nanoparticles of various origins will be used in medicine in the way implying their targeted and systematic administration into living organism [7,11].

Known nanoparticles are designed microscopic objects <100 nm. They are subdivided into the following groups [9]: liposomes, emulsions, polymers, ceramics, metals, and carbons (fullerenes and nanotubes). The accumulated experience and prospects of their clinical use are reviewed somewhere [9,10].

Extensive development of nanotechnology is not accompanied by adequate knowledge on the effect of nanoparticles on human health, which is virtually absent. However, even the first studies revealed the novel general and biological properties of the known materials, which they acquire when transformed into nanoparticles. For example, they penetrate into the cells and are selectively accumulated in various types of cells or in the compartments of similar cells. Nanoparticles can cross the epithelial and endothelial cell by transcytosis. Moreover, they travel along the dendrites and axons and the blood and lymphatic vessels provoking oxidative stress and inflammation [9,11]. Logically, the new academic discipline appeared and currently develops under the name of "nanotoxicology", which is determined as "the science examining the effects of artificially designed nanostructures and the nanomechanisms on the living organisms [11].

Elaboration of the adequate approaches to prognosis of the risk of nanoparticles of various natures for human health is closely related to the study of the fundamental relationships in manifestations of their biological effects, and it is impossible to elaborate such approaches without comprehensive studies of this problem. The study of most general relationships in manifestations of the biological and toxic effects of nanoparticles depending on their shape, size, origin material, surface area, electric charge, physicochemical peculiarities of the structure, dosage, administration route, concentration in the target organ, and duration of action should be considered as the most important and actual funda-

V. V. Zakusov State Research Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow. ***Address for correspondence:*** adurnev@aport.ru. A. V. Durnev

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mental problem of nanoparticle toxicology requiring immediate examination.

Of particular importance is evaluation of the delayed effects of nanoparticles, including their effects on genome, immunity, and antenatal and postnatal development of the progeny. However, there are virtually no published data on these aspects.

The theoretically outlined avenue of the wide use of nanoparticles in the development and production of new drugs needs principally novel approaches to the preclinical safety assessment (PSA) of "nanodrugs". Existing PSA system is targeted to assess toxicity of chemical agents, but not toxicity of nanoparticles. The therapeutic preparations and nanoparticles designed on their basis can be principally different in the toxic properties due to significant peculiarities in kinetics and bioavailability *in vivo* [11] and possibly due to integration of the toxic and pharmacological effects of the initial chemical substance and its derivative nanoparticles.

The defects of existing PSA system can be demonstrated with the cases documented during the study of cytogenetic effects of the chrysotile asbestos fibers and zeolite particles. Adverse genetic effects of these agents were revealed only by special methods, while routine methods were ineffective. Although these experiments used particles somewhat greater (2-10 μ) than nanoparticles, both kind of particles had similar toxic mechanisms related to the prooxidant effects and activation of oxidative stress. Hence, some important parameters of corpuscular mutagenesis (dosage, size, administration route, duration of action, and the presence in the organism [1-3]) can be considered as the key factors in the analysis of genotoxicity and general toxicity of nanoparticles. In this analysis, the principal feature is advantage of *in vivo* over *in vitro* experiments.

The same data suggest that examination of genotoxicity of nanoparticles leads to the problem of tissue specificity of the effects determined by the peculiarities of antioxidant protection and production of endogenous mutagens [4], which cannot be simulated *in vitro*. This problem can be solved by using DNA-comet assay in some modifications that can reliably detect DNA damages in virtually all tissues of the organism [5].

It should be stressed that other fields of toxicology accumulated pronounced experience in the study of toxic effects of particles of various size including airborne ultra small corpuscles, which can be used in the development of the methods of PSA of the therapeutic nanodrugs. It is important that the ultrasmall particles are heterogenic by their chemical composition, shape, and size, while the artificially produced nanoparticles are standardized by these parameters. This peculiarity can be of principal importance, although the common prooxidant toxic mechanism is a good ground to believe in efficiency of such approach.

Two aspects of nanotoxicology should be mentioned, which concerns the safety of nanodrugs. First, the patients will use the nanodrug particles, and it explains the need to examine their toxic profile not only in healthy organism, but also on animal models of particular diseases. Second, the wide spread of the genetic polymorphisms in human population suggests that some part of this population can be extremely sensitive to the action of nanoparticles. This hypothesis agrees with the preliminary data on the role of oxidative stress in the realization of the toxic effects of nanoparticles and genetically determined heterogeneity of the antioxidant and other protective systems [6]. This explains the necessity of 1) early prognosis of anomalous sensitivity of the persons, who systematically contact with nanoparticles by professional or environmental reasons, based on determination of the significant genetic polymorphisms and 2) the development of methods for correction of the undesirable action of nanoparticles. We previously summarized the positive experience in solving such problems concerning the chemical and corpuscular mutagens based on examination of the related molecular and pharmacogenetic mechanisms [4].

For adequate evaluation of the toxic effects of nanostructures, two prerequisite stages could be necessary, although they can delay the therapeutic use of nanodrugs: 1) elaboration of the related methodology that needs long time for its development and 2) the corresponding experimental studies. Certain hopes on acceleration of these procedures originate from the use of "omics" technologies and related specific toxicity markers in the toxicological studies [12,13]. However, insufficiently verified basis of these methods in PSA will delay their use in the immediate future.

The development of nanotechnologies, which goes far ahead of the toxic assessment of their products, can be surely and responsibly assessed as a negative trend in modern science. Apart from the ethic aspects and unexpected medical long-term after-effects, the feasible financial losses are envisaged because of underestimation of this problem. It is known that creation of a new drug needs 800 million USA dollars, while near 40% new drugs are sorted out at the stage of preclinical assessment [12]. Evidently, only timely study of fundamental and practical aspects of nanotoxicology can diminish the risk of possible losses.

Thus, the above considerations stress extreme scientific importance of the studies in nanotoxicology in general and in toxicology of the nanodrugs in particular. Moreover, they attest to appearance of a novel vector in the development of general and drug toxicology.

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