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Reproductive toxicity of carbon nanostructured material - a promising carrier of drugs in laboratory mice

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INTRODUCTION

Currently, to the prospects of nanotechnology is given an increasing worldwide attention. However, nanomaterials might have very different physical and chemical properties and biological (including toxic) effect than substance in the usual physical and chemical condition that is why they are refered to new types of materials and products. Among the actual and potential areas of their application - microelectronics, micromechanics, energy, environment, agriculture, etc. Especially we focus on medical applications – such as carbon nanotubes, due to its unique properties which is a high strength, hydrophobicity, chemical inertness, high penetrating power, are ideal carriers for drug delivery, providing targeted, the preservation of the active components in the internal environment of an organism , prolongation of action [1]. In a short while a close contact of humans and other biological objects are expected and this problem is one of the most considered issues of the science nowadays. At the same time, the question of the toxicity of carbon nanotubes is the subject of ongoing debate [2]. There are number of papers which demonstrate the negative impact of these structures on living organisms [3,4,5]. More over, the issues of reproductive toxicity of carbon nanotubes are studied improperly. At the same time, the purpose of this study was to evaluate the reaction of the reproductive system on the carbon nanostructured material "Taunit (multi-walled carbon nanotubes), that was injected to laboratory mice. Nutritional path was selected as a way of injection as it is the most possible method of proceeding nanomaterials into a body [6].

OBJECTS AND METHODS

The object of research - a carbon nanomaterial "Taunit" (multiwalled carbon nanotubes), which is produced on an industrial scale LLC NanoTechCenter (Tambov). This material is one-dimensional, nanoscale, filamentous formation of polycrystalline graphite, a cylindrical shape with an internal channel in the form of loose powder black. Hydrophobic, chemically inert, purity - more than 98%. Granules of nanomaterial of micrometric dimensions have a structure of a tangled bundles of multiwalled tubes (Fig. 1), method of obtaining - chemical vapor deposition on a metal catalyst or CVD-process. "Taunit" is a promising material for the aerospace Industry, nuclear, space technology, medicine, pharmaceutics, production of supercomputers, video equipment, flat screen monitors, filters, multi-purpose. Addition of "Taunit" improves the quality of lubricants, structural composites and building materials. Granules "Taunita" can serve as carriers of catalysts or drugs, as well as adsorbents, cold electron emission sources [7].

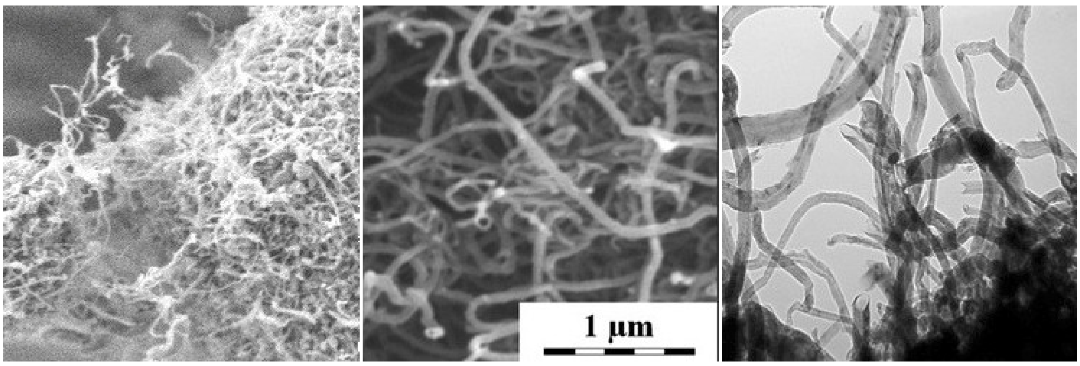


Fig. 1. Electron micrographs of nanostructured carbon material "Taunit". Photos courtesy LLC "NanoTechCenter", Tambov

The experiment consisted of two parts: the first assessed the physiological effect of the investigated nanomaterials in males, in the second - on female laboratory mice.

1. To study the effects of nanomaterials on male reproductive function formed by two coeval group of animals (experimental and control groups) consisting of 10

adult male non-linear laboratory mice each. Throughout the experiment, all animals were kept in standard conditions. Quarantined for 10 days.

Within 30 days of the experimental group was administered orally by UNM "Taunit" by replacing the drinking water in colloidal aqueous solution. The solution was prepared in distilled water using ultrasonic installation. The sample initial CNM prepared for TEM as follows. 25 mg of nanomaterial placed on a surface of liquid pitch (Epon 812), poured in a test tube, centrifuged 3 min at 6000 ×g and polymerized by a standard technique. Ultrathin cuts filled in Epon investigated samples methods TEM and diffractions of electrons by means of appearing through electronic microscopes JEM-1011 (JEOL) with digital camera GATAN ES500W and LEO 912AB (Carl Zeiss).

The average daily dose of the material for each male in the experimental group was 30 mg / kg. Assess the overall condition of the animals.

The control group consisted of mice injected with distilled water in similar quantities.

Upon expiration of the exposure to each male were sat down to 3 Virginy unexposed females. Noted the presence of sexual behavior. Replanting of females to male guinea was performed weekly for three weeks. Separated females were dissected after 15-17 days. Estimated number of pregnant females, females with living fetus, with a dead fetus, the number of living and dead fetuses per litter.

2. To assess the actions of nanomaterial on the reproductive function of females formed two coeval group of animals (experimental and control groups) consisting of 10 adult females, non-linear laboratory mice each. Throughout the experiment, all animals were kept in standard conditions. Quarantined for 10 days. Colloidal aqueous solution of nanomaterials for watering animals prepared as above. After several days of sharing content with the mature unexposed males, females were separated by individual cells and from that moment passed by watering test fluid. The experiment was completed after the end of the nursing offspring. Assessed the following indicators:% of female deaths (overall and for each day of the experiment),% mortality of young during the first three days of life;% not given birth

to females, the number of dead embryos in females, fertility, and general condition of the females.

At each stage, in addition to the experimental group, and contained a similarly studied control group of mice, which is used for drinking distilled water.

RESULTS AND DISCUSSION

1. Preliminary by us it has been spent characterization of structure of nanomaterial. On images structure of CNM (fig. 2A) - conglomerates of MWCNT is visible. Morphological features MWCNT are well visible in drawing 2B. The site with MWCNT, not containing graphitized carbon (fig. 2C), has been characterised by the method of electrons diffraction. As is shown in fig. 2D, MWCNT thanks to the ordered periodic packing of atoms of carbon form on electronogram rings, characteristic for polycrystalline samples.

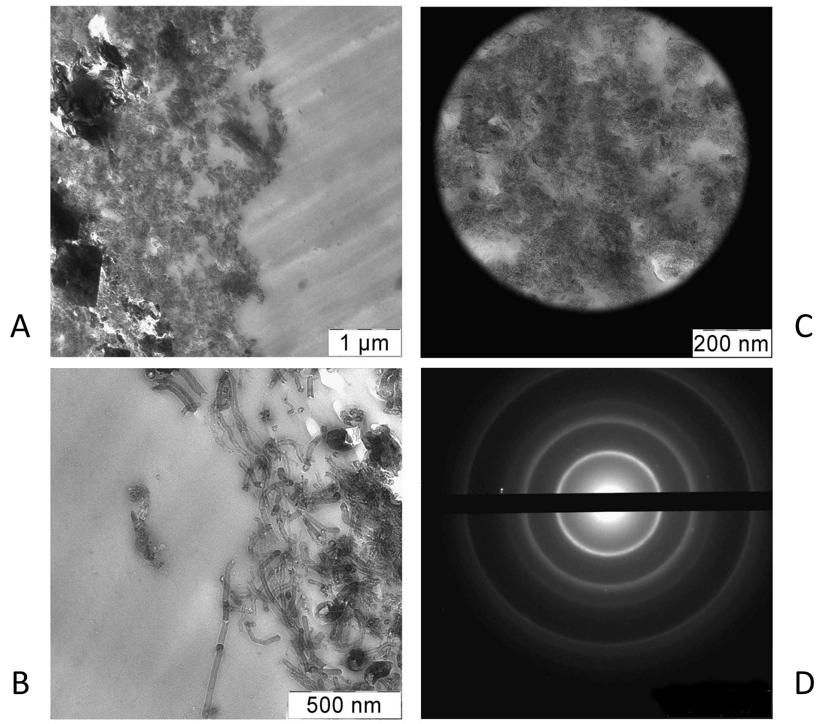
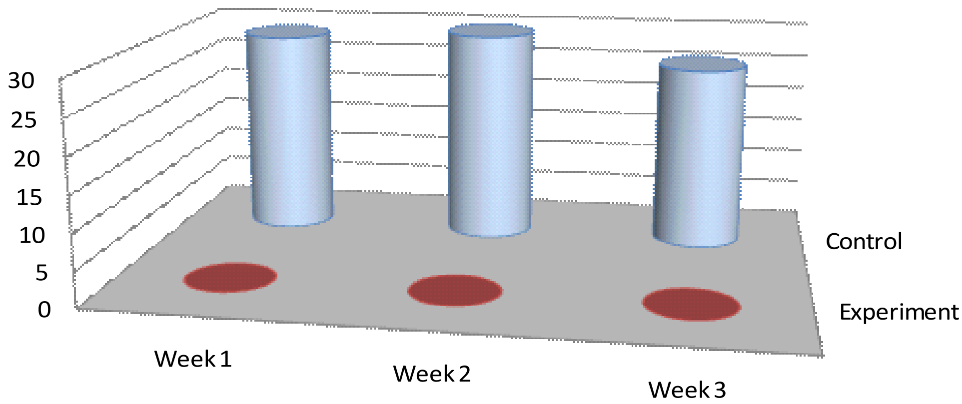


Fig. 2. The structural characteristic of nanomaterial. Explanatories in the text

2.According to the method of study to males from the experimental and control groups during the 3 weeks of sit down Virginy unexposed females of reproductive age. In both groups, there were the presence of normal sexual behavior. External lesions in the experimental group was noted. Follow-up for females revealed that the carbon nanomaterial, introduced orally in a dosage study, causes complete male sterility in laboratory mice (Fig. 3).



3.Fig. 3. The number of successfully inseminated females during the experiment

Study of histological sections of testes of experimental animals showed significant structural damage in comparison with the control group (Fig. 4). The result can indicate that, along with bodies such as the liver, spleen and lungs testes are target organs for the nanoparticles.

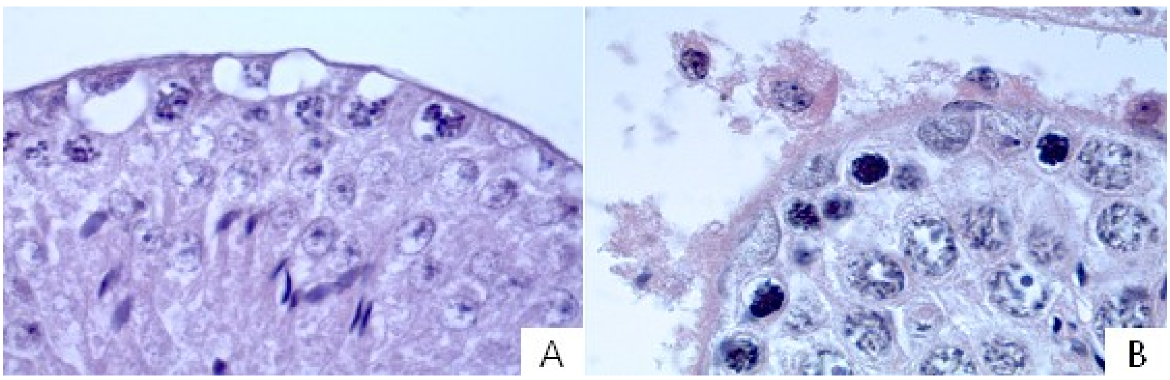


Fig. 4. Histological sections of testes of mice from the control (A) and experimental (B) groups. The right image shows disturbance seminiferous tubules, numerous necrotic cells. The

photos were made members of the Biological Faculty of Moscow State University. MV Lomonosov Moscow State University under the guidance of professor of cell biology and histology, Dr. G. Onishchenko

A possible mechanism of toxicity of carbon nanotubes is oxidative stress. Carbon nanotubes are cylindrical in shape. Presence in the tissue long enough and hard (Multilayer) of nanotubes causes a "failure" in the behavior of macrophages [8]. These cells are unable to swallow "such a large particle, and only emit toxic environment oxygen species (ROS) and hydrolytic enzymes, causing an inflammatory reaction [8]. Oxidative stress can cause infertility in males. Hyperproduction of reactive oxygen species leads to a decrease in cell viability in semen that leads to an inability to fertilize [9].
In the course of nanomaterial toxicity may cause chromosomal aberrations. Most of them occur in the chromosomes derived from the father [10]. Perhaps it is these violations occurred during the experiment, which ultimately led to reduced viability or sperm, or cause damage to spermatogenic tissue, which prevented the normal formation of germ cells. As a result, males of both experimental groups could lose the ability to fertilize.

Stress resulting from mechanical injury or poisoning of nanomaterials may be accompanied by increased levels of stress hormones - corticosteroids and catecholamines. Hormonal changes that accompany stress can cause pathological or adaptive changes at the level of the CNS, particularly in the hypothalamus, resulting in possible violation of the secretion of the hormone GnRH in it, it reduces the release of luteinizing hormone, acting in the testis are Leydig cells, which in response secrete the hormone testosterone. This may subsequently cause dysfunction of the reproductive system [11]. Thus, hormonal imbalance under the influence of nanomaterials could lead to suppression of reproductive function at the level of humoral regulation of spermatogenesis.

2. To study the effect of nanomaterials on female reproductive function, after the joint maintenance of a mature unexposed males and females during pregnancy

and nursing were treated with test fluid. Pathological abnormalities in the appearance and behavior of experimental females have been recorded, on the contrary, they are more heavily recruited body weight than females of the control group.
The positive trend was observed in the analysis of the studied indicators of reproductive activity. It was found that when exposed to the organism UNM "Town, administered orally in a dosage of the study is an increase in female fertility by 30% reduction in mortality of young animals by 46% and a decrease in the proportion of individuals not given birth by 17% (Fig. 5).

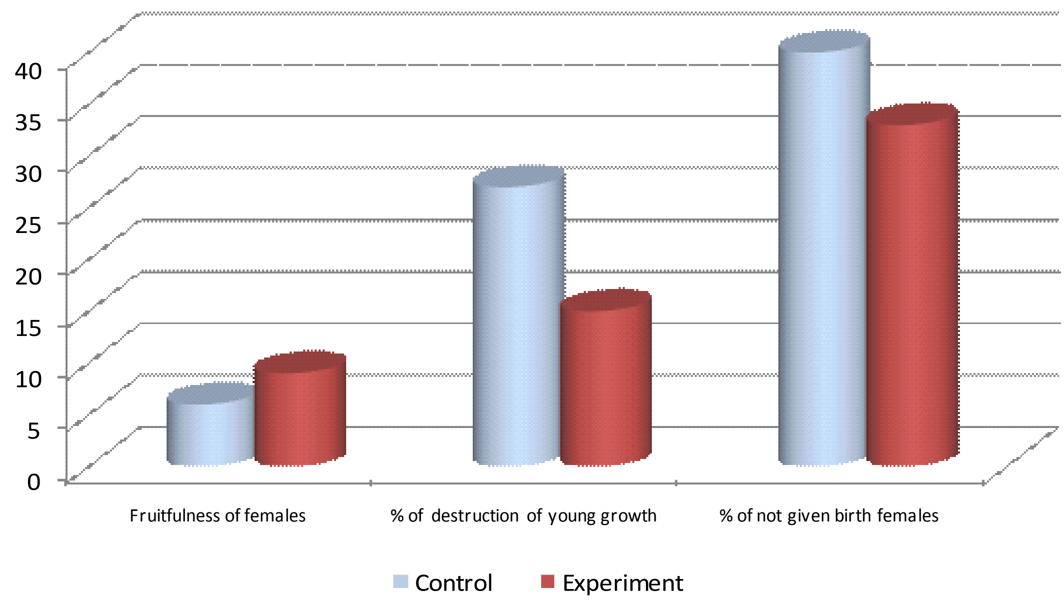


Fig. 5. Comparison srednegruppovyh indicators of female fertility, the proportion who died young, none gave birth to female mice in the control and experimental groups.

A similar effect can be explained as follows. Different reactions to the same effect in the first and second experiments, possibly connected with the peculiarities of physiology of male and female organisms, which are expressed in dissimilar norms of reaction, specific to each gender [12]. For example, the above-described possible hormonal imbalance in the male body can cause spermatoksichesky effect, while in the female body similar hormonal pattern may stimulate the activity of the reproductive system. Anyway, the mechanisms of observed changes we require deeper investigation.

CONCLUSIONS

Thus, study the effect of industrial carbon produced by the nanostructured material on the reproductive function of laboratory mice. Shown that oral administration of colloidal aqueous solution of carbon nanomaterial "Taunit" at a dosage of 30 mg / kg of body weight is a cause of infertility in male mice. At the opening of potentially pregnant females, none in the uterine horns, there were no signs of pregnancy, which constitutes a serious violation of the reproductive function of males under the influence of nanomaterials. At the same time, studied the dosage of nanomaterial stimulates increase fertility in females, leads to a reduction in mortality of young animals, as well as a decrease in the proportion of individuals not given birth.

The results can be taken into account when developing content standards of carbon nanomaterials in the environment, contact with animals and humans, as well as the creation based on multiwalled carbon nanotubes, next-generation drugs.

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