UDC 616.36+616.411]-091.8:[546.57+546.59]-022.513.2 https://doi.org/10.26641/2307-0404.2023.1.275855

O.M. Kaleinikova [1],
V.O. Kurovska [2 *],
I.V. Byelinska [2],
N.V. Kutsevol [2],
T.V. Blashkiv [1]

MORPHOLOGICAL CHANGES OF SPLEEN AND LIVER UNDER THE IMPACT OF DEXTRAN-POLYACRYLAMIDE POLYMERS AND THEIR EFFECTS AS CARRIERS OF SILVER AND GOLD NANOPARTICLES

Bogomoletz Institute of Physiology [1]
Bogomoletz str., 4, Kyiv, 01024, Ukraine
Taras Shevchenko National University of Kyiv [2]
Volodymyrska str., 64/13, Kyiv, 01601, Ukraine
Інститут фізіології ім. О.О. Богомольця [1]
вул. Богомольця, 4, Київ, 01024, Україна
Київський національний університет ім. Т. Шевченка [2]
вул. Володимирська, 64/13, Київ, 01601, Україна
[*]*e-mail: valentynakurovska@knu.ua*

Цитування: Медичні перспективи. 2023. Т. 28, № 1. С. 28-36
Cited: Medicni perspektivi. 2023;28(1):28-36

Key words: *dextran-polyacrylamide polymers, silver and gold nanoparticles, liver, spleen, toxicity*
Ключові слова: *декстран-поліакриламідні полімери, наночастинки срібла та золота, печінка, селезінка, токсичність*

Abstract. Morphological changes of liver and spleen under the impact of dextran-polyacrylamide polymers and their effects as carriers of silver and gold nanoparticles. Kaleinikova O.M., Kurovska V.O., Byelinska I.V., Kutsevol N.V., **Blashkiv T.V.** *The possibility of usage of polymer nanocomposites is being intensively studied today with a purpose of their application in medicine, espessialy in oncology. At the experimental stage it is important to determine the mechanisms of the influence of such compounds on the body and their own possible undesirable effects. Aim – to study the effect of the treatment with maximal doses of the dextran-polyacrylamide polymers and their effect as carriers of silver and gold nanoparticles on the spleen and liver. Histological examination of micropreparations of the spleen and liver by the standard method with hematoxylin-eosin staining was made. As a result of the treatment with nonionic (D-g-PAA) and anionic (D-g-PAA (PE)) polymer matrices, changes which occurred in the spleen indicate an increase in the production of all blood cells. These phenomena were absent when silver and gold nanoparticles were included in the matrix. In the liver, treatment with D-g-PAA and D-g-PAA (PE) caused a disorder of hepatic circulation, focal infiltration by inflammatory cells and death of hepatocytes by necrosis. The addition of nanoparticles triggered other mechanisms of alteration, which manifested themselves in excessive accumulation of glycogen, fatty infiltration of hepatocytes, and cell death, mainly through apoptosis. However, along with this, signs of an incomplete regenerative response of the liver were revealed. Morphological changes caused by the treatment with maximal doses of the tested substances indicate their toxic effect, especially on the liver. Further researches are needed to establish the optimal doses and the frequency of their administration, which can be used for therapeutic purposes, including the interaction of studied polymers with blood cells.*

Реферат. Морфологічні зміни печінки та селезінки під впливом декстран-поліакриламідних полімерів та їх ефект як носіїв наночастинок срібла та золота. Калейникова О.М., Куровська В.О., Бєлінська І.В., Куцевол Н.В., Блашків Т.В. *Можливість використання полімерних нанокомпозитів з метою їх практичного застосування в медицині, особливо в онкології, сьогодні інтенсивно вивчається. На етапі експерименту є важливим встановити механізми впливу таких сполук на організм та їхні можливі небажані ефекти. Мета – дослідити ефекти введення максимальних доз декстран-поліакриламідних полімерів та їх ефекти, як носіїв наночастинок срібла та золота, на селезінку та печінку. Проведено гістологічне дослідження мікропрепаратів селезінки та печінки, виготовлених стандартним методом із фарбуванням гематоксил-еозином. У результаті введення неіонних (D-g-PAA) та іонних (D-g-PAA (PE)) полімерних матриць у селезінці зафіксовано зміни, які вказують на збільшення продукування всіх типів клітин крові. Ці явища відсутні, коли в матриці було включено наночастинки срібла та золота. У печінці введення D-g-PAA та D-g-PAA (PE) зумовило погіршення печінкового кровотоку, фокальну інфільтрацію нейтрофілами та загибель гепатоцитів шляхом некрозу. Додавання наночастинок зумовило інші механізми пошкодження, які проявились у надлишковому акумулюванні глікогену,*

жировій інфільтрації гепатоцитів та їх загибелі, переважно шляхом апоптозу. Однак поруч із цим наявні ознаки неповної регенераторної відповіді печінки. Морфологічні зміни, які викликані введенням максимальних доз досліджуваних речовин, вказують на їхній токсичний ефект, особливо на печінку. З метою встановлення оптимальних доз та частоти їх введення, які можуть бути використані з терапевтичною метою, необхідні подальші дослідження, зокрема ті, що включають взаємодію досліджуваних полімерів з клітинами крові.

The ideal therapeutic agent in oncology is one that targetingly destroys cancer cells and has no effect on surrounding healthy tissue. In the development of such agents, among other studies, works are underway to create drugs based on macromolecules of soluble biopolymers [1, 2]. Polymer nanocomposites are being recognized as promising agents for the use in medicine due to their unique properties and multifunctionality of their matrix. The polymers are non-toxic and biocompatible. They are supposed to be used as nanocontainers for the delivery of anticancer medicine, which would specifically destroy tumor cells.

Nanocarriers on the base of branched dextran-polyacrylamide polymers (D-*g*-PAA) were synthesized in our laboratory, described, and tested. It has been shown that these nanocarriers are actively captured by phagocytic cells being not cytotoxic [3].

Among substances that can be used in oncology there are metal nanoparticles (NPs) as well, in particular gold and silver [4, 5]. However, taking into account that nanoparticles have a tendency to aggregate due to their large surface energy, different stabilizing agents are needed to prevent this phenomenon. Branched polymer macromolecules are among them.

The previously mentioned nanocarriers, synthesized in our laboratory were used as nanocontainers for silver and gold nanoparticles. Their effects on cultures of cancer cells had been tested in our previous studies. It had been shown that treatment of K-562 (human chronic myelogenous leukemia cell line), and U-937 (human histiocytic lymphoma cell line) with anionic form of polymer nanoparticles loaded with nanosilver caused the cytotoxic effect on both cell lines [3]. As well as, treatment of MT-4 cells (human T cell leukemia) with polymer loaded with gold nanoparticles had initiated dose-dependent production of singlet oxygen in toxic concentration upon laser irradiation [6].

The effects of synthesized polymers as carriers of nanoparticles on entire organism is needed to be studied with an aim of future perspectives of their usage in oncology.

Particularly, the possible negative effect on tissues and organs is important to be established on the stage of experiment. It will help to find a specific practical application, to determine optimal internal structure and correct dosage of polymers, to establish the best mode of a therapeutic agent release from incapsulated molecule. Regarding this, the researchers with the usage of animals are expedient.

It is known that organs accumulate NPs not at the same amount and exhibit different degree of structural damages. The liver is on the first line of defense against toxic impact on the organism. There are data that gold NPs the most intensively accumulate in the organs of reticuloendothelial system: macrophages of the liver (90%) and spleen (10%) [7]. The number of studies has been reported that nanoparticles of gold and silver provoke effects of apoptosis through mechanisms of disturbance of mitochondrial membrane potential and generation of reactive oxygen species [8, 9, 10, 11].

In our research, it was decided to establish whether synthesized polymers can be toxic in case of treatment in maximal doses? Will a damaging effect on organs be detected during the prolonged treatment?

The aim of our research is to estimate structural changes in the liver and spleen under the fivefold intravenous administration of D-*g*-PAA polymer matrices and nanoparticles of gold and silver in these matrices (D-*g*-PAA/AuNPs and D-*g*-PAA/AgNPs) in male Albina mice.

MATERIALS AND METHODS OF RESEARCH

The branched copolymers were used as nanocarriers. The choice of polymers was made among a number of samples previously synthesized during our researches. Branched copolymers used as nanocarriers were obtained by grafting polyacrylamide chains on dextran (M_w=7×10^4, g×mol^{-1}) backbone by ceric-ion-reduce initiation method. This redox process initiates free radical sites exclusively on the polysaccharide backbone, thereby preventing the formation of homopolymer polyacrylamide [12, 13].

Nonionic form of star-like polymer matrices D-*g*-PAA consists of a dextran backbone and grafted polyacrylamide chains. Anionic forms of the matrices (dextran-polyacrylamide polyelectrolyte – (D-PAA (PE)) were obtained by saponification of D-*g*-PAA copolymer by alkaline hydrolysis using NaOH which resultied in creation of branched polyelectrolyte. Hence, D-PAA (PE) also consist of a dextran backbone and grafted partially hydrolyzed polyacrylamide chains. An alkaline hydrolysis changes part of the amide groups to hydroxyl groups, which determines the negative charge of the macromolecule. The degree of saponification of carbamide groups to

carboxylate groups was determined by potentiometric titration, being equal 43% [2]. The hydrodynamic sizes of both types of macromolecules are 70-80 nm.

The silver nanoparticles (Ag NPs) were synthesized by the chemical reduction of Ag precursor $AgNO_3$. Sodium borohydride and hydrazine hydrate were used for the chemical reduction of silver nitrate dissolved in polymer solutions. The reddish-brown color of solution indicated the formation of Ag NPs [3, 14]. Silver nanoparticles are characterized by a spherical shape. The size of Ag NPs synthesized in D-*g*-PAA is 8-15 nm.

The gold nanoparticles (Au NPs) were synthesized by the reduction of Au precursor $HAuCl_4$ dissolved in polymer aqueous solution. For chemical reduction NaBH4 was used. The ruby-red color of final solution indicated the formation of Au NPs [6, 15]. Gold nanoparticles are characterized by a spherical shape. The size of Au NPs loaded into D-*g*-PAA is 2-5 nm.

The experiments were carried out in compliance with the Law of Ukraine "On the protection of animals against cruelty" (from 21.02.2006), the principles of the "International European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), and the conclusion of the biomedical ethics committee of Bogomoletz Institute of Physiology (protocol No. 5/21 from 23.12.2021). The objective status of the animals was assessed before and during the experiment: appearance, general motor activity, need for food and water. The body weight was measured twice per week. Experiments were carried out using 25 males of white laboratory Albino mice. Age of animals is 10 weeks, weight is 25-30 g. The animals were divided into the following groups: I – control group to which saline was administered (n=5); II – D-*g*-PAA was administered (n=5); III – D-*g*-PAA (PE) was administered (n=5); IV – D-*g*-PAA/AuNPs was administered (n=5); V – D-*g*-PAA/AgNPs was administered (n=5). Polymer matrices, gold and silver nanoparticles included in polymer matrices were diluted with 0.3 ml of saline and injected intravenously (into the tail vein) once a day. Saline was administered to control mice in the same amount and frequency. The following doses were used: for D-*g*-PAA and D-*g*-PAA (PE) – 10.00 mg/kg, for D-*g*-PAA/AuNPs – 9.78 mg/kg, and for D-*g*-PAA/AgNPs – 5.35 mg/kg. The used doses could be converted into their equivalents for a human. The dose of 10 mg/kg of body weight in mice is equivalent to a human dose of 0,81 mg/kg of body weight, what is equivalent to approximately 50 mg for a 60 kg person. Following this rule, 10.00 mg/kg of D-*g*-PAA (and D-*g*-PAA (PE)) in mice is equivalent to a human dose of 0.81 mg/kg of body weight, this corresponds to approximately 50 mg (48.6 mg) for a 60 kg person (or 56.7 mg for a 70 kg person). For D-*g*-PAA/AuNPs 9.78 mg/kg the doses are 47.53 mg/60 kg and 55.45 mg/70 kg respectively; for D-*g*-PAA/AgNPs 5.35 mg/kg: 21.14 mg/60 kg and 30.33 mg/70 kg, respectively. On the third day after the last (fifth) administration, the animals were withdrawn from the experiment by cutting the spinal cord under ether anesthesia in compliance with the rules of euthanasia.

The right lobe of the liver and spleen were removed from the animals immediately after sacrifice. The organs were fixed 4 times in Bouin's solution for 7 days, after then embedded in paraffin, and finally slices 5-6 μm thick were made. Slides were stained with hematoxylin-eosin according to the standard technique and analyzed at the light-optical level (microscope Olympus BX-41, camera Olympus C-5050 Zoom, Olympus Europe GmbH, Japan).

RESULTS AND DISCUSSION

Synthetic biopolymers are expedient in the use in oncology as drug delivery agents. Comparatively to natural biopolymers obtained from animal-, plant-, and microbial sources they are not immunogenic. Synthetic biopolymers are characterized by stability, biocompatibility, and biodegradability. They protect deliverable agent in circulation and purposefully destroy cancer cells [16]. Although, it is important to know about their possible toxic action on organs. Au and AgNPs while entering blood circulation may result in unwanted negative effects as well.

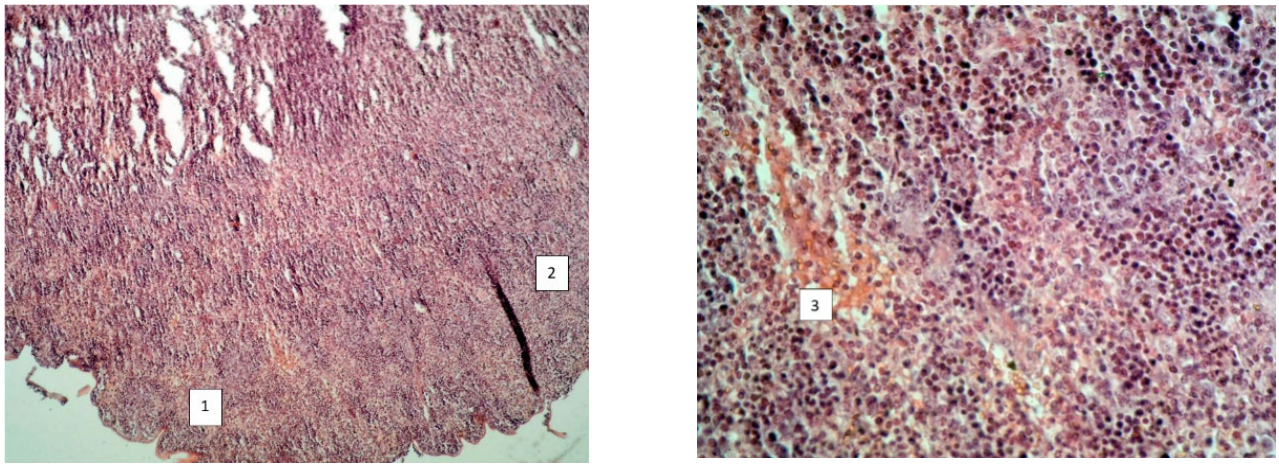
Histological examination of spleen

In the control group, the structure of spleen was typical for this type of animals without changes. The red and white pulp with centers of erythropoiesis and leukopoiesis, a large number of lymphocytes, occasionally megakaryocytes, were observed.

The spleen of animals of the II group (D-*g*-PAA) were characterized by a relative hyperplasia of the red pulp, expansion of sinusoids, and an increase in number of lymphocytes and megakaryocytes (Fig. 1a, 1b). This may indicate the stimulation of erythropoiesis, thrombocytopoiesis, and lymphopoiesis, this, in turn, may be signs of increased hemolysis, blood clotting, or inflammation.

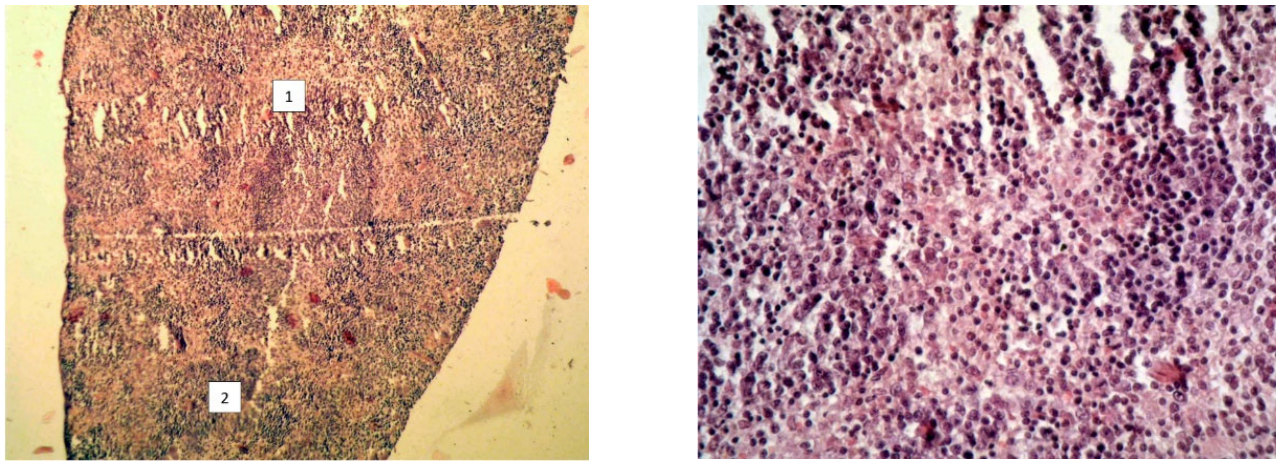
An even more pronounced hyperplasia of the red pulp was observed in animals of the group III (D-*g*-PAA (PE)) (Fig. 2a, 2b).

The ratio of white and red pulp in groups IV (D-*g*-PAA/AuNPs) and V (D-*g*-PAA/AgNPs) had no difference with the control group.



a) b)

Fig. 1. Spleen of mice of group II (D-*g*-PAA): a) – red (1) and white (2) pulp (×100); b – expansion of sinusoids (3) (× 400)



a) b)

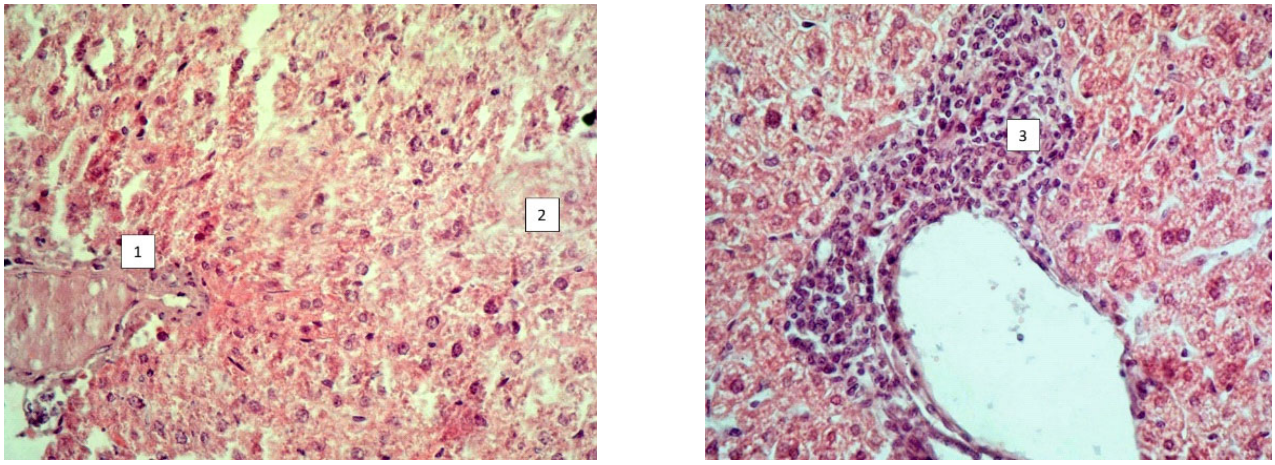
Fig. 2. Spleen of mice of group III (D-*g*-PAA (PE)): a - red (1) and white (2) pulp (×100); b – (×400)

Therefore, the adminiatration of both D-*g*-PAA and D-*g*-PAA (PE) may cause an increase in blood clotting, hemolysis, it initiated inflammation, which resulted in increased erythro-, thrombocyto- and lymphopoiesis in the spleen. The introduction of metal nanoparticles into the D-*g*-PAA matrices neutralized the changes caused by D-*g*-PAA separately.

Histological examination of the liver

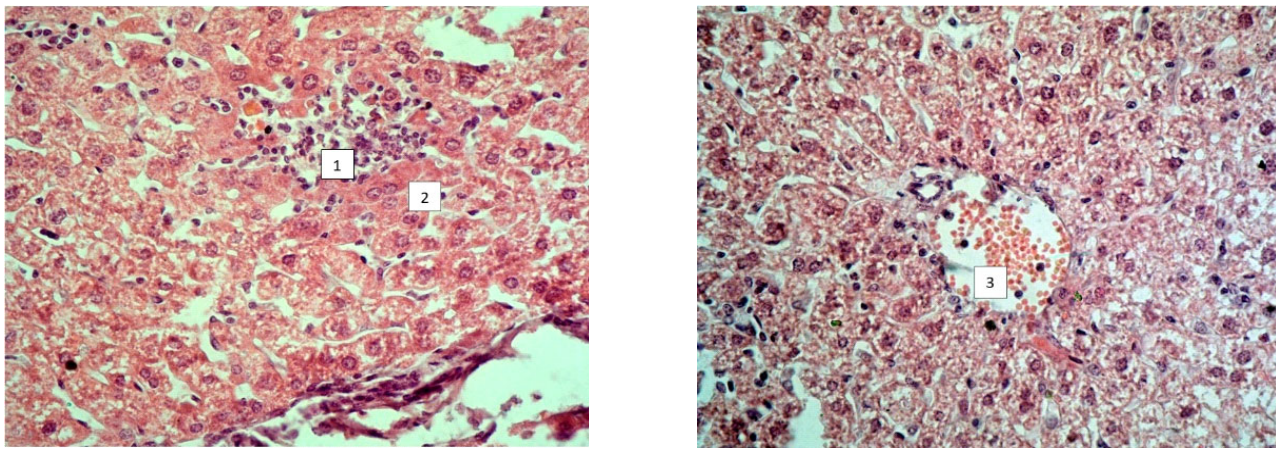
A structure of mice liver of the control group was typical for this species and had no features of pathological processes. In contrast, pronounced blood stasis in central veins and neutrophilic infiltration around them were observed in the livers of animals of the II group (D-*g*-PAA) (Fig. 3a, 3b). These sings demonstrate inflammatory processes and portal hypertension. Collagen deposits around the central veins, necrosis in the parenchyma of the centrilobular zone, and an increase of eosinophilia of the hepatocytes' cytoplasm were noted in this group as well. All these changes point out inflammatory processes in the liver and the death of hepatocytes in the centrilobular zone. They are also specific for ischemia and the action of certain drugs and toxins [17].

In group III (D-*g*-PAA (PE)) focal neutrophilic infiltration, increased eosinophilia of cytoplasm, focal necrosis, occasionally stasis in the central veins were observed (Fig. 4a, 4b). Hyperchromic small nuclei and acidophilic apoptotic bodies were noted as well, being signs of cell apoptosis. These changes are similar to those in the previous group and indicate toxic damage to the liver and death of its cells.



a) b)

Fig. 3. Liver of mice of group II (D-*g*-PAA): a) - collagen deposits around the central vein (1), necrosis (2); b) - neutrophilic infiltration around the central vein (3) (× 400)

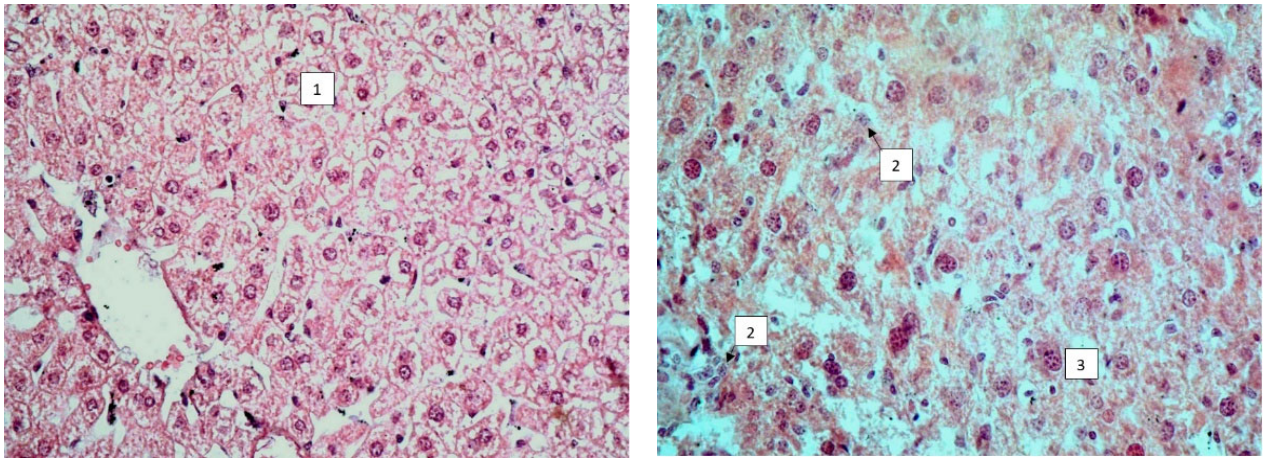


a) b)

Fig. 4. Liver of mice of group III (D-*g*-PAA (PE)): a) - focal neutrophilic infiltration (1), eosinophils alteration (2); b) – blood stasis (3) (× 400)

In group IV (D-*g*-PAA/AuNPs) the alteration of cells in the form of excessive accumulation of glycogen and small-drop fatty inclusions were observed (Fig. 5a, b). There were inclusions in Kupffer's cells which could be metal particles. In some micropreparations karyomegaly was noted; this may be evidence of a toxic effect on the liver and its abnormal regenerative response (when an increase in ploidy and/or karyokinesis is not accompanied by cytokinesis). Also, a focal necrosis, diffuse infiltration with macrophages, signs of apoptosis in form of pyknotic nuclei and eosinophilic alteration of hepatocytes (bright pink cells with pyknotic nuclei and uneven wrinkled edges) were observed. The described changes indicate toxic damage to the liver and cell death mainly by apoptosis, its perverted regeneration.

In group V (D-*g*-PAA/AgNPs) (Fig. 6) common signs of apoptosis in the form of eosinophilic alteration of hepatocytes, focal infiltration with neutrophils and necrosis, blood stasis in the central veins, alteration in the form of excessive accumulation of glycogen and small-drop fatty degeneration, hepatocellular hypertrophy, accompanied by compression of the sinusoids have been observed. The latest one is a sign of the liver's compensatory responses to damage (hypertrophic regeneration). That is, the changes are somewhat similar to those in group IV – toxic damage to the organ and cell death mainly by apoptosis, regenerative response of liver.



a) **b)**

Fig. 5. Liver of mice of group IV (D-*g*-PAA/AuNPs): a) - excessive accumulation of glycogen and small-drop fatty inclusions (1); b) – inclusions in Kupffer's cells (2), karyomegaly (3) (× 400)

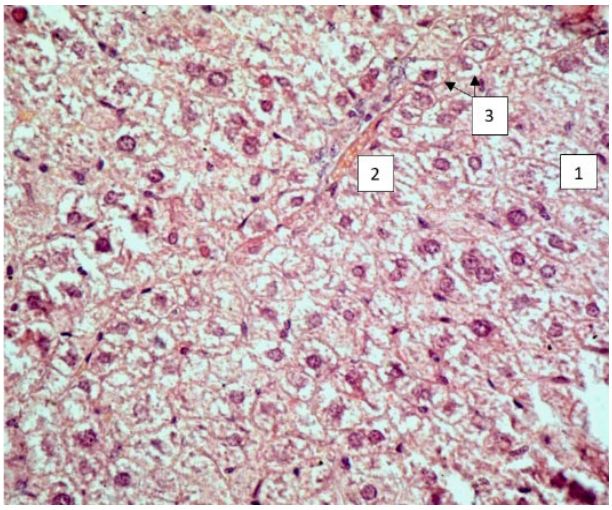


Fig. 6. Liver of mice of group V (D-*g*-PAA/AgNPs): necrosis (1), blood stasis (2), excessive accumulation of glycogen, small-drop fatty degeneration (3) (×400)

The morphological changes of mice liver that occurred as a result of the influence of the tested substances are summarized in Table. As seen from the Table the liver has been undergoing influences that initiate its toxic damage.

Studying the effects of NPs on cancer cells demonstrates their promising potential in oncology due to the provoking of cellular damage. NPs elicit changes in cell morphology, reduction in ATP levels, production of reactive oxygen species, DNA damage. From our data it is seen that such harmful effect is observed in healthy tissues when a limit of adaptive mechanisms of organs is exceeded.

As it was mentioned, there are data on the most intense accumulation of gold NPs in the organs of reticuloendothelial system [7]. Meanwhile, under the introduction of silver NPs, histological examination of spleen did not reveal changes compared with control, no changes were found in the brain, testicles and lungs as well. At the same time, these researchers assessed the effect of silver NPs on lung cancer cells and the induction of apoptosis in these cells was observed [18]. According to others, gold NPs predominantly accumulated in the liver, while silver NPs – in the heart, lungs, and kidneys [19]. Kupffer cells play a crucial role in accumulation of different type of NPs [7, 20].

Contrary, there were histological studies of mice spleen and liver, which did not establish any changes relative to control on 28 day after intravenous injection of gold and silver NPs twice a week [19]. All these contradictions could be explained by the

different nature of nanoparticles, different methods of their introduction, and influence on cells. The impact of internal factors of body and the state of its metabolism in general could be assumed.

According to our data, an increase in erythro-, thrombocyto- and lymphopoiesis was observed in spleen under the treatment with both D-*g*-PAA and D-*g*-PAA (PE). Unexpectedly, the spleen tissue has no difference from control under the treatment with D-*g*-PAA/AuNPs and D-*g*-PAA/AgNPs. In our opinion, the obtained data reflect the reactivity of the spleen and it may depend on the matrix charge and the size of NPs. It could also reflect changes that occur in the body as a whole in response to the introduction of such copolymers.

Structural changes of the liver under the impact of D-*g*-PAA, D-*g*-PAA (PE), D-*g*-PAA/AuNPs, D-*g*-PAA/AgNPs

Structural changes	Control	D-*g*-PAA	D-*g*-PAA (PE)	D-*g*-PAA/AuNPs	D-*g*-PAA/AgNPs
Hepatocellular hypertrophy	-	-	-	-	+
Excessive glycogen accumulation	-	-	-	++	+
Eosinophilic alteration of hepatocytes cytoplasm	-	+/-	+	++	+
Blood stasis	-	++	+		+
Inclusions in Kupffer cells	-	-	-	++	-
Diffuse neutrophilic infiltration	-	-	-	+	-
Focal neutrophilic infiltration	-	+++	++	-	+
Collagen deposits	-	+	-	-	-
Small-drop fatty dystrophy	-	-	-	+	+
Karyomegaly	-	-	-	+	-
Apoptosis	-	-	+	+	+
Necrosis	-	+	+	+	+

Notes: degree of phenomenon: "-" – not observed, "+" – solitary or mild, "++" – moderately expressed, "+++" – pronounced.

The morphological changes in liver tissue indicate the damaging effect of maximal doses of D-*g*-PAA, D-*g*-PAA (PE), D-*g*-PAA/AuNPs, and D-*g*-PAA/AgNPs. Death of hepatocytes, mainly by necrosis, and, to a lesser degree of apoptosis, was noted. However, signs of incomplete regenerative reactions of the organ were was noted. There are data that damaging effect of NPs on liver and spleen depends on their size. An injection of gold NPs different in size initiate more significant changes in the liver in case of small sized NPs (5 nm), while in the spleen essential pathological alterations of architectonics were observed as a result of the action of medium (20 nm) and large (50 nm) sized gold NPs [21]. Although, our NPs are characterized by smaller size they have revealed toxic effect.

To sum up, the picture of structural changes in liver we obtained is quite mosaic. The signs of apoptosis and necrosis, but, at the same time, of regeneration were observed on the histological specimens. If apoptosis and necrosis indicate the damaging effect of NPs, the signs of regeneration raise questions about the time of their appearance. It should be noted that regeneration is the initial response of hepatocytes, which develops at the first stages of damage and indicates an attempt of cells to fight the ongoing processes. In this case, it may point out the presence of mechanisms that operated in this cell and allowed it to avoid death. Administration of both D-*g*-PAA and D-*g*-PAA (PE) predominantly causes violations of the hepatic circulation, focal infiltration by inflammatory cells and death of hepatocytes, in the main by necrosis, principally in the centrilobular zones. Apparently, the addition of metals triggers other mechanisms which responsible for cells damage and death. An excessive accumulation of glycogen and fatty degeneration of hepatocytes, cell death predominantly by apoptosis, and regenerative response of the organ, albeit inadequate take place. Besides, gold NPs were actively

accumulated by liver's macrophages, while silver NPs were not. This can be explained by more strong biological effect of the latter and the death of cells that have accumulated any significant amounts of it.

Hence, our results demonstrate that maximal doses of studied substances cause harmful effect on liver and spleen. The optimal dosages, which could be used with therapeutic aim as well as frequency of their administration are needed to be studied. For deeper understanding of mechanisms realized in organism under the influence of tested polymers, further investigations, including *in vitro*, are required. It is reasonable to study the interaction of D-*g*-PAA matrices with blood proteins and cells, first of all, with erythrocytes and platelets.

The obtained results demonstrate that tested substances are characterized by toxic effect not only on cancer cells, as it was shown in our previous researches, but are quite devastating in maximal doses. Regarding this, in future the ways and modes of their application are recommended to be studied on cancer models in animals.

CONCLUSIONS

1. Under the administration of both D-g-PAA and D-g-PAA (PE) an increase in erythro-, thrombocyto- and lymphopoiesis was observed in the spleen; under the D-g-PAA/AuNPs and D-g-PAA/AgNPs administration the spleen tissue did not been differ from the control.

2. The data we received indicate the damaging effect of D-g-PAA, D-g-PAA (PE) and D-g-PAA/AuNPs, D-g-PAA/AgNPs on the liver: death of hepatocytes was observed mainly by necrosis and, to a lesser extent, apoptosis, however, at the same time signs of an incomplete regenerative reaction of the liver took place.

Contributors:

Kaleinikova O.M. – investigation, methodology, project administration, resources, writing – original draft, writing – review&editing;

Kurovska V.O. – conceptualization, data curation, funding acquisition, investigation, project administration, visualization, writing – original draft, writing – review&editing;

Byelinska I.V. – formal analysis, investigation, project administration, resources, writing – original draft, writing – review&editing;

Kutsevol N.V. – conceptualization, data curation, writing – original draft, writing – review&editing;

Blashkiv T.V. – conceptualization, data curation, methodology, supervision, validation, writing – original draft, writing – review&editing.

Funding. This research received no external funding.

Conflict of interests. The authors declare no conflict of interest.

REFERENCES

1. Wang H, Rempel GL. Introduction of polymer nanoparticles for drug delivery applications. J Nanotechnol Nanomed Nanobiotechnol. 2015;2:008.
doi: https://doi.org/10.24966/NTMB-2044/100008

2. Kutsevol N, Bezuglyi M, Bezugla T, et al. Star-like dextran-graft-(polyacrylamide-co-polyacrylic acid) copolymers. Macromolecular Symposia. 2014;335(1):12-6. doi: https://doi.org/10.1002/masy.201200115

3. Telegeev G, Kutsevol N, Chumachenko V, et al. Dextran-graft-polyacrylamide as matrices for creation of anticancer nanocomposite. International Journal of Polymer Science. 2017;2017:ID4929857.
doi: https://doi.org/10.1155/2017/4929857

4. Chugh H, Sood D, Chandra I, et al. Role of gold and silver nanoparticles in cancer nano-medicine. Artificial Cells, Nanomedicine and Biotechnology. 2018;46(1):1210-20. doi: https://doi:10.1080/21691401.2018.1449118

5. Sehgai S, Kumar J. Nishtha Involvement of gold and silver nanoparticles in lung cancer nanomedicines: a review. Materials Today: Proceeding. 2022;62(12):6468-76. doi: https://doi.org/10.1016/j.matpr.2022.04.199

6. Kutsevol N, Naumenko A, Harahuts Yu, et al. New hybrid composites for photodynamic therapy: synthesis, characterization and biological study. Applied Nanoscience. 2019;9:881-8.
doi: https://doi.org/10.1007/s13204-018-0768-y

7. Sadauskas E, Wallin H, Stoltenberg M, et al. Kupffer cells are central in the removal of nanoparticles from the organism. Particle and fibre toxicology. 2007;4:10. doi: https://doi.org/10.1186/1743-8977-4-10

8. Zhao MX, Cai ZC, Zhu BJ, et al. The apoptosis effect on liver cancer cells of gold nanoparticles modified with lithocholic acid. Nanoscale Research Letters. 2018;13:304. doi: https://doi.org/10.1186/s11671-018-2653-8

9. Yuan YG, Zhang S, Ji-Yoon, Hwang JY, et al. Silver nanoparticles potentiates cytotoxicity and apoptotic potential of camptothecinin human cervical cancer cells. Oxidative Medicine and Cellular Longevity. 2018 Dec 12;2018:6121328.
doi: https://doi.org/10.1155/2018/6121328

10. Yao Y, Zang Y, Qu J, et al. The toxicity of metallic nanoparticles on liver: the subcellular damages, mechanisms, and outcomes. International Journal of Nanomedicine. 2019;14:8787-804.
doi: https://doi.org/10.2147/IJN.S212907

11. Huang Q, Zhang J, Zhang Y, et al. Adaptive changes induced by noble-metal nanostructures in vitro and in vivo. Theranostics. 2020;10(13):5649-70. doi: https://doi.org/0.7150/thno.42569

12. Kutsevol N, Bezugla T, Bezuglyi M, et al. Branched dextran-graft-polyacrylamide copolymers as perspective materials for nanotechnology. Macromolecular Symposia. 2012;317-318(1):82-90. doi: https://doi.org/10.1002/masy.201100087

13. Bezuglyi M, Kutsevol N, Rawiso M, et al. Water-soluble branched copolymers dextran-polyacrylamide and their anionic derivates as matrices for metal nanoparticles in-situ synthesis. Chemik. 2012;8(66):865-7.

14. Chumachenko V, Kutsevol N, Rawiso M, et al. In situ formation of silver nanoparticles in linear and branched polyelectrolyte matrices using various reducing agents. Nanoscale Research Letters. 2014;9:164. doi: https://doi.org/10.1186/1556-276X-9-164

15. Chumachenko V, Naumenko A, Yeshchenko O, et al. Synthesis, morphology, and optical properties of Au/CdS hybrid nanocomposites stabilized by branched polymer matrices. Journal of Nanomaterials. 2016;2016:ID1439437. doi: https://doi.org/10.1155/2016/1439437

16. Gagliardi A, Giuliano E, Venkateswararao E, et al. Biodegradable polymeric nanoparticles for drug delivery to solid tumors. Front Pharmacol. 2021 Feb 3;12:601626. doi: https://doi.org/10.3389/fphar.2021.601626

17. Krishna M. Patterns of necrosis in liver disease. Clinical Liver Disease. 2017;10(2):53-6. doi: https://doi.org/10.1002/cld.653

18. Kanipandian N, Li D, Kannan S. Induction of intrinsic apoptotic signaling pathway in A549 lung cancer cells using silver nanoparticles from Gossypiumhirsutum and evaluation of in vivo toxicity. Biotechnology reports. 2019;23:1-11. doi: https://doi.org/10.1016/j.btre.2019.e00339

19. Yang L, Kuang H, Zhang W, et al. Comparisons of the biodistribution and toxicological examinations after repeated intravenous administration of silver and gold nanoparticles in mice. Scientific reports. 2017;7:3303. doi: https://doi.org/10.1038/s41598-017-03015-1

20. Colino CI, Lanao JM, Gutierrez-Millan C. Targeting of hepatic macrophages by therapeutic nanoparticles. Frontiers in Immunology. 2020;11:1-17. doi: https://doi.org/10.3389/fimmu.2020.00218

21. Ibrahim KE, Al-Mutary MG, Bakhietand AO, et al. Histopathology of the liver, kidney, and spleen of mice exposed to gold nanoparticles. Molecules. 2018;23:1848. doi: https://doi.org/10.3390/molecules23081848

Стаття надійшла до редакції
21.07.2022