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Review

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CELL STRESS RESPONSE TO COMBINED IONIZING AND NON-IONIZING RADIATION AND MAGNETIC FIELDS: A REVIEW BASED ON HUMAN BUCCAL EPITHELIUM CELLS

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Background: The impact of low-dosed ionizing radiation (IR) itself and in combination with the other damaging physical factors such as extremely high frequency (EHF) microwaves and magnetic fields (MF) is currently the object of numerous researches. Results of those investigations, however, still didn't lead to certain unequivocal conclusions.

Objectives: This paper presents the review and analysis of previously conducted experimental series in comparison with adjacent-aimed works to make a step forward in understanding the role of low doses of ionizing, non-ionizing radiation and magnetic field in the development of cellular effects.

Results: Ultra-low doses of both IR itself and with EHF and MF have triggering effects which included variability of IR effect modification; the significance of even non-ionizing radiation effects was shown on the example of ultra-wideband microwaves irradiation. Combined effects from gamma-IR with EHF microwaves and MF on chromatin led to decrease of heterochromatin granules quantity (HGQ) but affected the cell membrane permeability (CMP) rate greater than IR itself. Mitochondrial activity inhibition and cytoplasm Ca^{2+} decrease was detected under exposure to both IR and EHF-microwaves and their combination; MF slightly increased mitochondrial membrane potential and showed no significant changes in Ca^{2+} migration to the nucleus when applied together with IR. Exposure to neutron radiation revealed the maximum of chromatin condensation rate and cell membrane permeability up to the dose 36.5 mSv. Further dose increase returned the state of chromatin and cell membrane to control levels.

Conclusions: Vague effect of ultra-low doses of IR with modifying abilities of EHF-microwaves and MF was shown on the example of HGQ. Effects of high doses of gamma-radiation were also modified by both EHF-microwaves and MF at indexes of HGQ (decrease), CMP (increase), mitochondrial activity (decrease) and Ca^{2+} nucleus/cytoplasm redistribution. Irradiation with fast neutrons in low-to-medium dose range led to the development of cell stress signs (HGQ/CMP increase) which were smoothed under the dose increase.

KEY WORDS: X-rays, gamma-radiation, neutron radiation, EHF-microwaves, static magnetic field, chromatin, membrane permeability, mitochondria activity

The problem the impact of physical factors on the human organism is one of the main tasks in both medicine and ecology because of continuous exposure to variable physical factors [1]. The uncertainty of the data on the biological effects of small doses of ionizing, non-ionizing radiation, and low-intensity magnetic fields requires detailed study. The reasons

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for conducting the further investigations are the presence of electromagnetic and radioactive environmental pollution; the application of electromagnetic, corpuscular radiation and magnetic fields in medicine according to existing and under-development methods and procedures; additionally, it is actual for investigations of possible responses of human body in possibly stressing conditions (spaceflight, submarine etc.).

Together with mentioned objectives the modifying effect of non-ionizing radiation (microwaves and low-frequency electromagnetic fields) in combination with ionizing radiation has been the object of research for quite a long time [2], as these factors are used in practical and experimental medicine, but the mechanisms of this effect and its consequences at the cell level are still not completely clarified. Some experimental data [3, 4] says that prolonged exposure to microwave radiation is able to cause changes in living tissues, however the other researches [5, 6] disproves that.

The other significant influence on human organism comes from magnetic fields (MF). The applications of MF in medicine and industry (alone and together with radiation of different spectrum range) [7] requires further investigations.

As the results of scientific data analysis shows the uncertainty of conclusions about the effects of low-dose ionizing radiation especially combined with the other environmental factors such as magnetic fields or non-ionizing radiation. Those mentioned factors have increasing impact on human so that is why the studies in this filed do not lose their importance.

CELL RESPONSE TO X-RAYS, GAMMA RADIATION AND COMBINED EXPOSURE WITH MICROWAVES AND MAGNETIC FIELD

The effects of different ranges of electromagnetic radiation spectrum have been of a great interest especially in case of ionizing radiation impact on living cell. One of the branches in these studies is dedicated to possibility of modification the effects caused by ionizing radiation with non-ionizing one (such as microwaves and low-frequency electromagnetic fields). This problem is also relevant in connection with application in medicine; however, it remains incompletely described. The data of early studies in this field are well-described and summarized in [8]. Separately special attention is paid to the study of modification possibilities for biological effects caused by doses of ionizing radiation (IR), which belong to the ranges of very low (<100 mGy) [9], low (<0.5 Gy) and medium (0.5–5 Gy) [10]. UNSCEAR ranging tells that doses <100 mGy are low, 0.1–1 Gy are moderate, and doses >1 Gy are high ones [11]. It is also important to note that ranges of doses in certain studies may vary due to the way of radiation application, for instance the monthly lethal dose for human which formally belongs to medium range is described in [12] as ultra-low. There is the data that summarizes the presence of the ionizing radiation biological effects on prokaryotic organisms [13] which includes also the signs of radiostimulation with relatively low doses (around 0.5 Gy) which may refer to hormesis concepts [14].

The problem of the cellular response to electromagnetic radiation (both ionizing and non-ionizing) is key in understanding its potentially harmful effects on human health [15] and at the same time understanding the possibilities of using these effects in medicine [16, 17]. The question of the response of both a whole organism and individual cells to the action of ionizing and non-ionizing radiation was considered by A.S. Pressman, in his experimental works the positive changes in the viability of animals under conditions of microwave irradiation before receiving a dose of ionizing radiation were described [1]. Recently, it has been established that non-ionizing radiation (for example, microwaves) and magnetic fields can cause certain biological effects. In particular, there are data on the presence of such effects in the cell nucleus [18]. There is also the evidence of the positive effect of the magnetic field on plants [19, 20]. The possibility of biological interaction of the magnetic field and ionizing radiation has also been shown [21, 22].

Known cytological impact caused by ionizing radiation include changes in the permeability of the cell membrane, swelling of both the majority of cell organelles and its entire volume of cytoplasm, chromosomal aberrations and cell cycle interruption. There are data confirming the relationship between the number of heterochromatin granules and the degree of the cell's stress response to electromagnetic radiation, RNA synthesis inhibitors, etc. [23]. The permeability of the cytoplasmic membrane is also an indicator of cell damage. An increase in the permeability of the cell membrane can be a sign of either apoptosis or necrotic. It has been shown that microwave radiation and a magnetic field can damage the membranes of plant cells [24]. In addition, an increase in membrane permeability was observed in human cells under the influence of electromagnetic radiation of the mobile frequency range [25]. The influence of the magnetic field used in medicine (for MRI and stimulation of regenerative processes) and industry also requires a more detailed study, especially in cases of combined exposure together with microwave and other types of radiation [26]. There are data on the ability of a low-frequency magnetic field to reduce the harmful effects of microwave radiation [27, 28]. In the development of the stress response of the cell to the action of ionizing radiation, a significant role is played by the signal response of the cell to the stress associated with irradiation [29].

It has been established that non-ionizing radiation is also able to cause a stress response, leading to the activation of signaling pathways [30], which, in turn, affect the activity of certain genes [31]. It has been shown that there is an increase in the ability of laboratory animals to survive after exposure to ionizing radiation, simultaneously with irradiation and during pretreatment with electromagnetic or by magnetic fields [1]. Together with that different results exist with the use of the combination of 900 MHz microwaves and gamma-radiation based on experimental object. A negative effect of microwaves on the proliferation of cells that were previously treated with gamma radiation has been revealed on SHG44 cells while in mice the microwaves as pre-treatment of gamma-radiation exposure showed protective features [32, 33]. Plant organisms instead such as guar has shown an increase of productivity high doses of gamma radiation and 900 MHz-microwaves [34]. Also there the possibility of metabolic product modification by different combinations of gamma-radiation and microwaves was shown [35].

For magnetic field it has been shown the absence of a reliable effect of a magnetic field with an induction of 1.42 mT and electromagnetic radiation with a frequency of 60 Hz (magnetic induction of 0.13 μT) on the mortality of mice that simultaneously received high doses of gamma radiation (3.0, 4.0 and 5.1 Gy) [36]. In some works, the role of ELF electromagnetic fields in the development of cancer, their influence on immunity and the functioning of nerve cells were studied, there is evidence of the positive effect of ELF and magnetic fields on bone structures, nerve tissue, wound healing and reperfusion processes [37].

The uncertainties and controversy mentioned above the further research of electromagnetic field impact on human organism is still actual, especially in the branch related to combined exposure of different physical factor such as ionizing and non-ionizing radiation ranges.

The series of experiments which are discussed in present analysis were conducted with use of X-rays [38] and gamma-radiation impact modified with microwave radiation and static magnetic field [39]. Buccal epithelium cells were used as the experimental object for their convenience in examining of cytological indexes such as heterochromatin granules quantity (HGQ) and cell membrane permeability (CMP). The methods of cell samples prepare and the procedure of irradiation are described in [40, 38]. Another series included the assessment of mitochondrial activity and Ca^{2+} ions migration between cell nucleus and cytoplasm [41].

Effects of X-rays with microwaves and magnetic field on chromatin condensation

The main conclusion of the experimental series with use of X-rays is about trigger effect of X-ray towards chromatin state. Even dose 1.4 μSv led to significant increase of HGQ index. However, this effect appeared without certain dependences in the range of very low doses. The absence of the trend also was observed up to 40 μSv in cells of 2 donors. And in general cell of both donors did not show similarities in response to mentioned dose range [38]. Still the presence of the trigger effect may mean the radiosensitivity in dose ranges that are even lower than low [42] or very low [9].

According to the data that the cytological effects of even short ultrawideband impulses has been shown as significant in ability to change the rate of chromatin condensation [18, 43, 44], the combinations of microwave radiation and X-rays were implemented as the variant of exposure for cell samples. Microwave radiation and static magnetic field ability to change HGQ index were also illustrated in [45]

The combined effect of microwave and X-ray radiation in most cases reduced the value of the HGQ index under the condition of cells post-treatment with microwave radiation after exposure to X-ray. Thus microwave radiation had a modifying effect, which appeared more clearly with the increase of the X-rays.

The biological effect caused by the permanent magnetic field, also had its own personalized features such as decrease or increase of HGQ in the cells of different donors. A protective effect of the magnetic field was observed in case of cells pre-treatment before X-ray irradiation. This effect was most clearly observed on cells of a 25-year-old donor. Post-treatment with magnetic field caused changes variable by donors' individual features (from absence of the effects to its increase in addition to X-rays). These results illustrate the uncertainty in the statements about possibility of direct impact of the magnetic field on any kind of cellular effect including oncogenesis [46]. Detected so-called protective properties of static magnetic field against ionizing radiation can be explained from the creation of smaller cell stress from MF which may prepare the cell to upcoming damage from radiation.

Gamma-radiation with microwaves or magnetic field impact on chromatin condensation, cell membranes permeability

The problem of biological effects from the combined effects of ionizing and non-ionizing radiation is not fully resolved; basing on data of our experiments with X-rays and microwaves the mentioned stochasticity may be present not only in the range of extremely low doses both for ionizing and non-ionizing radiation, the same may be predicted also for simultaneous impact of magnetic field with ionizing radiation. In our opinion, the cellular response to the combination of these factors is determined by the genotype of the cell and the intensity of the effect, which is the reason for the difference in the experimental data obtained by different authors.

Cells of the human buccal epithelium obtained from different donors have individual characteristics of the reaction to the action of gamma radiation. These features are similar to those that occur under the action of small doses of X-ray and microwave radiation. Results of samples gamma-irradiation revealed predictable increase of HGQ; however the highest doses have led to non-linear plateau-like dependency [47]. Statistically significant increase in the level of chromatin condensation (HGQ index) in cells of all donors was detected at a dose of gamma radiation of 2 Sv and higher. With use of this threshold dose of 2 Sv the further modification of the cell effects on chromatin condensation, plasmatic membranes permeability, mitochondrial activity and Ca^{2+} redistribution between nucleus and cytoplasm was carried out.

The application of a constant magnetic field and microwaves in most cases after treatment with γ-radiation led to a decrease in the stress response of cells according to the HGQ index. General modifying effect of EHF-microwaves was also related either to the decrease of HGQ or no significance in the impact toward γ-radiation. Results obtained in our experiments correspond to general uncertainty about possibility of non-ionizing radiation to induce the adverse changes in living matter (including carcinogenesis) [48]. Also there was no difference between intensities of microwave radiation (0,1 or 1 W/m^2) in their effect before/after ionizing irradiation [40, 49]. There is the data about development of the oxidative stress however without significant outcome [49], so in our cases changes in cells nuclei membrane may appear as indirect illustration of EHF microwaves low impact on general cell stress development induced by ionizing radiation.

When the cells were exposed to microwave radiation in combination with ionizing radiation and static magnetic field, a tendency to decrease the permeability of the cell membrane was observed, but this effect was not pronounced among the cells of all donors. For instance, cell of one of the donors demonstrated greater amount of damage in plasmatic membranes under combined exposure of γ-radiation with magnetic field as well as the in combination with microwaves regardless of the sequence or intensity of EHF-irradiation. Due to expressivity of plasmatic membrane permeability changes under various damaging factors it can be concluded that both questionable microwaves influence on human [49] (but stated as possible on bacteria [9]) and magnetoreception [46] can be revealed under condition enhanced with such clearly damaging factor as gamma-radiation.

Ca^{2+} redistribution and mitochondria activity under gamma-radiation exposure combined with microwaves

The magnetic field has a weak positive effect on the membrane potential of mitochondria and is able to facilitate the transfer of Ca^{2+} ions from the cytoplasm to the nucleus; in combination with gamma radiation, this effect is neutralized.

EHF-microwaves and gamma radiation lead to a decrease in the activity of mitochondria in terms of their membrane potential and mutually reinforce each other, also leading to the accumulation of Ca^{2+} in the cell nucleus. Thus, this combination turned out to be the most significant among the studied physical factors with proapoptotic potential. Our results correspond with conclusion of works [50, 51] about radiation-induced oxidative stress; microwave radiation appeared to be a potent enhancer of ionizing radiation effects related to suppression of oxidative phosphorylation. Despite the clear difference in destructive impact of gamma rays on cell structures the non-ionizing showed even more expressive signs of oxidative stress comparing to pure IR exposure but at the same time the sustainability of such modifying effect should be researched furthermore.

With experimental data obtained, it is possible to make an assumption about the mutual reinforcement of the effects of gamma radiation and microwaves in relation to the redistribution of Ca^{2+} ions from the cytoplasm to the nucleus. In combination with the previously shown ability of EHF-waves and gamma-rays to a decrease in the membrane potential of mitochondria, this may indicate the beginning of the process of induced apoptosis in the cells of the buccal epithelium. However, taking into account the processes of restoration of cell membranes and reduction of the degree of chromatin condensation demonstrated above, at this stage of our research, the reversibility of the pro-apoptotic state of the cell should be noted [41]. Also the data about sensitization of the tissues to ionizing radiation by microwaves is present in recent studies [52] but in our case the changes in the mitochondria activity and Ca^{2+} ions location may doubtfully depend on thermal effects.

CELL RESPONSE TO NEUTRON RADIATION EXPOSURE

The study of the influence of neutron radiation on biological objects is necessary for the general characterization of the processes occurring during the interaction of tissues with corpuscular radiation, including for determining the relationship between indicators of the cell's response to stress and its functional (proliferative) activity, with the aim of practical application in medicine. It is known that the development of cellular stress depends on both the intensity and the type of radiation.

The medical value of neutron radiation is considered in [52], where the high efficiency of neutron exposure in the treatment of brain tumors was demonstrated. Biological effects of neutron radiation, occurring at all levels of the organization of living matter, have various manifestations. The problem of using neutrons in medicine is related to the absorption of accompanying low-intensity radiation by the tissues surrounding the tumor. Studying the state of cells under the influence of neutron radiation is of practical importance for clarifying the characteristics of possible side effects of radiotherapy. The work [54] shows the high efficiency of neutron radiation in anticancer therapy with neutron capture by boron ^{10}B. Slow neutrons are inferior to gamma radiation in terms of biological effectiveness [55], but it has long been established that their effect outweighs the effects of X-ray radiation [56]. At the same time, it should be noted that despite the established distribution of RBE (relative biological efficiency) of neutrons corresponding to their energy range, some reviews provide a set of data indicating no change in the RBE indicator, for example, for fast neutrons in relation to their effect on inducing apoptosis [57].

There are also quite contradictory data that indicate an increased risk of carcinogenesis under the influence of, including, neutrons [58], on the one hand, and the insignificance of the influence of neutron radiation on the occurrence of cancer [59] on the other. Neutron radiation at small absorbed doses has significant destructive properties for cells, which can be manifested in the weakening of gene activity, while X-ray radiation can have both suppressing and enhancing effects [60], the nature of which is not completely understood.

Separately, we should take into account the evidence about the weak influence of neutron radiation on the survival of patients [61], that is, the effects of neutrons at the cellular level were more pronounced than at the organismic level. The effect of large doses of neutron radiation on living objects is well studied. Studies show a clear dependence of the effect on the dose, albeit nonlinear, using the example of rat [62] and human [63] cells. There are different views on the biological effect of neutron radiation, which indicate both hormetic [56] and damaging effects [64, 65]. But since there are still no final conclusions determining the biological effects of small doses of neutron radiation, the question of a scientific solution to this problem arises separately. But at the same time, according to some data, it is claimed that there is an increased risk of carcinogenesis [66] and an increase in the frequency of chromosomal aberrations [57] in the range of small doses of ionizing radiation (including neutrons), according to others, that this risk is not significant [59]. There are also scientific data on the positive effect of neutron radiation on animal organisms [67]. All of the above requires further research to clarify the biological impact of neutron radiation depending on the dose range.

Low doses of neutron radiation appeared to be able to increase the degree of chromatin condensation (from 4.6 mSv) and the permeability of the cell membrane (from 9.2 mSv) with the maximum values of indicators at a dose of 36.5 mSv, but these processes have individual characteristics and character and depend from the characteristics of a specific donor. A further increase in the dose (73.1–146 mSv) caused the opposite changes such as chromatin decondensation and a decrease in the permeability of cell membranes. At the same time, the content of heterochromatin granules and the permeability of the cell membrane for vital dyes decreases to the control level and in some samples show even lower values [68, 69, 70, 71]. Such non-linear response may be explained by numerous cell protective mechanisms that are described in [72] or from the point of view of radiation hormesis as the stimulating effect of lower doses of neutron radiation (up to 36.5 mSv) with the subsequent development of the adaptive response of the cell to the stress factor of higher doses (73.1–146 mSv). There is a point of view about pro-inflammatory response of immune system to very low IR doses which changes to anti-inflammatory with the increase of dose to low-to-moderate range [73], so similar variations exactly on the border of dose ranges may take place in other cells (e.g. buccal epithelium). Also the case of protective effects of IR against chemical damaging factor were observed [74], and in our case due to elongated procedure of irradiation the dose received in the beginning of the exposure could appear as protection-activating against the upcoming doses.

At the same time the donors' sensitivity to neutron radiation had also individual features of response. Considering the noted similarity of reactions to different types and dose ranges of ionizing radiation, which were described both in experiments with gamma radiation and with neutrons, we can make an assumption about the similarity of individual adaptation reactions of donors to different types and doses of ionizing radiation.

There can be two points of view on the recorded wave-like changes in the state of chromatin: the development of a stress reaction with the loss of the cell's ability to further chromatin condensation with an increase in the dose of ionizing radiation due to irreversible DNA damage or cell repair and, accordingly, the stimulating effect of small doses of neutron radiation with the activation of biosynthetic processes. The second way may resemble the gradual acquired radioresistance to upcoming irradiation observed exactly at low-to-moderate doses (as it was recently shown in experiments with *Drosophila melanogaster* [9]) by analogy with higher ones [75]. In general, non-monotonic dependences of the effect on ultra-low doses of ionizing radiation have been known in radiobiology for many years.

CONCLUSIONS

According to the results of our research, it was primarily postulated that very low doses range cannot give the certain "dose-effect" dependency, the low doses of neutron radiation revealed non-linear features of cell response and the high doses may lead to plateau threshold in the effects toward chromatin condensation including the doses that are closes to lethal.

The effect of 2 Sv gamma-radiation dose is partially reduced by applying a constant magnetic field and microwaves before or after gamma radiation treatment. Individual differences in the reaction of the HGQ indicator in donor cells to different treatment regimes were revealed. Changes in the permeability of cell membranes of different donors under the exposure of gamma radiation have individual characteristics and in general statistically are less significant than the HGQ index. The microwave radiation and magnetic field in combination with gamma radiation has a weak but reliable additive effect, which is expressed in further increase of cell membranes permeability.

The transmembrane potential of mitochondria is significantly decreased under the influence of both microwave and gamma radiation, while increasing the dose of gamma radiation led to wave-like fluctuations in mitochondrial activity. The magnetic field had no significant effect on this index. Gamma radiation, unlike microwave radiation, did not cause a significant increase in the content of Ca^{2+} ions in cell nuclei, however the combined effect of microwave and gamma radiation led to an effect that was more expressive than the one after exposure of microwaves.

Neutron radiation caused wave-like changes in cell membrane permeability and chromatin condensation in the nucleus of target cells in the dose range of 2.3–146.0 mSv with the maximum effect at a dose of 36.5 mSv. A further increase in the dose of neutron radiation reduces the HGQ index and the permeability of the cell membrane to control levels and even below.

Since the cells of the buccal epithelium are sensitive even to extremely small doses of ionizing radiation, and also demonstrate modification of the effects of irradiation during the action together with a magnetic field and microwaves, it is proposed to continue using the cells of the human buccal epithelium as a test system for studying the effects of both ionizing and non-ionizing radiation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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СТРЕСОВА ВІДПОВІДЬ КЛІТИН НА КОМБІНОВАНУ ДІЮ ІОНІЗУЮЧОГО, НЕІОНІЗУЮЧОГО ВИПРОМІНЮВАННЯ ТА МАГНІТНОГО ПОЛЯ: ОГЛЯД НА ПРИКЛАДІ КЛІТИН БУКАЛЬНОГО ЕПІТЕЛІЮ ЛЮДИНИ

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Актуальність. Вплив малих доз іонізуючого випромінювання (ІВ) як такого та в поєднанні з іншими шкідливими фізичними факторами, такими як надвисокочастотні (НВЧ) мікрохвилі та магнітні поля (МП), в даний час є об'єктом численних досліджень. Проте результати цих досліджень все ще не мають однозначних висновків.
Мета роботи. Представлено огляд та аналіз раніше проведених серій експериментів у порівнянні з суміжними цільовими роботами для покращення розуміння ролі малих доз іонізуючого, неіонізуючого випромінювання та магнітного поля у розвитку ефектів клітинного стресу.
Результати. Наднизькі дози як самого ІВ, так і НВЧ і МП проявляли тригерні ефекти, які включають варіабельність модифікації ефекту ІВ. На прикладі ультраширокосмугового мікрохвильового опромінення показано значущість впливу навіть надмалих доз неіонізуючого випромінювання. Комбінований вплив гамма-випромінювання з НВЧ-мікрохвилями та МП на стан хроматину призвів до зменшення вмісту гранул гетерохроматину (ВГГ), але вплинув на зростання проникності клітинної мембрани (ПКМ) більше, ніж саме ІВ. Виявлено пригнічення активності мітохондрій та зниження Ca^{2+} в цитоплазмі при дії як ІВ, так і НВЧ-мікрохвиль та їх комбінацій. МП дещо підвищувало мембранний потенціал мітохондрій та не показало значних змін у перерозподілі Ca^{2+} до ядра при застосуванні разом з ІВ. При дії нейтронного випромінювання виявлено максимум показника ВГГ та проникності клітинної мембрани при дозі 36,5 мЗв. Подальше збільшення дози повертало стан хроматину та клітинної мембрани до контрольного рівня.
Висновки. На прикладі ВГГ показано невиразний ефект надмалих доз ІВ із модифікуючою здатністю НВЧ-мікрохвиль та МП. Ефекти високих доз гамма-випромінювання також були модифіковані як НВЧ-мікрохвилями, так і МП за показниками ВГГ (зменшення), ПКМ (збільшення), мітохондріальної активності (зменшення) і Ca^{2+}-перерозподілу між ядром та цитоплазмою. Опромінення швидкими нейтронами в діапазоні низьких і середніх доз призводило до розвитку ознак клітинного стресу (підвищення ВГГ та ПКМ), які згладжувалися при збільшенні дози.
КЛЮЧОВІ СЛОВА: рентгенівське випромінювання; гамма-випромінювання; нейтронне випромінювання; НВЧ-мікрохвилі; постійне магнітне поле; хроматин; проникність мембрани; активність мітохондрій.