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## Submicroscopic changes in hippocampal neurocytes of rats with induced colon adenocarcinoma under conditions of nanomaterial correction

**The aim of the work:** to investigate ultrastructural changes in hippocampal neurocytes under conditions of DMH-induced colon carcinogenesis and following correction with an Au/Ag/Fe nanocomposite.

**Materials and Methods.** The study was conducted on 35 white male laboratory rats with an average weight of 180–200 g, which were kept in standard vivarium conditions. The animals were divided into three groups: intact, rats with induced adenocarcinoma, and animals that received nanoparticles for 21 days. After the experiment was completed, the animals were removed from it by decapitation. Before that, they were intraperitoneally injected with a 10 % solution of sodium thiopental (Arterium, Ukraine) at a dose of 50 mg/kg.

**Results.** In rats with tumor intoxication, hypochromic and hyperchromic neurocytes predominated, demonstrating characteristic pathological alterations, including dilation of the granular endoplasmic reticulum cisternae, mitochondrial destruction, chromatin marginalization, and accumulation of autophagosomes and protein aggregates. In normochromic cells, signs of ultrastructural damage were also detected. Administration of the nanocomposite resulted in a reduction in the proportion of pathologically altered cells, stabilization of the ultrastructure of the neuroplasm, and restoration of ribosome number, as well as mitochondrial and karyoplasmic structure.

**Conclusions.** Under conditions of DMH-induced colon adenocarcinoma, hypochromic and hyperchromic neurocytes with pronounced ultrastructural damage predominate in the rat hippocampus, indicating oxidative stress and neuroinflammation. The application of the Au/Ag/Fe nanomaterial composition contributes to partial restoration of neuronal structure and demonstrates a neuroprotective effect.

**Key words:** hippocampus; brain; neurocytes; carcinogenesis; adenocarcinoma; nanoparticles; electron microscopy.

### Problem Statement and Recent Research

**Analysis.** The hippocampus is a complexly organized structure of the central nervous system that performs numerous functions, particularly cognitive ones. Structurally, the hippocampus includes the dentate gyrus and the CA (Cornu Ammonis) fields: CA1, CA2, and CA3. The CA1 field is considered to be responsible for the retrieval of memories related to spatiotemporal information and for encoding spatial information. This allows memories to be organized in the correct temporal sequence of events. In addition, CA1 integrates information from CA3 and the entorhinal cortex into output pathways and participates in the extinction of context-specific responses, such as conditioned fear [1–4]. The CA2 field performs a specific function related to social memory and also modulates aggressive behavior. Some authors describe CA2 as a “metaplastic switch,” due to the ability of neurons in this region to influence synaptic plasticity between CA1 and CA3, facilitating transmission under certain conditions while limiting excessive activation of CA3 neurons [5–7]. CA2 neurons are particularly sensitive to glucocorticoids and stress due to the presence of corresponding receptors, which subsequently affect the electrophysiological and

synaptic properties of neurons in this part of the hippocampus [8]. Neurons of the CA3 field form a network that functionally supports associative memory and the rapid formation of short-term memory. This enables the generation of memories even when only partial cues are present. When incoming signals are incomplete or distorted, CA3 can activate a complete memory through its intrinsic connections. CA3 neurons receive excitatory input from the entorhinal cortex and the CA1 field, which enhances the flexibility of information processing [9–11].

The hippocampal fields are highly sensitive to pathological influences originating both from the central nervous system and from peripheral organs. For example, the accumulation of beta-amyloid in CA1 neurons, which is typical for Alzheimer’s disease, leads to impaired plasticity of CA3–CA1 synapses and consequently to deficits in learning and memory [12]. Amyloid accumulation in CA2 reduces GABAergic activity and disrupts synaptic plasticity, which may affect social memory and network integration [13]. Studies modeling the effects of chronic stress on the hippocampus have demonstrated inhibition of oxidative phosphorylation in neurons,

which subsequently impairs cognitive functions. A pathological influence of growth hormone on this region has also been reported, leading to alterations in spatial perception by the brain [14, 15].

Neurons of hippocampal fields undergo ultrastructural changes under pathological conditions affecting the cardiovascular system, lungs, gastrointestinal tract, and other organs. In particular, heart and respiratory failure lead to hypoxia, resulting in the accumulation of electron-dense “dark material” in the neuroplasm, predominantly beneath the plasma membrane, especially in neuronal bodies and proximal dendrites, as well as polysome disaggregation. Glucose deficiency, dietary fiber deficiency, chronic obstructive pulmonary diseases, and disturbances of the intestinal microbiota affect neuronal volume, leading to neuronal shrinkage and synaptic loss, which is subsequently manifested as an overall reduction in hippocampal mass. Structural alterations of synapses under such conditions are associated with microglial activation. Oxidative stress in the organism results in mitochondrial dysfunction in hippocampal neurocytes (increased mitochondrial volume, destruction of cristae), dendritic remodeling (reduced diameter and altered shape), accumulation of protein aggregates in the cytoplasm, and lysosomal alterations [16–19].

Data regarding ultrastructural changes in neurocytes of hippocampal CA fields in the context of induced colon adenocarcinoma remain limited. Currently, there is growing scientific interest in the influence of nanoparticles on the state of brain cells in general and on the hippocampus in particular. Studies demonstrate a beneficial effect of gold nanoparticles on inflammatory processes in nervous tissue. They reduce oxidative stress and mitochondrial dysfunction and decrease the intensity of apoptosis [20]. Experimental studies have shown that gold nanoparticles reduce the level of reactive oxygen species and lipid peroxidation, thereby stabilizing cellular metabolism [21]. Iron and silver nanoparticles influence microglia and also reduce manifestations of neuroinflammation, stabilize neuronal membranes, and increase the proportion of cells that do not undergo apoptosis or degeneration [22]. Silver nanoparticles may stimulate neurogenesis in stroke models and act as “nano-chaperones,” suppressing amyloid accumulation [23]. Therefore, determining the effects of nanoparticles on neurons of the CA1, CA2, and CA3 hippocampal fields under conditions of induced carcinogenesis is of significant scientific interest.

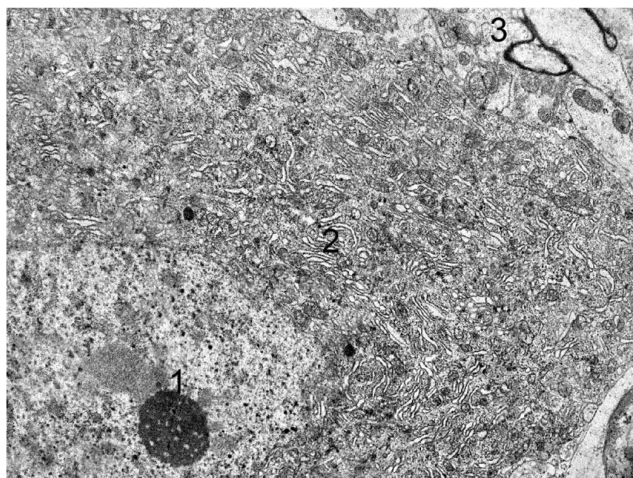
**The aim of the work:** to investigate ultrastructural changes in hippocampal neurocytes under conditions of DMH-induced colon carcinogenesis and following correction with an Au/Ag/Fe nanocomposite.

**Materials and Methods.** The study was conducted on 35 white laboratory male rats with an average body weight of 180–200 g, which were kept under standard vivarium conditions in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and in compliance with the ethical principles of animal experimentation (Kyiv, 2013). The animals were divided into three groups. The first group served as the control. The second group was experimental, in which colon adenocarcinoma was induced. The third group was the correction group, in which a composition of Au/Ag/Fe nanomaterials was used.

Tumor induction in groups 2 and 3 was performed by weekly subcutaneous administration of N,N-dimethylhydrazine (DMH) at a dose of 7.2 mg/kg body weight into the interscapular region for 7 months. Correction in the third group was carried out for 21 days. The animals received an aqueous dispersion of Au/Ag/Fe nanoparticles diluted with sterile distilled water at a ratio of 1:10 and administered intragastrically once daily. The daily dose of nanoparticles was 0.842 mg of silver, 0.0526 mg of iron, and 1.625 µg of gold per 1 kg of body weight of the experimental rat. After completion of the experiment, the animals were euthanized by decapitation. Prior to this, they were anesthetized by intraperitoneal administration of a 10 % solution of sodium thiopental (Arterium, Ukraine) at a dose of 50 mg/kg. The brain was removed, and hippocampal specimens were prepared according to standard methods followed by electron microscopic examination. The samples were fixed using standard procedures, after which ultrathin sections were prepared using an LKB 4801 A ultramicrotome. The sections were contrasted with uranyl acetate and lead citrate according to the Reynolds method and examined using a PEM-125 K transmission electron microscope.

**Results.** Electron microscopic examination of neurocytes in rats of the control group showed that normochromic cells predominated. The neurons contained a rounded nucleus with moderate electron density, clearly defined karyolemma membranes, a non-expanded perinuclear space, and visible nuclear pores. In the karyoplasm, active, optically light euchromatin predominated, and relatively large electron-dense nucleoli were observed. The neuroplasm also exhibited moderate electron density and contained numerous ribosomes and well-developed cisternae of the rough endoplasmic reticulum. Cisternae and vesicles of the Golgi complex were identified in the perinuclear region. Mitochondria

had a round to oval shape with clearly defined membranes, well-outlined cristae, and a matrix of low electron density (Fig. 1).



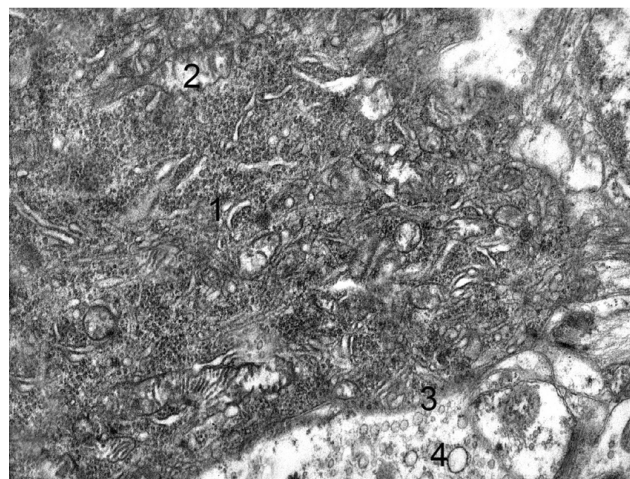
**Fig. 1.** Submicroscopic structure of a hippocampal neurocyte in an intact animal: 1 – nucleus with nucleolus, 2 – numerous cisternae of the rough endoplasmic reticulum in the neuropil, 3 – neuropil.  $\times 7000$ .

In the experimental group exposed to the carcinogen, at the 7th month of the experiment the proportion of alteratively changed neurocytes increased, particularly due to disturbances of their ultrastructure, reflecting a destructive response to carcinogenesis and the development of neurodysfunction. The proportion of normochromic cells markedly decreased, and these cells exhibited significant ultrastructural alterations. The plasmalemma was indistinct and often fragmented. The cisternae of the rough endoplasmic reticulum were dilated and vacuolated, and the number of ribosomes on their membranes was reduced. In the Golgi complex, thickening of the cisternae was observed, while microvesicles and occasional vacuoles disappeared. Mitochondria were swollen, with a clarified matrix and reduced cristae. In the nuclei, chromatin marginalization was observed; it appeared markedly osmiophilic, accompanied by a reduction or complete absence of nucleoli and local widening of the perinuclear space.

In “light” cells with low electron density of the neuropil, destructured organelles were observed, as well as ectasia of the cisternae of the rough endoplasmic reticulum and Golgi apparatus, and a sharp decrease in polysomes. Mitochondria showed partially fragmented cristae and an optically light matrix, indicating an increase in organelle volume. Accumulation of protein aggregates and fragmented remnants was observed in the neuropil,

accompanied by an increased number of autophagosomes. The nuclear envelope had indistinct contours with homogeneous osmiophilic zones, and euchromatin predominated in the karyoplasm. The nucleolus was markedly reduced or absent.

Hyperchromic neurocytes were characterized by neuropil and karyoplasm of high electron density, giving them the appearance of “dark” cells. The cisternae of the rough endoplasmic reticulum and Golgi apparatus were predominantly short and narrowed; however, the karyoplasm contained numerous ribosomes and polysomes. In mitochondria, disaggregation of cristae and vacuole-like changes in organelle shape were observed. The nuclei of these neurocytes demonstrated high osmiophilicity, large nucleoli were present, and the contours of the nuclear membranes were indistinct and poorly delineated (Fig. 2).

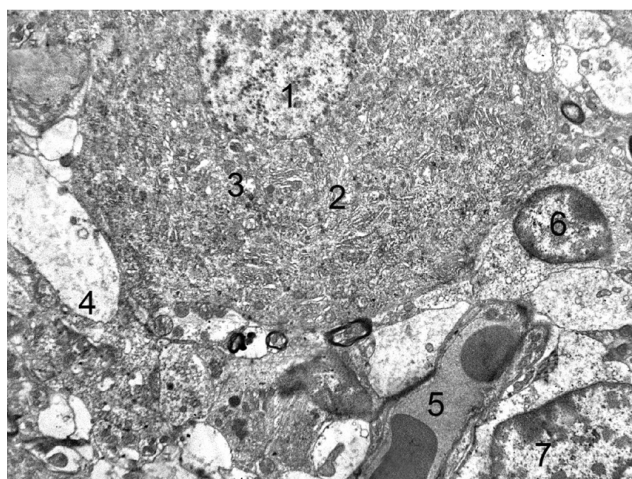


**Fig. 2.** Submicroscopic changes of a “dark” hippocampal neurocyte under conditions of modeled carcinogenesis: 1 – short cisternae of the endoplasmic reticulum 2 – in osmiophilic neuropil, altered mitochondrion, 3 – indistinct karyolemma, 4 – neuropil.  $\times 21000$ .

The identified changes in neurocytes of the hippocampal fields are caused by the effects of oxidative stress and endoplasmic reticulum stress, disturbances in energy metabolism, and dyscoordination of inter-organelle interactions that arise in response to the development of DMH-induced colon adenocarcinoma. In neurocytes, disruption of membrane integrity and destruction of organelles were observed, reflecting an increase in the intensity of oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, activation of autophagy, enhanced production of free radicals, and damage to organelle membranes. These processes lead to inhibition of the synthetic and energetic functions of neurons under the toxic influence of dimethylhydrazine.

Similar changes can be observed under other pathological conditions or influences. For example, experimental damage to neuronal mitochondria disrupts calcium metabolism regulation and initiates apoptosis [24]. Neuronal pathology, such as in amyotrophic lateral sclerosis, provokes ultrastructural alterations of the endoplasmic reticulum and its interaction with mitochondria, leading to metabolic disturbances and neurodegeneration [25, 26]. Chromatolysis (dissolution of Nissl substance), manifested by chromatin condensation and marginalization, nuclear fragmentation, and karyorrhexis, represents a cellular response to toxic effects and a manifestation of apoptosis. Similar changes have been confirmed in studies by Felix J. B. Bäuerlein et al. (2020) investigating neurodegenerative processes in the central nervous system [27].

During the study of hippocampal neurocytes in rats of group 3, which received correction with a composition of Au/Ag/Fe nanomaterials, a change in the ratio of neurocyte types was observed: the number of normochromic cells increased due to a reduction in hypo- and hyperchromic neurons within the hippocampal fields. In normochromic neurocytes, the severity of ultrastructural disturbances decreased; the integrity of the plasmalemma was restored, the cisternae of the endoplasmic reticulum were not dilated, and the number of ribosomes associated with them recovered. The nuclei were moderately osmiophilic, nuclear pores were clearly visible, and the nucleolus was moderately expressed. These findings indicate normalization of cellular metabolism and restoration of protein synthesis (Fig. 3).



**Fig. 3.** Ultrastructural changes of a hippocampal neurocyte in an animal under conditions of modeled carcinogenesis and treatment with a composition of Au/Ag/Fe nanometals: 1 – neuronal nucleus, 2 – cisternae of the rough endoplasmic reticulum in the neuropil, 3 – mitochondrion, 4 – neuropil, 5 – hemocapillary, 6 – oligodendrocyte, 7 – astrocyte.  $\times 7000$ .

**Discussion.** Hypochromic cells demonstrated a decrease in the dilation of the cisternae of the Golgi apparatus, a reduction in the size of the endoplasmic reticulum cisternae, and an increase in the number of ribosomes and polysomes. At the same time, the number of cytoplasmic autophagosomes decreased, and the structure of mitochondrial cristae was partially restored. The nuclei of such cells acquired clearer contours; a small but distinct nucleolus appeared, and euchromatin predominated.

The organelles of hyperchromic hippocampal neurocytes contained intact membranes, while dilation of the endoplasmic reticulum cisternae or Golgi apparatus was observed only rarely. The karyoplasm of the nuclei contained a small number of massive heterochromatin aggregates, and the karyolemma membranes had relatively clear contours with visible nuclear pores. A decrease in mitochondrial vacuolization and fragmentation of cristae was also observed.

Numerous studies demonstrate that Au, Ag, and Fe nanoparticles possess antioxidant properties, as they reduce the production of free radicals, stabilize cellular membranes, and decrease lipid peroxidation. Consequently, this may prevent mitochondrial swelling, cristae degradation, and rupture of the endoplasmic reticulum [28]. Gold and silver nanoparticles can support ribosomal activity and stabilize calcium homeostasis, thereby preserving the structure of the endoplasmic reticulum and the Golgi apparatus. They also inhibit apoptosis by increasing the expression of the Bcl-2 protein. Dimethylhydrazine activates caspases in neurocytes and induces nuclear destruction, whereas gold and iron nanoparticles can block the initiation of apoptosis by inhibiting caspase-3, stabilizing the mitochondrial membrane potential, and maintaining nuclear chromatin integrity [22, 29]. In addition, iron oxide increases the levels of nestin, a protein involved in axonal growth, and the transcription factor Sox-2 in neurons, which enhances neurogenesis and synaptogenesis [21].

**Conclusions.** Rats with DMH-induced colon adenocarcinoma showed a predominance of hyperchromic and hypochromic neurocytes in the hippocampal fields compared with the data of the control group. Under conditions of DMH-induced carcinogenesis, pronounced disturbances of the neuronal ultrastructure were observed: damage to membrane integrity, destruction of organelles, swelling and reduction of mitochondrial cristae, dilation of the endoplasmic reticulum, chromatin marginalization, and activation of autophagy, which indicates neuroinflammation and oxidative stress against the background of colon adenocarcinoma in situ. The application of a composition of Au/Ag/Fe nanomaterials

contributed to the restoration of the ultrastructure of neurocytes, an increase in the proportion of normochromic cells, normalization of the state of organelles, and activation of protein-synthetic processes, which indicates the neuroprotective effect of this correction. The obtained data indicate the prospects of using nanomaterials for the correction of neuronal changes caused by tumor intoxication.

**Conflict of Interest.** The authors declare no conflict of interest.

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**Authors' contribution.** Chebernina I. O. – literature review, formulation of the research aim and concept, data collection, analysis and interpretation of results, visualization, writing, editing, and preparation for publication. Nebesna Z. M. – supervision, interpretation of results, visualization, formulation of conclusions, writing, and editing.

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### СУБМІКРОСКОПІЧНІ ЗМІНИ НЕЙРОЦИТІВ ГІПОКАМПА ЩУРІВ З ІНДУКОВАНОЮ АДЕНОКАРЦИНОМОЮ ТОВСТОЇ КИШКИ ТА ЗА УМОВ КОРЕКЦІЇ НАНОМАТЕРІАЛАМИ

**Мета роботи:** вивчити ультраструктурні зміни нейроцитів гіпокампа на фоні ДМГ-індукованого канцерогенезу товстої кишки та за умов корекції наноконструктивом Au/Ag/Fe.

**Матеріали і методи.** Дослідження проведено на 35 білих лабораторних щурах-самцях середньою масою 180–200 г, яких утримували у стандартних умовах віварію. Тварин поділили на три групи: інтактні, щури з індукованою аденокарциномою, а також тварини, які отримували наночастинки упродовж 21 доби. Після завершення експерименту тварин виводили з нього шляхом декапітації. Перед цим їм внутрішньочеревно вводили 10 % розчин тіопенталу натрію (Arterium, Україна) в дозі 50 мг/кг.

**Результати.** У щурів із пухлинною інтоксикацією переважали гіпохромні та гіперхромні нейроцити, які демонстрували характерні патологічні зміни: розширення каналців гранулярної ендоплазматичної сітки, деструкцію мітохондрій, маргіналізацію хроматину, накопичення аутофагосом та протеїнових агрегатів. У нормохромних клітинах також виявлялися ознаки ушкодження ультраструктури. Застосування наноконструктиву привело до зменшення частки патологічно змінених клітин, стабілізації ультраструктур нейроплазми, відновлення кількості рибосом, структури мітохондрій і каріоплазми.

**Висновки.** За умов ДМГ-індукованої аденокарциноми товстої кишки в гіпокампі щурів переважають гіпо- та гіперхромні нейроцити з вираженими ультраструктурними ушкодженнями, що свідчить про оксидативний стрес і нейрозапалення. Застосування композиції наноматеріалів Au/Ag/Fe сприяє частковому відновленню структури нейронів і проявляє нейропротекторний ефект.

**Ключові слова:** гіпокамп; головний мозок; нейроцити; канцерогенез; аденокарцинома; наночастинки; електронна мікроскопія.

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