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NANOSIZED TITANIUM DIOXIDE MATERIAL. MODULATION OF SPONTANEOUS MOTILITY AND GABA-DEPENDENT REGULATION OF FUNCTIONS OF STOMACH SMOOTH MUSCLES *IN VIVO*

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Electron scanning microscopy was used to obtain the image and identify the size of TiO_2 nanoparticles. Using the tenzometric method in the isometric mode, it was established that chronic effect of TiO_2 on stomach smooth muscles led to redistribution of the amplitudes of spontaneous contractions in terms of their frequencies. An increase in frequency of their contractions, decrease in the duration of contraction–relaxation cycle, the disturbance of the asymmetry of the duration of contraction–relaxation development, a reduction in Montevideo index of contractions and Alexandria index of contractions were demonstrated. It was also shown the existance of the divergence in numerical values of frequency-amplitude complexes, TiO_2-modified spontaneous contractive activity of smooth muscles of stomach and *caecum*. In the conditions of long-term chronic influence (100 days), TiO_2 removes the regulatory mechanisms of depressing a release of inhibition neuromediators from neurons of the intramural nervous interlacement, mediated by $GABA_A$- and $GABA_C$-receptors, in smooth muscles of stomach and *caecum*.

Keywords: stomach smooth muscle, titanium dioxide nanoparticles, mechanokinetics, GABA-dependent regulation, spontaneous and induced contractions.

INTRODUCTION

Current development of high technologies, became the foundation for extensive production of nanosized materials, in particular, titanium dioxide (TiO_2), whose application takes a large sector of different kinds of industry, including pharmacological industry, the sphere of food production and medicine. This means that using TiO_2 in technologies, pertaining to microelectronics, biosensorics, production of plastic masses, creation of dyes, biocompatible implant materials, medicinal preparations, food dyes (E171), food products, others. Nanosized TiO_2 material is present in the form of three crystal structures: rutile, anatase, and brookite, but the first two forms are predominantly used in the industrial production (usually in the form of their mixture with different stoichiometry of components) [18, 24]. TiO_2 used in the form of anatase is much more chemically active, compared to rutile; when exposed to ultraviolet, it generates reactive oxygen intermediaries [10, 15]. Similar effects occur inside the tissue cells due to the interaction between TiO_2 nanoparticles and macromolecules [7, 17]. The intake of TiO_2 to human organism takes place with food, water, and air, and the main ways of its transportation are gastrointestinal tract (average daily amount of consumed TiO_2 (0.002–5) mg and respiratory tracts (daily amount of consumed TiO_2 – 0.0007 mg) [14, 16, 22], which in the global practice may already be referred to the nanohazard problems in the sphere of Environmental and Health Safety (protection of environment and human health from harmful impact of some objects, including nanoscaled). Our studies, conducted *in vitro* using stomach smooth muscles (SM) [19], demonstrated that nanosized TiO_2 material changed the energetic and calcium homeostasis of smooth muscle mitochondria, the conductivity of their plasmatic membrane for Ca^{2+} and cholinergic excitation. At the same time, the mechanisms of releasing these cations from rianodine- and IP_3-sensitive stores of sarcoplasmic reticulum were not sensitive to the impact of TiO_2. It was demonstrated [21] that *in vitro* TiO_2 in smooth muscles of large intestines modulated histamine and nicotine-induced mechanisms of regulating its functional activity. It was stated that the intake route of nanosized TiO_2 material to human organism via the gastrointestinal tract is the most probable, and food impact in the gastric cavity is the longest compared to other gastrointestinal tract parts. The aim of this work was to study changes *in vivo* in spontaneous motility and GABA-dependent regulation of functions of stomach smooth muscles, caused by chronic effect of nanosized TiO_2 material.

MATERIALS AND METHODS

8-week-old Wistar rats of both genders were used for *in vivo* experiments. The rats were kept in standard conditions of the vivarium (room temperature of 20±2 °C, relative humidity – 50–70 %, light-darkness cycle – 12:12 h). All manipulations with animals were carried out in accordance with the International Convention of animals and the Law of Ukraine "On protection of animals from cruelty". Protocol N 2 (October 20, 2016) of the meeting of Bioethics Committee of Educational and Scientific Centre "Institute of Biology and Medicine" Taras Shevchenko KNU. Killing of animals carried out by the injection of lethal dose of anesthetic protocol (Sigma).

TiO_2 nanoparticles were dispersed in the distilled water using ultrasound for 15 min; to obtain the homogenic suspension the latter was additionally stirred with the mechanical stirrer prior to each use. The intragastric dose was selected according to the data about the intake of TiO_2 with food products in Great Britain: 5 mg per person daily, that is equivalent to 0.1 mg/kg of weight per day [22]. Due to this, every day the rats were intragastrically administrated the suspension of TiO_2 with the consideration of 0.1 mg/kg in the first experimental group for 30 days and in the second experimental group for 100 days. The bodyweight of rats was estimated every 4–6 days.

The experiments were conducted using the isolated preparations of circular smooth muscles of rats' antrum, loaded with TiO_2. The registration of spontaneous contractibility of smooth muscle stripes (SMS) of *caecum* and myometrium was performed by the tenzometric method in the isometric mode with the following calculations: frequencies of preparation contractions for 10 min; averaged value of contraction-relaxation cycle;

duration of some contraction fragments: contraction phase, relaxation phase; asymmetry coefficient; Montevideo index of contractions (MU); Alexandria index (AU) of contractions. The method [4, 11] was also used to conduct the kinetic analysis of spontaneous contractions-relaxations of muscle preparations and the ones, induced by high potassium Krebs solution, with the estimation of normalized maximal velocities of contractions (V_{nc}) – relaxations (V_{nr}).

The performed experiments involved the use of normal Krebs solution (NRS) with the following concentration of components (in mmol/l): NaCl – 120.4; KCl – 5.9; $NaHCO_3$ – 15.5; NaH_2PO_4 – 1.2; $MgCl_2$ – 1.2; $CaCl_2$ – 2.5; glucose – 11.5; pH 7.4. High potassium Krebs solution with the concentration of K^+ ions (80 mmol/l) was prepared by replacing the required amount of Na^+ ions in standard Krebs with the equimolar amount of K^+ ions. Acetylcholine in concentration of 10^{-5} mol/l (Sigma-Aldrich) was also used in the experiments; gamma-aminobutyric acid (GABA) was used in oncentrations of (10^{-8}–10^{-5}) mol/l (Sigma-Aldrich).

Statistical analysis of the experiment results was performed using OriginPro 8 program. The unpaired version of Student's *t*-test was used to determine the reliable differences between the mean values of two samples. Multiple comparisons were performed using the parametric one-way ANOVA. The results were considered significant on condition of the probability value of p under 5 % ($p < 0.05$). The results were presented as the arithmetic mean ± standard error of the mean value, n – number of experiments.

The nanoparticles of TiO_2 (PlasmaChem GmbH, D-12489 Berlin, Germany) were used in the form of nanopowder (mixture of rutile and anatase) with the average size of particles (21±5) nm (Fig. 1). The measurements were conducted using the scanning electron microscope Tescan Mira 3 LMU, kindly provided for our work by NanoMedTech LLC) (Fig. 1), specific area (50±10) sq.m./g; purity > 99.5 %, content of Al_2O_3 < 0.3 wt; SiO_2 < 0.2 wt. The nanopowder of TiO_2 was previously resuspended in dimethylsulfoxide (DMSO) assuming the presence of 0.25 % DMSO in the final volume. Likewise, all the control solutions contained 0.25 % DMSO. The destruction of the aggregates of TiO_2 nanoparticles in the suspension was performed using the ultrasound processing for 2 min at the frequency of 37 kHz. The zeta-potential of TiO_2 nanoparticles, estimated using the Zetasizer nano device (kindly provided by NanoMedTech LLC), was (-7.93) mV.

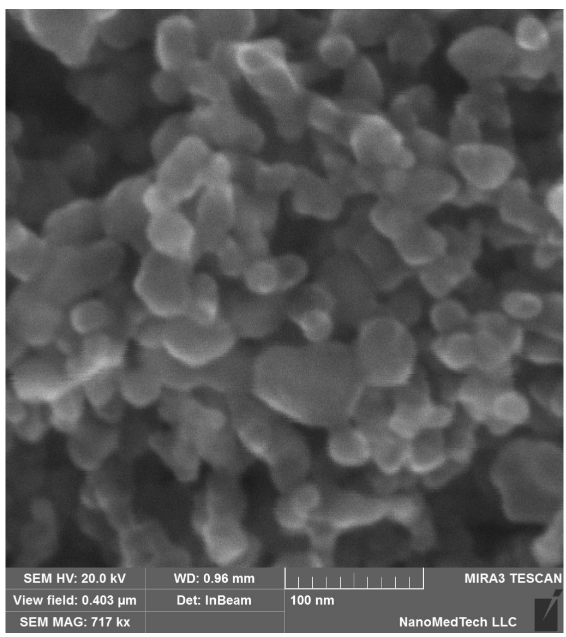

Fig.1. Micropicture of titanium dioxide nanoparticles
Рис.1. Мікрофотографія наночастинок діоксиду титану

RESULTS AND DISCUSSION

Our previous *in vivo* studies [20] demonstrated that TiO_2 used in nanosized form is an efficient modulator of the activity related to the functioning of pace-maker cells [6, 9, 23], spontaneous contractive activity of stomach smooth muscles of rats. The elemental analysis of the content of micro- and macro-elements in rat tissues [20] demonstrated that TiO_2 is bioavailable for cells of different organs, with the highest non-uniform accumulation in smooth muscles of gastrointestinal tract: in caecum and stomach. In this work, the tenzometric method in the isometric mode was used to study the spontaneous contractive activity of isolated smooth muscle stripes of circular smooth muscles of antrum of three groups of rats: control group (n = 6) and two groups of animals (6 per group), loaded with the suspension of nanosized TiO_2 material in the abovementioned concentration for 30 and 100 days. Similarly to the previous experiments, the duration of registration of spontaneous contractions in both groups of rats was 60 min. During this time period, the level of basal tone of muscle preparations remained stable. Fig. 2, *A* presents the results of tenzometric measurements in control and experimental groups of rats loaded with TiO_2. There was the distribution of amplitudes of spontaneous contractions of smooth muscles by frequencies with three significant maxima in the control. The contractions with the amplitude of (14.8±1.0) mN, n = 12.3 were registered with the highest frequency (13±0.8) %. The frequency of muscle preparation contractions, calculated in the control (Fig. 3), for 10 min was (12±0.6) %; the averaged value for the duration of the contraction-relaxation cycle (contraction act) was (48±3.4) s, the duration of some contraction fragments was as follows: contraction phase – (16.2±0.9) s, relaxation phase – (31.8±1.7) s; assymetry coefficient – (0.53±0.03); MU index of contractions – (143.8±7.2); AU index of contractions – (6900±483).

The following series of experiments involved the study of the changes in spontaneous contractive activity of stomach smooth muscles of rats, loaded with TiO_2 for 30 days (Fig. 2, *B*). In these conditions, compared to the control, in the dependency chart, “the amplitude of contractions – the frequency of the incidence of contractions with this amplitude”, there is a shift towards their smaller amplitudes with three significant peaks. The highest incidence (10.5±0.4) %, n = 12 was noted for contractions with the following amplitudes: (6.5±0.4) mN (two maxima) and (4.6±0.24) mN. The calculations of parameters of these spontaneous contractions (Fig. 3) demonstrated that in these conditions their frequency for 10 min, compared to the control, increases and amounts to (16±0.8) s; the duration of the contraction-relaxation cycle decreases almost 1.5 times and is (26.4±1.3) s. There was also a decrease in the duration of some contraction fragments: contraction phase – (11.2±0.7) s, relaxation phase – (15.2±0.9) s; asymmetry coefficient – (0.82±0.05); MU index of contractions – (93.6±6.5); AU index of contractions – (2470±148).

The study of spontaneous contractions of smooth muscle stripes of rats, loaded with TiO_2 suspension for 100 days, demonstrated (Fig. 2, *C*) that, compared to the control, there is further transformation of their amplitude-frequency characteristics. The amplitudes of such contractions cover the range from 3 to 6.5 mN, n = 12: the highest incidence (13.2±0.7) % was registered for contraction with the amplitude of (4.4±0.31) mN, as stated above, at the same frequency in the control its value was (14.8±1.0) mN, n = 12. The frequency of contractions of muscle preparations, calculated in these conditions for 10 min, was (19±1.2) %; the value of the contraction-relaxation cycle – (30±1.8) s; the duration of the relaxation phase of spontaneous contractions, the value

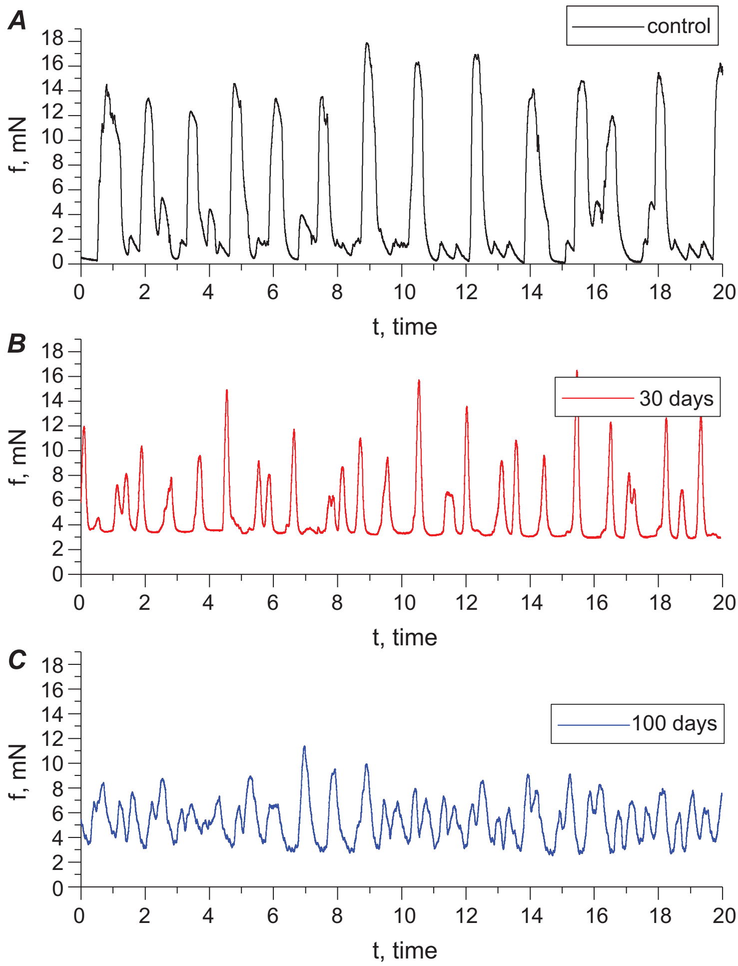

Fig. 2. Spontaneous contractive activity of circular smooth muscles of antrum of the control group rats (*A*) and the group of rats, burdened with the suspension of titanium dioxide for 30 (*B*) and 100 days (*C*).

Рис. 2. Спонтанна скорочувальна активність кільцевих гладеньких м'язів антрального відділу шлунка щурів контрольної групи (*А*) та групи щурів, навантажених суспензією діоксиду титану впродовж 30 (*В*) та 100 діб (*С*)

of which was (16.8±0.9) s continued decreasing, whereas the duration of the contraction phase had no statistically significant differences from the control. There is also noteworthy impairment of such an important index of spontaneous contractive activity, as asymmetry coefficient, at the effect of TiO_2 suspension in the rats of group two (duration of load with TiO_2 – 30 days) and three (duration of load with TiO_2 – 100 days): while in the control its value was (0.53±0.03), in group two – (0.82±0.05), in group three its value approximated 1 (1.07±0.06), which is likely related to the fact that this nanosized material modulates mutually coordinated mechanisms of increasing and decreasing the intracellular concentration of calcium ions in the interstitial cells of stomach smooth muscles, the pace-maker activity of which is known [23] to be determined by cyclic processes of releasing these cations from sarcoplasmic reticulum and their being absorbed by mitochondria. The fluctuation frequency of the processes is of the same order as pace-maker currencies and amplitude-frequency characteristics of spontaneous contractions of smooth muscles. The calculation of the MU index of contractions, the spontaneous contractive activity of muscle preparations of rats, loaded with TiO_2 for 100 days, demonstrated that this parameter was (92.4±6.5), and the AU index of contractions – (2772±138) which was almost 2.5 times less than the control. A considerable decrease in MU and AU indices, compared to the control, demonstrated that the overall effectiveness of contractive activity of stomach smooth muscles of rats in the presence of TiO_2 decreased.

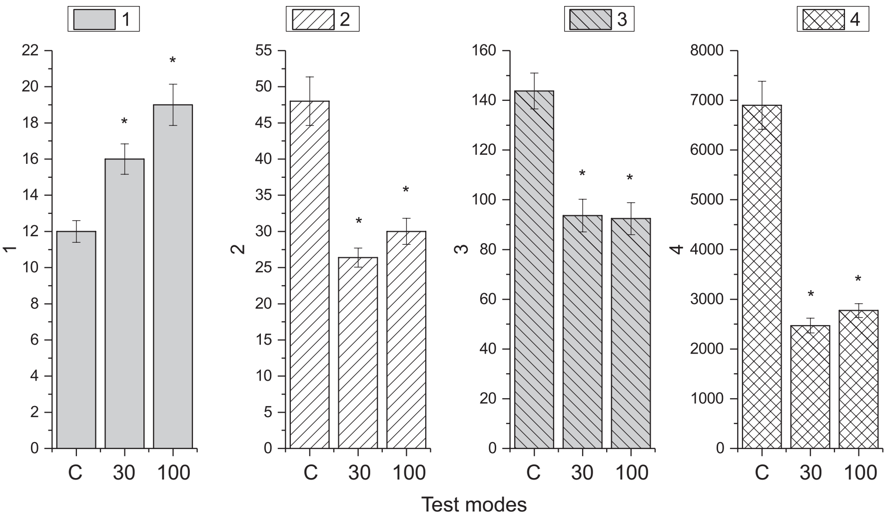

Fig. 3 Histograms of parameters of the kinetic analysis for spontaneous contractive activity of circular smooth muscles of antrum (C – control; 30 and 100 – term (days) of burdening the rats with the suspension of titanium dioxide nanosized material): 1 – frequency of preparation contractions during 10 min; 2 – averaged value of the duration of the contraction-relaxation cycle; 3 – MU index of contractions; 4 – AU index of contractions. * – $p<0.05$

Рис. 3. Гістограми параметрів кінетичного аналізу спонтанної скорочувальної активності кільцевих гладеньких м'язів шлунка (С – контроль; 30 та 100 – термін (діб) навантаження щурів суспензією нанорозмірного матеріалу діоксиду титану): 1 – частота скорочення препаратів за 10 хв; 2 – усереднене значення тривалості циклу скорочення–розслаблення (с); 3 – показник скоротливого індексу в одиницях Монтевідео; 4 – показник скоротливого індексу в Олександрійських одиницях. * $p<0,05$ – зміни вірогідні щодо контролю

Taking the abovementioned results into consideration, it was interesting to analyze the divergence in numerical values between some parameters of frequency-amplitude complexes of spontaneous contractive activity of circular smooth muscles of stomach and smooth muscles of *caecum*, modified by TiO_2 *in vivo* (the results of experimental studies *in vivo* using smooth muscles of *caecum* are presented in our work [20]). The calculations of the parameter value ratio (PVR) for the frequency-amplitude complexes of spontaneous activity of smooth muscles of stomach and *caecum* demonstrated considerable differences in the mechanisms of their formation. In control, these values for such parameters as contraction frequency, duration of contraction-relaxation cycle, AU index of contractions differed considerably for different muscles. The comparative analysis demonstrated that in the control the frequency of contractions of *caecum* preparations exceeded the same parameter for stomach smooth muscles considerably, and their ratio was far from 1, amounting to (0.27±0.01), n = 12. The value of this ratio was the same in conditions of loading the rats with TiO_2 for 30 and 100 days. As for PVR for such parameters as duration of contraction-relaxation cycle and AU index of contractions for the mentioned muscles, their difference in the values was also noted, especially for smooth muscles of rats, loaded with TiO_2 for 30 days. For instance, in control, PVR by the index of the duration of contraction-relaxation cycle was (3.8±0.2), n = 12, whereas at the effect of TiO_2 for 30 days it was twice higher. There was also a double increase in the PVR value for AU index of contractions compared to the control. Taking the abovementioned into consideration, it is possible to assume some differences in the mechanisms of the formation of spontaneous contractive activity of smooth muscles of stomach and intestines in the control and at the effect of TiO_2.

GABA is a neuromediator of both central and peripheral nervous systems [1, 2, 13]. Our studies [12] using the method of molecular docking of nanosized TiO_2 material to the extracellular part of GABA-receptor we have determined potentially probable sites of binding nanosized TiO_2 material of different affinity and analyzed the character of bonds, stabilizing them according to their amino acid composition. It is known [2, 8] that GABA-receptors ($GABA_A$ and $GABA_C$) of neurons of intramural nervous system are involved in NO-dependent regulation of functions of smooth muscles of gastrointestinal tract. It was interesting to study the participation of this neuromediator of non-adrenergic non-cholinergic neurons of stomach smooth muscles in the formation of the tonic component of high potassium contraction and its modulation with TiO_2. It was demonstrated (Fig. 4, *A*) that in response to the application of high potassium (80 mmol/l) solution, smooth muscle stripes developed contractions-relaxations with the phase component of (23±1.5) mN, n = 12; here, the ratio of the phase component of contraction to the tonic component was (1.3±0.08). The kinetic analysis of the curves for high potassium contraction and the calculations of normalized maximal velocities for separate contraction and relaxation phases demonstrated that such parameter as V_{nc} acquires the value of (7.7±0.4) min^{-1}, where as V_{nr} – (1.8±0.31) min^{-1}. Then, the plateau of the tonic component of high potassium contraction was consecutively applied high potassium solution in the abovementioned concentration with the content of GABA in the concentrations of (10^{-8}–10^{-5}) mol/l. It was determined (Fig. 4, *B*) that the application of GABA in these conditions was accompanied with fluctuations in the basic level of the tonic component of high potassium contraction according to acid concentration. The substitution of the abovementioned composition with normal Krebs solution was accompanied with the restoration of the initial level of the basal tone of muscle preparations. The study of changes in K^+-induced (80 mmol/l) contraction-relaxation of smooth muscle stripes of rats, loaded with the suspension of nanosized TiO_2 material for 30 days in the abovementioned concentration, demonstrated (Fig. 4, *C*) that its amplitude remained in the range of the control, whereas the velocity of relaxation increases (V_{nr} – (2.98±0.03) min^{-1}, n = 12), compared to the control. At the same time, the value of V_{nc} (6.16±0.61) min^{-1} remained unchanged. In these conditions, there was a decrease in the tonic component of high potassium contraction, accompanied with the decrease in the ratio of its components, which was (1.05±0.05), compared to the control. The application of GABA (10^{-8}–10^{-5}) mol/l on the tonic component of high potassium contraction was accompanied with insignificant increase in the level of its plateau (Fig. 4, *D*).

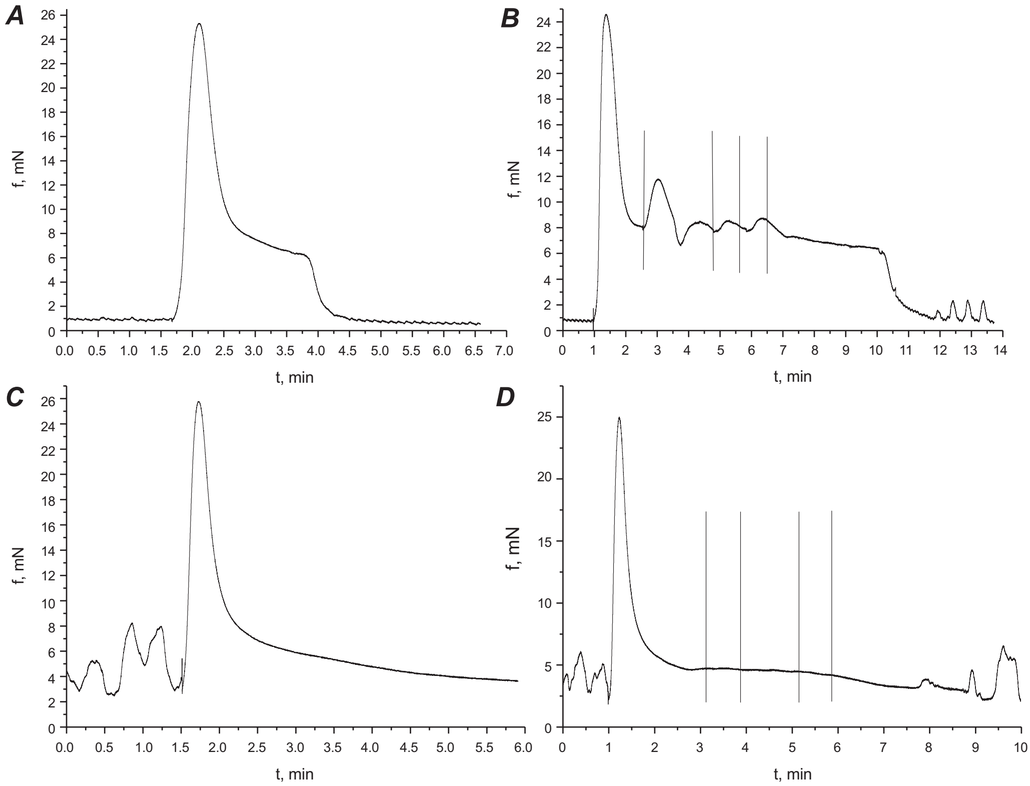

Fig. 4. High potassium (80 mmol/l) contraction (HPC) of circular smooth muscles of antrum of the control group rats (*A*); *B* – in conditions of application of gamma-aminobutyric acid (10^{-8}–10^{-5}) mol/l on the tonic component of this contraction; *C*, *D* – the same for the experimental group of rats, burdened with nanosized titanium dioxide material for 100 days

Рис. 4. Гіперкалієва (80 ммоль/л) контрактура кільцевих гладеньких м'язів антрального відділу шлунка контрольної групи щурів (*A*); *B* – за умов аплікації на тонічній складовій цього скорочення γ-аміномасляної кислоти (10^{-8}–10^{-5}) моль/л. *C*, *D* – те ж саме дослідної групи щурів, навантажених нанорозмірним матеріалом діоксиду титану впродовж 100 діб

It is known [3, 5] that acetylcholine, an agonist of muscarinic cholinoreceptors, participates in the parasympathetic control of contractive activity of smooth muscles along with inhibition neuromediators. Taking the abovementioned into consideration, the contraction of preparations of circular smooth muscles of antrum, activated by acetylcholine in the concentration of 10^{-5} mol/l, was registered in the work. It was determined (Fig. 5, *A*) that the averaged value of the phase component of such contraction was (26.3±1.8) mN, n=12, and its ratio to the tonic component – (1.25±0.07). Here the estimated maximal velocity of the contraction phase was (7.25±1.17) min^{-1}, whereas the normalized maximal velocity of the relaxation phase – (1.47±0.33) min^{-1}. Then, the plateau of tonic component of acetylcholine contraction was consecutively applied Krebs solution with the GABA in the concentrations of (10^{-8}–10^{-5}) mol/l (Fig. 5, *B*). It was determined that in these conditions there was an increase in the basic level of the tonic component, the plateau of which witnessed the increase in spontaneous contractions of smooth muscles. We also studied of acetylcholine-induced contractions of circular smooth muscles

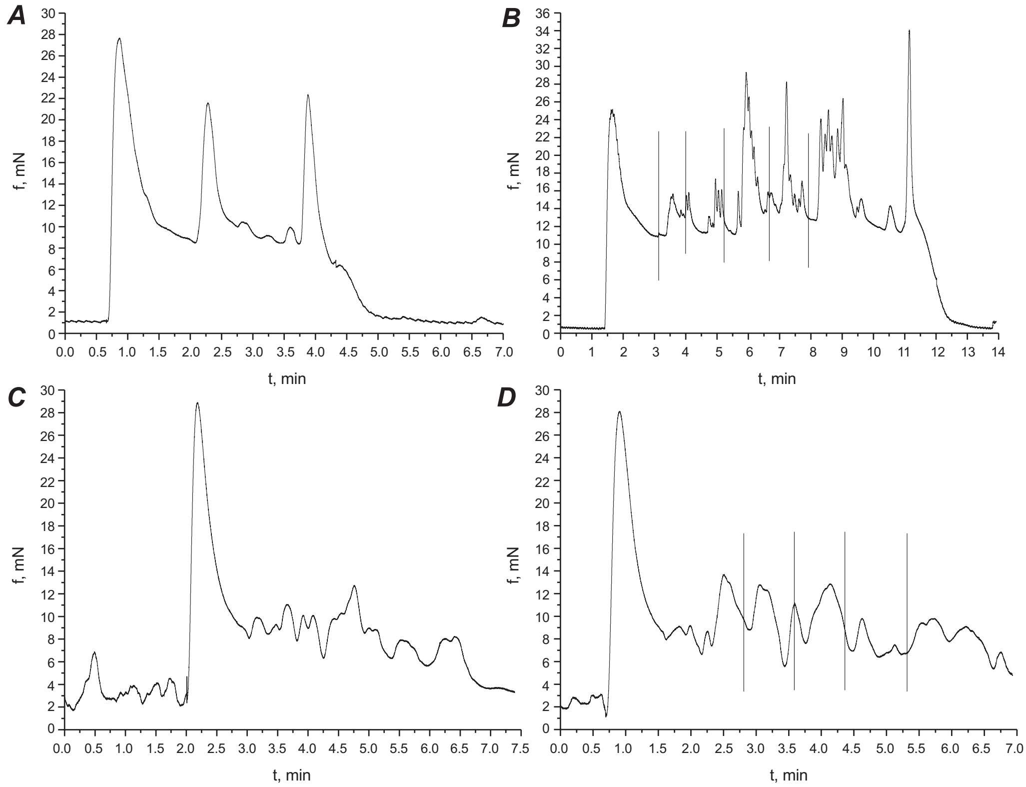

Fig. 5. Acetylcholine-induced (10^{-5} mol/l) contractions of circular smooth muscles of antrum of the control group rats (*A*); *B* – in conditions of application of gamma-aminobutyric acid (10^{-8}–10^{-5}) mol/l on the tonic component of this contraction; *C*, *D* – the same for the experimental group of rats, burdened with nanosized titanium dioxide material for 100 days

Рис. 5. Викликані ацетилхоліном (10^{-5} моль/л) скорочення кільцевих гладеньких м'язів антрального відділу шлунка контрольної групи щурів (А); *В* – за умов аплікації на тонічній складовій γ-аміномасляної кислоти (10^{-8}–10^{-5}) моль/л. *С*, *D* – те ж саме дослідної групи щурів, навантажених нанорозмірним матеріалом діоксиду титану впродовж 100 діб

of antrum (in the abovementioned concentration) of the group of rats (n = 6), which were loaded with the suspension of nanosized TiO_2 material for 100 days (Fig. 5, *C*). It was determined that, compared to the control group of animals, the value of the phase component of acetylcholine contraction of smooth muscles had no changes. The ratio of the phase component of acetylcholine contraction to its tonic component and the values of maximal velocities of contraction and relaxation for smooth muscle stripes also remained in the range of the control. The application of GABA in the abovementioned concentrations on the tonic component of acetylcholine of contractions caused no significant changes. For comparison, similar studies were conducted *in vivo* using smooth muscles of *caecum*. It was determined (Fig. 6, *A*, *B*) that in the control GABA (10^{-5}) mol/l, applied to the plateau of the tonic component of high potassium contraction, causes a considerable increase in its level, which exceeds the values of the similar parameter in stomach smooth muscles. Similarly to our previous studies [20], smooth muscles of *caecum*, loaded with TiO_2 for 30 days, had an increase in the phase component of high potassium contraction,

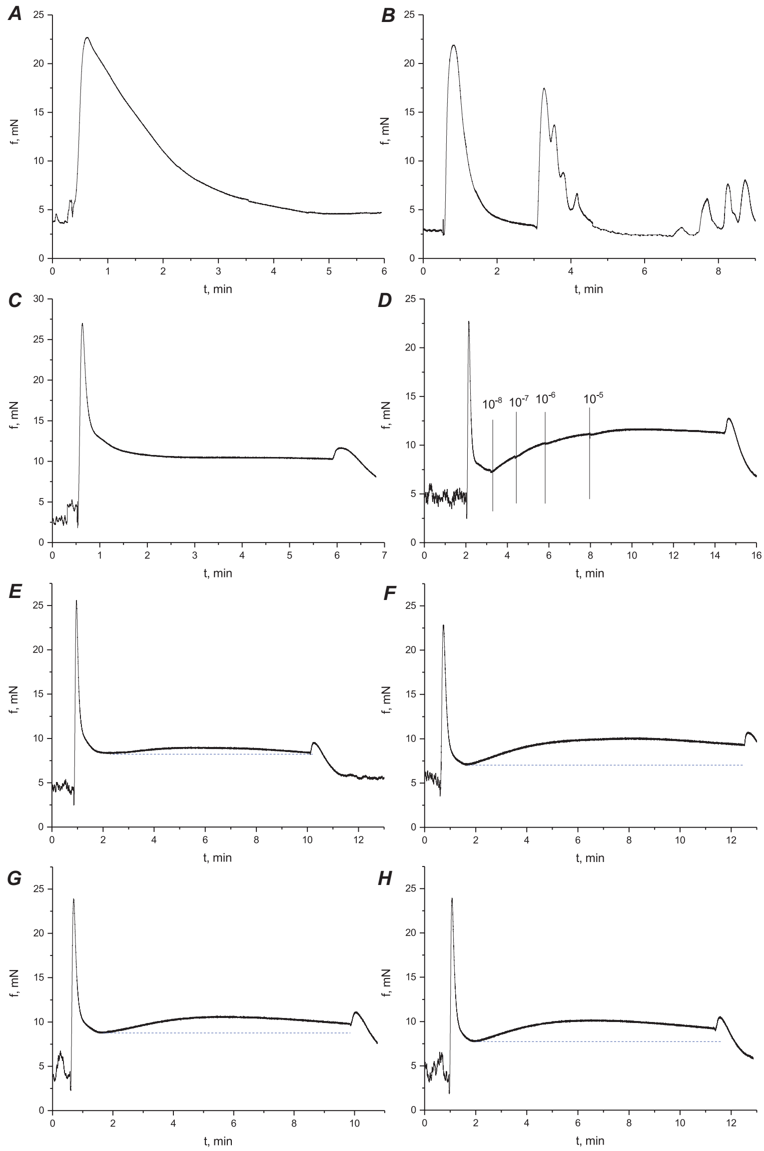

Fig. 6. High potassium (80 mmol/l) contraction of circular smooth muscles of antrum in the control group rats (*A*); *B* – in conditions of application of gamma-aminobutyric acid (GABA) (10^{-5}) mol/l on the tonic component of this contraction; *C*, *D* – the same for the experimental group of rats, burdened with nanosized titanium dioxide material for 30 days and the cumulative effect of GABA (10^{-8}–10^{-5}) mol/l in the same conditions; *E*, *F*, *G*, *H* – non-cumulative effect of GABA on the tonic component at the effect of TiO_2 for 30 days

Рис. 6. Гіперкалієва (80 ммоль/л) контрактура кільцевих гладеньких м′язів антрального відділу шлунка контрольної групи щурів (*A*); *B* – за умов аплікації на тонічній складовій цього скорочення γ-аміномасляної кислоти (ГАМК) (10^{-5}) моль/л. *C*, *D* – те ж саме дослідної групи щурів, навантажених нанорозмірним матеріалом діоксиду титану впродовж 30 діб та відповідно за даних умов кумулятивна дія ГАМК (10^{-8}–10^{-5}) моль/л; *E*, *F*, *G*, *H* – некумулятивна дія ГАМК на тонічну складову за дії TiO_2 упродовж 30 діб the increase in the normalized maximal velocity of the contraction phase and relaxation phase compared to the control group of rats, and the increase in the ratio of the phase component and the tonic component (Fig. 6, *C*). The data of the cumulative effect of GABA in the concentrations of (10^{-8}–10^{-5}) mol/l on the tonic component of high potassium contraction of *caecum* in the control group of rats, presented in Fig. 6, *D*, demonstrate a considerable increase in the level of its plateau. Thus, the obtained data of experimental studies testify to the relevant role of the mediator of intramural nervous system, nitrogen oxide, in the mechanisms of relaxation of smooth muscles of *caecum* and stomach, activated with high potassium solution or acetylcholine. Similar to stomach smooth muscles of rats, loaded with TiO_2 for 100 days, in smooth muscles of caecum this nanosized material removes the mechanisms of inhibiting the release of NO from neurons of intramural nervous system, mediated via $GABA_A$ and $GABA_C$ receptors.

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НАНОРОЗМІРНИЙ МАТЕРІАЛ ДІОКСИДУ ТИТАНУ. МОДУЛЯЦІЯ СПОНТАННОЇ МОТОРИКИ ТА ГАМК-ЗАЛЕЖНОЇ РЕГУЛЯЦІЇ ФУНКЦІЙ ГЛАДЕНЬКИХ М'ЯЗІВ ШЛУНКА *IN VIVO*

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Застосування електронної скануючої мікроскопії дало змогу одержати зображення та визначити розміри наночастинок TiO_2. Тензометричним методом в ізометричному режимі встановлено, що результатом хронічної дії діоксиду титану на гладенькі м'язи шлунка є перерозподіл амплітуд спонтанних скорочень за їх частотами, збільшення частоти їх скорочень, зменшення тривалості циклу скорочення–розслаблення, порушення асиметрії тривалості розвитку скорочення–розслаблення, зменшення показника скоротливого індексу Монтевідео та показника скоротливого індексу в Олександрійських одиницях. У роботі з'ясовано також розходження чисельних значень параметрів частотно-амплітудних комплексів, модифікованої TiO_2 спонтанної скорочувальної активності гладеньких м'язів шлунка та гладеньких м'язів кишечника (*caecum*). Встановлено, що за умов тривалої хронічної дії (100 діб) у гладеньких м'язах шлунка та *caecum* діоксид титану усуває опосередковані через $ГАМК_A$- та $ГАМК_C$-рецептори регуляторні механізми пригнічення вивільнення нейромедіаторів гальмування з нейронів інтрамурального нервового сплетення.

Ключові слова: гладенькі м'язи шлунка, наночастинки діоксиду титану, механокінетика, ГАМК-залежна регуляція, спонтанні та викликані скорочення.

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