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MODULATION OF RAT AORTIC CONTRACTIONS BY ULTRADISPERSE TiO_2 NANOPARTICLES OF CRYSTALLINE FORMS OF ANATASE AND RUTILE

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Background. The nanopowder of titanium dioxide (TiO_2) is among the most demanded industrial nanomaterials; thus, it is widely used in the food industry, medicine, cosmetics production, and agriculture. It creates preconditions for constant, daily input of these particles into the organism. TiO_2 nanoparticles are known to impact the functioning of the vascular endothelium cells, changing their response to acetylcholine. However, there is almost no information about possible effects of this nanomaterial on the processes of inducing the contractile function of the vessels, using epinephrine and the activation of voltage-gated Ca^{2+}-channels. Another interesting issue is the study of polymorph-dependent effects of TiO_2 nanoparticles (NPs).

This study was aimed at investigating the effect of ultradisperse TiO_2 nanoparticles of crystalline forms of anatase and rutile on the contractions of smooth muscle preparations of rat aorta, induced by the depolarization of the plasma membranes of myocytes and epinephrine-activated contractions.

Materials and Methods. The commercial preparations of TiO_2 nanoparticles (PlasmaChem GmbH, D-12489 Berlin, Germany) in the form of nanopowder with the average size of particles of 1–3 nm (crystalline form of rutile) and 4–8 nm (crystalline form of anatase) were used in the study. The determination of the average hydrodynamic diameter of TiO_2 nanoparticles in the suspension involved the method of dynamic light scattering.

The tenzometric experiments were conducted in the isometric and isotonic registration modes using the rings of rat thoracic aorta with preserved endothelium. The contractions of aortic isolated preparations were induced by the application of a high-potassium solution (80 mM), the activator of L-type voltage-gated Ca^{2+}-channels Bay K8644, and a non-selective agonist of adrenoreceptors, epinephrine. The contractions were analysed by the methods of mechanokinetic analysis with the estimation of maximal velocities of the contraction and relaxation phases.

Results. It was determined that both polymorphs of TiO_2 (at the fixed concentration of 10^{-4} mg/mL and 30 min pre-incubation) equally (approximately by one-third) activated the isometric and isotonic contractile responses of the aortic isolated preparations to the application of the high-potassium solution (80 mM) and the activator of Ca^{2+}-channels Bay K8644 (5 μM). In all cases, the parameters of the normalized maximal velocities of the phases of contraction and relaxation (Vn_C and Vn_R) remained at the control level. It was also found that under similar conditions of application, both types of TiO_2 NPs equally (more than twice as compared to the control) inhibited the amplitude of epinephrine-induced (1 μM) contractions of the aortic preparations.

Conclusions. Ultradisperse TiO_2 NPs in a polymorph-independent manner enhance aortic contractions in the case of potential-dependent input of Ca^{2+} ions. These nanoparticles also induce the inhibition of catecholaminergic contractions of aortic smooth muscles, which may occur due to the chelating of catecholamines by TiO_2.

Keywords: aorta, ultradisperse nanoparticles of titanium dioxide, voltage-gated Ca^{2+}-channels, epinephrine, mechanokinetic parameters

INTRODUCTION

Modern industrial technologies envisage active application of micro- and nanomaterials. These compounds have unique physical and chemical properties, which make them irreplaceable, for instance, in the energy sector and machine-building (Eker *et al.*, 2024). At present, nanomaterials are also actively used in the production of food, medical preparations, cosmetics, and agriculture. One of the most commonly applied nanopowders is titanium dioxide (TiO_2), which is the main pigment of white color. The global volumes of TiO_2 production amount to over 6 million tons a year (Khan *et al*., 2025). Although the larger part of the produced TiO_2 powder is used in plastic, paper, and rubber production, about 10% of its total produced volume is used in food, medical, and cosmetic industries. In particular, TiO_2 material as a food additive received a code E171; it is used to color many food products, tablets, different creams, and toothpastes white. Also, since TiO_2 is a biocompatible material, it is used in the production of orthopedic and dental implants.

Therefore, there are objective prerequisites for considerable constant input of TiO_2 into the organism and its accumulation in the tissues and organs. For instance, while fifteen years ago, the approximate daily consumption of E171 with food in industrially developed countries was 0.2–0.7 mg/kg for adults and 1–2 mg/kg for children, in 2021, it increased to the indices of 6.7 mg/kg and 11.5 mg/kg respectively (Weir *et al*., 2012; Khan *et al*., 2025). According to the data of B. Jovanović (Jovanović, 2015), less than 1% of digested TiO_2 penetrates the inner environment of the organism, yet the prerequisites are created for considerable accumulation of this material in the organism tissues. It is noteworthy that industrially produced powder E171 contains at least one-third of

nanosize particles of TiO_2 (Silva *et al*., 2013; Musial *et al*., 2020), so their small size allows for enhanced possibilities to penetrate the inner environment of the organism.

A large volume of information about the biological effects and mechanisms of TiO_2 toxicity, including genotoxicity and carcinogenicity, has been accumulated. Therefore, since January 2022, it has been prohibited to use E171 as a food additive in the European Union, while in other countries of the world, this additive is still used (Shabbir *et al*., 2021; Baranowska-Wójcik *et al*., 2022; Khan *et al*., 2025). The main reason for TiO_2 toxicity is its high ability to enhance the production of reactive oxygen species (ROS) in cells, to cause oxidative stress, and induce apoptosis (Baranowska-Wójcik *et al*., 2022; Khan *et al*., 2025; Pokharkar *et al*., 2025). Due to the effect of TiO_2 nanoparticles (NPs), there are impairments of some intracellular signalling pathways, as shown using the models of nervous cells, for instance; there is also excessive activation of signalling pathways p38-Nrf-2 and ERK1/2/MAPK with the inhibition of brain-derived neurotrophic factor – tropomyosin kinase receptor B (BDNF-TrkB) instead (Domingues *et al*., 2024; Tripathy *et al*., 2025). Also, TiO_2 NPs can activate tumor metastases (Mu *et al*., 2023).

TiO_2 material can be present in three crystalline forms: rutile, anatase, and brookite (Domingues *et al*., 2024; Khan *et al*., 2025). In the industry, E171 is mostly obtained by chemical methods, which lead to the formation of particles in the form of rutile or a mixture of anatase and rutile (Jovanović, 2015; Tripathy *et al*., 2025). TiO_2 NPs in the form of anatase can activate a considerably higher rate of ROS generation (Duan *et al.*, 2023); however, in some cases, higher cytotoxicity was found in NPs of the rutile form (Cheng *et al*., 2021; Hadrup *et al*., 2024).

It is known that in the case of the dominant pathway of penetrating the organism via the digestive system, TiO_2 NPs overcome the intestine barrier, causing changes in the motility regulation mechanisms for smooth muscles in the stomach and intestines (Tassinari *et al*., 2023; Tsymbalyuk *et al*., 2019, 2023), then they spread along the blood circulation system. While interacting with the endothelium of the vascular walls, TiO_2 NPs cause inflammation and dysfunctional impairments, an increase in the ROS rate and inhibition of nitrogen oxide synthesis (Chen *et al*., 2013; Cao *et al*., 2018). So far, the results of only several studies aimed at investigating the effect of these NPs on the contractile function of the vessels have been published (LeBlanc *et al*., 2009; Nurkiewicz *et al*., 2009; Loft & Møller, 2011; Mikkelsen *et al*., 2011; Jensen *et al*., 2018). For instance, the *in vitro* and *in vivo* investigations of rats (with peroral intake of TiO_2 NPs) found enhanced responses in the aortic rings – acetylcholine-induced vasodilation and serotonin-induced vasoconstriction (Jensen *et al*., 2018). The opposite effects regarding acetylcholine vasodilation were obtained using the segments of the murine aorta with atherosclerosis, induced by the knockout of apolipoprotein E (in case of inhaling administration of TiO_2 NPs) (Mikkelsen *et al*., 2011). The preparations of subepicardial arterioles of rats, which were administered TiO_2 NPs by inhalation, were used to determine the increase in spontaneous tone and the inhibition of vasodilation, induced by acetylcholine or caused by high concentrations of Ca^{2+}-ionophore A23187 (LeBlanc *et al*., 2009). Similarly, a considerable inhibition of the response to A23187 was observed in the preparations of arterioles of the spine trapezius muscle of rats, which were administered TiO_2 NPs by inhalation. There was also a considerable inhibition of the response to A23187, and, under the action of ultradisperse NPs – the inversion of A23187 effect from relaxation to contraction (Nurkiewicz *et al*., 2009). The model of human aortic myocyte culture was used to demonstrate that TiO_2 NPs can affect

the functioning of the smooth muscle cells of vascular walls, leading to a considerable increase in the reactive oxygen species (ROS) synthesis, the accumulation of Zn^{2+} ions in cells, and the stress of sarcoplasmic reticulum (Wang *et al*., 2018).

Thus, despite the current accumulation of a significant amount of data from *in vivo* and *in vitro* studies, and regularities of pharmacokinetics and pharmacodynamics of TiO_2 NPs, some regularities and mechanisms of their effect on specific organism tissues are yet to be fully elucidated. For instance, the issue of the possible impact of TiO_2 NPs on the contractile function of vessels induced by the depolarization of the plasma membrane of myocytes and epinephrine is yet to be solved.

The aim of this study was to investigate the effects of ultradisperse TiO_2 nanoparticles of crystalline forms of anatase and rutile on the contractions of smooth muscle preparations of rat aorta, induced by the depolarization of the plasma membranes of myocytes and epinephrine-activated contractions.

MATERIALS AND METHODS

Characterization of NPs and preparation of their suspensions. Commercial preparations of TiO_2 NPs (PlasmaChem GmbH, D-12489 Berlin, Germany) in the form of nanopowder with the average size of particles of 1–3 nm (crystalline form of rutile) and 4–8 nm (crystalline form of anatase) were used in the study. To prepare the stock solutions of TiO_2, their nanopowders were re-suspended in the distillate in the concentration of 1 mg/mL, mixed using the laboratory shaker Vortex4 and treated with ultrasound for 5 min.

To determine the average hydrodynamic diameter of TiO_2 NPs in the suspension, we used the method of dynamic light scattering with the laser correlation spectrometer "ZetaSizer-3" (Malvern Instruments, Great Britain), equipped with He-Ne laser LGN-111 (P = 25 mW, λ = 633 nm; the measuring range of the device is from 1 nm to 20 μm). The registration and statistical processing of the laser irradiation, dissipated from aqueous (n = 1.33) suspension of NPs, were conducted five times in the course of 60 s at the temperature of +22 °C under the dissipation angle of 90°. The obtained results of the measurements were processed using PCS-Size servicing software, mode v1.61.

Aortic rings preparation and tenzometric studies. The studies were conducted using Wistar rats which were kept with a standard diet and under standard conditions: temperature of 20±2 °C, relative air humidity 50–70%, light regime – light:darkness = 12:12 h. All the manipulations with the animals were conducted according to the International Convention for the Protection of Animals and the Law of Ukraine "On Protection of Animals from Cruelty" (the Minutes of the meeting of bioethics commission of SSC Institute of Biology and Medicine No. 8 dated December 26, 2024). The animals were euthanized by the displacement of cervical vertebrae after combined anesthesia with thiazol and xylazine.

The tenzometric experiments were conducted using the rings of the rat thoracic aorta with preserved endothelium. Aortic rings (2–3 mm wide) were placed into the working chamber (the volume of 2 mL) with the flowing Krebs solution (the flow rate of 8 mL/min), and thermostated at 37 °C. The preparations were provided with passive tension at the rate of 10 mN and left at least for 1 h. The contractile activity was studied in the isometric mode (using the force sensing device) and the isotonic mode (using the movement sensing device). The signals were registered with an analogue-to-digital transformer.

Krebs solution was used in the experiments (mM): 120.4 NaCl; 5.9 KCl; 15.5 $NaHCO_3$; 1.2 NaH_2PO_4; 1.2 $MgCl_2$; 2.5 $CaCl_2$; 11.5 glucose; pH of the solution was 7.4. The high-potassium solution (HPS), containing K^+ ions in the concentration of 80 mM, was prepared by isotonic replacement of the required amount of Na^+ ions in the initial Krebs with the equimolar amount of K^+ ions. The non-selective agonist of adrenoreceptors, a neurotransmitter epinephrine (in the applied concentration of 1 μM, Sigma) and the agonist of voltge-gated Ca^{2+}-channels of L-type, Bay K8644 (in the applied concentration of 5 μM, Sigma) were used in the study.

The stock solutions of TiO_2 NPs (1 mg/mL) were prepared by re-suspending with the laboratory shaker in the distillate, with the subsequent treatment with ultrasound for 5 min. The aliquotes of the stock solutions were added to the working solutions (the normal Krebs and high-potassium solutions) and applied in a concentration of 100 μg/mL.

Mechanokinetic analysis of contractions. Since the aorta generates contractile responses, which slowly (up to 30 min) reach the maximal value, these were determined three minutes after the contraction activation to ensure a unified comparison of the amplitude parameters of F_{max} and ΔL_{max}.

The contractions of the aortic preparations, registered in the isometric mode, were analyzed according to the method of multiparameter analysis of the complex mechanokinetic analysis (Kosterin *et al*., 2021). To analyze the complete profile of single spontaneous contractions, they were linearized in the coordinates $\left[\ln\left(\frac{F_R}{F_C}\right); \ln + \Delta t/t\right]$, where F and t – instant values of force and time at the level of the contraction cycle (C and R – symbols for the phases of contraction and relaxation, respectively), F_C and F_R – the values of the force at the inflexion points of the mechanogram at the level of the phases of contraction (from the beginning of the increase in the force to its maximal value F_{max}) and relaxation (from the maximal value of the force F_{max} at the time moment τ_0 and until its return to the basal level), Δt – arbitrarily fixed time interval (which varied within 15–50 s). The linearization charts were used to determine the characteristic constants k and n, which were further used to calculate the parameters: force (F_{max}, F_C and F_R) and velocity (V_C and V_R). Here V_C *and* V_R – maximal velocities of the phases of contraction and relaxation, respectively.

The contractions of the aortic preparations, registered in the isotonic mode, were analyzed according to the method of complex mechanokinetic analysis (Kosterin & Tsymbalyuk, 2023). To analyze the complete profile of single spontaneous contractions, they were linearized in the coordinates $\left[\ln\left(\frac{L_R}{L_C}\right); \ln + \Delta t/t\right]$, where L and t – instant values of length (diameter of aortal ring) and time at the level of the contraction cycle (C and R – symbols for the phases of contraction and relaxation, respectively), L_C and L_R – the values of the contraction (shortening) of the muscle preparation at the inflexion points of the mechanogram at the level of the phases of contraction (from the beginning of the contraction to its maximal value L_{max}) and relaxation (from the maximal value of the contraction ΔL_{max} at the time moment τ_0 and until its return to the length of the preparation at rest, to the basal level), Δt – arbitrarily fixed time interval. The linearization charts were used to determine the characteristic constants k and n, which were further used to calculate the parameters: contraction (ΔL_{max}, ΔL_C and ΔL_R) and velocity (V_C and V_R). Based on the analytical dependencies, which involved the indices n, k and the amplitude, the

energy parameters of contractions were estimated: $\Delta A_{max} = \Delta A_{\tau 0}$, τ_C, the averaged power N_m at the level of the contraction phase, the maximal power $N_{max} = N$.

The method of kinetic analysis, elaborated by Kosterin–Burdyga, was also used in the study (Burdyga & Kosterin, 1991). During the analysis, the phases of contraction and relaxation were separately linearized within the coordinates $\left\{\ln\left(\frac{f_m - f}{f}\right); \ln t\right\}$; the linearized charts were used to determine τ and n, further used to estimate the normalized maximal velocities of the phases of contraction (V_{nc}) and relaxation (V_{nr}), which did not depend on the amplitude of contractile responses.

Statistical analysis. The experimental data were processed by variation statistics methods using OriginPro 2018 program. The samples were checked in terms of belonging to normally distributed general populations according to Shapiro–Wilk's test. The one-way analysis of variances (ANOVA) with multiple post-hoc comparisons with Turkey test was used to determine reliable differences between the mean values of samplings. The results were considered significant on the condition of the probability value $p < 0.05$. The validation analysis of data approximation while using the mechanokinetic analysis method by the linear function was performed using Fisher's criterion; determination coefficients (R^2) were at least 0.96 in all cases. The results were presented as the arithmetic mean ± standard error of the mean value, n – number of experiments.

RESULTS AND DISCUSSION

The characteristics of suspensions of TiO_2 nanoparticles. The study using the method of dynamic light scattering determined that both samplings of TiO_2 NPs formed stable monodisperse systems (**Figs. 1** and **2**). For instance, the average hydrodynamic diameter of rutile NPs in the aqueous suspension was 33.2 nm, and its distribution in terms of sizes was as follows: the largest number (44.3 %) of particles –16.7 nm, 20.0 % of particles – 10.6 nm, 29.2 % of particles – 26.1 nm, and the hydrodynamic diameter of the remaining 6.5% was more than 26.1 nm (**Fig. 1**).

NPs with the certified size of 4–8 nm (the crystalline structure of anatase) in the aqueous solution were characterized by the average value of the hydrodynamic diameter of 8.9 nm (**Fig. 2**). In terms of sizes, its distribution was as follows: the largest number (40.9 %) of particles – 7.5 nm, 17.8 % of particles – 5.5 nm, 30.0 % of particles – 10.3 nm and the hydrodynamic diameter of the remaining 11.4% was larger, but not exceeding 36.1 nm (**Fig. 2**).

Also, NPs of the certified size of 1–3 nm (polymorph rutile) were characterized by some aggregation, while the aggregation of the particles of 4–8 nm (polymorph anatase) was minimal. In both cases, the suspended NPs corresponded to the ultradisperse NPs (Calderón-Garcidueñas & Ayala, 2022).

The contractions of aortic isolated preparations, induced by the input of the extracellular Ca^{2+}, at the effect of TiO_2 NPs, polymorphs rutile (1–3 nm) and anatase (4–8 nm). The main pathway of activating the excitation of myocytes in the vascular wall is the potential-dependent input of Ca^{2+} ions from the extracellular space, i.e. so called electromechanical excitation–contraction coupling (Eckert *et al*., 2000). A convenient model for its investigation is the depolarization of the plasma membrane of myocytes using the high-potassium solution.

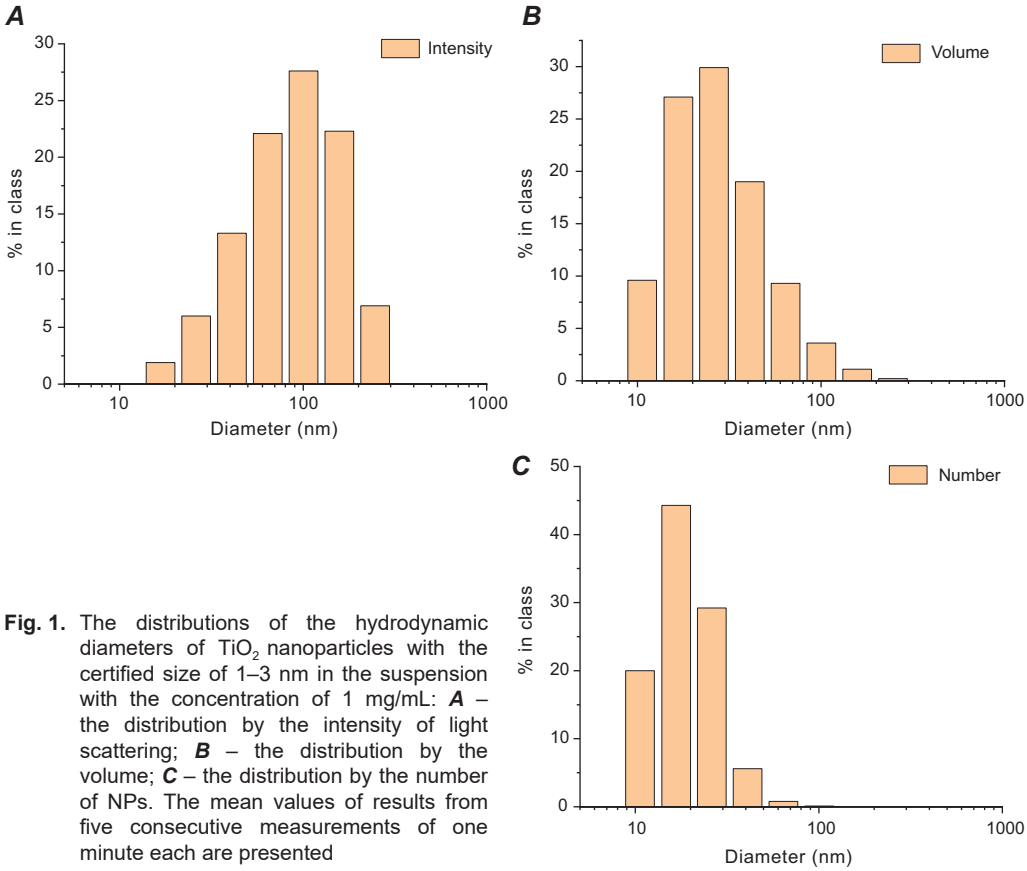

Fig. 1. The distributions of the hydrodynamic diameters of TiO_2 nanoparticles with the certified size of 1–3 nm in the suspension with the concentration of 1 mg/mL: ***A*** – the distribution by the intensity of light scattering; ***B*** – the distribution by the volume; ***C*** – the distribution by the number of NPs. The mean values of results from five consecutive measurements of one minute each are presented

The addition of the suspensions of TiO_2 NPs of both polymorph forms (both in the concentration of 10^{-4} mg/mL) to the washing solution and the preliminary incubation for 30 min did not cause any changes in the basal tension and the diameter of aortic isolated preparations at rest in the case of isometric and isotonic modes of registration.

However, under the action of both types of TiO_2 NPs, activation of isometric and isotonic contractions of preparations in response to the application of the high-potassium solution (80 mM) was observed (**Fig. 3**). In all modes of registration and polymorph forms of NPs, the magnitude of the activation of contractions was significant ($p < 0.05$) and, as compared to the control values, amounted to: for isotonic contractions – 137.2±10.5 % (at the background of NPs of 1–3 nm) and 127.4±4.6 % (at the background of NPs of 4–8 nm) and for isometric contractions – 121.8±5.3 % (at the background of NPs of 1–3 nm) and 159.5±12.4 % (at the background of NPs of 4–8 nm) (**Fig. 4**, **6**).

Further on, to get a deeper understanding of the changes in the dynamics of the force and contraction at the effect of TiO_2 NPs and to foresee possible cell targets for the action of this xenobiotic, the mechanograms of the contraction-relaxation cycles were analyzed using the methods of the mechanokinetic analysis (Burdyga & Kosterin, 1991; Kosterin *et al*., 2021; Kosterin & Tsymbalyuk, 2023). It was determined that both polymorphs of TiO_2 equally (and similar to the amplitude values of ΔL_{max}) increased the parameters of aortic preparation contraction at the inflexion points of the mechanogram at the level

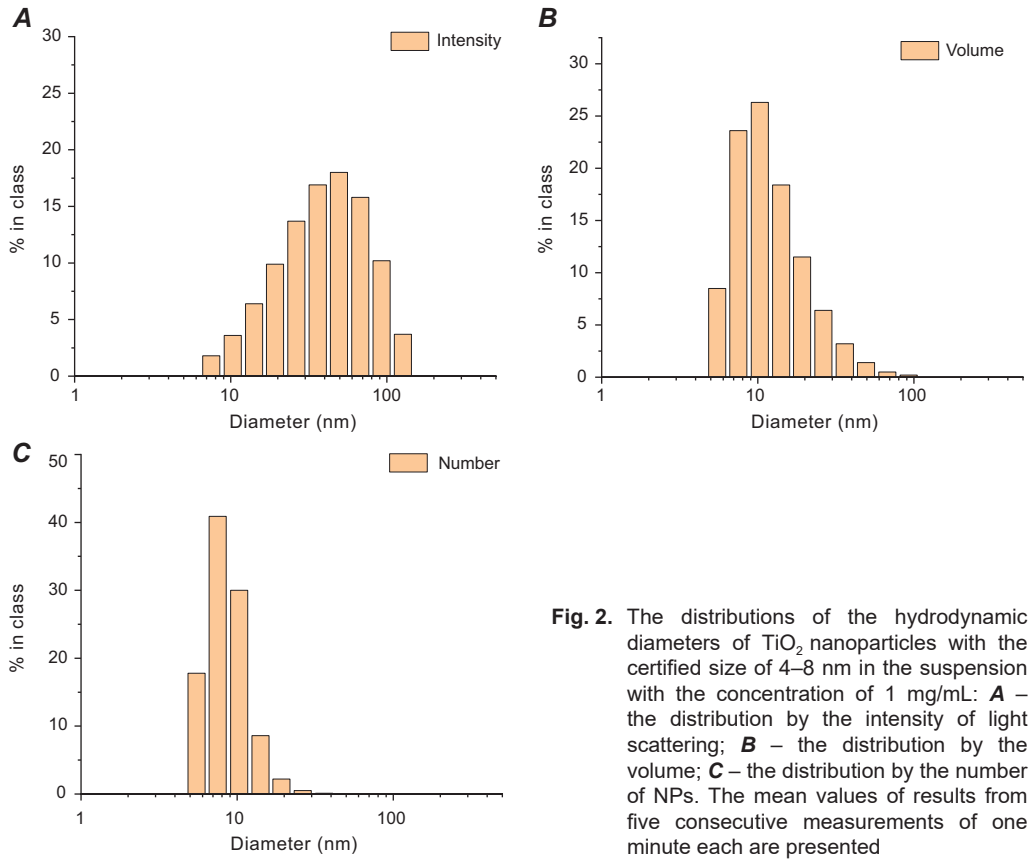

Fig. 2. The distributions of the hydrodynamic diameters of TiO_2 nanoparticles with the certified size of 4–8 nm in the suspension with the concentration of 1 mg/mL: ***A*** – the distribution by the intensity of light scattering; ***B*** – the distribution by the volume; ***C*** – the distribution by the number of NPs. The mean values of results from five consecutive measurements of one minute each are presented

of the phases of contraction and relaxation (L_C and L_R, respectively) (**Fig. 4*A***). There were differences between the effects of polymorphs on the parameters of the maximal velocities of the phases of contraction and relaxation (Vn_C and Vn_R) of the isotonic contractions: in case of rutile of 1–3 nm, there was an equal increase in both velocities (by one-third, on average), while at the effect of anatase NPs of 4–8 nm, the velocities did not significantly differ from the control values (**Fig. 4*B***).

The energy parameters were also estimated for the isotonic contractions of aorta, induced by the high-potassium solution in the control, and under the effect of TiO_2 NPs. It was determined that at the effect of both polymorphs of TiO_2, there was a considerable increase in both work indices (maximal ΔA_{max} and average ΔA_m). The power indices (except for the maximal power N_{max} against the background of rutile NPs) remained at the level of control values (**Fig. 5**).

Similarly to the isotonic contractions, there was a reliable increase in all the power parameters for the isometric contractions of aortic smooth muscle isolated preparations under the effect of rutile and anatase nanoparticles (**Fig. 6**). Contrary to the isotonic contractions, in the isometric mode of registration, TiO_2 NPs did not change the velocity parameters (V_C and V_R) of the contractions induced by the high-potassium solution. Yet, in the case of the maximal velocities normalization regarding the amplitude of contractions in both modes of registering the contractile activity of the aorta, we did not observe any considerable differences as compared to the control values (**Fig. 4*C*** and **6*C***).

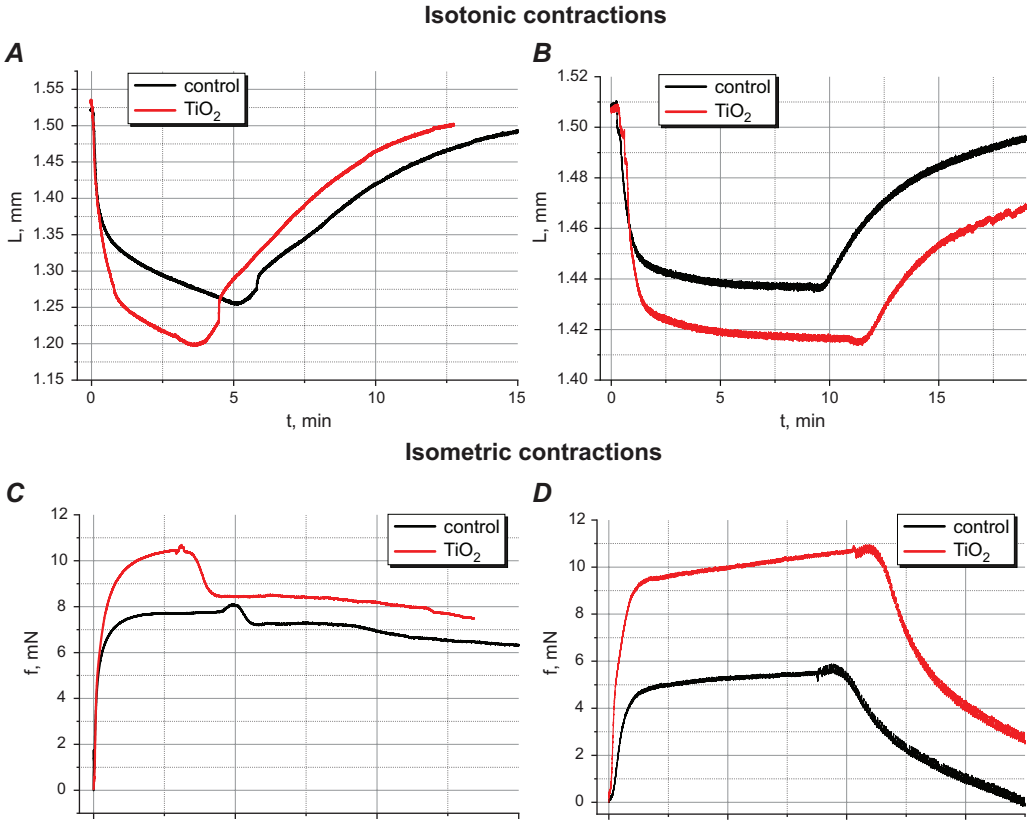

Fig. 3. The typical mechanograms of isotonic (***A*** and ***B***) and isometric (***C*** and ***D***) contractions of the isolated preparations of rat aorta, induced by the application of the high-potassium solution (80 mM), at the control and preliminary effect of TiO_2 nanoparticles (10^{-4} mg/mL, the preincubation throughout of 30 min): ***A*** and ***C*** – at the background of the NPs suspension of 1–3 nm (rutile); **B** and ***D*** – at the background of the NPs suspension of 4–8 nm (anatase)

Thus, under the effect of TiO_2 NPs with the average size of 1–3 nm (rutile) and 4–8 nm (anatase) there was an increase in the contractions, activated by the depolarization of the plasma membrane in smooth muscle cells, which showed no critical differences by the amplitude (F_{max}, F_C and F_R; ΔL_{max}, ΔL_C and ΔL_R) and velocity (Vn_C and Vn_R) parameters. These effects allow us to infer that TiO_2 NPs increase the voltage-gated input of Ca^{2+} ions from the extracellular space in a polymorph-independent manner (Eckert *et al*., 2000). It is known that in the plasma membrane of the aortic myocytes, there are voltage-gated Ca^{2+}-channels of L- and T-types which get activated under these conditions and determine the predominant contribution into the processes of activation of the contractile response of the muscle preparations (Wani *et al*., 2018, 2020). This assumption may be confirmed by the investigations (Nurkiewicz *et al*., 2008) that found a considerable decrease in the vasodilation response to the introduction of Ca^{2+}-ionophore A23187 in the arterioles of the spinal trapezius muscle of rats (the animals were administered thin-disperse and ultradisperse TiO_2 NPs by inhalation) up to the change in the response of the vessels to the vasoconstriction, due to the activation of the Ca^{2+} input into the myoplasm at the effect of TiO_2.

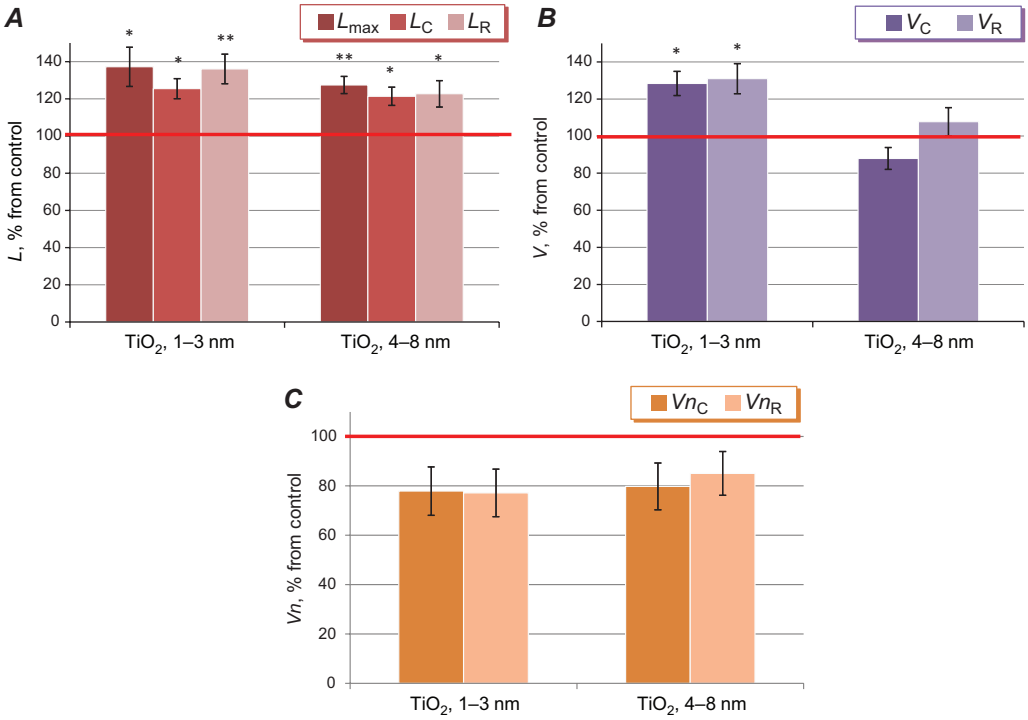

Fig. 4. The relative changes in the parameters of the isotonic contractions of the rat aortic isolated preparations, caused by the application of the high-potassium solution (80 mM) at the preliminary effect of TiO_2 nanoparticles with the average sizes of 1–3 nm (rutile) and 4–8 nm (anatase) (10^{-4} mg/mL, the pre-incubation throughout of 30 min): ***A*** – contraction parameters (ΔL_{max}, ΔL_C and ΔL_R); ***B*** – velocity parameters (V_C and V_R); ***C*** – normalized maximal velocities of the phases of contraction and relaxation (Vn_C and Vn_R). The parameters of muscle contractions in the control were taken as 100 %, and are indicated by a red line in the diagrams. n = 5; * – p <0.05; ** – p <0.01 – the difference is significant as compared to the control

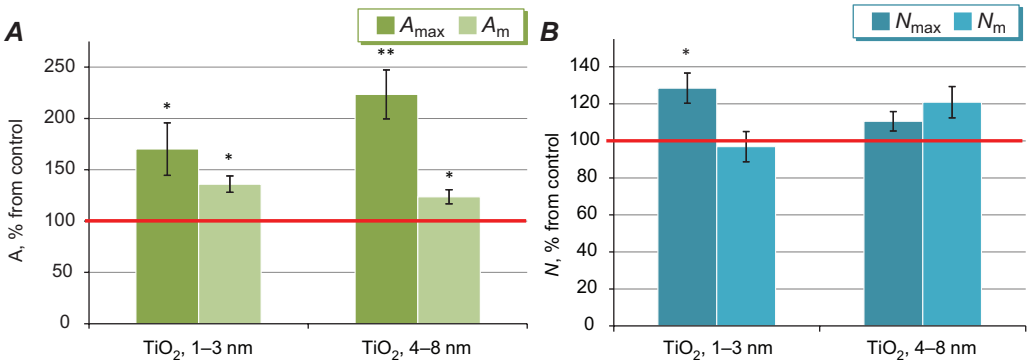

Fig. 5. The relative changes in the parameters of the isotonic contractions of the rat isolated aortic preparations, caused by the application of the high-potassium solution (80 mM) at the preliminary effect of TiO_2 nanoparticles with the average sizes of 1–3 nm (rutile) and 4–8 nm (anatase) (10^{-4} mg/mL, the pre-incubation throughout of 30 min): ***A*** – work parameters for the maximal ΔA_{max} and average ΔA_m; ***B*** – power parameters for the maximal N_{max} and average N_m). The parameters of muscle contractions in the control were taken as 100%, and are indicated by a red line in the diagrams. n = 5; * – p <0.05; ** – p <0.01 – the difference is significant as compared to the control

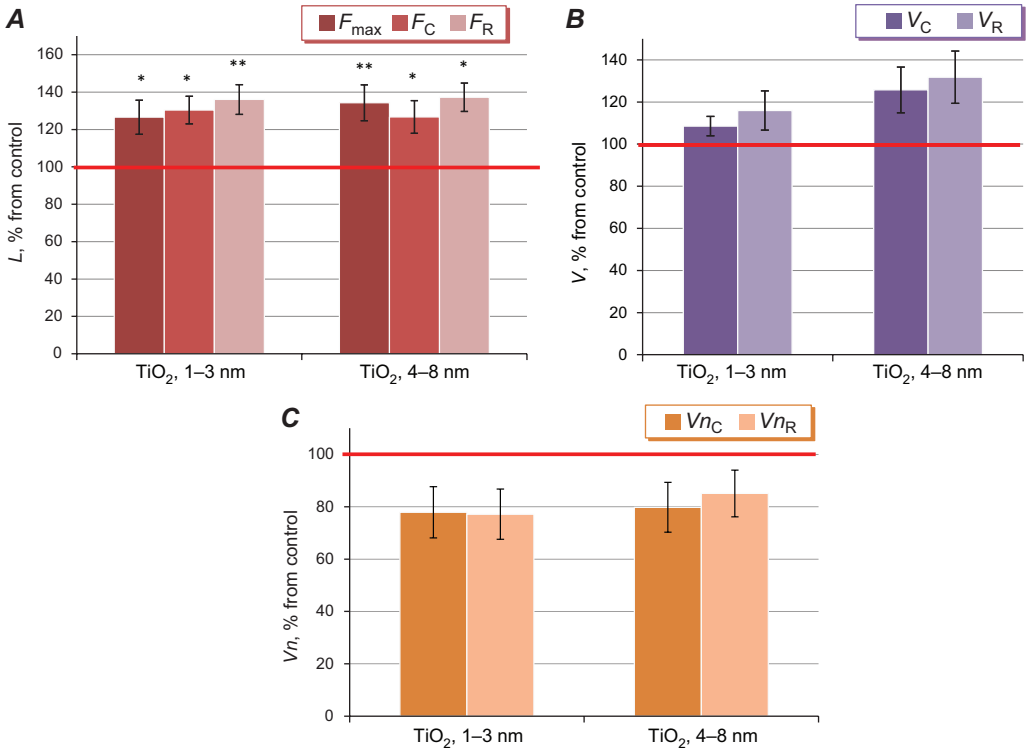

Fig. 6. The relative changes in the parameters of the isometric contractions of the rat aortic isolated preparations, caused by the application of the high-potassium solution (80 mM) at the preliminary effect of TiO_2 nanoparticles with the average sizes of 1–3 nm (rutile) and 4–8 nm (anatase) (10^{-4} mg/mL, the pre-incubation throughout of 30 min): ***A*** – force parameters (F_{max}, F_C and F_R); ***B*** – velocity parameters (V_C and V_R); ***C*** – normalized maximal velocities of the phases of contraction and relaxation (Vn_C and Vn_R). The parameters of muscle contractions in the control were taken as 100%, and are indicated by a red line in the diagrams. n = 5; * – p <0.05; ** – p <0.01 – the difference is significant as compared to the control

To check the assumption that TiO_2 NPs can increase the contractions of the aortic rings, induced by the high-potassium solution, precisely due to the activation of the input of Ca^{2+} ions via voltage-gated Ca^{2+}-channels of the plasma membrane, we studied the effect of these nanoparticles on the contractions of the rat aortic preparations activated by the selective activator of voltage-gated Ca^{2+}-channels of L-type, Bay K8644 (5 μM).

It was found that the preliminary incubation (for 30 min) of the smooth muscle isolated preparations of aorta with the suspensions of TiO_2 NPs was accompanied with a considerable increase in the amplitude (F_{max} and ΔL_{max}, respectively) of isometric and isotonic contractile responses to Bay K8644 without a significant effect on the parameters of the normalized maximal velocities of the phases of contraction and relaxation (**Fig. 7*A*** and ***B***). Thus, we can expect that the effects of the increase in the high-potassium contracture of the aorta under the impact of TiO_2 NPs are conditioned by the activation of the extracellular calcium via voltage-gated Ca^{2+}-channels of L-type.

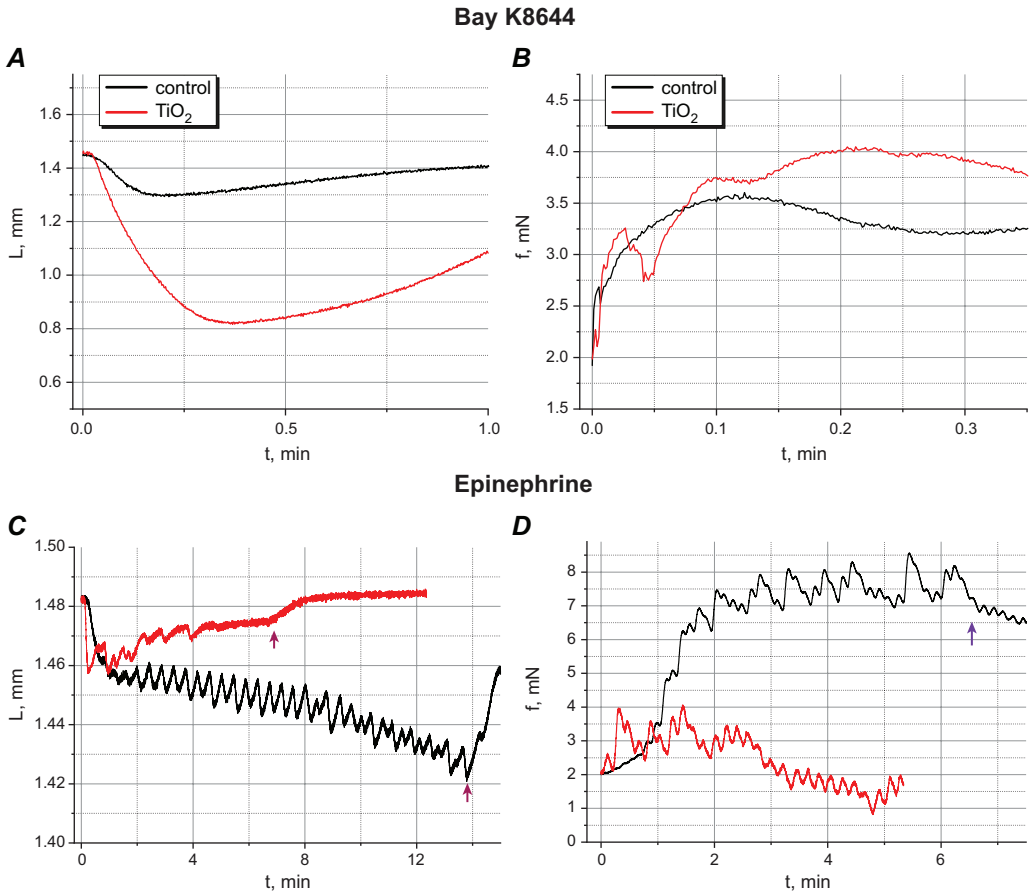

Fig. 7. The typical mechanograms of isotonic (***A*** and ***C***) and isometric (***B*** and ***D***) contractions of the rat aortic isolated preparations, induced by the application of the activator of voltage-gated Ca^{2+}-channels of L-type, Bay K8644 (5 μM), and epinephrine (1 μM) under the preliminary effect of TiO_2 NPs of 1–3 nm (rutile): ***A*** and ***B*** – Bay K8644; ***B*** and ***D*** – epinephrine

The contractions of aortic preparations, induced by epinephrine, under the effect of TiO_2 NPs, polymorphs rutile (1–3 nm) and anatase (4–8 nm). The contractile responses of the vascular smooth muscles under the effect of epinephrine are a typical example of the activation via the pharmacomechanical excitation-contraction coupling. Mostly, they are implemented by the stimulation of the adrenoreceptors of α_1-type, coupling with $G_{q/11}$-proteins (Eckert *et al*., 2000). It should be noted that the receptors of $\alpha_{1A/C}$- and α_{1D}-subtypes are expressed in the aortic myocytes of rats, but the latter dominate functionally (Eckert *et al*., 2000; Lee *et al*., 2024).

The application of epinephrine (1 μM) was accompanied by isotonic contractions of the aortic rings, which were characterized by the following average amplitude parameters (three minutes after the start of epinephrine application): ΔL_{max} -0.025±0.0018 mm and F_{max} 5.06±0.43 mN (n = 5). There was a considerable inhibition of the epinephrine-induced aortic contractions in the presence of TiO_2 NPs of both polymorphs in the solution washing the smooth muscle preparations. For instance, NPs with the average size

of 1–3 nm (rutile) caused the decrease in the amplitude parameters of the contractions on average down to: ΔL_{max} -0.0011±0.0001 mm and F_{max} 1.12±0.14 mN (n = 5, p <0.01 as compared to the corresponding control values) (**Fig. 7*C*** and ***D***). Under the effect of NPs with the average size of 4–8 nm (anatase), the amplitude values of epinephrine-induced contractions of aortic preparations were as follows: ΔL_{max} -0.0012±0.0001 mm and F_{max} 1.04±0.13 mN (n = 5, p <0.01 as compared to the corresponding control values). No significant differences were observed between the effects of different polymorphs of TiO_2 (p >0.05). The introduction of TiO_2 caused a two-fold inhibition of epinephrine-induced contractions as compared to the control.

The epinephrine-induced contractions of the vascular smooth muscles are contributed to by both Ca^{2+} ions, released from the sarcoplasmic reticulum, and the ions, incoming from the extracellular space via Ca^{2+}-channels (Creutz & Chou, 2008). At the first glance, there is a considerable contradiction between the effects of TiO_2 NPs regarding the contractions, induced by the high-potassium solution and epinephrine. However, these differences may be explained by the ability of TiO_2 to selectively chelate the enediol-containing compounds, including biologically active catecholamines (epinephrine, norepinephrine, dopamine) (Tae *et al*., 2005). In particular, these nanoparticles are currently used to elaborate sensors which would determine the content of epinephrine in biological fluids (Wu *et al*., 2007). Thus, it can be inferred that a considerable inhibition of the responses of the aortic isolated preparations to epinephrine can be explained by the binding of the molecules of this agonist to TiO_2 NPs.

In general, catecholamines play an important role in the regulation of tone and contractile activity of both vascular and visceral smooth muscles. Norepinephrine, by activating α-adrenoceptors of vascular smooth muscle to a greater extent, causes vasoconstriction and increased vascular resistance (Fernández-Reina *et al*., 2018). Dopamine at low concentrations predominantly activates Gs-protein-coupled D_1-like (subtypes D_1 and D_5) receptors in resistance arteries, causing vasodilation, while at high concentrations (under model experimental conditions) it can stimulate not only dopamine receptors, but also β_1- and α_1-adrenoceptors (Zeng *et al.*, 2008; Yang *et al.*, 2024). The motility of the smooth muscles of the digestive tract is controlled by the main excitatory neurotransmitter acetylcholine (via muscarinic cholinergic receptors of the M_2- and M_3-subtypes), as well as by dopamine and norepinephrine (Zizzo *et al.*, 2020). Additionally, catecholamines, in particular dopamine and norepinephrine, can take on a compensatory role of normalizing the motor function when cholinergic neurotransmission in the digestive tract wall deteriorates in the initial stages of Parkinson's disease (Zhu *et al.*, 2012; Murillo *et al.*, 2023). However, the death of enteric dopaminergic neurons is observed as the disease progresses (Natale *et al.*, 2017). Adrenergic neurotransmission in smooth muscles is diverse, which is due to the selective expression of certain types of adrenoceptors. Thus, α_1-adrenoceptors, which are coupled with $G_{q/11}$-proteins, are predominantly expressed in smooth muscle cells of blood vessels and the urinary tract, and their stimulation with epinephrine and norepinephrine causes a contractile response. Stimulation of α_1-adrenoceptors (with the selective agonist phenylephrine) causes relaxation of smooth muscle cells of the gastrointestinal tract due to activation of Ca^{2+}-activated K^+-channels of small conductance (Traserra *et al.*, 2025). Therefore, we can expect that the penetration of TiO_2 NPs into the internal environment of the body may also cause a weakening of the effects of catecholamines in the regulation of the contractile function of vascular and visceral smooth muscles.

CONCLUSIONS

The suspensions of TiO_2 NPs (1–3 nm, rutile, and 4–8 nm, anatase) were used to investigate their effect on aortic contractions. It was determined that both polymorphs of TiO_2 (used in the concentration of 10^{-4} mg/mL) equally activated the isometric and isotonic contractile responses of the aortic isolated preparations to the application of the high-potassium solution (80 mM) and the activator of the voltage-gated Ca^{2+}-channels of L-type, Bay K8644 (5 μM), not affecting the parameters of the normalized maximal velocities of the phases of contraction and relaxation (Vn_C and Vn_R). These effects are likely related to the immediate activation of the input of Ca^{2+} ions by TiO_2 NPs in a potential-dependent way.

It was found that both samplings of TiO_2 NPs (10^{-4} mg/mL) equally inhibited the amplitude of the epinephrine-induced (1 μM) contractions of the aortic isolated preparations by more than two times. A probable reason for this inhibition is the ability of TiO_2 to selectively chelate catecholamines, including epinephrine.

The results, obtained in our work, may be useful for deeper understanding of the toxic effect of TiO_2 NPs on living organisms, for instance, by foreseeing the mechanisms of impairments in the functioning of the cardiovascular system and the concentrations of the neurotransmitters of the central nervous system at the effect of this xenobiotic.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: the authors declare that they have no conflict of interest.

Human Rights: this article does not contain any studies with human subjects performed by any of the authors.

Animal Studies: all international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [O.T.; V.S.]; methodology, [P.Z.; O.T.; O.C.; T.D.; S.M.; K.S.; I.V.; O.T.; S.S.; V.S.]; research, [P.Z.; O.T.; O.C.; T.D.; S.M.; K.S.; I.V.; O.T.; S.S.; V.S]; resources, [P.Z.; O.T.; A.C.; T.D.; S.M.; I.V.; V.S.]; data processing, [P.Z.; O.T.; O.C.; T.D.; S.M.; K.S.; I.V.; O.T.; S.S.; V.S.]; writing – preparation of the original project, [O.T.; V.S.]; writing – review and editing, [P.Z.; O.T.; A.C.; T.D.; S.M.; K.S., I.V.; V.S.]; visualization, [O.T.; A.C.] supervision, [O.T.; V.S.]; project management, [O.T.; V.S.]; funding search, [–].

REFERENCES

Baranowska-Wójcik, E., Szwajgier, D., & Winiarska-Mieczan, A. (2022). A review of research on the impact of E171/TiO_2 NPs on the digestive tract. *Journal of Trace Elements in Medicine and Biology*, *72*, 126988. doi:10.1016/j.jtemb.2022.126988
Crossref ● PubMed ● Google Scholar

Burdyga, T. V., & Kosterin, S. A. (1991). Kinetic analysis of smooth muscle relaxation. *General Physiology and Biophysics*, 10(6), 589–598.
PubMed ● Google Scholar

Calderón-Garcidueñas, L., & Ayala, A. (2022). Air pollution, ultrafine particles, and your brain: are combustion nanoparticle emissions and engineered nanoparticles causing preventable fatal neurodegenerative diseases and common neuropsychiatric outcomes? *Environmental Science & Technology*, 56(11), 6847–6856. doi:10.1021/acs.est.1c04706
Crossref ● PubMed ● Google Scholar

Cao, Y., Gong, Y., Liao, W., Luo, Y., Wu, C., Wang, M., & Yang, Q. (2018). A review of cardiovascular toxicity of TiO_2, ZnO and Ag nanoparticles (NPs). *BioMetals*, 31(4), 457–476. doi:10.1007/s10534-018-0113-7
Crossref ● PubMed ● Google Scholar

Chen, T., Hu, J., Chen, C., Pu, J., Cui, X., & Jia, G. (2013). Cardiovascular effects of pulmonary exposure to titanium dioxide nanoparticles in ApoE knockout mice. *Journal of Nanoscience and Nanotechnology*, 13(5), 3214–3222. doi:10.1166/jnn.2013.7147
Crossref ● PubMed ● Google Scholar

Cheng, W., Xu, X., Lang, Y., Cheng, Z., Rizwan, M., Tang, X., Xie, L., Liu, Y., Xu, H., & Liu, Y. (2021). Anatase and rutile TiO_2 nanoparticles lead effective bone damage in young rat model via the IGF-1 signaling pathway. *International Journal of Nanomedicine*, 16, 7233–7247. doi:10.2147/ijn.s333632
Crossref ● PubMed ● PMC ● Google Scholar

Creutz, C., & Chou, M. H. (2008). Binding of catechols to mononuclear titanium(IV) and to 1- and 5-nm TiO_2 nanoparticles. *Inorganic Chemistry*, 47(9), 3509–3514. doi:10.1021/ic701687k
Crossref ● PubMed ● Google Scholar

Domingues, L. A. C. S., Carriello, G. M., Pegoraro, G. M., & Mambrini, G. P. (2024). Synthesis of TiO_2 nanoparticles by the solvothermal method and application in the catalysis of esterification reactions. *Anais da Academia Brasileira de Ciencias*, 96(3), e20240096. doi:10.1590/0001-3765202420240096
Crossref ● PubMed ● Google Scholar

Duan, S., Wang, H., Gao, Y., Wang, X., Lyu, L., & Wang, Y. (2023). Oral intake of titanium dioxide nanoparticles affect the course and prognosis of ulcerative colitis in mice: involvement of the ROS-TXNIP-NLRP3 inflammasome pathway. *Particle and Fibre Toxicology*, 20(1), 24. doi:10.1186/s12989-023-00535-9
Crossref ● PubMed ● PMC ● Google Scholar

Eckert, R. E., Karsten, A. J., Utz, J., & Ziegler, M. (2000). Regulation of renal artery smooth muscle tone by α_1-adrenoceptors: role of voltage-gated calcium channels and intracellular calcium stores. *Urological Research*, 28(2), 122–127. doi:10.1007/s002400050149
Crossref ● PubMed ● Google Scholar

Eker, F., Duman, H., Akdaşçi, E., Bolat, E., Sarıtaş, S., Karav, S., & Witkowska, A. M. (2024). A comprehensive review of nanoparticles: from classification to application and toxicity. *Molecules*, 29(15), 3482. doi:10.3390/molecules29153482
Crossref ● PubMed ● PMC ● Google Scholar

Fernández-Reina, A., Urdiales, J. L., & Sánchez-Jiménez, F. (2018). What we know and what we need to know about aromatic and cationic biogenic amines in the gastrointestinal tract. *Foods*, 7(9), 145. doi:10.3390/foods7090145
Crossref ● PubMed ● PMC ● Google Scholar

Hadrup, N., Vogel, U., & Jacobsen, N. R. (2024). Biokinetics of carbon black, multi-walled carbon nanotubes, cerium oxide, silica, and titanium dioxide nanoparticles after inhalation: a review. *Nanotoxicology*, 18(8), 678–706. doi:10.1080/17435390.2024.2431242
Crossref ● PubMed ● Google Scholar

Jensen, D. M., Christophersen, D. V., Sheykhzade, M., Skovsted, G. F., Lykkesfeldt, J., Münter, R., Roursgaard, M., Loft, S., & Møller, P. (2018). Vasomotor function in rat arteries after *ex vivo* and intragastric exposure to food-grade titanium dioxide and vegetable carbon particles. *Particle and Fibre Toxicology*, 15(1), 12. doi:10.1186/s12989-018-0248-2
Crossref ● PubMed ● PMC ● Google Scholar

Jovanović, B. (2015). Critical review of public health regulations of titanium dioxide, a human food additive. *Integrated Environmental Assessment and Management*, 11(1), 10–20. doi:10.1002/ieam.1571
Crossref ● PubMed ● PMC ● Google Scholar

Khan, J., Kim, N. D., Bromhead, C., Truman, P., Kruger, M. C., & Mallard, B. L. (2025). Hepatotoxicity of titanium dioxide nanoparticles. *Journal of Applied Toxicology*, 45(1), 23–46. doi:10.1002/jat.4626
Crossref ● PubMed ● PMC ● Google Scholar

Kosterin, S, & Tsymbalyuk, O. (2023) Mechanokinetics and power of the spontaneous isotonic contraction of visceral smooth muscles. *Series on Biomechanics*, 37(3), 43–56, doi:10.7546/sb.07.03.2023
Crossref ● Google Scholar

Kosterin, S., Tsymbalyuk, O., & Holden, O. (2021). Multiparameter analysis of mechanokinetics of the contractile response of smooth muscles. Series *on Biomechanics,* 35(1), 14–30.
Google Scholar

LeBlanc, A. J., Cumpston, J. L., Chen, B. T., Frazer, D., Castranova, V., & Nurkiewicz, T. R. (2009). Nanoparticle inhalation impairs endothelium-dependent vasodilation in subepicardial arterioles. *Journal of Toxicology and Environmental Health, Part A*, 72(24), 1576–1584. doi:10.1080/15287390903232467
Crossref ● PubMed ● PMC ● Google Scholar

Lee, S. H., Park, K. E., Eum, K., Hwang, Y., Ok, S. H., Sim, G., Perera, D., Ravald, H. K. M., Park, Y., Wiedmer, S. K., & Sohn, J. T. (2024). Effect of lipid emulsion on vasoconstriction induced by epinephrine or norepinephrine in isolated rat aorta. *Korean Journal of Anesthesiology*, 77(5), 555–564. doi:10.4097/kja.24093
Crossref ● PubMed ● PMC ● Google Scholar

Mikkelsen, L., Sheykhzade, M., Jensen, K. A., Saber, A. T., Jacobsen, N. R., Vogel, U., Wallin, H., Loft, S., & Møller, P. (2011). Modest effect on plaque progression and vasodilatory function in atherosclerosis-prone mice exposed to nanosized TiO_2. *Particle and Fibre Toxicology*, 8(1), 32. doi:10.1186/1743-8977-8-32
Crossref ● PubMed ● PMC ● Google Scholar

Minghui, F., Ran, S., Yuxue, J., & Minjia, S. (2023). Toxic effects of titanium dioxide nanoparticles on reproduction in mammals. *Frontiers in Bioengineering and Biotechnology*, 11, 1183592. doi:10.3389/fbioe.2023.1183592
Crossref ● PubMed ● PMC ● Google Scholar

Mu, X., Hu, K., Wei, A., Bai, J., Feng, L., & Jiang, J. (2023). TiO_2 nanoparticles promote tumor metastasis by eliciting pro-metastatic extracellular vesicles. *Journal of Nanobiotechnology*, 21(1), 392. doi:10.1186/s12951-023-02142-4
Crossref ● PubMed ● PMC ● Google Scholar

Murillo, M. D. P., Johansson, E., Bryntesson, V., Aronsson, P., Tobin, G., Winder, M., & Carlsson, T. (2023). 6-OHDA-induced changes in colonic segment contractility in the rat model of Parkinson's disease. *Gastroenterology Research and Practice*, 2023, 9090524. doi:10.1155/2023/9090524
Crossref ● PubMed ● PMC ● Google Scholar

Musial, J., Krakowiak, R., Mlynarczyk, D. T., Goslinski, T., & Stanisz, B. J. (2020). Titanium dioxide nanoparticles in food and personal care products – what do we know about their safety? *Nanomaterials*, 10(6), 1110. doi:10.3390/nano10061110
Crossref ● PubMed ● PMC ● Google Scholar

Natale, G., Ryskalin, L., Busceti, C. L., Biagioni, F., & Fornai, F. (2017). The nature of catecholamine-containing neurons in the enteric nervous system in relationship with organogenesis, normal human anatomy and neurodegeneration. *Archives Italiennes de Biologie*, 155(3), 118–130. doi:10.12871/00039829201733
Crossref ● PubMed ● Google Scholar

Nefedova, A., Svensson, F. G., Vanetsev, A. S., Agback, P., Agback, T., Gohil, S., Kloo, L., Tätte, T., Ivask, A., Seisenbaeva, G. A., & Kessler, V. G. (2024). Molecular mechanisms in metal oxide nanoparticle – tryptophan interactions. *Inorganic Chemistry*, 63(19), 8556–8566. doi:10.1021/acs.inorgchem.3c03674
Crossref ● PubMed ● PMC ● Google Scholar

Nurkiewicz, T. R., Porter, D. W., Hubbs, A. F., Cumpston, J. L., Chen, B. T., Frazer, D. G., & Castranova, V. (2008). Nanoparticle inhalation augments particle-dependent systemic microvascular dysfunction. *Particle and Fibre Toxicology*, 5(1), 1. doi:10.1186/1743-8977-5-1
Crossref ● PubMed ● PMC ● Google Scholar

Nurkiewicz, T. R., Porter, D. W., Hubbs, A. F., Stone, S., Chen, B. T., Frazer, D. G., Boegehold, M. A., & Castranova, V. (2009). Pulmonary nanoparticle exposure disrupts systemic microvascular nitric oxide signaling. *Toxicological Sciences*, 110(1), 191–203. doi:10.1093/toxsci/kfp051
Crossref ● PubMed ● PMC ● Google Scholar

Pokharkar, V., Chandak, S., Pawar, R., & Khandke, A. (2025). The implications of the EU ban on titanium dioxide: a comprehensive review of safety concerns and alternatives. *Annales Pharmaceutiques Francaises*, 83(3), 438–444. doi:10.1016/j.pharma.2024.11.002
Crossref ● PubMed ● Google Scholar

Silva, R. M., Teesy, C., Franzi, L., Weir, A., Westerhoff, P., Evans, J. E., & Pinkerton, K. E. (2013). Biological response to nano-scale titanium dioxide (TiO_2): role of particle dose, shape, and retention. *Journal of Toxicology and Environmental Health, Part A*, 76(16), 953–972. doi:10.1080/15287394.2013.826567
Crossref ● PubMed ● PMC ● Google Scholar

Tae, E. L., Lee, S. H., Lee, J. K., Yoo, S. S., Kang, E. J., & Yoon, K. B. (2005). A strategy to increase the efficiency of the dye-sensitized TiO_2 solar cells operated by photoexcitation of dye-to-TiO_2 charge-transfer bands. *The Journal of Physical Chemistry B*, 109(47), 22513–22522. doi:10.1021/jp0537411
Crossref ● PubMed ● Google Scholar

Tassinari, R., Tammaro, A., Martinelli, A., Valeri, M., & Maranghi, F. (2023). Sex-specific effects of short-term oral administration of food-grade titanium dioxide nanoparticles in the liver and kidneys of adult rats. *Toxics*, 11(9), 776. doi:10.3390/toxics11090776
Crossref ● PubMed ● PMC ● Google Scholar

Traserra, S., Grao, M., Trujillo, S., Jiménez-Altayó, F., Vergara, P., & Jimenez, M. (2025). Pharmacological characterization of alpha adrenoceptor-mediated motor responses in the rat colon. *Neurogastroenterology and Motility*, 37(1), e14921. doi:10.1111/nmo.14921
Crossref ● PubMed ● PMC ● Google Scholar

Tripathy, D. B., Pradhan, S., Gupta, A., & Agarwal, P. (2025). Nanoparticles induced neurotoxicity. *Nanotoxicology*, 1–28. doi:10.1080/17435390.2025.2488310
Crossref ● PubMed ● Google Scholar

Tsymbalyuk, O. V., Davydovska, T. L., Naumenko, A. M., Voiteshenko, I. S., Veselsky, S. P., Nyporko, A. Y., Pidhaietska, A. Y., Kozolup, M. S., & Skryshevsky, V. A. (2023). Mechanisms of regulation of motility of the gastrointestinal tract and the hepatobiliary system under the chronic action of nanocolloids. *Scientific Reports*, 13(1), 3823. doi:10.1038/s41598-023-30958-5
Crossref ● PubMed ● PMC ● Google Scholar

Tsymbalyuk, O. V., Naumenko, A. M., & Davidovska, T. L. (2019). Influence of nano-TiO_2 on the functioning of gastric smooth muscles: *in vitro* and *in silico* studies. *Studia Biologica,* 13(1), 3–26, doi:10.30970/sbi.1301.592
Crossref ● Google Scholar

Wang, M., Yang, Q., Long, J., Ding, Y., Zou, X., Liao, G., & Cao, Y. (2018). A comparative study of toxicity of TiO_2, ZnO, and Ag nanoparticles to human aortic smooth-muscle cells. *International Journal of Nanomedicine*, 13, 8037–8049. doi:10.2147/ijn.s188175
Crossref ● PubMed ● PMC ● Google Scholar

Wani, S. A., Khan, L. A., & Basir, S. F. (2018). Role of calcium channels and endothelial factors in nickel induced aortic hypercontraction in Wistar rats. *Journal of Smooth Muscle Research*, 54(0), 71–82. doi:10.1540/jsmr.54.71
Crossref ● PubMed ● PMC ● Google Scholar

Wani, S. A., Khan, L. A., & Basir, S. F. (2020). Cobalt-induced hypercontraction is mediated by generation of reactive oxygen species and influx of calcium in isolated rat aorta. *Biological Trace Element Research*, 196(1), 110–118. doi:10.1007/s12011-019-01890-5
Crossref ● PubMed ● Google Scholar

Weir, A., Westerhoff, P., Fabricius, L., Hristovski, K., & von Goetz, N. (2012). Titanium dioxide nanoparticles in food and personal care products. *Environmental Science & Technology*, 46(4), 2242–2250. doi:10.1021/es204168d
Crossref ● PubMed ● PMC ● Google Scholar

Wu, H. P., Cheng, T. L., & Tseng, W. L. (2007). Phosphate-modified TiO_2 nanoparticles for selective detection of dopamine, levodopa, adrenaline, and catechol based on fluorescence quenching. *Langmuir*, 23(14), 7880–7885. doi:10.1021/la700555y
Crossref ● PubMed ● Google Scholar

Yang, Z., Li, Y., Huang, M., Li, X., Fan, X., Yan, C., Meng, Z., Liao, B., Hamdani, N., Yang, X., Zhou, X., El-Battrawy, I., & Akin, I. (2024). Roles and mechanisms of dopamine receptor signaling in catecholamine excess induced endothelial dysfunctions. *International Journal of Medical Sciences*, 21(10), 1964–1975. doi:10.7150/ijms.96550
Crossref ● PubMed ● PMC ● Google Scholar

Zeng, C., Armando, I., Luo, Y., Eisner, G. M., Felder, R. A., & Jose, P. A. (2008). Dysregulation of dopamine-dependent mechanisms as a determinant of hypertension: studies in dopamine receptor knockout mice. *American Journal of Physiology – Heart and Circulatory Physiology*, 294(2), H551–H569. doi:10.1152/ajpheart.01036.2007
Crossref ● PubMed ● PMC ● Google Scholar

Zhang, X., Song, Y., Gong, H., Wu, C., Wang, B., Chen, W., Hu, J., Xiang, H., Zhang, K., & Sun, M. (2023). Neurotoxicity of titanium dioxide nanoparticles: a comprehensive review. *International Journal of Nanomedicine*, 18, 7183–7204. doi:10.2147/ijn.s442801
Crossref ● PubMed ● PMC ● Google Scholar

Zhu, H. C., Zhao, J., Luo, C. Y., & Li, Q. Q. (2012). Gastrointestinal dysfunction in a Parkinson's disease rat model and the changes of dopaminergic, nitric oxidergic, and cholinergic neurotransmitters in myenteric plexus. *Journal of Molecular Neuroscience*, 47(1), 15–25. doi:10.1007/s12031-011-9560-0
Crossref ● PubMed ● PMC ● Google Scholar

Zizzo, M. G., Bellanca, A., Amato, A., & Serio, R. (2020). Opposite effects of dopamine on the mechanical activity of circular and longitudinal muscle of human colon. *Neurogastroenterology and Motility*, 32(6), e13811. doi:10.1111/nmo.13811
Crossref ● PubMed ● Google Scholar

МОДУЛЯЦІЯ СКОРОЧЕНЬ АОРТИ ЩУРІВ УЛЬТРАДИСПЕРСНИМИ НАНОЧАСТИНКАМИ TiO_2 КРИСТАЛІЧНИХ ФОРМ АНАТАЗУ І РУТИЛУ

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Обґрунтування. Нанопорошок діоксиду титану (TiO_2) є одним із найбільш затребуваних промислових наноматеріалів, також його широко використовують у виробництві продуктів харчування, медичних і косметичних засобів, у сільському господарстві. Це створює передумови постійного, щоденного надходження цих частинок в організм. Відомо, що наночастинки TiO_2 впливають на функціонування клітин ендотелію судин, змінюючи їхню реакцію на ацетилхолін. Втім, на сьогодні практично немає інформації про ймовірні ефекти цього наноматеріалу на процеси активації скорочувальної функції судин епінефрином і на активацію потенціалкерованих Ca^{2+}-каналів. Також цікавим питанням залишається дослідження поліморфзалежних ефектів НЧ TiO_2.

Метою роботи було дослідити вплив ультрадисперсних наночастинок TiO_2 кристалічних форм анатазу і рутилу на скорочення гладеньком'язових препаратів аорти щурів, викликані деполяризацією плазматичної мембрани міоцитів, а також на епінефрин-активовані скорочення.

Матеріали і методи. У дослідженнях використовували комерційні препарати наночастинок TiO_2 (PlasmaChem GmbH, D-12489 Berlin, Germany) у формі нанопорошку зі середнім розміром частинок 1–3 нм (кристалічна форма рутил) і 4–8 нм (кристалічна форма анатаз). Для визначення середнього гідродинамічного діаметра наночастинок TiO_2 у суспензії було застосовано метод динамічного розсіювання світла.

Тензометричні досліди проводили в ізометричному й ізотонічному режимах реєстрації на препаратах кілець грудної аорти щурів зі збереженим ендотелієм. Скорочення ізольованих препаратів аорти індукували аплікуванням гіперкалієвого розчину (80 мМ), активатора потенціалкерованих Ca^{2+}-каналів L-типу Bay K8644 та неселективного агоніста адренорецепторів епінефрину. Скорочення аналізували методами механокінетичного аналізу з розрахунком максимальних швидкостей фаз скорочення і розслаблення.

Результати. Встановлено, що обидва поліморфи TiO_2 (за фіксованої концентрації 10^{-4} мг/мл і часу передінкубації 30 хв) однаковою мірою (приблизно на третину) спричиняють активацію ізометричних та ізотонічних скорочувальних відповідей ізольованих препаратів аорти на аплікування гіперкалієвого розчину (80 мМ) і активатора потенціалкерованих Ca^{2+}-каналів L-типу Bay K8644 (5 мкМ). У всіх випадках параметри нормованих максимальних швидкостей фаз скорочення і розслаблення (Vn_C і Vn_R) залишалися на контрольному рівні. Також виявлено, що за

аналогічних умов аплікування обидва типи НЧ TiO_2 однаковою мірою (більш ніж удвічі щодо контролю) пригнічують амплітуду епінефрин-викликаних (1 мкМ) скорочень препаратів аорти.

Висновки. Ультрадисперсні наночастинки TiO_2 поліморфнезалежним чином посилюють скорочення аорти і надходження іонів Ca^{2+} потенціалзалежним шляхом. Також наночастинки TiO_2 обумовлюють пригнічення катехоламінергічних скорочень гладеньких м'язів аорти, ймовірно, внаслідок хелатування катехоламінів.

***Ключові слова**:* аорта, ультрадисперсні наночастинки діоксиду титану, потенціалкеровані Ca^{2+}-канали, епінефрин, механокінетичні параметри

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