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Abstract

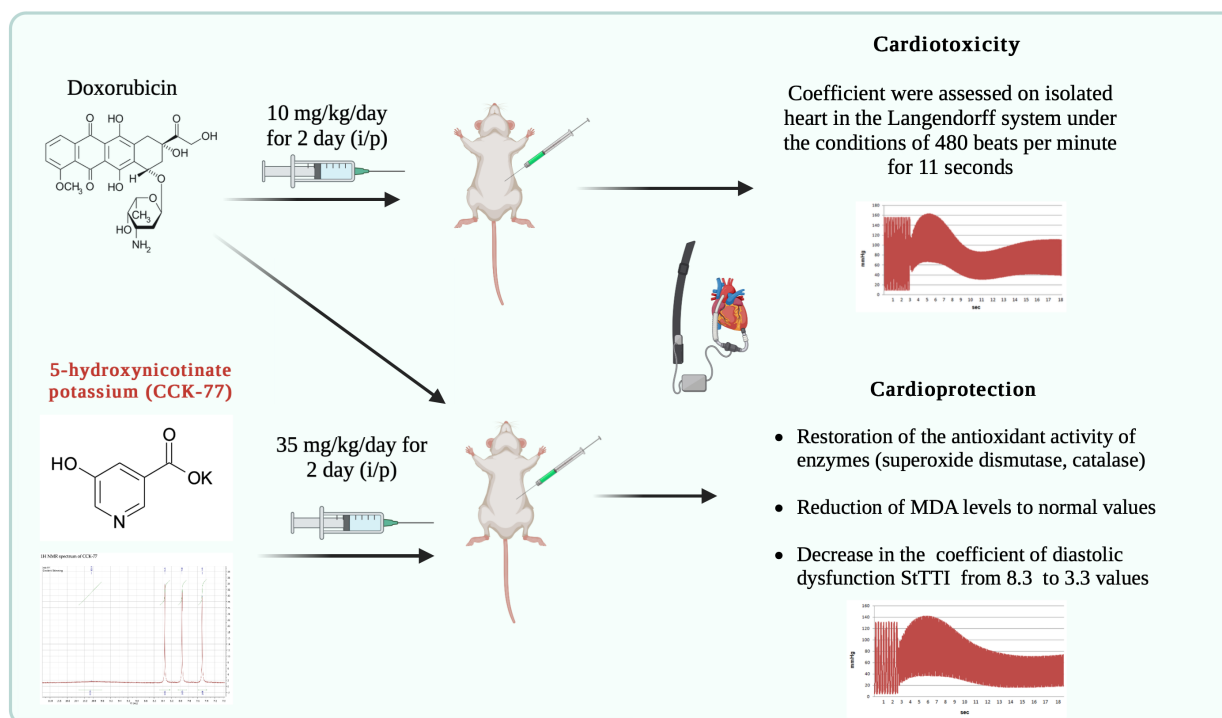
Introduction: Doxorubicin (DOX) is an anthracycline antibiotic with considerable significance in clinics as an anticancer agent, which is limited by its cardiotoxicity, though. A large number of possible therapeutic strategies for reducing cardiotoxicity with doxorubicin have been studied. However, none of them fully meets the requirements of clinical practice. **The aim of the study:** to evaluate the cardioprotective effects of a new original heterocyclic compound, a pyridine-3-carboxylic acid derivative potassium 5-hydroxynicotinate.

Materials and Methods: Cardiac injury was induced by intraperitoneal administration of doxorubicin (DOX) at a dose of 20 mg/kg. After 48 hours, the parameters of left ventricular contractility and S_{IT1} coefficient were assessed on isolated heart in the Langendorff system under the conditions of 480 beats per minute for 11 seconds. Additionally, specific markers of myocardial injury were determined. The lipid peroxidation products and SOD activity were measured as well to challenge whether the compound is able to reduce oxidative stress.

Results: The study showed that pretreatment by potassium 5-hydroxynicotinate (35 mg/kg, 48 h) attenuated DOX-induced damage, resulting in a significant decrease in the S_{IT1} coefficient to 3.3 values and in the restoration of the antioxidant activity of enzymes.

Conclusion: The obtained data totally demonstrate the protective effects of potassium 5-hydroxynicotinate in DOX-induced cardiomyopathy. A significant role in potassium 5-hydroxynicotinate-mediated cardioprotection is, apparently, related to the reduction of oxidative stress and down-regulation of the level of intracellular calcium.

Graphical abstract



Keywords

potassium 5-hydroxynicotinate, doxorubicin, coefficient StTTI, oxidative stress, Wistar rats

Introduction

The mechanism of cardiotoxic effect of DOX has yet to be elucidated in details. Various pathways contributing to cardiomyopathy are considered, but the most discussed mechanism is intracellular calcium overload, launching cell's death cascades (Awad et al. 2021; Wu et al. 2022). A number of studies have confirmed DOX-mediated formation of reactive oxygen species (ROS), affecting normal calcium homeostasis in various types of muscle cells via disruption of the normal functioning of the sarcoplasmic reticulum (Wallace et al. 2020; Shi et al. 2023;). Furthermore, DOX is known to promote calcium release from the sarcoplasmic reticulum, contributing to Ca²⁺ channels opening as well as inhibition of Ca²⁺ ATPases by reducing the expression of SERCA2a mRNA (Adeyemi et al. 2024). Since the release of ROS is central to the mechanisms of DOX-induced myocardial damage, it is reasonable to consider antioxidants as the main candidates for counteracting the toxic effects of DOX. Resveratrol and the β -blocker, carvedilol, have been studied as compounds with antioxidant activity (Neves 2023; Zhang et al. 2023). A number of flavonoids in experimental murine studies were shown to decrease cardiotoxicity of DOX without affecting its antitumor effect (Shabalala et al. 2017; Ma et al. 2017; Qi et al. 2020).

However, no ideal cardioprotective agent has yet been found to reduce DOX toxicity.

Nicotinic acid has been used for decades to treat dyslipidemias. Recently, its clinical use has been somewhat limited due to some side effects, primarily due to flushing (Benyó et al. 2006). A recent highlight of the G protein receptor GPR109A (PUMA-G and HM74) as a nicotinic acid receptor has provided a better understanding of the mechanisms underlying the metabolic and vascular effects of nicotinic acid (Gille et al. 2008). Since then, new strategies have been developed to more effectively use its pharmacological potential. New agents acting through the nicotinic acid receptor or related receptors, as well as new nicotinic acid derivatives, may soon be presented as a new avenue for the treatment of various diseases. For instance, Acipimox (5-methylpyrazinecarboxylic acid 4-oxide) is a lipid-lowering drug based on nicotinic acid, which is used clinically to treat atherogenic dyslipidemias (Hadigan et al. 2006). Nicotinic acid amides have found application as drugs for the treatment of cardiovascular diseases (Danilenko et al. 2018; Mateusz et al. 2020); esters of nicotinic acid and nicotinic acid salts have been used as agents for correction of retinal damage and ischemia of traumatic brain injury (Peresyphkina et al. 2020; Shcheblykina et al. 2022). In a series of

experimental studies, 6-hydroxynicotinic acid and 4-hydroxypyridine were reported to have a number of positive effects such as gastroprotection, increased pulmonary ventilation in bronchospasm and antidiabetic properties in rats with alloxan-induced hyperglycemia (Stetinová and Grossmann 2000). Notably, all compounds of **nicotinic acid** are characterized by low toxicity and lack of cardiodepressive action. Therefore, there are a growing number of premises to search for cardioprotective agents among novel derivatives of **nicotinic acid**. In particular, these molecules might show a protective effect after usage of anthracycline antibiotics in oncology.

The aim of this study was to assess the cardioprotective activity of a new original heterocyclic compound, a pyridine-3-carboxylic acid derivative, potassium 5-hydroxynicotinate, in a rat model of acute doxorubicin-induced cardiomyopathy.

Materials and Methods

Methods to obtain and analyze the substance

The chemical reagents, used for synthesis of the compound, were purchased from commercial suppliers that have a certificate for chemical products (Sigma-Aldrich, USA). The route to the synthesis of potassium 5-hydroxynicotinate compound, chemical formula ($C_6H_4NO_5K$) consisted of the following steps: 3.17 g (0.0564 m) of potassium hydroxide and 7.84 g (0.0564 m) of 5-hydroxynicotinic acid were dissolved in 32 mL of water. The solution was stirred at 80-85 °C for 5-10 minutes. Then 0.8 g of active carbon was added and resulting solution was stirred for 10 min, filtered, cooled to +5-7°C; then 12 mL of acetone was added and stirred for 2 hours. The precipitate was separated, washed with 5 mL of acetone, and dried resulting in 7.80 g of powdered hygroscopic 5-hydroxynicotinate potassium.

$T_{\text{degr}} 300$ °C. found, %: C 39,93; H 2,75; N 7,76. $C_6H_4NO_5K$; calculated, %: C 39,97; H 2,40; N 7,78; UV-spectrum, cm⁻¹: 2975, 2850, 1615, 1600, 1385 (chromatography-mass spectrometer (GCMS-QP2010 Ultra, Shimadzu, Japan)). UV spectrum was detected at 284 nm (water) (spectrophotometer SpectroDirect, UK). Structural formula of the chemical compound is presented in Figure 1.

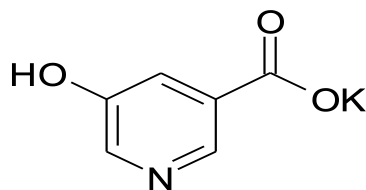


Figure 1. Structural formula of the chemical compound (5-hydroxynicotinate potassium – CCK77).

To confirm the structure of the synthesized compound, nuclear magnetic resonance spectroscopy was performed. ¹H NMR spectra was measured in DMSO-D₆ solutions on a broadband pulse spectrometer (Agilent MR400), operating at frequencies of 400 and 100 MHz using the σ -scale of chemical shifts (ppm). All procedures related to chemical synthesis and analysis were carried out in the Research Laboratory of Organic Synthesis and NMR Spectroscopy of Belgorod State National Research University.

Animal groups

Experiments were approved by the Local Ethics Committee of Belgorod State National Research University, Belgorod, Russia (Minutes No. 19/23 dated 29.03.23). The animal studies were carried out in accordance with the European Union (EU) legislation "On the protection of animals used for scientific purposes».

Wistar rats were randomly assigned to five groups. There were 10 animals in each group:

1) intact group – rats were treated with saline intraperitoneally (i/p) once a day for 2 days;

2) control – rats were treated with **DOX** i/p at a cumulative dose of 20 mg/kg over a period of 2 days, i/p (10 mg/kg/day);

3) 5-hydroxynicotinate potassium – rats were treated with **DOX** (20 mg/kg) + 5-hydroxynicotinate potassium at a dose of 35 mg/kg/day (I/p);

4) carvedilol – rats were treated with **DOX** (20 mg/kg) + carvedilol at a dose of 30 mg/kg/day (I/p);

5) **nicotinic acid** – rats were treated with **DOX** (20 mg/kg) + **nicotinic acid** at a dose of 3.7 mg/kg/day i/p.

DOX-induced cardiac injury

DOX dissolved in saline was administered i/p at a cumulative dose of 20 mg/kg for 2 days. After 48 hours, the rats were anesthetized with Zoletil, Virbac (Tiletamine-Zolazepam, 60 mg/kg); their hearts were excised and placed in ice-cold (2–4°C) Krebs–Henseleit bicarbonate buffer. The fluid-filled latex balloon which was connected to a pressure sensor was inserted into the left ventricle for the real-time recording of the contraction waves (MP150; BiopacSystems, California, USA). Data were recorded using AcqKnowledge software (BiopacSystems, California, USA). Forced acceleration of the heart rate to the frequency of the 480 beats per minute was used for evaluation of the dynamics of ventricular diastolic tension. Forced heart rhythm was achieved via electrical stimulation for 11 seconds using the STM 200-1 stimulator (BiopacSystems, Inc, California, USA). Additionally, the S_{ITTI} coefficient, calculated as the total area under the curve of the rise in end-diastolic pressure, was used for evaluation of diastolic dysfunction (Danilenko et al. 2018).

Finally, specific markers of cardiac injury were measured. MB isoenzyme of creatine kinase (CK-MB) and Rat cardiac troponin I (Tn-I) commercial kits were purchased from CUSABIO BIOTECH (China), and lactate dehydrogenase (LDH) kit was purchased from Vector-Best (Russia). Colorimetric analysis was conducted with use of universal microplate reader ELX800 (Bio-TekInstruments, Inc, USA).

Determination of malondialdehyde (MDA)

The levels of MDA, the end product of lipid peroxidation, was measured in the homogenates of cardiac tissue. Measurement was based on colorimetric determination of colored orange-red trimethine or trimethylsilyl complex, the terminal products of the reaction of MDA with thiobarbituric acid (Sigma-Aldrich, USA) (Tsikas 2017). In brief, 0.2 mL of each sample (homogenate of myocardium tissue) and 0.2 mL of 0.7% thiobarbituric acid (TBA) were mixed with 0.6 mL 1.3 % H₃PO₄ and 0.04 mL 0.6% FeSO₄*7H₂O. Next, the mixture was boiled

at 100 °C in a water bath for 30 min. After centrifugation (ELMI CM-6MT, Latvia) at 3000 rpm for 15 min, the supernatant was collected for measurement of light absorbance at 532 nm with use of spectrophotometer Helios γ («TermoElectronCorporation», England). The lipid peroxide levels were compared with a standard curve representing the signal of distilled water added instead of a homogenate specimen. The calculation of the MDA concentration was performed using the molar extinction coefficient ($1.56 \cdot 10^5 \text{ cm}^{-1}\text{M}$), expressed in (nmol/g tissue).

Determination of antioxidant enzymes activity

Superoxide dismutase (SOD) activity was determined by a degree of inhibition of quercetin oxidation according to V.A. Kostukov's method. SOD activity was expressed as units/mL, whereas one unit of SOD activity defines the amount of enzyme required to inhibit 50% of quercetin oxidation. Catalase activity was determined according to hydrogen peroxide decomposition rate as described in (Beutler et al. 1975).

Statistical analysis

For all data, descriptive statistics were used, and the data were checked for normal distribution. The distribution type was determined by using the Shapiro–Wilk test. In the case of the normal distribution, the average value (M) and standard deviation (SD) were calculated. In cases of the abnormal distribution, the median (Me) and the quartile range (QR) were calculated. In the normal distribution, the intergroup comparison was performed using one-way ANOVA and post-hoc analysis according to Tukey. In other cases, the intergroup comparison was performed using Kruskal–Wallis and Dunn's post-hoc tests. Statistical analyses were performed using R programming language.

Results

Chemistry

The compound under the laboratory code SSK-77 was obtained with a yield of 71%; then its structure was confirmed on the basis of its spectroscopic data. IR spectrum, cm^{-1} : 3500, 3450, 3350, 1660, 1610, 1575, 1295, 1260, 1160; UV spectrum, nm: 290. The formula of the chemical compound is presented in Figure 1.

¹H NMR spectrum of CCK-77 compound (Fig. 2):

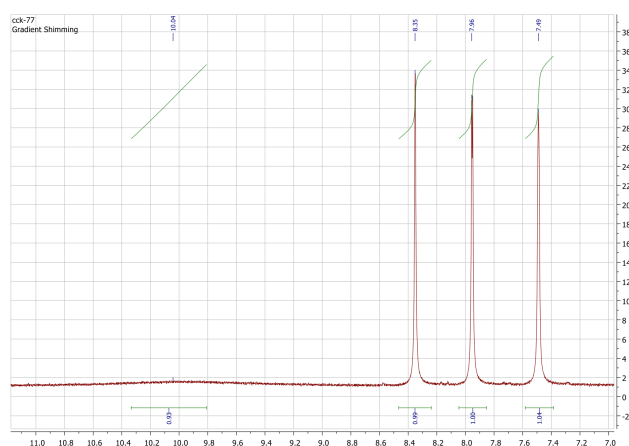


Figure 2. ¹H NMR spectrum of CCK-77 compound, ¹H NMR (400 MHz, DMSO) δ 10.04, 8.35, 7.96, 7.49.

In the ¹H NMR spectrum of the compound SSK-77, the signals of the protons of the pyridine nucleus appear in the form of three singlets with an integrated intensity of one proton each, with chemical shifts of 8.35, 7.96, 7.49 ppm, corresponding to protons in positions 2, 6 and 4 of the pyridine nucleus. The singlet of the hydroxyl group proton in position 5 of the pyridine nucleus is strongly broadened and weakly visible in the survey spectrum; however, it clearly manifests itself in the analysis of integral intensities in the region of 10 ppm.

CCK-77 prevents DOX-induced heart injury

DOX-induced cardiotoxicity was characterized by eccentric remodeling of the left ventricle and a decrease in myocardial contractility. Cardiac function was characterized by a decrease in the LVP and contractility as well as the significant increase in diastolic blood pressure, indicating impaired myocardial relaxation (Table 1).

Table 1. Indicators of the cardiac contractile function in the control DOX group (M \pm m; n=10)

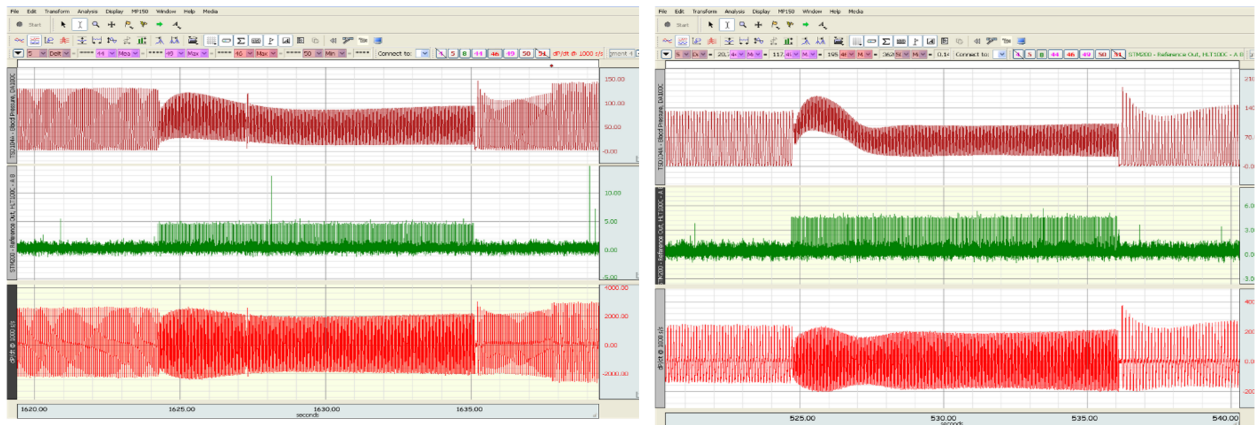
Experimental groups	LVP	+dp/dt _{max}	-dp/dt _{max}	HR
Intact	87.3 \pm 9.2	1423 \pm 122.2	-1265.2 \pm 173.2	248 \pm 32.1
DOX (20 mg/kg) (Control)	64.5 \pm 11.2*	1025.7 \pm 114.3*	-931.1 \pm 159.4*	247 \pm 29.4

Note: LVP – left ventricular pressure (mm Hg); +dp/dt_{max} – maximum rate of contraction (mm Hg/sec); -dp/dt_{max} – maximum rate of relaxation (mm Hg/sec); HR – heart rate (beats/min). * – p<0.05 when comparing with the intact group.

After 11-seconds of forced acceleration of heart rate (480 beats/min) for an assessment of Ca²⁺ pump functioning, untreated DOX-induced cardiomyopathy group demonstrated a decrease in the contractile myocardium activity. Figure 3 shows representative records of the functional tests with high-frequency stimulation in the intact group (Fig. 3a) and the control DOX group (Fig. 3b). The coefficient of diastolic dysfunction S_{TTI} was 8.3 \pm 0.3 in the control group against 1.4 \pm 0.1 in the intact one, representing dramatic 8-fold difference. Hereby, S_{TTI} is a high-sensitive indicator of myocardial damage, reflecting imbalance between the level of cardiac Ca²⁺ load and Ca²⁺-pump capacity.

CCK-77 (35 mg/kg/day) attenuated the coefficient of diastolic dysfunction S_{TTI} resulting in level 2.1 \pm 0.1, which was significantly lower than the levels in the control untreated group (Fig. 4 A). In contrast, the reference agents carvedilol (30 mg/kg/day) and nicotinic acid (3.7 mg/kg/day) resulted in a milder decrease in S_{TTI} coefficient: 4.6 \pm 0.1 и 7.1 \pm 0.2, respectively. Thus, according to data of the functional tests, the cardioprotective activity of the studied drugs decreases in the following sequence: CCK-77 > carvedilol > nicotinic acid.

Next step, the levels of CK-MB, LDH and troponin-I were determined. It was shown that treatment with CCK-77 resulted in a 2-fold decrease in CK-MB, LDH and Troponin-I compared to the untreated group (Fig. 4 B, C, D). Carvedilol (30 mg/kg) decreased the levels of CK-MB, LDH and Troponin by 26%, 44% and 42%, respectively, compared to the control group (Fig. 4 A, B, C, D). In contrast, nicotinic acid did not cause significant changes in biochemical markers (Fig. 4 A, B, C, D).



A

B

Figure 3. Representative records of loading tests with submaximal electrostimulation of the isolated rat hearts in Langendorff's system. *Note:* **A** – intact group; **B** – control DOX group. The dynamics of pressure in the left ventricle (mm Hg) with the cardiac stimulation (480 beats per minute) for 11 seconds. From top to bottom: scale 1 – left ventricular pressure (LVP in mm Hg); scale 2 – stimulation rate (480 beats per minute for 11 seconds); scale 3 – the rate of change of the LVP (+dP/dtmax, -dP/dtmax, mm Hg/sec).

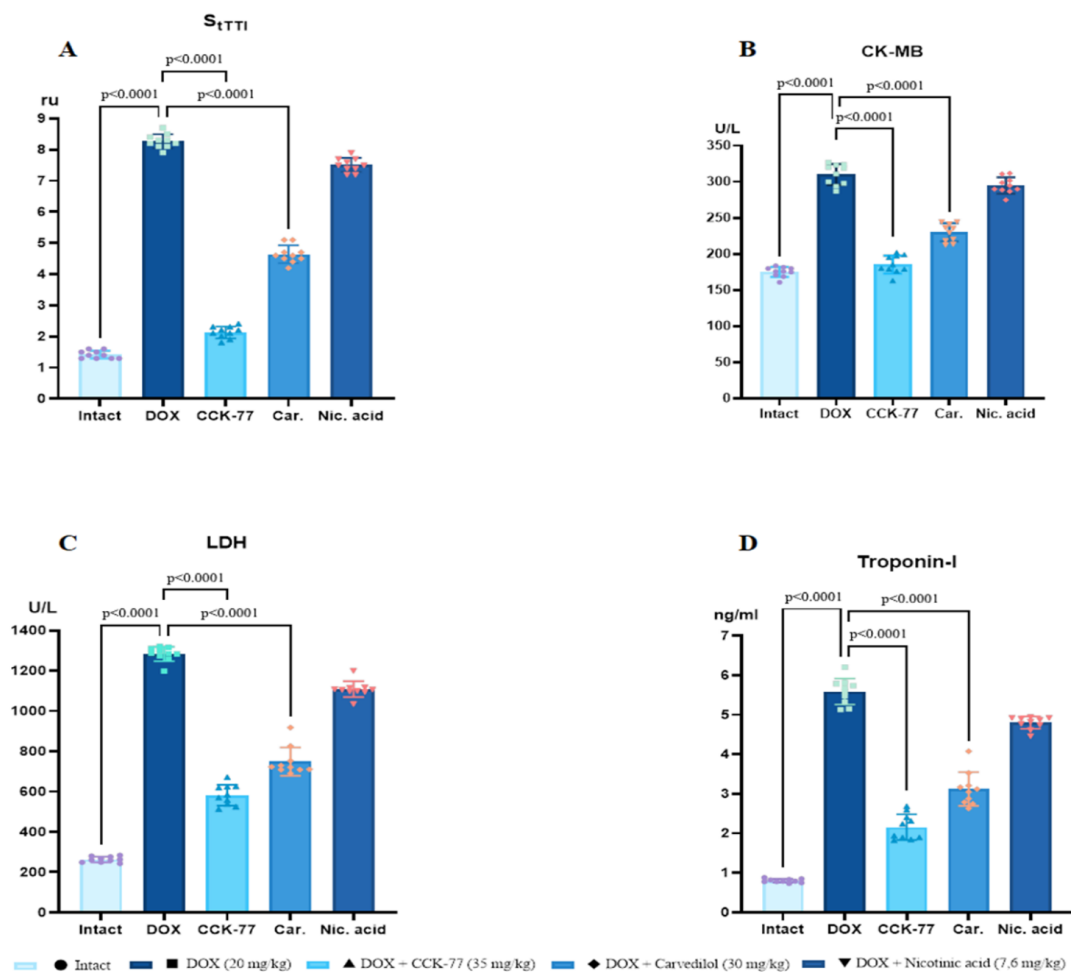


Figure 4. Cardioprotective effects of CCK-77 (35 mg/kg), carvedilol (30 mg/kg), nicotinic acid (3.7 mg/kg) in a rat model of DOX-induced cardiotoxicity (20 mg/kg). After 48 hours, the coefficient of diastolic dysfunction S_{tTTI} [dynamics of pressure in the left ventricle (mm Hg) on the background of cardiac electrostimulation (480 beats per minute) for 11 seconds and calculating the area under the curve of the rise in end-diastolic pressure was evaluated] (**A**). The levels of biochemical markers creatine kinase MB (CR-MB) (**B**), lactate dehydrogenase (LDH) (**C**), Troponin-I (**D**) was measured as well. Statistical analysis was performed with subsequent use of ANOVA and Tukey tests (Data presented as $M \pm SEM$; * $p < 0.05$; ** $p < 0.01$).

Thus, the functional and biochemical tests against the background of DOX-induced cardiomyopathy confirmed a pronounced cardioprotective effect of CCK-77, which was markedly higher than carvedilol (30 mg/kg) and nicotinic acid (3.7 mg/kg) had shown.

CCK-77 prevents oxidative stress induced by DOX in rat

Oxidative stress plays a crucial role in the processes of DOX-induced myocardial injury causing cell membrane damage and increased permeability as well as intracellular Ca²⁺ overload and subsequent activation of proteolytic enzymes (Antonucci et al. 2021). We observed highly increased MDA levels in the control DOX group, 45% higher than in the intact group, whereas CCK-77 treatment abolished this change (Fig. 5 A).

Similarly, CCK-77 increased the SOD level by 19% higher than in the control DOX group, which resulted in the values similar to intact group. Carvedilol increased the studied indicator by 11% compared to the control group of rats, while nicotinic acid did not significantly influence SOD levels (Fig. 5 B). Finally, CCK-77 also rescued catalase levels resulting in a 1.5-fold increase in comparison to control group. Carvedilol showed a less pronounced activity, increasing the levels of catalase by 34%. Nicotinic acid did not increase catalase levels (Fig. 5 C).

Discussion

Many reports showed that DOX affects mitochondrial function, causing generation of free radicals in the electron transport chain, especially in the myocardium (Rawat et al. 2021; Kong et al. 2022; Mao et al. 2023; Vitale R et al. 2024).

In our study, we predictably observed that DOX affected diastolic function, most probably via oxidative stress and impaired calcium dynamics. It is known that an increase in the heart rate promotes calcium accumulation due to shortening the diastole which serves as a period for

restoration from Ca²⁺-overload (Numata and Takimoto 2023). In this regard, endurance in response to forced acceleration of the heart rate reflects the functioning of Ca²⁺-pump, allowing to estimate diastolic function/dysfunction. Notably, simulating DOX-induced cardiomyopathy, we observed significant impairment of diastolic function. Additional criterion for an assessment of Ca²⁺-pumps capacity, the coefficient of diastolic dysfunction S_{ETI} confirmed incomplete diastolic relaxation.

In this study, we report CCK-77 ameliorates cardiac function in DOX-induced cardiomyopathy, which was confirmed by a decrease in the S_{ETI} coefficient as well as down-regulation of biochemical markers of myocardial damage and oxidative stress. Carvedilol also prevented DOX-induced myocardial damage, but its efficacy was quite milder. Nicotinic acid had modest cardioprotective effect and did not lead to a significant decrease in the S_{ETI} coefficient.

Evidently, one of the most probable mechanisms of cardioprotective action for the studied drugs is antioxidant defense. Normally, 1–2% of the electrons leak out of the respiratory chain causing ROS formation (Gnaiger and Kuznetsov 2002). Slight generation of ROS is required for various cellular process such as regulation of transcription and cell proliferation (Xie et al. 2021), but higher levels promote cell death (Pan et al. 2021; Ping et al. 2023; Wei et al. 2023). To protect itself, cell launches various mechanisms for preventing ROS accumulation. SOD inactivates the superoxide anion (O₂⁻) in the cytosol (Cu/Zn-SOD) and in mitochondria (Mn-SOD) (Hsieh et al. 2022). The resulting H₂O₂ is removed by catalase, glutathione peroxidase, and peroxiredoxin (Bauer 2017).

CCK-77 restricted LPO processes and restored the activity of antioxidant enzymes SOD and catalase. This finding highlights antioxidant properties as important feature for cardioprotection mediated by nicotinic acid derivatives. The results of the pharmacological study of the substance CCK-77 in DOX-induced cardiomyopathy make it possible to consider this compound as a promising basis for creating a drug for the prevention and treatment of complications arising during DOX treatment in oncology.

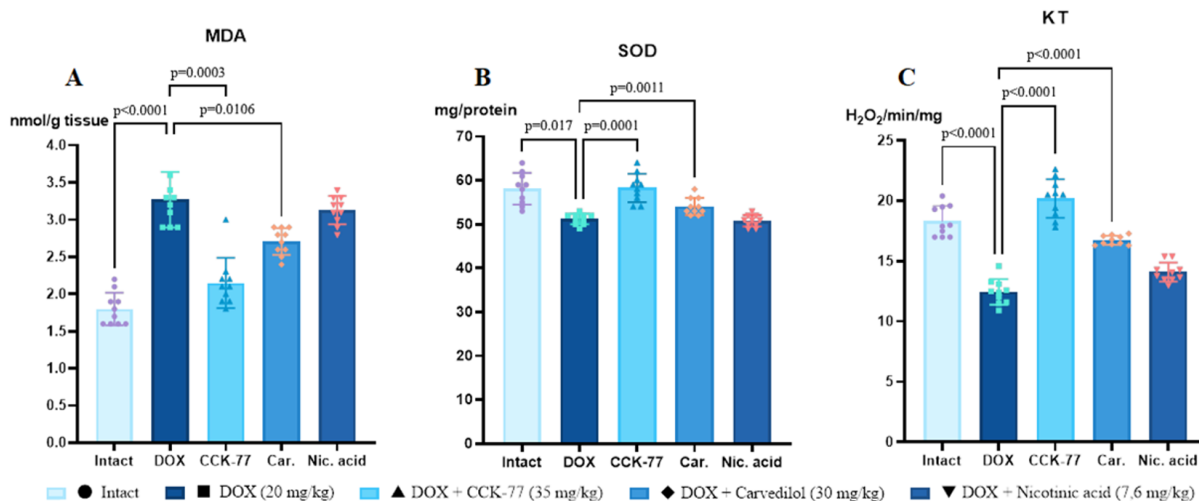


Figure 5. Effects of CCK-77 (35 mg/kg), carvedilol – Car (30 mg/kg), nicotinic acid – Nik. Acid (3.7 mg/kg) on the values of malondialdehyde – MDA (A), superoxide dismutase – SOD (B), catalase – CT (C). Statistical analysis was performed with subsequent use of ANOVA and post-hoc Tukey tests. Data are presented as M±SEM (* p<0.05; ** p<0.01).

Conclusion

CCK-77 (35 mg/kg), a heterocyclic compound derived from pyridine-3-carboxylic acid, attenuates DOX-induced cardiomyopathy in rats, improving functional and biochemical markers and reducing oxidative stress. Altogether these data allow considering derivatives of nicotinic acid as novel candidate group for protection against DOX-induced cardiotoxicity.

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Conflict of interests

The authors declare that they have no conflicts of interests.

Data availability

All of the data that support the findings of this study are available in the main text.

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