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Mechanisms of the cardioprotective effect of lithium

Mukhomedzyanov A.V.[1], Plotnikov E.V.[2,3,4], Maslov L.N.[1], Chernov V.I.[2,5], Naryzhnaya N.V.[1], Slidnevskaya A.S.[1], Yusubov M.S.[2], Larkina M.S.[2,3], Artamonov A.A.[6], Belousov M.V.[2,3]

[1]*Cardiology Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences 111 A, Kievskaya Str., Tomsk, 634012 Russian Federation*

[2] *National Research Tomsk Polytechnic University (NR TPU) 30, Lenina Av., Tomsk. 634050, Russian Federation*

[3] *Siberian State Medical University 2, Moscow Trakt, Tomsk, 634050, Russian Federation*

[4] *Mental Health Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences 4, Aleutskaya Str., Tomsk, 634021, Russian Federation*

[5] *Cancer Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences 5, Kooperativny Str., Tomsk, 634009, Russian Federation*

[6] *Institute of Biomedical Problems, Russian Academy of Sciences 76 A, Khoroshevskoe Highway, Moscow, 123007, Russian Federation*

ABSTRACT

Background. A study of the mechanisms of infarct size-limiting effects of lithium chloride (LiCl) on a model of myocardial infarction *in vivo*. Myocardial infarction is one of the main causes of death among the adult working population in economically developed countries. Currently, there are no drugs in clinical practice that would effectively protect the myocardium against ischemia – reperfusion injury, so there is a need to develop new drugs that can limit infarct size and reduce mortality.

Aim. To study the mechanisms of infarct size-limiting effects of lithium chloride.

Materials and methods. A study was performed in anesthetized Wistar rats with coronary artery occlusion (45 min) and reperfusion (120 min). The molecular mechanism of the protective effects of LiCl was examined in this model using appropriate blockers, including non-selective and selective blockers of ATP-sensitive potassium channel and NO synthase.

Results. Administration of LiCl before ischemia significantly reduced infarct size as well as the as the incidence of ventricular arrhythmias. Administration of LiCl after ischemia also promoted a decrease in infarct size. NO synthase, cycloxigenase-2, protein kinase C, and endogenous opioids were not involved in the cardioprotective effect of lithium. The cardioprotective effect of LiCl is mediated via sarcolemmal ATP-sensitive potassium channel ($sarcK_{ATP}$ channel) opening.

Conclusion. LiCl reduced infarct size and prevented reperfusion cardiac injury. The main cellular ways of the infarct size-limiting effects of LiCl are mediated through the $sarcK_{ATP}$ channel opening.

Keywords: lithium, myocardial infarction, cardioprotection, potassium channels, ischemia/reperfusion

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✉ *Plotnikov Evgenii V.,* Plotnikov.e@mail.ru

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Механизмы кардиопротекторного эффекта лития

Мухомедзянов А.В.[1], Плотников Е.В.[2, 3, 4], Маслов Л.Н.[1], Чернов В.И.[2, 5], Нарыжная Н.В.[1], Слидневская А.С.[1], Юсубов М.С.[2], Ларькина М.С.[2, 3], Артамонов А.А.[6], Белоусов М.В.[2, 3]

[1] Научно-исследовательский институт (НИИ) кардиологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634012, г. Томск, Киевская, 111а

[2] Национальный исследовательский Томский политехнический университет (НИ ТПУ)
Россия, 634050, г. Томск, пр. Ленина, 30

[3] Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

[4] Научно-исследовательский институт (НИИ) психического здоровья, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634021, Россия, Томск, ул. Алеутская, 4

[5] Научно-исследовательский институт (НИИ) онкологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634009, г. Томск, пер. Кооперативный, 5

[6] Институт медико-биологических проблем (ИМБП) Российской академии наук (РАН)
Россия, 123007, г. Москва, Хорошёвское шоссе, 76а

РЕЗЮМЕ

Цель. Исследование механизмов инфаркта – лимитирующего действия хлорида лития (LiCl) на модели инфаркта миокарда *in vivo*. Инфаркт миокарда является одной из основных причин смерти взрослого трудоспособного населения в экономически развитых странах. В настоящее время в клинической практике не существует препаратов, которые с высокой эффективностью защищали бы миокард от ишемии/реперфузии, поэтому имеется необходимость в разработке новых лекарственных средств, способных ограничить размер инфаркта и снизить смертность.

Материалы и методы. Моделирование инфаркта миокарда проводили на крысах линии Вистар путем окклюзии коронарной артерии (45 мин) и реперфузии (120 мин). Молекулярный механизм защитного действия хлорида лития исследовали на модели инфаркта с помощью соответствующих блокаторов, в том числе неселективных и селективных блокаторов АТФ-чувствительного калиевого канала и NO-синтазы.

Результаты. Введение LiCl до ишемии значительно уменьшало размер инфаркта, при этом NO-синтаза, циклоксигеназа-2, протеинкиназа С, эндогенные опиоиды не были вовлечены в кардиопротекторный эффект лития. Кардиопротекторный эффект LiCl опосредован через открытие сарколеммального АТФ-чувствительного калиевого канала (саркКАТФ-канала).

Заключение. Хлорид лития может предотвратить ишемическое и реперфузионное повреждение сердца. Основные клеточные пути инфаркт-лимитирующего действия LiCl реализуются в основном через открытие саркКАТР-каналы.

Ключевые слова: литий, инфаркт миокарда, кардиопротекция, калиевые каналы, ишемия/реперфузия

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Acute myocardial infarction (AMI) is one of the main causes of death among patients with cardiovascular diseases [1, 2]. Lethality in ST-segment elevation myocardial infarction (STEMI) is 4.6–6.8% [3, 4], and in patients with cardiogenic shock within 30 days, it exceeds 20% [5, 6]. The probability of death in patients with AMI is primarily related to infarct size, concomitant rhythm disturbances, and the time of pharmacologic or surgical reperfusion. Reperfusion provides restoration of coronary blood flow, but also contributes to reperfusion damage of the heart.

Currently in clinical practice, there are no drugs that can significantly increase cardiac resistance to reperfusion and, consequently, reduce infarct size. The most effective method of treatment of AMI is percutaneous coronary intervention; nevertheless, mortality remains at a high level [3, 4, 7, 8]. Therefore, there is an urgent need to develop new drugs that can reduce infarct size. Lithium (Li^+) and its salts are of particular interest in this regard. Lithium has a wide range of biological activities, including normothymic, cytoprotective, antioxidant, and antiapoptotic effects [9–11].

It has been previously reported that Li^+ can increase the resistance of rat heart to ischemia – reperfusion injury *in vitro* [12, 13]. However, it was unclear whether Li^+ could limit infarct size *in vivo*. The receptor and signaling mechanisms of the infarct size-limiting effect of Li^+ have not yet been studied in detail. A number of studies have shown that the cardioprotective effect of LiCl depends on the activation of cyclooxygenase [12, 13]. There are data that indicate the participation of opioid receptors (ORs) in the antinociceptive effect of Li^+, and that Li^+ is able to activate ATP-sensitive K^+ -channels (K_{ATP}-channels) [14, 15]. K_{ATP}-channels, ORs, protein kinase C (PKC), cyclooxygenase-2 (COX-2), and NO synthase (NOS) are known to play important roles in the mechanisms of cardiac tolerance to ischemia – reperfusion [16–20]. In the present study, we investigated the infarct size-limiting effect of lithium and determined the molecular mechanism of cardioprotection in *in vivo* models.

MATERIALS AND METHODS

The study design was planned according to ARRIVE guidelines 2.0 for reporting animal studies [21]. Outbred male Wistar rats weighing 250–300 g were used. One animal was considered as one experimental unit. The animals were maintained under standardized conditions at 24 ± 2 °C. The rats received pellets of normal feed and drinking water *ad libitum*. Division of animals into groups was done randomly. Simple randomization was used, with animals numbered and assigned to groups by selecting a set of numbers for each group using a random number generator. Twelve experimental animals were included in each experimental group and were processed by parametric statistical methods.

The control group (ischemia – reperfusion injury model without pharmacologic treatment) consisted of 12 experimental rats. The study was conducted using the blinding strategy. Surgical procedures and infarct size measurements were performed by different specialists who did not know to which group the animal belonged. Experimental procedures were performed in accordance with Directive 2010/63/EU of the European Parliament and the Guidelines for the Care and Use of Laboratory Animals. Pharmacologic effects in the experimental groups included the use of lithium salts and other pharmacologic agents described in detail below. LiCl solution was administered intravenously as a bolus in a volume of 1 mL of saline solution. Lithium solution

was administered 15 minutes before coronary occlusion. Other pharmacologic agents were administered intravenously 25 min before coronary artery occlusion.

The animals were anesthetized with α-chloralose (50 mg / kg, intraperitoneally) and connected to a SAR-830 ventilator (CWE Inc., Ardmore, USA). Blood pressure (BP) was recorded using an SS13L pressure transducer (Biopac System Inc., Goleta, USA) paired with an MP35 electrophysiologic study device (Biopac System Inc., Goleta, USA). This device was also used for ECG recording. Coronary occlusion (45 min) was performed according to the method of Neckar et al [22]. The animals underwent thoracotomy and pericardium removal, then ligature was applied to the coronary artery. After 45 minutes of ischemia, the ligature was removed, the restoration of blood flow was confirmed by the appearance of epicardial hyperemia. The duration of reperfusion was 2 hours.

After completion of the reperfusion period, the hearts were removed and flushed with saline solution through the aorta. The risk zone was determined by staining the myocardium through the aorta with 5% potassium permanganate solution. Then slices perpendicular to the longitudinal axis of the heart (1 mm thick) were made. The area of necrosis was distinguished from the area at risk by staining with 1% 2,3,5-triphenyltetrazolium chloride solution [22]. Heart slices were scanned and infarct area was calculated using the ImageJ program (NIH, USA). Myocardial infarct size was expressed as a percentage from the risk area size as the ratio of infarct area to risk area.

The compounds used were lithium chloride, L-NAME, glibenclamide, naltrexone, 5-GD and celecoxib (Sigma-Aldrich, USA), chelerythrine (MedChemExpress, USA), and hydroxypropyl β-cyclodextrin (Tocris Bioscience, UK). HMR 1098 was synthesized and provided by Sanofi-Aventis Deutschland GmbH (Frankfurt, Germany). Drug solutions for administration were prepared in saline *ex tempore*. Water-insoluble compounds (glibenclamide, chelerythrine, celecoxib) were first dissolved in 0.1 ml of dimethyl sulfoxide, and then 0.9 ml of 20% hydroxypropyl β-cyclodextrin was added.

We have previously found that hydroxypropyl β-cyclodextrin has no effect on animal hemodynamics, heart rhythm, and infarct size. Lithium chloride was used at doses of 40 mg / kg and 200 mg / kg intravenously. The other drugs were also administered intravenously. Naltrexone (a nonselective OR antagonist) was administered at a dose of 5 mg / kg. Chelerythrine (a selective PKC inhibitor) was administered at a dose of 5 mg / kg. The NOS inhibitor L-NAME was administered at a dose of 10 mg / kg. The non-selective K_{ATP} -channel blocker glibenclamide was administered at a concentration of 1 mg / kg. 5-Hydroxydecanoate (5-HD, a blocker of mitochondrial K_{ATP} ($mitoK_{ATP}$) channels) was administered at a dose of 5 mg / kg. HMR 1098 (a selective blocker of sarcolemmal ($sarK_{ATP}$) channels) was administered at a dose of 3 mg / kg. The selective COX-2 inhibitor celecoxib was administered at a concentration of 0.24 mg / kg. A.M. Stevens et al. demonstrated that celecoxib at this dose inhibits COX-2 [23].

The results of the study were processed using the Statistica 13.0 program (Stat Soft, USA). Data were presented as the mean and the standard deviation $M \pm \sigma$. Normality was checked by the Shapiro – Wilk test. One-factor analysis of variance (ANOVA) with the Bonferroni correction was used to compare differences between the groups. The differences between the groups were considered statistically significant at $p < 0.005$.

RESULTS

No significant changes in hemodynamic parameters were detected in animals of the control group (Table). L-NAME increased systolic blood pressure and decreased heart rate. The other drugs had no effect on hemodynamic parameters (Table).

Table

HR (beats / min) and BP (mm.Hg) in rats during coronary occlusion (45 min) and reperfusion (120 min)

Group	Dose, mg / kg	Before ischemia		45 min of ischemia		30 min reperfusion		120 min reperfusion	
		HR	AD	HR	AD	HR	AD	HR	AD
Control		363 ± 4	124 ± 3	357 ± 4	120 ± 3	352 ± 5	117 ± 3	342 ± 6	113 ± 4
LiCl	200	364 ± 4	126 ± 3	359 ± 4	121 ± 4	355 ± 3	116 ± 4	346 ± 5	111 ± 6
LiCl	40	361 ± 4	122 ± 3	355 ± 5	118 ± 3	350 ± 4	114 ± 3	341 ± 5	110 ± 6
Celecoxib	0.24	364 ± 3	121 ± 3	357 ± 4	117 ± 3	350 ± 4	113 ± 3	340 ± 5	109 ± 4

Table (continued)

Group	Dose, mg / kg	Before ischemia		45 min of ischemia		30 min reperfusion		120 min reperfusion	
		HR	AD	HR	AD	HR	AD	HR	AD
L-NAME	10	364 ± 4	125 ± 3	334 ± 5*	145 ± 3*	326 ± 6*	147 ± 4*	320 ± 6*	149 ± 6*
Chelerythrine	5	363 ± 4	123 ± 3	357 ± 3	120 ± 4	353 ± 4	115 ± 5	340 ± 6	109 ± 4
Glibenclamide	1	367 ± 3	122 ± 4	363 ± 4	119 ± 3	357 ± 4	115 ± 5	347 ± 4	110 ± 4
HMR 1098	3	365 ± 4	122 ± 3	359 ± 5	119 ± 4	355 ± 5	120 ± 4	347 ± 5	112 ± 5
5-HD.	5	362 ± 5	124 ± 4	358 ± 3	120 ± 3	353 ± 4	117 ± 4	341 ± 4	114 ± 5
Naltrexone	5	365 ± 4	126 ± 4	361 ± 4	122 ± 3	356 ± 3	118 ± 4	345 ± 4	113 ± 5

Note: LiCl – lithium chloride; 5-HD – 5-hydroxydecanoic acid; HR – heart rate, BP –blood pressure; * $p < 0.005$ compared to the control group.

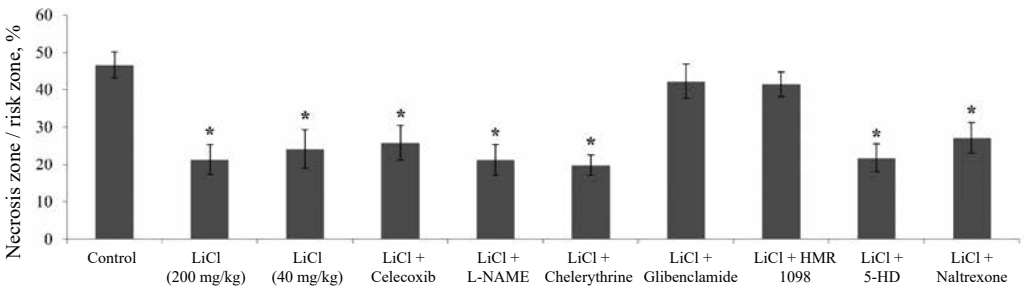

Fig. 1. Participation of COX-2, NO synthase, protein kinase C, K_{ATP}-channels, and opioid receptors in the infarct size-limiting effect of LiCl. Here and in Fig.2, the data are shown as M ± σ. * $p < 0.005$ compared to the control group

Pre-injection of LiCl (40 mg / kg) statistically significantly ($p = 0.00045$) reduced the necrosis zone / risk zone ratio by 48% compared to the controls (Fig. 1). Increasing the dose of lithium chloride to 200 mg / kg did not significantly enhance the cardioprotective effect (Fig. 1). Therefore, in further studies, lithium chloride was used at a concentration of 40 mg / kg.

As shown in Fig. 1, the COX-2 inhibitor celecoxib and the NOS inhibitor L-NAME did not affect the infarct size-limiting effect of LiCl, i.e., there was a statistically significant reduction in the infarct size compared to the controls ($p = 0.00088$ and $p = 0.00021$, respectively). A similar result was observed with the PKC inhibitor chelerythrine ($p = 0.00011$). However, glibenclamide (a non-selective blocker of K_{ATP}-channels) and HMR 1098 (a selective blocker of sarcK_{ATP}-channels) abolished the cardioprotective effect of lithium chloride (Fig. 1), in both cases the infarct zone size was not significantly different from the control values ($p = 0.303$ and $p = 0.206$, respectively). Pre-administration of the selective mitoK_{ATP}-channel inhibitor 5-HD did not affect lithium-induced cardiac tolerance to ischemia – reperfusion injury (a statistically significant reduction in infarct area was observed, $p = 0.00041$). The OR antagonist naltrexone also did not affect the infarct size-limiting effect of lithium chloride ($p = 0.0035$) (Fig. 1). All inhibitors used had no significant effect on the size of the infarct area (Fig. 2)

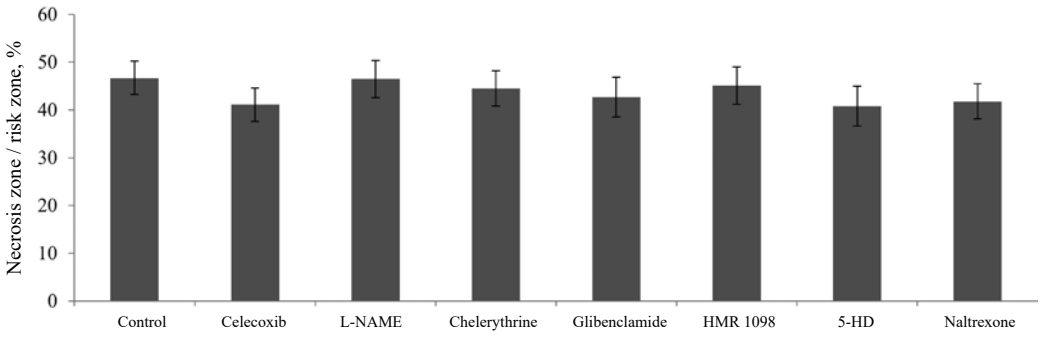

Fig. 2. Estimation of the intrinsic effect of the drugs used (inhibitors) on myocardial infarction size

DISCUSSION

The cardioprotective effect of lithium was previously shown in *ex vivo* studies [12, 13]. Cyclooxygenase may be involved in the realization of the infarct size-limiting effect of lithium [13]. Several studies have shown that COX-2 activation improves cardiac tolerance to ischemia [19, 20, 24]. We found that celecoxib (COX-2 inhibitor) did not eliminate the cardioprotective effect of LiCl. This may be due to the fact that M.Faghihi et al. conducted their studies on the isolated rat heart and used the non-selective COX inhibitor indomethacin, which also inhibits COX-1 [13].

We hypothesized that COX-1 is involved in the cardioprotective effect of LiCl. However, this hypothesis contradicts the current opinion that COX-2 activation increases cardiac tolerance to ischemia [19, 20]. Activation of PKC definitely plays an important role in the cardioprotective effect of ischemic preconditioning [16] and opioids [25]. Therefore, it was surprising that PKC is not involved in the infarct size-limiting effect of LiCl, since chelerythrine exposure did not affect the efficacy of lithium. NOS has been reported to be involved in the development of delayed (24 h) ischemic preconditioning [20]. However, the NOS inhibitor L-NAME did not affect the LiCl-induced increase in cardiac tolerance to ischemia – reperfusion.

The results of our study are in agreement with the data of Y. Terashima et al. who showed that the infarct size-limiting effect of LiCl *ex vivo* is independent of PKC activation [12]. Our data are in agreement with the work of M. Faghihi et al. [13], where it was shown that L-NAME does not attenuate lithium cardioprotection *in vitro.*

K_{ATP}-channels are known to be involved in cardioprotection due to ischemic pre- and postconditioning [16, 17]. It has been reported that LiCl can induce the opening of K_{ATP}-channels [15]. Summarizing the obtained results, we concluded that the infarct size-reducing effect of LiCl is partially realized through K_{ATP}-channels. This version is confirmed by the revealed effects of non-selective blocker of K_{ATP}-channels glibenclamide and selective blocker of sarcK_{ATP}-channels HMR 1098, which completely eliminated the cardioprotective effect of LiCl. Hence, sarK_{ATP}-channels are involved in the infarct size-limiting effect of LiCl. In this case, it remains unclear whether activation of the sarK_{ATP}-channel is the result of a direct action of Li^+ on this channel or whether its opening is mediated by the effect of kinases.

In our study, lithium chloride demonstrated an infarct size-limiting effect. The antinociceptive effect of lithium chloride depends on the release of endogenous opioids [17]. However, the results showed that endogenous opioids were not involved in the cardioprotective effect of LiCl. Lithium carbonate is used orally in psychiatry with achieving blood concentrations of 0.4–1.2 mmol / l in patients [26]. This concentration is comparable to the dose of LiCl used in our study. Consequently, these results indicate the feasibility of conducting a clinical trial on the treatment of AMI with lithium salts.

CONCLUSION

It has been shown that lithium chloride reduces the myocardial infarction zone *in vivo* and increases cardiac resistance to ischemia – reperfusion. The infarct size-limiting effect of LiCl is associated with the opening of sarK_{ATP}-channels. PKC, NOS, COX-2, endogenous opioids, and mitoK_{ATP}-channels are not involved in the cardioprotective effect of LiCl. The obtained data indicate the need for further study of the mechanism of cardioprotective effect of lithium.

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Authors' contribution

Mukhomedzyanov A.V. – performance of in vivo operations. Plotnikov E.V. – conception, carrying out of research. Maslov L.N. – research design, interpretation of the results. Chernov V.I. – analysis and interpretation of the data. Naryzhnaya N.V. – analysis of hemodynamics. Slidnevskaya A.S. – processing of heart slices. Yusubov M.S. – analysis of lithium compounds, processing of the results. Larkina M.S. – statistical analysis and data processing. Artamonov A.A. – graphic design of the results. Belousov M.V. – analysis and interpretation of the research results. All authors contributed to drafting of the article and final approval of the manuscript for publication.

Authors' information

Mukhomedzyanov Alexander V. – Cand. Sci. (Med.), Researcher, Laboratory for Experimental Cardiology, Cardiology Research Institite, Tomsk NRMC, Tomsk, sasha_m91@mail.ru, http://orcid.org/0000-0003-1808-556X

Plotnikov Evgenii V. – Cand. Sci. (Chemistry), Associate Professor, Research School of Chemical and Biomedical Technologies, NR TPU, Tomsk, plotnikov.e@mail.ru, http://orcid.org/0000-0002-4374-6422

Maslov Leonid N. – Dr. Sci. (Med.), Professor, Head of the Laboratory for Experimental Cardiology, Cardiology Research Institite, Tomsk NRMC, Tomsk, Maslov@cardio-tomsk.ru, http://orcid.org/0000-0002-6020-1598

Naryzhnaya Natalya V. – Dr. Sci. (Med.), Principal Researcher, Laboratory for Experimental Cardiology, Cardiology Research Institite, Tomsk NRMC, Tomsk, nataalynaar@yandex.ru, http://orcid.org/0000-0003-2264-1928

Slidnevskaya Alisa S. – Senior Laboratory Assistant, Laboratory for Experimental Cardiology, Cardiology Research Institite, Tomsk NRMC, Tomsk, alisaslidnevskaa@gmail.com, http://orcid.org/0009-0004-2215-5414

Chernov Vladimir I. – Corresponding Member of the Russian Academy of Sciences, Dr. Sci. (Med.), Professor, Deputy Director for Research and Innovation, Tomsk NRMC; Head of the Department of Radionuclide Diagnostics, Cancer Research Institute, Tomsk NRMC, Tomsk, chernov@tnimc.ru, http://orcid.org/0000-0002-5524-9546

Yusubov Mehman S. – Dr. Sci. (Chemistry), Professor, Research School of Chemical and Biomedical Technologies, NR TPU, Tomsk, yusubov@mail.ru, http://orcid.org/0000-0001-9233-1824

Larkina Maria S. – Dr. Sci. (Pharmaceut.), Professor, Division of Pharmaceutical Analysis, Siberian State Medical University, Tomsk, larkina.ms@ssmu.ru, http://orcid.org/0000-0003-1176-2441

Artamonov Anton A. – Senior Researcher, Institute of Medical and Biological Problems, Russian Academy of Sciences, Moscow, anton.art.an@gmail.com, http://orcid.org/0000-0002-7543-9611

Belousov Mikhail V. – Dr. Sci. (Pharmaceut.), Professor, Head of the Pharmaceutical Analysis Division, Siberian State Medical University, Tomsk, belousov.mv@ssmu.ru, http://orcid.org/0000-0002-2153-7945

(✉) **Plotnikov Evgenii V.,** Plotnikov.e@mail.ru

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