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EXPERIMENTAL ARTICLES

Indices of Blood Free Radical Balance during Stimulation of Central Neuromediator Systems

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Abstract—Activation of brain neurotransmitter systems can change the intensity of free radical processes in peripheral tissues and organs. We studied the parameters of free radical balance in the blood of mature male rats under conditions of stimulation of the central neurotransmitter systems (noradrenergic, NAS; serotonergic, SRS; dopaminergic, DPS). The level of products reacting with thiobarbituric acid, catalase activity in plasma, and erythrocyte hemolysate were determined by conventional methods in animals after stimulation of NAS (maprotiline, 10 mg/kg), SRS (5-hydroxytryptophan, 50 mg/kg and fluoxetine, 3 mg/kg), and DPS (L-Dopa and amantadine, 20 mg/kg each). In half of the animals of each group, the indices were determined after a single injection of the β-adrenergic receptor blocker anaprilin (2 mg/kg). Quadruple administration of drugs activating NAS, SRS, and DPS was accompanied by a decrease in the concentration of free radical oxidation products and an increase in the catalase activity of erythrocytes and blood plasma. The administration of a β-adrenergic blocker during stimulation of neurotransmitter systems increases the concentration of free radical oxidation products to a lesser extent but potentiates the catalase activity of erythrocytes. After DPS stimulation, the general shifts in the free radical balance of blood are more pronounced; after stimulation of NAS, they are smaller; and only when SRS is activated, the direction of changes in some indices deviates from the general trends. Thus, administration of drugs activating NAS, SRS, and DPS is accompanied by adaptive changes in the free radical balance of the blood and predominantly weakens its response to the administration of a β-adrenergic receptor blocker.

Key words: TBA-reactive substances, catalase activity, erythrocytes, blood plasma, noradrenergic, dopaminergic, serotonergic neurotransmitter systems, beta-blocker

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INTRODUCTION

The central neurotransmitter systems, CNTS (noradrenergic, serotonergic, and dopaminergic), play important roles in the formation of behavior, in the realization of cognitive functions and emotions, and negative states such as depression, anxiety, fear, and dyskinesias also depend on changes in their activity [1–4]. Drugs affecting the metabolism and reception of neurotransmitters are used to treat neurodegenerative diseases and depressive and other disorders of the nervous system [1–5]. Often, on the recommendation of doctors or on their own initiative, people decide to take these drugs in order to increase mental and physical performance. In all cases, it is important to understand that drugs that affect the metabolism of neurotransmitters can affect not only cognitive processes and emotional state, but also visceral functions and general metabolism, which can be seen in the literature [7–11]. Changes in the metabolism of neurotransmitters can result in the intensification of free radical oxidation (FRO), which is a universal mechanism of damage to membrane structures [12], and, according to [3, 12, 13], accelerates aging, leading to the development of various, including cerebral, pathologies. Despite a significant number of studies on free radical oxidation in the nervous tissue and its role in the pathogenesis of nervous disorders, this continues to be the subject of discussion. The reason for this is the inconsistency of the available data. On the one hand, it was shown that neurotransmitters, biogenic amines, can be sources of reactive oxygen species [14, 15], influence the activity of phospholipases, and stimulate the degradation of membrane phospholipids. The resulting modification of the composition and physicochemical properties of membranes is reflected in the cellular reception of monoamines and the activation of signaling cascades in cells [12, 16]. On the other hand, there is evidence that neurotransmitters, monoamines, exhibit antiradical activity, acting as the first line of antioxidant defense during oxidative stress [17, 18]. This controversy is supported by the fact that pharmacological drugs used to treat depression and

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neurodegenerative disorders can also exhibit both prooxidant [4] and antioxidant properties [19, 20].

It is known that pharmacological stimulation of the CNTS changes the level of monoamines both in the corresponding structures of the CNS and in the blood [4–6, 21]. This may change some properties of blood cells [7, 9, 10], and the activity of their enzyme systems, including the systems involved in antioxidant protection [4, 20].

The ambiguity of data on general and specific changes in free radical processes after administration of drugs that excite the CNS makes relevant the analysis of the relationship between neurotransmitter metabolism in the CNS and free radical processes in the blood. Research in this direction can complement the understanding of the effect of regulatory monoamines on free radical processes, the relationship between the central apparatus of regulation and processes at the level of peripheral organs and tissues, and will also allow the development of easy methods for monitoring changes in the body when taking drugs that activate CNTS.

Here, we analyzed changes in some indices of the free radical balance in the blood of male rats during stimulation of the central neurotransmitter systems (CNTS) and the administration of a beta-blocker.

MATERIALS AND METHODS

The work was performed with 54 male non-linear white rats weighing 220–270 g (vivarium of the Research Institute for the Study of Leprosy of the Ministry of Health of Russia), kept in the laboratory vivarium of Astrakhan State University with a 12-hour light regime, in plastic cages with wooden bedding, on a standard diet in the form of granulated feed for laboratory animals PK-120 GOST 50258-92 (Laboratorkorm, Russia) with free access to water and food. The experiments were performed in accordance with the National Standard of the Russian Federation GOST R-53434-2009 "Principles of Good Laboratory Practice", Order of the Ministry of Health of the Russian Federation of April 1, 2016, No. 199n "On Approval of the Rules of Good Laboratory Practice" and the European Convention Directive 2010/63/EU of 22 September 2010. Research was performed during the autumn-winter period.

The animals were divided into three experimental groups: (1) a group with stimulation of the noradrenergic system (NAS, n = 12) by norepinephrine reuptake inhibitor maprotiline (Maprotiline, 10 mg/kg) [5]; (2) a group with stimulation of the serotonergic system (SRS, n = 12) by 5-hydroxytryptophan (5-HTP, 50 mg/kg) [6] in combination with fluoxetine (Fluoxetine, 3 mg/kg) [1, 5]; (3) a group with activation of the dopaminergic system (DPS, n = 12) by the dopamine precursor L-dihydroxyphenylalanine (L-Dopa, 20 mg/kg) [4, 6, 21] in combination with amantadine (Amantadine, 20 mg/kg), which stimulates the release and inhibits the reuptake of dopamine in synapses [1]. The choice of drugs (maprotiline, fluoxetine, 5-hydroxytryptophan, L-dopa) and doses was based on the literature data on their ability to increase the level of major neurotransmitters (noradrenaline, serotonin, dopamine) in the CNS, as well as in the blood plasma after single and long-term administration [1, 4–6, 20, 21]. We used the drug administration scheme we developed for the study of the wave characteristics of the heart rhythm (project no. 14-04-00912, supported by the Russian Foundation for Basic Research) and presented in previous publications [9, 10]. In accordance with this scheme, drugs manufactured by Sigma Aldrich were administered intraperitoneally, daily for 4 days in the morning (8.00–10.00). During the subsequent 1.5–2 h, characteristic changes in behavior and heart rate variability were observed in animals, which indicated the development of central and peripheral effects of the drugs and a fairly stable change in neurotransmitter metabolism [9, 10]. Since changes in heart rate indicated an increase in adrenergic influences to some extent, in the conditions of this experimental model, we decided to evaluate changes in the parameters of blood free radical balance. On the fourth day, 1.5–2 h after drug administration, the animals were taken out of the experiment by decapitation under Nembutal anesthesia (40 mg/kg) and blood was taken for further study. To assess the possible role of β-adrenoception in the development of changes in the free radical balance during stimulation of the CNTS, 6 animals from each group received a single injection of the non-selective β-blocker Anapriline (2 mg/kg) [22] 30 min before decapitation. Animals of the control group (C, n = 18) received injections of physiological saline (1 mL/kg) in the same regime that the experimental animals received drugs to stimulate the central neurotransmitter systems (CNTS).

To obtain plasma, whole blood was collected in tubes with an anticoagulant (heparin), mixed, and centrifuged for 15 min at 2000 rpm. Blood plasma was taken into clean dry test tubes, and erythrocytes were washed twice with cold saline followed by centrifugation. The resulting erythrocyte mass was used to obtain a hemolysate (0.2 mL of distilled water + 0.1 mL of washed erythrocytes).

The intensity of lipid peroxidation (LPO) was evaluated using the content of products interacting with 2-thiobarbituric acid, TBA-reactive substances (TBARS) in blood plasma (in nmol/L) [13] and erythrocyte hemolysate (nmol/mL of erythrocyte mass) [23]. Determination of catalase activity in the plasma and erythrocyte hemolysate was performed according to the standard method [24]. The optical density of the samples was measured on a PD-303UV Apel UV spectrophotometer (Japan).

Table 1. Effect of stimulation of the central neurotransmitter systems and β-adrenergic blocker on the parameters of blood free radical balance in rats, $M \pm m$

Indices	Groups	After CNTS stimulation	After administration of β-adrenoblocker
TBARS in erythrocytes, nmole/mL erythrocytes	Control	4.0 ± 0.4	7.4 ± 1.4*
	NAS	1.6 ± 0.1^^^	2.9 ± 0.4 ($p < 0.1$*), ^
	SRS	3.3 ± 0.3	1.7 ± 0.2***, ^^
	DPS	1.2 ± 0.3^^^	2.2 ± 0.3^
TBARS in blood plasma, nmole/L	Control	1.4 ± 0.3	2.9 ± 0.4*
	NAS	0.6 ± 0.1	0.6 ± 0.1^^^
	SRS	0.4 ± 0.1^	1.0 ± 0.1***, ^^
	DPS	0.5 ± 0.1^	0.7 ± 0.1*, ^^^
Catalase activity in erythrocytes, μkat/mL erythrocytes	Control	240.0 ± 8.0	278.1 ± 6.8*
	NAS	249.0 ± 1.3	293.9 ± 3.9***
	SRS	335.1 ± 1.0^^^	311.6 ± 6.9**, ^^
	DPS	308.3 ± 4.3^^^	327.7 ± 3.3**, ^^^
Catalase activity in plasma, μkat/mL	Control	51.7 ± 4.0	73.2 ± 3.7**
	NAS	49.7 ± 1.0	30.6 ± 6.6^^^
	SRS	60.6 ± 10.0	85.9 ± 10.0
	DPS	101.7 ± 6.9^^^	61.4 ± 6.4**

The significance of differences was determined using the Mann–Whitney U-test: *, **, ***, significance of changes after administration of β-blocker at $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively; ^, ^^, ^^^, significance of differences compared to control, $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively. The β-blocker was administered to 6 animals from each group.

Statistical analysis of the results was performed using the Statistica 12.0 software. Significance of differences was calculated using the Mann–Whitney U-test. Differences were considered statistically significant at $p < 0.05$. The data in the Table 1 are presented as mean values with standard measurement errors ($M \pm m$ or $M \pm$ SEM), the figure shows the degree of changes (in %) in the indices from the average values.

RESULTS

According to our data (Table 1), in animals of the control group, the average TBARS concentration and catalase activity in erythrocyte hemolysate and blood plasma corresponded to the results of previous studies [25].

In animals with NAS stimulation (Table 1), the level of TBARS in erythrocytes was 2.5 times lower ($p < 0.001$), and in blood plasma, 2 times lower ($p < 0.1$) compared with the control. At the same time, the catalase activity of erythrocytes and blood plasma did not differ from the control.

In the series with SRS stimulation, the level of TBARS was reduced only in blood plasma, by almost 3.5 times ($p < 0.001$) in comparison with the control. Along with this, the catalase activity in erythrocytes exceeded the control by 30% ($p < 0.001$).

After DPS activation, the concentration of TBARS in erythrocytes was 3.3 times lower compared to the control ($p < 0.001$), and, in blood plasma, it was 2.8 times lower ($p < 0.001$). At the same time, catalase activity increased both in erythrocytes (by 28%, $p < 0.001$) and in blood plasma (by 2 times, $p < 0.001$).

Thus, modeling increased CNTS activity induced a general trend towards a decrease in the level of TBARS and an increase in catalase activity both in erythrocytes and in blood plasma. The downward difference with the control in terms of the level of TBARS in the erythrocyte mass ranged from 18 to 70%, and in blood plasma, from 58 to 71%; the increase in erythrocyte catalase activity ranged from 4 to 40%, and in blood plasma, from 0 to 96%. To the greatest extent, the parameters of the free radical balance of the blood changed during DPS stimulation, and to the least extent, during the NAS stimulation.

Data shown in Table. 1 and Fig. 1 suggest that administration of a β-blocker to rats of the control group led to an increase in the concentration of TBARS in erythrocytes and blood plasma (by 85% and 107%, respectively, $p < 0.05$). At the same time, catalase activity increased in erythrocytes by 16% ($p < 0.05$) and in blood plasma by 42% ($p < 0.01$). The latter may indicate an increase in the lability of erythrocyte membranes as a result of FRO intensification.

After NAS stimulation, the administration of anapriline caused a trend towards an increase in the concentration of TBARS in erythrocytes (by 81%, $p < 0.1$), but no changes were noted in blood plasma (Table 1, Fig. 1). Catalase activity in this series increased only in erythrocytes (by 18%, $p < 0.01$).

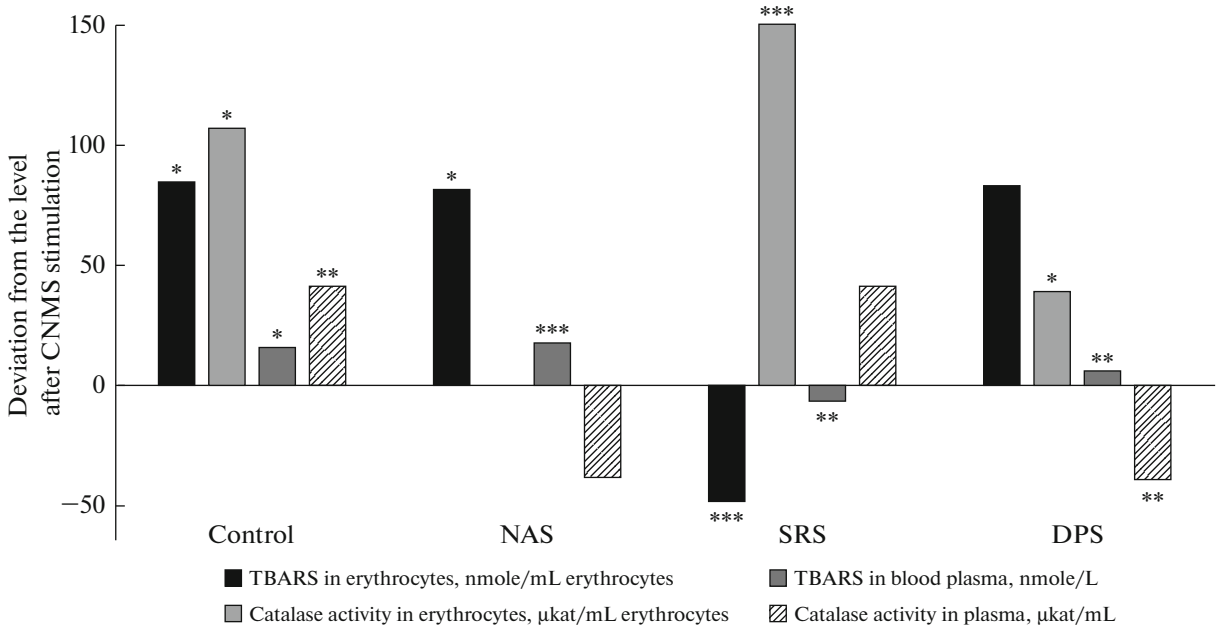

Fig. 1. Changes in the parameters of blood free radical balance in animals of the control and experimental groups after a single injection of β-blocker. Abscissa axis, changes in indices in the control and experimental groups; Ordinate axis, % deviation of indices from the values for which they were taken in the control series, minus the values of the indices after the administration of saline; in the experimental groups, the indices against the background of stimulation of NAS, SRS, DPS . The significance of differences was calculated using the Mann–Whitney test. *, **, and *** significant changes after β-blocker administration at $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

In rats with stimulated SRS after administration of the β-blocker, the level of TBARS in erythrocytes decreased by almost 50% ($p < 0.001$), and in blood plasma it increased by 150% ($p < 0.001$). Similarly, but to a lesser extent, catalase activity changed: in erythrocytes, it decreased by 7% ($p < 0.01$), in blood plasma, by 42% ($p < 0.2$) (Table 1, Fig. 1).

Finally, in the series with DPS activation after the administration of anapriline, an increase in the concentration of TBARS in erythrocyte hemolysate by 83% ($p < 0.1$) and in plasma by 40% ($p < 0.05$) was also found. The catalase activity of erythrocytes, which increased after DPS stimulation, increased by another 6% ($p < 0.01$) and turned out to be the highest among all experimental series. Catalase activity in blood plasma, on the contrary, became lower by 40% ($p < 0.01$).

In general, administration of the β-adrenergic blocker, both in the control and in the experimental series, increased the concentration of TBARS in erythrocytes and blood plasma, however, after stimulation of the central nervous system, the absolute values remained significantly lower than in the control: in the hemolysate of erythrocytes, the difference reached 60–77% ($p < 0.01$), in plasma, it was 66–79% ($p < 0.01$). The catalase activity of erythrocytes mainly increased, and in all series with CNTS activation it exceeded the control values by 6–16% ($p < 0.1$–0.001). However, the catalase activity in the blood plasma after the administration of the β-blocker changed in opposite directions, and the difference with the control series towards a decrease (by 58%, $p < 0.001$) was revealed only in the series with NAS stimulation. Consequently, as a result of the CNTS activation, the reaction of blood components to substances complementary to adrenoreceptors changed, affecting the processes of free radical oxidation and antioxidant protection.

DISCUSSION

According to the literature, drugs used for pharmacological activation of neurotransmitter systems (maprotiline, fluoxetine, 5-hydroxytryptophan, and L-dopa), administered in comparable doses, cause an increase in the concentration of the corresponding biogenic monoamines both in the central nervous system and in the blood within several hours of administration [4–6, 21]. Our own observations of changes in behavior, heart rate variability, and adrenoreactivity of erythrocytes in experimental animals confirmed that changes in the level of biogenic amines in the CNS and peripheral blood flow took place [9, 10].

Against this background, the animals showed a decrease in the level of FRO products and an increase in catalase activity in erythrocytes and blood plasma. These changes may be considered as a consequence of (1) the antiradical properties of the biogenic amines themselves, which have the ability to quench free rad-

icals by successive electron transfer with the loss of a proton [17, 18]; (2) the antioxidant activity of drugs used to stimulate CNTS (fluoxetine, [19], L-dopa [20]); or (3) adaptation at the molecular-cellular level to an increased level of biogenic amines, since they are similar to adaptive changes in FRO and antioxidant protection of nervous tissue, previously identified in stress and cerebral pathologies [12, 16].

It is important to note that shifts in the intensity of FRO and catalase activity occurred not only in blood plasma, where these parameters are determined by changes in various organs and tissues, but also in erythrocytes in a relatively short time (up to 4 days). This is consistent with the data on changes in the characteristics of erythrocytes and their reception of regulatory substances when subjected to CNTS [7, 9, 10]. An increase in the catalase activity of erythrocytes under these conditions may indicate the modulating effect of biogenic amines on the activity of the antioxidant defense enzyme through intracellular signaling molecules.

At the same time, the general changes in the level of FRO products and catalase activity in erythrocytes and blood plasma had some features in each experimental series. Thus, they turned out to be the most significant under conditions of DPS stimulation, which could be the result of a combination of the antiradical effects of dopamine and L-dopa [20]. On the other hand, taking into account previous data [3, 4], it is possible that this result originates from more rapid adaptive changes in membrane structures and enzyme systems as a result of a significant intensification of FRO after DPS activation. Under conditions of NAS and SRS stimulation, only some of the studied parameters changed significantly in the presence of general trends. In the SRS series, the more pronounced antioxidant properties of serotonin [8, 26] and fluoxetine [19] could be a possible cause. In addition, a marked increase in the adrenoreactivity of erythrocytes after SRS stimulation may be important for increasing the catalase activity of erythrocytes, as shown previously [9]. Apparently, the specific properties of the corresponding monoamines determine the severity and rate of development of general shifts in the parameters of the free radical balance of blood under conditions of stimulation of each of the neurotransmitter systems.

As for the effects of the β-blocker, it turned out that single administration caused an increase in the intensity of FRO, which probably resulted in an increase in the catalase activity of erythrocytes and blood plasma. These changes should obviously be considered as an urgent response to the blockade of β-adrenergic receptors, which leads to an increase in the level of free catecholamines in the blood due to the limitation of their binding to receptors on the membrane of erythrocytes [9] and cells of other tissues. Free catecholamines, upon reaching a certain critical concentration and autoxidation, probably, become sources of reactive oxygen species and cause oxidative stress [14]. Obviously, normal binding of catecholamines to the β-adrenergic receptors of erythrocytes and other elements reduces the risk of oxidative stress and is an important mechanism for maintaining blood free radical balance.

With this in mind, under conditions of CNTS stimulation, which leads to an increase in the concentration of monoamines in the blood [4–6, 21], it is possible to expect a significant increase in FRO during blockade of β-adrenergic receptors. Indeed, an increase in the level of TBARS in the blood occurred, but in all experimental series it was much lower than in control animals: SRS ≤ DPS < NAS < Control. The smallest changes were noted upon NAS stimulation, oppositely directed changes were noted after SRS activation, and a moderate unidirectional increase was noted after stimulation of the DPS. The catalase activity of erythrocytes also increased or remained at a high level, and after CNTS stimulation, the index remained higher than in the control: Control < NAS < SRS < DPS. We consider these results in favor of the fact that the main cause of the decrease in the intensity of FRO and the increase in the catalase activity of erythrocytes under conditions of CNS stimulation is the formation of adaptive resistance of membranes to a high level of biogenic amines [12, 13, 16], as well as a change in the sensitivity and reactivity of erythrocytes to ligands, taking into account previously obtained data [9, 10]. The role of the antioxidant properties of fluoxetine and L-dopa [19, 20] may be important for maintenance of a low FRO intensity, but in this case it seems to be less significant, since the shifts turned out to be more significant after SRS and DPS activation than after NAS stimulation, while no descriptions of the antioxidant properties of maprotiline were found in the literature.

With regard to the catalase activity of the plasma after administration of a β-adrenergic blocker, it changed in different directions: it increased in the control and after SRS activation but decreased with stimulation of NAS and DPS; in the experimental series it corresponded or was lower than in the control, especially after the stimulation of NAS: NAS < DPS ≤ Control < SRS. Apparently, in the series with activation of NAS and DPS, the ability of β-blocker to increase the resistance of erythrocyte membranes was clearly manifested, as noted previously [25]. However, after SRS stimulation, plasma catalase activity increased after the administration of anapriline and was the highest among all groups, which may reflect membrane instability and some depletion of the antioxidant protection of erythrocytes. The possibility of these changes is confirmed by the data [9] on a significant increase in erythrocyte adrenoreactivity after SRS stimulation.

CONCLUSIONS

Our results suggest that pharmacological modeling of increased activity of the noradrenergic, serotonergic, and dopaminergic systems is accompanied by a decrease in the concentration of FRO products and an increase in the catalase activity of erythrocytes and blood plasma. A single injection of a β-adrenergic blocker, which can cause an increase in the concentration of FRO products and catalase activity in erythrocytes, during stimulation of the central nervous system does not cause a sharp increase in the level of FRO products, which remains relatively low, and the catalase activity of erythrocytes increases even stronger. This gives a basis to consider changes in the free radical balance of the blood during CNTS stimulation as a manifestation of adaptive processes at the level of membranes and enzyme systems, which are associated with changes in the reception and reactivity of blood cells to monoamines. To the greatest extent, the changes are appeared after DPS activation and, to a lesser extent, after NAS stimulation. After SRS stimulation, the changes are multidirectional, which may be determined by the antiradical characteristics of specific monoamines, as well as drugs that stimulate their metabolism. The results of our study confirm the participation of biogenic amines in the modulation of blood free radical balance, but a more definite role of each could be assessed using specific agonists and antagonists of subtypes of adreno-, serotonin- and dopamine receptors.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare no conflict of interest.

Ethical approval. This study was performed with laboratory animals in compliance with ethical standards in accordance with the National Standard of the Russian Federation GOST R-53434-2009 "Principles of Good Laboratory Practice," Order of the Ministry of Health of the Russian Federation dated April 1, 2016 No. 199n "On Approval of the Rules of Good Laboratory Practice" and the European Convention Directive 2010/63/EU of 22.09.2010.

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