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METABOLIC ACCOMPANIMENT OF URINA LITHOGENICITY IN FEMALE RATS

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Background. We have previously discovered connections between the lithogenicity index of urine and a number of components of its composition. The aim of this study is to determine the relationship between the urine lithogenicity index and a number of metabolic components of plasma. **Materials and Methods**. Experiment was performed on 60 healthy old female Wistar rats 220-300 g. Ten animals remained intact, using daily water from drinking ad libitum. Other animals for 6 days were loaded through the tube with daily and various mineral waters at a dose of 1,5 mL/100 g of body mass. The day after the completion of the drinking course collected daily urine and estimate its lithogenicity. We determined plasma levels of electrolytes, nitric metabolites, glucose, amylase, cholesterol and lipids peroxidation parameters. **Results**. The lithogenicity of urine is upregulated by the plasma level of uric acid, bilirubin, potassium, malondialdehyde and catalase, but it is downregulated by calciumemia. The rate of determination of lithogenicity is 45,7%. **Conclusion**. Both lithogenic and litholytic factors are present in the plasma. This gives grounds for finding ways to correct lithogenicity.
Keywords: urine lithogenicity, plasma metabolites, drinking mineral waters, Truskavets' spa, female rats.

INRODUCTION

We have previously discovered connections between the lithogenicity index of urine and a number of components of its composition. Medium molecular polypeptides, catalase, sodium, phosphates and urea has been identified as prolithogenic factors while tubular reabsorption of water as litholytic factor [4]. The aim of this study is to determine the relationship between the urine lithogenicity index and a number of metabolic components of plasma.

MATERIALS AND METHODS

Experiment was performed on 60 healthy old female Wistar rats 220-300 g. Ten animals remained intact, using daily water from drinking ad libitum. Other animals for 6 days were loaded through the tube with daily and mineral waters at a dose of 1,5 mL/100 g of body mass [4].

The day after the completion of the drinking course animals were placed in individual chambers with perforated bottom for collecting daily urine and estimate its lithogenicity [4].

The experiment was completed by decapitation of rats in order to collect as much blood as possible.

We determined plasma levels of electrolytes: calcium (by reaction with arsenase III), magnesium (by reaction with colgamite), phosphates (phosphate-molybdate method), chloride (mercury-rhodanidine method), sodium and potassium (both in plasma and in erythrocytes) by flamming photometry; nitric metabolites: creatinine (by Jaffe's color reaction by Popper's method), urea (urease method by reaction with phenolhypochlorite), uric acid (uricase method), medium molecular polypeptides/middle mass molecules (by spectrophotometric method), bilirubin (by diazoreaction using the Jedrashik-Kleghorn-Grof method); cholesterol (by a direct method after the classic reaction by Zlatkis-Zack) [6], lipids peroxidation products: diene conjugates (spectrophotometry of the heptane phase of the lipids extract) [5] and malondyaldehide (in the test with thiobarbituric acid) [1], antioxidant enzymes: superoxide dismutase erythrocytes (according to the degree of inhibition of reduction of nitroblue tetrazolium in the presence of N-methylphenazonium metasulphate and NADH) [2,11] and catalase plasma (at the rate of decomposition of hydrogen peroxide) [10], as well as amylase (Karavay's amyloclastic method with starch substrate) and glucose (glucose-oxidase method) [6].

The analyzers "Pointe-180" ("Scientific", USA) and "Reflotron" (Boehringer Mannheim, BRD) were used with appropriate sets and a flaming spectrophotometer "СФ-47".

Digital material is statistically processed on a computer using the software package "Statistica 64".

RESULTS AND DISCUSSION

As a result of the screening of the correlations of urinary lithogenicity with plasma metabolic parameters, a matrix was created (Table 1).

Table 1. Matrix of correlations between urine lithogenicity and plasma metabolic parameters

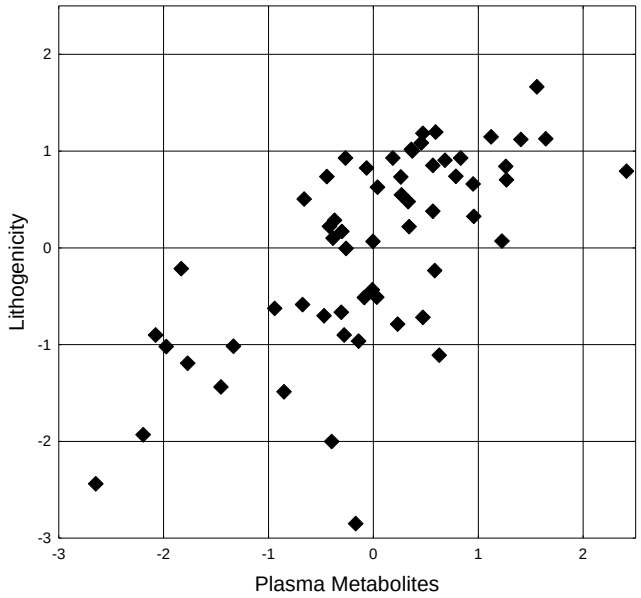
Variable	Lith
Na Er	0,33
Bilirubin	0,34
Amylase	-0,21
Uric acid	0,35
Katalase	0,35
MDA	0,42
DC	0,23
K P	0,29
Ca P	-0,28

Next, a regression model was built by stepwise exclusion of variables until the maximum value of Adjusted $R^2$was reached (Table 2).

Table 2. Regression Summary for Dependent Variable: Lithogenicity

N=60	R=,676; R^2=,457; Adjusted R^2=,395; F(6,5)=7,4; p<,00001; Std.Error of estimate: ,197					
	Beta	St. Err. of Beta	B	St. Err. of B	t(53)	p-value
Intercpt			0,2511	0,1707	1,47	0,147
Bilirubin	0,238	0,116	0,0280	0,0137	2,05	0,045
Uric acid	0,329	0,108	0,0002	0,0001	3,05	0,004
Katalase	0,135	0,116	0,7246	0,6250	1,16	0,251
MDA	0,227	0,110	0,0020	0,0010	2,06	0,045
K P	0,223	0,104	0,0714	0,0332	2,15	0,036
Ca P	-0,200	0,107	-0,0571	0,0305	-1,87	0,067

It was found that the lithogenicity of urine is upregulated by the plasma level of uric acid, which is quite expected, as well as bilirubin, potassium, malondialdehyde and catalase, but it is downregulated by calciumemia, which seems strange, because urinary calcium together with uric acid is a lithogenic factor. The rate of determination of lithogenicity is 45,7% (Table 2 and Fig. 1).



$R=0,676$; $R^2=0,457$; $\chi^2_{(6)}=33,5$; $p<10^{-5}$; Λ Prime=0,543

Fig. 1. Scatterplot of canonical correlation between plasma metabolic components (X-line) and urine lithogenicity (Y-line)

Table 3. Factor structure of plasma and urine canonical Roots

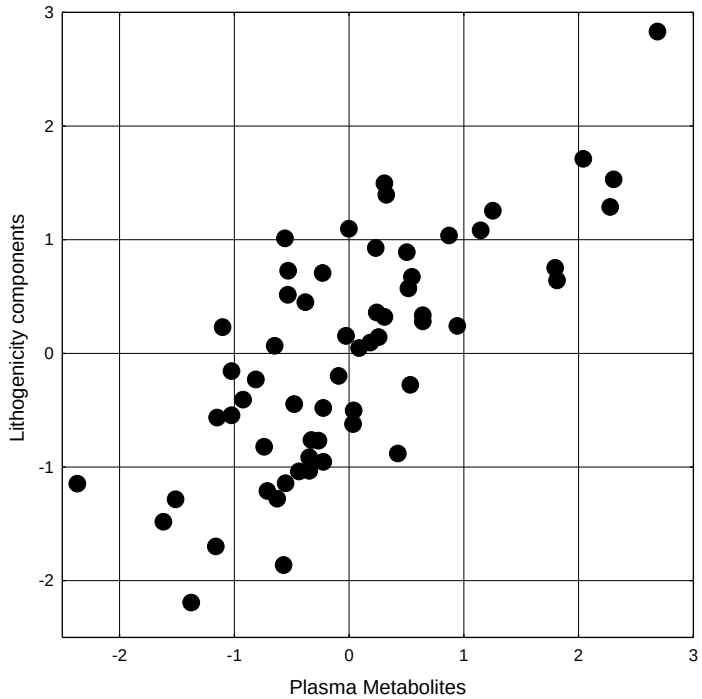
Root Variable	left set R
Bilirubin	0,416
Uric acid	0,515
Katalase	0,588
MDA	0,678
K P	0,434
Ca P	-0,331

Root Variable	right set
	R
Lith	0,894
CrU	-0,247
MgU	-0,746
CaU	0,437
UAU	0,615

Root Variable	Correlations, left set with right set				
	Lith	CrU	MgU	CaU	UAU
Bilirubin	0,344	-0,378	-0,239	0,297	-0,094
Uric acid	0,347	0,186	-0,429	-0,233	0,556
Katalase	0,348	-0,374	-0,208	0,469	0,009
MDA	0,416	-0,002	-0,310	0,262	0,413
K P	0,286	-0,135	-0,274	0,139	0,120
Ca P	-0,277	0,078	0,131	-0,279	-0,097

A more detailed analysis revealed (Table 3) that all plasma lithogenic factors downregulate magnesium concentration in urine; bilirubin and catalase also downregulate creatinine concentration. On the other hand, the concentration in urine of uric acid (more precisely, urate, because urine is alkaline in rats) is upregulated by uricemia and malondialdehyde, and the concentration of calcium is upregulated by the latter, catalase, and bilirubin. Interestingly, plasma calcium and uric acid have a downregulatory effect on urinary calcium.

We are aware that correlations do not necessarily reflect cause-and-effect relationships, but can be a manifestation of the regulatory influence of other factors, primarily hormonal. This will be the subject of the next article. Now let's limit ourselves to stating the fact that the constellation of metabolic plasma variables determines the lithogenicity of urine in general and its components in particular by 55,2% (Fig. 2).



$R=0,743$; $R^2=0,552$; $\chi^2_{(30)}=89$; $p<10^{-6}$; Λ Prime=0,187

Fig. 2. Scatterplot of canonical correlation between plasma metabolic components (X-line) and urina lithogenicity components (Y-line)

Discriminant analysis [9] is another approach to identifying plasma metabolic parameters characteristic of qualitatively different states of urinary lithogenicity. The forward stepwise program included ten variables in the discriminant model, including the weight of the animal as an integral metabolic state (Tables 4 and 5).

Table 4. Discriminant Function Analysis Summary. Metabolic variables currently in the model

Step 10, N of Variables currently in the model: 10; Grouping: 3 groups
Wilks' Lambda: 0,4350; approx. $F_{(21)}$=2,48; p=0,0018

Variables currently in the model	Groups (n)				Parameters of Wilks' Statistics				
	Intact rats (10)	Lith - (13)	Lith ± (40)	Lith + (7)	Wilks' Λ	Partial Λ	F-remove (2,48)	p-level	Tolerancy
Sodium Erythrocytes, mM/L	22,01 0	21,10,96 -0,20	22,21,01 +0,04	27,41,25 +1,22	0,480	0,907	2,47	0,096	0,833
Malondyaldehide Plasma, µM/L	63,31 0	61,50,97 -0,08	74,51,18 +0,52	85,31,35 +1,02	0,482	0,903	2,58	0,086	0,435
Uric Acid Plasma, µM/L	662 1 0	568 0,86 -0,28	711 1,07 +0,14	902 1,36 +0,70	0,477	0,912	2,31	0,110	0,730
Cholesterol Plasma mM/L	1,57 1 0	1,40 0,89 -0,36	1,64 1,04 +0,14	1,66 1,06 +0,19	0,459	0,947	1,35	0,270	0,857
Chloride Plasma, mM/L	94,31 0	91,20,97 -0,44	93,00,99 -0,18	94,11,00 -0,03	0,490	0,887	3,06	0,056	0,638
Potassium Plasma, mM/L	4,23 1 0	3,25 0,77 -1,39	3,66 0,87 -0,81	4,23 1,00 +0,01	0,542	0,802	5,92	0,005	0,666
Calcium Plasma, mM/L	3,35 1 0	2,94 0,88 -0,40	2,71 0,81 -0,62	1,91 0,57 -1,42	0,484	0,898	2,72	0,076	0,734
Glucose Plasma, mM/L	4,95 1 0	5,53 1,12 +0,53	5,29 1,07 +0,31	5,20 1,05 +0,23	0,467	0,931	1,79	0,178	0,773
Diene conjugates Plasma, E^{232}/mL	1,35 1 0	1,30 0,97 -0,11	1,49 1,10 +0,35	1,35 1,00 +0,01	0,482	0,902	2,62	0,083	0,365
Body Mass, g	263 1 0	272 1,04 +0,34	258 0,98 -0,16	269 1,02 +0,22	0,469	0,927	1,89	0,162	0,834

Note. In each column, the first line is the average value, the second is the fraction of the norm, and the third is the Z-score. The intact group is not subject to discriminant analysis.

Table 5. Summary of Stepwise Analysis. Variables ranged by criterion Lambda

Variables currently in the model	F to enter	p-level	Λ	F-value	p-level
Sodium Erythrocytes, mM/L	4,93	0,011	0,852	4,93	0,011
Calcium Plasma, mM/L	2,53	0,088	0,782	3,67	0,008
Potassium Plasma, mM/L	3,61	0,034	0,691	3,72	0,002
Body Mass, g	3,24	0,047	0,617	3,69	0,001
Chloride Plasma, mM/L	1,32	0,275	0,588	3,23	0,001
Uric Acid Plasma, µM/L	1,53	0,227	0,555	2,97	0,001
Cholesterol Plasma mM/L	1,35	0,269	0,527	2,75	0,002
Diene conjugates Plasma, E^{232}/mL	1,30	0,281	0,501	2,58	0,002
Malondyaldehide Plasma, µM/L	1,76	0,183	0,467	2,52	0,002
Glucose Plasma, mM/L	1,79	0,178	0,435	2,48	0,002

The rest of the metabolic variables were outside the model (Table 6), despite the fact that some of them are carriers of characteristic information.

Table 6. Discriminant Function Analysis Summary. Metabolic variables currently not in the model

Variables	Groups (n)				Parameters of Wilks' Statistics				
	Intact rats (10)	Lith - (13)	Lith ± (40)	Lith + (7)	Wilks' Λ	Partial Λ	F to enter	p-level	Tolerancy
Bilirubin Plasma, µM/L	4,63 1 0	3,92 0,85 -0,28	4,46 0,96 -0,07	6,31 1,36 +0,66	0,429	0,986	0,32	0,725	0,755
Middle Mass Molecules Plasma, units	154 1 0	129 0,84 -0,49	146 0,95 -0,15	164 1,06 +0,20	0,430	0,989	0,25	0,779	0,852
Phosphate Plasma, mM/L	0,72 1 0	1,05 1,46 +0,72	0,90 1,26 +0,40	0,85 1,19 +0,29	0,434	0,997	0,07	0,936	0,755
Amylase Activity Plasma, g/h•L	152 1 0	164 1,08 +0,49	155 1,02 +0,11	137 0,90 -0,62	0,435	0,999	0,01	0,989	0,666
Creatinine Plasma, µM/L	72,5 1 0	78 1,07 +0,21	79 1,09 +0,27	98 1,35 +1,07	0,426	0,981	0,47	0,630	0,698
Urea Plasma, mM/L	7,42 1 0	8,04 1,08 +0,36	8,63 1,16 +0,71	8,99 1,21 +0,91	0,430	0,987	0,30	0,743	0,616
Katalase Activity Plasma, µM/h•L	103 1 0	109 1,06 +0,19	124 1,20 +0,75	170 1,64 +2,37	0,427	0,982	0,43	0,653	0,730
Magnesium Plasma, mM/L	0,88 1 0	0,75 0,86 -0,21	0,85 0,97 -0,05	0,94 1,07 +0,11	0,417	0,960	0,99	0,380	0,620
Superoxide Dismutase Erythrocytes, un/mL	58,0 1 0	55,4 0,95 -0,24	56,1 0,97 -0,18	51,9 0,89 -0,57	0,429	0,986	0,33	0,720	0,748
Potassium Erythrocytes, mM/L	87,0 1 0	85,7 0,98 -0,19	87,2 1,00 +0,03	86,1 0,99 -0,14	0,424	0,976	0,58	0,563	0,771
Sodium Plasma, mM/L	128,6 1 0	129,1 1,00 +0,10	129,1 1,00 +0,10	128,9 1,00 +0,07	0,431	0,991	0,22	0,806	0,109

The dividing information contained in 10 variables is condensed in 2 canonical discriminant roots (Table 7). The major root contains 80,9% of discriminative opportunities (r*=0,688; Wilks' Λ=0,435; $\chi^2_{(20)}$=44; p=0,002) and the minor root 19,1% (r*=0,418; Wilks' Λ=0,825; $\chi^2_{(9)}$=10; p=0,345).

Table 7. Standardized and Raw Coefficients for Canonical Variables

Coefficients	Standardized		Raw	
Variables	Root 1	Root 2	Root 1	Root 2
Sodium Erythrocytes, mM/L	-0,303	-0,627	-0,068	-0,140
Calcium Plasma, mM/L	0,539	-0,086	0,633	-0,101
Potassium Plasma, mM/L	-0,772	0,297	-1,023	0,393
Body Mass, g	0,219	-0,609	0,010	-0,027
Chloride Plasma, mM/L	0,605	0,157	0,109	0,028
Uric Acid Plasma, µM/L	-0,502	-0,082	-0,0012	-0,0002
Cholesterol Plasma mM/L	-0,227	0,464	-0,558	1,138
Diene conjugates Plasma, E^{232}/mL	0,626	0,694	1,463	1,621
Malondyaldehide Plasma, µM/L	-0,680	-0,158	-0,024	-0,006
Glucose Plasma, mM/L	0,422	-0,180	0,539	-0,230
	Constants		-14,61	3,072
	Eigenvalues		0,898	0,211
Cumulative Proportions			0,809	1

The calculation of the discriminant root values for each animal as the sum of the products of raw coefficients (Table 7) to the individual values of discriminant variables together with the constant enables the visualization of each rat in the information space of the roots (Fig. 3).

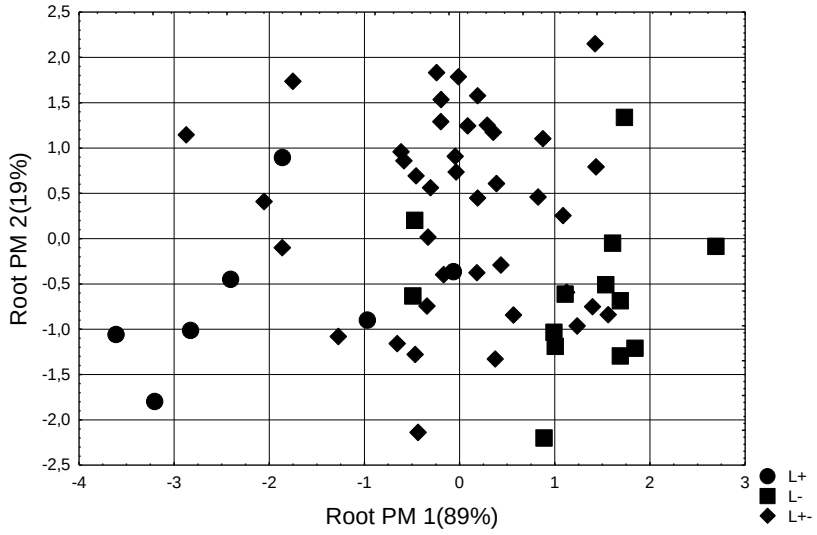


Fig. 3. Individual values of the first and second roots of the plasma metabolic parameters in rats with different levels of lithogenicity

Rats with **normal** lithogenicity are naturally located along the axis of the major root, as a rule, in its quasi-zero zone. This reflects, with few exceptions, quasi-zero Z-scores of plasma metabolic variables. Localization in the left axis zone of rats with **increased** lithogenicity reflects their above-normal or sample-maximum levels of variables that correlate **positively** with lithogenicity, as well as below-normal or sample-minimum levels of variables that correlate **negatively** with lithogenicity. At the opposite pole of the axis are localized rats with **reduced** lithogenicity of urine, which is accompanied by minimum for sampling or reduced

levels of **lithogenic** metabolites and maximum for sampling or increased levels of **litholytic** metabolites.

Table 8. Factor Structure Matrix and Means of Roots and Variables

	Correlations Variables-Roots		Lith+ (7)	Lith± (40)	Lith- (13)
Root 1 (80,9%)	**R1**	**R2**	**-2,13**	-0,02	**+1,22**
Sodium Erythrocytes	-0,416	-0,292	**+1,22**	+0,04	**-0,20**
Malondyaldehide Plasma	-0,257	0,158	**+1,02**	+0,52	**-0,08**
Uric Acid Plasma	-0,231	0,048	**+0,70**	+0,14	**-0,28**
Bilirubin Plasma			**+0,66**	-0,07	**-0,28**
Cholesterol Plasma	-0,194	0,361	**+0,19**	+0,14	**-0,36**
Middle Mass Molecules			**+0,20**	-0,15	**-0,49**
Chloride Plasma	-0,186	0,008	**-0,03**	-0,18	**-0,44**
Potassium Plasma	-0,389	0,063	**+0,01**	-0,81	**-1,39**
Calcium Plasma	0,360	0,197	**-1,42**	-0,62	**-0,40**
Glucose Plasma	0,129	-0,159	**+0,23**	+0,31	**+0,53**
Phosphate Plasma			**+0,29**	+0,40	**+0,72**
Amylase Activity Plasma			**-0,62**	+0,11	**+0,49**
Root 2 (19,1%)	**R1**	**R2**	-0,61	**+0,32**	-0,67
Diene conjugates Plasma	-0,040	**0,413**	+0,01	**+0,35**	-0,11
Body Mass	0,054	**-0,591**	+0,22	**-0,16**	+0,34

Along the axis of the minor root, rats with normal lithogenicity are usually located higher than the rest of the animals. This reflects slightly higher than average levels of diene conjugates and the fact that both increased and decreased urinary lithogenicity are accompanied by slightly higher than average body weight.

Despite the visually noticeable interpenetration of members, the demarcation of clusters turned out to be statistically significant (Table 9).

Table 9. Squared Mahalanobis Distances between groups (over diagonal), F-values (df=10,5) and p-levels (under diagonal)

Groups	Lith+ (7)	Lith- (13)	Lith± (40)
Lith+	**0,0**	11,2	5,43
Lith-	**4,30** 10^{-4}	**0,0**	2,41
Lith±	**2,72** **0,010**	**1,99** **0,056**	**0,0**

However, the accuracy of the classification based on the parameters of table 10 is not high enough (table 11).

Table 10. Coefficients and Constants for Classification Functions

Variables currently in the model	Lith + (p=0,117)	Lith - (p=0,217)	Lith ± (p=0,667)
Sodium Erythrocytes, mM/L	1,168	0,934	0,888
Calcium Plasma, mM/L	15,05	17,16	16,28
Potassium Plasma, mM/L	-20,47	-23,88	-22,24
Body Mass, g	0,728	0,759	0,722
Chloride Plasma, mM/L	6,723	7,091	6,982
Uric Acid Plasma, µM/L	-0,015	-0,019	-0,018
Cholesterol Plasma mM/L	16,30	14,50	16,25
Diene conjugates Plasma, E^{232}/mL	37,10	42,09	41,79
Malondyaldehide Plasma, µM/L	-0,241	-0,323	-0,298
Glucose Plasma, mM/L	15,62	17,41	16,53
Constants	-582,2	-628,8	-605,9

Table 11. Classification Matrix
Rows: Observed classifications; Columns: Predicted classifications

Groups	Percent correct	Lith+ (7)	Lith- (13)	Lith± (40)
		p=,117	p=,217	p=,667
Lith+ (7)	57,1	**4**	0	3
Lith- (13)	69,2	0	**9**	4
Lith± (40)	90,0	1	3	**39**
Total	81,7	5	12	43

CONCLUSION

So, we found that the lithogenicity of the urine is quite significantly related to the metabolic parameters of the blood, some of which are upregulating/lithogenic, and others are dawnregulating/litholytic. In particular, it has been shown that oxidative stress negatively affects both lithogenicity and kidney function [3,7]. This gives grounds for searching for methods of reducing lithogenicity, in particular by using antioxidants.

CONFORMITY TO ETHICAL STANDARDS

Experiments on animals have been carried out in accordance with the provisions of the Helsinki Declaration of 1975, revised and supplemented in 2002 by the Directives of the National Committees for Ethics in Scientific Research.

The carry out of experiments was approved by the Ethics Committee of the USR Institute of Medicine of Transport. The modern rules for the maintenance and use of laboratory animals complying with the principles of the European Convention for the Protection of Vertebrate Animals used for scientific experiments and needs are observed (Strasbourg, 1985).

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