

Influence of diabetes mellitus on free radical processes in the heart in rats with Guerin's carcinoma and characteristics of malignant lesions depending on the gender of animals

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Abstract

Aims: To study the intensity of lipid peroxidation (LPO) and the activity of the main antioxidant protection enzyme: superoxide dismutase (SOD) in heart tissues and tumors in rats of both genders with Guerin's carcinoma (GC) and the tumor growth against the background of diabetes mellitus (DM).

Materials and methods. Our research work was carried out in 80 outbred albino male and female rats, divided into 4 groups, with 10 animals of each gender in a group. The animals of two groups, namely, an intact animal group and a group of rats treated with alloxan DM (with a 5-fold increase in glucose levels) were subcutaneously transplanted with the Guerin's carcinoma (GC) strain cells, and at the same time we used one group of the intact rats and another group of the animals with DM as the references. The content of malondialdehyde (MDA), diene conjugates (DC), and the SOD activity in the heart and the tumor tissues were determined by conventional spectrophotometric methods.

Results. The most pronounced changes were found in the heart in the female rats with isolated GC and GC growing against the background of DM: a more than threefold increase in MDA, with a significant increase in DC and a multiple increase in the SOD activity as compared with the intact animals. In the GC tissue, the dependence of the severity of the increase in the MDA content on the size of the tumor was traced: the

maximum increase in both parameters was observed in males with GC tumor growing against the background of DM. In the males, the volume of the subcutaneous tumor nodes was 1.8 times greater than that in the reference group and in the females with combined pathology, while in the females with combined pathology the volume of their tumors was 1.3 times less than that in the reference group, although the area of tumor lesions in them was maximum due to extensive metastasizing.

Conclusion. DM has changed the specifics of oncogenesis depending on the gender of the animals. The identified gender differences in the redox status of the heart and the tumor in rats with combined pathology contribute to specifics of oncogenesis in males and females and determines their life expectancy.

Keywords

Heart, Free radical oxidation, Superoxide dismutase, Diabetes, Guerin's carcinoma, Male and female rats

Imprint

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Introduction

Cancer and diabetes are comorbid pathologies [1, 2]. Diabetes mellitus (DM) causes multiple organ dysfunction and aggravates the course of malignant pathology [3] as well as heart diseases including cardiovascular dysfunction [4]. It has been shown that in DM, the risk of developing heart failure is higher both in males and females [4].

The basis of cellular homeostasis is the balance of redox processes. The role of oxidative stress in the development and the course of both malignant pathology [5–8] and DM [9–12] is beyond doubt.

The evidence data available in the reference literature on the dynamics of changes in the activity of antioxidant enzymes during the development of DM in

blood of patients and tissues of experimental animals are inconsistent [10], and in case of a tumor growth against the background of diabetes, comprehensive experimental studies of the oxidative status of different tissues have not been carried out.

Both in malignant pathology and in DM, the dependence of the course of some pathological processes and the metabolic change features on the gender of experimental animals has been identified. Thus, certain significant gender differences were found in the regulation of the plasminogen system and the timing of the formation of experimental melanoma in mice against the background of chronic neurogenic pain [13], the functioning of the hypothalamic-pituitary-adrenal axes in the body in male and female mice with transplanted melanoma [14], and the effect of knockout of the urokinase gene on the growth of melanoma in the experiment [15]. Only in males with DM, a decrease in insulin-like growth factors and the IGFBP-1 carrier protein was observed in the heart tissue [16]. A rat model of gestational DM has shown the presence of the gender differences in the regulation of lipid metabolism in the fetal liver [17].

Taking into account the role of free radical processes and the dependence of the course of the pathological processes on the gender of experimental animals, as well as the pronounced effect of DM on the development of heart diseases, the aim of our work was to study the intensity of lipid peroxidation (LPO) and indicators of the anti-oxidant protection in the heart of rats of both genders with DM, Guerin's carcinoma (GC) and their combined pathology.

Materials and methods

The study included outbred albino rats of both genders weighing 180-220 g originated from the stock kept by the "Research Center of Biomedical Technologies" (Branch Andreevka, Moscow Region). All manipulations with the animals were in full compliance with *Directive 86/609/EEC* on the Protection of Animals Used for Experimental and Other Scientific Purpose. The record of the experimental study was approved by the Commission on Bioethics at the National Medical Research Center for Oncology of the Ministry of Health of Russia, Record No. 21/99 by the Ethics Committee dated September 1, 2020.

The animals were divided into 4 groups (10 animals of each gender per group): 1) intact animals; 2) animals with DM; 3) animals with growth of

transplanted Guerin's carcinoma cells; 4) animals with growth of transplanted Guerin's carcinoma cells against the background of DM. To reproduce experimental diabetes, alloxan was intraperitoneally injected at a single dose of 150 mg/kg of body weight, and blood glucose levels were measured during a week. At the time of tumor transplantation in the animals of the fourth group, the average blood glucose level was 25.4 ± 1.2 mmol/l, while in the group of intact animals it was 5.2 ± 0.3 mmol/l. The rats of the third and fourth groups after 1 week of persistent hyperglycemia were subcutaneously injected with 0.5 ml of a suspension of the Guerin's tumor cells in a 1:5 dilution with saline solution. 3 days after the injection of the suspension of Guerin's carcinoma strain cells, the subcutaneous tumor growth was recorded. The animals of all groups were slaughtered with a guillotine 10 days after tumor transplantation in group 3 and 4.

The intensity of lipid peroxidation (LPO) processes was evaluated by the tissue contents of primary products - diene conjugates (DC) and TBA-positive products in terms of malondialdehyde (MDA) as the most stable secondary product of LPO. The activity of superoxide dismutase (SOD) was determined by the degree of inhibition of the reduction of nitroblue tetrazolium in the presence of the superoxide radical produced from the reaction of reduction of molecular oxygen by adrenaline in an alkaline medium; the enzyme activity was expressed in U/g of tissue. All indicators were determined in the 10% tissue homogenates by conventional spectrophotometric methods [18].

Statistical processing of the results was carried out with STATISTICA 10.0 using the Student's t-test for two independent samples, as well as using the non-parametric Mann-Whitney test. The compliance of the samples with the normal distribution was assessed using the Shapiro-Wilk test. In the tables, the data are presented as the mean value \pm standard error of the mean ($M \pm m$), the median and the values of the lower and upper quartiles are also indicated: Me (Q25; Q75). Differences were considered statistically significant at $p < 0.05$ and tending towards statistical significance at $0.05 < p < 0.1$.

Results

The content of LPO products: MDA and DC, as well as the activity of SOD in the heart of the rats are presented in Table 1 herein.

Table 1

The content of malondialdehyde, diene conjugates and the activity of superoxide dismutase in the heart tissue of rats with diabetes mellitus during the development of Guerin's carcinoma

Parameters M±m Me (Q25; Q75) n=10	Intact animals	Diabetes mellitus	Guerin's carcinoma	Diabetes mellitus + Guerin's carcinoma
MDA, nmol/g males	16.03±1.96 17.37(13.59;19.86)	14.87±2.66 13.4(6.81;20.43)	14.86±1.2 14.86 (12.72;17.01)	12.86±1.13 12.48(9.04;16.14)
MDA, nmol/g females	14.46±1.3 14.66(11.19;17.17)	43.24±2.56 43.03(38.71;46.29) p=0.000000 p ₃ =0.000000	46.89±2.23 47.39(41.67;51.91) p=0.000000 p ₃ =0.000000	46.88±3.09 45.11(39.23;56.27) p=0.000000 p ₃ =0.000000
DC, μmol/g males	20.61±2.17 21.62(14.87;25.94)	24.5± 1.71 24.49(19.34;27.56)	42.05±1.5 42.05(37.94;46.16) p=0.000000 p ₁ =0.000000	23.75±1.52 22.92(19.15;26.44) p ₂ =0.000000
DC, μmol/g females	20.69±0.81 21.07(18.41;21.6)	15.05±1.06 15.22(12.31;16.42) p=0.000515 p ₃ =0.000206	36.37±3.62 34.21(28.38;45.19) p=0.000505 p ₁ =0.000023	28.38±1.39 28.5(25.39;31.14) p=0.000147 p ₁ =0.000000 p ₂ =0.053960 p ₃ =0.037093
SOD, U/g males	30.29±3.43 31.72(28.29;37.25)	14.02±1.58 13.07(10.18;18.29) p=0.000419	8.95±0.82 8.85(7.61;11.09) p=0.000010 p ₁ =0.010572	8.69±0.93 8.46(6.17;11.66) p=0.000010 p ₁ =0.009317
SOD, U/g females	8.38±0.82 8.38(7.45;9.68) p ₃ =0.000007	10.71±1.33 10.71(8.19;12.66)	46.17±10.86 47.6(13.81;71.5) p=0.002739 p ₁ =0.004540 p ₃ =0.003078	52.88±4.6 58.08(37.82;64.8) p=0.000000 p ₁ =0.000000 p ₃ =0.000000

Notes: Statistical significance of the differences: p - compared with the group of intact animals, p₁ - compared with the group of animals with diabetes mellitus, p₂ - compared with the group of animals with Guerin's carcinoma, p₃ - between males and females.

In the intact animals, there were no gender differences in the content of lipid peroxidation products in the heart reported. In the males, the MDA level remained unchanged both during the development of diabetes mellitus and the growth of Guerin's carcinoma and in case of comorbidity, i.e. the malignant growth in diabetic rats. In contrast to the males, the females showed a sharp increase in the content of MDA in the heart tissue under all conditions studied. In diabetes mellitus, the level of MDA increased by a factor of 3, and with the growth of Guerin's carcinoma, both against the background of diabetes and without the latter, it was found to be 3.2 times greater as compared with the intact animals. At the same time, a highly significant excess of the MDA content in the females against the males was observed: in diabetes mellitus it was 2.9 times greater, in case of Guerin's carcinoma it was 3.2 times greater, and under comorbidity it was 3.6 times higher (p = 0.000000 in all cases).

The content of DC in DM in the heart of the males did not change significantly, and in the fe-

males it turned out to be reduced by 27.3% (p = 0.0005) as against the intact animals that resulted in the appearance of the gender differences: in the males, the level of this LPO product became higher than that in the females by 38.8% (p=0.0002). With Guerin's carcinoma, an increase in the DC content was observed in the animals of both genders: in the males by 104% (p=0.000000), and in the females by 75.8% (p=0.0005) versus the intact animals of the corresponding gender. At the same time, with Guerin's carcinoma, the DC level was higher than that found in the animals with DM: in the males by 71.6% and in the females by 141.7% (p≤0.00002). With the growth of Guerin's carcinoma against the background of DM, the content of DC was lower than that in the animals with the malignant growth only: in the males by 43.5% (p=0.000000) and in the females by 22% (p=0.05). In this case, the level of the above mentioned product in the females remained higher by 37.2% than that recorded in the intact females (p=0.0001) and exceeded the level in the males

with combined pathology by 19.5% ($p=0.037$). In the males with combined pathology, no significant differences from the intact animals were observed.

Particularly pronounced differences between the males and the females were observed in the activity of SOD as the main antioxidant enzyme, which largely determined the severity of oxidative stress and also labially responded to the level of the LPO intermediates. In the males, there was a decrease in the SOD activity under all the studied pathological condition: the most pronounced reduction by 70.5% under the malignant growth of Guerin's carcinoma only and by 71.3% with the tumor growth against the background of DM ($p = 0.00001$), while as in DM itself, the SOD activity was lower by 53.7% than that in the intact males ($p=0.0004$) and higher than in both groups with Guerin's carcinoma by 56.6-61.3% ($p=0.01$). In the females, in which the SOD activity in the heart in the intact state was 3.6 times lower than that found in the males ($p = 0.000007$), with the growth of Guerin's carcinoma, the SOD activation was observed on average by a factor of 5.5-6. With the development of the tumor in the animals with DM, an increase in the enzyme activity was recorded to be 6.3 times versus the intact females and 4.8 times against the animals with DM ($p=0.000000$ in both cases).

An increase in the content of MDA was also demonstrated in the mitochondrial fraction of the heart in the female rats with DM by a factor of 1.9 and in those with the growth of Guerin's carcinoma against the background of DM by a factor of 1.7 [19,20].

Having identified the significant gender differences in the severity of the changes in lipid peroxidation products and the SOD activity in the heart during the growth of Guerin's carcinoma against the background of DM and in the animals without DM, taking into account the importance of free radical processes in a tumor invasion, we compared the data obtained with the characteristics of the tumor growth in males and females in the presence and absence of DM in the animals.

As can be seen from Table 2 herein, in the males with DM, the average tumor volume was by 75.4% ($p=0.0041$) larger than that found in the animals with the growth of Guerin's carcinoma in the males without DM, while in the females, on the contrary, there was a tendency to inhibition of the tumor growth. In this case, in the females with DM, the average tumor volume was 3 times ($p=0.0001$) less than that recorded in the males. A distinctive feature of the tumor process developing against the background of DM in the females was a combination of small sizes of subcutaneous primary tumor nodes with a generalization of the process, accompanied by metastatic lesions of the parietal and visceral peritoneum, ovaries, kidneys and the development of ascites.

The study of the LPO parameters in the tumor tissue revealed some differences between the males and females. The content of MDA in the tissue of Guerin's carcinoma, which developed against the background of DM, was 86.7% ($p=0.0025$) higher in the males than in the tumor of the animals without DM, and

Table 2

The content of malondialdehyde, diene conjugates and the activity of superoxide dismutase in tumor tissue of rats with diabetes mellitus during the development of Guerin's carcinoma

Parameters M±m Me (Q25; Q75) n=10	MALES		FEMALES	
	Guerin's carcinoma	Mellitus + Guerin's carcinoma	Guerin's carcinoma	Mellitus + Guerin's carcinoma
V tumor, cm ³	68.14±8.38	119.5±12.4 $p=0.004113$	50.41±5.22	39.33±3.84 $p_1=0.000097$
MDA, nmol/g	0.722±0.076 0.71(0.56;0.86)	1.348±0.162 1.12(0.9;1.6) $p=0.002548$	0.447±0.043 0.42(0.38;0.49) $p_1=0.005742$	0.387±0.081 0.30(0.19;0.69) $p_1=0.000047$
DC, μmol/g	33.34±5.65 26.63(20.9;38.4)	24.27±1.54 24.27(19.6;27.7)	25.56±2.86 24.02(20.6;30.4)	19.72±1.14 20.15(16;22.6) $p=0.074148$ $p_1=0.029023$
SOD,U/g	5.64±0.745 5.96(3.63;7.65)	9.59±1.717 8.27(5.49;13.59) $p=0.049200$	8.638±0.743 8.5(6.26;10.84) $p_1=0.010726$	10.39±0.717 10.39(8.6;11.4)

Notes: Statistical significance of differences: p - compared with the group of animals with Guerin's carcinoma, p_1 - between males and females.

in the females there were no significant differences between these groups. As to the content of DC, only a tendency to a lower level (by 13.4%, $p=0.074$) was revealed with the tumor growth against the background of DM in the females. At the same time, in the tumor tissue of the males, the level of MDA and DC was higher than that found in the females, with the tumor growth in the animals with DM, the differences in MDA reached 3.5 times ($p = 0.00005$), and for DC the difference was 23.1% ($p=0.029$). This indicates a higher intensity of lipid peroxidation in the tumor tissue of the males compared with that in the females, especially in comorbidities. The SOD activity in the tumor of the males with DM was increased by 70% ($p=0.049$), and no significant differences therein were found in the tumor of the females (see Table 2 herein).

Discussion

Our comparative analysis of the content of the lipid peroxidation products in the heart showed that in DM the changes were detected only in the females and consisted of a 3-fold increase in MDA and a decrease in DC by 27%. In both groups with Guerin's carcinoma, we observed in the females an accumulation of both LPO products and a multiple increase in the SOD activity in most animals, while the malignant growth in the males did not lead to an increase in the content of MDA, and the level of DC was increased only under the independent growth of Guerin's carcinoma that was accompanied by a decrease in the SOD activity by a factor of 3.4-3.5 as compared with the intact males. Thus, as opposed to the males, the females were characterized by a sharp intensification of lipid peroxidation in the heart, which, under the conditions of the multiply increased SOD activity, indicates the development of pronounced oxidative stress in this most important organ.

In this case, the males with DM are characterized by a highly significant threefold excess of the tumor volume compared with the females. It can be assumed that one of the factors that ensure the greatest tumor growth in the males with DM is the intensification of lipid peroxidation and the activation of SOD in the tumor tissue, which protects tumor cells from the development of oxidative stress. The dependence of the tumor growth on the oxidative status has been also shown in earlier studies

conducted by our Research Center [21-24]. This mechanism of the tumor progression is discussed by the latest reviews published in the reference papers abroad [25,26]. While in the females, generalization of the malignant process became possible due to a pronounced intensification of free radical processes in the cardiovascular system, and, consequently, damage to the vascular wall facilitating the extravasation of circulating tumor cells from the bloodstream into the tissues. It is the hematogenous route of metastasizing that is most likely appears in case of tumor cell dissemination to the kidneys, ovaries, and peritoneum, which is characteristic of the female rats with the development of a tumor process against the background of DM. Oxidative damage to the heart in the females with the malignant growth against the background of DM can contribute to a decrease in life expectancy, the average duration of which in case of Guerin's carcinoma in the females with DM was 1.6 times shorter than that recorded in the females without DM.

Conclusions

1. Intensification of free radical processes in the heart in the female rats during the growth of Guerin's sarcoma against the background of DM may reflect or rather contribute to the deterioration of the health state in the animals, leading to a more pronounced tumor invasion in them and resulting in their accelerated death.
2. Intensification of lipid peroxidation in the tumor itself, which is typical only for the males with DM, is one of the factors for increasing the size of the primary tumor, which has been found 3 times larger in the males than that recorded in the females with DM.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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