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Insulin-like growth factors and their binding proteins in the heart in rats in experimental diabetes mellitus, growing Guerin's carcinoma and under their combination

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Abstract

Diabetes mellitus is an additional risk factor for the development of heart diseases, cardiovascular dysfunction and malignant tumors. The aim of the study was to analyze levels of IGF and IGFBP in heart samples of animals with diabetes mellitus and/or growing Guerin's carcinoma. The study included white outbred rats of both genders weighing 180-220 g. The rats of each gender were divided into groups of 8 animals: the intact group; test groups 1 (with diabetes) and 2 (with transplanted Guerin's carcinoma); the main group (transplanted Guerin's carcinoma growing in the presence of diabetes mellitus). Levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-2 were measured by ELISA (Mediagnost, Germany) in heart homogenates in animals of all groups.

Results

The levels of IGF were not changed in female rats with diabetes and/or Guerin's carcinoma; however, diabetes mellitus upregulated IGFBP1 and downregulated IGFBP2. The levels of IGF-I, IGF-II and IGFBP2 decreased in males with diabetes mellitus and/or Guerin's carcinoma, and IGFBP1 decreased only in males with diabetes.

Conclusion

The study has demonstrated that the system of insulin-like growth factors and binding proteins in the heart has a gender specificity, which probably determines the pathogenetic mechanisms of diabetes-induced damage to the heart muscle. The metabolic characteristics typical of this endocrine disease dominate in the IGF-heart system over the changes caused by the growth of a malignant tumor, thereby determining the possible mechanisms for the stability or restoration of the heart function in various pathological conditions.

Keywords

Diabetes mellitus, Guerin's carcinoma, Heart, IGF, IGFBP

Imprint

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Introduction

One of the primary causes of death of the population in the modern world is cardiovascular diseases (CVD) including heart insufficiency, diabetes mellitus (DM) and malignant neoplasms [1]. As is shown by research studies, the above pathologies are often found in a combination. While DM cannot be recognized as an immediate cause of death, it is responsible for polyorganic dysfunction, which may include nephropathy, retinopathy, neuropathy, atherosclerosis, heart diseases and cardiovascular dysfunction [2]. The existing approaches to the proper interpretation of mutual relations between various comorbid states and the main pathogenic factor require complex methodological techniques from most advanced digital technology of cardiometry, which implies non-invasive assessments of hemodynamics, heart metabolism and heart energetics, to molecular markers of the heart performance, which offer a differentiated estimation of pathogenetic mechanisms based on models of the tumor growth [3-6]. In addition, available epidemiologic data support that there are interrelations between DM and malignant tumors [7].

An aggravation of oxidative stress and the metabolism dysfunction, which develop in DM, may lead to DNA damaging and diabetic cardiomyopathy, which may result in alterations of the myocardial tissue, metabolic disorders and abnormalities in the vegetative function of the heart [8]. Heart failure is found approximately in 20-30% of the diabetes mellitus pa-

tients that considerably increases risk of disease incidence and death [9]. Alterations in the heart muscle metabolism and insulin signal transduction are the key disorders connected with hyperglycemia as well as development and progression of cardiovascular complications [2, 10]. So, the risk of development of heart failure in DM increases both in males and females as against those patients who do not suffer from DM [1].

Some clinical studies focus on investigations devoted to diabetes and its causal connection with a neoplasm. There are some epidemiologic research works which demonstrate that the patients suffering from DM have a higher risk of various types of cancer [7]. The states like hyperglycemia, hyperinsulinemia and inflammation are considered to be of primary importance for progression of cancer in case of diabetes. Actually, diabetes mellitus and cancer share many common risk factors including ageing, hyperlipidemia, obesity and gender. Diabetes mellitus of both types I and II is interconnected with a higher risk of cancer progression [7].

Cancer can cause signs similar to those found in diabetes, which include a higher level of insulin and insulin-like growth factors, secretion of leptin/adiponectin and immune-related disorders. Moreover, malignant cells increase use of glucose to maintain proliferation [11]. The insulin-like growth factor (IGF) demonstrates its higher levels in patients with diabetes and can promote cancer progression due to its powerful mitogenic and anti-apoptotic activity [2,7,9,12]. Recent discoveries made in vitro and in vivo have shown that IGFBP can operate independent of IGF as independent growth modulators [13,14]. The IGF system has a pleiotropic effect on the organism: it participates in the tissue restoration due to anti-apoptotic, pro-angiogenic and fibrosis-modulating mechanisms that results in its cardioprotective and neuroprotective action at one end of the scale and in a risk of cancerogenesis at the other [2,15].

At present it becomes apparent that the growing incidence rate of diabetes mellitus on a global scale represents a major threat to public health care systems, since it is a severe comorbidity which may accompany and/or provoke diseases like cancer and cardiovascular insufficiency [1,2,10]. Much thought should be given to modifiable risk factors in the context of the diabetes mellitus epidemic observed nowadays throughout the world. As to the future medicine, the most prevalent should be a variant thereof which implies a prevention version adjusted to a human individual having a non-optimal health state, with the presence of a number of comorbid pathologies (prior to manifestation of a tumor disease). Some experimental studies have demonstrated an essential effect produced by concomitant chronic neurogenic pain on the malignant tumor growth [16]. For a better understanding of pathogenesis of the malignant tumor growth against the background of diabetes mellitus as a comorbid disease required are further experimental investigations in vivo [17]. The aim of our study was to investigate the IGF and IGFBP levels in the heart samples in animals suffering from diabetes mellitus and / or having growing Guerin's carcinoma as well in the rodents with the combination thereof.

Materials and methods

Our study has been conducted with the use of white outbred rats of both gender, with an individual body mass of 180-200 g, which have been delivered by the Federal State Medical & Biological Institution "Research Center of Biomedical Technologies" (Branch Andreevka, Moscow Region) at the Federal Medical & Biological Agency and which have been kept under natural lighting conditions with no restrictions on their access to water and food. The research in animals was completed in accordance with the Directive 86/609/EEC on the Protection of Animals Used for Experimental and Other Scientific Purpose, as well as in accordance with the International Guiding Principles for Biomedical Research Involving Animals and Order No. 267 "Approval of the Rules of Laboratory Practice" dated June, 19, 2003 issued by the Ministry of Health of the Russian Federation. The experimental research record was approved by the Commission on Bioethics at the Federal State Budgetary Institution "National Medical Research Center of Oncology", the Ministry of Health of the Russian Federation, Record No. 21/99 dated 01.09.2020.

The male and female animals have been assigned to groups, 8 animals in each, as follows: the group of the intact animals; test group 1 with rodents having diabetes mellitus and test group 2 of animals inoculated with Guerin's carcinoma cells; the main group covering the animals with growing Guerin's carcinoma against the background of diabetes mellitus. To reproduce experimental diabetes mellitus, the animals were given an intraperitoneal injection of Alloxan at a single dose of 150 mg/kg of an individual body mass.

Later, within the week, their blood glucose concentrations were measured. At the time of the inoculation with Guerin's carcinoma cells, the animals in the main group have been recorded to have an average glucose concentration level of 25,4±1,2 mmol/l, while the reference intact animal group values have been recorded to be 5,2±0,3 mmol/l.

Each rat in the group with the independently growing tumor, upon expiration of 1 week of stable hyperglycemia, has received a subcutaneous injection of 0,5 ml suspension of the Guerin's carcinoma cells in a 1:5 dilution with saline solution. Three days after the inoculation of the Guerin's carcinoma cells suspension, a subcutaneous tumor became detectable. Upon expiration of the 10-day period, the animals were decapitated with the guillotine. In the heart homogenates in the animals of all groups using the ELISA method we have measured the amounts of IGF-I, IGF-II, IGFBP-1 and IGFBP-2 (Mediagnost, Germany).

The Statistica 10.0 software has been utilized for the purpose of statistical analysis of the obtained data. The data are presented in the M±m form, where M is the arithmetic mean. The data have been analyzed for their compliance with the normal distribution law using the Shapiro-Wilk test. Significance of differences between independent samplings has been assessed with the Mann-Whitney U test. In this case, $p<0.05$ has been taken as the level of statistical significance.

Results

It has been found that in the heart in the intact male rats the levels of IGF-I, IGF-II and IGFBP-1 are 1,6, 1,7 and 1,8 times lower ($p<0,05$) as compared with the respective data recorded in the intact female animals (see Table 1 and 2 herein).

Considering the influence made by diabetes on the heart in the female rats, we have recorded no changes in the amount of IGF-I and IGF-II, however we have established that there is a multidirectional change in the IGFBP-1 and IGFBP-2 levels (see Table 1 herein): the IGFBP-1 level has increased by 1,9 times as against the respective values in the intact animals, while the IGFBP-2 level has decreased by 1,5 times ($p<0,05$). Accordingly, the IGF-to-binding proteins ratio values IGF-I/IGFBP1 and IGF-I/IGFBP2 have decreased by 1,9 times, while IGF-II/IGFBP2 has increased by 1,4 times.

The growing Guerin's carcinoma has induced a decrease in the IGFBP-1 level by 1,9 times only, while the other indicators remain within their normal value ranges. Accordingly, reported have been the 1,8-fold values of ratios IGF-I/IGFBP2 and IGF-II/IGFBP2 ($p<0,05$). As a result from the growing Guerin's carcinoma against the background of diabetes mellitus in the heart in female rats, no changes in the IGF level have been detected, but the amount of IGFBP-1 has increased by 2,3 times, while the IGFBP-2 level has decreased by 1,9 times as against the respective indicators in the intact animals, in a similar manner as it is the case with the processes typical of independently developing diabetes mellitus.

It is intriguing that in the female rats with the growth of the malignant tumor against the background of endocrine comorbidity, namely, induced diabetes mellitus, the changes in the values in ratio IGH to their binding proteins have integrated both signs of the independent diabetes mellitus and the independent malignant tumor growth. So, the values of ratios IGF-I/IGFBP1 and IGF-II/IGFBP1 have decreased by more than 2 times as against the independent tumor growth process and the respective indicators in the intact animals, similarly to the processes found in independent diabetes mellitus, while the values of ratios IGF-I/IGFBP2 and IGF-II/IGFBP2 have increased by 1,9 and 1,8 times, respectively, in the same manner that is the case with the processes under the independently growing malignant tumor.

A completely different type of the response produced by the IGF axis factors to the independently developing diabetes mellitus and the Guerin's carcinoma has been detected in male rats (see Table 2 herein). In the male rats with diabetes mellitus, in their heart samples, we have found a reduction in the levels of IGF-I and IGF-II as well as IGFBP1 and IGFBP-2 by 1,8 times on average as compared with the respective data recorded in the intact animals. In this case, no changes in the ratios between IGF and the binding proteins have been revealed. The Guerin's carcinoma growth has initiated the changes in the amounts of IGF-I, IGF-II and IGFBP2 in the same direction that is the case with those found in diabetes mellitus, except for the absence of changes in the IGFBP1 concentration; we have detected a decrease in the above amounts by 1,6, 1,3 and 1,5 times, respectively, as against the values reported for the intact animals. As a result, we have observed in the male rats with the independently growing Guerin's carcinoma in the heart samples the reduced values of the IGF-I/IGFBP1 and IGF-II/IG-

Table 1
Concentration of insulin-like growth factors and their binding proteins (ng/g tissue), and ratios between the insulin-like growth factors and the binding proteins in the heart in female rats

	Intact animals	DM	Guerin's carcinoma	Main group
IGF-1	1422,7±123,4	1377,45±128,3	1380,2±121,7	1497,0±140,3
IGF-2	215,8±18,7	212,8±20,1	215,4±16,4	213,5±20,5
IGFBP-1	11,5±9,5	21,4±1,71	10,0±0,92	22,8±2,11
IGFBP-2	251,4±24,3	167,5±15,41	131,1±12,21	135,8±11,71
IGF-1/IGFBP-1	123,7±11,7	64,4±6,21	138,0±11,92	65,7±5,91
IGF-1/IGFBP-2	5,7±0,54	5,5±0,45	10,5±0,71,2	11,0±0,81,2
IGF-2/IGFBP-1	18,8±1,5	9,9±0,871	21,5±1,52	9,4±0,761
IGF-2/IGFBP-2	0,9±0,06	1,3±0,111	1,6±0,141	1,6±0,151

Notes: statistically significant differences as against: [1] - the intact animal values; [2] - the animals with diabetes mellitus (p<0,05)

Table 2
Concentration of insulin-like growth factors and their binding proteins (ng/g tissue), and ratios between the insulin-like growth factors and the binding proteins in the heart in male rats

	Intact animals	DM	Guerin's carcinoma	Main group
IGF-1	877,6±69,9	468,7±43,11	546,7±53,11	437,1±41,11
IGF-2	124,4±11,2	71,1±6,71	94,2±8,91,2	80,3±7,71
IGFBP-1	6,3±0,60	3,5±0,311	6,6±0,572	5,2±0,462
IGFBP-2	224,5±21,2	126,4±11,11	150,4±14,41	125,6±12,41
IGF-1/IGFBP-1	139,3±13,1	133,9±12,4	82,8±7,61,2	84,1±7,61,2
IGF-1/IGFBP-2	3,9±0,30	3,7±0,32	3,6±0,33	3,5±0,34
IGF-2/IGFBP-1	19,7±1,8	20,3±1,9	14,3±1,41,2	15,4±12,21,2
IGF-2/IGFBP-2	0,6±0,05	0,6±0,05	0,6±0,06	0,6±0,05

Notes: statistically significant differences as against: [1] - the intact animal values; [2] - the animals with diabetes mellitus (p<0,05)

FBP-1 ratios by 1,7 times and 1,4 times, respectively, as compared with those in the intact animals and in the DM rodents.

In the male rats with the growing Guerin's carcinoma against the background of diabetes mellitus no significant differences from the indicators in the heart in independently developing diabetes mellitus or the independently growing Guerin's carcinoma with respect to IGF-I, IGF-II and IGFBP-2 have been detected; the only exception is IGFBP1, the level of which has been found 1,5 times lower, as compared with that in diabetes mellitus, and 1,3 times lower as against that found under the growing Guerin's carcinoma. The values of the ratios between IGF and their binding proteins under the growing Guerin's carcinoma against the background of diabetes mellitus show no significant variances from the respective data recorded in the group with the independent growth of the tumor only, however the values of ratios IGF-I/IGFBP1and IGF-II/IGFBP-1 have been reported to be 1,6 and 1,3 times lower, respectively.

Discussion

We have derived from our studies that the levels of IGF-I, IGF-II and IGFBP-1 recorded in the heart samples of the female rats are higher than those found in the male rodents. The peculiar features can be explained by differences in the level of their gender-specific steroids. It is well known that IGFs participate in the maintenance of the structure and performance of the heart, make influence on the lipid parameters and reduce coronary disease risk and rate of the aorta growth; in this case the effect produced by estradiol modifies this influence [2,7,15,18,19]. The CVD risk is known to considerably experience an increase in woman after menopause that bears witness to the protective role of estrogens [20]. We can find more and more experimental data confirming the fact that estrogens do much to shape the gender specificity found in the cardiac muscle contractility [21]. It is suggested that both diabetes mellitus and CVD have some common genetic and ecological factors, which are considered as contributors to development of the above diseases [1,2]. It is thought that diabetes is linked with the microcirculation dysfunction and heart insufficiency as well as fluctuations in the insulin and IGF1 levels [10,22].

In the course of our study we have revealed an interesting regularity: in the female rats neither diabetes mellitus nor the growing Guerin's carcinoma, including the combination of both diseases, has made any impact on IGF amounts, while in the male rats we have detected a decrease in the IGF amount in the heart samples as a response to induced DM, the growing Guerin's carcinoma and their combined action. As multi-fac-

tor studies of various biological markers have shown, the IGF/IGFBP system is most closely connected with the development of DM; the next contributors thereto should be hormones and pathways of their regulations. It is assumed that the involvement of the additional biomarkers of system-related pathway IGF/IGFBP, like IGF-1, IGF-2, IGFBP-1 and IGFBP-3 would be useful for an assessment of the contribution of this system to the DM and CVD risks [2,7]. It has been found that the overexpression of IGF-II accelerates the differentiation of parthenogenetic stem cells (PSC) into cardiomyocytes, but at the same time it inhibits their proliferation via signal transduction IGF-II / IGF1R that is evidence for the protective role of IGF [12,23]. The insulin-like IGF-1 signal transduction regulates contractility, metabolism, hypertrophy, autophagy, ageing and apoptosis in the heart. The IGF-1 deficiency is connected with a higher CVD risk [10,24]. On the other hand, thyroid hormones, insulin, IGF-1 and estrogens are usually linked with the physiological hypertrophy of the heart, however they are capable of counteracting a pathological response [25]. So, insulin and IGF-1 are powerful activators of PI3K/Akt1 in cardiomyocytes. It has been demonstrated that an increased production of the heart-associated IGF-1 in sport athletes is connected with the physiological hypertrophy found in the heart in them. It turns out that there is a relationship between the low levels of the heart-related IGF-I and a higher risk of developing heart insufficiency [25]. IGF-I –Akt involved to produce a cardioprotective effect is capable of accelerating and enhancing the transcriptional re-programming of fibroblasts to the functional cardiomyocytes that is a potential approach to restore the cardiac function after damage of the myocardium [26].

In the female rats in the heart samples, as a response to induced DM, we have detected multidirectional changes in the amount in the binding proteins of type 1 and 2, while for the male rats reported is a decrease therein. The growing Guerin's carcinoma has initiated a reduction in the IGFBP2 concentration found in the heart, while the IGFBP1 level in the animals of both genders has remained unchanged. In the main group, where we have observed the growing Guerin's carcinoma against the DM background, the amount of the binding proteins in the heart in the female rats is in compliance with the pattern under diabetes mellitus, while in the male rodents the pattern is in correspondence with that recorded in the male rodents both in case with DM and the tumor growth.

Initially, the role of IGFBP was limited to their binding function to prolong the life time of circulating IGF in all tissues only. But at the present time, the concept has been changed: it turns out that most of IGFBP compete for the IGF activity at the level of the receptors and counteract the IGF function, while some of them (for example IGFBP2) enhance the IGF signal transduction [27].

IGFBPs coordinate and control biological activity of IGF by several methods: 1) transport of IGF in blood plasma and control of its diffusion / discharge from the vascular space; 2) prolongation of time of half-life and regulation of IGFs clearance; 3) provision for sites of specific binding of IGF in the extra- and pericellular space; and 4) modulation of interaction between IGF and their receptors. IGFBPs bind IGF-I and IGF-II, but they do not bind insulin. IGFBP-1 binds IGF-I and IGF-II with a similar affinity, while IGFBP-2 shows a higher binding affinity for IGF-II [28]. The IGFBP levels can fluctuate and are variable due to different physiological or pathological states that may include day cycle variations, physical loading, pregnancy, DM and ageing, among them hormones, which modulate the levels of some IGFBP in blood serum and other bio-fluids [29]. It is assumed that IGFBP are tumor growth retardants inhibiting the IGF action, including proliferation, survival, migration/invasion and stimulation of apoptosis [27]. However, on the contrary, other studies have demonstrated a pro-tumorigenic action of some IGFBP, among them promotion to cell survival and migration/invasion. Specifically, presumably IGFBP-2 is mainly cancerogenic for a number of the cancer types, including glioma, and its circulating levels are found in good correlation with aggressiveness and other well-defined tumor markers found in prostate, breast and ovarian cancer [14,29].

The IGFBP2 expression is regulated by the transcription factor induced by hypoxia (HIF-1α), the expression of which, in its turn, is controlled by O2 concentration in the cells [14]. In our research work, we have revealed that there is a decrease in the IGFBP2 level in the heart samples in the animals of both genders in all experimental groups (DM, the growing Guerin's carcinoma and the growing Guerin's carcinoma against the DM background). We have detected that an introduction of IGFBP-2 can prevent adipogenesis and show anti-diabetic properties [14]. This evidence confirms the pathogenetic significance of changes in the IGFBP2 amounts both in case of DM and the malignant tumor growth.

In general, the completed study shows that the system of the insulin-like growth factors and their binding proteins in the heart has its own gender-specific feature, which probably governs the pathogenic mechanisms of cardiac muscle damaging against the DM background. The metabolism specificity, typical of this sort of the endocrine disease, predominates in the IGF system in the heart over those changes, which are induced by the growing malignant tumor that may identify possible mechanisms to provide the required stable heart performance or to restore the latter under different pathology states.

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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