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The structural rearrangement of testicular arteries in case of chronic ethanol intoxication

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Prolonged poisoning of the body with ethanol damages almost all its organs and systems. Structural changes in testicular arteries under the influence of chronic ethanol intoxication have not been fully studied.

Purpose – to analyze the morphometric parameters of the small caliber arteries of the right and left testicles of rats in case of chronic ethanol intoxication.

Materials and methods. 62 laboratory sexually mature male rats was performed. The animals were divided into two groups. The Group 1 (control) included 30 rats, the Group 2 (experimental) – 32 animals. The experimental rats, which were conducted to the experiment, were injected intragastrically with a 30% ethanol solution at the rate of 2 ml per 100 g of body weight for 28 days once a day. Animals were euthanized by heart bleeding under thiopental anesthesia. Histological micro-sections were made from the left and right testicles. Morphometrically, the outer and inner diameters of the arteries, media thickness, adventitia, Vogenvoort and Kernogan indices, the height of endotheliocytes, the diameter of their nuclei, the nuclear-cytoplasmic ratio in these cells, and the relative volume of damaged endotheliocytes were determined morphometrically in small-caliber arteries. Statistical processing of digital data was carried out using Excel (Microsoft, USA) and STATISTICA 6.0 (Statsoft, USA) software.

Results. It was established that in case of simulated experimental conditions of chronic ethanol intoxication, the investigated morphometric parameters of the arteries of the left and right testicles changed significantly. In case of chronic intoxication with ethanol in rats, pronounced structural rearrangement of testicular vessels, mainly small arteries, characterized by thickening of the blood vessel's wall, narrowing of vessels' lumen, rearrangement of endothelial cells, and an increase in the relative volume of the damaged cells of intima, is established, and is dominant in the left testis.

Conclusions. In case of chronic intoxication with ethanol the structural changes in testicular tissues are dominant in the left testis. Pronounced remodeling of small caliber testicular arteries causes endothelial dysfunction, deterioration of blood supply to the testicles, hypoxia, dystrophic and necrobiotic tissue changes, infiltrative and sclerotic processes, which are the pathomorphological basis of male infertility.

When carrying out experiments with laboratory animals, all bioethical norms and recommendations were observed.

No conflict of interests was declared by the authors.

Keywords: morphometry, testis, testicular arteries, ethanol intoxication.

Структурна перебудова артерій сім'яників в умовах хронічної етанолової інтоксикації

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Тривале отруєння організму етанолом пошкоджує майже всі його органи та системи. Структурні зміни артерій сім'яників під впливом хронічної етанолової інтоксикації повністю не вивчені.

Мета – проаналізувати морфометричні показники артерій дрібного калібру правого та лівого сім'яників щурів за умови хронічної інтоксикації етанолом.

Матеріали та методи. Морфометрично вивчали артерії дрібного калібру сім'яників 62 білих щурів-самців, поділених на дві групи. Перша (контрольна) група становила 30 тварин, друга – 32 щури, яким внутрішньошлунково вводили 30% розчин етанолу з розрахунку 2 мл на 100 г маси тіла протягом 28 діб один раз на добу. Евтаназію тварин здійснювали кровопусканням із серця в умовах тіопенталового наркозу. З лівого та правого сім'яників виготовляли гістологічні мікропрепарати. Морфометрично в артеріях дрібного калібру визначали зовнішній та внутрішній діаметри артерій, товщину медії, адвентиції, індекси Вогенворта та Керногана, висоту ендотеліоцитів, діаметр їхніх ядер, ядерно-цитоплазматичні відношення в цих клітинах, відносний об'єм пошкоджених ендотеліоцитів. Статистичну обробку цифрових даних проводили за допомогою програм Excel (Microsoft, США) та STATISTICA 6.0 (Statsoft, США).

Результати. Встановлено, що за умови хронічної інтоксикації етанолом відмічається виражена структурна перебудова судин сім'яників, переважно артерій дрібного калібру, що характеризується потовщенням стінки судин, звуженням їхнього просвіту, перебудовою ендотеліоцитів і зростанням відносного об'єму пошкоджених ендотеліоцитів, домінує у лівому сім'янику. Виявлено виражене ремоделювання артерій дрібного калібру сім'яників, яке зумовлює ендотеліальну дисфункцію, погіршення кровопостачання досліджуваних органів, гіпоксію, дистрофічні та некробіотичні зміни клітин і тканин, інфільтративні й склеротичні процеси, які є патоморфологічною основою порушень сперматогенезу.

Під час проведення експериментів із лабораторними тваринами дотримано всіх біоетичних норм і рекомендацій.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: морфометрія, сім'яники, артерії, етанолова інтоксикація.

Introduction

Almost 60% of the population in the world consumes alcoholic beverages [29]. According to a survey by the European Commission, in 2020, 76% of citizens in Europe drank alcoholic beverages [8]. According to the National Institute on Alcohol Abuse and Alcoholism, about 26% of the adult population of the United States of America is addicted to alcohol [19]. Ukraine is also characterized by high levels of alcohol consumption and negative trends in their growth, in particular, over the past 20 years, the consumption of alcoholic beverages has increased by 45.8%, which is an unfavorable prognostic indicator in the field of health care [31]. According to the WHO, alcohol is the cause of more than 200 diseases and is the cause of 5.3% of all deaths in the world, or even 13.5% in younger age groups [30]. In Poland, over the past two decades, 25% of premature deaths were related to alcohol, while alcohol consumption has practically doubled over the past ten years [32]. It has been scientifically proven that excessive alcohol consumption is associated with an increased incidence of various types of cancer [26], cardiovascular disease [10], liver disease [7], birth defects [9] and mental disorders [24].

Drinking alcohol can cause fertility problems in men. In a study by S. Grover et al. with long-term alcohol consumption, a decrease in gonadotropin release, testicular atrophy, and a decrease in testosterone and sperm production were found [11]. Another study by R.A. Condorelli et al. showed an increase in the level of gonadotropins and estradiol with a decrease in the level of testosterone in men who abuse alcohol [4]. Alcoholism is a disease, which is associated with dysfunction of the liver, and it can lead to hormonal disoders due to the inability to estrogen metabolize. A decrease in the quality of sperm parameters is also found in men who abuse alcohol [12]. In addition, alcohol abuse and acute alcohol intoxication have been found to be associated with sexual dysfunction, including problems with arousal, as well as erectile and ejaculatory dysfunction, which can lead to difficulty conceiving if men are unable to have effective intercourse [22,28].

Although a number of experimental and clinical studies have shown the effect of alcohol consumption on reproductive hormonal regulation, sperm quality, gene transcription, genetics and epigenetics, the question of structural changes in testicular tissues and the characteristics of their blood supply in men in case of chronic ethanol intoxication remains debatable.

The **purpose** of this study – to analyze the morphometric parameters of the small caliber arteries of the right and left testicles of rats in case of chronic ethanol intoxication.

Materials and methods of the study

The work was performed on 62 laboratory sexually mature male rats, weighing 195–200 g. Laboratory animals were kept on the standard ration of the vivarium of I. Horbachevsky Ternopil National Medical University, all manipulations were carried out in compliance with the rules of the «European Convention on the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes» [5].

The experimental animals are divided into two groups: the Group 1 (control) – 30 animals – were injected intragastrically with water at the rate of 2 ml per 100 g of body weight for 28 days once a day; the Group 2 (experimental) – 32 rats – animals were injected intragastrically with a 30% ethanol solution at the rate of 2 ml per 100 g of body weight for 28 days once a day [16]. Animals were euthanized by heart bleeding under thiopental anesthesia.

Table

Morphometric characteristics of small testicular arteries of experimental animals (M±m)

Index	Left testicle			Right testicle		
	Group 1 (n=30)	Group 2 (n=32)	dynamics	Group 1 (n=30)	Group 2 (n=32)	dynamics
OD, µm	41.20±0.42	43.20±0.39*	↑4.85%	41.15±0.42	43.00±0.39*	↑4.5%
ID, µm	24.10±0.21	19.15±0.8***	↓20.5%	24.07±0.21	19.40±0.18***	↓19.4%
MT, µm	6.65±0.12	10.14±0.12***	↑52.5%	6.60±0.03	9.60±0.12***	↑45.4%
TA, µm	4.30±0.03	8.89±0.12***	↑106.7%	4.30±0.03	8.86±0.12***	↑106%
WI, %	292.2±3.6	528.9±6.2***,#	-↑80.0%	292.3±3.3	491.2±5.6***	-↑68%
KI, %	34.2±0.18	19.60±0.12***	↓42.7%	34.2±0.15	20.30±0.12***	↓40.6%
EH, µm	6.15±0.11	5.12±0.09***	↓16.7%	6.12±0.11	5.14±0.08***	↓16%
DN, µm	3.08±0.03	3.07±0.03	-	3.06±0.04	3.02±0.03	-
NCR	0.252±0.003	0.360±0.004***	↑42.8%	0.250±0.003	0.345±0.004***	↑38%
RVDE, %, times	2.10±0.02	35.20±0.21***,#	-↑16.76 times	2.05±0.04	30.60±0.18***	-↑14.9 times

Notes: the difference is reliable between the Groups 1 and 2: * – p<0.05; ** – p<0.01; *** – p<0.001; # – the difference is reliable between the data of the same group. OD – outer diameter, ID – inner diameter, MT – media thickness, AT – adventitia thickness, WI – Wogenworth index, KI – Kernogan index, EH – endothelial cells' height, DN – diameter of the endothelial cells' nuclei, NCR – nuclear cytoplasmic ratio in the cells, RVDE – relative

Cut pieces of the left testis (LT) and right testis (RT) were fixed in Bouin's solution, passed through ethyl alcohols of increasing concentration and placed in paraffin blocks. After deparaffinization, microtome sections with a thickness of 5–6 µm were stained with hematoxylin and eosin according to Van Gieson, Mallory, Masson, and toluidine blue [3]. Small arteries (outer diameter 26–50 µm) were studied by quantitative morphological methods. Morphometrically it was determined: outer (OD) and inner (ID) diameters of arteries, media thickness (MT), adventitia thickness (AT), Wagenworth index (WI) and Kernogan index (KI), endothelial cells' height (EH), diameter of the endothelial cells' nuclei (DN), nuclear-cytoplasmic ratio (NCR) in these cells, relative volume of damaged endothelial cells (RVDE) [14]. Morphometry was performed with the help of a light microscope «Olimpus BX-2» with a digital video camera and a package of application programs «Video Test 5.0» and «Video size 5.0».

Statistical processing of digital data was carried out using Excel (Microsoft, USA) and STATISTICA 6.0 (Statsoft, USA) software. The analysis of the research results was carried out using parametric statistical methods, the choice of which was based on the correctness of the distribution of values. The processing of the results was carried out in the systematic statistical research Department of I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine. For all indices, the average arithmetic mean of the sample (M) and the error of the average arithmetic mean (m) were calculated. The reliability of the difference in values between independent quantitative values was determined in the case of a normal distribution according to the Student's t-test, and it was considered statistical at a value of p<0.05.

Results

It was established that in case of simulated experimental conditions of chronic ethanol intoxication, the investigated morphometric parameters of the arteries of the left and right testicles changed significantly (Table).

Thus, the thickness (outer diameter) of the arteries in the left testicle of male rats in case of chronic ethanol intoxication significantly increased by 4.85%, the thickness of the media – by 52.5%, the adventitia thickness – by 106.7%, the Wagenworth index – by 81.0%, in the right testicle the given morphometric parameters changed by 4.4%, 45.4%, 106.0%, 68.0%, respectively (p<0.05). It is worth noting that the Wagenworth index is significantly higher in the left testicle compared to the right one by 7.67%.

The lumen (inner diameter) of the left testicular small arteries decreased by 20.5% with a pronounced statistically significant difference during chronic ethanol intoxication, the Kernogan index – by 14.6%, in the right testis the indicated quantitative morphological indices changed by 19.4% and 13.9% (p<0.001). It should be noted that the marked decrease in the lumen of the small caliber arteries of the left and right testicles in case of ethanol intoxication, the Kernogan index, and the increase in the Wagenworth index indicated a significant decrease in the permeability of the studied vessels and the deterioration of the organs blood supply [14].

The structural rearrangement of the endotheliocytes of the small arteries of the left and right testicles in case of chronic ethanol intoxication was confirmed by characteristic morphometric changes: the height of the endotheliocytes of the specified arteries significantly decreased by 16.7% and 16.0%, respectively, with a pronounced increase in the nuclear-cytoplasmic ratio, respectively, by 42.8% and 38.0%, which indicated arterial damage and disruption of cellular structural homeostasis. The above-mentioned changes were accompanied by a significant increase in the small caliber arteries of the testes of RVDE. Thus, in the left testicle the specified morphometric parameter increased statistically significantly by 16.76 times, in the right testicle by 14.90 times ($p<0.001$), while in the left testicle the studied index was 15.03% higher in relation to the data on the right one. Nuclear-cytoplasmic ratios in endotheliocytes and relative volumes of their damage indicate that structural changes in the left testis were more pronounced compared to the right.

It is worth noting that pronounced changes in the nuclear-cytoplasmic ratio in the endothelial cells of small testicular arteries indicated their damage and disruption of cellular structural homeostasis. This was also confirmed by the morphometric parameters of the arteries (outer, inner diameters, media thickness, adventitia thickness, Wagenworth and Kernogan indices).

Discussion

A complex morphometric study of the arteries of the left and right testicles at the organ, tissue and cellular levels during the action of toxic factors on the body of experimental animals was not found in the analysis of modern medical and biological literature. Some authors studied disorders of reproductive function [1,2,4], others sexual dysfunction [11,22], peculiarities of spermatogenesis [12], venous vessels [8] of testicles under the action of toxic factors on the body. O.M. Herman et al.[13] studied the structural damage of the parenchyma and blood flow disorders in the testes of white rats during long-term exposure to high doses of prednisolone. They established the thickening of the arterial wall and the reduction of the lumen, which was complicated by a marked violation of hemodynamics in the examined organ.

Excessive alcohol consumption affects virtually every organ and tissue in the body, with multifactorial effects on cellular and molecular functions, altering biological function either through direct interaction with cellular components or through direct biochemical effects on alcohol metabolism [2].

Moreover, it has long been known that chronic consumption of ethanol can cause changes in the male reproductive organs of mammals. In a few experimental studies, they found evidence of testicular damage as the main changes resulting from long-term use of ethanol [1,2,25,27]. D.I. Akinloye et al. investigated the effects of alcohol on the degree of lipid peroxidation, testicular morphology, and sperm quality assessment in Wistar rats and discribe that in histological specimens of testes the pathological prosesses included mild testicular degeneration, degenerated tubules with distortion, detached intratubular mass of germ cells, testicular hypoplasia, and few layers of germinal epithelium, which was present in the wall of the seminiferous tubules [2]. This damage to the testes may be due to increased production of acetaldehyde, which «attacks» the polyunsaturated fatty acids in the testicular membrane, creating more free radicals, thus leading to loss of testicular structure and function. The researchers concluded that the structural rearrangement and impairment of the testicular function could be the result of excessive oxidative damage caused by alcohol.

O.A. Adaramoye et al. investigated ethanol-induced reproductive toxicity (3g/kg body weight during 21 days) in male Wistar rats and found that chronic ethanol intoxication led to a significant decrease in the relative weight of the animals' testicles [1]. In spermatozoa, chronic ethanol intoxication resulted in a decrease in testicular protein content, motility, and sperm count by 54%, 21%, and 38%, respectively. In addition, the introduction of ethanol increased the process of lipid peroxidation, which was assessed by the accumulation of malondialdehyde in the testicles. Namely, the level of malondialdehyde was increased by 121% in the testes of ethanol-treated rats compared to the control. In addition, testicular glutathione levels and the activity of testicular antioxidant enzymes such as catalase and superoxide dismutase were significantly decreased in ethanol-treated rats. Histopathologically, intensive degenerative morphological changes of the seminiferous tubules and loss of sperm cells were present in the testes of ethanol-treated rats.

F.E. Martinez et al. analyzed the changes in the epididymis and testes in a specific group, which includes the alcohol-intoxicated rats to contribute to our understanding of the effects of chronic alcohol intoxication on reproduction [18]. The epididymis and testes of such animals' groups were studied using macroscopy investigation, light and electron microscopy, morphological analysis. As a result, the UCh rats showed epithelial atrophy and decreased testicular and epididymal weight,enlarged liver and fatty infiltration, and changes in the hypothalamic-pituitary axis. Ethanol causes changes in testicular and epididymal weights and epithelium and in the hypothalamic-pituitary axis in UCh rats. Furthermore, chronic alcohol intoxication may be the cause of the ductus deferens changes analyzed in

UCh ethanol drinking rats by J.H. Rissato et al [23]. Distal and proximal parts of the vas deferens of 20 rats were studied using macroscopic, microscopic and ultramicroscopic methods also as morphometric analysis. The vas deferens epithelium atrophy and alterations of the hypothalamus-pituitary axis were found in the UCh rats. Ethanol induces changes in the ductus deferens epithelium and hypothalamic-pituitary axis in UCh rats were indicated.

In order to study the effect of chronic administration of ethanol on the antioxidant system of the testes and the activity of steroidogenic enzymes, male rats treated with ethanol at a dose of 1.6 g/kg of body weight per day for four weeks were studied [17]. In addition to a sharp decrease in the weight of the testicles, a decrease in ascorbic acid, a decrease in the level of glutathione and the activity of superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase were observed in the tissue of the testes in animals. At the same time, the activity of lipid peroxidation and glutathione-S-transferase increased. The activity of 3-beta-hydroxysteroid dehydrogenase and 17-beta-hydroxysteroid dehydrogenase also decreased. Thus, the researchers demonstrated that chronic administration of ethanol led to an increase in oxidative stress and a decrease in the activity of steroidogenic enzymes in the testes of rats.

The results obtained by us indicate that chronic ethanol intoxication leads to structural rearrangement of the small caliber arteries of the left and right testicles of rats. At the same time, the degree of remodeling of the studied vessels dominates in the left testicle. A more pronounced structural rearrangement of the vessels of the left testicle is probably explained by the anatomical features of the blood supply of the studied organ [13].

Testicular hemocirculation is an important aspect of testicular physiology. Functionally, it provided a stable environment for the transport of nutrients and secretory products in the testicles [6]. Pronounced remodeling of the small caliber arteries of the testicles leads to the development of dysfunction of the endothelial cells and deterioration of the testes blood supply. Endothelial dysfunction, in turn, is accompanied not only by a violation of the local synthesis of nitric oxide (NO), but also by the formation of an excess amount of the endothelium-dependent superoxide anion radical, which inactivates the synthesized NO molecules, stimulates the oxidation of low-density lipoproteins and contributes to the damage of endothelial cell membranes by peroxynitrite and hydroxyl radicals. Under these conditions, the permeability of the intima of vessels increases, which in turn leads to infiltration of the subendothelial layer by lymphocytes and macrophages, as a result of which the endothelium begins to produce mediators of further damage to the vascular wall. Subsequently, hypoxia develops, dystrophic and necrobiotic changes in the tissues of the testicles, which culminate in their sclerosis and loss of function [20].

Conclusions

In case of chronic intoxication with ethanol in rats, structural rearrangement of testes' blood vessels, mainly small arteries, characterized by thickening of their wall, narrowing of the vessels lumen, rearrangement of endothelial cells, and an increase of the relative volume of the damaged endothelial cells, is established, and is dominant in the left testis. Pronounced remodeling of small testicular arteries causes endothelial dysfunction, deterioration of blood supply to the testes, hypoxia, dystrophic and necrobiotic tissue changes, infiltrative and sclerotic processes, which are the pathomorphological basis of male infertility. The media thickness in the small-caliber arteries of the left testicle increased by 52.5%, the thickness of the advertisement by 106.7%, the nuclear-cytoplasmic ratio in the endotheliocytes by 42.8%, the Kernoghan index decreased by 42.7, in the right testicle, these indicators changed accordingly – by 45.4%, 106.0%, 38% and 40.6%.

The work is a fragment of scientific research work of the Clinical Anatomy and Operative Surgery Department of the I. Horbachevsky Ternopil National Medical University «Structural and functional regularities of the course of adaptive and compensatory processes in organs and systems during surgical interventions on abdominal organs and chest cavity under the influence of toxic endogenous and exogenous factors» (registration number 0122 U 000031).

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