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Experimental androgen deficiency and associated structural changes in the muscle tissue of the external anal sphincter

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Abstract

Aim. We aimed to study the histological and ultramicroscopic structure of the striated muscle tissue of the external anal sphincter (EAS) of mature male rats under experimental androgen deficiency.
Materials and methods. The study included 10 male laboratory rats aged 8 months, which were randomly divided into 2 groups of 5 each. The experimental group underwent bilateral orchiectomy to create testosterone deficiency. After 45 days, rats were sacrificed. We studied the concentration of testosterone in histological sections of EASs using light microscopy and ultramicroscopy. We also determined the diameter of muscle fibers and the thickness of endomysium, the area of muscle fibers, connective tissue, myofibrils and cytoplasm, identification of glycogen granules in the cytoplasm and intermyofibrillar space, as well as changes in mitochondria.
Results. In the experimental group, on the 45th day after surgical castration, the testosterone level was 2.5 times lower than in the control group 2.69 (2.52; 2.73) nmol/l vs. 7.20 (6.83; 7.21) nmol/l, $p = 0.008$. Using morphometric analysis, we found that in the experimental group after surgical castration the diameter of the muscle fibers was statistically significantly smaller than in the control group: 6.56 (3.96; 7.24) μm vs. 9.52 (8.88; 10.44) μm, $p < 0.001$, while the thickness of the endomysium in the experimental group was greater: 3.34 (3.11; 3.78) μm vs. 1.62 (1.51; 1.86) μm, $p < 0.0001$. The ratio of muscle fiber area/connective tissue area was statistically significantly lower in the group after castration: 1.64 (1.50; 1.78) vs. 4.00 (3.17; 5.25), $p < 0.0001$. The ratio of myofibril area/cytoplasmic area changed in the experimental group towards the predominance of cytoplasm 0.79 (0.67; 0.79) vs. 5.25 (5.25; 7.33), $p < 0.0001$. With an increase in cytoplasmic volume, an increase in the number of glycogen granules was observed; pathological forms of mitochondria were identified: swelling, destruction of cristae and vacuolization of their matrix.
Conclusion. Under conditions of testosterone deficiency, along with atrophic processes, compensatory and adaptive mechanisms are formed in the striated skeletal muscle tissue of the EAS, aimed at restoring its metabolic and functional organization.

Keywords: anal sphincter insufficiency; striated muscle tissue; hypogonadism; testosterone deficiency; muscle fiber; interstitium
MeSH terms:
HYPOGONADISM – PATHOLOGY
ANAL CANAL – PATHOLOGY
MUSCLE, STRIATED – PATHOLOGY
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Ethics statements. The study complies with the standards of the EU Directive for the Protection of the Vertebrate Animals used for Experimental and other Scientific Purposes. All manipulations with animals were approved by the Local Bioethics Committee of the Samara State Medical University, No. 195 of 10.10.2018.
Data availability. The data that support the findings of this study are available from the corresponding authors on reasonable request. Data and statistical methods used in the article were examined by a professional biostatistician on the Sechenov Medical Journal editorial staff.
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Структурные изменения мышечной ткани наружного сфинктера прямой кишки на фоне экспериментальной андрогенной недостаточности

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Аннотация

Цель. Изучить гистологическое и ультрамикроскопическое строение поперечнополосатой мышечной ткани наружного сфинктера прямой кишки (НСПК) половозрелых крыс-самцов в условиях экспериментальной андрогенной недостаточности.
Материалы и методы. Исследование выполнено на 10 лабораторных крысах-самцах в возрасте 8 месяцев, которые были рандомно разделены на 2 группы по 5 в каждой. Экспериментальной группе проводили двухстороннюю орхиэктомию для формирования дефицита тестостерона. На 45-е сутки крыс выводили из эксперимента. Проводили исследование концентрации тестостерона, гистологических срезов НСПК с помощью световой микроскопии и ультрамикроскопии. Определяли диаметр мышечных волокон и толщину эндомизия, площадь мышечных волокон, соединительной ткани, миофибрилл и цитоплазмы, выявление гранул гликогена в цитоплазме и межмиофибриллярном пространстве, а также изменения в митохондриях.
Результаты. В экспериментальной группе на 45-е сутки после кастрации уровень тестостерона был в 2,5 раза ниже, чем в контрольной группе: 2,69 (2,52; 2,73) нмоль/л vs. 7,20 (6,83; 7,21) нмоль/л; p = 0,008. При проведении морфометрического анализа установлено, что в группе после кастрации диаметр мышечных волокон был статистически значимо меньше, чем в контрольной группе: 6,56 (3,96; 7,24) мкм vs. 9,52 (8,88; 10,44) мкм; $p < 0,001$, при этом в экспериментальной группе толщина эндомизия была больше: 3,34 (3,11; 3,78) мкм vs. 1,62 (1,51; 1,86) мкм; $p < 0,0001$. Отношение «площадь мышечных волокон / площадь соединительной ткани» было статистически значимо ниже в группе после кастрации: 1,64 (1,50; 1,78) vs. 4,00 (3,17; 5,25); $p < 0,0001$. Отношение «площадь миофибрилл / площадь цитоплазмы» изменялось в экспериментальной группе в сторону преобладания цитоплазмы: 0,79 (0,67; 0,79) vs. 5,25 (5,25; 7,33); $p < 0,0001$. С увеличением объема цитоплазмы наблюдался рост количества гранул гликогена; выявлялись патологические формы митохондрий: набухание, деструкция крист и вакуолизации их матрикса.
Заключение. В поперечнополосатой скелетной мышечной ткани НСПК в условиях дефицита тестостерона наряду с атрофическими процессами формируются компенсаторно-приспособительные механизмы, направленные на восстановление ее метаболической и функциональной организации.

Ключевые слова: недостаточность анального сфинктера; скелетная мышечная ткань; гипогонадизм; дефицит тестостерона; мышечное волокно; интерстиций

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Соответствие принципам этики. Исследование проведено с соблюдением положений Европейской конвенции о защите позвоночных животных, которые используются для экспериментальных и других научных целей. Все манипуляции с животными проведены в соответствии с разрешением Локального этического комитета ФГБОУ ВО «Самарский государственный медицинский университет» Минздрава России (№ 195-10.10.2018).
Доступ к данным исследования. Данные, подтверждающие выводы этого исследования, можно получить у авторов по обоснованному запросу.
Данные и статистические методы, представленные в статье, прошли статистическое рецензирование редактором журнала – сертифицированным специалистом по биостатистике.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Финансирование. Исследование не имело спонсорской поддержки (собственные ресурсы).

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Abbreviations:

EAS – external anal sphincter

Hypogonadism is a life quality-impairing clinical syndrome with numerous organs affected via receptor insensitivity to androgens and biochemical signs of low testosterone content[1]. Indeed, primary hypogonadism originates from an inadequate testicular function resulting in decreased testosterone levels. In experiments, the condition can be easily achieved by bilateral orchidectomy.

Generally, androgen deficiency in men is common. For instance, studies in Europe and the USA reveal the prevalence of hypogonadism among middle-aged and older men at 2.1 to 12.8%. Besides, patients with concomitant diseases had higher prevalence, for example, 51 % for type 2 diabetes mellitus and 15 to 78.8 % for obesity [1].

Indeed, anabolic steroids such as testosterone are crucial not only in puberty, sexual activity, and reproduction but also in the normal function of skeletal muscles [2]. Thus, testosterone in muscle tissues enhances protein synthesis and inhibits its loss. It also directs mesenchymal pluripotent cells into myogenesis and provokes the synthesis of contractile proteins to permit hypertrophic muscular development [3–5]. Some sources report related sarcopenia occurring in low androgen content in the blood serum [6,7].

Due to the muscular changes, faecal incontinence remains a serious clinical challenge, where external anal sphincter (EAS) dysfunction occurs, as it consists of striated muscles [8]. Our colleagues modelled faecal incontinence via ovariectomy in female rats, while

[1] Dedov I.I., Mokrysheva N.G., Melnichenko G.A. et al. Recommendations on diagnosis and treatment of testosterone deficiency (hypogonadism) in men. FGBU "Endocrinology Research Center" of the Ministry of Health of Russia. 2016. P. 19 (In Russian). https://www.endocrincentr.ru/sites/default/files/specialists/science/clinic-recomendations/hypogon.pdf?ysclid=lneu1n3onn251612089 (date of access: 03.08.2023) / Дедов И.И., Мокрышева Н.Г., Мельниченко Г.А. и др. Рекомендации по диагностике и лечению дефицита тестостерона (гипогонадизма) у мужчин. ФГБУ «Эндокринологический научный центр» Минздрава России. 2016. С. 19. https://www.endocrincentr.ru/sites/default/files/specialists/science/clinic-recomendations/hypogon.pdf?ysclid=lneu1n3onn251612089 (дата обращения: 03.08.2023).

testosterone administration led to recovery [9]. Further investigation is needed to understand the EAS structure and metabolism in testosterone deficiency.

The study aimed to examine the microscopic and ultramicroscopic structure of striated muscles in EAS of mature male rats in experimental androgen deficiency.

MATERIALS AND METHODS

We used ten healthy mature 8-month-aged male rats with a body mass of 300–350 g to study the effects of testosterone deficiency. Experiments with animals took place at the Laboratory of Experimental Medicine and Biotechnology Institute of Samara State Medical University, Russia. The rodents stayed at constant temperature (22±1 °C), humidity (55±10 %), and 12/12-h-light/dark cycle in polypropylene cages with granular filler with food and water ad libitum.

At time point 1, we randomized the males into 2 groups (5 rats in each group): intact animals (controls) and experimental animals with a model of androgen insufficiency via bilateral orchidectomy (Fig. 1). All surgeries were performed after intramuscular anaesthesia of tiletamine anaesthetics and zolazepam (Virbac C.A., France) at a dose of 15 mg/kg of body mass and xylazine hydrochloride (Bioveta, Czech Republic) at a dose of 6 mg/kg of body mass. We then made incisions in the scrotums of the rats to remove the testes, and ligate and cut off the spermatic cords. At time points 1, 2 (Day 30), and 3 (Day 45) after orchidectomy, we checked the testosterone levels in the blood serum of rats by chemiluminescence immunoassay (ACCESS 2, Beckman Coulter Inc, USA) (Fig. 1)

On Day 45 we collected materials for the histological study of the modelled hypogonadism after medication-induced euthanasia (an intracardiac injection of drugs used at point 1 in lethal doses) and according to the recommendations of the European Commission on euthanasia of experimental animals. We isolated the rectum with the cutaneous part of the anus, thus fixing the lower third of the rectum in 10% neutral buffered (pH 7.4, which was followed by alcohol dehydration in increasing concentrations (30º, 50º, 70º, 90º, 96º(I), 96º(II), absolute alcohol) and paraffinized.

We cut slices of 5–7 μm with a Sakura Accu-Cut SRM 200 rotary microtome (Japan) and stained the slides according to the standard procedure with haematoxylin and eosin. We examined the slides via a Leica DM3000 light microscope (Germany) with a digital camera and software for morphometrics., and then determined the diameter of muscle fibres and endomysium thickness with a planimetric 25-point grid by G.G. Avtandilov. The area of muscle fibres and connective tissue was calculated by stereometric methods.

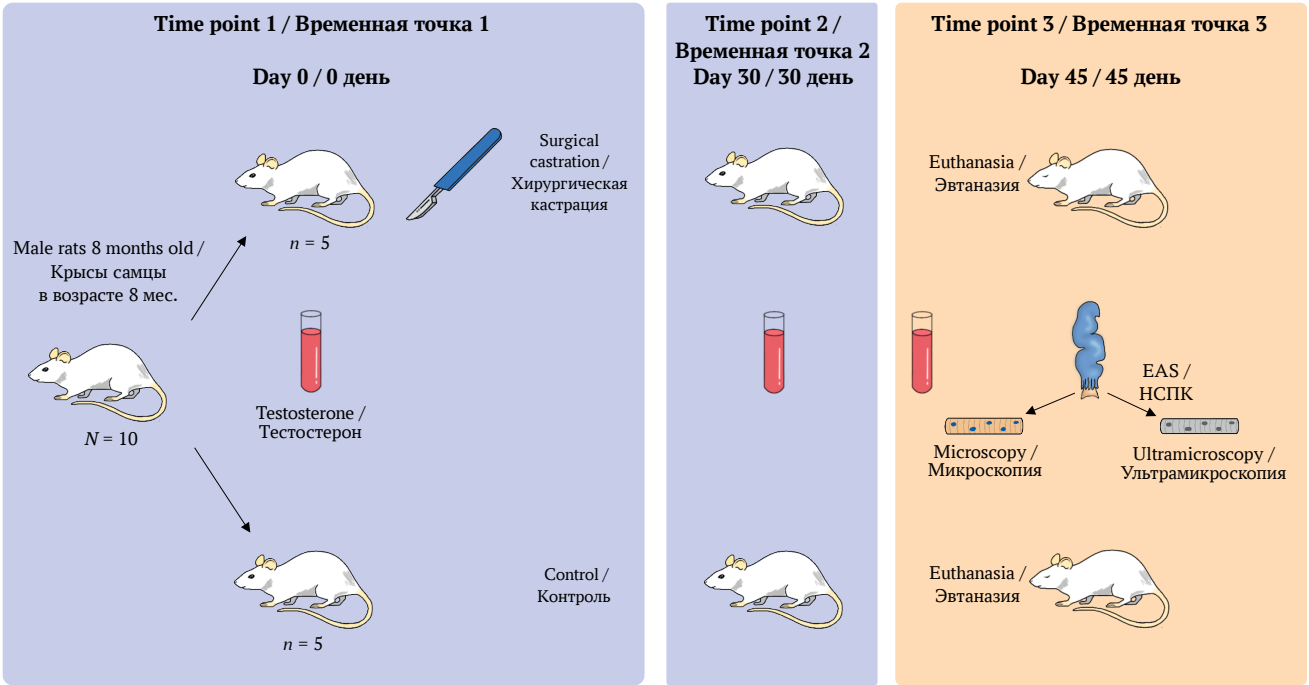

FIG. 1. Experimental design: study of the external anal sphincter after modeling androgen deficiency in mature male rats.
РИС. 1. Схема эксперимента: изучение наружного сфинктера прямой кишки после моделирования андрогенной недостаточности у половозрелых крыс-самцов.

Note: EAS – external anal sphincter.
Примечание: НСПК – наружный сфинктер прямой кишки.

For ultrastructural analysis, we fixed the material in 1 % glutaraldehyde (pH 7.4) for 12 hours. Later, the material was transferred into a 2.5 % solution of glutaraldehyde for 4 hours and then placed into 1 % osmium tetroxide for 2 hours. The dehydration was carried out through alcohols of increasing concentration and propylene oxide. We employed epoxy resins to get cutting blocks and obtained ultrathin sections of 60–80 nm with Leica UC7 microtome (Germany), then placed the slices onto copper meshwork and stained for 20 minutes with a saturated solution of uranyl acetate and 5 minutes with lead citrate.

We used a Hitachi HT 7700 Exalens electron microscope (Hitachi High-Tech Corporation, Japan) for transmission electron microscopy at the Laboratory of Electron Microscopy of Analytical Microscopy Interdisciplinary Centre at Kazan Federal University. Ultrastructural study of muscle fibres allowed us to calculate the area of myofibrils and cytoplasm, to detect glycogen granules in the cytoplasm and spaces between myofibrils, and to determine mitochondrial changes.

Statistical analysis

Continuous data from the study are given as median and interquartile range (25th; 75th percentiles). We used the non-parametric Mann–Whitney criterion to reveal the statistical significance of the differences between the values in the experimental group and the control group. The differences were considered significant at $p<0.05$. Statistical data analysis is performed using the software IBM SPSS v. 23.0 (SPSS: An IBM Company, USA).

RESULTS

The baseline testosterone levels in both groups did not differ. In the experimental group, the testosterone level after castration decreased by 2.5 times by Day 30 and there was no change until 45 days. In the control group, the testosterone concentration did not change significantly during the experiment (Table 1).

Light optical examination of the samples revealed that the composition of EAS (common striated structure of locomotive type muscle tissue) differs between the experimental and control groups by the number of muscle fibres and connective tissue amount (Fig. 2).

Morphometrics showed that the diameter of EAS muscle fibres was 1.5 times smaller in animals with experimentally modelled hypogonadism than those from the control group (Table 1). Moreover, this diameter decrease (for muscle fibres in the experimental male rats) was accompanied by an increase of endomysium thickness around 2 times greater than the corresponding values in the control group (Table 1). However, no cell pools differed between the groups in the endomysium samples, and standard loose connective tissue always formed the endomysium.

Testosterone-deficient rats also exhibited 1.3 times smaller muscle tissue area and 1.9 times greater

Table. **Testosterone concentration and changes in the external anal sphincter of male rats in a model of hypogonadism**
Таблица. **Концентрация тестостерона и изменения в наружном сфинктере прямой кишки крыс-самцов в модели гипогонадизма**

Parameter / Параметр	Experimental group / Экспериментальная группа	Control group / Контрольная группа	*p* value / Значение *p*
Testosterone, nmol/l / Тестостерон, нмоль/л			
initially / исходно	6.86 (6.75; 7.15)	7.19 (6.85; 7.29)	0.421
in 30 days / через 30 дней	2.77 (2.65; 2.79)[a]	7.23 (6.80; 7.24)	0.008
in 45 days / через 45 дней	2.69 (2.52; 2.73)[a]	7.20 (6.83; 7.21)	0.008
Diameter of muscle fibers, μm / Диаметр мышечных волокон, мкм	6.56 (3.96; 7.24)	9.52 (8.88; 10.44)	<0.001
Endomysium thickness, μm / Толщина эндомизия, мкм	3.34 (3.11; 3.78)	1.62 (1.51; 1.86)	<0.0001
Muscle fiber area, % / Площадь мышечных волокон, %	62 (60; 64)	80 (76; 84)	<0.0001
Connective tissue area, % / Площадь соединительной ткани, %	38 (36; 40)	20 (16; 24)	<0.0001
Muscle fiber area / connective tissue area / Площадь мышечных волокон / площадь соединительной ткани	1.64 (1.50; 1.78)	4.00 (3.17; 5.25)	<0.0001
Myofibril area, % / Площадь миофибрилл, %	44 (40; 44)	84 (84; 88)	<0.0001
Cytoplasm area, % / Площадь цитоплазмы, %	56 (56; 60)	16 (12; 16)	<0.0001
Myofibril area / Cytoplasm area / Площадь миофибрилл / площадь цитоплазмы	0.79 (0.67; 0.79)	5.25 (5.25; 7.33)	<0.0001

Note: [a] – $p < 0.01$ compared with the initial level.
Примечание: [a] – $p < 0,01$ при сравнении с исходным уровнем.

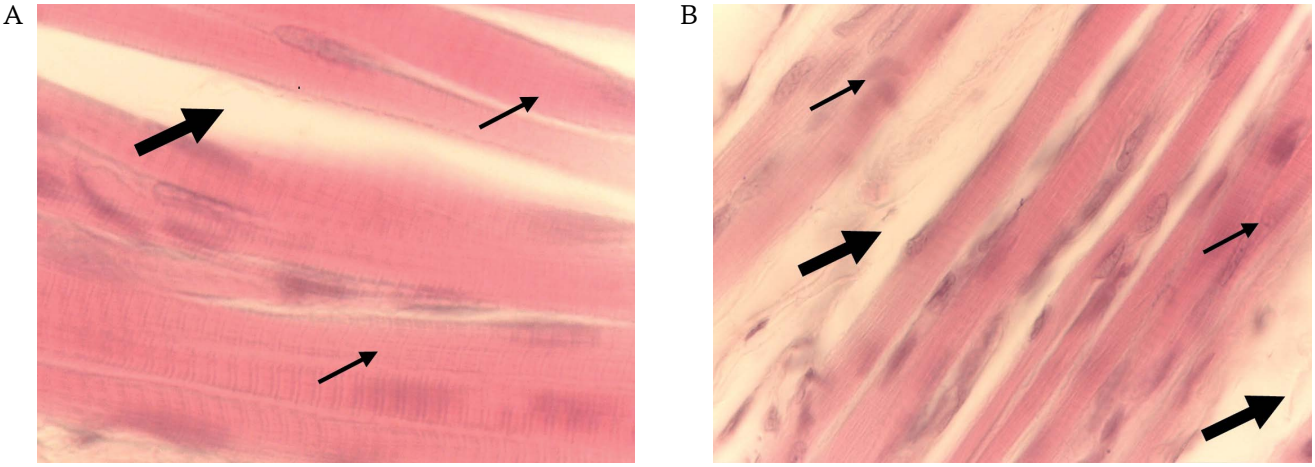

FIG. 2. Microscopic image of striated muscle tissue of the external anal sphincter in rats on the 45th day of simulated hypogonadism. Magnification 1000, ob. 100, oc. 10.
Thin arrows – muscle fibers, thick arrows – interstitium.
A – control group.
B – group with experimental hypogonadism on day 45.
РИС. 2. Микроскопическая картина поперечнополосатой мышечной ткани наружного сфинктера прямой кишки у крыс на 45-е сутки моделированного гипогонадизма. Ув. 1000, об. 100, ок. 10.
Тонкие стрелки – мышечные волокна, толстые стрелки – интерстиций.
A – контрольная группа.
B – группа с экспериментальным гипогонадизмом на 45-е сутки.

connective tissue area compared to those of the control group animals. Thus, the ratio between muscle fibre area and connective tissue area at EAS region remained 2.5 times less in the experimental group than in the control group.

Ultrastructural study of EAS striated muscle tissue revealed that animals of the experimental group had 1.9 times smaller myofibril area and 3.5 times larger cytoplasm area than the control group had. The ratio between myofibril area and cytoplasm area remained 6.6 times less in the experimental group than in the control group (Table 1).

In the experimental group, muscle fibres increased not only in the cytoplasm area but also in the number of glycogen granules. These granules were found between myofibrils, between myofilaments, and even around the nuclei. Besides, we observed pathological mitochondria with swelling, cristae destruction, and matrix vacuolization (Fig. 3).

DISCUSSION

Our light optical and ultramicroscopic study of modelled hypogonadism and confirmed testosterone deficiency (levels 2.5 times less than in the control group) showed that on Day 45 experimental mature male rats decreased their EAS striated muscle fibre diameter by 1.5 times compared with the control group. We believe that these atrophic muscle fibre changes result in compensatory connective tissue growth by 2 times compared to the control group.

This EAS muscle fibre atrophy might be explained by the anabolic effects of testosterone in skeletal muscle tissues with numerous androgen receptors. Such an androgen deficiency probably suppresses protein synthesis in muscles with no myofibril construction available [10].

Moreover, the decrease of myofibril content and impaired myofilament binding are accompanied by damaged mitochondrial structure with no adequate ATP supply. Later, sarcoplasm is filled by glycogen granules, and we assume these modifications to be compensatory and adaptive mechanisms of EAS striated muscle tissue in testosterone deficiency.

However, several different factors of testosterone deficiency probably led to the mitochondrial changes in the experimental group (swelling, cristae destruction, and matrix vacuolization). Some sources report that testosterone deficiency causes a decreased catabolism of energy substrates (glucose and fatty acids) in mitochondria during ATP production and heating. As a result, there is an extra energy substrate in the cytoplasm of muscle fibres, which may modify the mitochondrial structure.

Besides, damaged mitochondrial structure is often associated with hypoxia. For instance, a castration-related androgen deficiency affects erythropoiesis [11]. Indeed, it shortens the oxygen supply, and cells experience hypoxia. Hypoxia switches the respiratory chain to glycolysis that leads to local acidosis, sodium overload, lack of calcium, and impaired ATP production.

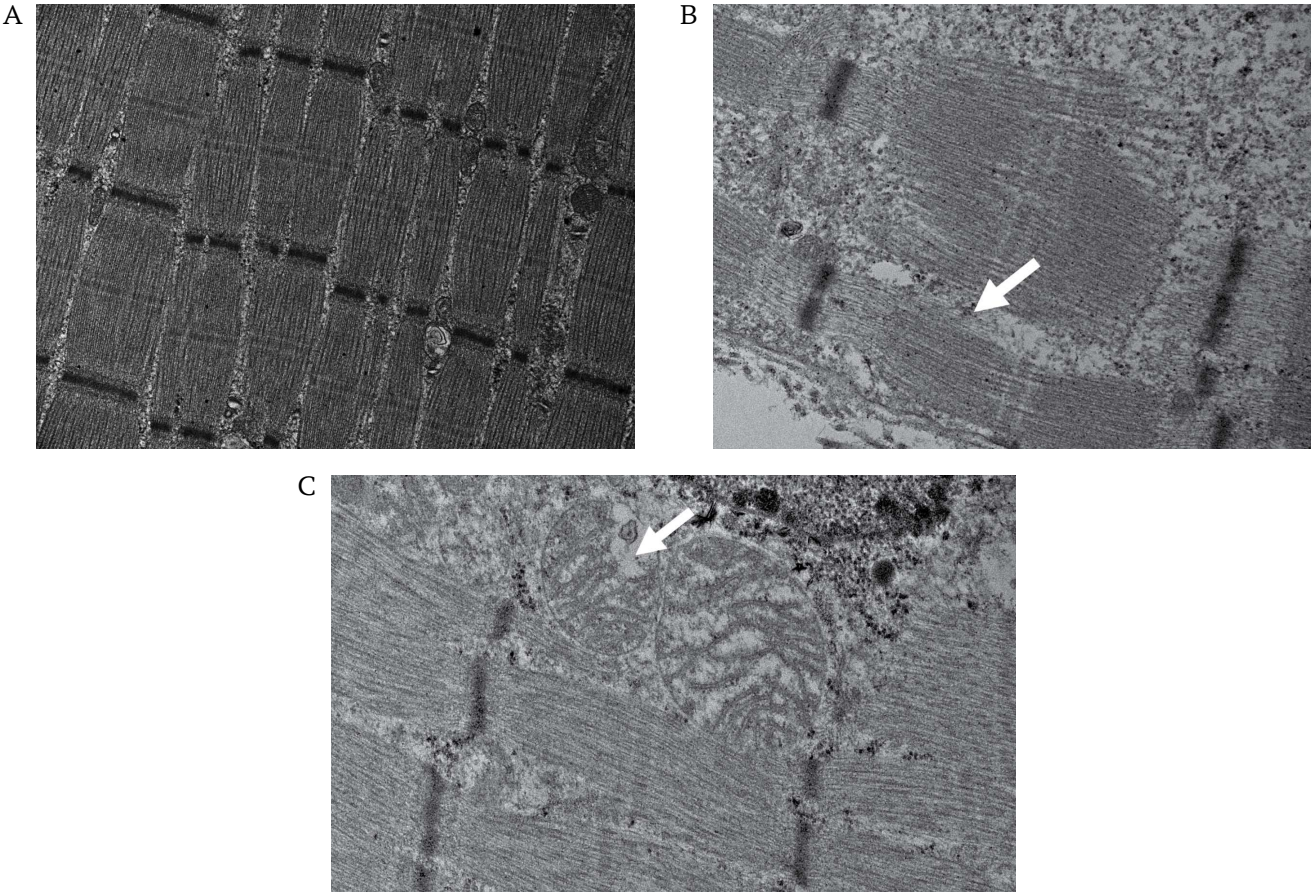

FIG. 3. Ultramicroscopic image of striated muscle tissue of the external anal sphincter in rats on the 45th day of simulated hypogonadism.
A – control group (magnification 12 000);
B – group with experimental hypogonadism on day 45 (magnification 20 000). Numerous glycogen granules in the cytoplasm and intermyofibrillar space (arrow);
C – group with experimental hypogonadism on day 45 (magnification 20 000). Changes in mitochondria: swelling, destruction of cristae and vacuolization of the matrix (arrow).
РИС. 3. Ультрамикроскопическая картина поперечнополосатой мышечной ткани наружного сфинктера прямой кишки у крыс на 45-е сутки моделированного гипогонадизма.
А – контрольная группа (ув. 12 000);
В – группа с экспериментальным гипогонадизмом на 45-е сутки (ув. 20 000). Многочисленные гранулы гликогена в цитоплазме и межмиофибриллярном пространстве (стрелка);
С – группа с экспериментальным гипогонадизмом на 45-е сутки (ув. 20 000). Изменения в митохондриях: набухание, деструкция крист и вакуолизации матрикса (стрелка).

Then, these mitochondrial hypoxia-caused changes result in increased permeability of the inner membrane, thereby to mitochondrial death or at least swelling [12]. In addition, an elevated content of reactive oxygen species accompanies decreased androgen levels. It may be another factor that provokes an impaired mitochondrial structure and enhances the oxidative damage in the respiratory chain [13].

Interestingly, previous studies reported that a decrease in androgen levels leads to muscle fibre mass loss with a shift to adipose tissue. Nonetheless, the replacement therapy results in the recovery of muscle mass [14, 15]. Our microscopic and ultramicroscopic findings expose atrophic muscle fibre changes in hypogonadism, while a partial loss of myofibrils and connective tissue growth occurs.

We should emphasize that our data differ from that of some other studies, for example, we found that glycogen content increases in muscle fibres in hypogonadism. However, a possible decrease of insulin sensitivity was previously reported for testosterone deficiency, leading to a reduced glucose intake and less intracellular glycogen accumulation [16]. We consider that the increased glycogen levels and dystrophic mitochondria in muscle tissue manifest an anaerobic switch of energy metabolism in testosterone deficiency. We assume these metabolic profile changes to be adaptive.

CONCLUSION

A modelled testosterone deficiency in male rats in puberty involves both atrophy of EAS striated muscles and compensatory adaptive machinery for metabolic and functional organization. Our results might promote an understanding of faecal incontinence in androgen deficiency to provide a benchmark for further studies.

AUTHOR CONTRIBUTIONS

Antonina S. Pronina: study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript. Galina N. Suvorova: study concept and design of the experiment, drafting of the manuscript. Natalya N. Vologdina: analysis and interpretation of data, drafting of the manuscript. All authors approved the final version of the publication.

ВКЛАД АВТОРОВ

А.С. Пронина внесла значительный вклад в разработку концепции идеи, проведение эксперимента и обработку данных, статистическую обработку результатов исследования, подготовку рукописи. Г.Н. Суворова внесла основной вклад в разработку концепции идеи и методологии проведения эксперимента, а также написание текста рукописи. Н.Н. Вологдина участвовала в обработке данных и редактировании текста статьи. Все авторы утвердили окончательную версию статьи.

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