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Testis morphophysiology of rats treated with nandrolone decanoate and submitted to physical training

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ABSTRACT. The mammalian testis is a complex organ with endocrine and exocrine functions. It consists of seminiferous tubules where the production of the male gametes called spermatogenesis occurs. This process is influenced by a number of factors including the use of physical performance-enhancing drugs. The objective of this study was to evaluate the effects of the anabolic steroid nandrolone decanoate on the morphofunctional structure of testes in sedentary rats and rats subjected to moderate aerobic exercise training. Twenty-four male rats were divided into four experimental groups: sedentary control, sedentary treated, trained control and trained treated. The training lasted eight weeks and consisted of running on a programmable ergometer treadmill, tailored to train eight rats simultaneously. Treated animals received intramuscular injections of nandrolone decanoate (0.5 mg kg⁻¹ body weight) during the last four weeks of physical training, while the control groups received intramuscular injections of vehicle (vegetable oil). The male reproductive system morphology showed that treatment with nandrolone decanoate, in both sedentary and trained rats, promoted morphological and functional changes that result in reduced efficiency of spermatogenesis.

Keywords: anabolic agent, testis, spermatogenesis, nandrolone decanoate.

Morfofisiologia testicular de ratos tratados com decanoato de nandrolona e submetidos ao treinamento físico

RESUMO. O testículo de mamíferos é um órgão complexo com funções endócrinas e exócrinas. É composto por túbulos seminíferos, local onde ocorre a espermatogênese, processo de produção dos gametas masculinos. Este processo é influenciado por uma série de drogas potencializadoras do desempenho físico, que são utilizadas para melhorar a performance. O objetivo deste estudo foi avaliar os efeitos do anabolizante esteróide decanoato de nandrolona sobre a estrutura morfofuncional de testículos de ratos sedentários e submetidos ao treinamento físico aeróbico moderado. Foram utilizados vinte e quatro ratos machos divididos em quatro grupos experimentais: sedentário controle, sedentário tratado, treinado controle e treinado tratado. O treinamento teve duração de oito semanas e consistiu de corrida em esteira ergométrica programável, adaptada para treinar oito ratos simultaneamente. Os grupos tratados receberam injeção intramuscular de decanoato de nandrolona (0,5 mg kg⁻¹) durante as quatro últimas semanas de treinamento físico, enquanto os grupos controles receberam injeção intramuscular do veículo (óleo vegetal). Os resultados mostraram que o tratamento com o decanoato de nandrolona, tanto em ratos sedentários como submetidos ao exercício físico, promove alterações morfofuncionais que resultam na redução da eficiência da espermatogênese.

Palavras-chave: anabolizante, testículo, espermatogênese, decanoato de nandrolona.

Introduction

The use of physical performance-enhancing drugs is an issue increasingly discussed throughout the world. Their importance is no longer restricted to high-level competitive sport, also reaching the areas of recreational sport and physical activity in general. In order to get a better physical performance and muscular appearance,

many young people seek resources that, in most cases, can bring harm to health, such as the indiscriminate use of anabolic androgenic steroids (AAS) (MARQUES et al., 2003; MIRKHANI et al., 2005).

AAS are a group of natural and synthetic compounds formed by testosterone and its derivatives (CUNHA et al., 2004; THIBLIN; PETERSSON, 2005). AAS has the primary

function to develop and maintain male sexual characteristics, besides its anabolic function that leads to increased protein synthesis and consequent increase in muscle mass (SOARES et al., 2011).

Many adverse effects, potentially serious, associated with high doses of anabolic steroids have been described, such as: (i) nervous system: increases aggressive behavior (SALAS-RAMIREZ et al., 2010), psychotic delusions and mood changes (SILVA et al., 2002; VENÂNCIO et al., 2008), (ii) cardiovascular system: leads to a reduction in HDL cholesterol and increases LDL cholesterol, which accelerates atherosclerosis (MIRKHANI et al., 2005; SANTOS et al., 2006), and lead to heart attacks and spills (SILVA et al., 2002); (iii) male reproductive system: reduction of follicle stimulating hormone circulating levels (FSH), luteinizing hormone (LH) and consequent decrease in circulating testosterone. It is also associated to a higher risk to develop prostate cancer (SILVA et al., 2002), lack of libido and impotence and morphological changes in the testis (NOORAFSHAN et al., 2005). The seminiferous epithelium is sensitive to the use of anabolic steroids, which severely affect sperm production (JOHNSON et al., 1997).

Studies have shown that the use of nandrolone decanoate in rats causes structural changes in the testis, the sperm quality and reduction in prostate weight (KARBALAY-DOUST; NOORAFSHAN, 2006). Administration of the AAS nandrolone decanoate to female rats causes alterations in the morphology of their uterus and a reduction in reproductive capacity (MOBINI-FAR et al., 2007; CAMARGO et al., 2009; ALMEIDA-CHUFFA et al., 2011). In addition, the pathological evaluation of the heart, testis and adrenal glands of rats subjected to treatment with AAS showed that these organs were severely damaged (TAKAHASHI et al., 2004).

It was established that exercise and high doses of anabolic-androgenic steroids might influence the hypothalamic-pituitary-gonadal axis and, consequently, lead to apoptosis of germ cells (SHOKRI et al., 2010).

The mammalian testis is a complex organ with exocrine and endocrine functions. Morphofunction features two compartments: (i) interstitial or intertubular, containing cells and fibers of connective tissue, blood and lymphatic vessels and Leydig cells, the main source of androgen in the body, (ii) tubular, formed by seminiferous tubules, which are structured with its outer portion to the internal: tunica propria, the seminiferous epithelium and lumen (ROOIJ,

1998). The seminiferous epithelium consists of two cell types: spermatogenic cells and Sertoli cells, which provide support for the germ cells, nutrition, phagocytosis and secretion of fluid that helps to transport the sperm. Among the various functions provided by them, they are responsible for the final testicular volume and sperm production of adult (RUSSELL et al., 1990).

Although the testes of mammals present standard structure for several species, there is great variation in relation to volumetric proportion of its various components, especially in relation to the seminiferous tubules, Leydig cells and proportion and disposition of vessels and lymphatics spaces (RUSSELL et al., 1990). The tubular compartment constitutes the majority of the testicular parenchyma, occupying, in most species of mammals about 70 to 90%, exerting great influence on the weight of the testes and sperm production. The interstitial compartment holds a percentage ranging from 10 to 30% in most mammals (FRANÇA; RUSSELL, 1998).

Taking into consideration that nandrolone decanoate is one of the most widely used anabolic steroids and that it can interfere with spermatogenesis (FOLETTTO et al., 2010) we aimed to evaluate the effects of AAS administration in Wistar rats submitted to physical training at testicular morphophysiology.

Material and methods

Experimental animals

Male Wistar rats, 50 days old, were kept in an animal facility at a room temperature of $23^{\circ} \pm 2^{\circ}\text{C}$, on a light:dark cycle of 12/12h (lights on at 6:30 a.m.) and free access to water and rodent chow (Nuvital®, Colombo, Paraná State, Brazil) distributed in polypropylene boxes ($46 \times 24 \times 20$ cm), six animals per each. The experimental procedures were approved by the Committee of Ethics in the Use of Experimental Animals – CEAE (Protocol no. 039/2008).

Experimental procedure

Twenty-four animals aging 45 days were allotted to four experimental groups: sedentary control (SCo), sedentary treated (STr), trained control (TCo) and trained treated (TTr), with six animals per group. The trained animals were subjected to a physical exercise program, which consisted in running (intensity of 60-65% of the VO_2 max.) in a programmable ergometer treadmill (Imbramed, model KT3000, Brazil)

adapted for rat training. Before the beginning of the training, the animals had a week of adaptation, during which the speed of the treadmill increased progressively from 0.3 to 0.6 km h⁻¹ at stages lasting two minutes each. After this period, the speed and the duration increased gradually until 60 min. day⁻¹ reaching an average speed of 1.0 km h⁻¹ (DUFLOTH et al., 1997). The training was performed four times a week, always at the same time of the day (7:30 to 8:30 a.m.), during nine weeks. The treatment with nandrolone decanoate began on the fifth week and consisted of the intramuscular injections (gastrocnemius muscle) of Deca-durabolin® (0.5 mg kg⁻¹) diluted in vegetal oil, five times a week, during five weeks (NOORAFSHAN et al., 2005). The control groups received intramuscular injections of the vehicle (vegetal oil). At the end of the training and treatment, the animals were anesthetized with sodium pentobarbital (Hypinol® 3%, 4 mg 100⁻¹ g bw, i.p.) and subjected to abdominal-pelvic laparotomy to remove the seminal vesicles and testicles, which were weighed. Finally, the animals were killed by anesthetic overload.

Histological processing of the testes

Testis samples were perfused-fixed with Karnovsky-fluid for 24 hours, at room temperature, and stored in 0.1 M phosphate buffer, pH 7.3 until histological processing. Samples of testis were dehydrated in progressive series of alcohols (70% -100%). After dehydration, infiltration was carried out in glycol metacrylate (GMA, Leica Instruments), at a concentration of 50%, remaining for 24 hours in refrigerator. Then the fragments were transferred to resin infiltration for 24 hours. Finally, the fragments were embedded in resin plus hardener. The blocks were cut with 4 µm thick histological sections and stained with periodic acid-Schiff, and finally counter-stained with hematoxylin (PAS-H).

Tubular diameter, height of seminiferous epithelium and total length of seminiferous tubules

The average diameter of seminiferous tubules was obtained of 24 animals as from as measurements of cross section of 30 seminiferous tubules that showed the contour more regular as possible. The height of the seminiferous epithelium was also obtained from the mean height of the seminiferous epithelium in 30 cross sections. The same cross sections used to measure the tubular diameter were utilized to measure the height of the seminiferous epithelium. All data were obtained

using an Olympus ocular micrometer 10 X, coupled in 10 X objective.

The total length of seminiferous tubules per testis was estimated using the formula determined by Attal et al. (1963) and Dorst and Sajonski (1974) from the knowledge of the volume (µL) occupied by seminiferous tubules in the testis and the tubular diameter.

Volumetric proportions (%) and volumes of the components of the testis (µL)

Volumetric proportions were estimated using reticle with 441 intersections (points) per animal, using a 10 X Olympus ocular micrometer coupled to a 40 X objective. For each animal were analyzed 15 fields, chosen at random, making a total of 6615 points. In tubular compartment were measured the tunica propria, the seminiferous epithelium and the lumen; while in the intertubular compartment were analyzed Leydig cells, blood and lymph vessels, mast cells and other components such as cells and fibers of connective tissue. The volume (µL) of each testicular component was estimated from the knowledge of the percentage occupied by them in the testis and knowledge of the net volume of the testis. The latter value was obtained by subtracting the weight of the tunica albuginea.

Individual volume of Leydig cells

The calculation of the individual volume of Leydig cells was investigated employing reticle with 441 intersections (points), using Olympus ocular micrometer 10 X, coupled in 100 X objective. Five hundred points over the cytoplasm and nucleus of Leydig cells were counted per animal for the purpose of determining the proportion (%) between nucleus and cytoplasm. In another step, the mean nuclear diameter of these cells was obtained with the aid of an ocular 10 X micrometer, coupled in 100 X objective. Fifteen nuclei of Leydig cells were measured in each animal. The nuclear volume, the volume of cytoplasm and, consequently, the volume of each Leydig cell were calculated from the data obtained previously. These values were expressed in cubic micrometers (µm³).

Statistical analysis

The statistical analysis was performed using the program Prism, v. 5.0 (GraphPad, USA). The comparison of means was made from analyse of variance (ANOVA), followed by Tukey's test, setting the significance level of 95% (p < 0.05).

Results

The weight of the testes and seminal vesicles of four experimental groups, calculated for 100 g of body weight, is shown in Table 1. Assessing the effect of training, it appears that trained animals had a higher testicular weight, compared to sedentary animals; however, this difference was only significant between the groups treated with anabolic steroid. The analysis of the treatment effect shows that the nandrolone decanoate did not affect significantly this parameter as observed in controls and treated animals, both sedentary and trained. In relation to the weight of the seminal vesicles, the anabolic caused significant increases in both sedentary and trained animals. The training, in turn, had no significant effect on the weight of seminal vesicles, independent of this animal to be treated or not with anabolic steroids.

Table 1. Effect of nandrolone decanoate on the weight of the testis and seminal vesicles (g 100⁻¹ g bw) of sedentary and trained rats. SCo: sedentary control; STR: sedentary treated; TCo: trained control; TTr: trained treated.

Weight	SCo	STR	TCo	TTr
Testes	0.36 ± 0.01	0.33 ± 0.02	0.39 ± 0.01*	0.40 ± 0.01*
Seminal Vesicle	0.30 ± 0.02	0.47 ± 0.03#	0.29 ± 0.02	0.51 ± 0.03#

Values express the mean ± sem; n = 6 animals for each experimental group. *p < 0.05 relative to group STR; #p < 0.001 relative to groups SCo and TCo.

Table 2 shows the mean values of the different components of the testis in trained and sedentary groups, treated or not with nandrolone decanoate. There was a significant reduction in the total percentage of seminiferous tubules from trained and sedentary rats treated with nandrolone. In assessing the percentage of the seminiferous epithelium, the effect of the drug is more pronounced, causing reductions of approximately 14% and, again, both in the sedentary and trained groups. The interference of the AAS in testicular development is also evident by examining the lumen of the seminiferous tubule, which increased significantly in the treated group. Finishing the analysis of the seminiferous tubules, we observed that the

tunica propria, as well as the lumen, were significantly increased in the groups that received nandrolone. The data show that the treatment with nandrolone increased the lumen of the seminiferous tubule and tunica propria, and decreased the seminiferous epithelium.

Table 2 also shows that the total volume of the interstitial compartment increased significantly in the testes of rats treated with nandrolone decanoate. This increase was 44.23% in the trained group and 41.58% in the sedentary group. Trained animals showed a slight decrease in the percentage of the interstitial compartment compared to sedentary ones, however, these differences were not significant in both experimental groups (control and treated). Noting further the results in Table 2, regarding the effect of treatment, there were significant reductions in the percentage of Leydig cells both in the STR and the TTR in relation to the SCo Group and TCo, respectively. The percentage of mast cells and blood vessels were not different between groups. However, the lymphatic space of the interstitial compartment of testes obtained from the trained rats that were treated with anabolic steroid was 56.36% higher compared with control rats. The anabolic steroid effect of this parameter was similar in sedentary rats, because treated rats had a reduction of 44.49%. Considering the percentage of other constituents of the interstitial compartment, referring to the fibers and connective tissue cells, there was a significant increase (p < 0.05) of 51.11% in the STR compared to the SCo. However, the physical training caused a significant decrease (p < 0.001) from 65.55% in TTR in relation to STR.

Table 3 shows the mean values for the diameter of the seminiferous tubule, seminiferous epithelium height and total length of seminiferous tubules (CTTS) per gram of testis. Given the values of tubular diameter and height of the seminiferous epithelium for trained rats, it is observed that the treatment promoted a significant reduction (p < 0.001) from 23.59% in the seminiferous tubule diameter and 35.08% at the height of seminiferous epithelium.

Table 2. Effect of nandrolone decanoate in the total seminiferous tubules (%) and interstitial compartment (%) of sedentary rats and subjected to physical training. SCo: sedentary control; STR: Sedentary treated; TCo: trained control; TTr: trained treated.

	SCo	STR	TCo	TTr
Total Seminiferous tubules	94.83 ± 0.30*	91.15 ± 0.35	95.46 ± 0.26**	91.86 ± 0.41
Tunica Propria	2.37 ± 0.07*	4.06 ± 0.24	2.89 ± 0.12**	3.75 ± 0.13
Seminiferous epithelium	87.87 ± 0.12*	73.67 ± 0.77	87.60 ± 0.99**	74.30 ± 0.66
Lumen	4.60 ± 0.59*	13.42 ± 0.28	4.97 ± 1.19**	13.81 ± 0.68
Interstitial Compartment	5.17 ± 0.30*	8.85 ± 0.35	4.54 ± 0.26**	8.14 ± 0.21
Leydig Cells	0.40 ± 0.05*	0.18 ± 0.03	0.56 ± 0.05**	0.22 ± 0.03
Mast Cells	0.19 ± 0.01	0.28 ± 0.04	0.16 ± 0.03	0.22 ± 0.03
Blood Vessels	0.27 ± 0.03	0.51 ± 0.09	0.37 ± 0.10	0.47 ± 0.05
Lymphatic Space	3.88 ± 0.32*	6.99 ± 0.29	3.02 ± 0.23**	6.92 ± 0.37
Other	0.44 ± 0.04#	0.90 ± 0.16	0.44 ± 0.04	0.31 ± 0.06*

Values express the mean ± sem; n = 6 animals for each experimental group. *p < 0.001 relative to group STR; **p < 0.001 relative to group TTr; #p < 0.05 relative to group STR.

Evaluations of these parameters in testes of sedentary rats confirmed these results, demonstrating that the anabolic steroid reduced ($p < 0.001$) in 19.24% of the seminiferous tubule diameter and 28.35% the height of the seminiferous epithelium. The training did not cause significant changes in these parameters in both control and treated rats. Completing the analysis of the results in Table 3, we observed that in the group of trained rats, the treatment caused a significant increase of 38.82% ($p < 0.001$) in CTTS. In the group of sedentary rats, the CTTS of treated rats was higher than the ones observed in the testes of control rats, however, did not differ significantly.

Table 3. Effect of treatment with nandrolone decanoate in diameter of the seminiferous tubule (μm), height of seminiferous epithelium (μm) and total length of the seminiferous tubule (CTTS) per gram of testis of sedentary rats and trained. SCo: sedentary control; Str: Sedentary treated; TCo: trained control; TTr: trained treated.

	SCo	STr	TCo	TTr
Diameter of the Seminiferous Tubule	318.55 \pm 3.74*	257.25 \pm 3.68	328.42 \pm 4.91**	250.95 \pm 3.16
Height of the Seminiferous Epithelium	117.81 \pm 2.10*	84.41 \pm 1.99	119.45 \pm 2.52**	77.55 \pm 1.49
Total Length of Seminiferous Tubules	11.71 \pm 0.12	14.55 \pm 2.95	11.00 \pm 0.25 [#]	17.98 \pm 0.21

Values express the mean \pm sem; n = 6 animals for each experimental group. * $p < 0.001$ relative to group STr; ** $p < 0.001$ relative to group TTr; [#] $p < 0.05$ relative to group TTr.

Table 4 shows the volume of Leydig cells (nuclear and cytoplasmic) of sedentary rats and submitted to physical training, treated or not with nandrolone decanoate. It is observed that the nuclear volume and cytoplasmic volume and, consequently, the total volume of Leydig cells, decreased significantly ($p < 0.001$) in treated animals, both when they were submitted to physical training, as in sedentary animals. The training interfere significantly in nuclear and cytoplasmic volume of control rats, causing an increase in these parameters ($p < 0.001$). In rats treated with anabolic steroids, the results did not differ significantly between trained and sedentary.

Table 4. Effect of nandrolone decanoate in Leydig cell morphometry (μm^3) of sedentary rats and trained. SCo: sedentary control; Str: Sedentary treated; TCo: trained control; TTr: trained treated.

	SCo	STr	TCo	TTr
Leydig Cell volume	5803.14 \pm 241.07*	1336.7 \pm 103.7	6974.77 \pm 188.06**	1733.4 \pm 76.86
Nuclear volume	1562.06 \pm 28.99*	987.26 \pm 64.12	1857.32 \pm 37.18** [#]	1183.05 \pm 71.94
Cytoplasmic volume	4241.07 \pm 221.75*	349.44 \pm 40.30	5117.45 \pm 174.34**	550.38 \pm 29.28

Values express the mean \pm sem; n = 6 animals for each experimental group. * $p < 0.001$ relative to group STr; ** $p < 0.001$ relative to group TTr; [#] $p < 0.01$ relative to group SCo.

Discussion

The size of the testis is an important parameter in the assessment of andrological mammals,

reflecting their normality and also allows to infer the rate of sperm production (FRANÇA; RUSSELL, 1998). Although the influence of body weight in testicular size, there is not significant correlation between the two measurements, and for each species, this can be determined in response to a variety of other factors. The number of Sertoli cells established during the period of testicular development is the main factor responsible for determining testicular size and sperm production (HESS et al., 1993).

This study evaluated the effect of the anabolic steroid nandrolone decanoate in the testicular weight of sedentary and trained rats. The results showed no significant effects in this parameter; however, when both factors are related (anabolic steroid and exercise) significant increases in testicular weight were observed. On the contrary, Noorafshan et al. (2005) found that this anabolic steroid caused a reduction in testes weight. It is important to note, the doses administered by these authors were much higher than those used in this study. The seminal vesicle was another structure whose size was compared between experimental groups and, unlike the testis, seminal vesicles weight increased significantly in treated animals, both in the trained and sedentary, demonstrating the high sensitivity of the reproductive structure to nandrolone decanoate.

Despite the testis of mammals present standard structure for several species, there is wide variation in relation to the volumetric proportion of its various components, especially in relation to the seminiferous tubules, Leydig cells and proportion and disposition of vessels and lymphatic spaces (RUSSELL et al., 1990).

The percentage of seminiferous tubules is one of the factors considered important in determining the spermatogenic efficiency in mammals. In this work, there was a reduction in the tubular compartment in treated animals compared to control animals. This result demonstrates changes in testicular structure and function, affecting the efficiency of spermatogenesis.

The tubular diameter is a parameter classically used as an indicator of spermatogenic activity in investigations involving testicular function (FRANÇA et al., 2000), there are positive correlations between the tubule diameter and spermatogenic activity of the testis (SINHÁ-HIKIM et al., 1998). Normally, the mean diameter of the seminiferous tubules did not change significantly in sexually mature animals that are in the reproductive period. However, the results obtained in this work demonstrate that the use of anabolic steroids

may interfere in this parameter, because rats treated with AAS showed a significant reduction of the diameter of this structure when compared to controls. It is likely that spermatogenic activity in animals treated was reduced, as was also observed reduction in mean height of the seminiferous epithelium in the animal groups treated both sedentary and trained. Therefore, considering a smaller tubular diameter and the reduction in height of the seminiferous epithelium is possible that this anabolic steroid is causing a reduction in the number of germ cells in the seminiferous tubules, thus decreasing the efficiency spermatogenic.

The Leydig cell is specialized in the production of androgens under stimulation of luteinizing hormone (LH). These androgens, particularly testosterone and dihydrotestosterone, are responsible for maintaining the functioning of the spermatogenic process, fertility and performance with successful reproduction (DOHLE et al., 2003). The need for testosterone for spermatogenic production and to maintain peripheral levels of androgens may be related to the compartment size of Leydig cells (SHARPE, 1994).

The results of this study demonstrated that treatment of sedentary and trained rats with nandrolone decanoate caused a decrease in the percentage of Leydig cells of the interstitial compartment, addition reduce its volume cytoplasmic and cellular. Naraghi et al. (2010) examined the combination effects of swimming exercise and supraphysiological doses of nadrolone decanoate on the ultra structural changes in rats' testes. The number and size of Leydig cells were considerably decreased in the interstitial space in the experimental rats. Koeva et al. (2003) investigated the effects of AAS on the activity of 3β hydroxysteroid dehydrogenase (3β HSD) in rat Leydig cells. In conclusion, they observed that the administration of AAS down regulated the steroidogenic enzyme activity.

Therefore, even low doses of anabolic steroids can cause significant impairment in testicular structures that are essential for male reproductive function. Such effect is probably due to a reduction in the hypothalamic secretion of GnRH (gonadotropin releasing hormone) and pituitary secretion of FSH (follicle stimulating hormone) and LH (luteinizing hormone), and as a consequence, in the endogenous secretion of testosterone by the testes.

Conclusion

The treatment with the AAS nandrolone decanoate caused a decrease on: a) tubular compartment, b) the diameter of the seminiferous tubules, c) the mean height of the seminiferous, d) the number of Leydig

cells and e) cytoplasmic and cellular volume of Leydig cells. Such changes in the structure and testicular function may compromise the efficiency of spermatogenesis in both sedentary and trained rats. It is also important to perform more experimental studies to clarify the effects of nandrolone decanoate on other structural and functional aspects of the spermatogenic process.

There are no conflicts of interest of a personal nature, business, political, academic or financial.

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