Differential effects of nandrolone decanoate in fast and slow rat skeletal muscles

WISSAM H. JOUMAA and CLAUDE LÉOTY

General Physiology Laboratory, CNRS E.P.1593, Faculty of Sciences and Technology, University of Nantes, 44322 Nantes, FRANCE

ABSTRACT

JOUMAA, W. H., and C. LÉOTY. Differential effects of nandrolone decanoate in fast and slow rat skeletal muscles. *Med. Sci. Sports Exerc.*, Vol. 33, No. 3, 2001, pp. 397–403. **Purpose:** We studied the effects of high doses of an anabolic-androgenic steroid, exercise training, and a combination of steroid and training on mammalian fast- and slow-twitch skeletal muscles at the cellular level. **Methods:** Thirty-two male rats were divided into sedentary and treadmill-trained groups (increased speed and time: 18 $m \cdot min^{-1}$, 0.5 $h \cdot d^{-1}$, 5 $d \cdot wk^{-1}$). Eight animals of each group were treated with nandrolone decanoate (ND) (15 $mg \cdot kg^{-1} \cdot wk^{-1}$), and others received the same doses of solvent. The animals were killed after 5 wk, and the contractile parameters for isolated small bundles of soleus and extensor digitorum longus (edl) fibers were estimated. **Results:** Muscle mass, twitches, and K^+ contractures were increased in soleus and edl muscles after the drug treatment and after the exercise training. Caffeine contractures were increased only after the exercise training. The combination of exercise with ND treatment produced greater effects, particularly a significant increase in sensitivity to caffeine and the amplitude of K^+ contractures as well as a shortening of the time required to restore contracture. These modifications were more marked in slow than fast muscle. **Conclusion:** These results show that 5 wk of exercise training produced changes in the contractile responses developed by isolated skeletal muscle cells. The combination of exercise training with ND treatment potentiated these effects, suggesting that there was some modification in the excitation-contraction coupling mechanism. ND treatment also produced a more potent effect in soleus than edl sedentary muscle. **Key Words:** ANABOLIC-ANDROGENIC STEROID, EXERCISE TRAINING, MALE RAT, TWITCH, SKELETAL MUSCLE, EXCITATION-CONTRACTION COUPLING

The classical therapeutic uses of anabolic-androgenic steroids (AAS) are associated with the correction of male hypogonadism of hereditary angioneurotic edema and stimulation of erythropoiesis and bone mineralization (32). These substances are also used by athletes to improve physical performance and/or increase muscle mass. Some studies have reported significant improvement when AAS are taken regularly at high doses during periods of intense training in combination with a high protein and caloric diet (10,29), whereas others have found that muscle strength or performance was not greatly affected (1,15). Studies carried out on animals have yielded contradictory results ranging from an insignificant effect (2) to improvement of physical working capacity (31), strength (6), and protein synthesis (22).

In skeletal muscle, tension is generated at the cellular level after propagation of the sarcolemmal action potential in the tubular system, resulting in the release of sarcoplasmic reticulum (SR) calcium (Ca^{2+}) into the myoplasm. The transduction of the sarcolemmal voltage signal into an intracellular calcium response is mediated by the voltage-sensor/dihydropyridine receptor, which activates the SR Ca^{2+} release channel/ryanodine receptor by a mechanism not fully understood. The reuptake of Ca^{2+} by SR is mediated by a Ca^{2+}-transporting ATPase, which causes muscle to relax by restoring intracellular Ca^{2+} concentration (28). In fact, Ca^{2+} plays a major role in cellular function, and any alteration in intracellular Ca^{2+} concentration can modify cellular response (28). Although the mechanisms of excitation-contraction (EC) coupling are identical in slow-twitch (type I) and fast-twitch (type II) mammalian muscle, differences in muscle relaxation, calcium binding protein, intracellular Ca^{2+} transient kinetics, and the sensitivity of SR Ca^{2+} release to caffeine have been reported (9,12). Therefore, changes in contractile response due to exercise training and nandrolone decanoate (ND) treatment could be related to alterations in the Ca^{2+} regulatory systems involved in EC coupling. In this context, the present study investigated the separate and combined effects of 5 wk of treatment with high doses of ND and an exercise program on the general components involved in EC coupling in soleus (slow-twitch) and extensor digitorum longus (edl) (fast-twitch) adult rat muscles.

MATERIALS AND METHODS

Animals. All procedures in this study were performed in accordance with the stipulations of the Helsinki Declarations and the policy statement of the American College of Sport Medicine for the care and use of laboratory animals. Thirty-two male Wistar rats (initial weight 365 ± 5 g) were divided into four groups of eight animals each. Two groups were trained, and two others served as sedentary controls.

0195-9131/01/3303-0397/$3.00/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

Submitted for publication November 1999.
Accepted for publication May 2000.

Rats were housed in a temperature-controlled room (22–24°C), with a 12–12 h light-dark cycle.

Hormone treatment. A group of trained animals and a sedentary group were treated for 5 wk with 17-hydroxy-4-oestren-3-on-17-decanoate [ND, Deca Durabolin® (50 $mg \cdot mL^{-1}$ Organon/Holland)] by a single injection at a supharmacological dose of 15 $mg \cdot kg^{-1}$ each week. The other groups were injected with the same quantity of sterile peanut oil. Changes in body weight during the experimental period were taken into account in calculating the injection doses.

Training program. Exercise was always performed midway through the light period of the light-dark cycle. Animals in training groups were exercised by running 5 $d \cdot wk^{-1}$ for 5 wk. The animals began exercise at 18 $m \cdot min^{-1}$, 0.5 $h \cdot d^{-1}$. The speed and duration of the daily exercise sessions were progressively increased until the rats were capable of running continuously for 1 h at 30 $m \cdot min^{-1}$ during the last week of exercise. These workloads were relatively similar in intensity ≅75% of maximal oxygen consumption (20).

Intact-fiber experiments. After 5 wk of training and hormone treatment, rats were anesthetized by an ether vapor flow. After respiratory arrest, the heart, soleus, and edl were quickly excised and weighed. Skeletal muscles were placed in the dissecting dish containing Ringer's solution (in mM): Na^+: 140; K^+: 6; Ca^{2+}: 3; Mg^{2+}: 2; Cl^-: 156; N-Z-hydroxyethylpiperazine-N'-Z-ethanesulfonic (HEPES): 5. pH was adjusted to 7.4 by addition of trisaminomethane solution.

After removal of connective tissue, isolated fibers or small bundles of 5 to 10 fibers were dissected along their entire length under the microscope. The preparation was then transferred onto a coverslip in a drop of physiological solution, placed in the experimental chamber, and mounted as described by Chapman and Léoty (4). Briefly, one tendon of the preparation was snared under a fine silver loop and fixed in the experimental chamber. The other tendon was fixed to the tip of a force transducer (Kaman kDa 2300 0.5 SU displacement measuring system, Colorado Springs, CO).

The preparation was perfused with physiological solution at 20 $mL \cdot min^{-1}$ and stimulated by electrical pulses at different frequencies. The fiber stimulated at 0.1 Hz was stretched until twitch reached its maximal amplitude. The experimental system was connected to a chart paper recorder (Goerz, Sevogor 120) and to a computer (DTK computer), which allowed storage of the results and estimation of the amplitude, the time to peak tension, and the time constant of relaxation. Amplitude was expressed in $mN \cdot mm^{-2}$. All experiments were performed at room temperature (19–20°C).

Potassium contractures were elicited by sudden exposure of fibers to a solution containing a high concentration of potassium (146 mM) in the absence of electrical stimulation. In this solution, the $[K^+][Cl^-]$ product was kept constant to allow rapid recovery of resting potential upon a return to Ringer's solution and the restoration of the amplitude of the tension response. For this reason, chloride was replaced by L-glutamate. $[K^+]$ concentrations larger than 146 mM were not used because of hypertonicity. After spontaneous relaxation of the contracture, K^+ solution was replaced by Ringer's. The time-course of repriming of K^+ contracture was determined by varying the time between conditioning and test exposures to high K^+ solution. When this approach was used, the amplitude of the different developed contractures showed a sigmoid curve fitted by means of a Boltzman equation. The time required for 50% recovery (Ec50) was calculated for each preparation.

Caffeine contractures were elicited by sudden exposure of fibers to solutions of different concentrations of caffeine (0.2, 0.5, 5, 10 mM) prepared by addition of caffeine to Ringer's solution. When the contractile response reached a maximum peak, the preparation was returned to the control solution and the amplitude of these contractures was estimated.

Statistical analyses. All values are expressed as means ± SEM for *N* observations. Data were analyzed by two-way ANOVA to test the two main effects (exercise training and ND administration) and their interaction. A standard computerized statistical program (Sigma) was used. When a significant *F*-value was obtained, Scheffé *post hoc* analysis was performed to determine specific differences. A level of $P < 0.05$ indicated statistical significance.

RESULTS

Body and muscle weights. The body weight curves (Fig. 1) clearly show that all animals steadily gained weight. After 5 wk of exercise training, body weight was less [trained control (TC)= 468 ± 6 g] in comparison with sedentary animals [sedentary control (SC)= 501 ± 7 g)]. Significant differences associated with ND treatment were detected [sedentary treated (ST) = 396 ± 15 g, trained treated (TT)= 434 ± 9 g; values are expressed as the mean ± SEM for $N = 8$ observations for each group]. As final body weight was different in every group, ratios of the muscle masses of soleus, edl, and heart (Fig. 2) to body

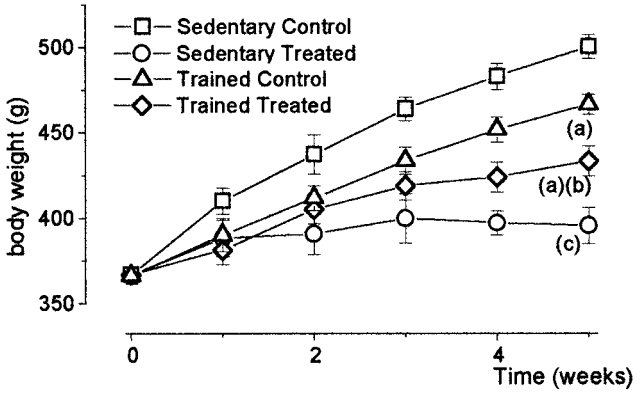

FIGURE 1—Time-dependent changes in body weight in sedentary control, sedentary ND-treated, in trained control, and in trained and ND-treated animals. (a) $P < 0.01$ trained vs. sedentary, (b) $P < 0.05$ ND trained vs. trained control, and (c) $P < 0.05$ sedentary ND-treated vs. sedentary control animals, $N = 8$. Data are expressed as means ± SEM, for *N* observations.

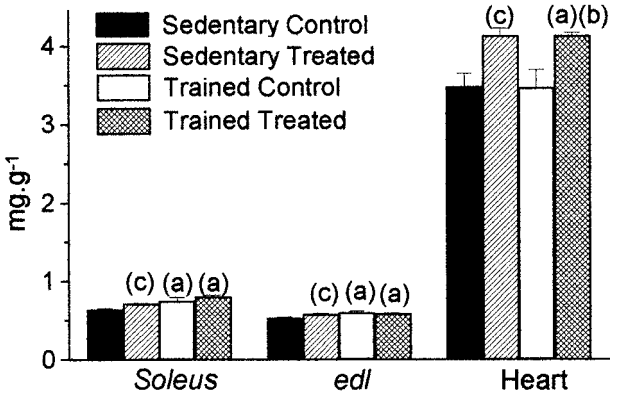

FIGURE 2—Ratio of soleus, edl, and heart weight to body weight after 5 wk of treatment with hormone and training program. (a) $P < 0.01$, trained vs. sedentary, $N = 8$; (b) $P < 0.05$, ND-trained vs. trained control, $N = 8$; and (c) $P < 0.05$ sedentary ND-treated vs. sedentary control animals, $N = 8$. Data are expressed as means ± SEM, for N observations.

weight were calculated. Five weeks of training resulted in an increase in the soleus (18%) and edl mass-to-body weight ratio (13%) as compared with sedentary animals. However, ND treatment showed a significant difference (12% and 8%, respectively) in the soleus and edl mass-to-body weight ratios, whereas no significant difference was observed in combination with treadmill exercise. The muscle mass-to-body weight ratio in heart was only increased by ND treatment (19% as compared with SC and TC animals).

Contractile parameters. Table 1A shows isometric twitch amplitude as measured in soleus and edl muscles of sedentary and trained animals, with and without hormone treatment. Exercise training caused significant changes in soleus and edl muscles. Twitch tension in soleus muscle was increased by 73% in TC animals, 20% in the trained group which received ND treatment (as compared with TC animals), and 41% in sedentary animals which received ND (as compared with SC animals). Neither exercise training nor administration of ND induced significant differences in time to peak tension in soleus muscle. In edl muscle, a significant effect was observed for trained animals (two-way ANOVA,

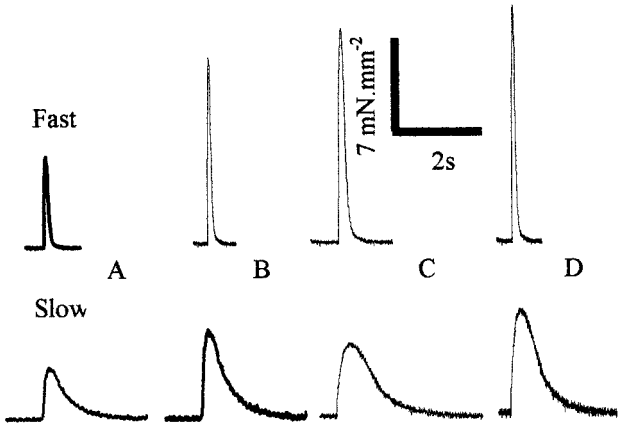

FIGURE 3—Recording of typical fast (edl)- and slow (soleus)-twitch responses from control (A), trained (B), treated (C), and trained and treated animals (D).

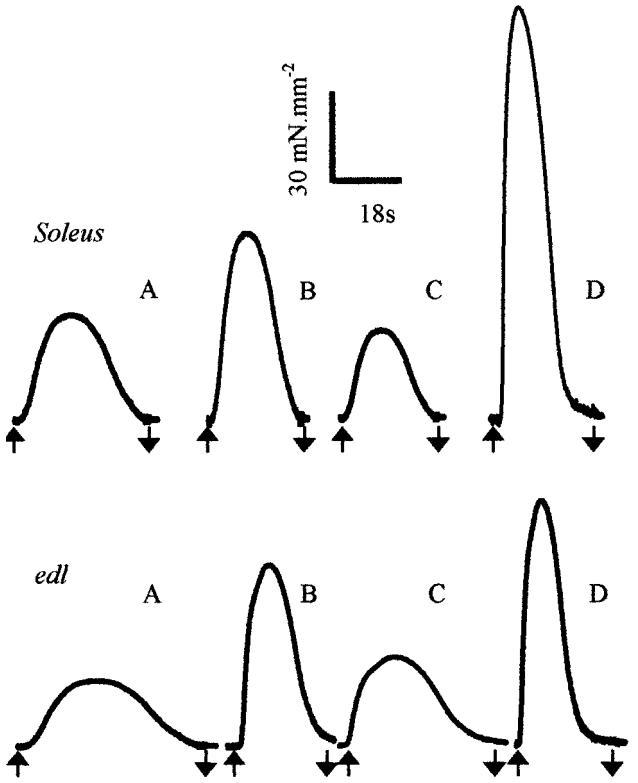

FIGURE 4—Recording of contractures developed by application of 146 mM of potassium solution after 5 wk of treatment, in soleus and edl muscles of sedentary controls (A), of trained controls receiving sterile peanut oil injection (B), treated (C), and trained and treated animals (D) receiving nandrolone decanoate injection.

$P < 0.01$). Twitch tension was increased by 104% in TC animals, whereas ND treatment potentiated this effect, increasing tension by 30% in comparison with TC animals. As with soleus muscle, intramuscular injection of ND for 5 wk induced significant increase in the twitch tension generated by small bundles of sedentary edl muscle (a 137% increase compared with SC animals; Fig. 3). In contrast with soleus muscle, 5 wk of endurance exercise produced a significant shortening in the time to peak tension of fast twitch muscle (44%).

Potassium contractures. In fast and slow muscles, a change from normal to high K^+ solution led to the development of transient contractile responses that reached a maximum and then relaxed in an exponential manner, even when perfusion was maintained by depolarization solution (Fig. 4) (16). The developed tension represented 80% of maximal response. Exercise training caused significant changes in soleus and edl muscles, enhancing the generated tension in soleus by 78% in TC animals (Table 1B) and by 117% in rats which received ND treatment (as compared with TC animals). In fast-twitch muscle, the response evoked in the trained group was significantly increased as compared to the sedentary group (Table 1B). Exercise training increased tension by 170% which was potentiated by 35% in combination with ND treatment (as compared with TC animals). In contrast to the effect produced in soleus muscle, injection of ND into sedentary animals led to a

TABLE 1. Soleus and edl contractile parameters.

	Soleus		edl	
	Tension ($mN \cdot mm^{-2}$)	TP (ms)	Tension ($mN \cdot mm^{-2}$)	TP (ms)
A				
Sedentary				
Control	4.1 ± 0.4	134 ± 11	7.0 ± 0.2	70 ± 7
Treated	5.8 ± 0.8[c]	144 ± 10	16.6 ± 0.8[c]	60 ± 6
Trained				
Control	7.1 ± 0.5[a]	134 ± 15	14.3 ± 1.4[a]	39 ± 5[a]
Treated	8.5 ± 0.4[a,b]	145 ± 9	18.6 ± 0.9[a]	39 ± 2[a]
N	16	16	14	14
B				
Sedentary				
Control	35.8 ± 4.5	6.2 ± 1.1	22.4 ± 1.4	8.7 ± 0.9
Treated	22.4 ± 1.4	4.5 ± 0.5[c]	29.5 ± 1.9[c]	6.6 ± 0.9[c]
Trained				
Control	63.8 ± 6.9[a]	4.5 ± 0.5[a]	60.5 ± 6.7[a]	4.4 ± 0.2[a]
Treated	138.3 ± 19.5[a]	3.5 ± 0.2[a,b]	81.4 ± 8.4[a,b]	3.8 ± 0.4[a]
N	16	16	14	14

TP, time to peak tension; TCR, time constant of relaxation.
A, twitch, B, K^+ contracture.
[a] $P < 0.01$ trained vs sedentary; [b] $P < 0.05$ ND trained vs trained control; [c] $P < 0.05$ sedentary ND treated vs sedentary control animals.
Data are expressed as means ± SEM, for *N* observations.

significant difference in edl muscle in the tension generated by exposure to high K^+ solutions (a 32% increase in comparison with SC animals). Exercise training induced a significant decrease in the time constant of relaxation (TCR) in both soleus and edl muscles (Table 1B). In soleus, the value was decreased by 27% for trained animals (as compared with SC animals) and by a further 22% with associated ND treatment (as compared with TC animals). Conversely, TCR was decreased by 27% in sedentary treated animals as compared with SC animals. In edl muscle, TCR was shortened by 49% in trained animals. Drug administration induced a significant decrease (14%) in comparison with TC animals. Similar to the results for soleus muscle, TCR was decreased by 24% in ST animals versus SC animals.

However, the recovery in amplitude of 146 mM K^+ contracture was slower in edl muscle of trained (56%) than sedentary animals (Table 2). Treatment with ND was decreased by 17% as compared with TC animals, and recovery tension in soleus was significantly accelerated (25%) for ND treatment associated with exercise training, as compared with no effect with exercise training alone.

Caffeine contractures. In fast- and slow-twitch muscles, a change from normal to caffeine solutions produced a dose-dependent contracture. Upon application of caffeine, the contracture reached a maximum peak and then relaxed in an exponential manner. Owing to the very slow relaxation of caffeine contractures, the perfusion with caffeine solution was maintained until the response reached its maximum peak (Fig. 5). In soleus muscle, the exercise training program produced a significant change in response through the application of different concentrations of caffeine solutions. Tension was increased by 156% for 0.2 mM, 273% for 0.5 mM, 80% for 5 mM, and 39% for 10 mM. ND treatment for the trained group affected tension, which was further potentiated by 152% for 0.2 mM, 102% for 0.5 mM, 98% for 5 mM, and 102% for 10 mM (Table 3A) (as compared with TC animals). Moreover, administration of ND produced a significant increase in the tension evoked at 0.2 mM (278%), 0.5 mM (436%), 5 mM (147%), and 10 mM (122%) in sedentary animals. In fast-twitch muscle, as in slow-twitch muscle, the exercise training induced an increase in response to caffeine at the different concentrations tested: 400%, 386%, 56%, and 84%, respectively, for 0.2, 0.5, 5, and 10 mM caffeine solutions. No change in generated tension as a result of training and ND treatment was

TABLE 2. Time of 50% recovery of K^+ contractures.

	Soleus Ec50 (s)	edl Ec50 (s)
Sedentary		
Control	88.8 ± 7.9	87.6 ± 3.8
Treated	97.9 ± 5.9	89.0 ± 4.2
Trained		
Control	85.5 ± 7.3	136.3 ± 4.9[a]
Treated	63.8 ± 4.1[a,b]	112.8 ± 6.1[a,b]
N	12	11

Time required for 50% recovery (Ec50) of K^+ contracture in soleus and edl muscle.
[a] $P < 0.01$ trained vs sedentary; [b] $P < 0.05$ ND trained vs trained control animals.
Data are expressed as means ± SEM, for *N* observations.

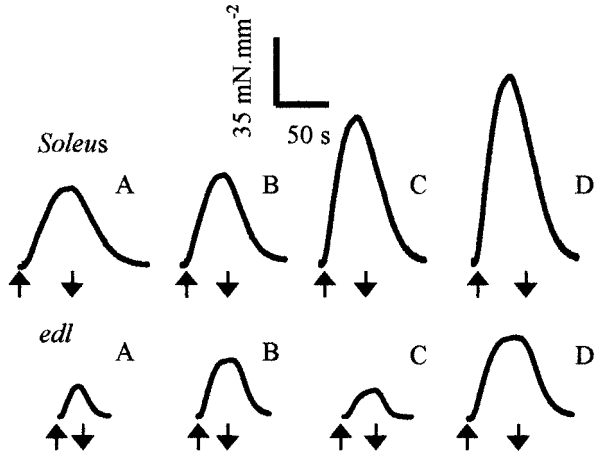

FIGURE 5—Recording of caffeine contractures developed by application of 10 mM of caffeine solution after 5 wk of treatment, in soleus and edl muscles of sedentary controls (A), of trained controls receiving sterile peanut oil injection (B), treated (C), and trained and treated animals (D) receiving nandrolone decanoate injection.

TABLE 3. Soleus and edl caffeine contractures.

	0.2 mM	0.5 mM	5 mM	10 mM
A				
Sedentary				
Control	0.9 ± 0.4	1.1 ± 0.3	25.7 ± 6.1	37.3 ± 5.8
Treated	3.4 ± 0.7[c]	5.9 ± 0.5[c]	63.6 ± 6.3[c]	82.7 ± 6.1[c]
Trained				
Control	2.3 ± 0.7[a]	4.1 ± 0.7[a]	46.2 ± 5.2[a]	51.9 ± 6.8[a]
Treated	5.8 ± 1.1[a,b]	8.3 ± 1.4[a,b]	91.7 ± 9.9[a,b]	104.6 ± 9.3[a,b]
N	12	12	11	11
B				
Sedentary				
Control	0.5 ± 0.3	0.7 ± 0.3	13.6 ± 1.7	17.3 ± 1.6
Treated	0.9 ± 0.3	1.2 ± 0.4	12.4 ± 1.2	15.1 ± 1.2
Trained				
Control	2.5 ± 0.3[a]	3.4 ± 0.7[a]	21.2 ± 3.1[a]	31.9 ± 3.4[a]
Treated	2.6 ± 0.3[a]	3.3 ± 0.6[a]	30.2 ± 4.5[a,b]	46.3 ± 4.8[a,b]
N	12	12	11	11

Tensions developed by application of 0.2, 0.5, 5, and 10 mM of caffeine solution in soleus A and edl B muscles.
[a] $P < 0.01$ trained vs sedentary; [b] $P < 0.05$ ND trained vs trained control; [c] $P < 0.05$ sedentary ND treated vs sedentary control animals. Data are expressed as means ± SEM, for *N* observations.

produced by application of 0.2 and 0.5 mM caffeine solutions. However, at high concentrations (5 and 10 mM) tensions were potentiated by 42% and 45%, respectively, in comparison with TC animals (Table 3B). In contrast with soleus muscle, drug administration did not affect the response to caffeine solutions in sedentary edl muscle.

DISCUSSION

Our results in healthy sedentary rats show that 5 wk of treatment with ND 15 $mg \cdot kg^{-1} \cdot wk^{-1}$ have a negative effect on body weight. Trained animals were also affected, and associated hormone treatment potentiated the effect. However, in comparison with the results of other studies, the body weight of adult male rats was not affected (23) or stunted in a dose-dependent manner. Exceeding the physiological level of androgens has been reported to decrease appetite (13), convert testosterone to estradiol excessively (11), reduce the natural production of testosterone (25) and down-regulate the androgen–binding receptor (24). Although all these factors could inhibit body growth, our study provided no indication of their relative participation.

Our data show that 5 wk of exercise training induced an increase in the ratio of muscle to body weight of soleus and edl muscles. Administration of ND to trained rats did not affect the ratio. Moreover, administration of drug to sedentary animals produced significant skeletal muscle modifications. Conversely, heart weight was only affected by AAS treatment. Although all skeletal muscle types responded to AAS, there was a considerable variation in sensitivity. The molecular basis of AAS action on skeletal muscle is not fully established, but it is generally assumed that the effects of AAS are mediated by intracellular receptor proteins that function as transcriptional regulatory factors. In fact, the differences in response to ND administration could have been partly related to the different levels of androgen-binding receptors in muscle cytosol, as reported by Dahlberg et al. (5), whereas administration of ND produced the same increase in the ratio of muscle to body weight as the training program. The combination of both factors did not cause a modification of the effect.

The effects of AAS on the different functions of skeletal muscle are controversial. In particular, changes in contractile parameters due to AAS have only been established in female rats (7), although similar treatment was also effective in male rats (17). However, these results were obtained when AAS treatment was combined with a training program (6,7,17,18). In general, these studies of AAS were influenced by factors which could have had an effect on the results, such as the species, gender and age of animals, the type of muscle studied (3,17,26), experimental conditions, the specific AAS used, doses, the mode and period of administration (11,14,19,23,30), diet (8), and the training program. All these factors make it difficult to compare our results with those in the literature.

In our study, the change in contractile response was estimated at the cellular level by analysis of twitch, high K^+ contractures, and caffeine contractures. The twitch evoked by direct stimulation depends on the interactions of different processes: the T-tubule action potential, the response of the voltage-sensor, the properties of the SR Ca^{2+} release channel, Ca^{2+} diffusion to and through myofibrils, Ca^{2+} binding to myoplasmic buffers, and Ca^{2+} removal by SR Ca^{2+} ATPase. Moreover, the transduction of the sarcolemmal voltage signal into an intracellular Ca^{2+} response is mediated by the voltage-sensor/dihydropyridine receptor, which activates the SR Ca^{2+} release channel/ryanodine receptor by a mechanism not clearly understood (27,28). Our data show that exercise training and ND treatment modified twitch in soleus and edl muscles and that the combination of both factors potentiated this effect. These modifications in twitch characteristics could have been related to changes in the different EC coupling steps.

Tension during K^+ depolarization depends on the activation of the voltage-sensor in the transverse tubule membrane. The slow relaxation of K^+ contracture during prolonged depolarization is assumed to depend on the inactivation of the process regulating calcium release from the SR and on the ability of the SR to pump calcium (21). Our study shows that 5 wk of training induced an increase in the amplitude and TCR of K^+ contractures in slow and fast muscle. These parameters were similarly modified by

ND treatment and amplified by combination of exercise training with ND treatment. These modifications in amplitude and the TCR of K^+ contractures could have been related to changes in activation-inactivation processes related to the voltage-sensor. Moreover, it is generally assumed that the repriming of EC coupling can be analyzed by studying time-dependency for the restoration of K^+ contractures. Our data show that 50% recovery in the amplitude of K^+ contractures (Ec50) was shorter in soleus only when training exercise was associated with ND treatment and that the exercise program alone or ND treatment induced no changes in this parameter. Conversely, in edl muscle, Ec50 was longer in edl of trained than sedentary animals. Furthermore, in trained and treated animals, Ec50 remained shorter than in the trained group. Thus, the restoration of EC coupling could have been modified by exercise training and ND treatment, which would have produced changes favorable to contractile response in the reactivation processes related to the voltage-sensor. However, further studies are needed to analyze the extent to which activation and/or inactivation processes of the voltage-sensor are modified by exercise training and ND treatment.

It is well-known that caffeine acts directly on ryanodine receptors by inducing the release of calcium from the SR. At low caffeine concentrations (0.2 and 0.5 mM), the contractures in our study were increased by exercise training in fast and slow muscles. In sedentary animals, ND treatment potentiated caffeine contractures in soleus, but no significant changes were observed in edl. Moreover, the combination of exercise training with ND treatment in slow-twitch muscle produced an added effect, although no changes were observed in fast-twitch muscle. Exercise training with or without associated ND treatment could have modified the sensitivity of ryanodine receptors to caffeine. At large concentrations of caffeine (5 and 10 mM), the tensions developed were increased in soleus and edl muscles by the training program. ND treatment increased the amplitude of caffeine contractures only in soleus muscle, but the combination of exercise training with ND treatment potentiated the effects in both soleus and edl, producing a greater effect in soleus. These changes in caffeine contractures could have been related to an increase in the Ca^{2+} content of the SR and/or to a faster Ca^{2+} release from the SR and/or to a change in the Ca^{2+} sensitivity of contractile proteins. However, further studies are required to determine which mechanisms were involved in these modifications.

It is known that endurance exercise training can produce changes in fast versus slow skeletal muscle fibers in relation to modifications in genetic expression. Such a change in muscle type could be partly responsible for the increase in K^+ contracture tensions and the caffeine sensitivity observed in edl muscle after training with and without associated ND treatment.

In conclusion, our results indicate that endurance exercise training can affect body mass, muscle mass, and contractile response. Although exercise training associated with ND treatment (anabolic-androgenic steroid) at supratherapeutic doses over a 5-wk period improved contractile responses more than training alone, this improvement may have been related to a change in EC coupling, especially at the voltage-sensor level, and/or in the mechanism involved in intracellular Ca^{2+} regulation. All these modifications depended on muscle type, and the effect was more marked in slow-twitch (soleus) than fast-twitch (edl). It was also determined that the administration of ND to sedentary animals induced a significant change in muscle mass and contraction.

This work was supported by the Foundation Langlois and was part of the Ph.D. studies of W. H. Joumaa, funded by the French Government. The authors are grateful to Organon Holland for supplying nandrolone decanoate.

Address for correspondence: Wissam H. Joumaa, Laboratoire de Physiologie Générale, Faculté des Sciences et des Techniques, Université de Nantes, 2 rue de la Houssinière, B.P. 92208, 44322 Nantes Cedex 3, France; E-mail: wjoumaa@yahoo.com.

REFERENCES

1. Alen, M., and K. Hakkinen. Androgenic steroid effects on serum hormones and on maximal force development in strength athletes. *J. Sports Med. Phys. Fitness* 27:38–46, 1987.
2. Bates, P. C., L. F. Chew, and D. J. Millward. Effects of the anabolic steroid stanozolol on growth and protein metabolism in the rat. *J. Endocrinol.* 114:373–381, 1987.
3. Bisschop, A., G. Gayan-Ramirez, H. Rollier, et al. Effects of nandrolone decanoate on respiratory and peripheral muscles in male and female rats. *J. Appl. Physiol.* 82:1112–1128, 1997.
4. Chapman, R. A., and C. Léoty. Proceedings: a method of mounting, perfusing and recording the tension generated by isolated mammalian cardiac trabeculae which overcomes their susceptibility to mechanical damage. *J. Physiol. (Lond.)* 258:1P–2P, 1976.
5. Dahlberg, E., M. Snochowski, and J. Gustafsson. Regulation of the androgen and glucocorticoid receptors in rat and mouse skeletal muscle cytosol. *Endocrinology* 108:1431–1440, 1981.
6. Elashoff, J. D., A. D. Jacknow, S. G. Shain, and G. D. Braunstein. Effects of anabolic-androgenic steroids on muscular strength. *Ann. Intern. Med.* 115:387–393, 1991.
7. Exner, G. U., H. W. Staudte, and D. Pette. Isometric training of rats: effects upon fast and slow muscle and modification by an anabolic hormone (nandrolone decanoate). II. Male rats. *Pflügers Arch.* 345: 15–22, 1973.
8. Fahey, T. D., and C. H. Brown. The effects of an anabolic steroid on the strength, body composition, and endurance of college males when accompanied by a weight training program. *Med. Sci. Sports* 5:272–276, 1973.
9. Fryer, M.W., and I. R. Neering. Actions of caffeine on fast- and slow-twitch muscles of the rat. *J. Physiol. (Lond.)* 416:435–454, 1989.
10. Haupt, H. A., and G. D. Rovere. Anabolic steroids: a review of the literature. *Am. J. Sports Med.* 12:469–484, 1984.
11. Hickson, R. C., and T. G. Kurowski. Anabolic steroids and training. *Clin. Sports Med.* 5:461–469, 1986.
12. Klein, M. G., L. Kovacs, B. J. Simon, and M. F. Schneider. Decline of myoplasmic Ca^{2+}, recovery of calcium release and sarcoplasmic Ca^{2+} pump properties in frog skeletal muscle. *J. Physiol. (Lond.)* 441:639–671, 1991.
13. Kochakian, C. D., and B. R. Endahl. Changes in body weight of normal and castrated rats by different doses of testosterone propionate. *Proc. Soc. Exp. Biol. Med.* 100:520–522, 1959.
14. Kopera, H. The history of anabolic steroids, and a review of clinical experience with anabolic steroids. *Acta Endocrinol.* 271s: 11–18, 1985.
15. Lamb, D. R. Anabolic steroids in athletics: how well do they work and how dangerous are they? *Am. J. Sports Med.* 12:31–38, 1984.

16. LÉOTY, C., and M. LÉAUTÉ. Membrane potential and contractures in segments cut from rat fast and slow twitch muscles. *Pflügers Arch.* 395:42–48, 1982.
17. LEWIS, M. I., M. FOURNIER, A. Y. YEH, P. E. MICEVYCH, and P. M. SIECK. Alterations in diaphragm contractility after nandrolone administration: an analysis of potential mechanisms. *J. Appl. Physiol.* 86:985–992, 1999.
18. LUBEK, B. M. Contractile responses of rat lateral gastrocnemius and soleus to dianabol (17 beta-hydroxy-17-methyl-1, 4-androstadien-3-one) and exercise. *Steroids* 44:485–495, 1984.
19. MARTINEZ, J. A., P. J. BUTTERY, and J. T. PEARSON. The mode of action of anabolic agents: the effect of testosterone on muscle protein metabolism in the female rat. *Br. J. Nutr.* 52:515–521, 1984.
20. MAZZEO, R. S., G. A. BROOKS, and S. M. HORVATH. Effects of age on metabolic responses to endurance training in rats. *J. Appl. Physiol* 57:1369–1374, 1984.
21. MÊME, W., and C. LÉOTY. Changes in voltage activation of contraction in frog skeletal muscle fibres as a result of sarcoplasmic reticulum Ca^{2+}-ATPase activity. *Acta Physiol. Scand.* 166:209–216, 1999.
22. MENSCHIKOWSKI, M., K. JUNG, P. JUNGHANS, K. J. PETZKE, and V. ALBRECHT. The influence of a steroid hormone and of physical exercise on protein metabolism in rats. *Exp. Clin. Endocrinol.* 92:341–348, 1988.
23. PREZANT, D. J., D. E. VALENTINE, E. I. GENTRY, B. RICHNER, J. CAHILL, and K. FREEMAN. Effects of short-term and long-term androgen treatment on the diaphragm in male and female rats. *J. Appl. Physiol.* 75:1140–1149, 1993.
24. RANCE, N. E., and S. R. MAX. Modulation of the cytosolic androgen receptor in striated muscle by sex steroids. *Endocrinology* 115:862–866, 1984.
25. RYAN, A. J. Anabolic steroids are fool's gold. *Fed. Proc.* 40:2682–2688, 1981.
26. SACHS, B. D., and R. E. LEIPHEIMER. Rapid effect of testosterone on striated muscle activity in rats. *Neuroendocrinology* 48:453–458, 1988.
27. SCHNEIDER, M. F., and B. J. SIMON. Inactivation of calcium release from the sarcoplasmic reticulum in frog skeletal muscle. *J. Physiol. (Lond.)* 405:727–745, 1988.
28. STEIN, R. B., J. BOBET, M. N. OGUZTORELI, and M. FRYER. The kinetics relating calcium and force in skeletal muscle. *Biophys. J.* 54:705–717, 1988.
29. STRAUSS, R. H., and C. E. YESALIS. Anabolic steroids in the athlete *Annu. Rev. Med.* 42:449–457, 1991.
30. TSIKA, R. W., R. E. HERRICK, and K. M. BALDWIN. Effect of anabolic steroids on skeletal muscle mass during hindlimb suspension. *J. Appl. Physiol.* 63:2122–2127, 1987.
31. VAN ZYL, C. G., T. D. NOAKES, and M. I. LAMBERT. Anabolic-androgenic steroid increases running endurance in rats. *Med. Sci. Sports Exerc.* 27:1385–1389, 1995.
32. WILSON, J. D., and J. E. GRIFFIN. The use and misuse of androgens. *Metabolism* 29:1278–1295, 1980.