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Test of the principle of initial value in rat genetic models of exercise capacity

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Koch, Lauren Gerard, Cheryl L. Green, Abraham D. Lee, Joseph E. Hornyak, George T. Cicila, and Steven L. Britton. Test of the principle of initial value in rat genetic models of exercise capacity. *Am J Physiol Regul Integr Comp Physiol* 288: R466–R472, 2005. First published November 4, 2004; doi:10.1152/ajpregu.00621.2004.—An inverse relationship between initial level of physical capacity and the magnitude of response to training is termed the principle of initial value. We tested the operation of this principle under experimental conditions of minimal genetic and environmental variation. Inbred rat strains previously identified as genetic models of low [Copenhagen (COP)] and high [Dark Agouti (DA)] intrinsic (untrained) exercise capacity were trained for 8 wk on a treadmill using two disparate protocols: 1) a relative mode where each rat exercised daily according to its initial capacity, and 2) an absolute mode where both strains received the same amount of training independent of initial capacity. Response to exercise was the change in running capacity as estimated by meters run to exhaustion before and after training. When trained with the relative mode, COP rats gained 88 m (+21%; NS) whereas DA rats increased distance run by 228 m (+36%; $P < 0.001$). When each strain trained with the same absolute amount of training, the COP strain showed essentially no change (–6 m, –2%) and the DA strain gained 325 m (+49%; $P < 0.009$). Differences in response to exercise between the COP and DA could not be explained by body mass differences, oxidative enzyme activity (citrate synthase or ATP), or spontaneous behavioral activity. Our data demonstrate that genetic factors causative of high response to exercise are not uniquely associated with genetic factors for low intrinsic capacity and thus are not in accord with the principle of initial value.

inbred; treadmill running

CONSIDERABLE VARIATION exists in the response to aerobic exercise training between individuals that is presumably related to a complex interaction of genetic and environmental factors (9). Twin studies in humans (11, 37) demonstrated approximately six to nine times more variation in the response to aerobic exercise training between pairs of monozygotic twins (genetic variance) than within pairs of monozygotic twins (environmental variance). These results are consonant with the tenet that genetics is a significant determinant for response to exercise.

Among the numerous environmental factors that affect response to aerobic training, the level of initial capacity appears to play a role (35, 36). According to the principle of initial values, if capacity is low then the percentage gain in capacity in response to training will be high, and vice versa (29, 42, 44). Test of principles that require information about the magnitude

of current capacity are difficult, especially when tested in human populations, because this value is a complex function of unknown genetic and environmental factors. The identification of inbred strains of rats that contrast in initial aerobic capacity provides a unique opportunity to test the applicability of this principle in near genetically uniform populations under closely controlled experimental conditions.

In previous work we evaluated treadmill aerobic running capacity in 11 inbred strains of rats. We found that Dark Agouti (DA) inbred rats have more than a twofold greater untrained (intrinsic) capacity for treadmill endurance running compared with Copenhagen (COP) inbred rats and thus can serve as genetic models of high and low endurance running capacity (3). We also found that aerobic running performance and isolated heart performance (3, 34) were correlated positively ($r = 0.86$) across the 11 strains. Cardiac output in the isolated hearts averaged ~50% greater in the DA compared with the COP strain. Subsequent studies show that the COP strain is lower for several other intermediates of cardiac function, including indexes of contractility (14), cardiac adenosine production (43), and autonomic control of both heart rate and blood pressure (27) compared with the DA strain.

The purpose of this study was to compare the response to exercise training between the COP and DA strains and test the hypothesis that the response to exercise is an inverse function of initial capacity. We applied two markedly different modes of training to test this hypothesis, and our results are not in general agreement with the principle of initial value. That is, in response to training, the intrinsically low-capacity COP strain improved less than the intrinsically high-capacity DA strain regardless of exercise protocol. Intermediate responses from an F_1 (COP \times DA cross) population were consistent with a genetic basis for these strain differences in response to exercise.

METHODS

Inbred strains of Copenhagen (COP/HsD) and Dark Agouti (DA/OlaHsD) rats were obtained from Harlan Sprague-Dawley (Indianapolis, IN) and maintained in breeding colonies at the Medical College of Ohio. The housing environments were uniform for both strains. Both strains were housed two per cage with littermates from the time of weaning in the same room. Rats were weaned between 26 and 28 days of age and fed pellet rodent diet (diet 5001, Purina Mills, Richmond, IN) and water ad libitum. Ambient environment for the animals was a controlled 12:12-h light-dark cycle with the light cycle occurring in the daytime and a target room temperature of 22°C. The Institutional Animal Care and Use Committee (IACUC) at the Med-

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ical College of Ohio approved all procedures before commencement of study.

The overall plan was to 1) pretest the rats for maximal treadmill running capacity, 2) train the rats for 8 wk, and 3) posttest the rats for maximal running capacity after the training. The measure for exercise capacity (5) was based on a speed-ramped treadmill run to exhaustion as described previously (3, 24, 25, 28). The response to exercise was calculated as the change in running capacity (m) before and after 8 wk of training. The pretraining capacity was estimated when the rats were 8–10 wk old. The entire protocol, from the pretesting period through training to the posttesting period, required 11 wk. Body mass was recorded after each running test and after each daily training session.

The primary objective was to estimate the influence of intrinsic exercise capacity on the response to training using two different modes of training. A relative but nonprogressive exercise protocol was applied to a population of COP and DA females ($n = 8$ per strain). These rats were trained five days per week with a speed-ramped protocol beginning at 10 m/min with a 1 m/min increase every 2 min for a duration equivalent to 80% relative of that reached pretraining. Another group of females ($n = 9$ COP and 8 DA) was evaluated as a control (sham trained) to assess the differences in intrinsic exercise capacity between the two strains as a function of time during sedentary behavior. An absolute and progressive mode of training was applied to another population that consisted of COP, DA, and first filial generation F_1 (COP \times DA cross) females ($n = 6$ each). Rats in this second population were trained three days per week with the same protocol. It was an absolute mode of training, in the sense that the DA, COP, and F_1 rats were trained identically at the same speed and for the same duration each training session.

Test of exercise capacity. During the first week of the protocol, each rat was educated to treadmill (Model Exer-4, Columbus Instruments, Columbus, OH) exercise for gradually increasing duration each day so that they could attain a minimum of 5 min of exercise at a speed of 10 m/min on a 15° slope. This amount of exposure to treadmill exercise is likely below that required to produce a significant increase in running capacity (2, 17).

The first day of education consisted of placing the rat on the treadmill belt that was moving at a velocity of 10 m/min (15° slope) for 1 min and picking the rat up and moving it forward if it started to slide off the back of the belt. During introductory *day 2*, rats unwilling to run at 10 m/min (15° slope) for 1 min would slide off of the moving belt and onto a shock grid that delivered 1.2 mA of current at 3 Hz. The rats were left on the grid for ~ 1.5 s and then moved back onto the moving belt. During introductory *days 3* and *4*, the exercise duration was increased to 5 min with all other training parameters unchanged. On introductory *day 5*, the rats exercised for 5 min with a change in belt speed that started at 10 m/min and increased 1 m/min every minute.

After the education week, all rats underwent a test for exercise running capacity on five consecutive days. Each daily running trial was performed at a constant slope of 15° with the starting velocity at 10 m/min and was evaluated at about the same time each day (between 9 AM and noon). Treadmill velocity was increased by 1 m/min every 2 min, and each rat was run until exhausted. Exhaustion was operationally defined as the third time the rat seemed to no longer keep pace with the speed of the treadmill and gave up to receiving shock rather than run. At the moment of exhaustion, the current to the grid was stopped, the rat was removed from the treadmill, and the time was recorded. The total distance run (m) to exhaustion was calculated and taken as the estimate of exercise capacity. For each rat, the single best day of performance of the five trials was considered the trial most closely associated with their genetic component of exercise capacity (28).

Exercise training protocols. Training protocols were devised to keep environments similar between the strains for the duration of training. For the relative protocol, each rat was exercised 5 days per week (Monday through Friday) using the same speed-ramped protocol

described above until the rat reached an endpoint equivalent to 80% of its single best trial. That is, each daily running session was performed at a constant slope of 15° and a starting velocity at 10 m/min with an increase by 1 m/min every 2 min until the 80% target distance for each individual rat was reached. The 80% level was chosen rather than repeated bouts to maximal capacity to lessen the likelihood of injury due to overtraining. If the rat was unable to reach the target distance and appeared exhausted, the rat was removed and the total distance run was calculated for that session. On average, the daily endpoint distance for the COP rats was 372 m, which was equivalent to a speed of 22 m/min over a 24-min training duration. The DA strain's endpoint distance was more than two times longer (780 m) and reached 30 m/min over a 40-min session. On average, the cumulative target distance run for all 40 sessions was 14,880 m for rats of the COP strain and 31,200 m for the DA strain.

Throughout the relative training period, the control (sham trained) rats were placed on a nonmoving treadmill daily for a duration that was on average equivalent to the training time spent by that strain. In preparation for the posttraining assessment of maximal exercise capacity, the rats in the sham-trained groups underwent a repeat week of education to treadmill running during the eighth week of training.

For the absolute training, rats from both strains ran 3 days a week (Monday-Wednesday-Friday) over 8 wk with an identical exercise protocol. The slope of the treadmill was set at 15°, and the first session was set at a constant speed of 10 m/min and duration of 20 min (200 m). Each session the duration was increased 0.5 min, and speed was raised 1 m/min every other session (Fig. 1). On *day 24*, training was performed at a rate of 20 m/min for 31.5 min (630 m). The cumulative training distance for the absolute protocol was 9,802 m.

At the completion of the training period, all rats underwent a second test of maximal treadmill running capacity. The posttraining measure was conducted in the same manner as the pretraining test for exercise capacity.

Enzyme activities. We tested if increases in oxidative enzyme activities are a prerequisite for improved running performance for either the COP or DA strain. To determine citrate synthase (CS) activity and levels of adenosine triphosphate (ATP), tissue samples of epitrochlearis muscle were prepared from the relative trained group and the corresponding control sham-trained group. Epitrochlearis muscle has been shown to adapt readily to exercise training such as swimming (38), treadmill running (41), and wheel running (39). Rats were anesthetized with pentobarbital sodium (5 mg/100 g body wt) injected intraperitoneally ~ 48 h after the last test to determine posttraining exercise capacity. Muscles were dissected out and immediately frozen with a metal tong that was cooled in liquid nitrogen. Samples were stored at -80°C for the subsequent measurements. Muscle ATP and CS were analyzed according to the methods described by Lowry and Passoneau (31).

Estimation of spontaneous activity. We tested the hypothesis that differences in spontaneous activity constituted a form of self-conditioning that could contribute to either the pretraining difference or the response to training between the COP and DA strains. Estimates of spontaneous activity were obtained during the normal housing condition of two rats per cage using the approach described by us previously (6). The rats' home cage was placed on a top-loading electronic balance that has a resolution of 0.1 g (model BP 6100; Sartorius, Edgewood, NY) and tared to zero. Rat movement was estimated from weight changes in grams that were sampled at 10 Hz and transmitted via an RS232 output port from the balance to a computer. The data were processed online using Labtech Notebook digital acquisition software (Labtech Notebook version 7.20; Laboratory Technologies, Wilmington, MA). Labtech Notebook was programmed to calculate the absolute value of the first difference, i.e., the absolute value of the difference between consecutive samples. Absolute values were calculated because upward movements registered positive values and downward movements registered negative values on the balance. The mean absolute values were calculated every 3 s

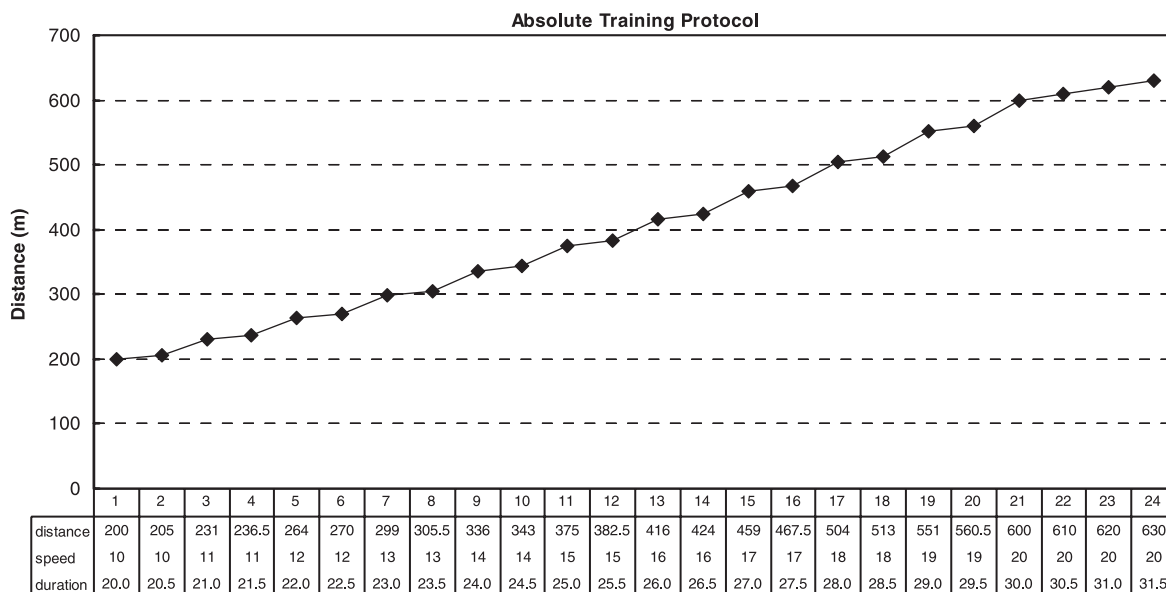


Fig. 1. Nomogram showing distance run (m) for the absolute treadmill exercise protocol over 8 wk of training (1–24 sessions). The slope of the treadmill was set at 15 degrees. The protocol started at speed of 10 m/min for a duration of 20 min. Each session the duration was increased 0.5 min and speed was incremented 1 m/min every other session.

(30 samples) and written to a file for analysis offline. The sum of the absolute values per unit time was taken as an estimate of spontaneous movement.

Estimates of spontaneous movement were obtained for 4-h durations (11 PM to 3 AM) on three consecutive nights at three points for the relative and sham-trained groups: 1) before the introduction to treadmill running, 2) halfway through the 8-wk training period, and 3) immediately after the posttraining test of exercise capacity. For each point of the study, the total activity (g) over the 4-h period was summed and the mean for each rat group and strain was determined.

Analysis of data. A one-way ANOVA was applied to evaluate possible differences for measurements of exercise capacity taken pretraining and posttraining both within and between strains. A Tukey post hoc procedure was used to identify multiple pairwise differences. Data are presented as means ± SE, and the 5% level of significance was arbitrarily assigned for declaring differences.

RESULTS

Neither the COP nor DA strain attained training levels equivalent to 80% of their initial treadmill running duration at the start of the relative training period (Fig. 2). The COP rats ran for duration not significantly different from 80% of their initial maximum on weeks 3, 5, 6, 7, and 8 of training, while the DA rats achieved values not different from the 80% level beginning at week 2. As a percentage of maximal effort, the training levels achieved by the COP and DA rats did not differ significantly for any of the 8 wk of relative training. Figure 3 summarizes the treadmill running capacity in both strains of rats, for both pre- and postrelative training. As expected (3, 27), the COP rats in the pretrained condition had less of an exercise capacity distance (mean = 425 ± 27 m, n = 8)

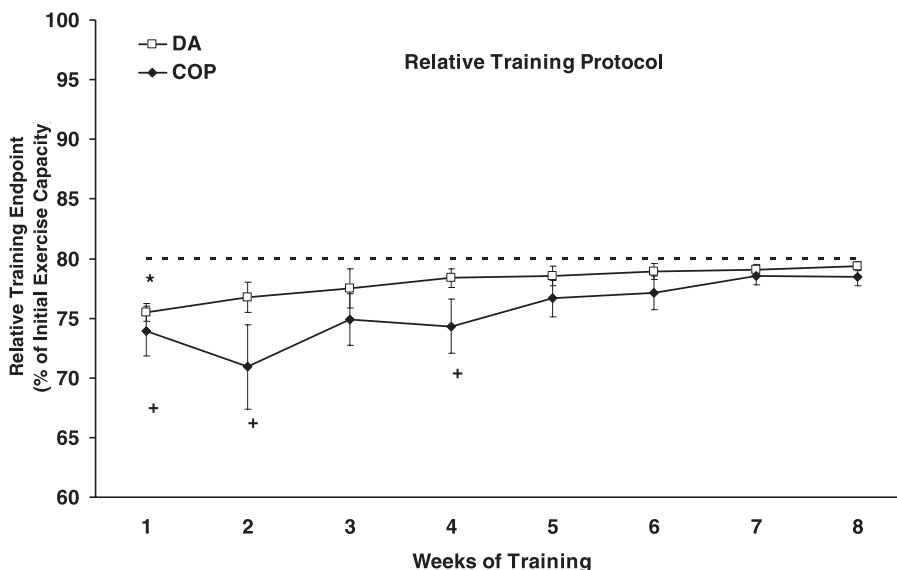


Fig. 2. Mean ± SE for percentage of initial exercise capacity during each week of relative training with a speed-ramped treadmill protocol. As a percentage of effort, the training performance between the Copenhagen (COP) and Dark Agouti (DA) rats did not differ significantly for any of the 8 wk of relative training. The COP rats trained for distances significantly below the 80% target endpoint during training weeks 1, 2, and 4, while the DA rats achieved values not different from the 80% level only during week 1. + Significantly (P < 0.05) different from 80% of initial exercise capacity for COP target level; *significantly (P < 0.05) different from 80% of initial exercise capacity for DA target level.

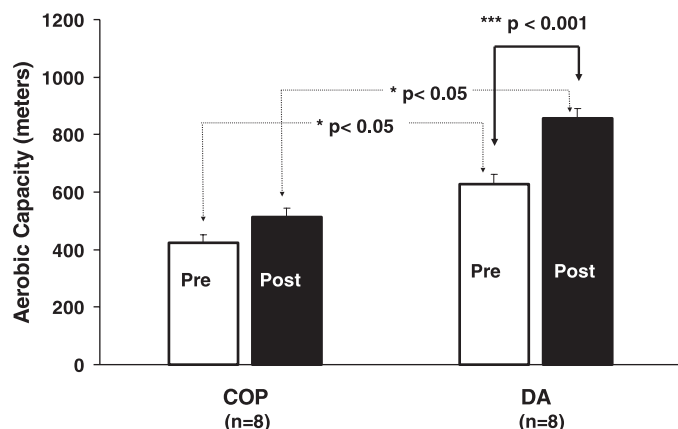


Fig. 3. Differences in pre- and posttreadmill running capacity (m) as an estimate of response to relative and nonprogressive training between COP and DA strains. Intrinsic (untrained) exercise capacity was significantly different between the COP and DA strains. After training, the low-capacity COP increased by 21% and high-capacity DA increased distance run by 36%. The DA strain demonstrated a greater change in exercise capacity in response to relative training compared with COP. Significant difference between groups: * $P < 0.05$, *** $P < 0.001$.

compared with the DA rats (mean = 629 ± 33 m, $n = 8$). Relative training increased the distance run to 513 ± 31 m [88 m gain, 21%, not significant (NS)] in the COP rats and to 857 ± 34 m (228 m gain, 36%, $P < 0.001$) in the DA rats. The COP sham-trained group exhibited a lesser decline in distance run of 89 m decrease (from 410 ± 21 to 321 ± 33 m) compared with 232 m (from 578 ± 82 to 346 ± 38 m) in the DA rats (Fig. 4). However, the change in meters run accompanying both control groups displayed relatively wide variation within strains and was not significantly different between the two strains.

The measures for CS activity and levels of ATP between the COP and DA strains for sham-trained and in response to relative-training are shown in Fig. 5. There was no significant difference in CS or ATP between the COP and DA sham-trained controls. With training, the COP strain had a significant increase in both CS (Fig. 5A) and ATP concentration (Fig. 5B). Although the DA strain demonstrated a significant gain in

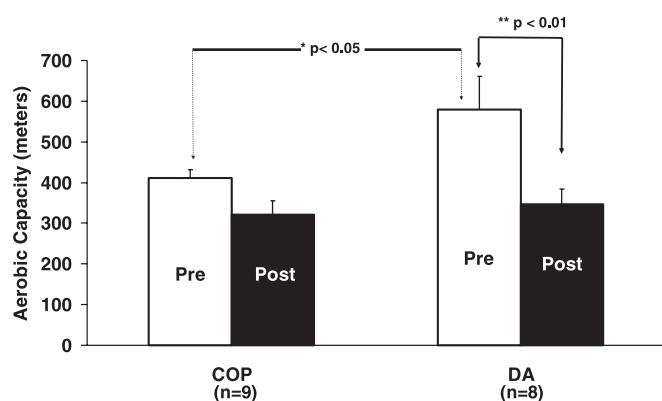


Fig. 4. Differences in pre- and posttreadmill running capacity (m) as an estimate of response to sham training (sedentary behavior) between COP and DA strains. The low-capacity COP decreased 22%, whereas high-capacity DA declined by 40% over 8 wk of sedentary behavior. Significant difference between groups: * $P < 0.05$, ** $P < 0.01$.

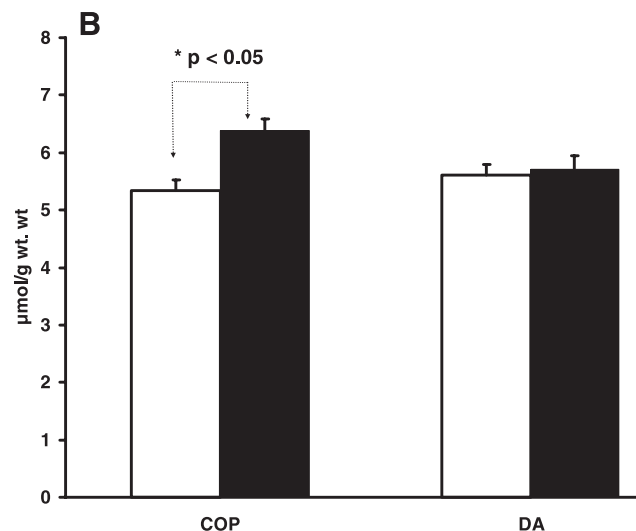
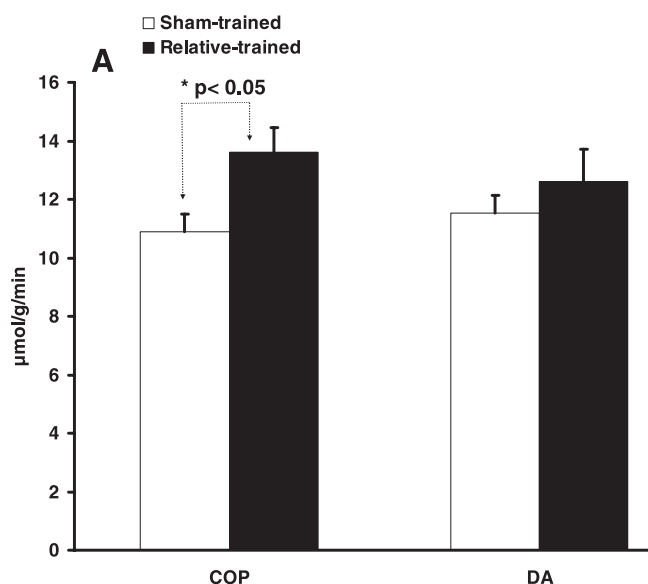


Fig. 5. Biochemical markers of skeletal muscle oxidative enzymes do not associate with strain difference for response to exercise. The COP strain showed a significant increase in citrate synthase activity (A) and levels of ATP (B) (* $P < 0.05$). There was no significant difference in enzyme activity between the COP and DA strains in the sham-trained group.

distance run after training, there was no difference in either CS or ATP compared with sham-trained controls.

Figure 6 shows pre- and posttreadmill running capacity when both inbred strains trained with an absolute protocol over 8 wk. On average, COP rats in the pretrained condition had an exercise capacity at less of a distance (412 ± 31 m) compared with the DA rats (662 ± 67 m). The F_1 (COP \times DA) rats ran intermediate to the parental strains and exhausted at 547 ± 41 m. In terms of duration, the COP rats ran to exhaustion in 25.7 min and a maximal speed of 23 m/min, whereas the DA capacity was exhausted by 35.6 min at a speed of 27 m/min. Events of these durations and intensities have aerobic capacity as a major but not exclusive element (12, 23). The absolute training protocol decreased the exercise capacity of the COP by 6 m (NS) but increased the capacity of the DA rats by 325 m

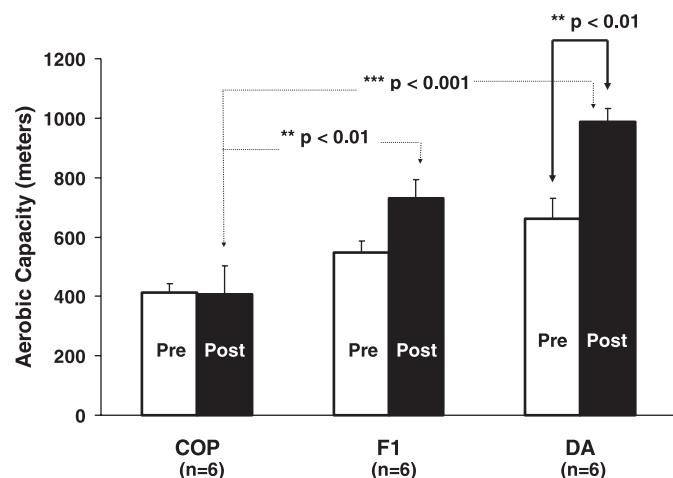


Fig. 6. Differences in pre- and posttreadmill running capacity (m) as an estimate of response to absolute and progressive training between COP and DA strains. When both inbred models trained uniformly over 8 wk, high-capacity DA increased by 49%, whereas low-capacity COP showed no significant change. An F₁ (COP and DA cross population) was intermediate to the parental strains for both pretraining capacity and posttraining capacity. Significant difference between groups: ** $P < 0.01$, *** $P < 0.001$.

(49%, $P < 0.01$). The F₁ (COP × DA) rats increased their exercise capacity after training to 730 ± 64 m (183 m gain; $P = 0.306$), intermediate to the parental strains.

There were no differences in body mass before training between COP and DA strains when comparisons were made within the three training groups (Table 1). All rats experienced a significant increase in body mass over the 8-wk training period. However, the DA proved to be on average ~6% lighter than the COP rats at the time of the posttraining test for exercise capacity.

Figure 7 summarizes the measures of spontaneous activity (g) taken before the education week (bar B), during the training period (bar D), and after the second exercise capacity test (bar A) for both strains in the relative and sham-trained control groups. These 12 sets are shown in Fig. 7, and only two of twelve sets had spontaneous activities that were significantly different from each other. The trained COP rats had a spontaneous activity of 295 ± 77 (g) during the posttest period that was significantly greater than that of the sham-trained COP rats (94 ± 52 g) during the before training period. These results suggest that the differences in initial exercise capacity or the

Table 1. Summary data for comparisons in body mass in all three training groups

Strain/Training Group	n	Age, wks	Body Mass, g		
			Pre	Post	Δ
COP					
Relative	8	8	140.9 ± 1.5	200.0 ± 2.2*	59.1 ± 3.1
Absolute	6	10	157.0 ± 3.1	198.5 ± 3.3*	41.5 ± 2.2
Sham	9	8	137.4 ± 2.6	190.6 ± 3.1*	53.2 ± 1.6
DA					
Relative	8	8	145.0 ± 1.6	185.2 ± 2.5*†	40.2 ± 1.2†
Absolute	6	10	155.8 ± 2.1	190 ± 2.1*	34.2 ± 3.8
Sham	8	8	142.6 ± 2.0	180.7 ± 0.5*†	38.1 ± 1.7†

Values are means ± SE. COP, Copenhagen; DA, Dark Agouti. * $P < 0.05$, significantly different Pre vs. Post; † $P < 0.05$, significantly different between strains.

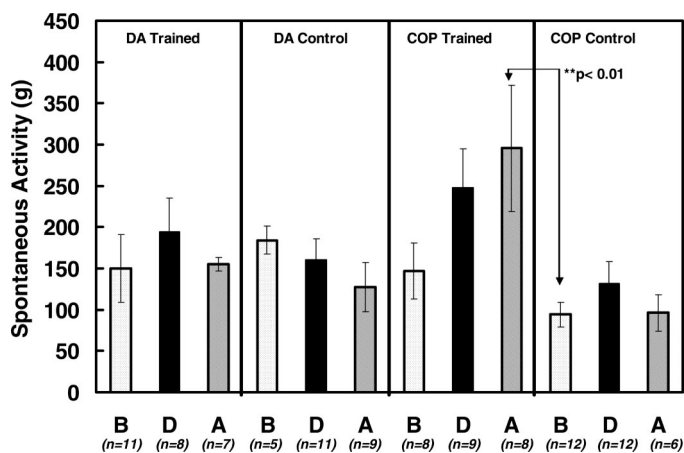


Fig. 7. Mean spontaneous activity (g) over 4-h periods (repeated on 3 days) for relative and sham-trained groups measured before training (bar B), during training (bar D), and after training (bar A). The only significant differences were between the COP rats after relative training and the COP rats before sham training ($n =$ number of cages monitored).

response to exercise training between the COP and DA rats are not explained by differences in spontaneous activity that would lead to self-conditioning.

DISCUSSION

Exercise capacity can be operationally divided into two components: 1) intrinsic (untrained), and 2) that acquired as a result of exercise training. Considerable variation exists between individuals for both the intrinsic and training components, presumably related to a complex interaction of genetic (G) and environmental (E) factors (9). A composite model of five factors that can influence the response to training has been put forth by Bouchard and Malina (10) and includes age, gender, previous experience with training, current phenotype, and genotype. The current phenotype is the most difficult part of this model to interpret because it is composed of undefined differential contributions of genotype and environment. In theory, the phenotypic variance can be estimated if one of the two components (G or E) is eliminated. Experimentally, genetic variance can be more closely controlled when using a highly inbred line with identical genotypes. Therefore, phenotypic variation within strain is produced by environmental factors, and between-strain variation is derived from genetic factors (26, 32). Our data support the hypothesis that genetic factors causative of high response to exercise are not uniquely associated with genetic factors for intrinsically low initial capacity. The major assumption with this approach is that the environmental variance is similar between inbred strains and that the genotypes respond similarly to the environment. This is problematic because of gene/environment interactions. Indeed, some mouse strains have been found to be more variable and sensitive to environmental differences for a given trait (16).

We applied two disparate types of training modes so that any differences in response to exercise between the COP and DA rats could not be explained exclusively by the type of training stimulus. We thought this was important because early exercise training studies in the rat by Gisolfi and colleagues (4) showed that rat strain is a significant factor in the response to exercise.

Exercise training protocols for a population can be applied relative (45) to the current capacity for each individual, or absolute (13), where each receives the same amount of training independent of current capacity. Protocols can also be progressive, with periodic adjustments for alterations in capacity, or nonprogressive. However, for any given protocol, more training does not always produce a greater response (15) and wide variation for response exists (8). This is predictable because each individual has a unique genotype that can respond best to one particular training environment.

The outcome of the exercise experiments presented here suggests that the COP strain is a nonresponding strain for two distinct types of exercise training modes. An implicit assumption of this work is that the difference in environmental variation between the strains approached zero. This is a reasonable assumption because for each experimental group, the strains were age matched, studied at the same time of day, and housed in the same room with random rotation of cage positioning. From this, we presume that both the greater initial capacity and response to exercise of the DA rats compared with the COP rats originated largely from as-of-yet undefined genetic differences. Consistent with this idea is the observation that measures of pre- and posttraining exercise capacity in the F_1 (COP \times DA) cross were midway between that of the parental strains. By operational definition, an F_1 phenotype that lies intermediate between parental strains suggests that the genetic variance depends on an additive effect of substituting one allele for another rather than a dominance variance which causes a phenotype to more closely resemble one strain.

Our measures of body mass changes, exercise capacity after 8 wk of sedentary behavior, and spontaneous activity further suggest that our results cannot be explained by differences in strain behavior that lead to self-conditioning as part of the current phenotype (Fig. 6). Although the measures of spontaneous activity showed wide variation, it was the low intrinsic capacity COP rats during the posttraining period that on average registered the most activity in their home cages. While the differences in body mass could arise from genetic or energetic factors (i.e., the DA trained at a higher level of intensity in the relative group), the mechanisms by which a lighter body mass could be causative of increased training response is unknown.

The age associated decline in maximal endurance capacity is a well-established phenomenon, and the rate of decline in humans is apparently similar whether one is fit or sedentary (40). It is interesting that distance run by the sham-trained DA rats decayed to a level (346 ± 38 m) not different from the sham-trained COP rats (321 ± 33 m) over the 8 wk of sham training. Nevertheless, the declines in performance associated with 8 wk of sedentary behavior (sham trained) were not significantly different ($P = 0.137$) between the two strains and demonstrated substantial variation.

Increases in peripheral oxidative enzyme capacity such as CS are routinely employed as markers for sufficiency of exercise intensity and evidence for training effect in rats (19, 20). Yet reports of large variation in CS activity (0–100%) with training, not explained by differences in exercise protocol, time course of exercise, or muscle type, suggests that a gain in response to exercise may not be exclusive to changes in oxidative potential (30). Additionally, it has been questioned in studies using models selectively bred for increased wheel-running or treadmill running capacity whether greater oxida-

tive capacity is a prerequisite for adaptation to exercise or a result of the exercise (21, 22). Here we report that the DA genotype demonstrated a significant change in running capacity but showed no significant increase in CS or ATP concentration in skeletal muscle. Conversely, the COP genotype had significant increases in both of these biomarkers but demonstrated no response to training. Given the myriad of molecular changes that could participate in adaptation to any exercise protocol (7), it is probably prudent not to consider any individual pathway as a standard measure for response to training.

Overall, our results suggest that training effects that follow the principle of initial value originate largely from environmental factors that influence the current phenotype. For example, Mazzeo et al. (33) found that maximum O_2 consumption ($\dot{V}O_{2\max}$) declined as a function of aging (3, 12, and 24 mo) in Fischer 344 rats. In response to 8 wk of exercise training, the percent improvement in $\dot{V}O_{2\max}$ was inversely related to age, which is consistent with the principle of initial value. Cardiac patients also commonly display an inverse relationship between baseline aerobic capacity and percent improvement with training (1). In contrast, Bouchard and colleagues (8) did not find a relationship between baseline $\dot{V}O_{2\max}$ and the change in $\dot{V}O_{2\max}$ in response to 14 wk of standardized exercise training performed on cycle ergometers in 481 presumably healthy subjects. This lack of relationship between baseline $\dot{V}O_{2\max}$ and response to training is consistent with the idea that these two phenotypes are determined by different genetic factors. As such, the principle of initial values appears to operate through somewhat stereotyped environmental factors such as age, health status, and body weight (18, 29).

Finally, we note that the generality of the principle of initial value may be overestimated because of an inappropriate use of regression analysis in both older (42) and newer literature (44). Regression analysis requires the variables be independent (46). Because the response to exercise (dependent variable) is sometimes presented as posttraining minus pretraining values (or as percent change), a significant negative slope is derived automatically as an associated function of pretraining (independent variable).

Given the complexity of traits for physical capacity, this study is one example on how well-defined animal models and experimental design for genetic and environmental uniformity will be useful in resolving the genetics of exercise.

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