Treadmill running produces both positive and negative physiological adaptations in Sprague-Dawley rats

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Moraska, Albert, Terrence Deak, Robert L. Spencer, David Roth, and Monika Fleshner. Treadmill running produces both positive and negative physiological adaptations in Sprague-Dawley rats. Am J Physiol Regulatory Integrative Comp Physiol 279: R1321–R1329, 2000.—Exercise training produces a vast array of physiological adaptations, ranging from changes in metabolism to muscle mitochondrial biogenesis. Researchers studying the physiological effects of exercise often use animal models that employ forced exercise regimens that include aversive motivation, which could activate the stress response. This study examined the effect of forced treadmill running (8 wk) on several physiological systems that are sensitive to training and stress. Forced treadmill running produced both positive and negative physiological adaptations. Indicative of positive training adaptations, exercised male Sprague-Dawley rats had a decrease in body weight gain and an increase in muscle citrate synthase activity compared with sedentary controls. In contrast, treadmill running also resulted in the potentially negative adaptations of adrenal hypertrophy, thymic involution, decreased serum corticosterone binding globulin, elevated lymphocyte nitrite concentrations, suppressed lymphocyte proliferation, and suppressed antigen-specific IgM. Such alterations in neuroendocrine tissues and immune responses are commonly associated with chronic stress. Thus treadmill running produces both positive training adaptations and potentially negative adaptations that are indicative of chronic stress. Researchers employing forced activity need to be aware that this type of exercise procedure also produces physiological adaptations indicative of chronic stress and that these changes could potentially impact other measures of interest.

immune function; exercise; corticosterone binding globulin; immunoglobulin; keyhole limpet hemocyanin

FORCED TREADMILL RUNNING is a common method of training used by researchers investigating physiological adaptations produced by exercise (2, 33, 45, 58, 61). Some benefits of this specific mode of training include the repeatability of training volume and consistency of changes that occur in muscle (skeletal and cardiac) as a result of training. This type of training, however, forces the animals to run according to the experimenters demands, that is, the experimenter chooses the time, duration, and intensity of the running that could chronically activate the stress response. Thus it is possible that stress-induced physiological changes could interact with and confound other physiological adaptations produced by exercise. This study therefore examined the effect of forced treadmill running on several measures indicative of training adaptations and of chronic stress.

Repeated bouts of exercise produces many physiological adaptations that allow an organism to perform greater amounts of work with improved efficacy. These changes are often referred to as training adaptations (4). Many of these training adaptations reported in the literature occur after 8 wk of gradually increasing treadmill training (40–43, 45, 55, 61). Two reported changes that are hallmarks of training are increased metabolic rate or energy expenditure and increased muscle mitochondrial biogenesis. A gross measure of increased metabolic rate or energy expenditure is a reduction in body weight. A commonly reported measure of improved muscle mitochondrial biogenesis is increased citrate synthase activity. Citrate synthase is an important rate-limiting enzyme in the energy-producing mitochondrial citric acid cycle or tricarboxylic acid cycle. An increase in this enzyme is believed to facilitate muscle energy output via oxidative metabolism.

In 1936 Seyle (53) first reported that chronic exposure to a wide variety of noxious agents or stressors produced a triad of common pathophysiological changes. Specifically, Seyle noted that with exposure to chronic stress, animals experienced adrenal hypertrophy, thymic involution, and gastrointestinal ulceration (54). More recently it has been recognized that the physiological systems affected by the stress response include nervous, endocrine, and immune, and that the nature of the responses of these systems is stressor dependent (32, 46). Importantly, in contrast to chronic stimulation, acute activation of the stress response is an adaptive physiological response that facilitates the fight-flight response and potentially survival after bodily injury (9, 22, 38, 39). Thus the initial fundamen-
Chronic exposure to psychological and/or physical stress can also result in maladaptive consequences of the stress response, such as suppression of many aspects of the immune response and an increased incidence of disease (29, 31, 49). Psychological challenges that are capable of activation of the stress response often share several common features, including “loss of control” and exposure to aversive events (37). In addition to the physical stress of exercise, forced treadmill running would seem likely to also produce chronic mental stress because the animals are both forced to run (loss of control) and often are aversively motivated (footshock, physical prodding, loud sounds, air and water spray). The demands of running at the intensity levels commonly used [i.e., 70–90% maximal O$_2$ consumption (Vo$_2$ max)] are known to produce short-term increases in muscle citrate synthase activity. This may produce a reduction in body weight gain and an increase in mesenteric blood flow at the outset of forced treadmill, but not voluntary free wheel, running. Elevations in peripheral blood pressure and heart rate are indicative of activation of the stress response (38). Psychological factors associated with physical activity also may contribute to the stress of activity that is measured in exercise and immune studies (25). Some investigators have specifically avoided forced exercise programs to study the effects of physical activity on specific immunity because of the stress associated with this type of activity (6). Indeed, 6 wk of treadmill exercise in mice resulted in decreased spleen weight and immune performance as measured by mitogen-stimulated splenocyte proliferation (26). Therefore, it is unlikely that the isolated effects of exercise are being measured in studies using a forced treadmill running activity program. Rather, the combined effects of psychological and physical stress are influencing the physiological measures that are then reported.

The following study therefore examined the effect of an 8-wk treadmill training regimen. The training regimen consisted of a gradually accelerating program that attained running for 60 min/day, 5 days/wk up to a velocity of 29.2 m/min at a 10% grade by the end of the study. The training program used involved running at intensities commonly reported in the literature (40–42). This training regimen has been reported previously to produce positive training adaptations such as reduced body weight gain, increased soleus muscle citrate synthase activity, and increased stress protein expression in myocardium (4, 40–43, 45, 55, 61). The treadmill training program in this study is expected to produce a reduction in body weight gain and an increase in muscle citrate synthase activity.

In addition, the following stress-sensitive measures were also taken: 1) thymus and adrenal weight, 2) serum corticosteroid binding globulin (CBG) levels, 3) antigen-specific immunoglobulin production, 4) lymphocyte proliferation, and 5) mitogen-stimulated lymphocyte nitric oxide (NO) production. Thymus and adrenal weight measures were taken because adrenal hypertrophy and thymic involution are part of Seyle’s triad of common pathophysiological changes produced by chronic stress. Serum CBG was measured because previous research has documented that chronic, and some types of acute, stressor exposure reduces serum levels of this corticosteroid carrier protein (8, 19, 56). Corticosterone was not measured in this study because stress-free blood sampling at the time of death was not possible. Antigen-specific immunoglobulin production and lymphocyte proliferation were measured because both measures of immune function are sensitive to suppression by stress (16, 21, 35, 38, 49). Splenic NO levels were measured because increases in leukocyte NO after psychological and/or physical acute or chronic stress have been reported previously (7, 14, 22, 34). If treadmill running chronically activates stress responsive systems, then treadmill training also would be expected to produce adrenal hypertrophy, thymic involution, decreased serum CBG, suppressed lymphocyte proliferation and antibody production, and increased nitrite production.

**MATERIALS AND METHODS**

**Animals**

Male Sprague-Dawley rats (320–350 g, 8 wk old) were purchased from Harlan Sprague Dawley (Indianapolis, IN). Rats were housed in a controlled temperature room (22°C) with a 12:12-h light-dark cycle (0600–1800 lights on) and access to laboratory rat chow (LabChow) and water ad libitum. To reduce the stress associated with shipping and acclimatization to the moderate altitude of Boulder, Colorado (elevation 5,400 feet), rats were individually housed in standard Plexiglas cages for 14 days before onset of any running activity. Care and use of the animals were in accordance with protocols approved by the University of Colorado Institutional Animal Care and Use Committee.

**Procedures**

**Exercise training.** Rats were either treadmill trained ($n = 10$) or remained sedentary ($n = 8$). Treadmill-trained rats were housed in clear plastic cages ($43 \times 21.6 \times 20.3$ cm) and followed a standard exercise training protocol shown to induce cardiovascular fitness in rats (41). The 8-wk exercise training protocol consisted of running on a motorized treadmill up a 10% grade five times per week with an incremental increase in treadmill velocity (17.4–29.2 m/min) and run duration (10–60 min) to accommodate increased fitness. The highest level of activity (29.2 m/min for 60 min) included two 5-min warm-up periods at 21.5 and 25.5 m/min, and the final 5 min consisted of a warm down at 21.5 m/min. Increases in velocity and/or duration were performed when the rats could maintain the current exercise intensity for 5 consecutive days. A shock grid at the back of the treadmill provided a mild but aversive footshock (1.6 mA) if the pace of the rat slowed below treadmill rate. Very few shocks were administered during a training session and occurred within the first week of training. In fact, Dunn et al. (11, 12) reported that treadmill-trained rats with no footshock have changes in central nervous system noradrenergic metabolism that are indicative of chronic stress (12). This training protocol resulted in a training intensity of 75% Vo$_2$ max (41). The sed-
ентary rats were handled identically to the treadmill-trained rats. At the same time of day, the sedentary rats were placed on a stationary treadmill, with the shock grid turned off, 5 days per week for the duration of the treadmill training session. Mean average distances run have been presented in part elsewhere (43).

Body weight. All rats were housed individually, and body weight was determined to the nearest gram on an Ohaus triple-beam balance at weekly intervals. Body weight data have been presented in part elsewhere (43).

Death. After 8 wk, both exercised and control rats were killed by decapitation. Exercise training ceased 18 h before death for treadmill-trained rats. Trunk blood was collected for CBG measurement. Serum was separated by centrifugation and stored at −20°C. The soleus muscle was dissected and flash frozen in liquid nitrogen. The spleen and mesenteric lymph nodes (MLN) were aseptically dissected and placed in cold medium (Iscoves, supplemented with 1% penicillin-streptomycin, Gibco). Thymus and adrenal glands were excised, rinsed, blotted dry, and weighed. Right tibia length was measured to the nearest millimeter using a micrometer. Thibia length measurement allowed for standardization of thymus and adrenal weight to an internal variable that would not be altered by exercise training.

Citrace synthase activity. Citrate synthase activity in soleus muscle samples was measured according to Srere (57) and measured at 30°C. These data have been presented in part elsewhere (43).

CBG assay. Serum CBG concentration from trunk blood obtained on death was assessed using a competitive binding assay adapted by Westphal (59). Serum samples initially were diluted 1:200 in buffer [10 mM Trizma base, 1.0 mM EDTA, 10% glycerol (vol/vol), and 1.0 mM dithiothreitol, pH 8.0], then mixed with [3H]corticosterone (15 nM) or unlabeled corticosterone (10 mM) at a final dilution of 1:600. Samples were incubated overnight at 4°C. Bound and unbound steroids were separated using activated charcoal (performed in duplicate). The bound fraction was mixed with scintillation cocktail and counted with a liquid scintillation counter (Tri-Carb 1600TR; Packard, Meriden, CT).

Lymphocyte proliferation. Cells from the spleen and MLN were dissociated from the tissues using a sterile modified glass tissue homogenizer. Cell enumeration was achieved using a Coulter counter. Spleen and MLN were washed in dissection medium and resuspended in Iscoves culture medium (Iscoves, supplemented with 1% penicillin-streptomycin, Gibco). Thymus and adrenal glands were excised, rinsed, blotted dry, and weighed. Right tibia length was measured to the nearest millimeter using a micrometer. Thibia length measurement allowed for standardization of thymus and adrenal weight to an internal variable that would not be altered by exercise training.

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NO production was determined by measuring nitrite levels in culture supernatants. Nitrite is a stable nitrogen intermediate formed from the degradation of NO in an aerobic environment. Nitrite was measured using the Greiss reagent assay. The Greiss reagent consisted of a 1:1 (vol/vol) solution of sulfanilamide (Sigma Chemical) in a 4.25% phosphoric acid solution (Mallinckrodt) and 0.1% N-(1-naphthyl)ethylendiamine dichloride (Sigma Chemical) in distilled deionized water. A standard curve was generated with a starting concentration of 2.5 mM sodium nitrite (Sigma Chemical) in culture medium. Standards (100 µl) were serially diluted 1:2, ten times, to obtain a standard curve. All standards were added to 96-well flat-bottom plates (Immulon 4, Dynatech Laboratories) in duplicate. Sample culture supernatants (100 µl) were also run in duplicate. Greiss reagent (100 µl) was added to each well and allowed to incubate at room temperature for 10 min. Absorbances were read at 540-nm wavelength using a microplate reader (MRX microplate reader, Dynatech Laboratories). Samples were compared with a standard curve containing serial dilutions of sodium nitrate.

Anti-KLH immunoglobulin. All rats were immunized with a 0.5-ml intraperitoneal injection containing 200 µg of KLH in sterile saline on days 0 and 49 of exercise training, stimulating a primary and secondary response, respectively. KLH is a benign, antigenic protein that will stimulate an antigenspecific immune responses without making the animal sick (15, 20, 21, 38).

Tail vein blood samples were quickly collected (within 2 min of touching the cage) by gently wrapping the rat in a small towel and lightly restraining it with a Velcro strapping apparatus. The tail was exposed, a small nick was made with a scalpel (No. 15 blade), and the blood sample (300 µl) was quickly milked from the tail vein. Serum levels of anti-KLH IgM and IgG were determined using an ELISA. The details of the ELISA procedures (using alkaline phosphatase, p-nitrophenyl phosphate disodium) have been presented previously (17, 18).

The primary anti-KLH IgM and IgG response was measured on days 7, 14, 21, 28, and 35 after KLH immunization. The secondary anti-KLH IgM and IgG response was measured on day 56, 1 wk after the second KLH challenge. Each anti-KLH IgM and anti-KLH IgG sample was calculated as a proportion of its plate positive, which is very nearly equal to 1.0 absorption unit. This is a standard transformation for data reported using ELISA (10). A negative control (serum from rats not challenged with KLH) was tested on each plate. Little nonspecific binding was found (OD < 0.1–0.2). Primary antibody data were presented for samples assayed at the 1:400 dilution for IgM and the 1:6,000 dilution for IgG. Because a secondary or memory antibody response is much greater than the primary response, samples were assayed at the 1:3,200 for IgM and 1:32,000 for IgG. These dilutions
were chosen so that samples fall within the linear range of the plate reader. Observed differences were consistent across dilutions.

Statistical Analysis

Repeated measures analysis of variances (ANOVAs) were used to analyze total distances run, body weight, anti-KLH immunoglobulin and proliferation data. Data for citrate synthase activity, thymus weight, adrenal weight, and CBG levels were analyzed using a two-group ANOVA. Nitrite production was analyzed by a 2 (treadmill vs. sedentary) × 2 (ConA vs. KLH) factorial ANOVA. Post hoc pairwise comparisons were performed using Fishers protected least-significant difference test. A statistical difference was accepted at \( P < 0.05 \). All data are reported as the means ± SE.

RESULTS

Running Activity

Weekly total running distance is presented in Fig. 1A. Because of the regimented treadmill training program, average weekly running distances were the same for all rats and continued to increase until week 7, at which point training was not increased over the final week.

Body Weight

The effect of treadmill running on body weight is depicted in Fig. 1B. Both sedentary and treadmill-trained rats gained weight over the 8 wk of the study (\( P \leq 0.0001 \)); however, treadmill runners gained overall statistically less weight than their matched sedentary controls (\( P \leq 0.05 \)). This decrease in body weight due to running was greatest during the final weeks of the study (\( P \leq 0.0001 \)).

Soleus Muscle Citrate Synthase Activity

Figure 2 clearly depicts an increase in citrate synthase activity in soleus muscle after 8 wk of treadmill running (\( P \leq 0.05 \)).

Thymus Gland Weight

Figure 3A presents thymus weight corrected for body weight. Clearly, 8 wk of treadmill training produced a large reduction in thymus weight (\( P \leq 0.001 \)). Treadmill rats had a 42% reduction in normalized thymus weight compared with sedentary controls. The results for thymus weight were the same when corrected for tibia length (data not shown).

Adrenal Gland Weight

Figure 3B presents adrenal gland weight corrected for body weight. Treadmill training produced a large increase in adrenal weight (\( P \leq 0.001 \)). The results for adrenal weight were the same when corrected for tibia length (data not shown).

CBG

Figure 4 presents the effect of treadmill running on CBG, the carrier protein for the stress hormone corticosterone. Eight weeks of treadmill running decreased serum CBG (\( P \leq 0.005 \)).

Lymphocyte Proliferation

Proliferation of mesenteric lymph node cells is shown in Fig. 5, A and B. Treadmill running suppressed both the ConA- (\( P = 0.08 \)) and KLH- (\( P \leq 0.005 \)) stimulated
proliferative response compared with sedentary controls. Although the suppression of ConA-stimulated proliferation was only trending to be statistically reliable, the suppression of KLH-specific proliferation was clearly suppressed. Treadmill running did not produce a reliable suppression of either ConA- or KLH-stimulated proliferation of splenocytes (Fig. 6, A-B).

**NO Production**

Nitrite concentrations were measured in supernatants of MLN cells and splenocytes (20.0 × 10^6 cells/ml) after 48 h of stimulation with either ConA or KLH (Fig. 7, A-B). Treadmill running did not affect nitrite production in the absence of in vitro antigen stimulation for either MLN or spleen (unstimulated). As shown in Fig. 7A, MLN ConA- or KLH-stimulated production of nitrite also was not affected by treadmill training. In contrast, splenocytes (Fig. 7B) stimulated with either ConA or KLH from treadmill-trained rats produced higher levels of nitrite compared with sedentary controls (P ≤ 0.05).

**Anti-KLH IgM and IgG**

Weekly serum levels of the primary KLH-specific immunoglobulin response is shown in Fig. 8, A-B. Treadmill running reduced the amount of anti-KLH IgM (Fig. 8A, P ≤ 0.05), but not anti-KLH IgG (Fig. 8B, P = 0.2). Interestingly, the secondary anti-KLH IgM (Fig. 9, P ≤ 0.01) but not secondary anti-KLH IgG (Fig. 9) response was also reduced in treadmill trained rats.
Running exercise is a frequently used training modality for rats, and treadmill running has the propensity to induce both psychological and physical stress. The purpose of this paper was to characterize effect of treadmill running on several training responsive and stress responsive physiological adaptations. The treadmill training protocol used in this study involves a gradual increase in running intensity and is commonly used in the literature. The results of this experiment were that treadmill running produced both positive or adaptive and potentially negative or maladaptive physiological changes. The positive adaptations reported here were reductions in body weight gain and increases in soleus citrate synthase activity. The potentially negative physiological adaptations exhibited were adrenal hypertrophy, thymic involution, decreased serum CBG, elevated lymphocyte nitrite concentrations, suppressed lymphocyte proliferation, and suppressed antigen-specific IgM.

The mechanisms and specific benefits of reductions in body weight gain and increases in muscle citrate synthase activity after training have been discussed elsewhere and are beyond the scope of this paper. There is evidence, however, that both changes result in benefits to the organism (4).

Classically stress-induced changes in adrenal and thymus weight occur because of long-term stimulation of the hypothalamic-pituitary-adrenal axis (54). In brief, repeated daily stressor exposure, through central nervous system inputs to the hypothalamus, stimulates hypothalamic corticotropin-releasing hormone, which stimulates pituitary to release adrenocorticotropic hormone (ACTH) into the peripheral circulation. ACTH stimulates adrenal production of corticosterone. Chronic stimulation of the adrenal gland by ACTH will result in proliferation of adrenal cortical cells and hence adrenal hypertrophy. Thymic involution is due to chronically elevated corticosterone (1, 27). Thymocytes are sensitive to corticosterone-induced apoptosis (5, 28). Thus chronically high-circulating corticosterone kills thymocytes and results in thymic involution.

Clearly short-term activation of the hypothalamic-pituitary-adrenal response is important for facilitating energy utilization during the stress response (44). However, chronically elevated glucocorticoids have been reported previously to result in negative consequences to the organism health (52, 56), including...
eventual adrenal exhaustion and a reduction in developing T cells (thymic involution). It should be noted, however, that others have proposed that an enlarged adrenal gland or the “sports adrenal” may be a positive training adaptation (4).

The mechanism(s) for stress-induced decreased serum CBG, elevated leukocyte nitrite concentration, suppressed lymphocyte proliferation, and suppressed antigen-specific IgM are not as clear. It has been proposed that both the elevation in NO and the reduction in CBG are indicative of stress-induced activation of the acute phase response (8, 22, 38). The acute phase response is a systemic response to pathogenic challenge and is characterized by a shift in liver protein metabolism and a facilitation of the inflammatory response (3). CBG is a “negative reactant” and is expected to decrease during the acute phase response, whereas leukocyte release of NO facilitates the inflammatory response (13). Thus a decrease in CBG and an increase in NO could be reflective of stimulation of the acute phase response. The functional consequences of an increase in antigen-mitogen-stimulated NO remains unknown. It is possible that the potentiated NO response could improve bactericidal killing by inflammatory cells (13). In contrast, it also is possible that the potentiated NO response could be detrimental to the organism by damaging normal cells (13, 22). In fact, it has been proposed that an increase in leukocyte NO could be a mechanism for stress-induced suppression in lymphocyte proliferation and anti-KLH antibody responses (7, 14, 22, 34). Although the precise mechanisms of these changes remain unknown, it is clear that they are associated with activation of the stress response (7, 9, 14, 19, 22, 34, 56). Therefore, the presence of these changes after 8 wk of treadmill running supports the conclusion that treadmill running chronically activates stress-responsive systems.

Are reduced serum CBG, elevated lymphocyte nitrite concentrations, suppressed lymphocyte proliferation, and suppressed antigen-specific IgM adaptive or maladaptive to the organism? As stated previously, a short-term reduction in CBG and elevation in NO is characteristic of activation of the acute phase response. In addition there is evidence that acute stressor activation of these responses is an adaptive response for the organism (8, 9, 22, 38). CBG is a carrier protein for corticosterone and serves to provide a reservoir of biologically inactive hormone that can be quickly made active. A short-term reduction in CBG can aid site-specific regulation of inflammatory responses (24). However, a long-term reduction in circulating CBG could lead to a chronic elevation in biologically free corticosterone that can become detrimental to health (52, 56). Clearly, reduced CBG after treadmill running was biologically relevant to the animal because it experienced a nearly 50% reduction in thymus size. Reductions in lymphocyte proliferation and generation of antigen-specific immune responses also are potentially maladaptive consequences to exposure to this training regimen. Importantly, the suppression in lymphocyte proliferation and the secondary anti-KLH IgM response occurred at the end of 8 wk of treadmill training. Studies that have reported the effect of acute
stress on lymphocyte proliferation and anti-KLH IgM production demonstrate that stressor exposure is no longer immunosuppressive if the KLH is administered (23) or the cells are removed (unpublished observation) within 2–7 days of stressor termination. This suggests that the immunosuppressive effect of treadmill running is not due to the initial novelty of the experience and that the effect is not habituating with repeated treadmill running. These findings may reflect a maladaptive adaptation as reductions in cellular proliferation and antibody production can increase disease susceptibility (30, 49).

The current study cannot address which particular components of treadmill exercise are responsible for producing the changes in stress-responsive systems. In addition to the previously discussed psychological (loss of control and aversive motivation) and physical (pushed to attain 75% VO2 max) stressors, rats trained on the treadmill are often forced to run during their light phase. Rats are normally most active during their dark phase (51). This difference in time of day of activity could lead to disruptions in biological rhythms that have been reported to activate stress-responsive systems (36). Although the current study cannot discern the source of the stress (e.g., exercise intensity, aversive motivation, fear, loss of control, disruption of biological rhythms, etc.), the results support the conclusion that the treadmill protocol tested in this study and commonly used by many researchers produces physiological adaptations that are indicative of chronic stress. Therefore, it is important to be aware of the potential negative impact that chronic activation of the stress response, due to forced treadmill running, can have on physiological measures of interest.

Chronic activation of the stress response may not occur as a consequence of all treadmill training protocols and could be dependent on exercise intensities, gender, time of training, or rat strains. In a recent paper by Palmer et al. (47), e.g., female Sprague-Dawley rats that were trained on a treadmill for 20 wk with a very gradual increase in running speed and duration, did not experience adrenal hypertrophy. In some circumstances, therefore, the stress-evoking effects of treadmill training can be minimized.

REFERENCES


