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Glucocorticoid Response to Forced Exercise in Laboratory House Mice (*Mus domesticus*)

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COLEMAN, M. A., T. GARLAND, JR., C. A. MARLER, S. S. NEWTON, J. G. SWALLOW AND P. A. CARTER. *Glucocorticoid response to forced exercise in laboratory house mice* (Mus domesticus). PHYSIOL BEHAV **63**(2) 279–285, 1998.—We examined the time course and sex differences of the glucocorticoid response to forced, moderate-intensity treadmill exercise in outbred laboratory house mice. Mice ($n = 64$ total) were divided into eight groups, each of four males and four females, which were run on a motorized treadmill at 1.0 km/h for either 0, 2, 5, 10, 15, 25, 40, or 60 min. Serum samples were taken immediately after exercise and corticosterone (CORT) concentration was determined by radioimmunoassay. Resting CORT levels ranged between 11.6 and 29.5 ng/mL for both sexes. CORT levels increased with length of exercise and then exhibited a plateau by 25 min in females and by 40 min in males. Females displayed a significantly more rapid increase in serum CORT levels and attained higher maximal CORT levels than males. Females also had significantly larger adrenal glands, both in absolute terms and relative to body mass. © 1998 Elsevier Science Inc.

Adrenal glands Corticosterone Exercise House mouse Locomotion *Mus* Treadmill

THE hypothalamus and pituitary secrete and respond to various chemical messengers (e.g., adrenocorticotropic hormone (ACTH), arginine vasopressin (AVP), oxytocin) that result ultimately in the secretion of glucocorticoids from the adrenal cortex. In vertebrates, glucocorticoids, such as cortisol or corticosterone (CORT), are involved in energy balance and regulation, both at rest and during physical activity (45,56,65). They are secreted continually at basal or maintenance levels and increased secretion in response to exercise has been demonstrated in several species of mammals (4,49,61,66). Glucocorticoid secretion in response to various other physical and psychological stressors is also well known (3,20,47,51,52,55).

In mammals, various hormones, including those of the hypothalamic-pituitary-adrenal (HPA) axis, are secreted during exercise (19,38,55,57,60,64,70). The particular combinations of hypothalamic-pituitary messengers responsible for stimulation of glucocorticoid secretion during exercise have yet to be established. Consequently, glucocorticoids themselves are often studied as an indicator of general HPA activity.

During prolonged exercise, glucocorticoids may promote maintenance of blood glucose levels by stimulating release of amino acids from muscle, stimulating gluconeogenesis, and enhancing mobilization of fat stores (55,60,61,70). Chronically elevated glucocorticoids can lead to muscle tissue loss (33), but both acute and chronic administration of exogenous glucocorticoids have also been shown to increase endurance and work performance in rats (25,36,53).

We have been developing house mice (*Mus domesticus*) as a model system for studying the genetics and evolution of exercise physiology (11,12,18). Here, we present initial studies aimed at elucidating endocrine mechanisms underlying activity and exercise. In future studies, we will compare various groups of house mice, e.g., trained versus untrained, genetically selected versus control (58), and wild versus domestic (13), with respect to hormonal responses to exercise.

The goals of the present experiment were twofold. First, we sought to establish the time course of the serum CORT response to moderate-intensity exercise. Second, we tested for sex differences in CORT levels in response to treadmill running. Corticosterone is the primary glucocorticoid secreted in rodents (44). Sex differences in adrenocortical function are well known in mammals (22,37,63) including house mice, but, to our knowledge, have not been studied in the context of physical exercise in rodents. We ran laboratory house mice at sustainable speeds for various periods of time, ranging from 2 min to 1 h, and measured serum CORT concentration immediately after exercise.

Compared with males, we predicted that females would have larger adrenal glands and a greater amplitude serum CORT response. These differences were predicted because previous studies of house mice have found females to have larger adrenal glands (35), because estrogen can increase activity of the HPA axis, whereas testosterone may suppress activity (30,37), and because female house mice are generally more active under laboratory conditions [(46) and unpublished results in our laboratory].

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MATERIALS AND METHODS

Animals

Study animals were derived from the Hsd:ICR strain of *Mus.* This outbred strain possesses relatively high levels of both genetic [(28) unpublished data] and phenotypic variation (18,29), and has been used extensively as a model for physiological and genetic studies (11,12,13,14,50). A total of 32 male and 32 female mice was used. These were from the eighth generation of selection for high voluntary wheel-running activity (58), with mice from control and selected lines equally represented. Mice were 94–105 days of age at treadmill testing (mean = 100 days).

Housing and Maintenance

Pups were weaned at 21 days and toe-clipped for individual identification. For standard maintenance, mice were housed in same-sex groups of four per cage (standard plastic cages 27.5 × 17 × 12 cm high in internal dimensions, with pine shavings for bedding, metal tops, metal food hoppers, and water bottles) at 23°C on a 12-h light cycle. Ten days before experimental procedures began, all mice were housed individually to reduce possible effects of aggression and/or dominance hierarchies (5). It is possible that group housing may differentially affect the stress response in males and females. If so, then an improvement for future studies would be to house animals individually from weaning. Access to food (Harlan Teklad Rodent Diet (W) 8604) and water was unrestricted.

Treadmill Exercise Protocol

For experimental trials, mice were placed individually in a small plexiglass chamber held just above the surface of the treadmill belt [inner dimensions of chamber running area were 13 × 6.3 × 5 cm high, with a wedge-shaped extension (for the electrified grid) that was 6-cm long × 6.3 cm wide × 5 cm at the highest and 2 cm at the lowest point (11)]. Mice were then run continuously for 2, 5, 10, 15, 25, 40, or 60 min at a speed of 1.0 km/h (the approximate mean running speed of these mice on voluntary running wheels). Resting serum CORT levels were determined for a separate group of eight mice that were removed from their cage and immediately decapitated. All trials were begun between 0800 and 1250 and the order of experimental trials was randomized to minimize time-of-day effects.

Based on the equation reported in Table 1 of (16), female mice with mean body mass of 27.8 g and male mice with mean body mass of 36.7 g running at 1 km/h are predicted to have $\dot{V}O_2$ of 193.8 mL/h and 261.1 mL/h, respectively. On the basis of data collected in our laboratory on mice of the same strain as studied herein (12,13,18,29,58), predicted $\dot{V}O_2$max is 284.4 mL/h for females and 337.4 mL/h for males. Thus, the female and male mice in this study, running at 1 km/h, were probably exercising at a moderate work intensity of approximately 68% and 77% $\dot{V}O_2$max, respectively.

Previous studies have shown that some individual laboratory house mice will refuse to run without stimulation (16). Therefore, as in previous studies (12,13,18,29,58), manual and controlled electrical (<10 mA delivered at approximately 70 V) stimulation were used for motivation when animals did not run voluntarily. Behavior data were recorded continuously during each trial. An apparent electrical stimulation event was recorded as occurring each time an animal touched the grid with its feet (this may or may not have resulted in an actual shock, depending on how the animal's feet touched the grid). The amount of manual stimulation was also scored subjectively on a scale from least (0) to most (2) stimulation required.

To separate potential responses to psychological stress [e.g., caused by a novel environment: (3,47)] from those related to exercise per se (55,61), animals were trained to run on the treadmill for 10 min on each of the 2 days prior to experimental trials. Preliminary studies showed that this training protocol reduced the amount of stimulation necessary to maintain running behavior during subsequent experimental trials. In addition, the number of fecal boluses produced during experimental trials was recorded as a potential indicator of emotionality [as in open-field tests (2,7,17,23,24,67)] and analyzed as a dependent variable (9,18,62). To control for the possible effects of stimulation, the number of electrical stimulation events and the subjective manual stimulation scores were used as covariates in all analyses.

Blood/Tissue Sampling and Hormone Assays

At the end of experimental trials, mice were rapidly decapitated and trunk blood was collected in 1.5-mL microcentrifuge tubes containing no anticoagulant. Decapitation was judged the best means of sampling because it was the fastest (time from end of trial to decapitation ranged from 11–60 s, with a mean of 28 s) and most humane means of obtaining relatively large samples for hormone assays. Anesthesia was not used because it may affect hormone levels (40).

Blood samples were immediately centrifuged at 1600 × *g* for 3.5 min, and serum was stored at −80°C until hormone assays were performed. CORT was measured by radioimmunoassay in the Protein and Steroid Hormone Assay Labs at the Wisconsin Regional Primate Research Center. Carcasses were frozen and, at a later date, right and left adrenal glands were dissected free and weighed to the nearest 0.1 mg.

Statistical Analyses

The primary goals of this study were to examine the time course and sex differences of serum CORT levels. A priori, we expected CORT levels to rise and then plateau (and possibly decline) at longer exercise times. Inspection of the data (see Fig. 3) and preliminary analyses indicated that the simplest model that adequately described the data was one in which CORT levels were log transformed and the relationship with length of exercise was fit by a second-degree polynomial. Hence, data were analyzed by analysis of covariance: sex was a dummy variable; time and z-transformed time squared were covariates. All three of these terms turned out to be highly statistically significant. This basic model was then used as a baseline to test for possible effects of additional covariates, including the subjective score for amount of manual stimulation, the logarithm of the number of (apparent) electrical stimuli, time of day at the start of the treadmill exercise, squared time of day, body mass, and mean adrenal gland mass (either absolute or relative to body mass). Number of fecal boluses was also analyzed as a dependent variable, following the foregoing strategy. All analyses were conducted with the SPSS/PC+ version 5.0 ANOVA or REGRESSION procedures.

RESULTS

As shown in Fig. 1, masses of right and left adrenal glands were positively correlated ($n = 64$, $r = 0.692$, two-tailed $p < 0.001$; females, $r = 0.524$, $p = 0.002$; males, $r = 0.297$, $p = 0.099$). In both sexes, however, the left adrenal tended to be larger than the right (paired $t = 0.566$, $p < 0.001$; females, $t = 0.392$, $p < 0.001$; males, $t = 4.02$, $p = 0.001$). Females had larger adrenal glands, both in absolute terms (Fig. 1) and relative to body mass (Fig. 2). Figure 2 also shows that males were larger in body mass than females.

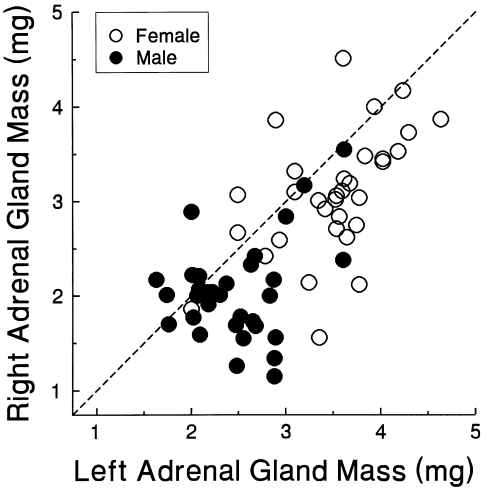


FIG. 1. Relationship between right and left adrenal gland mass.

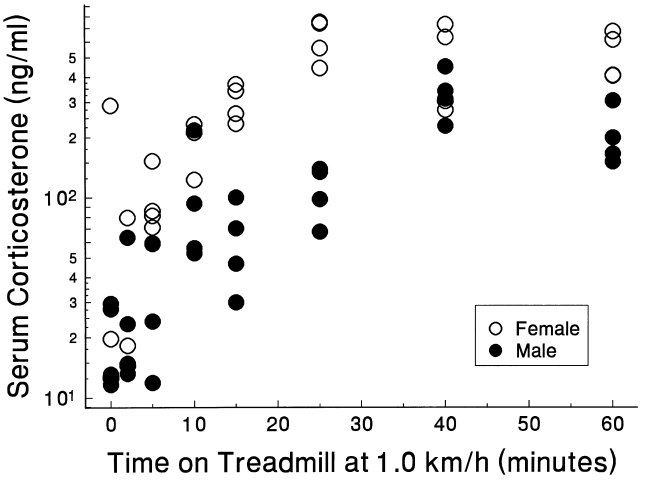


FIG. 3. Serum corticosterone levels in relation to length of treadmill exercise.

Figure 3 shows serum CORT levels as a function of time spent exercising on the treadmill. With one exception (a female with 288.12 ng/mL), values for resting animals were in the range 11.6–29.5 ng/mL (mean = 18.1, SE = 2.90). As expected, values for exercised animals were higher than for resting animals, and females tended to have higher values than males. Values for females reached a plateau by 25 min, but values for males did not plateau until 40 min.

On the basis of inspection of Fig. 3, we first analyzed data with a relatively simple model, including sex as a main effect and both time on treadmill and squared time on treadmill as covariates. Analysis of covariance on log-transformed data indicated a highly significant effect of sex (females higher $F(1, 60) = 28.6$, $p < 0.001$), time on treadmill (positive: $F(1, 60) = 137.9$, $p < 0.001$), and time^2 (negative, indicating that a plateau was reached: $F(1, 60) = 38.6$, $p < 0.001$). Results were similar when the one high 0-time individual was deleted from the data set: sex ($F(1, 59) = 28.3$, $p < 0.001$), time on treadmill ($F(1, 59) = 172.8$, $p < 0.001$), and time^2 ($F(1, 59) = 51.1$, $p < 0.001$).

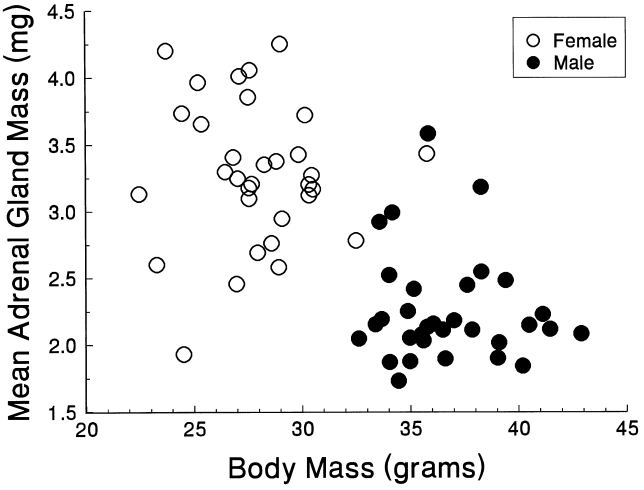


FIG. 2. Adrenal gland mass in relation to body mass.

More complicated models were also analyzed. Various combinations of several additional covariates were added to the model described in the previous paragraph. These additional covariates were the subjective score of amount of manual stimulation, the logarithm of the number of (apparent) electrical stimuli, time of day at the start of the treadmill exercise, squared time of day, body mass, and mean adrenal gland mass (either absolute or relative to body mass). None of these covariates was ever statistically significant at $p < 0.05$. Figure 4 shows the absence of a relationship between residual $\log_{10}$ serum CORT concentration and time of day.

Figure 3 suggests that the rate of increase in serum CORT levels was higher in females than in males. To test this, we excluded both males and females at 60 min and females at 40 min, i.e., after the plateaus had occurred, as well as the one female with high 0-time CORT. We then regressed log CORT on time on treadmill plus a cross-products term computed as time multiplied

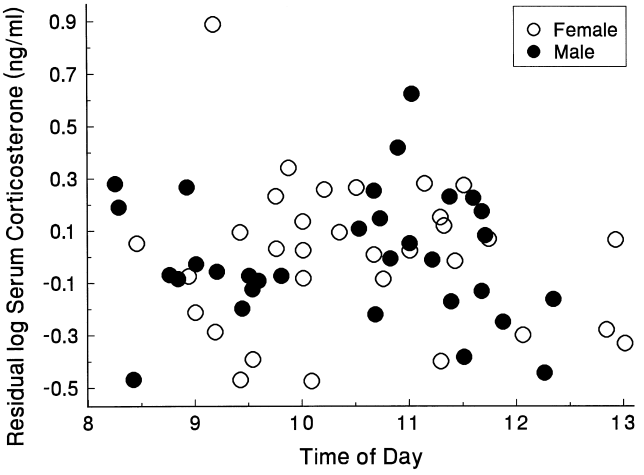


FIG. 4. Plot of residual $\log_{10}$ serum corticosterone versus time of day at sacrifice; no statistically significant relationship exists. For this figure, residuals were computed from a model containing eight dummy variables, one for sex and seven for length of exercise (as compared with resting levels).

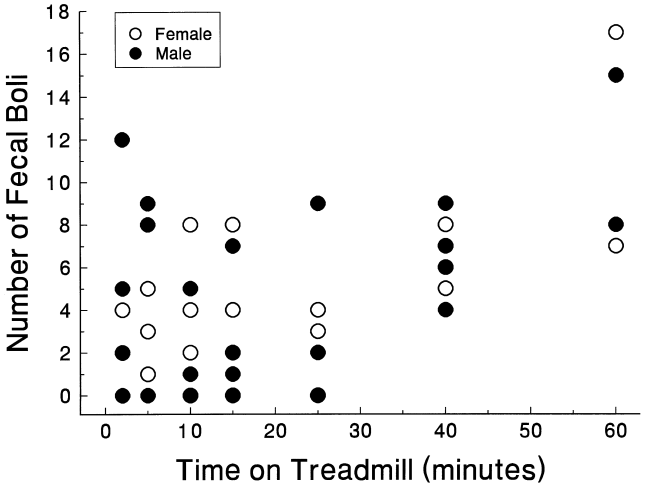


FIG. 5. Relationship between number of fecal boluses produced during a treadmill exercise trial and length of trial.

by the 0–1 dummy variable for sex. This model includes a common *Y*-intercept for the two sexes, an increase in CORT with time on treadmill, and a different slope between the sexes. The slope difference was statistically significant ($n = 51$, $F(1, 48) = 52.2$, $p < 0.0001$); thus, serum CORT levels increased more rapidly in response to forced exercise in females than in males.

Figure 5 shows the relationship between the number of fecal boluses produced and time on the treadmill. Analysis of covariance indicated a highly significant effect of time on treadmill (positive: $F(1, 51) = 7.8$, $p = 0.007$), time on treadmill squared (positive: $F(1, 51) = 8.2$, $p = 0.006$), and time of day at which the trial started (positive: $F(1, 51) = 8.9$ $p = 0.004$), but not of sex ($F(1, 51) = 0.2$, $p = 0.655$). Several additional covariates were tested and found not to be statistically significant predictors of number of fecal boluses (subjective score of amount of manual stimulation, logarithm of the number of electrical stimuli, squared time of day, body mass).

Finally, we tested for a correlation between log serum CORT level and fecal bolus production at the individual level. After controlling for effects of sex and length of exercise, we found no relationship between serum CORT levels and fecal bolus production on an individual basis (Fig. 6). This lack of relationship also held within each of the seven different exercise-length groups (all two-tailed $p > 0.19$).

DISCUSSION

Because serum CORT levels increase in response to both stressors and exercise (see ''Introduction''), it is important to consider what, exactly, our experimental protocol elicited. We presumed that the 2 days of exposure to and training on the treadmill would reduce, if not eliminate, effects of novelty in the treadmill environment, and hence reduce psychological stress [but see (30,31) on sensitization]. In addition, we also recorded the number of fecal boluses produced during experimental trials (9,18,62) because defecation is frequently interpreted as a measure of ''emotionality'' in novel and/or stressful situations [as in open-field tests, e.g., (7,2,67,17)].

Fecal bolus production increased only after 25 min of treadmill running, and no sex difference was apparent (Fig. 5). This pattern is very different from that exhibited by serum CORT levels, which rose more rapidly, then reached a plateau that was significantly higher in females than in males (Fig. 3). Moreover, we found no relationship between serum CORT levels and fecal bolus production on an individual basis (Fig. 6). This is in contrast to studies of rats that have found a consistent positive relationship between fecal production during open-field tests (and other stressors) and serum CORT levels at the end of the test (typically 10-min in duration) (22,23). Indeed, (24) concluded that ''Defecation score was . . . a valid parameter; it could be indicated as a barometer for [plasma] corticosterone''concentration at the end of a 10-min open-field exposure. Also, (23) concluded that ''Defecation score has once again been shown as another valuable parameter for the determination of stress experienced by an animal, reflecting very consistently differences observed in stress-hormone plasma concentrations.''In our mice, we found no relationship between serum CORT and fecal boluses after 10-min of exercise ($n = 8$, $r = -0.151$) or for the entire data set (Fig. 6). In summary, the difference in response pattern between fecal bolus production (Fig. 5) and serum CORT levels (Fig. 3) and the lack of correlation on an individual basis (Fig. 6) both suggest that serum CORT levels, as measured in our protocol, do not simply reflect a stress response to novelty. Instead, by elimination, serum CORT levels measured herein would seem chiefly to indicate a response to exercise.

Our serum CORT values for mice not run on the treadmill are comparable with, or somewhat lower than, resting values reported in other studies of laboratory house mice (e.g., 5,15,26,30–32, 43,72). Our highest values for exercised females are similar to the highest values reported for electrically shocked female house mice (30).

Time Course of Glucocorticoid Response

This study is, to our knowledge, the first attempt to establish a time course for the glucocorticoid response to exercise in house mice. Serum CORT rose from resting levels of about 18 ng/mL to a maximum of 621 ng/mL in females at 25 min (34 times resting levels) and 332 ng/mL in males at 40 min (18 times resting levels). This information will facilitate future comparisons of groups of house mice that differ genetically or with respect to physical conditioning, housing or other environmental conditions (13,15,20,58,71).

One study of male rats showed a time course similar to that observed here (Fig. 3), with a flattening of the curve beginning at

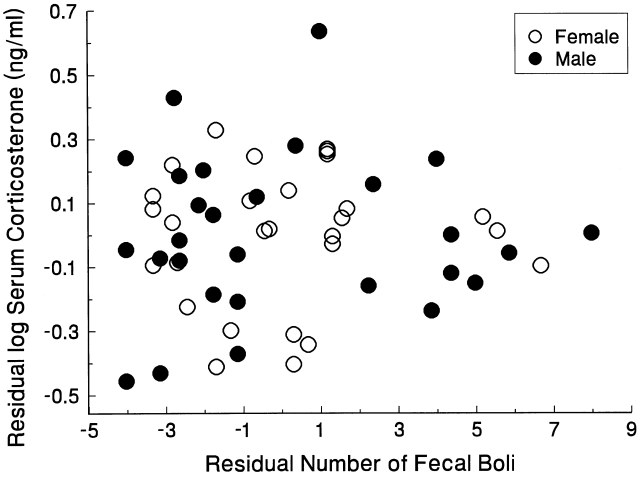


FIG. 6. Absence of relationship between residual $\log_{10}$ serum corticosterone (as in Fig. 4) and residual fecal bolus production. For both variables, residuals were produced by a regression on seven dummy variables, one for sex and six for length of exercise as compared with 2-min values (0-time values were excluded; time of day was not a significant predictor of fecal production once the length of exercise dummy variables were considered).

about 30 min of exercise (71), and norepinephrine and epinephrine showed a similar time course. Because that study and several others (27,38,69) suggest that training affects (often reduces) hormonal response to exercise, we studied untrained mice.

The time course of glucocorticoid responses to exercise has also been studied in dogs and humans. Levels of cortisol, ACTH, β-endorphin, epinephrine, and norepinephrine were studied in cerebrospinal fluid of dogs exercising on a treadmill at two intensities (49). At both intensities, plasma cortisol levels rose steadily for 90 min, with no obvious plateau, at which time exercise was terminated. Although exercise intensity in terms of percent $\dot{V}O_2$max was not reported (49), the relative exercise intensity of their low- and high-intensity exercise groups probably bracket the intensity used herein (see ''Materials and Methods''). Thus, the glucocorticoid response curve to treadmill exercise appears to occur more rapidly and to peak earlier in mice than in dogs. Humans show somewhat variable plasma cortisol responses that are affected by both intensity and duration of exercise (55,57). Typically, plasma cortisol levels peak within approximately 30 min of high intensity treadmill running and within 45 min of moderate intensity running (41). In any case, comparisons of our results with those for dogs and humans are problematic because house mice are much smaller and have lower mass-specific metabolic rates, in addition to being only distantly related (21).

Temporal Effects on Serum Corticosterone Levels

In many mammals, resting glucocorticoid secretion shows a diurnal rhythm (1,10,39,42,48,68). In nocturnal rodents, this pattern shows a peak that corresponds to the beginning of the dark period, when activity is generally greatest (42). The lowest glucocorticoid concentrations occur near the end of the dark period or the beginning of the light period, when nocturnal rodents are least active (42). In rats, this low glucocorticoid concentration persists for several hours (42).

To minimize effects of diurnal rhythms, we performed experiments during a restricted time period. Specifically, we chose the first 5 h (Fig. 4) after the onset of the light phase, which corresponds to an expected period of low glucocorticoid concentration in laboratory rats (42). In addition, experimental trials of different lengths were randomized with respect to time of day. Time of day did not have a statistically significant effect on serum CORT levels during treadmill running, and a plot of residual log CORT concentration in relation to time of day (Fig. 4) suggests no consistent effect of time of day. Therefore, within the 5-h period covered by our experiments, circadian secretion rhythms appear not to have had an important influence on CORT levels in response to treadmill exercise.

Sex Differences and Adrenal Gland Asymmetry

In this study, left adrenals were larger than right adrenals in both sexes (Fig. 1). This observation is consistent with a large body of data on other mammalian species (35).

Previous studies have addressed sex differences in the glucocorticoid responses to exercise in humans (55,54), but we are unaware of such studies in rodents. We found that female house mice respond significantly more rapidly and have higher levels of serum CORT after various periods of treadmill running, as compared with males. For females, Fig. 3 indicates a plateau after about 25 min of exercise, whereas in males the plateau occurs later, around 40 min. Our ongoing studies have also shown that females run significantly more than males when given access to activity wheels [unpublished results, see also (46)]. Whether the sex difference in corticosterone response to moderate-intensity exercise is related to the sex difference in wheel running is unclear, but 1.0 km/h (as studied herein) is similar to the speed of mice running voluntarily on wheels in our laboratory [(13) and unpublished results].

In house mice, females have been reported to exhibit higher plasma CORT levels than males under resting conditions and in response to various stressors, including novelty and electrical shock (30). In rats, females also exhibit higher resting CORT levels and higher maximal CORT levels in response to novelty and ether stress than do males (6). In golden hamsters, on the other hand, which are less closely related to house mice, males exhibit higher levels of glucocorticoids (22), which appears to be attributable to unusual effects of testosterone on the HPA axis (22,34). Determining whether these differences are adaptive (e.g., related to variation in social structure or mating system) or possibly fall out along phylogenetic lines (e.g., *Mus* and *Rattus* are more closely related to each other than to hamsters) will require additional comparative studies (21,44).

What accounts for the sex differences in CORT levels observed herein? One obvious possibility is the larger adrenal glands of females, both in absolute size and relative to body mass (Fig. 2), although direct and indirect effects of gonadal hormones are another possibility (30,37). Sex differences in adrenal size and histology in mice, other rodents, and other mammals have been reported previously [(8,37,59) and Table I in (35)]. However, females are not always the sex with larger adrenals. In golden hamsters, for instance, males have larger adrenals (34).

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