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ORIGINAL ARTICLE

Day-to-day variability in voluntary wheel running among genetically differentiated lines of mice that vary in activity level

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Abstract This study examined the day-to-day variability in voluntary wheel-running behavior among three genetically distinct lines of young male and female mice. Daily wheel revolutions were recorded at an age of 6–8 weeks in 10 males and 10 females from each of 3 lines: selectively bred line for high wheel running (Line 8), selectively bred for high wheel-running activity and fixed for a Mendelian recessive allele that reduces hind-limb muscle mass by 50% (Line 3), non-selected control (Line 2). There were significant mean differences in revolutions/day among weeks ($P = 0.003$), but the effect size was small (10%). Significant main effects for wheel running were also revealed for *sex* and *line* ($P < 0.001$). The grand mean ± SD for the coefficient of variation (CV) of intra-individual wheel running was 23.0 ± 10.8%. Although a significant main effect for the CV was found for *week*, the effect size was low (7%) (age 6 weeks, 23.4 ± 10.9%; age 7 weeks, 25.1 ± 13.2%; age 8 weeks, 20.1 ± 7.8%). The overall mean CV was similar between females (21.4 ± 9.8%) and males (24.4 ± 12.0%) and among lines (Line 2, 23.4 ± 9.8%; Line 3, 20.4 ± 7.6%; and Line 8, 25.0 ± 14.4%). These findings are consistent with our previous work in young humans and lend further support for the hypothesis that biological mechanisms influence daily levels of physical activity.

Keywords Activitystat · Energy expenditure · Exercise, experimental evolution · Physical activity · Variability

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Introduction

Habitual, free-living physical activity is an important component of total energy expenditure and energy regulation. The phenotypic variation in physical activity behavior, at least in humans, has been studied from several aspects, including sex, race, geographic, and seasonal effects (Sallis et al. 2000; Westerterp and Speakman 2008). In the past few years, we have pursued a better understanding of the phenotypic variation in the habitual, free-living locomotor activity and energy expenditure phenotypes among human children and adolescents (Wickel and Eisenmann 2006, 2007a, b; Wickel et al. 2007). In so doing, we have included reports on the day-to-day variability using a variety of physical activity assessment tools (activity diaries, pedometers, and accelerometers) (Wickel and Eisenmann 2006; Wickel et al. 2007). In general, the results show small differences in the mean day-to-day physical activity levels and a mean coefficient of variation (CV) of daily physical activity that approximates 25%. Furthermore, these results are independent of age, sex, and geographic location. For example, the mean CV of locomotor behavior

as determined by pedometer steps per day was similar among males and females ages of 6–12 years from Australia, United States, and Sweden (Wickel et al. 2007). In addition, it was recently shown that the CV for accelerometry activity counts approximated 23% among 11–12 year old British children over 3 measurement periods within 1 year (Mattocks et al. 2007). We are intrigued by the consistent nature of the CV for locomotor behavior across studies and irrespective of sex, age, country, season, etc., and we interpret these findings as evidence for a biological basis for locomotor behavior (and energy regulation) during the first two decades of human life.

In this paper, we attempt to extend our previous research on young human beings by examining the day-to-day variability in wheel-running behavior among young male and female mice from three genetically differentiated lines: (1) control, (2) selected for high voluntary wheel running, and (3) selected for high wheel running and fixed for a Mendelian recessive allele that causes a 50% reduction in hind-limb muscle mass (i.e., mini-muscle) (Garland et al. 2002; Girard et al. 2001; Hannon et al. 2008; Middleton et al. 2008; Swallow et al. 1998, 1999). Although the gene that underlies the mini-muscle phenotype has not yet been identified, it has been fine-mapped to a 2.6335-Mb interval on MMU11. This region harbors ~100 expressed or predicted genes, many of which have known roles in muscle development or function (Hartmann et al. 2008).

The present study represents a novel approach to expanding our understanding of the development of the physical activity phenotype because the animals used herein were selectively bred for the trait of interest (i.e., voluntary physical activity). More specifically, the mice selectively bred for high voluntary wheel running provide the opportunity to test the hypothesis in a group of animals known to exhibit extraordinarily high levels of physical activity. Therefore if they display a similar CV across days, then it suggests that the mechanism controlling physical activity levels on a daily or weekly basis is similar not only across species but also among genetically differentiated populations that vary in activity level. We hypothesized that the day-to-day variability in wheel revolutions would be similar between males and females and among the three lines. If the CV of voluntary physical activity in control mice and those selectively bred for high wheel running are similar to those found in human populations, then it provides an important observation for future studies aimed at understanding the biological basis for this variation in free-living habitual physical activity levels. Results of the present study are important for basic understanding of the relation of physical activity to energy balance and obesity, as well as elucidating reasons for the success versus failure of physical activity/exercise interventions commonly employed in schools.

Methods

Experimental animals and study design

Mice used in this study were sampled from generation 43 of a long-term artificial selection experiment for high voluntary wheel running. Full details of the selection experiment are provided elsewhere (Swallow et al. 1998). In brief, the mice were originally derived from the outbred, genetically variable Hsd:ICR strain (Harlan-Sprague-Dawley, Indianapolis, IN). Mice were randomly mated for two generations, paired, and assigned to eight closed lines (10 pairs in each line). In each successive generation, when the offspring were 6–8 weeks old, they were housed individually with Wahman-type running wheels (circumference 1.12 m) for 6 days. Daily wheel-running activity was monitored with a computer-automated system. Wheel running was quantified as the total number of revolutions on days 5 and 6. In the "selected" lines (S), the highest-running male and female were chosen from each family as breeders. In the "control" lines (C), a male and female were randomly chosen from each family. Within all lines the chosen breeders were randomly paired, except that sibling matings were disallowed.

For the current investigation, a total of 59 (29 males, 30 females) mice from three separate lines (lab-designated Lines 2, 3, and 8) were analyzed. Line 2 is a control line, not selectively bred for high wheel-running behavior. Line 3 is a selected line, fixed for a Mendelian recessive allele that reduces hind-limb muscle mass by ~50% (Garland et al. 2002). Line 8 is another selected line for high wheel-running behavior, but with normal muscles. Ten males and 10 females were from each line. These 20 mice/line came from 10 families, i.e., 1 male and 1 female from each family (with the exception of Line 3, where one family had two males and two females chosen). Mice were randomly chosen at weaning (21 days of age) and placed directly into a cage with a wheel attached but blocked. One male in Line 8 died early in the study. All mice were granted access to the running wheel on 16 September 2005, at approximately 35 days of age. We were most interested in the day-to-day variation around the age at which the selective breeding protocol is routinely applied (Swallow et al. 1998), and therefore we analyzed running at 6–8 weeks (42–63 days) of age. In general, this approximates late adolescence/young adulthood in humans (Tanner 1962).

Rooms housing the animals were controlled for temperature (~22°C) and photoperiod 12/12 h light/dark cycle (lights on at 0700). All mice were provided standard chow (Harlan Teklad Rodent Diet 8604) and water ad libitum. The study was approved by the University of California, Riverside IACUC, and all procedures were consistent with guidelines in the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

Table 1 Descriptive characteristics separated by sex and line

	Line 2		Line 3		Line 8		Total	
	Male (n = 10)	Female (n = 10)	Male (n = 10)	Female (n = 10)	Male (n = 9)	Female (n = 10)	Male (n = 29)	Female (n = 30)
Week 6 (42–48 days old)								
Mean rev/day	3,632 ± 2,457	8,344 ± 2,718	12,733 ± 3,315	18,358 ± 5,287	11,630 ± 6,639	14,696 ± 5,422	9,252 ± 5,958	13,800 ± 6,148
Mean CV (%)	24.6 ± 12.7	25.3 ± 12.0	22.2 ± 6.9	15.1 ± 5.9	22.8 ± 13.6	30.4 ± 8.5	23.2 ± 11.0	23.6 ± 10.9
Min-max	12.5–52.9	7.8–54.9	13.5–36.0	6.2–28.9	5.9–45.5	16.6–47.8	5.9–52.9	6.2–54.9
Week 7 (49–55 days old)								
Mean rev/day	4,111 ± 2,428	8,802 ± 3,118	13,458 ± 3,178	18,752 ± 5,448	11,709 ± 5,564	14,045 ± 5,568	9,692 ± 5,611	13,866 ± 6,240
Mean CV (%)	25.1 ± 12.5	24.5 ± 6.0	27.7 ± 6.2	18.9 ± 8.9	31.0 ± 25.5	24.1 ± 12.2	27.8 ± 16.0	22.5 ± 9.4
Min-max	10.9–51.6	10.2–30.3	16.2–34.2	8.5–31.4	10.5–90.4	8.7–49.3	10.5–90.4	8.5–49.3
Week 8 (56–62 days old)								
Mean rev/day	4,938 ± 2,819	9,128 ± 3,199	13,638 ± 2,990	19,300 ± 6,133	13,717 ± 5,463	15,254 ± 4,885	10,663 ± 5,641	14,561 ± 6,352
Mean CV (%)	20.3 ± 6.9	20.6 ± 7.2	21.7 ± 4.7	16.6 ± 6.5	24.3 ± 9.0	17.6 ± 10.9	22.0 ± 6.9	18.3 ± 8.3
Min-max	11.4–32.2	11.6–34.2	13.8–27.0	9.7–31.6	9.9–37.1	5.5–44.4	9.9–37.1	5.5–44.4
Total (Weeks 6–8)								
Mean rev/day	4,226 ± 2,543	8,758 ± 2,931	13,276 ± 3,078	18,803 ± 5,451	12,351 ± 5,765	15,253 ± 4,884	9,868 ± 5,702	14,075 ± 6,186
Mean CV (%)	23.3 ± 10.9	23.4 ± 8.7	23.9 ± 6.4	16.9 ± 7.1	26.0 ± 17.1	24.0 ± 11.5	24.4 ± 12.0	21.4 ± 9.8
Min-max	15.4–30.6	9.9–37.7	19.5–32.4	11.3–30.5	10.5–43.0	15.0–47.2	10.5–43.0	9.9–47.2

See "Results" section for significant main effects and interactions. Values are mean ± SD and minimum and maximum for the coefficient of variation (CV)

Assessment of wheel-running behavior

As described above, animals were housed individually with Wahman-type running wheels (circumference 1.12 m). Wheel-running activity was monitored daily during 6 through 8 weeks of age with a computer-automated system and expressed as revolutions/day (Swallow et al. 1998, 1999). Mean weekly levels of physical activity (revolutions/day) were calculated for individual animals.

Statistical analysis

Two-way (*sex* × *line*) repeated-measures analysis of variance (RMANOVA) was used to examine the mean difference in revolutions/day and CV. Specific mean differences between groups were further explored using Bonferroni post hoc tests. The effect size (ES) was calculated using partial eta squared to determine the meaningfulness of results. The CV was calculated for each individual [CV = (SD/mean)100] to describe the day-to-day variability within an individual. A relatively low CV suggests that daily wheel-running behavior is consistent, while a relatively high CV implies that wheel running is quite variable among days. Data analysis was conducted with SPSS v. 14.0. An alpha level of 0.05 was used for judging statistical significance.

Results

Descriptive statistics (mean ± SD) are presented in Table 1 according to line, sex, and week. The RMANOVA revealed significant mean differences in revolutions/day among weeks [$F(2,106) = 6.0$, $P = 0.003$, effect size (ES) = 0.10]. Pair-wise comparisons indicated that the mean revolutions/day were lower during week 6 (11,565 ± 6,426) and week 7 (11,812 ± 6,252) as compared to week 8 (12,665 ± 6,276) ($P < 0.05$). However, the ES is relatively low and suggests that only 10% of the variance in revolutions/day could be explained by the specific week. A significant main effect in revolutions/day was revealed for *sex* [$F(1,53) = 14.2$, $P < 0.001$, ES = 0.21] and *line* [$F(2,53) = 27.7$, $P < 0.001$, ES = 0.51]. Mean revolutions/day were higher among female mice (14,075 ± 6,186) compared to male mice (9,869 ± 5,702). This trend (female > male) in revolutions/day was observed within each line (2, 3, and 8) and at each weekly interval (weeks 6, 7, and 8) ($P < 0.05$). Significant mean differences in revolutions/day were found among lines (Line 2: 6,492 ± 3,553; Line 3: 16,040 ± 5,199; Line 8: 13,569 ± 5,519). Revolutions/day were significantly lower in Line 2 compared to Lines 3 and 8 ($P < 0.01$), while revolutions/day were significantly higher in Line 3 (fixed for the mini-muscle gene) compared to Line 8 ($P < 0.01$). Figure 1 shows individual raw data for "representative" mice from each of the three

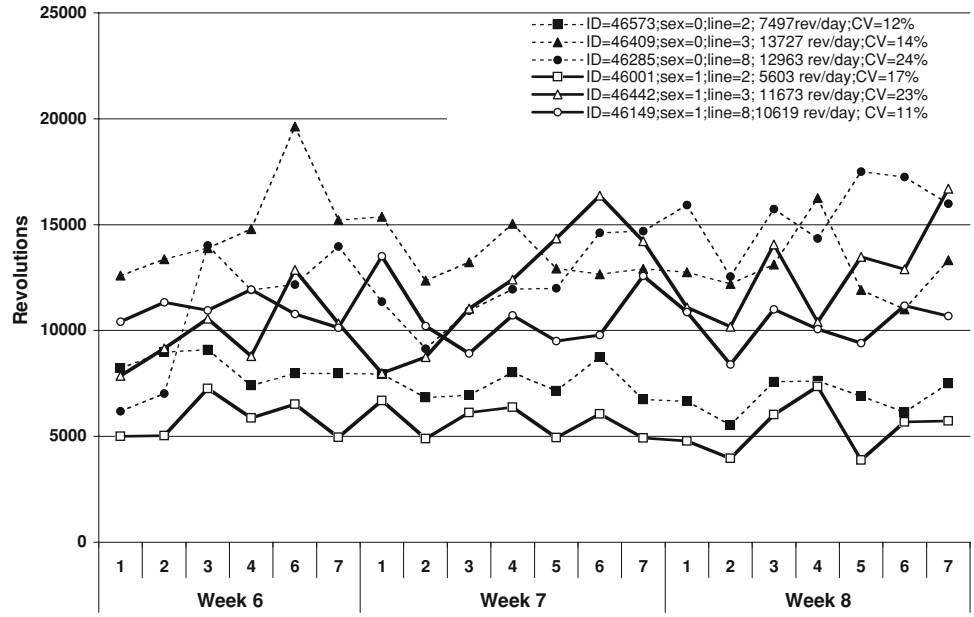

Fig. 1 Individual raw data for a representative male and female mouse from each of the 3 lines over a 21-day period (6–8 weeks of age). Sex = 0, females; sex = 1, males; Line 2 = control line, not selectively bred for high wheel-running behavior; Line 3 = selected line, fixed for a Mendelian recessive allele that reduces hind-limb muscle mass by ~50%; Line 8 = selected line, but with normal muscles

lines over the 21 days (weeks 6–8 of age) reported herein.

Group differences in the mean CV and the minimum and maximum values are also shown in Table 1. The grand mean ± SD for CV was 23.0% ± 10.8. A significant main effect for CV was found for *week* [$F(2,159) = 4.2$, $P = 0.02$]. The mean CV was higher in week 6 (23.4% ± 10.9) and week 7 (25.1% ± 13.2) compared to week 8 (20.1% ± 7.8); however, the ES was 0.07 indicating that approximately 7% of the variance could be attributed to a particular week. The overall mean CV was similar between females (21.4% ± 9.8) and males (24.4% ± 12.0) [$F(1,53) = 2.4$, $P = 0.13$] and among lines (Line 2, 23.4% ± 9.8; Line 3, 20.4% ± 7.6; and Line 8, 25.0% ± 14.4) [$F(2,53) = 2.0$, $P = 0.14$). None of the interaction terms were significant for either dependent variable (revolutions/day or the CV).

Discussion

Although day-to-day variation in such traits as resting metabolic rate (Haugen et al. 2003) and blood pressure (Iberall 1984) have been examined, few studies have addressed the fundamental question of how much natural, intra-individual, day-to-day variability occurs in physical activity of non-human animals. Examining the day-to-day variability in habitual locomotor activity is a fundamental aspect of better understanding the physical activity/energy expenditure phenotype, and may also shed light on the biological basis of physical activity (Rowland 1998). The results here support the hypothesis that the intra-individual variation in locomotor behavior as determined by wheel running is similar between sexes and among three genetically differentiated lines of house mice, and is also similar to our previous results in human children, adolescents, and young adults using a variety of tools to assess habitual physical activity (Wickel and Eisenmann 2006; Wickel et al. 2007).

Previous studies of these lines of mice from earlier generations have demonstrated that daily wheel-running distances increase for approximately 5 weeks following first exposure to wheels at weaning (3 weeks of age) or shortly thereafter (Swallow et al. 1999; Morgan et al. 2003). In the present study, we analyzed data from a later generation and considered weeks 3–5 of wheel access (6–8 weeks of age), in order to parallel our previous studies of human adolescents and young adults (Wickel and Eisenmann 2006, 2007a, b; Wickel et al. 2007). As interest in examining the CV of individual values for daily activity levels in human beings occurred after publication of the previous papers on these lines of mice, they did not present such statistics. Given that the age-related changes in wheel running had previously been described for these lines of mice from earlier generations, we focus our attention on the intra-individual variability in wheel-running behavior across time.

The mean difference between weeks 6 and 8 was 1,100 revolutions/day and statistically significant, but the effect size was small (0.10). As expected for mice of this age, some increase in physical activity level occurs as they are still undergoing physical maturation (Swallow et al. 1999; Morgan et al. 2003). This age-related trend makes it difficult to interpret the daily variability in raw wheel revolutions with respect to normal maturation versus inherent control (regulation) of physical activity level. However, examination of the CV (=SD/mean) for each week allows us to account for maturational changes by standardizing for

mean differences within a given week. Indeed, the overall mean day-to-day CV in wheel running for all animals was approximately 23% during each of the 3 weeks; thus, the week-to-week variability in wheel running remains consistent at approximately 23%. However, we also acknowledge the inter-individual variability in CV as well (see minimum and maximum values in Table 1).

The mean CV was also comparable between sexes and among lines. To our knowledge, no other study of non-human animals provides similar data for comparison [although other studies have reported CVs for single days of wheel running, e.g., (Friedman et al. 1992)]. This mean CV is comparable with previous studies of physical activity of human children and adolescents (Mattocks et al. 2007; Wickel et al. 2007). For example, we observed an absolute mean difference in pedometer steps per day that ranged from 55 to 958 steps, and the mean CV was similar across three separate countries (US, 22.1%; Sweden, 22.5%; Australia, 21.8%) and between sexes (boys, 21.2%; girls, 22.7%). And, similar to the results here, there were no statistically significant interactions. More specifically, there were no statistically significant interactions in the results described above for human children (age × country × sex) or in the results for the mice studied here (age in weeks × line × sex). Recently, Wilkin and colleagues (Wilkin et al. 2006) have used a myriad of results to support the hypothesis of central biological regulation of physical activity in children, including: (a) no difference between weekday/weekend day and year-on-year activities; (b) no significant difference in total activity among three groups of schoolchildren from (1) private preparatory school in which 9 h per week of physical education, (2) school in a village which participated in a physical activity promotion program in which there were 2 h per week of physical education, and (3) inner city school receiving 2 h physical education per week, despite a fivefold variation in timetabled physical education; (c) no difference in total activity between children that walked to school and those that did not walk to school; and (d) weekly activity recorded by children in Plymouth was the same as that recorded in Glasgow, 800 km away. Although these results show no mean differences in physical activity in a variety of settings and populations, in many ways the hypothesis still remains to be tested. For example, what happens to the physical activity level of an individual when he/she is moved from one situation to another?

One consideration regarding the expression of habitual physical activity by wheel-running revolutions per day and linking it to evidence for a biological basis for locomotor behavior and energy regulation needs some mention. The mean CV of approximately 23% for physical activity in our previous reports in human children and adolescents and for wheel running in mice reported herein is higher than those found for total daily energy expenditure in human beings. We (Wickel and Eisenmann 2006) and others (Black and Cole 2000; Goran et al. 1993) have shown a mean within-individual CV in total daily energy expenditure for free-living human males and females that approximates 12%. Maximum rate of energy assimilation in response to extreme cold exposure in mice produced a mean CV of 6.5% (Koteja et al. 2000). In the context of the present paper and its broader implications, it is important to recognize that free-living, habitual physical activity (or wheel running) is only one component of total energy expenditure and may not encompass the entire activity energy expenditure (Rezende et al. 2009, in press). More specifically, we did not consider cage activity nor the wheel-running intensity or time spent at varying intensities, all of which would impact total daily energy expenditure (Rezende et al. 2009, in press), which is hypothesized to be governed by the 'activitystat' (Rowland 1998). Importantly, mice from the selected lines exhibit elevated home-cage activity when they are housed without wheels (Malisch et al. 2009), but it is not yet known if cage activity is elevated when wheels are present. We are merely raising this point because it is important to consider that wheel running is but one component of total energy expenditure. Presently it is not known whether the control of physical activity and total energy expenditure are coupled or separate.

Although we have shown consistency in the mean CV across genetically differentiated lines of mice that vary in activity level and similarity to values previously found in diverse samples of human children, adolescents, and young adults, the intra-and inter-individual variation in CV should be recognized. Indeed, some individual animals show little daily variation, whereas others show more than a twofold variation (see Fig. 1; Table 1). The causes of this variation could include systematic and random error. Furthermore, random error exists as both analytical and biological variation. In terms of wheel-running revolutions, systematic error occurs when the measured revolutions consistently under or overestimates the true revolutions. To determine the amount of systematic error involved in wheel-running behavior, the actual number of revolutions accumulated is compared to the value obtained from the electronic wheel counts. The amount of analytical error can be reduced by using assessment tools with low inter-device variability. Assuming that the inter-instrument error between running wheels are low, it can be assumed that biological variation is the primary contributor of random variation. Biological variation, which is the main concern of the present study, occurs when the actual level of physical activity changes between measurements. Therefore, if total energy expenditure is tightly controlled, then perhaps on days of lower wheel activity there was greater home-cage activity. As previously mentioned, this could also relate to the intensity

of wheel running, if whereby lower wheel counts were exhibited on days of more intense activity of shorter duration. Another important consideration related to this topic is that the variability could suggest that some individuals possess greater inherent control of physical activity. This latter point should be further investigated, as it may have important implications for energy balance and weight gain.

In conclusion, the results found here along with findings from previous studies provide some evidence that locomotor behavior is regulated in a similar manner in young mammals of various species. Although several human studies have focused on social and environmental issues (Sallis 2000) to explain variability in physical activity, the biological basis of habitual physical activity has been largely ignored (Rowland 1998; Thorburn and Proietto 2000). Given that evidence exists for biological mechanisms controlling energy intake and resting metabolic expenditure (Keys et al. 1950), it is plausible that biological mechanisms are also operating to control habitual physical activity via an 'activitystat'. In a compelling review, Rowland (1998) provides several lines of evidence suggesting that a control center exists in the central nervous system that regulates daily energy expenditure (i.e., activitystat). In animals, support for the biological basis involves several lines of evidence, including experimentally induced lesions or administration of neuropeptides into either the forebrain or hypothalamus, which influence physical activity levels (Novak and Levine 2007), as well as results from the selective breeding experiment that supplied mice for the present study (Belke and Garland 2007; Girard et al. 2001; Rhodes et al. 2003, 2005; Vaanholt et al. 2008). Additional research is clearly warranted to explore intra-individual regulatory mechanisms of physical activity in mammals. This might include (1) more sophisticated statistical models, such as time series analysis, (2) attempts to discriminate between setpoint and critical limit models of regulation, (3) determining whether activity levels or energy expenditure are being controlled, (4) examination of possible regulation of duration versus intensity of activity, and (5) experimental perturbations of daily activity levels combined with analysis of how rapidly they return to pre-manipulation levels.

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