

The Biological Basis of Physical Activity in Children: Revisited

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Habitual physical activity among humans is a complex trait that is determined by the interaction of biological and psycho-social factors and the physical environment. The definition of *physical activity* is now accepted as “any bodily movement produced by skeletal muscles that results in a substantial increase in energy expenditure above resting metabolic rate and includes leisure time physical activity, exercise, sport, occupational work, and household and other chores” (10). Furthermore, physical activity as a whole has been broken down into the components of spontaneous (i.e., activity associated with daily living), obligatory (i.e., activity we are forced to do to survive), and voluntary (i.e., exercise; 52). In sum, these components represent the activity energy expenditure and when included with the energy cost of growth, thermic effect of food, and resting energy expenditure equal the total daily energy expenditure.

These two constructs of human movement—habitual physical and total daily energy expenditure—are of considerable interest given concerns for lack of adequate amounts of daily physical activity, energy imbalance, and the relationship between low levels of physical activity and energy expenditure with several chronic diseases (57). Among youth, physical activity plays an important role in normal growth, maturation, and development (48). Indeed, physical activity is a central concept to the field of pediatric exercise science; thus, understanding why a child is active or inactive is essential.

Although considerable attention has been placed on examining how active youth are, it is also important to understand the sources of variation, or the correlates or determinants in the physical activity phenotype (e.g., why youth are active). Malina et al. (30) have categorized the factors associated with physical activity in children and adolescents as biological, psychological, social, and the physical environment. Among these factors, the psycho-social aspects have been extensively studied and reviewed elsewhere (43), and more recent work has focused on the physical environment and, in particular, the “built environment” (42). In contrast, little attention has been devoted to understanding the biological basis of physical activity in children, which was the focus of the seminal review and commentary by Rowland 10 years ago (39). In this article, we would like to revisit Rowland’s paper and provide an update on the progress on this topic in the past 10 years. In considering the “biological determinants” of physical activity,

we imply that these factors are biologically inherent (e.g., heredity, sex, adiposity, sexual maturity, etc.). It is also our hope that revisiting the idea of a biological basis will stimulate scholars and practitioners in the field of pediatric exercise and health science to consider this topic when examining the habitual physical activity levels of young people.

A Summary of Rowland's Ideas: The Biological Basis of Physical Activity Revisited

At the time of Rowland's paper in 1998, there was considerable interest in the topic given the public health efforts with regards to habitual physical activity as evident in the Surgeon General's Report on Physical Activity and Health (57) and Centers for Disease Control and Prevention/American College of Sports Medicine physical activity recommendations (36). Rowland established his argument for an inherent control center, or activity regulatory center, within the central nervous system by asking a pertinent question: Is there any reason to believe *a priori* that biological mechanisms should exist that control the amount of one's physical movement? He provided insight into this question via the energy homeostasis concept and relates his idea of energy homeostasis to regulatory stats (temperature, pH, osmolarity, etc.) within the body and coins the term "activity stat." Furthermore, he acknowledged the evolutionary basis of energy homeostasis that is often ignored in the physical activity sciences.

To examine the scientific basis of an activity stat, Rowland identified that the hypothalamic appetite center regulates energy intake and mentions the recent identification of leptin in this process. In terms of energy expenditure, he cites the early starvation studies and its impact on basal metabolic rate (30% decrease), the well-known temporal change in physical activity with age which parallel changes in resting metabolic rate, experimental central nervous system lesions and pharmacological interventions in animals, the child with attention deficit hyperactivity disorder (ADHD), and heritability. As concluded by Rowland, "the evidence . . . leaves little doubt that a biological control center exists within the central nervous system that governs, to a certain extent, how much an individual engages in regular physical activity." The remainder of this article will provide a brief overview on papers related to this topic in the past 10 years.

Key Reviews Since 1998

Since 1998, four reviews have suggested the importance of this subject (5,34,54,55). Perhaps the strongest arguments for a biological basis of physical activity came from Bouchard and Rankinen (5) who state "Unfortunately the interest in the biological basis of physical activity does not have a long history . . . referring to the 'rooted paradigms' that psych-social and built environment factors influence physical activity levels." Bouchard and Rankinen echoed much of the same tenets as Rowland but expanded (mainly from a genetic perspective) and posited seven lines of evidence to support the hypothesis that biology plays a role in determining physical activity levels (Table 1). This evidence, along with other, will be briefly considered herein.

Table 1 Lines of Evidence Supporting the Hypothesis the Biological Basis of Physical Activity Levels. Taken From Bouchard and Rankinen, 2006.

1.	Current models that do not include biological factors account for only a moderate portion of the total variance in physical activity levels.
2.	Low adherence rates to physical activity programs.
3.	Evidence from family studies and twin studies.
4.	Estimated heritability coefficients are significant and meaningful.
5.	Genome-wide scans have identified several chromosomal regions which harbor genes and DNA sequence variation that contribute to physical activity.
6.	Association studies indicate differences in physical activity levels for a few candidate genes.
7.	Epigenetic mechanisms (e.g., maternal-fetal interactions) in animal models show altered physical activity during postnatal life.

The Age-Related Decline in Physical Activity and the Influence of Biological Maturity Status

We begin with a discussion of what Sallis (41) noted as “the most consistent finding in physical activity epidemiology”—that is, the decline in physical activity with chronological age. In particular, the decline in physical activity is quite prominent during the adolescent years. In the same series of papers, Ingram (20) stated that the evidence indicating an age-related decline in physical activity among all species suggests a biological basis of physical activity with a probable mechanism in the dopamine system given its role in the regulation of motivation for locomotion. Ingram clearly outlined evidence that shows that the age-related decline in physical activity appears to be related to altered neurotransmission involving the central dopamine system by either reduced dopamine release or loss of dopamine receptors. Aspects of the dopamine receptor system will be considered elsewhere in this paper as it relates to the genetics of physical activity.

Another consideration of the decline in physical activity during adolescence as it relates to the neuro-endocrine aspects of puberty is the neural development of the brain since it is influenced by hormones (47). Indeed, Tanner (52) suggested that puberty itself is a brain driven event. Futhermore, Malina et al. (30) have also noted that “Although many factors can exert an influence on the level of physical activity in children and adolescents, notably lacking are indicators of growth and maturity.” (p. 471). Indeed, although the decline in physical activity with chronological age is widely known, few studies have examined the maturity-related differences or maturity-related changes in physical activity during adolescence. A rationale for studying the variation in physical activity by maturity group (early, average, late) or longitudinally during puberty is that a key biological feature of the adolescent period is the maturation of the hypothalamic-pituitary-gonadal axis and the neural rewiring of the brain (47). The hypothalamic-pituitary-gonadal axis mediates the release of gonadotropins, which result in neural reorganization and rapid changes in body size and composition, both which may directly or indirectly influence physical activity.

The process of maturity varies considerably between individuals and there are obvious sex differences. Often times in studies that compare physical activity levels between boys and girls, or across age groups, the variation in biological maturation is ignored as youth are aligned according to chronological age. As mentioned above, the results from these studies consistently report an age-related decline in physical activity and higher levels of physical activity among boys compared with girls. However, when youth are aligned according to a biological age (i.e., years from peak height velocity) significant sex differences in physical activity at each age group tend to disappear (44,53). This observation demonstrates the importance of accounting for the distinct sex difference in the timing of biological maturation.

A related question is whether physical activity differs by maturity status. Romon et al. (38) grouped 10–16 yr old children by pubertal stage (e.g., Tanner stages) and reported pedometer steps/day to be greater among boys in Tanner stage 1 (mean = 10,509 steps/day) compared with Tanner stage 5 (mean = 8103 steps/day); however, the boys in Tanner stage 5 were also older, and thus the difference in physical activity (steps/day) may be age- and/or size-related rather than

maturity-related. We have recently examined this issue in three separate samples of youth. In our studies, maturity status was estimated within each gender based on their predicted age at peak height velocity obtained from the maturity offset method (32). In one study, mean pedometer steps were compared between early, average, and late maturing boys ($n = 65$) and girls ($n = 74$) aged 13–14 yrs (61). This limited age range was selected because of the considerable variability in pubertal status at this chronological age. Results indicated no significant mean differences in physical activity between maturity groups. However, we did observe a step-wise trend among early (12,427 steps/day, $n = 6$), average (9982 steps/day, $n = 62$), and late maturing girls (8642 steps/day, $n = 6$) but this did not reach statistical significance due to small sample size ($n = 6$ for early and late maturers). This result is opposite of the hypothesized direction and may be due to the small sample size as we have recently shown significant maturity group differences with early maturing girls showing lower activity levels compared with average or late maturers in a larger sample of younger girls (mean age = 10.3 years; Drenowatz et al., in press). These results were significant when controlling for leg length; however, when controlling for BMI, differences in mean steps per day by maturity group were no longer significant perhaps suggesting either psycho-social and/or biological factors are involved. In a subsequent study of 161 (76 boys, 85 girls) 9–14 yr olds using an accelerometer to capture moderate-to-vigorous physical activity there were no significant mean differences in moderate-to-vigorous physical activity between early, average, and late maturing boys and girls (64).

The cross-sectional design used in studies mentioned above does not allow for the examination of the effect that biological maturation has on subsequent levels of physical activity. Some insight into this question can be gained from a recent longitudinal study of 143 girls (1). In this study, girls at age 11 were classified as early ($n = 41$) or later maturers ($n = 102$) according to a composite maturity measure based on blood estradiol levels, Tanner breast staging criteria, and parental report of pubertal development. At baseline, early-maturing girls had significantly lower self-reported levels of physical activity compared with their later maturing counterparts. This trend was also observed when physical activity levels were reassessed two years later. At age 13, early maturing girls accumulated fewer minutes of moderate-to-vigorous physical activity, vigorous physical activity, and accelerometer counts per day compared with later maturing girls. Early-maturing girls had significantly lower self-reported physical activity and accumulated fewer minutes of moderate to vigorous (31 ± 12 v. 38 ± 16) and vigorous physical activity (3 ± 2 min/day v. 5 ± 5 min/day) and accelerometer counts per day at age 13 than later maturing girls. Although the mean moderate physical activity was five minutes per day lower (28 ± 10 v. 33 ± 12 min/d), the results were not significantly different. These effects were independent of differences in percentage body fat and self-reported physical activity at age 11. In a subsequent publication, the authors addressed if the reason for the lower physical activity of the early maturing girls was due to psychological factors (15). Using structural equation modeling, they showed that more advanced pubertal development at age 11 was associated with lower psychological well-being at age 13, which predicted lower enjoyment of physical activity at age 13 and in turn lower moderate-to-vigorous physical activity. Although the results and psycho-social aspects of maturity and physical activity should not be discounted, biological factors were largely ignored by the authors.

Given the paucity of data, continued work on the age- and maturity-related changes in physical activity are warranted. Although comparing physical activity levels between maturity groups provides some initial insight into the role of biological maturation, additional studies are needed throughout the entire adolescent period to examine changes in neuroendocrine anatomy and physiology and biomarkers with maturation and how this may influence the “activitystat.”

Genetics

Several studies have indicated that the physical activity phenotype can partly be explained by genetic factors (5). In general, the estimated heritability of physical activity varies considerably (range 18–69%) due to differences in measurement and expression of physical activity (e.g., retrospective questionnaire vs. accelerometer, sports participation vs. moderate-to-vigorous physical activity, etc.) and race (Whites, Blacks, Hispanics). Given the completion of the Human Genome Project (11), research is now in the early stages of identifying and testing candidate genes for physical activity. Among adults, three physical activity phenotypes (inactivity, moderate to strenuous physical activity, and total daily activity level) have shown encouraging linkage for both physical activity (chromosome 2p22-p16) and inactivity (chromosomes 7p11.2, 20q13.1; 44). There is also evidence suggesting that the dopamine D2 receptor gene (45) and melanocortin-4 receptor gene (28) are associated with physical activity in adults. In the only study involving children, Cai et al. (8) found that the percentage time in sedentary, light or moderate activity and total activity counts mapped to markers on chromosome 18, which harbors the melanocortin 4 receptor gene. To date, no studies have specifically examined the association between candidate genes and level of physical activity in children or adolescents.

Related to the findings discussed above, it is also conceivable that there are differential levels of environmental and biological control for the various components of physical activity (spontaneous, obligatory, and voluntary). For example, Carlsson et al. (9) suggested that as participation in organized sport reflects an active choice, the genetic influence on physical activity may be more important than in the past when obligatory activity was higher. Stubbe et al. (49) also showed that the environment is the major determinant of voluntary activity in adolescence, and genetics are the most important determinant in adult life. However, others have argued that childhood is a period when genetic influences may be more robust (29). Further cross-sectional and longitudinal research is warranted to partition the role of genetic and environmental influences on the various components of physical activity and energy expenditure.

Artificial Selection Experiments in Animals: Mice Selectively Bred for High Voluntary Wheel Running

Since 1995, Garland and colleagues (18) have studied the genetics and evolution of physical activity by undertaking an artificial selection experiment to increase levels of voluntary *wheel*-running behavior in house mice with the first publication coming in the same year as Rowland's paper (50). Several research questions are being explored using this model; however, central to the project is the biologi-

cal basis of physical activity. This model may prove particularly useful for understanding the biological basis of physical activity since psycho-social and built environment components are all but removed as factors that influence physical activity behavior.

A brief description of the selection protocol is as follows. The mice were originally derived from the 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 running wheels for 6 days. Wheel running was quantified with a computer-automated system and expressed as the total number of revolutions on days 5 and 6. In the “selected” lines the highest running male and females were chosen from each family as breeders. In the “control” lines 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. Currently, the animals are in generation 47 (April 2008). The wheel running difference between the selected and control lines appears at weaning and persists during the juvenile phase as the shape and position of the wheel-running ontogeny changes until the difference peaks at about 250% at 6–8 weeks (33,51).

The selected mice show not only increased wheel-running behavior but also motor impulsivity and hyperactivity even when housed without a wheel or when the wheel is provided but locked (personal communication with T. Garland). These observations certainly attest to the biological basis of physical activity and resemble to some regards the nature of physical activity in young children (and ADHD children). These activity phenotypes are also characterized by alterations in brain morphology and physiology. More specifically, Rhodes et al. (37) showed higher levels of brain activity in the hippocampus in selected mice when denied access to wheels in regions associated with arousal, reward, and initiation of locomotion. Alterations of dopamine receptor expression levels have also been shown in the selected lines compared with controls (7). Thus, the genetic architecture of running motivation likely involves the dopaminergic system as well as central nervous system signaling machinery.

Does Variation in Physical Activity Lie Within the Child and Not His Environment?

Although much attention to understanding the physical activity phenotype is on between-individual differences, exploring the intraindividual variability is an approach that can also be used to study the central processes that regulate daily energy expenditure. If a central control system regulates daily physical activity we would expect the level of control, or the amount of variation in this case, to be similar among children regardless of gender or environment.

In a recent paper (65; as titled by this section), researchers from the EarlyBird Study explored the intrinsic control of physical activity in children. As suggested by Rowland in 1998, Wilkin and colleagues conceive the activitystat to be “a neuro-humoral loop with a set-point possibly located in the hypothalamus, able to integrate activity carried out by as yet unknown means, and to control further physical activity accordingly.” To test the hypothesis that habitual activity in

young children is centrally rather than environmentally regulated, accelerometers were used to measure physical activity in a variety of settings and populations including (1) 5 yr old children enrolled in the Earlybird Study, (2) 3 groups of schoolchildren from (a) private preparatory school in which 9 hr per week of physical education, (b) school in a village which participated in a physical activity promotion program in which 2 hr per week of physical education, and (c) inner city school receiving 2 hr physical education per week, and (3) children from Glasgow. Physical activity was considered as the total amount during weekday and weekends, during transport to school, in school and after school. The authors used a myriad of results to support their hypothesis of central biological regulation of physical activity including: (a) no difference between weekday/weekend day and year-on-year activities, (b) no significant difference in total activity despite a fivefold variation in timetabled physical education between school 2a-c above, (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 (to within $<0.3\%$) as that recorded independently in Glasgow, 800 km away.

Although the results of the EarlyBird study shows no mean difference in total physical activity assessed by accelerometry in a variety of settings and populations, in some ways the hypothesis remains to be tested. That is, what happens to the physical activity of an individual child when he/she is moved from one situation to another. For example, what happens to the physical activity of an individual children if he/she walks to school on day 1 and then does not walk to school on day 2; or what happens to the physical activity of an individual child if he/she resides in a larger community and attends a private preparatory school in which 9 hr per week of physical education are offered and then moves to a village and attends a school which participated in a physical activity promotion program in which 2 hr per week of physical education, etc. Other studies have provided some insight into these scenarios. We have examining the contribution of youth sports to total daily physical activity and found that MVPA decreased 30 min (11 min moderate and 19 min vigorous) and sedentary time increased by 40 min on a non-sport day compared with a sport day (60). Thus, MVPA was not maintained on a nonsport day contrary to the hypothesis that physical activity is biologically regulated. Dale et al. (14) has shown that removal of opportunity to be active in the school day did not lead to compensatory increases in after school activity. However, the time scale over which compensation (if it does exist) may occur needs to be considered. The previous two studies cited assessed only one to two days of restriction or dose and one to two days of "normal" activity. It may be possible that the balance of physical activity may take longer to occur, which would explain the lack of compensation observed in these studies. Furthermore, the magnitude of the physical activity deprivation or dose that may induce compensation is not known, and presumably this would have to be outside of the limits of normal day to day variability of that child's activity. In addition, some of their results are not supported by previous work. For example, other have shown that physical activity on weekend days is less than weekdays (19,40), and children who walk to school have higher activity levels than children who do not walk to school (12,19). Insight into relocation has recently been addressed in Australian adults (56). This study investigated the extent and pattern of one-year tracking of pedometer-determined

physical activity in adults who relocated within the same metropolitan area. Overall, there was a small nonsignificant decrease in steps/day (-81 steps/day, 95%CI -259 – 97) between time 1 and time 2 (relocation) and adults held their rank position to a moderate to moderately high extent over 1 year. Further work is obviously needed to examine the influence of change in environmental settings and daily schedules on habitual physical activity and total daily energy expenditure in youth.

Another approach to studying this problem is using the coefficient of variation ($CV = (sd/mean) \times 100$), a useful statistic to summarize the variability within an individual and also to compare levels of variability across studies using different assessment tools. We used this approach to examine the mean CV values between boys and girls from three separate countries (United States: 195 boys, 254 girls; Sweden: 257 boys, 252 girls; Australia: 229 boys, 256 girls) who wore a pedometer over four consecutive days (Monday through Thursday; 61). The absolute mean difference between days ranged from 55 to 958 steps and the overall mean CV among participants approximated 22% and was similar across countries (US: 22.1%; Sweden: 22.5%; Australia: 21.8%) and between sexes (boys: 21.2%; girls: 22.7%). Others have also shown a similar mean CV in youth (31), and we have also shown a similar CV in daily wheel running revolutions recorded over three weeks (weeks 6–8; representing adolescence/late adolescence) in 20 mice (10 males, 10 females) from a selectively bred line for high endurance capacity, 20 mice (10 males, 10 females) from a selectively bred line fixed for a Mendelian recessive allele that reduces hindlimb muscle mass by 50%, and 20 mice (10 males, 10 females) from a control line (Eisenmann et al., 2009). This study represented a novel approach to expanding our understanding of the development of the physical activity phenotype because the animals were selectively bred for the trait of interest (i.e., voluntary physical activity). The mean CV was comparable during adolescence (week 6: 23%; week 7: 25%; week 8: 20%), between males (24%) and females (22%), and between lines (control: 23%; reduced hindlimb muscle mass: 20%; and high endurance capacity: 25%). Thus, given that they displayed a similar CV across days 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 lines of mice that vary in activity level.

Although we have shown consistency in the mean CV of locomotor behavior across diverse samples of human children, adolescents, and young adults and genetically different lines of mice, there was a considerable amount of interindividual variation in day-to-day CVs. For example, the day-to-day CV among the children from Australia, U.S., and Sweden ranged from ~ 2 –88%. Indeed, some individuals show little daily variation, whereas others show more than a great amount of variation. This may suggest that some individuals possess greater inherent control of physical activity compared with others. In terms of the “activity-stat” it is more than likely total energy expenditure that is tightly controlled, therefore it is also possible that this variation is due to a change in the nonlocomotor (or nonmeasurable) tasks that increase energy expenditure. For example, there may have been greater home-cage activity in the mice on days of lower wheel activity, and in the humans there may have been greater fidgeting, etc. on days of lower walking. This could also related to the intensity of locomotor behavior,

whereby lower wheel counts or steps per day were exhibited on days of more intense activity. This latter point is addressed in the paragraph below.

Since daily physical activity is a behavior, we would also expect to observe some regulatory effect on daily energy expenditure and its components. Using the Bouchard activity diary, we found little day-to-day variation in total energy expenditure among 277 young adults (125 males, 152 females) under free-living conditions (62). In this study, the mean CV for total energy expenditure approximated 12%, which is comparable to the mean CV reported in a meta-analysis of 21 doubly labeled water studies (4). Despite the relatively low amount of variation we reported in total energy expenditure, a large degree of variation was found in the energy expended through moderate-to-vigorous physical activity (mean CV >80%). This observation suggests that on days when MVPA levels are high, there is a reduced amount of low-intensity activity, and conversely on days when MVPA levels are low, there is an increased amount of low intensity activity. The CV for activity energy expenditure in this study was 32%, which is higher than the mean CV for the pedometer study (22%), however the difference between mean CVs can likely be attributed to the distinct methodological differences between pedometers (objective device based on mechanical movement) and activity diaries (subjective tools that may be influenced by memory recall or report bias). It is also possible that the higher CVs in this study is because adult's physical activity is less stable and consequently needs a longer measurement period to obtain a reliable estimate of habitual activity.

Collectively, the data on CVs suggests some similarities in mean day-to-day variability across groups. However, no study has demonstrated evidence of compensation for imposed or restricted activity on a within-child basis. Thus, further research is warranted to determine if compensation occurs, and if it varies across ages, sexes, activity level, etc. Additional studies are also needed in children using DLW and accelerometry to explore the variability of TEE, AEE, and MVPA.

Nonexercise Activity Thermogenesis (NEAT)

In 1999, Levine introduced the concept of nonexercise activity thermogenesis (NEAT; 24). NEAT is defined as the energy expended for everything we do that is not sleeping, eating or sports-like exercise, and includes the energy expended walking to school, typing, performing household chores, and fidgeting (24). In the context of children, the latter activity—fidgeting (and any other spontaneous-type movements)—seem relevant.

In the first paper, Levine and colleagues overfed adult subjects an extra 1000 kcal/day for 8 weeks. Subjects displayed compensatory changes in NEAT ranging from -98 to +692 kcal/day (26). Two thirds of the increase in total daily energy expenditure was due to increased nonexercise activity thermogenesis (NEAT). In early reviews Levine (24,25) commented that although the observation that NEAT increases during positive energy balance and varies between individuals, the mechanism that regulates NEAT is unknown. However, the author also acknowledged that biological underpinnings were perhaps at the root of the issue. For example, the author stated:

By understanding how NEAT is regulated we may come to appreciate that spontaneous physical activity is not spontaneous at all but carefully programmed.

It then becomes intriguing to dissect mechanistic studies that delineate how NEAT is regulated by neural, peripheral and humoral factors. NEAT may be a *carefully-regulated 'tank' of physical activity*. (25)

Based on this premise, Levine and colleagues (34) have conducted a series of studies in mature rats to explore the possible neuroendocrine mechanisms that may regulate energy expenditure. One study examined the effects of hyperthyroidism by continuous infusion of high-dose triiodothyronine and found mean spontaneous physical activity and NEAT increased in the hyperthyroid rats from 24 ± 7 to 36 ± 6 activity units/min and 8 ± 3 to 20 ± 5 kcal/day, respectively, but did not increase in the controls (23 ± 7 vs. 22 ± 4 activity units /min; 9 ± 3 vs. 9 ± 2 kcal/day; 27). Other studies have used hypothalamic paraventricular nucleus or arcuate nucleus cannulation to administer microinjections of selected neuropeptides (orexin and neuromedin U; 22, 35). These studies show a dose-dependent increase in spontaneous physical activity. Furthermore, injections of orexin receptor antagonist SB-334867 into the paraventricular nucleus were associated with decreases in spontaneous physical activity and attenuated the effects of paraventricular nucleus-injected orexin A. Thus orexin A can act in the paraventricular nucleus to increase nonfeeding-associated physical activity, suggesting that this neuropeptide might be a mediator of NEAT. Taken together, these studies coupled with several others (for review see Levine 2007) demonstrate that the hypothalamus is a key structure in regulating physical activity and that several biomolecules and neuropeptides are important in regulating physical activity. However, their application to the growing and maturing child is unknown, but may prove relevant given the aforementioned morphological and physiological changes in the brain associated with puberty.

Prenatal Environmental, Epigenetic, and Physical Activity

In the last decade or so, there has been considerable attention on the link between the in utero environment (namely the outcome of low birthweight—i.e., the Barker or fetal origins of adult disease hypothesis) and offspring chronic disease (2). This process has been also been termed “fetal programming.” Although several studies have examined the in utero environment and chronic disease outcomes, few have considered physical activity. Using the model of maternal undernutrition throughout pregnancy in the rat, Vickers et al. (58) investigated whether prenatal influences may lead to alterations in postnatal locomotor behavior. In this study, rats were mated and randomly assigned to receive food either ad libitum (ad libitum group) or at 30% of ad libitum intake (undernourished group). At weaning, offspring were assigned to one of two diets (control or hypercaloric consisting of 30% fat). At 35 days, 145 days, and 420 days, voluntary locomotor activity in offspring from undernourished mothers was significantly less than offspring born of normal birth weight for all parameters measured, independent of postnatal

nutrition. Furthermore, locomotor behavior in programmed offspring was exacerbated by postnatal hypercaloric nutrition. This work is the first to clearly separate prenatal from postnatal effects and shows that locomotor behavior may have a prenatal origin. Moreover, the prenatal influence may be permanent as offspring of undernourished mothers were still significantly less active compared with normal offspring at an advanced adult age, even in the presence of a healthy diet throughout postnatal life. To our knowledge, no epidemiological studies have examined the association between in utero environment on physical activity during childhood.

The observed decline in physical activity of offspring born under poor in utero circumstances may be explained by epigenetic mechanisms. This phenomena refers to the epigenetic processes involved in the unfolding developmental biology of the organism in which heritable changes in gene function occurs without a change in the sequence of nuclear DNA which includes, as described above, how environmental factors affecting a parent can result in changes in the way genes are expressed in the offspring (6). In recent years, there has been rapid progress in understanding epigenetic mechanisms that include differences in DNA methylation and chromatin structure. Epigenetic mechanisms have been widely studied in cancer and more investigations are considering the role of epigenetics in complex diseases in the past five or so years (3,13,21,59). However, no study has directly related epigenetic models to the study of physical activity. Given the initiation of the National Children's Study in the United States (23), future studies can examine the prenatal aspects of childhood physical activity.

Attention Deficit Hyperactivity Disorder (ADHD)

As previously mentioned, Rowland also pointed to the study of ADHD as a model for studying the biological basis of physical activity. He highlighted the proposed explanations for a biological basis of ADHD coming from either inadequate inhibition of impulses within the reticular activating system, frontal lobe dysfunction, and/or central nervous system neurotransmitter depletion. Since his review, about 130 papers have been published and indexed in PUBMED using the keywords "physical activity and ADHD"; however, few studies have been conducted that focus specifically on the question of a biological basis of physical activity. Instead, many of these papers are clinical in nature or aimed at elucidating the actions, efficacy, or safety of pharmaceutical agents. Hence, it seems that despite the recognition of the ADHD child as a model for the study of a biological basis of physical activity, few pediatric exercise researchers have pursued this avenue.

Summary and Conclusions

In his seminal paper, Rowland clearly outlined the rationale, evidence, and implications for the biological control of physical activity. Ten years later, there has been some progress in this area related to childhood physical activity with perhaps the greatest progress being made in the areas of genetics and the neuroendocrinology of physical activity. It is clear that heredity contributes to the physical activity (and inactivity) phenotype and candidate genes are now being identified. Furthermore, animal models indicate that maternal exposure to various environmental

factors may alter offspring physical activity. Although the mechanisms of this maternal-fetal interaction are unknown, it may involve the development programming of anatomical structures or biophysical pathways involved in energy homeostasis. In this regard, it is also clear that key brain structures and biomolecules involved in motivation, reward, and/or energy balance are also critical to understanding the biological basis of physical activity. Given the potential links between the neuro-endocrine and body composition changes during puberty and the decline in physical activity during this period, future multidisciplinary research in the human child and postnatal animal should be encouraged to provide a better understanding of the biological basis of physical activity during early life. Finally, there are also clear links between the neuro-endocrine and body composition changes during puberty and the decline in physical activity with psycho-social factors. Thus, there should also be emphasis on understanding the “biocultural” development of the child and its influence on the physical activity phenotype.

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