Long–Lasting Effects of Early-Onset Exercise on the Prevention of Obesity and Its Related Lifestyle Diseases

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Decreased physical activity and increased obesity during childhood have recently emerged as significant social problems. Since long-term exposure to risk factors contributes to the development of lifestyle diseases, determining effective early-age prevention strategies is essential. Regular exercise and increased physical activity are well known to prevent obesity and insulin resistance in both animals and humans. However, although physical activity during childhood has a well-known direct effect on child health, the long-term consequences of childhood exercise on adult health and morbidity have not been well studied due to the difficulties of following subjects long-term. To address this, many researchers use rodents or other animal models. Previous studies have suggested that exercise has long-lasting effects on body weight after exercise cessation. In this review, studies examining the long-lasting effects of childhood exercise on obesity and metabolic diseases later in life using animal models are summarized, and the importance of exercise in childhood in preventing obesity and its related comorbidities is highlighted.

Key words: early-onset exercise, primordial prevention, long-lasting effect, obesity, metabolic disease

Introduction

The prevalence of obesity and other lifestyle diseases has dramatically increased in both adults and children in recent decades. According to a 2013 report by the Centers for Disease Control and Prevention in the U.S. 12.7 million children and adolescents aged 2-19 years old were considered obese (http://www.cdc.gov/obesity/data/childhood.html). In Japan, the prevalence of obesity increased threefold in Japanese children and adolescents aged 5–17 between 1978 and 2007. Since long-term exposure to risk factors contributes to the development of lifestyle diseases, determining effective early-age prevention strategies is essential. A number of previous studies have demonstrated that overweight children are more likely to be overweight as adults compared to normal weight children, with 40–60% of overweight children becoming overweight adults. In addition, the Bogalusa heart study suggested that 77% of obese, and presumably sedentary, children remained obese during adulthood. Therefore, maintaining a normal weight and body fat percentage during childhood may be important for long-term health.

Although the main risk factors of lifestyle diseases include genetic and environmental factors, diet and exercise are commonly recommended for the prevention and amelioration of obesity and lifestyle diseases. However, the majority of dietary alterations fail in humans, and adults generally regain lost weight in the months and years following diet cessation. Similarly, weight-reduced rats quickly regain lost weight when allowed free
access to food\textsuperscript{8}-\textsuperscript{11}. Weight regain in humans and rodents may be partly attributed to the chronic reduction in resting metabolic rate associated with weight loss\textsuperscript{12}. On the other hand, exercise affects energy balance, and those who successfully maintain weight loss for several years have reported maintaining high levels of physical activity\textsuperscript{13} \textsuperscript{14}. Although the control of energy balance by exercise and diet is still not well understood, access to a running wheel modulated both food intake and body weight in studies examining rodent obesity\textsuperscript{15}. In addition, in some rodent models, long-lasting effects of exercise on feeding and body weight have been identified\textsuperscript{16} \textsuperscript{17}. Overall, these studies suggest that exercise is an effective way to maintain weight loss, and that physical activity levels have a strong influence on obesity and related lifestyle diseases.

Nonetheless, decreased physical activity in childhood has recently emerged as a significant social problem. However, little data exists regarding the effects of physical activity in childhood on adult health and mortality in humans. In addition, while multiple studies have examined the effects of exercise on energy homeostasis in adult rodents\textsuperscript{15} \textsuperscript{18}, few have examined the effect of early-onset exercise in juvenile animals on the development of obesity\textsuperscript{16} \textsuperscript{17} \textsuperscript{19} \textsuperscript{20}. The mechanisms by which exercise exerts long-term effects are also unknown at present. In this review, studies examining the long-lasting effects of childhood exercise on obesity and metabolic diseases using animal models are summarized, and the importance of exercise in childhood for the prevention of obesity and its related comorbidities is highlighted.

The importance of physical activity in childhood

Physical inactivity (lack of physical activity) has been identified as leading cause of death, and leads to decreased physical fitness. Convincing evidence suggests that the risk for all-cause and cardiovascular-related disease mortality is increased in the absence of moderate or high levels of cardiorespiratory fitness in adults\textsuperscript{21}. In addition, decreased physical activity in children has emerged as a significant social problem. Maffeis \textit{et al.}\textsuperscript{22} reported that time spent on sedentary activities was positively correlated to body fat percentage in 9 year-old boys, and that 8-10 year-old obese children were more sedentary and spent less time performing non-sedentary activities compared to age-matched non-obese children\textsuperscript{23}. The World Health Organization (WHO) has recommended that children and adolescents aged 5-17 should accumulate at least 60 minutes of moderate- to vigorous-intensity physical activity daily. However, Troiano \textit{et al.}\textsuperscript{24} found that 58% of children aged 6-11 and 92% of adolescents fail to meet these recommendations.

Blair \textit{et al.}\textsuperscript{25} presented three possible models by which enhanced physical activity in childhood may improve health in adults: (1) childhood physical activity influences adult physical activity, which in turn can affect adult health, (2) childhood physical activity has a direct beneficial effect on childhood health, which predicts adult health, and (3) childhood physical activity has a direct beneficial effect on adult health. These models are supported by several other studies. A longitudinal study suggested that high levels of physical activity during childhood were positively correlated to physical activity patterns 21 years later\textsuperscript{26}. Moreover, a similar study revealed that individuals who had high levels of physical activity as adults were more likely to have lower waist circumferences, and were more likely to have been highly active during childhood\textsuperscript{27}. These results suggest that physical activity in childhood and adolescence has an indirect effect on abdominal obesity through the maintenance of physical activity during adulthood. Therefore, establishing high levels of physical activity during childhood, and continuing high levels of physical activity into adulthood may combat the development of lifestyle diseases. Although there have been many epidemiologic studies, including the ones described above, the effects of childhood physical activity on adult health are difficult to establish due to the challenges of following subjects through their entire lifespans.

Experimental models by using animal to study the effect of early-onset exercise

To examine whether exercise habits in childhood contribute to health or morbidity in later life, many researchers have used experimental animal models. In the case of rats, they are weaned from the mother at approximately 3 weeks of age, and are used for breeding from 10-12 weeks of age.
Although matching ages between species is difficult, Goto\textsuperscript{28} described that a 6-month-old rat is roughly equivalent to a 15-20-year-old human. Therefore, the first of rat’s life is roughly equivalent to human children/adolescence, so to examine the effects of early-onset exercise on health during adulthood, animals must engage in exercise during this period.

Experimental models of exercise cessation have often been used to explore how long-lasting the effects of early-onset exercise are and the mechanisms by which long-lasting effects occur. The rodent wheel lock (WL) model was developed by Rhodes \textit{et al.}\textsuperscript{29}, and involves housing young rats in cages equipped with voluntary running wheels. After a short period of voluntary running (3 to 6 weeks), the wheels are locked, removing the rats' primary source of physical activity. Using this model, a number of researchers have examined how different organ systems in juvenile rats respond to cessation of daily physical activity. Roberts \textit{et al.}\textsuperscript{30} recently reviewed the evidence regarding the effects of exercise cessation on various physiological variables, including body weight, glucose and lipid metabolism, insulin resistance, and vascular function using the WL model\textsuperscript{30}. However, the longest studies using the WL model have only tracked rats for 173 hours after exercise cessation, and to determine the long-lasting effects of early-onset exercise, animals must be monitored over long periods of time. Several studies have examined the effects of exercise for more than 10 weeks using various models, and these results will be summarized in the next section.

The long-lasting effects of early-onset exercise on obesity and its related metabolic diseases

In a number of rodent obesity models, early-onset access to a running wheel and the subsequent increase in physical activity normalized body weight in diet-induced obesity (DIO) and type 2 diabetic, Otsuka Long-Evans Tokushima Fatty (OLETF) rats\textsuperscript{15,31,32}. OLETF rats represent a well-established animal model of obesity and type 2 diabetes, and are characterized by hyperphagia and obesity, which begin during early childhood\textsuperscript{33}. OLETF rats go on to develop hyperglycemia after 18 weeks of age. Since several reports have shown that running activity can prevent obesity in OLETF rats, but not Zucker fatty rats\textsuperscript{34}, OLETF rats have been used to examine the effects of exercise on the prevention of obesity and metabolic diseases.

In addition, some animal models suggest that early-onset exercise has long-lasting effects on body weight (Table-1). Interestingly, adult rats placed on similar exercise regimens did not sustain their weight loss after exercise cessation\textsuperscript{35}. Shima \textit{et al.}\textsuperscript{19} reported that exercise had long-lasting preventive effects on obesity and type 2 diabetes development in OLETF rats. Bi \textit{et al.}\textsuperscript{18} also demonstrated that the effects of exercise on body weight were long lasting, and that these effects might be mediated by central energy homeostasis regulating pathway, including neuropeptide Y (NPY) signaling in the dorsomedial hypothalamus (DMH). Patterson \textit{et al.}\textsuperscript{16} examined the duration of early running wheel activity necessary to produce sustained suppression of body weight and adiposity after exercise cessation, and determined that three weeks of exercise was sufficient to prevent obesity 10 weeks after wheel removal. In contrast, Chao \textit{et al.}\textsuperscript{17} examined the effects of a high-fat diet on body weight in OLETF rats that had prior access to running wheels for 4 weeks, and determined that the high-fat diet offset the long-lasting effects of exercise on body weight. In addition, Shindo \textit{et al.}\textsuperscript{20} observed the long lasting effects of exercise on weight gain for the longest period, and determined that higher levels of citrate synthase (CS), succinate dehydrogenase (SDH), phosphofructokinase (PFK) activity and uncoupling protein (UCP-3) mRNA in skeletal muscle were found after long-term exercise cessation. Research from our own lab also suggests that the lower body weight and glucose levels are sustained after exercise cessation in OLETF rats compared with sedentary animals. In addition, we observed that exercise completely prevented increase in serum lipid parameters (e.g. triglyceride and total cholesterol), even after cessation (unpublished data).

Taken together, these studies suggest that early-onset exercise has long-lasting effects on the prevention of obesity and its related metabolic diseases through the regulation of central energy homeostasis pathway, and by increasing the activity of enzymes participating in energy metabolism. Further studies are needed to determine the underlying mechanisms by which early-onset exercise prevent obesity and...
Studies on the long-term effects of early-onset exercise and exercise cessation on obesity and lifestyle disease development are difficult to perform in humans. Therefore, animal models provide a translational tool that can be used to identify preventative methods that can be utilized in children to prevent obesity and lifestyle diseases later in life. The information in this review establishes the importance and necessity of physical activity in childhood for the prevention of adult obesity and lifestyle diseases.

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Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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