Rewired to be thin? When exercise hits the brain

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IN THIS ISSUE OF THE American Journal of Physiology—Regulatory, Comparative and Integrative Physiology, the article by Patterson et al. (17) demonstrates that just 3 wk of voluntary exercise in the postnatal period mitigates weight gain in obesity-prone rats for at least 10 wk after cessation of the exercise. These novel findings suggest that a behavioral modification as simple as short-term exercise, in a critical developmental period, could alter brain circuits that otherwise promote obesity. This information is compelling news in the fight against obesity, in which current approaches appear to be losing ground to the ever-increasing obesigenic environment. The task of reducing obesity may be much more difficult than preventing obesity, and thus, major preventive efforts are under way in schools and communities to this end (20). Notwithstanding, childhood obesity has been increasing at alarming rates worldwide (24), and thus, new information on what types of approaches may work in children are needed.

In this study, the authors compared the relative effects of exercise in two sets of young rats: those that are resistant to obesity (diet-resistant, or DR) and those that are obesity prone (diet-induced obesity, or DIO). These rats were selectively bred based on their propensity to become obese on a high-fat diet, such that obese rats were mated with obese, and lean with lean. The obesity-prone rats gain excess weight and adiposity when placed on a high-fat diet, whereas the obesity-resistant rats remain lean (12). This is an attractive animal model of obesity because the late-onset and diet-induced obesity phenotype mirrors that which occurs in humans. Further, the obesity is not a result of a single gene defect, but rather polygenic, like most human obesity.

Previous work has shown that lack of compensatory caloric intake for the energy expenditure produced during exercise reduces adiposity in adult rats, but only during the time in which the exercise occurs (10, 11, 16). Once the exercise stops, adult obesity-prone rats return to their normal body weight gain trajectory. Contrary to adult rats, postnatal DIO rats appear particularly sensitive to the obesity-protective effects of exercise, and this sensitive period extends for at least 10 wk beyond exercise cessation (17, 18). Thus, time of onset appears crucial in determining length of the exercise effect on obesity resistance, and as some brain development is still occurring in rats during this time period, it is intriguing to speculate that brain circuitry favoring a lean phenotype has been created.

Importantly, the investigators verified that the extended obesity resistance in the exercised DIO rats was not solely a carryover of reduced caloric intake and increased energy expenditure during the exercise period, by including an additional group of weight-matched food-restricted control rats to mirror the same general “energy deficit” as the exercised animals. Cessation of the food restriction occurred simultaneously with removal of running wheels from the cages of exercised animals. Unlike exercised DIO rats, which maintained reduced adiposity for 10 wk following exercise, the previously food-restricted rats overshot the adiposity levels of nonrestricted controls. Thus, in stark contrast to the effect of exercise during this period, which appears to create obesity-resistant conditions, food restriction during this period sets up an obesigenic state. Of interest but not measured in this study, is whether levels of spontaneous activity during the nonexercise period were different between sedentary and exercised rats or altered by the exercise period and whether this could have contributed to extended obesity resistance in DIO rats. Routine exercise in rats has been shown to elevate spontaneous physical activity during nonexercise periods (6, 22, 26), and spontaneous activity has been shown to be a significant factor in energy balance (13, 23).

Not only is time of exercise onset important, but duration of exercise also appears to be significant. DIO rats exercised for only 2 wk before the sedentary period were not afforded the same protection from obesity as were those exercised for 3 wk. Although this appears to suggest that a 3-wk, rather than a 2-wk, period is the critical factor, it is unclear from these data whether it was the cumulative effect of the 3rd wk or the timing of that 3rd wk that was the crucial element in retaining obesity resistance. During that 3rd wk, the rats were about 6 wk of age, in both the “2-wk” and “3-wk” exercised rats. Previous work by this laboratory has shown that changes in the hypothalamic pituitary-adrenal axis occur during the 3- to 5-wk period in DIO rats (14). As the exercise effect in the current study encompassed the entire 3- to 6-wk period and was not apparent after exercise during the 3- to 5-wk period, it would be informative to determine whether 1 wk of exercise during this particular time in development—postnatal week 6—would result in the same obesity-resistant phenotype as those rats exercised for 3 wk in the present study.

Others have also investigated effects of exercise in the postnatal developmental period on obesity in rats (7, 9, 15, 21, 25). The Moran laboratory has shown that 8 wk of exercise in a slightly later developmental period (8 wk vs. 4 wk in the current study) reduces obesity in obese-prone Otsuka Long-Evans Tokushima Fatty (OLETF) rats, which lack the short-term satiety signaling CCK-A receptor (3, 16). Subsequent body weight gain was reduced in these OLETF rats for 6 wk (3, 16). This is similar to the current data, although the exercise period was longer, and the data were followed out for a shorter time. Other studies using rat strains with different genetic backgrounds have not shown any obesity-protective effect of exercise, suggesting that genetic background may be critical in the results observed (2, 8, 9). Human studies on this topic are lacking, although it has been shown that in children, reduced time in sedentary activities and increased time in physical activity would result in a significant reduction in adiposity (24).

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activity reduces their future propensity for obesity (5), and infants classified as highly active were shown to remain lean during development (19).

The current work further sought to identify neural factors that might explain the reduced propensity for obesity in the exercised DIO rats. Previous data had indicated that several neuropeptides important to appetite regulation, including corticotrophin-releasing factor, proopiomelanocortin (POMC), and neuropeptide Y are affected by exercise (3, 4). Thus, the investigators looked at gene expression of several appetite-related factors in many brain areas important to energy balance. Surprisingly, many expected changes in appetite neuropeptides did not occur, which may be related to the difficulty in anticipating responses in postnatal rats based on previous work in adult rats. However, gene expression for hypothalamic arcuate nucleus POMC was elevated in 6-wk exercised rats, which may yield an enhanced satiety-signaling milieu and suppress eating in a postexercise period. There are inherent difficulties in making conclusions regarding brain system function based on gene expression data, although these data should be useful in determining stable changes. Other issues such as timing of measurement may have also impacted these data, and there are likely other neurotransmitters or compounds important to plasticity that may be relevant to the results observed, but that were not measured in the current study.

Another limitation, which is a constraint of all rat studies, is the difficulty in extrapolating these data to humans, since brain development in rats and humans occurs at different rates, and much that occurs in the postnatal period in rats does not occur in humans (1). However, these data are proof of concept that, just as brain insults during critical developmental periods can have devastating behavioral effects, behavioral changes in developmentally susceptible periods can favor positive long-term outcomes related to body weight. Further, there is still substantial brain development after the birth in humans through the teenage years, and as evidenced by the success of physical rehabilitation after brain damage and the recent evidence showing new neuron formation in the adult brain, significant remodeling of brain circuits can occur in adulthood. Thus, the current data set should provide new hope in the efforts at combating obesity in children and throughout the lifespan. The practical implication is that increased exercise in children will not only afford them the caloric advantage of increased energy expenditure but may also have the more important effect of rewiring brain circuits to reduce their susceptibility to obesity as an adult.

The current paper also lays the groundwork for many additional questions: how long is the obesity resistance maintained after exercise cessation? If the resistance endures throughout the lifespan, this would suggest a permanent rewiring that affords an advantage in this obesigenic environment. Or does the obesity resistance subside over time? This would suggest a more temporary change in the brain milieu important to energy balance. Another exciting set of questions is related to the potential brain changes that occur as a result of exercise in the postnatal period. Plasticity is difficult to measure, but recent advances have yielded approaches that can help answer these questions.

The paper by Patterson et al. (17) has made important headway into understanding the influence of early exercise on future obesity propensity, and what happens to brain circuits as a result of this exercise. The future of work in this area looks promising.

REFERENCES