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Role of Exercise in the Central Regulation of Energy Homeostasis and in the Prevention of Obesity

Christa M. Patterson[a, b] Barry E. Levin[a–c]

[a]Department of Neurology and Neurosciences, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, and [b]Graduate School of Biomedical Sciences, University of Medicine and Dentistry of New Jersey, Newark, N.J., and [c]Neurology Service, Veterans Administration Medical Center, East Orange, N.J., USA

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Energy homeostasis, central regulation · Exercise role, energy homeostasis/obesity prevention · Obesity prevention

Abstract
Many of the small percentage of previously obese humans who successfully maintain weight loss report high levels of physical activity, suggesting a role for exercise in the maintenance of their lower body weights. The rat model of diet-induced obesity (DIO) has been particularly useful, since it shares several common characteristics with human obesity and, unlike the human condition, allows a thorough investigation of the effects of exercise on the central pathways which regulate energy homeostasis. In rats with DIO, voluntary wheel running selectively reduces adiposity without causing a compensatory increase in energy intake. These effects are likely mediated by signals generated by the exercising body such as interleukin-6, fatty acids, and heat which feed back on the brain to regulate central neuropeptide systems involved in the regulation of energy homeostasis. While exercise provides temporary reductions in obesity in adult rats, early postweaning exercise reduces adiposity in high-fat-fed DIO rats long after exercise is terminated. This suggests that early-onset exercise may permanently alter the development of the central pathways which regulate energy homeostasis. Therefore, identification of exercise-induced central and peripheral factors and elucidation of their interactions with central modulatory pathways may aid in the identification of new targets for the pharmacological treatment of human obesity.

The long-term treatment of human obesity has been largely unsuccessful, because a high percentage of individuals regain lost body weight within months to years following treatment [1, 2]. Likewise, calorically restricted obese rodents rapidly increase their food intake and regain lost body weight and adiposity when allowed to eat ad libitum [3–6]. There are several potential causes for this high rate of recidivism. While there are strong psychosocial motivations driving ingestive behavior, the most likely physiological reason for these relapses is that the mammalian system has evolved to avidly preserve energy stores, even when energy intake is limited. Thus, weight loss in both humans and rodents is accompanied by a chronic reduction in the resting metabolic rate [7–9] that is likely driven by the accompanying fall in plasma leptin and insulin levels which occur during both acute and chronic states of negative energy balance [10, 11]. In rodents, leptin and insulin relay information to the brain concerning the body's fat stores. A reduction in these hormones leads to the activation of the anabolic system – e.g., arcuate nucleus (ARC) neuropeptide Y (NPY)/agouti-

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Barry E. Levin
Neurology Service (127C), VA Medical Center
385 Tremont Avenue
East Orange, NJ 07018-1095 (USA)
Tel. +1 973 676 1000, ext. 1442, Fax +1 973 395 7112, E-Mail levin@umdnj.edu

related peptide – and to the inactivation of the catabolic system – e.g., ARC pro-opiomelanocortin (POMC). Such changes in these two neuronal systems result in a decreased resting energy expenditure and in a strong 'metabolic' drive to seek and ingest food [12–16]. Although the effect of exercise on short- and long-term regulation of body weight is controversial, many humans who maintain weight loss for over 2 years self-report high levels of physical activity [17–20]. Therefore, it has been suggested that exercise may prevent the lowering of the resting metabolic rate accompanied by weight loss [21, 22]. However, few studies have examined the relationship between exercise and central regulation of energy homeostasis [23, 24].

Because of the many difficulties in assessing brain function in human, much of the work regarding exercise and central energy homeostasis regulation has been carried out in rodents. The rat model of diet-induced obesity (DIO) shares several common characteristics with human obesity and can be used to examine the effects of exercise on body weight gain and energy homeostasis. Similar to human obesity, rodent DIO is an inherited polygenic trait that is exacerbated by exposure to high-fat, energy-dense diets and is accompanied by insulin and leptin resistance, hyperlipidemia, and hypertension [25]. When outbred Sprague-Dawley rats are placed on a 31% high-energy (HE) diet, approximately half become hyperphagic and develop DIO, whilst the remainder are diet-resistant (DR) and do not become obese [26, 27]. Selective breeding of the highest and lowest weight gainers on HE diet has led to the development of DIO and DR rat substrains that have bred true to their metabolic phenotype for over 30 generations [28].

In adult DIO rats, voluntary wheel running can lower the defended body weight gain and adiposity. However, exercise selectively decreases body weight gain and adiposity only in obese rodents [23, 29–32]. It is likely that this differential effect of exercise can be accounted for by the fact that exercise leads to a preferential loss of adiposity, presumably by increasing white adipose tissue (WAT) lipolysis via an increase in WAT sympathetic activity [33]. Exercise-induced loss of adipose tissue lowers plasma leptin levels which should drive these animals to increase their food intake [23, 32, 34]. However, no such compensation occurs in obese rats [23, 24, 32, 34]. There is currently no known mechanism for this uncompensated loss of adiposity induced by exercise.

For this reason, we have used DIO and DR rats to study the mechanisms by which exercise alters the central regulation of the energy homeostasis. As with most rodent strains, both outbred and selectively bred DIO and DR rats display a wide individual variability in their degree of voluntary wheel running. However, even before selectively bred DIO rats are placed on a HE diet and become obese, these rats run only half as much as DR rats in a wheel [23]. This differs from outbred DIO and DR rats which show no differences in wheel-running rates or activity in an open field before DIO rats are made obese on HE diet [23, 35]. Furthermore, both outbred and selectively bred DIO rats show no correlation between the distance of wheel running and their exercise-induced reductions in body weight gain or adiposity. Instead, they appear to regulate body weight and fat mass by adjusting their food intake in response to the increased energy expenditure associated with running [23, 32]. While neither exercising juvenile nor adult DIO rats compensate for their negative levels of energy balance by increasing the energy intake, exercising outbred DR rats do make appropriate adjustments and fail to lose significant amounts of body weight or adiposity [32]. This effect is very similar to the relative lack of correction made by DIO rats when they are exposed to the increased fat content and caloric density of the HE diet as compared with the rapid downregulation of intake by DR rats [36]. However, the adjustment of intake during exercise is not uniform among all exercising rodents; the amount of food consumed can either increase, decrease, or be unchanged, depending upon strain, dietary fat content, and palatability of the diet consumed [31, 37–41]. Therefore, it appears that many obese rodents adjust their food intake to maintain a lowered level of energy balance instead of altering the intensity of their running-wheel activity. But there are exceptions to this 'rule'. For example, when exercise is combined with chronic caloric restriction, DIO rats reduce their running rates to compensate for the additional loss of energy stores imposed by dieting [23]. It is likely that variations in the intensity of running-wheel activity may serve more as an indication of the rewarding properties of physical activity than as a signal of energy balance.

The combination of exercise and caloric restriction is a common therapeutic regimen for the treatment of obesity. In DIO rats, exercise plus caloric restriction produces an additive effect on reducing adiposity that is greater than that of exercise or caloric restriction alone [23]. Although calorically restricted exercising rats reduce their energy expenditure by decreasing their running-wheel activity by half, they still lose more adiposity than similarly restricted sedentary rats. Exercise also appears to lower the level of body weight and adiposity about which

obese rats regulate their body weight set point. For example, when calorically restricted sedentary rats are allowed to feed ad libitum, they increase their adiposity to the level of unrestricted sedentary rats, while previously restricted exercising rats regain the lower level of adiposity of unrestricted exercising rats. This suggests that exercise has lowered the defended level of adiposity [23]. Hypothalamic neuropeptide expression serves as a central correlate of this compensatory response to exercise. Caloric restriction of sedentary rats to the levels of adiposity seen in exercising rats causes an increase in anabolic ARC NPY and a decrease in catabolic ARC POMC mRNA expression. However, the reduced adiposity associated with exercise fails to significantly alter the expression of these peptides despite considerable lowering of their plasma leptin levels [23]. Furthermore, while intense exercise can lead to an increased orexigenic ARC NPY mRNA expression, such rats still fail to compensate for lost energy stores by increasing their intake [42]. Taken together, these data strongly suggest that exercise provides some unknown signals to the brain that allow rats to override the usually potent stimulation of anabolic NPY and inhibition of catabolic POMC expression provided by the lowering of leptin levels during weight loss. As a result, they fail to compensate for lost adiposity by increasing their caloric intake, and they avidly defend their adiposity at a new lower set point.

Unfortunately, as with many humans, the loss of adiposity caused by exercise in adult rats does not persist after exercise termination [39]. One exception to this is the long-lasting effect of exercise in adult Otsuka Long-Evans Tokushima fatty rats which have an inborn deletion of their cholecystokinin A receptors [24]. On the other hand, exercise begun early during the postweaning period in DIO rats can have permanent effects on lowering body weight gain, adiposity, and leptin levels for several weeks after exercise is terminated [34]. This 'permanent' lowering of the body weight set point is associated with long-term changes in hypothalamic neuropeptide expression and leptin signaling [unpubl. data]. Even though the development of ARC NPY/agouti-related peptide and POMC neuronal projections to their targets in the paraventricular nucleus and lateral hypothalamic area are largely completed by the 2nd week of life [43, 44], the fact that postweaning exercise can produce permanent lowering of the defended body weight suggests that the critical period of hypothalamic development may actually extend beyond weaning. Such hypothetical remodeling may occur by continued pruning and retraction of these pathways, persisting even after their targets are reached. If this hypothesis is correct, it would provide a mechanism by which early-onset exercise could positively influence the properties of hypothalamic circuit formation to foster a lowering in the body weight set point. Since the formation of these hypothalamic pathways is highly dependent upon the presence of leptin signaling [45], the increased hypothalamic leptin sensitivity produced by early-onset exercise [unpubl. data] may provide one mechanism for the permanent lowering of the defended body weight.

Such studies raise the question of what signals produced by exercise aid in the lowering of the defended body weight and adiposity and prevent compensatory increases in energy intake. Although little is known about the relationship between exercise and the hypothalamic pathways that control the energy homeostasis, many studies have focused on the effects of exercise on other brain functions that are influenced by neurotransmitters and other factors that are also involved in body weight regulation. Among these systems are catabolic corticotropin-releasing factor (CRF), serotonin (5-HT), brain-derived neurotrophic factor (BDNF), anabolic norepinephrine, and γ-aminobutyric acid [46–53]. Exercise increases corticosteroid production and therefore alters the catabolic CRF expression. Several studies have implicated CRF in the anorectic effects of exercise. Exercising Otsuka Long-Evans Tokushima fatty rats display increased CRF levels in the hypothalamic dorsomedial nucleus during the initial period of exercise, suggesting that CRF in this nucleus may play a role in the inhibition of feeding compensation [24]. Because BDNF has catabolic properties and has been widely implicated in neurogenesis and plasticity, it is another possible agent for exercise-induced alterations in body weight regulation [48, 52]. Not only may BDNF play a role in the failure of exercising rats to increase their energy intake, but BDNF might also positively alter the wiring of the hypothalamic circuits that control energy homeostasis. Transient changes in ventromedial nucleus BDNF expression during the postnatal period have implicated BDNF in the early development of the hypothalamus [54]. Moreover, leptin can induce the expression of BDNF in the ventromedial nucleus, and both interleukin-6 (IL-6) and the melanocortin system induce BDNF mRNA, further suggesting a potential role for BDNF in the regulation of the energy homeostasis [55–57] and in the perpetuation of the lowered body weight set point seen with early-onset exercise.

While such changes in central pathways are well described, the peripheral signals responsible for these alterations are not well defined. Figure 1 is a hypothetical

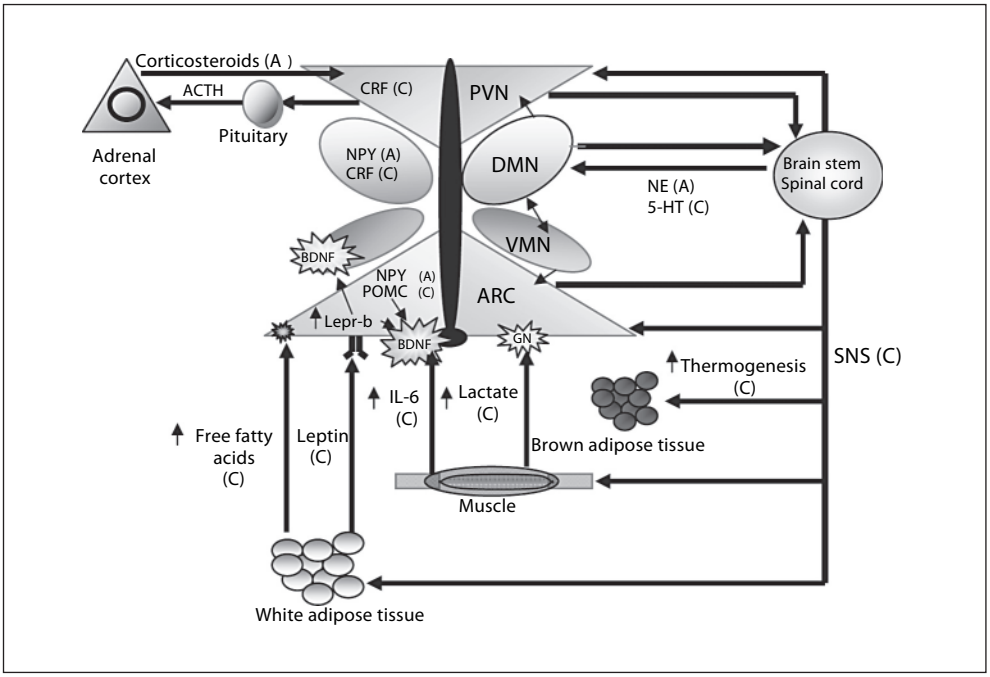

Fig. 1. Model of potential exercise-induced central and peripheral factors that may alter the pathways involved in energy homeostasis. Catabolic factors (C) decrease food intake and increase energy expenditure. Anabolic factors (A) increase food intake and decrease energy expenditure. An upregulation of leptin receptors (Lepr-b) within the arcuate nucleus may cause an increase in central leptin sensitivity, leading to a reduction in food intake and to an increase in energy expenditure. Free fatty acids may act on specialized sensing neurons within the hypothalamus and may be interpreted as an excess of energy stores. Interleukin-6 (IL-6), leptin, and α-melanocyte-stimulating hormone released from pro-opiomelanocortin (POMC) neurons within the arcuate nucleus may increase brain-derived neurotrophic factor (BDNF) mRNA expression in arcuate (ARC) and ventromedial (VMN) nuclei. Lactate may act on specialized glucosensing neurons (GN) within the hypothalamus to alter their firing rate and to decrease food intake. ACTH = Adrenocorticotropic hormone; CRF = corticotropin-releasing factor; NPY = neuropeptide Y; PVN = paraventricular nucleus; DMN = dorsomedial nucleus; NE = norepinephrine; 5-HT = serotonin (5-hydroxytryptamine); SNS = sympathetic nervous system.

model of some of the factors that might act as signals from the exercising body to the brain. Release of fatty acids by exercise-induced activation of WAT sympathetic activity is one possible signal, since specialized hypothalamic neurons can sense and respond to free fatty acids to alter energy homeostasis [58, 59]. Exercise also increases plasma and brain lactate levels, and lactate may act on glucosensing neurons that use it as an alternate fuel to glucose to decrease food intake and alter their firing rate [60, 61]. Increased brain lactate levels may be sensed by hypothalamic neurons as an excess of energy stores. IL-6 is another potential signal connecting exercise to energy homeostasis. Muscle-derived IL-6 released into the plasma can increase markedly during exercise, and such increases can persist long after exercise termination [62]. IL-6 increases in the brain and plasma following exercise can raise energy expenditure and thermogenesis associated with decreased energy intake [63–65]. Although fatty acids, lactate, and IL-6 are reasonable candidates as exercise-derived signals from the periphery to the brain, significantly more information will be needed to definitively implicate these or other signals as critical determinants of the effects of exercise on lowering the defended body weight.

In summary, exercise can selectively lower the defended body weight gain and adiposity in DIO versus DR rats. Importantly, this reduction occurs in the absence of compensatory increases in food intake that would be expected based on their increase in energy expenditure. Furthermore, this effect is not dependent upon the amount of running-wheel activity, but correlates highly with caloric intake. This suggests that rats monitor their energy balance not by their amount of activity, but by utilizing exercise-generated signals from the periphery that allow

them to regulate caloric intake. Exercise and caloric restriction have an additive effect on lowering body weight gain and adiposity. Additionally, exercise produces a very different array of hypothalamic neuropeptide expression than caloric restriction, showing that exercise provides a unique mechanism for altering energy homeostasis. Unlike exercise in the adult rat, early-onset exercise during the postweaning period can produce long-lasting reductions in adiposity that persist even after exercise termination. These observations raise several important issues. First, since exercising rats do not compensate for their lost adiposity by increasing their energy intake, there must be some signal from the exercising body which prevents such compensation. Second, one or several of these signals must be responsible for the unique effects of postweaning exercise on long-lasting reductions in body weight gain and adiposity, and other neural systems are likely to play a role in this effect. Even if the effects of exercise in rodents do not directly parallel the effects of exercise in humans, identification of exercise-induced central and peripheral factors and how they interact to modulate energy homeostasis may aid in the identification of new targets for the pharmacological treatment of human obesity.

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