Neurobiology of Exercise

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Abstract

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Voluntary physical activity and exercise training can favorably influence brain plasticity by facilitating neurogenerative, neuroadaptive, and neuroprotective processes. At least some of the processes are mediated by neurotrophic factors. Motor skill training and regular exercise enhance executive functions of cognition and some types of learning, including motor learning in the spinal cord. These adaptations in the central nervous system have implications for the prevention and treatment of obesity, cancer, depression, the decline in cognition associated with aging, and neurological disorders such as Parkinson's disease, Alzheimer's dementia, ischemic stroke, and head and spinal cord injury. Chronic voluntary physical activity also attenuates neural responses to stress in brain circuits responsible for regulating peripheral sympathetic activity, suggesting constraint on sympathetic responses to stress that could plausibly contribute to reductions in clinical disorders such as hypertension, heart failure, oxidative stress, and suppression of immunity. Mechanisms explaining these adaptations are not as yet known, but metabolic and neurochemical pathways among skeletal muscle, the spinal cord, and the brain offer plausible, testable mechanisms that might help explain effects of physical activity and exercise on the central nervous system.

Key words: brain and behavior, energy balance, neural plasticity, neurotrophins, stress

Introduction

There is growing evidence that insufficient physical activity associated with the modern sedentary lifestyle is a major contributor to increased risks of incident obesity, cardiovascular diseases, type 2 diabetes, osteoporosis, cancer, and depression. There is also growing evidence that increased physical activity, or reinstatement of normal levels, reduces the risks of these diseases (1–3). One way by which physical inactivity increases the risk of disease is through disturbances of energy balance. Obesity has been identified as a major risk factor for type 2 diabetes and cardiovascular disease, and both too high ($\geq$30 kg/m^2) and too low ($<$18.5 kg/m^2) BMIs are associated with an increased mortality rate (4). However, there is also clear evidence for beneficial health effects of physical activity that are independent of effects on energy balance.

Although the general physiology of exercise has been a very active area of research during the past 40 years, the neurobiology of exercise has been virtually absent from public health discourse (5). This is surprising because emerging evidence suggests that physical activity may confer health protective benefits for several neurological diseases including Parkinson's disease (6), Alzheimer's dementia (7), and ischemic stroke (8), as well as injuries from falls attributable to neuromuscular declines associated with

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physical inactivity among the elderly (9). There is also emerging evidence about the adaptability of neurobiological systems and their influence on performance and health during physical exertion in adverse conditions such as heat (10), hypoxia (11), and military combat (12).

It is now accepted that the brain controls mental, physiological, and behavioral processes; that brain functioning is controlled by genes; that social, developmental, and environmental factors can alter gene expression; and that alterations in gene expression induce changes in brain functioning and behavior (13). Brain neural circuits that regulate feeding, mood, pleasure, pain, memories about reward for behavior, and cognitions such as wanting, liking, and executive functions have been elaborated (14–16). Also, some of the neural circuits regulating effort-related decision-making have been identified (17). In contrast, relatively little is known about mechanisms underlying the influence of physical activity and exercise on the form and function of central and peripheral neural systems (18–23).

As an initial step toward advancing study and knowledge in this area of inquiry, an expert workshop on "The Neurobiology of Exercise" was held at the Pennington Biomedical Research Center, Baton Rouge, LA, on December 6 and 7, 2004. Twenty-three prominent researchers made formal presentations, and another 25 guest scientists participated actively in the discussions. The objective was to bring together established leaders in neurobiology and exercise science to begin discussions of this emerging field of study. The focus was on how exercise affects cognition, motivation, mood, stress, immunity, and energy balance, as well as the ability to learn a motor skill and the putative mechanisms through which these effects are mediated.

The purpose of this paper is to present a consensus view that reflects the content and consensus of the workshop. Our goal is to offer a foundation that will help accelerate and expand research in the field of exercise neurobiology and related fields of study.

Effects of Exercise on Brain and Behavior

Cognitive Functions

Chronic physical activity improves brain health. Among humans, regular exercise has a beneficial impact on depression (24–27), quality of sleep (28), and cognitive function in older adults (29–35). The positive effects on cognition occur generally and even more so for those processes requiring greater executive control (i.e., processes involved in scheduling, planning, monitoring, and task coordination). Both long-term research from cross-sectional studies and short-term research from randomized clinical trials suggest positive influences of physical activity and fitness training on human brain structure and function. Some evidence further suggests that there can be beneficial effects of fitness training on cognition across the life span, although the optimal amount and kind of physical activity for sustaining optimal brain function will likely vary across the life span. Animal studies using behavioral models of depression (36–38) and learning/memory (39–41) have corroborated and suggested neurobiological explanations (42–44) for some of the positive clinical outcomes of exercise observed among humans.

Neurotrophic Effects

Chronic physical activity increases the expression of brain growth factors. In rats and mice, chronic exercise can increase the expression of genes that encode several brain neurotrophins such as brain-derived neurotrophic factor (BDNF)[1] (45–49), nerve growth factor (47,50), and galanin (51).

Chronic physical activity may also have neurogenerative and neuroprotective influences on the brain by stimulating the growth and development of new cells (52,53) and protecting against ischemic neuronal damage in the hippocampal formation (8) and neurotoxic damage in the neostriatum (6,54).

Some putative mechanisms by which exercise affects cognition have been identified. For example, learning capacity is mediated by the action of BDNF on synaptic plasticity, which has the potential to underlie cognition (23,55,56). Periods as short as 1 week of voluntary wheel running can increase the capacity for learning and memory in rats (57). It is now understood that the action of exercise on the BDNF system modulates the function of intracellular signaling systems such as calcium-calmodulin kinase II and mitogen-activated protein kinase, with endpoint effects on the production and function of cAMP response element binding protein (CREB). Enhanced learning after chronic activity wheel running has also been accompanied by decreases in extracellular amyloid-β plaques and proteolytic fragments of amyloid precursor protein in a transgenic mouse model of Alzheimer's disease (39).

A central question that remains to be answered is whether, or how, physical activity elicits processes of energy metabolism to selectively impact neuronal plasticity underlying cognitive function. It has recently been found that, in the hippocampus, exercise significantly increases the levels of the mitochondrial uncoupling protein 2, an energy-balancing factor concerned with the maintenance of calcium homeostasis, ATP production, and free radical management (58). Uncoupling protein 2 seems to modulate BDNF production by hippocampal cells, as well as molecular systems downstream to BDNF action (e.g., CREB, synapsin I, calcium-calmodulin kinase II) that are important for learning and memory. These studies suggest fundamental mechanisms by which exercise affects key elements of

[1] Nonstandard abbreviations: BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; NE, norepinephrine; 5-HT, 5-hydroxytryptamine; DRN, dorsal raphe nucleus; LC, locus coeruleus; CNS, central nervous system.

energy metabolism that modulate substrates of synaptic plasticity underlying learning and memory.

Treadmill exercise training has been accompanied by increased gene expression for BDNF and nerve growth factor concomitantly with reduced brain infarct volume after focal ischemia by middle cerebral artery occlusion in rats (50,59,60), and it has mitigated caspase-dependent apoptosis in hippocampal neurons after transient global ischemia in the gerbil (61). Exercise can also improve the outcome of traumatic brain injury, but the timing, and probably the intensity, of its application is important for effectiveness. For example, exercise provided 2 weeks, but not immediately, after concussive brain injury attenuates the effects of the injury through a BDNF-mediated mechanism (62). Neuroprotection by prior locomotory training against chemical lesioning of nigro-neostriatal dopamine neurons seems to result, in part, from an increase in the availability of the trophic factor, glial cell line-derived neurotrophic factor, which can, in turn, stimulate certain cell signaling cascades, including the activation of extracellularly regulated kinases (6).

Counteracting the Effects of Stress

Chronic physical activity mitigates several harmful consequences of acute exposure to stress that are observable at different levels of function, including behavioral/emotional, immunologic, neural, and cellular levels. Chronic wheel running in rats prevents the behavioral consequences of uncontrollable stress such as learned helplessness (37,63,64), an established animal model of stress-induced affective dysregulation that exhibits features of both depression and anxiety. Chronic wheel running before exposure to uncontrollable stress also protects against the suppression of natural killer cell activity (65) and T helper cell-dependent keyhole limpet hemocyanin antibody (66–68) observed in sedentary rats after exposure to uncontrollable stress, possibly through alteration in immune modulation by splenic norepinephrine (NE) (69,70).

Neural consequences of wheel running that may contribute to these stress-protective effects include alterations in serotonergic [5-hydroxytryptamine (5-HT)] and NE systems (37,64,71,72). Chronic activity wheel running or treadmill running results in small increases in basal levels of 5-HT in the dorsal raphe nucleus (DRN) (63) and increased turnover of 5-HT in brain cortex (38). Chronic wheel running also attenuates stress-induced c-Fos induction in 5-HT neurons of the DRN (37,64) and increases levels of 5-HT_{1A} inhibitory autoreceptor mRNA in the DRN (37,73). Because learned helplessness is thought to be produced by hyperactivation and subsequent sensitization of 5-HT neurons in the DRN (74), chronic wheel running could prevent learned helplessness by producing resistance to increases in the synthesis or release of 5-HT, thereby mitigating excessive DRN 5-HT responses to stress.

Exercise may also act through the NE system. Wheel running and treadmill running lead to increased basal levels of NE in the locus coeruleus (LC) (63) and the frontal cortex, along with down-regulation of cortical β-adrenoreceptors (38); increased mRNA for the NE modulator, galanin, in the LC (41,75); blunted release of NE in the frontal cortex (76); and blunted depletion of NE levels in the LC, hippocampus, hypothalamus, and amygdala (77) in response to uncontrollable stress. Hence, adaptations of the brain NE system after chronic exercise also may mitigate an exaggerated stress response.

The protective cellular stress protein, heat shock protein 72, is increased in the human brain after prolonged (i.e., 3 hours) submaximal exercise (78). Also, chronic wheel running produces a larger and faster response of heat shock protein 72 in the brain, spleen, heart, liver, and lymph nodes in rats after exposure to a variety of stressors, including bacterial challenge (79) and tail shock or forced exhaustive exercise (80).

In Search of Mechanisms

An understanding of the influence of the central nervous system (CNS) on motor neurons is emerging, especially as it applies to limitations to neuromuscular performance (21,81). Corollaries of motor command or effort are available at multiple levels in the CNS and are likely to sustain multiple functions (e.g., motor, sensory, cardiovascular, respiratory, hormonal) during physical activity. However, their influences on CNS functions (e.g., executive cognitive function, learning, emotional responding, and motivated aversive or appetitive behavior) other than those dedicated to controlling locomotion and supporting its resultant increase in metabolism are not known and have received little study. Nonetheless, several metabolic and neurochemical pathways among skeletal muscle, the spinal cord, and the brain suggest ways by which physical activity and exercise might influence the CNS (Figure 1).

For example, lactate taken up from skeletal muscle seems to act as an intercellular energy shuttle within the brain during high-intensity exercise (82), and changes in oxidative enzymes in skeletal muscle after exercise could have indirect effects on brain metabolism. Both short-term high-intensity and prolonged low-intensity exercise increase pyruvate dehydrogenase kinase-4 transcription (PDK4) in active skeletal muscle, thus inhibiting the entry of carbohydrate-derived fuel into the mitochondria for oxidation and limiting the use of glucose as a fuel for skeletal muscle, subsequently protecting the increased metabolic needs of the brain during and after exercise (83).

Whether brain metabolic responses to acute physical activity extend beyond regions specifically involved with skeletal motor, sensory, and cardiovascular autonomic control is not as yet clear (84,85). Transient increases in local cerebral glucose use in the motor cortex, cerebellum, stria-

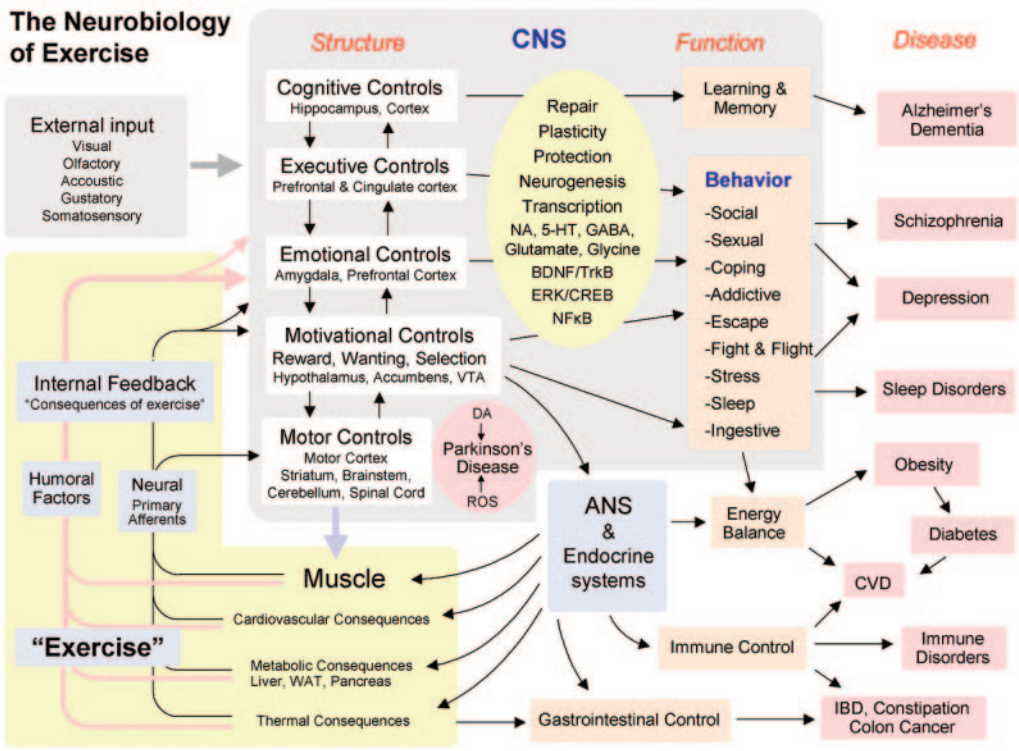

Figure 1: A heuristic diagram for understanding the neurobiology of exercise and physical activity. ANS, autonomic nervous system; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CREB, cyclic adenosine monophosphate response element-binding protein; CVD, cardiovascular disease; DA, dopamine; ERK, extracellular signal-regulated kinase; 5-HT, 5-hydroxytryptamine; GABA, gamma amino butyric acid; IBD, inflammatory bowel disease; NA, noradrenaline; NFκB, nuclear factor of kappaB; ROS, reactive oxygen species; TrkB, tyrosine residue kinase receptor-type 2; VTA, ventral tegmental area; WAT, white adipose tissue.

tum, thalamus, hippocampus, the somatosensory, auditory, and visual cortices, and dorsal raphe, and in specific areas of the hypothalamus, amygdala, and hippocampus have been reported in response to acute strenuous treadmill running (of unclear novelty) in the rat (86). Also, the discharge rate of a select pool of hippocampal cells (~12% of recorded CA1 cells) has been observed to increase as running velocity increases (87). However, it is not known whether these cells are activated directly by physical exertion or whether, similar to place cells, their activation depends on spatial-temporal cues. Moreover, oxidative capacity after chronic voluntary activity wheel running is increased only in the striatum and limb representations in the motor cortex and not in the hippocampus of rats (88). In humans, cerebral blood flow is transiently increased in the thalamus, anterior cingulate, insula, and sensorimotor cortex during static handgrip (89) and in the thalamus and insula during dynamic cycling exercise (90).

The influence of central motor command on autonomic cardiovascular responses during exercise has been shown by increases in perceived exertion, blood pressure, and heart rate, concomitantly with increased cerebral blood flow to insular and thalamic regions, after hypnotic suggestion of increased work during constant-load cycling exercise (91). Epidural anesthesia sufficient to cause cutaneous sensory loss and paralysis of the legs during electrically induced dynamic exercise suggests that neural and humoral mechanisms exert redundant control of circulating catecholamines, growth hormone, and adrenocorticotropic hormone. In contrast, neural input from motor centers and feedback from active muscles both seem important for glucose production and lipolysis during exercise in humans (92). Also, during complete paralysis by curarization, heart rate, blood pressure, and perceived effort still increase during attempted contraction of skeletal muscles, indicating that central motor command can operate independently of somatosensory inflow to the CNS (93).

Energy Balance

Exercise selectively reduces body weight and/or adiposity in obese compared with lean rodents (94), and exercise is associated with increased resting metabolic rate in rats (95). However, the role of exercise in lowering the defended

body weight in obese humans is controversial (96–98). Among the small number of obese individuals who successfully maintain significant weight loss for >2 years, a select group report that they engage in a high level of exercise; this seems to prevent the chronic reduction in resting metabolic rate usually associated with chronic weight loss in sedentary obese individuals (99–101). There is no evidence that an effect of exercise in promoting weight loss is sustained once exercise ceases. There are data suggesting that lean and obese individuals do not readily compensate for the increased energy expenditure of exercise by increasing energy intake (102–104).

When exercise is begun in the early post-weaning period and continued for several weeks in obese rats, there is a prolonged reduction in weight and adipose tissue once exercise ceases (105). Depending on strain and sex, some rats do not increase their energy intake sufficiently to compensate for the loss of body weight and adiposity (105,106). Exercise induces compensatory changes in central neuropeptide systems involved in the regulation of energy homeostasis (106). Chronic exercise also seems to offer some protection against the effects of poor lifestyle such as those elicited by consumption of a bad diet rich in saturated fat (107). The protective function of exercise on the brain seems to be achieved by an impact on molecular systems similar to the impact on systems disrupted by dietary factors, such as upstream and downstream regulation of BDNF signaling systems (108).

During prolonged exercise in humans, the cytokine interleukin-6 is released from the brain (109) and from active skeletal muscle, where it has glucostatic effects (110). Thus, it is plausible that interleukin-6 could play a role in CNS modulation of energy balance between expenditure and intake.

Is Physical Activity Regulated?

Neurobiological aspects of the regulation of physical activity by the CNS are poorly understood and have been studied mainly to understand central fatigue (i.e., a progressive decline in the drive to motor neurons) during exhaustive exercise in rats (111) and humans (21) and during prolonged strenuous exercise in humans under conditions of hyperthermia and hypoglycemia (10,112). *Homo sapiens* has evolved a large cerebral cortex with expanded motor and executive regions, as well as an elaborate distribution of direct and indirect corticospinal connections with motor neurons that supports prolonged physical activity such as sustained running (113). One consequence of this evolution is the ability, through central drivers from the motor cortex, locomotory circuits, or motor neurons, to override strong somatic, visceral, and "homeostatic' circuits, which, if activated, would stop ongoing exercise. Putative brain mechanisms of impaired voluntary activation of motor neurons during prolonged strenuous exercise include an effective decrease in supraspinal motor drive to motor neurons (21), which may be associated with increased brain 5-HT activity, elevated ammonia levels, brain glycogen depletion, decreased striatal dopamine, and inhibitory feedback from the exercising muscles (10). The reduction in spinal motor neuron activation results from altered inflow from muscle spindle, tendon organ, and group III and IV muscle afferents that innervate the fatiguing muscle and that act predominantly at supraspinal sites rather than directly on motor neurons (21,114).

It is also known that spinal motor learning that is specific to a practiced task (e.g., standing or stepping) can occur within the neuronal networks in the lumbosacral spinal cord in mice, rats, cats, and humans that have a transected spinal cord (20). This learning involves the two major inhibitory neurotransmitter systems within the spinal cord: glycine and gamma amino butyric acid. Spinal cord transection results in augmentation of these systems above normal levels, but training to step reduces these levels back toward normal levels. Administration of 5-HT agonists enhances stepping in mice that have complete spinal transections and facilitates learning to step when combined with training. The functional properties of the lumbosacral spinal cord and the general mechanisms by which locomotion is controlled in humans (115) seem to be qualitatively similar to those described for several laboratory animals (20,116–119).

The effects of neural activation of skeletal muscle are also becoming clearer. As few as 4 minutes of daily total stimulation, under isometric conditions, of otherwise electrically silent skeletal muscles are sufficient to maintain the mass of a fast extensor muscle. The importance of the motor activity associated with the support of body weight seems to be critical in maintaining basal levels of neurotrophins and neuroplasticity in the spinal cord (120) and the body's normal endocrine responses to exercise. For example, the chronic absence of weight-supporting activity results in a depression of the normal release of a pituitary derived trophic factor, which has some growth hormone–like properties, in response to modest exercise (121).

In contrast to the study of factors that limit skeletal muscle control of locomotion under conditions of impairment, the neurobiological regulation of voluntary non-strenuous physical activity by healthy animals has received little study. For example, mice (122) and rats (123) have been selectively bred for voluntary wheel running or treadmill running, but genes that might help explain motivated running have yet to be identified. The tight relationship between increased body mass and decreased spontaneous activity levels among rats and mice, irrespective of fat mass, has led to a hypothesis that a reduction in spontaneous activity is a symptom of obesity (124), but how body mass might be sensed to regulate voluntary physical activity is not known.

Reduced dopamine release or loss of dopamine receptors in the brain seems to be related to the age-related decline in physical activity observed among many species (125). The ventral-tegmental-nucleus accumbens dopamine system is a critical component of the forebrain circuitry that regulates activational aspects of motivation (17). Accumbens dopamine depletions decrease spontaneous, stimulant-induced, and food-induced motor activity, depending on the work requirements of the task. Antagonists of dopamine and depletions of accumbens dopamine cause rats to reallocate their instrumental behavior away from food-reinforced tasks that have high work requirements and toward the selection of less effortful types of food-seeking (126), implicating dopamine brain circuitry in energy-related decision-making.

Electrical self-stimulation of the ventral tegmental area has been used to motivate treadmill running (127) and weight lifting (128) in rats, but little is known about the role of the meso-limbic dopamine system (e.g., ventral tegmental area and the nucleus accumbens) in the motivation of voluntary physical activity such as wheel running. Treadmill running acutely increases dopamine release (129) and turnover (130) and chronically up-regulates D2 receptors (131) in the striatum of rats, but the effects of exercise on striatal dopamine activity have not yet been shown in humans (132).

Fos expression is increased in the medial region of the rostral and central striatum and in the dorsal region of the caudal striatum after acute treadmill running (133). A recent study found that c-fos and ΔfosB in the nucleus accumbens were activated during wheel-running in rats, and mice that overexpress ΔfosB selectively in striatal dynorphin-containing neurons increased their daily running compared with control littermates (134).

Methodological Issues

Physical activity is bodily movement produced by skeletal muscles that results in varying amounts and rates of energy expenditure that are positively related to physical fitness depending on the stimulus features of physical activity such as the type, intensity, regularity, and timing of the activity. Physical activity can occur in short bursts of low to high intensity or long, sustained periods of lower intensity, depending on the type of activity and the fitness of the organism. Exercise is a specific form of physical activity that is structured and repetitive, with the goal of improving or maintaining physical fitness, function, or health.

A problem with the interpretation of much of the aforementioned evidence derived from the predominant use of animal models has been the lack of uniformity in the description and control of the various features of the physical activity stimulus, such as training length (acute vs. chronic), modality and control of the exercise (e.g., voluntary wheel running vs. forced treadmill training or swimming), intensity of the exercise (self-selected vs. manipulated), and duration of the exercise. For example, the duration, and not necessarily the distance or intensity, of wheel running seems to be a critical factor in determining selected behavioral (e.g., learned helplessness) and neurochemical (e.g., serotonergic) effects of wheel running. The type of exercise (running wheel, treadmill, swimming) and the extent to which it is voluntary are both likely to be major determinants of the effects of exercise on energy homeostasis and the central pathways that regulate it. Also, most researchers studying exercise in rodents have used wheel-running or treadmill tasks. In contrast, most of the motivational research has involved lever pressing or maze tasks. It may be interesting to integrate these behavioral methodologies so that intramodal and intermodal comparisons between exercise training and motivation tasks can be made.

Outflow from the CNS to organ systems that support locomotion for a particular task must change over time as the musculoskeletal system changes in response to changes in the amounts or types of physical activity. Hence, it necessarily follows that some of the CNS changes in response to physical activity must directly reflect the altered central drive to execute the same external task. This fact adds to the difficulty of interpreting all CNS changes that accompany chronic physical activity or chronic exercise training sufficient to elicit changes in exercise capacity or capability (i.e., physical fitness).

It is also important to distinguish acute (i.e., transient) responses to a single episode of physical activity from chronic effects (i.e., long-term adaptation) of repetitive physical activity. This is especially pertinent to the appropriate time-point for killing experimental animals after completion of the exercise protocol. Also, it is important to continue to consider whether neurobiological outcomes of enhanced physical activity are specific to increased physical exertion or are a non-specific response to stress or some other psychological state that might be an unintended consequence of the exercise regimen. For example, casting one forelimb results in an increase in the use of the contralateral forelimb, but this "exercise" also causes a stress response. Similarly, it is important to determine in studies of chronic exercise whether the restriction of access to an activity wheel prior (e.g., 24 hours) to death, for the purpose of minimizing acute effects of physical activity, may have unintended effects of eliciting stress responses in specific CNS and neuroendocrine variables.

Studies of treadmill running or swimming in rats or mice have often confounded the exertional stress of physical activity with the emotional stress of coercion, thus making it difficult to distinguish general stress effects from effects unique to exercise. Thus, when treadmill training is a preferred mode of physical activity for a specific question, care should be taken to minimize other stressors [i.e., shock, training in the light (sleep) cycle of rodents].

The CNS adaptations to increases in physical activity are commonly interpreted in comparison with sedentary humans and with rodents whose housing typically constrains their spontaneous activity. Hence, it has been unclear in most studies of rats and mice whether differences in CNS outcomes between active and sedentary subjects reflect augmented responses by active subjects or an abnormal status among the sedentary controls.

Another limitation of the cumulative evidence stems from the limited use of animal models of disease. The selection, or development, of appropriate experimental animal models of disease is likely to greatly accelerate the identification of mechanisms by which physical activity may alter health. Also, when studying potential mechanisms by which physical activity affects behavior and neurobiology, it is particularly important to include modifying variables such as obesity, aging, exposure to stress, infection, and degenerative diseases, rather than assessing responses only under basal conditions. Finally, much more effort is needed to study the neurobiology of exercise and fitness from various levels of integration ranging from genes to cognition to behavior.

Future Research Directions

Although a great deal has been learned about the neurobiology of exercise during the past few decades, much additional information is necessary if we are ultimately going to be able to provide adequately for human health and well-being. The following are some of the key areas that our workshop identified as critical areas for future research.

1. There is a need to more fully characterize the features of the physical activity or exercise stimulus on specific outcome measures of CNS form and function in both humans and experimental animal models of health and disease. For example, we need to know how the impact of exercise is influenced by the type of exercise, whether or not it is voluntary, its intensity, the timing and duration of a single session, and the number and frequency of sessions.
2. Studies of the impact of exercise usually look for changes immediately after the exercise experience and seldom examine subjects months or years later. We need to know how long the effects last and whether there is a "priming effect," whereby prior exercise might potentiate the impact of later exercise.
3. Most studies are done on young, healthy humans or experimental animals. We need to know more about the impact of exercise on various disease states or models; we also need to know whether factors such as age and sex modify the effects of exercise.
4. More experimental studies are needed of potential mechanisms that may explain changes in behavior, cognition, mood, and stress resistance that are elicited by physical activity and exercise.
5. Studies of physical activity and mental or behavioral disorders should model dysfunctions in specific brain circuitries that are established for those disorders.
6. It will be important to reconsider the use of isolated or forced inactive animals as "normal" controls in studies of physical activity and exercise.
7. There is a need to better translate information from animal studies to the human condition. Where possible, more opportunities should be taken to study the CNS in humans (e.g., using in vivo neuroimaging and postmortem analyses of brains from donation repositories) to examine whether neural function and morphology are associated with physical activity status.
8. Studies should examine the mechanistic similarities, interactions, and differences among different exercise training paradigms, cognitive training, and dietary interventions on brain function.
9. There is a need is to determine genes that regulate physical activity, genes that require physical activity to normalize metabolic systems, and genes that mis-express proteins having metabolic functions in physically inactive humans.

Some examples of specific questions about the neurobiology of exercise are as follows.

1. What are the mechanisms that explain the positive effects of chronic exercise on cognitive function, depression, sleep, and fatigue-related disorders?
2. What are the central and peripheral mechanisms that elicit voluntary physical activity?
3. How do meso-limbic structures involved with reward-motivated behavior (e.g., the ventral tegmental area and the nucleus accumbens of the ventral striatum) synergize with other components of the forebrain neural circuitry involved in the regulation of effort during physical activity?
4. How are body mass and work sensed to possibly modulate the level of physical activity?
5. Is there an endocrine signal from muscle that is equivalent to leptin and other metabolic signals generated from adipose tissue?
6. What is the signal from muscle or other peripheral organs that prevents the brain from increasing food intake to compensate for lost adiposity after increased physical activity?
7. Can chronic exercise facilitate the growth of axons and their accuracy in reaching functionally appropriate neural targets?
8. What repair strategies related to physical activity can be developed to improve regenerative and other plastic processes that could enhance motor recovery?

Summary

Voluntary physical activity and exercise training are clearly beneficial to health in many ways. It has been known

for some time that regular physical activity, through its influence on energy balance and mitigation of obesity, can decrease the risk for type 2 diabetes, cardiovascular diseases, and many other obesity-related problems. Regular physical activity can also mitigate central and peripheral sympathetic activity and selectively modulate NE content in peripheral tissues, thereby plausibly reducing hypertension, heart failure, oxidative stress, and immunosuppression. More recently, convincing evidence has accumulated that physical activity and regular exercise can reduce depression, reduce the decline in cognition associated with aging, and provide protection against ischemic, traumatic, and toxic brain insults through influences on synaptic plasticity and axonal growth. It is obvious that the action of exercise on the CNS is mediated by multiple mechanisms involving highly integrated responses of all physiological systems. The study of mechanisms involved in CNS changes that are associated with exercise is essential for the timely development of more efficacious and rapid treatments for several neural and metabolic disorders. Understanding these mechanisms is perhaps even more important for identifying appropriate guidelines for physical activity and exercise that can positively affect public health.

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